Total Synthesis of the Teicoplanin Aglycon

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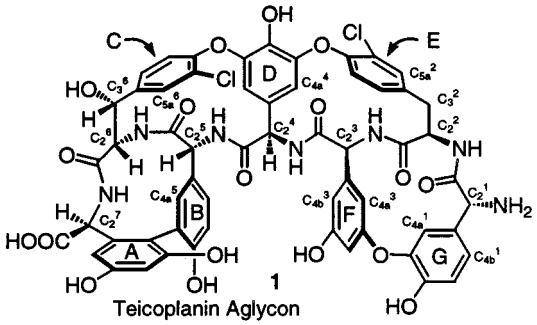
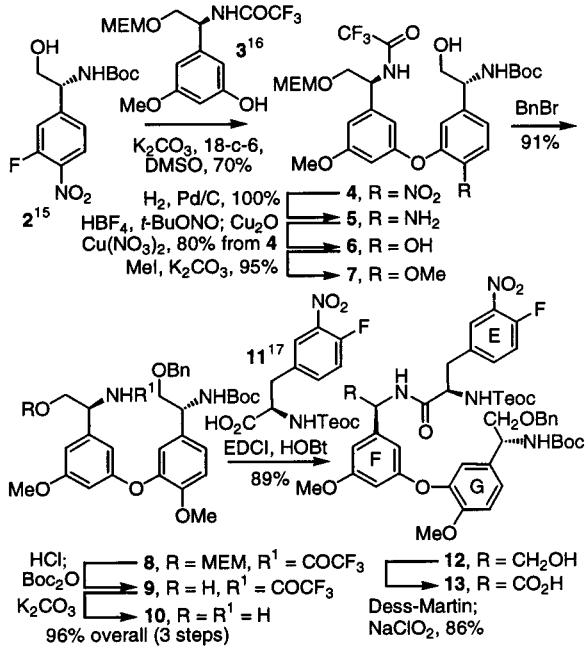
Teicoplanin[1,2] is a complex of five antibiotics isolated from *Actinoplanes teichomyceticus* that are related to vancomycin[3−8] which is enlisted as the drug of last resort for treatment of resistant bacterial infections or for patients allergic to β-lactam antibiotics.[6] It is 2−8-fold more potent, possesses a lower toxicity, exhibits a longer half-life in man (40 vs 6 h), and is easier to administer and monitor than vancomycin.

Herein we describe the first total synthesis of the teicoplanin aglycon (**1**).[9−12] Although teicoplanin bears the identical ABCD



ring system and the same CDE atropisomer stereochemistry as vancomycin, it contains a DE ring system that lacks the β-hydroxy group of the vancomycin E-ring substituted phenylalanine (C^2 residue) and incorporates an especially racemization prone substituted phenylglycine C^3 residue.[13] Most significantly, it contains the additional 14-membered FG ring system not found in vancomycin. Key elements of the approach include sequential DE and FG ring system introductions onto the common vancomycin/teicoplanin ABCD ring system providing a late stage divergent total synthesis of the two classes of glycopeptide antibiotics. The ring systems were introduced enlisting a nucleophilic aromatic substitution reaction of an *o*-fluoronitroaromatic

Scheme 1



for macrocyclization and formation of the 16-membered DE diaryl ether and a macrolactamization[14] of the *N*-terminus amide for closure of the 14-membered FG ring system. With the respective order of closures, the choice of substrates, and the conditions enlisted, no epimerization of the sensitive $C_2{}^3$ center was observed.

Because of the facile $C_2{}^3$ epimerization observed within the confines of the teicoplanin FG ring system,[13] the FG diaryl ether was formed using an intermolecular nucleophilic aromatic substitution reaction with acyclic phenylglycinol substrates incapable of epimerization. Thus, coupling of **2**[15] and **3**[16] (6 equiv of K_2CO_3, 5 equiv of 18-c-6, 0.1 M DMSO, 14 h, 25 °C) provided **4** (70%), Scheme 1. Reactions conducted in DMSO were substantially faster than those conducted in DMF and the

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(15) (a) Prepared by Sharpless AA of 4-fluoro-3-nitrostyrene[15b] (3 equiv of BocNClNa, 0.04 equiv of $K_2OsO_2(OH)_4$, 0.06 equiv of $(DHQD)_2PHAL$, 75%, 90% ee). (b) Rama Rao, A. V.; Gurjar, M. K.; Lakshmipathi, P.; Reddy, M. M.; Nagarajan, M.; Pal, S.; Sarma, B. V. N. B. S.; Tripathy, N. K. *Tetrahedron Lett.* **1997**, *38*, 7433.

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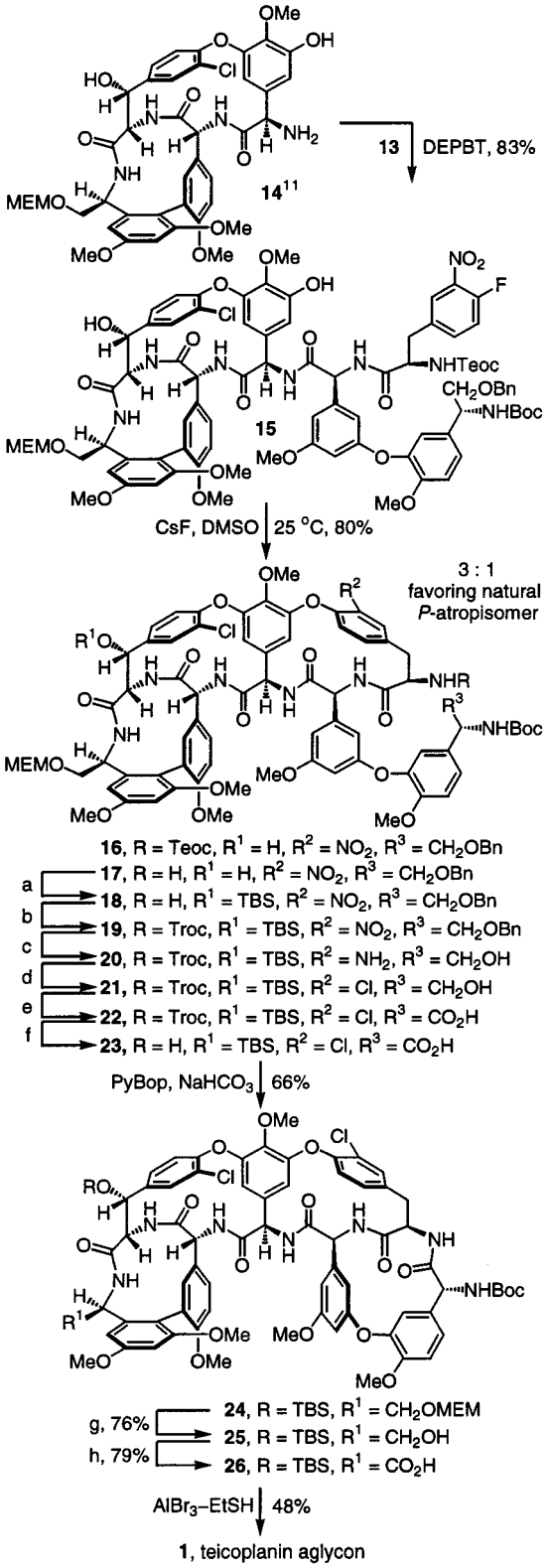
Scheme 2



(a) $CF_3CONMeTBS$, 89%. (b) TrocCl, 93%. (c) H_2, Pd/C, 1% Cl_3CCO_2H−MeOH. (d) *t*-BuONO, HBF_4; CuCl−$CuCl_2$, 66% from **19**. (e) Dess-Martin; $NaClO_2$, 79%. (f) 10% Zn−Pb, 89%. (g) *B*-Bromocatecholborane; Boc_2O, 76%. (h) Dess-Martin; $NaClO_2$, 79%.

conversions improved with inclusion of 18-c-6, 4 Å MS, or $CaCO_3$. Conversion of **4** to **10**, coupling with **11**,[17] and subsequent oxidation of **12** to the carboxylic acid **13** as detailed in Scheme 1 provided the key EFG tripeptide.

Coupling of **13** with **14**[11] was effected by DEPBT[18] (3.5 equiv, THF, 0 °C, 2 h, 83%) in good conversion without detectable epimerization (Scheme 2). Macrocyclization upon treatment of **15** with CsF (15 equiv, 0.007 M DMSO, 25 °C, 10 h) proceeded in superb conversions (74−80%) to provide a separable 3:1 mixture of *P*:*M* atropisomers favoring the natural stereochemistry. Under these conditions, *N*-Teoc deprotection was effected providing the amine **17** directly and only trace quantities of the corresponding *N*-Teoc derivative **16** were isolated (6−13%).[19] Protection of the secondary alcohol as its OTBS ether (30 equiv of $CF_3CONMeTBS$, CH_3CN, 10 h, 25 °C, 89%), *N*-Troc formation (2 equiv of TrocCl, 30 equiv of $NaHCO_3$, CH_2Cl_2, 1.5 h, 25 °C, 93%), nitro reduction and *O*-benzyl deprotection (H_2−10% Pd/C, 1% Cl_3CCO_2H−CH_3OH, 1 h, 25 °C), diazotization (1.3 equiv of *t*-BuONO and HBF_4, CH_3CN−H_2O, 5 min, 0 °C), and Sandmeyer substitution (50 equiv of CuCl, 160 equiv of $CuCl_2$, H_2O, 45 min, 0−25 °C) provided the key intermediate **21** (66% from **19**) and set the stage for FG ring closure.

Two-step primary alcohol oxidation (10 equiv of Dess-Martin periodinane, CH_2Cl_2; 15 equiv of $NaClO_2$, aqueous NaH_2PO_4−*t*-BuOH, resorcinol, 2 h, 25 °C) cleanly provided **22** (79%), which was subjected to *N*-Troc deprotection (10% Zn−Pb,[20] 1 N aqueous NH_4OAc/THF, 10 h, 25 °C, 89%) to provide **23**, the key amino acid for FG macrolactamization. The closure was conducted with slow addition of **23** (1 h, 0.001 M final concentration) to a solution of PyBop (66%) or FDPP (62%) in the presence of $NaHCO_3$ which provided excellent conversions to **24** (10−50% DMF−CH_2Cl_2) with only a trace of $C_2{}^1$ epimer generation. In each case, the use of *i*-Pr_2NEt versus $NaHCO_3$ led to competitive or extensive $C_2{}^1$ epimerization. MEM deprotection (10 equiv of *B*-bromocatecholborane, CH_2Cl_2, 2.5 h, 0 °C) followed by protection of the *N*-terminus amine with Boc_2O (3 equiv, aqueous $NaHCO_3$, 1 h, 25 °C) provided **25** (76%, 2 steps). Two-step alcohol oxidation (10 equiv of Dess-Martin periodinane, CH_2Cl_2, 3 h, 25 °C; $NaClO_2$, NaH_2PO_4, DMSO−H_2O, resorcinol, 30 min, 25 °C) provided the carboxylic acid **26** (79%). The use of resorcinol in DMSO proved superior to isobutene/*t*-BuOH and prevented competitive aromatic chlorination. Exhaustive deprotection of **26** enlisting $AlBr_3$−EtSH[9] (25 °C, 3 h), which served to cleave the six aryl methyl ethers, the $C_3{}^6$ OTBS ether, and the *N*-BOC group, provided the teicoplanin aglycon (48%) identical in all respects with authentic material.

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Supporting Information Available: Full characterization data for **1**−**4**, **6**−**13**, **15**−**19**, and **21**−**26** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Prepared by Sharpless AA of 3-benzyloxy-5-methoxystyrene[16b] (3 equiv of CbzNClNa, 0.04 equiv of $K_2OsO_2(OH)_4$, 0.05 equiv of $(DHQ)_2PHAL$, 78%, 80% ee) followed by (i) 6 equiv of MEMCl, 8 equiv of *i*-Pr_2NEt, CH_2Cl_2, 0−25 °C, 20 h, 92%; (ii) H_2, 10% Pd/C, MeOH, 1 h, 25 °C.; (iii) 2 equiv of TFAA, 3 equiv of pyridine, 0−25 °C, 2.5 h, 93% for 2 steps. (b) Prepared in two steps from 3-hydroxy-5-methoxybenzaldehyde (Ben, I.; Castedo, L.; Saá, J. M.; Seijas, J. A.; Suau, R.; Tojo, G. *J. Org. Chem.* **1985**, *50*, 2236): 1.5 equiv of BnBr, 1.5 equiv of K_2CO_3, DMF, 3 h, 60 °C, 89%; 2.8 equiv of $Ph_3P{=}CH_2$, THF, −78 to 25 °C, 2 h, 87%.

(17) (a) Prepared by *N*-Teoc protection of (*R*)-4-fluoro-3-nitrophenylalanine methyl ester[17b] (1.5 equiv of Teoc-OBt, 1.5 equiv of Et_3N, 50% dioxane−H_2O, 25 °C, 19 h, 92%) followed by methyl ester hydrolysis (1.3 equiv of $LiOH{\cdot}H_2O$, 33% H_2O−*t*-BuOH, 0 °C, 30 min, 100%). (b) Bois-Choussy, M.; Neuville, L.; Beugelmans, R.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 9309.

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(19) An analogous treatment of the unnatural $C_2{}^3$ diastereomer derived from coupling **14** with diastereomerically impure **13** provided the $C_2{}^3$ diastereomer of **17** as a mixture of two atropisomers (75%, ca. 1:1 *P*:*M*) which were chromatographically and spectroscopically distinguishable from **17** ensuring that the closure of **15** proceeds without detectable $C_2{}^3$ epimerization.

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