bility. Consistent with the view that full electron transfer does not play a significant role in the mechanism of sensitization, we find no evidence for the formation of $Ir(bpy\text{-}N,N')_2(bpy\text{-}C,N')^+$ upon flash photolysis of **1** and **2** in CH_3CN.[16]

Acknowledgment. We thank Dr. Guillermo Ferraudi of the Notre Dame Radiation Laboratory for performing exploratory flash photolysis experiments. Financial support from the National Science Foundation (Grant CHE-8210558) is gratefully acknowledged.

(16) The electronic absorption spectrum of the reduced iridium complex has been reported.[3c] Also see: Cohen, H.; Slama-Schwok, A.; Rabani, J.; Watts, R. J.; Meyerstein, D. *J. Phys. Chem.* **1985**, *89*, 2465.

Synthesis of (-)-Bertyadionol

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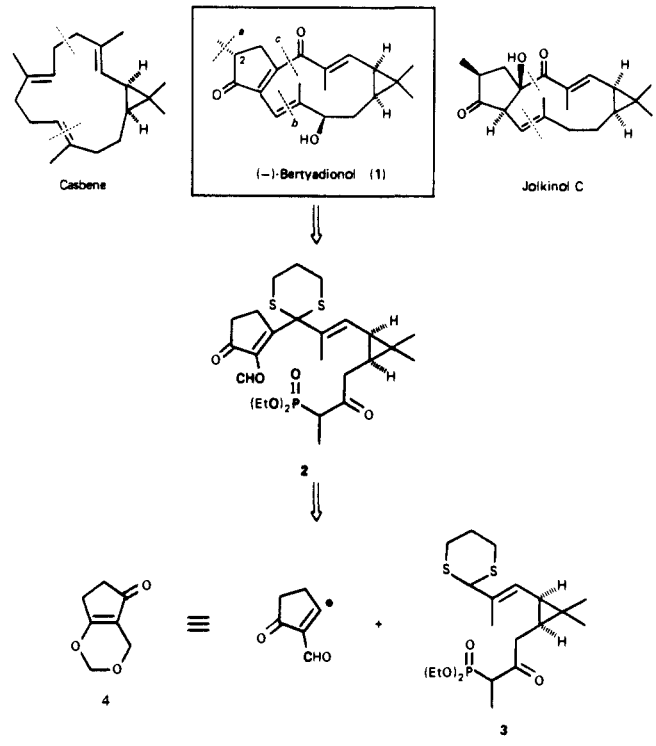
We disclose here a unified strategy that recently culminated in a total synthesis of (-)-bertyadionol (**1**), the first member of the lathyrane diterpenes to succumb to synthesis.[3] Our interest in this class[4] stems from the close structural relationship to the pharmacologically important *Crotonoideae* subfamily,[5] members of which display proinflammatory and tumor-promoting activity.[6]

Bertyadionol (**1**) was isolated by Jefferies from *Bertya cupressoidea* (*Euphorbiaceae*), a plant endemic to Western Australia. A preliminary report including a tentative structure appeared in 1970.[7] Several years later the relative and absolute stereochemistries were secured through a combination of degradation and double-resonance NMR experiments.[8] Of considerable importance from the synthetic perspective was the reported instability of bertyadionol toward mild acid, base, and ultraviolet light, as well as to both nucleophiles and electrophiles.[7,8]

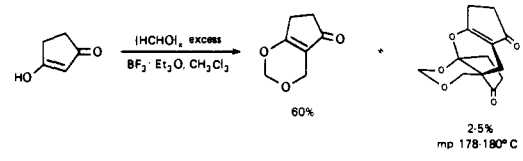
Our approach, applicable to other macrocyclic diterpenes within the casbene-lathryane class, called for union of **3**, derived from (-)-*cis*-chrysanthemic acid, with an appropriately functionalized cyclopentenyl synthon.[9] For bertyadionol (**1**), vinylogous ester



4[10] (a vinyl cation equivalent) appeared ideal.[11] Intramolecular keto phosphonate cyclization generating the requisite *E* configuration at C(5,6) would then provide the macrocyclic ring.[12,13] Finally, introduction of the stereocenters at C(2) and C(7) was envisioned to take advantage of the inherent stereochemical bias of the macrocyclic skeleton.[14]

With this as background, preparation of **3** began with (-)-*cis*-chrysanthemic acid (**5**, 88-92% ee).[15] Arndt-Eistert homologation[16] followed by regioselective allylic oxidation [SeO_2, pyr][17] and then careful[18] dithioacetal formation [propylene dithiol,

(10) Although unknown, vinylogous ester **4** was prepared in analogy to several closely related derivatives as illustrated below; see: Bolte, M. L.; Crow, W. D.; Yoshida, S. *Aust. J. Chem.* **1982**, *35*, 1411. The structure of the propellane was secured via X-ray analysis.[25]



(1) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983; National Institutes of Health (National Cancer Institute) Career Development Awardee, 1980-1985; J. S. Guggenheim Fellow, 1985-1986.

(2) American Cancer Society Postdoctoral Fellow, 1983-1985.

(3) The total synthesis of (-)-bertyadionol was first announced at the 190th National Meeting of the American Chemical Society, Chicago, IL, Sept 1985; paper ORGN 27.

(4) Other members of the lathyrane family include the jolkinols (Ghisalbert, E. L.; Jefferies, P. R.; Toia, R. F.; Worth, G. K. *Tetrahedron* **1974**, *30*, 3269) and diterpene D (Uemera, D.; Nobuhara, K.; Nakayama, Y.; Shizuri, Y.; Hirata, Y. *Tetrahedron Lett.* **1976**, 4593).

(5) For a comprehensive review, see: Evans, F. J.; Taylor, S. E. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: Wien, New York, 1983; Vol. 44, pp 2-99.

(6) Schmidt, R. J.; Evans, F. J. *Arch. Toxicol.* **1980**, *44*, 279. Kupchan, S. M.; Uchida, I.; Branfman, A. R.; Dailey, R. G.; Yefei, B. *Science (Washington, D.C.)* **1976**, *191*, 571.

(7) Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G.; Worth, G. K. *Tetrahedron Lett.* **1970**, 4599.

(8) Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G.; Worth, G. K. *Tetrahedron* **1973**, *29*, 403.

(9) To test the feasibility of this unified strategy, we initially completed a total synthesis of (-)-casbene employing the TBS-ether of 6-chloro-4-methyl-4-hexen-1-ol and **3**; unpublished results of M. S. Malamas and T. Maeda.

(11) For examples of 1,2-additions of dithianes to a vinylogous esters, see: Quesada, M. L.; Schlessinger, R. H. *Synth. Commun.* **1976**, *6*, 555. Tobin, P. S.; Basu, S. K.; Gosserode, R. S.; Wheeler, D. M. S. *J. Org. Chem.* **1980**, *45*, 1250.

(12) Dauben, W. G.; Robbins, J. D. *Tetrahedron Lett.* **1975**, 151 and references cited therein. Lang, M.; Prasad, K.; Holick, W.; Gosteli, J.; Ernest, I.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6296. Ernest, I.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6301. Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. Aristoff, P. A. *Synth. Commun.* **1983**, *13*, 145.

(13) (a) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. (b) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (d) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.

(14) (a) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (b) Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127 and references cited therein.

(15) Resolution of (±)-chrysanthemic acid was achieved by preparation of the (-)-*N*-methylephedrin salt and then fractional recrystallization (hexanes).

(16) Horner, L.; Spietschka, E. *Chem. Ber.* **1952**, *85*, 225. For a review, see: Meier, H.; Zeller, K.-P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32.

(17) Camps, F.; Coll, J.; Parente, A. *Synthesis* **1978**, 215.

(18) If dithioacetal formation is attempted at temperatures >-23 °C, a Lewis acid promoted rearrangement takes place.

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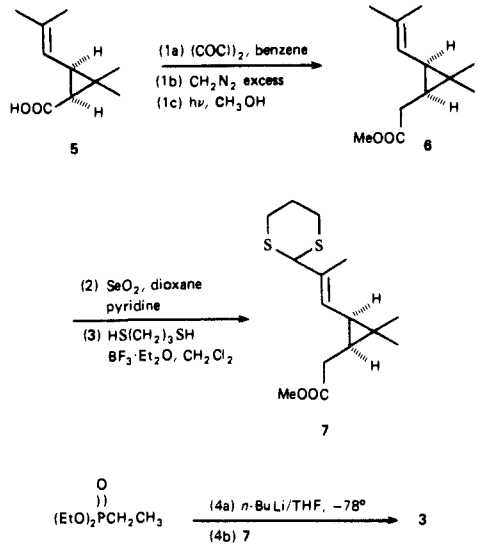
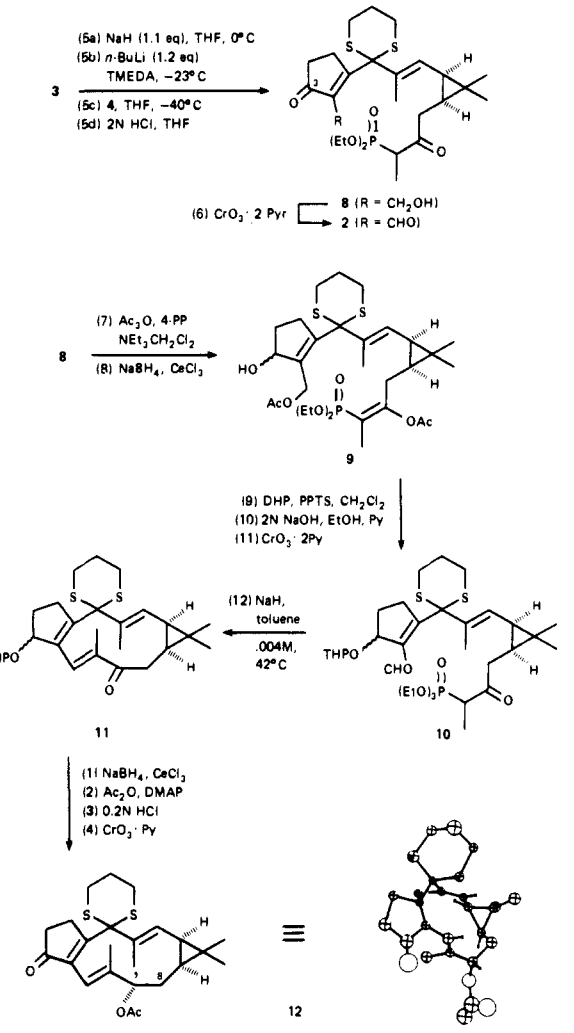
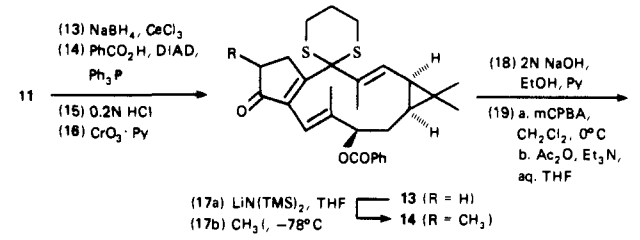
$BF_3{\cdot}Et_2O$][19] afforded **7**.[20a] Subsequent condensation with lithioethyl diethylphosphonate provided **3**[20] in 90% yield as a 1:1 diastereomeric mixture. The overall yield for this four step sequence was 35%.



With **3** in hand, we turned to its union with vinylogous ester **4**.[11] Treatment of **3** with sodium hydride (1.1 equiv 0 °C, 1 h) followed by the *n*-butyl lithium/TMEDA complex (1.2 equiv −78 → −23 °C, 2.5 h) resulted in a homogeneous deep purple solution (0.35 M in THF), presumably indicative of the dianion. Rapid addition of **4** at −40 °C followed immediately by acid treatment (2 N HCl) afforded enone **8**[20] in 58% yield. Collins oxidation[21] then provided keto aldehyde **2**[20a] ready for macrocyclization. All attempts to effect the intramolecular Horner–Wittig reaction,[13] however, on what proved to be a highly unstable enone–enal, led only to rapid destruction of the starting material. To circumvent the problem, the oxidation level at C(3) was adjusted so as to be more compatible with the macrocyclization conditions. Specifically, acetylation [Ac_2O, 4-pyrrolidinopyridine (4-PP), Et_3N] followed by reduction ($NaBH_4$, $CeCl_3$)[22] gave a 1:1 mixture of allylic alcohols (**9**).[20a] Since C(3) was destined to become a trigonal center its stereochemistry was expected to be of little consequence. Formation of the THP ether (DHP, PPTS, CH_2Cl_2) followed by acetate removal [2 N NaOH, pyr, EtOH (1:1:2)] and Collins oxidation[21] provided enal **10**[20] poised for macrocyclization. In this case, slow addition of **10** to a suspension of sodium hydride (5.0 equiv) in toluene (0.004 M, 42 °C) over a 10-h period[13c] resulted in enone **11**[20a] as the only isolable product. The yield ranged from 28% to 32%. Somewhat surprisingly, removal of the THP group (PPTS, aqueous THF, 93%) provided a 5:1 mixture of alcohols epimeric at C(3).[23] Presumably one of the C(3) epimers undergoes the Horner–Wittig cyclization in preference to the other.

At this point there remained only reduction of the C(7) carbonyl, introduction of the C(2) methyl group, and removal of the dithiane unit to complete the bertyadionol synthesis. Conformational analysis, including molecular mechanics calculations,[24] suggested that peripheral attack at C(7) would lead to the undesired α-carbinol, Correction by inversion, however, could be anticipated. Toward this end, reduction ($NaBH_4$–$CeCl_3$)[22] of **11** afforded a single C(7) alcohol (92%), the stereochemistry of which was initially assigned by NMR. Confirmation came via single-crystal X-ray analysis of **12**[20,25] obtained from **11**. With the C(7) stereochemistry secure, inversion via a Mitsunobu reaction [$PhCO_2H$, Ph_3P, diisopropyl azodicarboxylate (DIAD), THF][26] followed by removal of the THP-ether and careful C(3)-oxidation afforded benzoate **13**.[20] The overall yield for this four-step operation was 50%.





Turning next to introduction of the C(2) methyl group, alkylation of **13** [$LiN(Me_3Si)_2$/THF/−78 °C] with methyl iodide gave a 4.3:1 mixture (HPLC) of monomethylated products. The stereochemistry of the major isomer was presumed to be β, on the basis of attack of methyl iodide from the least hindered (convex) side of **13**.

At this juncture two major obstacles were encountered. First, we learned that it was not possible to convert bertyadionol benzoate

(19) Seebach, D.; Jones, N. R.; Corey, E. J. *J. Org. Chem.* **1968**, *33*, 300.

(20) (a) The structure assigned to each new compound is in accord with its infrared and 250-MHz ^1H NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. Purity (>97%) was accessed by either NMR or HPLC. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or chromatography (LC or TLC), gave satisfactory C and H combustion analysis within 0.4%.

(21) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

(22) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(23) The Mosher ester of the major alcohol obtained via hydrolysis of **11** was determined to be 88% ee by using ^{19}F NMR; see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(24) We thank Professor W. Clark Still (Columbia University) for the molecular mechanics program (Model 1.3).

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

(26) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. Mitsunobu, O. *Synthesis* **1981**, 1.

to bertyadionol;[27] complete destruction of the molecule, to say nothing of epimerization, occurred. Second, all attempts to remove the dithioketal exploiting most, if not all, of the known procedures (ca. 23),[28] proved uniformly unsuccessful. Fortunately, a deprotection–dithioketal hydrolysis protocol was eventually developed. The sequence involved removal of the benzoate [2 N NaOH, MeOH, Pyr (1:2:2), 63%], oxidation of the dithioketal functionality (*m*-CPBA, CH_2Cl_2, 0 °C) to the monosulfoxide, and then a "Pummerer-like" hydrolysis [Ac_2O, Et_3N, aqueous THF (3:4:10), 40 °C]. The result was a thermodynamic mixture (45:55) of bertyadionol (**1**) and its C(2) epimer,[20a] which was readily separable by HPLC (15% hexane–ethyl acetate, Ultrasphere-SI). The yield for the oxidative-hydrolysis maneuver was 28–37%. That in fact synthetic (−)-bertyadionol [mp 157–158.5 °C; lit.[8] 159–160 °C; $[\alpha]^{24}_D$ −318° (*c* 0.04, benzene, 89% ee), authentic **1** $[\alpha]^{24}_D$ −356° (*c* 0.10, benzene)],[27] was in hand derived from careful comparison (^{1}H NMR, TLC, HPLC, mp, mmp, and GC/MS) with an authentic sample of natural (−)-bertyadionol kindly provided by Professor Jefferies.[27]

In summary, the first total synthesis of a lathyrane diterpene, (−)-bertyadionol, has been achieved. The synthesis delivered the target in homochiral form. Of particular interest is the rapid assembly of the carbon skeleton, the viability of the intramolecular ketophosphonate construction of the 11-membered ring, and the oxidative protocol for the hydrolysis of dithioketals. Studies to exploit this strategy for the synthesis of other members in this class will be reported in due course.

Acknowledgment. Support for this investigation was provided by the National Institutes of Health through Grant GM-29028 and by Merck Sharp & Dohme Research Laboratories.

Supplementary Material Available: Physical data for selected intermediates (2 pages). Ordering information is given on any current masthead page.

(27) We thank Professor P. R. Jefferies (University of Western Australia) for the generous samples of (−)-bertyadionol and (−)-bertyadionol acetate.
(28) For an excellent review, see: Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

Total Synthesis of (+)-Rosaramicin Aglycone and Its Diacetate†

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Received December 10, 1985

Rosaramicin, a macrocyclic lactone isolated from the fermentation broth of *Micromonospora rosaria* NRRL-3718, is a potent broad spectrum antibiotic of considerable clinical interest.[3] This natural product is characteristic of its class and provides an interesting test of an anti-selective aldol method developed in these laboratories.[4]

Our construction of **1** commences with the key tactical component, namely, combination of the vinylogous urethane **3**, via its lithium enolate, with the chiral aldehyde **4** to obtain the lactone **5**, This substance leads to the acid **6** which on esterification with the alcohol aldehyde **7** followed by cyclo-olefination, alcohol deprotection, and epoxidation completes the synthesis of **1**, permitting, for the first time, the characterization of this aglycone.[5]

Deprotonation of **3**[6] (LDA, THF, 0.75 M, −78 °C, 90 min) generates the enolate **8**[7] which on treatment with the aldehyde **4**[6] (THF, 1.4 M, −78 °C, 30 min; 0 °C, 10 h) affords an 8:1 mixture of lactone products epimeric at C_4. The major isomer **5**, $[\alpha]_D$ +54.3° (*c* 1.0, CH_2Cl_2), was separated from its epimer by flash chromatography (70%). **5** was reduced and methylated (Li, NH_3; CH_3I) and the resulting saturated β-amino lactone converted into its *N*-oxide and eliminated (*m*-CPBA/Et_3N) to give (60% from **5**) the unsaturated lactone **9**, $[\alpha]_D$ +44.3° (*c* 1.5, CH_2Cl_2).

Conversion of **9** into the saturated lactone **10** was accomplished by diisobutylaluminum hydride reduction of the lactone to give a mixture of lactol anomers. Without purification, this material was persilylated with trimethylsilyl chloride under basic conditions (C_5H_5N, CH_2Cl_2) to give (88% from **9**) compound **11**, $[\alpha]_D$ +37.4° (*c* 1.0, CH_2Cl_2). The trisubstituted olefinic residue of **11** was then reduced, although not without difficulty, by using rhodium 5% on alumina (THF, 22 °C, H_2 >2000 psi, 120 h). Treatment of the crude reduction product with methanolic K_2CO_3 (22 °C, 3 h) to remove the trimethylsilyl groups followed, again without purification, by Collins oxidation (22 °C, 30 min) resulted (90% yield from **11**) in the aldehyde lactone **10**, $[\alpha]_D$ +31.7° (*c* 1.5, CH_2Cl_2), as a single substance carrying the C_2 methyl group in the required β-configuration.

We next converted the aldehyde portion of **10** into its dimethyl acetal analogue using trimethyl orthoformate and pyridinium *p*-toluenesulfonate in toluene. This intermediate was then treated with *p*-toluenesulfonic acid in methanol (0 °C, 1 h), which not only ring-opened the lactone into a methyl ester but also caused the conversion of the acetal residue into a five-membered-ring lactolide as well as removed the *tert*-butyldimethylsilyl group present on the side chain of **10**. The product formed by this process, **12**, $[\alpha]_D$ +36.3° (*c* 1.5, CH_2Cl_2), was obtained (66% yield from **10**) as a 6;1 mixture of anomers.[8] Interestingly, the direct conversion of **10** into **12**, while possible, occurred in significantly lower yield. The methyl ester residue of **12** reacted smoothly (90% yield) with dimethyl (lithiomethyl)phosphonate to give **13**, $[\alpha]_D$ +62.2° (*c* 1.0, CH_2Cl_2).

Jones oxidation (−20 °C) of **13** gave the acid **6**[9] which was immediately esterified with the alcohol aldehyde **7** through the agency of DCC and 4-(dimethylamino)pyridine in CH_2Cl_2 to give (66% yield from **13**) the ester **14**, $[\alpha]_D$ +63.3° (*c* 1.0, CH_2Cl_2), after flash chromatography.[10] Cyclo-olefination of **14** into **15**, $[\alpha]_D$ −11.3° (*c* 1.0, CH_2Cl_2), occurred in gratifying yield (85% after flash chromatography), using K_2CO_3 and 18-crown-6 in toluene (70 °C, 5 h).[11]

After considerable experimentation, it was found that **16**, $[\alpha]_D$ +7.8° (*c* 1.42, CH_2Cl_2), as a 3:1 mixture of anomers, could be obtained from **15** by employing 90% trifluoroacetic acid (0 °C, 10 min). Epoxidation of **16** using an aqueous pH 8 buffer (*m*-CPBA, CH_2Cl_2, 0 °C, 7 h), [12] afforded **1**, $[\alpha]_D$ +20.0° (*c* 1.10, CH_2Cl_2), as a 3:1 mixture of anomers, mp 212–213 °C, from **15**

† Dedicated to Professor Marshall D. Gates on the occasion of his 70th birthday.
(1) Hooker Corp. Fellow, Sherman Clarke Fellow, ACS Graduate Fellow in Organic Chemistry.
(2) Sherman Clarke Fellow.
(3) (a) Wagman, G. H.; Waitz, J. A.; Muarwski, A.; Oden, E. M.; Testa, R. T.; Weinstein, M. J J. *Antibiot.* **1972**, *21*, 641. (b) Stamm, W. E.; Holmes, K. K. *Abstract from Sexually Transmitted Diseases*, 2nd Meeting, Helsinki, Finland, Aug 9–10, 1979. (c) Maragoni, F.; Dainelli, B.; Magni, A.; Scazzocchio, F.; Repetto, A.; Filadoro, F. *Chemioterapia* **1983**, *2*, 56.
(4) For other applications of this anti-selective aldol method within the context of a total synthesis, see: (a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777. (b) Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357.
(5) A synthesis of the 3-deoxy aglycone of rosaramicin has been reported by: Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Somewhat to our surprise, however, rosaramicin aglycone, **1**, has never been described.
(6) Details for the preparation of all new materials mentioned in the text together with spectral data on them are available as supplemental material.
(7) Data supporting the structure of enolate **8** will be submitted for publication, manuscript in preparation.
(8) This 6:1 anomeric mixture is maintained throughout the reaction sequence leading to **1** until the penultimate step.
(9) For a leading reference, see: Ziegler, F. E.; Berger, G. D. *Synth. Commun.* **1979**, *9*, 539.
(10) The workup procedure for this reaction followed that outlined in the literature by: Muller, R. H; DiPardo, R. M. *J. Org. Chem.* **1977**, *42*, 3210.
(11) For leading references, see: (a) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.
(12) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351.

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