SYNTHESIS OF THE POLYETHER FRAGMENT A/B-RING SYSTEM OF TETRONOMYCIN

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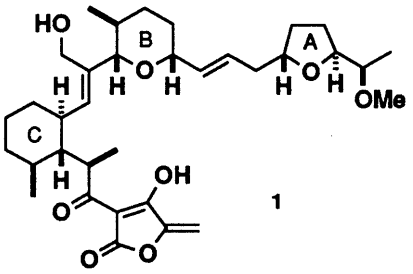
The polyether fragment **18** of tetronomycin (**1**) that contains the tetrahydrofuryl and tetrahydropyranyl groups has been synthesized *via* a Lewis acid-catalyzed coupling of a 2-methoxytetrahydrofuran **16** with a 2-(1-trimethylsilyl-2-propen-1-yl)tetrahydropyran **15**.

KEYWORDS allylsilane; allylation; ionophore antibiotic; total synthesis; tetronomycin.

In a previous paper,[1] we reported the synthesis of the enantiomeric polyether fragment of tetronomycin (**1**),[2] in which a Julia coupling was used to connect the two oxygen-containing heterocycles **2** and **3**. Here we describe the synthesis of the A/B ring system (**18**) having the correct absolute stereochemistry. The strategy involves the use of allylsilane chemistry for the stereospecific, high-yield formation of the central double bond, in contrast to the Julia method that provided a 2:1 *E/Z* mixture in a modest yield.



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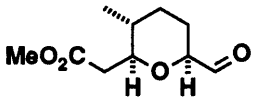

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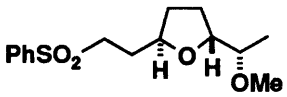

3

Synthesis of tetrahydropyran subunit **12** began with bishomologation of (*R*)-3,4-dihydroxybutyrate acetonide (**4**) derived from L-ascorbic acid[3a] or dimethyl (*R*)-malate[3b] (Chart 1). Thus, compound **4** was converted to **5**,[4] $[\alpha]_D^{26}$ -14.4° (*c*= 2.89, $CHCl_3$) in 83% yield by a 3-step sequence of reactions: reduction with 1.1 eq diisobutylaluminum hydride (DIBAL) in ether at -90 °C; Wittig reaction with $Ph_3P{=}CHCO_2Me$ in refluxing MeCN; and catalytic hydrogenation (H_2, 10% Pd-C, AcOEt). The ester **5** was hydrolyzed (KOH in MeOH-H_2O, room temperature), and the resulting carboxylic acid was allowed to react with (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone (1.1 eq) in the presence of dicyclohexylcarbodiimide (1.2 eq) and 4-dimethylaminopyridine (DMAP) (a catalytic amount) in CH_2Cl_2 at room temperature to give

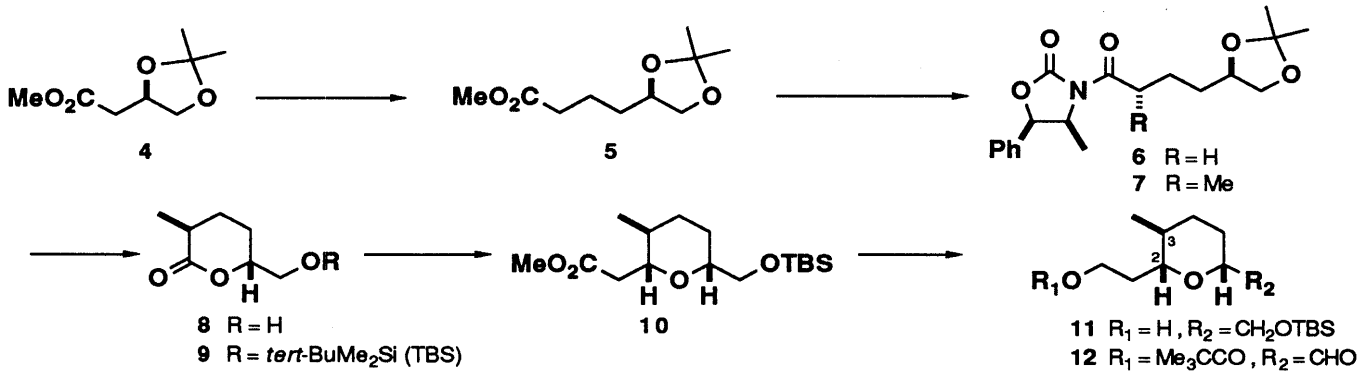

Chart 1

N-acyloxazolidinone **6**, mp 128-129°C, $[\alpha]_D^{26}$ -41.2° (*c*= 2.85, $CHCl_3$), in 70% yield from **5**. Treatment of **6** with 1.1 eq $NaN(Me_3Si)_2$ in tetrahydrofuran (THF) at -80 °C, then with 3 eq MeI at -80 to -30 °C (Evans protocol)[5] provided *ca.* a 8:1 mixture of **7** and its α-Me isomer (not shown in the Chart) in 99% yield. Treatment of this material with LiOH and H_2O_2 in aq.THF and then acidification (HCl) produced δ-lactone **8**,[6] which on silylation with *tert*-butyldimethylsilyl (TBS) chloride gave **9**[6] in 87% yield. Compound **9** was transformed into **10** according to the procedures used to prepare the enantiomer:[1,7] Dibal reduction; Wittig reaction with $Ph_3P{=}CHCO_2Me$; and treatment with methanolic KOH, then with *tert*-BuOK in THF (61% overall yield of a mixture of **10** and α-Me epimer). The mixture was separated by silica gel chromatography after Dibal reduction of the ester group. The stereochemically homogeneous alcohol **11** thus obtained in 73% yield was protected by *O*-trimethylacetylation, and the product was converted to aldehyde **12**,[14] $[\alpha]_D^{26}$ +119.7° (*c*=1.40, $CHCl_3$), *via* desilylation and Swern oxidation[9] (86% overall yield).

The reaction of **12** with vinylmagnesium bromide in THF at room temperature afforded vinyl carbinol **13** (86% yield), which, on treatment with 2 eq thionyl chloride in ether, afforded the rearranged allyl chloride **14** in 52% yield (Chart 2). Treatment of **14** with 2.5 eq Me_3SiCu-Me_2S by the method of J.G. Smith[10] afforded the desired allylsilane **15**[11,14] in 96% yield. The reaction[12] of **15** with the tetrahydrofuran fragment **16**[13] in the presence of 1 eq BF_3-Et_2O in CH_2Cl_2 at -40 to -20 °C for 3 h proceeded cleanly to afford exclusively (*E*)-olefin **17** in 92% yield as a 95:5 mixture of epimers **17a** and **17b**. The epimers were readily separated by silica gel chromatography after desilylation (*n*-Bu_4NF, THF), and the hydroxyl compound obtained from **17a** was subjected to *O*-methylation (8 eq NaH, 4 eq Me_2SO_4, THF, room temperature) to provide the target A/B system **18**,[14] $[\alpha]_D^{26}$ +38.0° (*c*=1.05, $CHCl_3$) in 63 % yield.

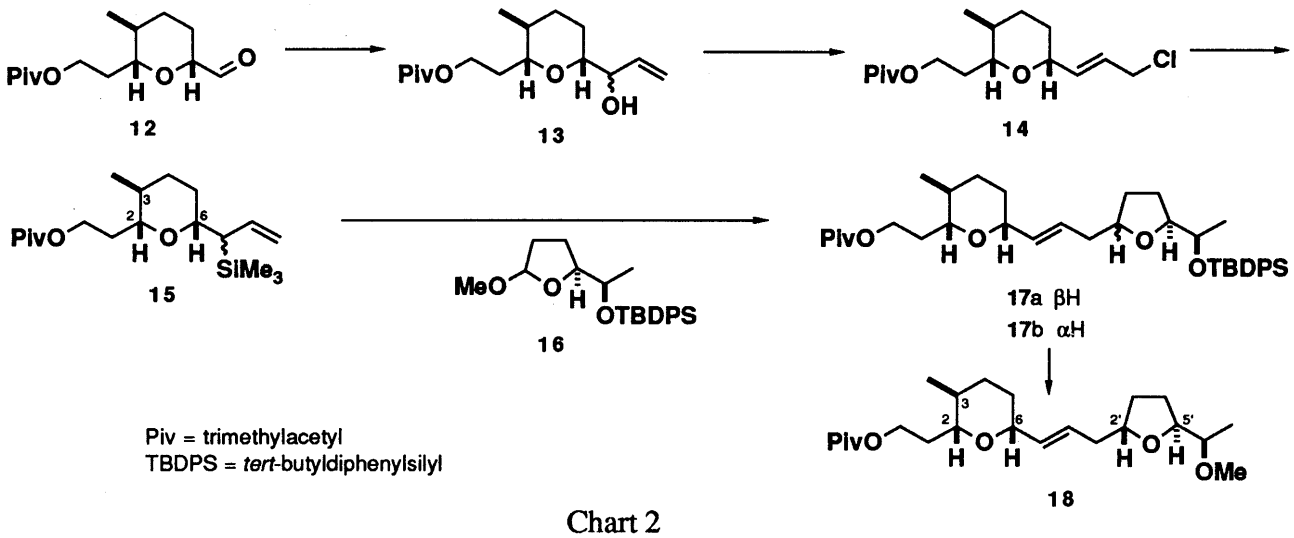

Chart 2

ACKNOWLEDGEMENT This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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6) Contaminated with C(3)-epimer (10~15%).

7) A comparable overall yield of **10** was realized by using the method of Kishi[8] that involves reaction of **9** with Li-enolate of $MeCO_2Me$ and subsequent treatment of the adduct with $Et_3SiH/BF_3{\cdot}Et_2O$.

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11) This compound was obtained as a mixture of epimers (*ca.* 70:30) which could not be separated.

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14) ^{1}H-NMR spectral data (270 MHz, $CDCl_3$).

12: δ 0.86 (3H, d, *J*=6.4 Hz, Me-3), 1.20 (9H, s, ^{t}Bu), 1.22-1.50 (3H, m), 1.69-1.92 (3H, m), 2.06 (1H, dddd, *J*=14.4, 8.1, 7.3, 2.4 Hz, C<u>H</u>HCH$_2$OPiv), 3.12 (1H, dt, *J*=9.3, 2.4 Hz, H-2), 3.74 (1H, dd, *J*=11.4, 2.7 Hz, H-6), 4.21 (1H, ddd, *J*=10.8, 8.1, 6.1 Hz, C<u>H</u>HOPiv), 4.29 (1H, ddd, *J*=10.8, 7.3, 5.0 Hz, CH<u>H</u>OPiv), 9.63 (1H, s, CHO).

15: δ (major isomer) 0.05 (9H, s, SiMe$_3$), 0.80 (3H, d, *J*=6.4 Hz, Me-3), 1.09-1.79 (7H, m), 1.19 (9H, s, ^{t}Bu), 1.90-2.02 (1H, m), 2.98 (1H, dt, *J*=9.0, 2.2 Hz, H-2), 3.42 (1H, dt, *J*=11.0, 2.7 Hz, H-6), 4.11 (1H, ddd, *J*=10.8, 8.8, 6.4 Hz, C<u>H</u>HOPiv), 4.26 (1H, ddd, *J*=10.8, 7.1, 4.6 Hz, CH<u>H</u>OPiv), 4.54 (1H, ddd, *J*=17.1, 2.4, 1.0 Hz, CH=C<u>H</u>H), 4.87 (1H, dd, *J*=10.5, 2.4 Hz, CH=CH<u>H</u>), 5.84 (1H, dt, *J*=17.1, 10.5 Hz, C<u>H</u>=CH$_2$).

18: δ 0.83 (3H, d, *J*=6.1 Hz, Me-3), 1.11-1.86 (8H, m), 1.12 (3H, d, *J*=6.3 Hz, CH(<u>Me</u>)OMe), 1.19 (9H, s, ^{t}Bu), 1.90-2.05 (3H, m), 2.15 (1H, ddd, *J*=13.9, 7.3, 6.0 Hz, CH=CH-C<u>H</u>H), 2.36 (1H, dt, *J*=13.9, 6.0 Hz, CH=CH-CH<u>H</u>), 3.05 (1H, dt, *J*=9.3, 2.4 Hz, H-2), 3.34 (1H, dq, *J*=6.3, 4.9 Hz, C<u>H</u>(Me)OMe), 3.37 (3H, s, OMe), 3.72 (1H, ddd, *J*=10.8, 5.0, 2.1 Hz, H-6), 3.90 (1H, dt, *J*=7.3, 4.9 Hz, H-5'), 3.99 (1H, ddt, *J*=8.0, 7.3, 6.0 Hz, H-2'), 4.17 (1H, ddd, *J*=10.5, 8.3, 7.9 Hz, C<u>H</u>HOPiv), 4.24 (1H, ddd, *J*=10.5, 7.8, 5.1 Hz, CH<u>H</u>OPiv), 5.53 (1H, dd, *J*=15.9, 5.0 Hz, C<u>H</u>=CH-CH$_2$), 5.63 (1H, dt, *J*=15.9, 6.0 Hz, CH=C<u>H</u>-CH$_2$).

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