Stereoselective Alkylations in Rigid Systems. Effect of Remote Substituents on π-Facial Additions to Lactam Enolates. Stereoelectronic and Steric Effects

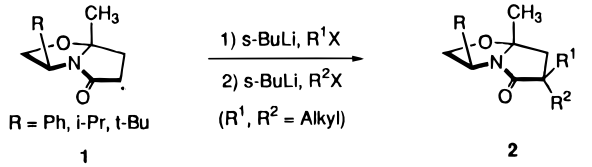
A. I. Meyers,*,† Mark A. Seefeld,† Bruce A. Lefker,‡ James F. Blake,‡ and Paul G. Williard§

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, Pfizer Central Research, Groton, Connecticut 06340, and Department of Chemistry, Brown University, Providence, Rhode Island 02912

Received February 23, 1998

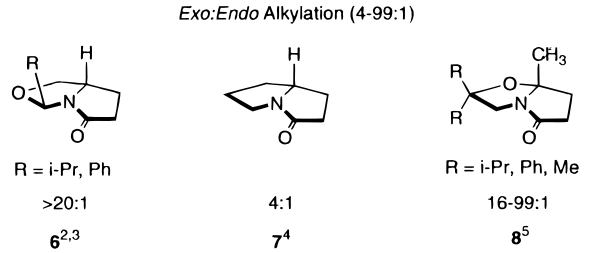
Abstract: A series of chiral bicyclic lactams has been studied by both experiment and ab initio molecular orbital calculations. The facial selectivity of the alkylation of their enolates shows a high degree of endo or exo entry, depending upon certain substituents and their positions in the lactams. The suggested reasons for the exo or endo selectivity for alkylation were determined to be purely electronic or purely steric in certain instances. The results of the selectivity study now allow the asymmetric synthesis of various ketones, acids, and pyrrolidines in either enantiomeric form based on the choice of lactam employed.

Chiral bicyclic lactams **1** are highly useful templates for the asymmetric construction of compounds containing quaternary carbon centers **3**−**5**.[1] The cornerstone of this methodology has



been the ability to alkylate **1** in a highly endo-selective manner. In the majority of cases, the preferred endo approach was 10−50:1 to give **2**.

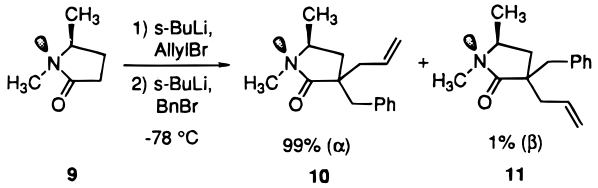
This is in stark contrast to a number of bicyclic lactams **6**−**8** that have been reported to alkylate in an exo-selective fashion.[2−5]



A combination of steric and electronic effects may be operative in defining the preferred trajectory for the incoming electrophile. Unfortunately, a satisfactory and consistent rationale has not yet been forthcoming to explain these observed reversals in selectivity.

Herein we report a series of experimental results and ab initio molecular orbital calculations which seem to support the hypothesis that an electronic preference for alkylation anti to the nitrogen lone pair (endo alkylation) is in competition with steric factors which have the potential to reverse the selectivity and thus favor exo alkylation. Additionally, we report the X-ray structure of the lithium enolate of lactam **6** (R = *i*-Pr). This enolate structure **12** (Figure 1A,B) provides information about the configuration and facial accessibility of this reactive species.

We chose to first investigate these stereoselective alkylations by focusing on the electronic aspects of lactam alkylation. We recently reported experimental and theoretical studies[6] on the monocyclic (±)-1,5-dimethylpyrrolidinone (**9**). Those studies



provided evidence that the nitrogen lone pair of the lactam enolate may introduce an electronic preference for alkylation anti to the nitrogen lone pair (α-entry). In this simple system, which is devoid of any significant steric biases, selectivities of

† Colorado State University.
‡ Pfizer Central Research.
§ Brown University.

(1) (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1.
(2) Lefker, B. A. Ph.D. Thesis, Colorado State University, 1988.
(3) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Yong, M. K. Y.; Kissick T. P. *J. Org. Chem.* **1986**, *51*, 3140.
(4) (a) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobl, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108. (b) Damm, L. G.; Eschenmoser, A. Ph.D. Dissertation, Eidgenossischen Technischen Hochscule, Zurich, Switzerland, 1979.
(5) Meyers, A. I.; Seefeld, M. A.; Lefker B. A. *J. Org. Chem.* **1996**, *61*, 5712. See also: Roth, G.; Leonard, S. F.; Tong L. *J. Org. Chem.* **1996**, *61*, 5710.
(6) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565.

S0002-7863(98)00614-3 CCC: $15.00
Published on Web 07/18/1998

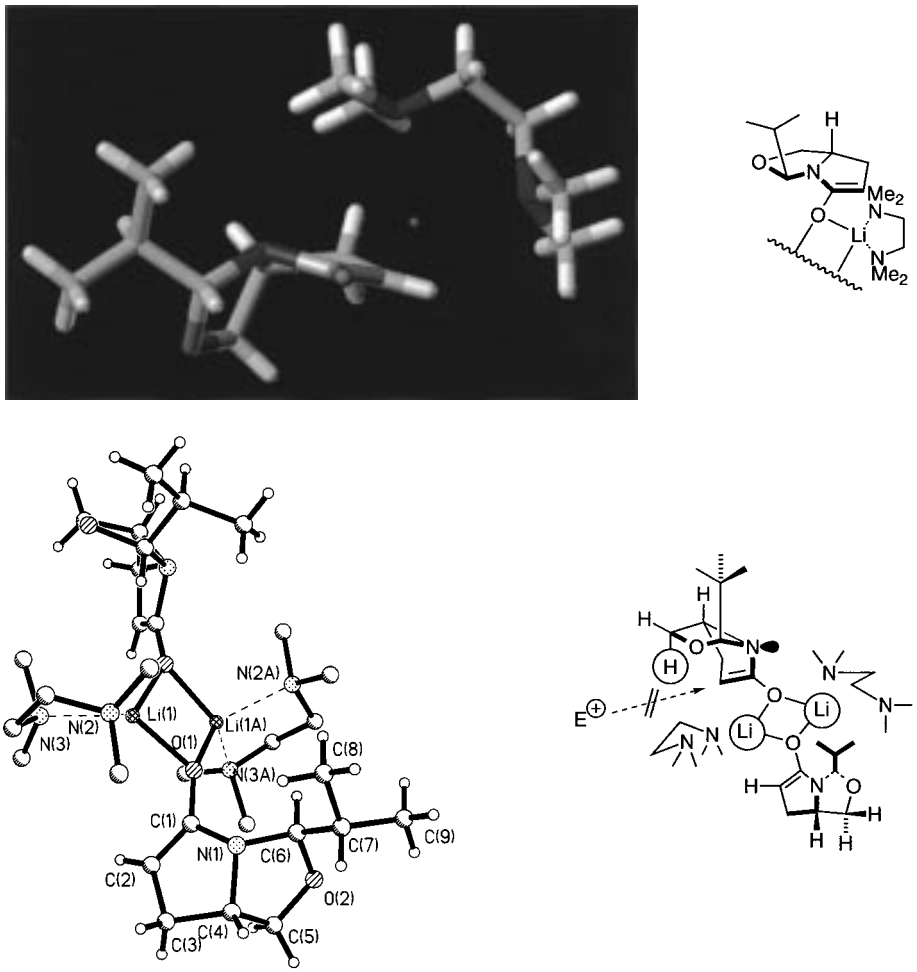
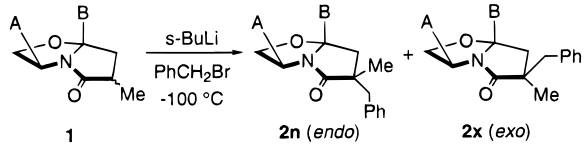


Figure 1. (A, top) Computer-generated X-ray structure of simplified lithium enolate **12** (from lactam **6**) with TMEDA complex. Only one-half of the dimer is shown; a complete structure is given in part B. Complete data are given in the Supporting Information. (B, bottom) ORTEP X-ray structure of dimeric lithium enolate·TMEDA (**12**).

Table 1. Effect of Exo Substituents on Endo/Exo Benzylation Ratios



1 **2n** (*endo*) **2x** (*exo*)

entry	A	B	%**2n** (endo)[a]	%**2x** (exo)[a]
a	*i*-Pr	Me	97	3
b	*t*-Bu	Me	98	2
c	*i*-Pr	Ph	98	2
d	*i*-Pr	H	80	20
e	H	Me	70	30
f	H	H	69	31

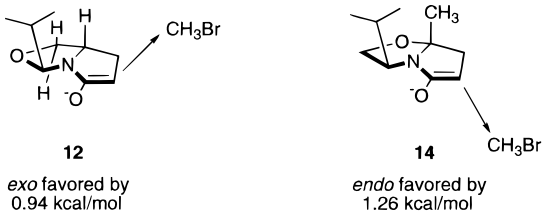
[a] Ratios detemined by NMR and are accurate to ±2%.

99:1 for compounds **10**:**11** were observed. Ab initio molecular orbital calculations on the β and α SN_2 transition states also predicted that α-face alkylation on this monocyclic lactam would be favored.

If a similar electronic effect can be extended to bicyclic lactams and alkylation anti to the nitrogen lone pair (endo) is mainly electronic in origin, then clearly additional steric and/or electronic factors are influencing the alkylation of bicyclic lactams **6**−**8**.

Previous studies[1] measuring alkylation selectivity in bicyclic lactams **1** have suggested that the angularly placed exo substituents do impart some steric bias for endo alkylation. Systematic replacement of the exo alkyl and aryl substituents (A and B, Table 1) on bicyclic lactam **1** with hydrogen results in an erosion of endo alkylation selectivity from 98:2 down to 69:31. However, endo alkylation is still preferred even when both A and B are hydrogens (entry f, Table 1). Thus, exo substituents (A and B) may be assumed to be only a minor factor in the determination of diastereofacial alkylation selectivity. This residual preference for endo alkylation in entry f can likely be attributed to an electronic effect or some yet to be observed steric factor. In an effort to further define this electronic effect, computational methodology similar to that described for the monocyclic (±)-dimethyl lactam **9** was applied.

A ground-state conformation for the lithium enolate of lactam **1** was calculated from X-ray parameters (Figure 1A), and the highly convex enolate structure **14** (Figure 2) appears to offer



significantly less access to the endo face than would have been predicted from the lactam structure prior to enolization. In an earlier study, we determined, in a prototypical system (lactam

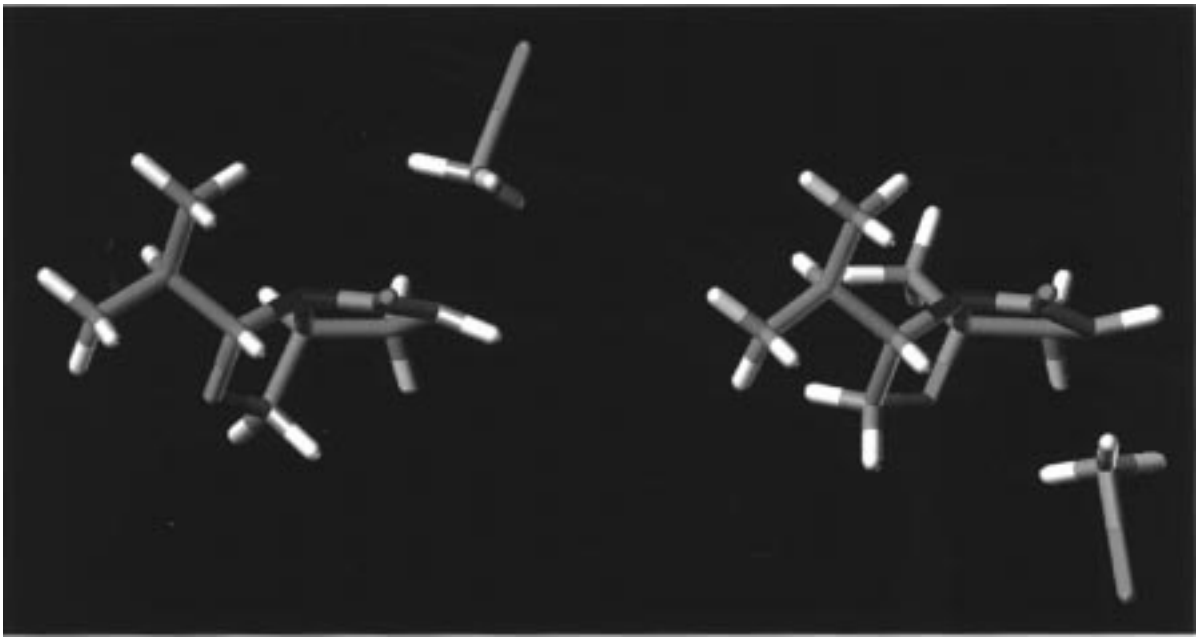
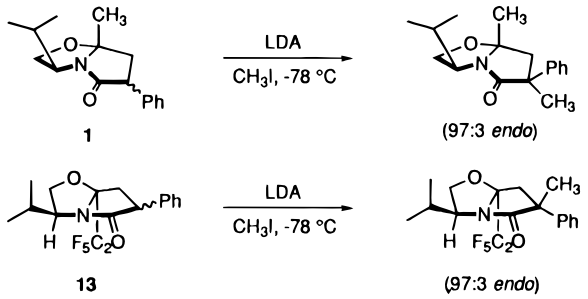


Figure 2. Exo addition is favored experimentally for **12**, as the endo face is encumbered by H atom. Endo addition is favored experimentally for **14**, although the exo face also appears to be unencumbered.

9), that the alkylation selectivity could be predicted via location of the SN_2 transition-state structures corresponding to the two modes (α and β) of attack.[6] This methodology has now been applied to the alkylation reaction involving enolate **14**. The transition-state structures corresponding to the endo and exo alkylation products of methyl bromide were determined (Figure 2). As with the enolate of lactam **9**, the endo mode of addition to **14** was predicted to be favored by ca. 1.26 kcal/mol, consistent with the results reported in Table 1 (entry a). It is interesting that the high endo selectivity displayed in this system is retained despite the concave nature of the bicyclic system. Clearly, the driving force for addition anti to the nitrogen lone pair is operative in this system.

In contrast to results obtained on alkylations with lactams **1**, the enolate **12** from lactam **6** (R = *i*-Pr) was reported[3] previously to alkylate with high exo selectivity. This reversal was surprising considering the only difference between enolates **12** and **14** is the position of the ring oxygen. To further our understanding about the factors governing selectivity, we chose to examine the specific configuration of the enolate **12**. To achieve this goal, the lithium enolate was successfully crystallized and studied by X-ray analysis. The structure of enolate **12** (Figure 1A,B) reveals a surprisingly convex bicyclic species which crystallized as a dimeric 1:1 complex with TMEDA. The plane designated by the three carbon atoms attached to nitrogen is 0.5 Å removed from the bridgehead nitrogen of the enolate structure. This indicates a substantial increase in pyramidalization from the starting bicyclic lactams **1** and **6** (0.1−0.3 Å) as determined from earlier X-ray analyses.[1] Alkylation of the lithio TMEDA/enolate **12** proceeded with the same selectivity as that observed in the absence of TMEDA. This is similar to earlier observations where addition of TMEDA or HMPA, altering the solvent polarity, or varying the counterion character[7,8] did not effect the facial alkylation selectivity of lactams **1**. In addition, the similar behaviors of lactams **1** and **13**[9] wherein the electrophile entered the corresponding lithio enolates anti to the angular methyl or trifluoromethyl (endo face) suggest that the Cieplak effect[10] is probably not applicable to this system.



Examination of the HOMO of the enolate **12** reveals a larger orbital coefficient on the endo face (Figure 3A), and thus, based on electronics alone, endo-facial alkylation for both lactam enolates might be expected. Similarly, the HOMO of enolate **14** reveals the larger orbital coefficient on the endo face (Figure 3B). Furthermore, the transition states for exo and endo attack on enolate **14** reveal no visible steric inhibition from either face (Figure 3C). However, comparison of the transition states for endo and exo alkylation reveals a reversal in the predicted stereoselectivity from **14**, with the exo addition product now favored by 0.94 kcal/mol (Figure 2). This result is in agreement with the earlier observed experimental preference for exo alkylation.[2,3]

Overlap of enolate **12** with the calculated enolate lactam **14** reveals only a 0.074 Å rms difference in structure between the non-hydrogen atoms forming the core enolate rings (Figure 4). A more meaningful analysis of this exo/endo paradox might be found by directly comparing the transition-state profiles for enolates **12** and **14**.

A comparison of the stereostructures of the valinol-derived enolate **14** with that of enolate **12** provides some interesting insight into endo-facial steric bias. The two structures are largely superimposable (Figure 4). The main structural differences lie in the position of their ether oxygens and their adjacent methylene groups. Calculations for the approach of methyl

(7) Liotta, D.; Durkin, K. A. *J. Am. Chem. Soc.* **1990**, *112*, 8162.
(8) Meyers, A. I.; Wallace, R. H.; Romo, D. Unpublished results.
(9) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509.
(10) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

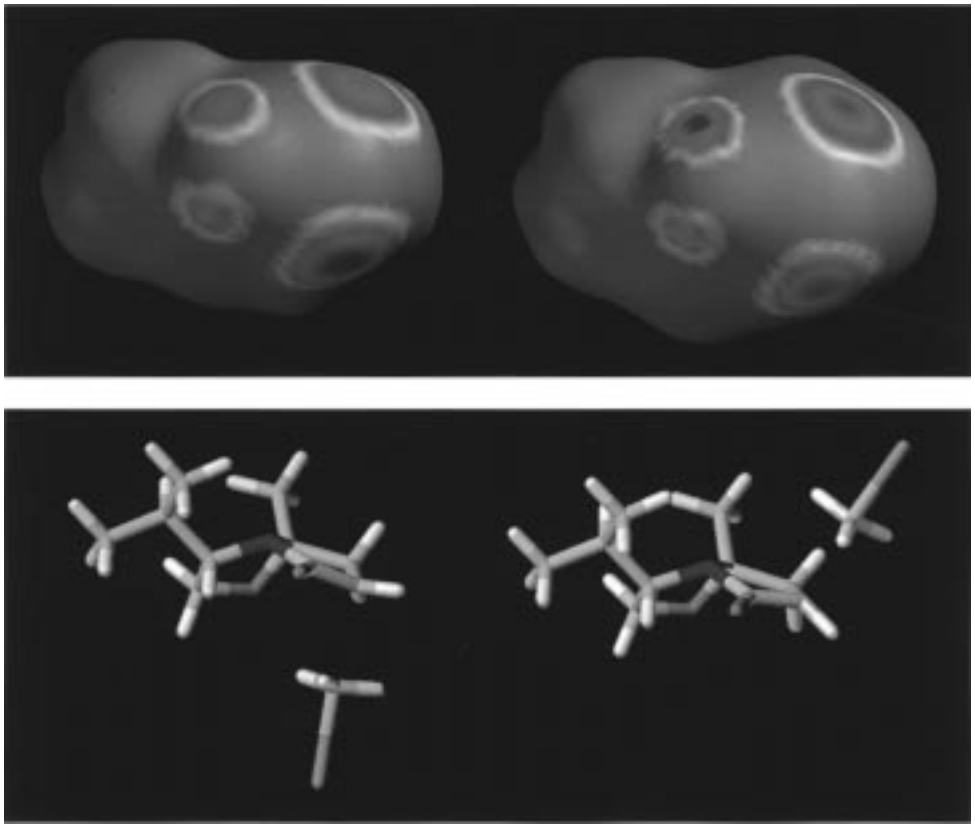


Figure 3. (A, top left) Electron density isosurface of the HOMO enolate **12**. (B, top right) Electron density isosurface of the HOMO of enolate **14**. (C, bottom) Calculated transition states for endo and exo approach of CH_3Br to enolate **14**.

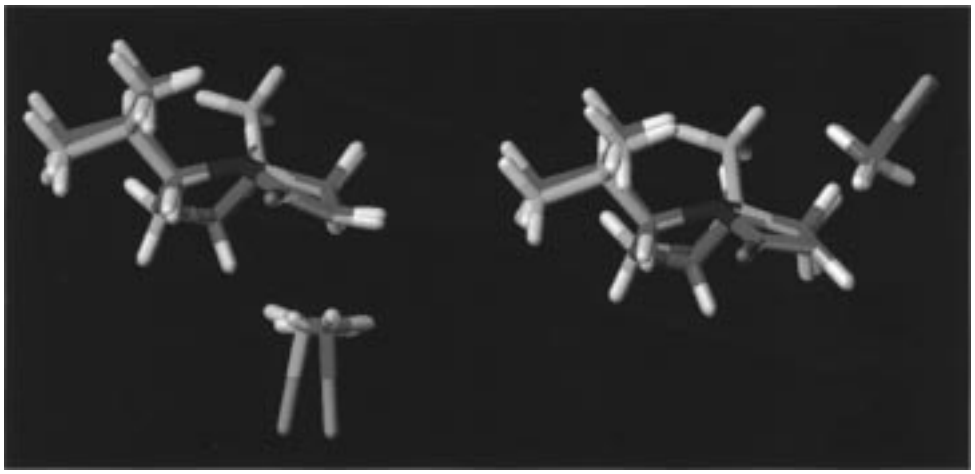


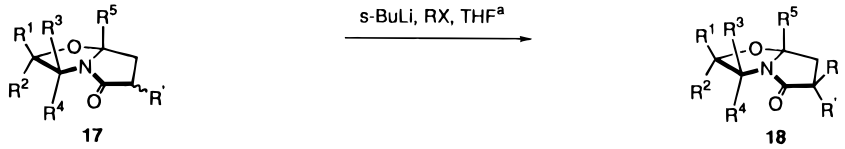
Figure 4. Overlapping enolates **12** (green) and **14** (gray) and their respective CH_3Br (green and gray) approach vectors for endo (left) and exo (right) entry.

bromide to enolate **12** indicate a difference in transition-state energies of 0.94 kcal/mol in favor of the exo approach model (Figure 2). Likewise, similar calculations predict a favored endo transition state for enolate **14** by 1.26 kcal/mol (Figure 2). Presumably some steric component, and one not present on the exo face of the bicyclic lactam **12**, must be overriding the electronic effect.

The approach vectors of methyl bromide to superimposed stereomodels of enolates **12** and **14** (Figure 4) indicate no visible steric bias on the exo faces of either of these enolates. In fact, the approach vectors to the exo face seem to be identical. However, the trajectory of the electrophile (CH_3Br) toward the endo face of enolate **12** is altered 10° relative to that of the valinol-derived enolate **14**. It appears the *endo*-methylene hydrogens of enolate **12** are interfering with the electrophile approach. By analogy, the deoxylactam **7** should show similar behavior on the basis of its endo hydrogens similarly protruding into the concave region, and exo entry was found to indeed be the case.[4]

Recently, we and others[5] reported that additional substitution on the endo face of related bicyclic lactams **8** could reverse the direction of entry and induce high levels of exo-facial alkylation. We concluded that a steric component provided by the newly placed endo substituent was responsible for this reversal in stereofacial alkylation. To test this hypothesis, racemic lactams **8**, each containing an endo substituent in the position β to the

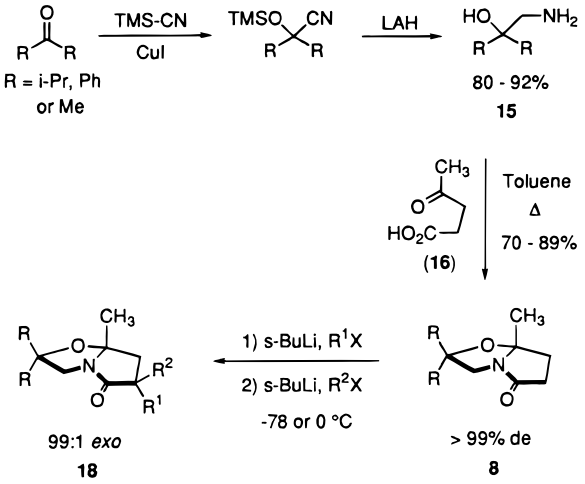
Table 2. Alkylation of Sutstituted Bicyclic Lactams



entry	R^1	R^2	R^3	R^4	R^5	R′	RX	R	R′	*T* (°C)	% yield[b]	exo:endo[c]
a	H	H	Me	Me	Me	H	BnBr	H	Bn	−78	86	1:99[d]
b	Me	Me	H	H	Me	Bn	allyBr	allyl	Bn	−78	89	99:1[d]
c	*i*-Pr	*i*-Pr	H	H	Me	H	BnBr	Bn	H	−78	91	96:4
d	*i*-Pr	*i*-Pr	H	H	Me	Bn	allylBr	allyl	Bn	−78	93	99:1[d]
e	*i*-Pr	*i*-Pr	H	H	Me	Bn	allylBr	allyl	Bn	0	90	99:1[d]
f	Ph	Ph	H	H	Me	H	BnBr	Bn	H	−78	94	94:6[e]
g	Ph	Ph	H	H	Me	Bn	allylBr	allyl	Bn	−78	95	99:1[d]
h	Ph	Ph	H	H	Me	Bn	allylBr	allyl	Bn	0	90	99:1[d]
i	H	Ph	CH_2O-TBDPS	H	Me	CH_3	BnBr	Bn	CH_3	−78	91	94:6
j	H	Ph	CH_2O-TBDPS	H	Me	Bn	allylBr	allyl	Bn	−78	87	98:2
k	H	Ph	CH_2O-TBDPS	H	Me	allyl	BnBr	Bn	allyl	−78	88	99:1[d]
l	H	Ph	CH_2O-TBDPS	H	Me	allyl	BnBr	Bn	allyl	0	77	99:1[d]
m	H	Ph	CH_2O-TBDPS	H	H	H	BnBr	Bn	H	−78	85	91:9
n	H	Ph	CH_2O-TBDPS	H	H	Bn	allylBr	allyl	Bn	−78	90	99:1[d]
o	Ph	Ph	Ph	H	Me	H	allylBr	allyl	H	−78	92	99:1[d]
p	Ph	Ph	Ph	H	Me	allyl	BnBr	Bn	allyl	−78	93	99:1[d]

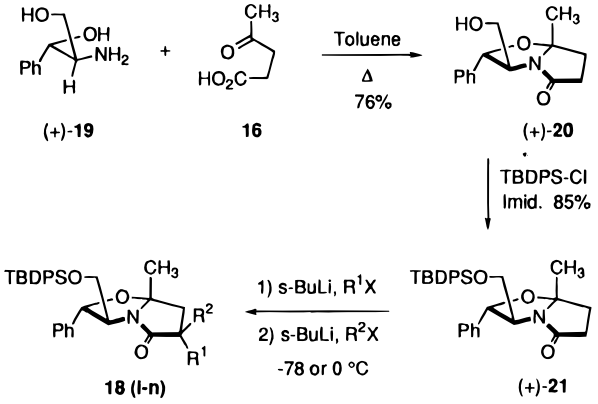
[a] Similar diastereomeric ratios and yields were also observed using LDA in THF. [b] Isolated yield of both diastereomers. [c] Diastereomeric ratio was determined by ^{1}H NMR at 300 MHz. [d] No minor diastereomer could be detected in the ^{1}H NMR spectrum. [e] Epimerization noted.

quaternary angular center, were prepared from levulinic acid (**16**) and their respective vicinal amino alcohols **15**.[11]



Alkylation of the lithium enolate of lactams **17** (Table 2, entries c and f) with benzyl bromide proceeded with high levels of exo selectivity. The *exo*-benzyl product gave rise to a diagnostic anisotropic shielding effect on the angular methyl substituent which was discernible by ^{1}H NMR. In two cases, complete exo selectivity was also observed at temperatures as high as 0 °C (Table 2, entries **18**e,h). Interestingly, the achiral lactam **17** containing *gem*-dimethyl substituents adjacent to nitrogen (entry a) displayed complete preference for endo alkylation. This is consistent with substituents adjacent to nitrogen in the enolates of **17** not interfering with the endo alkylation trajectory as much as substituents placed β to the ring nitrogen. In every instance shown in Table 2 where an endo substituent (R^2) was other than H, complete (or nearly so) exo alkylation occurred (entries **18**b−p).

To further substantiate the relative stereoselectivities which were assigned to **18** on the basis of anisotropic shielding of the angular substituent, chiral nonracemic lactams were constructed that could be further carried on to previously known, chiral, nonracemic products. To perform this task, lactam **21** was synthesized by condensing the commercially available amino diol (+)-**19** and levulinic acid to afford chiral lactam (+)-**20**. The hydroxyl group in the latter was silylated smoothly with TBDPS-Cl in 85% yield. Lactam (+)-**21**, on being subjected to the usual enolate formation, also exhibited a strong preference for exo alkylation to **18** at both −78 and 0 °C (Table 2, entries i−n) when alkyl halides were sequentially introduced.



The absolute stereochemistry for these systems was verified by chemical correlation as follows. Subjecting both lactam **21** and valinol-derived lactam **1** (R = *i*-Pr) separately to reverse-order alkylations followed by heating in butanol and H_2SO_4 resulted in the formation of an identical ketoester **22**.[12] Further stereochemical confirmation was provided by the conversion of **1** and **21** into the same cyclopentenone (−)-**23** when both substituents were introduced in reverse order to **21** and **1**,

(11) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

(12) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146.

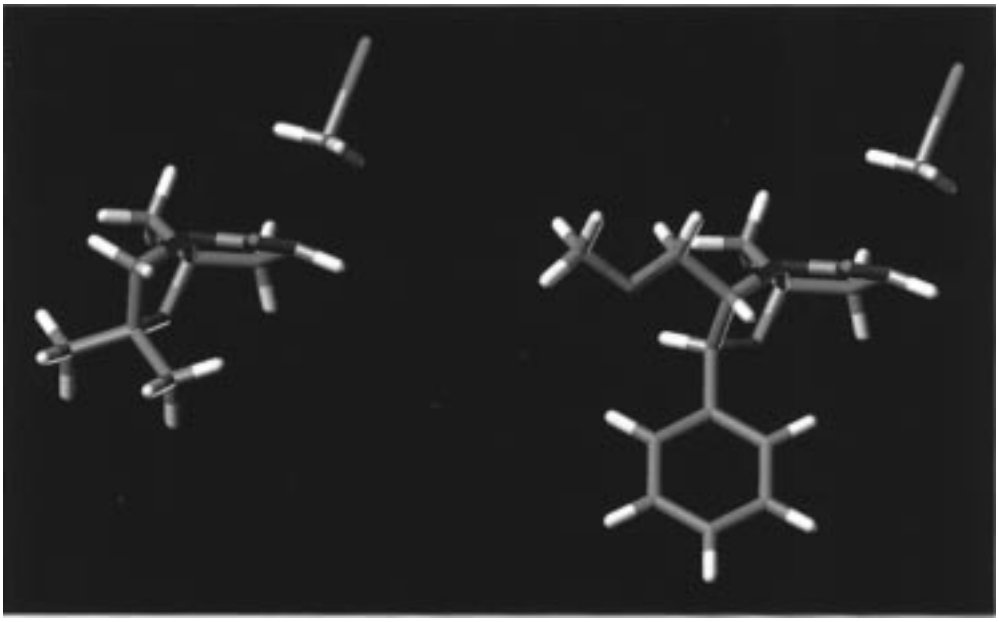
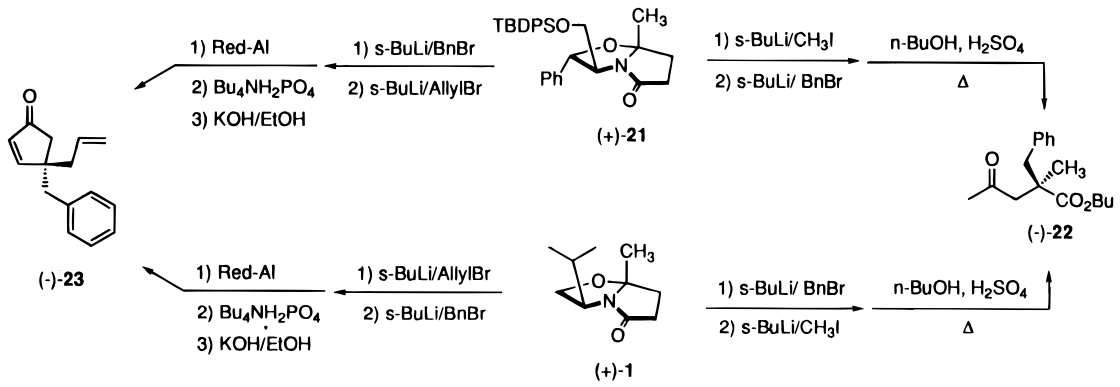
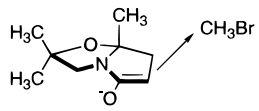


Figure 5. Calculated transition states for exo approach to enolates **24** and **25**.



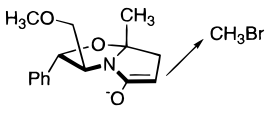
respectively.[13] This clearly showed that (+)-**21**, with an *endo*-phenyl substituent alkylated on the exo face, whereas (+)-**1**, with no endo substituent, alkylated on the endo face. Since a reverse sequence of electrophiles was employed, both modes of alkylation gave identical stereochemical results.

To rationalize the exo entry as the main mode of alkylation on the lactams in Table 2 (**17**h−p), stereomodels of the corresponding enolates **24** and **25** were studied as their transition



24

exo favored by 0.93 kcal/mol



25

exo favored by 0.49 kcal/mol

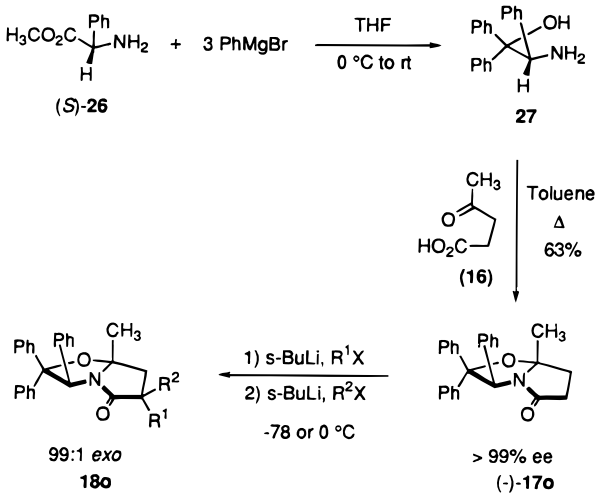
states toward alkylation. They clearly show the effect of having a substituent on the endo face (Figure 5). The transition-state energies of lactam enolates **24** and **25** with respect to the approach of methyl bromide should reflect the preference for exo alkylation, and this was indeed found to be the case. Racemic lactam enolate **24** is favored to give exo alkylation (0.93 kcal/mol), and the chiral lactam enolate **25** is also favored to provide exo alkylated products (0.49 kcal/mol). This is consistent with the experimental results for exo alkylation as shown in Table 2 (**17**b−**18**b; **17**i−**18**i) where, in every case, a substituent (R_2) projected down into the endo face.

It was now desirable to assess the feasibility of having ready access to a chiral nonracemic bicyclic lactam which is closely related to **1**, except it will selectively alkylate on the exo face. This was implemented by using (*S*)-phenylglycinate as the chiral auxiliary. Thus, chiral, nonracemic lactam (−)-**17o** was constructed in two steps from phenylmagnesium bromide and (*S*)-2-phenylglycine methyl ester (**26**) followed by simple reflux with levulinic acid in toluene. The enantiopurity of the lactam was determined from chiral HPLC analysis and found to be >99% ee. As with all the other similarly substituted lactams, the highly crystalline lactam **17o** displayed excellent exo alkylation selectivity when metalated and alkylated sequentially with allyl and benzyl bromide to give **18** (entries o and p, Table 2).

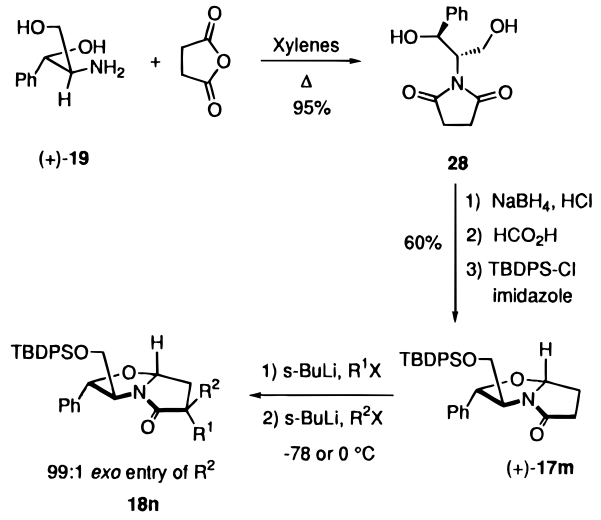
In an earlier report[14] we described the use of the bicyclic lactams in the preparation of chiral pyrrolidines.[1b] In this regard, it was deemed necessary to have access to a chiral lactam which would also alkylate exo and therefore lead to the enantiomeric series of pyrrolidines. We, therefore, prepared the angular hydrogen-substituted lactam **17m** which was constructed by heating amino diol **19** and succinic anhydride in xylenes. After recrystallization, the enantiomerically pure succinamide **28** was reduced with $NaBH_4$ followed by formic acid mediated cyclization and silylation to afford the crystalline lactam **17m**.

(13) Meyers, A. I.; Wanner, K. Th. *Tetrahedron Lett.* **1985**, *26*, 2047.

(14) Westrum, L. J.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 973.



The latter also alkylated in high exo-diastereofacial selectivity at both −78 and 0 °C (entries **18**m,n, Table 2). This suggests that the angular substituent in the bicyclic lactams (H vs Me) has little effect on the approach trajectory of the electrophile and the major factor in determining facial entry still remains the substituent R^2 in **17** (Table 2).



Computational Methods

Restricted Hartree−Fock calculations were carried out for the endo and exo alkylation reactions of enolates **12**, **14**, **24**, and **25** with methyl bromide. The geometries for each series of molecules were fully optimized by means of analytical energy gradients with the 6-31+G(d) basis set. The ab initio molecular orbital calculations were carried out with the Gaussian 94 series of programs on a Silicon Graphics computer.[15] Vibrational frequencies were calculated at the 6-31+G(d) level for all stationary structures. The existence of transition states or minima was confirmed by the presence of either one or zero negative eigenvalues in the analytical second-derivative matrix. The scaled vibrational frequencies[16] were used to compute the enthalpies and entropies of each molecule at 195.15 K. Electron correlation energies were computed via third-order Møller−Plesset perturbation theory (MP3) with the 6-31+G(d) basis set. All energetic values reported herein are given as enthalpies at 195.15 K computed from the MP3 (MP2 for 25)/6-31G+(d) energies.[17]

Summary

Through ab initio molecular orbital calculations and experimentation, we have determined the basis of diastereofacial alkylation for a series of bicyclic lactams, which appears to be governed by electronics and/or steric control. We have also prepared a number of easily accessible chiral, nonracemic bicyclic lactams that display excellent exo alkylation and should be of complementary use in the asymmetric construction of quaternary compounds and chiral pyrrolidines and piperidines. Further investigations into the application of chiral bicylic lactams toward asymmetric syntheses are continuing.

Experimental Section

General Experimental Procedures. All reactions were carried out under argon in septum-stoppered flasks. Unless otherwise noted, reagents were added by syringe and organic extracts were dried over anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator at aspirator pressure (20−40 mm). Flash chromatography was performed with ASA (200−400 mesh) silica gel. Thin-layer chromatography (TLC) was performed with Merck F-254 silica gel plates.

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and ether were distilled under N_2 from sodium/benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2) and toluene were distilled from CaH_2 immediately prior to use. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA.

General Procedure for Pyrrolidinone Dialkylation. Lactam (10). Lactam **9** (2.26 g, 20.00 mmol) was dissolved in THF (30 mL) and cooled to −78 °C. *s*-BuLi (18.0 mL, 1.1 M in hexane) was added dropwise over 5 min to the solution. After 1 h benzyl bromide (3.60 g, 21.0 mmol) was added to the stirred −78 °C solution. Thirty minutes after the addition of benzyl bromide, the solution was quenched with saturated aqueous NH_4Cl solution (10 mL). Ethyl acetate (20 mL) was added to the mixture, and the resulting solution was separated, dried, and concentrated. Filtration through silica (hexanes/EtOAc, 1:1) afforded 3.86 g of a crude colorless oil. The crude dried oil (2.40 g, 11.8 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. *s*-BuLi (10.9 mL, 1.1 M in hexane) was added dropwise to the solution. After 1 h, allyl bromide (1.80 g, 15.0 mmol) was added dropwise, and after an additional 15 min, the solution was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). Ethyl acetate (30 mL) was added to the mixture, and the resulting solution was separated, dried, and concentrated. Purification on silica (hexanes/EtOAc, 2:1) gave lactam **10** (2.72 g, 95%) as a light yellow oil. IR (neat) 3027, 2966, 1686 cm^{-1}. ^1H NMR (300 MHz): δ 0.77 (d, $J = 6.3$, 3H), 1.57 (dd, $J = 13.2$, 6.7, 1H), 2.11 (dd, $J = 13.4$, 8.1, 1H), 2.25 (dd, $J = 13.4$, 8.4, 1H), 2.58 (dd, $J = 13.4$, 6.4, 1H), 2.66 (d, $J = 13.4$, 1H), 2.80 (s, 3H), 3.20 (dd, $J = 13.4$, 1H), 3.41 (m, 1H), 5.15 (d, $J = 9.9$, 1H), 5.20 (d, $J = 18.0$, 1H), 5.83 (ddd, $J = 18.0$ 9.9, 5.3, 1H), 7.24−7.37 (m, 5H). ^{13}C NMR (75 MHz): δ 20.1, 27.5, 34.6, 43.2, 43.4, 49.9, 52.6, 118.7, 126.6, 128.3, 130.6, 134.1, 138.3, 177.2. MS (FAB^+): *m/z* 243 [$(M + H)^+$], 202, 152. HRMS calcd for $C_{16}H_{21}NO$: [$(M + H)^+$] 243.1623. Found: 243.1616.

Lactam (11). Isolated as a light yellow oil. IR (neat): 3027, 2966, 1685 cm^{-1}. ^1H NMR (300 MHz): δ 1.02 (d, $J = 6.0$, 3H), 1.54 (dd, $J = 12.0$, 7.1, 1H), 2.14 (m, 2H), 2.33 (dd, $J = 13.0$, 8.7, 1H), 2.55 (m, 1H), 2.60 (s, 3H), 3.07 (d, $J = 12.9$, 1H), 5.15 (d, $J = 10.1$, 1H), 5.18 (d, $J = 17.1$, 1H), 5.80 (ddd, $J = 17.1$, 10.1, 5.9, 1H), 7.18−7.33

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision B.3*; Gaussian, Inc.: Pittsburgh, PA, 1995.

(16) A scale factor of 0.91 was applied to all vibrational frequencies. Scaled vibrational frequencies below 500 cm^{-1} were treated as classical rotations, while imaginary frequencies were ignored. Grev, R. S.; Janssen, C. L.; Schaefer, H. F., III. *J. Chem. Phys.* **1991**, *95*, 5128.

(17) For a detailed discussion of this procedure, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(m, 5H). ^{13}C NMR (75 MHz): δ 20.3, 27.2, 35.7, 42.7, 43.8, 49.4, 52.1, 118.4, 126.6, 127.9, 129.8, 134.2, 137.6, 177.3. MS (FAB$^+$): *m*/*z* 243 [(M + H)$^+$], 202, 152. HRMS calcd for $C_{16}H_{21}NO$ [(M + H)$^+$]: 243.1623. Found: 243.1616.

General Procedure for Bicyclic Lactam Formation. Lactam (17a). 2-Amino-2-methyl-1-propanol (2.45 g, 27.0 mmol) and levulinic acid (3.13 g, 27.0 mmol) were dissolved in toluene (50 mL). The flask was equipped with a Dean−Stark trap, and the solution was heated to reflux. After 16 h the solution was cooled, washed with saturated aqueous $NaHCO_3$, dried, and concentrated. Chromatography on silica gel (hexane/EtOAc, 1:1) afforded 3.83 g (84%) of lactam **17a** as a colorless solid, mp = 37−38 °C (hexanes/EtOAc). IR (neat): 2975, 1698 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.39 (s, 3H), 1.47 (s, 3H), 1.54 (s, 3H), 2.04 (m, 2H), 2.43 (m, 1H), 2.65 (m, 1H), 3.94 (d, J = 8.6, 1H), 4.02 (d, J = 8.6, 1H). ^{13}C NMR (75 MHz): δ 23.4, 24.2, 26.5, 35.5, 36.0, 57.9, 81.7, 101.0, 172.9. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.65; H, 8.90.

Lactam (8, R = Me). Isolated as yellow oil in 89% yield. IR (neat): 2974, 1713 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.98 (s, 3H), 1.24 (s, 3H), 1.30 (s, 3H), 2.06 (m, 2H), 2.37 (m, 1H), 2.53 (m, 1H), 2.81 (d, J = 11.6, 1H), 3.74 (d, J = 11.6, 1H). ^{13}C NMR (75 MHz): δ 26.6, 27.7, 28.0, 32.3, 34.8, 52.8, 81.3, 99.4, 177.4. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.95; H, 8.97.

Lactam (17c). Isolated as light yellow oil in 90% yield. IR (neat): 2974, 1713 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.79 (d, J = 6.7, 3H), 0.83 (d, J = 6.7, 3H), 0.90 (d, J = 6.7, 3H), 0.95 (d, J = 6.7, 3H), 1.42 (s, 3H), 1.76 (m, 1H), 2.03 (m, 1H), 2.15 (m, 2H), 2.36 (m, 1H), 2.61 (m, 1H), 2.95 (d, J = 12.2, 1H), 3.72 (d, J = 12.2, 1H). ^{13}C NMR (75 MHz): δ 17.9, 18.0, 18.4, 18.6, 27.0, 32.7, 33.3, 33.8, 35.8, 44.0, 92.2, 99.4, 175.0. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.30; H, 10.29. Found: C, 69.19; H, 10.34.

Lactam (17f). Isolated as colorless solid in 87% yield, mp 95−96 °C (hexane/EtOAc). IR (neat): 2977, 1716 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.47 (s, 3H), 2.09 (m, 3H), 2.48 (m, 1H), 3.41 (d, J = 12.3, 1H), 4.90 (d, J = 12.3, 1H), 7.11−7.33 (m, 10H). ^{13}C NMR (75 MHz): δ 27.1, 32.8, 34.6, 53.0, 89.0, 101.0, 126.1, 126.8, 127.7, 128.0, 128.80, 128.82, 144.1, 145.3, 177.7. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.66; H, 6.61.

Lactam (20). Isolated as colorless crystals in 76% yield, mp 89−90 °C (hexanes/EtOAc). $[\alpha]^{23}_D$: +65.3° (*c* 1.4, EtOH). IR (neat): 3407, 2978, 1686 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.65 (s, 3H), 2.39 (m, 2H), 2.60 (m, 1H), 2.85 (m, 2H), 3.70 (m, 1H), 3.76 (m, 2H), 5.14 (d, J = 7.6, 1H), 7.35 (m, 5H). ^{13}C NMR (75 MHz): δ 24.8, 33.4, 35.3, 63.1, 65.0, 82.9, 100.1, 126.3, 128.7, 128.8, 178.6. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.12; H, 6.97.

General Silylation Procedure. Lactam (21). To a CH_2Cl_2 solution (100 mL) of lactam **20** (8.0 g, 33.7 mmol) and TBDPS-Cl (11.1 g, 40.5 mmol) was added neat imidazole (2.8 g, 41.0 mmol) with stirring. After 24 h at 25 °C the slurry was filtered through Celite and concentrated. Recrystallization from hexanes/ethyl acetate afforded lactam **21** (13.9 g, 28.6 mmol) in 85% yield as colorless crystals, mp 127−128 °C (hexanes/EtOAc). $[\alpha]^{23}_D$: +38.7 (*c* 2.0, EtOH). IR (neat): 3409, 2976, 1687 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.00 (s, 9H), 1.53 (s, 3H), 2.23 (m, 2H), 2.49 (m, 1H), 2.74 (m, 1H), 3.75 (m, 1H), 3.87 (m, 2H), 5.30 (d, J = 6.7, 1H), 7.30 (m, 9H), 7.61 (m, 6H). ^{13}C NMR (75 MHz): δ 19.5, 25.3, 26.8, 27.1, 33.6, 34.9, 63.9, 64.0, 83.1, 100.5, 126.8, 127.9, 128.0, 128.5, 128.8, 129.8, 130.0, 130.1, 133.1, 133.3, 135.0, 135.8, 135.9, 139.3, 178.3. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 74.19; H, 7.26. Found: C, 74.04; H, 7.31.

Lactam (17m). Succinic anhydride (5.2 g, 51.5 mmol) and (+)-2-amino-1-phenyl-1,3-propanediol (**19**) (8.6 g, 51.5 mmol) were dissolved in xylenes (1 L), and the mixture was heated to reflux for 1 h. Triethylamine (15 mL) was added, and the reaction mixture was further heated for 36 h, after which the volatiles were removed by atmospheric distillation. The resulting colorless oil was triturated with EtOH/EtOAc to give a colorless solid **28**. The crude colorless compound was dissolved in ethanol (100 mL) and cooled to 0 °C. $NaBH_4$ (9.5 g, 250 mmol) was added with stirring. Hydrochloric acid (2 M) in ethanol was added (∼0.15 mL per minute) over a 3-h period until 1 equiv of acid was added (51.5 mmol). The solution was acidified to a pH of 1−3 by addition of 2 M HCl in ethanol, affording a white suspension which was stirred an additional 3 h at room temperature. The mixture was quenched by the addition of 125 mL of saturated $NaHCO_3$ solution and then extracted with 3 × 75 mL of EtOAc. The combined extracts were dried (K_2CO_3), and the solvent was removed to give a yellow oil. The crude oil was dissolved in CH_2Cl_2 (300 mL) to which 88% formic acid (6 mL) was added with stirring. After 16 h the reaction was quenched by the addition of saturated $NaHCO_3$ solution. The organics were separated off, dried, and concentrated. Silyl ether formation (TBDPS) as in the preceding procedure followed by recrystallization (hexane/EtOAc) afforded lactam (**17m**) as a colorless solid in 60% yield from **19**, mp = 90−91 °C (hexane/EtOAc). $[\alpha]^{23}_D$: +28.2 (*c* 1.5, EtOH). IR (neat): 2930, 1719 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.06 (s, 9H), 2.17 (m, 1H), 2.37 (m, 1H), 2.60 (m, 2H), 3.78 (m, 1H), 3.95 (m, 2H), 5.15 (d, J = 5.8, 2H), 5.36 (dd, J = 6.1, 2.1, 1H), 7.16−7.42 (m, 11H), 7.61 (m, 4H). ^{13}C NMR (75 MHz): δ 19.2, 24.3, 26.9, 31.3, 63.5, 63.9, 82.6, 93.1, 126.3, 127.8, 127.9, 128.3, 128.6, 129.8, 129.9, 133.0, 135.6, 135.7, 139.1, 179.3. Anal. Calcd for $C_{29}H_{34}SiNO_2$: C, 73.85; H, 7.05. Found: C, 73.72; H, 7.08.

Bicyclic Lactam (17o). (*S*)-2-Phenylglycine methyl ester (**26**) (10.0 g, 60.6 mmol) was dissolved in THF (250 mL) and cooled to 0 °C. Phenylmagnesium bromide (61 mL, 3 M in ether) was added to the solution dropwise over 20 min with vigorous stirring. After the addition was complete the cooling bath was removed and the reaction stirred for 18 h at room temperature under Ar. The reaction slurry was quenched at 0 °C by careful addition of saturated NH_4Cl solution (100 mL), extracted with EtOAc (3 × 100 mL), dried, and concentrated to give a yellow oil. This oil was immediately reacted with levulinic acid using the general lactam procedure, providing, after chromatography on silica (EtOAc), lactam (**17o**) as a light yellow solid in 63% yield, mp 126−128 °C (hexane/EtOAc). $[\alpha]^{23}_D$: −118.2 (*c* 1.1, EtOH). IR (neat): 3060, 1713 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.69 (s, 3H), 1.75 (m, 1H), 1.93 (m, 1H), 1.97 (d, J = 12.5, 1H), 2.46 (m, 1H), 6.17 (s, 1H), 6.94 (m, 10H), 7.17 (m, 1H), 7.27 (t, J = 7.0, 2H), 7.54 (d, J = 7.3, 2H). ^{13}C NMR (75 MHz): δ 27.9, 33.0, 37.2, 64.9, 93.8, 101.6, 127.0, 127.1, 127.2, 127.3, 127.7, 127.8, 128.0, 128.7, 129.0, 137.3, 142.4, 144.7, 177.7. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27. Found: C, 81.19; H, 6.30.

General Procedure for Bicyclic Lactam Alkylation. Lactam (18a). Lactam **17a** (280 mg, 1.66 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. *s*-BuLi (1.50 mL, 1.1 M in hexane) was added dropwise to the solution over 5 min. After 2 h benzyl bromide (0.31 g, 1.82 mmol) was added dropwise over 5 min to the stirred −78 °C solution. The reaction solution was quenched after an additional 2 h by addition of saturated aqueous NH_4Cl solution (4 mL). Ethyl acetate (20 mL) was added to the mixture, and the resulting solution was separated, dried, and concentrated. Purification on silica (hexanes/EtOAc, 1:1) afforded 370 mg (86%) of **18a** as a colorless oil. IR (neat): 2974, 1698 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.45 (s, 6H), 1.54 (s, 3H), 1.81 (app t, J = 11.9, 1H), 2.13 (m, 1H), 2.68 (dd, J = 13.7, 9.5, 1H), 3.06 (m, 1H), 3.27 (dd, J = 13.8, 4.3, 1H), 3.92 (d, J = 8.5, 1H), 4.03 (d, J = 8.5, 1H), 7.19−7.35 (m, 5H). ^{13}C NMR (75 MHz): δ 23.6, 24.7, 26.6, 36.6, 42.7, 48.2, 58.3, 81.6, 98.6, 126.5, 128.7, 129.3, 139.6, 173.9. MS (FAB$^+$): *m*/*z* 260 [(M + H)$^+$], 244, 182. HRMS calcd for $C_{16}H_{22}NO_2$ [(M + H)$^+$]: 260.1651. Found: 260.1655.

Lactam (18b). Isolated as a colorless oil in 89% yield. IR (neat): 2976, 1707 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.61 (s, 3H), 1.30 (s, 3H), 1.44 (s, 3H), 1.98 (d, J = 13.7, 1H), 2.40 (m, 2H), 2.75 (d, J = 13.7, 1H), 2.94 (d, J = 11.5, 1H), 3.04 (d, J = 13.4, 1H), 3.81 (d, J = 11.7, 1H), 5.17 (m, 2H), 5.84 (m, 1H), 7.21 (m, 5H). ^{13}C NMR (75 MHz): δ 27.7, 28.6, 42.0, 42.3, 43.4, 52.8, 53.2, 80.7, 96.9, 119.2, 126.7, 128.3, 131.4, 133.8, 137.4, 180.4. MS (FAB$^+$): *m*/*z* 300 [(M + H)$^+$], 284. HRMS calcd for $C_{19}H_{26}NO_2$ [(M + H)$^+$]: 300.1964. Found: 300.1967.

Lactam (18c). Isolated as a colorless oil in 91% yield. IR (neat): 2965, 1707 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.88 (app t, J = 7.0, 6H), 0.99 (app t, J = 7.0, 6H), 1.23 (s, 3H), 1.81 (m, 1H), 2.05 (m, 2H), 2.43 (dd, J = 14.0, 10.1, 1H), 3.01 (m, 4H), 3.89 (d, J = 12.2, 1H), 7.27 (m, 5H). ^{13}C NMR (75 MHz): δ 17.9, 18.1, 18.5, 18.6, 28.8, 33.4, 33.6, 37.5, 38.7, 45.3, 46.9, 91.3, 98.5, 126.5, 128.4, 129.1, 138.6, 178.1. MS (FAB$^+$) *m*/*z* 316 [(M + H)$^+$]: 272. HRMS calcd for $C_{20}H_{30}NO_2$ [(M + H)$^+$]: 316.2276. Found: 316.2269.

Lactam (18d). Isolated as a colorless solid in 93% yield, mp 65−66 °C (hexanes). IR (neat): 2962, 1709 cm^{-1}. ^1H NMR (300 MHz): δ 0.53 (d, $J = 6.7$, 3H), 0.74 (d, $J = 6.7$, 3H), 0.95 (m, 6H), 1.50 (s, 3H), 2.02 (m, 2H), 2.32 (d, $J = 13.4$, 1H), 2.47 (m, 2H), 2.74 (d, $J = 13.7$, 1H), 2.96 (d, $J = 11.9$, 1H, 3.05 (d, $J = 13.7$, 1H), 3.84 (d, $J = 11.9$, 1H), 5.20 (m, 2H), 5.93 (m, 1H), 7.25 (m, 5H). ^{13}C NMR (75 MHz): δ 17.0, 19.1, 19.2, 28.2, 31.8, 34.6, 40.3, 42.8, 44.0, 45.2, 52.9, 90.5, 96.2, 118.8, 126.4, 128.0, 131.2, 133.6, 137.3, 179.0. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36. Found: C, 77.89; H, 9.34.

Lactam (18f). Isolated as a yellow oil in 94% yield. IR (neat): 3026, 2978, 1714 cm^{-1}. ^1H NMR (300 MHz): δ 1.24 (s, 3H), 1.91 (dd, $J = 14.3$, 4.8, 1H), 2.40 (m, 1H), 2.62 (m, 1H), 2.79 (m, 1H), 2.95 (dd, $J = 13.5$, 4.8, 1H), 3.57 (d, $J = 12.2$, 1H), 4.98 (d, $J = 11.9$, 1H), 7.09−7.38 (m, 15H). ^{13}C NMR (75 MHz) δ 27.3, 37.0, 37.2, 44.9, 53.9, 87.7, 99.3, 125.5, 126.0, 126.4, 127.1, 127.3, 128.1, 128.3, 129.0, 138.3, 144.0, 145.0, 180.3. MS (FAB^+) *m/z* 384 [$(M + H)^+$]: 201. HRMS calcd for $C_{26}H_{26}NO_2$ [$(M + H)^+$]: 384.1963. Found: 384.1959.

Lactam (18 g). Isolated as a yellow oil in 95% yield. IR (neat): 3027, 2977, 1712 cm^{-1}. ^1H NMR (300 MHz): δ 1.54 (s, 3H), 1.79 (d, $J = 11.8$, 1H), 1.86 (d, $J = 12.0$, 1H), 2.15 (m, 1H), 2.40 (dd, $J = 13.5$, 6.4, 1H), 2.52 (d, $J = 14.0$, 1H), 2.67 (d, $J = 13.7$, 1H), 3.58 (d, $J = 11.9$, 1H), 5.11 (m, 2H), 5.76 (m, 1H), 7.03 (m, 2H), 7.19−7.48 (m, 13H). ^{13}C NMR (75 MHz): δ 27.3, 41.5, 41.8, 42.8, 51.3, 52.9, 87.8, 97.8, 118.8, 125.5, 126.4, 126.6, 127.2, 127.5, 128.0, 128.30, 128.33, 130.5, 133.9, 137.2, 143.7, 145.3, 181.4. MS (FAB^+) *m/z* 424 [$(M + H)^+$]: 241. HRMS calcd for $C_{29}H_{30}NO_2$ [$(M + H)^+$]; 424.2277. Found: 424.2278.

Lactam (17j). Isolated as colorless oil in 91% yield. $[\alpha]^{23}_D$: −35.1 (*c* 1.1, EtOH). IR (neat): 1711 cm^{-1}. ^1H NMR (300 MHz): δ 0.64 (s, 3H), 1.08 (s, 9H), 1.72 (app t, $J = 11.9$, 1H), 2.01 (m, 1H), 2.47 (dd, $J = 11.9$, 10.3, 1H), 2.91 (m, 1H), 3.30 (dd, $J = 14.1$, 4.0, 1H), 3.82 (dd, $J = 9.2$, 7.7, 1H), 3.93 (dd, $J = 9.4$, 7.6, 1H), 4.30 (app q, $J = 7.6$, 1H), 4.96 (d, $J = 7.6$, 1H), 7.11−7.44 (m, 16H), 7.74 (m, 4H). ^{13}C NMR (75 MHz): δ 19.1, 19.4, 23.4, 26.7, 27.0, 36.5, 42.3, 46.3, 59.8, 67.9, 76.0, 97.9, 126.3, 126.6, 127.4, 127.6, 127.7, 127.8, 127.9, 128.1, 128.5, 128.8, 129.5, 129.6, 129.8, 133.2, 133.7, 134.9, 135.5, 136.0, 136.1, 139.5, 139.8, 178.4. MS (FAB^+) *m/z* 576 [$(M + H)^+$]: 519, 498, 135. HRMS calcd for $C_{37}H_{42}NO_3Si$ [$(M + H)^+$]: 576.2934. Found: 576.2928.

Lactam (18i). Isolated as a colorless oil in 91% yield. $[\alpha]^{23}_D$: −66.2 (*c* 1.5, EtOH). IR (neat): 3069, 2962, 1711 cm^{-1}. ^1H NMR (300 MHz): δ 1.05 (s, 9H), 1.06 (s, 3H), 1.37 (s, 3H), 2.00 (d, $J = 14.0$, 1H), 2.31 (d, $J = 14.0$, 1H), 2.65 (d, $J = 13.5$, 1H), 3.10 (d, $J = 13.4$, 1H), 3.52 (m, 1H), 4.25 (dd, $J = 11.2$, 3.6, 1H), 4.70 (dd, $J = 11.6$, 4.6, 1H), 4.98 (d, $J = 8.3$, 1H), 7.05−7.72 (m, 20H). ^{13}C NMR (75 MHz): δ 19.1, 26.9, 27.4, 43.8, 49.3, 58.3, 64.5, 82.2, 97.2, 126.3, 126.7, 127.7, 127.8, 128.3, 128.4, 129.7, 129.8, 130.5, 133.0, 133.3, 135.8, 135.9, 137.8, 139.6, 179.0. MS (FAB^+) *m/z* 590 [$(M + H)^+$]: 532, 512. HRMS calcd for $C_{38}H_{44}NO_3Si$ [$(M + H)^+$]: 590.3090. Found: 590.3087.

Lactam (18j). Isolated as a colorless oil in 87% yield. $[\alpha]^{23}_D$: +63.8 (*c* 1.9, EtOH). IR (neat): 3067, 2965, 1709 cm^{-1}. ^1H NMR (300 MHz): δ 1.12 (s, 9H), 1.60 (s, 3H), 2.09 (d, $J = 13.8$, 1H), 2.60 (m, 4H), 3.24 (d, $J = 13.4$, 1H), 3.81 (m, 2H), 3.94 (m, 1H), 5.15 (d, $J = 6.7$, 1H), 5.23 (m, 2H), 5.93 (m, 1H), 6.81 (d, $J = 8.0$, 2H), 7.19−7.44 (m, 14H), 7.71 (m, 4H). ^{13}C NMR (75 MHz): δ 19.3, 26.3, 27.0, 41.2, 41.7, 44.1, 53.5, 64.0, 64.9, 81.6, 97.3, 119.3, 126.5, 127.9, 128.0, 128.2, 128.5, 128.6, 129.9, 130.0, 131.3, 133.0, 133.2, 133.7, 135.7, 135.8, 135.9, 137.7, 139.3, 181.7. MS (FAB^+) *m/z* 616 [$(M + H)^+$]: 574. HRMS calcd for $C_{40}H_{46}NO_3Si$ [$(M + H)^+$]: 616.3247. Found: 616.3245.

Lactam (18k). Isolated as a colorless oil in 88% yield. $[\alpha]^{23}_D$: +11.8 (*c* 1.3, EtOH). IR (neat): 3067, 2965, 1709 cm^{-1}. ^1H NMR (300 MHz): δ 0.87 (s, 3H), 1.05 (s, 9H), 2.06 (d, $J = 14.4$, 1H), 2.27 (m, 1H), 2.44 (d, $J = 14.3$, 1H), 2.59 (m, 1H), 2.65 (d, $J = 13.5$, 1H), 3.08 (d, $J = 13.4$, 1H), 3.71−3.98 (m, 3H), 5.05 (d, $J = 7.0$, 1H), 5.15 (m, 2H), 5.73 (m, 1H), 7.19 (m, 10H), 7.35 (m, 6H), 7.68 (m, 4H). ^{13}C NMR (75 MHz): δ 19.1, 24.8, 26.7, 40.7, 43.2, 44.0, 53.2, 63.8, 64.9, 80.9, 97.3, 119.3, 126.2, 126.7, 127.7, 128.0, 128.1, 128.3, 129.7, 130.4, 132.8, 133.9, 135.5, 137.0, 139.3, 182.1. MS (FAB^+) *m/z* 616 [$(M + H)^+$]: 574. HRMS calcd for $C_{40}H_{46}NO_3Si$ [$(M + H)^+$]: 616.3247. Found: 616.3247.

Lactam (18m). Isolated as a colorless solid in 85% yield, mp 109−110 °C (hexane/EtOAc). $[\alpha]^{23}_D$: = +8.2 (*c* 0.8, EtOH). IR (neat): 3029, 2930, 1716 cm^{-1}. ^1H NMR (300 MHz): δ 1.06 (s, 9H), 2.07 (m, 1H), 2.25 (m, 1H), 2.80 (dd, $J = 13.7$, 9.1, 1H), 3.04 (m, 1H), 3.19 (dd, $J = 13.7$, 4.5, 1H), 3.78 (m, 1H), 3.90 (m, 1H), 4.05 (m, 1H), 5.06 (d, $J = 6.1$, 1H), 5.14 (dd, $J = 4.6$, 1.2, 1H), 7.20 (m, 10H), 7.34 (m, 6H), 7.64 (d, $J = 6.5$, 4H). ^{13}C NMR (75 MHz): δ 19.1, 26.8, 29.3, 37.7, 44.2, 63.5, 64.5, 82.3, 91.5, 126.2, 126.5, 127.7, 128.1, 128.4, 128.5, 128.9, 129.7, 129.8, 132.8, 135.5, 138.3, 139.1, 181.4. Anal. Calcd for $C_{36}H_{39}NO_3Si$: C, 76.97; H, 7.00. Found: C, 76.63; H, 6.95.

Lactam (18n). Isolated as a yellow oil in 90% yield. $[\alpha]^{23}_D$: = +60.0 (*c* 1.0, EtOH). IR (neat): 3069, 2929, 1706 cm^{-1}. ^1H NMR (300 MHz): δ 1.02 (s, 9H), 2.20 (m, 3H), 2.50 (dd, $J = 13.4$, 6.4, 1H), 2.63 (d, $J = 13.4$, 1H), 3.15 (d, $J = 13.4$, 1H), 3.65 (m, 2H), 3.91 (dd, $J = 10.7$, 3.6, 1H), 5.05 (d, $J = 6.5$, 1H), 5.11 (m, 2H), 5.81 (m, 1H), 6.73 (dd, $J = 7.9$, 2.1), 7.10−7.38 (m, 16H), 7.60 (m, 4H). ^{13}C NMR (75 MHz): δ 19.3, 26.9, 33.9, 42.5, 44.0, 53.7, 62.9, 63.7, 82.5, 90.3, 119.1, 126.3, 126.5, 127.8, 127.9, 128.2, 128.4, 128.5, 129.9, 130.0, 131.1, 132.9, 133.4, 135.6, 135.7, 137.6, 139.0, 179.9. MS (FAB^+) *m/z* 602 [$(M + H)^+$]: 544, 524, 135. HRMS calcd for $C_{39}H_{44}NO_3Si$ [$(M + H)^+$]: 602.3090. Found: 602.3087.

Lactam (18o). Isolated as a light yellow solid in 92% yield, mp 118−119 °C (hexane/EtOAc). $[\alpha]^{23}_D$: −114.5 (*c* 0.4, $CHCl_3$). IR (neat): 3062, 1713 cm^{-1}. ^1H NMR (300 MHz): δ 1.81 (s, 3H), 1.96 (d, $J = 13.3$, 1H), 2.13−2.30 (m, 3H), 2.50 (m, 1H), 5.02 (d, $J = 4.9$, 1H), 5.08 (s, 1H), 5.69 (m, 1H), 6.34 (s, 1H), 7.07 (m, 10H), 7.27 (t, $J = 6.9$, 1H), 7.35 (t, $J = 7.0$, 2H), 7.66 (d, $J = 7.4$, 2H). ^{13}C NMR (75 MHz): δ 31.0, 36.2, 40.2, 43.6, 66.1, 93.0, 99.8, 117.2, 126.9, 127.0, 127.2, 127.4, 127.6, 127.7, 128.3, 129.0, 135.3, 136.8, 142.1, 144.3, 181.0. MS (FAB^+) *m/z* 410 [$(M + H)^+$]: 227. HRMS calcd for $C_{28}H_{28}NO_2$ [$(M + H)^+$]: 410.2120. Found: 410.2113.

Lactam (18p). Isolated as a light yellow solid in 93% yield, mp 155−156 °C (hexane/EtOAc). $[\alpha]^{23}_D$: −131.2 (*c* 0.4, $CHCl_3$). IR (neat): 3062, 3029, 1712 cm^{-1}. ^1H NMR (300 MHz) δ 1.25 (s, 3H), 2.19 (dd, $J = 13.9$, 7.5, 1H), 2.27 (d, $J = 14.2$, 1H), 2.51 (d, $J = 14.2$, 1H), 2.93 (d, $J = 13.4$, 1H), 3.20 (d, $J = 13.4$, 1H), 5.01 (dd, $J = 17.0$, 1.2, 1H), 5.12 (dd, $J = 10.0$, 1.2, 1H), 5.56 (m, 1H), 6.57 (s, 1H), 7.00 (d, $J = 7.3$, 2H), 7.17−7.29 (m, 8H), 7.41−7.56 (m, 6H), 7.62 (t, $J = 7.7$, 2H), 7.93 (d, $J = 7.3$, 2H). ^{13}C NMR (75 MHz): δ 29.2, 41.9, 42.7, 43.8, 52.0, 66.4, 93.1, 98.0, 118.9, 126.7, 127.2, 127.5, 127.6, 127.8, 128.3, 128.4, 128.5, 130.7, 133.3, 137.1, 137.5, 141.8, 144.3, 182.2. MS (FAB^+) *m/z* 500 [$(M + H)^+$]: 317. HRMS calcd for $C_{35}H_{34}NO_2$ [$(M + H)^+$]: 500.2590. Found: 500.2595.

Lactam (2, R = *i*-Pr, R^1 = Bn, R^2 = CH_3). Isolated as a colorless oil in 91% yield. $[\alpha]^{23}_D$: −74.2 (*c* 1.2, EtOH). IR (neat): 2960, 1710 cm^{-1}. ^1H NMR (300 MHz): δ 0.73 (s, 3H), 0.81 (d, $J = 6.7$, 3H), 1.03 (d, $J = 6.7$, 3H), 1.25 (s, 3H), 1.47 (m, 1H), 1.97 (d, $J = 14.1$, 1H), 2.15 (d, $J = 14.1$, 1H), 2.55 (d, $J = 13.1$, 1H), 3.05 (d, $J = 13.4$, 3H), 3.60 (m, 2H), 4.11 (m, 1H), 7.14−7.29 (m, 5H). ^{13}C NMR (75 MHz): δ 18.9, 20.7, 23.8, 27.1, 34.3, 43.5, 45.2, 49.1, 62.5, 70.0, 96.6, 126.7, 128.2, 130.3, 137.6, 183.9. MS (FAB^+) *m/z* 288 [$(M + H)^+$]: 272. HRMS calcd for $C_{18}H_{26}NO_2$ [$(M + H)^+$]: 288.1964. Found: 288.1964.

Ketoester (22). Isolated as a colorless oil in 71% yield from lactam (**21**). $[\alpha]^{23}_D$: −5.3 (*c* 1.1, $CHCl_3$). IR (neat): 2960, 1718, 1684 cm^{-1}. ^1H NMR (300 MHz): δ 0.91 (t, $J = 7.4$, 3H), 1.22 (s, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 2.09 (s, 3H), 2.55 (d, $J = 18.0$, 1H), 2.79 (d, $J = 18.0$, 1H), 2.92 (m, 2H), 4.05 (t, $J = 6.4$, 2H), 7.06 (m, 2H), 7.26 (m, 3H). ^{13}C NMR (75 MHz): δ 13.6, 19.1, 22.2, 30.5, 44.2, 44.6, 50.3, 64.4, 126.6, 128.0, 130.3, 137.0, 176.3, 206.2. MS (FAB^+) *m/z* 277 [$(M + H)^+$]: 203. HRMS calcd for $C_{17}H_{25}O_3$ [$(M + H)^+$]: 277.1804. Found: 277.1809.

Cyclopentenone (23). To a −78 °C THF solution (60 mL) of lactam (**21**) (4.02 g, 6.54 mmol) was added Red-Al (1.95 mL, 3.4 M in toluene) over 15 min. The −78 °C bath was replaced with a 0 °C cooling bath, and the reaction was monitored for the disappearance of starting material by TLC. After 6 h the reaction was quenched by the addition of methanol (1.5 mL), concentrated, extracted with EtOAc (3 × 50 mL),

washed with 10% aqueous NaOH and H_2O, then dried and concentrated. The resulting crude residue was dissolved in EtOH (125 mL) and aqueous 1 M $Bu_4NH_2PO_4$ solution (125 mL) and stirred at room temperature for 36 h. The reaction solution was concentrated, extracted with ether, dried, and concentrated. The resulting yellow oil was dissolved in 100 mL of THF, and 1.5 mL of 1 M KOH in ethanol was added. After 2 h the reaction solution was diluted with ether (75 mL), washed with H_2O, dried, and concentrated. Purification on silica (hexane/EtOAc, 4:1) afforded cyclopentenone (**23**) as a colorless oil in 69% yield. $[\alpha]^{23}_D$: −62.6 (*c* 1.7, EtOH), (lit.[13] $[\alpha]_D^{23}$ −64.1). IR (neat): 3028, 2916, 1714 cm^{-1}. ^1H NMR (300 MHz): δ 2.27 (d, J = 1.5, 2H), 2.30 (m, 2H), 2.77 (d, J = 3.4, 1H), 2.90 (d, J = 3.4, 1H), 5.06 (m, 2H), 5.65 (m, 1H), 6.04 (d, J = 5.8, 1H), 7.07 (m, 2H), 7.25 (m, 3H), 7.44 (d, J = 5.8, 3H). ^{13}C NMR (75 MHz): δ 42.8, 44.6, 45.3, 49.1, 119.3, 126.7, 128.2, 130.3, 133.2, 133.4, 136.7, 170.2, 213.0. MS (FAB^+) *m*/*z* 213 $[(M + H)^+]$: 171. HRMS calcd for $C_{25}H_{16}O$ $[(M + H)^+]$:213.1279. Found: 213.1278.

Acknowledgment. This paper is dedicated to Professor E. J. Corey on the occasion of his 70th birthday. A.I.M. and M.A.S. are grateful to the National Institutes of Health and the National Science Foundation for financial support of this study.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all compounds, complete X-ray structural parameters (bond angles, etc.) for **12**, and chiral HPLC of lactam **17o**, both enantiomers (62 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA980614S