First and Second Generation Total Synthesis of the Teicoplanin Aglycon

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Abstract: Full details of studies leading to the total synthesis of the teicoplanin aglycon are provided. Key elements of the first generation approach (26 steps from constituent amino acids, 1% overall) include the coupling of an EFG tripeptide precursor to the common vancomycin/teicoplanin ABCD ring system and sequential DE macrocyclization of the 16-membered ring with formation of the diaryl ether via a phenoxide nucleophilic aromatic substitution of an *o*-fluoronitroaromatic (80%, 3:1 atropisomer diastereoselection) followed by 14-membered FG ring closure by macrolactamization (66%). Subsequent studies have provided a second generation total synthesis which is shorter, more convergent, and highly diastereoselective (22 steps, 2% overall). This was accomplished by altering the order of ring closures such that FG macrolactamization (95%) preceded coupling of the EFG tripeptide to the ABCD ring system and subsequent DE ring closure. Notably, DE macrocyclization via diaryl ether formation on substrate **57**, the key intermediate in the latter approach incorporating the intact FG ring system, occurred with exceptional diastereoselection for formation of the natural atropisomer (>10:1, 76%) without problematic C_2^3 epimerization provided the basicity of the reaction is minimized.

Teicoplanin (**1**, Figure 1)[1,2] is a complex of five closely related, clinically useful glycopeptide antibiotics isolated from *Actinoplanes teichomyceticus* (ATCC 31121) 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 2−20-fold more potent than vancomycin against Gram-positive bacteria,[9] possesses a lower toxicity than vancomycin,[1,10] exhibits a longer half-life (40 vs 6 h) in man,[11] and is easier to administer and monitor.[12,13] These characteristics along with its structural complexity, the interest in defining the structural features of glycopeptide antibiotics contributing to cell wall biosynthesis inhibition in sensitive bacteria,[7] the emergence of clinical resistance and the determination of its origin,[8] and the potential of reengineering the glycopeptide antibiotics to overcome this resistance have

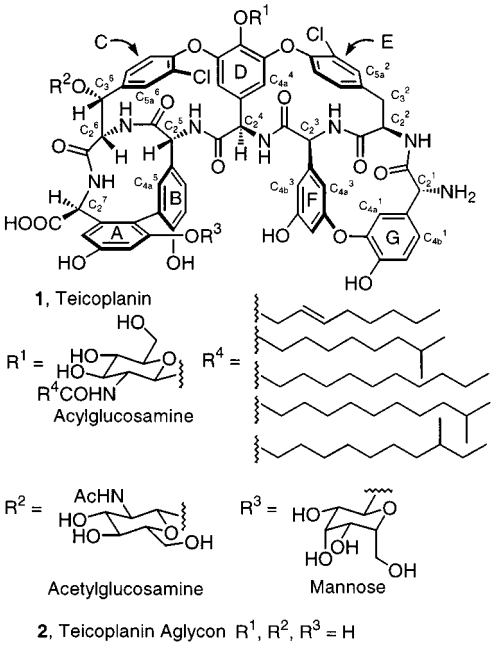

Figure 1.

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generated considerable interest in teicoplanin, vancomycin, and related agents.

Herein we provide full details of the development of the first total synthesis of the teicoplanin aglycon (**2**),[14] and the subsequent efforts which have provided an improved second generation total synthesis. The teicoplanin aglycon bears the same ABCD ring system and the same CDE atropisomer stereochemistry as vancomycin, but contains a DE ring that lacks the sensitive β-hydroxy group of the vancomycin E-ring substituted phenylalanine (C^2 residue) and incorporates a racemization prone substituted phenylglycine C^3 residue.[15] It also contains the additional 14-membered diaryl ether FG ring system not found in vancomycin, making it an even more challenging synthetic target than vancomycin.

Complementary to the efforts of Evans[16] and Nicolaou,[17] we recently described a total synthesis of the vancomycin aglycon,[18,19] enlisting a defined order to introduction of its CD, AB, and DE ring systems that permitted selective thermal atropisomerism of the newly formed ring systems or their immediate precursors.[20−22] In addition to the diastereoselection that was achieved in two of the three ring closures, this order permitted the recycling of any undesired atropisomer for each ring system and provided reliable control of the stereochemistry throughout the synthesis, funneling all synthetic material into the natural atropisomer. A special attraction of this approach was the recognition that the common ABCD ring system of vancomycin and teicoplanin constituted a key intermediate providing, as realized herein, access to both classes of natural products from a common advanced synthetic intermediate.

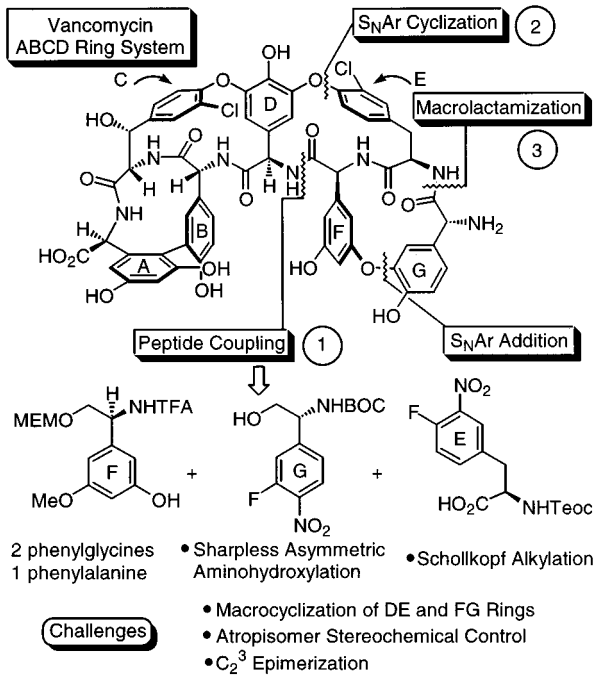

Figure 2. First generation total synthesis.

The most conservative implementation of this approach to teicoplanin was judged to entail sequential introduction of the DE and FG ring systems onto this preformed ABCD ring system (Figure 2). Closure of the DE ring system without the constraints of the FG ring system was expected to permit its mild thermal atropisomerism to adjust its final stereochemistry should this prove necessary without affecting the AB or CD atropisomer stereochemistry (E_a = 37.8 and 30.4 kcal/mol, respectively). We recently disclosed studies defining the relative ease of selective DE atropisomerism of teicoplanin aglycon derivatives (E_a = 29.3 kcal/mol) as well as derivatives cleaved at the N-terminus amide (FG ring system cleaved, E_a = 24.8 kcal/mol).[22] Although a necessary adjustment in the DE ring system atropisomer stereochemistry could be conducted with the FG ring system intact, that conducted with the acyclo FG precursors proceeds with greater ease. More significant, the C_2^3 center of teicoplanin readily epimerizes (1% aqueous $NaHCO_3$, 80 °C) to its more stable (>95:5) unnatural *R*-configuration under mildly basic conditions,[15,22] and we have shown that this epimerization occurs less readily on acyclo FG teicoplanin derivatives.[22] The diaryl ether ring closure of the DE ring system in the absence of the constraints of the FG ring system was expected to minimize C_2^3 epimerization under the required basic conditions. Thus, the more conservative first generation total synthesis enlisted a diastereoselective (3:1) aromatic nucleophilic substitution macrocyclization with formation of the diaryl ether[20,23] for closure of the DE ring system under racemization free conditions and a subsequent macrolactamization reaction for cyclization of the 14-membered FG ring system. The diaryl ether linkage in the 14-membered FG ring system was also anticipated to arise from a phenoxide nucleophilic substitution reaction of an *o*-fluoronitroaromatic. Although this could

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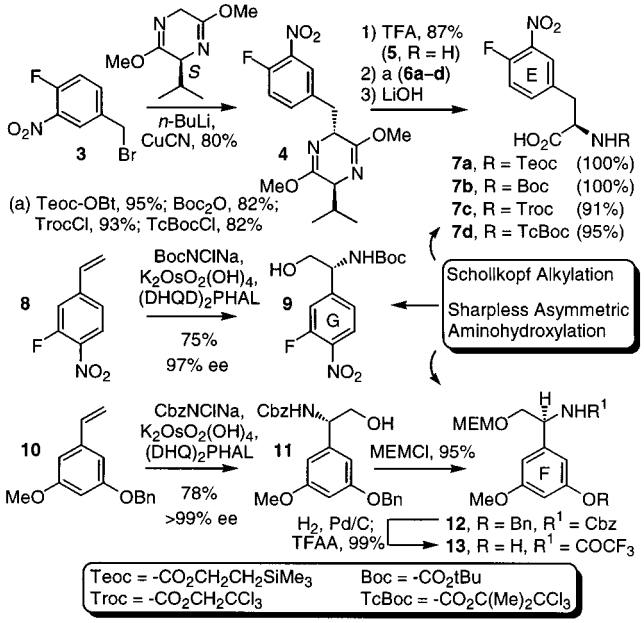
Scheme 1

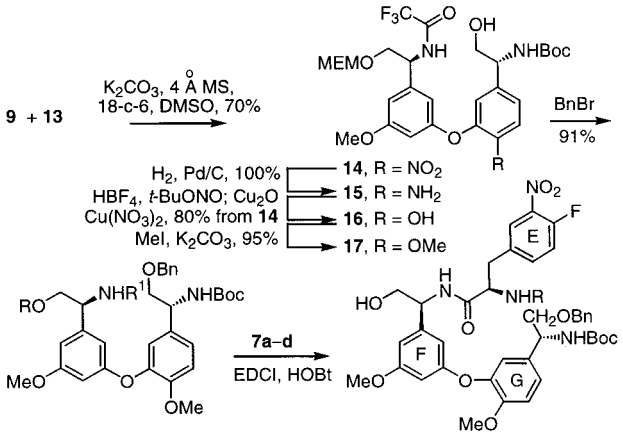


constitute the key macrocyclization reaction used to close the FG ring system, its propensity for C_2^3 epimerization and the basic conditions required of the reaction suggested problems may arise in such an approach. Therefore, an intermolecular coupling was implemented, enlisting substituted phenylglycinol derivatives to ensure no racemization would be possible.

The development of a shorter, second generation total synthesis of **2** reversing the order of FG and DE ring system macrocyclizations is also described. This less secure route was found to proceed with superb diastereoselection (>10:1) in the DE macrocyclization precluding the need for thermal equilibration of DE ring system atropisomers and, more importantly, may be implemented under select conditions without competitive C_2^3 epimerization.

Synthesis of Precursors to the Teicoplanin Residues 1−3. The requisite E-ring (*R*)-(4-fluoro-3-nitrophenyl)alanine **7** (residue 2) was prepared through Schollkopf alkylation of bromide **3** via the transmetalated cuprate[24] and the Teoc, Boc, Troc, and TcBoc derivatives **7a**−**d** were examined in our studies (Scheme 1). The F and G ring phenylglycine precursors were prepared employing the Sharpless asymmetric aminohydroxylation (AA) reaction.[25] Thus, the styrenes **8**[26] and **10**[27] were converted to the (*R*)- and (*S*)-phenylglycinols **9** (75%, 97% ee) and **11** (78%, >99% ee) using the complementary $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ catalysts, respectively. Notably, the quality of $CbzNH_2$ greatly affected the AA reaction of **10**, and freshly recrystallized material substantially increased the conversion (78% vs 33%). The product **9** of the Sharpless AA reaction of **8** was incorporated directly into the synthesis and **11** was further converted to **13** in three steps. Both the F ring and G ring amino acid precursors (residues 3 and 1) were utilized as the reduced phenylglycinols to avoid α-center racemization throughout the synthesis and oxidized to the corresponding carboxylic acids immediately prior to use in an amide coupling. Experience derived from our efforts on vancomycin suggested the requisite oxidations could be conducted without difficulty.[18]

Scheme 2



Preparation of **14.**

base (equiv)	additive	solvent (conc), conditions	**14**
CsF (6.0)	none	DMSO (0.11 M), 25 °C, 10 h	56%
CsF (8.5)	4 Å MS	DMSO (0.20 M), 25 °C, 13 h	57%
K_2CO_3 (4.0)	4 Å MS	DMF (0.05 M), 40 °C, 20 h	28%
K_2CO_3 (5.0)	4 Å MS	DMF (0.06 M), 80 °C, 17 h	34%
K_2CO_3 (4.8)	4 Å MS	DMSO (0.07 M), 40 °C, 3 h	60%
K_2CO_3 (5.6)	4 Å MS, 18-c-6	DMSO (0.07 M), 25 °C, 6 h	63%
K_2CO_3 (6.0)	4 Å MS, 18-c-6	DMSO (0.07 M), 25 °C, 15 h[a]	70%

[a] 2 equiv of **9**, yield based on **13**.

Synthesis of the FG Diaryl Ether. Because of concerns over the C_2^3 epimerization observed within the confines of the teicoplanin FG ring system, we elected to form the FG diaryl ether by an intermolecular aromatic nucleophilic substitution reaction using acyclic substrates which are incapable of epimerization. Thus, coupling of **9** and **13** (K_2CO_3, DMSO, 25 °C) provided **14** (60−63%), Scheme 2. Reactions conducted in DMSO could be run at room temperature and were substantially faster than those conducted in DMF, and the conversions improved with inclusion of 18-c-6 and 4 Å MS (Scheme 2). The former serves to accelerate the reaction rate, and 4 Å MS serves to moderate the basicity of the liberated fluoride, and presumably this improves the overall conversions. Utilizing the more accessible G ring precursor **9** in excess (2 equiv) further improved the conversion based on **13** (70%). Nitro reduction (H_2, Pd/C), diazotization of **15** (*t*-BuONO, HBF_4), and phenol introduction ($Cu_2O-Cu(NO_3)_2$) proceeded in superb conversions (80%) on a large scale, provided that the reaction was vigorously stirred, and subsequent selective phenol versus primary alcohol *O*-methylation of **16** (CH_3I, K_2CO_3) provided **17**. Protection of the primary alcohol (BnBr, NaH, 17−20% DMF−THF), MEM and *N*-Boc deprotection of **18** (4 N HCl−EtOAc), and reinstallation of the Boc-protecting group (Boc_2O, $NaHCO_3$) afforded **19**. Notably, longer reaction times were required, and lower conversions were obtained when the benzylation was conducted

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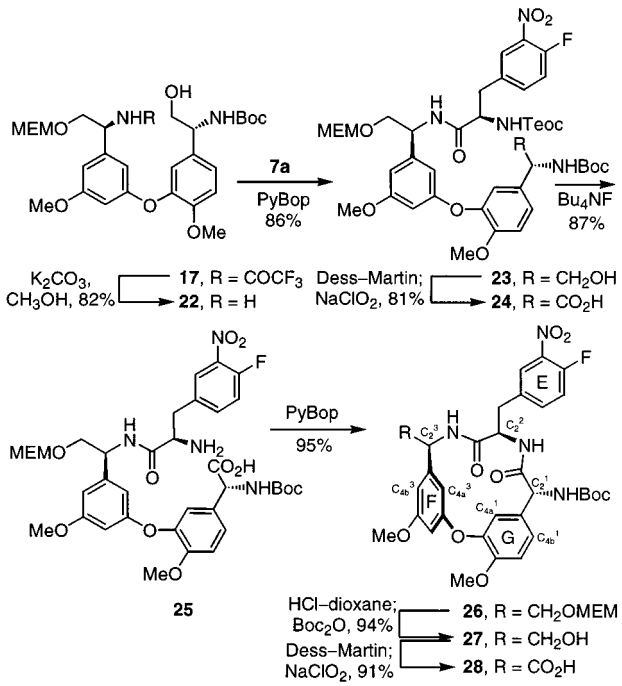
Scheme 3



in THF, whereas reactions conducted in DMF or >20% DMF−THF led to additional competitive *N*-benzylation. *N*-Trifluoroacetamide hydrolysis (K_2CO_3, CH_3OH-H_2O) followed by coupling of **20** with **7a-d** provided the substrates **21** on which both DE and FG macrocyclizations could be examined.

FG Ring System Macrolactamization. Essential to implementation of the approach was the closure of the FG ring system at the amide bond linking residues 1 and 2. Both Chakraborty[28] and Pearson[29] independently conducted macrolactamizations on teicoplanin or ristocetin model systems and illustrated their success. In our own efforts, we examined teicoplanin aglycon derivatives containing acyclic FG ring systems with cleavage of the residue 1 and 2 amide bond.[22] Their macrolactamization closure established its viability on advanced intermediates capable of mild C_2^3 epimerization and ultimately provided intermediates enlisted in the total synthesis (see Scheme 8). With **17** in hand, we examined its coupling with **7a**, subsequent conversion to **25**, and its macrolactamization. Thus, hydrolysis of **17** (K_2CO_3, H_2O-CH_3OH, 82%), coupling of **22** with **7a** to provide **23** (PyBop,[30] 86%), two-step oxidation of the primary alcohol **23** to the carboxylic acid **24** (Dess−Martin periodinane; $NaClO_2$ buffered with NaH_2PO_4 in the presence of resorcinol, 81%), and Teoc deprotection (Bu_4NF, THF, 87%) provided **25** (Scheme 3). Macrolactamization effected by treatment with PyBop[30] ($NaHCO_3$, 10% DMF−CH_2Cl_2, 95%) provided **26** in superb conversions consistent with related observations made on advanced synthetic intermediates, and without detectable epimerization. Simultaneous MEM and *N*-Boc deprotection of **26** (4 N HCl−dioxane, −5 °C), reinstallation of the *N*-Boc protecting group (Boc_2O, $NaHCO_3$; 94% for two steps), and low-temperature, two-step oxidation of the primary alcohol **27** (Dess−Martin periodinane, DMF; $NaClO_2$, 20% H_2O−DMSO buffered with NaH_2PO_4 in the presence of resorcinol) provided the carboxylic acid **28** (91%). This latter oxidation was sensitive to epimerization and degradation at the stage of the intermediate aldehyde analogous to the corresponding acyclo FG derivatives **31** described below. The availability of **28** provided the opportunity to examine the DE ring system introduction on substrates containing the preformed FG ring system, and it constitutes a key intermediate in our second generation total synthesis. Analogous to the FG ring system in the natural product itself, **26** displayed a sharp ^1H NMR spectrum indicative of a single predominant conformation and 2D $^1H-^1H$ NMR (CD_3OD, 293 K, 500 MHz) cross-peaks consistent with that of the natural product. Strong nOe's between C_2^1-H/C_{4b}^1-H, C_{4a}^1-H/C_{4a}^3-H, and C_2^3-H/C_{4b}^3-H, only a weak C_2^1-H/C_{4a}^1-H nOe, and the absence of a C_2^3-H/C_{4a}^3-H nOe established the orientation of the diaryl ether and its relationship to the backbone peptide chain as shown in Scheme 3.

Model DE Ring System Studies. Key to implementation of the approach was the construction of the DE ring system by an intramolecular phenoxide nucleophilic substitution reaction of an *o*-fluoronitroaromatic for formation of the 16-membered diaryl ether. Necessary issues to address upfront included the inherent ease of C_2^3 racemization under the range of ring closure conditions available, the establishment of the intrinsic atropisomer diastereoselection of the ring closure reaction outside the confines of the preformed ABCD ring system, the relative ease of the thermal equilibration and thermodynamic ratio of the DE ring system atropisomers, and subtle substituent effects that might contribute to the success of the approach.

Thus, two-step oxidation of **21** to the corresponding carboxylic acids **31** and subsequent coupling with the free amine **30** derived from **29**[20,31] provided the substrates **32** necessary for examining the DE ring closure (Scheme 4). The oxidation reaction proved surprisingly sensitive to C_2^3 epimerization at the stage of the intermediate aldehyde. Even the use of aqueous $NaHCO_3$ in the workup of the Dess−Martin oxidation produced substantial epimerization. As a matter of practice, workup of the Dess−Martin oxidation was conducted at 0 °C in the absence of base. Under these conditions, little or no epimerization was observed (>20:1), and this could be established by $TMSCHN_2$ esterification of **31** to provide the corresponding methyl ester[32] whose stereochemical integrity could be established by ^1H NMR. Alternative direct oxidation of **21c** to provide **31c** was also examined utilizing TEMPO−NaOCl/KBr and provided the

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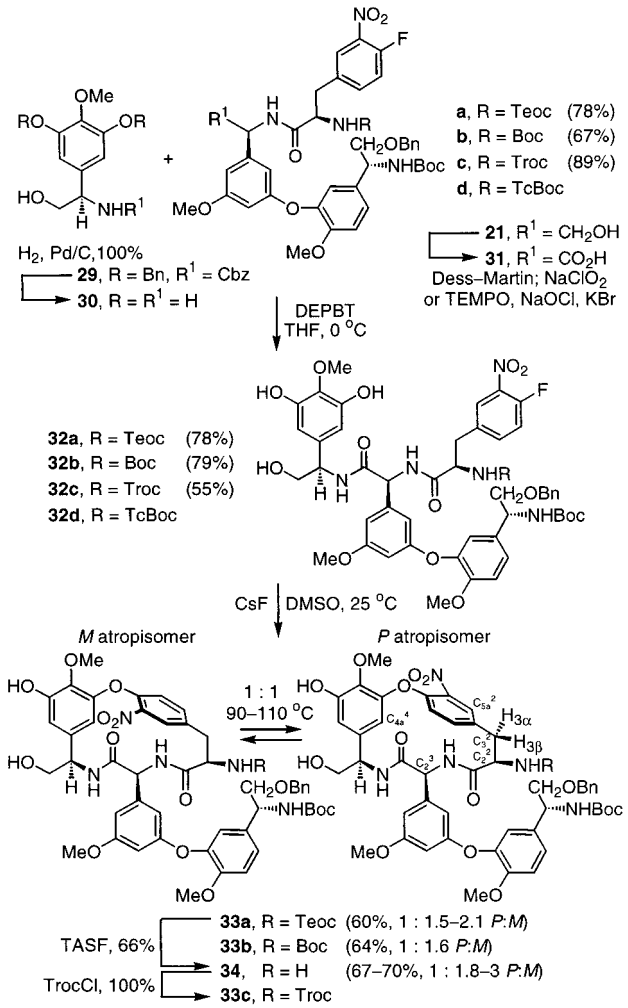
(30) Abbreviations: PyBop = benztriazol-1-yl-oxy-tris(pyrrolidino)-phosphonium hexafluorophosphate; FDPP = pentafluorophenyl diphenylphosphinate; HATU = 2-(1*H*-7-azabenzotriazol)-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate; Bop = (1-benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluoride; EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide; HOBt = 1-hydroxybenzotriazole; HOAt = 1-hydroxy-7-azabenzotriazole; PyBrop = bromo-tris(pyrrolidino) phosphonium hexafluorophosphate; TFFH = fluoro-*N,N,N′,N′*-tetramethylformamidinium hexafluorophosphate, DPPA = diphenyl phosphorazidate.

(31) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *J. Org. Chem.* **1996**, *61*, 3561.

(32) For the methyl ester of **31a**: ^1H NMR (CD_3OD, 600 MHz) δ 7.91 (d, J = 5.2 Hz, 1H, C_{5a}^2-H), 7.48 (m, 1H, C_{5b}^2-H), 7.31−7.05 (m, 9H), 6.51 (s, 1H, C_{4a}^3-H), 6.37 (s, 1H, C_{4b}^3-H), 6.29 (s, 1H), 5.35 (s, 1H), 4.82 (m, 1H), 4.50−4.30 (m, 5H), 4.07 (m, 2H), 3.83 (br s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H, CO_2CH_3), 3.03 (dd, J = 6.6, 13.6 Hz, 1H), 2.88 (dd, J = 8.8, 13.6 Hz, 1H), 1.36 (s, 9H), −0.02 (s, 9H); Diagnostic signals for the C_2^3 epimer: (CD_3OD, 600 MHz) δ 8.00 (d, J = 5.3 Hz, 1H, C_{5a}^2-H), 7.60 (m, 1H, C_{5b}^2-H), 6.62 (s, 1H, C_{4a}^3-H), 6.46 (s, 1H, C_{4b}^3-H), 3.67 (s, 3H, CO_2CH_3). For the methyl ester of **31c**: ^1H NMR (CD_3CN, 600 MHz) δ 7.93 (d, 1H, J = 6.8 Hz, C_{5a}^2-H), 7.48 (m, 1H, C_{5b}^2-H), 7.40−7.20 (m, 6H), 7.15 (dd, J = 2.2, 4.9 Hz, 1H), 7.07 (d, J = 4.9 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.51 (s, 1H, C_{4a}^3-H), 6.41 (s, 1H, C_{4b}^3-H), 6.36 (s, 1H), 5.33 (s, 1H), 4.73−4.65 (m, 4H), 4.50 (d, J = 12.3 Hz, 1H), 4.47 (d, J = 12.3 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H, CO_2CH_3), 3.63−3.56 (m, 2H), 3.12 (dd, J = 4.9, 14.5 Hz, 1H), 2.92 (dd, J = 9.2, 14.5 Hz, 1H), 1.36 (s, 9H); Diagnostic signals for the C_2^3 epimer: (CD_3CN, 600 MHz) δ 7.97 (d, J = 6.6 Hz, 1H, C_{5a}^2-H), 7.58 (m, 1H, C_{5b}^2-H), 6.58 (s, 1H, C_{4a}^3-H), 6.46 (s, 1H, C_{4b}^3-H), 3.65 (s, 3H, CO_2CH_3). The stereochemical integrity of **31b** and **31d** could be assessed directly.

Scheme 4



33a: E_a = 17.2 kcal/mol, $\Delta H^{\ddagger}$ = 18.0 kcal/mol, $\Delta S^{\ddagger}$ = −13.8 eu
33b: E_a = 16.2 kcal/mol, $\Delta H^{\ddagger}$ = 16.3 kcal/mol, $\Delta S^{\ddagger}$ = −18.2 eu

compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
33a	90 °C, *o*-$Cl_2C_6H_4$	0.12	2.5
33a	105 °C, *o*-$Cl_2C_6H_4$	0.30	0.96
33b	90 °C, *o*-$Cl_2C_6H_4$	0.13	2.2
33b	105 °C, *o*-$Cl_2C_6H_4$	0.32	0.89

carboxylic acid with little or no epimerization but in lower and erratic conversions (0−43%). Finally, the coupling reaction of **30** with **31**, like those of analogous substrates in the vancomycin series, proved challenging, providing occasional low conversions or significant racemization, depending on the reagents or reaction conditions.[33] However, the use of the Goodman DEPBT reagent[34] (0 °C, THF) uniformly provided the best results, affording good to superb conversions and, importantly, no detectable racemization.

The macrocyclization of both **32a** and **32b** provided **33a** or **33b** in superb conversions (60−70%) upon treatment with CsF (10 equiv, DMSO, 25 °C, 0.01−0.007 M, 14−18 h) as a mixture of two atropisomers of which the unnatural stereochemistry was slightly preferred (*P*:*M* 1:1.5−2.1). *N*-Teoc deprotection of **33a** (6 equiv of TASF, DMSO, 25 °C, 20 h) served to generate the free amine **34**. More conveniently, enlisting a larger excess of freshly predried CsF (25−40 equiv) and longer reaction times (DMSO, 25 °C, 0.007 M, 13−16 h) with **32a** led to cyclization and subsequent in situ deprotection of the *N*-Teoc with direct generation of the free amine **34** as a separable mixture of two atropisomers (67−70%, 1:1.8−3 *P*:*M*) and minor amounts of **33a** (5−18%). The use of freshly dried CsF was found to be important for achieving these conversions and especially important for the *N*-Teoc deprotection. Untreated CsF provided slower conversions and little *N*-Teoc deprotection. Similarly, treatment of **32a** with K_2CO_3 (10 equiv, 4 Å MS, 0.006 M DMF, 40 °C, 12 h) did not lead to cyclization and provided only recovered starting material notably without detectable epimerization. An analogous closure of the $C_2{}^3$ epimer[33] of **32a** obtained as a minor component of the coupling of diastereomerically impure **31a** provided cyclized products[35] (30 equiv CsF, 0.007 M DMSO, 25 °C, 13 h, 90%, *P*:*M* of 1.6:1) that were both chromatographically (lower R_f) and spectroscopically distinguishable from the two atropisomers of **34**. Importantly, this confirmed that no detectable $C_2{}^3$ epimerization accompanied the cyclization of **32**. Reprotection of **34** as its *N*-Troc derivative (TrocCl, $NaHCO_3$) provided the DE ring system suitably protected to serve as models for the total synthesis. The atropisomer stereochemical assignments were established through 2D ^{1}H−^{1}H NMR of *P*- and *M*-**34** with observation of diagnostic nOe's for the natural *P*-atropisomer of $C_{3\alpha}{}^2$−H (δ 3.35)/$C_{5a}{}^2$−H (7.78) (s), $C_{3\beta}{}^2$−H (2.90)/$C_{5b}{}^2$−H (7.80) (s), $C_{3\alpha}{}^2$−H (3.35)/$C_{3\beta}{}^2$−H (2.90) (s), and $C_{3\alpha}{}^2$−H (3.35)/$C_2{}^2$−H (3.89) (m), and for the unnatural *M*-atropisomer of $C_{3\alpha}{}^2$−H (3.38)/$C_{5b}{}^2$−H (7.40) (s), $C_{3\beta}{}^2$−H (2.98)/$C_{5a}{}^2$−H (8.09) (s), $C_{3\alpha}{}^2$−H (3.38)/$C_{3\beta}{}^2$−H (2.98) (s), and $C_{3\alpha}{}^2$−H (3.38)/$C_2{}^2$−H (3.90) (m).

Conversion of the nitro group of *P*-**33b** to the corresponding chloride *P*-**35** by reduction to the aniline (H_2, 10% Pd/C), diazotization (*t*-BuONO, HBF_4), and Sandmeyer substitution ($CuCl-CuCl_2$) proceeded with complete maintenance of the atropisomer stereochemistry and provided the fully functionalized DE ring system (Scheme 5).

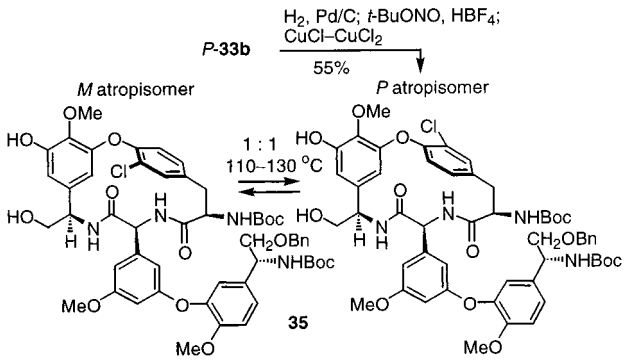
In contrast, both **32c** and **32d** (Scheme 4) failed to close upon exposure to a range of macrocyclization conditions and provided products derived from base-catalyzed cyclization of the *N*-Troc or *N*-TcBoc onto the adjacent backbone amide. Consistent with these observations, studies with **21c** (10 equiv $K_2CO_3-CaCO_3$, 4 Å MS, DMSO, 25 °C, 5 h, quantitative) and **21d** (8 equiv CsF, DMSO, 25 °C, 1 h, quantitative) revealed that treatment with mild base led to intramolecular *N*-Troc or *N*-TcBoc cleavage by the adjacent amide precluding their use in macro-

(33) For the $C_2{}^3$ epimer of **32a**: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.98 (d, J = 8.5 Hz, 1H), 7.52−7.50 (m, 1H), 7.28−7.24 (m, 6H), 7.16−7.12 (m, 2H), 7.06 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.38 (s, 2H), 6.29 (s, 1H), 5.49 (br s, 1H), 4.73 (dd, J = 5.9, 9.2 Hz, 1H), 4.55 (s, 1H), 4.51 (s, 2H), 4.47−4.42 (m, 2H), 4.11−4.02 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.64 (dd, J = 5.5, 11.3 Hz, 1H), 3.62−3.59 (m, 3H), 3.14 (dd, J = 5.9, 12.5 Hz, 1H), 2.90 (dd, J = 9.2, 12.5 Hz, 1H), 1.40 (s, 9H), −0.03 (s, 9H).

(34) Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91. DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one.

(35) For the $C_2{}^3$ epimer of **34**: *P*-diastereomer: ^{1}H NMR (CD_3OD, 600 MHz) δ 7.78 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 2.2, 8.3 Hz, 1H), 7.28−7.24 (m, 5H), 7.15 (d, J = 8.3 Hz, 1H), 7.14 (dd, J = 2.2, 7.9 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.75 (s, 1H), 6.62 (s, 1H), 6.53 (s, 1H), 6.22 (s, 1H), 5.52 (s, 1H), 5.34 (br s, 1H, NH), 5.30 (s, 1H), 4.76 (br s, 1H), 4.60−4.58 (m, 1H), 4.51 (s, 2H), 3.94 (s, 3H), 3.79−3.77 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.62−3.59 (m, 2H), 3.30−3.20 (m, 1H, partially obscured by CD_2HOD), 2.80 (dd, J = 8.3, 11.3 Hz, 1H), 1.41 (s, 9H); MALDIFTMS (DHB) *m*/*z* 946.3469 (M^+ + Na, $C_{48}H_{53}N_5O_{14}$ requires 946.3481). *M*-diastereomer: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.06 (d, J = 2.2 Hz, 1H), 7.43 (dd, J = 2.2, 8.5 Hz, 1H), 7.27−7.24 (m, 6H), 7.14 (dd, J = 2.2, 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.70 (s, 1H), 6.61 (br s, 1H), 6.57 (s, 1H), 6.22 (s, 1H), 5.62 (s, 1H), 5.31 (s, 1H), 4.71−4.69 (m, 1H), 4.60 (m, 1H), 4.51 (s, 2H), 3.93 (s, 3H), 3.86−3.83 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.60−3.58 (m, 2H), 3.30−3.20 (m, 1H, partially obscured by CD_2HOD), 2.82−2.80 (m, 1H), 1.41 (s, 9H); MALDIFTMS (DHB) *m*/*z* 946.3463 (M^+ + Na, $C_{48}H_{53}N_5O_{14}$ requires 946.3481). The atropisomer stereochemistry is tentatively assigned on the basis of 1D ^{1}H NMR.

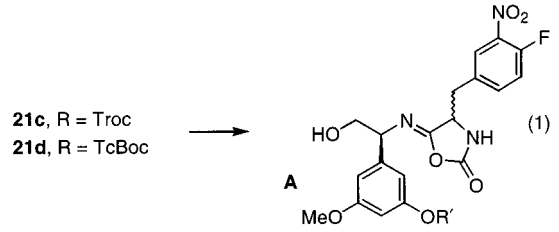
Scheme 5



35: E_a = 20.0 kcal/mol, $\Delta H^{\ddagger}$ = 20.3 kcal/mol, $\Delta S^{\ddagger}$ = −10.2 eu

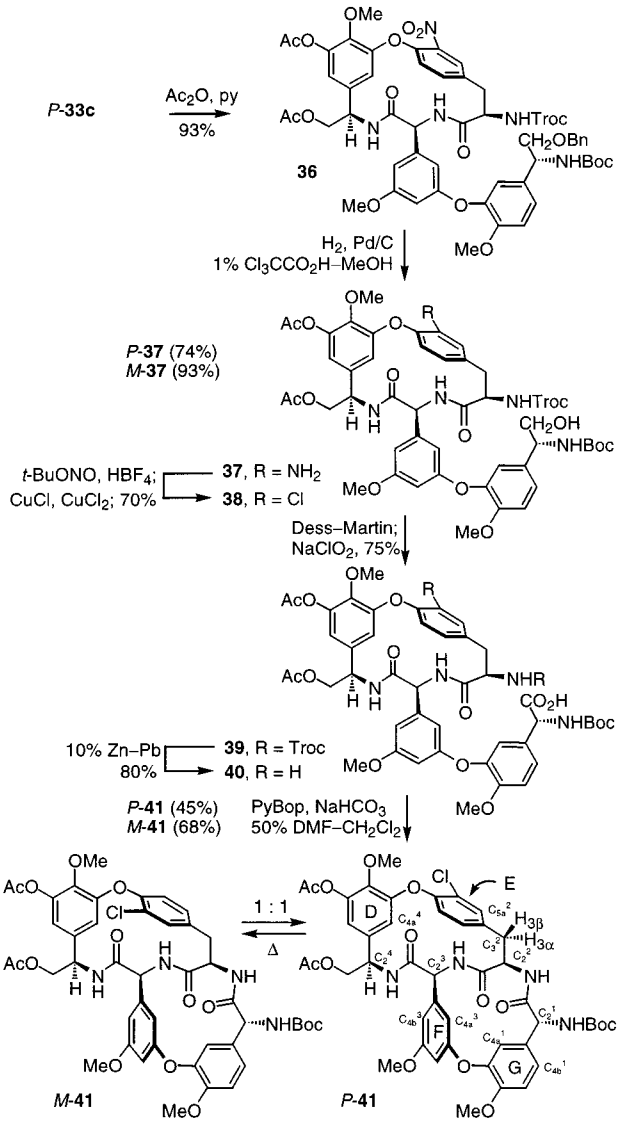
compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
35	120 °C, *o*-$Cl_2C_6H_4$	0.31	0.93
35	130 °C, *o*-$Cl_2C_6H_4$	0.58	0.50

cyclization reactions (eq 1).[36] Both **21a** and **21b** with the *N*-Teoc and *N*-Boc were stable to such base treatment and the former, because it constitutes an orthogonal protecting group to the N-terminus Boc group, was enlisted in the natural product total synthesis.



Preparation of a Fully Functionalized DEFG Ring System. The viability of an approach employing sequential DE and FG ring closures was examined with **33c**, resulting in the preparation of **41** constituting a fully functionalized teicoplanin DEFG ring system. Acetylation of the primary alcohol and phenol of **33c** provided **36**, and simultaneous nitro reduction and benzyl ether deprotection (H_2, 10% Pd/C, 1% $Cl_3CCO_2H-CH_3OH$, 25 °C, 15 min, 74−93%) was accomplished under mild conditions that had no effect on the reduction-sensitive *N*-Troc group (Scheme 6). Reduction in the absence of an acid catalyst was problematic, leading to reduction of the *N*-Troc group competitive with the slow *O*-debenzylation. Other catalysts ($Pd(OH)_2$, Pt(0)) or conditions were less successful or unsuccessful at converting **36** to **37**. The use of 1% $HOAc-CH_3OH$ proved marginally successful at accelerating the *O*-debenzylation relative to *N*-Troc reduction, and this was found to be successively improved with use of stronger acid catalysts: 1% $Cl_3CCO_2H-CH_3OH$ > 1% Cl_2CHCO_2H > 1% $ClCH_2CO_2H$ > 1% CH_3CO_2H. In the course of our use of these conditions, it also appeared as if the use of freshly dried anhydrous Cl_3CCO_2H (hygroscopic) provides the best results although this was not investigated in detail.[37] Not previously examined, the introduction of these conditions (1% $Cl_3CCO_2H-CH_3OH$) for conducting hydrogenolysis reactions in the presence of a *N*-Troc-protecting group serves to address a long-standing incompatibility[37] and extends its utility as an orthogonal amine-protecting group. Diazotization and Sandmeyer introduction of the aryl chloride provided **38** without loss of the atropisomer stereochemistry, establishing conditions for implementation in the total synthesis and providing a key substructure upon which FG ring closure and comparative thermal atropisomerism studies could be conducted. Without optimization, two-step oxidation of the alcohol **38** to the carboxylic acid **39**, *N*-Troc deprotection enlisting 10% Zn−Pb[38] (1 N aqueous NH_4OAc/THF), and FG macrolactamization under the conditions prescribed for **26** (see Scheme 3) provided **41** in satisfactory conversions and without detectable epimerization.

Scheme 6



41: E_a = 23.3 kcal/mol, $\Delta H^{\ddagger}$ = 23.0 kcal/mol, $\Delta S^{\ddagger}$ = −5.6 eu

compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
41	130 °C, *o*-$Cl_2C_6H_4$	0.15	1.92
41	140 °C, *o*-$Cl_2C_6H_4$	0.31	0.93

Atropisomerism Studies. With samples of **33**, **35**, and **41** in hand, their relative ease of thermal atropisomerism and

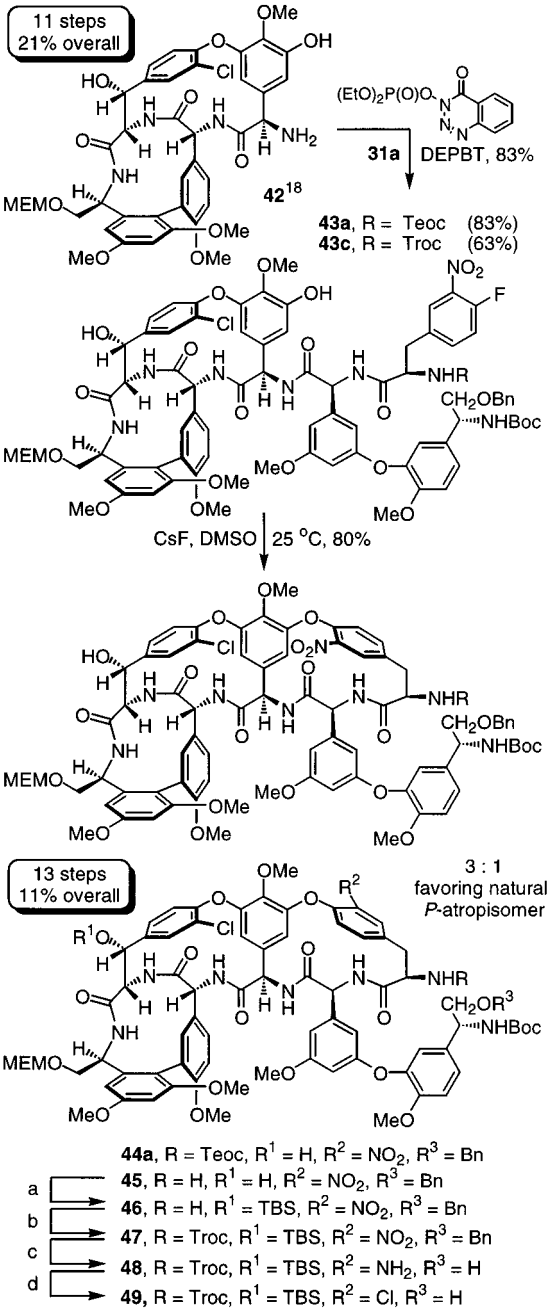
(36) For **A**: ^{1}H NMR (CD_3CN, 600 MHz) δ 7.90 (dd, J = 2.6, 8.3 Hz, 1H), 7.46 (m, 1H), 7.31−7.26 (m, 5H), 7.21 (dd, J = 8.3, 11.4 Hz, 1H), 7.13 (dd, J = 2.2, 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.38 (br s, 1H, NH), 6.33 (s, 1H), 6.32 (s, 1H), 6.26 (s, 1H), 5.81 (br s, 1H, NH), 4.85 (dd, J = 4.8, 8.8 Hz, 1H), 4.75 (br s, 1H, OH), 4.49 (d, J = 12.3 Hz, 1H), 4.46 (d, J = 12.3 Hz, 1H), 4.34 (m, 1H), 4.18 (m, 1H), 3.82 (m, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.60 (dd, J = 4.9, 10.1 Hz, 1H), 3.56 (dd, J = 7.4, 10.1 Hz, 1H), 3.11 (dd, J = 4.9, 14.1 Hz, 1H), 3.08 (dd, J = 5.7, 7.0 Hz, 1H), 3.03 (dd, J = 5.3, 14.1 Hz, 1H), 1.35 (s, 9H); MALDIFTMS (DHB) *m/z* 797.2834 (M^+ + Na, $C_{40}H_{43}N_4FO_{11}$ requires 797.2810).

(37) Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249. Cl_3CCO_2H was dried under vacuum in the presence of P_2O_5 (25 °C) prior to use.

thermodynamic preferences were established. In each instance, the thermal isomerism proceeded with ease to provide a nonselective 1:1 mixture of atropisomers with experimental E_a's of 17.2 (**33a**), 16.2 (**33b**), 20.0 (**35**), and 23.3 (**41**) kcal/mol comparable to or slightly higher than those observed with the corresponding derivatives of the isolated vancomycin DE ring system ($ArNO_2$ E_a = 16.4−18.8 kcal/mol; ArCl E_a = 18.7 kcal/mol). As anticipated, the aryl nitro derivatives **33** isomerize more readily than the aryl chloride **35**, and the constraints of the FG ring system have a decelerating effect on the rate of isomerism with **41** proceeding more slowly than **33** or **35**. Analogous observations have been made with the teicoplanin aglycon derivatives.[22] Moreover, even comparisons between an isolated vancomycin DE ring system (E_a = 18.7 kcal/mol) and its rate of DE atropisomerism within the constraints of a vancomycin aglycon derivative (E_a = 23.6 kcal/mol) are nearly identical to those observed with teicoplanin except that the latter are typically slower. Most importantly, the isomerism studies of **33**, **35**, and **41** revealed that they occur without problematic $C_2{}^3$ epimerization and under conditions where the stereochemistry of the CD (E_a = 30.4 kcal/mol)[20] and *O*-methylated AB (E_a = 37.8 kcal/mol)[18] ring systems would be unaffected. Most remarkable of these observations is that the 16-membered vancomycin and teicoplanin DE ring systems isomerize at similar rates relatively independent of the nature of the substituents or the presence of the teicoplanin FG ring system. Both isomerize much more readily than the 16-membered CD ring system even in the absence of the confines of the AB ring system. The structural similarity of the teicoplanin DE ring system and the CD ring system, especially in the absence of the confines of the AB or FG ring systems, might suggest that the two would have behaved comparably.

First Generation Total Synthesis of the Teicoplanin Aglycon. The coupling of **42**[18] with **31a** was effected by DEPBT[34] (THF, $NaHCO_3$, 0 °C, 2 h, 68−83%) in excellent conversion and without detectable epimerization (Scheme 7). This is especially notable since this coupling involves the use of an activated phenylglycine derivative prone to racemization. In contrast to DEPBT, typical reagents and conditions including those enlisted for vancomycin[18] provided near 1:1 mixtures of the $C_2{}^3$ diastereomers. Macrocyclization upon treatment of **43a** with freshly dried 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.[39] Under these conditions, *N*-Teoc deprotection was effected providing the free amine **45** directly requiring a smaller excess of CsF and shorter reaction times than the model substrate **32a** and only trace quantities of the corresponding *N*-Teoc derivative **44a** were detected (6−13%). The stereochemistry of the DE ring system and the stereochemical integrity of the ABCD ring system within **45** were established by 2D $^1H-^1H$ NMR with the observation of diagnostic nOe's for the natural *P*-atropisomer of $C_{5a}{}^2$−H (7.92)/$C_{3\alpha}{}^2$−H (3.42) (s), $C_3{}^6$−H (5.24)/$C_{5a}{}^6$−H (7.56) (m), $C_3{}^6$−H (5.24)/ $C_2{}^6$−H (4.07) (s), $C_{4a}{}^5$−H (7.01)/$C_2{}^6$−H (4.07) (s), $C_2{}^5$−H (4.59)/$C_2{}^6$−H (4.06) (s), $C_2{}^5$−H (4.59)/$C_{4a}{}^5$−H (7.01) (w), and for the unnatural *M*-atropisomer of $C_{5a}{}^2$−H (8.06)/$C_{3\beta}{}^2$−H (2.95) (s), $C_{5b}{}^2$−H (7.90)/$C_{3\alpha}{}^2$−H (3.45) (m), $C_2{}^6$−H (4.05)/$C_{5a}{}^6$−H (7.57) (m), $C_2{}^6$−H (4.05)/$C_{4a}{}^5$−H (7.00) (s), $C_2{}^6$−H (4.05)/$C_3{}^6$−H (5.22) (s), $C_{4a}{}^5$−H (7.00)/$C_2{}^5$−H (4.60) (s), $C_3{}^6$−H (5.22)/$C_{5a}{}^6$−H (7.57) (s), $C_2{}^5$−H (4.60)/$C_2{}^6$ (4.05) (s). An analogous treatment of the unnatural $C_2{}^3$ diastereomer[40] derived from coupling **42** with diastereomerically impure **31a** provided the $C_2{}^3$ diastereomer of **45**[41] as a mixture of two atropisomers (75%, ∼1:1 *P*:*M*) which were chromatographically and spectroscopically distinguishable from **45** ensuring that the closure proceeds without detectable $C_2{}^3$ epimerization. Like observations documented with the model DE ring system studies, treatment of **43c**[42] bearing the *N*-Troc protecting group with CsF or even

Scheme 7[a]

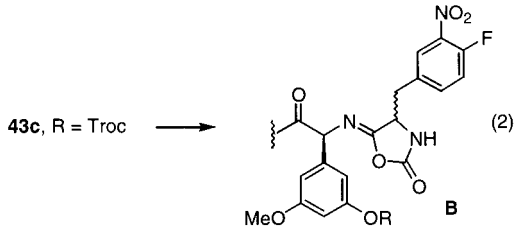


[a] (a) $CF_3CONMeTBS$, 89%; (b) TrocCl, 93%; (c) H_2, Pd/C, 1% Cl_3CCO_2H−EtOAc; (d) *t*-BuONO, HBF_4; CuCl−$CuCl_2$, 66% from **47**.

(38) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833. 10% Zn−Pb couple was prepared in the same manner as 10% Cd−Pb couple which has been described: yellow lead oxide (PbO, 108 mg, 0.49 mmol) was dissolved in 5 mL of warm 50% aqueous HOAc (45 °C), and the solution was slowly added to a vigorously stirred suspension of Zn dust (320 mg, 4.9 mmol) in deionized water (10 mL). The Zn darkened, as Pb deposited on its surface, and formed clumps that were gently broken up with a glass rod. The dark Zn−Pb was collected by filtration, washed with H_2O and then acetone, vacuum-dried, crushed, and stored in a closed vessel. See: Dong, Q.; Anderson, C. E.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 5681.

(39) Conducting the reaction at lower temperature (40 equiv of CsF, 0.007 M 20% DMF−DMSO, 5 °C, 48 h) did not significantly alter the atropisomer ratio, *P*:*M* = 2.6:1 (64%).

K_2CO_3 ($CaCO_3$, 4 Å MS, 0.08 M DMSO, 25 °C. 3.5 h) failed to provide evidence of cyclization, but rather provided the cyclic carbamate derived from reaction with the adjacent backbone amide (eq 2).[42] Protection of the secondary alcohol as its OTBS ether **46** ($CF_3CONMeTBS$, 89%), *N*-Troc formation (TrocCl, $NaHCO_3$, 93%), aryl nitro reduction to the arylamine and simultaneous *O*-benzyl deprotection (H_2−Pd/C, 1% Cl_3CCO_2H−CH_3OH), diazotization (*t*-BuONO, HBF_4), and Sandmeyer substitution (CuCl−$CuCl_2$) provided the key intermediate **49** (66% from **47**) and set the stage for closure of the FG ring system. Analogous to observations made with the model DE ring system, conversion of **47** to **48** was unsuccessful in the absence of an acid catalyst, leading to preferential *N*-Troc reduction versus *O*-debenzylation and only modestly successful employing 1% HOAc−CH_3OH (50−60%). The use of 1% Cl_3CCO_2H−CH_3OH provided clean and rapid nitro reduction and *O*-debenzylation without detection of competitive *N*-Troc reduction.



This set the stage for the final steps of the first generation total synthesis (Scheme 8). Two-step primary alcohol oxidation (Dess−Martin periodinane, CH_2Cl_2; $NaClO_2$, aqueous NaH_2PO_4, *t*-BuOH, in the presence of resorcinol) cleanly provided the carboxylic acid **50** (74%) which was subjected to *N*-Troc deprotection (10% Zn−Pb,[38] 1 N aqueous NH_4OAc/THF, 25 °C, 89%) to provide **51**, the key amino acid for FG ring closure by macrolactamization. The *N*-Troc deprotection was examined with a range of reagents including Zn (1 M NaH_2PO_4−THF, 25 °C, 2 h, 50−55%), Cd (1 M NaH_2PO_4−THF, 25 °C, 12−16 h, 58−83%), and 10% Cd−Pb (1 N NH_4OAc/THF, 25 °C, 3−7 h, 50−70%) with the Zn−Pb couple providing the best results. The closure of **51** was conducted with slow addition of the substrate (1 h, 0.001 M final concentration) to a solution of the coupling reagents (Scheme 8). PyBop[30] (66%) and FDPP[30] (62%) in the presence of $NaHCO_3$ provided excellent conversions of **51** to **52** in 10−50% DMF−CH_2Cl_2 with only trace generation of a C_2[1] epimer. HATU[30] and Bop[30] were nearly as effective, but PyBrop,[30] TFFH,[30] EDCI,[30] and DPPA[30] were substantially less effective or unsuccessful. In each case, the use of *i*-Pr_2NEt in place of $NaHCO_3$ led to more competitive C_2[1] epimerization. MEM deprotection (*B*-bromocatecholborane, CH_2Cl_2, 0 °C) followed by reprotection of the N-terminus amine with Boc_2O (THF/aqueous $NaHCO_3$, 25 °C) provided **53** (76%, two steps). Two-step alcohol oxidation (Dess−Martin periodinane, CH_2Cl_2; $NaClO_2$, DMSO−H_2O, in the presence of resorcinol), provided the carboxylic acid **54** (79%) which was also esterified with $TMSCHN_2$ (20% CH_3OH−toluene, 25 °C) to afford **55** (74%, three steps). The use of resorcinol in DMSO proved superior to isobutene/*t*-BuOH and prevented a competitive aromatic chlorination under the reaction conditions. Completion of the synthesis was accomplished from either **54** or **55** with the former being two steps shorter and proceeding with the highest overall conversion. Treatment of **54** with $AlBr_3$−EtSH served to cleave the six methyl ethers, the C_3[6] OTBS ether and *N*-Boc group providing **2** (48%) in superb conversion. Alternatively, deprotection of the C_3[6] OTBS ether of **55** (Bu_4NF−HOAc, THF, 25 °C, 78%) under conditions that suppress base-catalyzed retro aldol cleavage of the CD ring system,[18,21] and subsequent exhaustive deprotection of the resulting **56** enlisting $AlBr_3$−EtSH (25 °C, 3 h), which served to cleave the six aryl methyl ethers, the C-terminus methyl ester, and the N-terminus *N*-Boc group, also provided the teicoplanin aglycon identical in all respects with authentic material.

Adjustment of the DE atropisomer stereochemistry could be accomplished at any one of several stages without competitive thermal isomerism of the AB or CD ring systems (Figure 3). Thermal equilibration of *M*-**46** bearing the C_3[6] OTBS ether could be accomplished under the mildest conditions (DMSO, 110 °C), permitting the recycling of the unnatural *M*-atropisomer into the synthesis. Additional derivatives bearing the DE aryl chloride and an acyclo FG ring system, and even the derivative **55** incorporating both the DE aryl chloride and the cyclized FG ring system exhibited selective DE atropisomerism albeit under increasingly more vigorous thermal conditions.[22]

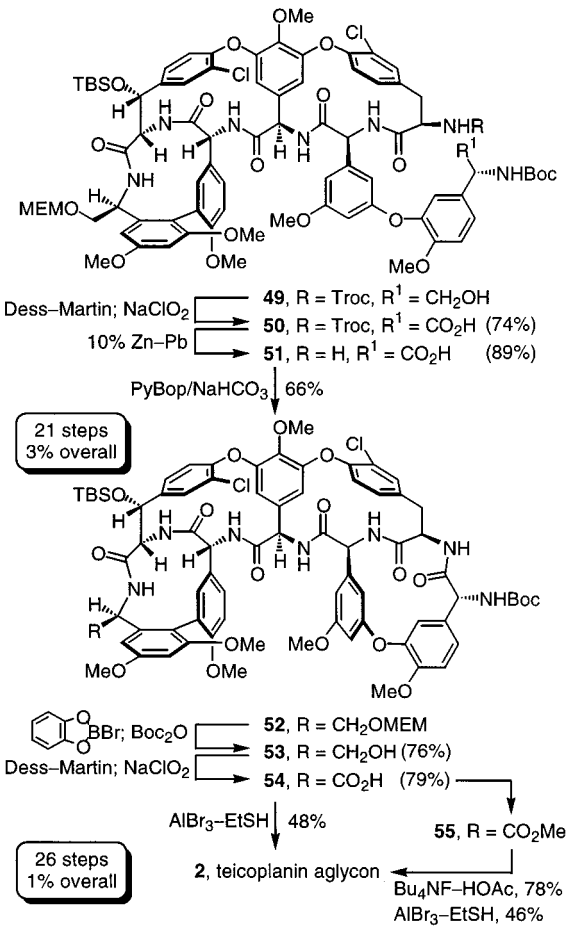
A Second Generation, More Convergent Total Synthesis of the Teicoplanin Aglycon. The alternative approach of forming the FG ring system prior to coupling with the ABCD

(40) For the C_2[3] diastereomer of **43a**: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.24 (br s, 1H, NH), 7.99 (br s, 1H), 7.61 (s, 1H), 7.55 (br s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.25−7.23 (m, 6H), 7.08−7.06 (m, 4H), 6.98 (s, 1H), 6.92−6.89 (m, 3H), 6.60 (s, 2H), 6.52 (s, 2H), 6.16 (br s, 1H), 5.97 (br s, 1H), 5.51 (s, 1H), 5.22 (s, 1H), 5.21 (s, 1H), 4.80−4.78 (m, 2H, partially obscured by H_2O), 4.76 (s, 2H), 4.72 (s, 1H), 4.48 (s, 2H), 4.35 (m, 1H), 4.06 (m, 4H), 3.93 (s, 3H), 3.88 (s, 3H), 3.74−3.70 (m, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.58−3.55 (m, 8H), 3.46 (s, 3H), 3.37 (s, 3H), 3.20 (dd, J = 6.5, 13.0 Hz, 1H), 2.94 (dd, J = 8.5, 13.0 Hz, 1H), 1.39 (s, 9H), −0.02 (s, 9H).

(41) For the C_2[3] diastereomer of **45**: *P*-atropisomer: ^{1}H NMR (CD_3OD, 315 K, 500 MHz) δ 7.82 (s, 1H), 7.66 (br s, 2H), 7.24−7.19 (m, 7H), 7.15 (d, J = 8.4 Hz, 1H), 7.10−7.08 (m, 3H), 7.04−7.00 (m, 2H), 6.95−6.90 (m, 2H), 6.93 (s, 1H), 6.81 (m, 1H), 6.61 (s, 1H), 6.59 (br s, 2H), 6.16 (br s, 1H), 5.60 (s, 1H), 5.43 (s, 1H), 5.35 (s, 1H), 5.27 (s, 1H), 5.13 (s, 1H), 4.76−4.74 (m, 2H), 4.58 (s, 1H), 4.47 (s, 2H), 4.35 (m, 1H), 4.13 (s, 3H), 4.08−4.05 (m, 2H), 3.96 (dd, J = 3.7, 10.6 Hz, 1H), 3.88 (s, 3H), 3.73−3.71 (m, 2H), 3.58−3.56 (m, 4H), 3.51 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.36 (s, 3H), 3.20−3.15 (m, 1H, partially obscured by CD_2HOD), 2.80 (m, 1H), 1.38 (s, 9H). *M*-atropisomer: ^{1}H NMR (CD_3OD, 315 K, 500 MHz) δ 8.06 (br s, 1H), 7.58−7.57 (m, 3H), 7.35 (br s, 1H), 7.28−7.19 (m, 7H), 7.10 (br s, 2H), 7.06 (d, J = 8.8 Hz, 1H), 7.00−6.95 (m, 3H), 6.90 (d, J = 8.8 Hz, 1H), 6.85 (br s, 1H), 6.59 (s, 1H), 6.37 (br s, 1H), 6.19 (br s, 1H), 5.80 (s, 1H), 5.34 (s, 1H), 5.25 (s, 1H), 5.13 (br s, 1H), 4.78−4.76 (m, 2H, partially obscured by H_2O), 4.49 (s, 2H), 4.34 (m, 1H), 4.11−4.05 (m, 3H), 4.06 (s, 3H), 3.96 (dd, J = 4.0, 10.3 Hz, 1H), 3.88 (s, 3H), 3.75−3.68 (m, 2H), 3.64 (s, 3H), 3.60 (s, 3H), 3.59 (s, 3H), 3.58−3.57 (m, 4H), 3.56 (s, 3H), 3.50 (m, 2H), 3.39 (s, 3H), 3.20−3.18 (m, 1H, partially obscured by CD_2HOD), 2.80 (m, 1H), 1.39 (s, 9H); ESIMS m/z 1584 (M^+ + Na, $C_{80}H_{85}ClN_8O_{23}$ requires 1584).

(42) For **43c**: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.92 (d, J = 6.7 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.49 (dd, J = 2.0, 8.4 Hz, 1H), 7.46 (br s, 1H), 7.28−7.20 (m, 6H), 7.11 (dd, J = 2.2, 8.4 Hz, 1H), 7.09−7.03 (m, 3H), 7.04 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.97 (br s, 1H), 6.93−6.92 (m, 3H), 6.63 (s, 1H), 6.62 (s, 1H), 6.53 (br s, 1H), 6.46 (s, 1H), 6.43 (s, 1H), 6.32 (s, 1H), 6.23 (s, 1H), 5.79 (s, 1H), 5.30 (s, 1H), 5.22 (s, 1H), 5.21 (s, 1H), 4.90 (s, 1H), 4.76 (s, 2H), 4.72 (s, 1H), 4.47 (s, 2H), 4.36−4.34 (m, 2H), 4.09−4.07 (m, 3H), 4.06 (dd, J = 8.1, 10.3 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.74−3.69 (m, 2H), 3.67 (s, 3H), 3.61 (s, 3H), 3.58−3.56 (m, 5H), 3.50 (s, 3H), 3.37 (s, 3H), 3.08 (dd, J = 6.9, 13.9 Hz, 1H), 2.91 (dd, J = 8.8, 13.9 Hz, 1H), 1.40 (s, 9H); MALDIFTMS (DHB) m/z 1777.4449 (M^+ + Na, $C_{83}H_{87}Cl_4FN_8O_{25}$ requires 1777.4418). For **B**: ^{1}H NMR (CD_3OD, 600 MHz) δ 8.30 (br s, 1H, NH), 7.83 (dd, J = 2.2, 7.9 Hz, 1H), 7.62 (d, J = 1.7 Hz, 1H), 7.49 (dd, J = 1.7, 8.8 Hz, 1H), 7.38 (m, 1H), 7.26−7.22 (m, 5H), 7.14 (dd, J = 2.2, 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.09−7.06 (m, 2H), 7.04 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.97 (d, J = 3.5 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H), 6.92 (d, J = 1.7 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.32 (s, 1H), 6.23 (s, 2H), 5.77 (s, 1H), 5.53 (s, 1H), 5.18 (s, 1H), 4.88 (s, 2H), 4.76 (s, 2H), 4.66 (s, 1H), 4.57 (s, 1H), 4.49 (s, 1H), 4.47 (s, 1H), 4.44 (m, 2H), 4.36 (m, 1H), 4.06 (m, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.74−3.72 (m, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 3.58−3.56 (m, 4H), 3.41 (s, 3H), 3.37 (s, 3H), 3.14 (dd, J = 4.3, 14.8 Hz, 1H), 3.08 (dd, J = 4.4, 14.8 Hz, 1H), 1.40 (s, 9H); MALDIFTMS (DHB) m/z 1629.5123 (M^+ + Na, $C_{81}H_{84}ClFN_8O_{24}$ requires 1629.5169).

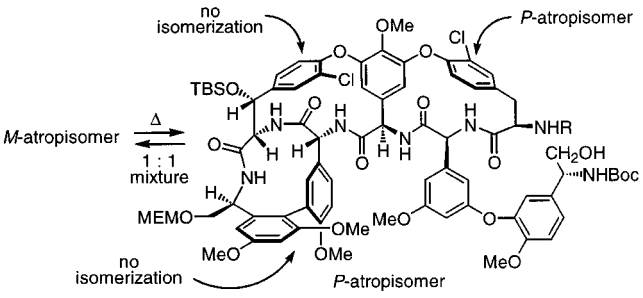
Scheme 8



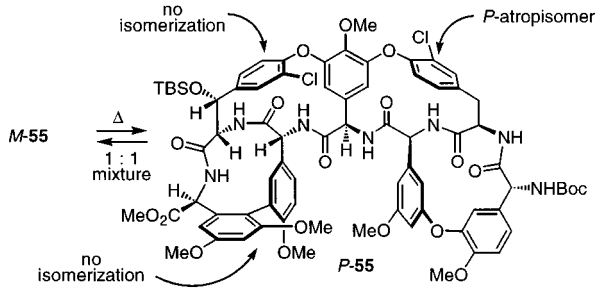
Macrolactamization of **51** to **52**.[a]

reagents (equiv)	solvent	% **52**	% C_2^1 epimer
PyBop/$NaHCO_3$ (5/5)	50% DMF–CH_2Cl_2	66%	6%
PyBop/$NaHCO_3$ (5/5)	10% DMF–CH_2Cl_2	65%	6%
PyBop/lutidine (5/5)	10% DMF–CH_2Cl_2	62%	9%
PyBop/*i*-Pr_2NEt (5/5)	50% DMF–CH_2Cl_2	57%	19%
FDPP/$NaHCO_3$ (5/5)	50% DMF–CH_2Cl_2	60%	4%
FDPP/$NaHCO_3$ (5/5)	10% DMF–CH_2Cl_2	61%	5%
HATU/*i*-Pr_2NEt (5/5)	50% DMF–CH_2Cl_2	47%	trace
Bop/*i*-Pr_2NEt (5/5)	50% DMF–CH_2Cl_2	47%	30%
EDCI (12)	DMF	–	33%
EDCI/HOBt (5/5)	25% DMF–CH_2Cl_2	29%	14%

[a] 25 °C, 1−5 h.



R = H (DMSO): E_a = 27.6 kcal/mol, $\Delta H^‡$ = 26.8 kcal/mol, $\Delta S^‡$ = −6.7 eu
R = Boc (*o*-$Cl_2C_6H_4$): E_a = 24.8 kcal/mol, $\Delta H^‡$ = 23.4 kcal/mol, $\Delta S^‡$ = −4.6 eu
R = Teoc (*o*-$Cl_2C_6H_4$): E_a = 25.2 kcal/mol, $\Delta H^‡$ = 23.6 kcal/mol, $\Delta S^‡$ = −4.2 eu



55: E_a = 29.3 kcal/mol, $\Delta H^‡$ = 27.8 kcal/mol, $\Delta S^‡$ = −4.7 eu

compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
55	130 °C, *o*-$Cl_2C_6H_4$	0.074	3.90
55	140 °C, *o*-$Cl_2C_6H_4$	0.18	1.57
55	150 °C, *o*-$Cl_2C_6H_4$	0.42	0.69

Figure 3.

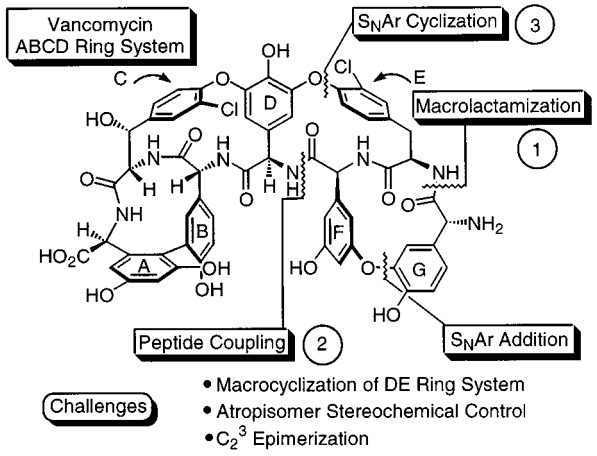


Figure 4. Second generation total synthesis.

ring system and DE macrocyclization was also examined (Figure 4). Although it was not clear at the onset of our studies, this approach proved not to suffer from a potentially problematic C_2^3 epimerization if the basicity of the reaction conditions of the DE cyclization reaction was minimized. Not only did this provide a shorter route to **2** removing four steps from the longest linear sequence from the constituent amino acids, but the DE ring closure proceeded with superb diastereoselection (>10:1), providing a further improvement over the first generation total synthesis.

Thus, coupling of **28** with **42**[18] (DEPBT,[34] THF, 0 °C, 72%) provided **57** without problematic competitive epimerization of the labile C_2^3 center. Subjection of **57** to tempered reaction conditions for DE macrocyclization (100 equiv CsF, 0.006 M DMF, 10 °C, 24 h) provided **58** as a single atropisomer which possessed the natural stereochemistry. Only trace amounts of an additional second product (18:1) were detected that possessed the molecular weight of **58**, but it was isolated in insufficient quantities for unambiguous identification. Either it constitutes the unnatural *M*-atropisiomer of the DE ring system (>10:1 diastereoselection), or it is an epimer of **58**. Consistent with the greater sensitivity of **57** and **58** toward base-catalyzed reactions, efforts to promote the closure of **57** under the required conditions enlisted for **43a** (30 equiv CsF, DMSO, 25 °C, 19 h) resulted in lower isolated yields of **58** (23−37%) and greater amounts of numerous epimeric or degradation products. Thus, the use of DMF versus DMSO as the reaction solvent and the lower reaction temperature (10 versus 25 °C) minimized the competitive degradation and epimerization reactions. Interestingly, the DE ring closure of **57** appears to proceed with greater ease than that of **43a**, allowing the effective use of these conditions. Especially notable is the substantial increase in the atropisomer diastereoselection for this ring closure (>10:1 *P*:*M*)

Table 1. Diastereoselection of DE Ring Closure

substrate	*P*:*M*	conversion (%)
32	1:2−3	65−70
43a	3:1	80
57	>10:1	76

over that observed with **43a** (3:1 *P*:*M*) and **32** (1:2−3 *P*:*M*). Not only does the diastereoselection improve when this ring closure is conducted with the FG ring system intact (>10:1 vs 3:1, **57** vs **43a**), but also when it is conducted within the confines of the ABCD ring system (3:1 vs 1:2−3, **43a** vs **32**), Table 1.

Conversion of the nitro group to the corresponding chloride by reduction, diazotization, and Sandmeyer substitution provided **60** without loss of the atropisomer stereochemistry. Protection of the C_3[6] alcohol as its OTBS ether ($CF_3CONMeTBS$, CH_3CN, 50 °C, 13 h) provided **52** (87%) junctioning with a key intermediate that was converted to **2** (five steps) in the first generation total synthesis.

Conclusions

First and second generation total syntheses of the teicoplanin aglycon were developed, and both enlist the common vancomycin/teicoplanin ABCD ring system as a key intermediate. The two complementary convergent approaches provide a means for reliable control of the atropisomer stereochemistry and are sufficiently concise and modular in nature to be implemented in the preparation of key structural analogues of either teicoplanin or vancomycin. Such studies are in progress and will be disclosed in due course.

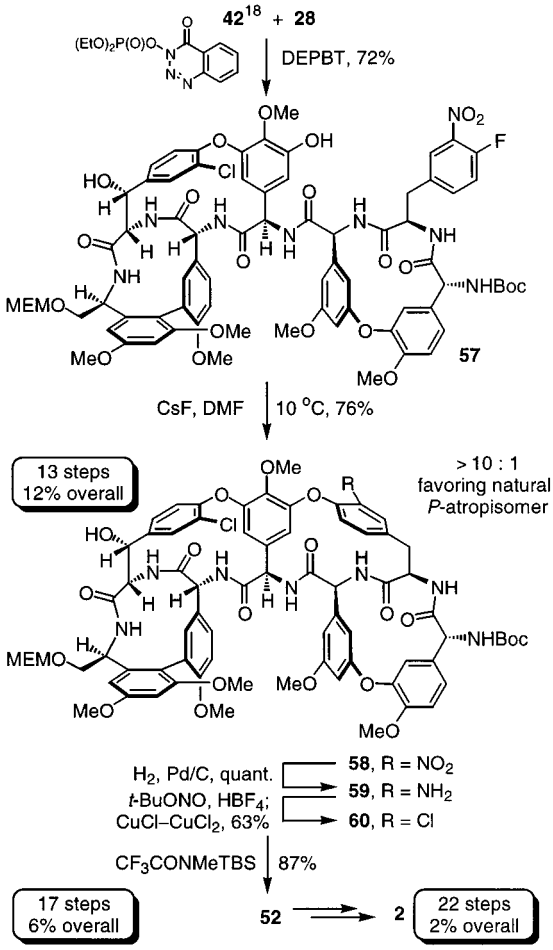
Experimental Section[43]

Full experimental details and characterization are provided in the Supporting Information.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA41101) and the Skaggs Institute for Chemical Biology, the sabbatical leave of Y.M. (Mitsubishi-Tokyo Pharmaceuticals, Inc., 1999-2001), and the award of a NIH postdoctoral fellowship (JJM, AI10367). We thank Dr. Harald Strittmatter for supplying quantities of the amino acid subunits, contributions to the supplies of the EFG tripeptide, and the initiation of studies detailed in Schemes 4 and 6.

(43) Full experimental details and characterization are provided in the Supporting Information.

Scheme 9



Supporting Information Available: Full experimental details and characterization are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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