Total Synthesis of Tartrolon B

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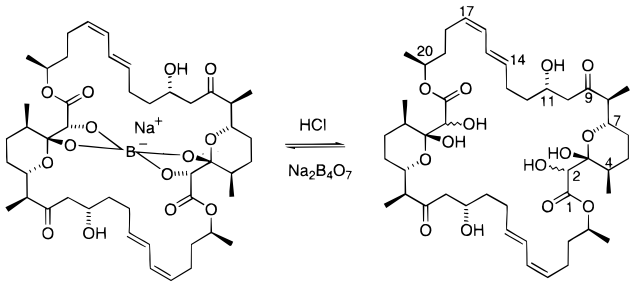
Five years ago Höfle et al.[1] reported the isolation, structural elucidation, and physiological properties of tartrolon B (**1**), a boron containing C_2-symmetrical macrodiolide, structurally related to boromycin,[2] aplasmomycin,[3] and borophycin.[4] Similar to these diolides, **1** is an inhibitor of Gram-positive bacteria with a broad antibiotic spectrum. Remarkably, the fermentation may be directed both to **1** and its boron-free precursors **2a**−**c** (tartrolon A1−A3,

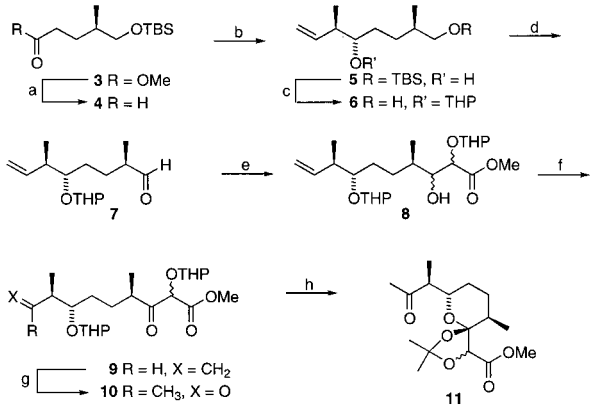


tartrolon B (**1**) tartrolon A1, A2, A3 (**2a-c**)

diasteromeric mixture) depending on the material of the reaction vessel (glassware vs stainless steel). Whereas **2a**−**c** undergo rapid epimerization at C2, these stereogenic centers are configurationally fixed in **1** by the template effect of the boron. This interesting phenomenon, combined with the remarkable ionophoric and antibiotic properties and the complex molecular architecture, makes **1** an attractive object for synthetic studies. We now report the first total synthesis of **1**, whose key features are aldoltype connections between C10/11 and C2/3, a chemoselective dimerizing esterification to form the protected seco acid **19** (Scheme 2) and a Yamaguchi macrolactonization to close the 42-membered diolide ring to **22**.

For the preparation of ketone **11**, ester **3**[5] was transformed into aldehyde **4** and then converted into the desired anti-crotyl-adduct **5** with >95% de using the Duthaler−Hafner crotylation protocol.[6] Alcohol protection and desilylation of **5** furnished alcohol **6**, which was oxidized[7] to aldehyde **7**. Aldol addition of the lithium enolate of methyl THP-oxyacetate to **7** furnished hydroxy ester **8** (as a

Scheme 1



Reagents and yields: (a) DIBAL-H, Et_2O, -90°C (89 %); (b) (4S,5S)-cyclopentadienyl-[(4,5- trans)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-O,O'] titanium chloride, crotylmagnesium chloride (1M in Et_2O), then **7** in Et_2O at -78°C, 3h, (81 %); (c) (i) DHP, cat. CSA, CH_2Cl_2 (96 %); (ii) HF/pyridine, pyridine, THF (97 %); (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then NEt_3 (97 %); (e) $THPOCH_2COOMe$, LDA, THF, -90°C (83 %); (f) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then NEt_3, (75 %); (g) $PdCl_2$, THF, DMF, Na_2HPO_4 buffer (84 %); (h) (i) PPTS, MeOH, THF, 50°C (96 %); (ii) P_2O_5, acetone (69 %).

mixture of all C2/C3-epimers), which was first oxidized to the 3-keto ester **9** and then converted to the methyl ketone **10** by Wacker oxidation.[8] Removal of the 2- and 7-OTHP groups followed by ketalization with acetone[9] led to a mixture of the C2-epimers of spiroketal **11** which were used without separation in the aldol addition to aldehyde **12** (prepared from (*S*) lactic acid as described previously).[10]

The substrate control was unpredictable in this aldol addition as the only stereocenter in **12** is too remote to exert any stereodirecting influence and all five stereogenic centers in the cyclic array of ketone **11** may contribute significantly to the overall asymmetric induction. Therefore, some external source of chirality was sought which could control facial selectivity in a more calculable manner, for instance, via Paterson's variation of the Mukaiyama aldol addition.[11] Thus, ketone **11** was converted into the enol borinate with (−)-chlorodiisopinocampheylborane and treated with aldehyde **12** to give the desired aldol adduct **13** with a surprisingly high overall 4:1 preference of the (11-*R*)- over the (11-*S*)-configuration.[12]

The carbon skeleton thus being completed, a crucial decision had to be made with respect to the C-9-C-11-hydroxycarbonyl structural element. Surely a protective group (e.g. MOM) had to be placed on the 11-OH to ensure chemoselective C-20-OH-lactonization later. However, this β-alkoxy ketone **14** turned out to be highly susceptible to β-elimination even under mildly acidic or basic conditions. So it was decided to reduce the 9-ketone to the alcohol **15**, which could be left unprotected, as model studies told us that both an (*R*)- and (*S*)-9-OH was sterically much less accessible for acylation than the C-20-OH function.

Turning to the question of the final ring closure we first attempted both dimerization and macrolactonization in one

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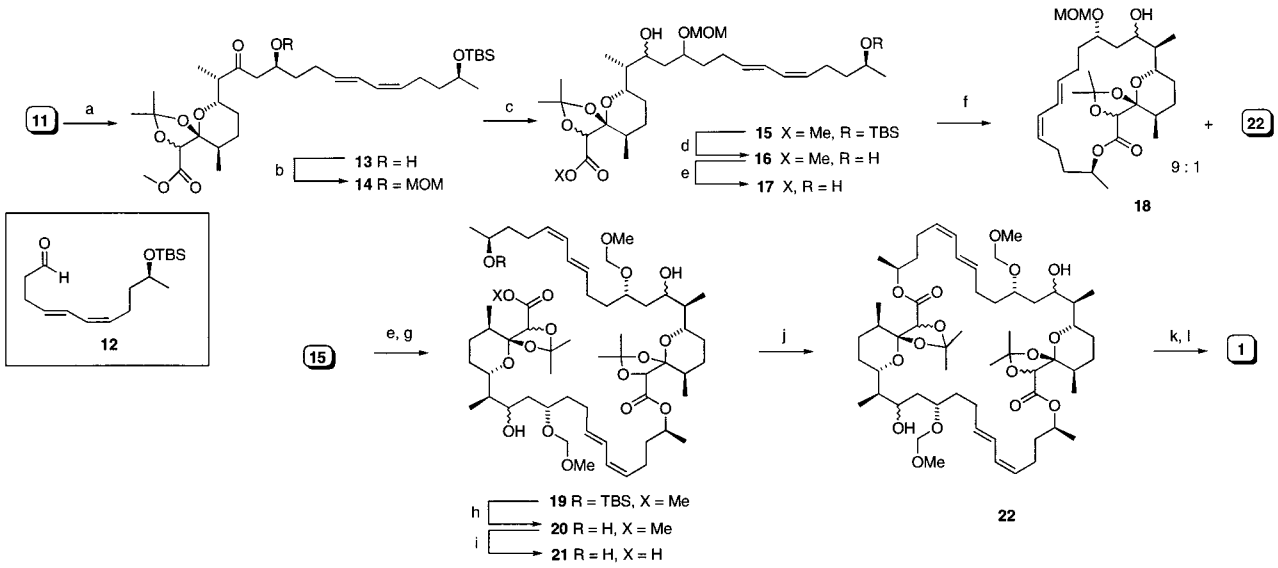
Scheme 2



Reagents and yields: (a) (-)-DIPCl, NEt_3,THF,-78°C, **12** (4:1, 72 %); (b) MOMCl, Hünig's base, CH_2Cl_2 (90%); (c) $NaBH_4$, MeOH, THF, -20°C to 0°C (89%); (d) HF/pyridine, THF, RT, 24 h (94 %); (e) $Ba(OH)_2 \cdot 8\ H_2O$, MeOH, 1 h; (f) $C_6H_2Cl_3COCl$, NEt_3, DMAP, toluene (89 % over 2 steps); (g) $C_6H_2Cl_3COCl$, NEt_3, DMAP toluene, then **16** (74 % over 2 steps); (h) HF/pyridine, THF, RT, 24h (96 %); (i); $Ba(OH)_2 \cdot 8\ H_2O$, MeOH, 15 min; (j) $C_6H_2Cl_3COCl$, NEt_3, DMAP, toluene, 35°C (82%); (k) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, -78°C (89%); (l) (i) Me_2BBr, CH_2Cl_2, -78°C (65%); (ii) $Na_2B_4O_7 \cdot 10\ H_2O$, MeOH, 60°C (41%).

operation. Thus desilylation and ester hydrolysis of **15** gave monomeric seco acid **17**, whose Yamaguchi lactonization[13] in 0.007 M toluene solution resulted in a 1:9 mixture of the desired diolide **22** together with the "monolide" **18** in 89% combined yield. No conditions could be found for improving the diolide/monolide ratio. Therefore, the hydroxy ester was divided in two portions one of which was desilylated to diol **16** while the other one was saponified. Yamaguchi esterification of **16** and the free acid of **15** in 0.015 M solution gave the desired dimer **19**. Desilylation (HF/pyridine) and selective saponification of the methyl ester (barium hydroxide in MeOH)[14] furnished the dimeric seco acid **21**, which was smoothly cyclized to the 42-membered lactone **22** (as a mixture of diastereomers) under Yamaguchi conditions. Reoxidation of the 9-OH and removal of the MOM-ether and the acetonide group in one step with Me_2BBr[15] delivered tartrolon A (**2a**−**c**) as a diastereomeric mixture. Treatment with $Na_2B_4O_7$ in methanol at 50 °C gave tartrolon B (**1**), which after HPLC purification (25% EtOAc in hexanes, Merck supersphere) was indistinguishable (^1H and ^{13}C NMR, IR, and MS spectra, HPLC) from an authentic sample.[16] The CD spectra of the synthetic and the natural material were superimposable, so that the absolute configuration of **1**, first confirmed by the X-ray structural analysis,[17] has now also been confirmed in the classical way, i.e., by total synthesis from starting materials with known configurations.

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Supporting Information Available: Experimental procedures and spectral data for the relevant intermediates of the synthesis of tartrolon B and ^1H-/^{13}C NMR spectra of **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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