Tandem [4 + 2]/[3 + 2] Cycloadditions: Facile and Stereoselective Construction of Polycyclic Frameworks

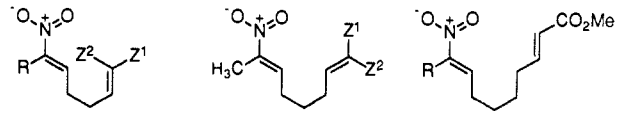
Scott E. Denmark,* Young-Choon Moon, and C. B. W. Senanayake

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801. *Received May 12, 1989*

Abstract: Di- and trisubstituted nitroalkenes tethered to dipolarophiles (unsaturated esters, nitriles) undergo tandem [4 + 2]/[3 + 2] cycloadditions with 2,3-dimethyl-2-butene or butyl vinyl ether in the presence of Lewis acids. For the dimethylene tether **1**, the tandem cycloadduct **4** is the direct reaction product. The *E* configuration of the dipolarophile is preferred, and the products arise selectively from a syn-endo pathway. For a trimethylene-tethered precursors **2** the initial [4 + 2] cycloadducts **9** are isolable and undergo the second [3 + 2]-dipolar cycloaddition upon brief warming via a syn-exo pathway. The resulting nitroso acetals (**4bB/B'** and **11aB/B'**) are cleaved with hydrogen and Raney nickel to afford the tricyclic lactams **12** and **14** stereoselectively in good yield.

Recent reports from these laboratories have demonstrated the utility of nitroalkenes as heterodienes in [4 + 2] cycloadditions.[1] These reactions succeed both intra- and intermolecularly with unactivated olefins in the presence of $SnCl_4$ (Scheme I). A variety of synthetically useful transformations of the cyclic nitronates that are produced have been described.[1b] Perhaps the most interesting of these is their reactions as 1,3-dipoles in [3 + 2] cycloadditions[1a,1b] (Scheme I).[2] This reaction was first discovered by Tartakovskii[3a] and was later developed by him[3b] as well as Carrie.[4] In addition, Torssell[5] has investigated 1,3-dipolar cycloadditions of silyl nitronates. In comparison to the enormous success of nitrones[6] and nitrile oxides,[7] these functions have found limited application in synthesis. We describe herein a simple strategy, which expands the utility of the nitronates by *intramolecularly* coupling a 1,3-dipolar cycloaddition[8,9] with the [4 + 2] process that creates them.[10]

Chart I



1a: R=H; Z=CO_2Me / H
1b: R=Me; Z=CO_2Me / H

2a: Z=CO_2R^1 / H
2b: Z=CN / H

3a: R=H
3b: R=Me

To explore the scope of this process we evaluated three structural variables: (1) length of the tether between the dipole and dipolarophile, (2) substitution on the nitronate, and (3) dipolarophile configuration. To eliminate the complications due to exo/endo isomers[1b] in the [4 + 2] cycloaddition, tetramethylethylene (T) was used as the dienophile. Since the nitroalkene cycloaddition requires $SnCl_4$, we were concerned about Lewis basic activating groups and initially used nitriles (vide infra). However, experimentation showed that unsaturated esters are fully compatible and served as our dipolarophiles.

Three families of substrates were studied that would create five- (**1**), six- (**2**), and seven- (**3**) membered rings. The precursors were prepared by sequential Wittig olefination and nitroolefination of terminally differentiated 1,4-,[11a] 1,5-,[11b] and 1,6-dialdehyde[11c] equivalents.[11] The results with substrates **1** are collected in Table I. For both di- and trisubstituted nitroalkenes the [4 + 2] cycloaddition proceeded rapidly in dichloromethane with $SnCl_4$ at −70 °C. In this solvent, however, a byproduct from Wagner-Meerwein rearrangement[1b] was also formed in significant amounts (10–15%). The formation of this byproduct was suppressed by using toluene as the solvent. The reactions were cleaner, but considerably slower in toluene, requiring warming to −20 °C for completion. In the *E*-enoate series *the second cycloaddition occurred spontaneously upon workup* to afford the tricyclic nitrosoacetals **4** *as single diastereomers*. The full stereostructure of the double cycloadducts was assured by an X-ray crystal structure determination of **4bT**. The all-cis ring fused arrangement arises from a syn-endo transition state,[12] which places the ester function exo. By contrast, the [4 + 2] cycloadducts from (*Z*)-**1a** and (*Z*)-**1b** could be isolated and underwent subsequent [3 + 2] cycloaddition upon brief warming. While **5aT** was formed as a mixture of three isomers (6:1:1.8), **5bT** was produced as a 95:5 mixture of endo-exo cycloadducts. That **4bT** and **5bT** possessed

(1) (a) Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306. (b) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971. (c) Denmark, S. E.; Sternberg, J. A.; Lueoend, R. *J. Org. Chem.* **1988**, *53*, 1251. (d) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Tetrahedron Lett.* **1986**, *27*, 3693.

(2) Seebach has described a similar tandem intermolecular process using silyl enol ethers as the dienophiles. (a) Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 836. See also: (b) Tohda, Y.; Yamawaki, N.; Matsui, H.; Kawashima, T.; Ariga, M.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 461.

(3) (a) Tartakovskii, V. A.; Chlenov, I. E.; Smagin, S. S.; Novikov, S. S. *Izv. Akad. Nauk SSSR, Ser. Khim. (Engl. Transl.)* **1964**, 583. (b) Shitkin, V. M.; Chlenov, I. E.; Tartakovskii, V. A. *Ibid.* **1977**, 187. (c) Tartakovskii, V. A. *Ibid.* **1984**, 147.

(4) (a) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron* **1976**, *32*, 675. (b) Gree, R.; Carrie, R. *Ibid.* **1976**, *32*, 683. (c) Gree, R.; Carrie, R. *J. Heterocycl. Chem.* **1977**, *14*, 965. (d) Gree, R.; Carrie, R. *J. Am. Chem. Soc.* **1977**, *99*, 6667.

(5) (a) Torssell, K.; Zeuthen, O. *Acta Chem. Scand. B* **1978**, *32*, 118. (b) Sharma, S. C.; Torssell, K. *Ibid.* **1979**, *33*, 379. (c) Mukerji, S. K.; Torssell, K. B. G. *Ibid.* **1981**, *35*, 643. (d) Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell K. B. G. *Ibid.* **1982**, *36*, 1. (e) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2227, 2247. (f) Andersen, S. H.; Sharma, K. K.; Torssell, K. B. G. *Ibid.* **1983**, *39*, 2241. (g) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988; Chapter 4.

(6) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 9. (b) DeShong, P.; Lander, S. W.; Leginus, J. M.; Dicken, C. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 87–128. (c) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

(7) (a) Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 3. (d) Curran, D. P. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 129–189. (c) Reference 5g, Chapter 2.

(8) Reviews of intramolecular [3 + 2] cycloadditions: (a) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 12. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(9) Only two examples of intramolecular cycloadditions of nitronates have been reported: (a) Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735. (b) Reference 5d.

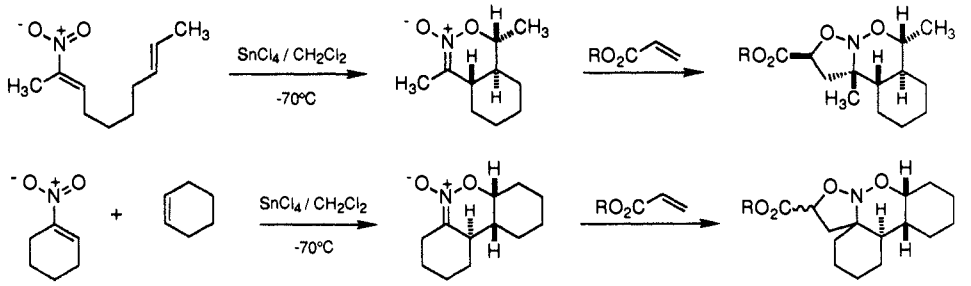
(10) For other examples of tandem [4 + 2]/[3 + 2] processes, see: (a) Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 1845. (b) Donegan, G.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1989**, *30*, 609, and references therein.

(11) (a) Bates, H. A.; Farina, J. *J. Org. Chem.* **1985**, *50*, 3843. (b) Woods, G. F. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 470. (c) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.

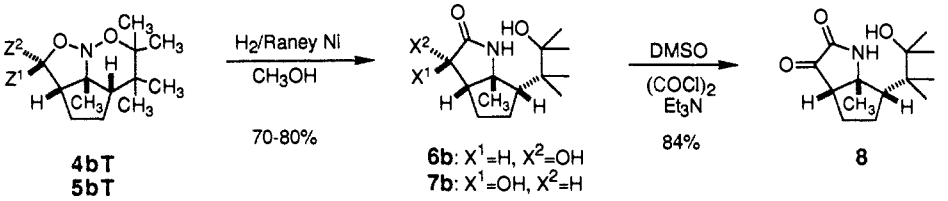
(12) For definition of these terms, see: Denmark, S. E.; Cramer, C. J.; Dappen, M. S. *J. Org. Chem.* **1987**, *52*, 877.

0002-7863/90/1512-311$02.50/0

Scheme I



Scheme II

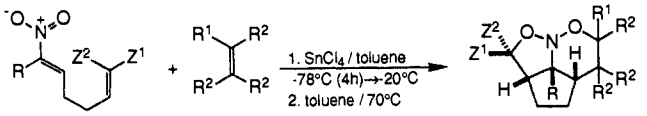


4bT
5bT

6b: X^1=H, X^2=OH
7b: X^1=OH, X^2=H

8

Table I. Tandem Cycloadditions with **1**



1a: R=H
1b: R=Me

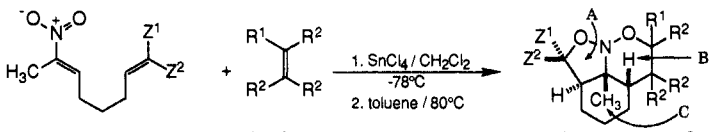
T: R^1=R^2=Me
B: R^1=*n*-BuO, R^2=H

4: Z^1=CO_2R^3, Z^2=H
5: Z^1=H, Z^2=CO_2R^3

educt	product	R	Z^1	Z^2	R^1	R^2	tim,[a] h	time,[b] h	ds[c]	yield, %
(*E*)-**1a**	**4aT**	H	CO_2Et	H	Me	Me	7	0	>100:1	68[d]
(*E*)-**1b**	**4bT**	Me	CO_2Et	H	Me	Me	7	0	>100:1	72
(*Z*)-**1a**	**5aT**	H	H	CO_2Me	Me	Me	8	2.5	*e*	76
(*Z*)-**1b**	**5bT**	Me	H	CO_2Me	Me	Me	8	3	20:1	78
(*E*)-**1b**[f]	**4bB/4bB'**	Me	CO_2Me	H	*n*-BuO[g]	H	1	0	>100:1	80

[a] [4 + 2] cycloaddition. Time at −20 °C. [b] [3 + 2] cycloaddition. [c] Determined by ^{1}H NMR. [d] Based on recovered starting material. [e] Three isomers (6:1:1:8). [f] $TiCl_2(O\text{-}i\text{-}Pr)_2/CH_2Cl_2$, −78 °C. [g] Mixture of anomers.

Table II. Tandem Cycloadditions with **2**



2a: Z=CO_2R / H
2b: Z=CN / H

T: R^1=R^2=Me
B: R^1=*n*-BuO, R^2=H

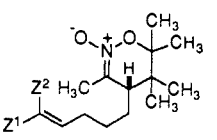
10: Z^1=CO_2R(CN), Z^2=H
11: Z^1=H, Z^2=CO_2R(CN)

educt	product	Z^1	Z^2	R^1	R^2	time,[a] min	yield,[b] %	time,[c] h	ds[d]	yield, %
(*E*)-**2a**	**10aT**	CO_2Et	H	Me	Me	10	66	14	2.6:1	90
(*Z*)-**2a**	**11aT**	H	CO_2Et	Me	Me	25	72	7	>100:1	93
(*E*)-**2b**	**10bT**	CN	H	Me	Me	25	83	20	2.8:1	97
(*Z*)-**2b**	**11bT**	H	CN	Me	Me	25	75	7	>100:1	95
(*Z*)-**2a**[e]	**11aB**	H	CO_2Me	*n*-BuO[f]	H	30	73	7[g]	32:1	93
	11aB'	H	CO_2Me	*n*-BuO[h]	H		11	7[g]	16:1	62

[a] [4 + 2] cycloaddition. [b] Isolated yield of **9**. [c] [3 + 2] cycloaddition. [d] Determined by ^{1}H NMR (300 MHz) and isolation. [e] $TiCl_2(O\text{-}i\text{-}Pr)_2/CH_2Cl_2$, −78 °C. [f] α isomer, more polar. [g] At 60 °C. [h] β isomer, less polar.

the same tricyclic stereostructure was confirmed by the reduction[5]/oxidation[13] sequence in Scheme II, which afforded the same α-keto lactam **8** from each. Thus, **4bT** and **5bT** differ only in the configuration of the ester-bearing carbon arising from *E*- or *Z*-enoates. Both the slower rate of [3 + 2] cycloaddition and erosion in stereoselectivity in the *Z* series are consequences of the well-established exo preference for dipolarophiles in reaction with nitronates.[1a,b,2a,3b,4]

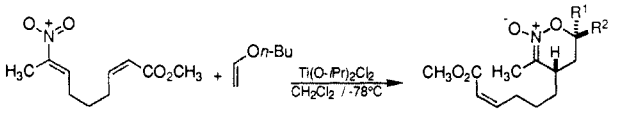
In the homologous series **2**, containing a trimethylene tether, we employed only trisubstituted nitroalkenes but compared carboethoxy (**2a**) and cyano (**2b**) activating groups. As with system **1**, the $SnCl_4$-induced cycloaddition proceeded rapidly at −78 °C in dichloromethane. In toluene the reactions were cleaner (71–89% yield) but much slower, so we opted to use dichloromethane since the byproduct was easily removed chromatographically. The results, Table II, were complementary to those from **1**. In this series, the [4 + 2] cycloadducts **9aT/9bT** could be isolated and



(*E/Z*)-**9aT/9bT**

(13) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

Scheme III



84%

R^1=O-*n*Bu, R^2=H: **9aB** (87)
R^1=H, R^2=O-*n*Bu: **9aB'** (13)

purified, and they all underwent subsequent cycloaddition at 80 °C. However in this case the *Z dienophiles reacted faster and with higher selectivity*. This divergent behavior was easily understood after the stereostructure of the cycloadducts was established by X-ray crystallographic analysis of **11bT**. The trans A/C cis B/C structure arises from a syn–exo transition state, which permits better staggering of the trimethylene tether. The exo-folding preference is reinforced in the *Z* series by simultaneously placing the ester/nitrile in the electronically preferred exo position. Both double cycloadducts **11aT** and **11bT** were formed stereoselectively in excellent yield. We were pleased that both dipolarophile activating functions were compatible. The nitriles cyclized more readily than the esters. The third series of substrates, **3**, underwent [4 + 2] cycloaddition to give cyclic nitronates with T and B (70–80% yield). However, they have thus far resisted attempts to induce the [3 + 2] process. This is not surprising, since the formation of a fused seven-membered ring by an intramolecular [3 + 2] cycloaddition has little precedent.[8a]

The problem of forming exo/endo isomers and regioisomers with unsymmetrically substituted alkenes presents a serious limitation. However, the synthetic utility of these reactions is enhanced by the observation that *n*-butyl vinyl ether (B) induces the tandem cycloaddition as well. For the more nucleophilic enol ethers we have followed Seebach's recommendation in the use of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ as the Lewis acid in dichloromethane solution. With this protocol, substrate (*E*)-**1b** afforded the double cycloadducts **4bB**/**4bB'** (Table I) as separable mixture of anomers in high yield. The anomer mixture was variable and was shown to be sensitive to reagent/substrate stoichiometry. Kinetic control of the anomeric center was not established. Similarly, (*Z*)-**2a** underwent [4 + 2] cycloaddition to afford **9aB**/**9aB'** as a separable (7:1) mixture of anomers (Scheme III). The separated isomers underwent facile cyclization to give the double cycloadducts **11aB** and **11aB'** (Table II).

Hydrogenation[5] of the separated isomers **4bB** and **4bB'** with Raney nickel at atmospheric pressure gave a single tricyclic lactam **12** (Scheme IV). Complete hydrogenolysis of **11aB** and **11aB'** required slightly higher pressure and gave the amino ester **13**.[14] Formation of the lactam **14** required heating due to the formation of trans ring fusion. These products arise from the sequence (1) N–O hydrogenolysis, (2) hemiacetal breakdown, (3) imine formation, (4) saturation, and (5) lactamization.[15] The stereoselective construction of these polycyclic compounds in two or three steps from readily prepared acyclic precursors bodes well for the application of this strategy in synthesis.

Finally, we have recently demonstrated that chiral, nonracemic vinyl ethers produce the double cycloadduct **12** with very high stereoselectivity (>90% ee).[16] Opportunities in this area and the selective manipulation of the cycloadducts are under current investigation.

Experimental Section

General Methods. See supplementary material. (NMR coupling constants, *J*, are given in hertz.)

Ethyl *rel*-(1*R*,3*S*,6a*R*,8a*R*,8b*S*)-5,5,6,6,8b-Pentamethyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (4bT). To a magnetically stirred, cold (−78 °C) solution of nitroalkene (*E*)-**1b** (106 mg, 0.491 mmol, 1.0 equiv) and 2,3-dimethyl-2-butene (84 mg, 0.994 mmol, 2.0 equiv) in dry toluene (5 mL, 0.1 M solution) was added freshly distilled tin(IV) chloride (115 μL, 0.994 mmol, 2.0 equiv). The solution was stirred at −78 °C for 4 h and at −20 °C for 7 h, quenched with 0.5 N NaOH in methanol (8 mL), and allowed to warm to room temperature. The mixture was then poured into saturated aqueous sodium bicarbonate (25 mL) and extracted with dichloromethane (3 × 25 mL). The dichloromethane extracts were washed with water (25 mL) and brine (25 mL), dried over magnesium sulfate, and concentrated under reduced pressure, and the residue was chromatographed on silica gel (hexane/EtOAc, 4/1) to afford 102 mg (75%) of **4bT** as a white solid, which was recrystallized with hexane. For **4bT**: mp 58–59 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 6.73, 1 H, HC(1)), 4.20 (q, *J* = 7.15, 2 H, $H_2C(15)$), 2.68 (q, *J* = 6.76, 1 H, HC(8a)), 2.22–1.75 (m, 5 H), 1.41 (s, 3 H, $CH_3C(5)$), 1.30 (s, 3 H, $CH_3C(5)$), 1.26 (t, *J* = 7.15, 3 H, $H_3C(16)$), 1.21 (s, 3 H, $H_3C(9)$), 1.19 (s, 3 H, $CH_3C(6)$), 0.98 (s, 3 H, $CH_3C(6)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.00 (C(14)), 86.31 (C(1)), 85.12 (C(5)), 80.48 (C(8b)), 61.01 (C(13)), 59.30 (C(8a)), 57.21 (C(6a)), 36.93 (C(6)), 31.37 (C(8)), 29.47 (C(9)), 29.38 (C(7)), 27.20/27.02 ($CH_3C(5)$), 25.95/24.30 ($CH_3C(6)$), 13.98 (C(14)); IR (CCl_4) 2982 (m), 2874 (w), 1757 (m), 1738 (m), 1446 (w), 1392 (w), 1377 (m), 1192 (m), 1169 (m), 1151 (m), 1041 (w), 850 (m) cm^{-1}; MS (70 eV) *m/z* 297 (M^+, 25), 224 (13), 167 (22), 166 (21), 136 (18), 96 (17), 95 (16), 83 (100), 81 (46), 69 (56), 57 (50), 55 (50), 43 (55); TLC R_f 0.68 (hexane/EtOAc, 4/1); GC t_R 7.84 min (COV-17 (50 m), 200 °C). Anal. Calcd for $C_{16}H_{27}NO_4$ (297.394): C, 64.62; H, 9.15; N, 4.71. Found: C, 64.69; H, 9.13; N, 4.75.

Methyl *rel*-(1*R*,3*R*,6a*S*,8a*S*,8b*R*)-5,5,6,6,8b-Pentamethyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (5bT). To a magnetically stirred, cold (−78 °C) solution of nitroalkene (*Z*)-**1b** (92 mg, 0.462 mmol, 1.0 equiv) and 2,3-dimethyl-2-butene (110 μL, 0.924 mmol, 2.0 equiv) in dry toluene (5 mL, 0.09 M solution) was added freshly distilled tin(IV) chloride (108 μL, 0.924 mmol, 2.0 equiv). The solution was stirred at −78 °C for 4 h and at −20 °C for 8 h, quenched with 0.5 N NaOH in methanol (8 mL), and allowed to warm to room temperature. The mixture was then poured into saturated aqueous sodium bicarbonate (25 mL) and extracted with dichloromethane (3 × 25 mL). The dichloromethane extracts were washed with water (25 mL) and brine (25 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in toluene (10 mL) and heated at 70 °C for 3 h. The solution was concentrated under reduced pressure, and the residue was chromatographed on silica gel (hexane/EtOAc, 4/1) to afford 96 mg (78%) of **5bT**, a white solid, as a 20:1 mixture of isomers. An analytical sample of the major isomer was obtained after recrystallization from hexane. For **5bT** (major): mp 99–100 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, *J* = 8.66, 1 H, HC(1)), 3.75 (s, 3 H, $H_3(C15)$), 2.96 (q, *J* = 8.91, 1 H, HC(8a)), 2.10–1.95 (m, 4 H), 1.72–1.67 (m, 1 H), 1.34 (s, 3 H, $CH_3C(5)$), 1.28 (s, 3 H, $CH_3C(5)$), 1.20 (s, 3 H, $H_3C(9)$), 1.13 (s, 3 H, $CH_3C(6)$), 0.95 (s, 3 H, $CH_3C(6)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.58 (C(14)), 84.25 (C(5)), 83.98 (C(1)), 80.79 (C(8b)), 57.21 (C(15)), 56.39 (C(8a)), 51.83 (C(6a)), 37.91 (C(6)), 30.44 (C(8)), 29.92 (C(9)), 29.28 (C(7)), 26.98 ($CH_3C(5)$), 25.62 ($CH_3C(5)$), 25.53 ($CH_3C(6)$), 24.46 ($CH_3C(6)$); IR (CCl_4) 2979 (m), 2901 (m), 2874 (w), 1772 (m), 1732 (m), 1460 (w), 1437 (w), 1392 (w), 1377 (m), 1370 (w), 1288 (w), 1257 (w), 1198 (m), 1175 (m), 1153 (m), 1099 (w), 1019 (w), 934 (w), 860 (m) cm^{-1}; MS (70 eV) *m/z* 283 (M^+, 11), 226 (11), 224 (11), 184 (20), 168 (20), 166 (29), 153 (15), 136 (25), 128 (11), 125 (49), 124 (12), 121 (12), 119 (10), 107 (19), 93 (24), 83 (89), 69 (76), 55 (71), 43 (87), 41 (100); TLC R_f 0.35 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{15}H_{25}NO_4$ (283.367): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.69, H, 8.83; N, 5.04.

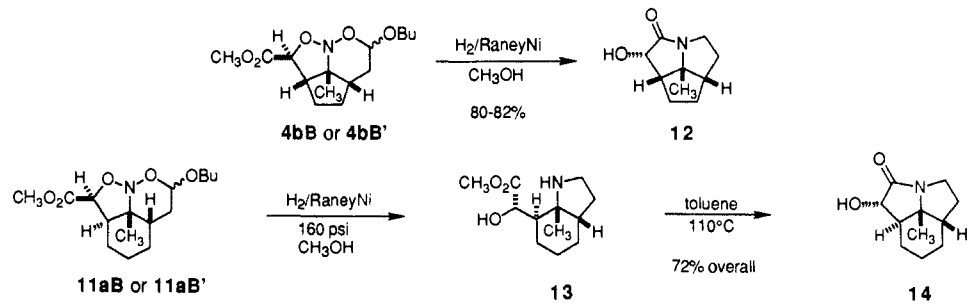
Ethyl 2-(*Z*)-5,6-Dihydro-2-oxido-3,5,5,6,6-pentamethyl-4*H*-1,2-oxazine-4-hexenoate (9aT). To a magnetically stirred solution of nitroalkene (*Z*)-2a (292 mg, 1.28 mmol, 1.0 equiv) and 2,3-dimethyl-2-butene (306 μL, 256 mmol, 2.0 equiv) in dichloromethane (10 mL, 0.12 M solution) was added freshly distilled tin(IV) chloride (302 μL, 2.56 mmol, 2.0 equiv) dropwise at −78 °C. After 25 min, the mixture was quenched with saturated aqueous sodium bicarbonate (5 mL) and ethyl acetate (30 mL) was added. The mixture was warmed to 10 °C slowly (~20 min) and diluted with saturated aqueous sodium bicarbonate (30 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL). The aqueous layers were back-extracted with ethyl acetate (2 × 40 mL) and the combined organic layers were dried over sodium sulfate, concentrated under reduced pressure, and chromatographed on silica gel (hexane/EtOAc, 5/3, 250 mL; hexane/EtOAc, 1/1, 250 mL; EtOAc, 500 mL) to afford 63.7 mg (16%) of rearranged product and 287.1 mg (72%) of **9aT** as white solids, which were recrystallized with hexane. For **9aT**: mp 52–53 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (dt, *J* = 11.6, 7.6, 1 H, HC(14)), 5.78 (d, *J* = 11.6, 1 H, HC(15)), 4.14 (q, *J* = 7.1, 2 H, $H_2C(17)$), 2.75–2.60 (m, 2 H, $H_2C(13)$), 2.21 (br s, 1 H, HC(4)), 2.06 (s, 3 H, $H_3C(19)$),

(14) The intermediate products from hydrogenolysis of **11aB** and **11aB'** have been characterized. This detail will be discussed in a full account of this work.

(15) Seebach has reported a similar, though more capricious transformation: Reference 2a.

(16) Ho, G.-D., unpublished results from these laboratories.

Scheme IV



1.68–1.59 (m, 2 H, $H_2C(12)$), 1.56–1.48 (m, 2 H, $H_2C(11)$), 1.29 (s, 3 H, $H_3C(7)$), 1.28 (s, 3 H, $H_3C(8)$), 1.26 (t, J = 7.1, 3 H, $H_3C(18)$), 0.96 (s, 3 H, $H_3C(9)$), 0.95 (s, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.04 (C(16)), 148.64 (C(14)), 124.19 (C(3)), 120.42 (C(15)), 86.25 (C(6)), 59.69 (C(17)), 45.79 (C(4)), 37.13 (C(5)), 29.71 (C(13)), 28.85 (C(11)), 27.63 (C(12)), 23.05 (CH_3), 21.66 (CH_3), 20.24 (CH_3), 18.23 (CH_3), 16.77 (C(9)), 14.09 (C(18)); IR (CCl_4) 2984 (m), 1721 (s), 1646 (w), 1597 (m), 1462 (w), 1416 (w), 1399 (w), 1383 (w), 1269 (m), 1237 (m), 1190 (s), 1165 (m), 1034 (w), 934 (w), 885 (w) cm^{-1}; MS (10 eV) m/z 312 (M^+ + 1, 25), 311 (M^+, 100), 281 (16), 254 (18), 253 (18), 239 (17), 238 (64), 236 (21), 192 (13), 181 (13), 180 (50), 179 (17), 153 (14), 152 (13), 150 (13), 140 (73), 122 (12), 121 (20), 120 (23), 111 (12), 110 (46), 106 (15), 84 (30), 59 (18); TLC R_f 0.08 (hexane/EtOAc, 1/1), 0.19 (EtOAc). Anal. Calcd for $C_{17}H_{29}NO_4$ (311.42): C, 65.57; H, 9.38; N, 4.50. Found: C, 65.52; H, 9.33; N, 4.46.

Ethyl *rel*-(1*R*,3*S*,6a*R*,9a*S*,9b*S*)-5,5,6,6,9b-Pentamethyldecahydro-1*H*-isooxazolo[2,3,4-*h*][2,1]benzoxazine-1-carboxylate (11aT). A stirred solution of **9aT** (138.8 mg, 0.46 mmol) in dry toluene (5 mL, 0.09 M solution) was briefly degassed twice at room temperature. The solution was heated to 80 °C for 7 h and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexane/EtOAc, 10/1, 100 mL; hexane/EtOAc, 5/1, 100 mL) to afford 129.1 mg (93%) of **11aT** as a viscous oil. For **11aT**: bp 130 °C (1.6×10^{-4} Torr) (bulb-to-bulb distillation); ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, J = 10.8, 1 H, HC(1)), 4.25–4.13 (m, 2 H, $H_2C(16)$), 3.25 (ddd, J = 13.2, 10.8, 3.1, 1 H, HC(9a)), 2.10–2.00 (m, 2 H), 1.82–1.57 (m, 5 H), 1.45–1.30 (m, 1 H), 1.37 (s, 3 H, H_3C), 1.25 (t, J = 7.1, 3 H, $H_3C(17)$), 1.14 (s, 3 H, H_3C), 1.10 (s, 3 H, H_3C), 1.08 (s, 3 H, H_3C), 0.81 (s, 3 H, H_3C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.82 (C(15)), 81.87 (C(5)), 78.83 (C(1)), 70.82 (C(9b)), 60.55 (C(16)), 46.39 (C(9a)), 42.26 (C(6a)), 37.60 (C(6)), 25.84 (CH_3), 23.88 (CH_2), 23.08 (CH_3), 22.42 (CH_3), 22.18 (CH_3), 21.87 (CH_2), 21.63 (CH_2), 19.63 (C(10)), 13.95 (C(17)); IR (CCl_4) 2982 (m), 2948 (m), 1759 (s), 1730 (m), 1470 (w), 1449 (w), 1395 (w), 1377 (w), 1368 (w), 1337 (w), 1266 (w), 1239 (w), 1188 (s), 1144 (w), 1109 (w), 1078 (w), 1028 (w), 970 (w), 938 (w), 909 (m), 884 (w), 853 (m), 839 (m) cm^{-1}; MS (10 eV) m/z 312 (M^+ + 1, 29), 311 (M^+, 99), 254 (26), 238 (21), 180 (100), 150 (21), 110 (80), 97 (27); TLC R_f 0.18 (hexane/EtOAc, 10/1), 0.29 (hexane/EtOAc, 5/1), 0.45 (hexane/EtOAc, 10/3). Anal. Calcd for $C_{17}H_{29}NO_4$ (311.42): C, 65.57; H, 9.38; N, 4.50. Found: C, 65.25; H, 9.34; N, 4.44.

Methyl *rel*-(1*R*,3*S*,5*R*,6a*R*,8a*R*,8b*S*)-5-Butoxy-8b-methyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (4bB) and Methyl *rel*-(1*R*,3*S*,5*S*,6a*R*,8a*R*,8b*S*)-5-Butoxy-8b-methyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (4bB'). To a magnetically stirred solution of titanium(IV) isopropoxide (645 μL, 2.258 mmol, 1.5 equiv) in dichloromethane (5.0 mL), was added freshly distilled titanium(IV) chloride (247 μL, 2.258 mmol, 1.5 equiv). The solution was stirred at room temperature for 0.5 h and cooled to −78 °C; then a cold (−78 °C) solution of nitroalkene (300 mg, 1.50 mmol, 1.0 equiv) and butyl vinyl ether (969 μL, 7.50 mmol, 5.0 equiv) in dichloromethane (2.5 mL) was added via cannula. The resulting pale yellow solution was stirred at −78 °C for 1 h, quenched with 0.5 N NaOH in methanol (10 mL), and allowed to warm to room temperature. The mixture was then poured into diethyl ether (25 mL) and washed with water (3 × 25 mL). The aqueous layers were extracted with diethyl ether (2 × 25 mL). The combined ether layer was dried ($MgSO_4/NaHCO_3$, 1/1) and concentrated under reduced pressure, and the residue was chromatographed on silica gel (hexane/EtOAc, 4/1) to afford 314 mg (70%) of **4bB** and 45 mg (10%) of **4bB'** as clear oils. For **4bB**: bp 105–108 °C (0.05 Torr); ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (dd, J = 3.48, 6.42, 1 H, HC(5)), 4.86 (d, J = 8.3, 1 H, HC(1)), 3.85 (dt, J = 9.63, 6.77, 1 H, HC(10)), 3.78 (s, 3 H, $H_3C(15)$), 3.51 (dt, J = 9.67, 6.72, 1 H, HC(10)), 2.72 (dt, J = 7.73, 2.64, 1 H, HC(8a)), 2.14–1.34 (m, 11 H), 1.31 (s, 3 H, $H_3C(9)$), 0.90 (t, J = 7.31, 3 H, $H_3C(13)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.07 (C(14)), 99.65 (C(5)), 86.63 (C(1)), 83.04 (C(8b)), 69.60 (C(10)), 57.28 (C(15)), 52.25 (C(8a)), 43.45 (C(6a)), 34.35 (C(6)), 31.76 (C(11)), 28.68 (C(8)), 27.94 (C(7)), 24.58 (C(9)), 19.09 (C(12), 13.77 (C(13)); IR (CCl_4) 2957 (m), 2934 (m), 2874 (m), 1761 (m), 1743 (m), 1439 (w), 1282 (w), 1252 (w), 1201 (w), 1180 (w), 1136 (m), 1097 (m), 1020 (w), 841 (m) cm^{-1}; MS (70 eV) m/z 299 (M^+), 269 (2), 163 (9), 135 (10), 107 (20), 81 (100), 57 (12), 41 (24); TLC R_f 0.66 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{15}H_{25}NO_5$ (299.376): C, 60.18; H, 8.42; N, 4.68. Found: C, 60.22; H, 8.46; N, 4.67. For **4bB'**: bp 105–108 °C (0.05 Torr); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (t, J = 7.43, 1 H, HC(5)), 4.78 (d, J = 7.92, 1 H, HC(1)), 3.81 (dt, J = 9.62, 6.86, 1 H, HC(10)), 3.72 (s, 3 H, $H_3C(15)$), 3.36 (dt, J = 9.62, 7.01, 1 H, HC(10)), 2.67 (m, 1 H, HC(8a)), 2.06–1.33 (m, 11 H), 1.28 (s, 3 H, $H_3C(9)$), 0.84 (t, J = 7.33, 3 H, $H_3C(13)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.14 (C(14)), 98.62 (C(5)), 87.27 (C(1)), 85.27 (C(8b)), 67.88 (C(10)), 56.72 (C(15)), 52.31 (C(8a)), 43.15 (C(6a)), 31.64 (C(6)), 31.51 (C(11), 28.69 (C(8)), 26.78 (C(7)), 23.68 (C(9)), 19.22 (C(12)), 13.08 (C(13)); IR (CCl_4) 2959 (m), 2874 (m), 1744 (m), 1439 (w), 1283 (w), 1254 (w), 1200 (w), 1183 (w), 1119 (m), 1088 (w), 1039 (w), 1010 (w) cm^{-1}; MS (70 eV) m/z 299 (M^+), 269 (3), 226 (10), 163 (12), 135 (16), 107 (25), 96 (12), 81 (100), 79 (16), 57 (12), 55 (12), 41 (29); TLC R_f 0.60 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{15}H_{25}NO_5$ (299.38): C, 60.18; H, 8.42; N, 4.68. Found: C, 60.08; H, 8.43; N, 4.78.

Methyl *rel*-(4*R*,6*R*)-2-(*Z*)-6-*n*-Butoxy-3-methyl-2-oxido-5,6-dihydro-4*H*-1,2-oxazine-4-hexenoate (9aB) and Methyl *rel*-(4*R*,6*S*)-2-(*Z*)-6-*n*-Butoxy-3-methyl-2-oxido-5,6-dihydro-4*H*-1,2-oxazine-4-hexenoate (9aB'). To a magnetically stirred, cold (−78 °C) solution of nitroalkene **2a** (198 mg, 0.93 mmol, 1.0 equiv) and butyl vinyl ether (240 μL, 1.85 mmol, 2.0 equiv) in dichloromethane (2.5 mL) was added dropwise a freshly prepared solution of titanium diisopropoxy dichloride (prepared as described in **4bB**, 3.7 mmol, 4.0 equiv) in dichloromethane (2 mL). After 30 min at −78 °C the reaction mixture was quenched with 0.5 N NaOH in methanol (8 mL) at −78 °C. The resulting white emulsion was diluted with dichloromethane (50 mL), 0.1 N NaOH (20 mL), and saturated aqueous sodium bicarbonate (30 mL). The organic layer was washed with 0.1 N NaOH (2 × 50 mL). The aqueous layers were back-extracted with dichloromethane (2 × 50 mL) and the combined organic layers were dried over sodium sulfate, concentrated under reduced pressure, and chromatographed on silica gel (CH_2Cl_2/EtOAc, 1/1) to afford 20.4 mg (7%) of **9aB'**, 85.3 mg (29%) of **9aB**/**9aB'** (6:1), and 139.5 mg (48%) of **9aB**. For **9aB**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (dt, J = 11.4, 7.6, 1 H, HC(14)), 5.78 (d, J = 11.4, 1 H, HC(15)), 5.24 (t, J = 4.2, 1 H, HC(6)), 3.95 (dt, J = 9.4, 6.6, 1 H, HC(7)), 3.67 (s, 3 H, $H_3C(17)$), 3.51 (dt, J = 9.4, 6.6, 1 H, HC(7)), 2.66 (q, J = 7.4, 2 H, $H_2C(13)$), 2.43 (quintet, J = 6.4, 1 H, HC(4)), 2.17 (ddd, J = 13.6, 7.7, 3.9, 1 H, $H_{eq}C(5)$), 2.03 (s, 3 H, $H_3C(18)$), 1.78 (dt, J = 13.6, 5.1, 1 H, $H_{ax}C(5)$), 1.63 (quintet, J = 7.4, 2 H, $H_2C(8)$), 1.50 (q, J = 7.1, 2 H, $H_2C(11)$), 1.46–1.38 (m, 2 H, HC(12)), 1.32 (q, J = 7.3, 2 H, $H_2C(9)$), 0.88 (t, J = 7.3, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.26 (C(16)), 149.17 (C(14)), 124.61 (C(3)), 119.61 (C(15)), 102.40 (C(6)), 69.18 (C(7)), 50.68 (C(17)), 34.56 (C(4)), 31.11 (2 CH_2), 29.60 (CH_2), 28.01 (C(11)), 25.72 (C(12)), 18.81 (C(9)), 16.30 (C(18)), 13.45 (C(10)); IR (CCl_4) 2957 (m), 2872 (m), 1761 (m), 1725 (s), 1646 (m), 1611 (s), 1549 (w), 1439 (w), 1408 (w), 1375 (w), 1337 (w), 1244 (m), 1200 (s), 1175 (s), 1121 (w), 1096 (w), 1057 (w), 1005 (w), 976 (w), 902 (w) cm^{-1}; TLC R_f 0.40 (EtOAc). For **9aB'**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (dt, J = 11.4, 7.6, 1 H, HC(14)), 5.78 (d, J = 11.4, 1 H, HC(15)), 5.25 (t, J = 2.6, 1 H, HC(6)), 3.91 (dt, J = 9.6, 6.7, 1 H, HC(7)), 3.68 (s, 3 H, $H_3C(17)$), 3.56 (dt, J = 9.6, 6.5, 1 H, HC(7)), 2.65 (q, J = 6.8, 2 H, $H_2C(13)$), 2.63–2.47 (m, 1 H, HC(4)), 2.02 (d, J = 0.9, 3 H, $H_3C(18)$), 2.01 (ddd, J = 13.5, 9.0, 2.0, 1 H, $H_{eq}C(5)$), 1.76 (dt, J = 13.5, 3.6, 1 H, $H_{ax}C(5)$), 1.75–1.66 (m, 1 H, HC(11), 1.56–1.46 (m, 2 H, $H_2C(8)$), 1.46–1.36 (m, 3 H, HC(11)), $H_2C(12)$), 1.31 (q, J = 7.3, 2 H, $H_2C(9)$), 0.87 (t, J = 7.3, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.65 (C(16)), 149.29 (C(14)), 124.65 (C(3)), 120.06

(C(15)), 101.04 (C(6)), 68.97 (C(7)), 51.10 (C(17)), 33.08 (C(4)), 31.78 (CH_2), 31.39 (CH_2), 30.43 (CH_2), 28.58 (C(11)), 25.49 (C(12)), 19.12 (C(9)), 16.60 (C(18)), 13.78 (C(10)); IR (CCl_4) 2957 (m), 2872 (m), 1763 (w), 1725 (s), 1647 (w), 1615 (m), 1547 (w), 1439 (m), 1408 (w), 1383 (w), 1335 (w), 1266 (m), 1200 (s), 1179 (m), 1119 (m), 1088 (m), 1040 (m), 984 (m), 905 (w) cm^{-1}; TLC R_f 0.52 (EtOAc).

Methyl *rel*-(1*R*,3*S*,5*R*,6a*R*,9a*S*,9b*S*)-5-*n*-Butoxy-9b-methylhexahydro-1*H*-isooxazolo[2,3,4-*hi*][2,1]benzoxazine-1-carboxylate (11aB). To a solution of nitronate **9aB** (226.6 mg, 0.72 mmol) in freshly distilled toluene (23 mL, 0.03 M solution) was added ~40 mg of anhydrous sodium bicarbonate. The solution was carefully degassed twice and then heated to 60 °C under N_2 for 7 h. The mixture was filtered and concentrated. The crude product ratio was determined by means of ^1H NMR (97:3), and the crude products were chromatographed on silica gel (hexane/EtOAc, 10/1, 200 mL; hexane/EtOAc, 7.5/1, 300 mL; hexane/EtOAc, 5/1, 200 mL; hexane/EtOAc, 5/2, 200 mL) to afford 190.5 mg (84%) of **11aB**. For **11aB**: bp 170 °C (1.2×10^{-3} Torr); ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, J = 10.8, 1 H, HC(1)), 4.66 (dd, J = 9.9, 2.0, 1 H, HC(5)), 3.93 (dt, J = 9.6, 6.7, 1 H, HC(11)), 3.73 (s, 3 H, $H_3C(16)$), 3.52 (dt, J = 9.6, 6.9, 1 H, HC(11)), 3.21 (ddd, J = 13.5, 10.8, 3.2, 1 H, HC(9a)), 2.20 (dt, J = 12.1, 5.9, 1 H, HC(6)), 2.06–2.00 (m, 1 H, HC(6)), 1.81–1.67 (m, 2 H), 1.61–1.44 (m, 3 H), 1.42–1.31 (m, 2 H), 1.15 (s, 3 H, $H_3C(10)$), 0.90 (t, J = 7.3, 3 H, $H_3C(14)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.19 (C(15)), 99.88 (C(5)), 79.39 (C(1)), 71.02 (C(9b)), 69.43 (C(11)), 51.80 (C(16)), 40.24 (C(9a)), 37.10 (C(6a)), 31.54 (C(6)), 30.10 (C(12)), 25.96 (C(7)), 22.63 (C(9)), 21.98 (C(8)), 19.02 (C(13)), 18.58 (C(10)), 13.76 (C(14)); IR (CCl_4) 2955 (s), 2869 (m), 2361 (w), 1763 (s) (C=O), 1736 (m) (C=O), 1549 (m), 1449 (w), 1437 (w), 1374 (w), 1331 (w), 1257 (m), 1200 (s), 1163 (s), 1078 (m), 1057 (m), 1003 (m), 922 (w), 901 (w), 837 (s) cm^{-1}; MS (10 eV) m/z 313 (M^+, 46), 255 (13), 254 (53), 209 (26), 191 (17), 184 (11), 183 (34), 182 (100), 180 (22), 155 (12), 123 (17), 121 (15), 95 (46); TLC R_f 0.08 (hexane/EtOAc, 10/1), 0.22 (hexane/EtOAc, 5/1), 0.35 (hexane/EtOAc, 10/3). Anal. Calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.69; N, 4.47. Found: C, 61.42; H, 8.75; N, 4.39.

Methyl *rel*-(1*R*,3*S*,5*S*,6a*R*,9a*S*,9b*S*)-5-*n*-Butoxy-9b-methylhexahydro-1*H*-isooxazolo[2,3,4-*hi*][2,1]benzoxazine-1-carboxylate (11aB′). To a solution of nitronate **9aB′** (84 mg, 0.26 mmol) in freshly distilled toluene (8.4 mL, 0.03 M solution) was added 30 mg of anhydrous sodium bicarbonate. The solution was carefully degassed twice and then heated to 60 °C under N_2 for 7 h. The mixture was filtered and concentrated. The crude product ratio was determined by means of ^1H NMR (93:7), and the crude products were chromatographed on silica gel (hexane/EtOAc, 10/1, 100 mL; hexane/EtOAc, 7.5/1, 100 mL; hexane/EtOAc, 5/1, 50 mL; hexane/EtOAc, 5/2, 50 mL) to afford 52.4 mg (62.4%) of **11aB′**. For **11aB′**: bp 165 °C (8.1×10^{-4} Torr); ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (d, J = 3.5, 1 H, HC(5)), 4.82 (d, J = 10.8, 1 H, HC(1)), 3.95 (dt, J = 9.5, 6.9, 1 H, HC(11)), 3.73 (s, 3 H, $H_3C(16)$), 3.43 (dt, J = 9.5, 6.6, 1 H, HC(11)), 3.16 (ddd, J = 11.8, 11.0, 3.2, 1 H, HC(9a)), 2.52 (dt, J = 12.6, 5.8, 1 H, HC(6)), 2.07 (dt, J = 12.6, 2.5, 1 H, HC(6)), 1.93 (dt, J = 13.3, 3.7, 1 H), 1.82–1.71 (m, 2 H), 1.62–1.30 (m, 8 H), 1.17 (s, 3 H, $H_3C(10)$), 0.91 (t, J = 7.3, 3 H, $H_3C(14)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.22 (C(15)), 99.44 (C(5)), 79.50 (C(1)), 71.02 (C(9b)), 66.62 (C(11)), 51.80 (C(16)), 40.35 (C(9a)), 33.63 (C(6a)), 31.32 (CH_2), 27.29 (CH_2), 25.66 (CH_2), 22.74 (CH_2), 21.53 (CH_2), 19.23 (C(13)), 18.75 (C(10)), 13.83 (C(14)); IR (CCl_4) 2957 (s), 2936 (s), 2866 (m), 1763 (s) (C=O), 1734 (m) (C=O), 1549 (m), 1451 (w), 1437 (w), 1383 (w), 1335 (w), 1264 (s), 1202 (s), 1115 (s), 1088 (m), 1040 (m), 1003 (m), 978 (m), 911 (w) cm^{-1}; MS (10 eV) m/z 313 (M^+, 26), 254 (24), 240 (38), 209 (19), 191 (17), 183 (26), 182 (100), 180 (14), 149 (24), 123 (17), 121 (15), 95 (32); TLC R_f 0.08 (hexane/EtOAc, 10/1), 0.22 (hexane/EtOAc, 5/1), 0.35 (hexane/EtOAc, 10/3). Anal. Calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.69; N, 4.47. Found: C, 61.33; H, 8.70; N, 4.47.

***rel*-(1*R*,3*S*,5a*R*,7a*R*,7b*S*)-1Hydroxy-7b-methyl-2-oxo-5a,6,7,7a-tetrahydrocyclopenta[1,2,3-*gi*]pyrrolidino[1,2-*a*]pyrrolidine (12).** To a solution of nitrosoacetal **4bB** (178 mg, 0.595 mmol) in methanol (3 mL) was added a catalytic amount of Raney nickel. The suspension was stirred under H_2 (1 atm) at room temperature for 24 h, filtered through a Celite pad, and concentrated, and the residue was chromatographed on silica gel (hexane/EtOAc, 1/3) to afford 87 mg (81%) of **12** as a white solid, which recrystallized with ethyl acetate. For **12**: mp 115–116 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (dd, J = 6.92, 2.31, 1 H, HC(1)), 3.93 (d, J = 2.9, 1 H, OH (exch D_2O)), 3.85 (ddd, J = 11.98, 8.47, 3.01, 1 H, HC(4)), 2.88 (dt, J = 11.90, 7.95, 1 H, HC(4)), 2.58 (q, J = 7.39, 1 H, HC(7a)), 2.22 (m, 1 H), 2.05 (m, 1 H), 1.72 (m, 3 H), 1.44 (m, 1 H), 1.26 (s, 3 H, $H_3C(8)$), 1.22 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.46 (C(2)), 75.56 (C(7b)), 72.85 (C(1)), 51.11 (C(7a)), 49.23 (C(5a)), 42.11 (C(4)), 31.48 (C(5)), 31.00 (C(7)), 24.85 (C(6)), 22.88 (C(8)); IR (KBr) 3337 (m), 2957 (m), 2864 (m), 1676 (s), 1558 (m), 1541 (m), 1456 (m), 1412 (m), 1336 (m), 1153 (m) cm^{-1}; MS (70 eV) m/z 182 ($M^+ + 1$, 48), 181 (M^+, 90), 166 (100), 138 (62), 124 (16), 110 (25), 107 (44), 96 (42), 82 (55), 67 (46), 55 (89), 41 (80), 39 (55); TLC R_f 0.11 (hexane/EtOAc, 2/1); GC t_R 7.6 min (220 °C HP-1, 50 m). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.23): C, 60.18; H, 8.42; N, 4.68. Found: C, 60.08; H, 8.43; N, 4.78.

***rel*-(1*R*,3*S*,5a*R*,8a*R*,8b*S*)-1-Hydroxy-8b-methyl-2-oxohexahydropyrrolidino[1,5,4-*hi*]indoline (14).** To a solution of nitrosoacetal **11aB** (89.5 mg, 0.29 mmol) in methanol (reagent grade, 18 mL, 0.016 M solution) was added Raney nickel (~150 mg). The solution was placed in a pressure bottle, which was twice degassed and filled with hydrogen gas (180 psi). The mixture was stirred for 16 h at room temperature under hydrogen pressure (140–180 psi). The crude product was filtered through Celite and concentrated under reduced pressure to afford 63.9 mg (98%) of a crude amino alcohol **13**, which was used for the next cyclization without purification. The amino alcohol (63.9 mg, 0.28 mmol) was dissolved in freshly distilled toluene (10 mL, 0.03 M solution in the presence of 4-Å molecular sieves, ~300 mg) and refluxed for 42 h. The mixture was filtered, concentrated under reduced pressure, and chromatographed on silica gel (hexane/EtOAc, 2/1) to afford 40.1 mg (73%) of a white solid, which was recrystallized with hexane. For **14**: mp 114–116 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 4.37 (dd, J = 10.9, 1.7, 1 H, HC(1)), 3.88 (dd, J = 11.9, 7.5, 1 H, $H_\alpha C(4)$), 3.12 (br s, 1 H, OH), 2.97 (td, J = 11.9, 5.4, 1 H, $H_\beta C(4)$), 2.14 (quintet, J = 6.14, 1 H, $H_\beta C(5)$), 1.91–1.72 (m, 5 H), 1.62–1.55 (m, 2 H), 1.44–1.20 (m, 2 H), 1.20 (s, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.45 (C(2)), 73.48 (C(1)), 62.96 (C(9b)), 50.24 (C(9a)), 45.17 (C(4)), 43.17 (C(6)), 34.90 (CH_2), 26.06 (CH_2), 22.47 (C(10)), 19.61 (CH_2), 17.61 (CH_2); IR (CCl_4) 3523 (w), 3391 (w), 2948 (m), 2878 (m), 1711 (s) (N—C=O), 1470 (w), 1381 (m), 1337 (m), 1302 (w), 1283 (w), 1235 (w), 1208 (w), 1165 (m), 1130 (w), 1111 (m), 1059 (w), 1024 (w), 995 (w), 955 (w), 909 (w), 872 (w) cm^{-1}; MS (10 eV) m/z 196 ($M^+ + 1$, 4), 195 (M^+, 22), 181 (11), 180 (100), 178 (3), 167 (9), 166 (5), 162 (9), 152 (13), 150 (18), 139 (3), 137 (3), 124 (8), 108 (3), 98 (4), 96 (5), 85 (3), 84 (6); TLC R_f 0.06 (hexane/EtOAc, 2/1), 0.12 (hexane/EtOAc, 1/1), 0.30 (EtOAc); GC t_R 9.1 min (HP-1, 50 m, 100 °C (5 min), 10° C/min, 250 °C (5 min)). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.18. Found: C, 67.52; H, 8.84; N, 7.10.

Acknowledgment. We gratefully acknowledge the financial support provided for this project by the National Institutes of Health (PHS GM-30938). Y.-C.M. gratefully acknowledges the University of Illinois for a Graduate Fellowship (1986–1989). S.E.D. also acknowledges support from the NSF [Presidential Young Investigator Award (1985–1990)] and the Alfred P. Sloan Foundation (1985–1989).

Supplementary Material Available: General methods and procedures and full characterization of **4aT, 6b, 7b, 8, 9bT,** and **11bT** and tables of crystal and positional parameters, bond lengths, bond angles, and torsional angles for **4bT** and **11bT** (21 pages). Ordering information is given on any current masthead page.