Tandem Inter [4 + 2]/Intra [3 + 2] Nitroalkene Cycloadditions. 4. Cycloadditions with (*E*)- and (*Z*)-1-Propenyl Ethers

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The tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkene 1 was initiated efficiently by 1-propenyl ethers as the dienophile. Ethyl (*E*)-1-propenyl ether reacted highly selectively to give a single nitroso acetal cycloadduct **6**. Hydrogenolysis of **6** afforded a single isomer of α-hydroxy lactam **8** wherein the newly installed methyl group occupied the β-configuration. Similarly, ethyl (*Z*)-1-propenyl ether produced an anomeric mixture of cycloadducts **7a** and **7b** which afforded a single α-hydroxy lactam **9** upon hydrogenolysis. The methyl group in **9** occupied the α-orientation. The high and complementary selectivity for production of **8** and **9** was explained on the basis of an extreme endo preference for the ethoxy group of the 1-propenyl ether in the [4 + 2] cycloaddition.

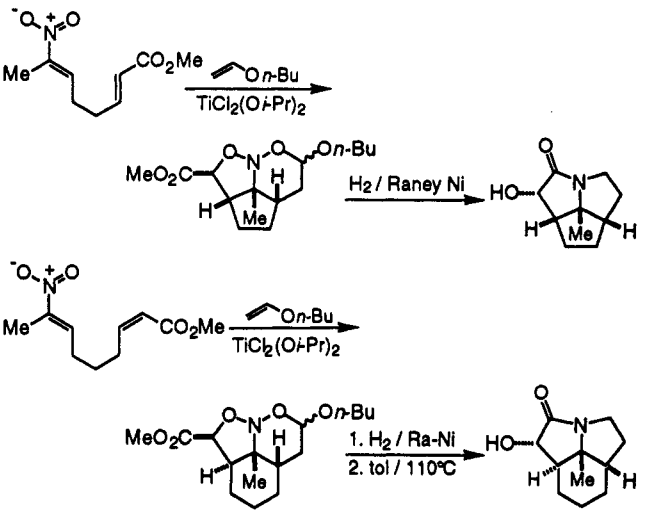
Introduction

Recent disclosures from these laboratories have documented the synthetic utility of the tandem [4 + 2]/[3 + 2] cycloaddition process of nitroalkenes for the stereoselective construction of polycyclic frameworks,[1] Scheme I. The reaction has proven general for the construction of five- and six-membered rings with >100:1 and >30:1 overall stereoselectivity, respectively. The nitroalkene can be di- or trisubstituted and the dipolarophile can be *E*- or *Z*-configured. Indeed, we have also shown that unactivated dipolarophiles will participate in the [3 + 2]-cycloaddition efficiently.[2] Furthermore, the hydrogenolysis of the nitroso acetals has proven to be a mild method for the conversion to synthetically useful products.

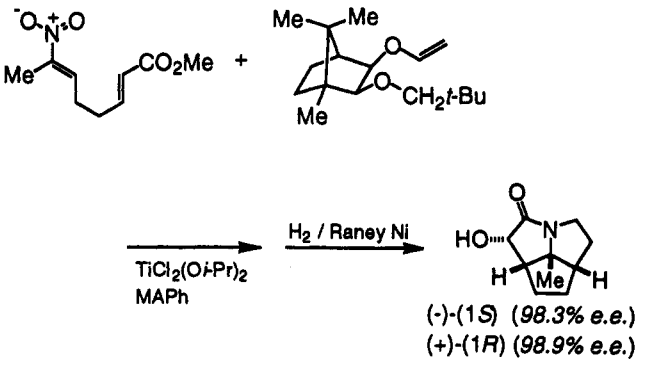
The tandem reaction is also capable of delivering the final α-hydroxy lactams in >98% enantiomeric excess by the use of chiral vinyl ethers derived from camphor or 2-phenylcyclohexanol.[3] Moreover, the absolute stereochemical course of the reaction can be controlled by the simple expedient of changing the Lewis acid activator, Scheme II.[4]

The extremely high diastereoselectivities observed with chiral vinyl ethers required that the dienophile combine with the nitroalkene with extreme endo ($Ti(O\text{-}i\text{-}Pr)_2Cl_2$) or exo (MAPh)[5] selectivity. However, this could not be unambiguously established because the configurationally labile anomeric center is the only stereochemical reporter. We therefore became interested in studying the cycloadditions of 1-propenyl ethers for two reasons: (1) the methyl group can serve as a permanent stereochemical marker preserving the memory of an exo or endo [4 + 2]-transition structure, and (2) the methyl group also installs an additional stereocenter which (if created selectively) further extends the synthetic utility of the reaction, Scheme III.

Scheme I



Scheme II



As the test substrate, our previously employed nitroalkene **1** was selected to allow direct comparison to the vinyl ether series. Furthermore, we were interested in examining the importance of enol ether geometry and chose for simplicity (*E*)- and (*Z*)-1-propenyl ethyl ether (**2**). In this report we describe the extremely high diastereoselectivities obtainable with simple 1-propenyl ethers and the mechanistic implications of the stereochemical outcome. Subsequent reports will describe the tandem cycloaddition with chiral propenyl ethers along with a detailed transition structure analysis.[6]

† Taken in part from: Senanayake, C. B. W. Ph.D. Thesis, University of Illinois, Urbana, IL, 1991.

(1) (a) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311. (b) Denmark, S. E.; Senanayake, C. B. W.; Moon, Y.-C.; Schnute, M. E.; Ho, G.-D.; Middleton, D. S. *Proceedings of the 5th International Kyoto Conference on Organic Chemistry*; Ohshiro, Y., Yoshida, Z.-I., Eds.; Kodansha Press: Tokyo, 1992; p 215.

(2) Denmark, S. E.; Senanayake, C. B. W. Manuscript in preparation.

(3) (a) Denmark, S. E.; Senanayake, C. B. W.; Ho. G.-D. *Tetrahedron* **1990**, *46*, 4857. (b) Schnute, M. E.; Middleton, D. S. Unpublished results from these laboratories.

(4) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738–6739.

(5) Yamamoto, H.; Maruoka, K. *Tetrahedron* **1988**, *44*, 5881.

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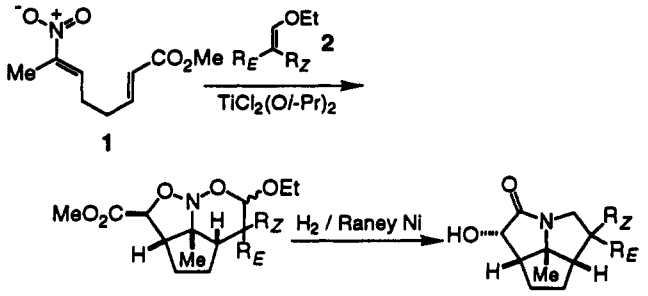
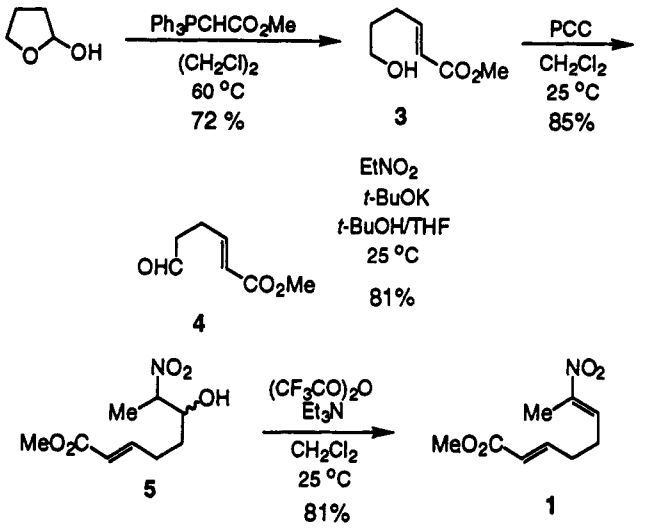
Scheme III



Scheme IV



Results

Preparation of Nitroalkene Substrate 1. The synthesis of nitroalkene 1 was very straightforward and presented no particular difficulties, Scheme IV. Reaction of 2-hydroxytetrahydrofuran with methyl triphenylphosphoranylideneacetate afforded alcohol 3 in 72% yield (>99% *E*-isomer by GC analysis). Alcohol 3 was oxidized to aldehyde 4 in 85% yield using pyridinium chlorochromate. This aldehyde was then transformed into the target nitroalkene 1 by the use of nitroolefination conditions developed and optimized in these laboratories.[7] The nitro alcohol 5 was prepared by potassium *tert*-butoxide catalyzed Henry reaction.[8,9] Dehydration of 5 was effected by treatment with trifluoroacetic anhydride/triethylamine at room temperature to afford 1 in 81% yield as a single geometrical isomer.

Cycloaddition with Ethyl 1-Propenyl Ethers (2). The effects of dienophile substitution and geometry on the tandem cycloaddition was initially studied using a 3:1 *E*/*Z* mixture of ethyl 1-propenyl ether. In the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$, the nitroalkene 1 reacted smoothly with 2 to give nitroso acetals as expected from previous studies. The ^1H NMR analysis of the product mixture indicated formation of nitroso acetals from each geometrical isomer

Scheme V

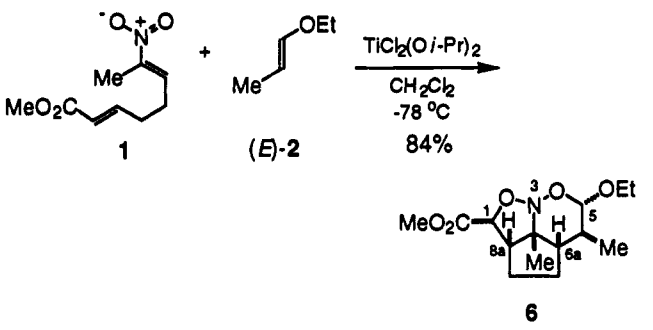


Table I. Effect of Reaction Time on the Anomer Ratio of 6 and 7[a]

entry	1-propenyl ether	time, h	OEt(C(5)), (α:β)
1	(*E*)-2	1	95:5[b]
2	(*E*)-2	3	95:5[b]
3	(*E*)-2	5	95:5[b]
4	(*E*)-2	8	95:5[b]
5	(*Z*)-2	1	1.3:1[c]
6	(*Z*)-2	3	1:8[c]

[a] At −78 °C. [b] By ^1H NMR. [c] By ^1H NMR and isolation.

confirming that closer investigation was warranted. Thus, a commercially available mixture of ethyl (*E*)- and (*Z*)-1-propenyl ether was separated by spinning band distillation, and the isomerically pure propenyl ethers were used for the cycloaddition study.

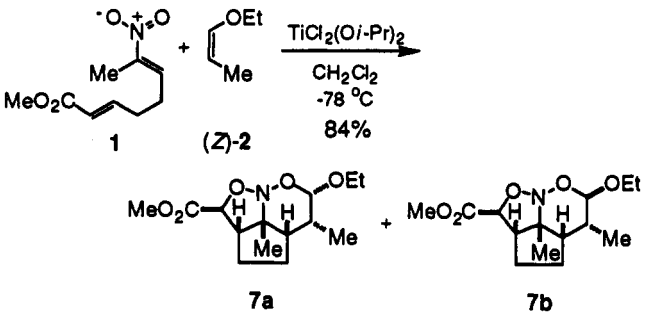
The reaction of nitroalkene 1 with ethyl (*E*)-1-propenyl ether ((*E*)-2) was performed in the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$ at −78 °C in CH_2Cl_2. The starting material was consumed within 10 min, and the isolated product 6 was isomerically homogeneous as judged by ^1H NMR analysis, Scheme V. A single cycloadduct was obtained even after longer reaction times, Table I. The ^1H NMR analysis of 6 revealed a doublet at 4.50 ppm (J = 6.7 Hz) for the anomeric proton (HC(5)) and a doublet at 4.80 ppm (J = 7.9 Hz) for HC(1), Table II. The configuration at C(6) is assigned on the basis of an endo orientation of the ethoxy group of (*E*)-2 during the [4 + 2]-cycloaddition thus placing the methyl group in a β-orientation. This assignment was corroborated by NOE studies on the α-hydroxy lactam (vide infra). The rest of the stereostructure of 6 is based on analogy to the nitroso acetals derived from *n*-butyl vinyl ether cycloaddition.[1a]

The cycloaddition of nitroalkene 1 with ethyl (*Z*)-1-propenyl ether ((*Z*)-2) was performed similarly in the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$ at −78 °C in CH_2Cl_2. The rate of cycloaddition was noticeably slower than that of (*E*)-2. The ^1H NMR analysis of the isolated product showed a mixture of two nitroso acetal isomers **7a** and **7b**, Scheme VI. The isomers **7a** and **7b** were shown to be anomers by their interconversion under the reaction conditions. In contrast to 6, the anomer ratio in 7 was dependent on the reaction time. With short reaction times, **7a** was the exclusive product and over extended periods of time, the amount of **7b** increased.

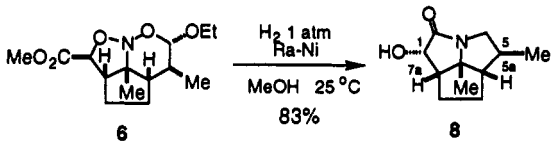
The separated anomers were analyzed by ^1H NMR spectroscopy. The ^1H NMR spectrum for **7a** displayed a doublet at 5.08 ppm (J = 6.8 Hz) for the anomeric proton (HC(5)) and a doublet at 4.82 ppm (J = 7.8 Hz) for HC(1). Similarly, **7b** showed two doublets at 4.53 ppm (J = 7.3 Hz) and 4.83 ppm (J = 8.1 Hz) for HC(5) and HC(1), respectively. The configuration at C(6) in **7a** and **7b** is based on the assumption of an endo orientation of the ethoxy group during the [4 + 2] cycloaddition, placing the

(6) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. Following paper in this issue.
(7) Moon, Y.-C., Ph.D. Thesis, University of Illinois, Urbana, IL, 1991.
(8) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1985**, *50*, 2603.
(9) For reviews on the Henry reaction see: (a) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (b) Rosini, G. In *Comprehensive Organic Synthesis: Additions to C–X π-Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.10.

Scheme VI



Scheme VII



methyl group on the α-face. This assumption was corroborated by NOE studies on the α-hydroxy lactam. Since **7a** isomerized to **7b**, we assign the α-anomeric configuration to **7a**. The spectroscopic data from Table II do not allow unambiguous assignment of anomeric configuration from coupling constants. However, the chemical shifts of HC(5) and C(5) follow similar patterns established for the butyl vinyl ether cycloadducts, entries 1 and 2, Table II. Thus, the high-field shift for HC(5) for **6** and **7b** along with the corresponding lower field shifts for C(5) in these compounds imply a pseudoequatorial orientation for the ethoxy groups. Accordingly, in **7a** the ethoxy group is axially disposed in a chair oxazine ring. Anomerization then places it in the preferred equatorial position in **7b**. The lack of crossover and unique structure for each of cycloadducts **6**, **7a**, and **7b** clearly shows that the dienophile geometry is preserved during the cycloaddition.

N–O Bond Cleavage. Our previous studies[1] had established the ready cleavage of the N–O bonds in nitroso acetals by hydrogenolysis. These substrates were no exception. The nitroso acetal **6** was subjected to hydrogenolysis in the presence of a catalytic amount of Raney nickel in methanol at atmospheric pressure of hydrogen at room temperature to afford α-hydroxy lactam **8** (83% yield) as a white solid, Scheme VII. The spectroscopic analysis of the product allowed the identification of the α-hydroxy lactam **8** as a single isomer, Table III. Primary among these was the appearance of the characteristic IR stretches for the lactam (1709 cm^{-1}) and hydroxyl functions (3389 cm^{-1}). In the ^1H NMR spectrum, peaks appeared at 4.63 ppm (d, J = 6.5 Hz) for HC(1) and at 2.78 (m) for HC(7a). The stereostructure of **8** (except at C(5)) is based on the spectroscopic comparison with products from the n-butyl vinyl ether cycloaddition (vide infra).

Similarly, nitroso acetals **7a** and **7b** were separately subjected to the hydrogenolysis conditions and both gave the same α-hydroxy lactam **9** as a single product, Scheme VIII. The diagnostic IR stretches for **9** appeared at 3372 and 1707 cm^{-1}. The ^1H NMR spectrum displayed resonances at 4.66 ppm (d, J = 7.9 Hz) for HC(1) and at 2.70 ppm (t, J = 8.3 Hz) for HC(7a). The rest of the stereostructure (except at C(5)) is based on spectroscopic comparison to the α-hydroxy lactam derived from n-butyl vinyl ether. Table III summarizes selected NMR data for α-hydroxy lactams. The lactams from both vinyl and propenyl ethers showed very similar ^1H NMR chemical shifts for HC(1) ($\Delta\delta$ = 0.04 ppm, d, J = 6.5–7.9 Hz) and very similar ^{13}C NMR chemical shifts for C(1) and C(2). These experiments confirmed that **7a** and **7b** differed only at the anomeric center.

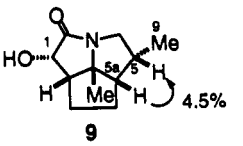


Figure 1.

Configurational Assignment for 8 and 9. The spectroscopic data (Table III) clearly indicated that **8** and **9** were two different compounds. In the ^{13}C NMR spectra, the chemical shifts for C(5) and C(9) showed the largest variation between the two compounds supporting the notion that the difference is due to the orientation of the methyl group at C(5).[10] However, the lack of sufficient structural analogies did not allow an unambiguous assignment. Thus the disposition of the methyl group was established by NOE studies of α-hydroxy lactam **9** as shown in Figure 1.

The ^1H NMR assignments for **8** and **9** were established by homonuclear decoupling and HETCOR experiments. The resonances of interest, HC(5) and HC(5a), could be located in **8**, but they were insufficiently resolved for a reliable NOE study. Fortunately, the analogous resonances in **9** were easily assigned and were well-resolved, thus facilitating an NOE experiment. The proton HC(5) appeared at 2.62 ppm and HC(5a) appeared at 2.08 ppm. Irradiation of the resonance at 2.62 ppm showed a 4.5% NOE enhancement for the peak at 2.08 ppm. Corresponding irradiation at 2.08 ppm showed a 4% NOE for the peak at 2.62 ppm. This confirmed that protons HC(5) and HC(5a) are cis related. Thus, the methyl group in **9** is assigned the β or exo orientation and that in **8** the α or endo orientation. Although not unambiguous, the strong downfield shifts for C(5) and C(9) in **8** compared to **9** are supportive of this assignment.[10]

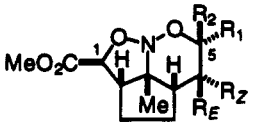
Discussion

The extremely selective and complimentary formation of **8** from (*E*)-**2** and **9** from (*Z*)-**2** was remarkable.[11] The configurational assignments for **8** and **9** allow the assertion that *both* (*E*)-**2** and (*Z*)-**2** initiate the tandem cycloaddition exclusively by an endo (ethoxy) mode [4 + 2] process, Scheme IX. The differences in the rate of cycloaddition support the assumption of the endo orientation of the alkoxy group. The faster rate of cycloaddition with (*E*)-**2** compared to (*Z*)-**2** can be explained by analyzing the transition structures for the [4 + 2] cycloadditions in Scheme IX. In the (*E*)-1-propenyl ether cycloaddition, the methyl group of the dienophile is oriented exo and does not suffer from nonbonded interactions with the nitroalkene. However, in the (*Z*)-1-propenyl ether cycloaddition, this methyl group is endo as well where nonbonded interaction with the heterodiene can occur. The additional nonbonded interactions experienced by (*Z*)-**2** slow the reaction relative to the (*E*)-**2** isomer.

(10) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987; Chapter 12.

(11) For similar observations with 1-oxabutadienes see: Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 1133.

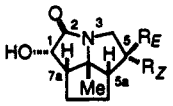
Table II. Selected NMR Data for Nitroso Acetals



acetal	R_1	R_2	R_E	R_Z	HC(5), ppm (*J*, Hz)	HC(1), ppm (*J*, Hz)	C(5), ppm
a	O-*n*-Bu	H	H	H	5.08 (dd, 6.4, 3.5)	4.86 (d, 8.3)	99.65
a	H	O-*n*-Bu	H	H	4.94 (t, 7.4)	4.78 (d, 7.9)	98.62
6	OEt	H	Me	H	4.50 (d, 6.7)	4.80 (d, 7.9)	104.92
7a	OEt	H	H	Me	5.08 (d, 6.8)	4.82 (d, 7.8)	101.62
7b	H	O-Et	H	Me	4.53 (d, 7.3)	4.83 (d, 8.1)	104.41

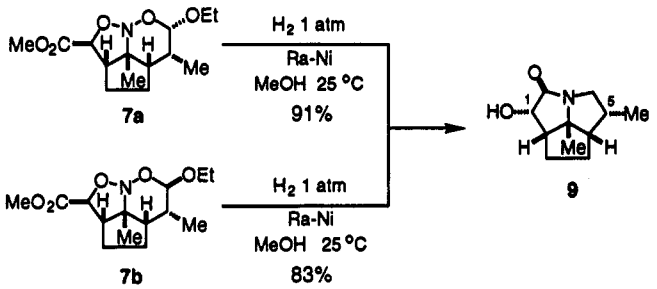
[a] From ref 1a.

Table III. Selected NMR Data for α-Hydroxy Lactams

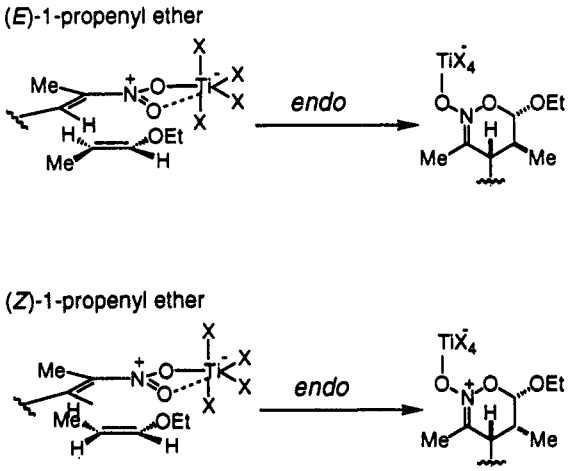


			^{1}H NMR, ppm (*J*, Hz)		^{13}C NMR, ppm			
lactam	R_E	R_Z	HC(1)	HC(5)	C(1)	C(2)	C(5)	C(9)
	H	H	4.67 (dd, 6.9, 2.3)	2.58	72.81	176.45		
8	Me	H	4.63 (d, 6.5)	1.75	72.45	176.07	42.08	17.52
9	H	Me	4.66 (d, 7.9)	2.62	71.95	177.22	34.05	14.92

Scheme VIII



Scheme IX



Nonetheless, (*Z*)-**2** must still experience an overall stabilizing interaction compared to the limiting exo transition structure in which no such non-bonded interactions would exist.

The extremely high selectivity for the formation of **9** from (*Z*)-**2** indicates that the stabilization must be significant and can be understood by consideration of two important features of the reaction. First, the endo preference for donor groups in inverse electron demand [4 + 2] cycloadditions is well documented.[12] In our previous studies with nitroalkenes we demonstrated the strong endo preference for the alkoxy groups of vinyl ethers and identified this preference as crucial in the asymmetric [4 + 2] cycloaddition with chiral vinyl ethers.[3] This preference may arise from the polarization of the transition state due to the electronic imbalance of the diene and dienophilic groups.[13] This electronic complimentarity can lead to an attractive stabilization between alkoxy and nitro groups in the carbon-carbon bond forming event. Second, the titanium-based Lewis acid is relatively small and can accommodate the alkoxy group in an endo orientation. Clearly, these two features conspire to allow the highly stereoselective introduction of the methyl group in either configuration by the simple expedient of changing the dienophile geometry.

Conclusions

The extension of the nitroalkene tandem [4 + 2]/[3 + 2] cycloaddition reaction to include 1-propenyl ethers allowed the creation of an additional stereogenic center in the α-hydroxy lactam product. Thus, of the six contiguous stereogenic centers created in the tandem process (including the anomeric center), three are formed in the [4 + 2] cycloaddition while three are created in the [3 + 2] cycloaddition. This study also allowed evaluation of an important stereocontrolling feature of the tandem cycloaddition, namely, the exclusive endo preference of the alkoxy group during the [4 + 2] stage. This strong preference dominated the steric interactions experienced by alkyl β-substituents and forced them to take up exo or endo positions as required by the dienophile geometry. The consequences of these features on the stereochemical

(12) (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; Chapter 7. (c) Bäckvall, J.-E.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 5347. (d) Posner, G. H.; Haces, A.; Harrison, W.; Kinter, C. M. *J. Org. Chem.* **1987**, *52*, 4836. (e) Posner, G. H. Switzer, C. *Ibid.* **1987**, *52*, 1642. (f) Desimoni, G.; Astolfi, L.; Cambieri, M.; Gamba, A.; Tacconi, G. *Tetrahedron* **1973**, *29*, 2627. (g) Daneo, S.; Pitacco, G.; Risaliti, A.; Valentin, E. *Ibid.* **1982**, *38*, 1499. (h) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *J. Org. Chem.* **1984**, *49*, 4741. (i) Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282.

(13) Secondary orbital interactions have been invoked to explain this behavior as well: Desimoni, G.; Gamba, A.; Monticelli, M.; Nicola, M.; Tacconi, G. *J. Am. Chem. Soc.* **1976**, *98*, 2947.

course of cycloadditions with chiral 1-propenyl ethers is the subject of the accompanying paper.

Experimental Section

General Information. ^1H NMR and ^{13}C NMR spectra were obtained at either 200 MHz ^1H (50.4 MHz ^{13}C), 300 MHz ^1H (75.5 MHz ^{13}C), or 400 or 500 MHz ^1H (125.8 MHz ^{13}C) in $CDCl_3$ with $CHCl_3$ as an internal standard (^1H δ = 7.26 ppm, ^{13}C δ = 77.07 ppm). Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (J) are reported in Hz. Infrared spectra (IR) were obtained in CCl_4 solution unless otherwise indicated. Peaks are reported in cm^{-1} with the following relative intensities; s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%). Electron impact (EI) mass spectra were obtained with ionization voltages of 70 or 10 eV. Data are reported in the form m/e (intensity relative to base = 100). Boiling points (bp) from bulb-to-bulb distillations refer to air bath temperature and are uncorrected. Melting points (mp) were determined in sealed capillaries and are corrected. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light, iodine, and/or sulfuric acid–vanillin–ethanol solution. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents; hexane, dichloromethane ($CaCl_2$), ether ($CaSO_4/FeSO_4$), ethyl acetate (K_2CO_3). Column chromatography was performed using 32–63-μm silica gel. Medium-pressure chromatography was performed using Merck Lobar columns. Capillary gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph fitted with a flame ionization detector, H_2 carrier gas 1 mL/min, using 50-m silicone OV-17 or HP-5 columns (2 mm). Retention times (t_R) and integrated ratios were obtained from a Hewlett-Packard 3390A integrator. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Brine refers to a saturated aqueous solution of sodium chloride. All reactions were performed in oven-dried and/or flame-dried glassware under an inert atmosphere of dry N_2.

Methyl (*E*)-6-Hydroxy-2-hexenoate (3). To a solution of 2-hydroxytetrahydrofuran (3.63 g, 41.20 mmol) in dichloroethane (50 mL) was added methyl triphenylphosphoranylideneacetate (13.78 g, 41.20 mmol, 1 equiv). The resulting clear solution was allowed to stir at ~80 °C for 12 h, concentrated, and diluted with pentane. The precipitate formed was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc (4:1–1:1)) to afford 4.276 g (72%) of ester **3** as a clear oil: bp 74–76 °C (0.2 Torr, air bath); ^1H NMR (300 MHz) 6.97 (dt, J_d = 15.6, J_t = 7.0, 1 H, HC(3)), 5.85 (d, J = 15.6, 1 H, HC(2)), 3.71 (s, 3 H, $H_3C(7)$), 3.66 (m, 2 H, $H_2C(6)$), 2.30 (q, J = 6.9, 2 H, $H_2C(4)$), 1.71 (m, 2 H, $H_2C(5)$); ^{13}C NMR (75.5 MHz) 167.12 (C(1)), 148.96 (C(3)), 121.13 (C(2)), 61.61 (C(7)), 51.38 (C(6)), 30.80 (CH_2), 28.47 (CH_2); IR (CCl_4) 3695 (m), 3490 (br, m), 2950 (m), 2878 (m), 1727 (s), 1659 (m), 1437 (m), 1323 (m), 1271 (m), 1201 (m), 1040 (m), 922 (w), 816 (m); MS (70 eV) 144 (M^+, 2), 114 (30), 113 (97), 112 (49), 111 (60), 98 (50), 95 (22), 87 (23), 85 (20), 84 (28), 83 (16), 81 (46), 71 (41), 67 (100), 59 (45), 55 (59), 40 (80), 38 (69); TLC R_f 0.10 (hexane/EtOAc (4:1)). Anal. Calcd for $C_7H_{12}O_3$ (144.17): C, 58.32; H, 8.39. Found: C, 58.56; H, 8.55.

Methyl (*E*)-6-Oxo-2-hexanoate (4). Pyridinium chlorochromate (31.55 g, 146 mmol, 2.0 equiv) was added to a three-neck round-bottom flask equipped with a mechanical stirrer and addition funnel and containing 4-Å molecular sieves (50.0 g). The solids were dissolved in 600 mL of CH_2Cl_2. A solution of ester **3** (E/Z = 9/1, 10.55 g, 73 mmol, 1.0 equiv) in 10.0 mL of CH_2Cl_2 was added dropwise over 5 min. The resulting dark brown solution was allowed to stir at room temperature for 1 h. The reaction mixture was filtered through Florisil, washed with MTBE (500 mL), CH_2Cl_2 (500 mL), and EtOAc (500 mL), and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc (3:1–1:1)) to afford 8.0 g of aldehyde (*E*)-**4** and 1.3 g of (*Z*)-**4** as clear oils in a combined yield of 89%. Data for (*E*)-**4**: bp 120 °C (0.1 Torr, air bath); ^1H NMR (400 MHz) 9.79 (s, 1 H, HC(6)), 6.93 (dt, J_d = 15.6, J_t = 6.6, 1 H, HC(3)), 5.85 (d, J = 15.6, 1 H, HC(2)), 3.72 (s, 3 H, $H_3C(7)$), 2.64 (t, J = 7.1, 2 H, $H_2C(5)$), 2.52 (q, J = 7.2, 2 H, $H_2C(4)$); ^{13}C NMR (100 MHz) 200.30 (C(6)), 166.58 (C(1)), 146.63 (C(3)), 121.85 (C(2)), 51.41 (C(7)), 41.67 (C(5)), 24.31 (C(4)); IR (CCl_4) 2996 (m), 2951 (s), 2901 (s), 2820 (s), 2720 (s), 1726 (s), 1660 (s), 1437 (s), 1412 (s), 1387 (m), 1319 (s), 1273 (s), 1201 (s), 1163 (s), 1103 (s), 1041 (s), 978 (s); MS (70 eV) 142 (M^+, 2), 124 (14), 114 (30), 113 (64), 111 (30), 110 (36), 87 (15), 83 (58), 82 (36), 81 (58), 71 (12), 68 (15), 59 (37), 55 (100), 53 (53), 51 (12), 43 (29), 42 (28), 40 (50); TLC R_f 0.65 (hexane/EtOAc (1:1)). Anal. Calcd for $C_7H_{10}O_3$ (142.154): C, 59.15; H, 7.09. Found: C, 58.84; H, 7.21.

Methyl (*E*)-6-Hydroxy-7-nitro-2-octenoate (5). To a solution of aldehyde **4** (1.50 g, 10.55 mmol) in *t*-BuOH (10.5 mL)/THF (10.5 mL) was added nitroethane (2.36 mL, 31.65 mmol, 3 equiv) and a catalytic amount of potassium *tert*-butoxide. The resulting clear solution was allowed to stir at room temperature. After 30 min, the solution was diluted with CH_2Cl_2 and washed with water and brine. The aqueous layers were back-extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc (4:1–1:1)) to afford 1.86 g (81%) of nitro alcohol **5** as a clear oil: ^1H NMR (300 MHz) 6.93 (dt, J_d = 15.7, J_t = 7.4, 1 H, HC(3)), 5.85 (d, J = 16.0, 1 H, HC(2)), 4.49 (m, 1 H, HC(7)), 3.91 (m, 0.5 H, HC(6)), 3.91 (m, 0.5 H, HC(6)), 3.72 (s, 3 H, $H_3C(9)$), 2.56–2.28 (m, 2 H), 1.69–1.47 (m, 2 H), 1.55 (d, J = 6.9, 3 H, $H_3C(8)$); ^{13}C NMR (75.5 MHz) 169.04 (C(1)), 147.86 and 147.80 (C(2)), 121.87 (C(3)), 87.80 and 86.34 (C(7)), 71.92 and 71.06 (C(6)), 51.63 (C(9)), 31.21 and 31.15 (CH_2), 28.37 and 27.88 (CH_2), 16.17 and 12.52 (C(1)); IR (CCl_4) 3567 (m), 2952 (m), 1728 (s), 1653 (m), 1553 (s), 1456 (m), 1392 (w), 1358 (w), 1320 (m), 1273 (m), 1202 (m), 1163 (m); TLC R_f 0.19 (hexane/EtOAc (4:1)).

Methyl (*E,E*)-7-Nitro-2,6-octadienoate (1). To a magnetically-stirred solution of nitro alcohol **5** (1.80 g, 8.25 mmol) in CH_2Cl_2 (10.5 mL) was added trifluoroacetic anhydride (1.278 mL, 8.70 mmol, 1.05 equiv), and triethylamine (2.42 mL, 17.39 mmol, 2.1 equiv) was added dropwise at 0 °C. After 1 h, the resulting pale brown solution was diluted with CH_2Cl_2 and washed with water, saturated aqueous NH_4Cl solution, and brine. The aqueous layers were back-extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4/1) to afford 1.32 g (81%) of **1** as a clear pale brown oil: bp 96–98 °C (0.05 Torr, air bath); ^1H NMR (300 MHz) 7.06 (t, J = 7.1, 1 H, HC(6)), 6.90 (dt, J = 15.6, 1 H, HC(3)), 5.86 (d, J = 15.5, 1 H, HC(2)), 3.72 (s, 3 H, $H_3C(9)$), 2.41 (m, 4 H), 2.16 (s, 3 H, $H_3C(8)$); ^{13}C NMR (75.5 MHz) 166.43 (C(1)), 148.28 (C(7)), 146.31 (C(3)), 133.98 (C(6)), 122.30 (C(2)), 51.45 (C(9)), 30.50 (C(5)), 26.44 (C(4)), 12.49 (C(8)); IR (CCl_4) 2952 (m), 2847 (w), 1730 (s), 1663 (m), 1559 (m), 1528 (s), 1437 (m), 1391 (m), 1333 (s), 1273 (m), 1207 (m), 1171 (m), 1042 (m), 972 (m), 843 (w); MS (70 eV) 168 (35), 152 (10), 121 (13), 109 (11), 100 (100), 99 (52), 94 (13), 93 (61), 91 (34), 81 (21), 79 (27), 77 (36), 72 (14), 71 (62), 69 (23), 68 (40), 67 (28), 65 (15), 59 (47), 55 (35) 53 (50), 42 (40), 40 (99), 38 (73); TLC R_f 0.43 (hexane/EtOAc (4:1)); GC t_R 13.74 min (HP-5, 150 °C(4 min), 10 °C/min, 250 °C). Anal. Calcd for $C_9H_{13}NO_4$ (199.21): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.10; H, 6.66; N, 7.03.

Methyl *rel*-(1*R*,3*S*,5*R*,6*R*,6a*R*,8a*R*,8b*S*)-5-Ethoxy-6,8b-dimethyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (6). To a cold (−78 °C), magnetically-stirred solution of nitroalkene **6** (200 mg, 1.00 mmol) in CH_2Cl_2 (3 mL) was added a freshly prepared solution of $TiCl_2(O\text{-}i\text{-}Pr)_2$ (3.00 mmol, 3.0 equiv) in CH_2Cl_2 (2 mL). The resulting pale yellow solution was stirred at −78 °C for 10 min, ethyl (*E*)-1-propenyl ether (223 μL, 2.00 mmol, 2.0 equiv) was added, and the mixture was stirred at −78 °C. After 2 h, the reaction was quenched with 0.5 N NaOH in methanol (12 mL) at −78 °C and allowed to warm to room temperature. The mixture was poured into Et_2O and washed with water and brine. The aqueous layers were back-extracted with Et_2O. The combined organic extracts were dried ($MgSO_4/NaHCO_3$ (1:1)), filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 (1:2)) to afford 239 mg (84%) of **6** as a clear oil: bp 129 °C (0.8 Torr, air bath); ^1H NMR (300 MHz) 4.80 (d, J = 7.9, 1 H, HC(1)), 4.50 (d, J = 6.7, 1 H, HC(5)), 3.92 (dq, J_d = 9.6, J_q = 7.1, 1 H, HC(11)), 3.75 (s, 3 H, $H_3C(14)$), 3.59 (dq, J_d = 9.7, J_q = 6.9, 1 H, HC(11)), 2.62 (q, J = 7.2, 1 H, HC(8a)), 1.98–1.66 (m, 6 H), 1.35 (s, 3 H, $H_3C(9)$), 1.90 (t, J =

7.1, 3 H, $H_3C(12)$), 1.03 (d, J = 7.1, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) 170.24 (C(13)), 104.92 (C(5)), 85.32 (C(1)), 82.77 (C(8b)), 65.39 (C(11)), 58.68 (C(8a)), 52.32 (C(14)), 50.93 (C(6a)), 37.22 (C(6)), 36.22 (C(8)), 28.44 (C(7)), 27.52 (C(9)), 17.96 (C(12)), 15.16 (C(10)); IR (CCl_4) 2973 (m), 2874 (m), 1745 (m), 1449 (m), 1381 (m), 1279 (m), 1199 (m), 1176 (m), 1039 (m), 999 (w), 908 (m); MS (70 eV) no M^+, 255 (9), 191 (16), 177 (13), 167 (34), 152 (23), 149 (52), 135 (15), 131 (19), 125 (17), 122 (23), 121 (95), 107 (35), 93 (52), 87 (20), 86 (95), 82 (58), 81 (100), 77 (23), 67 (37), 58 (100), 55 (83), 41 (100), 39 (42); TLC R_f 0.43 (hexane/EtOAc (4:1)); GC t_R 10.40 min (HP-5, 200 °C (2 min), 10 °C/min, 250 °C). Anal. Calcd for $C_{14}H_{23}NO_5$ (285.34): C, 58.93; H, 8.12; N, 4.91. Found: C, 58.73; H, 8.13; N, 4.93.

Methyl *rel*-(1*R*,3*S*,5*R*,6*S*,6a*R*,8a*R*,8b*S*)-5-Ethoxy-6,8b-dimethyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hf*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (7a) and Methyl *rel*-(1*R*,3*S*,5*S*,6*S*,6a*R*,8a*R*,8b*S*)-5-Ethoxy-6,8b-dimethyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hf*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (7b). To a cold (−78 °C), magnetically-stirred solution of nitroalkene 1 (200 mg, 1.00 mmol) in CH_2Cl_2 (3.0 mL) was added a freshly prepared solution of $TiCl_2(O\text{-}i\text{-}Pr)_2$ (3.00 mmol, 3.0 equiv) in CH_2Cl_2 (2.0 mL). The resulting pale yellow solution stirred at −78 °C for 10 min, ethyl (*Z*)-1-propenyl ether (223 μL, 2.00 mmol, 2.0 equiv) was added, and the mixture was stirred at −78 °C. After 2 h, the reaction was quenched with 0.5 N NaOH in methanol (12 mL) at −78 °C and was then allowed to warm to room temperature. The mixture was poured into Et_2O and washed with water and brine. The aqueous layers were back-extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$/$NaHCO_3$ (1:1)), filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 (1:2)) to afford 134 mg (47%) of **7a** and 107 mg (37%) of **7b** as clear oils. Data for **7a**: bp 125 °C (0.6 Torr, air bath); ^1H NMR (300 MHz) 5.08 (d, J = 6.8, 1 H, HC(5)), 4.82 (d, J = 7.8, 1 H, HC(1)), 3.82 (dq, J_d = 9.8, J_q = 7.1, 1 H, HC(11)), 3.74 (s, 3 H, $H_3C(14)$), 3.49 (dq, J_d = 9.8, J_q = 7.1, 1 H, HC(11)), 2.69 (td, J_t = 7.6, J_d = 2.6, 1 H, HC(8a)), 2.18–2.06 (m, 2 H), 1.90–1.69 (m, 4 H), 1.27 (s, 3 H, $H_3C(9)$), 1.14 (t, J = 7.0, 3 H, $H_3C(12)$), 0.95 (d, J = 7.2; 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) 170.30 (C(13)), 101.62 (C(5)), 86.63 (C(1)), 84.78 (C(8b)), 65.80 (C(11)), 56.65 (C(8a)), 52.20 (C(14)), 50.01 (C(6a)), 30.98 (C(6)), 29.61 (C(8)), 28.25 (C(7)), 24.02 (C(9)), 15.25 (C(12)), 13.21 (C(10)); IR (CCl_4) 2976 (m), 2880 (m), 1743 (s), 1439 (m), 1377 (m), 1323 (w), 1266 (m), 1203 (m), 1178 (m), 1024 (m), 908 (w), 885 (w), 843 (m); MS (70 eV) 285 (1), 191 (11), 177 (11), 167 (69), 152 (36), 149 (39), 135 (11), 131 (17), 121 (99), 107 (30), 93 (55), 86 (90), 81 (100), 77 (29), 67 (39), 58 (100), 55 (79), 43 (79), 41 (100), 39 (45); TLC R_f 0.43 (hexane/EtOAc (4:1)); GC t_R 10.50 min (HP-1, 50 m, 200 °C (2 min), 10 °C/min, 250 °C). Anal. Calcd for $C_{14}H_{23}NO_5$ (285.34): C, 58.93; H, 8.12; N, 4.91. Found: C, 58.87; H, 8.15; N, 4.86. Data for **7b**: bp 132 °C (0.7 Torr, air bath); ^1H NMR (300 MHz) 4.83 (d, J = 8.1, 1 H, HC(1)), 4.52 (d, J = 7.3, 1 H, HC(5)), 3.92 (dq, J_d = 9.9, J_q = 7.0, 1 H, HC(11)), 3.77 (s, 3 H, $H_3C(14)$), 3.49 (dq, J_d = 9.8, J_q = 7.0, 1 H, HC(11)), 2.73 (m, 1 H, HC(8a)), 1.97 (m, 1 H), 1.84 (br, s, 5 H), 1.34 (s, 3 H, $H_3C(9)$), 1.22 (t, J = 7.1, 3 H, $H_3C(12)$), 1.08 (d, J = 6.9, 3 H, $H_3C(10)$); ^{13}C NMR (75.5 MHz) 170.22 (C(13)), 104.41 (C(5)), 87.22 (C(1)), 86.05 (C(8b)), 63.80 (C(11)), 56.59 (C(8a)), 52.42 (C(14)), 49.81 (C(6a)), 32.11 (C(6)), 28.30 (C(8)), 28.15 (C(7)), 23.83 (C(9)), 17.10 (C(12)), 15.08 (C(10)); IR (CCl_4) 2967 (m), 2876 (m), 1765 (m), 1744 (m), 1458 (w), 1439 (m), 1377 (w), 1282 (w), 1200 (m), 1107 (s), 1017 (m), 964 (w), 891 (w), 824 (m); MS (70 eV) 240 (56), 212 (28), 191 (13), 180 (10), 177 (14), 167 (96), 152 (72), 149 (47), 121 (100), 111 (53), 107 (44), 96 (58), 95 (50), 86 (100), 81 (100), 72 (42), 68 (58), 67 (60), 58 (100), 43 (100), 41 (100), 39 (63); TLC R_f 0.29 (hexane/EtOAc (4:1)); GC t_R 10.75 min (HP-5, 200 °C(2 min), 10 °C/min, 250 °C). Anal. Calcd for $C_{14}H_{23}NO_5$ (285.34): C, 58.93; H, 8.12; N, 4.91. Found: C, 58.97; H, 8.17; N, 4.91.

***rel*-(1*R*,3*S*,5*R*,5a*R*,7a*R*,7b*S*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (8).** To a solution of nitroso acetal **6** (120 mg, 0.42 mmol) in methanol (3.0 mL) was added a catalytic amount of Raney nickel. The suspension was allowed to stir at room temperature under a hydrogen atmosphere (1 atm). After 17 h, the mixture was filtered through a Celite pad and concentrated, and the residue was purified by column chromatography (silica gel, hexane/EtOAc (1:1)) to afford 68 mg (83%) of **8** as a white solid. An analytical sample was prepared by recrystallization from hexane/EtOAc: mp 90–91 °C (hexane/EtOAc); ^1H NMR (300 MHz) 4.63 (d, J = 6.5, 1 H, HC(1)), 3.99 (dd, J = 11.7, 7.3, 1 H, HC(4)), 3.71 (br, 1 H, OH), 2.41 (m, 2 H, HC(4), HC(7a)), 1.75 (m, 1 H, HC(5)), 1.57 (m, 1 H, HC(5a)), 1.46 (m, 2 H, HC(6), HC(7)), 1.28 (s, 3 H, $H_3C(8)$), 1.02 (d, J = 6.6, 3 H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 176.07 (C(2)), 75.34 (C(7b)), 72.45 (C(1)), 58.17 (C(5a)), 51.94 (C(7a)), 50.47 (C(4)), 42.08 (C(5)), 30.87 (C(7)), 25.30 (C(6)), 24.17 (C(8)), 17.52 (C(9)); IR (CCl_4) 3389 (br, w), 2961 (m), 2872 (w), 1709 (s), 1462 (w), 1453 (w), 1404 (m), 1379 (w), 1335 (m), 1289 (w), 1266 (w), 1210 (m), 1140 (w), 1096 (w), 1047 (w); MS (70 eV) 195 (M^+, 61), 180 (100), 167 (11), 152 (58), 138 (13), 124 (11), 122 (13), 111 (48), 110 (24), 93 (31), 82 (32), 81 (37), 77 (12), 69 (15), 67 (24), 57 (28), 56 (13), 55 (54), 43 (29), 42 (19), 41 (60), 39 (31); TLC R_f 0.19 (hexane/EtOAc (1:1)); GC t_R 19.29 min (HP-1, 100 °C (2 min), 10 °C/min, 250 °C). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.83; H, 8.87; N, 7.24.

***rel*-(1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (9).** To a solution of nitroso acetal **7a** (158 mg, 0.55 mmol) in methanol (3 mL) was added a catalytic amount of Raney nickel. The suspension was allowed to stir at room temperature under an atmosphere of hydrogen (1 atm). After 44 h, the mixture was filtered through a Celite pad and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc (3:1)) to afford 98 mg (91%) of **9** as a white solid. An analytical sample was obtained by recrystallization from hexane/EtOAc: mp 134–135 °C (hexane/EtOAc); ^1H NMR (300 MHz) 4.66 (d, J = 7.9, 1 H, HC(1)), 3.79 (br, 1 H, OH), 3.15 (d, J = 8.9, 2 H, $H_2C(4)$), 2.70 (t, J = 8.3, 1 H, HC(7a)), 2.62 (m, 1 H, HC(5)), 2.10 (m, 2 H, HC(5a), HC(7) or HC(6)), 1.55 (m, 2 H, HC(6), HC(7)), 1.32 (s, 3 H, $H_3C(8)$), 1.12 (m, 1 H, HC(7), or HC(6)), 0.99 (d, J = 6.9, 3 H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 177.22 (C(2)), 77.50 (C(7b)), 71.95 (C(1)), 54.29 (C(5a)), 50.34 (C(7a)), 47.39 (C(4)), 34.05 (C(5)), 25.50 (C(7)), 24.85 (C(6)), 22.04 (C(8)), 14.92 (C(9)); IR (CCl_4) 3372 (br, w), 2965 (w), 2878 (w), 1707 (s), 1479 (w), 1453 (w), 1406 (w), 1363 (w), 1325 (m), 1147 (m), 1068 (w); MS (70 eV) 196 (M^+ + 1, 27), 195 (100), 180 (84), 167 (19), 152 (26), 111 (28); TLC R_f 0.16 (hexane/EtOAc (1:1)). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.79; H, 8.86; N, 7.04.

***rel*-(1*R*,3*S*,5*S*,5a*R*,7a*R*,7b*S*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (9).** To a solution of nitroso acetal **7b** (100 mg, 0.35 mmol) in methanol (3.0 mL) was added a catalytic amount of Raney nickel. The suspension was allowed to stir at room temperature under an atmosphere of hydrogen (1 atm). After 44 h, the mixture was filtered through a Celite pad and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc (3:1)) to afford 56 mg (82%) of **9** as a white solid. An analytical sample was obtained by recrystallization from hexane/EtOAc: mp 134–135 °C (hexane/EtOAc); ^1H NMR (300 MHz) 4.66 (d, J = 7.9, 1 H, HC(1)), 3.73 (br, 1 H, OH), 3.15 (d, J = 8.9, 2 H, $H_2C(4)$), 2.70 (t, J = 8.3, 1 H, HC(7a)), 2.62 (m, 1 H, HC(5)), 2.12 (m, 2 H, HC(5a), HC(7) or HC(6)), 1.60 (m, 2 H, HC(7), HC(6)), 1.31 (s, 3 H, $H_3C(8)$), 1.10 (m, 1 H, HC(6), or HC(7)), 0.98 (d, J = 7.0, 3 H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 177.24 (C(2)), 77.50 (C(7b)), 71.94 (C(1)), 54.26 (C(5a)), 50.32 (C(7a)), 47.37 (C(4)), 34.03 (C(5)), 25.49 (C(7)), 24.84 (C(6)), 22.03 (C(8)), 14.92 (C(9)); IR (CCl_4) 3348 (br, w), 2965 (s), 2876 (m), 1705 (s), 1479 (w), 1453 (w), 1406 (m), 1381 (m), 1364 (m), 1325 (m), 1302 (m), 1210 (w), 1184 (m), 1147 (m), 1117 (w), 1086 (w), 997 (m); MS (70 eV) 195 (M^+, 64), 180 (100), 167 (11), 152 (54), 138 (14), 122 (13), 111 (63), 110 (26), 96 (16), 93 (38), 82 (38), 81 (45), 67 (31), 57 (36), 55 (55), 53 (22), 43 (43), 41 (71), 39 (32); TLC R_f 0.21 (hexane/EtOAc (1:1)). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.61; H, 8.88; N, 7.17.

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