I. MOLECULAR RECOGNITION WITH SYNTHETIC RECEPTORS

II. DEVELOPMENT OF NEW CHIRAL AUXILIARIES

by

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Finally, I would like to thank my family for their love and support. This thesis is dedicated to my wife, Jungwon, for her unfinished degree.

To my wife, Jungwon.

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Submitted to the Department of Chemistry
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ABSTRACT

A series of synthetic molecular receptors with functional groups complementary to adenines, cytosines, diketopiperazines, barbiturates, and hydantoins is described. The receptors feature functional groups and suitably placed aromatic surfaces to permit simultaneous hydrogen bonding and aromatic stacking interactions. The general features and energetics of complexation between the synthetic receptors and heterocycles mentioned above are established by NMR techniques involving chemical shift changes and NOE experiments. Hydrogen bonding affinities are studied in $CDCl_3$ compared for the functional groups; imide vs lactam, amide vs acid. Chiral recognition is achieved by optically active receptors with diketopiperazines ($\Delta\Delta G$ = 2-3 kcal/mol) and hydantoins ($\Delta\Delta G$ = 0.5-1.4 kcal/mol) in $CDCl_3$.

New chiral auxiliaries derived from Kemp's triacid are introduced for stereocontrolled asymmetric synthesis. The synthesis of the new systems is outlined and their applications are described in alkylations and α-unsubstituted aldol reactions.

Thesis Supervisor: Julius Rebek, Jr.
Title: Professor of Chemistry

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PART I

MOLECULAR RECOGNITION WITH SYNTHETIC RECEPTORS

Introduction

Molecular recognition is a fundamental process in biological systems. The ability of individual molecules to recognize and discriminate between closely related partners is a key determinant of enzyme catalysis, gene regulation and many other processes.[1] However, natural systems such as nucleic acids and proteins are usually so complex that it is hard to understand and identify specific functions.

In order to circumvent the difficulties of natural systems, model systems have been extensively studied for the last twenty years. The design of synthetic receptors capable of the specific recognition requires the correct manipulation of the energetic features of the weak non-covalent forces: hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions. To date, most of the synthetic models have been based on macrocyclic molecules. For examples, cyclodextrins[2] and cyclophanes[3] form inclusion complexes with organic molecules through hydrophobic interactions. Crown ethers[4] and several other related molecules[5] such as spherands and cryptands have been studied and the

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1 Dugas, H. *Bioorganic Chemistry*; Springer-Verlag: New York, 1988.

2 a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. b) Dugas, H. *Bioorganic Chemistry*; Springer-Verlag: New York, 1988; p 350-366.

3 a) Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* **1983**, *113*, 145-183. b) Franke, J.; Vögle, F. *Top. Curr. Chem.* **1986**, *132*, 135-170. c) Diederich, F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 362-386.

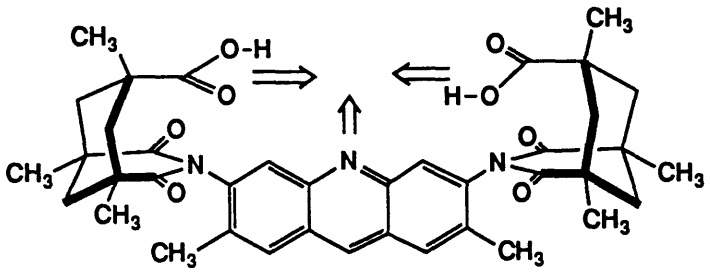
4 a) Pederson, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021-1027. b) Dugas, H. *Bioorganic Chemistry*; Springer-Verlag: New York, 1988; p 262-323.

5 a) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009-1020. b) Lehn, J. M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89-112.

binding of ionic substrates through ion-dipole and hydrogen bonding interactions has been assessed.

The main problem of these macrocyclic models is the limited functionalization of these systems. Slight modifications require multistep syntheses. Despite the tedious synthesis, divergence of the binding cavity and the functional group is usually a feature of these macrocyclic models, unlike natural systems, which involve convergence of functional groups.

In 1984, Rebek introduced a new model, the so-called molecular cleft, to bioorganic chemistry.[6] One significant advantage of this system is the convergence of useful functional groups.



Rebek's acridine diacid

For example, the acridine diacid features one basic and two acidic groups which converge and resemble the active sites of enzymes. The acridine diacid recognizes substrates of complementary size, shape and functionality through hydrogen bonding and aromatic stacking interactions.[7]

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6 Rebek, J., Jr.; Marshall, L.; Wolak, R. McManis, J. *J. Am. Chem. Soc.* **1984**, *106*, 1170-1171.

7 a) Rebek, J., Jr. *Science (Washington, D. C.)* **1987**, *235*, 1478-1484. b) Rebek, J., Jr. *Top. Curr. Chem.* **1988**, *149*, 189-210.

It is also efficient for transport of amino acids across a liquid membrane[8] and the catalytic cleavage of hemiacetals.[9]

The present study extends the convergent functional group approach to the recognition of nucleic acid components and the asymmetric complexation of neutral substrates.

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8 Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2342-2434.

9 Wolfe, J.; Nemeth, D.; Costero, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 983-984.

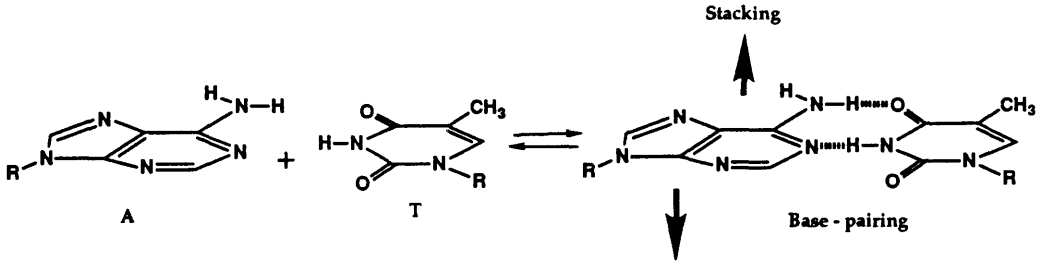
Chapter 1

Molecular Complexation of Adenine Derivatives

1.1 Receptors with Imide Group

The hereditary material, deoxyribonucleic acid (DNA), is a linear polymer built up of monomeric units, the nucleotides. A nucleotide consists of three molecular fragments: a sugar, a heterocycle and a phosphate. DNA forms antiparallel double helices, which are held together by hydrogen bonds within base pairs and stacking forces between adjacent base pairs (A-T, G-C).[10] In the chemistry of nucleic acids, Watson-Crick base pairs[11] are the classical example of molecular recognition. The base pairing between adenine and thymine is shown below (Eq 1).

Eq 1



Compared to natural systems, synthetic models must offer simplicity and interpretability without changing rules of intermolecular interactions. The new receptors[12] presented here have an imide functional group similar

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10 Saneger, W. *Principle of Nucleic Acid Structure*; Springer-Verlog: New York, 1984; chapter 6.

11 Watson, J. D.; Crick, F. H. C. *Nature (London)* **1953**, *171*, 737.

12 a) Rebek, J., Jr.; Williams, K.; Ballester, P.; Jeong, K.-S. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1244-1245. b) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jonces, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082-1090. c) Williams, K.; Askew, B.; Ballester,

to thymine. Therefore, both synthetic and natural systems have the same patterns of hydrogen bonding. An adjacent aromatic group can provide aromatic stacking forces resembling those of DNA (Figure 1).

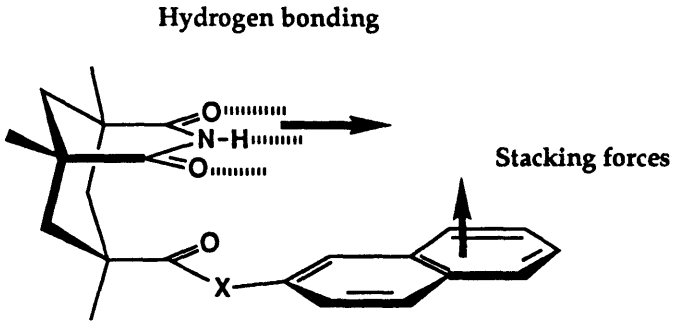


Figure 1 Hydrogen bonding and stacking forces in synthetic receptors

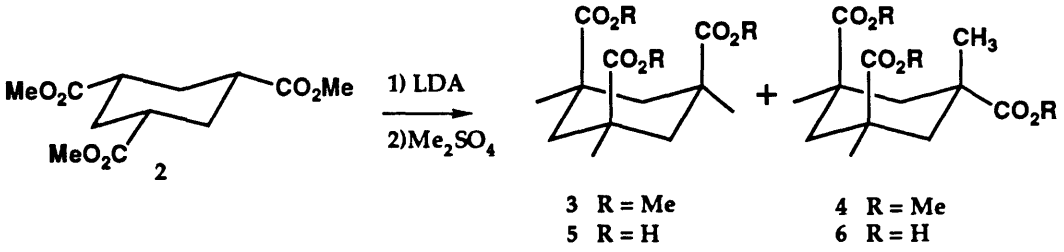
1.1.1 Synthesis

Model systems presented here are based on Kemp's triacid **5**,[13] in which three carboxyl groups are conformationally related by a U-turn. Hydrogenation and esterification of the commercially available trimesic acid **1** provide trimethyl 1,3,5-cyclohexane-caboxylate **2**, which is alkylated with dimethylsulfate to afford a mixture of cis-cis triester **3** and cis-trans triester **4**. After separation of two isomers, triesters **3** and **4** are hydrolyzed to give the corresponding triacids **5** and **6** (Scheme 1).

P.; Buhr, C.; Jeong, K. S.; Jonces, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090-1094.

13 a) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1982**, *46*, 5140-5143. b) For modified synthesis, see: Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426-2431.

Scheme 1

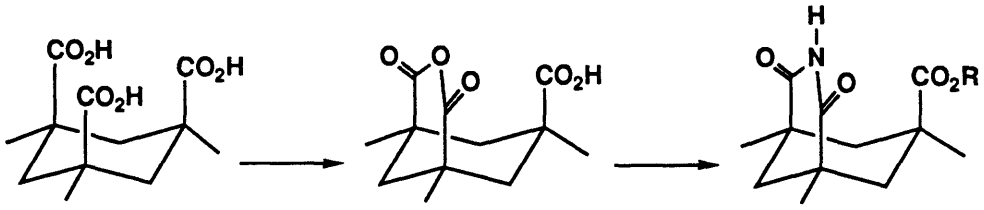


3 R = Me
5 R = H

4 R = Me
6 R = H

Triacid **5** is merely heated in xylene or sublimed to give the anhydride acid **7**. Refluxing of the anhydride acid **7** in concentrated ammonium hydroxide gives the imide acid **8**. Alternatively, compound **8** can be conveniently made by heating triacid **5** with urea. The imide acid **8** is treated with thionyl chloride ($SOCl_2$) to give the imide acid chloride **9** (Scheme 2).

Scheme 2



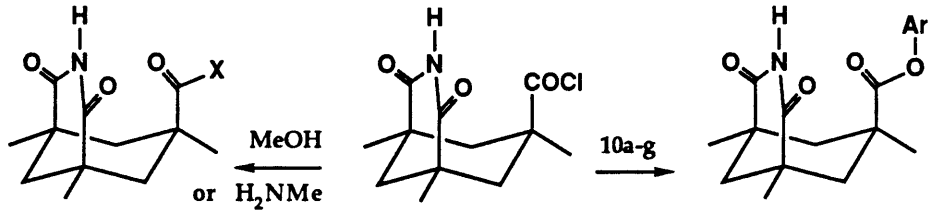
5

7

8 R = H
9 R = Cl

The imide acid chloride **9** is acylated with the various alcohols **10a-f** to give the U-shaped receptors **11a-h** for adenine derivatives (Scheme 3).

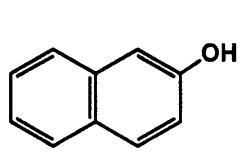
Scheme 3



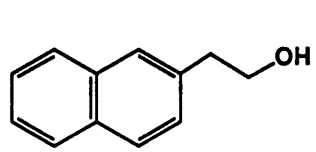
11g X = OMe
11h X = NHMe

9

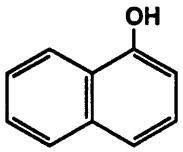
11a-f



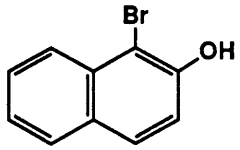
10a



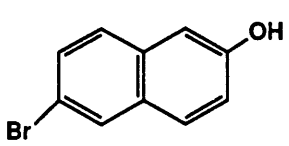
10b



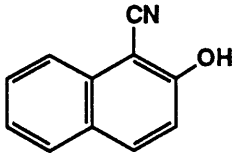
10c



10d



10e

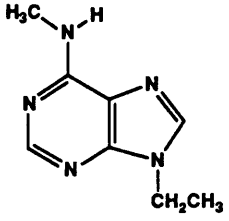


10f

1.1.2 Results and Discussion

All binding affinities reported here were obtained from ^1H NMR studies. Guest molecules were 9-ethyladenine **12** and 9-ethyl-N_6-methyladenine **13**.

12



13

All spectra at various concentrations[14] of hosts and guests showed only time-averaged signals of complexed and uncomplexed molecules in the ^1H NMR spectra. The association constants (K_a's) shown in Table 1 were determined from the Eadie-Hofstee plots.[15] The data from these studies were treated as follows: If the association of the host (H) with a guest (G) yields a 1:1 complex (HG), then

$$H + G \rightleftharpoons HG$$

and can be described by an association constant K_a

$$K_a = [HG]/[H][G] \quad (1)$$

When $[H]_o$ and $[G]_o$ are the total concentrations of host and guest,

$$[H] = [H]_o - [HG] \quad (2)$$

$$[G] = [G]_o - [HG] \quad (3)$$

The ratio of [HG] to $[H]_o$ is termed P_c, the degree of association of host with guest. It follows that [HG] equals $P_c[H]_o$. If the species H, G, and HG are in rapid equilibrium on the NMR time scale, the chemical shift δ of the proton being observed follows the rule

$$\delta = \delta_o + P_c\delta_c$$

with δ_o being the chemical shift of noncomplexed (free) host, and δ_c being the chemical shift of fully complexed host. Since $\delta - \delta_o = \Delta\delta$, and $\delta_c - \delta_o = \Delta\delta_{max}$, it follows that

$$P_c = \Delta\delta/\Delta\delta_{max} = [HG]/[H]_o \quad (4)$$

A rearrangement of equations 1, 2, and 3 yields a linear form shown in equation 5.

$$\Delta\delta = \Delta\delta/[G]\,K_a - \Delta\delta_{max} \quad (5)$$

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14 In most cases, initial concentrations of hosts and guests in titrations were ~ 0.01 M and ~0.1 M in $CDCl_3$, respectively.

15 a) Eadie, G. S. *J. Biol. Chem.* **1942**, *146*, 85-93. b) Hofstee, B. H. J. *Nature (London)* **1959**, 1296-1298.

The titration data was treated by the application of the Eadie-Hofstee plot (equation 5) , plotting $\Delta\delta$ vs. $\Delta\delta/[G]$ to get the association constants (K_a = -1/slope).

The chemical shift of the signal for the imide NH of the host usually moved from 7.6 ppm to > 12 ppm on the addition of 20-30 equivalents of guest. The signals for aromatic resonances generally involved 0.1-0.3 ppm upfield shifts during titration. These spectroscopic changes indicate that hydrogen bonding occurs between the adenine and the imide. Additionally, the upfield shifts of the aromatic protons in complex indicate that stacking interactions occur between the aromatic surfaces of receptors and guests. In order to obtain association constants (Ka's), $\delta_{complex}$ = 13.2 ppm for the imide NH of complex was assumed in Eadie plots. This is the experimentally determined maximal chemical shift of an imide NH in similar studies.[16] A typical saturation curve and Eadie plot are shown in Figure 2 for the specific case of naphthyl ester imide **11a** and 9-ethyladenine **12** in the relatively noncompeting solvent (in the hydrogen-bonding sense), $CDCl_3$[17], at 296 °K.

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16 Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jonces, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090-1094.

17 In a relatively low dielectric solvent such as chloroform, the bases primarily form hydrogen bonds, while in aqueous solution base stacking is favored. Solvents with low dielectric constants provide an environment similar to the interior of nucleic acid double helices. See: Williams, N. G.; Williams, L. D.; Shaw, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 7205-7209 and references therein.

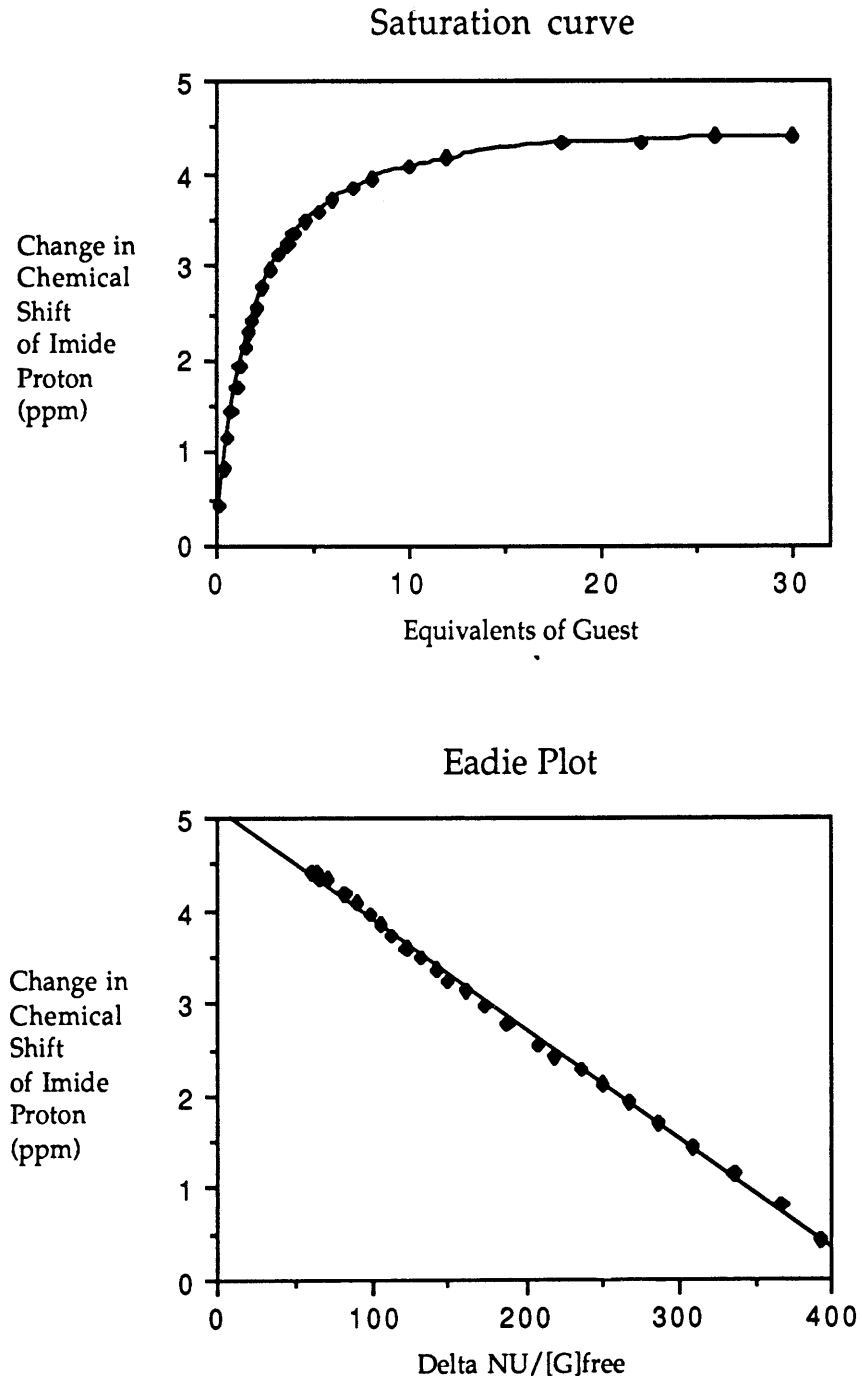
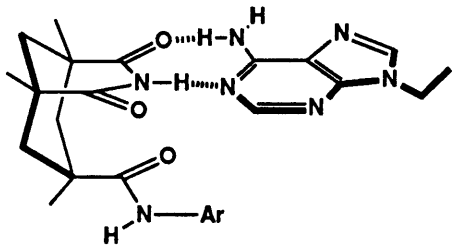


Figure 2 Saturation curve and Eadie plot in the titration of naphthyl ester imide **11a** with 9-ethyladenine **12**.

Table 1 Association Constants (K_a's) of Hosts **11a-h** with Guests **12** and **13**.

Imide	$K_a \pm 10\%$ (M^{-1}) with **12**	$K_a \pm 10\%$ (M^{-1}) with **13**
11a	90	45
11b	80	38
11c	70	40
11d	64	-
11e	80	-
11f	91	-
11g	45	-
11h	45	-

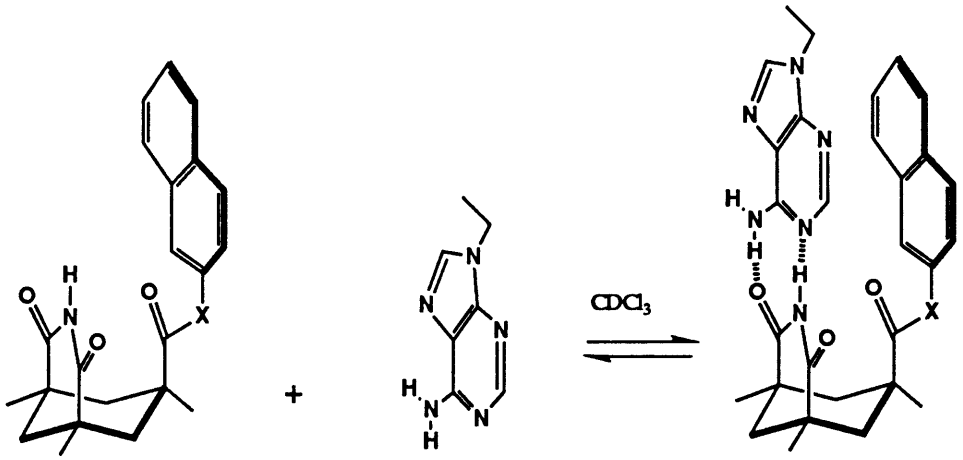
The associations of methyl ester imide **11g** and methylamide imide **11h** with 9-ethyladenine **12** are evaluated in order to determine the H-bonding contribution to the formation of complexes. In other imide hosts which show > 45 M^{-1} of association constants, their complexes involve the additional binding forces, such as π-stacking interactions which are not present in the imides **11g** and **11h**. Privious studies[12b] of this system clearly showed the effect of aromatic surface area on the complexation event. In structures shown below, hydrogen bonding is expected to contribute a constant amount but the different aromatic surfaces offer various degrees of π-stacking stabilization.



Ar = phenyl Ka = 101 M^{-1}
Ar = 2-naphthyl Ka = 220 M^{-1}
Ar = 2-anthryl Ka = 440 M^{-1} in $CDCl_3$

The Ka of naphthyl ester imide **11a** is only 90 M^{-1}, while the naphthylamide imide **15a** is 220 M^{-1} (Eq 2).

Eq 2



11a X = O
15a X = NH

12

X = O Ka = 90 M^{-1}
X = NH Ka = 220 M^{-1}

This difference in binding may be due to three factors: bifurcated hydrogen bonding, structural differences, and polarizabilities of the aromatic surfaces.

The bifurcated hydrogen bond[18] (Figure 3), three-center hydrogen bonds, was established by NMR techniques[19], specifically heteronuclear intermolecular nuclear Overhauser effects (NOE).

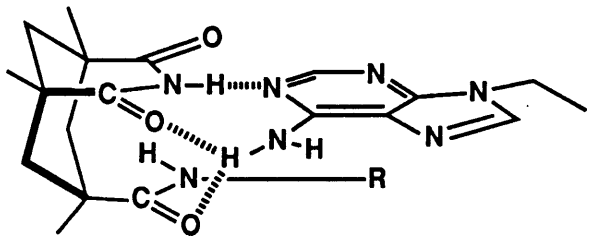


Figure 3 Bifurcated hydrogen bonding in synthetic receptors

Upon irradiation of the adenine NH_2 signal in the complexes, enhancements in the ^{13}C signals are observed. The results are shown in the Table 2.

Table 2 Results of the Heteronuclear Intermolecular NOE Experiments

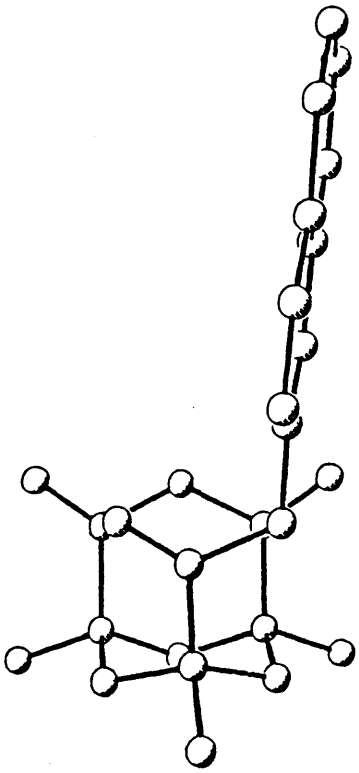
	% NOE	
Receptor	**Imide ^{13}C signal**	**Amide or Ester ^{13}C signal**
methyl ester **11g**	24	4
methyl amide **11h**	26	33
2-naphthyl ester **11a**	19	0
2-anthraquinone-amide[18]	20	24

18 a) Jeffery, G. A.; Maluszynska, H. *Int. J. Biol. Macromol.* **1982**, *4*, 173-185. b) Taylor, R.; Kennard, O.; Werner, V. *J. Am. Chem. Soc.* **1984**, **106**, 244-248.

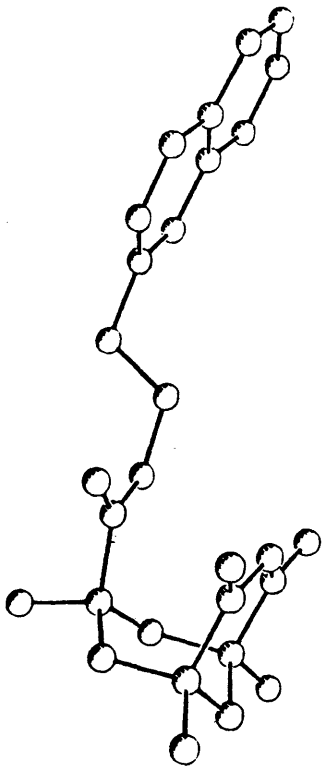
19 Rebek, J. Jr.; Askew, B.; Ballester, P.; Buhr, C.; Costero, A.; Jonces, S.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 6866-6867.

As seen in Table 2, the enhancements are observed at the ^{13}C signals of both the imide and amide carbonyl groups for receptors with amide functionality. The NOEs indicate simultaneous binding of the adenine NH to the both imide and amide carbonyl oxygens, *i.e.*, bifurcated hydrogen bonding. In contrast, ester host **11a** give no evidence for such interaction between the ester carbonyl and the NH of the adenine **12**, *i.e.*, bifurcation does not appear to contribute to the complexation of **11a** with adenine. This may be due to the reduced basicity of esters compared to the amides, although the methyl ester **11g** shows a small enhancement of the ester carbonyl group.

The difference of Ka's may be also attributed to the structural differences of the ester **11a** and amide **15a**. The crystallographic structures for the 2-naphthyl ester **11a** and 2-naphthylethyl ester imide **11b** are shown below.



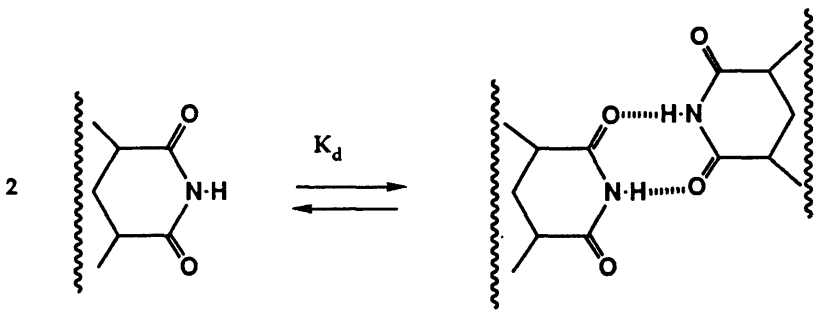
X-ray structure of **11a**



X-ray structure of **11b**

For the host **11a** and **11b**, intermolecular self-association is observed in the solid state involving imide dimerization with complementary hydrogen bonding and stacking interactions to a third molecule. However, in solution ($CDCl_3$), the dimerization (Eq 3) is negligible because these systems[20] show dimerization constants (K_d's) in the 2-4 M^{-1} range in $CDCl_3$.

Eq 3



While the aromatic plane of 2-naphthylamide imide **15a** is almost parallel to that of the imide function,[21] the crystal structure of the 2-naphthyl ester imide **11a** shows that the plane of imide group is nearly perpendicular to that of the aromatic group. This is, in part, due to repulsion between the ortho hydrogen and the carbonyl oxygen. However, NOE experiments of imide **11a** shows that irradiation of the imide NH resulted in comparable enhancements of H_1 (1.2 %) and H_3 (1.8 %). This indicates that rapid rotation of the indicated bond may occur in solution ($CDCl_3$) at room temperature (Eq 4).

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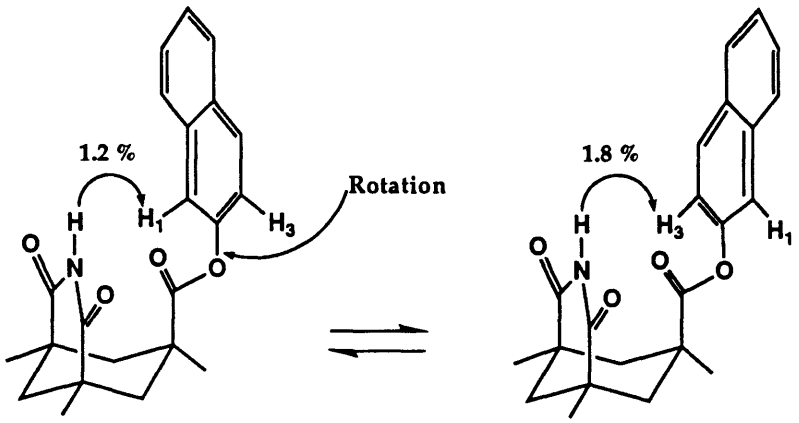
20 Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jonces, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090-1094.

21 Crystallographic analysis of **15a** was not be performed. For a similar example, see the crystal structure of **16a** in Chapter 2.

Eq 4



The repulsion between the ortho hydrogens and the carbonyl oxygen must be overcome to achieve face to face stacking . The contribution of this repulsion may be large in the 1-bromo-2-naphthyl ester imide **11d**, negligible in the 2-naphthylethyl ester imide **11b**. The latter has the flexible two extra carbons, which contribute an unfavorable entropic term during the complexation. The association constants in Table 1 are accord with these explanations.

Thymine and adenine bases form Watson-Crick, reverse Watson-Crick, Hoogsteen, and reverse Hoogsteen base pairs[22]. In this study it is not possible to distinguish between the Watson-Crick and reverse Watson-Crick, and between the Hoogsteen and reverse Hoogsteen binding modes in the complexes of receptors and adenine. Preference for Watson-Crick vs Hoogsteen base pairing (Figure 4) was determined by two experiments.

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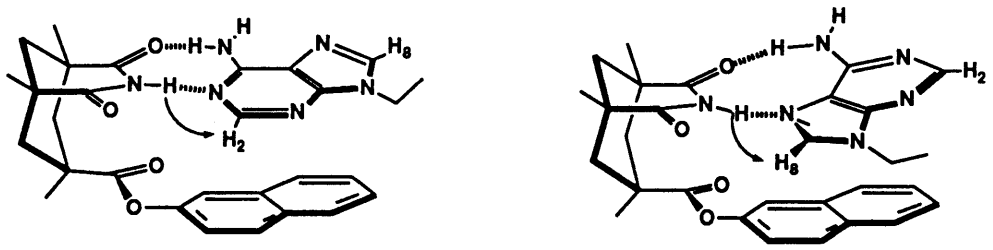
22 a) Hoogsteen, K. *Molecular Associations in Biology;* Pullman, B., Ed.; Academic: New York, 1968; p 21-38. b) Saneger, w. *Principle of Nucleic Acid Structure;* Springer-Verlog: New-York, 1984; chapter 6.



Watson-Crick Mode Hoogsteen Mode

Figure 4 Watson-Crick and Hoogsteen modes in the complex of 2-naphthyl ester imide **11a** with 9-ethyladenine **12**.

First, in a NOE experiment, irradiation of the imide NH in the complex of 2-naphthyl ester imide **11a** and 9-ethyladenine **12** caused enhancements of 1.9 and 2.1 %, respectively, in H_2 and H_8 of the 9-ethyladenine. Even though these data are difficult to place on a quantitative level, it appears that roughly equal amounts of two modes of hydrogen bonding are present.[23]

Secondly, the preference for Watson-Crick vs Hoogsteen modes can be seen from the comparison of the association constants. The association constants (K_a's) of receptors with **13** in Table 1 are reduced by ~ 50 % from the values for the unsubstituted adenine **12**. In the N_6-methyladenine derivative **13**, the methyl group is directed away from N_7 due to both Van der Waals

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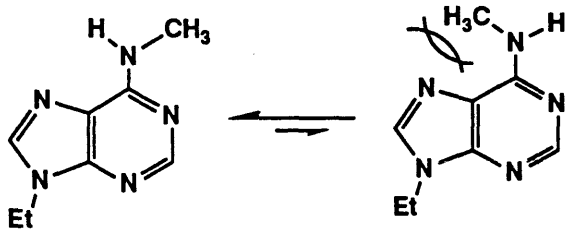
23 For comparison, the complex of cyclohexyluracil with 9-ethyladenine were examined under same conditions. Irradiation of H_2 and H_8 in 9-ethyladenine gave 1.4 and 0.9 %, respectively, enhancements of the 1-cyclohexyluracil NH. Saturation transfer was observed on the irradiation of the 1-cyclohexyluracil NH, while it was not observed on the irradiation of the imide NH of receptors. This may be due to increased acidity of the 1-cyclohexyluracil NH compare to the imide NH of receptors.

repulsion and intramolecular hydrogen bonding, and the Hoogsteen mode is strongly favored in its complexes (Eq 5).[24]

Eq 5



13

The Watson-Crick hydrogen bonding mode is removed in cases that N_6-methyladenine derivative **13** is employed as guest molecule. NOE experiments also gave evidence for mostly Hoogsteen base pairing. For example, the irradiation of the imide NH now showed enhancements of < 0.5 and 3.4 %, respectively, in H_2 and H_8 of the adenine **13** in its complex with **11a**. This suggests that roughly equal amounts of Watson-Crick and Hoogsteen base pairing exist in the complex between **11a** and **12**. Due to the small stacking contribution, receptors **11b** and **11c** do not show a clear preference for the two base-pairing modes, even though **11b** is expected to favor Watson-Crick and **11c** to favor Hoogsteen because of better orientation of the aromatic stacking surface.

The thermodynamic parameters (ΔH, ΔS) were obtained from temperature dependent studies using Van't Hoff plots.[25] It was assumed that the chemical shift for the fully complexed imide, NH, was temperature-

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24 Dodin, G.; Dreyfus, M.; Dubois, J. E. *J. Chem. Soc. Perkin trans. 2*, **1979**, 439.

25 Barrow, G. M. *Physical Chemistry*; McGraw Book Co.: New York, 1979, p 257.

independent. The enthapies (-ΔH's) and entropies (-ΔS's) of **11a** and **11b** were, respectively, 7.7 Kcal/mol, 17 eu and 9.2 Kcal/mol, 22 eu on the complexation with 9-ethyladenine **12**. These values indicate that the host **11b** has more favorable stacking interaction than the host **11a**, but is less favored entropically. The magnitudes of ΔH and ΔS are quite reasonable for these types of hydrogen bonds.[26]

1.2 Receptors with Lactam Group.

1.2.1 Synthesis

2-Aminonaphthalene **14a** was acylated with imide acid chloride **9** to afford the corresponding imide **15a**. Reduction[27] of imide **15a** with $NaBH_4$ gave hydroxylactam **16a** which was further reduced with triethylsilane (Et_3SiH) under acidic conditions (CF_3CO_2H) to provide 2-naphthylamide lactam **17** (Scheme 4).[28]

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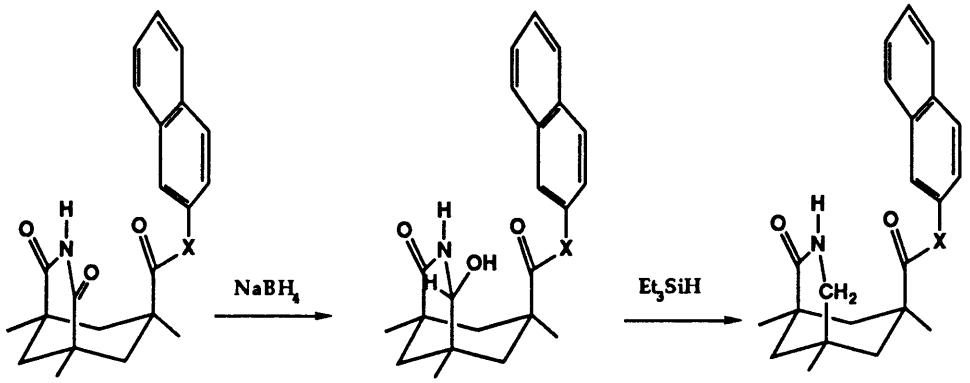
26 Pohorille, A.; Burt, S. K.; MacElroy, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 402-409.

27 Kyogoku, Y.; Lord, R. C.; Rich, A. *Science (Washington, D. C.)* **1966**, *154*, 518-520.

28 Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1969**, *34*, 4-6. For a review of ionic hydrogenation, see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis*, **1974**, 633-651.

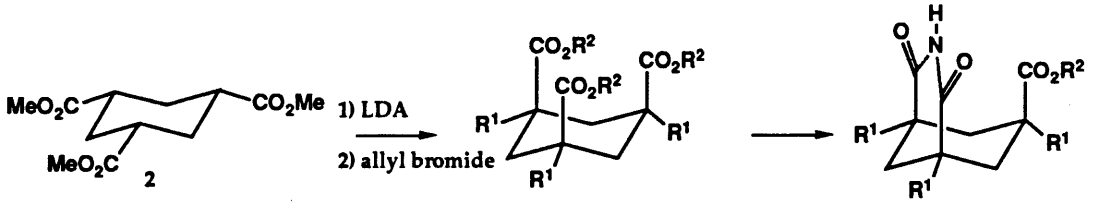
Scheme 4



15a 16a 17

A new triacid **20** was prepared to enhance the solubility of the diimide derivatives in $CDCl_3$.[29] Allylation of trimethyl 1,3,5-cyclohexanecarboxylate **2** with allyl bromide gave only the cis-cis isomer of the triallyl triester **18**. The hydrogenation and hydrolysis of **18** provided the tripropyl triacid **20**. Condensation with urea gave the imide acid **21** which was converted to the acid chloride **22** with $SOCl_2$ (Scheme 5).

Scheme 5



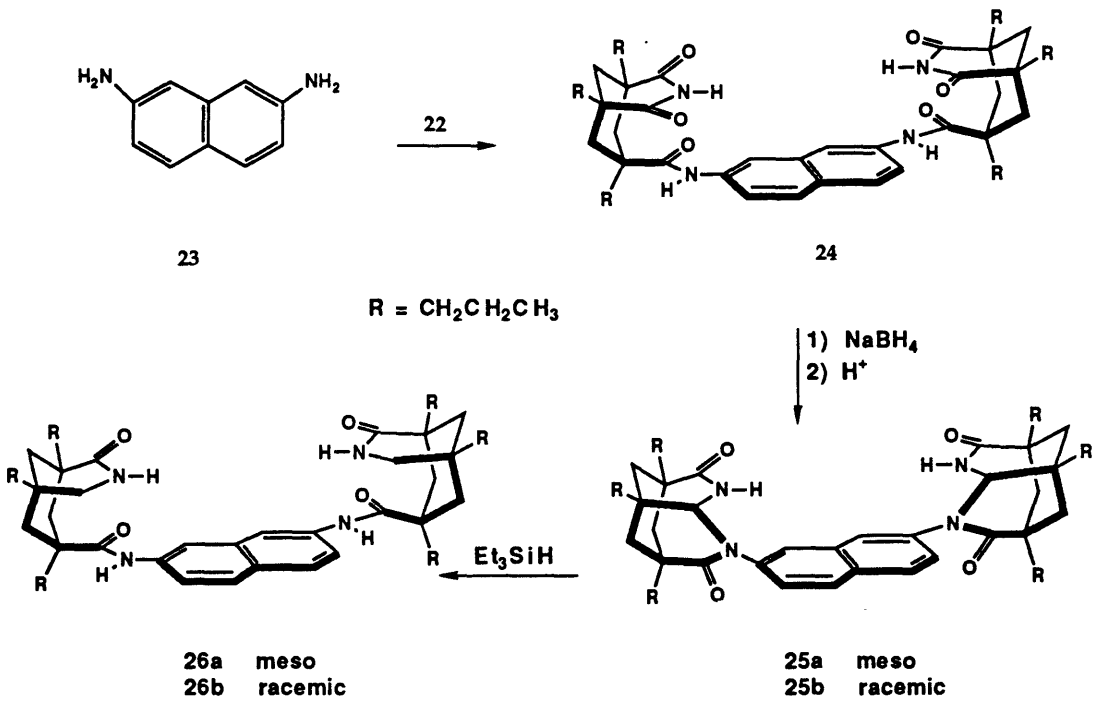
2

18 $R^1 = CH_2CHCH_2$, $R^2 = CH_3$
19 $R^1 = CH_2CH_2CH_3$, $R^2 = CH_3$
20 $R^1 = CH_2CH_2CH_3$, $R^2 = H$
21 $R^1 = CH_2CH_2CH_3$, $R^2 = H$
22 $R^1 = CH_2CH_2CH_3$, $R^2 = Cl$

29 Several diimide systems derived from Kemp's (trimethyl) triacid are hardly soluble in $CDCl_3$. For examples, see Chapter 4.

2,7-Diaminonaphthalene **23** was acylated with **22** to give the diimide **24** which was highly soluble in $CHCl_3$. Reduction and cyclization of the diimide **24** provided the diastereomeric mixture of the tricyclic dilactams **25a** and **25b**. The diastereomers were then separated by flash chromatography.[30] The meso **25a** and racemic **25b** were further reduced to give the appropriate dilactams **26a** and **26b** (Scheme 6).

Scheme 6



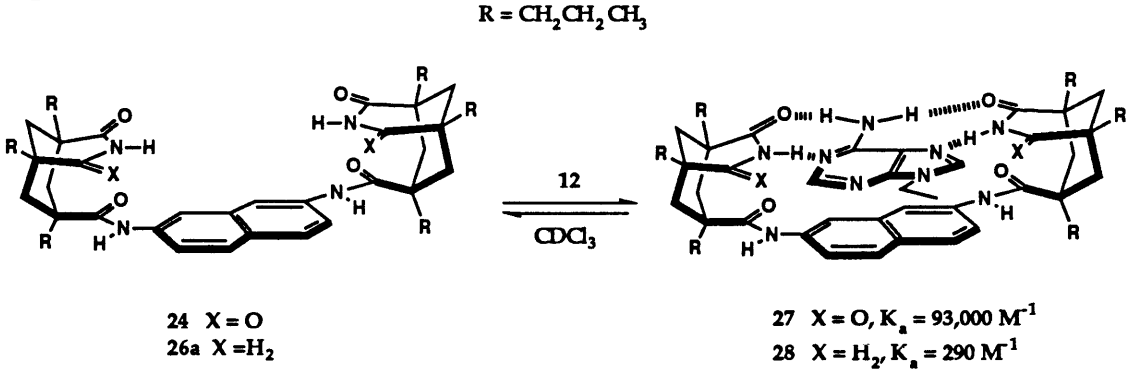
30 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

1.2.2 Results and Discussion

Titration of 2-naphthylamide lactam **17** with 9-ethyladenine **12** showed a shift of the signal for the lactam NH moved from 5.39 ppm to 7.10 ppm and an upfield shift at the aromatic resonances of naphthalene (<0.1 ppm). The titration data was treated with nonlinear least squares curve fit[31] which yielded the association constant (K_a = 15 M^{-1}) and chemical shift of complex (δc = 8.53 ppm). Hydrogen-bonding affinities of imides to adenine were shown in previous section. The association constant of 2-naphthylamide imide **15a** is 220 M^{-1} in $CDCl_3$.

Both diimide **24** and dilactam **26a** can form simultaneous Watson-Crick and Hoogsteen modes of base pairing, along with aromatic stacking (Eq 6).

Eq 6



24 X = O
26a X = H_2

27 X = O, K_a = 93,000 M^{-1}
28 X = H_2, K_a = 290 M^{-1}

---

31 Eadie treatment requires the chemical shift (δ_c) of complex which can not be experimentally obtained in this case due to low binding affinity. The initial concentrations of lactam **17** and guest **12** are 9 x 10^{-3} and 9 x 10^{-2} M in $CDCl_3$, respectively. However, δ_c is not prerequisite and is an unknown parameter in nonlinear least squares curve-fit method which is written by G. Deslongshamps in this group. For other examples, see: a) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett*, **1986**, 5563-5566. b) Petti, M. A.; Shepodd, T. J.; Barrans, R. E.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825-6840.

During the titration of **24** with 9-ethyladenine **12**, the signal for the imide NH of receptor **24** shifted from 7.54 ppm to 13.5 ppm. Additionally, the signals for aromatic protons of both naphthalene and adenine moved upfield (0.3-0.6 ppm) during the formation of complex **27**. The association constant from nonlinear least squares curve fit is 93,000 M^{-1} ± (15 %) in $CDCl_3$ at 296 °K.[32] The association constant[33] of the corresponding meso dilactam **26a** with 9-ethyladenine **12** is only 290 M^{-1} under the same conditions.

The enhanced affinities of imides compared to lactams toward adenine arise from several factors. The most apparent factor is the statistical probabilities. Imide receptors have twice as many modes as lactams for binding to 9-ethyladenine. However, these statistical factors can not explain the large reductions of the association constants in lactam receptors.

The second consideration is the increased acidities of the imide proton vs the lactam proton. Association constants for hydrogen bonding increase with increasing acidity of the hydrogen-bonding donor and increasing basicity

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32 Initial concentrations of **24** and **12** were 1.5 x 10^{-3} M and 5.3 x 10^{-3} M. During titration, the imide NH signals disappeared until ~ 75 % saturation occured, and the aromatic signals of receptor **24** were slightly broadened due to slow exchange of complexed and uncomplexed species in NMR time scale. The association constant from the imide NH of diimide **24**, covering 75-100 % of the saturation range is 104,000 $M^{-1}$and that from the aromatic H_2 of adenine **12** with covering 15-100 % of saturation range is 82,000 M^{-1}.

33 Intial concentrations of dilactam **26a** and adenine **12** are 3.8 x 10^{-3} M and 3.2 x 10^{-2} M in $CDCl_3$. The signal for lactam NH moved from 5.33 ppm to 9.02 ppm upon addition of ~ 10 equivalents of guest. Titration data was treated with nonlinear least squares curve-fit program which yielded δ_c = 9.66 ppm.

of the hydrogen-bonding acceptor.[34] This factor will be described later in detail.

Thirdly, carbon atoms act as proton donors in hydrogen bonding. Even through this subject has been controversial for many years, crystallographic studies have provided the evidence for C–H···O hydrogen bonds.[35] Usually these types of hydrogen bonds occur at carbon atoms adjacent to neutral or positively charged nitrogen atoms. These additional hydrogen bonds are possible in imide systems, but not in lactam systems (Figure 5).

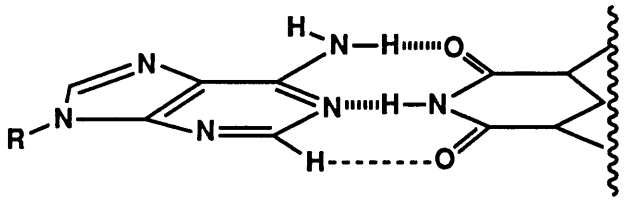

Figure 5 Possible C—H·····O hydrogen bonding between adenine **12** and imide functional group

1.3 Binding Affinities of Amides and Acids with Adenine

1.3.1 Synthesis.

Tripropyl triacid **20** was merely heated with 2,3-diaminonaphthalene **29** to give the rigid acid **30** in quantitative yield. Sequential treatment of acid

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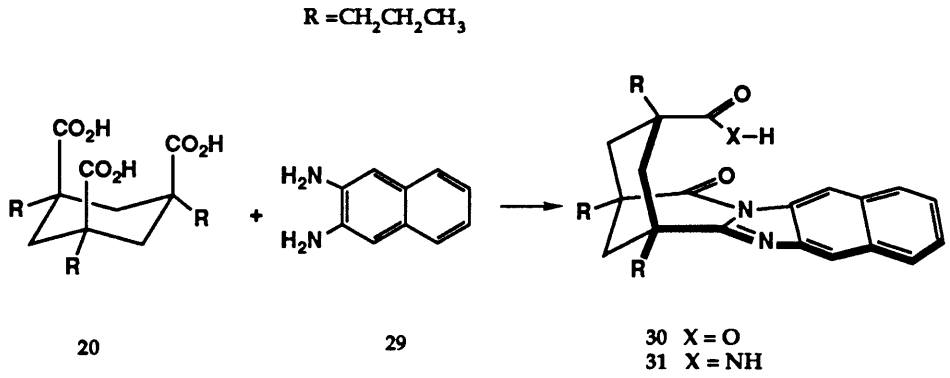
34 a) Hine, J.; Hahn, S.; Hwang, J. *J. Org. Chem.* **1988**, *53*, 884-887. b) Povsic, T. J.; Dervan, P. B. *J. Am. Chem. Soc.* **1989**, *111*, 3059-3061.

35 a) Saenger, W. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 591-601. b) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1984**, *104*, 5063-5070.

30 with thionyl chloride and ammonia provided the corresponding amide **31** (Scheme 7).

Scheme 7



1.3.2 Results and Discussion

Hydrogen bonds of acid and amide functional groups are important for the specific interactions between proteins and nucleic acids.[36] Some amino acids contain amide (Asn, Gln) and carboxylate groups (Asp, Glu) in the side chains which form hydrogen bonds with bases in nucleic acids. Recently, binding affinities of synthetic models with bearing amide or acid groups to adenine have been studied by Hamilton,[37] Wilcox,[38] and Zimmerman,[39] yet comparisons were not made between the different functional groups.

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36 Saneger, W. *Principle of Nucleic Acid Structure;* Springer-Verlag: New York, 1984; chapter 18.

37 Goswami, S.; Hamilton, A. D.; van Engen, D. *J. Am. Chem. Soc.* **1989,** *111,* 3425-3426.

As mentioned earlier, binding affinities in hydrogen bonds depend on the acidities of the hydrogen-bonding donors and the basicities of the hydrogen-bonding acceptors. It is very difficult to predict the relative strength of acid vs amide complexes with adenine. Both systems can form two hydrogen bonds. The carbonyl group of the amide is a better proton acceptor than that of the carboxylic acid, and the NH of the amide is a worse proton donor than the OH of the carboxylic acid.

First, binding studies of acid **30** were performed with 9-ethyladenine **12**. Titration[40] of **12** with **30** showed that the signal for adenine H_2 shifted from 8.38 to 7.18 ppm, adenine H_8 from 7.82 to 6.70 ppm, and N_9-CH_2 of adenine from 4.28 to 3.60 ppm. Additionally, signals for aromatic protons of acid **30** showed 0.2-0.3 ppm upfield shifts. Saturation curves shown in Figure 6 indicate that 1:2 stoichiometry between adenine **12** and acid **30** are formed in the complex **32**. The large upfield shifts of signals for adenine protons also indicate that adenine may be sandwiched between naphthalene chromophores in the complex **32** (Figure 7).

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38 Wilcox, C. S.; Adrian, J. C., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 8055-8077.

39 Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054-8055.

24 Initial concentrations of **12** and **30** are 4.0×10^{-3} M and 4.1×10^{-2} M in $CDCl_3$ at 296 °K, respectively.

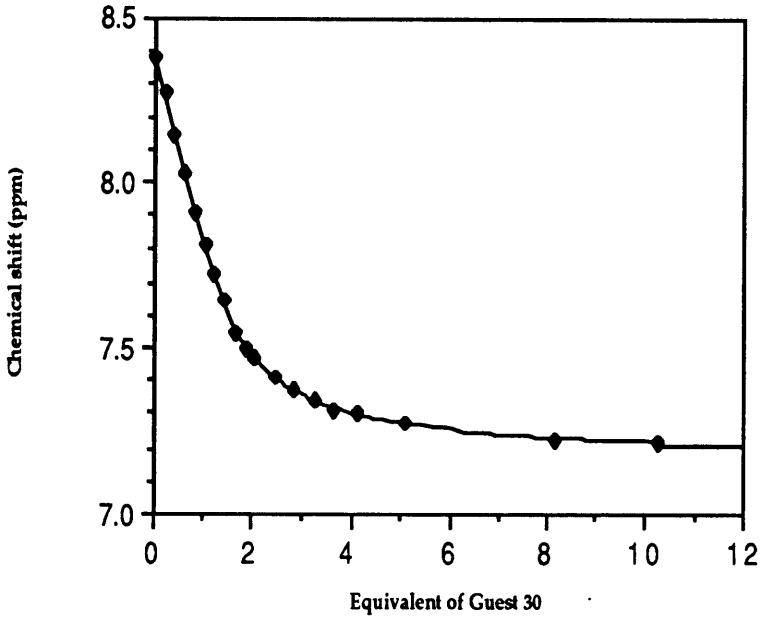

Figure 6 Saturation curve of the titration of **12** (H_2) with **30**.

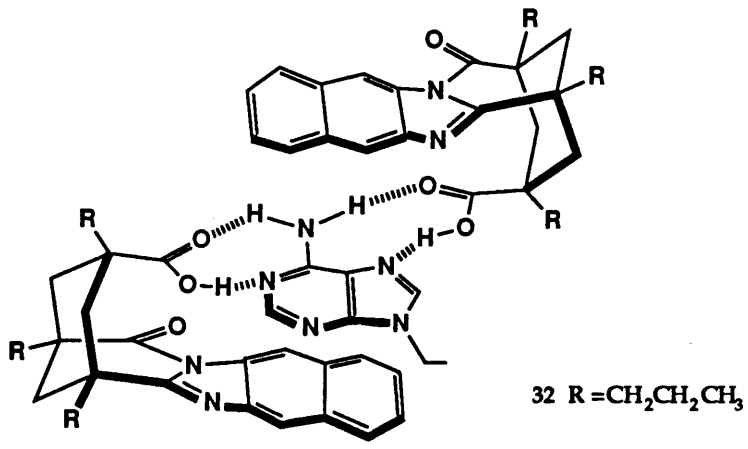

Figure 7 Proposed structure of complex **32** between receptor **30** and **12**.

Several methods such as Hill plots[41] and nonlinear square curve fits[42] were employed to determine the association constants of the complex. Association constants could not be obtained by these methods due to uncertainties in some parameters, especially $\delta_{complex}$ for 1:1 stoichiometry.

Due to these complexities, N_6-methyladenine **13** was used for this study in which only 1:1 complexation is possible with the Hoogsteen mode strongly favored. Titration[43] of acid **30** with **13** showed an association constant of 4900 ± 400 M^{-1} in $CDCl_3$ (Eq 7), and upfield shifts (~ 0.3 ppm) in the aromatic regions of the NMR spectra indicate aromatic stacking interactions. Under the same conditions, the association constant[44] of amide **31** with **13** is only 13 ± 2 M^{-1}.

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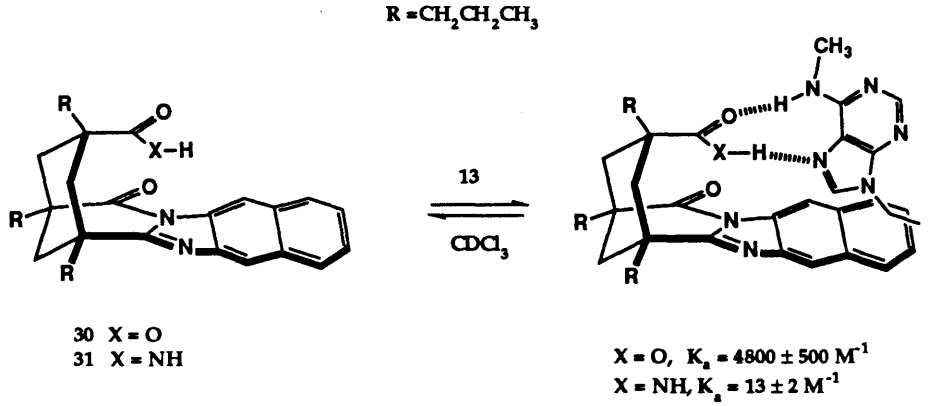
41 Hill, A. V. *Biochem. J.* **1913**, *7*, 471. b) Connors, C. A. *Binding Constants*; Wiley: New York, 1987; p 61.

42 A nonlinear least squares curve-fit program for 1:2 complex of host and guest was written by G. Deslongchamps. For another program employed here, see: Friedrichsen, B. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 9232-9234.

43 Initial concentrations of **30** and **13** are 2.2 x 10^{-3} M and 2.3 x 10^{-2} M in $CDCl_3$ at 296 °K, respectively. Association constants from two singlet aromatic protons of acid **30** are 4,500 M^{-1} and 5,300 M^{-1}.

44 Initial concentrations of **31** and **13** are 2.2 x 10^{-3} M and 2.3 x 10^{-2} M, respectively. Association constants from two singlet aromatic protons of amide **31** are 11 M^{-1} and 11 M^{-1}, and that from NH_2 signal is 16 M^{-1}.

Eq 7



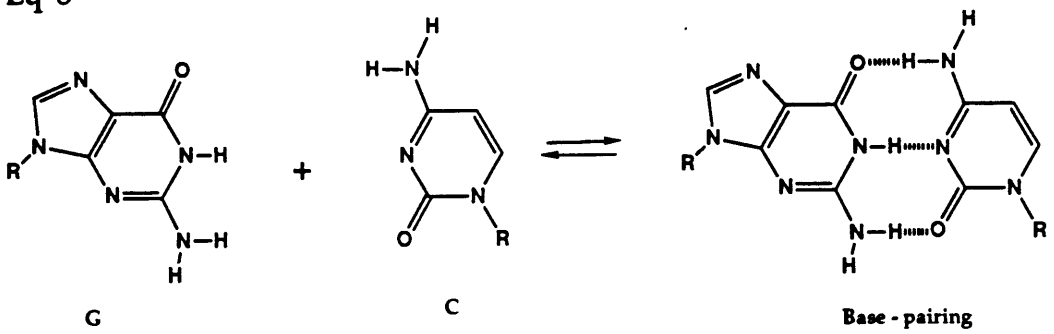
These association constants indicate that, in the formation of the complex, the increase of proton-donor ability seems to be much more important than the decrease of proton-acceptor ability when an amide group is compared with a carboxylic acid for adenine bases. The considerable reduction of association constant in amide **31** may be mainly attributed to the lower acidity of the amide group.

Chapter 2

Synthetic Receptors for Cytosine Derivatives

Guanine and cytosine bases form three hydrogen bonds as shown below (Eq 8). However, extensive studies of interactions between these two bases have not been carried out due to the limited solubilities of cytosine and guanine derivatives in nonpolar solvents. In 1966, Rich reported that association constant between guanosine and cytidine derivatives was in the range of 10^4 M^{-1} in $CDCl_3$.[45]

Eq 8



As a result of the single modification of an imide functional group which forms the complementary hydrogen bonds with adenine, receptors for cytosine were generated in this study.[46] These also feature three hydrogen bonds (Figure 8).

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45 Kyogoku, Y.; Lord, R. C.; Rich, A. *Science (Washington, D. C.)* **1966**, *154*, 518-520.

46 Jeong, K.-S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 3327-3328.

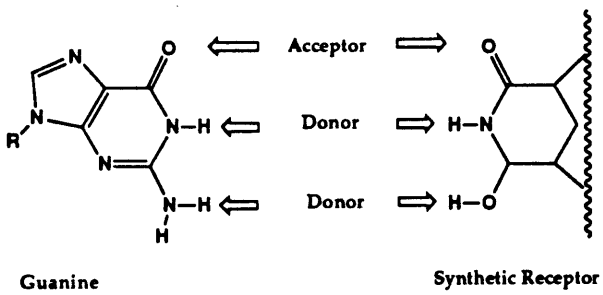
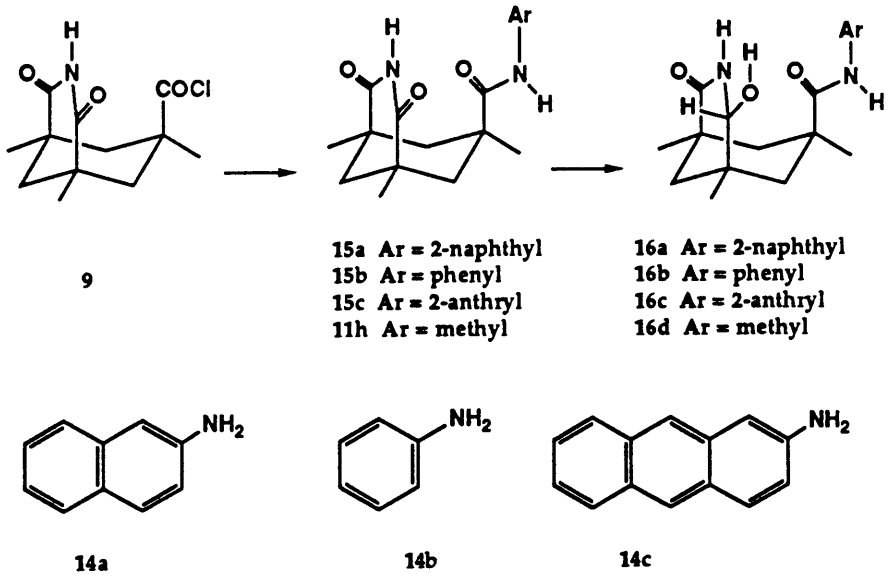


Figure 8 Hydrogen bonding patterns of guanine and receptors.

2.1 Synthesis and Structural Features

The aromatic amines were acylated with imide acid chloride **9**. The resulting imides **15a-d** were reduced at 0 °C by $NaBH_4$[47] to give the corresponding hydroxylactams **16a-d** which could provide simultaneous hydrogen bonds and aromatic stacking forces (Scheme 8).

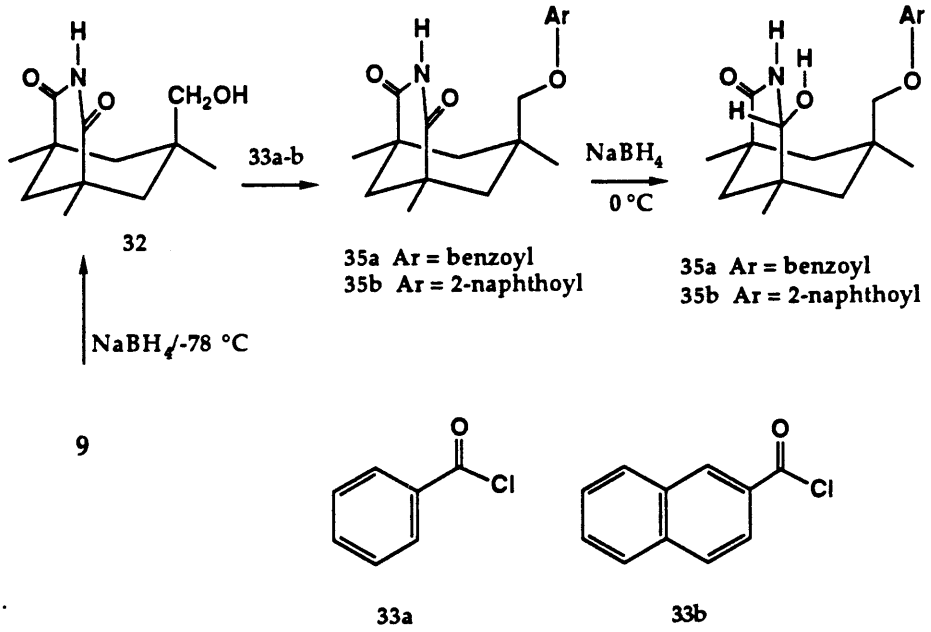
Scheme 8



47 Hubert, J. C.; Wijinberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437-1441.

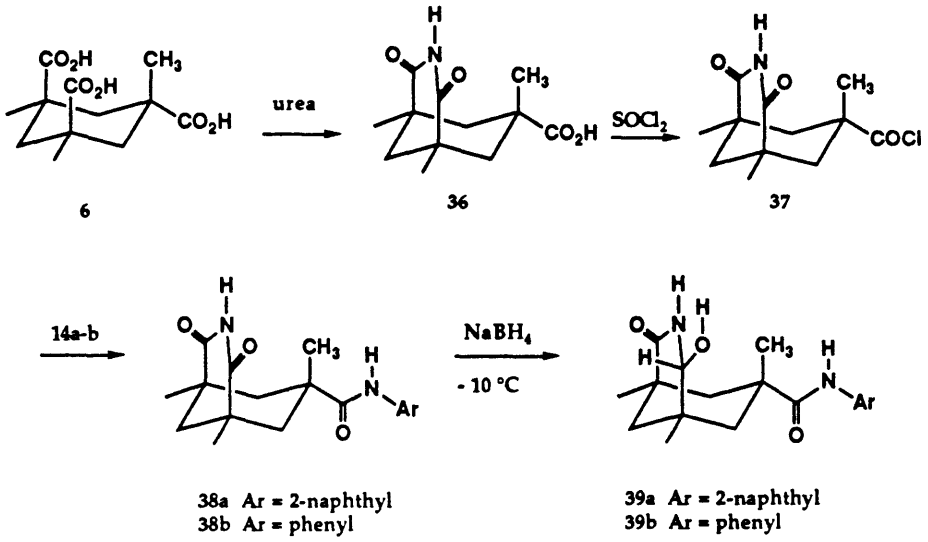
Acid chloride **9** was selectively reduced by $NaBH_4$ at -78 °C to give the imide alcohol **32**, which was acylated with aromatic acid chlorides, **33a** and **33b**. Reductions of imides **34a** and **34b** gave hydroxylactams **35a** and **35b**, respectively (Scheme 9).

Scheme 9



The synthesis of the cis-trans triacid **6** was described in the previous chapter. Heating of **6** with urea provided the cis-trans imide acid **36**, which was converted to the acid chloride **37** with $SOCl_2$. Cis-trans isomers **39a** and **39b** were prepared in a fashion parallel to the cis-cis isomers (Scheme 10).

Scheme 10

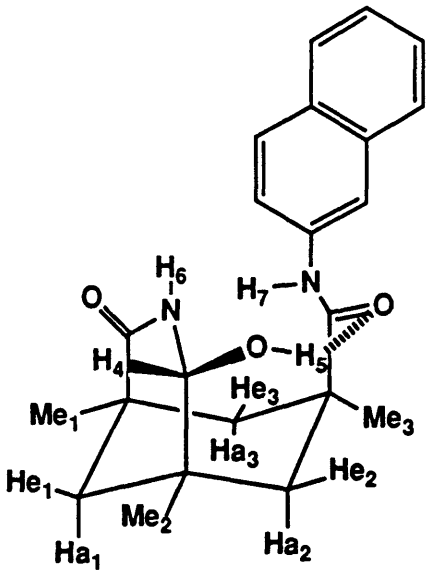


6 36 37

38a Ar = 2-naphthyl
38b Ar = phenyl

39a Ar = 2-naphthyl
39b Ar = phenyl

The structural features were determined by spectroscopic studies and crystallographic analysis. Specifically, hydroxylactam, **16a** was investigated.



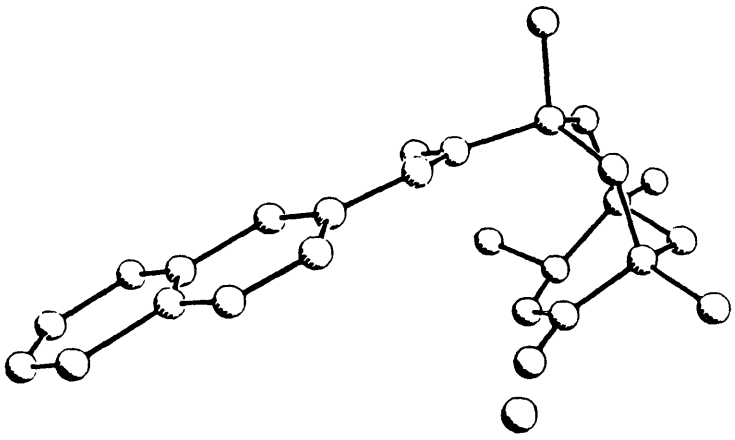
16a

An intramolecular hydrogen bond is revealed by a large coupling constant (13 Hz) between the hydroxyl proton H_5 (5.16 ppm) and the methine proton H_4 (4.17 ppm) in $CDCl_3$, while the coupling constant in the corresponding cis, trans isomer **38a** is only 6 Hz, and the chemical shifts of the OH and CH are, respectively, 3.07 and 4.85 ppm. The intramolecular NOE experiments also indicate that this intramolecular hydrogen bond limits considerably the internal rotations in the structure. The NOE results are summarized on the Table 3.

Table 3. Intramolecular NOE's of **16a**.

Irradiation	NOE (%)
H_7	He_3 (11)
H_6	H_5 (4.3), H_4 (7.3)
H_5	H_4 (2.8), He_2 (7.3)
H_4	H_6 (5.1), H_5 (8.6), He_1 (4), Me_2 (5)
He_2	H_5 (16), Ha_2 (28)
He_3	H_7 (22.2), Ha_3 (23)
He_1	H_4 (5.4), Ha_1 (22)

The crystal structure of **16a**, shown below, confirms the NOE results and shows a water molecule hydrogen bonded to the carbonyl group of the lactam.



X-ray structure of **16a**

2. 2 Results and Discussion

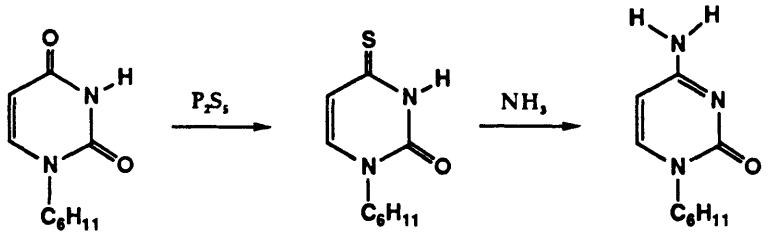
The titration[48] of each host with 1-cyclohexylcytosine **42**, made from 1-cyclohexyluracil **40** (Scheme 11),[49] in $CDCl_3$ gives changes consistent with simultaneous hydrogen bonding and stacking interactions.

---

48 Typical initial concentrations of receptors and guest **42** are 5×10^{-3} M and $1.3\text{-}1.8 \times 10^{-2}$ M in $CDCl_3$. Association constants reported in Table 4 are the average values of three signals monitored (NH, OH, CH). Individual values are of K_a's within ± 10 % of average values.

49 Okano, T.; Goya, S.; Takahashi, T. *Yakugaku Zasshi.* **1968**, *88*, 1112-1117. (*Chem. Abs.* **1969**, *70*, 37756x). See, also: Fox, J. J.; van Praag, D.; Wempen, I.; Doerr, I. L.; Cheong, L.; Knoll, J. E.; Eidinoff, M. L.; Bendich, A.; Brown, G. B. *J. Am. Chem. Soc.* **1959**, *81*, 178-187.

Scheme 11



40 41 42

Upon titration of **16a** with **12**, downfield shifts of the signals of the amide (5.9 ppm, 5.5 to 11.4 ppm), hydroxyl (2.8 ppm, 5.2 to 8.0 ppm), methine proton (0.38 ppm, 4.58 to 4.96 ppm), and upfield shifts in the aromatic protons were observed. Other hosts show similar shifts. Association constants are obtained from Eadie plots, and are shown in Table 4.

Table 4. Association Constants of Hosts with **42** in $CDCl_3$ at 296 ± 1 °K

Host	Ka (M^{-1})	Host	Ka (M^{-1})
16a	260	**35a**	366
16b	100	**35b**	362
16c	290	**39a**	2325
16d	32	**39b**	2170

In hosts, **16a-d**, hydrogen bonding is expected to contribute a constant amount but the different aromatic surfaces offer various degrees of π-stacking interactions. The naphthalene surface appears to offer the maximum stacking interactions available in this system. The titration could also be followed by observing the change in coupling constant between the hydroxyl

and methine proton; this decreases from 13 to 3 Hz during complexation. The changes of the coupling constant are shown in Figure 9 for the specific case of 2-naphthylamide hydroxylactam **16a** and 1-cyclohexyl cytosine **42**.

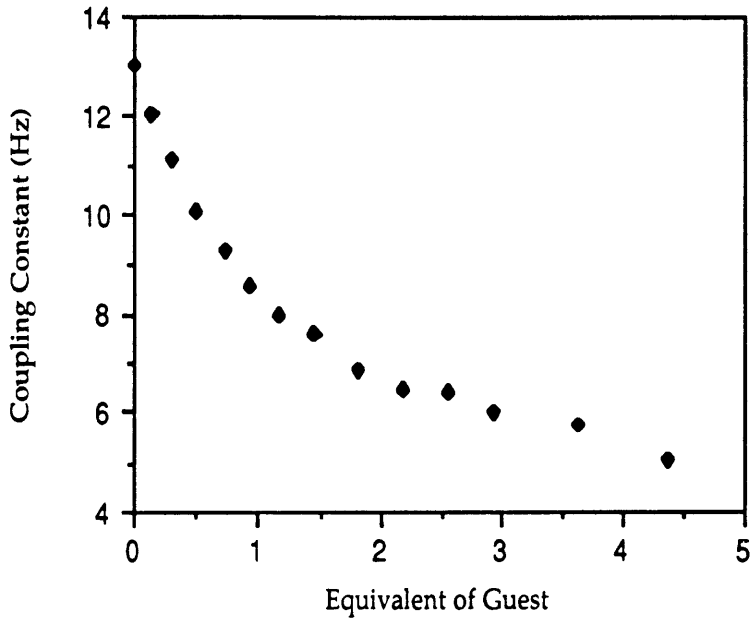
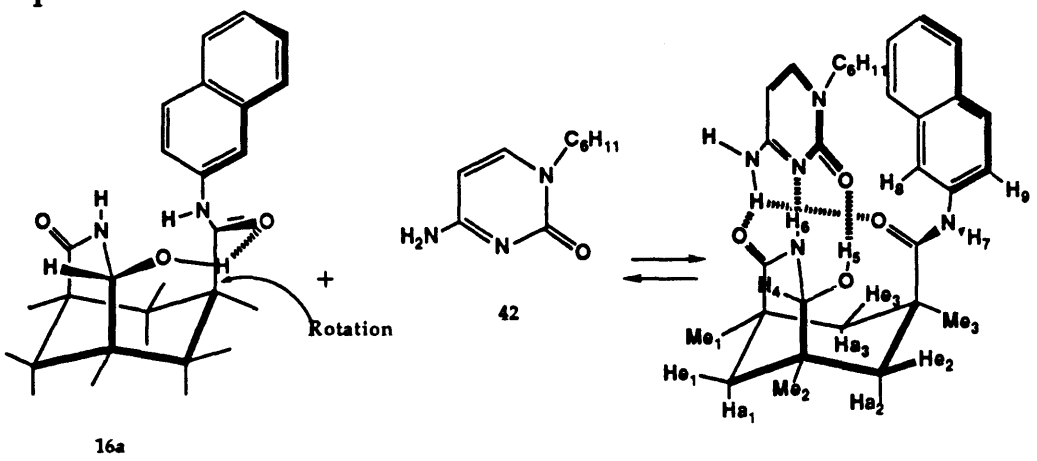


Figure 9 Change of coupling constant (Hz) in the titration of **16a** with **42**.

The signal for the equatorial proton He_2 shifts from 2.96 to 2.67 ppm and He_3 shifts from 2.33 to 2.98 ppm with increasing concentration of complex in the titration. This suggests that the bond indicated in the complex (Eq 9) is rotated on the complexation in order that bifurcation of the amine proton of 1-cyclohexylcytosine **19** and both amide carbonyl oxygens of host **16a** can be achieved.

Eq 9



Rotation for bifurcated hydrogen bonding is also revealed in the NOE experiments. In the mixture of **16a/42** (1:1), which has approximately 63 % complex ($CDCl_3$, 9.22 ppm (NH), $\Delta\delta_{obs}$ = 3.72 ppm, $\Delta\delta_{max}$ = 5.9 ppm), the NOE ratio of both equatorial protons, He_2 and He_3, on the irradiation of H_7 is consistent with the amount of complex in the mixture (He_2/He_3 = 42/58). Similarly, the NOE ratio of the signals for the equatorial protons (He_2/He_3 = 34/66) on the irradiation of H_7 is also consistent with amounts of complex (70 %, 9.66 ppm (NH), $\Delta\delta_{obs}$ = 4.16 ppm, $\Delta\delta_{max}$ =5.9 ppm) in the mixture (**16a/42** = 1:4). Therefore, it can be considered that the NOE of He_2 comes from the free **16a** and the NOE of He_3 from the complex. The NOE results are summarized in Table 5.

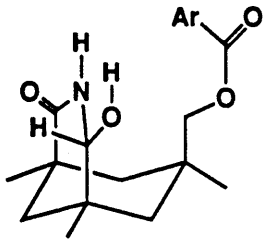
Table 5. Intramolecular NOE's of Receptor **16a** upon Complexation with **42**.

Irradiation	NOE (%) **16a/42** = 1:1	NOE (%) **16a/42** = 1:4
H_7	He_2 (8.5), He_3 (6.2)	He_2 (10), He_3 (5.1)
	H_8 (4.1), H_9 (10.9)	H_8 (4.4), H_9 (11.9)
H_4	He_1 (2.7), Me_2 (4.1)	He_1 (3.1), Me_2 (5.1)
	H_6 (3.8)	H_6 (4.5)
He_2	H_7 (8.7), Ha_2 (30.6)	H_7 (12.3), Ha_2 (23.3)
He_3	H_7 (7.4), Ha_3 (29)	H_7 (6.1), Ha_3 (25)

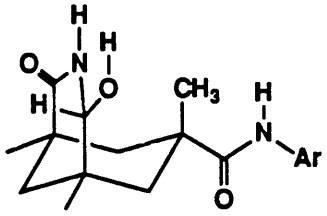
As mentioned earlier, there is an intramolecular hydrogen bond between the hydroxyl and the neighboring carbonyl group in the receptors, but in complexes it is destroyed by rotation of the C—C=O bond indicated in Eq 20. Therefore, only two hydrogen bonds are created during the complexation. As a result, the association constants are in the hundreds rather than the thousands expected for three net hydrogen bonds. This can be also recognized in the thermodynamic parameters. Studies at various temperatures (273-323 °K) with **16a** and **42** give ΔH = -8.65 Kcal/mol and ΔS = -18 eu.

This intramolecular hydrogen bond must be broken to get the maximum intermolecular association in this system. It is well shown in the association of hosts **39a** and **39b** with **42**. The association constants are 2250 ±

100 M^{-1} for the net three hydrogen bonds. Recently, others[50] have reported that the association constant was in the range of 10^3-10^4 M^{-1} for the guanosine and cytidine derivatives in chloroform.



35a Ar = phenyl
35b Ar = 2-naphthyl



39a Ar = 2-naphthyl
39b Ar = phenyl

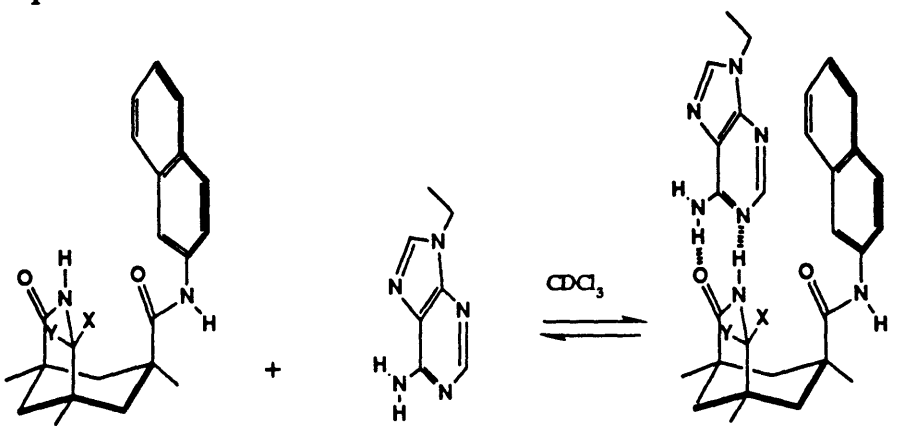
The hosts, **35a-b**, were synthesized not only to remove an intramolecular hydrogen bond but also to achieve a simultaneous π-stacking interaction. However, these hosts still possess an intramolecular hydrogen bond even though the distances between the hydroxyl and carbonyl group are longer than those in hosts **16a-d**. In hosts, **35a** and **35b**, the coupling constant between the hydroxyl and methine proton is 11.2 Hz. Additionally, in IR spectroscopy, the stretching absorption band of the ester carbonyl of hydroxylactam **35b** is 1713 cm^{-1}, while the corresponding band of the imide **34b** is 1721 cm^{-1}. This shift is caused by the intramolecular hydrogen bond between the proton of the hydroxyl and the oxygen of the adjacent ester carbonyl group. The association constants of **35a** and **35b** with **42** are similar (~360 M^{-1}) and there is no stacking advantage in **35b** with the larger aromatic surface. These hosts, **35a** and **35b** may not involve stacking interactions in the

50 a) Hamilton, A. D.; Pant, N. *J. Chem. Soc., Chem. Comm.* **1988**, 795-796.
b) Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245-255.

formations of complexes because of the improper orientation of the aromatic ring.

The selectivity of an imide and corresponding hydroxylactam for 9-ethyladenine was investigated (Eq 10).

Eq 10



15a X = Y = O
16a X = OH, Y = H

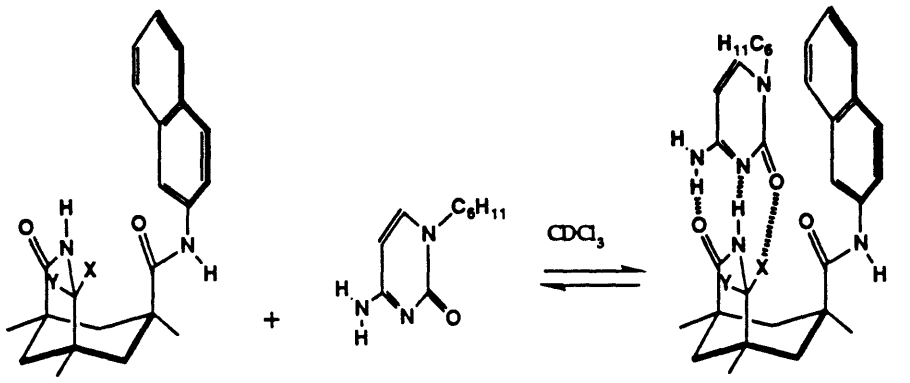
12

X = Y = O Ka = 220 M^{-1}
X = OH, Y = H Ka = ~ 25 M^{-1}

The association constant of the 2-naphthylamide hydroxylactam **16a** with 9-ethyladenine **12** is 220 M^{-1}. Titration of naphthylamide hydroxylactam **16a** with 9-ethyladenine **12** gave a value of ~ 25 M^{-1}. In contrast to the association with **16a** and cyclohexylcytosine **42**, the coupling constant between the hydroxyl and the methine proton does not change on the titration of **16a** with 9-ethyladenine **12**, indicating that the hydroxyl group does not participate in the complexation. The selectivity of adenine **12** between these systems is, therefore, approximately 9-fold.

Reverse selectivity between imide and hydroxylactam was observed for the cytosine base (Eq 11).

Eq 11



15a X = Y = O
16a X = OH, Y = H

42

X = Y = O Ka = < 10 M^{-1}
X = OH, Y = H Ka = 260 M^{-1}

The association constant of the 2-naphthylamide hydroxylactam **16a** with 9-ethyladenine **12** is 260 M^{-1}, but the mismatched interaction[51] of 2-naphthylamide imide **15a** with cyclohexylcytosine **42** shows an association constant of only <10 M^{-1}.

Imide systems prefer adenine to cytosine bases at least 20-fold and hydroxylactam systems prefer cytosine to adenine bases approximately 10-fold. This study shows that quite striking selectivities in molecular recognition can be achieved by altering a single hydrogen bonding site.

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51 For a similar mismatch, see: Williams, L. D.; Shaw, B. R.; *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 1779-1983.

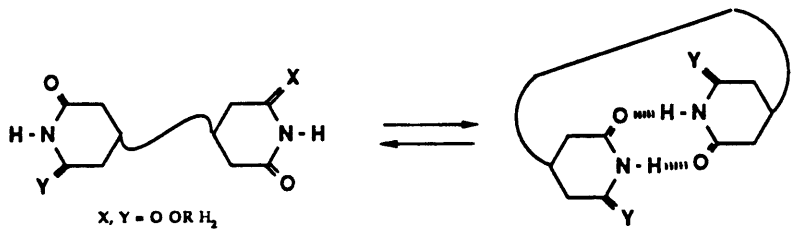
Chapter 3

Relative Hydrogen Bonding Affinities of Imides and Lactams

Hydrogen bonding is one of the most important interactions for specific recognition and catalysis in biological systems.[52] For this reason, a key goal in molecular recognition is finding the best functional groups in synthetic receptors for maximum intermolecular interactions.

In this study,[53] the relative hydrogen-bonding affinities between imide-imide, imide-lactam, and lactam-lactam systems are examined. Even through the self-association of imide or lactam functional groups has been studied in non-polar solvents,[54] it is difficult to determine the relative affinities due to the low association constants. By arranging an intramolecular (cyclization) model (Eq 12), it is possible to magnify the association to a conveniently measurable level.

Eq 12



52 a) Blow, D. M. *Acc. Chem. Res.* **1976**, *9*. 145-152. b) Fersht, A. R. *Trends Biochem. Sci.* **1984**, *9*, 145-147. c) Fersht, A. R. *Trends Biochem. Sci.* **1987**, *12*, 301-304.

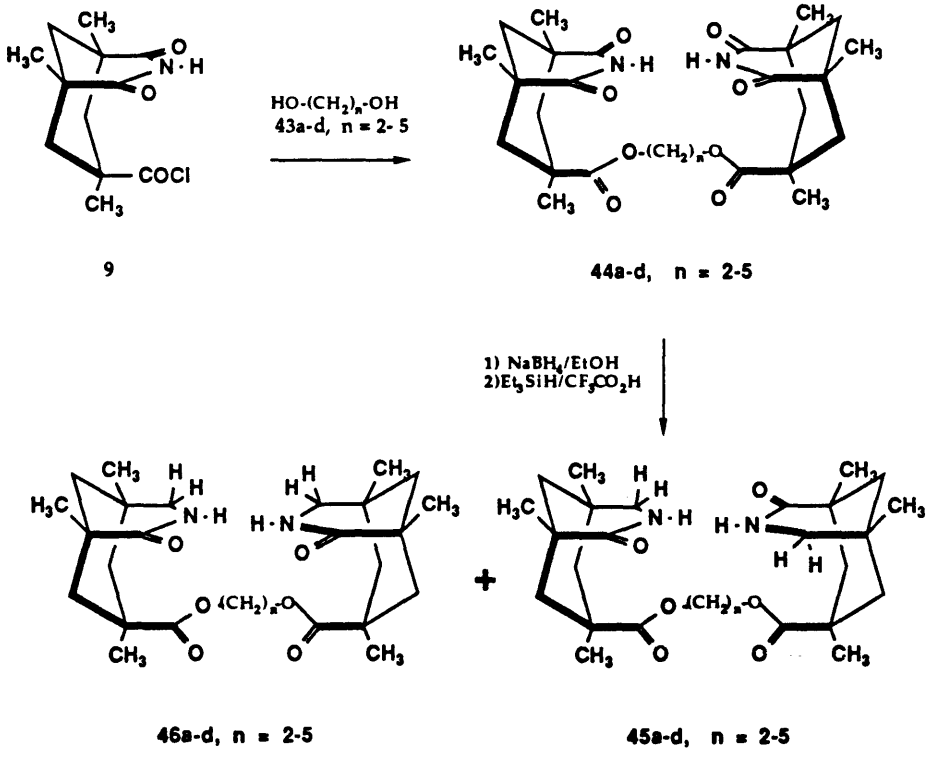
53 Jeong, K.-S.; Tjivikua, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3215-3217.

54 a) Walmsley, J. A. *J. Phys. Chem.* **1978**, *82*, 2031-2035. b) Krikorian, S. E. *J. Phys. Chem.* **1982**, *86*, 1875-1881. c) Hine, J.; Hahn, S.; Hwang, S. *J. Org. Chem.* **1988**, *53*, 884-887.

3.1 Synthesis

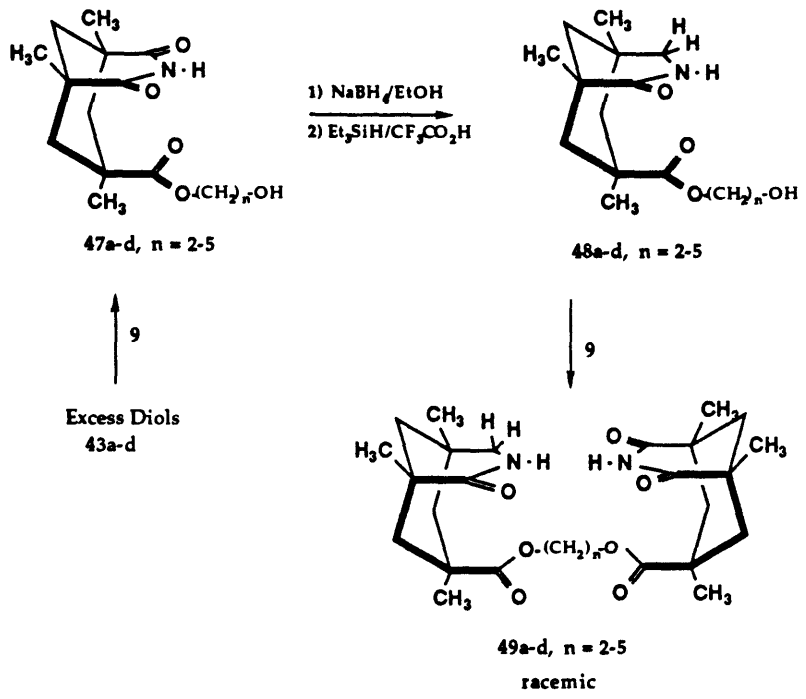
Various α,ω-diols **43a-d** were acylated with imide acid chloride **9** to give the series of the corresponding diimides **44a-d** in a high yield (65-85 %). Reductions of the diimides **44a-d** with excess $NaBH_4$, and then Et_3SiH/CF_3CO_2H led to the mixture of racemic **45a-d** and meso dilactams **46a-d**, which were separated by flash chromatography (Scheme 12).

Scheme 12



Finally, esterification of imide acid chloride **9** with excess diols **43a-d** gave imide alcohols **47a-d** in a high yield (67-87 %). **47a-d** were reduced to lactam alcohols **48a-d**, which were again acylated with **9** to afford imide-lactam systems **49a-d** (Scheme 13).

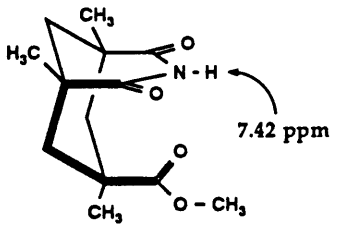
Scheme 13



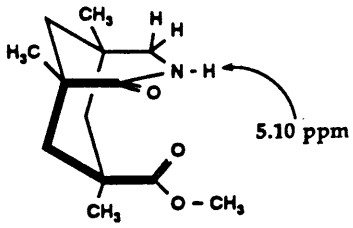
3.2 Results and Discussion

The cyclization constants, K_C, were determined by following the chemical shifts for the ^1H NMR signals of imide and/or lactam NH's at 295 °K. The ^1H NMR resonances for the free imide (7.42 ppm) and lactam NH's (5.10 ppm) were determined by the dilutions of methyl ester imide **11g** and methyl ester lactam **50**[55] at 295 °K.

55 The synthesis of lactam methyl ester **50** is described in Chapter 5.



11g



50

In **44a-d**, **45a-d**, and **49a-d**, the chemical shifts of the exchangeable protons (NH's) were concentration independent at 295 °K, suggesting that intermolecular associations are negligible in these systems. The chemical shifts for the completely cyclized forms were obtained by cooling solutions of the corresponding C_3 molecules **44b**, **45b** and **49b**, which showed the most cyclic forms at 295 °K, until no further downfield shifts were observed. These values and the cyclization constants are reported in Table 6.

Since all systems have the flexible alkyl spacers, it was assumed that two hydrogen bonds were formed in the cyclic forms. For comparison with other equilibria, the cyclization constants K_c's for the imide-imide systems must be statistically corrected because there are two ways for intramolecular cyclization (Eq. 13).

Eq 13

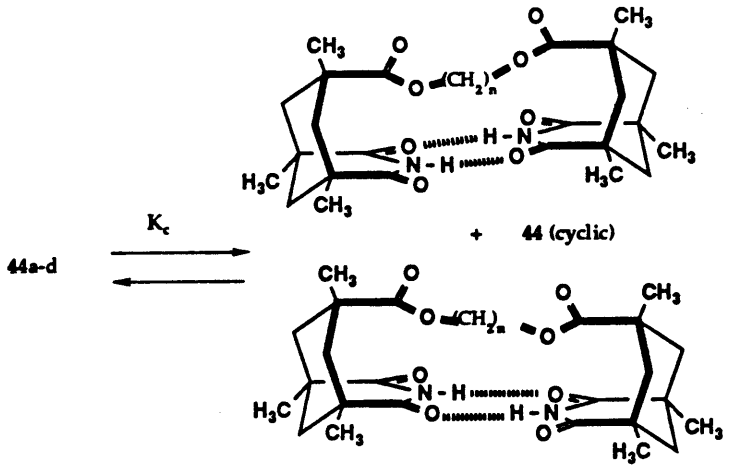
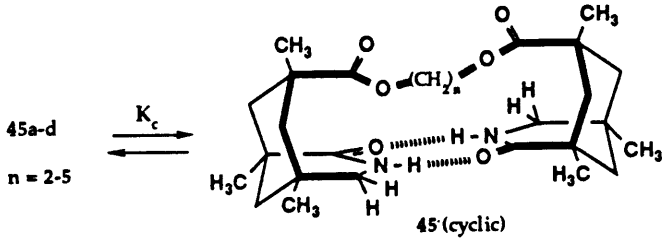


Table 6 Cyclization Data in $CDCl_3$ at 295 ° K

	Imide-Imide (Eq 13)				Lactam-Lactam (Eq 14)			Imide-Lactam (Eq 15)		
δ_{free}	7.42				5.1			5.1	7.42	
δ_{cyclic}	10.40				8.6			7.54	11.93	
	Imide-Imide (Eq 13)				Lactam-Lactam (Eq 14)			Imide-Lactam (Eq 15)		
n	δ_{obsd}	% cyclic	K_{obsd}	K_{calcd} (corr)	δ_{obsd}	% cyclic	K_{calcd}	δ_{obsd}	% cyclic	K_{calcd}
2	9.29	63	1.7	0.85	8.11	86	6.1	6.92/10.87	75	3
3	9.90	83	5.2	2.6	8.47	96	24	7.23/11.47	87-90	8
4	8.36	32	0.45	0.22	6.76	48	0.92	5.75/9.42	27-44	0.43-0.78
5	8.59	39	0.64	0.32	7.04	55	1.2	6.06/9.46	39-45	0.66-0.82

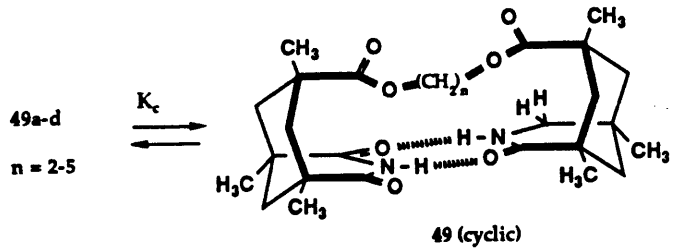
In dilactam systems, the observed chemical shifts of racemic dilactams **45a-d** were used to determine the cyclization constants, K_c's (Eq.14) since meso dilactams[56] could not form simultaneously two intramolecular hydrogen bonds. The lactams **45a-d** consistently show higher tendency to cyclize than the corresponding imides **44a-d**, even though the latter have a statistical advantage.

Eq 14



In the imide-lactam systems **49a-d** (Eq 15), the cyclization constants, K_c's, are values between those of the corresponding diimides **44a-d** and dilactams **45a-d**.

Eq 15



56 The meso forms of dilactams **46a-d** showed NH resonances between 5.26 and 6.00 ppm.

The K_c's reported for imide-lactam systems are calculated independently from the two chemical shifts (imide NH's, lactam NH's). The range may indicate that some single hydrogen bonds exist in the C_4 and C_5 species of Eq. 15.

The overall results show that the dilactams have a greater tendency to self-associate than imide-lactams, which in turn self-associated better than diimides. These results appear to be opposite to the higher binding affinities of adenines to imides over lactams. The enhanced acidity of the imide is of little advantage in hydrogen bonding to imides or lactams. Jorgensen[57] has recently proposed that secondary interactions alter the effective strength of hydrogen bonds. As shown in Figure 10, the additional repulsive interactions between the oxygens are expected to destabilize the hydrogen-bonded array in imide-lactams and diimides. If this is the cause, each such interaction costs the system ~ 0.4 kcal/mol under these conditions.

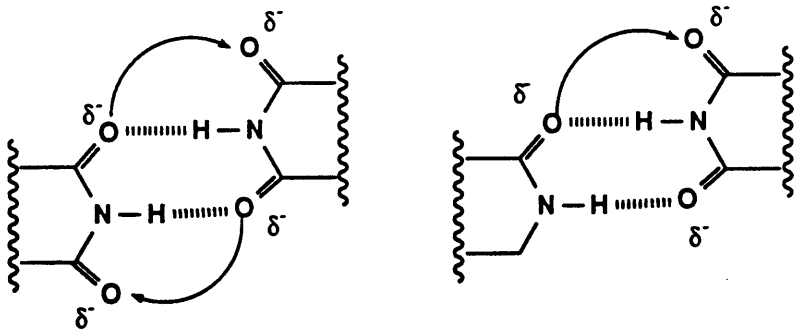


Figure 10 Secondary hydrogen bonding interactions of diimides (left) and imide-lactams (right).

57 Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008-2010.

Chapter 4

Molecular Recognition with Chiral Receptors

Chiral resolution of neutral substrates with synthetic receptors is one of the important issues in molecular recognition. Recently, several studies[58] have been reported in this area. Chiral recognition using new synthetic molecules can provide further development of the enantiomer separation in chromatography[59] and transport[60]. The major forces in chiral discrimination are steric interactions. Also different hydrogen bonds occur between the two enantiomers in the diastereomeric complexes.

In this study, new receptors[61] are prepared for biologically important substrates such as diketopiperazines, hydantoins, and barbiturates. These substrates are broad classes of drugs and have similarities in their structures as shown below.

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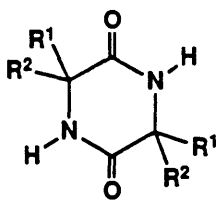
58 a) Feibush, B.; Figueroa, A.; Charles, R.; Onan, K. D.; Feibush, P.; Karger, B. L. *J. Am. Chem. Soc.* **1986**, *108*, 3310-3318. b) Rebek, J., Jr.; Askew, B.; Ballester, P.; Doa, M. *J. Am. Chem. Soc.* **1987**. *109*, 4119-4120. c) Dharanipragada, R.; Ferguson, S. B.; Diederich, F. *J. Am. Chem. Soc.* **1988**, *110*, 1679-1690. d) Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835-5838. e) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184-5186.

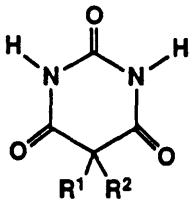
59 Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347-362.

60 Pirkle, W. H.; Doherty, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 4113-4114.

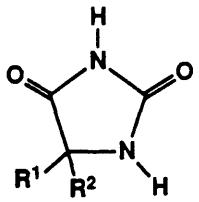
61 a) Jeong, K. -S.; Muehldorf, A. V.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144-6145. b) Jeong, K. -S.; Tjivikua, T.; Muehldorf, A. V.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc. in press.*



Diketopiperazines



Barbiturates

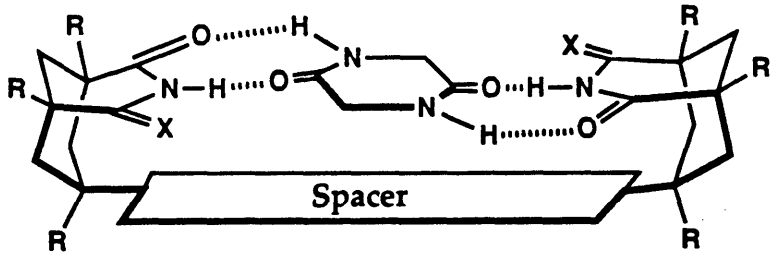


Hydantoins

4.1 Asymmetric Complexation of Diketopiperazines

4.1.1 Design and Syntheses of Receptors

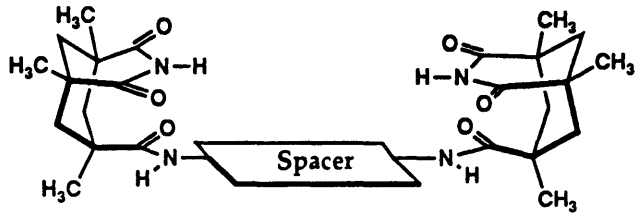
Diketopiperazines have two C_2 symmetric lactam functional groups. The first choice of functional group in receptors for complementary hydrogen bonding to diketopiperazine was the imide since it is easily synthesized and converted to chiral lactams. Spacer can be selected to yield highly preorganized molecular clefts of complementary size and shape for the recognition of diketopiperazines (Figure 11).



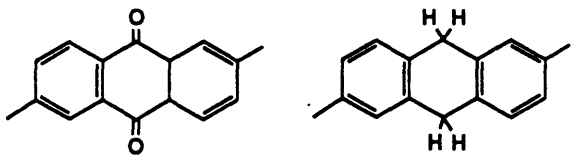
X = O, H_2

Figure 11 General structures of the complexes between receptors and diketopiperazine.

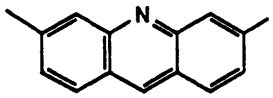
Three receptors were synthesized for initial binding studies of diketopiperazine derivatives. Receptor **52** was prepared by refluxing a solution of 9,10-dihydro-2,6-anthracenediamine **56** and imide acid chloride **9** in pyridine. Receptors **51** and **53** were prepared by heating a solid phase mixture of the corresponding diamines and imide acid chloride **9** to 230 °C.



Spacer =



51 52



53

However, receptors **51** and **52** were insoluble in most organic solvents[62] and not suitable for binding studies. Receptor **53** is slightly soluble in chloroform, but the spectra are very broad due to possible self-association.

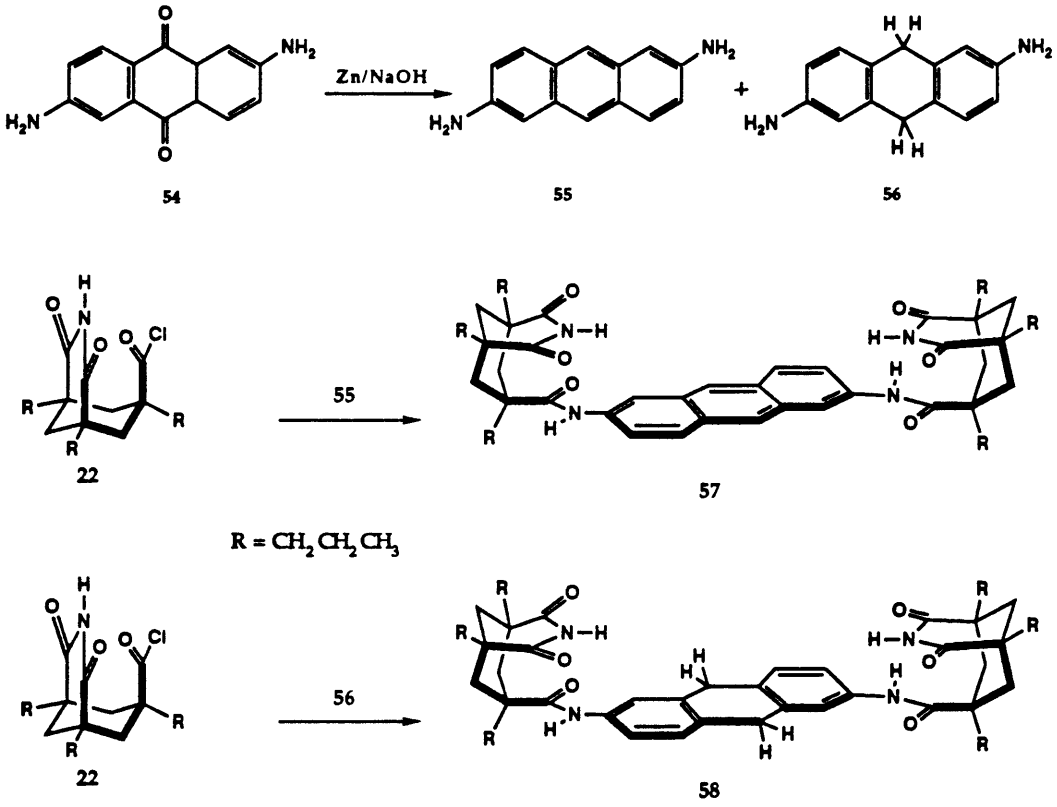
The solubility problem of receptors was solved by using tripropyl triacid derivatives. As shown in Scheme 14, 2,6-anthraquinone-diamine **54** was reduced with zinc to afford a mixture (~ 1:1) of two aromatic diamines **55**

---

62 Receptors **51** and **52** were insoluble in methylene chloride, chloroform, acetonitrile, tetrohydrofuran, but soluble in dimethyl sulfoxide.

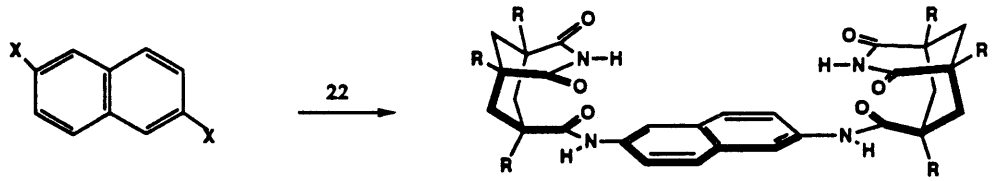
and 56,[63] which were acylated with tripropyl imide acid chloride **22** to give diimides **57** and **58**, respectively.

Scheme 14



63 For a reduction of anthraquinonedicarboxylic acid, see: Caluwe, P.; Pepper, T. *J. Org. Chem.* **1988**, *53*, 1786-1790 and references contained therein.

Scheme 15



59 R = OH
60 R = NH_2

61 R = $CH_2CH_2CH_3$

2,6-Naphthalenediamine **60** was prepared by Bucherer reaction of the corresponding diol **59** (Scheme 15).[64] Acylation of **60** with tripropyl imide acid chloride **22** gave diimide **61** which turned out to be an ideal receptor for diketopiperazine. Diimides **61** was reduced to dilactams **64a-b**, **65** for chiral recognition (Scheme 16). The racemic tricyclic dilactam[65] **62** was separated by flash chromatography from the meso form **63**, and then each diastereomer was further reduced to the corresponding dilactams. The enantiomers, **64a** and **64b**, were resolved by preparative HPLC using a Pirkle column.[66]

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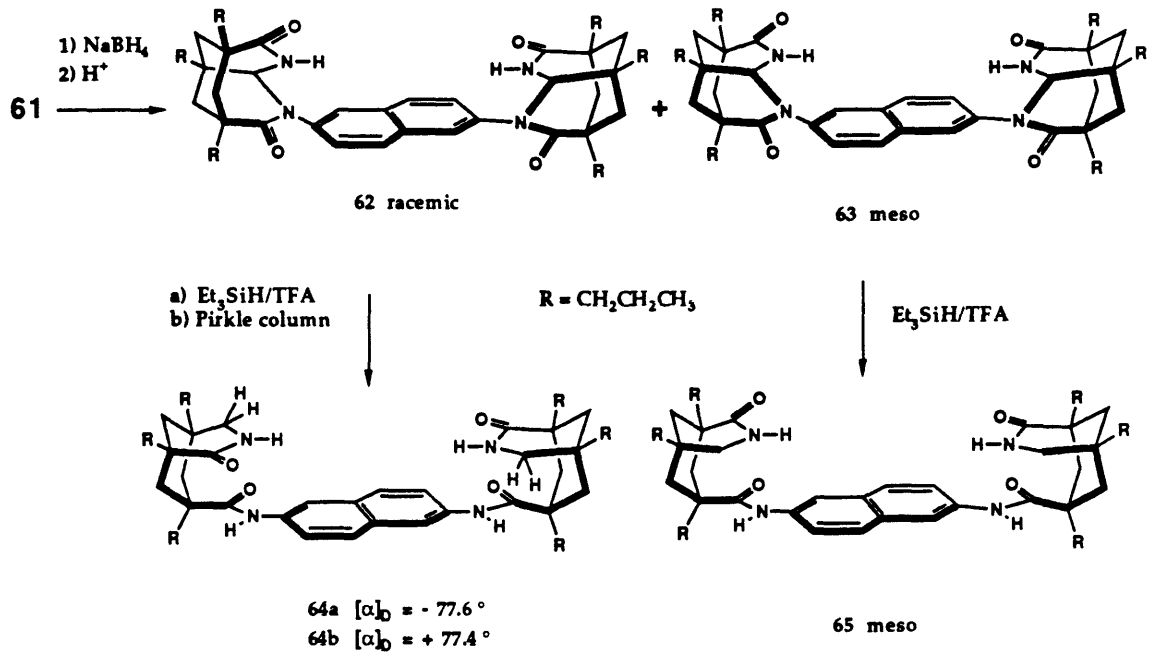
64 Chatt, J.; Wynne, P. *J. Chem. Soc.* **1943**, 33-36.

65 Tricyclic dilactams, **62** and **63** were prepared for the convenient separation by flash chromatography. After reduction of diimides **61**, the resulting hydroxylactams could be directly treated with Et_3SiH/TFA to give a mixture of racemic **64a-b** and meso dilactams **65**, which could not be separated by flash chromatography since they were appeared as one spot on TLC in several different solvent systems.

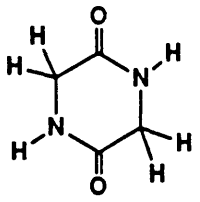
66 Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352-354. Columns are purchased from Regis Chemical Co.

Scheme 16

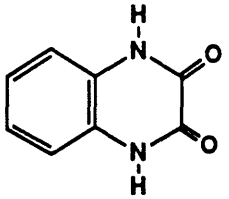


4.1.2 Results and Discussion

The binding properties of these receptors were examined by solid-liquid extractions. These procedures are useful when either receptors or substrates are not soluble in chloroform. The receptors are highly soluble, but substrates glycine anhydride **66** and quinoxalinedione **67** are insoluble in chloroform.



66



67

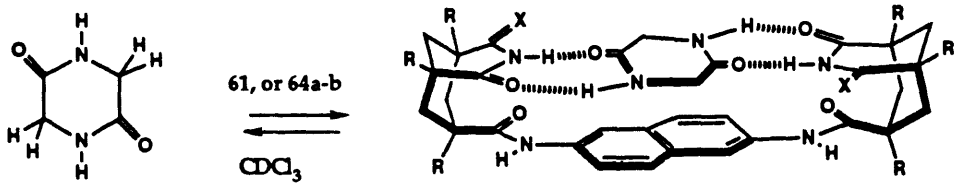
For the solid-liquid extractions, an excess of finely powered solid substrate is extracted at ambient temperature with a $CDCl_3$ solution of receptor by ultrasonic irradiation until the extraction equilibrium is established. The excess solid is filtered and the amount of substrate in solution measured by integration of the appropriate signals in ^1H NMR. When the solubility of substate is known, the association constant can be obtained by solid-liquid extractions. However, the solubilities of substrates, **66** and **67** are unknown in chloroform, and therefore association constants (Ka's) between receptors and substrates are not determined in this study. The results of solid-liquid extractions are shown in Table 7.

Table 7 Solid-Liquid Extractions of Glycine Anhydride **66** and Quinoxalinedione **67** with Receptors in $CDCl_3$ at 295 ± 1 °K.

Receptor	Equivalent of **66** dissolved	Equivalent of **67** dissolved
57	< 0.05	-
58	0.4	-
61	0.7	0.5
64a	0.8	0.3
64b	0.8	0.32
65	0.45	0.65

The distance between the two imide functional groups in the receptor is the dominant factor in solid-liquid extractions. The anthracene spacer is simply too large to simultaneously form four hydrogen bonds between anthracene diimide **57** and glycine anhydride **66**, dissolved. However, the receptor **58** can fold enough to accommodate the guest **66**. On the other hand, naphthalene dimide **61** dissolves 0.7 equivalent of glycine anhydride **66**. CPK molecular models show that four hydrogen bonds can be formed in the complex of receptors **61, 64a-b** and substrate **66**. The naphthalene dilactams **64a** and **64b** dissolve glycine anhydride **66** more efficiently than the corresponding diimide **61** (Eq 16). As discussed in the previous Chapter, this is due to secondary repulsions in diimide **61**.

Eq 16



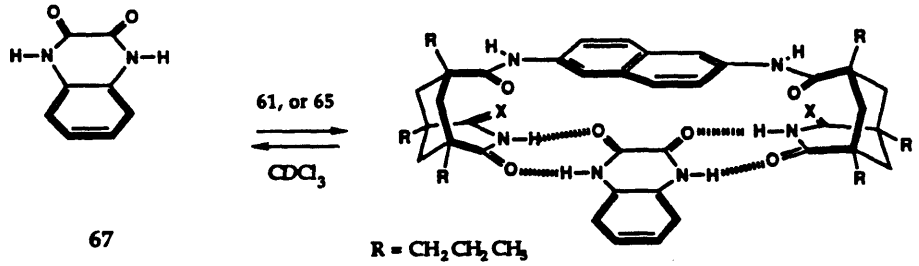
66

R = $CH_2CH_2CH_3$

X = O, 0.7 equiv.
X = H_2, 0.8 equiv.

The meso naphthalene dilactam **65** can form only three hydrogen bonds with glycine anhydride **66**, but can form four hydrogen bonds with quinoxalinedione **67**. The meso form **65** dissolves 0.65 equivalent of quinoxalinedione **67**. The optically active dilactams **64a-b** can form three hydrogen bonds with quinoxalinedione **67** and dissolve only 0.3 equivalent of **67** in chloroform. Secondary interactions are possibly the reason for the ability of meso dilactam **65** to solubilize quinoxalinedione **67** better than the diimide receptor, even though both systems can form four hydrogen bonds to quinoxalinedione (Eq 17).

Eq 17

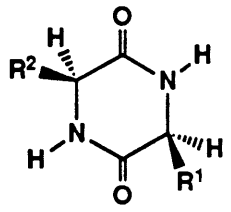


67

R = $CH_2CH_2CH_3$

X = O, 0.5 equiv
X = H_2, 0.65 equiv

A more quantitative determination of the affinity of the receptors for the cyclic dipeptides can be obtained by NMR titration.[67] The cyclic peptides studied were cyclo-L-leucyl-glycine **68** and cyclo-L-leucyl-L-leucine **69**, both of which are soluble in chloroform. Since both cyclic dipeptides are chiral molecules, the asymmetric complexations can be studied with chiral lactams **64a** and **64b**.



68 $R^1 = H, R^2 = i\text{-butyl}$

69 $R^1 = R^2 = i\text{-butyl}$

Titration[68] of naphthalene diimide **61** with cyclo(Leu-Gly) **68** showed a shift of the signal for the imide proton of receptor **61** from 7.51 to 11.46 ppm. This signal was very broad until approximately 1 equivalent of **68** was added. The association constant obtained from non-linear least squares fit of the titration data was 50,000 M^{-1}. During the titration[69] of naphthalene (-)-dilactam **64a** with **68**, the lactam NH resonance disappeared until approximately 1 equivalent of **68** was added. Association was monitored by

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67 All titrations were performed in $CDCl_3$ at 296 ± 1 °K and were not repeated. Estimated error of K_a's are within ± 20 %. All association constants for this study were determined from the nonlinear least squares fits of the saturation plots.

68 The initial concentrations of receptor **61** and cyclo(Leu-Gly) **68** were 1.76 x 10^{-3} M and 3.65 x 10^{-3} M, respectively.

69 The initial concentrations of receptor **64a** and cyclo(Leu-Gly) **68** were 2.0 x 10^{-3} M and 2.9 x 10^{-3} M, respectively.

following the singlet aromatic proton (shifted from 8.01 to 8.60 ppm) of the naphthalene spacer. The K_a was determined to be 73,000 M^{-1}. The association constant for (+)-dilactam **64b** and **68** was only 2,900 ± 200 M^{-1}.[70] This indicates an enantiomeric selectivity of 25-fold for cyclo(Leu-Gly), a 1.9 kcal/mol difference in binding energy. All results are reported in Table 8.

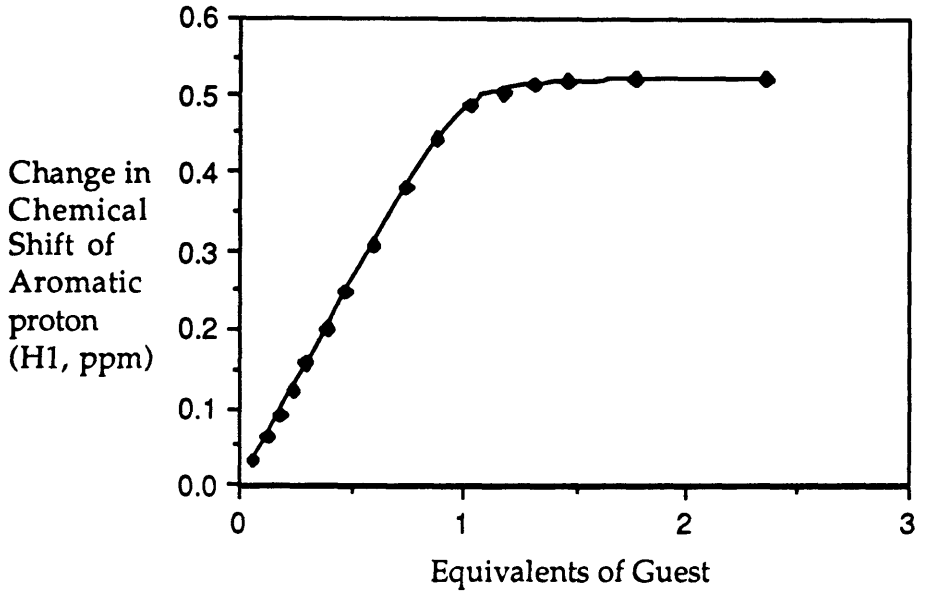
Table 8 Association Constants (K_a's) of Receptors with Cyclic Dipeptides at 296 ± 1 °K

Entry	Receptor	Substrate	Solvent	K_a (M^{-1})
1	**58**	**68**	$CDCl_3$	4,800
2	**61**	**68**	$CDCl_3$	50,000
3	**64a**	**68**	$CDCl_3$	73,000
4	**64b**	**68**	$CDCl_3$	2,900
5	**65**	**68**	$CDCl_3$	6,700
6	**61**	**69**	$CDCl_3$	12,000
7	**64a**	**69**	$CDCl_3$	82,000
8	**64b**	**69**	$CDCl_3$	840
9	**64a**	**68**	CD_3OD	46

The titration data of **64a** and **64b** with cyclo(Leu-Leu) **69** with theoretically generated curves are shown in Figure 12.

---

70 The initial concentrations of receptor **64b** and cyclo(Leu-Gly) **68** were 2.0 x 10^{-3} M and 2.9 x 10^{-3} M, respectively. The association constant from the lactam NH (shifted from 5.35 to 8.12 ppm) was 2,710 M^{-1} and from the singlet aromatic proton (shifted from 8.01 to 8.32 ppm) was 3,080 M^{-1} in $CDCl_3$.



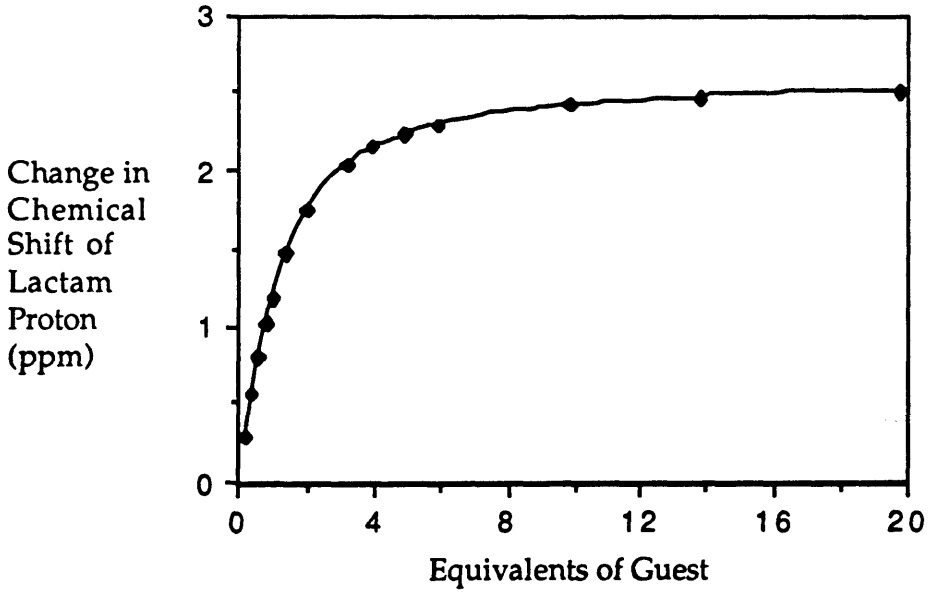


Figure 12 Titration data and calculated curves for **64a** (above) and **64b** (below) with cyclo(Leu-Leu) **69**.

The association constants[71] of (-)-dilactam **64a** and (+)-dilactam **64b** with cyclo(Leu-Leu) **69**[72] were 82,000 M^{-1} and 840 M^{-1}, respectively. The enantiomeric selectivity for cyclo(Leu-Leu) was ~100-fold, and indicated $\Delta\Delta G$ of 2.7 kcal/mole. These are among the largest observed for the chiral recognition of neutral substrates. Interestingly, the complex between **64a** and **69** is also stable enough to withstand chromatography. A mixture (1/1) of **64a** and **69** showed one spot (R_f = 0.67) on silica TLC (eluted with 50 % EtOAc in $CHCl_3$, R_f = 0.44 for **64a**, R_f = 0.10 for **69**).[73]

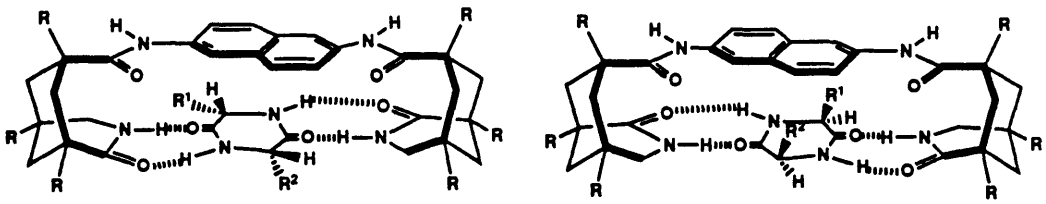
A rationale for high enantiomeric selectivities is in the proposed structure for the complex. With the appropriate match shown in Figure 13, four hydrogen bonds can be had without unfavorable steric contacts elsewhere in the complex of (-)-dilactam **64a** and cyclic dipeptides, **68** and **69**. However, in the complex between (+)-dilactam **64b** and cyclic dipeptides, **68** and **69** , four hydrogen bonds can not be formed due to the steric repulsions between the naphthalene ring of **64b** and the side chains, R^1 and R^2 of **68** and **69**.

---

71 In titration of (-)-dilactam **64a** with cyclo(Leu-Leu) **69**, the initial concentrations of **64a** and **69** were 2.18 x 10^{-3} M and 3.22 x 10^{-3} M, respectively. Since lactam protons were invisible until ~ 1 equivalent of **69** was added, the titration was monitered by the signal for the singlet aromatic proton (shifted from 8.01 to 8.53 ppm). In titration of (+)-dilactam **64b** with cyclo(Leu-Leu) **69**, the initial concentrations of **64b** and **69** were 1.76 x 10^{-3} M and 1.73 x 10^{-2} M, respectively. The signal for lactam protons of **64b** shifted from 5.33 to 7.84 ppm. Non-linear curve fit program gave $\delta_{complex}$ = 8.13 ppm.

72 Cyclo(Leu-Leu) was prepared by catalytic hydrogenation and cyclization of cBz-L-Leu-L-Leu-OEt in methanol. The author greatly thanks Professor Kemp's group for the generous gift of CBZ-L-Leu-L-Leu-OEt.

73 For another example of this behavior, see: Seto, C. T.; Whitesides, G. M. *J. Am. Soc. Chem.* **1990**, *112*, 6409-6411.

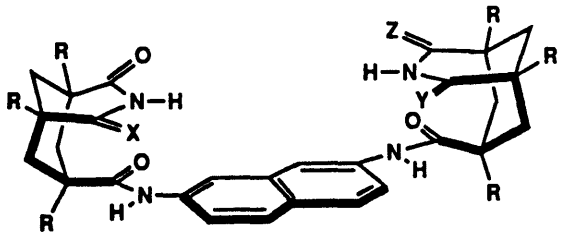


R = $CH_2CH_2CH_3$, R^1 = i-butyl, R^2 = H, or i-butyl

Figure 13 Proposed structures for the complexes of (-)-dilactam **64a** (left) and (+)-dilactam **64b** (right) with cyclic dipeptides **68** and **69**.

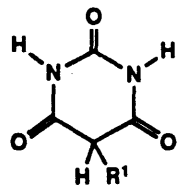
4.2 Molecular Recognition of Barbiturates and Hydantoins

CPK molecular models showed that barbiturates[74] **70** and **71** could form four hydrogen bonds with either the 2,7-naphthalene diimide **24** or meso dilactam **26a**. The syntheses of these 2,7-naphthalene derivatives were previously described in Chapter 1.



R = $CH_2CH_2CH_3$

24 X = Y = Z = O
26a X = Y = H_2, Z = O, meso
26b X = Z = H_2, Y = O, racemic



70 R^1 = H
71 R^1 = n-butyl

74 For an excellent macrocyclic receptor, see: Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318-1319.

Modelling studies were confirmed by solid-liquid extractions. Receptors **24** and **26a** dissolved barbituric acid **70** quite effectively into chloroform as shown Table 9. Additionally, a liquid-liquid extraction showed that the meso dilactam **26a** was capable of extracting ~ 0.7 equivalent of barbituric acid **70** from its saturated aqueous solution (1 N HCl) into $CDCl_3$.

Table 9 Solid-liquid Extractions and Association Constants with Barbiturates.

Receptor	Equivalent of **70** dissolved	K_a's (M^{-1}) with **71**
24	0.75	17,000
26a	1.0	32,400
26b	0.35	890

Titrations[75] were performed with a chloroform soluble derivative, n-butyl barbiturate **71**.[76] The racemic dilactam **26b** can form only three hydrogen bonds with **71**, and shows lower affinity, while the diimide **24** and meso dilactam **26a** can form four hydrogen bonds to the substrate. Diimide **24** shows lower binding affinity than the meso dilactam **26a** due to the secondary interactions. The proposed structures for the complexes are shown in Figure 14.

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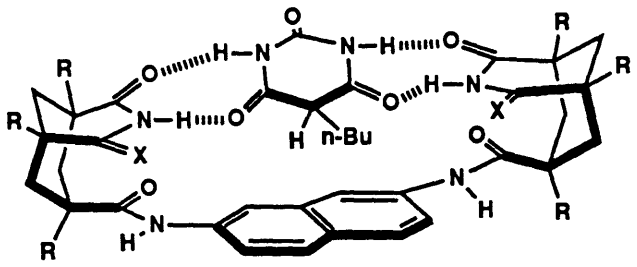
75 Initial concentrations of receptors, **24**, **26a-b**, and barbitrate **71** are 1.5-1.7 x 10^{-3} M and 2.2-2.6 x 10^{-3} M in $CDCl_3$ at 295 °K. Titrations were followed by the exchangeable protons (imide or lactam NH) and association constants were calculated by nonlinear least squares fits.

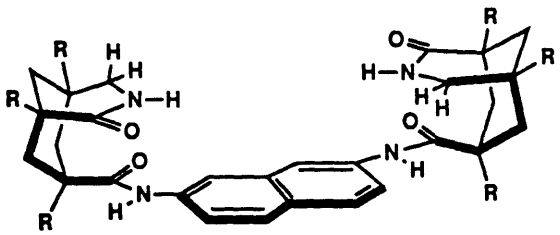
76 For a synthesis of barbituric acid, see: Dickey, J. B.; Gray, A. R. *Org. Synth. Coll. Vol. II*, **1943**, 60.



R = $CH_2CH_2CH_3$, X = O, or H_2

Figure 14 Proposed structures of complexes between receptors **24** and **26a** and n-butyl barbituric acid **71**.

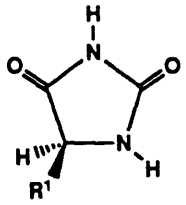
The chiral recognition of hydantoins **72a-d** was investigated with 2,7-naphthalene dilactam **26b**. The racemic dilactam **26b** was resolved on a chiral Pirkle column.



R = $CH_2CH_2CH_3$

(-)-26b $[\alpha]_D$ = - 63 °

(+)-26b $[\alpha]_D$ = + 64 °



72a $R^1 = CH_2Ph$

72b $R^1 = CH_2CH(CH_3)_2$

72c $R^1 = CH(CH_3)_2$

72d $R^1 = CH(CH_3)CH_2CH_3$

All hydantoins were prepared from the corresponding L-amino acids using literature procedures[77] and were recrystallized three times from either ethanol or ethanol/water. Titrations were followed by monitoring the lactam protons of the receptors, which usually shifted from 5.31 to ~ 8.0 ppm. The association constants are summarized in Table 10.

Table 10 Association Constants of (±)-Dilactam **26b** with Hydantoins **72a-d** in $CDCl_3$ at 295 °K

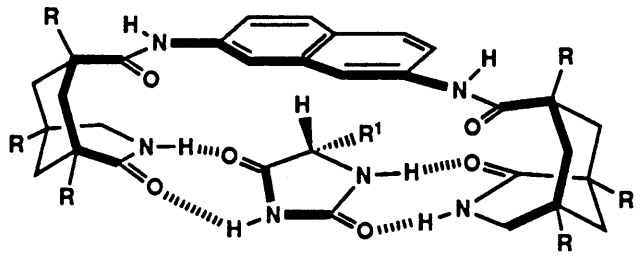
	K_a's (± 10 %, M^{-1})		
Guest	**(-)-26b**	**(+)-26b**	ΔΔG (kcal/mol)
72a	4800	1720	0.45
72b[78]	1050	390	0.58
72c	7080	705	1.35
72d	7070	650	1.40

CPK molecular models show that (-)-dilactam **26b** can form four hydrogen bond with hydantoins **72a-b**. However, one hydrogen-bond distance in the complex is relatively longer than the others. This would explain why the association constants in Table 10 are in the range of 10^3 M^{-1} rather than 10^4 M^{-1}. The selectivities between the two enantiomers is highly dependent on the side chains of hydantoins. For example, ΔΔG = ~ 0.5

77 Suzuki, T.; Igarashi, K.; Hase, K.; Tuzimura, K. *Agr. Biol. Chem.* **1973**, *37*, 411-416. **72a**; mp = 182-184 °C, $[\alpha]_D$ = -132 ° (EtOH). **72b**; mp = 221-223 °C, $[\alpha]_D$ = -82 ° (EtOH). **72c**; mp = 149-150 °C, $[\alpha]_D$ = -99 ° (EtOH). **72d**; mp = 138-140 °C, $[\alpha]_D$ = -74 ° (EtOH).

78 Titration was performed in 10 % THF-d_4/$CDCl_3$.

kcal/mole for **72a** and **72b**., while $\Delta\Delta G$ = ~ 1.4 kcal/mole for **72c** and **72d** in which secondary alkyl groups are directly attached to the 5-position of the hydantoins. The association constant decreased in a more polar environment (10 % THF-d_4 in $CDCl_3$), but selectivity was not changed in the titrations of **26b** with **72b**. The proposed structures for the complexes between (-)-**62b** and hydantoins are shown in Figure 15, in which the alkyl chain at the 5-position of the hydantoins is positioned away from the naphthalene ring to avoid the unfavorable steric interaction.



R = $CH_2CH_2CH_3$

Figure 15 Proposed structure of complexes between **(-)-26b** and hydantoins **72a-d**.

PART II

DEVELOPMENT OF NEW CHIRAL AUXILIARIES

Introduction

One of the main synthetic challenges in organic chemistry is the control of enantio- and diastereoselectivity of reactions.[79] Since the practical asymmetric synthesis (80-90 ee) in 1961 was achieved by H. C. Brown in the hydroboration of cis-2-butene with tetrapinanyldiborane,[80] the ongoing search for chemical reactions of ever-increasing selectivity has led to the development of systems that couple catalysis with chiral selectivity.[81] Chiral auxiliaries provide one means of controlling the stereoselectivities in chemical reactions. E. Eliel[82] has outlined three criteria of a useful auxiliary: 1) It must lead to the desired enantiomer in both high optical and chemical yield. 2) The chiral product must be readily separable from the chiral auxiliary reagent that is needed in synthesis. 3) Unless the chiral auxiliary reagent is very much cheaper than the desired product, the auxiliary reagent must be capable of being recovered in good yield and undiminished optical purity. A number of synthetically useful chiral auxiliaries are known in various reactions. Representative examples include Evans's oxazolidinones[83], Oppolzer's sultams[84], and Davies's iron complexes[85].

---

79 a) Evans, D. A. *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic press: New York, 1984, Vol 3, Chap 1. b)Heathcock, C. H.*ibid* Chap 2.

80 Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486-487.

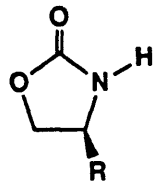
81 For a review, see: Brown, J. M. *Chem. Britain* **1989**, *25(3)*, 276-280 and references therein.

82 Eliel, E. L. *Tetrahedron* **1974**, *30*, 1503-1513.

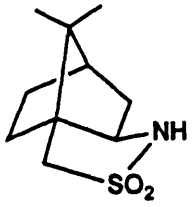
83 For a review, see: Evans, D. A. *Science* **1988**, *240*, 420-426 and references therein.

84 For a review, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969-2004 and references therein.

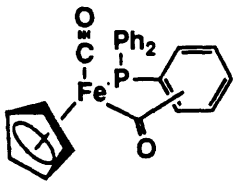
85 For a review, see: Davies, S. G. *Aldrichim. Acta* **1990**, *23(2)*, 31-37 and references therein.



Evans



Oppolzer



Davies

Here, preliminary studies of alkylations and aldol condensations using new chiral auxiliaries derived from Kemp's triacid will be presented.

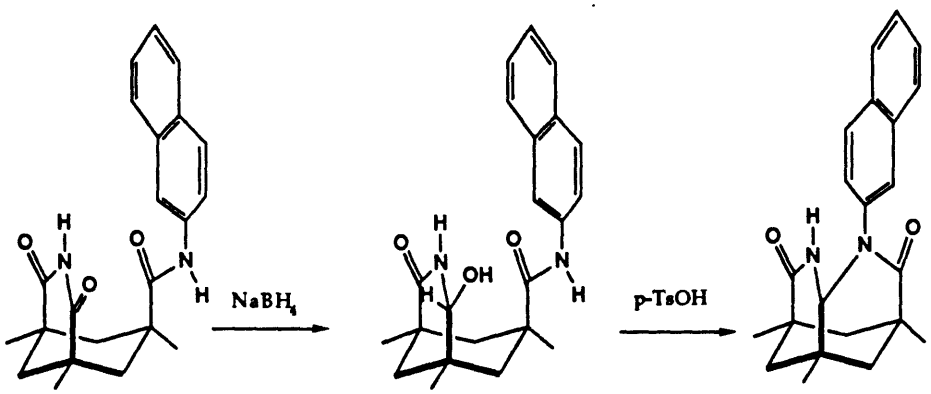
Chapter 5

Alkylation and Aldol Condensation with New Chiral Auxiliaries

5.1 Syntheses of Chiral Auxiliaries

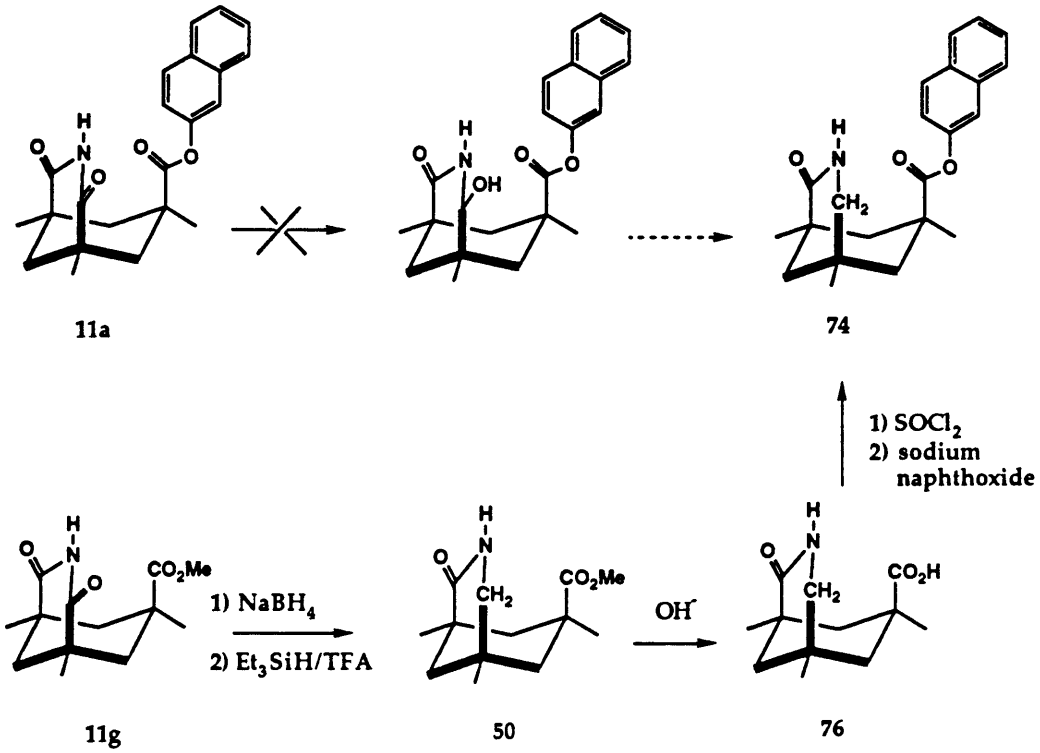
The 2-naphthylamide imide **15a** was reduced with $NaBH_4$ to afford the hydroxylactam **16a**, which was cyclized with a catalytic amount of p-TsOH to give a racemic **73** (Scheme 17).

Scheme 17



Direct reduction of the naphthyl ester imide **11a** with $NaBH_4$ failed to give the corresponding hydroxylactam, the precursor to naphthyl ester lactam **74**. The naphthyl ester lactam **74** was synthesized as outlined in Scheme 18; the methyl ester imide **11g** was reduced with $NaBH_4$, and the resulting methyl ester hydroxylactam **75** was treated with Et_3SiH/CF_3CO_2H to yield methyl ester lactam **50**. After hydrolysis of **50**, the resulting racemic lactam acid **76** was treated with $SOCl_2$ and sodium naphthoxide to give the racemic naphthyl ester lactam **74**.

Scheme 18

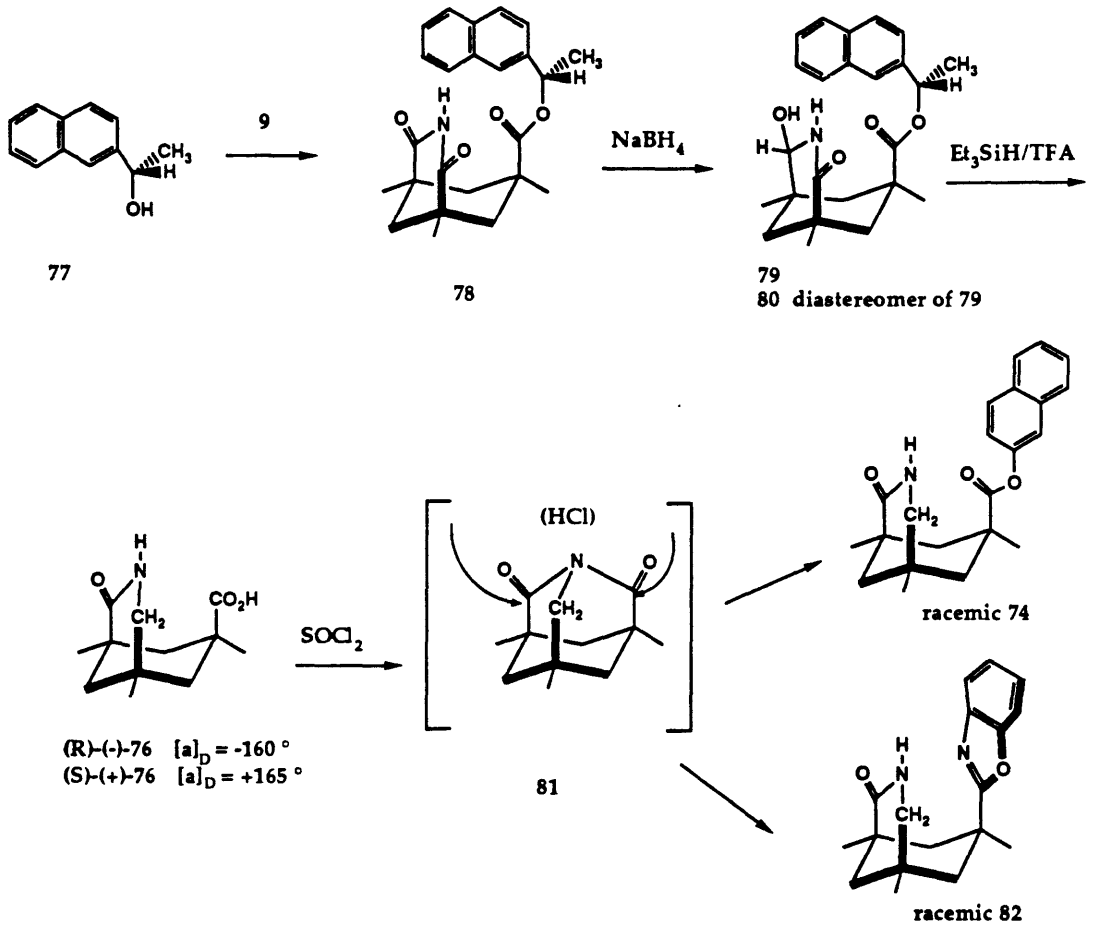


Optically active lactam acid **76** was prepared as a precursor of an enantiomerically pure **74** as shown in Scheme 19.

Commercially available (S)-α-methyl-2-naphthalenemethanol **77** was acylated with imide acid chloride **9**. The resulting imide **78** was reduced to a mixture (**79**/**80** = 4/1) of hydroxylactams which were separated by flash chromatography. The relative configurations of **79** and **80** were determined by crystallographic analysis. Each diastereomer was treated with Et_3SiH/TFA to give the optically pure lactam acid **74**. Surprisingly, activation with thionyl chloride followed by coupling with 2-naphthol gave a racemic lactam **74**. Coupling with o-hydroxyaniline also gave a racemic lactam benzoxazole **82**.

The racemization probably occurs via the tricyclic intermediate **81**, a non-planar imide (Scheme 19).[86]

Scheme 19

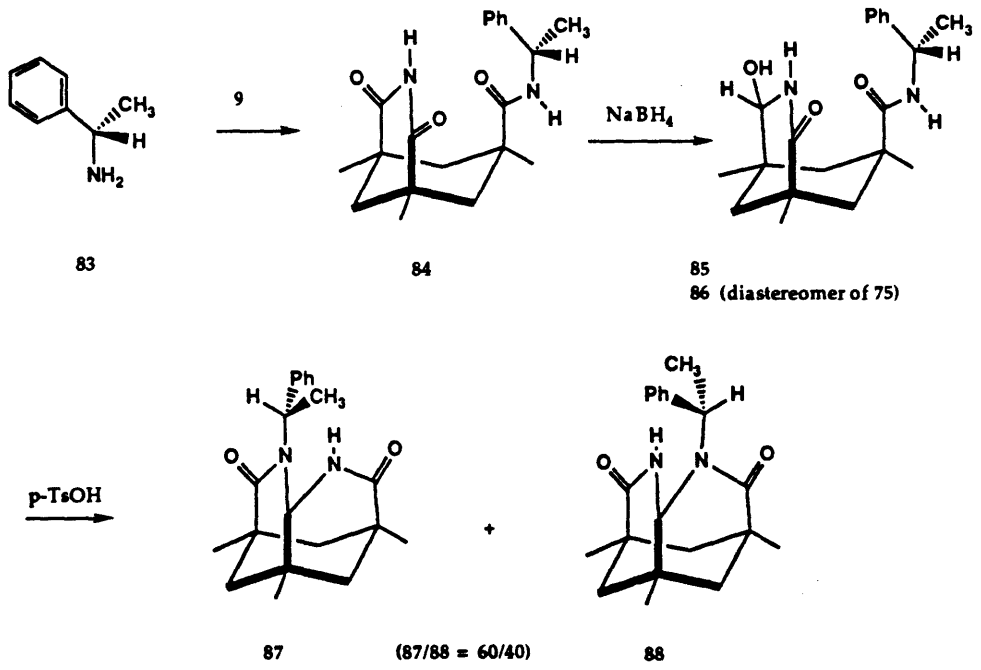


Because auxiliaries **73**, **74**, and **82** are racemic, and additional steps are required to prepare their enantiomerically pure forms, other easily accessible auxiliaries were synthesized. The imide acid chloride **9** was treated with (S)-

86 Ballester, P.; Tadayoni, B. M.; Branda, N.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3685-3686.

(-)-α-methylbenzylamine **83** and the resulting imide **84** was reduced at 0 °C with $NaBH_4$ to give a mixture of two diastereomeric hydroxylactams, **85** and **86**. Without separation of these two diastereomers, the mixture is cyclized with a catalytic amount of p-TsOH to give the diastereomeric mixture of dilactams (87/88 = 3/2) in a quantitative yield (Scheme 20). The two diastereomers are easily separated through flash chromatography to give the optically pure compounds.

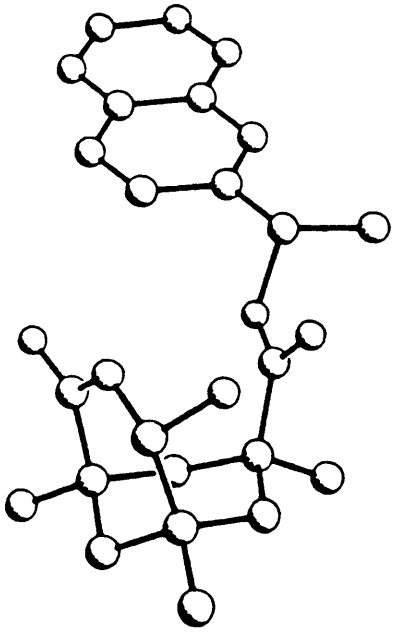
Scheme 20



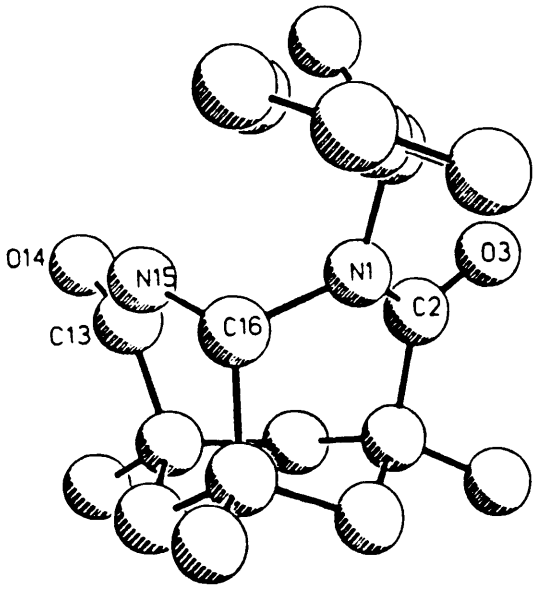
5.2 Alkylation

5.2.1 Benzylation

The crystal structures of **79** and **88**, which are the minor isomers, are shown below.



X-ray structure of **79**

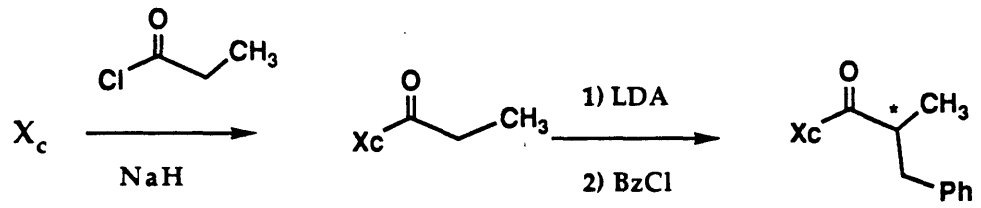


X-ray structure of **88**

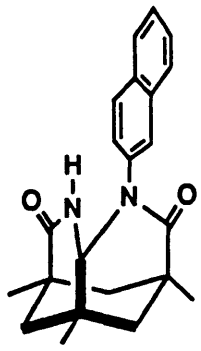
The auxiliaries **73**, **74**, **87**, and **88** (**87** and **88** are enantiomerically pure, and **73** and **74** are racemic) were acylated with NaH/propionyl chloride to give the corresponding N-propionyllactams **89a-92a**, which are treated with base (LDA, -78 °C, THF) to generate enolates. These enolates are alkylated with benzyl bromide (2 equivalents) at 0 °C (3-5 h) (Scheme 21). All of the

alkylations proceeded cleanly under these reaction conditions. Only alkylated products and unreacted starting materials were observed in the reaction mixtures. When the reaction temperature was raised up to ~ 5 °C, a trace amount (<5 %) of an unidentified side product was observed. The results are summarized in Table 11.

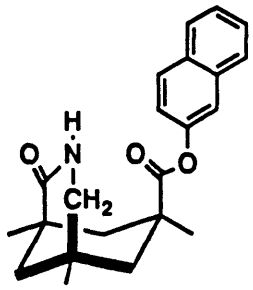
Scheme 21



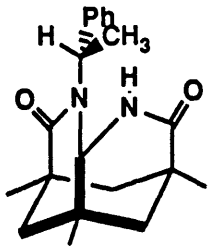
73	89a Xc =73	89b Xc =73
74	90a Xc =74	90b Xc =74
87	91a Xc =87	91b Xc =87
88	92a Xc =88	92b Xc =88



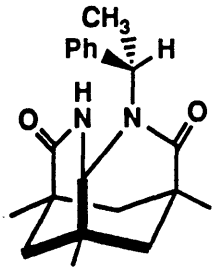
73



74



87



88

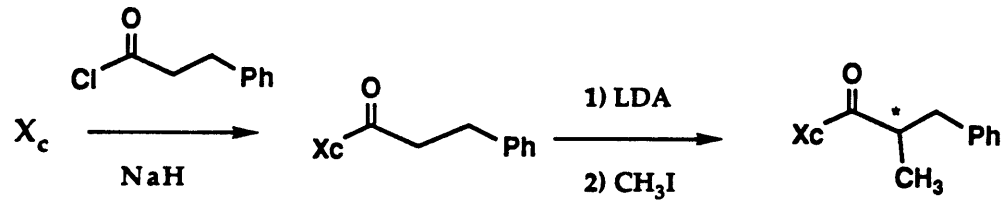
Table 11. The Results of Benzylation

Entry	X_c	Selectivity (89b-92b)	Yield (%)
1	73	97:3	76
2	74	>99:1	63
3	87	37:63 (R)	81
4	88	>99 (S):1	56

5.2.2 Methylation

The experimental method used for methylation was the same as that for benzylation. The acylation and alkylation reagents were hydrocinammoyl chloride and methyl iodide, respectively (Scheme 22). The results are summarized in Table 12.

Scheme 22



73
74
87
88

89c Xc =73
90c Xc =74
91c Xc =87
92c Xc =88

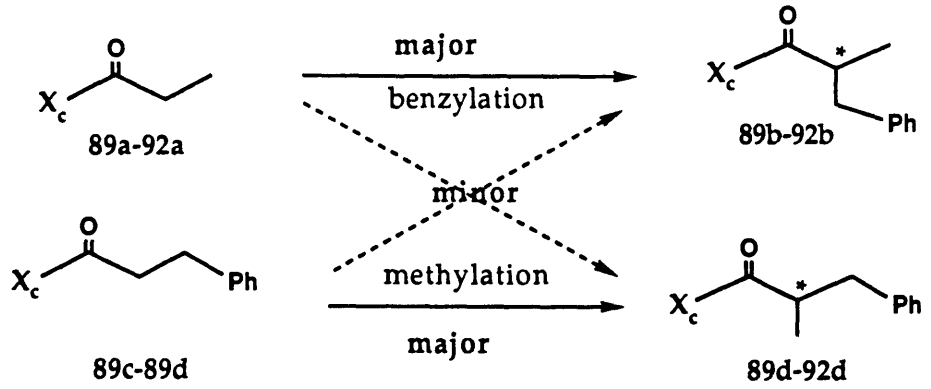
89d Xc =73
90d Xc =74
91d Xc =87
92d Xc =88

Table 12. The Results of Methylation.

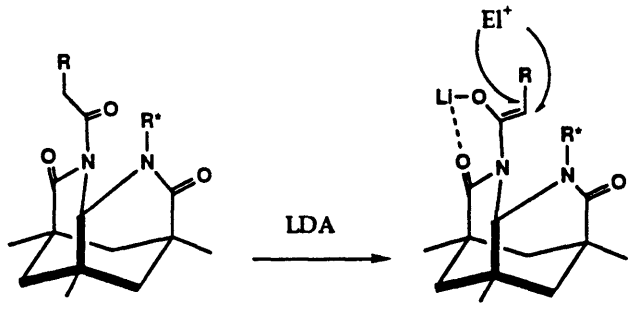
Entry	X_c	Selectivity (89d-92d)	Yield (%)
1	73	96:4	70
2	74	98:2	73
3	87	>99 (S):1	84
4	88	1:>99 (R)	64

5.2.3 Discussion

Diastereomeric analysis of the reaction mixture **89b-92b** was carried out by ^1H NMR spectroscopy (500 MHz, $CDCl_3$) and HPLC. Usually, the analyzed peak in ^1H NMR is the characteristic sharp singlet proton of methyl or methine groups. Since the major diastereomers of the benzylations of **89a-92a** correspond to the minor diastereomers of the methylations of **89c-92c** as shown below, diastereomeric ratios of alkylations can be easily determined by either NMR or HPLC without ambiguity.



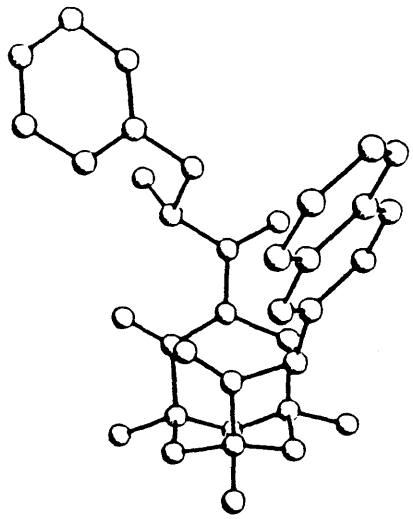
From the experimental results, enolate formation occurs stereoselectively (>99:1) under these conditions (THF, -78 °C, LDA). The chelated Z-enolates[87] such as **93**, in which lithium metal may be chelated to the carbonyl oxygen, may be involved in the creation of a diastereofacial bias in the alkylation.



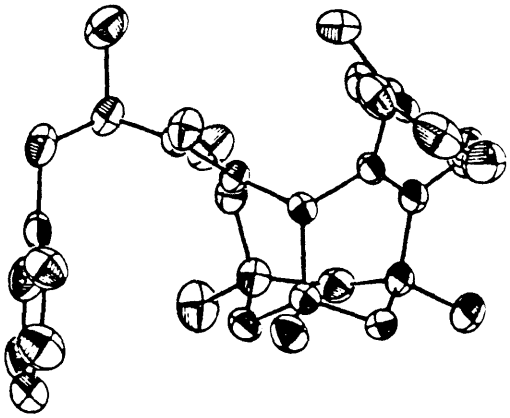
93

87 The assignment of the Z-enolate geometry to these systems has not been rigorously established; however, it is fully consistent with an interpretation of the obtained results in this and other similar studies see: a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129. b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *ibid* **1982**, *104*, 1737-1739.

In enolates **93**, the electrophile may approach to the Re face (outside) rather than to the Si face (inside) which is sterically hindered. The resulting alkylation products lose the lithium ion, and the N-acyl bond is rotated to release the unfavorable dipole-dipole repulsion of carbonyl groups. This explanation is consistent with two crystal structures of akylation products **90b** (entry 2 in Table 11) and **92d** (entry 4 in Table 12), shown below.



X-ray structure of **90b**



X-ray structure of **92d**

Chiral auxiliaries must be easily removable and recoverable from the reactions. Indeed, treatment[88] of alkylation products (**92b**, **91d**, and **92d**) with

88 Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.

$LiOH/H_2O_2$ gave the optically pure carboxylic acid[89] and auxiliaries in a high yield (90-100 %).

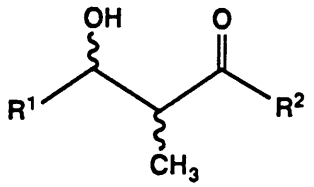
In summary, the new auxiliaries show the high stereoselection of the enolate faces which are fixed by chelation of lithium ion to the adjacent carbonyl group. Especially, optically pure **87** and **88** are easily prepared from the commercially available Kemp's triacid, and are very stable in reaction conditions of alkylation and deprotection.

---

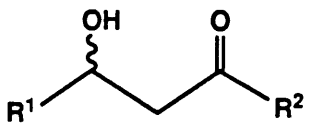
89 The (S)- and (R)-2-methyl-3-phenylpropionic acids released from **92b**, **91d**, and **92d**, were coupled with optically pure (S)-(-)-(a)-methylbenzylamine; ^1H NMR analysis showed >99:1 optical purity.

5.3 Aldol Reactions of α-Unsubstituted Enolates.

The aldol reaction is the classical method for the formation of carbon-carbon bond with functionality in 1,3-relationships. For their direct construction by enantio- and diastereoselective aldol reactions, usually via carboxylic acid derivatives, excellent solutions have been found for the case of α-substituted aldols.[90]



α-substituted aldol



α-unsubstituted aldol

However, the transition from the α-substituted enolate to the α-unsubstituted enolate is accompanied by the almost total loss of the ability of the latter to discriminate between the enantiotopic faces of an aldehyde, so that the specific preparation of given α-unsubstituted diastereomer is not easily accessible.[91] This prompted us to study aldol reactions of α-unsubstitued enolates using the new chiral auxiliaries.

---

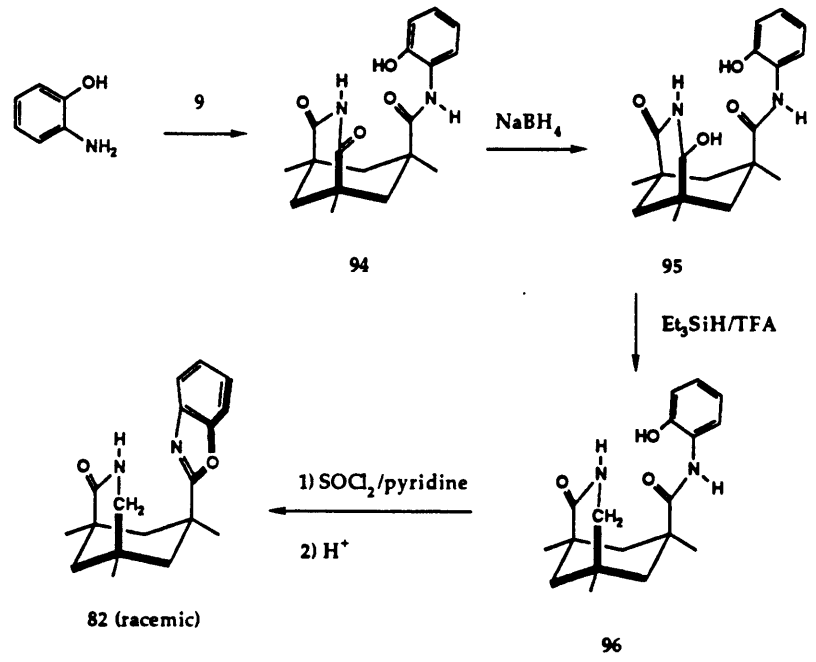
90 Heathcock, C. H. *Asymmetric Synthesis* Morrison, J. D. Ed.; Academic Press: New York 1984, Chap. 3.

91 a) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 874-875. b) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281. c) Braun, M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24-37. d) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297-300. e) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493-5495. f) Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 495--497.

5.3.1 Resolution of the Racemic Lactambenzoxazole 82[92]

The alternative synthesis of the racemic lactambenzoxazole **82** was described in Scheme 23.

Scheme 23



The racemic lactambezoxazole **82** was acylated with (-)-menthyl chloroformate to provide a diastereomeric mixture of **97a** and **97b**, which was seperated by flash chromatography (15 % EtOAc in hexanes). Treatment of **97a** or **97b** with sodium methoxide provided compound **98**. The recovery of the optically active lactambenzoxazole **82** was achieved by treatment with CF_3CO_2H in 80-83 % yield (Scheme 24).

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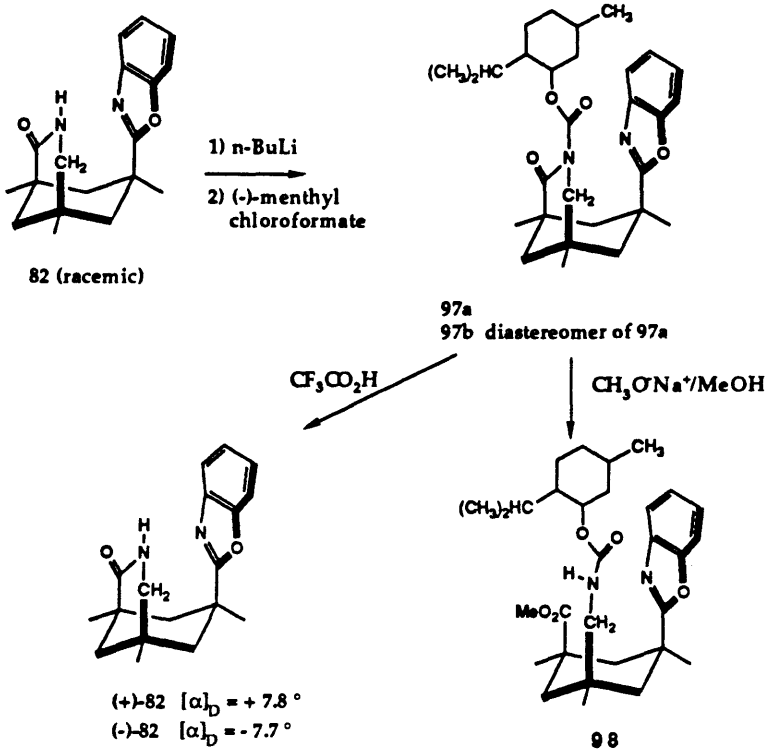
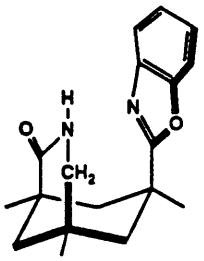
92 Author greatly thanks Dr. P. Ballester for the resolution of the racemic lactambenzoxazole **82**.

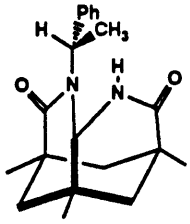
Scheme 24


1) n-BuLi
2) (-)-menthyl chloroformate
82 (racemic)
97a
97b diastereomer of 97a
CF_3CO_2H
$CH_3O^-Na^+/MeOH$
(+)-82 $[\alpha]_D$ = + 7.8 °
(-)-82 $[\alpha]_D$ = - 7.7 °
98

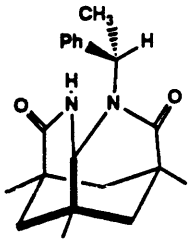
5. 3. 2 Results



82



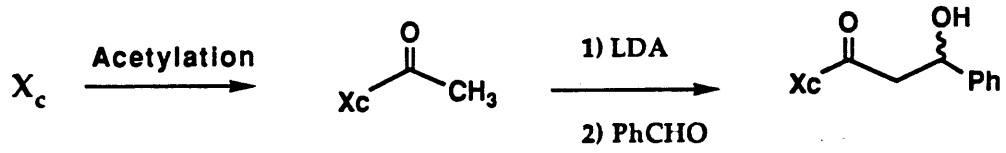
87



88

The auxiliaries **82**, **87**, and **88** were acylated with Ac_2O, or AcCl. The enolates were generated with LDA followed by addition of aldehyde (Scheme 25). Diastereomeric analysis of the reaction mixture **99b-101b** was carried out by ^1H NMR spectroscopy (500 MHz, $CDCl_3$) and HPLC. The results of the aldol reactions are listed on Table 3.

Scheme 25



82	**99a Xc =82**	**99b Xc =82**
87	**100a Xc =87**	**100b Xc =87**
88	**101a Xc =88**	**101b Xc =88**

Table 13 The Results of Aldol Reactions

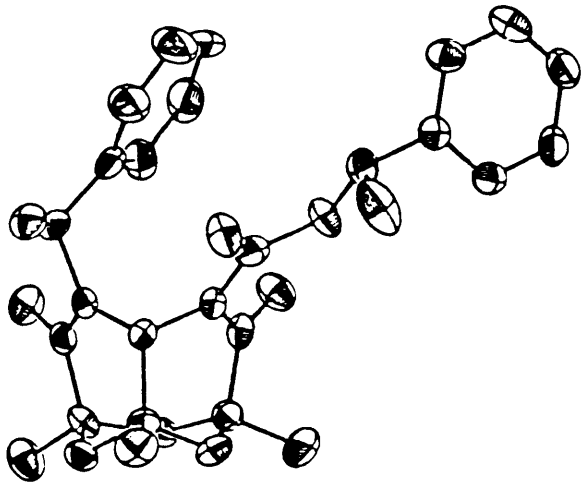
Entry	Xc	Base/Solvent	Temp/Time	S/R	Yield (%)
1	**87**	LDA/THF	-78 (°C)/3 min	80/20	94
2	"	"	-78 (°C)/10 min	80/20	92
3	"	"	-78 (°C)/30 min	80/20	90
4	"	"	-10 (°C)/30 min	62/38	61***
5	"	"	-98 (°C)/30 min	86/14	96
6	"	"	-78 to -10 (°C)/ 10 min	76/24	90
7	"	LDA/toluene	-78 (°C)/30 min	83/16	92
8	"	LDA, Et_2AlCl* THF	-78 (°C)/30 min	13/87	80
9	**88**	LDA/THF	-78 (°C)/30 min	16/84**	92
10	**(-)-82**	LDA/THF	-78 (°C)/30 min	95(S)/5	95***
11	**rac-82**	LDA/THF	-78 (°C)/10 min	95/5**	92
12	"	LDA/THF	-10 (°C)/10 min	64/36**	40****

* Transmetalation was performed at -40 °C for 1 h, and then the reaction was cooled to -78 °C followed by the addition of aldehyde. ** The ratios are more polar vs.less polar products (eluent; 25% EtOAc in hexanes).

*** Recryatallization of the reaction mixture from benzene gave one pure isomer in 73 % yield. The absolute stereochemistry in the new stereogenic center of the major aldol product was determined by the optical rotation of 3-phenyl-3-hydroxypropionic acid ($[\alpha]_D$ = -14.4 °, c = 1.3 in EtOH). See ref. 95b ($[\alpha]_D$ = -14.9 °, c = 1.94 in EtOH). **** Acylated compounds **94a** and **95a** were decomposed to give **82** and **87**, respectively.

5. 3. 3 Discussion

The stereochemistry of the aldol reactions in entry 1-8 on Table 13 was determined by x-ray analysis. The (R)-diastereomer, which is a minor isomer, is shown below.

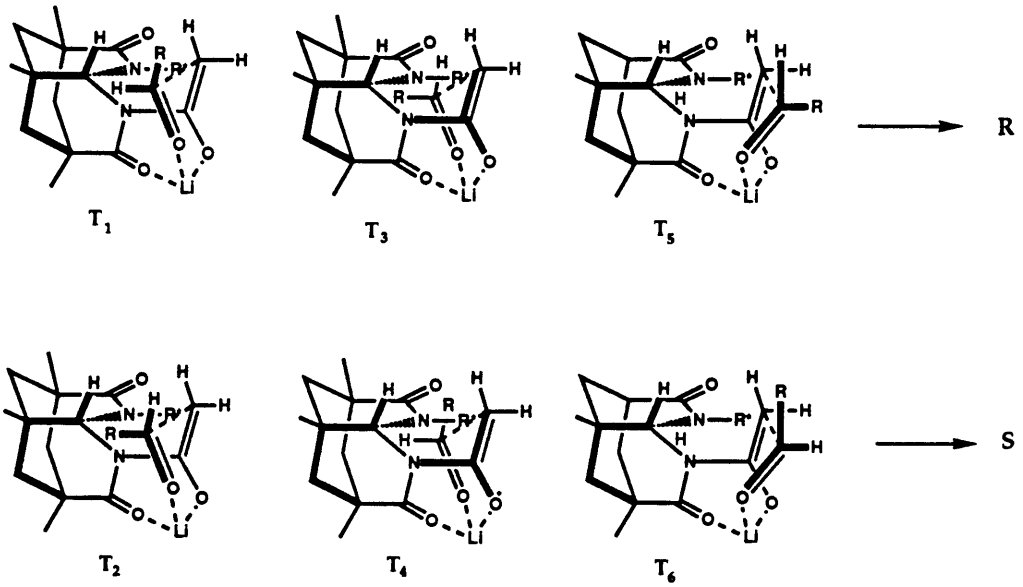


The crystal structure of (R)-isomer
in Table 13 (entry 1-8)

Variation of reaction time (3-30 min, entry 1-3) did not alter the diastereomer ratio, but changes in temperature (-10 - -98 °C,, entry 3-5) had large effects. In entry 6, the ratio was changed only within the range of the experimental error when the reaction was warmed up to -10 °C, and then quenched with ammonium chloride solution. This indicates that retro-aldolization does not occur and kinetic product ratios are observed in the reaction conditions. The reverse diastereoselectivity is observed when the counterion is changed from lithium to aluminum (entry 3 and 8). This may

be due to the fact that the carbonyl oxygen of aldehyde can not be chelated to tetra-coordinated aluminum ion in the transition state.[93]

Several transition states have been proposed for aldol reaction. The most popular one is the closed or chelated transition state first proposed by Zimmerman and Traxler.[94]



When it is assumed that the lithium cation of enolate is chelated to both carbonyl groups of the imide and aldehyde, four chair transition states (T_1-T_4) are possible. However, we can exclude the transition states T_3 and T_4 because R* (α-methylbenzyl) and incoming aldehyde group have a significant steric repulsion. The transition state T_1 simply gives the wrong diastereomer

93 Liebeskind, L. S.; Welker, M. E. *Tetrahedron Lett.* **1984**, *25*, 4341-4344.

94 a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923. b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *ibid* **1981**,*103*, 3099-3111.

of aldol adduct. In the remaining transition state T_2, the bulky phenyl group is axial so that large steric repulsion exists between the phenyl ring of the aldehyde and the cyclohexane portions of auxiliary. Therefore, the twist boat transition states T_5, T_6 must be considered. In these transition states, it may be favorable when the phenyl group of the aldehyde is in pseudo-equatorial position like in T_6. At this stage, it is not apparent whether transition states T_2, T_6 or even other possibilities[95] are favorable for these systems.

Again, treatment of aldolization product **101b** with $LiOH/H_2O_2$ gave the optically active (S)-3-phenyl-3-hydroxypropionic acid (86-96 %) and auxiliaries **(-)-82** (99 %) and **87** (100 %), respectively.

In summary, the new auxiliaries **82**, **87** and **88** for the α-unsubstituted aldolization show moderate diastereoselectivities (60-90 de), but these values are among the highest seen with lithium enolates to date.[96] Additional studies are needed to understand the transition state in these systems and to develop a more convenient preparation of auxiliary **82** in optically active form.

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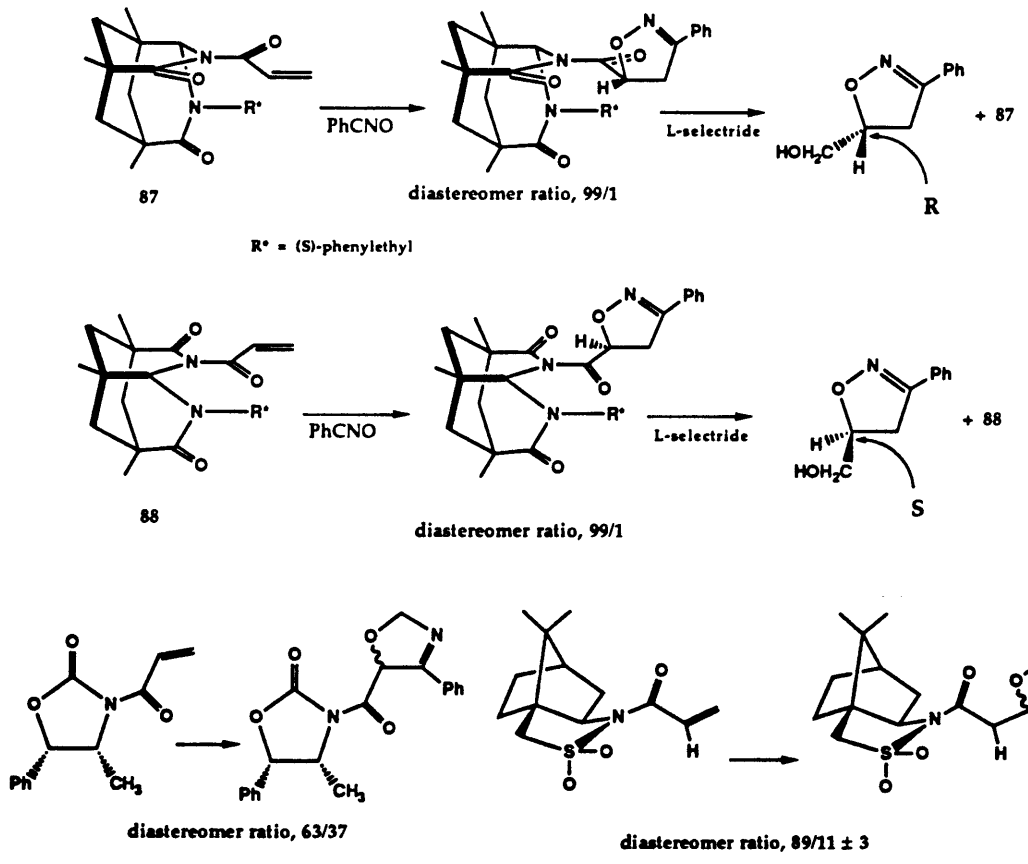
95 For a review of transition state of the aldol addition reaction, see: Heathcock, C. H. *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic press: New York, 1984, Vol 3, p 154-159.

96 a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129. b) Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699-1703. c) Davies, S. G.; Dordor, I. M.; Warner, P. *J. Chem. Soc. Chem. Commun.* **1984**, 956-957.

5.4 Other Applications

Curran et al[97] have shown that these new chiral auxiliaries 87 and 88 provided unprecedentedly high levels of diastereoselectivity in cycloadditions of nitrile oxides. These are notoriously unselective because of the minimal interaction between the incoming nitrile oxide and the auxiliary, that is, the oxygen bears no substituents. The representative results are shown in Scheme 26.

Scheme 26



97 Curran, D. P.; Jeong, K. S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 9238-9240.

Chapter 6

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories Knoxville Tenn. Mass spectra were obtained on a VG instruments SE-20 (low resolution), a Varian CH-5 instrument and Finnegan MAT 8200 (high resolution). IR spectra were obtained on an IBM IR/32 FTIR. ^1H NMR spectra were taken on a Bruker 250 MHz, 300 MHz or 500 MHz instrument with chemical shift values reported relative to tetramethylsilane. Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Column chromatography was performed on Merck or Baker silica gel (230-40 mesh ASTM).

Titrations. Typically, a solution (2 mL, concentrations were indicated in footnotes) of host in dry $CDCl_3$ was prepared. A 500 μL aliquot was transferred to a 5 mm NMR tube and a spectrum was recorded. Aliquots of a $CDCl_3$ solution (concentrations were indicated in footnote) of guest were added (10-20 μL at first, then 50-100 μL close to saturation) with spectra recorded after each addition. Addition of guest was continued until the chemical shift of the host signals remained constant. Association constants were obtained by Eadie-Hofstee plot and non-linear least-squares fit of the saturation plot to the 1:1 binding isotherm. Typical titration data are shown in Table 14 for the specific case of naphthyl ester imide **11a** (0.01 M, 500 mL) and 9-ethyladenine **12** (0.1 M) in $CDCl_3$, at 296 ^oK.

Table 14 Titration Data of Naphthyl Ester Imide **11a** and 9-Ethyladenine **12**

Entry	Guest **12** Total (μL)	Chemical Shift Imide (NH, ppm)	Entry	Guest **12** Total (μL)	Chemical Shift Imide (NH, ppm)
1	0	7.6191	15	180	10.8674
2	10	8.0441	16	200	10.9809
3	20	8.4380	17	230	11.1220
4	30	8.7710	18	260	11.2301
5	40	9.0518	19	300	11.3382
6	50	9.3156	20	350	11.4738
7	60	9.5391	21	400	11.5654
8	70	9.7370	22	500	11.6954
9	80	9.9092	23	600	11.7871
10	90	10.0393	24	700	11.8654
11	100	10.1675	25	900	11.9556
12	120	10.3947	26	1100	11.9813
13	140	10.5907	27	1300	12.0289
14	160	10.7483	28	1500	12.0307

Thermodynamic Studies. An equimolar solution of host and guest in $CDCl_3$ were made up in a volumetric flask (2 mL). A 500 μL portion of this solution was added to a 5-mm-o.d. NMR tube and cooled to 273 °K. The chemical shift of the imide NH proton was recorded at this temperature and at every 5 °K temperature increment as the sample was warmed to 323 °K (equilibrium time at each temperature was ~ 5 min). The van't Hoff plot of the K_a calculated each temperature gave $-\Delta H$ and $-\Delta S$. In order to ensure that reasonable range of the saturation plot was covered, the initial solution concentration was adjusted such that, over the range of temperatures studied, $0.2 \leq$ fraction saturation≤ 0.8 was maintained. A typical van't Hoff plot is

shown in Figure 16 for the specific case of naphthylester imide **11a** (0.01 M, 500 mL) and 9-ethyladenine **12** (0.01 M) in $CDCl_3$.

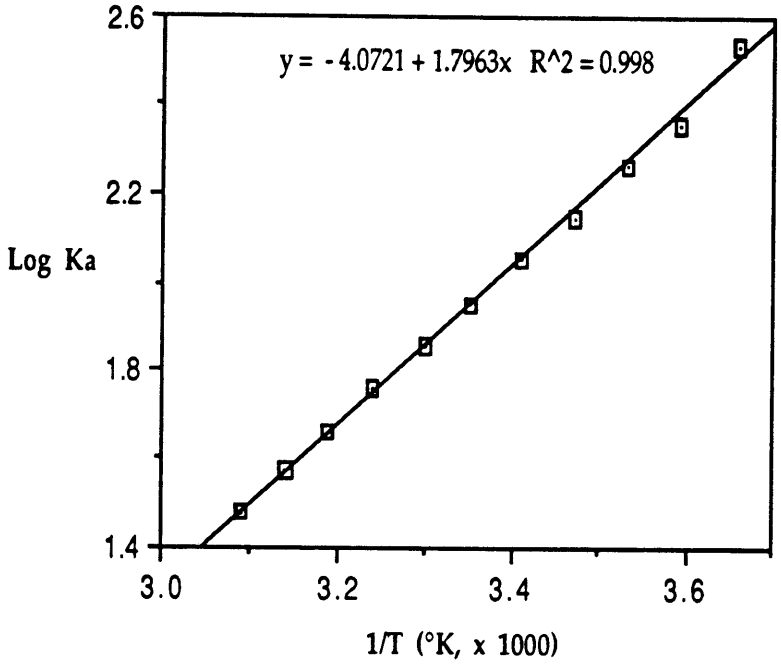


Figure 16 The van't Hoff plot of naphthylester imide **11a** (0.01 M, 500 mL) and 9-ethyladenine **12** (0.01 M) in $CDCl_3$.

Extractions. a) Solubilization of glycine anhydride **66** and barbituric acid **70** in $CDCl_3$: To a 3 mM solution of receptor in dry $CDCl_3$ (1 mL) was added **66** (3 mg), or **70** (3 mg). The mixture was sonicated for 10 min at room temperature and filtered. The amount of **66** or **70** dissolved was calculated by integration of the appropriate ^1H NMR signals of the filtrate.

b) Extraction of **70** from aqueous solution: 2,7-Naphthalenediamide meso-dilactam **65** (1.5 mg) was dissolved in $CDCl_3$ (1 mL). Barbituric acid **70**

(0.5 g) was suspended in 5 ml of neutral or acidic (1 N HCl) water, stirred for 10 min at room temperature and filtered. The aqueous solution was combined with the $CDCl_3$ solution and the mixture was shaken for 5 min. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The amount of **70** dissolved was calculated by integration of the appropriate ^1H NMR signals of the filtrate.

c) Solubilization of quinoxalinedione **67**: To a 2 mM solution of receptor in dry $CDCl_3$ (1 mL) was added **67** (6-8 mg). The mixture was sonicated (Branson 2200) for 10 min at room temperature and filtered. To this solution was added ca. 50 μL of DMSO-d_6 to resolve the signal of the complex. The amount of **67** dissolved was calculated by integration of the appropriate ^1H NMR signals of the filtrate.

Trimethyl 1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylate 3 and 4. 1,3,5-Trimethyl cyclohexane-1,3,5-tricarboxylate **2** was prepared from trimesic acid **1** by following literature procedure.[13b] Lithium isopropylamide (LDA) was generated at 0 °C by the addition of 10 M n-butyllithium (51 mL, 0.51 mol, 3.3 equiv) to dry diisopropylamine (72 mL, 0.51 mol, 3.3 equiv) in dry diethyl ether (400 mL). After the LDA solution was stirred for 30 min at 0 °C, a solution of triester **2** (40 g, 0.16 mol) in dry diethyl ether (400 mL) was dropwise added over 40 min. The mixture was stirred at 0 °C for 1 h, then dimethyl sulfate (76 mL, 0.80 mol, 5.0 equiv) was added in a portion. The reaction was stirred for 3 h at 0 °C and overnight at room temperature. The reaction was diluted with diethyl ether (500 mL) and water (200 mL). The organic layer was washed with 1 N HCl and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure to give a yellow oil, which was distilled under vacuum (ca. 1 mm Hg, 145-165 °C) to give a 85:15 mixture (42 g, 75%) of cis-cis, and cis-trans isomers. The solid cis-cis isomer (21 g, 45%) was purified by recrystallization from pentane: mp 80-81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.62 (s, 9 H), 2.70 (d, 3 H, J = 14 Hz), 1.20 (s, 12 H), 0.95 (d, 3 H, J = 14 Hz). The mother liquid was concentrated by rotary evaporation and the mixture was directly hydrolyzed without further purification.

1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic Acid 5 and 6. a) from pure triester **3**: The triester **3** (15 g, 50 mmol) was dissolved in a mixture of methanol (150 mL) and 3 N NaOH aqueous solution (150 mL). The solution was heated at 65-70 °C for 12 h. Methanol was removed at reduced pressure and the aqueous solution was carefully acidified to pH 1. The triacid appeared as a white precipitate (12.4 g, 96%): mp = 240-247 °C (decomp); ^{1}H NMR (pyridine-d_5, 300 MHz) δ 3.3 (d, 3 H, J = 14 Hz), 1.56 (d, 3 H, J = 14 Hz), 1.54 (s, 9

H), b) from mixture **3** and **4**: A mixture triester (20 g, 33 mmol) was dissolved in a solution of methanol (50 mL) and 3 N NaOH aqueous solution(150 mL). The mixture was heated at reflux for 6 h, the methanol was removed at reduced pressure. The aqueous solution was carefully acidified to pH 1 and the resulting precipitate was collected by filtration. The mixture of triacids was suspended to diethyl ether (500 mL), stirred rapidly for 30 min, and then filtered. This was repeated three times. The cis-cis triacid (combined yield, 9.0 g) was hardly soluble in diethyl ether, while the cis-trans triacid **6** was dissolved. The remaining mother liquors were concentrated to 300 mL, filtered to remove the cis-cis isomer, and then concentrated to a solid, which was recrystallized from ethanol to give pure cis-trans isomer **6** (5 g): mp 241-245 °C (decomp); IR 3200-2200, 1690, 1466, 1406, 1290, 1182 cm^{-1}; 1H NMR (pyridine-d_5, $CDCl_3$) δ 3.32 (d, 1 H, J = 14 Hz), 2.72 (d, 2 H, J = 14 Hz), 2.57 (d, 2 H, J = 14 Hz), 1.75 (d, 1 H, J = 14 Hz), 1.72 (s, 3 H), 1.67 (s, 6 H)

Cis-Cis Anhydride Acid 7. Triacid **5** (20.0 g, 0.0775 mol) was suspended in xylene (200 mL) and heated to reflux for 10 h with a Dean-Stark trap under N_2. The resulting mixture was concentrated and traces of remaining solvent were removed under vacuum to give **7** (16.6 g, 100%). The anhydride acid **3** could also be prepared by sublimation of the triacid **5** at 190 °C (0.5 mmHg): mp 252-254 °C; IR 3200-2200, 1790, 1759, 1693, 1466, 1277, 1210, 1182, 1136, 1095, 1001 cm^{-1}; ^1H NMR (pyridine-d_5, 300 MHz) δ 2.95 (d, 2 H, J = 14.1 Hz), 2.05 (d, 1 H, J = 13.2 Hz), 1.41-1.21 (m, 12 H, including 1.37 [s, 6 H] and 1.31 [s, 3 H]). Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; O, 33.30. Found: C, 60.12; H, 6.78; O, 33.10.

Cis-Cis Imide Acid 8. Method a). To a stirred solution of concentrated aqueous ammonium hydroxide (NH_4OH, 500 mL) containing a catalytic amount of 4-dimethylaminopyridine (DMAP) was added solid anhydride acid **7** (16 g, 0.067 mmol). The reaction was heated at 80 °C for 12 h and then

carefully concentrated to ~ 100 mL. The resulting mixture was cooled in an ice water bath, and then the pH of the mixture adjusted to ~ 1.0 using concentrated HCl. After 5 min, the colorless solid was collected by filtration and thoroughly washed with 1 N HCl solution. The product was dried on a vacuum , affording 14.5 g (91%) of **8**.

Method b). Triacid **5** (1.00 g, 3.88 mmol) and urea (0.26 g, 0.43 mmol, 1.1 equiv.) were heated to 200 °C in triglyme (5 mL) for 2 h. The solution was cooled to room temperature and poured into 1 N HCl (50 mL). The solid was collected by filtration and thoroughly washed with hexanes and 1 N HCl solution. The product was dried on a vacuum, affording 0.85 g (92%): mp > 300 °C (from MeOH); IR 3300-2500, 3140, 2971, 1730, 1717, 1456, 1383, 1311, 1219, 1184 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.19 (s, 1H, CO_2H), 10.36 (s, 1 H, NH), 2.36 (d, 2 H, J = 13.3 Hz), 1.88 (d, 1 H, J = 12.8 Hz), 1.38 (d, 1 H, J = 13 Hz), 1.18 (d, 2 H, J = 13.8 Hz), 1.11 (s, 3 H), 1.08 (s, 6 H); HRMS m/z for $C_{12}H_{17}NO_4$ $[M]^+$ calcd 239.1157, found 239.1156.

Imide Acid Chloride 9. The imide acid **8** (10 g, 0.042 mol) was added to fleshly distilled thionyl chloride (50 mL). The stirred reaction was heated at reflux under a nitrogen atmosphere for 3 h. The solution was carefully concentrated under reduced pressure and the resulting solid was recrystallized from hexanes/toluene to yield white solid **9** (9.9 g, 92%): mp 182-184 °C; IR 3200, 3094, 2987, 1780, 1721, 1696, 1462, 1385, 1205, 924, 897, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 (s, 1 H, NH), 2.78 (d, 2 H, J = 14.0 Hz), 2.04 (d, 1 H, J = 13.4 Hz), 1.45-1.25 (m, 12 H, including 1.32 [s, 3 H] and 1.29 [s, 6 H]); HRMS m/z for $C_{12}H_{16}NO_3Cl$ $[M]^+$ calcd 257.0819, found 257.0820.

2-Naphthyl Ester Imide 11a. To a magnetically stirred solution of 2-naphthol **10a** (73 mg, 0.506 mmol) in dry THF (15 mL) was added sodium hydride (NaH, 18 mg, 1.5 equiv). The reaction was stirred under nitrogen

atmosphere for 20 min and then a solution of imide acid chloride **9** (129 mg, 0.500 mmol, 1.0 equiv.) in dry THF (15 mL) was added dropwise over 10 min. Stirring was continued for 2 h and then the reaction was quenched with 2-3 drops of 1 N HCl solution. The solution was then concentrated and the resulting solid was taken up in CH_2Cl_2 and washed sequentially with water, satd $NaHCO_3$, satd brine, and water. The organic portion was then dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography using hexanes:EtOAc (2:1) affording **11a** as a colorless crystals (153 mg, 84%): mp 214-216 °C; IR 3208, 3096, 2968, 1750, 1697, 1205, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 3 H), 7.62 (s, 1 H, NH), 7.50 (d, 1 H, J = 2 Hz), 7.47 (m, 2 H), 7.16(dd, 1 H, J = 9.0, 2.0 Hz), 2.88 (d, 2 H, J = 14 .1 Hz), 2.07 (d, 1 H, J = 13.0 Hz), 1.49 (s, 3 H), 1.46 (d, 1 H, J = 13.0 Hz), 1.33 (s, 6 H), 1.33 (d, 2 H, J = 14.1 Hz); HRMS m/z for $C_{22}H_{23}NO_4$ $[M]^+$ calcd 365.1627, found 365.1627.

2-(2-Naphthalene)ethyl Ester Imide 11b. To a stirred solution of 2-(2-naphthalene)ethanol **10b** (0.50 g, 2.90 mmol) in CH_2Cl_2 (20 mL) containing dry pyridine (1.0 mL) and a catalytic amount of DMAP was added **9** (0.820 g, 3.18 mmol, 1.1 equiv.). The reaction was heated at reflux under a nitrogen atmosphere overnight. The solution was allowed to cool to room temperature, and then washed with 3 N HCl, water, satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The resulting solid was recrystallized from toluene to give colorless crystals of **11b** (0.89 g, 78%): mp 192-194 °C; IR 3219, 3094, 2967, 2932, 1728, 1695, 1508, 1462, 1381, 1238, 1205, 1178, 1093, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (m, 3 H), 7.66 (d, 1 H, J = 1.9 Hz), 7.53 (s, 1 H, NH), 7.45 (m, 2 H), 7.34 (dd, 1 H, J = 8.1, 1.9 Hz), 4.30 (t, 2 H, J = 7.1 Hz), 3.08 (t, 2 H, J = 7.2 Hz), 2.68 (d, 2 H, J = 14.0 Hz), 1.98 (d, 1 H, J = 13.1 Hz), 1.36 (d, 1 H, J = 13.0 Hz), 1.26 (s, 6 H), 1.14 (d, 2 H, J = 14.0 Hz), 1.10 (s, 3 H); HRMS m/z for $C_{24}H_{27}NO_4$ $[M]^+$ calcd 393.1940, found 393.1940.

The other ester imides **11c-f** were prepared using the method described for the preparation of **11a** by using the corresponding aromatic alcohols **10c-f**. The spectroscopic data and melting points for these imides are given below.

1-Naphthyl Ester Imide 11c. A colorless solid (79% yield): mp 241-245 °C; IR 3202, 3099, 2966, 2932, 1751, 1721, 1697, 1462, 1362, 1316, 1201, 1140, 1085, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (m, 1 H), 7.68 (m, 2 H), 7.65 (s, 1 H, NH), 7.48 (m, 3 H), 7.25 (m, 1 H), 2.95 (d, 2 H, J = 14.0 Hz), 2.10 (d, 1 H, J = 13.1 Hz), 1.50 (s, 3 H), 1.49 (d, 1 H, J = 13.0 Hz), 1.39 (d, 2 H, J = 14.1 Hz), 1.34 (s, 6 H); HRMS m/z for $C_{22}H_{23}NO_4$ $[M]^+$ calcd 365.1627, found 365.1627.

1-Bromo-2-Naphthyl Ester Imide 11d. A colorless solid (70% yield): mp 267-269 °C; IR 3198, 3088, 2974, 2914, 1757, 1722, 1698, 1595, 1502, 1462, 1385, 1205, 1130, 1074, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, 1 H, J = 1.2 Hz), 7.84 (dd, 1 H, J = 8.0, 1.2 Hz), 7.82 (d, 1 H, J = 8.2 Hz), 7.68 (s, 1 H, NH), 7.59 (t, 1 H, J = 8.0 Hz), 7.51 (t, 1 H, J = 8 Hz), 7.28 (d, 1 H, J = 8.2 Hz), 2.91 (d, 2 H, J = 13.0 Hz), 2.09 (d, 1 H, J = 12.9 Hz), 1.56 (s, 3 H), 1.47 (d, 1 H, J = 12.8 Hz), 1.36 (d, 2 H, J = 13.0 Hz), 1.33 (s, 6 H); HRMS m/z for $C_{22}H_{22}{}^{81}BrNO_4$ $[M]^+$ calcd 445.0712, found 445.0713.

6-Bromo-2-Naphthyl Ester Imide 11e. A colorless solid (81% yield): mp 222-224 °C; IR 3218, 2970, 2932, 1750, 1727, 1698, 1589, 1501, 1460, 1381, 1360, 1237, 192, 1150, 1082, 903, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, 1 H, J = 1.9 Hz), 7.33 (dd, 1 H, J = 8.0, 1.2 Hz), 7.67 (s, 1 H, NH), 7.55 (dd, 1 H, J = 8.0, 1.2 Hz), 7.50 (d, 1 H, J = 1.9 Hz), 7.19 (dd, 1 H, J = 8.0, 1.2 Hz), 2.86 (d, 1 H, J = 13.4 Hz), 2.07 (d, 1 H, J = 13.0 Hz), 1.48 (s, 3 H), 1.46 (d, 1 H, J = 13.0 Hz), 1.33 (s, 6 H), 1.33 (d, 2 H, J = 13.4 Hz); HRMS m/z for $C_{22}H_{22}{}^{81}BrNO_4$ $[M]^+$ calcd 445.0713, found 445.0713.

1-Cyano-2-Naphthyl Ester Imide 11f. 1-Cyano-2-naphthol **10f** was synthesized in three steps. To a solution of 1-bromo-2-naphthol (3.00 g, 0.014

mol) and the phase transfer catalyst tetrabutylammonium iodide ($n\text{-}Bu_4N^+I^-$) in 20 mL of methylene chloride (CH_2Cl_2) were added 3 N NaOH (16 mL) and dimethyl sulfate (Me_2SO_4, 7 mL). After stirring at room temperature for 1 h, the organic layer was sequentially washed with 4 N NH_4OH, 2 N NaOH solution, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The solid was dried under vacuum affording 1-bromo-2-methoxynaphthalene as a colorless solid (3.00 g, 94%): mp 80-82 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, 1 H, J = 8.6 Hz), 7.83 (d, 1 H, J = 9.0 Hz), 7.79 (d, 1 H, J = 8.6 Hz), 7.57 (t, 1 H, J = 7.2 Hz), 7.40 (t, 1 H, J = 7.2 Hz), 7.29 (d, 1 H, J = 9 Hz), 4.04 (s, 3 H); HRMS m/z for $C_{11}H_9BrO$ $[M]^+$ calcd 235.9837, found 235.9837.

A solution of 1-bromo-2-methoxynaphthalene (2.00 g, 8.44 mmol) and cuprous cyanide (1.50 g, 2 equiv.) in dry DMF (20 mL) was heated at reflux for 5 h under a nitrogen atmosphere.[97] Upon cooling to 80 °C, 10% HCl (50 mL) containing $FeCl_3 \cdot H_2O$ (3.00 g) and toluene (100 mL) was added to the reaction mixture, heated to 100 °C for 3 h to decompose the copper-complex. The aqueous layer was extracted with toluene. The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography using 33% EtOAc in hexanes affording 1.1 g (71%) of 1-cyano-2-methoxynaphthalene as a colorless solid: mp 93-95 °C; IR, 2211, 1624, 1576, 1508, 1476, 1287, 1149, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, 1 H, J = 8.5 Hz), 8.05 (d, 1 H, J = 9.2 Hz), 7.84 (d, 1 H, J = 8.5 Hz), 7.65 (t, 1 H, J = 7.2 Hz), 7.47 (t, 1 H, J = 7.2 Hz), 7.29 (d, 1 H, J = 9.2 Hz), 4.09 (s, 3 H); HRMS m/z for $C_{12}H_9NO$ $[M]^+$ calcd 183.0684, found 183.0684.

A solution of 1-cyano-2-methoxynaphthalene (1.00 g, 5.46 mmol) in iodic acid (47-51 %, 15 mL) and glacial acetic acid (12 mL) was refluxed

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overnight with a $CaCl_2$ drying tube. After concentration in vacuo, the resulting oily liquid was taken up in ether. The ethereal solution was washed with water, satd aq. $NaHCO_3$, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The crude product was subjected to flash chromatography using 67% Et_2O in hexanes affording 1-cyano-2-naphthol **10f** (0.40 g, 43%) as a colorless solid: mp 151-153 °C; IR, 3191, 2226, 1626, 1576, 1516, 1286 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, 1 H, J = 8.5 Hz), 7.97 (d, 1 H, J = 9.1 Hz), 7.83 (d, 1 H, J = 8.1 Hz), 7.65 (t, 1 H, J = 7.9 Hz), 7.47 (t, 1 H, J = 7.9 Hz), 7.19 (d, 1 H, J = 9.0 Hz) 6.45 (s, 1 H, OH); HRMS m/z for $C_{11}H_7NO$ $[M]^+$ calcd 169.0534, found 169.0534.

The 1-cyano-2-naphthyl ester imide **11f** was prepared by the method described for the preparation of **11a** with using 1-cycno-2-naphthol **10f**. The spectroscopic data and melting point for imide **11f** are given below.

A colorless solid (65% yield): mp 276-279 °C; IR 3221, 2972, 2932, 2855, 2233, 1759, 1728, 1692, 1205, 1132, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, 1 H, J = 8.3 Hz), 8.08 (d, 1 H, J = 9.0 Hz), 7.73 (s, 1 H, NH), 7.69 (t, 1 H, J = 7.2 Hz), 7.62 (t, 1 H, J = 7.3 Hz), 7.36 (d, 1 H, J = 9.0 Hz), 2.90 (d, 2 H, J = 14.6 Hz), 2.10 (d, 1 H, J = 13.4 Hz), 1.63 (s 3 H), 1.49 (d, 1 H, J = 13.5 Hz) 1.39 (d, 2 H, J = 14.6 Hz), 1.34 (s, 6 H); HRMS m/z for $C_{23}H_{22}N_2O_4$ $[M]^+$ calcd 390.1580, found 390.1580.

Methyl Ester Imide 11g. To a solution of anhydrous methanol (15 mL) and sodium methoxide (0.10 g, 1.94 mmol, 2.5 equiv.), which was stirred at room temperature under a nitrogen atmosphere, was added imide acid chloride **9** (0.2 g, 0.78 mmol) in one portion. After stirring for 2 h, the reaction mixture was concentrated affording a crude product. The crude product was taken up in 20 mL of $CHCl_3$, and the solution was washed with satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The resulting

solid was purified by flash chromatography using 30% EtOAc in $CHCl_3$ to afford 0.17 g (87 %) as a colorless solid: mp 212-214 °C; IR 3194, 3094, 2965,, 1721, 1698, 1464, 1379, 1325, 1209, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (s, 1 H, NH), 3.61 (s, 3 H), 2.70 (d, 2 H, J = 14.0 Hz), 1.98 (d, 1 H, J = 13.1 Hz), 1.37 (d, 1 H, J = 13 Hz), 1.26 (s, 6 H), 1.22 (s, 3 H), 1.17 (d, 2 H, J = 14.0 Hz); HRMS m/z for $C_{13}H_{19}NO_4$ $[M]^+$ calcd 253.1314, found 253.1314.

Methylamide Imide 11f. A solution of **9** (1.00 g, 3.89 mmol) in anhydrous THF (90 mL) containing a catalytic amount of DMAP was treated with a slow stream of gaseous methylamine (CH_3NH_2) with vigorous stirring at room temperature for 1 h. After stirring for an additional 1 h, the solution was evaporated and the residue was subjected to flash chromatography using EtOAc. This gave 65% yield of **11f**: mp 260-261 °C; IR 3306, 3194, 3094, 1699, 1684, 1522, 1373 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 7.61 (s,1 H, NH), 5.54 (s, 1 H, NH), 2.71 (d, 3 H, J= 4.7 Hz), 2.55 (d, 2 H, J = 13.6 Hz) 1.99 (d, 1 H, J = 13.3 Hz), 1.37 (d, 1 H, J= 13.3 Hz), 1.27 (s, 6 H), 1.21 (s, 3 H), 1.21(d, 2 H, J=13.5 Hz); HRMS m/z for $C_{13}H_{20}N_2O_2$ $[M]^+$ calcd 252.1474, found 252.1475.

2-Naphthylamide Imide 15a. A solution of **9** (0.30 g, 1.17 mmol), 2-aminonaphthalene **14a** (0.20 g, 1.4 mmol), catalytic amount of DMAP , and pyridine (1 mL) in dry $CHCl_3$ (20 mL) was stirred overnight at room temperature. The solution was subsequently washed with 10% HCl, water, satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4). After concentration, the crude product was purified by flash chromatography (1:4 EtOAc:CH_2Cl_2) affording **15a** as colorless solid (0.26 g, 62%): mp 281-283 °C (from EtOAc); IR 3486, 3366, 3200, 3092, 2963, 1719, 1690, 1547, 1470, 1385, 1363, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, 1 H, J = 1.9 Hz), 7.75 (m, 4 H), 7.42 (m, 4 H), 2.70 (d, 2 H, J = 13.7 Hz), 1.92 (d, 1 H, J = 13.4 Hz), 1.39 (d, 1 H, J = 13.4 Hz), 1.35 (s, 3 H), 1.35 (d, 2 H, J = 13.8 Hz), 1.28 (s,6 H); HRMS m/z for $C_{22}H_{24}N_2O_3$ $[M]^+$

calcd 364.1787, found 364.1788. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69; O, 13.17. Found: C, 72.50; H, 6.57; N, 7.73; O, 13.20.

Imides **15b** and **15c** were prepared by the method described above using the appropriate aromatic amines. The spectroscopic data and melting points are given below.

Phenylamide Imide 15b. A colorless solid (78% yield): mp 244-246 °C; IR 3375, 3200, 3100, 2697, 1720, 1688, 1601, 1541, 1437, 1321, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 7.62 (s, 1 H, NH), 7.40 (d, 2 H, J = 7.9 Hz), 7.29 (t, 2 H, J = 7.4 Hz), 7.10 (t, 1 H, J = 7.4 Hz), 2.67 (d, 2 H, J = 13.7 Hz), 2.02 (d, 1 H, J = 13.2 Hz), 1.43 (d, 1 H, J = 13.3 Hz), 1.34 (d, 2 H, J = 13.7 Hz), 1.32 (s, 3 H), 1.30 (s, 6 H); HRMS m/z for $C_{18}H_{22}N_2O_3$ $[M]^+$ calcd 314.1630, found 314.1630.

2-Anthrylamide Imide 15c. A off-white solid (67% yield): mp 280-281 °C (from EtOAc); IR 3368, 3194, 3052, 2965, 1696, 1541, 1522, 1562, 1429, 1381, 1360, 1312, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 2 H), 8.31 (d, 1 H, J = 1.8 Hz), 7.95 (m, 3 H), 7.61 (s, 1 H, NH), 7.42 (m, 4 H), 2.73 (d, 2 H, J = 14.5 Hz), 2.02 (d, 1 H, J = 12.8 Hz) , 1.56 - 1.25 (m, 12 H, including 1.38 [s, 3 H] and 1.32 [s, 6 H]); HRMS m/z for $C_{26}H_{26}N_2O_3$ $[M]^+$ calcd 414.1493, found 414.1493.

2-Naphthylamide Hydroxylactam 16a. A solution of 2-naphthylamide imide **15a** (0.20 g, 0.55 mmol) and excess $NaBH_4$ (0.4 g) in anhydrous EtOH (50 mL) was stirred at 0 °C for 5 h. The cooled solution was poured into ice-water (300 ml) and extracted with $CHCl_3$ (3 x 100 mL). The organic layer was washed with water and dried with anhydrous sodium sulfate. After concentration at reduced pressure, the crude product was subjected to flash chromatography (2:1 EtOAc/$CHCl_3$) affording 0.19 g (95%) of **16a** as colorless crystals: mp 186-189 °C (decomp); IR 3280, 2959, 2924, 1716, 1650,1600, 1576, 1558, 1506, 1471, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 8.03 (d, 1 H, J = 1.8 Hz), 7.80 (m, 3 H), 7.68 (s, 1 H, NH), 7.46 (m, 3 H), 5.56 (s, 1 H, NH), 5.15 (d, 1 H, OH, J = 13.1 Hz), 4.56

(d, 1 H, J = 13.1 Hz), 2.96 (d, 1 H, J = 14.9 Hz), 2.33 (d, 1 H, J = 15.0 Hz), 1.82 (d, 1 H, J = 13.4 Hz), 1.54 (d, 1 H, J = 15.0 Hz), 1.38 (s, 3 H), 1.36 (d, 1 H, J = 13.4 Hz), 1.24 (s, 3 H), 1.09 (s, 3 H), 0.96 (d, 1 H, J = 14.9 Hz); HRMS m/z for $C_{22}H_{26}N_2O_3$ $[M]^+$ calcd 366.1943, found 366.1944.

Hydroxylatams **16b-d** were synthesized using the identical procedure described for **16a**. The spectroscopic data and melting points for these compounds are given below.

Phenylamide Hydroxylactam 16b. A colorless solid in quantitative yield: mp 201-204 °C (decomp); IR 3232, 2927, 2874, 1660, 1645, 1595, 1538, 1417, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49 (s, 1 H, NH), 7.43 (d, 2 H, J = 7.6 Hz), 7.33 (t, 2 H, J = 7.7 Hz), 7.18 (t, 1 H, J = 7.2 Hz), 5.50 (s, 1 H, NH), 5.18 (d, 1 H, OH, J = 13.0 Hz), 4.57 (d, 1 H, J = 13.0 Hz), 2.92 (d, 1 H, J = 14.8 Hz), 2.27 (d, 1 H, J = 15.0 Hz), 1.83 (d, 1 H, J= 13.4 Hz), 1.52 (d, 1 H, J = 15.0 Hz), 1.35 (d, 1 H, J = 13.5 Hz), 1.33 (s, 3 H), 1.23 (s, 3 H), 1.08 (s, 3 H), 0.94 (d. 1 H, J = 14.9 Hz); HRMS m/z for $C_{18}H_{24}N_2O_3$ $[M]^+$ calcd 316.1787, found 316.1788.

2-Anthrylamide Hydroxylactam 16c. A off-white solid (87% yield): mp 223-225 °C; IR 3300, 3053, 2964, 2928, 2872, 1661, 1544, 1524, 1461, 1290, 1219, 1117, 1064, 892, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 8.38 (s, 1 H), 8.37 (s, 1 H), 8.24 (s, 1 H), 7.76 (m, 3 H), 7.43 (m, 3 H), 5.70 (s, 1 H, NH), 5.21 (d, 1 H, OH, J = 13.1 Hz), 4.54 (d, 1 H, J = 13.0 Hz), 2.96 (d, 1 H, J = 15.1 Hz), 2.35 (d, 1 H, J = 14.9 Hz), 1.76 (d, 1 H, J = 13.3 Hz), 1.52 (d, 1 H, J =14.9 Hz), 1.38 (s, 2 H), 1,33 (d, 1 H, J = 13.3 Hz), 1.22 (s, 3 H), 1.07 (s, 3 H), 0.96 (d, 1 H, J = 15.0 Hz); HRMS m/z for $C_{26}H_{28}N_2O_3$ $[M]^+$ calcd 416.2100, found 416.2101.

Methylamide Hydroxylactam 16d. A colorless solid (89% yield): mp 183-186 °C; IR, 3260, 2961, 2926, 1661, 1555, 1478, 1404, 1381, 1342, 1296, 1223, 1156, 1120, 1078, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.92 (s, 1 H, NH), 5.70 (d, 1 H, OH, J = 13.0 Hz), 5.48 (s, 1 H, NH), 4.56 (d, 1 H, J = 13.0 Hz), 2.85 (d, 1 H, J

= 15.0 Hz), 2.76 (d, 3 H,J = 5.4 Hz), 2.08 (d, 1 H, J = 15.1 Hz), 1.78 (d, 1 H, J = 14.0 Hz), 1.39 (d, 1 H,J = 15.1 Hz), 1.29 (d, 1 H, J = 14.0 Hz), 1.23 (s, 3 H), 1.16 (s, 3 H), 1.06 (s, 3 H), 0.85 (d, 1 H, J = 15.0 Hz); HRMS m/z calcd 254.1630, found 254.1630.

2-Naphthylamide Lactam 17. A solution of 2-naphthylamide hydroxylactam **16a** (0.15 g, 0.41 mmol) in dry CH_2Cl_2 (5 mL) containing CF_3CO_2H (0.5 mL) and Et_3SiH (0.1 mL) was stirred for 2 h at room temperature. The reaction mixture was carefully washed with saturated $NaHCO_3$ and brine, then dried (Na_2SO_4). The solvent was removed in vacuo to yield pure **11** in quantitative yield as a white solid: mp 214-216 °C; IR 3427, 3276, 3190, 2957, 2908, 2868, 1663, 1539, 1469, 1193, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.08(d, 1 H, J = 1.8 Hz), 7.77 (m, 3 H), 7.57 (s, 1 H, NH), 7.51-7.38 (m, 3 H), 5.39 (s, 1 H, NH), 3.18 (dd, 1 H, J = 11.5, 1.3 Hz), 2.97 (d, 1 H, J = 11.5 Hz), 2.88 (d, 1 H, J = 13.9 Hz), 2.31 (d, 1 H, J = 15.2 Hz), 1.76 (d, 1 H, J = 12.8 Hz), 1.44 (d, 1 H, J = 12.8 Hz), 1.34 (s, 3 H), 1.30 (dd, 1 H, J = 15.1, 1.3 Hz), 1.25 (s, 3 H), 1.04 (dd, 1 H, J = 13.9, 1.3 Hz), 0.99 (s, 3 H); HRMS m/z for $C_{22}H_{26}N_2O_2$ $[M]^+$ calcd 350.1994, found 350.1994.

Cis-Cis Trimethyl 1,3,5-Triallylcyclohexane-1,3,5-tricarboxylate 18. Trimethyl 1,3,5-cyclohexanetricarboxylate **2** (23 g, 89 mmol) in dry toluene (1000 mL) was cannulated over 2.5 h to the stirred solution of lithium diisopropylamide (321 mmol, 3.6 equivalents, commercially available 1.5 M in cyclohexane as monotetrahydrofuran complex) in dry toluene (400 mL) at 0 °C under argon atmosphere. After the addition was complete, the solution was stirred at 0 °C for 30 min, allyl bromide (46 mL, 535 mmol, 6.0 equivalents) was added in a single portion. The ice bath was removed and the temperature was slowly raised to 75 °C over 1 h and maintained for 40 min. After cooling to room temperature, 1 N NH_4Cl solution (200 mL) was

added and the organic layer was sequentially washed with 1 N HCl (3 x 100 mL), brine, satd $NaHCO_3$, and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was distilled under vacuum (0.1 mm Hg, 170-175 °C) to yield **18** as a pale yellow oil (27 g), which was recrystallized from hexanes (22 g, 65%): mp 78-79 °C; IR 3078, 2951, 2914, 1737, 1430, 1211, 1156, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5,51 (m, 3 H), 5.00 (m, 6 H), 3.57 (s, 9 H), 2,59 (d, 3 H, J = 14.0 Hz), 2.24 (d, 6 H, J = 8.0 Hz), 0.94 (d, 3 H, J = 14.0 Hz); HRMS m/z for $C_{21}H_{30}O_6$ $[M]^+$ calcd 378.2042, found 378.2040.

Trimethyl 1,3,5-Tripropylcyclohexane-1,3,5-tricarboxylate 19. Distilled triallyl compound **18** (16.1 g, 43 mmol) was dissolved in ethyl acetate (50 mL) and briefly refluxed with 5 % Pd/C (1.0 g). The solution was filtered and placed in a Parr hydrogenation apparatus along with 10% Pd/C (0.5 g). Hydrogenation was complete at room temperature under 50 psi H_2 for 3 h. The catalyst was filtered off through celite, and the solvent was evaporated to yield a pale yellow semisolid. This was recrystallized from hexanes (75 mL) to give pure tripropyl ester **19** as large blocky crystals (12.1 g, 73% from crude **18**): mp 115.5 °C; IR 2952, 2852, 1732, 1433, 1177, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.94 (s, 9 H), 2.83 (s, 6 H), 1.43 (m, 6 H), 1.16 (m, 6 H), 0.90 (d, 3 H, J = 14.0 Hz), 0.84 (t, 9 H, J = 8.0 Hz); HRMS m/z for $C_{20}H_{33}O_5$ $[M\text{-}OCH_3]^+$ calcd 353.2328, found 353.2326.

1,3,5-Tripropylcyclohexane-1,3,5-tricarboxylic Acid 20. Tripropyl triester **19** (12 g, 31 mmol) was suspended in ethanol (150 mL). Potassium hydroxide (10 g, 150 mmol) in water (40 mL) was added, and the mixture was heated at reflux for 12 h. The ethanol was removed in vacuo and the aqueous residue was diluted with water (60 mL) and carefully acidified to pH < 2 with concentrated HCl in an ice bath. The mixture was filtered and a white solid

was dried in vacuo to give pure tripropyl triacid **20** (10.4 g, 97%): mp 205-210 (decomp); IR 3500-2500, 2960, 2874, 1707, 1467, 1457, 1404, 1255, 1237, 1178, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.80 (d, 3 H, J = 14. 6 Hz), 1.48 (m, 6 H), 1.30 (m, 6 H), 0.96 (d, 3 H, J = 14.6 Hz), 0.88 (t, 9 H, J = 7.0 Hz); HRMS m/z for $C_{18}H_{29}O_5$ $[M\text{-}OH]^+$ calcd 325.2015, found 325.2012.

Tripropyl Imide Acid 21. Tripropyl triacid **20** (4.5 g, 13.2 mmol) in triglyme (20 ml) was heated with urea (1.5 g, 25 mmol) at 180 °C for 2 h under N_2 atmosphere. The hot solution was poured into 1 N HCl aqueous solution. (200 ml) and cooled to room temperature with stirring. After filtration, a white solid was dried in vacuo to yield pure **21** (4.1 g, 96%): mp 262-263 °C; IR 3145, 3071, 2949, 2910, 2875, 1707, 1661, 1465, 1367, 1202, 1177, 872, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 10.61 (s, 1 H, NH), 2.62 (d, 2 H, 13.3 Hz), 2.18 (d, 1 H, J = 13.1 Hz), 1.94 (m, 2 H), 1.49-1.13 (m, 13 H), 0.93-0.81 (m, 9 H); HRMS m/z for $C_{18}H_{29}NO_4$ $[M]^+$ calcd 323.2096, found 323.2095.

Tripropyl Imide Acid Chloride 22. Tripropyl imide acid **21** (4.1 g, 12.7 mmol) was heated at reflux in thionyl chloride ($SOCl_2$, 10 mL) under N_2 atmosphere for 2 h. Excess $SOCl_2$ was removed in vacuo to give an off-white solid which was recrystallized from carbon tetrachloride/hexanes to yield pure **22** (4.1 g, 95%): mp 157.5-158.5 °C; IR 3194, 3100, 2962, 2918, 2876, 1785, 1696, 1440, 1200, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.61 (s, 1 H, NH), 2.66 (d, 2 H, J = 13.6 Hz), 2.21 (d, 1 H, J =13.1 Hz), 1.93 (m, 2 H), 1.57 (m, 2 H), 1.40-1.15 (m, 11 H), 0.92 (m, 9 H); HRMS m/z for $C_{18}H_{28}NO_3Cl$ $[M]^+$ calcd 341.1758, found 341.1757.

2,7-Naphthalenediamide Diimide 24. A solution of 2,7-diaminonaphthalene **23** (46 mg, 0.29 mmol), imide acid chloride **22** (0.20 g, 0.58 mmol) and a catalytic amount of DMAP in dry pyridine (10 mL) was heated at reflux overnight under N_2 atmosphere. The solution was

concentrated in vacuo and the residue was taken up in CH_2Cl_2 (30 mL) and the organic phase was washed with 1 N HCl solution, brine, then dried with anhydrous Na_2SO_4. The crude product was purified by flash chromatography using 33% EtOAc in $CHCl_3$ to yield pure **24** (0.18 g, 81%) as a white solid: mp 329-331 °C; IR 3447, 3360, 3155, 2962, 2934, 2875, 1700, 1652, 1539, 1520, 1496, 1457, 1387, 1381, 1188, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.86 (d, 2 H, J = 1.8 Hz), 7.66 (d, 2 H, J = 8.9 Hz), 7.53 (s, 2 H), 7.39 (dd, 2 H, J = 8.9, 1.8 Hz), (7.30 (s, 2 H), 2.63 (d, 4 H, J = 14.3 Hz), 2.24 (d, 2 H, J = 13.1 Hz), 1.98 (m, 4 H), 1.52-0.85 (m, 44 H); HRMS m/z for $C_{46}H_{64}N_4O_6$ $[M]^+$ calcd 768.4825, found 768.4825.

2,7-Naphthalenediamide Dilactams 26a-b. A solution of 2,7-naphthalenediamide diimide **24** (0.14 g, 0.18 mmol) in ethanol (20 ml) was stirred with $NaBH_4$ (0.13 g) at room temperature for 23 h under Ar atmosphere. The ethanolic solution was poured into water (250 ml) and extracted with $CHCl_3$. The organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2 (10 ml) and a catalytic amount of p-TsOH was added. The mixture was stirred for 2.5 h and diluted with CH_2Cl_2 (70 ml). The mixture was washed with saturated $NaHCO_3$ and brine, then dried with anhydrous $MgSO_4$. The diastereomeric mixture was separated by flash chromatography (16% EtOAc in CH_2Cl_2) to yield meso **25a** (less polar, 48 mg, 37%) and racemic tricyclic compound **25b** (more polar, 54 mg, 40%). Each isomer was dissolved in CH_2Cl_2 (2 ml). CF_3CO_2H (1 ml) and Et_3SiH (81 mg) were added to the solution. The mixture was stirred for 18 h at room temperature and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (30 ml), and the solution was washed with saturated $NaHCO_3$ and brine, then dried with anhydrous $MgSO_4$. The solvent was removed to yield the desired products in quantitative yield as white solids. Meso isomer **26a**: mp 308-310 °C; IR 3393,

3155, 2961, 2933, 2920, 2874, 1653, 1624, 1506, 1491, 1448, 1380, 1095, 1033, 1010, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.03 (d, 2 H, J = 1.8 Hz), 7.67 (d, 2 H, J = 8.8 Hz), 7.58 (s, 2 H, NH), 7.38 (dd, 2 H, J = 8.8, 1.8 Hz), 5.38 (s, 2 H, NH), 3.18 (d, 2 H, J = 11.3 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.90 (d, 2 H, J = 14.3 Hz), 2.23 (d, 2 H, J = 15.6 Hz), 1.99 (m, 2 H), 1.84 (d, 2 H, J = 12.7 Hz), 1.61-0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ $[M]^+$ calcd 740.5240, found 740.5240. Racemic isomer **26b**: mp 175-177 °C; IR 3154, 2961, 2932, 2921, 2874, 1653, 1648, 1471, 1457, 1381, 1096, 1033, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.04 (d, 2 H, J = 1.8 Hz), 7.67 (d, 2 H, J = 8.8 Hz), 7.57 (s, 2 H, NH), 7.38 (dd, 2 H, J = 8.8,1.8 Hz), 5.44 (s, 2 H, NH), 3.19 (d, 2 H, J = 11.3 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.90 (d, 2 H, J = 14.3 Hz), 2.24 (d, 2 H, J = 15.6 Hz), 1.99 (m, 2 H), 1.84 (d, 2 H, J = 12.7 Hz), 1.61-0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ $[M]^+$ calcd 740.5240, found 740.5240. The racemic mixture **26b** was resolved on a Pirkle column (L-3,5-dinitrophenylglycine, Regis Chem. Co.) using 5% isopropanol in chloroform to yield a less polar enantiomer ($[a]_D$ = -63 °, c = 0.40 in CH_2Cl_2) and a more polar enantiomer ($[a]_D$ = +64 °, c = 0.40 in CH_2Cl_2).

Tripropyl 2,3-Naphthylwall Acid 30. A finely ground mixture of tripropyl triacid **20** (85 mg, 0.25 mmol)and 2,3-diaminonaphthalene **29** (39 mg, 0.25 mmol) was heated at 200-210 °C for 2 h under argon atmosphere. The crude product was purified by flash chromatography (8% MeOH in $CHCl_3$) to give a off-white solid (0.10 g, 95%): mp 145-147 °C; IR 3500-2500, 2960, 2934, 2873, 1726, 1696, 1558, 1441, 1362, 1317, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.70 (s, 1 H), 8.11 (s, 1 H), 7.91-7.98 (m, 2 H), 7.43-7.48 (m, 2 H), 2.65 (d, 1 H, J = 12.5 Hz), 2.60 (d, 1 H, J = 12.2 Hz), 2.42 (d, 1 H, J = 11.6 Hz), 1.70-2.35 (m, 3 H), 1.27-1.55 (m, 7 H), 0.95-1.01 (m, 9 H), 0.81 (t, 6 H, J = 7.1 Hz).

Tripropyl 2,3-Naphthylwall Amide 31. A solution of tripropyl 2,3-naphthylwall acid **30** (52 mg, 0.12 mmol) and excess thionyl chloride (0.5 mL)

in dry CH_2Cl_2 (5 mL) was heated at reflux for 3 h under nitrogen atmosphere. After concentration in vacua, the residue was dissolved in dry CH_2Cl_2 (10 mL), and ammonia gas was bubbled for 5 min at 0 °C. The solution was stirred for 20 min at room temperature and concentrated in vacuo. The crude product was purified by flash chromatography (6% MeOH in $CHCl_3$) to give pure **31** as a white solid (44 mg, 85 %): mp 135-137 °C; IR 3470, 3337, 3184, 2959, 2933, 2872, 1718, 1657, 1558, 1440, 1403, 1319, 1193, 873, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.73 (s, 1 H), 8.10 (s, 1 H), 7.93-7.99 (m, 2 H), 7.44-7.48 (m, 2 H), 4.94 (s, br, 1 H, NH), 4.36 (s, br, 1 H, NH), 2.74 (d, 1 H, J = 14.3 Hz), 2.17-2.47 (m, 4 H), 0.97-1.90 (m, 15 H), 0.81 (t, 6 H, J = 7.0 Hz).

Imide Alcohol 32. To a solution of **9** (1.00 g, 3.88 mmol) in anhydrous ethanol (100 mL) was added excess $NaBH_4$ (1.00 g) at -78 °C. After stirring at -78 °C for 10 h, the reaction was carefully quenched with 2 N HCl aqueous solution and the solution was concentrated at reduced pressure. The resulting solid was taken up in $CHCl_3$ (100 mL) and the chloroform layer was washed with water, satd brine, water. The organic layer was dried with anhydrous Na_2SO_4, and concentrated. The crude product was subjected to flash chromatography (40% EtOAc in CH_2Cl_2) to give a colorless solid **32** (0.51 g, 58%): mp 158-160 °C; IR 3346, 3208, 2970, 2909. 1716, 1694, 1467, 1362, 1209, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (s, 1 H, NH), 3.32 (s, 2 H), 2.04 (d, 3 H, J = 14.5 Hz), 1.82 (s, 1 H, OH), 1.40 (d, 1 H, J = 14.5 Hz), 1.26 (s, 6 H), 1.17 (d, 2 H, J = 14.4 Hz), 1.01 (s, 3 H); HRMS m/z for $C_{11}H_{17}NO_2$ $[M]^+$ calcd 195.1259, found 195.1250

Benzoyl Ester Imide 34a. A solution of imide alcohol **32** (0.20 g, 0.89 mmol), benzoyl chloride **33a** (0.25 g, 1.78 mmol 1.2 equiv), DMAP (20 mg), and pyridine (2 mL) in dry CH_2Cl_2 (15 mL) was heated at reflux for 5 h. The reaction mixture was sequentially washed with 3 N HCl, satd aq. $NaHCO_3$,

satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (2:2:1 hexanes/CH_2Cl_2/EtOAc) affording **34a** (0.26 g, 90%) as a colorless solid: mp 142-143 °C; IR 3227, 3095, 2970, 2932, 1723, 1705, 1434, 1383, 1318, 1271, 1111, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, 2 H, J = 8.0 Hz), 7.89 (s, 1 H, NH), 7.56 (t, 1 H, J = 7.1 Hz), 7.43 (t, 2 H, J = 7.1 Hz), 4.09 (s, 2 H), 2.15 (d, 2 H, J = 15.1 Hz), 2.07 (d, 1 H, J = 13.2 Hz), 1.43 (d, 1 H, J = 13.2 Hz), 1.30 (d, 2 H, J = 15.1 Hz), 1.28 (s, 6 H), 1.12 (s, 3 H); HRMS m/z for $C_{19}H_{23}NO_4$ $[M]^+$ calcd 329.1627, found 329.1627.

2-Naphthoyl Ester imide 34b. The preparative method of **34b** is the same as that described for **34a** except that 2-naphthoyl chloride **33b** was used instead of **33a**. A colorless solid (96% yield): mp 180-182 °C; IR 3235, 3021, 2967, 2932, 1721, 1630, 1462, 1433, 1358, 1318, 1284, 1226, 1196, 987, 779, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 1 H), 8.02-7.95 (m, 2 H), 7.87 (m, 3 H, including NH), 7.62-7.51 (m, 2 H), 4.17 (s, 2 H), 2.20 (d, 2 H, J = 15.1 Hz), 2.07 (d, 1 H, J = 13.1 Hz), 1.45 (d, 1 H, J = 13.2 Hz), 1.34 (d, 2 H, J = 15.2 Hz), 1.30 (s, 6 H), 1.17 (s, 3 H); HRMS m/z for $C_{23}H_{27}NO_4$ $[M]^+$ calcd 381.1940, found 381.1940.

Benzoyl Ester Hydroxylactam 35a. A solution of 2-benzoylester imide **34a** (0.15 g, 0.46 mmol) and excess $NaBH_4$ (0.3 g) in anhydrous EtOH (15 mL) was stirred at -10 °C for 2 h. The cooled solution was poured into ice-water (300 ml) and extracted with $CHCl_3$ (3 x 100 mL). The organic layer was washed with water and dried with anhydrous sodium sulfate. Removal of solvent gave a pure **35a** (0.14 g, 93%) as colorless crystals: mp >165 °C (decomp); IR 3336, 2961, 2911, 1717, 1651, 1436, 1316, 1098, 1054, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, 2 H, J = 7.7 Hz), 7.57 (t, 1 H, J = 7.3 Hz), 7.44 (t, 2 H, J = 7.8 Hz), 6.08 (s, 1 H, NH), 5.06 (d, 1 H, J = 11.4 Hz), 4.71 (d, 1 H, J = 10.5 Hz), 4.55 (d, 1 H, OH, J = 10.7 Hz), 3.83 (d, 1 H, J = 11.2 Hz), 2.08 (d, 1 H, J = 15.6 Hz), 1.99 (d, 1 H, J = 14.4 Hz), 1.77 (d, 1 H, J = 13.3 Hz), 1.32 (d, 1 H, J = 13.3 Hz), 1.28 (d, 1 H, J =

14.4 Hz), 1.16 (s, 3 H), 1.12 (s, 3 H), 1.05 (s, 3 H), 0.96 (d, 1 H, J = 15.5 Hz); HRMS m/z for $C_{19}H_{25}NO_4$ $[M]^+$ calcd 331.1784, found 331.1784.

2-Naphthoyl Ester Hydroxylactam 35b. The preparative method of **35b** is the same as that described for **35a** with using **34a**. A colorless solid in quantitative yield: mp >160 °C (decomp); IR 3339, 3060, 2959, 2924, 1713, 1657, 1468, 1372, 1354, 1285, 1231, 1198, 1071, 984, 779, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.62 (s 1 H), 8.05 (dd, 1 H, J = 8.5, 1.6 Hz), 7.96 (d, 1 H, J = 7.8 Hz), 7.89 (d, 2 H, J = 8.5 Hz), 7.63-7.53 (m, 2 H), 6.06 (s, 1 H, NH), 5.22 (d, 1 H, J = 11.3 Hz), 4.73 (d, 1 H, J = 11.2 Hz), 4.62 (d, 1 H, J = 11.2 Hz), 3.82 (d, 1H, J = 11.3 Hz), 2.12 (d, 1H, J = 15.6 Hz), 2.03 (d, 1H, J = 14.4 Hz), 1.80 (d, 1 H, J = 13.3 Hz), 1.35 (d, 1 H, J = 13.3 Hz), 1.34 (d, 1 H, J = 14.4 Hz), 1.19 (s, 6 H), 1.07 (s, 3 H), 0.99 (d, 1 H, J = 15.5 Hz); HRMS m/z for $C_{23}H_{29}NO_4$ $[M]^+$ calcd 383.2096, found 383.2096.

Cis-Trans Imide Acid 36. Cis-Trans triacid **6** (2.00 g, 7.76 mmol) and urea (0.52 g, 0.86 mmol, 1.1 equiv.) were heated to 200 °C in triglyme (10 mL) for 2 h. The solution was cooled to room temperature and poured into 1 N HCl (100 mL). The solid was collected by filtration and thoroughly washed with hexanes and 1 N HCl solution. The product was dried on a vacuum, affording 1.46 g (79%): mp > 300 °C; IR 3300-2500, 1763, 1693, 1385 cm^{-1}; ^1H NMR (pyridine-d_5, 300 MHz) δ 12.50 (s, 1H), 2.20 (d, 2 H, J = 13.0 Hz), 2.10 (d, 2 H, J = 13.0 Hz), 2.05 (d, 1 H, J = 13.0 Hz) 1.36 (s, 6 H), 1.34 (s, 3 H), 1.31 (d, 2 H, J = 13.0 Hz); HRMS m/z for $C_{12}H_{17}NO_4$ $[M]^+$ calcd 239.1157, found 239.1156.

Cis-Trans Imide Acid Chloride 37. A solution of cis-trans imide acid **36** (1.4 g, 5.85 mmol) in excess thionyl chloride (10 mL) was heated at reflux for 2 h under nitrogen atmosphere. The reaction then concentrated. The resulting yellow solid was taken up in hot $CHCl_3$ (~ 10 mL) and precipitated with hexanes (~ 100 mL) as a colorless solid (1.29 g, 86%): mp 170-175 °C; IR 3350, 2970, 1730, 1690, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (s, 1 H), 2.12 (d, 2

H, J = 14.0 Hz), 2.10 (d, 1 H, J = 14.0 Hz), 1.85 (d, 2 H, J = 14.0 Hz), 1.39 (s, 3 H), 1.30 (s, 6 H), 1.25 (d, 2 H, J = 14.0 Hz); HRMS m/z for $C_{12}H_{16}NO_3Cl$ $[M]^+$ calcd 257.0819, found, 257.0820.

Cis-Trans 2-Naphthylamide Imide 38a. A solution of **37** (0.30 g, 1.17 mmol), 2-aminonaphthalene **14a** (0.20 g, 1.4 mmol), catalytic amount of DMAP , and pyridine (1 mL) in dry $CHCl_3$ (20 mL) was stirred overnight at room temperature. The solution was subsequently washed with 10 % HCl, water, satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4). After concentration, the crude product was purified by flash chromatography (20% EtOAc in CH_2Cl_2) affording **38a** as colorless solid (0.35 g, 81%): mp 255-256 °C; IR 3368, 3300, 1699, 1678, 1555, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, 1 H, J = 1.9 Hz), 7.79 (m,4 H), 7.45 (m, 3 H), 7.32 (s, 1 H, NH), 2.08 (m, 5 H), 1.50 (d, 1 H, J = 13.3 Hz), 1.45 (s, 3 H), 1.35 (s, 6 H); HRMS m/z for $C_{22}H_{24}N_2O_3$ $[M]^+$ calcd 364.1787, found 364.1787.

Cis-Trans Phenylamide Imide 38b. This was prepared with using **37** and **14b** by the method described for **38a**. A colorless solid (81% yield): mp > 260 °C; IR 3364, 3196, 3086, 2970, 1695 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (s, 1 H, NH), 7.48 (d, 2 H, J = 8 Hz), 7.34 (t, 2 H, J = 7.6 Hz), 7.14 (s, 1 H, NH), 7.13 (t, 1 H, J = 7.3 Hz), 2.03 (m, 5 H), 1.54 (d, 1 H, J = 13.5 Hz), 1.40 (s, 3 H), 1.33 (s, 6 H); HRMS m/z for $C_{18}H_{22}N_2O_3$ $[M]^+$ calcd 314.1630, found 314.1630.

Cis-Trans 2-Naphthylamide Hydroxylactam 39a. The cis-trans 2-naphthyl amide imide **38a** (0.25 g, 0.69 mmol) was dissolved at -10 °C in EtOH (60 mL) with excess $NaBH_4$ (0.5 g). After stirring at -10 °C for 3 h with adding 2 N HCl (in EtOH) at regular intervals (mostly 15 min), the cooled solution was poured into ice-water (300 mL), which was extracted with $CHCl_3$ (3 x 100 mL). The $CHCl_3$ layer was washed with water and dried with anhydrous Na_2SO_4. After concentration, the crude product was purified by

flash chromatography (50% acetone in $CHCl_3$) affording a colorless solid **39a** (0.21 g, 82 %): mp > 110 °C (decomp); IR 3325, 3070, 2961, 2925, 1676, 1663, 1653, 1539, 1506, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 8.24 (s, 1 H) 7.78 (m, 3 H), 7.57 (s, 1 H, NH), 7.45 (m, 3 H), 6.13 (s, 1 H, NH), 4.85 (d, 1 H, J = 6.2 Hz), 3.07 (d, 1 H, OH, J = 6.2 Hz), 2.16 (d, 1 H, J = 15.4 Hz), 2.02 (s, 2 H), 1.87 (d, 1 H, J= 15.0 Hz), 1.74 (d, 1 H, J = 13.4 Hz), 1.59 (s, 3 H), 1.44 (d, 1 H, J = 13.5 Hz), 1.25 (s, 3 H), 1.18 (s, 3 H).

Cis-Trans Phenylamide Hydroxylactam 39b. This was prepared with using **38b** by the method described for **39a**. The crude product was purified by flash chromatography (40 % acetone in $CHCl_3$) affording **19b** in a 65% yield: mp > 110 °C (decomp); IR 3347, 2959, 2926, 1652, 1598, 1500, 1437, 1103, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, 2 H, J = 7.4 Hz), 7.33 (m, 3 H, including NH), 7.11 (t, 1 H, J = 7.6 Hz), 6.02 (s, 1 H, NH), 4.83 (d, 1 H, J = 6.7 Hz), 2.89 (d, 1 H, OH, J = 6.7 Hz), 2.10 (d, 1H, J = 14.8 Hz), 1.97 (s, 2 H), 1.82 (d, 1 H, J = 14.9 Hz), 1.72 (d, 1 H, J= 13.4 Hz), 1.53 (s, 3 H), 1.41 (d, 1 H, J = 13.5 Hz), 1.22 (s, 3 H), 1.16 (s, 3 H).

1-Cyclohexyl-4-thiouracil 41. A solution of 1- cyclohexyluracil **40** (0.10 g, 0.52 mmol) and phosphorus pentasulfide (0.13 g, 0.57 mmol, 1.2 equiv) in pyridine (30 mL) was refluxed with stirring for 5 h. The solution was concentrated and the resulting solid was dissolved in $CHCl_3$ (50 mL). The solution was washed with water, satd brine water, dried (Na_2SO_4), filtered, and concentrated. The crude product was separated by flash chromatography (50 % EtOAc in hexanes) to give **41** as yellow needles (86 mg, 80%): mp 196 - 197 °C (lit.[48]191 - 192 °C); IR 3205, 3104, 2932, 2857, 1682, 1610, 1451, 1385, 1341, 1271, 1246, 1177, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.40 (s, 1 H, NH), 7.07 (d, 1 H, J = 7.6 Hz), 6.41 (dd, 1 H, J = 7.6, 2.1 Hz), 4.43 (tt, 1 H, J = 11.6, 3.4 Hz), 1.92 (m, 4 H), 1.75 (d, 1 H, J = 12.8 Hz), 1.44 (m, 4 H), 1.17 (tt, 1 H, J = 12.9, 3.6

Hz); HRMS m/z for $C_{10}H_{14}N_2OS$ $[M]^+$ calcd 210.0827, found 210.0826.

1-Cyclohexylcytosine 42. 1-Cyclohexyl-4-thiouracil **41** (0.08 g, 0.38 mmol) was treated with 30 ml of ethanolic ammonia (previously saturated at 0 °C) in a sealed tube at 120 - 130 °C for 48 h. The solvent was removed at reduced pressure and the resulting solid was dissolved in $CHCl_3$ (30 mL). The organic layer was washed with satd $NaHCO_3$, satd brine, water, and dried with anhydrous sodium sulfate. The solvent was removed at reduced pressure and the resulting solid was dried under vacuum affording 0.070 g (96%) as a colorless solid: mp 268 - 270 °C; IR, 3463, 3291, 3094, 2932, 2855, 1647, 1607, 1526, 1483, 1400, 1371, 1282, 1188, 1132, 893, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 7.34 (d, 1 H, J = 7.3 Hz), 5.67 (d, 1 H, J = 7.3 Hz), 5.28 (s, br, 2 H, NH_2), 4.62 (tt, 1 H, J = 11.9, 3.2 Hz), 1.95 (m, 4 H), 1.86 (d, 1 H, J= 13.4 Hz), 1.60- 1.36 (m, 4 H), 1.17 (tt, 1 H, J = 12.8, 3.6 Hz); HRMS $[M]^+$ m/z for $C_{10}H_{15}N_3O$ calcd 193.1214, found 193.1214.

General Procedure of the Preparations of Alkane Diester Diimides 44a-d. A solution of imide acid chloride **9** (2.1 equiv), α,ω-diols **43a-d** (1 equiv), DMAP (0.5 equiv) and excess Et_3N in dry CH_2Cl_2 was heated at reflux overnight under N_2 atmosphere. The solution was washed with 1 N HCl, brine, and dried over anhydrous Na_2SO_4. The crude product was subjected to flash chromatography (1:3:6 MeOH/hexanes/EtOAc) to give a pure diester diimides **44a-d.**

1,2-Ethane Diester Diimide 44a; white solid (84% yield): mp > 300 °C; IR 2957, 2929, 2871, 1728, 1693, 1462, 1286, 1123 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.26 (s, 2 H, NH), 4.14 (s, 4 H), 2.71 (d, 4 H, J = 14.2 Hz), 1.96 (d, 2 H, J = 13.3 Hz), 1.36 (d, 2 H, J = 13.3 Hz), 1.26 (s, 12 H), 1.24 (s, 6 H), 1.17 (d, 4 H, J = 14.2 Hz). HRMS m/z for $C_{26}H_{36}N_2O_8$ $[M]^+$ calcd 504.2471, obsd 504.2469.

1,3-Propane diester diimide 44b; white solid (85% yield): mp = 223-225

°C; IR 3201, 2967, 2932, 1728, 1691, 1464, 1208, 1173 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.90 (s, 2 H, NH), 4.05 (t, 4 H, J = 6.2 Hz), 2.70 (d, 4 H, J = 13.0 Hz), 1.93 (d, 2 H, J = 12.2 Hz), 1.37-1.12 (m, 26 H), including 1.24 [s, 12 H], 1.21 [s, 6 H]). HRMS m/z for $C_{27}H_{38}N_2O_8$ $[M]^+$ calcd 518.2628, obsd 518.2630.

1,4-Butane diester diimide 44c; white solid (62% yield): mp = 218-219 °C; IR 2959, 2930, 2872, 1729, 1691, 1464, 1275, 1209, 1179 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.34 (s, 2 H, NH), 4.02 (m, 4 H), 2.72 (d, 4 H, J = 14.2 Hz), 1.97 (d, 2 H, J = 13.3 Hz), 1.65 (m, 4 H), 1.35 (d, 2 H, J = 13.3 Hz), 1.25 (s, 12 H), 1.21 (s, 6 H), 1.16 (d, 4 H, J = 14.2 Hz). HRMS m/z for $C_{28}H_{40}N_2O_8$ $[M]^+$ calcd 532.2784, obsd 532.2785.

1,5-Pentane diester diimide 44d; white solid (89% yield): mp >235 °C; IR 3214, 2964, 2930, 1723, 1692, 1427, 1184 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.57 (s, 2 H, NH), 4.01 (t, 4 H, J = 6.9 Hz), 2.70 (d, 4 H, J = 14.2 Hz), 1.95 (d, 2 H, J = 13.2 Hz), 1.65 (m, 4 H), 1.37-1.24 (m, 4 H), 1.24 (s, 12 H), 1.21 (s, 6 H), 1.16 (d, 4 H, J = 14.2 Hz). HRMS m/z for $C_{29}H_{42}N_2O_8$ $[M]^+$ calcd 546.2941, obsd 546.2938.

General Procedure for the Preparation of Alkane Diester Dilactams 45a-d (racemic) and 46a-d (meso). A solution of alkane diester diimides **44a-d** (0.1 g) and $NaBH_4$ (10-20 equiv.) in EtOH was stirred at 0 °C for 6-12 h. The solution was poured into cold brine and the aqueous solution was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a white solid. The solid was dissolved in dry CH_2Cl_2 and excess CF_3CO_2H and Et_3SiH were added. The solution was stirred for 2-5 h at ambient temperature and concentrated in vacuo. The resulting oily liquid was taken up in CH_2Cl_2 and the organic layer was washed with saturated $NaHCO_3$, brine, then dried over anhydrous Na_2SO_4. The crude mixture (racemic/meso 50/50) was subjected to flash chromatography to give

the pure dilactams as white solids. The racemic dilactams **45a-d** were less polar than the meso dilactams **46a-d**. Total yields of **45a-d** and **46a-d** from **44a-d** were in the range of 85-94%.

1,2-Ethane Diester Dilactam 45a (racemic, less polar): mp 223-226 °C; IR 3197, 2954, 2928, 1724, 1663, 1491, 1456, 1241, 1175, 1089 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.11 (s, 2 H), 4.25-4.09 (m, 4 H), 3.19 (d, J = 12.1 Hz, 2 H), 2.97 (d, J = 12.1 Hz, 2 H), 2.53 (d, J = 13.7 Hz, 4 H), 1.69 (d, J = 12.7 Hz, 2 H), 1.23-0.99 (m, 6 H), 1.17 (s, 6 H), 1.07 (s, 6 H), 0.94 (s, 6 H); HRMS m/z for $C_{26}H_{40}N_2O_6$ $[M]^+$ calcd 476.2886, obsd 476.2885. **1,2-Ethane Diester Dilactam 46a (meso, more polar)**: mp > 280 °C; IR 3197, 2953, 2912, 1715, 1688, 1646, 1440, 1261 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.41 (s, 2 H), 4.36 (m, 4 H), 4.10 (m, 2 H), 3.17 (d J = 11.7 Hz, 2 H), 3.03 (d, J = 11.7 Hz, 2 H), 2.70 (d, J = 13.9 Hz, 2 H), 2.50 (d, J = 14.1 Hz, 2 H), 1.73 (d, J = 12.8 Hz, 2 H), 1.25-1.02 (m, 6 H), 1.18 (s, 6 H), 1.15 (s, 6 H), 0.98 (s, 6 H); HRMS m/z for $C_{26}H_{40}N_2O_6$ $[M]^+$ calcd 476.2886, obsd 476.2885.

1,3-Propane Diester Dilactam 45b (racemic, less polar): mp 213-215 °C; IR 3209, 2955, 2927, 1723, 1666, 1471, 1456, 1257, 1174, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.47 (s, 2 H), 4.33 (m, 2 H), 4.18 (m, 2 H), 3.24 (d, J = 12.1 Hz, 2 H), 2.99 (d, J = 12.1 Hz, , 2 H), 2.59-2.51 (m, 4 H), 2.03 (m, 2 H), 1.69 (d, J = 12.5 Hz, 2 H), 1.21-1.00 (m, 6 H), 1.14 (s, 6 H), 1.10 (s, 6 H), 0.95 (s, 6 H); HRMS m/z for $C_{26}H_{40}N_2O_6$ $[M]^+$ calcd 476.2886, obsd 476.2885. **1,3-Propane Diester Dilactam 46b (meso, more polar)**: mp 185-187 °C; IR 3300, 2954, 2924, 1723, 1663, 1491, 1456, 1273, 1257, 1175 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.01 (s, 2 H), 4.21-3.98 (m, 4 H), 3.18 (d, J = 11.5 Hz, 2 H), 3.03 (d, J = 11.5 Hz, 2 H), 2.63 (d, J = 13.9 Hz, 2 H), 2.51 (d, J = 14.0 Hz, 2 H), 1.72 (d, J = 12.9 Hz, 2 H), 1.25-1.01 (m, 6 H), 1.16 (s, 6 H), 1.14 (s, 6 H), 0.97 (s, 6 H); HRMS m/z for $C_{26}H_{40}N_2O_6$ $[M]^+$ calcd 476.2886, obsd 476.2885.

1,4-Butane Diester Dilactam 45c (racemic, less polar): mp 172-174 °C; IR

3223, 2950, 2927, 1715, 1653, 1472, 1448, 1174, 1089 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.76 (s, 2 H), 4.20 (m, 2 H), 3.91 (m, 2 H), 3.19 (d, J = 11.7 Hz, 2 H), 2.99 (d, J = 11.7 Hz, 2 H), 2.63-2.50 (m, 4 H), 1.80-1.55 (m, 4 H), 1.25-1.00 (m, 6 H), 1.15 (s, 6 H), 1.12 (s, 6 H), 0.96 (s, 6 H); HRMS m/z for $C_{28}H_{44}N_2O_6$ $[M]^+$ calcd 504.3199, obsd 504.3198. **1,4-Butane Diester Dilactam 46c (meso, more polar)**: mp 201-203 °C; IR 3197, 2952, 2916, 1717, 1645, 1439, 1258, 1177 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.64 (s, 2 H), 4.09-3.93 (m, 4 H), 3.17 (d, J = 11.5 Hz, 2 H), 3.00 (d, J = 11.5 Hz, 2 H), 2.65 (d, J = 14.1 Hz, 2 H), 2.51 (d, J = 13.9 Hz, 2 H), 1.75-1.57 (m, 4 H), 1.25-1.01 (m, 6 H), 1.16 (s, 6 H), 1.15 (s, 6 H), 0.97 (s, 6 H); HRMS m/z for $C_{28}H_{44}N_2O_6$ $[M]^+$ calcd 504.3199, obsd 504.3198.

1,5-Pentane Diester Dilactam 45d (racemic, less polar): mp 161-163 °C; IR 3206, 2954, 2925, 1719, 1655, 1448, 1257, 1186, 1089 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.98 (s, 2 H), 3.97 (m, 4 H), 3.19 (d, J = 11.8 Hz, 2 H), 2.96 (d, J = 11.8 Hz, 2 H), 2.58-2.50 (m, 2 H), 1.75-1.65 (m, 4 H), 1.39 (t, J = 7.0 Hz, 2 H), 1.22-0.97 (m, 6 H), 1.15 (s, 6 H), 1.11 (s, 6 H), 0.96 (s, 6 H); HRMS m/z for $C_{29}H_{46}N_2O_6$ $[M]^+$ calcd 518.3356, obsd 518.3357. **1,5-Pentane Diester Dilactam 45d (meso, more polar)**: mp 178-180 °C; IR 3193, 2953, 2927, 1723, 1668, 1448, 1257, 1175, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.23 (s, 2 H), 4.07 (m, 2 H), 3.90 (m, 2 H), 3.17 (d, J = 11.5 Hz, 2 H), 3.01 (d, J = 11.5 Hz, 2 H), 2.60 (d, J = 13.9 Hz, 2 H), 2.50 (d, J = 14.0 Hz, , 2 H), 1.74-1.60 (m, 6 H), 1.41-1.00 (m, 8 H), 1.16 (s, 6 H), 1.15 (s, 6 H), 0.98 (s, 6 H); HRMS m/z for $C_{29}H_{46}N_2O_6$ $[M]^+$ calcd 518.3356, obsd 518.3357.

General Procedure for the Preparations of Alkane Monoester Imides 47a-d. A solution of imide acid chloride **9** (0.15 g, 1 equiv), excess α,ω-diol **43a-d** (10 equiv), DMAP (0.5 equiv) and excess Et_3N in dry CH_2Cl_2 was heated at reflux overnight under N_2 atmosphere. The solution was washed with 1 N HCl, brine, and dried over anhydrous Na_2SO_4. The crude product **47a-d** was

purified by flash chromatography.

2-Hydroxyethyl Ester Imide 47a; white solid (67% yield): mp 140-142 °C; IR 3410, 3077, 2977, 2873, 1728, 1691, 1464, 1317, 1196, 1179, 1078 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 4.17 (m, 2 H), 3.79 (m, 2 H), 3.34 (t, J = 6.8 Hz, 1 H), 2.71 (d, J = 14.1 Hz, 2 H), 2.01 (d, J = 13.4 Hz, 1 H), 1.38 (d, J = 13.4 Hz, 1 H), 1.27 (s, 6 H), 1.23 (s, 3 H), 1.19 (d, J = 14.1 Hz, 2 H).

3-Hydroxypropyl Ester Imide 47b; white solid (80% yield): mp 133-135 °C; IR 3510, 3203, 3097, 2967, 2933, 1727, 1697, 1463, 1382, 1318, 1199, 1056 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 4.12 (t, J = 5.3 Hz, 2 H), 3.69 (m, 2 H), 2.69 (d, J = 14.1 Hz, 2 H), 2.57 (t, J = 6.5 Hz, 1 H), 1.99 (d, J = 13.2 Hz, 1 H), 1.38 (d, J = 13.2 Hz, 1 H), 1.26 (s, 6 H), 1.23 (s, 3 H), 1.19 (d, J = 13.9 Hz, 2 H).

4-Hydroxybutyl Ester Imide 47c; oily liquid (81% yield): IR 3462, 3220, 3099, 2964, 2933, 1729, 1697, 1463, 1381, 1318, 1208 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 4.05 (t, J = 6.1 Hz, 2 H), 3.67 (q, J = 5.7 Hz, 2 H), 2.69 (d, J = 14.2 Hz, 2 H), 1.97 (d, J = 13.3 Hz, 1 H), 1.70-1.61 (m, 3 H, including OH), 1.36 (d, J = 13.3 Hz, 1 H), 1.24 (s, 6 H), 1.21 (s, 3 H), 1.17 (d, J = 14.2 Hz, 2 H).

5-Hydroxyethyl Ester Imide 47d; white solid (86% yield): mp 142-144 °C; IR 3445, 2961, 2931, 1727, 1696, 1448, 1318, 1196, 1207 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 7.72 (s, 1 H), 4.02 (t, J = 6.3 Hz, 2 H), 3.67 (q, J = 5.9 Hz, 2 H), 2.70 (d, J = 14.5 Hz, 2 H), 1.97 (d, J = 13.4 Hz, 1 H), 1.82-1.28 (m, 8 H), 1.25 (s, 6), 1.22 (s, 3 H), 1.17 (d, J = 14.5 Hz, 2 H).

General Procedure for the Preparation of Alkane Monoester Lactams 48a-d. The reductions of **47a-d** were performed following the same procedure as that described for the preparation of **46a-d** and **47a-d**. Yields of **48a-d** from **47a-d** were in the 80-93 % range.

2-Hydroxyethyl Ester Lactam 48a; oily liquid: IR 3403, 2959, 2931, 1724, 1653, 1189, 1082 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 3.89-3.65 (m, 4

H), 3.16 (d, J = 11.6 Hz,1 H), 3.06 (d, J = 11.6 Hz, 1 H), 2.63 (d, J = 14.0 Hz, 2 H), 2.55 (d, J = 13.9 Hz, 1 H), 1.73 (d, J = 12.7 Hz, 1 H), 1.30-1.02 (m, 3 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 1.00 (s, 3 H).

3-Hydroxypropyl Ester Lactam 48b; white solid: mp 123-125°C; IR 3321, 2958, 2931, 1722, 1654, 1457, 1258, 1188 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.48 (s, 1 H), 4.30 (s, 1 H), 4,14 (m, 1 H), 4.10 (m, 1 H), 3.75-3.51 (m, 2 H), 3.22 (d, J = 11.6 Hz, 1 H), 3.01 (d, J = 11.6 Hz, 1 H), 2.61-2.50 (m, 2 H), 1.81-1.70 (m, 3 H), 1.27-1.01 (m, 6 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 0.99 (s, 3 H).

4-Hydroxybutyl Ester Lactam 48c; white solid: mp 155-157 °C, IR 3403, 3203, 2960, 2929, 1719, 1652, 1242, 1190, 1083 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.37 (s, 1 H), 4.24 (m, 1 H), 3.92 (m, 1 H), 3.77 (m, 1 H), 3.58 (m, 1 H), 3.21 (d, J = 11.6 Hz, 1 H), 3.01 (d, J = 11.6 Hz, 1 H), 2.62 (d, J = 13.9 Hz, 1 H), 2.53 (d, J = 13.9 Hz, 1 H), 1.78-1.55 (m, 3 H), 1.27-1.01 (m, 3 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 0.99 (s, 3 H).

5-Hydroxypentyl Ester Lactam 6, n=5; white solid: mp 103-105 °C; IR 3312, 2952, 2931, 1723, 1663, 1458, 1188, 1088 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.32 (s, 1 H), 4.15-3.91 (m, 2 H), 3.71-3.60 (m, 2 H), 3.20 (d, J = 11.6 Hz, 1 H), 3.01 (d, J = 11.6 Hz, 1 H), 2.61 (d, J = 14.0 Hz, 1 H), 2.53 (d, J = 13.9 Hz, 1 H), 1.74-1.40 (m, 7 H), 1.17 (s, 3 H), 1.14 (s, 3 H), 0.98 (s, 3 H).

General Procedure for the Preparations of Alkane Diester Imide Lactams 49a-d. A solution of imide acid chloride **9** (0.50 g, 1.1 equiv), **48a-d** (1 equiv), DMAP (0.5 equiv) and excess Et_3N in dry CH_2Cl_2 was heated at reflux overnight under N_2 atmosphere. The solution was washed with 1 N HCl, brine, and dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography to give pure **49a-d**.

1,2-Ethane Diester Lactam Imide 49a; white solid (64% yield): mp 248-250 °C; IR 3303, 3252, 2965, 2932, 2872, 1728, 1697, 1652, 1464, 1197, 1175 cm^{-1}; ^1H

NMR (250 MHz, $CDCl_3$) δ 10.87 (s, 1 H), 6.91 (s, 1 H), 4.30-4.04 (m, 4 H), 3.19 (d, J = 11.7 Hz, 1 H), 2.98 (d, J = 11.7 Hz, 1 H), 2.77-2.49 (m, 4 H), 1.93 (d, J = 13.3 Hz, 1 H), 1.69 (d, J = 13.6 Hz, 1 H), 1.36-1.01 (m, 18 H), 0.96 (s, 3 H); HRMS m/z for $C_{26}H_{38}N_2O_7$ $[M]^+$ calcd 490.2679, obsd 490.2678.

1,3-Propane Diester Lactam Imide 49b; white solid (83% yield): mp 222-224 °C; IR 3292, 3244, 2965, 2930, 1726, 1693, 1650, 1453, 1176 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 11.47 (s, 1 H), 7.22 (s, 1 H), 4.27-4.15 (m, 2 H), 3.98-3.84 (m, 2 H), 3.22 (d, J = 11.6 Hz, 1 H), 2.97 (d, J = 11.6 Hz, 1 H), 2.77-2.50 (m, 6 H), 2.00-1.90 (m, 3 H), 1.67 (d, 1 H, J = 12.7 Hz), 1.38-0.84 (m, 24 H); HRMS m/z for $C_{27}H_{40}N_2O_7$ $[M]^+$ calcd 504.2835, obsd 504.2833.

1,4-Butane Diester Lactam Imide 49c; white solid (91 % yield): mp 178-180 °C; IR 3218, 2965, 2933, 1728, 1697, 1665, 1464, 1183 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.42 (s, 1 H), 5.75 (s, 1 H), 4.07-3.98 (m, 4 H), 3.20 (d, J = 11.6 Hz, 1 H), 3.00 (d, J = 11.6 Hz, 1 H), 2.73-2.50 (m, 4 H), 1.96 (d, J = 13.3 Hz, 1 H), 1.76-1.55 (m, 5 H), 1.36-0.96 (m, 24 H); HRMS m/z for $C_{28}H_{42}N_2O_7$ $[M]^+$ calcd 518.2992, obsd 518.2990.

1,5-Pentane Diester Lactam Imide 49d; white solid (86% yield): mp 175-177 °C; IR 3247, 2962, 2931, 1727, 1697, 1654, 1462, 1184 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 6.06 (s, 1 H), 4.04-3.93 (m, 4 H), 3.20 (d, J = 11.6 Hz, 1 H), 2.97 (d, J = 11.6 Hz, 1 H), 2.75-2.49 (m, 4 H), 1.95 (d, J = 13.3 Hz, 1 H), 1.76-0.0.96 (m, 30 H); HRMS m/z for $C_{29}H_{44}N_2O_7$ $[M]^+$ calcd 532.3148, obsd 532.3149.

Methylester Lactam 50. Methylester imide **11g** (1.50 g, 5.88 mmol) was reduced with excess $NaBH_4$ (1.50 g) in anhydrous EtOH at 0 °C to give the corresponding hydroxylactam in quantitative yield as a colorless solid by following procedure described for **16a**: mp >125 °C (decomp); IR, 3435, 3254, 2963, 2928, 1701, 1668, 1261, 1116, 1078 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.42 (s, 1 H, NH), 4.66 (d, 1 H, OH, J = 13.0 Hz), 4.55 (d, 1 H, J = 13.0 Hz), 3.68 (s, 3 H),

2.68-2.18 (m, 2 H), 1.75 (d, 1 H, J = 13.4 Hz), 1.29 (d, 1 H, J = 13.5 Hz), 1.15-0.96 (m, 11 H); HRMS m/z for $C_{13}H_{21}NO_4$ calcd 255.1470, found 255.1470. A solution of methyl ester hydroxylactam (1.50 g, 5.84 mmol) in dry CH_2Cl_2 (15 mL) containing CF_3CO_2H (2 mL) and Et_3SiH (2 mL) was stirred for 2 h at room temperature. The reaction mixture was carefully washed with satd $NaHCO_3$, satd brine, water, then dried (Na_2SO_4). The removal of solvent gave 1.40 g (99 %) of **50** as a colorless solid: mp 141-143 °C; IR, 3198, 2958, 2924, 1722, 1671, 1448, 1202, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.30 (s, 1 H, NH), 3.61 (s, 3 H), 3.16 (d, 1 H, J = 11.5 Hz), 3.02 (d, 1 H, J = 11.5 Hz), 2.61 (d, 1 H, J = 13.9 Hz), 2.51 (d, 1 H, J = 14.0 Hz), 1.72 (d, 1 H, J = 12.9 Hz), 1.27-0.98 (m, 12 H); HRMS m/z for $C_{13}H_{21}NO_3$ $[M]^+$ calcd 239.1521, found 239.1521.

Anthraquinone 2,6-Diamide Diimide 51 (trimethyl derivative). The suspension of 2,6-diaminoanthraquinone (0.10 g, 0.44 mmol) and imide acid chloride (0.24 g, 0.94 mmol) in triglyme (5 mL) was heated at reflux for 2 h under argon atmosphere. After cooling to room temperature, the reaction was poured into hexanes (50 mL), then filtered. The filter cake was washed with hot 1 N HCl (10 mL) and CH_2Cl_2 (50 mL) to give a tan solid **51** (0.24 g, 84%): mp > 300 °C; ^1H NMR (DMSO-d_6, 250 MHz) δ 10.37 (s, 2 H, NH), 9.79 (s, 2 H, NH), 8.36 (s, 2 H), 8.15 (s, 4 H), 2.72 (d, 4 H, J = 14.4 Hz), 1.91 (d, 2 H, J = 12.9 Hz), 1.42 (d, 2 H, J = 12.9 Hz), 1.29 (d, 4 H, J = 14.4 Hz), 1.21 (s, 6 H), 1.13 (s, 12 H).

9,10-Dihydro 2,6-Anthracenediamide Diimide 52 (trimethyl derivative). 2,6-Diamino-9,10-dihydroanthracene was prepared as follows: The suspension of 2,6-diaminoanthraquinone (1.00 g, 4.20 mmol) and zinc dust (2.50 g) in 5% NaOH aqueous solution (50 mL) was refluxed for 3 h. The hot solution was filtered, and filter cake contained zinc derivatives was dissolved in hot acetone (500 mL), and then filtered. The solution was dried with anhydrous Na_2SO_4 and concentrated to give a yellow solid, which was a

mixture of 2,6-diamino-9,10-dihydroanthracene **56** (52%) and 3,6-diaminoanthracene **55** (48%). A yellow solid was stirred in hot $CHCl_3$ (500 ml) for 5 min and the solution was cooled to room temperature, and then filtered ($CHCl_3$ solution; >80% of 2,6-diamino 9,10-dihydroanthracene, filter cake; 80 % of 2,6-diaminoanthracene). The solution was concentrated and the crude product was purified with flash chromatography (40 % EtOAc in CH_2Cl_2) to give pure 2,6-Diamino 9, 10-dihydroanthracene **56**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.04 (d, 2 H, J = 7.9 Hz), 6.63 (d, 2 H, J = 2.3 Hz), 6.53 (dd, 2 H, J= 7.9, 2.3 Hz), 3.75 (s, 4 H), 3.55 (s, 4 H, NH_2). A solution of 2,6-diamino-9,10-dihydroanthracene (0.21 g, 1.0 mmol) and imide acid chloride **9** (0.52 g, 2 mmol)in dry CH_2Cl_2 (30 mL) containing Et_3N (1 mL)was stirred for 10 h at room temperature under N_2 atmosphere. The solution was concentrated and the resulting solid was washed with 1 N HCl and CH_2Cl_2, then dried in vacuo to a off-white solid **52** (0.51 g, 78%). mp > 300 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 10.31 (s, 2 H, NH), 9.10 (s, 2 H, NH), 7.42 (s, 2 H), 7.20 (s, 4 H), 3.81 (s, 4 H), 2.66 (d, 4 H, J = 14.2 Hz), 1.87 (d, 2 H, J = 12.9 Hz), 1.39 (d, 2 H, J = 12.9 Hz), 1.21 (d, 4 H, J = 14.2 Hz), 1.16 (s, 6 H), 1.11 (s, 12 H).

Acridine 3,6-Diamide Diimide 53 (trimethyl derivative). A finely ground mixture of 3,6-diaminoacridine (0.10 g, 0.48 mmol) and imide acid chloride **9** (0.25 g, 0.97 mmol) was heated at 225 °C for 3 h under Ar atmosphere. The solid was dissolved in $CHCl_3$ (250 ml) and subjected to flash chromatography (12% MeOH in $CHCl_3$) to give a yellow solid **53** (0.23 g, 73%). mp > 300 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 10.45 (s, 2 H, NH), 9.55 (s, 2 H, NH), 8.84 (s, 1 H), 8.31 (s, 2 H), 8.00 (d, 2 H, J = 8.7 Hz), 7.65 (d, 2 H, J = 8.7 Hz), 2.75 (d, 4 H, J = 13.9 Hz), 1.92 (d, 2 H, J = 12.9 Hz), 1.43 (d, 2 H, J = 12.9 Hz), 1.29 (d, 4 H, J = 13.9 Hz), 1.25 (s, 6 H), 1.14 (s, 12 H).

2,6-Anthracenediamide Diimide 57. A solution of 2,6-

diaminoanthracene **55** (44 mg, 0.21 mmol), imide acid chloride **22** (0.15 g, 0.44 mmol) and a catalytic amount of DMAP in dry pyridine (20 ml) was heated at reflux for 7 h under N_2 atmosphere. The solution was concentrated in vacuo, and the residue was taken up in CH_2Cl_2 (30 ml) and the organic layer was washed with 1 N HCl solution, brine, then dried with anhydrous Na_2SO_4. The crude product was purified by flash chromatography (20% EtOAc in $CHCl_3$) to yield a pure **57** (0.12 g, 69 %) as a yellow solid: mp > 300 °C; IR 3450, 3189, 2955, 2934, 2871, 1725, 1689, 1553, 1507, 1448, 1385, 1181, 869 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.29 (d, 2 H, J = 1.9 Hz), 8.25 (s, 2 H), 7.88 (d, 2 H, J = 9.1 Hz), 7.60 (s, 2 H, NH), 7.32 (s, 2 H, NH), 7.30 (dd, 2 H, J = 9.1, 1.9 Hz), 2.64 (d, 2 H, J = 14.3 Hz), 2.23 (d, 2 H, J = 13.0 Hz), 1.99 (m, 4 H), 1.56 - 1.24 (m, 44 H); HRMS m/z for $C_{50}H_{66}N_4O_6$ $[M]^+$ calcd 818.4982, found 818.4979.

9,10-Dihydro 2,6-Anthracenediamide Diimide 58. The preparation of **58** is the same as that described for **57** except that 9,10-dihydro 2,6-diaminoanthracene **56** (33 mg, 0.16 mmol) was used instead of 2,6-diaminoanthracene **55**. The crude product was purified by flash chromatography (33% EtOAc/CH_2Cl_2) to yield pure **58** (0.11 g, 78%) as a white solid: mp > 300 °C; IR 3378, 2958, 2933, 2871, 1700, 1521, 1496, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.48 (d, 2 H, J = 1.8 Hz), 7.47 (s, 2 H, NH), 7.17 (s, 4 H), 7.11 (s, 2 H), 3.85 (s, 4 H), 2.58 (d, 2 H, J = 15.2 Hz), 2.22 (d, 2 H, J = 13.0 Hz), 1.99 (m, 4 H), 1.56 - 1.24 (m, 44 H); HRMS m/z for $C_{50}H_{68}N_4O_6$ $[M]^+$ calcd 820.5138, found 820.5135.

2,6-Naphthalenediamide Diimide 61. 2,6-Diaminonaphthalene **60** was prepared from 2,6-dihydroxynaphthalene **59**. The preparation of **61** is the same as that described for **57** except that 2,6-diaminonaphthalene **60** (0.22 g, 1.39 mmol) was used instead of 2,6-diaminoanthracene **55**. The crude product was purified by flash chromatography (20% EtOAc/CH_2Cl_2) to yield pure **61**

(0.92 g, 86%) as white solid: mp > 300 °C; IR 3454, 3201, 3073, 2957, 2934, 2872, 1717, 1689, 1539, 1461, 1180, 875 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.06 (d, 2 H, J = 1.7 Hz), 7.70 (d, 2 H, J = 8.8 Hz), 7.49 (s, 2 H, NH), 7.31 (dd, 2 H, J = 8.8, 1.7 Hz), 7.26 (s, 2 H, NH) 2.61 (d, 2 H, J = 14.1 Hz), 2.24 (d, 2 H, J = 13.0 Hz), 1.99 (m, 4 H), 1.56 - 1.24 (m, 44 H); HRMS m/z for $C_{46}H_{64}N_4O_6$ $[M]^+$ calcd 768.4825, found 768.4825.

2,6-Naphthalenediamide Tricyclic Dilactams 62 and 63. A solution of **61** (0.70 g, 0.91 mmol) in EtOH (60 mL) and THF (60 mL) was stirred with $NaBH_4$ (1.40 g) at room temperature for 24 h. The solution was poured into water (200 mL) and the aqueous solution was extracted with $CHCl_3$ (2 x 200 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was taken up in CH_2Cl_2 (50 mL). A catalytic amount of p-TsOH was added and the mixture was stirred for 3 h at room temperature. The solution was washed with saturated $NaHCO_3$ and brine, then dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the resulting mixture of two diastereomers was separated by flash chromatography (16% EtOAc/CH_2Cl_2) to yield meso **63** (0.30 g, 45 %) and racemic tricyclic dilactam **62** (0.26 g, 39%) as white solids. Racemic tricyclic dilactam **62** (more polar): mp > 300 °C; IR 3345, 2957, 2929, 2872, 1693, 1646, 1457, 1383, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.89 (d, 2 H, J = 8.9 Hz), 7.70 (d, 2 H, J = 1.8 Hz), 7.31 (dd, 2 H, J = 8.9, 1.8 Hz), 5.88 (d, 2 H, NH, J = 3.1 Hz), 4.68 (d, 2 H, J = 3.1 Hz), 2.22 (d, 2 H, J = 14.1 Hz), 2.09-0.80 (m, 50 H); HRMS m/z for $C_{46}H_{64}N_4O_4$ $[M]^+$ calcd 736.4927, found 736.4927. Meso tricyclic dilactam **63** (less polar): mp 298-300 °C; IR 3220, 2958, 2931, 2871, 1676, 1440, 1376, 1259, 1084, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.89 (d, 2 H, J = 8.9 Hz), 7.70 (d, 2 H, J = 1.8 Hz), 7.31 (dd, 2 H, J = 8.9, 1.8 Hz), 5.88 (d, 2 H, NH, J = 3.1 Hz), 4.70 (d, 2 H, J = 3.1 Hz), 2.22 (d, 2 H, J = 14.1 Hz), 2.09-

0.80 (m, 50 H); HRMS m/z for $C_{46}H_{64}N_4O_4$ $[M]^+$ calcd 736.4927, found 736.4927.

2,6-Naphthalenediamide Dilactams 64a-b (racemic). Racemic tricyclic dilactam **62** (0.20 g, 0.27 mmol) was dissolved in CF_3CO_2H (3 mL) and Et_3SiH (0.2 mL). The mixture was stirred overnight at room temperature. The mixture was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (15 mL), the organic phase was washed with saturated $NaHCO_3$, brine, then dried with anhydrous Na_2SO_4. The crude product was purified by flash chromatography (80% EtOAc in CH_2Cl_2) to yield pure **64a-b** (racemic, 0.13 g, 64 %) as a white solid. mp 174-176 °C; IR 3432, 3197, 2957, 2917, 2871, 1684, 1662, 1585, 1525, 1457, 1393, 1269, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.00 (d, 2 H, J = 1.7 Hz), 7.71 (d, 2 H, J = 8.7 Hz), 7.60 (s, 2 H, NH), 7.46 (dd, 2 H, J = 8.7, 1.7 Hz), 5.34 (s, 2 H, NH), 3.17 (d, 2 H, J = 11.9 Hz), 2.99 (d, 2 H, J = 11.9 Hz), 2.89 (d, 2 H, J = 13.6 Hz), 2.24 (d, 2 H, J = 15.1 Hz), 2.00 (m, 2 H), 1.85 (d, 2 H, J = 12.2 Hz), 1.61-0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ $[M]^+$ calcd 740.5240, found 740.5240. The racemic mixture was resolved on a Pirkle column (L-3,5-dinitrophenylglycine, Regis Chem. Co.) with using 5% isopropanol in chloroform to yield a less polar enantiomer **64a** ($[a]_D$ = -77.6 °, c = 1.13 in CH_2Cl_2) and a more polar enantiomer **64b** ($[a]_D$ = +77.4 °, c = 1.31 in CH_2Cl_2).

2,6-Naphthalenediamide Dilactam 65 (meso). The preparation of **65** is the same as that described for **64a** and **64b** except that the less polar diastereomer **63** (0.20 g, 0.27 mmol) was used instead of the more polar diastereomer **62**. A white solid (0.12 g, 60%): mp > 300 °C; IR 3438, 3174, 2956, 2845, 1675, 1635, 1605, 1539, 1456, 1283 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.00 (d, 2 H, J = 1.7 Hz), 7.71 (d, 2 H, J = 8.7 Hz), 7.60 (s, 2 H, NH), 7.46 (dd, 2 H, J = 8.7, 1.7 Hz), 5.34 (s, 2 H, NH), 3.17 (d, 2 H, J = 11.9 Hz), 2.99 (d, 2 H, J = 11.9 Hz), 2.89 (d, 2 H, J = 13.6 Hz), 2.24 (d, 2 H, J = 15.1 Hz), 2.00 (m, 2 H), 1.85 (d, 2 H, J =

12.2 Hz), 1.61-0.88 (m, 46 H); HRMS m/z for $C_{46}H_{68}N_4O_4$ $[M]^+$ calcd 740.5240, found 740.5240.

n-Butyl Barbituric Acid 71. A solution of diethyl butylmalonate (1.00 g, 4.62 mmol), urea (0.28 g, 4.63 mmol), and sodium ethoxide (9.25 mmol) in absolute ethanol (40 mL) was refluxed for 6 h under N_2 atmosphere. The mixture was concentrated in vacuo and the residue was triturated with 1 N HCl (100 mL) and filtered to yield a white solid. The mother liquor was saturated with NaCl and extracted with $CHCl_3$ (2 x 100 mL). The organic phase was dried with anhydrous Na_2SO_4. and concentrated in vacuo. The combined crude product was recrystallized from hot $CHCl_3$ to yield a white solid (0.53 g, 63%): mp 211-212 °C; IR 3227, 2960, 2926, 2863, 1684, 1419, 1337, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.05 (s, 2 H, NH), 3.99 (d, 2 H, J = 9.5 Hz), 1.93-1.60 (m, 6 H), 1.00 (d, 6 H, J = 6.2 Hz), 0.95 (d, 6 H, J = 6.2 Hz); ; HRMS m/z for $C_8H_{12}N_2O_3$ $[M]^+$ calcd 350.1994, found 350.1994.

2-Naphthyl dilactam 73. A solution of hydroxylactam **16a** (0.2 g, 5.75 mmol) in dry CH_2Cl_2 (10 mL) containing a catalytic amount of p-TsOH was stirred at room temperature for 2 h. The reaction mixture was washed with satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The colorless solid was dried under vacuum to give pure **73** in quantitative yield: mp 198-200 °C; IR 3280, 3058, 2965, 2927, 2868, 1683, 1634, 1598, 1507, 1470, 1398, 1271, 1199, 1105, 1060 cm^{-1}; ^1H NMR ($CDCl_3$), δ 7.89 (d, 1 H, J = 8.7 Hz), 7.84 (m, 2 H), 7.68 (d, 1 H, J = 1.8 Hz), 7.51 (m, 2 H), 7.27 (dd,1 H, J = 8.7, 1.9 Hz), 5.97 (d, 1 H, NH, J = 3.5 Hz), 4.73 (d, 1 H, J = 3.5 Hz), 2.21 (d, 1 H, J = 12.8 Hz), 2.14 (d, 1 H, J = 14.7 Hz), 2.02 (d, 1 H, J = 12.7 Hz), 1.52 (d, 1 H, J =12.7 Hz), 1.43 (d, 1 H, J = 12.7 Hz), 1.43 (s, 3 H), 1.39 (d, 1 H, J = 14.6 Hz) , 1.28 (s 3 H), 1.26 (s, 3 H); HRMS m/z for $C_{22}H_{24}N_2O_2$ $[M]^+$ calcd 348.1838, found 348.1837.

Lactam acid 76 (racemic). A solution of **50** (1.20 g, 5.02 mmol) in 3 N

NaOH (20 mL) and MeOH (40 mL) was heated at reflux with stirring for 24 h. Methanol was removed at reduced pressure, the remaining aqueous solution was carefully acidified up to pH 1 in ice-water bath. After filtration, the white solid was dried on a vacuum affording 1.04 g (92%) of **76**: mp >270 °C; IR 3400-2500, 3253, 3173, 2960, 2929, 1699, 1626, 1462, 1283, 1181, 989 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.36 (s, br, 1 H, CO_2H), 8.63 (s, br, 1 H, NH), 3.29 (d, 1 H, J = 11.9 Hz), 3.02 (d, 1 H, J = 12.0 Hz), 2.65 (d, 1 H, J = 13.6 Hz), 2.43 (d, 1 H, J = 14.1 Hz), 1.70 (d, 1 H, J = 12.9 Hz), 1.25-0.98 (m, 12 H, including 1.20 [s, 3 H)], 1.15 [s, 3 H], and 0.98 [s, 3 H]); HRMS m/z for $C_{12}H_{19}NO_3$ $[M]^+$ calcd 225.1365, found 225.1366.

2-Naphthyl Ester Lactam 74. A solution of lactam acid **76** (0.20 g, 0.89 mmol) in thionyl chloride ($SOCl_2$, 2 mL) was heated at 60 °C for 3 h. Excess $SOCl_2$ was removed at reduced pressure. The residue was dissolved in dry THF (5 mL) and was added dropwise to a solution of 2-naphthol (0.25 g, 1.77 mmol, 2 equiv.) and NaH (47 mg, 1.96 mmol) in dry THF (5 mL) under nitrogen atmosphere. After stirring at room temperature for 1 h, CF_3CO_2H (1 mL) and water (1 mL) were added, and stirring was continued for 2 days at room temperature. The reaction mixture was carefully washed with satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (33%EtOAc in $CHCl_3$) affording **27a** (0.22 g, 71%) as a colorless solid: mp 82-84 °C; IR 3330, 2959, 2958, 1745, 1665, 1460, 1159, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 3 H), 7.65 (d, 1 H, J = 2.0 Hz), 7.45 (m, 2 H), 7.27 (dd, 1 H, J = 8.1, 2.0 Hz), 5.28 (s, 1 H, NH), 3.20 (d, 1 H, J = 11.5 Hz), 3.05 (d, 1 H, J = 11.6 Hz), 2.88 (d, 1 H, J = 14.1 Hz), 2.61 (d, 1 H, J = 14.0 Hz), 1.82 (d, 1 H, J = 12.9 Hz), 1.45 (s, 3 H), 1.37-1.15 (m, 6 H, including 1.27 [s, 3 H]) and 1.02 [s, 3 H); HRMS m/z for $C_{22}H_{25}NO_3$ $[M]^+$ calcd 351.1834, found 351.1834.

(S)-(α)-Methyl-2-naphthalenemethyl Ester Imide 78. A solution of imide acid chloride **9** (1.00 g, 3.89 mmol), (S)-(α)-methyl-2-naphthalenemethanol (0.74 g, 4.28 mmol), and N, N-dimethylaminopyridine (DMAP, 0.2 equiv) in dry CH_2Cl_2 (25 mL) containing pyridine (1 mL) was heated to reflux for 12 h under nitrogen atmosphere. The solution was diluted with CH_2Cl_2 (30 mL) and sequentially washed 1 N HCl, satd aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in a vacuo. The crude product was purified by chromatography to give a colorless solid **78** (1.05 g, 69%). mp 160-162 °C; IR 3209, 3095, 2970, 2932, 1728, 1696, 1462, 1184, 1175, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.78 (m, 5 H), 7.49-7.44 (m, 3 H), 5.93 (q, 1 H, J = 6.6 Hz), 2.77 (d, 1 H, J = 13.8 Hz), 2.71 (d, 1 H, J = 15.0 Hz), 1.60 (d, 3 H, J = 6.6 Hz), 1.37 (d, 1 H, J = 13.3 Hz), 1.27-1.10 (m, 11 H).

(S)-(α)-Methyl-2-naphthalenemethyl Ester Hydroxylactam 79, 80. A solution of **78** (1.05 g, 2.67 mmol) in anhydrous EtOH (100 mL) containing $NaBH_4$ (2.00 g) was stirred for 12 h at 0 °C. The solution was poured into ice-water (300 mL) and extracted with $CHCl_3$ (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated in a vacuo. The crude product was purified by chromatography (2:1:2 hexanes/EtOAc/CH_2Cl_2)to give **79** (0.78 g, 74 %) and **80** (0.19 g, 18%) as a colorless solid. **79** (more polar): mp 147-150 °C (decomp); IR 3422, 3265, 2964, 2931, 1695, 1669, 1451, 1256, 1177, 1063, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.75 (m, 4 H), 7.49-7.44 (m, 3 H), 5.92 (q, 1 H, J = 6.6 Hz), 5.46 (s, 1 H, NH), 4,77 (d, 1 H, OH, J = 13.0 Hz), 4.59 (d, 1 H, J = 13.0 Hz), 2.74 (d, 1 H, J = 14.0 Hz), 2.61 (d, 1 H, J = 15.1 Hz), 1.79 (d, 1 H, J = 13.4 Hz), 1.66 (d, 3 H, J = 6.6 Hz), 1.31 (d, 1 H, J = 13.4 Hz), 1.20 (s, 3 H), 1.19 (d, 1 H, J = 13.9 Hz), 1.13 (s, 3 H), 1.06 (s, 3 H), 0.94 (d, 1 H, 15.1 Hz). **80** (less polar): mp 140-142 °C (decomp); 3368, 3253, 3058, 2963, 2906, 1693, 1602, 1471,

1381, 1180, 1065, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96-7.80 (m, 4 H), 7.54 (dd, 1 H, J = 8.6, 1.7 Hz), 7.48-7.43 (m, 2 H), 5.89 (q, 1 H, J = 6.6 Hz), 4.77 (s, 1 H, NH), 4,43 (d, 1 H, OH, J = 13.0 Hz), 4.36 (d, 1 H, J = 13.0 Hz), 2.73-2.62 (m, 2 H), 1.69 (d, 1 H, J = 13.4 Hz), 1.64 (d, 3 H, J = 6.6 Hz), 1.26 (d, 1 H, J = 13.3 Hz), 1.26 (s, 3 H), 1.19 (d, 1 H, J = 14.0 Hz), 1.14 (s, 3 H), 1.00 (s, 3 H), 0.96 (d, 1 H, 15.1 Hz).

Lactam acid 76 (optically active). A solution of hydroxylactam **79** and **80** (0.73 g, 1.86 mmol), Et_3SiH (1 mL), and CF_3CO_2H (1.5 mL) in dry CH_2Cl_2 (10 mL) was stirred overnight at room temperature. The solution was concentrated and the resulting oily liquid was taken in CH_2Cl_2 (10 mL) and 2 N NaOH (10 ml). The aqueous layer was carefully acidified with concentrated HCl in ice water bath and filtered to give optically pure lactam acid **76** as a white solid. Additionally, the filtrate was saturated with sodium chloride and extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over Na_2SO_4, and concentrated to give **76**; combined yield (0.38 g, 92%): mp > 280 °C; IR 3400-2500, 3253, 3173, 2960, 2929, 1699, 1626, 1462, 1283, 1181, 989 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.5 (s, br, 1 H, CO_2H), 8.62 (s, 1 H, NH), 3.24 (d, 1 H, J = 12.2 Hz), 3.03 (d, 1 H, J = 12.2 Hz), 2.67 (d, 1 H, J = 13.7 Hz), 2.43 (d, 1 H, J = 14.0 Hz), 1.70 (d, 1 H, J = 12.9 Hz), 1.20-0.99 (m, 12 H); HRMS m/z for $C_{12}H_{19}NO_3$ $[M]^+$ calcd 225.1365, found 225.1366. (R)-Lactam acid **76** (from **79**); $[\alpha]_D$ = -160 ° (c = 4.0 in $CHCl_3$). (S)-Lactam acid **76** (from **80**); $[\alpha]_D$ = +165 ° (c = 4.1 in $CHCl_3$).

Lactam benzoxazole 82. a) from lactam acid **76**: A solution of lactam acid **76** (racemic, or optically active, 0.50 g, 2.22 mmol) and $SOCl_2$ (0.47 mL, 6.60 mmol) in dry CH_2Cl_2 (20 mL) was heated at reflux for 2 h under nitrogen atmosphere. The solution was carefully concentrated and dried in vacuo. The resulting residue was dissolved in dry CH_2Cl_2 (15 mL) , and o-aminophenol (0.48 g, 4.44 mmol) and dry pyridine (1 ml) were added. The reaction was stirred for 4 h at room temperature under nitrogen atmosphere.

The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with 1 N HCl (3 x 50 mL), brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified with chromatography (EtOAc) to give o-hydroxyphenylamide lactam **96** as a white solid (0.57 g, 81%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, br, 1 H, OH), 7.35 (s, 1 H, NH), 7.28 (dd, 1 H, J = 8.0, 1.4 Hz), 7.10 (td, 1 H, J = 8.3, 1.6 Hz), 6.99 (dd, 1 H, J = 8.0, 1.3 Hz), 6.87 (td, 1 H, J = 7.8, 1.5 Hz), 5.52 (s, 1 H, NH), 3.20 (d, 1 H, J = 12.0 Hz), 3.02 (d, 1 H, J = 12.0 Hz), 2.81 (d, 1 H, J = 14.0 Hz), 2.27 (d, 1 H, J = 15.1 Hz), 1.80 (d, 1 H, J = 12.8 Hz), 1.47 (d, 1 H, J = 15.1 Hz), 1.35-1.02 (m, 11 H).

b) from imide acid chloride **9**: A solution of imide acid chloride **9** (1.75 g, 6.8 mmol), 2-aminophenol (0.88 g, 8.1 mmol), and pyridine (0.75 mL) in dry CH_2Cl_2 (60 mL) was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give (o-hydroxyphenyl)amide imide **94** (2.2 g, 98%) as white solid. mp 254-255 °C; IR 3336, 3184, 3099, 2968, 2929, 1722, 1684, 1496, 1209, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.82 (s, br, 1 H), 7.72 (s, br, 1 H), 7.23 (m, 1 H), 7.12 (dd, 1 H, J = 7.2, 1.5 Hz), 7.09 (dd, 1 H, J = 7.2, 1.5 Hz), 6.91 (m. 1 H), 2.77 (d, 2 H, J = 13.6 Hz), 1.54 (d, 2 H, J = 13.5 Hz), 1.49 (d, 2 H, J = 13.5 Hz), 1.46 (s, 3H), 1.41 (s, 6 H).

To a solution of (o-hydroxyphenyl)amide imide **94** (2.2 g, 6.7 mmol) in MeOH (450 mL) at 0 °C was added excess $NaBH_4$ (10 g), the mixture was stirred at 0 °C for 14 h and poured into water (1000 mL). The aqueous solution was extracted with $CHCl_3$ (5 x 100 mL). The aqueous layer was acidified with concentrated HCl (pH 4-5), saturated with NaCl, and extracted with chloroform (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give (o-hydroxyphenyl)amide

imide **95** (2.1 g, 95%) as white solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.20 (s, 1 H), 7.56 (s, 1 H), 7.25 (dd, 1 H, J = 8.1, 1.5 Hz), 7.12 (m, 1 H), 6.98 (dd, 1 H, J = 8.1, 1.4 Hz), 6.86 (m. 1 H), 5.75 (s, br, 1 H), 5.24 (d, 1 H, J = 13.2 Hz), 4.58 (d, 1 H, J = 13.1 Hz), 2.89 (d, 1 H, J = 15.1 Hz), 2.33 (d, 1 H, J = 13.4 Hz), 1.53-1.36 (m, 3 H), 1.36 (s, 3 H), 1.23 (s, 3H), 1.08 (s, 3 H), 0.96 (d, 1 H, J = 15.0 Hz).

A solution of (o-hydroxyphenyl)amide imide **95** (2.1 g, 6.3 mmol) in CF_3CO_2H (20 mL)/Et_3SiH(8 mL) was stirred for 6 h at room temperature. The reaction was diluted with CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ (100 mL). Solid $NaHCO_3$ was added to the solution until CO_2 gas was not evolved. The organic layer was separated and the aqueous layer was extracted with CH2Cl2. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give (o-hydroxyphenyl)amide imide **96** (2.1 g, 95%) as white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, br, 1 H, OH), 7.35 (s, 1 H, NH), 7.28 (dd, 1 H, J = 8.0, 1.4 Hz), 7.10 (td, 1 H, J = 8.3, 1.6 Hz), 6.99 (dd, 1 H, J = 8.0, 1.3 Hz), 6.87 (td, 1 H, J = 7.8, 1.5 Hz), 5.52 (s, 1 H, NH), 3.20 (d, 1 H, J = 12.0 Hz), 3.02 (d, 1 H, J = 12.0 Hz), 2.81 (d, 1 H, J = 14.0 Hz), 2.27 (d, 1 H, J = 15.1 Hz), 1.80 (d, 1 H, J = 12.8 Hz), 1.47 (d, 1 H, J = 15.1 Hz), 1.35-1.02 (m, 11 H).

o-Hydroxyphenylamide lactam **96** (0.50 g, 1.58 mmol) was suspended in dry toluene (20 ml). To this solution, $SOCl_2$ (1 mL) and dry pyridine (1.5 mL) were added and the reaction was heated up to 60 °C for 1 h. The solution was concentrated and the resulting oily liquid was taken up in CH_2Cl_2 (30 mL). The organic layer was washed with water, saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The crude product was purified by chromatography (EtOAc) to give **82** (racemic) as a white solid (0.45 g, 96%). mp 225-227 °C; IR IR 3363, 3090, 2960, 2907, 1671, 1559, 1455, 1247, 1153, 1068, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (m, 1 H), 7.50 (m, 1 H), 7.26 (t, 2 H, J = 4.6 Hz), 4.62 (s, 1 H, NH), 3.25 (d, 1 H, J = 11.5 Hz), 3.02-2.90 (m, 3 H), 1.75 (d, 1 H, J = 12.8 Hz),

1.45-1.33 (m, 6 H), 1.22 (s, 3 H), 1.07 (s, 3 H); HRMS m/z $C_{18}H_{22}N_2O_2$ $[M]^+$ calcd 298.1681, found 298.1681.

(S)-(-)-(α)-Methylbenzylamide Imide 84. A solution of imide acid chloride **9** (1.00 g, 3.88 mmol), (S)-(-)-(α)-methylbenzylamide **83** (0.57 g, 4.66 mmol, 1.2 equiv.) and dry pyridine (1 mL) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h under a nitrogen atmosphere. The reaction mixture was sequentially washed with 1 N HCl, satd $NaHCO_3$, satd brine, water, then dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (50% EtOAc in $CHCl_3$) affording pure **84** (1.20 g, 87%) as a colorless solid: mp 113-115 °C; IR 3370, 3225, 3105, 2969, 2872, 1678, 1649, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.25 (m, 5 H), 7.12 (s, 1 H, NH), 5.62 (d, 1 H, NH, J = 7.0 Hz), 5.01 (m, 1 H), 2.64 (d, 1 H, J = 14.3 Hz), 2.45 (d, 1 H, J = 12.5 Hz), 1.96 (d, 1 H, J = 13.3 Hz), 1.46 (d, 3 H, J = 7.0 Hz), 1.37-1.14 (m, 12 H); HRMS m/z for $C_{20}H_{26}N_2O_3$ $[M]^+$ calcd 342.1936, found 342.1936.

(S)-(-)-(α)-Methylbenzyl Dilactams 87 and 88. The reduction of **84** (1.20 g, 3.51 mmol) with excess $NaBH_4$ (1.50 g) at 0 °C in anhydrous EtOH (30 mL) for 6 h gave a diastereomeric mixture of hydroxylactams **85** and **86**. The work-up procedure is the same as that described for **16a**. Without separation of the diastereomeric mixture, a solution of **85** and **86** in dry CH_2Cl_2 (15 mL) containing a catalytic amount of anhydrous p-TsOH was stirred at room temperature for 3 h. The reaction mixture was washed satd $NaHCO_3$, satd brine, water, dried (Na_2SO_4), filtered, and concentrated. The two diastereomers **87** and **88** were separated by flash chromatography (17% EtOAc in CH_2Cl_2, then 60 % EtOAc in CH_2Cl_2) affording **87** (less polar, 0.63 g, 62%) and **88** (more polar, 0.39 g, 38%). The isolated total yield from **84** is 89%. **87** (less polar): $[a]_D$ = -260 ° (c = 1.0 in CH_2Cl_2 at 295 °K); mp 107-109 °C; IR 3376, 3291, 2928, 1690, 1657, 1471, 1450, 1381, 1267, 1207, 1156 cm^{-1}; ^1H NMR ($CDCl_3$,

300 MHz) δ 7.45-7.34 (m, 5 H), 5.99 (q, 1 H, J = 7.0 Hz), 4.42 (d, 1 H, J = 3.4 Hz), 4.17 (s, 1 H, NH), 1.94 (d, 1 H, J = 14.6 Hz), 1.75 (d, 1 H, J = 11.0 Hz), 1.72 (d, 1 H, J = 11.0 Hz), 1.48 (d, 3 H, J = 7.0 Hz), 1.32 -1.07 (m, 12 H, including 1.25 [s, 3 H], 1.24 [s, 3 H], and 1.07 [s, 3 H)]); HRMS m/z for $C_{20}H_{26}N_2O_2$ $[M]^+$ calcd 326.1994, found 326.1994. **88** (more polar): $[a]_D$ = +84 ° (c = 1.1 in CH_2Cl_2 at 295 °K); mp 187-188 °C; IR 3227, 2969, 2928, 1682, 1655, 1453, 1271, 1205, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.24 (m, 5 H), 5.68 (m, 1 H), 5.59 (s, 1 H, NH), 4.16 (d, 1 H, J = 3.6 Hz), 1.98 (d, 1 H, J = 14.7 Hz), 1.78 (d, 1 H, J = 12.5 Hz), 1.71 (d, 1 H, J = 14.0 Hz), 1.63 (d, 3 H, J = 7.1 Hz), 1.29-1.24 (m, 6 H), 1.17 (s, 3 H), 0.80 (s, 3 H); HRMS m/z for $C_{20}H_{26}N_2O_2$ $[M]^+$ calcd 326.1994, found 326.1994.

(S)-(-)-(α)-Methylbenzyl Propionyl Dilactam 91a. A solution of **87** (0.10 g, 0.31 mmol) and NaH (8.8 mg, 0.37 mmol, 1.2 equiv.) in dry THF (10 mL) was stirred for 10 min under a nitrogen atmosphere. Propionyl chloride (34 mg, 0.37 mmol, 1.2 equiv.) was syringed into the solution, and the solution was stirred for 3 h at room temperature. The reaction was quenched with 1 N HCl, and the solution was concentrated at reduced pressure. The resulting solid was taken up in $CHCl_3$ (20 mL), and the solution was washed with satd $NaHCO_3$, satd brine, water , and dried with anhydrous sodium sulfate. After concentration, the crude product was purified by flash chromatography (2:2:1 $CHCl_3$/hexanes/EtOAc) affording **91a** (97 mg, 83%) as a colorless solid: mp 217-219 °C; IR 2979, 2915, 2867, 1720, 1693, 1646, 1449, 1369, 1272, 1153, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.14 (m, 5 H), 6.23 (s, 1 H), 5.55 (q, 1 H, J = 7.2 Hz), 2.10-1.83 (m, 7 H, including two equatorial protons), 1.64 (d, 3 H, J = 7.2 Hz), 1.62 (d, 1 H, J = 12.7 Hz), 1.43-1.21 (m, 12 H, including 1.30 [s, 3 H], 1.22 [s, 3 H)], and 1.21 [s, 3 H]), 0.81 (t, 3 H, J = 7.5 Hz).

The other acylations were performed following the same procedure as that described for the preparation of **91a**. In the preparation of **89c-92c**, the

acylating reagent is hydrocinnamoyl chloride. The spectroscopic data and melting points for these compounds are given below.

2-Naphthyl Propionyl Dilactam 89a. A colorless solid (87% yield): mp 193-194 °C; IR, 3057, 2969, 2930, 2869, 1720, 1702, 1678, 1467, 1253, 1174, 1106, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 3 H), 7.54 (d, 1 H, J = 1.8 Hz), 7.45 (m, 2 H), 7.13 (dd, 1 H, J = 8.7, 1.8 Hz), 6.36 (s, 1 H), 2.66 (m, 1 H), 2.40-2.20 (m, 3 H, including two equatorial protons) 1.82 (d, 1 H, J = 13.1 Hz), 1.57 (d, 1 H, J = 13.1 Hz), 1.47-1.39 (m, 5 H, including 1.43 [s, 3 H]), 1.34 (s, 3 H), 1.26 (s, 3 H), 0.81 (t, 3 H, J = 7.3 Hz).

2-Naphthyl Ester Propionyl Lactam 90a. Isolated an oily liquid (81% yield): IR, 3059, 2968, 2935, 1747, 1695, 1462, 1374, 1358, 1151, 1080, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 3 H), 7.46 (m, 3 H), 7.07 (dd, 1 H, J = 8.9, 2.3 Hz), 4.02 (dd, 1 H, J = 13.4, 2.5 Hz), 3.31 (dd, 1 H, J = 13.4, 1.7 Hz), 2.88-2.71 (m, 3 H), 2.42 (m, 1 H), 1.84 (d, 1 H, J = 13.0 Hz), 1.46 (s, 3 H), 1.45-1.15 (m, 9 H), 0.75 (t, 3 H, J = 7.4 Hz).

(S)-(-)-(α)-Methylbenzyl Propionyl Dilactam 92a. A colorless solid (82% yield): mp 114-116 °C; IR, 2970, 2930, 2870, 1726, 1693, 1659, 1450, 1372, 1266, 1213, 1173, 1152, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.26 (m, 5 H), 5.71 (s, 1 H), 5.53 (q, 1 H, J = 8.1 Hz), 2.61 (m, 1 H), 2.37 (m, 1 H), 2.07 (d, 1 H, J = 14.3 Hz), 1.76 (d, 1 H, J = 12.7 Hz), 1.55 (d, 1 H, J = 13.1 Hz), 1.44 (d, 3 H, J = 7.2 Hz), 1.36-1.19 (m, 9 H), 1.09 (t, 3 H, J = 7.3 Hz), 0.90 (s, 3 H).

In the preparation of **89c-92c**, acylations were performed following the same procedure as that described for the preparation of **91a**.except that the acylating reagent is hydrocinnamoyl chloride. The spectroscopic data and melting points for these compounds are given below.

2-Naphthyl Hydrocinnamoyl Dilactam 89c. A colorless solid (87% yield): mp 168-171 °C; IR, 3027, 2965, 2929, 1720. 1679, 1453, 1470, 1272, 1152, 750

cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 3 H), 7.55 (d, 1 H, J = 1.8 Hz), 7.47 (m, 2 H), 7.22-7.01 (m, 6 H), 6.30 (s, 1 H), 2.84-2.53 (m, 5 H), 2.24-2.17 (m, 2 H, two equatorial protons), 1.51-1.25 (m, 12 H, including 1.35 [s, 3 H], 1.27 [s, 3 H], and 1.25 [s, 3 H]).

2-Naphthyl Ester Hydrocinnamoyl Lactam 90c. Isolated a colorless solid (79%): mp 188-189 °C; IR 3051, 2968, 2931, 1747, 1690, 1381, 1149, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) d 7.83-7.78 (m, 3 H), 7.53-7.44 (m, 3 H), 7.13 (dd, 1 H, J = 8.9, 2.3 Hz), 7.07-7.03 (m, 3 H), 6.75-6.72 (m, 2 H), 4.02 (dd, 1 H, J = 13.4, 2.3 Hz), 3.30 (dd, 1 H, J = 13.4, 1.4 Hz), 3.17 (m, 1 H), 2.85-2.63 (m, 4 H), 2.27 (m, 1 H), 1.83 (d, 1 H, J = 13.0 Hz), 1.46 (s, 3 H), 1.46-1.25 (m, 6 H), 1.15 (s, 3 H).

(S)-(-)-(α)-Methylbenzyl Hydrocinnamoyl Dilactam 91c. A colorless solid (96% yield): mp 145-146 °C; IR, 3027, 2963, 2926, 2868, 1720, 1684, 1656, 1500, 1371, 1269, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.06 (m, 10 H), 6.18 (s, 1 H), 5.56 (q, 1 H, J = 7.2 Hz), 2.68-2.57 (m, 2 H), 2.44-2.33 (m, 1 H), 2.20-2.12 (m, 1 H), 2.05 (d, 1 H, J = 14.4 Hz), 1.82 (d, 1 H, J = 12.5 Hz), 1.65 (d, 3 H, J = 7.2 Hz), 1.39-1.15 (m, 12 H, including 1.24 [s, 3 H], 1.19 [s, 3 H], and 1.14 [s, 3 H]).

(S)-(-)-(α)-Methylbenzyl Hydrocinnamoyl Dilactam 92c. A colorless solid (79% yield): mp 73-75 °C; IR, 3028, 2966, 2928, 2869, 1725, 1658, 1452, 1374, 1265, 1210, 1150, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.15 (m, 10 H), 5.67 (s, 1 H), 5.52 (q, 1 H, J = 7.1 Hz), 2.93-2.63 (m, 5 H), 2.03 (d, 1 H, J = 14.0 Hz), 1.73 (d, 1 H, J = 12.7 Hz), 1.40 (d, 3 H, J = 7.1 Hz),1.32-1.09 (m, 9 H, including 1.23 [s, 3 H] and 1.15 [s, 3 H]), 0.85 (s, 3 H).

General Procedure of Alkylations. Lithium diisopropylamide (LDA) was purchased from Aldrich Chem. Co. as the monotetrahydrofuran complex, 1.5 M in cyclohexane. Tetrahydrofuran was distilled from sodium benzophenone ketyl or dianion under argon atmosphere. Methyl iodide and benzyl bromide were distilled before use.

To a solution of LDA (1.2 equiv.) in THF (1 mL) was dropwise added a solution of acylated auxiliaries **89a-92a, 89c-92c** (50-100 mg, 1 equiv.) in THF (1-5 ml) at -78 °C. After 30 min stirring at -78 °C, the appropriate electrophile (2 equiv.) was syringed in to the solution. The reaction was stirred for 10 min at -78 °C and 3-5 h at 0 °C, quenched with 0.1 N HCl, and then concentrated in vacuo. The residue was taken up in $CHCl_3$ (10 mL) and sequentially washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was dried under vacuum and the diastereomer ratio measured by ^1H NMR or HPLC. The spectroscopic data and melting points of major products from alkylations are given below.

89b (benzylation of 89a): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81-7.75 (m, 3 H), 7.58 (s, 1 H), 7.47-7.40 (m, 2 H), 7.25-7.09 (m, 7 H), 6.39 (s, 1 H), 3.32-3.25 (m, 1 H), 2.98 (dd, 1 H, J = 13.3, = 4.0 Hz), 2.25 (d, 2 H, J = 13.3 Hz), 1.96 (dd, 1 H, J = 13.3, 10.0 Hz), 1.83 (d, 1 H, J = 12.9 Hz), 1.58 (d, 1 H, J = 13.0 Hz), 1.49-1.41 (m, 5 H), 1.38 (s, 3 H), 1.27 (s, 3 H), 0.80 (d, 3 H, J = 6.8 Hz).

90b (benzylation of 90a); colorless crystal: mp 173-175 °C; IR 3027, 2965, 2931, 1748, 1685, 1462, 1373, 1147, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73-7.69 (m, 3 H), 7.51 (d, 1 H, J = 2.4 Hz), 7.40-7.36 (m, 3 H), 7.16 (dd, 1H, J = 9.0, 2.4 Hz), 7.07-7.01 (m, 3 H), 6.86-6.83 (m, 2 H), 4.06 (dd, 1H, J = 13.7, 2.3 Hz), 3.48 (m, 1 H), 3.02 (dd, 1 H, J =13.7, 1.5 Hz), 2.88 (d, 1 H, J = 14.1 Hz), 2.75 (d, 1 H, J =14.3 Hz), 2.42 (dd, 1 H, J = 13.4, 2.9 Hz), 2.06 (dd, 1 H, J = 13.4, 11.2 Hz), 1.87 (d, 1 H, J = 13.1 Hz), 1.48 (s, 3 H), 1.46 (dd, 1H, J = 13.2, 2.3 Hz). 1.36 (dd, 1H, J = 14.3, 1.5 Hz), 1.30 (s, 3 H), 1.27 (d, 1H, J = 14.1 Hz), 1.18 (s, 3 H), 0.92 (d, 3 H, J = 6.7 Hz).

91b (benzylation of 91a); oily liquid: IR 3056, 2996, 2967, 2922, 1718, 1685, 1452, 1360, 1119, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.20 (m, 10 H), 6.19 (s, 1 H), 5.16 (q, 1 H, J = 7.1 Hz), 3.50-3.17 (m, 1 H), 2.71 (dd, 1 H, J = 13.4, 4.6

Hz), 2.28 (dd, 1 H, J = 13.4, 9.9 Hz), 2.08 (d, 1 H, J = 14.7 Hz), 1.86 (d, 1 H, J = 11.9 Hz), 1.57 (d, 3 H, J = 7.1 Hz), 1.70-1.16 (m, 13 H), 0.87 (d, 3 H, J = 7.0 Hz).

92b (benzylation of 92a); IR 3058, 2992, 2966, 2922, 1719, 1685, 1462, 1375, 1220, 1175, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.17 (m, 10 H), 5.64 (s, 1 H), 5.55 (q, 1 H, J = 7.2 Hz), 3.45 (m, 1 H), 3.15 (dd, 1 H, J = 13.3, 6.4 Hz), 2.53 (dd, 1 H, J = 13.3, 8.3 Hz), 2.08 (d, 1 H, J = 14.2 Hz), 1.73 (d, 1 H, J = 12.8 Hz), 1.53 (d, 1 H, J = 12.4 Hz), 1.35-1.20 (m, 9 H), 1.13 (d, 3 H, J = 7.2 Hz), 0.99 (d, 3 H, J = 6.8 Hz), 0.86 (s, 3 H).

89d (methylation of 89c): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.76 (m, 3 H), 7.55-7.43 (m, 3 H), 7.23-6.29 (m, 6 H), 6.03 (s, 1 H), 3.23-3.17 (m, 1 H), 2.70-2.49 (m, 2 H), 2.17-2.05 (m, 3 H), 1.55-1.28 (m, 3 H), 1.19 (s, 3 H), 1.12 (s, 3 H), 1.01 (s, 3 H), 0.99 (d, 3 H, J = 7.0 Hz), 0.85 (d, 1 H, J = 13.0 Hz), 0.55 (d, 1 H, J = 13.0 Hz).

90d (methylation of 90c); oily liquid: IR 3027, 2965, 2932, 1748, 1685, 1462, 1360, 1148, 1071, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77-7.67 (m, 3 H),7.44-7.39 (m, 3 H), 7.26-7.17 (m, 5 H), 7.09 (dd, 1 H, J = 8.8, 2.2 Hz), 3.86 (dd, 1 H, J = 13.3, 1.9 Hz), 3.72 (m, 1 H), 3.00-2.93 (m, 2 H), 2.85 (d, 1 H, J = 14.1 Hz), 2.61 (d, 1 H, J = 14.3 Hz), 2.45 (dd, 1 H, J = 12.8, 7.8 Hz), 1.46 (d, 1 H, J = 12.9 Hz), 1.42 (s, 3 H), 1.29-1.19 (m, 6 H), 1.04 (s, 3 H), 0.70 (d, 3 H, J = 6.6 Hz).

91d (methylation of 91c); white solid: mp 194-195 °C; IR 3060, 2992, 2966, 2922, 2860, 1717, 1683, 1653, 1452, 1355, 1221, 1170, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.06 (m, 10 H), 5.90 (s, 1 H), 5.05 (q, 1 H, J = 7.1 Hz), 3.03 (m, 1 H), 2.79 (dd, 1 H, J = 12.6, 11.2 Hz), 2.58 (dd, 1 H, J = 12.7, 4.4 Hz), 1.93 (d, 1 H, J = 14.4 Hz), 1.72 (d, 1 H, J = 13.0 Hz), 1.64 (d, 3 H, J = 7.1 Hz), 1.26-0.98 (m, 14 H), 0.76 (d, 1 H, J = 13.1 Hz), 0.36 (d, 1 H, J = 13.1 Hz).

92d (methylation of 92c); colorless crystal: mp 170-171 °C; IR 3063, 2996, 2965, 2922, 2860, 1715, 1680, 1460, 1365, 1176, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500

MHz) δ 7.41-7.04 (m, 10 H), 5.59 (q, 1 H, J = 7.3 Hz), 5.38 (s, 1 H), 3.09 (m, 1 H), 2.89 (dd, 1 H, J = 12.7, 11.9 Hz), 2.59 (dd, 1 H, J = 12.7, 3.9 Hz), 1.94 (d, 1 H, J = 14.1 Hz), 1.62 (d, 1 H, J = 12.8 Hz), 1.32-1.13 (m, 12 H), 0.98 (s, 3 H), 0.62 (s, 3 H), 0.15 (d, 1 H, J = 13.2 Hz).

General Procedure of the Deprotection (92b, 91d, 92d). A 0.05 M solution of the alkylation product in 3:1 THF/H_2O was treated at 0 °C with 10 equiv of 30% H_2O_2 followed by 2.0 equiv of LiOH. The mixture was stirred at room temperature for 4-24 h, and the excess peroxide (peracid) was quenched at 0 °C with excess of 1.5 N aqueous Na_2SO_3. After buffering to pH 9-10 with aqueous $NaHCO_3$ and evaporation of the THF, the chiral auxiliaries (**87, 88**) were recovered by CH_2Cl_2 extraction in quantitative yield. The carboxylic acid was obtained by extraction of the acidified (pH 1-2) aqueous layer in a high yield (90-100%) as an oily liquid, which was used for next coupling reaction without further purification. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33-7.18 (m, 5 H), 3.08 (dd, 1 H, J = 13.1, 6.1 Hz), 2.81-2.64 (m, 2 H), 1.18 (d, 3 H, J = 6.7 Hz).

Coupling Reactions with (S)- (-)-(α)-Methylbenzylamine. To a solution of carboxylic acid (1 equiv) and N-methylmolpholine (1.2 equiv) in THF (2 ml) at -10 °C was added isobutylchloroformate (1 equiv). The solution was stirred for 1-2 min and then (S)-(-)-(α)-methylbenzylamine (3 equiv) was syringed. The reaction was stirred at -10 °C for 2 h and partitioned between EtOAc (5 mL) and NaH_2PO_4 (1 M, 5 mL). The organic layer was washed with saturated $NaHCO_3$, brine, and dried, then concentrated to give a colorless solid, which was used for HPLC analysis with 20% EtOAc in hexanes as eluent. (S,S; carboxylic acid from deprotection of **92b** and **91d**): mp 119-120 °C; IR 3310, 3065, 2977, 2924, 1641, 1538, 1446, 1246, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.41-6.98 (m, 10 H), 5.38 (s, 1 H, NH), 5.05 (m, 1 H), 2.94 (dd, 1 H, J = 13.4, 8.8 Hz), 2.67 (dd, 1 H, J = 13.4, 5.9 Hz), 2.42 (m, 1 H), 1.41 (d, 3 H, J = 6.8 Hz),

1.22 (d, 3 H, J = 6.8 Hz). (R,S; carboxylic acid from deprotection of **92d**): mp 88-89 °C; IR 3276, 3029, 2972, 2924, 1642, 1551, 1453, 1252, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33-7.17 (m, 10 H), 5.29 (s, 1 H, NH), 5.02 (m, 1 H), 2.94 (dd, 1 H, J = 12.6, 9.3 Hz), 2.71 (dd, 1 H, J = 14.4, 5.7 Hz), 2.40 (m, 1 H), 1.23 (d, 3 H, J = 6.9 Hz), 1.18 (d, 3 H, J = 6.9 Hz).

N-Menthylfomyl Lactambenzoxazoles 97a and 97b. To a solution of the racemic benzoxazole 82 (0.80 g, 2.68 mmol) in dry THF (70 mL) at -78 °C was dropwise added n-butyllithium (1.2 M solution in hexanes, 1.1 equiv) under argon atmosphere. After additional 15 min stirring, menthyl chloroformate (0.63 g, 2.91 mmol) was syringed and the solution was stirred for 30 min at -78 °C and 1 h at 0 °C. The reaction was quenched with saturated aqueous ammonium chloride and THF was removed at reduced pressure. The residue was diluted with CH_2Cl_2 and the organic layer was washed with saturated aqueous $NaHCO_3$, brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give a mixture of **97a and 97b**, which were separated by flash chromatography (15% EtOAc in hexanes).

97a (less polar isomer, 0.57 g, 44%); white solid: mp 100-102 °C; IR 2957, 2938, 2870, 1711, 1561, 1459, 1270, 1200, 1162, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.59 (m, 1 H), 7.47 (m. 1 H), 7.25 (m, 2 H), 4.14 (dd, 1 H, J = 10.8, 4.4 Hz), 3.75 (d, 1 H, J = 12.0 Hz), 3.26 (d, 1 H, J = 12.6 Hz), 3.05 (d, 1 H, J = 14.0 Hz), 2.99 (d, 1 H, J = 14.4 Hz), 1.88 (m, 1 H), 1.82 (d, 1 H, J = 13.0 Hz), 1.55-0.56 (m, 7 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 0.81 (d, 3 H, J = 7.0 Hz), 0.75 (d, 3 H, J = 6.4 Hz), 0.58 (d, 3 H, J = 6.9 Hz), -0.03 (q, 1 H, J = 11.4 Hz).

97b (more polar isomer, 0.56 g, 43%); white solid: mp 132-133 °C; IR 2959, 2870, 1773, 1669, 1430, 1210, 1167, 987, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.58 (m, 1 H), 7.47 (m. 1 H), 7.27 (m, 2 H), 4.15 (dd, 1 H, J = 10.8, 4.1 Hz), 3.76 (dd, 1 H, J = 12.5, 2.0 Hz), 3.12 (dd, 1 H, J = 12.6, 1.4 Hz), 3.06 (d, 1 H, J = 14.2

Hz), 2.96 (d, 1 H, J = 14.0 Hz), 1.80 (m, 1 H), 1.82 (d, 1 H, J = 13.0 Hz), 1.77-1.13 (m, 7 H), 1.33 (s, 3 H), 1.29 (s, 3 H), 1.13 (s, 3 H), 0.94-0.82 (m, 1 H), 0.86 (d, 3 H, J = 6.9 Hz), 0.80 (d, 3 H, J = 8.5 Hz), 0.52 (q, 1 H, J = 10.8 Hz), 0.49 (d, 3 H, J = 6.8 Hz).

Optically Active Lactambenzoxazole 82. A solution of **97a** or **97b** in CF_3CO_2H (5 mL) was stirred for 24 h at room temperature. Trifluoroacetic acid was removed at reduced pressure and the residue was taken up in CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$, brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give a yellowish solid, which were purified by flash chromatography (15 % EtOAc in hexanes) to give optically active lactambenzoxazole **82**. $[\alpha]_D$ = -7.7 ° (c = 4 in $CDCl_3$, from **97a**); $[\alpha]_D$ = +7.8 ° (c = 4 in $CDCl_3$ from **97b**); mp 185-187 °C; IR 3363, 3090, 2960, 2907, 1671, 1559, 1455, 1247, 1153, 1068, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (m, 1 H), 7.50 (m, 1 H), 7.26 (t, 2 H, J = 4.6 Hz), 4.62 (s, 1 H, NH), 3.25 (d, 1 H, J = 11.5 Hz), 3.02-2.90 (m, 3 H), 1.75 (d, 1 H, J = 12.8 Hz), 1.45-1.33 (m, 6 H), 1.22 (s, 3 H), 1.07 (s, 3 H)

N-Acetyllactam Benzoxazole 99a. To a solution of lactam benzoxzole **82** (0.10 g, 0.34 mmol) in dry THF (5 mL) at -78 °C was dropwise added 1 equiv of n-BuLi under argon atmosphere. After 10 min stirring, acetyl chloride (30 mg, 0.37 mmol) was syringed and the reaction was stirred at -78 °C for 30 min and at 0 °C for 10 min. The reaction was quenched with saturated aqueous NH_4Cl and concentrated in a vacua. The residue was diluted with CH_2Cl_2 (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, and dried with Na_2SO_4, and concentrated. The product was purified with chromatography (EtOAc) to give **99a** (0.11g, 92%) as a colorless solid: mp = 189-190 °C; IR 3034, 2962, 2908, 2847, 1693, 1536, 1455, 1245, 1175, 1153, 1104, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.59 (m, 1 H), 7.43 (m, 1 H), 7.26 (m, 2

H), 3.87 (dd, 1 H, J = 13.7, 2.5 Hz), 3.06 (d, 2 H, J = 13.7 Hz), 2.95 (d, 1 H, J = 14.3 Hz), 1.79 (d, 1 H, J = 13.0 Hz), 1.50-1.38 (m, 6 H), 1.38 (s, 3 H), 1.28 (s, 3 H), 1.15 (s, 3 H).

N-Acetyl N-(S)-(α)-Methylbenzyl Dilactam 100a. A solution of N-(S)-(α)-methylbenzyl dilactam **87** (1.00 g, 3.07 mmol) in acetic anhydride (15 mL) was refluxed for 4 h. After concentration in vacuo, the residue was taken up in CH_2Cl_2 (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was purified by chromatography (50% EtOAc in hexanes) to give pure **100a** as a white solid (1.07 g, 95 %): mp 172-173 °C; IR 2968, 2870, 1725, 1696, 1655, 1559, 1497, 1450, 1368, 1267, 1227, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.29-7.15 (m, 5 H), 6.20 (s, 1 H), 5.51 (q, 1 H, J = 7.1 Hz), 2.08 (d, 1 H, J = 14.5 Hz), 1.85 (d, 1 H, J = 12.8 Hz), 1.72 (s, 3 H), 1.66-1.62 (m, 4 H), 1.43-1.27 (m, 6 H), 1.22 (s, 3 H), 1.20 (s, 3 H); HRMS m/z for $C_{22}H_{28}N_2O_3$ $[M]^+$ calcd 368.2100, found 368.2100.

N-Acetyl N-(S)-(α)-Methylbenzyl Dilactam 101a. In the preparation of **101a**, acylations were performed by following the same procedure as that described for the preparation of **100a** except that dilactam **88** was used instead of **87**. The spectroscopic data and melting points for this compound are given below. mp 120-122 °C; IR 2967, 2929, 2869, 1728, 1691, 1658, 1451, 1370, 1267, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40-7.25 (m, 5 H), 5.68 (s, 1 H), 5.53 (q, 1 H, J = 7.1 Hz), 2.18 (s, 3 H), 2.07 (d, 1 H, J = 14.3 Hz), 1.78 (d, 1 H, J = 12.8 Hz), 1.57 (d, 1 H, J = 13.0 Hz), 1.45 (d, 3 H, J = 7.1 Hz), 1.66-1.62 (m, 4 H), 1.33-1.15 (m, 9 H), 0.92 (s, 3 H)

General Procedure of the α-Unsubstituted Aldol Reaction. Lithium diisopropylamide (LDA) was purchased from Aldrich Chem. Co. as a monotetrahydrofuran complex, 1.5 M in cyclohexane. Tetrahydrofuran and

toluene were distilled from sodium benzophenone ketyl or dianion under argon atmosphere. Benzaldehyde was washed with 10 % Na_2SO_4 prior to vacuum distillation. To a solution of LDA (1.1 equiv) in THF (1 mL) was dropwise added a solution of **99a-101a** (0.1 g, 1 equiv) in THF (2-3 mL) at -78 °C. After 30 min stirring at -78 °C, benzaldehyde (1.1 equiv) was syringed in to solution. The reaction was stirred at -78 °C for a certain time (3-30 min), and quenched with saturated aqueous NH_4Cl at -78 °C and warmed up to ambient temperature. After the solution was concentrated, the residue was taken up in CH_2Cl_2 (10 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was dried on a vacuum and the diastereomeric ratio was measured by ^1H NMR or HPLC.

Transmetallation. To a solution of LDA (1.1 equiv) in THF (1 mL) was dropwise added a solution of **100a** (0.1 g, 1 equiv.) in THF (2 mL) at -78 °C. After 30 min stirring at -78 °C, Et_2AlCl (2 equiv, 1.0 M solution in hexanes) was syringed and the temperature was warmed to -41 °C, and the solution was stirred for 1 h at -41 °C. The solution was cooled to -78 °C and benzaldehyde (1.1 equiv) was syringed in to the solution. The reaction was stirred at -78 °C for 30 min. Work-up was performed by following the same procedure as that described for general procedure. The spectroscopic data and melting points of major products from aldol reactions are given below.

99b (aldol reaction of **99a** with benzaldehyde, entry 10-13 in Table 13); colorless crystal: mp = 157-159 °C; IR 3522, 2964, 2912, 1697, 1559, 1429, 1245, 1149 750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.52 (m, 1 H), 7.37 (m, 1 H), 7.24 (m, 2 H), 3.81 (dd, 1 H, J = 13.5, 2.4 Hz), 3.42 (m, 1 H), 3.05-2.85 (m, 3 H), 2.65 (dd, 1 H, J = 17.3, 2.4 Hz), 2.11 (d, 1 H, OH, J = 2.8 Hz), 1.73 (d, 1 H, J = 12.9 Hz), 1.47-0.77(m, 14 H), 0.69 (t, 3 H, J = 7.4 Hz).

100b (aldol reaction of **100a** entry 1-7 in Table 13); white solid: mp 152-153 °C; IR 3432, 2997, 2930, 2835, 1745, 1653, 1437, 1355, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40-7.20 (m, 10 H), 6.17 (s, 1 H), 5.55 (q, 1 H, J = 7.1 Hz), 4.84 (m, 1 H), 3.24 (d, 1 H, OH, J = 2.6 Hz), 2.47 (dd, 1 H, J = 17.3, 3.5 Hz), 2.29 (dd, 1 H, J = 17.3, 9.4 Hz), 2.07 (d, 1 H, J = 14.3 Hz), 1.85 (d, 1 H, J = 12.9 Hz), 1.67 (d, 3 H, J = 7.2 Hz), 1.48 (d, 1 H, J = 13.2 Hz), 1.42-1.14 (m, 12 H).

100b (aldol reaction of **100a** with transmetallation, entry 8 in Table 13); colorless crystal: mp 163-164 °C; IR 3445, 3028, 2967, 2928, 2869, 1725, 1647, 1436, 1371, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35-7.20 (m, 10 H), 6.20 (s, 1 H), 5.72 (q, 1 H, J = 7.1 Hz), 4.74 (m, 1 H), 3.28 (d, 1 H, OH, J = 3.8 Hz), 2.39 (dd, 1 H, J = 17.5, 9.2 Hz), 2.17 (dd, 1 H, J = 17.5, 2.5 Hz), 2.07 (d, 1 H, J = 14.3 Hz), 1.84 (d, 1 H, J = 12.7 Hz), 1.67 (d, 3 H, J = 7.1 Hz), 1.46-1.16 (m, 13 H).

101b (aldol reaction of **101a**, entry 9 in Table 13); major product: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35-7.23 (m, 5 H), 6.22 (s, 1 H), 5.51 (q, 1 H, J = 7.1 Hz), 3.56 (m, 1 H), 2.99 (d, 1 H, OH, J = 3.3 Hz), 2.32 (dd, 1 H, J = 17.1, 2.1 Hz), 2.15-1.87 (m, 3 H), 1.72 (d, 3 H, J = 7.1 Hz), 1.68-1.32 (m, 8 H), 1.27 (s, 3 H), 1.23 (s, 3 H), 0.88 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.8 Hz). Minor product: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.28-7.11 (m, 5 H), 6.21 (s, 1 H), 5.79 (q, 1 H, J = 7.1 Hz), 3.38 (m, 1 H), 2.63 (d, 1 H, OH, J = 3.3 Hz), 2.12-1.24 (m, 12 H), 1.24 (s, 3 H), 1.21 (s, 3 H), 0.85 (d, 3 H, J = 6.8 Hz), 0.80 (d, 3 H, J = 6.8 Hz).

Deprotection of 100b (major product from entry 1-7 in Table 13). A solution of **100b** (0.10 g, 0.21 mmol) in 3:1 THF/H_2O (5 mL) was treated at 0 °C with 10 equiv of 30 % H_2O_2 followed by 2.0 equiv of LiOH. The mixture was stirred for 20 min at 0 °C, and the excess peroxide (peracid) was quenched at 0 °C with an excess of 1.5 N aqueous Na_2SO_3 (5 mL). After buffering to pH 9-10 with aqueous $NaHCO_3$ (5 mL) and evaporation of the THF, the chiral auxiliary **87** was recovered by CH_2Cl_2 extraction (3 x 10 mL) in quantitative

yield. The carboxylic acid was obtained by extraction of the acidified (pH 1-2) aqueous with ethyl acetate (3 x 10 mL). The ethyl acetate was removed at reduced pressure to give (S)-3-phenyl-3-hydroxy propionic acid (34 mg, 96%) as a white solid. mp 115-116 °C; $[\alpha]_D$ = -16.3 ° (c=1.0 in EtOH) ; IR 3600-2300, 1740, 1710, 1635, 1451, 1282, 1204, 1163, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.39 (m, 5 H), 5.16 (dd, 1 H, J = 8.7, 4.0 Hz), 2.81 (m, 3 H).