Thermal Atropisomerism of Teicoplanin Aglycon Derivatives: Preparation of the *P*,*P*,*P* and *M*,*P*,*P* Atropisomers of the Teicoplanin Aglycon via Selective Equilibration of the DE Ring System

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Abstract: The degradation of teicoplanin to a series of key aglycon derivatives, including those containing a cleaved FG ring system, and a study of their thermal atropisomerism are detailed. In all cases, selective equilibration of the DE ring system was observed to provide a 1:1 mixture of *P:M* atropisomers under conditions in which the AB and CD atropisomer stereochemistry were unaffected. The DE atropisomer equilibration was found to occur with an E_a of 29.3 and 24.8−25.2 kcal/mol for **6a** (FG ring system intact) and **10/12** (cleaved FG ring system), respectively, which is comparable to that of a vancomycin aglycon DE ring system (E_a = 23.6 kcal/mol) and more facile than the CD (E_a = 30.4 kcal/mol) or *O*-methylated AB ring system (E_a = 37.8 kcal/mol). Consistent with intuitive expectations, the intact teicoplanin FG ring system slowed the rate of isomerization, contributing ca. 4.0 kcal/mol to the E_a (**6a** vs **10**), and the bulky $C_2{}^3$ substituent on teicoplanin acyclo FG derivatives had a much less significant effect, contributing only 1−1.5 kcal/mol to the E_a relative to the vancomycin aglycon. Neither precludes selective equilibration of the DE ring system, and neither had an effect on the thermodynamic ratio of the resulting atropisomers (1:1). Resynthesis of the teicoplanin aglycon (*P*,*P*,*P*-**2**) from **8** as a prelude to the synthesis of the teicoplanin aglycon unnatural DE atropisomer (*M*,*P*,*P*-**17**) from **13** is described and provides the final stages of a teicoplanin aglycon total synthesis and a key structural analogue. The comparative evaluation of **2** and **17** revealed that the DE atropisomer stereochemistry substantially impacts the antimicrobial activity (**2** > **17**, 50-fold) and the binding affinity for *N*,*N*′-Ac_2-L-Lys-D-Ala-D-Ala (**2** > **17**, $K_a = 2.4 \times 10^6$ vs 1.9×10^4 M^{-1}, 125 times).

Teicoplanin (**1**, Figure 1) is a complex of five closely related natural products isolated from *Actinoplanes teichomyceticus*[1,2] (ATCC 31121) that are related to vancomycin.[3−8] It is 2−20-fold more potent than vancomycin against Gram-positive bacteria,[9,10] possesses a lower toxicity than vancomycin,[1,11,12] exhibits a longer half-life in man (40 h vs 6 h),[13,14] and is easier to administer[15] and monitor.[16] The teicoplanin aglycon bears the identical ABCD ring system and the same ABCDE atropisomer stereochemistry of vancomycin but contains a DE

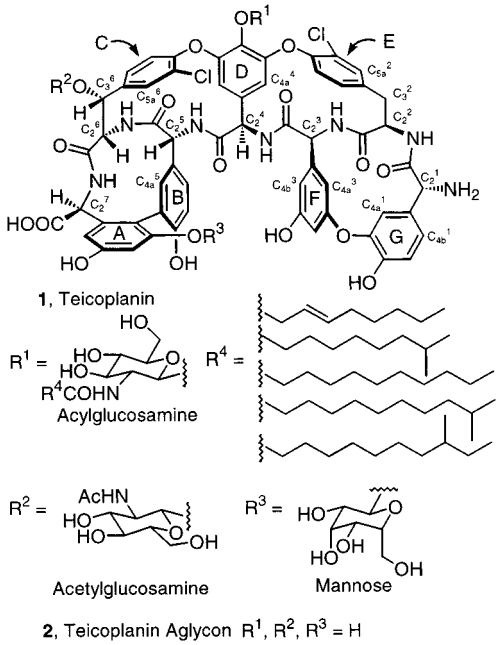

Figure 1.

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ring system that lacks the sensitive β-hydroxy group of the E-ring-substituted phenylalanine (residue 2) and incorporates an especially racemization-prone substituted phenylglycine (residue 3).[17] Most significantly, it contains the additional 14-membered diaryl ether FG ring system that is not found in vancomycin. We recently disclosed a total synthesis[18−22] of the vancomycin aglycon, complementary to those of Evans and Nicolaou, which enlisted a defined order to the introduction of its CD, AB, and DE ring systems, which permits selective thermal atropisomerism of the newly formed ring systems or their immediate precursors.[23−27] In addition to the diastereoselection that was achieved in each of the ring closures, this order permitted the recycling of any undesired atropisomer for each ring system and provided a means for 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 could serve as a key intermediate to both classes of natural products.

Prior to implementing this approach for teicoplanin[20] and in efforts to address a concern over its viability, we examined the thermal atropisomerism of a series of teicoplanin aglycon derivatives. The added constraints that the teicoplanin FG ring system imposes on the conformational properties of the structure were not clear, and it was expected to have a significant impact on the ease of DE atropisomerism and could also alter the thermodynamic atropisomer preference. Optimally, the DE ring system would be capable of selective isomerism without affecting the AB or CD atropisomer stereochemistry. Anticipating that the constraints of the FG ring system might preclude selective thermal DE atropisomer equilibration, we examined derivatives of the teicoplanin aglycon containing both the intact and cleaved FG ring system. This approach provided the added benefit that we could establish the relative sensitivity of both types of derivatives toward C_2[3] epimerization, which is known to be especially facile for teicoplanin derivatives.[17]

Herein we provide details of studies that have defined conditions suitable for selective teicoplanin DE versus CD or AB atropisomerism and that provided appropriately functionalized teicoplanin aglycon derivatives which served as relay intermediates in a total synthesis of the natural product. Thus, thermal atropisomerism of **6a** or **10** and **12** provided 1:1 mixtures of the *P*,*P*,*P* and *M*,*P*,*P*-atropisomers **13**, **14**, and **15**, respectively, in which the DE atropisomers selectively equilibrate. We also describe the conversion of **8** to the teicoplanin aglycon, which constitutes the final stages of its total synthesis and the conversion of *M*,*P*,*P*-**13** to *M*,*P*,*P*-**17**, the corresponding teicoplanin aglycon which possesses the unnatural DE antropisomer stereochemistry.

Teicoplanin Degradation. The degradation of **1** to a series of aglucoteicoplanin derivatives is summarized in Scheme 1. The removal of the three carbohydrates was accomplished by treatment with 10% concentrated HCl−HOAc (80 °C, 1 h)[29] or 80% aqueous H_2SO_4, DMSO (85−90 °C, 30 h).[30] Although the aglycon **2** could be isolated in pure form by semipreparative reverse-phase HPLC, it proved to be more convenient to carry the crude material forward without purification. *N*-Boc formation (Boc_2O, $NaHCO_3$, DMF, 25 °C), followed by methyl ester formation (CH_3I, $NaHCO_3$, DMF, 25 °C) conducted in situ without isolation of the carboxylic acid **3**, provided **4a** (50% overall from **1**). Exhaustive methylation of the six phenols (CH_3I, K_2CO_3, DMF, 25 °C) and *O*-silylation of the C_3[6] alcohol of **5a** ($CF_3CONMeTBS$, CH_3CN, 45 °C) afforded **6a**. Methyl ester reduction ($LiBH_4$, $(MeO)_3B$, THF, 45 °C), followed by MEM protection of the primary alcohol **7** (MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C), provided **8**. This sequence was also conducted with formation of the benzyl versus methyl ester ($PhCH_2Br$, $NaHCO_3$, 45% overall from **1**), providing **4b**, an intermediate which is often easier to purify than **4a**.

For access to derivatives that lack the FG ring system, the N-terminus amide was reductively cleaved following a modification to protocols disclosed in studies conducted on *N*-Boc aglucoteicoplanin.[31] Thus, treatment of **8** with $LiBH_4$ (10% H_2O−EtOH, 25 °C) cleanly led to reductive cleavage of the FG ring system at the N-terminus amide to provide **9** (66%,

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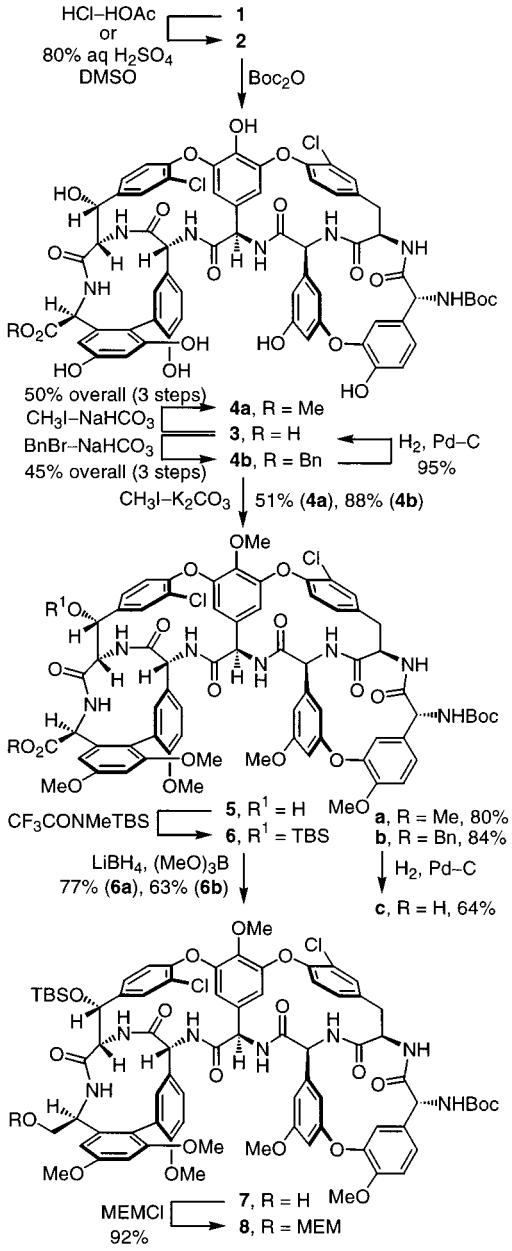
Scheme 1

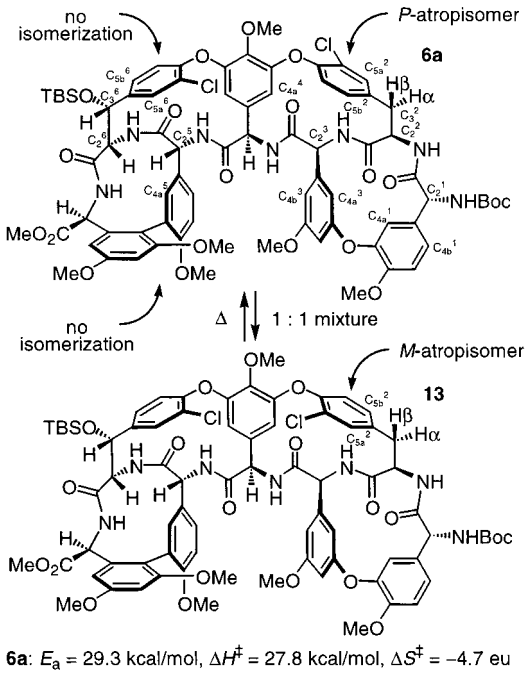


Scheme 1). However, the conversion was much lower following the conditions disclosed for *N*-Boc aglucoteicoplanin ($NaBH_4$, 10% H_2O−EtOH, 25 °C, 72 h)[31] in which substantial competitive C_2^3 epimerization of **8** (50%), generation of the C_2^3 epimerized reductive cleavage product,[32] and further reduction products were observed.

In studies related to synthetic efforts on teicoplanin, the liberated free amine in **9** was protected as the Boc derivative **10** (Boc_2O, $NaHCO_3$, CH_2Cl_2), the Troc derivative **11** (TrocCl, $NaHCO_3$, CH_2Cl_2), and the Teoc derivative **12** (Teoc−OBt, Et_3N, dioxane−H_2O).

Thermal Atropisomerism. Given the anticipated thermal instability of teicoplanin and the fact that it is a mixture of five components, no effort was made to study the thermal equilibration of **1**. The thermal isomerization of **6a** was examined in detail, and it contains protecting groups not only for the C-terminus carboxylic acid, the N-terminus amine, and all six

(32) The identity of this product was examined by independent synthesis; see Scheme 5.



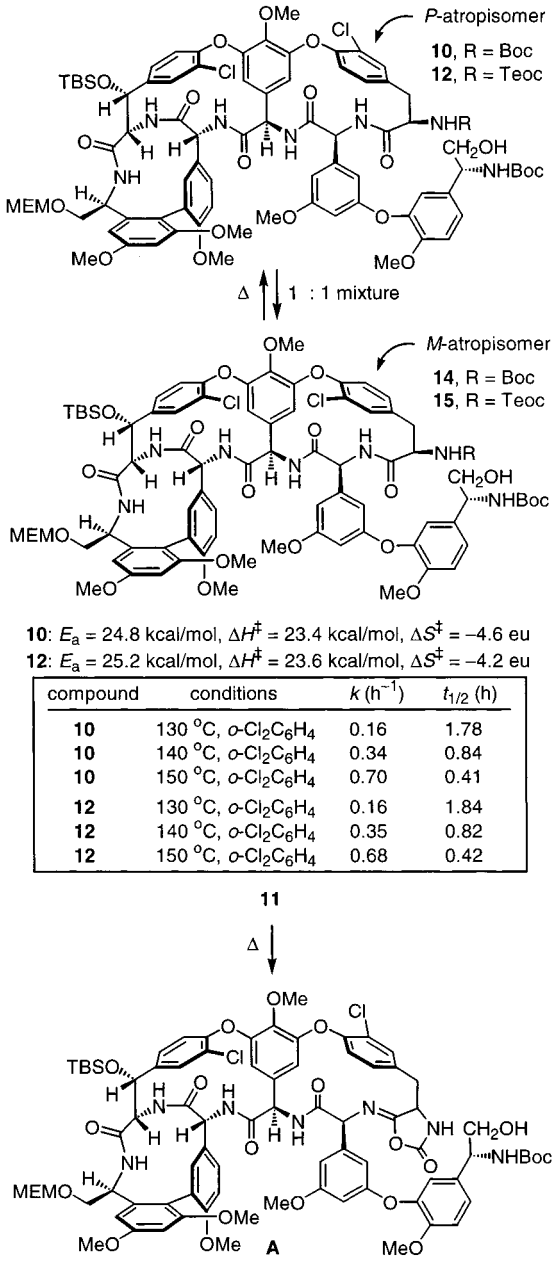
6a: E_a = 29.3 kcal/mol, $\Delta H^{\ddagger}$ = 27.8 kcal/mol, $\Delta S^{\ddagger}$ = −4.7 eu

compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
6a	130 °C, *o*-$Cl_2C_6H_4$	0.074	3.90
6a	140 °C, *o*-$Cl_2C_6H_4$	0.18	1.57
6a	150 °C, *o*-$Cl_2C_6H_4$	0.42	0.69

Figure 2.

phenols, but also for the C_3^6 secondary alcohol which was found to suffer a thermally slow retro aldol reaction within the vancomycin aglycon.[27] Clean, selective equilibration of the DE atropisomers was observed for **6a** under relatively mild conditions (130−150 °C, *o*-$Cl_2C_6H_4$), which provided a 1:1 mixture of **6a** and **13** without detectable isomerization of either the AB or CD ring system atropisomers (Figure 2).[28] The thermal equilibration occurs with a greater E_a (29.3 kcal/mol vs 23.6 kcal/mol) and longer half-life (140 °C, 1.6 vs 0.8 h) than the vancomycin aglycon DE equilibration, which also provided a 1:1 mixture of *P*:*M* atropisomers.[27] Thus, the teicoplanin FG ring system, including the sterically bulky C_2^3 side chain, does slow the rate of atropisomerism, but it does not preclude selective equilibration of the DE ring system; nor does it alter the atropisomer thermodynamic ratio. The isolation of **13** and its thermal reequilibration with **6a** established their relationship as interconverting atropisomers. Diagnostic of the DE atropisomer stereochemistry, the 2D $^1H-^1H$ NMR (Roesy, CD_3OD, 600 MHz, 313 K) of **6a** revealed natural atropisomer NOEs corresponding to $C_{3\beta}^2$−H (δ 3.00)/C_{5b}^2−H (δ 7.41) (s, strong), $C_{3\alpha}^2$−H (3.31)/C_{5a}^2−H (7.36) (s) and C_{4a}^4−H (5.68)/C_{6b}^2−H (7.03,) (w, weak), and C_{4a}^4−H (5.68)/C_{5a}^2−H (7.36) (w), whereas **13** revealed unnatural atropisomer NOEs corresponding to $C_{3\alpha}^2$−H (3.34)/C_{5b}^2−H (7.25) (m, medium), $C_{3\beta}^2$−H (2.95)/C_{5a}^2−H (7.58) (m), and C_{4a}^4−H (5.66)/C_{5b}^2−H (7.25) (w). Diagnostic NOE cross-peaks indicative of the CD and AB ring system stereochemistry were unperturbed: C_3^6−H/C_{5a}^6−H, C_2^6−H/C_{5a}^6−H, C_{4a}^5−H/C_2^6−H, C_2^5−H/C_{4a}^5−H, and C_2^5−H/C_2^6−H.

These observed NOEs and assignments for **6a** and related structures were analogous to those that Malabarba[29] made on the teicoplanin aglycon. In addition, **2** (DMF-d_7, 500 MHz, 323 K) exhibited a C_2^1−H/C_{4b}^1−H NOE much stronger than C_2^1−H/C_{4a}^1−H, a C_{4a}^1−H/C_{4a}^3−H NOE but no C_{4b}^1−H/C_{4a}^3−H NOE, and C_2^3−H exhibited a NOE with C_{4b}^3−H but not with



compound	conditions	k (h^{-1})	$t_{1/2}$ (h)
10	130 °C, *o*-$Cl_2C_6H_4$	0.16	1.78
10	140 °C, *o*-$Cl_2C_6H_4$	0.34	0.84
10	150 °C, *o*-$Cl_2C_6H_4$	0.70	0.41
12	130 °C, *o*-$Cl_2C_6H_4$	0.16	1.84
12	140 °C, *o*-$Cl_2C_6H_4$	0.35	0.82
12	150 °C, *o*-$Cl_2C_6H_4$	0.68	0.42

Figure 3.

$C_{4a}{}^3$−H. Similarly, **8** (DMSO-d_6, 600 MHz, 333 K) exhibited $C_2{}^1$−H/$C_{4a}{}^1$−H and $C_2{}^1$−H/$C_{4b}{}^1$−H NOEs, a $C_{4a}{}^1$−H/$C_{4a}{}^3$−H NOE but no $C_{4b}{}^1$−H/$C_{4a}{}^3$−H NOE, and $C_2{}^3$−H exhibited a NOE with $C_{4b}{}^3$−H, but not with $C_{4a}{}^3$−H. These observations suggest a well-defined FG conformation for **2** and related compounds in polar aprotic solvents which has not been previously established for teicoplanin or a teicoplanin aglycon derivative. The behavior of **8** and, presumably, related agents was slightly different in CD_3OD (313 K, 500 MHz), with $C_2{}^3$−H exhibiting NOEs with both $C_{4a}{}^3$−H and $C_{4b}{}^3$−H, $C_2{}^1$−H exhibiting NOEs with both $C_{4a}{}^1$−H and $C_{4b}{}^1$−H but still exhibiting only a $C_{4a}{}^1$−H/$C_{4a}{}^3$−H NOE and no $C_{4b}{}^1$−H/$C_{4a}{}^3$−H NOE.

The analogous thermal equilibration of **10** which contains the cleaved FG ring system occurred with greater ease, requiring temperatures of 130−150 °C (*o*-$Cl_2C_6H_4$) and proceeding with an E_a of 24.8 kcal/mol and $t_{1/2}$ of 0.84 h (140 °C) or 1.78 h (130 °C), which produced a separable 1:1 mixture of DE ring system atropisomers (Figure 3). No detectable isomerism of either the AB or CD ring system atropisomers was observed. Thus, the added conformational constraints of **6a** relative to **10** imposed by the FG ring system resulted in a greater barrier to thermal isomerism. Isolation of the unnatural DE atropisomer **14** and its thermal reequilibration with **10** established the relationship of **10** and **14** as interconverting atropisomers. Diagnostic of the DE atropisomer stereochemistry, the 2D ^{1}H−^{1}H NMR (Roesy, CD_3OD, 500 MHz, 313 K) of **10** revealed natural atropisomer NOEs corresponding to $C_{3\alpha}{}^2$−H (3.41)/$C_{5a}{}^2$−H (7.42) (s), whereas **14** revealed unnatural atropisomer NOEs corresponding to $C_{3\alpha}{}^2$−H (3.34)/$C_{5b}{}^2$−H (7.25) (m), $C_{3\beta}{}^2$−H (2.95)/$C_{5a}{}^2$−H(7.58) (m), and $C_{4a}{}^4$−H (5.66)/$C_{5b}{}^2$−H (7.25) (w). Diagnostic NOE cross-peaks indicative of the CD and AB ring system stereochemistry were unperturbed: $C_3{}^6$−H/$C_{5a}{}^6$−H, $C_2{}^6$−H/$C_{5a}{}^6$−H, $C_{4a}{}^5$−H/$C_2{}^6$−H, and $C_2{}^5$−H/$C_{4a}{}^5$−H.

The corresponding *N*-Teoc derivative **12** behaved similarly (130−150 °C, *o*-$Cl_2C_6H_4$), providing a 1:1 mixture of *P*:*M* DE atropisomers with no evidence of AB or CD ring system isomerism (Figure 3), but the *N*-Troc derivative **11** preferentially closed to the imino carbamate **A**[33] faster than DE ring system equilibration. Diagnostic of the DE atropisomer stereochemistry for the equilibration of **12**, the 2D ^{1}H−^{1}H NMR (Rosey, CD_3OD, 500 MHz, 313 K) of **12** revealed natural atropisomer NOEs corresponding to $C_{3\alpha}{}^2$−H (3.43)/$C_{5a}{}^2$−H (7.51) (s), whereas **15** revealed unnatural atropisomer NOEs corresponding to $C_{3\alpha}{}^2$−H (3.44)/$C_{5b}{}^2$−H (7.34) (m), $C_{3\beta}{}^2$−H (2.89)/$C_{5a}{}^2$−H (7.50) (w), and $C_{4a}{}^4$−H (5.76)/$C_{6b}{}^2$−H (7.28) (w). NOE cross-peaks indicative of the CD and AB ring system stereochemistry were unperturbed: $C_3{}^6$−H/$C_{5a}{}^6$−H, $C_2{}^6$−H/C_{5a}6−H, $C_{4a}{}^5$−H/$C_2{}^6$−H, and $C_2{}^5$−H/$C_{4a}{}^5$−H.

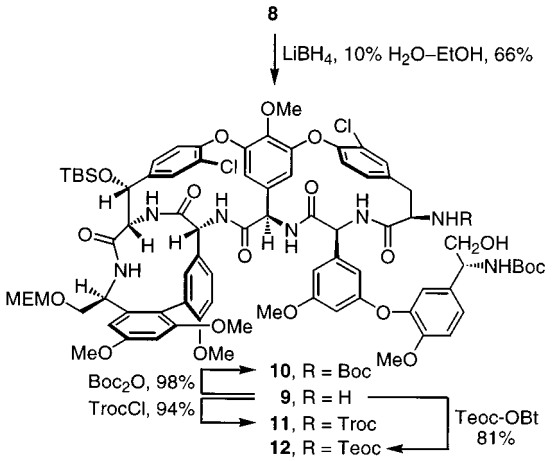
Although not investigated in detail, initial attempts at the thermal equilibration of **9** led to conversion to a second product (*o*-$Cl_2C_6H_4$) that did not reequilibrate with **9** and most likely constitutes an epimerized diastereomer. However, the equilibration could be conducted in DMSO, albeit with some degradation, resulting in a 70% recovery of a 1:1 mixture of DE ring system atropisomers at 130 °C: E_a = 27.6 kcal/mol, $t_{1/2}$ = 1.1 h (120 °C), 0.45 h (130 °C), and 0.16 h (140 °C).

Finally, studies conducted with **5a** revealed that its DE atropisomerism, even in nonpolar solvents (*o*-$Cl_2C_6H_4$) which suppress retro aldol cleavage of the CD ring system,[27] did not proceed sufficiently well at the lower temperatures (130 °C) to permit respectable rates of equilibration or product recoveries. Instead, an unidentified product was observed that possessed the same molecular weight and the same diagnostic NOEs as **5a**, but that exhibited chemical shift perturbations in $C_{6b}{}^6$−H and $C_6{}^5$−OMe. Thus, useful interconversions do not appear to be possible with **5a**.

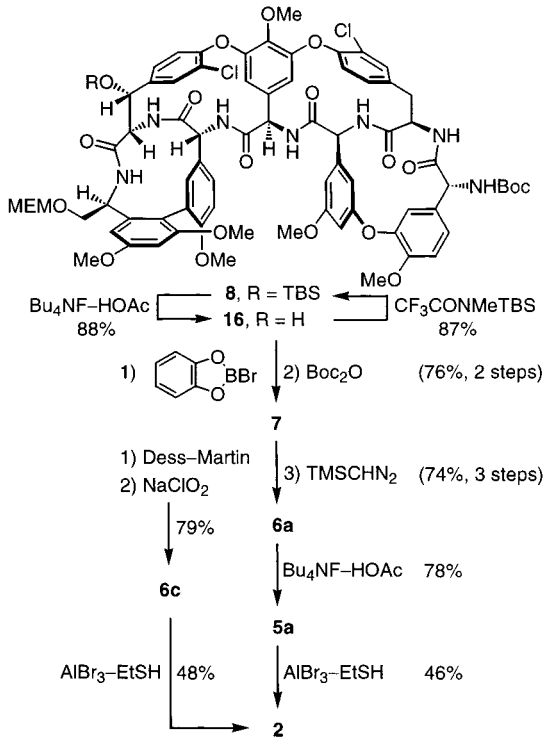
Synthesis of the Teicoplanin Aglycon from 8. The preparation of the teicoplanin aglycon from **8** or its corresponding $C_3{}^6$ free alcohol **16** was conducted to establish the final steps of a total synthesis and as a prelude to preparing the teicoplanin aglycon unnatural DE atropisomer (Scheme 3). Thus, $C_3{}^6$ OTBS deprotection enlisting Bu_4NF in the presence of HOAc (10 equiv) cleanly provided the secondary alcohol **16** (88%) without competitive retro aldol ring cleavage.[27] Reprotection of **16** as its $C_3{}^6$ OTBS ether ($CF_3CONMeTBS$, CH_3CN, 50 °C), followed by aqueous acid workup, provided **8** (87%). MEM deprotection (*B*-bromocatecholborane, CH_2Cl_2, 0 °C), followed by reprotection of the N-terminus amine with Boc_2O (aqueous $NaHCO_3$, 25 °C), provided **7** (76% for 2 steps). Two-step alcohol oxidation (Dess−Martin periodinane, CH_2Cl_2; $NaClO_2$, DMSO−H_2O in

(33) Full characterization is provided in Supporting Information.

Scheme 2



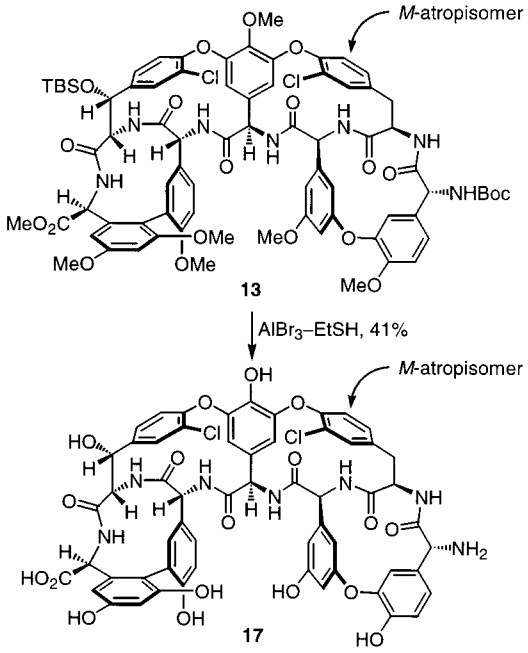
Scheme 3



the presence of resorcinol) provided the carboxylic acid, which was esterified upon treatment with $TMSCHN_2$ (20% MeOH−toluene, 25 °C) to afford **6a** (74% for 3 steps). The use of resorcinol in DMSO−H_2O proved to be superior to isobutene/*t*-BuOH and prevented competitive aromatic chlorination under the reaction conditions. Deprotection of the C_3^6 OTBS ether (Bu_4NF−HOAc, THF, 25 °C, 78%), followed by exhaustive deprotection of **5a** enlisting $AlBr_3$−EtSH (25 °C, 3 h, 46%),[21] which served to cleave the six aryl methyl ethers, the C-terminus methyl ester, and the N-terminus Boc group, provided the teicoplanin aglycon identical in all respects with authentic material.[34]

A more concise sequence for the final conversions, which eliminates two steps and improves the overall conversion, entailed two-step alcohol oxidation of **7** (Dess−Martin periodinane, CH_2Cl_2; $NaClO_2$, DMSO−H_2O in the presence of resorcinol) to provide the carboxylic acid **6c** (79%) and direct

Scheme 4



treatment of the purified carboxylic acid **6c** with $AlBr_3$−EtSH (25 °C, 3 h), which served to deprotect the six aryl methyl ethers, the C_3^6 OTBS ether, and the N-terminus Boc, to provide **2** (48%).

Preparation of the Teicoplanin Aglycon Unnatural DE Atropisomer 17. Following the route detailed for **2**, **13** was obtained from preparative thermal isomerism of **6a** and converted to **17**, aglucoteicoplanin that possesses the unnatural *M*-atropisomer of the DE ring system. Thus, treatment of **13** with $A1Br_3$ (EtSH, 25 °C, 3 h) led to exhaustive deprotection of the nine protecting groups and provided **17** directly (41%) (Scheme 4).

The unnatural DE atropisomer of the teicoplanin aglycon (**17**) was compared to the natural teicoplanin aglycon **2** in representative antimicrobial assays and in cell free binding assays with *N*,*N*′-diacetyl-L-Lys-D-Ala-D-Ala and *N*,*N*′-diacetyl-L-Lys-D-Ala-D-Lac. In the antimicrobial assays, **17** was found to be 50 times less potent than **2** (Table 1). Unlike teicoplanin itself, both its aglycon **2**, as well as **17**, exhibited diminished activity against Van B *Enterococcus faecalis*.

The binding of **2** and **17** with both *N*,*N*′-Ac_2-L-Lys-D-Ala-D-Ala and *N*,*N*′-Ac_2-L-Lys-D-Ala-D-Lac was examined following established protocols (Table 2). The binding of **17** with the D-Ala-D-Ala ligand was reduced 125 times relative to the natural teicoplanin aglycon (**2**), indicating that the DE atropisomer stereochemistry substantially impacts the tripeptide binding affinity. This observation is consistent with the relative antimicrobial potency of the two compounds. Both **2** and **17**, like vancomycin, exhibited very substantial reductions in binding affinity to the D-Ala-D-Lac ligand that were consistent with their loss of antimicrobial activity against vancomycin resistant strains of *E. faecalis*.

These observations may help clarify the role of the residue 2 chlorine substituent. Recent proposals have suggested a role for promoting antibiotic dimerization enhancing the cooperative D-Ala-D-Ala binding.[35] However, teicoplanin represents the exception for which antibiotic dimerization is not observed.

(34) The resynthesis of the teicoplanin aglycon from **8** and **11** confirmed that **9**−**12** possess the natural C_2^3 stereochemistry.

(35) Gerhard, U.; Mackay, J. P.; Maplestone, R. A.; Williams, D. H. *J. Am. Chem. Soc.* **1993**, *115*, 232.

Table 1. Antimicrobial Activity

	MIC (μg/mL)				
	Staphylococcus aureus	*Enterococcus faecium*		*Enterococcus faecalis*	
compound	(ATCC 25923)	(ATCC 35667)	vanco. resist.	Van A (BM 4166)	Van B (ATCC 51299)
vancomycin	1.25	2.5	500	2850	125
1, teicoplanin	0.15	1.25	60	2560	1.25
2, teicoplanin aglycon	≤0.30	1.25	>640	>640	10
17	16	66	>534	>534	534

Table 2. Association Constants[a]

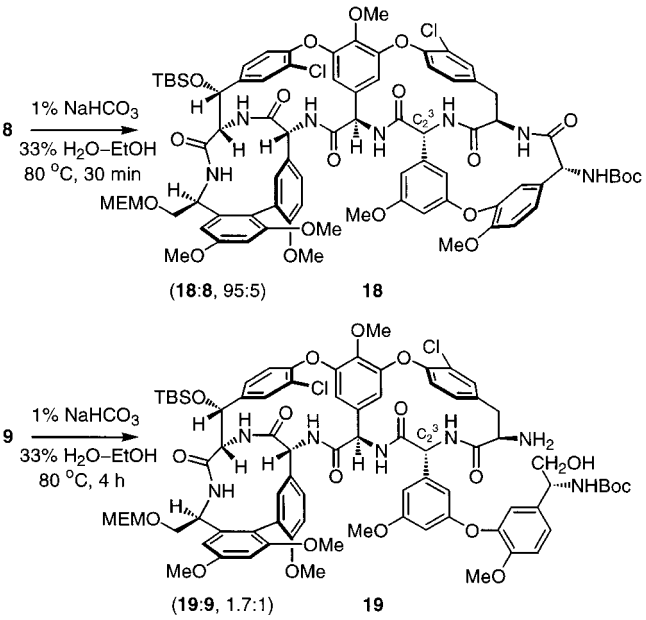
ligand	K_a, M^{-1}		
	vancomycin	**2**, teicoplanin aglycon	**17**
N,N′−Ac_2−L−Lys−D−Ala−D−Ala	3.1×10^5	2.4×10^6	1.9×10^4
N,N′−Ac_2−L−Lys−D−Ala−D−Lac	3.3×10^{2b}	2.0×10^2	4.8×10^2

[a] 0.11 mM compound, 25 °C, 0.02 M sodium citrate, pH = 5.1. Perkins, H. R. *Biochem. J.* **1969**, *111*, 195. Nieto, M.; Perkins, H. R. *Biochem. J.* **1971**, *123*, 773. Scrimin, P., et al. *J. Org. Chem.* **1996**, *61*, 6268. [b] Popieniek, P. H.; Pratt, R. F. *Anal. Biochem.* **1987**, *165*, 108.

Instead, enhancement of its antimicrobial properties is derived from the membrane-anchoring effects provided by the residue 4 glucosamine acyl lipid. That the reduction in the antimicrobial activity of **17** correlated with its reduced binding affinity for D-Ala-D-Ala with an antibiotic that does not dimerize suggests a primary, direct role for the residue 2 chlorine. The distinct behavior of **17** vs **2** may be derived from a chlorine-enhanced D-Ala-D-Ala binding of **2**, a chlorine-diminished binding of **17**, or a combination of the two effects. The binding of the corresponding DE dechloro teicoplanin aglycon with *N,N*′-Ac_2-L-Lys-D-Ala-D-Ala has been examined in the work of Malabarba[36] and was found to exhibit a $K_a = 3.5 \times 10^4$ M^{-1}, which is only slightly greater than that of **17** (1−2 times) and approximately 70-fold lower than the teicoplanin aglycon. Thus, the residue 2 chlorine, with only the natural atropisomer stereochemistry, enhances the D-Ala-D-Ala binding affinity relative to its removal (70 times) and its incorporation with the unnatural stereochemistry has little additional effect (1.8 times, 125 times total). This is a direct effect on the binding affinity of the teicoplanin monomer and is independent of any additional role the substituent might play in promoting dimerization of other antibiotics in the class, or its role in orienting the residue 4-bound carbohydrates.

Teicoplanin Aglycon Epimerization. In studies leading to the structure elucidation of teicoplanin, Williams and coworkers[17] detailed a facile C_2^3 epimerization that occurs under mild conditions (3% aqueous $NaHCO_3$, 80 °C, 5 h or 20% *n*-$BuNH_2$−CH_3OH, 80 °C, 3−6 h) to provide the unnatural C_2^3 (*R*)-isomer as the near exclusive product of the equilibration. Although equilibrated diastereomer ratios were not reported, the unnatural C_2^3 (*R*)-diastereomers were isolated in yields up to 80%. Consequently, we examined the analogous epimerization of **8** and **9** to provide an in-house sense of their relative ease of isomerization and to provide authentic samples for comparison. Thus, while exposure of **8** to 1% $NaHCO_3$ in 33% H_2O−EtOH at 25 °C or 50 °C (5 h) had no effect, its exposure at 80 °C (30 min) led to a presumed C_2^3 epimerization to **18** (52%) and a second additional minor isomer (16%) whose structure was not established, with only a trace of **8** remaining (≥ 95:5 **18**:**8**) (Scheme 5). By contrast, **9** epimerized more slowly, and a 4-h versus 30-min exposure of **9** to 1% $NaHCO_3$ in 33% H_2O−EtOH at 80 °C led to a 1:1.7 mixture of **9**:**19**, and **19** appears to possess the unnatural C_2^3 (*R*)-stereochemistry. More vigorous

Scheme 5



basic conditions of 3% K_2CO_3 in 33% H_2O−EtOH, even at 45 °C, produced a 3:1 mixture of **19**:**9** with the unnatural C_2^3 (*R*)-diastereomer predominating. Thus, the ease of epimerization of **9** is lower than **8**, and the preference for the unnatural C_2^3 (*R*) versus (*S*) diastereomer appears to be less pronounced, and this observation has significant strategic implications in the planning of a total synthesis of the teicoplanin aglycon. However, both **8** and **9** epimerize with an ease that should raise concerns in synthetic efforts. Notably, **19** was identical to the epimerized reduction product that was derived from reductive cleavage of **8** with $NaBH_4$ (10% H_2O−EtOH, 26%). In the case of both **18** and **19**, the ^1H NMR chemical shifts most affected by the epimerization were C_2^3−H and C_2^4−H and the exact site of epimerization was not unambiguously established in our studies. That of **18** might be safely extrapolated from the work of Williams,[17] and that of **19** deduced from correlation with the epimerized reduction product. However, no effort was made to unambiguously establish the assignments, and it is possible that they could involve C_2^4 versus C_2^3 epimerization.

Discussion. Most remarkable of the observations is the ease of the teicoplanin DE atropisomerism and the relative lack of impact the constraints of the additional 14-membered FG ring system have on the rate of isomerism or the thermodynamic

(36) Malabarba, A.; Spreafico, F.; Ferrari, P.; Kettenring, J.; Strazzolini, P.; Tarzia, G.; Pallanza, R.; Berti, M.; Cavalleri, B. *J. Antibiot.* **1989**, *42*, 1684.

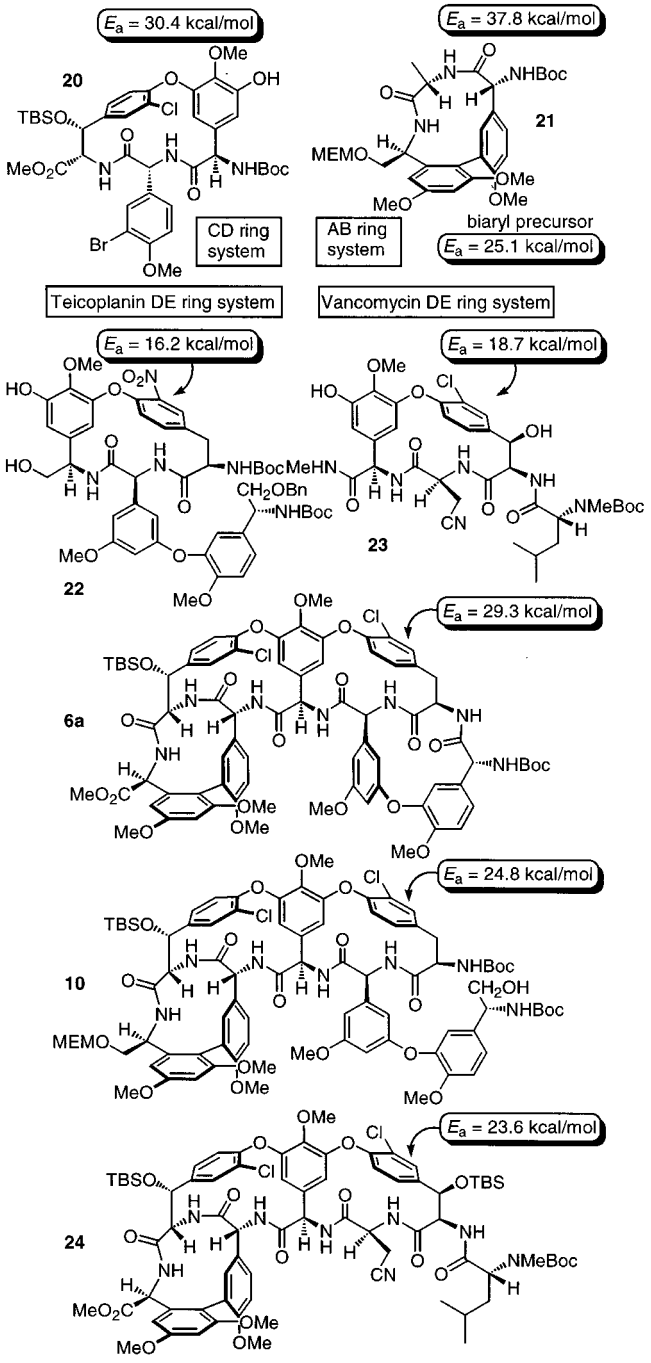


Figure 4.

ratio of atropisomers. Summarized in Figure 4 are the comparison parameters that have been established to date on related systems. Considering the relative substituent effects (NO_2 faster than Cl),[23] the isolated teicoplanin and vancomycin 16-membered DE ring systems isomerize with essentially the same ease (**22** versus **23**). The constraints of the intact FG ring system substantially slow the rate of DE ring system equilibration, whereas the bulky C_2[3] substituent of FG acyclo teicoplanin derivatives has only a modest effect (**6a** versus **10** relative to **24**). However, neither precludes selective DE ring system equilibration. The isomerism of the DE ring system in both teicoplanin and vancomycin is slowed by the fusion with the ABCD ring system by roughly 3.6−6.0 kcal/mol. Remarkably, each of these interconversions is substantially faster than the isomerism of the isolated 16-membered CD ring system **20**, even without the constraints of the AB ring system, and the origin of these distinctions is not obvious. Similarly, each of the DE ring systems isomerizes much more readily than the *O*-methylated AB ring system **21**, but is comparable to its isolated acyclic biaryl precursor. In contrast, the isolated AB ring system bearing the free phenols isomerizes even at room temperature.[21] Unlike the deprotected natural AB ring system (≥ 95:5) or its cyclic biaryl precursor (3:1),[20] the CD ring system (1:1) and both the vancomycin DE (1:1) and teicoplanin DE ring systems (1:1) exhibit no thermodynamic atropisomer preference.

Experimental Section

4a. Teicoplanin[37] (**1**, 1.32 g) in HOAc (90 mL) was treated with conc. HCl (10 mL), and the resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into Et_2O (700 mL), and the resulting precipitate was collected by filtration, washed with EtOAc (200 mL) and dried under vacuum to afford aglucoteicoplanin (**2**) as a crude residue. A solution of the crude **2** in DMF (15 mL) was treated sequentially with $NaHCO_3$ (159 mg, 1.89 mmol) and Boc_2O (276 mg, 1.26 mmol) at 0 °C. The reaction mixture was slowly warmed to 25 °C and stirred for 5 h before the dropwise addition of CH_3I (0.158 mL, 2.54 mmol) at 25 °C. The reaction mixture was stirred at 25 °C under Ar for 8 h. The mixture was cooled to 0 °C; quenched by the addition of H_2O (40 mL), followed by 10% aqueous HCl (5 mL); and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (30 mL) and saturated aqueous NaCl (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 2.5 × 20 cm, 14% CH_3OH−$CHCl_3$) afforded **4a**[33] (509 mg, 50% for 3 steps) as a white film.

4b. Teicoplanin[37] (**1**, 5.2 g) was dissolved in 41.6 mL of DMSO and 1.04 mL of 80% aqueous H_2SO_4 (v/v). The solution was warmed at 85 °C for 30 h, cooled to 25 °C, and 65 mL of H_2O was added. Activated charcoal (520 mg) was added to the cloudy solution, which was stirred for 1 h and filtered. The filtrate was neutralized (pH 7) under stirring by the addition of 10% aqueous NaOH, and the suspension that was obtained was cooled and left overnight at 5 °C. The solid was collected by filtration and dried under vacuum overnight to provide 4.8 g of crude teicoplanin aglycon. A sample of crude **2** (100 mg) prepared as described above was purified by semipreparative reverse-phase HPLC (Nova Pak C_{18}, 2.5 × 10 cm, CH_3CN−0.07% TFA/H_2O 18:82, 10 mL/min, t_R = 20 min) to afford pure aglucoteicoplanin (**2**, 29.0 mg) as a white film.[33] The crude aglycon was placed in DMF (15 mL) and treated with $NaHCO_3$ (697 mg, 8.3 mmol) and Boc_2O (905 mg, 4.15 mmol) at 25 °C for 2 h before $NaHCO_3$ (600 mg, 7.14 mmol) and benzyl bromide (3.31 mL, 27.8 mmol) were added. The mixture was stirred at 25 °C for 10 h, cooled to 0 °C, and 936 μL of HOAc was added to neutralize the mixture (pH 7). Most of the DMF was removed in vacuo, H_2O (50 mL) was added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL) and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (SiO_2, 7 × 20 cm, 10−15% MeOH−CH_2Cl_2 gradient elution) afforded **4b**[33] (1.74 g, 45% for 3 steps) as a white solid.

3: from 4b. 1 mg of 10% Pd/C was placed in MeOH (0.5 mL) and the mixture was saturated with H_2. A solution of **4b** (10 mg, 7.21 μmol) in MeOH (0.5 mL) was added and the mixture was stirred under 1 atm H_2 at 25 °C for 12 h. The Pd/C was removed by filtration through Celite, and the solvent was evaporated in vacuo to afford **3**[33] (8.9 mg, 95%) as a white powder.

5a. A solution of **4a** (509 mg, 0.387 mmol) in DMF (4 mL) was treated sequentially with K_2CO_3 (535 mg, 3.87 mmol) and CH_3I (0.48 mL, 7.8 mmol). The reaction mixture was stirred at 25 °C for 4.5 h, diluted with EtOAc (100 mL), cooled to 0 °C, quenched by the addition of 10% aqueous HCl (80 mL) at 0 °C, and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (40 mL) and saturated aqueous NaCl (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 2.5 × 20 cm, 6% CH_3OH−$CHCl_3$ gradient elution) afforded **5a**[33] (275 mg, 51%) as a white solid.

5b. A solution of **4b** (740 mg, 0.54 mmol) at 0 °C in DMF (8.5 mL) was treated with K_2CO_3 (723 mg, 5.4 mmol) and CH_3I (0.663

(37) Purchased from Advanced Separation Technologies Inc.

mL, 10.8 mmol). The mixture was stirred at 25 °C for 2 h, cooled to 0 °C, and 0.4 mL of HOAc was added (pH ~ 7). Most of the DMF was removed in vacuo, H_2O (30 mL) was added, and the mixture was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with H_2O (3 × 80 mL) and saturated aqueous NaCl (40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (SiO_2, 3.0 × 20 cm, 5% MeOH−CH_2Cl_2) provided **5b**[33] (692 mg, 88%) as a white solid.

6a. A solution of **5a** (219 mg, 0.16 mmol) in anhydrous CH_3CN (4 mL) was treated with $CF_3CONMeTBS$ (1.12 mL, 4.76 mmol) under Ar, and the resulting mixture was stirred at 45 °C for 13 h. The reaction mixture was poured into EtOAc−20% aqueous citric acid (3:1, 40 mL) and stirred at 25 °C for 30 min. The two layers were separated, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 2.5 × 20 cm, 50−75% EtOAc−hexane gradient elution) afforded **6a**[33] (190 mg, 80%) as a white film.

6b. A solution of **5b** (692 mg, 0.47 mmol) in anhydrous CH_3CN (15 mL) was treated with $CF_3CONMeTBS$ (2 mL, 8.48 mmol) at 45 °C for 11 h. The reaction mixture was cooled to 25 °C, and 3 mL of EtOAc and 1 mL of 5% aqueous citric acid were added. The mixture was stirred for 5 min at 25 °C. The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (SiO_2, 3.0 × 20 cm, 0−2% MeOH−CH_2Cl_2 gradient elution) yielded **6b**[33] (628 mg, 84%) as a white solid.

6c. A 2-mg sample of 10% Pd/C was placed in EtOH (0.5 mL), and the mixture was saturated with H_2. A sample of **6b** (9 mg, 5.7 μmol) was added, and the mixture was stirred under 1 atm H_2 at 25 °C for 12 h. The Pd/C was removed by filtration, and the solvent was evaporated in vacuo to provide **6c**[33](5.4 mg, 64%) as a pale yellow powder.

7: from 6a. A solution of **6a** (36.7 mg, 24 μmol) in anhydrous THF (2 mL) was treated sequentially with $LiBH_4$ (2 M solution in THF, 0.486 mL, 0.97 mmol) and $(MeO)_3B$ (32.7 μL, 0.29 mmol) at 0 °C. The reaction mixture was stirred at 45 °C for 9 h, cooled to 0 °C, quenched by the addition of 10% aqueous HCl (10 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (10 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 2.5 × 10 cm, 75−80% EtOAc−hexane gradient elution) afforded **7**[33] (27.6 mg, 77%) as a white solid.

7: from 6b. A solution of **6b** (360 mg, 0.23 mmol) in anhydrous THF (15 mL) was treated sequentially with $LiBH_4$ (2 M solution in THF, 4.51 mL, 9.02 mmol) and $(MeO)_3B$ (306 μL, 2.7 mmol) at 0 °C. The reaction mixture was stirred at 45 °C for 12 h, cooled to 0 °C, quenched by the addition of 5% aqueous HCl (10 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (10 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 3.0 × 20 cm, 75−80% EtOAc−hexane gradient elution) afforded **7**[33] (213 mg, 63%) as a white solid.

8. A solution of **7** (80.0 mg, 54 μmol) in anhydrous CH_2Cl_2 (2 mL) was treated sequentially with *i*-Pr_2NEt (564 μL, 3.24 mmol) and MEMCl (277 μL, 2.43 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 13 h, diluted with EtOAc (50 mL), cooled to 0 °C, quenched by the addition of 1% aqueous HCl (10 mL), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 15 cm, 0−75% EtOAc−hexane gradient elution) afforded **8**[33] (72.2 mg, 92%) as a white solid.

9. A solution of **8** (15.8 mg, 0.0l mmol) in 10% H_2O−EtOH (333 μL) was treated with $LiBH_4$ (9.0 mg, 0.41 mmol), and the mixture was stirred at 25 °C for 48 h. A solution of 1% HOAc−EtOH was added to adjust pH = 7, then EtOAc (30 mL) and saturated aqueous NH_4Cl were added. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 10 cm, 5−10% MeOH−CH_2Cl_2 gradient elution) afforded **9**[33] (10.4 mg, 66%) as a white solid.

10. A solution of **9** (2.4 mg, 1.5 μmol) in anhydrous CH_2Cl_2 (0.2 mL) was treated sequentially with $NaHCO_3$ (0.2 mg, 2.4 μmol) and Boc_2O (0.4 mg, 1.8 μmol) at 25 °C. The mixture was stirred at 25 °C for 3 h, cooled to 0 °C, and 1% aqueous HOAc was added to adjust the pH = 7. The mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 5% MeOH−CH_2Cl_2) afforded **10**[33] (2.5 mg, 98%) as a white powder.

11. A solution of **9** (7.5 mg, 4.8 μmol) in anhydrous CH_2Cl_2 (0.5 mL) was treated sequentially with $NaHCO_3$ (0.4 mg, 5.2 μmol) and TrocCl (0.72 μL, 5.3 μmol) at 25 °C. The mixture was stirred at 25 °C for 14 h, cooled to 0 °C, and 1% aqueous HOAc was added to adjust to pH = 7. The mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 0.7 × 6 cm, 5% MeOH−CH_2Cl_2) yielded **11**[33] (7.8 mg, 94%) as a white solid.

12. A solution of **9** (8.9 mg, 6.4 μmol) in 50% dioxane−H_2O was treated sequentially with Et_3N (1.3 μL, 9.5 μmol) and Teoc−OBt (2.7 mg, 9.5 μmol) at 25 °C. The mixture was stirred at 25 °C for 3 h before it was concentrated in vacuo. The residue was dissolved in EtOAc (20 mL), and the EtOAc phase was washed with 10% aqueous citric acid (2 × 10 mL), H_2O (5 mL), and saturated aqueous NaCl (5 mL); dried (Na_2SO_4); and concentrated in vacuo. Chromatography (SiO_2, 0.7 × 6 cm, 5% MeOH−CH_2Cl_2) yielded **12**[33] (7.9 mg, 81%) as a white solid.

16. A solution of **8** (10.8 mg, 6.9 μmol) in THF (300 μL) was treated with *n*-Bu_4NF−HOAc (1:1.2, 1 M solution in THF, 69 μL, 69 μmol) at 25 °C. The mixture was stirred at 25 °C for 15.5 h and quenched by the addition of 1% aqueous HCl (5 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 2 h and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 9% CH_3OH−$CHCl_3$) afforded **16**[33] (8.8 mg, 88%) as a white film.

Preparation of 8 from 16. A solution of **16** (1.8 mg, 1.24 μmol) in anhydrous CH_3CN (0.2 mL) was treated with $CF_3CONMeTBS$ (14.6 μL, 61.8 μmol) under Ar, and the resulting mixture was stirred at 50 °C for 13 h. The reaction mixture was poured into EtOAc−20% aqueous citric acid (3:1, 10 mL) and stirred at 25 °C for 1 h. The two layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 80% EtOAc−hexane) afforded **8**[33] (1.7 mg, 87%) as a white film.

Preparation of 7 from 8. A solution of **8** (6.1 mg, 3.8 μmol) in anhydrous CH_2Cl_2 (0.3 mL) was treated with *B*-bromocatecholborane (0.2 M in CH_2Cl_2, 195 μL, 37.8 μmol) at 0 °C for 2.5 h under Ar. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and stirred for 30 min. The two layers were separated, and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting amino alcohol was dissolved in THF (0.6 mL), and saturated aqueous $NaHCO_3$ (145 μL), followed by Boc_2O (2.5 mg, 11.3 μmol), was added. The reaction mixture was stirred at 25 °C for 1 h, diluted with EtOAc (5 mL), and quenched by the addition of 1% aqueous HCl (5 mL) at 0 °C. The two layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 80% EtOAc−hexane) afforded **7**[33] (4.3 mg, 76%) as a white film.

Preparation of 6a from 7. A solution of **7** (2.9 mg, 2.0 μmol) in anhydrous CH_2Cl_2 (0.6 mL) was treated with Dess−Martin periodinane (8.3 mg, 20 μmol) at 25 °C for 3 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched by the addition of saturated aqueous $NaHCO_3$−10% aqueous $Na_2S_2O_3$ (1:1, 1 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous NaCl (4 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting aldehyde in DMSO (0.4 mL) was treated sequentially with resorcinol (2.2 mg, 20 μmol) and a solution of $NaClO_2$ (80%, 1.1 mg, 10 μmol) and $NaH_2PO_4 \cdot 2H_2O$ (1.36

mg, 10 μmol) in H_2O (0.1 mL). The reaction mixture was stirred at 25 °C for 30 min, diluted with EtOAc (10 mL), and quenched by the addition of 1% aqueous HCl (2 mL) at 0 °C. The two layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 9% $CH_3OH-CHCl_3$) afforded the carboxylic acid, which was dissolved in toluene/CH_3OH (5:1, 1.2 mL) and treated with $TMSCHN_2$ (2.0 M solution in hexane) until the yellow color persisted. The mixture was stirred at 25 °C for 30 min, and concentrated in vacuo. PTLC (SiO_2, 75% EtOAc−hexane) afforded **6a**[33] (2.2 mg, 74%) as a white film.

Preparation of 5a from 6a. A solution of **6a** (6.2 mg, 4.1 μmol) in THF (200 μL) was treated with *n*-$Bu_4NF-HOAc$ (1:1.2, 1 M solution in THF, 41 μL, 41 μmol) at 25 °C. The resulting mixture was stirred at 25 °C for 15 h, diluted with EtOAc (5 mL), and quenched by the addition of 1% aqueous HCl (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 6% $CH_3OH-CHCl_3$) afforded **5a**[33] (4.4 mg, 78%) as a white film.

Preparation of 2 from 5a. A vial charged with **5a** (9.8 mg, 7.0 μmol) was treated with $AlBr_3$ (63 mg, 0.24 mmol) in EtSH (0.5 mL) under Ar. The resulting mixture was stirred at 25 °C for 3 h, diluted with $CHCl_3$ (0.5 mL), cooled to 0 °C, and quenched by addition of MeOH (0.1 mL). The solvent was removed by a stream of N_2. The crude mixture was purified by PTLC (SiO_2, EtOAc−MeOH−H_2O (5:2.5:1)) and semipreparative reverse phase HPLC (Nova Pak C_{18}, 2.5 × 10 cm, $CH_3CN-0.07\%$ TFA/H_2O 18:82, 10 mL/min, t_R = 20 min) to afford pure aglucoteicoplanin **2**[33] (4.2 mg, 46%) as a white film.

Preparation of 6c from 7. A solution of **7** (3.9 mg, 2.6 μmol) in anhydrous CH_2Cl_2 (1.0 mL) was treated with Dess−Martin periodinane (11 mg, 26.0 μmol) at 25 °C for 1 h. The reaction mixture was diluted with EtOAc (5 mL) and quenched by the addition of saturated aqueous $NaHCO_3$−10% aqueous $Na_2S_2O_3$ (1:1, 1 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous NaCl (4 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting aldehyde in DMSO (0.5 mL) was treated sequentially with resorcinol (6.1 mg, 55.4 μmol) and a solution of $NaH_2PO_4 \cdot 2H_2O$ (3.0 mg, 19.36 μmol) in H_2O (2 mL) and $NaClO_2$ (80%, 1.6 mg, 22.1 μmol) in H_2O (0.2 mL). The reaction mixture was stirred at 25 °C for 1 h, diluted with EtOAc (10 mL), and quenched by the addition of 1% aqueous HCl (2 mL) at 0 °C. The two layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 10% $CH_3OH-CH_2Cl_2$) afforded **6c**[33] (3.1 mg, 79%).

Preparation of 2 from 6c. A flask charged with $AlBr_3$ (125 mg, 0.47 mmol) was treated with anhydrous EtSH (2.0 mL). After the mixture was stirred for 10 min, **6c** (21.4 mg, 14.3 μmol) was added. The resulting mixture was stirred at 25 °C for 3 h, cooled to 0 °C, and quenched by addition of MeOH (2 mL). The solvents were removed in vacuo. The crude mixture was washed with ether (3 × 1 mL) and CH_2Cl_2 (3 × 1 mL) to yield a white solid. The solid was purified by semipreparative reverse-phase HPLC (Nova Pak C_{18}, 2.5 × 10 cm, $CH_3CN-0.07\%$ TFA/H_2O 18:82, 10 mL/min, t_R = 20 min) to afford pure aglucoteicoplanin **2**[33] (8.4 mg, 48%) as a white powder.

Preparation of 17 from 13. A vial charged with $AlBr_3$ (49.0 mg, 0.18 mmol) was treated with anhydrous EtSH (0.5 mL) under Ar. After the mixture was stirred for 10 min at room temperature, **13** (4.0 mg, 2.9 μmol) was added. The resulting mixture was stirred at 25 °C for 3 h, cooled to 0 °C, diluted with CH_2Cl_2, and quenched by the addition of MeOH (1 mL). The solvent was removed by a stream of N_2. The crude mixture was washed with Et_2O (3 × 0.5 mL) and CH_2Cl_2 (3 × 0.5 mL) to give a white solid. The solid was purified by semipreparative reverse-phase HPLC (Nova Pak C_{18}, 2.5 × 10 cm, $CH_3CN-0.07\%$ TFA/H_2O 17:83, 10 mL/min, t_R = 24.0 min) to afford pure **17**[33] (1.4 mg, 41%) as a white powder.

Thermal Interconversion of the Atropisomers 6a and 13. A solution of **6a** (6.3 mg, 4.2 μmol) in *o*-dichlorobenzene (0.6 mL) was warmed to 150 °C for 9 h. The solvent was removed under a stream of N_2. PTLC (SiO_2, 3% MeOH−CH_2Cl_2, developed two times) afforded 2.9 mg (46%) of pure **13**[33] as a white film and 3.0 mg (48%) of recovered **6a** as a white film.

Thermal Interconversion of the Atropisomers 10 and 14. A solution of **10** (6.8 mg, 4.1 μmol) in *o*-dichlorobenzene (0.6 mL) was warmed to 140 °C for 10 h. The solvent was removed under a stream of N_2. PTLC (SiO_2, 3% MeOH−CH_2Cl_2, developed three times) afforded **14**[33](2.9 mg, 43%) and recovered **10** (3.5 mg, 51%). Longer equilibration time provided an equilibrium 1:1 ratio of **10**:**14**.

Thermal Interconversion of the Atropisomers 12 and 15. A solution of **12** (6.1 mg, 3.5 μmol) in *o*-dichlorobenzene (0.6 mL) was warmed to 140 °C for 10 h. The solvent was removed under a stream of N_2. PTLC (SiO_2, 3% MeOH−CH_2Cl_2, developed three times) afforded **15**[33](2.5 mg, 41%) and recovered **12** (3.1 mg, 51%). Longer equilibration time provided an equilibrium 1:1 ratio of **12**:**15**.

Thermal Interconversion of the DE Atropisomers of 9. A solution of **9** (2.0 mg, 1.27 μmol) in DMSO-d_6 (0.4 mL) was warmed to 130 °C for 2 h. The solvent was removed under a stream of N_2. PTLC (SiO_2, MeOH−CH_2Cl_2−EtOAc 1:4.5:4.5, developed two times) afforded the DE atropisomer of **9**[33] (0.7 mg, 35%) as a white powder and recovered **9** (0.7 mg, 35%) as a white powder.

Epimerization of 8 to 18. A solution of **8** (3.1 mg, 1.98 μmol) in 33% H_2O−EtOH (3 mL) was treated with 30 mg of $NaHCO_3$. The mixture was stirred at 80 °C for 30 min and concentrated in vacuo. The mixture was dissolved in EtOAc (10 mL) and H_2O (5 mL), and the H_2O phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with H_2O (2 × 5 mL) and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 5% $CH_3OH-CH_2Cl_2$, developed two times) afforded **18**[33] (1.6 mg, 52%) as a white powder. HPLC (Nova PakC_{18}, 3.9 × 300 mm, $CH_3CN-0.07\%$ TFA/H_2O 75:25, 1.0 mL/min) of the crude mixture revealed a 95:5 mixture of **18** (t_R = 5.30 min) and **8** (t_R = 8.96 min).

Epimerization of 9 to 19. A solution of **9** (5.0 mg, 3.2 μmol) in 33% H_2O−EtOH (1 mL) was treated with 10.0 mg of $NaHCO_3$. The mixture was stirred at 80 °C for 4 h and concentrated in vacuo. The mixture was dissolved in EtOAc (10 mL) and H_2O (5 mL), and the H_2O phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with H_2O (2 × 5 mL), saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 5% $CH_3OH-CH_2Cl_2$, developed 3×) to afford **19**[33] (1.5 mg, 30%) as a white solid and 0.9 mg of recovered **9**.

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Supporting Information Available: Full characterization data for **2**, **3**, **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **6c**, **7**−**19**, and **A** are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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