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Total Synthesis of Teicoplanin Aglycon

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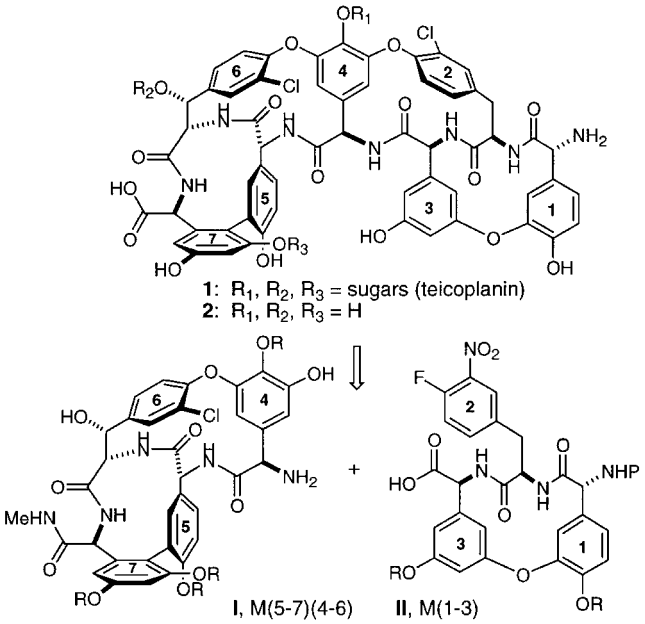
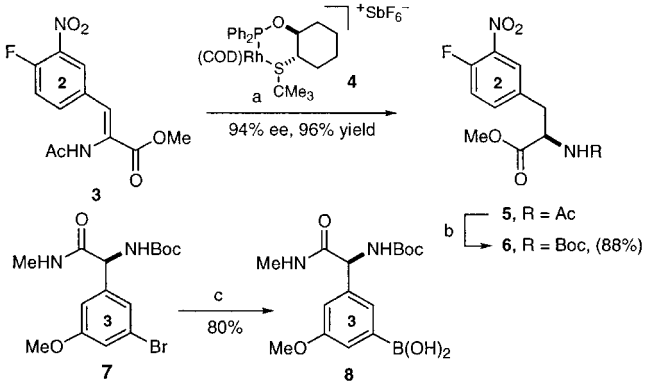
Teicoplanin (**1**),[1] isolated in 1978 from *Actinoplanes teichomyceticus*, is a member of a large family of glycopeptide antibiotics which includes vancomycin.[2] Teicoplanin and vancomycin are the only two representatives of this family that are used clinically for the treatment of methicillin-resistant *Staphylococcus aureus* infections and are considered to be the antibiotics of last resort against this pathogen.[3] The emergence of bacterial strains resistant to treatment by these glycopeptides,[4] and the challenging structural features of these natural products, have prompted extensive investigations into the total syntheses of both vancomycin[5] and teicoplanin (**1**).[6] In this Communication, we report the total synthesis of teicoplanin aglycon (**2**) from the peptidic subunits **I** and **II** (Scheme 1). One of the major goals in the development of this synthesis has been to incorporate each of the amino acid subunits in their correct oxidation states. This objective has now been met for the first time.

The teicoplanin and vancomycin aglycons share a common bicyclic tetrapeptide subunit **I** that includes amino acids **4**−**7** (Scheme 1). With the exception of ring-6 substitution, which varies in the level of chlorination, this subunit is structurally invariant throughout the family of antibiotics. The additional complexity inherent in the teicoplanin aglycon is derived from the replacement of the position-3 asparagine and position-1 leucine residues in the vancomycin aglycon with two additional racemization-prone arylglycine residues.[7] Furthermore, these two amino acid residues are cross-linked to form a new 14-membered macrocycle. The heightened base lability of the teicoplanin skeleton is consistent with the observation that arylglycine residue-3 is exceptionally prone to epimerization.[8] This problem was recognized in our construction of the M(1−3) diaryl ether macrocyclic subunit **II**.[9] While the use of nucleophilic aromatic substitution has been the method of choice for construction of the diaryl ethers in the M(2−4) and M(4−6) ring systems,[10] we felt that our $Cu(OAc)_2$ mediated diaryl ether synthesis from

Scheme 1



Scheme 2[a]



[a] Key: (a) 1 atm H_2, 1 mol% **4**, THF, room temperature. (b) Boc_2O, DMAP, THF, room temperature; then N_2H_4, MeOH, room temperature. (c) MeMgCl (5 equiv), THF, 0 °C; then *t*-BuLi (5 equiv), −78 °C; then $B(OMe)_3$ (10 equiv), 0 °C.

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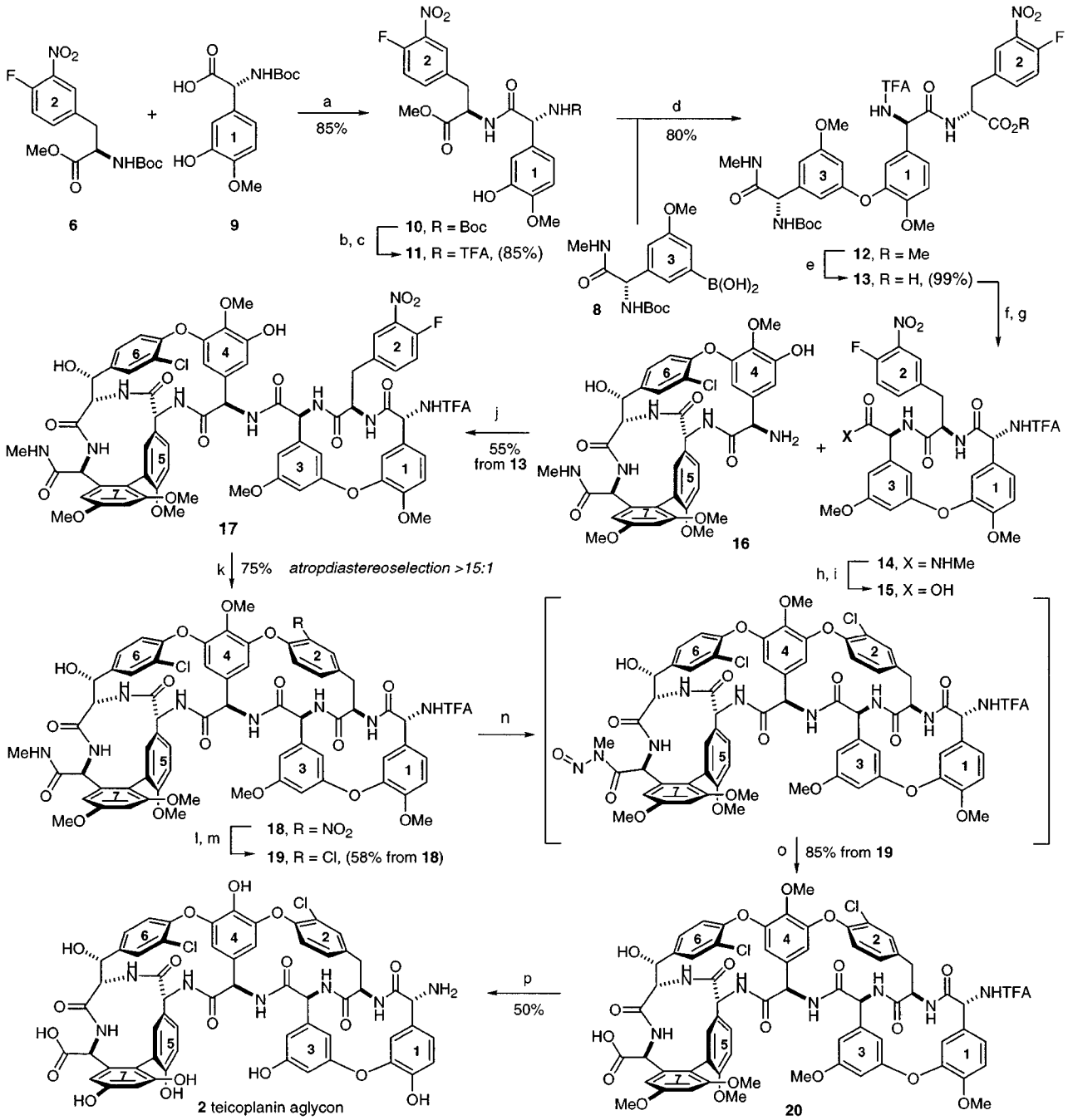
Scheme 3[a]



[a] Key: (a) **6**, TFA, DMS, CH_2Cl_2, 0 °C; then **9**, EDCI, HOAt, THF, 0 °C to room temperature. (b) TFA, DMS, CH_2Cl_2, 0 °C. (c) TFAA, 2,6-lutidine, CH_2Cl_2, 0 °C. (d) **8**, $Cu(OAc)_2$, pyridine, 4 Å sieves, O_2, CH_2Cl_2, room temperature. (e) LiOH, 3:1 MeOH:H_2O, 0 °C. (f) TFA, DMS, CH_2Cl_2, 0 °C. (g) HATU, HOAt, 19:1 CH_2Cl_2:DMF, 0 °C to room temperature. (h) N_2O_4, DMF, 0 °C. (i) 2:1 DMF:H_2O, 60 °C, 6 h. (j) DEPBT, DMF, −5 °C. (k) CsF, DMF, 10 °C. (l) 1 atm H_2, 10% Pd/C, 6:1 EtOAc:EtOH, room temperature. (m) *t*-BuONO, HBF_4, MeCN, 0 °C; then CuCl, $CuCl_2$, H_2O, 0 °C. (n) N_2O_4, DMF, 0 °C. (o) 2:1 DMF:H_2O, 60 °C, 7 h. (p) $AlBr_3$, CH_2Br_2, 0 °C; then EtSH, room temperature.

phenols and arylboronic acid coupling partners[11] might effect this bond construction without arylglycine epimerization.

The synthesis of the M(1−3) macrocycle **II** began with the asymmetric hydrogenation of dehydroamino acid **3**[12] catalyzed by 1 mol % of the chiral Rh(I) complex **4**[13] (1 atm H_2, THF) to afford the 4-fluoro-3-nitrophenylalanine ester **5** (94% ee, 96% yield, Scheme 2). Exchange of the amine protecting group by the procedure of Burk[14] (DMAP, Boc_2O, THF; then N_2H_4, MeOH)[15] provided carbamate **6**. The boronic acid coupling partner **8** was accessed from aryl bromide **7**[16] via metal−halogen exchange, followed by trapping with trimethyl borate (MeMgCl, THF; then *t*-BuLi; then $B(OMe)_3$). Deprotonation of both amidic N−H protons in **7** by Grignard reagent, prior to exposure to *t*-BuLi, is critical to the success of this reaction.

In preparation for the assembly of the M(1−3) macrocyclic subunit **II**, phenylalanine **6** was deprotected (TFA, DMS,

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(12) Compound **3** was prepared from commercially available 4-fluoro-3-nitrobenzaldehyde ($(MeO)_2P(O)CH(CO_2Me)NHAc$, TMG, THF, 99%).

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(14) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054−7057.

CH_2Cl_2) and coupled with **9**[17] (EDCI, HOAt, DMF) to afford dipeptide **10** (Scheme 3). Installation of the *N*-trifluoroacetamide protecting group (TFA, DMS, CH_2Cl_2; then TFAA, 2,6-lutidine, CH_2Cl_2)[18] afforded phenolic dipeptide **11**, which was now positioned for the Cu(II)-promoted phenolic arylation. Diaryl ether coupling between **8** and **11** ($Cu(OAc)_2$, pyridine, 4 Å sieves, O_2, CH_2Cl_2) proceeded smoothly to provide **12** in 80% yield. In accord with our previous study,[11a] no epimerization of either arylglycine residue was detected. Saponification of the methyl ester in **12** was accomplished with LiOH (3:1 MeOH:H_2O, 0 °C), again without any detectable nucleophilic aromatic substitution or epimerization, providing macrocyclization precursor **13**.

After Boc deprotection of **13** (TFA, DMS, CH_2Cl_2), initial attempts at macrolactamization of the amino acid derived from **13** (HATU, HOAt, CH_2Cl_2-DMF) resulted in low isolated yields (<5%) of macrolactam **14**. It was quickly realized that the desired macrolactam is almost completely insoluble in standard solvents (including MeOH, CH_2Cl_2, THF, EtOAc, MeCN, H_2O and mixtures thereof), and could be manipulated only in DMF or DMSO. We reasoned that the low yields resulted from material loss during the isolation and purification. Indeed, amide **14** precipitated from the reaction mixture during amide formation under high dilution (1×10^{-5} M in 19:1 CH_2Cl_2:DMF) and could be isolated by simple filtration of the entire reaction mixture. Purification was effected by dissolution of **14** in DMF followed by precipitation of the desired material by the addition of H_2O. Mass recovery of over 90% was consistently obtained when using this procedure. Further attempts to purify **14** by normal or reverse-phase chromatography resulted in substantial material loss.

Deprotection of the *N*-methylamide moiety in monocycle **14**, in preparation for coupling with the M(4−6)(5−7) bicycle **16**, proved challenging. We had anticipated using our two-step nitrosation/hydrolysis procedure,[19] which had previously proven successful for complex peptidic systems.[20] Yet, nitrosation with N_2O_4 in CH_2Cl_2 or MeCN failed, presumably due to the insolubility of **14**. We then turned to DMF as a nitrosation solvent (N_2O_4, 0 °C) in the presence of sodium acetate as an acid scavenger. These conditions led to sluggish nitrosation and incomplete conversion. However, *in the absence of added base*, very clean and complete mono-nitrosation could be effected in DMF. Conversion of the intermediate nitrosamide to the carboxylic acid with LiOOH (3:1 THF:H_2O, 0 °C) resulted in extensive decomposition and apparent epimerization of residue-3. On the other hand, clean hydrolysis was observed by heating of the nitrosamide in 2:1 DMF:H_2O (6 h, 60 °C). This procedure resulted in quantitative mass recovery of unpurified **15**. Macrocyclic acid **15** displayed solubility characteristics similar to those exhibited by amide **14** and was used without purification.

In agreement with observations by Boger,[6] peptide coupling of **15** and **16**[21] utilizing DEPBT[22] (DMF, −5 °C) in the absence of base afforded tricycle **17** in good yield as an inseparable 12:1 mixture of position-3 epimers. This coupling procedure was far superior to other coupling agents screened, such as HATU/2,6-lutidine, which promoted extensive epimerization and provided only a 3:1 mixture of position-3 epimers. Nucleophilic aromatic substitution (CsF, DMF, 10 °C)[6b,10] proceeded with high atropdiastereoselectivity (>15:1) to afford **18** as a single diastereomer after purification containing the entire tetracyclic core of teicoplanin aglycon. The favorable selectivity noted here strongly suggests that the M(1−3) diaryl ether macrocycle present in **17** enhances the atropdiastereoselectivity noted for closure of the M(2−4) macrocycle. The analogous ring closure first precedented in our vancomycin synthesis proceeded with only 5:1 atropdiastereoselectivity.[5a,5b]

Reduction of the nitro moiety in **18** (1 atm H_2, 10% Pd/C, 6:1 EtOAc:EtOH) and Sandmeyer reaction (*t*-BuONO, HBF_4, MeCN; then CuCl, $CuCl_2$, H_2O) afforded **19** bearing the requisite chlorine substituent on ring-2. Deprotection of the carboxy-terminal *N*-methylamide **19** to acid **20** was then accomplished in 85% yield by successive nitrosation (N_2O_4, DMF, 0 °C) and pH neutral hydrolysis, as previously described in the transformation of **14** → **15** (2:1 DMF:H_2O, 7 h, 60 °C). The high site selectivity and yield of this amide deprotection sequence demonstrates that amidic protection of carboxylic acids is a viable strategy for complex molecules containing multiple amides. Finally, global demethylation and *N*-terminal trifluoroacetamide hydrolysis were effected by treatment with $AlBr_3$ and EtSH (CH_2Br_2, 0 °C to room temperature) to provide teicoplanin aglycon **2** that was spectroscopically and analytically identical with material derived from natural sources.[23]

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Supporting Information Available: Spectral data for all compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Abbreviations: TFA = trifluoroacetic acid; DMS = dimethyl sulfide; EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide; HOAt = 1-hydroxy-7-azabenzotriazole; TFAA = trifluoroacetic anhydride; HATU = 2-(1-*H*-7-azabenzotriazol)-1−1,1,3,3-tetramethyluronium hexafluorophosphate; DEPBT = 3-(diethyloxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one.

(16) 3-bromo-5-methoxy-phenylglycine **7** was synthesized in 3 steps from 3-bromo-5-methoxy-styrene: i) Sharpless asymmetric amino-hydroxylation (BocNClNa, $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, *n*-PrOH, H_2O, 80%), See: Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217; ii) oxidation to the carboxylic acid (TEMPO, NaOCl, KBr, acetone, H_2O); iii) protection of the carboxylic acid as its *N*-methyl amide (*i*-BuOC(O)Cl, NMM, EtOAc; then $MeNH_2$, 60−65% for 2 steps).

(17) Compound **9** was synthesized in four steps from commercially available 3-benzyloxy-4-methoxy benzaldehyde: i) Wittig olefination (Ph_3PCH_3Br, KHMDS, THF, 96%); ii) Sharpless AA (BocNClNa, $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, *n*-PrOH, H_2O); iii) oxidation to the carboxylic acid (TEMPO, NaOCl, KBr, acetone, H_2O, 70−81% for 2 steps); iv) hydrogenolysis (1 atm H_2, 10% Pd/C, EtOH, quant.).

(18) Because urethanes are highly susceptible to nitrosation, a protecting group change at this point is required in advance of the carboxyl deprotection step (**19**→**20**).

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(20) Evans, D. A.; Barrow, J. C.; Watson, P. S.; Ratz, A. M.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M.; Ellman, J. A.; Rychnovsky, S. D.; Lacour, J. *J. Am. Chem. Soc.* **1997**, *119*, 3419−3420. See also ref 5b.

(21) Bicycle **16** was synthesized in analogy with previously published M(4−6)(5−7) bicyclic systems, see ref 5b.

(22) Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91−93.

(23) Teicoplanin aglycon was obtained by acidic hydrolysis of natural teicoplanin complex (80% H_2SO_4, DMSO, 85 °C, 48 h), See: Boger, D. L.; Weng, J.-H.; Miyazaki, S.; McAtee, J. J.; Castle, S. L.; Kim, S. H.; Mori, Y.; Rogel, O.; Strittmatter, H.; Jin, Q. *J. Am. Chem. Soc.* **2000**, *122*, 10047−10055.