Total Synthesis of (±)-Methyl Atis-16-en-19-oate via Homoallyl−Homoallyl Radical Rearrangement

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Abstract: Total synthesis of (±)-methyl atis-16-en-19-oate (**5c**), a tetracyclic diterpenoid possessing a bicyclo[2.2.2]octane ring system, was accomplished. Intramolecular Diels−Alder reaction of tetraene **14** was employed in a construction of kaurene skeleton **13**. The pivotal step involved a homoallyl−homoallyl radical rearrangement process of (±)-methyl 12-hydroxykaur-16-en-19-oate monothioimidazolide **12**, which led to **5c** in good yield. Interestingly, treatment of methyl 12-oxo-kaur-16-en-19-oate **30** with hydrazine monohydrate in the presence of KOH in bis(ethylene glycol) at 200 °C resulted in cyclopropanation to furnish, directly, trachyloban-19-oic acid (**4b**), together with kaur-16-en-19-oic acid (**6b**).

Introduction

Atisirenoic acid (**5b**) was first isolated from *Helichrysum chionosphaerum* as the corresponding methyl ester **5c** by Bohlmann in 1980;[1] however, partial synthesis of **5c** from isosteviol was reported by Coates as early as 1969.[2] Although some kaurene- and trachylobane-type diterpenoids display a wide range of interesting biological activities, including antimicrobial,[3] antitumor,[4] antifeedant,[5] gibberellin-like,[6] and anti-HIV (neotripterifordin **8**)[7] properties, relatively little is known about the substantial biological activities of **5c** and its relatives (**5a**,**b**).[8] However, the unique bicyclo[2.2.2]octane subunit of **5**, constituting its CD ring system, has provided considerable impetus for the development of new synthetic strategies in the elaboration of the atisirene family.[9]

According to the hypothesis of diterpene biogenesis, originally proposed by Wenkert in 1955,[10] diterpenes belonging to hibaene (**7**), kaurene (**6a**), trachylobane (**4a**), and atisirene (**5a**) families all might arise from (−)-copalyl pyrophosphate (**1**) via nonclassical carbocations such as **2** and its hydrogen shift (C12 to C16) isomer **3** as common intermediates (Scheme 1).[11] Based on this scheme, interconversions and rearrangements of the bicyclooctane subunit of these diterpenes have been extensively studied.[12] In most cases, however, reactions proceed via Wagner−Meerwein rearrangements of carbocations, analogous to **2**/**3**, which is generated under acid-catalyzed conditions. Therefore, mixtures of products are frequently obtained.

To achieve such a transformation under mild conditions with satisfactory selectivity, we designed cyclopropylcarbinyl radical **9** as an alternative to **2**/**3** because it can rearrange to homoallyl radicals **10** and **11**, and furthermore, the introduction of hydrogen at C17, if possible, affords **4a**.[13] Rearrangement of a cyclopropylcarbinyl radical via 3-exo fragmentation[14] usually results in the predominant formation of a thermodynamically more stable homoallyl radical if the concentration of the hydrogen source is sufficiently low.[15] Thus, we expected that homoallyl radical **10**, which possesses a relatively strained five-membered ring moiety, would undergo homoallyl−homoallyl radical rearrangement via **9** to produce **11** (Scheme 2).

Synthetic Plan

Our synthetic strategy for **5c** is outlined in Scheme 3 in which the Pd(II)-promoted cycloalkenylation reaction[16] of silyl enol ether **16** and the intramolecular Diels−Alder reaction of **14** were employed for the construction of the kaurene skeleton. Herein, we describe our investigation of novel skeletal rearrangements

(1) Bohlman, F.; Abraham, W.; Sherdlick, W. S. *Phytochemistry* **1980**, *19*, 869−871.
(2) (a) Coates, R. M.; Bertram, E. F. *J. Chem. Soc., Chem. Commun.* **1969**, 797−798. (b) *Idem. J. Org. Chem.* **1971**, *36*, 2625−2631.
(3) Mitscher, L. A.; Rao, G. S. R.; Veysoglu, T.; Drake, S.; Hass, T. *J. Nat. Prod.* **1983**, *46*, 745−746.
(4) Ryu, S. Y.; Ahn, J. W.; Han, Y. N.; Han, B. H.; Kim, S. H. *Arch. Pharm. Res.* **1996**, *19*, 77−78.
(5) Daniewski, W. M.; Skibicki, P.; Bloszyk, E.; Budesinsky, M.; Holub, M. *Polish J. Chem.* **1993**, *67*, 1255−1259.
(6) Katsumi, M.; Phinney, B. O.; Jefferies, P. R.; Henrick, C. A. *Science* **1964**, *144*, 849−850.
(7) (a) Chen, K.; Shi, Q.; Fujioka, T.; Zhang, D.-C.; Hu, C.-Q.; Jin, J.-Q.; Kilkuskie, R. E.; Lee, K.-H. *J. Nat. Prod.* **1992**, *55*, 88−92. (b) Chen, K.; Shi, Q.; Fujioka, T.; Nakano, T.; Hu, C.-Q.; Jim, J.-Q.; Kilkuskie, R. E.; Lee, K.-H. *Bioorg. Med. Chem.* **1995**, *3*, 1345−1348. Total synthesis: Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929−9930.
(8) Villalobos, N.; Martin, L.; Macias, M. J.; Mancheno, B.; Grande, M. *Phytochemistry* **1994**, *37*, 635−639.
(9) (a) Recent synthesis: Berettoni, M.; Chiara, G. D.; Iacoangeli, T.; Surdo, P. L.; Bettolo, R. M.; di Mirabello, L. M.; Nicolini, L.; Scarpelli, R. *Helv. Chim. Acta* **1996**, *79*, 2035−2041 and references therein. (b) Our own synthetic study: Ihara, M.; Toyota, M.; Fukumoto, K.; Kamitani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151−2161 and references therein.
(10) Wenkert, E. *Chem. Ind. (London)* **1955**, 282−284.
(11) Although a face-protonated, trachlobane-type intermediate is employed in ref 10, we prefer the bridged ions **2** and **3** that are now widely accepted, see: Coates, R. M.; Bertram, E. F. *J. Org. Chem.* **1971**, *36*, 3722−3729 and references therein.
(12) Recent examples: Garcia-Granados, A.; Duenas, J.; Guerrero, A.; Martinez, A.; Parra, A. *J. Nat. Prod.* **1996**, *59*, 124−130 and references therein.
(13) In some cases, the cyclopropylcarbinyl radical can be trapped to give the cyclopropane derivative. For example, see: Srikrishna, A.; Sharma, V. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 177−181 and references therein.
(14) For reviews, see: (a) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347−359. (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091−2115.
(15) (a) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *38*, 4525−4528. (b) Stork, G.; Mook, R., Jr. *Ibid.* **1986**, *38*, 4529−4532.
(16) (a) Ito, Y.; Aoyama, H.; Hirao, T.; Machizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494−496. (b) Kende, A. S.; Roth, B.; Sanfilippo, P. J. *Ibid.* **1982**, *104*, 1784−1785.

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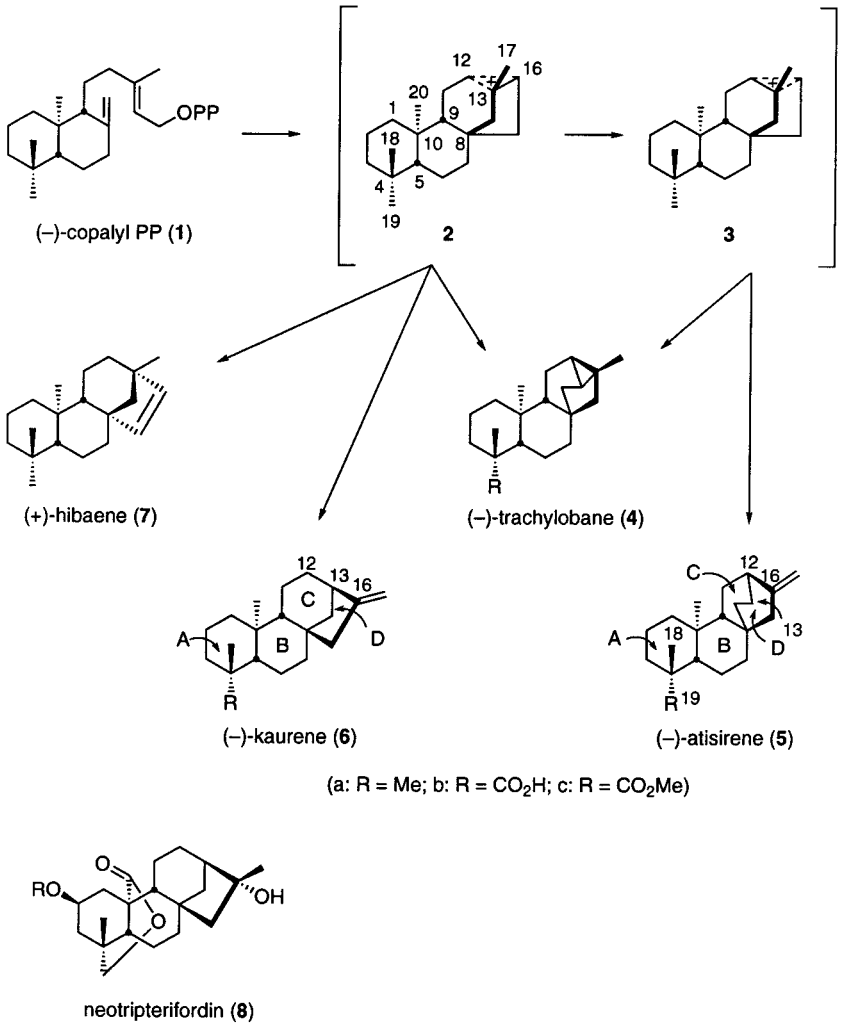
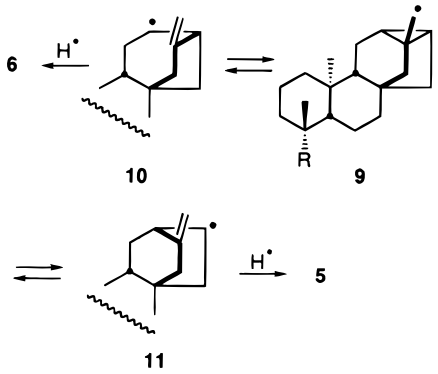
Scheme 1



Scheme 2



of a kaurene derivative **12**, leading to the first total synthesis of (±)-methyl atis-16-en-19-oate (**5c**).

Pd(II)-Catalyzed Cycloalkenylation Reaction

During the course of investigations directed toward a total synthesis of gibberellin A_{12}, we recently reported a route to the bicyclo[3.2.1]octane derivative **15**[17b] which utilized a Pd(II)-promoted cyclization reaction of silyl enol ether **16a** (Table 1). A stoichiometric amount of $Pd(OAc)_2$ allows the aforesaid cycloalkenylation reaction to proceed under mild conditions; however, this process suffers from low yield on a large scale probably due to tarry Pd(0) species produced by reductive elimination. This is a serious limitation in the application of cycloalkenylation reaction involving Pd(II).

To address this issue, reproducible catalytic processes become highly desirable. We demonstrate the viability of such a process as exemplified by the conversion of cross-conjugated silyl enol ethers **16** to bicyclo[3.2.1]octenone **15**. Substrates **16** were synthesized by the basic treatment of **17**[17] followed by silylation. A number of different reaction parameters, such as silyl groups, amount of $Pd(OAc)_2$, concentrations, and solvents were evaluated in order to optimize the reaction (Table 1). Since DMSO has been recently reported to be an excellent solvent for Pd(II)-catalyzed dehydrosilylation of silyl enol ethers,[18] the first attempt to perform cycloalkenylation reaction was made by employing **16a** in the presence of 10 mol % of $Pd(OAc)_2$ under O_2 (1 atm) in DMSO and resulted in the formation of the desired compound **15** in 62% yield along with dienone **19** (21%) (run 1). For evaluation of the effect of the silyl protecting group, we performed the same reaction using **16b**, in which adduct **15** was isolated in 76% yield (run 2). Switching to TBDMS further enhanced the yield to 81% (run 3). The dependence of the

(17) (a) Toyota, M.; Wada, T.; Nishikawa, Y.; Yanai, K.; Fukumoto, K. *Synlett* **1994**, 597−598. (b) Toyota, M.; Wada, T.; Nishikawa, Y.; Yanai, K.; Fukumoto, K.; Kabuto, C. *Tetrahedron* **1995**, *51*, 6927−6940. (c) Toyota, M.; Wada, T.; Fukumoto, K. *Heterocycles* **1995**, *41*, 1135−1138.

(18) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423−2426. For mechanistic studies, see: Larock, R. C.; Lee, N. H. *Ibid.* **1991**, *42*, 5911−5914 and references therein.

Scheme 3

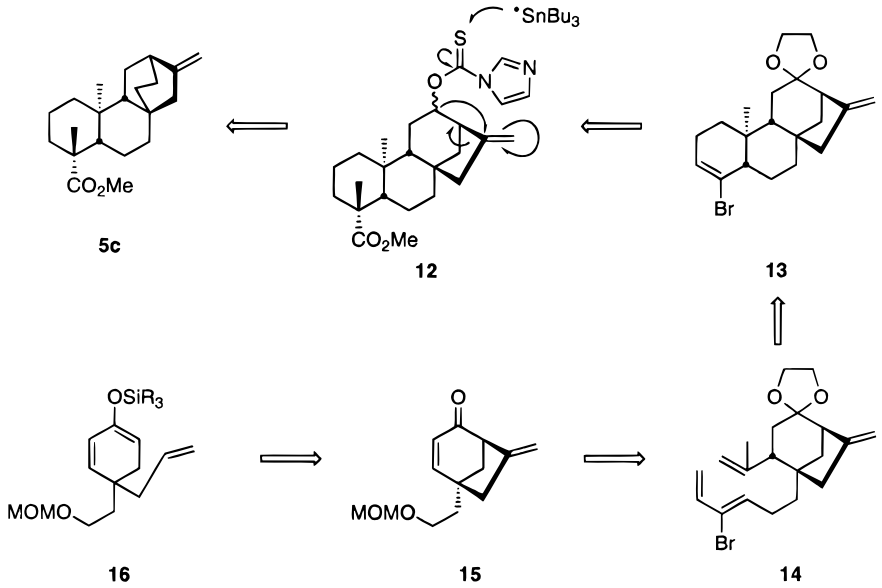
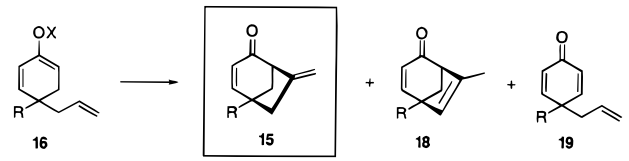


Table 1. Pd-Catalyzed Cycloalkenylation Reaction of Cross-Conjugated Silyl Enol Ethers (**16**)[a]

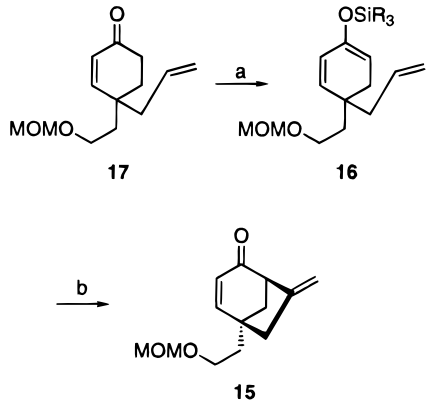


					yield (%)			
run	X	$Pd(OAc)_2$ (mol %)	solvent (mol/L)	time (h)	**15**	**18**	**19**	**16**
1	TMS	10	DMSO (0.05)	17	62	trace	21	
2	TES	10	DMSO (0.05)	11	76	trace	14	
3	TBDMS	10	DMSO (0.05)	19	81	4	5	
4	TBDMS	5	DMSO (0.05)	4	82	3	3	
5	TBDMS	3	DMSO (0.05)	22	81	5	trace	
6	TBDMS	1	DMSO (0.05)	26	18	trace	trace	64
7	TBDMS	10	DMSO (0.1)	5	89	2	3	
8	TBDMS	10	DMSO (0.3)	15	78	3	5	
9	TBDMS	10	DMSO−H_2O[b] (0.05)	4.5	63	trace	trace	
10	TBDMS	10	MeCN (0.05)	13	37	trace	trace	57

[a] All reactions were carried out at 45 °C under O_2 (1 atm). [b] DMSO:H_2O (10:1 v/v).

amount of $Pd(OAc)_2$ on the reaction was next investigated. As a result, cycloalkenylation reactions were conveniently carried out by heating a mixture of **16c** with a catalytic amount (3∼10 mol %) of $Pd(OAc)_2$ at 45 °C for 4−22 h (runs 3−5). In contrast to the dehydrosilylation,[18] even at a higher concentration (0.3 M), the hydrolysis of silyl enol ether was not observed and the major product was still **15** (runs 7 and 8). The cycloalkenylation reaction also tolerated the presence of water (run 9). The effects of solvents were briefly examined. Unfortunately, MeCN was not suitable for this catalytic system (run 10) (Scheme 4).[19]

Scheme 4[a]



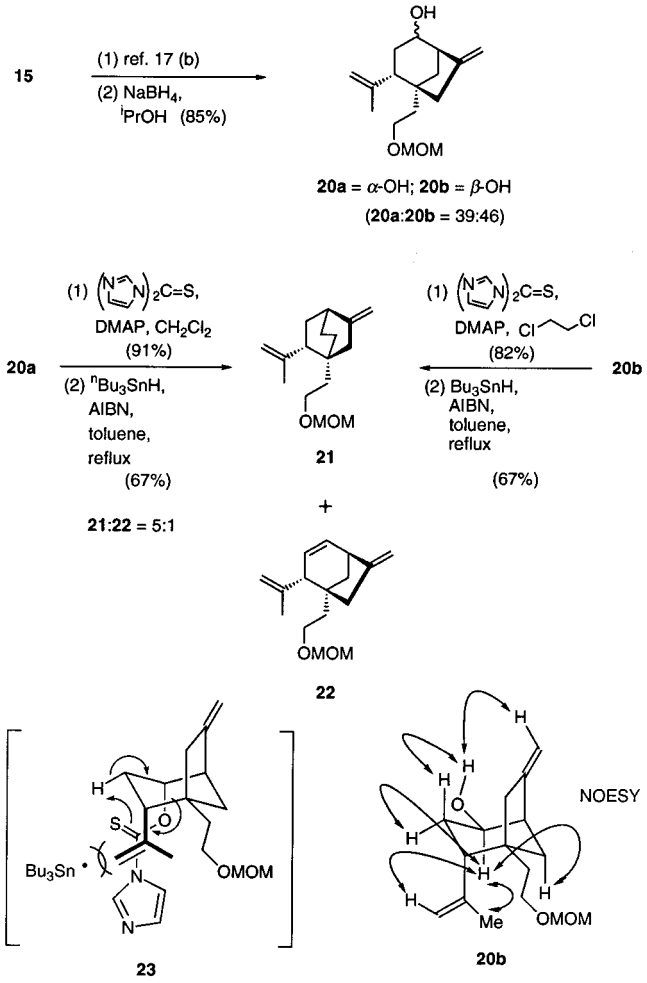
[a] (a) LDA, THF, −78 °C, then R_3SiCl, HMPA, −78 to 0 °C. (b) See Table 1.

Homoallyl−Homoallyl Radical Rearrangement Reaction Leading to Bicyclo[2.2.2]octane

To explore the feasibility of the designed synthetic strategy, the novel homoallyl−homoallyl radical rearrangement reaction of the corresponding α- and β-thioimidazolides of **20** was first examined. The requisite substrates **20** were readily prepared by sequential stereoselective 1,4-conjugate addition[20] of the

(19) To prove the effect of the solvent, we used HMPA (to give **15**, 36%) and DMPU (to give **15**, 45%) as polar solvents.

Scheme 5



isopropenyl group followed by $NaBH_4$ reduction. Column chromatography of **20** on silica gel (hexanes−EtOAc = 5:1) provided two fractions. The first fraction gave **20a** (α-OH), and on the other hand, the second one afforded **20b** (*β*-OH). The structure assigned to **20b** is supported by its IR spectrum which shows a band at 3450 cm^{-1} (hydroxyl) and the phase-sensitive NOESY experiment in the NMR spectrum (Scheme 5). The radical deoxygenation reaction[21] of **20b** via the corresponding thioimidazolide proceeded smoothly, giving rearranged product **21** as a sole product. The spectral properties of the rearranged product were consistent with structure **21**.[22] When **20a** was subjected to the same conditions, however, **21** was obtained together with **22** (Chugaev-type elimination product) (**21**:**22** = 5:1). The generation of **22** could be due to the nonbonded interaction between the isopropenyl group in **23** and $Bu_3Sn^•$ as shown in Scheme 5.

To provide some understanding of the previous results, the calculations were performed on a system involving radical species **24** by means of the semiempirical Hamiltonian PM3 in MOPAC 7.0.[23] As shown in Figure 1, the steric congestion between the isopropenyl group and α-radical in **24A**, generated from **20a**, makes it less favorable than the alternative **24B**, which gives rise to the desired compound **21** (Figure 1).

To circumvent the above problem, we planned to construct the bicyclo[2.2.2]octane ring system of **5c** by the homoallyl−homoallyl radical rearrangement process after intramolecular Diels−Alder reaction.

Intramolecular Diels−Alder Reaction Oriented toward Perhydrophenanthrene Construction

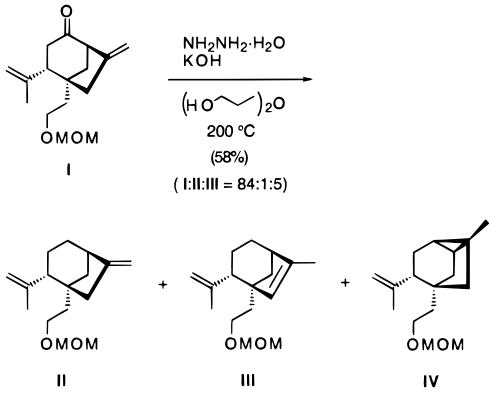
Tosylation of alcohol **25**,[17] followed by cyanation, gave cyanide **26** in 97% overall yield in two steps, which was then subjected to successive partial reduction with DIBALH (91%) and Wittig olefination (92%) to afford **27** as mixture of geometrical isomers (*Z*:*E* = 5:1). Reduction of **27** with DIBALH enabled the separation of each isomer as the corresponding alcohol, and the desired *Z*-isomer obtained (74%) was oxidized with MnO_2, followed by methylenation, to give rise to tetraene **14** in 83% overall yield in two steps. An intramolecular Diels−Alder reaction[24] of **14** was conducted in toluene at 200 °C for 45 h in a sealed tube to afford the desired perhydrophenanthrene derivative **13** and its stereoisomer **28** in 74% yield as a 5.7:1 mixture. Although recrystallization of the above mixture from Et_2O−hexane gave pure **13**, the separation of stereoisomers **13** and **28** was tedious at this stage. However, it was found that the desired major isomer was easily separated as the corresponding saturated ester **29**. Accordingly, the above cycloadducts were subjected to carbomethoxylation (70%) followed by conjugate reduction (94%) with Mg in MeOH[25] without further purification.

The stereoselectivity observed for the above cycloaddition can be rationalized by considering two conformers (**14A**,**B**). The major product **13** arises via conformer **14A**. In the alternative conformer **14B**, the diene unit suffers from unfavorable steric interactions with the axial hydrogen as shown in Figure 2. Finally, the stereochemistry of the major isomer was established by transformation into **5c**.

(20) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025−4028.

(21) (a) Barton, D. H. R.; Ferreira, J. A.; Jaszberenyi, J. C. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York,-1997; pp 15−172. (b) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc*. **1997**, *119*, 6949−6950.

(22) Deoxygenated compound **II** was synthesized by the Wolff−Kishner reduction of **I** (ref 17b) to make sure that the structure of **21** is correct. It is worth while to note that a small amount of tricyclo[3.2.1.$0^{2,7}$]octane derivative **IV** and endo-olefin **III** was produced under these reaction conditions.



(23) Minimum energy structures were located by the global search program GMMX (Version 1.0) (Serena software, Bloomington, IN). The lowest energy structure **24C** located in this fashion was then subjected to molecular mechanics minimization using the MMX force field (Gajewski, J. J.; Gilbert, K. E.; Mckelvey, J. In *Advances in Molecular Modeling*; Liotta, D., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 65−92) in the computer program PCMODEL (Version 5.01) (Serena software, Bloomington, IN). Finally, this molecular mechanics structure was reminimized by employing the PM3 model in the program MOPAC (Version 7.0) (Serena software, Bloomington, IN).

(24) For intramolecular Diels−Alder reactions of Br-containing trienes, see: Roush, W. R.; Kageyama, M.; Rita, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem*. **1991**, *56*, 1192−1210 and references therein.

(25) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409−2412.

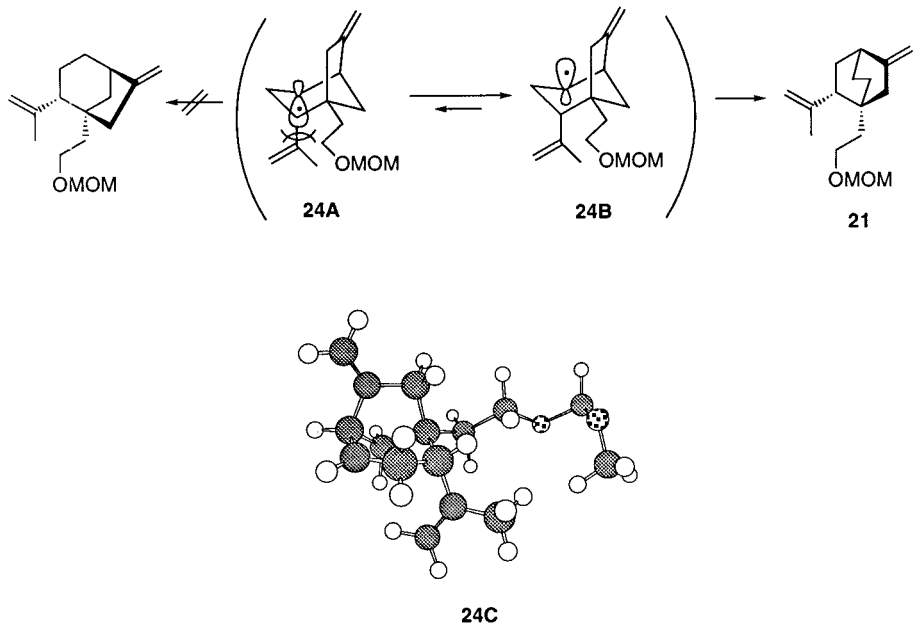


Figure 1.

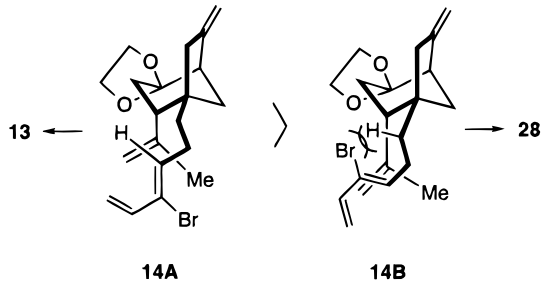


Figure 2.

Total Synthesis of (±)-Methyl Atis-16-en-19-oate (5c)

With the efficient synthesis of **29** realized, the stage was now set for the completion of the synthesis. Ester **29** was converted to **30** via stereoselective methylation (84%) and hydrolysis of the ethylene acetal moiety (100%). To confirm the stereochemistry of keto ester **30**, it was subjected to Wolff−Kishner reduction. Namely, treatment of **30** with excess $NH_2NH_2 \cdot H_2O$ and KOH in bis(ethylene glycol) at 200 °C furnished the desired (±)-methyl kaur-16-en-19-oate (**6c**)[26] (51% in two steps) after reesterification with CH_2N_2. It is surprising that (±)-methyl trachyloban-19-oate (**4c**)[27,28] was also obtained in 11% overall yield in two steps.[29] It should be further noted that the present approach employing the intramolecular Diels−Alder reaction of the bromo diene **14** provides an efficient route for these diterpenes.

Finally, **30** was transformed into (±)-**5c** as shown in Scheme 7. Reduction of **30** with $NaBH_4$ produced **31** in 93% yield as a 1:3.6 mixture in which the β-oriented hydroxyl group was predominant.[30] Hydroxyesters **31** were then acylated with 1,1′-thiocarbonyldiimidazole to afford **12**, which was submitted to a deoxygenation reaction;[21] Bu_3SnH and catalytic amounts of AIBN in toluene were added to **12** in toluene (0.01 M) over a period of 3 h. Under these reaction conditions, the homoallyl radical generated from **12** was smoothly rearranged, as expected, via successive 3-exo-trig cyclization and 3-exo fragmentation, to furnish **5c** as the *sole* product in 68% overall yield in two steps.[31] The spectral properties (^{1}H NMR and IR) of (±)-**5c** were identical in all respects to those of (−)-**5c** provided by Coates.

Conclusions

We have synthesized racemic methyl kaur-16-en-19-oate (**6c**), methyl trachyloban-19-oate (**4c**), and methyl atis-16-en-19-oate (**5c**) via a common intermediate **30**. The key step in the synthesis of **5c** is a homoallyl−homoallyl radical rearrangement that allowed, in a one-pot process, the construction of the atisirene skeleton without isomerization of the exomethylene moiety. Moreover, this successful approach opens a novel pathway for the syntheses of other atisirene-type diterpenoids and diterpene alkaloids such as atisine.

Experimental Section[32]

General Method for the Preparation of Silyl Enol Ethers (16a−c). To a stirred solution of LDA (1.2 mmol) in THF (2 mL) cooled to −78 °C was added dropwise a solution of substrate **17**[17] (1.0 mmol) in THF (1 mL). After 45 min, a solution of TBDMSCl (1.5 mmol) and HMPA (1.2 mmol) in THF (1 mL) was added at the same temperature, and the resulting mixture was allowed to warm to 0 °C. After removal of the solvent, the residue was diluted with hexane, washed with H_2O and brine, and dried over K_2CO_3. Removal of the solvent and chromatography of the crude product on silica gel with hexanes−EtOAc (20:1 v/v) afforded the TBDMS enol ether as a colorless oil (yields of 95−100%). TMS/TES enol ethers were prepared in the same manner as the corresponding TBDMS enol ethers, by quenching the lithium enolates with chlorotrimethylsilane (1.5 equiv)/chlorotriethylsilane (1.5 equiv). TMS enol ether was purified by bulb-to-bulb distillation.

(26) Mori, K.; Matsui, M. *Tetrahedron Lett.* **1966**, 175−180; *Tetrahedron* **1968**, *24*, 3095−3111.

(27) Pyrek, J. S. *Tetrahedron* **1970**, *26*, 5029−5032.

(28) (a) Cory, R. M.; Naguib, Y. M. A.; Rasmussen, M. H. *J. Chem. Soc., Chem. Commun.* **1979**, 504−506. (b) Cory, R. M.; Chan, D. M. T.; Naguib, Y. M. A.; Rastall, M. H.; Renneboog, R. M. *J. Org. Chem.* **1980**, *45*, 1852−1863 and references therein.

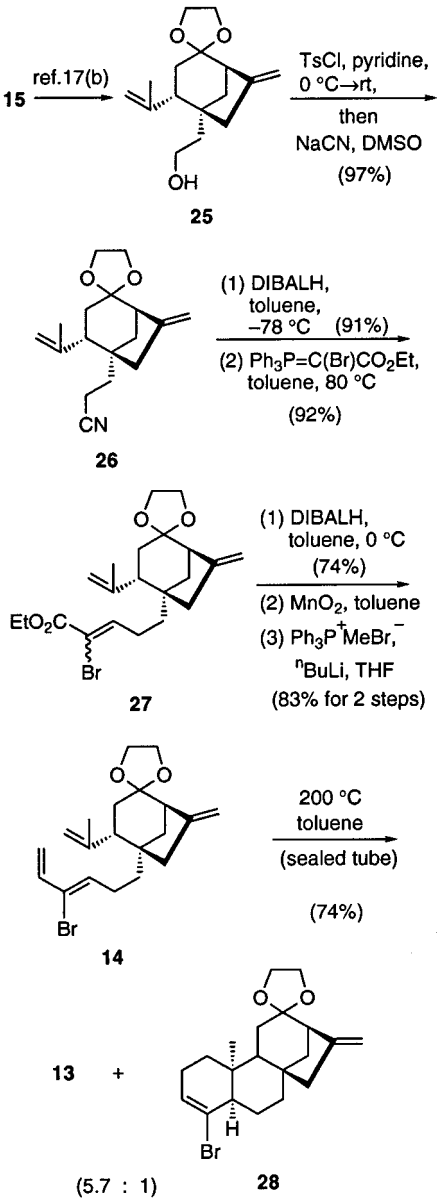
(29) For a possible mechanism, we propose a sigmatropic elimination of N_2 from a β-oriented diazene intermediate (CH−N=NH).

(30) Lewis, N. J.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1270−1278.

(31) Although deoxygenation of the corresponding thiobenzoate, prepared from naturally occurring 12α-acetoxykaur-16-en-19-oic acid, was performed for degradation purposes, the reported product was (−)-kaurenoic acid (mass spectral analysis), see: Beale, M. H.; Bearder, J. R.; MacMillan, J.; Matsuo, A.; Phinney, B. O. *Phytochemistry* **1983**, *22*, 875−881.

(32) See the Experimental Section of ref 17b.

Scheme 6



(±)-2-(*tert*-Butyldimethylsiloxy)-5-(2-(methoxymethoxy)ethyl)-5-(2-propenyl)cyclohexa-1,3-diene (16c). IR: 1670 and 1040 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 0.22 (6H, s), 1.07 (9H, s), 1.75 (1H, dt, J = 13.5 and 7.0), 1.86 (1H, dt, J = 13.5 and 7.0), 2.11−2.30 (4H, m), 3.27 (3H, s), 3.65 (2H, t, J = 7.0), 4.56 (2H, s), 4.85−4.93 (1H, m), 5.04−5.16 (2H, m), 5.55 (1H, d, J = 10.0), and 5.77−5.93 (2H, m). ^{13}C NMR (75 MHz, C_6D_6): δ −4.24, 18.30, 25.96, 32.87, 36.63, 38.27, 43.61, 54.89, 64.69, 96.56, 101.27, 117.51, 125.77, 135.17, 136.73, and 147.86. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12. Found: C, 67.35; H, 10.04.

(±)-5-(2-(Methoxymethoxy)ethyl)-5-(2-propenyl)-2-(trimethylsiloxy)cyclohexa-1,3-diene (16a). IR: 1680, 1650, and 1020 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 0.19 (9H, s), 1.60−1.80 (2H, m), 2.19 (2H, d, J = 5.5), 2.06−2.24 (2H, m), 3.35 (3H, s), 3.51−3.66 (2H, m), 4.59 (2H, s), 4.72−4.80 (1H, m), 4.96−5.09 (2H, s), 5.55 (1H, d, J = 10.0), 5.65 (1H, dd, J = 10.0 and 2.0), and 5.70−5.83 (1H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 0.32, 32.86, 36.63, 38.36, 43.70, 54.90, 64.71, 96.56, 101.00, 117.47, 125.83, 135.19, 136.76, and 147.76. Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 64.53; H, 9.36.

(±)-5-(2-(Methoxymethoxy)ethyl)-5-(2-propenyl)-2-(triethylsiloxy)-cyclohexa-1,3-diene (16b). IR: 1655 and 1050 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 0.76 (2H, q, J = 7.7), 1.10 (3H, t, J = 7.7), 1.76 (1H, dt, J = 13.5 and 7.3), 1.87 (1H, dt, J = 13.5 and 7.3), 2.12−2.30 (4H, m), 3.27 (3H, s), 3.66 (2H, t, J = 7.3), 4.57 (2H, s), 4.90 (1H, dt, J = 4.0 and 2.0), 5.05−5.18 (2H, m), 5.55 (1H, d, J = 10.0), 5.85 (1H, ddt, J = 17.5, 10.0, and 7.5), and 5.91 (1H, dd, J = 10.0 and 2.0). ^{13}C NMR (75 MHz, C_6D_6): δ 5.43, 7.00, 32.92, 36.64, 38.29, 43.64, 54.90, 64.72, 96.59, 100.56, 117.51, 125.80, 135.22, 136.76, and 147.91. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12. Found: C, 67.32; H, 10.42.

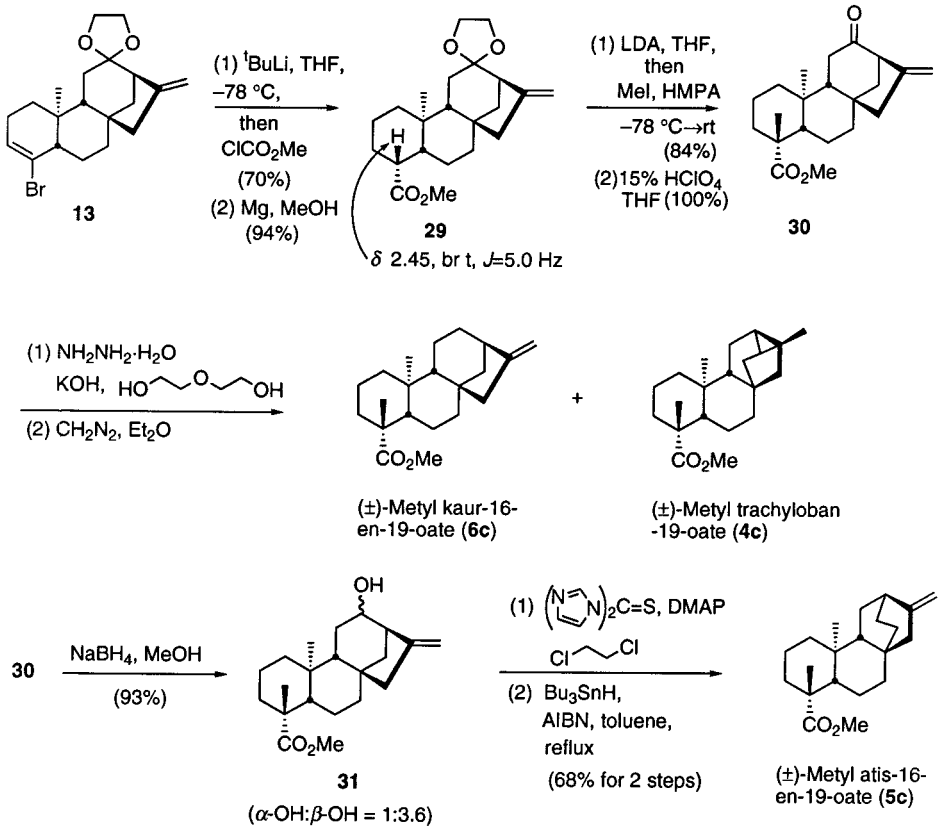
Palladium-Catalyzed Cycloalkenylation Reaction. (±)-5-(2-(Methoxymethoxy)ethyl)-7-methylidene-*cis*-bicyclo[3.2.1]oct-3-en-2-one (15)[17b] (as a Typical Procedure; Run 4). To a stirred solution of TBDMS enol ether **16c** (78.7 mg, 0.233 mmol) in DMSO (4.6 mL) was added $Pd(OAc)_2$ (2.60 mg, 11.6 μmol) at room temperature, and the resulting solution was again stirred under O_2 (1 atm) for 4 h. The reaction mixture was diluted with Et_2O and filtered through Celite to remove Pd black. H_2O (50 mL) was added to the filtrate, and the layers were separated. The aqueous layer was further extracted with Et_2O, and the combined organic layers were washed with ice-cold 10% HCl, saturated $NaHCO_3$ and brine and dried. After removal of the solvent, the residue was chromatographed. Elution with a 2:1 mixture of hexane−EtOAc furnished **15**[17b] (42.4 mg, 82%), **18** (1.7 mg, 3%), and **19** (1.6 mg, 3%), each as a colorless oil.

(±)-5-(2-(Methoxymethoxy)ethyl)-7-methyl-*cis*-bicyclo[3.2.1]octa-3,6-dien-2-one (18). IR: 1675 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 1.78 (3H, d, J = 1.8), 1.96 (1H, dt, J = 14.0 and 6.5), 2.10 (1H, dt, J = 14.0 and 6.5), 2.46 (1H, ddd, J = 9.5, 4.5, and 1.8), 2.56 (1H, d, J = 9.5), 3.15 (1H, br d, J = 4.5), 3.36 (3H, s), 3.66 (2H, t, J = 6.6), 4.62 (2H, s), 5.35 (1H, dd, J = 10.0 and 1.8), 6.01 (1H, br s), and 7.25 (1H, dd, J = 10.0 and 1.8). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 15.67, 35.38, 51.08, 55.47, 55.67, 62.18, 64.74, 96.60, 121.71, 139.19, 142.85, 160.01, and 199.99. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.20; H, 8.10.

(±)-4-(2-(Methoxymethoxy)ethyl)-4-(2-propenyl)-cyclohexa-2,5-dien-1-one (19). IR: 1665 and 1625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (2H, br t, J = 7.0), 2.38 (2H, d, J = 7.3), 3.29 (3H, s), 3.37 (2H, br t, J = 7.0), 4.50 (2H, s), 5.00−5.12 (2H, m), 5.50−5.67 (1H, m), and 6.32 (2H, dt, J = 10.5 and 2.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.67, 44.21, 44.50, 55.38, 64.12, 96.55, 119.20, 129.88, 131.80, 153.75, and 186.20. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.00; H, 8.44.

(1*R,2*R**,4*S**,5*S**)-5-((Methoxymethoxy)ethyl)-4-(methylethenyl)-7-methylidenebicyclo[3.2.1]octan-2-ol (20a) and (1*R**,2*S**,4*S**,5*S**)-5-((Methoxymethoxy)ethyl)-4-(methylethenyl)-7-methylidenebicyclo-[3.2.1]octan-2-ol (20b).** To a stirred solution of ketone **15**[17b] (134 mg, 0.508 mmol) in 2-propanol (5 mL) was added $NaBH_4$ (193 mg, 5.09 mmol) at room temperature, and then the mixture was stirred at room temperature for 12 h. After removal of the solvent, saturated brine (7 mL) was added. The resulting mixture was extracted with $CHCl_3$, and then the organic layer was dried and evaporated to leave an oil, which was chromatographed. Elution with a 5:1 mixture of hexane−EtOAc afforded α-alcohol **20a** (52.9 mg, 39%) followed by β-alcohol **20b** (62.4 mg, 46%), each as a colorless oil. **20a**: IR: 3450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (1H, br dd, J = 11.5 and 5.0), 1.52 (1H, d, J = 14.5), 1.56 (1H, ddd, J = 14.0, 8.5, and 6.0), 1.77 (1H, br s), 1.93 (3H, d, J = 0.6), 2.03 (1H, ddd, J = 14.0, 8.5, and 5.5), 2.08 (1H, ddd, J = 14.0, 8.5, and 4.5), 2.22 (1H, d, J = 8.5), 2.28−2.34 (2H, m), 2.44 (1H, dd, J = 11.5 and 1.5), 2.71 (1H, dd, J = 5.0 and 3.5), 3.35 (1H, br s), 4.82−4.91 (3H, m), and 5.04−5.07 (1H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 23.71, 31.55, 32.94, 37.93, 43.85, 45.07, 48.85, 49.76, 55.15, 64.79, 72.24, 96.43, 105.67, 113.32, 149.37, and 152.40. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.13; H, 9.84. Found: C, 72.17; H, 9.80. **20b**: IR: 3450 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.40 (1H, ddd, J = 14.0, 11.5, and 8.0), 1.44 (1H, ddd, J = 12.0, 8.0, and 5.5), 1.60 (1H, br s), 1.78 (1H, ddd, J = 15.0, 9.0, and 5.5), 1.78−1.81 (3H, m), 1.84 (1H, ddd, J = 15.0, 9.0, and 5.5), 1.89 (1H, dd, J = 12.0 and 1.5), 2.27 (1H, br d, J = 8.0), 2.32 (1H, dt, J = 12.0 and 2.5), 2.61 (1H, br dd, J = 5.5 and 3.5), 3.35 (3H, s), 3.47 (1H, ddd, J = 13.5, 9.0, and 6.7), 3.58 (1H, ddd, J = 13.5, 9.0, and 5.5), 3.88 (1H, ddd, J = 11.5, 6.0, and 3.5), 4.60 (2H, s), 4.76 (1H, br s), 4.82 (1H, br s), 4.90 (1H, br s), and 4.91 (1H, br s). ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 24.62, 35.09, 37.37, 38.31, 44.21, 44.74, 50.45, 50.67, 55.22, 64.89, 70.20, 96.45, 106.58, 114.24, 147.95, and 150.94. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.94; H, 9.91.

Scheme 7



2-[(1*S,2*S**,4*S**)-1-(2-(Methoxymethoxy)ethyl)-5-methylidenebicyclo[2.2.2]octan-2-yl]prop-1-ene (21). (A) From 20b:** To a stirred solution of **20b** (40.3 mg, 0.151 mmol) in 1,2-dichloroethane (1 mL) was added 1,1′-thiocarbonyldiimidazole (90.8 mg, 0.459 mmol) at room temperature, and then the mixture was again stirred at room temperature for 13 h. After removal of the solvent, the residue was chromatographed. Elution with a 2:1 mixture of hexane−EtOAc gave the thioimidazolide (46.8 mg, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (1H, ddd, J = 12.5, 6.0, and 2.0), 1.62 (1H, ddd, J = 14.0, 9.0, and 6.0), 1.85−2.11 (7H, m), 2.26 (1H, dd, J = 16.0 and 2.0), 2.40−2.51 (2H, m), 3.00 (1H, dd, J = 6.0 and 3.0), 3.34 (2H, s), 3.48−3.70 (2H, m), 4.86−4.88 (1H, m), 4.92 (1H, t, J = 1.5), 4.96−5.03 (2H, m), 5.08 (1H, ddd, J = 9.0, 6.0, and 3.0), 7.02 (1H, dd, J = 1.1 and 1.5), 7.62 (1H, t, J = 1.5), and 8.33 (1H, t, J = 1.1). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.37, 29.23, 37.70, 38.04, 44.28, 44.31, 46.57, 50.43, 55.27, 64.68, 83.26, 96.53, 108.30, 115.13, 118.02, 130.88, 136.89, 147.18, 149.58, and 183.48. HRMS calcd for $C_{20}H_{28}N_2O_3S$ (M^+): 376.1819. Found: 376.1772.

To a stirred solution of the above thioimidazolide (24.4 mg, 64.8 μmol) in degassed toluene (3 mL) was slowly added a degassed toluene solution (0.3 mL) of Bu_3SnH (0.025 mL, 90.2 μmol) and AIBN (0.6 mg, 3.7 μmol) over a period of 2.5 h under reflux. After 1 h of refluxing, Et_2O (5 mL) was added, and the resulting mixture was successively washed with 5% HCl (2 mL), saturated $NaHCO_3$ and brine, dried, and evaporated to yield an oil, which was chromatographed. Elution with a 30:1 mixture of hexane−EtOAc afforded **21** (10.8 mg, 67%) as a colorless oil. IR ($CHCl_3$): 1639 and 1650 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (1H, ddd, J = 11.5, 4.5, and 2.0), 1.34 (1H, ddd, J = 11.5, 5.0, and 2.0), 1.40−1.81 (9H, m), 2.05−2.13 (1H, m), 2.17−2.24 (3H, m), 3.33 (3H, s), 3.53 (2H, dt, J = 9.0 and 6.0), 4.57 (2H, s), 4.60 (1H, q, J = 2.0), 4.73 (1H, q, J = 2.0), 4.76−4.78 (1H, m), 4.79−4.81 (1H, m). ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 21.76, 26.76, 26.82, 33.95, 35.30, 36.05, 37.62, 42.39, 48.91, 55.26, 64.40, 96.55, 105.33, 113.62, 147.74, and 151.94. HRMS calcd for $C_{16}H_{26}O_2$: 250.1931. Found: 250.1939.

(B) From 20a: To a stirred solution of **20a** (28.8 mg, 0.108 mmol) in CH_2Cl_2 (2 mL) were added 1,1′-thiocarbonyldiimidazole (58.4 mg, 0.328 mmol) and DMAP (41.9 mg, 0.235 mmol) at room temperature, and then the resulting yellowish mixture was again stirred at room temperature for 20 h. After removal of the solvent, the residue was chromatographed. Elution with a 3:1 mixture of hexane−EtOAc furnished the thioimidazolide (36.8 mg, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (1H, dd, J = 11.5 and 5.0), 1.64 (1H, ddd, J = 12.5, 8.0, and 6.0), 1.89 (3H, d, J = 0.6), 1.88−1.99 (1H, m), 2.15 (1H, ddd, J = 12.5, 7.5, and 5.0), 2.26−2.44 (5H, m), 3.15 (1H, br dd, J = 5.0 and 3.0), 3.36 (3H, s), 3.46−3.64 (2H, m), 4.60 (2H, s), 4.96 (1H, t, J = 1.5), 4.99 (1H, br s), 5.02 (1H, br s), 5.09 (1H, br t, J = 2.5), 5.51 (1H, br t, J = 4.0), 7.03 (1H, dd, J = 1.4 and 0.8), 7.65 (1H, t, J = 1.4), and 8.34 (1H, br s). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.15, 27.99, 33.92, 37.54, 43.79, 45.22, 45.66, 47.59, 55.24, 64.58, 83.78, 96.49, 108.18, 113.14, 118.17, 130.89, 137.04, 147.01, 149.88, and 183.59. HRMS calcd for $C_{20}H_{28}N_2O_3S$: 376.1819. Found: 376.1819.

To a stirred solution of the above thioimidazolide (31.7 mg, 84.2 μmol) in degassed toluene (4 mL) was slowly added a degassed toluene solution (0.4 mL) of Bu_3SnH (34 μL, 0.123 mmol) and AIBN (1 mg, 6 μmol) over a period of 2 h under reflux. After 1 h of refluxing, the solvent was evaporated to give an oil, which was directly chromatographed. Elution with a 30:1 mixture of hexane−EtOAc provided **21** (11.8 mg, 56%) and **22** (2.4 mg, 11%) as a colorless oil. **22:** IR ($CHCl_3$): 1645 and 1660 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (1H, br ddd, J = 10.5, 3.5, and 1.0), 1.77 (3H, dd, J = 1.2 and 0.6), 1.61 (1H, ddd, J = 13.0, 9.0, and 5.5), 1.81−1.92 (2H, m), 2.20 (1H, br dq, J = 16.0 and 2.0), 2.40 (dt, J = 16.0 and 2.0), 2.72 (1H, dd, J = 3.5 and 1.5), 2.91 (1H, dd, J = 6.5 and 3.5), 3.58 (3H, s), 3.56 (1H, dt, J = 9.0 and 5.5), 3.72 (1H, dt, J = 9.0 and 5.0), 4.55 (1H, br s), 4.61 (2H, s), 4.71−4.76 (1H, m), 4.81−4.84 (1H, m), 4.86−4.90 (1H, m), 5.27 (1H, dd, J = 9.0 and 3.5), and 5.98 (1H, dddd, J = 9.0, 6.5, 1.5, and 1.0); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 22.26, 37.29, 38.41, 43.42, 44.35, 44.39, 55.27, 57.16, 64.68, 96.50, 101.37, 115.02, 127.96, 132.92, 146.33, and 157.11. HRMS calcd for $C_{16}H_{24}O_2$ (M^+): 248.1776. Found: 248.1782.

3-[Spiro[(1*R,4*S**,5*S**)-4-(methylethenyl)-7-methylidenebicyclo-[3.2.1]octan-2,2′-1′,3′-dioxolan]-5-yl]propanenitrile (26).** To a solution of **25**[17b] (1.70 g, 6.44 mmol) in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (1.16 g, 8.41 mmol) at 0 °C, and then the

mixture was placed in a refrigerator for 14 h. After the addition of H_2O (20 mL), the resulting solution was extracted with Et_2O. The ethereal layer was washed in succession with 10% $CuSO_4$ (10 mL × 3), H_2O (5 mL), and brine, dried, and evaporated to leave the tosylate (2.75 g) as a white solid, which was used in the next step without further purification.

To a stirred solution of the above tosylate (2.75 g) in DMSO (16 mL) was added powdered NaCN (442 mg, 8.57 mmol) at room temperature, and then the resulting clear solution was again stirred at room temperature for 24 h. After addition of H_2O (30 mL), the mixture was extracted with Et_2O. The ethereal layer was washed with H_2O (16 mL) and brine, dried, and evaporated to give a white solid, which was chromatographed. Elution with a 5:1 mixture of hexane−EtOAc afforded **26** (1.71 g, 97% for 2 steps) as a white solid. An analytical sample, obtained as colorless prisms by recrystallization of a small amount of this material from Et_2O−hexane, exhibited mp 89.0−90.5 °C. IR ($CHCl_3$): 2260 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (1H, ddd, J = 12.0, 5.5, and 1.5), 1.57 (1H, dd, J = 15.0 and 1.5), 1.65 (1H, ddd, J = 13.5, 10.5, and 6.0), 1.94 (3H, s), 1.97 (1H, ddd, J = 13.5, 10.5, and 5.5), 2.10 (1H, dd, J = 15.0 and 9.5), 2.19−2.46 (6H, m), 2.60 (1H, dd, J = 5.5 and 1.5), 3.86−4.04 (4H, m), 4.80 (1H, br s), 4.86 (1H, br s), 4.93 (1H, br s), and 5.05 (1H, br s). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.5, 22.17, 34.14, 34.86, 36.69, 44.00, 44.32, 49.71, 50.87, 63.88, 64.70, 108.80, 110.24, 114.96, 120.40, 148.32, and 148.99. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.54; H, 8.44; N, 4.89.

Ethyl 2-Bromo-3-[spiro[(1*R,4*S**,5*S**)-4-(methylethenyl)-7-methylidenebicyclo[3.2.1]octan-2,2′-1′,3′-dioxolan]-5-yl]pent-2-en-1-oate (27).** To a stirred solution of **26** (186 mg, 0.680 mmol) in toluene (5 mL) was added dropwise DIBALH (0.85 mL, 0.95 M in hexane, 0.808 mmol) at −78 °C. After 5 min, saturated NH_4Cl (2 mL) was added at −78 °C, and then the mixture was allowed to warm to room temperature over a period of 10 min. After addition of 10% HCl (20 drops) at room temperature, the resulting mixture was extracted with Et_2O. The ethereal layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated to provide an oil, which was chromatographed. Elution with a 7:1 mixture of hexane−EtOAc furnished the aldehyde (172 mg, 91%), as a colorless oil, which was immediately used in the next reaction. IR ($CHCl_3$): 1722 and 2730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (1H, ddd, J = 11.0, 5.0, and 1.7), 1.50−1.64 (2H, m), 1.85 (1H, ddd, J = 14.0, 8.0, and 5.0), 1.92 (3H, s), 2.09 (1H, dd, J = 14.5 and 8.5), 2.20−2.43 (5H, m), 2.5 (1H, ddd, J = 10.5, 5.0, and 1.6), 2.59 (1H, br d, J = 5.0), 3.85−4.03 (4H, m), 4.74−4.78 (1H, m), 4.87 (1H, d, J = 1.5), 4.91 (1H, br s), 5.01−5.05 (1H, m), 9.75 (1H, t, J = 1.6). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.40, 30.05, 35.02, 36.84, 40.04, 43.87, 44.64, 50.11, 51.20, 63.85, 64.67, 108.36, 114.51, 148.79, and 204.84. HRMS calcd for $C_{17}H_{24}O_3$ (M^+): 276.1725. Found: 276.1724.

A mixture of the above aldehyde (143.5 mg, 0.519 mmol) and the Wittig reagent[33] (326 mg, 0.793 mmol) in toluene (2 mL) was heated at 80 °C for 4 h. After further addition of the Wittig reagent (64.6 mg, 0.157 mmol), heating of the resulting mixture was continued at 80 °C for 1 h. The solvent was removed under reduced pressure, and the residue was chromatographed. Elution with a 7:1 mixture of hexane−EtOAc gave rise to **27** (204 mg, 92%) as a mixture of *Z*- and *E*-isomers in the ratio 5:1. IR: 1630, 1660, 1718 (middle, C═O of *E*-ester), and 1730 (strong, C═O of *Z*-ester) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (2.5H, t, J = 7.2; 3H for *Z*-ester), 1.34 (0.5H, t, J = 7.2; 3H for *E*-ester), 1.28−1.42 (1H, m), 1.52−1.62 (1H, m), 1.65−1.83 (1H, m), 1.92 (0.5H, s; 3H for *E*-ester), 1.93 (2.5H, s; 3H for *Z*-ester), 2.04−2.16 (1H, m), 2.20−2.62 (8H, m), 3.87−4.02 (4H, m), 4.26 (2H, q, J = 7.2), 4.75−4.82 (1H, m), 4.87−4.95 (2H, m), 5.00−5.06 (1H, m), 6.60 (0.17H, t, J = 8.4; 1H for *E*-ester), and 7.24 (0.83H, t, J = 8.4; 1H for *Z*-ester). HRMS calcd for $C_{21}H_{29}BrO_4$ (M^+): 424.1248. Found: 424.1246.

(1*R,4*S**,5*S**)-5-[(*Z*)-4-Bromohexa-3,5-dienyl]-4-(methylethenyl)-7-methylidenebicyclo[3.2.1]octane-2-one 2-Ethylene Acetal (14).** To a stirred solution of **27** (195 mg, 0.458 mmol) in toluene (5 mL) was added dropwise DIBALH (1.0 mL, 0.95 M hexane, 0.95 mmol) at 0 °C. After 10 min of stirring at 0 °C, H_2O (1 mL) was added at 0 °C. The mixture was diluted with hexane (3 mL) and Et_2O (3 mL), and the resulting mixture was again stirred at room temperature until a heavy white precipitate began to form. After addition of $MgSO_4$ at 0 °C, the mixture was filtered through Celite. The filtrate was concentrated to produce an oil, which was chromatographed. Elution with a 5:4 mixture of hexane−Et_2O afforded the desired *Z*-isomer (129 mg, 74%) and then the *E*-isomer (24.9 mg, 14%), each as a colorless oil. *Z*-isomer: IR: 3400 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (1H, dt, J = 12.5 and 5.0), 1.36 (1H, ddd, J = 12.0, 5.0, and 1.5), 1.57 (1H, d, J = 15.0), 1.67 (1H, dt, J = 12.5 and 5.0), 1.93 (3H, s), 2.10 (1H, dd, J = 15.0 and 9.5), 2.27−2.40 (6H, m), 2.44 (1H, d, J = 9.5), 2.59 (1H, br d, J = 5.0), 3.86−4.04 (4H, m), 4.22 (2H, d, J = 6.0), 4.74−4.82 (1H, m), 4.92 (2H, br s), 4.99−5.07 (1H, m), and 5.95 (1H, t, J = 7.0). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.60, 26.70, 34.86, 36.57, 39.77, 44.35, 44.44, 49.60, 51.03, 63.57, 64.42, 67.98, 107.85, 110.45, 114.08, 126.27, 129.93, 148.34, and 149.82. Anal. Calcd for $C_{19}H_{27}BrO_3$: C, 59.53; H, 7.10; Br, 20.85. Found: C, 59.40; H, 7.10; Br, 20.74. *E*-isomer: IR: 3450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (1H, dt, J = 12.5 and 4.5), 1.34 (1H, ddd, J = 11.5, 5.5, and 1.5), 1.56 (1H, dd, J = 15.0 and 1.5), 1.65 (1H, dt, J = 12.5 and 4.5), 1.85 (1H, br t, J = 6.0), 1.93−2.34 (6H, m), 2.42 (1H, br d, J = 9.5), 2.58 (1H, br d, J = 5.5), 3.86−4.02 (4H, m), 4.28 (2H, d, J = 6.0), 4.81 (1H, dd, J = 1.5 and 0.5), 4.89 (1H, d, J = 1.5), 4.91 (1H, s), 5.02−5.04 (1H, m), and 5.99 (1H, t, J = 8.0). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.43, 25.62, 35.03, 37.09, 38.08, 44.41, 44.71, 49.81, 51.06, 62.55, 63.77, 64.58, 108.08, 110.42, 114.06, 124.19, 135.31, 148.95, and 149.71. HRMS calcd for $C_{19}H_{27}BrO_3$ (M^+): 382.1143. Found: 382.1166.

A mixture of the above *Z*-isomer (33.6 mg, 87.7 μmol) and MnO_2 (379 mg) in toluene (3 mL) was stirred at room temperature for 4 h. After filtration through Celite, the filtrate was concentrated to afford the aldehyde, which was immediately used without purification.

To a stirred ylide, prepared from methyltriphenylphophonium bromide (63.9 mg, 0.179 mmol) and BuLi (80.0 μL, 10% in hexane, 0.125 mmol), in THF (1 mL) was added dropwise a THF solution (1.5 mL) of the above aldehyde at room temperature. After 15 min of stirring at room temperature, saturated NH_4Cl (2 mL) was added, and the resulting mixture was extracted with Et_2O. The ethereal layer was washed with H_2O (2 mL) and brine, dried, and evaporated to furnish an oil, which was chromatographed. Elution with a 15:1 mixture of hexane−EtOAc afforded **14** (27.7 mg, 83%) as a colorless oil. IR: 1600, 1630, and 1655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23−1.42 (2H, m), 1.57 (1H, dd, J = 15.0 and 1.5), 1.70 (1H, ddd, J = 13.5, 11.5 and 5.5), 1.93 (3H, s), 2.10 (1H, dd, J = 15.0 and 9.5), 2.16−2.43 (5H, m), 2.45 (1H, dd, J = 9.5 and 1.0), 2.59 (1H, br d, J = 5.5), 3.85−4.05 (4H, m), 4.73−4.82 (1H, m), 4.86−4.96 (2H, m), 5.00−5.07 (1H, m), 5.15 (1H, d, J = 10.3), 5.51 (1H, d, J = 16.5), 5.93 (1H, t, J = 7.0), and 6.28 (1H, dd, J = 16.5 and 10.3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.67, 27.52, 34.96, 36.61, 36.82, 44.49, 44.53, 49.74, 51.20, 63.74, 64.56, 107.98, 114.27, 117.29, 125.34, 135.90, 138.84, and 150.26. Anal. Calcd for $C_{20}H_{27}BrO_2$: C, 63.33; H, 7.17; Br, 21.06. Found: C, 63.25; H, 7.13; Br, 20.95.

(±)-19,20-Dinor-4-bromokaur-3,16-dien-12-one 12-Ethylene Acetal (13). A toluene solution (16 mL) of **14** (155 mg, 0.409 mmol) was heated at 200 °C in a sealed tube for 45 h. After removal of the solvent, the residue was chromatographed. Elution with a 15:1 mixture of hexane−Et_2O afforded 114 mg (74%) of **13** + **28** (5.7:1 mixture by ^1H NMR) as a solid. Recrystallization of the Diels−Alder adducts (**13** + **28**) from Et_2O−hexane provided an analytical sample of **13** as colorless prisms, mp 136.0−137.5 °C. IR ($CHCl_3$): 1638 and 1655 cm^{-1}. **13**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (3H, s), 1.23 (1H, ddd, J = 11.0, 5.0 and 1.5), 1.30 (1H, d, J = 8.5), 1.34−1.85 (9H, m), 1.87 (1H, dd, J = 14.0 and 8.5), 2.42 (1H, dd, J = 12.0 and 1.5), 2.60 (1H, d, J = 5.0), 3.80−4.05 (4H, m), 4.95−5.02 (1H, m), and 5.97−6.05 (1H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.34, 25.22, 25.28, 29.51, 34.92, 37.82, 39.18, 39.60, 42.93, 49.37, 51.76, 51.88, 52.88, 52.77, 63.69, 64.64, 107.55, 110.43, 128.30, 128.39, and 150.02. Anal. Calcd for $C_{20}H_{27}BrO_2$: C, 63.33; H, 7.17; Br, 21.06. Found: C, 63.33; H, 7.17; Br, 21.16. **13** + **28** (5.7:1): IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85−1.10 (1H, m), 1.02 (2.6H, s), 1.17−1.38 (2H, m), 1.25 (0.4H, s), 1.56−2.24 (12H, m), 2.35 (0.15H, d, J =

(33) Denny, D. B.; Ross, S. T. *J. Org. Chem.* **1961**, *27*, 998−1000.

12.0), 2.43 (0.85H, d, J = 12.0), 2.60 (1H, br d, J = 5.0), 3.70 (2.6 H, s), 3.72 (0.4H, s), 3.86−4.03 (4H, m), 4.84 (0.15H, br s), 4.87 (0.85H, br s), 4.95−5.01 (1H, m), 6.48−6.55 (0.85H, m), 6.67−6.72 (0.15H, m). HRMS clacd for $C_{22}H_{30}O_4$ (M^+): 358.2142, found: 358.2144.

(±)-Methyl 20-Nor-12-oxokaur-16-en-19-oate 12-Ethylene Acetal (29). To a stirred solution of a 5.7:1 mixture of the Diels−Alder adducts **13** and **28** (68.0 mg, 0.179 mmol) and 2,2′-dipyridyl (a crystal as indicator) in THF (3 mL) was added dropwise ^{t}BuLi (0.22 mL, 1.64 M in hexane, 0.361 mmol) at −78 °C. The reaction mixture remained a red color for 40 min. When methyl chloroformate (80.0 μL, 1.04 mmol) was added at −78 °C, the color dissipated. After 0.5 h of stirring, saturated NH_4Cl (2 mL) was added at −78 °C. The resulting mixture was extracted with Et_2O, and then the ethereal layer was washed with brine, dried, and evaporated to provide an oil, which was chromatographed. Elution with a 7:1 mixture of hexane−EtOAc gave the α,β-unsaturated ester (44.6 mg, 70%) as a colorless oil.

To a stirred solution of the above material (8.9 mg, 24.8 μmol) in MeOH (1 mL) was added Mg (turnings) (68.0 mg, 2.63 mmol) at room temperature. After the addition was completed, the mixture was irradiated with ultrasound for 1 min until gas evolution was apparent; the mixture was then stirred at room temperature for 7 h. After addition of saturated NH_4Cl (2 mL) and 10% HCl (5 drops), the resulting mixture was extracted with Et_2O. The ethereal layer was washed with brine, dried, and evaporated to yield a solid, which was chromatographed. Elution with a 10:1 mixture of hexane−EtOAc gave rise to the saturated ester (8.4 mg, 94%). Recrystallization from Et_2O−hexane gave **29**, mp 151.5−152.8 °C, as a single isomer. IR (Nujol): 1735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (1H, dt, J = 13.7 and 4.0), 0.99 (3H, s), 1.16−2.00 (15H, m), 2.09−2.19 (3H, m), 2.28 (1H, d, J = 12.0), 2.45 (1H, br t, J = 5.0), 2.57 (1H, br d, J = 5.0), 3.65 (3H, s), 3.84−4.02 (4H, m), 4.85 (1H, br s), and 4.95−4.99 (1H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.18, 18.52, 26.93, 28.51, 29.34, 36.90, 38.60, 40.02, 40.28, 43.14, 49.12, 49.55, 51.11, 52.28, 55.58, 63.63, 64.53, 107.30, 110.54, 150.35, and 175.94. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.59; H, 8.94.

(±)-Methyl 12-Oxokaur-16-en-19-oate (30). To a stirred solution of diisopropylamine (0.240 mL, 1.71 mmol) in THF (1.5 mL) at 10 °C was added dropwise BuLi (1.0 mL, 10 wt % in hexane, 1.56 mmol). After the solution was stirred for 0.5 h at −10 °C, it was cooled to −78 °C, and a THF solution (2 mL) of the above saturated ester (62.3 mg, 0.173 mmol) was slowly added over a period of 20 min. The mixture was again stirred at −78 °C for 1 h; HMPA (0.03 mL, 0.172 mmol) was rapidly added. After 8 min of stirring, MeI (1 mL, 16 mmol) was quickly added at −78 °C, and the resulting mixture was stirred at −78 °C for 10 min and at 0 °C for 2 h. After addition of saturated NH_4Cl (4 mL) and H_2O (1 mL) at 0 °C, the mixture was extracted with Et_2O. The ethereal layer was washed with saturated $Na_2S_2O_4$ and H_2O, dried, and evaporated to afford a solid, which was chromatographed. Elution with a 10:1 mixture of hexane−EtOAc provided the ester (54.6 mg, 84%) as a white solid. Subjection of this material to recrystallization from Et_2O−hexane gave needles, mp 165.0−165.5 °C. IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72−0.86 (1H, m), 0.96 (3H, s), 1.17 (3H, s), 0.92−1.86 (15H, m), 2.12−2.22 (3H, m), 2.29 (1H, d, J = 12.0), 2.57 (1H, br d, J = 5.5), 3.63 (3H, s), 3.84−4.02 (4H, m), 4.85 (1H, br s), and 4.95−5.00 (1H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.49, 19.03, 21.88, 28.85, 29.58, 36.90, 38.09, 38.95, 40.46, 40.61, 42.98, 43.88, 49.05, 51.21, 52.24, 55.99, 56.92, 63.63, 64.53, 107.27, 110.58, 150.40, and 178.03. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.74; H, 9.07.

To a stirred solution of the above ester (54.6 mg, 0.146 mmol) in THF (3 mL) was added 15% $HClO_4$ (1.5 mL) at room temperature, and then the mixture was stirred at room temperature for 1 h. After addition of saturated $NaHCO_3$ at room temperature, the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to leave a solid, which was chromatographed. Elution with a 6:1 mixture of hexane−EtOAc furnished **30** (48.1 mg, 100%) as a white solid. Recrystallization of a small amount of this material from Et_2O−hexane yielded **30**, mp 116.0−117.0 °C (prisms). IR ($CHCl_3$): 1705 and 1718 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.69 (3H, s), 0.80 (1H, dt, J = 12.0 and 5.0), 1.01 (1H, dt, J = 12.0 and 4.0), 1.17 (1H, dd, J = 11.0 and 2.0), 1.19 (3H, s), 1.48−1.64 (4H, m), 1.68−1.96 (5H, m), 2.13−2.22 (1H, m), 2.22 (1H, d, J = 16.0), 2.34−2.44 (3H, m), 2.55 (1H, dd, J = 16.0 and 9.0), 3.22 (1H, d, J = 4.5), 3.63 (3H, s), 4.87 (1H, br s), and 5.00 (1H, t, J = 2.0). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.38, 18.66, 21.47, 28.61, 35.88, 37.78, 38.99, 39.48, 39.56, 39.78, 43.76, 44.05, 48.12, 51.25, 56.33, 56.73, 60.58, 107.89, 148.93, 177.77, and 211.60. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.11.

(±)-Methyl Kaur-16-en-19-oate (6c) and (±)-Methyl Trachyloban-19-oate (4c). 30 (43.7 mg, 0.132 mmol) was dissolved in bis-(ethylene glycol) (4 mL), and then $NH_2NH_2{\cdot}H_2O$ (1 mL, 20.62 mmol) was added. The resulting mixture was refluxed at 135 °C for 2 h. After cooling to room temperature, KOH (83.1 mg, 1.26 mmol, 85%) was added at room temperature, and the mixture was allowed to warm to 200 °C over a period of 2 h. After 6.5 h of heating, 5% HCl (4 mL) was added at room temperature, and then the resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O (2 mL) and brine, dried, and evaporated to leave a white solid (32.1 mg), which was taken up into Et_2O (2 mL). The resulting solution was treated with an ethereal solution of diazomethane at room temperature. After 1 h of stirring at room temperature, AcOH was added until the evolution of nitrogen gas ceased. Saturated K_2CO_3 (1 mL) was added, and the mixture was extracted with Et_2O. The ethereal layer was washed with brine, dried, and evaporated to afford a white solid. Chromatography of the residue on a column of silica gel impregnated with 30% silver nitrate with a 1:3 mixture of benzene−petroleum ether as solvent furnished **4c** (4.6 mg, 11%) and **6c** (21.3 mg, 51%). **6c**, whose spectral data were consistent with those reported,[34] exhibited mp 89.5−90.0 °C (prisms). IR: 1650 and 1715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (3H, s), 1.17 (3H, s), 2.26−2.66 (1H, m), 4.73 (1H, br s), 4.77−4.81 (1H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 15.55, 18.52, 19.29, 22.05, 28.88, 33.23, 38.23, 39.54, 39.79, 40.89, 41.40, 43.94, 44.33, 49.06, 51.21, 55.18, 57.16, 103.05, 155.97, and 178.16. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.89; H, 10.17. **4c**: IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.56−0.59 (2H, m), 0.76 (3H, s), 1.12 (3H, s), 1.14 (3H, s), and 3.63 (3H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.45, 18.89, 19.82, 20.66, 21.94, 22.50, 24.35, 28.80, 33.20, 38.23, 38.75, 39.33, 39.57, 40.84, 43.85, 50.44, 51.21, 52.80, 57.07, and 178.09. Comparison of spectral data recorded for synthetic **4c** with those provided by Professor R. M. Coates comfirmed that the total synthesis of **4c** had indeed been accomplished.

(±)-Methyl 12-Hydroxykaur-16-en-19-oate (31). To a stirred solution of **30** (16.6 mg, 50.2 μmol) in MeOH (2 mL) was added $NaBH_4$ (16.1 mg, 0.462 mmol) at room temperature, and then the mixture was again stirred at room temperature for 20 min. After removal of the solvent, $CHCl_3$ (5 mL), saturated brine (2 mL) and 10% HCl (5 drops) were added. After separation, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried, and evaporated to provide an oil, which was chromatographed. Elution with a 4:1 mixture of hexane−EtOAc gave rise to **31** (15.6 mg, 93%) as a colorless oil. IR ($CHCl_3$): 1720 and 3450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (0.65H, s; 3H for β-OH), 1.00 (2.35H, s; 3H for α-OH), 1.17 (3H, s), 2.27 (1H, d, J = 12.0), 2.61 (0.22H, br d, J = 5.0; 1H for β-OH), 2.64 (0.78H, br d, J =5.0; 1H for α-OH), 3.64 (3H, s), 3.78 (1H, t, J = 5.0), 4.75−4.79 (0.78H, m), 4.83−4.86 (0.78H, m), and 4.87−4.92 (0.44H, m). HRMS calcd for $C_{21}H_{32}O_3$ (M^+): 332.235. Found: 332.2347.

(±)-Methyl Atis-16-en-19-oate (5c). To a stirred solution of **31** (15.0 mg, 45.1 μmol) in CH_2Cl_2 (1 mL) were added 1,1′-thiocarbonyldiimidazole (21.6 mg, 90%, 0.109 mmol) and DMAP (14.0 mg, 0.115 mmol), and the resulting yellowish solution was stirred at room temperature for 12 h. After removal of the solvent, the residue was chromatographed. Elution with a 4:1 mixture of hexanes−EtOAc afforded the thioimidazolide (16 mg) a colorless oil, which was pure enough for the subsequent step.

To a stirred solution of the previous thioimidazolide (16 mg) in degassed toluene (4 mL) was slowly added a degassed toluene solution

(34) Mitscher, L. A.; Rao, G. S. R.; Veysoglu, T.; Drake, S.; Haas, T. *J. Nat. Prod.* **1983**, *46*, 745−746.

(0.4 mL) of Bu_3SnH (0.02 mL, 72.1 μmol) and AIBN (1.3 mg, 7.9 μmol) over a period of 3 h under reflux. After 11.5 h of refluxing, the solvent was removed, and then the residue was chromatographed. Elution with a 30:1 mixture of hexane−EtOAc provided **5c** (9.7 mg, 68% for two steps) as colorless prisms, mp 102.5−105.0 °C. IR ($CHCl_3$): 1718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (3H, s), 1.18 (3H, s), 3.65 (3H, s), 4.57 (1H, q, J = 2.0), and 4.73 (1H, q, J = 2.0). ^{13}C NMR (75.3 MHz, $CDCl_3$): δ 11.99, 18.90, 20.40, 27.32, 28.36, 28.76, 28.85, 33.58, 36.66, 38.25, 38.31, 39.71, 39.80, 43.92, 48.24, 51.23, 52.17, 57.22, 104.56, 152.87, and 178.04. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.90; H, 10.14. Synthetic (±)-**5c** was in all respects (^1H NMR, ^{13}C NMR, and IR) indistinguishable from an authentic sample of (−)-**5c** provided by Professor T. Kato.

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