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First Synthesis and Structural Elucidation of (−)-Presphaerene[1]

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The first total synthesis of (−)-presphaerene (**1**) was achieved from (*R*)-glyceraldehyde **9** in 19 steps, demonstrating the novel "folding and allylic strain-controlled" intramolecular ester enolate S_N2' alkylation strategy could be extended to the stereoselective synthesis of cyclopentanoid natural products. The present study also established the relative and absolute stereochemistry of **1**, and the absolute structures of co-occurring sphaeroanes from the red alga *Sphaerococcus coronopifolius*.

Introduction

The sphaeroanes with a skeleton of 2,7-cycloneodolabellane such as (−)-presphaerene (**1**), (+)-presphaerol (**2**), (+)-isosphaerodiene 1 (**3**), and (+)-isosphaerodiene 2 (**4**) were isolated from the red alga *Sphaerococcus coronopifolius* by Fattorusso and co-workers (Figure 1).[2] The structures of these natural products were determined by a combination of chemical correlation, NMR spectroscopy, and X-ray crystallography except for their absolute configurations and the C-7 stereochemistry of **1**. In detail, the relative configuration of **3** was resolved by X-ray crystallography. The chemical transformation of **2** into a mixture of **3** and **4** by treatment with acetyl chloride in refluxing xylene, coupled with NMR spectroscopy, led to the tentative assignment of **2**. Aromatization of **2** with SeO_2 also produced **1**.

Previously, we reported the application of the novel and highly stereoselective "folding and allylic strain-controlled" intramolecular enolate S_N2' alkylation methodology to the synthesis of cyclohexanoid natural products.[3] Encouraged by the report that some of the sphaeroanes are biologically active,[4] we set out to examine the feasibility of the internal S_N2' alkylation for the construction of highly functionalized cyclopentane systems with a particular emphasis on the stereochemical outcome. Described herein is the first total synthesis and complete structural elucidation of **1** utilizing a folding and allylic strain-controlled[5] intramolecular ester enolate S_N2' alkylation and an intramolecular Friedel−Crafts acylation as key steps.

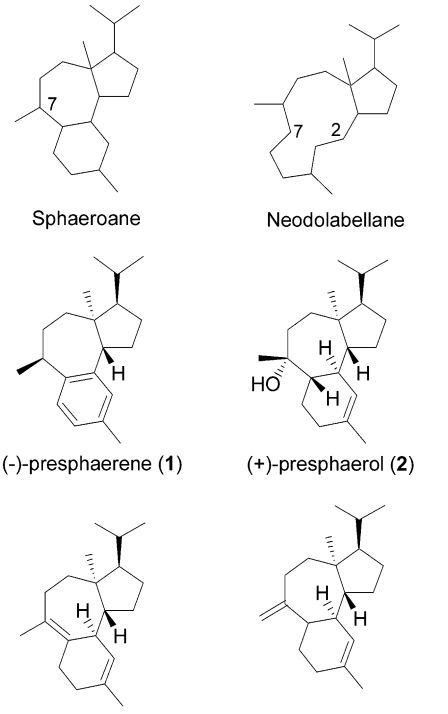

FIGURE 1. Structures of **1**−**4**.

Results and Discussion

Our retrosynthetic analysis for **1** (Scheme 1) called for the intermediacy of tricyclic ketone **5** and highly functionalized cyclopentanecarboxylate **7** as key intermediates, which could be constructed by intramolecular

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(1) Taken in part from the doctoral thesis of J. Lee, Seoul National University, 2001.

(2) (a) Cafieri, F.; Napoli, L. D.; Fattorusso, E.; Piattelli, M.; Sciuto, S. *Tetrahedron Lett.* **1979**, *20*, 963. (b) Cafieri, F.; Fattorusso, E.; Blasio, B. D.; Pedone, C. *Tetrahedron Lett.* **1981**, *22*, 4123. (c) Cafieri, F.; Ciminiello, P.; Santacroce, C.; Fattorusso, E. *Phytochemistry* **1983**, *22*, 1824. (d) Cafieri, F.; Napoli, L. D.; Fattorusso, E.; Santacroce, C. *Phytochemistry* **1987**, *26*, 471.

(3) (a) Kim, D.; Choi, W. J.; Hong, J. Y.; Park, I. Y.; Kim, Y. B. *Tetrahedron Lett.* **1996**, *37*, 1433. (b) Kim, D.; Lim, J. I.; Shin, K. J.; Kim, H. S. *Tetrahedron Lett.* **1993**, *34*, 6557. (c) Kim, D.; Kim, H. S.; Yoo, J. Y. *Tetrahedron Lett.* **1991**, *32*, 1577. (d) Jo, H.; Lee, J.; Kim, H.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, *44*, 7043. (e) For a review of the S_N2' reaction, see: Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

(4) Engler, M.; Anke, T.; Sterner, O. *Phytochemistry* **1998**, *49*, 2591.

(5) (a) Tokoroyama, T.; Okada, K.; Iio, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1572. (b) Asao, K.; Iio, H.; Tokoroyama, T. *Tetrahedron Lett.* **1989**, *30*, 6397.

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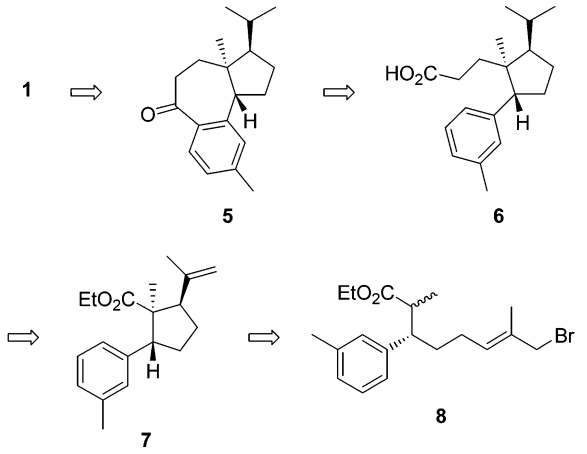
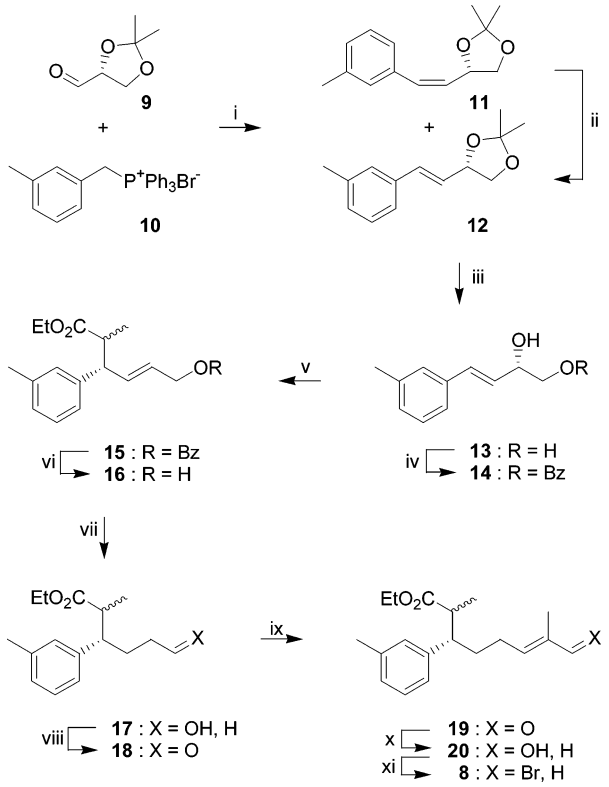
SCHEME 1. Retrosynthetic Analysis of 1



Friedel−Crafts acylation and S_N2' alkylation from acyclic precursors **6** and **8**, respectively.

The requisite intramolecular S_N2' alkylation substrate **8** was prepared from readily available (*R*)-glyceraldehyde **9**[6] by a straightforward manner as depicted in Scheme 2. (*R*)-Glyceraldehyde **9** was transformed to an easily separable mixture of *Z*-olefin **11** and *E*-olefin **12** (11:1) by a Wittig reaction with *m*-tolylphosphonium bromide **10**[7] in a total 90% yield. *Z*-Olefin **11** could be cleanly isomerized to *E*-olefin **12** by treatment with thiophenol in the presence of AIBN in refluxing benzene according to the protocol described by Schwarz[8] in 76% yield. It is worthwhile to mention the stereoselective access to both *Z*- and *E*-olefin is an important factor for the determination of the absolute stereochemistry of **1** in our synthetic scheme. Removal of the acetonide group of olefin **12**, followed by a selective monobenzoylation[9] of the resulting diol **13** (>95% ee),[10] furnished monobenzoate **14** in 88% yield for the two steps. Subjection of allylic alcohol **14** to Johnson ortho ester Claisen rearrangement conditions[11] and subsequent deprotection of the benzoyl protecting group of the resulting diester **15** by a transesterification led to the formation of hydroxy ester **16** in 85% overall yield. Catalytic hydrogenation of olefin **16** using PtO_2 and PCC oxidation of the resulting alcohol **17** produced the corresponding aldehyde **18** in 74% yield for the two steps. The aldehyde **18** was elaborated to the cyclization precursor **8** by a convenient three-step sequence. Wittig reaction of aldehyde **18** with 2-(triphenylphosphoranylidene)propionaldehyde, $NaBH_4$ reduction of the corresponding α,β-unsaturated aldehyde **19**, and finally bromination of the resulting allylic alcohol **20** by the protocol described by Hooz[12] afforded the desired allylic bromide **8** in 69% overall yield over the three steps.

SCHEME 2 [a]



[a] Reagents and conditions: (i) *t*-BuOK, THF, −78 to −30 °C, 90%; (ii) PhSH, AIBN, benzene, reflux, 3 h, 76%; (iii) 60% aqueous AcOH, rt, 6 h, 97%; (iv) BzCl, Et_3N, CH_2Cl_2, −40 °C, 4 h, 91%; (v) $CH_3CH_2CH(OEt)_3$, phenol, toluene, reflux, 20 h, 87%; (vi) NaOEt, EtOH, rt, 7 h, 98%; (vii) PtO_2, H_2, EtOH, rt, 7 h, 88%; (viii) PCC, NaOAc, CH_2Cl_2, 0 °C, 2 h, 84%; (ix) $Ph_3P{=}C(CH_3)CHO$, toluene, reflux, 8 h; (x) $NaBH_4$, EtOH, 0 °C, 0.5 h, 78% for two steps; (xi) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 2 h, 89%.

Allylic bromide **8** underwent a smooth S_N2' cyclization upon treatment with LHMDS in THF for 22 h at room temperature to afford a highly functionalized cyclopentanecarboxylate, **7**, as a major component along with diastereomeric **7-*iso*** and **7-*cis*** in a 9.9:3.3:1 ratio (capillary GLC analysis) in a total 86% yield. These stereoisomers could be separated by preparative HPLC, and the relative stereochemistry of the cyclized products was established by NOE experiments as shown in Scheme 3. In addition, the second major isomer, **7-*iso***, could be converted to the desired isomer **7** by a straightforward three-step sequence (ozonolysis, epimerization, Wittig reaction) as described in Scheme 3, which reinforces our structural assignment.

The observed stereoselectivity can best be rationalized by considering that the reaction proceeds via chairlike "*double H-eclipsed*" transition-state geometry **21** where the nucleophilic ester enolate moiety and electrophilic allylic bromide assume a "*H-eclipsed*" conformation with

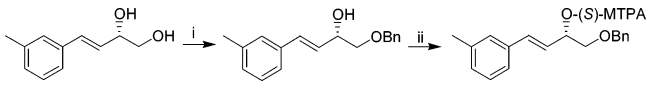
(6) (a) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056. (b) (*R*)-Glyceraldehyde **9** prepared according to the protocol described by Schmid[5a] is commercially available now.

(7) Friedrich, K.; Henning, H. G. *Chem. Ber.* **1959**, *92*, 2756.

(8) Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260.

(9) Schlessinger, R. H.; Lopes, A. C. *J. Org. Chem.* **1981**, *46*, 5252.

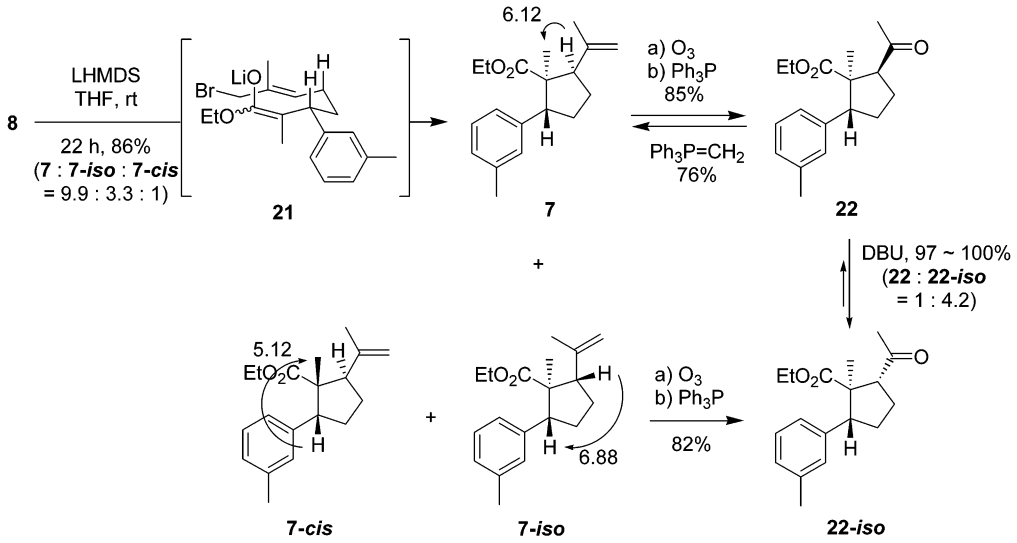
(10) The ee of dio1 **13** was calculated by the analysis of the ^1H 500 MHz NMR spectrum of the corresponding (*S*)-MTPA ester, which was prepared from diol **13** by a two-step sequence [(i) NaH, BnBr, DMF, rt, 5 h, 58%; (ii) (*S*)-(+)-MTPC, DMAP, CH_2Cl_2, rt, 4 h, >95% ee, 100%]. Anderson, R. J.; Adams, K. G.; Chinn, H. R.; Henrick, C. A. *J. Org. Chem.* **1980**, *45*, 2229.



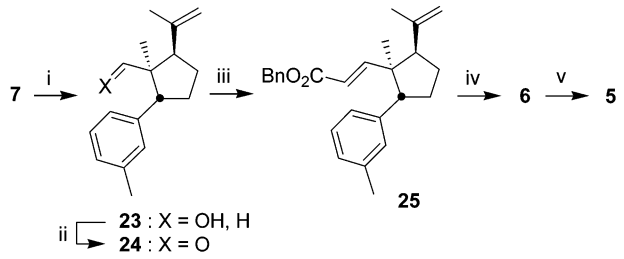
(11) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Takano, S.; Sugihara, T.; Samizu, K. *Chem. Lett.* **1989**, 1781.

(12) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

SCHEME 3



SCHEME 4[a]



[a] Reagents and conditions: (i) DIBALH, toluene, −78 to −30 °C, 93%; (ii) PCC, NaOAc, 0 °C, 2.5 h, 77%; (iii) $TMSCH_2CO_2Bn$, LDA, THF, −25 °C, 2 h; (iv) PtO_2, H_2, EtOAc, rt, overnight, 92% for two steps; (v) PPA, 90 °C, overnight, 89%.

the bulky *m*-tolyl appendage in an equatorial position, affording a cyclopentanecarboxylate with three contiguous stereogenic centers.[3]

Treatment of the desired cyclopentanecarboxylate **7** with DIBALH led to the formation of primary alcohol **23** (Scheme 4), which was further oxidized with PCC to the corresponding aldehyde **24** (72% overall yield). Peterson olefination[13] of aldehyde **24** with benzyl (trimethylsilyl)-acetate[14] yielded α,*β*-unsaturated benzyl ester **25**, and then simultaneous catalytic hydrogenation of olefin and hydrogenolysis of benzyl ester with PtO_2 afforded carboxylic acid **6** in 92% overall yield. It is quite interesting to note that the Peterson olefination yielded *E*-olefinic ester in an exclusive manner. Intramolecular Friedel−Crafts acylation[13a,15] of carboxylic acid **6** with PPA gave the desired seven-membered tricyclic ketone **5** in high yield (89%).

To establish unambiguously the configuration of the secondary methyl group at C-7, tricyclic ketone **5** was first treated with methyllithium and $SOCl_2$ to provide a 5:1 mixture of *endo*-olefin **26** and *exo*-olefin **27** as depicted in Scheme 5 .[16] Examination of the most stable conformation of *endo*-olefin **26**, which was generated by a systematic Monte Carlo conformational search and subsequent energy minimization using MM2 calculation, revealed the *β*-face of the olefin is distinctively less hindered as shown in Figure 2.[17] As we expected, catalytic hydrogenation of *endo*-olefin **26** with 10% Pd/C produced exclusively a quantitative yield of the 7-α-methyl isomer, which turned out to be 7-*epi*-presphaerene (**1′**). However, use of PtO_2 as catalyst instead of Pd/C for the hydrogenation of *endo*-olefin **26** yielded a small amount (10%) of **1**, the desired 7-*β*-methyl isomer, in addition to **1′** as a major product (90%). These two isomeric compounds could be separated by column chromatography on $AgNO_3$-impregnated silica gel, and their structure was fully determined by the analyses of their NOE, DEPT, $^1H-^1H$ COSY, and $^1H-^{13}C$ COSY spectra. Moreover, the spectrum of the minor 7-*β*-methyl isomer was in agreement with the spectral data of natural **1** reported in the literature.[2c,e]

Since it was not so obvious from the inspection of the most stable conformation of *exo*-olefin **27** (Figure 2) which side of the *exo*-methylene double bond is more hindered,[17] we hoped that we had a better chance of obtaining the desired 7-*β*-methyl isomer from *exo*-olefin **27** as a major product. The catalytic hydrogenation of *exo*-olefin **27**, also prepared from tricyclic ketone **5** by a Wittig reaction in high yield, with 10% Pd/C produced only **1′** in almost quantitative yield. We reasoned that the reduction with Pd catalyst might proceed through *endo*-olefin **26** via in situ isomerization.[18]

Taking advantage of these experimental findings, *exo*-olefin **27** was hydrogenated in ethanol using PtO_2 as

(13) (a) Budhram, R. S.; Palaniswamy, V. A.; Eisenbraun, E. J. *J. Org. Chem.* **1986**, *51*, 1402. (b) For a review of Peterson olefination, see: Ager, D. J. *Org. React.* **1990**, *38*, 1. (c) For a review of alkene synthesis, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Seoul, 1991; Vol. 1, pp 729−817.

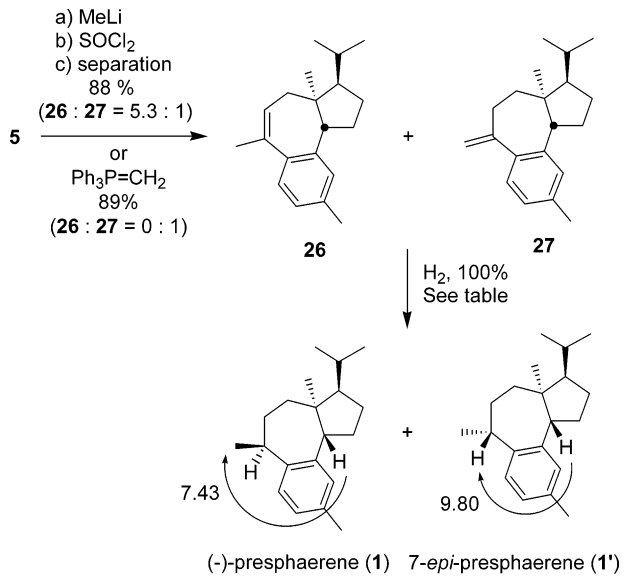
(14) (a) Benzyl (trimethylsilyl)acetate was prepared from ethyl (trimethylsilyl)acetate by titanate-mediated transesterification in 80% yield. See: Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138. (b) For other preparations of benzyl (trimethylsilyl)acetate, see: Emde, H.; Simchen, G. *Synthesis* **1977**, 867. Emde, H.; Simchen, G. *Liebigs Ann. Chem.* **1983**, 816. Maruoka, K.; Banno, H.; Yamamoto, H. *Synlett* **1991**, 253. Soderberg, B. C.; Bowden, B. A. *Organometallics* **1992**, *11*, 2220.

(15) (a) Anderson, C. L.; Horton, W. J.; Walker, F. E.; Weiler, M. R. *J. Am. Chem. Soc.* **1955**, *77*, 598. (b) Corey, E. J.; Behforouz, M.; Ishiguro, M. *J. Am. Chem. Soc.* **1979**, *101*, 1608.

(16) Olah, G. A.; Wu, A.; Farooq, O. *J. Org. Chem.* **1989**, *54*, 1375.

(17) All calculations were performed on MacroModel/BATCHMIN (version 6.0).

SCHEME 5



Catalyst	Substrate	Solvent	Products (**1** : **1'**)
10% Pd/C	**26**	EtOH	0 : 100
PtO_2	**26**	EtOH	10 : 90
10% Pd/C	**27**	EtOH	0 : 100
PtO_2	**27**	*n*-BuOH	75 : 25
PtO_2	**27**	*n*-PrOH	75 : 25
PtO_2	**27**	*i*-PrOH	71 : 29
PtO_2	**27**	EtOH	75 : 25
PtO_2	**27**	MeOH	57 : 43
PtO_2	**27**	EtOAC	60 : 40
PtO_2	**27**	hexane	57 : 43
Pt/C	**27**	EtOH	50 : 50
Pt/Al_2O_3	**27**	EtOH	50 : 50

catalyst, which is known to be less prone to isomerization,[18] to give rise to a 3:1 mixture of **1** and **1′**, to our delight (Scheme 5). Use of other solvents such as MeOH, EtOAc, and *n*-hexane exhibited somewhat decreased stereoselectivity than ethanol. It is interesting to note that use of Pt/C or Pt/Al_2O_3 for the hydrogenation of *exo*-olefin **27** afforded a 1:1 mixture of **1** and **1′**.

In summary, the first total synthesis and structure determination of **1** have been accomplished from (*R*)-glyceraldehyde **9** employing a folding and doubly allylic strain-controlled intramolecular ester enolate S_N2' alkylation and an intramolecular Friedel−Crafts acylation as key steps. The present synthesis also established the absolute structures of co-occurring sphaeroanes from the red alga *S. coronopifolius* such as **2**−**4** as a result. More importantly, we have demonstrated that the internal S_N2' methodology is a viable method for the stereoselective construction of highly functionalized cyclopentanoid natural products, though the observed stereoselectivity seems to be slightly inferior to that of the corresponding six-membered cases. During the course of the study we introduced benzyl (trimethylsilyl)acetate[14] for the purpose of introducing a two-carbon acetic acid unit to a very hindered position and observed a very interesting interplay of catalyst and molecular geometry in the catalytic

(18) (a) Nishimura, S.; Sakamoto, H.; Ozawa, T. *Chem. Lett.* **1973**, 855. (b) For a review for heterogeneous catalytic hydrogenation, see: Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Seoul, 1991; Vol. 8, pp 417−442.

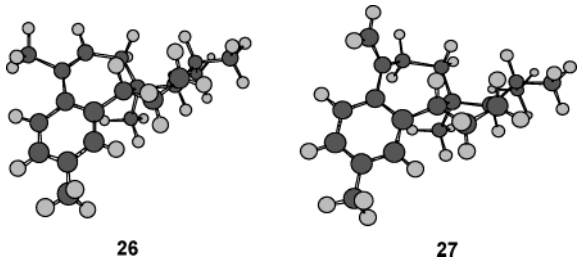


FIGURE 2. The most stable conformations of *endo*-olefin **26** and *exo*-olefin **27** by a systematic Monte Carlo conformational search and subsequent energy minimization using MM2 calculation.[17]

hydrogenation. Currently, efforts are being made to apply this internal S_N2' alkylation strategy to the syntheses of various biologically active natural products in our laboratories.

Experimental Section

(*Z*/*E*,4*S*)-2,2-Dimethyl-4-(2-*m*-tolylvinyl)[1,3]dioxolane (11 and 12). To a mixture of *m*-tolylphosphonium bromide **10** (1374 mg, 3.07 mmol) and anhydrous THF (5.1 mL) was added a 1.0 M solution of *t*-BuOK (2.76 mL) in THF at 0 °C. After 1 h at ambient temperature, the mixture was cooled to −78 °C, and a solution of (*R*)-glyceraldehyde **9** (180.0 mg, 1.38 mmol) in THF (1.5 mL) was added. The mixture was stirred and slowly warmed to −30 °C over 3 h. The reaction mixture was quenched with a few drops of saturated aqueous NH_4Cl solution and filtered through a pad of silica gel. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 15:1) to afford *Z*-olefin **11** (247.0 mg) and *E*-olefin **12** (22.5 mg) in a total 90% yield. Data for *Z*-olefin **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.07 (s, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 11.6 Hz, 1H), 5.68 (dd, J = 11.5, 8.9 Hz, 1H), 4.91 (dddd, J = 8.8, 7.6, 6.3, 1.2 Hz, 1H), 4.14 (dd, J = 8.1, 6.1 Hz), 3.66 (t, J = 7.9 Hz, 1H), 2.35 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 136.1, 134.1, 129.4, 128.9, 128.2, 128.1, 125.7, 109.3, 72.4, 69.7, 26.8, 25.9, 21.4; IR (neat) 1604, 1454, 1060 cm^{-1}; $[\alpha]^{20}_D$ = −37.3 (*c* 3.04, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1313. Data for *E*-olefin **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.18 (m, 3H), 7.06 (br d, J = 6.6 Hz, 1H), 6.63 (dd, J = 15.8, 0.6 Hz, 1H), 6.14 (dd, J = 15.8, 7.6 Hz, 1H), 4.67 (dddd, J = 8.5, 7.6, 6.4, 1.1 Hz, 1H), 4.15 (dd, J = 8.1, 6.2 Hz, 1H), 3.67 (t, J = 8.0 Hz, 1H), 2.33 (s, 3H), 1.47 (d, J = 0.5 Hz, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 136.2, 133.4, 128.7, 128.4, 127.3, 126.5, 123.8, 109.4, 77.2, 69.5, 26.7, 25.9, 21.3; IR (neat) 1604, 1454, 1059 cm^{-1}; $[\alpha]^{20}_D$ = +58.5 (*c* 2.02, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1305.

***E*-Olefin 12 from *Z*-Olefin 11.** To a solution of *Z*-olefin **11** (2094 mg, 9.59 mmol) in benzene (9.6 mL) were added thiophenol (0.49 mL, 4.77 mmol) and AIBN (236 mg, 1.44 mmol). The reaction mixture was refluxed for 3 h. Removal of the solvent and column chromatography of the resulting residue on silica gel (hexane/EtOAc, 30:1) gave *E*-olefin **12** (1582 mg) in 76% yield.

(2*S*)-4-*m*-Tolylbut-3-ene-1,2-diol (13). A mixture of *E*-olefin **12** (645.7 mg, 2.96 mmol) and 60% aqueous acetic acid (5.9 mL) was stirred for 6 h at room temperature. After neutralization with saturated aqueous NaOH solution, the mixture was extracted with EtOAc (30 mL × 5). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc/MeOH, 8:16:1) to give diol **13** (510.0 mg) in 97% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.17 (m, 3H), 7.07 (d, J = 7.1 Hz, 1H),

6.65 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 6.4 Hz, 1H), 4.41 (dt, J = 6.5, 3.5 Hz, 1H), 3.74 (dd, J = 11.2, 3.5 Hz, 1H), 3.59 (dd, J = 11.2, 7.4 Hz, 1H), 2.45 (br s, 1H), 2.34 (s, 3H), 2.23 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 136.2, 131.7, 128.4, 128.3, 127.4, 127.2, 123.5, 73.2, 66.4, 21.2; IR (neat) 3389, 1074 cm^{-1}; $[\alpha]^{20}_D$ = +29.5 (*c* 1.91, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{11}H_{14}O_2$ (M^+) 178.0994, found 178.0993.

Benzoic Acid (*E*,2*S*)-2-Hydroxy-4-*m*-tolylbut-3-enyl Ester (14). To a solution of diol **13** (245.0 mg, 1.38 mmol) in CH_2Cl_2 (6.9 mL) were added Et_3N (0.57 mL, 4.09 mmol) and benzoyl chloride (0.24 mL, 2.07 mmol) at −78 °C. The mixture was stirred for 4 h at −40 °C and cooled to −78 °C. A 3% aqueous HCl solution (1.0 mL) was added to the mixture at −78 °C with vigorous agitation. After 1 h, the mixture was poured into brine and extracted with EtOAc (30 mL × 4). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to produce benzoate **14** (352.5 mg) in 91% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.59−7.55 (m, 1H), 7.45 (dd, J = 8.1, 7.5 Hz, 2H), 7.23−7.19 (m, 3H), 7.08 (dd, J = 6.9, 1.3 Hz, 1H), 6.74 (dd, J = 16.0, 1.2 Hz, 1H), 6.25 (dd, J = 15.9, 6.2 Hz, 1H), 4.72−4.68 (m, 1H), 4.50 (dd, J = 11.4, 3.7 Hz, 1H), 4.37 (dd, J = 11.4, 7.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 138.2, 136.2, 133.2, 132.6, 129.8, 129.7, 128.8, 128.5, 128.4, 127.3, 126.9, 123.8, 71.1, 68.5, 21.3; IR (neat) 3443, 1714, 1275 cm^{-1}; $[\alpha]^{20}_D$ = +3.4 (*c* 0.79, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{18}H_{18}O_3$ (M^+) 282.1256, found 282.1247.

Benzoic Acid (*E*,4*S*)-5-Ethoxycarbonyl-4-*m*-tolylhex-2-enyl Ester (15). To a solution of benzoate **14** (352.5 mg, 1.25 mmol) in toluene (6.2 mL) were added triethylorthopropionate (2.5 mL, 12.4 mmol) and phenol (12 mg, 0.13 mmol) at room temperature. The reaction mixture was refluxed for 20 h and cooled to room temperature. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 15:1) to afford allylic benzoate **15** (399.4 mg) in 87% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04−8.00 (m, 2H) 7.57−7.53 (m, 1H), [7.43 (t, J = 7.7 Hz) and 7.42 (t, J = 7.6 Hz), 2 H], [7.21 (t, J = 7.5 Hz) and 7.17 (t, J = 7.8 Hz), 1H], [7.04 (d, J = 7.2 Hz) and 7.01−6.98 (m), 3H], [6.03 (dd, J = 15.4, 8.6 Hz) and 5.96 (dd, J = 15.3, 9.3 Hz), 1H], [5.79 (td, J = 15.3, 6.2 Hz) and 5.72 (td, J = 15.3, 6.3 Hz), 1H], [4.82−4.74 (m) and 4.73 (dd, J = 6.3, 1.0 Hz), 2H], [4.10 (q, J = 7.1 Hz) and 3.94−3.85 (m), 2H], [3.51 (t, J = 9.6 Hz) and 3.44 (t, J = 9.6 Hz), 1H], 2.84−2.77 (m, 1H), [2.34 (s) and 2.31 (s), 3H], [1.21 (t, J = 6.4 Hz) and 0.98 (t, J = 7.0 Hz), 3H], [1.22 (d, J = 5.8 Hz) and 0.97 (d, J = 7.0 Hz), 3H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 175.0, 166.2, 141.7, 140.8, 138.3, 137.9, 136.7, 135.7, 132.9, 132.8, 130.2, 129.52, 129.50, 128.7, 128.6, 128.5, 128.29, 128.26, 128.23, 127.6, 127.4, 126.1, 125.0, 124.9, 124.6, 65.09, 65.07, 60.3, 60.0, 52.4, 52.3, 45.3, 44.9, 21.38, 21.35, 15.8, 15.6, 14.2, 13.8; IR (neat) 1725, 1271 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{23}H_{26}O_4$ (M^+) 366.1831, found 366.1845.

(*E*,3*S*)-6-Hydroxy-2-methyl-3-*m*-tolylhex-4-enoic Acid Ethyl Ester (16). Sodium ethoxide (1.82 mL, 1.0 M solution in ethanol) was added to a solution of allylic benzoate **15** (222 mg, 0.61 mmol) in ethanol (1.2 mL). The mixture was stirred for 7 h at room temperature under an argon atmosphere and neutralized with saturated aqueous NH_4Cl solution. The solvent was removed at reduced pressure, and the resulting residue was dissolved in EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to afford allylic alcohol **16** (156 mg) in 98% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.20 (t, J = 7.5 Hz) and 7.16 (t, J = 7.8 Hz), 1H], [7.04 (d, J = 7.2 Hz and 7.00−6.97 (m), 3H], [5.87 (dd, J = 15.2, 8.6 Hz) and 5.81 (dd, J = 15.4, 9.1 Hz), 1H], [5.73 (td, J = 15.2, 5.3 Hz) and 5.66 (td, J = 15.3, 5.6 Hz), 1H], [4.18−4.11 (m) and 3.93−3.86 (m), 2H], [4.12 (t, J = 5.7 Hz) and 4.05 (t, J = 5.4 Hz, 2H], [3.46 (t, J = 9.5 Hz) and 3.40 (t, J = 9.7 Hz), 1H], 2.82−2.75 (m, 1H), [2.34 (s) and 2.31 (s), 3H], [1.34 (t, J = 6.0 Hz) and 1.28 (t, J = 6.1 Hz), 1H], [1.26 (t, J = 7.2 Hz) and 0.98 (t, J = 7.1 Hz), 3H], [1.21 (d, J = 6.9 Hz) and 0.96 (d, J = 6.9 Hz), 3H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 175.3, 142.1, 141.2, 138.2, 137.8, 133.3, 132.1, 131.3, 130.1, 128.7, 128.5, 128.4, 128.2, 127.4, 127.3, 124.9, 124.6, 63.13, 63.08, 60.3, 60.0, 52.3, 52.2, 45.4, 45.0, 21.4, 21.3, 15.8, 15.5, 14.2, 13.8; IR (neat) 3444, 1732 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_2$ (M^+ − H_2O) 244.1463, found 244.1464.

(3*S*)-6-Hydroxy-2-methyl-3-*m*-tolylhexanoic Acid Ethyl Ester (17). To a solution of allylic alcohol **16** (264.0 mg, 1.01 mmol) in ethanol (2.0 mL) was added PtO_2 (5 mg) at room temperature. After 7 h at room temperature under a hydrogen atmosphere, the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to afford alcohol **17** (235.1 mg) in 88% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.18 (t, J = 7.7 Hz) and 7.15 (t, J = 8.1 Hz), 1H], [7.02 (d, J = 7.4 Hz) and 6.99 (d, J = 7.6 Hz), 1H], 6.96−6.92 (m, 2H), [4.18 (q, J = 7.1 Hz) and 3.92−3.86 (m), 2H], [3.57 (t, J = 6.3 Hz) and 3.54 (t, J = 6.3 Hz), 2H], [2.79 (ddd, J = 11.8, 8.4, 3.4 Hz) and 2.73 (dt, J = 10.4, 4.2 Hz), 1H], 2.68−2.60 (m, 1H), [2.33 (s) and 2.31 (s), 3H], [1.89−1.82 (m) and 1.68−1.59 (m), 2H], 1.39−1.25 (m, 3H), 1.29 (t, J = 7.1 Hz) and 0.99 (t, J = 7.1 Hz), 3H], [1.21 (d, J = 6.9 Hz) and 0.90 (d, J = 6.9 Hz), 3H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 175.6, 142.4, 141.9, 137.9, 137.5, 129.00, 128.95, 128.2, 128.0, 127.3, 127.1, 125.2, 125.1, 62.6, 62.4, 60.3, 59.9, 48.6, 48.3, 46.1, 46.0, 30.6, 30.5, 27.8, 21.4, 16.2, 14.8, 14.2, 13.8; IR (neat) 3437, 1731 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{16}H_{24}O_3$ (M^+) 264.1725, found 264.1725.

(3*S*)-2-Methyl-6-oxo-3-*m*-tolylhexanoic Acid Ethyl Ester (18). To a solution of alcohol **17** (236.7 mg, 0.90 mmol) in dry CH_2Cl_2 (9.0 mL) were added NaOAc (490 mg, 5.97 mmol), molecular sieves (4 Å, 400 mg), and PCC (429 mg, 1.99 mmol) at 0 °C. After 2 h at 0 °C, the mixture was diluted with ether. The mixture was stirred for 0.5 h and filtered through a pad of Florisil. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 7:1) to afford aldehyde **18** (198.0 mg) in 84% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ [9.66 (t, J = 1.1 Hz) and 9.60 (t, J = 1.4 Hz), 1H], [7.19 (t, J = 7.5 Hz) and 7.15 (t, J = 7.7 Hz), 1H], [7.04 (d, J = 7.5) and 7.01 (d, J = 7.5 Hz), 1H], 6.93−6.90 (m, 2H), [4.19 (q, J = 7.1 Hz) and 3.93−3.84 (m), 2H], 2.80−2.61 (m, 2H), [2.33 (s) and 2.31 (s), 3H], [2.28−2.13 (m) and 2.00−1.93 (m), 3H], 1.90−1.78 (m, 1H), [1.30 (t, J = 7.2 Hz) and 0.98 (t, J = 7.1 Hz), 3H], [1.25 (d, J = 6.9 Hz) and 0.91 (d, J = 6.8 Hz), 3H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 175.2, 141.4, 140.8, 138.2, 137.8, 128.9, 128.8, 128.4, 128.2, 127.6, 127.5, 125.2, 125.1, 60.4, 59.9, 48.3, 47.9, 46.0, 45.8, 42.0, 41.9, 26.8, 24.1, 21.4, 21.3, 16.3, 14.9, 14.1, 13.8; IR (neat) 2723, 1730 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1569.

(*E*,3*S*)-8-Hydroxy-2,7-dimethyl-3-*m*-tolyloct-6-enoic Acid Ethyl Ester (20). A mixture of 2-(triphenylphosphoranylidene)-propionaldehyde (226 mg, 0.71 mmol), aldehyde **18** (155.2 mg, 0.59 mmol), and toluene (2.0 mL) was refluxed for 8 h. The mixture was filtered through a pad of silica gel, and the filtrate was concentrated to give crude enal **19**. The crude product was dissolved in ethanol (2.0 mL), and $NaBH_4$ (45 mg, 1.19 mmol) was added at 0 °C. After 0.5 h at the same temperature, the mixture was quenched with saturated aqueous NH_4Cl, and ethanol was removed at reduced pressure. The resulting residue was dissolved in EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to afford allylic alcohol **20** (140.0 mg) in 78% yield from aldehyde **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.18 (t, J = 7.5 Hz) and 7.15 (t, J = 7.9 Hz), 1H], [7.02 (d, J = 7.5 Hz) and 6.99 (d, J = 7.9

Hz), 1H], 6.95−6.91 (m, 2H), [5.33 (t, J = 6.5 Hz) and 5.29 (t, J = 6.9 Hz), 1H], [4.17 (q, J = 6.9 Hz) and 3.95−3.86 (m), 4H], [2.78 (ddd, J = 11.3, 8.5, 2.9 Hz) and 2.72 (dt, J = 10.2, 4.3 Hz), 1H], 2.67−2.58 (m, 1H), [2.33 (s) and 2.31 (s), 3H], [1.87−1.78 (m) and 1.70−1.62 (m), 4H], [1.50 (s) and 1.48 (s), 3H], [1.29 (dt, J = 7.1, 0.5 Hz) and 0.99 (dt, J = 7.2, 0.5 Hz), 3H], [1.20 (d, J = 6.7 Hz) and 0.89 (d, J = 6.8 Hz), 3H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 175.6, 142.3, 141.8, 137.7, 137.3, 134.93, 134.91, 129.0, 128.1, 127.8, 127.1, 127.0, 125.4, 125.3, 125.2, 125.1, 68.5, 60.2, 59.8, 48.4, 48.2, 46.1, 45.9, 34.2, 31.4, 25.31, 25.26, 21.32, 21.27, 16.1, 14.7 14.1, 13.8, 13.4; IR (neat) 3443, 1731 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{28}O_3$ (M^+) 286.1933, found 286.1937.

(*E*,3*S*)-8-Bromo-2,7-dimethyl-3-*m*-tolyloct-6-enoic Acid Ethyl Ester (8). To a solution of allylic alcohol **20** (105.0 mg, 0.34 mmol) in CH_2Cl_2 (3.4 mL) were added CBr_4 (229 mg, 0.69 mmol) and Ph_3P (136 mg, 0.52 mmol) at 0 °C. After 2 h, the mixture was diluted with hexane and filtered through a pad of silica gel. The filtrate was concentrated, and the resulting residue was purified by column chromatography (hexane/EtOAc, 20:1) to give allylic bromide **8** (112.7 mg) in 89% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.18 (t, J = 7.5 Hz) and 7.15 (t, J = 7.9 Hz), 1H], [7.02 (d, J = 7.5 Hz) and 6.99 (d, J = 8.0 Hz), 1H], 6.94−6.90 (m, 2H), [5.53 (t, J = 6.7 Hz) and 5.49 (t, J = 6.9 Hz), 1H], [4.18 (q, J = 7.1 Hz) and 3.94−3.86 (m), 4H], [2.76 (ddd, J = 11.7, 8.6, 3.0 Hz) and 2.71 (dt, J = 9.8, 5.0 Hz), 1H], 2.66−2.57 (m, 1H), [2.33 (s) and 2.31 (s), 3H], 1.85−1.75 (m, 3H), 1.70−1.62 (m, 2H), [1.57 (s) and 1.55 (s), 3H], [1.29 (t, J = 7.1 Hz) and 1.00 (t, J = 7.1 Hz), 3H], [1.20 (d, J = 7.0 Hz) and 0.89 (d, J = 6.8 Hz), 3H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 175.5, 142.1, 141.6, 137.9, 137.5, 132.3, 132.2, 130.9, 129.16, 129.14, 128.3, 128.0, 127.3, 127.2, 125.3, 125.2, 60.3, 59.9, 48.5, 48.2, 46.11, 46.06, 41.8, 41.7, 33.7, 31.0, 26.1, 26.0, 21.44, 21.41, 16.3, 14.8, 14.5, 14.3, 13.9; IR (neat) 1730 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{28}BrO_2$ (MH^+) 367.1273, found 367.1268.

Cyclization of Allylic Bromide 8. To a solution of allylic bromide **8** (62.0 mg, 0.17 mmol) in THF (17 mL) was added LHMDS (0.84 mL, 1.0 M solution in THF) at 0 °C. After 22 h at room temperature, the mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution. The solvent was removed at reduced pressure, and the residue was dissolved in EtOAc. The mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 20:1) to give a mixture of **7**, **7-*iso***, and **7-*cis*** (9.9:3.3:1, by capillary GLC analysis) in a total 86% yield, and the isomers were separated by NP-preparative HPLC. Data for cylopentanecarboxylate **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6, 1H), 6.96 (s, 1H), 6.96 (d, J = 7.6 Hz), 1H], 4.83 (t, J = 1.6 Hz, 1H), 4.79 (d, J = 0.8 Hz, 1H), 4.16−4.04 (m, 2H), 3.96 (dd, J = 11.5, 6.8 Hz, 1H), 2.48 (t, J = 8.7 Hz, 1H), 2.31 (s, 3H), 2.11−2.05 (m, 1H), 2.04−1.96 (m, 1H), 1.96−1.90 (m, 2H), 1.77 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 145.3, 141.1, 137.4, 129.4, 127.8, 127.0, 125.6, 111.9, 60.4, 59.5, 55.6, 51.8, 30.0, 29.5, 23.3, 22.9, 21.5, 14.2; IR (neat) 1719 cm^{-1}; $[\alpha]^{20}_D$ = +46.5 (c 0.43, $CHCl_3$); HRMS (EI) m/z calcd for $C_{19}H_{26}O_2$ (M^+) 286.1933, found 286.1932. Data for **7-*iso***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, J = 7.9 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.93 (br s, 2H), 4.87 (q, J = 1.4 Hz, 1H), 4.77 (d, J = 0.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.73 (t, J = 10.1 Hz, 1H), 3.27 (t, J = 9.8 Hz, 1H), 2.30 (s, 3H), 2.13−2.08 (m, 2H), 2.01−1.95 (m, 2H), 1.65 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 144.4, 139.6, 137.4, 129.2, 127.8, 127.4, 125.3, 111.9, 60.5, 55.6, 55.0, 54.9, 26.5, 25.6, 23.2, 21.5, 14.2, 11.3; IR (neat) 1726 cm^{-1}; $[\alpha]^{20}_D$ = −25.1 (c 0.25, $CHCl_3$); HRMS (EI) m/z calcd for $C_{19}H_{26}O_2$ (M^+) 286.1933, found 286.1935. Data for **7-*cis***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, J = 7.7 Hz, 1H), 7.00 (s, 1H), 6.99 (d, J = 7.4 Hz, 2H), 4.86 (d, J = 0.9 Hz, 1H), 4.78 (s, 1H), 3.54 (dq, J = 7.1, 1.6 Hz, 2H), 3.38 (dd, J = 12.5, 5.9 Hz, 1H), 2.93 (dd, J = 11.4, 7.0 Hz, 1H), 2.31 (s, 3H), 2.09 (dq, J = 11.9, 6.0 Hz, 1H), 2.03−1.98 (m, 1H), 1.96 (dq, J = 6.0, 1.2 Hz, 1H), 1.79 (dq, J = 12.2, 6.3 Hz, 1H), 1.63 (s, 3H), 1.18 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 145.0, 141.1, 137.1, 129.2, 127.6, 127.3, 125.5, 111.3, 60.1, 59.1, 55.0, 52.8, 30.8, 29.1, 23.5, 21.4, 13.6; IR (neat) 1727 cm^{-1}; $[\alpha]^{20}_D$ = +15.5 (c 0.075, $CHCl_3$); HRMS (EI) m/z calcd for $C_{19}H_{26}O_2$ (M^+) 286.1933, found 286.1930.

(1*R*,2*S*,5*R*)-2-Acetyl-1-methyl-5-*m*-tolylcyclopentanecarboxylic Acid Ethyl Ester (22). To a solution of cyclopentanecarboxylate **7** (11.0 mg, 0.038 mmol) in EtOAc (1 mL) were added a few drops of saturated ozone solution in EtOAc every 20 min at −78 °C until the starting material disappeared on TLC. After removal of excess ozone by a stream of nitrogen, Ph_3P (30 mg, 0.11 mmol) was added to the mixture. It was stirred overnight and filtered through a pad of silica gel. The filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give ketone **22** (9.4 mg) in 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.99 (d, J = 7.5 Hz, 1H), 4.12 (dq, J = 7.1, 1.4 Hz, 2H), 3.68 (dd, J = 9.8, 6.7 Hz, 1H), 2.85 (t, J = 8.1 Hz, 1H), 2.33 (s, 3H), 2.17 (s, 3H), 2.20−2.00 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 176.5, 140.3, 137.4, 129.8, 127.8, 127.3, 125.9, 63.4, 60.7, 54.7, 52.2, 30.0, 29.9, 27.8, 22.5, 21.5, 14.0; IR (neat) 1712, 1233 cm^{-1}; $[\alpha]^{20}_D$ = +56.4 (c 0.70, $CHCl_3$); HRMS (EI) m/z calcd for $C_{18}H_{24}O_3$ (M^+) 288.1725, found 288.1721.

(1*R*,2*R*,5*R*)-2-Acetyl-1-methyl-5-*m*-tolylcyclopentanecarboxylic Acid Ethyl Ester (22-*iso*). To a solution of cyclopentanecarboxylate **7-*iso*** (24.6 mg, 0.086 mmol) in EtOAc (1 mL) were added a few drops of saturated ozone solution in EtOAc every 10 min for 2 h, and 0.5 mL of saturated ozone solution in EtOAc was added to the mixture every 1 h for 4 h at −78 °C. After removal of excess ozone by a stream of nitrogen, Ph_3P (68 mg, 0.26 mmol) was added to the mixture. The mixture was stirred overnight and filtered through a pad of silica gel. The filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give ketone **22-*iso*** (14.0 mg) in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.76 (br s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.71 (t, J = 9.5 Hz, 1H), 3.66 (dd, J = 12.1, 8.2 Hz, 1H), 2.38−2.29 (m, 1H), 2.31 (s, 3H), 2.17 (dq, J = 12.2, 6.3 Hz, 1H), 2.06 (s, 3H), 2.10−2.03 (m, 1H), 1.95 (dtd, J = 13.2, 9.5, 6.3 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 176.5, 138.2, 137.5, 129.2, 127.9, 127.8, 125.4, 61.1, 61.0, 55.3, 30.1, 26.7, 22.4, 21.4, 14.2, 12.8; IR (neat) 1712, 1268 cm^{-1}; $[\alpha]^{20}_D$ = −87.3 (c 0.48, $CHCl_3$); HRMS (EI) m/z calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1725.

Epimerization of Ketone 22 to 22-*iso*. A mixture of ketone **22** (7.0 mg, 0.024 mmol) and DBU (0.5 mL) was stirred for 20 h at room temperature and filtered through a pad of silica gel to give a mixture of ketone **22** and epimer **22-*iso*** (6.8 mg, 1:4.2 by 400 MHz ^{1}H NMR analysis) in a total 97% yield. The mixture was separated by column chromatography on silica gel (hexane/EtOAc, 10:1).

Epimerization of Ketone 22-*iso* to 22. A mixture of ketone **22-*iso*** (5.5 mg, 0.019 mmol) and DBU (0.5 mL) was stirred for 36 h at room temperature and then filtered through a pad of silica gel to give a mixture of ketone **22-*iso*** and epimer **22** (5.5 mg, 4.2:1 by 400 MHz ^{1}H NMR analysis). The mixture was separated by column chromatography on silica gel (hexane/EtOAc, 10:1).

Cyclopentanecarboxylate 7 from 22. A mixture of methyltriphenylphosphonium iodide (56 mg, 0.14 mmol) and *n*-BuLi (0.078 mL, 1.6 M solution in hexane) in THF (1.0 mL) was stirred for 30 min at −78 °C. To the mixture was added a solution of ketone **22** (8.1 mg, 0.028 mmol) in THF (0.5 mL) at −78 °C, and the mixture was stirred for 10 h at room temperature. The reaction mixture was quenched with a few drops of saturated aqueous NH_4Cl solution and filtered

through a pad of silica gel. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 20:1) to afford cyclopentanecarboxylate **7** (6.1 mg) in 76% yield.

((1*S*,2*R*,5*R*)-2-Isopropenyl-1-methyl-5-*m*-tolylcyclopentyl)methanol (23). To a solution of cyclopentanecarboxylate **7** (13.0 mg, 0.045 mmol) in dry toluene (0.9 mL) was added DIBALH (0.27 mL, 1.0 M solution in hexane) at −78 °C. The reaction mixture was stirred and slowly warmed to −30 °C over 3 h. The mixture was cooled to −78 °C again, and methanol (0.5 mL) was added to the mixture. The mixture was stirred overnight at room temperature and filtered through a pad of Celite. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to afford alcohol **23** (10.2 mg) in 93% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, J = 7.8 Hz, 1H), 7.02−6.99 (m, 3H), 4.98 (t, J = 1.5 Hz, 1H), 4.96 (s, 1H), 3.45 (br d, J = 4.1 Hz, 2H), 3.20 (dd, J = 10.9, 7.7 Hz, 1H), 2.37 (dd, J = 10.9, 6.9 Hz, 1H), 2.33 (s, 3H), 2.05−1.95 (m, 2H), 1.92 (s, 3H), 1.91−1.86 (m, 1H), 1.85−1.78 (m, 2H), 0.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 141.9, 137.4, 129.9, 127.8, 126.9, 126.0, 111.7, 68.4, 56.1, 50.4, 48.7, 29.7, 24.6, 23.0, 21.5; IR (neat) 1040 cm^{-1}; $[\alpha]^{20}_D$ = +15.2 (*c* 0.35, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M^+) 244.1827, found 244.1828.

(1*S*,2*R*,5*R*)-2-Isopropenyl-1-methyl-5-*m*-tolylcyclopentanecarbaldehyde (24). To a solution of alcohol **23** (12.0 mg, 0.050 mmol) in dry CH_2Cl_2 (1 mL) were added NaOAc (26 mg, 0.32 mmol), molecular sieves (4 Å, 22 mg), and PCC (24 mg, 1.08 mmol) at 0 °C. After 2.5 h at the same temperature, the mixture was diluted with ether and filtered through a pad of Florisil. The filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 15:1) to afford aldehyde **24** (9.2 mg) in 77% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.00 (d, J = 7.5 Hz), 6.90 (d, J = 7.9 Hz, 1H), 6.89 (s, 1H), 4.92 (t, J = 1.4 Hz, 1H), 4.92 (d, J = 1.4 Hz, 1H), 3.65 (dd, J = 11.5, 6.7 Hz, 1H), 2.54 (dd, J = 11.5, 6.7 Hz, 1H), 2.31 (s, 3H), 2.16 (dtd, J = 12.3, 6.2, 1.7 Hz, 1H), 2.10 (dq, J = 11.7, 6.2 Hz, 1H), 1.97 (dtd, J = 12.7, 6.4, 1.7 Hz, 1H), 1.88 (dq, J = 11.9, 6.7 Hz, 1H), 1.72 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 143.0, 140.2, 137.7, 129.4, 128.0, 127.2, 125.6, 113.1, 58.7, 57.3, 48.9, 30.0, 29.9, 23.4, 21.5, 19.8; IR (neat) 2710, 1721 cm^{-1}; $[\alpha]^{20}_D$ = +39.7 (*c* 0.22, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{17}H_{22}O$ (M^+) 242.1671, found 242.1672.

3-((1*S*,2*R*,5S)-2-Isopropyl-1-methyl-5-*m*-tolylcyclopentyl)propionic Acid (6). To a solution of benzyl (trimethylsilyl)acetate (46 mg, 0.21 mmol) in THF (1.0 mL) was added LDA (0.21 mL, 0.5 M solution in THF) at −78 °C. After 0.5 h, a solution of aldehyde **24** (10.0 mg, 0.041 mmol) in THF (0.5 mL) was added to the mixture at the same temperature, and the mixture was stirred for 2 h at −25 °C. The mixture was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give crude benzyl ester **25**. The crude product was dissolved in EtOAc (2.0 mL), and PtO_2 (1 mg) was added. The mixture was stirred overnight at ambient temperature under a hydrogen atmosphere. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to afford carboxylic acid **6** (11.0 mg) in 92% overall yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.94 (s, 1H), 2.91 (t, J = 7.5 Hz, 1H), 2.49−2.35 (m, 2H), 2.33 (s, 3H), 2.11−1.98 (m, 2H), 1.89−1.73 (m, 3H), 1.72−1.65 (m, 1H), 1.60−1.50 (m, 2H), 0.96 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 144.4, 137.2, 130.0, 127.7, 126.6, 126.1, 56.3, 53.9, 46.7, 30.9, 30.1, 29.9, 28.6, 27.8, 24.1, 23.5, 22.2, 21.5; IR (neat) 1708, 1297 cm^{-1}; $[\alpha]^{20}_D$ = +38.2 (*c* 1.03, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{19}H_{28}O_2$ (M^+) 288.2089, found 288.2087.

(3*R*,3a*S*,10b*S*)-3-Isopropyl-3a,9-dimethyl-2,3,3a,4,5,10b-hexahydro-1*H*-benzo[*e*]azulen-6-one (5). A mixture of carboxylic acid **6** (25.3 mg, 0.089 mmol) and PPA (1 mL) was stirred overnight at 90 °C. Crushed ice was added, and the mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 20:1) to give ketone **5** (21.0 mg) in 89% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.07 (s, 1H), 3.18 (dd, J = 12.4, 5.5 Hz, 1H), 2.83 (t, J = 6.4 Hz, 1H), 2.83 (t, J = 7.2 Hz, 1H), 2.38 (s, 3H), 2.14 (dt, J = 12.8, 6.4 Hz, 1H), 2.09 (dt, J = 10.9, 5.5 Hz, 1H), 1.98 (ddd, J = 11.4, 5.7, 5.7 Hz, 1H), 1.85−1.73 (m, 3H), 1.41−1.25 (m, 2H), 0.97 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 142.2, 142.1, 137.2, 127.85, 127.82, 126.9, 59.8, 53.0, 43.7, 41.6, 33.7, 30.1, 29.4, 28.5, 27.7, 23.5, 22.2, 21.7; IR (neat) 1673 cm^{-1}; $[\alpha]^{20}_D$ = −140.9 (*c* 0.64, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{19}H_{26}O$ (M^+) 270.1984, found 270.1984.

(3*R*,3a*S*,10b*S*)-3-Isopropyl-3a,6,9-trimethyl-1,2,3,3a,4,-10b-hexahydrobenzo[*e*]azulene (26). To a solution of ketone **5** (8.0 mg, 0.030 mmol) in ether (1.0 mL) was added methyllithium (0.2 mL, 1.5 M solution in ether) at −78 °C, and the mixture was stirred for 1 h at the same temperature. $SOCl_2$ (0.04 mL, 0.54 mmol) was then added to the mixture. After 10 min at −78 °C, the mixture was stirred for 1 h at room temperature, poured into ice, and extracted with ether (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane) to afford a mixture of *endo*-olefin **26** and *exo*-olefin **27** (7.0 mg, 5.3:1 by 500 MHz ^{1}H NMR analysis) in a total 88% yield. The *endo*-olefin **26** and *exo*-olefin **27** were separated by column chromatography on $AgNO_3$-impregnated silica gel (hexane). Data for *endo*-olefin **26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 5.85−5.83 (m, 1H), 2.83 (t, J = 9.3 Hz, 1H), 2.57 (br d, J = 15.8 Hz, 1H), 2.35 (s, 3H), 2.20 (t, J = 1.5 Hz, 3H), 2.21−2.15 (m, 1H), 1.92−1.88 (m, 1H), 1.84−1.79 (m, 1H), 1.77−1.68 (m, 1H), 1.30−1.19 (m, 2H), 0.97 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.8, 135.4, 130.5, 128.4, 126.6, 126.0, 125.9, 59.6, 53.6, 42.3, 41.2, 30.6, 28.3, 27.7, 27.2, 25.7, 23.6, 22.8, 21.3; IR (neat) 1574, 1496 cm^{-1}; $[\alpha]^{20}_D$ = −320.1 (*c* 0.10, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{20}H_{28}$ (M^+) 268.2191, found 268.2190.

Reduction of *endo*-Olefin 26 with 10% Pd/C. A mixture of *endo*-olefin **26** (2.3 mg, 0.0086 mmol) and 10% Pd/C (2 mg) in ethanol (1 mL) was stirred for 1 h at 15 °C under a hydrogen atmosphere. The mixture was filtered over a pad of Celite to give only 7-*epi*-presphaerene (**1′**) (2.3 mg) in quantitative yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.95 (s, 1H), 3.14 (dd, J = 12.6, 5.2 Hz, 1H), 3.05−2.98 (m, 1H), 2.36 (s, 3H), 1.93−1.82 (m, 4H), 1.82−1.72 (m, 2H), 1.65 (td, J = 14.0, 1.0 Hz, 1H), 1.47−1.30 (m, 3H), 1.34 (d, J = 7.0 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.9, 134.4, 126.3, 126.0, 123.8, 59.2, 53.3, 40.3, 38.7, 35.6, 32.3, 30.0, 27.80, 27.75, 25.1, 24.2, 21.9, 21.6, 21.1; IR (neat) 1455 cm^{-1}; $[\alpha]^{20}_D$ = −91.8 (*c* 0.20, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{20}H_{30}$ (M^+) 270.2348, found 270.2348.

Reduction of *endo*-Olefin 26 with PtO_2. A mixture of *endo*-olefin **26** (2.5 mg, 0.0093 mmol) and PtO_2 (1 mg) in ethanol (1 mL) was stirred for 1 h at 15 °C under a hydrogen atmosphere. The mixture was filtered over a pad of Celite to give a mixture of (−)-presphaerene (**1**) and **1′** (2.5 mg, 1:9 by 400 MHz ^{1}H NMR analysis) in quantitative yield.

(3*R*,3a*S*,10b*S*)-3-Isopropyl-3a,9-dimethyl-6-methylene-1,2,3,3a,4,5,6,10b-octahydrobenzo[*e*]azulene (27). A mixture of methyltriphenylphosphonium iodide (112 mg, 0.28

mmol) and *n*-BuLi (0.15 mL, 1.6 M solution in hexane) in THF (2.0 mL) was stirred for 0.5 h at −78 °C. To the mixture was added ketone **5** (10.7 mg, 0.040 mmol) in THF (1.0 mL) at the same temperature. After 2 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl solution and filtered through a pad of silica gel. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane) to give *exo*-olefin **27** (9.5 mg) in 89% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 5.11 (dd, J = 2.2, 1.3 Hz, 1H), 4.86 (d, J = 2.5 Hz, 1H), 2.95 (dd, J = 12.7, 5.5 Hz, 1H), 2.45 (td, J = 13.2, 4.1 Hz, 1H), 2.35−2.29 (m, 1H), 2.33 (s, 3H), 1.95 (td, J = 12.8, 4.0 Hz, 1H), 1.90−1.81 (m, 3H), 1.80−1.71 (m, 2H), 1.42−1.37 (m, 1H), 1.33−1.24 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 141.4, 139.9, 136.3, 127.3, 126.1, 113.7, 59.3, 54.8, 40.8, 39.9, 32.4, 29.7, 27.9, 27.8, 24.7, 24.2, 24.8, 21.4; IR (neat) 1628, 1448 cm^{-1}; $[\alpha]^{20}_D$ = −165.3 (*c* 0.46, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{20}H_{28}$ (M^+) 268.2191, found 268.2193.

Reduction of *exo*-Olefin 27 with 10% Pd/C. A mixture of *exo*-olefin **27** (2.3 mg, 0.0086 mmol) and 10% Pd/C (2 mg) in ethanol (1.0 mL) was stirred for 1 h at 15 °C under a hydrogen atmosphere. The mixture was filtered over a pad of Celite to give **1′** (2.3 mg) in quantitative yield.

Reduction of *exo*-Olefin 27 with PtO_2. A mixture of *exo*-olefin **27** (9.5 mg, 0.035 mmol) and PtO_2 (1 mg) in ethanol (2.0 mL) was stirred for 3 h at 15 °C under a hydrogen atmosphere. The mixture was filtered through a pad of Celite to give a mixture of **1** and **1′** (9.5 mg, 3:1 by 500 MHz ^{1}H NMR analysis) in quantitative yield. **1** and **1′** were separated by column chromatography on $AgNO_3$-impregnated silica gel (hexane). Data for **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (d, J = 7.5 Hz, 1H), 6.92 (s, 1H), 6.87 (d, J = 7.4 Hz, 1H), 3.20 (dd, J = 12.2, 5.6 Hz, 1H), 3.09−3.04 (m, 1H), 2.28 (s, 3H), 2.03−1.93 (m, 2H), 1.90−1.77 (m, 4H), 1.74−1.66 (m, 2H), 1.44−1.33 (m, 2H), 1.31 (d, J = 7.6 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.9, 135.0, 129.5, 127.6, 126.2, 58.9, 53.3, 41.7, 41.6, 32.9, 28.6, 28.5, 28.2, 27.9, 24.2, 24.0, 21.3, 21.2, 18.3; IR (neat) 1455 cm^{-1}; $[\alpha]^{20}_D$ = −90.2 (*c* 0.40, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{20}H_{30}$ (M^+) 270.2348, found 270.2347.

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Supporting Information Available: ^{1}H NMR comparison of natural and synthetic **1** and **1′**, the most stable conformations of *endo*-olefin **26** and *exo*-olefin **27**, along with copies of the ^{1}H and ^{13}C NMR spectra for **1**, **1′**, **5**−**20**, and **22**−**27**, ^{1}H−^{1}H COSY, ^{1}H−^{13}C COSY, and DEPT spectra for **1**, **1′**, **5**, **7**, **7-*iso***, and **7-*cis***, and NOE spectra for **1**, **1′**, **7**, **7-*iso***, and **7-*cis*** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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