STUDIES TOWARDS A SYNTHESIS OF SESBANIMIDE

by

A thesis submitted to the Faculty of Graduate Studies and Research of McGill University in partial fulfilment of the requirements for the Degree of Doctor of Philosophy

Department of Chemistry
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Montreal, Quebec
Canada

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To my parents,

Tian You Tan and Chu Hui Chuao Tan

To my brothers,

Ah-Ti, Francis, Sammy, William and George

To my sisters,

Ah-Bi, Victoria and Estrella

ABSTRACT

A general method of transforming aldehydes via α,β-unsaturated esters to the 3-substituted glutarimide ring was developed and was applied to the construction of ring A of (-)-sesbanimide A (1) and the AB ring moiety of (+)-sesbanimide A (2). The phase-transfer-catalyzed methylenation reaction of dihydroxy dithioacetal **46** brought about a 1,4-migration of the *t*-butyldiphenylsilyl group to provide 1,3-dioxolane derivative **49**.

Model studies towards the synthesis of (+)-sesbanimide (**2**) and C-15 desmethyl sesbanimide **93** were carried out using allylsilanes **74**, **79** and **94**, with aldehydes **56a** and **85**.

The synthesis of 8-*O*-benzyl-13-*O*-*t*-butyldimethylsilyl sesbanimides **88**, 13-deoxychloro sesbanimide **89**, 8-*O*-benzyl-13-*O*-*t*-butyldimethylsilyl-15-desmethyl sesbanimide **91**, 13-deoxychloro-15-desmethyl sesbanimide **92**, 8-*O*-benzyl-13-*O*-*t*-butyldiphenylsilyl-15-desmethyl sesbanimide **96** and 13-*O*-*t*-butyldiphenylsilyl-15-desmethyl sesbanimide **97** are described.

RÉSUMÉ

Une méthode générale de la transformation d'aldehydes aux glutarimides substitués correspondants par l'intermediare des esters α,β-insaturés a été développée. Cette méthode fut employée pour la synthèse du cycle A du (+)-sesbanimide A (1) de même que pour la synthèse des cycles adjacents A et B du (+)-sesbanimide A (2). Une migration-1,4 du groupement *t*-butyldiphénylsilyle a été observée lors de la catalyse par transfert de phase de la methylènation du dithioacétal dihydroxyle **46**. Le dérivé **49**, un dioxolane-1,3, fut ainsi obtenu.

Des études préliminaires à la synthèse du (+)-sesbanimide (**2**) et du sesbanimide 15-desmethylé **93** ont été effectués à l'aide de la réaction des silanes allylés **74**, **79**, et **94** avec les aldéhydes **56a** et **85**.

La synthèse des sesbanimides suivants est également décrite: les 8-*O*-benzyl-13-*O*-*t*-butyldiméthylsilyl sesbanimides **88**, le déoxychloro-13 sesbanimide **89**, le 8-*O*-benzyl-13-*O*-*t*-butyldiméthylsilyl desméthyl-15 sesbanimide **91**, le deoxychloro-13 desméthyl-15- sesbanimide **92**, le 8-*O*-benzyl-13-*O*-*t*-butyldiphenylsilyl desméthyl-15 sesbanimide **96** et le 13-*O*-*t*-butyldiphénylsilyl desméthyl-15 sesbanimide **97**.

ACKNOWLEDGEMENTS

I would especially like to express my gratitude to Dr. George Just, without whose understanding, patience and encouragement, this work would not have been completed.

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All my co-workers for their friendship and helpful discussions.

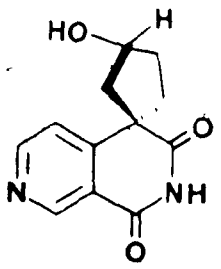
TABLE OF CONTENTS

Glossary of Abbreviations

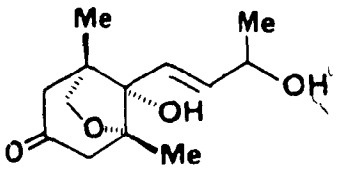
Ac	acetyl	m	multiplet
b	broad	Me	methyl
bs	broad singlet	mL	milliliter
Bn	benzyl	mmol	millimole
Bu	butyl	m.p.	melting point
ca.	circa.	^{1}H NMR	proton nuclear magnetic resonance
C.I.	chemical ionization		
d	doublet	Ph	phenyl
DEA	diethanolamine	pp.	page
dec.	decomposes	ppm	parts per million
DMF	dimethylformamide	q	quartet
E.I.	electron-impact ionization	ref.	reference
		s	singlet
Et	ethyl	t	triplet
FAB	fast atom bombardment	tert	tertiary
		THF	tetrahydrofuran
g	gram	TLC	thin-layer chromatography
gly	glycerol		
Hz	Hertz	x	times
IR	infrared		

INTRODUCTION

In 1976, Powell and co-workers[1] reported that the ethanolic extracts from defatted seed of three legumes, *Sesbania vesicaria* (JACQ.) ELL., *Sesbania punicea* (CAV) BENTH and *Sesbania drummondii* (RYD) CORY exhibited significant activity against P-388 lymphocytic leukemia in vivo.[2] Further work with the extracts from the seeds of *Sesbania drummondii* led to the isolation and structural elucidation of sesbanine[3,4] and drummondol[4] The structure of the former has since been confirmed by total synthesis[5,6,7,8]



sesbanine



drummondol

1 R G Powell, C R Smith, Jr and R V Madrigal, *Planta Med*, 30, 1 (1976)

2 R I Geran, N H Greenberg, M M McDonald, A M Schumacker and B J Abbott, *Cancer Chemother Rep*, Part 3, 3, 1 (1972)

3 R G Powell, C R Smith, Jr and David Weisleder, *J Am Chem Soc*, 101, 2784 (1979)

4 R G Powell and C R Smith, Jr, *J Nat Prod*, 44, 86 (1981)

5 A S Kende and T P Demuth, *Tet Lett*, 715 (1980)

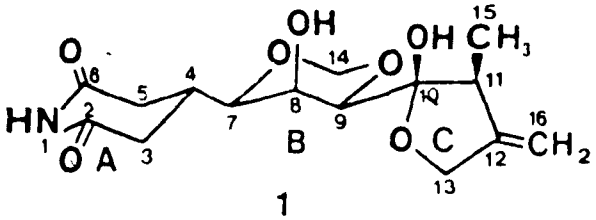
6 J C Bottaro and G A Berchtold, *J Org Chem*, 45, 1176 (1980)

7 M J Wanner, G Koomen and U K Pandit, *Heterocycles*, 15, 377 (1981)

8 K Tomioka and K Koga, *Tet Lett*, 2321 (1981)

Although the chromatographic fractions from which sesbanine and drummondol were isolated were cytotoxic, the pure compounds themselves were essentially devoid of antitumour activity.

In 1983, Powell *et al*[9] disclosed the structure of sesbanimide I (1), a potent antitumour compound, isolated after complicated chromatographic techniques from extracts of seeds of *Sesbania drummondii* in 8 x 10^{-6} % yield. This substance was the correct active ingredient which accounted for the high activity observed previously in extracts from *Sesbania* seeds. The structure was determined from high field proton and carbon nuclear magnetic resonance spectrometric and infrared spectroscopic studies and X-ray experiments which revealed its relative (but not absolute) stereochemistry. Sesbanimide I (1) has a structure in which three rings are linked by single bonds. The glutarimide, lactone and lactol rings are labelled respectively as A, B and C.



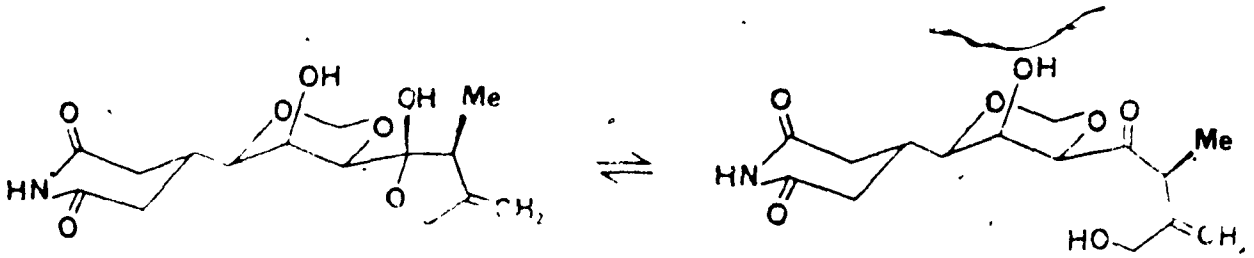
1

A year later, Gorst-Allman *et al*[10] also reported their structural work on sesbanimide, after its isolation from the seeds of *Sesbania punicea*. They confirmed the structure of 1, after an extensive application of high field proton and carbon NMR supplemented with nuclear Overhauser effect studies. These investigators also

9 R G Powell, C R Smith, Jr, D Weisleder, G K Matsumodo and J Clardy, *J Am Chem Soc*, **105**, 3739 (1983)

10 C P Gorst-Allman, P S Steyn, R Vleggar and N Grobbelaar, *J Chem Soc Perkin Trans I*, 1311 (1984)

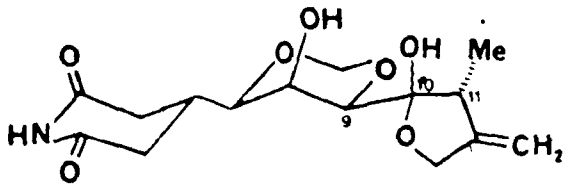
that in solvents more polar than chloroform such as methanol, pyridine and dimethyl sulfoxide, sesbanimide exists as an equilibrium mixture of the hemiacetal form 1 and the ring-opened 7-hydroxyketone 1a



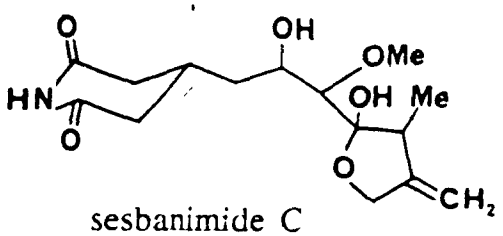
1 1a

In a full paper published by Powell and co-workers[11] in 1984, 1 was renamed sesbanimide A [12] Furthermore, two other antitumour active compounds, sesbanimide B and sesbanimide C, were described. Whereas the configuration about the C-10 carbon of sesbanimide A is fixed, sesbanimide B exists as anomers differing in their configuration at C-10

1



sesbanimide B



sesbanimide C

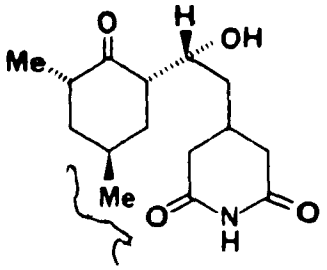
Whether 1 is a fungal metabolite or a higher plant product remains to be determined The biosynthesis of sesbanimide has yet to be investigated. It does however, bear a structural resemblance to the glutarimide antibiotics, the more

11 R G Powell, C R Smith and D Weisleder, *Phytochemistry*, 23, 2789 (1984)

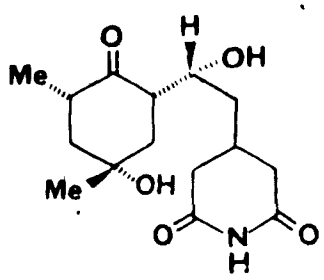
12. For convenience, sesbanimide A will be simply referred to as sesbanimide from hereon

prominent members of this class of natural products being cycloheximide, streptovitacin A, and streptimidone.

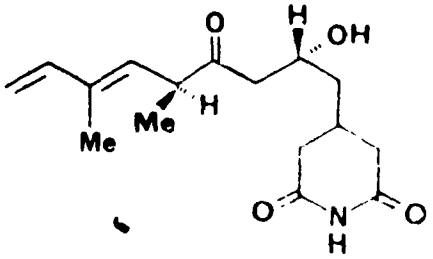
Glutarimide Antibiotics



cycloheximide



streptovitacin A



streptimidone

Cycloheximide is known to be a potent inhibitor of protein synthesis. This compound, and streptimidone are also active antifungal agents. Streptovitacin A, on the other hand, possesses strong antitumour activity.[13]

There is some structural resemblance of the lactol C-ring of sesbanimide to the α-methylene-γ-butyrolactone ring. The latter moiety is an integral building block of many natural products, especially the sesquiterpene lactones, which exhibit interesting biological properties. A large number of these active lactones, including vernolepin,[14] aromaticin,[15] and elephantopin[16] have been isolated from plant extracts which show tumour inhibiting activity. However, none of these terpenoid antitumour agents has been used clinically owing to their extreme toxicity. Attempts to increase the antitumour activity by chemical modifications have, so far, been unsuccessful.

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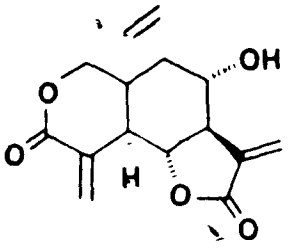
13 H.D Sisler and M R Siegel, *Antibiot (Mech Action)*, **1**, 283 (1967)

14 L. Sequeira, R.J Hemingway and S M Kupchan, *Science*, **161**, 789 (1968)

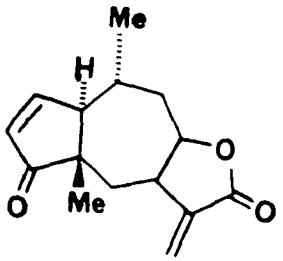
15. S.M Kupchan, M.A Eakin and M Thomas, *J Med Chem*, **14**, 1147 (1971)

16. S M Kupchan, Y Aynehchi, J M Cassady, H.K Schnoes and A L. Burlingame, *J Org Chem*, 34, 3867 (1969)

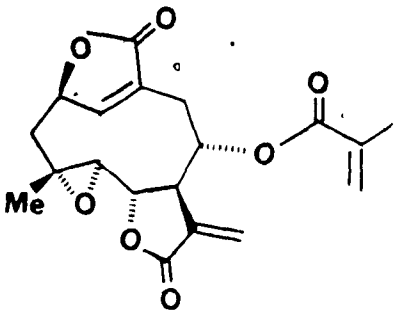
Sesquiterpene Lactones



vernolepin



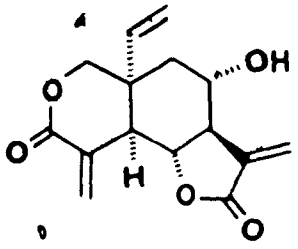
aromaticin



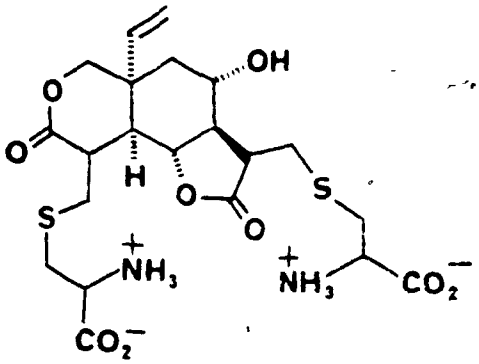
elephantopin

With few exceptions, almost all known cytotoxic sesquiterpene lactones possess an α,β-unsaturated lactone structure, and the double bond must be exocyclic in order for them to exhibit activity. Biological studies performed by Kupchan *et al.*[17,18] have demonstrated α-methylene-γ-butyrolactones to be alkylating agents which are biologically active because they undergo Michael reactions with biological nucleophiles such as L-cysteine or thiol-containing enzymes. In their studies, it was found that the exposure of vernolepin, elephantopin and eupatundin to L-cysteine resulted in the recovery of their corresponding monocysteine adducts.

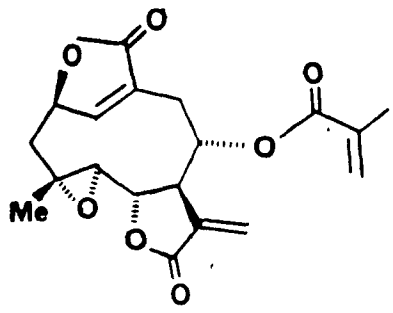
Addition Products



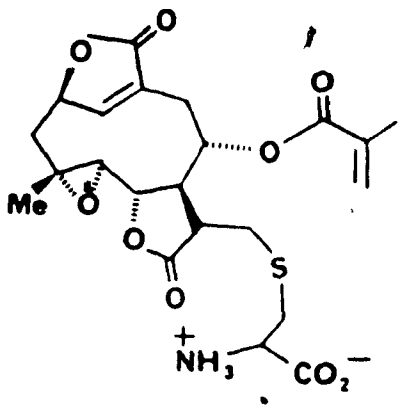
vernolepin

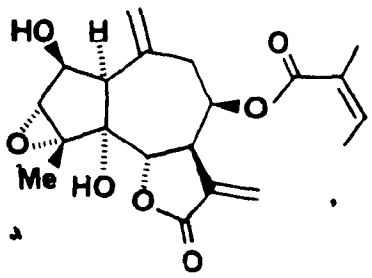


17. S.M. Kupchan, D.C. Fessler, M.A. Eakin and T.J. Giacobbe, *Science*, 168, 376 (1970).
18. R.L. Hanson, H.A. Lardy and S.M. Kupchan, *Science*, 168, 378 (1970).

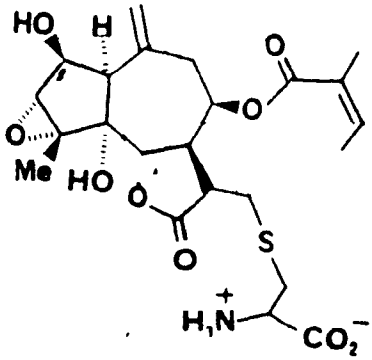


elephantopin



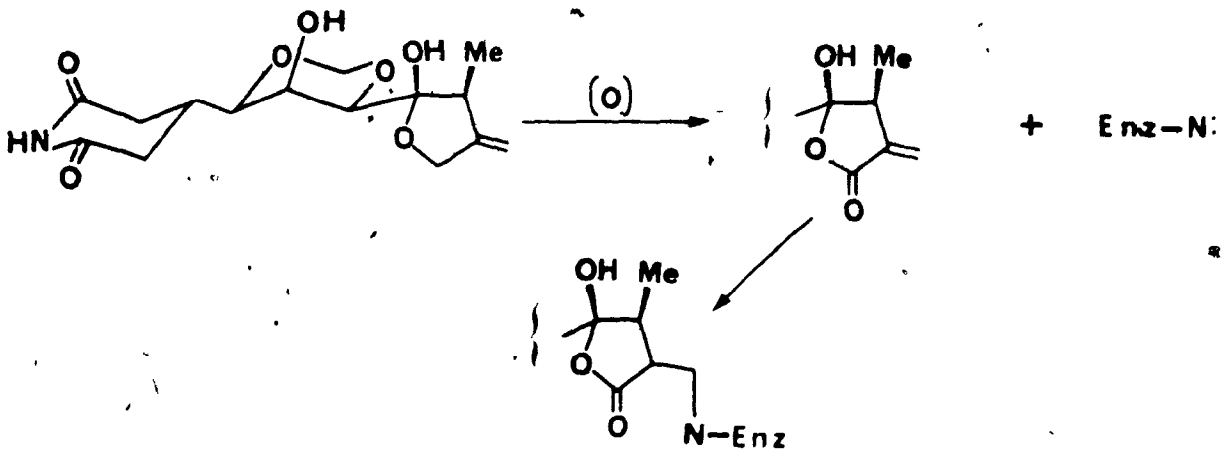


eupatundin



Based on this information, one could postulate that the antitumour mechanism of sesbanimide might involve prior enzymic oxidation of the C-ring at the allylic carbon, followed by attack of the exocyclic double bond by biological nucleophiles (Scheme I).

Scheme I



It should be emphasized that the above mode of action is highly speculative.

Since sesbanimide was isolated in extremely low yields, a thousand pounds of starting seed material being needed to obtain milligram quantities, the full spectrum of its biological activity profile could only be studied after its total synthesis. With this in mind, as well as the novelty exhibited by its tricyclic structure linked by single bonds, and the exceptionally strong antitumour activity of sesbanimide, we were attracted to attempt a synthesis of sesbanimide and if successful, some of its analogues.

Chapter 1

Introduction

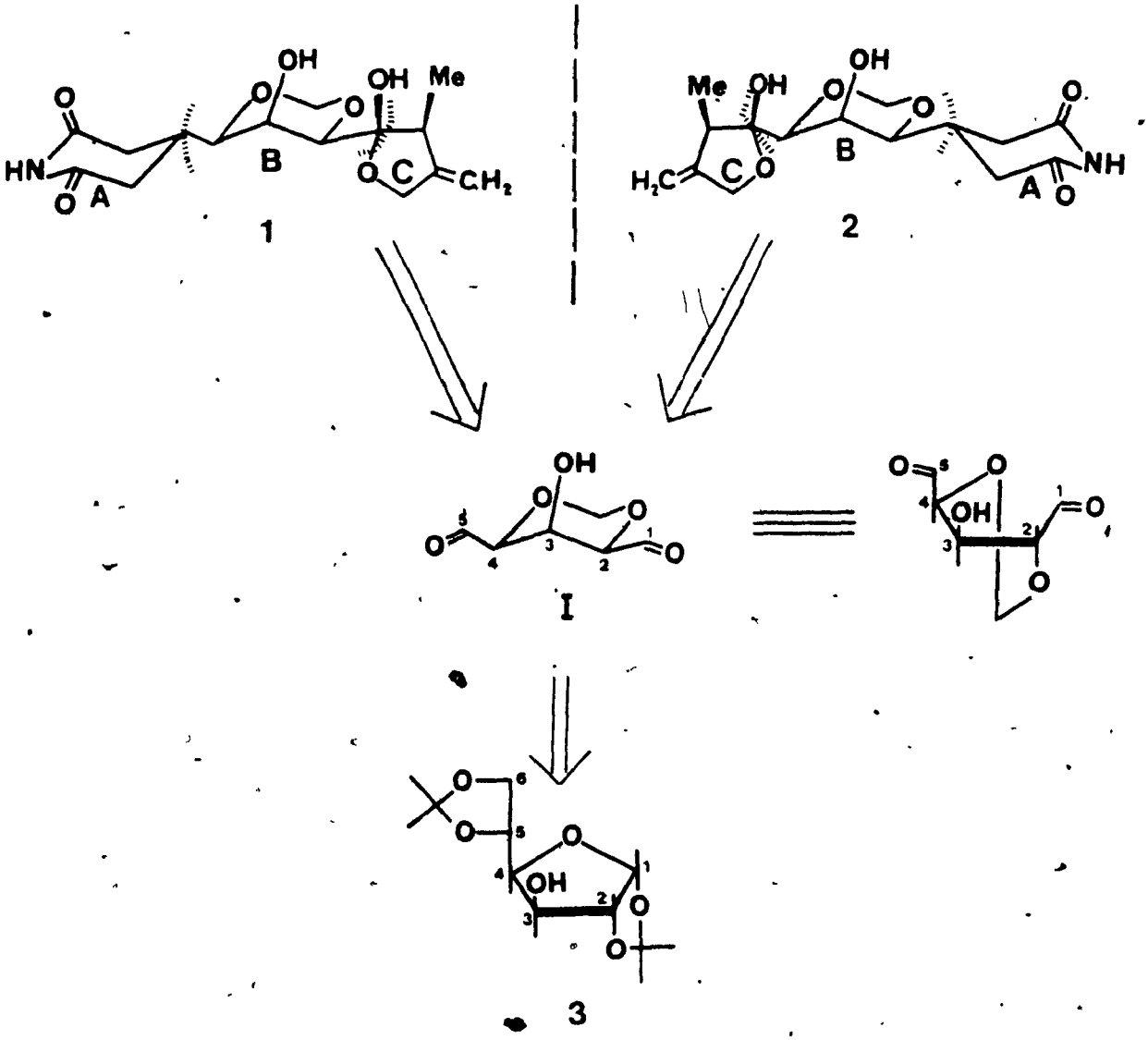
In this chapter, we describe model studies toward the synthesis of the glutarimide moiety (ring A) of sesbanimide.

Part I begins with our retrosynthetic rationale for the synthesis of sesbanimide. Furthermore, we discuss some investigations of acyclic imides and their phosphonates, in addition to the synthesis of some α,β-unsaturated imides and their attempted cyclization.

Part II is concerned with our efforts to react certain nucleophiles with halides or to add them in a conjugative manner to α,β-unsaturated compounds, which could presumably give the glutarimide ring after further elaboration. Finally, the development of a general procedure for introducing the glutarimide functionality is described.

Part I

The first published structure identification of sesbanimide by Powell *et al.*[9] tentatively depicted it as enantiomer **1**, having the relative (7R, 8S, 9R, 10S, 11S)[19] stereochemistry. However, since either **1** or its mirror image **2** was natural sesbanimide, any starting material we chose to chemically modify should be able to provide either enantiomeric form.



19. The (R) descriptor was assigned in error to C-10 in ref. 9.

A retrosynthetic analysis shows that the middle 1,3-dioxane ring of sesbanimide is perfectly symmetrical about its x-axis. Disconnecting this middle ring from the glutarimide ring (ring A) and the lactol ring (ring C), reveals a dialdehyde intermediate I.

Diacetone glucose 3 has all the necessary functionalities which would allow for its appropriate chemical transformation to this intermediate. A potential aldehyde exist at C-1 and at C-5, while its chiral centers at C-2, C-3 and C-4 have the same configuration as carbons 2, 3 and 4 in 3. Thus, both possible enantiomers 1 and 2 could in principle be derived from a suitably protected intermediate I, followed by the systematic elaboration of the glutarimide ring or the lactol ring about this middle ring to complete the total synthesis. The synthesis of each desired enantiomer is dependent on which side of the middle ring, rings A and C are placed. Roughly speaking, enantiomer 1 has ring A on the left and ring C to the right of ring B, which effectively means its synthesis would involve the elaboration of the glutarimide functionality at C-1, and the construction of the lactol moiety at C-5 of glucose. The opposite would hold true for its mirror image 2.

After a careful examination of the structure of sesbanimide and because of the reported extreme lability of the lactol ring towards base,[9] we thought it would be desirable to construct the lactol moiety at the final stage. With that in mind, we first set forth to devise a useful methodology for the synthesis of glutarimide rings from aldehydes. Studies on the construction of the other two rings will be discussed in chapters two and three.

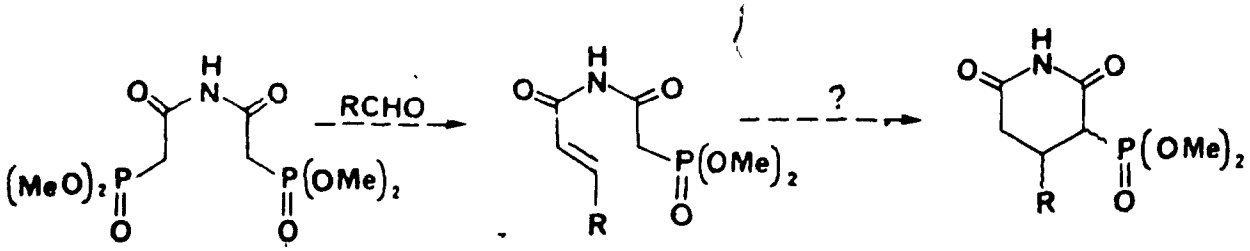
Although there is much chemical literature accounting for the synthesis of glutarimide derivatives,[20,21,22] that specifically describing 3-monosubstituted

20. M.K. Hargreaves, J G. Pritchard and H R Dave, Chem. Rev., 70, 439 (1970)
21. O.W. Wheeler in Ch. 7 of "*The Chemistry of Amides*", Ed. J. Zabicky, (1970), John Wiley & Sons Ltd.
22. S.R. Sandler and W Karo, Org. Group. Prep., 3, Ch. 7, pp.252, Academic Press, Inc. 1972.

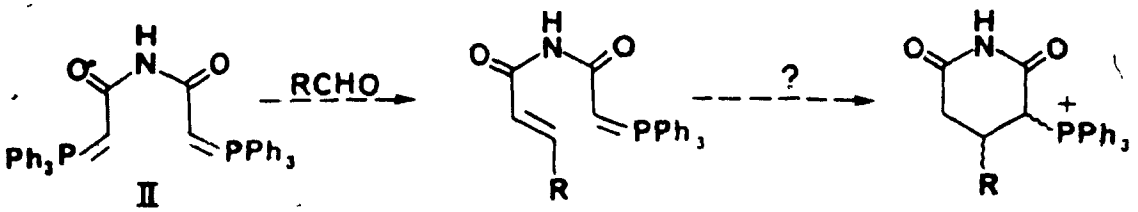
glutarimide rings is sparse. The papers mainly involve studies pertaining to the cycloheximide class of antibiotics.[23,24,25,26] All their preparations require multi-step sequences, with some of the steps involving strong acid and extremely high temperature conditions (>200°) The need for a mild and expeditious synthesis of the glutarimide was therefore obvious

Almost all procedures for ring cyclization of cyclic imides involve formation of the carbonyl-carbon-nitrogen bond as a last step We thought it might be interesting and challenging to devise a short route for forming cyclic imides through intramolecular conjugate addition reactions of acyclic imides

It was felt that an acyclic imide in the form of a bisphosphonate ester **5** could react with an aldehyde to form *trans*-olefin phosphonate **A**. Cyclization of the anion of **A** may then lead to glutarimide **B**. The second phosphonate group of compound **A**, the role of which was to impart appreciable acidity to its α-methine hydrogen to enable carbanion formation, would be removed later after the envisaged cyclization.



5 A B



II

23 D D Philips, M.A Acitelli and J Meinwald, *J. Am. Chem Soc*., 79, 3517 (1957).

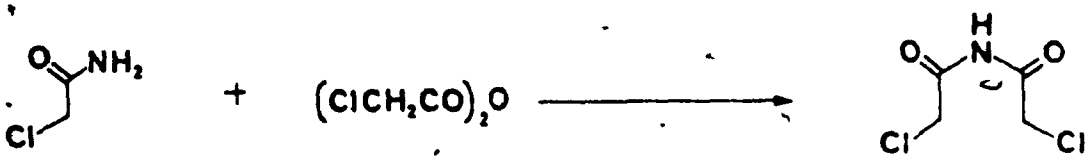
24. B C Lawes, *J Am Chem Soc*., 82, 6413 (1960).

25. F Johnson, *J Org Chem*., 27, 3658 (1962).

26. M. Suzuki, Y Egawa and T Okuda, *Chem. Pharm. Bull*., 11, 589 (1963)

This same sequence of events could theoretically be achieved by its phosphonium ylide homologue **II**, but this idea was abandoned because phosphonium ylides are known to be less nucleophilic than the phosphonate carbanions. Even if the first olefination step could be successfully performed, the ensuing Michael addition step would be less apt to proceed compared to the phosphonate anion of **I**.

In order to synthesize bisphosphonate ester **5** the starting dichloroimide **4** had to be prepared. According to the recommendations of March,[27] "the best synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100° catalyzed by sulfuric acid". This statement was based on Petterson's[28] extensive studies on the monoacylation of amides using a procedure earlier developed by Davidson and Skovronek.[29] Thus, the formation of bis(chloroacetyl)amine **4** was achieved in 65% yield by reacting 2-chloroacetamide and chloroacetic anhydride, with 100% sulfuric acid. That **4** was indeed obtained, was confirmed by mass spectral, infrared, and ^1H NMR evidence. Furthermore, spectroscopic details of this symmetrical imide were identical to those reported by Booth and Noori.[30]



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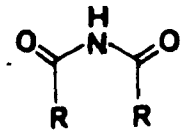
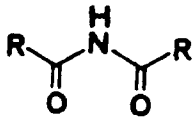
27. J. March in "Reactions, Mechanisms, and Structure" 3rd Ed., pp.379 (1985), John Wiley & Sons
28. R.C. Petterson, K. Barburao, A.M. Costello and G.E. Sander, *J. Chem. Soc. (C)*, 2779 (1968)
29. D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, 80, 376 (1958).
30. B.L. Booth and F.M. Noori, *J. Chem. Soc. Perkin Trans I*, 2894 (1980)

Before proceeding with the discussion of the formation of bisphosphonate ester **5** from the symmetrical imide **4**, one should note with interest that assuming coplanarity of the -CONHCO- structure, three possible rotational isomers are possible for any acyclic imides. They are shown in Figure 1.

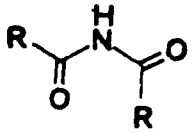
Figure 1



cis-cis



trans-trans



trans-cis

The *trans-trans* structure was tentatively assigned by us to bis(chloroacetyl)amine 4 based on the following arguments from evidence collected from an infrared spectrum taken of a crystalline sample; (1) a band at 1520 eliminates its existence as the *cis-cis* rotomer. Succinimide[31,32] and glutarimide,[33] because of their cyclic nature, cannot exist in any configuration other than the *cis-cis* form[34] and do not exhibit any strong band in the 1450 to 1600 cm^{-1} region; (2) its infrared spectra was quite similar to that reported by Uno and Machida[35,36] for the *trans-trans* isomer of diacetamide and for four other *trans-trans* saturated acyclic imides, determined in their crystalline states and

31 J Chouteau, *Bull. Soc. Chim. France*, (5) 20, 1149 (1953)

32. A.W. Baker, *J Phys. Chem.*, 61, 453 (1957).

33. R.L. Frank and J B. McPherson, Jr., *J. Am. Chem. Soc.*, 71, 1389 (1949).

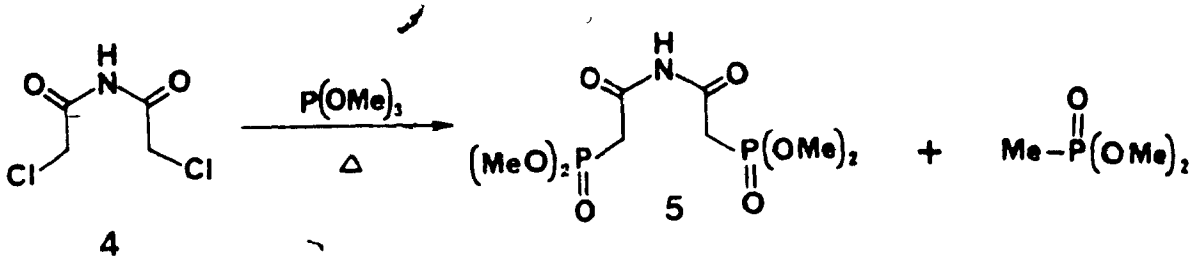
34. H.K. Hall and R. Zbinden, *J. Am. Chem. Soc.*, 80, 6428 (1958).

35. T. Uno and K. Machida, *Bull. Chem. Soc. Jpn*, 34, 545 (1961).

36. T Uno and K. Machida, *Bull. Chem. Soc. Jpn*, 34, 551 (1961).

(3) the IR spectra of imide **4** also failed to reveal any band in the 1690-1695 cm^{-1} region, which is characteristic of acyclic imides possessing the *trans-cis* geometry.

The first attempt at forming bisphosphonate **5**, by simply refluxing bis(chloroacetyl)amine **4** with a six-fold excess of trimethyl phosphite for *ca.* 18 hours, gave a mixture of predominantly undesired side product dimethyl methyl-phosphonate, and a trace amount of the required bis(dimethyl phosphonoacetyl)amine **5**, identified by ^1H NMR. That considerable amounts of dimethyl methylphosphonate were formed reflect the ease of interaction of methyl chloride (generated during the second step of the Abuzov reaction) with trimethyl phosphite in contrast to the latter's low reactivity with starting material **4**. Because the molar quantity of dimethyl methylphosphonate obtained vastly exceeded that of used starting material, this suggests that only a catalytic amount of chloride was required for generating the former compound.



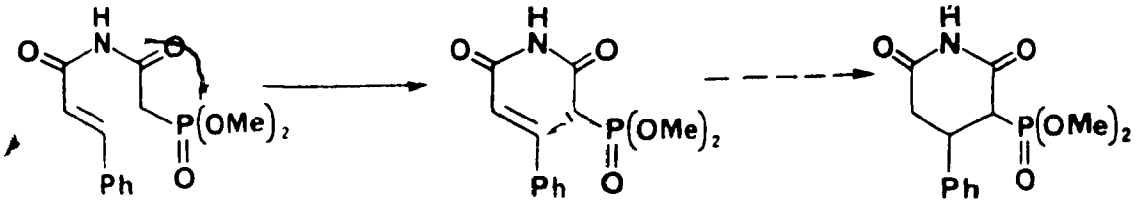
4 **5**

Literature precedents[37,38] are available indicating that "where the alkyl halide employed is not identical with the one eliminated during the second stage of the reaction, a mixture may be formed," as shown by the equations

37. A. K. Bahattacharya and G Thyagarajan, *Chem. Rev*, **81**, 415 (1981)
38. G M. Kosolapoff, *J Am. Chem. Soc.*, **66**, 109 (1944)

Thus, it was felt that if methyl chloride formed in the reaction was to be removed as rapidly as possible from the reaction mixture, the course of the reaction should be cleaner. This problem was resolved by bubbling nitrogen into the solution vigorously during the refluxing period. Consequently, formation of dimethyl methyl phosphonate was greatly diminished and after its removal along with excess trimethyl phosphite by vacuum distillation, the remaining residue, bis(dimethyl phosphonoacetyl)amine **5** was judged by its ^{1}H NMR spectrum, to be sufficiently pure (>95%) for the next step. Bisphosphonate ester **5** was well-characterized by its ^{1}H NMR, infrared and mass spectral data.

Now that the desired bisphosphonate was obtained, the next step would be a model study involving the reaction of this compound with benzaldehyde. We were hoping that the following transformations would occur in a one-pot reaction:
(1) Olefin formation as a result of the Wittig-Horner reaction of the first phosphonate carbanion with benzaldehyde giving **6** and (2) subsequent addition of the second anion in an internal fashion to provide glutarimide **C**, which also satisfies Baldwin's rule,[39] which states that 6-endo-trigonal ring closures are favoured

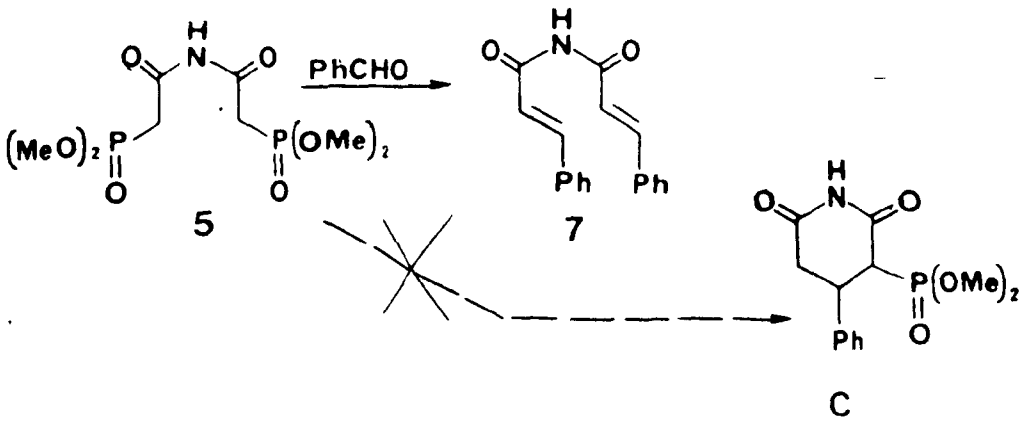


6 **C**

In the first reaction where one equivalent each of benzaldehyde and bis(dimethyl phosphonoacetyl)amine were treated with two equivalents of sodium

39 J E Baldwin, *J Chem Soc , Chem Comm* , 734 (1976).

hydride in THF at room temperature, almost all the benzaldehyde was transformed into *trans*-cinnamimide 7, yielding no desired cyclized product C.



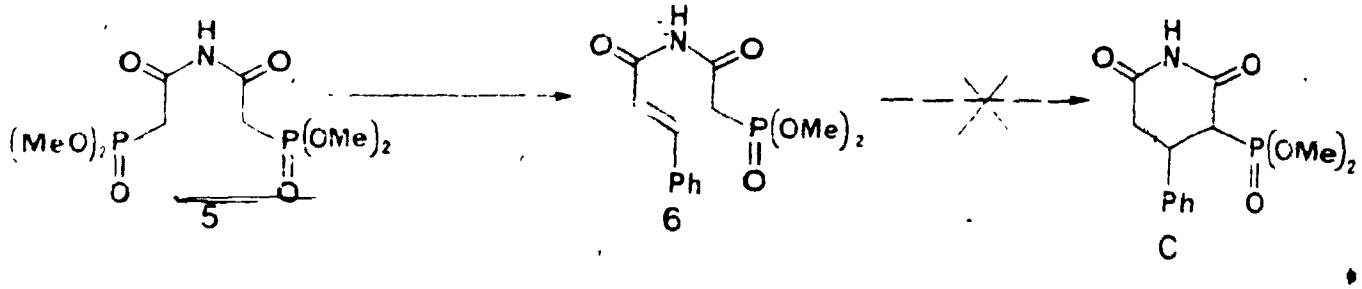
5 7 C

Confirmation of the structure of *trans*-cinnamimide 7 was based on mass spectral, infrared and ^1H NMR data. Its mass spectral data, in addition to displaying the molecular ion peak m/e 277, also displayed two prominent sets of triads among other peaks, in close agreement with Lalonde and Davis[40] results. The first of these triads was located at m/e 206, 205 and 204 and thesecond at 180, 179 and 178. One set only of AB quartet protons centered at 7.62 ppm with a coupling constant of 15 Hz was indicative of the E-geometry about both newly established olefinic double bonds.

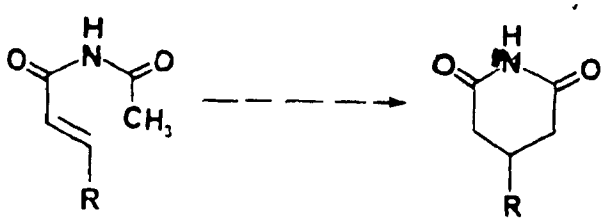
After failing to obtain C in a one-pot method, a two step synthesis was attempted in an effort to form the glutarimide ring. Our aim was to first form and then isolate the monophosphonate ester 6, before making its anion in an effort to cyclize it. After repeating the reaction with different stoichiometric quantity of reactants (one equivalent of benzaldehyde, two equivalents of bis(dimethyl phosphonoacetyl)amine, one equivalent of sodium hydride) at the same temperature and condition, we were

40. R.T. Lalonde and C.B. Davis, *Can. J Chem*, 47, 3250 (1969).

successful in isolating the desired monophosphonate 6 in appreciable yield (61% with respect to benzaldehyde). Attempted closure of this moiety *via* its anion to the 2,3-disubstituted glutarimide ring C was unfortunately unsuccessful.

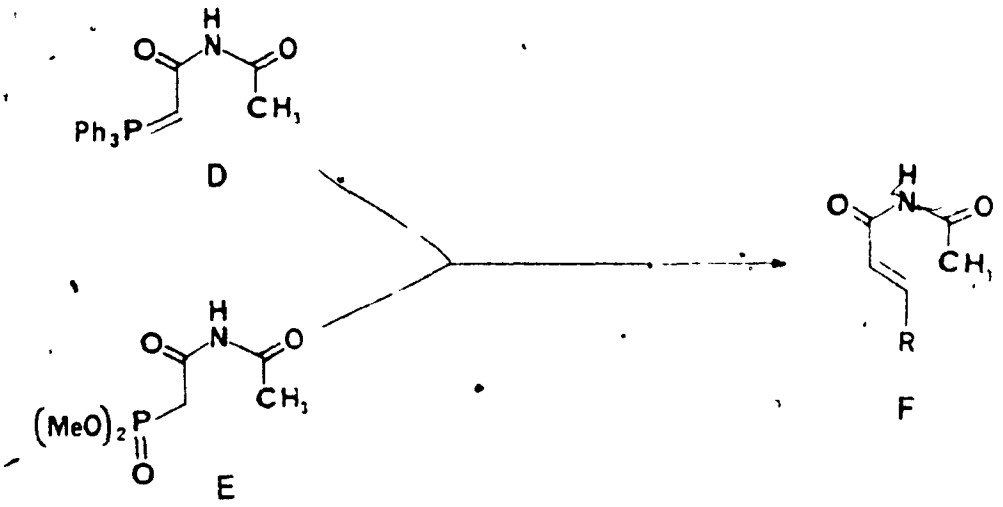


At about the same time, we also investigated the formation and the possible closure of simpler α,β-unsaturated imides without the second phosphonate group.

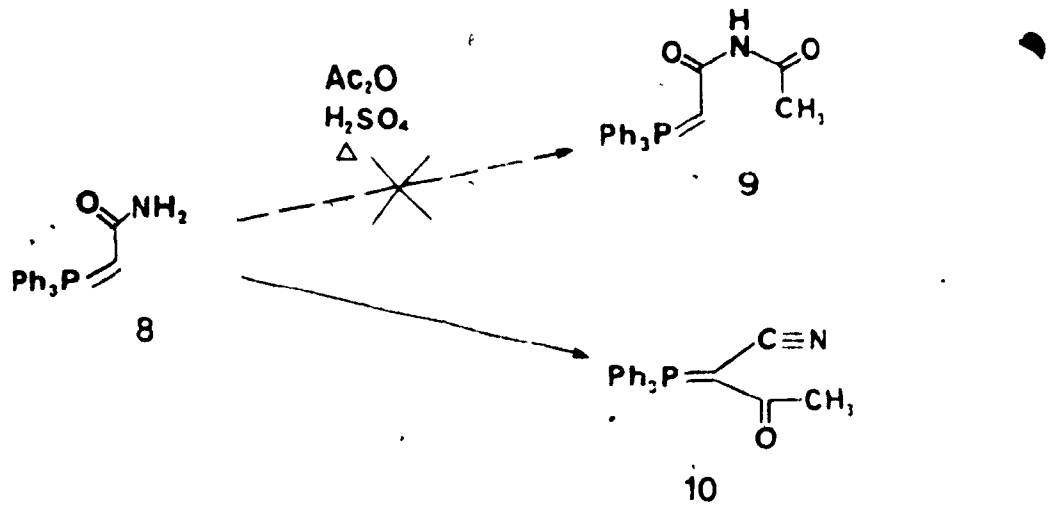


Therefore, a phosphorane or phosphonate imide was needed as starting material. More explicitly, an extension of an aldehyde *via* its stabilized Wittig reaction with a phosphorane ylide **D** or phosphonate anion **E** should lead to the required *N*

acylated α,β-unsaturated amide F, ready for the attempted closure to the 3-substituted glutarimide.



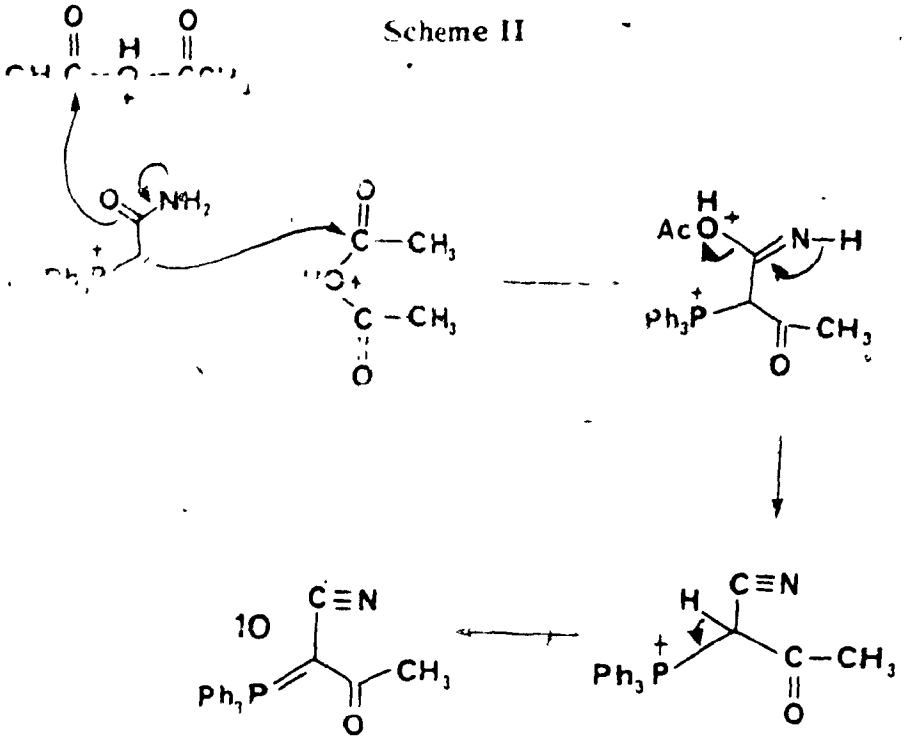
Since the known reagent carbamoyltriphenylphosphorane 8[41] could be conveniently prepared in one step, we tried to chemically modify it into its N-acyl-derivative 9, in the usual manner. Treatment of 8 with acetic anhydride and a catalytic amount of fuming sulfuric acid gave a less polar product as observed on TLC. After workup, we did not obtain the expected imide, but isolated instead the following nitrile **10**.



41. S. Trippett and D.M. Walker, *J. Chem. Soc.*, 3874 (1959)

The probable mechanism for its formation is shown in Scheme II.

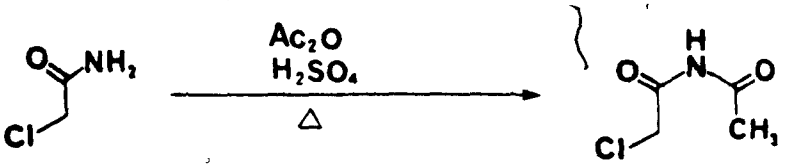
Scheme II



Structure **10** was confirmed by ^1H NMR, mass spectral, and infrared data. The ^1H NMR showed a methyl singlet at 2.37 ppm and an aromatic multiplet centered at 7.60 ppm, and the absence of the imide N-H proton. Its infrared spectrum showed an absorption at 2170 cm^{-1}, characteristic of a nitrile functionality. There was also a carbonyl absorption at 1585 cm^{-1}. No bands were found at 1740-1670 cm^{-1} associated with carbonyl absorptions for imides (taken in the solid state), nor were any N-H band found near 3250 cm^{-1}. In addition, the mass spectrum of **10** showed a peak at m/e 343 which corresponds to its molecular ion, rather than m/e 361 expected for **9**.

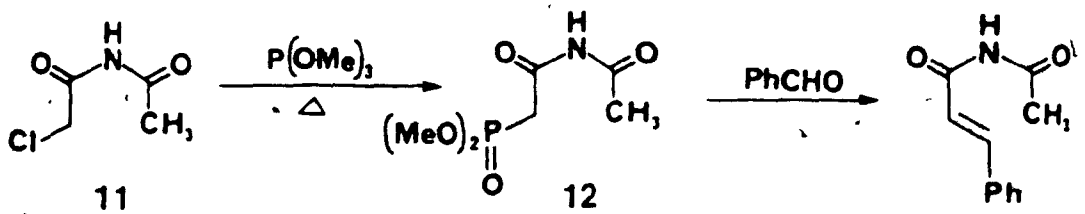
Because of this surprising and rather unexpected result, we elected to synthesize the phosphonate derivative **12**. This could conceivably come from the heating of trimethyl phosphite with *N*-2-chloroacetylacetamide **11**. Adopting again the general procedure published by Petterson *et al.*[28] for the acylation of amides, **11** was made in 81% yield by heating a mixture of acetic anhydride and 2-chloroacetamide with a catalytic amount of fuming sulfuric acid. It should be noted that Polya and

Spotswood[42] had previously synthesized this compound using 2-chloroacetamide and acetic anhydride in the presence of acetyl chloride as catalyst, resulting in lower yield (50%).



11

After obtaining the asymmetrical imide **11**, the synthesis of dimethyl *N*-acetylphosphonoacetamide **12** was pursued by heating imide **11** with trimethyl phosphite. For reasons discussed earlier during the preparation of bisphosphonate **5**, a stream of nitrogen was required to diminish the production of undesired dimethyl methylphosphonate.



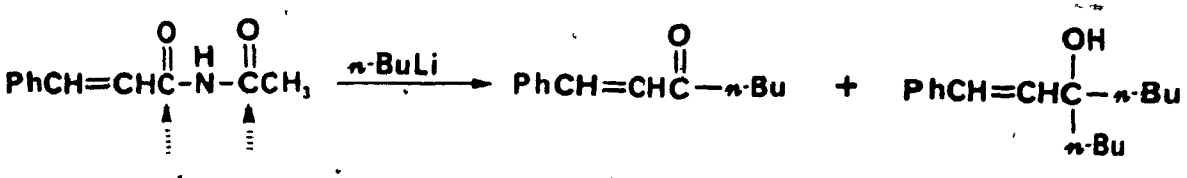
11 **12** **13**

We then proceeded to test this phosphonate's anion reactivity with benzaldehyde as the model aldehyde. The phosphonate carbanion of **12** reacted smoothly with benzaldehyde giving *N*-acetylcinnamamide **13** in 70% yield. A proton coupling constant of approximately 16 Hz certified that the condensation had resulted in pure *trans*-olefination.

42. J.B Polya and T. M Spotswood, *Rec. Trav. chim* , **67**, 927 (1948).

With regards to this successful Wittig-Horner condensation and the earlier mentioned bisphosphonate **5** anion reaction with benzaldehyde, we believe it to be the first time phosphonates containing imide groups have been involved in providing a useful route to α,β-unsaturated imides. Prior to now, there was only one small note of phosphonates containing secondary and tertiary amides reacting with aldehydes and ketones to afford α,β-unsaturated secondary and tertiary amides.[43]

The next step was to effect its cyclization. We envisaged that the cyclization would occur after formation of its dianion. Treatment of **13** with 2.2 molar equivalents of n-butyllithium in THF at -78° immediately led to the disappearance of starting material giving two very non-polar products and a third highly polar product on TLC, all of them highly UV sensitive. These two non-polar products were identified as ketone **14** and alcohol **15** by ^{1}H NMR. The latter was formed as a result of the addition of n-BuLi to ketone **14**. The third and most polar compound was identified as cinnamamide after a comparison of its R_f value with an authentic sample on TLC. That both **15** and cinnamamide are products of this reaction attests to the susceptibility of both carbonyl centers towards nucleophilic attack by n-butyllithium. The side products, acetamide and 2-hexanone were not observed probably due to their loss during aqueous workup and during solvent removal.

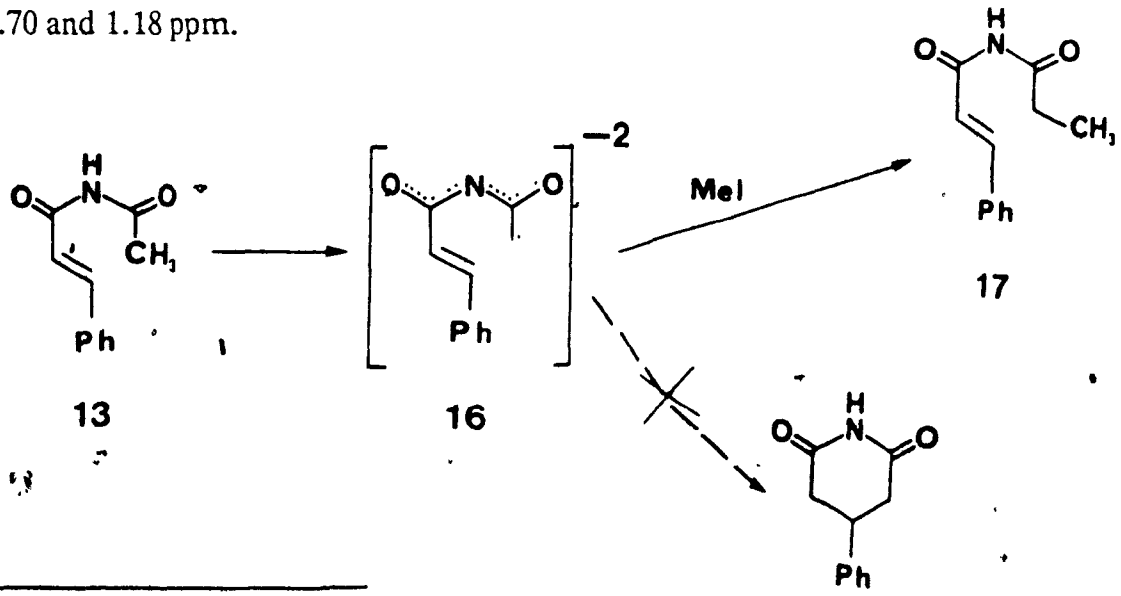


13 **14** **15**

43 I. Shahak, J. Almog and E.D. Bergmann, *Isr J Chem.*, 7, 585 (1969).

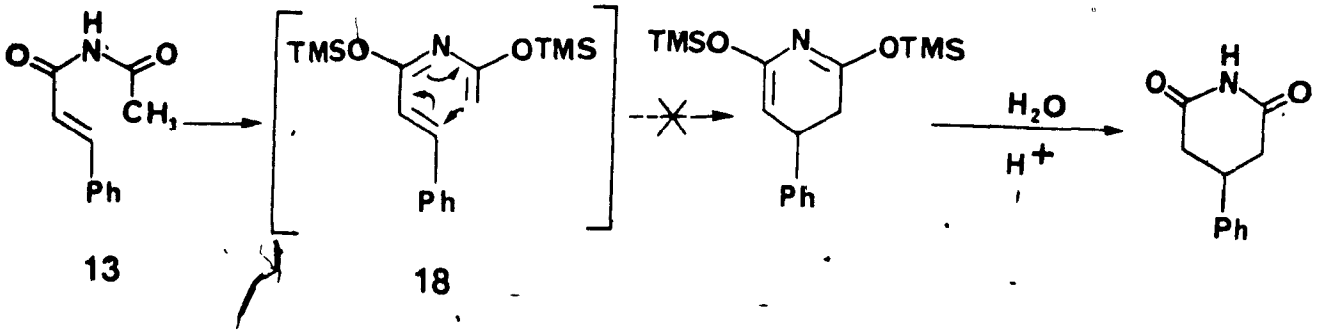
While this work was in progress, Czarnocki and Wrobel[44] also reported that treatment of several acyclic and cyclic imides with phenyllithium led to ketones and amides, products corresponding to nucleophilic attack of phenyllithium on the carbonyl centers of the imide. Our findings confirm their observations regarding treatment of imides with organolithium compounds.

Therefore, the need for a non-nucleophilic and more sterically hindered base was warranted in order to convert **13** to its dianion. We found lithium bistrimethylsilylamide[45] (prepared in situ from hexamethyldisilazane and n-butyllithium at -78°) suitable for generating dianion **16**, as little or no undesired by-products were formed even after warming the reaction mixture to ~50°. Unfortunately, the cyclization of **16** could not be effected either. Proof of dianion formation was obtained by quenching the reaction mixture with methyl iodide to yield **17**. The isolated product indicated that the condensation took place only at the methyl carbon even though the N-H proton was assumed to have been abstracted as well. Thus, the methyl resonance which had appeared at 2.47 ppm in the ^{1}H NMR spectrum of **16** was replaced by a methylene quartet and a methyl triplet centered respectively at 2.70 and 1.18 ppm.



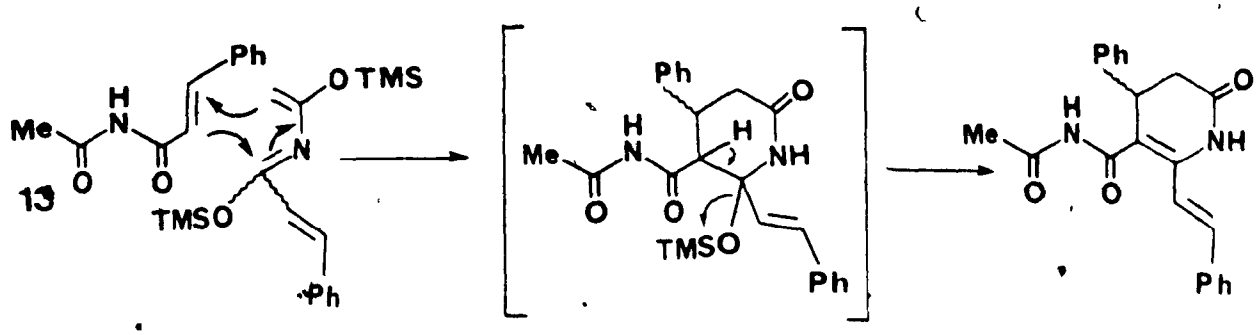
44. Z. Czarnocki and J.T. Wrobel, *Bull. Pol. Acad Sci., Chem*, 32, 335 (1984)
45. J C Stowell, "Carbanions in Organic Synthesis", John Wiley & Sons, New York, 1979, p. 15.

In another attempt at cyclization of *N*-acetylcinnamamide, **13** was reacted with 2.2 equivalents each of trimethylsilyl trifluoromethanesulfonate and triethylamine to generate the 2-aza-1,3,5-triene **18** intermediate, hoping that the intermediate would cyclize. We knew beforehand that treatment of diacetamide with trialkylsilyl triflates resulted in the formation of 2-aza-1,3-dienes, which acted as powerful dienophiles in cycloaddition reactions.[46] We could not predict however, the consequence of placing a third olefin in conjugation with the 2-aza-1,3-dienophile system. Optimistically speaking, a successful cyclization of the type depicted by **18** could in principle, provide the sought after glutarimide ring after an acid hydrolysis workup.



Treatment of **13** with trimethylsilyl trifluoromethanesulfonate and triethyl amine led to two products after purification by flash chromatography.[47] The less polar product had an R_f exactly equal to the starting material. It could not be identified. The second product **19** apparently resulted from a Diels-Alder reaction between two molecules of **13**. The course of the reaction is outlined below.

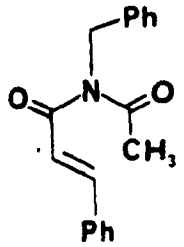
46. F. Sainte, B.S Serckx-Poncin, A.-M. Hesbain-Frisque and L. Ghosez, *J. Am. Chem. Soc.*, 104, 1428 (1982).
47. W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 43, 2923 (1978)



18 19

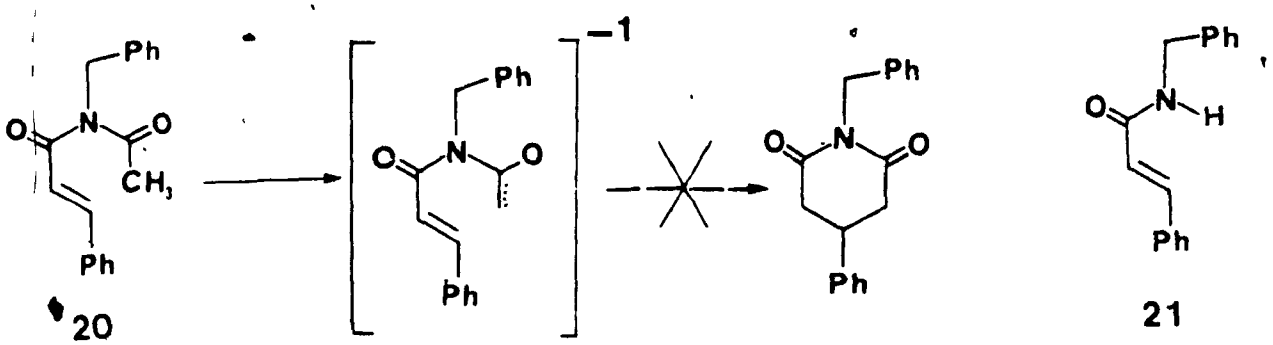
Even though we were not able to isolate the highly reactive intermediate **18**, isolation of the Diels-Alder product **19** was ample proof of its formation. The ^1H NMR, mass spectrum and high resolution mass spectrum were in accord with the proposed structure of **19**.

The decision was then made to alkylate *N*-acetylcinnamamide with benzyl bromide. It was based on the highly tentative assumption that the removal of the acidic N-H proton would result in a more electron deficient double bond. The benzyl group was chosen because of its facile removal by catalytic hydrogenation, assuming a successful cyclization took place. Treatment of *N*-acetylcinnamamide with sodium hydride and benzyl bromide in DMF resulted in its conversion to tertiary amide **20**. Its infrared spectra demonstrated a doublet between the 1600 to 1700 cm^{-1} range, giving credence to the fact that the product isolated was strictly *N*-alkylated (and not *O*-alkylated).

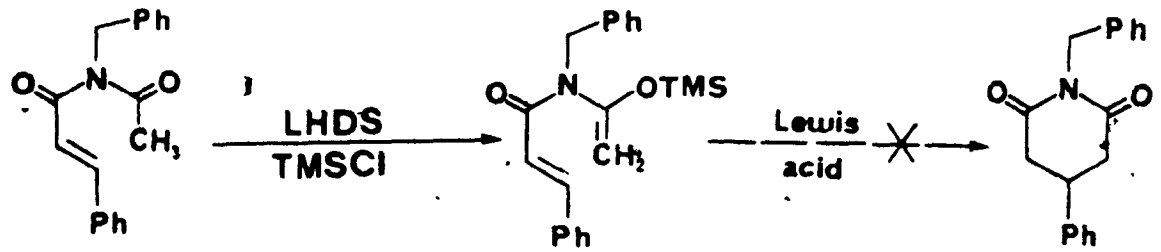


20

However, treatment of **20** with non-nucleophilic bases such as lithium hexamethyldisilazide or lithium diisopropylamide in THF or potassium *t*-butoxide in *t*-butanol at room temperature failed to cyclize the compound, and only starting material was recovered. Upon prolonged heating with the *t*-butoxide/*t*-butanol system, we could only obtain the secondary amide **21** resulting from acyl cleavage, along with products of decomposition.

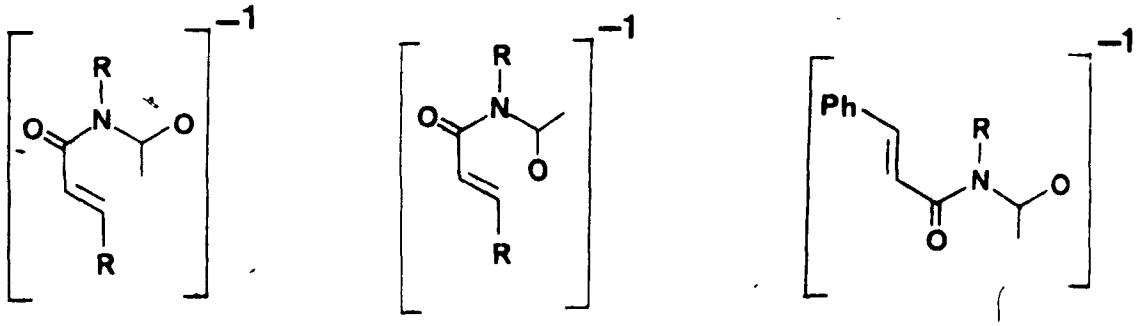


We then went on to explore the chemistry of its silyl enol ether **22**. It was felt that a Lewis acid would coordinate with the carbonyl oxygen of this compound, thereby activating the α,β-unsaturated system towards an internal Michael addition, and hopefully resulting in closure. The synthesis of silyl enol ether **22** was achieved by quenching the enolate anion of **20** generated by lithium hexamethyldisilylamide with chlorotrimethylsilane.



This silyl enol ether was identified by ^1H NMR alone. Owing to the extreme susceptibility of the compound to moisture, no mass spectrum was obtained. Highly apparent in its ^1H NMR spectrum are two sets of doublets (J = 1.8 Hz) centered at 4.03 and 4.20 ppm corresponding to the two vinyl protons, in addition to other signals. Once isolated, it was immediately treated either with titanium tetrachloride or with aluminum chloride, in an effort to effect Lewis acid promoted cyclization. Again, the cyclization attempt was thwarted for only unreacted α,β-unsaturated amide **20** was recovered.

In conclusion, we would like to suggest that the failure of the anion of **20** to undergo an internal Michael condensation is due to the poor electrophilic character of the olefinic bond of the α,β-unsaturated system. Another possible reason is the failure of the enolate anion to be in the proper orientation with respect to the double bond to allow for closure, since three possible configurations are permissible as depicted below.

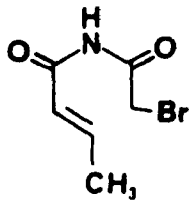


Unfortunately, studies of rotational barriers have not been carried out so far, and this latter explanation is speculative.

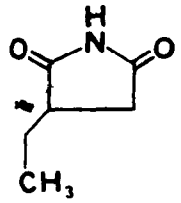
Dr. G. Sacripante[48] in our laboratory, found that treatment of *N*-2-bromoacetylcrotonamide **23** with AIBN gave exclusively 2-ethylsuccinimide **24**.[49]

48. G. Sacripante, Ph.D. Thesis, Dept of Chemistry, McGill University, 1987
49. G Sacripante, C Tan and G Just, *Tet. Lett.*, 5643 (1985).

resulting from a 5-exo-trig addition of the radical to the olefinic bond, with some reduction product.



23



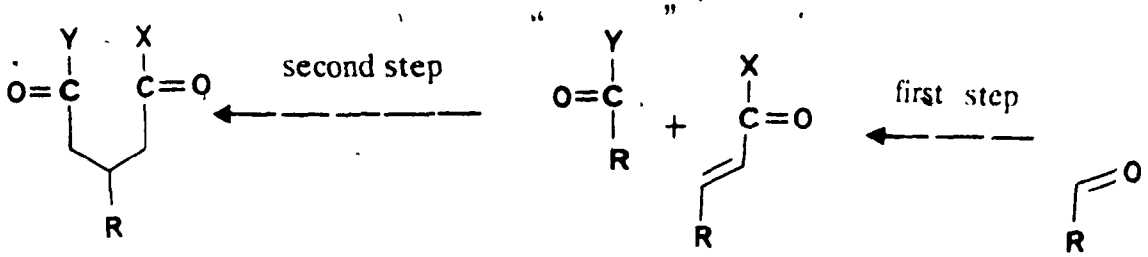
24

Failure of all our aforementioned attempts at cyclizing the α,β-unsaturated imides to the corresponding glutarimides compelled us to investigate other approaches, which are discussed in part II of this chapter.

Part II

In view of the failure to effect cyclization of α,β-unsaturated imides, we investigated other possibilities for the construction of the glutarimide ring of sesbanimide.

Our approach described in this second part of the first chapter is directed towards finding the shortest route possible to constructing a bifunctional carbonyl derivative of type **III**, starting from an aldehyde functionality. Transformation of any initial aldehyde to **III** could be envisaged to occur in two steps, the first step incorporating a two-carbon unit homologation and the second step implicating another two-carbon unit addition to the starting aldehyde's carbonyl carbon. Moreover, this pair of two-carbon units should bear an ester, amide or aldehyde terminus, allowing for the required chemical modifications, before or after the cyclization step to the glutarimide ring.



III X,Y = OR, NHR, Cl, H

Many methods are available to accomplish the first two-carbon unit homologation. Wittig-type reagents are especially attractive because they are rapid and high yield reactions. Furthermore, the ensuing α,β-unsaturated compound is a potential Michael acceptor for subsequent nucleophilic addition of the second two-carbon unit.

For the second two-carbon unit condensation, we first considered the use of masked "acetamide" synthons. Anions of *N,O*-bis(trimethylsilyl)acetamide (hereafter denoted as BSA) have been known to add to ketones and aldehydes affording β-hydroxy acetamides in excellent yield.[50,51] Likewise, the same products could be synthesized using the dianion of *N*-(trimethylsilyl)acetamide. The latter is known also to alkylate methyl iodide, n-butyl bromide and benzyl chloride, and also participate in acylation reactions giving keto amides.[52] Unfortunately, there has been no mention whatsoever regarding their chemical behaviour towards α,β-unsaturated compounds. If either one of them behaves as a Michael donor, the resulting adducts **III** would only need some small chemical modifications to make the glutarimide ring. For example, if they were to add in a 1,4 fashion to α,β-unsaturated aldehydes, we would be able to obtain the corresponding amide-aldehydes **G**. This amide-aldehyde is known to exist in tautomeric equilibrium with the carbinolamine **H** in which **H** is the preferred form.[53] Furthermore, there is available in the literature, a method for the oxidation of this carbinolamine moiety with manganese dioxide to the glutarimide.[54] On the other hand, a successful 1,4 addition by an acetamide synthon to the corresponding ester would provide the monoamide **I**, which could then be cyclized by known literature methods.[55,56]

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50 T. Morwick, *Tet. Lett.*, 3227 (1980)

51 D.A. Evans and R.Y. Wong, *J. Org. Chem.*, **42**, 350 (1977)

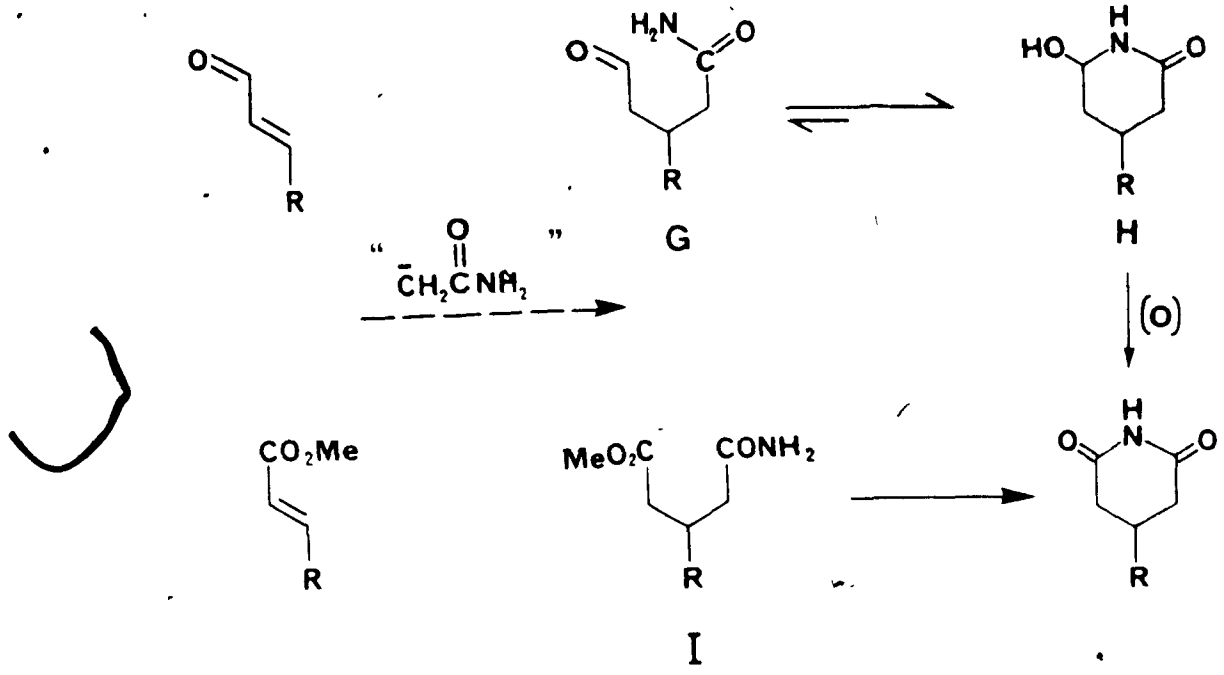
52 T.M. Harris, P.C. Kuzma and L.E. Brown, *J. Org. Chem.*, **49**, 2015 (1984)

53 J.C. Hubert, J.B.P.A. Wijnberg and W.N. Speckamp, *Tetrahedron* **31** 1437 (1975)

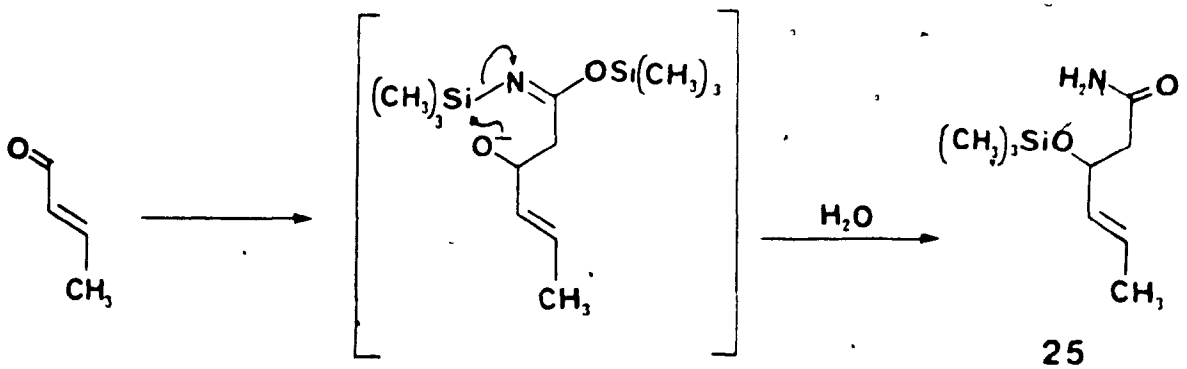
54 P. de Mayo and S.T. Reid, *Chem. and Ind. (Lond.)*, 1756 (1962)

55 S.R. Sandler and W. Karo, Org. Group Prep., 3 Ch. 7, pp. 252, Academic Press, Inc. 1972

56 M.K. Hargreaves, J.G. Pritchard and H.R. Dave, *Chem. Rev.*, **70** 441 (1969) and references cited therein



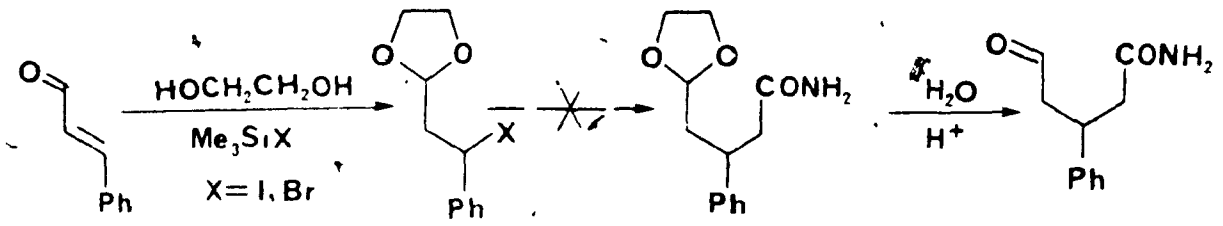
In a model study reaction involving the BSA anion and crotonaldehyde, silyl ether **25** was obtained rapidly. The newly created alkoxide becomes silylated, either by internal silyl transfer or by a second molecule of BSA.



Because the α,β-unsaturated aldehyde reacted with the BSA anion by 1,2 rather than 1,4-addition, it was decided to attempt an analogous reaction with a β-haloacetal. A recent procedure by Gil[57] describing the one-pot synthesis of β-halides of acetals from

57 G. Gil, *Tet. Lett.*, 3805 (1984)

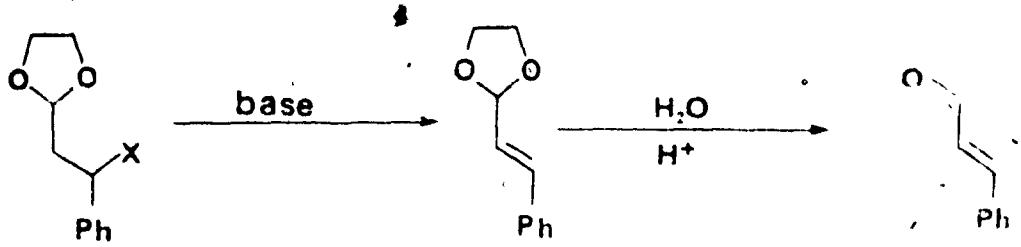
α,β-unsaturated aldehydes was available; therefore, we then formed the acetal halides **26** and **27** by reacting cinnamaldehyde with ethylene glycol and the appropriate trimethylsilyl halide.



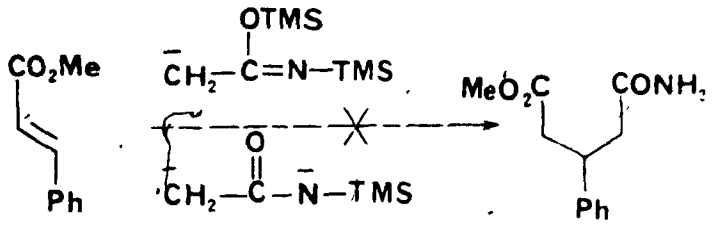
26 X=I **IV** **G**
27 X=Br

Once the halide was obtained, its displacement by "masked" acetamide derivatives could in principle, be performed to give the amide-aldehyde **G** after an acid hydrolysis step. An unknown factor of importance in this approach was the nucleophilicity of the acetamide equivalents towards secondary halides. In their studies with the dianion of *N*-(trimethylsilyl)acetamide, Harris *et al*[52] noted the successful alkylation reactions of the latter with primary and benzyl halides. No mention however, was made regarding its reactivity with other classes of halides, such as secondary halides.

Unfortunately, the experimental results were quite disappointing. Firstly, β-iodoacetal **26** was very unstable and its immediate treatment with the anion of BSA or the dianion of *N*-trimethylsilylacetamide at -78° failed to afford **IV** but yielded only cinnamaldehyde. Secondly, reactions involving these "masked" acetamide anions with the more stable β-bromoacetal **27** also gave cinnamaldehyde, in addition to unreacted starting material. In these reactions, cinnamaldehyde was presumably formed after base induced elimination of HX (X=Br, I), followed by acid hydrolysis of the acetal moiety.



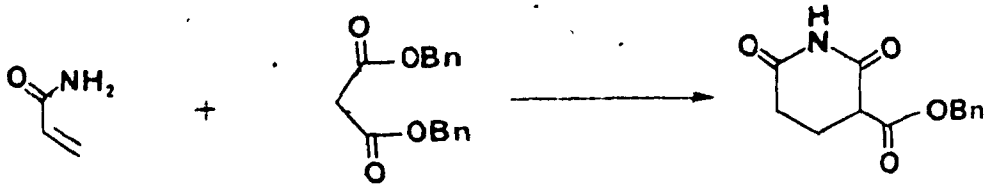
In experiments involving reactions between anions of BSA and dianions of *N*-trimethylsilylacetamide with methyl cinnamate, only methyl cinnamate and surprisingly, a trace amount of *N*-acetylcinnamamide were recovered. No Michael addition products were isolated.



Primary α,β-unsaturated amides as Michael acceptors are rarely reported in the literature. Until now in this class of compounds, only acrylamide[58,59,60] and

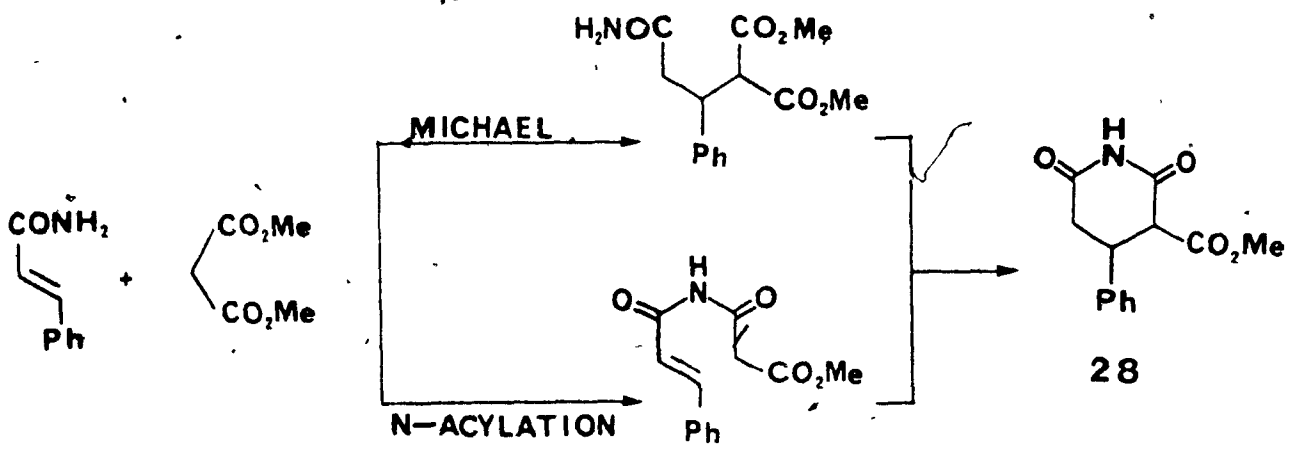
58. Bruson, U.S. P 2, 370, 142, *Chem Abs*, 39, 3544 (1945)
59. D Elad and D Ginsburg, *J Chem Soc.*, 4137 (1953)
60. T. Kametani, W Taub and D Ginsburg, *Bull Chem Soc Jpn*, 31, 857 (1958).

methacrylamide[61] have been reported to undergo Michael condensations. For example, Ginsburg *et al.*[60] condensed the dibenzyl malonate anion with acrylamide, to provide the following glutarimide derivative.



We decided to try this reaction with *trans*-cinnamamide as the α,β-unsaturated amide and dimethyl malonate as the Michael donor. Condensation of cinnamamide with dimethyl malonate in the presence of sodium methoxide gave glutarimide ring 28 directly, albeit in low and variable yields of approximately 15-25% in addition to methyl cinnamate, triester 29 and much unreacted cinnamamide. An explanation for the products recovered is outlined in Scheme III and Scheme IV.

Scheme III



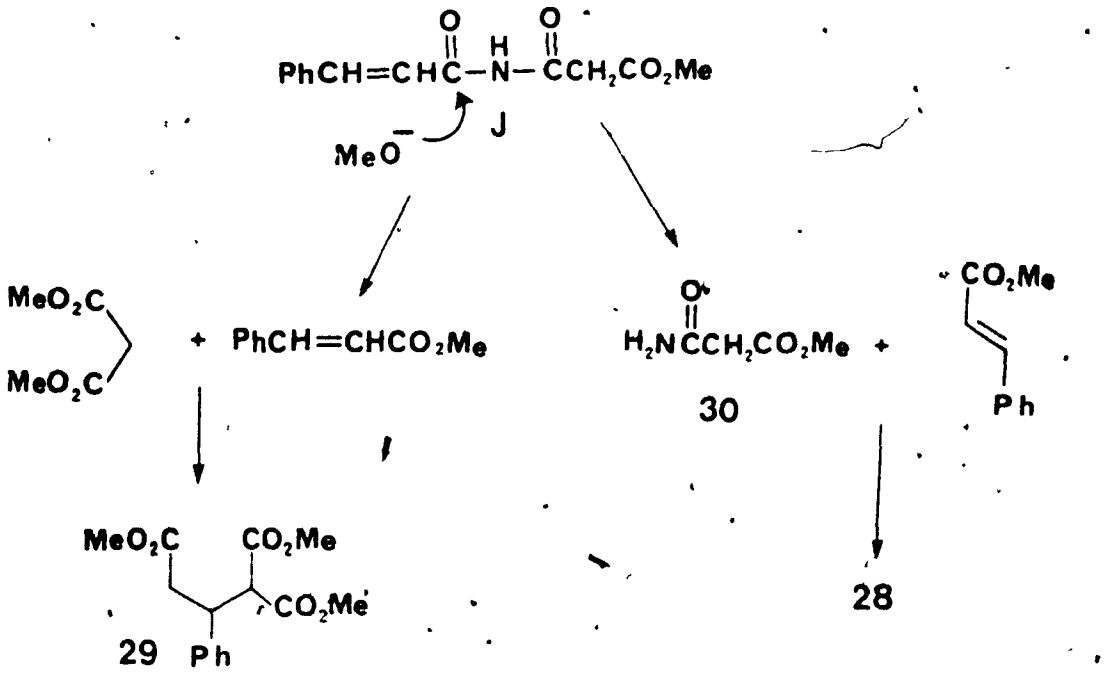
J

61. Oesterr A.G. Stickstoffwerke, Austrian pat. 176,845 [*C.A.*, 48, 10772 (1954)].

The reaction proceeded either by (1) *N*-acylation resulting from the condensation of the anion from cinnamamide with dimethyl malonate, followed by subsequent cyclization or, (2) direct addition of the carbanion of dimethyl malonate to the β-carbon of cinnamamide, followed by formation of the imido structure.

The formation of methyl cinnamate may be explained by the nucleophilic attack of sodium methoxide on the hypothetical acyclic imide intermediate J, which in turn could also act as a Michael acceptor for dimethyl malonate anion, accounting for the formation of the triester by-product **29**. This is outlined in Scheme IV.

Scheme IV



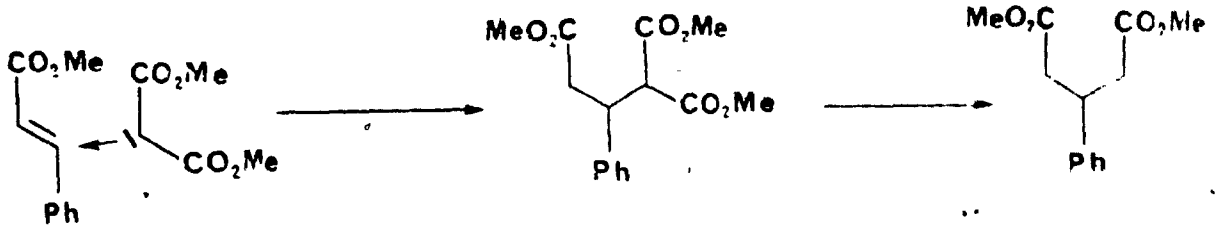
A third plausible mechanism for the formation of glutarimide ring 28 suggests involvement of by-products in Scheme IV. Presumably, the half amide of malonate ester **30** may also add in a 1,4 manner to methyl cinnamate (itself a by-product), followed by N-C bond formation to afford the disubstituted glutarimide **28** (see Scheme IV). Because of the low yield nature of this reaction, we decided to investigate other approaches.

The result of this work convinced us that α,β-unsaturated amides are poor Michael acceptors and therefore, the acceptor would have to come in the form of an α,β-unsaturated ester. What was required was an acetate synthon, for the acetamide synthon was earlier found incapable of adding. We decided upon dimethyl malonate as the acetate synthon after giving careful thoughts to the following considerations. Methyl acetate or ethyl acetate existing as their lithio enolates or enol silyl ethers would be ideal synthons provided that they would add in a 1,4 fashion. However, it has been noted that the quenching of anions of methyl acetate[62,63] and ethyl acetate with chlorotrimethylsilane gives a mixture of *C*- and *O*-silylated products. Furthermore, their treatment with Lewis acids results in self-polymerization, prohibiting their use. The lithio enolate of methyl acetate has been shown to add 1,2 to α,β-unsaturated ketone (and not 1,4) by Ravid and Ikan.[64] Another compound, *O*-methyl-*C*,*O*-bis(trimethylsilyl)ketene acetal, synthesized by Matsuda and co-workers,[65] is described to add in a Michael fashion to α,β-unsaturated ketone upon treatment with $TiCl_4$, but has not been tested yet for its action on α,β-unsaturated esters. Moreover, making this reagent requires two steps, and assuming that the addition product could be formed, a protodesilylation step would still be required.

The anions of malonates gives exclusively conjugate addition to α,β-unsaturated carbonyl systems, as evidenced by the great number of pertinent references cited in Bergmann's[66] review article regarding Michael reactions. A model study was then attempted with the goal of making 3-phenyl glutarimide, starting from the 1,4-addition

62. C. Ainsworth, F. Chen and Y N. Kuo, *J. Organomet Chem.*, **46**, 59 (1972)
63. M.W. Rathke and D F Sullivan, *Syn Comm.*, 3, 67 (1973)
64. U Ravid and R. Ikan, *J Org. Chem.*, **39**, 2637 (1974).
65. I. Matsuda, S. Murata, and Y Izumi, *J Org. Chem.*, **45**, 237 (1980)
66. E D Bergmann, D Ginsburg and R Pappo, *Org React.*, **10**, 179 (1959)

of dimethyl malonate anion to methyl cinnamate in refluxing methanolic sodium methoxide solution.



31 32

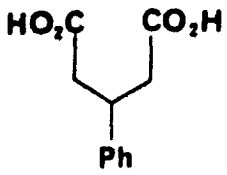
The resulting Michael product, triester **31** was obtained in approximately 60% yield after purification by flash chromatography.

Now that the triester was at hand, a method was required to demethylate and decarboxylate one of the geminal ester groups. This problem was resolved neatly in one step by Krapcho's method[67] of decarbalkoxylation, affording the desired dimethyl 3-phenylglutarate **32** in 60% yield. It should be noted that the mechanism of this reaction is not yet entirely understood.[68,69,70] Thus, the introduction of a two-carbon unit methyl acetate synthon was accomplished successfully in two steps.

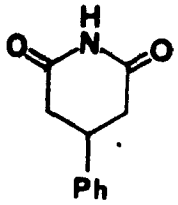
We then turned our attention to the activation of the glutarate ring into the required 3-phenylglutarimide **34**. There was a vast wealth of published literature dealing with the conversion of glutarates to cyclic imides, but all of them would entail at least a two-step sequence procedure. We finally decided on one which would involve (1) hydrolysis of the diester to dicarboxylic acid **33** and (2) heating the diacid

67. A.P. Krapcho and A.J. Lovey, *Tet Lett.*, 957 (1973).
68. A.P. Krapcho, E.G.E. Jahngen, A.J. Lovey and F.W. Short, *Tet. Lett.*, 1091 (1974)
69. C.L. Liotta and F L. Cook, *Tet. Lett*, 1095 (1974).
70. J.E. McMurray, *Org React*, 24, 190 (1976).

with urea.[71] They gave respective yields of 55 and 70%. The overall non-optimized yield in four steps, starting from the Michael reaction was about 15%.



33



34

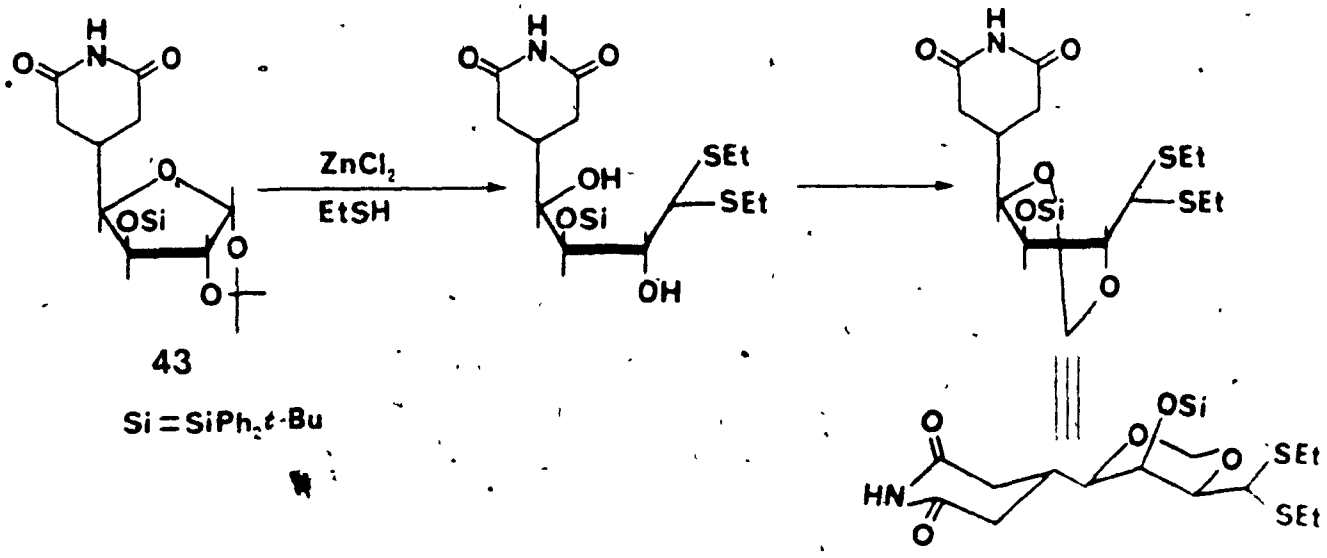
71. G.C. Crockett, B.J. Swanson, D.R. Anderson and T.H. Koch, *Syn. Comm.*, 447 (1981).

Chapter 2

Part I

Synthesis of Ring A of Sesbanimide

Since the glutarimide ring had only been grafted onto simple aldehydes, we next investigated if it could also be added to a molecule of higher complexity. Our choice was the readily available diacetone glucose, which not only can serve as a model, but can in principle also be further elaborated to enantiomer 1 of sesbanimide, provided that the molecule obtained would be resistant to further manipulation. This plan for the synthesis of enantiomer 1 was to first construct the A (glutarimide) ring onto the yet unformed B (1,3-dioxane) ring, followed by elaboration of ring B and addition of ring (lactol) C. The success of this scheme depends on the ability of the glutarimide moiety to survive the reaction conditions it would be encountering later, such as its forecasted exposure to zinc chloride/ethanethiol or the yet undetermined condition for the methylenation reaction required to bridge the C-2 and C-4 hydroxyl groups. Our immediate synthetic goal was therefore glutarimide derivative 43, where the construction of the glutarimide ring would take place about C-5 of diacetone glucose.

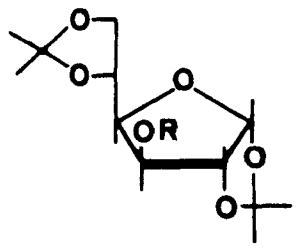


43

Si = $SiPh_2t$-Bu

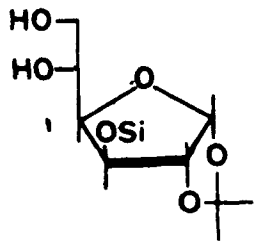
The crucial factor involved the selection of a suitable protecting group at C-3 of this glucose. The protecting group had to be both acid- and base-stable to survive the reaction conditions that were to employed in the synthetic scheme. Acetates are susceptible to facile migration and elimination, and furthermore, are sensitive to zinc chloride/ethanethiol, reagents likely to be employed later. Benzyl ethers could be removed by hydrogenation, but the removal conditions may be incompatible with the preservation of olefins. They could also be cleaved chemically, but these would involve use of "harsh" chemical reagents such as trimethylsilyl iodide,[72] which could possibly destroy the 1,3-dioxane ring system as well. Eventually, the relatively acid- and base-stable *t*-butyldiphenylsilyl group was chosen for the protection of the hydroxyl group at C-3 of diacetone glucose. It can be removed by the action of fluoride ion.[73,74]

Silylation of diacetone glucose **3** with *t*-butyldiphenylsilyl chloride and imidazole in dimethylformamide gave silyl ether **35**, which was selectively hydrolyzed to its corresponding diol **36** with 70% aqueous acetic acid. Subsequent treatment of diol **36** with lead tetraacetate yielded aldehyde **37**.



3 R=H

35 R=SiPh$_2$*t*-Bu =Si



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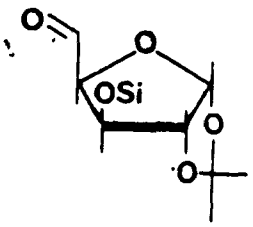


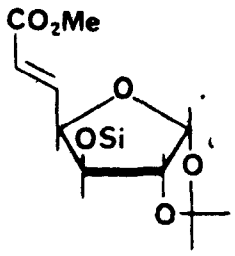
37

Evidence for the formation of aldehyde **37** came from its infrared spectrum, which had the aldehydic carbonyl absorbing at 1735 cm^{-1}, and from its ^{1}H NMR spectrum, which

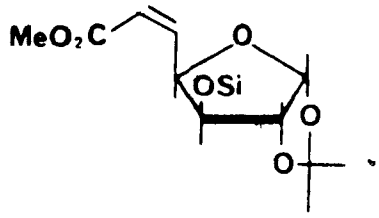
72. M E. Jung and M.A Lyster, *J Org Chem*, 42, 3761 (1977).
73. S. Hanessian and P Lavallee, *Can J Chem*, 53, 2975 (1975).
74. S Hanessian and P Lavallee, *Can J Chem*, 55, 562 (1977)

displayed an aldehydic low field proton at 9.70 ppm with a small coupling constant of J = 1.2 Hz with 4-H. An item of interest revealed by the 200 MHz ^{1}H NMR of this aldehyde is the absence of any proton-proton coupling between the 2-H and 3-H protons, which is indicative of a 90° dihedral angle. Its electron ionization mass spectrum gave fragments which appeared at m/e 361, 311 and 283 corresponding to the respective losses of a *t*-butyl radical, [*t*-butyl + acetone] and [*t*-butyl + acetone + CO]. It should be noted that in many subsequent electron ionization mass spectra taken of *t*-butyldiphenylsilyl protected compounds, many fragments involved the ready loss of *t*-butyl radicals, owing to the greater capacity of silicon than carbon to accommodate a positive charge.[75]

Aldehyde **37** could be elaborated to the glutarimide ring, following the methodology we had developed earlier. Treatment of the aldehyde with the stabilized ylide methoxycarbonylmethylenetriphenylphosphorane, gave *trans*-ester **38a** and *cis*-ester **38b**.



38a



38b

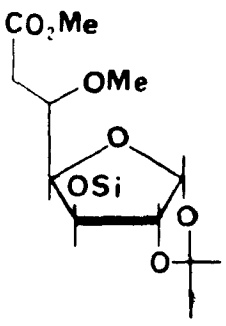
Si = SiPh$_2$*t*-Bu

These geometric isomers had similar mobilities and they could not be cleanly separated by flash chromatography. However, it was possible to isolate a small amount of the two components in sufficient purity to assign them as *cis*- and *trans*-isomers on the basis of their ^{1}H NMR data. The least polar spot was the *cis*-isomer, as evidenced

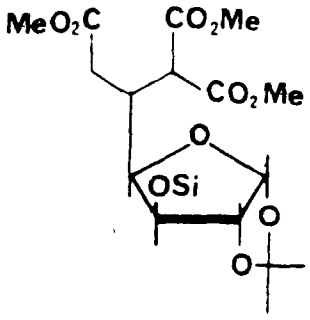
75 M R Litzow and T R Spalding, Mass Spectrometry of Inorganic and Organometallic Compounds, Chapter 3, (1973) Elsevier, N Y

by a coupling constant between the two olefinic protons of *ca.* 10.5 Hz. The more polar isomer, displayed a coupling constant of *ca.* 15 Hz, indicative of a *trans*-relationship. The total yield for the two products was approximately 81% from aldehyde **37**. Preparation of the α,β-unsaturated ester on a larger scale was achieved by treating the same aldehyde with the carbanion of trimethyl phosphonoacetate, which resulted in exclusive *trans*-olefination to afford *trans*-ester **38a** as the sole product. By employing trimethyl phosphonoacetate in a Wittig-Horner reaction instead of the corresponding phosphorane, we managed to avoid the purification step required to remove triphenylphosphine oxide.

Some difficulties were encountered during the addition step of dimethyl malonate anion to the α,β-unsaturated esters **38a** and **38b**, when the reaction was conducted in refluxing methanolic sodium methoxide medium. On TLC, we observed a rapid disappearance of the *cis*-ester, whereas much of the *trans*-ester remained virtually untouched. Moreover, chromatographic separation of the products yielded an undesired methyl ether **39** resulting from methoxide addition to the double bond, in addition to recovering starting *trans*-ester **38a** and triester **40**.



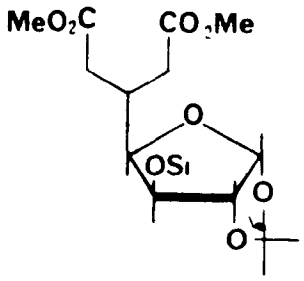
39



40

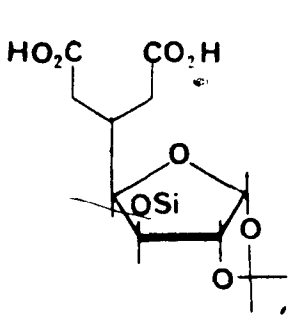
The problem was rectified by replacing sodium and methanol with a refluxing non-hydroxylic system comprised of toluene, solid anhydrous potassium carbonate and dicyclohexano-18-crown-6. The malonate anion of this mixture added to *trans*-ester **38a**, to provide triester **40**. Without purification, the triester was heated in brine-

175° for 8 h following Krapcho's method[67] to give dimethyl glutarate **41**. The yield obtained in two steps from the α,β-unsaturated ester was 83%.



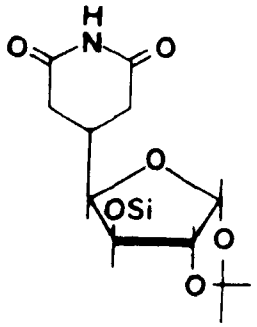
41

The hydrolysis of the 3-substituted glutarate to dicarboxylic acid **42** was achieved by treating the diester with lithium hydroxide.[76] The use of this reagent resulted in a cleaner reaction compared to hydrolysis with a system of aqueous sodium hydroxide and methanol.



42

Si = SiPh$_2$*t*-Bu



43

Finally, the glutarimide derivative **43**[49] was obtained after heating the diacid with excess urea[71] at 175° for 4 h. An examination of its infrared spectrum showed that the extremely broad hydroxyl stretching absorption in the region of 3100 to 3700 cm^{-1} belonging to the dicarboxylic acid **42** precursor had been replaced by a narrower imide N-H absorption band centered at 3250 cm^{-1}. This imidic proton was also observed on the ^{1}H NMR spectrum as a broad singlet resonating at 7.95 ppm.

76 E.J. Corey, J. Szekely and C.S. Shiner, *Tet. Lett.*, 3529 (1977).

In parallel studies, we had at that time established that the formation of the 1,3-dioxane ring did not proceed well under acid-catalyzed conditions, but required strong base. Since the glutarimide ring would certainly not survive these strong basic conditions, this pathway was not further explored.

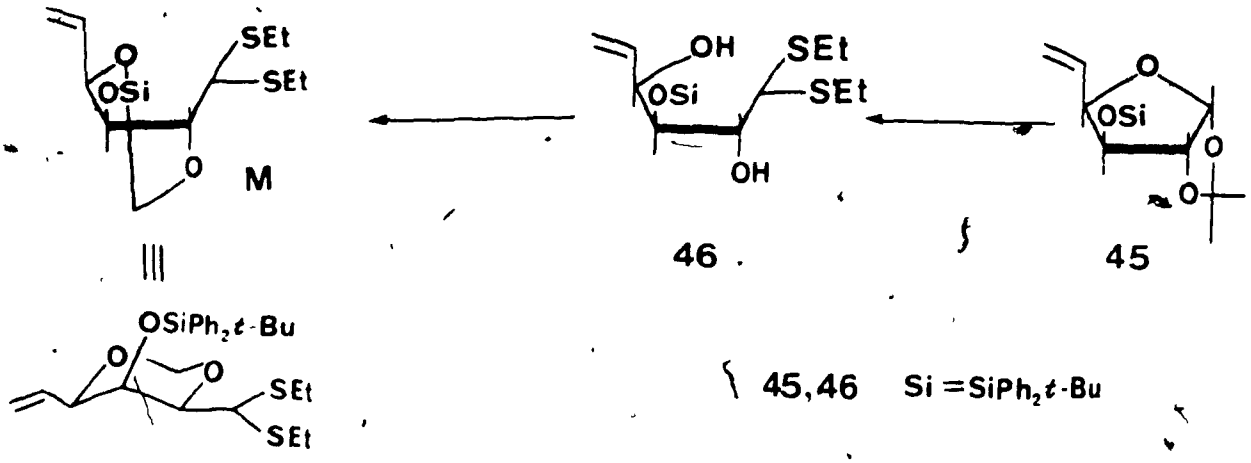
Part II

Synthesis of the AB Ring System of Sesbanimide: Unexpected 1,4-Silyl Shift

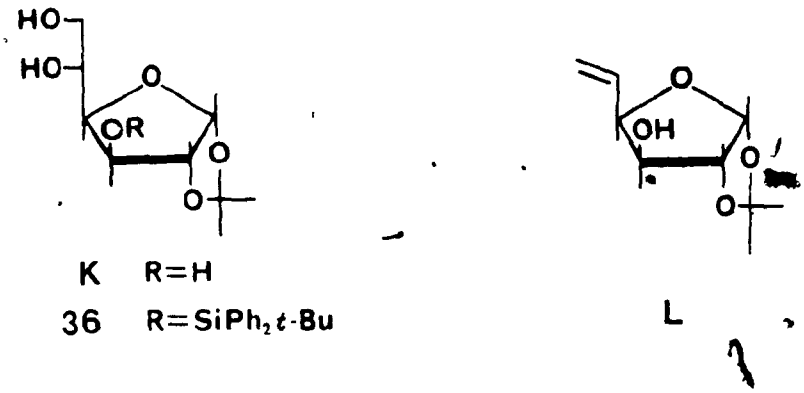
At the time that we did this work, the absolute stereochemistry of sesbanimide was unknown. Since sesbanimide had been represented as enantiomer **1**, we decided to synthesize its mirror image **2**, in the belief that most research groups would first attempt to prepare **1**. Indeed, two years later, Upendra K. Pandit[77] provided us a copy of his paper in advance of publication, reporting that his group had achieved the synthesis of enantiomer **1**. They noted that this enantiomer had an optical rotation equal in magnitude, but opposite in sign to that of natural sesbanimide.

For the synthesis of the natural enantiomer, we felt it would be appropriate to obtain a middle ring dialdehyde intermediate, with the C-1 and C-5 aldehydic sites of the diacetone glucose skeleton masked differently. The decision was made to convert the 5,6-diol system of diacetone glucose into its corresponding olefin **45**. At the required moment, the olefin could be converted to the required C-5 aldehyde after an ozonolysis reaction. The C-1 site, we envisaged, would be protected as a diethyl dithioacetal, as have been known to occur after treatment of 1,2-isopropylidene derivatives of sugars with zinc chloride/ethanethiol. The decision to protect the 3-hydroxy function of diacetone glucose as the *t*-butyldiphenylsilyl ether was discussed previously. Thus, a synthesis of an intermediate such as **M** was warranted and could be derived presumably, *via* dihydroxy dithioacetal **46** and olefin **45**.

77. M.J. Wanner, N.P. Willard, G.-J. Koomen and U.K. Pandit, *J. Chem. Soc., Chem. Comm.*, 396 (1986).



Two synthetic routes were possible for the synthesis of olefin **45**. The first would involve the silylation of 1,2-acetonide **L**, a derivative which could be made in three steps starting with triol **K**.[78,79]



K R=H

36 R=SiPh$_2$*t*-Bu

L

The second route involves silylation of diacetone glucose, selective hydrolysis of the 5,6-acetonide, and conversion of the 5,6-diol system to carbon-carbon double bonds. Since the first two steps of this latter possibility had been performed earlier, and a sufficient quantity of 5,6-diol **36** was available, we decided to convert the diol to its olefin **45**. There are many methods to carry out this kind of transformation. Prominent ones are (1) the Corey-Winter method[80,81] of thiocarbonylation followed by

78 J.K.N. Jones and A.L. Thompson, *Can. J. Chem.*, **35**, 955 (1957) and references cited

79 M. Pietraszkiewicz and P. Sinay, *Tet. Lett.*, 4741 (1979).

80 E.J. Corey and R.A.E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963)

81. E.J. Corey and R.A.E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965).

heating in trimethyl phosphite, (2) Hanessian's method[82] involving the formation of the 1-dimethylamino(methylene)acetal and treatment with methyl iodide and (3) Josan and Eastwood's procedure[83,84] of converting the diol to a cyclic orthoester and subsequent pyrolysis with catalytic amount of benzoic or triphenylacetic acid.

The first method was not applied in our case because of the high cost of the thiocabonylating reagent, thiocarbonyldiimidazole, precluded its use in large quantities. Furthermore, this procedure requires two reaction steps, in which the second step requires a prolonged heating time of about 60 hours.

We focused instead our attention on the latter two procedures which are also essentially one-pot methods. Our first attempt at olefination using Hanessian's method gave unsatisfactory results. As detected on TLC, treatment of the diol with *N,N*-dimethylformamide dimethylacetal in methylene chloride as solvent gave a less polar compound. Without characterization, methylene chloride was replaced with toluene, methyl iodide was added and the mixture refluxed for the prescribed amount of time as described by Hanessian. As visualized by TLC, another spot less polar appeared, as expected. After workup, however, only orthoester **44** was obtained; no trace of olefinic compound was detected.

We then decided to use Josan and Eastwood's procedure to convert the diol to its olefin. The acetic acid catalyzed reaction of the 5,6-diol with trimethyl orthoformate gave quantitatively its corresponding diastereomeric orthoesters **44**.

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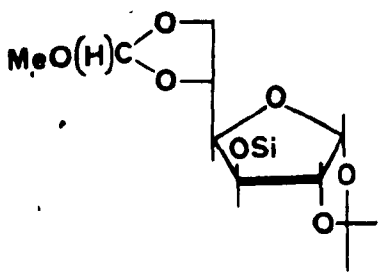
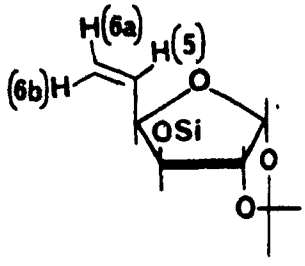
82. S. Hanessian, A. Bargiotti and M. LaRue, *Tet. Lett.*, 737 (1978).
83. J.S. Josan and F W Eastwood, *Carbohyd Res*, 7, 161 (1968)
84. J S, Josan and F W Eastwood, *Aust J Chem*, 21, 2013 (1968)



44 Si=SiPh$_2$*t*-Bu

In the 200 MHz ^{1}H NMR spectrum, the orthoformyl proton was observed as two signals resonating at 5.73 and 5.79 ppm, the integrated areas of which were in the approximate ratio 3:1, and the total integral of which corresponded to one proton.

Heating this mixture of orthoesters **44** in the presence of benzoic acid at 155-175° for 20 h afforded the olefin **45** in 73% yield, based on diol **36**. The ^{1}H NMR spectrum of **45** showed the presence of vinylic protons.[85] The two coupling constants between the *cis* 6a-H and 5-H protons, and *trans* 6b-H and 5-H protons, were about 10.3 and 17.7 Hz, respectively.



45

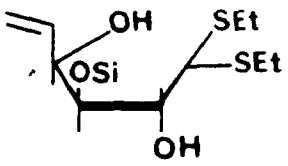
The next step was the formation of dihydroxy diethyl dithioacetal **46**. Earlier workers[86,87] in our laboratory had discovered that dithioacetals could be formed from

85 J.A. Pople, W G. Schneider and H.J Bernstein, High – resolution Nuclear Magnetic Resonance, pp 240, McGraw-Hill Book Company, Inc. (1959).

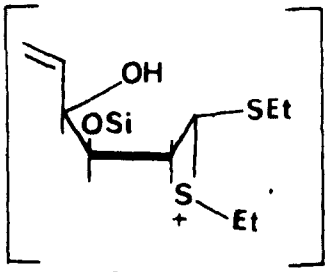
86. C Luthe, Ph D Thesis, McGill University, 1981

87 H Oh, Ph D Thesis, McGill University, 1981

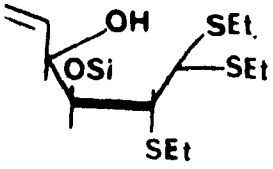
their corresponding ribose 1,2-acetonide derivatives without prior deprotection of the isopropylidene group by simply exposing them to zinc chloride/ethanethiol. Thus, **45** was treated with zinc chloride/ethanethiol[88,89] at 0° for 15-25 min to afford dithioacetal **46**. It should be noted that the reaction mixture was immediately quenched by rapid addition of a 1N HCl solution within the time period specified. If the reaction time was prolonged, there was rapid formation of a side product, just slightly less polar than the expected dithioacetal. This product was determined to be **48**, presumably formed *via* an episulfonium ion **47**.[90]



46



47



48

Si= SiPh$_2$*t*-Bu

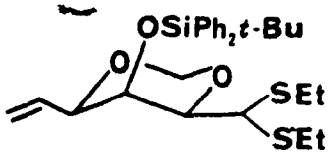
The next step in the synthetic sequence was the linkage of the 1,3-diol dithioacetal **46** *via* a methylene unit to form the 1,3-dioxane ring **M**. Literature methods for synthesis of methylene acetals report that they are conducted in neutral, acidic or basic conditions.

In neutral media, a diol is treated with NBS or bromine in DMSO,[91,92,93] a reaction which involves a Pummerer rearrangement. This type of acetalization was not

88. P J. Barry and B M Craig, *Can J Chem*, 33, 716 (1955)
89. H. Zinner, H Brandner and G Rembarz, *Chem. Ber*, **89**, 800 (1956)
90. M.L. Wolfrom and W von Bebenburg, *J. Am Chem Soc*, **82**, 2817 (1960).
91. S. Hanessian, G Yang-Chun, P Lavallee and A.G. Pernet, *J. Am. Chem. Soc.*, 94, 8929 (1972)
92. S. Hanessian and A G Pernet, *Carbohyd. Res.*, **26**, 258 (1973).
93. R M. Munavu, *J Org Chem*, 45, 3341 (1980)

attempted because of possible interference from the brominating reagents on the dithioacetal moiety of **46**. The first attempt at methylenation employing a refluxing solution of 1,3-diol **48**, s-trioxane and p-toluenesulfonic acid failed to afford the desired 1,3-dioxane ring. A second attempt using powdered KOH and methylene bromide in DMSO[94] gave many products, which we did not try to isolate.

The third attempt using phase-transfer condition described by Szarek and Kim,[95] calls for heating the diol concerned at 60-65°, in a heterogeneous solution of methylene bromide and 50% aqueous sodium hydroxide, in the presence of tetrabutylammonium bromide as phase-transfer catalyst. This method seemed promising after a TLC taken from the organic phase showed a major non-polar product, as expected, and also two minor spots (more polar than the starting material) which we did not attempt to isolate. After workup and purification by flash chromatography, this major product was isolated in approximately 55-57% yield. This product was first thought to be the required B ring intermediate **M**.



M

The 200 MHz ^{1}H NMR could reasonably be interpreted in terms of **M**. The chemical shifts of the vinylic protons, as well as the other ring protons, all seemed to be in the proper location. The methylene protons of the 1,3-dioxane ring appeared as singlets at 4.86 and 5.05 ppm. The lack of any coupling was rationalized at that point by

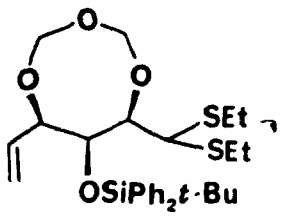
94. A. Liptak, V.A. Olah and J. Kerekgyarto, *Synthesis*, 421 (1982)
95. K.S. Kim and W.A. Szarek, *Synthesis*, 48 (1978).

postulating that the steric bulk of the *t*-butyldiphenylsilyl protecting group had altered the conformation of the six-membered ring, and hence the value of the coupling constants. The mass spectrum fragmentation pattern was also in accord with M. Although no molecular ion peak was detected, there was a prominent peak at m/e 445($M^{+\cdot}$ - *t*-Bu·), and another one at m/e 353($M^{+\cdot}$ - *t*-Bu· - H_2CO - EtSH). We therefore proceeded to transform this intermediate to the corresponding glutarimide ring containing AB ring system.

Large scale preparation of M led to some problems with erratic yields varying between 12-25%. Since methylene bromide assumed the role of both solvent and reactant in this phase-transfer reaction, we thought that an appropriate dilution with a co-solvent such as 1,2-dichloroethane could lead to higher yields of this product. Unfortunately, dilution with this co-solvent inhibited any desired reaction. A dilution with toluene also did not afford better yields of **M**.

It was then felt that lower base concentration might provide better yield of M However, the reaction failed to proceed in systems where the aqueous base concentration was lower than 40% (w:w). An attempt carried out at room temperature, instead of heating at the recommended temperature (60-65°) resulted in long reaction times in order to consume all of the starting material. Furthermore, this also resulted in the recovery of substantial amount of a side-product just slightly more polar than the required one. With the exception of two extra protons observed as singlets on the 200 MHz ^1H NMR spectrum, the rest of the spectrum of this side product was superimposable with that of M. The observed fragmentation pattern from the mass spectrum of this by-product was also similar to that displayed by the major product but many of its fragments were shifted higher by 30 mass units. Fragments which appeared at m/e 445 and 353 in M were replaced by fragments in this side product appearing at m/e 475 and 383. The mass spectrum of this by-product also exhibited another peak at m/e 415 which could be interpreted in terms of the loss of

[t-Bu· + 2 H_2CO] from the molecular ion.. In other words, this side-product contained an extra formaldehyde unit. We thus assigned it as 1,3,5-trioxepan **N**. Since we could not find the right condition to increase the yields during large scale preparation, the required transformation was accomplished by carrying it out on 5 g batches.

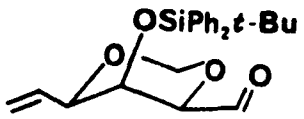


N

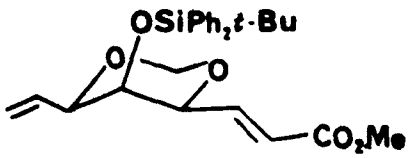
Mercury ion-mediated ($HgO/HgCl_2$) hydrolysis of dithioacetal **M** only gave low yields (31%) of aldehyde **O**, and much starting dithioacetal was recovered after silica-gel chromatography . It was necessary to unmask this dithioacetal group in a different manner. This was achieved by treating **M** with $NCS/AgNO_3$ in aqueous acetonitrile.[96] As monitored by thin layer chromatography, the hydrolysis reaction was extremely rapid, all of the starting material being consumed almost immediately. The workup failed to remove the silver chloride salts completely and the ^1H NMR spectrum, though not definitive, revealed a downfield aldehyde peak at 9.63 ppm.

We did not purify the aldehyde but instead, we proceeded to conduct a Wittig-Horner condensation of this aldehyde with the carbanion of trimethyl phosphonoacetate. This reaction yielded only the *trans*-ester **P**, as evidenced by a coupling constant of *ca.* 16 Hz. The yield obtained was 55%, based on dithioacetal **M**.

96. E.J. Corey and B.W. Erickson, *J. Org. Chem.*, 36, 3553 (1971).

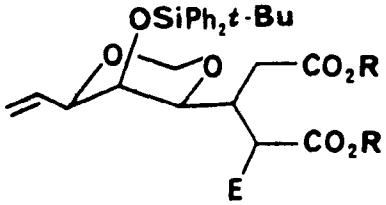


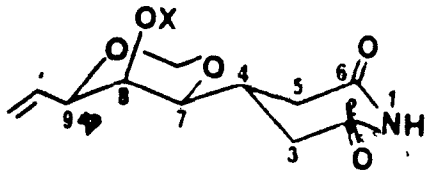
O



P

Now that the α,β-unsaturated ester was obtained, the next step would be the addition of the anion of dimethyl malonate. Using the procedure developed earlier on glucose derivative **37**, we then undertook the conversion of α,β-unsaturated ester **P** to glutarimide **T**. The anion of dimethyl malonate was added to **P**, forming triester **Q**. The triester was conveniently demethoxycarbonylated by Krapcho's method[97] to dimethyl glutarate **R**. This diester was subsequently hydrolyzed to dicarboxylic acid **S** after treatment with lithium hydroxide and then heated with urea to form the 3-substituted glutarimide **T**. The sequence from ester **P** to glutarimide **T** gave an overall yield of 56%.



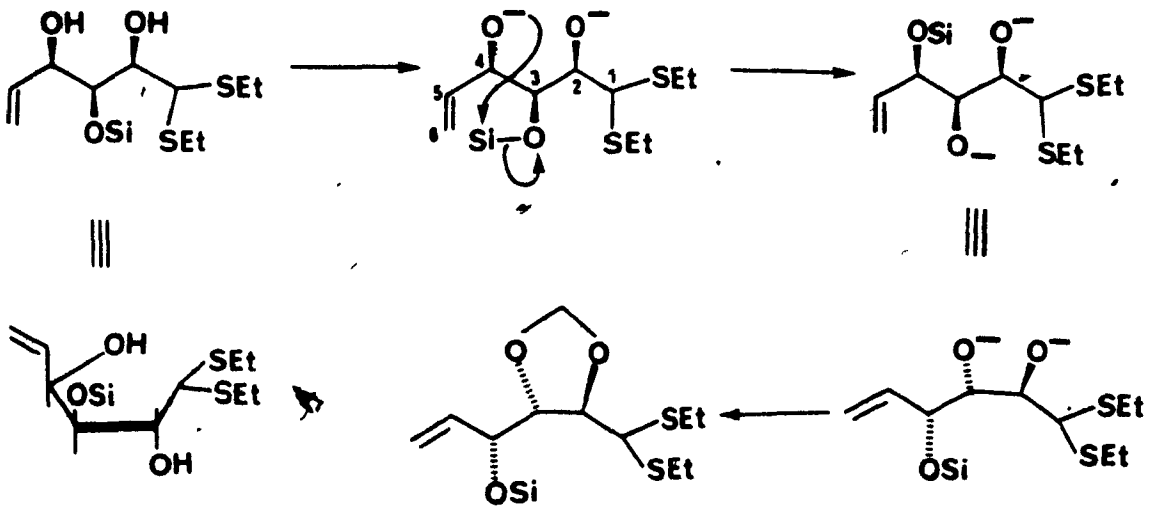


Q	R=Me, E=CO_2Me	**T**	X=SiPh, *t*-Bu
R	R=Me, E=H	**U**	X=H
S	R=H, E=H		

Throughout the sequence of chemical modifications and structure identifications from **M** to **T**, the proton-proton coupling constants of the methylene acetal protons varied between zero and two Hz, but never exceeded 2 Hz. Even after the deprotection of the *t*-butyldiphenylsilyl group of **T** to alcohol **U**, the methylene acetal protons remained as two singlets. That these methylene protons had a coupling constant of $J=0$ Hz was therefore not due to the steric bulk of the *t*-butyldiphenylsilyl

protecting group. Moreover, the ^1H NMR signal of the allylic proton (9-H of U) appeared as a multiplet centered at 4.16 ppm, instead of the expected doublet of doublet. Cookson *et al.*[97,98] listed a series of compounds possessing methylenedioxy groups the protons of which have different chemical shifts. In five-membered 1,3-dioxolane rings the coupling constant was between zero and 2 Hz, whereas in six-membered 1,3-dioxane rings it was about 6 Hz. The former value was the type which we had observed throughout the products **M** to **T**. Obviously, a selective 1,4 silyl shift must have occurred with concomitant acetalization during the phase-transfer reaction step involving the methylenation step of dithioacetal **M**. Instead of the expected 1,3 acetalization, we had a 1,4-migration of the *t*-butyldiphenylsilyl group from the C-3 (OH) to the C-4 (OH) of the glucose skeleton followed by a 1,2 acetalization reaction, giving the five-membered dioxolane ring **49**.

Scheme V

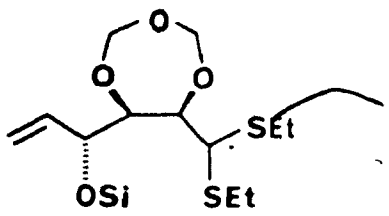


49

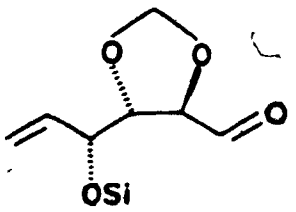
97. T.A. Crabb and R.C. Cookson, *Tet. Lett.*, 679 (1964).
98. R.C. Cookson, T.A. Crabb, J.J. Frankel and J. Hudec, *Tetrahedron* (Suppl. 7), 355 (1967).

We therefore had unknowingly operated on a series of 1,3-dioxolane ring derivatives instead of the 1,3-dioxane derivatives. Mass spectral and high resolution mass spectral data of these series of 1,3-dioxolane products, not unexpectedly, failed to distinguish them from the required 1,3-dioxane ring homologues. Mass spectral fragmentation patterns would not have differed due to similar functionalities, and high resolution mass spectral data of these 1,3-dioxolane substances gave results expected of the 1,3-dioxanes since they are isomeric. Because the error made concerning the structural assignments of these series of compounds had only been discovered at such a late stage, we decided to use the glutarimide intermediate **56** as a model for studies on the final C-ring synthesis and possibly for the synthesis of some analogues.

Structure Reassignments

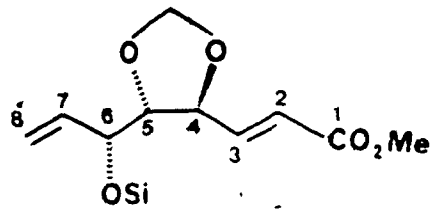


50



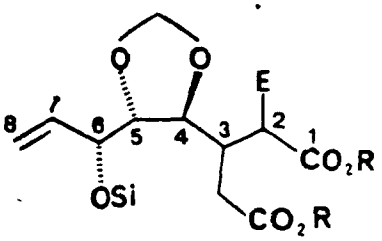
51

Si = $SiPh_2t$-Bu



P

52



Q

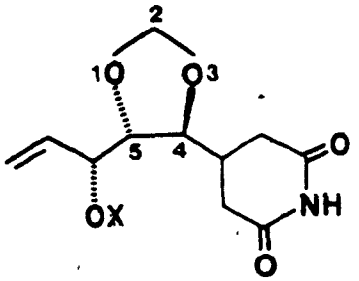
53 R=Me, E=CO_2Me

R

54 R=Me, E=H

S

55 R=H, E=H



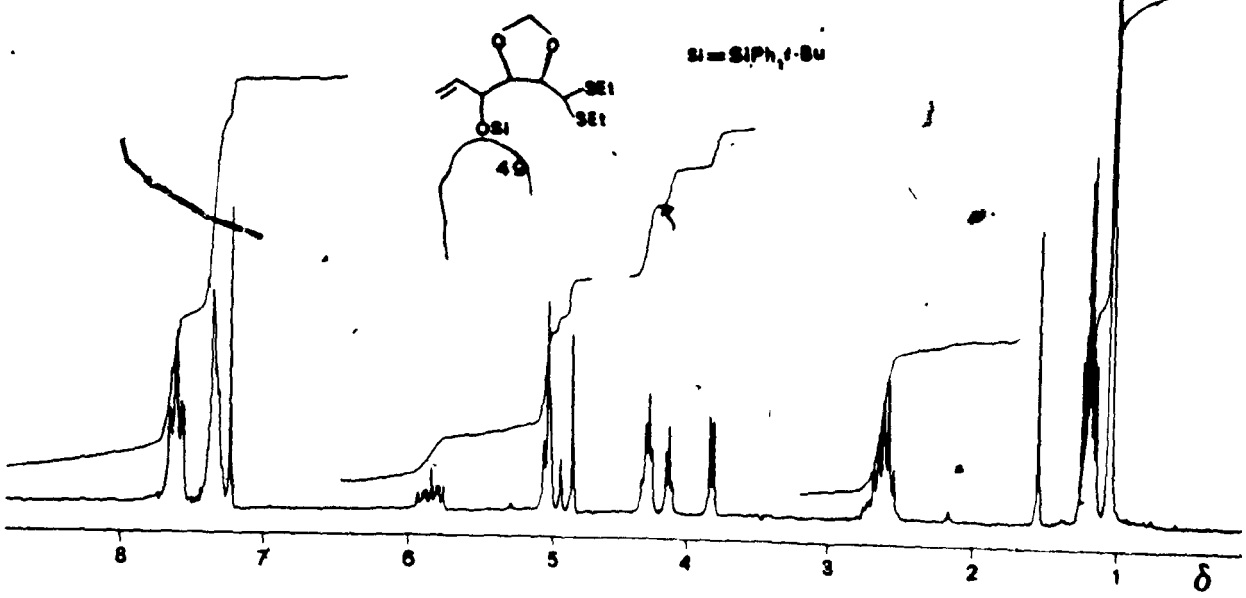
T

56 X=Si

U

57 X=H

Si=$SiPh_2t$-Bu

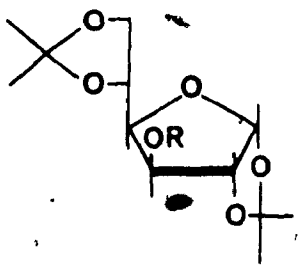


200 MHz ^{1}H NMR spectrum of compound **49** ($CDCl_3$).

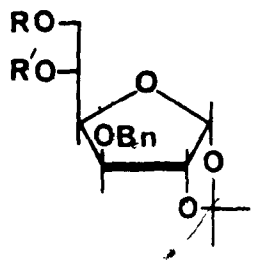
Part III

Synthesis of the AB Ring Moiety of Sesbanimide

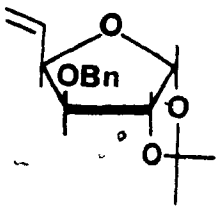
In view of the failure to form the 1,3-dioxane middle ring because of the selective migration of the *t*-butyldiphenylsilyl group from the C-3 hydroxy to C-4 hydroxy, a different protecting group was required for protection of the alcohol function at C-3 of glucose. The choice of protecting groups being rather limited, we decided to protect diacetone glucose with a benzyl group. Following literature methods, the transformation of diacetone glucose **3** was accomplished in four steps to olefin **61**. The first step involved the benzylation of the C-3 hydroxy of diacetone glucose to benzyl ether **58** by the method of Czernecki *et al.*[99] using sodium hydride, tetrabutylammonium iodide and benzyl bromide. Selective hydrolysis of the 5,6-isopropylidene group gave the corresponding 5,6-diol **59**,[100] which was readily converted to orthoester **60** [101] after refluxing the diol in trimethyl orthoformate and a catalytic amount of acetic acid. Finally, **60** was pyrolyzed using triphenylacetic acid as a catalyst to afford olefin **61**.



3 R=H
58 R=Bn



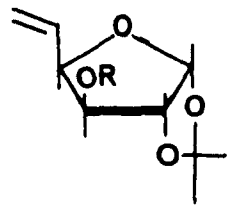
59 R=R'=H
60 RR'=MeOCH



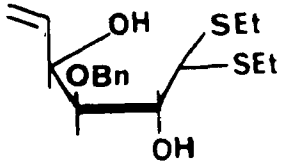
61

99. S Czernecki, C. Georgoulis and C. Provelenghiou, *Tet. Lett*, 3535 (1976).
100. R L. Whistler and W.C. Lake, *Methods Carbohyd. Chem.*, **6**, 288 (1972).
101. D. Horton, J K. Thompson and C.G. Tindall, Jr., *Methods Carbohyd Chem*, **6**, 300 (1972)

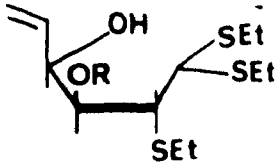
In the usual manner, acetonide **61** was treated with zinc chloride and ethanethiol providing diethyl dithioacetal **62** in quantitative yield. In contrast to its silyl ether homologue **45** where the reaction time was crucial to avoid the formation of by-product **48**, by-product **V** was not detected even after prolonged exposure of **61** to ethanethiol/$ZnCl_2$.



45 R=SiPh$_2$*t*-Bu
61 R=Bn

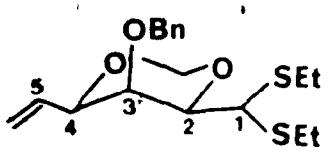


62



48 R=SiPh$_2$*t*-Bu
V R=Bn

The methylenation reaction of Szarek and Kim[95] was then successfully employed on dithioacetal **62** to provide the potential dialdehyde intermediate **63**, appropriately masked at C-1 and at C-5, as a dithioacetal and an olefin, respectively.

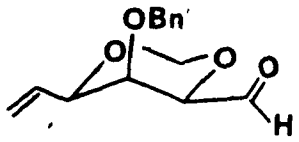


63

About a 75% yield of 1,3-dioxane **63** was obtained after workup and purification by flash chromatography. The ^1H NMR and mass spectral data were in accord with proposed structure **63**. The methylene protons were clearly observed as two sets of doublets centered at 4.79 and 5.28 ppm, each with a coupling constant of J = 6.4 Hz. The 3-H proton of this ring was displayed as a broad singlet on a 200 MHz or 300 MHz

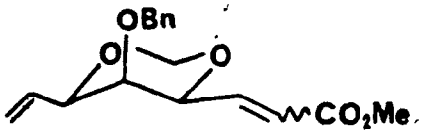
^{1}H NMR spectrum. The coupling constant observed between 3-H and 2-H or between 3-H and 4-H of this 1,3-dioxane compound and of subsequent 1,3-dioxane intermediates, was always less than 2 Hz. That there is very little or no apparent coupling between 3-H, and 2-H and 4-H, is indicative of dihedral angles of close to 90°, and implies that 2-H and 4-H occupy axial positions, since the benzyloxy group is assumed to be axial in the chair conformation of the 1,3-dioxane.

The dithioacetal was hydrolyzed to its corresponding aldehyde **64**, using mercuric chloride/mercuric oxide. Its ^{1}H NMR spectrum showed a singlet at 9.60 ppm for the aldehyde proton among other peaks.



64

Treatment of aldehyde **64** with the anion of trimethyl phosphonoacetate gave both *trans*-ester and *cis*-ester **65**.

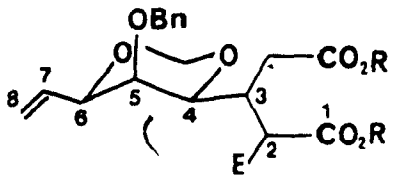


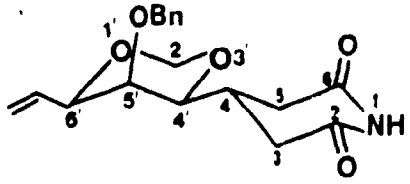
65

The *cis*-ester was less polar than the *trans*-ester and both geometric isomers were easily separated by flash chromatography. The *cis*-ester did not crystallize whereas the *trans*-

ester crystallized readily (mp 91-92°). The former adduct revealed a proton-proton coupling constant of 11.7 Hz and the latter displayed a coupling constant of 16.0 Hz. The total yield of the isomers was about 93%, consisting of one-fifth *cis* and four-fifths *trans* isomers.

Having obtained the α,β-unsaturated esters, we proceeded with the synthesis of the glutarimide moiety. The esters were reacted with the sodium anion of dimethyl malonate to provide triester **66**, followed by heating the triester in aqueous dimethyl sulfoxide and sodium chloride at 160-175° for 4 h to give dimethyl glutarate **67**. Lithium hydroxide hydrolysis of **67** provided dicarboxylic acid **68**, which in turn was converted to glutarimide **69** after heating with urea. The yield obtained after the four step transformation of the α,β-unsaturated esters to the AB ring synthon **69** was approximately 60%.





66 R=Me, E=CO_2Me

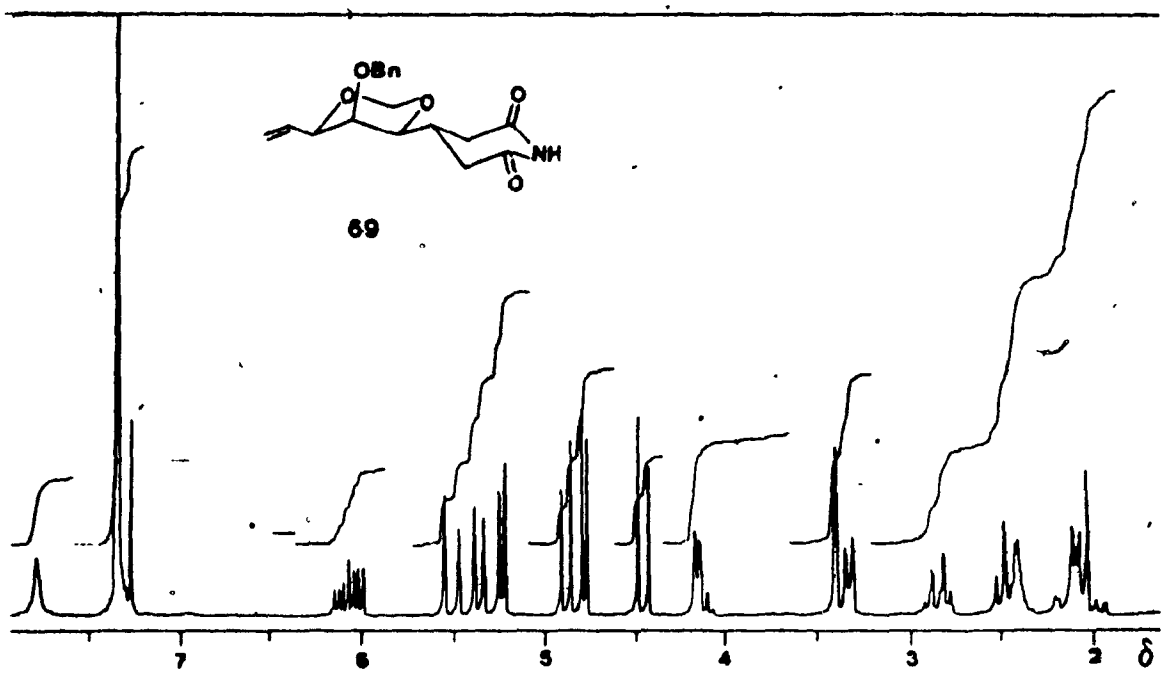
67 R=Me, E=H

68 R=H, E=H

69

Satisfactory spectral and analytical data were obtained for the AB ring system. A broad singlet at 7.77 ppm corresponding to the N-H proton was displayed on the ^1H NMR spectrum. The methylene protons of the 1,3-dioxane ring were observed as two doublets (J=6.4 Hz) centered at 4.77 and 5.22 ppm; the 5′-H proton as usual, appeared as a singlet at 3.40, while the 4′-H and 6′-H protons were observed as doublets of doublets respectively centered at 3.33($J_{4',5}$ =1.2, $J_{4,4'}$ =7.3 Hz) and 4.15($J_{4',5}$ = 1.3,

$J_{5',6'}$ =6.2 Hz) ppm. The ammonia chemical ionization mass spectrum showed peaks at m/e 349($(M + NH_4)^+$) and 322(MH^+). The high resolution chemical ionization mass spectrum analysis gave the recorded value of 332.1499 for MH^+ compared to the calculated value of 332 1498. An infrared spectrum showed the carbonyl band at 1708 and the N-H band at 3373 cm^{-1}.



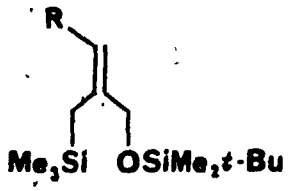
200 MHz ^1H NMR spectrum of compound **69** ($CDCl_3$).

Chapter 3

Part I

Model Studies Involving the Condensation of Allylsilanes to the AB Ring System using 1,3-Dioxolane 56a

In order to construct the C-ring of sesbanimide, a five-carbon unit had to be added to the aldehyde carbonyl carbon. We felt that this addition would be conveniently achieved by using allylsilanes. For instance, an allylsilane protected as its *t*-butyldimethylsilyl ether **74** would lead to the desmethyl analog of sesbanimide, in which we were also interested, whereas allylsilane **79** would be useful for the synthesis of sesbanimide itself.



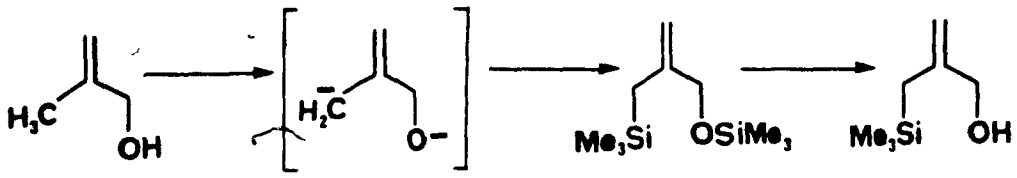
74 R=H

79 R=Me

Allyl alcohol **73** was prepared in two steps according to a procedure developed by Trost *et al.*[102,103] The commercially available 2-methyl-2-propen-1-ol **70** was first converted to its dianion **71** using n-butyllithium and tetraethylenediamine as base,

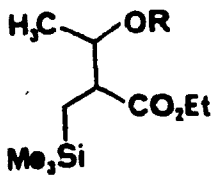
102. B.M. Trost and P. Renaut, *J Am. Chem. Soc.*, **104**, 6668 (1982).
103. B.M. Trost and D.M.T Chan, *J. Am. Chem. Soc.*, **105**, 2315 (1983).

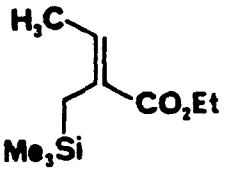
followed by quenching with chlorotrimethylsilane to provide 72. Trimethylsilyl ether 72 was then hydrolyzed to its alcohol 73.

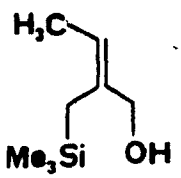


70 71 72 73

Allyl alcohol 78 was synthesized according to the method of Vedejs and co-workers.[104] The anion of ethyl 3-(trimethylsilyl)propionate[105] was condensed with acetaldehyde to afford alcohol 75. This was followed by a one pot reaction in which alcohol 75 was mesylated to 76, and the mesylate function eliminated using DBU as a base to give ester-olefin 77. Subsequent diisobutylaluminum reduction of 77 gave the corresponding alcohol 78.







75 R=H
76 R=Ms

77

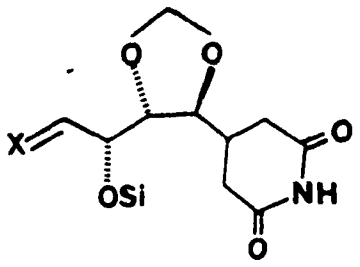
78

104. E. Vedejs, J.B. Campbell, Jr., R.C. Gadwood, J.D. Rodgers, K.L. Spear and Y. Watanabe, *J. Org. Chem.*, 47, 1534 (1982).

105. B.M. Trost and D.M.T. Chan, *J. Am. Chem. Soc.*, 105, 2326 (1983).

Allylsilanes 74 and 79 were formed after silylation of the respective allyl alcohols 73 and 78 with *tert*-butyldimethylsilyl chloride[106] and imidazole in dimethylformamide.

Preliminary studies were carried out with these allylsilanes on models involving the aldehyde derived from the unexpected 1,3-dioxolane product **56**. Thus, olefin **56** was first converted to the aldehyde intermediate **56a**, after ozonolysis at -78°, followed by reduction with dimethyl sulfide[107] for 16 h at room temperature.

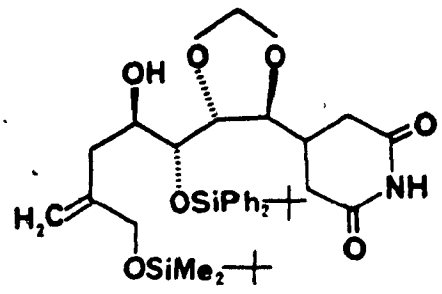


56 X=CH$_2$

56a X=O

Si=SiPh$_2$*t*-Bu

Condensation of allylsilane **74** with aldehyde intermediate **56a** using boron trifluoride etherate as catalyst at -78° for 1 hour and then at -45° for another 19 hours gave alcohol **80** in 52% yield.

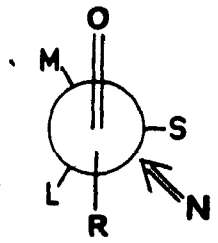


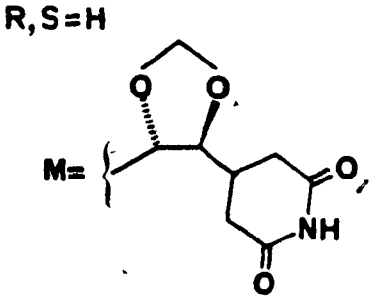
80

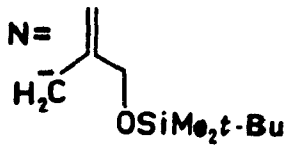
106. E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94, 6190 (1972).

107. J.J. Pappas, W.P. Keaveney, E. Grancher and M. Berger, *Tet. Lett.*, 4273 (1966).

A TLC of the reaction mixture showed only a single product of higher mobility compared to the aldehyde. According to the 200 MHz ^{1}H NMR of this compound, this was a single diastereomer. The R-configuration was assigned to the newly created chiral center after application of Cram's rule[108] (or Felkin-Anh model). Our assumption was substantiated by a report authored by Reetz and Kesseler,[109] who experimentally determined that non-chelation-controlled (Felkin-Anh) products would result from the nucleophilic addition to chiral α-alkoxy aldehydes when catalyzed by boron trifluoride etherate. Furthermore, Danishefsky and DeNinno[110] reported that reactions of allylsilane with aldosuloses under catalysis by boron trifluoride etherate gave high diastereofacial excess of Felkin-Anh type products. A fast atom bombardment spectrum of **80** using a diethanolamine (DEA) matrix showed a peak at m/e 773 which corresponds to $(M + DEAH)^+$.



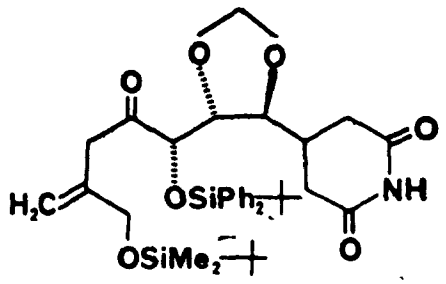




L=OSiPh$_2$*t*-Bu

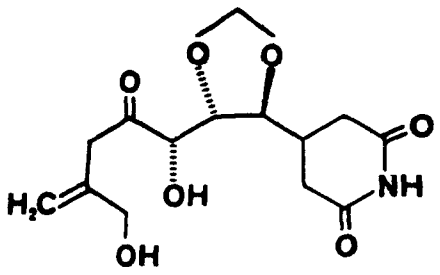
Oxidation of alcohol **80** was carried out with chromium trioxide and pyridine in methylene chloride to give ketone **81** in almost quantitative yield.

108. D.J. Cram and F.A. Abd Elhafez, *J. Am. Chem. Soc.*, 74, 5828 (1952).
109. M.T. Reetz and K. Kesseler, *J. Chem. Soc., Chem. Comm.*, 1079 (1984).
110. S. Danishefsky and M. DeNinno, *Tet. Lett.*, 823 (1985).



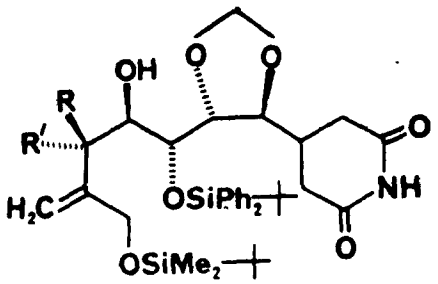
81

The 200 MHz ^{1}H NMR and FAB mass spectra were in accord with the proposed structure **81**. The ^{1}H NMR signals for **81** showed the presence of the two silyl groups, a multiplet accounting for the five C-H protons of the glutarimide ring at 2.08-2.65, a broad singlet downfield N-H proton at 7.80 ppm, two doublet of doublet signals at 3.74 (J=4.5, 5.5 Hz) and 3.89 ppm (J=4.2, 5.5 Hz) for the 4-H and 5-H protons, as well as two methylene acetal singlets at 4.80 and 4.91 for the 1,3-dioxolane ring portion. There was a doublet at 4.33 ppm (J=4.2 Hz) for the single C*H*OSiPh$_2$ proton. Two methylene protons α to the keto group appeared as an AB quartet centered at 3.28 ppm with coupling constants of J=19.5 Hz. The two olefinic protons were found as doublets with coupling constants of 1.5 Hz centered at 4.76 and 5.20 ppm, and the CH_2 protons of the CH_2OSiMe_2 moiety as a singlet at 3.96 ppm. The FAB spectrum of ketone **81** using a diethanolamine (DEA) matrix gave a peak at m/e 771 corresponding to (M + DEAH)$^+$. Unfortunately, treatment of **81** with fluoride ions did not give the expected analog **82** but instead gave two products which could not be identified after an examination of their ^{1}H NMR spectrum.



82

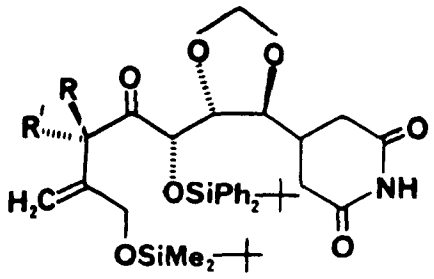
After having successfully carried out the the addition of allylsilane **74** to the model aldehyde, followed by oxidation of the resulting alcohol, we next sought to repeat these steps using allylsilane **79** to the same aldehyde. When allylsilane **79** was condensed with aldehyde **56a**, three products less polar than the starting aldehyde were observed on thin layer chromatography. After workup, they were separated by flash chromatography. The product with the highest mobility on TLC could not be identified. The other two were the required diastereomeric alcohols **83a** and **83b**, as shown by ^{1}H NMR. The less polar component and the more polar component were isolated in the ratio of 1:4. The total yield was 42%.



83a R=Me R′=H
83b R=H R′=Me

Because of the non-chelation-control nature of the boron trifluoride etherate catalyzed addition, we expected to form only diastereomers **83a** and **83b**, both of which possess the R-configuration about the C-OH center, but are epimeric about the C-CH_3 carbon center. When these separated alcohols were oxidized to ketones **84a** and **84b** with

chromium trioxide/pyridine, each corresponding ketone provided different optical rotation values.



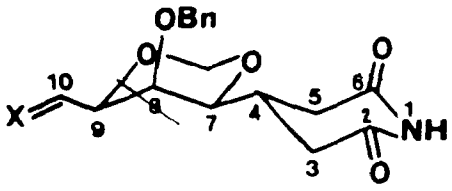
84a R= Me R'=H
84b R= H R= Me

The oxidation product of the less polar alcohol had an optical rotation of $[\alpha]_D^{23}$ +20.8° whereas oxidation of the more polar alcohol led to a ketone with $[\alpha]_D^{23}$ −58.2°. This proves that the two isolated alcohols were indeed epimeric at the carbon methyl position and not at the carbon hydroxy position. Unfortunately, no facile methods were available to determine the stereochemistry at the C-CH_3 center. Therefore, we decided to stop at this point, satisfied that allylsilanes could serve as the five-carbon unit synthon for the construction of the C-ring of sesbanimide.

Part II

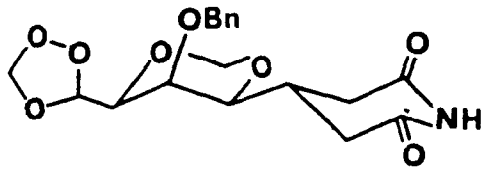
Attempted Synthesis of Desmethyl Sesbanimide: Synthesis of Disubstituted Furan 98

In order to construct the C-ring , a five-carbon unit had to be introduced to the C-10 carbon. Ozonolysis of **69** at -78° followed by reduction with dimethyl sulfide for 16 h at room temperature, yielded aldehyde **85** [111] and minor amounts of a by-product the R_f value of which was identical to the starting olefin **69**. The ^1H NMR of the required aldehyde displayed a singlet for the aldehydic proton at 9.76 ppm, amongst other peaks. That there is no apparent coupling between the aldehydic proton and 9-H is indicative of a 90° dihedral angle.



69 X = CH_2

85 X = O



86

The by-product of the ozonolysis reaction was separated from the aldehyde by flash chromatography. It was identified as ozonide **86**. The three protons of the ozonide ring appeared on the ^1H NMR spectrum as singlets at 5.02 and 5.39 ppm, corresponding to the two methylene protons, and a doublet at 5.60 ppm with a coupling constant J = 7.5 Hz. Fragments in the chemical ionization mass spectrum appeared at m/e 334, 226 and 196, corresponding to the losses of OCH_2O, [OCH_2O + $C_6H_5CH_2OH$] and [OCH_2O + $C_6H_5CH_2OH$ + CH_2O], respectively, from MH^+.

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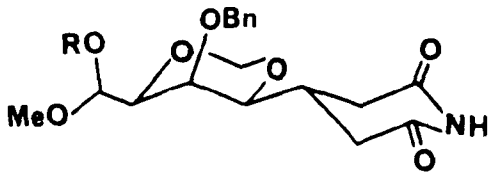
111. Starting with this aldehyde, the numbering system patterned after sesbanimide (see ref. 9) will be utilized.

Unfortunately, the ozonide by-product persisted even after prolonged exposure to dimethylsulfide; therefore, separation by flash chromatography was necessary to afford the aldehyde. It should be noted that methanol had to be avoided as eluant during the purification process. A first attempt at separating the aldehyde from the ozonide using methanol-methylene chloride (1/19) as eluant, gave substantial amounts of a compound the TLC mobility of which was slightly greater than that of aldehyde **85**. Although generally uninformative, the ^{1}H NMR spectrum of this compound showed additional methoxy peaks at 3.42, 3.46 and 3.51. This unknown compound may well be hemiacetal **X** or acetal **Y**.

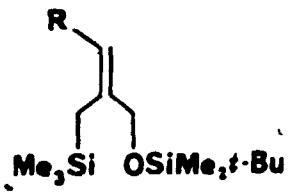


X R = H

Y R = Me

Presumably, silica gel was sufficiently acidic to catalyze the addition of methanol to the aldehyde. When this product was kept in ethyl acetate at room temperature overnight, aldehyde **85** was recovered from it.

After having obtained the required crucial intermediate **85**, the stage was set for the condensation steps involving allylsilanes **74** and **79**.

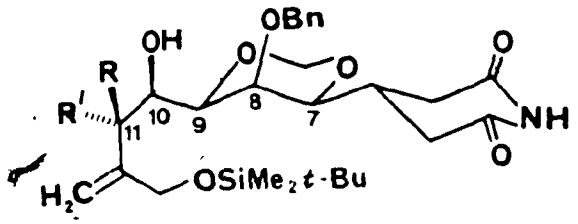


74 R = H

79 R = Me

A condensation involving allylsilane **79** to aldehyde **85** should provide an intermediate alcohol, which upon further elaboration would lead to the natural sesbanimide. On the other hand, addition of allylsilane **74** to aldehyde **85**, would provide the alcohol precursor, which could be later transformed to the desmethyl analogue of sesbanimide.

Boron trifluoride etherate mediated condensation of allylsilane **79** with aldehyde **85** gave three compounds that were detected by TLC. The compound with the highest mobility could not be identified. The two more polar compounds gave proper spectroscopic data (200 MHz ^{1}H NMR, C.I. mass spectrum) for the anticipated diastereomeric alcohols **87**(a,b). Because of non-chelation-control, these substances are epimeric about the C-11 carbon, and both isomers are assumed to possess the R-configuration about the C-10 center. The diastereomers were isolated in the ratio of 3.5/2. The total yield of the diastereomers was approximately 40-45%.

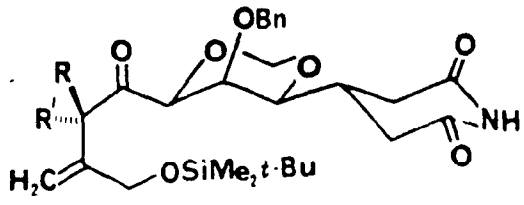


87a R = Me, R' = H

87b R = H, R' = Me

It was not possible to assign the stereochemistry at this epimeric C-11 center for each of the isolated compound at this stage. We felt it was only possible to assign them, after having subsequently transformed them to the natural products.

Oxidation of both diastereomers employing chromium trioxide/pyridine gave their corresponding ketones **88**.



88a R=Me, R'=H

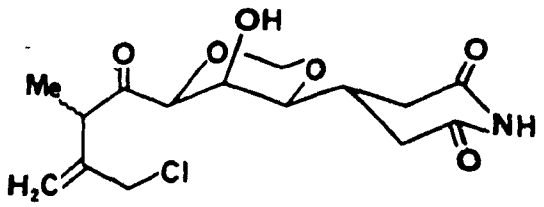
88b R=H, R'=Me

The reactivity of the diastereomers towards oxidation was poor and also differed significantly. Oxidation of the less polar alcohol and more polar component gave the corresponding ketones in only 4 and 21%, respectively. There was also much side product formation, along with recovered starting material. The poor oxidation yields of these diastereomers is in sharp contrast to the oxidation of the alcohols in the corresponding 1,3-dioxolane systems (**80**, **83a**, **83b**), where yields recovered were essentially quantitative. Attempted oxidation of these alcohols **87** using other oxidizing systems such as oxalyl chloride/Et_3N/DMSO,[112] NCS/methyl sulfide/Et_3N[113], pyridinium dichromate[114], and by the Fetizon[115] reaction all failed to afford the required ketones.

Despite the low yield of the oxidation step, we did have a sufficient quantity of one of the isomeric ketones to proceed with the next step, namely the removal of the benzyl group. We felt that the exposure of **88** to boron trichloride[116] would lead to deprotection of both benzyl and silyl protecting groups. Instead, after exposure of one of the ketones to boron trichloride at -78°, we were surprised to find that in addition to

112. A.J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978)
113. E.J. Corey and C.U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).
114. E.J. Corey and G. Schmidt, *Tet. Lett.*, 399 (1979).
115. M. Fetizon and M. Golfier, *Compt. rend.*, **267**, 900 (1968).
116. F. Seela and S. Menkhoff, *Liebigs Ann. Chem.*, 813 (1982).

removing the benzyl group, the *t*-butyldimethylsilyloxy moiety was also displaced by a chloride, to give the allyl chloride derivative **89**.

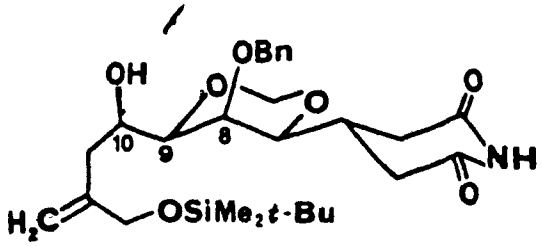


89

The structure of **89** was confirmed by ^{1}H NMR and mass spectral data. Only two dissociable protons were observed after D_2O exchange experiments were performed.

Also, during this time, Terashima and Matsuda,[117] published the first total synthesis of natural sesbanimide A and sesbanimide B, which was very similar to our proposed synthesis. Thus, instead of continuing with our work towards completion of the synthesis of sesbanimide, we focused our attention towards its C-15 desmethyl analogue.

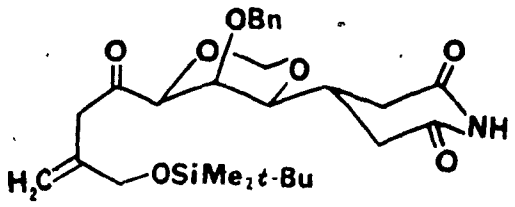
In the usual manner, the aldehyde intermediate **85** was condensed with allylsilane **74** using boron trichloride at -78°. Only one alcohol was isolated after purification by flash chromatography. Presumably, this was derivative **90**, the alcohol with R-configuration at C-10.



90

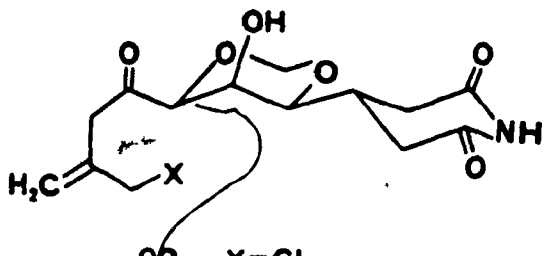
117. F. Matsuda and S. Terashima, *Tet. Lett.*, 3407 (1986).

Oxidation of this alcohol to its corresponding ketone **91**, when monitored by TLC plates was somewhat deceiving, because both alcohol and ketone had identical R_f values. When we treated this alcohol with the recommended amount of 12 equivalents of pyridine and 6 equivalents of chromium trioxide per equivalent of alcohol, only *ca.* 30% of alcohol was oxidized, as determined by ^1H NMR integration of relevant protons. Much starting alcohol remained unoxidized. An infrared spectrum of this product could not detect this newly made carbonyl center, its absorption being obscured by the carbonyl absorptions of the glutarimide ring moiety. Since the polarities of both starting alcohol and ketone product were identical, a clean separation could not be effected, to isolate enough product for the subsequent step. Fortunately, the problem was resolved by treating **90** with two to three times the recommended amount of pyridine (24-36 eq.) and chromium trioxide (12-18 eq.) in order to effect a quantitative oxidation of **90**.



91

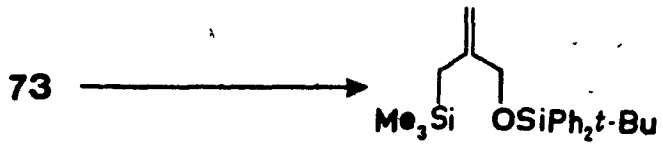
The next step would be to deprotect the benzyl and silyl group using boron trichloride. Exposure of ketone 91 to boron trichloride resulted in the cleavage of the benzyl group, but again, the *t*-butyldimethylsilyloxy moiety was replaced by a chloride function to yield allyl chloride **92**. All subsequent attempts aimed at displacing the chloro with a hydroxy group failed to provide the required alcohol functionality at C-13; therefore the C-15 desmethyl analogue of sesbanimide **93** could not be obtained in this manner.



92 X=Cl

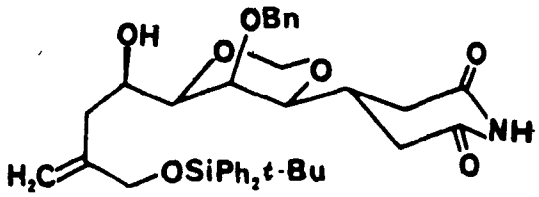
93 X=OH

It was decided that the use of a protecting group more resistant than the *t*-butyldimethylsilyl protecting group towards boron trichloride would be warranted. Therefore, allyl alcohol 73 was silylated to the more stable *t*-butyldiphenylsilyl ether, by heating with *t*-butyldiphenylsilyl chloride and imidazole in dimethylformamide at 60°, providing 94.



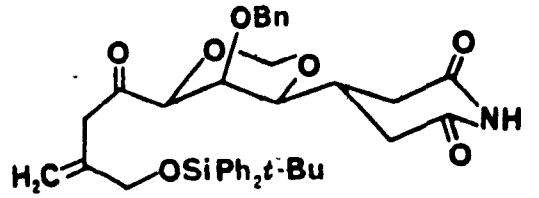
94

The addition of allylsilane 94 to the aldehyde intermediate 85 in the usual manner with boron trifluoride etherate, gave a 44% yield of alcohol 95 after purification by flash chromatography. A 200 MHz ^{1}H NMR of this alcohol indicated that it was a single diastereomer. Applying Cram's rule, the stereochemistry about the C-10 carbon was assigned the R-configuration.



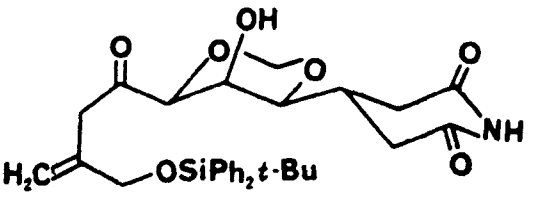
95

The oxidation of this alcohol was carried out in the same manner as previously described for the *t*-butyldimethylsilyl protected homolog **90**, employing pyridine and chromium trioxide (24 eq. py/12 eq. CrO_3 for each eq of alcohol) at room temperature to obtain the corresponding ketone **96** in 44% yield.



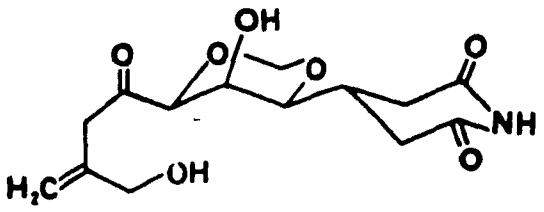
96

As we had predicted, exposure of this compound to boron trichloride resulted in selective cleavage of the benzyl group and afforded the required alcohol **97**. The *t*-butyldiphenylsilyl group was not removed.

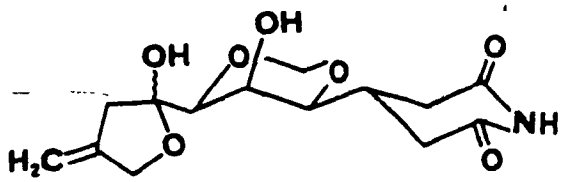


97

The next step would be the treatment of silyl ether **97** with *tetra-n*-butylammonium fluoride in tetrahydrofuran to give C-15 desmethyl sesbanimide either as the ring-opened hydroxy ketone **93** or ring-closed lactol **93a**.

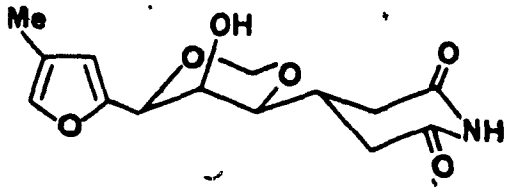


93



93a

A single more polar spot was detected by thin layer chromatography immediately after exposure of **96** to fluoride ion. Within 15 min the reaction was essentially complete; the tetrahydrofuran was evaporated at 0°, and the mixture was immediately purified by flash chromatography. This product, however, was not the expected β,γ-unsaturated ketone, but the disubstituted furan **98**.



98

This furan compound when subjected to a chemical ionization mass spectroscopy analysis decomposed in the probe. However, a satisfactory FAB mass spectrum was obtained.

Our suspicions were raised when a TLC of this product taken from the NMR solvent, was markedly different from that of the sample originally recovered after flash

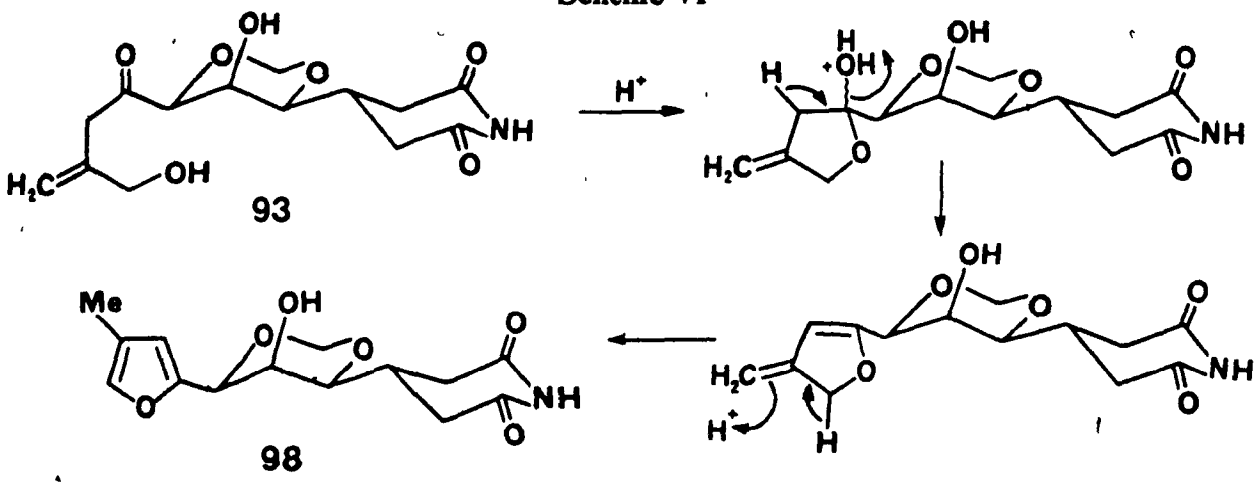
chromatography. The sample which was isolated after purification had an R_f value equal to 0.20 (in methanol-methylene chloride 1:19), but after its dissolution in the NMR solvent, the R_f increased to R_f=0.32. This coincidentally, was also the R_f value of the starting silyl ether **97**. Therefore, we knew that the as yet uncharacterized sample, observed to form during the desilylation step, had been converted to furan **98** once dissolved in the NMR solvent.

When we repeated the same desilylation procedure, using silica gel pre-washed with triethylamine, and conducted the ^1H NMR analysis using deuterated chloroform treated with sodium bicarbonate, an extremely complicated ^1H NMR spectrum was observed, in which integration of the vinylic protons gave much less than the two protons expected. The ^1H NMR spectrum of this unknown substance also showed a doubling of the usual methylene acetal doublet which suggested that isomers were involved, but it was not possible to assign the vast number of signals recorded to any specific structure. A TLC of this NMR sample revealed only one spot and it decomposed in the probe during chemical mass spectral analysis. A FAB spectrum displayed only a weak MH^+ but a prominent $MH^+ - H_2O$ fragment.

When the sample that gave rise to the complicated ^1H NMR spectrum was subsequently treated with a catalytic amount of acetic acid, furan **98** was obtained again, in a clean and rapid manner. It is quite possible that the unknown substance is indeed, desmethyl sesbanimide existing as a mixture of ring-opened γ-hydroxy ketone **93**, and ring-closed anomers **93a**. This would account for the great number of signals recorded in the ^1H NMR spectrum.

The desmethyl C-ring, once exposed to the smallest trace of acid, presumably, is dehydrated to the furan ring. The mechanism for the formation of furan **98** is proposed below.

Scheme VI



98

In view of the fact that satisfactory spectral data could not be obtained for desmethyl sesbanimide, the above suggestions, are however, highly speculative.

During the course of our work, synthetic studies of sesbanimide by many other investigators have led to the synthesis of ring A,[118,119] ring C[120,121] and the AB ring system[122,123,124,125,126,127] of sesbanimide. In addition, Terashima and Matsuda[117] have completed the total synthesis of natural (+)-sesbanimide, and the syntheses of its

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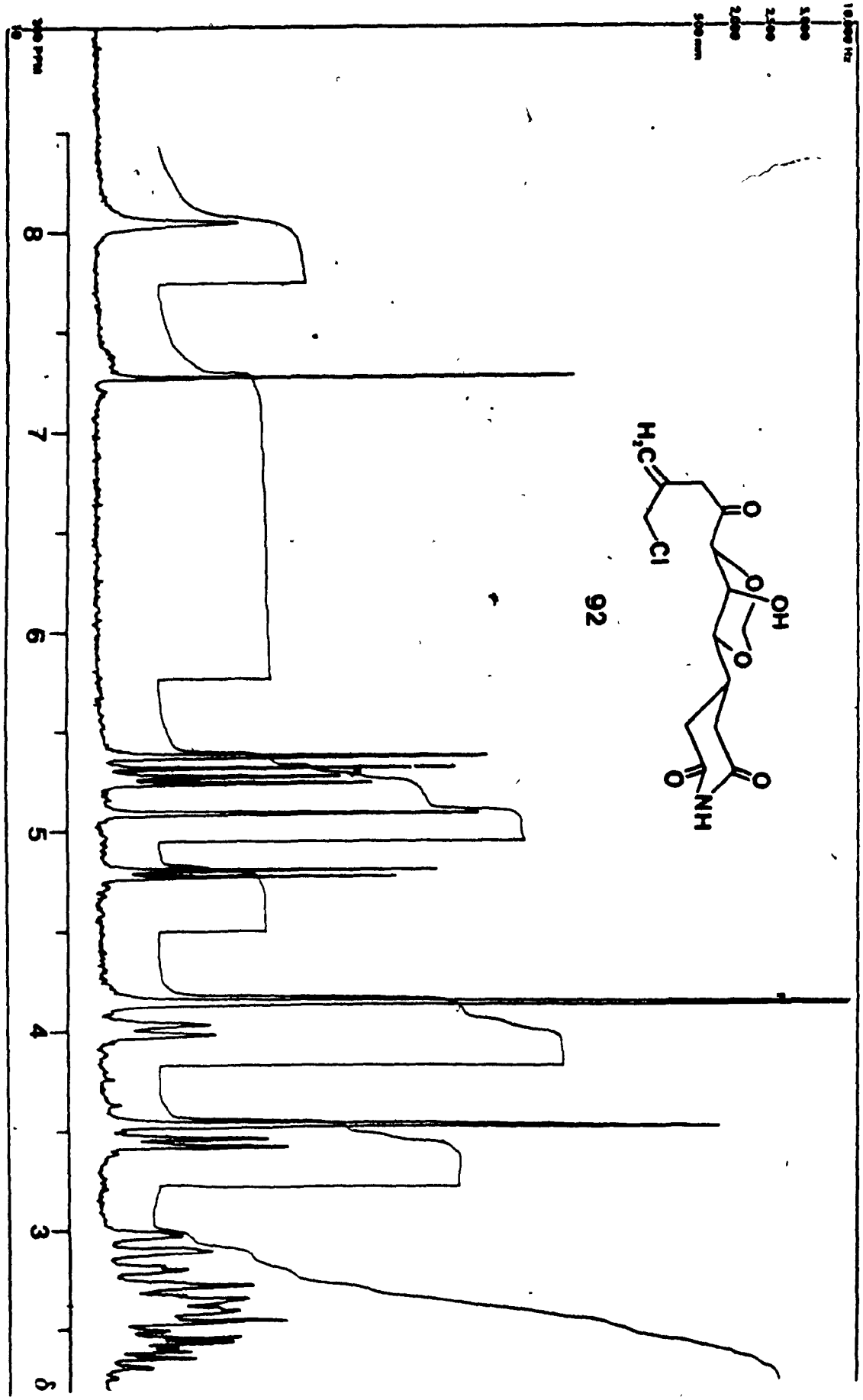
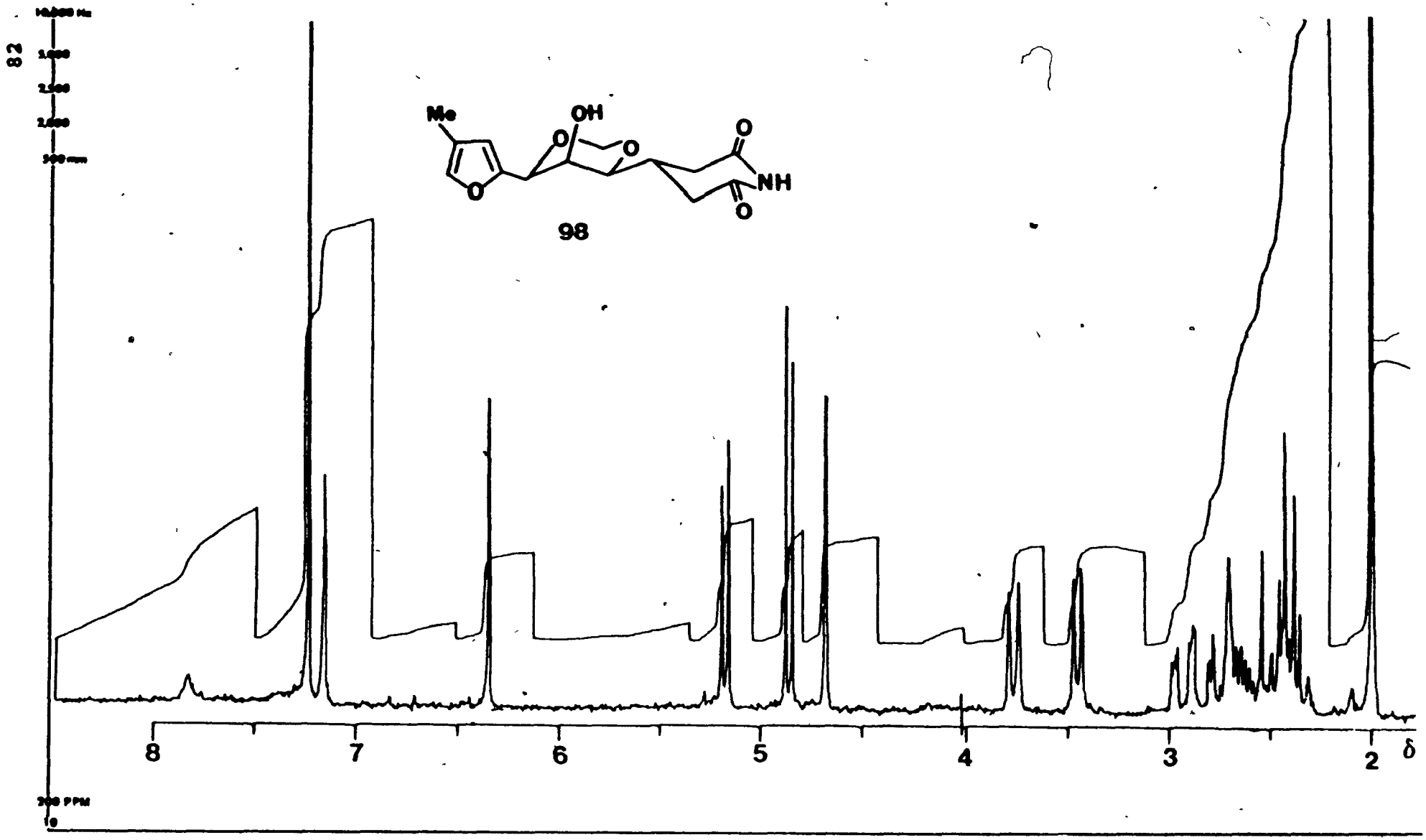
118. K. Tomioka and K. Koga, *Tet. Lett.*, 1599 (1984).
119. T. Kometani, T. Fitz and D. Watt, *Tet. Lett.*, 919 (1986).
120. N. Willard, M.J. Wanner, G.-J. Koomen, and U. K. Pandit, *Heterocycles*, 23, 51, (1985)
121. A.V Rama Rao, J.S. Yadav, A.M. Naik and A.G. Chaudhary, *Tet. Lett.*, 993 (1986).
122. M.J. Wanner, G.-J. Koomen and U K. Pandit, *Heterocycles*, 22, 1483 (1984).
123. G.W.J. Fleet and T.K.M Shing, *J. Chem. Soc., Chem. Comm.*, 835 (1984).
124. M. Shibuya, *Heterocycles*, 23, 61 (1985).
125. F. Matsuda, M. Kawasaki and S. Terashima, *Tet. Lett.*, 4639 (1985).
126. W.R. Roush and M.R. Michaelides, *Tet. Lett.*, 3353 (1986).
127. A.V. Rama Rao, J.S. Yadav, A.M. Naik and A.G. Chaudhary, *Ind. J. Chem.*, 25B, 579 (1986).

enantiomer have been described by Pandit *et al.*[77] and by Schlessinger and Wood.[128] All these syntheses followed a sequence very similar to our proposed synthesis, and differed mainly in the choice of protecting groups, and the exact nature of the five-carbon unit necessary for the construction of the C-ring. The fact that the total synthesis of the C-15 desmethyl analogue of sesbanimide has yet to be reported, may be due to similar problems which we encountered during its construction, namely the unstable nature of the C-15 desmethyl C-ring moiety.

128. R.H. Schlessinger and J.L. Wood, *J. Org. Chem.*, 51, 2623 (1986).



200 MHz ^{1}H NMR spectrum of compound **92** ($CDCl_3$).



200 MHz ^{1}H NMR spectrum of compound **98** ($CDCl_3$).

CONTRIBUTION TO KNOWLEDGE

1. A general procedure for transforming aldehydes to the corresponding glutarimides was developed.

2. After subjecting dihydroxy dithioacetal **46** to the phase-transfer conditions prescribed by Szarek and Kim,[95] 1,3-dioxolane derivative **49** was formed. This was explained by the migration of the *t*-butyldiphenylsilyl group from the C-3 (OH) to the C-4 (OH) of **46**, followed by acetalization of the C-2 (OH) and C-3 (OH) 1,2-diols.

3. The synthesis of the AB ring moiety of sesbanimide was carried out.

4. The synthesis of 8-*O*-benzyl-13-*O*-*t*-butyldimethylsilyl sesbanimides **88**, 13-deoxychloro sesbanimide **89**, 8-*O*-benzyl-13-*O*-*t*-butyldimethylsilyl-15-desmethyl sesbanimide **91** and 13-deoxychloro-15-desmethyl sesbanimide **92** were described.

5. 13-*O*-*t*-Butyldiphenylsilyl-15-desmethyl sesbanimide **97** was synthesized. Subsequent desilylation of **97** gave compounds which could not be identified, but which were easily converted to a single furan derivative **98** upon exposure to acetic acid.

GENERAL EXPERIMENTAL

Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Mass spectra (ms) were obtained on a Hewlett Packard 5984A or a Dupont 21-492 B mass spectrometer, in the direct inlet mode unless otherwise indicated. Fast Atom Bombardment (FAB) spectra were recorded on a VG ZAB HS mass spectrometer. Infrared (IR) spectra were obtained on a Perkin Elmer 297 spectrophotometer or Analect Instruments AQS-18 FT-IR, and specific rotations ($[\alpha]_D$) on a JASCO DIP-140 digital polarimeter (Na vapour lamp 589 line). Proton magnetic resonance (^{1}H NMR) were recorded on Varian T-60, T-60A, XL-200 and XL-300 spectrometers as specified, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in the δscale in parts per million (ppm). Doublets (d), triplets (t), and quartets (q) were recorded at the center of the peaks, and multiplets (m) as their range of absorptions, other abbreviations used: singlet (s), broad (b) and broad singlet (bs). Chemical shifts are described as they appeared even though they might represent more complex patterns.

Analytical thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} aluminum-backed plates and was visualized by dipping into a solution of ammonium molybdate (25 g) and ceric sulfate (1 g) in c-H_2SO_4/H_2O (10 mL/90 mL) and heating on a hot plate. Merck Silica Gel 60 (230-400 mesh, 40-60 m) was used for flash chromatography, performed according to the procedure of Still *et al* [47]

Solvents were reagent grade unless otherwise specified. Petroleum ether refers to that fraction having a boiling point of 30 to 60°. Dry tetrahydrofuran (THF) was obtained by refluxing with sodium metal and benzophenone. All evaporations were carried out under reduced pressure (water aspirator) with a bath temperature of 25 – 40° unless otherwise specified.

CHAPTER 1 - EXPERIMENTAL

Bis(chloroacetyl)amine **4**

Concentrated sulfuric acid (fuming (30% SO_3), 1.1 g, 11 mmol) was added to a mixture of 2-chloroacetamide (10.1 g, 108 mmol) and chloroacetic anhydride (15.4 g, 90 mmol) with stirring. The reaction mixture was then heated at 105°, the solution upon heating became yellowish and then brownish until precipitation occurred after 1 h. It was heated for an extra 1 h at 120°, cooled to room temperature and then ice cold water was added. The crystalline material was filtered and rinsed repeatedly from 5% $NaHCO_3$ solution and ice-cold water. Recrystallization from hot acetonitrile gave 10.3 g (67%) of bis(chloroacetyl)amine **4** as light brown crystals, m.p. 196-198° (dec.) (Lit. m.p. Booth and Noori[30] give 191-193°). ^{1}H NMR (60 MHz, DMSO-d_6) δ: 3.77(s, 4H, $C(O)CH_2Cl$). ^{1}H NMR (60 MHz, acetone-d_6) δ: 2.77(s, 1H, N-H, D_2O exch.), 4.50(s, 4H, $C(O)CH_2Cl$). Mass spectrum (70 eV, E.I., 172°) m/e (rel. int %) 169(0.3, $M^{+\cdot}$), 134(7.1, $M^{+\cdot}$ - Cl·), 93(6.8, $M^{+\cdot}$ - ClCH=CO), 77(70.2, Cl-CH_2CO^+), 76(11.9, $M^{+\cdot}$ - CO - $ClCH_2O$·), 49(100, $CH_2=Cl^+$), 44(11.9, $M^{+\cdot}$ - ClCH=CO $ClCH_2$·), 42(50.3), 41(12.0). High resolution molecular weight determination (60°), calcd. for $C_4H_3O_2{}^{35}ClN$ (M - Cl): m/e 134.0009; found: m/e 134.0029; calcd. for $C_4H_3O_2{}^{37}ClN$ (M - Cl): m/e 135.9980; found: m/e 136.0002. IR (KBr disc): 3260 and 3180(N-H), 1750(C=O), 1550, 1520, 1160(imide III band) cm^{-1}.

Bis(dimethyl phosphonoacetyl)amine **5**

Nitrogen was bubbled vigorously into a refluxing solution of bis(chloroacetyl)amine **4** (3.40g, 20 mmol) in 30 mL of trimethyl phosphite for 7 h. The resulting solution was cooled and a ^1H NMR spectrum of the crude mixture identified the formation of two products - the required bis(dimethyl phosphonoacetyl)amine **5** and a by-product, dimethyl methylphosphonate. A vacuum distillation (0.5 mmHg) removed *ca.* 2 g of dimethyl methylphosphonate (b.p. 37-38°), purification of the remaining light brown syrup by flash chromatography using methanol-methylene chloride (1/19) as eluant gave bis(dimethyl phosphono)acetylamine (4.1 g, 65%) as a colourless and viscous liquid. ^1H NMR (60 MHz, $CDCl_3$) δ. 3.37(d, 4H, J=22 Hz, $CH_2P(O)(OMe)_2$, 3.83(d, 6H, J=12 Hz, $P(O)(OCH_3)_2$), 10.10(bs, 1H, NH). Mass spectrum (70 eV, E.I., 150°) m/e (rel. int. %) : 317(0.2, $M^+\cdot$), 151(49.3, $(MeO)_2P(O)CH_2CO^+$), 124(100, $(MeO)_2P(=CH_2OH^+\cdot)$, 109(44.2, $(MeO)_2P(O)^+$), 94(66.5, $MeOP(O)HCH_3^+\cdot$), 93(8.0, $MeOP(O)CH_3^+$), 79(39.7, $MeP(O)OH^+$). IR (neat): 3220(NH), 1680 and 1730(b) (C=O), 1250(b) (P=O), 1020(b) (P-O-CH_3)cm^{-1}.

A substantial amount of the undesired by-product, dimethyl methylphosphonate (*ca.* 10 g) was obtained in addition to much unreacted starting material, offering little of the desired bis(dimethyl phosphonoacetyl)amine **5**, if the process of bubbling nitrogen gas into the refluxing solution had been omitted. Presumably, nitrogen introduction rapidly removed methyl chloride (itself a by-product) from the reaction mixture, minimizing the latter's reaction with the excess trimethyl phosphite; therefore, this slight modification allowed the reaction to proceed to completion.

N-2-(Dimethyl phosphonoacetyl)cinnamamide **6**

To a solution of bis(dimethyl phosphonoacetyl)amine (317 mg, 1 mmol) in 50 ml of dry tetrahydrofuran under a nitrogen atmosphere, was added a sodium hydride dispersion (20 mg, 0.5 mmol, 60% dispersion); after 15 min at room temperature the reaction mixture was cooled to 5° and a tetrahydrofuran (10 mL) solution of benzaldehyde (53 mg, 0.5 mmol) was added over a 1.75 h period. The ice-bath was removed and the mixture was magnetically stirred at room temperature overnight. Evaporation of the solvent and purification by flash chromatography using methanol-methylene chloride (1/19) as eluant gave 90 mg (61 % yield with respect to benzaldehyde) of *N*-2-dimethyl phosphonoacetylcinnamamide **6** as a white solid. Recrystallization from ethyl acetate-petroleum ether afforded white crystals, m.p. 98-100°. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 3.50(d, 2H, J = 22 Hz, $CH_2P(O)$), 3.77(d, 6H, J = 11 Hz, OCH_3), 7.07-7.60(m, 5H, C_6H_5), 7.30(ABq, 2H, J = 15 Hz, CH=CH-Ph), 9.93(bs, 1H, NH). Mass spectrum (70 eV, E.I., 70°) m/e (rel. int. %) : 151(95.8, $(MeO)_2P(O)CH_2CO^+$), 131(12.9, $Ph\text{-}CH{=}CHCO^+$), 124(67.2, $(MeO)_2P(=CH_2)OH^+\cdot$), 109(92.7, $(MeO)_2P(O)^+$), 103(29.4, $Ph\text{-}CH{=}CH^+$), 79(76.5, $MeP(O)OH^+$), 77(53.2, $C_6H_5^+$).

trans-Cinnamimide **7**

To a solution of 270 mg (0.852 mmol) of bis(dimethyl phosphonoacetyl)amine **5** in 60 mL of dry THF was added NaH (68 mg(60 % oil disp.), 1.70 mmol); hydrogen evolution was immediate, and the suspension became clear. After 30 min at room temperature, the reaction mixture was cooled to 0°, and a THF (10 mL) solution of benzaldehyde (90 mg, 0.852 mmol) was added over a 1 h period. The solution was allowed to further proceed for an extra 30 min at room temperature. Evaporation of the solvent and purification by flash chromatography using ethyl acetate as eluant gave

60 mg of cinnamimide **7** as white crystals, m.p. 198.5-199.5°(lit.[129] m.p. 198.5-199°) as the undesired by-product and only 38 mg (17% yield with respect to benzaldehyde) of *N*-2-(dimethyl phosphonoacetyl)cinnamamide **6**. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 7.17-7.90(m, 10H, $2C_6H_5$), 7.62(ABq, 4H, J = 15 Hz, C*H*=C*H*Ph), 8.88(bs, 1H, NH). Mass spectrum (70 eV, E.I., 277°) m/e (rel. int. %) : 277(11.3, $M^+\cdot$), 206(9.6, $C_{16}H_{14}^+$), 205(31.7, $C_{13}H_{13}^+$), 180(8.5, $C_{14}H_{12}^+$), 179(7.7, $C_{14}H_{11}^+$), 178(1.6, $C_{14}H_{10}^+$), 131(91.5, Ph-CH=CH-CO^+), 103(92.8, Ph-CH=CH^+), 77(100, $C_6H_5^+$), 51(54.2). High resolution molecular weight determination (170°), calcd. for $C_{18}H_{15}O_2N$: m/e 277.1102; found: m/e 277.1061.

Carbamoylmethylenetriphenylphosphorane **8**[41]

According to the method of Trippett and Walker, 9.35 g (0.1 mmol) of 2-chloroacetamide and triphenylphosphine (26.2 g, 0.1 mmol) was refluxed for 24 h in 250 mL of nitromethane. The reaction mixture was cooled in ice, and filtered to give carbamoylmethylphosphonium chloride (30.1 g, 85%). 25 g of this chloride was dissolved in 500 mL of water, cooled to 0°, and then made alkaline with 2 N NaOH solution. With minimal delay, the resulting precipitate was filtered, washed with water and dried *in vacuo* to give 21.3 g of phosphorane **8** (95% yield) (m.p. 172-175°, lit. 177-178°).

Nitrile **10**

A mixture of 100% fuming sulfuric acid (123 mg, 1.25 mmol), acetic anhydride (1.53 g, 15 mmol) and carbamoylmethylenetriphenylphosphorane **8** (4 g, 12.5 mmol) was heated for about 5 h at 100° and then for an extra 3 h at 150°. The mixture was

129. Q.E. Thompson, *J. Am. Chem. Soc.*, 73, 5841 (1951).

cooled and then ice-water was added to the black and tarry syrup. The product was extracted with ethyl acetate; the ethyl acetate extract wash washed with saturated sodium bicarbonate solution, water and brine before drying with $MgSO_4$. Evaporation of the solvent *in vacuo* yielded a white crystalline compound (m.p. 203-208°). ^1H NMR (60 MHz, $CDCl_3$) δ: 2.37(s, 3H, $C(O)CH_3$), 7.27-7.93(m, 15H, C_6H_5) Mass spectrum (70 eV, E.I., 292°) m/e (rel. int. %) : 344(26.4, $M^{+\cdot}$ + 1), 343(19.0, $M^{+\cdot}$), 330(23.4), 329(100, 344 - $CH_3^{\cdot}$). High resolution molecular weight determination (240°), calcd. for $C_{22}H_{18}ONP$: 343.1126; found: 343.1093. IR (KBr disc): 3070 and 3040(aromatic C-H stretch), 2170(C≡N stretch), 1585(C=O) cm^{-1}.

N-Acetyl-2-chloroacetamide **11**

2-Chloroacetamide (37.4 g, 0.4 mol) was added to a solution of H_2SO_4 (3.9 g, 2 mL-containing 30% SO_3) in acetic anhydride (49 g, 0.48 mol) under nitrogen. After 20 minutes of stirring at 60°, the initial clear golden-coloured solution became cloudy with precipitate. The white solid cake was heated for an extra 40 minutes at 60° to ensure completion of the reaction. Cold ice water was added to destroy the excess acetic anhydride; the product was extracted with ethyl acetate (3 x 500 mL), washed with saturated $NaHCO_3$ solution (2 x 150 mL) and brine (150 mL) before drying with $MgSO_4$. Evaporation of the solvent *in vacuo* and recrystallization from ethyl acetate gave 43.7 g of the imide (81% yield), m.p. 111-113°. Lit.[42] m.p. 106°. ^1H NMR (60 MHz, $CDCl_3$) δ: 2.40(s, 3H, CH_3), 4.33(s, 2H, CH_2Cl), 9.05(bs, 1H, NH). Mass spectrum (70 eV, E.I., 120°) m/e (rel. int. %) : 135(0.1, $M^{+\cdot}$), 93(1.5, $M^{+\cdot}$ - CH_2CO), 77(1.6, $ClCH_2CO^+$), 49(6.7, $Cl\text{-}CH_2^+$), 44(10.9, $HO\text{-}CNH^+$), 43(100, CH_3CO^+), 42(12.5, $CH_3CN\text{-}H^+$). High resolution molecular weight determination (40°), calcd for $C_4H_6O_2Cl_2{}^{35}N$ (M): m/e 135.0087; found: m/e 135.0123. IR (KBr disc): 3262

and 3180 (N-H), 1748(C=O), 1540, 1508(C-N), 1378(s), 1230 and 1164(imide III bands) cm^{-1}.

N-Acetyl-dimethyl phosphonoacetamide **12**

Imide **11** (6.78 g, 50 mmol) was added to trimethyl phosphite (24.8 g, 200 mmol) and the reaction mixture was then heated under reflux for 5.5 h. The reaction was monitored by TLC. The apparatus was then arranged for vacuum distillation to remove the excess trimethyl phosphite and dimethyl methyl phosphonate, a major by-product of the reaction. The resulting phosphonate **12** (a viscous oil) could not be purified by vacuum distillation; it was left behind and was found to be 95% pure by ^1H NMR. To obtain even purer phosphonate **12**, a Kugelrohr distillation (200-230^0, 1.8 mm Hg) afforded a colourless oil in 68% yield. ^1H NMR (60 MHz, $CDCl_3$) δ: 2.37(s, 3H, CH_3), 3.22(d, 2H, J=22 Hz, $(MeO)_2P(O)CH_2$-, 3.83(d, 6H, J=11.5 Hz, $(MeO)_2P(O)$), 9.30(bs, 1H, NH). Mass spectrum (70 eV, E.I., 180^0) m/e (rel. int. %) : 209(0.3, $M^{+}\cdot$), 194(10.4, $M^{+}\cdot$ - $CH_3\cdot$), 167(5.8, $M^{+}\cdot$ - CH_2CO), 151(62.2, $(MeO)_2P(O)H_2CO^+$, 124(59.0, $(MeO)_2P(=CH_2)OH^{+}\cdot$), 109(50.8, $(MeO)_2P(O)^+$, 94(50.8, $MeOP(O)HCH_3^{+}\cdot$), 93(8.0, $MeOP(O)CH_3^+$), 79(39.7, $MeP(O)OH^+$). IR (neat): 3180(NH), 1780-1660(C=O), 1510 cm^{-1}.

N-Acetylcinnamamide **13**

Sodium hydride (1.2 g, 50 mmol) was added to a solution of phosphonate **12** (10.45 g, 50 mmol) in dry methylene chloride (P_2O_5) at -20^0 under a nitrogen atmosphere. The mixture was kept stirring for 10 minutes resulting in precipitation. Benzaldehyde (4.42 g, 42 mmol) in 20 mL of dry methylene chloride was added dropwise to the mixture over a 15 minute period. The solution became clear and after

30 minutes at -20°, the reaction was kept for an extra 1.5 h at room temperature before quenching with water. The product was extracted with methylene chloride (2 x 200 mL), washed with water (2 x 70 mL) and dried over magnesium sulfate. Evaporation of the solvent yielded a crude crystalline residue. Three crops of pure product were obtained by precipitating the crystals with petroleum ether from a concentrated ethyl acetate solution, reevaporating the mother liquors and repeating the process. The three crops were weighed (5.51 g, 70% yield) and melted at 127-128° (lit. m.p. Thompson[129] give 131-132°, Polya *et al.*[130] 127°). The fourth crop was contaminated with benzaldehyde. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 2.47(s, 3H, CH_3), 6.87(d, 1H, J = 16 Hz, $CH{=}CHC_6H_5$), 7.17-7.67(m, 5H, C_6H_5), 7.78(d, 1H, J = 16 Hz, $CH{=}CHC_6H_5$), 9.33(bs, 1H, NH). Mass spectrum (70 eV, E.I.,240°) m/e (rel. int. %): 189(58.0, $M^{+\cdot}$), 147(20.2, $M^{+\cdot}$ - CH_2CO), 146(65.6, $M^{+\cdot}$ - 43), 131(100, Ph-CH=CHCO$^+$), 103(74.2, Ph-CH=CH^+), 102(48.3), 77(56.0, $C_6H_5^+$), 51(35.9, $C_6H_5^+$ - C_2H_2), 43(80.4, CH_3CO^+). High resolution molecular weight determination (70°), calcd. for $C_{11}H_{11}O_2N$ (M): m/e 189.0790; found: m/e 189.0835. IR (KBr disc): 3000-3280(b) (N-H), 1630(C=C) cm^{-1}.

Isolated ketone **14** *and alcohol* **15**

1.4 mL of n-butyllithium (2.2 mmol, 1.6 M in hexane) was added to a -78° solution of *N*-acetylcinnamamide **13** in 5 mL of dry THF under N_2. The clear colourless solution immediately became orange-brown. After an extra 15 min. at -78°, the reaction mixture was warmed to room temperature, 5 mL of water was added and the bulk of the tetrahydrofuran removed *in vacuo*. The products were extracted with diethyl ether (1 x 20 mL); the ether extract was washed with water (1 x 7 mL) and dried over magnesium sulfate. Evaporation of the solvent and purification by flash

130. M.R. Atkinson, E.A. Parkes and J.B. Polya, *J. Chem. Soc.*, 4256 (1954).

chromatography (ethyl acetate-petroleum ether : 1/19) gave 55 mg of alcohol **15** (R_f=0.53) and 29 mg of ketone **14** (R_f=0.42). ^{1}H NMR (60 MHz, $CDCl_3$) of alcohol **15** δ: 0.57-1.90(m, 18H, 2 C_4H_9), 6.30(ABq, 2H, J=16 Hz, CH=CH), 6.90-7.37(m, 5H, C_6H_5). ^{1}H NMR (60 MHz, $CDCl_3$) of ketone **14** δ: 1.0-2.0(m, 7H, $(CH_2)_2CH_3$), 2.62(t, 2H, J=7 Hz, $C(O)CH_2$), 7.05(ABq, 2H, J=16 Hz, CH=CH), 6.90-7.60(m, 5H, C_6H_5).

Methylation of the dianion of N-acetylcinnamamide **13**: *formation of N-propionylcinnamamide* **17**

A solution of *N*-acetylcinnamamide **13** (189 mg, 1 mmol) in THF (3 mL) was added at -78^o to 2.2 equivalent of lithium hexamethyldisilazide (generated *in situ* from hexamethyldisilazane and n-butyllithium at -78^o) in THF (5 mL). The colour of the reaction mixture immediately became reddish-brown. It was allowed to warm to 0^o and further stirred for 30 min at 0^o. Then methyl iodide (0.14 mL, 2.2 mmol) was added via a syringe and the colour of the solution became a pale orange. After stirring for 1 h at 0^o, 10 mL of ice-cold 1 N HCl solution was added to the reaction. The solution was extracted with ethyl acetate, dried with magnesium sulfate and evaporated to give 28 mg (14%) of *N*-propionylcinnamamide **17** (white crystals, m.p. 130-132^o) and 18 mg of starting material after column chromatography (ethyl acetate-petroleum ether : 1/4). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.18(t, 3H, J=7.0 Hz, CH_3), 2.70(q, 2H, J=7.0 Hz, CH_2), 6.88(d, 1H, J=15 Hz, C*H*=CHPh), 7.03-7.57(m, 5H, C_6H_5), 7.65(d, 1H, J=15 Hz, CH=C*H*Ph).

Compound **19**

To an ice-bath cooled (0^{o}) solution of *N*-acetylcinnamamide **13** (189 mg, 1 mmol) in 2 mL of dry methylene chloride, under a nitrogen atmosphere, was added trimethylsilyl trifluoromethanesulfonate (445 mg, 2 mmol). The reaction mixture was stirred for 15 min at 0^{o} followed by the addition of triethylamine (223 mg, 2.2 mmol). Immediately, the solution became bright yellow. It was left for an extra 1 h at 0^{o}, warmed to room temperature and maintained for 1.5 h before 1 N HCl (3 mL) was added. The solution was extracted with methylene chloride (20 mL); the organic extract was washed with 1 N HCl (7 mL), saturated sodium bicarbonate (7 mL) and water (7 mL) and dried with $MgSO_4$. After flash chromatography using ethyl acetate-petroleum ether (1/1) as eluant, 68 mg of **19** was obtained as a yellow powder, along with 47 mg of an unidentified by-product which had the same R_f value as the starting material. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.36(s, 3H, $COCH_3$), 2.73(dd, 1H, J=4 and 16 Hz, $CH_AH_BC(O)$), 3.05(dd, 1H, J=8 and 16 Hz, $CH_AH_BC(O)$), 4.07(dd, 1H, J=4 and 8 Hz, C_6H_5CH), 7.20-7.50(m, 10H, $2C_6H_5$), 7.30(ABq, 2H, J=16 Hz, CH=CHPh), 8.09(bs, 1H, NH), 8.69(bs, 1H, NH). Mass spectrum (70 eV, E.I.) m/e (rel. int. %) : 360(1.6, $M^{+\cdot}$), 318(5.9, $M^{+\cdot}$ - CH_2CO), 317(10.1, $M^{+\cdot}$ - HN=C=O), 302(23.9, $M^{+\cdot}$ - CO - $CH_3NH\cdot$), 301(100, $M^{+\cdot}$ - CH_3CONH_2), 275(7.6, $M^{+\cdot}$ - CH_2CO - HN=C=O), 274(30.7, $M^{+\cdot}$ - CH_2CO - $NH_2CO\cdot$), 273(22.0), 272(22.7), 245(13.5), 244(19.0). High resolution molecular weight determination (195^{o}), calcd. for $C_{22}H_{20}O_3N_2$ (M): m/e 360.1473; found: m/e 360.1528.

N-Acetyl-N-benzylcinnamamide **20**

To *N*-acetylcinnamamide **20** (189 mg, 1 mmol) in 2 mL of dry DMF, under a nitrogen atmosphere, was added NaH (60 mg(60 % oil disp.), 1.5 mmol); hydrogen evolution was immediate, and the suspension became clear. After 30 min of stirring at

room temperature, the reaction mixture was cooled to 0° and benzyl bromide (257 mg, 1.5 mmol) was added dropwise *via* a syringe. The solution immediately became pale yellow and after 30 min, it became a white suspension. The mixture was allowed to warm to room temperature and maintained for an extra 1 h. The solution was then diluted with 20 mL of water, and the mixture was extracted with diethyl ether (3 x 30 mL), washed with water (4 x 20 mL) and dried over $MgSO_4$. Purification by flash chromatography using ethyl acetate-petroleum ether (1/4: v/v) as eluant gave *N*-acetyl-*N*-benzylcinnamamide **20** as a semi-solid (148 mg, 53 %). Recrystallization from diethyl ether afforded white crystals, m.p. 91-92°. ^1H NMR (60 MHz, $CDCl_3$) δ: 2.50(s, 3H, CH_3), 5.07(s, 2H, CH_2Ph), 7.03(d, 1H, J=16 Hz, CH=CHPh), 7.03-7.67(m, 10H, $2C_6H_5$), 7.77(d, 1H, J=16 Hz, CH=CHPh). Mass spectrum (70 eV, E.I., 250°) m/e (rel. int. %) : 279(28.5, $M^+\cdot$), 148(94.1, $M^+\cdot$ - 131), 132(12.6, CH_3 - $\overset{+}{N}$-CH_2Ph), 131(100, $PhCH=CHCO^+$), 106(86.4), 103(65.0, $PhCH=\overset{+}{C}H^+$), 91(32.0, $C_6H_5CH_2^+$), 77(47.5, $C_6H_5^+$), 51(18.4, $C_6H_5^+$ - C_2H_2), 43(52.5, CH_3CO^+). High resolution molecular weight determination (120°), calcd. for $C_{18}H_{17}O_2N$: m/e 279.1259; found: m/e 279.1281. IR (KBr disc): 1667 and 1695(C=O) cm^{-1}.

N-Benzylcinnamamide **21**

Potassium t-butoxide (30 mg, 0.267 mmol) was added to *N*-acetyl-*N*-benzylcinnamamide (68 mg, .244 mmol) in 3 mL of dry t-butanol and the mixture was heated at 70° for 1.5 h during which all starting material had disappeared. The product was diluted with 15 mL of diethyl ether and 3 mL of 0.1 N HCl was added. The organic layer was separated form the aqueous layer, washed with water (2 x 5 mL) and dried over $MgSO_4$ before removal *in vacuo*. Purification by flash chromatography using ethyl acetate-petroleum ether (1/3) gave 14 mg of *N*-benzylcinnamamide **21**. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.54d, 2H, J=5.4 Hz, CH_2Ph), 5.18(bs, 1H, NH), 6.43(d,

1H, J=15.4 Hz, C*H*=CHPh), 7.19-7.56(m, 10H, $2C_6H_5$), 7.66(d, 1, J=15.4 Hz, CH=C*H*Ph). Mass spectrum (70 eV, E.I.) m/e (rel. int. %) : 237(99.1, $M^{+}\cdot$), 160(6.2, $M^{+}\cdot - C_6H_5\cdot$), 131(100, $PhCH=CHCO^{+}$), 10637.3, $C_7H_8N^{+}$), 103(52.4, $PhCH=CH^{+}$). IR ($CHCl_3$): 1647(C=O), 1627(C=C) cm^{-1}.

Silyl enol ether **22**

A dry flask charged with 1,1,1,3,3,3-hexamethyldisilazane (194 mg, 1.2 mmol) and 4 mL of dry tetrahydrofuran under a nitrogen atmosphere was cooled to -78°. n-BuLi (1.2 mmol, 1.60 M in hexane) was added dropwise, and the mixture stirred for 30 min at -78°. To this was added a solution of *N*-acetyl-*N*-benzylcinnamamide **20** (279 mg, 1 mmol) in 2 mL of dry tetrahydrofuran. The resulting bright yellow solution was stirred for a further 20 min before quenching with excess chlorotrimethylsilane (520 mg, 4.8 mmol). The solution (now a pale yellow colour) was poured into dry hexane (freshly distilled over P_2O_5) and formation of a white precipitate (LiCl) was observed. The precipitate was filtered off and evaporation of the solvent *in vacuo* afforded the silyl enol ether **22** in quantitative yield as a colourless oil. ^1H NMR (60 MHz, $CDCl_3$) δ: 0.23(s, 9H, $Si(CH_3)_3$), 4.03 and 4.20(2d, 2H, J=1.8 Hz, $C=CH_2$), 4.77(s, 2H, CH_2Ph), 7.07(d, 1H, J=16 Hz, C*H*=CHPh), 7.15-7.53(m, 5H, C_6H_5), 7.77(d, 1H, J=16 Hz, CH=C*H*Ph).

Silyl ether amide **25**

n-Butyllithium (5 mmol, 1.6 M in hexane) was added to a solution of bis(trimethylsilyl)acetamide (1.02 g, 5 mmol) in 15 mL of dry THF at -78° under nitrogen. The resulting milky solution was stirred for 20 min before proceeding with the dropwise addition of crotonaldehyde (350 mg, 5 mmol) in THF (10 mL) over a

period of 15 min. The mixture was then stirred for an extra 30 min at -78° and warmed to -40°. It was maintained at -40° for another 1 h. After warming to 0°, the reaction was quenched with 20 mL of saturated ammonium chloride solution. The THF was removed *in vacuo* and the solution was extracted with ethyl acetate (2 x 60 mL); the ethyl acetate extracts were washed once with brine and dried over magnesium sulfate. 800 mg of the product substance was recovered as an oil (80 %). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.00(s, 9H, $OSi(CH_3)_3$), 1.60(d, 3H, J=4.8 Hz, CH_3), 2.28(d, 2H, J=5.5 Hz, CH_2CONH_2), 4.42(dt, 1H, J=6.0 and 6.0 Hz, $CHOSi(CH_3)_3$), 5.20-6.00(m, 2H, $CH=CH$), 6.37(bs, 2H, $CONH_2$).

β-Iodoacetal **26**

According to the method of Gil,[57] iodotrimethylsilane (4.4 g, 22 mmol) and ethylene glycol (1.24 g, 20 mmol) were added to cinnamaldehyde (1.32 g, 10 mmol) in 40 mL of dry methylene chloride at 0° under a nitrogen atmosphere. After 5 min of stirring, 50 mL of 5% $NaHCO_3$ solution was added to the mixture. The product was extracted with diethyl ether (2 x 80 mL); the ether extracts were washed with 10% sodium thiosulfate solution (3 x 40 mL), 5% $NaHCO_3$ (1 x 40 mL) and water and dried with magnesium sulfate. After removal of the solvent, 2.76 g (91%) of this highly unstable product was recovered as an oil and was used as such with minimal delay. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 3.07-3.03(m, 2H, CH_2CHI), 3.73-4.14(m, 4H, $CH(O_2CH_2)_2$), 4.93(t, 1H, J=4 Hz, $CH(O_2CH_2)_2$), 5.33(t, 1H, J=7 Hz, $CHIPh$), 7.00-7.67(m, 5H, C_6H_5).

β-Bromoacetal **27**

According to the method of Gil,[57] bromotrimethylsilane (842 mg, 5.5 mmol) was added to cinnamaldehyde (330 mg, 2.5 mmol) in 10 mL of dry methylene chloride at 0° under N_2 and the solution was stirred for 20 min. To this was added ethylene glycol (310 mg, 5 mmol) dissolved in 5 mL of methylene chloride and the clear colourless mixture became green. The reaction was maintained for 1.5 h at 0°, then 20 mL of 5% $NaHCO_3$ solution was added to quench the reaction. The product was extracted with diethyl ether (1 x 60 mL); the ether extract was washed with 10 mL of brine and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave β-bromoacetal **27** as an oil in quantitative yield. ^1H NMR (200 MHz, $CDCl_3$) δ 2.27-2.48(m, 1H, CH_AH_BCHBr), 2.66(ddd, 1H, J=5.0 Hz, 8.8 and 13.6 Hz, CH_AH_BCHBr), 3.75-4.08(m, 4H, $H(O_2CH_2)_2$), 4.95(t, 1H, J=3.7 Hz, $CH(O_2CH_2)_2$), 5.07-5.24(m, 1H, $CHBrPh$), 7.19-7.51(m, 5H, C_6H_5). Mass spectrum (70 eV, E.I.) m/e (rel int. %) 177(0.9, $M^{+\cdot}$ - $Br^{\cdot}$), 176(0.9, $M^{+\cdot}$ - HBr), 73(100, $(CH_2O)_2CH^+$).

2-Methoxycarbonyl-3-phenyl-glutaramide **28**

To a refluxing solution of methanolic sodium methoxide (103 mg of sodium, 4.5 mmol) and dimethyl malonate (595 mg, 4.5 mmol) was added cinnamamide (441 mg, 3 mmol) in dry methanol, and the mixture refluxed further for 23 h. The mixture was poured into 10 % acetic acid solution (10 mL), and the products were extracted with ethyl acetate (1 x 30 mL); the ethyl acetate extract was washed once with brine and dried with $MgSO_4$. Removal of the solvent gave a crude residue which was subsequently purified by flash chromatography using 300 mL of ethyl acetate-petroleum ether (1/3) as eluant for the first three less polar products, followed by ethyl acetate alone for eluting out the very polar cinnamamide (starting material). The products recovered in increasing order of polarity are methyl cinnamate (40 mg),

triester **29** (55 mg), 2,3-disubstituted glutarimide **28** (175 mg, 24%) and cinnamamide (173 mg). ^{1}H NMR (60 MHz, $CDCl_3$) of glutarimide derivative **28** δ: 2.70-3.17(m, 2H, $CH_2(O)$), 3.37-3.97(m + s(OCH_3), 5H, $CHCO_2CH_3$), $CHPh$ and CO_2CH_3), 6.93-7.47(m, 5H, C_6H_5). Mass spectrum (70 eV, E.I., 125°) m/e (rel. int. %) : 247(10.0, $M^{+\cdot}$), 216(3.7, $M^{+\cdot}$ - $CH_3O\cdot$), 215(2.2, $M^{+\cdot}$ - CH_3OH), 189(34.8, $M^{+\cdot}$ - $\cdot CH_2CONH_2$), 188(100, $M^{+\cdot}$ - $CH_3O\cdot$ - CO), 187(6.1, $M^{+\cdot}$ - CH_3OH - CO), 171(12.7), 161(13.9, $M^{+\cdot}$ - $\cdot CH_2CONH_2$ - CO), 160(34.1, $M^{+\cdot}$ - $CH_3O\cdot$ - 2CO). High resolution molecular weight determination (135°), calcd. for $C_{13}H_{13}O_4N$: 247.0844; found: 247.0855.

Dimethyl 2-(methoxycarbonyl)-3-phenyl-glutarate **31**

To a solution of dimethyl malonate (1.98 g, 15 mmol) and sodium methoxide (810 mg, 15 mmol) in anhydrous methanol (5 mL) was added a solution of *trans*-methyl cinnamate (1.62 g, 10 mmol) in methanol. The mixture was refluxed for 19 h under nitrogen, cooled and acidified with 1N HCl until pH 1. Methanol was removed *in vacuo*, the product extracted with diethyl ether (2 x 30 mL), washed once with brine (10 mL), and dried ($MgSO_4$). The crude residue, after evaporation of the solvent *in vacuo*, was chromatographed on silica gel. Elution with ethyl acetate-petroleum ether (1:4, v/v) afforded triester **31** (1.61 g, 55%) as a transparent liquid. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 2.70-3.00 (m, 2H, $CH_2CO_2CH_3$), 3.50 (s, 3H, CO_2CH_3), 3.55 (s, 3H, CO_2CH_3), 3.77 (s, 3H, $CH_2CO_2CH_3$), 3.80-4.00 (m, 2H, PhC*H* and $CH(CO_2CH_3)_2$), 7.27 (s, 5H, C_6H_5). Mass spectrum (70 eV, E.I., 45°) m/e (rel. int. %) : 294(6.4, $M^{+\cdot}$), 263(4.3, $M^{+\cdot}$ - CH_3O), 234(28.8, $M^{+\cdot}$ - CH_3OH - CO), 231(7.9, M+· - CH_3OH - $CH_3O\cdot$), 203(8.3, 231 - CO), 202(42.0, $M^{+\cdot}$ - $2CH_3OH$ - CO), 189(7.0, $M^{+\cdot}$ - $\cdot CH_2CO_2CH_3$ - CH_3OH), 176(26.8), 175(100, 203 - CO), 174(33.0, $M^{+\cdot}$ - $2CH_3OH$ -

2CO). High resolution molecular weight determination (45°), calcd. for $C_{15}H_{18}O_6$: 294.1103; found: 294.1103. IR (neat): 1735(b) (C=O), 1430(phenyl) cm^{-1}.

Dimethyl 3-phenylglutarate **32**

Triester **31** (1.47 g, 5 mmol), sodium chloride (526 mg, 9 mmol) and water (252 mg, 14 mmol) in 2.5 mL of dimethyl sulfoxide was heated at 165-170° for 2 h, following Krapcho's procedure[67] for demethoxycarbonylation. The mixture was cooled, 30 mL of water was added, and the product was extracted with diethyl ether (3 x 20 mL). The organic layer was washed once with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave a crude solid which was recrystallized from diethyl ether to give dimethyl 3-phenyl glutarate **32** (703 mg, 60%), m.p. 85-87° (Lit. value[131] 85-87°). ^1H NMR (200 MHz, C_6D_6) δ: 2.33-2.70(m, 4H, 2 C*H*$_2$CO$_2$CH$_3$), 3.23(s, 6H, CO_2CH_3), 3.50-4.07(m, 1H, PhC*H*), 7.07(s, 5H, C_6H_5). Mass spectrum (70 eV, E.I., 130°) m/e (rel. int. %) : 236(7.8, $M^{+\cdot}$), 205(16.7, $M^{+\cdot}$ - $\cdot OCH_3$), 204(8.6, $M^{+\cdot}$ - CH_3OH), 177(12.2, $M^{+\cdot}$ - CO - $\cdot OCH_3$), 176(100, $M^{+\cdot}$ - CH_3OH - CO), 131(26.5, $M^{+\cdot}$ - $\cdot CH_2CO_2CH_3$ - CH_3OH), 121(48.2), 118(49.0, PhCH($\dot{C}H_2$)CH_2^+), 117(17.6, PhC(=CH_2)CH_2^+), 104(17.3, Ph$\dot{C}HCH_2^+$), 103(20.2, PhCH=CH^+), 91(17.9, $C_7H_7^+$), 78(11.6, $C_6H_6^{+\cdot}$), 77(15.8, $C_6H_5^+$), 59(36.1, CH_3O-C≡O^+). IR ($CHCl_3$): 1720(b) (C=O), 1420(phenyl) cm^{-1}.

3-Phenylglutaric acid **33**

To a stirring solution of dimethyl 3-phenylglutarate **32** (1.56 g, 6.61 mmol) in 20 mL of reagent grade methanol was added 5 mL of a 10 N NaOH solution. The solution was stirred for 30 min at room temperature and then acidified with 1N HCl

131. G.P. Schiemenz and H. Engelhard, *Chem. Ber.* **95**, 195 (1962).

solution. The methanol was removed *in vacuo* and the product was extracted with ethyl acetate (2 x 100 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give the crude diacid. Recrystallization from water afforded the diacid (735 mg, 54%). M.p. 137-139° (Lit. value[131] 139-141°). ^{1}H NMR (200 MHz, CD_3CN) δ: 2.58(dd, 2H, J=8.5, 15.9 Hz, CH_AH_BCOOH), 2.72(dd, 2H, J=6.5, 15.9 Hz, CH_AH_BCOOH), 3.40-3.58(m, 1H, PhC*H*), 7.28(s, 5H, C_6H_5). IR (KBr disc): 3000(COOH), 1700(b) (C=O) cm^{-1}.

3-Phenylglutarimide **34**

3-Phenylglutaric acid **33** (690 mg, 3.32 mmol) and finely ground urea (219 mg, 3.65 mmol) were mixed in a round bottom flask (10 mL), and the flask was immersed in an oil bath preheated to 170°. A magnetic stirring bar was added and the melted solution was stirred for 3 h. After cooling, the crude residue was recrystallized from absolute ethanol to afford 436 mg (69%) of 3-phenylglutarimide. m.p. 175-177° (lit.[132] m.p. 175-177°). ^{1}H NMR (200 MHz, CD_3CN) δ: 2.75(d, 4H, J=8.0 Hz, $CH_2C(O)$), 3.32-3.55(m, 1H, PhC*H*), 7.19-7.47(m, 5H, C_6H_5), 8.78(bs, 1H, NH). Mass spectrum (70 eV, E.I., 265°) m/e (rel. int. %) : 189(100, $M^{+\cdot}$), 161(8.9, $M^{+\cdot}$ - CO), 160(19.7), 131(57.3, $M^{+\cdot}$ - $\cdot CH_2CONH_2$), 118(19.0, $M^{+\cdot}$ - HNCO - CO), 117(15.2, $PhC(=CH)CH_2^+$), 115(10.7), 104(77.8, $PhCH_2CH_2^+$), 103(33.7, $PhCH=CH^+$), 91 (16.3, $C_7H_7^+$), 78(40.3, $C_6H_6^{+\cdot}$), 77(25.8, $C_6H_5^+$). IR (neat): 3180(N-H), 1680-1728(C=O) cm^{-1}.

132. A. Burger and A. Hofstetter, *J. Org. Chem.*, 24, 1290 (1959).

CHAPTER 2 - EXPERIMENTAL

3-O-t-Butyldiphenylsilyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **35**

A solution of diacetone glucose 3 (40 g, 169 mmol), *t*-butylchlorodiphenylsilane[73] (46.5 g, 169 mmol) and imidazole (23 g, 338 mmol) in dry dimethylformamide (40 mL) was stirred at 85° under N_2 for 17 hours. Water (500 mL) was then added and the solution extracted with ether (3 x 200 mL). The ether extracts were washed with water (2 x 150 mL) and brine, dried ($MgSO_4$) and concentrated to give silyl ether **35** as a crude solid. Recrystallization from hexane gave 68.3 g of product (89% yield, m.p. 98-100°). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08(s, 3H, CH_3), 1.09(s, 9H, $C(CH_3)_3$, 1.33, 1.39, and 1.42(3s, 9H, $3CH_3$), 4.00(dd, 1H, J=6, 8.5 Hz, 6a-H), 4.03(dd, 1H, J=3, 8.5 Hz, 4-H), 4.06(d, 1H, J=3 Hz, 2-H), 4.17(dd, 1H, J=6, 8.5 Hz, 6b-H), 4.43(d, 1H, J=3 Hz, 3H), 4.45-4.50(m, 1H, 5-H), 4.81(d, 1H, J=4 Hz, 1-H), 7.37-7.90(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 69°) m/e (rel. int. %): 483(8.4, $M^{+\cdot} - CH_3\cdot$), 383(4.7, $M^{+\cdot} - CH_3\cdot - H_2C{=}C{=}O - (CH_3)_2CO$), 325(15.5, $M^{+\cdot}$ - t-Bu· - $2(CH_3)_2CO$), 297(8.1), 283(8.1), 253(100), 199(41.7, Ph_2SiOH^+), 101(16.3, $(CH_3)_2COCH_2CHO^+$).

3-O-t-Butyldiphenylsilyl-1,2-O-isopropylidene-α-D-glucofuranose **36**

Silyl ether **35** (15 g, 30 mmol) was heated in 70% aqueous acetic acid (75 mL) for 3-4 hours at 70-75°. The solution was diluted with 100 mL of water and then extracted with methylene chloride (2 x 300 mL); the extracts were washed with

saturated sodium bicarbonate solution (3 x 100 mL), water (1 x 100 mL) and brine before drying over magnesium sulfate. Evaporation of the solvent gave the crude diol in quantitative yield which was used without purification in the next step. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.08 (s, 3H, CH_3), 1.11(s, 9H, t-Bu), 1.39(s, 3H, CH_3), 2.10-2.77(m, 2H, 2OH, D_2O exch.), 3.63-4.13(m, 4H, 4-H, 5-H, 6a-H and 6b-H), 4.23(d, 1H, J=4 Hz, 2-H), 4.50(bs, 1H, 3-H), 5.80(d, 1H, J=4 Hz, 1-H), 7.20-7.87(m, 10H, 2 C_6H_5). IR(neat): 3450(OH) cm.$^{-1}$.

3-O-t-Butyldiphenylsilyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose **37**

To diol **36** (1.03 g, 2.25 mmol) in chloroform (20 mL) at room temperature, was added dropwise lead tetraacetate (1.29 g, 2.92 mmol, 1.3 eq) in 20 mL of chloroform over a period of fifteen minutes. The solution was maintained for 1 hour and then filtered through a bed of Celite. The product was extracted with chloroform (2 x 120 mL); the extracts were washed with saturated sodium bicarbonate solution (2 x 40 mL) and then with water (2 x 40 mL). The chloroform extracts were dried over magnesium sulfate, whereafter evaporation of the solvent gave the aldehyde as a yellow oil in quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.03(s, 9H, $C(CH_3)_3$), 1.13 and 1.36(2s, 6H, $C(CH_3)_2$), 4.20(d, 1H, J=4 Hz, 2-H, 4.51(dd, 1H, J=1.2 and 3 Hz, 4-H), 4.69(d, 1H, J=3 Hz, 3-H), 6.08(d, 1H, J=4 Hz, 1-H), 7.32-7.86(m, 10H, $2C_6H_5$), 9.70(d, 1H, J=1.2 Hz, 5-H). Mass spectrum (70 eV, E.I., 200°) m/e (rel. int. %) : 369(8.1, M^+·- t-Bu·), 311(33.2, M^+·- t-Bu·- $(CH_3)_2CO$), 283(33.0, M^+·- t-Bu·- $(CH_3)_2CO$ - CO), 253(75.4), 199(100, Ph_2SiOH^+).

Methyl esters of 3,5,6-trideoxy-3-[(1,1-dimethylethyl)-diphenylsilyl]-1,2-O-(1-methylethylidene)-α-D-xylo-hept-5-enofuranuronic acid **38a** *and* **38b**

698 mg of aldehyde **37** (1.64 mmol) in 8 mL of dry methanol was treated with 548 mg (1.64 mmol) of methyl (triphenylphosphoranylidene)acetate. After 30 min at room temperature, 2 components of higher R_f were observed on TLC. The methanol was removed *in vacuo* and after purification by flash chromatography (ethyl acetate-petroleum ether: 1/9), it was possible to obtain a small amount of the two components in sufficient purity to identify them as *cis* (minor and less polar) and *trans* (major and more polar) isomers. The total yield of the purified mixture of isomers was 639 mg (81%). ^1H NMR (60 MHz, $CDCl_3$) of *cis*-ester **38b** δ: 1.07(s, 9H, $C(CH_3)_3$), 1.18 and 1.45(2s, 6H, $C(CH_3)_2$), 3.58(s, 3H, $COOCH_3$, 4.33(d, 1H, J=4 Hz, 2-H), 4.65(d, 1H, J=3 Hz, 3-H), 5.60(m, 1H, 4-H), 5.75(dd, 1H, J=1.5 and 10.5 Hz, CH=C*H*CO_2CH_3), 5.96(d, 1H, J=4 Hz, 1-H), 6.38(dd, 1H, J=7 and 10.5 Hz, C*H*=$CHCO_2CH_3$), 7.10-7.80(m, 10H, 2 C_6H_5). $[\alpha]_D^{23}$ -0.53° (c 3.15, $CHCl_3$); ^1H NMR (60 MHz, $CDCl_3$) of *trans* ester **38a** δ: 1.03(s, 9H, $(CH_3)_3$), 1.20 and 1.41(2s, 6H, $C(CH_3)_2$, 3.68(s, 3H, $COOCH_3$), 4.32(d, 1H, J=2.5 Hz, 3-H), 4.36(d, 1H, J=3.5 Hz, 2-H), 4.68(m, 1H, 4-H), 5.96(d, J=3.5 Hz, 1-H), 6.12(dd, 1H, J=1.5 and 15 Hz, CH=C*H*CO_2CH_3), 6.83(dd, 1H, J=5 and 15 Hz, C*H*=$CHCOOCH_3$), 7.27-7.82(m, 10H, 2 C_6H_5). Mass spectrum of both *trans*- and *cis*-ester (70 eV, E.I., 170°) m/e (rel. int. %) : 425(100, M^+·- t-Bu·), 407(7.1, M^+·- CH_3·- CH_3COOH), 367(23.6, M^+·- t-Bu·- $(CH_3)CO$), 349(7.3, 367 - H_2O), 335(29.0, 335 - MeOH), 325(17.8, 367 - $H_2C=C=O$), 253(44.5), 213(19.4), 199(44.8, Ph_2SiOH^+). IR (neat) of the *cis*-ester: 1725(C=O), 1655(C=C) cm^{-1}. IR (neat) of the *trans*-ester: 1722(C=O), 1660(C=C) cm^{-1}.

Alternatively, in order to synthesize the *trans*-ester exclusively, the following procedure was used. To sodium hydride (0.34 g, 14.2 mmol, pre-washed with hexane) in dry THF (30 mL), under a nitrogen atmosphere, was added trimethyl phosphonoacetate (2.73 g, 14.2 mmol); hydrogen evolution was immediate and after 30

min at room temperature, the initially clear solution became a white suspension. To this well-stirred suspension was added 4.04 g (9.48 mmol) of aldehyde **37** in 40 mL of THF *via* a drop funnel. The suspension became clear and after stirring for an extra 1.5 hours, water (30 mL) was added to the reaction. The bulk of the THF was removed *in vacuo* and the product was extracted with diethyl ether (3 x 90 mL); the ether extracts were washed with water (3 x 30 mL) and dried with $MgSO_4$. Evaporation of the solvent gave 4.35 g (93%) of α,β-unsaturated ester **38a**, exclusively in the *trans* geometry, as a pale yellow syrup.

Methyl ester of 3,5,6-trideoxy-3-[(1,1-dimethylethyl)-diphenylsily!]-5-methoxy-1,2-O-(1-methylethylidene)-α-D-xylo-heptofuranuronic acid **39**

Esters **38a** and **38b** (165 mg, 0.342 mmol) and dimethyl malonate (50 mg, 0.377 mmol) were refluxed in a methanolic sodium methoxide solution (2 mL MeOH, ~8 mg of Na) for 20 h. The solution was acidified with HCl (0.1N); the mixture was extracted with ether (2 x 50 mL), washed with water (2 x 15 mL) and dried over magnesium sulfate. 6 mg of methyl ether **39** and 53 mg of triester **40** were recovered after purification by flash chromatography (1/19 : ethyl acetate/petroleum ether). ^{1}H NMR of methyl ether **39** (200 MHz, $CDCl_3$) δ: 1.05(s, 3H, CH_3), 1.09(s, 9H, $C(CH_3)_3$), 1.38(s, 3H, CH_3), 2.66(dd, 1H, J=6.0 and 16 Hz, $CH_AH_BCO_2CH_3$), 2.92(dd, 1H, J=3.8 and 16 Hz, $CH_AH_BCO_2CH_3$), 3.31(s, 3H, OCH_3), 3.70(s, 3H, CO_2CH_3), 4.11(d, 1H, J=4 Hz, 2-H), 4.14-4.29(m, 1H, 5-H), 4.15(d, 1H, J=3 Hz, 4-H), 4.48(d, 1H, J=3 Hz, 3-H), 5.69(d, 1H, J=4 Hz; 1-H), 7.27-7.91(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 180°) m/e (rel. int. %) : 499(3.4, $M^+\cdot - \cdot CH_3$), 483(3.2, $M^+\cdot - \cdot OCH_3$), 457(100, $M^+\cdot$ - t-Bu·), 425(9.0, 457 - MeOH), 407(11.7, $M^+\cdot - \cdot CH_3 - CH_3COOH - CH_3OH$), 397(3.8, 425 - CO), 339(6.1, 367 -CO), 325(20.1, $M^+\cdot - CH_3CO_2CH_3$ - t-Bu· - $(CH_3)_2CO$). IR (neat): 1738(C=O) cm^{-1}.

Methyl ester of 3,5,6-trideoxy-3-[(1,1-dimethylethyl)-diphenylsilyl]-6-(methoxycarbonyl)-5-(2-methoxy-2-oxoethyl)-1,2-O-(1-methylethylidene)-α-D-gluco-heptofuranuronic acid **40**

A mixture of α,β-unsaturated ester **38a** (1.17 g, 2.42 mmol), dimethyl malonate (384 mg, 2.91 mmol), anhydrous potassium carbonate (2.49 g, 18 mmol) and dicyclohexano-18-crown-6 (64 mg, 0.242 mmol) in 5 mL of dry toluene was heated at the reflux temperature for 22 hours under a nitrogen atmosphere. Potassium carbonate was filtered off to give triester **40**, which was use in the next step without prior purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06(s, 3H, CH_3), 1.07(s, 9H, $C(CH_3)$), 1.35(s, 3H, CH_3), 2.56(ABX system, 2H, J=4.5, 7.5 and 16 Hz, $CH_{6a}H_{6b}CO_2Me$), 3.20-3.38(m, 1H, 5-H), 3.60(s, 3H, $H_{6a}H_{6b}CO_2CH_3$), 3.72(s, 6H, $CH(CO_2CH_3)_2$), 4.03(d, 1H, J=4.8 Hz, $CH(CO_2CH_3)_2$, 4.22(d, 1H, J=3.6 Hz, 2-H), 4.23-4.33(m, 2H, 3-H and 4-H), 5.65(d, 1H, J=3.6 Hz, 1-H), 7.32-7.77(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 212°) m/e (rel. int. %) : 583(8.9, $M^+ \cdot - \cdot OCH_3$), 557(100, $M^+ \cdot$ - t-Bu·), 525 (39.4, 557 - CH_3OH), 499(8.4, 557 - $(CH_3)_2CO$), 467(5.9, $M^+ \cdot$ - t-Bu· - $(CH_3)_2CO$ - CH_3OH), 427(6.0), 397(5.5, $M^+ \cdot$ - $\cdot CH(CH(CO_2Me)_2)CH_2CO_2Me$).

Methyl ester of 3,5,6-trideoxy-3-[(1,1-dimethylethyl)-diphenylsilyl]-5-(2-methoxy-2-oxoethyl)-1,2-O-(1-methylethylidene)-α-D-xylo-heptofuranuronic acid **41**

Krapcho's method[67] for demethoxycarbonylation was used. Sodium chloride (255 mg, 4.36 mmol) was added to a magnetically stirred mixture of triester **40** (1.49 g, 2.42 mmol) and water (122 mg, 6.78 mmol) in 30 mL of DMSO and the solution was heated to 150°. Monitoring by TLC showed the formation of the required product (less polar). After 8 hours of heating, the reaction mixture was cooled and diluted with 300 mL of water. The product was extracted with diethyl ether (3 x 100 mL); the ether

extracts were washed with water (3 x 30 mL) and dried over $MgSO_4$. After removal of the solvent and purification by flash chromatography (ethyl acetate-petroleum ether: 1/5), 1.1 g of diester **41** was recovered as a colourless syrup (83% yield in two steps from α,β-unsaturated ester **38a**). $[\alpha]_D^{23}$ -5.5° (c 4.70, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.07(s, 9H, $C(CH_3)_3$, 1.26 and 1.37(2s, 6H, $C(CH_3)_2$), 2.37(d, 2H, J=6.4 Hz, CH_2CO_2Me), 2.70(ABX system, 2H, J=3.8, 7.2 and 16 Hz, $CH_AH_BCO_2Me$), 2.71-3.00(m, 1H, 5-H), 3.63 and 3.65(2s, 6H, $2CO_2CH_3$), 4.08(dd, 1H, J=2.5 Hz and 10 Hz, 4-H), 4.23(d, 1H, J=2.5 Hz, 3-H), 4.27(d, 1H, J=3.8 Hz, 2-H), 5.72(d, 1H, J=3.8 Hz, 1-H), 7.26-7.80(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 200°) m/e (rel. int. %) : 525(8.9, $M^+ \cdot - \cdot OCH_3$), 499(100, $M^+ \cdot$ t-Bu·), 441(12.2, $M^+ \cdot$ - t-Bu· - $(CH_3)_2CO$), 381(17.2, 441 - CH_3OH - CO), 367(18.8, 441 - $CH_3CO_3CH_3$), 339(18.2, M+· - $\cdot CH(CH_2O_2Me)_2$ - $(CH_3)_2CO$), 253(13.0), 199(23.4, Ph_2SiOH^+).

5-(Carboxymethyl)-3,5,6-trideoxy-3-[(1,1-dimethylethyl)-diphenylsilyl]-1,2-O-(1-methylethylidene)-α-D-xylo-heptofuranuronic acid **42**

Diester **41** (392 mg, 0.705 mmol) dissolved in a solution of THF:MeOH:H_2O (3/2/1) was treated with lithium hydroxide monohydrate[76] (65 mg, 1.55 mmol) and the reaction was magnetically stirred at room temperature for 24 hours. The solution was then acidified (until pH 2), concentrated (to ~2 mL) and extracted with ethyl acetate (3 x 15 mL); the ethyl acetate extracts were washed with water (5 mL) and brine (5 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded **42** as a white foam in quantitative yield which was used without purification in the next step. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.05(s, 9H, $C(CH_3)_3$), 1.05 and 1.24(2s, 6H, $C(CH_3)_2$), 2.26-2.80(m, 5H, $2CH_2COOH$ and 1-H), 4.50(m, 1H, 4-H), 4.68(d, 1H, =4.0 Hz, 2-H), 4.75(d, 1H, J=3.5 Hz, 3-H), 5.91(d, 1H, J=4.0 Hz, 1-H), 7.22-7.93(m, 10H, 2 C_6H_5), 10.93(bs, 2H, 2COOH). IR (neat): 3150-3680(OH), 1710(C=O) cm^{-1}.

4-[6-[(1,1-Dimethylethyl)-diphenylsilyl]tetrahydro-2,2-dimethylfuro[2,3-d]-1,3-dioxol-5-yl]-2,6-piperidinedione **43**

Dicarboxylic acid **42** (372 mg, 0.705 mmol) and finely ground urea[71] (64 mg, 1.06 mmol) were immersed in an oil bath pre-heated to 165°. When the mixture had melted, a magnetic stirring bar was added, and the reaction stirred for 2 hours. Another 42 mg (1.00 mmol) of urea was added and heating was maintained for an extra 2 hours. After cooling the mixture to room temperature, the product was extracted with ethyl acetate (3 x 20 mL); the ethyl acetate extracts were washed once with pH 4.0 buffer (6 mL) and brine (6 mL), dried over $MgSO_4$, and evaporated to give the 3-substituted glutarimide **43** in 73% yield (261 mg), after flash chromatography (petroleum ether/ethyl acetate : 3/2). $[\alpha]_D^{23}$ -20.3° (c 2.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06(s, 9H, $C(CH_3)_3$), 1.11 and 1.37(2s, 6H, $C(CH_3)_2$), 2.18, 2.46, 2.49, 2.61-2.78 and 3.00(dd + dd + d + m(5-H) + bd, 5H, J=11.6, 16.7 Hz; J=7.0, 17.1; J=17.1 Hz; J=17.1 Hz, $CH_2C(O)NHC(O)CH_2$ and 5-H)), 3.78(dd, 1H, J=2.4 and 8.7 Hz, 4-H), 4.19(d, 1H, J=2.4 Hz, 3-H), 4.35(d, 1H, J=3.7 Hz, 2-H), 5.80(d, 1H, J=3.7 Hz, 1-H), 7.37-7.80(m, 10H, 2 C_6H_5), 7.95(bs, 1H, NH). Mass spectrum (70 eV, E.I., 292°) m/e (rel. int. %) : 452(100, M^+· - t-Bu·), 394(8.2, M^+· - t-Bu· - $(CH_3)_2CO$), 352(49.4, 394 - C_2H_2O or NCO), 322(8.9), 274(13.7), 253(43.2), 199(32.9, Ph_2SiOH^+). High resolution ms (180°) calcd. for $C_{24}H_{26}N)_6Si$ (M - t-Bu): m/e 452.1529; found: m/e 452.1489. IR (neat): 3250(b) (NH), 1710(C=O), 1262(C-N stretching and N-H bending vibrations) cm^{-1}.

3-O-t-Butyldiphenylsilyl-1,2-O-isopropylidene-5,6-O-methoxymethylidene-α-D-glucofuranose **44**

The general directions of Josán and Eastwood[83,84] were used. 3-*O*-t-Butyldiphenylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranose **36** (2.29 g, 5 mmol),

trimethylorthoformate (2.65 g, 25 mmol), and one drop of glacial acetic acid were refluxed for 4 hours under a nitrogen atmosphere. After evaporation of the excess trimethylorthoformate *in vacuo*, the mixture of diastereomeric orthoformic esters was obtained as a colourless oil in quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06 and 1.07(2s, 6H, $C(CH_3)_2$), 1.10(s, 9H, t-Bu), 1.37(s, 3H, CH_3), 3.29 and 3.30(2s, 3H, OCH_3), 4.05-4.74(m, 6H, 2-H, 3-H, 4-H, 5-H, 6a-H and 6b-H), 5.73 and 5.79(2s, 1H, C*H*OCH_3, ratio 1:3), 5.80(d, 1H, J=3 Hz, 1-H), 7.30-7.86(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 187^o) m/e (rel. int. %): 469(8.9, $M^+ \cdot - \cdot OCH_3$), 383(15.1, $M^+ \cdot$ - HCO_2Me -t-Bu·), 325(19.7, 383 - $(CH_3)_2CO$), 253(100), 199(33.8, Ph_2SiOH^+), 103(23.7, $CH_3OCHCOCH_2CHO^+$).

3-O-t-Butyldiphenylsilyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose **45**

According to the literature method of Josan and Eastwood,[83,84] the crude mixture of cyclic orthoformates **44** (2.50 g, 5 mmol) and benzoic acid (15 mg) was heated from 155^o to 175^o over a period of 20 hours, during which time methanol and carbon dioxide were evolved. The residue was dissolved in ether, solid potassium carbonate was added and after stirring for 1 hour, the suspension was filtered, and the filtrate was evaporated to dryness. The brown syrup could be used as such in the next step without further purification. Alternatively, purification of the crude olefin by flash chromatography (petroleum ether/ethyl acetate : 19/1) gave 1.56 g of product as a clear colourless oil (73% yield from the diol). $[\alpha]_D^{23}$ -26.9^o (c 4.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08(s, 9H, t-Bu), 1.16 and 1.43(2s, 6H, 2t-Bu), 4.25(d, 1H, J=3.5 Hz, 2-H), 4.26(d, 1H, J=3.5 Hz, 3-H), 4.52(dd, 1H, J=2.4, 7.2 Hz, 4-H), 5.24(d, 1H, J=10.3 Hz, 6a-H), 5.36 (d, 1H, J=17.7 Hz, 6b-H), 5.91-6.08(m, 1H, 5-H), 7.34-7.77(m, 10H, 2 C_6H_5). Mass spectrum (70eV, E.I., 195^o) m/e (rel. int. %): 367(19.7, $M^+ \cdot$ - t-

Bu·), 309(8.7, M^{+}· - t-Bu· - $(CH_3)_2CO$), 267(56.3), 253 (100), 199(24.8, Ph_2SiOH^{+}), 135 (13.7), 115(25.3). High resolution ms (55°) calcd. for $C_{21}H_{23}O_4Si$ (M^{+}· - t-Bu·): m/e 367.1365; found: m/e 367.1247. IR (neat): 3080(olefinic C-H stretch) cm^{-1}.

Dihydroxy diethyl dithioacetal **46**

A solution of vinyl acetonide **45** (6.25 g, 14.7 mmol) in ethanethiol (12 mL) was cooled to -15° in an ice-salt bath. To this was added anhydrous $ZnCl_2$ (10.0 g, 73.7 mmol). The flask was stoppered and the mixture was magnetically stirred for 15 min at -15°. The reaction was treated with 0.5 N HCl (30 mL) and then excess ethanethiol was removed by bubbling nitrogen through the flask into a series of 3 Erlenmeyer flasks filled with NaOH and potassium permanganate solution for about 1 hour. The solution was extracted with ethyl acetate (3 x 90 mL), washed with 0.5 N HCl (30 mL), and water (30 mL) before drying with $MgSO_4$. Filtration followed by evaporation of the filtrate gave the product in quantitative yield. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07(s, 9H, t-Bu), 1.13 and 1.19(2t, 6H, J=7.2 Hz, $2SCH_2CH_3$), 2.02(d, 1H, J=5.4 Hz, 4-HCO*H*), 2.43-2.72(m, 4H, $2SCH_2CH_3$), 2.86(d, 1H, J=5.2 Hz, 2-HCO*H*), 3.67(ddd, 1H, J=3.0, 5.2, 8.5 Hz, 2-H), 3.95(d, 1H, J=8.5 Hz, 1-H), 4.19(dd, 1H, J=2.9, 5.6 Hz, 3-H), 4.22-4.32(m, 1H, 4-H), 6.11-6.35(m, 2H, 6a-H and 6b-H), 5.72-5.90(m, 1H, 5-H), 7.34-7.86(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 215°) m/e (rel. int. %) : 433(0.3, M^{+}· - t-Bu·), 415(3.0, M^{+}· - t-Bu· - H_2O), 371(3.6, M^{+}· - t-Bu· - EtSH), 329(23.8), 303(17.8), 285(52.6), 267(79.8, M^{+}· - EtSH - CH_2=CHOH - t-Bu·), 253(58.8), 199(57.1, Ph_2SiOH^{+}), 135(100, $(EtS)_2CH^{+}$), IR(neat) : 3500(OH), 3080(olefinic C-H stretch) cm^{-1}.

Dithioacetal by-product **48**

During the transformation of **45** to dihydroxy diethyl dithioacetal **46**, it was found that a longer reaction time resulted in a substantial amount of undesired by-product **48**. It has the following spectral data: ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.08(t, 3H, J=7 Hz, SCH_2CH_3), 1.12(s, 9H, t-Bu), 1.17(t, 6H, J=7 Hz, 2 SCH_2CH_3), 2.08-2.87(m, 7H, OH and 3 SCH_2CH_3), 3.33(dd, 1H, J=4 and 9 Hz, 2-H), 3.67-4.03(m, 2H, 1-H and 3-H), 4.13-4.50(m, 1H, 4-H), 4.63-5.20(m, 2H, 2 6-H), 5.40-6.10(m, 1H, 5-H), 7.13-7.97(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 230°) m/e (rel. int. %) : 477(8.5, M^+ - t-Bu·), 473(3.3, M^+ - EtS·), 415(39.9, M^+ - t-Bu· - EtSH), 368(13.5), 353(22.5, M^+ - t-Bu· - 2EtSH), 329(68.6), 135(100, $(EtS)_2CH^+$).

4-O-t-Butyldiphenylsilyl-5,6-dideoxy-2,3-O-methylene-diethyl mercaptyl-α-D-xylo-hex-5-enofuranose **49**

According to the method described by Szarek and Kim,[95] a mixture of dihydroxy diethyl dithioacetal **46** (2.97 g, 6.06 mmol), *tetra-n*-butylammonium bromide (390 mg, 1.21 mmol), methylene bromide (60 g) and 50% aqueous sodium hydroxide (100 g) was vigorously stirred at 60-65°. The reaction was monitored by TLC of the organic layer. After 45 min the starting material had disappeared. The organic layer was separated from the 50% aqueous NaOH layer and then diluted with 40 mL of methylene chloride, washed with water (30 mL), brine, and dried over magnesium sulfate. Evaporation of the filtrate gave an oily residue which was purified by flash chromatography using hexane-methylene chloride (1:1) as eluant. to afford 1.65 g (54%) of product. $[\alpha]_D^{23}$ -12.8° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.08(s, 9H, t-Bu), 1.21 and 1.23(t and t, 6H, J=7.4 Hz, $2SCH_2CH_3$), 2.63 and 2.65(q and q, 4H, J=7.4 Hz, $2SCH_2CH_3$), 3.83(d, 1H, J=5.1 Hz, 1-H), 4.16(dd, 1H, J=4.9, 4.9 Hz, 3-H), 4.30(dd, 1H, J=4.9, 5.1 Hz, 2-H), 4.32(dd, 1H, J=4.9, 7.4 Hz, 4-H), 4.86(s,

1H, OCH_AH_BO), 4.90-5.13 and 5.05(m + s(OCH_AH_BO), 3H, 6a-H, 6b-H and OCH_AH_BO), 5.86(ddd, 1H, J=7.2, 10.4, 17 Hz, 5-H), 7.28-7.82(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., ~205°) m/e (rel. int. %) : 445(16.7, $M^{+\cdot}$ - t-Bu·), 353(33.9, $M^{+\cdot}$ - t-Bu· - H_2CO - EtSH), 295(14.6, $H_2CH=CH-CH=\overset{+}{O}$-Si(t-Bu)$Ph_2$), 267(14.6) 135(100, $(EtS)_2CH^+$).

By-product **50**

A mixture of 7.22 g of dithioacetal **46**, methylene bromide (147 g), 50% NaOH (235g), tetrabutylammonium bromide and 200 mL of toluene was stirred overnight at 23°. The sodium hydroxide layer was separated from the organic layer; the organic layer was diluted with 300 mL of diethyl ether and washed once with water (120 mL), and dried over magnesium sulfate. After separation by flash chromatography (ethyl acetate-petroleum ether : 3/97), 2.1 g of dithioacetal **49** and 0.93 g of dithioacetal **50** were recovered. NMR of by-product **50** (200 MHz, $CDCl_3$) δ: 1.07(s, 9H, t-Bu), 1.24(t, 6H, J=7.5 Hz, 2 CH_2CH_3), 2.51-2.80(m, 4H, 2 CH_2CH_3), 3.88(d, 1H, J=5.8 Hz, 1-H), 4.16-4.44(m, 3H, 1-H, 2-H and 3-H), 4.94(ABq, 2H, J=5.0 Hz, OCH_2O), 5.04 and 5.11(2s, 2H, OCH_2O), 5.16-5.38(m, 2H, 6a-H and 6b-H), 5.70-5.94(m, 1H, 5-H), 7.24-7.78(m, 10H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 95°) m/e (rel. int. %) : 475(4.8, $M^{+\cdot}$ - t-Bu·), 445(1.9, $M^{+\cdot}$ - t-Bu· - CH_2O), 415(4.6, 445 - CH_2O), 377(21.6), 353(3.6, 415 - EtSH).

Methyl 6R-t-butyldiphenylsilyloxy-4S,5R-dihydroxy-4,5-O-methylene-octa-2E,7-dienoate **52**

A solution of diethyl dithioacetal **49** (3.45 g, 6.87 mmol) in acetonitrile (10 mL) was added quickly to a well-stirred solution of NCS[96] (2.90 g, 21.8 mmol) and silver

nitrate (4.16 g, 24.5 mmol) in aqueous 80% acetonitrile (60 mL) at -5° (salt-ice bath). Silver chloride separated immediately as a voluminous white precipitate. The mixture was stirred for 5-10 min and treated successively at 1-min intervals with saturated aqueous sodium sulfite, saturated aqueous sodium carbonate, and brine (7 mL each); 1:1 hexane-methylene chloride (100 mL) was added and the mixture filtered through Celite. The Celite cake was washed thoroughly with 1:1 hexane-methylene chloride (100 mL) and the organic layer was washed once with brine (60 mL). After drying ($MgSO_4$) and removal of the solvent, some 4.39 g of material (aldehyde **51**) remained contaminated with silver chloride and water. The ^1H NMR spectrum, though uninformative generally, showed a weak peak at δ9.63. Without further purification of this material, the crude product was azeotroped twice with benzene (20 mL), dissolved in 40 mL of dry THF and added quickly to a stirring suspension of trimethylphosphonoacetate (1.97g, 10.8 mmol) and sodium hydride (526 mg(50% oil dispersion), 10.8 mmol) in 120 mL of dry THF at 20° under nitrogen. The solution was kept stirring for 30 min before addition of water (30 mL). The solution was then concentrated (to 30 mL) and the product was extracted with ethyl acetate (3 x 60 mL), washed with brine (2 x 20 mL) and dried ($MgSO_4$). The residual oil was purified by flash chromatography (petroleum ether (30-60°)/ethyl acetate : 9/1) to yield 1.75 g (56% yield in two steps from diethyl dithioacetal **49**) of the α,β-unsaturated ester existing exclusively in the *trans* geometry as a transparent oil. $[\alpha]_D^{23}$ +21.1° (c 14.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.08(s, 9H, t-Bu), 3.60(dd, 1H, J=6.5, 6.5 Hz, 5-H), 3.74(s, 3H, CO_2CH_3), 4.38(dd, 1H, J=5.5, 6.5 Hz, 6-H), 4.49(ddd, 1H, J=1.2, 4.7, 6.5 Hz, 4-H), 4.90(s, 2H, OCH_2O), 5.11-5.30(m, 2H, 8a-H and 8b-H), 5.74-5.94(m, 1H, 7-H), 5.99(dd, 1H, J=1.2, 16 Hz, 3-H), 6.77(dd, 1H, J=4.7, 16 Hz, 2-H), 7.25-7.72(m, 10H, 2 C_6H_5). Mass spectrum (70eV, E.I., 90°) m/e (rel. int. %): 395(7.1, $M^{+\cdot}$ - t-Bu·), 365(38.7, $M^{+\cdot}$ - t-Bu· - H_2CO), 339(4.2), 333(7.8, $M^{+\cdot}$ - t-Bu· - H_2CO - MeOH), 309(39.2), 295(48.9, $H_2C{=}CH{-}CH{=}\overset{+}{O}Si(t\text{-}Bu)Ph_2$), 199(76.7, Ph_2SiOH^+). IR (neat):

3080(olefinic C-H stretch; terminal), 1728(C=O), 1665(terminal C=C), 1618(conj. C=C) cm^{-1}.

Methyl 6R-t-butyldiphenylsilyloxy-4S,5R-dihydroxy-4,5-O-methylene-2-(methoxycarbonyl)-3-(2-methoxy-2-oxoethyl)-octa-7-enoate **53**

Sodium methoxide (418 mg, 7.73 mmol) was added to a stirring solution of α,β-unsaturated ester **52** (1.75 g, 3.86 mmol) and dimethyl malonate (1.02 g, 7.73 mmol) in 2 mL of dry THF under a nitrogen atmosphere. The solution was refluxed for 3.5 hours, cooled, and acidified with 1 N HCl until pH 2. The THF was removed and the product extracted with ethyl acetate (3 x 50 mL), washed with brine (15 mL), and dried over magnesium sulfate. Concentration of the solvent gave the diastereomeric mixture of triesters as an oil in quantitative yield and was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06(s, 9H, t-Bu), 2.37-2.74(m, 2H, CH_2CO_2Me), 3.53-3.87(m (singlets at 3.61, 3.65, 3.67 and 3.68), 11H, 2-H, 5-H and $3COCH_3$), 4.12-4.31(m, 2H, 4-H and 6-H), 4.57, 4.71, 4.81, and 4.85(4s, 2H, OCH_2O), 4.94-5.14(m, 2H, 8a-H and 8b-H), 5.69-5.96(m, 1H, 7-H), 7.24-7.76(m, 10H, 2 C_6H_5). Mass spectrum (70eV, E.I., 120°) m/e (rel. int. %): 527(41.6, $M^{+\cdot}$ - t-Bu·), 497(4.6, 527 - H_2CO), 495(8.6, 527 - MeOH), 465(3.8, $M^{+\cdot}$ - t-Bu· - MeOH - H_2CO), 441(8.7), 395(6.2, $M^{+\cdot}$ - t-Bu· - $MeO(OH)C{=}CHCO_2Me$), 367(5.8, $M^{+\cdot}$ - $\cdot CH(CH_2CO_2Me)(CH(CO_2Me)_2)$), 365(56.3, 395 - H_2CO), 363(9.5, 395 - MeOH).

Methyl 6R-t-butyldiphenylsilyloxy-4S,5R-dihydroxy-4,5-O-methylene-3-(2-methoxy-2-oxo-ethyl)-octa-7-enoate **54**

Crude triester **53** (2.25 g, 3.86 mmol), sodium chloride (406 mg, 6.95 mmol), and water (195 mg, 10.8 mmol) were dissolved in 5 mL of dimethyl sulfoxide and the

solution was heated for 4 hours at 160-170°,[67] cooled, and diluted with 60 mL of water. The product was extracted with ethyl acetate (3 x 50 mL); the ethyl acetate extracts were washed with water (2 x 15 mL), and brine (15 mL). The organic layer was further extracted with ethyl acetate (2 x 60 mL) and the organic layers combined and dried over $MgSO_4$. After purification by flash chromatography (petroleum ether (30-60°)/ethyl acetate:85/15), 1.69 g of dimethyl glutarate **54** was obtained as a clear colourless oil (83% yield in two steps from the α,β-unsaturated ester). $[\alpha]_D^{23}$ -1.95° (c 3.95, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.06(s, 9H, $C(CH_3)_3$), 2.19-2.41(m, 4H, $2CH_2CO_2CH_3$), 2.41-2.61(m, 1H, 3-H), 3.63 and 3.64(2s, 6H, CO_2CH_3), 3.69(dd, 1H, J=4.5, 4.5 Hz, 5-H), 3.98(dd, 1H, J=4.5, 4.5 Hz, 4-H), 4.22(dd, 1H, J=4.5, 4.5 Hz, 6-H), 4.62 and 4.81(2s, 2H, OCH_2O), 5.00-5.16(m, 2H, 8a-H and 8b-H), 5.70-5.92(m, 1H, 7-H), 7.27-7.49(m, 5H, C_6H_5), 7.56-7.75(m, 5H, C_6H_5). Mass spectrum (70 eV, E.I., 135°) m/e (rel. int. %) : 469(29.0, $M^{+\cdot}$ - t-Bu·), 439(7.8, 469 - H_2CO), 437(5.2, 469 - CH_3OH), 407(4.6, 437 - H_2CO), 383(25.6), 365(41.5, 439 - $H_2CC(OH)OMe$). High resolution ms (150°) calcd. for $C_{25}H_{29}O_7Si$ ($M^{+\cdot}$ - t-Bu·): m/e 469.1682; found: m/e 469.1661.

6R-t-Butyldiphenylsilyloxy-3-(carboxymethyl)-4S,5R-dihydroxy-4,5-O-methylene-octa-7-enoic acid **55**

A solution of diester **54** (526 mg, 1 mmol) in a mixture of reagent grade methanol (15 mL) and water (15 mL) was treated with lithium hydroxide monohydrate[76] (420 mg, 10 mmol) for 20 hours at 20°. The solution was acidified with 1 N HCl until pH 2 and methanol was removed *in vacuo*. The product was extracted with ethyl acetate (3 x 15 mL), washed once with brine (15 mL), and dried over magnesium sulfate. Evaporation of the solvent yielded 506 mg of dicarboxylic acid **55** as a viscous oil which could be used without prior purification in the next step.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.09(s, 9H, t-Bu), 2.06-2.74(m, 5H, 3-H and 2CH_2COOH), 3.67(dd, 1H, J=4.8, 4.8 Hz, 5-H), 3.86(dd, 1H, J=4.8, 4.8 Hz, 4-H), 4.32(dd, 1H, J=4.8, 5.5 Hz, 6-H), 4.74(s, 1H, OCH_AH$_B$O), 4.88(s, 1H, OCH$_A$$H_B$O), 5.08-5.27(m, 2H, 8a-H and 8b-H), 5.72-6.00(m, 1H, 7-H), 7.28-7.82(m, 6H, 2 C_6H_5). Mass spectrum (70 eV, E.I., 290°) m/e (rel. int. %) : 441(1.8, $M^{+\cdot}$ - t-Bu·), 393(25.0, $M^{+\cdot}$ - t-Bu· - H_2O - H_2CO), 351(22.2, $M^{+\cdot}$ - t-Bu· - $C_2H_4CO_2$ - H_2O), 295(76.4, H_2C=CH-CH=$\overset{+}{O}$Si(t-Bu)Ph$_2$), 199(100, Ph_2SiOH^+).

Glutarimide derivative **56**

The general procedure described by Crockett *et al.*[71] for the preparation of aliphatic imides was used. Dicarboxylic acid **55** (498 mg, 1 mmol) and finely ground urea (180 mg, 3 mmol) were mixed well in a 10 mL round-bottom flask. A magnetic spin bar was added and the flask was immersed in an oil bath preheated to 155-160°. The melted mixture was stirred for 2 hours, cooled and the imide purified by flash chromatography using ethyl acetate-petroleum ether (1:1) as eluant. 326 mg (68%) of crystalline glutarimide **56** was obtained, m.p. 51-56°. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.08(s, 9H, C(CH_3)$_3$), 2.04-2.22(m, 1H, CH(CH_2C(O))$_2$NH), 2.22-2.67(m, 4H, CH_2C(O)NHC(O)CH_2), 3.58(dd, 1H, J=5.5, 5.5 Hz, 5-H), 3.83(dd, 1H, J=3.7, 5.5 Hz, 4-H), 4.38(ddd, 1H, J=1.5, 4.0, 5.5 Hz, CH(OSiPh$_2$*t*-Bu), 4.69 and 4.86(2s, 2H, OCH_2O), 5.14-5.36(m, 2H, CH=CH_2), 5.68-6.00(m, 1H, CH=CH$_2$), 7.25-7.81(m, 10H, 2 C_6H_5), 7.94(bs, 1H, NH). Mass spectrum (70 eV, E.I., 266°) m/e (rel. int. %) : 422(69.2, $M^{+\cdot}$ - t-Bu· and/or $M^{+\cdot}$ - H_2CO - C_2H_3·), 410(100), 393(4.2, $M^{+\cdot}$ - ·CH_2CONH_2 - CO), 392(8.2, 422 - H_2CO), 391(4.2, M+· - ·CH_2CONH_2 - H_2CO), 337(8.2, $M^{+\cdot}$ - t-Bu· - CO - CH_2CONH), 336(36.9), 295(30.1, H_2C=CH-CH=$\overset{+}{O}$-Si(t-Bu)Ph$_2$), 199(29.7, Ph_2SiOH^+). High resolution molecular weight determination,

calcd. for $C_{24}H_{28}O_4SiN$ (M - H_2CO - C_2H_3): 422.1787; found: 422.1821. IR (neat): 3250(NH), 3080(C-H of olefin), 1735 and 1710(C=O) cm^{-1}.

Glutarimide alcohol **57**

Tetra-n-butylammonium fluoride (101 mg, 0.388 mmol) was added to glutarimide **56** in 2 mL of dry THF at room temperature under a nitrogen atmosphere. After 2 h, the solvent was removed *in vacuo*, and after purification by flash chromatography (using ethyl acetate as eluant), 57 mg of alcohol **57** was obtained. NMR (200 MHz, $CDCl_3$) δ: 2.22-2.42(m, 1H, C*H*$(CH_2CO)_2NH$)), 2.42-2.90(m, 5H, CH$(CH_2CO)_2$NH and OH), 3.79(dd, 1H, J=5.5 and 5.5 Hz, 4-H), 3.86(dd, 1H, J=5.5 and 5.5 Hz, 5-H), 4.05-4.31(m, 1H, C*H*OH), 4.98 and 5.02(2s, 2H, OCH_2O), 5.27-5.52(m, 2H, CH=CH_2), 5.84(ddd, 1H, J=5.5 ,12 and 17 Hz, C*H*=CH_2), 8.48(bs, 1H, NH). Mass spectrum (isobutane C.I.) m/e (rel. int. %): 242(50.7, MH^+), 224(18.6, MH^+ - H_2O), 194(100, MH^+ - H_2O - CH_2O).

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **58**[99]

To a solution of diacetone glucose (39 g, 150 mmol) in 250 mL of dry tetrahydrofuran (0^o, N_2) were added sodium hydride (7.3 g (50 % oil dispersion), 152 mmol), tetrabutylammonium iodide (540 mg, 1.5 mmol), and benzyl bromide (25.8 g, 151 mmol). The mixture was stirred magnetically at 23^o for 2 h. Florisil (10 g, Fisher grade, 60/100 mesh) was then added and the tetrahydrofuran was removed *in vacuo*. The solution was filtered through a sintered glass funnel and the Florisil rinsed with pentane. Removal of the solvent yielded benzyl ether **58** quantitatively, which was used without purification in the next step. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.30, 1.37, 1.42 and 1.49(4s, 12 H, $C(CH_3)_2$), 4.00 - 4.29 and 4.37 - 4.50(2m, 5H, 3-H, 4-H, 5-H,

6a-H and 6b-H), 4.58(d, 1H, J=3.4 Hz, 2-H), 4.65(s, 2H, $CH_2C_6H_5$), 5.89(d, 1H, J=3.4 Hz, 1-H), 7.33(bs, 5H, C_6H_5).

3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose **59**[100]

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **58** (35 g, 100 mmol) was selectively hydrolyzed by the addition of a solution of 96 mL of acetic acid and 64 mL of water, followed by stirring at 40° for 16 h. The acetic acid was carefully neutralized by the slow addition of 10 g of solid potassium and then with saturated potassium carbonate solution (until pH=5). The product was extracted with methylene chloride (3 x 100 mL); the combined methylene chloride extracts were washed with 10% sodium chloride and dried with anhydrous magnesium sulfate. Concentration of the methylene chloride solution under diminished pressure gave 29.6 g of syrup (95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.32 and 1.48(2s, 6H, $C(CH_3)_2$), 2.12 and 2.54(2bs, 2H, 2OH, D_2O exch.), 3.59-3.93(m, 2H, 6a-H and 6b-H), 3.95-4.25 and 4.10(m+s, 3H, 3-H and 5-H), 4.627(d, 1H, J=3.8 Hz, 2-H), 4.632(ABq, 2H, J =11.7Hz, $PhCH_2$), 5.93(d, 1H, J=3.8 Hz, 1-H), 7.34(s, 5H, C_6H_5).

Compounds **60** and **61** were prepared by methods described in references 100 and 101.

3-O-Benzyl-1,2-O-isopropylidene-5,6-O-methoxymethylidene-α-D-glucofuranose **60**

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose **59** (3.1 g, 10 mmol), trimethyl orthoformate (2.33 g, 22 mmol), and 0.2 mL of acetic acid were magnetically stirred and heated for 45 min. at the reflux temperature. Excess reagents were then removed by evaporation under diminished pressure followed by evaporating three 15 mL portions of toluene from the product. The resultant mixture of diastereomeric orthoformic esters **60** were used in the next step without further purification. ^{1}H NMR

(200 MHz, $CDCl_3$) δ: 1.30 and 1.48(2s, 6H, $C(CH_3)_2$), 3.33(s, 3H, OCH_3), 4.00-4.70(m, 8H, 2-H, 3-H, 4-H, 5-H, 6a-H, 6b-H and CH_2Ph), 5.74 and 5.76(2s, 1H, MeOC*H*), 5.89 and 5.90(2d, 1H, J=3.4 Hz, 1-H), 7.33(s, 5H, C_6H_5).

3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose **61**

Triphenylacetic acid (867 mg, 3 mmol) was added to the syrupy mixture of ortho esters **60** (21.1 g, 60 mmol) and the round bottom flask fitted with a condenser in a distillation setup. The mixture was stirred and heated for 6 h at 170°, during which methanol distilled from the mixture. The resultant product was dissolved in 200 mL of ether, solid sodium bicarbonate was added, and the mixture was kept overnight. The mixture was filtered, and the filtrate was washed twice with saturated aqueous sodium bicarbonate, dried with anhydrous magnesium sulfate, and evaporated. The product was distilled at 0.2mmHg and the pure alkene **61** was collected over the range 140-165°; yield 14.9 g (90% as a colourless oil). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.32 and 1.50(2s, 6H, $C(CH_3)_2$); 3.88(d, 1H, J=3.2 Hz, 3-H), 4.48-4.74(m + ABq(CH_2Ph centered at 4.59), 4H, J=12.4 Hz, 2-H, 4-H and CH_2Ph), 5.23-5.50(m, 2H, 6a-H and 6b-H), 5.89-6.13(m + d(1-H centered at 5.96), 2H, J=3.8 Hz, 5-H and 1-H), 7.31(s, 5H, C_6H_5).

Dihydroxy diethyl dithioacetal **62**

A solution of 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropyl-idene-α-D-*xylo*-hex-5-enofuranose **61** (16.9 g, 61 mmol) in ethanethiol (45 mL)was cooled to 0° in an ice bath. To this was added anhydrous $ZnCl_2$ (33.3 g, 244 mmol). The flask was stoppered and allowed to stand for 15 min at 0°. The reaction was treated with 1 N HCl (100 mL) and then excess ethanethiol was removed by bubbling nitrogen through

the flask into a series of 3 Erlenmeyer flasks filled with NaOH and potassium permanganate solution for about 1.5 h. The solution was extracted with ethyl acetate (2 x 250 mL), washed with 1 N HCl (2 x 200 mL), water (200 mL), saturated sodium bicarbonate (250 mL), and brine (200 mL) before drying with $MgSO_4$. Filtration followed by evaporation of the filtrate gave the product as a yellowish oil in quantitative yield. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.24 and 1.26(2t, 6H, J=7.2 Hz, $2SCH_2CH_3$), 2.52(d, 1H, J=4.6 Hz, OH), 2.55-2.76(m, 4H, $2SCH_2CH_3$), 3.13(d, 1H, J=4.9 Hz, OH), 3.76(ddd, 1H, J=2.7, 4.7, 7.6 Hz, 2-H), 3.91(dd, 1H, J=2.7, 5.3 Hz, 3-H), 4.00(d, 1H, J=7.6 Hz, 1-H), 4.34-4.48(m, 1H, 4-H), 4.81(ABq, 2H, J=11.2 Hz, CH_2Ph), 5.20 - 5.50(m, 2H, 6a-H and 6b-H), 5.87 - 6.08(m, 1H, 5-H), 6.29 - 6.46(m, 5H, C_6H_5). Mass spectrum (NH_3 CI, ~200°) m/e (rel. int.) : 281(81.4, MH^+ - EtSH), 263(14.1, MH^+ - EtSH - H_2O), 236(100, M + NH_4^+ - 2EtSH), 195(27.0), 175(94.0). High resolution ms (NH_3 CI,110°) calcd. for $C_{17}H_{30}O_3NS_2$ (M + NH_4^+) : m/e 360.1677; found : m/e 360.1669.

Methylenation[95] *of dihydroxy diethyl dithioacetal 62 to methylene acetal diethyl dithioacetal 63: preparation of 3-O-benzyl-5,6-dideoxy-2,4-O-methylene-diethyl mercaptyl-α-D-xylo-hex-5-enofuranose* **63**

A mixture of dihydroxy diethyl dithioacetal **62** (1.71 g, 5 mmol), *tetra-n*-butylammonium bromide (160 mg, 0.5 mmol), methylene bromide (50 g), and 50 % aqueous sodium hydroxide (80 g) was stirred vigorously at 60-65°. After 30 min, the organic phase was separated, diluted with methylene chloride (30 mL), washed with water (25 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate : 9/1) to yield 1.2 g (69%) of **63** as a yellowish amorphous solid. $[\alpha]_D^{23}$ -17.2° (c 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.22 and 1.23(2t, 6H, J=7.5 Hz, $2SCH_2CH_3$),

2.50-2.83(m, 4H, $2SCH_2CH_3$), 3.59(dd, 1H, J=1.4, 10.3 Hz, 2-H), 3.90(s, 1H, 3-H), 4.12(d, 1H, J=5.5 Hz, 4-H), 4.17(d, 1H, J=10.3 Hz, 1-H), 4.76(ABq, 2H, J=11.2 Hz, CH_2Ph), 4.79(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.19 - 5.45(m, 2H, 6a-H and 6b-H), 5.28(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.87 - 6.11(m, 1H, 5-H), 7.26 - 7.46(m, 5H, C_6H_5). Mass spectrum (70 eV, E.I., ~250°) m/e (rel. int. %) : 354(8.2, $M^{+\cdot}$), 325(2.7, $M^{+\cdot}$ - $H^{\cdot}$ - CO), 293(9.3, $M^{+\cdot}$ - EtS·), 267(37.9, $M^{+\cdot}$ - 2H· - CH_2=CHCH=$\overset{+}{O}$-CH=O), 207(31.5, M+· - H_2C=CHCHO - H_2CO - EtS·), 177(7.0), 135(100, $(EtS)_2CH^+$). Mass spectrum (NH_3 CI, 163°) m/e (rel. int. %) : 372(0.9, $(M + NH_4)^+$), 355(0.5, MH^+), 293(100, MH^+ - $C_6H_5CH_2OH$), 263(3.6, 293 - H_2CO), 147(31.4).

Preparation of 3S-O-Benzyl-2R,4R-dihydroxy-2,4-O-methylene-5-hexenal **64**

To diethyl dithioacetal **63** (7.08 g, 20 mmol) in acetone:water (90 mL: 10 mL) were added mercuric oxide (10.8 g, 50 mmol) and mercuric chloride (10.9 g, 40 mmol); the heterogeneous mixture was stirred at room temperature for 3 hours and then filtered through a bed of Celite. The solution was evaporated to near dryness and taken up in chloroform; the precipitated chloride was filtered a second time through Celite. The product was extracted with chloroform (2 x 100 mL), washed with 5% potassium iodide solution (3 x 30 mL) and brine,and dried ($MgSO_4$). Evaporation of the solvent and purification of the product by flash chromatography using ethyl acetate/petroleum ether (2/3) as eluant gave aldehyde **64** as a white solid (3.69 g, 74%). M.p. 75-78°. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.83(s, 1H, 3-H), 4.11(d, 1H, J=2.5 Hz, 2-H), 4.16(d, 1H, J=7.3 Hz, 4-H), 4.53(ABq, 2H, J=11.3 Hz, CH_2Ph), 4.87(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.21 and 5.34(m + d, 3H, J=6.4 Hz, 6a-H, 6b-H and OCH_AH_BO), 5.84-6.08(m, 1H, 5-H), 7.14-7.42(m, 5H, C_6H_5), 9.60(s, 1H, 1-H).

Methyl 5S-O-Benzyl-4S,6R-dihydroxy-4,6-O-methylene-octa-2E(~20% 2Z),7-dienoate **65**

A sodium hydride dispersion (854 mg(50% oil disp.), 17.8 mmol) was added to trimethyl phosphonoacetate (3.25 g, 17.8 mmol) in 125 mL of dry tetrahydrofuran under a nitrogen atmosphere. Immediately, hydrogen evolution was observed and after stirring for 30 min at room temperature, the solution became a heterogeneous mixture. To this mixture was added aldehyde **64** (3.69 g, 14.9 mmol) in 50 mL of tetrahydrofuran *via* a drop funnel, and the reaction mixture gradually became homogeneous. After further stirring for an additional 1.5 h, water (30 mL) was added to quench the reaction. The bulk of the tetrahydrofuran was removed *in vacuo*, and the product was extracted with ethyl acetate (3 x 100 mL); the ethyl acetate extracts were washed with water (2 x 30 mL) and brine (30 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (ethyl acetate/petroleum ether : 1/4) gave .88 g of the *cis*-ester, (which crystallized slowly over a period of several weeks) and 3.31 g of the *trans*-ester, m.p. 91-92^{o} (white crystals from methylene chloride/petroleum ether). The total yield of the mixed fractions was 93%. ^{1}H NMR of the *trans*-ester (200 MHz, $CDCl_3$) δ: 3.43(s, 1H, 5-H), 3.74(s, 3H, CO_2CH_3), 4.17(dd, 1H, J=1.3, 5.6 Hz, 6-H), 4.32(m, 1H, 4-H), 4.53(ABq, 2H, J=11.3 Hz, CH_2Ph), 4.84(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.19-5.50(m, 2H, 8a-H and 8b-H), 5.25(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.83-6.05(m, 1H, 7-H), 6.14(dd, 1H, J=4.4, 16.0 Hz, $CHCO_2Me$), 6.79(dd, 1H, J=4.4, 16.0 Hz, 3-H), 7.26(s, 5H, C_6H_5). Mass spectrum of the *trans*-ester (NH_3 CI, 185^{o}) m/e (rel. int. %) : 322(100, $(M + NH_4)^+$), 108(32.2, $C_6H_5CH_2OH^+$). High resolution ms (NH_3 CI, 165^{o}) calcd. for $C_{17}H_{21}O_5$ (MH^+) : m/e 305.1389; found: m/e 305.1389. ^{1}H NMR of the *cis*-ester (200 MHz, $CDCl_3$) δ: 3.69(s, 3H, CO_2CH_3), 3.75(s, 1H, 5-H), 4.25(dd, 1H, J=1.4, 6.1 Hz, 6-H), 4.50(ABq, 2H, J=11.7 Hz, CH_2Ph), 4.86(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.14-5.53(m, 3H, 2-H, 8a-H and 8b-H), 5.20(d, 1H, J=6.4 Hz, OCH_AH_BO), 5.66(dd, 1H, J=1.9,

11.7 Hz, 2-H), 5.85-6.06(m, 1H, 7-H), 6.31(dd, 1H, J=6.6, 11.7 Hz, 3-H), 7.25(s, 5H, C_6H_5). Mass spectrum of the *cis*-ester (NH_3 CI, 175°) m/e (rel. int. %) : 322(100, (M + NH_4^+)), 305(49.3, MH^+), 197(15.9, MH^+ - $C_6H_5CH_2OH$), 157(25.9, MH^+ - $C_6H_5CH_2OH$ - C_3H_4), 108(48.8, $C_6H_5CH_2OH^+$). High resolution ms (NH_3 CI, 95°) calcd for $C_{17}H_{24}O_5N$ (M + NH_4^+): m/e 322.1654; found: m/e 322.1658.

Methyl 5S-O-Benzyl-4S,6R-dihydroxy-4,6-O-methylene-2-(methoxycarbonyl)-3-(2-methoxy-2-oxoethyl)-octa-7-enoate **66**

552 mg of sodium was dissolved in 20 mL of dry methanol in a 100 mL round-bottom flask. Dimethyl malonate (3.17 g, 24 mmol) was added and the reaction mixture was refluxed for 30 min. Removal of the methanol under reduced pressure gave the sodium salt of dimethyl malonate as a white powder. The sodium salt was resuspended in 50 mL of dry tetrahydrofuran. To this cloudy white suspension was added 6.08 g (20 mmol) of *trans*-ester **65** under a nitrogen atmosphere; the solution became clear over a period of 20 hours and a TLC showed only one spot having a lower R_f value. The reaction mixture was neutralized with 1 N HCl (until pH~2) and the bulk of tetrahydrofuran removed *in vacuo*. The product was extracted with ethyl acetate (3 x 150 mL); the ethyl acetate extracts were washed once with brine (50 mL) and dried with magnesium sulfate. Evaporation of the solvent followed by flash chromatography (ethyl acetate/petroleum ether: 1/3), gave 7.15 g of triester **66** as an amorphous solid (82%). A parallel reaction involving the dimethyl malonate addition to the *cis*-ester also gave triester **66**. ^1H NMR (200 Mhz, $CDCl_3$) δ: 2.41(dd, 1H, J=5.1, 16.9 Hz, $CH_AH_BCO_2Me$), 2.54(dd, 1H, J=6.3, 16.9 Hz, $CH_AH_BCO_2Me$), 3.13(m, 1H, 3-H), 3.51(bs, 1H, 5-H), 3.60(s, 3H, $CH_AH_BCO_2CH_3$), 3.68 and 3.69(2s, 6H, $CH(CO_2CH_3)_2$), 3.92(dd, 1H, J=1.3, 8.9 Hz, 4-H), 3.98(d, 1H, J=4.5 Hz, $CH(CO_2CH_3)_2$), 4.16 (dd, 1H, J=1.3, 5.7 Hz, 6-H), 4.65(ABq, 2H, J=11.1 Hz,

CH_2Ph), 4.72 and 5.14(2d, 2H, J=6.4 Hz, OCH_2O), 5.22-5.56(m, 2H, 8a-H and 8b-H), 5.93-6.16(m, 1H, 7-H), 7.22-7.44 (m, 5H, C_6H_5). Mass spectrum (isobutane CI) m/e (relative intensity %) : 437(45.2, MH^+), 405(82.8, $MH^+ - CH_3OH$), 329(100, $MH^+ - C_6H_5CH_2OH$), 313(43.7, $MH^+ - 3CH_3OH - CO$), 299(40.1, $MH^+ - C_6H_5OH - CH_2O$), 289(45.0, $MH^+ - 2CH_3OH - 3CO_2$).

Methyl 5S-O-Benzyl-4S,6R-dihydroxy-4,6-O-methylene-3-(2-methoxy-2-oxoethyl)-octa-7-enoate **67**

Krapcho's[67] method for decarbomethoxylation was used. A mixture of triester **66** (7.15 g, 16.4 mmol), sodium chloride (1.73 g, 29.5 mmol) and water (830 mg, 45.9 mmol) in 8 mL of dimethyl sulfoxide was heated for 4 hours at 160-170°. The reaction mixture was cooled and diluted with 150 mL of water. The product was extracted with diethyl ether (3 x 100 mL); the ether extracts were washed with water (3 x 30 mL) and dried over magnesium sulfate. Evaporation of the solvent and purification by flash chromatography using ethyl acetate-petroleum ether (1/3) as eluant gave 5.04 g (81.3%) of diester **67**, m.p. 73-75° (ethyl acetate-petroleum ether). $[\alpha]_D^{23}$ +20.5° (c 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 2.22-2.83(m, 5H, 3-H and $2CH_2CO_2Me$), 3.50(s, 1H, 5-H) 3.62(s, 3H, CO_2CH_3), 3.71(dd, 1H, J=1.5, 7.8 Hz, 4-H), 4.16(dd, 1H, J=1.2, 5.7 Hz, 6-H), 4.68(ABq, 2H, J=11.3 Hz, CH_2Ph), 4.76 and 5.19(2d, 2H, J=6.0 Hz, OCH_2O), 5.24-5.55(m, 2H, 8a-H and 8b-H), 5.95-6.15(m, 1H, 7-H), 7.20-7.39(m, 5H, C_6H_5). Mass spectrum (isobutane CI, 135°) m/e (relative intensity) : 379(56.4, MH^+), 347(100, MH^+ - MeOH), 317(52.6, MH^+ - MeOH - H_2CO), 299(49.9, M + $C_2H_5^+ - C_6H_5CH_2OH$), 271(73.9, $MH^+ - C_6H_5CH_2OH$). High resolution ms (NH_3 CI) calcd. for $C_{20}H_{27}O_7$ (MH^+) : m/e 379.1756; found : m/e 379.1753. IR ($CHCl_3$): 3010(C-H aromatic), 1730(C=O) cm^{-1}.

5S-O-Benzyl-3-(carboxymethyl)-4S,6R-dihydroxy-4,6-O-methylene-octa-7-enoic acid **68**

A solution of 1.46 g of 3-substituted dimethyl glutarate **67** (3.85 mmol) in a mixture of 18.8 mL of methanol and 6.2 mL of water was magnetically stirred at room temperature, in the presence of 1.62 g of lithium hydroxide monohydrate[76] (1.62 g, 38.5 mmol) for 6 hours. The solution was then acidified with 1 N HCl until pH=2, the methanol was removed *in vacuo*, the product extracted with diethyl ether and dried over $MgSO_4$. Evaporation of the solvent afforded dicarboxylic acid **67** in quantitative yield, m.p. 123-124°. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.12-3.00 and 2.76(m + bs(1-H), 5H, 2CH_2COOH and 3-H), 3.49(s, 1H, 5-H), 3.62(d, 1H, J=7.2 Hz, 4-H), 4.17(d, 1H, J=7.0 Hz, 6-H), 4.69(ABq, 2H, J=11.3 Hz, CH_2Ph), 4.84 and 5.22(2d, 2H, J=6.0 Hz, OCH_2O), 5.23-5.58(m, 2H, 8a-H and 8b-H), 5.91-6.17(m, 1H, 7-H), 7.13-7.45(m, 5H, C_6H_5), 10.45(bs, 2H, 2COOH).

4-[5'S-O-Benzyl-6'R-vinyl-1',3'-dioxan-4'S-yl]-2,6-piperidinedione **69**

According to the general procedure described by Crockett *et al.*[71] for the preparation of aliphatic imides, dicarboxylic acid **68** (1.35 g, 3.86 mmol) and finely ground urea (463 mg, 7.71 mmol) were well-mixed and heated at 175°. When the mixture had melted, a magnetic spin bar was added and it was stirred for an extra 2 hours. After cooling, a solid black residue remained. Purification by flash chromatography (ethyl acetate-petroleum ether: 3/1) gave 1.13 g of 3-substituted glutarimide **69** (89%), m.p. 141-142° (from hot benzene). $[\alpha]_D^{23}$ +77.8° (c 2.35, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.94-2.26, 2.32-2.59 and 2.74-2.96(3m, 5H, 3-H, 4-H and 5-H), 3.33(dd, 1H, J=1.2, 7.3 Hz, 4'-H), 3.40(bs, 1H, 5'-H), 4.15(dd, 1H, J=1.3 and 6.2 Hz, 6'-H), 4.67(ABq, 2H, J=12.0 Hz, CH_2Ph), 4.77 and 5.22(2d, 2H, J=6.4 Hz, 2'-H), 5.30-5.62(m, 2H, CH=CH_2), 5.98-6.19(m, 1H, CH=CH$_2$), 7.33(s, 5H, C_6H_5), 7.77(bs, 1H, NH). Mass spectrum (NH_3 CI, 236°) m/e (rel. int. %) : 349(100,

($M + NH_4^+$)), 332(80.2, MH^+). High resolution ms (NH_3 CI, 35°) calcd for $C_{18}H_{22}O_5N$ (MH^+) : m/e 332.1498; found: m/e 332.1499.

CHAPTER 3 - EXPERIMENTAL

3-[5R-[(1S-t-Butyldiphenylsilyloxy)formylmethyl]-1,3-dioxolan-4S-yl]glutarimide **56a**

Ozone was bubbled through a solution of 1,3-dioxolane derivative **56** (105 mg, 0.219 mmol) in ethyl acetate (15 mL) at -78°. Excess ozone was flushed out with nitrogen, 1 mL of methyl sulfide was added, and the reaction was stirred for 16 h at room temperature. After removing the ethyl acetate under reduced pressure and purification by flash chromatography (ethyl acetate/petroleum ether-1:1), 79 mg (75%) of aldehyde **56a** was recovered as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.12(s, 9H, t-Bu), 2.02-2.10(m, 1H, $CH(CH_2C(O))_2NH$), 2.10-2.73(m, 4H, $CH(CH_2C(O))_2NH$), 3.82(dd, 1H, J=4.5 and 4.5 Hz, 4-H), 3.95(dd, 1H, J=4.5 and 5 Hz, 5-H), 4.10(dd, 1H, J=1.5 and 5 Hz, $CHOSiPh_2$t-Bu), 4.88 and 4.94(2s, 2H, OCH_AH_BO), 7.30-7.76(m, 10H, 2 C_6H_5), 8.25(bs, 1H, NH), 9.70(d; 1H, J=1.5 Hz, CHO). The assignments were made with the help of decoupling experiments.

(2-[(Trimethylsiloxy)methyl)-3-allyl)trimethylsilane **72**[102,103]

A 500-mL three-necked flask equipped with mechanical stirring, nitrogen inlet, and septum was charged with n-butyllithium (1.6 M in hexane, 154 mL, 246 mmol). The bulk of the hexane was removed by using an aspirator at 15-20 mmHg and with gentle warming at a temperature no higher than 45°. Anhydrous ether (135 mL) and *N,N,N',N'*-tetramethylethylenediamine (40 mL, 264 mmol) were added at 0°. 2-Methyl-2-propen-1-ol **70** (8.7 g, 121 mmol) was added dropwise over 15 min. THF was

then introduced, and the reaction turned from cloudy to clear yellowish orange. The reaction was allowed to warm up to room temperature over 5-7 h and then was stirred for an additional 13 h. The reaction was quenched with chlorotrimethylsilane (65 mL, 512 mmol) at 0°. The dark reaction mixture was allowed to stir for 10 min before being diluted with 1 L of ether. The mixture was washed with saturated sodium bicarbonate (250 mL), water (250 mL), saturated $CuSO_4$ (2 x 250 mL), water (100 mL), and brine (200 mL) and dried over anhydrous potassium carbonate. The solvent was removed *in vacuo* carefully, and the orange residue was then distilled *via* a Vigreux column to give 11.5 g (44%) of the title compound as a colourless oil (99-102° (15 mmHg)). ^1H NMR (60 MHz, $CDCl_3$) δ: .02(s, 9H, $CH_2Si(CH_3)_3$), 0.10(s, 9H, $OSi(CH_3)_3$), 1.43(bs, 2H, $CH_2Si(CH_3)_3$), 3.87(bs, 2H, $CH_2OSi(CH_3)_3$, 4.53 and 4.83(2m, 2H, $C=CH_2$). These assignments correspond closely to the data reported in the literature.

[2-(Hydroxymethyl)-3-allyl]trimethylsilane **73**[102,103]

To a solution of **72** (5.4 g, 25 mmol) in 60 mL of THF was added 12 mL of 1 N H_2SO_4. The mixture was stirred vigorously for approximately 30 min at room temperature. Anhydrous potassium carbonate was added carefully until bubbling subsided. The reaction was diluted with 200 mL of ether, washed with saturated sodium bicarbonate (40 mL) and brine (40 mL), and dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield 3.6 g (100%) of crude colourless alcohol, which was carried on to the next step without further purification. ^1H NMR (60 MHz, $CDCl_3$) δ: 0.00(s, 9H, $Si(CH_3)$), 1.53(s, 3H, $CH_2Si(CH_3)_3$), 1.79(bs, 1H, OH), 3.91(bs, 2H, CH_2OH), 4.60 and 4.80(2m, 2H, $C=CH_2$). These ^1H NMR assignments were similar to the ones reported in the literature.

[2-((t-Butyldimethylsilyloxy)methyl)-3-allyl]trimethylsilane **74**

To alcohol **73** (600 mg, 4.17 mmol) in dry DMF (6 mL) under N_2 were added t-butyldimethylsilyl chloride[106] (942 mg, 6.25 mmol) and imidazole (624 mg, 9.2 mmol); the reaction mixture was then stirred at 50-55° for 21 h. Water (100 mL) was added and the product was extracted with ether (3 x 30 mL) and dried over magnesium sulfate. Evaporation of the solvent and purification by flash chromatography gave 566 mg (53%) of silylated alcohol **74**. ^1H NMR (60 MHz, $CDCl_3$) δ: 0.010(s, 9H, $Si(CH_3)_3$), 0.14(s, 6H, $Si(CH_3)_2$), 1.00(s, 9H, $C(CH_3)_3$), 1.55(bs, 2H, $CH_2Si(CH_3)_3$), 4.02(m, 2H, CH_2OSi), 4.67 and 4.97(2m, 2H, $C=CH_2$). High resolution molecular weight determination (150°), calcd. for $C_{13}H_{30}OSi_2$ (M): m/e 258.1879; found: m/e 258.1857.

Ethyl 3-(Trimethylsilyl)propionate[105]

A dry 2-L three-necked flask equipped with a 250 mL addition funnel, nitrogen inlet, thermometer, and mechanical stirrer was charged with lithium (ca. 8.0 g, 1153 mmol, in the form of small pieces of ribbon). THF (550 mL) was added, and the reaction was rigorously stirred for 1 h under nitrogen. Chlorotrimethylsilane (140 mL, 1109 mmol) was then added dropwise at ice-bath temperature. The mixture was stirred for 45 min. A solution of ethyl acrylate (42 g, 420 mmol) in 50 mL of THF was then added over 5 h, with the temperature of the reaction maintained between 4 and 8°. The cloudy mixture was warmed to room temperature and stirred for an additional 40 h. The reaction was allowed to settle, and the supernatant liquid was cannulated into a 1-L flask. The solid residue (lithium chloride and unreacted lithium) was rinsed with ether. The combined organic solution was concentrated *in vacuo*. Dilute hydrochloric acid (3%, 300 mL) was added and the mixture stirred vigorously for 45 min. Ether (200 mL) was then added, and the aqueous layer was extracted with ether

(100 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue distilled *via* a Vigreux column to give 41 g of a light yellow liquid (bp 89-100° (15 mmHg)). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.00(s, 9H, $Si(CH_3)_3$), 0.50-0.93(m, 2H, $CH_2CH_2Si(CH_3)_3$), 1.17(t, 3H, J=7.0 Hz, OCH_2CH_3), 2.00-2.43(m, 2H, $CH_2CH_2Si(CH_3)_3$), 3.98(q, 2H, J=7.0 Hz, OCH_2CH_3).

Ethyl 2-[(Trimethylsilyl)methyl]-3-hydroxybutanoate **75**[104]

A dry 250-mL flask cooled under a stream of nitrogen was charged with 9.27 mL (66.1 mmol) of diisopropylamine (distilled from CaH_2) and 75 mL of dry THF. After the mixture was cooled to -78°, n-BuLi (39.0 mL, 63 mmol, 1.6M in hexane) was added dropwise. After the mixture was stirred for 15 min at -78°, a solution of ethyl 3-(trimethylsilyl)propionate[105] (10.35, 59.5 mmol) in 15 mL of THF was added over a period of 2 h. The resulting yellow solution was stirred for 1 h at -78°. Freshly distilled acetaldehyde (5.07 mL, 90 mmol) in 20 mL of THF was then added over a period of 15 min. After the mixture was stirred for 1.5 h at -78°, the cooling bath was removed and the solution stirred for an extra 30 min. The reaction was quenched by pouring the mixture into 150 mL of 0.5 N HCl at 0°. The aqueous phase was saturated with sodium chloride followed by separation of the layers and extraction of the aqueous phase with ether (3 x 25 mL). The combined organic layer was washed once with 50 mL of brine, followed by drying over anhydrous sodium sulfate. The solvents were removed by rotary evaporation, with the residual liquid being distilled to yield 8.2 g (37.6 mmol, 63%) of the colourless ester: bp 87-92° (15 mmHg). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.05(s, 9H, $Si(CH_3)_3$), 0.78-1.03(m, 1H, $CH_2Si(CH_3)_3$), 1.18(d, 3H, J=6.0 Hz, $CH(OH)CH_3$), 1.30(t, 3H, J=7.0 Hz, OCH_2CH_3), 2.33-2.65(m, 2H, $CHCO_2Et$ and OH), 3.84(q, 1H, J=6.0 Hz, CH(OH)), 4.13(q, 2H, J=7.0 Hz, OCH_2CH_3).

Ethyl 2-[(trimethylsilyl)methyl]-2-butenoate **77**[104]

To an ice-bath cooled (0°) solution of ethyl 2-[(trimethylsilyl)methyl]-3-hydroxybutanoate **75** (8.2 g, 37.6 mmol) in 50 mL of ether was added 3.1 mL of methanesulfonyl chloride (40 mmol). Immediately, triethylamine (distilled from CaH_2; 5.57 mL, 39.5 mmol) was added. The white suspension was stirred for 30 min at 0° followed by dilution with 60 mL of hexane. The mixture was filtered through Celite with several portions of 1:1 ether/hexane. The solvent was removed by rotary evaporation while the temperature was maintained below 35°. The resulting crude yellow oil was taken up in 70 mL of dry THF, and 13.5 mL of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, Aldrich, 90.3 mmol) was added all at once. The reaction mixture was warmed to 40° and stirred for 30 h. After the mixture was cooled to room temperature, ether (40 mL) and H_2O (40 mL) were added. The layers were separated, and the organic phase were washed with saturated $CuSO_4$ (2 x 60 mL) to remove the excess DBU. After a final wash with 60 mL of brine, drying ($MgSO_4$), and removal of the solvents, the residual liquid was distilled to give 4.86 g (24.3 mmol, 65%) of **77** as a colourless oil: bp 55-65° (0.5 mmHg). ^1H NMR (60 MHz, $CDCl_3$) δ: 0.00(s, 9H, $Si(CH_3)_3$), 1.25(t, 3H, J=7.0 Hz, OCH_2CH_3), 1.79(bs, 2H, $CH_2Si(CH_3)_3$), 4.09(q, 2H, J=7.0 Hz, OCH_2CH_3), 6.55(q, 1H, J=7.0 Hz, $C=CHCH_3$).

2-[(Trimethylsilyl)methyl]-2-buten-1-ol **78**[104]

To a -78° solution of ethyl 2-[(trimethylsilyl)methyl]-2-butenoate **77** (1.0 g, 5.0 mmol) in 12 mL of dry THF was added dropwise 7.33 mL of diisobutylaluminum hydride (Aldrich, 11.0 mmol, 1.5 M in toluene). After being stirred 2 h at -78° and 1 h at 0°, the solution was poured with stirring into 40 mL of 0° 1N H_2SO_4 solution. The mixture was stirred for 30 min, followed by saturating the aqueous phase with sodium chloride and adding 50 mL of ether. The layers were separated and the aqueous phase

was extracted with ether (2 x 20 mL). The combined ether layer was dried (Na_2SO_4) and condensed, and the crude alcohol was purified by flash chromatography using ethyl acetate-petroleum ether (1:9) as eluant, to afford 0.759 g (96%) of **78** as a yellowish oil. ^1H NMR (60 MHz, $CDCl_3$) δ: 0.00(s, 9H, $Si(CH_3)_3$), 1.51(s, 2H, $CH_2Si(CH_3)_3$), 1.52(d, 3H, J=7.0 Hz, $C=CHCH_3$), 3.82(bs, 2H, CH_2OH), 5.25(q, 1H, J=7.0 Hz, $C=CHCH_3$).

2-[(Trimethylsilyl)methyl]-1-(tert-butyldimethylsilyloxy)-2-butene **79**

To 2-[(Trimethylsilyl)methyl]-2-buten-1-ol **78** (759 mg, 4.80 mmol) in dry DMF (5 mL) under N_2 were added t-butyldimethysilyl chloride[106] (1.09 g, 7.20 mmol) and imidazole (719 mg, 10.6 mmol); the reaction mixture was then stirred at 50° for 45 min to effect complete silylation. Water (60 mL) was added and the product was extracted with ether (3 x 20 mL); the ether extracts were washed with water (2 x 7 mL), dried over $MgSO_4$ and evaporated. After purification by flash chromatography with petroleum ether as eluant, it was possible to obtain a small amount of the two components in sufficient purity to identify them as Z (major) and E (minor) isomers. The total yield of the purified mixture of isomers was 1.16 g (89%); **Z isomer**: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.01(s, 9H, $Si(CH_3)_3$), 0.05(s, 6H, $Si(CH_3)_2$), 0.90(s, 9H, $C(CH_3)_3$), 1.51(s, 2H, $CH_2Si(CH_3)_3$), 1.55(d, 3H, J=6.9 Hz, CH_3), 3.95(s, 2H, $CH_2OSi(CH_3)_2$), 5.37(q, 1H, J=6.9 Hz, C=CH); **E isomer**: ^1H NMR (200 MHz, $CDCl_3$) δ: -.002(s, 9H, $Si(CH_3)_3$), 0.05(s, 6H, $Si(CH_3)_2$), 1.57(s, 2H, $CH_2Si(CH_3)_3$), 1.59d, 3H, J=7.2 Hz, CH_3), 4.10(s, 2H, $CH_2OSi(CH_3)_2$), 5.10(q, 1H, J=7.2 Hz, C=CH). High resolution molecular weight determination (150°), calcd. for $C_{10}H_{23}OSi_2$ (M - C_4H_9): m/e 215.1288; found: m/e 215.1260.

3-[[5R-[4-((t-Butyldimethylsilyloxy)methyl)-1R-t-butyldiphenylsilyloxy-2R-hydroxy]-4-pentenyl]-1,3-dioxolan-4S-yl]glutarimide **80**

Aldehyde **56a** and allylsilane **74** were dissolved in 1 mL of dry methylene chloride and the mixture was cooled to -78°. $BF_3{\cdot}Et_2O$ dissolved in 0.5 mL of methylene chloride was added via a syringe over a 2 min period. After stirring the solution at -78° for 1 hour, the mixture was warmed to -45° and maintained at this temperature for a further 17 hours. Saturated sodium bicarbonate solution was added, and the product was extracted with 10 mL of methylene chloride (2 x 10 mL) and dried with magnesium sulfate. After purification by flash chromatography (ethyl acetate:petroleum ether / 3:7), 45 mg (52%) of **80** was recovered as white crystals (m.p. 48-52°). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.07 and 0.08(2s, 2H, $SiMe_2$), 0.90 and 1.08(2s, 18H, 2 t-Bu), 1.94-2.74(m, 7H, $CH(CH_2C(O))_2NH$ and CH_2CHOH), 3.43(d, 1H, J=4 Hz, OH), 3.61(dd, 1H, J=4 and 6.5 Hz, 4-H), 3.69-3.92 and 3.73(m($CHOH$) + dd($CHOSiPh_2$), 2H, J=4 and 6.5 Hz), 4.00(dd, 1H, J=4 and 6.5 Hz, 5-H), 4.10(s, 2H, CH_2OSiMe_2t-Bu), 4.55(s, 1H, OCH_AH_BO), 4.81(s, 1H, OCH_AH_BO), 4.93 and 5.11(2 d, J=1.5 Hz, $C=CH_2$), 7.27-7.87(m, 10H, 2 C_6H_5), 7.80(bs, 1H, NH). FAB spectrum (8 kV xenon, diethanolamine matrix, room temp.). 773(2.05, M + $DEAH^+$), 743(0.38, 773 - CH_2O).

3-[[5R-[4-((t-Butyldimethylsilyloxy)methyl)-1R-t-butyldiphenylsilyloxy-2-oxo]-4-pentenyl]-1,3-dioxolan-4S-yl]glutarimide **81**

Chromium trioxide (27 mg, 0.27 mmol), was added to a magnetically stirred solution of pyridine (43 mg, 0.54 mmol) in 0.68 mL of dry methylene chloride under a nitrogen atmosphere at room temperature. The solution was stirred for 15 min at room temperature. At the end of this period, a solution of alcohol **80** (30 mg, 0.045 mmol) in 0.60 mL of methylene chloride was added in one portion. After 20 min at

room temperature, it was diluted with 5 mL of ether, and the contents filtered through Celite. The rinsing and filtration was repeated an additional three times, each time with 5 mL of ether. Purification by flash chromatography using ethyl acetate petroleum (3/7) as eluant gave *ca.* 26 mg of ketone **81**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.02 and 0.04(2 s, 6H, 2 $SiMe_2$), 0.89 and 1.12(2 s, 18H, 2 t-Bu), 1.92-2.08(m, 1H, $CH(CH_2C(O))_2NH$), 3.28(ABq, 2H, J=19.5 Hz, $COCH_2C(=CH_2)$), 3.74(dd, 1H, J=4.5 and 5.5 Hz, 4-H), 3.89(dd, 1H, J=4.2 and 5.5 Hz, 5-H), 3.96(s, 2H; CH_2OSiMe_2t-Bu), 4.33(d, 1H, J=4.2 Hz, $CHOSiPh_2$t-Bu), 4.76(d, 1H, J=1.5 Hz, $C=CH_AH_B$), 4.80(s, 1H, OCH_AH_BO), 4.91(s, 1H, OCH_AH_BO), 5.20(d, 1H, J=1.5 Hz, $C=CH_AH_B$), 7.30-7.75(m, 10H, 2 C_6H_5), 7.80(bs, 1H, NH). FAB spectrum (8 kV xenon, diethanolamine matrix, room temp.): 771(5.10, M + $DEAH^+$), 665(0.18, M).

3-[[5R-[4-((t-Butyldimethylsilyloxy)methyl)-1R-t-butyldiphenylsilyloxy-2R-hydroxy-3-methyl]-4-pentenyl]-1,3-dioxolan-4S-yl]glutarimide **83(a,b)**

Boron trifluoride etherate (50 mg, 0.35 mmol) was added to a solution of aldehyde **56a** and allylsilane **79** in 1 mL of methylene chloride at -78° under N_2. The reaction mixture was stirred at -78° for 1 h and at -40° for 21 h, then poured into a cold (0°) saturated sodium bicarbonate solution (40 mL). The products were extracted with 30 mL of methylene chloride and dried over magnesium sulfate. Purification by flash chromatography using ethyl acetate-petroleum ether (1/3) as eluant gave two alcohols (12 mg of the less polar component and 38 mg of the more polar substance). The total yield was 42%. Spectroscopic data for the major alcohol component $[\alpha]_D^{20}$ −14.2° (c 1.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.02 and 0.04(2 s, 6H, $SiMe_2$), 0.91 and 1.08(2 s, 18H, 2 t-Bu), 1.14(d, 1H, J=6.8 Hz, CH_3), 2.10-2.68(m, 7H, $CH(CH_2C(O))_2NH$, $CHCH_3$ and OH), 3.40-3.54(m, 1H, CHOH), 3.60-4.06(m + 2 s at 3.87(2H, CH_2OSiMe_2) and 3.96(1H, OCH_AH_BO), 7H, CH_2OSiMe_2, OCH_AH_BO, 4-

H, 5-H and C*H*OSiPh$_2$), 4.56(s, 1H, OCH$_A$H$_B$O), 4.70 and 5.13(2s, 2H, C=CH$_2$), 7.34-7.82(m, 10H, 2 C$_6$H$_5$), 7.96(s, 1H, NH). Mass spectrum (NH$_3$ C.I., 335°) m/e (rel. int. %) : 682(8.6, MH$^+$), 624(100, MH+ - 58). High resolution ms (NH$_3$ C.I., 245°) calcd. for $C_{37}H_{56}O_7NSi_2$ (MH$^+$): m/e 682.3595; found: m/e 682.3596. IR(CHCl$_3$): 3565(OH) and 3373(NH), 1711(C=O)cm^{-1}. Spectroscopic data of the minor alcohol: $[\alpha]_D^{20}$ +5.4° (c 0.5, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ: 0.04(s, 6H, SiMe$_2$), 0.86(s, 9H, t-Bu), 0.97(d, 1H, J=6.7 Hz, CH$_3$), 1.04(s, 9H, t-Bu), 1.90-2.83(m, 7H, C*H*(C*H*$_2$C(O))$_2$NH, C*H*CH$_3$ and OH), 3.64-3.80(m, 4H, 4-H, 5-H, C*H*OSiPh$_2$ and C*H*OH),3.96(s, 2H, C*H*$_2$OSiMe$_2$), 4.48(s, 1H, OC*H*$_A$H$_B$O), 4.68(s, 1H, C=C*H*$_A$H$_B$), 4.75(s, 1H, OCH$_A$*H*$_B$O), 5.00(s, 1H, C=CH$_A$*H*$_B$), 7.24-7.85(m + s(NH), 11H, 2 C$_6$H$_5$ and NH). Mass spectrum (NH$_3$ C.I., 330°) m/e (rel. int. %): 682(16.5, MH$^+$), 624(100, MH$^+$ - 58). High resolution ms (NH$_3$ C.I., 215°) calcd. for $C_{33}H_{46}O_7NSi_2$ (M - t-Bu): m/e 624.2812; found: m/e 624.2812. IR(CHCl$_3$): 1707(C=O)cm^{-1}.

3-[[5R-[4-((t-Butyldimethylsilyloxy)methyl)-1R-t-butyldiphenylsilyloxy-3-methyl-2-oxo]-4-pentenyl]-1,3-dioxolan-4S-yl]glutarimide **84(a,b)**

Alcohols **83(a,b)** were oxidized to ketones **84(a,b)** in the same manner as described for the conversion of alcohol **80** to ketone **81**. Spectroscopic data for the keto product resulting from the oxidation of the major and also more polar alcohol **83**: $[\alpha]_D^{23}$ −58.2° (c 0.85, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ: 0.014(2s, 6H, SiMe$_2$), 0.86(s, 9H, t-Bu), 0.97(d, 3H, J=7.0 Hz, CH$_3$), 1.06(s, 9H, t-Bu), 2.15-2.70(m, 5H, CH(CH$_2$C(O))$_2$NH), 3.27(q, 1H, J=7.0 Hz, C*H*CH$_3$), 3.62(dd, 1H, J=3.4 Hz and 5.2 Hz, 4-H), 3.83(bs, 2H, C*H*$_2$OSiMe$_2$), 4.10(dd, 1H, J=5.2 and 5.6 Hz, 5-H), 4.26(d, 1H, J=5.6 Hz, C*H*OSiPh$_2$), 4.50(s, 1H, OC*H*$_A$H$_B$O), 4.75(s, 1H, C=C*H*$_A$H$_B$), 4.81(s, 1H, OCH$_A$*H*$_B$O), 5.17(s, 1H, C=CH$_A$*H*$_B$), 7.30-7.50 and 7.55-7.75(2m, 10H, 2 C$_6$H$_5$),

7.85(bs, 1H, NH). IR($CHCl_3$): 3373(NH) and 1711(C=O)cm^{-1}. Spectral data of the ketone resulting from the oxidation of the minor (less polar) alcohol component: $[\alpha]_D^{23}$ +20.8° (c 0.23, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 0.01 and 0.03(2s, 6H, $SiMe_2$), 0.88(s, 9H, t-Bu), 1.08(d, 1H, J=6.5 Hz, CH_3), 1.09(s, 9H, t-Bu), 1.92-2.80(m, 5H, $CH(CH_2C(O))_2NH$), 3.61(q, 1H, J=6.5 Hz, $CHCH_3$), 3.81-4.00(m, 4H, 4-H, 5-H and CH_2OSiMe_2), 4.48(d, 1H, J=4.8 Hz, $CHOSiPh_2$), 4.59(s, 1H, OCH_AH_BO), 4.61(s, 1H, $C=CH_AH_B$), 4.82(s, 1H, OCH_AH_BO), 5.04(s, 1H, $C=CH_AH_B$), 7.26-7.85(m, 10H, 2 C_6H_5).

Aldehyde **85** *and ozonide* **86**

Ozone and nitrogen were bubbled for approximately 45 min through a solution of glutarimide **69** (497 mg, 1.5 mmol) in ethyl acetate 30 mL) at -78°. Excess ozone was flushed out with nitrogen, 4 mL of methyl sulfide was added at -78° and the mixture allowed to stir for 24 h at ambient temperature under a nitrogen atmosphere. Removal of the ethyl acetate gave crude aldehyde **85** as a foam, contaminated with ozonide **86**. The R_f value of **86** was identical to olefin **69**. Purification by flash chromatography using methanol-methylene chloride (1/19) as eluant resulted in the formation of either hemiacetal **X** or dimethyl acetal **Y**. Aldehyde **85** was eventually separated from ozonide **86** by flash chromatography using ethyl acetate as eluant. Aldehyde **85** was isolated in approximately 70 to 75% yield. ^1H NMR (200 MHz, $CDCl_3$) of aldehyde **85**; δ: 2.00-3.00(m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.33(d, 1H, J =7.3 Hz, 7-H), 3.92(s, 1H, 8-H), 4.10(s, 1H, 9-H), 4.52(ABq, 2H, J=12.4 Hz, CH_2Ph), 4.79 and 5.31(2d, 2H, J=6.4 Hz, 14a-H and 14b-H), 7.17-7.54(m, 5H, C_6H_5), 8.32(bs, 1H, NH), 9.76(s, 1H, 10-H). ^1H NMR (200 MHz, $CDCl_3$) of ozonide **86**; δ: 1.90-3.00(m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.25(d, 1H, J=6.4 Hz, 7-H), 3.56(dd, 1H, J=1.6 and 7.5 Hz, 9-H), 3.64(s, 1H, 8-H), 4.72(d, 1H, J=6.4 Hz, 14a-H),

4.78(ABq, 2H, J=11.7 Hz, CH_2Ph), 5.02(s, 1H, OCH_AH_BO), 5.20(d, 1H, J=6.4 Hz, 14b-H), 5.39(s, 1H, OCH_AH_BO), 5.60(d, 1H, J=7.5 Hz, 10-H), 7.38(s, 5H, C_6H_5), 7.77(bs, 1H, NH). Mass spectrum of ozonide **86** (isobutane C.I.) m/e (rel. int. %): 334(0.8, $MH^+ - OCH_2O\cdot$), 226(56.9, $MH^+ - OCH_2O\cdot - C_6H_5CH_2OH$), 196(100, 226 - CH_2O).

Alcohols **87(a,b)**

Boron trifluoride etherate (216 mg, 1.52 mmol) was added to a mixture of aldehyde **85** (422 mg, 1.27 mmol) and allylsilane **79** (414 mg, 1.52 mmol) in 5 mL of dry methylene chloride at -78° under nitrogen. The reaction mixture was stirred at -78° for 1.5 h. Cold saturated sodium bicarbonate solution (5 mL) was added to the mixture and the solution was extracted with methylene chloride (2 x 15 mL); the methylene chloride extracts were dried over magnesium sulfate and evaporated. After purification by flash chromatography using ethyl acetate-petroleum ether (2/3), 174 mg of the less polar alcohol and 108 mg of the more polar alcohol were obtained (42% yield). Spectroscopic data of the less polar alcohol: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.13 and 0.16(2s, 6H, $SiMe_2$), 0.93(s, 9H, t-Bu), 1.24(d, 3H, J=7.2 Hz, 15-H), 2.72-2.91(m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.02(m, 1H, 11-H), 3.09(d, 1H, J=7.0 Hz, 7-H), 3.31(d, 1H, J=9.4 Hz, 9-H), 3.68(m + bs(8-H), 2H, 8-H and 10-H), 4.08(ABq, 2H, J=11 Hz, 13a-H and 13b-H), 4.50(d, 1H, J=10.2 Hz, OH, D_2O exch.), 4.56(d, 1H, J=6.0 Hz, 14a-H), 4.82(ABq, 2H, J=11.7 Hz, CH_2Ph), 5.01(d, 1H, J=2.0 Hz, 16a-H), 5.09(d, 1H, J=2.0 Hz, 16b-H), 5.13(d, 1H, J=6.0 Hz, 14b-H), 7.26-7.48(m, 5-H, C_6H_5), 7.85(bs, 1H, N-H). FAB spectrum (8 kV xenon, glycerol matrix, room temp.): 718(0.09, MH^+ + 2 gly), 626(0.22, M + $glyH^+$), 553(0.29, M + $glyH^+$ - HNCO - CH_2O), 534(1.52, MH^+), 461(0.50, MH^+ - HNCO - CH_2O), 402(0.52, MH^+ - $HOSiMe_2$t-Bu), 369(1.47). Mass spectrum (isobutane C.I.) m/e (rel. int. %): 534(7.0,

MH^+), 474(7.3), 402(100, MH^+ - $HOSiMe_2t$-Bu). Spectral data of the more polar alcohol: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.00(s, 6H, $SiMe_2$), 0.94(s, 9H, t-Bu), 1.04(d, 3H, J=6.8 Hz, 15-H), 1.80-2.95(m, 6H, 3a-H, 3b-H, 4-H, 5a-H, 5b-H and 11-H), 3.26(d, 1H, J=6.9 Hz, 7-H), 3.45(d, 1H, J=9.6 Hz, 9-H), 3.67(m + s, 2H, 8-H and 10-H), 3.93(d, 1H, J=9.9 Hz, 10-H), 4.15(ABq, 2H, J=12.6 Hz, 13-H), 4.19(d, 1H, J=5.1 Hz, OH), 4.69(d, 1H, J=6.4 Hz, 14a-H), 4.81(ABq, 2H, J=11.9 Hz, CH_2Ph), 5.07(s, 1H, 16a-H), 5.14(s, 1H, 16b-H), 5.17(d, 1H, J=6.4 Hz, 14b-H), 7.26-7.47(m, 5H, C_6H_5), 7.66(bs, 1H, NH). Mass spectrum (isobutane C.I.) m/e (rel. int. %): 534(100, MH^+), 426(6.8, MH^+ - $C_6H_5CH_2OH$), 402(100, MH^+ - $HOSiMe_2t$-Bu).

8-O-Benzyl-13-O-t-butyldimethylsilyl sesbanimides **88**

Chromium trioxide (146 mg, 1.2 mmol) was added to a magnetically stirred solution of pyridine (190 mg, 2.4 mmol) in 3 mL of dry CH_2Cl_2 (from P_2O_5) under N_2. The resulting deep burgundy solution was stirred for 15 min at room temperature. At the end of this period, a solution of the less polar alcohol **87** (104 mg, 0.20 mmol) in 1.5 mL of CH_2Cl_2 was added in one portion. A tarry, black deposit separated immediately. After stirring an additional 15 min at room temperature, the solution was diluted with ether and filtered through Celite. Purification by flash chromatography using petroleum ether-ethyl acetate (3:1) as eluant, gave 4 mg (4%) of ketone as an oil. Much starting material was recovered along with other unidentified products. Oxidation of the more polar alcohol was carried out in the same manner except that the yield of the corresponding ketone obtained was higher (21%). ^1H NMR (200 MHz, $CDCl_3$) of the ketone obtained from the less polar alcohol **87** δ: 0.06(s, 6H, $SiMe_2$), 0.89(s, 9H, t-Bu), 1.26(d, 3H, J=6.9 Hz, 15-H), 1.95-3.00(m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.30(dd, 1H, J=1.6 and 8.2 Hz, 7-H), 3.66(q, 1H, J=7.3 Hz, 11-H), 3.78(s, 1H, 8-H), 4.13(s, 2H, 13-H), 4.56(ABq, 2H, J=11.7 Hz, CH_2Ph), 4.64(s, 1H, 9-

H), 4.93(d, 1H, J=6.4 Hz, 14a-H), 4.96(s, 1H, 16a-H), 5.02(d, 1H, J=6.4 Hz, 14b-H), 5.24(s, 1H, 16b-H), 7.35(s, 5H, C_6H_5), 7.75(bs, 1H, NH). Mass spectrum of the ketone derived from the less polar alcohol (isobutane C.I.) m/e (rel. int. %): 532(50.0, MH^+), 424(31.0, MH^+ - $C_6H_5CH_2OH$), 400(65.5, MH^+ - $HOSiMe_2t$-Bu), 394(18.5, 424 - CH_2O), 382(56.3), 292(37.5, 400 - $C_6H_5CH_2OH$), 262(100, 292 - CH_2O). Oxidation of the more polar alcohol **87** gave the ketone with the following spectral data: NMR (200 MHz, $CDCl_3$) δ: 0.14(s, 6H, $SiMe_2$), 0.96(s, 9H, t-Bu), 1.26(d, 3H, J=6.9 Hz, 15-H), 3.44(d, 1H, J=7.5 Hz, 7-H), 3.67(q, 1H, J=6.9 Hz, 11-H), 3.81(s, 1H, 8-H), 4.20(s, 2H, 13-H), 4.58(ABq, 2H, J=11.7 Hz, CH_2Ph), 4.66(d, 1H, J=6.4 Hz, 14a-H), 4.77(s, 1H, 9-H), 4.92(s, 1H, 16a-H), 5.08(d, 1H, J=6.4 Hz, 14b-H), 5.24(s, 1H, 16b-H), 7.20-7.46(m, 5H, C_6H_5), 7.90(bs, 1H, NH). Mass spectrum (isobutane C.I.) m/e (rel. int. %): 532(60.2, MH^+), 424(17.6, MH^+ - $C_6H_5CH_2OH$), 400(100, MH^+ - $HOSiMe_2t$-Bu), 382(70.0), 370(16.4, 400 - CH_2O), 292(47.5, 400 - $C_6H_5CH_2OH$), 262(30.7, 292 - CH_2O).

13-Deoxychloro sesbanimide **89**

To ketone **88** (57 mg, 0.110 mmol)(which was obtained after oxidation of the more polar alcohol **87**) in 1.0 mL of dry methylene chloride at -78° under N_2 was added 0.14 mL of 1 N BCl_3 (in CH_2Cl_2) *via* a syringe. After 40 min at -78°, the reaction mixture was poured into 2 mL of a cold (0°) and well-stirred saturated sodium bicarbonate solution. The product was extracted with methylene chloride and dried over magnesium sulfate. Evaporation under reduced pressure and purification by flash chromatography using methanol-methylene chloride (1:25) as eluant, gave ~2 mg of **89** (20%) as a white foam. NMR (200 MHz, $CDCl_3$) δ: 1.28(d, 3H, J=7.0 Hz, 15-H), 2.23-2.97(m + d(OH) at 2.62, 6H, J=12 Hz, 3a-H, 3b-H, 4-H, 5a-H, 5b-H and OH), 3.49(dd, 1H, J=1.3 and 8.4 Hz, 7-H), 3.81(q, 1H, J=7.0 Hz, 11-H), 4.00(d, 1H, J=12

Hz, 8-H), 4.13(ABq, 2H, J=1.6 Hz, 13-H), 4.63(d, 1H, J=1.7 Hz, 9-H), 4.72(d, 1H, J=6.7 Hz, 14a-H), 5.04(d, 1H, J=6.7 Hz, 14b-H), 5.12(s, 1H, 16a-H), 5.37(s, 1H, 16b-H), 7.79(bs, 1H, NH). Mass spectrum (isobutane C.I.) m/e (rel. int. %): 346(100, MH^+), 328(12.4, $MH^+ - H_2O$), 316(11.9, $MH^+ - CH_2O$), 310(72.4, MH^+ - HCl), 300(12.9, 328 - CO), 298(40.3, 316 - H_2O), 280(37.8, 310 - CH_2O), 264(13.2, 310 - CO - H_2O), 262(15.7, 280 - H_2O).

Alcohol **90**

Boron trifluoride etherate (369 mg, 2.6 mmol) was syringed into a well-stirred solution of aldehyde **85** (666 mg, 2 mmol) and 2-[(trimethylsilyl)methyl]-3-tert-butyldimethylsiloxy-1-propene **74** (774 mg, 3.0 mmol) in 12 mL of methylene chloride at -78° under a nitrogen atmosphere. Immediately, a white suspension was formed in the reaction mixture which became a homogeneous solution after 10 min of further stirring. After the mixture was stirred 2 h at -78°, it was poured into a cold (0°) rapidly stirring saturated sodium bicarbonate solution. After warming to room temperature, the product was extracted with CH_2Cl_2 (2 x 90 mL), washed once with water (40 mL), and dried over $MgSO_4$. 467 mg (45%) of alcohol **90** was recovered as a white solid after flash chromatography (ethyl acetate-petroleum ether/1:1). m.p. 148-151°; $[\alpha]_D^{23}$ +63.0° (c 0.40, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 0.13(s, 6H, $Si(CH_3)_2$), 0.93(s, 9H, t-Bu), 1.82-1.98 and 2.13-2.50(2m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.17(d, 1H, J=6.5 Hz, 7-H), 3.30(d, 1H, J=9.5 Hz, 9-H), 3.73(s, 1H, 8-H), 3.80-4.00(m, 1H, 10-H), 4.12(s, 2H, 13-H), 4.29(d, 1H, J=4.0 Hz, OH, D_20 exch.), 4.65(d, 1H, J=6.0 Hz, 14a-H), 4.81(ABq, 2H, J=11.8 Hz, CH_2Ph), 5.03(s, 1H, 16a-H), 5.15(s, 1H, 16b-H), 5.16(d, 1H, J=6.0 Hz, 14b-H), 7.26-7.48(m, 5H, C_6H_5), 7.77(s, 1H, NH). FAB spectrum (8 kV xenon, glycerol matrix, 22°) m/e (rel. int. %): 612(0.069,MH^+ + gly),

520(0.520, MH^+), 462(0.113, MH^+ - CO - H_2CO), 459(0.084, MH^+ - HNCO - H_2O), 431(0.063, MH^+ - HNCO - CO - H_2O).

8-O-Benzyl-13-O-t-butyldimethylsilyl-15-desmethyl sesbanimide **91**

Chromium trioxide (240 mg, 2.40 mmol) was added to a magnetically stirred solution of pyridine (380 mg, 4.81 mmol) in 7 mL of dry CH_2Cl_2 (from P_2O_5) under N_2. The resulting deep burgundy solution was stirred for 15 min at room temperature. At the end of this period, a solution of alcohol **90** (104 mg, 0.20 mmol) in 3 mL of CH_2Cl_2 was added in one portion. A tarry, black deposit separated immediately. After stirring an additional 15 min at room temperature, the solution was decanted from the residue. The residue was further rinsed with small portions of methylene chloride (total 20 mL). The combined extracts were washed with 1 N HCl (2 x 10 mL), saturated $NaHCO_3$ (10 mL), 5% sodium bisulfite (2 x 10 mL), and water (10 mL) before drying with magnesium sulfate. Purification by flash chromatography using petroleum ether-ethyl acetate (2:3) as eluant, gave 57 mg (55%) of ketone **91** as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.02(s, 6H, $SiMe_2$), 0.87(s, 9H, t-Bu), 2.00-2.93(m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.29(d, 1H, J=6.8 Hz, 7-H), 3.47(ABq, 2H, J=16.9 Hz, 11a-H and 11b-H), 3.93(s, 1H, 8-H), 4.08(d, 1H, J=1.3 Hz, 9-H), 4.13(s, 2H, 13-H), 4.50(ABq, 2H, J=11.9 Hz, CH_2Ph), 4.73(d, 1H, J=6.5 Hz, 14a-H), 4.89 and 5.24(2d, 2H, J=1.0 Hz, 16a-H and 16b-H), 5.29(d, 1H, J=6.5 Hz, 14b-H), 7.24-7.41(m, 5H, C_6H_5), 7.81(bs, 1H, NH). Mass spectrum (isobutane C.I., 282°) m/e (rel. int. %): 518(100, MH^+), 460(7.7, MH^+ - CO - CH_2O), 410(10.7, MH^+ - $C_6H_5CH_2OH$), 402(10.1, 460 - $CH_2C(O)NH_2$), 388(12.6), 386(47.4, MH^+ - $HOSiMe_2$t-Bu), 380(55.4, 410 - H_2CO), 368(15.8), 362(13.4), 356(19.9, 386 - H_2CO), 278(15.1, 386 - $C_6H_5CH_2OH$), 248(32.2, 278 - H_2CO).

13-Deoxychloro-15-desmethyl sesbanimide **92**

To ketone **91** (57 mg, 0.110 mmol) in 1.0 mL of dry methylene chloride at -78° under N_2 was added 0.55 mL of 1 N BCl_3 (in CH_2Cl_2) *via* a syringe. After 1 h at -78°, the reaction mixture was poured into 3 mL of a cooled (0°) and well-stirred saturated sodium bicarbonate solution. After warming the total mixture to room temperature, the product was extracted with ethyl acetate (3 x 10 mL), washed with H_2O (1 x 3 mL), and brine before drying over magnesium sulfate. Evaporation under reduced pressure and purification by flash chromatography using methanol-methylene chloride (1:19) as eluant, gave 26 mg of **92** (68%) as a white foam. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.29-3.03 and 2.62(m + d(OH), 6H, J = 10.0 Hz, 3a-H, 3b-H, 4-H, 5a-H, 5b-H, and OH, D_2O exch.), 3.44(d, 1H, J = 7.2 Hz, 7-H), 3.53(s, 2H, 11-H, 4.00(d, 1H, J = 10.0 Hz, 8-H), 4.16(s, 3H, 9-H and 13-H), 4.80(d, 1H, J = 6.5 Hz, 14a-H), 5.10(s, 1H, 16a-H), 5.25(d, 1H, J = 6.5 Hz, 14b-H), 5.38(s, 1H, 16b-H), 8.05(bs, 1H, NH, D_2O exch.). Mass spectrum (NH_3 C.I., 230°) m/e rel. int. %) : 349/351(28.1/7.7, $(M + NH_4^+)$), 332(2.2, MH^+), 331/333(3.0/1.3, $(M + NH_4)^+ - H_2O$), 314(15.3, $MH^+ - H_2O$), 313(100, $(M + NH_4)^+ - HCl$), 296(13.5, $MH^+ - HCl$), 266(7.6, 296 - H_2CO), 265(7.4), 248(4.7, 266 - H_2O). High resolution ms (NH_3 C.I., 210°) calcd. for $C_{14}H_{22}O_6ClN_2$ $(M + NH_4^+)$: m/e 349.1166; found: m/e 349.1169.

[2-((t-Butyldiphenylsilyloxy)methyl)-3-allyl]trimethylsilane **94**

Alcohol **73** (2.88 g, 20 mmol), t-butylchlorodiphenylsilane (8.2 g, 30 mmol) and imidazole (3.00g, 44 mmol) in 30 mL of dry DMF were heated for 19 h at 50-55°. The mixture was diluted with 350 mL of water and the solution was extracted with diethyl ether (3 x 120 mL); the ether extracts were washed with water (3 x 40 mL) and brine and dried over $MgSO_4$. After flash chromatography, 5.4 g of silyl ether **94** was obtained. ^1H NMR (60 MHz, $CDCl_3$) δ: -.007(s, 9H, $Si(CH_3)_3$), 1.07(s, 9H,

$C(CH_3)_3$), 1.43(s, 2H, $CH_2Si(CH_3)_3$), 4.00(m, 2H, CH_2OSi), 4.65 and 5.07(2m, 2H, $C=CH_2$), 7.17-7.77(m, 10H, C_6H_5). High resolution molecular weight determination (80°), calcd. for $C_{19}H_{25}OSi_2$ (M - C_4H_9): m/e 325.1444; found: m/e 325.1457.

Alcohol **95**

Boron trifluoride etherate (86 mg, 0.61 mmol) was added *via* a syringe to a mixture of aldehyde **85** (120 mg, 0.36 mmol) and allylsilane **94** (268 mg, 0.70 mmol) at -78° under a nitrogen atmosphere and the reaction was stirred for 1.5 h. The mixture was then poured into a cold saturated sodium bicarbonate solution; the product was extracted with methylene chloride (2 x 30 mL). The methylene chloride extracts were washed with water (1 x 10 mL), dried over magnesium sulfate and evaporated. After purification by flash chromatography, 100 mg of alcohol **94** (43%) was recovered as a foam. $[\alpha]_D^{23}$ +50.7° (c 1.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.08(s, 9H, t-Bu), 2.09-2.53, 2.63-2.96 and 2.82-2.99(3m, 7H, 3a-H, 3b-H, 4-H, 5a-H, 5b-H, 11a-H and 11b-H), 3.15(d, 1H, J=7.0 Hz, 7-H), 3.29(d, 1H, J=8.9 Hz, 9-H), 3.70(s, 8-H and OH), D_2O exch.), 3.82-4.00(m, 1H, 10-H), 4.12(s, 2H, 13-H), 4.61(d, 1H, J=6.0 Hz, 14a-H), 4.78(ABq, 2H, J=11.9 Hz, CH_2Ph), 5.04(s, 1H, 16a-H), 5.13(d, 1H, J=6.0 Hz, 14a-H), 5.18(s, 1H, 16b-H), 7.18-7.93(m+s(NH), 16H, $CH_2C_6H_5$, $Si(C_6H_5)_2$ and NH, D_2O exch.). Mass spectrum (NH_3 C.I., 150°), m/e (rel. int. %) : 661(100, $(M + NH_4)^+$), 644(35.9, MH^+), 566(22.7). High resolution ms. (NH_3 C.I., 300°) calcd. for $C_{37}H_{46}O_7NSi$ (MH^+): m/e 644.3044; found: m/e 644.3046.

8-O-Benzyl-13-O-t-butyldiphenylsilyl-15-desmethyl sesbanimide **96**

Chromium trioxide (56 mg, 0.56 mmol) was added to pyridine (89 mg, 1.12 mmol) in 1.5 mL of dry methylene chloride and the solution was stirred for 15 min at room temperature. To this solution was added alcohol **94** (34 mg, 0.047 mmol) in 1 mL of methylene chloride. After 30 min, the solution was decanted and the solvent removed. The product was purified by flash chromatography (ethyl acetate-petroleum ether : 5/3) to yield 20 mg of **96** (67%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.04(s, 9H, t-Bu), 1.85-2.95(m, 5H, 3a-H, 3b-H, 4-H, 5a-H and 5b-H), 3.14(bs, 1H, 7-H), 3.45(ABq, 2H, J = 17.7 Hz, 11-H), 3.88(s, 1H, 8-H), 3.98s, 1H, 9-H), 4.16(s, 2H, 13-H), 4.42(ABq, 2H, J = 11.6 Hz, CH_2Ph), 4.63(d, 1H, J = 6.2 Hz, 14a-H), 4.92(s, 1H, 16a-H), 5.20(d, 1H, J = 6.2 Hz, 14b-H), 5.35(s, 1H, 16b-H), 7.09-7.74(m, 15H, $CH_2C_6H_5$ and $Si(C_6H_5)_2$), 7.86(bs, 1H, NH). Mass spectrum (NH_3 C.I., ~120°) m/e rel. int. %) : 659(100, $(M + NH_4)^+$), 455(9.5), 426(15.9), 403(23.0, 659 - $HOSiPh_2$t-Bu), 338(9.5). High resolution ms (NH_3 C.I., 305°) calcd. for $C_{37}H_{47}O_7N_2Si$ ($(M + NH_4)^+$): 659.3152; found 659.3156.

13-O-t-Butyldiphenylsilyl-15-desmethyl sesbanimide **97**

Boron trichloride (0.07 mL, 1 N in methylene chloride) was added to a solution of alcohol **96** in 1 mL of methylene chloride at -78° under nitrogen. The reaction mixture was stirred for 30 min at -78°, then poured into a cold saturated sodium bicarbonate solution (5 mL). The product was extracted with methylene chloride (1 x 15 mL), washed with water (1 x 5 mL) and dried with $MgSO_4$. After purification by flash chromatography (ethyl acetate-petroleum ether : 1/1), 10 mg of **97** (60%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06(s, 9H, t-Bu), 2.29-3.05m, 6H, 3a-H, 3b-H, 4a-H, 5a-H, 5b-H and OH), 3.33(d, 1H, J = 8.3 Hz, 7-H), 3.34(ABq, 2H, J = 16.6 Hz, 11a-H and 11b-H), 3.93(d, 1H, J = 10.3 Hz, 8-H), 4.03(s, 1H, 9-H), 4.17(s, 2H, 13-H),

4.66(d, 1H, J=6.4 Hz, 14a-H), 5.00(s, 1H, 16-H), 5.16(d, 1H, J=6.4 Hz, 14b-H), 5.34(s, 1H, 16b-H), 7.33-7.86(m, 10H, 2 C_6H_5), 7.89(bs, 1H, NH). Mass spectrum (NH_3 C.I., 271°) m/e (rel. int. %) : 569(88.8, $(M + NH_4)^+$), 504(64.8, $MH^+ - H_2O - CH_2O$), 478(100), 460(94.4), 400(79.2). High resolution ms (NH_3 C.I., 230°) calcd. for $C_{30}H_{38}O_7NSi$ (MH^+): 552.2419; found 552.2418.

Furan **98**

To a solution of of silyl ether **97** (28 mg, 0.05 mmol) in dry THF (0.5 mL) was added *tetra-n*-butylammonium fluoride (0.076 mmol) at room temperature. Only one major spot was observed on TLC and it had an R_f value equal to 0.20. After 15 min, the solvent was removed at 0° and the mixture was immediately purified by flash chromatography using silica gel pre-washed with triethylamine and methanol-methylene chloride (1/19) as eluant. A ^1H NMR spectrum was obtained using deuterated chloroform treated with sodium bicarbonate as solvent and it gave rise to a spectrum with a vast number of signals. However, upon exposure of this sample to a catalytic amount of acetic acid, the spot with R_f=0.20 became replaced with one less polar (R_f=0.32). This less polar compound was furan **98**. ^1H NMR (200 MHz, $CDCl_3$) of furan **98** δ: 1.99(s, 3H, CH_3), 2.27-3.00(m + d(OH), 6H, J=9.5 Hz, 3a-H, 3b-H, 4-H, 5a-H, 5b-H and OH, D_2O exch.), 3.45(d, 1H, J=7.5 Hz, 7-H), 3.77(d, 1H, J=9.5 Hz, 8-H), 4.69(s, 1H, 9-H), 4.86(d, 1H, J=6.4 Hz, 14a-H), 5.17(d, 1H, J=6.4 Hz, 14b-H), 6.35(s, 1H, furan γ-H), 7.15(d, 1H, J=1 Hz, furan α-H), 7.83(bs, 1H, NH, D_2O exch.). FAB spectrum (8 kV xenon, glycerol matrix, room temp.): 388(6.9, M + $glyH^+$), 296(17.1, MH^+), 266(7.0, $MH^+ - CH_2O$). High resolution FAB spectrum (8 kV xenon, glycerol matrix, room temp.): calcd. for MH^+: 296.1135; found: 296.1066.