Tandem α-Cyano Enamine/Enolate Alkylations on Bicyclic Lactams: Asymmetric Carbocycle and Heterocycle Synthesis

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The alkylation of cyano enamines **1** and **7** with α,ω-dihalides (or dihalide equivalents), followed by hydrolysis to reveal the lactam carbonyl, provided lactams **8** and **10** containing a tethered electrophile. Intramolecular cyclization of the pendant halide onto the lactam enolate provided tricyclic lactams **9** and **13**, which were subjected to a second enolate alkylation to form a quaternary stereocenter. In the case of *nor*-ephedrine tricyclic lactam **13**, the intermolecular was highly *endo* selective, and the resultant lactams **14** were subjected to partial reduction and hydrolytic auxiliary cleavage to provide enantiopure octalones **16** and **17**. From this chemistry came the synthesis of the "Woodward ketone" **19**, an intermediate in the total synthesis of a number of steroids. Finally, the methoxymethyl bicyclic (or tricyclic) lactams **33** were shown to undergo nonreductive cleavage of the chiral auxiliary to provide 3,4-dihydropyridones containing a quaternary center.

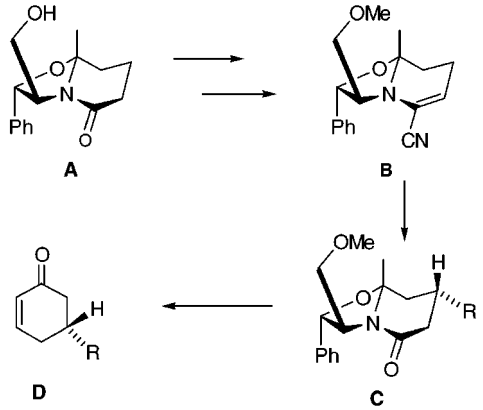
Introduction

We recently reported the preparation of an α-cyano enamine **B** from a chiral bicyclic lactam that, when metalated, underwent completely stereoselective alkylation at the γ-carbon (Scheme 1).[1] Hydrolysis of the alkylated cyano enamine revealed the lactam carbonyl, and subsequent reduction and auxiliary cleavage provided enantiopure 5-substituted cyclohexenones **D**. It was envisioned that if β-substituted lactams **C** contained a pendant electrophilic component, formation of the lactam enolate and intramolecular cyclization would provide tricyclic lactams of various ring sizes. Bicyclic lactams have previously been shown to undergo a variety of carbocyclic ring-forming reactions with high diastereoselectivity.[2] Hence, cyclobutanes,[3] cyclopentanes,[4] cyclopentenes,[5] and cyclohexenes[6] have been appended to 5,5-bicyclic lactams and were subsequently transformed to enantiopure bicyclic carbocycles and heterocycles. This paper will discuss our efforts to construct tricyclic lactams from systems of type **C** and elaborate them to useful chiral, nonracemic products.

Results and Discussion

A. Allylation of Cyano Enamine 1 Leading to Formation of a Cyclobutane. It was envisioned that β-allyl bicyclic lactam **2**,[1] prepared by allylation/hydrolysis of cyano enamine **1**, could be elaborated to a cyclobutane-fused tricyclic lactam (Scheme 2). First, a benzyl group was installed via an enolate alkylation of **2** using

Scheme 1



LDA and benzyl chloride at −78 °C to afford **3** as a 3:1 mixture of epimers (determined by ^{1}H NMR integration of the angular methyl singlets). Pure *exo*-diastereomer was isolated by chromatography and used for characterization in the synthetic sequence. Subsequent oxidative cleavage of the terminal olefin in **3** with catalytic OsO_4 and periodate,[7] followed by in situ reduction of the aldehyde by sodium borohydride (MeOH, 0 °C), gave hydroxy lactam **4** in 66% yield. Bromination of **4** (NBS/PPh_3)[8] proceeded smoothly (84%), and following enolization of **5** with LDA in THF/HMPA at 0 °C, the cyclobutane **6** was formed in 69% yield. As expected, the positioning of the benzyl moiety on the β-face of **6** resulted in an extreme upfield signal for the angular methyl group (0.5 ppm), a phenomenon observed earlier[9] in bicyclic lactam enolate alkylations.

B. Alkylation of Cyano Enamine Anion with α,ω-Dihalides. A more expedient route for annulation than the oxidation/bromination sequence involving a terminal

(1) Schwarz, J. B.; Meyers, A. I. *Tetrahedron* **1997**, *53*, 8795.
(2) For reviews of the chemistry of bicyclic lactams, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.
(3) (a) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306. (b) Meyers, A. I.; Tschantz, M. A.; Brengel, G. P. *J. Org. Chem.* **1995**, *60*, 4359.
(4) Brengel, G. P.; Rithner, C.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 5144.
(5) Meyers, A. I.; Bienz, S.; Kwon, H.-B.; Wallace, R. H. *Helv. Chim. Acta* **1996**, *79*, 1026.
(6) Meyers, A. I.; Busacca, C. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299.
(7) Reinecke, M. G.; Kray, L. R.; Francis, R. F. *J. Org. Chem.* **1972**, *37*, 3489.
(8) Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446. Castro, B. R. *Org. React.* **1983**, *29*, 1.
(9) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936.

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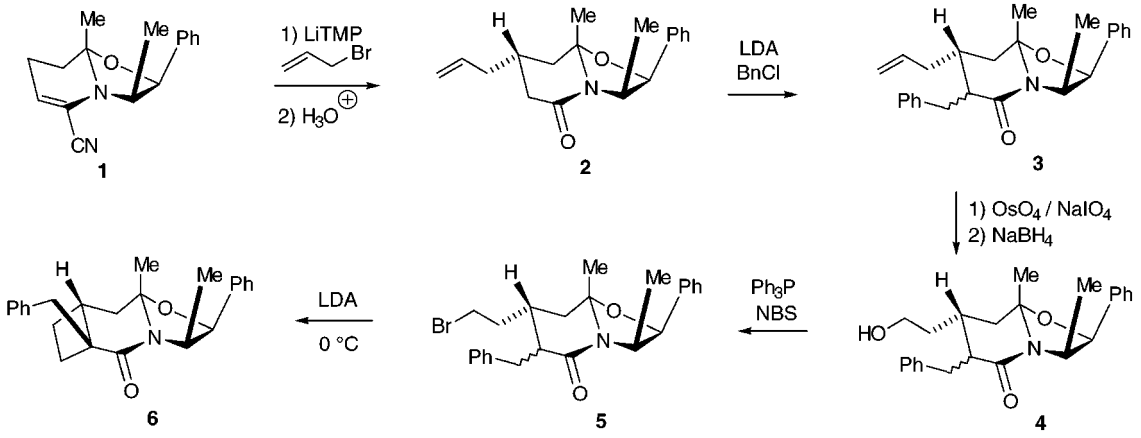
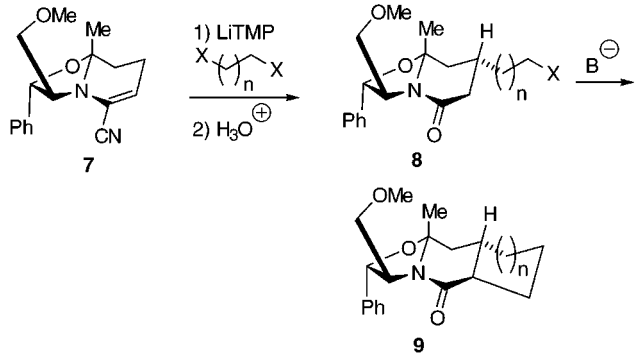
Scheme 2



olefin described above was sought. If cyano enamine **1** or **7** could be monoalkylated with an α,ω-dihalide, the pendant alkyl or allylic halide in **8** would then be available for further use in an enolate alkylation to furnish tricyclic lactams of type **9**. Indeed, this proved to be the case. Table 1 describes the results with various dihalide electrophiles.



Some interesting observations may be gleaned from Table 1. First, use of a chloro/iodoalkane for alkylation of **7** rather than a diiodoalkane resulted in markedly improved yields for the three- and four-carbon electophiles (Table 1, entries 1−4). Longer carbon chains (C_5, C_6) containing a terminal chloride or iodide could also be introduced (Table 1, entries 5−7). An unsaturated chlorinated side chain could be incorporated into **7**, but not an aromatic dihalide (Table 1, entries 8, 9, and 12). Optimal results were obtained using method B (Table 1, entries 8, 10−12). Thus, a combination of more cosolvent (2.0 vs 1.3 equiv of HMPA), less electrophile (1.5 vs 2.0 equiv of dihalide) and the use of inverse addition of the base to the cyano enamine all contributed to a marked improvement in yields of products. Presumably, this is the result of a more reactive cyanoallyl anion from **7** and/or fewer byproducts that result from competitive halide elimination.

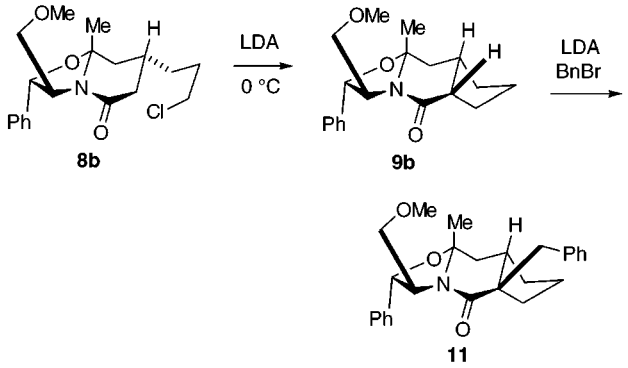
C. Intramolecular Enolate Alkylation Annulations. With the β-haloalkyl and allylic substituents incorporated into lactams **8** and **10**, the ring-forming enolate cyclizations were examined. Unfortunately, seven- or eight-membered rings (from lactams **8e** or **8g**) did not form using LDA in THF/HMPA at ambient temperature. Cyclopentane-fused tricyclic lactam **9b** was formed readily from chlorolactam **8b** in 74% yield as a single diastereomer (as determined by ^{1}H NMR and GLC analysis). Formation of an α-quaternary center was effected with LDA/benzyl bromide in THF/HMPA at 0 °C, furnishing **11** in 54% yield. The extreme upfield shift exhibited for the angular methyl of **11** (0.7 ppm) indicated that the benzyl halide entered the enolate from the β-face. The selectivity may be attributed to two factors: (a) both groups, fused cyclopentane and the phenyl, hinder approach of the electrophile to the α-face, and (b) the five-membered ring can assume a *cis*-fusion if the benzyl group enters the enolate from the β-face.

The six-membered ring analogue of **9b**,**d** was also formed as a single diastereomer (57%), but HMPA was required to promote the cyclization. Alkylation of tricycle **9d** resulted in not only a low conversion to product **12**

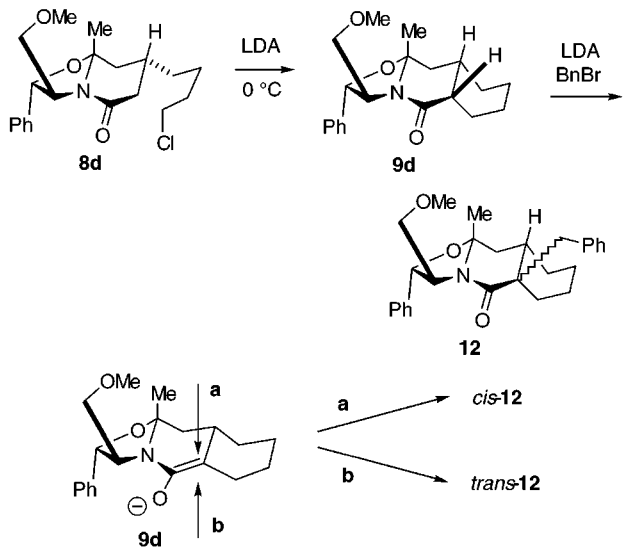
Table 1. Alkylation of Cyano Enamines 1 and 7 with α,ω-Dihalides

Entry	Cyano-enamine	Dihalide	Method[a]	Lactam	Yield(%)[b]
1	**7**	I∼∼I	A	**8a**	31
2	**7**	I∼∼Cl	A	**8b**	49
3	**7**	I∼∼∼I	A	**8c**	37
4	**7**	I∼∼∼Cl	A	**8d**	53
5	**7**	I∼∼∼∼I	A	**8e**	47
6	**7**	I∼∼∼∼Cl	A	**8f**	48
7	**7**	I∼∼∼∼∼I	A	**8g**	50
8	**7**	Cl∼=∼Cl	A	**8h**	49
9	**7**	Br, Br (o-xylyl)	A	--	0
10	**1**	I∼∼∼Cl	A	**10a**	45
11	**1**	I∼∼∼Cl	B	**10a**	68
12	**1**	Cl∼=∼Cl	B	**10b**	67

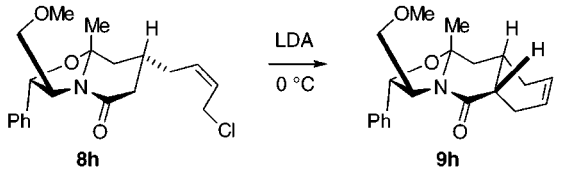
[a] Method A: Addition of the cyano enamine in THF to 1.3 equiv of LiTMP and 1.3 equiv of HMPA at −78 °C, followed by addition of 2.0 equiv of dihalide. Method B: Addition of a solution of 1.3 equiv of LiTMP and 2.0 equiv of HMPA in THF to the cyano enamine at −78 °C, followed by addition of 1.5 equiv of dihalide, see the Experimental Section. [b] Isolated yield of single diastereomer (^{1}H NMR) after flash chromatography.



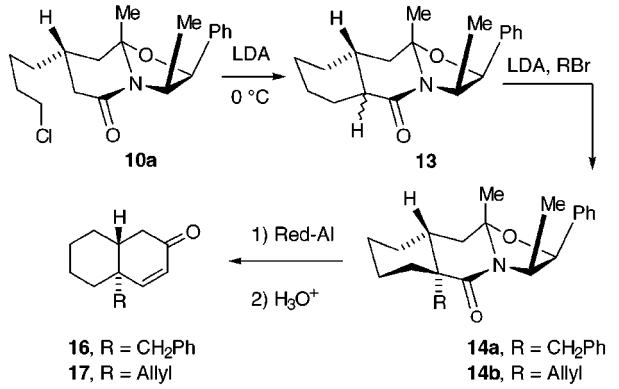
(ca. 50%) but also poor stereoselectivity (3:1, *exo*:*endo* as determined by the angular methyl shifts in the ^{1}H NMR spectra). Again, two factors may contribute to the stereoselectivity: (a) *exo*-alkylation was favored because of the presence of two groups on the α-face, (b) there may have been no preference to the facial approach of the enolate since both are expected to have similar transition-state energies. Furthermore, the 6,6-ring fusion (decalin) is known to have only a small thermodynamic preference for trans.[10]



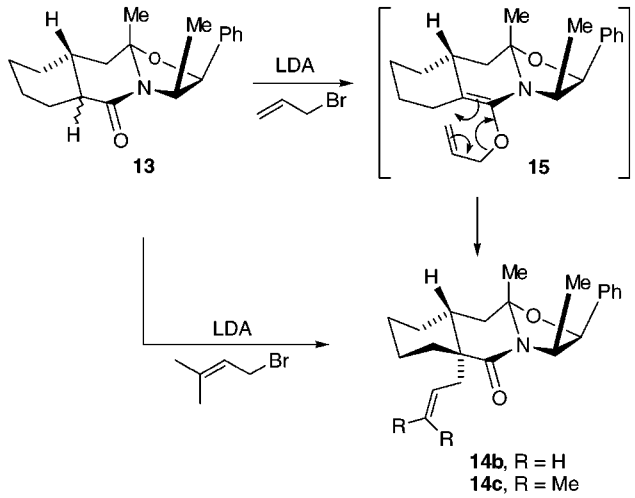
Lactam **8h**, containing a pendant allylic chloride, ring-closed upon enolization in the absence of HMPA to furnish tricyclic lactam **9h** as a single diastereomer in 49% yield (31% of starting lactam **8h** was also recovered). The unsaturation in the system would potentially be amenable to further manipulation to provide more complex systems, but the lack of selectivity in the quaternary alkylation step in lactam **9d** could potentially diminish the utility of the process.



Chlorolactam **10a**, derived from *nor*-ephedrine, cyclized smoothly (82%) with LDA in THF/HMPA at 0 °C to provide tricycle **13** as a 1:1 mixture of diastereomers (determined by ^{1}H NMR and GLC analysis). This result was in contrast to the ring closures of the earlier systems **8** in which a single diastereomer was formed. One potential rationale for the lack of selectivity could be that the position of the phenyl group on the β-face in the *nor*-ephedrine series diminishes the steric crowding on the α-face, thus providing equal facial bias for the approaching tether. Of course, the stereoselectivity of the ring closure was of no consequence as enolization and alkylation to provide the quaternary carbon was to be performed. Unlike the earlier analogue **9d**, alkylation of the enolate of **13** gave a single diastereomer **14a** (GLC) corresponding to *endo*-approach of the benzyl group in 82% yield. As with previous examples, benzyl bromide was chosen as the electrophile to verify the stereochemistry of addition. The absence of an upfield angular methyl group shift in the ^{1}H NMR spectrum (1.6 ppm) indicated that the benzyl group occupied the α-face of lactam **14a**.



Interestingly, deprotonation of **13**, followed by quench with allyl bromide at −78 °C, afforded only a 2:1 mixture of *exo*/*endo* tricyclic lactams **14b**. The possibility existed

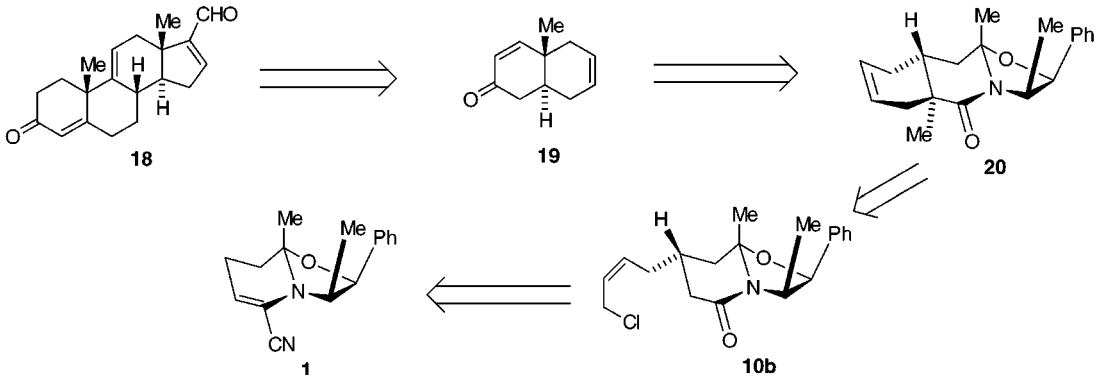


that one of the epimers of **14b** may have been formed via a Claisen rearrangement of *O*-allylated intermediate **15**. The thio-Claisen rearrangement of related bicyclic thiolactams is known to occur at the *exo*-face.[11] Hence, competing allylation at oxygen and carbon would account for the alkylation on both faces of **13**. If the Claisen pathway was indeed operational, replacement of allyl

(10) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons, Inc: New York, 1994.

(11) Devine, P. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 2633.

Scheme 3

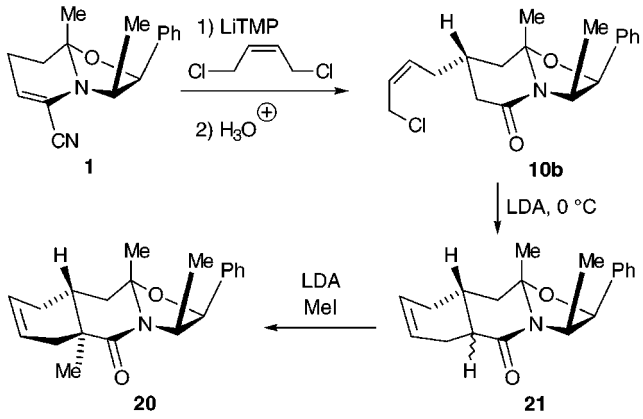


bromide with the more-hindered prenyl bromide should (a) eliminate the rearrangement pathway or (b) lead to the isomeric allylated product. When lactam **13** was treated with LDA and prenyl bromide using the same conditions for allylation, only SN_2 product **14c** was isolated in excellent yield (88%) as a single diastereomer. Thus, the alkylation with prenyl was far superior to allyl, which may be due to the more sterically endowed electrophile. Also, for further synthetic manipulation, the high stereoselectivity of the prenyl alkylation would provide much greater utility than the allyl halide.

D. Reduction/Hydrolysis of Tricyclic Lactams To Provide Enantiopure Octalones. To demonstrate the versatility of tricyclic lactams **14** toward more generally useful chiral products, they were shown to reduce cleanly with Red-Al (THF, 0 °C to ambient temperature) to the carbinolamines, which were not isolated but directly subjected to hydrolysis with tetrabutylammonium dihydrogen phosphate (EtOH−H_2O, reflux). The intermediate keto aldehyde was not isolated and underwent spontaneous aldol cyclization to afford octalones **16** and **17**. Because racemization at either the quaternary or tertiary stereocenters was highly unlikely in the reduction/hydrolysis sequence, the octalones were presumed to be optically pure and were obtained in overall yields of 72−79% from lactams **14**. From the cyano enamine **1**, the octalones were produced in ca. 30% overall yield for the six-step sequence.

E. Asymmetric Synthesis of a Steroid Intermediate (The "Woodward Ketone"). As an extension of the asymmetric carbocycle synthesis described above, it was envisioned that bicyclic ketone **19** could be obtained by a predictable sequence (Scheme 3). Enone **19** was used as a racemate by Woodward in the synthesis of *dl*-$\Delta^{9(11),16}$-bisdehydro-20-norprogesterone (**18**) in 1952.[12] The steroid nucleus **18** has been transformed into progesterone, desoxycorticosterone, testosterone, androsterone, cholesterol, and cortisone. Although enone **19** was later prepared as a single enantiomer via a kinetic resolution,[13] no asymmetric synthesis has been reported to date. In a retrosynthetic sense, reduction and hydrolytic cleavage of tricyclic lactam **20** would provide the desired enone, whereas lactam **20** would be obtained from annulation and stereoselective methylation of allylic chloride **10b**. The prerequisite bicyclic precursor **10b** would arise from stereoselective alkylation of *nor*-ephedrine-derived cyanoenamine **1** with *cis*-1,4-dichloro-2-butene.

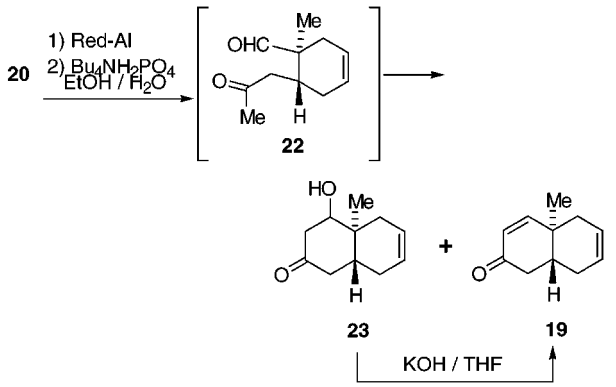
The sequence was initiated by allylation of the lithiated cyanoenamine from **1**, providing the necessary chlorolactam **10b** in 68% yield after hydrolysis (1 N HCl/THF). Cyclization of **10b** with 1.5 equiv of LDA at 0 °C in the presence of 1.5 equiv of HMPA resulted in the tricyclic lactam **21** as a 1:1 mixture of diastereomers. This was determined by integration of the proton α to nitrogen in each epimer in the ^1H NMR spectrum. Once again, the mixture was of no consequence as alkylation (LDA, MeI, 0 °C) gave **20** as a single stereoisomer, presumably due to *endo* approach of the electrophile as observed earlier for the saturated lactams **13**. Lactam **20** was formed in 63% overall yield from chlorolactam **10b**.



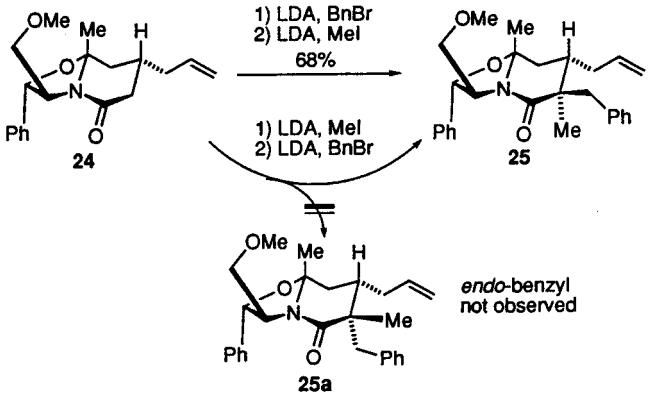
With the chiral precursor to the Woodward ketone in hand, the reduction/hydrolysis step was investigated. Partial reduction of lactam **20** with Red-Al, as before, provided the carbinolamine, which was not isolated but directly hydrolyzed (phosphate buffer, EtOH/H_2O, reflux). Two products were isolated by chromatography following the hydrolysis, the desired enone **19** (40%) and hydroxy ketone **23** (35%), which failed to spontaneously dehydrate under the reaction conditions employed. However, when **23** was subjected to base-catalyzed aldol conditions (KOH, THF, reflux), the enone **19** was obtained in 90% yield. Including the aldol step, the Woodward ketone was obtained from tricyclic lactam **20** in 72% overall yield. The optical rotation of synthetic **19**, $[\alpha]^{23}_D$ +226 (*c* 1.00, $CHCl_3$), matched well with the literature value,[13] $[\alpha]^{23}_D$ −239 (*c* 1.00, $CHCl_3$), indicating that no unexpected racemization of either the quaternary or the tertiary stereocenter occurred during the reduction/hydrolysis sequence. From cyano enamine **1**, the steroid intermediate **19** was synthesized in 31% yield over seven steps. The (−)-enantiomer of **19** was used by the Monsanto

(12) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.
(13) Speziale, A. J.; Stephens, J. A.; Thompson, Q. E. *J. Am. Chem. Soc.* **1954**, *76*, 5011.

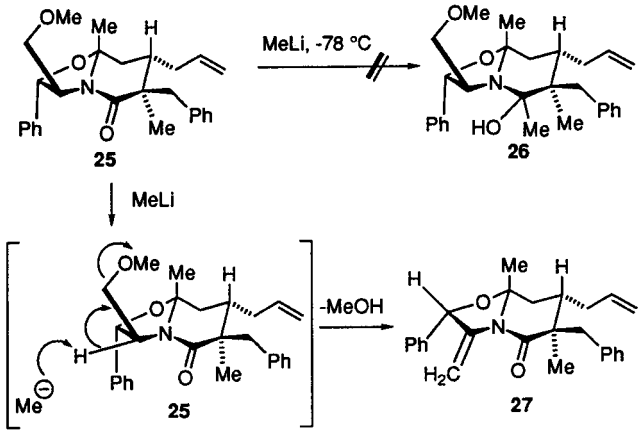
group[13] to synthesize norprogesterones with the same absolute configuration as rings C and D in natural steroids.



F. An Asymmetric Route to Chiral Heterocycles. Nonreductive Auxiliary Cleavage. Sequential intermolecular alkylation of β-allyl lactam **24**[1] with benzyl bromide followed by methyl iodide afforded trisubstituted lactam **25** as a single diastereomer. The stereochemistry was confirmed by an X-ray crystal structure. The *endo*-selectivity was consistent with previous studies[9] using the lactams containing a free hydroxyl group. However, when the order of alkylation was reversed, no product corresponding to *endo*-benzylation was observed. This result was in accordance with the attempted benzylation of tricyclic lactams **9b** and **9d**, which gave poor selectivity favoring *exo*-alkylation. Apparently, a steric barrier to *endo*-alkylation of the β-substituted systems exists that could be overcome by a methyl, but not a benzyl, electrophile. Further studies of the steric requirements for alkylation of these systems should prove to be interesting and are currently under investigation.

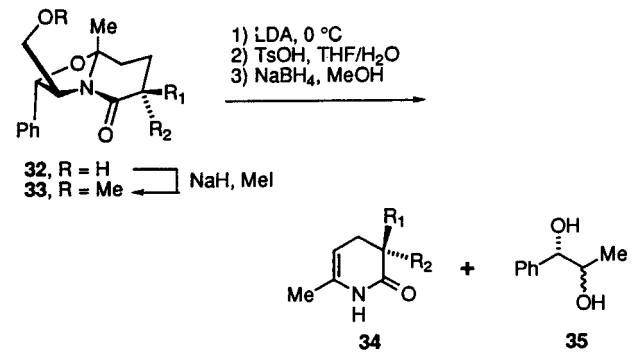


Lactam **25** was treated with methyllithium in an attempt to transform it into a carbocyclic system as described above for the *nor*-ephedrine series. However, no addition to the lactam carbonyl was observed. In fact, the product obtained corresponded to loss of methanol by ^{1}H NMR and GC/MS analysis, suggesting enamide **27** as the product, formed in nearly quantitative yield. A similar elimination was reported recently by Kodama *et al.*[14,15] using benzyl ethers. These authors assumed that an anion was generated at the benzylic position and abstracted a proton β to the ether oxygen, similar to the [2,3]-Wittig rearrangement. There exists the possibility that the elimination of methanol in **25** proceeds in a similar fashion, as opposed to direct deprotonation, and this mechanism should not be ruled out.



Treatment of enamide **27** with *p*-toluenesulfonic acid in refluxing THF/H_2O appeared to result in angular cleavage to **28**, with concomitant hydrolysis of the imine **29** to liberate dihydropyridone **30** (76%) and α-hydroxy ketone **31** (Scheme 4). The optical rotation of **31**, $[\alpha]^{23}_D$ +413 (*c* 0.82, $CHCl_3$), matched well with the literature value,[16] $[\alpha]^{23}_D$ +400 (*c* 1.00, $CHCl_3$), indicating that no racemization of the hydroxyl-bearing carbon occurred under the hydrolytic conditions employed. Presumably, dihydropyridone **30** was formed with a high degree of optical purity since any racemization of the stereocenters present was unlikely.

To evaluate the applicability of the nonreductive auxiliary-cleavage protocol toward simpler systems, hydroxy lactams **32** synthesized previously[9,17] were examined. Thus, the α-benzyl/allyl,[9] benzyl/methyl,[9] and ethyl/allyl[17] derivatives of **32** were subjected to the nonreductive strategy. First, the free hydroxyl was methylated (NaH/MeI) to provide lactams **33** in 80−86% yield. Lactams **33** were then treated with strong base (LDA, 0 °C), and the resulting enamide was hydrolyzed (TsOH, THF/H_2O, reflux). Since the resulting pyridones **34** and hydroxy ketone **31** were found to be inseparable, the mixture containing the ketone was reduced ($NaBH_4$, MeOH, 0 °C) to afford diol **35**, which was readily separated by flash chromatography. The pyridones **34** were obtained in overall yields from lactams **33** in 52−64% yields. The results are described in Table 2.



Furthermore, tricyclic lactam **11**, prepared by cyano enamine alkylation of **7** with 1-chloro-3-iodopropane,

(14) Matsushita, M.; Nagaoka, Y.; Hioki, H.; Fukuyama, Y.; Kodama, M. *Chem. Lett.* **1996**, 1039.
(15) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117.

Scheme 4

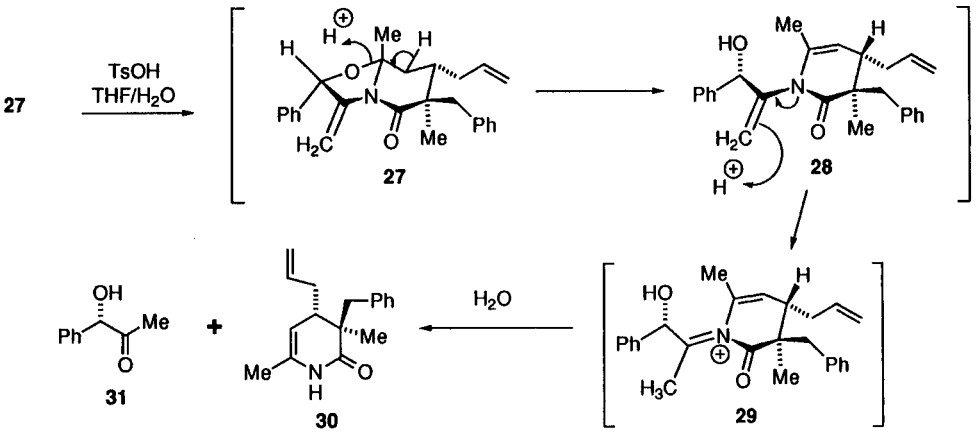
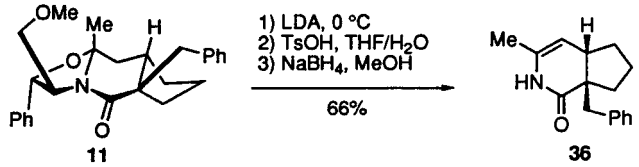


Table 2. Transformation of Lactams 33 to Dihydropyridones 34

entry	lactam	R_1	R_2	pyridone	yield (%)	$[\alpha]^{23}_D$
1	**33a**	allyl	Bn	**34a**	53	+12.7
2	**33b**	Bn	allyl	**34b**	64	−10.6
3	**33c**	Bn	Me	**34c**	56	−18.9
4	**33d**	Et	allyl	**34d**	52	−5.9

intramolecular ring closure to **9b**, and subsequent *exo*-benzylation as described earlier, was subjected to the deprotonation/hydrolysis conditions. After the reductive workup and flash chromatography, bicyclic dihydropyridone **36** was obtained in 66% overall yield from **11**.



In summary, the scope of the α-cyano enamine alkylations described earlier[1] has been expanded to include polycyclic ketone and dihydropyridones in high enantiomeric excess. Alkylation of cyano enamines **1** or **7** with α,ω-dihalides and subsequent hydrolysis provided lactams **8** or **10** containing a tethered electrophile for enolate alkylations. The alkylations of *nor*-ephedrine tricyclic systems **13** and **21** were highly stereoselective, and the resultant quaternary substituted lactams **14** and **20** were amenable to hydride reduction/hydrolysis to provide enantiopure carbocycles. An extension of this chemistry was used to construct the enantiomer of the Woodward ketone (+)-**19** in an efficient manner. Finally, a novel, nonreductive cleavage of the amino diol auxiliary was examined and applied toward the synthesis of optically pure di- and trisubstituted dihydropyridones.

Experimental Section

Thin-layer chromatography (TLC) and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230−400 mesh). All reagents were purchased from Aldrich. All nonaqueous reactions were conducted under an argon atmosphere in a flame-dried apparatus. Tetrahydrofuran was distilled from sodium−benzophenone ketyl under argon atmosphere prior to use. HMPA was distilled from calcium hydride under reduced pressure prior to use. Alkyl halides were passed through a plug of basic Al_2O_3 prior to use.

α-Benzyl-β-allyl Bicyclic Lactam 3. To a stirred solution of diisopropylamine (0.32 mL, 2.28 mmol) in 3.0 mL of THF at 0 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.95 mL, 2.19 mmol) dropwise. The mixture was stirred for 5 min at 0 °C and then transferred dropwise via cannula to a stirred solution of lactam **2**[1] (0.52 g, 1.82 mmol) in 6.0 mL of THF at −78 °C. Stirring was continued at −78 °C for 15 min, at which time benzyl chloride (0.26 mL, 2.28 mmol) was added dropwise. The mixture was allowed to warm slowly to ambient temperature over 12 h and then was partitioned between ether (20 mL) and saturated NH_4Cl (aq, 20 mL). The phases were separated, and the aqueous phase was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue provided 0.16 g (23%) of *exo*-α-benzyl lactam **3** as a single diastereomer and 0.23 g (34%) of a 5.3:1 mixture of *exo*:*endo*-α-benzyl diastereomers. The stereochemistry of the newly introduced benzyl group was determined by integration of the angular methyl singlets in the ^{1}H NMR spectrum. Pure lactam **3**: $[\alpha]^{23}_D$ +121 (*c* 1.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, J = 7.0 Hz, 3H), 0.89 (s, 3H), 1.37 (app t, J = 13.2 Hz, 1H), 1.79 (m, 1H), 1.95 (m, 2H), 2.27 (m, 1H), 2.45 (m, 1H), 2.91 (dd, J = 4.5, 13.5 Hz, 1H), 3.40 (dd, J = 5.1, 13.5 Hz, 1H), 4.81 (quint, J = 6.9 Hz, 1H), 5.01 (br s, 1H), 5.05 (m, 1H), 5.07 (d, J = 4.2 Hz, 1H), 5.73 (m, 1H), 7.24 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.68, 27.49, 31.25, 36.46, 39.15, 40.32, 47.65, 54.89, 79.40, 92.16, 117.6, 126.0, 126.6, 127.6, 128.2, 128.3, 130.1, 135.1, 136.7, 138.3, 170.4; IR (neat) 1642 cm^{-1}; HRMS (FAB, M + H) calcd for $C_{25}H_{29}NO_2$ 376.2277, found 376.2275. A significant amount of starting lactam **2** (0.10 g, 19%) was also recovered.

α-Benzyl-β-hydroxyethyl Lactam 4. To a stirred, cloudy solution of lactam **3** (0.15 g, 0.40 mmol) in THF:H_2O (1:1, 6.0 mL) was added osmium tetraoxide (2.5 wt % solution in *tert*-butyl alcohol, 0.41 mL, 0.04 mmol), resulting in a clear solution that darkened rapidly. The solution was stirred for 15 min, at which time sodium periodate (0.26 g, 1.20 mmol) was added in one portion, and a colorless precipitate appeared. After 1 h, methanol (3.0 mL) was added, the mixture was cooled to 0 °C, and sodium borohydride (0.03 g, 0.80 mmol) was added in one portion, resulting in a black mixture. The mixture was stirred vigorously at 0 °C for 20 min and then poured into 10 mL of saturated $NaHCO_3$ (aq, 10 mL). The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (4:1 ethyl acetate−hexanes) to provide 0.10 g (66%) of alcohol **4** as a colorless foam: $[\alpha]^{23}_D$ +98.3 (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 7.0 Hz, 3H), 0.88 (s, 3H), 1.37 (app t, J = 12.3 Hz, 1H), 1.47 (m, 1H), 1.66 (m, 1H), 1.77 (m, 1H), 1.97 (m, 2H), 2.44 (m, 1H), 2.91 (dd, J = 4.5, 13.5 Hz, 1H), 3.40 (dd, J = 5.1, 13.2 Hz, 1H), 3.69 (m, 2H), 4.82 (quint, J = 7.2 Hz, 1H), 5.01 (d, J = 5.7 Hz, 1H), 7.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.59, 27.32, 28.01, 36.50, 38.15, 40.58, 48.48, 54.88, 59.96, 79.35, 92.11, 126.0, 126.6, 127.6, 128.2, 130.2, 136.6, 138.1,

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170.4; IR (neat) 3403, 1615 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2136.

α-Benzyl-β-bromoethyl Lactam 5. To a stirred solution of hydroxy lactam **4** (95 mg, 0.25 mmol) in 5.0 mL of CH_2Cl_2 at 0 °C was added triphenylphosphine (99 mg, 0.38 mmol), followed by *N*-bromosuccinimide (67 mg, 0.38 mmol). The mixture was stirred for 60 min and then diluted with CH_2Cl_2 (15 mL) and washed with water (20 mL). The phases were separated, and the organic phase washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (1:1 hexanes−ethyl acetate) to give 93 mg (84%) of bromo lactam **5** as a colorless oil: $[\alpha]^{23}_D$ +58.8 (*c* 1.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 7.0 Hz, 3H), 0.85 (s, 3H), 1.30 (app t, J = 12.6 Hz, 1H), 1.71 (m, 1H), 2.07 (m, 3H), 2.40 (m, 1H), 2.85 (dd, J = 4.2, 13.5 Hz, 1H), 3.42 (m, 3H), 4.81 (quint, J = 7.2 Hz, 1H), 5.00 (d, J = 5.7 Hz, 1H), 7.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.57, 27.25, 29.73, 30.60, 36.28, 37.69, 39.39, 48.17, 54.88, 79.41, 91.93, 126.0, 126.8, 127.7, 128.2, 128.3, 130.3, 136.6, 137.8, 169.8; IR (neat) 1642 cm^{-1}.

Cyclobutane-Fused Tricyclic Lactam 6. To a stirred solution of diisopropylamine (0.05 mL, 0.36 mmol) in 1.0 mL of THF at 0 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.14 mL, 0.32 mmol), followed by HMPA (0.06 mL, 0.34 mmol). The mixture was stirred at 0 °C for 15 min and then transferred dropwise via cannula to a stirred solution of bromo lactam **5** (93 mg, 0.21 mmol) in 1.0 mL of THF at 0 °C. The solution was stirred for 30 min at 0 °C and then warmed to ambient temperature and stirred 6 h. The mixture was partitioned between ether (10 mL) and saturated NH_4Cl (aq, 10 mL), and the phases were separated. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (2:1 hexanes−ethyl acetate) to yield 52 mg (69%) of tricyclic lactam **6** as a colorless oil: $[\alpha]^{23}_D$ +125 (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.51 (s, 3H), 0.74 (d, J = 6.7 Hz, 3H), 1.46 (m, 1H), 1.76 (app t, J = 12.0 Hz, 1H), 2.11 (m, 2H), 2.35 (m, 3H), 2.89 (d, J = 12.9 Hz, 1H), 3.46 (d, J = 13.2 Hz, 1H), 4.79 (quint, J = 6.9 Hz, 1H), 5.04 (d, J = 5.7 Hz, 1H), 7.24 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.46, 20.79, 26.29, 30.12, 31.47, 40.95, 42.58, 46.19, 54.15, 79.10, 92.79, 126.1, 126.7, 127.6, 128.2, 130.1, 136.6, 137.7, 172.5; IR (neat) 1637 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{27}NO_2$ 361.2042, found 361.2039. A significant amount of starting bromo lactam **5** (17 mg, 18%) was also recovered.

General Procedure for Alkylation of Cyano Enamines 7 with α,ω-Dihalides (Method A). β-Chlorobutyl Lactam 8d. To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.22 mL, 1.33 mmol) in 3.5 mL of THF at −78 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.56 mL, 1.28 mmol) followed by HMPA (0.22 mL, 1.28 mmol). The solution was stirred for 5 min at −78 °C, warmed to 0 °C, stirred 1.5 min, and then cooled to −78 °C, at which time cyano enamine **7**[1] (0.28 g, 0.99 mmol) in 1.5 mL of THF was added dropwise over 1 min. The solution was stirred at −78 °C for 20 min, and 1-chloro-4-iodobutane (0.24 mL, 1.97 mmol) was added dropwise. The mixture was stirred for 6 h at −78 °C and quenched with saturated $NaHCO_3$ (10 mL). The mixture was diluted with ether (15 mL), and the phases were separated. The aqueous phase was extracted with ether (15 mL), and the combined organic phases concentrated. To the crude chlorocyano enamine were added THF (15 mL) and 1 N HCl (aq) (15 mL), and the mixture was stirred at ambient temperature 24 h. The mixture was concentrated, the residue was extracted with ether (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (1:1 hexanes−ethyl acetate) provided 0.19 g (53%) of β-chlorobutyl lactam **8d** as a colorless oil: $[\alpha]^{23}_D$ +23.9 (*c* 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 5H), 1.58 (s, 3H), 1.69 (m, 2H), 1.99 (m, 2H), 2.21 (m, 1H), 2.65 (app q, J = 11.1 Hz, 1H), 3.35 (s, 3H), 3.53 (t, J = 6.6 Hz, 2H), 3.59 (dd, J = 3.3, 10.2 Hz, 1H), 3.78 (dd, J = 5.4, 10.2 Hz, 1H), 5.23 (d, J = 7.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.76, 24.37, 29.39, 32.28, 35.50, 37.76, 42.03, 44.55, 59.06, 63.04, 70.44, 78.08, 93.31, 126.4, 128.1, 128.3, 139.1, 168.8; IR (neat) 1647 cm^{-1}; HRMS (FAB, M + H) calcd for $C_{20}H_{28}NO_3Cl$ 366.1836, found 366.1833. For ^{37}Cl calcd 368.1807, found 368.1815.

β-Iodopropyl lactam 8a was obtained from 1,3-diiodopropane and **7** in 31% yield as a colorless oil: $[\alpha]^{23}_D$ +21.2 (*c* 1.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 3H), 1.58 (s, 3H), 1.87 (app quint, J = 7.5 Hz, 2H), 2.01 (m, 2H), 2.20 (m, 1H), 2.64 (app q, J = 11.1 Hz, 1H), 3.18 (t, J = 6.9 Hz, 2H), 3.35 (s, 3H), 3.58 (dd, J = 3.0, 10.5 Hz, 1H), 3.78 (dd, J = 5.4, 10.2 Hz, 1H), 4.04 (m, 1H), 5.23 (d, J = 7.8 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 5.97, 24.54, 28.97, 30.54, 37.24, 37.87, 42.21, 59.25, 63.25, 70.50, 78.21, 93.40, 126.6, 128.3, 128.6, 139.1, 168.8; IR (neat) 1649 cm^{-1}; HRMS (FAB, M + H) calcd for $C_{19}H_{26}NO_3I$ 444.1036, found 444.1032.

β-Chloropropyl lactam 8b was obtained from 1-chloro-3-iodopropane and **7** in 49% yield as a pale yellow oil: $[\alpha]^{23}_D$ +22.7 (*c* 1.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.51 (m, 3H), 1.58 (s, 3H), 1.82, (app quint, J = 7.2 Hz, 2H), 1.98 (app t, J = 10.2 Hz, 1H), 2.02 (m, 1H), 2.21 (m, 1H), 2.65 (app q, J = 11.4 Hz, 1H), 3.35 (s, 3H), 3.54 (t, J = 6.6 Hz, 2H), 3.58 (dd, J = 3.0, 10.2 Hz, 1H), 3.78 (dd, J = 5.4, 10.5 Hz, 1H), 4.04 (m, 1H), 5.23 (d, J = 7.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.46, 29.18, 29.66, 33.64, 37.81, 42.13, 44.67, 59.18, 63.18, 70.46, 78.17, 93.35, 126.6, 128.3, 128.5, 139.1, 168.7; IR (neat) 1647 cm^{-1}.

β-Iodobutyl lactam 8c was obtained from 1,4-diiodobutane and **7** in 37% yield as a colorless oil: $[\alpha]^{23}_D$ +26.4 (*c* 1.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 5H), 1.59 (s, 3H), 1.82 (m, 2H), 1.99 (m, 2H), 2.21 (m, 1H), 2.65 (app q, J = 11.1 Hz, 1H), 3.18 (t, J = 6.6 Hz, 2H), 3.35 (s, 3H), 3.59 (dd, J = 3.0, 10.5 Hz, 1H), 3.78 (dd, J = 5.1, 10.2 Hz, 1H), 4.04 (m, 1H), 5.23 (d, J = 7.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 6.43, 24.45, 27.40, 29.40, 33.13, 35.23, 37.85, 42.12, 59.15, 63.10, 70.47, 78.14, 93.37, 126.5, 128.2, 128.4, 139.1, 168.9; IR (neat) 1647 cm^{-1}; HRMS (FAB, M + H) calcd for $C_{20}H_{28}NO_3I$ 458.1192, found 458.1195.

β-Iodopentyl lactam 8e was obtained from 1,5-diiodopentane and **7** in 47% yield as a pale yellow oil: $[\alpha]^{23}_D$ +21.1 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 7H), 1.59, (s, 3H), 1.82 (m, 2H), 1.98 (m, 2H), 2.20 (m, 1H), 2.64 (app q, J = 11.1 Hz, 1H), 3.18 (t, J = 6.9 Hz, 2H), 3.35 (s, 3H), 3.59 (dd, J = 3.0, 10.5 Hz, 1H), 3.78 (dd, J = 5.4, 10.5 Hz, 1H), 4.04 (m, 1H), 5.23 (d, J = 7.8 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 6.77, 24.49, 25.46, 29.45, 30.30, 33.18, 36.17, 37.94, 42.19, 59.19, 63.15, 70.54, 78.18, 93.46, 126.6, 128.2, 128.5, 139.2, 169.1; IR (neat) 1648 cm^{-1}. Anal. Calcd for $C_{21}H_{30}NO_3I$: C, 53.51; H, 6.42. Found: C, 53.38; H, 6.45.

β-Chloropentyl lactam 8f was obtained from 1-chloro-5-iodopentane and **7** in 48% yield as a colorless oil: $[\alpha]^{23}_D$ +23.2 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 7H), 1.58 (s, 3H), 1.76 (m, 2H), 1.97 (m, 2H), 2.19 (m, 1H), 2.63 (app q, J = 11.4 Hz, 1H), 3.34 (s, 3H), 3.51 (t, J = 6.6 Hz, 2H), 3.58 (dd, J = 3.0, 10.5 Hz, 1H), 3.78 (dd, J = 5.4, 10.2 Hz, 1H), 4.04 (m, 1H), 5.22 (d, J = 8.1 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.48, 25.84, 26.74, 29.48, 32.35, 36.23, 37.96, 42.22, 44.83, 59.19, 63.16, 70.56, 78.20, 93.47, 126.6, 128.2, 128.5, 139.2, 169.1; IR (neat) 1647 cm^{-1}.

β-Iodohexyl lactam 8g was obtained from 1,6-diiodohexane and **7** in 50% yield as a colorless oil: $[\alpha]^{23}_D$ +18.5 (*c* 1.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 9H), 1.58 (s, 3H), 1.81 (m, 2H), 1.98 (m, 2H), 2.19 (m, 1H), 2.64 (m, 1H), 3.17 (t, J = 6.9 Hz, 2H), 3.35 (s, 3H), 3.59 (dd, J = 3.3, 10.2 Hz, 1H), 3.78 (dd, J = 5.4, 10.2 Hz, 1H), 4.04 (m, 1H), 5.22 (d, J = 8.1 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 6.88, 24.46, 26.32, 28.39, 29.49, 30.24, 33.27, 36.26, 37.96, 42.21, 59.16, 63.10, 70.53, 78.15, 93.44, 126.5, 128.2, 128.4, 139.2, 169.1; IR (neat) 1648 cm^{-1}.

β-Chlorobutenyl lactam 8h was obtained from *cis*-1,4-dichloro-2-butene and **7** in 49% yield as a pale yellow oil: $[\alpha]^{23}_D$ +27.2 (*c* 1.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.53 (app t, J = 12.3 Hz, 1H), 1.58 (s, 3H), 2.12 (m, 5H), 2.65 (dd, J = 4.5, 16.5 Hz, 1H), 3.35 (s, 3H), 3.58 (dd, J = 3.0, 10.5 Hz, 1H), 3.78 (dd, J = 5.4, 10.5 Hz, 1H), 4.04 (m, 1H), 4.06 (d, J = 8.1 Hz, 2H), 5.23 (d, J = 7.8 Hz, 1H), 5.61 (ddd, J = 7.5, 10.8 Hz, J = 15.0 Hz, 1H), 5.78 (ddd, J = 8.1, 10.8, 15.9 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.45, 29.78, 33.39, 37.52, 38.81, 41.74,

59.16, 63.15, 70.44, 78.18, 93.35, 126.6, 127.7, 128.3, 128.5, 131.2, 139.0, 168.6; IR (neat) 1649 cm^{-1}.

General Procedure for Intramolecular Enolate Alkylation of Lactams 8b and 8h. Cyclopentane-Fused Tricyclic Lactam 9b. To a stirred solution of diisopropylamine (0.07 mL, 0.50 mmol) in 1.0 mL of THF at 0 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.21 mL, 0.48 mmol). The mixture was stirred at 0 °C for 15 min and then transferred dropwise via cannula to a stirred solution of chlorolactam **8b** (0.11 g, 0.32 mmol) in 2.0 mL of THF at 0 °C and stirred at 0 °C for 90 min. The mixture was partitioned between ether (10 mL) and saturated NH_4Cl (aq, 10 mL). The phases were separated, and the aqueous phase was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (2:1 hexanes−ethyl acetate) provided 75 mg (76%) of tricyclic lactam **9b** as a colorless oil: $[\alpha]^{23}_D$ +43.1 (*c* 1.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (m, 1H), 1.43 (app t, J = 13.2 Hz, 1H), 1.52 (m, 1H), 1.55 (s, 3H), 1.67 (m, 1H), 1.98 (m, 3H), 2.28 (dd, J = 5.7, 12.3 Hz, 1H), 2.49 (m, 1H), 2.75 (app q, J = 9.3 Hz, 1H), 3.33 (s, 3H), 3.52 (dd, J = 2.7, 10.5 Hz, 1H), 3.82 (dd, J = 4.8, 10.5 Hz, 1H), 4.01 (m, 1H), 5.24 (d, J = 7.8 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.23, 25.36, 29.15, 33.87, 34.00, 42.37, 43.89, 59.25, 63.04, 69.51, 78.41, 93.95, 126.7, 128.3, 128.5, 138.9, 172.0; IR (neat) 1647 cm^{-1}.

Cyclohexene-Fused Tricyclic Lactam 9h was obtained from chlorolactam **8h** in 49% yield as a colorless crystalline solid: mp = 93−94 °C; $[\alpha]^{23}_D$ +84.3 (*c* 1.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.62 (s, 3H), 1.92 (m, 1H), 2.01 (dd, J = 3.6, 13.2 Hz, 1H), 2.12 (dd, J = 8.4, 12.9 Hz, 1H), 2.32 (m, 4H), 2.63 (dd, J = 6.9, 11.1 Hz, 1H), 3.34 (s, 3H), 3.64 (dd, J = 3.3, 10.5 Hz, 1H), 3.80 (dd, J = 5.7, 10.2 Hz, 1H), 4.03 (m, 1H), 5.18 (d, J = 7.8 Hz, 1H), 5.67 (m, 2H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.18, 26.45, 27.98, 29.13, 38.54, 39.20, 59.13, 69.39, 71.22, 78.54, 93.38, 124.9, 125.1, 126.6, 128.2, 128.5, 139.4, 172.1; IR (neat) 1661, 1647 cm^{-1}. A significant amount of starting chloro lactam **8h** was also recovered (31%). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70. Found: C, 73.22; H, 7.68.

Cyclohexane-Fused Tricyclic Lactam 9d. To a stirred solution of diisopropylamine (0.10 mL, 0.74 mmol) in 1.0 mL of THF at 0 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.31 mL, 0.72 mmol), followed by HMPA (0.12 mL, 0.70 mmol). The mixture was stirred at 0 °C for 15 min and then transferred dropwise via cannula to a stirred solution of chlorolactam **8d** (0.17 g, 0.46 mmol) in 1.5 mL of THF at 0 °C and stirred at 0 °C for 6 h. The mixture was partitioned between ether (20 mL) and saturated NH_4Cl (aq, 20 mL). The phases were separated, and the aqueous phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (2:1 hexanes−ethyl acetate) provided 0.09 g (59%) of tricyclic lactam **9d** as a colorless crystalline solid: mp = 89−91 °C; $[\alpha]^{23}_D$ +61.1 (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23−1.79 (m, 10H), 1.61 (s, 3H), 1.91 (m, 2H), 2.19 (app q, J = 12.0 Hz, 1H), 2.27 (m, 1H), 2.43 (m, 1H), 3.34 (s, 3H), 3.64 (dd, J = 3.3, 10.2 Hz, 1H), 3.78 (dd, J = 6.0, 10.5 Hz, 1H), 4.04 (m, 1H), 5.19 (d, J = 7.5 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.36, 25.34, 25.40, 26.18, 29.57, 30.51, 37.52, 41.91, 59.13, 63.18, 71.29, 78.62, 93.53, 126.6, 128.2, 128.5, 139.6, 172.8; IR (neat) 1647 cm^{-1}.

α-Benzyl Tricyclic Lactam 11. To a stirred solution of diisopropylamine (0.04 mL, 0.28 mmol) in 1.0 mL of THF at 0 °C was added *n*-butyllithium (2.30 M solution in hexanes, 0.12 mL, 0.27 mmol), followed by HMPA (0.05 mL, 0.27 mmol). The mixture was stirred at 0 °C for 15 min and then transferred dropwise *via* cannula to a stirred solution of tricyclic lactam **9b** (0.07 g, 0.23 mmol) in 1.0 mL of THF at 0 °C and stirred at 0 °C for 30 min, at which time benzyl bromide (0.03 mL, 0.27 mmol) was added dropwise. The mixture was allowed to warm slowly to ambient temperature over 12 h and partitioned between ether (20 mL) and saturated NH_4Cl (aq, 20 mL). The phases were separated, and the aqueous phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (4:1 hexanes−ethyl acetate) provided 0.05 g (56%) of lactam **11** as a colorless oil that crystallized upon standing: mp 100−102 °C; $[\alpha]^{23}_D$ −40.9 (*c* 1.51, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.69 (s, 3H), 1.53 (dt, J = 13.5 Hz, 1H), 1.55 (app t, J = 13.2 Hz, 1H), 1.78 (m, 2H), 1.92 (m, 2H), 2.18 (m, 3H), 2.57 (d, J = 12.9 Hz, 1H), 3.33 (d, J = 13.2 Hz, 1H), 3.36 (s, 3H), 3.68 (m, 2H), 4.10 (m, 1H), 5.09 (d, J = 7.8 Hz, 1H), 7.23 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.92, 22.86, 31.02, 35.68, 37.51, 41.24, 43.77, 55.75, 58.89, 62.68, 70.60, 78.57, 92.86, 126.5, 126.6, 128.0, 128.1, 128.4, 130.3, 138.2, 139.3, 173.4; IR (neat) 1637 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{31}NO_3$ 285.1604, found 285.1597. A significant amount of starting lactam **33b** was also recovered (32%).

Alkylation of Cyano Enamine 1 with α,ω-Dihalides (Method B). β-Chlorobutyl Lactam 10a. To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.49 mmol) in 3.0 mL of THF at −78 °C was added *n*-butyllithium (2.25 M solution in hexanes, 0.64 mL, 1.43 mmol), followed by HMPA (0.38 mL, 2.20 mmol). The mixture was warmed to 0 °C for 1.5 min, cooled to −78 °C, and transferred dropwise via cannula to a stirred solution of cyano enamine **1**[1] (0.28 g, 1.10 mmol) in 3.0 mL of THF at −78 °C. Stirring was continued at −78 °C for 30 min, at which time 1-chloro-4-iodobutane (0.20 mL, 1.65 mmol) was added in one portion. The solution was stirred for 3 h at −78 °C and then quenched with saturated $NaHCO_3$ (aq, 10 mL). The mixture was diluted with ether (15 mL), and the phases were separated. The aqueous phase was extracted with ether (15 mL), and the combined organic phases concentrated. To the residue was added THF:1 N HCl (1:1, 40 mL) and the mixture stirred 24 h at ambient temperature. The mixture was concentrated and the residue extracted with ether (2 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (2:1 to 1:1 hexanes−ethyl acetate) gave 0.25 g (68%) of chlorolactam **10a** as a pale yellow oil: $[\alpha]^{23}_D$ +49.3 (*c* 1.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 7.0 Hz, 3H), 1.43 (m, 5H), 1.64 (s, 3H), 1.75 (m, 2H), 2.02 (m, 3H), 2.67 (dd, J = 7.5, 17.4 Hz, 1H), 3.52 (t, J = 6.9 Hz, 2H), 4.72 (quint, J = 6.9 Hz, 1H), 5.07 (d, J = 5.7 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.85, 23.92, 27.97, 28.46, 32.31, 36.29, 36.41, 41.31, 44.64, 54.74, 79.44, 92.68, 126.0, 127.6, 128.2, 136.5, 168.3; IR (neat) 1650 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{26}NO_2Cl$ 336.1732, found 336.1735.

Tricyclic Lactam 13. To a stirred solution of diisopropylamine (0.12 mL, 0.83 mmol) in 1.0 mL of THF at 0 °C was added *n*-butyllithium (2.25 M solution in hexanes, 0.35 mL, 0.80 mmol) followed by HMPA (0.14 mL, 0.80 mmol). The solution was stirred for 15 min and then transferred dropwise via cannula to a stirred solution of lactam **10a** (0.18 g, 0.54 mmol) in 2.0 mL of THF at 0 °C. The mixture was allowed to warm to ambient temperature with stirring over 12 h and then partitioned between ether (20 mL) and saturated NH_4Cl (20 mL). The phases were separated, and the organic phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (4:1 hexanes−ethyl acetate) to give 0.13 g (81%) of tricyclic lactam **13** as a 1:1 mixture of α-*exo*:*endo* epimers as a colorless oil. The diastereomeric ratio was determined by integration of the proton α to nitrogen in the ^1H NMR spectrum of each epimer.

General Procedure for Alkylation of Lactam 13: α-Prenyl Tricyclic Lactam 14c. To a stirred solution of diisopropylamine (0.07 mL, 0.50 mmol) in 1.0 mL of THF at 0 °C was added *n*-butyllithium (2.25 M solution in hexanes, 0.21 mL, 0.48 mmol) followed by HMPA (0.08 mL, 0.46 mmol). The solution was stirred for 15 min and then transferred dropwise via cannula to a stirred solution of lactam **13** (96 mg, 0.32 mmol) in 2.0 mL of THF at 0 °C. The mixture was stirred at 0 °C for 60 min and then cooled to −78 °C, at which time 4-bromo-2-methyl-2-butene (0.07 mL, 0.61 mmol) was added in one portion. The solution was allowed to warm to ambient temperature with stirring over 12 h and then partitioned between ether (10 mL) and saturated NH_4Cl (10 mL). The phases were separated, and the organic phase was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (4:1 hexanes−ethyl acetate) to give 0.10 g (85%) of tricyclic lactam **14c** as a colorless oil: $[\alpha]^{23}_D$ −4.7 (*c* 1.91, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.40 (m, 4H), 1.63 (s,

3H), 1.68 (s, 3H), 1.70 (s, 3H), 1.79 (m, 5H), 2.11 (m, 2H), 2.29 (dd, J = 7.5, 14.7 Hz, 1H), 2.42 (dd, J = 7.5, 14.7 Hz, 1H), 4.64 (quint, J = 7.2 Hz, 1H), 5.08 (d, J = 6.6 Hz, 1H), 5.26 (dt, J = 7.5 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.82, 18.05, 21.05, 26.02, 26.20, 27.70, 30.30, 30.36, 33.52, 38.70, 39.60, 44.89, 56.14, 80.74, 93.01, 121.2, 126.1, 127.6, 128.3, 132.5, 137.7, 174.2; IR (neat) 1645 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{33}NO_2$ 368.2591, found 368.2592.

α-Allyl tricyclic lactam 14b was obtained from lactam **13** as a 3:2 mixture of *exo*:*endo* epimers (determined by integration of the internal olefin proton in the ^{1}H NMR spectrum) as a colorless oil in 80% yield. Pure *endo* epimer **14b** could be isolated by flash chromatography (4:1 hexanes−ethyl acetate) as a colorless oil that crystallized upon standing: mp = 84−86 °C; $[\alpha]^{23}_D$ +26.4 (*c* 1.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3H), 1.41 (m, 7H), 1.68 (s, 3H), 1.85 (m, 2H), 2.05 (m, 1H), 2.19 (m, 1H), 2.34 (dd, J = 6.9, 14.4 Hz, 1H), 2.43 (dd, J = 7.8, 14.4 Hz, 1H), 4.64 (quint, J = 7.2 Hz, 1H), 5.02 (br s, 1H), 5.06 (m, 1H), 5.11 (d, J = 6.3 Hz, 1H), 5.95 (m, 1H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.76, 20.57, 25.82, 27.32, 30.32, 32.17, 35.42, 38.75, 39.44, 44.86, 55.99, 80.74, 92.82, 116.7, 126.0, 127.5, 128.2, 135.2, 137.6, 173.6; IR (neat) 1646 cm^{-1}. Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61. Found: C, 77.77; H, 8.62.

α-Benzyl tricyclic lactam 14a was obtained from lactam **13** as a single diastereomer in 82% yield as a colorless oil: $[\alpha]^{23}_D$ −70.3 (*c* 1.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 7.0 Hz, 3H), 1.42 (m, 3H), 1.60 (s, 3H), 1.75 (m, 3H), 1.92 (m, 4H), 2.24 (m, 1H), 2.88 (d, J = 13.5 Hz, 1H), 3.28 (d, J = 13.8 Hz, 1H), 4.07 (d, J = 6.6 Hz, 1H), 4.44 (quint, J = 6.9 Hz, 1H), 7.23 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 16.46, 21.12, 26.33, 27.62, 30.09, 35.87, 38.37, 38.51, 40.20, 47.20, 55.75, 79.94, 92.71, 125.9, 126.6, 127.4, 127.9, 128.1, 131.0, 137.6, 139.2, 172.9; IR (neat) 1637 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{31}NO_2$ 389.2355, found: 389.2350.

General Procedure for Reduction/Hydrolysis of Tricyclic Lactam 38: *trans*-2-Keto-10-benzyl-Δ^3-octahydronaphthalene (16). To a stirred solution of lactam **14a** in 2.0 mL of THF at 0 °C was added Red-Al (3.4 M solution in toluene, 0.13 mL, 0.43 mmol). The mixture was stirred at 0 °C for 2 h, warmed to ambient temperature and stirred 6 h, and then quenched by cautious dropwise addition of methanol (1 mL) and concentrated. The residue was dissolved in hexanes−ether (1:1, 20 mL), washed with 10% NaOH (aq, 20 mL) and water (20 mL), and concentrated. To the crude carbinolamine were added tetrabutylammonium dihydrogenphosphate (1.0 M solution in water, 4.20 mL, 4.20 mmol) and absolute ethanol (4.2 mL), and the mixture was heated to reflux for 12 h. The mixture was cooled and extracted with ether (3 × 15 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (8:1 hexanes−ethyl acetate) to provide 40 mg (79%) of octalone **17a** as a colorless crystalline solid: mp = 105−107 °C; $[\alpha]^{23}_D$ +212 (*c* 1.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (dt, J = 13.2 Hz, 1H), 1.59 (m, 7H), 2.07 (m, 1H), 2.28 (dd, J = 3.9, 18.0 Hz, 1H), 2.50 (dd, J = 14.4, 18.0 Hz, 1H), 2.69 (d, J = 13.2 Hz, 1H), 3.13 (d, J = 12.6 Hz, 1H), 5.93 (dd, J = 0.6, 10.2 Hz, 1H), 6.41 (d, J = 10.2 Hz, 1H), 7.09 (m, 2H), 7.22 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.50, 25.85, 27.25, 32.58, 35.24, 39.44, 40.83, 44.34, 126.4, 127.6, 128.0, 130.5, 137.2, 161.4, 199.9; IR (neat) 1684 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.89; H, 8.44.

***trans*-2-Keto-10-allyl-Δ3-octahydronaphthalene 17** was obtained from tricyclic lactam **14b** in 72% yield as a colorless oil: $[\alpha]^{23}_D$ +192 (*c* 1.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 4H), 1.55 (m, 2H), 1.75 (m, 1H), 1.85 (m, 1H), 1.97 (m, 1H), 2.17 (m, 2H), 2.37 (dd, J = 13.8, 17.7 Hz, 1H), 2.56 (dd, J = 8.1, 13.2 Hz, 1H), 5.03 (m, 1H), 5.07 (br s, 1H), 5.71 (m, 1H), 5.87 (dd, J = 0.9, 10.2 Hz, 1H), 6.72 (d, J = 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.91, 25.58, 27.16, 33.31, 34.63, 38.73, 40.76, 43.80, 118.2, 127.7, 133.4, 161.0, 199.8; IR (neat) 1684 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.95; H, 9.47.

***β*-Chlorobutenyl Lactam 10b.** To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.64 mL, 3.77 mmol) in 4.0 mL of THF at −78 °C was added *n*-butyllithium (2.25 M solution in hexanes, 1.61 mL, 3.63 mmol), followed by HMPA (0.97 mL, 5.58 mmol). The mixture was warmed to 0 °C for 1.5 min, cooled to −78 °C, and transferred dropwise via cannula to a stirred solution of cyanoenamine **1**[1] (0.71 g, 2.79 mmol) in 8.0 mL of THF at −78 °C. Stirring was continued at −78 °C for 20 min, at which time 1,4-dichloro-2-butene (0.44 mL, 4.19 mmol) was added in one portion. The solution was stirred for 3 h at −78 °C and quenched with saturated $NaHCO_3$ (aq, 20 mL). The mixture was diluted with ether (20 mL), and the phases were separated. The aqueous phase was extracted with ether (20 mL) and the combined organic phases were concentrated. To the residue was added THF−1 N HCl (1:1, 60 mL) and the mixture stirred 24 h at ambient temperature. The mixture was concentrated and the residue extracted with ether (2 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (2:1 to 1:1 hexanes−ethyl acetate) gave 0.63 g (68%) of chloro lactam **10b** as a colorless oil: $[\alpha]^{23}_D$ +40.9 (*c* 1.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 7.0 Hz, 3H), 1.45 (app t, J = 12.3 Hz, 1H), 1.63 (s, 3H), 2.13 (m, 5H), 2.66 (app q, J = 11.1 Hz, 1H), 4.04 (d, J = 7.8 Hz, 2H), 4.72 (quint, J = 6.9 Hz, 1H), 5.06 (d, J = 5.7 Hz, 1H), 5.58 (m, 1H), 5.75 (m, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.91, 28.06, 28.76, 34.15, 35.96, 38.88, 41.03, 54.88, 79.61, 92.68, 126.1, 127.7, 127.7, 128.3, 131.3, 136.5, 168.0; IR (neat) 1647 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{24}NO_2Cl$ 334.1575, found 334.1578.

Cyclohexene-Fused Tricyclic Lactam 21. To a stirred solution of diisopropylamine (0.40 mL, 2.88 mmol) in 3.0 mL of THF at 0 °C was added *n*-butyllithium (2.25 M solution in hexanes, 1.24 mL, 2.79 mmol), followed by HMPA (0.48 mL, 2.79 mmol). The mixture was stirred for 15 min and then transferred dropwise via cannula to a stirred solution of chloro lactam **10b** (0.62 g, 1.86 mmol) in 6.0 mL of THF at 0 °C. The solution was stirred for 5 min at 0 °C and then warmed to ambient temperature and stirred 12 h. The mixture was partitioned between ether (30 mL) and saturated NH_4Cl (aq, 30 mL). The organic phase was washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The crude ^{1}H NMR showed a 1:1 mixture of epimers determined by integration of the proton α to nitrogen in each epimer. The crude tricyclic lactam **21** was subjected to alkylation without further purification.

α-Methyl Tricyclic Lactam 20. To a stirred solution of diisopropylamine (0.17 mL, 1.20 mmol) in 2.0 mL of THF at 0 °C was added *n*-butyllithium (2.25 M solution in hexanes, 0.52 mL, 1.16 mmol), followed by HMPA (0.20 mL, 1.16 mmol). The solution was stirred for 15 min at 0 °C and then transferred dropwise to a stirred solution of crude lactam **21** (0.23 g, 0.77 mmol) in 2.0 mL of THF at 0 °C. The mixture was stirred at 0 °C for 1 h, at which time iodomethane (0.10 mL, 1.54 mmol) was added in one portion, and stirring was continued at 0 °C for 30 min. The solution was partitioned between ether (15 mL) and saturated NH_4Cl (aq, 15 mL), and the phases were separated. The organic phase was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (4:1 hexanes−ethyl acetate) provided 0.15 g (63% from *β*-chlorobutenyl lactam **10b**) of tricyclic lactam **20** as a pale yellow oil: $[\alpha]^{23}_D$ +151 (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3H), 1.13 (s, 3H), 1.67 (s, 3H), 1.86 (m, 3H), 2.15 (m, 3H), 2.34 (m, 1H), 4.70 (quint, J = 7.2 Hz, 1H), 5.08 (d, J = 6.3 Hz, 1H), 5.64 (m, 2H), 7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.40, 17.75, 28.82, 29.82, 34.36, 35.30, 38.03, 40.13, 55.79, 80.25, 92.41, 125.5, 126.0, 126.0, 127.5, 128.2, 137.3, 174.9; IR (neat) 1652, 1638 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{25}NO_2$ 312.1965, found 312.1964. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09. Found: C, 77.04; H, 8.10.

***β*-Hydroxy Ketone 23.** To a stirred solution of lactam **20** (0.21 g, 0.67 mmol) in 9.0 mL of THF at 0 °C was added Red-Al (3.4 M solution in toluene, 0.40 mL, 1.35 mmol). The mixture was stirred for 2 h at 0 °C and then warmed to ambient temperature and stirred for 1 h. The reaction was

quenched by cautious dropwise addition of methanol (3.0 mL) and concentrated. The residue was dissolved in ether−hexanes (30 mL) and washed with 10% NaOH (aq, 30 mL) and water (30 mL), and the organic phase was concentrated. To the crude carbinolamine were added tetrabutylammonium dihydrogenphosphate (1.0 M solution in water, 13.5 mL, 13.5 mmol) and absolute ethanol (13.5 mL), and the mixture was heated to reflux for 12 h. The mixture was extracted with ether (3 × 20 mL), and the combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue provided 43 mg (40%) of enone **19** and 42 mg (35%) of hydroxy ketone **23** as colorless oils. *β*-Hydroxy ketone **23**: ^{1}H NMR ($CDCl_3$) *δ* 0.97 (s, 3H), 1.62−2.25 (m, 8H), 2.51 (m, 1H), 2.54 (br s, 1H), 3.56 (m, 1H), 5.63 (m, 2H).

***trans*-2-Keto-10-methyl-Δ^{3,6}-hexahydronaphthalene (19).** To a solution of *β*-hydroxy ketone **23** in 3.0 mL of THF was added KOH (1.0 M solution in ethanol, 3 drops). The mixture was heated to reflux for 2 h, cooled, and concentrated. The residue was purified by flash chromatography (4:1 hexanes−ethyl acetate) to provide 34 mg (90%) of enone **19** as a colorless oil: $[\alpha]^{23}_D$ +226 (*c* 1.00, $CHCl_3$) [lit.[13] $[\alpha]_D$ −239 (*c* 1.00, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) *δ* 0.99 (s, 3H), 2.14 (m, 7H), 5.63 (m, 2H), 5.84 (dd, *J* = 0.6, 9.9 Hz, 1H), 6.68 (d, *J* = 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 16.10, 29.07, 34.32, 37.76, 37.94, 40.38, 124.7, 126.0, 126.8, 159.6, 199.7; IR (neat) 1674 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O$: C, 82.06; H, 9.53. Found: C, 81.95; H, 9.47.

Bicyclic Lactam 25. To a stirred solution of diisopropylamine (0.10 mL, 0.72 mmol) in 2.5 mL of THF at −78 °C was added *n*-butyllithium (1.89 M solution in hexanes, 0.38 mL, 0.72 mmol). The mixture was stirred at −78 °C for 15 min, at which time lactam **24**[1] (0.21 g, 0.67 mmol) in 0.7 mL of THF was added dropwise. The solution was stirred at −78 °C for 15 min, and benzyl bromide (0.08 mL, 0.69 mmol) was added dropwise. Stirring was continued for 2 h, and the reaction mixture was partitioned between ether (10 mL) and saturated NH_4Cl (aq, 10 mL). The phases were separated, and the organic phase was dried ($MgSO_4$) and concentrated. The above sequence was repeated using iodomethane (0.05 mL, 0.80 mmol) as the electrophile. Flash chromatography of the residue (4:1 hexanes−ethyl acetate) provided 0.19 g (68%) of trisubstituted lactam **24** as a colorless oil that crystallized upon standing: mp 85−87 °C; $[\alpha]^{23}_D$ −52.3 (*c* 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 0.85 (s, 3H), 1.23 (s, 3H), 1.51 (app t, *J* = 12.3 Hz, 1H), 1.84 (m, 2H), 2.01 (dd, *J* = 1.5, 12.6 Hz, 1H), 2.43 (m, 1H), 2.61 (d, *J* = 13.5 Hz, 1H), 3.34 (s, 3H), 3.37 (d, *J* = 13.5 Hz, 1H), 3.65 (m, 2H), 4.11 (m, 1H), 5.05 (m, 1H), 5.08 (d, *J* = 8.1 Hz, 1H), 5.09 (br s, 1H), 5.72 (m, 1H), 7.22 (m, 10H); ^{13}C NMR ($CDCl_3$) *δ* 21.02, 23.52, 32.91, 34.11, 36.25, 42.94, 47.86, 58.91, 63.18, 70.83, 78.35, 92.20, 117.0, 126.4, 126.5, 127.9, 128.0, 128.4, 130.2, 136.3, 137.7, 139.4, 173.5; IR (neat) 1640 cm^{-1}. Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93. Found: C, 77.20; H, 7.93.

General Procedure for *O*-Methylation of Hydroxy Lactams 32. Bicyclic Lactam 33a. To a stirred solution of lactam **32a**[9] (0.15 g, 0.38 mmol) in 3.0 mL of THF at 0 °C was added sodium hydride (14 mg, 0.58 mmol) in one portion. The suspension was stirred for 1 h at 0 °C, at which time iodomethane (0.05 mL, 0.80 mmol) was added in one portion. The mixture was allowed to warm to ambient temperature, stirred for 3 h, and quenched with saturated NH_4Cl (aq, 5 mL). The mixture was partitioned between ether (15 mL) and water (5 mL), and the phases were separated. The organic phase was washed with saturated $Na_2S_2O_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (4:1 hexanes−ethyl acetate) to yield 0.13 g (84%) of lactam **33a** as a colorless crystalline solid: mp 85−87 °C; $[\alpha]^{23}_D$ +44.5 (*c* 1.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 0.84 (m, 1H), 1.44 (s, 3H), 1.66 (m, 1H), 1.85 (m, 2H), 2.06 (dd, *J* = 9.0, 12.9 Hz, 1H), 2.50 (d, *J* = 12.9 Hz, 1H), 2.67 (dd, *J* = 5.1, 13.2 Hz, 1H), 3.35 (s, 3H), 3.42 (d, *J* = 12.9 Hz, 1H), 3.67 (dd, *J* = 3.0, 10.2 Hz, 1H), 3.76 (dd, *J* = 5.4, 10.2 Hz, 1H), 4.06 (m, 1H), 5.11 (m, 3H), 5.67 (m, 1H), 7.26 (m, 10H); ^{13}C NMR ($CDCl_3$) *δ* 24.06, 25.91, 32.95, 45.76, 46.42, 46.46, 59.25, 63.79, 70.77, 78.77, 93.55, 102.7, 119.0, 126.7, 128.2, 128.4, 128.4, 130.0, 134.0, 138.5, 139.7, 172.4; IR (neat) 1634 cm^{-1}. Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.00; H, 7.71. Found: C, 76.85; H, 7.73.

Bicyclic lactam 33b was obtained from lactam **32b**[9] in 86% yield as a colorless oil: $[\alpha]^{23}_D$ −38.4 (*c* 1.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 0.72 (s, 3H), 1.80 (m, 4H), 2.34 (dd, *J* = 8.1, 13.5 Hz, 1H), 2.43 (d, *J* = 12.9 Hz, 1H), 2.71 (dd, *J* = 6.6, 13.2 Hz, 1H), 3.27 (d, *J* = 12.9 Hz, 1H), 3.34 (s, 3H), 3.66 (m, 2H), 4.11 (m, 1H), 5.07 (d, *J* = 7.5 Hz, 1H), 5.14 (m, 2H), 5.85 (m, 1H), 7.22 (m, 10H); ^{13}C NMR ($CDCl_3$) *δ* 22.98, 24.52, 33.49, 45.07, 45.31, 47.05, 58.98, 63.00, 70.86, 78.77, 93.44, 118.4, 126.6, 126.7, 128.0, 128.2, 128.5, 130.8, 134.5, 137.5, 139.6, 172.3; IR (neat) 1633 cm^{-1}.

Bicyclic Lactam 33c was obtained from lactam **32c**[9] in 86% yield as a colorless crystalline solid: mp 74−75 °C; $[\alpha]^{23}_D$ −84.0 (*c* 2.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 0.87 (s, 3H), 1.35 (s, 3H), 1.53 (m, 1H), 1.87 (m, 3H), 2.44 (d, *J* = 12.9 Hz, 1H), 3.34 (s, 3H), 3.35 (d, *J* = 13.2 Hz, 1H), 3.66 (d, *J* = 4.5 Hz, 2H), 4.09 (m, 1H), 5.10 (d, *J* = 8.1 Hz, 1H), 7.25 (m, 10H); ^{13}C NMR ($CDCl_3$) *δ* 23.05, 27.38, 28.00, 32.91, 43.80, 46.46, 58.98, 62.97, 70.86, 78.71, 93.47, 126.4, 126.6, 127.9, 128.1, 128.4, 130.5, 137.8, 139.4, 173.3; IR (neat) 1641 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70. Found: C, 75.82; H, 7.77.

Bicyclic lactam 33d was obtained from lactam **32d**[17] in 80% yield as a colorless oil: $[\alpha]^{23}_D$ +54.8 (*c* 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 0.85 (t, *J* = 7.3 Hz, 3H), 1.40 (m, 1H), 1.58 (s, 3H), 1.83 (m, 4H), 2.04 (m, 1H), 2.25 (dd, *J* = 7.8, 13.5 Hz, 1H), 2.53 (dd, *J* = 6.9, 13.5 Hz, 1H), 3.33 (s, 3H), 3.63 (dd, *J* = 3.0, 10.5 Hz, 1H), 3.75 (dd, *J* = 5.4, 10.5 Hz, 1H), 4.11 (m, 1H), 5.09 (m, 2H), 5.22 (d, *J* = 7.5 Hz, 1H), 5.78 (m, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) *δ* 8.77, 23.98, 25.58, 32.20, 33.34, 44.07, 45.62, 59.16, 63.27, 70.72, 78.60, 93.56, 117.9, 126.6, 128.2, 128.5, 134.7, 139.5, 173.3; IR (neat) 1638 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51. Found: C, 73.54; H, 8.56.

General Procedure for Conversion of Lactams 33 to Dihydropyridones 34. Dihydropyridone 34b. To a stirred solution of diisopropylamine (0.18 mL, 1.26 mmol) in 2.0 mL of THF at 0 °C was added *n*-butyllithium (2.25 M solution in hexanes, 0.54 mL, 1.22 mmol) dropwise. The mixture was stirred for 5 min at 0 °C and then transferred dropwise via cannula to a stirred solution of lactam **33b** at 0 °C. The lactam solution gradually turned orange during the addition. When the addition was complete, the reaction was immediately quenched with water (2 mL), resulting in a colorless mixture. The mixture was partitioned between ether (15 mL) and saturated NH_4Cl (aq, 10 mL). The phases were separated, and the organic phase was concentrated. To the crude bicyclic enamide weres added *p*-toluenesulfonic acid monohydrate (0.16 g, 0.81 mmol), THF (3.0 mL), and water (3.0 mL), and the mixture was heated to reflux for 3 h. The mixture was cooled and partitioned between ether (10 mL) and saturated $NaHCO_3$ (aq, 10 mL), the phases were separated, and the organic phase was washed with brine (10 mL) and concentrated. The residue was dissolved in methanol (4.0 mL) and cooled to 0 °C, and sodium borohydride (46 mg, 1.22 mmol) was added in one portion. After being stirred for 20 min at 0 °C, the cooling bath was removed, and 10% NaOH (aq, 6 mL) and CH_2Cl_2 (6 mL) were added. The mixture was stirred vigorously for 45 min, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:1:1 hexanes−ether:CH_2Cl_2) to yield 0.13 g (67%) of dihydropyridone **34b** as a colorless oil: $[\alpha]^{23}_D$ −10.6 (*c* 1.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 1.73 (m, 3H), 2.07 (m, 3H), 2.48 (dd, *J* = 5.1, 14.1 Hz, 1H), 2.69 (d, *J* = 13.5 Hz, 1H), 3.02 (d, *J* = 13.2 Hz, 1H), 4.69 (m, 1H), 5.04 (m, 2H), 5.82 (m, 1H), 7.21 (m, 5H), 7.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) *δ* 18.56, 28.95, 39.54, 40.86, 44.61, 99.32, 118.3, 126.4, 127.8, 130.6, 131.7, 134.2, 137.2, 174.8; IR (neat) 3223, 1697, 1666 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO$ 241.1467, found 241.1465. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.36; H, 7.87.

Dihydropyridone 34c was obtained from lactam **33c** in 56% yield as a pale yellow oil: $[\alpha]^{23}_D$ −18.9 (*c* 1.91, $CHCl_3$);

^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.78 (m, 3H), 1.91 (m, 1H), 2.11 (m, 1H), 2.70 (d, J = 12.9 Hz, 1H), 2.94 (d, J = 12.9 Hz, 1H), 4.74 (m, 1H), 6.93 (br s, 1H), 7.20 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.71, 22.35, 31.75, 40.92, 42.01, 99.48, 126.4, 127.8, 130.6, 132.1, 137.1, 176.3; IR (neat) 3217, 1694, 1664 cm^{-1}; HRMS (FAB, M + H) calcd for $C_{14}H_{17}NO$ 216.1388, found 216.1387.

Dihydropyridone 34d was obtained from lactam **33d** in 52% yield as a pale yellow oil: $[\alpha]^{23}_D$ −5.9 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.6 Hz, 3H), 1.56 (m, 2H), 1.74 (m, 3H), 2.21 (m, 4H), 4.68 (m, 1H), 5.01 (m, 1H), 5.06 (br s, 1H), 5.75 (m, 1H), 6.78 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.24, 18.70, 27.71, 30.06, 39.12, 53.45, 99.33, 117.9, 131.2, 134.2, 174.9; IR (neat) 3224, 1697, 1668 cm^{-1}; HRMS (EI) Calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1305.

Dihydropyridone 30 was obtained from lactam **25** in 76% yield as a colorless oil: $[\alpha]^{23}_D$ +101 (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.80 (m, 3H), 1.94 (m, 1H), 2.16 (m, 2H), 2.69 (d, J = 13.2 Hz, 1H), 3.08 (d, J = 13.2 Hz, 1H), 4.78 (m, 1H), 4.95 (br s, 1H), 4.99 (m, 1H), 5.65 (m, 1H), 7.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 18.31, 18.77, 34.08, 38.40, 42.24, 45.19, 103.8, 116.6, 126.5, 128.0, 130.5, 131.0, 136.1, 137.1, 176.1; IR (neat) 3222, 1696, 1668 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.85; H, 8.29; N, 5.42.

Dihydropyridone 36 was obtained from tricyclic lactam **11** in 66% yield as a colorless oil: $[\alpha]^{23}_D$ +16.9 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.41 (m, 2H), 1.61 (m, 2H), 1.65 (m, 3H), 1.90 (m, 1H), 2.33 (m, 2H), 2.63 (d, J = 13.2 Hz, 1H), 3.05 (d, J = 13.5 Hz, 1H), 4.68 (m, 1H), 6.99 (br s, 1H), 7.18 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.86, 21.78, 33.04, 34.96, 41.39, 42.12, 52.72, 104.1, 126.4, 127.9, 129.9, 130.3, 137.5, 175.7; IR (neat) 3225, 1661 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO$ 242.1546, found 242.1547.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all compounds (66 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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