

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

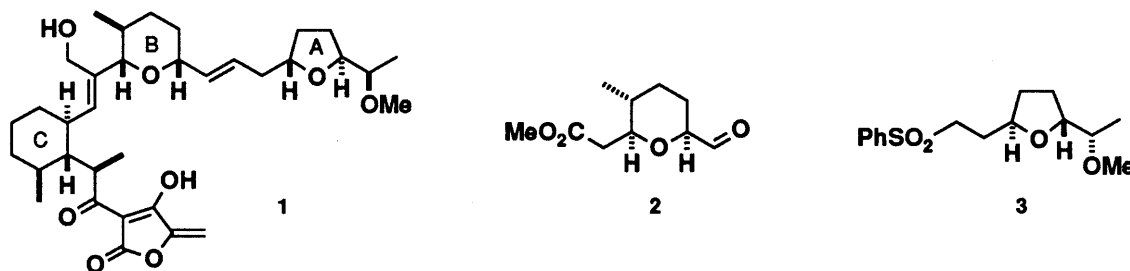
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The polyether fragment **18** of tetroneycin (**1**) that contains the tetrahydrofuryl and tetrahydropyranyl groups has been synthesized *via* a Lewis acid-catalyzed coupling of a 2-methoxytetrahydrofuran **16** with a 2-(1-trimethylsilyl-2-propen-1-yl)tetrahydropyran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

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

In a previous paper,¹⁾ we reported the synthesis of the enantiomeric polyether fragment of tetroneycin (**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.



Synthesis of tetrahydropyran subunit **12** began with bishomologation of (*R*)-3,4-dihydroxybutyrate acetone (4) derived from L-ascorbic acid^{3a)} or dimethyl (*R*)-malate^{3b)} (Chart 1). Thus, compound **4** was converted to **5**,⁴⁾ $[\alpha]_D^{26} -14.4^\circ$ ($c=2.89$, 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 $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ in refluxing MeCN; and catalytic hydrogenation (H_2 , 10% Pd-C, AcOEt). The ester **5** was hydrolyzed (KOH in MeOH-H₂O, 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

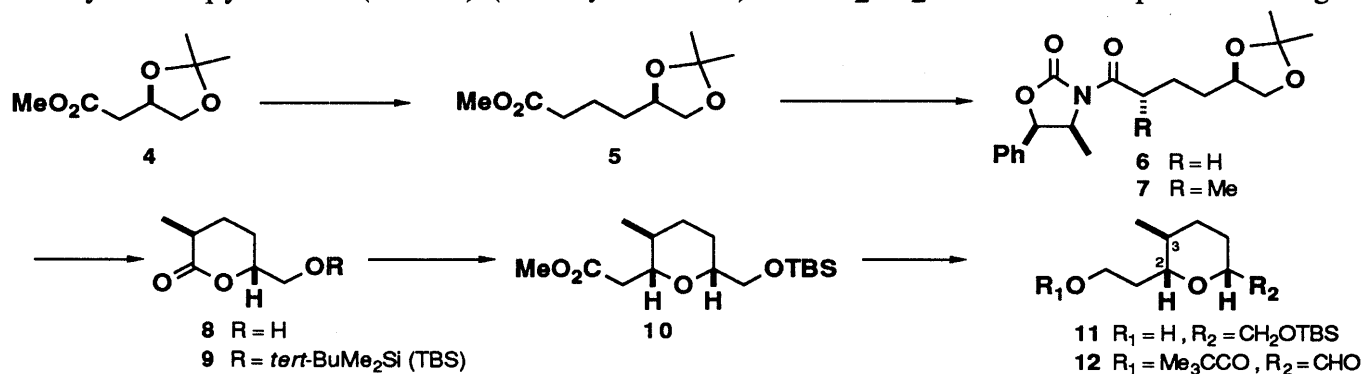


Chart 1

N-acyloxazolidinone **6**, mp 128-129°C, $[\alpha]_D^{26}$ -41.2° ($c=2.85$, CHCl₃), in 70% yield from **5**. Treatment of **6** with 1.1 eq NaN(Me₃Si)₂ in tetrahydrofuran (THF) at -80 °C, then with 3 eq MeI at -80 to -30 °C (Evans protocol⁵) 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 H₂O₂ 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 Ph₃P=CHCO₂Me; 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° ($c=1.40$, CHCl₃), *via* desilylation and Swern oxidation⁹) (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 Me₃SiCu-Me₂S by the method of J.G. Smith¹⁰ afforded the desired allylsilane **15**^{11,14} in 96% yield. The reaction¹² of **15** with the tetrahydrofuran fragment **16**¹³ in the presence of 1 eq BF₃-Et₂O in CH₂Cl₂ 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*-Bu₄NF, THF), and the hydroxyl compound obtained from **17a** was subjected to *O*-methylation (8 eq NaH, 4 eq Me₂SO₄, THF, room temperature) to provide the target A/B system **18**,¹⁴ $[\alpha]_D^{26}$ +38.0° ($c=1.05$, CHCl₃) in 63 % yield.

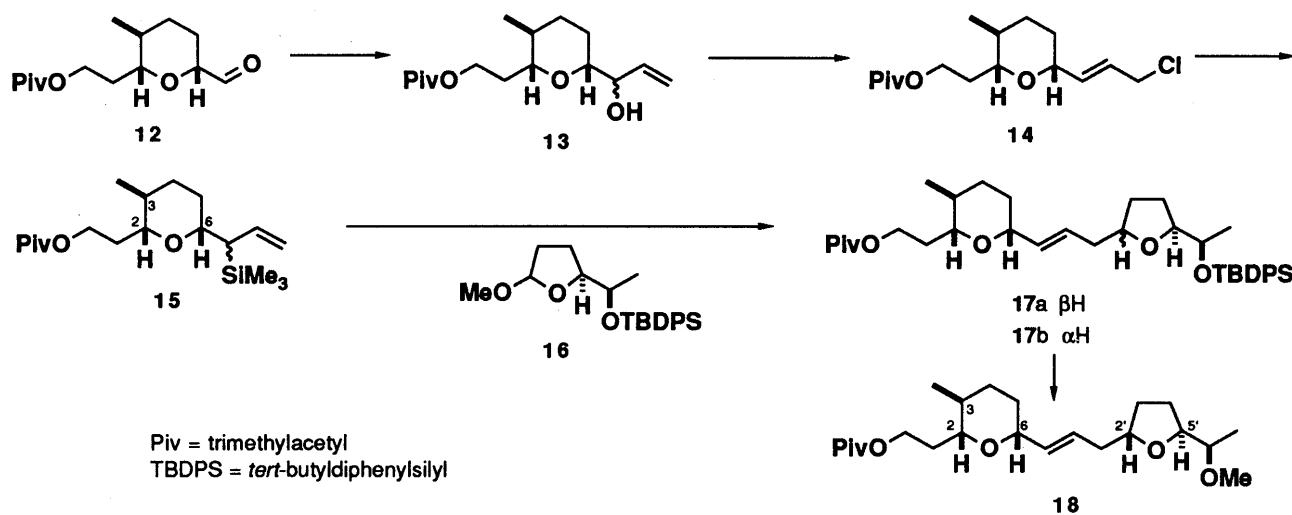


Chart 2

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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- 7) A comparable overall yield of **10** was realized by using the method of Kishi⁸⁾ that involves reaction of **9** with Li-enolate of MeCO₂Me and subsequent treatment of the adduct with Et₃SiH/BF₃•Et₂O.
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- 11) This compound was obtained as a mixture of epimers (*ca.* 70:30) which could not be separated.
- 12) Reaction of γ -lactol with allyltrimethylsilane: C. Brückner, H. Lorey and H-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, **25**, 556(1986).
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- 14) ¹H-NMR spectral data (270 MHz, CDCl₃).
 - 12**: δ 0.86 (3H, d, $J=6.4$ Hz, Me-3), 1.20 (9H, s, ^tBu), 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, CHHCH₂OPiv), 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, CHHOPiv), 4.29 (1H, ddd, $J=10.8, 7.3, 5.0$ Hz, CHHOPiv), 9.63 (1H, s, CHO).
 - 15**: δ (major isomer) 0.05 (9H, s, SiMe₃), 0.80 (3H, d, $J=6.4$ Hz, Me-3), 1.09-1.79 (7H, m), 1.19 (9H, s, ^tBu), 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, CHHOPiv), 4.26 (1H, ddd, $J=10.8, 7.1, 4.6$ Hz, CHHOPiv), 4.54 (1H, ddd, $J=17.1, 2.4, 1.0$ Hz, CH=CHH), 4.87 (1H, dd, $J=10.5, 2.4$ Hz, CH=CHH), 5.84 (1H, dt, $J=17.1, 10.5$ Hz, CH=CH₂).
 - 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(Me)OMe), 1.19 (9H, s, ^tBu), 1.90-2.05 (3H, m), 2.15 (1H, ddd, $J=13.9, 7.3, 6.0$ Hz, CH=CH-CHH), 2.36 (1H, dt, $J=13.9, 6.0$ Hz, CH=CH-CHH), 3.05 (1H, dt, $J=9.3, 2.4$ Hz, H-2), 3.34 (1H, dq, $J=6.3, 4.9$ Hz, CH(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, CHHOPiv), 4.24 (1H, ddd, $J=10.5, 7.8, 5.1$ Hz, CHHOPiv), 5.53 (1H, dd, $J=15.9, 5.0$ Hz, CH=CH-CH₂), 5.63 (1H, dt, $J=15.9, 6.0$ Hz, CH=CH-CH₂).

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