Facile Synthesis of Spirocyclic Systems through the Intramolecular Addition of Ketyl Radicals via the Sodium/Ammonia Reduction of δ,ϵ-Unsaturated Carboxylic Esters

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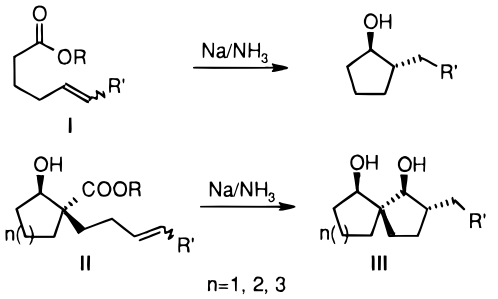
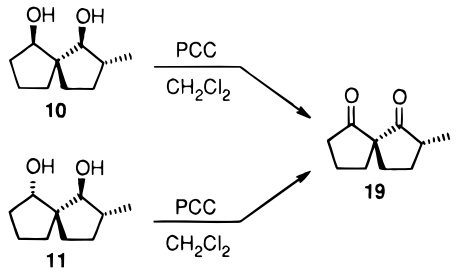
Received December 31, 1997

Cyclization of δ,ϵ-unsaturated radicals is a very fast process that leads to cyclopentylmethyl or cyclohexyl radicals. Convenient methods to prepare the key radical intermediate include the reduction of functional groups such as halides, haloketals, or thioethers. Similarly, ketyl radicals arising from the reduction of δ,ϵ-unsaturated ketones and aldehydes, utilizing alkali metals in liquid ammonia,[1] TMSCl/Zn,[2a] TMSCl/Mg,[2b] Bu_3SnH,[3] SmI_2,[4] cathode reduction,[5] or photochemically induced electron transfer,[6] are cyclized efficiently and lead to the corresponding substituted cyclopentanols.[7] Alternatively, esters can be reduced by dissolved metals in liquid ammonia,[8] amines,[7c] or HMPA,[9] at the cathode,[10] by SmI_2[11] in the presence of H_2O,[12] or by photochemically induced electron transfer from HMPA.[13] Although it has been known for a long time that the Bouveault−Blanc reduction[14] of carboxylic esters and the acyloin condensation[15] proceed via ketyl radical anion intermediates, these latter have not yet been used in additions to alkenes or alkynes.

Scheme 1



Scheme 2



Here, we report that δ,ϵ-unsaturated carboxylic esters react with Na in liquid ammonia (Na/NH_3) and undergo cyclization with the formation of cyclopentanols with good diastereoselectivity (enantioselectivity) and that β-hydroxyesters of type **II** (Scheme 1) can be transformed to spirocyclic diols with excellent regio- and stereoselectivity. The results are summarized Table 1.

Treatment of β-hydroxy ester **1** by Na (6 equiv) in NH_3 afforded the spirocyclic compound **10** (95%). The 300 MHz ^1H NMR analysis of the crude reaction mixture did not reveal any other product. The relative configuration of centers C-6, C-5, C-1, and C-2 was determined by NOE differences in the ^1H NMR spectrum and was confirmed by single-crystal X-ray diffraction studies. The high regio- and stereoselectivity as well as the high yield observed for this process led us to explore the synthetic potential of this new reductive cyclization reaction. Reduction of esters **2**−**5** with Na/NH_3 led to the corresponding spirocyclic products **11**−**14**,[16] respectively, in good yield and high diastereoselectivity. On the contrary, when compound **6** was treated with Na/NH_3, the spirocyclic compound **15** was isolated (45%), accompanied by a diastereoisomeric spirocyclic alcohol **15′**[17] (30%). The relative stereochemistry of the substituents in compound **11** was established by oxidation of **10** and **11**, which led to the same dione **19** (Scheme 2).

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(1) (a) Stork, G.; Malhotra, S.; Thompson, H.; Uchibayashi, M. *J. Am. Chem. Soc.* **1965**, *87*, 1148. (b) Stork, G.; Boeckmann, R. K., Jr.; Taber, D. F.; Still, W. C.; Singh, J. *J. Am. Chem. Soc.* **1979**, *101*, 7107. (c) Pradhan, S. K.; Subhash, R. K.; Kohle, J. N.; Radhakrishnan, T. V.; Sohani, S. V.; Thaker, V. B. *J. Org. Chem.* **1981**, *46*, 2622.

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(9) (a) Deshayes, H.; Pete, J. P. *J. Chem. Soc., Chem. Commun.* **1978**, 567. (b) Mukhopadhyaya, J. K.; Mukhopadhyaya, C.; Ghatak, U. R. *Indian J. Chem.* **1994**, *33B*, 132.

(10) Chaussard, J.; Combellas, C.; Thiebault, A. *Tetrahedron Lett.* **1987**, *28*, 1173.

(11) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *28*, 4437. (b) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4477. (c) Bartelts, A.; Jones, P. G.; Liebscher, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1539.

(12) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, 1495.

(13) Portella, C.; Deshayes, H.; Pete, J. P.; Scholler, D. *Tetrahedron* **1984**, *40*, 3635.

(14) (a) Bouveault, L.; Blanc, G. *C. R. Acad. Sci. Paris* **1903**, *136*, 1676. (b) Chablay, E. *C. R. Acad. Sci. Paris* **1913**, *156*, 1020. (c) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 150−151.

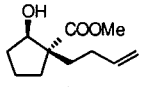
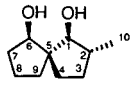
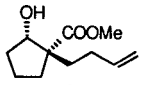
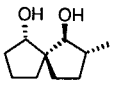
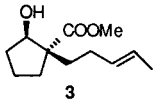
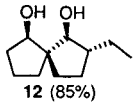
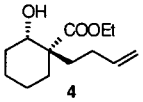
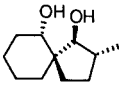
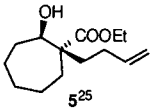
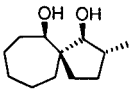
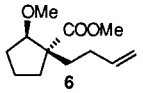
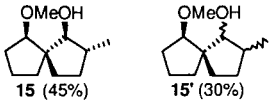
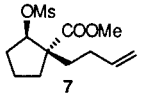
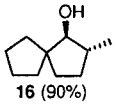
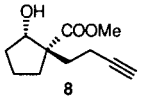
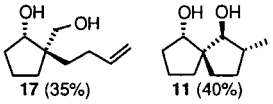
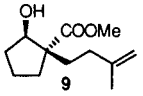
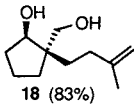
(15) (a) McElvain, S. M. *Org. React.* **1948**, *4*, 256. (b) Finley, K. T. *Chem. Rev.* **1964**, *64*, 573. (c) Ruhlmann, K. *Synthesis* **1971**, 236. (d) Bloomfield, J. J.; Owsley, D. C.; Nelke J. M. *Org. React.* **1976**, *23*, 259.

(16) By analogy to compound **10**, the same configuration can be assigned respectively, to compounds **12**, **14** and **11**, **13**.

(17) The stereochemistry of compound **15′** could not be determined.

S0022-3263(97)02339-6 CCC: $15.00
Published on Web 04/11/1998

Table 1. Reduction of Unsatured β-Hydroxy Ester of Type II

Starting material[a]	Products (yield)
 **1**	 **10** (95%)
 **2**	 **11** (90%)
 **3**	 **12** (85%)
 **4**	 **13** (83%)
 **5**[25]	 **14** (85%)
 **6**	 **15** (45%) **15'** (30%)
 **7**	 **16** (90%)
 **8**	 **17** (35%) **11** (40%)
 **9**	 **18** (83%)

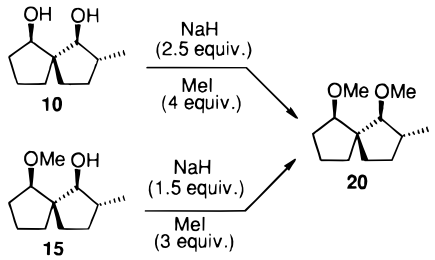
[a] All compounds are racemic.

Furthermore, as the dimethoxy compound **20** could be obtained from **10** [NaH (2.5 equiv), MeI (4 equiv)] as well as from **15** [NaH (1.5 equiv), MeI (3 equiv)], the relative stereochemistry of the substituents in spirocyclic compound **15** has been established by comparison of the spectral data of the dimethoxy compound obtained from **10** (Scheme 3).

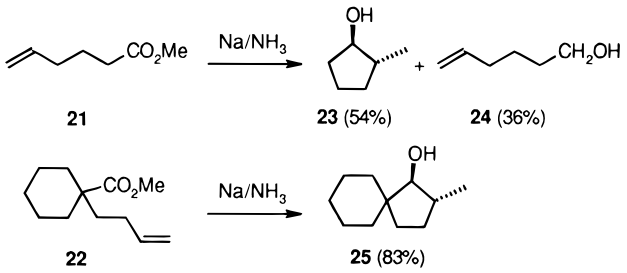
Under similar conditions, mesylate **7** gave the spirocyclic alcohol **16** in which the mesylate has been reduced.[18] When several functional groups are present in the starting ester, electron transfer from the donor might occur selectively to the most reducible group. Not unexpectedly, treatment of the acetylenic ester **8** with Na/NH_3 furnished a 46/54 mixture of reduced products **17**/**11** (75% yield), the acetylenic moiety being reduced concomitantly with the ester moiety. Under the same reduction conditions, **9** provided diol **18** (83%) as a unique product, showing that cyclization may not compete with Bouveault-Blanc reduction of the ester, possibly due to steric reasons.

(18) For a similar reduction by alkali metals in HMPA see: Cuvigny, T.; Larcheveque, M. *J. Organomet. Chem.* **1974**, *64*, 315.

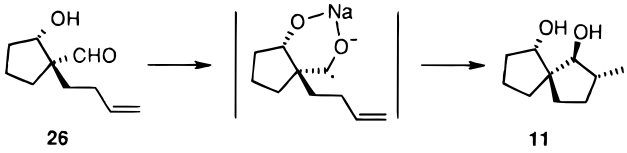
Scheme 3



Scheme 4



Scheme 5



Discussion

Except for compounds **8** and **9**, which underwent Bouveault−Blanc reduction faster than cyclization, all the products of cyclization followed an *exo-trig* mode. This indicates that when one-electron transfer occurs, the cyclization process is faster than hydrogen transfer from the solvent. The reaction is very sensitive to steric effects as the treatment of **9** led only to diol **18**. We should point out that no cyclized product was detected in the crude reaction mixture. The cyclization of unsaturated esters is sensitive to the Thorpe−Ingold effect as compound **21**[2b] provides the cyclic alcohol **23**[19] and the unsaturated primary alcohol **24** in a ratio of 6/4 (yield = 90%)[20] in contrast to the unsaturated ester **22**,[21] which led only to a single spirocyclic alcohol **25** (83%) (Scheme 4).

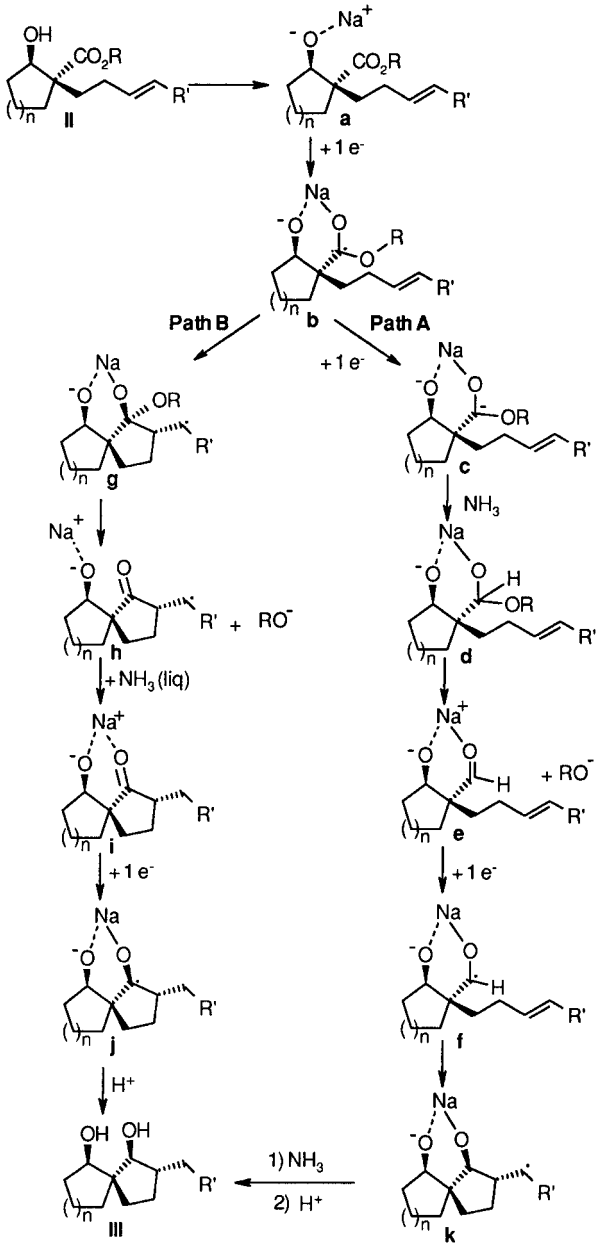
In the case of the acetylenic hydroxy ester **8**, the diol **17** and the spirocyclic diol **11** were formed (Scheme 5), but no product resulting from a 5-*exo-dig* process was detected. This result seems to indicate that under these reaction conditions, the acetylenic functionality is slightly more reducible than the ester group.

(19) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532.

(20) ^1H and ^{13}C NMR data of **23** and **24** were identical with the literature values, and the structure of alcohol **23** was confirmed by the reduction of 2-methylcyclopentanone. The ratio of 6:4 was determined by comparison of the integrals between $CHCH_3$ and CH_2OH in the proton NMR spectrum.

(21) (a) Cossy, J.; Pete, J. P.; Portella, C. *Tetrahedron Lett.* **1989**, *30*, 7361. (b) Shono, T.; Masuda, H.; Murase, H.; Shimomura, M.; Kashimura, S. *J. Org. Chem.* **1992**, *57*, 1061.

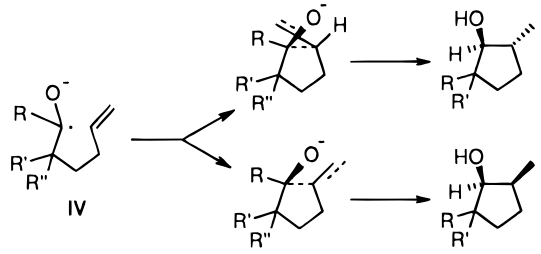
Scheme 6



When an ester is treated with Na/NH_3, an electron transfer takes place in what might be considered as a classical redox process (Scheme 6). In the treatment of β-hydroxy esters of type **II** by Na/NH_3, the alcoholate **a** should be formed and the ester group should be reduced by Na/NH_3 to produce intermediate **b**, which could be transformed (path A) to aldehyde **e** via intermediates **c** (second electron transfer) and **d** (hydrogen abstraction to NH_3). The aldehyde **e** should be then reduced and the ketyl radical **f** should cyclize to produce the observed spirocyclic compound of type **III**. This hypothesis was verified by the reduction of hydroxy aldehyde **26**[22] by Na/NH_3, which led to the spirocyclic diol **11** in 67% yield. In the case of **1** and **26**, only one spirocyclic alcohol was detected in the reaction mixture. This experiment seems to be in favor of intermediate **f**.

However, a second mechanism (path B), where the cyclization of the ketyl radical takes place to produce intermediate **g**, cannot be excluded. The resulting hydroxy ketone **h** could be reduced to the spirocyclic diol of type **III** via intermediates **i** and **j**.

Scheme 7



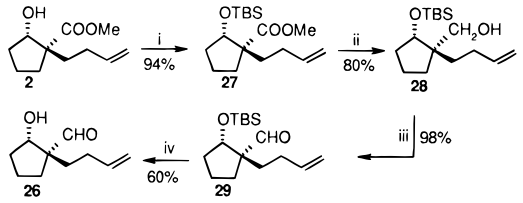
The relative stereochemistry of the newly created stereocenters deserves further comments. In the special case of a ketyl radical anion intermediate of type **IV** (Scheme 7), the stereoselectivity is well rationalized considering repulsive electrostatic interactions between negative oxygen and partial negative charge carried by the terminal sp^2 carbon atom in the C5 cyclic transition state, according to the stereoelectronic approach to this transition state. In other words, the stereochemistry will be governed by the size of the dihedral angle between the C−O bond and the olefinic bond in the transition state. The transition state[5c,23] that has the greater dihedral angle will be favored. Furthermore, the relative stereochemistry between the two hydroxy groups (in compounds **1**−**5**) is due to the complexation of the two alcoholates by the sodium.

In summary, the readily available unsaturated β-hydroxy esters are reduced very efficiently to produce substituted cycloalkanols or spirocyclic diols. The reaction is general when an olefinic bond is present but is somewhat sensitive to steric hindrance. Furthermore, because unsaturated β-hydroxy esters can be synthesized with good enantioselectivity,[24] the spirocyclic compounds could be obtained with good enantioselectivity.

Experimental Section

General. All experiments were run under an argon atmosphere. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie. Mass spectra were run on a coupled analysis GC−MS device and were obtained at 70 eV. Uncorrected melting points were taken on a Kofler bank. Flash chromatographies were carried out on Kieselgel 60 (230−400 mesh) with petroleum ether (PE) and ethyl acetate. Analytical thin layer chromatographies (TLC) were accomplished on Merck silica Kieselgel 60 GF_{254}. Solvents such as THF or Et_2O were freshly distilled from sodium/benzophenone. Diisopropylamine, DMSO, dichloromethane, propane-1,3-diamine (APA), and triethylamine were distilled from CaH_2 and MeOH from magnesium.

(22) Compound **26** was synthesized according to the following scheme [(i) TBSCl, imidazole, DMF, rt; (ii) Dibal-H, CH_2Cl_2, −78 °C to room temperature; (iii) PCC, molecular sieves 4 Å, CH_2Cl_2, rt; (iv) TBAF, THF, rt]:



(23) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(24) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383. (c) Cossy, J.; Ibhi, S.; Kahn, P. H.; Tacchini, L. *Tetrahedron Lett.* **1995**, *43*, 7877. (d) Chitkul, B.; Pinyopronpanich, Y.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1994**, *35*, 1099.

Synthesis of Starting Materials. Compounds 1−3 and 9. Methyl 2-oxocyclopentanecarboxylate (6.0 mmol, 1.0 equiv) was added dropwise to a stirred solution of *t*-BuOK (0.7 g, 6.5 mmol, 1.1 equiv) in dry DMSO (30 mL). After the mixture was stirred at room temperature for 1 h, the alkyl bromide (6.6 mmol, 1.1 equiv) was added dropwise. After 12 h at room temperature, the solution was diluted with a saturated aqueous solution of NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in MeOH (20 mL), and $NaBH_4$ (0.3 g, 7.2 mmol, 1.2 equiv) was added at 0 °C in small portions. When the reaction was complete, the reaction mixture was mixed with water. After evaporation of MeOH, the aqueous layer was acidified with an aqueous solution of HCl 10% and extracted with Et_2O. The organic layers were washed with water, dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography.

(±)-(1*RS*,2*SR*)-Methyl 1-(but-3-enyl)-2-hydroxycyclopentane-1-carboxylate (1). R_f 0.24 (petroleum ether (PE)/AcOEt 90/10); yellow oil; yield 72%; IR 3480, 1725, 1640 cm^{-1}; ^1H NMR δ 1.45−1.72 (m, 5H), 1.82−2.00 (m, 4H), 2.02−2.15 (m, 1H), 2.55 (s, 1H), 3.64 (s, 3H), 4.25 (dd, 1H, J = 5.8, 5.9 Hz), 4.75−4.94 (m, 2H), 5.64−5.81 (m, 1H); ^{13}C NMR δ 19.8 (t), 29.6 (t), 31.0 (t), 31.2 (t), 32.2 (t), 51.6 (q), 57.3 (s), 76.8 (d), 114.3 (t), 138.2 (d), 176.9 (s); EI MS $C_{11}H_{18}O_3$ *m/z* (relative intensity) 166 (3, M − MeOH), 157 (64), 126 (40), 125 (100), 97 (55), 81 (65), 79 (86), 65 (55), 55 (81), 53 (64); HRMS calcd for $C_{11}H_{17}O_2$ (M − OH) 181.1229, found 181.1228.

Compounds 5 and 29. These compounds were prepared as compounds **1**−**3** and **9** from ethyl 2-oxocycloheptanecarboxylate and were purified by flash chromatography (PE/AcOEt 90/10).

(±)-(1*RS*,2*SR*)-Ethyl 1-(but-3-enyl)-2-hydroxycycloheptane-1-carboxylate (5): R_f 0.28 (PE/AcOEt 90/10); yellow oil; yield 22%; IR 3500, 1730, 1640 cm^{-1}; ^1H NMR δ 1.26 (t, 3H, J = 7.0 Hz,), 1.30−1.60 (m, 7H), 1.60−1.88 (m, 4H), 1.88−2.20 (m, 3H), 2.75−2.79 (m, 1H), 4.01 (dd, 1H, J = 2.6, 7.0 Hz), 4.18 (q, 2H, J = 7.0 Hz), 4.85−5.00 (m, 2H), 5.73−5.77 (m, 1H); ^{13}C NMR δ 14.0 (q), 22.3 (t), 22.3 (t), 24.8 (t), 28.8 (t), 31.7 (t), 32.2 (t), 32.8 (t), 52.9 (s), 60.5 (t), 75.2 (d), 114.3 (t), 138.4 (d), 177.5 (s); EI MS $C_{14}H_{24}O_3$ *m/z* (relative intensity) 240 ($M^{\bullet+}$, 1), 199 (58), 168 (29), 153 (100), 107 (27), 83 (20), 81 (55), 79 (28), 67 (26), 55 (43). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H 10.06. Found: C, 69.80; H, 10.18.

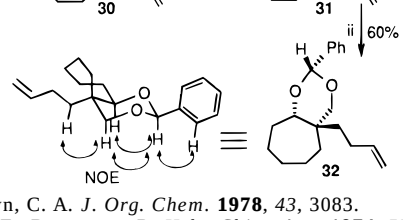
(±)-(1*SR*,2*SR*)-Ethyl 1-(but-3-enyl)-2-hydroxycyclohexane-1-carboxylate (4).[24] Ethyl 2-oxocyclohexanecarboxylate (1.0 g, 6.0 mmol, 1.0 equiv) was dissolved in MeOH (20 mL) and $NaBH_4$ (0.3 g, 7.2 mmol, 1.2 equiv) was added at 0 °C in small portions. When the reaction was complete, the reaction mixture was mixed with water (20 mL). MeOH was removed in vacuo, and the remaining aqueous layer was acidified with an aqueous solution of HCl 10% and extracted with Et_2O. The organic layers were washed with water, dried over $MgSO_4$, and evaporated. The residue was dissolved in THF (4 mL), and the solution was added to a stirred solution of LDA [diisopropylamine (1.5 g, 14.4 mmol, 2.4 equiv) and *n*-BuLi (1.6 M hexane solution, 9.0 mL, 14.3 mmol, 2.4 equiv)] in THF (6 mL) at − 70 °C. After 10 min, a solution of 4-bromobut-1-ene (1.0 g, 7.6 mmol) in HMPA (5 mL) was added at −15 °C. The reaction mixture was stirred at room temperature for 30 min, poured onto a cold aqueous NH_4Cl solution (10%), and extracted with Et_2O. The organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford an oily residue. The crude product was purified by flash chromatography and provided a colorless oil (0.4 g, yield = 30%): R_f 0.25 (PE/AcOEt 90/10); IR 3510, 1700, 1640 cm^{-1}; ^1H NMR δ 1.24 (t, 3H, J = 7.0 Hz), 1.02−1.29 (m, 3H), 1.30−1.50 (m, 2H), 1.52−1.70 (m, 2H), 1.80−2.18 (m, 5H), 3.44 (dd, 1H, J = 9.9, 3.3 Hz), 3.41−3.55 (m, 1H), 4.19 (q, 2H, J = 7.0 Hz), 4.91−4.93 (m, 1H), 5.00−5.05 (m, 1H), 5.74−5.77 (m, 1H); ^{13}C NMR δ 14.1 (q), 22.4 (t), 23.6 (t), 28.3 (t), 31.4 (t), 32.1 (t), 36.1 (t), 51.1 (s), 60.3 (t), 74.6 (d), 114.5 (t), 138.1 (d), 176.9 (s); EI MS $C_{13}H_{22}O_3$ *m/z* (relative intensity) 226 ($M^{\bullet+}$, 2), 208 (M − H_2O, 1), 185 (86), 154 (2), 139 (100), 93 (47), 67 (53), 55 (47).

(±)-(1*RS*,2*SR*)-Methyl 1-(But-3-enyl)-2-methoxycyclopentane-1-carboxylate (6). To a stirred suspension of NaH (0.3 g, 7.5 mmol, 1.5 equiv) in THF (30 mL) at 0 °C was added dropwise a solution of **2** (5 mmol, 1.2 g, 1.0 equiv) in THF (5 mL). The solution was stirred at room temperature for 1 h, and iodomethane (0.6 mL, 10.0 mmol, 2.0 equiv) was added. After 12 h at room temperature, the reaction mixture was diluted with Et_2O (50 mL) and neutralized with an aqueous saturated solution of NH_4Cl. The organic layer was washed with water and dried over $MgSO_4$. The combined organic extracts were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to give a yellow oil (1 g, 95% yield): R_f 0.35 (PE/AcOEt 90/10); IR 1725, 1640 cm^{-1}; ^1H NMR δ 1.15−1.30 (m, 1H), 1.40−1.78 (m, 6H), 1.80−2.00 (m, 2H), 2.05−2.21 (m, 1H), 3.25 (s, 3H), 3.60 (s, 3H), 3.83 (dd, 1H, J = 2.6, 5.1 Hz), 4.86−4.99 (m, 2H), 5.65−5.70 (m, 1H); ^{13}C NMR δ 20.8 (t), 29.4 (t), 29.9 (t), 31.6 (t), 33.0 (t), 51.6 (q), 56.9 (q), 58.9 (s), 85.5 (d), 114.1 (t), 138.5 (d), 176.7 (s); EI MS $C_{12}H_{20}O_3$ *m/z* (relative intensity) 197 (M − CH_3, 3), 171 (11), 158 (19), 141 (30), 139 (36), 126 (56), 121 (42), 111 (53), 109 (72), 79 (100), 72 (46), 71 (52), 67 (46), 53 (40). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89, H, 9.49. Found: C, 67.80; H, 9.16.

(±)-(1*RS*,2*SR*)-Methyl 1-(but-3-enyl)-2-(methylsulfonyloxy)cyclopentane-1-carboxylate (7). 4-DMAP (0.05 g, 0.04 mmol, 0.02 equiv) was added to a stirred solution of **2** (0.4 g, 2.0 mmol, 1.0 equiv) and triethylamine (0.35 mL, 2.50 mmol, 1.10 equiv) in CH_2Cl_2 (1 mL). The reaction mixture was cooled to −40 °C, and mesyl chloride (0.2 mL, 2.5 mmol, 1.1 equiv) was added dropwise. The solution was warmed at room temperature, diluted with Et_2O, and neutralized by a saturated aqueous solution of NH_4Cl. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography to give a yellow oil (0.4 g, 96% yield): R_f 0.30 (PE/AcOEt 90/10); IR 1725, 1640, 1355 cm^{-1}; ^1H NMR δ 1.54−2.09 (m, 9H), 2.18−2.33 (m, 1H), 2.99 (s, 3H), 3.67 (s, 3H), 4.89−4.97 (m, 2H), 5.26 (dd, 1H, J = 3.1, 4.9 Hz), 5.64−5.80 (m, 1H); ^{13}C NMR δ 20.5 (t), 29.5 (t), 31.8 (t), 32.1 (t), 32.5 (t), 38.3 (q), 52.1 (q), 58.2 (s), 86.0 (d), 114.7 (t), 137.5 (d), 174.6 (s); EI MS $C_{12}H_{20}O_5S$, *m/z* (relative intensity) 180 (M − CH_3-SO_3H, 6), 151 (7), 126 (50), 121 (60), 93 (43), 79 (100), 77 (38), 67 (48), 55 (22). Anal. Calcd for $C_{12}H_{20}O_5S$: C, 52.16; H, 7.29. Found: C, 52.06; H, 7.14.

(±)-(1*SR*,2*SR*)-Methyl 1-(but-3-ynyl)-2-hydroxycyclopentane-1-carboxylate (8). KH (1.2 g, 28.8 mmol, 4.0 equiv) was added to APA (25 mL) at 0 °C.[26] After 30 min at room temperature, the reaction mixture was cooled at 0 °C and (±)-(1*SR*,2*SR*)-methyl 1-(3-chlorobut-3-enyl)-2-hydroxycyclopentane-1-carboxylate (1.7 g, 7.2 mmol, 1.0 equiv) (prepared as compound **1** with 1-iodo-3-chlorobut-2-ene[27]) was added. After 1 h at room temperature, the reaction mixture was poured into a solution of ice/water (50 mL), acidified with a solution of HCl 10%, and extracted with Et_2O. The combined organic extracts were washed with water and dried over $MgSO_4$, and the solvent was removed in *vacuo*. The crude product, identified as (±)-(1*SR*,2*SR*)-1-(but-2-ynyl)-2-hydroxycyclopentanoic acid, was isomerized to (±) (1*SR*,2*SR*)-1-(but-3-ynyl)-2-hydroxycyclopentane carboxylic acid by KAPA (Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.78; H, 7.84). The obtained alkyne (0.7 g, 3.6 mmol, 1.0 equiv) was dissolved in acetone (30 mL) and was treated with anhydrous K_2CO_3 (0.8 g, 5.4 mmol, 1.5 equiv) and iodomethane (1.5 g, 10.8 mmol, 3.0 equiv). After 12 h at 23 °C, the resulting mixture was quenched with an aqueous solution of NH_4Cl and extracted with Et_2O. The combined

(25) The relative stereochemistry of the ester group and the hydroxy groups was determined by NOE differences in the ketal **32** [(i) $LiAlH_4$, Et_2O, Δ; (ii) PhCHO, cat. PPTS, toluene, Δ, Dean−Stark]:



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organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography to provide a colorless oil (0.35 g, 25% yield): R_f 0.26 (PE/AcOEt 80/20); IR 3450, 3300, 2120, 1720 cm^{-1}; ^1H NMR δ 1.52−1.91 (m, 6H), 1.92−2.02 (m, 2H), 2.13−2.28 (m, 3H), 2.79 (s, 1H), 3.71 (s, 3H), 4.02 (dd, 1H, J = 4.4, 6.2 Hz); ^{13}C NMR δ 14.0 (t), 20.2 (t), 31.0 (t), 32.2 (t), 35.0 (t), 51.7 (q), 57.8 (s), 68.4 (d), 79.2 (d), 83.5 (s), 175.7 (s); EI MS $C_{11}H_{16}O_3$ *m/z* (relative intensity) 164 (M − MeOH, 6), 157 (85), 139 (39), 125 (100), 97 (44), 79 (72), 55 (31). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.26; H, 8.25.

Preparation of Compound 26.[22] To a solution of **2** (2.3 g, 11.6 mmol, 1.0 equiv) in dry THF (20 mL) were added imidazole (2.0 g, 29.0 mmol, 2.5 equiv) and *tert*-butyldimethylsilyl chloride (2.1 g, 14.0 mmol, 1.2 equiv). After 12 h at room temperature, the reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The ethereal extracts were washed with water and dried over $MgSO_4$. Removal of the solvent in vacuo gave the desired product (±)-(1*SR*,2*SR*)-methyl 2-(*tert*-butyldimethylsiloxy)-1-(but-3-enyl)cyclopentane-1-carboxylate **(27)** as a colorless oil (3.4 g, 94% yield): R_f 0.36 (PE/AcOEt 98/2); IR 1730, 1640, 1260, 835, 725 cm^{-1}; ^1H NMR δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.49−1.81 (m, 6H), 1.83−2.01 (m, 3H), 2.11−2.24 (m, 1H), 3.65 (s, 3H), 3.98 (m, 1H), 4.89−4.98 (m, 2H), 5.78−5.85 (m, 1H); ^{13}C NMR δ −5.2 (q), −4.7 (q), 17.8 (s), 20.7 (t), 25.6 (q), 29.8 (t), 31.9 (t), 33.9 (t), 51.4 (q), 58.7 (s), 77.4 (d), 113.9 (t), 138.5 (d), 176.8 (s); EI MS $C_{17}H_{32}O_3Si$ *m/z* (relative intensity) 297 (M − CH_3, 1), 256 (20), 255 (M − *t*-Bu, 100), 223 (20), 185 (5), 121 (14), 89 (76), 75 (83), 73 (78), 59 (42), 57 (36); Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.37; H, 10.27.

A solution of Dibal-H in hexane (12.8 mL, 12.8 mmol, 4.0 equiv) was added dropwise to a solution of ester **27** (1.0 g, 3.2 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at −78 °C. After 1 h at room temperature, the solution was diluted with CH_2Cl_2 (60 mL) and poured into a solution of ice/water (20 mL). The aqueous layer was acidified with a solution of HCl 10%, and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by flash chromatography and provided (±)-(1*RS*,2*SR*)-2-(*tert*-butyldimethylsiloxy)-1-(but-3-enyl)cyclopentanemethanol **(28)** as a yellow oil (0.73 g, 80% yield): R_f 0.25 (PE/AcOEt 60/10); IR 3380, 1640, 1260, 840, 770 cm^{-1}; ^1H NMR δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.19−1.78 (m, 7H), 1.79−1.95 (m, 2H), 1.95−2.17 (m, 2H), 3.39 (d, 1H, J = 10.8 Hz), 3.53 (d, 1H, J = 10.8 Hz), 4.00 (t, 1H, J = 6.6 Hz), 4.91−4.95 (m, 1H), 5.01−5.04 (m, 1H), 5.81−5.85 (m, 1H); ^{13}C NMR δ −5.2 (q), −4.2 (q), 17.8 (s), 19.7 (t), 25.7 (q), 28.2 (t), 28.5 (t), 29.8 (t), 32.9 (t), 49.1 (s), 67.9 (t), 79.0 (d), 113.7 (t), 139.7 (d); EI MS $C_{16}H_{32}O_2Si$ *m/z* (relative intensity) 253 (M − CH_2OH, 1), 227 (M − *t*-Bu, 19), 209 (3), 185 (100), 171 (7), 135 (30), 107 (14), 93 (35), 75 (98). Anal. Calcd For $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.76; H, 11.30.

To a stirred suspension of PCC (0.4 g, 1.6 mmol, 1.5 equiv) and molecular sieves 4 Å (0.3 g) in dry CH_2Cl_2 (2 mL) was added dropwise a solution of **28** (0.3 g, 1.1 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL). After 30 min, Et_2O (10 mL) was added, and the reaction mixture was filtered through Florisil. The filtrate was concentrated in vacuo to give (±)-(1*SR*,2*SR*)-2-(*tert*-butyldimethylsiloxy)-1-(but-3-enyl)cyclopentanemethanal **(29)** as a colorless oil (0.3 g, 98% yield), which was used directly in the next step; R_f 0.40 (PE/AcOEt 90/10); IR 1725, 1640, 1260, 840, 770 cm^{-1}; ^1H NMR δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.44−1.82 (m, 7H), 1.82−2.06 (m, 3H), 4.26 (dd, 1H, J = 4.8, 4.4 Hz), 4.93−5.05 (m, 2H), 5.75−5.90 (m, 1H), 9.51 (s, 1H); ^{13}C NMR δ −5.1 (q), −4.5 (q), 17.8 (s), 20.8 (t), 25.6 (q), 28.2 (t), 29.1 (t), 29.2 (t), 34.2 (t), 62.3 (s), 74.9 (d), 114.4 (t), 138.4 (d), 205.2 (s); EI MS $C_{16}H_{30}O_2Si$ *m/z* (relative intensity) 265 (1), 241 (1), 225 (M − *t*-Bu, 11), 207 (1), 183 (100), 171 (36), 157 (4), 141 (8), 133 (18), 129 (9), 115 (13), 105 (10), 91 (29), 75 (79), 73 (59); HRMS calcd for $C_{12}H_{21}O_2Si$ (M − C_4H_9) 225.1310, found 225.1310.

To a solution of **29** (0.30 g, 1.06 mmol, 1.00 equiv) in THF (10 mL) was added a solution of TBAF (1.6 mL, 1.0 M in THF, 1.6 mmol, 1.5 equiv). After 1 h at room temperature, the reaction mixture was diluted with Et_2O, washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave (±)-(1*SR*,2*SR*)-1-(but-3-enyl)-2-hydroxypentane-1-methanal **(26)** (0.11 g, 60% yield): R_f 0.30 (PE/AcOEt 80/20); IR 3400, 1720, 1640 cm^{-1}; ^1H NMR δ 0.80−2.25 (m, 10H), 3.30 (m, 1H), 4.15 (t, 1H, J = 5.9 Hz), 4.84−5.12 (m, 2H), 5.69−5.92 (m, 1H), 9.70 (s, 1H); ^{13}C NMR δ 20.4 (t), 29.0 (t), 29.3 (t), 33.7 (t), 33.9 (t), 62.1 (s), 80.2 (d), 114.9 (q), 138.1 (d), 206.8 (d); EI MS $C_{10}H_{16}O_2$ *m/z* (relative intensity) 150 (M − H_2O, 1), 127 (2), 114 (12), 111 (10), 109 (12), 96 (28), 81 (100), 79 (35), 67 (26), 55 (3). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.65.

Reductive Cyclization by Na/NH_3. Compounds 10. Small pieces of sodium (0.3 g, 12.0 mmol, 6.0 equiv) were added to liquid ammonia at −78 °C (150 mL). After 15 min, a solution of β-hydroxy ester (2.0 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. The reaction mixture was warmed to −33 °C and stirred in refluxing ammonia for 10 min. The excess of Na was then destroyed by addition of ammonium chloride, and the ammonia was evaporated under a stream of nitrogen (fume hood). Et_2O was added, and the reaction mixture was neutralized by a solution of HCl (10%). The residue was extracted with Et_2O. The organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude oil was purified by crystallization in pentane or by flash chromatography.

(±)-(1*SR*,2*RS*,5*SR*,6*RS*)-2-Methyl-spiro[4.4]nonane-1,6-diol (10): R_f 0.10 (PE/AcOEt 50/50); purification by crystallization in pentane; mp 132−133 °C; yield 95%; IR 3310 cm^{-1}; ^1H NMR δ 1.05 (d, 3H, J = 6.6 Hz), 1.12−1.25 (m, 1H), 1.26−1.38 (m, 1H), 1.39−1.70 (m, 5H), 1.72−2.09 (m, 6H), 3.45 (d, 1H, J = 5.1 Hz), 4.20 (dd, 1H, J = 9.6, 7.7 Hz); ^{13}C NMR δ 18.7 (q), 19.1 (t), 28.1 (t), 29.9 (t), 30.9 (t), 35.0 (t), 43.8 (d), 54.8 (s), 75.3 (d), 87.3 (d); EI MS $C_{10}H_{18}O_2$ *m/z* (relative intensity) 152 (M − H_2O, 8), 137 (28), 134 (44), 119 (44), 108 (59), 97 (32), 94 (42), 93 (65), 81 (100), 79 (56), 67 (48), 57 (51), 55 (58), 53 (38). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.41; H, 10.54.

Synthesis of compounds 19, 20 and 32. (±)-(2*RS*,5*SR*)-2-methylspiro[4−4]nonane-1,6-dione (19). To a stirred suspension of PCC (0.4 g, 2.0 mmol, 2.0 equiv) and molecular sieves 4 Å (0.4 g) in dry CH_2Cl_2 (3 mL) was added dropwise a solution of **10** (0.2 g, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL). After 30 min, Et_2O (10 mL) was added, and the reaction mixture was filtered through florisil. The filtrate was concentrated in vacuo to give a colorless oil (0.31 g, 94% yield). R_f 0.34 (PE/AcOEt 90/10); IR 1740, 1720 cm^{-1}; ^1H NMR δ 1.09 (d, 1H, J = 7.3 Hz), 1.37−1.56 (m, 1H), 1.63−1.98 (m, 3H), 2.08−2.48 (m, 7H); ^{13}C NMR δ −13.9 (q), 19.6 (s), 28.5 (s), 32.1 (s), 34.8 (s), 38.2 (s), 44.6 (t), 64.1 (q), 217.1 (q), 217.4 (q); EI MS $C_{10}H_{14}O_2$ *m/z* (relative intensity) 166 ($M^{\bullet+}$, 56), 151 (4), 148 (5), 123 (12), 111 (39), 110 (100), 109 (18), 97 (35), 95 (22), 68 (37), 67 (39), 55 (34), 53 (28); HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0995. Compound **19** was also obtained by the same reaction from compound **11**.

(±)−(1*SR*,2*RS*,5*SR*,6*RS*)-1,6-dimethoxy-2-methylspiro-[4−4]nonane (20). To a stirred suspension of NaH (0.3 g, 3.0 mmol, 1.5 equiv) in THF (13 mL) at 0 °C was added dropwise a solution of **15** (0.4 g, 2.0 mmol, 1.0 equiv) in THF (2 mL). The solution was stirred at room temperature for 1 h, and iodomethane (0.4 mL, 6.0 mmol) was added. After 2 h at room temperature, an aqueous saturated solution of NH_4Cl and Et_2O were added. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed in vacuo, and a yellow oil was obtained (0.36 g, 90%). R_f 0.85 (PE/AcOEt 80/20); IR 1460 cm^{-1}; ^1H NMR δ 1.10 (d, 3H, J = 7.0 Hz), 1.30−1.42 (m, 1H), 1.45−1.72 (m, 5H), 1.76−2.06 (m, 5H), 2.83 (d, 1H, J = 6.3 Hz), 3.31 (s, 3H), 3.39 (s, 3H), 3.69 (dd, 1H, J = 5.2, 5.9 Hz); ^{13}C NMR δ 20.4 (q), 20.6 (t), 29.6 (t), 30.7 (t), 31.0 (t), 36.8 (t), 39.9 (d), 56.2 (s), 56.9 (q), 58.6 (q), 83.8 (d), 95.4 (d); EI MS $C_{12}H_{22}O_2$ *m/z* (relative intensity) 198 ($M^{\bullet+}$, 1), 166 (7), 151 (12), 134 (100), 125 (14), 119 (23), 108 (89), 93 (36), 85 (23), 72 (14), 71 (41). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.51; H, 11.46. Compound **20** was also obtained by treating **10** with NaH (2.5 equiv) and MeI (4.0 equiv).

Preparation of compound 32. To a stirred suspension of $LiAlH_4$ (0.7 g, 18.0 mmol, 6.0 equiv) in Et_2O (40 mL) at 0 °C was added dropwise a solution of **30** (0.7 g, 3.0 mmol, 1.0 equiv) in Et_2O (10 mL). After 1 h at room temperature, the mixture

was heated under reflux for 2 h. After being cooled at 0 °C, the solution was quenched with water (0.7 mL) and an aqueous solution of NaOH (15%) (0.7 mL), which was followed by addition of water (2 mL). The white suspension was filtered on Celite. The filtrate was concentrated in vacuo to give (±)-(1*RS*,2*SR*)-2-hydroxy-1-(but-3-enyl)cycloheptanemethanol **(31)** as a colorless oil (0.56 g, 94% yield): R_f 0.28 (PE/AcOEt 80/20); IR 1640 cm^{-1}; ^1H NMR δ 1.20−2.23 (m, 14H), 2.97 (s, 2H), 3.32 (d, 1H, J = 11.4 Hz), 3.71 (d, 1H, J = 9.2 Hz), 3.78 (d, 1H, J = 11.4 Hz), 4.96−4.98 (m, 1H), 5.01−5.06 (m, 1H), 5.88−5.94 (m, 1H); ^{13}C NMR δ 21.9 (t), 25.2 (t), 27.8 (t), 29.6 (t), 31.4 (t), 33.8 (t), 34.0 (t), 42.9 (s), 67.3 (t), 80.4 (d), 114.0 (t), 139.3 (d); EI MS $C_{12}H_{22}O_2$ *m*/*z* (relative intensity) 199 (M + 1, 3), 168 (2), 149 (9), 133 (14), 121 (13), 109 (17), 107 (17), 95 (36), 94 (37), 81 (100), 67 (54), 55 (58). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.64; H, 11.00.

A mixture of **31** (0.4 g, 2.0 mmol, 1.0 equiv), benzaldehyde (0.3 mL, 3.0 mmol, 1.5 equiv), and PPTS (0.05 g, 0.20 mmol, 0.10 equiv) in dry toluene (20 mL) was heated under reflux for 2 h in a Dean Stark apparatus. After being cooled at room temperature, the solution was neutralized with $NaHCO_3$ (0.08 g, 1.00 mmol), diluted in Et_2O, and washed with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo and the residue was purified by flash chromatography to provide the ketal (±)-(2*RS*,4a*RS*,9a*SR*)-4a-(but-3-enyl)-2-phenyl-4,-4a,5,6,7,8,9,9a-octahydrocyclohepta-1,3-dioxine **(32)** (0.34 g, 60% yield): R_f 0.25 (PE/AcOEt 98/2); IR 1640 cm^{-1}; ^1H NMR δ 1.22−1.25 (m, 1H), 1.45−1.88 (m, 8H), 1.89−2.13 (m, 4H), 2.46−2.49 (m, 1H), 3.73 (d, 1H, J = 10.8 Hz), 3.78 (m, 1H), 3.92 (d, 1H, J = 10.8 Hz), 5.01 (d, 1H, J = 10.3 Hz), 5.04−5.09 (m, 1H), 5.53 (s, 1H), 5.85−5.90 (m, 1H), 7.34−7.45 (m, 3H), 7.53−7.57 (m, 2H); ^{13}C NMR δ 19.8 (t), 21.0 (t), 26.6 (t), 27.1 (t), 29.1 (t), 29.9 (t), 32.8 (t), 38.6 (s), 78.3 (t), 82.8 (d), 101.8 (d), 114.5 (t), 126.2 (d), 128.2 (d), 128.7 (d), 138.7 (d), 138.9 (s); EI MS $C_{19}H_{26}O_2$ *m*/*z* (relative intensity) 286 ($M^{\bullet+}$, 6), 285 (7), 268 (5), 202 (2), 180 (4), 162 (17), 149 (7), 147 (7), 135 (11), 133 (9), 121 (19), 107 (7), 105 (89), 81 (100), 79 (64), 77 (70), 67 (82), 55 (71). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.63; H, 8.95.

Acknowledgment. We thanks the Ministère de la Recherche et de l'Enseignement Supérieur for financial support (B.G.) and J.-E. Devos (STOE-Oxford Cryosystems-INSTO) for single crystal X-ray diffraction studies.

Supporting Information Available: The characterization data of **2**, **3**, **9**, **11**−**18**, **25**, and **30**, the ^1H NMR spectra of **1**, **15′**, **29**, and **30**, ORTEP drawing for **10**, and details of the data acquisition (12 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.

JO972339I