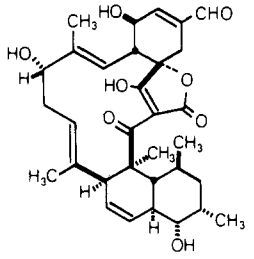
A Synthetic Approach to the Macrolide Nucleus of Tetronolide

Summary: Synthesis of compound **4**, the 14-membered macrolide nucleus of tetronolide (**1**), has been achieved via a base-catalyzed intramolecular cyclization of α-sulfonyl ω-aldehyde **15a** under controlled conditions.

Sir: Tetronolide (**1**) and kijanolide (**2**), a close analogue of **1**, are the aglycons of the tetronic acid containing antibiotics tetrocarcins[1] and kijanimicin,[2] respectively. Since



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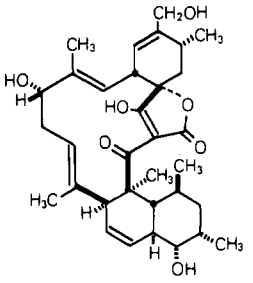

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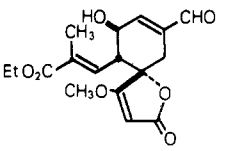
the discovery and structural determination of the antibiotics in 1980, total synthesis of these novel 14-membered macrolides has been a subject of considerable interest for synthetic chemists, yielding our recent synthesis of the top-half **3** of **1**[3,4] and Marshall's elegant approaches to the bottom octalin fragment (Chart I) by utilization of an intramolecular Diels–Alder reaction.[5] Thus, the remaining major problem in the total synthesis of **1** is how to construct the macrocyclic ring by assembling these two fragments. However, there has been no report dealing with this subject, except our unsuccessful attempt in the macrocyclization of model compound **5**.[6] We report here an efficient entry to the basic nucleus **4** employing, as a key step, an intramolecular condensation of α-sulfonyl ω-carbaldehyde intermediate **15a** which is obtainable through coupling of the top and bottom halves **7** and **8**.

The Diels–Alder reaction product of methyl (2*E*,4*E*)-3-methylhepta-2,4,6-trienoate with methacrolein,[6] a ca. 5:1 mixture of **6** and its diastereomer (exo-mode adduct), was transformed into the bottom-half **7** in good yield by four steps (Scheme I): acetalization with ethane-1,2-diol; reduction to an alcohol with *i*-Bu_2AlH (2.4 equiv);[6] phenylsulfenylation with diphenyl disulfide and *n*-Bu_3P in pyridine[8] (78% yield for the three steps), followed by

Chart I[7]



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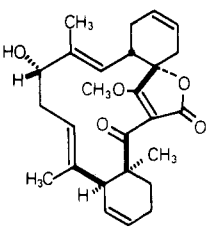

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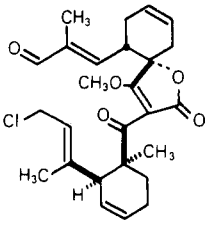

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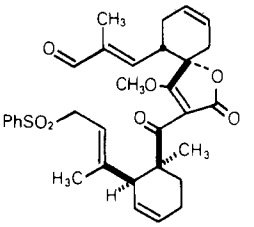
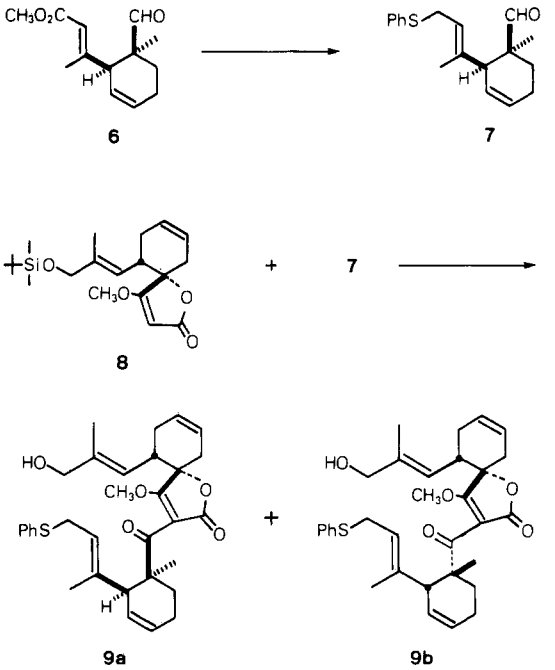


15a

Scheme I[7]



6 **7** **8** **9a** **9b**

separation of the resulting phenyl sulfide diastereomers by MPLC; deacetalization (Pyr-TsOH, aqueous acetone, reflux, ~100%).

α-Lithiation of the top-half tetronate **8** with LDA (THF, −78 °C, 30 min) followed by addition of **7** produced a carbinol product (75% yield), which on Swern oxidation using trifluoroacetic anhydride/Me_2SO[9] and subsequent desilylation with HF in acetonitrile[10] provided a mixture of diastereomeric α-acyltetronates. Separation of the isomers was cleanly achieved at this stage by MPLC, giving **9a** and **9b** in 29% and 23% yields from **8**, respectively. Assignment of the less polar isomer to **9a** was tentatively made from the results of the base-induced cyclization

(1) (a) Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Tetrahedron Lett.* **1980**, *21*, 2559. (b) Tomita, F.; Tamaoki, T.; Shirahata, K.; Kasai, M.; Morimoto, M.; Ohkubo, S.; Mineura, K.; Ishii, S. *J. Antibiot.* **1980**, *33*, 668. (c) Tomita, F.; Tamaoki, T. *Ibid.* **1980**, *33*, 940. (d) Tamaoki, T.; Kasai, M.; Shirahata, K.; Ohkubo, S.; Morimoto, M.; Mineura, K.; Ishii, S.; Tomita, F. *Ibid.* **1980**, *33*, 946. (e) Tamaoki, T.; Kasai, M.; Shirahata, K.; Tomita, F. *Ibid.* **1982**, *35*, 979.

(2) (a) Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938. (b) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D. *Ibid.* **1981**, *103*, 3940. (c) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497.

(3) Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1986**, *1197*.

(4) For approaches to the top-half of chlorothricolide having a similar spirotetronic acid structure to that found with **2**, see: Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.

(5) Marshall, J. A.; Grote, J.; Shearer, B. G. *J. Org. Chem.* **1986**, *51*, 1633. Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893.

(6) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K. Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673.

(7) All compounds are racemic. One enantiomer corresponding to **1** is depicted for graphic simplicity.

(8) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

(9) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. Huang, S. S.; Omura, K.; Swern, D. *Ibid.* **1976**, *41*, 3329.

(10) Newton, R. F.; Reynolds, D. P.; Finchi, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

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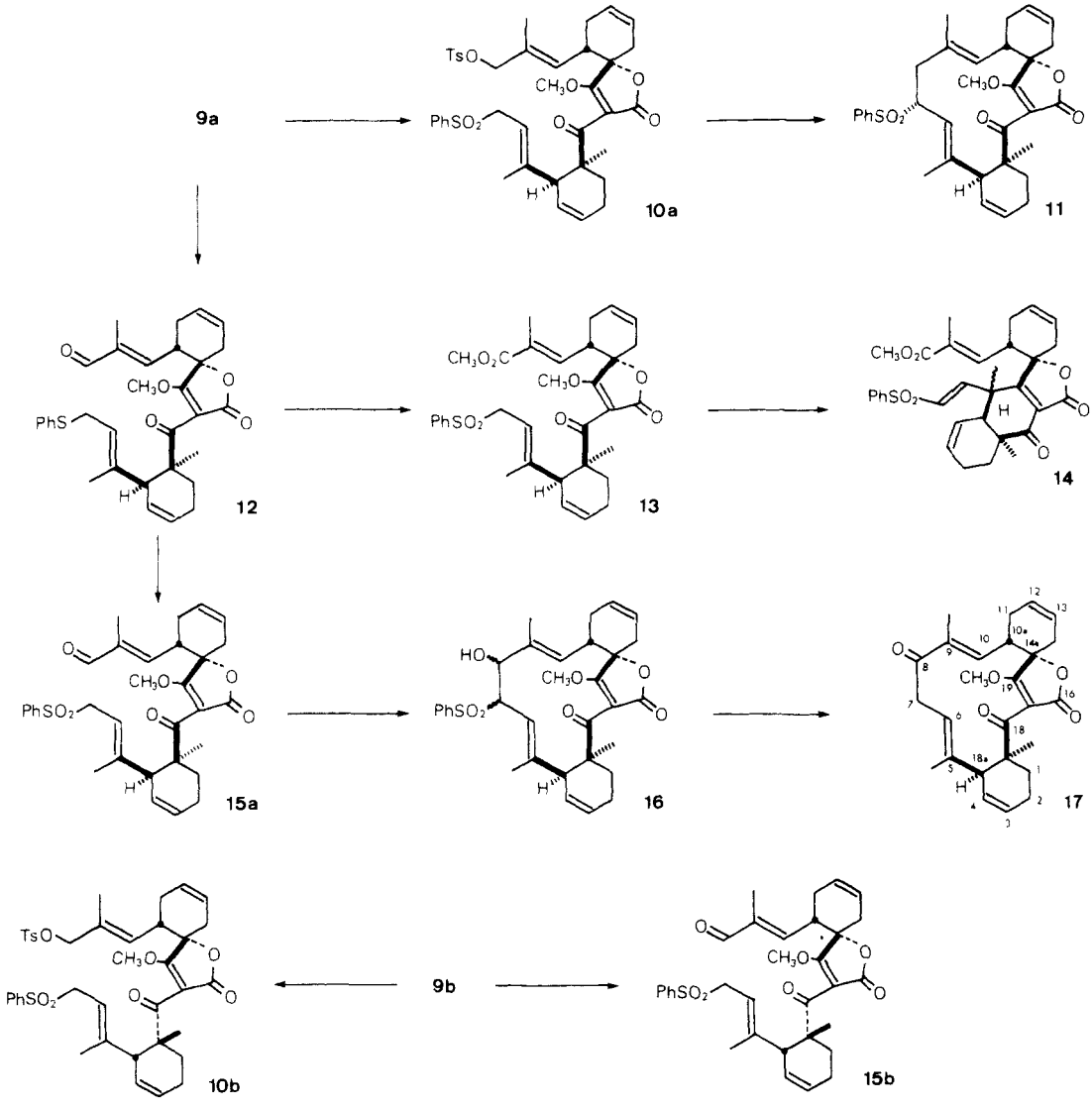
Scheme II[7]



performed on the corresponding sulfone/tosylate isomers **10a,b**, which were prepared from **9a,b** by tosylation with *p*-toluenesulfonic anhydride (Et_3N, CH_2Cl_2) and subsequent oxidation with MCPBA (ca. 65%). Treatment of compound **10a** (ca. 4×10^{-3} M in THF) with 1 equiv of potassium bis(trimethylsilyl)amide[11] at 20 °C for 1 h afforded the cyclization product **11**[12] in 45% isolated yield. On the other hand, the isomer **10b**, whose intramolecular S_N2 reaction is expected to be sterically less favorable by comparison of the transition states with molecular models, was largely recovered unchanged. This stereochemical assignment was later verified by X-ray crystallographic analysis of the derivatives **15a** and **15b**.

Our first attempt aimed at the synthesis of **4** was made by employing the sulfonyl ester **13** derived from **9a** through the following three-step reaction (Scheme II): active MnO_2 oxidation[13] (95% yield of **12**); transformation of the aldehyde group to the methyl ester by a modified method of Corey[14] (Me_3SiCN, catalytic KCN and 18-crown-6, CH_2Cl_2; then MnO_2 in MeOH, 83%); and MCPBA oxidation (96%). Treatment of **13** with a variety of amide and alkoxide bases, however, did not produce the desired compound **17**. Instead, there was obtained a vinyl sulfone, to which the structure **14** was assigned on the basis of the mass and ^1H NMR spectral analyses.

Our attention was then directed to a base-catalyzed intramolecular condensation of the α-sulfonyl ω-aldehyde **15a** which was obtained by MCPBA oxidation of **12** (65%). The stereostructures of **15a** and its diastereomer **15b** were confirmed by X-ray crystallographic analysis (**15a** in Figure 1, **15b** in supplementary material). After extensive investigation on the reaction conditions, we finally have established a highly effective and yet simple procedure as follows. To a stirred solution of **15a** (31 mg) in dry benzene (10.8 mL, concentration 5×10^{-3} M) under nitrogen atmosphere at 20 °C was syringed a solution of sodium *tert*-amyloxide (0.3 M in benzene, 1 equiv) over a period of ca. 10 min. Shortly after addition of the base had been completed, the reaction was quenched with acetic acid and then subjected to standard workup followed by chromatographic purification of the product to afford **16** as a diastereomeric mixture in quantitative yield. Use of THF

(11) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

(12) The configuration of the sulfonyl group was assigned on the basis of a vicinal coupling constant ($J_{7,8}$ = 12.2 Hz) of the sulfonyl methine proton (δ 3.88) in the ^1H NMR. For configuration of the macrocycle, see ref 1a.

(13) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Wolkea, T. *J. Chem. Soc.* **1952**, 1094.

(14) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

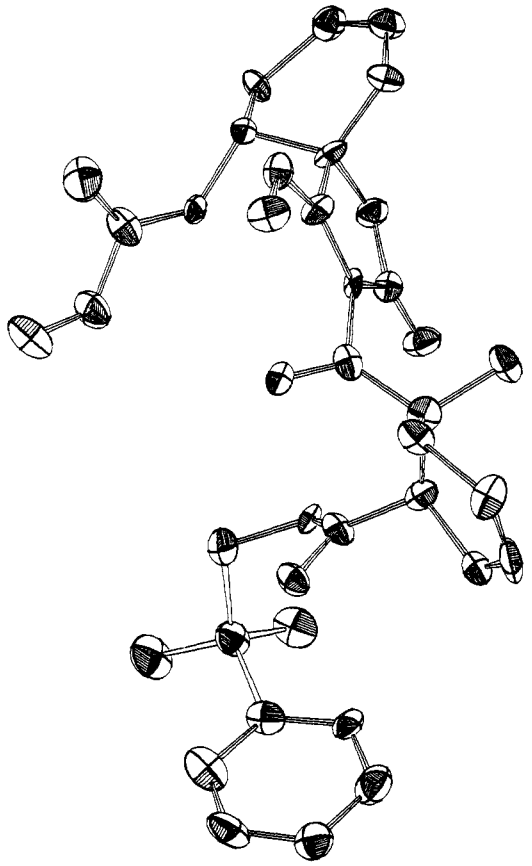


Figure 1. ORTEP drawing of compound **15a**.

as a solvent in place of benzene resulted in dramatic decrease in the yield of **16**.

Oxidation of **16** with pyridinium chlorochromate[15] in the presence of 3-Å molecular sieves[16] gave α-sulfonyl ketone (82%), which was submitted to reductive desulfonylation with Al–Hg in aqueous THF[17] to afford the ketone **17** (66%), mp 227–228 °C, whose structure was confirmed by spectral analysis.[18] Finally, reduction of **17** with sodium borohydride in MeOH proceeded stereoselectively to afford **4** in 31% yield,[19] no epimeric alcohol being detected by ^{1}H NMR (270 MHz). Resonance of the carbinyl proton in the ^{1}H NMR was observed at 4.23 ppm with $J_{w/2}$ = 9.9 Hz (coupling with the vicinal methylene protons) in accordance with axial orientation of the hydroxy group as reported for **1** and **2**.[1a,2b,c] Confirmation of the molecular structure of **4** was obtained by X-ray analysis as shown in Figure 2.

In conclusion, we could have established an efficient methodology for the construction of the macrocyclic ring of tetronolide and kijanolide. It utilizes in the key step (**15a** to **16**) an intramolecular aldol reaction between α-sulfonyl carbanion and aldehyde groups, the technique having so far been ignored or unsuccessful in large-ring synthesis.

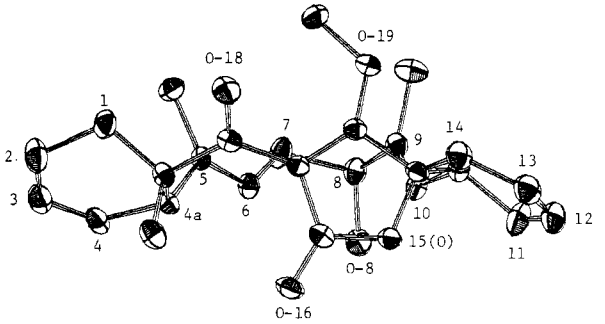


Figure 2. ORTEP drawing of compound **4**.

Acknowledgment. Support of this work by the Tamura Foundation for the Promotion of Science and Technology is gratefully acknowledged.

Registry No. **1**, 76705-48-1; (±)-**4**, 104995-64-4; (±)-**5** (isomer 1), 98993-13-6; (±)-**6** (isomer 2), 99094-70-9; (±)-**7**, 104995-47-3; (±)-**7** (ethylene acetal) (isomer 1), 104995-59-7; (±)-**7** (ethylene acetal) (isomer 2), 105086-99-5; (±)-**8**, 104995-48-4; (±)-**9a**, 104995-49-5; **9a**-ol (TBDMS), 104995-60-0; (±)-**9a** (TBDMS), 104995-61-1; (±)-**9a** (tosylate), 104995-62-2; (±)-**9b**, 105086-96-2; (±)-**9b** (TBDMS), 105087-00-1; (±)-**10a**, 104995-50-8; (±)-**10b**, 105086-97-3; (±)-**11**, 105018-31-3; (±)-**12**, 104995-51-9; (±)-**13**, 104995-52-0; (±)-**13** (sulfide), 104995-63-3; **14**, 104995-53-1; (±)-**15a**, 104995-54-2; (±)-**15b**, 105086-98-4; **16**, 104995-55-3; (±)-**16**-one, 104995-56-4; (±)-**17**, 104995-57-5; (±)-**17** (desmethoxylated), 104995-65-5; (*E*,*E*)-CH_2=CHCH=CHC(CH_3)=CHCOOCH_3, 98993-08-9; 4-(1,3-dioxolan-2-yl)-3-[1-hydroxy-3-methyl-2-propen-1-yl]-4-methylcyclohexene, 104995-58-6; methacrolein, 78-85-3.

Supplementary Material Available: Experimental details of compounds prepared (11 pages). Ordering information is given on any current masthead page.

Kei Takeda, Makoto Urahata, Eiichi Yoshii*
Faculty of Pharmaceutical Sciences
Toyama Medical and Pharmaceutical University
Sugitani 2630, Toyama 930-01, Japan

Hiroaki Takayanagi, Haruo Ogura
School of Pharmaceutical Sciences
Kitasato University
Shirokane, Minato-ku, Tokyo 108, Japan
Received April 4, 1986

(15) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(16) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.
(17) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(18) IR (KBr) 1755, 1665, 1590 cm^{-1}; MS, *m/e* (relative intensity) 422 (50, M^+), 404 (37, $M^+ - H_2O$), 315 (45, $M^+ - C_8H_{11}$, derived from a retro-Diels–Alder fragmentation of the bottom-half and α-cleavage of the (α-methylene)ketone group), 69 (100); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.32 (s, 3 H, 18a-CH_3), 1.42 (s, 3 H, 5-CH_3), 1.70 (dt, J = 14.0, 8.9 Hz, 1 H, H-1), 1.75 (d, J = 1.2 Hz, 3 H, 9-CH_3), 1.87 (ddd, J = 14.0, 4.6, 3.5 Hz, 1 H, H-1), 2.10–2.25 (m, 4 H, H-2, -11, and -14), 2.30–2.45 (m, 1 H, H-11), 2.72 (dm, J = 18.3 Hz, 1 H, H-14), 3.12 (td, J = 10.8, 6.1 Hz, 1 H, H-10a), 3.13 (ddd, J = 15.4, 5.1, 1.2 Hz, 1 H, H-7), 3.31 (dd, J = 15.4, 9.8 Hz, 1 H, H-7), 3.83 (s, 3 H, OCH_3), 3.88 (dm, J = 5.2 Hz, 1 H, H-4a), 5.28 (ddt, J = 9.8, 5.2, 2.2 Hz, 1 H, H-4), 5.68–5.81 (m, 3 H, H-3, -6, and H-12 or -13), 5.81–5.90 (m, 1 H, H-12 or -13), 6.21 (dq, J = 10.8, 1.2 Hz, 1 H, H-10).
(19) A major side reaction was hydrogenolytic elimination of the methoxy group with the ketone group unattacked.

New Methylseleno-Promoted Ketene–Imine Cycloaddition Reaction. A Simplified Stereoselective Synthesis of Penam[1]

Summary: A simplified stereoselective synthesis of penam-type β-lactams **5a–e** has been accomplished by utilizing a new methylseleno-promoted ketene–imine cycloaddition reaction and reductive elimination of the methylseleno group with *n*-Bu_3SnH.

Sir: β-Lactams can be synthesized in a practical way by the ketene–imine cycloaddition reaction,[2] but this reaction

(1) Presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, Japan, April 4, 1985; abstract paper p 630.

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