Hz), 4.26 (1 H, dd, J = 12.7, 7.3 Hz), 3.26 (2 H, AB, J = 18.0 Hz), 2.25-2.42 (2 H, m), 2.14 (1 H, ddd, J = 13.0, 7.2, 2.0 Hz), 1.83 (1 H, m), 1.6 (1 H, br s), 0.94 (9 H, s), 0.24 (3 H, s), 0.23 (3 H, s); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.5 (s), 133.9 (s), 129.6 (d), 123.5 (d), 122.0 (d), 119.5 (d), 102.0 (s), 100.9 (s), 85.3 (s), 85.1 (s), 77.4 (s), 59.9 (t), 36.8 (t), 29.0 (t), 25.9 (q), 24.9 (t), 18.3 (s), -2.7 (q), -2.9 (q); HRMS calcd for $C_{21}H_{28}O_2Si$ - tBu ($C_{17}H_{19}O_2Si$) 283.1154, found m/e 283.1156.

Conversion of the Allyl Alcohol 36 into Its Derived Thioacetate 36. To a solution of the alcohol **36** (106 mg) in dichloromethane (10 mL) was added Et_3N (450 μL) and the mixture cooled to -12 °C. Methanesulfonyl chloride (90 μL) was added and the mixture stirred for 15 min. A solution of freshly prepared sodium thioacetate (300 mg, 10 equiv) in methanol (2 mL) was added to the above mixture. After 1 h at 20 °C the mixture was poured into water (5 mL) and extracted with dichloromethane (2 × 5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue chromatographed over silica gel, eluting with 20% ether/petroleum ether, to give **37** (114.2 mg, 92%) as a colorless oil: IR (film) 2958, 2930, 2860, 1695, 1255, 1130, 840, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73-5.79 (4 H, m), 3.60-3.70 (2 H, ABX, J_{AB} = 13.5 Hz), 3.31 (1 H, d, J = 17.2 Hz), 3.25 (1 H, d, J = 17.2 Hz), 2.33 (3 H, s), 2.32 (2 H, m), 2.12 (1 H, m), 1.80 (1 H, ddd, J = 13.0, 9.5, 7.9 Hz), 0.91 (9 H, s), 0.22 (3 H, s), 0.20 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5 (s), 144.0 (s), 133.6 (s), 130.3 (d), 123.6 (d), 121.9 (d), 115.2 (d), 102.0 (s), 100.9 (s), 85.3 (s), 85.0 (s), 71.5 (s), 37.1 (t), 30.4 (q), 28.6 (t), 28.2 (t), 25.9 (q), 24.9 (t), 18.3 (s), -2.8 (q), -3.0 (q); HRMS calcd for $C_{23}H_{30}O_2SiS$ 398.1736, found m/e 398.1718.

***S*-Benzyl Trisulfide Adduct 38.** Treatment of a solution of the thioester **37** (11.4 mg) in ether (1.5 mL) with lithium aluminum hydride (35 μL, 1 M solution) at 0 °C for 10 min followed by warming to 20 °C for 0.5 h gave intermediate thiol **37a**, which was not isolated but used directly. Treatment of the thiol with *N*-(benzylthiosulfenyl)phthalimide (20 mg) in dichloromethane (0.8 mL) at 20 °C for 1 h gave the trisulfide **38** (13.4 mg, 92%) after purification by PLC, eluting with 10% ether/petroleum ether: IR (film) 2960, 2935, 2858, 1458, 1252, 1138, 1112, 836, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (5 H, m), 5.89 (1 H, m), 5.78 (1 H, d, J = 9.4 Hz), 5.75 (1 H, d, J = 9.4 Hz), 5.75 (1 H, m), 4.08 (2 H, J_{AB} = 2.7 Hz), 3.56-3.65 (2 H, ABX, J_{AB} = 12.7 Hz), 3.40 (1 H, d, J = 17.1 Hz), 3.26 (1 H, d, J = 17.1 Hz), 2.24-2.40 (2 H, m), 2.13 (1 H, m), 1.85 (1 H, ddd, J = 13.0, 9.3, 7.9 Hz), 0.93 (9 H, s), 0.23 (3 H, s), 0.21 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1 (s), 136.6 (s), 133.8 (s), 130.4 (d), 129.5 (d), 128.6 (d), 127.6 (d), 123.6 (d), 121.9 (d), 115.4 (d), 102.2 (s), 100.9 (s), 85.3 (s), 85.1 (s), 71.7 (s), 43.1 (t), 37.24 (t), 37.23 (t), 28.7 (t), 25.9 (q), 24.9 (t), 18.3 (s), -2.7 (q), -2.9 (q); HRMS calcd for $C_{28}H_{34}OSiS_3$ 510.1540, found m/e 510.1525. *S*-Methyl derivative: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (1 H, m), 5.78 (3 H, m), 3.40 (1 H, d, J = 17 Hz), 3.28 (1 H, d, J = 17 Hz), 2.43 (3 H, s), 2.36 (2 H, m), 2.36 (2 H, m), 2.17 (1 H, m), 1.86 (1 H, m), 0.95 (9 H, s), 0.23 (3 H, s), 0.21 (3 H, s).

Cyclic Sulfide 40. To a solution of the alcohol **36** (11.9 mg, 36.8 μmol) in dichloromethane (1.5 mL) at -15 °C were added triethylamine (50 μL) and methanesulfonyl chloride (10 μL). After 15 min potassium ethylxanthate (50 mg) was added and the mixture warmed to 20 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (2 × 5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by PLC, eluting with 20% ether/petroleum ether, to give the xanthate **39** (12.5 mg, 80.5%). The xanthate **39** (11.8 mg) in dichloromethane (0.5 mL) was treated with ethylenediamine (0.5 mL) at 20 °C for 1 h. Evaporation in vacuo and chromatography of the residue over silica gel gave the cyclic sulfide **40**: 6 mg, 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (1 H, dd, J = 10.9, 3.0 Hz), 6.14 (1 H, ddd, J = 3.4, 2.1, 0.7 Hz), 5.96 (1 H, ddd, J = 8.9, 8.0, 1.1 Hz), 5.52 (1 H, m), 5.44 (1 H, dd, J = 10.9, 2.1 Hz), 3.75 (1 H, dd, J = 13.2, 5.9 Hz), 3.48 (2 H, m), 2.92 (1 H, dd, J = 13.2, 8.0 Hz), 2.33 (2 H, m), 2.05 (1 H, m), 1.83 (1 H, dt, J = 13.2, 3.4 Hz), 0.93 (9 H, s), 0.22 (3 H, s), 0.19 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 140.6, 137.3, 129.6, 129.5, 127.2, 114.0, 113.4, 104.8, 90.7, 72.5, 39.9, 35.5, 26.5, 25.9, 24.0, 18.2, -3.0, 3.1; HRMS calcd for $C_{21}H_{28}OSiS$ 356.1630, found m/e 356.1624.

Acknowledgment. The National Institutes of Health (CA 50512), National Science Foundation, and Robert A. Welch Foundation are thanked for their support of this research. Dr. Jason Elliott is thanked for earlier contributions to this work.

Supplementary Material Available: Details of the X-ray structure determination of **13**, **22**, and **23** and tables of fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond lengths, bond angles (58 pages). Ordering information is given on any current masthead page.

Applications of an Asymmetric [2 + 2]-Photocycloaddition. Total Synthesis of (-)-Echinosporin. Construction of an Advanced 11-Deoxyprostaglandin Intermediate

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Contribution from the Department of Chemistry, the Monell Chemical Senses Center, and the Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received September 16, 1991*

Abstract: The first total synthesis of the novel antitumor metabolite (-)-echinosporin (**1**) has been achieved. Asymmetric [2 + 2]-photocycloaddition of dihydrofuran acetonide (+)-**8** to 2-cyclopentenone (**7**) constituted the cornerstone of the synthetic strategy. Mitsunobu lactonization of hemiacetal acid **43** generated the tricyclic framework of **1**, which embodies a strain energy of ca. 17 kcal/mol as estimated by MNDO calculations. The successful synthetic venture permitted assignment of the absolute configuration of echinosporin. Construction of the Corey 11-deoxyprostaglandin intermediate (+)-**49** further demonstrated the utility of (+)-**8** as a chiral building block.

The isolation of (-)-echinosporin (XK-213) from the fermentation broth of *Streptomyces echinosporus* was reported by a group from the Kyowa Hakko Kogyo Co. (Japan) in 1981.[1] The structure of **1**, initially deduced via spectroscopic and chemical methods, was later confirmed by a single-crystal X-ray analysis.[2] Although **1** displays modest activity against Gram-negative bacteria, its efficacy against several rodent tumor models appears promising.[3] Moreover, in vitro studies have implicated the in-

(1) (a) Iida, T. N.; Hirayama, N.; Shirahata, K. *Abstr. Papers, 44th Annu. Meeting Jpn. Chem. Soc.*, October 12, 1981, 1E-18, pp 403. Kyowa Hakko Kogyo Co., Ltd. *Jpn. K. Tokkyo Koho* **1981**, *59*, 777. (b) Sato, T.; Kawamoto, I.; Oka, T.; Okachhi, R. *J. Antibiot.* **1982**, *35*, 266.

(2) Hirayama, N.; Iida, T.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 287.

(3) Morimoto, M.; Imai, R. *J. Antibiot.* **1985**, *38*, 490.

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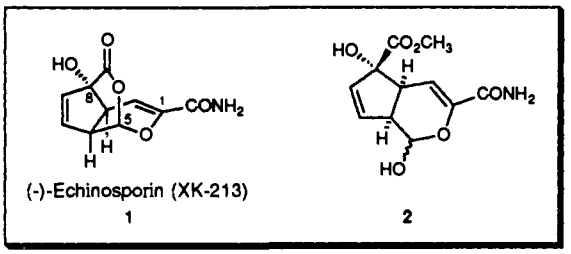
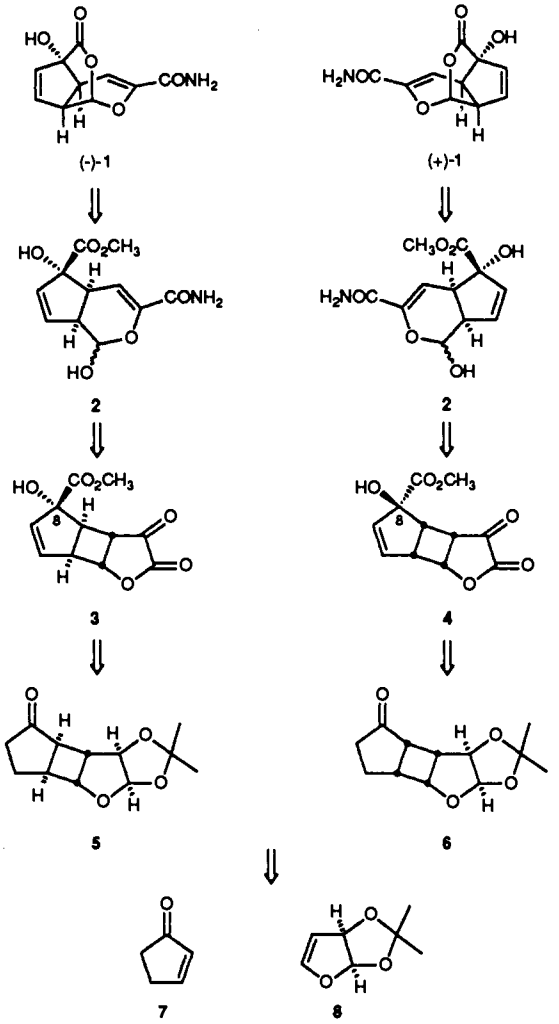
hibition of DNA synthesis as a likely mechanism for the observed cytotoxicity.[3]



The strained and highly functionalized architecture of echinosporin presents a formidable synthetic challenge.[4] Significant bond angle distortions provide one measure of the anticipated difficulty in assembling the tricyclic framework. For example, the C(8)–C(3)–C(4) cyclopentene bond angle is only 98.5°, whereas the C(2)–C(1)–C(6) value of 123.2° is unusually large. Indeed, MNDO calculations revealed a 17 kcal/mol increase in strain energy upon conversion of bicyclic hemiacetal ester **2** to the tricyclic skeleton of **1**.[5] A viable synthetic strategy for echinosporin must also orchestrate installation of the four contiguous stereocenters; to control absolute stereochemistry, we sought to devise a new asymmetric [2 + 2]-photocycloaddition employing dihydrofuran (+)-**8** as a chiral template. Herein we describe the implementation of this approach, culminating in the first, and to date only, total synthesis of echinosporin.[6] The utility of our asymmetric photoreaction is further demonstrated by the construction of advanced 11-deoxyprostaglandin intermediate (+)-**49**.

Scheme I



Synthetic Strategy. Our analysis of the echinosporin problem inspired a novel enantiodivergent strategy (Scheme I), employing as a chiral building block dihydrofuran **8**, readily available from L-ascorbic acid. A [2 + 2]-photocycloaddition of 2-cyclopentenone (**7**) with **8** was predicted to furnish a mixture of anti and syn tetracyclic adducts **5** and **6**. We would then exploit the concave–convex nature of the latter structures to secure the correct relative and absolute stereochemistry of the C(8) α-hydroxy ester moiety. Deprotection of the diol and oxidation would then provide the corresponding α-keto lactones **3** and **4**, which upon treatment with ammonia would induce a de Mayo fragmentation–cyclization sequence,[7] affording acetal **2**. Finally, lactonization of **2** or the corresponding carboxylic acid would generate echinosporin.

Construction of (+)- and (−)-Dihydrofuran 8: Useful Chiral Templates. We envisioned that dihydrofuran **8** would be prepared most readily by dehydration of the known alcohol **12**, a ketalized derivative of threose **10** which in turn is accessible via degradation of various carbohydrates. By suitable selection of the starting sugar, both enantiomers of **8** were thus anticipated to be available. Following the procedure of Perlin,[8] treatment of D-galactose (**9**) with lead tetraacetate in acetic acid afforded a mixture of **10** and the derived formate **11** (Scheme II). The resultant mixture furnished the corresponding acetonides **12** and **13** in a combined yield of 34% upon exposure to 1% sulfuric acid in acetone. The formate was readily converted to alcohol (−)-**12** upon treatment with potassium carbonate in methanol (89% yield).

The (+) isomer was prepared from methyl L-threonate (**16**), obtained via a Hoffmann–La Roche three-step sequence (Scheme III).[9] The latter entailed conversion of L-ascorbic acid to the 5,6-isopropylidene derivative **14**, followed by Isbell–Frush oxidation[10] and methylation to provide **16** in 54% overall yield. Hydroxyl protection as a THP ether and ester reduction then gave aldehyde (+)-**18**, whereupon methanolysis followed by acetonide formation produced the crystalline alcohol (+)-**12** (53% yield from **16**).

Turning to the dehydration of **12**, we found that several standard procedures were completely ineffective. We therefore explored a less direct alternative involving Bamford–Stevens reduction[11] of the corresponding tosylhydrazone **20** (Scheme III). Oxidation of alcohol **12** to furanone **19** proceeded uneventfully, but attempted purification generated the known furanone dimer.[12] Isolation of the reactive furanone could be avoided by in situ generation of **20**.[13] The hydrazone likewise was not purified, but instead

(4) Previous synthetic studies: (a) Kinsella, M. A.; Kalish, V. J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 105. (b) Deprez, D.; Margraff, R.; Bizot, J.; Pulicani, J. P. *Tetrahedron Lett.* **1987**, *28*, 4679. (c) Taschner, M. J.; Rach, N. L. *Abstracts of Papers*, 190th National Meeting of the American Chemical Society, Chicago, IL, September 1985; American Chemical Society: Washington, DC, 1985; ORGN 97. (d) Wincott, F. E. Ph.D. Thesis, Yale University, New Haven, CT, 1989.

(5) The enthalpies of lactonization for the unstrained model system 5-hydroxyvaleric acid → δ-valerolactone and for **43** → **1** were determined via the MINDO method, providing an estimate of the strain incurred upon lactonization of **43**. Wood, J. L., University of Pennsylvania. Unpublished results.

(6) Preliminary communication: Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039.

(7) The de Mayo photocycloaddition–fragmentation–cyclization tactic has been exploited widely in complex molecule synthesis. For reviews, see: de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. Baldwin, S. W. *Synthetic Aspects of [2+2] Cycloadditions of α,β-Unsaturated Carbonyl Compounds*; Padwa, A., Ed.; Marcel Dekker, Inc.: New York, 1981; Vol. 5, Chapter 2. Also see: Büchi, G.; Carlson, J. A.; Powell, J. E.; Tietz, L.-F. *J. Am. Chem. Soc.* **1970**, *92*, 2165.

(8) (a) Perlin, S. A. *Methods Carbohydr. Chem.* **1968**, *1*, 68. (b) Perlin, S. A.; Brice, C. *Can. J. Chem.* **1955**, *33*, 1216.

(9) Chung, C. W.; De Bernardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3462.

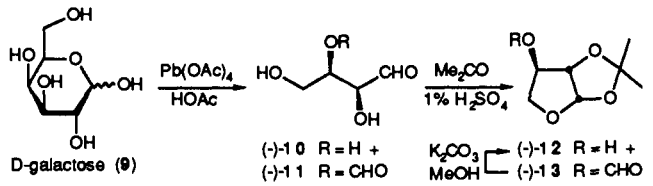
(10) (a) Isbell, H. S.; Frush, H. L. *Carbohydr. Res.* **1979**, *72*, 301. (b) Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta* **1986**, *69*, 1273.

(11) (a) Gianturco, M. A.; Friedel, P.; Flanagan, V. *Tetrahedron Lett.* **1965**, 1847. (b) Shapiro, R. H. *Org. React.* **1976**, *23*, 405.

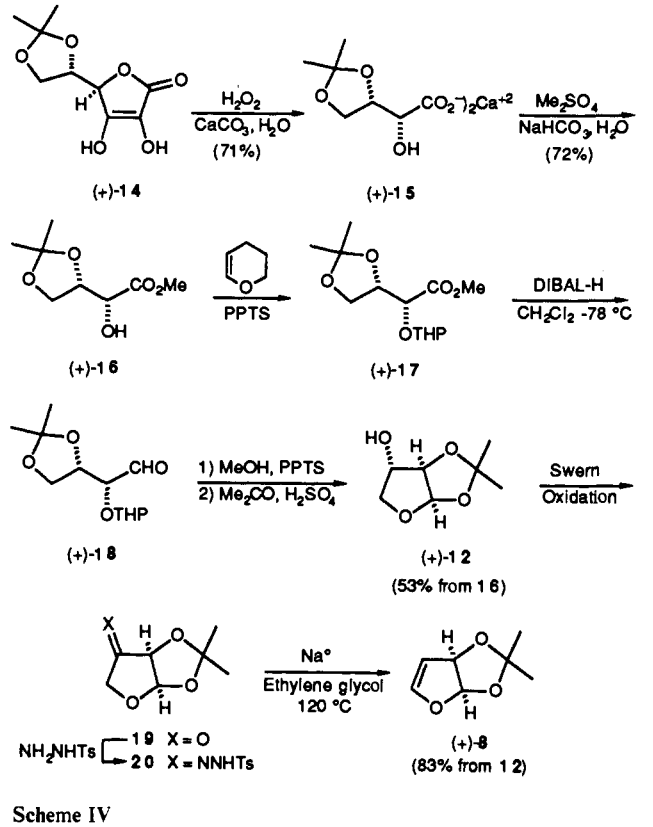
(12) (a) Nachman, R.; Honel, M.; Williams, T. H.; Halaska, R. C.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 4802. (b) Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3.

(13) (a) Swern, D.; Omura, K. *Tetrahedron* **1978**, *34*, 1651. (b) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

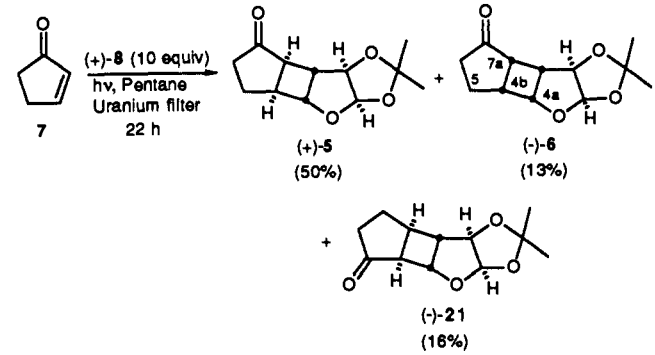
Scheme II



Scheme III



Scheme IV

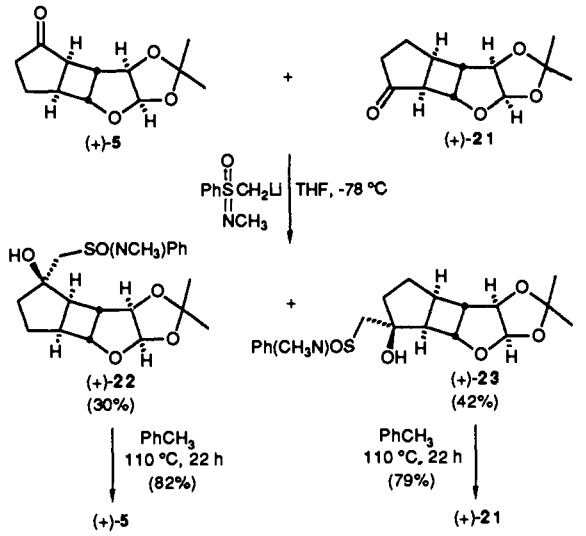


used directly in the Bamford–Stevens reaction under protic conditions to afford dihydrofuran **8**. The two-step process proved to be both efficient (80–85% overall yield) and amenable to large-scale work. Importantly, both (+)- and (−)-**8** are now readily available from alcohols (+)- and (−)-**12**, respectively.

Asymmetric Photocycloaddition of Dihydrofuran (+)-8 to 2-Cyclopentenone (7). With an efficient synthesis of dihydrofuran (+)-**8** in hand, we next addressed the [2 + 2]-photocycloaddition with 2-cyclopentenone (**7**). We anticipated the head-to-tail regioselectivity characteristic of photocycloadditions involving enones and enol ethers.[14] The addition was also expected to occur from the less hindered exo face of the bicyclic dihydrofuran. Finally,

(14) (a) de Mayo, P.; Pete, J.-P.; Tchir, M. *J. Am. Chem. Soc.* **1967**, *89*, 5712. (b) Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50. (c) Ermont, D.; De Keukeleire, D.; Vandewalle, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2349.

Scheme V



literature precedent suggested the probable generation of approximately equal amounts of anti and syn adducts **5** and **6**.[15] Both isomers were viewed as potentially useful for the synthesis of echinosporin (vide supra).

Photocycloadditions of electron-rich olefins with **7** are typically carried out with a 10- to 20-fold excess of the olefin in a nonpolar solvent.[14] Our best results were obtained by irradiation of cyclopentenone (0.03 M) and dihydrofuran (+)-**8** (0.3 M) in pentane at room temperature for 22 h, using a 450-W Hanovia lamp with a uranium-glass filter. This protocol generated a 4:1.2:1 mixture of three photoadducts in 79% yield (Scheme IV), with 80–90% recovery of excess (+)-**8**. Flash chromatography furnished only one of the minor isomers in pure form (vide infra). Fortunately, the major product readily crystallized; single-crystal X-ray analysis revealed the head-to-tail, cis-anti-cis structure (+)-**5**.[16] Separation of the second minor isomer from **5** required chemical manipulation. To this end, addition of the α-lithio derivative of (−)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine to a ca. 1:1 mixture of **5** and the minor isomer afforded carbinols (+)-**22** and (+)-**23** (Scheme V).[17] Following purification by flash chromatography, thermolysis of the chromatographically more mobile alcohol **22** (toluene, 110 °C) regenerated the major photoadduct **5**. Thermolysis of **23** in turn furnished a white crystalline solid, identified as the head-to-head, cis-anti-cis isomer (−)-**21** via single-crystal X-ray analysis.[16]

The third photoadduct, obtained in pure form via flash chromatography of the ternary mixture, was initially characterized by NMR analysis. A combination of ^{1}H decoupling and a two-dimensional, phase-sensitive COSY experiment led to assignment of the head-to-tail, cis-syn-cis structure (−)-**6** (Scheme IV). The head-to-tail regiochemistry was deduced from the C(4b)–C(5) and C(4a)–C(4b) proton–proton couplings (J = 8.3 and 4.9 Hz, respectively), whereas the W coupling (J = 3.0 Hz) between the C(4a) and C(7a) protons provided support for the syn stereochemistry. The formulation of **6** was later confirmed by X-ray analysis of a more advanced intermediate (vide infra).

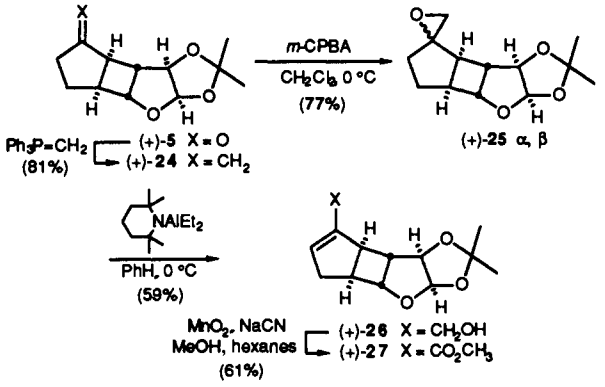
Generation of Hemiacetal (+)-2, the Penultimate Intermediate. Elaboration of the major photoadduct (+)-**5** initially entailed homologation to enoate **27**. We first explored the oxidation of allylic alcohol **26**, available by base-induced rearrangement of epoxide **25** (Scheme VI). Reaction of cyclopentanone **5** with methylenetriphenylphosphorane and epoxidation of the resultant olefin [(+)-**24**] with *m*-CPBA provided a 6:1 mixture of α- and

(15) For an example of a photocycloaddition of dihydrofuran, see: Bauslaugh, P. G. *Synthesis* **1970**, 287, ref 29.

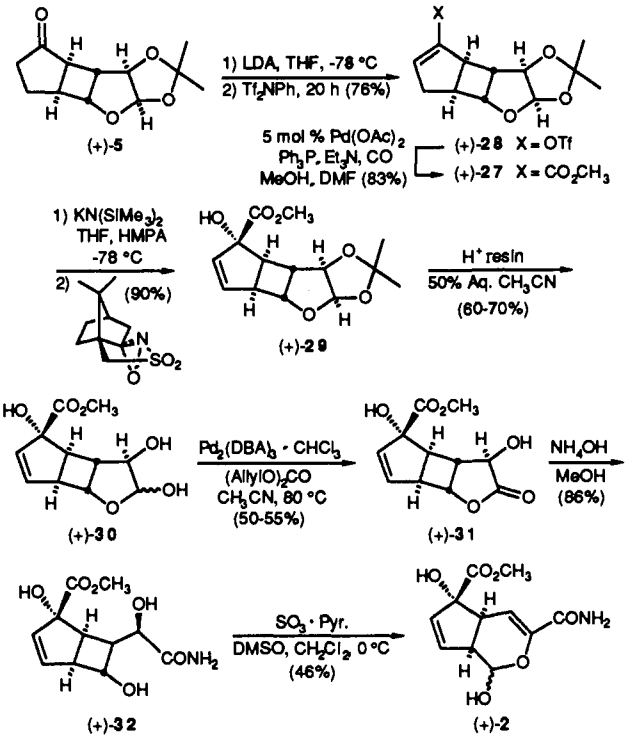
(16) Unpublished results of Dr. P. Carroll, University of Pennsylvania X-ray Crystallographic Facility.

(17) (a) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021. (b) Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, 1225.

Scheme VI



Scheme VII

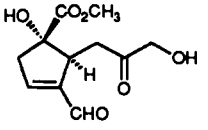


β-epoxides **25** in 74% yield. Treatment of the mixture with diethylaluminum 2,2,6,6-tetramethylpiperidide gave allylic alcohol (+)-**26** in 59% yield,[18] and in turn oxidation (MnO_2, MeOH, NaCN, hexanes) furnished the requisite enoate (+)-**27** (61% yield).

Concerned with the overall length of this sequence, we devised a more efficient scheme for conversion of **5** to **27** via the palladium-mediated carbonylation of enol triflate (+)-**28** (Scheme VII).[19] The latter tactic involved only two steps and afforded enoate **27** in 63% overall yield, whereas the former sequence required four operations and provided **27** in only 26% overall yield.

Exposure of enoate **27** to strong base was expected to generate the corresponding dienolate, and oxidation of the latter would then introduce the C(8) α-hydroxy group with the desired relative stereochemistry (Scheme VII). We elected to utilize the Davis 2-(phenylsulfonyl)-3-phenyloxaziridine as the source of electrophilic oxygen.[20] Whereas the lithium dienolate (LDA, THF, −78 °C, 2 h) was initially unreactive, addition of HMPA did lead to the carbinol (+)-**29**, albeit in low yield (ca. 20%).[21] After further optimization, oxidation of the potassium dienolate [$KN(SiMe_3)_2$, 20% HMPA/THF, −78 °C, 2 h] with the (+)-(camphorylsulfonyl)oxaziridine reproducibly furnished **29** in 90–94% yield.

We next turned our attention to the key rearrangement sequence designed to generate the potentially delicate hemiacetal **2**. Hydrolysis of isopropylidene (+)-**29** with BioRad AG50W-X2 acidic resin in 50% aqueous CH_3CN provided triol (+)-**30** (60–70%) (Scheme VII).[22] Chemoselective oxidation of the lactol in the presence of the secondary and tertiary hydroxyls initially proved problematic: the Fetizon reagent gave a mixture of a diol cleavage product and the desired hydroxy lactone **31** in low yield, whereas attempted ruthenium-mediated dehydrogenation [$(Ph_3P)_3RuH_2$, $PhCH_3$, reflux, 2 h] provided enal **33** via an overall isomerization process involving oxidation of the secondary alcohol and reduction of the aldehyde.[23] Selective oxidation of the lactol hydroxyl was finally achieved via palladium-catalyzed dehydrogenation [$Pd_2(DBA)_3 \cdot CHCl_3$ (10 mol %), diallyl carbonate, acetonitrile, 80 °C], affording (+)-**31** in 50–55% yield.[24]



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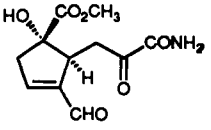

(+)-**34**

Further oxidation of **31** to keto lactone **3** with MnO_2 gave variable results; moreover, exposure of **3** to methanolic ammonia resulted in complete decomposition. We therefore devised a successful variation of this strategy (Scheme VII) involving initial ammonolysis of (+)-**31** (NH_4OH, MeOH) to furnish cyclobutanol **32** (86% yield). Oxidation of the latter (SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2)[25] induced the desired fragmentation–cyclization sequence, providing the key hemiacetal intermediate (+)-**2** in 46% yield. However, exposure of **2** to base or silica gel led to ring opening and olefin migration to afford isomer (+)-**34**, a compound of no great utility. Careful reverse-phase chromatography did, however, enable us to isolate and characterize the sensitive hemiacetal.

A parallel series of transformations was next explored in an effort to convert the cis-syn-cis photoadduct (−)-**6** to the enantiomeric hemiacetal (−)-**2** (vide supra). Functionalization of the cyclopentane ring, diol deprotection, and oxidation to hydroxy lactone **39** proceeded essentially as described for the cis-anti-cis series (Scheme VIII). Ammonolysis of **39** expectedly generated the δ-lactone **40**; the latter structure was secured by single-crystal X-ray analysis.[16] Efforts to convert **40** to echinosporin, however, were unfruitful.

Lactonization Studies: Final Elaboration of (−)-Echinosporin (1). At this juncture we were able to correlate synthetic hemiacetal (+)-**2** with natural (−)-echinosporin. Methanolysis of the latter furnished a sample of **2** which was indistinguishable from the totally synthetic material by 500-MHz ^1H NMR and 125-MHz ^{13}C NMR analysis. Furthermore, the optical rotations, +53.0° (*c* 0.8, MeOH) for synthetic **2** and +64.6° (*c* 0.8, MeOH) for **2** derived from natural **1**,[26] permitted us to assign the previously unknown absolute configuration of the natural product as depicted in **1**.

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(19) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

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(21) (a) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433. (b) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, *13*, 4249.

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(24) (a) Tsuji, J.; Minami, I. *Tetrahedron* **1987**, *43*, 3903. (b) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269.

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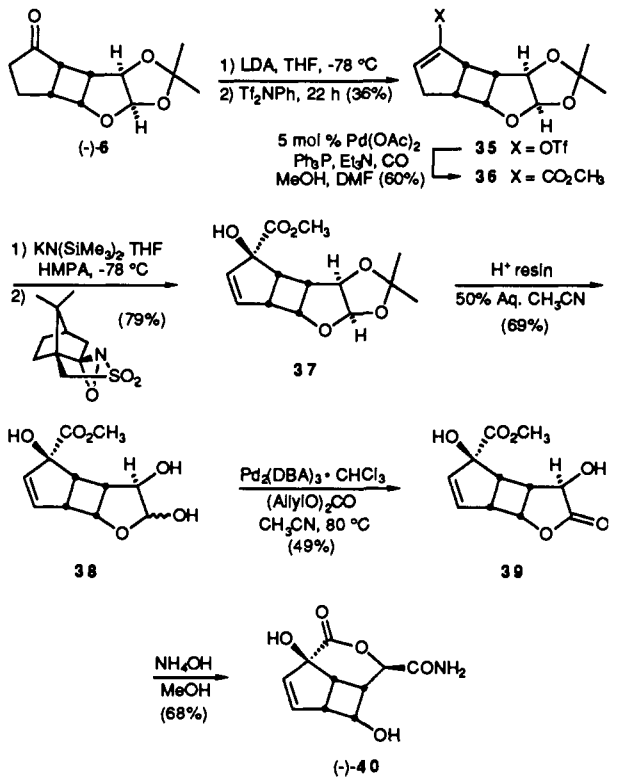
(26) The difference in optical rotation values for synthetic and naturally derived **2** apparently reflects variations in temperature and/or anomer ratio. The rotations of synthetic and natural echinosporin are virtually identical (vide infra).

Scheme VIII



All that remained to complete the total synthesis of (−)-echinosporin was lactonization of hemiacetal ester (+)-**2**. In initial experiments, exposure of **2** to various acidic conditions with concomitant removal of methanol led to no reaction or decomposition, whereas basic conditions gave either decomposition or enal (+)-**34**.

The reluctance of **2** to lactonize raised concerns about the conformation of the bicyclic ring system as well as the configuration of the hemiacetal hydroxyl group. Examination of molecular models suggested that the α- and β-anomers could each adopt two flattened half-chair conformations, illustrated in Figure 1 along with the calculated H_1–H_2 coupling constants.[27] Experimentally, $J_{1,2}$ for the major anomer (ca. 20:1 mixture) proved to be 7.88 Hz. Thus, comparison with the calculated couplings indicated that the major epimer contained an α-hydroxy in a pseudoequatorial conformation.

Further support for this assignment was derived from acetylation studies (Scheme IX). Exposure of hemiacetal **2** to the Mitsunobu[28] protocol (HOAc, Ph_3P, DIAD, THF) furnished two anomeric acetates in 74% yield. The β-configuration of the major product [(+)-**41**β] was deduced from the observed 6% nuclear Overhauser enhancement between H_1 and H_2. In addition, acetylation of **2** (Ac_2O, pyridine, 4-PP, CH_2Cl_2) provided diacetate (+)-**42** almost quantitatively, and acetylation of the minor Mitsunobu product, (+)-**41**α, gave the same diacetate. These results not only buttressed the assignment of the anomeric configuration for **2** but also suggested that echinosporin might be generated via intramolecular Mitsunobu lactonization of the corresponding hydroxy acid.

To this end, acidic hydrolysis (3.6 N HCl) of the methyl ester moiety of **2** furnished carboxylic acid **43** quantitatively (Scheme X). The acid was purified via ion-exchange chromatography on DEAE Sephadex followed by lyophilization. With ample quantities of **43** in hand, we explored a range of phosphorus reagents [e.g., Ph_3P, $(MeO)_3P$, $(Me_2N)_3P$, and Me_3P] and reaction conditions for the proposed Mitsunobu lactonization. The best results were obtained by addition of a preformed tri-*n*-butylphosphine–DEAD complex to a solution of **43** in THF containing 4-Å molecular sieves at −15 °C. Additional reagent was added after 1 h at −15 °C, and the mixture was then allowed to stir overnight at room temperature. This protocol furnished (−)-echinosporin (**1**) in 28–31% yield. The synthetic echinosporin was identical with a sample of natural material, kindly provided by Dr. Fumio Suzuki of Kyowa Hakko Kogyo Co., as judged by ^1H NMR and IR spectra and optical rotation data {$[\alpha]_D$ −402° (*c* 0.08, CH_3OH); natural: $[\alpha]_D$ −400° (*c* 0.10, CH_3OH)}.

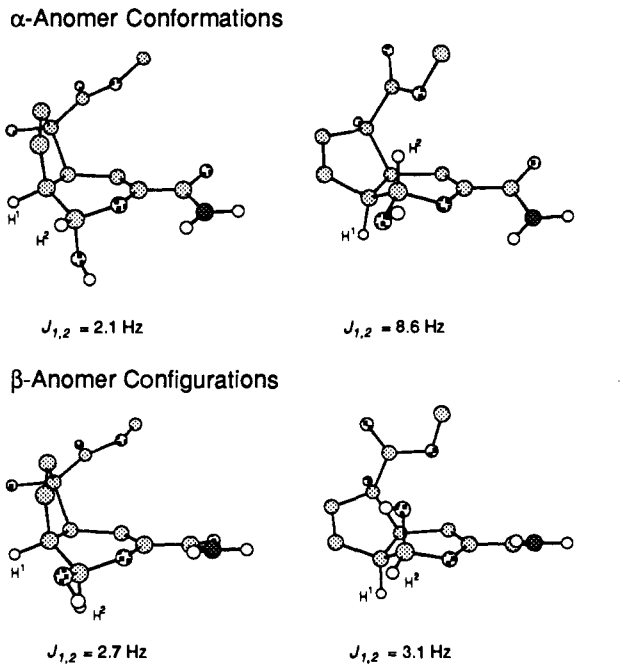
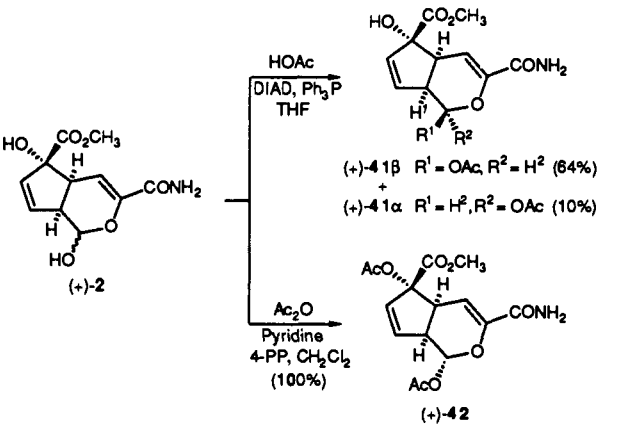
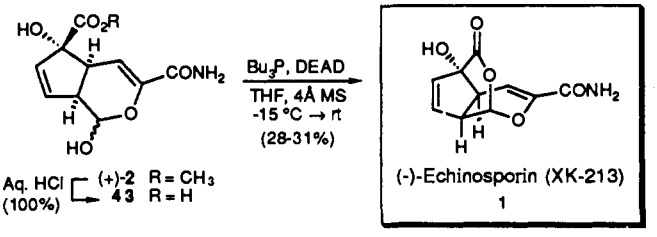


Figure 1. Calculated H_1–H_2 coupling constants for the half-chair conformers of the α- and β-anomers of hemiacetal (+)-**2**.

Scheme IX



Scheme X



(27) The coupling constants were calculated with the MacroModel program (version 2.5). Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. Department of Chemistry, Columbia University, New York, NY 10027.

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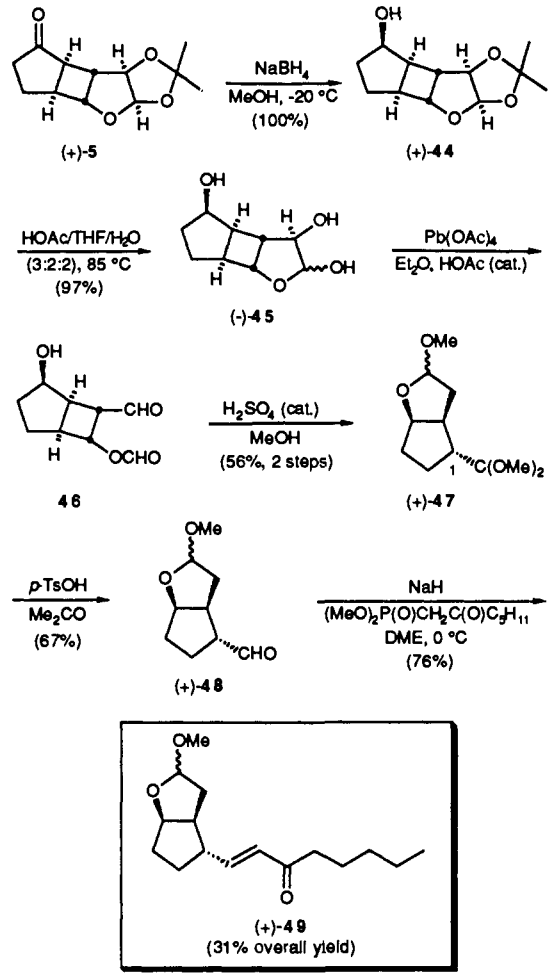
Scheme XI



Asymmetric Synthesis of an 11-Deoxyprostaglandin Intermediate. To further demonstrate the utility of dihydrofuran **8** as a chiral template, we sought to prepare **49**, the versatile Corey intermediate for the synthesis of 11-deoxyprostaglandins.[29] We envisioned a six-step route beginning with the cis-anti-cis photoadduct **5** (Scheme XI).[30]

Stereoselective sodium borohydride reduction of ketone (+)-**5** followed by acidic hydrolysis afforded triol (−)-**45** almost quantitatively. Oxidative diol cleavage with lead tetraacetate was performed in diethyl ether rather than pyridine or acetic acid to minimize decomposition of formate aldehyde **46** upon removal of the solvent. The latter intermediate was immediately subjected to acidic methanolysis. In the ensuing sequence of transformations, initial alcoholysis of the formate induced fragmentation and hemiacetal formation; C(1) epimerization, followed by acetal formation, then furnished (+)-**47** in 56% overall yield from **45**.[31] Transketalization with *p*-TsOH in acetone gave aldehyde (+)-**48**, whereupon the Corey protocol was employed to incorporate the lower side chain in (+)-**49** with excellent stereocontrol.[29c] The antipode of **49** would likewise be available from dihydrofuran (−)-**8**. Importantly, the six-step sequence can be carried out with only a single chromatographic purification.

Experimental Section[32]

Oxidation of D-Galactose (9). A mixture of D-galactose **9** (10 g, 55 mmol) and glacial acetic acid (750 mL) was heated to dissolution and allowed to cool to room temperature, and lead tetraacetate (51.2 g, 115 mmol) was added in portions (ca. 5 g) over a 5-min period. The reaction mixture was stirred at room temperature for 10 min, and then oxalic acid (12.6 g) was added. The suspension was stirred for 1 h and filtered through Celite. Following concentration in vacuo, the residual oil was dissolved in acetone (200 mL). The solution was cooled to 0 °C, concentrated sulfuric acid (1 mL) was added, and the reaction mixture was stirred overnight. Anhydrous potassium carbonate (2 g) was then introduced, and the mixture was stirred for 2 h, filtered, and concentrated in vacuo. Flash chromatography with hexane/ethyl acetate (2:1) as eluant afforded 1.9 g (18% yield) of (−)-**13** and 1.4 g (16% yield) of (−)-**12**.

(−)-**13**: mp 40.5–42.5 °C; R_f 0.57 (1:1 hexanes/EtOAc); $[\alpha]^{25}_D$ −39.8° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 3000 (m), 2970 (m), 2950 (w), 1735 (s), 1455 (w), 1390 (s), 1380 (s), 1170 (s), 1100 (s), 1020 (s), 960 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (s, 3 H), 1.43 (s, 3 H), 3.92 (d, J = 10.90 Hz, 1 H), 4.10 (dd, J = 10.90, 2.90 Hz, 1 H), 4.52 (d, J = 3.71 Hz, 1 H), 5.17 (d, J = 2.83 Hz, 1 H), 5.89 (d, J = 3.73 Hz, 1 H), 7.97 (s, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 189.0766 [(M + H)$^+$, calcd for $C_8H_{13}O_5$ 189.0762].

(−)-**12**: mp 83.0–84.0 °C; R_f 0.15 (1:1 hexanes/EtOAc); $[\alpha]^{25}_D$ −10.6° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3018 (m), 3000 (m), 2960 (m), 2880 (m), 1750 (s), 1460 (m), 1445 (m), 1390 (m), 1380 (m), 1250–1200 (br s), 1130 (s), 1080 (s), 1040 (s), 970 (m), 910 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.49 (s, 3 H), 2.28 (d, J = 5.30 Hz, 1 H), 3.87 (dd, J = 2.7, 10.15 Hz, 1 H), 4.27 (m, 1 H), 4.57 (d, J = 3.67 Hz, 1 H), 5.95 (d, J = 3.68 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 161.0823 [(M + H)$^+$, calcd for $C_7H_{13}O_4$ 161.0814].

Hydrolysis of (−)-13. A solution of formate (−)-**13** (1.9 g, 10.1 mmol), methanol (25 mL), and a catalytic amount of potassium carbonate (ca. 10 mg) was stirred for 14 h. The mixture was then concentrated in vacuo and the product purified by flash chromatography (2:1 hexanes/EtOAc) to afford the acetal (−)-**12** (1.44 g, 89% yield), obtained as a colorless solid and identical in all respects to (−)-**12** prepared above.

Tetrahydropyranyl Ether (+)-17. A solution of methyl ester **16**[9] (53 g, 0.279 mol), dichloromethane (1 L), dihydropyran (100 mL, 0.558 mol), and pyridinium *p*-toluenesulfonate (1 g) was stirred for 12 h at room temperature. The reaction mixture was then washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography (4:1 hexane/EtOAc) gave tetrahydropyranyl ether **17** (78 g, 100% yield) as a colorless oil: $[\alpha]^{25}_D$ +24.3° (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3018 (m), 3000 (m), 2960 (m), 2880 (m), 1750 (s), 1460 (m), 1445 (m), 1390 (m), 1380 (m), 1250–1200 (s), 1130 (s), 1080 (s), 1040 (s), 970 (m), 910 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35, 1.36 (s, s, diastereomers, 3 H), 1.41, 1.43 (s, s, diastereomers, 3 H), 1.58 (br m, 3 H), 1.75 (br m, 2 H), 1.85 (m, 1 H), 3.48 (m, 1 H), 3.75, 3.76 (s, s, diastereomers, 3 H), 3.90, 4.06 (m, m, diastereomers, 3 H), 4.14 (dd, d, diastereomers, J = 11.2, 6.09

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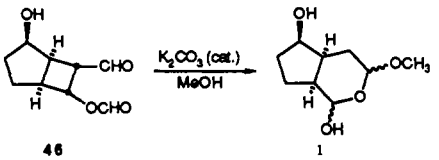
(30) For the achiral version of this approach to 11-deoxyprostaglandins, see: Ogino, T.; Yamada, K.; Isogai, K. *Tetrahedron Lett.* **1977**, 2445.

(31) Basic conditions included an undesired rearrangement of (+)-**46** to i.



(32) **Materials and Methods.** All reactions were carried out under an argon atmosphere using dry, freshly distilled solvents and oven-dried glassware, unless otherwise noted. Tetrahydrofuran was distilled from sodium/benzophenone; dichloromethane and benzene were distilled from calcium hydride. Triethylamine and diisopropylamine were distilled from calcium hydride and stored over potassium hydroxide. Dimethyl sulfoxide and hexamethylphosphoramide were distilled from calcium hydride and stored over 4-Å molecular sieves. Acetone, acetonitrile, dimethylformamide, and methanol were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm). Reverse-phase chromatography was performed with the indicated solvents using prepacked RP-8 LOBAR columns. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are corrected unless otherwise noted. ^1H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane or CD_3OD. GLC analyses were performed with a Hewlett-Packard 5790A chromatograph equipped with a 12 m × 0.2 mm × 0.33 mm HP-1 (cross-linked methyl silicone gum) column. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center by John Dykins on a VG Micromass 70/70H or VG ZAB-E spectrometer. The single-crystal X-ray diffraction analyses were performed by Dr. Patrick Carroll of the University of Pennsylvania using an Enraf Nonius CAD-4 diffractometer.

Hz, J = 6.85 Hz, 1 H), 4.46, 4.36 (m, m, diastereomers, 1 H), 4.81, 4.73 (t, t, diastereomers, J = 2.27 Hz, J = 3.31 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 292.1778 [$(M + NH_4)^+$, calcd for $C_{13}H_{26}O_6N$ 292.1760].

Aldehyde (+)-18. A solution of methyl ester **17** (23 g, 91 mmol) and dichloromethane (400 mL) was cooled to −78 °C and treated dropwise with a solution of diisobutylaluminum hydride (1.0 M in hexanes, 100 mL, 100 mmol). The resultant mixture was stirred for 1 h at −78 °C, and then methanol (5 mL) and a saturated solution of Rochelle salts (200 mL) were added. After the solution was stirred for an additional 30 min at room temperature, the aqueous layer was extracted with methylene chloride (3 × 300 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to furnish aldehyde **18** (23 g, 100% yield) as a colorless oil: $[\alpha]^{25}_D$ +30.0° (c 0.71, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2960 (m), 2880 (m), 2860 (m), 1740 (s), 1460 (w), 1445 (w), 1390 (m), 1380 (m), 1265 (m), 1210 (s), 1130 (s), 1080 (s), 1035 (s), 910 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35, 1.36 (s, s, diastereomers, 3 H), 1.42, 1.43 (s, s, diastereomers, 3 H), 1.50–1.65 (m, 3 H), 1.65–1.90 (m, 3 H), 3.50 (m, 1 H), 3.75–4.10 (m, 3 H), 4.14, 4.27 (d, d, diastereomers, J = 4.52 Hz, J = 6.86 Hz, 1 H), 4.48, 4.30 (m, m, diastereomers, 1 H), 4.82, 4.73 (m, m, diastereomers, 1 H), 9.71, 9.76 (d, d, diastereomers, J = 1.10 Hz, J = 1.87 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 262.1632 [$(M + NH_4)^+$, calcd for $C_{12}H_{24}NO_5$ 262.1654].

Alcohol (+)-12. A solution of aldehyde **18** (23 g, 94 mmol), methanol (800 mL), and pyridinium p-toluenesulfonate was stirred for 3 h at room temperature and then concentrated in vacuo. The resultant oil was successively taken up in three 100-mL portions of acetone, and the resultant solutions were concentrated in vacuo. The oil was then dissolved in acetone (500 mL), and the solution was cooled to 0 °C and treated dropwise with concentrated sulfuric acid (2.5 mL). The mixture was stirred at room temperature for 2 h and then sodium bicarbonate (18 g) was added. After an additional 24 h, the mixture was filtered through Celite and concentrated in vacuo. The resulting yellow solid was purified via flash chromatography (2:1 hexanes/EtOAc), affording acetal (+)-**12** (7.62 g, 53% yield) as a white solid. Recrystallization from hexanes/ether (3:1) furnished a white solid: mp 83.0–84.0 °C; $[\alpha]^{25}_D$ +12.7° (c 0.15, acetone); IR ($CHCl_3$) 3590 (m), 3560–3200 (br w), 2990 (m), 2940 (m), 2890 (w), 1390 (m), 1380 (m), 1200–1250 (br m), 1165 (m), 1080 (s), 1015 (s), 925 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.49 (s, 3 H), 2.28 (d, J = 5.3 Hz, 1 H), 3.87 (dd, J = 10.15, 2.7 Hz, 1 H), 4.09 (dd, J = 10.15, 2.76 Hz, 1 H), 4.27 (m, 1 H), 4.50 (d, J = 3.67 Hz, 1 H), 5.95 (d, J = 3.68 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 161.0825 [$(M + H)^+$, calcd for $C_7H_{12}O_4$ 161.0814]. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.62; H, 7.55.

Tosylhydrazone 20. A solution of oxalyl chloride (12.0 mL) in dichloromethane was cooled to −78 °C, and a solution of DMSO (20.4 mL, 287 mmol) in dichloromethane (60 mL) was added dropwise. The solution was stirred for 10 min, alcohol (+)-**12** (20 g, 125 mmol) dissolved in dichloromethane (60 mL) was introduced, and the resultant mixture was stirred for 15 min. Triethylamine (88 mL) was then added, and the mixture was allowed to warm to 0 °C and treated with p-toluenesulfonohydrazide (23.2 g, 125 mmol). After stirring at room temperature for an additional 10 min, the reaction was diluted with water (300 mL) and extracted with dichloromethane (3 × 600 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to furnish hydrazone **20**, which was used directly in the next reaction. A sample was purified by flash chromatography (1:1 hexanes/EtOAc) for characterization: mp 151.0–153.0 °C; IR ($CHCl_3$) 3300 (w), 3200 (w), 3030 (w), 3000 (w), 1605 (w), 1460 (w), 1410 (w), 1390 (m), 1380 (m), 1355 (m), 1250–1200 (br m), 1170 (s), 1100 (m), 1025 (m), 960 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.36 (s, 3 H), 2.44 (s, 3 H), 4.50 (AB q, J_{AB} = 15.22, $\Delta\nu_{AB}$ = 18.55 Hz, 2 H), 4.84, 4.97 (d, d, diastereomers, J = 3.91 Hz, J = 4.51 Hz, 1 H), 5.87, 5.92 (d, d, diastereomers, J = 3.73 Hz, J = 4.53 Hz, 1 H), 7.33 (d, J = 8.06 Hz, 2 H), 7.82 (d, J = 8.04 Hz, 2 H), 8.43 (br, s 1 H); high-resolution mass spectrum (CI, NH_3) m/z 327.1025 [$(M + H)^+$, calcd for $C_{14}H_{19}N_2O_5S$ 327.1008].

Dihydrofuran (+)-8. Hydrazone **20** was dissolved in a solution containing the sodium salt of ethylene glycol (6 g of sodium dissolved in 300 mL of ethylene glycol), and the resultant mixture was heated to 120 °C for 1 h. Dihydrofuran **8** was then isolated by a short-path distillation at reduced pressure (15 mmHg) and collected in a vessel cooled to −78 °C. The product was next purified by flash chromatography (10:1 pentane/diethyl ether) to afford dihydrofuran **8** (14.7 g, 83% yield) as a colorless oil: $[\alpha]^{25}_D$ +14.1° (c 0.88, acetone); IR ($CHCl_3$) 3020 (w), 2990 (m), 2940 (w), 1612 (s), 1545 (w), 1385 (s), 1378 (s), 1340 (w), 1320 (w), 1290 (w), 1250 (s), 1150 (s), 1110 (s), 1045 (s), 1025 (s), 1000 (m), 945 (m), 910 (s), 890 (m), 825 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.48 (s, 3 H), 5.28 (m, 2 H), 6.04 (d, J = 5.01 Hz, 1 H), 6.50 (d, J = 1.70 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.7, 27.7, 82.6, 102.8, 105.7, 112.1, 149.1; λ_{max} (pentane) 220.8 (ϵ 2.97 × 10^4) nm; high-resolution mass spectrum (CI, isobutane) m/z 143.0713 [$(M + H)^+$, calcd for $C_7H_{11}O_3$ 143.0708].

[2 + 2]-Photocycloaddition of (+)-8 with 2-Cyclopentenone (7). Argon was passed through a solution of 2-cyclopentenone (**7**) (631 mg, 7.70 mmol) and dihydrofuran **8** (11 g, 77 mmol) in pentane (240 mL) for 0.5 h. The solution was then irradiated at room temperature with a 450-W medium-pressure mercury lamp through a uranium-glass filter for 22 h under an atmosphere of argon. The pentane was then removed via simple distillation. Flash chromatography (gradient elution, 10:1 pentane/diethyl ether → 2:1 hexanes/EtOAc) afforded 8.5 g (78% yield) of starting dihydrofuran **8**, 278 mg (16% yield) of **6**, and 1.092 g (ca. 63% yield) of a 4:1 mixture of **5** and **21**, as determined by GLC analysis. The major regioisomer **5** was selectively crystallized from petroleum ether/ether (1:1).

6: white solid; mp 85.0–86.0 °C; R_f 0.21 (4:1:1 hexanes/CH_2Cl_2/Et_2O); $[\alpha]^{25}_D$ −118.2° (c 0.22, acetone); IR ($CHCl_3$) 3020 (m), 2990 (m), 2950 (m), 1728 (s), 1455 (w), 1388 (m), 1378 (m), 1250–1220 (br m), 1165 (m), 1080 (m), 1060 (s), 1015 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 1 H), 1.43 (s, 1 H), 1.93 (m, 1 H), 2.18 (m, 1 H), 2.34 (m, 1 H), 2.51 (m, 1 H), 2.89 (app t, J = 8.09 Hz, 1 H), 2.99 (ddd, J = 8.34, 8.34, 4.82 Hz, 1 H), 3.17 (dd, J = 9.66, 4.85 Hz, 1 H), 4.84 (d, J = 3.84 Hz, 1 H), 4.92 (ddd, J = 4.85, 4.85, 2.98 Hz, 1 H), 5.78 (d, J = 3.87 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.3, 26.9, 27.3, 37.9, 39.7, 44.4, 46.0, 81.2, 81.9, 109.2, 112.0, 219.9; high-resolution mass spectrum (CI, NH_3) m/z 225.1138 [$(M + H)^+$, calcd for $C_{12}H_{17}O_4$ 225.1127]. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.18.

5: white solid; mp 104.5–105.0 °C; R_f 0.13 (4:1:1 hexanes/CH_2Cl_2/Et_2O); $[\alpha]^{25}_D$ +191.2° (c 0.08, acetone); IR ($CHCl_3$) 3010 (m), 3000 (w), 2940 (w), 1735 (s), 1380 (m), 1370 (m), 1225 (m), 1160 (s), 1070 (s), 1020 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.45 (s, 3 H), 1.93–1.99 (m, 1 H), 2.14–2.22 (m, 1 H), 2.31–2.38 (m, 1 H), 2.52–2.63 (m, 2 H), 2.74 (m, 1 H), 2.95 (app t, J = 4.85 Hz, 1 H), 4.66 (d, J = 4.99 Hz, 1 H), 4.72 (d, J = 3.53 Hz, 1 H), 6.08 (d, J = 3.52 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.0, 27.2, 27.8, 37.3, 42.3, 44.3, 46.1, 83.7, 85.7, 107.8, 113.4, 218.7; high-resolution mass spectrum (CI, NH_3) m/z 224.1132 [$(M + H)^+$, calcd for $C_{12}H_{17}O_4$ 224.1127]. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.38; H, 7.09.

Sulfoximine Adducts (+)-22 and (+)-23. A solution of (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (1.54 g, 9.11 mmol) and THF (20 mL) was cooled to 0 °C, and *n*-BuLi (2.4 M in hexanes, 2.4 mL, 10.0 mmol) was added dropwise. The reaction was stirred at 0 °C for 5 min. The solution was then cooled to −78 °C, and a solution of regioisomers **5** and **21** (ca. 1:1, 1.86 g, 8.28 mmol) in THF (5 mL) was added. The mixture was stirred for 20 min at −78 °C and then poured into a saturated solution of ammonium chloride (15 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (gradient elution, 2:1 → 1:1 hexanes/EtOAc) afforded 595 mg of **22** (18% yield) and 973 mg of **23** (30% yield) as amorphous solids. The remaining material consisted of a mixture of **22** and **23** (784 mg, ca. 26% yield).

22: R_f 0.29 (1:1 hexanes/EtOAc); $[\alpha]^{25}_D$ +26.0° (c 0.46, $CHCl_3$); IR ($CHCl_3$) 3400–3100 (br m), 3000 (m), 2950 (m), 2880 (w), 2810 (w), 1450 (m), 1385 (m), 1375 (m), 1230 (s), 1150 (s), 1070 (s), 880 (m), 850 (m), 690 (m), 630 (m), 570 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.47 (s, 3 H), 1.57–1.65 (br m, 4 H), 2.03 (m, 1 H), 2.48 (m, 1 H), 2.60 (s, 3 H), 3.17 (d, J = 7.11 Hz, 1 H), 3.14 (AB q, J_{AB} = 13.86 Hz, $\Delta\nu_{AB}$ = 16.58 Hz, 2 H), 4.62 (d, J = 3.60 Hz, 1 H), 5.03 (dd, J = 5.63, 1.02 Hz, 1 H), 6.10 (d, J = 3.60 Hz, 1 H), 7.56–7.63 (m, 3 H), 7.85 (m, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 394.1695 [$(M + H)^+$, calcd for $C_{20}H_{28}NO_5S$ 394.1692].

23: R_f 0.23 (1:1 hexanes/EtOAc); $[\alpha]^{25}_D$ +69.1° (c 0.18, $CHCl_3$); IR ($CHCl_3$) 3400–3080 (br m), 3060 (m), 3020–3000 (s), 2950 (s), 2890 (m), 2820 (w), 1455 (s), 1480–1450 (br s), 1390 (s), 1380 (s), 1340 (m), 1240 (s), 1160 (s), 1110 (s), 1070 (s), 1025 (s), 880 (m), 860 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.46 (s, 3 H), 1.75 (m, 2 H), 2.00 (m, 2 H), 2.29 (app t, J = 7.40 Hz, 1 H), 2.63 (s, 3 H), 2.69 (dd, J = 13.38, 6.86 Hz, 1 H), 3.20 (m, 1 H), 3.11 (AB q, J_{AB} = 13.93, $\Delta\nu_{AB}$ = 103.83 Hz, 2 H), 4.46 (d, J = 5.30 Hz, 1 H), 4.55 (d, J = 3.55 Hz, 1 H), 5.95 (d, J = 3.51 Hz, 1 H), 7.56–7.65 (m, 3 H), 7.85 (m, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 394.1708 [$(M + H)^+$, calcd for $C_{20}H_{28}NO_5S$ 394.1692].

Ketone (−)-21 via Thermolysis of Sulfoximine Adduct (+)-23. A solution of sulfoximine adduct **23** (239 mg, 0.69 mmol) in toluene (10 mL) was heated at reflux for 12 h. Concentration in vacuo followed by flash chromatography (2:1 hexanes/EtOAc) afforded ketone **21** (122 mg, 79% yield) as an oil which crystallized upon standing: white solid, mp

98.0–99.0 °C; $[\alpha]^{25}_D$ −193.4° (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 3020 (w), 2990 (m), 2940 (m), 1735 (s), 1455 (w), 1410 (w), 1385 (m), 1375 (m), 1335 (w), 1250–1200 (br m), 1165 (s), 1080 (s), 1070 (s), 1030 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.43 (s, 3 H), 2.05 (m, 2 H), 2.39 (dd, *J* = 18.56, 8.8 Hz, 1 H), 2.54 (m, 1 H), 2.63 (d, *J* = 6.39 Hz, 1 H), 2.76 (dd, *J* = 12.37, 6.38 Hz, 1 H), 2.91 (app t, *J* = 4.91 Hz, 1 H), 4.61 (d, *J* = 4.88 Hz, 1 H), 4.70 (d, *J* = 3.53 Hz, 1 H), 6.07 (d, *J* = 3.53 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.4, 27.2, 27.8, 36.6, 36.8, 48.6, 52.6, 79.4, 85.6, 108.2, 113.3, 217.5. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.35; H, 7.02.

Olefin (+)-24. A suspension of methyltriphenylphosphonium bromide (3.98 g, 11.1 mmol) in toluene (40 mL) was treated with *n*-BuLi (2.4 M in hexanes, 4.46 mL, 11.1 mmol), and the resulting orange solution was stirred at room temperature for 1.5 h. A solution of ketone **5** (500 mg, 2.23 mmol) in THF (2 mL) was added dropwise, and the mixture was then heated at reflux for 5 h. After stirring overnight at room temperature, the mixture was diluted with 1 M HCl (20 mL), and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10:1 hexanes/EtOAc) provided olefin **24** (403 mg, 81% yield) as a colorless solid: mp 64.0–65.0 °C; $[\alpha]^{25}_D$ +165.1° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3020 (w), 3000 (w), 2950 (m), 2870 (w), 1660 (w), 1460 (w), 1445 (w), 1390 (m), 1210 (s), 1165 (m), 1070 (s), 1020 (m), 895 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 3 H), 1.42 (s, 3 H), 1.62–1.73 (m, 2 H), 2.47–2.72 (m, 5 H), 4.47 (d, *J* = 5.27 Hz, 1 H), 4.67 (d, *J* = 3.59 Hz, 1 H), 4.77 (br s, 1 H), 4.81 (br s, 1 H), 6.03 (d, *J* = 3.58 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 223.1351 [(M + H)$^+$, calcd for $C_{13}H_{19}O_3$ 223.1333].

Epoxides (+)-25α and (+)-25β. A solution of olefin **24** (289 mg, 1.30 mmol) in dichloromethane (5 mL) was cooled to 0 °C, and *m*-CPBA (270 mg, 1.56 mmol) was added. After stirring at 0 °C for 0.5 h, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then diluted with saturated sodium bicarbonate (10 mL), the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) afforded 238 mg of epoxide **25α** (77% yield) and 40 mg of epoxide **25β** (13% yield) as colorless solids.

25α: mp 72.5–74.0 °C; R_f 0.40 (3:1 hexanes/EtOAc); $[\alpha]^{25}_D$ +95.0° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) 3030 (s), 2950 (w), 1390 (w), 1380 (w), 1215 (s), 1170 (m), 1085 (s), 1020 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (s, 3 H), 1.38 (s, 3 H), 1.48 (dd, *J* = 13.96, 7.59 Hz, 1 H), 1.71 (dd, *J* = 13.12, 7.75 Hz, 1 H), 1.92 (m, 2 H), 2.25 (m, 1 H), 2.63 (m, 2 H), 2.80 (AB q, J_{AB} = 4.24 Hz, $\Delta\nu_{AB}$ = 18.22 Hz, 2 H), 4.43 (d, *J* = 5.33 Hz, 1 H), 4.53 (d, *J* = 3.54 Hz, 1 H), 5.98 (d, *J* = 3.54 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.0, 27.6, 27.7, 31.5, 43.3, 45.3, 45.5, 47.5, 67.5, 82.8, 85.8, 107.5, 112.8; high-resolution mass spectrum (CI, NH_3) *m/z* 239.1268 [(M + H)$^+$, calcd for $C_{13}H_{19}O_4$ 239.1283]. Anal. Calcd for $C_{13}H_{18}O_3$: C, 65.53; H, 7.61. Found: C, 65.33; H, 7.60.

25β: mp 46.0–47.5 °C; R_f 0.38 (3:1 hexanes/EtOAc); $[\alpha]^{25}_D$ +90.4° (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2950 (s), 2880 (m), 1490 (m), 1465 (m), 1410 (m), 1390 (s), 1380 (s), 1345 (m), 1320 (m), 1210–1240 (br s), 1170 (s), 1080 (s), 1010 (s), 985 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.46 (s, 3 H), 1.60–1.93 (m, 3 H), 2.07 (dd, *J* = 6.91, 4.34 Hz, 1 H), 2.19 (m, 1 H), 2.56 (app t, *J* = 6.96 Hz, 1 H), 2.84 (AB q, J_{AB} = 5.25 Hz, $\Delta\nu_{AB}$ = 9.80 Hz, 2 H), 3.03 (app t, *J* = 4.74 Hz, 1 H), 4.56 (m, 2 H), 6.02 (d, *J* = 3.51 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.3, 26.9, 27.7, 30.1, 39.8, 43.4, 44.6, 56.2, 66.2, 83.2, 86.0, 107.4; high-resolution mass spectrum (CI, NH_3) *m/z* 239.1238 [(M + H)$^+$, calcd for $C_{13}H_{19}O_4$ 239.1283].

Allylic Alcohol (+)-26. Lithium tetramethylpiperidide was prepared at 0 °C by the addition of *n*-BuLi (2.5 M in hexanes, 0.80 mL, 1.98 mmol) to a solution of tetramethylpiperidine (0.33 mL, 1.98 mmol) in benzene (3 mL). The solution was stirred for 15 min and treated with diethylaluminum chloride (1.80 M in toluene, 1.10 mL, 1.98 mmol). The resultant white suspension was stirred for an additional 0.5 h, and a solution of epoxides **25α** and **25β** (6:1 α/β, 118 mg, 0.49 mmol) in benzene (1 mL) was then added. After stirring for 15 min, the reaction mixture was carefully poured into 1 M HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) provided alcohol **26** (69 mg, 59% yield) as a colorless oil: $[\alpha]^{25}_D$ +25.4° (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 3620 (w), 3580–3230 (br w), 3020 (m), 3000 (m), 2970 (m), 2860 (w), 1390 (m), 1380 (m), 1215 (s), 1165 (s), 1080 (s), 1030 (m), 975 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.44 (s, 3 H), 2.38 (m, 1 H), 2.64 (m, 2 H), 2.89 (m, 2 H), 2.99 (m, 1 H), 4.23 (m, 2 H), 4.54 (dd, *J* = 5.60, 1.34 Hz, 1 H), 4.72 (d, *J* = 3.65 Hz, 1 H), 5.65 (br s, 1 H), 6.08 (d, *J* = 3.65 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 239.1310 [(M + H)$^+$, calcd for $C_{13}H_{19}O_4$ 239.1283].

Enol Triflate (+)-28. Lithium diisopropylamide was generated at −78 °C by the addition of *n*-BuLi (2.4 M in hexanes, 2.04 mL, 4.90 mmol) to a solution of diisopropylamine (0.69 mL, 4.90 mmol) in THF (8 mL). After the mixture was stirred for 0.5 h, a solution of ketone **5** (1.00 g, 4.46 mmol) in THF (2 mL) was added. The reaction was stirred for an additional 0.75 h, and a solution of *N*-phenyltrifluoromethanesulfonimide (1.75 g, 4.90 mmol) in THF (4 mL) was introduced. The resultant mixture was then stirred for 10 h at −20 °C, warmed to room temperature, and stirred overnight. The reaction was quenched with saturated ammonium chloride (15 mL), and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with 1 M NaOH (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10:1 hexanes/EtOAc) furnished triflate **28** (1.21 g, 76% yield) as a colorless oil: $[\alpha]^{25}_D$ +15.0° (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2990 (m), 2940 (m), 2850 (w), 1650 (m), 1425 (s), 1390 (s), 1380 (s), 1335 (m), 1245 (s), 1200 (s), 1140 (s), 1115 (s), 1070 (s), 1020 (m), 975 (s), 915 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.45 (s, 3 H), 2.41 (m, 1 H), 2.73 (br m, 2 H), 3.11 (m, 1 H), 3.19 (app t, *J* = 3.73 Hz, 1 H), 4.62 (dd, *J* = 5.70, 1.74 Hz, 1 H), 4.69 (d, *J* = 3.61 Hz, 1 H), 5.70 (br s, 1 H), 6.06 (d, *J* = 3.62 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 357.0653 [(M + H)$^+$, calcd for $C_{13}H_{16}O_6F_3S$ 357.0628]. Anal. Calcd for $C_{13}H_{15}F_3O_6S$: C, 43.82; H, 4.24. Found: C, 43.96; H, 4.35.

Ester (+)-27. Method 1. A suspension containing alcohol **26** (45 mg, 0.147 mmol), methanol (0.5 mL), NaCN (1 mg), MnO_2 (1 g), and hexanes (3 mL) was stirred for 2 days at room temperature. The reaction mixture was diluted with dichloromethane (5 mL) and filtered through Celite. Concentration in vacuo and flash chromatography (2:1 hexanes/EtOAc) provided methyl ester **27** (24 mg, 61% yield) as a colorless solid.

Method 2. A stream of carbon monoxide was passed through a solution of enol triflate **28** (4.065 g, 11.41 mmol), methanol (20 mL), $Pd(OAc)_2$ (87 mg, 0.84 mmol), Ph_3P (174 mg, 0.66 mmol), and triethylamine (3.1 mL) in DMF (50 mL) for 0.5 h. A carbon monoxide-filled balloon was then fit to the reaction flask, and stirring was continued for an additional 20 h. The reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (4 × 75 mL), and the combined extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) furnished methyl ester **27** (2.51 g, 83% yield) as white needles: mp 75.5–77.0 °C; $[\alpha]^{25}_D$ +40.4° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2980 (m), 1715 (s), 1625 (w), 1445 (m), 1390 (m), 1380 (m), 1300 (m), 1280 (m), 1240 (s), 1160 (m), 1070 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.43 (s, 3 H), 2.51 (m, 1 H), 2.72 (m, 1 H), 2.80 (m, 1 H), 2.92 (app t, *J* = 4.41 Hz, 1 H), 3.23 (m, 1 H), 3.74 (s, 3 H), 4.54 (dd, *J* = 5.66, 1.80 Hz, 1 H), 4.78 (d, *J* = 3.57 Hz, 1 H), 6.08 (d, *J* = 3.56 Hz, 1 H), 6.78 (br s, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 267.1225 [(M + H)$^+$, calcd for $C_{14}H_{19}O_5$ 267.1232]. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.75; H, 7.09.

Alcohol (+)-29. A solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 20.0 mL, 10.0 mmol) in THF (26 mL) and HMPA (10 mL) was stirred for 10 min at 0 °C and cooled to −78 °C. After the addition of methyl ester **27** (2.417 g, 9.075 mmol) dissolved in THF (10 mL), the mixture was stirred for 2 h. The resultant enolate was treated with (+)-(camphorylsulfonyl)oxaziridine (4.162 g, 18.15 mmol) in THF (15 mL). After 5 min, the reaction mixture was poured into a saturated solution of ammonium chloride (25 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with water (50 mL) and brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was triturated with Et_2O (3 × 10 mL), and the Et_2O extracts were then combined and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) provided carbinol **29** (2.35 g, 90% yield) as colorless needles: mp 127.0–129.0 °C; $[\alpha]^{25}_D$ +80.5° (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 3590 (w), 3560–3100 (br w), 3020 (m), 3000 (m), 2960 (m), 1740 (s), 1660 (w), 1460 (w), 1445 (w), 1390 (m), 1380 (m), 1345 (s), 1210 (s), 1170 (s), 1070 (s), 1020 (m), 960 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.42 (s, 3 H), 2.55 (app t, *J* = 5.48 Hz, 1 H), 2.78 (app t, *J* = 5.01 Hz, 1 H), 3.31 (m, 1 H), 3.85 (s, 3 H), 4.53 (d, *J* = 5.00 Hz, 1 H), 4.57 (d, *J* = 3.56 Hz, 1 H), 5.96 (m, 1 H), 6.09 (d, *J* = 3.55 Hz, 1 H), 6.13 (dd, *J* = 5.25, 2.41 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 27.9, 44.2, 48.2, 52.0, 52.7, 81.0, 85.0, 87.4, 108.6, 112.9, 133.3, 136.6, 173.0; high-resolution mass spectrum (CI, NH_3) *m/z* 283.1165 [(M + H)$^+$, calcd for $C_{14}H_{19}O_6$ 283.1182]. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.16; H, 6.69.

Triol (+)-30. A mixture of carbinol **29** (500 mg, 1.77 mmol), Bio-Rad AG50W-X2 resin (400 mg), and 50% aqueous CH_3CN (20 mL) was stirred for 3 days at room temperature. Filtration, concentration in

vacuo, and flash chromatography (10:1 $CHCl_3$/MeOH) afforded triol **30** (297 mg, 69% yield) as a white foam: $[\alpha]^{25}_D$ +40.4° (*c* 0.58, MeOH); IR (KBr) 3700–3040 (br s), 2960 (m), 1730 (s), 1445 (m), 1400 (m), 1380 (m), 1310 (m), 1150 (s), 790 (m) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.37, 2.43 (app t, app t, diastereomers, J = 5.36 Hz, J = 5.27 Hz, 1 H), 2.47, 2.94 (app t, app t, diastereomers, J = 5.16 Hz, J = 5.20 Hz, 1 H), 3.23, 3.36 (m, m, diastereomers, 1 H), 3.87 (s, 3 H), 3.88, 4.03 (s, s, diastereomers, 1 H), 4.19, 4.33 (d, d, diastereomers, J = 5.70 Hz, J = 5.62 Hz, 1 H), 5.46, 5.57 (d, d, diastereomers, J = 0.56 Hz, J = 2.96 Hz, 1 H), 5.93, 5.96 (m, m, diastereomers, 1 H), 6.06 (m, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 260.1155 [$(M + NH_4)^+$, calcd for $C_{11}H_{18}NO_6$ 260.1134].

Enal 33. A stream of argon was passed through a solution of triol **30** (38 mg, 0.16 mmol), methyl allyl carbonate (91 mg, 0.78 mmol), and $(Ph_3P)_3RuH_2$ (2 mg) in toluene (3 mL) for 0.5 h. The reaction mixture was then brought to reflux for 2 h, cooled to room temperature, and concentrated in vacuo. Flash chromatography (10:1 $CHCl_3$/MeOH) afforded enal **33** (12 mg, 32% yield) as a yellow oil: IR ($CHCl_3$) 3580 (w), 3580–3200 (br w), 3020 (m), 2940 (w), 2830 (w), 1740 (s), 1685 (s), 1625 (w), 1445 (w), 1405 (w), 1370 (w), 1285 (m), 1230 (m), 1055 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.53 ($^1/_2$ ABX, J = 18.53, 10.85 Hz, 1 H), 2.84 (ddd, J = 19.48, 2.78, 0.75 Hz, 1 H), 3.07 ($^1/_2$ ABX, J = 18.48, 3.64 Hz, 1 H), 3.23 (ddd, J = 19.50, 1.87, 1.87 Hz, 1 H), 3.71 (s, superimposed on m, 4 H), 4.21 (AB q, J_{AB} = 18.73, $\Delta\nu_{AB}$ = 44.34 Hz, 2 H), 6.88 (m, 1 H), 9.71 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.5, 45.2, 50.8, 52.9, 67.9, 83.5, 145.2, 150.0, 174.0, 189.0, 208.7; high-resolution mass spectrum (CI, NH_3) m/z 260.1169 [$(M + NH_4)^+$, calcd for $C_{11}H_{18}NO_6$ 260.1134].

Lactone (+)-31. A stream of argon was passed through a solution of triol **30** (1.455 g, 6.00 mmol) in CH_3CN (150 mL) for 0.5 h. Diallyl carbonate (2.24 mL, 15.61 mmol) and $Pd_2(DBA)_3{\cdot}CHCl_3$ (553 mg, 0.60 mmol) were added, and the mixture was heated to 80 °C for 3 h. After the mixture was cooled to room temperature and concentrated in vacuo, flash chromatography (10:1 $CHCl_3$/MeOH) followed by medium-pressure reverse-phase chromatography (RP-8, LOBAR, gradient elution, $H_2O \rightarrow 5\%$ CH_3CN/H_2O) provided lactone **31** (777 mg, 54% yield) as a white solid: mp 90.5–92.0 °C; $[\alpha]^{25}_D$ +121.5° (*c* 0.13, MeOH); IR ($CHCl_3$) 3580 (w), 3550–3000 (br m), 3020 (m), 1780 (s), 1738 (s), 1645 (w), 1350 (w), 1255 (m), 1210 (m), 1170 (m), 1110 (w), 1055 (s), 1020 (w), 1010 (w), 1000 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.69 (app t, J = 5.48 Hz, 1 H), 2.86 (app t, J = 5.40 Hz, 1 H), 3.02 (br s, 1 H, OH), 3.14 (br s, 1 H, OH), 3.58 (m, 1 H), 3.87 (s, 3 H), 4.32 (s, 1 H), 4.68 (d, J = 5.43 Hz, 1 H), 6.05 (dd, J = 5.49, 0.85 Hz, 1 H), 6.17 (dd, J = 5.47, 2.42 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.9, 49.3, 51.9, 53.0, 72.8, 79.5, 87.3, 134.8, 134.9, 172.8, 177.6; high-resolution mass spectrum (CI, NH_3) m/z 258.0948 [$(M + NH_4)^+$, calcd for $C_{11}H_{16}NO_6$ 258.0978].

Amide (+)-32. A solution of lactone **31** (50 mg, 0.208 mmol) in methanol (5 mL) was cooled to 0 °C and treated with ammonium hydroxide (4 drops). The mixture was stirred at room temperature for 20 h and then concentrated in vacuo. Flash chromatography (10:1 $CHCl_3$/MeOH) gave amide **32** (46 mg, 86% yield) as colorless needles: mp 158.5–160.0 °C; $[\alpha]^{25}_D$ +63.3° (*c* 0.18, MeOH); IR (KBr) 3580–3000 (br s), 2980 (w), 2960 (w), 2940 (w), 2920 (w), 2890 (w), 1720 (s), 1645 (s), 1445 (m), 1410 (m), 11350 (w), 1290 (m), 1210 (m), 1180 (m), 1150 (m), 1110 (w), 1090 (w) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.43 (m, 1 H), 3.03 (app t, J = 6.45 Hz, 1 H), 3.26 (m, 1 H), 3.73 (s, 3 H), 3.96 (d, J = 6.67 Hz, 1 H), 4.26 (d, J = 7.57 Hz, 1 H), 5.86 (ddd, J = 5.54, 1.40, 0.70 Hz, 1 H), 6.13 (dd, J = 5.50, 2.29 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 43.8, 49.5, 52.7, 53.3, 71.1, 71.4, 88.9, 135.4, 137.3, 174.6, 179.3; high-resolution mass spectrum m/z 258.1005 [$(M + H)^+$, calcd for $C_{11}H_{16}NO_6$ 258.0978].

Hemiacetal (+)-2. A solution of amide **32** (42 mg, 0.163 mmol) in DMSO (0.60 mL) and dichloromethane (0.40 mL) was cooled to 0 °C, treated with triethylamine (0.160 mL, 1.146 mmol), and stirred for 5 min. A sulfur trioxide–pyridine complex (105 mg, 0.660 mmol) was added, and the mixture was stirred for 1 h and then quenched with water (1 mL). Concentration in vacuo and medium-pressure reverse-phase chromatography (RP-8, LOBAR, gradient elution, $H_2O \rightarrow 5\%$ CH_3CN/H_2O) afforded hemiacetal **2** (19 mg, 46% yield) as an oil: $[\alpha]^{25}_D$ +53.0° (*c* 0.80, MeOH); IR (KBr) 3700–3000 (br s), 2970 (m), 1745 (s), 1690 (s), 1650 (s), 1600 (m), 1445 (m), 1415 (m), 1345 (m), 1320 (m), 1290 (m), 1230 (m), 1145 (m), 1075 (s), 965 (m) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.94 (m, 1 H), 3.04 (dd, J = 8.07, 4.19 Hz, 1 H), 3.76, 3.66 (s, s, diastereomers, 3 H), 4.84 (d, J = 7.90 Hz, 1 H), 5.85 (dd, J = 5.82, 1.52 Hz, 1 H), 6.05 (d, J = 4.36 Hz, 1 H), 6.13 (dd, J = 5.46, 2.55 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 50.3, 50.6, 52.7, 90.3, 97.8, 106.6, 135.7, 136.1, 146.2, 166.3, 174.5; high-resolution mass spectrum (CI, NH_3) m/z 256.0875 [$(M + H)^+$, calcd for $C_{11}H_{14}NO_6$ 256.0821].

Methanolysis of Echinosporin (1). A solution of echinosporin (**1**) (75 mg, 0.336 mmol) in methanol (6 mL) containing concentrated HCl (2 drops) was stirred for 23 h at room temperature. Dilution with water (1 mL), concentration in vacuo, and medium-pressure reverse-phase chromatography (gradient elution, $H_2O \rightarrow 5\%$ CH_3CN/H_2O) furnished hemiacetal methyl ester **2** (76 mg, 88% yield) as an amorphous solid: $[\alpha]^{25}_D$ +64.6° (*c* 0.82, MeOH); IR (KBr) 3700–3000 (s), 2960 (m), 1740 (s), 1690 (s), 1645 (s), 1600 (m), 1420 (m), 1345 (m), 1320 (m), 1290 (m), 1275 (m), 1225 (m), 1140 (m), 1070 (s), 960 (m) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.94 (m, 1 H), 3.03 (dd, J = 7.96, 4.07 Hz, 1 H), 3.76, 3.66 (s, s, diastereomers, 3 H), 5.25, 4.84 (d, d, diastereomers, J = 3.05 Hz, J = 7.88 Hz, 1 H), 5.85 (dd, J = 5.84, 1.34 Hz, 1 H), 6.05 (d, J = 4.10 Hz, 1 H), 6.13 (dd, J = 5.75, 2.52 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 50.2, 50.6, 52.7, 90.3, 97.8, 106.7, 135.7, 136.1, 146.2, 166.3, 174.5; high-resolution mass spectrum (CI, NH_3) m/z 256.0798 [$(M + H)^+$, calcd for $C_{11}H_{14}NO_6$ 256.0821].

Ammonolysis of Lactone 39. A solution of lactone **39** (75 mg, 0.291 mmol) in methanol (4 mL) was cooled to 0 °C, treated with ammonium hydroxide (4 drops), and then stirred at room temperature for 16 h. Concentration in vacuo and flash chromatography (10:1 $CHCl_3$/MeOH) provided lactone **40** (41 mg, 68% yield) as a solid. Recrystallization from EtOAc gave colorless needles: mp 202.0–203.0 °C dec; $[\alpha]^{25}_D$ −88.0° (*c* 0.19, MeOH); IR (KBr) 3600–3100 (br m), 2960 (w), 2900 (w), 1750 (s), 1600 (s), 1460 (m), 1350 (w), 1285 (m), 1255 (m), 1235 (s), 1140 (m), 1125 (m), 1105 (m), 1075 (s) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.65 (dd, J = 8.72, 5.42 Hz, 1 H), 3.04 (m, 1 H), 3.92 (m, 1 H), 4.50 (app t, J = 7.83 Hz, 1 H), 5.26 (d, J = 11.43 Hz, 1 H), 5.86 (d, J = 5.48 Hz, 1 H), 6.47 (dd, J = 5.53, 2.61 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.2, 41.0, 54.9, 62.4, 75.3, 83.8, 134.7, 141.5, 173.3, 173.4; high-resolution mass spectrum (CI, NH_3) m/z 226.0691 [$(M + H)^+$, calcd for $C_{10}H_{12}NO_5$ 226.0716].

Enal (+)-34. A solution of hemiacetal **2** (10 mg, 0.039 mmol) and triethylamine (0.03 mL) in dichloromethane (3 mL) was stirred at room temperature for 0.5 h. Concentration in vacuo and flash chromatography (20:1 CH_2Cl_2/MeOH) provided enal **34** (7 mg, 70% yield) as a yellow oil: $[\alpha]^{25}_D$ +2.6° (*c* 0.5, MeOH); IR ($CHCl_3$) 3520 (w), 3410 (w), 3020 (w), 2940 (w), 2930 (w), 1740 (m), 1715 (s), 1685 (m), 1570 (w), 1365 (m), 1310 (m), 1190 (w), 1010 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.62 (s, 1 H, OH), 2.82 (dd, J = 19.47, 2.83 Hz, 1 H), 3.04 (dd, J = 18.86, 9.54 Hz, 1 H), 3.25 (d, J = 19.44 Hz, 1 H), 3.32 (dd, J = 18.90, 4.97 Hz, 1 H), 3.68 (m, 1 H), 3.72 (s, 3 H), 5.54 (br m, 1 H, NH), 6.80 (br m, 1 H, NH), 6.88 (m, 1 H), 9.70 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.1, 44.8, 50.7, 53.0, 83.6, 145.4, 149.7, 161.5, 174.1, 189.0, 196.7; high-resolution mass spectrum (CI, NH_3) m/z 273.1084 [$(M + NH_4)^+$, calcd for $C_{11}H_{17}NO_6$ 273.1087].

Acetates 41α and 41β. Hemiacetal **2** (114 mg, 0.448 mmol), Ph_3P (470 mg, 1.79 mmol), and acetic acid (0.103 mL, 1.79 mmol) were dissolved in THF (8 mL), and a solution of DIAD (0.352 mL, 1.79 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 10 min at room temperature and concentrated in vacuo. Flash chromatography (gradient elution, $CH_2Cl_2 \rightarrow$ 20:1 CH_2Cl_2/MeOH) afforded 14 mg of **41α** (10% yield) and 85 mg of **41β** (64% yield) as colorless oils.

41α: R_f 0.38 (10:1 $CHCl_3$/MeOH); $[\alpha]^{25}_D$ +112.0° (*c* 1.1, MeOH); IR ($CHCl_3$) 3530 (m), 3410 (m), 3010 (w), 2960 (w), 1770 (s), 1740 (s), 1705 (s), 1665 (s), 1580 (m), 1445 (w), 1405 (m), 1370 (w), 1320 (w), 1290 (w), 1280 (w), 1225 (s), 1115 (s), 1065 (s), 1050 (s), 970 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 3 H), 3.22 (m, 2 H), 3.77 (s, 3 H), 5.79 (br s, 1 H, NH), 5.89 (m, 2 H), 6.06 (dd, J = 5.68, 1.54 Hz, 1 H), 6.13 (d, J = 3.13 Hz, 1 H), 6.37 (br s, 1 H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 46.3, 48.2, 53.2, 88.4, 93.0, 106.4, 133.9, 135.5, 143.9, 169.3 (2C), 173.4; high-resolution mass spectrum (CI, NH_3) m/z 315.1215 [$(M + NH_4)^+$, calcd for $C_{13}H_{19}N_2O_7$ 315.1190].

41β: R_f 0.35 (10:1 $CHCl_3$/MeOH); $[\alpha]^{25}_D$ +5.5° (*c* 0.20, MeOH); IR ($CHCl_3$) 3530 (m), 3410 (m), 3020 (m), 2960 (w), 1740 (s), 1705 (s), 1665 (s), 1580 (m), 1440 (w), 1400 (m), 1375 (w), 1280 (m), 1210 (s), 1055 (s), 1015 (m), 955 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3 H), 3.19 (dd, J = 7.73, 4.05 Hz, 1 H), 3.57 (m, 1 H), 3.80 (s, 3 H), 5.66 (br s, 1 H, NH), 5.96 (dd, J = 5.84, 2.13 Hz, 1 H), 6.00 (d, J = 4.03 Hz, 1 H), 6.14 (d, J = 3.44 Hz, 1 H), 6.17 (dd, J = 5.79, 1.95 Hz, 1 H), 6.33 (br s, 1 H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 46.6, 47.8, 52.9, 87.9, 91.3, 107.9, 133.7, 134.6, 143.2, 162.7, 169.2, 173.2; high-resolution mass spectrum (CI, NH_3) m/z 315.1179 [$(M + NH_4)^+$, calcd for $C_{13}H_{19}N_2O_7$ 315.1190].

Diacetate (+)-42. A solution of hemiacetal **2** (13 mg, 0.051 mmol), pyridine (0.012 mL, 0.153 mmol), and 4-pyrrolidinopyridine (ca. 2 mg) in dichloromethane (1 mL) was cooled to 0 °C and treated with acetic anhydride (0.014 mL, 0.153 mmol). The mixture was stirred for 14 h at room temperature and then concentrated in vacuo. Flash chromatography (gradient elution, $CH_2Cl_2 \rightarrow$ 20:1 CH_2Cl_2/MeOH) provided

diacetate **42** (20 mg, 100% yield) as a colorless oil: $[\alpha]^{25}_D$ +180.4° (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 3520 (w), 3010 (w), 2910 (w), 2960 (w), 1750 (s), 1705 (m), 1670 (m), 1580 (m), 1440 (w), 1400 (w), 1375 (m), 1325 (w), 1285 (m), 1255 (m), 1220 (m), 1125 (w), 1110 (w), 1060 (m), 975 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.09 (s, 3 H), 2.14 (s, 3 H), 3.28 (m, 1 H), 3.37 (dd, *J* = 7.18, 3.89 Hz, 1 H), 3.76 (s, 3 H), 5.64 (br s, 1 H, NH), 6.00 (d, *J* = 3.85 Hz, 1 H), 6.06 (d, *J* = 5.00 Hz, 1 H), 6.11 (dd, *J* = 5.88, 2.16 Hz, 1 H), 6.32 (br s, 1 H, NH), 6.37 (dd, *J* = 5.85, 2.29 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 20.9, 43.3, 45.8, 52.7, 91.7, 92.2, 105.4, 133.5, 135.5, 143.7, 162.4, 168.9, 169.2, 170.1; high-resolution mass spectrum (CI, NH_3) *m/z* 340.0093 [(M + H)$^+$, calcd for $C_{15}H_{18}NO_8$ 340.1032].

Acid 43. A solution of hemithioacetal methyl ester **2** (67 mg, 0.263 mmol) in 3.6 N HCl (35 mL) was stirred for 2 days at room temperature and then passed through an ion-exchange column (DEAE Sephadex, 40–120 μm). Lyophilization furnished carboxylic acid **43** (63 mg, 100% yield), which was used without further purification: IR (KBr) 3720–2500 (br s), 1750–1690 (br s), 1655 (s), 1610 (m), 1420 (s) cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 2.89 (m, 1 H), 2.93 (dd, *J* = 7.87, 4.10 Hz, 1 H), 4.80 (d, *J* = 7.38 Hz, 1 H), 5.76 (dd, *J* = 5.66, 1.24 Hz, 1 H), 5.88 (d, *J* = 3.89 Hz, 1 H), 6.03 (dd, *J* = 5.80, 2.32 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 47.8, 48.4, 88.7, 95.7, 107.0, 134.1, 135.7, 143.7, 166.0, 175.5; high-resolution mass spectrum (CI, NH_3) *m/z* 242.0703 [(M + H)$^+$, calcd for $C_{10}H_{12}NO_6$ 242.0665].

(−)-Echinosporin (1). A mixture of carboxylic acid **43** (25 mg, 0.102 mmol), 4-Å molecular sieves (269 mg), and THF (8 mL) was cooled to −15 °C and treated with a preformed complex of *n*-Bu_3P and DEAD [formed by addition of DEAD (0.038 mL, 0.255 mmol) to a solution of *n*-Bu_3P (0.064 mL, 0.255 mmol) in THF (8 mL) at −15 °C]. After the mixture was stirred for 1 h, a second portion (0.255 mmol) of *n*-Bu_3P·DEAD complex was added, and the reaction was stirred overnight at room temperature. The mixture was then diluted with water (20 mL) and washed with Et_2O (2 × 10 mL), and the washings were extracted with water (2 × 10 mL). Concentration of the aqueous extracts and reverse-phase chromatography (LOBAR, RP-8, gradient elution, H_2O → 5% CH_3CN/H_2O) afforded (−)-echinosporin (7 mg, 30% yield) as a white solid: $[\alpha]^{25}_D$ −402.0° (*c* 0.08, CH_3OH); IR (KBr) 3460 (s), 3330 (s), 1760 (s), 1700 (s), 1670 (s), 1615 (m), 1415 (m), 1375 (w), 1335 (w), 1190 (s), 1145 (m), 1010 (m), 925 (m) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 3.01 (m, 1 H), 3.14 (td, *J* = 5.56, 1.33 Hz, 1 H), 6.00 (app t, *J* = 1.54 Hz, 1 H), 6.22 (d, *J* = 5.77 Hz, 1 H), 6.27 (d, *J* = 5.78 Hz, 1 H), 6.44 (dd, *J* = 5.58, 3.41 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 39.0, 47.8, 83.8, 96.3, 105.6, 133.3, 141.7, 142.7, 161.7, 171.8; high-resolution mass spectrum (CI, NH_3) *m/z* 224.0572 [(M + H)$^+$, calcd for $C_{10}H_{10}NO_5$ 224.0559].

Alcohol (+)-44. A solution of ketone **5** (1.0 g, 4.5 mmol) in methanol (100 mL) and tetrahydrofuran (10 mL) was cooled to −20 °C, and sodium borohydride (171 mg, 4.5 mmol, 4.0 equiv) was added. After 30 min, the reaction was quenched with water (0.4 mL). Following concentration in vacuo and azeotropic removal of residual water with benzene, flash chromatography (5:1 chloroform/methanol) provided 1.0 g (100% yield) of alcohol **44** as a white solid: mp 71.5 °C; $[\alpha]^{25}_D$ +37.0° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3610 (s), 3470 (b), 2940 (s), 2870 (w), 1430 (s), 1380 (s), 1370 (s), 1230 (b), 1160 (s), 1065 (b) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.46 (s, 3 H), 1.53 (m, 4 H), 1.99 (m, 1 H), 2.40 (dt, *J* = 3.70, 2.91 Hz, 2 H), 2.98 (t, *J* = 3.10 Hz, 1 H), 4.25 (dt, *J* = 6.50, 6.12 Hz, 1 H), 4.43 (d, *J* = 5.23 Hz, 1 H), 4.58 (d, *J* = 3.64 Hz, 1 H), 6.04 (d, *J* = 3.64 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 112.9, 107.7, 86.6, 83.9, 74.3, 44.3, 41.4, 39.9, 32.2, 27.9, 27.2, 25.8; high-resolution mass spectrum (CI, NH_3) *m/z* 227.1270 [(M + H)$^+$, calcd for $C_{12}H_{19}O_4$ 227.1298]. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.45; H, 7.97.

Triol (−)-45. A solution of alcohol **44** (1.0 g, 4.5 mmol) in acetic acid/tetrahydrofuran/water (3:2:2, 150 mL) was heated to 85 °C for 6 h, cooled to room temperature, and concentrated in vacuo. Flash chromatography (1:1 methanol/chloroform) furnished 812 mg (97% yield) of triol **45** as a white solid: mp 141–142 °C; $[\alpha]^{25}_D$ −12.7° (*c* 0.35, MeOH); IR (KBr) 3330 (b), 2980 (s), 2950 (s), 2930 (s), 2850 (w), 1450 (w), 1420 (s), 1320 (s), 1150 (w), 1080 (b) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.51–1.72 (m, 4 H), 1.89 (m, 2 H), 2.59 (d, *J* = 4.18 Hz, 1 H), 2.55 (t, *J* = 6.78 Hz, 1 H), 2.61 (t, *J* = 4.12 Hz, 1 H), 2.72 (t, *J* = 4.70 Hz, 1 H), 4.01 (s, 1 H), 4.13 (td, *J* = 6.43, 2.91 Hz, 2 H), 4.26 (d, *J* = 5.76 Hz, 1 H), 5.42 (s, 1 H); ^{13}C NMR (125.8 MHz, CD_3OD) δ 107.9, 86.2, 81.8, 74.8, 47.3, 44.2, 42.3, 32.7, 27.4; high-resolution mass spectrum (CI, NH_3) *m/z* 204.1250 [(M + NH_4)$^+$, calcd for $C_9H_{18}O_4N$ 204.1236]. Anal. Calcd for $C_9H_{14}O_4$: C, 58.07; H, 7.52. Found: C, 58.23; H, 7.75.

Formate Aldehyde 46. Triol **45** (97.8 mg, 0.52 mmol) was added to a slurry of Celite (117 mg) in diethyl ether (26 mL) and treated with glacial acetic acid (10 drops) followed by lead tetraacetate (279.8 mg, 0.63 mmol, in two portions). After stirring for 5 min, the reaction was quenched with oxalic acid (132 mg), stirred for 1 h, neutralized to pH 7.0 with solid $NaHCO_3$, and filtered. Concentration by gentle distillation (760 mm) provided formate **46** as a colorless oil, which was used directly in the next reaction: IR ($CHCl_3$) 3530 (w), 3440 (b), 2950 (s), 1735 (b), 1380 (w), 1340 (w), 1180 (b) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.63–1.84 (m, 4 H), 2.68 (m, 2 H), 3.25 (q, *J* = 7.71 Hz, 1 H), 3.58 (t, *J* = 8.26 Hz, 1 H), 4.38 (d, *J* = 7.13 Hz, 1 H), 5.11 (d, *J* = 8.17 Hz, 1 H), 8.01 (s, 1 H), 9.81 (s, 1 H).

Bisacetal (+)-47. A solution of crude formate **46** (140 mg, 0.76 mmol) in methanol (8 mL) was cooled to 0 °C, and concentrated sulfuric acid (10 drops) was added dropwise. The mixture was warmed to room temperature and stirred for 45 min. The reaction then was neutralized with solid $NaHCO_3$, and the resultant suspension was stirred overnight. After the addition of water, the mixture was extracted with ether, and the combined extracts were washed with brine and dried over $MgSO_4$. Following concentration by distillation (760 mm), preparative thin-layer chromatography (1:4 ether/pentane) gave 90 mg (52% yield overall from **45**) of dimethyl acetal **47** as an oil: $[\alpha]^{25}_D$ +77.9° (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 2950 (s), 2820 (w), 1450 (w), 1370 (b), 1100 (s), 1045 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37–1.46 (m, 1 H), 1.56–1.78 (m, 3 H), 1.83 (m, 1 H), 2.15–2.25 (m, 1 H), 2.89 (m, *J* = 8.3 Hz, 1 H), 3.29 (s, 3 H), 3.32 (s, 3 H), 3.33 (s, 3 H), 4.25 (d, *J* = 8.7 Hz, 1 H), 4.56 (t, *J* = 6.7 Hz, 1 H), 4.99 (d, *J* = 4.6 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.3, 105.6, 83.2, 54.1, 53.0, 52.3, 44.5, 41.8, 33.8, 32.5, 25.0; high-resolution mass spectrum (CI, CH_4) *m/z* 185.1207 [(M − OMe)$^+$, calcd for $C_{10}H_{17}O_3$ 185.1178]. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.07; H, 9.32. Found: C, 61.06; H, 9.31.

Aldehyde (+)-48. A solution of dimethyl acetal **47** (223 mg, 1.99 mmol) and *p*-TsOH (21 mg, 0.19 mmol) in acetone (50 mL) was heated to 60 °C for 2 h. The reaction mixture was then cooled to room temperature, neutralized with $NaHCO_3$, and filtered through a plug of neutral alumina. Concentration by distillation (760 mm) provided 118 mg (67% yield) of aldehyde **48** as an oil: $[\alpha]^{25}_D$ +22.8° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 2970 (s), 1730 (s), 1210 (s), 1100 (s), 1050 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43–2.08 (m, 6 H), 2.78 (m, *J* = 7.51 Hz, 1 H), 3.17 (m, *J* = 7.82 Hz, 1 H), 3.30 (s, 1 H), 4.63 (t, *J* = 6.43 Hz, 1 H), 5.01 (dd, *J* = 5.02, 4.69 Hz, 1 H), 9.78 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 202.4, 105.7, 83.3, 55.7, 54.2, 41.3, 35.2, 31.9, 23.2; high-resolution mass spectrum (CI, NH_3) *m/z* 139.0768 [(M − OMe)$^+$, calcd for $C_8H_{11}O_2$ 139.0768]. Anal. Calcd for $C_9H_{14}O_3$: C, 63.48; H, 8.29. Found: C, 63.41; H, 8.01.

Enone (+)-49. A solution of dimethyl (2-oxoheptyl)phosphonate (76.8 mL, 0.37 mmol) in DME (2 mL) was added dropwise to a suspension of 80% NaH (9 mg, 0.37 mmol) in DME (2 mL). After stirring for 1 h at room temperature, the suspension was cooled to 0 °C, and a solution of aldehyde **48** (42.1 mg, 0.25 mmol) in DME (1.5 mL) was slowly added dropwise. The reaction was stirred for 1.5 h, warmed to room temperature, and stirred for an additional 30 min. After quenching with saturated NH_4Cl, the mixture was extracted with ether, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (5:1 hexane/ethyl acetate) gave 50 mg (76% yield) of enone **49** as an oil: $[\alpha]^{25}_D$ +37.3° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 2995 (s), 2980 (s), 1670 (b), 1630 (s), 1450 (b, w), 1105 (w), 1040 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3 H), 1.24–1.35 (cm, 4 H), 1.51–1.77 (m, 5 H), 1.83–2.01 (m, 2 H), 2.52 (m, 3 H), 2.68 (m, 1 H), 2.96 (m, *J* = 7.95 Hz, 1 H), 3.29 (s, 3 H), 4.62 (t, *J* = 4.32 Hz, 1 H), 4.97 (d, *J* = 4.34 Hz, 1 H), 6.15 (dd, *J* = 16.0, 2.15 Hz, 1 H), 6.83 (dd, *J* = 16.78, 2.13 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 200.5, 146.2, 130.4, 105.6, 83.4, 54.1, 45.3, 44.2, 40.4, 32.5, 31.4, 27.2, 23.9, 22.4, 13.8; high-resolution mass spectrum (CI, NH_3) *m/z* 284.2204 [(M + NH_4)$^+$, calcd for $C_{16}H_{30}O_3N$ 284.2226]. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.13; H, 9.84. Found: C, 71.97; H, 9.95.

Acknowledgment. Support for this work was provided by the National Institutes of Health (National Cancer Institute and Institute of General Medical Sciences) through Grants CA-22807 and GM-29028. We thank Dr. Fumio Suzuki of Kyowa Hakko Kogyo Co. for a generous sample of natural echinosporin. We also thank Dr. John L. Wood for obtaining the two-dimensional COSY spectrum of (−)-**6**. Dr. Christopher S. Shiner provided helpful suggestions and critical comments.

Supplementary Material Available: Tables of experimental details, positional parameters, and thermal parameters for X-ray analyses of (+)-**5** and (−)-**40** (18 pages). Ordering information is given on any current masthead page.