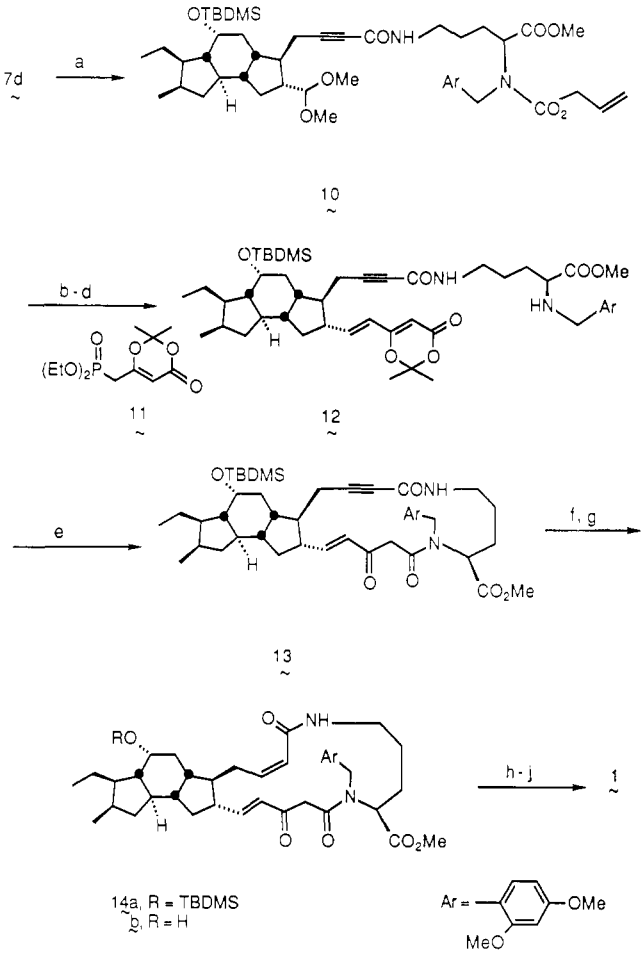
Scheme III[a]



[a] (a) K_2CO_3, MeOH, H_2O; 2,4,6-$(CH_3)_3PhSO_2Cl$, THF; DMAP, **9**; (b) acetone, (TsOH); (c) $KN(TMS)_2$, **11**, THF; (d) $Pd(PPh_3)_4$, PPh_3, HOAc, THF; (e) toluene, 110 °C, 4 h; (f) H_2 (1 atm), 5% Pd-$BaSO_4$, quinoline; (g) 48% HF, CH_3CN; (h) $CH_3OC(O)NSO_2NEt_3$, C_6H_6, Δ; (i) *t*-BuOK (1 equiv), *t*-BuOH; (j) CF_3CO_2H, 65 °C, 10 min.

(58%, Scheme III). Transketalization with dry acetone, conditions found necessary to avoid concomitant deblocking of the silyl ether functionality, made possible condensation with phosphonate **11**[11] and ensuing cleavage of the allyl carbamate under mild conditions [catalytic $(Ph_3P)_4Pd$[12] in the presence of HOAc;[13] THF solution]. Heating dilute solutions of **12** in boiling toluene for 4 h liberated the acyl ketene and induced smooth macrocyclization (65% from **10**). Semisaturation of the acetylenic double bond was next achieved by the Lindlar method (76%). Successive desilylation with 48% hydrofluoric acid (85%) and dehydration of **14b** with the Burgess reagent[14] (40%) proceeded to introduce the requisite B ring double bond.[5]

Completion of the total synthesis was realized by Dieckman cyclization in *t*-BuOH containing 1 equiv of *t*-BuOK[4a] (70%) followed by CF_3COOH-promoted removal of the 2,4-$(MeO)_2$-benzyl group (45%).[15] The IR and ^1H NMR spectra of the synthetic material were identical with those recorded for the natural product.[3,16]

With completion of this convergent and stereoselective route to (+)-ikarugamycin, the focus of attention may perhaps be directed to the preparation of capsimycin, a related natural tetramic acid of some note.[17]

Acknowledgment. We thank the National Institutes of Health for financial support (Grant GM-28468). A helpful exchange of information with Professor R. K. Boeckman, Jr. and his willingness to publish his results simultaneously[18] are deeply appreciated. Professor A. I. Meyers (Colorado State Univ.) as well as Drs. K. Drauz and H. Lotter (Degussa) have made generous samples of L-*tert*-leucine available.

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Total Synthesis of Natural (−)-Echinosporin. Determination of the Absolute Configuration

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In 1981 Hirayama and co-workers[1] reported the isolation and characterization of echinosporin (**1**), a new antibiotic-antitumor agent produced by *Streptomyces echinosporus* MK-213.[2] The novel, highly oxygenated tricyclic structure, initially deduced by chemical derivatization and NMR analysis, was later confirmed by single-crystal X-ray analysis;[3] however, the absolute configuration remained undefined. Intrigued by the unique tricyclic skeleton, we initiated a program directed toward the enantioselective total synthesis of **1**. Given the unknown absolute stereochemistry, a unified strategy leading to both enantiomers was considered highly desirable (vide infra). Herein we disclose the first total synthesis of natural (−)-echinosporin.[4]

From the retrosynthetic perspective, lactol **2** appeared to be an ideal penultimate intermediate. Of concern here were the three contiguous stereocenters which punctuate the cyclopentene ring. Two of these were anticipated to arise via a [2 + 2] photocycloaddition of cyclopentenone (**5**) to dihydrofuran **6**.[5] Elaboration of the functionality at C(8) in **4** would then involve a palladium-catalyzed carbomethoxylation of the derived enol triflate,[6] followed by a stereocontrolled deconjugative α-hydroxylation. Removal of the acetonide, oxidation of the diol, and ammonolysis of the resultant α-ketolactone (i.e., **3**) were then

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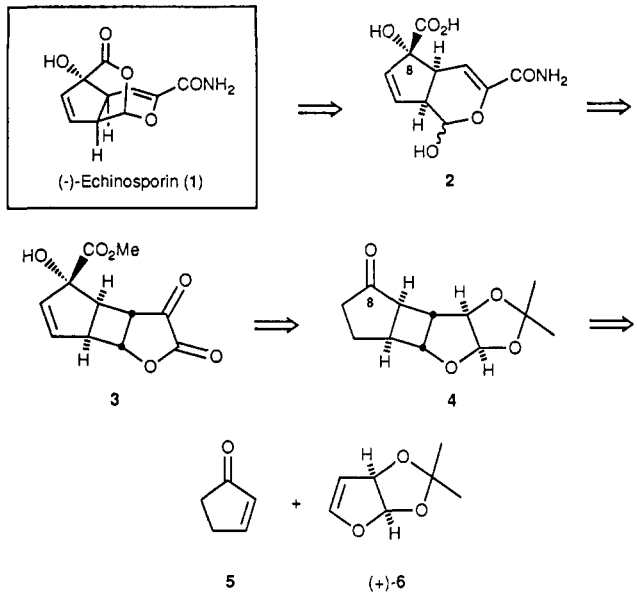
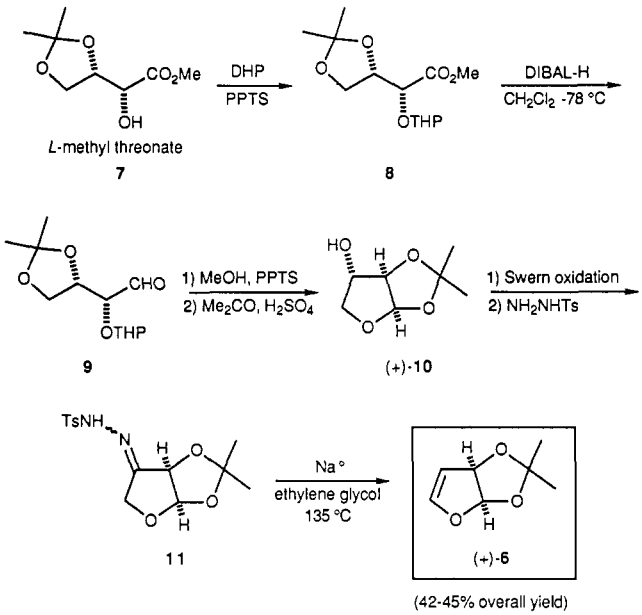
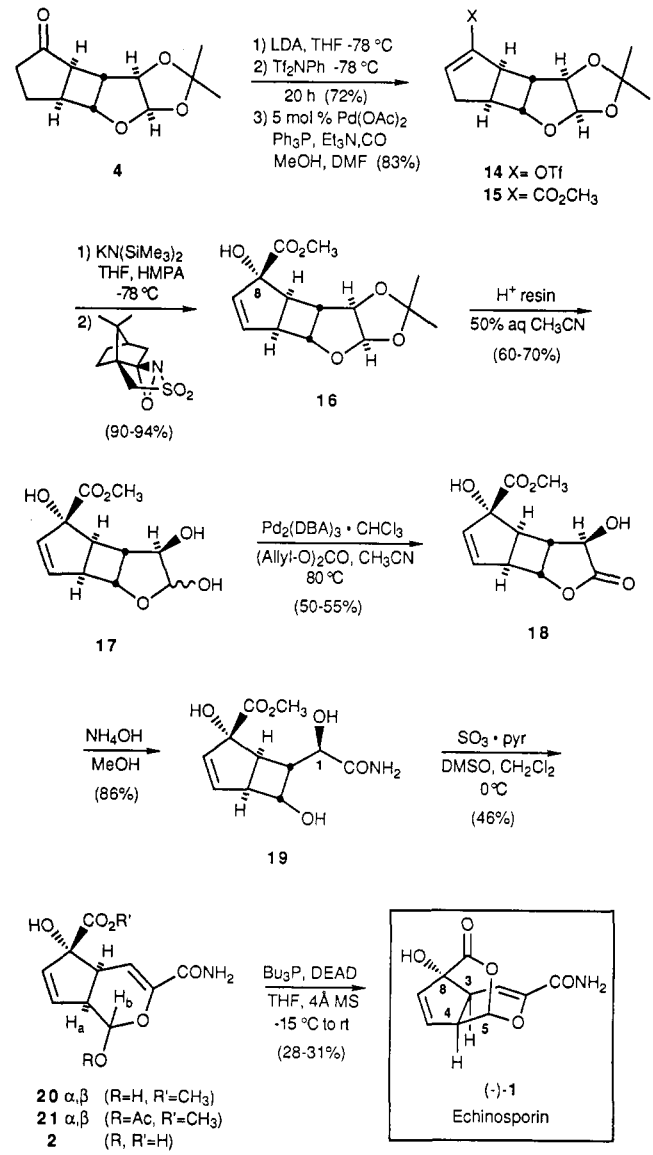
Scheme I



Scheme II



Scheme III



expected to serve as prelude to the cornerstone of the synthetic strategy, namely fragmentation of the derived cyclobutanol ring followed by cyclization. Hydrolysis of the methyl ester would then furnish lactol **2**.[7]

The dextrorotary enantiomer of dihydrofuran **6** proved to be especially amenable to large-scale preparation. Accordingly, the synthesis (+)-**6** began with L-methyl threonate (**7**), readily available from L-ascorbic acid in three steps as described by Weigele (Scheme II).[8] Following the straightforward conversion of **7** to (+)-**10**,[9,10] formal dehydration of the latter to (+)-dihydrofuran **6**[10a] was best achieved via Swern oxidation,[11,12] followed by Bamford–Stevens reduction of the derived tosylhydrazone.[13] The sequence proceeded in 42–45% overall yield for the six steps.

With a viable synthesis of dihydrofuran in hand, photocycloaddition of cyclopentenone (**5**) to (+)-**6** provided three adducts.[14,15] As expected from earlier work,[5] the major product (ca. 50% yield) was the desired cis–anti–cis adduct **4**,[10] the structure of which was confirmed by single-crystal X-ray analysis.[16] The minor adducts proved to be the cis–syn–cis (15%) and the cis–anti–cis (14%) isomers (-)-**12**[10] and (-)-**13**,[10] respectively.[17]

Introduction of the carbomethoxy and hydroxyl groups comprising the C(8)-stereogenic center required three steps. First, generation of the enolate of **4** (LDA, THF, −78 °C) followed by treatment with Tf_2NPh (−78 to −20 °C, 12 h)[18] provided enol

(7) For a review of the related de Mayo enone photoannulation–cyclobutanol fragmentation tactic, see: de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41.

(8) Wei, C. C.; De Barnardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3462.

(9) (a) For a similar synthesis of (+)-**10**, see: Gätzi, K.; Reichstein, T. *Helv. Chim. Acta* **1938**, *21*, 195. (b) The enantiomer (-)-**10** is available in two steps from D-galactose: Perlin, S. A. *Methods Carbohydr. Chem.* **1968**, *1*, 68.

(10) (a) The structure assigned to each new compound is in accord with its infrared and high field (250 or 500 MHz) ^1H NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or liquid chromatography, gave satisfactory C and H combustion analysis within 0.4%.

(11) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

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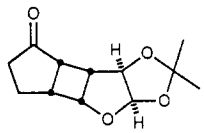
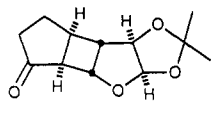
(15) A degassed solution of **5** and **6** (10 equiv) in pentane (0.1 M in **5**) was irradiated for 22 h through a uranium glass filter with a 450-W Hanovia source. Unreacted **8** could be recovered by flash chromatography (81%).

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

(17) A similar synthetic strategy is expected to provide (+)-echinosporin (**1**) from the cis–syn–cis photoadduct (-)-**12**.



(-)-12



(-)-13

triflate **14**.[10] Palladium-catalyzed carbomethoxylation was then achieved via the protocol described by Ortar.[6] Finally, oxidation of the dienolate derived from **15**[10] [$KN(SiMe_3)_2$, 20% HMPA/THF, -78 °C][19] with the Davis (+)-(camphorsulfonyl)oxaziridine[20] furnished carbinol **16**.[10] The overall yield for the three steps was 55%. Removal of the isopropylidene group (Bio-Rad AG50W-X2 acidic resin, 50% aq CH_3CN) then afforded triol **17**.[10a,21]

We next confronted the task of oxidizing the diol unit in **17**. This transformation was best accomplished in a stepwise fashion, first by using the palladium-catalyzed dehydrogenation developed by Tsuji [$Pd_2(DBA)_3 \cdot CHCl_3$ (10 mol %), diallyl carbonate, acetonitrile at 80 °C];[22] the result was hydroxylactone **18**[10a] obtained in 50-55% yield. Subsequent oxidation of **18** with MnO_2 provided α-ketolactone **3**,[10a] albeit with variable efficiency. These results, in conjunction with the general instability of **3**, prompted us to explore a useful variation of the oxidation-fragmentation tactic. Thus, ammonolysis of **18** (NH_4OH in MeOH)[23] provided cyclobutanol **19**[10a,24] (86%) which in turn was subjected to oxidation.[25] The latter led via fragmentation[7] and recyclization to **20**,[10a] obtained as a 20:1 anomeric mixture.[26] The structure of **20**, and in particular the α-configuration of the anomeric hydroxyl, was secured by preparation of the corresponding acetates (**21**), exploiting the Mitsunobu protocol (DIAD, Ph_3P, HOAc in THF).[27] The major acetate was assigned the β-configuration (i.e., **21**β)[10a] on the basis of an observed 6% nuclear Overhauser enhancement between H_a and H_b.[28]

The success of the latter transformation suggested that an intramolecular Mitsunobu lactonization would lead to echinosporin (**1**). After considerable experimentation, acid **2**[10a] was prepared by hydrolysis of methyl ester **20** (3.6 N HCl, 2 days), followed by ion-exchange chromatography (DEAE Sephadex) and immediate lyophilization. Without further purification, **2** was subjected to the Mitsunobu reaction,[29] whereupon reverse phase chromatography provided (-)-echinosporin (**1**) in 28-31% yield for the two steps.[30] That indeed synthetic (-)-echinosporin was in hand derived from detailed comparison of synthetic (-)-**1** with natural material (i.e., 500 MHz ^1H and 125 MHz ^{13}C NMR, IR, HRMS, and TLC comparison in four solvent systems).[31] The optical rotation of synthetic echinosporin {$[\alpha]^{25}_D$ -402° (*c* 0.08, CH_3OH)} was also identical with that of natural (-)-echinosporin {$[\alpha]^{25}_D$ -400 °C (*c* 0.1, CH_3OH)}. Thus the absolute configuration of (-)-echinosporin is assigned as 3*R*, 4*R*, 5*S*, and 8*R*.[3b]

In summary, we have completed an enantioselective total synthesis of (-)-echinosporin and thereby have defined the absolute configuration of this potentially important antibiotic-antitumor agent. Progress concerning the preparation of (+)-echinosporin from cycloadduct (-)-**12** as well as further demonstration of the synthetic utility of dihydrofurans (+)- and (-)-**6** will be reported in due course.

Acknowledgment. Support for this work was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-22807.

Supplementary Material Available: Spectral (IR, ^1H NMR, and ^{13}C NMR) and analytical (elemental analysis) data for **1**, **2**, **4**, **6**, **12-21**, and **i** (4 pages). Ordering information is given on any current masthead page.

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(24) Compound **19** was homogeneous by ^{13}C NMR; however, the assignment of stereochemistry at C(1) remains tentative.

(25) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(26) Prolonged exposure of **20** to either basic oxidation conditions or silica gel resulted in facile conversion to enal **i**.[10a] These observations necessitated isolation of **20** by reverse-phase chromatography (LOBAR RP-8, gradient elution, water → 5% CH_3CN/water).

20 i

(27) Mitsunobu, O. *Synthesis* **1981**, 1. Also, see: Smith, III, A. B.; Hale, K. J.; Rivero, R. A. *Tetrahedron Lett.* **1986**, *27*, 5813 and references cited therein.

(28) This assignment was further supported by the chemical shifts and coupling constants of the anomeric hydrogens. The major acetal hydrogen displayed a chemical shift of δ 4.84 and a coupling constant J = 7.88 Hz, while the minor acetal hydrogen appeared at δ 5.25 with a coupling constant J = 3.05 Hz.

(29) The optimal conditions for the desired ring closure entailed preformation of the Mitsunobu complex at -15 °C [Bu_3P (2.5 equiv), DEAD (2.5 equiv), THF] followed by addition of the complex to a solution of **2** in THF (4 Å molecular sieves) at -15 °C. Addition of the Mitsunobu complex (2.5 equiv) was repeated after 1 h, and the resultant mixture was then stirred overnight at room temperature.

(30) The low yield obtained in the Mitsunobu ring closure is attributable to the instability of carboxylic acid **2** and the strained character of the lactone. With use of the MNDO method, the strain energy incurred upon lactonization of **2** was calculated to be 17 Kcal/mol.

(31) We thank Dr. Fumio Suzuki of Kyowa Hakko Kogyo Co. for a generous sample of natural echinosporin.

Preparation and Structure of a New Ternary Transition-Metal Zintl Compound Containing High Spin $Mn^{III}Bi_4$ Tetrahedra

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Several rational approaches to solid-state synthesis have been proposed and may lead to a large number of new compounds.[1-3] Such a rational approach is seen in the Zintl concept,[2,4,5] which has been applied to intermetallics,[2,5] ternary main-group compounds,[6,7] ternary transition-metal chalcogenides,[8] and ternary lanthanide transition-metal pnictides.[9] The Zintl concept can

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