Studies on the Synthesis of the Diterpenoid Mold Metabolite Sordaricin. Exploration of a Prospective Biogenetic Intramolecular [4 + 2] Cycloaddition

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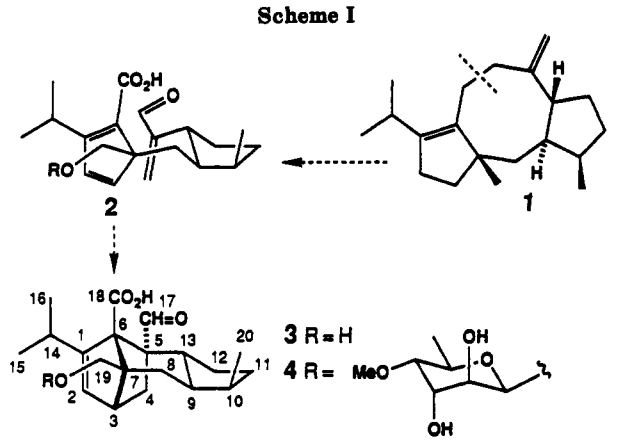
In a model study directed toward the synthesis of the diterpenoid sordaricin 3, the main carbon skeleton was established via intramolecular [4 + 2] cycloadditions of the 5,5-cyclopentadienyl derivatives 24 and 30. These intermediates were prepared by two similar routes, beginning with the alkylation of either the norbornenyl ester 14 or its enantiomer with iodide 16. The oxygenated two-carbon bridge in each of the resulting adducts was then cut away by a sequence of oxidative processes to form the diene component for the cycloadditions. For 24 this began with the Bayer–Villiger oxidation (21 → 22) and for 30, Vedejs α-hydroxylation of 27, followed by periodate cleavage. In the latter case, the benzyloxy group was introduced into the dienophile moiety by selective epoxidation of the isopropenyl group followed by amide-initiated elimination.

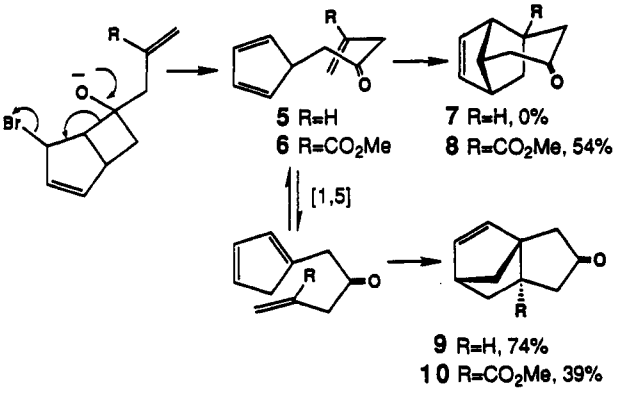
Sordarin (4) is an unusual diterpene glycoside with antifungal properties isolated from the ascomycete *Sordaria araneosa* Cain.[2] The structures of both the sugar residue and the aglycon, sordaricin (3), are unique,[3] although the biosynthetic precursor of the latter, cycloaraneosen (1),[4] shares a common skeleton with the fusicoccin diterpenes.[5] It is tempting to speculate that the biogenetic route from 1 to 4 might conceivably proceed by means of an enzyme mediated intramolecular [4 + 2] cycloaddition akin to the conversion 2 → 3.[6,7] as indicated in Scheme I (the point at which the sugar moiety is appended and the precise level of oxidation are indeterminant). We have accordingly commenced an exploration of this prospect within the context of a total synthesis of 4, the details of which are reported in this paper.[8]

A positive outcome for the desired Diels–Alder process was far from assured, given the propensity for [1,5] sigmatropic shifts in cyclopentadienyl systems.[9] The simple trienone 5, for example, affords only 9 (Scheme II), although the more reactive dienophile moiety in 6 leads to a 3:2 mixture of cycloadducts 8 and 10.[10] There is a much more favorable gap between the activation energies required for rearrangement and cycloaddition in 5,5-dialkylcyclopentadienes,[11] and this has been exploited by Fallis and co-workers in a synthesis of sinularene based on the cyclization of 11 to 12 (Scheme III).[12] It was of some concern, however, that although 11 and its C(4) epimer react at 67 °C, the 4*S*,5*S* and 4*R*,5*S* diastereomers failed to react at temperatures as high as 180 °C. Moreover, the parent system lacking both the isopropyl and alkoxy groups was found to be inert at 195 °C.[13]

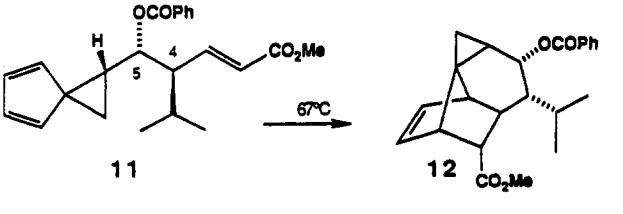
Scheme I



Scheme II



Scheme III



(1) Present address: Pfizer Central Research, Eastern Point Road, Groton, CT 06340.

(2) Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 1178–1190.

(3) Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972.

(4) Borschberg, H. J. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1975.

(5) Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Sharma, R. P.; *J. Chem. Soc., Perkin Trans. 1* **1973**, 1590–1599.

(6) It was considered unlikely that 4 was an artefact of a thermally induced cycloaddition.

(7) For other speculations regarding biogenetic intramolecular [4 + 2] cycloadditions, see: Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509–1511. Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429–3432. Takeda, K.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903–3906 and references cited therein.

(8) We are grateful to Professors Vasella and Arigoni for bringing this problem to our attention and for helpful discussions and suggestions.

(9) Ciganek, E. *Org. React.* **1984**, *32*, 1–374.

(10) Wallquist, O.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 1891–1901.

(11) Activation parameters for the rearrangement of 1,5,5-trimethylcyclopentadiene: $\Delta H^{\ddagger} = 40.3$ kcal mol^{-1}, $\Delta S^{\ddagger} = -1$ eu (De Haan, J. W.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 298–307).

(12) Antczak, K.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1985**, *63*, 993–995.

(13) Gallacher, G.; Ng, A. S.; Attah-Poku, S. K.; Antczak, K.; Alward, S. J.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 1709–1716.

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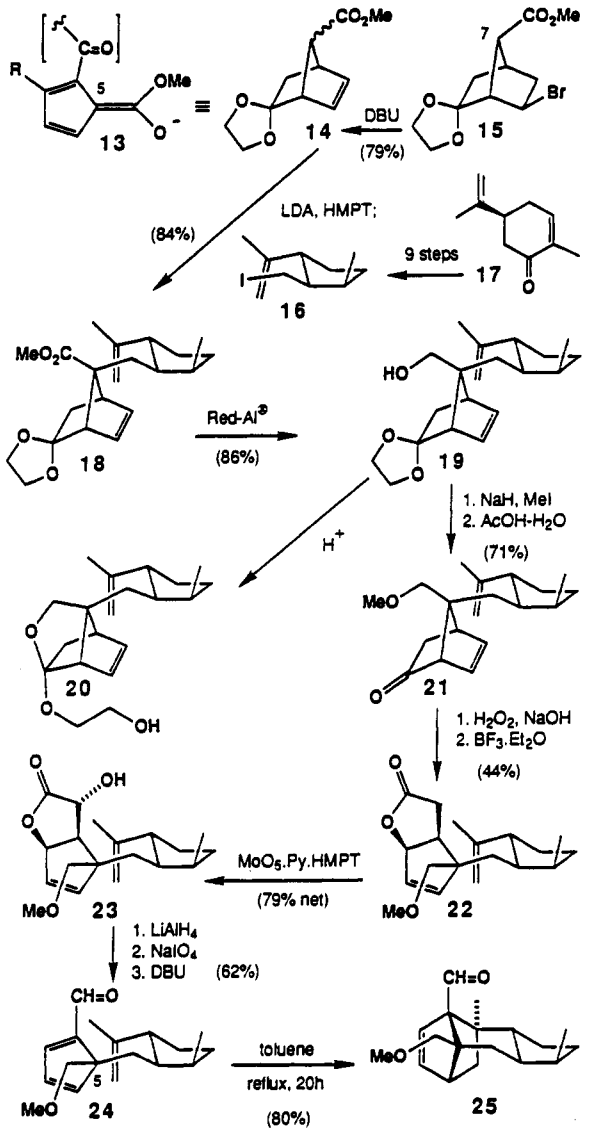
Scheme IV



The formation of **3** was expected to be favored on the basis of both frontier molecular orbital and geometrical considerations (the product of the alternative dienophile orientation requires the C-ring to adopt a boat conformation). However, inspection of a molecular model of **2** shows that the trans relationship between the functionalized side chains attached to the cyclopentane ring forces the dienophile moiety away from what might be assumed to be the preferred geometry for the transition-state structure leading to **3**.[14] There are also three contiguous quaternary centers in **3** generating steric strain, which is aggravated by the buttressing interaction between the isopropyl group and the carboxyl.[15] Given these uncertainties, we chose first to study the intramolecular Diels–Alder reactions of the model system **24** which could be expected to be more reactive than **2** and could be more easily prepared (Scheme IV).

Regardless of biosynthetic considerations, retrosynthetic analysis of **3** and its analogues guided by the Diels–Alder transform[16] leads logically to an efficient, convergent strategy based in a formal sense on the C(5)-alkylation of the cyclopentadienyl ester enolate **13** with alkyl halide **16**, which may be prepared as the racemate from citral in four steps,[17] or enantiomerically pure from (+)-carvone (**17**) in nine steps.[18] Because both regio- and stereoselectivity could be expected to be problematical in the alkylation of **13**, however, we sought an operationally equivalent molecule to the cyclopentadienyl system which would resolve both of these control problems. C-Methylation of bromo ester **15** at C(7) [equivalent to C(5) in **13** and **24**] has been reported to proceed with good diastereofacial selectivity anti to the bromo group in 78% yield (up to 10% of the 7-epimer was also formed).[19] We could envisage that one of the two-carbon bridges in the norbornyl moiety could be cleaved with deletion of one carbon center while the remaining carbon would become the carbonyl group in **24**. Moreover, both enantiomers of **15** were readily available from norbornadiene,[20] allowing a useful degree of flexibility in our synthetic planning. Alkylation of (±)-**15** with (±)-**16**, however, furnished a mixture of four diastereomers in which the facial selectivity was only ~2:1, an outcome that was attributed to the greater bulk of **16** and the higher temperature required for this conversion. We therefore proceeded to examine the equivalent alkylation of ester **14**, which was obtained as a mixture of 7-epimers by treatment of **15** with DBU. In this case, the π-facial selectivity was complete: reaction of (+)-**14** with (−)-**12** produced only (+)-**18** in 84% yield. The configuration at C(7) in this product was inadvertently confirmed when reduction by Red-Al (Aldrich) furnished not only carbinol **19**, but the isomeric ketal **20** as well.[21] The merest traces of water in the reaction medium or any subsequent exposure to acid led to the formation of variable amounts of the latter compound.

After protection of the hydroxy function in **19** as the methyl ether, the ketone function was liberated to afford **21**, and the oxygenated bridge of the norbornenyl moiety cleaved by means of a Baeyer–Villiger reaction under alkaline conditions. The resulting hydroxy acid was then lactonized by means of an intramolecular S_N2'-like process to form **22**.[22] The superfluous atoms in the lactone ring were excised by a sequence beginning with a Vedejs hydroxylation[23] to form **23**, followed by reduction to the hydroxy lactol and cleavage with sodium periodate to the β-formyloxy aldehyde. The task was then completed by heating with DBU, which gave the cyclopentadienyl carboxaldehyde **24**. In spite of all our trepidations, this product underwent a smooth [4 + 2] cycloaddition in toluene at reflux, affording only a single product after 20 h. ^1H and ^{13}C NMR spectra were fully consistent with the assignment of structure **25**.[24]

(14) Townshend, R. E.; Rammuni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190–2198.

(15) MM2 calculations on structures **3**, **25**, and further analogues using the Still–Steliou program MODEL indicate a destablizing energy of ~6 kcal mol^{-1} associated with the three angular groups plus a further ~4 kcal mol^{-1} from the isopropyl substituent.

(16) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley Interscience: New York, 1989.

(17) Prepared from the parent aldehyde which was obtained by the method of Cookson, R. C.; Hudec, J.; Knight, S. A.; Whitear, B. R. D. *Tetrahedron* **1964**, *19*, 1995–2007.

(18) Obtained from the parent methyl ester, which was prepared by the method of Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247–1261.

(19) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111–4123.

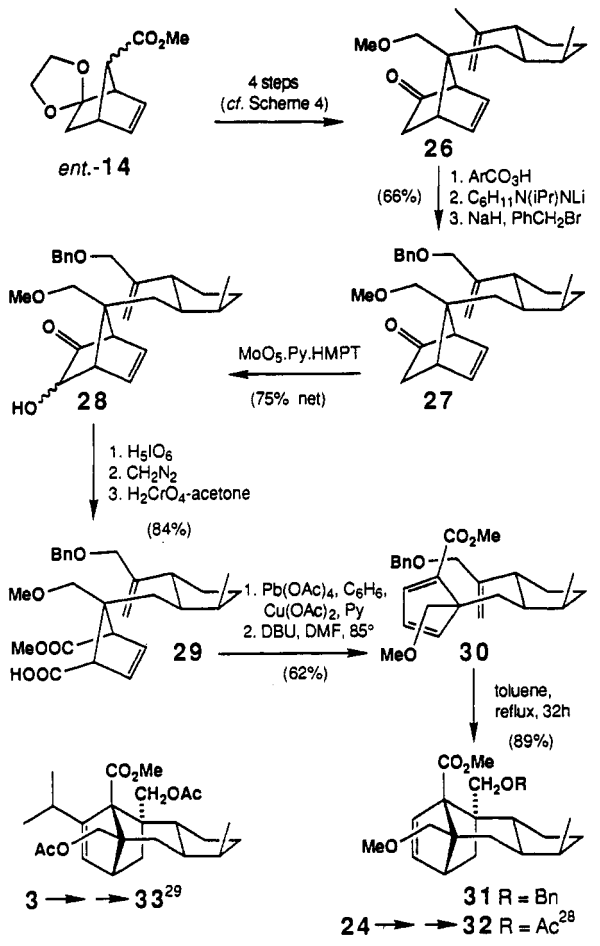
(20) Peel, R.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1974**, 151–153.

(21) Formation of ketal **20** occurred more easily when $LiAlH_4$ was used as the reducing agent.

(22) This procedure is based on a sequence described in ref 19. Yields are reduced because of a competing reaction involving the isopropenyl group.

(23) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.

Scheme V

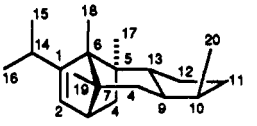


Having established the feasibility of the cycloaddition in this way, we proceeded to explore methods for hydroxylation of the isopropenyl group and to develop a more efficient procedure for the oxidative fission of the norbornenone moiety. The successful outcome of these investigations is outlined in Scheme V.

The new sequence, for which yields were consistently good to excellent, began with the (−)-enantiomer of **14**. This was converted into ketone **26** in the same way as for the preparation of the previously employed diastereomer **21**. Alkene bonds in norbornenes tend to react very readily with electrophiles, but presumably because of the deactivating influence of the adjacent carbonyl group in **26**, the propenyl group could be selectively oxidized to a mixture of diastereomeric epoxides, which was treated with lithium cyclohexyl(isopropyl)amide (LICA)[25] to afford the desired allylic alcohol. This was protected as the benzyl ether **27** and converted by the Vedejs reagent[23] into a mixture of epimeric α-ketols **28** (*exo*/*endo* = ~2:3). These were cleaved by periodic acid,[26] and the resulting carboxy aldehyde was isolated as its methyl ester. Oxidative decarboxylation of the derived acid **29** with lead tetraacetate[27] afforded a mixture of allylic acetates, which were cleanly eliminated with DBU to the cyclopentadiene **30**. The intramolecular cycloaddition then proceeded with equal facility as before to give **31** in an excellent overall yield. Spectroscopic comparison of **31** and **32**[28] with **33** [obtained by degradation of sordaricin (**3**)],[29] indicated that the respective skeletons were the same, apart from the isopropyl group. ^{13}C NMR spectra (Table I)[30] were especially diagnostic and showed excellent agreement, after making allowance for the expected discrepancies arising from the minor differences between the two structures. The only apparent anomaly in these comparisons is the downfield shift for C(13) in **33** relative to **31** and **32**. However, it seems reasonable to assume that C(13) in the latter compounds is shifted upfield by ca. 4 ppm because of the antiperiplanar relationship between what appears to be the preferred orientation of the γ-oxygen substituent and the C(5)–C(13) bond.[31] In **33**, this conformation would be disfavored by nonbonded interaction with the isopropyl group, and so the shift of 45.2 ppm for this compound then matches that of the desoxy analogue, **25** (45.7 ppm).

The possibility that **4** was an artefact of a simple, thermally induced cycloaddition was never considered to be likely, but may now be fully discounted. The formation of **25** and **31** at relatively moderate temperatures, however, is consistent with an enzyme-catalyzed conversion for the biosynthetic intermediate, a prospect that is the subject of a continuing investigation. Our efforts to utilize **31** as

Table I. ^{13}C NMR Data (δ)



sordaricane

carbon	25	31	32	33
1	128.6	130.7	130.8	149.2
2	139.3	138.6	139.7	130.5
3	49.6	47.5	47.9	45.8
4	36.0	32.0	32.5	32.5
5	47.9	50.2	49.1	49.3
6	70.7	64.4	65.4	70.1
7	67.3	67.2	67.5	67.3
8	32.2	31.6	32.3	31.2
9	42.3	41.1	41.7	41.6
10	32.8	32.0	31.9	31.7
11	27.3	26.7	27.1	27.8
12	29.7	28.8	29.2	29.2
13	45.7	40.3	41.4	45.2
14				28.4
15				21.5
16				22.7
17	22.7	75.1	69.3	70.3
18	205.4	172.8	173.1	173.0
19	78.6	77.9	78.2	70.8
20	18.0	17.6	18.0	18.0

(24) The racemic C(5) diastereomeric mixture was available from preliminary experiments and when a solution in toluene was heated under reflux for an extended period, 5-*epi*-**24** was recovered largely unchanged, although a very small amount of an impure isomeric cycloadduct assumed to arise from this isomer was obtained.

(25) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345–443.

(26) Only the exo isomer was cleaved by $NaIO_4$.

(27) Kochi, J. *Org. React.* **1972**, *19*, 279–421.

(28) In an exploratory study to determine the optimal stage for the introduction of the 17-OH group, the isopropylene group in **24** was selectively oxidized to give a mixture of epimeric epoxides, following which, treatment with LICA and cycloaddition gave a modest overall yield of the 17-hydroxy derivative of **25**. Because of the low yields in this sequence we had transferred our attention to the alternative and more efficient approach outlined in Scheme V, but the availability of this compound enabled us to prepare **32** (via acetylation, oxidation, and methylation) so as to allow additional spectroscopic comparisons with **33**.

(29) This sample was kindly provided by Professors Arigoni and Borschberg, Eidegenossischen Technischen Hochschule, Zurich.

(30) The trivial name sordaricane is proposed for the carbon skeleton of sordaricin derivatives. The numbering system follows that used by Vasella (ref 2).

(31) Eliel, E. L.; Bailey, W. F.; Kopp, L. D.; Willer, R. L.; Grant, D. M.; Bertrand, R.; Christensen, K. A.; Dallin, D. K.; Duch, M. W.; Wenkert, E.; Schell, F. M.; Cochran, D. W.; *J. Am. Chem. Soc.* **1975**, *97*, 323–330.

an intermediate in the total synthesis of sordaricin 3 will be described later.

Experimental Section

Organic extracts were routinely dried over anhydrous $MgSO_4$. Chromatography refers to "flash chromatography" on Merck Kieselgel 60. Optical rotations and IR spectra were measured in $CHCl_3$ solutions. NMR spectra were recorded in $CDCl_3$ at 200 MHz (^1H).

Methyl (1′*S*,4′*R*)-Bicyclo[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane-7′ξ-carboxylate (14). A degassed solution of bromo ketal **15** (3.41 g, 11.7 mmol) in *p*-xylene (13.5 mL) and DBU (17 mL) was heated at reflux under argon for 11.5 h. The cooled mixture was diluted with ether and washed with 1 N HCl and brine. The product was dissolved in methanol (70 mL) and treated with ethereal CH_2N_2 until TLC indicated disappearance of carboxylic acid, and then the solvent was removed under reduced pressure. Chromatography on SiO_2 with 1:1 Et_2O/hexane as eluant furnished ester **14** as a ~1:1 mixture of 7-epimers (1.94 g, 79%), $[\alpha]^{20}_D$ +116.7° (*c* 4.82), ν_{max} 1730 cm^{-1}. ^1H NMR (*syn* (7*S*) epimer) 1.57 (d, 1 H, *J* = 13.7 Hz, H3α), 1.99 (dd, 1 H, *J* = 13.7, 3.9 Hz, H3β), 2.97 (s, 1 H, H7), 3.03 (br s, H4), 3.19 (br s, H1), 3.62 (s, 3 H, OMe), 3.9 (m, 4 H, OCH_2CH_2O), 6.07 (dd, 1 H, *J* = 5.4, 2.7 Hz, H5), 6.31 (dd, 1 H, *J* = 5.4, 2.7 Hz, H6); (*anti* (7*R*) epimer) 1.57 (dd, 1 H, *J* = 13.7, 2.8 Hz, H3α), 1.99 (dd, 1 H, *J* = 13.7, 3.7 Hz, H3β), 2.77 (br s, 1 H, H7), 3.07 (br s, H4), 3.19 (br s, H1), 3.68 (s, 3 H, OMe), 3.9 (m, 4 H, OCH_2CH_2O), 6.16 (dd, 1 H, *J* = 5.8, 2.9 Hz, H5), 6.31 (dd, 1 H, *J* = 5.8, 2.9 Hz, H6). MS *m*/*z* 210 (M^+, 33): 195 (5), 151 (100), 86 (45). HRMS: calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0894.

[(1*R*,2*R*,5*R*)-5-Methyl-2-(1′-methylethenyl)cyclopentyl]methyl Iodide (16). *p*-Toluenesulfonyl chloride (1.7 g, 8.9 mmol) was added to a cooled solution of carbinol in pyridine at 0 °C under argon. The sealed mixture was allowed to stand for 3 days at 4 °C then poured onto ice and extracted with ether. The ether extract was washed with $NaHCO_3$ solution (2×), 1 N HCl, $NaHCO_3$, and brine. A solution of this product in DMF (27 mL) at 0 °C was treated with $NaHCO_3$ (0.54 g, 6.42 mmol) and LiI (2.55 g, 19.05 mmol), stirred at 0 °C for 1 h and 10 min, and then warmed to 75 °C. After 7 h the mixture was kept at room temperature overnight, diluted with ether, and washed with $NaHCO_3$, H_2O (3×), and brine. The product was chromatographed on silica (3 × 17 cm) with hexane as eluant to afford pure iodide **16** (1.50 g, 86%), $[\alpha]^{23}_D$ −54° (*c*, 5.41, hexane), ν_{max} 1640 cm^{-1}. ^1H NMR: 0.87 (d, 3 H, CH-*Me*), 1.68 (d, 3 H, *J* = 0.7 Hz, =CMe), 2.90 (apparent t, 1 H, *J* = 10.3 Hz, CH_2I), 3.23 (dd, 1 H, *J* = 5.9, 3.6 Hz, CH_2I), 4.72, 4.74 (2 br s, 2 × 1 H, $=CH_2$). ^{13}C NMR: 7.7 (CH_2I), 14.9 (Me), 19.2 (Me), 30.5 (CH_2), 32.1 (CH_2), 36.4 (CH), 49.8 (CH), 51.0 (CH), 111.5 ($=CH_2$), 146.8 (=C). HRMS: calcd for $C_{10}H_{17}I$ 264.0375, found 264.0375.

Methyl (1′*S*,4′*R*,7′*R*,1″*R*,2″*R*,5″*R*)-7′-[[5″-Methyl-2″-(1‴-methylethenyl)cyclopentyl]methyl]bicyclo[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane-7′-carboxylate (18). A solution of *n*-BuLi in hexane (1.6 M, 12.8 mL, 20.5 mmol) was added to a mixture of THF (40 mL) and diisopropylamine (2.85 mL, 20.3 mmol) at −30 °C under an argon atmosphere, stirring was continued at −30 to −20 °C over a period of 0.5 h, and then the temperature was lowered to −78 °C. A solution of ester **14** (3.77 g, 17.93 mmol) in THF (40 mL) (dried over 4-Å molecular sieves) was injected dropwise at a rate of 0.3 mL/min with the aid of a syringe pump. After the mixture was stirred at −78 °C for 75 min, HMPT (3.6 mL, 20.7 mmol) was added, and the resulting mixture was warmed to 0 °C. A solution of iodide **16** (5.6 g, 21.2 mmol) in THF (dried over 4-Å molecular sieves) (6 mL + 6 mL rinse) was added, and the mixture was stirred at room temperature overnight (16 h). After the reaction was quenched with H_2O (5 mL), the THF was removed in vacuo and the residue taken up in ether, and washed with H_2O (2×) and brine. The crude product was chromatographed on silica gel (5 × 17 cm) using 3:2 hexane/ether as eluant. The pure ketal ester **18** was obtained as a viscous oil, 5.21 g (84%), $[\alpha]^{22}_D$ +6.9° (*c* 3.24), ν_{max} 1727, 1640 cm^{-1}. ^1H NMR: 0.72 (d, 3 H, *J* = 7.3 Hz, CHMe), 1.56 (d, 3 H, *J* = 0.5 Hz, =CMe), 2.75 (br s, 1 H, H4), 3.03 (br s, 1 H, H1), 3.64 (s, 3 H, OMe), 3.8–3.9 (m, 4 H, OCH_2CH_2O), 4.62, 4.67 (2 br s, 2 × 1 H, $=CH_2$), 6.07 (dd, 1 H, *J* = 5.7, 3.2 Hz, H5), 6.24 (dd, 1 H, *J* = 5.7, 2.9 Hz, H6). ^{13}C NMR: 15.7 (Me), 18.4 (Me), 27.3 (CH_2), 29.1 (CH_2), 33.1 (CH_2), 35.4 (CH), 39.3 (CH_2), 44.3 (CH), 50.9 (OMe), 51.2 (CH), 57.0 (CH), 64.3, 64.4 (OCH_2CH_2O), 72.0 (C), 111.2 ($=CH_2$), 116.9 (OCO), 132.3 (=CH), 137.3 (=CH), 147.4 (=C), 175.3 (CO). MS: *m*/*z* 346 (M^+, 0.2), 287 (2), 209 (13), 175 (10), 86 (100). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.99; H, 8.64.

(1′*S*,4′*R*,7′*R*,1″*R*,2″*R*,5″*R*)-7′-(Hydroxymethyl)-7′-[[5″-methyl-2″-(1‴-methylethenyl)cyclopentyl]methyl]bicyclo[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane (19). To a solution of ester **18** (3.34 g, 9.64 mmol) in dry toluene (10 mL, freshly distilled over $LiAlH_4$) was added a solution of Red-Al (8 mL, 70% in toluene). The mixture was heated at reflux under argon in an oil bath (140 °C) for 17 h, and after cooling to 0 °C, quenched by dropwise addition of H_2O. Ether was added, the mixture was filtered through Celite, the solvents were removed, and the residual clear oil was chromatographed on silica gel (5 × 13 cm) using 1.25:1 hexane/ether as eluant. The pure hydroxy ketal **19** was obtained as a colorless oil (2.63 g, 86%), $[\alpha]^{23}_D$ +16.7° (*c* 4.32), ν_{max} 3540, 1640 cm^{-1}. ^1H NMR: 0.78 (d, 3 H, *J* = 7.1 Hz, CH*Me*), 1.68 (s, 3 H, =CMe), 2.52, 2.54 (2 br s, 2 × 1 H, H1, H4), 3.58 (d, 1 H, *J* = 12 Hz, CH_2OH), 3.83 (m, 5 H, OCH_2CH_2O + CH_2OH), 4.71, 4.74 (2 br s, 2 × 1 H, $=CH_2$), 6.12, 6.18 (2 m, 2 × 1 H, H5, H6). ^{13}C NMR: 15.2 (Me), 18.5 (Me), 27.2 (CH_2), 28.8 (CH_2), 33.2 (CH_2), 35.7 (CH), 39.7 (CH_2), 44.0 (CH), 46.5 (CH), 50.7 (CH), 55.2 (CH), 63.2 (CH_2OH), 64.3 (OCH_2CH_2O), 66.7 (C), 110.9 ($=CH_2$), 117.7 (OCO), 132.9 (=CH), 136.8 (=CH), 147.8 (=C). MS: *m*/*z* 318 (M^+, 0.4), 201 (23), 149 (25), 123 (20), 86 (100).

Further elution afforded **20** (200 mg, 6%). ^1H NMR: 0.76 (d, 3 H, *J* = 7.1 Hz, CH*Me*), 1.60 (s, 3 H, =CMe), 2.57, 2.68 (2 br s, 2 × 1 H, H-1, H4), 3.70 (s, 2 H, OCH_2), 3.70, 3.78 (2 m, 2 × 2 H, OCH_2CH_2O), 4.65, 4.70 (2 br s, 2 × 1 H, $=CH_2$), 5.91 (dd, 1 H, *J* = 5.6, 2.7 Hz, H5), 6.33 (dd, 1 H, *J* = 5.6, 2.7 Hz, H6). ^{13}C NMR: 15.7 (Me), 18.8 (Me), 27.2 (CH_2), 27.9 (CH_2), 33.3 (CH_2), 36.1 (CH), 38.9 (CH_2), 43.8 (CH), 48.0 (CH), 51.5 (CH), 56.0 (CH), 62.5 (CH_2O), 68.5, 69.3 (OCH_2CH_2O), 70.8 (C), 111.5 ($=CH_2$), 112.8 (OCO), 128.2 (=CH), 140.4 (=CH), 147.5 (=C). MS: *m*/*z* 318 (M^+, 1), 287 (5), 201 (54), 123 (40), 86 (100).

(1′*S*,4′*R*,7′*R*,1″*R*,2″*R*,5″*R*)-7′-(Methoxymethyl)-7′-[[5″-methyl-2″-(1‴-methylethenyl)cyclopentyl]methyl]bicyclo[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane. A suspension of NaH in oil (55–60%, 3.7 g, ca. 85 mmol) under argon was washed with dry hexane, and then THF (20 mL) was added. To this suspension was then added a solution of the ketal alcohol **19** (6.73 g, 21.13 mmol) in THF (40 mL) by cannulation. After the mixture was stirred at room temperature for 15 min, methyl iodide (8.3 mL, 133 mmol) was added and stirring was continued overnight (21 h). The mixture was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution, and concentrated in vacuo. The residue was dissolved in ether and washed with H_2O and then brine. The crude methyl ether was obtained as a slightly yellow oil (7.07 g, 100%) and used without further purification in the next step. An analytical sample was obtained by chromatography on silica gel using 3:1 hexane/ether as eluant to afford pure methyl ether (365 mg, 92%) as a clear oil, $[\alpha]^{20}_D$ +33.2° (*c* 3.11), ν_{max} 1640 cm^{-1}. ^1H NMR: 0.78 (d, 3 H, *J* = 7.1 Hz, CH*Me*), 1.64 (s, 3 H, =CMe), 2.45 (br s, 1 H, H4), 2.53 (br s, 1 H, H1), 3.31 (s, 3 H, OMe), 3.54, 3.70 (AB d, 2 H, *J* = 9.8 Hz, CH_2OMe), 3.79–3.98 (m, 4 H, OCH_2CH_2O), 4.67 (br s, 2 H, $=CH_2$), 6.06 (m, 1 H, H6), 6.18 (m, 1 H, H5). ^{13}C NMR: 15.3 (Me), 18.7 (Me), 27.1 (CH_2), 27.4 (CH_2), 33.3 (CH_2), 36.1 (CH), 39.8 (CH_2), 44.5 (CH), 47.1 (CH), 51.1 (CH), 55.2 (CH), 58.9 (OMe), 63.7, 64.7 (OCH_2CH_2O), 65.3 (C), 73.3 (CH_2OMe), 111.1 ($=CH_2$), 118.2 (OCO), 133.1 (=CH), 137.2 (=CH), 147.9 (=C). MS: *m*/*z* 332 (M^+, 11), 287 (11), 246 (9), 214 (18), 201 (100), 145 (14), 123 (35), 86 (73). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.64; H, 9.54.

(1*S*,4*R*,7*R*,1′*R*,2′*R*,5′*R*)-7-(Methoxymethyl)-7-[[5′-methyl-2′-(1″-methylethenyl)cyclopentyl]methyl]bicyclo[2.2.1]hept-5-en-2-one (21). A heterogeneous mixture of the ketal (9.70 g, 29.17 mmol) in AcOH (70 mL) plus H_2O (160 mL) was heated in an oil bath at 100 °C for 6.25 h. After being cooled to 0 °C the mixture was made alkaline (pH 9) by addition of NaOH (49 g in 80 mL H_2O) followed by solid Na_2CO_3. The mixture was diluted with H_2O and extracted three times with ether. Pure **21**, $[\alpha]^{23}_D$ +385° (*c* 4.27), was obtained as an oil (6.45 g, 77%) by chromatography on silica gel (5 × 13 cm) using 3:1 hexane/ether as eluant, ν_{max} 1736, 1640 cm^{-1}. ^1H NMR: 0.82 (d, 3 H, *J* = 7.1

Hz, CH*Me*), 1.63 (s, 3 H, =CMe), 2.72 (br s, 1 H, H4), 2.99 (br s, 1 H, H1), 3.28 (s, 3 H, OMe), 3.33 (s, 2 H, C*H*$_2$OMe), 4.66, 4.69 (2 s, 2 × 1 H, =CH$_2$), 5.93 (m, 1 H, H5), 6.49 (m, 1 H, H6). ^{13}C NMR: 15.4 (Me), 18.7 (Me), 26.9 (CH$_2$), 27.5 (CH$_2$), 33.4 (CH$_2$), 36.0 (CH$_2$), 36.3 (CH), 44.2 (CH), 46.3 (CH), 51.3 (CH), 59.3 (OMe), 62.3 (CH), 66.3 (C), 74.0 (*C*H$_2$OMe), 111.3 (=CH$_2$), 127.7 (=CH), 143.7 (=CH), 147.7 (=C), 214.4 (CO). MS: *m/z* 288 (M$^+$, 0.6), 171 (13), 145 (15), 132 (15), 131 (15), 123 (50), 105 (50), 91 (100). Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.13; H, 9.99.

(3a*S*,6a*S*,1′*R*,2′*R*,5′*R*)-4-[[2′-(1″-Methylethenyl)-5′-methylcyclopentyl]methyl]-4-(methoxymethyl)-2,3,3a,4-tetrahydro-6a*H*-cyclopenta[*b*]furan-2-one (22). To a cooled solution of ketone **21** (430 mg, 1.49 mmol) in MeOH (5 mL), H$_2$O (3 mL), and THF (5 mL) were added 10% NaOH (1.8 mL) and 30% H$_2$O$_2$ (1.4 mL), and the mixture was stirred at 0–5 °C for 25 h, after which time further 30% H$_2$O$_2$ (0.6 mL) was added, and stirring was continued for a further 3.5 h. The mixture was acidified to pH 5.5 and quenched with Na$_2$SO$_3$ (3 g). The hydroxy acid product was obtained by extraction into EtOAc and employed directly in the next stage. The residue after removal of solvent was dissolved in CH$_2$Cl$_2$ (18 mL), cooled to 0 °C under argon, and treated with BF$_3$·OEt$_2$ (6 μL). After 45 min additional BF$_3$·OEt$_2$ (50 μL) was added and after 1 h and 15 min the solution was diluted with CH$_2$Cl$_2$ and washed with brine. The product was chromatographed on silica gel using 2:1 hexane/ether as eluant. The product obtained appeared to be contaminated by a carboxylic acid and so was treated with ethereal CH$_2$N$_2$ and then rechromatographed to afford lactone **22** (201 mg, 44%), $[\alpha]^{20}_D$ −104.9° (*c* 3.70), ν_{max} 1765, 1640 cm^{-1}. ^{1}H NMR: 0.82 (d, 3 H, *J* = 7.1 Hz), 1.63 (d, 3 H, *J* = 0.7 Hz, =CMe), 2.54 (dd, 1 H, *J* = 5.9, 2.7 Hz, CHCO$_2$), 2.72 (m, 1 H, CHCO$_2$), 3.26 (s, 3 H, OMe), 4.67, 4.73 (2 br s, 2 × 1 H, =CH$_2$), 5.43 (d, 1 H, *J* = 7.1 Hz, H1), 5.91 (s, 2 H, H2 + H3). ^{13}C NMR: 15.7 (Me), 18.8 (Me), 27.5 (CH$_2$), 30.7 (CH$_2$), 33.3 (CH$_2$), 35.6 (CH$_2$), 35.9 (CH), 42.6 (CH), 44.6 (CH), 51.5 (CH), 55.5 (C), 58.8 (OMe), 76.1 (*C*H$_2$OMe), 88.7 (CHOCO), 111.7 (=CH$_2$), 128.6 (=CH), 143.5 (=CH), 147.0 (=C), 177.5 (CO). MS: *m/z* 304 (M$^+$, 1), 259 (46), 199 (18), 137 (39), 123 (41), 107 (38), 91 (49), 81 (62), 45 (100). HRMS: calcd for $C_{19}H_{28}O_3$ 304.2038, found 304.2052.

(2*R*,3a*S*,6a*S*,1′*R*,2′*R*,5′*R*)-3-Hydroxy-4-[[2′-(1″-methylethenyl)-5′-methylcyclopentyl]methyl]-4-(methoxymethyl)-2,3,3a,4-tetrahydro-6a*H*-cyclopenta[*b*]furan-2-one (23). Into a solution of LDA in THF formed from *i*Pr$_2$NEt (0.14 g, 1.0 mmol) and *n*-BuLi (1.6 M, 0.63 mL) at −78 °C was canulated dropwise a solution of lactone **22** (185 mg, 0.61 mmol) in THF (5 mL + 2 mL rinse). The mixture was stirred for 1.5 h at −70 °C, and then MoO$_5$·py·HMPT (434 mg, 1.0 mmol) was added in one portion. After 2.5 h, during which time the temperature was allowed to rise from −70 °C to −35 °C, the reaction was quenched with saturated Na$_2$SO$_3$ solution (4 mL) and the mixture warmed to room temperature. Ether was added, and the mixture was washed with brine. Chromatography on silica gel with 1:1 hexane/ether as eluant afforded starting material (81 mg) and hydroxy lactone **23** as a colorless oil (87 mg, 45%, 79% net), $[\alpha]^{23}_D$ −109.7° (*c* 4.65), ν_{max} 3460, 1777, 1640 cm^{-1}. ^{1}H NMR: 0.82 (d, 3 H, *J* = 7.1 Hz, =C*Me*), 1.62 (s, 3 H, =CMe), 2.76 (t, 1 H, *J* = 6.8 Hz, H5), 3.33 (s, 3 H, OMe), 3.48 (s, 2 H, C*H*$_2$OMe), 3.65 (e, 1 H, OH), 4.45 (d, 1 H, *J* = 6.4 Hz, C*H*(OH)CO), 4.47, 4.67 (2 br s, 2 × 1 H, =CH$_2$), 5.49 (d, 1 H, *J* = 7.1 Hz, H1), 5.90 (s, 2 H, H2 + H3). ^{13}C NMR: 15.7 (Me), 18.8 (Me), 27.5 (CH$_2$), 33.4 (CH$_2$), 35.8 (CH), 36.2 (CH$_2$), 42.8 (CH), 51.7 (CH), 54.5 (CH), 54.6 (C), 59.2 (OMe), 69.6 (CHOH), 75.9 (*C*H$_2$OMe), 86.3 (COCHOH), 111.9 (=CH$_2$), 129.1 (=CH), 142.7 (=CH), 147.1 (=C), 177.3 (CO). MS: *m/z* 275 (M$^+$ − 45, 10), 213 (30), 201 (23), 137 (58), 123 (60), 107 (44), 45 (100). HRMS: calcd for $C_{19}H_{28}O_4$ 320.1983, found 320.1987.

(5*S*,1′*R*,2′*R*,5′*R*)-5-[[2′-(1″-Methylethenyl)-5′-methylcyclopentyl]methyl]-5-(methoxymethyl)cyclopenta-1,3-diene-1-carboxaldehyde (24). LiAlH$_4$ (24 mg) was added in two portions to a solution of hydroxy lactone **23** (104 mg, 0.33 mmol) in Et$_2$O (7 mL), and when TLC indicated consumption of starting material, a few drops of saturated Na$_2$SO$_4$ soln was added followed by anhydrous MgSO$_4$. The filtered mixture was reduced to dryness, dissolved in dioxane/H$_2$O (3:2, 5 mL) and treated with NaIO$_4$ (100 mg). After the mixture was stirred overnight (dark, 15 h), H$_2$O was added and the product was extracted into ether, which was then washed with brine. After removal of solvent the residue was dissolved in benzene (5 mL), DBU (8 drops) was added, and the mixture was heated at reflux under argon for 10 min. After removal of solvent, the residue was chromatographed on silica gel using 3:1 hexane/ether as eluant. Triene **24** (55 mg, 62%) was obtained as a colorless oil, $[\alpha]^{23}_D$ −172.3° (*c* 2.69), ν_{max} 1659 cm^{-1}. ^{1}H NMR: 0.78 (d, 3 H, *J* = 7.0 Hz), 1.48 (s, 3 H, =CMe), 3.25 (d, 1 H, overlapped, C*H*$_2$OMe), 3.26 (s, 3 H, OMe), 3.87 (d, 1 H, *J* = 8.4 Hz, C*H*$_2$OMe), 4.62, 4.69 (2 br s, 2 × 1 H, =CH$_2$), 6.52 (dd, 1 H, *J* = 2.3, 5.4 Hz, H3), 7.05 (d, 1 H, *J* = 5.4 Hz, H4), 7.34 (dd, *J* = 2.3, 0.9 Hz, H2), 9.72 (d, 1 H, *J* = 0.9 Hz, CH=O). ^{13}C NMR: 15.1 (C20), 18.3 (C17), 27.6 (C11), 29.3 (C8), 32.8 (C12), 36.0 (C10), 42.6 (C9), 51.0 (C13), 62.1 (C7), 77.1 (C19), 111.3 (C4), 130.1 (C2), 146.9 (C5), 150.5 (C6), 151.2 (C3), 154.6 (C1), 185.6 (C18). HRMS: calcd for $C_{18}H_{26}O_2$ 274.1933; found 274.1939.

19-Methoxy-14,15,16-trisnorsordaric-1-en-18-al (25). A degassed solution of triene **24** (13 mg) in toluene (3.5 mL) was heated at reflux under an atmosphere of argon for 20 h. After removal of solvent the residue was chromatographed on silica gel with 7:3 hexane/ether as eluant to afford **25** as a colorless oil, $[\alpha]^{23}_D$ −45.0° (*c* 0.52), ν_{max} 2862, 1700 cm^{-1}. ^{1}H NMR: 0.53 (d, 1 H, *J* = 12.4 Hz, H4α), 0.86 (d, 3 H, *J* = 6.8 Hz, 10Me), 0.93 (s, 3 H, 5 Me), 2.52 (t, 1 H, *J* = 3.7 Hz, H3), 3.18 (s, 3 H, OMe), 3.25, 3.43 (AB d, 2 × 1 H, *J* = 9.0 Hz, H19), 6.12 (d, 1 H, *J* = 5.9 Hz, H1), 6.32 (dd, 1 H, *J* = 5.6, 3.4 Hz, H2), 10.13 (s, 1 H, H18). ^{13}C NMR: see table. MS: *m/z* 274 (M$^+$, 2), 242 (17), 229 (100), 121 (33), 107 (50). HRMS: calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1939.

Methyl (1′*R*,4′*S*,7′*S*,1″*R*,2″*R*,5″*R*)-7′-[[5″-Methyl-2″-(1‴-methylethenyl)cyclopentyl]methyl]bicyclo[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane-7′-carboxylate (*epi*-18). This ester was prepared on a 6-g scale from *ent*-**14** as described for the diastereomer **18** and obtained as a viscous oil (87% yield), $[\alpha]^{20}_D$ −69.3° (*c* 2.83), ν_{max} 1727, 1640 cm^{-1}. ^{1}H NMR: 0.69 (d, 3 H, *J* = 6.8 Hz CH*Me*), 1.50 (d, 1 H, *J* = 12.7 Hz, H3α), 1.61 (s, 3 H, =CMe), 2.31 (dd, 1 H, *J* = 12.7, 3.6 Hz, H3β), 2.80 (m, 1 H, H4), 2.97 (m, 1 H, H1), 3.82 (s, 3 H, OMe), 3.85 (m, 4 H, OCH$_2$CH$_2$O), 4.62, 4.67 (2 br s, 2 × 1 H, =CH$_2$), 6.04 (m, 1 H, H5), 6.17 (dd, 1 H, *J* = 5.8, 3.2 Hz, H6). ^{13}C NMR: 15.2 (Me), 18.8 (Me), 27.3 (CH$_2$), 29.1 (CH$_2$), 33.2 (CH$_2$), 34.8 (CH), 38.9 (CH$_2$), 44.2 (CH), 45.8 (CH), 51.0 (CH), 51.2 (OMe), 56.3 (CH), 64.3 (OCH$_2$CH$_2$O), 70.8 (C), 111.3 (=CH$_2$), 117.5 (OCO), 131.8 (=CH), 137.3 (=CH), 147.5 (=C), 175.7 (CO). MS: *m/z* 346 (M$^+$, 2), 287 (2), 209 (13), 175 (10), 86 (100). HRMS: calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2143.

(1′*R*,4′*S*,7′*S*,1″*R*,2″*R*,5″*R*)-7′-(Hydroxymethyl)-7′-[[5″-methyl-2″-(1‴-methylethenyl)cyclopentyl]methyl]bicyclo-[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane (*epi*-19). This intermediate was prepared on a 6-g scale from *epi*-**18** as described for the diastereomer **19** and obtained as a viscous oil (87% yield), $[\alpha]^{20}_D$ −105.0° (*c* 1.67, CH$_2$Cl$_2$), ν_{max} 3530, 1640 cm^{-1}. ^{1}H NMR: 0.78 (d, 3 H, *J* = 6.8 Hz, CH*Me*), 1.50 (d, 1 H, *J* = 13.2 Hz, H-3α), 1.67 (d, 3 H, *J* = 0.5 Hz, =CMe), 2.19 (dd, 1 H, *J* = 13.2, 3.6 Hz, H3β), 2.55 (m, 2 H, H1 + H4), 3.85 (m, 4 H, OCH$_2$CH$_2$O), 4.70 (m, 2 H, =CH$_2$), 6.07 (dd, 1 H, *J* = 5.3, 3.1 Hz, H5), 6.25 (dd, 1 H, *J* = 5.3, 2.2 Hz, H6). ^{13}C NMR: 15.2 (Me), 18.7 (Me), 27.3 (CH$_2$), 28.8 (CH$_2$), 33.2 (CH$_2$), 35.9 (CH), 39.3 (CH$_2$), 44.0 (CH), 47.1 (CH), 51.0 (CH), 54.6 (CH), 63.8 (CH$_2$OH), 64.6, 64.7 (OCH$_2$CH$_2$O), 66.6 (C), 110.7 (=CH$_2$), 118.3 (OCO), 132.0 (=CH), 138.2 (=CH), 148.3 (=C). MS: *m/z* 332 (M$^+$, 2), 287 (5), 246 (5), 214 (11), 201 (77), 145 (16), 123 (39), 86 (100). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.51, H. 9.28.

(1′*R*,4′*S*,7′*S*,1″*R*,2″*R*,5″*R*)-7′-(Methoxymethyl)-7′-[[5″-methyl-2″-(1‴-methylethenyl)cyclopentyl]methyl]bicyclo-[2.2.1]hept-5′-ene-2′-spiro-2-[1,3]dioxolane. This intermediate was prepared on a 4-g scale from *epi*-**19** as described for the diastereomer and obtained as a clear oil in 96% yield, $[\alpha]^{20}_D$ −96.5° (*c* 3.0), ν_{max} 1640 cm^{-1}. ^{1}H NMR: 0.75 (d, 3 H, *J* = 7.1 Hz, CH*Me*), 1.47 (d, 1 H, *J* = 13.1 Hz, H3α), 1.65 (s, 3 H, =CMe), 2.13 (dd, 1 H, *J* = 13.1, 3.7 Hz, H3β), 2.46 (m, 1 H, H4), 2.52 (m, 1 H, H1), 3.29 (s, 3 H, OMe), 3.38, 3.85 (AB d, 2 H, *J* = 10 Hz, C*H*$_2$OMe), 3.81 (m, 4 H, OCH$_2$CH$_2$O), 4.69 (s, 2 H, =CH$_2$), 6.07 (m, 1 H, H5), 6.26 (m, 1 H, H6). ^{13}C NMR: 15.0 (Me), 18.3 (Me), 27.0 (CH$_2$), 27.1 (CH$_2$), 33.0 (CH$_2$), 35.8 (CH), 39.0 (CH$_2$), 44.0 (CH), 47.6 (CH), 50.7 (CH), 54.8 (CH), 58.7 (OMe), 63.5, 64.5 (OCH$_2$CH$_2$O), 65.0

(C), 73.0 (CH_2OMe), 110.8 (=CH_2), 118.5 (OCO), 132.2 (=CH), 137.6 (=CH), 147.5 (=C). MS: m/z 332 (M^+, 10), 287 (10), 246 (9), 201 (100), 86 (73). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.87; H, 9.41.

(1*R*,4*S*,7*S*,1′*R*,2′*R*,5′*R*)-7-(Methoxymethyl)-7-[[5′-methyl-2′-(1″-methylethenyl)cyclopentyl]methyl]bicyclo[2.2.1]hept-5-en-2-one (26). This intermediate was prepared on a 10-g scale as described for the diastereomer **21** and obtained as a clear oil in 81% yield, $[\alpha]^{20}_D$ −451.3° (*c* 2.97), ν_{max} 1735, 1640 cm^{-1}. ^1H NMR: 0.74 (d, 3 H, *J* = 7.1 Hz, CH*Me*), 1.66 (s, 3 H, =CMe), 1.85 (d, 1 H, *J* = 16.9 Hz, H3α), 2.20 (dd, 1 H, *J* = 16.9, 3.2 Hz, H3β), 2.76 (br s, 1 H, H4), 2.90 (br s, 1 H, H1), 3.27 (s, 3 H, OMe), 3.28, 3.30 (AB d, 2 H, *J* = 10.6 Hz, CH_2OMe, partly obscured), 4.72 (br s, 2 H, =CH_2), 5.91 (m, 1 H, H5), 6.55 (dd, 1 H, *J* = 5.4, 2.7 Hz, H6). ^{13}C NMR: 15.10 (Me), 18.37 (Me), 26.13 (CH_2), 27.13 (CH_2), 33.00 (CH_2), 35.30 (CH_2), 35.56 (CH), 43.65 (CH), 46.66 (CH), 50.68 (CH), 58.04 (OMe), 61.55 (CH), 65.96 (C), 72.76 (CH_2O), 111.13 (=CH_2), 126.81 (=CH), 144.13 (=CH), 147.16 (=C), 214 (CO). MS: m/z 288 (M^+, 0.6), 171 (11), 145 (12), 132 (16), 131 (15), 123 (56), 105 (52), 91 (100). Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.41; H, 9.50.

(1*R*,4*S*,7*S*,1′*R*,2′*R*,5′*R*)-7-[[2′-[1″-(Hydroxymethyl)ethenyl]-5′-methylcyclopentyl]methyl]-7-(methoxymethyl)bicyclo[2.2.1]hept-5-en-2-one. To a stirred solution of the ketone **26** (2.0 g, 6.93 mmol) in CH_2Cl_2 (100 mL) and suspended solid $NaHCO_3$ at room temperature was added small portions of *m*-CPBA (80–90%, 2.67 g, ca. 12.5 mmol) over a period of 40 min. A solution of Na_2SO_3 (15 g) in H_2O (150 mL) was then poured into the reaction vessel, and the resulting mixture was stirred vigorously. After addition of ether and further stirring, the organic fraction was separated and washed with 3% NaOH solution (2 × 125 mL), H_2O, and brine. The crude epoxide was dissolved in dry ether (15 mL) and cannulated into a solution of LICA in ether prepared by addition of *n*-BuLi/hexane (1.6 M 21.7 mL, 34.7 mmol) to a solution of cyclohexylisopropylamine (5.7 mL, 34.7 mmol) in ether (25 mL) at 0 °C. The mixture was stirred at room temperature for 6.25 h, cooled to 0 °C, and quenched with saturated aqueous NH_4Cl solution (25 mL). Following dilution with ether, the solution was washed sequentially with H_2O and brine. The crude product was chromatographed on a column of silica gel (3 × 18 cm) using 3:1 ether/hexane as eluant to provide the pure allylic alcohol (1.72 g, 82%) as a colorless oil, $[\alpha]^{20}_D$ −464.2° (*c* 3.7), ν_{max} 3600, 3460, 1735, 1640 cm^{-1}. ^1H NMR: 0.73 (d, 3 H, CH*Me*), 2.76 (m, 1 H, H4), 2.91 (m, 1 H, H1), 3.26, 3.40 (AB d, 2 H, *J* = 10.8 Hz, CH_2OMe), 3.29 (s, 3 H, OMe), 4.07 (br s, OH), 4.93, 5.09 (2 s, 2 × 1 H, =CH_2), 5.93 (m, 1 H, H5), 6.57 (dd, 1 H, *J* = 5.8, 2.9 Hz, H6). ^{13}C NMR: 15.0 (Me), 26.2 (CH_2), 28.9 (CH_2), 32.8 (CH_2), 35.3 (CH_2), 35.5 (CH), 44.6 (CH), 46.7 (CH), 47.2 (CH), 59.2 (OMe), 61.7 (CH), 64.7 (CH_2OH), 65.9 (C), 72.6 (CH_2OMe), 110.1 (=CH_2), 126.8 (=CH), 144.3 (=CH), 151.8 (=C), 214.5 (CO). MS: m/z 213 (M^+ − 91, 5), 213 (10), 171 (11), 157 (18), 131 (19), 123 (22), 105 (32), 91 (100). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.88; H, 9.58.

(1*R*,4*S*,7*S*,1′*R*,2′*R*,5′*R*)-7-[[2′-[1″-[(Benzyloxy)methyl]ethenyl]-5′-methylcyclopentyl]methyl]-7-(methoxymethyl)bicyclo[2.2.1]hept-5-en-2-one (27). Sodium hydride suspension (55–60% in oil) (1 g, ca. 23 mmol) was placed in a dry flask and washed with hexane. A solution of the alcohol prepared above (2.64 g, 8.67 mmol) in DMF (50 mL) was added by cannulation and shortly afterward, benzyl bromide (2.7 mL, 22.7 mmol) was injected. After the mixture had been stirred at room temperature for 5 h the excessive NaH was quenched by slow dropwise addition of saturated aqueous NH_4Cl solution. The mixture was diluted with ether (ca. 500 mL) and washed three times with H_2O and once with brine. The crude product was chromatographed on silica gel (3 × 19 cm) using 3:1 hexane/ether as eluant to obtain pure **27** (2.77 g, 81%) as a colorless oil, $[\alpha]^{20}_D$ −357.4° (*c* 2.86), ν_{max} 1735, 1640 cm^{-1}. ^1H NMR: 0.73 (d, 3 H, *J* = 7.1 Hz, CH*Me*), 2.76 (e, 1 H, $W_{1/2}$ = 5 Hz, H4), 2.87 (e, 1 H, $W_{1/2}$ = 5 Hz, H1), 3.23 (s, 3 H, OMe), 3.22, 3.32 (AB d, 2 × 1 H, *J* = 8.5 Hz, CH_2OMe), 3.97 (s, 2 H, CH_2OBn), 4.51 (s, 2 H, PhCH_2O), 4.97, 5.13 (2 s, 2 × 1 H, =CH_2), 5.90 (m, 1 H, H5), 6.51 (dd, 1 H, *J* = 5.4, 2.9 Hz, H6), 7.33 (m, 5 H, ArH). ^{13}C NMR: 15.0 (Me), 26.2 (CH_2), 28.7 (CH_2), 32.7 (CH_2), 35.2 (CH_2), 35.5 (CH), 44.4 (CH), 46.5 (CH), 46.7 (CH), 59.0 (OMe), 61.6 (CH), 65.9 (C), 72.1, 72.3, 72.6 (3 × CH_2O), 110.9 (=CH_2), 126.0, 127.5, 128.3 (ArH), 127.5 (=CH), 138.4 (Ar), 144.0 (=CH), 148.5 (=C), 214.3 (CO). MS: m/z 303 (M^+ − 91, 5), 285 (4), 271 (5), 243 (5), 131 (19), 123 (42), 105 (50), 91 (100). Anal. Calcd for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.01; H, 8.83.

(1*R*,3*S*,4*S*,7*S*,1′*R*,2′*R*,5′*R*)-7-[[2′-[1″-[(Benzyloxy)methyl]ethenyl]-5′-methylcyclopentyl]methyl]-3-hydroxy-7-(methoxymethyl)bicyclo[2.2.1]hept-5-en-2-one and 3*R* Epimer (28). A solution of ketone **27** (3.52 g, 8.92 mmol) in THF (45 mL) was cannulated under argon into a solution of LDA in THF (20 mL) prepared from diisopropylamine (1.4 mL, 9.99 mmol) and *n*-BuLi in hexane (1.6 M, 6.3 mL, 10.03 mmol) at −78 °C. The mixture was stirred at −78 °C for 1.5 h and then warmed to −23 °C (dry ice/CCl_4 bath). Solid MoO_5·py·HMPT (5.81 g, 13.38 mmol) was added in one portion with vigorous stirring. After continued stirring at −23 °C for 0.5 h, the reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (40 mL) and allowed to warm to room temperature. The mixture was diluted with brine and extracted twice with ether. The combined organic fractions were washed with aqueous 1 N HCl and then brine. The crude product was subjected to flash chromatography on a column of silica gel (3 × 20 cm) using 3:2 ether/hexane as eluant. Eluted first was a small amount of the starting ketone **27** (0.42 g, 12%) followed by small amounts of two unidentified side products. Eluted next was hydroxy ketone 3*S*-**28** (0.95 g, 26%), $[\alpha]^{20}_D$ −306.7° (*c* 3.55), which overlapped somewhat with the more polar isomer, 3*R*-**28** (1.46 g, 40%), $[\alpha]^{20}_D$ (*c* 2.56).

3*S*-**28**: ν_{max} 3600, 3420, 1747, 1642 cm^{-1}. ^1H NMR: 0.74 (d, 3 H, *J* = 6.8 Hz, CH*Me*), 2.81 (dd, 1 H, *J* = 2.2, 1.9 Hz, H4), 3.00 (br s, 1 H, H1), 3.25 (s, 3 H, OMe), 3.54 (s, 2 H, CH_2OMe), 3.76 (d, 1 H, *J* = 6.3 Hz, H3), 3.97 (s, 2 H, CH_2OBn), 4.52 (s, 2 H, PhCH_2O), 4.97, 5.15 (2 s, 2 × 1 H, =CH_2), 5.96 (m, 1 H, H5), 6.33 (dd, 1 H, *J* = 5.4, 3.2 Hz, H6), 7.33 (m, 5 H, ArH). ^{13}C NMR: 15.1 (Me), 27.5 (CH_2), 28.5 (CH_2), 32.8 (CH_2), 35.5 (CH), 44.4 (CH), 46.9 (CH), 54.0 (CH), 58.8 (OMe), 59.9 (CH), 65.3 (C), 70.0 (CHOH) 72.3 (2 CH_2O) 73.6 (CH_2O) 111.3 (=CH_2), 127.6, 128.3, 129.3 (=CH + ArH), 138.3 (Ar), 140.8 (=CH), 148.4 (=C), 212.5 (CO). MS: m/z 382 (M^+ − 18, 5). Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 75.97; H, 8.50.

3*R*-**28**: ν_{max} 3600, 1743, 1644 cm^{-1}. ^1H NMR: 0.76 (d, 3 H, *J* = 6.8 Hz, CH*Me*), 2.96 (m, 2 H, H4 + H1), 3.21, 3.36 (AB d, 2 × 1 H, *J* = 10.8 Hz, CH_2OMe), 3.22 (s, 3 H, OMe), 3.96 (s, 2 H, CH_2OBn), 4.25 (e, 1 H, $W_{1/2}$ = 5 Hz, H3), 4.51 (s, 2 H, OCH_2Ph), 4.95, 5.14 (2 br s, 2 × 1 H, =CH_2), 5.93 (m, 1 H, H5), 6.49 (dd, 1 H, *J* = 5.6, 2.7 Hz, H6), 7.33 (m, 5 H, ArH). ^{13}C NMR: 15.1 (Me), 26.2 (CH_2) 28.6 (CH_2) 32.8 (CH_2) 35.5 (CH) 44.1 (CH) 46.8 (CH) 51.4 (CH) 58.9 (OMe) 60.9 (C) 62.2 (C), 70.0 (CHOH), 72.2 (CH_2O), 72.3 (CH_2O), 72.7 (CH_2O), 111.2 (=CH_2), 126.9, 127.6, 128.3 (=CH + ArH), 138.3 (Ar), 140.8 (=CH), 148.4 (=C), 212.5 (CO). MS: m/z 382 (M^+ − 18, 5). Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 76.22; H, 8.57.

(1*R*,4*S*,5*S*,1′*R*,2′*R*,5′*R*)-5-[[2′-[1″-[(Benzyloxy)methyl]ethenyl]-5′-methylcyclopentyl]methyl]-5-(methoxymethyl)cyclopent-2-ene-1,4-dicarboxylic Acid 1-Methyl Ester (29). To a solution of the endo-enriched hydroxy ketone **28** (2.63 g, 6.41 mmol) in ether (120 mL) was added powdered H_5IO_6 (2.43 g, 10.7 mmol). The mixture was stirred at room temperature for 1 h. After dilution with additional ether, the solution was washed once with 50% saturated aqueous NaCl solution and then treated at 0 °C with an excess of ethereal diazomethane prepared by a standard procedure from Diazald. The solution was immediately concentrated, and the residue was dissolved in acetone (150 mL), cooled to 0 °C, and treated dropwise with Jones reagent (2.5 mL). After 1 h at room temperature, the excess oxidant was quenched with iPrOH (1 mL); stirring was continued for 0.5 h. The mixture was filtered through Celite, washing with acetone, the resulting solution was concentrated, and the residue was taken up in EtOAc and washed successively with H_2O and brine. The pure acid **29** (2.44 g, 84%), $[\alpha]^{20}_D$ 38.8° (*c* 1.73) was obtained by chromatography of the crude product on silica gel (3 × 19 cm) using 1:1 Et_2O/hexane to elute high R_f colored impurities and then EtOAc as eluant. Similar treatment of the exo-enriched hydroxy ketone with H_5IO_6 over 2 h provided, after esterification and oxidation, the same acid **29**, ν_{max} 1740, 1703 cm^{-1}. ^1H NMR: 0.78 (d, 3 H, CH*Me*), 3.11 (s, 3 H, CH_2OMe), 3.34 (d, 2 H, overlapped, H1 + H4), 3.42 (CH_2OMe), 3.57 (CO_2Me), 3.99 (s, 2 H, CH_2OBn), 4.51

(s, 2 H, PhCH_2O), 5.00, 5.16 (2 s, 2 × 1 H, =CH_2), 5.80 (m, 2 H, H2 + H3), 7.32 (m, 5 H, ArH). ^{13}C NMR: 15.6 (Me), 28.6 (CH_2), 33.4 (CH_2), 36.0 (CH_2), 36.2 (CH), 43.6 (CH), 48.2 (CH), 51.7 (CO_2*Me*), 54.4 (C), 57.1 (CH), 57.8 (CH), 58.3 (OMe), 72.26 (CH_2O), 72.32 (CH_2O), 73.0 (CH_2O), 112.1 (=CH_2), 127.6, 127.7, 128.7 (ArH), 130.4, 131.0 (=CH), 138.4 (Ar), 148.5 (=C), 173.4 (CO_2Me), 177.6 (CO_2H). MS: *m/z* 456 (M^+, 1). Anal. Calcd for $C_{27}H_{35}O_6$: C, 71.03; H, 7.62. Found: C, 71.19; H, 7.62.

Methyl (5*S*,1′*R*,2′*R*,5′*R*)-5-[[2′-[1″-[(Benzyloxy)methyl]-ethenyl]-5′-methylcyclopentyl]methyl]-5-(methoxymethyl)cyclopenta-1,3-diene-1-carboxylate (30). To a solution of the acid **29** (2.44 g, 5.34 mmol) in benzene (50 mL) was added $Cu(OAc)_2$ H_2O (10 mg) and pyridine (0.54 mL, 6.68 mmol). The mixture was stirred in the dark at room temperature for 0.5 h, $Pb(OAc)_4$ (2.96 g, 6.68 mmol) was added, and stirring was continued for 3 h. The mixture was then heated at reflux (no longer in the dark) for 1 h, cooled, and quenched with aqueous ethylene glycol (4.5 mL made up to 15 mL with H_2O). After dilution with ether, the mixture was washed twice with H_2O and once with brine. A solution of the crude β-acetoxy ester (brown oil, 2.45 g) in DMF (60 mL), containing DBU (7.8 g, 51.2 mmol) was heated under argon in an oil bath at 85 °C for 3 h, cooled, and poured into H_2O (400 mL). The mixture was extracted twice with ether, and the aqueous layer was diluted to a volume of ca. 1 L, acidified to pH 1 with concd HCl, and extracted further with ether. The ether extracts were washed with H_2O (2×), 1 N aqueous HCl, and brine. The crude product was chromatographed on silica gel (3 × 19 cm) using 4:1 hexane/ether as eluant. The pure cyclopentadiene derivative **30** (1.33 g, 62% from **29**) was obtained as a colorless oil, $[\alpha]^{20}_D$ −85.7° (*c* 1.85), ν_{max} 1700, 1636, 1592 cm^{-1}. ^{1}H NMR: 0.79 (d, 3 H, CH*Me*), 3.18 (d, 1 H, *J* = 8.7 Hz, CH_2OMe), 3.27 (s, 3 H, OMe), 3.69 (s, 3 H, CO_2Me), 3.84 (s, 2 H, CH_2OMe), 3.89 (d, 1 H, *J* = 8.7 Hz, CH_2OMe), 4.48 (s, 2 H, PhCH_2O), 4.80, 5.05 (2 s, 2 × 1 H, =CH_2), 6.38 (dd, 1 H, *J* = 5.4, 2.3 Hz, H3), 6.88 (dd, 1 H, *J* = 5.4, 1.4 Hz, H4), 7.33 (m, 6 H, ArH + H2). ^{13}C NMR: 15.1 (Me), 29.1 (CH_2), 29.3 (CH_2), 32.6 (CH_2), 35.9 (CH), 43.4 (CH), 47.1 (CH), 50.8 (CO_2*Me*), 59.4 (OMe), 62.6 (C), 72.0 (CH_2O), 72.8 (CH_2O), 77.5 (CH_2OMe), 110.5 (=CH_2), 127.3, 127.5, 128.2 (ArH), 129.1 (C3), 138.6 (Ar), 140.3 (C1), 148.3 (=C), 151.7 (C2), 163.5 (CO). HRMS: calcd for $C_{28}H_{34}O_4$ 410.2455, found 410.2457.

Methyl 17-(Benzyloxy)-19-methoxy-14,15,16-trisnorsordaric-1-en-18-oate (31). A degassed solution of the cyclopentadiene **30** (1.33 g, 3.24 mmol) was heated in toluene (310 mL) at reflux under argon for 31.5 h. The toluene was removed, and the residue was chromatographed on silica gel (3 × 19 cm) using 4:1 hexane/ether as eluant to obtain pure **31** as a crystalline solid, 1.18 g (89%). An analytical sample, mp 85–86 °C, $[\alpha]^{20}_D$ −41.8° (*c* 1.13), was obtained by recrystallization from methanol. Further elution of the column provided a small amount of slightly impure **31**, 106 mg (8%). ν_{max} 1739 cm^{-1}. ^{1}H NMR: 0.45 (d, 1 H, *J* = 12.3 Hz, H-4α), 0.92 (d, 3 H, CH*Me*), 2.60 (m, 1 H, H3), 3.14, 3.51 (AB d, 2 × 1 H, *J* = 8.7 Hz, CH_2OMe), 3.21 (s, 3 H, OMe), 3.61 (s, 3 H, CO_2Me), 4.40 (s, 2 H, PhCH_2O), 6.12 (d, 1 H, *J* = 5.9 Hz, H1), 6.30 (dd, 1 H, *J* = 5.9, 3.1 Hz, H2). ^{13}C NMR: see table. Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 76.10; H, 8.76.

(5*S*,1′*R*,2′*R*,5′*R*)-5-[[2′-[1″-(Hydroxymethyl)ethenyl]-5′-methylcyclopentyl]methyl]-5-(methoxymethyl)cyclopenta-1,3-diene-1-carboxaldehyde. ^{1}H NMR: 0.78 (d, 3 H, *J* = 6.8 Hz, CH*Me*), 3.19 (d, 1 H, CH_2OMe), 3.26 (s, 3 H, OMe), 3.85 (d, 1 H, CH_2OMe), 3.92 (br s, 2 H, CH_2OH), 4.79, 5.08 (2 s, 2 × 1 H, =CH_2), 6.54 (dd, 1 H, *J* = 5.3, 2.3 Hz, H3), 7.07 (br d, 1 H, *J* = 5.1 Hz, H4), 7.38 (dd, 1 H, *J* = 2.3, 1.2 Hz, H2), 9.69 (d, 1 H, *J* = 0.9 Hz, H18).

17-Hydroxy-19-methoxy-14,15,16-trisnorsordaric-1-en-18-al. ^{1}H NMR: 0.28 (d, 1 H, *J* = 12.4 Hz, H4α), 0.86 (d, 3 H, *J* = 6.5 Hz, 10-Me), 2.59 (br t, 1 H, *J* = 5.2 Hz, H3), 3.21 (s, 3 H, OMe), 3.33, 3.44 (AB d, 2 × 1 H, *J* = 8.7 Hz, CH_2OMe), 3.37 (s, 2 H, CH_2OH), 6.12 (d, 1 H, *J* = 5.9 Hz, H1), 6.36 (dd, 1 H, *J* = 5.6, 3.1 Hz, H2), 10.2 (s, 1 H, H18).

17-Acetoxy-19-methoxy-14,15,16-trisnorsordaric-1-en-18-al. ^{1}H NMR: 0.48 (d, 1 H, *J* = 12.8 Hz, H4α), 0.89 (d, 3 H, *J* = 7.0 Hz, 10-Me), 2.00 (s, 3 H, OAc), 2.63 (br t, 1 H, *J* = 3.1 Hz, H3), 3.17 (s, 3 H, OMe), 3.304, 3.306 (AB d, 2 H, *J* = 9.3 Hz, CH_2OMe), 3.81, 3.83 (AB d, 2 H, *J* = 11.3 Hz, CH_2OAc), 6.15 (d, 1 H, *J* = 5.3 Hz, H1), 6.37 (dd, *J* = 5.6, 3.1 Hz, H2), 10.2 (s, 1 H, H18). ^{13}C NMR: 18.0 (C20), 26.7 (C11), 29.8 (C12), 32.2 (C8), 32.5 (C4 + C10), 40.8 (C13), 42.1 (C9), 49.2 (C3), 50.6 (C5), 68.1 (C17), 69.3 (C7), 70.0 (C6), 77.9 (C19), 128.6 (C1), 140.0 (C2), 203.3 (C18).

Methyl 17-Acetoxy-19-methoxy-14,15,16-trisnorsordaric-1-en-18-oate (32). ^{1}H NMR: 0.56 (d, 1 H, *J* = 12.4 Hz, H4α), 0.88 (d, 3 H, *J* = 6.8 Hz, 10-Me), 1.98 (s, 3 H, OAc), 2.64 (br t, 1 H, *J* = ~3 Hz, H3), 3.17, 3.52 (AB d, 2 H, *J* = 9.3 Hz, CH_2OMe), 3.22 (s, 3 H, OMe), 3.70 (s, 3 H, CO_2Me), 3.82, 3.97 (AB d, 2 H, *J* = 11.3 Hz, CH_2OAc), 6.08 (d, 1 H, *J* = 5.7 Hz, H1), 6.35 (dd, *J* = 5.7, 3.4 Hz, H2). ^{13}C NMR: see table. MS: *m/z* 362 (M^+, 1), 330 (5), 302 (17), 285 (10), 270 (40), 257 (56), 211 (47), 121 (56), 105 (64), 91 (50), 45 (100).

Methyl 17,19-Diacetoxysordaric-1-en-18-oate (33). ^{1}H NMR: 0.56 (d, 1 H, *J* = 12.4 Hz, H4α), 1.98 (s, 3 H, OAc), 2.64 (br t, 1 H, *J* = 3.1 Hz, H3), 3.17 (d, 1 H, *J* = 8.7 Hz, CH_2OMe), 3.22 (s, 3 H, OMe), 3.52 (d, 1 H, *J* = 8.7 Hz, CH_2OMe), 3.71 (s, 3 H, CO_2*Me*), 3.80, 3.98 (AB d, 2 × 1 H, *J* = 11.3 Hz, CH_2OAc), 6.07 (d, 1 H, *J* = 5.6 Hz, H1), 6.35 (dd, 1 H, *J* = 5.6, 3.1 Hz, H2). ^{13}C NMR: see table.

Supplementary Material Available: ^{1}H NMR spectra for all compounds and ^{13}C NMR spectra for all fully characterized compounds except **14** and **19** (55 pages). Ordering information is given on any current masthead page.