First Synthesis of Cytotoxic 8,9-Secokaurene Diterpenoids. An Enantioselective Route to (−)-*O*-Methylshikoccin and (+)-*O*-Methylepoxyshikoccin

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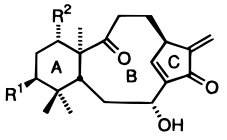
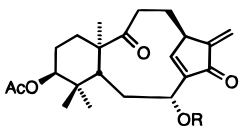
Abstract: A practical route for the total synthesis of 8,9-secokaurene diterpenes is described. The central step is the [3.3]sigmatropic rearrangement of spirocyclic intermediates such as **35**, **40**, and **41**. All three compounds must necessarily respond identically to properly install the absolute configuration of the bridgehead methine carbon. The total synthesis of (−)-*O*-methylshikoccin (**2b**) was realized in 8% overall yield from the Wieland−Miescher ketone **9**. Its naturally occurring epoxide **47** was prepared with comparable efficiency. The preparative route developed herein should provide a general entry into this important class of diterpenoids.

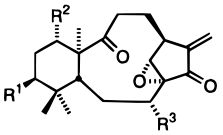
Rabdolatifolin (**1b**),[1] shikodomedin (**1c**),[2] and *O*-methylshikoccin (**2b**)[3] are the most well-known members of a relatively small group of structurally unusual 8,9-seco-*ent*-kaurenes. These *Rabdosia* metabolites, their close relatives such as rabdoumbrosanin (**1a**),[4] shikoccin (**2a**),[5] rabdoshikoccin A and B,[6] and the corresponding epoxides **3** are reputed to exhibit potent cytotoxicity against HeLa, KB, and FM 3A/B cells, Ehrlich ascites and Walker intramuscular carcinomas, and P388 lymphocytic leukemia.[7] This biological activity has been attributed to the ability of **1**−**3** to act as Michael acceptors of bionucleophiles. On this basis, the exo- and endocyclic double bonds must both be responsive since both classes of compounds are cytotoxic.[8]



1a, R^1 = H, R^2 = OH
b, R^1 = R^2 = OH
c, R^1 = R^2 = OAc



2a, R = H
b, R Me



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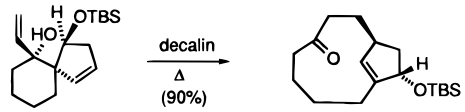
As crucial as the C-ring domain in these diterpenoids is to their potentially useful biological activity, it is the structural ensemble that poses interesting synthetic challenges from several directions. From one perspective, the four trigonal carbons in ring C form a rather planar cyclopentenone platform to which the remainder of the alicyclic framework is attached in a 1,3-cyclophane arrangement. A strategy and supporting technology must be developed for the enantiocontrolled construction of this framework, with proper introduction of the bridgehead double bond.[9] Moreover, all of the oxygen-containing functional groups must be capable of being correctly positioned without the inducement of unwanted transannular bond formation.

In light of our previous finding that the bicyclo[7.2.1]-dodecene **5**, closely related in structural detail to the B/C composite of **1**−**3**, could be quickly elaborated by the thermal [3.3]sigmatropic rearrangement of **4**,[10] we wished to explore related, more advanced application of this process to the synthesis of **2b** and its epoxide. In so doing, we were unaware at the outset that the need would develop to devise an expedient alternative to the assembly of spirocyclic systems related to **4**. In fact, the total syntheses detailed herein[11] proved to be a particularly informative setting for evaluating the usefulness of this new methodology.



4 **5**

Results

Studies Oriented toward Spirocycle Construction. Our first generation solution to the construction of **4** took advantage of sequential intramolecular Claisen rearrangement and allyl-

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

(1) Takeda, Y.; Fujita, T.; Ueno, A. *Phytochemistry* **1983**, *22*, 2531.

(2) (a) Fujita, T.; Takeda, Y.; Shingu, T. *Phytochemistry* **1979**, *18*, 299. (b) Fujita, T.; Takeda, Y.; Shingu, T.; Kido, M.; Taira, Z. *J. Chem. Soc., Chem. Commun.* **1982**, 162.

(3) (a) Node, M.; Ito, N.; Fuji, K.; Fujita, E. *Chem. Pharm. Bull.* **1982**, *30*, 2639. (b) Node, M.; Ito, N.; Uchida, I.; Fujita, E.; Fuji, K. *Chem. Pharm. Bull.* **1985**, *33*, 1029.

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(9) For an overview of our past research involving the synthesis of natural products endowed with bridgehead olefinic centers, consult Paquette, L. A. *Chem. Soc. Rev.* **1995**, *24*, 9.

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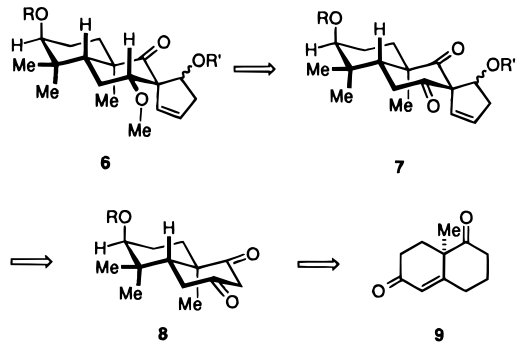
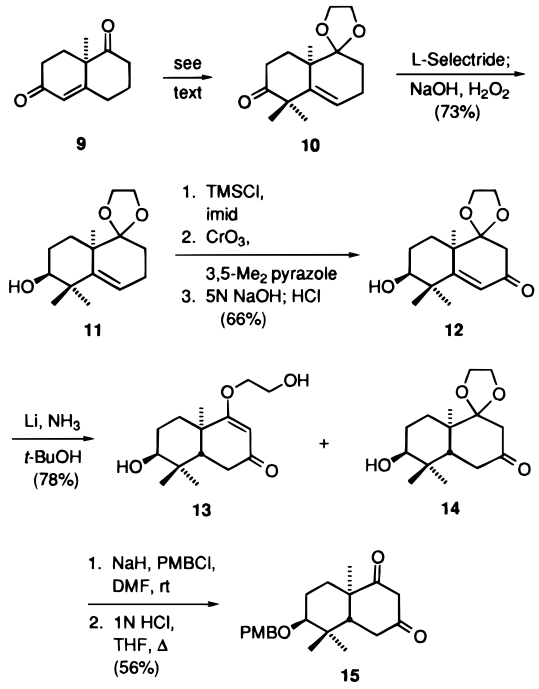
(11) Preliminary communication: Paquette, L. A.; Backhaus, D.; Braun, R. *J. Am. Chem. Soc.* **1996**, *118*, 11990.

S0002-7863(97)01527-8 CCC: $14.00

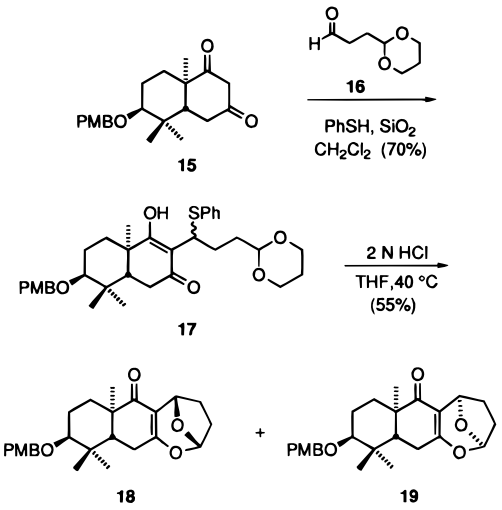
Scheme 1



Scheme 2



Scheme 3



silane-carboxaldehyde cyclization steps. Although this protocol proved to be very efficient and highly stereocontrolled, the framework is insufficiently oxygenated for the present purposes. An alternate plan, designed to incorporate an additional methoxyl group as projected retrosynthetically in Scheme 1, begins with the Wieland−Miescher ketone **9**.[12] Following functional group manipulation, including buildup of the 1,3-dicarbonyl system resident in **8**, the needed spiroalkylation as in **7** should set the stage for arrival at **6**. When preliminary studies revealed to us that the **8** → **7** transposition could not be accomplished as before, a new approach that suitably melded the stereochemical demands with the resident functionality was developed.

In practice, protection of the saturated carbonyl group in *R*-**9** (≥98% ee) was achieved readily by either the transketalization method of Pietrasantra[13] or the direct ketalization tactic reported by Kametani.[14] Subsequent Woodward methylation[15,16] provided **10** efficiently (Scheme 2). Reduction of **10** with L-Selectride proceeded with high stereoselectivity (>95:5) to deliver the β-alcohol **11**. Protection of this hydroxyl group is necessary to facilitate the allylic oxidation programmed to follow. Formation of the trimethylsilyl ether in advance of exposure to the chromium trioxide/3,5-dimethylpyrazole complex[17] is adequate to allow progression to **12** in 66% overall yield. Subsequent dissolving metal reduction of **12** resulted in clean establishment of the trans ring fusion. Most often, the basic conditions that develop during the lithium-liquid ammonia procedure were adequate to induce β-elimination with opening of the ketal ring as in **13**. Occasionally, a modest amount of **14** could be isolated simultaneously. This feature was inconsequential since treatment of either **13** or **14** with excess sodium hydride and *p*-methoxybenzyl chloride afforded doubly protected **13**. Direct acidic hydrolysis of this intermediate provided **15**, which was destined to serve as a key intermediate *en route* to the shikoccins.

Conventional Knoevenagel reactions involving cyclic 1,3-diketones and *aliphatic* aldehydes cannot be arrested at the monoaddition level because of very rapid second-stage 1,4-addition of the enolate anion with formation of bis-adducts.[18] In order to redirect the latter phases of this multistep condensation in a useful direction, we have previously demonstrated that simple stirring of a three-component mixture consisting of the two reactants and thiophenol results in interception by the sulfur nucleophile to give a polyfunctional adduct.[19] Especially noteworthy is the fact that the phenylthio substituent resides at a position ideally suited to subsequent introduction of the cyclopentene double bond via sulfoxide thermolysis.

Application of this procedure to **15**, bifunctional aldehyde **16**,[20] and thiophenol in the presence of silica gel did indeed give rise to adduct **17** (Scheme 3). Submission of **17** to the hydrolysis-cyclization conditions earlier found to be highly successful for achieving the desired ring closure in many analogues led instead to the generation of the diastereomeric acetals **18** and **19**. The structural assignments to these products were confirmed by a combination of NMR experiments. Thus, an LR-COSY 90 study revealed the singlets at δ 0.94 and 0.97

(12) (a) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215. (b) Li, Y.; Bahman, N.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2349. (c) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53. (d) Buchschacher, P.; Fürst, A. *Org. Syn., Coll. Vol. 7* **1990**, 368.

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(17) (a) Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4459. (b) Wright, J.; Drtina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806.

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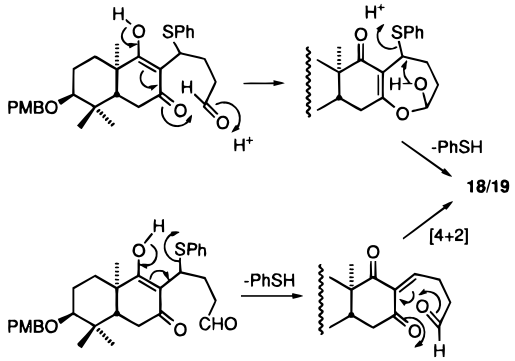
Scheme 4



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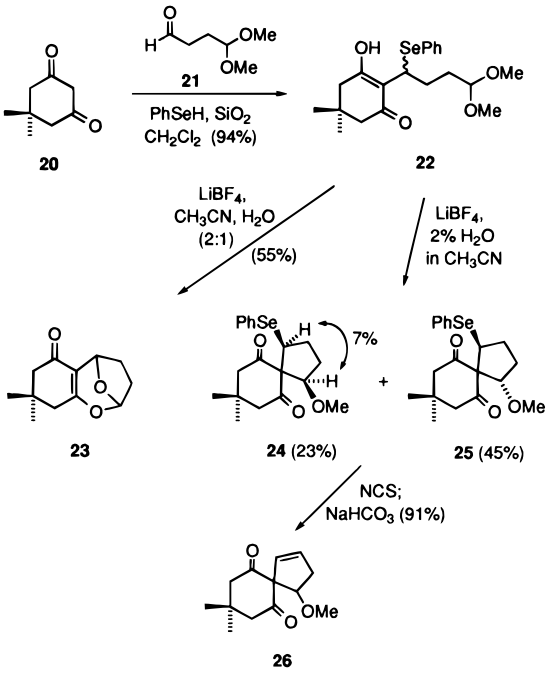
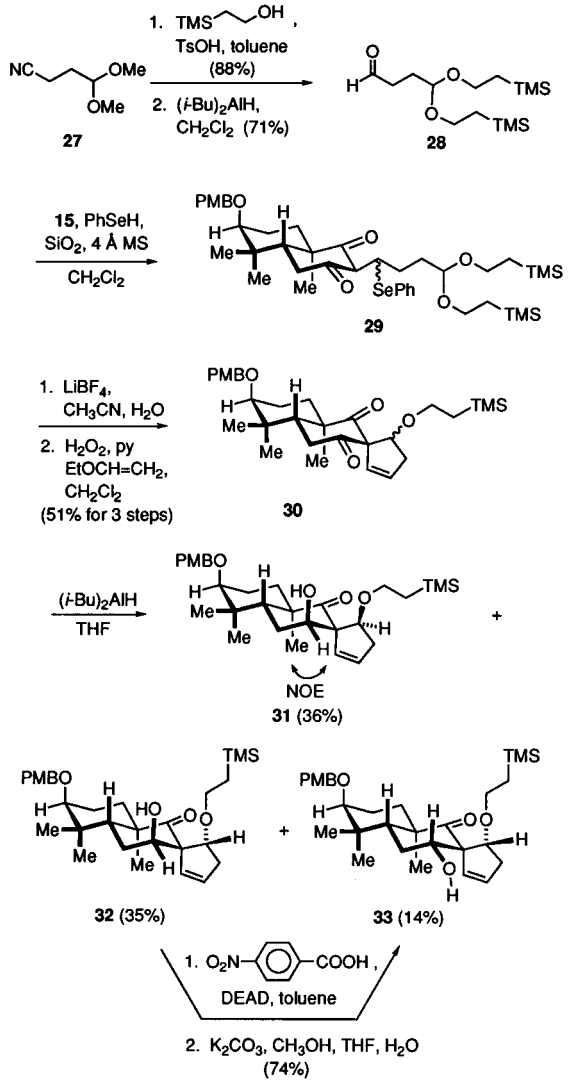


Scheme 6



to belong to the angular methyl groups in the major (**18**) and minor acetals (**19**), respectively. This information was then utilized in a 7.5 Hz-tuned semiselective DEPT 45 experiment that established the proximity of these methyl substituents to the carbonyl functionality via $^3J_{C-H}$ coupling. On this basis, isomeric structures in which the more sterically congested carbonyl group had been incorporated into the heterocyclic network could be ruled out. The two mechanistic options outlined in Scheme 4 account concisely for this phenomenon. While we have not distinguished between them, it is clear that the β-dicarbonyl part structure plays a key role.

Alternate conditions had to be found for effecting the critical spirocyclization. Concomitantly, the discovery was made that the temperatures required for bringing about sulfoxide elimination in model systems were unduly destructive. Because selenoxides are lost with much greater ease than sulfoxides, the substitution of PhSeH for PhSH was implemented as well. Not surprisingly, dimedone (**20**) reacted rapidly with aldehyde **21**[21] and phenylselenol in the presence of silica gel to deliver **22** in good yield (Scheme 5). When diketone **22** was subjected to the action of lithium tetrafluoroborate in acetonitrile containing 2% water,[22] ionization of the dimethyl acetal was effected, and intramolecular cyclization to give **24** and **25** occurred more rapidly than complete hydrolysis to the aldehyde. The latter reaction course dominates when additional water is present; at the 33% level, **23** is formed as the exclusive product. The minor spirocycle was identified as the cis isomer **24** on the strength of a significant NOE interaction between the two methine protons shown. The conversion of **24** and **25** to **26** was most efficiently performed by the method of Detty.[23]

Stereoselection during Spirocyclization. The success associated with the expedient generation of **26** led to two important matters now requiring immediate attention. The first was the replacement of the methoxy group by an alternative substituent that could ultimately be smoothly deprotected to the free hydroxy level. Of the several candidates that were carried through careful exploratory studies, 2-(trimethylsilyl)ethoxy emerged as the candidate of choice. Additionally, for the proposed approach to be successful, it was imperative that the spirocyclization be accomplished in a highly stereoselective manner since, as will be demonstrated below, *the configuration of the stereogenic center generated in the ten-membered ring during oxy-Cope rearrangement depends entirely on the configuration of the spirocyclic carbon.*

Acetal exchange involving **27** and 2-(trimethylsilyl)ethanol proceeded efficiently under acidic conditions. Arrival at aldehyde **28** was accomplished by controlled reduction of the nitrile functionality with Dibal-H (Scheme 6). Following the standard-

(21) Prepared by Dibal-H reduction of **27**, the product of S_N2 displacement by cyanide ion on β-bromoacetaldehyde dimethylacetal.

(22) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267.

(23) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 274.

ized conditions developed earlier, diketone **15** underwent smooth condensation with aldehyde **28** in the presence of phenylselenol to make alkylated diketone **29** available. Without purification, this diastereomeric mixture was cyclized in the presence of lithium tetrafluoroborate as before and immediately subjected to selenoxide elimination. The applied conditions led to the isolation of **30** in 51% overall yield as a 1:1 mixture of epimers. Although chromatographic separation was not feasible at this stage, proof that the two products differed in stereochemistry uniquely at the site of the protected hydroxyl was ultimately derived from subsequent chemical interconversions and an X-ray crystallographic analysis of **34**.

We see therefore that intramolecular aldolization in this conformationally restricted *trans*-decalindione carboxaldehyde exhibits a marked preference for carbon−carbon bond formation on the equatorial π-surface of the intermediate enol. While we are unaware of other closely parallel aldol analogies, previous studies of Claisen rearrangements,[24] cationic 3-aza-Cope reactions,[25] and [2.3]sigmatropic isomerizations[26] all have been shown to evince a similar preference for bonding to the equatorial face of cyclohexane systems. Consequently, the generation of **30** which necessarily must also pass through a cyclic transition state can be regarded as precedented. Evidently the groups on the carbons resident on the cyclic assembly involved in the bond-forming process can lead to marked energetic differences in the available diastereomeric transition states, with ring closure from the equatorial direction representing that of minimal enthalpic cost.

With **30** in hand, attention was next directed to the considerable difference in steric shielding surrounding its two carbonyl groups. The anticipation was that Dibal-H would attack the "front" carbonyl chemoselectively and skirt approach to the doubly neopentylic "rear" alternative. Indeed, the three alcohols **31**−**33** were formed, and these could be conveniently obtained in individually pure condition only when the 2-(trimethylsilyl)-ethyl protecting group was in place. In that diastereomer of **30** in which the C-ring oxygen is projected β and toward the site of reduction, steric approach control operates with delivery of hydride from below as seen in **31**. In contrast, the α-diastereomer gives rise to both **32** and **33**.

This triad of aldols proved to be fascinatingly distinctive in certain chemical properties. Thus, while **31** is surprisingly resistant to epimerization, **32** and **33** are slowly interconverted in methanol containing potassium carbonate. For this reason, no accurate assessment can be made of the stereoselectivity with which their diketone precursor is reduced. This widely different susceptibility to retroaldolization gains importance because of the pending need to methylate these hydroxylic sites. Despite the sensitivity of **32**, it proved possible to effect its epimerization to **33** under Mitsunobu conditions[27] such that the net proportion of **31** and **33** ultimately approximated 1:1. In order to accomplish this epimerization effectively, saponification of the *p*-nitrobenzoate intermediate had to be carefully controlled.

Oxy-Cope Rearrangement and Arrival at *O*-Methylshikoccin. The kinetic instability of **33** under strongly basic conditions required that conversion to the *O*-methyl derivative **34** be effected with silver(I) oxide and methyl iodide in the presence of calcium sulfate.[28] The highly crystalline nature of **34** proved

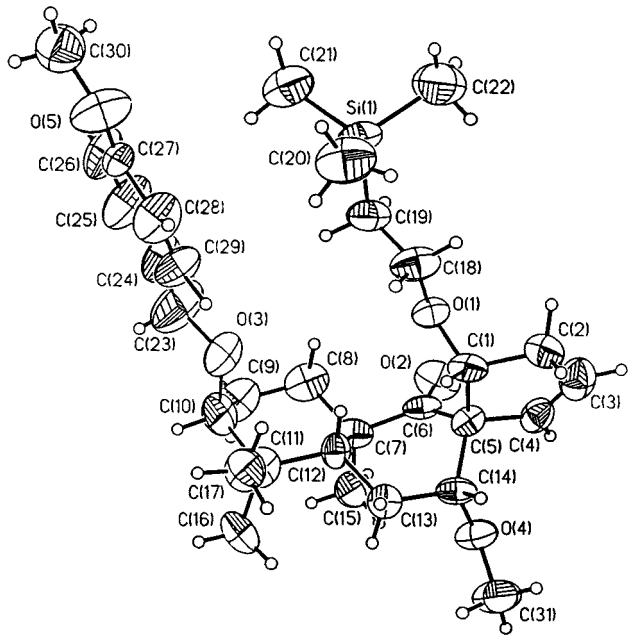


Figure 1. Crystallographically determined molecular structure of **34** as drawn with 50% thermal ellipsoids.

conducive to X-ray diffraction analysis. As seen in Figure 1, this study confirmed the absolute configurational assignments made above. Addition of vinylmagnesium bromide to **34** proceeded from that direction opposite to the methoxy substituent (NOE analysis). When attempts to induce diene **35** into anionically accelerated oxy-Cope rearrangement resulted in decomposition, recourse was made instead to purely thermal conditions. Of the solvents examined, DMF proved to be the most effective solvent of those examined. When **35** was heated at 230−240 °C for 19 h in DMF, only one cyclodecenone was formed. This compound was inferred to be **36a** as a result of consideration of transition states, a conclusion later confirmed by a successful synthesis. At this point, cesium fluoride was introduced, and the reaction mixture brought back to 210 °C (6 h) in order to effect hydroxyl deprotection directly. Subsequent oxidation of **36b** so obtained with the Dess−Martin periodinane reagent[29] led to diketone **37**. Extensive COSY and NOE studies on **37** served to corroborate the three-dimensional structural features of this advanced intermediate (Figure 2).

The mechanistic details of the [3.3] sigmatropic shifts associated the **35** → **36a**, **40** → **42**, and **41** → **43a** transformations (the latter two to be discussed below) hold particular relevance (Scheme 8). When the double bonds involved are arranged trans as in **35**, only in the chair−boat−chair arrangement is their proximity realized. Conformation **B** reveals that these sites of unsaturation are too distal to permit necessary interaction. Accordingly, the expectation is that **A** will evolve into the (*Z*)-configured enol **C** and subsequently to ketone **D**. In those examples in which an α-vinyl substituent is present, rearrangement is likely to proceed via both **E** and **F**. In accordance with these transition state models, the chair−chair−chair arrangement **E** would give rise to the (*E*)-enol **G**, whereas adoption of the higher energy chair−boat−boat construct **F** would lead directly to the (*Z*)-enol **H**. Tautomerism in **F** and **H** results in convergence to **I**. The important issue here is that the absolute configuration of the newly formed bridgehead carbon in **D** and **I** (note arrows) is uniquely dependent on the configuration of the spirocyclic carbon. Stated differently, **35**, **40**, and **41** *must respond identically in installing this key element*

(24) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86.
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(26) (a) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453. (b) Mander, L. N.; Turner, J. V. *Aust. J. Chem.* **1980**, *33*, 1559.
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Scheme 7

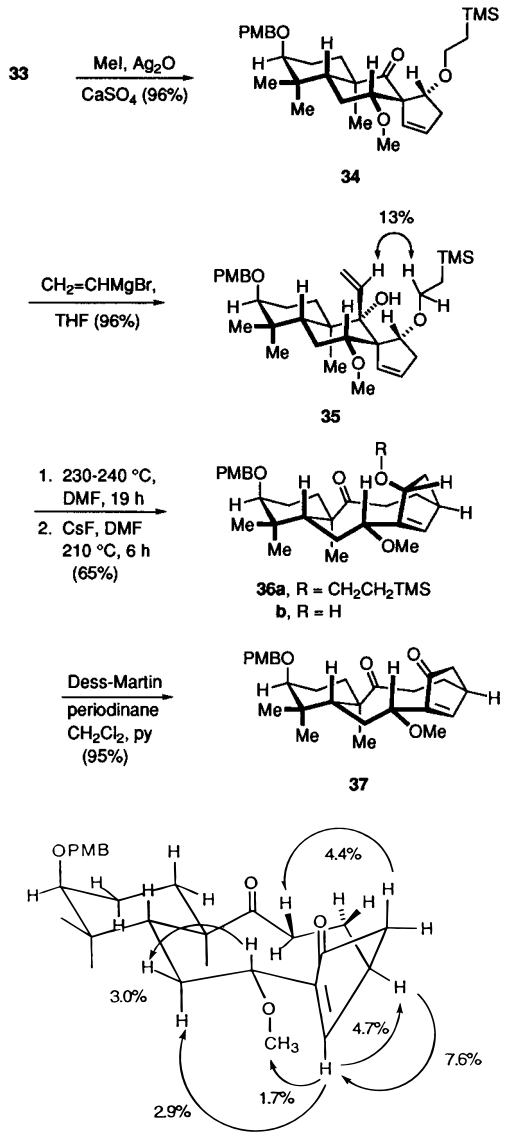


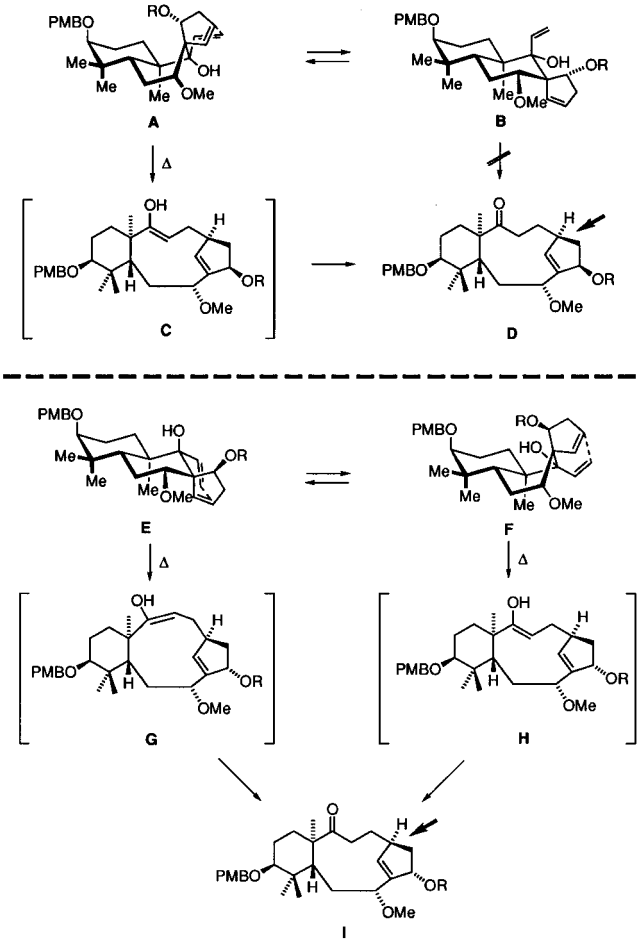
Figure 2. NOE interactions determined for **37**.

of ent-secokaurene chirality, irrespective of the transition state adopted.

In this light, the efficiency of the overall conversion to **37** would be reinforced significantly if its elaboration from **31** could also be implemented. These studies, detailed in Scheme 9, drew in large part on the earlier successes. Interestingly, vinylmagnesium bromide underwent 1,2-addition to **31** exclusively from the α-face, thus making possible direct experimental assessment of the postulate advanced in Scheme 8. The necessary inversion of alcohol stereochemistry, best deferred until after the vinylation step, was most effectively accomplished by oxidation of **38** to ketone **39** with subsequent hydride reduction. Regiocontrolled O-methylation of diol **41** was brought about with sodium hydride and methyl iodide under conditions of proper stoichiometric control.

The synthesis of **43b** was easily completed from two directions. The oxy-Cope rearrangements of **40** and **41** were accomplished with comparably modest efficiency, although **40** was unquestionably the more reactive compound. With arrival at **43a**, unmasking of the hydroxyl group was undertaken as before. Perhaps because steric crowding is not now extant, elimination of the exo-oriented trimethylsilylethyl group was accomplished only in an unoptimized yield of 22%. Sufficient

Scheme 8



material was produced in this manner to allow linkup with cyclodecenone **37**.

Once Scheme 9 had been reduced to practice, attention was turned to the preparation of *O*-methylshikoccin (**2b**). The highly regioselective conversion of **37** into its *exo*-methylene derivative began by conversion to silyl enol ether **44** (Scheme 10). No tendency was seen under ordinary conditions for this cyclopentadiene to undergo one or more [1.5] hydrogen shifts. Condensation of **44** with Eschenmoser's salt in DMF at 50 °C[30] followed by conversion of the Mannich product to the methiodide in advance of Hoffmann elimination delivered **45** in a satisfactory 66% overall yield. Deprotection[31] /acetylation of **45** afforded high quality samples of natural (levorotatory) *O*-methylshikoccin (**2b**), which was identical in all respects to an authentic specimen provided by Professor Fujita.[32]

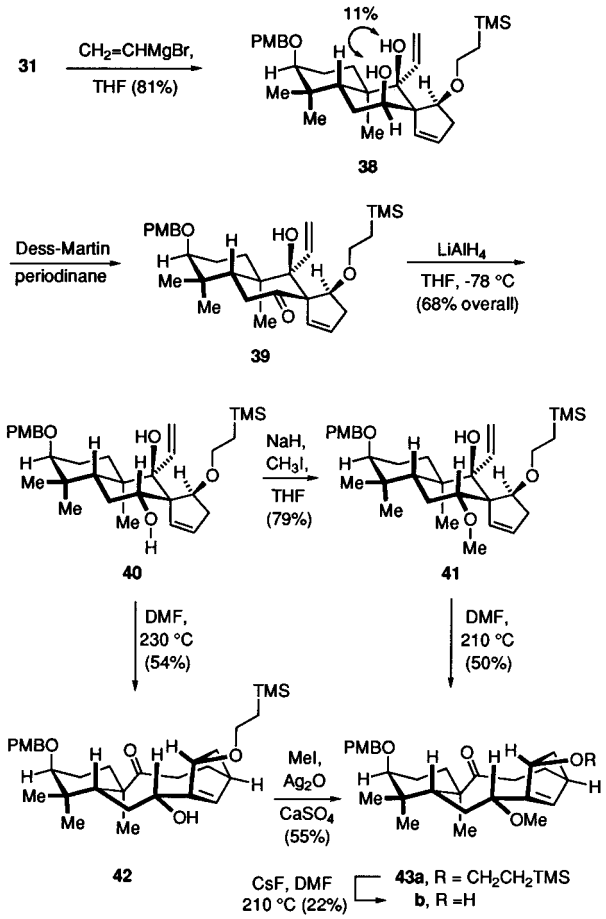
Synthesis of (+)-*O*-Methylepoxyshikoccin. The challenge of introducing an oxiranyl oxygen into **2b** was answered in a straightforward manner. While repeating the three-step sequence associated with the conversion of **44** into **45**, the Mannich base was purified by chromatography on silica gel. This protocol had been utilized before. Presently, however, a quantity of ether that had experienced a buildup in peroxide content was inadvertently employed as eluant. Epoxidation took place

(30) (a) Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* **1979**, *35*, 613. (b) Caputo, R.; Ferreri, C.; Mastroianni, D.; Palumbo, G.; Wenkert, E. *Synth. Commun.* **1992**, *22*, 2305.

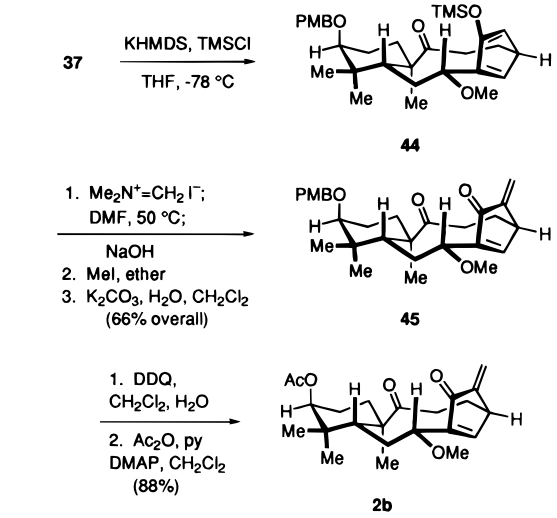
(31) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(32) In the original report,[3b] the signals due to H-3 (δ 3.20) and OCH_3 (δ 3.26) were erroneously claimed to appear at δ 3.34 and 3.18, respectively. The spectra graciously provided by the Japanese group and our re-recording of these data revealed the source of the confusion to be typographical.

Scheme 9



Scheme 10

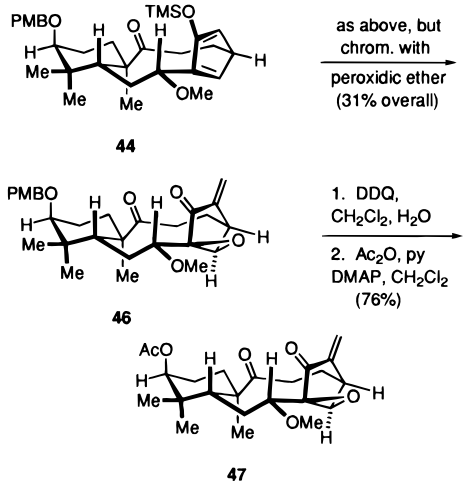


smoothly to deliver **46** ultimately two steps later (Scheme 11). Evidently, the bridgehead double bond is sufficiently strained to be more reactive than the tertiary nitrogen under these circumstances. Conversion of the PMB group in **46** into an acetate as before delivered dextrorotatory **47**. This material could not be distinguished spectroscopically from the natural specimen.

The synthesis of **2b** summarized herein was sufficiently efficient that adequate quantities of advanced intermediates were available for additional biosynthetic-like interconversions.[33] The overall yield of enantiopure *O*-methylshikoccin was approximately 8% when **31**−**33** were all brought forward. The route

(33) Backhaus, D.; Paquette, L. A. *Tetrahedron Lett.* **1997**, *38*, 29.

Scheme 11



also allows convenient access to the epoxy derivative **47**. Much has been learned about the chemical nature of secokaurene-like structures and about polycyclic analogues *en route* to this interesting diterpenoid framework.

Experimental Section[34]

(4a*R*,6*S*,8s*R*)-Hexahydro-6-[(*p*-methoxybenzyl)oxy]-5,5,8a-trimethyl-1,3(2*H*,4*H*)-naphthalenedione (15). A solution of **13** (5.00 g, 18.6 mmol) in dry DMF (50 mL) was added to a suspension of sodium hydride (1.34 g, 55.8 mmol) in the same solvent (30 mL), and the mixture was stirred at 20 °C for 1 h, cooled to 0 °C, and treated with *p*-methoxybenzyl chloride (7.6 mL, 55.8 mmol). After overnight stirring, an additional 0.89 g (37.2 mmol) of sodium hydride and 5.1 mL (37.2 mmol) of *p*-methoxybenzyl chloride were introduced, and stirring was continued for a total of 36 h. The reaction mixture was hydrolyzed at 0 °C by the careful addition of water (10 mL) and partitioned between ether (300 mL) and water (100 mL). The separated aqueous phase was extracted with ether (3×), and the combined organic layers were washed with brine, dried, and evaporated. The residue was subjected to Kugelrohr distillation at 100 °C and 0.2 Torr to remove unreacted *p*-methoxybenzyl chloride and the corresponding alcohol. The nonvolatile portion was dissolved in THF (450 mL), refluxed with 1 N HCl (180 mL) for 18 h, cooled to 0 °C, and neutralized with saturated $NaHCO_3$ solution (220 mL). After the removal of THF on a rotary evaporator, the aqueous solution was extracted with ethyl acetate (5×) and CH_2Cl_2 (3×), and the combined organic phases were washed with brine, dried, and concentrated. The white solid was triturated with ether/hexanes (1:1), cooled to 0 °C, and filtered to give 3.05 g (48%) of **15**. The filtrate was evaporated and resubjected to Kugelrohr distillation to remove residual volatiles. Crystallization of the residue as above gave an additional 0.51 g (total of 56%) of **15** as colorless crystals, mp 185 °C (from ethyl acetate): IR ($CHCl_3$, cm^{-1}) 1735, 1710, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2 H), 6.89−6.84 (m, 2 H), 4.52 (d, J = 11.2 Hz, 1 H), 4.27 (d, J = 11.2 Hz, 1 H), 3.80 (s, 3 H), 3.43 (d, J = 18.3 Hz, 1 H), 3.33 (d, J = 18.3 Hz, 1 H), 3.15 (br s, 1 H), 2.55 (2d, J = 9.3 Hz, 2 H), 2.16 (t, J = 9.3 Hz, 1 H), 2.04−1.90 (m, 2 H), 1.82−1.71 (m, 1 H), 1.64−1.57 (m, 1 H), 1.17 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 208.2, 205.0, 159.1, 138.8, 129.2, 113.7, 81.9, 70.7, 55.3, 54.4, 47.1, 38.6, 38.5, 37.5, 27.9, 26.4, 22.1, 19.5, 17.4; FAB MS ($M^+ + H$) calcd 345.5, obsd 345.5; $[\alpha]^{20}_D$ +67.8° (*c* 0.5, chloroform).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 72.23; H, 8.19. Found: C, 72.98; H, 8.20.

(2*S*,4a*R*,6*S*,8a*R*)-2-[4,4-[2-(trimethylsilyl)ethoxy]-1-(phenylseleno)butyl]hexahydro-6-[(*p*-methoxybenzyl)oxy]-5,5,8a-trimethyl-1,3-(2*H*,4*H*)-naphthalenedione (29). A solution of **27** (810 mg, 6.27 mmol) and 2-(trimethylsilyl)ethanol (3.0 g, 4 equiv) in toluene (20 mL) was treated with 20 mg of *p*-toluenesulfonic acid and heated in a Dean-Stark trap so that methanol could be removed by azeotropic distillation.

(34) For general experimental procedures, see: Wang, T.-Z.; Pinard, E.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 1309.

As the toluene distilled off, it was replaced with fresh solvent. After 5 h, the reaction mixture was cooled, diluted with ether (100 mL), and washed with saturated $NaHCO_3$ solution and brine prior to drying and solvent evaporation. The residual material was purified by flash chromatography on silica gel (elution with 10% ether in petroleum ether) to provide 1.66 g (88%) of the corresponding bis(trimethylsily) acetal as a colorless oil: IR (neat, cm^{-1}) 2249; ^1H NMR (300 MHz, $CDCl_3$) δ 4.53 (t, J = 5.2 Hz, 1 H), 3.71−3.63 (m, 2 H), 3.55−3.43 (m, 2 H), 2.26 (t, J = 7.4 Hz, 2 H), 1.90 (td, J = 7.4, 5.2 Hz, 2 H), 0.90 (t, J = 8.2 Hz, 4 H), 0.00 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 119.4, 100.3, 64.2, 29.7, 18.2, 12.3, −1.5; MS *m/z* (M^+) calcd 301.1893, obsd 301.1899.

A solution of this nitrile (21.7 g, 72 mmol) in CH_2Cl_2 (250 mL) was cooled to −78 °C and treated dropwise with Dibal-H (86 mL of 1 M in hexanes, 86 mmol) within 30 min. The reaction mixture was allowed to warm to room temperature during 6 h, diluted with CH_2Cl_2 (400 mL) and saturated sodium potassium tartrate solution (200 mL) with ice bath cooling, and stirred overnight at 20 °C. The separated organic layer was washed with water and, brine, dried, evaporated to leave a residue that was diluted with CH_2Cl_2 and filtered through a plug of silica gel. After concentration of the filtrate, purification was realized by flash chromatography on silica gel. Elution with 10% ethyl acetate in hexanes furnished 16.2 g (71%) of **28** as a colorless oil: IR (neat, cm^{-1}) 1723; ^1H NMR (300 MHz, C_6D_6) δ 9.39 (t, J = 1.3 Hz, 1 H), 4.34 (t, J = 5.3 Hz, 1 H), 3.67 (dt, J = 8.7, 2.5 Hz, 2 H), 3.46 (dt, J = 8.7, 7.5 Hz, 2 H), 2.13 (dt, J = 7.0, 1.3 Hz, 2 H), 1.82 (dt, J = 7.0, 5.3 Hz, 2 H), 0.91 (t, J = 7.8 Hz, 4 H), 0.01 (s, 18 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.3, 102.0, 33.1, 26.8, 18.4, −1.2; MS *m/z* (M^+) calcd 304.1890, obsd 304.1876.

Anal. Calcd for $C_{14}H_{32}O_3Si_2$: C, 55.21; H, 10.59. Found: C, 55.33; H, 10.61.

Three-Step Conversion to (1*S*,4′a*R*,6′*S*,8′a*R*)-4′a,5′,6′,7′,8′,8′a-Hexahydro-6′-[(*p*-methoxybenzyl)oxy]-5′,5′,8′a-trimethyl-5-[2-(trimethylsilyl)ethoxy]spiro[2-cyclopentene-1,2′(1′*H*)-naphthalene]-1′,3′(4′*H*)-dione (30). A flame-dried flask was charged with **15** (300 mg, 0.87 mmol), powdered 4 Å molecular sieves (1.2 g), TLC grade silica gel (3.0 g), CH_2Cl_2 (15 mL), and a solution of benzeneselenol in CH_2Cl_2 (2.8 mL of 1.1 M, 3.0 mmol). The suspension was stirred at room temperature as aldehyde **28** (2.4 mL of 0.41 M in CH_2Cl_2, 1.0 mmol) was added. After 2 h, the solvent was removed under reduced pressure and the slightly yellow powder was placed atop a pad of silica gel housed in a Buchner funnel. Fast elution with 10−50% ether in hexanes (400 mL total) gave **29** in the more polar fractions. Solvent evaporation from these combined fractions gave 650 mg (95%) of **29** as a yellow foam which was immediately carried on to the next step.

The above sample was dissolved in acetonitrile (27 mL) and 2% aqueous acetonitrile (0.36 mL), cooled to −10 °C, and treated with a solution of lithium tetrafluoroborate in acetonitrile (0.82 mL of 1 M). The reaction mixture was warmed to 0 °C during 1.5 h and stirred at 20 °C for an additional 1.5 h, at which point it was diluted with ether (100 mL) and hexanes (70 mL) and washed with saturated $NaHCO_3$ solution, water (2×), and brine. After drying and solvent evaporation, the crude material was rapidly purified by chromatography on silica gel (elution with 15% ether in hexanes). There was obtained 409 mg (74%) of a pale yellow foam that was directly oxidized.

A 381 mg (0.57 mmol) sample of the spiro compound was dissolved in CH_2Cl_2 (15 mL), cooled to 0 °C, and treated sequentially with pyridine (0.09 mL, 1.14 mmol), ethyl vinyl ether (1.63 mL, 30 equiv), and 10% hydrogen peroxide (0.27 mL, 1.4 equiv). The reaction mixture was stirred vigorously overnight at room temperature, diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution and brine, then dried, and concentrated. Chromatography on silica gel (elution with 20% ether in hexanes) gave 212 mg (73%) of **30** as a colorless, oily 1:1 mixture of diastereomers: IR ($CHCl_3$, cm^{-1}) 1720, 1691; ^1H NMR (300 MHz, $CDCl_3$) (β-isomer) δ 7.25−7.20 (m, 2 H), 6.84−6.81 (m, 2 H), 6.09−6.03 (m, 1 H), 5.45−5.43 (m, 1 H), 4.51 (d, J = 11.9 Hz, 2 H), 4.31 (d, J = 11.9 Hz, 2 H), 4.19 (dd, J = 6.3, 5.3 Hz, 1 H), 3.77 (s, 3 H), 3.51−3.31 (m, 2 H), 3.09 (br s, 1 H), 2.87 (dd, J = 13.3, 6.2 Hz, 1 H), 2.72 (dd, J = 19.0, 6.2 Hz, 1 H), 2.69−2.47 (m, 3 H), 2.04−1.63 (m, 4 H), 1.01 (s, 3 H), 0.97 (s, 3 H), 0.92 (s, 3 H), 0.89−0.82 (m, 2 H), −0.12 (s, 9 H); (α-isomer) δ 7.24−7.21 (m, 2 H), 6.87−6.83 (m, 2 H), 6.12−6.08 (m, 1 H), 5.40−5.37 (m, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 4.34 (dd, J = 6.6, 4.4 Hz, 1 H), 4.30 (d, J = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.52−3.29 (m, 2 H), 3.16 (m, 1 H), 2.71−2.50 (m, 4 H), 2.03−1.64 (m, 4 H), 1.03 (s, 6 H), 0.98 (s, 3 H), 0.88−0.78 (m, 2 H), −0.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (β-isomer) ppm 210.9, 109.8, 158.9, 133.6, 131.1, 129.0, 128.8, 113.6, 85.9, 81.3, 78.8, 70.3, 68.0, 55.1, 47.1, 38.5, 38.0, 36.2, 30.3, 27.6, 26.2, 22.0, 19.9, 17.8, 17.7, −1.5; MS *m/z* (M^+) calcd 512.2957, obsd 512.2963.

Anal. Calcd for $C_{30}H_{44}O_5Si$: C, 70.28; H, 8.64. Found: C, 70.19; H, 8.69.

Hydride Reduction of 30. Dibal-H (4.14 mL of 1 M in hexanes, 4.14 mmol) was added dropwise at −10 °C to 752 mg (1.48 mmol) of **30** in 170 mL of THF. After 1.5 h of stirring at this temperature, the excess reducing agent was destroyed by the careful addition of methanol. After treatment with 10% citric acid and dilution with ether (150 mL), the organic layer was separated and washed with water, saturated $NaHCO_3$ solution, and brine. After drying and solvent evaporation, the residue was subjected to flash chromatography on silica gel. Elution with 18% ethyl acetate in petroleum ether resulted in the isolation of three pure diastereomers: 271 mg (36%) of **31**, 101 mg (14%) of **33**, and 258 mg (35%) of **32**.

For **31**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3505, 1694; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.22 (m, 2 H), 6.87−6.82 (m, 2 H), 5.80−5.76 (m, 1 H), 5.71−5.68 (m, 1 H), 4.65 (dd, J = 5.5, 1.7 Hz, 1 H), 4.53 (d, J = 11.6 Hz, 1 H), 4.28 (d, J = 11.6 Hz, 1 H), 4.22 (m, 1 H), 4.08 (br s, 1 H), 3.80 (s, 3 H), 3.68−3.62 (m, 1 H), 3.47−3.38 (m, 1 H), 3.03 (br s, 1 H), 2.71 (m, 1 H), 2.50 (dd, J = 11.7, 4.0 Hz, 1 H), 2.40 (m, 1 H), 1.98−1.70 (m, 5 H), 1.50−1.44 (m, 1 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 0.93 (s, 3 H), 0.96−0.90 (m, 2 H), −0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.6, 158.8, 131.5, 131.3, 131.0, 129.0, 113.4, 82.8, 81.9, 71.9, 70.5, 70.4, 66.5, 55.2, 48.5, 38.3, 37.8, 37.6, 28.2, 27.6, 25.8, 22.5, 20.1, 19.2, 18.6, −1.5; MS *m/z* (M^+) calcd 514.3114, obsd 514.3146; $[\alpha]^{21}_D$ +164.2° (*c* 0.92, chloroform).

Anal. Calcd for $C_{30}H_{46}O_5Si$: C, 70.00; H, 9.01. Found: C, 69.95; H, 8.95.

For **32**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3570, 1703; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24−7.20 (m, 2 H), 6.87−6.82 (m, 2 H), 6.08−6.05 (m, 1 H), 5.48−5.44 (m, 1 H), 4.51 (d, J = 12.3 Hz, 1 H), 4.33 (d, J = 12.3 Hz, 1 H), 4.27 (dd, J = 5.4, 2.6 Hz, 1 H), 4.02 (dd, J = 8.2, 7.6 Hz, 1 H), 3.80 (s, 3 H), 3.52−3.31 (m, 2 H), 3.01 (br s, 1 H), 2.53-2.45 (m, 3 H), 2.20 (m, 1 H), 1.85−1.56 (m, 6 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.92 (s, 3 H), 0.88−0.78 (m, 2 H), −0.11 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.2, 158.9, 134.3, 131.3, 131.1, 129.1, 113.5, 81.4, 80.0, 72.5, 70.2, 68.4, 67.0, 55.2, 46.2, 40.1, 38.1, 36.5, 27.8, 27.0, 26.7, 21.8, 20.1, 19.8, 17.6, −1.5; MS *m/z* (M^+) calcd 514.3114, obsd 514.3103; $[\alpha]^{22}_D$ −30.0° (*c* 1.02, chloroform).

Anal. Calcd for $C_{30}H_{46}O_5Si$: C, 70.00; H, 9.01. Found: C, 69.80; H, 8.94.

For **33**: white crystals, mp 125 °C (from ether−petroleum ether); IR ($CHCl_3$, cm^{-1}) 3610, 1702; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2 H), 6.86−6.83 (m, 2 H), 5.98−5.94 (m, 1 H), 5.79−5.76 (m, 1 H), 4.51 (d, J = 11.8 Hz, 1 H), 4.28 (d, J = 11.8 Hz, 1 H), 4.06 (dd, J = 6.7, 5.1 Hz, 1 H), 3.86 (t, J = 6.7 Hz, 1 H), 3.79 (s, 3 H), 3.60−3.36 (m, 2 H), 3.03 (br s, 1 H), 2.70 (m, 1 H), 2.53 (m, 1 H), 2.19 (ddd, J = 13.5, 7.1, 3.7 Hz, 1 H), 2.06 (dd, J = 13.4, 3.6 Hz, 1 H), 1.85−1.51 (m, 6 H), 1.16 (s, 3 H), 1.01 (s, 3 H), 0.91 (s, 3 H), 0.93−0.83 (m, 2 H), −0.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.5, 158.8, 133.1, 131.2, 131.0, 129.1, 113.4, 83.3, 81.8, 71.5, 70.4, 70.3, 67.3, 55.1, 47.2, 38.4, 38.2, 37.2, 28.2, 28.1, 27.3, 22.3, 20.1, 19.2, 17.8, −1.4; MS *m/z* (M^+) calcd 514.3114, obsd 514.3115; $[\alpha]^{22}_D$ +13.5° (*c* 1.14, chloroform).

Anal. Calcd for $C_{30}H_{46}O_5Si$: C, 70.00, H, 9.01. Found: C, 69.91; H, 8.95.

Mitsunobu Inversion on 32. A solution of **32** (198 mg, 0.385 mmol) in benzene (10 mL) was treated successively with triphenylphosphine (202 mg, 0.77 mmol), *p*-nitrobenzoic acid (116 mg, 0.69 mmol), and diethyl azodicarboxylate (0.12 mL, 0.77 mmol). The reaction mixture was stirred at room temperature for 4 h and transferred directly to the top of a prepacked silica gel column. Following elution with 20% ether in petroleum ether, the *p*-nitrobenzoate ester (254 mg) was dissolved in 5:3 methanol/THF (10 mL), and a solution of potassium carbonate (110 mg) in water (1 mL) was added. This mixture was stirred for 2 h, diluted with ether (100 mL), and washed successively with water (2×) and brine. After drying and solvent

evaporation, the residue was subjected to flash chromatography on silica gel (elution with 18% ethyl acetate in petroleum ether) to give 145 mg (74%) of **33** and return 22 mg (11%) of unreacted **32**.

(1*R*,3′*R*,4′a*R*,5*R*,6′*S*,8′a*R*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-3′-methoxy-6′-[(*p*-methoxybenzyl)oxy]-5′,5′,8′a-trimethyl-5-[2-(trimethylsilyl)ethoxy]spiro[2-cyclopentene-1,2′(1′*H*)-naphthalen]-1′-one (34). A solution of **33** (255 mg, 0.495 mmol) in methyl iodide (4 mL) was treated with silver oxide (230 mg, 0.99 mmol) and calcium sulfate (500 mg), stirred in the dark for 20 h, diluted with ether, and filtered through a plug of Celite. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel. Elution with 15% ether in petroleum ether afforded **34** (253 mg, 96%) as white crystals, mp 119 °C (from ether−petroleum ether): IR ($CHCl_3$, cm^{-1}) 1702; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2 H), 6.86−6.83 (m, 2 H), 5.85−5.77 (m, 2 H), 4.51 (d, J = 11.8 Hz, 1 H), 4.28 (d, J = 11.8 Hz, 1 H), 4.02 (dd, J = 6.7, 4.8 Hz, 1 H), 3.80 (s, 3 H), 3.56−3.38 (m, 2 H), 3.33 (s, 3 H), 3.31 (m, 2 H), 2.71−2.62 (m, 1 H), 2.55−2.45 (m, 1H), 2.21−2.08 (m, 1 H), 2.07 (dd, J = 12.9, 4.0 Hz, 1 H), 1.79−1.56 (m, 5 H), 1.13 (s, 3 H), 1.02 (s, 3 H), 0.92 (s, 3 H), 0.90−0.82 (m, 2 H), −0.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.5, 158.8, 132.8, 131.3, 130.4, 129.1, 113.5, 83.2, 81.8, 80.9, 70.3, 69.8, 67.3, 57.3, 55.2, 47.2, 38.3 (2 C), 37.1, 28.2, 27.4, 23.4, 22.3, 20.1, 19.3, 17.8, −1.4; MS *m/z* (M^+) calcd 528.3271, obsd 528.3255; $[\alpha]^{22}_D$ −10.7° (*c* 1.33, chloroform).

Anal. Calcd for $C_{31}H_{48}O_5Si$: C,70.41; H, 9.15. Found: C, 70.46; H, 9.17.

(1*R*,1′*S*,3′*R*,4′a*R*,5*R*,6′*S*,8′a*R*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-3′-methoxy-6′-[(*p*-methoxybenzyl)oxy]-5′,5′,8′a-trimethyl-5-[2-(trimethylsilyl)ethoxy]-1′-vinylspiro[2-cyclopentene-1,2′(1′*H*)-naphthalen]-1′-ol (35). A solution of **34** (172 mg, 0.325 mmol) in dry THF (2 mL) was treated at 0 °C with vinylmagnesium bromide (10 mL of 0.55 M in THF, 5.5 mmol), stirred at room temperature for 12 h, returned to 0 °C, and treated successively with isopropyl alcohol (1 mL) and saturated NH_4Cl solution (25 mL). After dilution with ether (100 mL), the organic phase was separated, washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Purification of the residue by flash chromatography on silica gel (elution with 10% ether in petroleum ether) gave 173 mg (96%) of **35** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3424; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.28 (m, 2 H), 6.89−6.85 (m, 2 H), 6.35 (dd, J = 16.8, 10.8 Hz, 1 H), 6.19−6.17 (m, 1 H), 6.04−6.02 (m, 1 H), 5.38−5.28 (m, 2 H), 4.65 (s, 1 H), 4.53 (d, J = 11.4 Hz, 2 H), 4.23 (d, J = 11.4 Hz, 2 H), 3.82 (s, 3 H), 3.60 (d, J = 4.1 Hz, 1 H), 3.41−3.17 (m, 3 H), 3.27 (s, 3 H), 3.01 (br s, 1 H), 2.50−2.43 (m, 1 H), 2.07 (dd, J = 16.0, 2.0 Hz, 1 H), 1.83−1.70 (m, 5 H), 1.28 (s, 3 H), 0.97 (s, 3 H), 0.86 (s, 3 H), 0.80−0.76 (m, 2 H), −0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.8, 140.6, 133.4, 131.8, 130.8, 128.9, 114.5, 113.5, 89.1, 84.7, 82.6, 81.3, 69.9, 67.4, 66.7, 57.6, 55.2, 43.0, 40.1, 39.0, 38.1, 28.7, 26.5, 23.8, 22.2, 20.3, 18.4, 17.3, −1.5; MS *m/z* (M^+ − $TMSCH_2CH_2OH$) calcd 438.2769, obsd 438.2762; $[\alpha]^{22}_D$ −34.6° (*c* 0.92, chloroform).

Anal. Calcd for $C_{33}H_{52}O_5Si$: C, 71.18; H, 9.41. Found: C, 71.32; H, 9.50.

(3*S*,4a*R*,6*R*,8*R*,10*S*,13a*R*)-1,2,3,4,4a,5,6,9,10,11,12,13a-Dodecahydro-6-methoxy-3-[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-8-[2-(trimethylsilyl)ethoxy]-10,7-metheno-7*H*-benzocycloundecen-13-(8*H*)-one (36a). A solution of **35** (100 mg, 0.18 mmol) in dry DMF (10 mL) was placed in a thick wall tube, deoxygenated by bubbling N_2 through for 5 min, sealed, and heated in a Woods metal bath at 230−240 °C for 16 h. After cooling, the reaction mixture was diluted with water (20 mL) and ether (40 mL). The layers were separated, the organic phase was washed twice with water, and the combined aqueous solutions were extracted with ether (3×). The ethereal layers were washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (elution with 15% ether in hexanes) to give 87 mg (87%) of **36a** as a colorless crystalline solid, mp 130 °C (from ether−petroleum ether): IR ($CHCl_3$, cm^{-1}) 1687; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.27 (m, 2 H), 6.89−6.84 (m, 2 H), 5.43 (br s, 1 H), 4.55 (d, J = 12.7 Hz, 1 H), 4.42 (d, J = 12.7 Hz, 1 H), 4.25 (br d, J = 8.4 Hz, 1 H), 3.81 (s, 3 H), 3.72 (dd, J = 11.8, 4.0 Hz, 1 H), 3.60−3.39 (m, 2 H), 3.20 (s, 3 H), 3.14 (dd, J = 17.3, 12.3 Hz, 1 H), 3.02 (br s, 1 H), 2.99−2.94 (m, 1 H), 2.55 (d, J = 5.3 Hz, 1 H), 2.49−2.24 (m, 3 H), 1.86−1.64 (m, 4 H), 1.36−1.09 (m, 4 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.96−0.88 (m, 2 H), 0.90 (s, 3 H), −0.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.9, 158.8, 142.9, 136.0, 131.6, 128.9, 113.5, 84.7, 80.8, 76.1, 69.4, 67.2, 55.9, 55.2, 54.0, 42.1, 39.4, 35.9, 35.2, 34.6, 31.0, 28.7, 28.2, 28.1, 23.5, 19.9, 18.3, 16.5, −1.5; MS *m/z* (M^+) calcd 556.3583, obsd 556.3581; $[\alpha]^{22}_D$ +16.8° (*c* 1.10, chloroform).

Anal. Calcd for $C_{33}H_{52}O_5Si$: C, 71.18; H, 9.41. Found: C, 71.09; H, 9.43.

(3*S*,4a*R*,6*R*,8*R*,10*S*,13a*R*)-1,2,3,4,4a,5,6,9,10,11,12,13a-Dodecahydro-8-hydroxy-6-methoxy-3-[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-10,7-metheno-7*H*-benzocycloundecen-13(8*H*)-one (36b). A 102 mg sample of **35** (0.18 mmol) in dry DMF (10 mL) was heated as described above for 19 h at 230−240 °C. The sealed tube was cooled, opened in order to allow cesium fluoride (10 equiv) to be introduced, resealed, and heated at 210 °C for 6 h. Workup in the predescribed manner afforded 60 mg (65% overall) of **36b** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3500, 1690, 1608, 1508, 1246, 1094; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 2 H), 6.91−6.85 (m, 2 H), 5.44 (s, 1 H), 4.66 (d, J = 8.8 Hz, 1 H), 4.58 (d, J = 11.4 Hz, 1 H), 4.31 (d, J = 11.4 Hz, 1 H), 3.81 (s, 3 H), 3.75 (dd, J = 11.8, 4.2 Hz, 1 H), 3.18 (s, 3 H), 3.14 (br s, 1 H), 3.10−2.90 (m, 2 H), 2.56 (dt, J = 14.8, 8.9 Hz, 1 H), 2.55−2.25 (m, 3 H), 1.90−1.70 (m, 5 H), 1.40−1.10 (m, 4 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.7, 158.7, 143.6, 136.4, 131.6, 128.6 (2 C), 113.5 (2 C), 82.6, 78.4, 76.0, 70.3, 56.0, 55.2, 53.8, 41.9, 39.1, 38.5, 36.3, 34.1, 31.1, 29.0, 27.0, 27.6, 22.1, 20.1, 16.7; MS *m/z* (M^+) calcd 456.2876, obsd 456.2884; $[\alpha]^{22}_D$ +41.5° (*c* 1.17, chloroform).

Anal. Calcd for $C_{28}H_{40}O_5$: C, 73.65; H, 8.83. Found: C, 73.76; H, 8.83.

(3*S*,4a*R*,6*R*,10*S*,13a*R*)-1,2,3,4,4a,5,6,9,10,11,12,13a-Dodecahydro-6-methoxy-3[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-10,7-metheno-7*H*-benzocycloundecene-8,13-dione (37). A solution of **36b** (41.1 mg, 9.0×10^{-5} mol) in CH_2Cl_2 (5 mL) was diluted with 1.8 mL of a 0.5 M solution of pyridine in CH_2Cl_2 and treated with the Dess−Martin periodinane reagent (76 mg, 1.8×10^{-4} mol). The reaction mixture was stirred for 1.5 h, diluted with ether (5 mL) and saturated $NaHCO_3$ (1 mL) and $Na_2S_2O_3$ solutions (1 mL), and poured into a 1:1 mixture of ether and water. The separated aqueous phase was extracted with ether (3×), and the combined organic layers were washed with brine, dried, and evaporated. Purification of the residue by chromatography on silica gel (elution with 30% ether in hexanes) provided 38.7 mg (95%) of **37** as a colorless oil: IR (neat, cm^{-1}) 1699, 1513, 1240, 1099; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.32 (m, 2 H), 7.23 (d, J = 2.9 Hz, 1 H), 6.96−6.91 (m, 2 H), 4.56 (d, J = 11.8 Hz, 1 H), 4.39 (d, J = 11.8 Hz, 1 H), 4.13 (dd, J = 11.7, 4.8 Hz, 1 H), 3.83 (s, 3 H), 3.26−3.20 (m, 1 H), 3.17 (s, 3 H), 3.12 (br s, 1 H), 2.58 (dd, J = 18.7, 6.1 Hz, 1 H), 2.48 (dd, J = 12.8, 3.7 Hz, 1 H), 2.44−2.33 (m, 1 H), 2.20 (td, J = 12.8, 5.1 Hz, 1 H), 2.01 (d, J = 18.7 Hz, 1 H), 1.95−1.55 (m, 6 H), 1.12 (td, J = 7.8, 1.4 Hz, 1 H), 1.12 (s, 3 H), 1.02−0.90 (m, 1 H), 0.97 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.0, 207.9, 164.7, 158.9, 144.7, 131.6, 128.1 (2 C), 113.6 (2 C), 81.8, 73.1, 70.0, 56.4, 55.3, 53.3, 40.4, 39.1, 37.5, 36.7, 33.5, 30.0, 29.2, 27.2, 25.2, 22.6, 20.0, 16.7; MS *m/z* (M^+) calcd 454.2719, obsd 454.2719; $[\alpha]^{22}_D$ +4.5° (*c* 0.77, chloroform).

Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.42. Found: C, 73.93; H, 8.50.

(1*R*,1′*R*,3′*S*,4′a*R*,5*S*,6′*S*,8′a*R*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-6′-[(*p*-methoxybenzyl)oxy]-5′,5′,8′a-trimethyl-5-[2-(trimethylsilyl)ethoxy]-1′-vinylspiro[2-cyclopentene-1,2′(1′*H*)-naphthalene]-1′,3′-diol (38). A solution of **31** (205 mg, 0.40 mmol) in dry THF (2 mL) was treated at 0 °C with vinylmagnesium bromide (10 mL of 0.55 M in THF), stirred at 20 °C for 12 h, cooled to 0 °C, and treated successively with isopropyl alcohol and saturated NH_4Cl solution. After dilution with ether, the organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Purification of the residue by flash chromatography on silica gel (elution with 10% ether in petroleum ether) gave **38** (176 mg, 82%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3438; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.27 (m, 2 H), 6.89−6.83 (m, 2 H), 5.78 (dd, J = 17.0, 10.9 Hz, 1 H), 5.78−5.70 (m, 2 H), 5.42 (dd, J = 17.0, 2.9 Hz, 1 H), 5.14 (dd, J = 10.9, 2.9 Hz, 1 H), 5.10 (d, J = 1.8 Hz, 1 H), 4.94 (s, 1 H), 4.58 (d, J = 11.7 Hz, 1 H), 4.39 (dd, J = 6.5, 1.7 Hz, 1 H), 4.28 (d, J = 11.7 Hz, 1 H), 4.08 (m,

1 H), 3.80 (s, 3 H), 3.65−3.56 (m, 1 H), 3.46−3.37 (m, 1 H), 3.01 (br s, 1 H), 2.51−2.41 (m, 2 H), 2.29−2.07 (m, 2 H), 1.84−1.60 (m, 5 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.95−0.89 (m, 2 H), 0.87 (s, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.7, 137.1, 133.6, 131.8, 130.6, 128.8, 116.3, 113.5, 84.3, 82.6, 81.0, 73.4, 70.2, 66.2, 63.3, 55.2, 42.5, 38.1, 37.8, 33.9, 28.6, 26.2, 25.6, 22.3, 20.2, 18.8, 18.3, −1.5; MS *m/z* ($M^+ + H$) calcd 543.3573, obsd 543.3529; $[\alpha]^{22}_D$ +87.0° (*c* 0.74, chloroform).

(1*R*,1′*R*,3′*R*,4′a*R*,6′*S*,8′a*R*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-6′-[(*p*-methoxybenzyl)oxy]-5′,5′,5′a-trimethyl-5-[1-(trimethylsilyl)ethoxy]-1′-vinylspiro[2-cyclopentene-1,2′(1′*H*)-naphthalene]-1′,3′-diol (40). A solution of **38** (174 mg, 0.321 mmol) in CH_2Cl_2 (10 mL) was treated successively with 1.3 mL of a 0.5 M solution of pyridine in CH_2Cl_2 (2 equiv) and 272 mg (0.642 mmol) of the Dess−Martin periodinane reagent. The suspension was stirred for 2 h and diluted with ether (20 mL), saturated $NaHCO_3$ solution (2 mL), and saturated $Na_2S_2O_3$ solution (2 mL). After several minutes of stirring, the reaction mixture became a clear solution. Following the addition of more ether (100 mL), the organic phase was separated, washed with water (2×) and brine, dried, filtered through a pad of Celite, and evaporated. The resulting yellowish, oily ketone **39** decomposed on attempted chromatographic purification and was therefore reduced directly: IR ($CHCl_3$, cm^{-1}) 3434, 1702, 1612, 1513, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2 H), 6.89−6.86 (m, 2 H), 5.93 (dd, J = 16.8, 10.5 Hz, 1 H), 5.97−5.86 (m, 2 H), 5.59 (dd, J = 16.8, 2.6 Hz, 1 H), 5.32 (dd, J = 2.9, 16.8 Hz, 1 H), 4.32 (s, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.31 (d, J = 12.0 Hz, 1 H), 4.26 (t, J = 8.3 Hz, 1 H), 3.82 (s, 3 H), 3.68−3.64 (m, 1 H), 3.48−3.42 (m, 1 H), 3.03 (br s, 1 H), 2.92 (dd, J = 13.0, 5.3 Hz, 1 H), 2.78−2.65 (m, 1 H), 2.55−2.27 (m, 3 H), 2.12−2.02 (m, 1 H), 1.87−1.68 (m, 3 H), 1.15 (s, 3 H), 1.05−0.90 (m, 2 H), 0.95 (s, 3 H), 0.87 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.0, 173.6, 158.7, 134.6, 131.9, 131.6, 129.0, 117.0, 113.5, 83.8, 82.9, 81.5, 70.1, 69.3, 67.2, 55.2, 42.1, 38.0, 37.8, 37.4, 34.3, 28.1, 25.3, 21.8, 20.0, 18.4, 16.9, −1.5; $[\alpha]^{22}_D$ −24.1° (*c* 1.18, chloroform).

The above material was dissolved in dry THF (10 mL), cooled to −78 °C, treated dropwise with a solution of lithium aluminum hydride in THF (0.96 mL of 0.5 M), and stirred at this temperature for 2 h. The reaction mixture was allowed to warm to 20 °C during 1 h, returned to −30 °C, and hydrolyzed by the careful addition of isopropyl alcohol. After dilution with ether (80 mL) and 10% aqueous citric acid (10 mL), the aqueous phase was separated and extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 15% ether in hexanes) gave 118 mg (68% overall) of **40** and returned 10 mg of **38** (ratio 11:1).

For **40**: colorless oil; IR (neat, cm^{-1}) 3486, 1613, 1513, 1258, 1078, 836; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2 H), 6.88−6.85 (m, 2 H), 5.99−5.90 (m, 3 H), 5.31 (dd, J = 17.1, 2.0 Hz, 1 H), 5.17 (dd, J = 10.9, 2.0 Hz, 1 H), 4.54 (d, J = 11.7 Hz, 1 H), 4.31−4.25 (m, 3 H), 4.16 (dd, J = 7.0, 3.4 Hz, 1 H), 3.80 (s, 3 H), 3.65−3.43 (m, 2 H), 2.99 (br s, 1 H), 2.44 (ddt, J = 16.7, 7.1, 2.0 Hz, 1 H), 2.29−2.15 (m, 3 H), 1.84−1.67 (m, 4 H), 1.56−1.43 (m, 1 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.97−0.87 (m, 2 H), 0.85 (s, 3 H), −0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.8, 138.9, 131.8 (2 C), 131.5, 129.0, 115.3, 113.5 (2 C), 83.8, 82.1, 81.6, 70.3, 70.0, 67.1, 66.2, 55.2, 42.4, 38.9 (2 C), 38.0, 28.7, 27.5, 25.8, 22.3, 20.1, 18.6, 17.8, −1.5; MS *m/z* (M^+) calcd 542.3427, obsd 542.3423.

Anal. Calcd for $C_{32}H_{50}O_5Si$: 70.81; H, 9.28. Found: C, 70.89; H, 9.35.

(1*R*,1′*R*,3′*R*,4′a*R*,5*S*,6′*S*,8′a*R*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-3′-methoxy-6′-[(*p*-methoxybenyzl)oxy]-5′,5′,5′a-trimethyl-5[2-(trimethylsilyl)ethoxy]-1′-vinylspiro[2-cyclopentene-1,2′(1′*H*)-naphthalen]-1′ol (41). A solution of **40** (93.5 mg, 0.172 mmol) in dry THF (4 mL) was blanketed with N_2, treated with methyl iodide (0.21 mL, 20 equiv) and sodium hydride (62 mg, 15 equiv), stirred for 24 h, and hydrolyzed by the addition of saturated NH_4Cl solution. After dilution with water and ethyl acetate, the separated aqueous layer was extracted with ethyl acetate (2×), and the combined organic layers were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel furnished 75.9 mg (79%) of **41** as a colorless oil: IR (neat, cm^{-1}) 3500, 1613, 1587, 1514, 1249, 1087; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.27 (m, 2 H), 6.89−6.85 (m, 2 H), 5.92−5.84 (m, 3 H), 5.45 (dd, J = 17.0, 2.7 Hz, 1 H), 5.24 (dd, J = 10.7, 2.7 Hz, 1 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.29 (d, J = 12.0 Hz, 1 H), 4.14 (t, J = 8.1 Hz, 1 H), 3.89−3.79 (m, 1 H), 3.81 (s, 3 H), 3.60−3.53 (m, 1 H), 3.50−3.35 (m, 1 H), 3.34 (s, 3 H), 3.25 (s, 1 H), 2.97 (br s, 1 H), 2.45−2.15 (m, 4 H), 2.01 (m, 1 H), 1.90−1.60 (m, 3 H), 1.35−1.15 (m, 1 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 1.00−0.85 (m, 2 H), 0.83 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.7, 140.1, 135.3, 132.5, 132.1, 131.7, 130.6, 129.1, 116.1, 113.4, 83.0, 82.3, 82.2, 79.1, 70.1, 66.2, 62.0, 42.5, 39.0, 38.0, 36.0, 28.8, 25.2, 23.6, 22.5, 20.0, 18.8, 17.7, −1.5; MS *m/z* (M^+) calcd 556.3584, obsd 556.3583; $[\alpha]^{22}_D$ +15.4° (*c* 1.03, chloroform).

(3*S*,4a*R*,6*R*,8*S*,10*S*,13*R*)-1,2,3,4,4a,5,6,9,10,11,12,13a-Dodecahydro-6-hydroxy-3-[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-8-[2-(trimethylsilyl)ethoxy]-10,7-metheno-7*H*-benzocycloundecen-13(8*H*)-one (42). A solution of **40** (35.8 mg, 6.6×10^{-6} mol) in DMF (10 mL) was placed in a thick-walled Carius tube, deoxygenated by bubbling N_2 through for several minutes, sealed, and heated at 230 °C in a Woods metal bath for 3 h. Workup in the predescribed manner (elution with 40% ether in hexanes) returned 7.9 mg of unreacted **40** and furnished 15.2 mg (54% corrected) of **42**, a colorless oil: IR (neat, cm^{-1}) 3431, 1695, 1513, 1248; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2 H), 6.90−6.85 (m, 2 H), 5.62 (d, J = 1.5 Hz, 1 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.50 (m, 1 H), 4.32 (d, J = 11.2 Hz, 1 H), 4.17 (dd, J = 11.5, 4.5 Hz, 1 H), 3.81 (s, 3 H), 3.79−3.49 (m, 1 H), 3.29−3.25 (m, 1 H), 3.18 (m, 1 H), 3.07 (m, 1 H), 2.45−2.20 (m, 3 H), 1.95−1.70 (m, 6 H), 1.30−1.10 (m, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.96 (s, 3 H), 1.00−0.80 (m, 3 H), −0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.2, 158.9, 147.0, 136.7, 131.5, 128.4, 113.6, 87.9, 82.3, 70.2, 67.2, 66.5, 55.2, 53.5, 42.4, 39.1, 37.7, 36.8, 36.6, 31.8, 27.5, 22.3, 19.9, 18.6, 18.0, 16.7, −1.4; MS *m/z* (M^+) calcd 542.3427, obsd 542.3439.

(3*S*,4a*R*,6*R*,8*S*,10*S*,13*R*)-1,2,3,4,4a,5,6,9,10,11,12,13a-Dodecahydro-6-methoxy-3-[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-8-[2-(trimethylsilyl)ethoxy]-10,7-metheno-7*H*-benzocycloundecen-13-(8*H*)-one (43a). A. *O*-Methylation of 42. A solution of **42** (15.2 mg, 0.028 mmol) in methyl iodide (1 mL) was stirred with silver(I) oxide (20 mg, 3 equiv) and calcium sulfate (20 mg, 0.15 mmol) in the dark for 3 days. An identical quantity of Ag_2O was added again after 4 and 9 days. On the 14th day, the reaction mixture was filtered through Celite, and the filter pad was washed with ether. The filtrate was evaporated and the residue was chromatographed on silica gel (elution with 9% ethyl acetate in hexanes) to give 8.5 mg (55%) of **43a** as a colorless oil: IR (neat, cm^{-1}) 1698, 1614, 1514, 1248, 1089; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.30 (m, 2 H), 6.90−6.85 (m, 2 H), 5.92 (d, J = 2.6 Hz, 1 H), 4.61 (d, J = 11.2 Hz, 1 H), 4.43 (m, 1 H), 4.32 (d, J = 11.2 Hz, 1 H), 3.82 (s, 3 H), 3.70 (dd, J = 11.6, 4.5 Hz, 1 H), 3.58−3.49 (m, 1 H), 3.37−3.22 (m, 1 H), 3.19 (s, 3 H), 3.19−3.06 (m, 2 H), 2.45−2.20 (m, 3 H), 2.00−1.65 (m, 6 H), 1.53−1.40 (m, 1 H), 1.35−1.10 (m, 2 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.95−0.80 (m, 3 H), −0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.9, 159.0, 144.4, 136.3, 131.6, 128.4, 113.6, 87.8, 82.4, 76.1, 70.2, 66.7, 56.0, 55.3, 53.6, 42.3, 39.1, 38.0, 36.2, 35.3, 31.7, 29.3, 27.7, 27.6, 22.3, 19.9, 18.6, 16.6, −1.3, MS *m/z* (M^+) calcd 556.3584, obsd 556.3546; $[\alpha]^{22}_D$ +37.0° (*c* 0.77, chloroform).

B. Sigmatropic Rearrangement of 41. A solution of **41** (26.6 mg, 4.78×10^{-5} mol) in DMF (8 mL) was deoxygenated by bubbling N_2 through for several minutes, sealed, and heated at 210 °C for 11 h. Workup in the customary fashion returned 11.0 mg of unreacted **41** and gave 7.8 mg (50% corrected) of **43a**.

Deprotection of 43a. A solution of **43a** (6.1 mg, 1.10×10^{-6} mol) in DMF (3 mL) was deoxygenated, treated with cesium fluoride (25 mg, 15 equiv), sealed, and heated at 210 °C for 6 h. The customary workup was followed by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) and provided 1.1 mg (22%) of **43b** as a white crystalline solid, mp 166−169 °C: IR (neat, cm^{-1}) 3442, 1695, 1613, 1513, 1092; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 2 H), 6.92−6.86 (m, 2 H), 5.54 (s, 1 H), 4.75 (m, 1 H), 4.58 (d, J = 11.5 Hz, 1 H), 4.35 (d, J = 11.5 Hz, 1 H), 3.83 (s, 3 H), 3.76 (dd, J = 11.3, 3.7 Hz, 1 H), 3.22 (s, 3 H), 3.16 (br s, 1 H), 3.08 (m, 1 H), 2.45−2.17 (m, 3 H), 2.10−1.95 (m, 1 H), 1.95−1.70 (m, 5 H), 1.55−1.10 (m, 3 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.96 (s, 3 H), 1.00−0.85 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.0, 158.8, 145.4, 136.8, 131.4, 128.6,

113.7, 82.0, 80.8, 76.3, 70.2, 56.0, 55.3, 53.3, 42.0, 41.0, 39.1, 36.4, 35.1, 31.5, 30.0, 27.5, 27.4, 22.3, 20.0, 16.6; MS *m/z* (M^+) calcd 456.2876, obsd 456.2887; $[\alpha]^{22}_D$ +33.4° (*c* 0.91, chloroform).

(3*S*,4a*R*,6*R*,10*R*,13a*R*)-1,2,3,4,4a,5,6,9,10,11,12,13a-Dodecahydro-6-methoxy-3-[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-9-methylene-10,7-metheno-7*H*-benzocycloundecene-8,13-dione (45). A nitrogen-blanketed solution of **37** (50.6 mg, 0.111 mmol) and chlorotrimethylsilane (0.28 mL, 20 equiv) in dry THF (7 mL) was cooled to −78 °C and treated dropwise with 0.78 mL of 0.5 M potassium hexamethyldisilazide (in toluene, 3.5 equiv). After 2 h of stirring at −78 °C, the reaction mixture was quenched with triethylamine (0.47 mL, 30 equiv), diluted with pentane (10 mL), allowed to warm to room temperature, and evaporated under reduced pressure. The residue was triturated with pentane, filtered through glass wool, and re-evaporated in vacuo to give **44** which was used directly: ^{1}H NMR (300 MHz, C_6D_6) δ 7.27−7.20 (m, 2 H), 6.91−6.85 (m, 1 H), 6.25 (t, J = 1.9 Hz, 1 H), 4.81 (t, J = 2.2 Hz, 1 H), 4.39 (d, J = 11.9 Hz, 1 H), 4.27 (dd, J = 11.5, 4.5 Hz, 1 H), 4.15 (d, J = 11.9 Hz, 1 H), 3.36 (s, 3 H), 3.36−3.34 (m, 1 H), 3.26 (s, 3 H), 2.90 (br s, 1 H), 2.73 (td, J = 12.5, 4.2 Hz, 1 H), 2.47 (dd, J = 17.0, 12.1 Hz, 1 H), 2.20−2.05 (m, 3 H), 1.85 (m, 1 H), 1.71 (t, J = 17.1 Hz, 1 H), 1.54−1.44 (m, 1 H), 1.29 (dd, J = 16.9, 6.3 Hz, 1 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 1.16−1.00 (m, 1 H), 0.79 (s, 3 H), 0.80−0.65 (m, 1 H), 0.23 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 213.9, 159.6, 156.6, 143.2, 139.5, 129.4, 114.0, 105.7, 82.3, 74.7, 70.4, 56.0, 54.8, 53.9, 46.5, 39.3, 38.0, 36.2, 29.5, 29.4, 27.8, 24.1, 23.3, 22.6, 20.2, 17.0, −0.20.

Eschenmoser's salt (103 mg, 5 equiv) was dissolved in dry DMF (6 mL), placed under N_2, and heated to 50 °C. A solution of the sample of **44** from above in DMF (2 mL) was added, and stirring was maintained at 50 °C for 2.5 h. At this point, 2.5 N sodium hydroxide (3 mL) was introduced, and the mixture was poured into 1:1 chloroform/water. The separated aqueous layer was extracted with chloroform (2×), and the combined organic phases were dried and concentrated. The residual DMF was removed by heating the sample to 60 °C and 1 Torr in a Kugelrohr distillation apparatus.

The amine was dissolved in ether (5 mL), stirred with methyl iodide (1 mL) for 24 h, and evaporated. The residue was dissolved in CH_2Cl_2 (6mL), stirred vigorously with 4 mL of saturated K_2CO_3 solution for 24 h, diluted with CH_2Cl_2, and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 15% ethyl acetate in hexanes) gave 34.2 mg (66% overall) of **45** as a colorless oil: IR (neat, cm^{-1}) 1698, 1651, 1513, 1246, 1099; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2 H), 7.14 (d, J = 2.4 Hz, 1 H), 6.94−6.90 (m, 2 H), 6.16 (s, 1 H), 5.41 (s, 1 H), 4.53 (d, J = 11.7 Hz, 1 H), 4.37 (d, J = 11.7 Hz, 1 H), 4.25 (dd, J = 11.8, 4.8 Hz, 1 H), 3.83 (s, 3 H), 3.61 (br s, 1 H), 3.18 (s, 3 H), 3.12 (br s, 1 H), 2.67−2.31 (m, 1 H), 2.45−2.31 (m, 1 H), 2.11 (td, J = 12.5, 5.3 Hz, 1 H), 1.93−1.82 (m, 1 H), 1.80−1.62 (m, 4 H), 1.57 (d, J = 6.4 Hz, 1 H), 1.30−1.10 (m, 2 H), 1.15 (s, 3 H), 0.97 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.2, 195.0, 159.0, 158.6, 146.6, 145.7, 131.6, 127.8, 116.5, 113.6, 82.1, 73.6, 70.0, 56.5, 55.3, 53.3, 44.3, 39.1, 36.8, 33.7, 30.7, 29.2, 27.0, 25.7, 22.6, 20.0, 16.8; MS *m/z* (M^+) calcd 466.2719, obsd 466.2718; $[\alpha]^{22}_D$ −58.1° (*c* 1.30, chloroform).

Anal. Calcd for $C_{29}H_{38}O_5$: C, 74.65; H, 8.20. Found: C, 74.40; H, 8.30.

(−)-*O*-Methylshikoccin (2b). To a solution of **45** (32.1 mg, 7.06 × 10^{-5} mol) in CH_2Cl_2 (10 mL) containing 3 drops of water was added DDQ (21 mg, 3 equiv). The reaction mixture was stirred for 1 h, quenched with saturated $NaHCO_3$ solution, and diluted with ethyl acetate. The separated aqueous layer was extracted with ethyl acetate (2×), and the combined organic layers were washed with brine, dried, and evaporated. The crude alcohol was dissolved in CH_2Cl_2 (2 mL) and treated with pyridine (1 mL), acetic anhydride (0.5 mL), and 4-(dimethylamino)pyridine (22 mg). After being stirred overnight, the reaction mixture was diluted with ethyl acetate and saturated $NaHCO_3$ solution. The aqueous phase was extracted with ethyl acetate (3×), and the combined organic layers were washed with 2 N HCl (2×), saturated $NaHCO_3$ solution, and brine prior to drying and solvent evaporation. After chromatography on silica gel (elution with 15 → 25% ethyl acetate in hexanes), there was isolated 24.0 mg (88%) of **2b** as a white solid, mp 161−165 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 2.3 Hz, 1 H), 6.15 (s, 1 H), 5.44 (s, 1 H), 4.74 (br s, 1 H), 4.17 (dd, J = 11.6, 4.9 Hz, 1 H), 3.65 (br s, 1 H), 3.17 (s, 3 H), 2.70−2.55 (m, 1 H), 2.48-2.35 (m, 1 H), 2.20−2.05 (m, 1 H), 2.11 (s, 3 H), 1.95−1.80 (m, 4 H), 1.43 (d, J = 6.3 Hz, 1 H), 1.30−1.00 (m, 2 H), 1.01 (s, 6 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.4, 195.3, 170.1, 159.3, 146.5, 146.0, 116.2, 77.0, 73.5, 56.5, 53.0, 42.3, 38.0, 36.7, 33.4, 30.8, 28.3, 27.2, 25.7, 21.9 (2 C), 20.9, 16.7; MS *m/z* (M^+) calcd 388.2250, obsd 388.2250; $[\alpha]^{22}_D$ −4.9° (*c* 0.41, methanol).

(3*S*,4a*R*,6*R*,7*R*,10*S*,13a*R*,14*R*)-7,14-Epoxydodecahydro-6-methoxy-3-[(*p*-methoxybenzyl)oxy]-4,4,13a-trimethyl-9-methylene-7,10-methano-2*H*-benzocycloundecene-8,13-dione (46). An 8.9 mg (1.96 × 10^{-5} mol) sample of **37** was converted to silyl enol ether **44** in the predescribed manner. Condensation of **44** with Eschenmoser's salt (18 mg, 5 equiv) in a parallel manner afforded the amine, which was chromatographed on silica gel. Elution was effected with ether *containing peroxides*. The epoxy amine which eluted was stirred with methyl iodide (0.2 mL) for 20 h and processed as before to give 2.9 mg (31% overall) of **46** as a colorless oil: IR (neat, cm^{-1}) 1727, 1698, 1642, 1243, 1104; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.32 (m, 2 H), 6.93−6.89 (m, 2 H), 6.28 (d, J = 1.0 Hz, 1 H), 5.46 (d, J = 1.0 Hz, 1 H), 4.55 (d, J = 11.6 Hz, 1 H), 4.39 (d, J = 11.6Hz, 1 H), 4.22 (dd, J = 12.0, 4.0 Hz, 1 H), 3.83 (s, 3 H), 3.64 (s, 1 H), 3.34 (s, 3 H), 3.19−3.16 (m, 2 H), 2.78−2.58 (m, 2 H), 2.23 (td, J = 13.0, 5.2 Hz, 1 H), 1.94−1.65 (m, 6 H), 1.30−1.10 (m, 2 H), 1.22 (s 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.7, 196.4, 158.7, 145.2, 131.6, 128.0, 122.5, 113.6, 82.5, 71.9, 70.2, 64.0, 60.1, 59.0, 55.3, 53.0, 40.0, 39.6, 35.6, 31.5, 31.3, 29.2, 26.8, 25.0, 22.3, 19.9, 16.6; MS *m/z* (M^+) calcd 482.2668, obsd 482.2669; $[\alpha]^{22}_D$ −24.6° (*c* 0.39, chloroform).

(+)-*O*-(Methylepoxy)shikoccin (47). Epoxy ketone **46** (2.2 mg, 4.9 × 10^{-6} mol) was dissolved in CH_2Cl_2 (2 mL) containing one drop of water, treated with DDQ (1.7 mg, 1.3 equiv), and stirred at room temperature for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and ethyl acetate. The separated aqueous phase was extracted with ethyl acetate (2×), and the combined organic layers were washed with brine, dried, and concentrated. The residue was dissolved in CH_2Cl_2 (1 mL) and pyridine (0.5 mL), treated with acetic anhydride (0.2 mL) and 4-(dimethylamino)pyridine (0.11 mg), and stirred overnight. Workup in the predescribed manner gave 1.5 mg (76%) of **47**: IR (neat, cm^{-1}) 1728, 1698, 1244, 1109; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, J = 0.9 Hz, 1 H), 5.52 (d, J = 1.2 Hz, 1 H), 4.78 (t, J = 2.5 HZ, 1 H), 4.14 (dd, J = 11.9, 4.4 Hz, 1 H), 3.65 (s, 1 H), 3.34 (s, 3H), 3.23 (br s, 1 H), 2.85−2.60 (m, 2 H), 2.25−2.15 (m, 1 H), 2.14 (s, 3 H), 2.10−1.55 (m, 6 H), 1.30−1.10 (m, 2 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 213.8, 197.0, 170.3, 145.7, 122.1, 77.2, 71.9, 63.9, 59.9, 59.1, 52.7, 40.0, 38.5, 35.5, 31.5, 31.1, 28.3, 27.0, 25.0, 21.9, 21.7, 20.9, 16.6; MS *m/z* (M^+) calcd 404.2199, obsd 404.2193; $[\alpha]^{22}_D$ +20.8° (*c* 0.71, methanol).

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Supporting Information Available: Experimental details for the preparation of **11**−**14**, **17**−**19**, and **22**−**26**, along with tables giving the crystal data and structure refinement information, bond lengths and bond angles, atomic and hydrogen coordinates, and isotropic and anisotropic displacement coordinates for **34** (16 pages). See any current masthead page for ordering and Internet access instructions.

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