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Total Synthesis of Tetronolide, the Aglycon of Tetrocarcins

Kei Takeda, Eiji Kawanishi, Hitoshi Nakamura, and Eiichi Yoshii*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University
Sugitani 2630, Toyama 930-01, JAPAN

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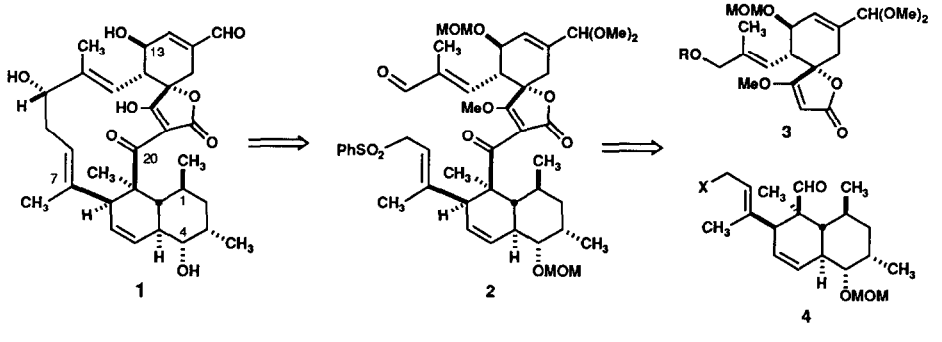
Abstract: *The first total synthesis of tetronolide (**1**) has been achieved via coupling of spirotetronate **3** with octahydronaphthalene aldehyde **17** and subsequent macrocyclization of ω-sulfone-α-aldehyde **2**, leading to confirmation of the absolute configuration of **1**.*

Tetronolide (**1**) is the aglycon of antitumor antibiotics tetrocarcins[1] which have been isolated from *Micromonospora chalcea*, and its stereostructure except absolute configuration was determined by X-ray analysis. This architecturally unusual molecule has attracted considerable attention[2,3,4] as a formidable synthetic target, together with the closely related aglycons kijanolide[5] and chlorothricolide[6]. In this Letter we wish to record the first total synthesis of the structure **1**, leading to the conclusion that tetronolide has the same absolute stereochemistry as of kijanolide.

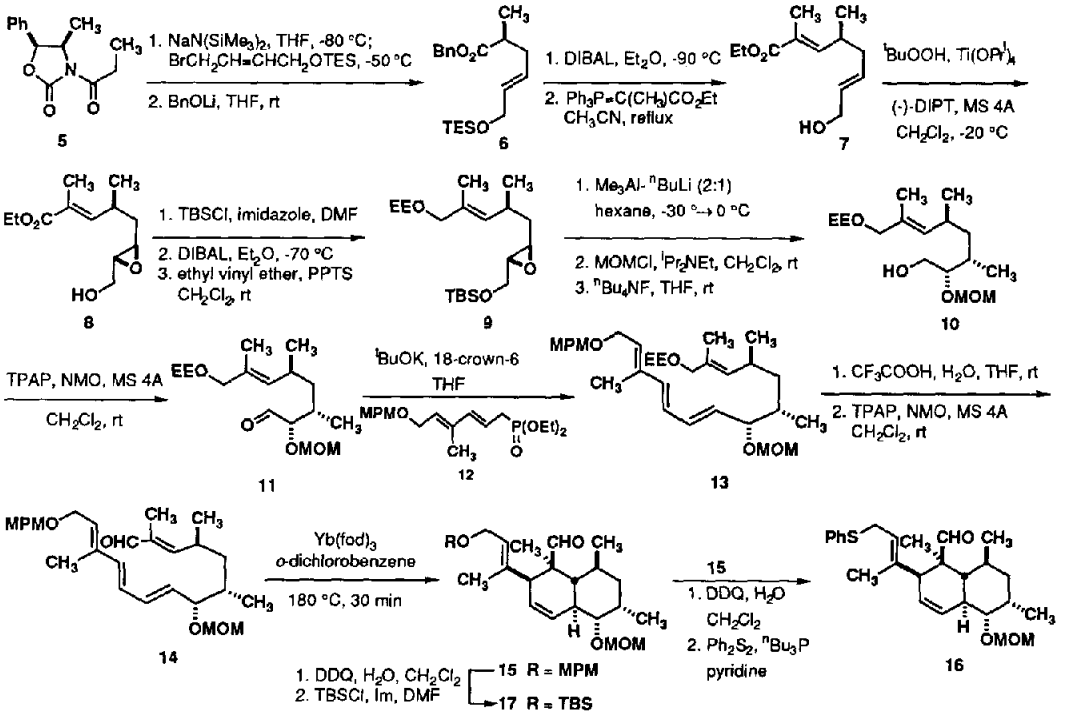
Our strategy for the construction of the macro-ring involves two key steps (Scheme 1): 1) aldol coupling of spirotetronate **3** (top-half) and octalinaldehyde **4** (bottom-half); 2) internal cyclization of ω-sulfone-α-aldehyde **2**. The top-half **3** has already been prepared by us in an enantiomerically pure form.[2a] Non-racemic bottom-half has also been prepared by us[2b] and others[7,8] via intramolecular Diels-Alder (IMDA) reaction of an appropriate 1,7,9,11-tetraene, but all of the reported protocols are unsuitable in terms of multigram preparation. The first task was therefore to establish a practical route to Diels-Alder precursor **14** (Scheme 2).



Scheme 1

Sharpless asymmetric epoxidation[9] of allylic alcohol **7**, prepared from *N*-propionyloxazolidinone **5** in 46% overall yield by standard procedures[10], afforded **8** in 95% yield which was transformed into **9** in 88% overall yield by the three-step sequence; *O*-silylation, ester reduction with *i*-Bu_2AlH (DIBAL), and hydroxyl protection as ethoxyethyl ether. Nucleophilic ring opening of the epoxide **9** using Me_3Al-*n*-BuLi (2:1)[11] oc-

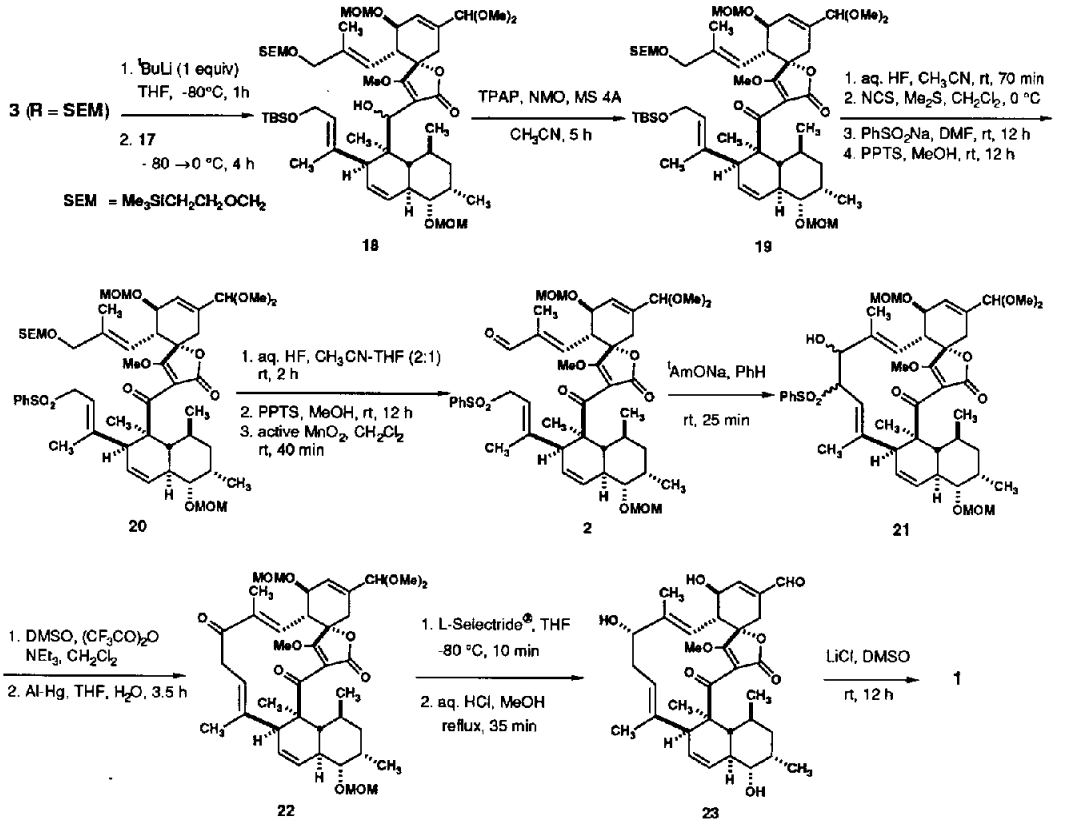
curred in highly regioselective manner affording **10** after protection-deprotection sequence (84% overall yield). Swern oxidation of the β-alkoxyalcohol **10** to aldehyde **11** resulted in poor yield (less than 30% yield). On the other hand, catalytic *n*-Pr_4NRuO_4 (TPAP) oxidation[12] using *N*-methylmorpholine-*N*-oxide (NMO) as a cooxidant proceeded cleanly to provide **11** in 92% yield. The next Horner-Emmons reaction of **11** with dienylphosphonate **12**[2b] (*t*-BuOK-THF) afforded homogeneous (*E,E,E*)-triene **13** in 27% yield along with a substantial amount of β-hydroxyphosphonate. Upon addition of 18-crown-6 to facilitate elimination of the intermediate much better yield was obtained, although triene product (90%) was contaminated with ca. 30% geometrical isomers. This difficult-to-separate mixture was used for the next step since the unwanted diastereomers were easily removed at the stage of ensuing IMDA reaction. Thus the impure **13** was subjected to sequential deprotection-TPAP oxidation to give crude **14** in 81% yield. It was then heated in *o*-dichlorobenzene at 180 °C for 30 min in the presence of $Yb(fod)_3$ (5 mol%). Chromatography of the reaction product provided *trans*-octalin **15**, $[\alpha]_D^{23} = -118°$ (c 0.31, $CHCl_3$), in 52% yield (38% from **13**) and unreacted tetraenal diastereomers (30%). The phenylsulfenyl derivative **16**was obtained from **15** by DDQ mediated removal of the MPM group followed by Hata's procedure.[13]



Scheme 2

Coupling of top and bottom-halves was first attempted with **3** (R = *t*-butyldiphenylsilyl) and **16** using mesityllithium for α-lithiation of the tetronate,[3b] which resulted in complete recovery of both partners. After extensive experimentation, the desired aldol reaction was realized by using *t*-BuLi as a base and SEM-protected top-half **3** (R = SEM) followed by reaction with TBS-protected bottom-half **17**, providing **18** in 67% yield (Scheme 3). The highly hindered carbinols (**18**) were resistant to oxidation to ketone with standard agents (DMSO/TFAA, PCC, active MnO_2). Only effective was stoichiometric TPAP oxidation in MeCN producing 81% yield of **19**. Manipulation of the silyloxy group in **19** to phenylsulfonyl was carried out by four steps: desilylation (1.2 equiv HF in MeCN-H_2O), Corey-Kim chlorination[14] of allyl alcohol, displace-

ment with $PhSO_2Na$, and acetalization (24%). Selective removal of the SEM group from **20** proved troublesome. Use of *n*-Bu_4NF produced a complex mixture. However, acceptable yields (~60%) could be secured by treatment with 15 equiv HF (5% in MeCN/THF/H_2O) for ca. 50% conversion and by recycling of the recovered starting material. Reacetalization followed by active MnO_2 oxidation afforded **2** in 50% overall yield from **20.**



Scheme 3

Macrocyclization of **2** was nicely achieved by treatment with 2 equiv *t*-AmONa (5 mM in benzene) at 18 °C for 25 min affording **21** (diastereomeric mixture) in quantitative yield. Swern oxidation followed by reductive removal of the sulfonyl group with Al-Hg afforded 13-membered ketone **22** (48% overall yield). Reduction of the ketone carbonyl with L-Selectride®, then hydrolysis of the MOM and acetal groups produced *O*-methyltetronolide (**23**) in 89% yield. Finally, treatment with excess LiCl in DMSO provided tetronolide in 90% yield. Its ^1H NMR[15] and TLC mobility were identical with those of an authentic sample obtained by an acid-catalyzed hydrolysis of tetrocarcin A. The observed sign in $[\alpha]_D^{22}$ = +49.6 °(c 0.76, acetone) of the compound was the same as that of the natural one, $[\alpha]_D^{26}$ = +79.3 ° (c 1.0, acetone), indicating that the absolute configuration of tetronolide is as shown structure **1**. The discrepancy in the optical rotations can be attributed to high ability for encapsulation of metal cations as observed in this class of molecules (e.g. kijanolide). Smaller difference was observed with tri-*O*-acetyl derivative: synthetic ($[\alpha]_D^{22}$ = +37.6 ° (c 0.94, acetone); natural ($[\alpha]_D^{26}$ = +42.0 ° (c 1.0, acetone)).

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15. mp 207 °C (natural 211-213 °C); ^{1}H NMR (270 MHz) δ 0.64 (3H, br d, Me-1), 1.04 (3H, d, J = 6.8 Hz, Me-3), 1.42 (3H, s, Me), 1.54 (3H, s, Me), 1.64 (3H, s, Me), 1.98-2.40 (5H, br m), 2.60 (1H, d, J = 18.6 Hz, H-16ax), 2.90 (1H, dt, J = 18.6, 2.7 Hz, H-16eq), 3.00 (1H, t, J = 9.8 Hz, H-12a), 3.29 (1H, br d, H-6a), 3.67 (1H, dd, J = 10.0, 5.9 Hz, H-4), 4.28 (1H, br s, H-10), 4.76 (1H, dm, J = 9.8 Hz, H-13), 5.18 (1H, br t, H-8), 5.38 (1H, dm, J = 9.8 Hz, H-12), 5.49 (1H, m, H-6), 6.07 (1H, dm, J = 10.3 Hz, H-5), 6.90 (1H, br s, H-14), 9.57 (1H, s, CHO).

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