Total Synthesis of (±)-Heptelidic Acid

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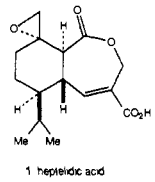
Abstract: The total synthesis of the title compound in 13 steps from 4-isopropylcyclohexanone has been accomplished. The key phases were the following: (i) the use of a cuprate derivative of a diprotected bis allylic alcohol for conjugate addition (see **19b** + **13** → **20**); (ii) the use of an allysilane (**22**) as a precursor for a methylenecyclohexane in which the silane was prepared by a $Ni(acac)_2$-catalyzed cross-coupling reaction of an enol phosphate with [(trimethylsilyl)methyl]magnesium chloride (**21** → **22**); (iii) the stereospecific epoxidation of a methylenecyclohexane derivative (**27**) with *tert*-butyl hydroperoxide–molybdenum hexacarbonyl. The stereochemical course of this epoxidation reaction is opposite to that brought about by *m*-chloroperoxybenzoic acid.

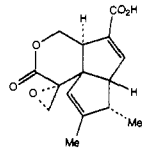
Background

Heptelidic acid (**1**),[1,2] previously called avocettin,[3] was isolated from the cultures of three fungi by Sankyo scientists as part of a screening program for new antibiotics. Subsequently, in the context of a screening program seeking microbially derived inhibitors of lipid biosynthesis, Endo and co-workers isolated koningic acid from a strain of *Trichoderma koningii*.[4] Structural studies disclosed heptelidic acid and koningic acid to be the same substance.

Biochemical investigations revealed the cholesterol-lowering properties of heptelidic acid to be indirect. The compound does not inhibit any known enzymes in the sterol biosynthesis pathway. Rather, its effect arises from its inhibition of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase. It thereby alters the balance of ATP generation. The effect on sterol biosynthesis arises from blockage of the conversion of mevalonate pyrophosphate to isopentenyl pyrophosphate. Though mediated by mevalonate pyrophosphate decarboxylase, this process is ATP dependent and is thus inhibited by **1**.



1 heptelidic acid

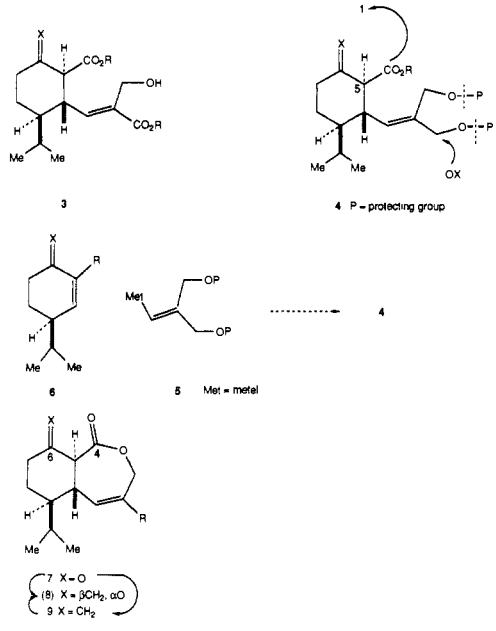


2 pentalenolactone

Another inhibitor of glyceraldehyde-3-phosphate dehydrogenase is the antibiotic pentalenolactone (**2**).[5] In very general terms, there are elements of structural similarity between hepteldic acid and pentalenolactone (epoxide, lactone, and α,β-unsaturated carboxyl functions). We had previously achieved the total synthesis of pentalenolactone, though only after a multistep effort, which was plagued by several low-yielding steps.[6a,b] Our hope in the case of heptelidic acid was to realize a total synthesis, which would not only produce significant amounts of the natural product but could also provide access to closely related congeners for probing structure–activity relationships.

Synthetic Planning

A proposal that contemplates reaching heptelidic acid via cyclization of the seco acid equivalent **3** must deal with control of



3 4 P = protecting group 6 5 Met = metal 7 X = O (8) X = βCH_2, αO 9 X = CH_2

the geometry of the double bond. While this could possibly be achieved, a simplification presented itself wherein the substrate to undergo cyclization would be a bis allylic alcohol of the type **4**. The cause of synthetic directness would be well served if access to the bis allylic alcohol moiety could be achieved via a consolidated unit **5**. In this expression, P refers to a suitable protecting group and Met implies a metal appropriate for mediating nucleophilic character. Reaction of **5** with **6** would generate the ensemble required to reach **4**. It seemed likely that the addition of **5** would occur anti to the isopropyl group of **6**.

The variation wherein X = O and R = carboalkoxy would presumably favor the efficiency of the 1,4-addition. It would also obviate the need for what might otherwise turn out to be an awkward de novo introduction of a carboxy equivalent at carbon 5[7a,b] via an unsubstituted version of **6**.

A potentially challenging substructural unit from a synthetic standpoint was the C_6–C_7 spiroepoxide entity β,γ to the C_4 carbonyl group.[8] When issues of stereochemistry are neglected for the moment, two obvious approaches suggested themselves. In one version the epoxide would arise via methenylation of a ketone (cf. **7** → **8**). Alternatively, the oxirane would arise from epoxidation of **9** (cf. **9** → **8**). In principle, the exocyclic methylene compound **9** might itself be derived from ketone **7**. Both of these approaches to the spiroepoxide via ketone **7** were not without potential difficulties in that they each would require carbon–carbon

(1) Itoh, Y.; Kodama, K.; Furuya, K.; Takahashi, S.; Haneishi, T.; Takiguchi, Y.; Arai, M. *J. Antibiot.* **1980**, *33*, 468–473. Itoh, Y.; Takahashi, S.; Tatsuo, H.; Arai, M. *Ibid.* 525–526.

(2) Stipanovic, R. D.; Howell, C. R. *Tetrahedron* **1983**, *39*, 1103–1107.

(3) Hagenbach, A. *Diss. Eidgenossische Technishce Hochschule, Zurich, Switzerland, Prom. N.* **1971**, 4674. Arigoni, D. *Pure Appl. Chem.* **1975**, *41*, 219–245.

(4) Endo, A.; Hasumi, K.; Sakai, K.; Kanbe, T. *J. Antibiot.* **1985**, *38*, 920–925.

(5) Hartman, S.; Neeff, J.; Mecke, D. *FEBS Lett.* **1978**, *93*, 339–342.

(6) (a) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536. *Ibid.* **1979**, *101*, 7020. (b) Parsons, W. H.; Schlessinger, R. H.; Quesada, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 889.

(7) (a) The numbers used in the discussion correspond to the crystallographic numbering system provided by Stipanovic.[2] (b) Cf.: Danishefsky, S. J.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *22*, 703.

(8) Still, W. C., Jr.; Lewis, A. J.; Goldsmith, D. *Tetrahedron Lett.* **1971**, 1421. Epstein, W. W.; Sonntag, A. C. *J. Org. Chem.* **1967**, *32*, 3390.

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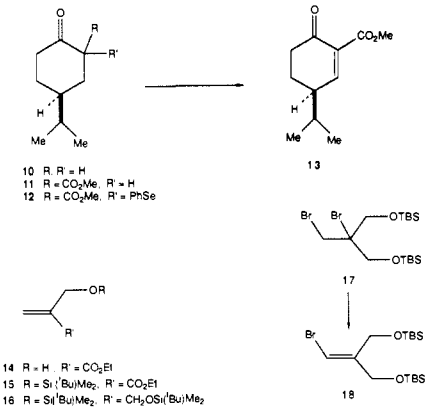
bond formation (7 → 8 or 7 → 9), utilizing the "ketone" of a likely enolizable β-keto ester (or lactone). Below we report a concise total synthesis of heptelidic acid. In this synthesis, the bis allylic alcohol is introduced in the manner contemplted, and the potentially serious complications associated with the "β-dicarbonyl" route to the spiroepoxide are satisfactorily resolved.

Discussion of Results

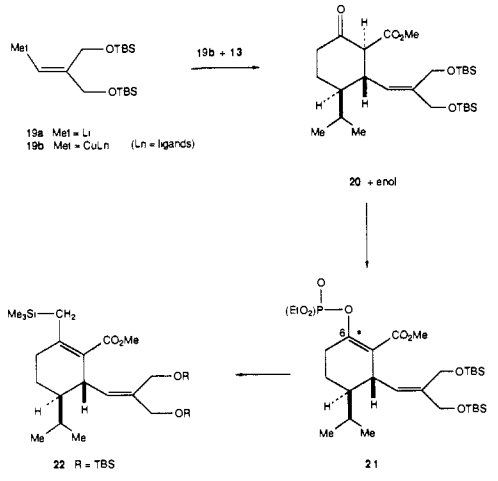
Commercially available 4-isopropylcyclohexanone (**10**)[9] was converted to **11** (90%) by carbomethoxylation under standard conditions.[10a] The selenenylated β-keto ester **12**, prepared in the



usual way,[10b] upon treatment with hydrogen peroxide provided the desired **13** (91% from **12**). With a satisfactory route to a specific version of electrophile **6** well in hand, attention was directed to obtaining a workable equivalent of **5**.

The plan called for synthesizing the bromoolefin **18**. In further pursuit of that goal the known ester alcohol **14**[11] was converted (96%) to its *tert*-butyldimethylsilyl derivative **15**. Reduction of **15** with DIBAH followed by protection, again with TBSCl, gave **16** in 86% overall yield. This compound after exposure to bromine in methylene chloride, gave rise to dibromide **17**. Treatment of **17** with DBU in benzene did indeed complete the route to the desired **18** (68% from **16**).

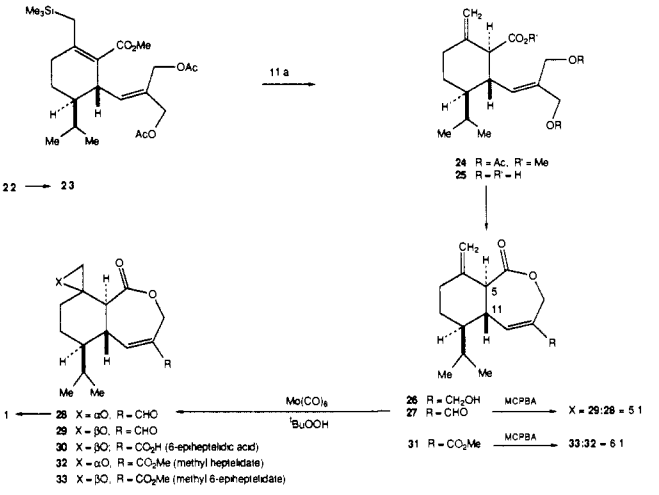
Bromide **18** was subjected to the action of 1.9 equiv of ^{t}BuLi in ether at −78 °C. The presumed lithium reagent, **19a**, was



treated with lithium 2-thienylcyanocuprate to generate, ostensibly, the higher order cuprate, **19b**.[12] Reaction of **19b** with freshly prepared **13**[13] in THF at −78 °C gave rise to the somewhat labile ester **20**. Compound **20** was obtained as a keto–enol mixture (of varying ratios), which was not suitable for purification by silica gel chromatography. Accordingly, the crude material was treated with sodium hydride and diethyl chlorophosphate, THF, from 0 °C to room temperature. There was thus obtained a 74% yield of the homogeneous enol phosphate **21**.[14]

The phosphorylation had served to confer stability on the adduct system. It served another valuable purpose in that it provided an exploitable electrophilic center at carbon 6 (see asterisk) for carbon–carbon bond formation at C_6 without interference from enolization. Indeed, a cross-coupling reaction[15] of **21** with [(trimethylsilyl)methyl]magnesium chloride[16] in the presence of catalytic Ni(acac)$_2$ in THF produced an 86% yield of the allylic silane **22**.

Prior to unveiling the exocyclic methylene group, it seemed prudent to arrange for base labile blocking groups on the bis allylic alcohol. This subgoal was readily accomplished through the action of ferric chloride–acetic anhydride[17] on **22** to give the diacetate **23**.



At this stage the plan called for unveiling the exocyclic methylene group by protodesilylation of the allylic silane.[18] In the event, reaction of **23** with trifluoracetic acid in methylene chloride gave a 70% yield of an excocylic methylene compound, formulated as **24**. Analysis of the crude reaction mixture indicated the presence of ca. 15% of another exocyclic methylene isomer, presumably the C_5 epimer of **24**. That the major compound is properly formulated as **24** is suggested from analysis of its high-field NMR spectrum where in the proton at C_5 is revealed to be axial ($\delta(H_5) = 2.92$; $J_{5,6} = 11$ Hz). The preferred formation of **24** can be rationalized in terms of axial protonation of the allylic silane. The possibility that **24** is being produced via thermodynamic control was not explored.

At this juncture the acetates were easily cleaved with aqueous sodium hydroxide. The resulting diol acid **25** was not characterized but instead was lactonized with bis(2-oxo-3-oxazolidinyl)phosphinic chloride.[19] This procedure provided a 70% yield of lactone **26**. To improve the possibilities for differentiation of the two double bonds of the diene with respect to electrophilic attack in the desired C_6–C_7 sense, the allylic alcohol function was oxidized to the enal. Jones reagent provided an 86% yield of the epoxidation substrate, **27**.

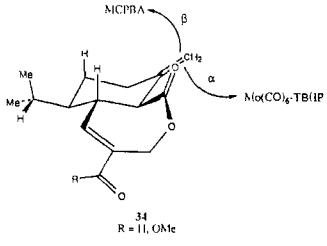
An early probe involving reaction of **27** with *m*-chloroperoxybenzoic acid proved to be discouraging. A mixture of two epoxides, ca. 5:1,[20] was obtained. Analysis of the ^{1}H NMR spectra of the

(9) 4-Isopropylcyclohexanone can be obtained from Pfaltz and Bauer Research Chemicals.
(10) (a) Ruest, L.; Blouin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6*, 169–174. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5446.
(11) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924–926.
(12) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945–948.
(13) Increasing amounts of the dienol form of **20** were produced upon standing.
(14) Alderdice, M.; Sum, F. W.; Weiler, L. *Org. Synth.* **1984**, *62*, 14–23.
(15) Armstrong, R. J.; Harris, F. L.; Weiler, L. *Can. J. Chem.* **1982**, *60*, 673–675.
(16) Available from Aldrich Chemical Co.
(17) Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *34*, 3728.
(18) Cf.: Seyferth, D.; Wuisthorn, K. R.; Mammarella, R. E. *J. Org. Chem.* **1977**, *42*, 3104.
(19) Diago-Meseguer, J.; Palomo-Coll, A. L. *Synthesis* **1980**, 547–551.
(20) This ratio was determined by analysis of the ^{1}H NMR (250 MHz) spectrum of the crude reaction mixture.

mixture in conjunction with the spectrum of heptelidic acid methyl ester suggested that it was the *minor* isomer that corresponded in its relative stereochemistry to the natural product. This view was subsequently confirmed (vide infra).

A much more satisfying result was obtained by recourse to *tert*-butyl hydroperoxide (TBHP)–molybdenum hexacarbonyl[21] in benzene under reflux. There was thus produced a 49% yield of **28**. At most only traces of **29**, the major product of the *m*-CPBA reaction, were produced in this reaction.[22] Lindgren oxidation[23] of **28** ($NaClO_2$; NaH_2PO_4, aqueous *tert*-butyl alcohol) afforded a 90% yield of *dl*-heptelidic acid (**1**). *The NMR and infrared spectra of fully synthetic* **1** *were identical with those of a sample of the natural product provided by Dr. R. D. Stipanovic.*[24] Similarly, Lindgren oxidation of **29** provided *dl*-6-epiheptelidic acid (**30**). The spectral properties of **30** differed from those obtained from the Stipanovic specimen. We also note that substantially the same results were realized when epoxidation reactions were carried out on the ene ester **31**.[25] Thus, epoxidation of **31** with MCPBA afforded a 6:1 ratio of methyl 6-epiheptelidate (**33**)[26] and methyl heptelidate (**32**). By contrast, epoxidation with $Mo(CO)_6$–TBHP cleanly afforded methyl heptelidate (**32**) in 57% yield.

Though the precise factors that produce the strikingly different results in the two epoxidations are not known, some insights in this matter may be gained from the crystal structure[2] of acid **1** reported by Stipanovic.[2] The assumption is made that the conformations of the ene compounds (**27** and **31**) are not materially different from those of the oxirane system **1**. The consistency of the 12-Hz coupling between H_5 and H_{11} in all three compounds supports this supposition. If it is further assumed that the solid-state conformation of **1** is simulated in solution, stereostructure **34** can be considered for the epoxidation precursors.



It seems that β-face attack corresponds to attack from the more hindered face than does α-face attack from two standpoints. β-Face epoxidation corresponds to axial entry of the oxidant at C_6. Moreover, the trajectory for this attack brings the electrophile relatively close to the C_5–lactonic carbonyl bond. The $Mo(CO)_6$–TBHP result (i.e., clean α-attack) is in accord with the expected approach of the oxidant from the much more open α-face.

The tendency of molybdenum-mediated oxidations to take on a sharply different diastereofacial course from that of MCPBA is precedented both with acyclic unsaturated alcohols and with cycloalkenes.[27a,b] Moreover, there is precedent for apparent axial preference in the attack of peracids on conformationally defined methylenecycloalkanes, though the reason for this preference is not clear.[28] The very high proclivity for β-face (more hindered) attack of MCPBA in the case of **27** and **31** may reflect an as yet undefined bonding stabilization between the peracid and the lactone, though this is not established by the data at hand.

In any case, a straightforward fully synthetic route to racemic **1** has been developed. By extension, a route to either antipode is also available. Pathways to the 6-epi system and to the Δ^6 system, neither of which was previously known, are also now available. From such compounds might well arise a fuller definition of the structural requirements for inhibition of glyceraldehyde-3-phosphate dehydrogenase.

Experimental Section

2-(Methoxycarbonyl)-4-(1-methylethyl)cyclohexan-1-one (11). To a stirred mixture of dimethyl carbonate (33.1 mL, 392 mmol), NaH (12.6 g, 471 mmol), and KH (627 mg, 17.7 mmol) in THF (200 mL) at room temperature was added approximately 7 mL of a THF (50 mL) solution of 4-isopropylcyclohexanone **10** (22 g, 157 mmol). The solution was heated to reflux, and the remaining substrate was added over a period of 30 min. After complete addition, the mixture was heated for an additional 50 min and cooled to 0 °C, and the reaction was carefully quenched with a 3% aqueous HOAc solution (100 mL). Extractive workup and distillation [83–84 °C (0.6 mmHg)] gave 28 g (90%) of **11** as a clear oil (enol form): IR ($CDCl_3$) 2960, 2875, 1740, 1715, 1660, 1615, 1445, 1355, 1310, 1270, 1230, 1210, 1100, 820 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 12.11 (s, 1 H), 3.74 (s, 3 H), 2.39–2.28 (m, 3 H), 1.93–1.75 (m, 2 H), 1.65–1.46 (m, 1 H), 1.37–1.20 (m, 2 H), 0.90 (d, 6 H, J = 7 Hz). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.90; H, 9.32.

2-(Methoxycarbonyl)-4-(1-methylethyl)cyclohex-2-en-1-one (13). β-Keto ester **11** (22.0 g, 111 mmol) was added dropwise to a stirred, cooled (0 °C) suspension of hexane-washed NaH (6.65 g of a 60% dispersion, 166 mmol) in THF (400 mL). After the addition was complete, the mixture was warmed to room temperature for 1 h and then cooled (0 °C). A solution of phenylselenyl chloride (25.5 g, 133 mmol) in THF (75 mL) was added in one portion. The reaction was warmed to room temperature and quenched with saturated aqueous $NaHCO_3$ (400 mL). Extractive workup (EtOAc) and flash chromatography (SiO_2, 10% hexane–EtOAc) gave 36.5 g (93%) of selenide **12** (thick oil) as a mixture of cis and trans isomers: ^1H NMR (90 MHz, $CDCl_3$) δ 7.78–7.55 (m, 2 H), 7.45–7.20 (m, 3 H), 3.75 and 3.68 (2 s, integrated ratio = 2:1, 3 H), 2.72–1.24 (m, 8 H), 190 (apparent t, 6 H).

To a vigorously stirred solution of selenide **12** (28 g, 79.2 mmol) in dichloromethane (150 mL) was added 5 mL of a solution of H_2O_2 (13.5 mL of a 30% aqueous solution, 119 mmol) in water (30 mL). After 10 min, the solution turned yellow and was cooled to 0 °C, and the remaining H_2O_2 was added dropwise. The mixture was stirred until a precipitate formed. Analysis by TLC indicated consumption of the starting material (ca. 20 min). Saturated aqueous $NaHCO_3$ (200 mL) was added, the mixture was extracted with dichloromethane, and the combined organic layers were successively washed with saturated aqueous $NaHCO_3$ and brine. Drying ($MgSO_4$) and concentration provided 15.3 g (98%) of enolate **13** (oil) as a 13:1 mixture of keto/enol forms. Attempts to further purify the product (distillation or SiO_2 chromatography) resulted in increasing enolization: IR ($CDCl_3$) 2960, 2870, 1740, 1715, 1685, 1280 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.62 (t, 1 H, J = 2 Hz), 3.79 (s, 3 H), 2.59 (dt, 1 H, J = 16, 4 Hz), 2.49–2.34 (m, 2 H), 2.12–1.72 (m, 3 H), 0.99 (d, 3 H, J = 3.6 Hz), 0.97 (d, 3 H, J = 3.6 Hz). HRMS (EI) for $C_{11}H_{16}O_3$, calcd 196.1099, found 196.1094.

1-(*tert*-Butyldimethylsiloxy)-2-[(*tert*-butyldimethylsiloxy)methyl]-2,3-dibromopropane (17). Triethylamine (79.6 mL, 571 mmol) and 4-(dimethylamino)pyridine (2.32 g, 19.0 mmol) were added to a stirred mixture of 2-(hydroxymethyl)ethyl acrylate[11] (24.8 g, 190 mmol) and *tert*-butyldimethylsilyl chloride (29.0 g, 192 mmol) in dichloromethane (400 mL) at 0 °C. After 1 h, the mixture was warmed to room temperature and stirred for an additional 9 h. The resulting slurry was filtered and successively washed with cold 1 N aqueous HCl (475 mL), saturated aqueous sodium bicarbonate (400 mL), and brine (200 mL). Drying ($MgSO_4$) and concentration gave 45 g (96%) of crude siloxy ethyl ester **15** as a clear oil: ^1H NMR (90 MHz, $CDCl_3$) δ 6.24 (s, 1 H), 5.87 (s, 1 H), 4.37 (s, 2 H), 4.21 (1, 2 H, J = 7 Hz), 1.30 (t, 3 H, J = 7 Hz),

(21) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1970**, *35*, 1839.

(22) The presence of **28** could not be detected by analysis of the ^1H NMR (250 MHz) spectrum of the crude reaction mixture.

(23) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. Bal, B. S.; Childeis, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(24) We thank Dr. R. D. Stipanovic (National Cotton Pathology Research Laboratory, U.S. Department of Agriculture—Agriculture Research Service, College Station, TX 77841) for a specimen of heptelidic acid. We note that the fully synthetic homogeneous racemic material melts at 201–202 °C. This is considerably higher than the melting points of the natural product reported by Itoh[1] and Stipanovic[2] (95 and 62–65 °C, respectively). The superimposability of the ^1H NMR (250 MHz) and the IR spectra of the fully synthetic material and the Stipanovic sample confirms the identity. The correctness of our assignments of aldehyde **28** was verified by an X-ray crystallographic determination.

(25) The ene methyl ester **31** was prepared by Lindgren oxidation of aldehyde **27** followed by esterification with diazomethane.

(26) The chemical shift difference of the spiroepoxymethylene protons as compared to the natural heptelidic acid methyl ester[1] led us to formulate structure **33** as the major product. The spectral properties of the minor product (**32**) compared closely with methyl heptelidate.[1]

(27) (a) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254. (b) Groen, M. B.; Zeelen, F. J. *Tetrahedron Lett.* **1982**, *23*, 3611.

(28) Sevin, A.; Cense, J.-M. *Bull. Soc. Chim. Fr.* **1974**, 963. Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363–1367.

0.96 (s, 9 H), 0.10 (s, 6 H). Diisobutylaluminum hydride (405 mL of a 1 M solution in hexanes) was added over 15 min to a stirred solution of crude **15** (45 g, 184 mmol) in THF (400 mL) at −78 °C. After 2 h, the mixture was warmed to 0 °C, stirred for 30 min, and then carefully quenched with 10 mL of H_2O. Rochelle's salt (400 mL) and ether (300 mL) were added, and the mixture was stirred at room temperature until the emulsion cleared. The layers were separated, and the aqueous portion was extracted with ether (50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 35.4 g of a clear oil, which was dissolved in CH_2Cl_2 (400 mL). To this solution was added triethylamine (73 mL, 525 mmol), 4-(dimethylamino)pyridine (2.13 g, 17.5 mmol), and *tert*-butyldimethylsilyl chloride (26.6 g, 176 mmol) at 0 °C. After 1 h, the mixture was warmed to room temperature and stirred for 10 h. The resulting slurry was filtered and successively washed with cold 1 N aqueous HCl (440 mL), saturated aqueous sodium bicarbonate (400 mL), and brine (200 mL). Drying ($MgSO_4$) and concentration gave 50 g (86%) of crude **16** as a clear oil, which was used directly in the next step: ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.08 (s, 2 H), 5.17 (s, 4 H), 0.90 (s, 18 H), 0.09 (s, 12 H).

Bromine (8.50 mL, 166 mmol) was added dropwise to a cooled (−78 °C) stirred solution of **16** (50 g, 158 mmol) in dichloromethane (250 mL). After 10 min, a solution of 2% aqueous sodium bisulfite (100 mL) was added, and the mixture was warmed to room temperature. Extractive workup and drying of the organic layers ($MgSO_4$) gave 72 g of a yellow oil after concentration. Purification by flash chromatography (300 g of dry packed SiO_2, elution with hexanes) gave 56 g (74%) of pure dibromide **17** as a clear oil: IR (neat) 2945, 2923, 2855, 1460, 1255, 1120, 840 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.85 (s, 4 H), 3.80 (s, 2 H), 0.90 (s, 18 H), 0.08 (s, 12 H).

1-Bromo-3-(*tert*-butyldimethylsiloxy)-2-[(*tert*-butyldimethylsiloxy)-methyl]-1-propene (18). A solution of dibromide **17** (55 g, 115 mmol) and DBU (69 mL, 462 mmol) in benzene (250 mL) was heated to reflux for 7.5 h. The reaction mixture was cooled to 0 °C, and 173 mL of 2 M HCl was added. The mixture was extracted with ether (2 × 100 mL), and the combined organic layers were successively washed with saturated aqueous $NaCO_3$ (100 mL) and brine. Drying (K_2CO_3), concentration, and flash chromatography (SiO_2, hexanes) gave 37.3 g (92%) of vinyl bromide **18** as a clear oil: IR (neat) 2945, 2925, 2880, 2850, 1640, 1470, 1360, 1255, 1100, 850, 780 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.20 (s, 1 H), 4.36 (s, 2 H), 4.25 (s, 2 H), 0.92 (s, 18 H), 0.10 (s, 12 H). Anal. Calcd for $C_{16}H_{35}BrO_2Si_2$: C, 48.59; H, 8.92. Found: C, 48.55; H, 9.00.

(3*SR*,4*RS*)-1-[(Diethoxyphosphoryl)oxy]-2-(methoxycarbonyl)-4-(1-methylethyl)-3-[3-(*tert*-butyldimethylsiloxy)-2-[(*tert*-butyldimethylsiloxy)methyl]prop-1-en-1-yl]cyclohex-1-ene (21). A 1.7 M solution of *tert*-butyllithium in pentane (18.0 mL, 30.5 mmol) was added dropwise to a stirred solution of vinyl bromide **18** (6.20 g, 15.7 mmol) in dry ether (60 mL) at −78 °C. After complete addition, the mixture was stirred for an additional 20 min and then added via a double-tipped needle over 20 min to a stirred 0.13 M solution of 2-thienylcyanocopperlithium in THF (120.6 mL, 15.7 mmol) at −78 °C. After 1 h at −78 °C, a solution of enoate **13** (2.20 g, 11.2 mmol) in THF (30 mL) was added over a period of 20 min, and the mixture was stirred for 3 h at −78 °C. A 20% solution of aqueous NH_4Cl–NH_4OH (200 mL) and ether (50 mL) was added, and the mixture was warmed to room temperature and stirred for 30 min. Extractive workup (ether), drying ($MgSO_4$), and concentration gave crude β-ketoester **20** (as a mixture of keto and enol forms), which was dissolved in THF (20 mL). This solution was added dropwise to a stirred slurry of hexane-washed NaH (60% dispersion, 672 mg, 16.8 mmol) in THF (40 mL) at 0 °C. The solution was warmed to room temperature for 20 min and cooled to 0 °C, and $(EtO)_2POCl$ (1.94 mL, 13.4 mmol) was added dropwise. After 2 h at 0 °C, the reaction was carefully quenched with saturated aqueous $NaHCO_3$ (80 mL) and extracted with ether. Drying ($MgSO_4$), concentration, and purification by flash chromatography (SiO_2, 40% EtOAc–hexanes) gave 5.35 g (74%) of enol phosphate **21** as a thick oil: IR ($CDCl_3$, NaCl) 2960, 2930, 2890, 2760, 1720, 1460, 1360, 1260, 1100, 840 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.18 (d, 1 H, J = 10 Hz), 4.31 (d, 1 H, J = 12 Hz), 4.23–4.07 (m, 7 H), 3.63 (s, 3 H), 3.52 (dd, 1 H, J = 10, 9 Hz), 2.60–2.44 (m, 2 H), 1.84–1.68 (m, 2 H), 1.60–1.44 (m, 1 H), 1.38–1.29 (m, 6 H), 1.28–1.14 (m, 1 H), 0.94 (d, 3 H, J = 7 Hz), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.81 (d, 3 H, J = 7 Hz), 0.064 (s, 3 H), 0.059 (s, 3 H), 0.024 (s, 3 H), 0.017 (s, 3 H). Anal. Calcd for $C_{31}H_{61}O_8PSi_2$: C, 57.37; H, 9.47. Found: C, 57.99; H, 9.33. HRMS (CI) for $C_{31}H_{61}O_8PSi_2$ (M^+ + 1), calcd 649.3722, found 649.3739.

(3*SR*,4*RS*)-2-(Methoxycarbonyl)-4-(1-methylethyl)-1-[(trimethylsilyl)methyl]-3-[3-(*tert*-butyldimethylsiloxy)-2-[(*tert*-butyldimethylsiloxy)methyl]prop-1-en-1-yl]cyclohex-1-ene (22). To a stirred mixture of enol phosphate **21** (5.35 g, 8.25 mmol) and $Ni(acac)_2$ (212 mg, 0.826 mmol) in THF (50 mL) at room temperature was added 0.25 equiv of a 1 M ethereal solution of [(trimethylsilyl)methyl]magnesium chloride[16] (2.06 mL, 2.06 mmol). This addition process was repeated every 1 h for a total of 11 h of reaction time and 2.5 equiv of Grignard reagent. The reaction was quenched with 30 mL of a 20% aqueous NH_4Cl solution and stirred for 45 min. Extractive workup (ether) and purification by flash chromatography (SiO_2, 5% EtOAc–hexanes) gave 4.14 g (86%) of allylsilane **22** as a thick oil: IR ($CDCl_3$) 2960, 2930, 2890, 2855, 1705, 1460, 1305, 1175, 845 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.13 (d, 1 H, J = 10 Hz), 4.33 (d, 1 H, J = 11 Hz), 4.16 (d, 1 H, J = 11 Hz), 4.14 (AB qd, 2 H, J = 13, 1.4 Hz, ν(AB) = 14 Hz), 3.58 (s, 3 H), 3.44 (dd, 1 H, J = 10, 8.7 Hz), 2.13–2.00 (m, 2 H), 2.02 (s, 2 H), 1.78–1.61 (m, 2 H), 1.39–1.20 (m, 1 H), 1.18–1.09 (m, 1 H), 0.93 (d, 3 H, J = 6.8 Hz), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.82 (d, 3 H, J = 6.8 Hz), 0.08 (s, 3 H), 0.076 (s, 3 H), 0.031 (s, 9 H), 0.026 (s, 3 H), 0.019 (s, 3 H). HRMS (EI) for $C_{31}H_{62}Si_3O_4$ (M^+), calcd 582.3956, found 582.3937.

(3*R*,4*RS*)-2-(Methoxycarbonyl)-4-(1-methylethyl)-1-[(trimethylsilyl)methyl]-3-[3-acetoxy-2-(acetoxymethyl)prop-1-en-1-yl]cyclohex-1-ene (23). $FeCl_3$ (343 mg, 2.11 mmol) was added in one portion to a vigorously stirred mixture of **22** in 4.74 mL of Ac_2O (4.10 g, 7.05 mmol) at 0 °C. After 7 min, $NaHCO_3$ (5 g) was added, and the mixture was warmed to room temperature. After 10 min hexane (50 mL) was added, and the mixture was filtered through Celite and thoroughly washed with hexane (100 mL). The organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (SiO_4, 25% EtOAc–hexanes) gave 2.70 g (88%) of **23** as a clear oil: IR ($CDCl_3$, NaCl) 2960, 2895, 1735, 1715, 1370, 1255, 860 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.41 (d, 1 H, J = 11 Hz), 4.85 (d, 1 H, J = 12 Hz), 4.64 (d, 1 H, J = 12 Hz), 4.53 (AB qd, 2 H, J = 12, 1 Hz, ν(AB) = 14 Hz), 3.60 (s, 3 H), 3.50 (dd, 1 H, J = 11, 8.4 Hz) 2.18–1.98 (m, 4 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 1.73–1.60 (m, 2 H), 1.42–1.15 (m, 2 H), 0.95 (d, 3 H, J = 6.8 Hz), 0.82 (d, 3 H, J = 6.8 Hz), 0.027, (s, 9 H); HRMS (EI) for $C_{23}H_{38}SiO_6$ (M^+), calcd 438.2437, found 438.2440.

(2*SR*,3*RS*,4*RS*)-2-(Methoxycarbonyl)-4-(1-methylethyl)-1-methylene-3-[3-acetoxy-2-(acetoxymethyl)propen-1-yl]cyclohexane (24). Trifluoroacetic acid (4.75 mL, 61.8 mmol) was added to a stirred solution of allylsilane (2.7 g, 6.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was warmed to room temperature, stirred for 48 h, and then cooled to 0 °C. $NaHCO_3$ (5.2 g, 61.8 mmol) was added, the slurry was stirred for 1 h, and then water (50 mL) was carefully added. Extractive workup (CH_2Cl_2) gave 2.31 g of crude **24** presumed to be a 4:1 mixture of epimers. Flash chromatography (SiO_2, 10% EtOAc–hexanes) gave 1.58 g (70%) of the major product **24** as a clear oil: IR ($CDCl_3$, NaCl) 2960, 2885, 1735, 1570, 1240, 1030 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.41 (d, 1 H, J = 11 Hz), 4.84 (s, 1 H), 4.79 (d, 1 H, J = 13 Hz) 4.60 (d, 1 H, J = 13 Hz), 4.54 (AB qd, 2 H, J = 12, 1 Hz, ν(AB) = 14 Hz), 4.51 (s, 1 H), 3.64 (s, 3 H), 2.92 (d, 1 H, J = 11 Hz), 2.67 (dd, 1 H, J = 11, 11 Hz) 2.46 (dt, 1 H, J = 13, 4 Hz) 2.05 (s, 6 H), 2.05–1.90 (m, 1 H), 1.83–1.68 (m, 2 H), 1.38–1.10 (m, 2 H), 0.91 (d, 3 H, J = 6.9 Hz), 0.69 (d, 3 H, J = 6.9 Hz). Anal. Calcd for $C_{20}H_{29}O_6$: C, 65.55; H, 8.25. Found: C, 65.72; H, 8.38.

(5a*RS*,6*RS*,9a*SR*)-1,3,5a,6,7,8,9,9a-Octahydro-4-(hydroxymethyl)-6-(1-methylethyl)-9-methylene-1-oxo-2-benzoxepin (26). A mixture of **24** (1.58 g, 4.32 mmol) and 10% aqueous NaOH (50 mL) was stirred at room temperature until homogeneous (48 h). The solution was cooled to 0 °C, acidified to pH 3 with concentrated HCl, saturated with NaCl, and extracted with EtOAc (5 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 1.09 g of crude dihydroxy acid **25** as an amorphous solid. 4-(Dimethylamino)pyridine (25 mg, 0.204 mmol) was added to a stirred mixture of crude dihydroxy acid **25** (1.09 g, 4.08 mmol), bis(2-oxo-3-oxazolidinyl)phosphonic chloride[19] (1.09 g, 4.29 mmol), and triethylamine (1.75 mL, 12.2 mmol) in CH_2Cl_2 (120 mL) at 0 °C. The mixture was warmed to room temperature, stirred for 12 h, and then cooled to 0 °C. Addition of 0.5 N aqueous HCl (30 mL) followed by extractive workup (CH_2Cl_2) gave 1.10 g of crude hydroxy lactone **26** as a clear oil. A small sample was purified (SiO_2, 50% EtOAc–hexane) for analysis: IR ($CHCl_3$) 3600, 3420 (br), 3020, 2960, 1780, 1390, 1180, 1130, 1055, 1010 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.99 (dd, 1 H, J = 4.5, 1.3 Hz), 5.33 (d, 1 H, J = 1.4 Hz), 5.03 (d, 1 H, J = 14 Hz), 5.02 (d, 1 H, J = 1.4 Hz), 4.55 (d, 1 H, J = 14 Hz), 4.23–4.02 (m, 2 H), 3.72 (d, 1 H, J = 12 Hz), 2.47 (dt, 1 H, J = 13, 4.2 Hz), 2.38 (dd, 1 H, J = 12, 10 Hz), 2.17–2.03 (m, 2 H), 1.79 (dq, 1 H, J = 12, 4 Hz), 1.69–1.57 (m, 2 H), 1.45 (tt, 1 H, J = 11, 4 Hz), 1.25 (qd, 1 H, J = 12, 4 Hz), 0.96 (d, 3 H, J = 7 Hz), 0.79 (d, 3 H, J = 7 Hz); HRMS (EI) for $C_{15}H_{22}O_3$ (M^+), calcd 250.1569, found 250.1568.

(5a*RS*,6*RS*,9a*SR*)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-9-methylene-1-oxo-2-benzoxepin-4-carboxaldehyde (27). Jones reagent[29]

(29) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(1.01 mL, 2.7 M) was added to a stirred solution of crude alcohol **26** (1.10 g, 4.08 mmol) in acetone (40 mL) at 0 °C. After 10 min, methanol (1 mL) was added, followed by saturated aqueous $NaHCO_3$ (40 mL). The mixture was filtered through Celite, the excess acetone was evaporated under reduced pressure, and the aqueous phase was extracted with EtOAc (2 × 50 mL). Drying ($MgSO_4$), concentration, and purification by flash chromatography (SiO_2, 25% EtOAc–hexanes) gave 685 mg (57% from **24**) of aldehyde **27** as a clear oil: IR ($CHCl_3$, NaCl) 3020, 2960, 2870, 1745, 1690, 1640, 1370, 1195, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.42 (s, 1 H), 6.96 (dd, 1 H, J = 4, 2 Hz), 5.45 (s, 1 H), 5.13 (d, 1 H, J = 15 Hz), 5.10 (s, 1 H), 4.97 (dt, 1 H, J = 15, 2 Hz), 3.84 (d, 1 H, J = 12 Hz), 2.66 (tt, 1 H, J = 11, 4 Hz), 2.51 (dt, 1 H, J = 14, 4 Hz), 2.24–2.05 (m, 2 H), 1.86 (dq, 1 H, J = 13, 4 Hz), 1.65–1.52 (m, 2 H), 1.36 (qd, 1 H, J = 12, 4 Hz), 1.01 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz).

(5a*RS*,6*RS*,9*SR*,9a*SR*)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-1-oxospiro[2-benzoxepin-9,2′-oxirane]-4-carboxaldehyde (28). A stirred mixture of olefin **27** (685 mg, 2.74 mmol), anhydrous *tert*-butyl hydroperoxide (5.48 mL, 1 M in benzene), and molybdenum hexacarbonyl (72 mg, 0.274 mmol) in benzene (5 mL) was heated to reflux for 3.5 h. The reaction was cooled to room temperature, dimethyl sulfide (1 mL) was added, and the mixture was stirred for 30 min. Concentration and purification by flash chromatography (SiO_2, 25% EtOAc–hexanes) gave 356 mg (49%) of epoxide **28** as a white solid: mp 161–162 °C (CH_2Cl_2–hexanes); IR ($CHCl_3$, NaCl) 3020, 2965, 2870, 1750, 1695, 1640, 1370, 1200, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.42 (s, 1 H), 6.93 (dd, 1 H, J = 2, 1.5 Hz), 5.12 (d, 1 H, J = 15 Hz), 4.91 (dt, 1 H, J = 15, 2 Hz), 3.83 (dd, 1 H, J = 5, 1.5 Hz), 3.56 (d, 1 H, J = 12 Hz), 2.74 (td, 1 H, J = 12, 4 Hz), 2.62 (d, 1 H, J = 5 Hz), 2.33–2.14 (m, 1 H), 2.04–1.90 (m, 1 H), 1.80–1.90 (m, 1 H), 975–1.42 (m, 3 H), 1.03 (d, 3 H, J = 7 Hz), 0.95 (d, 3 H, J = 7 Hz). HRMS (CI) for $C_{15}H_{20}O_4$ (M^+ + 1), calcd 265.1440, found 265.1455.

(5a*RS*,6*RS*,9*SR*,9a*SR*)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-1-oxospiro[2-benzoxepin-9,2′-oxirane]-4-carboxylic Acid ((±)-Heptelidic Acid) (1). To a stirred mixture of aldehyde **28** (304 mg, 1.15 mmol), *tert*-butyl alcohol (12 mL), and 2-methyl-2-butene (9 mL) at 0 °C was added a solution of $NaClO_2$ (1.04 g, 11.5 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.58 g, 11.5 mmol) in water (4.2 mL). The mixture was warmed to room temperature and stirred for 2 h. HOAc (1 mL) and 2 g of NaCl were added, and the mixture was extracted with EtOAc (4 × 25 mL), dried (Na_2SO_4), and concentrated. Benzene was added, and the mixture was concentrated in vacuo to remove the excess HOAc. The crude product was dissolved in 2 mL of THF and purified by flash chromatography (SiO_2, 1% HOAc–EtOAc) to give 306 mg (95%) of (±)-heptelidic acid (**1**) as a crystalline solid: mp 201–202 °C (THF–hexanes); IR ($CDCl_3$) 3400, 2980, 1760, 1720, 1440, 1380, 1295, 1265, 1180, 1075 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (d, 1 H, J = 3 Hz), 5.08 (AB q, 2 H, J = 14.6 Hz, ν(AB) = 14.2 Hz), 3.86 (d, 1 H, J = 5 Hz), 3.58 (d, 1 H, J = 12 Hz), 2.65 (t, br, 1 H, J = 12 Hz), 2.61 (d, 1 H, J = 5 Hz), 2.23–2.07 (m, 1 H), 2.00–1.77 (m, 2 H), 1.68–1.35 (m, 3 H), 1.00 (d, 3 H, J = 7 Hz), 0.91 (d, 3 H, J = 7 Hz). HRMS (CI) for $C_{15}H_{21}O_5$ (M^+ + 1), calcd 281.1389, found 281.1412.

(5a*RS*,6*RS*,9*RS*,9a*RS*)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-1-oxospiro[2-benzoxepin-9,2′-oxirane]-4-carboxaldehyde (29). To a stirred solution of olefin **27** (19 mg, 0.076 mmol) in CH_2Cl_2 (mL) at 0 °C was added *m*-CPBA (16 mg, 0.092 mmol) in one portion. The mixture was warmed to room temperature and stirred for 4.5 h. Dimethylsulfide (0.5 mL) was added, and the mixture was stirred for 10 min. Addition of saturated aqueous $NaHCO_3$ (2 mL), extractive workup (EtOAc), drying (Na_2SO_4), and concentration gave 22 mg of an oil residue. Analysis of the crude ^1H NMR indicated a 5:1 ratio of **29** and **28**. Purification by flash chromatography (SiO_2, EtOAc–hexanes) gave 1.5 mg of **28** and 15 mg of **29**. **29**: IR ($CDCl_3$) 2960, 1750, 1695, 1645, 1380, 1225, 1090 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.43 (s, 1 H), 7.00 (dd, 1 H, J = 5, 1 Hz), 5.08 (d, 1 H, J = 14.5 Hz), 4.90 (d, 1 H, J = 14.5 Hz), 3.54 (d, 1 H, J = 12 Hz), 3.43 (d, 1 H, J = 5 Hz), 3.05 (ddd, 1 H, J = 12, 12, 5 Hz), 2.62 (d, 1 H, J = 5 Hz), 2.24–2.10 (m, 1 H), 2.03–1.58 (m, 4 H), 1.45 (dt, 1 H, J = 13, 3 Hz), 1.02 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz). HRMS (CI) for $C_{15}H_{21}O_4$ (M^+ + 1), calcd 265.1440, found 265.1450.

(5a*RS*,6*RS*,9*RS*,9a*SR*)-1,3,5a,6,7,8,9,9a-Octahydro-6-(1-methylethyl)-1-oxospiro[2-benzoxepin-9,2′-oxirane]-4-carboxylic Acid ((±)-9-Epiheptelidic Acid) (30). To a stirred solution of aldehyde **29** (10 mg, 0.038 mmol), *tert*-butyl alcohol (0.40 mL), and 2-methyl-2-butene (0.30 mL) at 0 °C was added a solution of $NaClO_2$ (3 mg, 0.38 mmol) and $NaH_2PO_4 \cdot H_2O$) (52 mg, 0.38 mmol) in water (0.14 mL). The solution was warmed to room temperature and stirred for 3 h. HOAc (0.3 mL) and brine (0.5 mL) were added, and the mixture was extracted with EtOAc (4 × 5 mL), dried (Na_2SO_4), and concentrated. Benzene was added, and the mixture was concentrated to remove excess HOAc. The crude product was purified by flash chromatography (SiO_2, 1% HOAc–Et_2O) to give 9.5 mg (90%) of (±)-9-epiheptelidic acid as a white solid: mp 205–206 °C (Et_2O); IR ($CDCl_3$) 3480, 2955, 1745, 1690, 1385, 1250, 1060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.46 (d, 1 H, J = 5 Hz), 5.07 (AB q, 2 H, J = 14 Hz, ν(AB) = 24 Hz), 3.45 (d, 1 H, J = 12 Hz), 3.38 (d, 1 H, J = 4.5 Hz), 3.06 2.98 (m, 1 H), 2.64 (d, 1 H, J = 4.5 Hz), 2.20–1.40 (m, 6 H), 1.01 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz).

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Registry No. (±)-**1**, 116782-03-7; **10**, 5432-85-9; (±)-**11** (enol), 116700-74-4; (±)-*cis*-**12**, 116700-75-5; (±)-*trans*-**12**, 116700-68-6; (±)-**13**, 116700-76-6; (±)-**13** (enol), 116700-69-7; **14**, 10029-04-6; **15**, 116700-77-7; **16**, 116700-78-8; **16** (R = H), 116700-73-3; **17**, 116700-79-9; **18**, 116700-80-2; **19a**, 116808-48-1; **19b**, 116783-46-1; (±)-**20**, 116700-81-3; (±)-**20** (enol), 116700-71-1; (±)-**21**, 116724-52-8; (±)-**22**, 116700-82-4; (±)-**23**, 116700-83-5; (±)-**24**, 116782-04-8; (±)-2-*epi*-**24**, 116700-70-0; (±)-**25**, 116700-84-6; (±)-**26**, 116700-85-7; (±)-**27**, 116700-86-8; (±)-**28**, 116700-87-9; (±)-**29**, 116782-05-9; (±)-**30**, 116782-06-0; (±)-**31**, 116700-88-0; (±)-**31** (acid), 116700-72-2; (±)-**32**, 116782-07-1; (±)-**33**, 116782-08-2.

Supplementary Material Available: Tables of protocols, fractional coordinates, anisotropic temperature factors, bond distances, torsional angles, and a computer-generated three-dimensional plot for the X-ray crystallographic determination of compound **28** (6 pages). Ordering information is given on any current masthead page.