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Studies Directed towards the Total Synthesis of the Antibiotic Macrodiolide Tartrolon: EPC Synthesis of the Protected Seco Acid

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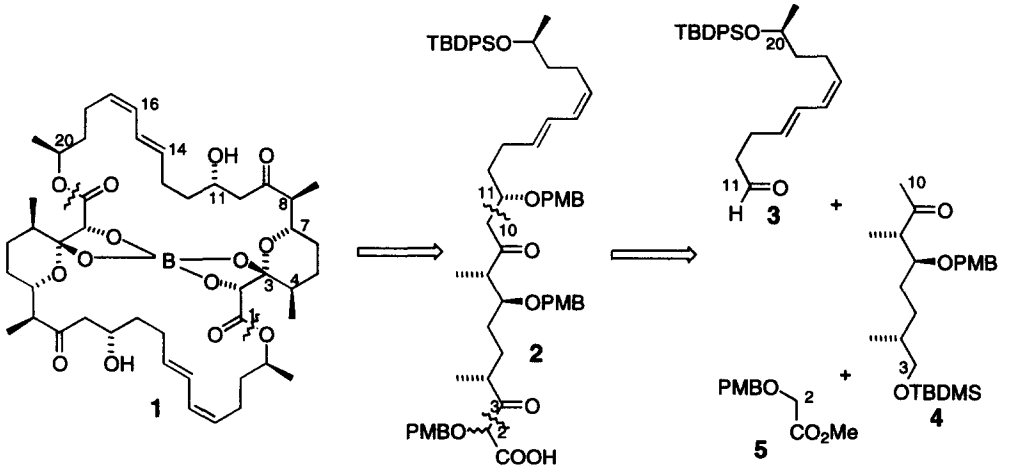
Abstract: An efficient synthesis of the protected seco acid **2** of the antibiotic macrodiolide tartrolon **1** is described. Key steps are a substrate controlled aldol-reaction, a Johnson-Claisen rearrangement, and a Horner-Wadsworth-Emmons olefination with subsequent Corey-Bakshi-Shibata (CBS) reduction.

Tartrolon **1**, first isolated by Höfle[1a] from *Sorangium cellulosum*, is a boron containing C_2-symmetrical macrodiolide structurally related to boromycin, aplasmomycin, and borophycin.[1b] Similar to these diolides, **1** is an inhibitor of Gram-positive bacteria with a broad antibiotic spectrum.[1c]

Retrosynthetic considerations (Scheme 1). In a total synthesis of **1** the macrolactonization-dimerization of a suitably protected seco acid (such as **2**) followed by deprotection may be envisaged as the final operation. In this letter we report an efficient synthesis of seco acid **2**; the dimerization-macrolactonization studies will be described later. Retrosynthetically **2** is disconnected by means of two aldol type additions, by which the C10-C11- and C2-C3-bonds are generated. This strategy leads back to aldehyde **3**, methyl ketone **4** and alkoxy acetate **5** as the key fragments. Our synthesis is based on the "chiral pool" concept. Thus, C-20 is taken from (*S*)-lactate, whereas C-4 and C-8 stem from (*R*)- and (*S*)-methyl 3-hydroxy-2-methylpropionate ("Roche's ester"), respectively.



Scheme 1

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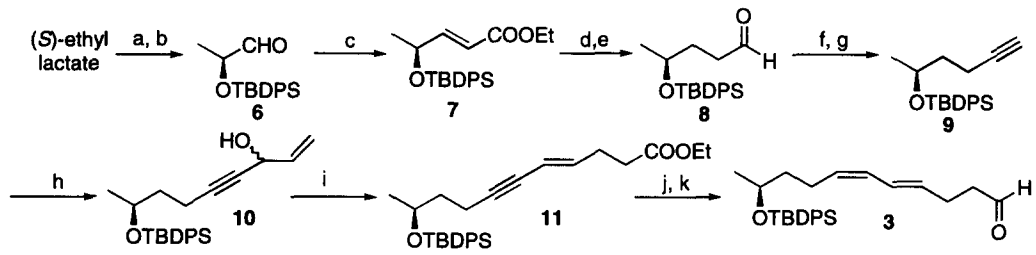
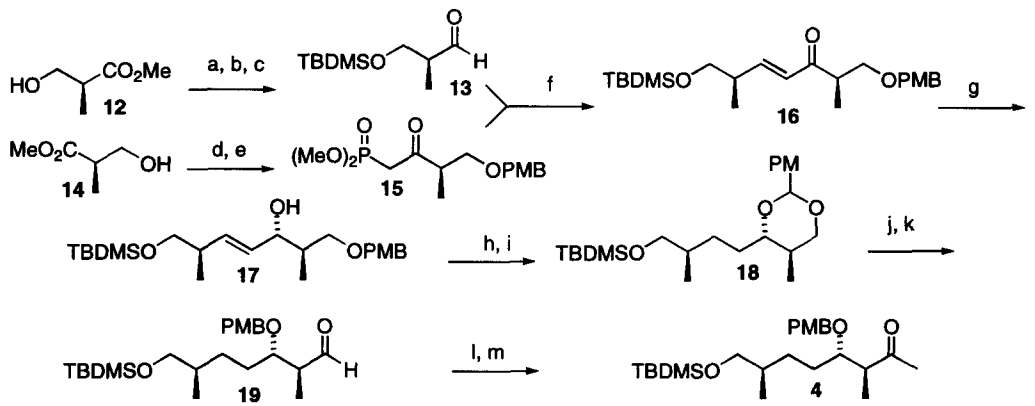
Synthesis of the C11-C21 fragment 3 (Scheme 2). (*S*)-Ethyl lactate was O-silylated and reduced to the aldehyde **6**, which was converted into enoate **7** by a Horner-Wadsworth-Emmons reaction. Catalytic hydrogenation of the double bond and reduction of the ester with DIBAH furnished aldehyde **8**, which was converted into alkyne **9** via a Corey-Fuchs sequence.[2] Addition of lithiated alkyne **9** to acrolein in presence of lithium bromide[3] gave allylalcohol **10**, which was transformed into the (*E*)-en-ynoate **11** via a Johnson-Claisen rearrangement.[4] *cis*-Selective alkyne reduction with activated zink[5] and DIBAH reduction of the ester furnished aldehyde **3** eventually in 31% overall yield from the lactate.



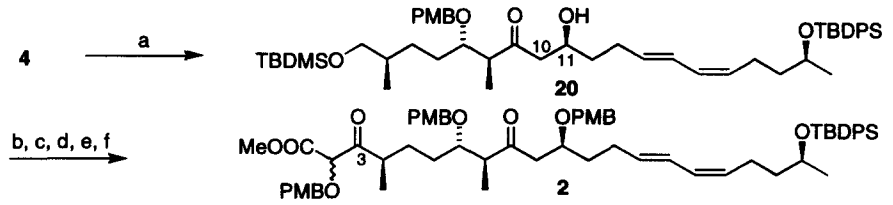
Scheme 2. *Reagents and conditions:* a) TBDPSCl, NEt_3, DMAP; b) DIBAH, Et_2O, -78°C; c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; d) Raney-Ni, H_2, 81% for 4 steps; e) DIBAH, Et_2O, -78°C; f) Zn, CBr_4, PPh_3; g) Mg, Et_2O, 64% for 3 steps; h) acrolein, BuLi, LiBr 0.5 eq, 89%; i) $(EtO)_3CCH_3$, cat. propionic acid, xylene, refl., 88%, *E/Z* 6:1; j) Zn, $BrCH_2CH_2Br$, CuBr, LiBr; THF; k) DIBAH, Et_2O, -78°C, 89% for 2 steps.

Synthesis of the C3-C10 fragment 4 (Scheme 3). (*S*)-(+)-Methyl 3-hydroxy-2-methylpropionate **12** was converted into the aldehyde **13**,[6] which was condensed with the β-ketophosphonate **15** in a Horner-Wadsworth-Emmons reaction.[7] Ketophosphonate **15** in turn was obtained from (*R*)-(-)-methyl 3-hydroxy-2-methylpropionate **14** in two steps.[8] The resulting enone **16** was reduced to the allylic alcohol **17** by the CBS protocol[9] with a diastereomer ratio of 6:1. Diimine reduction[10] of the double bond followed by ketalization of the hydroxy groups at C-10 and 12 led to the cyclic ketal **18**, which was regioselectively opened with DIBAH at the primary position. Swern oxidation[11] of the resulting primary alcohol gave aldehyde **19**. Addition of methylmagnesium bromide followed by Swern oxidation furnished methylketone **4** in 26% overall yield from **16**.

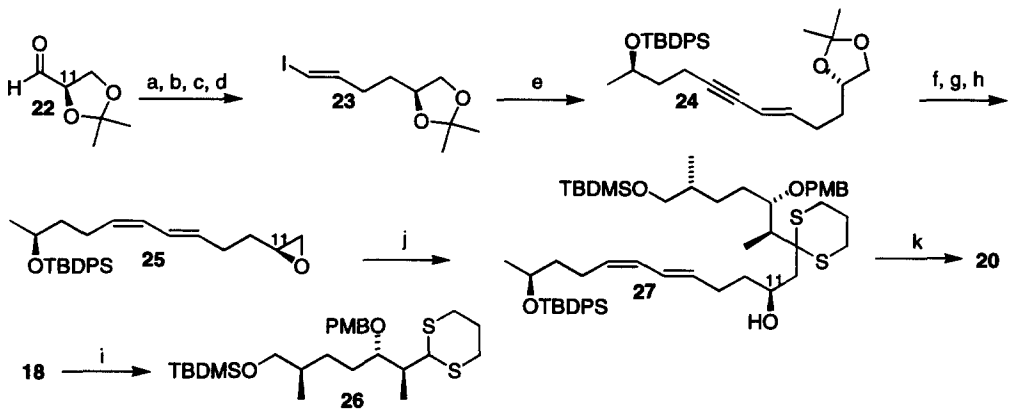


Scheme 3. *Reagents and conditions*: a) TBDMSCl, imidazole, DMF; b) DIBAH, THF; c) $(COCl)_2$, DMSO, $NEt(iPr)_2$, 74% for 3 steps; d) $PMBOC(NH)CCl_3$, cat. CSA, CH_2Cl_2; e) LDA, $CH_3P(O)(OMe)_2$, THF, 80% for 2 steps; f) LiOH, THF, 87%; g) CBS reduction, *anti/syn* 6:1; h) H_2NNH_2, O_2, cat. $Cu(OAc)_2$, 55% for 2 steps; i) DDQ, MS 4A, CH_2Cl_2; j) DIBAH, CH_2Cl_2, -20°C, 62% for 2 steps ; k) $(COCl)_2$, DMSO, NEt_3; l) MeMgBr, Et_2O, -10°C; m) $(COCl)_2$, DMSO, NEt_3, 78% for 3 steps.

Coupling of fragments 3 and 4 by aldol addition and final steps (Scheme 4). Methylketone **4** was converted into the enol borinate with (-)-chloro-diisopinocampheylborane and treated with aldehyde **3** to give the desired aldol adduct **20** with 95:5 diastereoselectivity. The same diastereoselectivity was observed with (+)-chloro-diisopinocampheyl-borane! This means that the stereochemistry in this addition is substrate controlled and independent of the reagent. The high substrate control results from the two mutually reinforcing effects which are exerted by the 8-methyl group (1,4-*syn*-direction)[12a] and by the 7-OPMB group (1,5-*anti*-direction) in the enol borinate.[12b] The stereogenic centers in **4** are too remote for stereochemical induction. Chain elongation via aldol type addition of a suitably protected C-3 aldehyde with the lithium enolate prepared from **5** eventually generated the fully protected seco acid **2**[13] after Swern oxidation. In consequence of the high C-H acidity of the 2-position **2** exists in form of two rapidly equilibrating epimers with respect to C-2.



Scheme 4. *Reagents and conditions:* a) $((-)\text{-Ipc})_2BCl$, Et_3N, THF, -78°C, then **3** , 83%, 95 :5; b) $PMBOC(NH)CCl_3$, cat. CSA, cyclohexane / CH_2Cl_2; c) Dowex-50, THF, RT; d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 68% for 3 steps; e) MeO_2CCH_2OPMB, LDA, THF, -78°C; f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 79% for 2 steps.



Scheme 5. *Reagents and conditions*: a) Ph_3PCHCO_2Me, MeOH; b) Raney-Ni, H_2; c) DIBAH, Et_2O, -78°C; d) CHI_3, $CrCl_3$, LAH, 37% for 4 steps; e) **9**, $BuNH_2$, cat. $Pd(PPh_3)_4$, CuI; f) Zn, $BrCH_2CH_2Br$, CuBr, LiBr; g) *p*-TosOH, MeOH; h) NaH, N-tosylimidazole, 46% for 4 steps; i) TMS-S$(CH_2)_3$S-TMS, cat. ZnI_2, 64%; j) **26**, *s*-BuLi, TMEDA, DMPU, THF, -40°C to -20°C, 39% ; k) NBS, $AgClO_4$, 0°C, acetone / H_2O, 55%.

An alternative approach to seco acid 2 (Scheme 5). It has surely been noted that the configuration of the stereogenic center at C-11 has not rigorously been assigned so far. Therefore, a second approach to key fragment **20** was designed to generate this center in a stereochemically unambiguous way. The hydroxyketone moiety at C-10 to C-12 was assembled by a dithiane anion epoxide ring opening[14] employing the components **25** and **26**, respectively. The synthesis of these fragments is shown in scheme 5.

Contrary to the previous synthesis the (*E*)-ene-alkyne moiety in **24** was prepared stereoselectively via a Stephens-Castro coupling[15] of the (*E*)-vinyl iodide[16] **23** with alkyne **9**. The addition of the lithiated dithiane[17] **26** to epoxide **25** proceeded regiospecifically under retention of configuration[18] to furnish **27**, which after

deketalization[19] gave **20**, indistinguishable (^{1}H and ^{13}C NMR, optical rotation and HPLC) from the material obtained from the first sequence.

REFERENCES AND NOTES

Dedicated to Professor Harry Kurreck on the occasion of his 65th birthday

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13. Data for **2** (mixture of C-2-epimers): **^{1}H NMR** δ (400 MHz, $CDCl_3$) = 0.80 (d, *J*= 6.8, 1.5H), 0.92 (d, *J*= 7.0, 1.5H), 1.04 (s, 15H), 1.05 (d, *J*= 6.1, 1.5H) 1.11 (d, *J*= 6.8, 3H), 1.20 (d, *J*= 6.8, 3H), 1.36-1.60 (m, 7H), 1.68-1.86 (m, 1H), 2.12 (m, 4H), 3.19 (m, 1H), 3.73 (s, 3H), 3.75 (s, 1.5H), 3.76 (s, 4.5H), 3,79 (s, 3H) 3.85 (s, 3H), 3.91 (m, 1H), 4.16 (d, *J*= 11.0, 0.5H), 4.24 (d, *J*=5.2, 1H), 4.27 (d, *J*=5.2, 1H), 4.36 (d, *J*= 11.0, 0.5H),4.38 (d, *J*= 1.8, 1H), 4.39 (d, *J*= 1.8, 1H), 4.57 (d, *J*= 5.1, 1H), 4.60 (d, *J*= 5.1), 4.81 (d, *J*= 2.2, 0.5H), 4.84 (d, *J*= 2.2, 0.5H), 5.16 (dt, *J*= 10.9, 7.5, 1H), 5.55 (dt, *J*= 15.1, 6.9), 5.85 (dd, *J*= 11.1, 10.9, 1H), 6.21 (dd, *J*= 15.1, 11.1, 1H), 6.78 (dt, *J*= 8.8, 2.0, 1H), 6.79 (dt, *J*= 8.4, 2.0, 1H), 6.82 (dt, *J*= 8.4, 2.0, 2H), 6.86 (dt, *J*= 8.8, 2.2, 1H), 6.88 (dt, *J*= 8.8, 2.2, 1H), 7.08 (dt, *J*= 8.8, 2.2, 1H), 7.14 (dt, *J*= 8.8, 2.2, 1H), 7.18 (dt, *J*= 8.4, 2.0, 1H), 7.19 (dt, *J*= 8.8, 2.0, 1H), 7.29 (dt, *J*= 8.4, 2.0, 2H), 7.32-7.42 (m, 6H), 7.66 (m, 4H); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 12.3; 12.4; 18.4; 18.6; 19.2; 27.0; 27.4; 27.6; 28.2; 28.7; 34.5; 39.4; 39.9; 40.4; 48.8; 49.6; 49.7; 53.9; 55.2; 69.2; 69.5; 71.5; 74.4; 80.3; 113.7; 114.0; 125.9; 127.4; 127.5; 128.5; 129.3; 129.4; 129.5; 129.9; 130.1; 130.4; 130.8; 133.8; 134.5; 134.8; 135.8; 135.9; 159.1; 201.6; 202.1; 212.3; **IR** (film) 2934; 1729; 1514; 1250; 1036 cm^{-1}.
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