Tetrahedron Letters, Vol. 34, No. 52, pp. 8439-8442, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthetic Studies on Oligomycins. Enantiospecific Synthesis of the Oligomycin B Spiroketal Portion and Establishment of the Absolute Stereochemistry of Oligomycin B

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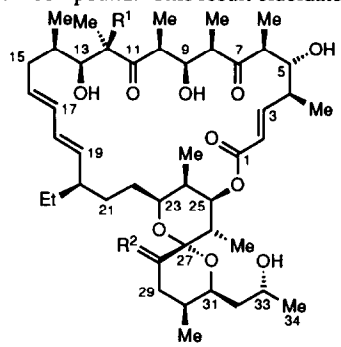
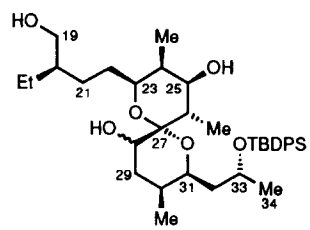
Abstract: The enantiospecific synthesis of the oligomycin B degradation product **2**, corresponding to the C19-C34 spiroketal portion, has been achieved by sequential coupling of the C19-C21, C22-C27, and C28-C34 subunits, establishing the absolute stereochemistry of oligomycin B.

Oligomycins A (**1a**), B (**1b**), and C (**1c**) were isolated in 1954 from a strain of *Streptomyces diastatochromogenes*.[1] They are antifungal antibiotics[1] and potent, specific inhibitors of oxidative phosphorylation.[2] The structure of **1** was elucidated by chemical degradation studies and an X-ray crystallographic analysis,[3] but the absolute stereochemistry has not been determined. We wish to describe here the enantiospecific synthesis of the oligomycin B degradation product **2**, corresponding to the C19-C34 spiroketal portion of **1b**, by sequential coupling of the C19-C21Wittig salt, the C22-C27 aldehyde, and the C28-C34 organotin compound. This result elucidated the absolute stereochemistry of **1b** as depicted below.[4]

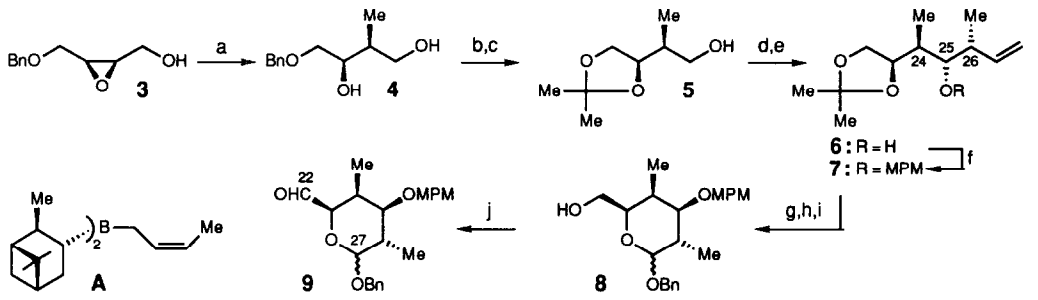


1a : Oligomycin A (R^1 = OH, R^2 = H_2)
1b : Oligomycin B (R^1 = OH, R^2 = O)
1c : Oligomycin C (R^1 = H, R^2 = H_2)

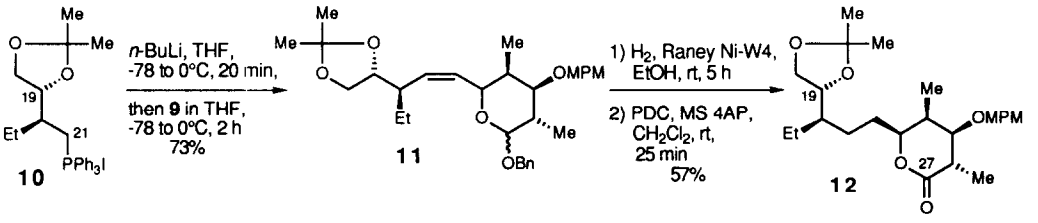


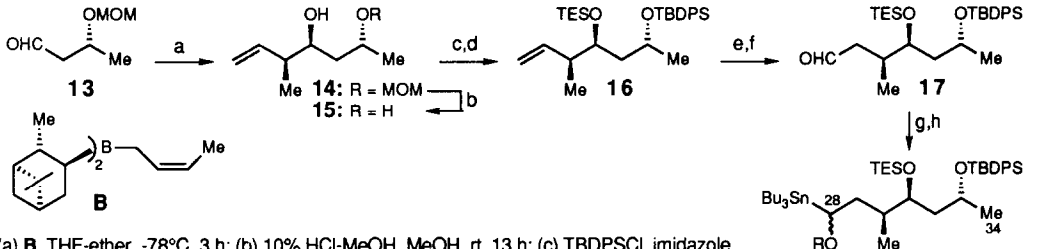
2

Our synthesis began with readily available epoxy-alcohol **3** (94% ee)[5] which was subjected to the regioselective epoxide-opening[6] with Me_2CuLi to afford a 4.5 : 1 mixture of **4**[7] and its regioisomer. Since this mixture could not be separated, it was subjected to $NaIO_4$-oxidation and from the resulting mixture the inert **4** was easily isolated by silica-gel column chromatography in 66% yield. Debenzylation of **4** followed by regioselective acetalization afforded alcohol **5**[7] in 75% yield. Swern oxidation (*i*-Pr_2NEt workup)[8] of **5** gave the crude aldehyde. The C25 and the C26 stereocenters[9] were then introduced with 15 : 1 selectivity by

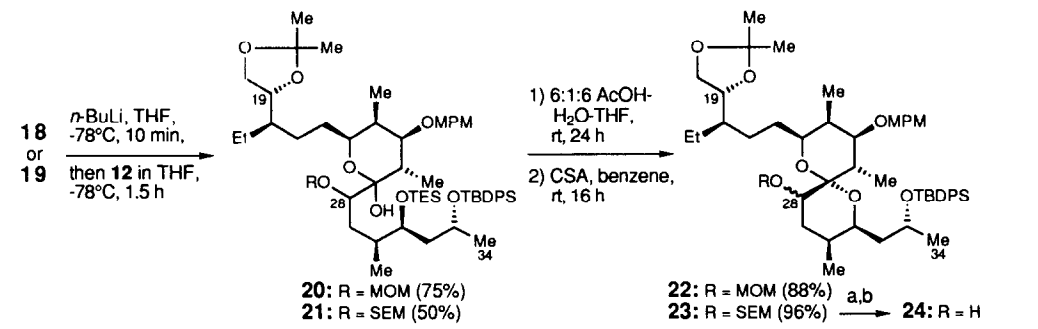


(a) Me_2CuLi, ether, -40°C, 1 h, then $NaIO_4$, aq THF, rt, 12 h, 66%; (b) H_2, $Pd(OH)_2$, MeOH, rt, 2 h, 92%; (c) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 20 h, 82%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 40 min, then *i*-Pr_2NEt, -78 to 0°C, 15 min; (e) **A**, THF-ether, -78°C, 1 h, 50% (2 steps); (f) MPMCl, NaH, DMF, rt, 20 h, 55%; (g) OsO_4, NMO, aq acetone, rt, 7 h, then $NaIO_4$, THF-pH 7 phosphate buffer, rt, 6 h; (h) 1 : 1 : 1 AcOH-H_2O-THF, rt, 15 h; (i) BnOH, CSA, CH_2Cl_2, rt, 15 h, 65% (4 steps); (j) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 30 min, then Et_3N, -78 to 0°C, 15 min, 100%.





(a) **B**, THF-ether, -78°C, 3 h; (b) 10% HCl-MeOH, MeOH, rt, 13 h; (c) TBDPSCl, imidazole, DMF, rt, 14 h; (d) TESCl, imidazole, DMF, rt, 20 min, 25% (4 steps); (e) dicyclohexylborane, THF, 0°C, 40 min, then H_2O_2-aq NaOH, 40°C, 20 min, 100%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 15 min, then Et_3N, -78 to 0°C, 20 min, 80%; (g) *n*-Bu_3SnH, LDA, THF, 0°C, 15 min, then **17**, -78°C, 40 min; (h) to **18**: MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 19 h, 75% (2 steps).
to **19**: 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl), *i*-Pr_2NEt, CH_2Cl_2, rt, 15 h, 72% (2 steps).



(a) *n*-Bu_4NF, MS 4AP, *N,N'*-dimethylpropyleneurea, 45°C, 1 d, 60%; (b) TBDPSCl, imidazole, DMF, 40°C, 5 h, 70%.

coupling of this aldehyde with (*Z*)-crotyldiisopinocampheylborane (**A**), prepared from *B*-(-)-methoxydiisopinocampheylborane.[10] The stereochemistry of the major diastereomer **6**,[7,11,12] isolated in 50% yield from **5**, was verified by conversion to **8**.[13] Protection of **6** [4-methoxybenzyl chloride (MPMCl), 55% yield] followed by cleavage of the terminal olefin of the resulting **7**[7] [OsO_4-4-methylmorpholine *N*-oxide (NMO), then $NaIO_4$] gave aldehyde, which was subjected to deacetalization and subsequent benzyl glycosylation to afford **8**[7] in 65% overall yield as a 3 : 1 mixture of α : β anomers, respectively.[13] Swern oxidation of **8** gave the C22-C27 aldehyde **9** in quantitative yield.

The C19-C21 Wittig salt **10**,[7] prepared from (2*R*,3*R*)-3-ethyl-1,2,4-butanetriol,[14] was treated with *n*-BuLi in THF and the resulting ylide was coupled with the above aldehyde **9** to afford **11**[7] in 73% yield. Further elaboration of this single (*Z*)-isomer **11** into the C19-C27 lactone **12**[7] was accomplished in 57% overall yield by selective hydrogenolysis[15] and hydrogenation followed by PDC oxidation of the intermediate lactol.

The synthesis of the C28-C34 organotin compound **18** or **19** began with aldehyde **13**.[16] Treatment of **13** with the Brown's reagent **B**, prepared from *B*-(+)-methoxydiisopinocampheylborane,[10] afforded a 3 : 1 mixture of **14** and the other syn isomer.[17] Deprotection of this mixture gave the desired diol **15**, separable from its stereoisomer by column chromatography, which was protected as its disilyl ether to give **16**[7] in 25% overall yield from **13**. Hydroboration of **16** with dicyclohexylborane followed by Swern oxidation afforded aldehyde **17** in 80% yield. Finally, addition of *n*-Bu_3SnLi[18] to **17** followed by etherification furnished the C28-C34 subunit **18** or **19** in 75% yield or 72% yield (each was a 1 : 1 mixture at the C28-position).

The coupling of the C19-C27 and the C28-C34 subunits was realized by lithiation[18] of **18** or **19** with *n*-BuLi followed by immediate addition of lactone **12** to afford the adduct **20** (75%) or **21** (50%). Each adduct was subjected to selective desilylation and cyclization to afford **22**[7] (88%) or **23**[7] (96%). Both **22** and **23** consisted of a 1 : 1 separable mixture at the C28-position. We believe that these compounds would be useful synthetic intermediates for the total synthesis of oligomycins. Selective deprotection[19] and re-silylation of one epimer of **23** furnished **24**, which was transformed to **2**[7,20] by the four-step sequence: (1) TsOH, MeOH, rt, 4 h; (2) $NaIO_4$, THF-pH 7 phosphate buffer, rt, 1 h; (3) $NaBH_4$, MeOH, rt, 0.5 h; (4) DDQ, aq CH_2Cl_2, rt, 20 min,[15] 75% overall yield. For securing the authentic sample of **2**, the degradation study of oligomycins was performed.[3d,21] Commercially available oligomycin A, B, and C mixture (A : B : C = 75 : 15 : 10, Aldrich) was subjected to silylation (TBDPSCl, imidazole, DMF, 33°C, 88 h), ozonolysis (O_3, EtOAc, -75°C, 5 min, then $NaBH_4$, THF, -70°C to rt, 21 h), and ester cleavage reaction (DIBAL, CH_2Cl_2, -75 to -40°C, 1 h). The obtained **2** (12% yield) consisted of a 10 : 1 separable mixture at the C28-position.[20] The synthetic **2** was identical in all respects (^1H NMR, IR, $[\alpha]_D$,[22] and TLC mobilities) with the naturally derived **2** (the major one), which implies that the absolute stereochemistry of oligomycin B (**1b**) is as depicted. Further efforts to complete the total synthesis of oligomycins are now in progress.

Acknowledgment: We would like to thank Emeritus Professor Mitsuhiro Kinoshita (Keio University) for helpful discussion and Nippon Kayaku Co., Ltd. for a generous gift of 44-homooligomycin B. We are grateful to the Institute of Microbial Chemistry for the generous support of our program.

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5. The % ee of **3** was determined by ^{1}H NMR shift analysis of the derived acetate with Eu(hfc)$_3$ in benzene-d_6, see footnote 9 in ref. 5a: a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; b) Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1154.
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7. Satisfactory analytical data (^{1}H NMR and IR spectra, elemental analyses and/or HRMS) were obtained for all new compounds.
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9. The numbering system used for **1** is employed in the discussion of all synthetic intermediates.
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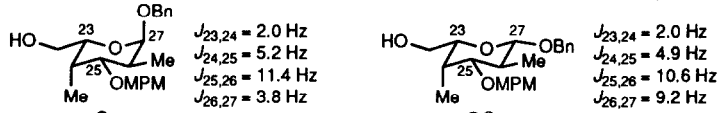
11. The minor isomer was assumed to be the other C25-C26 syn product.
12. The coupling between the same aldehyde and (*Z*)-crotyldiisopinocampheylborane (**B**), prepared from *B*-(+)-methoxydiisopinocampheylborane,[10] afforded **6** and the other C25-C26 syn product in a 1 : 1 ratio. According to these experiments, the optical purity of **6** was determined to be 97% ee.
13. The ^{1}H NMR *J* analysis confirmed the complete stereochemistry in **8**α and **8**β, and hence in **6**.



8α **8**β

14. (2*R*,3*R*)-3-Ethyl-1,2,4-butanetriol was prepared from (*R*)-malic acid by the Seebach protocol: (1) MeOH, H_2SO_4, 65°C, 8 h; (2) LDA, THF, -78°C, 0.5 h, then EtI, -78 to 0°C, 8 h; (3) DIBAL, toluene, 0°C, 1 h, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1.5 h; (4) NaOMe, MeOH, rt, 0.5 h, 24% overall yield [Wasmuth, D.; Arigoni, D.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 344]. The C19-C21 Wittig salt **10** was obtained from this triol by the three-step sequence: (1) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 1 h; (2) I_2, Ph_3P, imidazole, CH_2Cl_2, rt, 1 h; (3) Ph_3P, MeCN, 75°C, 25 h, 27% overall yield.
15. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
16. Aldehyde **13** was obtained from (*R*)-methyl 3-hydroxybutyrate by the three-step sequence: (1) chloromethyl methyl ether (MOMCl), *i*-Pr_2NEt, CH_2Cl_2, rt, 42 h; (2) $LiAlH_4$, THF, 0°C, 1 h; (3) PCC, MS 4AP, CH_2Cl_2, rt, 0.5 h, 75% overall yield.
17. The stereochemistries of both compounds were established by conversion of them to the 6-membered glycosides. The details will be published in a full account.
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20. The C28-configuration of **2** has not been determined.
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22. Optical rotation of the synthetic **2**: $[\alpha]_D^{30}$ -35.1° (c 0.08, $CHCl_3$). Optical rotation of the naturally derived **2**: $[\alpha]_D^{30}$ -54.8° (c 0.08, $CHCl_3$), -41.9° (c 0.54, $CHCl_3$). The synthetic **2** was contaminated with a small quantity of an inseparable byproduct.

(Received in Japan 18 August 1993; accepted 12 October 1993)