JOC*Article*

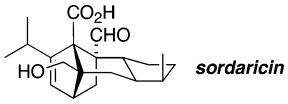
Total Synthesis of Sordaricin

Lewis N. Mander* and Regan J. Thomson

Research School of Chemistry, The Australian National University, Canberra, ACT 0200, Australia

mander@rsc.anu.edu.au

Received October 12, 2004



sordaricin

An enantioconvergent total synthesis of sordaricin (**3**), the diterpene aglycon of an important class of antifungal compounds, is described. Two approaches were explored, the first of which utilized a possible biogenetic intramolecular [4 + 2] cycloaddition to form the complete carbon skeleton of the target molecule as a single regioisomer **30**. A second approach employed a tandem cycloreversion/intramolecular [4 + 2] cycloaddition process to afford not only the desired product **30** but also significant quantities of the undesired regioisomer *iso*-**30**. An investigation into the reasons for the difference in regioselectivity between these two reactions revealed the intervention of a cycloreversion/cycloaddition pathway at elevated temperatures leading to the formation of *iso*-**30**. Experimental evidence supports the hypothesis that *iso*-**30** is the more thermodynamically stable of the two regioisomers.

Introduction

The sordarins are an emerging class of potent antifungal compounds, of which sordarin (**4**),[1] isolated in 1971 from the ascomycete *Sordaria araneosa* Cain, is the structural prototype. The sordarins exhibit remarkable in vitro activity against a wide range of fungal pathogens such as *Candida albicans*,[2] the causative agent of the common thrush infection. Additionally, sordarins show encouraging in vivo activity against several pathogenic fungi, including *Pneumocystis carnii*,[2] the major cause of lethal pneumonia among immunocompromised patients. Unlike the other major antifungals, which are targeted against fungal ergosterol biosynthesis, the sordarins are selective inhibitors of fungal protein synthesis through a specific interaction with Elongation Factor 2 (EF2),[3] a remarkable feat considering the high degree of EF2 homology (85%) between fungi and higher order Eukaryotes. The combination of potent biological activity and a novel mode of action have made the sordarins lead compounds for the development of new antifungal agents.

We were interested in the sordarins not only because of their potent biological activity but also because of their unusual structures[4] and possible biosynthesis (Figure 1).[5] Borschberg demonstrated that sordaricin (**3**), the diterpene aglycon common to all sordarins, was biosynthetically derived from cycloaraneosene (**1**), a member of the fusicoccin class of diterpenes. It is tempting to speculate that the conversion of **1** to **3** might proceed by means of

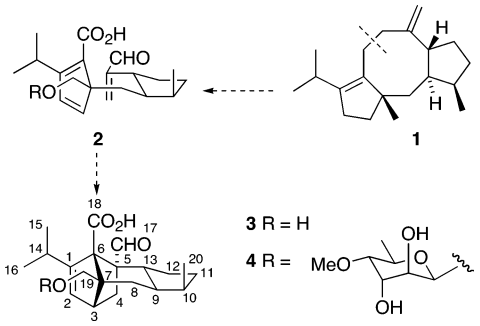


FIGURE 1. Proposed biosynthesis of the sordarins from cycloaraneosene **1**.

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

(2) For a review of sordarin biological activity, see: Gargollo-Viola, D. *Curr. Opin. Anti-Infect. Invest. Drugs* **1999**, *1*, 297.

(3) Justice, M. C.; Hsu, M. J.; Tse, B.; Ku, T.; Balkovec, J.; Schmatz, D.; Neilsen, J. *J. Biol. Chem.* **1998**, *273*, 3148.

(4) Sordarin: Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972. Zofimarin: Ogita, T.; Hiyashi, A.; Sato, S.; Furutani, W. JP Patent 6240292, 1987; *Chem. Abstr.* **1987**, *107*, 5745. GR135402: (a) Kinsman, O. S.; Chalk, P. A.; Jackson, H. C.; Middleton, R. F.; Shuttleworth, A.; Rudd, B. A. M.; Jones, C. A.; Noble, H. M.; Wildman, H. G.; Dawson, M. J.; Stylli, C.; Sidebottom, P. J.; Lamont, B.; Lynn, S.; Hayes, M. V. *J. Antibiot.* **1998**, *51,* 41. (b) Kennedy, T. C.; Webb, G.; Cannell, R. J. P.; Kinsman, O. S.; Middleton, R. F.; Sidebottom, P. J.; Taylor, N. L.; Dawson, M. J.; Buss, A. D. *J. Antibiot.* **1998**, *51,* 1012. Hypoxysordarin: Daferner, M.; Mensch, S.; Anke, T.; Sterner, O. *Z. Naturforsch.* **1999**, *54c,* 474. Neosordarin and Hydroxysordarin: Davoli, P.; Engel, G.; Werle, A.; Sterner, O.; Anke, T. *J. Antibiot.* **2002**, *55,* 377.SCH57404/Xylarin: (c) Coval, S. J.; Puar, M. S.; Phife, D. W.; Terracciano, J. S.; Patel, M. *J. Antibiot.* **1995**, *48,* 1171. (d) Schneider, G.; Anke, H.; Sterner, O. *Nat. Prod. Lett.* **1995**, *7,* 309. BE-31405: Okada, H.; Kamiya, S.; Shiina, Y.; Suwa, H.; Nagashima, M.; Nakajima, S.; Shimokawa, H.; Sugiyama, E.; Kondo, H.; Kojiri, K.; Suda, H. *J. Antibiot.* **1998**, *51,* 1081.

10.1021/jo048199b CCC: $30.25
Published on Web 01/25/2005

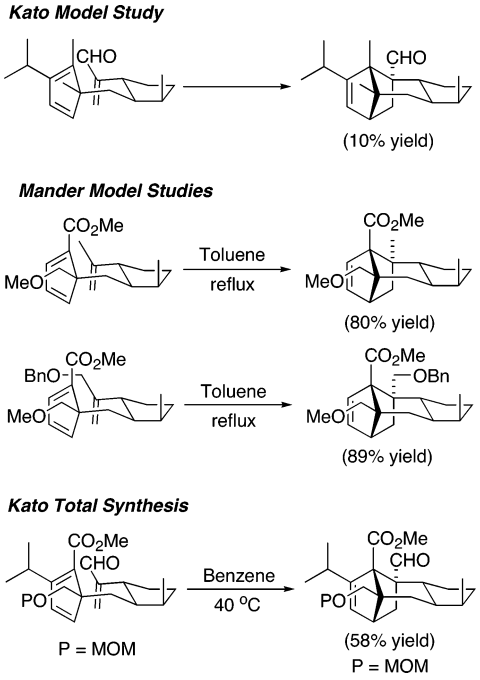


FIGURE 2. Previous cycloadditions related to sordaricin.

an intramolecular [4 + 2] cycloaddition, such as that shown by the conversion of **2** to **3**. Contemporaneously, Mander and Kato independently demonstrated the feasibility of such a transformation on simplified model systems,[6] both of which reported formation of the desired product as a single regioisomer. Shortly thereafter, Kato[7] disclosed the first total synthesis of sordaricin methyl ester based upon this transformation (Figure 2).

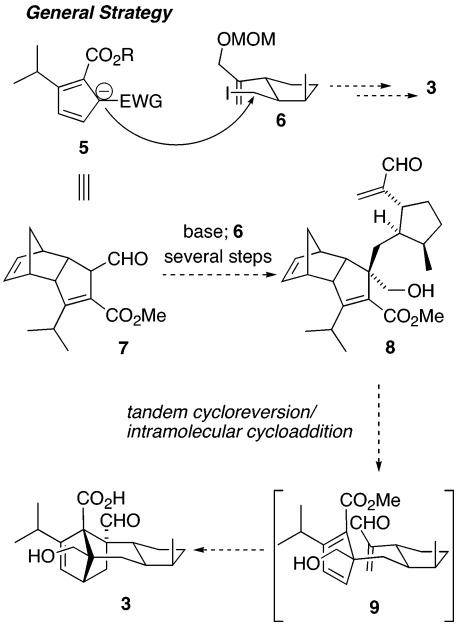
Recently, we communicated our efforts in this area, which culminated in an enantioconvergent total synthesis of sordaricin (**3**).[8] Two successful approaches utilizing intramolecular [4 + 2] cycloadditions were detailed: one that provided sordaricin methyl ester as a single regioisomer and a second that afforded a mixture of regioisomeric cycloadducts. Narasaka has since disclosed a total synthesis of racemic sordaricin based upon an intramolecular Tsuju−Trost reaction to form the norbornene system.[9]

This paper provides a full account of our research and also describes the results of a study into the interesting outcomes of previously mentioned cycloadditions.

Results and Discussion

Synthetic Strategy. Regardless of biosynthetic considerations, retrosynthetic analysis of sordaricin (**3**) guided by the Diels−Alder transform leads to a strategy based upon a formal alkylation of cyclopentadienyl enolate **5** with iodide **6**. Because both regio- and diastereofacial selectivity were expected to be poor for the alkylation of enolate **5**, use of an operational equivalent of

SCHEME 1

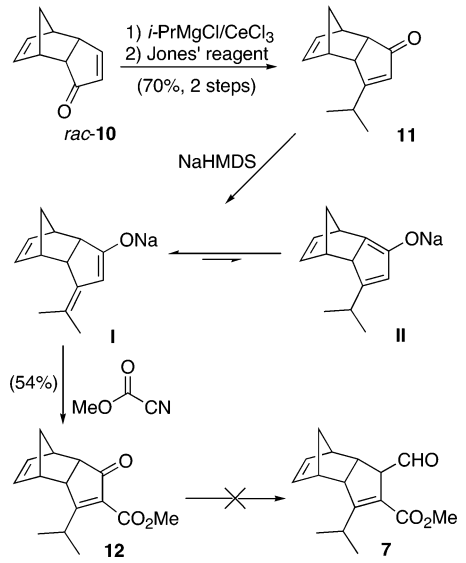


this enolate was deemed essential. In the model study previously published from our group,[6a] a norbornene ester served as an operational equivalent of **5**, but this approach did not lead to a successful synthesis due to problematic late-stage transformations.[10] The revised strategy (Scheme 1) we chose to employ for the synthesis of sordaricin (**3**) involved alkylation of aldehyde **7** with iodide **6**, which could be expected to give **8** after some simple manipulations. We hoped that aldehyde **8** would undergo a tandem cycloreversion/intramolecular [4 + 2] cycloaddition[11] to form the sordaricin carbon skeleton in a single operation. Demethylation of the resultant ester would then afford the natural product **3**. As the coupling of racemic **6** and **7** would be expected to give a mixture of diastereomers, we planned to prepare **6** and **7** in enantiopure form. With ready access to both enantiomers of enone **10**,[12] we envisaged sequences that might allow iodide **6** and aldehyde **7** to be prepared from the (−)- and (+)-enantiomers of **10**, respectively (cf. Schemes 2−4).

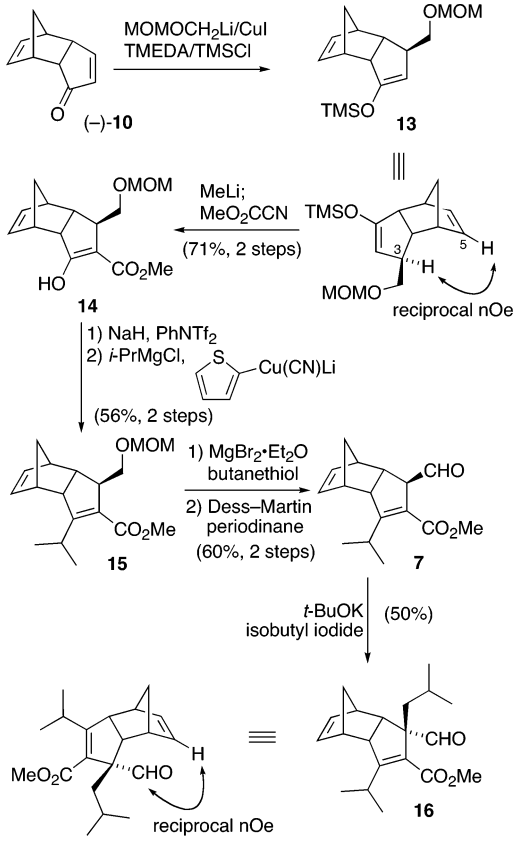
Synthesis of the Aldehyde 7. Because the alkylation of aldehyde **7** with iodide **6** was expected to be nontrivial we focused our attention on developing a straightforward synthesis of *rac*-**7**, with a view to carrying out a simple model alkylation with isobutyl iodide as a surrogate for **6**. Our initial approach to aldehyde **7**, outlined in Scheme 2, involved the cerium trichloride mediated 1,2-addition of isopropylmagnesium chloride to enone *rac*-**10**,[12] followed by oxidative transposition with Jones' reagent to afford **11** in good yield (70%, two steps). The use of cerium trichloride[13] is essential as exposure of **10** to the Grignard

(5) Borschberg, H. J. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1975.
(6) (a) Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595. (b) Kato, N.; Wu, X.; Takeshita, H. *Chem. Express* **1991**, *6*, 687.
(7) Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002.
(8) Mander, L. N.; Thomson, R. J. *Org. Lett.* **2003**, *5*, 1321.
(9) Kitamura, M.; Chiba, S.; Narasaka, K. *Chem. Lett.* **2004**, *33*, 942.
(10) Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 5718.
(11) For a recent review on retro-Diels−Alder reactions, see: Rickborn, B. *Org. React.* **1998**, *52*, 1. For examples of tandem processes in synthesis, see: Ho, T.-L. *Tandem organic reactions*; Wiley: New York, 1992; and references therein.
(12) This initial approach was carried out on racemic **10**. All subsequent work utilized enantiopure substrates; see: (a) Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636. (b) Takano, S.; Moriya, M.; Tanaka, K.; Ogasawara, K. *Synthesis* **1994**, 687.
(13) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

SCHEME 2

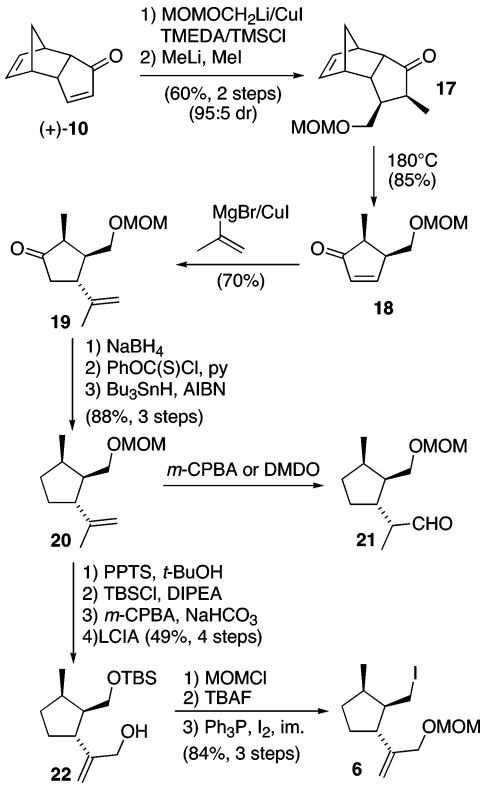


SCHEME 3



reagent alone leads to quantitative 1,4-addition. Next, we hoped to install the carboxyl group by acylation of the linear dienolate derived from **11**. The C-selective acylation of cross-conjugated enolates using methyl cyanoformate is well established,[14] but to the best of our knowledge the acylation of a linear dienolate has not yet been reported. On the grounds of thermodynamic stability we expected enolate **I** to form in preference to enolate

SCHEME 4



II if equilibrating conditions were used during enolate generation.[15] Also, formation of **II** would result in a high degree of torsional strain, thereby lowering the intrinsic acidity of the α proton. After significant experimentation, we found that treatment of enone **11** with NaHMDS (1.5 equiv) in THF (−78 °C → rt, 3 h), followed by the addition of methyl cyanoformate (1.5 equiv, −78 °C) gave a 54% isolated yield of the desired ester **12**. Our next intention was to form aldehyde **7** by homologation of the ketone functionality within **12**. Unfortunately, a variety of methods, including Wittig and Horner−Wittig homologations, failed to give rise to useful amounts of the desired product, and we therefore sought an alternative route to **7**.

Our second, and ultimately successful, route to aldehyde **7**, this time working with enantiopure material, is shown in Scheme 3. 1,4-Addition of the cuprate derived from $MOMOCH_2Li$[16] to enone (−)-**10** in the presence of TMSCl gave the expected silyl enol ether **13**, which was then treated with MeLi followed by methyl cyanoformate to afford *β*-keto ester **14** (71% over two steps from (−)-**10**) as a mixture of enol and keto tautomers (6:1, respectively). The expected *exo* addition of the cuprate was proven by NOE experiments carried out on **13** (reciprocal interactions between H-3 and H-5). Next, installation of the isopropyl group was achieved by converting **14** into the corresponding triflate followed by addition of the higher order mixed cuprate derived from

(14) (a) Mander, L. N.; Sethi, S. P.; *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256.

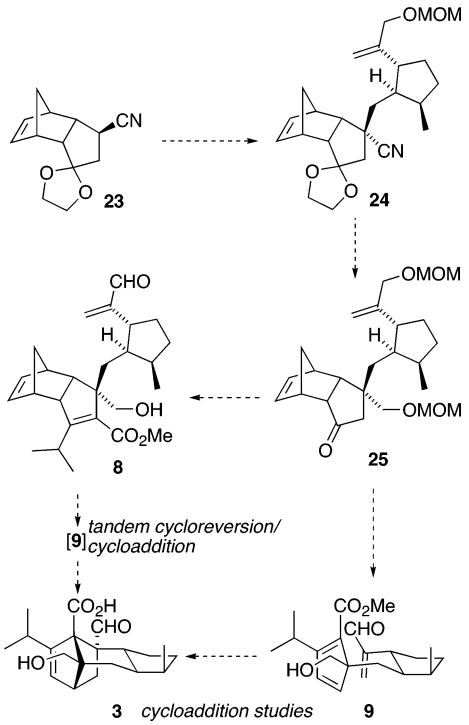
(15) For relevant examples of C-selective acylation of enolates generated under equilibrating conditions, see: (a) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F.; *J. Am. Chem. Soc.* **1985**, *107*, 2730. (b) Schuda, P. F.; Phillips, J. L.; Morgan, T. M. *J. Am. Chem. Soc.* **1986**, *51*, 2742

(16) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495.

isopropylmagnesium chloride and 2-Th(Cu)CNLi (56% yield of **15** over two steps).[17] Removal of the MOM group using $MgBr_2 \cdot Et_2O$ and butanethiol,[18] and subsequent oxidation with Dess−Martin periodinane,[19] afforded the desired aldehyde **7** (60% over two steps). Alkylation of **7** with isobutyl iodide was carried out using *t*-BuOK to afford **16** as a single stereoisomer in moderate yield (50%), the *exo* selectivity of the alkylation being proven by the presence of an NOE correlation between the aldehyde CH and norbornene olefinic proton.

Synthesis of the Iodide 6. Having developed a synthesis of aldehyde **7** and demonstrated a successful model alkylation, we focused our efforts on iodide **6**. As shown in Scheme 4, the synthesis of iodide **6** commenced with the 1,4-addition of the cuprate derived from $MOMOCH_2Li$[16] to enone (+)-**10** in the presence of TMSCl to give the expected silyl enol ether, which was then treated with MeLi followed by methyl iodide, to afford the *syn*-substituted tricycle **17** (60% over two steps, 95:5 dr). The selectivity of the alkylation was assumed at this stage but was later proven by comparison to a known compound (vide infra). Heating **17** at reflux in 1,2-dichlorobenzene under a stream of dry nitrogen effected smooth cycloreversion to cyclopentenone **18** (85%).[20] The next task in the synthesis was to conduct a 1,4-addition of a nucleophile that would correspond to the allylic ether substituent present in the target fragment. Initially, it was hoped that this conversion might be achieved by the direct addition of the dianion derived from 2-bromo-prop-2-en-1-ol,[21] but this was unsuccessful, as were attempts to add protected versions of this nucleophile. After investigating several other possible nucleophiles, the copper-promoted 1,4-addition of isopropenylmagnesium bromide was carried out with the intention of functionalizing the alkenyl substituent at a later time. Thus, the trisubstituted cyclopentanone **19** was obtained in good yield (70%) as a single diastereomer. Addition of the cuprate was assumed to have occurred on the less hindered α-face of the enone, placing the isopropenyl group *anti* to the existing substituents. So as to avoid epimerization of the methyl substituent in **19**, carbonyl deletion was carried out over three steps by borohydride reduction followed by the Barton−McCombie reaction[22] to give the key cyclopentane **20** in good overall yield (88%). We had hoped to install the required allylic hydroxyl group via an epoxide, which could be opened by treatment with a lithium alkylamide base. Unfortunately, and surprisingly, epoxidation of the alkene bond present in **20** was invariably followed by a facile [1,2] hydride shift to form aldehyde **21**, even under the neutral conditions allowed by employing dimethyl dioxirane (DMDO). However, conversion of the MOM ether **20** to the corresponding TBS ether and subsequent treatment with *m*-CPBA gave an excellent yield of the desired epoxide (formed as an inseparable mixture of diastereomers). The mixture of epoxides was subsequently converted to allylic alcohol **22** (49% from **20**) upon exposure to lithium cyclohexyl isopropyl amide (LCIA). This sequence also served to confirm the stereochemistry of our earlier alkylations, because the alcohol formed by deprotection of **20** was identical with the one which had been prepared previously from carvone.[23] Protection of the hydroxy group in **22** as a MOM ether, followed by TBS ether removal with TBAF, gave the parent alcohol which was readily converted into the target iodide **6** (84% over three steps) using iodine/Ph_3P/imidazole.[24]

SCHEME 5

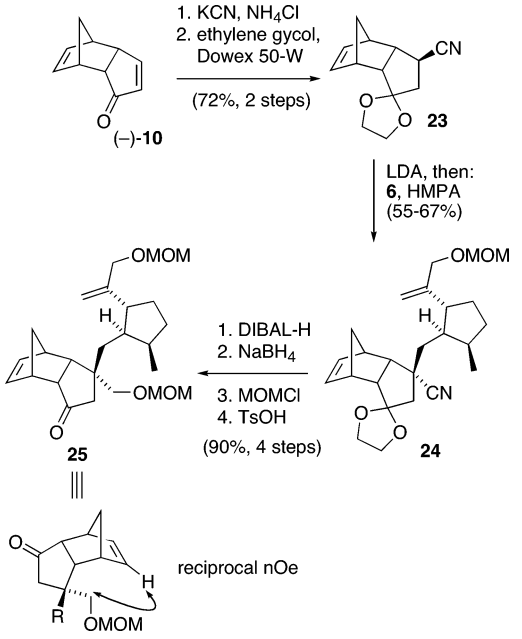


Attempted Alkylation of Aldehyde 7. Having already established a procedure for the alkylation of **7** with isobutyl iodide, these conditions were the first choice for the initial attempt using iodide **6**. Although consumption of aldehyde **7** was observable, ^1H NMR spectra of the reaction mixture showed only unchanged iodide **6** and no signals corresponding to the desired product. Further experimentation did not improve this situation.

Revised Synthetic Strategy. The failure of **7** to yield any alkylated product led us to consider the use of nitrile **23** as the substrate for the alkylation step (Scheme 5). In this case, we felt that the simplified structure and more reactive nitrile anion[25] would allow for an efficient coupling with **6** to afford **24**. Although this revised strategy was less convergent than that outlined in Scheme 1, it provided a more flexible approach to the natural product. Thus, nitrile **24** could be converted into the originally targeted aldehyde **8**, which should then undergo the tandem cycloreversion/intramolecular cycloaddition process. Of additional interest, however, would be the conversion of ketone **25** into aldehyde **9** in

(17) Lipshultz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.
(18) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183.
(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(20) For a review pertaining to similar cycloreversions, see: Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163.
(21) (a) Corey, E. J.; Widiger, G. N. *J. Org. Chem.* **1975**, *40*, 2975. (b) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.
(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(23) Robinson, R. Unpublished work.
(24) Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883.
(25) For a review on the reaction of nitrile stabilized carbanions, see: Arseniyadis, S.; Kyler, K. S. *Org. React.* **1984**, *31*, 1.

SCHEME 6

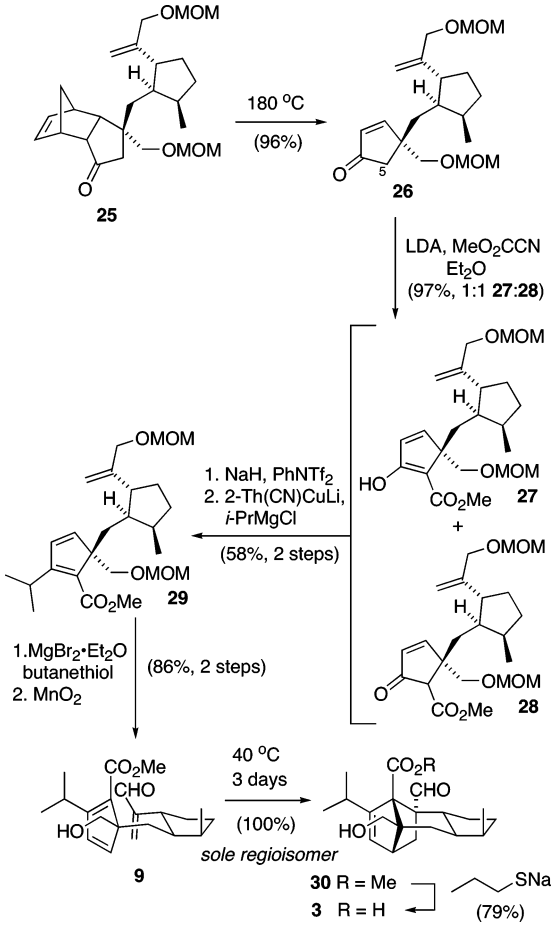


a controlled stepwise manner, which would allow for further study of the cycloaddition process.

Alkylation of Nitrile 23 and Conversion to Ketone 25. First, nitrile **23** was synthesized by 1,4-addition of cyanide anion to enone **10**,[26] followed by protection of the ketone function as the corresponding ketal (72% over two steps, Scheme 6). Examination of the required alkylation could now be addressed. After extensive experimentation, a set of reliable conditions was found, whereby the desired product **24** could be obtained, as a single diastereomer, in yields between 55% and 67%, based on iodide consumption. In this transformation, 2 equiv of the nitrile **23** were utilized in order to effect complete consumption of the iodide **6**. Unchanged nitrile **23** could be readily recovered during product purification by flash column chromatography. The nitrile group in **24** was then reduced over two steps to afford the corresponding alcohol which was protected as the MOM ether and then converted into ketone **25** following ketal hydrolysis (90% over four steps). The presence of an NOE correlation within **25** between the alkoxymethyl protons and the norbornene olefinic proton confirmed that alkylation had occurred on the less hindered *exo* face of nitrile **23**.

Total Syntheses of Sordaricin. With the ketone **25** now in hand we chose first to explore the route to sordaricin via aldehyde **9** (Scheme 7) before attempting the proposed cycloreversion/cycloaddition sequence. To this end, ketone **25** underwent smooth cycloreversion to afford cyclopentenone **26** (96%) upon heating under reflux in 1,2-dichlorobenzene. The next step in the synthesis required the introduction of a carboxyl group by selective C-acylation of the enolate derived from **26**. Methyl cyanoformate is highly regioselective for C vs O acylation in most systems, but O-acylation may predominate with enolates that are sterically hindered as in the present situation. If diethyl ether is used as the solvent instead of the more commonly used THF, however, then C-

SCHEME 7



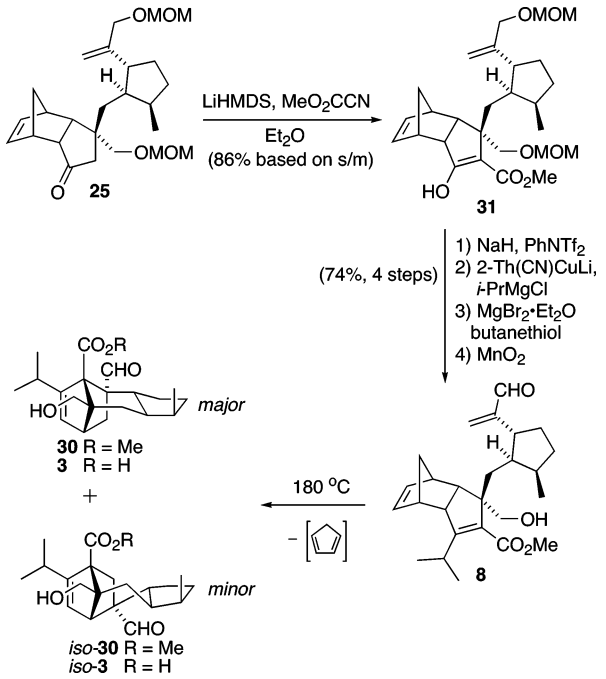
acylation is usually ensured.[14b] In view of these considerations, acylation of enone **26** was carried out using LiHMDS/hexanes in diethyl ether, followed by the addition of MeO_2CCN to afford the desired β-keto ester in excellent yield (97%, 1:1 ratio of enol **27** and ketone **28**). Installation of the isopropyl substituent was achieved by converting **27**/**28** into the corresponding enol triflate and subsequent addition of the higher order mixed cuprate derived from isopropylmagnesium chloride and 2-Th(Cu)-CNLi (58% over two steps).[17] Concomitant removal of both MOM protecting groups with $MgBr_2 \cdot Et_2O$)/*n*-butanethiol,[18] followed by selective allylic oxidation with MnO_2,[27] afforded the target aldehyde **9** in excellent yield (86% over 2 steps). Aldehyde **9** cyclized over 3 days at 40 °C to give **30** as a single regioisomer in quantitative yield, which could be demethylated with propanethiolate to give sordaricin (**3**), mp 189−191 °C, $[\alpha]_D$ −55 (*c* 0.2, MeOH); authentic sample $[\alpha]_D$ −58 (*c* 0.2, MeOH) [lit.[12] mp 190−191 °C, $[\alpha]_D$ −62 (*c* 0.2, MeOH)] (79% yield); spectroscopic data (^1H and ^{13}C NMR, MS, IR) were identical to those of natural material.

Investigation into the possible tandem cycloreversion/intramolecular [4 + 2] cycloaddition approach to sordaricin (**3**) began with the previously described ketone, **25** (Scheme 8). Installation of the requisite carboxyl and isopropyl groups was achieved in a manner similar to that detailed for the synthesis of **29** from **25** (see Scheme 7). In this case, however, acylation of **25** did not proceed

(26) Bugel, J. P.; Ducos, P.; Gringore, O.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1972**, 4371.

(27) Babler, J. H.; Martin, M. J. *J. Org. Chem.* **1977**, *42*, 1799.

SCHEME 8



with the high levels of C-selectivity observed for **26**. Under optimized conditions, a mixture of C- to O-acylated products was obtained in a ratio of 6:1. Typically, the unpurified reaction mixture was exposed to K_2CO_3/MeOH, converting the unwanted enol carbonate back into ketone **25**, and in this manner an 86% yield of **31** was obtained on the basis of recovered starting material. Transformation of **31** into **8** then proceeded in good overall yield (74% over four steps) using the chemistry developed previously.

Heating **8** in 1,2-dichlorobenzene at 180 °C for 1 h gave a 4:1 mixture of the desired product **30** and a second compound identified as the regioisomer *iso*-**30** (76% combined yield). Further experimentation did not lead to any improvement in the product ratio. Demethylation of the mixture and subsequent separation by preparative HPLC afforded **3** (38%) and *iso*-**3** (25%). Structural assignment of *iso*-**3** was made on the basis of the NOE data, the key correlations of which are shown in Figure 3, and by the appearance of an isolated AB spin system due to the protons on C5 (2.49 and 2.84 ppm, J = 12.7 Hz).

Cycloaddition Studies. Formation of this alternative regioisomer was totally unexpected, given our observations for the cyclization of **9**, and on the previous studies of both Kato and Mander.[6,7] This result prompted us to explore the cyclizations of diol intermediates **33** and **34** in order to gain a better understanding of the cycloaddition process (Figure 4). Cyclization of the diol **32**,

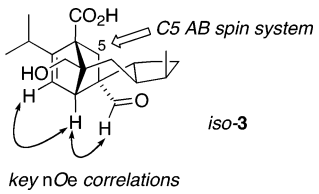


FIGURE 3. Key ^{1}H NMR signals for *iso*-**3**.

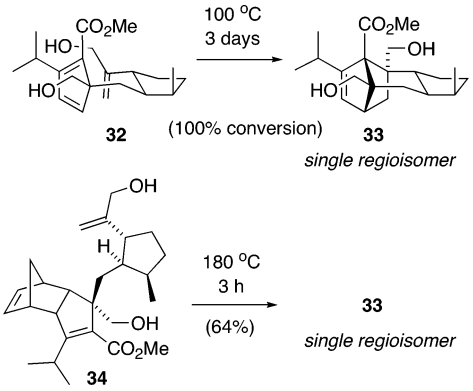


FIGURE 4. Regioselective cycloadditions of diols **32** and **34**.

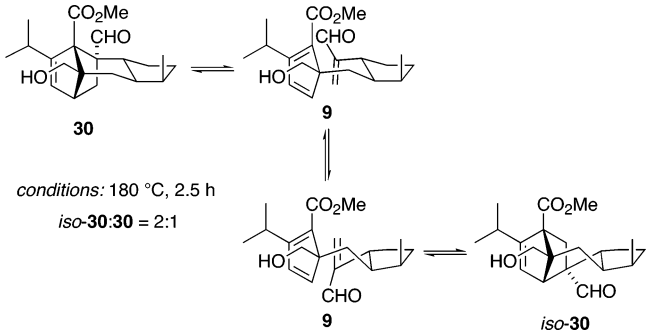


FIGURE 5. Thermal interconversion of **30** and *iso*-**30**.

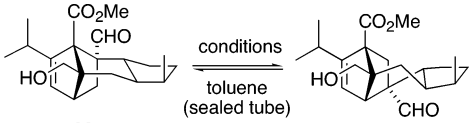
prepared en route to **3**, proceeded to afford **33** as a single regioisomer, but in order to achieve a significant rate of reaction, heating at 100 °C was necessary, and even then, a period of 3 days was required for complete conversion. In sharp contrast to aldehyde **8**, the cycloreversion/intramolecular [4 + 2] cycloaddition of diol **34** rendered **33** as a single regioisomer (64%).

Given that the formation of ester **30** from aldehyde **9** was completely regioselective at 40 °C, we considered the possibility that *iso*-**30** was being formed from **30** by a retro-Diels−Alder process that occurs at the elevated temperatures necessary to induce the initial cycloreversion. To validate this hypothesis, isomerically pure **30** was heated in 1,2-dichlorobenzene at 180 °C for 2.5 h to afford a 2:1 mixture of *iso*-**30** and **30**, respectively (Figure 5). The excess of *iso*-**30** indicated that it is probably more thermodynamically stable than **30**.

To establish the energy difference experimentally between the two isomers and to obtain some information regarding the activation energy necessary to induce the isomerization, a series of experiments were performed, the results of which are summarized in Table 1.

Clearly, the activation energy corresponds to a temperature somewhere between 120 and 150 °C. The exact position of the equilibrium was difficult to establish as prolonged heating led to significant decomposition. After heating **30** for 72 h a 3:1 ratio of *iso*-**30** to **30** was obtained. Conversely, heating pure *iso*-**30** at 150 °C for 24 h gave a 4:1 ratio of isomers. These results indicate an equilibrium ratio of 3−4:1 providing a ΔG of approximately 1 kcal/mol at 150 °C. The stability of *iso*-**30** relative to **30** is clearly the result of an alleviation of the nonbonding interactions of the aldehyde substituent with both the carboxyl and isopropyl groups. Minimizing these

TABLE 1. Isomerization of 30 into *iso*-30 over Time



30 *iso*-**30**

T (°C)	time (h)	*iso*-**30/30**
120	6	0:100
150	5	25:75
150	20	50:50
150	46	66:34
150	72	72:28

TABLE 2. Frontier Orbital Energies for Model Dienophiles and Diene

	Frontier orbital energies (eV)[a]	
	HOMO	***LUMO***
	**-9.88**	**1.80**
	**-10.89**	**0.60**
	**-9.41**	**1.99**

[a] Values taken from: Smith, M. B. *Organic Synthesis*; McGraw-Hill Book Co.: Singapore, 1994.

interactions results in an overall lowering of energy despite the fact that the B-ring is then forced to adopt a boatlike conformation.

Modeling predicted that *iso*-**33** should also be more stable than **33**, and hence it should be possible to induce isomerization at elevated temperatures. Given that the isomeric structure was not observed during the sequential cycloreversion/cycloaddition process for diol **32** at 180 °C, the diol was heated at 200 °C, but unfortunately, this led only to decomposition and no data could be obtained.

Rationalizing the Kinetic Outcomes of the Cycloadditions. The dramatic difference in the rates of cyclization for aldehyde **9** and diol **32** may not have been easy to predict at the outset of this study. However, the reactivity of both aldehyde **9** and diol **32** may be rationalized in terms of frontier molecular orbital (FMO) analysis[28] using simple model compounds whereby sorbic acid represents the diene portion of both substrates, and the dienophile portion of **9** and **32** is represented by acrolein and propene, respectively.

Inspection of Table 2 reveals that the favored orbital interactions for both aldehyde **9** and diol **32** will be the HOMO of the diene and the LUMO of the dienophile (−11.21 eV for $HOMO_{(sorbic\ acid)}$-$LUMO_{(propene)}$, and −10.01 eV for $HOMO_{(sorbic\ acid)}$-$LUMO_{(acrolein)}$, compared with −12.27 eV and −12.88 eV, respectively, for the alternative arrangement.). From these data it is clear that the reaction of acrolein and sorbic acid is more favorable, due to a smaller energy gap between the participating orbitals, and hence would proceed at a lower temperature than the equivalent reaction involving propene and sorbic acid. Therefore, from these models it would be predicted that **9** should cyclize at a lower temperature than diol **32**, as observed experimentally.

The observed regioselectivity for the low-temperature cyclizations is in line with what would be expected based on FMO analysis for Diels−Alder reactions between such reacting partners.

Summary and Conclusions

An enantioconvergent total synthesis of sordaricin (**3**) has been achieved in 26 steps (longest linear sequence) from (+)-**10** in 3% overall yield, using (−)-**10** and (+)-**10** as starting materials. Alkylation of nitrile **23** with iodide **6** afforded, after elaboration, **25**, which served as a common intermediate for the alternative syntheses. The first of these syntheses involved the construction of aldehyde **9**, which underwent regioselective cycloaddition to generate **30** and, following demethylation, sordaricin (**3**). Given the ease with which this cycloaddition occurs, the question of it's role in the biosynthesis of **3** or **4** remains moot. Enzymatic catalysis could be involved as was recently shown by Sterner and co-workers for the biosynthesis of galiellalactone,[29] but would not appear to be necessary. The second synthesis made use of the tandem cycloreversion/intramolecular cycloaddition of **8**, which afforded the desired compound **30** as well as the alternative regioisomer, *iso*-**30**. Subsequent studies revealed that formation of *iso*-**30** is the result of a thermodynamically driven cycloreversion/cycloaddition process which **30** undergoes at temperatures over 150 °C.

Experimental Section

NMR spectra were recorded in $CDCl_3$ at 300 MHz (^1H), unless stated otherwise.

(1*RS*,3a*RS*,4*SR*,7*RS*,7a*SR*)-1-Isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoinden-1-ol. $CeCl_3 \cdot 7H_2O$ (7.0 g, 18.7 mmol) was heated at 130 °C under vacuum for 2 h, cooled to room temperature, and crushed into a fine powder. The powder was then heated with stirring at 130 °C under vacuum for 2 days, after which time the flask was charged with nitrogen gas and cooled to room temperature. THF (130 mL) was added in a single volume and the suspension stirred for 5 h. Isopropylmagnesium chloride/THF (2.0 M, 9.4 mL, 18.7 mmol) was added dropwise to the stirred suspension at 0 °C and stirring continued for 1.5 h before a solution of ketone (±)-**10** (2.5 g, 17.0 mmol) in THF (20 mL) was added. A 2.0 M aqueous acetic acid solution (25 mL) was added after 30 min and the reaction mixture stirred for 10 min. When all of the solid had dissolved, the solution was extracted three times with diethyl ether (100 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 25% ethyl acetate in petroleum spirits as the eluant, afforded the alcohol (2.7 g, 83%) as a colorless oil. IR (film) ν: 3480, 3044, 2962, 2874, 1468, 1370, 1341, 1166, 1075, 1024, 774 cm^{-1}. ^1H NMR δ: 0.88 (d, 3 H, $J = 6.8$ Hz, CH*Me*), 0.93 (d, 3 H, $J = 6.7$ Hz, CH*Me*), 1.36 (s, 1 H, OH), 1.46 (d, 1 H, $J = 8.1$ Hz), 1.58 (dt, 1 H, $J = 7.7$, 1.6 Hz), 1.74 (sep, 1 H, $J = 6.9$ Hz, C*H*Me_2), 2.65 (dd, 1 H, $J = 7.8$, 3.0 Hz), 2.86 (m, 2 H, H4 + H7), 3.19

(28) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. See also: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: Chicester, 1996.

(29) Johansson, M.; Köpcke, B.; Anke, H.; Sterner, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 2158. For other examples of enzyme-catalyzed Diels−Alder reactions, see: (a) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748. (b) Katayama, K.; Kobayashi, T.; Oikawa, H.; Honma, M.; Ichihara, A, A. *Biochim. Biophys. Acta* **1998**, *1384*, 387. (c) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van denHeever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519. (d) Witter, D. J.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 2613.

(m, 1 H), 5.43 (dd, 1 H, J = 5.8, 1.7 Hz, H3), 5.55 (dd, 1 H, J = 5.7, 2.0 Hz, H2), 5.86 (dd, 1 H, J = 5.6, 3.2 Hz), 6.18 (dd, 1 H, J = 5.6, 2.8 Hz). ^{13}C NMR δ: 16.5 (Me), 17.1 (Me), 37.5 (CH), 45.4 (CH), 46.3 (CH), 49.5 (CH), 52.4 (CH_2), 53.7 (CH), 86.3 (C), 133.2, 134.4, 134.5, 136.8 (4 × =CH). MS *m/z*: 190 ($M^{+\cdot}$, 14), 172 (32), 157 (37), 147 (52), 129 (38), 124 (45), 119 (24), 109 (100), 91 (40), 81 (46). HRMS: calcd for $C_{13}H_{18}O_1$ 190.1358, found 190.1355.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-3-Isopropyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (11). Jones' reagent was added dropwise to a stirred solution of the alcohol (1.4 g, 7.2 mmol) in acetone (70 mL) at 0 °C, until no starting material remained by TLC. Propan-2-ol (5 mL) was added, and the resulting blue-green solution diluted with water (100 mL) and extracted twice with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant afforded the enone **11** (940 mg, 70%) as a colorless oil. IR (film) ν: 2966, 2872, 1694, 1601, 1466, 1337, 1267, 1180, 770 cm^{-1}. ^{1}H NMR δ: 1.13 (d, 1 H, J = 6.9 Hz, CH*Me*), 1.16 (d, 1 H, J = 7.0 Hz, CH*Me*), 1.58 (br d, 1 H, J = 8.4 Hz), 1.75 (dt, 1 H, J = 8.4, 1.2 Hz), 2.45 (sep, 1 H, J = 6.7 Hz, C*H*Me$_2$), 2.85 (t, 1 H, J = 5.2 Hz), 3.00 (m, 1 H, H4), 3.18 (m, 1 H), 3.37 (td, 1 H, J = 4.4, 1.1 Hz), 5.69 (s, 1 H, H2), 5.75 (dd, 1 H, J = 5.5, 3.1 Hz), 5.98 (dd, 1 H, J = 5.5, 3.1 Hz). ^{13}C NMR δ: 20.3 (Me), 21,1 (Me), 30.9 (CH), 43.8 (CH), 43.9 (CH), 48.3 (CH), 51.2 (CH), 52.1 (CH_2), 130.0 (CH), 131.6, 133.1 (2 × =CH), 133.1 (C), 210.0 (C, CO). MS *m/z*:188 ($M^{+\cdot}$, 48), 173 (46), 160 (21), 145 (48), 123 (34), 117 (48), 105, 17), 91 (32), 77 (27), 66 (100). HRMS: calcd for $C_{13}H_{16}O_1$ 188.1201, found 188.1199.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-Methyl-3-isopropyl-1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (12). NaHMDS/THF (1.0 M, 15.1 mL, 15.1 mmol) was added dropwise to a stirred solution of enone **11** (1.9 g, 10 mmol) in THF (100 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1.5 h and cooled to −78 °C and methyl cyanoformate (2.4 mL, 30 mmol) added. After 30 min, water (25 mL) was carefully added and the reaction mixture allowed to warm to room temperature, diluted with water (75 mL), and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 30% ethyl acetate in petroleum spirits as the eluant to afford ester **12** (1.8 g, 73%) as an oil. IR (film) ν: 2971, 2876, 1739, 1703, 1606, 1468, 1432, 1335, 1288, 1234, 1187, 1125, 1028 cm^{-1}. ^{1}H NMR δ: 1.19 (d, 3 H, J = 7.4 Hz, CH*Me*), 1.22 (d, 3 H, J = 7.4 Hz, CH*Me*), 1.62 (br d, 1 H, J = 8.5 Hz), 1.77 (dt, 1 H, J = 8.5, 1.8 Hz), 2.9 (dd, 1 H, J = 4.8, 4.8 Hz), 3.14 (m, 1 H, H4), 3.24 (m, 1 H, H7), 3.36 (sep, 1 H, J = 7.4 Hz, C*H*Me$_2$), 3.42 (dd, 1 H, J = 5.8, 4.1 Hz, H3a), 3.78 (s, 3 H, CO_2*Me*), 5.78 (dd, 1 H, J = 5.6, 2.6 Hz), 6.05 (dd, 1 H, J = 5.6, 3.0 Hz). ^{13}C NMR δ: 20.9 (Me), 21.2 (Me), 30.6 (CH), 44.4 (CH), 46.0 (CH), (51.2 (CH), 51.9 (OMe), 52.8 (CH_2), 132.1, 134.0 (2 × =CH), 134.6 (C), 164.1 (C, *C*O_2Me), 190.7 (C), 204.2 (C, CO). MS *m/z*: 246 ($M^{+\cdot}$, 25), 214 (26), 181 (40), 171 (26), 149 (100), 122 (21), 115 (15), 91 (26), 66 (81). HRMS: calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1254.

(3*S*,3a*R*,4*R*,7*S*,7a*R*)-(3-Methoxymethoxymethyl-3a,4,7,7a-tetrahydro-3*H*-4,7-methanoinden-1-yloxy)trimethylsilane (13). *n*-BuLi/hexanes (1.6 M, 13.7 mL, 21.8 mmol) was added dropwise to a stirred solution of *n*-Bu_3SnCH_2-OMOM (8.0 g, 21.8 mmol) in THF (60 mL) at −78 °C under a nitrogen atmosphere. After 5 min, the reaction mixture was transferred via a cannula to a stirred solution of CuI (2.1 g, 10.9 mmol) and TMEDA (5.0 mL, 32.7 mmol) in THF (20 mL) at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min before TMSCl (4.2 mL, 32.7 mmol) and a solution of (−)-**10** (1.6 g, 10.9 mmol) in THF (20 mL) were added consecutively. After 45 min, the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and allowed to warm to room temperature. Following dilution with water (100 mL) and 10% aqueous ammonia solution (5 mL), the mixture was extracted twice with diethyl ether (150 mL), and the combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using petroleum spirits, then 5% ethyl acetate in petroleum spirits as the eluant, afforded the unstable silyl enol ether **13** (2.23 g, 73%) which was used immediately in the next reaction.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-3-hydroxy-1-methoxymethoxymethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (14). MeLi/diethyl ether (1.0 M, 6.2 mL, 8.8 mmol) was added dropwise to a solution of silyl enol ether **13** (2.23 g, 8.0 mmol) in THF (70 mL) at −20 °C under a nitrogen atmosphere. Stirring was continued at −20 °C for 30 min, and then after cooling to −78 °C methyl cyanoformate (1.3 mL, 16.0 mmol) was added. After 20 min, water (10 mL) was carefully added and the solution allowed to warm to room temperature. The mixture was further diluted with water (100 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 10%, increasing to 20% ethyl acetate in petroleum spirits as the eluant, to afford **14** (1.6 g, 71%) as an inseparable mixture of enol:keto (6:1) tautomers. $[\alpha]^{20}_D$: −131.0 (*c* 0.78 $CHCl_3$). IR (film) ν: 2952, 1756, 1731, 1661, 1619, 1445, 1358, 1342, 1243, 1217, 1150, 1111, 1041, 917 cm^{-1}. ^{1}H NMR (key signals for keto) δ: 1.47 (d, 1 H), 1.62 (d, 1 H), 6.16 (m, 2 H, H5 + H6); (key signals for **14**) δ: 1.30 (d, 1 H, J = 8.2 Hz), 1.52 (d, 1 H, J = 8.2 Hz), 2.37 (m, 1 H), 2.55 (m, 1 H), 3.00 (br s, 1 H), 3.08 (br s, 1 H), 3.29 (t, 1 H, J = 8.2 Hz, H3), 3.34 (s, 3 H, OMe), 3.69 (m, 5 H, CO_2*Me* + CH_2OMOM), 4.60 (AB d, 2 H, J = 6.6 Hz, OCH_2OMe), 5.97 (m, 1 H), 6.02 (m, 1 H), 10.40 (br s, 1 H, OH). ^{13}C NMR (key signals for keto) δ: 52.5 (CH_2), 69.2 (CH_2), 96.1 (CH_2), 135.2, 136.4 (2 × =CH), 168.0 (C, *C*O_2Me), 209.7 (C, CO); (key signals for **14**) δ: 50.0 (CH_2), 70.8 (CH_2), 96.3 (CH_2), 101.1 (C), 133.5, 134.5 (2 × = CH), 169.6 (C), 177.6 (C, *C*O_2Me). MS *m/z* 280 ($M^{+\cdot}$, 6), 243 (13), 215 (14), 205 (47), 183 (52), 173 (12), 154 (71), 139 (70), 122 (46), 107 (66), 66 (100). HRMS: calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1311.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-1-methoxymethoxymethyl-3-trifluoromethanesulfonyloxy-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate. NaH (60% w/w in oil, 214 mg, 5.4 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.4 g, 4.0 mmol) were carefully added to a stirred solution of **14** (1.0 g, 3.6 mmol) in THF (36 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h after which time water (5 mL) was carefully added at 0 °C. The resulting mixture was further diluted with water (80 mL) and extracted twice with diethyl ether (75 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, to afford the triflate (1.14 g, 77%) as a colorless oil. $[\alpha]^{20}_D$: −13.6 (*c* 0.96 $CHCl_3$). IR (film) ν: 3440, 2953, 2887, 1725, 1660, 1661, 1427, 1343, 1231, 1212, 1143, 1041, 947 cm^{-1}. ^{1}H NMR δ: 1.28 (d, 1 H, J = 8.5 Hz), 1.60 (d, 1 H, J = 8.5 Hz), 2.57 (m, 1 H), 2.67 (m, 1 H), 3.06 (br s, 2 H, H4 + H7), 3.33 (s, 3 H, OMe), 3.52 (m, 2 H, H1 + CH_2OMOM), 3.66 (dd, 1 H, J = 5.6, 3.9 Hz, CH_2OMOM′), 3.74 (s, 3 H, CO_2*Me*), 4.59 (AB d, 2 H, J = 6.7 Hz, OCH_2OMe), 6.07 (m, 1 H), 6.11 (m, 1 H). ^{13}C NMR δ: 42.1 (CH), 44.7 (CH), 44.7 (CH), 46.0 (CH), 49.6 (CH_2), 51.6, 51.8 (CH + OMe), 55.1 (CO_2*Me*), 69.5 (CH_2), 96.4 (CH_2), 118.3 (C, q, J = 320 Hz, *C*F_3), 123.6 (C), 134.1, 134.9 (2 × =CH), 156.2 (C), 162.2 (*C*O_2Me). MS *m/z*: 412 ($M^{+\cdot}$, 3), 380 (3), 347 (40), 315 (67), 285 (44), 153 (24), 66 (100). HRMS: calcd for $C_{16}H_{19}O_7F_3S$ 412.0804, found 412.0805.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-3-isopropyl-1-methoxymethoxymethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (15). *n*-BuLi/hexanes (1.6 M, 5.2 mL, 8.2 mmol) was added to a stirred solution of thiophene (660 μL, 8.2 mmol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. After 20 min, the resulting solution was transferred via a cannula to a stirred suspension of CuCN (738 mg, 8.2 mmol) in THF (10 mL) at −78 °C. The mixture was allowed to slowly warm to −40 °C and stirred for a further 30 min, after which time the solution was cooled to −78 °C. Isopropylmagnesium chloride/THF (2.0 M, 4.12 mL, 8.2 mmol) was added, followed by the addition of a solution of the triflate (1.7 g, 4.1 mmol) in THF (15 mL). After 1 h, aqueous ammonium chloride solution (10 mL) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (100 mL) and 10% aqueous ammonia solution (5 mL) and then extracted three times with diethyl ether (150 mL). The combined organic extracts were washed with 1.0 M HCl (200 mL) and brine (200 mL) and dried ($MgSO_4$). Concentration in vacuo followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant afforded **15** (919 mg, 73%) as a colorless oil. $[\alpha]^{20}_D$: −110.2 (*c* 0.68 $CHCl_3$). IR (film) *ν*: 2949, 1707, 1618, 1465, 1434, 1337, 1231, 1150, 1111, 1041 cm^{-1}. ^1H NMR *δ*: 1.10 (apparent t, 6 H, 2 × CH*Me*), 1.29 (m, 1 H), 1.50 (dt, 1 H, *J* = 8.1, 1.9 Hz), 2.52 (m, 2 H, H1 + H7a), 3.05 (m, 2 H, H4 + H7), 3.29 (d, 1 H, *J* = 7.8 Hz, CH_2OMOM), 3.35 (s, 3 H, OMe), 3.40 (m, 1 H, H3a), 3.54 (sep, 1 H, *J* = 7.0 Hz, C*H*Me_2), 3.64 (m, 1 H, CH_2OMOM'), 3.66 (s, 3 H, CO_2Me), 4.60 (AB d, 2 H, *J* = 6.6 Hz, OCH_2OMe), 5.90 (dd, 1 H, *J* = 5.7, 2.8 Hz), 6,04 (dd, 1 H, *J* = 5.7, 2.9 Hz). ^{13}C NMR *δ*: 21.3 (Me), 21.5 (Me), 27.8 (CH), 43. ((CH), 45.7 (CH), 45.7 (CH), 47.1 (CH), 48.9 (CH), 50.2 (CH_2), 50.8 (CH), 54.7, 54.9 (OMe + CO_2Me), 71.4 (CH_2), 96.3 (CH_2), 127.3 (C), 133.5, 135.2 (2 × =CH), 165.8, 166.0 (*C*O_2Me + C3). MS *m/z*: 306 ($M^{+\cdot}$, 27), 274 (13), 260 (45), 243 (33), 231 (24), 180 (100), 165 (24), 134 (28), 105 (26). 66 (15). HRMS: calcd for $C_{18}H_{27}O_4$ ($[M + H]^+$) 307.1909, found 307.1904.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-1-hydroxymethyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate. A solution of MOM ether **15** (160 mg, 0.52 mmol), $MgBr_2{\cdot}Et_2O$ (1.35 g, 5.2 mmol), and 1-butanethiol (504 μL, 4.7 mmol) in diethyl ether (5 mL) was stirred at room temperature for 24 h. The resulting solution was then diluted with 1.0 M HCl (10 mL) and extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 50% ethyl acetate in hexanes as the eluant to afford the alcohol (113 mg, 83%) as a colorless oil. $[\alpha]^{20}_D$: −104.0 (*c* 0.65 $CHCl_3$). IR (film) *ν*: 3401, 2963, 1697, 1615, 1434, 1338, 1231, 1100, 1035 cm^{-1}. ^1H NMR *δ*: 1.10 (m, 6 H, 2 × CH*Me*), 1.29 (d, 1 H, *J* = 8.1 Hz), 1.51 (dt, 1 H, *J* = 8.2, 1.8 Hz), 2.39 (m, 1 H, H7a), 2.46 (m, 1 H, H1), 3.00 (br s, 2 H, H4 + H7), 3.39 (m, 1 H, H3a), 3.46 (m, 1 H, C*H*Me_2), 3.59 (m, 2 H, CH_2OMOM), 3.70 (s, 3 H, CO_2Me), 5.90 (dd, 1 H, *J* = 5.7, 2.9 Hz), 6.02 (dd, I H, *J* = 5.9, 2.9 Hz). ^{13}C NMR *δ*: 21.5 (Me), 21.7 (Me), 28.4 (CH), 43.4 (CH), 45.6 (CH), 47.2 (CH), 50.1 (CH_2), 51.2 (CH + OMe), 54.5 (OMe), 67.3 (CH_2), 127.9 (C, C2), 133.6, 135.5 (2 × =CH), 167.0 (C3 + *C*O_2Me). MS *m/z*: 262 ($M^{+\cdot}$, 4), 231 (4), 196 (40), 178 (29), 166 (100), 151 (44), 135 (19), 119 (51), 91 (36), 66 (28). HRMS: calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

(1*S*,3a*R*,4*S*,7*R*,7a*S*)-Methyl-1-formyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (7). Dess−Martin periodinane (366 mg, 0.86 mmol) was added to a stirred solution of the alcohol (113 mg, 0.43 mmol) in DCM (5 mL) at room temperature. After 1 h, the reaction mixture was diluted with DCM (5 mL) and then treated with 1.0 M sodium thiosulfate (5 mL) and saturated aqueous sodium bicarbonate (5 mL). After vigorous stirring for 10 min, the reaction mixture was diluted with water (20 mL) and extracted three times with DCM (20 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 15% ethyl acetate in hexanes as the eluant to afford **7** (80 mg, 72%) as a colorless oil. $[\alpha]^{20}_D$: −18.7 (*c* 0.46). IR (film) *ν*: 2967, 1719, 1619, 1467, 1434, 1344, 1228, 1193, 1109, 1030 cm^{-1}. ^1H NMR *δ*: 1.13 (m, 6 H, 2 × CH*Me*), 1.35 (d, 1 H, *J* = 8.4 Hz), 1.57 (dt, 1 H, *J* = 8.2 Hz), 2.76 (m, 1 H, H7a), 3.04 (br s, 1 H, H7), 3.07 (br s, 1 H, H4), 3.12 (d, 1 H, *J* = 3.1 Hz, H1), 3.44(m, 1 H, H3a), 3.66 (m, 1 H, C*H*Me_2), 3.67 (s, 3 H, CO_2Me), 5.96 (dd, 1 H, *J* = 6.0, 2.6 Hz), 6.05 (dd, 1 H, *J* = 5.7, 2.9 Hz), 9.57 (d, 1 H, *J* = 2.8 Hz, CHO). ^{13}C NMR *δ*: 21.4 (Me), 21,7 (Me), 28.2 (CH), 40.0 (CH), 45.5 (CH), 47.1 (CH), 50.4 (CH_2), 51.3 (CH), 55.2 (CO_2Me), 61.0 (CH), 124.3 (C, C2), 133.4, 135.8 (2 × = CH), 164.8 (C, C3), 170.2 (*C*O_2Me), 201.7 (CHO). MS *m/z* 260 ($M^{+\cdot}$, 5), 233 (20), 195 (76), 166 (100), 151 (85), 133 (48), 119 (52), 107 (56), 91 (66), 77 (38), 66 (97). HRMS: calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1410.

(1*R*,3a*R*,4*S*,7*R*,7a*S*)-Methyl-1-formyl-1-isobutyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (16). ^{t}BuOK/THF (1.0 M, 115 μL, 115 μmol) was added to a stirred solution of aldehyde **7** (25 mg, 96 μmol) in THF (1.0 mL) at 0 °C under a nitrogen atmosphere. After 5 min, isobutyl iodide (33 μL, 288 μmol) was added and the reaction mixture allowed to warm to room temperature. After 2.5 h, the mixture was diluted with water (10 mL) and extracted twice with diethyl ether (10 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 5% ethyl acetate in hexanes as the eluant to afford **16** (15 mg, 50%) as a single stereoisomer. $[\alpha]^{20}_D$: −78.4 (*c* 0.26 $CHCl_3$). IR (film) *ν*: 2917, 1715, 1606, 1466, 1342, 1226, 1082, 1024 cm^{-1}. ^1H NMR *δ*: 0.76 (d, 3 H, *J* = 6.6 Hz, CH*Me′*), 0.94 (d, 3 H, *J* = 6.7 Hz, CH*Me′*), 1.15 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.16 (d, 3 H, *J* = 6.9 Hz, CH*Me*), 1.31 (d, 1 H, *J* = 8.4 Hz), 1.41 (m, 1 H, C*H*Me_2′), 1.58 (br d, 1 H, *J* = 8.2 Hz), 1.74 (m, 2 H, CH_2CHMe_2), 2.59 (dd, 1 H, *J* = 8.1, 4.0 Hz, H7a), 2.97 (br s, 1 H), 3.14 (br, s, 1 H), 3.52 (dd, 1 H, *J* = 8.2, 4.3 Hz, H3a), 3.66 (sep, 1 H, *J* = 7.0 Hz, C*H*Me_2), 3.68 (s, 3 H, CO_2Me), 5.80, 5.88 (2 × m, 1 H, H5 + H6), 9.61 (s, 1 H, CHO). ^{13}C NMR *δ*: 21.3 (Me), 21.5 (Me), 24.3 (Me), 24.5 (Me), 25.5 (CH), 28.6 (CH), 45.2 (CH), 45.7 (CH_2), 47.5 (CH), 50.6 (CH), 51.5 (CH), 51.5 (CH), 51.5 (CH_2), 52.6 (OMe), 63.5 (C), 129.2 (C), 134.3, 135.3 (2 × =CH), 169.4 (C3 + *C*O_2Me), 205.9 (CHO). MS *m/z*: 316 ($M^{+\cdot}$, 10), 298 (10), 260 (28), 248 (20), 222 (100), 207 (20), 179 (88), 147 (50), 119 (50), 91 (42), 66 (38). HRMS: calcd for $C_{20}H_{26}O_3$ 316.2038, found 316.2037.

(2*S*,3*S*,3a*S*,4*S*,7*R*,7a*S*)-3-Methoxymethoxymethyl-2-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (17). MeLi/diethyl ether (1.0 M, 6.4 mL, 6.4 mmol) was added dropwise to a solution of silyl enol ether *ent*-**13** (1.87 g, 6.4 mmol) in THF (50 mL) at −20 °C under a nitrogen atmosphere. Stirring was continued at −20 °C for 30 min, and then after the mixture was cooled to −78 °C, HMPA (5.5 mL, 32 mmol) and MeI (1.98 mL, 32 mmol) were added. After 30 min, the reaction mixture was allowed to gradually warm to −20 °C and stirred for a further 1 h before aqueous ammonium chloride solution (10 mL) was carefully added. The mixture was allowed to warm to room temperature, diluted with water (100 mL), and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (75 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, gave the ketone **17** (95:5 dr, 881 mg, 60%) as a colorless oil. $[\alpha]^{20}_D$: +131.7 (*c* 0.67 $CHCl_3$). IR (film) *ν*: 2933, 1730, 1455, 1182, 1149, 1108, 1052, 917 cm^{-1}. ^1H NMR *δ*: 0.95 (d, 3 H, *J* = 7.3 Hz, CH*Me*), 1.41 (dt, 1 H, *J* = 8.2, 1.4 Hz), 1.53 (dt, 1 H, *J* = 8.2, 1.6 Hz), 2.01 (m, 1 H, H3), 2.18 (m, 1 H, H2), 2.70 (ddd, 1 H, *J* = 9.2, 4.1, 2.2 Hz, H3a), 2.91 (dd, 1 H, *J* = 9.2, 4.7 Hz, H7a), 3.05 (m, 1 H, H4), 3.18 (m, 1 H, H7), 3.34 (s, 3 H, OMe), 3.45, 3.53 (AB

d, 2 H, J = 9.3 Hz, CH_2OMOM), 4.55 (s, 2 H, OCH_2OMe), 6.07 (dd, 1 H, J = 5.6, 2.9 Hz, H6), 6.22 (dd, 1 H, J = 5.6, 3.0 Hz, H5). ^{13}C NMR δ: 9.5 (Me), 39.7 (CH), 44.1 (CH), 46.9 (CH), 47.1 (CH), 47.3 (CH), 52.4 (CH_2), 53.4 (CH), 55.3 (OMe), 69.3 (CH_2), 96.5 (CH_2), 134.6, 136.0 (2 × =CH), 220.8 (C, CO). MS *m/z*: 236 ($M^{+\cdot}$, 5), 191 (3), 171 (48), 139 (50), 109 (47), 91 (32), 81 (39), 66 (100). HRMS: calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1415.

(4*S*,5*S*)-4-Methoxymethoxymethyl-5-methylcyclopent-2-enone (18). Nitrogen was bubbled through a stirred solution of ketone **17** (800 mg, 3.4 mmol) in 1,2-dichlorobenzene (6 mL) at reflux for 7 h. After being cooled to room temperature, the reaction mixture was subjected to flash chromatography on a column of silica gel using petroleum spirits, then 50% ethyl acetate in petroleum spirits as the eluant, to give the enone **18** (507 mg, 85%) as a colorless oil. $[\alpha]^{20}_D$ +234.9 (*c* 0.48 $CHCl_3$). IR (film) ν: 2883, 1709, 1588, 1458, 1383, 1354, 1187, 1150, 1109, 1036 cm^{-1}. ^1H NMR δ: 1.15 (d, 3 H, J = 7.6 Hz, CH*Me*), 2.52 (m, 1 H, H5), 3.52 (m, 1 H, H4), 3.35 (s, 3 H, OMe), 3.55 (dd, 1 H, J = 10.5, 7.0 Hz, CH_2OMOM), 3.70 (dd, 1 H, J = 9.6, 6.9 Hz, CH_2OMOM'), 4.60 (s, 2 H, OCH_2OMe), 6.24 (dd, 1 H, J = 5.9, 2.0 Hz, H2), 7.67 (dd, 1 H, J = 5.9, 2.6 Hz, H3). ^{13}C NMR δ: 10.5 (Me), 42.1 (CH), 45.) (CH), 55.4 (OMe), 67.0 (CH_2), 96.5 (CH_2), 133.5 (CH), 164.2 (CH), 211.8 (C, CO). MS *m/z*: 170 ($M^{+\cdot}$, 15), 140 (100), 125 (5), 108 (34), 95 (21), 81 (51), 75 (39), 67 (29). HRMS: calcd for $C_9H_{14}O_3$ 170.0943, found 170.0943.

(2*S*,3*S*,4*R*)-4-Isopropenyl-3-methoxymethoxymethyl-2-methylcyclopentanone (19). Isopropenylmagnesium bromide/THF (0.5 M, 345 mL, 2.4 mmol) was added to a stirred suspension of CuI (224 mg, 1.2 mmol) in THF (10 mL) at −78 °C under a nitrogen atmosphere. After 5 min, TMSCl (298 μL, 2.4 mmol) and a solution of enone **18** (345 mg, 2.0 mmol) in THF (5 mL) were added dropwise. After the mixture was stirred for 15 min, a solution of aqueous ammonium chloride (5 mL) was added and the reaction mixture allowed to warm to room temperature. The solution was diluted with water (50 mL) and 10% aqueous ammonia (2 mL) and then extracted three times with ethyl acetate (30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant to afford olefin **19** (300 mg, 70%) as a single diastereoisomer. $[\alpha]^{20}_D$: −19.2 (*c* 1.02 $CHCl_3$). IR (film) ν: 2933, 1740, 1645, 1454, 1377, 1149, 1108, 1042 cm^{-1}. ^1H NMR δ: 1.07 (d, 3 H, J = 7.3 Hz, CH*Me*), 1.78 (m, 3 H, =C*Me*), 2.26 (ddd, 1 H, J = 18.8, 7.5, 1.5 Hz), 2.40−2.60 (m, 3 H, H2), 2.72 (dd, 1 H, J = 14.4, 6.9 Hz, H4), 3.35 (s, 3 H, OMe), 3.56 (AB d, 2 H, J = 5.6 Hz, CH_2OMOM), 4.58 (s, 2 H, OCH_2OMe), 4.76, 4.82 (m, 2 × 1 H, $=CH_2$). ^{13}C NMR δ: 9.8 (Me), 20.2 (=C*Me*), 41.8 (CH_2), 42.9 (CH), 43.5 (CH), 43.8 (CH), 55.3 (OMe), 67.3 (CH_2), 96.5 (CH_2), 110.8 (=CH_2), 145.3 (=*C*Me), 219.4 (CO). MS *m/z* 212 ($M^{+\cdot}$, 55), 180 (40), 167 (39), 152 (41), 137 (53), 121 (56), 107 (82), 93 (74), 81 (62), 68 (92), 55 (100). HRMS: calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1410.

(1*R*,2*R*,3*R*)-1-Isopropenyl-2-methoxymethoxymethyl-3-methylcyclopentane (20). $NaBH_4$ (106 mg, 2.8 mmol) was added to a stirred solution of ketone **19** in MeOH (10 mL) at 0 °C. After 20 min, water (5 mL) was added and the mixture stirred for a further 5 min. The reaction mixture was diluted with water (20 mL) and extracted three times with ethyl acetate (25 mL). The combined organic extracts were then washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a 2:1 mixture of diastereomeric alcohols which was used in the next reaction without further purification. ^1H NMR δ: (major) 1.04 (d, 3 H, J = 7.2 Hz, CH*Me*), 1.70 (m, 3 H, =C*Me*), 3.39 (s, 3 H, OMe), 3.98 (m, 1 H, C*H*OH); (minor) 0.94 (d, 3 H, J = 7.2 Hz, CH*Me*), 1.73 (m, 3 H, =CHC*Me*), 3.35 (s, 3 H, OMe), 3.87 (q, 1 H, J = 5.7 Hz, C*H*OH). Pyridine (280 μL, 3.5 mmol) and phenyl chlorothionoformate (211 μL, 1.5 mmol) were added successively to a stirred solution of the crude alcohols in DCM (5 mL) at room temperature under a nitrogen atmosphere. After 2 h, the reaction mixture was diluted with a 1.0 M aqueous HCl solution (30 mL) and extracted three times with DCM (20 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (25 mL) and brine (25 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded an inseparable 2:1 mixture of thionocarbonates (435 mg, 88%). ^1H NMR δ: (major) 5.59 (m, 1 H, C*H*OC(S)OPh); (minor) 5.28 (m, 1 H, C*H*OC(S)OPh). *n*-Bu_3SnH (398 μL) and AIBN (cat.) were added to a stirred solution of thionocarbonates (435 mg, 1.2 mmol) in benzene (5 mL) at reflux under a nitrogen atmosphere. After 30 min the reaction mixture was allowed to cool to room temperature and the solvent removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using petroleum spirits and then 10% ethyl acetate in petroleum spirits as the eluant, to afford cyclopentane **20** (258 mg, 100%) as a colorless oil. $[\alpha]^{20}_D$: −42.8 (*c* 0.80 $CHCl_3$). IR (film) ν: 2950, 1642, 1454, 1377, 1213, 1147, 1110, 1048 cm^{-1}. ^1H NMR δ: 0.93 (d, 3 H, J = 7.2 Hz, CH*Me*), 1.24−1.38 (m, 1 H), 1.42−1.58 (m, 1 H), 1.70 (m, 3 H, =C*Me*), 1.78−1.90 (m, 2 H), 2.02−2.12 (m, 1 H, H1), 2.20−2.36 (m, 2 H), 3.37 (s, 3 H, OMe), 3.44 (m, 2 H, CH_2OMOM), 4.60 (AB d, 2 H, J = 6.4 Hz, OCH_2OMe), 4.69 (m, 2 H, $=CH_2$). ^{13}C NMR δ: 15.5 (Me), 19.2 (=C*Me*), 29.7 (CH_2), 33.4 (CH_2), 35.0 (CH), 45.7 (CH), 48.2 (CH), 55.2 (OMe), 68.0 (CH_2), 96.6 (CH_2), 110.0 ($=CH_2$), 147.5 (=*C*Me). MS *m/z* 198 ($M^{+\cdot}$, 1), 167 (11), 153 (15), 136 (68), 123 (100), 107 (55), 95 (62), 81 (84), 67 (35). HRMS: calcd for $C_{12}H_{22}O_2$ 198.1620, found 198.1620.

(1*R*,2*R*,5*R*)-(2-Isopropenyl-5-methylcyclopentyl)methanol. A solution of ether **20** (80 mg, 0.4 mmol) and PPTS (624 mg, 2.4 mmol) in ^{t}BuOH (8 mL) was heated at reflux for 20 h. After cooling to room temperature, the reaction mixture was diluted with a 1.0 M aqueous HCl solution (10 mL) and extracted three times with ethyl acetate (15 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 40% ethyl acetate in petroleum spirits as the eluant to give the alcohol (50 mg, 80%) as a pale yellow oil. Identical with spectra obtained from (*S*)-(+)-carvone.[30]

(1*R*,2*R*,5*R*)-*tert*-Butyl[2-isopropenyl-5-methylcyclopentylmethoxy)dimethylsilane. TBSCl (3.5 g, 23.3 mmol) was added to a stirred solution of the alcohol (3.0 g, 19.4 mmol) and DIPEA (4.7 mL, 27.2 mmol) in DMF (50 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stir for 12 h, after which time the mixture was diluted with water (250 mL) and 1.0 M HCl (250 mL) and then extracted three times with diethyl ether (100 mL). The combined organic extracts were washed with brine (200 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant to give the TBS ether (5 g, 96%) as an oil. $[\alpha]^{20}_D$: +10.1 (*c* 0.24 $CHCl_3$). IR (film) ν: 2954, 2858, 1643, 1471, 1462, 1387, 1255, 1098 cm^{-1}. ^1H NMR δ: 0.03 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si^{t}Bu), 0.94 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.22−1.50 (m, 2 H), 1.70 (m, 3 H, =C*Me*), 1.75−1.98 (m, 3 H), 2.21 (m, 1 H, H5), 2.35 (q, 1 H, J = 8.8 Hz, H2), 3.53 (m, 2 H, CH_2OTBS), 4.67 (m, 2 H, $=CH_2$). ^{13}C NMR δ: −5.3 ($SiMe_2$), 15.5 (Me), 18.3 (Si*C*Me_3), 19.5 (=C*Me*), 26.0 (SiC*Me*$_3$), 30.1 (CH_2), 33.7 (CH_2), 35.4 (CH), 48.0 (2 × CH), 62.8 (CH_2), 109.5 ($=CH_2$), 148.2 (=*C*Me). MS *m/z*: 211 ([M − ^{t}Bu]$^{+\cdot}$, 45), 193 (5), 181 (8), 169 (18), 135 (12), 89 (18), 75 (100). HRMS: calcd for $C_{12}H_{23}OSi$ 211.1518, found 211.1516.

(1*R*,2*R*,5*R*)-*tert*-Butyldimethyl[2-methyl-5-(2′-methyloxiranyl)cyclopentylmethoxy]silane. To a stirred solu-

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

tion of the olefin (7.5 g, 28.8 mmol) and $NaHCO_3$ (25 g) in DCM (300 mL) was added small portions of *m*-CPBA (57−86%) until all the starting material was consumed, as judged by TLC. A solution of Na_2SO_3 (15 g) in water (150 mL) was added and the resulting mixture stirred vigorously for 10 min. The reaction mixture was diluted with diethyl ether (200 mL) and washed twice with 3% aqueous NaOH solution (500 mL). The combined organic extracts were washed with brine (200 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 5% ethyl acetate in petroleum spirits as the eluant, to afford an inseparable mixture of epoxides (7.6 g, 98%) as a colorless oil. IR (film) *ν*: 2954, 2858, 1472, 1387, 1255, 1094 cm^{-1}. ^1H NMR (key signals) *δ*: 0.04 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si^tBu), 0.92 (m, 3 H, CH*Me*), 1.30 (s, 3 H, Me′), 1.30−1.90 (m, 6 H), 2.10 (m 1 H, H2), 2.53, 2.61 (AB d, 2 H, *J* = 7.2 Hz, H1′), 3.57 (m, 2 H, CH_2OTBS). MS *m/z*: 284 ([M+H]$^{+\bullet}$, 2), 267 (8), 227 (52), 209 (8), 197 (17), 153 (12), 135 (100), 121 915), 93 (30), 75 (70). HRMS: calcd for $C_{12}H_{23}O_2Si$ 227.1467, found 227.1469.

(1′*R*,2′*R*,3′*R*)-[2′-(*tert*-Butyldimethylsilanyloxymethyl)-3′-methylcyclopentyl]prop-2-en-1-ol (22). A solution of the epoxides (2.0 g, 7.0 mmol) in diethyl ether (20 mL) was transferred via a cannula into a stirred solution of LCIA, prepared by addition of *n*-BuLi/hexane (1.6 M, 26.4 mL, 42.0 mmol) to a solution cyclohexylisopropylamine (6.9 mL, 42.0 mmol) in diethyl ether (100 mL) at 0 °C. The mixture was stirred at room temperature for 6.5 h, cooled to 0 °C, and quenched with saturated aqueous ammonium chloride solution (25 mL). The resulting mixture was diluted with water (125 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were then washed with 1.0 M HCl (150 mL) and brine (150 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, afforded allylic alcohol **22** (1.28 g, 64%) as a colorless oil. $[\alpha]^{20}_D$: −30.6 (*c* 0.32 $CHCl_3$). IR (film) *ν*: 3369, 2953, 1647, 1471, 1462, 1388, 1254, 1096, 1056 cm^{-1}. ^1H NMR *δ*: 0.05 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si^tBu), 0.90 (obscured d, 3 H, CH*Me*), 1.28 (m, 1 H), 1.51 (m, 1 H), 1.78−2.50 (m, 4 H), 2.47 (m, 1 H), 2.54 (br s, 1 H, OH), 3.52 (dd, 1 H, *J* = 10.0, 7.2 Hz, CH_2OTBS), 3.65 (dd, 1 H, *J* = 9.8, 6.0 Hz, CH_2OTBS'), 4.10 (apparent t, 2 H, *J* = 13.6 Hz, CH_2OH), 4.90, 5.00 (br s, 2 × 1 H, $=CH_2$). ^{13}C NMR *δ*: −5.5, −5.4 ($SiMe_2$), 15.3 (Me), 18.2 (C, Si*C*Me_3), 25.9 (SiC*Me*$_3$), 31.2 (CH_2), 33.5 (CH_2), 35.4 (CH), 44.5 (CH), 49.0 (CH), 63.6 (CH_2), 65.1 (CH_2), 108.5 (=CH_2), 152.1 (=C). MS *m/z*: 227 ([M − ^{t}Bu]$^{+\cdot}$, 22), 135 (35), 107 (46), 93 (85), 75 (100). HRMS: calcd for $C_{12}H_{23}O_2Si$ 227.1467, found 227.1465.

(1*R*,2*R*,5*R*)-*tert*-Butyl-[2-(1′-methoxymethoxymethylvinyl)-5-methylcyclopentylmethoxy]dimethy-silane. To a stirred solution of alcohol **22** (4.5 g, 16.0 mmol) and DMAP (193 mg, 1.6 mmol) in DCM (150 mL) at 0 °C under a nitrogen atmosphere were added DIPEA (6.06 mL, 35.2 mmol) and MOMCl (2.4 mL, 32.0 mmol). The reaction mixture was allowed to stir at room temperature for 13 h, diluted with 1.0 M HCl (100 mL), and extracted twice with diethyl ether (150 mL). The combined organic extracts were washed with brine (150 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant to give the MOM ether (5.0 g, 94%) as a colorless oil. $[\alpha]^{20}_D$: −40.3 (*c* 0.33 $CHCl_3$). IR (film) *ν*: 2953, 1647, 1471, 1463, 1388, 1255, 1151, 1100, 1055 cm^{-1}. ^1H NMR *δ*: 0.03 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, Si^tBu), 0.94 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.22 (m, 1 H), 1.47 (m, 1 H), 1.75−2.04 (m, 4 H), 2.23 (sep, 1 H, *J* = 7.3 Hz, H5), 2.40 (q, 1 H, *J* = 8.6 Hz, H2), 3.38 (s, 3 H, OMe), 3.55 (m, 2 H, CH_2OTBS), 4.02 (s, 2 H, CH_2OMOM), 4.64 (s, 2 H, OCH_2OMe), 4.94, 5.05 (br s, 2 × 1 H, $=CH_2$). ^{13}C NMR *δ*: −5.5, −5.4 ($SiMe_2$), 15.4 (Me), 18.1 (C, Si*C*Me_3), 25.9 (SiC*Me*$_3$), 31.1 (CH_2), 33.6 (CH_2), 35.3 (CH), 44.2 (CH), 48.6 (CH), 55.1 (OMe), 62.6 (CH_2), 69.1 (CH_2), 95.4 (CH_2), 109.7 (=CH_2), 148.6 (=C). MS *m/z*: 297 ([M − OMe]$^{+\cdot}$, 2), 267 (20), 209 (18), 179 (20), 147 (95), 135 (30), 119 (75), 105 (70), 89 (80), 75 (100). HRMS: calcd for [M + H] $C_{18}H_{37}O_3Si$ 329.2512, found 329.2521.

(1*R*,2*R*,5*R*)-[2-(1′-Methoxymethoxymethyl-vinyl)-5-methyl-cyclopentyl]-methanol. TBAF/THF (1.0 M, 45.6 mL, 45.6 mmol) was added dropwise to a stirred solution of the TBDMS ether (5.0 g, 15 mmol) in THF (50 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 16 h, then diluted with water (150 mL) and extracted three times with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant, to give the alcohol (3.1 g, 93%) as an oil. $[\alpha]^{20}_D$ −40.7 (*c* 0.70 $CHCl_3$). IR (film) *ν*: 3435, 2950, 2874, 1649, 1456, 1399, 1214, 1150, 1050 cm^{-1}. ^1H NMR *δ*: 0.92 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.24−1.36 (m, 1 H), 1.42−1.58 (m, 1 H), 1.8−2.25 (m, 3 H), 1.85 (br s, 1 H, OH), 2.26 (sep, 1 H, *J* = 6.7 Hz, H5), 2.41 (q, 1 H, *J* = 8.8 Hz, H2), 3.38 (s, 3 H, OMe), 3.62 (m, 2 H, CH_2-OH), 4.04 (s, 2 H, CH_2OMOM), 4.64 (s, 2 H, OCH_2OMe), 5.02, 5.08 (br s, 2 × 1 H, $=CH_2$). ^{13}C NMR *δ*: 15.3 (Me), 31.2 (CH_2), 33.3 (CH_2), 34.9 (CH), 44.6 (CH), 49.3 (CH), 55.1 (OMe), 62.9 (CH_2), 69.5 (CH_2), 95.4 (CH_2), 110.9 (=CH_2), 148.5 (=C). MS *m/z*: 183 ([M − MeOH]$^{+\cdot}$, 3), 169 (10), 151 (49), 137 (35), 123 9100), 107 (65), 91 (38), 81 (74), 67 (45). HRMS: calcd for [M − MeOH] $C_{11}H_{18}O_2$ 182.1307, found 182.1309.

(1*R*,2*R*,3*R*)-2-Iodomethyl-1-(1′-methoxymethoxymethylvinyl)-3-methylcyclopentane (6). Iodine (3.6 g, 14.0 mmol) was added to a stirred solution of the alcohol (2.0 g, 9.3 mmol) and triphenylphosphine (3.7 g, 14.0 mmol) in 3:1 diethyl ether: acetonitrile (80 mL) at room temperature under a nitrogen atmosphere. After 30 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (100 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting residue was taken up in diethyl ether and the insoluble triphenylphosphine oxide removed by filtration. The mother liquor was evaporated and the residue subjected to flash chromatography on a column of silica gel using 5% diethyl ether in hexanes as the eluant to give **6** (2.9 g, 96%) as a colorless oil. $[\alpha]^{20}_D$: −64.7 (*c* 0.30 $CHCl_3$). IR (film) *ν*: 2953, 1646, 1464, 1428, 1378, 1211, 1150, 1104, 1052 cm^{-1}. ^1H NMR *δ*: 0.88 (d, 3 H, *J* = 6.7 Hz, CH*Me*), 1.37 (m, 1 H), 1.60 (m, 1 H), 1.86 (m, 1 H), 2.05 (m, 1 H), 2.31 (m, 3 H), 2.93 (apparent t, 1 H, *J* = 9.8 Hz, CH_2I), 3.28 (dd, 1 H, *J* = 9.5, 3.5 Hz, CH_2I'), 3.39 (s, 3 H, OMe), 4.01 (s, 2 H, CH_2OMOM), 4.64 (s, 2 H, OCH_2OMe), 4.97, 5.13 (br s, 2 × 1 H, $=CH_2$). ^{13}C NMR *δ*: 7.3 (CH_2I), 14.7 (Me), 31.5 (CH_2), 31.6 (CH_2), 36.0 (CH), 47.0 (CH), 50.2 (CH), 55.4 (OMe), 69.0 (CH_2), 95.6 (CH_2), 111.5 (=CH_2), 147.2 (=C). MS *m/z*: 279 ([M − 45]$^{+\cdot}$, 27), 264 (6), 235 (36), 165 (18), 147 (42), 135 (64), 121 (32), 107 (64), 95 (90), 81 (100), 67 (59). HRMS: calcd for $C_{12}H_{21}O_2I$ 324.0586, found 324.0590.

(1*S*,3a*R*,4*S*,7*R*,7a*S*)-3-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoindene-1-carbonitrile. To a stirred solution of potassium cyanide (2.23 g, 34.2 mmol) and ammonium chloride (1.54 g, 28.8 mmol) in water (35 mL) at 0 °C under a nitrogen atmosphere was added a solution of enone (−)-**10** (2.5 g, 17.1 mmol) in DMF (35 mL). The reaction mixture was stirred at room temperature for 48 h, diluted with water (400 mL), and extracted three times with ethyl acetate (200 mL). The combined organic extracts were washed with water (300 mL) and brine (300 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 60% ethyl acetate in petroleum spirits as the eluant, afforded the nitrile (2.8 g, 95%) as a white solid. Mp: 48−50 °C (petroleum spirits, ethyl acetate). $[\alpha]^{20}_D$: −149.5 (*c* 0.66 $CHCl_3$). IR (film) *ν*: 2977, 223, 1735, 1453, 1404, 1332, 1228, 1186, 1133, 840 cm^{-1}. ^1H NMR *δ*: 1.52 (d, 1 H, *J* = 8.6 Hz), 1.67 (dt, 1 H, *J* = 8.6, 1.6 Hz), 2.42 (dd, 1 H, *J* = 18.5, 10.1

Hz, H2), 2.56 (ddd, 1 H, J = 18.5, 6.9, 1.6 Hz, H4′), 2.66 (m, 1 H, H1), 3.11, 3.35 (m, 2 × 1 H, H4 +H7), 3.23, 3.35 (m, 2 × 1 H, H3a + H7a), 6.17 (dd, 1 H, J = 5.7, 3.1 Hz), 6.23 (dd, 1 H, J = 5.7, 3.1 Hz). ^{13}C NMR δ: 25.6 (CH), 44.5 (CH_2), 46.2 (CH), 46.3 (CH), 46.6 (CH), 52.1 (CH_2), 53.6 (CH), 121.9 (CN), 133.5, 137.5 (2 × =CH), 214.1 (CO). MS *m/z*: 173 ($M^{+\cdot}$, 5), 144 (10), 130 (32), 117 (12), 103 (20), 92 (30), 91 (100), 77 (36). HRMS: calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0834. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1. Found: C, 76.0; H, 6.1; N, 8.0.

(1′*S*,3a′*R*,4′*S*,7′*R*,7a′*S*)-2′,3′,3a′,4′,7′,7a′-Hexahydro-1*H*-4′,7′-methanoindene-1′-cyano-3′-spiro-2-[1,3]dioxolane (23). A solution of the nitrile (950 mg, 5.5 mmol), ethylene glycol (766 μL, 13.8 mmol), and Dowex-50W resin (285 mg, 30% w/w) in benzene (50 mL) was heated at reflux through a Soxhlet apparatus ($MgSO_4$) under a nitrogen atmosphere. After 6 h, the reaction mixture was cooled to room temperature and filtered and the solvent removed in vacuo. The remaining residue was taken up in ethyl acetate (100 mL) and washed twice with water (100 mL), and then the combined aqueous extracts were extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant, afforded ketal **23** (1.02 g, 85%) as a white solid. Mp: 106 °C (petroleum spirits, ethyl acetate). $[\alpha]^{20}_D$: −38.0 (*c* 1.15 $CHCl_3$). IR (film) ν: 2985, 2231, 1479, 1430, 1338, 1140, 1107, 1067, 901 cm^{-1}. ^{1}H NMR δ: 1.33 (d, 1 H, J = 8.4 Hz), 1.50 (dt, 1 H, J = 8.4, 1.8 Hz), 1.96 (apparent d, 2 H), 2.42 (td, 1 H, J = 6.7 Hz, H′1), 2.80 (dd, 1 H, J = 9.2, 4.1 Hz, H′3a), 2.90, 2.95 (m, 2 × 1 H, H′4+ H′7), 3.03 (m, 1 H, H′7a), 3.80−4.00 (m, 4 H, H4, 4′ + H5, 5′), 6.05 (dd, 1 H, J = 5.6, 2.9 Hz), 6.23 (dd, 1 H, J = 5.7, 3.1 Hz). ^{13}C NMR δ: ′27.2 (CH), 41.5 (CH_2), 44.9 (CH), 45.2 (CH_2), 48.9 (CH), 51.8 (CH_2), 53.7 (CH), 63.7 CH_2), 64.6 (CH_2), 115.6 (C), 122.6 (CN), 132.0, 138.5 (2 × =CH). MS *m/z* 217 ($M^{+\cdot}$, 56), 177 (11), 164 (33), 151 (40), 124 (65), 99 (69), 88 (60), 66 (100). HRMS: calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1104. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 72.2; H, 7.0; N, 6.4.

(1′*R*,3a′*R*,4′*S*,7′*R*,7a′*S*,1″*R*,2″*R*,5″*R*)-1′-[2″-(1‴-Methoxymethoxymethylvinyl)-5″-methylcyclopentylmethyl]-2′,3′,3a′,4′,7′,7a′-hexahydro-1*H*-4′,7′-methano-indene-1′-cyano-3′-spiro-2-[1,3]dioxolane (24). A solution of LDA/THF (1.0 M, 23.1 mL, 23.1 mmol) was added dropwise to a stirred solution of nitrile **23** (2.0 g, 9.25 mmol) in THF (60 mL) at −78 °C under a nitrogen atmosphere. After 30 min, the reaction mixture was allowed to warm to room temperature and stir for 1 h before being cooled to −78 °C. HMPA (1.6 mL, 9.25 mmol) and a solution of iodide 158 (1.5 g, 4.63 mmol) in THF (40 mL) were added, and the mixture was stirred at −78 °C for 2 h. A saturated solution of aqueous ammonium chloride (10 mL) was added and the mixture warmed to room temperature, diluted with 1.0 M HCl (300 mL), and extracted three times with diethyl ether (150 mL). The combined organic extracts were washed with brine (500 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 15% ethyl acetate in petroleum spirits as the eluant, afforded the desired product **24** (1.1 g, 58% based on iodide) as a pale yellow oil. Further elution afforded recovered nitrile **23** (1.2 g, 5.53 mmol). Product yield based on recovered nitrile **23** was 73%: $[\alpha]^{20}_D$ −19.9 (*c* 0.84 $CHCl_3$). IR (film) ν: 2951, 2230, 1646, 1431, 1334, 1210, 1150, 1113, 1052 cm^{-1}. ^{1}H NMR δ: 0.89 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.27 (d, 1 H, J = 8.2 Hz), 1.34−1.54 (m, 4 H), 1.68−2.08 (m, 4 H), 1.88 (d, 1 H, J = 13.8 Hz, H′2), 2.14 (d, 1 H, J = 13.9 Hz, H′2′), 2.28−2.46 (m, 2 H), 2.71 (m, 2 H), 2.93, 3.09 (s, 2 × 1 H, H′4 + H′7), 3.38 (s, 3 H, OMe), 3.78−3.94 (m, 4 H, H4,4′ + H5, 5′), 4.04 (s, 2 H, CH_2OMOM), 4.65 (s, 2 H, OCH_2OMe), 5.01, 5.15 (s, 2 × 1 H, =CH_2), 6.22 (dd, 1 H, J = 5.7, 3.1 Hz), 6.41 (dd, 1 H, J = 5.6, 2.9 Hz). ^{13}C NMR δ: 15.0 (Me), 28.2 (CH_2), 32.9 (CH_2), 35.0 (CH), 37.3 (C), 44.4 (CH), 46.0 (CH), 46.8 (CH), 47.5 (CH), 47.6 (CH_2), 51.0 (CH_2), 53.7 (CH), 54.3 (CH), 55.1 (OMe), 63.6 (CH_2), 64.2 (CH_2), 68.6 (CH_2), 95.4 (CH_2), 1115.5 (=CH_2), 115.8 (C), 123.7 (CN), 133.4, 137.6 (2 × =CH), 147.3 (=C). MS: *m/z* 413 ($M^{+\cdot}$, 3.2), 284 (14), 268 (83), 352 (55), 316 (23), 286 (100), 261 (35), 229 (64), 216 (39), 164 912), 89 (30), 66 (78). HRMS: calcd for $C_{25}H_{36}NO_4$ 414.2622, found 414.2643.

(1′*R*,3a′*R*,4′*S*,7′*R*,7a′*S*,1″*R*,2″*R*,5″*R*)-1′-[2″-(1‴-Methoxymethoxymethylvinyl)-5″-methylcyclopentylmethyl]-2′,3′,3a′,4′,7′,7a′-hexahydro-1*H*-4′,7′-methanoindene-1′-formyl-3′-spiro-2-[1,3]dioxolane. To a stirred solution of nitrile **24** (1.5 g, 3.6 mmol) in DCM (50 mL) at −78 °C under a nitrogen atmosphere was added DIBAL-H/hexane (1.0 M, 9.0 mL, 9.0 mmol). After 30 min, the reaction mixture was quenched with 0.5 M aqueous oxalic acid (5.0 mL) and allowed to warm to room temperature. The mixture was further diluted with 0.5 M aqueous oxalic acid (50 mL) and extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with a saturated solution of potassium sodium tartrate (300 mL) and brine (300 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford the aldehyde (1.5 g, 100%) which was used in the next reaction without further purification. For the purpose of characterization a portion of the aldehyde was subjected to flash chromatography on a column of silica gel using 15% ethyl acetate in petroleum spirits as the eluant to afford analytically pure aldehyde. $[\alpha]^{20}_D$: −28.1 (*c* 0.76 $CHCl_3$). IR (film) ν: 2954, 1720, 1645, 1454, 1435, 1333, 1244, 1211, 1150, 1111, 1052 cm^{-1}. ^{1}H NMR δ: 0.83 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.18 (d, 1 H, J = 8.1 Hz), 1.26−2.10 (m, 9 H), 2.20 (m, 1 H), 2.62 (dd, 1 H, J = 8.8, 4.0 Hz), 2.75 (m, 1 H), 2.88, 2.98 (br s, 2 × 1 H, H′4 + H′7), 3.37 (s, 3 H, OMe), 3.75−3.90 (m, 6 H), 4.63 (s, 2 H, OCH_2-OMe), 4.89, 5.10 (br s, 2 × 1 H, =CH_2), 5.76 (dd, 1 H, J = 5.7, 2.9 Hz), 6.10 (dd, 1 H, J = 5.6, 2.9 Hz), 9.54 (s, 1 H, CHO). ^{13}C NMR δ: 14.6 (Me), 28.3 (CH_2), 32.9 (CH_2), 35.8, 36.0 (CH), 41.0, 43.7 (CH), 44.4 (CH), 44.8 (CH), 47.9 (CH), 51.3 (CH_2), 53.4 (CH), 54.0 (CH), 55.2 (OMe), 56.6 (CH_2), 63.4 (CH_2), 64.2 (CH_2), 68.6 (CH_2), 95.6 (CH_2), 111.5 (=CH_2), 116.3 (C), 132.5, 147.8 (2 × =CH), 147.8 (=C), 204.9 (CHO). MS *m/z*; 371 ([M − $CH_2OMe]^{+\cdot}$, 5), 327 (10), 310 (100), 295 (20), 267 (58), 250 (48), 220 (66), 206 (25), 176 (20), 148 (78), 121 (40), 66 (32). HRMS: calcd for ([M − $CH_2OMe]^{+\cdot}$ $C_{25}H_{31}O_4$ 371.2222, found 371.2221.

(3′*S*,3a′*S*,4′*R*,7′*S*,7a′*R*,1″*R*,2″*R*,5″*R*)-3′-Hydroxymethyl-3′-[2″-(1‴-methoxymethoxymethylvinyl)-5″-methylcyclopentylmethyl]-2′,3′,3a′,4′,7′,7a′-hexahydro-4′,7′-methanoindene-1′-spiro-2-[1,3]dioxolane. To a stirred solution of the aldehyde (1.5 g, 3.6 mmol) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (275 mg, 7.2 mmol) in portions. After 30 min, the reaction was quenched with water (15 mL) and stirred for 10 min. The reaction mixture was further diluted with water (50 mL) and extracted three times with ethyl acetate (60 mL). The combined organic extracts were washed with brine (500 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford the crude alcohol (1.46 g, 97%) which was used directly in the next reaction. For the purpose of characterization a portion of the alcohol was subjected to flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant to afford pure alcohol. $[\alpha]^{20}_D$: −50.1 (*c* 0.63 $CHCl_3$). IR (film) ν: 3498, 2950, 1644, 1470, 1334, 1211, 1150, 1110, 1048 cm^{-1}. ^{1}H NMR δ: 0.92 (d, 3 H, J = 6.9 Hz, CH*Me*), 1.18−1.26 (m, 2 H), 1.36−1.53 (m, 5 H), 1.69−1.98 (m, 4 H), 2.10 (m, 1 H), 2.36−2.44 (m, 3 H), 2.79 (m, 1 H), 2.84, 3.01 (m, 2 × 1 H, H′4 + H′7), 3.23 (d, 1 H, J = 11.7 Hz, CH_2OH), 3.40 (s, 3 H, OMe), 3.45 (d, 1 H, J = 11.7 Hz, CH_2OH′), 3.76−3.98 (m, 4 H, H4, 4′ + H5, 5′), 4.04 (m, 2 H, CH_2OMOM), 4.67 (s, 2 H, OCH_2OMe), 5.06, 5.16 (br s, 2 × 1 H, =CH_2), 6.15 (apparent t, 2 H, J = 1.9 Hz, 2 × =CH). ^{13}C NMR δ: 14.3 (Me), 27.5, 33.5, 34.1 (2 × CH_2 + C), 36.7 (CH), 43.6 (CH_2), 43.8 (CH), 45.2 (CH), 45.4 (CH), 45.6 (CH_2), 49.0 (CH), 52.1 (CH_2), 54.0 (CH), 55.4 (OMe), 56.0 (CH), 63.3 (CH_2), 63.8 (CH_2), 64.9 (CH_2), 68.5 (CH_2), 95.9 (CH_2), 114.4 (=CH_2), 117.1 (C), 133.3, 137.1

(2 × =CH), 148.5 (=C). MS *m/z*: 418 ($M^{+\cdot}$, 13), 387 (28), 373 (12), 357 (18), 321 (35), 291 (27), 277 (15), 234 (20), 221 (77), 157 (25), 139 (34), 91 (64), 66 (100). HRMS: calcd for ($[M + H]^{+\cdot}$ $C_{25}H_{39}O_5$ 419.2798, found 419.2789.

(3′*S*,3a′*S*,4′*R*,7′*S*,7a′*R*,1″*R*,2″*R*,5″*R*)-3′-Methoxymethoxymethyl-3′-[2″-(1‴-methoxymethoxymethylvinyl)-5″-methylcyclopentylmethyl]-2′,3′,3a′,4′,7′,7a′-hexahydro-4′,7′-methanoindene-1′-spiro-2-[1,3]dioxolane. To a stirred solution of the alcohol (1.46 g, 3.5 mmol) and DMAP (64 mg, 0.53 mmol) in DCM (35 mL) at 0 °C under a nitrogen atmosphere were added DIPEA (3.3 mL, 19.3 mmol) and MOMCl (1.33 mL, 17.5 mmol). The reaction mixture was allowed to stir at room temperature for 24 h, diluted with 1.0 M HCl (100 mL), and extracted twice with diethyl ether (150 mL). The combined organic extracts were washed with brine (150 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting crude ether (1.58 g, 97%) was used directly in the next reaction. For the purpose of characterization a portion of the ether was subjected to flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant to afford pure MOM ether. $[\alpha]^{20}_D$: −47.9 (*c* 0.40 $CHCl_3$). IR (film) *ν*: 2949, 1646, 1466, 1335, 1211, 1149, 1107, 1050 cm^{-1}. ^1H NMR *δ*: 0.88 (d, 3 H, *J* = 6.9 Hz, CH*Me*), 1.19 (d, 1 H, *J* = 7.6 Hz), 1.36−2.14 (m, 14 H), 2.32 (m, 1 H), 2.45 (dd, 1 H, *J* = 8.9, 3.7 Hz, H), 2.73 (dd, 1 H, *J* = 8.9, 4.5 Hz), 2.82 (br s, 2 × 1 H, H′4 + H′7), 3.32 (AB d, 2 H, *J* = 9.4 Hz, CH_2OMOM), 3.37, 3.38 (s, 2 × 3 H, 2 × OMe), 3.76−3.84 (m, 4 H, H4, 4′ + H5, 5′), 4.03 (s, 2 H, $=CCH_2OMOM$), 4.58, 4.64 (s, 2 × 2 H, 2 × OCH_2OMe), 4.99, 5.10 (br s, 2 × 1 H, $=CH_2$), 6.09 (dd, 1 H, *J* = 5.6, 2.9 Hz), 6.15 (dd, 1 H, *J* = 5.4, 2.9 Hz). ^{13}C NMR *δ*: 15.0 (Me), 28.3, 33.4, 35.4 (2 × CH_2 + C), 36.5 (CH), 44.0 (CH), 44.2 (CH_2), 45.1 (2 × CH), 46.7 (CH_2), 47.7 (CH), 52.1 (CH_2), 54.0 (CH), 54.3 (CH), 55.2 (OMe), 55.4 (OMe), 63.4 (CH_2), 63.8 (CH_2), 68.9 (CH_2), 71.8 (CH_2), 95.6 (CH_2), 96.9 (CH_2), 110.6 ($=CH_2$), 117.1 (C), 133.0, 137.4 (2 × =CH), 148.5 (=C). MS *m/z*: 462 ($M^{+\cdot}$, 10), 421 (5), 417 (15), 401 (40), 387 (64), 365 (20), 321 (50), 265 (64), 201 (25), 89 (84), 66 (100). HRMS: calcd for ($[M + H]^{+\cdot}$ $C_{27}H_{43}O_6$ 463.3060, found 463.3065.

(3′*S*,3a′*S*,4′*R*,7′*S*,7a′*R*,1″*R*,2″*R*,5″*R*)-3-Methoxymethoxymethyl-3-[2′-(1″-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one (25). A solution of the bisMOM ether (1.6 g, 3.4 mmol) and toluene-4-sulfonic acid (1.29 g, 6.8 mmol) in acetone (50 mL) was stirred at room temperature for 30 min. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed twice with saturated aqueous sodium bicarbonate solution (100 mL). The combined aqueous residues were washed three times with ethyl acetate (75 mL), and the combined organic extracts were washed with brine (200 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, afforded the ketone **25** (1.35 g, 90% over four steps) as a pale yellow oil. $[\alpha]^{20}_D$: −150.5 (*c* 0.50 $CHCl_3$). IR (film) *ν*: 2948, 1732, 1645, 1465, 1404, 1213, 1149, 1108, 1047 cm^{-1}. ^1H NMR *δ*: 0.80 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.30−1.55 (m, 6 H), 1.70−2.30 (m, 8 H), 2.63 (dd, 1 H, *J* = 8.5, 3.5 Hz, H3a), 2.93 (dd, 1 H, *J* = 8.5, 3.5 Hz, H7a), 3.06, 3.14 (br s, 2 × 1 H, H4 + H7), 3.36, 3.39 (s, 2 × 3 H, 2 × OMe), 3.40 (AB d, 2 H, *J* = 9.4 Hz, CH_2OMOM), 3.97 (s, 2 H, $=CCH_2OMOM$), 4.62 (s, 4 H, 2 × OCH_2OMe), 4.92, 5.09 (br s, 2 × 1 H, $=CH_2$), 6.02 (dd, 1 H, *J* = 5.7, 3.1 Hz, =CH), 6.20 (dd, 1 H, *J* = 5.4, 2.8 Hz, =CH). ^{13}C NMR *δ*: 15.5 (Me), 28.1, 33.2, 37.8 (2 × CH_2 + C), 35.8 (CH), 42.9 (CH), 45.5 (CH), 46.5 (CH), 48.2 (CH), 50.2 (CH), 50.2 (CH_2), 52.9 (CH_2), 53.8 (CH), 55.2 (OMe), 55.5 (OMe), 68.7 (CH_2), 71.9 (CH_2), 95.6 (CH_2), 96.6 (CH_2), 111.3 ($=CH_2$), 134.6, 135.6 (2 × =CH), 147.7 (=C), 220.1 (CO). MS *m/z* 418 ($M^{+\cdot}$, <1), 373 (1), 321 (54), 291 (22), 229 (15), 187 (17), 159 (23), 121 (30), 107 (39), 91 (44), 66 (100). HRMS: calcd for $[M + H]^{+\cdot}$ $C_{25}H_{39}O_5$ 419.2798, found 419.2790.

(4*S*,1′*R*,2′*R*,5′*R*)-4-Methoxymethoxymethyl-4-[2′-(1″-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]cyclopent-2-enone (26). A solution of ketone **25** (300 mg, 0.72 mmol) in 1,2-dichlorobenzene (3.0 mL) was heated at 180 °C under a stream of nitrogen gas from a cylinder for 24 h. After being cooled to room temperature, the mixture was subjected to flash chromatography on a column of silica gel using 40% ethyl acetate in hexanes as the eluant to afford enone **26** (243 mg, 96%) as an oil. $[\alpha]^{20}_D$: −31.3 (*c* 0.75 $CHCl_3$). IR (film) *ν*: 2949, 1715, 1675, 1587, 1465, 1442, 1379, 1213, 1150, 1109, 1044 cm^{-1}. ^1H NMR *δ*: 0.80 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.25−2.10 (m, 8 H), 2.23 (m, 1 H), 2.24 (s, 2 H, H5), 3.30 (s, 3 H, OMe), 3.34 (s, 3 H, OMe), 3.45 (AB d, 2 H, *J* = 9.2 Hz, CH_2OMOM), 3.94 (s, 2 H, $=CCH_2OMOM$), 4.55, 4.60 (s, 2 × 2 H, 2 × OCH_2OMe), 4.89, 5.08 (s, 2 × 1 H, $=CH_2$), 6.11 (d, 1 H, *J* = 5.7 Hz, H2), 7.50 (d, 1 H, *J* = 5.7 Hz, H3). ^{13}C NMR *δ*: 15.6 (Me), 28.8 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 35.2 (CH), 42.9 (C), 43.3 (CH_2), 47.6 (CH), 49.7 (CH_2), 55.4 (2 × OMe), 68.9 (CH_2), 73.7 (CH_2), 95.7 (CH_2), 96.5 (CH_2), 112.1 ($=CH_2$), 134.0 (CH, C2), 147.5 (=C), 169.0 (CH, C3), 209.0 (CO). MS *m/z*: 352 ($M^{+\cdot}$, 1), 291 (10), 277 (65), 217 (50), 159 (45), 122 (78), 107 (98), 95 (100), 67 (45). HRMS: calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2247.

(5*S*,1′*R*,2′*R*,5′*R*)-Methyl-2-hydroxy-5-methoxymethoxymethyl-5-[2′-(1″-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]cyclopenta-1,3-dienecarboxylate (27) and (2*S*,1′*R*,2′*R*,5′*R*)-Methyl-2-methoxymethoxymethyl-2-[2′-(1″-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]-5-oxocyclopent-3-enecarboxylate (28). LDA/diethyl ether (1.0 M, 2.76 mL, 27.6 mmol) was added to a stirred solution of enone **26** (243 mg, 6.9 mmol) in diethyl ether (7.0 mL) at −78 °C under a nitrogen atmosphere. After 2 h, methyl cyanoformate (438 *μ*L, 27.6 mmol) was added and the mixture allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with water (2 mL), and after further dilution with water (20 mL) extracted three times with diethyl ether (15 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 20%, increasing to 40% ethyl acetate in hexanes as the eluant, afforded an inseparable mixture of **27** and **28** (280 mg, 97%) as a pale yellow oil. ^1H NMR *δ*: 3.69, 3.73 (s, 3 H, 2× CO_2Me), 6.19 (d, 1 H, *J* = 5.7 Hz), 6.28 (d, 1 H, *J* = 5.7 Hz), 6.86 (d, 1 H, *J* = 5.7 Hz), 7.53 (d, 1 H, *J* = 5.7 Hz).

(5*S*,1′*R*,2′*R*,5′*R*)-Methyl-5-methoxymethoxymethyl-5-[2′-(1″-methoxymethoxymethyl-vinyl)-5′-methylcyclopentylmethyl]-2-trifluoromethanesulfonyloxycyclopenta-1,3-dienecarboxylate. NaH (60% w/w in oil, 137 mg, 3.4 mmol) and *N*-phenyltrifluoromethanesulfonimide (488 mg, 1.36 mmol) were carefully added to a stirred solution of **27/28** (280 mg, 0.68 mmol) in THF (7.0 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, after which time water (5 mL) was carefully added at 0 °C. The resulting mixture was further diluted with water (80 mL) and extracted twice with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 5%, increasing to 10% ethyl acetate in hexanes as the eluant, to afford the triflate (230 mg, 62%) as a colorless oil. $[\alpha]^{20}_D$: −62.6 (*c* 0.74 $CHCl_3$). IR (film) *ν*: 2953, 1713, 1615, 1535, 1431, 1375, 1213, 1143, 1108, 1044 cm^{-1}. ^1H NMR *δ*: 0.75 (d, 3 H, CH*Me*), 1.20−1.40 (m, 3 H), 1.60−2.20 (m, 6 H), 3.26 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.51 (d, 1 H, CH_2OMOM), 3.76 (s, 3 H, CO_2Me), 3.87 (AB d, 2 H, *J* = 13.2 Hz, $=CCH_2OMOM$), 4.00 (d, 1 H, *J* = 8.9 Hz, CH_2OMOM'), 4.50, 4.60 (s, 2 × 2 H, 2 × OCH_2OMe), 4.78, 5.02 (br s, 2 × 1 H, $=CH_2$), 6.32 (d, 1 H, *J* = 5.7 Hz, H3), 6.96 (d, 1 H, *J* = 5.7 Hz, H4). ^{13}C NMR *δ*: 14.7 (Me), 28.9, 29.4, 32.7 (2 × CH_2 + C), 35.8 (CH), 43.4 (CH), 47.1 (OMe), 51.4 (OMe), 55.2 (OMe), 60.8 (CH_2), 68.9 (CH_2),

71.6 (CH_2), 95.6 (CH_2), 96.6 (CH_2), 110.7 (=CH_2), 118.4 (q, J = 319.9 Hz, CF_3), 125.8 (C), 129.4 (CH), 147.6 (=C), 151.6 (C), 153.7 (C), 160.9 (CO_2Me). MS *m/z*: 542 ($M^{+\cdot}$, <1), 448 (10), 435 (32), 333 (85), 301 (100), 271 (70), 241 (86), 213 (88), 121 (55), 93 (62), 67 (41). HRMS: calcd for $C_{26}H_{33}O_9F_3S$ 542.1797, found 542.1792.

(5*S*,1′*R*,2′*R*,5′*R*)-Methyl-2-isopropyl-5-methoxymethoxymethyl-5-[2′-(1″-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]cyclopenta-1,3-dienecarboxylate. *n*-BuLi/hexanes (1.6 M, 398 μL, 0.63 mmol) was added to a stirred solution of thiophene (76 μL, 0.63 mmol) in THF (1.0 mL) at 0 °C under a nitrogen atmosphere. After 20 min, the resulting solution was transferred via a cannula to a stirred suspension of CuCN (57 mg, 0.63 mmol) in THF (2.0 mL) at −78 °C. The mixture was allowed to slowly warm to −40 °C and stirred for a further 30 min after which time the solution was cooled to −78 °C. Isopropylmagnesium chloride/THF (2.0 M, 318 μL, 0.63 mmol) was added, followed by the addition a solution of the triflate (230 mg, 0.42 mmol) in THF (3.0 mL). After 1 h, aqueous ammonium chloride solution (2.0 mL) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (20 mL) and 10% aqueous ammonia solution (10 mL) and then extracted three times with diethyl ether (25 mL). The combined organic extracts were washed with 1.0 M HCl (50 mL) and brine (50 mL) and dried ($MgSO_4$). Concentration in vacuo followed by flash chromatography on a column of silica gel using 10% ethyl acetate in hexanes as the eluant, afforded the product (170 mg, 93%) as an oil. $[\alpha]^{20}_D$: −88.2 (*c* 0.68 $CHCl_3$). IR (film) *ν*: 2950, 1698, 1647, 1603, 1530, 1465, 1435, 1377, 1238, 1150, 1106, 1046 cm^{-1}. ^1H NMR *δ*: 0.71 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.07 (d, 3 H, CH*Me*$_2$), 1.08 (d, 3 H, *J* = 6.9 Hz, CH*Me*$_2$′), 1.10−1.35 (m, 6 H), 1.56 (m, 1 H), 1.70−2.16 (m, 5 H), 3.24 (s, 3 H, OMe), 3.30 (obscured d, 1 H, CH_2OMOM), 3.31 (s, 3 H, OMe), 3.65 (s, 3 H, CO_2Me), 3.70−3.80 (m, 2 H), 3.83 (d, 1 H, *J* = 7.6 Hz, =CCH_2OMOM), 3.98 (d, 1 H, *J* = 8.9 Hz, =CCH_2OMOM′), 4.49 (AB d, 2 H, *J* = 7.0 Hz, OCH_2OMe), 4.56 (AB d, 2 H, *J* = 6.6 Hz, OCH_2OMe′), 4.73, 4.98 (br s, 2 × 1 H, =CH_2), 6.42 (d, 1 H, *J* = 5.4 Hz, H3), 6.75 (d, 1 H, *J* = 5.4 Hz, H4). ^{13}C NMR *δ*: 14.7 (Me), 21.5 (Me), 21.8 (Me), 27.2 (CH), 28.8, 29.2, 32.7 (2 × CH_2 + C), 35.6 (CH), 43.5 (CH), 47.2 (CH), 50.4 (OMe), 55.0 (OMe), 55.1 (OMe), 62.5 (CH_2), 68.7 (CH_2), 73.1 (CH_2), 95.5 (CH_2), 96.5 (CH_2), 110.1 (=CH_2), 129.3 (CH), 129.8 (C), 147.8 (=C), 149.9 (CH), 164.3 (C), 167.2 (CO_2Me). MS *m/z*: 436 ($M^{+\cdot}$, 5), 404 915), 374 (26), 342 (73), 329 (83), 297 (99), 269 (78), 253 (55), 179 (54), 147 (94), 133 (86), 119 (100), 91 (87). HRMS: calcd for $C_{25}H_{40}O_6$ 436.2825, found 436.2826.

(5*S*,1′*R*,2′*R*,5′*R*)-Methyl-5-hydroxymethyl-5-[2′-(1″-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]-2-isopropylcyclopenta-1,3-dienecarboxylate (32). A solution of the bisMOM ether (160 mg, 0.37 mmol), $MgBr_2{\cdot}Et_2O$ (948 mg, 3.7 mmol), and 1-butanethiol (472 μL, 4.4 mmol) in diethyl ether (10 mL) was stirred at room temperature for 24 h. A further portion of reagents was added and the mixture stirred a further 24 h. The resulting solution was then diluted with 1.0 M HCl (50 mL) and extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 20%, increasing to 70% ethyl acetate in hexanes as the eluant, to afford **32** (110 mg, 86%) as a colorless oil. $[\alpha]^{20}_D$: −143.3 (*c* 0.81 $CHCl_3$). IR (film) *ν*: 3400, 2952, 1674, 1601, 1527, 1464, 1436, 1377, 1325, 1244, 1192, 1055 cm^{-1}. ^1H NMR *δ*: 0.76 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.09 (d, 3 H, *J* = 6.7 Hz, CH*Me*$_2$), 1.13 (d, 3 H, *J* = 6.7 Hz, CH*Me*$_2$′), 1.10−1.36 (m, 3 H), 1.56−1.86 (m, 4 H), 2.02−2.18 (m, 2 H), 2.71 (br s, 2 H, 2 × OH), 3.63 (obscured m, 1 H, C*H*Me$_2$), 3.67 (AB d, 2 H, *J* = 10.4 Hz, CH_2OH), 3.74 (s, 3 H, OMe), 3.92 (AB d, 2 H, *J* = 14.4 Hz, =CCH_2OH), 4.73, 5.02 (br s, 2 × 1 H, =CH_2), 6.47 (d, 1 H, *J* = 5.4 Hz, H3), 6.59 (d, 1 H, *J* = 5.4 Hz, H4). ^{13}C NMR *δ*: 15.2 (Me), 21.8 (Me), 21.9 (Me), 27.6 (CH), 28.4, 28.6, 23.9 (2 × CH_2 + C), 35.9 (CH), 43.7 (CH), 47.5 (CH), 51.3 (OMe), 64.0 (CH_2), 64.6 (CH_2), 67.4 (CH_2), 108.8 (=CH_2), 130.3 (CH), 131.1 (C), 149.3 (CH, C4), 151.5 (=C), 166.4 (C), 167.0 (CO_2Me). MS *m/z*: 348 ($M^{+\cdot}$, 5), 330 (40), 300 (42), 285 (57), 241 (45), 225 (37), 178 (47), 133 (70), 119 (100), 105 (94), 91 (91). HRMS: calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2301.

(5*S*,1′*R*,2′*R*,5′*R*)-Methyl-5-[2′-(1″-formylvinyl)-5′-methylcyclopentylmethyl]-5-hydroxymethyl-2-isopropylcyclopenta-1,3-dienecarboxylate (9). Manganese dioxide (250 mg) was added to a solution of diol **32** (50 mg, 0.15 mmol) in diethyl ether (2 mL) at room temperature. After 30 min, the solution was filtered through a pad of Celite and the solvent removed in vacuo to afford pure **9** (50 mg, 100%). $[\alpha]^{20}_D$: −180.0 (*c* 0.38 $CHCl_3$). IR (film) *ν*: 3435, 2954, 1639, 1527, 1464, 1435, 1377, 1324, 1241, 1191, 1096 cm^{-1}. ^1H NMR *δ*: 0.80 (d, 3 H, *J* = 6.9 Hz, CH*Me*), 1.11 (d, 3 H, *J* = 6.7 Hz, CH*Me*$_2$), 1.15 (d, 3 H, *J* = 6.7 Hz, CH*Me*$_2$′), 1.20−1.42 (m, 3 H), 1.64−2.00 (m, 5 H), 2.55 (m, 1 H), 3.54 (d, 1 H, *J* = 10.4 Hz, CH_2OH), 3.65 (obscured m, 1 H, C*H*Me$_2$), 3.74 (s, 3 H, OMe), 3.75 (obscured d, 1 H, CH_2OH′), 5.91 (s, 1 H, =CH_2), 6.09 (s, 1 H, =CH_2′), 6.49 (d, 1 H, *J* = 5.4 Hz, H3), 6.58 (d, 1 H, *J* = 5.4 Hz, H4), 9.48 (s, 1 H, CHO). ^{13}C NMR *δ*: 14.7 (Me), 21.7 (Me), 21.9 (Me), 27.6 (CH), 28.7, 29.3, 32.9 (2 × CH_2 + C), 36.1 (CH), 41.9 (CH), 44.1 (CH), 51.1 (OMe), 62.5 (CH_2), 67.3 (CH_2), 130.3 (CH), 131.1 (=CH_2), 133.4 (C), 149.2 (CH), 153.3 (=C), 166.0 (CO_2Me), 166.8 (C), 194.4 (CHO). MS *m/z*: 346 ($M^{+\cdot}$, 13), 328 (38), 316 (40), 284 (100), 269 (36), 256 (44), 241 (34), 180 (57), 147 (83), 133 (57), 119 (79), 105 (65), 91 (72). HRMS: calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2147.

Methyl 19-Hydroxy-17-oxosordaric-1-en-18-oate (30). A solution of aldehyde **9** (60 mg, 0.17 mmol) in d_8-toluene (1.5 mL) was heated at 40 °C for 3 days after which time the solvent was removed, in vacuo to give pure ester **30** (60 mg, 100%). $[\alpha]^{20}_D$ synthetic: −65.1 (*c* 0.38 $CHCl_3$), natural: −66.4 (*c* 0.38 $CHCl_3$). IR (film) *ν*: 3434, 2955, 2869, 1721, 1435, 1382, 1291, 1268, 1066 cm^{-1}. ^1H NMR *δ*: 0.79 (d, 3 H, *J* = 7.2 Hz, H20), 0.89, 1.05 (d, 2 × 3 H, *J* = 6.9 Hz, H15 + H16), 1.24 (m, 3 H), 1.70−1.80 (m, 3 H), 1.90−2.12 (m, 5 H), 2.25 (sep d, 1 H, *J* = 6.9, 1.0 Hz, H14), 2.58 (t, 1 H, *J* = 4.1 Hz, H3), 3.53, 3.90 (AB d, 2 × 1 H, *J* = 11.3 Hz, CH_2OH), 3.80 (s, 3 H, OMe), 6.08 (dd, 1 H, *J* = 3.5, 1.3 Hz, H2), 9.64 (s, 1 H, CHO). ^{13}C NMR *δ*: 17.4 (Me, C20), 21.0, 22.1 (2 × Me, C15 + C16), 26.5 (CH_2, C11), 27.8 (CH, C14), 27.9, 30.0 (2 × CH_2, C8 + C12), 31.1 (CH, C10), 32.0 (CH_2, C4), 41.3, 41.4, 47.0 (3 × CH, C3, C9 + C13), 52.3 (C, C5), 66.8, 66.9 (2 × C, C6 + C7), 72.6 (CH_2, C19), 130.5 (CH, C2), 147.8 (C, C1), 173.6 (C, C18), 203.7 (CH, C17). MS *m/z*: 346 ($M^{+\cdot}$, 34), 328 (36), 315 (50), 284 (100), 269 (32), 255 (37), 239 (24), 180 (48), 147 (84), 133 (50), 119 (74), 105 (60), 91 (74). HRMS: calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2144.

Sordaricin (3). Freshly distilled propanethiol (700 μL, 7.72 mmol) was added to a stirred suspension of NaH (240 mg, 10 mmol) in HMPA (5.0 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 2 h and then allowed to stand for 1 h to give a 1.35 M solution of propanethiolate. To a dried flask containing the ester **30** (60 mg, 0.17 mmol) and a stirrer bar was added a solution of propanethiolate/HMPA (1.35 M, 2.0 mL, 2.7 mmol) and the solution stirred under a nitrogen atmosphere for 48 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed twice with water (30 mL). The combined aqueous extracts were extracted twice with ethyl acetate (20 mL), and then the combined organic extracts were washed with brine (25 mL) and dried ($MgSO_4$). Concentration in vacuo followed by flash chromatography on a column of silica gel using 20% ethyl acetate in hexanes, then 60% ethyl acetate in hexane as the eluant afforded sordaricin (**3**) (45 mg, 79%) as a white solid that was identical in all respects to an authentic sample of sordaricin (**3**). Mp: 189−191 °C (diethyl ether, DCM and hexanes) (lit.[3] mp 190−191 °C). $[\alpha]^{20}_D$ synthetic: −55.3 (*c* 0.19 MeOH), natural: −58.4 (*c* 0.19 MeOH) [lit.[31] −64 (*c* 0.374 MeOH)]. IR (film) *ν*: 3350, 2954, 2868, 1712, 1446, 1378, 1289,

1234, 1017 cm^{-1}. ^1H NMR (d_5-pyridine) δ: 0.80 (d, 3 H, J = 6.6 Hz, H20), 1.08 (m, 6 H, H15 + H16), 1.48 (d, 1 H, J = 12.5 H, H4α), 1.74 (m, 1 H), 1.95 (m, 5 H), 2.20−2.50 (m, 3 H), 2.72 (sep, 1 H, J = 6.7 Hz, H14), 2.97 (t, 1 H, J = 3.8 Hz, H3), 4.20, 4.37 (AB d, 2 × 1 H, J = 10.5 Hz, CH_2OH), 6.13 (d, 1 H, J = 3.1 Hz, H2), 8.85 (variable br s, 1 H, CO_2H), 10.24 (s, 1 H, CHO). ^{13}C NMR (d_5-pyridine) δ: 17.7 (Me, C20), 21.3, 22.7 (2 × Me, C15 + C16), 26.9 (CH_2, C11), 28.2 (CH, C14), 29.1, 29.7 (2 × CH_2, C8 + C12), 31.6 (CH, C10), 32.4 (CH_2, C4), 41.9, 42.0, 47.1 (3 × CH, C3, C9 + C13), 59.4 (C, C5), 66.9, 67.5 (2 × C, C6 + C7), 73.8 (CH_2, C19), 130.9 (CH, C2), 148.9 (C, C1), 176.0 (C, C18), 204.8 (CH, C17). MS *m/z*: 332 ($M^{+\cdot}$, 24), 314 (33), 302 (40), 284 (90), 256 (37), 241 (40), 227 (35), 166 (64), 147 (67), 119 (64), 105 (72), 91 (100). HRMS: calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1986. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.3; H, 8.5. Found: C, 70.9; H, 8.7. Anal. Calcd for $C_{20}H_{29}O_4$: C, 70.4; H, 8.6.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-3-hydroxy-1-methoxymethoxymethyl-1-[2′-(1′′-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (31). LiHMDS/hexanes (1.0 M, 2.15 mL, 2.15 mmol) was added to a stirred solution of ketone **25** (600 mg, 1.43 mmol) in diethyl ether (2.0 mL) at 0 °C under a nitrogen atmosphere. After 3 h, the solution was cooled to −78 °C and diluted with diethyl ether (4 mL) and methyl cyanoformate (1.1 mL, 14.4 mmol) added. After 20 min, the reaction mixture was allowed to warm to room temperature and stirred for a further 30 min. The reaction mixture was diluted with water (100 mL) and extracted three times with diethyl ether (50 mL). The combined organic residues were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was dissolved in methanol (15 mL) and potassium carbonate (500 mg) added. After 30 min, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 1.0 M HCl (50 mL). The aqueous layer was extracted twice with ethyl acetate (50 mL), and the combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration in vacuo, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded the ester **31** (360 mg, 86% based on recovered starting material) as an oil. Increasing to 20% ethyl acetate in petroleum spirits as the eluant, afforded starting material **25** (230 mg). $[\alpha]^{20}_D$: −111.7 (*c* 0.41 $CHCl_3$). IR (film) ν: 2952, 1766, 1651, 1609, 1443, 1342, 1281, 1256, 1230, 1208, 1107, 1047 cm^{-1}. ^1H NMR δ: 0.90 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.25−1.55 (m, 7 H), 1.60−2.20 (m, 7 H), 2.42 (dd, 1 H, J = 8.5, 3.7 Hz, H7a), 3.10, 3.30 (br s, 2 × 1 H, H4 + H7), 3.34 (m, 1 H, H3a), 3.36 (s, 3 H, OMe), 3.40 (m, 1 H, CH_2OMOM), 3.44 (s, 3 H, OMe), 3.63 (s, 3 H, CO_2Me), 3.65 (m, 1 H, CH_2OMOM'), 3.85 (AB d, 2 H, J = 13.0 Hz, =CCH_2OMOM), 4.60, 4.66 (s, 2 × 2 H, 2 × OCH_2OMe), 4.76, 4.98 (br s, 2 × 1 H, =CH_2), 5.93 (dd, 1 H, J = 5.7, 3.1 Hz), 6.08 (dd, 1 H, J = 5.4, 2.5 Hz), 10.96 (br s, 1 H, OH). ^{13}C NMR δ: 16.4 (Me), 28.8, 29.8, 33.5, 36.1 (3 × CH_2 + C), 36.5 (CH), 42.8 (CH), 45.2 (CH), 46.0 (CH), 47.7 (CH), 48.5 (CH), 49.1 (CH_2), 50.8 (CH), 51.3 (OMe), 52.0 (CH_2), 55.3 (OMe), 55.6 (OMe), 68.9 (CH_2), 73.6 (CH_2), 95.7 (CH_2), 97.3 (CH_2), 104.5 (C), 110.3 (=CH_2), 133.8, 134.4 (2 × =CH), 148.2 (=C), 170.5 (C), 179.1 (*C*O_2Me). MS *m/z*: 445 ([M − OMe]$^{+\cdot}$, 7), 399 (14), 369 (37), 351 (23), 339 (53), 307 (50), 261 (60), 229 (69), 191 (56), 159 (76), 91 (100). HRMS: calcd for ([M − OMe]$^{+\cdot}$ $C_{26}H_{37}O_6$ 445.2590, found 445.2584.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-1-methoxymethoxymethyl-1-[2′-(1′′-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]-3-trifuoromethanesulfonyloxy-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate. NaH (60% w/w in oil, 277 mg, 7.0 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.2 g, 2.8 mmol) were carefully added to a stirred solution of **31** (660 mg, 1.4 mmol) in THF (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, after which time water (5 mL) was carefully added at 0 °C. The resulting mixture was further diluted with water (80 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 5%, increasing to 10%, ethyl acetate in petroleum spirits as the eluant to afford the triflate (740 mg, 89%) as a colorless oil. $[\alpha]^{20}_D$: −17.8 (*c* 1.02 $CHCl_3$). IR (film) ν: 2952, 2251, 1723, 1647, 1426, 1337, 1292, 1212, 1144, 1048 cm^{-1}. ^1H NMR δ: 0.88 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.28 (d, 1 H, J = 8.4 Hz), 1.34−1.62 (m, 4 H), 1.76−2.00 (m, 4 H), 2.16 (m, 2 H), 2.58 (dd, 1 H, J = 8.4, 3.7 Hz), 3.08, 3.25 (br s, 2 × 1 H, H4 + H7), 3.37 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.53 (m, 2 H, H3a + CH_2OMOM), 3.67 (s, 3 H, CO_2Me), 3.78 (d, 1 H, J = 9.7 Hz, CH_2OMOM'), 3.92 (AB d, 2 H, J = 13.2 Hz, =CCH_2OMOM), 4.63, 4.64 (s, 2 × 2 H, 2 × OCH_2OMe), 4.87, 5.04 (br s, 2 × 1 H, =CH_2), 5.96 (dd, 1 H, J = 5.6, 2.9 Hz), 6.17 (dd, 1 H, J = 5.7, 2.8 Hz). ^{13}C NMR δ: 15.8 (Me), 28.4, 33.3 (CH), 36.3 (CH), 36.7, 43.2 (CH), 45.4 (CH), 46.0 (CH), 47.7 (CH), 47.9 (CH), 50.6 (OMe), 51.0 (CH_2), 51.5 (CH), 51.6 (CH_2), 55.2 (OMe), 55.7 (OMe), 68.9 (CH_2), 72.1 (CH_2), 95.5 (CH_2), 97.3 (CH_2), 111.0 (=CH_2), 118.1 (q, J = 319.3 Hz, CF_3), 126.6 (C), 134.1, 135.1 (2 × =CH), 147.9 (=C), 156.6 (C), 161.9 (*C*O_2Me). MS *m/z*: 607 ($M^{+\cdot}$, 2), 501 (12), 434 (12), 369 (20), 348 (58), 301 (41), 241 (40), 215 (41), 79 (40), 66 (100). HRMS: calcd for ([M + H]$^{+\cdot}$ $C_{28}H_{39}O_9F_3S$ 608.2267, found 608.2266.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-3-isopropyl-1-methoxymethoxymethyl-1-[2′-(1′′-methoxymethoxymethylvinyl)-5′-methylcyclopentylmethyl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate. *n*-BuLi/hexanes (1.6 M, 357 μL, 0.58 mmol) was added to a stirred solution of thiophene (91 μL, 0.58 mmol) in THF (1.0 mL) at 0 °C under a nitrogen atmosphere. After 20 min, the resulting solution was transferred via a cannula to a stirred suspension of CuCN (51 mg, 0.58 mmol) in THF (2.0 mL) at −78 °C. The mixture was allowed to slowly warm to −40 °C and stirred for a further 30 min, after which time the solution was cooled to −78 °C. Isopropylmagnesium chloride/THF (2.0 M, 285 μL, 0.58 mmol) was added, followed by the addition a solution of the triflate (170 mg, 0.29 mmol) in THF (3.0 mL). After 1 h, aqueous ammonium chloride solution (2.0 mL) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (20 mL) and 10% aqueous ammonia solution (10 mL) and then extracted three times with diethyl ether (25 mL). The combined organic extracts were washed with 1.0 M HCl (50 mL) and brine (50 mL) and dried ($MgSO_4$). Concentration in vacuo followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant afforded the product (130 mg, 90%) as a pale yellow oil. $[\alpha]^{20}_D$: −110.5 (*c* 0.76 $CHCl_3$). IR (film) ν: 2952, 1705, 1645, 1604, 1434, 1229, 1150, 1107, 1047 cm^{-1}. ^1H NMR δ: 0.88 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.06 (d, 3 H, J = 7.2 Hz, CH*Me*$_2$), 1.10 (d, 3 H, J = 7.2 Hz, CH*Me*$_2$′), 1.20−2.00 (m, 9 H), 2.18 (m, 2 H), 2.44 (dd, 1 H, J = 8.4, 3.7 Hz, H7a), 3.04, 3.12 (br s, 2 × 1 H, H4 + H7), 3.17 (sep, 1 H, J = 6.7 Hz, C*H*Me_2), 3.33, 3.34 (s, 2 × 3 H, 2 × OMe), 3.36 (m, 1 H, H3a), 3.45 (d, 1 H, J = 9.5 Hz, CH_2OMOM), 3.56 (s, 3 H, CO_2Me), 3.60 (d, 1 H, J = 9.5 Hz, CH_2OMOM'), 3.87 (AB d, 2 H, J = 13.9 Hz, =CCH_2OMOM), 4.59, 4.60 (s, 2 × 2 H, 2 × OCH_2-OMe), 4.80, 5.00 (br s, 2 × 1 H, =CH_2), 5.75 (dd, 1 H, J = 5.7, 2.9 Hz), 6.06 (dd, 1 H, J = 5.6, 2.8 Hz). ^{13}C NMR δ: 16.0 (Me), 21.6 (Me), 21.7 (Me), 28.4 (C), 28.8 (CH), 33.6 (CH_2), 36.5 (CH_2), 37.0 (CH_2), 43.1 (CH), 45.8 (CH), 47.8 (CH), 48.2 (CH), 48.3 (CH), 50.5 (CH), 52.2 (CH_2), 53.3 (OMe), 53.7 (CH_2), 55.2 (OMe), 55.5 (OMe), 68.6 (CH_2), 73.2 (CH_2), 95.6 (CH_2), 97.3 (CH_2), 110.6 (=CH_2), 131.2 (C), 134.5, 135.2 (2 × =CH), 148.1 (=C), 165.0 (C), 166.1 (*C*O_2Me). MS *m/z*: 502 ($M^{+\cdot}$, 3), 404 (37), 374 (52), 342 (100), 300 (90), 269 (39), 243 (55), 119 (40), 81 (40), 66 (52). HRMS: calcd for $C_{30}H_{46}O_6$ 502.3294, found 502.3298.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-1-hydroxymethyl-1-[2′-(1″-hydroxymethylvinyl)-5′-methylcyclopentylmethyl]-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (34). A solution of the MOM ether (200 mg, 0.4 mmol), $MgBr_2{\cdot}Et_2O$ (823 mg, 3.2 mmol), and 1-butanethiol (299 μL, 2.8 mmol) in diethyl ether (10 mL) was stirred at room temperature for 24 h. A further portion of reagents was added and the mixture stirred a further 24 h. The resulting solution was then diluted with 1.0 M HCl (50 mL) and extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was subjected to flash chromatography on a column of silica gel using 20%, increasing to 70% ethyl acetate in hexanes as the eluant, to afford **34** (153 mg, 92%) as a colorless oil. $[\alpha]^{20}_D$: −78.6 (*c* 0.59 $CHCl_3$). IR (film) *ν*: 3429, 2955, 1765, 1702, 1436, 1252, 1121, 1042 cm^{-1}. ^1H NMR *δ*: 0.88 (d, 1 H, *J* = 7.0 Hz, CH*Me*), 1.05 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$), 1.13 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$′), 1.26 (d, 1 H, *J* = 8.1 Hz), 1.38 (m, 2 H), 1.50 (d, 1 H, *J* = 8.1 Hz), 1.60−1.90 (m, 5 H), 2.20 (m, 2 H), 2.43 (dd, 1 H, *J* = 8.4, 3.8 Hz, H7a), 2.97, 3.07 (br s, 2 × 1 H, H4 + H7), 3.23 (sep, 1 H, *J* = 6.9 Hz, C*H*Me$_2$), 3.39 (dd, 1 H, *J* = 8.4, 4.5 Hz, H3a), 3.56 (d, 1 H, *J* = 11.3 Hz, CH_2OH), 3.66 (s, 3 H, OMe), 3.75 (d, 1 H, *J* = 11.3 Hz, CH_2OH′), 3.98 (AB d, 2 H, *J* = 14.4 Hz, $=CCH_2OH$), 4.78, 5.03 (br s, 2 × 1 H, $=CH_2$), 5.73 (dd, 1 H, *J* = 5.7, 2.9 Hz), 6.04 (dd, 1 H, *J* = 5.7, 2.9 Hz). ^{13}C NMR *δ*: 16.2 (Me), 21.6 (Me), 21.8 (Me), 28.0, 28.9 (CH), 33.6, 35.7, 36.5 (CH), 42.4 (CH), 45.3 (CH), 47.8 (CH), 48.5 (2 × CH), 51.4 (CH), 52.5 (CH_2), 52.8 (Me), 54.6 (CH_2), 64.0 (CH_2), 66.9 (CH_2), 109.4 ($=CH_2$), 132.0 (C), 134.1, 134.3 (2 × =CH), 151.9 (=C), 165.0 (C), 168.1 (*C*O_2Me). MS *m/z*: 382 ([M − MeOH]$^{+\cdot}$, 17), 357 (13), 287 (26), 244 (83), 215 (42), 197 (48), 121 (50), 109 (75), 91 (100), 66 (75). HRMS: calcd for ([M − MeOH]$^{+\cdot}$ $C_{25}H_{34}O_3$ 382.2508, found 382.2505.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-1-[2′-(1″-formylvinyl)-5′-methylcyclopentylmethyl]-1-hydroxymethyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindene-2-carboxylate (8). Manganese dioxide (600 mg) was added to a solution of diol **34** (120 mg, 29.0 mmol) in diethyl ether (3 mL) at room temperature. After 30 min, the solution was filtered through a pad of Celite and the solvent removed in vacuo to afford pure **8** (120 mg, 100%). $[\alpha]^{20}_D$: −133.8 (*c* 0.50 $CHCl_3$). IR (film) *ν*: 3467, 2957, 1694, 1601, 1466, 1434, 1345, 1233, 1122, 1016 cm^{-1}. ^1H NMR *δ*: 0.90 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.04 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$), 1.13 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$′), 1.23 (d, 1 H, *J* = 7.2 Hz), 1.40−1.52 (m, 4 H), 1.73 (dd, 1 H, *J* = 14.4, 8.4 Hz), 1.80−1.98 (m, 3 H), 2.24 (m, 1 H), 2.37 (dd, 1 H, *J* = 8.5, 3.8 Hz, H7a), 2.58 (m, 1 H), 2.91, 3.06 (br s, 2 × 1 H, H4 + H7), 3.20 (sep, 1 H, *J* = 7.0 Hz, C*H*Me$_2$), 3.28 (br s, 1 H, OH), 3.36 (dd, 1 H, *J* = 8.4, 4.4 Hz, H3a), 3.49 (br d, 1 H, CH_2OH), 3.64 (s, 3 H, OMe), 3.70 (d, 1 H, *J* = 11.3 Hz, CH_2OH′), 5.71 (dd, 1 H, *J* = 5.7, 2.9 Hz), 5.88, 6.12 (br s, 2 × 1 H, $=CH_2$), 6.00 (dd, 1 H, *J* = 5.6, 2.9 Hz), 9.43 (s, 1 H, CHO). ^{13}C NMR *δ*: 15.8 (Me), 21.5 (Me), 21.8 (Me), 28.7 (CH_2), 28.9 (CH), 29.7, 33.6, 35.9 (2 × CH_2 + C), 37.1 (CH), 43.4 (CH), 43.5 (CH), 45.1 (CH), 47.9 (CH), 48.4 (CH), 51.2 (CH), 52.5 (CH_2), 52.6 (OMe), 54.4 (CH_2), 66.6 (CH_2), 132.1 ($=CH_2$), 134.1 (2 × =CH), 153.5 (C, =*C*CHO), 165.6 (C), 167.8 (*C*O_2Me), 194.3 (CHO). MS *m/z*: 412 (M$^{+\cdot}$, <1), 380 (5), 346 (9), 328 (45), 284 (100), 256 (30), 180 (35), 147 (55), 119 (50), 91 (52), 66 (56). HRMS: calcd for $C_{26}H_{36}O_4$ 412.2614, found 412.2615.

Methyl 19-Hydroxy-17-oxo-sordaric-1-en-18-oate (33) and Isomethyl 19-Hydroxy-17-oxosordaric-1-en-18-oate (*iso*-30). A solution of aldehyde **8** (30 mg, 73 μmol) in dichlorobenzene (1.0 mL) was heated at 180 °C under a stream of nitrogen gas from a cylinder for 1 h. After being cooled to room temperature, the mixture was subjected to flash chromatography on a column of silica gel using 100% hexanes then 15% ethyl acetate in hexanes as the eluant, to afford an inseparable 4:1 mixture of **30** and *iso*-**30** (19 mg, 76%) as a white solid. The mixture was then used in the next reaction.

Sordaricin (3) and *iso*-Sordaricin (*iso*-3). Freshly distilled propanethiol (700 μL, 7.72 mmol) was added to a stirred suspension of hexane-washed NaH (240 mg, 10 mmol) in HMPA (5.0 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 2 h and then allowed to stand for 1 h to give a 1.35 M solution of propanethiolate. To a dried flask containing a 1:1 mixture of **30** and *iso*-**30** (70 mg, 0.2 mmol) and a stirrer bar was added a solution propanethiolate/HMPA (1.35 M, 2.5 mL, 3.4 mmol) and the solution stirred under a nitrogen atmosphere for 48 h. The reaction mixture was diluted with ethyl acetate (15 mL) and washed twice with water (50 mL). The combined aqueous extracts were extracted twice with ethyl acetate (15 mL), then the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). Concentration in vacuo followed by flash chromatography on a column of silica gel using 20% ethyl acetate in hexanes and then 60% ethyl acetate in hexane as the eluant afforded a mixture of sordaricin (**3**) and isosordaricin (*iso*-**3**, 50 mg combined). The mixture was dissolved in HPLC grade acetonitrile (3 mL) and 50:50:0.05 water/acetonitrile/acetic acid (5 drops) and subjected to semipreparative HPLC separation using a mixture of 55% acetonitrile (containing 0.005% acetic acid) and 45% water (containing 0.005% acetic acid), at a flow rate of 5.0 mL/min. The compounds were detected at 210 nm. Concentration of the fractions containing the first eluting compound afforded isosordaricin (*iso*-**3**, 17 mg, 25% from mixture of esters). Concentration of the fractions containing the second eluting compound afforded sordaricin (**3**, 25 mg, 38%), which was identical in all respects to an authentic sample. **Isosordaricin (*iso*-3).** $[\alpha]^{20}_D$: −35.7 (*c* 0.23 $CHCl_3$). IR (film) *ν*: 3413, 2956, 1703, 1649, 1465, 1255, 1096, 1017, 800 cm^{-1}. ^1H NMR (d_5-pyridine) *δ*: 0.73 (d, 3 H, *J* = 7.0 Hz, H20), 1.07, 1.09 (2 × d, 2 × 3 H, *J* = 6.7 Hz, H15 + H16), 1.11 (obscured m, 2 H), 1.40 (m, 1 H), 1.55 (m, 1 H), 1.75−2.08 (m, 6 H), 2.39 (d, 1 H, *J* = 12.7 Hz), 2.49 (d, 1 H, *J* = 12.7 Hz, *exo*-H5), 2.84 (d, 1 H, *J* = 12.7 Hz, *endo*-H5), 2.95 (m, 1 H, H14), 3.50 (d, 1 H, *J* = 3.2 Hz, H3), 4.26, 4.41 (2 × AB d, 2 × 1 H, *J* = 10.5 Hz, H19,19′), 5.68 (br s, 1 H, H2), 6.85 (variable br s, 1 H, CO_2H), 9.80 (s, 1 H, H17). ^{13}C NMR (d_5-pyridine) *δ*: 17.7 (Me, C20), 20.9, 22.1 (2 × Me, C15 + C16), 26.2 (CH_2), 28.4 (CH, C14), 28.6 (CH_2), 29.8 (CH, C10), 34.3 (CH_2), 37.8 (C, C6), 46.3 (CH), 46.4 (CH_2, C5), 46.8 (CH), 49.6 (CH), 58.3 (C, C4), 65.3 (CH_2, C19), 69.5 (C, C7), 121.3 (CH, C2), 158.4 (C, C1), 175.8 (C, C18), 203.9 (CH, C17). MS *m/z*: 332 (M$^{+\cdot}$, 7), 314 (25), 302 (72), 284 (100), 274 (44), 256 (40), 241 (34), 227 (25), 166 (51), 147 (62), 133 (37), 105 (50), 91 (66). HRMS: calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1985.

Methyl 17,19-Dihydroxysodaric-1-en-18-oate (33). A solution of diol **34** (15 mg, 36 μmol) in 1,2-dichlorobenzene (1.0 mL) was heated at 180 °C under a stream of nitrogen gas from a cylinder for 3 h. After being cooled to room temperature, the mixture was subjected to flash chromatography on a column of silica gel using 100% hexanes then 30%, increasing to 50%, ethyl acetate in hexanes as the eluant to afford diol **33** (8 mg, 64%) as a white solid. $[\alpha]^{20}_D$: −70.4 (*c* 0.27 $CHCl_3$). IR (film) *ν*: 3400, 2953, 1718, 1697, 1435, 1295, 1270, 1028 cm^{-1}. ^1H NMR *δ*: 0.21 (d, 1 H, *J* = 12.5 Hz, H4α), 0.76 (d, 3 H, *J* = 6.7 Hz, H20), 0.87, 1.12 (d, 2 × 3 H, *J* = 6.6 Hz, H15 + H16), 1.20 (obscured m, 3 H), 1.60−2.10 (m, 9 H), 2.47 (sep, 1 H, *J* = 6.6 Hz, H14), 2.55 (t, 1 H, *J* = 4.3 Hz, H3), 3.24, 3.37 (AB d, 2 × 1 H, *J* = 12.2 Hz, H17), 3.67, 3.72 (AB d, 2 × 1 H, H19), 3.78 (s, 3 H, OMe), 5.95 (d, 1 H, *J* = 2.2 Hz, H2). ^{13}C NMR *δ*: 17.5 (Me, C20), 20.9, 22.4 (2 × Me, C15 + C16), 26.2 (CH_2, C11), 27.7 (CH, C14), 28.9 (CH_2, C12), 31.8 (CH, C10), 31.9, 32.2 (2× CH_2, C4 + C8), 41.5, 42.5, 45.0 (3 × CH, C3, C9 + C13), 50.4 (C, C5), 52.2 (OMe), 67.1, 67.2, 68.4, 71.4 (2 × C + 2 × CH_2, C6, C7, C17 + C19), 128.7 (CH, C2), 149.0 (C, C1), 176.7 (C, C18). MS *m/z*: 348 (M$^{+\cdot}$, 5), 330 (70), 317 (46), 299 (59), 285 (100), 257 (40), 225 (26), 197 (32), 147 (70), 119 (78), 105 (70), 91 (86), 81 (75). HRMS: calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2298.

Acknowledgment. We thank Dr. Jim Balkovec (Merck) for an authentic sample of sordaricin. Amano Pharmaceuticals is thanked for supplying the lipase used for the preparation of enantiopure **10**.

Supporting Information Available: All experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048199B