Synthesis of Carbocycles via Intramolecular Conjugate Additions: Another Solution to the Terpenoid Side Chain Stereochemistry Problem

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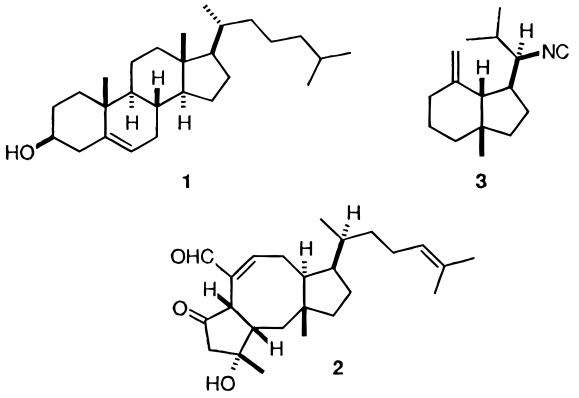
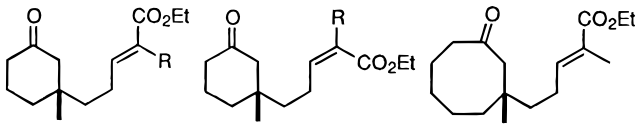
Intramolecular conjugate additions of keto esters **7**−**11**, mediated by pyrrolidine−acetic acid, provide perhydroindans or bicyclo[6.3.0]undecanes with high levels of diastereoselectivity at the acyclic stereogenic center. Levels of acyclic diastereoselection depend on starting unsaturated ester olefin geometry.

Many terpenoids contain side chains attached to carbocyclic ring systems via a stereogenic carbon. Cholesterol (**1**),[1] ophiobolin C (**2**),[2] and axisonitrile-1 (**3**)[3] are only three of numerous examples that could be cited. The problem of establishing stereochemistry at the side chain stereogenic center, relative to stereogenic centers in the carbocycle, is a long-standing problem in organic synthesis, and a number of creative solutions have been developed over the years.[4,5] Of course, no general solution has been developed because the stereochemical relationships required by one natural product or another are quite different. Nonetheless, any solution to this problem usually has a certain set of natural products for which it is relevant. During the course of a synthesis of axamide-4 and related natural products, we discovered an intramolecular conjugate addition reaction that afforded a carbocycle with an appended side chain in which both the ring and side chain stereogenic centers were established with an excellent level of relative stereochemical control.[6] Specifically, it was found that treatment of ketone **4** with pyrrolidine and acetic acid in tetrahydrofuran gave perhydroindans **5** (15%) and **6** (60%) (Scheme 1). The high degree of stereocontrol in the formation of **6** was surprising. Since this observation obviously offered another potential solution to the terpenoid side chain stereochemistry problem, we decided to investigate the generality of the process. The results of this study are reported herein.

Ketones **7**−**11** were selected as substrates for study. It was felt that substrates **7** and **9** would complement one another somewhat in terms of stereochemistry at the acyclic stereogenic center, substrates **8** and **10** would examine the importance of olefin geometry on the stereochemical course of the cyclization, and substrate **11** would determine whether results obtained in the perhydroindan-producing systems could be extrapolated to other fused carbocyclic systems.





7 R = Me **8** R = Me **11**
9 R = $(CH_2)_2CH{=}CMe_2$ **10** R = $(CH_2)_2CH{=}CMe_2$

Cyclization substrates **7**−**10** were prepared as described in Scheme 2. Peterson olefination of aldehyde **12** using the enolate derived from ethyl 2-(trimethylsilyl)-propanoate provided a 1:1 mixture of unsaturated esters **13** and **14**.[6,7] On the other hand, Wittig olefination of **12** using the appropriate stabilized phosphorane gave an 8:1 mixture of **13** and **14**, respectively.[8] Although the isomeric esters were inseparable by chromatography, stereochemical assignments were easily made on the basis of the chemical shift of the vinylic proton, which was much further upfield for **14** (δ 5.90) than for **13** (δ 6.75) due to steric inhibition of resonance in **14**. Acid-promoted hydrolysis of the aforementioned mixtures of **13** and **14** provided a 78% yield of a mixture of keto esters **7** and **8** which could be separated by column chromatography. In addition, isomerization of **8** to **7** was ac-

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1996.

(1) For one synthesis that addresses the side chain stereochemistry problem, see: Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907.

(2) For syntheses that address the side chain stereochemistry problem, see: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735 and references cited therein.

(3) For a synthesis that addresses the side chain stereochemistry problem, see: Guevel, A.-C.; Hart, D. J. *Synlett* **1994**, 169; *J. Org. Chem.* **1996**, *61*, 473−479.

(4) For reviews, see: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. Redpath, B. J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75.

(5) For a categorization of more recent methods, see: Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412. For some additional methods, see: Mandai, T.; Matsumoto, T.; Kawada, M. Tsuji, J. *J. Org. Chem.* **1992**, *57*, 6090. Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986**, *108*, 7055. Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. Ficini, J.; D'Angelo, J.; Noire, J. *J. Am. Chem. Soc.* **1974**, *96*, 1213.

(6) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Lai, C.-S. *J. Org. Chem.* **1992**, *57*, 2018. This article also describes the preparation of aldehyde **12**.

(7) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288. For overviews of the Peterson olefination, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon Press: New York, 1991; Vol. 1, p 729. Chan, T.-H. *Acc. Chem. Res.* **1977**, *10*, 442.

(8) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.

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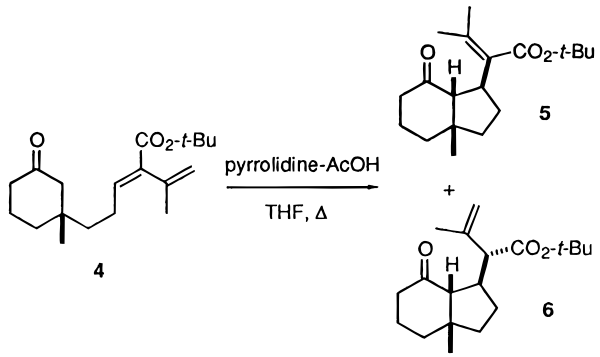
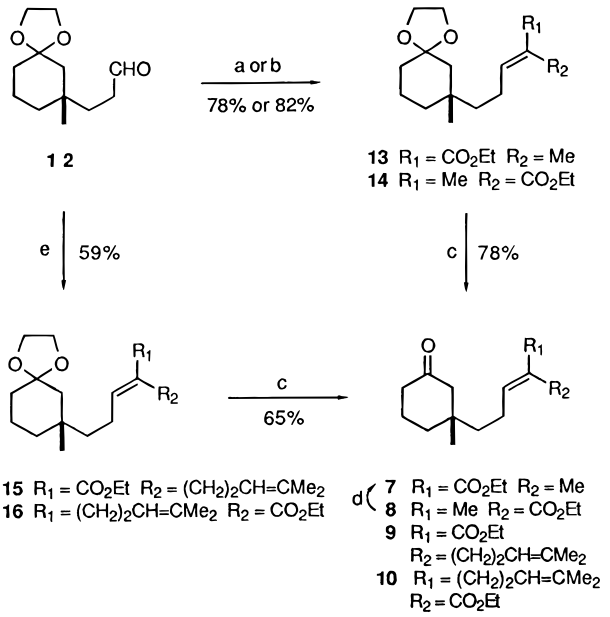
Scheme 1



Scheme 2

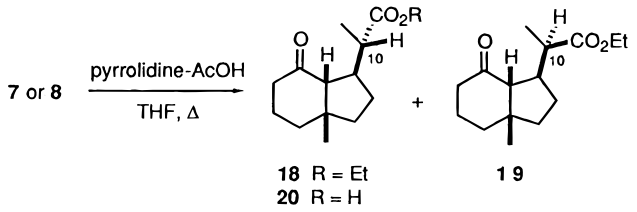


(a) $Me_3SiCH(Me)CO_2Et$–LDA, THF (**13**:**14** = 1:1) (b) $Ph_3P{=}C(Me)CO_2Et$, PhH, Δ (**13**:**14** = 8:1) (c) HCl, *t*-BuOH, Et_2O (d) PhSH, AIBN, PhH, Δ (e) $Me_2C{=}CH(CH_2)_2CH(SiMe_3)CO_2Et$ (**17**)–LDA, THF (**15**:**16** = 1:4)

complished in 91% yield using catalytic amounts of thiophenol and AIBN in benzene at reflux.[9] The syntheses of **9** and **10** were accomplished from **12** in a similar manner. Thus, ester **17** was prepared in 53% yield by alkylating the lithium enolate of ethyl 2-(trimethylsilyl)-acetate with 1-iodo-4-methyl-3-pentene.[10] Peterson olefination of aldehyde **12** with **17** provided a 4:1 mixture of unsaturated esters **16** and **15**, respectively, in 59% yield. Once again, stereochemical assignments were based on the chemical shifts of the vinylic protons which appear at δ 5.83 and 6.74 for **16** and **15**, respectively. Hydrolysis of the mixture of ketals provided a mixture of ketones **9** and **10** in 65% yield. Once again, these cyclization substrates were separated and purified by chromatography over silica gel.

With cyclization substrates **7**−**10** in hand, their pyrrolidine-mediated cyclizations were examined under several conditions.[11] No cyclization occurred when substrates were treated with 1 equiv of either pyrrolidine or acetic acid in tetrahydrofuran at reflux for 6 h. If 1 equiv of pyrrolidine and a catalytic amount of acetic acid were used, cyclization occurred slowly, but mass balance upon product isolation was low. In addition, it was found that the *Z*-olefins isomerized to the *E*-olefins to some extent under these conditions. It was eventually determined that these substrates were all converted to perhydroindans in a timely manner upon treatment with 1 equiv of pyrrolidine and 2.3 equiv of acetic acid in tetrahydrofuran at reflux, followed by an aqueous acidic workup. For example, these conditions isomerized substrate **7** to a 99:1 mixture (by GC) of perhydroindans **18** and **19**, respectively in 78% yield (Scheme 3). When substrate **8** was subjected to the same reaction conditions, a separable 3:1 mixture (by GC) of **18** and **19** was obtained in 55% yield. The stereochemistry of **18** was determined by X-ray crystallographic analysis of carboxylic acid **20**, prepared in 93% by hydrolysis of **18** using lithium hydroxide in aqueous methanol.[12] The stereochemistry of **19** was determined by epimerization experiments. Thus, treatment of **18** with an excess of sodium ethoxide in ethanol at reflux afforded a 1:1 mixture of **18** and **19**.[13] In a similar manner, substrate **9** was converted to perhydroindan **21** in 43% yield and **10** was isomerized to a separable 6:1 mixture of **21** and **22**, respectively, in 72% yield (Scheme 4). The stereochemical assignments for the perhydroindans were based on analogy with results obtained with substrates **7** and **8**.

Scheme 3



Substrate	% Yield	18:19
7	78%	99:1
8	55%	3:1

It is interesting to note the similarity between the systems studied. In each case, cyclization of the *E*-isomer (**7** and **9**) was highly diastereoselective, whereas cyclization of the *Z*-isomer (**8** and **10**) gave a mixture of epimers at C_{10}. In each case the major product was the same

(9) Henrick, C. A.; Willy, W. E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1. Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260. Annuziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674.

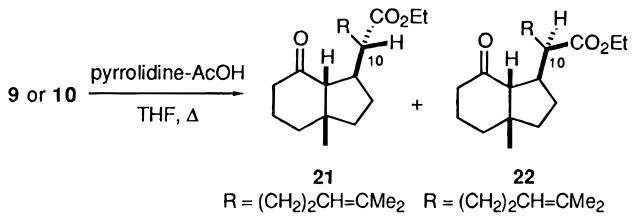
(10) Biernacki, W.; Gdula, A. *Synthesis* **1979**, *37*.

(11) For pioneering studies related to the stereochemical course of intramolecular conjugate additions, see: Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. For reviews of relevant conjugate additions, see: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. Hickmott, P. W.; *Tetrahedron* **1982**, *38*, 3363. Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Ed.; Wiley: New York, 1991; Vol. 26. Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4. Whitesell, J. K. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 6, p 703. For specific articles of interest, see: Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1984**, 715. Hirai, Y.; Hagiwara, A.; Yamazaki, T. *Heterocycles* **1986**, *24*, 571. D'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459. Kozikowski, A. P.; Greco, M. N.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 6873. Pandit, U. K.; Juisman, H. O. *Tetrahedron Lett.* **1967**, *8*, 3901. D'Angelo, J.; Guingant, A.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1988**, *29*, 2667. Guingant, A. *Tetrahedron: Asymmetry* **1991**, *2*, 415. Hori, K.; Kazuno, H.; Nomura, K.; Yoshii, E. *Tetrahedron Lett.* **1993**, *34*, 2183. Yoshii, E.; Hori, K.; Nomura, K.; Yamaguchi, *Synlett* **1995**, 568.

(12) We thank Dr. Judith C. Gallucci for performing X-ray crystallographic analyses of acids **20** and **36** at The Ohio State University Crystallography Facility.

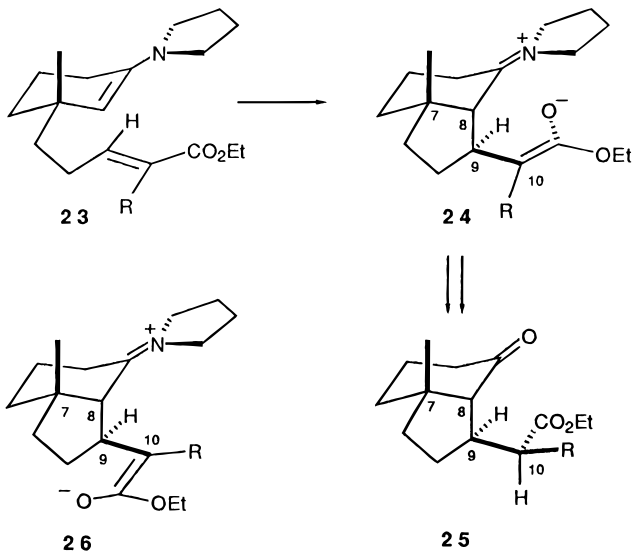
(13) It has previously been established that perhydroindans of type **18** are thermodynamically more stable as the cis isomers.[6] Thus, the observed epimerization is surely occurring at adjacent to the carbethoxy group.

Scheme 4



Substrate	% Yield	21:22
9	43%	100:0
10	72%	6:1

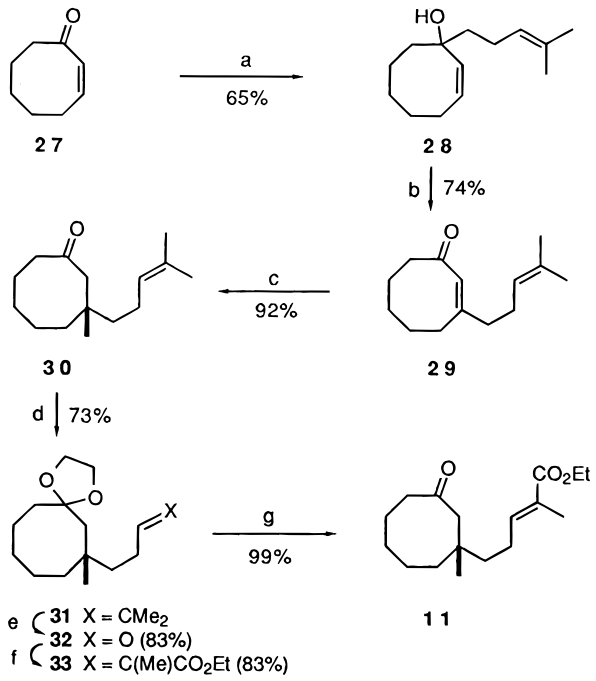
Scheme 5



diastereomeric perhydroindan, regardless of starting olefin geometry. Moreover, the mixtures obtained from these cyclizations appeared to be the result of kinetic protonation, since no isomerization was observed when the products were resubjected to the reaction conditions, whereas base-promoted isomerization led to a 1:1 mixture of epimers at C_{10} as described above.

Although more effort is required to determine the true origin of the diastereoselectivity observed in these cyclizations, one rationalization of the results is shown in Scheme 5. Upon treatment with pyrrolidine and acetic acid, ketones **7** and **9** might be converted into enamines of type **23**. Subsequent conjugate addition would lead to the formation of an axial C_8-C_9 bond, to avoid developing $A^{1,3}$ strain.[14] Moreover, the resulting enolate or enol might be born in conformation **24**, which minimizes development of charge separation.[15] Subsequent protonation would afford products of type **25** upon workup. The relative stereochemistry at C_7, C_8, and C_9 is consistent with results previously reported by Heathcock and follows from Seebach's topological rule for intermolecular conjugate additions.[16,17] The acyclic diastereoselection observed at C_{10} might arise from kinetic protonation of **24** from the α-face because the β-face of the enolate or enol is blocked by the iminium ion.

Scheme 6



(a) $Li(CH_2)_2CH=CMe_2$, $CeCl_3$, THF (b) PCC, CH_2Cl_2
(c) Me_2CuLi, Me_3SiCl, THF; TBAF, THF (d) $HOCH_2CH_2OH$, *p*-TsOH, $(MeO)_3CH$ (e) O_3, $NaHCO_3$, MeOH-CH_2Cl_2
(f) $Ph_3P=C(Me)CO_2Et$, PhH, Δ (g) HCl, THF

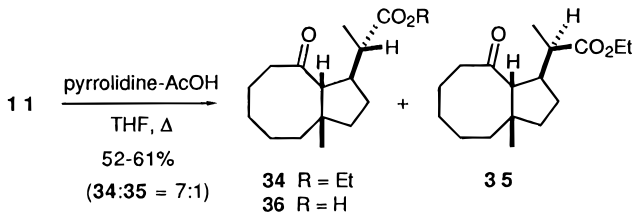
How might these arguments be used to rationalize the reduced selectivity observed with **8** and **10**? Cyclization of enamines derived from these ketones in a manner that minimizes $A^{1,3}$ strain would necessarily lead to **26** or its geometrical isomer. Although **26** is simply a C_9-C_{10} conformer of **24**, its geometrical isomer could never adopt a conformation that enjoys electrostatic stabilization. Thus, it is possible that the diastereofacial bias present in **24** might not be accessible to at least a portion of the reactive intermediates derived from cyclization of **8** and **10**, the result being less stereoselectivity in the protonation of C_{10}.

Regardless of the origin of stereoselectivity, we wanted to see if this argument could be extrapolated to the preparation of other ring systems. With an eye on members of the ophiobolin and ceroplastol family of sesterterpenes, we prepared substrate **11** as described in Scheme 6. Thus, cyclooctenone was converted to **28** in 65% yield upon treatment with the cerium reagent derived from (4-methyl-3-pentenyl)lithium.[18,19] Oxidative rearrangement of **28** using pyridinium chlorochromate gave **29** in 74% yield.[20] Treatment of **29** with lithium dimethylcuprate in the presence of chlorotrimethylsilane gave **30** (92%) which was converted to ketal **31** in 73% yield.[21] Ozonolysis of **31** afforded aldehyde **32** in 83% yield, and Wittig olefination provided α,β-unsaturated ester **33** in 80% yield along with 3% of the corresponding *Z*-isomer. Ketal hydrolysis completed the synthesis of **11**.

Cyclization substrate **11** was much less reactive that substrates **7**–**10**. In fact, only traces of conversion to

(14) Johnson, R. *Chem. Rev.* **1968**, *68*, 375. Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(15) Although the structures depicted in Scheme 5 are enolates, the same types of arguments could also be advanced for the corresponding enols.
(16) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165.
(17) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637.
(18) Lansbury, P. T.; Haddon, V. R.; Stewart, R. C. *J. Am. Chem. Soc.* **1974**, *96*, 896. Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166.
(19) Imamoto, T.; Kusumoto, T.; Tawarayama, T.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.
(20) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
(21) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

Scheme 7



cyclized materials were observed when **11** was exposed to the optimal conditions for cyclizing **7**−**10**. Eventually it was found that warming **11** with 1.3 equiv of pyrrolidine and 2.3 equiv of acetic acid in a minimal amount of tetrahydrofuran at 110 °C for 17 h gave a 7:1 mixture of **34** and **35** in 52% yield along with 38% of recovered **11** (Scheme 7). The structure of **34** was determined by X-ray crystallographic analysis of carboxylic acid **36**, obtained by hydrolysis of the aforementioned mixture of **34** and **35** using lithium hydroxide in aqueous methanol.[12,22] Thus, it appears that the stereoselectivity observed in the perhydroindan synthesis will extrapolate to other systems, although stereoselectivity may erode slightly if more vigorous cyclization conditions are required as was the case with **11**.[23]

Finally, it is notable that the cyclization of substrates **7** and **11** could be catalyzed by potassium *tert*-butoxide (15 mol%) in benzene at 60−78 °C for 2 h. Although keto ester **7** gave an 85% yield of a 15:1 mixture of **18** and **19**, respectively, keto ester **11** gave only a 9% yield of a 2:1 mixture of **34** and **35**. In terms of stereochemistry, these results qualitatively parallel those obtained using pyrrolidine−acetic acid. It is clear, however, that the pyrrolidine−acetic acid mediated reactions provide better selectivity in both cases and superior yields in the case of **11**.

In summary, a diastereoselective procedure for preparing fused carbocyclic systems with appended side chains has been developed and some of the limitations of the process have been defined. An application of this process to sesquiterpene synthesis is presented in the following article in this journal.

Experimental Section

All melting points are uncorrected as are all boiling points. ^{1}H NMR spectra are reported on the δ scale as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad), coupling constants in hertz, integration, interpretation]. ^{13}C NMR spectra are recorded in parts per million from internal chloroform or dimethyl sulfoxide on the δ scale. The ^{13}C NMR spectra are reported as follows: chemical shift (multiplicity determined from DEPT spectra). Mass spectra were obtained using EI at an ionization energy of 70 eV unless stated otherwise. Compounds for which an exact mass is reported exhibited no significant peaks at *m/e* greater than that of the parent.

Solvents and reagents were dried and purified prior to use when deemed necessary: THF, Et_2O, benzene, and pyrrolidine were distilled from sodium metal; chlorotrimethylsilane, CH_2Cl_2, diisopropylamine, triethylamine, and toluene were distilled over calcium hydride. Purification of CuI was accomplished according to the literature procedure.[24] Reactions requiring an inert atmosphere were run under argon. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM Laboratory silica gel (70−230 mesh). Medium pressure liquid chromatography (MPLC) was performed using EM Laboratories Lobar prepacked silica gel columns. All organolithium reagents were titrated prior to use with (±)-menthol using 1,10-phenanthroline as the indicator.[25]

Ethyl (±)-(*E*)-2-Methyl-5-(7-methyl-1,4-dioxaspiro[4.5]-dec-7-yl)-2-pentenoate (13) and Ethyl (±)-(*Z*)-2-Methyl-5-(7-methyl-1,4-dioxaspiro[4.5]dec-7-yl)-2-pentenoate (14). A. Peterson Olefination. To a solution of 1.60 mL (11.4 mmol) of diisopropylamine in 15 mL of THF at 0 °C was added 13 mL (13.0 mmol) of *n*-BuLi (1.0 M in hexane). The solution was stirred for 15 min at 0 °C and then cooled to −78 °C. A solution of 2.00 g (11.5 mmol) of ethyl 2-(trimethylsilyl)acetate[7] in 20 mL of THF was added dropwise via an addition funnel, and the mixture was stirred for 1 h. A solution of 1.97 g (9.27 mmol) of aldehyde **12**[6] in 12 mL of THF was added dropwise via an addition funnel over a 35 min period, and the mixture was stirred at −78 °C for 3 h, followed by an additional 18 h during which the temperature was slowly raised to rt. The reaction was quenched with 12 mL of saturated NH_4Cl, and the solution was diluted with 150 mL of Et_2O. The organic phase was washed with two 15-mL portions of brine, and the combined washes were extracted with two 10-mL portions of Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc−petroleum ether, 1:9) to afford 2.14 g (78%) of a 1:1 mixture of stereoisomers **13** and **14** by integration of selected peaks in ^{1}H NMR spectrum: IR (neat) 1711, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.95 and 0.97 (two s, 3H, CH_3), 1.30−1.80 (m, 13H), 1.85 and 1.90 (two s, 3H, =CCH_3), 2.10 (m, 1H), 2.40 (m, 1H), 3.91 (bs, 4H, $(OCH_2)_2$), 4.18 and 4.20 (two q, J = 7.1 Hz, 2H, OCH_2), 5.90 (t, J = 7.5 Hz, 0.5H, =CH), 6.75 (t, J = 7.4 Hz, 0.5H, =CH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.0 and 14.2 (two q), 14.1 and 20.5 (two q), 19.5 and 19.6 (two t), 23.1 and 24.0 (two t), 25.3 and 25.7 (two q), 34.4 (two s), 34.8 and 34.9 (two t), 36.9 and 37.1 (two t), 40.5 and 41.9 (two t), 44.5 and 44.7 (two t), 59.8 and 60.2 (two t), 63.8 (two t), 63.9 (two t), 109.2 and 109.3 (two s), 126.5 and 127.2 (two s), 142.7 and 143.3 (two d), 168.0 and 168.1 (two s); exact mass calcd for $C_{17}H_{28}O_4$ *m/e* 296.1988; found *m/e* 296.1989. **B. Wittig Reaction.** To a solution of 302 mg (1.42 mmol) of aldehyde **12** in 26 mL of dry benzene under argon was added 1.14 g (3.15 mmol) of (1-carbethoxyethylidene)triphenylphosphorane in one portion. The resulting solution was heated under reflux for 4.8 h, and the solvent was removed in vacuo. The residue was chromatographed over 45 g of silica gel (eluted with petroleum ether−EtOAc, 9:1) to afford 345 mg (82%) of an 8:1 mixture of **12** and **13** by integration of selected peaks in ^{1}H NMR spectrum.

Ethyl (±)-(*E*)-2-Methyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (7) and Ethyl (±)-(*Z*)-2-Methyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (8). A. Preparation from 13 and 14. To a solution of 2.35 g (7.93 mmol) of a 1:1 mixture of **13** and **14** in 16.4 mL of a 1:1 mixture of Et_2O and *tert*-butyl alcohol was added 20.4 mL of 1 N aqueous HCl. The reaction mixture was stirred at rt for 6.5 h, diluted with 90 mL of Et_2O, and washed with 15 mL of water, followed by two 15-mL portions of saturated aqueous $NaHCO_3$. The organic phase was washed with two 30-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. This residue was a 1:1 mixture of *E*- and *Z*-isomers, by integration of selected peaks in the ^{1}H NMR spectrum of the mixture. Separation by MPLC (eluted with EtOAc−hexanes, 1:13) afforded 0.6 g (30%) of **7**, 0.6 g (30%) of **8**, and 0.36 g (18%) of a mixture of **7** and **8**.

(22) These conditions have been used to hydrolyze similar esters without epimerization at an adjacent stereogenic center. For example, see: Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(23) For an approach to bicyclo[6.3.0]undecanes that affords transfused structures, see: Brooker-Milburn, K. I.; Thompson, D. F. *Synlett* **1993**, 592. Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Narasaka, K. *Chem. Lett.* **1993**, 545.

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Ester **7**: IR (neat) 1713, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (s, 3H, CH_3), 1.29 (t, J = 7.1 Hz, 3H, CH_3), 1.30−2.30 (m, 15H), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.71 (t, J = 7.4 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ 12.2 (q), 14.2 (q), 22.1 (t), 22.9 (t), 24.8 (q), 35.8 (t), 38.6 (s), 40.29 (t), 40.9 (t), 53.5 (t), 60.4 (t), 128.0 (s), 141.6 (d), 168.1 (s), 211.6 (s); exact mass calcd for $C_{15}H_{24}O_3$ *m/e* 252.1725, found *m/e* 252.1670. Ester **8**: IR ($CDCl_3$) 1702, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.94 (s, 3H, CH_3), 1.27 (t, J = 7.1 Hz, 3H, CH_3), 1.30−2.50 (m, 15H), 4.19 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.87 (t, J = 7.5 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.3 (q), 20.6 (q), 22.0 (t), 23.8 (t), 24.8 (q), 35.6 (t), 38.6 (s), 40.9 (t), 41.1 (t), 53.7 (t), 60.0 (t), 127.3 (s), 142.4 (d), 167.9 (s), 211.9 (s); exact mass calcd for $C_{15}H_{24}O_3$ *m/e* 252.1725, found *m/e* 252.1674. **B. Preparation of 7 from 8.** To a solution of 154 mg (0.61 mmol) of **8** in **7** mL of benzene was added 16 μL (0.15 mmol) of thiophenol. The reaction mixture was degassed and heated under reflux, and 10 mg (0.07 mmol) of AIBN was added. Another 10 mg of AIBN was added after 1 h, and again after 30 min. After a total of 2.8 h at reflux, the mixture was concentrated in vacuo and chromatographed over silica gel (eluted with hexanes−EtOAc, 9:1) to afford 140 mg (91%) of **7**.

Ethyl 6-Methyl-2-(trimethylsilyl)hept-5-enoate (17). To a solution of 4.2 mL (30 mmol) of diisopropylamine in 20 mL of THF at 0 °C was added 21 mL (33 mmol) of *n*-BuLi (1.6 M in hexanes). The solution was cooled to −78 °C and stirred between −78 and −35 °C for 30 min. A solution of 4.03 g (25.2 mmol) of ethyl 2-(trimethylsilyl)acetate[7] in 25 mL of THF was added dropwise via an addition funnel over a 20 min period. The mixture was stirred for 1.5 h at −30 °C, and 11.3 g (69.4 mmol) of 1-iodo-4-methyl-3-pentene[10] was added neat in one portion. The resulting mixture was stirred for 6 h at a temperature ranging from −20 °C to rt and 2 h at rt. The reaction was quenched with 1.8 mL of glacial acetic acid and 20 mL of water. The mixture was diluted with 70 mL of Et_2O. The organic phase was washed with two 35 mL portions of brine. The combined aqueous washes were extracted with two 35 mL portions of Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The low-boiling impurities were removed by distillation. The resulting dark brown pot material was chromatographed over 90 g of silica gel (eluted with EtOAc−hexane, 1:49) to afford 3.22 g (53%) of the ester **17** as a clear colorless liquid: IR (neat) 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 9H, $(CH_3)_3Si$), 1.23 (t, J = 7.1 Hz, 3H, CH_3), 1.28−1.51 (m, 2H), 1.57 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.72−2.10 (m, 3H), 4.09 (q, J = 7.1 Hz, 2H, OCH_2), 5.06 (bt, J = 6.6 Hz, 1H, CH=); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −2.9 (q), 14.3 (q), 17.4 (q), 25.5 (q), 26.7 (t), 28.6 (t), 37.1 (d), 59.3 (t), 123.6 (d), 132.1 (s), 175.1 (s); exact mass calcd for $C_{13}H_{26}SiO_2$ *m/e* 242.1702, found *m/e* 242.1702.

Ethyl (±)-6-Methyl-2-[(*E*)-3-(7-methyl-1,4-dioxaspiro-[4.5]dec-7-yl)propylidene]-5-heptenoate (15) and Ethyl (±)-6-Methyl-2-[(*Z*)-3-(7-methyl-1,4-dioxaspiro[4.5]dec-7-yl)propylidene]-5-heptenoate (16). To a solution of 1.7 mL (12.1 mmol) of diisopropylamine in 18 mL of THF at 0 °C was added 8.8 mL (14.1 mmol) of *n*-BuLi (1.6 M in hexanes). The solution was cooled to −78 °C and stirred at that temperature for 45 min. A solution of 3.22 g (13.3 mmol) of **17** in 20 mL of THF was added dropwise via syringe pump over a 15 min period, and the mixture was stirred for 1.5 h at −70 °C. A solution of 2.41 g (11.3 mmol) of **12** in 20 mL of THF was added dropwise via syringe pump over a 15 min period, and the mixture was stirred between −78 and 15 °C for 20 h. The reaction was quenched with 15 mL of saturated NH_4Cl, and the solution was diluted with 100 mL of Et_2O. The mixture was washed with two 10 mL portions of brine, and the combined washes were extracted with two 10 mL portions of Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−petroleum ether, 1:9) to afford, along with a mixed fraction containing **15**, **16**, and **17** (**15**+**16**: **17** = 1:4), 2.42 g (59%) of a 4:1 mixture of **16** and **15**, respectively, by integration of selected peaks in the ^1H NMR spectrum: ^1H NMR ($CDCl_3$, 250 MHz) δ 0.97 and 0.98 (two s, 3H, CH_3), 1.23−1.68 (m, 19H), 2.04−2.43 (m, 6H), 3.90−3.94 (m, 4H, $(OCH_2)_2$), 4.11−4.25 (m, 2H, OCH_2CH_3), 5.09 (m, 1H, $CH=CMe_2$), 5.83 (*Z*-isomer) and 6.74 (*E* isomer) (t, J = 7.5 Hz, 1H, $CH=CCO_2Et$). This mixture was used in the following reaction without further characterization.

Ethyl (±)-6-Methyl-2-[(*E*)-3-(1-methyl-3-oxocyclohexyl)propylidene]-5-heptenoate (9) and Ethyl (±)-6-Methyl-2-[(*Z*)-3-(1-methyl-3-oxocyclohexyl)propylidene]-5-heptenoate (10). To a solution of 645 mg (1.77 mmol) of a 4:1 mixture of **16** and **15**, respectively, in 4 mL of a 1:1 mixture of Et_2O and *tert*-butyl alcohol was added 4.6 mL of 1 N aqueous HCl. The reaction mixture was stirred at rt for 17 h, diluted with 30 mL of Et_2O, and washed with 5 mL of water, followed by two 7-mL portions of saturated aqueous $NaHCO_3$. The organic phase was washed with two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo to give 508 mg (90%) of a 4:1 mixture of **10** and **9**, respectively, by integration of selected peaks in the ^1H NMR spectrum. Separation by MPLC (eluted with hexane−EtOAc, 13:1) afforded 283 mg of **10** and 64 mg of **9**, along with 20 mg of a mixture of **10** and **9**. Ester **9**: IR ($CDCl_3$) 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.96 (s, 3H, CH_3), 1.29 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.33−1.42 (m, 3H), 1.59 (s, 3H, $=CCH_3$), 1.68 (s, 3H, $=CCH_3$), 1.55−1.71 (m, 3H), 1.89 (m, 2H), 2.04−2.18 (m, 5H), 2.24−2.34 (m, 3H), 4.19 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.13 (m, 1H, $CH=CMe_2$), 6.69 (t, J = 7.5 Hz, 1H, $CH=CCO_2Et$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (q), 17.6 (q), 22.0 (t), 22.8 (t), 24.7 (q), 25.7 (q), 26.9 (t), 27.7 (t), 35.8 (t), 38.6 (s), 40.7 (t), 40.9 (t), 53.5 (t), 60.3 (t), 123.6 (d), 132.2 (two s), 141.9 (d), 167.8 (s), 211.5 (s); exact mass calcd for $C_{20}H_{32}O_3$ *m/e* 320.2339, found *m/e* 320.2346. Ester **10**: IR ($CDCl_3$) 1704, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (s, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.57 (s, 3H, $=CCH_3$), 1.67 (s, 3H, $=CCH_3$), 1.22−2.46 (m, 16H), 4.20 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.08 (m, 1H, $CH=CMe_2$), 5.81 (t, J = 7.5 Hz, 1H, $HC=CCO_2Et$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.3 (q), 17.6 (q), 22.1 (t), 23.9 (t), 24.9 (q), 25.6 (q), 27.8 (t), 34.8 (t), 35.6 (t), 38.6 (s), 41.0 (t), 41.2 (t), 53.7 (t), 60.0 (t), 123.5 (d), 131.9 (s), 132.1 (s), 141.5 (d), 167.9 (s), 212.0 (s); exact mass calcd for $C_{20}H_{32}O_3$−EtOH *m/e* 274.1933, found *m/e* 274.1957.

Ethyl (±)-(α*S,1*R**,3a*R**,7a*S**)-Hexahydro-α-methyl-3a-methyl-7-oxo-1-indanacetate (18). A. Pyrrolidine-Mediated Cyclization of 7.** To a solution of 143 mg (0.57 mmol) of keto ester **7** in 2.5 mL of THF were added 50 μL (0.59 mmol) of pyrrolidine and 80 μL (1.4 mmol) of glacial acetic acid. The reaction mixture was heated under reflux for 6 h and diluted with 8 mL of Et_2O. The reaction was quenched with 0.8 mL of 5% aqueous HCl, and the solution was stirred for 15 min at rt. The aqueous phase was extracted with three 10 mL portions of Et_2O. The combined organic phases were diluted with 40 mL of Et_2O, washed with 10 mL of water, 20 mL of saturated aqueous $NaHCO_3$, and two 20 mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo to give 143 mg (100%) of a pale yellow oil. The residue was chromatographed over silica gel (eluted with petroleum ether−EtOAc, 13:1) to give 112 mg (78%) of a 99:1 mixture of diastereoisomers whose major component was **18**: IR (neat) 1732, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.06 (s, 3H, CH_3), 1.10 (d, J = 7.0 Hz, 3H, CH_3), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.30−2.73 (m, 13H), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.2 (q), 15.4 (q), 23.0 (t), 25.8 (q), 28.3 (t), 33.4 (t), 38.0 (t), 39.9 (t), 44.8 (d), 45.3 (d), 48.7 (s), 60.1 (t), 64.8 (d), 175.6 (s), 215.1 (s); exact mass calcd for $C_{15}H_{24}O_3$ *m/e* 252.1726, found *m/e* 252.1705. **B. KO-*t*-Bu-Mediated Cyclization of 7.** To a solution of 6 mg (0.05 mmol) of *t*-BuOK in 0.3 mL of *t*-BuOH was added 85 mg (0.34 mmol) of **7** in 0.2 mL of benzene. The resulting mixture was heated between 60 and 78 °C for 2 h and cooled to rt, and the reaction was quenched with 3 μL of glacial acetic acid. The mixture was diluted with 20 mL of water and extracted with two 25 mL portions of ether. The combined organic layers were washed with 20 mL of saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo to afford 72 mg (85%) of a residual crude oil. This material was a 15:1 mixture of **18** and **19**, as estimated by ^1H NMR spectroscopy. Traces of **7** could also be detected.

Ethyl (±)-(α*R,1*R**,3a*R**,7a*S**)-Hexahydro-α-methyl-**

3a-methyl-7-oxo-1-indanacetate (19). To a solution of 173 mg (0.69 mmol) of **8** in 2 mL of THF were added 60 μL (0.72 mmol) of pyrrolidine and 90 μL (1.6 mmol) of glacial acetic acid. The reaction mixture was heated under reflux for 5 h and diluted with 10 mL of Et_2O. The reaction was quenched with 0.7 mL of 5% aqueous HCl, and the solution was stirred for 20 min at rt. The aqueous phase was extracted with three 10 mL portions of Et_2O. The combined organic phases were diluted with 40 mL of Et_2O, washed with 10 mL of water, 20 mL of saturated aqueous $NaHCO_3$, and two 20 mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo to give 160 mg (92%) of a mixture of perhydroindans. Separation by MPLC (eluted with hexane−EtOAc, 49:1) afforded 72 mg (42%) of **18** and 22 mg (13%) of diastereoisomer **19**. Ester **19**: IR ($CDCl_3$) 1720, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 3H, CH_3), 1.14 (d, J = 7.0 Hz, 3H, CH_3CH), 1.23 (t, J = 7.1 Hz, 3H, CH_3), 1.40−2.03 (m, 8H), 2.01 (d, J = 9.6 Hz, 1H, CH), 2.13−2.20 (m, 1H, CH), 2.32 (m, 1H, CH), 2.51−2.60 (m, 1H, CH), 2.68−2.71 (m, 1H, CH), 4.04 (q, J = 7.1 Hz, 1H, OCHH), 4.05 (q, J = 7.2 Hz, 1H, OCHH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (q), 15.1 (q), 22.9 (t), 26.0 (q), 27.2 (t), 33.7 (t), 37.7 (t), 39.8 (t), 43.9 (d), 45.3 (d), 48.3 (s), 60.3 (t), 65.6 (d), 175.7 (s), 214.5 (s); exact mass calcd for $C_{15}H_{24}O_3$ *m/e* 252.1726, found *m/e* 252.1747.

(±)-(α*S,1*R**,3a*R**,7a*S**)-Hexahydro-α-methyl-3a-methyl-7-oxo-1-indanacetic Acid (20).** To a solution of 109 mg (0.43 mmol) of **18** in 2.2 mL of methanol was added 1.75 mL (3.7 mmol) of 5% aqueous lithium hydroxide in one portion. The reaction mixture was heated at 50 °C for 1.7 h, and the reaction was quenched with 50 mL of 1 N aqueous HCl in 50 mL of CH_2Cl_2. The aqueous phase was extracted with 50 mL of CH_2Cl_2, and the combined extracts were washed with 25 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give 90 mg (93%) of **20** as a pale yellow solid. Recrystallization of a sample from petroleum ether−Et_2O−CH_2Cl_2 gave acid **20** as a white solid: mp 81−82 °C; IR ($CHCl_3$) 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 3H, CH_3), 1.15 (d, J = 6.9 Hz, 3H, CH_3), 1.20−2.70 (m, 13H), the acidic proton was not recorded; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 15.4 (q), 22.8 (t), 26.0 (q), 28.3 (t), 33.7 (t), 38.1 (t), 39.9 (t), 44.2 (d), 45.3 (d), 48.3 (s), 64.5 (d), 179.9 (s), 215.6 (s); exact mass calcd for $C_{13}H_{20}O_3$ *m/e* 224.1413, found *m/e* 224.1428.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93. Found: C, 69.66; H, 9.00.

Ethyl (±)-(α*S,1*R**,3a*R**,7a*S**)-Hexahydro-3a-methyl-α-(4-methyl-3-pentenyl)-7oxo-1-indanacetate (21).** To a solution of 127 mg (0.40 mmol) of **9** in 2 mL of THF were added 40 μL (0.48 mmol) of pyrrolidine and 55 μL (0.94 mmol) of glacial acetic acid. The reaction mixture was heated under reflux for 6.1 h and diluted with 40 mL of Et_2O, and the reaction was quenched with 25 mL of saturated $NaHCO_3$. The aqueous phase (pH 7) was extracted with two 20 mL portions of Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with petroleum ether−EtOAc, 24:1) to afford 55 mg (43%) of **21**, along with traces of unidentified byproducts, one of which (15 mg) was removed from the silica gel by flushing the column with EtOAc. This byproduct lacked the isopropylidene moiety, as seen in the ^1H NMR spectrum. Ester **21**: IR (neat) 1729, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.05 (s, 3H, CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.30−1.70 (m, 7H), 1.56 (s, 3H, =CCH_3), 1.66 (d, J = 0.8 Hz, 3H, =CCH_3), 2.05 (d, J = 9.3 Hz, 1H, CHC(O)), 1.84−2.00 (m, 5H), 2.20−2.37 (m, 2H), 2.43−2.71 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.04 (bt, J = 7.1 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.3 (q), 17.6 (q), 22.9 (t), 25.7 (q), 26.0 (q), 26.1 (t), 27.8 (t), 30.7 (t), 33.6 (t), 38.2 (t), 39.8 (t), 44.5 (d), 48.7 (s), 50.8 (d), 60.1 (t), 65.2 (d), 123.5 (d), 132.1 (s), 175.1 (s), 215.0 (s); exact mass calcd for $C_{20}H_{32}O_3$ *m/e* 320.2351, found *m/e* 320.2360.

Ethyl (±)-(α*R,1*R**,3a*R**,7a*S**)-Hexahydro-3a-methyl-α-(4-methyl-3-pentenyl)-7-oxo-1-indanacetate (22).** To a solution of 320 mg (1.0 mmol) of **10** in 7 mL of THF were added 0.1 mL (1.2 mmol) of pyrrolidine and 0.14 mL (2.4 mmol) of glacial acetic acid. The reaction mixture was heated under reflux for 12 h and diluted with 15 mL of Et_2O. The reaction was quenched with 1.5 mL of 5% aqueous HCl, and the solution was stirred for 5 min at rt. The aqueous phase was extracted with three 20 mL portions of Et_2O. The combined organic phases were diluted with 50 mL of Et_2O, washed with 20 mL of water, 40 mL of saturated aqueous $NaHCO_3$, and two 40 mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo to give 260 mg of a mixture of perhydroindans **21** and **22**. Separation of 219 mg by MPLC (eluted with hexane−EtOAc, 49:1) afforded 168 mg (62%) of **21** and 28 mg (10%) of diastereomer **22**. Ester **22**: IR (neat) 1727, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.02 (s, 3H, CH_3), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.29−2.25 (m, 15H), 1.56 (s, 3H, =CCH_3), 1.66 (d, J = 0.9 Hz, 3H, =CCH_3), 2.48−2.76 (m, 2H), 4.03 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.04 (bt, J = 7.1 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (q), 17.6 (q), 23.1 (t), 25.6 (q), 25.7 (q), 25.9 (t), 28.1 (t), 31.2 (t), 33.6 (t), 37.6 (t), 39.6 (t), 44.9 (d), 48.7 (s), 50.6 (d), 60.1 (t), 65.8 (d), 123.5 (d), 132.2 (s), 175.0 (s), 214.3 (s); exact mass calcd for $C_{20}H_{32}O_3$ *m/e* 320.2351, found *m/e* 320.2393.

(±)-(*Z*)-1-(4-Methyl-3-pentenyl)-2-cycloocten-1-ol (28). Cerium trichloride (1.31 g, 5.31 mmol) was dried at 140 °C/0.1 mmHg for 4.5 h. The flask was cooled to rt and vented to a dry argon atmosphere. Dry THF was added (10 mL), and the suspension was stirred at rt under argon for 15.5 h. The light grey slurry was then cooled to −78 °C, and a solution of *t*-BuLi (1.7 M in pentane) was added until an orange color was obtained. Meanwhile, to a solution of 642 mg (3.94 mmol) of 1-bromo-4-methyl-3-pentene[10] in 10 mL of THF, stirred under argon at −70 °C, was added dropwise 3.25 mL (3.90 mmol) of a 1.2 M solution of *t*-BuLi in pentane. The resulting pale yellow solution was stirred for another 20 min and then transferred via cannula into the $CeCl_3$ slurry. The resulting mixture was stirred at −70 °C for 55 min, and 257 mg (2.07 mmol) of 2-cyclooctenone[26] in 5 mL of THF was added. The resulting mixture was stirred at −70 °C for 6 h, the reaction was quenched with 25 mL of saturated aqueous NH_4Cl, and the solution was diluted 25 mL of Et_2O. The aqueous phase was extracted with three 25-mL portions of ether. The combined organic phases were dried (Na_2SO_4) and concentrated to afford 398 mg of a yellow oil. Purification by column chromatography (eluted with petroleum ether−EtOAc, 9:1 + 0.25% triethylamine) afforded 280 mg (65%) of alcohol **28** as a clear colorless oil: IR (neat) 3416, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39−1.79 (m, 8H), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.81−1.90 (m, 2H), 2.05 (q, J = 8.0 Hz, 2H, CH_2), 2.12−2.23 (m, 2H, CH and OH), 2.41−2.52 (m, 1H, CH), 5.12 (bt, J = 7.1 Hz, 1H, CH=CMe_2), 5.46−5.56 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.5 (q), 22.3 (t), 22.4 (t), 24.6 (t), 24.8 (t), 25.5 (q), 26.9 (t), 39.6 (t), 44.1 (t), 75.4 (s), 124.3 (d), 127.9 (d), 131.5 (s), 136.7 (d); exact mass calcd for $C_{14}H_{24}O$ *m/e* 208.1827, found *m/e* 208.1833.

(*E*)-3-(4-Methyl-3-pentenyl)-2-cycloocten-1-one (29). To a bright orange slurry of 1.26 g (5.84 mmol) of pyridinium chlorochromate in 10 mL of CH_2Cl_2 was added in one portion, under argon, 599 mg (2.88 mmol) of alcohol **28** in 8 mL of CH_2Cl_2. The resulting dark brown mixture was stirred at rt for 4.5 h and diluted with 25 mL of ether. The residual black polymer was rinsed further with three 20 mL portions of ether. The combined organic phases were washed successively with 40 mL of 1 N aqueous sodium hydroxide, 40 mL of 1 N aqueous HCl, and two 20 mL portions of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to afford 549 mg of a pale orange oil. Purification by column chromatography over 40 g silica gel (eluted with petroleum ether−EtOAc, 9:1) afforded 439 mg (74%) of enone **29** as a clear colorless oil: IR (neat) 1650, 1621 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40−1.55 (m, 6H), 1.49 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.59−1.68 (m, 2H, CH_2), 2.07 (bs, 2H, CH_2CO), 2.50 (t, J = 6.6 Hz, 2H, =CCH_2), 2.61 (t, J = 7.1 Hz, 2H, =CCH_2), 4.97 (bs, 1H, CH=CMe_2), 5.92 (s, 1H, =CHCO); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.5 (q), 22.8 (t), 23.5 (t), 23.9 (t), 25.4 (q), 26.0 (t), 31.9 (t), 41.3 (t),

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41.8 (t), 122.8 (d), 130.4 (d), 132.2 (s), 156.3 (s), 203.6 (s); exact mass calcd for $C_{14}H_{22}O$ *m/e* 206.1670, found *m/e* 208.1672.

(±)-3-Methyl-3-(4-methyl-3-pentenyl)cyclooctanone (30). To a suspension of 1.08 g (5.64 mmol) of CuI in 8 mL of dry Et_2O at 4 °C was added dropwise 8.50 mL (9.10 mmol) of 1.07 M ethereal methyllithium. The resulting mixture was cooled to −70 °C and stirred for 10 min. To this mixture was added dropwise 0.55 mL (4.4 mmol) of TMSCl, followed by 438 mg (2.12 mmol) of enone **29** in 8 mL of ether. The resulting mixture was stirred for 7 h between −70 and 5 °C and then poured onto 50 mL of chilled 10% aqueous NH_4Cl. The resulting mixture was stirred for 2.5 h, and the aqueous layer was separated and extracted with three 50-mL portions of ether. The combined organic phases were washed with 50 mL of brine, dried ($MgSO_4$), and concentrated to afford 543 mg of a mixture of silyl enol ether (mainly) and ketone (trace). This mixture was dissolved in 11 mL of THF, and 3.5 mL (3.5 mmol) of tetra-*n*-butylammonium fluoride (1M in THF) was added under argon. The mixture was stirred at rt for 50 min, the reaction was quenched with 40 mL of saturated aqueous NH_4Cl, and the solution was diluted with 40 mL of ether. The aqueous layer was extracted with two 25 mL portions of ether, and the combined organic phases were washed with 40 mL of brine, dried ($MgSO_4$), and concentrated to afford 432 mg (92%) of ketone **30** as a pale yellow oil which was used as such in the next step: IR (neat) 1696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 3H, CH_3), 1.21−1.58 (m, 8H), 1.61 (s, 3H, CH_3), 1.67 (d, J = 1.0 Hz, 3H, CH_3), 1.88−2.07 (m, 4H), 2.10 (d, J = 11.0 Hz, 1H, C*H*(H)CO), 2.30 (m, 2H, CH_2CH_2CO), 2.42 (d, J = 11.0 Hz, 1H, C*H*(H)CO), 5.10 (bt, J = 6.5 Hz, 1H, CH=CMe_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.4 (q), 20.0 (t), 21.7 (t), 22.3 (t), 25.5 (q), 25.9 (q), 28.8 (t), 37.1 (t), 38.6 (s), 42.0 (t), 45.2 (t), 48.8 (t), 124.5 (d), 131.1 (s), 214.7 (s); exact mass calcd for $C_{15}H_{26}O$ *m/e* 222.1984, found *m/e* 222.1985.

(±)-7-Methyl-7-(4-methyl-3-pentenyl)-1,4-dioxaspiro-[4.7]dodecane (31). A solution of 432 mg (1.95 mmol) of ketone **30**, 2.5 mL (44.8 mmol) of ethylene glycol, 12 mL of dry benzene, 1.9 mL (17.4 mmol) of trimethyl orthoformate, and 21 mg (1.1 mmol) of *p*-toluenesulfonic acid monohydrate was stirred at rt for 6 h and diluted with 50 mL of Et_2O, and the reaction was quenched by addition of 30 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with two 30 mL portions of ether. The combined organic phases were washed with 50 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residual liquid was chromatographed over 50 g of silica gel (eluted with petroleum ether−EtOAc, 60:1) to give 381 mg (73%) of ketal **31** as a clear colorless liquid: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3H, CH_3), 1.13 (ddd, J = 13.4, 11.9, 5.2 Hz, 1H, C*H*(H)), 1.24−1.69 (m, 11H), 1.59 (s, 3H, =CCH_3(Me)), 1.66 (bs, 3H, =CCH_3(Me)), 1.76−1.79 (m, 2H), 1.83−1.98 (m, 2H), 3.86 (m, 4H, $(OCH_2)_2$), 5.08 (bt, J = 6.5 Hz, 1H, CH=CMe_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.4 (q), 22.3 (t), 22.5 (t), 23.3 (t), 25.6 (q), 27.4 (q), 30.7 (t), 34.4 (s), 36.2 (t), 38.3 (t), 40.9 (t), 42.6 (t), 63.7 (t), 64.2 (t), 112.8 (s), 125.3 (d), 130.5 (s); exact mass calcd for $C_{17}H_{30}O_2$ *m/e* 266.2246, found *m/e* 266.2247.

(±)-7-Methyl-1,4-dioxaspiro[4.7]dodecane-7-propionaldehyde (32). Through a stirred solution of 381 mg (1.43 mmol) of alkene **31** and $NaHCO_3$ (spatula tipfull) in 11.3 mL of CH_2Cl_2 and 2.3 mL of methanol at −78 °C was passed a stream of ozone (Welsbach ozone generator) at a flow rate of 1.0 mmol min^{-1}. When the reaction mixture maintained a blue color for 1 min, the stream of ozone was replaced by argon and the solution was stirred until the color dissipated (1 h). To the resulting clear reaction mixture was added 1.7 mL of dimethyl sulfide. The reaction mixture was stirred for 24 h, at a temperature ranging from −78 °C to rt. The solvent was removed in vacuo, and the residual crude liquid was chromatographed over 40 g silica gel (eluted with hexane−EtOAc, 9:1) to give 286 mg (83%) of aldehyde **32** as a clear colorless oil: IR (neat) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.85 (s, 3H, CH_3), 1.42−1.84 (m, 14H), 2.40 (dddd, J = 16.3, 10.7, 5.4, 2.0 Hz, 2H, CH_2CHO), 3.82−3.94 (m, 4H, $(OCH_2)_2$), 9.76 (t, J = 2.0 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.5 (t), 23.2 (t), 27.5 (q), 30.6 (t), 33.8 (t), 34.1 (s), 35.9 (t), 38.5 (t), 39.0 (t), 40.6 (t), 63.5 (t), 64.5 (t), 112.5 (s), 203.2 (d); exact mass calcd for $C_{14}H_{24}O_3$ *m/e* 240.1726, found *m/e* 240.1716.

Ethyl (±)-(*E*)-2-Methyl-5-(7-methyl-1,4-dioxaspiro[4.7]-dodec-7-yl)-2-pentenoate (33). To a solution of 130 mg (0.542 mmol) of aldehyde **32** in 10 mL of dry benzene under argon was added 433 mg (1.20 mmol) of (1-carbethoxyethylidene)triphenylphosphorane in one portion. The resulting solution was heated under reflux for 4.5 h, and the solvent was removed in vacuo. The residue was chromatographed over 35 g of silica gel (eluted with petroleum ether−EtOAc, 24:1) to afford 6 mg (3%) of the *Z*-isomer of **33** and 141 mg (80%) of ester **33** as a clear colorless oil. Ester **33**: IR (neat) 1709, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3H, CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.18−1.28 (m, 1H, CH), 1.41−1.79 (m, 13H), 1.82 (s, 3H, =CCH_3), 2.04−2.20 (m, 2H), 3.82−3.90 (m, 4H, $(OCH_2)_2$), 4.16 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.74 (t, J = 7.5 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.1 (q), 14.2 (q), 22.5 (t), 23.3 (t), 27.5 (q), 30.2 (t), 30.7 (t), 34.5 (s), 36.0 (t), 38.5 (t), 40.7 (t), 40.8 (t), 60.2 (t), 63.5 (t), 64.4 (t), 112.6 (s), 127.0 (s), 143.0 (d), 168.2 (s); exact mass calcd for $C_{19}H_{32}O_4$ *m/e* 324.2301, found *m/e* 324.2304. *Z*-Isomer of **33**: IR (neat) 1714, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3H, CH_3), 1.20−1.31 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.42−1.66 (m, 11H), 1.77−1.79 (2H, CH_2), 1.87 (d, J = 1.3 Hz, 3H, =CCH_3), 2.38−2.51 (m, 2H), 3.83−3.91 (m, 4H, $(OCH_2)_2$), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.90 (dt, J = 7.4, 1.4 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (q), 20.6 (q), 22.5 (t), 23.3 (t), 24.2 (t), 27.4 (q), 30.7 (t), 34.5 (s), 36.2 (t), 38.3 (t), 40.8 (t), 41.9 (t), 59.8 (t), 63.7 (t), 64.3 (t), 112.7 (s), 126.3 (s), 143.8 (d), 168.1 (s); exact mass calcd for $C_{19}H_{32}O_4$ *m/e* 324.2301, found *m/e* 324.2285.

Ethyl (±)-(*E*)-2-Methyl-5-(1-methyl-3-oxocyclooctyl)-2-pentenoate (11). To a solution of 303 mg (0.93 mmol) of ketal **33** in 17 mL of THF was added 8 mL of 0.3 N aqueous HCl. The reaction mixture was stirred at rt for 4.2 h, diluted with 50 mL of Et_2O, and neutralized with 25 mL of saturated aqueous $NaHCO_3$ (until pH 7). The organic layer was separated, and the aqueous phase was extracted with three 25 mL portions of ether. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford 258 mg (99% crude) of keto ester **11** as a colorless oil which was used as such in the next step: IR (neat) 1708, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 3H, CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.34−1.57 (m, 8H), 1.83 (bs, 3H, =CCH_3), 1.87−1.96 (m, 2H, CH_2), 2.01−2.39 (m, 6H), 4.16 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.73 (bt, J = 7.5 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.2 (q), 14.3 (q), 20.1 (t), 21.7 (t), 23.3 (t), 26.3 (q), 28.8 (t), 37.2 (t), 38.7 (s), 40.0 (t), 45.3 (t), 48.5 (t), 60.4 (t), 127.7 (s), 142.2 (d), 168.2 (s), 214.7 (s); exact mass calcd for $C_{17}H_{28}O_3$ *m/e* 280.2039, found *m/e* 280.2014.

Ethyl (±)-(α*R,1*R**,3a*R**,7a*S**)-Decahydro-α,3a-dimethyl-9-oxo-1*H*-cyclopentacyclooctene-1-acetate (34).** To a solution of 100 mg (0.36 mmol) of **11** in 0.15 mL of THF was added 38 μL (0.45 mmol) of pyrrolidine followed by 47 μL (0.82 mmol) of glacial acetic acid. The resulting mixture was heated in a sealed tube at 110 °C for 17 h, cooled to rt, diluted with 25 mL of ether, and washed with 15 mL of saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous phase was extracted with two 25 mL portions of Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with petroleum ether−EtOAc, 9:1) to give, along with 38.5 mg (38%) of recovered **11**, 52 mg (52%) of cyclization products **34** and **35**. This material was a 7:1 mixture of isomers (**34:35**) by integration of the selected peaks in the ^1H NMR spectrum of the mixture. The ^{13}C NMR spectrum also showed one major isomer and one very minor isomer: IR (neat) 1731, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.03 (s, 0.36H, CH_3), 1.05 (d, J = 7.0 Hz, 2.64H, $CHCH_3$), 1.06 (s, 2.64H, CH_3), 1.11 (d, J = 7.0 Hz, 0.36H, $CHCH_3$), 1.21 (t, J = 7.1 Hz, 0.36H, OCH_2CH_3), 1.22 (t, J = 7.1 Hz, 2.64H, OCH_2CH_3), 1.23−1.59 (m, 8H), 1.61−1.80 (m, 4H), 2.25−2.31 (m, 2H), 2.33−2.45 (m, 1H, CH), 2.55 (bd, J = 6.4 Hz, 1H, CHC(O)), 2.69−2.82 (m, 1H, CH), 4.05 (q, J = 7.1 Hz, 0.24H, OCH_2CH_3), 4.07 (q, J = 7.1 Hz, 1.76H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz, peaks for **34**) δ 14.1 (q), 15.4 (q), 24.3 (t), 24.5 (t), 26.5 (q), 27.4 (t),

28.0 (t), 36.3 (t), 42.5 (t), 44.5 (d), 47.1 (t), 47.6 (s), 47.8 (d), 60.0 (t), 60.9 (d), 175.7 (s), 217.7 (s); exact mass calcd for $C_{17}H_{28}O_3$ *m/e* 280.2039, found *m/e* 280.2039.

(±)-(αR*,1*R,3a*R**,7a*S**)-Decahydro-α,3a-dimethyl-9-oxo-1*H*-cyclopentacyclooctene-1-acetic Acid (36).** To a solution of 74 mg (0.26 mmol) of a mixture of esters **34** and **35** (7:1) in 1.4 mL of methanol was added 0.9 mL (1.9 mmol) of 2.07 M aqueous lithium hydroxide in one portion. The mixture was stirred at rt for 8.5 h and poured into 15 mL of 1 N aqueous HCl in 25 mL of CH_2Cl_2. The phases were separated, and the aqueous layer (pH 1) was extracted with 25 mL of CH_2Cl_2 and 15 mL of saturated brine, dried ($MgSO_4$), and concentrated in vacuo to afford 61 mg (93%) of a pale yellow oil which crystallized upon standing. Recrystallization from CH_2Cl_2−hexane afforded 41 mg of pure **36**, and the mother liquor contained a mixture of isomers. Acid **36**: mp 108−110 °C; IR ($CDCl_3$) 3300−2500 (broad), 1740, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 3H, CH_3), 1.11 (d, J = 7.0 Hz, 3H, $CHCH_3$), 1.26−1.48 (m, 5H), 1.51−1.66 (m, 3H), 1.68−1.93 (m, 4H), 2.24−2.50 (m, 3H, CH and CH_2C=O), 2.59 (d, J = 6.3 Hz, 1H, CHC=O), 2.79 (m, 1H, $CHCO_2H$), acidic proton not recorded; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.4 (q), 24.4 (t), 24.5 (t), 26.5 (q), 27.4 (t), 28.0 (t), 36.3 (t), 42.4 (t), 44.1 (d), 46.9 (t), 47.4 (d), 47.6 (s), 61.1 (d), 181.4 (s), 217.6 (s); exact mass calcd for $C_{15}H_{24}O_3$ *m/e* 252.1726, found *m/e* 252.1719. The relative stereochemistry of **36** was determined by X-ray crystallography.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.58. Found: C, 71.16; H, 9.54.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds studied (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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