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Syntheses of (−)-Funebrine and (−)-Funebral, Using Sequential Transesterification and Intramolecular Cycloaddition of a Chiral Nitrone

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The first syntheses of (−)-funebrine [(−)-**1**] and (−)-funebral [(−)-**2**] are described. The syntheses feature sequential formation of nitrone **VI** from methyl glyoxylate (**5**) with oxime **6**, transesterification of nitrone **VI** with (*E*)-crotyl alcohol (**4**), and intramolecular cycloaddition of the resulting nitrone **VII** bearing crotyl ester to afford cycloadduct **7** as a major product. The adduct **7** was readily elaborated to amino lactone (−)-**3**, the key synthetic intermediate of (−)-**1** and (−)-**2**.

Introduction

Near Oaxaca, Mexico, fragrant flowers of *Quarabribea funebris* have been used as an additive to chocolate drinks since pre-Columbian times, and they have also been used as a folk medicine for treating various diseases. In 1984, (−)-funebrine [(−)-**1**], a unique pyrrole alkaloid, and amino lactone (−)-**3** were isolated from the flowers,[1] and (−)-funebral [(−)-**2**] was also isolated from these flowers in 1986 (Figure 1).[2] In 1999, Le Quesne et al. synthesized (±)-funebrine [(±)-**1**] and (±)-funebral [(±)-**2**] via (±)-amino lactone (±)-**3**,[3] which was prepared by Bartlett's ester enolate Claisen rearrangement of Boc-protected glycine crotyl ester[4] followed by iodolactonization[4,5] as key steps. However, there has been no report on an asymmetric synthesis of (−)-**1**. The intriguing origin, insufficient natural supplies of (−)-**1**, (−)-**2**, and (−)-**3** from the flowers, and interest in their unidentified biological profiles prompted us to undertake syntheses of these compounds. We report here the first asymmetric synthesis of (−)-funebrine [(−)-**1**] via (−)-funebral [(−)-**2**] and (−)-amino lactone (−)-**3**.

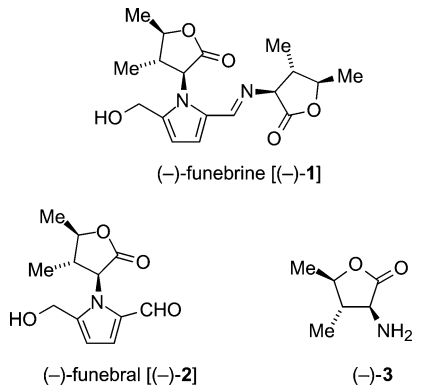

FIGURE 1. Structures of (−)-funebrine [(−)-**1**], (−)-funebral [(−)-**2**], and amino lactone (−)-**3**.

Results and Discussion

Amino lactone (−)-**3**, the key component of (−)-**1** and (−)-**2**, can be regarded as a derivative of γ-hydroxyleucine **I**. Bond connections between the β-methyl group and a carboxyl oxygen atom and between the γ-hydroxy group and amino group provide a bicyclic compound **II**, which would be obtained by diastereoselective intramolecular cycloaddition of *C*-crotyloxycarboyl nitrone **III** having a chiral auxiliary R* at the nitrogen atom (Scheme 1). We previously reported[6] that protected L-gulose oxime **V** reacted with methyl glyoxylate (**5**) to give nitrone **IV**, which, in turn, underwent transesterification with an allyl alcohol in the presence of a titanium catalyst and molecular sieves 4A (MS 4A) to afford a cycloadduct via intramolecular cycloaddition of *C*-allyloxycarbonyl *N*-glosylnitrone.[7,8] We assumed that this sequential meth-

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(1) Raffauf, R. F.; Zennie, T. M.; Onan, K. D.; Le Quesne, P. W. *J. Org. Chem*. **1984**, *49*, 2714.

(2) Zennie, T. M.; Cassady, J. M.; Raffauf, R. F. *J. Nat. Prod*. **1986**, *49*, 695.

(3) Dong, Y.; Pai, N. N.; Ablaza, S. L.; Yu, S.-X.; Bolvig, S.; Forsyth, D. A.; Le Quesne, P. W. *J. Org. Chem*. **1999**, *64*, 2657.

(4) (a) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett*. **1982**, *23*, 619. (b) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem*. **1982**, *47*, 3933.

(5) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc*. **1978**, *100*, 3950.

(6) Tamura, O.; Mita, N.; Kusaka, N.; Suzuki, H.; Sakamoto, M. *Tetrahedron Lett*. **1997**, *38*, 429.

(7) For use of *N*-glycosyl nitrones, see: (a) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am.Chem. Soc*. **1986**, *108*, 4647. See also: (b) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730. (c) Mancini, F.; Piazza, M. G.; Trombini, C. *J. Org. Chem*. **1991**, *56*, 4246. (d) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem*. **1994**, *59*, 6103. (e) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett*. **1994**, *35*, 1011. (f) Lantos, I.; Flisak, J.; Liu, L.; Matsuoka, R.; Mndelson, W.; Stevenson, D.; Tubman, K.; Tucker, L.; Zhang, W.-Y.; Adams, J.; Sorenson, M.; Garigipati, R.; Erhardt, K.; Ross, S. *J. Org. Chem*. **1997**, *62*, 5385. (g) Mita, N.; Tamura, O.; Ishibashi, H.; Sakamoto, M. *Org. Lett*. **2002**, *4*, 1111. (h) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2002**, *41*, 3054.

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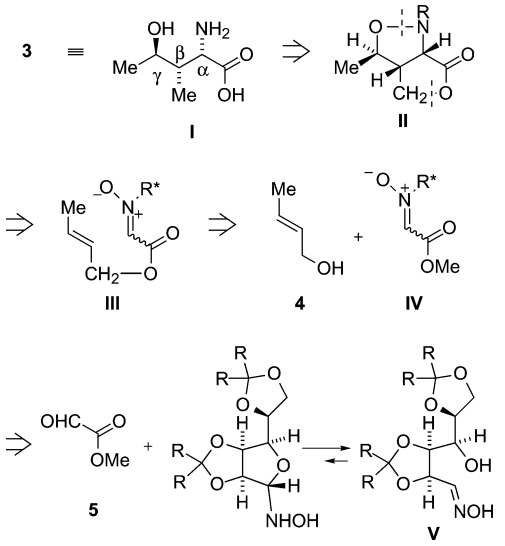
SCHEME 1



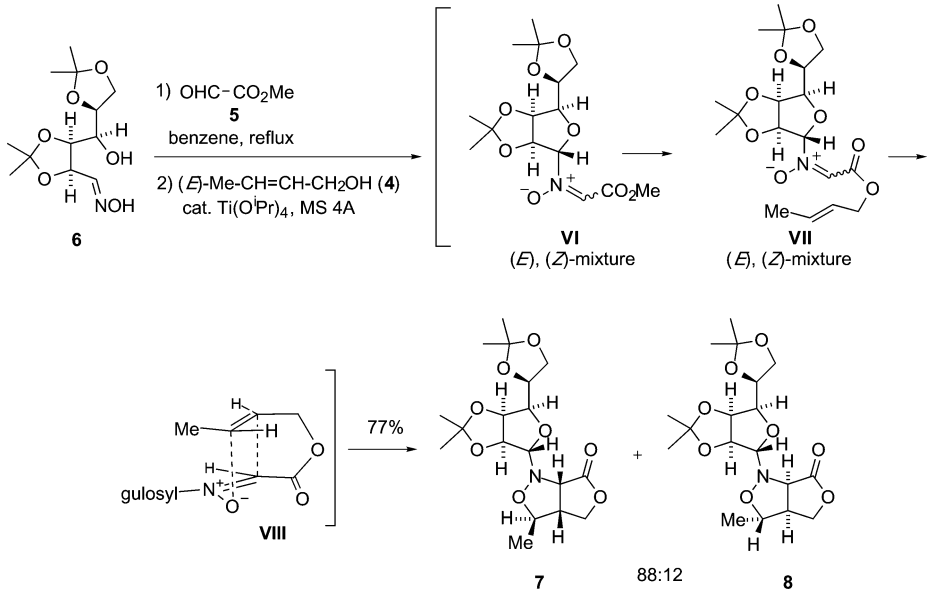
odology[9] would be suitable for the preparation of cycloadduct **II**.

Our synthesis of (−)-**3** started with intramolecular cycloaddition of **VII** prepared from oxime **6**,[7g,10] methyl glyoxylate (**5**), and (*E*)-crotyl alcohol (**4**)[11] (Scheme 2). Heating oxime **6** with aldehyde **5** in boiling benzene with azeotropic removal of water generated nirone **VI**, which was treated with alcohol **4** in the presence of a catalytic amount of $Ti(O^iPr)_4$ and MS 4A to cause sequential transesterification and intramolecular cycloaddition of the resulting nitrone **VII** leading to an 88:12 mixture of cycloadducts **7** (via transition state **VIII**) and **8** in 77% yield. It is worth noting that this reaction constructed three contiguous stereogenic centers required for the synthesis of (−)-**3** in one step.

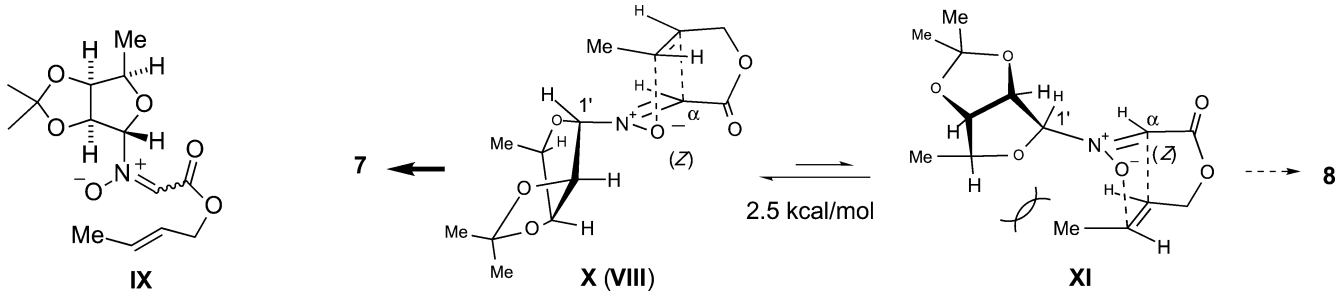
To better understand the stereoselectivity of this cycloaddition, the possible transition states were subjected to computation (Scheme 3).[12] For the computation, the structure of intermediate **VII** was simplified as **IX**. Transition state geometries were calculated by using PM3,[13] and then single point energy calculations were performed with 6-31**.[14] The calculations showed that transition state **X** (corresponding to **VIII**) is more stable than is the alternate transition state **XI** by 2.5 kcal/mol. In each transition state, C1′-H occupies a position close to Cα−H to minimize $A^{1,3}$-strain,[15,16] and transition state **XI** has steric repulsion between the methyl group and tetrahydrofuran ring. Accordingly, the intramolecular cycloaddition should proceed via **VIII** (corresponding to **X**) to give **7** as the major isomer.

Compound **7** was next elaborated to (−)-**3**. Heating **7** with $Mo(CO)_6$ in CH_3CN-H_2O[17] followed by treatment with aqueous 1% HCl caused reductive cleavage of the *N*−*O* bond, hydrolysis of the anomeric position of the sugar moiety, and translactonization of amino alcohol **XII** to generate amino lactone **XIII**. Without isolation, lactone **XIII** was exposed to Boc_2O to afford Boc-protected amino

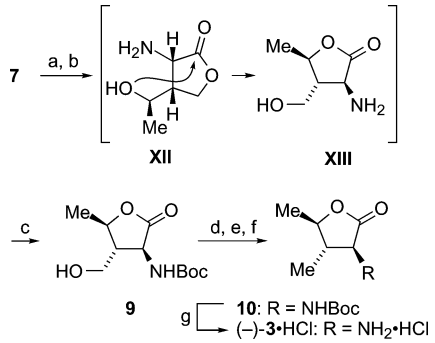
SCHEME 2



SCHEME 3



SCHEME 4[a]

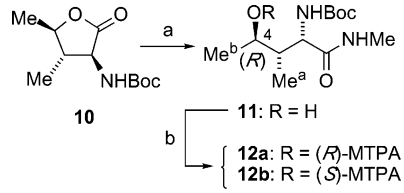


[a] Reagents and conditions: (a) $Mo(CO)_6$, $MeCN-H_2O$; (b) 1% HCl−MeCN; (c) Boc_2O, $NaHCO_3$, 89% from **7**; (d) MsCl, Et_3N, CH_2Cl_2; (e) NaI, DME; (f) Bu_3SnH, 82% from **9**; (g) 35% HCl, 96%.

lactone **9** in 83% yield from **7**. After mesylation of the hydroxyl group of **9**, the resulting mesylate was successively treated with NaI and Bu_3SnH[18] to yield amino lactone **10** in 82% yield from **9**. Finally, the Boc group of **10** was removed with hydrochloric acid to afford (−)-**3**·HCl in 96% yield (Scheme 4).

The mp and ^1H and ^{13}C NMR spectra of synthesic (−)-**3**·HCl were identical with those reported for natural (−)-**3**·HCl, but the optical rotation {$[\alpha]^{22}_D$ −1.89 (*c* 1.00, MeOH)} of synthetic (−)-**3**·HCl is significantly different from that reported for natural (−)-**3**·HCl {$[\alpha]^{25}_D$ −14.8 (*c* 0.695, MeOH)}.[1] To confirm the optical purity and absolute configuration of synthetic (−)-**3**·HCl, the modified Mosher method[19] was employed on amide **11** derived from Boc-protected lactone **10** (Scheme 5). Lactone **10** was transformed to *N*-methyl amide **11** by using Weinreb's protocol.[20] Without isolation of **11**, the hydroxyl group of amide **11** was acylated with (*R*)-MTPA to give

SCHEME 5[a]



[a] Reagents and conditions: (a) $MeNH_2$·HCl, Me_3Al, toluene, reflux; (b) (*R*)- or (*S*)-MTPA, DCC, DMAP, CH_2Cl_2, rt.

SCHEME 6

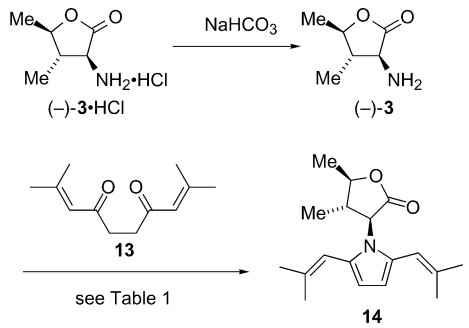


TABLE 1. Preparation of Pyrrole 14 from Lactone (−)-3 and Diketone 13

		yield (%)	
entry	conditions	**14**	recovery of **13**
1	**13**, $Ti(O^iPr)_4$ (1 equiv), (−)-**3**, toluene, reflux, 30 h	5−15	>80
2	**13**, $Ti(O^iPr)_4$ (1 equiv), toluene, rt, 1 h; then (−)-**3**, reflux, 30 h	22	76
3	**13**, $Ti(OEt)_4$ (1 equiv), toluene, rt, 1 h; then (−)-**3**, reflux, 6 h	48	47

ester **12a** in 56% yield from lactone **10**. In a similar manner, ester **12b** (51%) was obtained from lactone **10**.[21] During MTPA-ester formation for each isomer the other isomer could not be detected, which indicated that the optical purity of amide **11** was sufficient.[22] In addition, the ^1H NMR spectrum of (*R*)-MTPA ester **12a** exhibited singlets at δ 0.93 (Me^a) and 1.26 (Me^b), whereas that of (*S*)-MTPA ester **12b** showed them at δ 0.86 (Me^a) and 1.36 (Me^b). These results proved that C4 of amide **11** has the (*R*)-configuration.[19]

With (−)-**3**·HCl bearing correct stereochemistry in hand, we next conducted a Paal−Knorr pyrrole synthesis[23] using diketone **13**[24] (Scheme 6, Table 1). With use of the previously reported method,[3] exposure of amino

(8) For a review on sugar-derived nitrones, see: Osborn, H. M. I.; Gemmell, N.; Harwood: L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.

(9) For sequential transesterification and intramolecular cycloaddition of *C*-methoxycarbonyl nitrone with allyl alcohols, see: (a) Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Noe, K.; Sakamoto, M. *Tetrahedron* **1995**, *51*, 107. (b) Tamura, O.; Mita, N.; Okabe, T.; Yamaguchi, T.; Fukushima, C.; Yamashita, M.; Morita, Y.; Morita, N.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2001**, *66*, 2602 and references therein.

(10) In our previous work (ref 6), dicyclohexylidene congener **V** [R, R = $-(CH_2)_5-$] of oxime **6** was used for a similar sequential transesterification and intramolecular cycloaddition. In this work, diisopropylidene-protected oxime **6** was employed for practical reasons such as its lower molecular weight and higher crystallinity than those of the dicyclohexylidene congener. For comparison of oxime **6** and its dicyclohexylidene congener in sequential cycloaddition, see the Supporting Information.

(11) Pickard, S. T.; Smith, H. E.; Polavarapu, P. L.; Black, T. M.; Rauk, A.; Yang, D. *J. Am. Chem. Soc.* **1992**, *114*, 6850.

(12) The calculations were carried out with MacSpartan version 2.0.

(13) Stewart, J. J. P. *J. Comput. Chem.* **1989**, 10, 209.

(14) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (b) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.

(15) For excellent reviews on $A^{1,3}$-strain, see: (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, UK, 1984; Vol. 3, pp 1−101. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(16) For Cartesian coodinates and heat of formations of **X** and **XI**, see the Supporting Information.

(17) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

(18) Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* **1983**, 795.

(19) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092 and references therein.

(20) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.

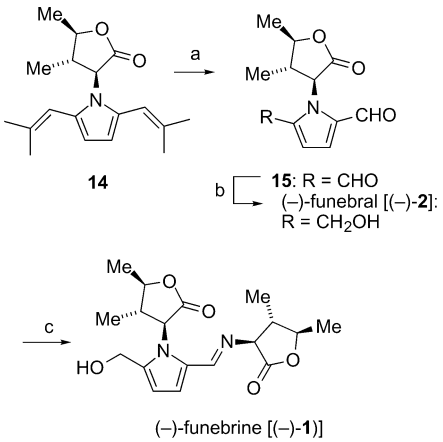
(21) During workup of amide formation, significant re-lactonization occurred to give the starting lactone **10**, and hence the yields of MTPA-esters **12a** and **12b** were moderate. Since the yields of both MTPA-esters were similar, it was strongly suggested that kinetic resolution did not occur during MTPA-ester formation.

(22) The difference between the specific rotation of natural (−)-**3**·HCl and that of synthetic (−)-**3**·HCl might be ascribed to the purity. Since the value of the specific rotation of (−)-**3**·HCl is quite small, the rotation is likely to be influenced by a trace of impurity.

(23) (a) Broadbent, H. S.; Burnham, W. S.; Olsen, R. K.; Sheeley, R. M. *J. Heterocycl. Chem.* **1968**, *5*, 757. (b) Yu, S.-X.; Le Quesne, P. W. *Tetrahedron Lett.* **1995**, *36*, 6205.

(24) (a) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912. (b) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *Chem. Pharm. Bull.* **1980**, *28*, 262.

SCHEME 7[a]



[a] Reagents and conditions: (a) OsO_4, $NaIO_4$, dioxane−H_2O, 48%; (b) $NaBH_3CN$, HCO_2H, H_2O−dioxane, 81%; (c) (−)-**3**, neat, 120 °C, 5 min, 77%.

lactone (−)-**3** to diketone **13** in the presence of $Ti(O^iPr)_4$ in refluxing toluene for 30 h gave only 15% yield of pyrrole **14** (entry 1). Repeated runs of this reaction revealed a lack of reproducibility (5−15%), and hence we reinvestigated this step. Diketone **13**, on treatment with MS 4A in toluene at room temperature, followed by (−)-**3** at reflux temperature for 30 h, slightly improved the yield (22%) of **14** (entry 2). The use of $Ti(OEt)_4$ in place of $Ti(O^iPr)_4$ required a shorter reaction period (6 h) and afforded a higher yield (48%) of **14** (entry 3).[25]

(−)-Funebral [(−)-**2**] and (−)-funebrine [(−)-**1**] were then synthesized from pyrrole **14** (Scheme 7). Oxidative cleavage of both side chains of pyrrole **14** was effected with OsO_4−$NaIO_4$ to give dialdehyde **15** in 48% yield. One of the two aldehydes of **15** was reduced with $NaBH_3CN$ in an acidic medium to afford (−)-funebral [(−)-**2**] in 81% yield, $[\alpha]^{23}_D$ −36.1 (*c* 1.00, MeOH) {lit.[2] $[\alpha]^{32}_D$ −19.0 (*c* 0.05, MeOH)}.[26] Condensation of (−)-**2** with (−)-**3** was readily achieved by simple heating under neat conditions for 5 min to give (−)-funebrine [(−)-**1**] in 77% yield, mp 236−237 °C, $[\alpha]^{26}_D$ −144 (*c* 1.00, Me_2SO) {lit.[1] mp 231−233 °C, $[\alpha]^{22.5}_D$ −215 (*c* 0.01, Me_2SO)}.[26]

In summary, we have achieved the synthesis of (−)-funebrine [(−)-**1**] in 6.6% overall yield via (−)-funebral [(−)-**2**] and amino lactone (−)-**3**. This synthesis features sequential nitrone formation from oxime **6** with methyl glyoxylate leading to a nitrone having an ester moiety, transesterification of the nitrone with (*E*)-crotyl alcohol, and intramolecular cycloaddition of the resulting nitrone. Pharmacological properties of these natural products are currently under investigation.

Experimental Section

Melting points are uncorrected. Flash column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque).

(3*S*,3a*R*,6a*S*)-1-(2′,3′:5′,6′-*O*-Diisopropylidene-α-L-gulofuranosyl)-3-methyltetrahydrofuru[3,4-*c*]isoxazol-6-one (7) and Its (3*R*,3a*S*,6a*R*) Isomer (8). A mixture of oxime **6** (5.84 g, 21.2 mmol) and methyl glyoxylate (**5**) (3.16 g, 29.8 mmol) in dry benzene (240 mL) was heated under reflux with azeotropic removal of water, using a Dean−Stark trap under an argon atmosphere. After 3.5 h, oxime **6** was consumed, and the Dean−Stark equipment was removed. To the mixture were added $Ti(O^iPr)_4$ (1.26 mL, 4.27 mmol), (*E*)-crotyl alcohol (**4**) (4.132 g, 57.30 mmol), and MS 4A (50 g), and the mixture was heated under reflux for 4 h. The mixture was diluted with $CHCl_3$ and filtered through a pad of Celite. To the filtrate was added a 10% aqueous solution of potassium sodium tartrate (2 mL), then the mixture was stirred. After 1 h, $MgSO_4$ and Celite were added to the mixture, and the mixture was further stirred for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel ($CHCl_3$−AcOEt, 10:1) to give an 88:12 mixture of **7** and **8** (6.31 g, 77%). Pure compound **7** was obtained by recrystallization from $^iPr_2O$−AcOEt (5:1). Recrystallization (*n*-hexane-AcOEt, 1:1) of a solid obtained by concentrating the mother liquor gave compound **8**. **7**: mp 178−180 °C; $[\alpha]^{26}_D$ −8.92 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 1790 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.37 (3H, s), 1.42 (3H, d, J = 6.3 Hz), 1.47 (6H, s), 2.97 (1H, dddd, J = 1.3, 5.9, 6.3, 8.6 Hz), 3.75 (1H, m), 4.03 (1H, quin, J = 6.3 Hz), 4.20 (1H, dd, J = 5.9, 9.9 Hz), 4.23 (1H, dd, J = 1.3, 9.9 Hz), 4.35 (2H, m), 4.42 (1H, dd, J = 5.9, 9.9 Hz), 4.49 (1H, d, J = 8.6 Hz), 4.56 (1H, s), 4.75 (1H, dd, J = 3.3, 5.9 Hz), 4.96 (1H, d, J = 5.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 25.0, 25.9, 26.3, 26.9, 49.0, 64.6, 66.3, 68.4, 76.0, 80.5, 80.8, 84.2, 84.5, 99.0, 110.2, 113.1, 174.5. Anal. Calcd for $C_{18}H_{27}NO_8$: C, 56.10; H, 7.06; N, 3.63. Found: C, 55.80; H, 7.12; N, 3.41. **8**: mp 161−164 °C; $[\alpha]^{25}_D$ +65.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1790 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (3H, s), 1.33 (3H, d, J = 5.9 Hz), 1.39 (3H, s), 1.45 (3H, s), 1.46 (3H, s), 2.97 (1H, m), 3.69 (1H, dd, J = 5.9, 8.3 Hz), 3.90 (1H, dq, J = 6.3, 5.9 Hz), 4.15−4.33 (4H, m), 4.41 (1H, d, J = 9.9 Hz), 4.43 (1H, d, J = 9.2 Hz), 4.71 (1H, dd, J = 4.3, 5.9 Hz), 5.00 (1H, d, J = 5.9 Hz), 5.01 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.6, 24.8, 25.5, 26.2, 27.1, 51.0, 62.7, 66.2, 68.3, 77.2, 79.8, 81.0, 84.4, 87.6, 97.7, 109.7, 112.9, 174.3. Anal. Calcd for $C_{18}H_{27}NO_8$: C, 56.10; H, 7.06; N, 3.63. Found: C, 55.82; H, 7.13; N, 3.63.

(3*S*,4*S*,5*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-4-hydroxymethyl-5-methyltetrahydro-2-furanone (9). To a solution of **7** (7.522 g, 19.52 mmol) in CH_3CN−H_2O (10:1, 215 mL) was added $Mo(CO)_6$ (10.67 g, 40.7 mmol), and the mixture was heated under reflux for 6 h. After the mixture was cooled to room temperature, 1% aqueous HCl−CH_3CN (3:1, 300 mL) was added, and the mixture was stirred for 16 h. The mixture was basified to pH 9 by adding powdered $NaHCO_3$. To the stirred mixture was added a solution of di-*tert*-butyl dicarbonate (24.15 g, 112.0 mmol) in CH_3CN (10 mL), and the mixture was stirred for 24 h. The mixture was extracted with AcOEt, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane-AcOEt, 1:1) to give **9** (4.08 g, 85%), mp 112−127 °C (*n*-hexane−AcOEt). $[\alpha]^{25}_D$ +58.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3430, 1779, 1698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (1H, d, J = 6.3 Hz), 1.46 (9H, s), 2.05 (1H, m), 2.79 (1H × $^1/_2$, br), 2.92 (1H × $^1/_2$, br), 3.64−3.92 (1H + $^1/_2$H, m), 4.04 (1H × $^1/_2$, br), 4.36−4.67 (2H, m), 5.42 (1H, br d, J = 6.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.2, 28.5, 53.0, 54.4, 58.4, 75.9, 81.5, 157.2, 174.7. Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87, H, 7.81, N, 5.71. Found: C, 53.59, H, 7.76, N, 5.61.

(3*S*,4*S*,5*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-4,5-dimethyltetrahydrofuranone (10). To a stirred solution of **9** (1.11 g, 4.52 mmol) and Et_3N (1.7 mL, 12.3 mmol) in CH_2Cl_2 (80 mL) was added MsCl (0.87 mL, 11.3 mmol) at room temperature. After 15 min, MeOH (4 mL) was added, and the

(25) In general, use of a strong Lewis acid for Paal−Knorr reaction gives a high yield of a pyrrole. However, lactone (−)-**3** was decomposed by the use of $TiCl_4$ as a strong Lewis acid, and then $Ti(OEt)_4$ having moderate Lewis acidity was employed.

(26) The differences in the specific rotations between synthetic products and natural products might be due to weighing errors in making the diluted solutions [*c* 0.05 for (−)-**2** and *c* 0.01 for (−)-**1**].

mixture was stirred for 15 min. Water was added, and the mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude mesylate, which was dissolved in DME (80 mL). To the solution was added NaI (2.09 g, 14.3 mmol), and the mixture was heated under reflux. After consumption of the mesylate (1.5 h), Bu_3SnH (2.9 mL, 10.8 mmol) was added, and the mixture was further heated under reflux for 3 h. After cooling to room temperature, the mixture was diluted with Et_2O. An 8% aqueous solution of KF was added, and the mixture was stirred vigorously for 16 h. The mixture was filtered, and the filtrate was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with *n*-hexane−AcOEt (4:1) to afford **10** (851 mg, 82%), mp 120−121 °C (*n*-hexane−AcOEt). $[\alpha]^{26}_D$ +17.5 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3438, 1781, 1717 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 6.6 Hz), 1.43 (3H, d, J = 6.3 Hz), 1.46 (9H, s), 2.00 (1H, m), 4.05−4.25 (2H, m), 4.99 (1H, br d, J = 6.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.4, 18.8, 28.6, 46.5, 58.1, 80.3, 80.9, 156.0, 175.0. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.60; H, 8.57; N, 5.81.

To confirm the optical purity and absolute configuration, a derivative was prepared. To a stirred suspension of $MeNH_2$·HCl (25.2 mg, 0.38 mmol) in toluene (1 mL) was added a 1.0 M solution of Me_3Al in *n*-hexane (0.38 mL, 0.38 mmol) at room temperature. After 1 h, a solution of **10** (20.0 mg, 87 μmol) in toluene−CH_2Cl_2 (1:2, 1.5 mL) was added to the mixture, and the mixture was heated under reflux for 1 h. After the mixture was cooled to room temperature, MeOH (three drops) and a saturated solution of $NaHCO_3$ (two drop) were added to the mixture, and the mixture was stirred for 30 min. The mixture was filtered though a pad of Celite, and the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.5 mL), and to the solution were added (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (33.2 mg, 0.14 mmol), dicyclohexylcarbodiimide (31.5 mg, 0.15 mmol), and DMAP (6.2 mg, 50 μmol). After being stirred for 15 h, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane−AcOEt, 3:1) to give (2*R*,1′*R*,2′*S*,3′*S*)-3′-[(*tert*-butyloxycarbonyl)-amino]-1′,2′-dimethyl-3′-methylcarbamoyl-2-methoxy-2-phenyl-2-trifluoromethyl acetate (**12a**) (23.4 mg, 56%), and **10** (5.6 mg, 28%) was recovered. **12a**: mp 93−96 °C. IR ($CHCl_3$) 3443, 1748, 1717, 1676 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 7.3 Hz), 1.45 (9H, s), 2.30 (1H, dquin, J = 3.3, 7.3 Hz), 2.77 (3H, d, J = 5.0 Hz), 3.54 (3H, s), 4.26 (1H, dd, J = 3.3, 8.9 Hz), 5.08 (1H, quin, J = 7.3 Hz), 5.15 (1H, d, J = 8.9 Hz), 5.95 (1H, br), 7.42 (3H, m), 7.57 (2H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.0, 17.5, 26.7, 28.7, 40.7, 55.5, 55.8, 75.8, 80.8, 85.0, 128.2, 128.9, 130.1, 132.4, 156.1, 166.1, 172.0.

With use of a procedure similar to that for the preparation of **12a**, (2*R*,1′*R*,2′*S*,3′*S*)-isomer **12b** (21.5 mg, 51%) was obtained from **10** (20.0 mg, 87 μmol), and **10** (6.0 mg, 30%) was recovered. **12b**: mp 87−89 °C. IR ($CHCl_3$) 3443, 1750, 1717, 1676 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 7.3 Hz), 1.43 (9H, s), 2.30 (1H, dquin, J = 3.0, 7.3 Hz), 2.74 (3H, d, J = 4.6 Hz), 3.60 (3H, s), 4.20 (1H, dd, J = 3.0, 8.6 Hz), 5.04 (1H, br d, J = 8.6 Hz), 5.11 (1H, quin, J = 7.3 Hz), 5.77 (1H, br), 7.35 (3H, m), 7.60 (2H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.2, 17.4, 26.3, 28.3, 40.2, 54.7, 55.5, 75.5, 80.3, 127.3, 128.4, 129.6, 132.6, 155.6, 165.5, 171.6.

(3*S*,4*S*,5*R*)-3-Amino-4,5-dimethyltetrahydrofuranone Hydrochloride [(−)-3·HCl]. To a stirred solution of **10** (3.53 g, 15.4 mmol) in MeOH (80 mL) was added 35% hydrochloric acid (80 mL) at 0 °C, and the mixture was allowed to warm to room temperature. After 2 h, the mixture was concentrated under reduced pressure to give the crude hydrochloride, which was recrystallized from MeOH−Et_2O to afford (−)-**3**·HCl (2.45 g, 96%), mp 212−215 °C. $[\alpha]^{22}_D$ −1.89 (*c* 1.00, MeOH) {lit.[1] mp 212−215 °C $[\alpha]^{25}_D$ −14.8 (*c* 0.695, MeOH)}; ^1H NMR [270 MHz, D_2O, 1,4-dioxane (δ 3.81 ppm) was used as an internal standard] δ 1.34 (3H, d, J = 6.3 Hz), 1.54 (3H, d, J = 5.9 Hz), 2.45 (1H, qdd, J = 6.3, 9.6, 11.6 Hz), 4.25 (1H, d, J = 11.6 Hz), 4.52 (1H, qd, J = 5.9, 9.6 Hz); ^{13}C NMR [67.8 MHz, D_2O, 1,4-dioxane (δ 66.5 ppm) was used as an internal standard] δ 12.3, 17.3, 42.6, 55.6, 82.3, 173.2. Anal. Calcd for $C_6H_{12}NO_2$-Cl: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.25; H, 7.39; N, 8.55. The spectral data shown above were identical with those reported.[1,3]

1-[(3*S*,4*S*,5*R*)-3-Amino-4,5-dimethyltetrahydrofuranone]-2,5-bis(isobutenyl)pyrrole (14) (Table 1, entry 3). Compound (−)-**3**·HCl (169.0 mg, 1.0 mmol) was partitioned between saturated aqueous $NaHCO_3$ (0.5 mL) and $CHCl_3$−Et_2O (10:1). The organic phase was dried and concentrated under reduced pressure to give (−)-**3** (128.3 mg). ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 6.6 Hz), 1.40 (3H, d, J = 6.3 Hz), 1.63 (2H, br), 1.78 (1H, qdd, J = 6.6, 9.6, 11.5 Hz), 3.24 (1H, d, J = 11.5 Hz), 4.05 (1H, qd, J = 6.3, 11.5 Hz). This compound was used for the next step without further purification.

To a stirred mixture of **13** (201.5 mg, 1.04 mmol) and MS 4A (6 g) in toluene (30 mL) was added $Ti(OEt)_4$ (0.2 mL, 1.0 mmol) at room temperature, and the mixture was further stirred at the same temperature for 1 h. A solution of (−)-**3** (128.3 mg, 0.99 mmol) in toluene (20 mL) was added to the mixture, and the mixture was heated under reflux for 6 h. After cooling, the mixture was filtered through a pad of Celite. To this filtrate was added a 10% aqueous solution of potasium sodium tartrate (0.5 mL), and the mixture was stirred for 1 h. To the mixture was added $MgSO_4$ and Celite, and the mixture was further stirred for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane−AcOEt (10:1) to give **14** (139.2 mg, 48%) along with recovered **13** (95.1 mg, 47%). **14**: mp 78−80 °C (*n*-hexane); $[\alpha]^{25}_D$ +242.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1782 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.6 Hz), 1.45 (3H, d, J = 6.3 Hz), 1.84 (6H, s), 1.86 (3H, s), 1.88 (3H, s), 2.46 (1H, qdd, J = 6.6, 9.6, 11.9 Hz), 4.15 (1H, qd, J = 6.3, 9.6 Hz), 4.66 (1H, d, J = 11.9 Hz), 5.80 (1H, s), 5.93 (1H, s), 6.03 (1H, s), 6.09 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.7, 19.6, 20.4, 26.7, 26.8, 45.1, 61.6, 80.4, 109.1, 110.9, 114.8, 116.0, 129.5, 132.1, 137.0, 139.6, 173.5. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 74.96; H, 8.89; N, 4.92. The spectral data described above are identical with those reported[3] for racemic **14**.

1-[(3*S*,4*S*,5*R*)-3-Amino-4,5-dimethyltetrahydrofuranone]-2,5-diformylpyrrole (15). To a solution of **14** (28.5 mg, 0.10 mmol) in 1,4-dioxane−H_2O (2:1, 2.4 mL) was added 4% aqueous OsO_4 (45 μL, 7.3 μmol). To the mixture was added $NaIO_4$ (33 mg, 0.155 mmol) in four portions (total 133 mg, 0.62 mmol) every 15 min. After the mixture was stirred at room temperature for 20 h, saturated aqueous $Na_2S_2O_3$ (2 mL) was added, and the mixture was stirred for 1 h. The mixture was filtered, and the filtrate was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with (*n*-hexane−AcOEt, 2:1) to give **15** (11.2 mg, 48%) as a crystalline solid, mp 86−88 °C. $[\alpha]^{25}_D$ +194.2 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1782, 1694, 1667 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (3H, d, J = 6.6 Hz), 1.61 (3H, d, J = 5.9 Hz), 2.64 (1H, qdd, J = 6.6, 9.6, 11.5 Hz), 4.30 (1H, qd, J = 5.9, 9.6 Hz), 6.45 (1H, d, J = 11.5 Hz), 7.09 (1H, d, J = 4.3 Hz), 7.16 (1H, d, J = 4.3 Hz), 9.74 (1H, s), 9.84 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.6, 18.8, 44.6, 62.4, 80.8, 124.3, 124.9, 136.3, 136.7, 171.6, 182.0, 183.4. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.08; H, 5.71; N, 5.78. The spectral data described above are identical with those reported[3] for racemic **15**.

1-[(3*S*,4*S*,5*R*)-3-Amino-4,5-dimethyltetrahydrofura-

none]-2-formyl-5-hydroxymethylpyrrole, (−)-Funebral [(−)-2]. To a stirred solution of **15** (58.1 mg, 0.25 mmol) in H_2O−1,4-dioxane−HCO_2H (1000:100:1, 11 mL) was added $NaBH_3CN$ (17.4 mg, 0.28 mmol) at room temperature, and the mixture was stirred for 15 h. The pH was adjusted to ca. 8 by adding $NaHCO_3$ (605 mg), and the mixture was extracted with $CHCl_3$−Et_2O (10:1). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with (*n*-hexane−AcOEt, 1:1) to give (−)-**2** (47.5 mg, 81%) as a colorless oil. $[\alpha]^{23}_D$ −36.1 (*c* 1.0, MeOH) {lit[2] $[\alpha]^{32}_D$ −19.0 (*c* 0.05, MeOH)}; IR ($CHCl_3$) 3594, 1780, 1663 cm^{-1}. Rotamers were observed in the ^1H NMR. ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.4 Hz), 1.25 (1H, br), 1.50 (1H × $^1/_5$, d, J = 5.9 Hz), 1.60 (3H × $^4/_5$, d, J = 6.3 Hz), 2.50−2.80 (1H, m), 4.27 (1H, qd, J = 6.3, 9.3 Hz), 4.45−4.70 (2H, m), 5.05 (1H × $^4/_5$, d, J = 11.7 Hz), 6.26 (1H × $^4/_5$, d, J = 4.4 Hz), 6.37 (1H × $^1/_5$, d, J = 3.9 Hz), 7.00 (1H × $^4/_5$, d, J = 4.4 Hz), 9.41 (1H × $^4/_5$, s), 9.49 (1H × $^1/_5$, s). Rotamers were observed in the ^{13}C NMR. ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 15.1, 18.9, 19.1, 30.1, 44.0, 46.9, 56.9, 57.1, 61.6, 63.1, 77.7, 81.1, 111.5, 113.6, 126.6, 126.8, 132.6, 143.2, 172.6, 179.3, 180.8; HRMS calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.1004. The spectral data described above are identical with those reported[2] for natural (−)-**2**.

(3*S*,4*S*,5*R*)-4,5-Dihydro-3-{2-(hydroxymethyl)-5-[*N*-[(3*S*,4*S*,5*R*)-tetrahydro-4,5-dimethyl-2-oxo-3-furyl]formimidoyl]-pyrrol-1-yl}-4,5-dimethyltetrahydrofuranone, (−)-Funebrine [(−)-1]. Compound (−)-**3**·HCl (158 mg, 0.952 mmol) was partitioned between saturated aqueous $NaHCO_3$ (0.5 mL) and $CHCl_3$−Et_2O (10:1). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give (−)-**3** (122.0 mg). The mixture of (−)-**2** (37.5 mg, 0.158 mmol) and (−)-**3** (122.0 mg) was heated at 120 °C for 5 min. After cooling, the crude product was purified by column chromatography on silica gel (Et_2O−*n*-hexane, 5:1) to afford (−)-**1** (42.3 mg, 77%). Mp 236−237 °C (*n*-hexane-$CHCl_3$); $[\alpha]^{26}_D$ −144 (*c* 1.00, Me_2SO), $[\alpha]^{26}_D$ −71.3 (*c* 1.00, $CHCl_3$) {lit.[1] mp 231−233 °C, $[\alpha]^{22.5}_D$ −215 (*c* 0.01, Me_2SO)}; IR ($CHCl_3$) 1777, 1647 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (6H, d, J = 6.6 Hz), 1.25 (1H, br), 1.45 (3H, d, J = 6.3 Hz), 1.49 (3H, d, J = 6.0 Hz), 2.51 (1H, m), 3.18 (1H, m), 3.62 (1H, d, J = 10.7 Hz), 4.16 (2H, m), 4.62 (1H, d, J = 13.9 Hz), 4.70 (1H, d, J = 13.9 Hz), 5.01 (1H, d, J = 11.6 Hz), 6.23 (1H, d, J = 4.0 Hz), 6.61 (1H, d, J = 4.0 Hz), 7.98 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2, 15.0, 18.6, 19.3, 43.2, 46.7, 57.6, 63.5, 76.8, 81.1, 81.3, 110.9, 121.0, 131.0, 139.9, 155.8, 173.0, 175.3; HRMS calcd for $C_{18}H_{24}N_2O_5$ 348.1685, found 348.1679. The spectral data described above are identical with those reported[1] for natural (−)-**1**.

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Supporting Information Available: Comparison between oxime **6** and its cyclohexylidene congener in sequential transesterification and intramolecular cycloaddition; computation of TSs **X** and **XI**; ^1H and ^{13}C NMR spectra for **7**, **8**, **9**, **10**, (−)-**3**, **12a**, **12b**, **14**, **15**, (−)-**2**, and (−)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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