Complete Diastereocontrol in Intramolecular 1,3-Dipolar Cycloadditions of 2-Substituted 5-Hexenyl and 5-Heptenyl Nitrones: Application to the Synthesis of the β-Lactam Antibiotic 1β-Methylthienamycin

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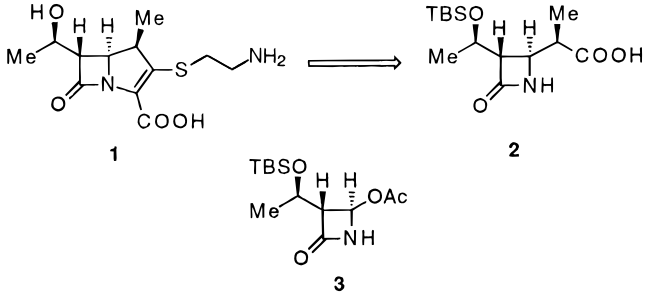
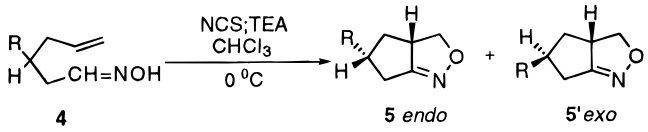
The diastereoselectivity of intramolecular 1,3-dipolar cycloadditions of 2-substituted 5-hexenyl and 5-heptenyl nitrones to give 6-substituted and 3,6-disubstituted perhydrocyclopenta[*c*]isoxazoles has been investigated. An alkyl or aryl substituent at C2 completely controls the stereochemistry of the ring juncture and, in the case of the 5-heptenyl systems, also the stereochemistry of the 3-methyl group. Thus one stereocenter controls the formation of the other three to give a product with four contiguous stereocenters. The use of an ethylene ketal substituent in these systems allows the reaction to be carried out at much lower temperatures, an example of the *gem*-dialkoxy effect. This cycloaddition process has been used in an efficient formal total synthesis of the potent β-lactam antibiotic, 1β-methylthienamycin.

Introduction

The development of thienamycin,[2] a potent broad spectrum β-lactam antibiotic isolated from *Streptomyces catteleya*, as a clinical drug candidate was unsuccessful because of its instability at high concentration and susceptibility to renal dehydropeptidase-I (DHP-I). Then, in 1984, Shih and co-workers at Merck[3] reported that the presence of a β-methyl group at the C1 position of the carbapenem skeleton, namely, 1β-methylthienamycin **1**, increased the chemical stability of thienamycin, prevented it from being readily metabolized by DHP-I enzyme, while retaining the antibacterial activity of thienamycin.



Since then, several approaches for the stereoselective synthesis of **1** have been reported.[4] Nearly every synthesis proceeds through the key intermediate **2** of the original synthesis reported by Shih *et al.*[3] Common synthetic approaches to **2** involve an aldol-type condensation of 4-acetoxy-2-azetidinone **3** with various kinds of enolates.[5] In our recent study of substituent effects on intramolecular dipolar cycloadditions of 3-substituted 5-hexenyl nitrile oxides, we observed good diastereoselectivity when C3 was monosubstituted.[6] When the nitrile oxide derived from the oximes **4** underwent intramolecular dipolar cycloaddition, it gave mainly the endo diastereomer **5** rather than the exo one **5′** in agreement with calculated transition structures for these reactions.[7] The size of the diastereoselectivity is in good agreement with the relative size of the substituents (Ph > Me > COOMe).[8]



4 **5** *endo* **5'** *exo*

Substrate	R	*endo/exo*
a	Ph	90:10
b	Me	87:13
c	COOMe	70:30

We have further investigated the diastereoselectivity of such 1,3-dipolar cycloadditions when C2 is monosubstituted and have utilized our findings in an efficient synthesis of the key intermediate **2** for the synthesis of 1β-methylthienamycin **1**. The recent report of Kang and Lee[9] of the synthesis of **2** *via* the intramolecular 1,3-dipolar cycloaddition of a 2-substituted 5-heptenyl nitrone prompts us to report the results of our study, which culminated in a formal total synthesis of 1β-methylthienamycin **1**.

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(4) (a) Yamamoto, Y.; Tsukada, T.; Shimada, T.; Gyoung, Y. S.; Asao, N. *J. Org. Chem.* **1995**, *60*, 143. (b) Yamamoto, Y.; Tsukada, T.; Asao, Naoki, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2102. (c) Nakai, T.; Shirai, F. *Chem. Lett.* **1989**, 445. (d) Ihara, M.; Masanobu, T.; Fukumoto, K.; Kametami, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2215. (e) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett.* **1988**, *44*, 1988. (f) Hatanaka, M. *Tetrahedron Lett.* **1987**, *28*, 83. (g) Shibasaki, M.; Iimori, T. *Tetrahedron Lett.* **1986**, *27*, 2149.

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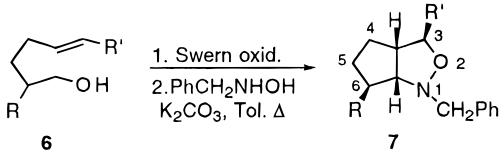
Results and Discussion

We examined the cyclizations of the 2-substituted nitrones prepared from the corresponding alcohols **6** by Swern oxidation[10] followed by condensation with *N*-benzylhydroxylamine[11] in the presence of anhydrous potassium carbonate. We prepared the alcohols **6a** and **6c** by alkylation of the lithium enolate of methyl phenylacetate with 4-bromo-1-butene (or 5-bromo-2-pentene[12]) followed by reduction with lithium aluminum hydride (LAH). Alkylation of dimethyl methylmalonate with 4-bromo-1-butene (or 5-bromo-2-pentene), followed by decarboalkoxylation using Krapcho's procedure[13] and reduction with LAH, furnished the alcohols **6b** and **6d**. Heating the nitrones derived from the alcohols **6a**−**d** in toluene at ∼100 °C for 12 h gave the bicyclic compounds **7a**−**d** in good yields as single diastereomers.[14] Thus the C2 stereochemistry completely controls the stereochemistry of the other three centers in the cyclization process. This complete diastereocontrol in the formation of four contiguous stereocenters of the bicyclic isoxazolidine led us to use this process as the key step in the synthesis of **2**.

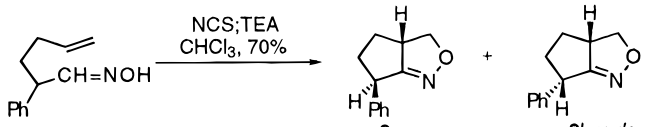
We also studied the cyclization of the nitrile oxides generated from the 2-substituted 5-hexenal oximes, but the observed diastereoselectivity was not as good as with the nitrones. Treatment of the oxime **8** with *N*-chlorosuccinimide and triethylamine in chloroform gave a mixture of diastereomers **9** and **9′** (81:19 ratio, favoring the *exo* isomer) *via* the nitrile oxide.[15] Presumably the larger bulk of the nitrone with its *N*-alkyl substituent causes one of the two diastereomeric transition states to



6 **7**

Compound	R	R'	Yield
a	Ph	H	82
b	Me	H	52
c	Ph	Me	83
d	Me	Me	73

be much more stable than the other while this effect is less pronounced in the less sterically demanding nitrile oxide.



8 **9** *exo* 81 : 19 **9'** *endo*

The bicyclic compound **7d** has the four contiguous stereocenters needed for the construction of **2** but needs to have the bond between C4 and C5 replaced by carbonyl groups and the N−O bond reductively cleaved. In order to introduce functionality in the molecule to carry out the eventual oxidative cleavage of the C4−C5 bond, we decided to utilize an ethylene ketal at C4 since it should not change the diastereocontrol observed in formation of **7**. Moreover, previous studies in our group indicated that the *gem*-dialkoxy group greatly facilitates cyclization of small-membered rings.[16] Thus our synthetic approach to **2** would involve the formation of the bicyclic compound **14** by intramolecular 1,3-dipolar cycloaddition of the nitrone **19** (Scheme 1). This bicyclic isoxazolidine ketal could then be taken on by either of two routes. In route A, the N−O bond of the isoxazole ring would be cleaved first to give the alcohol and amine functional groups. With these two groups protected, the ethylene ketal would then be removed with subsequent ozonolysis of the corresponding silyl enol ether and construction of the β-lactam ring. In route B, the ethylene ketal would be removed first with the alcohol and amine functional groups remaining masked until the cleavage of the silyl enol ether to give the carboxylic acid moiety; reduction and cyclization would then afford the desired β-lactam.

We began the synthesis of **2** with the addition of the dianion generated from 3-chloro-2-methyl-1-propanol to crotonaldehyde to give the diol **10** in 74% yield, using the procedure of Seebach.[17] Normant *et al.*[18] also re-

(5) (a) Maslerz, H.; Menard, M. *J. Org. Chem.* **1994**, *59*, 3223. (b) Hirai, K.; Iwano, Y.; Mikoshiba, I.; Koyama, H.; Nishi, T. *Heterocycles* **1994**, *38*, 277. (c) Uyero, S.; Itani, H. *Tetrahedron Lett.* **1994**, *35*, 4377. (d) Choi, W. B.; Churchill, H. R. O.; Lynch, J. E.; Thompson, A. S.; Humprey, G. R.; Volante, R. P.; Reider, P. J.; Shinkai, I. *Tetrahedron Lett.* **1994**, *35*, 2275. (e) Miura, T.; Murayama, T.; Yoshida, A.; Kobayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2271. (f) Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Tereshima, S. *Tetrahedron* **1991**, *47*, 2801. (g) Ueyo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143. (h) Noyori, R.; Hsiao, Y.; Kitamura, M. *Tetrahedron Lett.* **1990**, *31*, 549. (i) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5492. (j) Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563. (k) Deziel, R.; Favreau, D. *Tetrahedron Lett.* **1986**, *27*, 5687. (l) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675. (m) Sugimura, Y.; Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y. *Tetrahedron Lett.* **1985**, *26*, 4739.

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(8) For example, the conformational free energy differences for these three groups in the axial vs equatorial position on a cyclohexane (*A* values) are (kcal/mol): CO_2Me, 1.3; Me, 1.7; Ph, 2.7. In addition, we have carried out calculations of the transition structures and energies for these nitrile oxide cycloadditions and they are in good agreement with the experimental results. The calculated ratios of **5**:**5′** are as follows: CO_2Me, 77:23; Me, 84:16; Ph, 90:10. Heitkamp, H. J. Ph.D. Thesis, UCLA, 1995.

(9) Kang, S. H.; Lee, H. S. *Tetrahedron Lett.* **1995**, *36*, 6713.

(10) (a) Swern, D.; Omura, K. *Tetrahedron* **1978**, *34*, 1651. (b) Swern, D.; Mancuso, A. J. *Synthesis* **1981**, 165.

(11) Both *N*-benzyl- and *N*-(*p*-methoxybenzyl)hydroxylamine were prepared according the literature procedure: Jencks, W. P.; Maskill, H. *J. Am. Chem. Soc.* **1987**, *109*, 2062.

(12) (*E*)-5-Bromo-2-pentene was prepared according to the literature procedure: Julia, M.; Julia, S.; Tchen, S. Y. *Bull. Soc. Chim. Fr.* **1961**, 1849. It contains ∼7% of the cis isomer which was carried through to **7c** and **7d**.

(13) Krapcho, A. P.; Weismaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(14) The relative stereochemistry of **7b**, **7d**, and **14a** was proven by NOESY experiments. The methyl group (not next to the oxygen, at the 6-position in the 1*H*-cyclopent[*c*]isoxazole numbering) was shown to be syn to the ring juncture hydrogens by NOESY, while the structures of **7a** and **7c** were assigned by analogy to **7b** and **7d**.

(15) (a) Grundmann, C.; Grunanger, P. *The Nitrile Oxides*; Springer-Verlag: New York, 1971. (b) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition*; Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, 1984; pp 291−392. (c) Curran, D. P. In *Advances in Cycloaddition*; JAI Press: Greewich, CT, 1988; Vol. 1, p 150. (d) The structures of compounds **9** and **9′** were assigned by analogy to similar compounds reported in the literature: Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277. Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259.

(16) (a) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrehedron Lett.* **1992**, *33*, 6719. (b) Jung, M. E.; Vu, B. T. Unpublished results.

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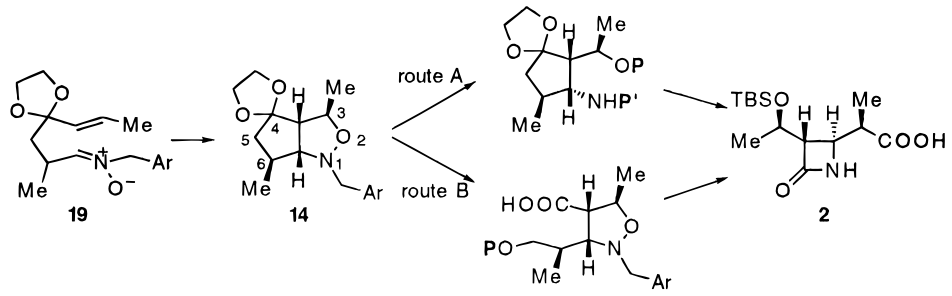
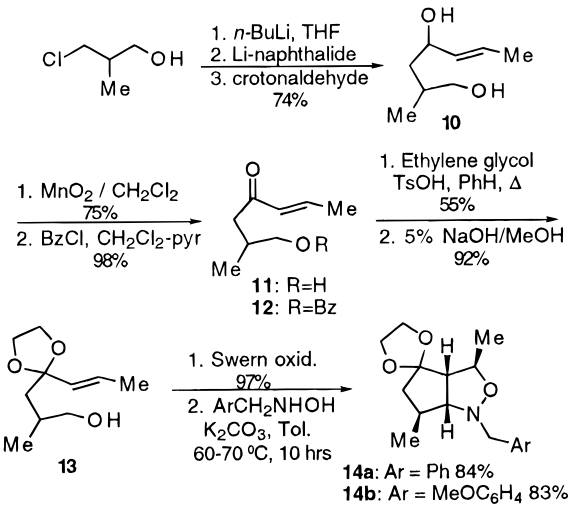
(18) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1978**, *19*, 3013.

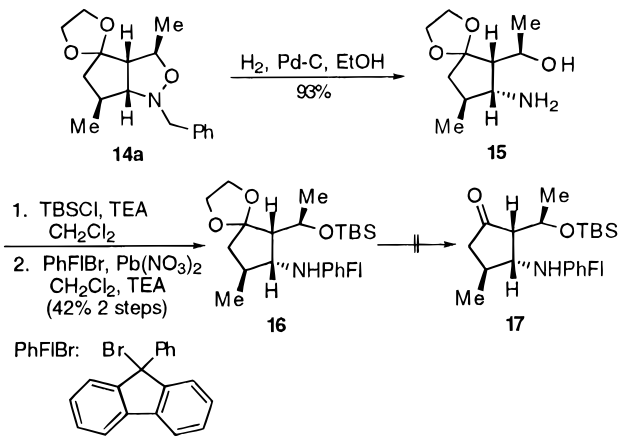
Scheme 1



Scheme 2



Scheme 3



ported a similar procedure using Grignard reagents. Both enantiomers of 3-chloro-2-methyl-1-propanol are commercial available or readily prepared from ethyl 3-hydroxy-2-methylpropionate.[17] The allylic alcohol of diol **10** was selectively oxidized by activated manganese oxide to the enone **11**, and the primary alcohol was protected as the benzoate to give **12** in 74% yield for the two steps. Ketalization with ethylene glycol and saponification gave the alcohol **13**.[19] Swern oxidation of the alcohol to the aldehyde and heating the aldehyde in toluene at 60−70 °C with *N*-benzylhydroxylamine and anhydrous potassium carbonate for 10 h gave the desired diastereomer **14a** in 84% yield as a single diastereomer (Scheme 2). Thus, as expected, the ketal did not affect the diastereocontrol and only the desired diastereomer was obtained. Moreover, the cyclization could be carried out under much milder conditions than that of **6**, presumably due to the *gem*-dialkoxy effect.

With **14a** in hand, we examined route A first (Scheme 3). The isoxazolidine was hydrogenated over Pd on activated carbon in ethanol to give the amino alcohol **15** in 93% yield. Hydrogenation in other solvents, such as ethyl acetate or benzene, failed to give **15**. The alcohol was then protected as a bulky silyl ether and the amine protected with the phenylfluorenyl group.[20] Rapoport reported that the phenylfluorenyl protecting group can be used as a steric pocket that shields the hydrogen on the α-carbon of amino acid derivatives.[20] In addition, the phenylfluorenyl group is much more stable to solvolysis than the trityl group.[21] However, several efforts at selective removal of the ketal protecting group failed.[22] For this reason, we abandoned this approach to 1β-methylthienamycin.

Since the first approach (route A) failed, we decided to keep the amine and alcohol functional groups masked as the isoxazolidine ring until the later steps (route B, see Scheme 4). After several failed attempts to remove the ethylene ketal of **14a** under mild conditions such as *p*-TsOH or pyridinium *p*-toluenesulfonate (PPTS) in acetone, we were able to obtain **18a** in 72% yield by heating **14a** with 50% H_2SO_4 in methanol for 4 h. Presumably the presence of the basic nitrogen in **14** requires the formation of a dicationic species in order to remove the ketal to give the ketone **18**, and thus strongly acidic conditions are necessary.

In order to allow greater possibilities for deprotection of the amine functionality later in the synthetic scheme, we also prepared the corresponding *N*-*p*-methoxybenzyl derivative. Thus reaction of the aldehyde derived by Swern oxidation of **13** with *N*-[(4-methoxyphenyl)methyl]-hydroxylamine[11] in toluene with potassium carbonate at 90 °C for 4 h afforded the desired bicyclic isoxazolidine ketal **14b** in 83% yield, again as a single diastereomer. Acidic hydrolysis of **14b** under the conditions described above for **14a** furnished the ketone **18b** in 82% yield. Comparison of the spectroscopic data of our sample of **18b** with that kindly provided by Professor Kang showed them to be identical. Since Kang and Lee reported the

(19) The alcohol **13** contains ~6−7% of the *cis* isomer resulting from isomerization of the double bond during ketalization, which was carried on to **14**.

(20) (a) Rapoport, H.; Christie, B. D. *J. Org. Chem.* **1985**, *50*, 1239. (b) Rapoport, H.; Lubell, W. D. *J. Am. Chem. Soc.* **1987**, *109*, 236.

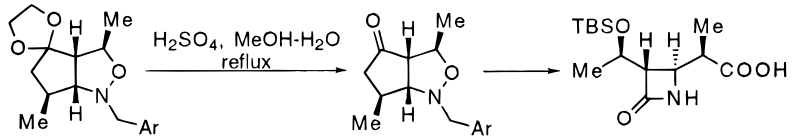
(21) Shorter, J.; Bolton, R.; Chapman, N. B. *J. Chem. Soc.* **1964**, 1895.

(22) In one case, with the amino being protected by the benzoyl group, only 31% of the desired ketone was obtained in *p*-TsOH and aqueous acetone conditions.

(23) Compound **6b** was prepared according to the literature procedure: Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 345.

(24) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

Scheme 4



14a: Ar = Ph
14b: Ar = $MeOC_6H_4$

18a: Ar = Ph 72 %
18b: Ar = $MeOC_6H_4$ 82%

2

synthesis of **2** in eight steps from **18b**, we have thus completed a formal total synthesis of both **2** and the β-lactam antibiotic 1β-methylthienamycin **1**.

Conclusion

Thus we have observed remarkable diastereocontrol in intramolecular 1,3-dipolar cycloadditions of 2-substituted 5-hexenyl and 5-heptenyl nitrones in which only one diastereomer of the 6-substituted and 3,6-disubstituted perhydrocyclopenta[*c*]isoxazoles is isolated. An alkyl or aryl substituent at C2 completely controls the stereochemistry of both the ring juncture and the 3-substituent, and thus one stereocenter controls the formation of the other three to give a product with four contiguous stereocenters. We have also observed a *gem*-dialkoxy effect in the cyclization of an analogous ethylene ketal. Finally this cycloaddition process has been used as the key step in an efficient formal total synthesis of the potent β-lactam antibiotic, 1β-methylthienamycin. Further work in the area of substituent effects—*gem* dialkyl, dialkoxy, dicarbalkoxy, etc.—is currently underway in our laboratory and will be described in due course.

Experimental Section

General. All reactions were carried out under argon with the exclusion of moisture. Reagents were purchased from Fisher Scientific Co. and Aldrich Chemical Co. and were used without further purification unless otherwise specified. The following solvents and reagents were distilled from the indicated agent under argon: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl, methylene chloride, benzene, and toluene from calcium hydride, and triethylamine from potassium hydroxide. Flash column chromatography was carried out in the indicated solvent system (in the percentage of volume) on 230−400 mesh silica gel. Analytical thin layer chromatography was done on Merck silica gel F_{254} 0.2 mm precoated plates.

2-Phenyl-5-hexen-1-ol (6a). To the solution of diisopropylamine (0.721 mL, 5.5 mmol) in 40 mL of THF at −78 °C was added *n*-butyllithium (5.5 mmol). After 15 min, methyl phenylacetate (0.719 mL, 5.0 mmol) was added. Stirring was continued for another 15 min, and then 4-bromo-1-butene (0.533 mL, 5.25 mmol) was added dropwise. After 1 h, the reaction was worked up with diethyl ether and saturated brine solution. Flash column chromatography (silica gel, 3−5% EtOAc−hexane) of the crude residue gave methyl 2-phenyl-5-hexenoate (547.1 mg, 54%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (5H, m), 5.78 (2H, m), 5.01 (2H, m), 3.65 (3H, s), 3.58 (1H, t, J = 7.6 Hz), 2.19 (1H, m), 2.01 (2H, m), 1.88 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.30, 138.80, 137.4, 128.50, 127.90, 127.20, 115.30, 51.90, 50.60, 33.40, 31.40; IR (neat) 3065, 2952, 1736, 1641, 1255, 1163.

The solution of methyl 2-phenyl-5-hexenoate (517.1 mg, 2.531 mmol) and LAH (115.3 mg, 3.037 mmol) in 30 mL of diethyl ether was refluxed for 3 h to give **6a** (379.2 mg, 85%) after chromatography (silica gel, 20% EtOAc−hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (2H, t, J = 7.0 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.27 (2H, d, J = 7.0 Hz), 5.83 (1H, m), 5.01 (2H, m), 3.79 (2H, m), 2.86 (1H, m), 2.02 (2H, m), 1.85 (1H, m), 1.75 (1H, m), 1.41 (1H, bt, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.91, 138.22, 128.58, 128.00, 126.70, 114.67, 67.36, 47.88, 31.25, 31.03; IR (neat) 3359, 3063, 3029, 2928, 1640, 1057, 1032.

2-Methyl-5-hexen-1-ol (6b):[21] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86 (1H, m), 5.02 (2H, m), 3.55 (1H, dd, J = 10.5, 5.8 Hz), 3.54 (1H, dd, J = 10.5, 5.8 Hz), 2.14 (2H, m), 1.64 (1H, m), 1.56 (1H, m), 1.51 (1H, m), 1.25 (1H, m), 0.97 (3H, d, J = 6.7 Hz).

(*E*)-2-Phenyl-5-hepten-1-ol (6c). To the solution of diisopropylamine (0.684 mL, 5.216 mmol) in 50 mL of THF at −78 °C was added *n*-butyllithium (5.216 mmol). After 15 min, methyl phenylacetate (0.625 mL, 4.346 mmol) was added. Stirring was continued for another 15 min, and then 5-bromo-2-pentene[12] (713.6 mg, 4.781 mmol) was added dropwise. After about 2 h, the reaction was worked up with diethyl ether and a saturated brine solution. Flash column chromatography (silica gel, 3−5% EtOAc−hexane) of the crude residue gave methyl 2-phenyl-5-heptenoate (503.1 mg, 53%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (5H, m), 5.39 (2H, m), 3.65 (3H, s), 3.56 (1H, t, J = 7.6 Hz), 2.18−1.80 (3H, m), 1.64 (3H, bd, J = 3.7 Hz), 1.35 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.41, 138.95, 129.88, 128.48, 127.88, 126.91, 125.88, 64.65, 51.83, 33.05, 30.21, 17.82.

Methyl 2-phenyl-5-heptenoate (503.1 mg, 2.304 mmol) was stirred with LAH (96.2 mg, 2.535 mmol) in 30 mL of diethyl ether overnight at room temperature to give **6c** (310 mg, 71%) after chromatography (silica gel, 15% EtOAc−hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.25 (5H, m), 5.42 (2H, m), 3.78 (2H, m), 2.85 (1H, m), 1.93 (2H, m), 1.79 (1H, m), 1.71 (1H, m), 1.67 (3H, bd, J = 5.3 Hz), 1.37 (1H, bs); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.07, 130.65, 128.54, 128.02, 126.63, 125.20, 67.40, 47.85, 31.71, 30.03, 17.81; IR (neat) 3358, 3028, 2921, 1603, 1029.

(*E*)-2-Methyl-5-hepten-1-ol (6d). To the solution of methyl methylmalonate (1.464 g, 10 mmol) in 100 mL of THF was added 60% sodium hydride in mineral oil (440 mg, 11 mmol). After 15 min, 5-bromo-2-pentene[12] (1.6396 g, 11 mmol) was added. The solution was refluxed for 10 h. A saturated NH_4Cl solution was then added, and the product was extracted with petroleum ether. The ethereal extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (silica gel, 5% EtOAc−hexane) of the crude residue gave dimethyl 2-methyl-2-(5-pentenyl)propanedioate (1.920 g, 90%). The solution of dimethyl 2-methyl-2-(5-pentenyl)propanedioate (1.920 g, 8.960 mmol), lithium chloride (1.520 g, 35.84 mmol), and water (0.160 mL, 8.960 mmol) in DMSO (20 mL) was refluxed for 2 h. Water was added, and the monoester was extracted with petroleum ether. The ethereal extracts were washed with saturated brine and dried over $MgSO_4$. Chromatography of the crude residue (silica gel, 5% EtOAc−hexane) gave methyl 2-methyl-5-heptenoate (1.1256 g, 80%).

The solution of methyl 2-methyl-5-heptenoate (1.0581 g, 6.772 mmol) and LAH (257 mg, 6.772 mmol) in ∼50 mL of diethyl ether was refluxed for 2 h to give the alcohol **6d** (801.2 mg, 92%) after chromatography (silica gel, 15% EtOAc−hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47 (2H, m), 3.55 (1H, dd, J = 10.5, 5.8 Hz), 3.46 (1H, dd, J = 10.5, 6.5 Hz), 2.08 (1H, m), 2.01 (1H, m), 1.68 (3H, bd, J = 3.5 Hz), 1.67 (1H, m), 1.51 (1H, m), 1.41 (1H, bs), 1.20 (1H, m), 0.96 (3H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 131.28, 124.85, 68.20, 35.14, 32.94, 29.90, 17.88, 16.45; IR (neat) 3341, 2919, 2857, 1657, 1038.

(3,3aα,4,5,6β,6aα)-Hexahydro-6-phenyl-1-(phenylmethyl)-1*H*-cyclopent[*c*]isoxazole (7a). Oxalyl chloride (122 μL, 1.402 mmol) was added to a solution of dimethyl sulfoxide (199

μL, 2.805 mmol) in 10 mL of methylene chloride at −78 °C. After 15 min, a solution of **6a** (100 mg, 0.561 mmol) in 1 mL of methylene chloride was added dropwise. Stirring was continued for 45 min, and the reaction was quenched with triethylamine (626 μL, 4.488 mmol). The cooling bath was removed, and the reaction flask was allowed to warm to about −20 °C. Workup involved addition of 1 M $NaHSO_4$ and extraction with petroleum ether. The organic layers were washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation of solvents gave the crude aldehyde (98 mg, 98%) which was used without further purification. To a solution of the aldehyde (98 mg, 0.556 mmol) in 10 mL of toluene were added potassium carbonate (154.7 mg, 1.112 mmol) and *N*-benzylhydroxylamine[11] (82.2 mg, 0.667 mmol). After the solution was heated at ∼100 °C for 12 h, the solids were then filtered out, and the solvent was removed in vacuo to give an oily residue. ^{1}H NMR of the crude oil shows only one diasteremer. Flash column chromatography (silica gel, 5% EtOAc−hexane) gave **7a** (127.4 mg, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (10H, m), 4.21 (1H, dd, *J* = 8.6, 7.6 Hz), 3.98 (1H, d, *J* = 13.2 Hz), 3.78 (1H, d, *J* = 13.2 Hz), 3.67 (1H, dd, *J* = 8.6, 3.6 Hz), 3.55 (1H, bdd, *J* = 8.0, 8.0 Hz), 3.23 (1H, m), 3.08 (1H, m), 2.15 (2H, m), 1.77−1.59 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.51, 137.26, 128.85, 128.20, 128.16, 127.25, 127.08, 125.97, 78.59, 72.40, 60.36, 50.68, 47.70, 33.85, 31.47; IR (neat) 3029, 2951, 2566, 1495, 1030; high-resolution MS (EI, *m*/*z*) 279.1620, calcd for $C_{19}H_{21}NO$ 279.1623.

(3,3aα,4,5,6β,6aα)-Hexahydro-6-methyl-1-(phenylmethyl)-1*H*-cyclopent[*c*]isoxazole (7b). Using the aldehyde from **6b** (61.2 mg, 0.545 mmol), the procedure used for the formation of **7a** from **6a** was followed to give **7b** (61.7 mg, 52%) after flash column chromatography (silica gel, 10% EtOAc−hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (2H, d, *J* = 7.1 Hz), 7.38 (2H, t, *J* = 7.3 Hz), 7.31 (1H, t, *J* = 7.2 Hz), 4.19 (1H, dd, *J* = 8.5, 7.9 Hz), 4.06 (1H, d, *J* = 12.9 Hz), 3.83 (1H, d, *J* = 12.9 Hz), 3.58 (1H, dd, *J* = 8.5, 4.5 Hz), 3.11 (1H, m), 3.01 (1H, dd, *J* = 8.4, 4.6 Hz), 1.94 (3H, m), 1.52 (1H, m), 1.23 (1H, m), 0.89 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.45, 129.08, 128.21, 127.20, 78.88, 72.53, 61.00, 47.02, 39.39, 33.19, 30.50, 18.00; IR (neat) 3063, 2953, 2868, 1455, 1030; high-resolution MS (EI, *m*/*z*) 217.1471, calcd for $C_{14}H_{19}NO$ 217.1467.

(3α,3aβ,4,5,6β,6aα)-Hexahydro-3-methyl-6-phenyl-1-(phenylmethyl)-1*H*-cyclopent[*c*]isoxazole (7c). Using the alcohol **6c** (77.7 mg, 0.408 mmol), the procedure used for the formation of **7a** from **6a** was followed to give **7c** (99.5 mg, 83%) after flash column chromatography (silica gel, 5% EtOAc−hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.10 (10H, m), 4.06 (1H, d, *J* = 13.8 Hz), 3.97 (1H, d, *J* = 13.8 Hz), 3.87 (1H, bdq, *J* = 6.9, 6.1 Hz), 3.54 (1H, dd, *J* = 8.8, 2.0 Hz), 3.08 (1H, m), 2.78 (1H, dq, *J* = 3.3, 7.8 Hz), 2.41 (1H, m), 1.96 (1H, m), 1.85 (1H, m), 1.66 (1H, m), 1.39 (3H, d, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.87, 137.50, 128.90, 128.23, 128.10, 127.29, 127.02, 125.92, 80.11, 79.97, 62.06, 56.28, 49.77, 34.15, 28.30, 18.33; IR (neat) 3029, 2931, 2868, 1496, 1454, 1117; high-resolution MS (EI, *m*/*z*) 293.1780, calcd for $C_{20}H_{23}NO$ 293.1780.

(3α,3aβ,4,5,6α,6aβ)-Hexahydro-3,6-dimethyl-1-(phenylmethyl)-1*H*-cyclopent[*c*]isoxazole (7d). Using the alcohol **6d** (123.5 mg, 0.963 mmol), the procedure used for the formation of **7a** from **6a** was followed to give **7d** (162.8 mg, 73%) after flash column chromatography (silica gel, 5% EtOAc−hexane): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (2H, dd, *J* = 7.5, 1.4 Hz), 7.25 (2H, tt, *J* = 7.6, 1.4 Hz), 7.16 (1H, tt, *J* = 7.4, 1.3 Hz), 4.09 (1H, d, *J* = 13.1 Hz), 3.86 (1H, d, *J* = 13.1 Hz), 3.65 (1H, bdq, *J* = 8.5, 6.1 Hz), 2.91 (1H, bd, *J* = 8.5 Hz), 2.51 (1H, dq, *J* = 1.8, 8.5 Hz), 2.01 (1H, m), 1.74 (2H, m), 1.47 (1H, m), 1.31 (1H, m), 1.27 (3H, d, *J* = 6.1 Hz), 0.73 (1H, d, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.42, 129.15, 128.09, 127.11, 80.74, 79.57, 62.41, 55.00, 37.99, 31.74, 27.19, 18.04, 17.76; IR (neat) 2955, 2869, 1455, 1100; high-resolution MS (EI, *m*/*z*) 231.1624, calcd for $C_{15}H_{21}NO$ 231.1623.

2-Phenyl-5-hexen-1-al Oximes 8. Oxalyl chloride (93 μL, 1.066 mmol) was added to a solution of dimethyl sulfoxide (151 μL, 2.133 mmol) in 10 mL of methylene chloride at −78 °C. After 15 min, a solution of **6a** (75.2 mg, 0.427 mmol) in 1 mL of methylene chloride was added dropwise. Stirring was continued for 1 h, and the reaction was quenched with triethylamine (476 μL, 3.416 mmol). The cooling bath was removed, and the reaction flask was allowed to warm to −20 °C. Workup involved addition of 1 M $NaHSO_4$ and extraction with petroleum ether. The organic layers were washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation of solvents gave the crude aldehyde (∼74 mg) which was used without further purification. The crude aldehyde was dissolved in 10 mL of pyridine, and hydroxylamine hydrochloride (44.5 mg, 0.641 mmol) was added. The reaction mixture was stirred overnight (∼12 h) and then worked up with 1 N HCl and diethyl ether. The ethereal extracts were washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated to give a oily residue. Flash column chromatography (silica gel, 20% EtOAc−hexane) of the crude residue gave **8** (66.2 mg, 82%) as a mixture of *Z* and *E* isomers. *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (1H, bs), 7.52 (1H, d, *J* = 6.9 Hz), 7.34 (2H, t, *J* = 6.2 Hz), 7.27 (1H, t, *J* = 6.1 Hz), 7.22 (2H, d, *J* = 6.1 Hz), 5.81 (1H, m), 5.03 (2H, m), 3.53 (1H, app q, *J* = 7.1 Hz), 2.03 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.05, 140.38, 137.67, 128.70, 127.76, 126.79, 115.19, 45.50, 32.43, 31.23; IR (neat) 3262, 3068, 2930, 1642, 1601.

(3aα,4,5,6β)-Tetrahydro-6-phenyl-3*H*-cyclopent[*c*]isoxazole (9). *N*-Chlorosuccinimide (22.1 mg, 0.165 mmol) was added to a solution of **8** (31.3 mg, 0.165 mmol) in chloroform (3 mL) at 0 °C. After 3 h, triethylamine (23 μl, 0.165 mmol) was added. The reaction was worked up after 12 h with water and methylene chloride. The CH_2Cl_2 layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. ^{1}H NMR of the crude residue showed a mixture of diastereomers (81:19 ratio). Preparative chromatography (silica gel, 20% EtOAc−hexane) gave 17.8 mg of **9** and 3.9 mg of **9′**. Yield: 70%. Compound **9**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (2H, bt, *J* =7.4 Hz), 7.32 (2H, bd, *J* = 7.5 Hz), 7.29 (1H, bt, *J* =7.2 Hz), 4.64 (1H, m), 4.04 (1H, app t, *J* = 8.5 Hz), 3.95 (2H, m), 2.90 (1H, m), 2.35 (1H, m), 2.22 (1H, m), 1.65 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.08, 140.52, 128.63, 126.83, 126.71, 74.73, 55.61, 39.45, 38.56, 28.13; IR (neat) 2936, 2870, 1603, 1497, 1269; high-resolution MS (EI, *m*/*z*) 187.1004, calcd for $C_{12}H_{13}NO$ 187.0997. Compound **9′**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20−7.15 (5H, m), 4.61 (1H, m), 4.00−3.90 (3H, m), 2.70 (1H, m), 2.33 (1H, m), 2.18 (1H, m), 1.76 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.50, 139.98, 128.52, 127.80, 126.89, 75.34, 54.77, 40.46, 37.79, 29.59.

(*E*)-2-Methyl-5-heptene-1,4-diol (10). *n*-Butyllithium (10 mmol) was added to a solution of 3-chloro-3-methyl-1-propanol (1.0858 g, 10 mmol) in 10 mL of THF at −78 °C under argon. After 15 min, a solution of lithium naphthalenide (prepared by stirring 173.4 mg of lithium and 3.2 g of naphthalene in 50 mL of THF overnight) was added via cannula. The reaction mixture was then stirred at −78 °C for 6−8 h. Crotonaldehyde (0.830 mL, 10 mmol) was then added dropwise. After an additional 2 h at −78 °C, the cooling bath was removed, and the reaction mixture was allowed to warm up to room temperature. After the solution was stirred at room temperature overnight, the reaction was quenched with saturated NH_4Cl solution, and the product was extracted with diethyl ether. The ethereal extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Flash column chromatography (silica gel, 50−60% EtOAc−hexane) of the crude residue gave 1.0713 g of the diol **10** as a ∼1:1 mixture of diastereomers. Yield: 74%. **10:** ^{1}H NMR of one diastereomer ($CDCl_3$, 400 MHz) δ 5.64 (1H, dd, *J* = 15.2, 6.3 Hz), 5.47 (1H, dm, *J* =15.2 Hz), 4.18 (1H, dt, *J* = 6.0, 6.2 Hz), 3.5 (4H, m), 1.81 (1H, m), 1.67 (3H, m), 1.52 (2H, m), 0.90 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.85, 126.42, 70.37, 67.81, 41.66, 31.97, 17.56, 17.12; IR (neat) 3334, 2919, 1675, 1040; high-resolution MS (EI, *m*/*z*) 143.1069 $(M - H)^+$, calcd for $C_8H_{15}O_2$ 143.1072.

(*E*)-7-Hydroxy-6-methyl-2-hepten-4-one (11). The solution of **10** (867 mg, 6.011 mmol) and activated manganese dioxide[24] (5.229 g, 60.108 mmol) in 60 mL of methylene chloride was stirred for 48 h at room temperature. The black solids were filtered out and washed with chloroform. The filtrate was then concentrated in vacuo and chromatographed on silica gel (neutralized with triethylamine, 40% EtOAc−

hexane) to give the enone **11** (641.2 mg, 75%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (1H, dq, J = 15.8, 6.9 Hz), 6.12 (1H, dq, J = 15.8, 1.6 Hz), 3.53 (1H, m), 3.42 (1H, m), 2.67 (1H, dd, J = 16.1, 6.6 Hz), 2.44 (1H, dd, J = 16.1, 6.6 Hz), 2.23 (1H, m), 2.20 (1H, bs), 1.89 (3H, dd, J = 6.8, 1.7 Hz), 0.93 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.71, 143.18, 132.16, 67.82, 44.13, 32.23, 18.25, 16.98; IR (neat) 3433, 2960, 2934, 2875, 1666, 1632, 1443, 1042; high-resolution MS (EI, m/z) 143.1073 (M − H)$^+$, calcd for $C_8H_{15}O_2$ 143.1072.

(*E*)-7-(Benzoyloxy)-6-methyl-2-hepten-4-one (12). To a solution of **11** (568 mg, 3.994 mmol) in 5 mL of methylene chloride and 1 mL of dry pyridine was added benzoyl chloride (1.0 mL, 8.615 mmol). After being stirred overnight at room temperature, the reaction mixture was worked up by addition of brine and extraction with petroleum ether. Pyridine was removed by washing the ethereal extracts with diluted HCl. Evaporation of ether gave an oily residue which after chromatography on a short column of silica gel (15% EtOAc−hexane) gave **12** (973.2 mg, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (2H, bd, J = 7.1 Hz), 7.54 (1H, bt, J = 7.5 Hz), 7.42 (2H, bt, J = 7.4 Hz), 6.83 (1H, dq, J = 15.8, 6.8 Hz), 6.12 (1H, dq, J = 15.8, 1.5 Hz), 4.18 (2H, m), 2.70 (1H, dd, J = 15.7, 5.6 Hz), 2.57 (1H, m), 2.45 (1H, dd, J = 15.7, 7.6 Hz), 1.85 (3H, dd, J = 6.8, 1.6 Hz), 1.03 (3H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.82, 166.38, 142.84, 132.87, 132.05, 130.11, 129.46, 128.28, 69.03, 43.66, 29.22, 18.14, 17.03; IR (neat) 2967, 1790, 1721, 1698, 1674, 1275, 1113; high-resolution MS (EI, m/z) 247.1329 (M + H)$^+$, calcd for $C_{15}H_{19}O_3$ 247.1334.

(*E*)-7-Hydroxy-6-methyl-2-hepten-4-one Ethylene Ketal (13). To the solution of **12** (1.0910 g, 4.429 mmol) in 40 mL were added ethylene glycol (1 mL, 16 mmol) and several crystals of *p*-TsOH. The reaction was refluxed for 12 h using a Dean−Stark trap. TLC (10% EtOAc−hexane) showed a mixture of **12** and the product. A saturated $NaHCO_3$ solution was added, and the products were extracted with ether. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (silica gel, 8−10% EtOAc−hexane) gave 325.1 mg (30%) of starting material and 429.9 mg (55% yield) of the ketal: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09 (2H, bd, J = 7.1 Hz), 7.60 (1H, bt, J = 7.1 Hz), 7.48 (2H, bt, J = 7.5 Hz), 5.87 (1H, dq, J = 15.4, 6.6 Hz), 5.43 (1H, dq, J = 15.4, 1.6 Hz), 4.34 (1H, dd, J = 10.7, 5.2 Hz), 4.17 (1H, dd, J = 10.6, 6.9 Hz), 3.99−3.89 (4H, m), 2.23 (1H, m), 1.94 (1H, dd, J = 14.4, 6.0 Hz), 1.75 (3H, dd, J = 6.7, 1.7 Hz), 1.70 (1H, dd, J = 14.4, 6.4 Hz), 1.13 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.63, 132.75, 130.81, 130.55, 129.52, 128.30, 126.81, 108.84, 69.94, 64.30, 64.22, 41.46, 28.59, 18.51, 17.31; IR (neat) 2961, 2886, 1717, 1603, 1452, 1280, 1115, 1028; high-resolution MS (EI, m/z) 291.1587 (M + H)$^+$, calcd for $C_{17}H_{23}O_4$ 291.1596.

The solution of the ketal (415.6 mg, 1.432 mmol) and 5 mL of 5% NaOH in 20 mL of MeOH was stirred at room temperature for 2 h. Workup involved removal of methanol by evaporation in vacuo, addition of water, and extraction with diethyl ether. The ethereal extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography (silica gel, 25−30% EtOAc−hexane) of the residue gave the alcohol **13** (240 mg, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (1H, dq, J = 15.4, 6.6 Hz), 5.37 (1H, dq, J = 15.4, 1.6 Hz), 3.99−3.84 (4H, m), 3.51 (1H, bm), 3.38 (1H, bm), 2.87 (1H, m), 1.89 (1H, m), 1.74 (2H, m), 1.70 (3H, dd, J = 6.6, 1.7 Hz), 0.92 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.38, 126.94, 108.82, 68.43, 64.37, 63.90, 42.87, 31.13, 18.88, 17.20; IR (neat) 3426, 2954, 2886, 11675, 1451, 1201, 1036; high-resolution MS (EI, m/z) 187.1327 (M + H)$^+$, calcd for $C_{10}H_{19}O_3$ 187.1334.

(3α,3a*β*,5,6α,6a*β*)-Hexahydro-3,6-dimethyl-1-(phenylmethyl)-4*H*-cyclopent[*c*]isoxazol-4-one Ethylene Ketal (14a). Oxalyl chloride (112 μL, 1.28 mmol) was added to a solution of dimethyl sulfoxide (182 μL, 2.56 mmol) in 6 mL of methylene chloride at −78 °C. After 15 min, a solution of the alcohol **13** (95.3 mg, 0.512 mmol) in 1 mL of methylene chloride was added dropwise. After the solution was stirred at −78 °C for 1 h, triethylamine (571 μL, 4.096 mmol) was added, and the cooling bath was removed. The reaction was worked up at −20 °C with addition of water, and the product was extracted with diethyl ether. The ethereal extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 94 mg of the crude aldehyde. The aldehyde was dissolved in 10 mL of toluene, and *N*-benzylhydroxylamine (75.6 mg, 0.614 mmol) and anhydrous potassium carbonate (141.5 mg, 1.024 mmol) were added. The reaction mixture was heated at 60−70 °C for 10 h. The solids were then filtered out, and toluene was removed in vacuo. Flash column chromatography (silica gel, 10% EtOAc−hexane) of the crude residue gave **14a** (124.5 mg, 84%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (2H, bd, J = 7.4 Hz), 7.36 (2H, bt, J = 7.5 Hz), 7.30 (1H, bt, J = 7.3 Hz), 4.16 (1H, m), 4.11 (1H, d, J = 13.2 Hz), 3.98−3.80 (5H, m), 3.07 (1H, d, J = 8.7 Hz), 2.52 (1H, dt, J = 1.2, 8.3 Hz), 2.38 (1H, dd, J = 13.5, 8.1 Hz), 1.81 (1H, m), 1.54 (1H, bd, J = 13.5 Hz), 1.33 (3H, d, J = 6.1 Hz), 0.92 (3H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.14, 129.15, 128.18, 127.26, 117.06, 78.89, 75.19, 64.49, 63.98, 62.21, 40.96, 34.51, 19.06, 18.82 (1 carbon not resolved); IR (neat) 2973, 2932, 2874, 1740, 1455, 1341, 1119, 1032; high-resolution MS (EI, m/z) 289.1667, calcd for $C_{17}H_{23}NO_3$.

(3α,3a*β*,5,6α,6a*β*)-Hexahydro-1-*N*-(4-methoxybenzyl)-3,6-dimethyl-4*H*-cyclopent[*c*]isoxazol-4-one Ethylene Ketal (14b). The alcohol **13** (92.3 mg, 0.495 mmol) was oxidized to give 88.5 mg of the corresponding aldehyde using the procedure described for **14a**. The aldehyde (88.5 mg, 0.480 mmol) was dissolved in toluene (5 mL), and *N*-(4-methoxyphenyl)methylhydroxylamine[11] (88.2 mg, 0.576 mmol) and potassium carbonate (132.7 mg, 0.960 mmol) were added. The reaction mixture was heated at 90−100 °C for 4 h. The solids were then filtered out, and toluene was evaporated in vacuo. Column chromatography (25% EtOAc−hexane) of the crude residue gave **14b** (127.6 mg, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (2H, d, J = 8.7 Hz), 6.85 (2H, d, J = 8.7 Hz), 4.10 (1H, m), 4.06 (1H, d, J = 12.9 Hz), 3.92 (1H, m), 3.85 (2H, m), 3.79 (3H, s), 3.77 (2H, m), 3.00 (1H, d, J = 8.7 Hz), 2.46 (1H, dt, J = 1.2, 8.3 Hz), 2.32 (1H, dd, J = 13.5, 8.1 Hz), 1.73 (1H, m), 1.45 (1H, bd, J = 13.5 Hz), 1.28 (3H, d, J = 6.1 Hz), 0.86 (3H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.87, 130.45, 129.10, 117.07, 113.57, 78.71, 75.14, 64.49, 63.98, 62.21, 61.70, 55.19, 40.92, 34.57, 19.03, 18.85; IR (neat) 2969, 2876, 1514, 1341, 1250, 1117, 1034; high-resolution MS (EI, m/z) 319.1785, calcd for $C_{18}H_{25}O_4$ 319.1784.

(±)-(2*S*,3*R*,4*S*)-3-Amino-2-((*R*)-1-hydroxyethyl)-4-methylcyclopentanone Ethylene Ketal (15). The isoxazole **14a** (280.8 mg, 0.970 mmol) was hydrogenated for 12 h in absolute ethyl alcohol (10 mL) over Pd−C under a balloon of hydrogen gas. The black solids were then filtered out and washed with ethyl acetate. Evaporation of solvents in vacuo gave the amino alcohol **15** (182.2 mg, 93%) which is sufficiently pure to be used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.14 (1H, dq, J = 8.1, 6.2 Hz), 4.00−3.87 (4H, m), 3.12 (1H, dd, J = 8.5, 4.9 Hz), 2.99 (3H, bs), 2.18 (1H, dd, J = 8.3, 8.3 Hz), 2.10 (1H, dd, J = 13.2, 7.7 Hz), 1.82 (1H, m), 1.33 (1H, dd, J = 13.2, 8.9), 1.28 (3H, d, J = 6.2 Hz), 1.08 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 116.45, 64.38, 64.29, 63.86, 59.04, 52.98, 43.04, 41.34, 22.01, 19.30.

(±)-(2*S*,3*R*,4*S*)-2-[(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-ethyl]-3-[(9-(9-phenylfluorenyl)amino]-4-methylcyclopentanone Ethylene Ketal (16). To a solution of **15** (182.2 mg, 0.905 mmol) in 10 mL of methylene chloride were added triethylamine (139 μL, 0.996 mmol), *tert*-butyldimethylsilyl chloride (150.7 mg, 0.996 mmol), and DMAP (4.9 mg, 0.04 mmol). The reaction mixture was stirred at room temperature for 24 h; then phenylfluorenyl bromide[20] (312 mg, 1.0 mmol), triethylamine (139 μL, 0.996 mmol), and $Pb(NO_3)_2$ (331.2 mg, 1.0 mmol) were added. The reaction mixture was stirred for another 24 h. The reaction was worked up with water and diethyl ether. The organic layers were washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and evaporated in vacuo to give an oil. Flash column chromatography of the crude residue gave the protected amino alcohol **16** (210.9 mg, 42%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (1H, d, J = 7.5 Hz), 7.66 (1H, d, J = 7.5 Hz), 7.50−7.12 (11H, m), 4.22 (1H, dq, J = 6.1, 6.2 Hz), 3.82−3.71 (3H, m), 3.69 (1H, bs), 3.55 (1H, m), 2.52 (1H, m), 2.13 (1H, dd, J = 13.9, 9.9 Hz), 1.74 (1H, m), 1.46 (1H, bt, J = 5.8 Hz), 1.13 (1H, m), 1.12 (3H, d, J = 6.2

Hz), 0.81 (9H, s), 0.56 (3H, d, J = 7.0 Hz), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.83, 146.10, 140.80, 140.14, 127.85, 127.80, 127.74, 127.29, 127.27, 126.68, 126.53, 126.23, 125.98, 119.62, 119.55, 116.47, 73.02, 68.00, 64.12, 63.07, 62.46, 52.88, 41.68, 35.97, 25.95, 24.67, 19.22, 18.00, −3.98, −4.33; high-resolution MS (EI, m/z) 555.3165, calcd for $C_{35}H_{45}NO_3$ 555.3165.

(3α,3aβ,5,6α,6aβ)-Hexahydro-3,6-dimethyl-1-(phenylmethyl)-4*H*-cyclopent[*c*]isoxazol-4-one (18a). The ketal **14a** (190 mg, 0.6565 mmol) was dissolved in 5 mL of methanol, and 2 mL of 50% sulfuric acid was added. The solution was heated at reflux for 4 h and then neutralized with dilute sodium hydroxide. The product was extracted with diethyl ether, washed with saturated solutions of $NaHCO_3$ and NaCl, and dried over anhydrous $MgSO_4$. The solvents were then removed in vacuo. Flash column chromatography (15% EtOAC−hexane) of the residue gave the ketone **18a** (116.8 mg, 72%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (5H, m), 4.07 (3H, m), 3.27 (1H, d, J = 7.4 Hz), 2.89 (1H, dd, J = 18.2, 8.0 Hz), 2.79 (1H, bdd, J = 7.4, 5.8 Hz), 2.11 (1H, m), 1.98 (1H, d, J = 18.2 Hz), 1.41 (3H, d, J = 6.13 Hz), 1.02 (3H, d, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.81, 136.90, 128.71, 128.24, 127.35, 76.49, 76.05, 61.79, 60.95, 44.06, 30.86, 20.03 (2 C's); IR (neat) 2973, 2930, 2872, 1740, 1456, 1380, 1103; high-resolution MS (EI, m/z) 245.1408, calcd for $C_{15}H_{19}NO_2$ 245.1416.

(3α,3aβ,5,6α,6aβ)-Hexahydro-3,6-dimethyl-1-[(4-methoxyphenyl)methyl]-4*H*-cyclopent[*c*]isoxazol-4-one (18b). To a solution of **14b** (100 mg, 0.313 mmol) in 4 mL of MeOH were added water (1 mL) and several drops of concentrated H_2SO_4. The reaction mixture was heated at reflux for 5 h. It was then neutralized with a saturated $NaHCO_3$ solution, and the product was extracted with diethyl ether. The ethereal extracts were washed with saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and concentrated. Column chromatography of the crude residue gave the ketone **18b** (70.6 mg, 82%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (2H, d, J = 8.6 Hz), 6.86 (2H, d, J = 8.7 Hz), 4.00 (1H, m), 3.99 (1H, d, J = 13.3 Hz), 3.98 (1H, d, J = 13.5 Hz), 3.80 (3H, s), 3.21 (1H, d, J = 7.5 Hz), 2.82 (1H, dd, J = 18.2, 8.0 Hz), 2.73 (1H, ddd, J = 7.5, 6.5, 1.5 Hz), 2.03 (1H, m), 1.94 (1H, bd, J = 18.2 Hz), 1.36 (3H, d, J = 6.2 Hz), 0.96 (3H, d, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.97, 158.98, 130.11, 128.94, 113.72, 76.43, 76.05, 61.90, 60.58, 55.22, 44.13, 30.99, 20.13, 20.10; IR (neat) 2961, 2872, 1740, 1613, 1514, 1250, 1034; high-resolution MS (EI, m/z) 275.1520, calcd for $C_{16}H_{21}NO_3$ 275.1521.

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Supporting Information Available: Copies of NMR spectra (42 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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