Total Synthesis of the Vancomycin Aglycon

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Abstract: Full details of a diastereoselective total synthesis of the vancomycin aglycon are described. Two key aromatic nucleophilic substitution macrocyclizations with formation of the 16-membered diaryl ethers were enlisted for sequential CD and DE ring formations, an effective macrolactamization was developed for closure of the 12-membered biaryl AB ring system, and the defined order of CD, AB, and DE ring closures permitted selective thermal atropisomerism of the newly formed ring systems or their immediate precursors. This indirect control of the atropisomer stereochemistry allowed all synthetic material to be funneled into the one of eight atropdiastereomers characterizing the natural product.

Vancomycin is the prototypical member of a class of clinically important glycopeptide antibiotics[1−3] enlisted as the drugs of last resort for the treatment of resistant bacterial infections or for patients allergic to β-lactam antibiotics.[4] Its structural complexity, the interest in defining its structural features responsible for cell wall biosynthesis inhibition in sensitive bacteria,[5] the emergence of clinical resistance,[6] and the determination of its molecular origin have generated considerable interest in vancomycin and related agents.[7−13] Complementary to the efforts of Evans and Nicolaou,[9−11] herein we provide full details of a convergent total synthesis of the vancomycin aglycon (**1**).[12] In earlier efforts, we established that the CD and DE ring systems are most effectively closed through formation of the diaryl ether linkage,[14] and we subsequently explored,[15] implemented,[16] and improved[17,18] methodology amenable to macrocyclization of the sensitive vancomycin CD and DE ring systems. In completing the studies needed to define an approach to **1**, we disclosed an unusually effective macrolactamization for closure of the 12-membered biaryl AB ring system, and we described an indirect strategy for controlling the three stereochemical elements of atropisomerism.[16,17,19−21] Thus, two aromatic nucleophilic substitution macrocyclizations of the 16-membered diaryl ethers are enlisted for sequential CD and DE ring formations, a key macrolactamization reaction is employed for cyclization of the AB ring system, and the defined order of CD, AB, and DE ring closures permits selective thermal atropisomerism of the newly formed ring systems or their immediate precursors (Figure 1). In addition to any diastereo-

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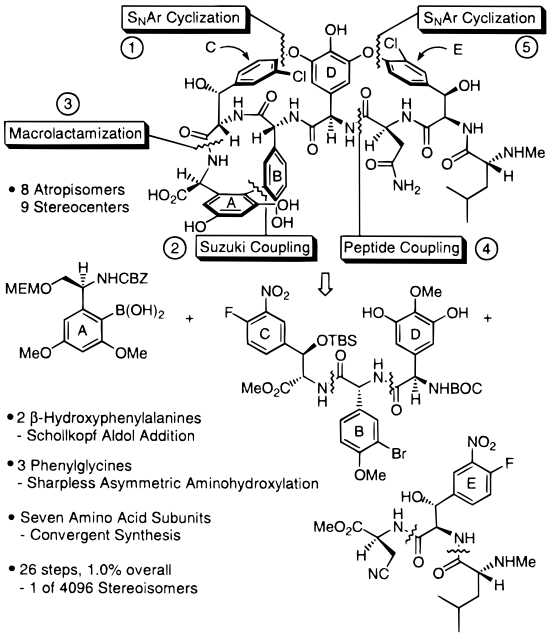


Figure 1.

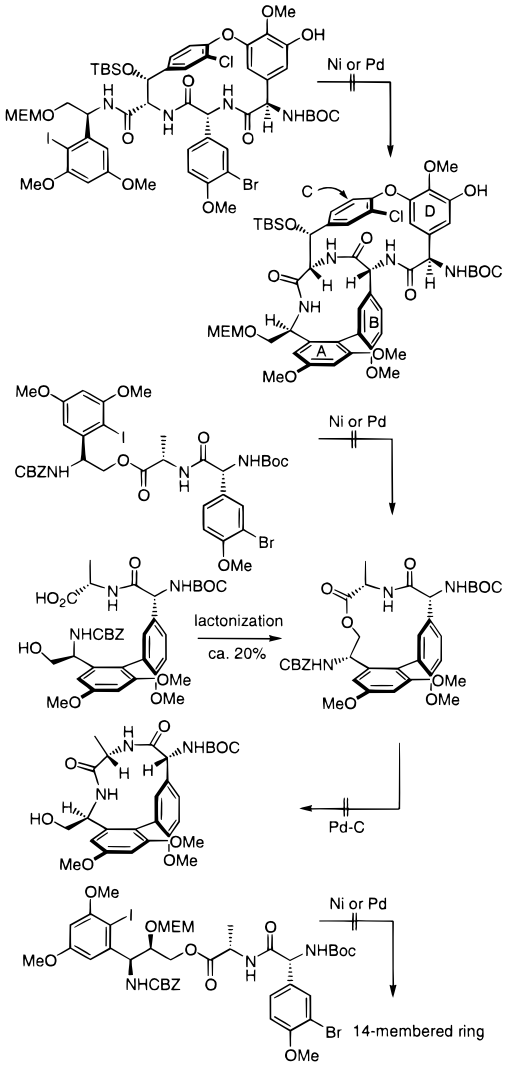
selection that may be achieved in the ring closures, this order permits the recycling of any undesired atropisomer for each ring system and provides predictable control of the stereochemistry, dependably funneling all synthetic material into the one of eight atropdiastereomers characterizing the natural product. Key to recognition of this order was our establishment of the thermodynamic parameters of atropisomerism: DE ring system (E_a = 18.7 kcal/mol) < AB biaryl precursor[12] (E_a = 25.1 kcal/mol) < CD ring system (E_a = 30.4 kcal/mol).[16,17,19−21]

Model AB Ring System Studies. Following studies that defined routes to the CD and DE ring systems and which established the activation parameters for their thermal atropisomerism,[16,17] only the development of an approach to the 12-membered biaryl AB ring system remained to be addressed. Initial attempts to close the AB ring system by an intramolecular biaryl coupling reaction on fully substituted model systems proved relatively unsuccessful. Not only were attempts to form the biaryl linkage with closure of the 12-membered ring unsuccessful, but preliminary efforts to first form a 13- or 14-membered ring followed by an intramolecular amination of a lactone also were not encouraging (Scheme 1).

Concurrent with these efforts, studies of a macrolactamization closure of the 12-membered ring were unusually successful. More importantly, the route proceeds through a noncyclized biaryl precursor that possessed atropisomerism activation parameters and a favorable thermodynamic ratio of atropisomers that exceeded those accessible through the biaryl cyclization route. These attributes led us to adopt the macrolactamization route in lieu of the biaryl cyclization route, although the latter might well prove successful with further study.

The A ring amino acid precursor was prepared by enlisting a Sharpless asymmetric aminohydroxylation reaction on 3,5-dimethoxystyrene, as detailed[23] (0.05 equiv of $(DHQ)_2PHAL$, 0.04 equiv of $K_2Os_2(OH)_4$, 3.1 equiv of $BnOCONH_2$, 3.05 equiv of *t*-BuOCl, 3.05 equiv of NaOH, *n*-PrOH/H_2O (1:1) 25 °C, 30 min, 60%, 92% ee). Regioselective aromatic bromination of **3**

Scheme 1



(1 equiv of NBS, CH_3CN, 0 °C, 30 min, 95%), MEM ether protection of **4** (3 equiv of MEMCl, 4 equiv of *i*-Pr_2NEt, CH_2Cl_2/THF (2:1), 25 °C, 22 h, 96%), and subsequent conversion of **5** to the boronic acid **6** (59%) provided the A ring precursor for Suzuki biaryl coupling (Scheme 2). This latter reaction entailed sequential carbamate deprotonation (1.5 equiv of *i*-PrMgBr, 0 °C, 30 min) and metal−halogen exchange (2.4 equiv of *t*-BuLi, −78 °C, 5−10 min), followed by trap of the intermediate aryllithium with $(MeO)_3B$ (8 equiv, −78 to 0 °C, 30 min) to provide **6** after hydrolytic workup.[24] Intermolecular Suzuki biaryl coupling of **6** with the model dipeptide **9**[25] incorporating the B ring amino acid proceeded unexpectedly well, given the steric congestion and electron-rich character of the coupling partners. Because the boronic acid was sensitive to typical reaction conditions, which resulted in its decomposition, the use of catalysts and conditions which accelerate the oxidative addition proved key to implementation of this coupling. Its success was largely dependent on the use of $Pd_2(dba)_3$ (0.3 equiv) in the presence of (*o*-tolyl)$_3$P (1.5 equiv), following protocols introduced by Hartwig,[26] and was found to be most effective in the toluene−CH_3OH−H_2O solvent system at 80 °C. Other catalysts including $(Ph_3P)_4Pd$ or other phosphine

(22) The natural AB atropisomers within the ABCD and ABCDE ring systems of vancomycin are also the thermodynamically most stable (≥95:5), ensuring that the subsequent DE equilibration does not affect the AB stereochemistry.

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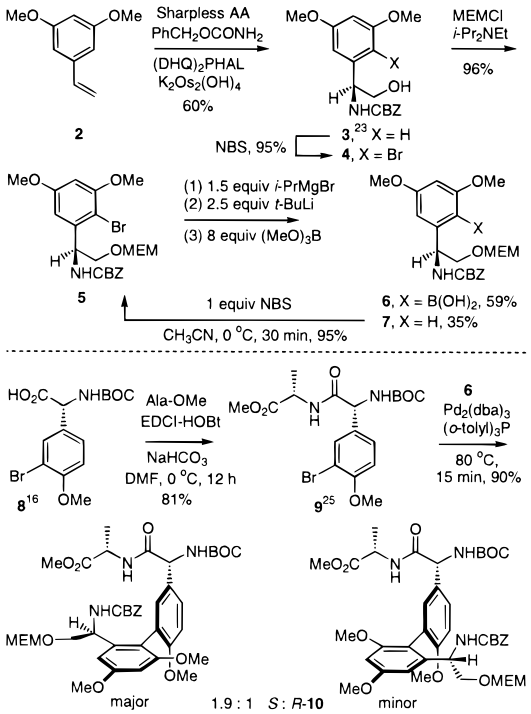
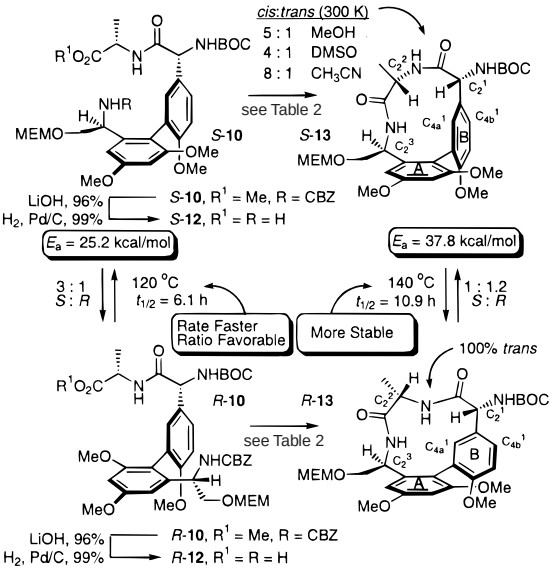
Scheme 2



Scheme 3



ligands shown to accelerate oxidative addition (DPPF, (*S*)-BINAP, tri-2-furylphosphine) and alternative reaction conditions (DMF) were less successful or failed altogether.

While the coupling provided a 2:1 mixture of biaryl atropisomers with the natural *S*-isomer predominating (Scheme 2), thermal equilibration at 120 °C provided an improved 3:1 mixture, with the natural *S*-isomer being the major product (Scheme 3). The fact that the atropisomers are stable at 25 °C but readily equilibrate at 120−130 °C (Table 1) with an energy of activation (E_a = 25.2 kcal/mol) that lies between those of the CD and DE ring systems (E_a = 30.4 and 18.7 kcal/mol, respectively) to provide a favorable 3:1 ratio of *S*:*R* atropisomers made this the ideal point at which to introduce and adjust the AB atropisomer stereochemistry.

Sequential ester hydrolysis and NCBZ deprotection of **10** provided the amino acid **12**, possessing the natural atropisomer stereochemistry, on which the key cyclization studies were

Table 1

compd	conditions	k (h^{-1})	$t_{1/2}$ (h)
10[a]	*o*-$Cl_2C_6H_4$, 120 °C	0.08	6.12
10	*o*-$Cl_2C_6H_4$, 140 °C	0.37	1.28
13[b]	*o*-$Cl_2C_6H_4$, 140 °C	0.029	10.9
13	*o*-$Cl_2C_6H_4$, 150 °C	0.087	3.66

[a] For **10** (*o*-$Cl_2C_6H_4$): E_a = 25.2 kcal/mol, $\Delta H^{\ddagger}$ = 24.2 kcal/mol, $\Delta S^{\ddagger}$ = −2.5 eu, $\Delta G^{\ddagger}$ (120 °C) = 25.2 kcal/mol. [b] For **13** (*o*-$Cl_2C_6H_4$): E_a = 37.8 kcal/mol, $\Delta H^{\ddagger}$ = 35.2 kcal/mol, $\Delta S^{\ddagger}$ = −19.1 eu, $\Delta G^{\ddagger}$ (130 °C) = 42.9 kcal/mol.

Table 2

reagents[27]	conditions (30 min addn, 25 °C)	yield of *S*-**13** (%)
HATU/*i*-Pr_2NEt, 1.5/3.0 equiv	0.001 M DMF	91
HATU/DMAP, 2.0/3.0 equiv	0.001 M DMF	90
EDCl/HOAt, 3.0/3.0 equiv	0.004 M 20% DMF−CH_2Cl_2	75[a]
EDCl/HOBt, 3.0/3.3 equiv	0.002 M DMF (4.5 h)	60[b]
PyBOP/DMAP, 2.0/3.0 equiv	0.001 M DMF	91
PyBOP/DMAP, 2.0/3.0 equiv	0.001 M THF	73[c]
PyBOP/DMAP, 2.0/3.0 equiv	0.001 M CH_2Cl_2	trace[d]

reagents[27]	conditions (30 min addn, 25 °C)	yield of *R*-**13** (%)
HATU/DMAP, 3.0/4.0 equiv	0.001 M DMF	81
PyBOP/DMAP, 3.0/4.0 equiv	0.001 M DMF	74

[a] 8% cyclic dimer. [b] 18% cyclic dimer. [c] 17% cyclic dimer. [d] 86% cyclic dimer.

conducted. Closure of *S*-**12** to **13** was unusually effective under a range of macrocyclization conditions (Table 2). The ring closure was fast and was conducted in DMF with slow addition (30 min) of the substrate to a dilute reaction mixture containing reagents. Under these conditions, the reaction was done essentially upon completion of the addition, providing *S*-**13** with little or no trace of cyclic dimer. The reaction proved sensitive to the choice of solvent (DMF), and ring closures conducted in CH_2Cl_2, THF, or mixed solvent systems of DMF−CH_2C1_2 were typically less successful. The comparisons of the PyBOP/DMAP[27] closures are notable in this regard, with the reaction conducted in DMF providing exclusively *S*-**13** (91%), while the reactions in THF and CH_2Cl_2 provided significant amounts of (17%, THF) or predominantly (86%, CH_2Cl_2) the cyclic dimer.[28] In only one instance was the epimerized $C_2{}^2$ diastereomer detected in small amounts, and these observations serve as interesting contrasts to those we made in closing the AB ring system within the confines of the preformed CD ring system.

In an analogous fashion, *R*-**12**, possessing the unnatural atropisomer stereochemistry, could be cyclized effectively to provide *R*-**13** (75−84%, Table 2), albeit with rates that were substantially slower (24 h vs 30 min). Thus, while the cyclization of *S*-**12** with HATU−DMAP[27] was complete upon addition (30 min), the closure of *R*-**12** under identical conditions gave no detectable product after 40 min but provided *R*-**13** in 81% yield after 24 h. In addition, the clean closure of *R*-**12** without $C_2{}^2$

(27) Abbreviations: PyBOP = benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; HATU = 2-(1*H*-7-azabenzotriazol-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate; EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole; HOAt = 1-hydroxy-7-azabenzotriazole; FDPP = pentafluorophenyl diphenylphosphinate.

(28) For cyclic dimer of *S*-**13**: ^{1}H NMR (CD_3OD, 600 MHz) δ 7.78 (br s, 1H, NH), 7.35 (br s, 2H), 7.01 (d, J = 8.7 Hz, 1H), 6.56 (s, 1H), 6.49 (s, 1H), 5.09 (br s, 1H), 4.63 (br s, 2H), 4.38 (d, J = 5.0 Hz, 1H), 4.28 (s, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.65 (s, 3H), 3.43−3.36 (m, 6H), 3.33 (s, 3H), 1.41 (s, 9H), 0.96 (d, J = 6.7 Hz, 3H); FABHRMS (NBA-CsI) m/z 1367.5012 (M^+ + Cs, $C_{62}H_{86}N_6O_{20}$ requires 1367.4951).

Scheme 4

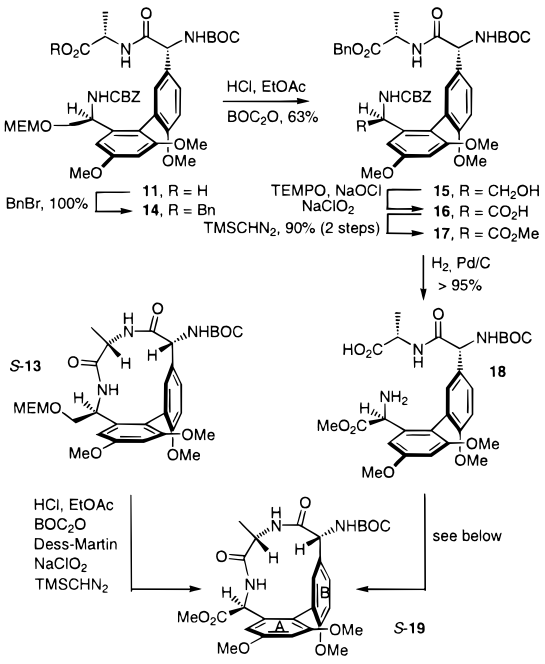


Table 3

reagents[27]	conditions (30 min addn, 25 °C)	yield of *S*-**19** (%)
HATU/DMAP 3.0/4.0 equiv	0.001 M 25% DMF−CH_2Cl_2	70
HATU/DMAP, 3.0/4.0 equiv	0.001 M DMF	63
EDCl/HOBt, 3.0/3.3 equiv	0.001 M DMF	35
PyBOP/DMAP, 3.0/4.0 equiv	0.001 M DMF	60

epimerization was observed, and this stands in contrast to the C_2[3] epimerization that accompanies closure of the unnatural atropisomer within the confines of the CD ring system.[10]

Significantly, the thermal atropisomerism of the cyclized AB ring system was much slower than that of the acyclic precursor, with an E_a = 37.8 kcal/mol and an equilibrium 1:1.2 mixture of isomers favoring the unnatural atropisomer (Table 1). Thus, the milder isomerization conditions and more favorable atropisomer ratio obtained with **10** versus **13** provided the basis for the decision to introduce and adjust the AB atropisomer stereochemistry on an acyclic precursor analogous to **10**. Following this introduction and adjustment of stereochemistry, its closure to the 12-membered AB ring system would then be expected to provide a thermally stable intermediate suitable for subsequent DE atropisomer introduction and equilibration.

The stereochemical assignments for *S*- and *R*-**13** were established by 2D ^{1}H NMR on the cyclic AB ring system. The natural *S*-atropisomer, which adopts a cis amide conformation between residues 1 and 2, exhibits a strong and diagnostic set of NOEs between $C_2{}^2$−H and both $C_2{}^1$−H and $C_{4a}{}^1$−H and between $C_2{}^1$−H and $C_{4a}{}^1$−H. The unnatural *R*-atropisomer adopts an all-trans amide conformation and exhibits a $C_2{}^1$−H /$C_{4b}{}^1$−H NOE but not the diagnostic $C_2{}^2$−H/$C_{4a}{}^1$−H or $C_2{}^1$−H/$C_{4a}{}^1$−H NOEs.

In addition, a more limited study of the cyclization of **18**, which possesses the C-terminus carboxylic acid protected as its methyl ester, was also conducted (Scheme 4). The amino acid *S*-**18** also closed effectively to *S*-**19** under a range of conditions, although typically the yields were lower and the rates of closure slower (Table 3). The correlation of *S*-**19** derived from cyclization of *S*-**18** with that derived from *S*-**13** confirmed that ring closure proceeded without epimerization of the methyl

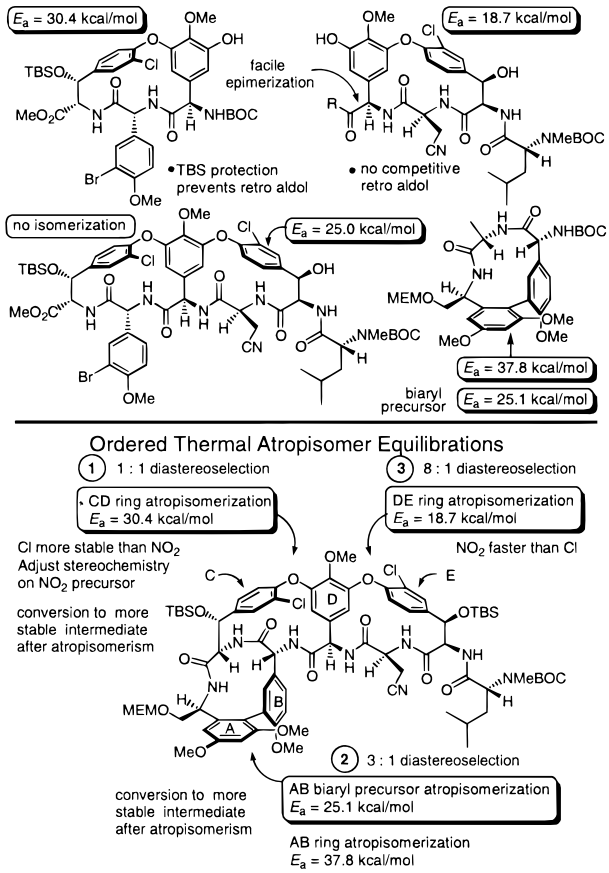


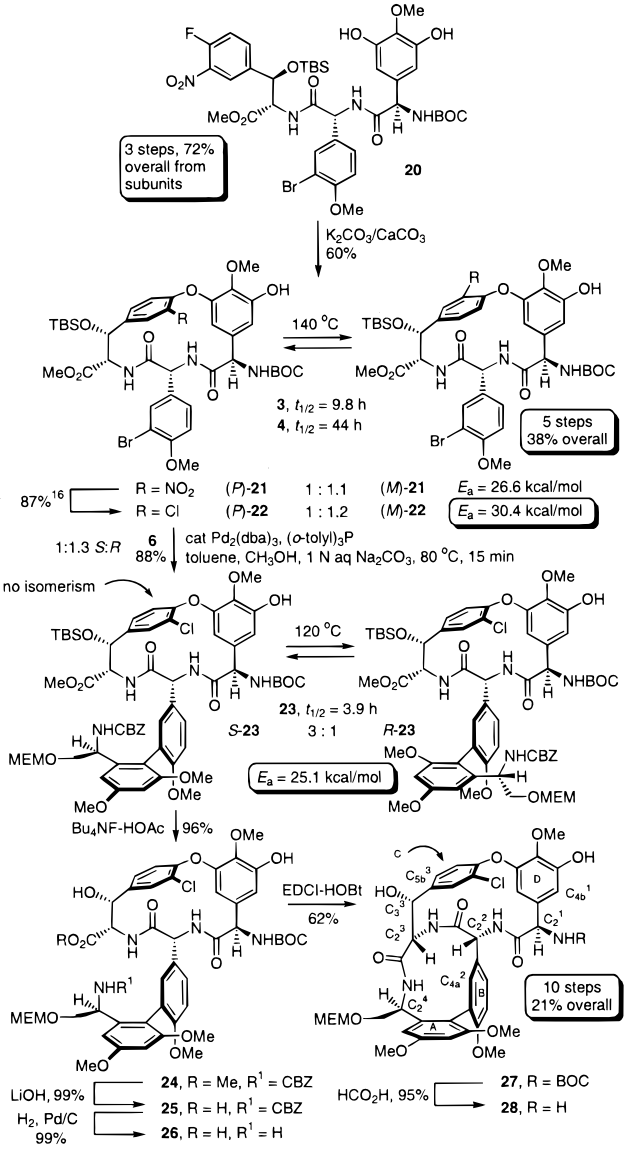
Figure 2. Key partial structures: model studies.

ester. This less effective closure of **18**, coupled with concerns that the C-terminus methyl ester might not withstand the conditions of DE ring closure (CsF, DMSO) without epimerization, and with this establishment that a precursor alcohol analogous to **13** could be oxidized to the corresponding carboxylic acid, provided the basis for the decision to implement the AB ring introduction with a C-terminus MEM-protected alcohol, even though this may not be required.

Total Synthesis of the Vancomycin Aglycon. When combined with the thermodynamic parameters we established for the atropisomerism of the CD and DE ring systems, the intermediate ease of isomerism of the acyclic AB biaryl precursor defined a rational order to the introduction of the three ring systems (Figure 2). Moreover, the greater ease of isomerism of a CD aryl nitro intermediate prior to introduction of the aryl chloride (E_a = 26.6 vs 30.4 kcal/mol), and the analogous greater stability of the cyclized AB ring system (E_a = 37.8 vs 25.1 kcal/mol), permit the adjustment of stereochemistry on an intermediate that readily equilibrates, followed by its subsequent conversion to a synthetic intermediate which is thermally more stable. Complementing these observations, we also recently disclosed the ease and extent (K_2CO_3, DMF, <5 min; *R*:*S* >99:1 to ≥3:97) with which the central D ring phenylglycine epimerizes within the isolated DE ring system, which would preclude the activation and coupling of its C-terminus carboxylic acid, required of an approach where the CD ring system introduction follows that of the DE ring system.

The tripeptide **20** was assembled in three steps (72% from the constituent amino acids) and cyclized to provide the CD ring system, bearing an aryl nitro group as a 1:1 mixture of *P*:*M* atropisomers. This was described in full detail previously[16] and was carried out under conditions (K_2CO_3/$CaCO_3$) that trap the liberated fluoride and prevent OTBS deprotection, which

Scheme 5



in turn is required in order to prevent retro aldol ring-opening under the subsequent thermal conditions of atropisomerism. Equilibration and recycling of the unnatural atropisomer *M*-**21** and two-step conversion of *P*-**21** to *P*-**22** were accomplished as disclosed (Scheme 5).[16,17] Both the ease of isomerization and the thermodynamic ratio of the atropisomers were more favorable with **21** versus **22**, such that the former was enlisted for equilibration while conversion to the latter enhanced the thermodynamic stability of the CD ring system throughout the synthesis (Table 4). This proved to be the only ring system for which no diastereoselection was achieved in its synthesis, but it occurs at an early stage in the synthesis, where all the unnatural atropisomer was funneled into the synthesis through this thermal atropisomerism. Suzuki biaryl coupling of *P*-**22** with **6** (0.3 equiv of $Pd_2(dba)_3$, 1.5 equiv of (*o*-tolyl)$_3$P, toluene/CH_3OH/1 M aqueous Na_2CO_3 10/3/1, 80 °C, 15 min) following protocols established with the model AB ring system provided a 1:1.3 mixture of *S*:*R* **23** in excellent yield (88%). More significantly than observed in the model coupling reaction, $(Ph_3P)_4Pd$ was unsuccessful at promoting this reaction. Analogous to observations made with a model AB precursor (Scheme 3), thermal equilibration of the separable atropdiastereomers under conditions where the CD atropisomer was stable provided

Table 4

compd	conditions	k (h^{-1})	$t_{1/2}$ (h)
21[a]	DMSO, 140 °C	0.082	3.52
21	DMSO, 155 °C	0.27	1.06
21	*o*-$Cl_2C_6H_4$, 140 °C	0.029	9.77
22[b]	*o*-$Cl_2C_6H_4$, 140 °C	0.0065	44.0
22	*o*-$Cl_2C_6H_4$, 150 °C	0.016	14.2
23[c]	*o*-$Cl_2C_6H_4$, 120 °C	0.13	3.88
23	*o*-$Cl_2C_6H_4$, 135 °C	0.41	1.02
33[d]	*o*-$Cl_2C_6H_4$, 120 °C	0.052	5.0
33	*o*-$Cl_2C_6H_4$, 140 °C	0.24	1.1
35[e]	*o*-$Cl_2C_6H_4$, 110 °C	0.033	8.24
35	*o*-$Cl_2C_6H_4$, 130 °C	0.11	2.78
35	*o*-$Cl_2C_6H_4$, 140 °C	0.35	0.82

[a] For **21** (DMSO): E_a = 26.6 kcal/mol, $\Delta H^{\ddagger}$ = 27.0 kcal/mol, $\Delta S^{\ddagger} = -1.7$ eu, $\Delta G^{\ddagger}$ (130 °C) = 27.7 kcal/mol. [b] For **22** (*o*-$Cl_2C_6H_4$): E_a = 30.4 kcal/mol, $\Delta H^{\ddagger}$ = 29.7 kcal/mol, $\Delta S^{\ddagger} = -2.7$ eu, $\Delta G^{\ddagger}$ (140 °C) = 30.8 kcal/mol. [c] For **23** (*o*-$Cl_2C_6H_4$): E_a = 25.1 kcal/mol, $\Delta H^{\ddagger}$ = 24.2 kcal/mol, $\Delta S^{\ddagger} = -1.6$ eu, $\Delta G^{\ddagger}$ (120 °C) = 24.8 kcal/mol. [d] For **33** (*o*-$Cl_2C_6H_4$): E_a = 24.8 kcal/mol, $\Delta H^{\ddagger}$ = 24.7 kcal/mol, $\Delta S^{\ddagger} = -2.3$ eu, $\Delta G^{\ddagger}$ (120 °C) = 25.6 kcal/mol. [e] For **35** (*o*-$Cl_2C_6H_4$): E_a = 23.6 kcal/mol, $\Delta H^{\ddagger}$ = 22.9 kcal/mol, $\Delta S^{\ddagger} = -6.2$ eu, $\Delta G^{\ddagger}$ (130 °C) = 25.4 kcal/mol.

Table 5

		yield (%)	
reagents[27]	conditions (25 °C)	**27**	*epi*-**27**
EDCl/HOBt, 5.5/5.0 equiv	0.002 M 20% DMF−CH_2Cl_2 (0 °C)	62	10−17
EDCl/HOBt, 5.0/5.0 equiv	0.002 M 20% DMF−CH_2Cl_2	51	15
EDCl/HOBt, 5.0/5.0 equiv	0.002 M DMF	16	54
EDCl/HOBt, 5.0/5.0 equiv	0.002 M CH_2Cl_2	trace	trace
EDCl/HOAt, 5.0/5.0 equiv	0.001 M 20% DMF−CH_2Cl_2	30	34
PyBOP/DMAP, 4.0/4.0 equiv	0.002 M DMF	trace	60
PyBOP/DMAP, 4.0/4.0 equiv	0.002 M 20% DMF−CH_2Cl_2	trace	60
HATU/DMAP, 5.0/5.0 equiv	0.002 M DMF (0 °C)	25	50
FDPP/DMAP, 5.0/5.0 equiv	0.002 M DMF	63	14

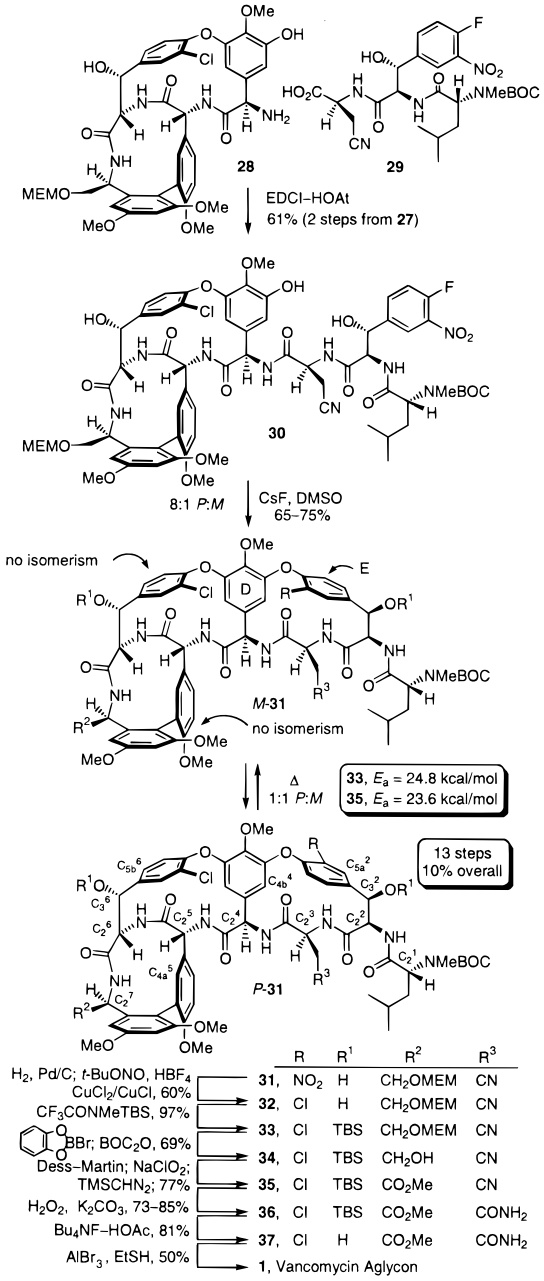
an equilibrium 3:1 ratio of *S*:*R* **23** in which the natural isomer predominated (Table 4). The minor, unnatural *R*-**23** was recycled through use of this thermal equilibration. Silyl ether deprotection of *S*-**23** under conditions that suppress retro aldol cleavage of the CD ring system (4 equiv of Bu_4NF, 5 equiv of HOAc, THF, 25 °C, 6 h, 96%),[16] methyl ester hydrolysis (LiOH, 99%), and NCBZ deprotection of **25** (H_2, catalytic 10% Pd/C, 99%) provided **26**, the precursor for AB cyclization. Enlisting conditions developed with the model tripeptide **12**, macrolactamization was effected by treatment with EDCI/HOBt[27] (5 equiv/5 equiv, CH_2Cl_2/DMF 5:1, 0.002 M, 0 °C, 16 h) to provide **27** (62%), possessing the natural vancomycin ABCD atropisomer stereochemistry (50% from **22** and 21% overall from the constituent amino acid subunits). The atropisomer stereochemistry and the stereochemical integrity of the labile C_2^3 center were established by 2D ^{1}H NMR, with the observation of C_2^2−H/C_{4a}^2−H, C_2^3−H/C_{4a}^2−H, C_2^2−H/C_2^3−H, C_2^3−H/C_{5a}^3−H, and C_3^3−H/C_{5a}^3−H NOEs. The closure of the AB ring system within the confines of the CD ring system proved more sensitive to the reaction conditions than the simpler model system. The most successful conditions enlisted EDCI/HOBt at 0 °C in 20% DMF−CH_2Cl_2, providing a 62% yield of **27** accompanied by the separable C_2^3 epimer (17%). Predominant or nearly exclusive closure with epimerization of the C_2^3 center was typically observed under conditions employing a strong base (DMAP) or when the reaction was conducted in DMF (Table 5). The exception to this generalization is the conditions similar to those

enlisted by Nicolaou and co-workers[10] (FDPP),[27] which in recent comparison studies we found provide near identical results with our EDCI/HOBt closure. Notably, the unnatural AB atropisomer derived from *R*-**23** failed to close effectively under comparable conditions, and the preliminary attempts at closing *R*-**26** provided multiple products and were not further pursued.

Although this was not examined in detail, the ABCD ring system **27** proved remarkably stable to attempts at thermal atropisomer interconversion, even at 140 °C, and only after 60−70 h was partial isomerism detected competitive with decomposition. From these studies, it appeared as if the CD ring system interconverts, albeit very slowly, without alteration of the AB stereochemistry. While this would be consistent with the relative ease of CD versus AB atropisomerism, it is also consistent with the observation that the natural AB atropisomer stereochemistry within the ABCD ring system is thermodynamically favored (≥95:5). More importantly, it ensures that a subsequent adjustment of the DE atropisomer stereochemistry may be thermally conducted without alteration of the AB or CD stereochemistry.

Selective NBOC deprotection of **27** ($HCO_2H-CHCl_3$ 1:1, 95%), followed by coupling of **28** with **29**[16] (1.6 equiv of EDCI, 1.6 equiv of HOAt, THF, 0 °C, 30 min, 61%), provided **30** and set the stage for DE macrocyclization. Much lower yields of **30** were obtained in coupling reactions conducted in DMF, where extensive epimerization of the β-cyanoalanine subunit was observed. Even in THF, this epimerization was problematic and responsible for the modest yields. Diaryl ether formation proceeded cleanly upon treatment of **30** with CsF (6 equiv, DMSO, 25 °C, 7−12 h, 65−75%) to provide an 8:1 mixture of *P*:*M* **31**, with the natural DE atropisomer predominating (Scheme 6). The atropisomer stereochemistry of the newly introduced DE ring system and the stereochemical integrity of the ABCD ring system were established by 2D ^1H NMR, with the observation of diagnostic C_3^2-H/C_{5b}^2-H NOEs for *P*-**31** and C_3^2-H/C_{5b}^2-H NOEs for *M*-**31**, along with C_2^5-H/C_{4a}^5-H, C_2^5-H/C_2^6-H, C_2^6-H/C_{4a}^5-H, C_3^6-H/C_{5a}^6-H, and C_2^6-H/C_{5a}^6-H NOEs. This preferential generation of the natural stereochemistry was first disclosed by Evans[8,9] with closely related substrates (5:1) but contrasts closures described by Nicolaou[10] (1:3), where the unnatural atropisomer predominated with an alternative substrate and method of closure. Thermal equilibration of the minor *M*-atropisomer provided a 1:1 mixture of *P*:*M* **31**, allowing the unnatural DE atropisomer to be recycled. Moreover, thermal atropisomerism of both **31** and **33** could be conducted without affecting the AB or CD stereochemistry, analogous to our prior observations with **35**,[21,22] and those conducted with **33** and **35** were much cleaner due to suppressed competing retro aldol reactions (Table 4).[21] Sandmeyer substitution with introduction of the E-ring chloride was accomplished without loss of the DE atropisomer stereochemistry (H_2, 10% Pd/C, EtOAc, 25 °C, 4 h; 1.3 equiv of *t*-BuONO, 1.3 equiv of HBF_4, CH_3CN, 0 °C, 10 min; 65 equiv of $CuCl_2$, 55 equiv of CuCl, H_2O-CH_3CN, 25 °C, 0.5 h, 60% overall).[16] In conversions that have been optimized since our preliminary disclosure, TBS protection of the secondary alcohols (65 equiv of $CF_3CONMeTBS$, CH_3CN, 55 °C, 22 h; aqueous citric acid, 25 °C, 13 h, 97%),[21] MEM ether deprotection (*B*-bromocatecholborane, CH_2Cl_2, 0 °C, 2 h; BOC_2O, 69% for two steps), and two-step alcohol oxidation (Dess−Martin periodinane, CH_2Cl_2, 0 °C, 15 min then 25 °C, 1 h; $NaClO_2$, 0.7 M NaH_2PO_4, isobutene/*t*-BuOH 1/4, 25 °C, 20 min), followed by immediate methyl ester formation ($TMSCHN_2$), provided **35** (77%, three steps), which was identical to material derived from natural vancomycin.[21] The final three steps in the conversion of **35** to **1** followed our disclosed sequence.[21] Significantly, the final step involves clean cleavage of the methyl ester and four methyl ethers, and NBOC deprotection under conditions first enlisted by Evans.[8]

Scheme 6



	R	R^1	R^2	R^3
31,	NO_2	H	CH_2OMEM	CN
32,	Cl	H	CH_2OMEM	CN
33,	Cl	TBS	CH_2OMEM	CN
34,	Cl	TBS	CH_2OH	CN
35,	Cl	TBS	CO_2Me	CN
36,	Cl	TBS	CO_2Me	$CONH_2$
37,	Cl	H	CO_2Me	$CONH_2$

The convergent assemblage of **1** from the seven individual amino acid subunits required 24 steps[30] (1.0% overall). Given the concise, modular nature of the synthesis and its reliable control of the atropisomer stereochemistry, it is especially suited for the preparation of key analogues and such studies are in progress.

The key partial structures and derivatives of the vancomycin aglycon were tested for antimicrobial activity against vancomycin sensitive and resistant bacteria (Table 6). The fully functionalized ABCD ring systems **27** and **28** were inactive, the vancomycin aglycon possessing the unnatural DE atrop-

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

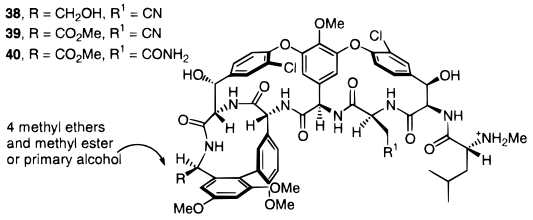
(30) Excluding as steps the thermal isomerization of the unnatural atropisomers.

Table 6

	MIC (μg/mL)				
	Staphylococcus aureus	*Enterococcus faecium*		*Enterococcus faecalis*	
compound	(ATCC 25923)	(ATCC 35667)	vancomycin resistant	Van A BM 4166	Van B ATCC 51299
27 (ABCD)	>842[a]	>842[a]	>842[a]	>842[a]	>842[a]
28 (ABCD)	>417[a]	>417[a]	>417[a]	>417[a]	>417[a]
38	0.7	1.4	<700[a]	22	5
39	<0.5	1.9	1.9	30	1.9
40	0.7	1.4	45	nd	nd
1	0.7	2.8	560	560	280
(*M*)-**1**	14	28	>1800[a]	nd	nd
vancomycin	1.25	2.5	250	1425	125

[a] Highest dose tested. [b] Not determined.

isomer stereochemistry (*M*-**1**) proved to be 10−20 times less active than the natural aglycon, and the deprotected derivatives of **32**, **35**, and **37** (**38**−**40**) were equipotent or more potent than the natural aglycon. Thus, the permethyl derivative **40**,[21] where



the four phenols were capped as methyl ethers and the *C*-terminus carboxylic acid was in the form of a methyl ester, was found to be 1−4 times more potent than the vancomycin aglycon. More significantly, the deprotected derivatives of **32** and **35** (**38** and **39**), containing the four phenol methyl ethers, the *C*-terminus primary alcohol or methyl ester, and the asparagine nitrile versus carboxamide, proved not only comparable or more potent than **1** in the vancomycin sensitive cell lines but essentially as effective against VanB *Enterococcus faecais*, which is vancomycin resistant due to the incorporation of the cell wall precursor peptidoglycan terminating in D-Ala-D-Lac. Thus, **38** and **39** showed little or no alteration in the MIC values for VanB *Enterococcus faecais* versus the vancomycin sensitive bacteria and both were ca. 100× more potent than the vancomycin aglycon and ca. 50× more potent than vancomycin itself. There were also surprisingly effective against VanA *Enterococcus faecais* which produces cell wall precursors terminating in D-Ala-D-Lac, D-Ala-D-Met, and D-Ala-D-Phe exhibiting inducible high level resistance to all glycopeptides. Thus **38** and **39** were 20−25× more potent than the vancomycin aglycon and 50−65× more potent than vancomycin itself. This suggests that alterations in the asparagine side chain may facilitate binding to D-Ala-D-Lac potentially by permitting adoption of complex bound conformations that avoid the destabilizing electrostatic interaction between the C_1[4] carbonyl oxygen and the D-Ala-D-Lac ester oxygen. Studies of such derivatives are in progress and will be disclosed in due course.

Experimental Section

***S*-23 and *R*-23.** A suspension of *P*-**22** (381 mg, 0.43 mmol), **6** (502 mg, 1.08 mmol), $Pd_2(dba)_3$ (119 mg, 0.13 mmol), and tri-*o*-tolylphosphine (198 mg, 0.65 mmol) in toluene (2.86 mL), CH_3OH (0.86 mL), and 1 M aqueous Na_2CO_3 (0.48 mL, 0.48 mmol) was degassed and warmed at 80 °C in a preheated oil bath with vigorous stirring for 15 min. The mixture was cooled to 25 °C, diluted with EtOAc (10 mL), and treated with 1 N aqueous HCl (2 mL) at 0 °C. The aqueous phase was extracted with EtOAc, and the combined organic solution was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 50−100% EtOAc−hexane gradient elution) afforded *S*-**23**[31] (168 mg, 32%) as a white film and *R*-**23**[31] (221 mg, 42%) as a pale yellow film (combined yield 74%; typically 70−88%).

Thermal Interconversion of the Atropisomers *S*-23 and *R*-23. A solution of *R*-**23** (398 mg, 0.33 mmol) in chlorobenzene (3.5 mL) was warmed to 120 °C for 12 h. The reaction mixture was concentrated in vacuo. Flash chromatography (SiO_2, 50−100% EtOAc−hexane gradient elution) afforded *S*-**23** (223 mg, 56%) as a white film and *R*-**23** (98.5 mg, 25%) as a pale yellow film (typical ratios of 2.2−3:1).

24. A solution of *S*-**23** (219 mg, 0.18 mmol) in THF (8 mL) was treated with Bu_4NF (0.80 mL, 0.80 mmol, 1 M solution in THF) and AcOH (56 μL, 0.97 mmol) at 25 °C. The resulting mixture was stirred for 6 h at 25 °C and poured into cold saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic solution was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3% CH_3OH−CH_2Cl_2) afforded **24**[31] (189 mg, 196 mg theoretical, 96%) as a white film.

25. A solution of **24** (189 mg, 0.17 mmol) in THF (8.5 mL) was treated with 0.2 N aqueous LiOH (1.5 mL) at 0 °C. The resulting solution was stirred for 1 h at 0 °C and quenched by the addition of 0.25 N aqueous HCl (3 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic solution was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% CH_3OH−CH_2Cl_2) afforded **25**[31] (188 mg, 190 mg theoretical, 99%) as a white film.

26. A stirred solution of **25** (188 mg, 0.17 mmol) in EtOH (10 mL) and EtOAc (25 mL) was treated with 10% Pd/C (55 mg) portionwise and stirred for 11 h at 25 °C under an atmosphere of H_2. The reaction mixture was diluted with EtOAc (30 mL), filtered through a pad of Celite (EtOAc, 2 × 20 mL), and concentrated in vacuo. Flash chromatography (SiO_2, 10−20% CH_3OH−CH_2Cl_2 gradient elution) afforded **26**[31] (128 mg, 160 mg theoretical, 80%, 99% based on recovered starting material) as a white film.

27. A solution of **26** (128 mg, 0.133 mmol) and HOBt (90 mg, 0.665 mmol) in CH_2Cl_2−DMF (5:1, 64 mL, 0.002 M) was treated dropwise with EDCI (128 mg, 0.665 mmol) in CH_2Cl_2−DMF (5:1, 4 mL) at 0 °C. The resulting solution was stirred for 15 h at 0 °C before H_2O (30 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic solution was washed with H_2O and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 5% CH_3OH−CH_2Cl_2) afforded **27**[31] (70 mg, 56%; typically 55−62%) as a white film and *epi*-**27**[31] (18 mg, 15%) as a white film.

30. A solution of **27** (39.0 mg, 41.6 μmol) in $CHCl_3$ (1.0 mL) was treated with HCOOH (1.0 mL) at 25 °C, and the reaction mixture was stirred for 7 h. The reaction mixture was diluted with $CHCl_3$ (10 mL), cooled to 0 °C, and quenched by the addition of H_2O (10 mL) and $NaHCO_3$ until pH = 8. The resulting mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 8−14% CH_3OH−$CHCl_3$ gradient elution)

(31) Full characterization data are provided in the Supporting Information.

afforded **28** (28.5 mg, 34.8 mg theoretical, 82%, typically 80−95%) as white powder.

A solution of **28** (28.6 mg, 34.2 μmol) and **29** (25.3 mg, 44.6 μmol) in THF (0.39 mL) was treated sequentially with HOAt (7.4 mg, 55 μmol) and EDCI (10.5 mg, 55 μmol) at 0 °C, and the reaction mixture was stirred for 30 min. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (3 mL), dried (Na_2SO_4), and concentrated in vacuo. Semipreparative reverse-phase HPLC (C18, 2.5 × 10 cm, CH_3CN-0.07% TFA/H_2O 55:45, 10 mL/min) afforded **30**[31] (29.7 mg, 47.3 mg theoretical, 63%) as a white film.

31. A solution of **30** (29.7 mg, 21 μmol) in DMSO (2.6 mL) was treated with CsF (19.5 mg, 128 μmol) at 25 °C, and the reaction mixture was stirred for 7.5 h. The reaction mixture was diluted with EtOAc (30 mL) and quenched by the addition of 1% aqueous HCl (10 mL). The water layer was extracted with EtOAc (2 × 30 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, 7% $CH_3OH-CH_2Cl_2$) afforded *P*-**31**[31] (20.2 mg, 29.3 mg theoretical, 69%; typically 65−75%) as a white film and *M*-**31** (4.3 mg contaminated with an inseparable impurity). *M*-**31**[31] was further purified by semipreparative reverse-phase HPLC (C18, 2.5 × 10 cm, $CH_3CN-0.07\%$ TFA/H_2O 52:48), providing 2.2 mg (8%) as a white film.

32. A solution of **31** (5.6 mg, 4.0 μmol) in EtOAc (1.6 mL) was treated with 10% Pd/C (1.6 mg) at 25 °C, and the reaction mixture was stirred under H_2 for 4 h. The reaction mixture was filtered through a pad of Celite (CH_3OH, 3 × 10 mL), and solvent was removed in vacuo to afford the crude aniline (5.2 mg, 5.4 mg theoretical, 96%) which was used in the subsequent step without purification.

A solution of the above crude aniline (5.2 mg, 3.9 μmol) in CH_3CN (0.3 mL) was treated with HBF_4 (0.1 mM solution in THF, 51 μL, 5.1 μmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min before the dropwise addition of *tert*-butylnitrite (0.1 mM solution in THF, 51 μL, 5.1 μmol). The resulting mixture was stirred at 0 °C for 5 min. The reaction mixture was cooled to −20 °C and immediately added to an aqueous solution (0.3 mL) containing CuCl (19.3 mg, 194 μmol) and $CuCl_2$ (31.4 mg, 234 μmol) at 0 °C, and the heterogeneous mixture was warmed to 25 °C and stirred for 30 min. EtOAc (10 mL) and H_2O (4 mL) were added to the reaction mixture, and the water layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (4 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 7% $CH_3OH-CHCl_3$) afforded **32**[31] (3.3 mg, 5.5 mg theoretical, 60%) as a white solid.

33. A solution of **32** (16.4 mg, 0.012 mmol) in anhydrous CH_3CN (205 μL) was treated with MTBSTFA (187 μL, 0.79 mmol, 65 equiv). The mixture was stirred at 55 °C under Ar for 22 h, cooled to 25 °C, poured into EtOAc/15% aqueous citric acid (3:1, 2 mL), and stirred for 15 h. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 10.5 cm, 2−5% $CH_3OH-CHCl_3$ gradient elution) afforded **33**[31] (18.6 mg, 19.2 mg theoretical, 97%) as a white film.

34. A solution of **33** (18.4 mg, 0.012 mmol) in anhydrous CH_2Cl_2 (470 μL) at 0 °C was treated with *B*-bromocatecholborane (0.2 M in CH_2Cl_2, 700 μL, 0.14 mmol, 12 equiv) and stirred at 0 °C under Ar for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ (3 mL), stirred for 15 min, and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with saturated aqueous NaCl (3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 5% $CH_3OH-CHCl_3$) afforded the intermediate amino alcohol, which was dissolved in dioxane/H_2O (2:1, 900 μL), cooled to 0 °C, and treated with $NaHCO_3$ (5.8 mg, 0.069 mmol, 6.0 equiv), followed by BOC_2O (13 mg, 0.060 mmol, 5.1 equiv). The mixture was stirred at 25 °C for 2.5 h, diluted with H_2O (2 mL), and extracted with EtOAc (4 × 4 mL). The combined organic layers were washed with saturated aqueous NaCl (4 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12.5 cm, 5% $CH_3OH-CHCl_3$) afforded **34**[31] (12.0 mg, 17.4 mg theoretical, 69%) as a white solid.

35. A solution of **34** (12.6 mg, 0.0084 mmol) in anhydrous CH_2Cl_2 (340 μL) at 0 °C was treated with Dess−Martin periodinane (14.2 mg, 0.033 mmol, 4.0 equiv), stirred at 0 °C for 15 min, and stirred at 25 °C for 1 h. Et_2O (0.5 mL) and saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1, 2 mL) were added to the mixture, and it was stirred until the cloudiness disappeared. The layers were separated, the aqueous layer was extracted with Et_2O (3 × 3 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous NaCl (3 mL), dried (Na_2SO_4), and concentrated in vacuo. This afforded the intermediate aldehyde, which was dissolved in *t*-BuOH/2-methyl-2-butene (4:1, 350 μL) and treated with a solution of 80% aqueous $NaClO_2$ (8.6 mg, 0.076 mmol, 9.0 equiv) and $NaH_2PO_4 \cdot H_2O$ (8.1 mg, 0.058 mmol, 7.0 equiv) in H_2O (80 μL). The mixture was stirred at 25 °C for 20 min, and the *t*-BuOH and 2-methyl-2-butene were removed in vacuo. The residue was diluted with H_2O (3 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. This afforded the intermediate acid, which was dissolved in benzene/CH_3OH (4:1, 0.5 mL) and treated with trimethylsilyldiazomethane (2.0 M in hexanes) until the yellow color persisted. The mixture was stirred at 25 °C for 30 min, concentrated in vacuo, and purified by flash chromatography (SiO_2, 1.5 × 15.5 cm, 2−5% $CH_3OH-CHCl_3$ gradient elution) to afford **35**[31] (9.9 mg, 12.8 mg theoretical, 77%) as a white film.

36. A solution of **35** (3.5 mg, 2.3 μmol) in DMSO (0.6 mL) at 25 °C was treated sequentially with H_2O_2 (10 μL, 98 μmol) and 10% aqueous K_2CO_3 (25.0 μL, 20 μmol). The resulting mixture was stirred at 25 °C for 3.5 h, diluted with EtOAc (15 mL), and quenched by addition of 0.1% aqueous HCl (2 mL). 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 (10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 6% $CH_3OH-CHCl_3$) afforded **36**[31] (2.6 mg, 3.5 mg theoretical, 73%; 73−85%) as a white film.

37. A solution of **36** (1.6 mg, 1.04 μmol) in THF (50 μL) was treated with $Bu_4NF-HOAc$ (1:1, 1 M solution in THF, 31 μL, 31 μmol) at 25 °C, and the resulting mixture was stirred at 25 °C. After 11 h, additional $Bu_4NF-HOAc$ (1:1, 1 M solution in THF, 31 μL, 31 μmol) was added. The reaction mixture was stirred for 18 h, quenched by the addition of H_2O (2 mL) at 0 °C, and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 9% $CH_3OH-CHCl_3$) afforded **37**[31] (1.1 mg, 1.4 mg theoretical, 81%) as a white film.

1. A vial charged with **37** (5.0 mg, 3.8 μmol) was treated with $AlBr_3$ (38.1 mg, 0.143 mmol) in EtSH (0.2 mL) under Ar. The resulting mixture was stirred at 25 °C for 5 h, diluted with $CHCl_3$ (0.5 mL), cooled to 0 °C, and quenched by addition of CH_3OH (0.1 mL). The solvent was removed by a stream of N_2. The crude mixture was purified by PTLC (SiO_2, 55% $CH_3OH-EtOAc$) and semipreparative reverse-phase HPLC ($CH_3CN-0.07\%$ TFA/H_2O 17:83, 10 mL/min, R_t = 18 min) to afford **1**[31] (2.4 mg, 4.8 mg theoretical, 50%) as a white film.

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Supporting Information Available: Full experimental details and characterization of **4**−**6**, **9**−**19**, and **38**−**40**, full characterization data for **23**−**27**, **29**−**37**, and **1**, and data on the thermal atropisomerism (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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