"Asymmetric Synthesis of Quaternary Carbon Centers"

By

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To my parents: BunHan & Neang Eng,
Sister: Ny-Yana; Brother-in-law: Sothun
And little brother: Bunthan
For their love, encouragement and support

Asymmetric Synthesis of Quaternary Carbon Centers

Bunda Hin

To my fiancé
Arun-Rasmey Chang,
For his love and encouragement

Abstract

The methodology of asymmetric synthesis of quaternary carbon centers is in the process of being developed. Two enolization techniques have been explored. First, the reduction of a cyclic glycolate lactone which involved various electron transfer reducing agents following a classical method did not seem to be promising, moreover the enolate alkylation chemistry of such system was too problematic that both resulted in an abandon of the first approach. The second strategy employed a technique so-called "directed enolization" toward an amide system. The first alkylation methodology of amides has been successfully developed, whereas the second alkylation rather occurred at the β-enolizable position due to the Complex-Induced Proximity Effects.

Résumé

La méthodologie de synthèse asymétrique des centres de carbone quaternaires est en voie d'être développée. Deux techniques d'énolisation ont été explorées. En premier lieu, la réduction suivant une méthode classique d'un système cyclique tel que la glycolate lactone avec une variété d'agents réductants, ne semblait pas prometteuse. De plus, la chimie des alkylations des énolates de ce système avait été trop problématique, qu'elle s'est soldée par un échec et un abandon de la première méthode. Au cours de l'exploration de la seconde stratégie appelée "énolisation dirigée" chez les amides, une première méthode d'alkylation a été développée avec succès. Cependant, une seconde alkylation était loin d'être atteinte: l'abstraction du proton par une base eût lieu plutôt à la position β (possédant des protons énolisables), dû aux effets de proximité d'induction du complexe.

Acknowledgements

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Figures Schemes, Tables and Spectra

Introduction

The creation of the quaternary carbon atoms present in many molecules poses a significant synthetic challenge. There exists a number of reactions that may be effectively employed for construction of these sterically crowded centers. The most commonly utilized methods for the formation of a fully substituted carbon atom involve the reaction of a suitable carbon electrophile with a tertiary carbon nucleophile.[1] The reaction of a "tertiary" enolate, derived from carbonyl compounds with carbon electrophiles such as alkyl halides is probably one of the most useful methodologies for the construction of the quaternary carbon atom. The carbanion employed for such reaction may be generated from available precursors by a) direct deprotonation of the α-proton with a strong and non-nucleophilic base; b) cleavage of the corresponding trimethylsilyl enol-ether or enol acetate with proper nucleophiles[2] or c) metal reduction of α-heteroatom-substituted carbonyl[3] (figure 1).

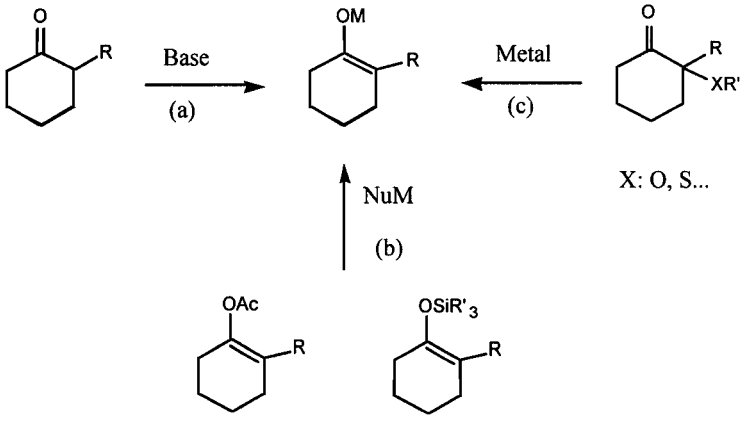


Figure 1. Generations of enolates by (a) deprotonation, (b) cleavage of O-silyl (or acyl), (c) metal reduction.

Control of the Enolate Geometry

Enolate alkylation is a powerful method for the asymmetric formation of the C-C bond. The procedure has allowed the synthesis of a variety of chiral, non-racemic substances, from molecules of small size such as substituted amino acids to the more complex ones

such as polypeptides, natural and non-natural products. Typically, such asymmetric alkylations are highly stereoregular occurring via a specific enolate geometry and conformation. The stereoselectivity depends upon the chiral sources, commonly referred to as chiral auxiliaries. When covalently or ionically attached to a substrate the chiral auxiliary renders enantiotopicity or diastereotopicity to the molecule. In addition to its capability for stereoselective alkylation, the chiral auxiliary also serves to control the enolate geometry during the deprotonation process thus allows the alkylation reactions to occur in a highly efficient and enantio- or diastereoselective manner.

The control of the enolate geometry (*E* versus *Z*) resulting from the deprotonation of monosubstituted carbonyl compounds is very well documented. Two of the most successful examples of asymmetric C-alkylation of enolate rely on Evans' *N*-acyl oxazolidinones[4a] and Oppolzer's camphor sultams[4b] as chiral auxiliaries. The enolate generated from Evan's oxazolidinone amides were observed to be at least 99% stereoselective for the *Z(O)*-enolate, which is metal-chelated to the oxazolidinone carbonyl oxygen to form a six membered-ring intermediate.[4a] The high selectivity of this enolate formation is rationalized in terms of the minimum of 1,3-diaxial interaction between the isopropyl group of the chiral auxiliary and the α-substituent of amides. This form of interaction would disfavour the formation of the *E(O)*-enolate. Similar selectivity and rationalization were given by Oppolzer for the high *Z(O)*-enolate formation when champhor was used as a chiral auxiliary.[4b] Generally, alkylation of such systems leads to a new asymmetric tertiary carbon center and proceeds in high degree of predictable stereoselectivity (Figure 2).

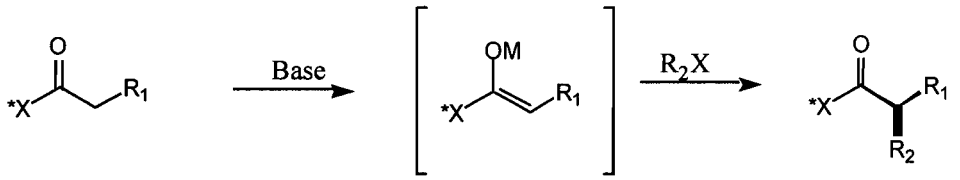


Figure 2. Asymmetric synthesis of tertiary carbon center

However, for the generation of quaternary carbon center, the major problem that arises is the control of the geometry of enolate, which is generated from the corresponding α,α-

disubstituted carbonyl compounds and will play an integral part in determining the stereochemistry of the newly formed asymmetric center (Figure 3).

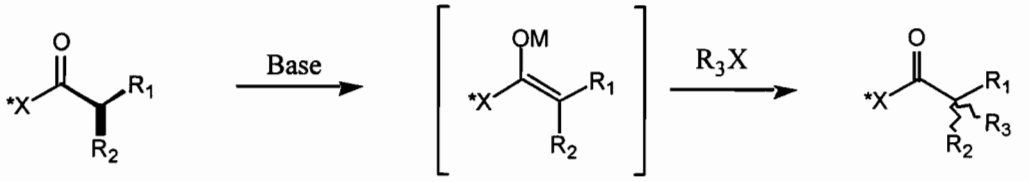


Figure 3. Asymmetric synthesis of quaternary carbon center

Although some solutions to this problem already exist, they are limited to specialized cases. In most reported cases, the geometry of enolates is controlled by cyclic systems, including heterocyclic rings and metal chelates via heteroatom substituent[5] (Figure 4a).

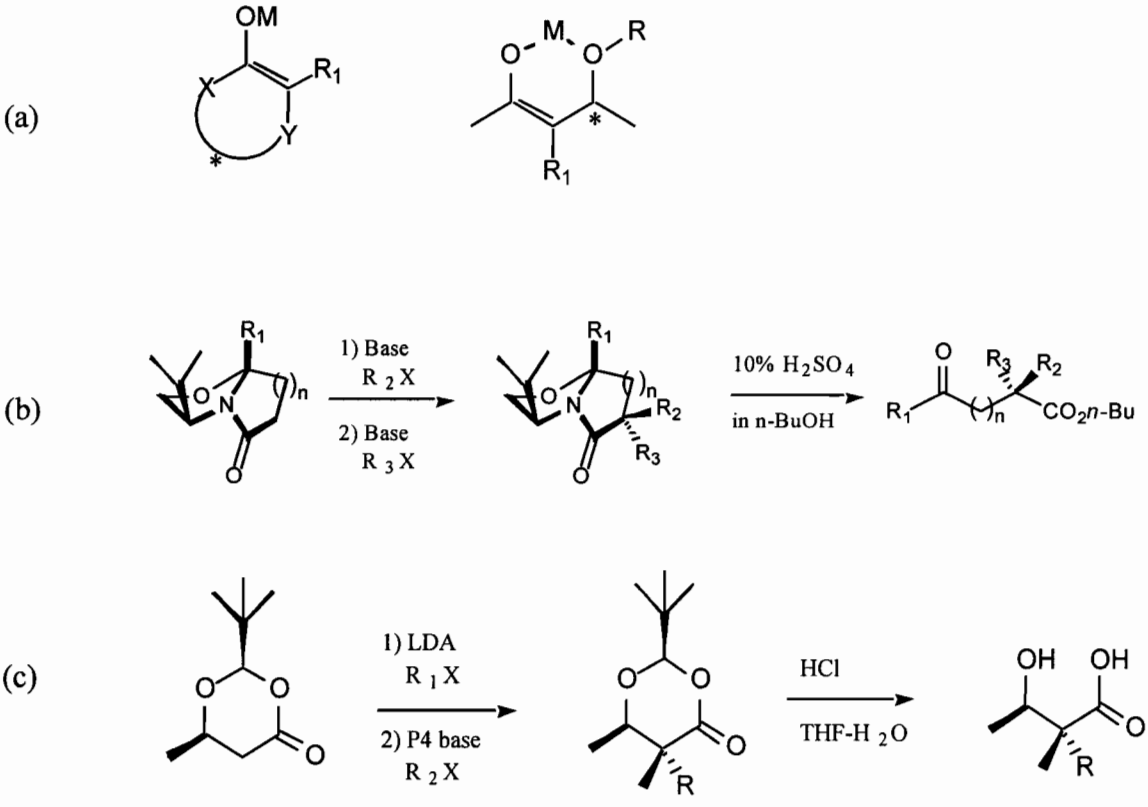
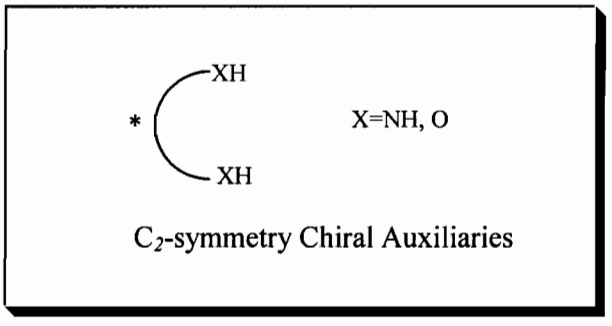


Figure 4. Intraligand asymmetric induction: (a) intraannular; chelate-enforced intraannular (b) Meyer's bicyclic lactams (c) Seebach's dioxanone.

For example, one of the most recent developments in synthetic methodology has been the use of chiral bicyclic lactams, as reported by Meyers, for the synthesis of a series of optically pure quaternary carbon substances derived from keto acids[5a] (figure 4b). For the same purpose Seebach has performed a diastereoselective synthesis of disubstituted β-hydroxy acids by employing chiral dioxanones (Figure 4c).[5b]

Unfortunately, the synthetic utility of these procedures for the construction of quaternary carbon centers is limited. In the absence of the heteroatom substituents, there is no general solution for the control of enolate geometry during the deprotonation of α,α-disubstituted carbonyl compounds.

It is the purpose of this project to develop an efficient and general methodology that enables the construction of asymmetric quaternary carbon centers through enolate alkylation reactions. Two separate strategies will be investigated. The first portion of our project (Chapter 1) will consist of exploring non-classical methods of enolate generation by reduction of chiral rigid cyclic glycolate lactones via single-election transfer reactions. The second part (Chapter 2) will be to develop chiral auxiliaries, which not only serve to control the diastereofacial selectivity in enolate alkylation but more importantly will incorporate functional groups which capable of directing intramolecular enolization. For both cases, only chiral auxiliaries that bear C_2-symmetry will be utilized.

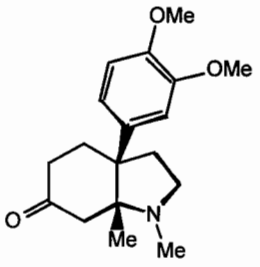


C_2-symmetry Chiral Auxiliaries

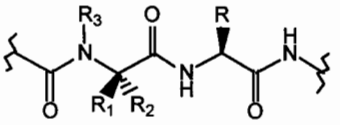
Potential Impacts of the Research

If successful, this method will provide an excellent opportunity to synthesize a variety of optically active compounds such as natural and non-natural products. For example:

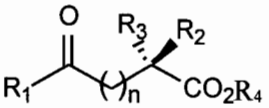
- The α,α-disubstituted Amino Acids having D or L configurations are often incorporated into polypeptides and peptidomimetic structures to lend conformational rigidity to a substrate.
- Natural products possessing complex molecular architecture are required in significant quantities so that their biological activity may be studied.
- The optically active compounds that are non-commercially available are in great demand for use as chiral synthons.



(+)-Mesembrine



α,α-disubstituted Amino Acids



α,α-disubstituted esters

Chapter 1

Enolization technique via reductive elimination

1.1. Introduction

A potentially elegant synthetic strategy for the generation of enolates would involve the reduction of carbonyl compounds possessing α-substituted heteroatoms with the aid of electron transfer agent. Several methods have been devised to achieve reductions of such compounds. Among the more widely utilized methods are: a) dissolving reducing metals in liquid ammonia (lithium, sodium) known as classical Birch conditions[6], b) lanthanide derivatives (*e.g* samarium iodide)[7] and c) metals intercalated in graphite (*e.g.* potassium graphite)[8]. Yamaguchi has reported a series of reactions in which a variety of α-oxygenated esters such as methyl α-methoxyphenylacetate were easily reduced to give the corresponding saturated esters in excellent yield with samarium iodide (SmI_2)[7c]. The reaction was carried out at room temperature in the presence of hexamethylphosphoramide (HMPA) and appropriate proton sources (figure5, path a).

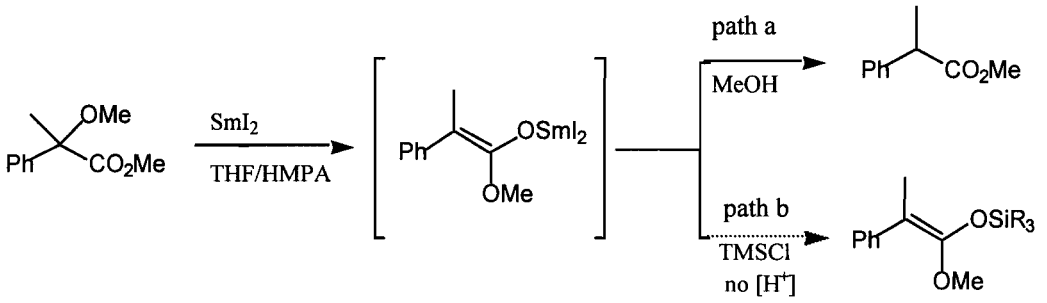


Figure 5. Reduction of methyl α-methoxyphenylacetate; path a. Yamaguchi's reduced product; path b. the proposed structure of the enolate intermediate

The mechanism of the reduction seems to proceed through two successive one-electron transfers to the ester carbonyl followed by β-elimination of the resulting β-oxygen-substituted carbanion to afford the corresponding ester enolate. At this stage, the enolate may be either protonated to yield the reduced product of Yamaguchi[7c] (figure 5, path a) or

possibly trapped as its silyl enol ether. A variety of subsequent reactions are possible after cleavage of the silyl group (figure 5, path b).

In our substrate design, a chiral rigid cyclic system such as glycolate lactone containing α-oxygen should be readily reduced under Yamaguchi's conditions to the corresponding ester enolate. Alkylation of this enolate with an electrophilic species would generate the desired quaternary carbon (figure 6).

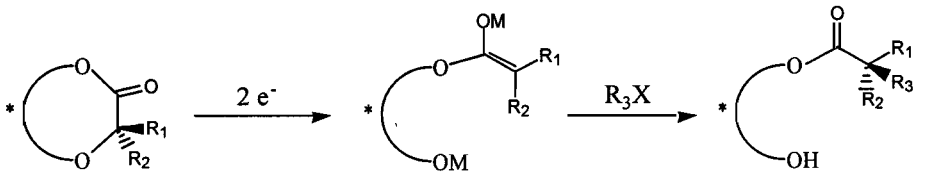


Figure 6. Acyclic structure of enolate generated from cyclic system

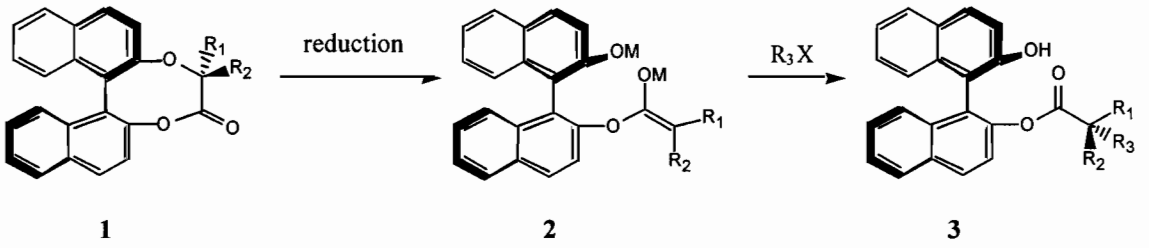
The ring backbone that constitutes the chiral auxiliary is expected to play two fundamental roles: 1. 1. It provides significant rigidity to maintain the α-substituents R_1 and R_2 at fixed positions in the ring (*i.e.* equatorial and axial), which is important for if the heteroatom contained in the ring is oxygen or sulfur, the geometry of the ring would be locked such as cylcohexane ring system, where upon exposure of the ring to reductive conditions, the orientation of the α-groups in the starting material relative to the carbonyl plane would be maintained upon enolate formation, thus should result in high E or Z selectivity; 2. The carbon framework is used as a chiral auxiliary for controlling diastereofacial selectivity of subsequent enolate alkylation reactions.

Our initial investigations will focus on the reduction of glycolate lactones as a non-classical method for generation of α,α-disubstituted enolates. The first part of our discussion will be the studies on glycolate lactones of 2,2-binaphthol, followed by the related system of glycolate lactones of *trans*-1,2-cyclohexane-diol. The nature of different reducing agents will also be explored.

1.2. Results and Discussion

1.2.1. Glycolate Lactone of *(R,R)*-2,2'-Binaphthol

For purposes of the first discussion, 2,2-diols systems were the first C_2-symmetric chiral auxiliaries to be employed as stereoinductor ligands. We first studied the glycolate lactones of *(R,R)*-2,2'-binaphtol which theoretically should provide a high degree of conformational rigidity, due to the restriction of rotation along Aryl-Aryl' bond. Calculations using MM2 molecular mechanics showed that the glycolate lactone of such system preferentially adopts a chair-like conformation as the favored structure.



1 **2** **3**

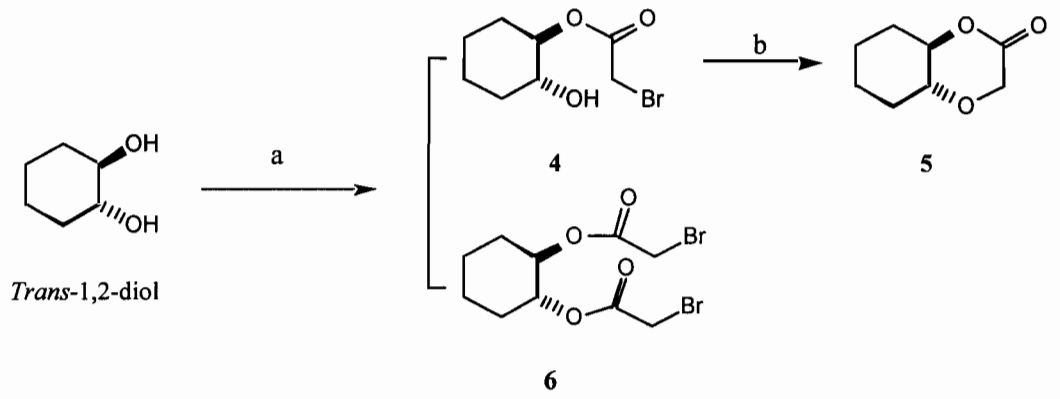
Figure 7. Glycolate lactone of *(R,R)*-2,2'-binaphthol

Alkylation of the monosubstituted binaphthyl enolates (**2**, R=H) is known to proceed with high levels of stereoselectivity.[9] Unfortunately this system was abandoned due to the unsuccessful synthesis of the 8-membered ring lactone **1** (figure 7).

1.2.2. Glycolate Lactone of *trans*-1,2-Cyclohexane-diol

The glycolate lactone of *trans*-1,2-cyclohexane-diol (**5**) was chosen as an alternative to **1** due to the fact that it has a six-membered ring, was thus perceived to be an easier target to prepare. During the first course of our synthesis, commercially available racemic *trans*-1,2-cyclohexane-diol was used in order to study the alkylation and reduction chemistry. Treatment of the racemic *trans*-1,2-diol at room temperature with bromoacetyl bromide using potassium carbonate in methylene chloride (CH_2Cl_2) afforded the desired monoester **4** and the diester **6** in respective 33% and 29% yields (scheme 1).

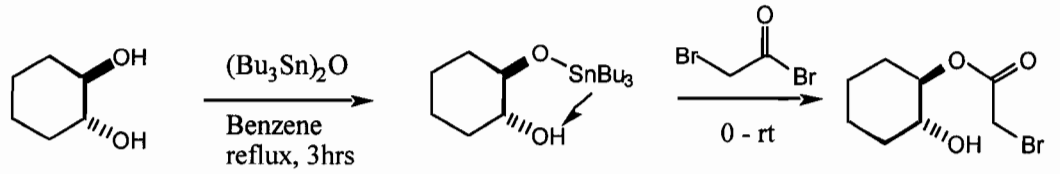
Scheme 1. Acylation of *trans*-1,2-cyclohexane-diol



Reagents: (a) $BrCOCH_2Br$, K_2CO_3, CH_2Cl_2, 25 °C; (b) NaH, THF, reflux.

The problem of the diacylation product was overcome by employing bis-tributyltinoxide, which allows a selective monoesterification of one hydroxyl group[10]. The reaction takes place in two separate steps, namely, an initial activation of one hydroxyl group through fast formation of a stannylether, followed by esterification with an acyl halide (scheme 2).

Scheme 2. Monoacylation of *trans*-1,2-cyclohexane-diol



4

84-88%

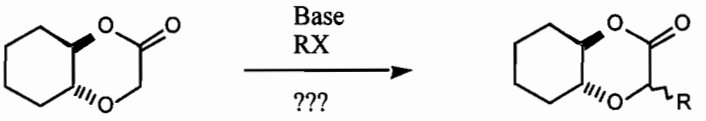
Hydrolytic workup of the corresponding acylation reaction followed by purification on column chromatography yielded 84-88% of monoester **4** as the major product. The latter compound readily cyclized when heated to reflux overnight in THF in the presence of sodium hydride to afford lactone **5** in moderate yield (57-60%, scheme 1).

1.2.3. Alkylation Chemistry

Having the glycolate lactone in hand, we undertook to study the enolate chemistry. The first alkylations employing various bases, such as lithium diisopropylamide (LDA), lithium hexamethyldisilazide (HMDS), potassium *tert*-butoxide (*tert*-BuOK) and alkylating agents failed to give the α-monosubstituted glycolate lactone (scheme 3a). Only a small amount (~12%) of the α-benzylated product was obtained when lithium diisopropylamide (LDA) was used in the presence of the co-solvent such as hexamethylphosphoramide (HMPA) or 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) in THF. The reaction appears to suffer from extensive decomposition of the enolate at temperature necessary for alkylation.

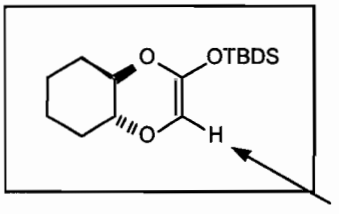
Scheme 3. (a) Alkylation of glycolate lactone (b) Studies of enolate formation

(a)



R: Me, Bn,

(b)



5.74 ppm

7

In order to confirm the formation of enolate, lactone **5** was subjected to the same reaction condition as mentioned (at -78 °C in THF and DMPU) and the reaction was quenched with *tert*-butyldimethylsilyl chloride (TBDMSCl). Analysis by ^{1}H NMR clearly showed a clean formation of the silylketene acetal (**7**), as evidenced by a signal at 5.74 ppm corresponding to the vinyl proton (scheme 3b). Thus the assumption made earlier for the formation, followed by the decomposition of the enolate was evidently correct.

Interestingly, when benzaldehyde was used as an electrophile, the aldol product **8** was isolated in 39% yield (23% if DMPU was omitted) as a mixture of four diastereomers (Scheme 4). This improvement arose effectively from the higher reactivity of the electrophile, which resulted in a higher rate for the aldol reaction than for enolate alkylation.

Scheme 4. Aldol reaction

5 **8**

Seeing that the alkylation chemistry was problematic because of the continuous decomposition of enolate, we moved to study the reduction chemistry which represents the key aspect of the project.

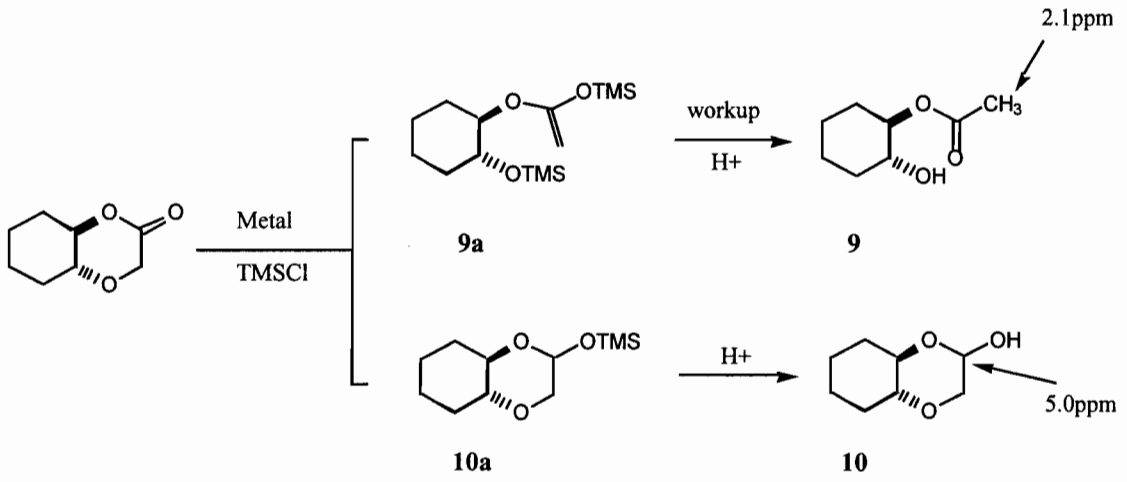
1.2.4. Reduction Chemistry

Reduction of the glycolate lactone **5** was carried out using potassium graphite C_8K. Potassium-graphite is easily prepared by heating the mixture of the two elements, under high vacuum, at 150 °C until bronze-colored solid appeared.[8] Addition of the lactone to a slury suspension of C_8K was followed by quenching with trimethylsilylchloride (TMSCl) and then an acid workup. A new product was isolated by column chromatography (3-8% yield). Detailed spectroscopic analyses (^{1}H NMR, GC and GC/MS) concluded that the product was a mixture of two compounds (**9**, **10**; ratio 1:2) having similar polarity, 1) the reduced product acetate ester **9** (from enolate quenching, **9a**) and 2) the glycolate lactol **10** (from incomplete reduction, **10a**) (scheme 5). ^{1}H NMR of the crude products showed two peaks characterizing the acetate protons at 2.03 ppm and the acetal proton of the incomplete reduced product at 5.02 ppm. GCMS analysis showed the presence of two products with the same molecular weight (158). A fragmentation at 115 corresponds to

the molecular weight of cyclohexane-diol presumably arising from the loss of the acetate group from the ester **9**; and the fragmentation at 140 was assumed to be the result of dehydration (loss of H_2O) of the lactol **10**.

The GC-MS results were confirmed by preparing authentic samples of **9** and **10**. The acetate ester of cyclohexane-diol, **9**, was obtained in 84% yield from a straightforward acylation of cyclohexane-diol with bis(tributyltin)oxide and acetyl chloride. The glycolate lactol **10** was prepared in 98% yield from reduction of the corresponding lactone (**5**) using diisobutylaluminiumhydride (DIBALH) in toluene at –78 °C. ^{1}H NMR and GC analyses confirmed the authenticity between the molecules obtained from reduction via electron transfers and from synthesis.

Scheme 5. Reduction of Glycolate lactone



Attempted reduction of **5** with SmI_2 gave only trace amounts (<2%) of reduced compounds **9** and **10**. No reduction was observed when dissolving metals such as Li/NH_3 and Li/Naphthalene were used.

1.3. Conclusion

The first synthetic strategy for the construction of quaternary carbon centers employing reduction chemistry was too problematic due to the low reactivity of the glycolate lactone toward a variety of reducing agents as well as the low yield of the alkylation product. Thus, this resulted in an abandon of the first technique.

Chapter 2

Generation of Enolate by Directed Enolization of Amides

2.1. Introduction

There are many possible methods that allow to construct the quaternary carbon atoms in a highly stereoselective manner. Ideally, the most straightforward method would be through the alkylation of carboxylic acid derivatives. However, a straightforward method for preparing α,α-disubstitued enolates through the direct enolization of esters or amides generally does not provide high E/Z selectivity, which results from the inability of lithium dialkylamide bases to discriminate between α-substituents in either a chair-like or open transition state. This makes impossible to control the stereoselectivity of quaternary carbon construction in acyclic systems via alkylation methods. It is proposed that the introduction of a pendant amines into chiral auxiliaries will allow for directed enolization through a complex induced proximity effect. Recently, Myers has reported diastereoselective alkylations of pseudoephedrine glycinamides to afford α-amino acids in highly enantiomeric purity.[12] The enolization of this particular molecule which contains three different acidic functional groups, was believed to proceed through two successive processes. The mechanism of the reaction started with kinetic abstraction of an amine proton at low temperature (-78 °C) by lithium diisopropyllamide.[12] Equilibration (lithiated amine ↔ enolate) presumably took place upon warming the reaction up to 0 °C. Myers attributed this result to the phenomenon of internal proton transfer from the thermodynamic proton α to the primary lithiated amine (figure 8).

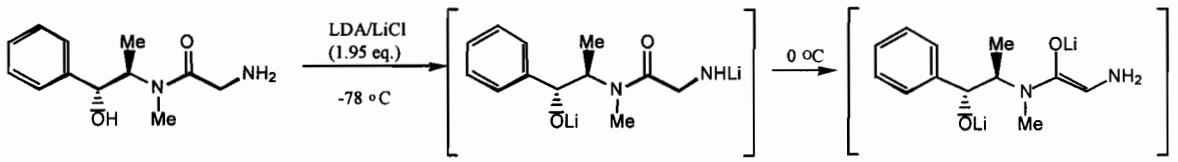
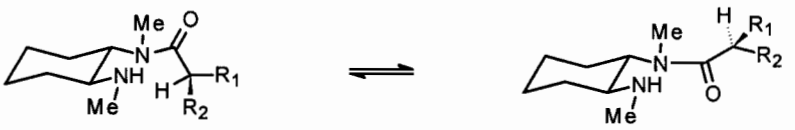


Figure 8. Enolization of Pseudoephedrine Glycinamide

In our substrate design, we hope that the process of enolization would occur in a similar manner (i.e. via internal proton transfer). *Trans*-1,2-diaminocyclohexane is proposed as a

first generation approach to directed enolization. This chiral ligand has been of particular interest of many chemists. One of the most recent synthetic methodologies developed by Davies was the use of *trans*-1,2-diaminocyclohexane as the bifunctional chiral auxiliaries for stereoselective alkylation of 1,3-diacylimidazolidin-2-ones derivatives to generate two tertiary carbon centers at a time.[11] Of our interest, we expect from this ligand, in addition to its ability to control the diastereofacial selectivity in enolate (enamine-like) functionalization reaction, it would also be capable of directing the intramolecular enolization of amides through the second amino group of the chiral auxiliary. Therefore, the intramolecular deprotonation of α-substituted amides, through amino group of *trans-1,2*-diaminocyclohexane would require reaction through *trans*-amide rotamer, whereas calculations using MM2 molecular mechanics has indicated a preference for the *cis*-amide rotamer by 3-5 kcal/mol (Figure 9).



trans *cis*

Figure 9. *Trans* and *cis* amide rotamers

It is expected that at low temperature the rotation might not be rapid enough for amide rotamer isomerization, thus the α-proton is found to point itself far away from the directing site. However, in order for the amide to adopt the right conformation (i.e. *trans*-rotamer) for the deprotonation to occur through the second directing amine, high temperature would be required. That way, the rotation along the amide bond is rapid enough that would place the relatively acidic α-proton face towards the directing amine.

The deprotonation may occur in several possible processes. It is well known that amines are capable of chelation or forming aggregates by hydrogen bonding with dialkylamide bases.[14] One of the proposed mechanisms for directed enolization would be the coordination of the amino group to lithium dialkylamide thus delivering the base from

one specific face of the amide (figure 10, path b). Alternatively, deprotonation of the secondary amine by a strong base (*n*-butyllithium or LDA) would lead to lithium alkylamide species that exists in either a dimeric form (a so-called homo-dimer) or in coordination with one equivalent of lithium dialkylamide (path b). In both cases, lithium alkylamide base is found in a favorable position to direct the intramolecular deprotonation of the amide (figure 10, paths a and b).

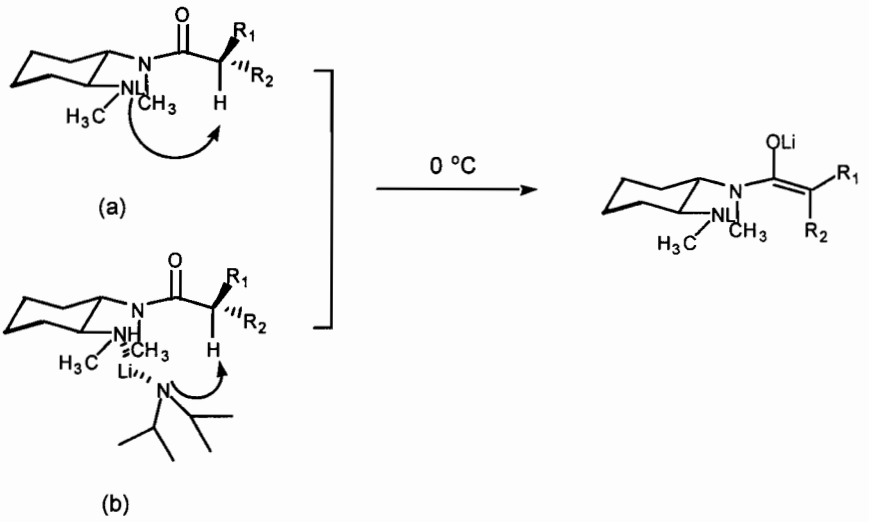


Figure 10. Proposed mechanisms for directed enolization of amides

The discussion in chapter 2 will focus on the development of chiral auxiliaries capable of directing the intramolecular enolization and inducing the stereoselectivity. For this purpose, the chemistry of amides will be investigated, which presents a good advantage due to the high stability of amide enolates over a wide range of conditions as compared in particular with ester enolate.

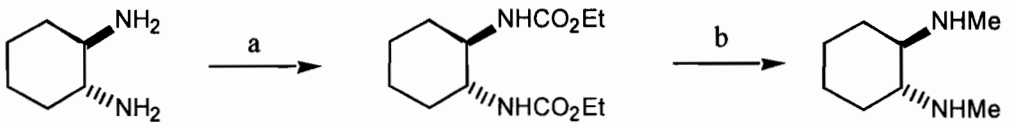
2.2. Results and Discussion

We first studied the model reactions which comprised: 1) the stereoselectivity expected from the first alkylation of amide enolate and 2) the chemistry of directed enolization. For this purpose, commercially available *trans*-1,2-diaminocyclohexane in racemic form was used for the synthesis of the first ligand.

2.2.1. Synthesis of racemic *trans-N,N'*-dimethyl-1,2-diaminocyclohexane

Racemic *Trans-N,N'*-dimethyl-1,2-diaminocyclohexane **12** was prepared according to a known procedure.[13] *Trans*-1,2-diaminocyclohexane was initially converted into its *N,N'*-dicarbamate **11** by reaction with ethylchloroformate in a biphasic mixture of aqueous sodium hydroxide and benzene. Dicarbamate **11** was obtained in 83-88% yield after recrystallization. Reduction of **11** with lithium aluminum hydride ($LiAlH_4$) in THF resulted the *N,N'*-dimethyl analog **12** in 76-96% yield.

Scheme 6



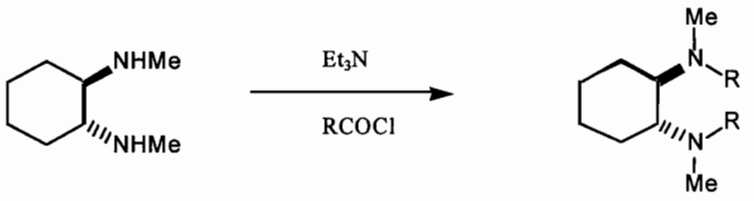
(R,R) **11** *(R,R)* **12**

Reagents. (a) $ClCO_2Et$, NaOH, C_6H_6, 0 °C-RT; (b) $LiAlH_4$, THF, reflux.

2.2.2. Mono-acylation of *trans*-1,2-dimethyldiaminocyclohexane

As we have seen in the first approach, monoesterification of *trans*-1,2-cyclohexane-diol with acyl chloride was selectively achieved through its dibutylstannylene derivative.[10] However, there are no known procedures for the selective monoacylation of a 1,2-diamine. Reaction of *N,N'*-dimethyl-1,2-diamine **12** with one equivalent of propionyl chloride gave the diacylated compound **13** which was isolated as the main product (scheme 7). The same result (compound **14**) was obtained even when a bulkier group such as *tert*-butoxycarbonyl (Boc) was employed as acylating agent.

Scheme 7. Attempted monoacylation of *N,N'*-dimethyl-1,2-diamine

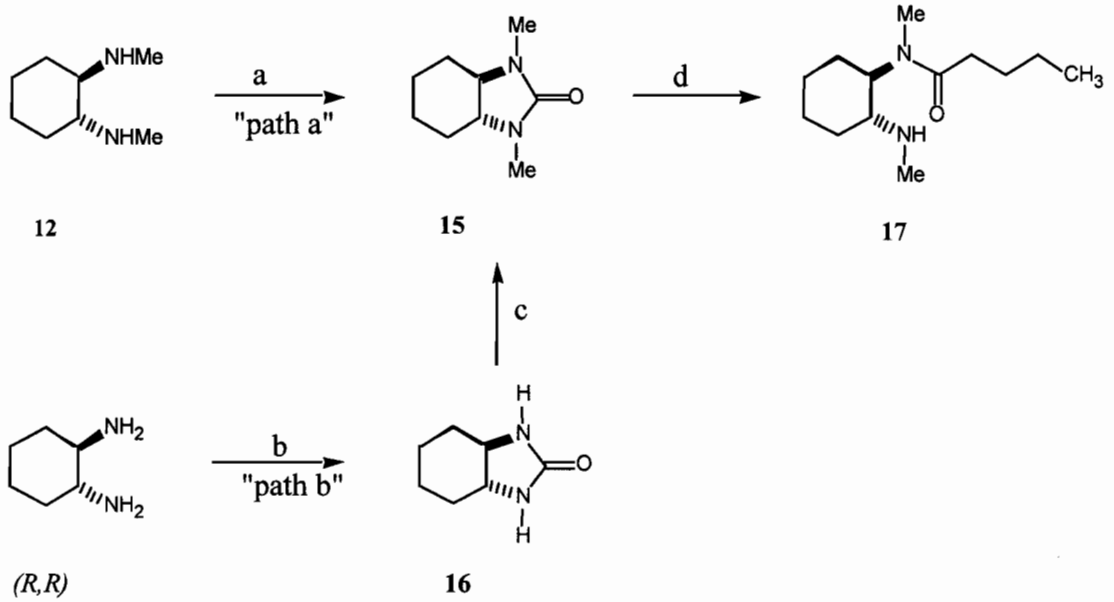


12

13, R = CH_3CH_2CO-
14, R = Boc

The problem of the overacylation was overcome with one additional step by first converting *(R,R)*-dimethyl-1,2-diaminocyclohexane **12** into its urea analog followed by the urea ring opening from nucleophilic addition of an organometallic reagent (scheme 8).

Scheme 8



12 **15** **17**

(R,R) **16**

Reagents. (a) and (b) $Cl_3CO(CO)OCCl_3$, Et_3N, CH_2Cl_2; (c) NaH, MeI; (d) i. *n*-BuLi, THF, ii. CH_3COCl, MeOH, (recrystallization) iii. 15% NaOH, CH_2Cl_2 (workup).

Conversion of **12** into into its urea analog **15** (Me-urea) was achieved in 51-60% yield by treating *N,N'*-dimethyl **12** with triphosgene in CH_2Cl_2 in the presence of triethylamine (path a). An alternative pathway for making urea **15** was to start with the available *trans*-

1,2-diaminocyclohexane. Treatment of this material with triphosgene (scheme 8, path b) led to imidazolidin-2-one **16** (*H*-urea) in 70% yield. The reaction was not reproducible since further attempt to duplicate the synthesis failed. Davies reported the similar problems which were attributed to the formation of polymeric material.[11b] *H*-urea **16** was *N*-methylated by reaction with sodium hydride and methyl iodide in THF to afford 57% yield of Me-urea **15**.

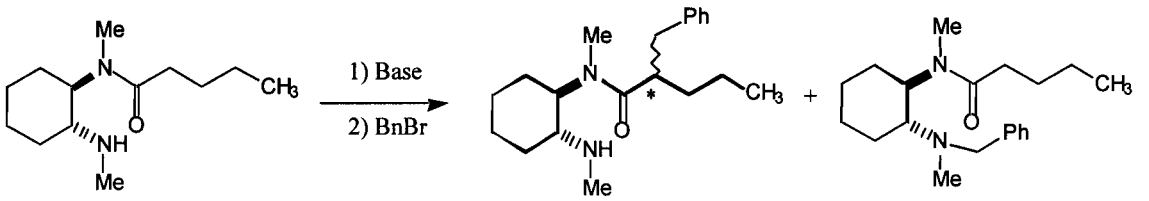
Addition of *n*-butyllithium at –78 °C to urea **15** furnished pentanamide **17** in 63% yield after purification. Care must be taken in order to get highly pure material, which is extremely important for the subsequent alkylation chemistry. Purification requires some additional tasks. First pentanamide **17** was converted to its amine hydrochloride salt. The procedure for such derivation was reported in the literature. Treatment of the crude pentanamide **17** with hydrochloric acid solution in methanol (prepared from addition of acetylchloride to methanol at 0 °C), followed by recrystallization in ethylacetate/hexanes (or hot toluene), provided the amine hydrochloride salt of **17** as a white powder. ^{1}H NMR showed two broad singlets at 9.05 and 9.30 ppm, indicating the two protons of NH_2Cl. The salt derivative was then subjected to a concentrated base workup (15-50% NaOH) in CH_2Cl_2 and the starting material **17** was quantitatively recovered (63% overall yield). ^{1}H NMR showed the presence of two rotamers as judged by the presence of four singlets in the region between 2.36-2.86 ppm (ratio of 2:1) assigned for both *N,N'*-dimethyl groups. Surprisingly, the change from simple amine to amine hydrochloride derivative induced change in rotameric ratio; only one singlet was observed at 3.0 ppm, assumed to be the methyl group that substituted the amine salt nitrogen ($\underline{Me}NH_2Cl$).

Unfortunately, attempts to make analogous propionamide by Grignard addition of ethylmagnesium halides (*e.g.* iodide, bromide) failed.

2.2.3 Alkylation of Pentanamide 17

The highly pure pentanamide **17** was subjected to alkylation reactions with benzyl bromide and varying bases and conditions. Table 1 shows the percentages of two main products isolated from the reaction mixtures.

Table 1. Diastereoselective alkylation of Pentanamide (**17**)



18 **19**

Base	Enolization time (-78°C/ 0°C) (min)	Alkylation Time (h)	*N*-Benzyl **19** (%)[a]	*C*-Benzyl **18** (%)[d]	*C*-Benzyl **18** de ratio
n-BuLi	20 / 20	6	---	---	---
LDA/LiCl	30 / 10	4	66[b]	---	---
LDA	20 / 20	1	3.4	1.9	2:1
LDA	10 / 30	1	3.5	0.3	2:1
LHMDS	20 / 30	6	0.7	26.2	2:1
LHMDS/LiCl	20 / 20	2	4.0	56.1	3:1
NaHMDS	25 / 20	1	0.3	81.0	2:1
NaHMDS	25 / 20	6	1.1	80.6	2:1
KHMDS	20 / 25	1	0.4	85.4	1:1.5
KHMDS	20 / 25	6	0.3	92.3	1:1.5
KDA	20 min at -78°C	1	Trace[c]	---	---
KDA	20 min at -78°C	6	0.3	23.4	1:1.5

[a] Values determined by Capillary GC analysis. [b] Yield determined by column chromatography. [c] Trace observed by ^{1}H NMR. [d] Yield and selectivity determined by Capillary GC analysis of the corresponding *N*-acetate. [e] Yield quantitated by column chromatography of the correspong *N*-Boc.

Reaction of amide **17** with lithium diisopropylamide (LDA) at –78 °C in the presence of lithium chloride in THF followed by the addition of benzyl bromide failed to give the α-substituted product **18**. Mainly the product of *N*-benzylation **19** was isolated in 66% yield after 4 h at 0 °C (Table 1, entry 2). The structure of the *N*-benzylated product was elucidated by spectroscopic analyses. The ^{1}H NMR spectrum of **19** displayed two signals at chemical shifts of 3.34 and 3.70 ppm as a doublet of doublets for the two benzylic protons. The observed large coupling constant of 13.3 Hz is characteristic of geminal coupling. In addition, the existence of *N*-Bn substituent was ascertained by the IR spectrum, which showed a complete disappearance of the absorption peak at 3450 cm^{-1} for the secondary amine N-H stretching, and supported for the formation of the tertiary amine.

No significant change was observed even with a variation of the conditions for enolization when lithium diisopropylamide was used as base (entries 3-4). Possible reasons to be considered are:

1. The *N*-benzylation product mainly obtained (entry 2) was due to the high nucleophilicity of the secondary amine thus resulted in a more rapid alkylation on the nitrogen atom, while the enolate did not have time to form.
2. The recovery of the starting material after 1 h (entry 3-4) could be the cause of a) too short reaction time to allow *N*-alkylation to occur and b) enolate quenching. As the time granted for enolization was longer and at higher temperature (0 °C), amide enolate was formed (Table 1, entry 3-4), followed by a rapid α-C re-protonation, either by external proton quenching or internal proton return (ipr). Recently, Vedejs[14] has studied the possibility of enantioselective ipr in amide-enolate complexes. The author has attributed the rapid protonation of lithium enolate-amine complexes to the small distance (about the hydrogen bonding distance) between ammonium-like N-H (from coordination amine-lithium ion, N-H-Li) and the enolate.[14] When an electrophile was added, the electron demand in the complex was believed to increase resulting the increased acidity of N-H bond and the rapid α-C protonation. However, this rationalization is not yet proven at this stage because of limited data.

Or

3. It is also possible that the amine NH is undergoing deprotonation and that the equilibrium constant for proton transfer does not favour the enolate relative to this species.

There was no reaction when LDA was replaced by *n*-butyllithium after 6 h at 0 °C (entry 1). Among bases, alkylations with hexamethyldisilazides seemed to give the most promising results. Thus, treatment of pentanamide **17** with lithium hexamethyldisilazide (LiHMDS) in THF for 20 min at –78 °C and 30 min at 0 °C followed by the addition of benzyl bromide gave the α-benzyl **18** in 26.2% yield along with 0.7% of *N*-benzyl **19** after 6 h. The selectivity of the reaction was 2:1 diastereomeric ratio as determined by capillary GC of the *N*-acetate derivatives (entry 5). The yield of desired product increased up to 56.1% within only 2 h of reaction time when the same reaction was carried out in the presence of anhydrous lithium chloride. Along with this result, the formation of the competing side product was found to increase from 0.7 to 4.0%. More interestingly, improvement in diastereoselectivity was also observed (3:1 diastereomeric ratio, entry 5). When increasing the size of hexamethyldisilazide counter ion from Li^+, Na^+ to K^+, the yields of the corresponding α-benzylated amide increased significantly (26.2%, 81.0% and 92.3% respectively) with only small variation in the amount of the side product (entry 5-10). The reactions were followed by taking aliquots after 1 h and 6 h and GC analysis after derivation to the corresponding *N*-acetates as previously described. It is important to point out the same selectivity (2:1) existed for reactions with NaHMDS as well as LiHMDS.

Surprisingly, alkylation reactions using potassium base (KHMDS) showed the major product with a reversed stereochemistry (1:1.5 diastereomeric ratio, entries 9-12). Alkylation of potassium enolate occurred at a faster rate as compared to the corresponding lithium and sodium species. This resulted in a higher yield up to 85.4% after only 1 h, and 92.3% after 6 h (by GC, entries 9-10). No further optimization was performed to increase the yield of the reaction.

Conversion of the *C*-benzylated amide **18** to the corresponding *N*-Boc derivative (Et_3N, Boc_2O, CH_2Cl_2) allowed the isolation of 76% of pure material by column chromatography. The latter (*N*-Boc amine) was subjected to acidic condition (trifluroacetic acid, TFA) to cleave the Boc group to get back to the amide **18** in a pure state. Analysis of the IR spectrum revealed one absorption band at 3450 cm^{-1} assigned as the N-H stretching band of the secondary amine, and the appearence of one additional band at 3025 cm^{-1} characteristic for the aromatic C-H stretching.

It should not be unnoticed that reactions of amide with a more reactive base such as potassium diisopropylamide (KDA) gave low yields (23.4%) of the *C*-alkylated product after 6 h with a conserved stereoselectivity at 1:1.5. Despite the positive results obtained when HMDS bases were employed, directed enolization was not studied yet. We were questioning whether the observed selectivity of the reactions with HMDS was the results of the directed enolization as we anticipated or the results of direct enolization, i.e. usual deprotonation. The latter proposition seems to be the more plausible explanation. According to the pKa values, hexamethyldisilazides (pKa ~29)[21] are not basic enough to abstract the proton of the secondary amine (pKa ~ 40) thus less probable for directed enolization to happen. Nevertheless, dialkyl diisopropylamides bases which have similar pKa values would potentially be more suitable for this purpose.

The low diastereomeric ratio (1:1.5) observed in the reaction with HMDS could be rationalized by the low discrimination of the chiral auxiliary to control the stereofacial approach of electrophile (alkylation). This first alkylation should occur only via *Z*-enolate, regardless the trajectory of the base to approach the α-protons, i.e. either from the front or the back face of diaminocyclohexane backbone. It is known that, for steric and perhaps stereoelectronic reason, deprotonation of unsubstituted amides proceeds more easily, which will not be the case of the substituted amide as we will see later.

In order to study the *E/Z* selectivity of the second enolization, one single and pure diastereomer was required. All attempts to isolate a single diastereomer by chromatography or recrystallization of either **18** or its derivatives (HCl salt, *N*-Boc or

enamine derivative) were unsuccessful. Our effort was now focused on an alternative synthesis for obtaining one single diastereomer.

2.2.4. Synthesis of Mono-Amide via Aminal intermediate

To prepare homochiral **18**, we envisioned mono-acylation of **12** with an enantiomerically pure acid derivative. As described earlier, mono-acylation of diamines is often difficult. We envisioned the use of an aminal as an *in situ* blocking group which would allow selective functionalization of diamine **12**. One possible mechanism is illustrated below (figure 11). The process of monoacylation may start with the nucleophilic attack of the nitrogen atom onto acyl carbonyl group which leads to a tetrahedral ammonium acyl chloride followed by a ring opening and hydrolysis under mild conditions to afford the mono-amide (figure 11).

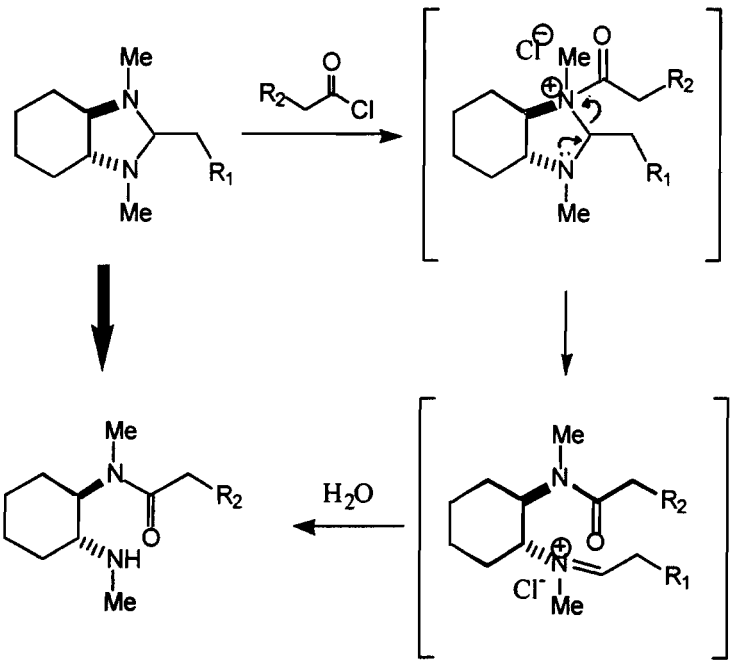
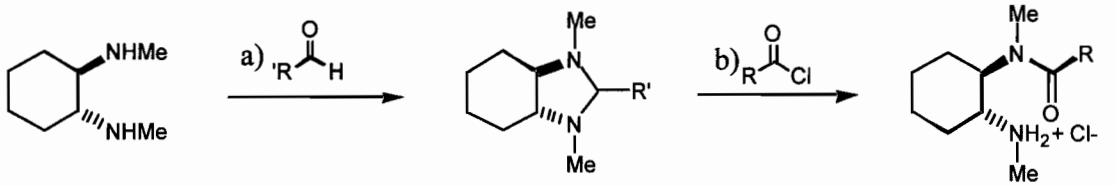


Figure 11. Proposed mechanism for monoacylation of *N,N'*-dimethyl-1,2-diamine via aminal intermediate.

Two different aldehydes were used for the purpose of synthesizing the corresponding aminals. Diaminocyclohexane-aminal of isobutyraldehyde **20** and diaminocyclohexane-aminal of benzaldehyde **21** were obtained in quantitative yields (confirmed by ^{1}H NMR) when the solutions of *trans-N,N'*-dimethyl-1,2-diaminocyclohexane in diethylether were treated with respective aldehydes in the presence of the 4 Å molecular sieves at room temperature. Both aminals **20** and **21** were without purification, used directly in subsequent acylation reactions. Surprisingly, precipitation was observed within 5 minutes upon addition of acyl chlorides onto a solution of aminal **20** in THF at room temperature (scheme 9).

Scheme 9. Monoacylation of *N,N'*-dimethyl via aminals



20 R'=-$CH(CH_3)_2$
21 R'=-C_6H_5

22 R=-CH_3
23 R=-CH_2CH_3

Precipitation was even more rapid (< 1 min) when the aminal of benzaldehyde (**21**) was used in place of the isobutyraldehyde (**20**). Recrystallization (hot toluene or ethylacetate/hexanes) afforded amine hydrochloride salts **22** and **23** as white powder in 72-76% yields. Regardless the number of carbons on the aliphatic chain, there was close similarity between the ^{1}H and ^{13}C NMR spectra of amine hydrochloride salt of acetamide (**22**) and propionamide (**23**) and the one previously obtained from hydrochloric acid treatment (pentanamide salt **17**).

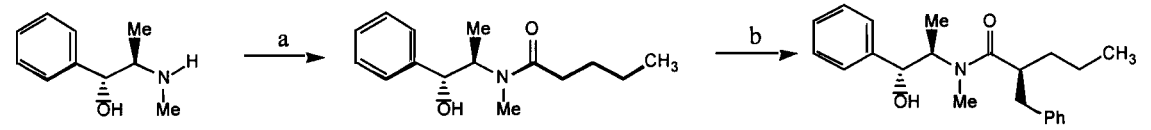
We wished to apply this method for synthesizing a single diastereomer of the α-benzylpentanamide of *trans-N,N'*-dimethyl-1,2-diaminocyclohexane. Enantiomerically pure *(R,R)*-1,2-diaminocyclohexane was obtained from chemical resolution via tartrate salt derivatives of the racemic *(R,R)*-1,2-diaminocyclohexane.[15] The corresponding *(R,R)-N,N'*-1,2-dimethyl was converted into *(R,R)*-aminal **21** following the two-step procedure

previously described. Let us now bring our attention to the synthesis of the other part of the molecule: *(S)*- α-benzylvaleryl acid chloride.

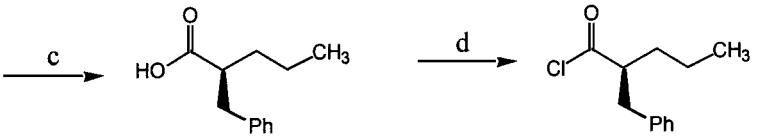
2.2.5. Synthesis of enantiomerically pure α-benzylvaleric acid chloride

The other part of the molecule, α-benzylvaleric acid was prepared in enantiomerically enriched form in three steps using the procedure of Myers.[16] (-)-Pseudoephedrine a commercially available material has been used as a chiral auxiliary for this synthesis. *N*-Acylation of (-)-pseudoephedrine with valeryl chloride was performed at 0 °C in THF with a slight excess of triethylamine to give the tertiary amide **24** in 92-95% yield (Scheme 10).

Scheme 10.



(-)-Pseudoephedrine **24** **25**



26 **27**

Reagents (a) $CH_3(CH_2)_3COCl$, Et_3N, CH_2Cl_2; (b) LDA, BnBr, LiCl, THF; (c) H_2SO_4/dioxane, reflux; (d) $(CO)_2Cl_2$, cat. DMF, CH_2Cl_2.

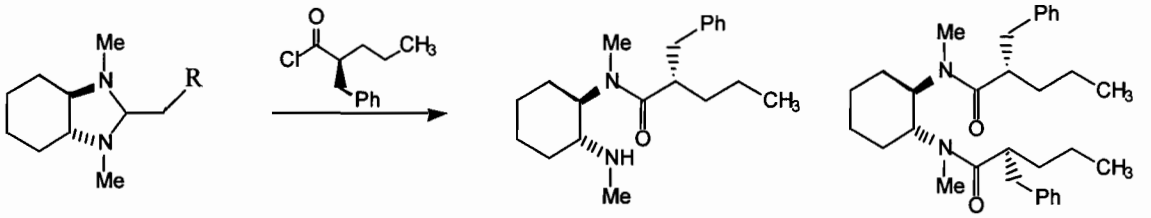
Alkylation of the pseudoephedrine amide was carried out by adding an excess (1.5 equiv) of benzyl bromide (procedure A of Myers)[16] to a solution of enolate derived from amide **24** and LDA in the presence of anhydrous LiCl in THF at –78 °C. The reaction produced pseudoephedrine α-benzylamide **25** in 86% yield. Hydrolysis to the corresponding carboxylic acid was effected in excellent yield (97.8%) simply by heating amide **25** at reflux in a 1:2 mixture of 9 N H_2SO_4/dioxane (Scheme 10). The enantiomeric excess of α-

benzylvaleric acid **26** was determined to be 97% by analysis on capillary GC of the corresponding *(S)*-(α-methylbenzyl) amide derivative. Treatment of acid **26** with oxalyl chloride in the presence of a catalytic amount of dimethylformamide (DMF) in CH_2Cl_2 afforded the α-benzylvaleryl chloride **27** in 94.5% yield after Kugelrohr distillation.

2.2.6. Attempted synthesis of α-benzylpentanamide via Aminal intermediate

Having the enantiomerically pure aminal **21** and α-benzylvaleryl chloride **27** in hand, it was time to combine both pieces together. Acid chloride **27** was added to a solution of amine **21** in THF at room temperature. Unexpectedly, no precipitation was observed even after long period of time. ^{1}H NMR spectrum showed the diacylated diaminocyclohexane **29** in 20% yield with only a small amount of the desired monoacylated product (**28**) formed after a reaction time of 30 minutes.

Scheme 11.



28 (trace) **29** (formed)

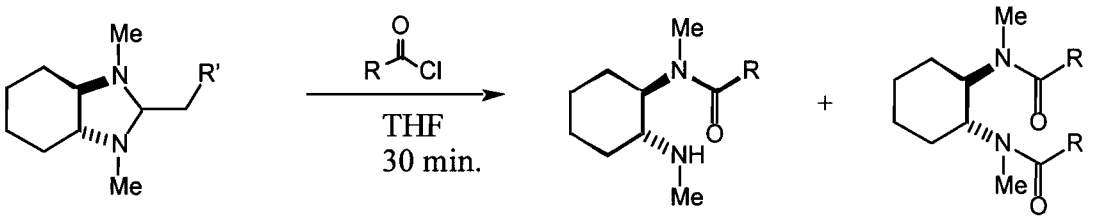
A possible reason for the formation of diacylation products is that the reaction between acid chloride **27** and the aminal may be slower, for the steric effect, than the prior examples utilizing simple acid chlorides. Thus, aminal **21** may be degraded to the diamine by trace of acid generated during the reaction. The latter species will undergo rapid diacylation, forming product **29**.

In order to study the steric effect, two reactions were carried out by using acid chlorides bearing α-substituent(s) such as isobutyryl and pivaloyl chlorides. As anticipated, with the methyl groups at the α-position, the reactions seemed to proceed very slowly to give

traces of the diacylated products after 30 minutes while no sign of the monoacylation product was observed.

This problem could be circumvented by selective monobenzylation followed by acylation of the corresponding *N*-benzyl-*N,N'*-dimethyl-1,2-diaminocyclohexane and final cleavage of the benzyl group.

Scheme 12. Studies of steric effect on aminal alkylation reaction

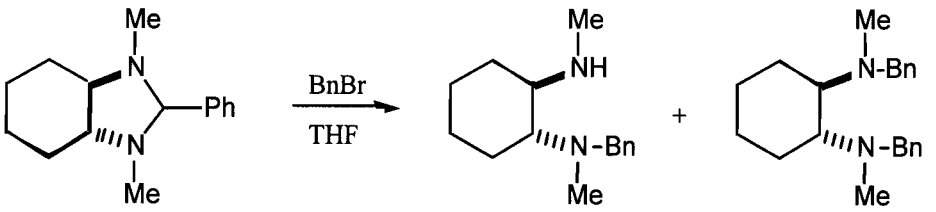


R=-$CH(CH_3)_2$ = -$C(CH_3)_3$ not formed trace

2.2.7. Synthesis of α-benzylpentanamide via *N*-benzyl-*N,N'*-dimethyldiamine

Treatment of *(R,R)*-aminal **21** with benzyl bromide at room temperature for 30 min resulted two products at a ratio of 3.8:1 (*N*-benzylation **30** versus *N,N'*-dibenzylation **31**, scheme 13), calculated by ^{1}H NMR. The two benzylic protons of the products **30** were displayed as two doublets with a coupling constant of 13.3 Hz at 3.42 and 3.62 ppm and **31** (J = 13.3 Hz) at 3.65 and 3.73 ppm respectively.

Scheme 13. Monobenzylation of aminal

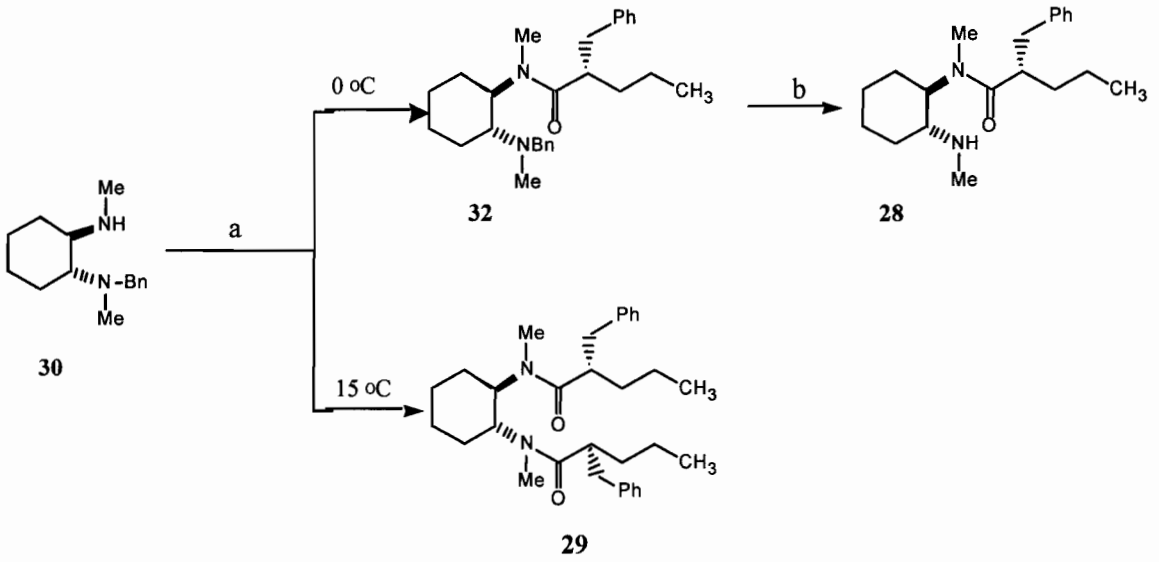


21 **30** **31**

The best yield of the mono *N*-benzylated product (81.6%) was obtained when a mixture of aminal and benzyl bromide was stirred for exactly 30 min (no more, no less) in THF at room temperature. After 30 min the crude product was extracted (1 N NaOH /CH_2Cl_2), dried and concentrated, then re-dissolved in CH_2Cl_2 for another acid/base workup. Unfortunately, isolation of a single *N*-benzylation compound was impossible. Therefore, the crude mixture was used for further reaction to delay the purification in the next step or so. Recently, Professor Gleason has obtained a clean mono *N*-benzylated product of *N,N'*-dimethyl-1,2-diaminocyclohexane by a simple reduction of benzaldehyde aminal **21** with sodium borohydride in ethanol.[17]

The crude mixture of the *N*-benzylated product obtained previously was treated with *(S)*-α-benzylvaleryl chloride in the presence of 1.2 equiv. of triethylamine in CH_2Cl_2. The reaction was complete in 5 minutes at 0 °C to yield 98.3% of *N*-benzyl-α-benzyl pentanamide **32** after purification by column chromatography (scheme 14). Temperature is an important factor in the reaction yield. When the same reaction was carried out at 15 °C after 1 h, mainly the di-acylated product **29** was isolated.

Scheme 14.



Reagents. (a) **27**, Et_3N, CH_2Cl_2; (b) Pd/C, HCO_2H-MeOH.

It was assumed that at high temperature the tertiary amine nitrogen is basic enough to undergo nucleophilic attack on another α-benzylvaleryl chloride molecule, which will result in the formation of an unstable tetrahedral quaternary amide intermediate as illustrated in figure 12. In result, the nitrogen-benzyl N-C bond will be readily cleaved by the attack of chloride anions on the benzylic carbon, to generate a second tertiary amide.

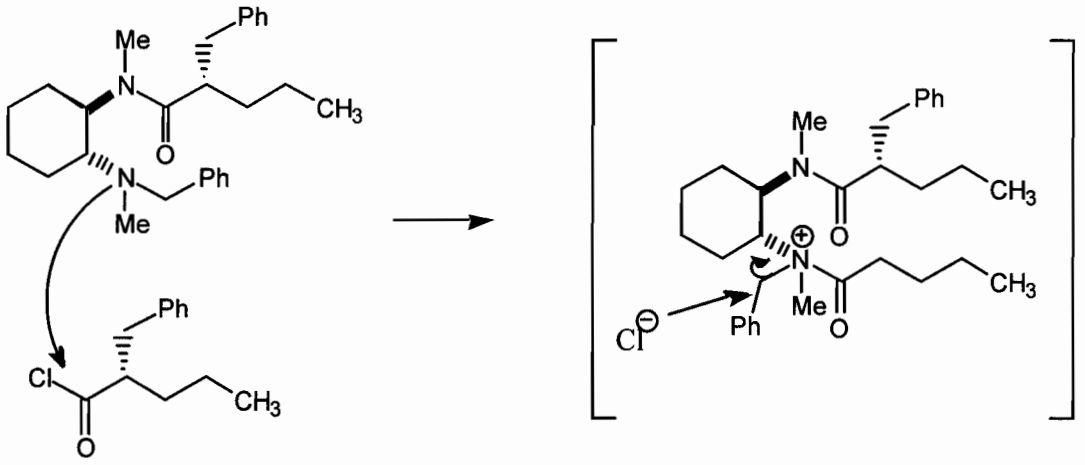


Figure 12. Proposed mechanism of diacylation with α-benzylvaleryl chloride

Interestingly, ^{1}H NMR of the *N*-benzyl-α-benzyl pentanamide **32** displayed only two singlet peaks for the two *N*-methyl groups as one single rotamer. Also, the two *N*-benzylic protons showed up as a singlet at 3.52 ppm.

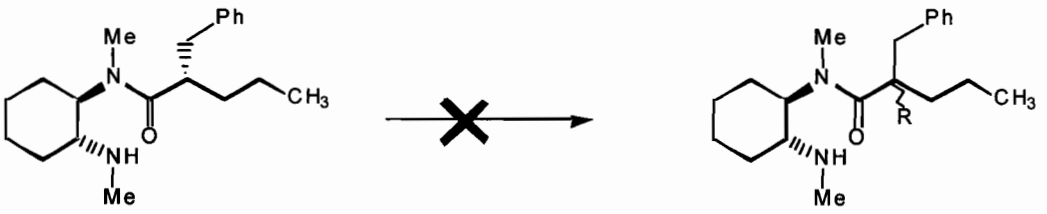
Hydrogenolysis of compound **32** was performed according to a known procedure in the literature.[18] Treatment with a catalytic amount of formic acid (4.4% in methanol) led to a complete removal of the benzyl *N*-protecting group after 45 h at room temperature (followed by TLC) and pentanamide **28** was isolated in 80.4% yield from acid/base workup. Reduction using normal condition (H_2-Pd/C, MeOH and pressure) was unsuccessful. The analytical data of the reduced product **28** indicated a close agreement between the single diastereomer **28** and the one obtained previously as a mixture of diastereomers **18** from the racemic 1,2-diaminocyclohexane. Having in hand the desired

α-substituted pentanamide, we wished to study the second alkylation chemistry via the technique of directed enolization.

2.2.8. Studies of the second alkylation via directed enolization

As we have seen previously of the first alkylation, pentanamide **18** underwent α-benzylation with a variable selectivity when hexamethyldisilazides were employed as bases. However, we could not explain this varied selectivity. Hopefully the second alkylation would help to do so since only one proton of amide remains to get abstracted. In this case, it was hoped that deprotonation would occur at one specific face through chelation of the base directed by the secondary amine of the auxiliary. The amide would be forced to adopt a conformation in which the single acidic proton would place itself face to the basic site. However, the α-proton of the substituted amide is expected to be more difficult to abstract than the ones of the unsubstituted amide on account of steric effect and maybe electronic effect as well. Hence the reactions would involve the use of stronger bases for this purpose.

Attempted alkylation of the α-benzylpentanamide **28** employing a variety of bases such as LDA, KHMDS and different additives (LiCl, HMPA) with methyl iodide failed to give the α,α-disubstituted amide. The starting material was recovered when KHMDS or LDA was used in the absence of coordinating agents. In contrast, in the presence of HMPA with LDA, alkylation took place at the amine as observed by ^{1}H NMR.



Moreover, reaction quenching with trimethylsilylchloride gave only trace of *N*-silylation plus the starting amide. Deuterium incorporation using D_2O also failed and only the

starting amide was recovered, which revealed once again unsuccessful enolization. Reaction with *n*-BuLi resulted in a cleavage of amide bond, which arose from nuclephilic addition of *n*-BuLi onto the amide's carbonyl. Reaction with *sec*-BuLi followed by TMSCl quenching gave rise to *N*-silylation as displayed by ^{1}H NMR. The starting material was cleanly recuperated upon hydrolysis (CH_3COCl/MeOH) and acid/base workup of this latter reaction. The result was even more complicated to interpret with the use of a more reactive and stronger base such as *tert*-BuLi.

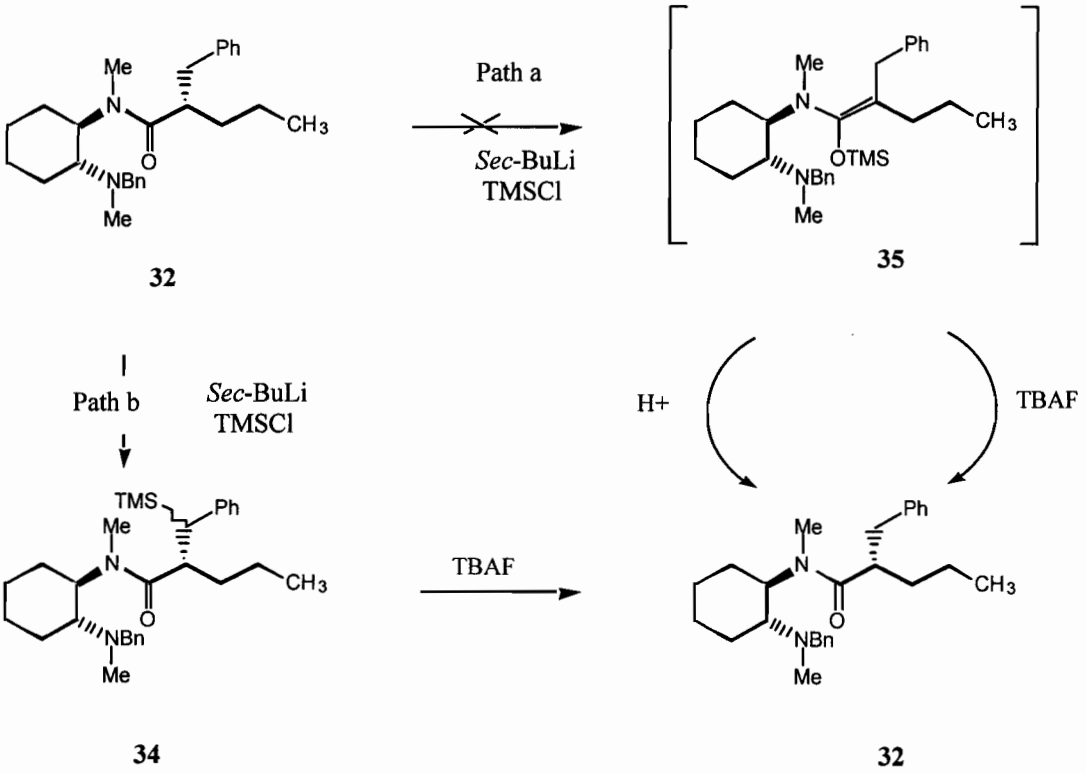
In conclusion, enolization of the substituted amide seemed to be quite problematic presumably owing to some steric (α-substituent) effects, which decreased the acidity of the remaining α-proton. As we have seen, the reactions did not proceed when a weak and bulky base such as KHMDS was employed. The second deprotonation would indeed require a stronger base such as LDA or BuLi. Now since reactions with LDA and *sec*-BuLi kinetically favor the alkylation at the nitrogen atom, a possible solution to this problem would be to protect the secondary amine. Benzyl group was chosen for this purpose because it was already attached to the molecule at one synthetic step less (compound **32**). At this point, it was anticipated that the benzyl group would not only act as amine protector but also be included as a part of the chiral auxiliary. Thus the selectivity of the alkylation reaction will be once again looked at after the introduction of the benzyl group.

2.2.9. Enolization of *N,N'*-dimethyl-*N'*-benzyl-1,2-diaminocyclohexane (32)

The procedures described above were repeated for enolization of the new system. Treatment of amide **32** with LDA followed by deuterium quenching in the presence of HMPA unfortunately gave back a clean starting material indicating the lack of enolate formation during the reaction. Likewise, treatment of amide **32** with *t*-BuLi, followed by TMSCl quenching, then hydrolysis (CH_3COCl/MeOH) of the crude reaction yielded once again the starting amide with no epimerization at the stereogenic center at the α-position. Surprisingly, when the same reaction was repeated with *sec*-BuLi, the colorless solution of amide **32** in THF at –78 °C turned to bright yellow upon addition of the base and rapidly to dark orange within minutes. The bright yellowish color faded spontaneously

upon addition of an excess amount of TMSCl. Detailed spectroscopic analysis as well as experimental observation determined that the silylation occurred at the β position (scheme 15, path b). ^{1}H NMR of the silylation reaction showed a loss of two protons at 2.95 ppm, assumed to be one of the *C*-benzylic protons and the α-proton, while a new signal, integrated for one proton, appeared as a ddd at 3.28 ppm. To better interprete these analytical results, the crude mixture was subjected to the TMS cleavage. Assuming that the intermediate were silylenolether **35** (scheme 15, path a), simple hydrolysis in acidic condition (CH_3COCl/MeOH) would easily cleave off the silyl group to give back the starting amide **32**. Unexpectedly, no reaction occurred upon treatment with HCl in MeOH after 14 h at room temperature.

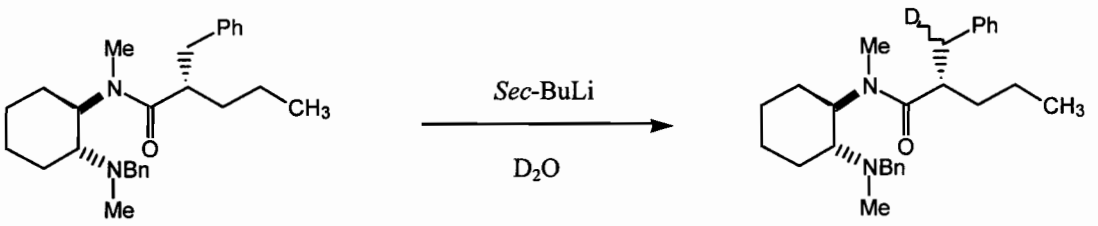
Scheme 15



However, when more harsh conditions were employed (tetrabutylammonium fluoride (TBAF), a reagent known for C-Si bond cleavage), the TMS group was removed within 1.25 h. This evidence hinted the structure of the silylation, which occurred at the benzylic

position that gave the intermediate **34** (scheme 15, path b). It has been also hypothesized that, for steric reason, the proton α would be less likely to get abstracted. As a matter of fact the deprotonation would preferentially take place at the benzylic carbon which contains two relatively acidic protons.

Scheme 16



32 **33**

To confirm the above hypothesis, the same enolization condition was performed but this time the reaction was quenched with deuterium oxide (scheme 16). ^{1}H NMR of the isolated material showed one proton missing at the region of 2.95 ppm when compared to the spectrum of the starting material. It was critical to assign an exact ^{1}H NMR chemical shift to each of the benzylic proton as well as the α-proton of the amide. More detailed spectroscopic data are important in understanding and probing the proton involved. A COSY spectrum of the starting amide **32** showed a strong coupling between the two overlapping protons at 2.95 ppm and at 2.70 ppm and a second interaction between the proton at 2.95 ppm and the aliphatic protons at around 1.4 and 1.8 ppm (see spectrum # 1). The latter coupling was presumed to be the interaction between the α-proton and the protons of the aliphatic carbon chain. According to the experiment on HMQC (correlation between ^{1}H NMR and ^{13}C NMR) one of the protons at 2.95 ppm belongs to a carbon at 44 ppm, assigned as the α-carbon, whereas the other proton at the same chemical shift and the one at 2.70 ppm correlate to the benzylic carbon at 40 ppm (see spectrum # 2). When one of the protons was replaced by deuterium, only the carbon at 40 ppm (benzylic carbon) was affected and appeared as a triplet for carbon-deterium coupling on the ^{13}C NMR. Whereas, the α-carbon at 44 ppm stayed intact. DEPT experiment once again

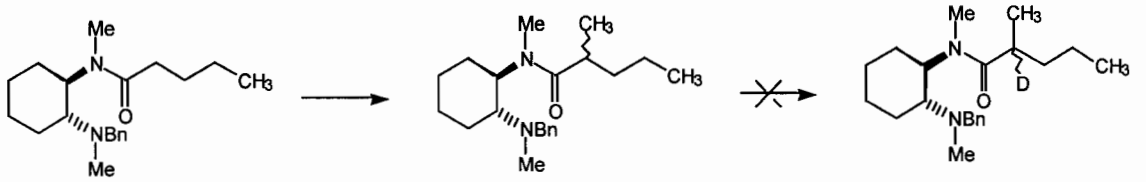
showed clear evidence of the deuteration at the benzylic carbon. The triplet signal of the benzylic carbon pointed toward the positive plane (of Y axis) just like other tertiary CH's signals, which was consistent with the loss of one proton at that position (spectrum # 3). Irradiation of the signal at 2.95 ppm (α-proton) was found to affect the one at 2.70 ppm (benzylic protons to a singlet) whereas irradiation at 2.70 ppm did not significantly disturb the multiplet at 2.95 ppm. On the other hand, M + H value obtained from HRMS was consistent with the calculated mass of the deuterated compound **33** (deuterium calculated as ^{2}H isotope). All the above information has confirmed the reactivity of the compound possessing acidic β-protons towards *sec*-BuLi. Beak et al. has communicated similar findings for the synthesis of β-substituted secondary carboxamides where secondary amides served as chiral auxiliaries. In Beak's case, the loss of acidity was due to the deprotonation of the secondary amide. In other words, the equivalent lithiated secondary amides have been found to provide complex-induced proximity effects, which rendered the α-proton less acidic.[14a-c] Consequently, alkylation occurred at the benzylic β-carbon, which resulted as a β-substituted product[14a]. Similar results were obtained when tertiary amides, such as *N,N*-diisopropyl, *N*-Boc-*N*-Aryl amides that contain acidic β protons such as allyl or benzyl substituents, were reacted with butyllithium.[14c]

To avoid the presence of an acidic proton at the β position and in order to study more specifically the deprotonation at the α-carbon, one methyl group was introduced to replace benzyl and the same experiments were repeated.

N-Benzyl-α-methyl pentanamide **36** was easily obtained in 82.7% with 2:1 diastereomeric ratio by treating *N*-benzylpentanamide **19** (obtained from *N*-benzylation of amide **17**) with *sec*-BuLi and methyl iodide in THF. The reaction time was much shorter (30 min at –78 °C and 30 min at 23 °C) than the time required for alkylation with KHMDS (6 h). Both diastereomers were not separable, thus the purified as diastereomeric mixture was used for alkylation reactions. Interestingly, ^{1}H NMR displayed the two benzylic protons as a doublet of the doublet for J = 13.1 Hz at 3.2-3.5 ppm. Whereas, the benzylic protons of the related *N*-Benzyl-α-benzyl pentanamide **32** showed up as a simple singlet. *N*-Benzyl-α-methyl pentanamide **36** was reacted with *sec*-BuLi according to the procedure already described for amide **32**. Reaction quenching with D_2O gave back unmodified

starting material (**36**), as analyzed by ^{1}H NMR. The addition of a coordinating agent such as *N,N,N',N'*-tetramethylethylenediamine did not seem to improve the reaction outcome. In contrast, only the starting amide plus some trace of the decomposition product (resulted from amide bond cleavage) were recuperated after D_2O quenching. Significant decomposition was observed when a more reactive base such as *n*-butylpotassium (*n*-BuK) was used.

Scheme 17



19 **36**

Reagents. (a) *sec*-BuLi, MeI; (b) *sec*-BuLi, D_2O

2.3. Conclusion of the second approach

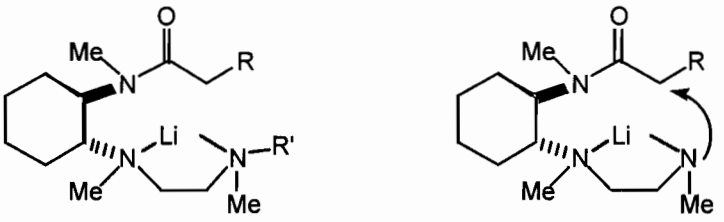
According to the results obtained so far, it is justified to say that the directed enolization technique is far from being developed. However, the first alkylation of pentanamide of *trans*-N,N'-dimethyl-1,2-diaminocyclohexane using HMDS bases was successfully developped. In addition, two important points have been rationalized:

1. It appeared to be impossible for the second enolization to occur even with strong base such as *sec*-BuLi. The secondary amine (*N*-H) as well as the tertiary amine (*N*-Bn) of the chiral auxiliary did not seem to contribute in the deprotonation process, probably owing to the long internal distance between the directing amine and the α-proton. In other words, for some conformational reason, the α-proton remained unreachable even though there is accessibility for dialkylamide base to coordinate to the amino groups.
2. Clean deprotonation occurred at the benzylic position.

These interesting results have somewhat helped to shed light on new synthetic strategies that will be the subject of future work.

2.4. Extension of the strategies

Firstly, extending the chiral auxiliary by simply adding two carbon unit chain possessing amine functionality would solve the first problem. The diamine **37** is generated from alkylation of the secondary amine with an aminoethylene unit.



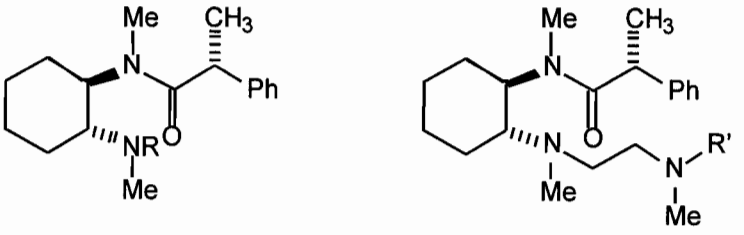
R'=Me, H

Figure 13. Extension of the chiral auxiliaries

The two amino groups, inserted in between by a two-carbon unit, resemble a bidentate ligand. For once the secondary amine got deprotonated, the resulting lithium amide (or an alternative tertiary amine) would internally coordinate to the tertiary amine as illustrated by figure 13. The resulting extended intramolecular chelate structure is expected to be able to reach the α-proton thus allow the intramolecular deprotonation of the amide. In addition, the carbon chain should function as a stereodirecting group that would force enolate alkylation to occur at the face opposite to the ethylenediamine unit.

Another strategy would be to consider a new amide system that possesses enolizable protons located at the α-carbon. By simply replacing the aliphatic four-carbon chain by a benzyl group, the enolization of the amide would occur at the α-carbon of amides in a faster rate due to the π-system of the benzene ring which allows α-carbanion stabilization (figure 13). Even though it is no more considered as a general solution for the synthesis

quaternary carbon center, the latter system would at least allow studying the model reaction of "directed enolization" as well as the selectivity associated.



R = Me, Benzyl R' = Me, H

Figure 14. Amide possessing enolizable benzylic proton

Conclusion

Examples of asymmetric synthesis of quaternary carbon centers are abundant. However, the majority of the methodologies are conceived for some specific cases. In this study, we have drawn our attention to develop a general solution using two enolization techniques for the construction of the quaternary carbon centers. The C_2-symmetry chiral auxiliaries were employed as device for this purpose. In the first part of our synthesis, the technique of enolization employing classical reduction chemistry has not been profoundly explored due to the difficulties connected to the low reactivity of glycolate lactones toward reducing agents and also to the unsuccessful alkylation reactions (decomposition of enolate). In contrast, the second investigation has brought us hope for success. However, the use of diamines as chiral auxiliaries presented a great disadvantage particularly at the purification stage. The first alkylation of amide has been explored and results have been successfully obtained when hexamethyldisilazides bases were used. Nevertheless, most of the reactions were not optimized. The second alkylation had appeared to be quite problematic. With *sec*-BuLi, alkylation occurred at the β position resulted from abstraction of the benzylic proton.

The future works will focus on the optimization of reaction conditions for better yields. The absolute stereochemistry of the major diastereomer obtained from the first alkylations also needs to be determined, which would help us to rationalize the resulting selectivity. Finally, the extended chiral auxiliary depicted in figure 12 should also be investigated, followed by the exploration of the key reactions in order to study the selectivity of the method. It would also be interesting to explore the alternative strategy for a system in which benzyl group replaces the aliphatic chain of amide (figure 13). Even though it turned out not to be a general solution, this idea would at least allow us to study directed enolization, a key synthesis process.

Experimental Section

General Procedure. Tetrahydrofuran and ether were distilled under nitrogen from sodium-benzophenone ketyl. Dichloromethane, diisopropylamine, chlorotrimethylsilane, hexanes, DMPU, HMPA and toluene were distilled under nitrogen from calcium hydride. Lithium chloride was flame-dried under vacuum immediately prior to use. Benzyl bromide and iodomethane were filtered through activated basic alumina (Brockman Grade 1) immediately prior to use. The molarity of *n*-butyllithium was determined by titration against 2,2'-bipyridyl as an indicator (average of three determinations)[20]. Enantiopure *(R,R)*-1,2-diaminocyclohexane was obtained from chemical resolution according to the literature procedure[15]. *(R,R)*-1,2-Diaminocyclohexane-*N,N'*-diethyl dicarbamate **11** and *(R,R)-N,N'*-Dimethyl-1,2-diaminocyclohexane **12** were prepared according the literature procedure[13]. All non-aqueous reactions were performed in flame-dried round bottom flasks fitted with rubber septa under a positive pressure of argon. All distilled solvents and reaction solutions were transferred via syringe.

Instrumentation. Melting points were recorded on a Buchi apparatus and are not corrected. IR spectra were recorded on Analect AQS-18 FT-IR and IFS-48 using NaCl cell in CH_2Cl_2. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL 270 MHz in the deuterated solvents using tetramethylsilane as internal reference. COSY and HMCQ NMR spectra were recorded on a Utility 500 MHz. Mass spectra were recorded on Kratos MS-25 RFA and HRMS ZAB 2F HS. Elemental analyses were performed by QTI Laboratories, New Jersey, USA. Flash chromatography was performed on 460-520 m^2/g silica gel (60 Geduran 35-75 μm). Chiral capillary gas chromatography (GC) analyses was carried out using Cl-Chirasil-Dex CB column under isothermal conditions, with a column head pressure of 14 psi. Diastereomeric ratio was determined on Chrompack Crosslinked 5% Ph-Me Siloxane normal column, with a column head pressure of 14 psi. Thin-layer chromatography plates (glass plates) were visualized by exposure to ultraviolet light, iodine and/or by immersion in a staining solution (ninhydrin, permanganate) followed by heating on a heat gun.

1-Bromoacetylester of *trans*-1,2-cyclohexanediol (4)

A mixture of racemic *trans*-cyclohexane-1,2-diol (5.0 g, 42.9 mmol, 1 equiv) and bis(tributyltin)oxide (19.2 g, 32.1 mmol, 0.75 equiv) in benzene (200 mL) was heated at reflux overnight under Dean-Stark condition in order to remove water formed during the reaction. After cooling to room temperature, the reaction mixture was concentrated and diluted with CH_2Cl_2 (180 mL). The reaction flask was cooled at 0 °C in an ice bath and bromoacetyl bromide (4.5 mL, 51.5 mmol, 1.2 equiv) was added. The reaction was stirred for 20 min at 0 °C and 1 h at to 21 °C, and quenched with a 1 N HCl solution (100 mL). The product was extracted with CH_2Cl_2 (3 x 100 mL); the organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Flash column chromatography (4:1-3:1 Hexanes/EtOAc) of the crude product yielded 8.96 g (88%) of bromoester (**4**) as a clear yellowish oil. ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 4.65 (m, 1H), 3.86 (d, 2H, *J*=2.24), 3.61 (m, 1H), 2.06 (m, 3H), 1.61-1.75 (m , 3H), 1.34 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5 , 80.2, 72.5, 33.0, 29.7, 26.3, 23.83, 23.75; FTIR (CH_2Cl_2, cm^{-1}) 3313 (s, OH), 1750 (s, C=O); LRMS calcd for $C_8H_{15}O_3$ (M + H) 237.0, found 237.0; Anal. Calcd for $C_8H_{13}BrO_3$: C, 40.53; H, 5.53. Found: C, 41.02; H, 5.68.

Glycolate lactone of *trans*-1,2-cyclohexane-diol (5)

To a solution of bromoacetylester (**4**) (2.3 g, 9.7 mmol, 1 equiv) in tetrahydrofuran at 0 °C was added sodium hydride (60% in mineral oil, 450 mg, 11 mmol, 1.1 equiv). The suspension was stirred at room temperature for 2.5 h and heated at reflux overnight. The solvent was removed and the crude mixture was treated with 1 N HCl (25 mL) and the product was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Flash column chromatography (4:1 hexanes/EtOAc) gave 0.88 g (58%) of glycolate lactone (**5**). ^{1}H NMR ($CDCl_3$) (*J* in hertz) δ 4.26-4.48 (dd, 2H, 17.8), 4.09 (m , 1H), 3.29 (m, 1H), 2.03 (m, 2H), 1.74 (m, 2H), 1.2-1.4 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 167.6, 82.0, 76.1, 66.2, 30.3, 29.7, 23.7, 23.4; Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.24; H, 7.68.

Glycolate-*tert*-butyldimethylsilylketene acetal (7)

A solution of *n*-butyllithium in hexanes (0.35 mmol, 1.1 equiv) was added to a cooled (0 °C) solution of diisopropylamine (0.35 mmol, 1.1 equiv) in tetrahydrofun (0.3 mL). The mixture was stirred for 3 min at 0 °C, and cooled to -78 °C where upon a solution of glycolate lactone (**5**) (50 mg, 0.32, 1 equiv) in tetrahydrofuran (0.6 mL) was added dropwise via canula. After 20 min -78 °C, a solution of *tert*-butyldimethylsilyl chloride (TBDMSCl, 0.35 mmol, 1.1 equiv) in hexanes was introduced into the reaction mixture, followed by the addition of DMPU freshly distilled (360 μL). The reaction was stirred for an additional 5 min at -78 °C, 45 min at room temperature, and quenched with a saturated sodium bicarbonate solution (2 mL) and diluted with cold hexanes (2 mL). The resulting solution was washed with water (2 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give an oil (complete reaction observed by ^{1}H NMR); ^{1}H NMR ($CDCl_3$) δ 5.74 (s, 1H), 3.61 (m, 1H), 3.30 (m, 1H), 2.10 (m, 2H), 1.76 (m, 2H), 1.30 (m, 4H), 0.93 (s, 9H), 0.18 (s. 6H).

α-(Hydroxybenzyl) glycolate lactone (8)

To a solution of diisopropylamine(76 mmol, 230 μL, 1.08 equiv) in tetrahydrofuran at -78 °C was added a solution of *n*-butyllithium in hexanes (1.76 mmol, 1.08 equiv). The mixture was stirred at -78 °C for 5 min, at 0 °C for 5 min and cooled back to -78 °C where upon DMPU (1.8 mL) was added via syringe, followed by the addition via canula a solution of lactone **5** (254 mg, 1.63 mmol) dissolved in a minimal amount tetrahydrofuran. The reaction mixture was stirred at -78 °C for 7.5 h, at 0 °C for 10 min and quenched with saturated sodium bicarbonate solution (3 mL), and diluted with cold hexanes (3 mL). The resulting two layers were separated; the organic layer was washed with water (2 x 3 mL), dried over anhydrous sodium sulfate and concentrated to give an oil which contains a mixture of four diastereomers of the aldol product **8** obtained after purification on column chromatography (155 mg, 36%). ^{1}H NMR ($CDCl_3$) (J in hertz) **isomer a** δ 7.37 (m, 5H), 5.22 (s, 1H), 4.71 (s, 1H), 4.40 (dd, 1H, J = 17.8), 4.14 (m, 1H), 3.35 (m, 1H), 2.12 (m, 2H), 1.84 (m, 2H), 1.32 (m, 4H); **Isomer b** δ 7.37 (m, 5H), 5.33 (d, 1H, 2.9 Hz), 5.14 (s, 1H), 4.70 (s, 1H), 4.63 (D, 1H, J = 3.2), 4.13 (m, 1H), 3.70 (m,

1H), 3.23 (m, 1H), 3.12 (m, 1H), 1.63-2.08 (m, 2H), 1.06-1.43 (m, 3H); **Isomer c** δ 7.47 (m, 5H), 5.23 (d, 1H, J = 2.7), 4.68 (d, 1H, J = 2.7), 3.92 (m, 1H), 3.43 (m, 1H), 2.05 (m, 2H), 1.80 (m, 2H), 1.30 (m, 4H); **Isomer d** δ 7.44 (m, 5H), 5.70 (d, 1H), 5.50 (d, 1H), 5.15 (d, 1H), 4.65 (m, 1H), 4.10 (m, 1H), 3.55 (m, 1H), 3.35 (m, 1H), 2.95 (m, 1H), 2.65 (m, 1H), 1.80 (m, 2H), 1.0 (m, 2H); ^{13}C NMR ($CDCl_3$) for the mixture of isomers δ 169.9, 140.1, 128.42, 128.32, 128.26, 128.15, 128.06, 127.2, 126.8, 126.6, 82.2, 81.6, 79.8, 75.95, 75.86, 75.0, 73.9, 52.8, 30.1, 29.7, 23.6, 23.3; FTIR (CH_2Cl_2, cm^{-1}) 3417 (m, OH), 1750 (s, C=O); HRMS calcd for $C_{15}H_{19}O_4$ (M + H) 263.12833, found 263.12828.

Reduction of lactone with potassium graphite (ester 9 and lactol 10)

Potassium (120 mg, 2.93 mmol, 2.2 equiv) was added in pieces to graphite (280 mg, 23.4 mmol, 17.6 equiv) prior degassed for 15-20 minutes under argon at 150-160 °C. When the potassium melted, the mixture was vigorously stirred by a magnetic stirring bar, thus yielding the bronze-colored C_8K within 10 minutes. After cooling to temperature and to 0 °C, THF (5 mL) was added, followed by TMSCl (510 µL, 3.99 mmol, 3 equiv) and the solution of lactone (200 mg, 1.33 mmol, 1 equiv) in 5 mL of THF. After stirring for 2 h, the reaction was quenched with saturated ammonium chloride solution (5 mL), and the resulting mixture was passed through a packed celite filter. The layers were separated, the organic layer was washed with 1 N HCl (5 mL x 2), dried and concentrated to give a yellowish oil. Column chromatography (Toluene:ethylacetate, 5:1 to 5:3) of the crude oil yielded a mixture of two isomers (ester **9** and lactol **10**) in a total weight of 6.1-16.3 mg (3-8%).

1-Hydroxy-2-acetate cyclohexan-ester (9)

A mixture of *trans*-cyclohexane-1,2-diol (203 mg, 1.75 mmol) and. bis(tributyltin)oxide (456 µL, 0.91 mmol, 0.52 equiv) in benzene (18 mL) was heated at reflux overnight. A Dean-Stark trap was used in order to remove water formed during the reaction. The solution was cooled to room temperature, concentrated and diluted with CH_2Cl_2 (3.5 mL). The reaction flask was cooled at 0 °C in an ice bath and acetylchloride (150 µL, 2.1 mmol, 1.2 equiv) was added. The reaction was stirred for 20 min at 0 °C and 1 h at room

temperature, quenched with a 1 N HCl solution (10 mL). The product was extracted with CH_2Cl_2 (3 x 10 mL); the organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Flash column chromatography (4:1-3:1 Hexanes/EtOAc) of the crude product yielded 230 mg (84%) of acetate ester (**9**) as a clear yellowish oil. ^{1}H NMR ($CDCl_3$) δ 5.60 (m, 1H), 3.57 (m, 1H), 2.30 (b, 1H), 2.11 (s, 3H), 2.06 (m , 2H), 1.72 (m, 2H), 1.34 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.3, 78.2, 33.0, 29.9, 23.8, 23.7, 21.3; FTIR (CH_2Cl_2, cm^{-1}) 3438 (s, OH), 1750 (s, C=O); Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.34; H, 8.87.

Glycolate lactol of *trans*-1,2-cyclohexane-diol (10)

A solution of glycolate lactone **5** (150 mg, 0.96 mmol, 1 equiv) in toluene (2 mL) was cooled at -78 °C. Di-isobutylaluminiumhydride (1.5 M, 1.2 mmol, 800 µL, 1.25 equiv) was introduced into the reaction flask. No significant change was observed by TLC after the first 10 minutes. After 1 h at –78 °C, EtOAc was added. The solution was kept stirring for an additional 10 min at -78 °C, and slowly brought to room temperature followed by the addition of diethylether (2 mL), toluene (2 mL) and a 0.5 M aqueous solution of potassium-sodium tartrate (2.4 mmol, 4.8 mL, 2.5 equiv). The mixture was vigorously stirred for 2 h at room temperature and two phases were observed. The two layers were separated. The organic layer was washed with water (4 mL) and kept aside after separation. The latter aqueous layer was extracted with diethylether (4 mL x 2). The combined organic layers was dried over anhydrous sodium sulfate and concentrated. Flash chromatography (3/1 hexanes/EtOAc) of the crude mixture yielded 149 mg (98%) of glycolate lactol (**10**) in a mixture of two epimers. ^{1}H NMR ($CDCl_3$) (J in hertz) δ 5.02 (dd, 1H, J = 4.0), 3.92 (dd, 1H, J = 2.7), 3.80 (m, 1H), 3.27 (m, 1H), 3.09 (m, 1H), 2.88 (b, 1H), 1.89 (m, 2H), 1.76 (m, 2H), 1.30 (m, 4H); ^{13}C NMR ($CDCl_3$) (mixture of diastereomers) δ 92.4, 90.2, 80.5, 78.7, 78.3, 71.9, 70.9, 69.9, 30.1, 29.7, 24.3, 24.2, 23.9; FTIR (CH_2Cl_2, cm^{-1}) 3375 (s, OH), disappearance of C=O band at 1750; HRMS calcd for $C_8H_{15}O_3$ (M + H) 159.10212, found 159.10205.

***Trans-N,N'*-Dimethyl-1,2-diaminocyclohexylurea (15)**

To a solution of racemic *trans-N,N'*-dimethyl-1,2-diaminocyclohexane (5.41 g, 38.08 mmol, 1 equiv) in CH_2Cl_2 (72 mL) was added triethylamine (80.0 mmol, 11.4 mL, 2.1 equiv) at room temperature. The solution was cooled at 0°C for 15min and triphosgene (3.76 g, 12.47 mmol, 0.33 equiv) was added portionwise (note: formation of HCl gas). The reaction mixture was stirred at 0 °C for 2 h and quenched by addition of a saturated ammonium chloride solution (30 mL). The product was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were dried over K_2CO_3, filtered and the solvent evaporated to give yellowish oil. Upon drying under high vacuum the product formed a foam. Recrystallization (EtOAc/Hexanes) yielded 60% of urea **15**.

Alternative synthesis: To a homogenous solution of racemic *H*-urea **16** (89.5 mg, 0.64 mmol, 1 equiv) in THF (5 mL) at 0 °C was added NaH (1.60 mmol, 2.5 equiv). After stirring for 25 min, methyl iodide was added dropwise via syringe. The suspension was stirred at 0 °C for 10 min, at room temperature for 5.5 h, and quenched with 1 N HCl (3 mL). The product was extracted with CH_2Cl_2 (3 mL x 2) and the combined organic layers were dried over K_2CO_3, filtered and the solvent evaporated to give a yellowish oil. Upon drying under high vacuum, the product formed foam. Recrystallization (EtOAc/Hexanes) yielded 57% of Me-urea (**15**). ^{1}H NMR($CDCl_3$) δ 2.7 (s, 3H), 2.54-2.60 (m, 1H), 1.98-2.06 (m, 1H), 1.84-1.92 (m, 1H), 1.22-1.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 165.0, 64.0, 29.7, 28.2, 24.4; HRMS calcd for $C_9H_{17}N_2O$ (M + H) 169.13409, found 169.13405.

***Trans*-1,2-diaminocyclohexyl-urea (*H*-urea) (16)**

To a cooled (0 °C) solution of racemic *trans*-1,2-diaminocyclohexane (5.0 g, 43.8 mmol) and triethylamine (131.4 mmol, 18.8 mL, 3 equiv) in CH_2Cl_2 (250 mL) was added triphosgene (4.39 g, 15.59 mmol, 0.33 equiv) in small portions. The mixture was stirred at 0 °C for 1.5 h and at room temperature for 4 h. The reaction was quenched with 1 N HCl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layer was dried over K_2CO_3, filtered and the solvent evaporated to give white foam as the crude product. Recrystallization in EtOAc/Hexanes gave a white powder of H-urea (**16**) (70-73%). Rf 0.41 (1:1 EtOAc/hexanes plus few drops of AcOH); MP 138-141 °C; ^{1}H NMR ($CDCl_3$) δ

165.5, 63.4, 61.1, 29.6, 24.1; FTIR (CH_2Cl_2, cm^{-1}) 3235 (b, m, NH), 1730 (b, s, C=O); HRMS calcd for $C_7H_{13}N_2O$ (M + H) 141.09, found 141.

***Trans-N,N'*-Dimethyl-1,2-diaminocyclohexane pentanamide (17)**

To a -78 °C solution of the racemic *trans-N,N'*-dimethyl-1,2-diaminocyclohexylurea (**15**) (1.75 g, 10.44 mmol, 1 equiv) in THF (55 mL) was added a solution of *n*-butyllithium in hexanes (10.65 mmol, 1.02 equiv) on the inner edge of the reaction flask such that the alkylation solution had cooled before mixing with the reaction mixture. After 1 h stirring at -78 °C, the reaction was warmed to 0 °C and stirred for 5 h. The reaction was quenched with 1 N HCl (35 mL) and washed with CH_2Cl_2 (35 mL). The aqueous layer was treated with 15% NaOH until pH~12, and the product was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over K_2CO_3, filtered and the solvent evaporated to give yellowish oil.

Purification

a) ***Amine hydrochloride salt derivative.*** To MeOH (30 mL) at 0 °C was added an excess of acetylchloride (1 mL). After 15 min stirring at O °C, the solution of the crude product (obtained previously) in MeOH (10 mL) was added via canula. The reaction mixture was stirred at 0 °C for 3 h, then MeOH evaporated. Recrystallization in EtOAc/Hexanes gave the amine-hydrochloride salt as a white powder (1.83 g, 66.7%).

^{1}H NMR ($CDCl_3$) δ 9.30 (s (br), 1H), 9.05 (s (br), 1H), 4.67 (m (br), 1H), 3.32 (m (br), 1H), 3.0 (s, 3H), 2.63 (t, 4H), 2.24-2.38 (m, 2H), 1.55-1.90 (m, 8H), 1.37 (m, 4H), 0.92 (t, 3H); Anal. Calcd for $C_{13}H_{27}N_2OCl$: C, 59.41; H, 10.35; N, 10.65. Found: C, 59.44; H, 10.64; N, 10.65. The salt derivative was treated with 15% NaOH (20 mL) and extracted with CH_2Cl_2 (20 mL x 2). The organic layers were combined, dried over K_2CO_3, filtered and the solvent evaporated to give yellowish oil. Toluene (2-3 mL) using as water chaser was added to the crude oil and the solution concentrated. The oil was dried for overnight under high vacuum to yield 1.49 g (63%) of the pure product (**17**).

b) ***N-Boc Derivative.*** Alternatively, amide **17** could be purified as followed: The crude mixture obtained previously was dissolved in CH_2Cl_2 and treated with Et_3N (2.1 equiv) followed by the addition of di-tert-butyl-dicarbonate (Boc_2O) (1.2 equiv) at room

temperature. Column chromatography of the resulting N-Boc amide afforded the pure material (HRMS calcd for $C_{18}H_{35}N_2O_3$ (M + H) 327.26477, found 327.26472).

Cleavage of Boc group was performed by treating the N-Boc amide with trifluoroacetic acid (TFA) at room temperature for 3 h to give back the starting amide in a pure form. ^{1}H NMR (2:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) δ 4.30 (m(br), 1H), 3.44 (m, 1H), 2.86* (s, 3H), 2.78 (s, 3H), 2.44* (m, 3H), 2.36 (m, 3H), 2.1-2.26 (m, 1H), 1.5-1.9 (m (br), 7H), 1.0-1.5 (m, 5H), 0.92 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 61.3, 59.6, 58.7, 33.9, 33.3, 33.0, 31.4, 31.0, 29.7, 29.5, 29.1, 28.0, 27.5, 27.2, 26.6, 25.5, 25.3, 25.0, 24.3, 22.6; FTIR (CH_2Cl_2, cm^{-1}) 3450 (b, w, RNH), 1625 (s, C=O); HRMS calcd for $C_{13}H_{27}N_2O$ (M + H) 227.20111, found 227.21241.

Alkylation procedure of *trans-N,N'*-Dimethyl-1,2-diaminocyclohexane-pentanamide (17); Synthesis of α-benzylpentanamide (18)

To a solution of potassium hexamethyldisilylazide in toluene (4.31 mL, 1.1 equiv) and THF (6 mL) at -78 °C, was added a -78 °C racemic pentanamide **17** (450 mg, 1.99 mmol, 1 equiv) solution in THF (6 mL) via canula. The reaction turned bright yellowish, indicating enolate formation. The mixture was stirred at -78 °C for 20 min, at 0 °C for 20 min and benzyl bromide added dropwise via syringe. After 6 h stirring at -78 °C the reaction was quenched with a 1 N HCl (10 mL) solution. The solution was poured in to a separatory funnel flask and EtOAc (10 mL) added. The aqueous layer was separated and treated with 15% NaOH until pH~12. The alkylated product was extracted from aqueous phase using CH_2Cl_2 (2 x 15 mL). Organic layers were combined, dried over K_2CO_3, filtered and concentrated to give a yellowish oil.

***Purification:* *N*-Boc derivative**: The solution of the crude product and triethylamine (4.09 mmol, 2.06 equiv) in CH_2Cl_2 (16 mL) was cooled and stirred at 0 °C for 15 min and di-tert-butyl-dicarbonate (651 mg, 2.99 mmol, 1.5 equiv) was added via syringe. The reaction was stirred for 2 h 15 at 0 °C and then overnight at room temperature, and quenched with a saturated solution of ammonium chloride (10 mL). The organic layer was separated and kept aside; the aqueous layer was washed once again with CH_2Cl_2 (10 mL). The organic layers were combined, dried over K_2CO_3, filtered and concentrated to give

yellowish oil. Column chromatography on silica gel using Hexanes/EtOAc (3:1) provided 630 mg (1.51 mmol, 76%) of the pure *N*-Boc-α-benzylpentanamide. Rf 0.52 (Hexanes/EtOAc 3:1); ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 5H), 4.63 (b, 1H), 4.12 (m, 2H), 2.88 (b, 2H), 2.85* (s, 1H), 2.66 (b, 1H), 2.64* (s, 1H), 2.47 (s, 2H), 2.06 (s, 1H), 1.72 (b, 4H), 1.41 (s, 5H), 1.38 (s, 4H), 1.26 (m, 2H), 0.86 (m, 3H); ^{13}C NMR δ 175.4, 156.2, 140.1, 129.0, 128.3, 128.2, 126.1, 79.1, 54.1*, 54.0, 52.6*, 52.1, 44.2, 43.9*, 39.8, 38.8*, 35.6, 34.3*, 29.74, 29.65, 29.1, 28.4, 25.3, 25.0*, 20.7, 20.6*, 14.3*, 14.2; HRMS calcd for $C_{25}H_{40}N_2O_3$ (M + H) 417.31172, found 417.31154. Cleavage of the Boc group using TFA (3.5 mL) in CH_2Cl_2 (3.5 mL) at room temperature for 3 h gave back to the clean material **18** (75% for overall purification process, de ratio 1.5:1). ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 5H), 4.28 (b, 1H), 3.46 (m, 1H), 3.06 (m, 1H), 2.91 (m, 1H), 2.74* (s, 1H), 2.72 (m, 1H), 2.48* (s, 2H), 2.36 (s, 2H), 2.15 (s, 1H), 2.05 (m, 1H), 1.8 (m, 3H), 1.1-1.45 (m, 6H), 0.88 (t, 3H); ^{13}C NMR ($CDCl_3$) δ176.5, 175.9, 175.8, 175.77, 140.4, 140.3, 140.2, 129.3, 129.0, 128.96, 128.4, 128.3, 128.2, 126.1, 126.0, 61.4, 61.2, 59.5, 59.2, 58.6, 56.0, 44.7, 44.5, 43.9, 43.6, 39.9, 39.8, 39.0, 36.4, 36.0, 35.7, 35.1, 34.1, 34.0, 33.2, 33.0, 31.5, 31.3, 31.0, 30.4, 29.4, 29.1, 28.6, 27.2, 27.0, 25.6, 25.3, 24.9, 24.6, 24.2, 20.7, 20.6, 14.4, 14.3, 14.2; FTIR (CH_2Cl_2, cm^{-1}) 3350 (b, w, NH), 2938 (s, aromatic CH), 1625 (s, C=O); HRMS calcd for $C_{20}H_{33}N_2O$ (M + H) 317.25929, found 317.25917. Capillary GC Analysis of the *N*-acetate derivative of **18** (obtained from **18** + pyridine + DMAP + acetic anhydride, room temperature, 3 h) showed a diastereomer ratio of 1.5:1.

General procedure for the formation of *Trans-N,N'*-Dimethyl-1,2-diaminocyclohexylaminal (20-21)

To a mixture of *trans-N,N'*-dimethyl-1,2-diaminocyclohexane (150 mg, 1.06 mmol, 1 equiv) in ether (3 mL) in presence of activated 4 Å molecular sieve was added aldehyde (PhCHO, $(CH_3)_2CHCHO$) (1 equiv). The reaction was complete within 3 h at room temperature. The molecular sieve was removed by filtration and the filtrate was dried over K_2CO_3 and concentrated. No further purification was required. **Isobutyraldehyde-aminal (20)** ^{1}H NMR ($CDCl_3$) δ2.74 (d, 1H), 2.44-2.56 (m, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 1.89-2.60 (m, 3H), 1.70-1.83 (m, 3H), 1.02-1.42 (m, 3H), 0.95 (t, 6H); ^{13}C NMR ($CDCl_3$) δ

96.4, 67.0, 66.3, 41.0, 39.6, 32.5, 29.8, 27.0, 25.1, 24.2, 19.6, 17.7; FTIR (CH_2Cl_2, cm^{-1}) 2775 (s, aliphatic CH); HRMS calcd for $C_{12}H_{24}N_2$ (M + H) 197.20177, found 197.20173.

Benzaldehyde-aminal (21) ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H), 4.24 (s, 1H), 2.50 (m, 1H), 2.21 (s, 3H), 2.06 (m, 1H), 1.93 (s, 3H), 1.83 (m (br), 2H), 1.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 140.1, 129.5, 128.1, 128.0, 90.0, 77.6, 77.1, 76.6, 69.5, 68.5, 37.6, 35.8, 29.1, 24.6, 24.5; FTIR (CH_2Cl_2, cm^{-1}) 2875 (s, aromatic CH), HRMS calcd for $C_{15}H_{23}N_2$ (M + H) 231.18612, found 231.18620.

General procedure for the formation of *Trans-N,N'*-Dimethyl- 1,2-diaminocyclohexane Amides (22-23)

Acylchlorides (1.05 equiv) were slowly added to solutions of aminal (**21** or **22**) (1 equiv) in THF at room temperature. Prompt precipitation was observed when unsubstituted acid chlorides were used (in ~5 min). After an additional 10 min stirring, THF was evaporated and the crude solid was recrystallized (EtOAc/Hexanes) to give a white power.

Acetamide (22) 76%; MP 151-151 °C; ^1H NMR ($CDCl_3$) δ 9.41 (s (br), 1H), 8.99 (s (br), 1H), 4.66 (m, 1H), 3.33 (m, 1H), 3.00 (s, 3H), 2.66 (s, 3H), 2.22 (s, 4H), 1.84 (q, 3H), 1.64 (q, 2H), 1.37 (q, 2H); ^{13}C NMR δ 173.3, 56.8, 28.8, 28.3, 26.7, 24.4, 24.0, 23.3; FTIR (CH_2Cl_2, cm^{-1}) 2750 (b, s, Me$\underline{NH_2}$Cl), 1625 (m, C=O); Anal. Calcd for $C_{10}H_{21}N_2OCl$: C, 54.41; H, 9.59; N, 12.69. Found: C, 54.34; H, 9.47; N, 12.36.

Propionamide (23) 74.8%; MP 135-136 °C; ^1H NMR ($CDCl_3$) δ9.35 (s (br), 1H), 8.95 (s (br), 1H), 4.65 (m (br), 1H), 3.30 (m (br), 1H), 2.97 (s, 3H), 2.64 (m, 4H), 2.30 (m, 2H), 1.79 (m, 3H), 1.61 (m, 2H), 1.31 (m, 2H), 1.11 (t, 3H); ^{13}C NMR δ176.2, 76.6, 56.9, 29.0, 27.8, 24.6, 24.1, 9.0; FTIR (CH_2Cl_2, cm^{-1}) 2935 (s, Me$\underline{NH_2}$Cl), 1625 (m, C=O);
Anal. Calcd for $C_{11}H_{23}N_2OCl$: C, 56.27; H, 9.87; N, 11.93. Found: C, 56.24; H, 9.67; N, 11.68.

Synthesis of *(-)*-Pseudoephedrinepentanamide (24)

A mixture of *(-)*-pseudoephedrine (5.0 g, 51.22 mmol, 1 equiv), Et_3N (51.22 mmol, 1.3 equiv) in THF (75 mL) was cooled at 0 °C and a solution of valerylchloride (4.13 mL, 34.83 mmol, 1.15 equiv) in THF (25 mL) was added via canula over a period of 5 min.

The reaction was complete after 10 min (followed by TLC) at 0 °C. After stirring for an additional 15 min, excess of acylchloride was quenched by addition of water (5 mL). The product mixture was partitioned between ehtyl acetate (100 mL) and brine (10 mL) and the organic layer was separated and extracted with brine (2 x 10 mL). The organic layers were dried over Na_2SO_4 and concentrated. Column chromatography on silica gel (3/2-3/3 Hexanes/EtOAc) provided 92-95% of the desired product. ^{1}H NMR ($CDCl_3$) δ (ratio of ratamers 3.5:1*), 7.31 (m, 5H), 4.4*-5.55 (t, 1H), 3.97 (m, 1H), 2.87* (s, 1H), 2.82 (s, 3H), 2.35* (ddd, 1H), 2.24 (ddd, 2H), 1.55 (qt, 2H), 1.30 (m, 2H), 1.06 (d, 3H), 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 175.7, 174.5*, 142.6, 141.5*, 129.0*, 128.4, 127.6, 127.0*, 126.4, 75.5, 60.0, 58.8, 58.4, 34.1, 33.5, 33.1, 27.6*, 27.2, 26.5, 22.7, 22.5, 21.0, 15.4, 14.5, 13.9; FTIR (CH_2Cl_2, cm^{-1}) 3400 (b, s, OH), 2960 (m, aromatic CH), 1625 (s, C=O); HRMS calcd for $C_{15}H_{24}NO_2$ (M + H) 250.18070, found 250.18074.

Alkylation of *(-)*-Pseudoephedrinepentanamide: synthesis of Pseudoephedrine α-benzyl pentanamide (25)

To a flame-dried flask containing dried LiCl (8.90 g, 210 mmol, 7.1 equiv) was added 80 mL of THF, followed by the addition of diisopropylamine (9.32 mL, 66.65 mmol, 2.25 equiv). The suspension was cooled to -78 °C and a solution of *n*-BuLi in hexanes (61.6 mmol, 2.08 equiv) was added dropwise. The resulting mixture was stirred at -78 °C for 5 min, at 0 °C for 5 min and cooled back to -78 °C, and a pseudoephedrine pentanamide (**24**) (7.38 g, 29.62 mmol, 1 equiv) solution in THF (50 mL) was added into the reaction flask via canula. The mixture was stirred at -78 °C for 1h, at 0 °C for 15 min, at room temperature for 5 min, and cooled back to 0 °C. Benzyl bromide (5.32 mL, 44.4 mmol, 1.5 equiv) was then added and the reaction was stirred at 0 °C for 20 min, quenched with a saturated ammonium chloride solution (60 mL) (precipitation observed). EtOAc was added (60 mL) and two layers separated. The organic layer was kept aside; the aqueous phase was washed again with EtOAc (50 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. Upon drying under high vacuum the product formed a white solid. Recrystallization in hot toluene yielded 6.09 g (86%) of white crystals. MP 109-110 °C; ^{1}H NMR ($CDCl_3$) δ7.26 (m, 10H), 4.50 (d, 2H),

3.92 (b, 1H), 2.85 (m, 2H), 2.73 (m, 1H), 2.57 (s, 3H), 1.74 (m, 1H), 1.47 (m, 1H), 1.27 (m, 1H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 177.9, 142.3, 140.0, 129.1, 129.0, 128.5, 128.4, 128.3, 127.0, 126.7, 126.6, 126.5, 44.8, 39.7, 35.4, 20.8, 14.4, 14.3; FTIR (CH_2Cl_2, cm^{-1}) 3375 (b, s, OH), 3000 (s, aromatic CH), 1625 (s, C=O); HRMS calcd for $C_{22}H_{30}NO_2$ (M + H) 240.22765, found 240.22754.

Hydrolysis of pseudoephedrine amide: route to α-benzylvaleric acid (26)

Pseudoephedrine α-benzyl pentanamide (**25**) (5.98 g, 17.63 mmol) obtained from the previous reaction was dissolved in dioxanes (27.5 mL) (partially soluble) and 9 N H_2SO_4 (12.5 mL) was added. The mixture was heated at reflux overnight. The pH of the mixture was adjusted to pH > 10 by the slow addition of 50% (w/w) aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water and CH_2Cl_2 (100 mL). The aqueous layer was separated and washed again with CH_2Cl_2 (100 mL). The aqueous layer was treated with 6 N H_2SO_4 solution until pH < 2 and extracted with CH_2Cl_2 (100 mL x 3). The latter organic extracts were combined and concentrated to a volume of 20 mL; the concentrate was washed with 1 N HCl solution to remove the residual dioxane. The two phases separated and the organic layer was dried over Na_2SO_4, filtered and concentrated to give yellowish oil (17.25 mmol, 97.8%). ^1H NMR ($CDCl_3$) δ 12.03 (b, 1H), 7.24 (m, 5H), 2.96 (m, 1H), 2.70 (m, 2H), 1.65 (m, 1H), 1.39 (m, 3H), 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 182.5, 139.2, 129.0, 128.5, 126.5, 47.3, 38.2, 34.0, 20.5, 14.0; FTIR (CH_2Cl_2, cm^{-1}) 3050 (b, s, COOH), 2915 (s, aromatic CH), 1665 (s, C=O); HRMS calcd for $C_{12}H_{17}O_2$ (M + H) 193.12285, found 193.12281.

Synthesis of α-benzylvaleric acid chloride (27)

Oxalylchloride (481 μL, 5.46 mmol, 1.05 equiv) was slowly added to a solution of α-benzylvaleric acid (**26**) (1.0 g, 5.2 mmol, 1 equiv) in CH_2Cl_2 (17 mL), followed by a catalytic amount of DMF (20 μL, 0.26 mmol, 0.05 equiv) which initiated gas evolution. The mixture was stirred at room temperature for 3 h and the solvent evaporated. Distillation (Kugelrohr) under high vaccum at 165 °C yielded a clear oil (4.91 g, 1.04 mmol, 94.5%). ^1H NMR ($CDCl_3$) δ 7.20 (m, 5H), 3.12 (dd, 2H), 2.85 (m, 1H), 1.75 (m,

1H), 1.58 (m, 1H), 1.39 (m, 2H), 0.95 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 176.7, 137.7, 129.0, 128.7, 127.0, 58.9, 38.0, 33.7, 20.1, 13.9; ; FTIR (CH_2Cl_2, cm^{-1}) 2940 (s, aromatic CH), 1685 (s, C=O).

_N_-Benzylation of benzaldehyde-aminal with benzyl bromide: Synthesis of _N_-Benzyl-_N,N'_-dimethyl-1,2-cyclohexanediamine (30).

To a solution of benzaldehyde-aminal **21** (2.148 g, 9.33 mmol, 1 equiv) in THF (50 mL) was added benzyl bromide (1.11 mL, 9.33 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 30 min and 1 N NaOH (50 mL) solution was added followed by CH_2Cl_2 (50 mL). The organic phase was separated, dried over K_2CO_3, filtered and concentrated to give a yellowish solid. The crude solid was dissolved in CH_2Cl_2 (20 mL) acidified with 10% HCl and the two layers were separated. The aqueous layer was treated with 50% NaOH solution until pH > 12, then extracted with CH_2Cl_2 (30 mL x 2). The latter organic layers were combined, dried over K_2CO_3, filtered and concentrated to give a clear oil (1.77 g, 7.61 mmol, 81.6%). ^{1}H NMR ($CDCl_3$) δ 7.4 (m, dialkylation), 7.2-7.3 (m, 5H), 3.6-3.75 (dd, dialkylation), 3.62 (d, 1H, 13.3 Hz); 3.42 (d, 1H, 13.3 Hz), 2.41 (s, 3H), 2.25 (s, 1H), 2.11 (s, 3H), 1.7-1.95 (m, 3H), 1.0-1.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 140.2, 128.8*, 128.7, 128.3, 128.0*, 126.8, 67.0, 64.0*, 60.5, 57.8*, 54.6, 36.2, 34.0, 31.5, 25.8, 24.8, 22.9; FTIR (CH_2Cl_2, cm^{-1}) 3375 (b, w, MeNH), 2915 (s, aromatic CH).

***Trans*-_N_-Benzyl-_N,N'_-dimethyl- 1,2-diaminocyclohexane α-benzyl pentanamide (32)**

The mixture of *N*-Benzyl-*N,N'*-dimethyl-1,2-cyclohexanediamine **30** (1.77 g, 7.61 mmol) and triethylamine (9.13 mmol, 1.2 equiv) in CH_2Cl_2 (42 mL) was stirred at 0 °C for 5 min and *(S)*- α-Benzylpentionyl chloride (1.69 g, 8.02 mmol, 1.05 equiv) was added via canula. The reaction mixture was stirred at 0 °C until the complete disappearance of the starting material (followed by TLC, approximately 30 min) and 1 N NaOH solution (20 mL) was added. The organic layer was kept aside and the aqueous phase was extracted again with CH_2Cl_2 (20 mL x 2), dried over K_2CO_3, filtered and concentrated to give a yellowish oil. Column chromatography on silica gel using Hexanes/EtOAc (3:1) yielded

3.04 g (7.48 mmol, 98.3%) of the clean product. Rf 0.65 (Hexanes/EtOAc 3:2); ^{1}H NMR ($CDCl_3$) δ 7.18-7.25 (m, 10), 4.65 (m, 1H), 3.52 (s, 2H), 2.95 (m, 2H), 2.70 (m, 1H), 2.47 (s, 3H), 2.05 (s, 3H), 1.65-1.95 (m, 4H), 1.10-1.45 (m, 8H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 175.0, 140.5, 140.0, 129.1, 128.6, 128.2, 128.0, 35.7, 35.6, 29.3, 28.9, 25.5, 22.8, 22.5, 20.8, 14.3; FTIR (CH_2Cl_2, cm^{-1}) 2915 (s, aromatic CH), 1625 (s, C=O); HRMS calcd for $C_{27}H_{39}N_2O$ (M + H) 407.30624, found 407.30616.

Removal of the benzyl group, synthetic route to the diastereomeric α-benzyl pentanamide (28)

To a suspension of Pd/C (3.03 g) in 30 mL of 4.4% formic acid-methanol was added a solution of *N*-Benzyl-*N,N'*-dimethyl-1,2-diaminocyclohexane α-benzyl pentanamide (**32**) (3.03 g, 7.47 mmol) in 150 mL of 4.4% HCOOH-MeOH) at 0 °C. The resulting suspension was stirred at room temperature for 45 h, the solution was filtered through a packed celite column and the filtrate was concentrated to a viscous oil. The crude oil was dissolved in EtOAc (30 mL) and 10% HCl solution (30 mL). The aqueous layer was separated and treated with 50% NaOH solution until pH>12 and extracted with EtOAc (30 mL x 2). The organic layer was dried over K_2CO_3, filtered and concentrated to give oil (1.90 g, 6.01 mmol, 80.4%). ^{1}H NMR ($CDCl_3$) δ 7.19-7.27 (m, 5H), 4.28 (b, 1H), 3.46 (m, 1H), 3.06 (m, 1H), 2.91 (m, 1H), 2.74 (s, 1H), 2.72 (m, 1H), 2.45 (s, 2H), 2.30 (s, 2H), 2.15 (s, 1H), 2.05 (m, 1H), 1.6-1.85 (m, 3H), 1.1-1.45 (m, 6H), 0.80 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 176.4, 176.0, 140.5, 140.3, 129.4, 129.1, 128.3, 126.2, 126.1, 61.2, 59.3, 58.6, 44.6, 43.6, 40.2*, 40.0, 39.1, 35.8, 35.1, 34.3*, 34.0, 33.1, 31.5, 31.3, 30.5, 29.3*, 28.6, 27.3, 25.6, 25.4, 25.0, 24.5, 20.8, 20.7, 14.33, 14.26; HRMS calcd for $C_{20}H_{33}N_2O$ (M + H) 317.25929, found 317.25917.

Preparation of *N*-benzyl-*N,N'*-dimethyl-1,2-diaminocyclohexane pentanamide (19)

To a cooled (0 °C) solution of the racemic pentanamide **17** (203 mg, 0.90 mmol, 1 equiv) and triethylamine (161 μL, 1.35 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL) was added benzyl bromide (160 μL, 1.35 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C until completion (followed by TLC). A solution of 1 N NaOH (10 mL) was added and the two

phases separated. The organic layer was kept aside and the aqueous phase was extracted again with CH_2Cl_2 (10 mL x 2). All the organic layers were combined, dried over potassium carbonate, filtered and concentrated to give yellowish oil. Column chromatography on silica gel (3:1 hexanes/EtOAc) provided 91% of the product. ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H), 4.68 (m, 1H), 3.34-3.70 (dd, 2H, 13.3 Hz), 2.83* (s, 1H), 2.80 (s, 2H), 2.50 (s, 3H), 2.30 (m, 2H), 2.11 (s, 3H), 2.0 (b, 1H), 1.55-1.85 (m, 5H), 1.10-1.45 (m, 6H), 0.92 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 140.5, 128.6, 128.5*, 128.1, 126.7, 63.4, 57.8, 53.1, 37.2*, 36.6, 34.0, 32.8, 31.5, 30.1, 29.5*, 27.6, 27.4*, 25.6, 25.5, 24.0*, 23.1, 22.7, 14.0; FTIR (CH_2Cl_2, cm^{-1}) 2925 (m, aromatic CH), 1625 (s, C=O); Anal. Calcd for $C_{20}H_{32}N_2O$: C, 75.90; H, 10.19; N, 8.85. Found: C, 75.70; H, 10.54; N, 8.81.

β-Deuterated *N*-benzyl-α-benzyl-pentanamide (33)

A solution of *sec*-butyllithium in cyclohexane (0.15 mmol, 2.0 equiv) was added dropwise to a -78 °C solution of *N*-benzyl-α-benzyl-pentanamide (**32**) (31 mg, 0.077 mmol, 1 equiv) in THF (2 mL). The solution turned from colorless to bright and to dark yellow within 10 min after the addition of the base. Deuterium oxide (1 mL) was then added. The dark yellow color immediately faded resulting in a colorless solution. The reaction was stirred at -78 °C for 10 min, at room temperature for 15 min and 1 N NaOH solution (5 mL) and CH_2Cl_2 (5 mL) were added; the two phases were separated; the organic layer was dried over K_2CO_3, filtered and concentrated. ^{1}H NMR (same spectrum of compound **32** with loss of one proton at 2.9 ppm). HMQC, COSY, DEPT, ^{13}C spectra are enclosed with this thesis (see appendix). HRMS calcd for $C_{27}H_{37}DN_2O$ (M + H) 408.31252, found 408.31265.

***Trans*-*N*-Benzyl-*N,N'*-dimethyl- 1,2-diaminocyclohexane α-methyl pentanamide (36)**

A *sec*-butyllithium solution in cyclohexane (0.322 mmol, 1.2 equiv) was added dropwise to a solution of *N*-Benzyl-*N,N'*-dimethyl-1,2-diaminocyclohexane pentanamide (**19**) (87.5 mg, 0.276 mmol, 1 equiv) in THF (3 mL) at -78 °C. After 10 min stirring, methyl iodide (21 µL, 322 mmol, 1.2 equiv) was added and the resulting mixture was stirred at -78 °C for 30 min, at 0 °C for 30 min, and quenched with a 1 N NaOH solution (3 mL); CH_2Cl_2

(3 mL) was added and the two phases separated. The organic layer was dried over potassium carbonate, filtered and concentrated to oil. Column chromatography on silica using Hexanes/EtOAc (3:1) afforded 75.5 mg (82.7%) of α-methyl pentanamide **36**. Rf 0.24 (3:1 hexanes/EtOAc); diastereomer ratio of 2:1; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), 4.70 (b, 1H), 3.41-3.67 (dd, 2H, 10.4 Hz), 2.84 (s, 3H), 2.73 (m, 1H), 2.55 (bt, 1H), 2.12 (s, 3H), 2.0 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.4, 128.5, 127.7, 127.5, 126.5, 80.5, 54.8, 53.5, 37.7, 37.5, 36.6, 30.5, 30.0, 25.5, 20.8, 17.7, 13.8; HRMS calcd for $C_{21}H_{35}N_2O$ (M + H), 331.27915 found 331.27908.

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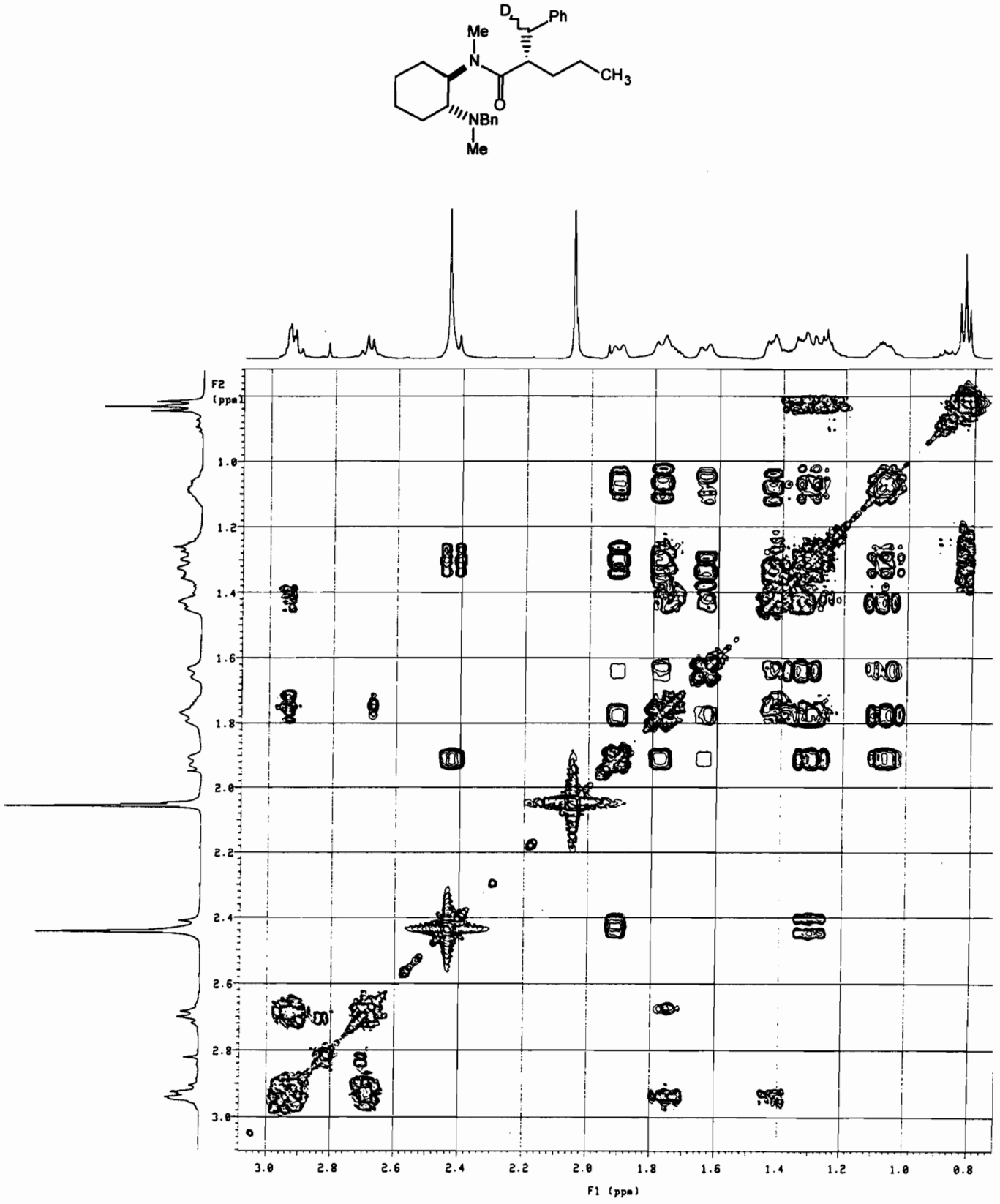
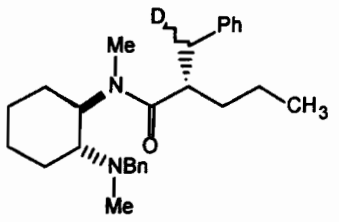
Appendice

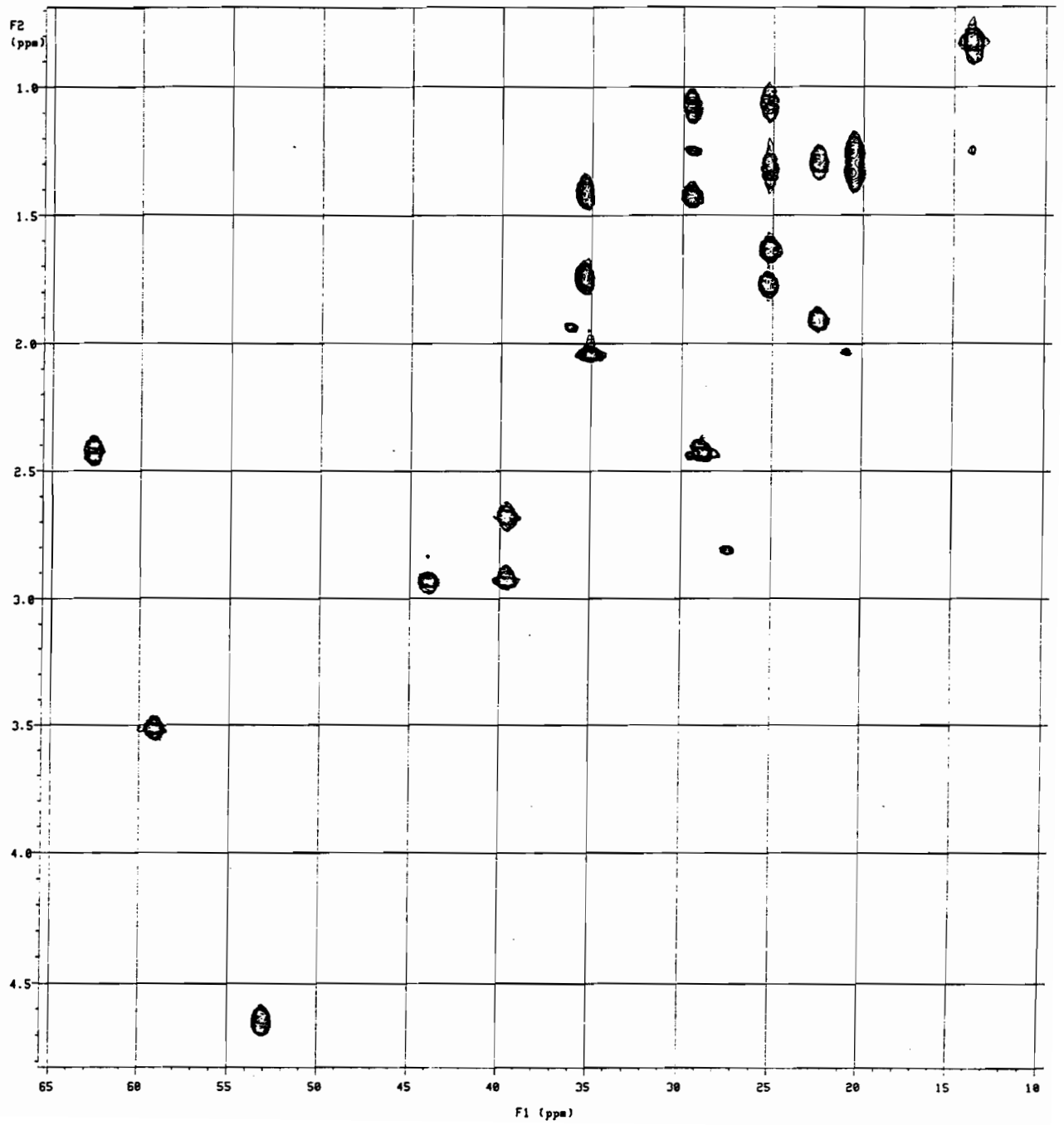
COSY, HMQC and DEPT Spectra

Spectrum # 1: COSY



Spectrum # 2: HMQC





Spectrum # 3: DEPT