Palladium-Promoted Synthesis of Ionophore Antibiotics. Strategy and Assembly of the Homochiral Tetrahydrofuran and Tetrahydropyran Portions of Tetronomycin

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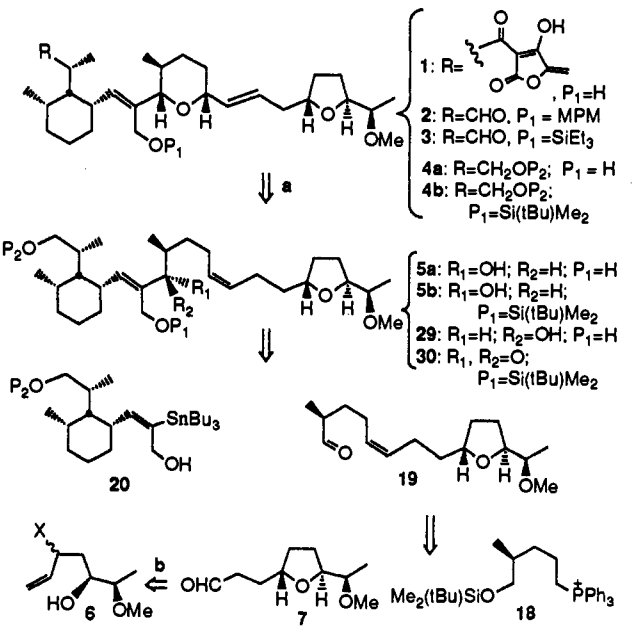
The ionophore antibiotics[1-3] such as tetronomycin (**1**) have structural features of particular relevance to our interests in methodology development[4] such as stereospecifically substituted tetrahydrofuran and tetrahydropyran units. The 10 stereocenters of tetronomycin are arranged in three separate groups: on the cyclohexane ring, on the tetrahydropyran ring, and on the tetrahydrofuran ring (Scheme 1). Our strategy considers each of these units separately, each homochiral.

Our approach is summarized in Scheme 1, culminating in formation of **2**, closely related to advanced intermediate **3** from a complete synthesis.[3a] A key step (a) is the Pd(II)-promoted cyclization/β-H elimination converting **5a** to **4a** and **5b** to **4b**.[4c] Another key step (b) is the Pd(II)-promoted alkoxycarbonylation of **6** to give a *trans*-2,5-disubstituted tetrahydrofuran which leads to **7**; X in **6** is a directing group devised to control the relative configuration of the 2,5-substituents.[4a,d] Key starting materials are homochiral diastereomers **8a** and **8b**, each being converted by different processes to **7**. The synthesis of **8a/b** began with D-arabinose and proceeded on a 60-g scale to **9** in 41% yield over six steps (Scheme 2).[5] The primary hydroxyl in **9** was removed by formation of the *p*-toluenesulfonate ester, epoxidation induced with base, and then ring opening of the epoxide with $LiAlH_4$. After methylation of the secondary hydroxyl group, the aldehyde (in **10**) was revealed. Addition of vinyllithium produced the diastereomers **8a/8b** (1:1 to 2:1 ratio) which were separated by HPLC on a multigram scale.[6] Based on our development of silyloxy *blocking* groups to control the relative configuration in formation of 2,5-disubstituted tetrahydrofurans,[4a,d] **8b** is the desired isomer, expected to lead to **11**. However, we also demonstrated that an unprotected allylic hydroxyl group can participate in alkoxycarbonylation through an *attractive* interaction, forming a lactone.[4a,b] For this purpose, **8a** is the proper reactant to give the 2,5-*trans* arrangement in the tetrahydrofuran product **12**.

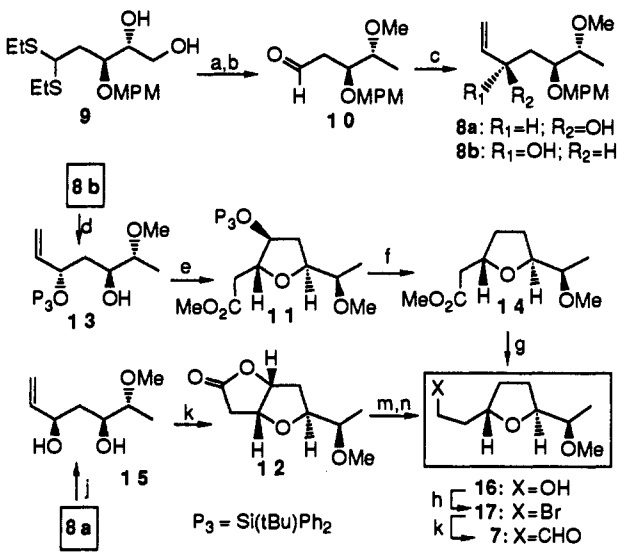
Isomer **8b** was silylated at the allylic OH and the MPM ether was cleaved to give **13** (Scheme 2). Pd(II)-promoted cyclization of **13** produced **11** in 55% yield and >98% diastereoselectivity.

Scheme 1



[a] In all structures, P_2 = Si(tBu)Ph_2.

Scheme 2



[a] Conditions: (a) (i) TsCl, py, −5 °C, (ii) NaOMe, ether, 0 °C, (iii) LAH, THF, 0 °C, (iv) NaH, MeI, THF, 0 °C (80%, 4 steps); (b) $HgCl_2$, $CaCO_3$, MeCN/H_2O, 0 °C, 94%; (c) vinyllithium, THF, −78 °C (65%); (d) (i) (tBu)Ph_2SiCl, imidazole, DMF, 60 °C, (ii) DDQ, CH_2Cl_2/H_2O, 0 °C (90%, 2 steps); (e) $Pd(OAc)_2$, CH_3OH, CO, 23 °C (55%); (f) (i) Bu_4NF, THF, 0 °C (100%), (ii) 2,2′-dibenzothiazolyl disulfide, Bu_3P, toluene, reflux, (iii) Bu_3SnH, AIBN, benzene, 80 °C (86%, 2 steps); (g) LAH, THF, 0 °C (91%); (h) CBr_4, PPh_3, CH_2Cl_2, 0 °C to 23 °C (98%); (j) (i) (tBu)Me_2SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, (ii) DDQ, CH_2Cl_2/H_2O, 0 °C, (iii) Bu_4NF, THF, 0 °C (83%, 3 steps); (k) $PdCl_2$; (k) $PdCl_2$, $CuCl_2$, NaOAc, AcOH, CO, 23 °C (86–95%); (m) (i) LAH,THF, 0 °C (97%), (ii) (tBu)Ph_2SiCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C (87%); (n) (i) PhOC(S)Cl, DMAP, pyridine, 70 °C, (ii) Bu_3SnH, AIBN, benzene, 80 °C, (iii) Bu_4NF, THF, 0 °C (60% over three steps); (p) (i) 2-lithio-1,3-dithiane, THF, −25 °C (67%), (ii) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (73%).

After desilylation and radical deoxygenation,[7] **14** was isolated (86% yield). Deprotection of diastereoisomer **8a** gave diol **15**, which was converted to lactone **12** with efficient Pd(II) catalysis

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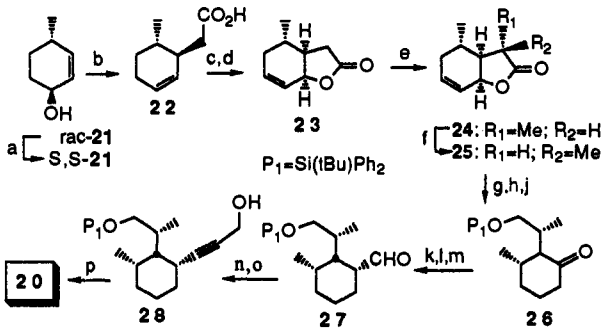
Scheme 3



[a] Conditions: (a) TBHP, $Ti(OiPr)_4$, (-)-DCDT, CH_2Cl_2, molecular sieves, -20 °C, 136 h (44%, 88% ee); (b) (i) $CH_3C(OEt)_3$, 2,4-dinitrophenol (catalyst), reflux, 3 days (92%), (ii) KOH, MeOH, reflux, 20 h (88%); (c) NBS, CH_2Cl_2, 25 °C, 12 h (92%); (d) DBU, xylene, reflux, 2 h (97%); (e) (i) LDA, THF, -78 °C, 1 h, (ii) MeI, THF, -78 °C, 0.5 h (97%); (f) (i) LDA, THF, -78 °C, 1 h, (ii) H^+, H_2O (91%); (g) (i) H_2 (25 psi), 5% Pd/C, Et_2O, 25 °C, 4 h, (ii) LAH, THF, -78 °C to 25 °C, 1 h (89%); (h) (tBu)Me_2SiCl, DMAP (catalyst), TEA, CH_2Cl_2, 0 °C, 2 h (98%); (j) PDC, CH_2Cl_2, 25 °C, 10 h (89%); (k) *n*-BuLi, $MeOCH_2P(O)Ph_2$, THF, 25 °C, 2 h (69%); (m) TCA, CH_2Cl_2, H_2O, 25 °C, 0.5 h (95%); (n) DBU, MeOH, reflux, 5 h (92%); (o) KOtBu, $N_2CHP(O)(OMe)_2$, THF, -78 °C to 0 °C, 12 h (100%); (p) nBuLi, $(HCHO)_n$, THF, -78 °C, 2 h (85%); (q) $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, 25 °C, 1 h (80%).

in yields of 86–95%. The *cis*-lactone arrangement in **12** was confirmed by a positive NOE between the H's at the ring fusion. Treatment of **12** with $LiAlH_4$ gave a diol which was selectively silylated at the primary OH, and the secondary OH was removed,[8] giving **16**. One-carbon chain extension of **16** gave the aldehyde **7** in 48% yield over a 3-step process via bromide **17**. The known phosphonium salt **18**[9] was converted to the phosphorane [NaN(TMS)$_2$, THF, 23 °C]; addition of aldehyde **7** (THF, -78 °C to 23 °C, 70%) led to a single alkene isomer (>95% from ^{1}H NMR) assumed to be of *Z*-stereochemistry.[10] Desilylation (TBAF, THF, -78 °C to 23 °C, 70%) followed by Swern oxidation (oxalyl chloride, DMSO, CH_2Cl_2, -78 °C then Et_3N, 96%) produced aldehyde **19**.

(*S*,*S*)-Cyclohexenol **21** was prepared in 88% ee[11] from racemic **21**[12] by kinetic resolution via Sharpless asymmetric epoxidation (Scheme 3).[13,14] Ireland–Claisen rearrangement[15] gave the *trans*-1,2-disubstituted cyclohexene **22**. Bromolactonization followed by dehydrobromination produced **23** in 91% yield; the *cis*-ring junction was confirmed by NOE studies. Introduction of a methyl group via the enolate gave exclusively the "wrong" methyl configuration in the new stereogenic center in **24**. The stereocenter could be inverted (11:1) by deprotonation and kinetic protonation at -78 °C to give lactone **25**. Hydrogenation of the double bond, reduction of the lactone to the diol, selective silylation of the primary hydroxyl group, and oxidation gave the ketone **26**. One-carbon homologation[16] to an aldehyde gave the (kinetic) "wrong" configuration, but the configuration could be inverted (98:2) by treatment with DBU to give **27**. Conversion of the aldehyde unit into an alkyne[17] and addition of formaldehyde to the alkyne anion yielded **28**. Palladium-catalyzed hydrostannation[18] produced **20** (Scheme 1) with high regioselectivity in 80% yield.

Vinylstannyl alcohol **20** was converted to the dilithio derivative via deprotonation of the hydroxyl group and tin–lithium exchange (nBuLi, -78 °C to -30 °C, 2 h),[19] which was then allowed to react with the homochiral aldehyde **19** (-20 °C to -10 °C, 4 h; refer to Scheme 1 for structures). A mixture of *anti* (**5a**) and *syn* (**29**) diastereoisomers[20] was obtained in 74% yield in a 1:2 ratio. After separation of most of the desired *anti* isomer **5a** by chromatography and selective protection of the primary hydroxyl group (tBuMe_2SiCl, Et_3N, DMAP, DMF, 35 h, 69%), the residual mixture (rich in the *syn* isomer **29**) was oxidized to the ketone **30** (Swern oxidation,[21] 75%). The ketone was then reduced with the oxazaborolidine catalyst[22,23] used in conjunction with catecholborane to give the desired *anti* isomer **5b**, with >96% high stereoselectivity, [(*S*)-*B*-methyl oxazaborolidine, catecholborane, -30 °C, 36 h, 50%]. The key palladium(II)-catalyzed cyclization with controlled β-hydride elimination was then performed on **5a** and **5b**. Under the standard conditions ($Pd(OAc)_2$, DMSO, 23 °C, 36 h),[4] but with addition of 8–10 mol equiv of acetic acid, the reaction produced **4a** and **4b** in 70-80% and 80% yields, respectively. On a small scale, the primary hydroxyl group in **4a** was protected as the MPM derivative (*p*-$MeOC_6H_4CH_2Br$, NaH, THF, 0 °C to 23 °C), the t$BuPh_2Si$ group was removed (Bu_4NF, THF, 0 °C), and oxidation (Swern[21]) produced aldehyde **2**. The key parts of the tetronomycin framework are in place, based on successful application of the alkoxypalladation technology.

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Supplementary Material Available: NMR, IR, and mass spectral data for compounds **2**, **4a**, **4b**, **5a**, **5b**, **8–30** and experimental procedures for the preparation of compounds **11** and **12** (72 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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