(q, 3 C), 27.65 (t), 31.39 (t), 31.47 (d), 32.17 (t), 33.83 (t), 36.63 (s), 36.86 (t), 38.03 (t), 38.62 (s), 41.57 (s), 49.57 (d), 51.71 (d), 55.35 (d), 65.14 (t), 72.23 (s), 73.41 (d), 75.28 (d), 94.36 (t), 122.06 (d), 139.92 (s), 177.88 (s); IR (KBr) 1721, 1171 cm^{-1}; high-resolution MS (CI, NH_3) calcd for $C_{36}H_{58}NO_5Si$ $(M + NH_4)^+$ m/z 564.4084, found m/z 564.4069. Anal. Calcd for $C_{32}H_{54}O_5Si$: C, 70.28; H, 9.95. Found: C, 70.04; H, 10.10.

Acknowledgment. We are grateful to the National Institutes of Health (Grant DK-30025) for financial support of this work. The National Science Foundation is also thanked for their partial support of a VG 70-250S high-resolution mass spectrometer.

Registry No. **5**, 123487-32-1; **6**, 123487-33-2; **7a**, 387-79-1; **7b**, 123487-34-3; **8**, 123487-35-4; **9**, 123487-36-5; **10**, 123487-37-6; **11a**, 1162-53-4; **11b**, 123487-38-7; **12**, 123487-39-8; **13a**, 123487-40-1; **13b**, 123487-41-2; **14a**, 123487-42-3; **14b**, 123487-43-4; **15**, 123487-44-5; **16**, 123538-42-1; **17b**, 123487-45-6; **18b**, 123487-46-7; **19a**, 123487-47-8; **20a**, 123487-48-9; **20b**, 123487-49-0; **21a**, 123487-50-3; SEM chloride, 76513-69-4; pivaloyl chloride, 3282-30-2.

Approaches to the Total Synthesis of the Antitumor Antibiotic Echinosporin

Mary A. Kinsella, Vincent J. Kalish, and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

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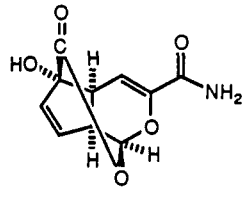
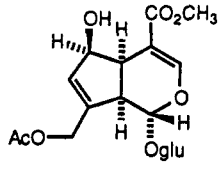
A strategy for the total synthesis of the structurally unique microbial metabolite echinosporin (1) has been tested. Readily available bromo ester **6** has been converted in a few steps to the TCBOC-protected α-keto ester norbornene system **14**. An alternative, shorter, but less reliable route to **14** has also been investigated starting from keto ester **15**. Cleavage of the unconjugated olefinic double bond of **14** yielded diacid **21a**, which was subsequently converted to α-keto ester **22**. Intermediate **22** was transformed to the key enol lactone **24**, which possesses the full carbon skeleton and two of the four chiral centers of echinosporin. Further manipulation of lactone **24** gave acetal unsaturated diester **29**. Despite considerable effort, **29** could not be converted to the required α-hydroxy ester **31** via dienolate **30**. Moreover, mesylate **33**, prepared from **29**, could not be eliminated to produce **31**. Thus, a modified route will have to be developed to construct the α-hydroxy-β,γ-unsaturated cyclopentenyl ester system of 1.

In 1981 Sato and co-workers reported the isolation of echinosporin from the actinomycete *Streptomyces echinosporus* discovered in the microbial screening of a Mexican soil sample.[1] A combination of chemical and spectroscopic studies established structure 1 for this compound, and subsequent X-ray crystallographic analysis confirmed the original formulation.[2] Echinosporin was found to possess antimicrobial activity as well as antitumor activity against systems such as leukemia P388, P388/VCR, and fibrosarcoma Meth 1.[3]



1



2

Echinosporin has a unique structure reminiscent of iridoids such as daphylloside (2).[4,5] However, it seems unlikely that these compounds share a common biogenetic origin.[5] To date, no studies on the biosynthesis of echinosporin have appeared.

Despite its similarity to the iridoids, echinosporin (1) poses a unique set of synthetic problems, in part due to its exceptionally high level of functionality.[6] In addition, most routes to echinosporin that one can devise would seem to require quite a number of chemoselective transformations. We envisioned a total synthesis of 1 shown retrosynthetically in Scheme I. We hoped to prepare 1 from lactone **3** via selective reduction of the enol lactone carbonyl group and α-hydroxylation of the cyclopentenyl ester functionality. Compound **3** would be synthesized from the nearly symmetrical tetracarbonyl compound **4**, which seemed accessible from oxidative double-bond cleavage of norbornyl system **5** or its equivalent. Intermediate **5** incorporates the requisite stereochemistry for enol lactone **3**. In this paper is described our progress in executing the strategy shown in Scheme I.

The synthetic route commenced with known bromo ester **6**, readily available from norbornadiene,[7] which was reduced to alcohol **7** (93%) and eliminated[7] to norbornene **8** (80%) (Scheme II). PCC/alumina oxidation[8] of **8** afforded aldehyde **9** (73%). A two-carbon homologation of

(1) Sato, T.; Kawamoto, I.; Oka, T.; Okachi, R. *J. Antibiot.* **1982**, *35*, 266.
(2) Hirayama, N.; Iida, T.; Shirahata, K.; Oshashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 287.
(3) Morimoto, M.; Imai, R. *J. Antibiot.* **1985**, *38*, 490.
(4) Inouye, H.; Ueda, S.; Hirabayashi, M.; Shimokawa, N. *Yakugaku Zasshi* **1966**, *86*, 943.
(5) For reviews, see: Taylor, W. I.; Battersby, A. R. *Cyclopentanoid Terpene Derivatives*; Marcel Dekker: New York, 1969. Erman, W. F. *Chemistry of the Monoterpenes, Part A*; Marcel Dekker: New York, 1985. Grayson, D. H. *Nat. Prod. Rep.* **1988**, *5*, 419.
(6) For some transformation chemistry of the amide group of 1, see: Deprez, D.; Margraff, R.; Bizot, J.; Pulicani, J. P. *Tetrahedron Lett.* **1987**, *28*, 4679.
(7) (a) Bindra, J. S.; Grodski, A.; Schaaf, T. K.; Corey, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 7522. (b) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C. J.; Majetich, G. *Ibid.* **1977**, *99*, 4111.
(8) Cheng, Y.; Liu, W.; Chen, S. *Synthesis* **1980**, 223.

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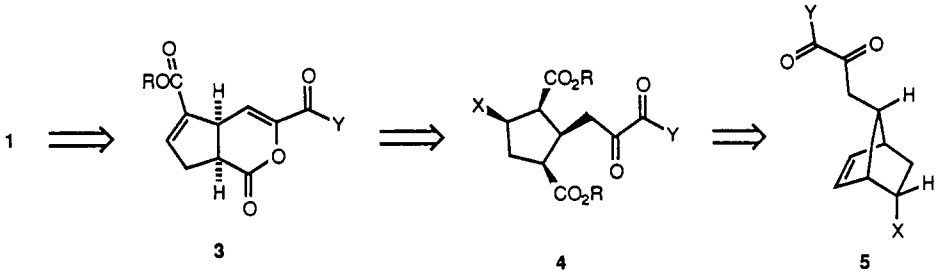
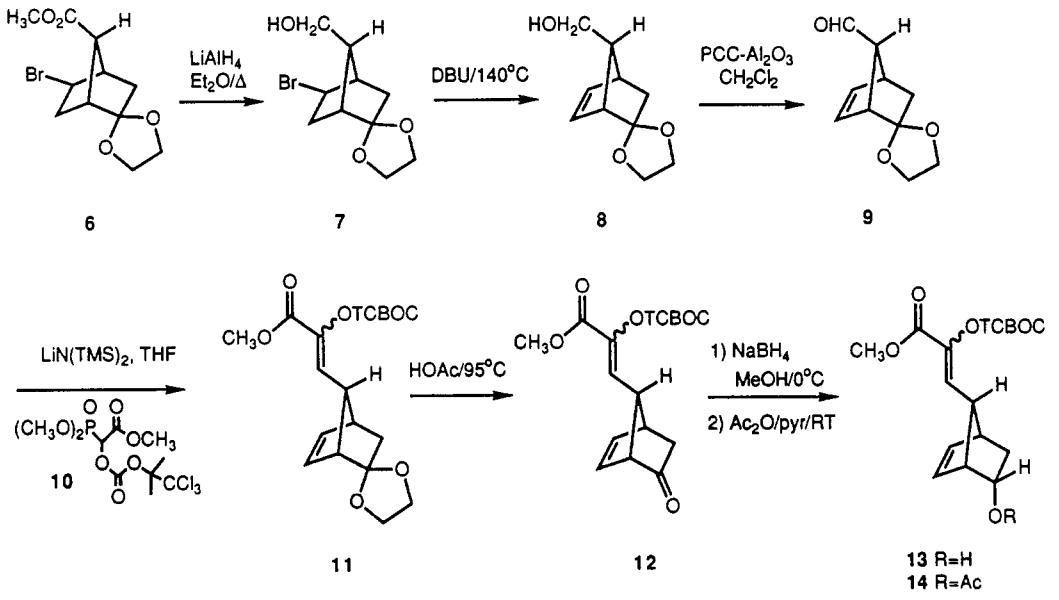
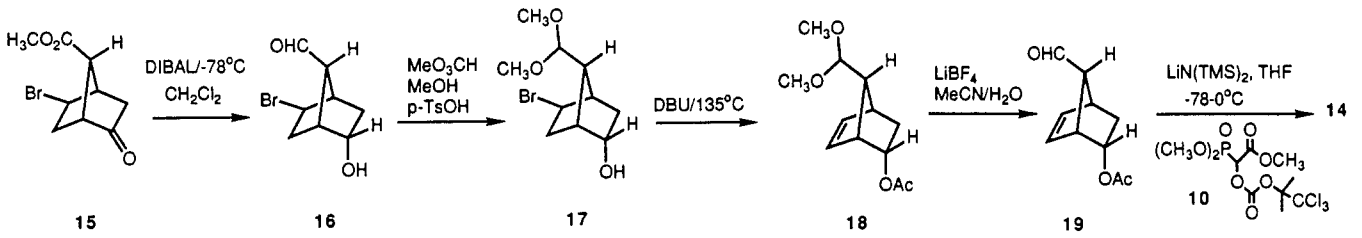
Scheme I



Scheme II



Scheme III



9 was required to produce the equivalent of α-keto ester **5**, and the best procedure for this transformation was that of Thompson and co-workers.[9] Thus, treatment of aldehyde **9** with the anion of phosphonate **10** afforded the trichloro-*tert*-butyl carbonate (TCBOC) protected α-keto ester **11** as an *E*/*Z* isomer mixture (77%). The ketal moiety of **11** was hydrolyzed to afford ketone **12** (90%), which was reduced to alcohol **13** (91%) and protected as acetate **14** (85%).

An alternative, somewhat shorter route to intermediate **14** was also explored (Scheme III). Ketone **15**[7] was reduced with 2 equiv of diisobutylaluminum hydride to hydroxy aldehyde **16** (75%). This compound was converted to acetal **17** (75%), which upon elimination and acetylation yielded **18** (80%). Removal of the acetal protecting group gave aldehyde **19** (90%) and subsequent condensation with phosphonate **10**[7] afforded **14**. One problem encountered with this route was irreproducibility in the initial DIBAL reduction of **15** to **16**. Therefore, it was preferable to prepare compound **14** via the procedure shown in Scheme II.

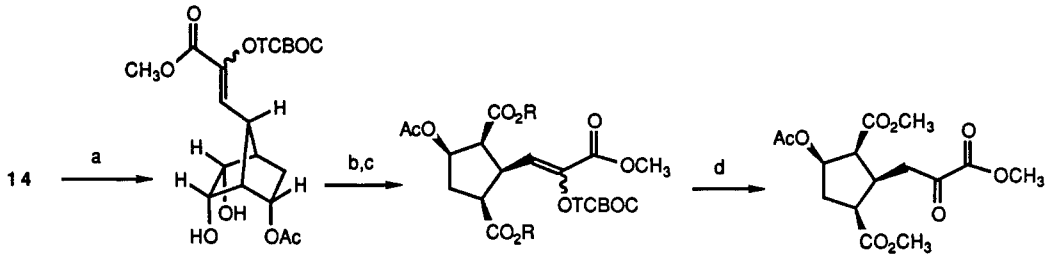
With **14** in hand, our next goal was to effect selective cleavage of the unconjugated norbornene ring double bond to produce the diacid (cf. **4**). Attempted cleavages with oxidants such as ozone, potassium permanganate, and ruthenium tetraoxide were apparently nonselective, giving only intractable material. However, the desired double bond could be cleaved via a two-step procedure. Hydroxylation of **14** with OsO_4/NMO[10] gave cis diol **20** (64%) (Scheme IV). Subsequent cleavage of **20** with a mixture of chromium trioxide/periodic acid gave diacid **21a**, presumably via the intermediate dialdehyde.[11] Methylation of **21a** with diazomethane yielded diester **21b** (77% from diol **20**). The TCBOC protecting group of **21b** could be removed with zinc as described previously,[9] giving α-keto ester **22** (60%).

(9) Horne, D.; Gaudino, J.; Thompson, W. J. *Tetrahedron Lett.* **1984**, *25*, 3529.

(10) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(11) (a) Perold, G. W.; Pachler, K. G. R. *J. Chem. Soc. C* **1966**, 1918. (b) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387.

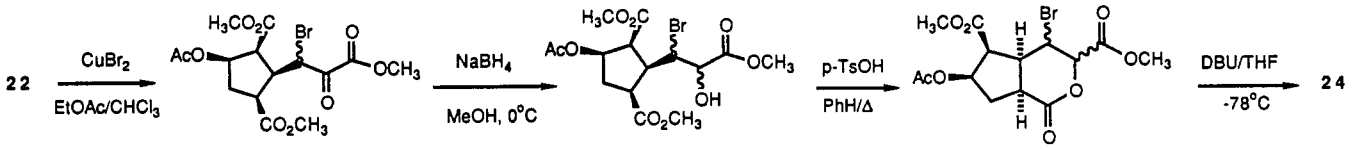
Scheme IV[a]



20 21a R=H 21b R=CH3 22

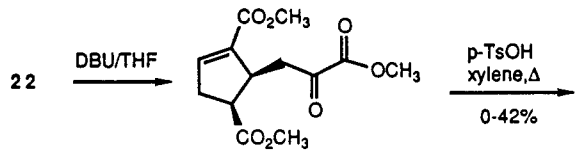
[a] (a) NMO/OsO_4, $Me_2CO/H_2O/t$-BuOH, room temperature; (b) H_5IO_6/CrO_3, Me_2CO/H_2O; (c) CH_2N_2/Et_2O; (d) $Zn/CH_3SiCl/THF$; HCl.

Scheme V

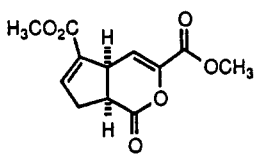


25 26 27

We next turned to closure of keto ester **22** to the required enol lactone system **3** (cf. Scheme I). It was found that treatment of **22** with DBU caused elimination to unsaturated ester **23** (eq 1). Upon heating **23** with *p*-



23



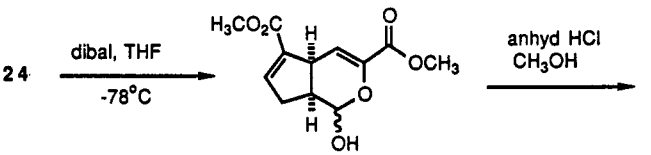
(Eq 1)

24

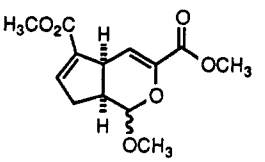
toluenesulfonic acid, varying amounts of the desired enol lactone **24** were produced along with unchanged starting material. Since we were unable to reproducibly obtain satisfactory yields of **24**, an alternative approach to this compound was developed.

Exposure of α-keto ester **22** to cupric bromide[12] afforded the bromo ketone **25** as a mixture of epimers (75%) (Scheme V). Reduction of **25** with sodium borohydride gave bromo alcohol **26**, which upon heating in the presence of *p*-toluenesulfonic acid provided lactone **27** (65%). It is not clear just why closure of this hydroxy ester is so regioselective. Treatment of **27** with DBU caused elimination of both HBr and acetic acid to yield the desired enol lactone **24** (76%). Compound **24** contains the complete carbon skeleton of echinosporin along with two of the four chiral centers.

Not surprisingly, the enol lactone carbonyl group of **24** was quite susceptible to nucleophilic attack. Thus, treatment of **24** with 1 equiv of diisobutylaluminum hydride afforded lactol **28** (eq 2). Although this compound was quite sensitive, it did not, as we had feared, spontaneously ring open to the corresponding α-keto ester al-



28

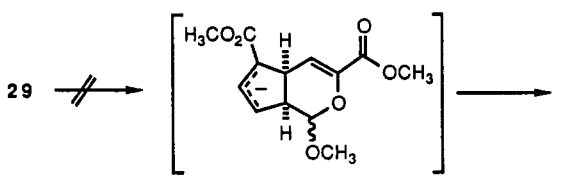


(Eq 2)

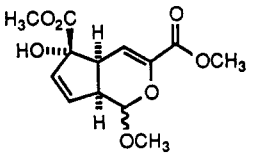
29

dehyde. It was, in fact, possible to convert lactol **28** to the relatively stable cyclic acetal **29** as an inseparable 5:1 mixture of epimers (62% from **24**).

It was our intention to next introduce the echinosporin cyclopentenyl hydroxyl group into diester **29** via oxidation of enolate **30** (eq 3).[13,14] We had hoped that a kinetically



30



(Eq 3)

31

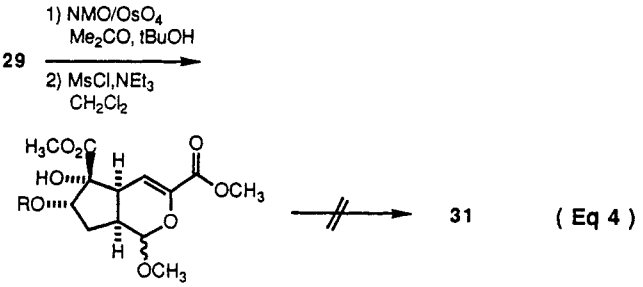
(12) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.

(13) Cf: Ortiz de Montellano, P. R.; Hsu, C. K. *Tetrahedron Lett.* **1976**, 4215. Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398. Baxter, E. W.; Labaree, D.; Chao, S.; Mariano, P. S. *J. Org. Chem.* **1989**, *54*, 2893.

(14) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. Rubottom, G. M.; Marrero, R. *Synth. Commun.* **1981**, *11*, 505.

controlled deprotonation of **29** might selectively provide this anion. A number of unsuccessful attempts were made to generate **30** using a wide variety of bases (e.g., LDA, LiTMP, KH, KOtBu, etc.) followed by quenching with one of several electrophiles (e.g., MoOPh, D_2O, CH_3I, TMSCl, etc). In no case was there any evidence that enolate **30** had actually been produced. Either uncharacterizable decomposition products or starting material were obtained in these experiments.

In an alternative attempt to prepare **31**, it was found that selective mono-hydroxylation of bis-unsaturated ester **29** could be effected with osmium tetraoxide[10] to afford diol **32** (45%) (eq 4). This diol was then converted to the



(Eq 4)

32 R=H
33 R=Ms

mono-mesylate **33** (71%). However, all attempts at promoting elimination of **33** to **31** using a number of bases failed. Moreover, attempts to displace the mesyl group of **33** with phenyl selenide anion were also unfruitful.

The work described here outlines a strategy for construction of the carbon framework of echinosporin along with most of the functionality of this interesting, biologically active molecule. We are hopeful that this approach can be suitably modified to allow introduction of the requisite cyclopentene ring functionality at an earlier stage.

Experimental Section

Melting points are uncorrected. Mass spectra were recorded at an ionizing voltage of 50–70 eV by electron impact.

Column chromatography was performed on E. M. Merck silica gel 60 (70–200 μm for gravity columns) and Baker silica gel (25–40 μm for flash columns[15]). Preparative thin-layer chromatography was done using E. M. Merck silica gel 60 PF-254.

All nonaqueous reactions were run under a positive pressure of nitrogen. All solvents were dried by standard methods before use. Activated zinc was prepared by successive washing with 6 N HCl, 5% HCl, distilled H_2O, 95% ethanol, and ether, followed by solvent removal in vacuo.

5-*exo*-Bromo-7-*syn*-(hydroxymethyl)bicyclo[2.2.1]heptan-2-one Ethylene Ketal (7). A solution of ester **6** (38.40 g, 0.13 mol) in ether (530 mL) was added dropwise to a suspension of lithium aluminum hydride (10.03 g, 0.26 mol) in ether (730 mL). The mixture was refluxed for 30 min, cooled to 0 °C, and quenched by successive addition of water (10 mL), 10% aqueous sodium hydroxide solution (10 mL), and water (10 mL). Suspended matter was removed by filtration and the filtrate was concentrated under reduced pressure to give alcohol **7** as a light yellow oil (32.2 g, 93%): IR (neat) 3400, 2970, 2880, 1475, 1440, 1330, 1210, 1160, 1110, 1070, 1035, 1020, 995, 975, 950, 915, 900, 840, 670, 625 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.02 (ddd, J = 1.1, 4.1, 8.0 Hz, 1 H), 3.75–3.99 (m, 6 H), 2.54–2.60 (m, 2 H), 2.33 (t, J = 8.0 Hz, 1 H), 2.19–2.20 (m, 1 H), 2.17 (s, 1 H), 2.11 (td, J = 4.3, 14.8 Hz, 1 H), 1.93 (dd, J = 5.3, 13.9 Hz, 1 H), 1.49 (d, J = 13.9 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 113.78, 64.53, 64.06, 60.30, 51.64, 49.63, 46.79, 46.68, 45.27, 33.88; MS m/z (rel intensity) 264 ($M^+(^{81}Br)$, 25), 262 ($M^+(^{79}Br)$, 25), 233 (92), 231 (94), 183 (100), 151 (61), 125 (82), 87 (53), 86 (82), 84 (60), 79 (55), 77 (42), 73 (37), 67 (35), 65 (50), 55 (33), 51 (44), 49 (94), 43 (47), 42 (45), 41 (37), 39 (42).

7-*anti*-(Hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-one Ethylene Ketal (8). A solution of bromide **7** (40.0 g, 0.15 mol) in DBU (69.4 g, 0.45 mol) was heated to 140 °C. After 2 h, the mixture was cooled, diluted with saturated aqueous ammonium chloride solution (100 mL), and extracted with ethyl acetate (2 × 300 mL). The extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (elution with 50% ethyl acetate/hexanes) to give alkene **8** as a light yellow oil (22.01 g, 80%): IR (neat) 3400, 3075, 2980, 2885, 1630, 1480, 1440, 1340, 1310, 1220, 1175, 1115, 1060, 1030, 975, 960, 900, 850, 840, 740, 725 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.20 (dd, J = 2.8, 5.6 Hz, 1 H), 5.97 (dd, J = 3.1, 5.6 Hz, 1 H), 3.88–3.97 (m, 4 H), 3.57 (d, J = 7.2 Hz, 2 H), 2.79 (br s, 1 H), 2.64 (d, J = 0.9 Hz, 1 H), 2.45 (t, J = 7.2 Hz, 1 H), 1.96 (dd, J = 3.7, 12.5 Hz, 1 H), 1.58 (m, 1 H, OH), 1.54 (d, J = 12.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.50, 130.04, 117.61, 64.59, 64.12, 62.34, 60.62, 51.30, 42.32, 41.21; HRMS m/z calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0942.

Synthesis of 7-*anti*-Formylbicyclo[2.2.1]hept-5-en-2-one Ethylene Ketal (9). A suspension of pyridinium chlorochromate (20.43 g, 94.8 mmol) and activated neutral alumina (102 g) in methylene chloride (275 mL) was mixed for 15 min. To the vigorously stirred dispersion was added dropwise a solution of alcohol **8** (11.5 g, 63.2 mmol) in methylene chloride (275 mL). After 14 h, the reaction mixture was diluted with ether (550 mL) and filtered, and the filtrate was concentrated under reduced pressure. The residue was passed through a short column of Florisil (elution with ether) and the filtrate was concentrated in vacuo to afford aldehyde **9** (8.25 g, 73%): IR (neat) 3080, 2980, 2890, 2880, 2720, 1720, 1480, 1440, 1335, 1300, 1220, 1170, 1110, 1070, 1040, 1015, 950, 895, 725 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.62 (d, J = 1.8 Hz, 1 H), 6.31 (dd, J = 2.8, 5.6 Hz, 1 H), 6.08 (dd, J = 2.9, 5.5 Hz, 1 H), 3.12–3.85 (m, 4 H), 3.20 (br s, 1 H), 3.03–3.04 (m, 1 H), 2.83 (br s, 1 H), 2.01 (dd, J = 4.1, 12.2 Hz, 1 H), 1.59 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 203.50, 137.41, 130.93, 116.77, 70.57, 64.88, 64.31, 50.63, 42.22, 40.63; HRMS m/z calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0775.

Homologation of Aldehyde 9. To a solution of hexamethyldisilazane (8.14 g, 50.4 mmol) in dry tetrahydrofuran (50 mL) at 0 °C was added 1.6 M *n*-butyllithium in hexane (31.5 mL, 50.4 mmol). After stirring for 30 min, the lithium hexamethyldisilazide solution was cooled to −78 °C and phosphonoglycolate ester **10** (18.41 g, 45.8 mmol) in tetrahydrofuran (50 mL) was added dropwise. After 20 min at −78 °C, a solution of aldehyde **9** (8.25 g, 45.8 mmol) in tetrahydrofuran (50 mL) was added rapidly. After 10 min, the mixture was warmed to 0 °C and stirred for an additional 30 min. Saturated aqueous ammonium chloride solution (100 mL) was then added and the mixture was extracted with ether (2 × 300 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure, and purified by chromatography on silica gel (elution with 40% ethyl acetate/hexanes) to give condensation product **11** (16.0 g, 77%) as a varying mixture of *E* and *Z* olefinic isomers. The major isomer solidified upon standing and could be precipitated from methanol to give a fluffy white solid (mp 103 °C): IR (neat) 3080, 2990, 2970, 2900, 1770, 1735, 1655, 1465, 1445, 1390, 1380, 1340, 1270, 1220, 1170, 1120, 1060, 1020, 980, 950, 895, 835, 810, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) major isomer δ 6.25 (dd, J = 2.8, 5.5 Hz, 1 H), 6.21 (d, J = 9.3 Hz, 1 H), 6.02 (dd, J = 3.0, 5.4 Hz, 1 H), 3.99–4.04 (m, 1 H), 3.85–3.96 (m, 3 H), 3.81 (d, J = 10.4 Hz, 1 H), 3.80 (s, 3 H), 2.87 (br s, 1 H), 2.71–2.72 (m, 1 H), 2.06 (dd, J = 3.7, 12.5 Hz, 1 H), 1.93 (s, 6 H), 1.57 (d, J = 12.5 Hz, 1 H); minor isomer δ 6.61 (d, J = 9.1 Hz, 1 H), 6.27 (dd, J = 2.8, 5.7 Hz, 1 H), 6.05 (dd, J = 3.1, 5.8 Hz, 1 H), 3.96–4.00 (m, 1 H), 3.83–3.91 (m, 3 H), 3.76 (s, 3 H), 3.19 (d, J = 9.1 Hz, 1 H), 2.83 (br s, 1 H), 2.67–2.68 (m, 1 H), 2.02 (dd, J = 3.7, 12.5 Hz, 1 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.58 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 161.68, 150.13, 138.00, 137.18, 134.12, 130.68, 117.12, 105.03, 90.77, 64.65, 64.30, 57.14, 54.71, 52.13, 46.45, 40.75, 20.93; minor isomer δ 161.87, 149.44, 138.59, 137.04, 130.86, 130.70, 117.07, 105.06, 91.01, 64.78, 64.25, 56.44, 54.11, 52.38, 45.72, 40.63, 20.99; HRMS m/z calcd for $C_{18}H_{21}O_7Cl_3$ 454.0353, found 454.0375. Anal. Calcd for $C_{18}H_{21}O_7Cl_3$: C, 47.44; H, 4.65. Found: C, 47.39; H, 4.91.

Conversion of Ketal 11 to Ketone 12. A mixture of ketal

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(16) **Note added in proof:** A total synthesis of echinosporin has recently appeared: Smith, A. B.; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039.

11 (13.23 g, 29.0 mmol) and 30% aqueous acetic acid (v/v) (72 mL) was heated to 95 °C. After 3 h, the reaction mixture was cooled to 0 °C, a solution of potassium hydroxide (48.3 g) in water (50 mL) was added, and solid sodium bicarbonate was introduced until the solution was weakly basic to pH paper. The resultant mixture was extracted with ethyl acetate (2 × 200 mL) and the organic solution was dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (elution with 30% ethyl acetate/hexanes) to afford ketone **12** as a mixture of olefinic isomers (10.7 g, 90%). The major isomer solidified upon standing and was recrystallized from methanol (mp 108–109 °C): IR (neat) 3075, 3000, 2950, 1770, 1750, 1730, 1660, 1460, 1440, 1390, 1375, 1320, 1270, 1220, 1160, 1120, 1055, 1020, 970, 915, 830, 800, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major isomer δ 6.50 (dd, J = 2.7, 5.6 Hz, 1 H), 6.30 (d, J = 9.2 Hz, 1 H), 6.03–6.06 (m, 1 H), 4.07 (d, J = 9.0 Hz, 1 H), 3.81 (s, 3 H), 3.23 (br s, 1 H), 3.08–3.09 (m, 1 H), 2.19 (dd, J = 3.2, 16.7 Hz, 1 H), 2.01 (d, J = 16.8 Hz, 1 H), 1.95 (s, 6 H); minor isomer δ 6.66 (d, J = 9.1 Hz, 1 H), 6.52 (dd, J = 2.7, 5.6 Hz, 1 H), 6.05–6.08 (m, 1 H), 3.79 (s, 3 H), 3.38 (d, J = 8.8 Hz, 1 H), 3.18 (d, J = 0.8 Hz, 1 H), 3.04–3.05 (m, 1 H), 2.14 (ddd, J = 0.8, 3.2, 16.7 Hz, 1 H), 2.01 (d, J = 16.9 Hz, 1 H), 1.97 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer δ 211.69, 161.45, 149.78, 140.76, 138.85, 131.63, 127.50, 104.91, 90.95, 60.39, 58.73, 52.27, 45.66, 37.91, 20.87; minor isomer δ 211.58, 161.54, 149.15, 140.62, 139.64, 127.73, 127.61, 104.91, 91.37, 59.93, 58.09, 52.58, 44.97, 37.82, 20.97; HRMS m/z calcd for $C_{16}H_{17}O_6Cl_3$ 410.0091, found 410.0100. Anal. Calcd for $C_{16}H_{17}O_6Cl_3$: C, 46.68; H, 4.16. Found: C, 46.88; H, 4.18.

Reduction of Ketone 12. To a solution of ketone **12** (10.68 g, 25.9 mmol) in methanol (70 mL) at 0 °C was added sodium borohydride (0.99 g, 25.9 mmol) in two portions. After 1 h, 5% aqueous sodium bicarbonate solution (20 mL) was added and the mixture was extracted with ethyl acetate (2 × 300 mL). The extract was dried ($MgSO_4$) and concentrated in vacuo and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate/hexanes) to give alcohol **13** as a mixture of olefinic isomers (9.80 g, 91%): IR (neat) 3420, 3060, 2950, 2900, 1770, 1730, 1660, 1460, 1440, 1390, 1370, 1330, 1270, 1220, 1160, 1120, 1070, 1010, 970, 910, 830, 800, 740, 670, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major isomer δ 6.35 (dd, J = 2.9, 5.7 Hz, 1 H), 6.18 (d, J = 9.4 Hz, 1 H), 5.99 (dd, J = 2.7, 5.7 Hz, 1 H), 4.55 (m, 1 H), 3.76 (s, 3 H), 3.35 (d, J = 9.4 Hz, 1 H), 3.02–3.04 (m, 1 H), 2.83 (br s, 1 H), 2.28 (ddd, J = 3.8, 8.2, 12.1 Hz, 1 H), 1.92 (s, 6 H), 1.41–1.45 (m, 1 H, OH), 0.87 (dd, J = 2.6, 12.6 Hz, 1 H); minor isomer δ 6.57 (d, J = 9.8 Hz, 1 H), 6.39 (dd, J = 3.0, 5.7 Hz, 1 H), 6.03 (dd, J = 2.8, 5.7 Hz, 1 H), 4.53 (m, 1 H), 3.75 (s, 3 H), 3.0 (br s, 1 H), 2.81 (br s, 1 H), 2.70 (d, J = 9.3 Hz, 1 H), 2.26 (ddd, J = 4.0, 8.2, 12.2 Hz, 1 H), 1.96 (s, 6 H), 1.37–1.39 (m, 1 H, OH), 0.88 (dd, J = 2.6, 12.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer δ 161.73, 150.08, 137.66, 137.59, 134.62, 128.75, 104.99, 90.80, 71.80, 56.12, 53.44, 52.08, 48.52, 38.12, 21.05, 21.00; minor isomer δ 161.82, 149.33, 138.41, 137.61, 130.61, 128.70, 104.99, 91.10, 71.75, 55.52, 52.85, 52.40, 47.95, 38.02, 21.02, 20.95; MS m/z (rel intensity) 412 (M^+, 0.23), 193 (28), 166 (35), 165 (29), 161 (45), 159 (39), 149 (31), 125 (41), 123 (56), 106 (100), 105 (60), 91 (94), 89 (36), 84 (33), 79 (42), 78 (31), 77 (42), 59 (32), 55 (29), 53 (33), 51 (30), 49 (52), 43 (26), 28 (58).

Acetylation of Alcohol 13. Alcohol **13** (9.80 g, 23.67 mmol) was mixed with pyridine (2.29 mL, 28.4 mmol) and acetic anhydride (323 mL) at room temperature. After being stirred for 12 h, the reaction mixture was diluted with methylene chloride (300 mL) and the resultant solution was washed with saturated aqueous ammonium chloride solution (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative HPLC on silica gel (elution with 40% ethyl acetate/hexanes) to afford acetate **14** as a mixture of olefinic isomers (9.12 g, 85%): IR (neat) 3070, 2980, 2950, 2870, 1770, 1730, 1660, 1460, 1440, 1390, 1380, 1370, 1330, 1270, 1250, 1160, 1120, 1060, 1020, 910, 830, 800, 740 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) major isomer δ 6.25 (dd, J = 3.0, 5.6 Hz, 1 H), 6.17 (d, J = 9.3 Hz, 1 H), 5.90 (dd, J = 2.7, 5.7 Hz, 1 H), 5.31–5.35 (m, 1 H), 3.78 (s, 3 H), 3.39 (d, J = 9.2 Hz, 1 H), 3.16–3.18 (m, 1 H), 2.86 (br s, 1 H), 2.33 (ddd, J = 4.0, 8.3, 12.3 Hz, 1 H), 1.97 (s, 3 H), 1.92 (s, 6 H), 1.03 (dd, J = 2.8, 12.7 Hz, 1 H); minor isomer δ 6.56 (d, J = 9.2 Hz, 1 H), 6.29 (dd, J = 3.0, 5.7 Hz, 1 H), 5.94 (dd, J = 2.8, 5.7 Hz, 1 H), 5.29–5.32 (m, 1 H), 3.76 (s, 3 H), 3.15 (br s, 1 H), 2.84 (br s, 1 H), 2.74 (d, J = 9.2 Hz, 1 H), 2.30 (ddd, J = 4.0, 8.4, 12.3 Hz, 1 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.04 (dd, J = 2.8, 12.8 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 170.98, 161.63, 150.04, 137.96, 136.06, 133.79, 129.22, 105.02, 90.83, 74.33, 74.05, 55.61, 52.14, 51.07, 47.89, 35.18, 21.02, 20.93; minor isomer δ 171.00, 161.76, 149.35, 138.73, 135.97, 130.05, 129.19, 105.00, 91.16, 73.91, 55.01, 52.42, 50.52, 47.33, 35.00, 21.01; HRMS m/z calcd for $C_{18}H_{21}O_7Cl_3$ 454.0353, found 454.0390.

Hydroxylation of Norbornene 14. A mixture of *N*-methylmorpholine *N*-oxide (1.48 g, 12.6 mmol), water (4 mL), acetone (2 mL), *tert*-butyl alcohol (0.8 mL), and a crystal of osmium tetraoxide was stirred for 5 min. A solution of alkene **14** (4.82 g, 10.6 mmol) in acetone (8 mL) was added dropwise at 0 °C and acetone was then added until the mixture became homogenous. The resultant solution was stirred at ambient temperature for 12 h and was then quenched by addition of an aqueous slurry of sodium dithionite and Florisil. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with water (200 mL), cooled to 0 °C, and acidified with concentrated sulfuric acid (12 drops). The mixture was extracted with ethyl acetate (2 × 300 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue on silica gel (elution with 50% ethyl acetate/hexanes) afforded diol **20** (3.33 g, 64%) as a mixture of olefinic isomers: IR (neat) 3440 (br), 2960, 1770, 1730, 1645, 1440, 1375, 1275, 1245, 1220, 1170, 1120, 1055, 1030, 980, 915, 835, 805, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3/D_2O$) major isomer δ 6.91 (d, J = 8.6 Hz, 1 H), 5.00 (td, J = 4.1, 10.3 Hz, 1 H), 4.44 (t, J = 5.4 Hz, 1 H), 4.00 (t, J = 5.0 Hz, 1 H), 3.80 (s, 3 H), 3.30 (d, J = 8.6 Hz, 1 H), 2.69 (d, J = 4.5 Hz, 1 H), 2.47 (d, J = 5.1 Hz, 1 H), 2.24 (ddd, J = 5.2, 10.4, 14.0 Hz, 1 H), 2.05 (s, 3 H), 1.95 (s, 6 H), 0.94 (dd, J = 3.7, 14.0 Hz, 1 H); minor isomer δ 7.18 (d, J = 8.1 Hz, 1 H), 4.97 (td, J = 5.0, 10.3 Hz, 1 H), 4.43 (t, J = 5.5 Hz, 1 H), 4.01 (t, J = 4.9 Hz, 1 H), 3.79 (s, 3 H), 2.67–2.72 (m, 2 H), 2.43 (d, J = 5.0 Hz, 1 H), 2.19 (ddd, J = 5.3, 10.4, 14.1 Hz, 1 H), 2.05 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 0.95 (dd, J = 3.8, 14.0 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 170.67, 161.77, 150.51, 136.54, 134.52, 104.94, 90.89, 75.24, 71.58, 69.44, 52.11, 51.75, 48.81, 44.47, 33.35, 20.93; minor isomer δ 170.61, 162.01, 149.58, 137.52, 130.57, 104.90, 91.21, 74.99, 71.42, 69.15, 52.49, 51.29, 48.32, 43.64, 33.15, 20.99, 20.93; MS m/z (rel intensity) 453 ($M^+ - 35(^{35}Cl)$, 0.14), 161 (25), 159 (29), 125 (21), 123 (29), 84 (22), 43 (100).

Cleavage of Diol 20. To a mixture of diol **20** (3.09 g, 6.30 mmol) in acetone (70 mL) at 0 °C was added a solution of periodic acid (5.75 g, 25.2 mmol) and chromium trioxide (1.89 g, 18.9 mmol) in water (70 mL). The mixture was warmed to ambient temperature and stirred for 12 h. Solid sodium bisulfite (2 g) was added and the reaction mixture was extracted with ethyl acetate (3 × 200 mL). The organic extract was washed with 10% aqueous sodium thiosulfate solution (20 mL), dried ($MgSO_4$), and then concentrated in vacuo to afford diacid **21a** as a mixture of olefinic isomers that was used in the next step without further purification: IR (neat) 3050 (br), 1770, 1740, 1450, 1390, 1275 (br), 1130, 1060, 920, 840, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major isomer δ 10.79 (m, 2 H), 6.28 (d, J = 11.1 Hz, 1 H), 5.45–5.55 (m, 1 H), 4.50–4.65 (m, 1 H), 3.77 (s, 3 H), 3.12–3.28 (m, 2 H), 2.40–2.69 (m, 1 H), 2.20–2.39 (m, 1 H), 2.04 (s, 3 H), 2.01 (s, 6 H); minor isomer δ 9.98 (m, 2 H), 6.68 (d, J = 11.4 Hz, 1 H), 5.48–5.60 (m, 1 H), 3.81–3.89 (m, 1 H), 3.77 (s, 3 H), 3.13–3.23 (m, 2 H), 2.51–2.56 (m, 1 H), 2.26–2.40 (m, 1 H), 2.06 (s, 3 H), 2.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer δ 175.74, 173.13, 170.17, 161.72, 150.06, 138.57, 129.23, 104.86, 90.88, 73.45, 52.22, 52.13, 46.35, 39.15, 33.15, 26.34, 21.01, 20.66; minor isomer δ 175.69, 172.99, 170.17, 161.64, 149.48, 139.28, 126.22, 104.97, 91.01, 73.17, 52.59, 52.48, 46.53, 39.10, 33.16, 20.96, 20.92, 20.71.

Esterification of Diacid 21a. A solution of diacid **21a** (3.28 g, 6.30 mmol) in ether (100 mL) was treated with an ethereal solution of diazomethane until evolution of nitrogen ceased and a yellow color persisted. The solution was stirred at ambient temperature for 3 h and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (elution with 40% ethyl acetate/hexanes) to give diester **21b** as a mixture of olefinic isomers (2.96 g, 77% from diol **20**): IR (neat) 3000, 2950, 2840, 1775, 1750, 1735, 1660, 1460, 1440, 1395, 1375, 1360, 1320, 1240 (br), 1170, 1135, 1115, 1050, 1025, 970, 930, 910, 835, 800,

780 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) major isomer δ 6.27 (d, J = 11.8 Hz, 1 H), 5.52 (dt, J = 4.3, 6.6 Hz, 1 H), 4.58 (ddd, J = 7.1, 7.5, 11.8 Hz, 1 H), 3.82 (s, 3 H), 3.68 (s, 3 H), 3.64 (s, 3 H), 3.13–3.20 (m, 2 H), 2.36–2.53 (m, 2 H), 2.06 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H); minor isomer δ 6.68 (d, J = 11.4 Hz, 1 H), 5.51 (dt, J = 3.8, 6.6 Hz, 1 H), 3.78 (s, 3 H), 3.68–3.80 (m, 1 H), 3.64 (s, 3 H), 3.62 (s, 3 H), 3.04–3.14 (m, 2 H), 2.33–2.52 (m, 2 H), 2.05 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 171.80, 170.01, 168.75, 161.71, 150.41, 138.33, 129.96, 104.99, 90.85, 73.59, 52.36, 52.15, 51.79, 46.48, 39.53, 33.16, 20.99; minor isomer δ 171.40, 169.89, 168.48, 161.52, 149.57, 138.83, 126.92, 105.00, 90.82, 73.31, 52.51, 52.33, 52.18, 51.83, 46.50, 39.48, 33.16, 21.00, 20.96; MS m/z (rel intensity) 515 (M$^+$ – 31(^{35}Cl), 0.31), 343 (56), 224 (58), 165 (53), 164 (22), 161 (36), 159 (35), 125 (29), 123 (37), 59 (25), 43 (100).

Cleavage of TCBOC Protecting Group of 21b. A rapidly stirred solution of enol carbonate **21b** (1.25 g, 2.28 mmol) and chlorotrimethylsilane (0.50 g, 4.56 mmol) in dry tetrahydrofuran (30 mL) was cooled to 0 °C and freshly activated zinc dust (2.98 g, 45.64 mmol) was added. The reaction mixture was stirred at ambient temperature or mixed in a Bransonic ultrasound water bath until TLC showed that no starting material remained. The mixture was then filtered through a fritted glass funnel and the zinc salt precipitate was washed with ethyl acetate (200 mL). The filtrate was washed with 5% aqueous hydrochloric acid solution (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 60% ethyl acetate/hexanes) to give α-keto ester **22** as a colorless oil (417 mg, 60%), which solidified upon standing. Recrystallization of this material from methanol afforded white needles (mp 69–69.5 °C): IR (neat) 2980, 2940, 2900, 2840, 1730, 1430, 1370, 1350, 1300, 1235, 1210, 1170, 1070, 1020, 970, 765 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.39 (ddd, J = 5.3, 6.7, 7.5 Hz, 1 H), 3.88 (s, 3 H), 3.63 (s, 6 H), 3.22–3.35 (m, 2 H), 3.04–3.12 (m, 2 H), 2.97 (dt, J = 7.4, 9.5 Hz, 1 H), 2.48 (ddd, J = 7.8, 9.3, 14.8 Hz, 1 H), 2.27 (ddd, J = 5.1, 9.8, 14.9 Hz, 1 H), 2.04 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 191.90, 172.87, 170.12, 170.09, 161.08, 73.39, 52.96, 52.02, 51.77, 50.69, 44.35, 36.99, 36.55, 33.16, 20.94, HRMS m/z calcd for $C_{15}H_{20}O_9$ 344.1107, found 344.1113. Anal. Calcd for $C_{15}H_{20}O_9$: C, 52.32; H, 5.86. Found: C, 51.77; H, 5.70.

Bromination of α-Keto Ester 22. To a refluxing mixture of cupric bromide (1.58 g, 7.09 mmol) in ethyl acetate (25 mL) was added a solution of α-keto ester **22** (0.81 g, 2.36 mmol) in chloroform (25 mL). The mixture was refluxed for 18 h, cooled, and filtered through a short column of silica gel (elution with ethyl acetate). Solvent was removed in vacuo and the residue was purified by chromatography on silica gel (elution with 40% ethyl acetate/hexanes) to give bromide **25** as a mixture of epimers (0.75 g, 75%): IR (neat) 2980, 2950, 2840, 1730 (br), 1435, 1370, 1230 (br), 1200, 1175, 1095, 1070, 1000, 855, 820, 785, 755, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) major isomer δ 5.60 (d, J = 11.4 Hz, 1 H), 5.22 (ddd, J = 7.1, 8.7, 9.6 Hz, 1 H), 3.97 (s, 3 H), 3.74 (s, 3 H), 3.66 (s, 3 H), 3.60–3.64 (m, 1 H), 3.11–3.21 (m, 2 H), 2.52–2.62 (m, 2 H), 2.04 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 182.38, 172.59, 171.17, 170.17, 159.59, 72.62, 53.46, 52.42, 52.01, 49.19, 45.81, 43.07, 40.52, 31.65, 20.70; MS m/z (rel intensity) 393 (M$^+$ – 31(^{81}Br), 0.84), 391 (M$^+$ – 31(^{79}Br), 0.86), 323 (16), 321 (16), 199 (34), 59 (22), 43 (100), 28 (38).

Reduction of α-Bromo Ketone 25. To a solution of α-bromo ketone **25** (0.40 g, 0.95 mmol) in methanol (6 mL) at 0 °C was added sodium borohydride (36 mg, 0.95 mmol) in one portion. After 1 h at 0 °C the solution was treated with 5% aqueous sodium bicarbonate solution (10 mL) and was extracted with ethyl acetate (2 × 100 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The crude hydroxy ester **26** was obtained as a mixture of isomers and was used in the next step without further purification: IR (neat) 3480 (br), 3020, 2960, 1735 (br), 1440, 1375, 1240, 1180, 1125, 1105, 1050, 905 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) major isomer δ 5.27–5.33 (m, 1 H), 5.15 (d, J = 11.6 Hz, 1 H), 4.91–4.93 (m, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.53–3.57 (m, 1 H), 3.16–3.18 (m, 1 H), 3.09 (dt, J = 3.6, 8.8 Hz, 1 H), 2.91–2.98 (m, 1 H), 2.69 (ddd, J = 3.6, 6.1, 14.5 Hz, 1 H), 2.42–2.51 (m, 1 H), 2.03 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 172.51, 172.35, 170.75, 170.16, 72.33, 71.39, 55.76, 53.25, 52.14, 51.76, 50.57, 46.33, 42.31, 33.64, 20.81; MS m/z (rel intensity) 395 (M$^+$ – 31(^{81}Br), 0.96), 393 (M$^+$ – 31(^{79}Br), 0.95), 327 (30), 271 (22), 199 (29), 181 (21), 59 (25), 43 (100).

Lactonization of Bromo Alcohol 26. A mixture of hydroxy ester **26** (0.40 g, 0.94 mmol), p-toluenesulfonic acid (5 mg), and benzene (15 mL) was refluxed for 3 h. The solution was cooled and concentrated in vacuo and the residue was dissolved in ethyl acetate (200 mL). The mixture was washed with saturated aqueous sodium bicarbonate solution (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (elution with 60% ethyl acetate/hexanes) to give lactone **27** as a mixture of isomers (0.24 g, 65% from ketone **22**): IR (neat) 3000, 2960, 2860, 1750 (br), 1440, 1375, 1230, 1175, 1130, 1080, 980, 935, 855, 820, 780, 765, 725, 695, 675 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) major isomer δ 5.28 (td, J = 5.9, 7.7 Hz, 1 H), 5.13 (d, J = 4.3 Hz, 1 H), 4.78 (dd, J = 4.3, 8.8 Hz, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.58 (ddd, J = 6.9, 9.1, 11.0 Hz, 1 H), 3.44 (dd, J = 6.0, 8.4 Hz, 1 H), 3.18 (td, J = 8.7, 11.0 Hz, 1 H), 2.48–2.56 (m, 1 H), 2.37 (ddd, J = 2.6, 9.0, 14.0 Hz, 1 H), 2.02 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 170.23, 169.83, 169.73, 167.62, 77.67, 73.45, 53.00, 52.21, 48.65, 43.68, 41.12, 39.56, 33.53, 20.72; MS m/z (rel intensity) 394 (M$^+$(^{81}Br), 0.18), 392 (M$^+$(^{79}Br), 0.18), 313 (14), 293 (12), 291 (13), 271 (15), 239 (14), 59 (15), 55 (15), 43 (100).

Elimination of Bromo Lactone 27. To a solution of lactone **27** (0.35 g, 0.892 mmol) in dry tetrahydrofuran (6 mL) at –78 °C was added dropwise a solution of DBU (0.27 g, 1.78 mmol) in tetrahydrofuran (6 mL). After 2 min, silica gel (7 g) and 50% ethyl acetate in hexanes (20 mL) was added to the mixture, which was then filtered rapidly through a short column of silica gel (elution with 50% ethyl acetate/hexanes). The filtrate was concentrated in vacuo to give enol lactone **24** (0.17 g, 76%): IR (neat) 3100, 2960, 2860, 1770, 1740, 1720, 1675, 1635, 1440, 1375, 1335, 1320, 1265, 1190, 1150, 1100, 995, 935, 920, 890, 865, 815, 780, 765, 720 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.82–6.83 (m, 1 H), 6.61 (d, J = 3.9 Hz, 1 H), 3.97–4.01 (m, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.43–3.56 (m, 1 H), 3.00–3.07 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.76, 163.55, 160.81, 142.49, 139.99, 135.51, 112.61, 52.66, 51.96, 41.97, 39.74, 37.88; MS m/z (rel intensity) 252 (M$^+$, 13), 225 (39), 211 (77), 193 (38), 165 (100), 151 (82), 137 (86), 105 (41), 79 (45), 77 (41), 59 (64), 43 (42).

Conversion of Enol Lactone 24 to Acetal 29. A solution of enol lactone **24** (0.27 g, 1.07 mmol) in dry tetrahydrofuran (25 mL) at –78 °C was treated with a 1.0 M solution of diisobutylaluminum hydride in toluene (1.6 mL, 1.60 mmol). After 30 min silica gel (9 g) was added, the mixture was rapidly filtered through a fritted glass funnel, and the silica gel was eluted with 50% ethyl acetate in hexanes (150 mL). The combined filtrates were concentrated in vacuo to give sensitive lactol **28**, which was used immediately in the next step.

Crude enol lactol **28** was treated with anhydrous 10% HCl in methanol (25 mL) and the mixture was stirred at ambient temperature for 3 h. Solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (elution with 40% ethyl acetate/hexanes) to give methyl acetal **29** as a mixture of epimers (0.18 g, 62% from lactone **24**): IR (neat) 3000, 2960, 2860, 1730 (br), 1650, 1635, 1445, 1380, 1350, 1310, 1260, 1225, 1210, 1175, 1140, 1095, 1070, 1030, 1005, 950, 930, 895, 785, 770, 755 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) major isomer δ 6.73–6.74 (m, 1 H), 6.45 (d, J = 3.6 Hz, 1 H), 4.87 (d, J = 3.0 Hz, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.67–3.76 (m, 1 H), 3.51 (s, 3 H), 2.52–2.74 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer δ 164.49, 163.23, 142.87, 139.16, 136.61, 114.60, 100.32, 56.33, 52.18, 51.67, 41.24, 39.13, 34.01.

Hydroxylation of Unsaturated Ester 29. A mixture of N-methylmorpholine N-oxide (0.06 g, 0.50 mmol), water (2 mL), acetone (0.06 mL), *tert*-butyl alcohol (0.06 mL), and a crystal of osmium tetraoxide was stirred for 5 min and then cooled to 0 °C. A solution of unsaturated ester **29** (0.09 g, 0.34 mmol) in acetone (0.6 mL) was added and additional acetone was introduced until the mixture became homogeneous. Stirring was maintained at ambient temperature for 30 min, and the mixture was cooled again to 0 °C. An aqueous slurry of sodium dithionite and Florisil was added and the mixture was filtered. The filtrate was concentrated in vacuo and the residue was passed through a plug of silica gel (elution with ethyl acetate). The filtrate was concentrated and purified by chromatography on silica gel (elution with 80% ethyl acetate/hexanes to give diol **32** as a mixture of acetal epimers

(0.045 g, 45%): IR (neat) 3460, 2950, 2920, 2840, 1730, 1645, 1435, 1370, 1270, 1140, 1100, 1070, 980, 955, 915, 805, 775, 760, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) major isomer δ 5.94 (d, J = 3.3 Hz, 1 H), 4.93 (d, J = 2.6 Hz, 1 H), 4.45–4.52 (m, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.46 (s, 3 H), 2.98 (dd, J = 3.5, 7.8 Hz, 1 H), 2.83–2.90 (m, 1 H), 2.36 (br s, 1 H, OH), 2.07–2.15 (m, 1 H), 1.70–1.94 (m, 1 H), 1.56 (br s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) major isomer δ 172.84, 162.79, 140.92, 110.25, 100.78, 83.33, 73.93, 56.20, 52.90, 52.33, 42.30, 37.43, 32.08; HRMS m/z calcd for $C_{13}H_{18}O_8$ 302.1002, found 302.1008.

Conversion of Diol 32 to Monomesylate 33. To a solution of diol **32** (0.035 g, 0.12 mmol) in methylene chloride (8 mL) at 0 °C was added triethylamine (0.035 g, 0.35 mmol). Methanesulfonyl chloride (3 drops) in methylene chloride (1 mL) was added dropwise at 0 °C until TLC analysis indicated that starting material had disappeared. The solution was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (elution with 80% ethyl acetate/hexanes) to give monomesylate **33** (0.031 g, 71%) as a mixture of acetal epimers: IR (neat) 3470 (br), 2960, 2840, 1730, 1650, 1440, 1370, 1280, 1180, 1150, 1110, 1075, 980, 925, 860, 810, 760 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) major isomer δ 5.90–5.91 (m, 1 H), 5.24 (dd, J = 6.9, 9.4 Hz, 1 H), 4.95 (d, J = 1.8 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.45 (s, 3 H), 3.05 (s, 3 H), 3.0–3.06 (m, 1 H), 2.95–3.00 (m, 1 H), 2.25 (dd, J = 6.6, 9.4 Hz, 1 H), 2.12–2.23 (m, 1 H), 1.65 (m, 1 H, OH); ^{13}C NMR (90 MHz, $CDCl_3$) major isomer δ 171.21, 162.52, 141.06, 109.00, 100.00, 83.11, 81.25, 56.22, 53.22, 52.44, 42.35, 38.04, 37.40, 30.05; HRMS m/z calcd for $C_{14}H_{20}O_{10}S$ 380.0777, found 380.0807.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **7**, **8**, **9**, **11** (major and minor isomers), **12** (major isomer), **21b** (minor isomer), **25**, and **32** (R = H) (18 pages). Ordering information is given on any current masthead page.

Synthesis, Configuration, and Chemical Shift Correlations of Chiral 1,3,2-Oxazaphospholidin-2-ones Derived from *l*-Serine

Charles M. Thompson,* Jeffrey A. Frick, and Diana L. C. Green

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

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The reaction between (*S*)-methyl *N*-benzylserinoate and phosphorous oxychloride leads to the diastereomeric chloro-1,3,2-oxazaphospholidin-2-ones. Reaction of the chloridates with alcohols or phenols in the presence of base affords the corresponding alkoxy (or aryloxy) derivatives (66–94%), which were readily separated by standard chromatographic methods. The stereochemical arrangement of these compounds was established by NMR chemical shift correlations (carbon-13 and phosphorus-31) and single-crystal X-ray analysis. The trans geometry of the carbomethoxy and exocyclic phosphorus ligand resulted in approximately a 1 ppm upfield shift in the phosphorus-31 spectra relative to the cis isomer. The carbon-13 NMR spectra revealed an opposite trend in the heteroatom-bound alkyl region with most of the trans isomer signals appearing downfield (0.2–1.2 ppm) from the corresponding cis isomer.

Introduction

The past two decades have witnessed explosive growth in the preparation, reactivity, and utility of the carbon-based chiral center. By comparison, our understanding of events involving the corresponding chiral phosphorus atom remains in its infancy. To a large extent, this is due to a paucity of methods available for preparing chiral phosphorus molecules. Two representative examples include (a) reaction of a racemic phosphoryl halide with a suitably substituted chiral amine,[1] separation of the diastereomeric amides, and displacement of the auxiliary by acidic alcohol solutions and (b) reaction of a phosphoryl dihalide with a bifunctional chiral auxiliary to afford cyclic diastereomers[2] capable of undergoing a series of specific displacement reactions. In the latter instance, Inch and co-workers have elegantly extended this methodology to a wide variety of substrates utilizing ephedrine, pseudoephedrine, and sugars as the chiral appendage.[3,4] Interest in chiral phosphorus molecules, in part, emanates from their known utility as insecticides and nerve gas agents where specific interactions with biomolecules may be dependent upon the configuration at phosphorus.[5,6] Despite the fact that many of these compounds contain a center of asymmetry at phosphorus, little work has been conducted to determine the contribution of the individual antipodes to the toxic event.[7] To understand better the stereochemical implications at phosphorus upon these events, it would be advantageous to construct and examine reactions of chiral phosphorus molecules appended to amino acid residues. This study outlines our preliminary approach to this problem and characterizes the stereochemistry of cyclic chiral phosphorus intermediates obtained from a suitably substituted serine derivative.

Results and Discussion

Synthesis. Initially, amide (benzoyl) and sulfonamide (toluenesulfonyl) nitrogen protecting group derivatives of (*S*)-methyl serinoate were examined. Unfortunately, these derivatives could not be induced to cyclize in good conversion and mostly polymeric material was obtained. The *N*-benzyl derivative **2** was chosen owing to its structural similarity to previously reported 1,3,2-oxazaphosphorus cyclic systems prepared from ephedrine.[3] A somewhat surprising drawback to this approach was a paucity of

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