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Stereodivergent Syntheses of Anisomycin Derivatives from D-Tyrosine

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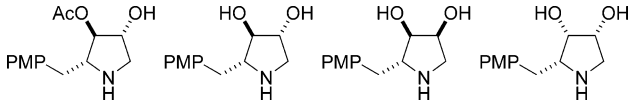

Enantiomerically pure 2-alkyl-3-acetoxy-4-iodopyrrolidines with all groups *cis*, and all adjacent groups *trans* (**10** and **17**), important precursors for the synthesis of pyrrolidinediols, have been prepared from D-tyrosine through regio- and diastereoselective reduction of a vinyl ketone and subsequent iodoamidation controlled by minimization of nonbonding steric interactions. Highly stereodivergent Woodward−Prevost methodology, applied to both iodopyrrolidines, yielded enantiomerically pure (2*R*,3*R*,4*R*)-, (2*R*,3*R*,4*S*)-, and (2*R*,3*S*,4*R*)-deacetylanisomycin (**3**, **4**, and **5**), each in excellent de. Incorporation of differential protection of the hydroxyl groups led to a one-pot synthesis of (2*R*,3*R*,4*R*)-anisomycin **2**.

Introduction

Anisomycin, first isolated from *Streptomyces* species in 1954,[1] exhibits a remarkably selective activity against several pathogenic protozoa[2] and fungi[3] because it specifically blocks peptide bond formation on 60S eukaryotic ribosomes[4] through inhibition of the peptidyl transferase.[4a,5] These properties have been used in the clinical treatment of amoebic dysentery[6] and vaginitis.[7] Anisomycin has also been shown to exhibit antiviral[8] and antitumor activities due to apoptotic activity.[9] Some anisomycin analogues, such as deacetylanisomycin, act as potential fungicides for bean mildew and other fungal plant infections,[2,10] and they are also expected to be inhibitors of some enzymes.[11,13a] Thus, much attention has been focused toward the development of convenient and efficient routes to anisomycin and its derivatives, and the following general methodologies have been used for this purpose: (i) the transformation of carbohydrates based on stereoselective reductive alkylation,[12] (ii) diastereoselective addition of cyclic imines and nitrones,[13] (iii) the combined application of Sharpless asymmetric

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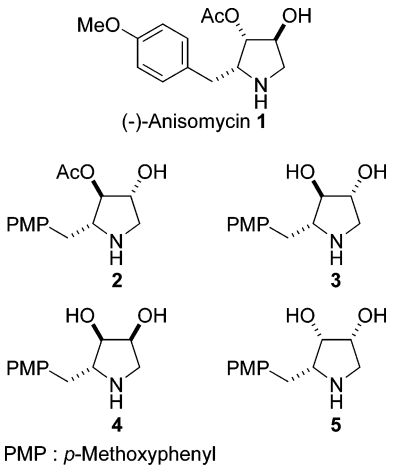


FIGURE 1. (−)-Anisomycin and its derivatives.

epoxidation from divinylcarbinol,[14] (iv) transformation of benzylpyrrole,[15] (v) the addition of electrogenerated anions,[16] (vi) the asymmetric dihydroxylation of unsaturated esters,[17] (vii) the aldol coupling of glycolate and tyrosinal,[18] and (viii) nucleophilic substitution along with aryl migration.[19] However, many of these routes suffer the disadvantage of either the use of nonstereoselective transformations[15] or having low overall yield, due to the large number of steps used.[16,19,20] Although the problem of enantioselectivity has been solved in a few cases,[12b,13a] a powerful synthetic methodology for construction of structurally diverse dihydroxylated pyrrolidines still remains to be fully developed.

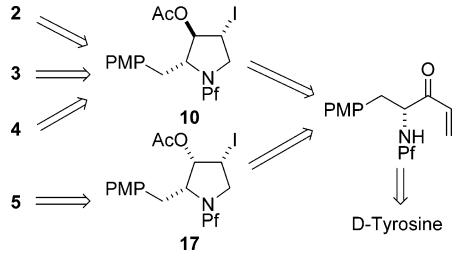
In a previous paper, we described a new approach to the stereodivergent synthesis of dihydroxylated pyrrolidine using the Woodward−Prevost reaction.[21] Therefore, as a continuation of our studies, we have directed our interest to investigating the stereoselective synthesis of (2*R*,3*R*,4*R*)-anisomycin **2**, and (2*R*,3*R*,4*R*)-, (2*R*,3*R*,4*S*)-, and (2*R*,3*S*,4*R*)-deacetylanisomycin (**3**, **4**, and **5**) (Figure 1).

The outline of the process is shown in Scheme 1, beginning with D-tyrosine and proceeding via selective reduction of vinyl ketone and iodocyclization[22] with anticipated total regio- and stereointegrity. The intermidate iodoacetates (**10** and **17**) should serve as a basis for the synthesis of a wide range of pyrrolidinediols.

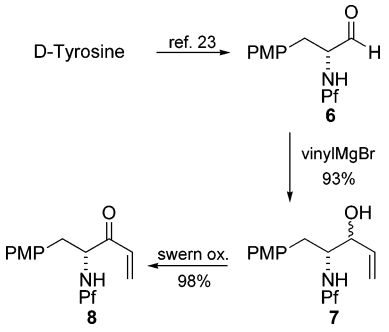
Results and Discussion

The numerous flaws in the available methodologies to synthesize pyrrolidinediols prompted us to undertake a thorough investigation into the use of a previously published novel intermediate as an alternative synthetic route, focusing on the synthesis of anisomycin derivatives.[22] This intermediate, generated from chiral α-amino acids, via an iodoamidation, is attractive for a number of reasons. First, although α-amino acids are an ideal starting point for an enantioselective synthesis of pyrrolidinediols as they are readily available and are of high enantiopurity, using this precursor, selective installation of both hydroxyl groups on the pyrorrolidine ring has proved difficult, with no general methodology being developed. It was envisioned that Woodward−Prevost (W−P) methodology could be used to overcome this problem easily. Second, if successful, this methodology would be highly stereodivergent as the Woodward−Prevost reaction gives access to a wide range of stereoisomers from common intermediates. Third, with the iodocyclization generating a *β*-iodoaceate stereo and regiospecifically, the usual issues of facial selectivity of epiiodination and regioselectivity of the subsequent ring opening would be overcome.

SCHEME 1. Retrosynthetic Plan for the Synthesis of Anisomycin Derivatives



SCHEME 2. Synthesis of α,*β*-Unsaturated Ketone 8



Synthesis of *β*-iodoacetates (**10** and **17**) was achieved simply in a small number of steps by the following reaction sequence. The aminoaldehyde **6** was synthesized in a high yield from homochiral amino acid, D-tyrosine, as previously described[23] in 65% yield. The 9-phenyl-9-fluorenyl (Pf) group was chosen for protection of the amine since it was expected not only to inhibit of deprotonation at the α-position of the α-amino aldehyde[24] but also to provide an electron-donating effect to the nitrogen atom, accelerating iodoamidation (Scheme 2).

Treatment of **6** with vinylmagnesium bromide yielded a fully separable mixture of the *syn* and *anti* isomers of allylic alcohol **7**, in a 1:1 ratio, in 93% total yield. To

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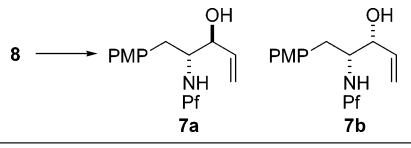
TABLE 1. Preparation of Enantiomerically Pure Allylic Alcohol[a]



entry	reagents	conditions	ratio[b] (**7a/7b**)	yield[c] (%)
1	BH_3-$(CH_3)_2S$	toluene, −78 °C	1:9	91[d]
2	(*S*)-BINAL	THF, −78 °C	>95:1	89
3	(*R*)-BINAL	THF, −78 °C	1:6	82
4	$NaBH_4$	THF, −10 °C		*e*
5	DIBAL-H	THF, −78 °C		*e*
6	L-Selectride	THF, −78 °C	1:5	45
7	KS-Selectride	THF, −78 °C	1:6	38
8	Red-Al	THF, −40 °C	1:8	20

[a] The reactions were all run at 0.1 M concentration. [b] Determined by ^{1}H NMR integration. [c] Isolated yield. [d] Based on 70% conversion of starting material. [e] 1,4-addition product.

improve the efficiency of this route, an efficient protocol for the conversion of the mixture of diastereoisomers to a single diastereoisomer of either **7a** or **7b** was investigated. It was envisioned that stereoselective reduction of the ketone moiety could achieve the desired goal. Accordingly, compound **7** was reoxidized using under Swern conditions to afford α, β-unsaturated ketone **8** (Scheme 2).

Initially, reduction of the ketone with $NaBH_4$ was attempted, but this gave reduction predominantly at the β position. A further attempt with DIBAL-H also gave the same result. However, it was shown that highly regio- and stereoselective reduction at the carbonyl moiety occurred when more complex reducing agents were used, and indeed, both epimers **7a** and **7b** were created in high diastereoselectivity and yields using this methodology (Table 1).

In general, the results are in accordance with the polar Felkin model, where the most electron-withdrawing substituent occupies the position usually adopted by the largest group in the classical Felkin−Ahn-type transition state. The nature of this group being perpendicular to the carbonyl adds extra delocalization in the transition state, allowing electron density from the nascent bond to overlap with the best acceptor orbital. Addition via transition state **B** is responsible for the major product, which is derived from attack of the nucleophile *syn* to the C−H bond at the Burgi−Dunitz angle, reducing steric effects and lowering its energy. The electrophilic reductant BH_3·SMe_2 was found to be the best reducing agent to give the Felkin product in terms of de and yield. On the other hand, **7a** was formed in an excellent enantioselective manner by the use of (*S*)-BINAL,[25] while the use of (*R*)-BINAL favored **7b** (Figure 2). Subsequent reaction with Ac_2O furnished the respective acetates in excellent yields.

With the vinylic acetate **9** in hand, treatment with I_2, leading to stereoselective formation of an epiiodonium ion in situ, followed by subsequent highly regioselective ring closure, furnished **10** in 90% yield (Scheme 3). The excellent selectivity of the iodination can be explained

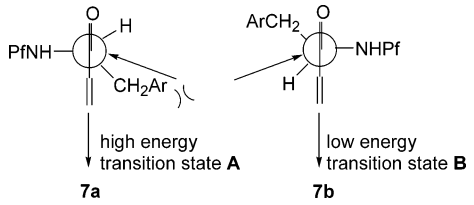
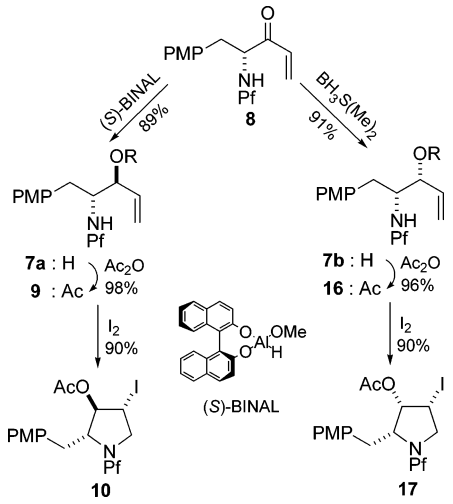


FIGURE 2. Comparison of Felkin−Ahn models for the selective reduction.

SCHEME 3. Synthesis of W−P Reaction Substrates 10 and 17



by minimizing the nonbonding steric interactions between the β-center and the proximal C−H of the vinyl group. The standard A1,3 strain model being of low importance in this system due to there being no *syn* alkyl substituent. The β-stereocenter was shown by Tamaru and co-workers to dominate over the α-center in an amide-based system.[26] Addition of I_2 to the least hindered face (away from NHPf group) generates the desired *epi*-iodonium ion, which when trapped out by the nitrogen lone pair electron gives the desired product (Figure 3). An analogous procedure repeated on **16** generated the expected all syn product, again that derived from the epiiodonium formed due to minimization of nonbonding steric interactions.

Key intermediate **10**, with a *trans* relationship between iodine and acetoxy groups, is now set up for W−P transformations, which proceed by neighboring group participation of the acetate. Treatment of **10** with wet $AgBF_4$ (Woodward conditions) gave a 1:1 mixture of easily separable β-hydroxy acetates **13a** and **13b** (Scheme 4). Proof that the two products differed only in the position of the acetate group was given by cleavage of a 1:1 mixture of acetates **13a** and **13b** to a single diol derivative **14** in >98% de. Subsequent hydrogenolysis yielded target compound (2*R*,3*R*,4*S*)-deacetylanisomycin **4**.

Formation of the C(4) epimer could be achieved using Prevost conditions, where water is excluded from the reaction mixture. Thus, treatment of **10** with AgOBz gave the corresponding differentially protected diester in excellent yield and with very high regioselectivity. Cleav-

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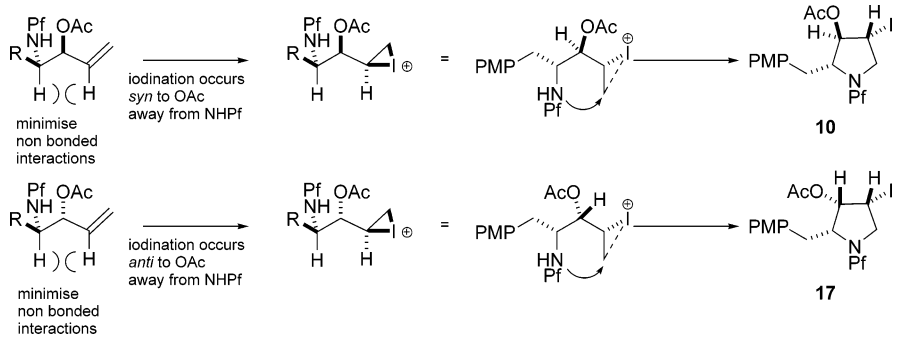
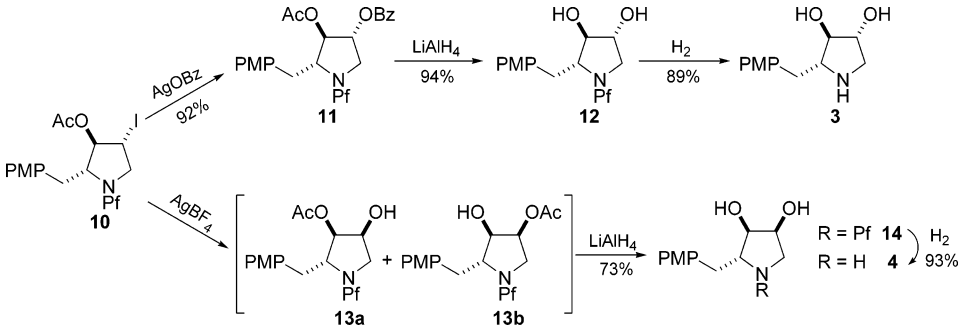
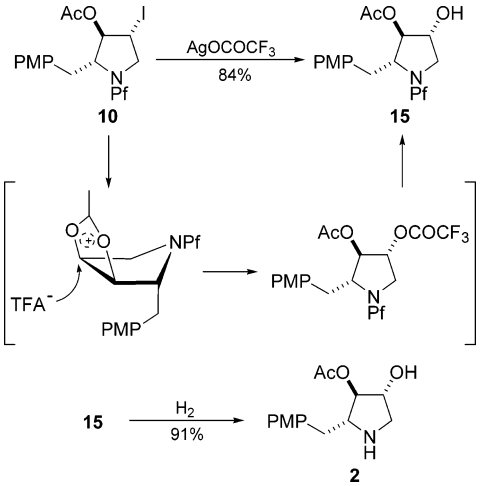


FIGURE 3. Proposed mechanism for the stereoselective iodoamidation.

SCHEME 4. Synthesis of Target Compounds 3 and 4



SCHEME 5. Synthesis of Target Compound 2



age of both ester protecting groups with $LiAlH_4$ gave **12**, which was easily deprotected to the (2*R*,3*R*,4*R*)-deacetylanisomycin **3** (Scheme 5). Under both reaction conditions, the reaction pathway relies upon activation of the iodide with the halophilic sliver(I) cation, allowing the acetate to displace the iodide to generate a cyclic acetoxonium ion, which was described extensively in our previous report.[21] With the methodology for highly selective manipulation of **10** demonstrated, and the principle of differential protection further established in the case of **11**, the synthesis of Anisomycin was attempted. Compound **10** was treated with $Ag(O_2CCF_3)$, using Prevost conditions. Trapping of the cyclic acetoxonium ion by triflouroacetate formed the *trans* diol derivative, with a labile protecting group installed regioselectively in the C4 position. Deprotection was easily effected during chromatography on silica gel to yield *N*-protected anisomycin **15** in 84% yield. Deprotection by hydrogenolysis furnished (2*R*,3*R*,4*R*)-anisomycin **2** in 91% yield. Thus the synthesis of anisomycin was accomplished from **10** in two steps in overall 76% yield.

With both stereoisomers of C2−C3 *trans* having been synthesized from **7a**, attention turned to the C2−C3 *cis* series. This series was thought to be accessible from iodoacetate **17**, which, unfortunately, has a *syn* arrangement about the two reacting groups, making it not totally ideal for the W−P reaction, as the departure of the nucleofuge cannot be assisted by the neighboring acetoxy group due to them being *syn* on a five-membered ring. Initial studies focused on the use of AgOBz as the Lewis acid, although this resulted only in the return of the starting material, and altering amount of Lewis acid and the temperature had no effect. However, in an analogous manner to that documented above, **17** was treated with $AgBF_4$ in aqueous conditions, and as observed previously, a 1:1 mixture of separable acetates **18a** and **18b** was generated (Scheme 6). Cleavage of acetyl group from the mixture **18a/18b** using $LiAlH_4$ gave the diol **19** as a single product again in 70% yield. Deprotection of **19** by hydrogenolysis furnished (2*R*,3*S*,4*R*)-deacetylanisomycin **5**.

Conformation of stereochemistries were obtained by 2D-NOESY experiments on **3**−**5** (Figure 4). Strong NOESY cross-peaks were observed between H_3−H_4 in

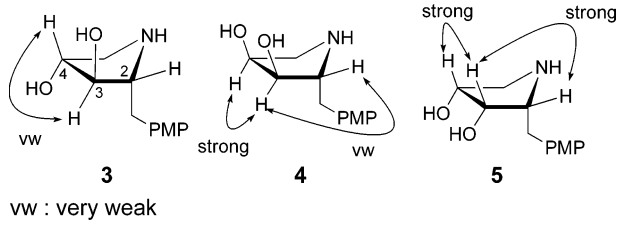
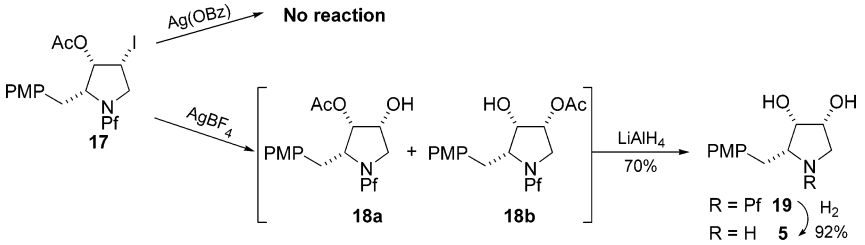


FIGURE 4. Selected NOESY correlation of **3**−**5**.

SCHEME 6. Synthesis of Target Compound 5



both compounds **4** and **5**, whereas a very weak cross-peaks was observed between H_3-H_4 in compound **3**.

In conclusion, a highly stereodivergent methodology for the synthesis of a range of stereoisomers of deacetylanisomycine has been demonstrated starting from a single homochiral amino acid, with each target being isolated in high yield and over a small number of steps, with excellent selectivity. This highly efficient methodology was further extended to a short enantioselective synthesis of anisomycin. The value of such stereodivergency can be seen in the relation of the relative stereochemistry of the hydroxyl groups on the pyrrolidine ring to the glycosidase inhibition of the natural anisomycin. Screening of the unnatural compounds for activity will allow the effects of such variations to be assessed in a systematic way, and endevours toward this and over bioactivity issues are currently underway within the group.

Experimental Section

(4*R*)-5-(*p*-Methoxyphenyl)-4-(*N*-9-phenylfluoren-9-yl)-aminopent-1-en-3-one (8). To a solution of **6** (1.21 g, 2.88 mmol) in THF (12 mL) was added 1.0 M vinylmagnesium bromide (3.4 mL, 3.43 mmol) at −40 °C. After being stirred for 30 min, the reaction mixture was quenched by addition of satd $NaHCO_3$. The resulting mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the resulting product was used for swern oxidation with oxalyl chloride (0.62 mL, 7.15 mmol), DMSO (0.81 mL, 11.44 mmol), and Et_3N (3.18 mL, 22.88 mmol) at −78 °C in CH_2Cl_2 (25 mL). The reaction mixture was quenched with satd $NaHCO_3$, and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexane/EtOAc = 15/1) to give compound **8** (1.16 g, 91%): $[\alpha]_D$ +109.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3052, 2982, 1718 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 2.57 (2H, m), 3.05 (1H, m), 3.82 (3H, s), 5.36 (1H, d, J = 10.6 Hz), 5.60 (1H, d, J = 17.5 Hz), 5.96 (1H, m), 7.62 ~ 6.77 (17H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 39.9, 55.2, 60.4, 73.0, 113.6, 119.4, 119.5, 125.3, 126.1, 126.9, 127.1, 127.5, 127.9, 128.2, 128.3, 129.6, 130.6, 133.7, 139.9, 140.9, 158.3. Anal. Calcd for $C_{31}H_{27}NO_2$: C, 83.57; H, 6.11; N, 3.14. Found: C, 83.64; H, 6.27; N, 3.22.

(3*S*,4*R*)-4-(*N*-9-Phenylfluoren-9-yl)amino-3-hydroxy-5-(*p*-methoxyphenyl)-1-pentene (7a). Unsaturated ketone **8** (0.3 g, 0.67 mmol) was mixed with 3 equiv of (*S*)-BINAL (2.0 mmol) in THF at −78 °C and allowed to stir at the same temperature for 1 h. The mixture was quenched by addition of water (0.1 mL), filtered through Celite 545, and evaporated. The residue was chromatographed on silica gel (hexane/EtOAc = 8/1) to give compound **7a** (0.26 g, 89%) as a solid: mp 53 °C; $[\alpha]_D$ −153.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3452, 2840 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 2.32 (2H, m), 2.52 (1H, m) 3.30 (1H, bs), 3.77 (3H, s), 5.03 (2H, m), 5.61 (1H, m), 7.62 ~ 6.28 (17H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ 33.8, 54.1, 57.8, 70.4, 71.1, 112.8, 114.1, 118.3, 118.8, 123.9, 124.0, 124.5, 126.0, 126.7, 126.9, 127.0, 127.2, 127.4, 129.2, 129.5, 135.9, 138.4, 139.6, 143.8, 147.2, 157.1. Anal. Calcd for $C_{31}H_{29}NO_2$: C, 83.19; H, 6.53; N, 3.13. Found: C, 83.29; H, 6.60; N, 3.24.

(3*R*,4*R*)-4-(*N*-9-Phenylfluoren-9-yl)amino-3-hydroxy-5-(*p*-methoxyphenyl)-1-pentene (7b). To a solution of **8** (0.3 g, 0.67 mmol) in toluene (2 mL) was added 2.0 M $BH_3(CH_3)_2S$ (0.67 mL, 1.3 mmol) at −78 °C. After being stirred for 30 min, the reaction mixture was quenched by addition of satd $NaHCO_3$ (4 mL). The resulting mixture was extracted with EtOAc (2 mL × 3), washed with brine, and dried over Na_2SO_4. The organic layer was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 8/1) to give compound **7b** (0.19 g, 91%, based on 70% conversion of starting material **8**): $[\alpha]_D$ − 115.3 (*c* 2.0, $CHCl_3$); IR (KBr) 3450, 3070, 2994, 1610 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 2.21 (1H, dd, J = 13.3, 5.1 Hz), 2.32 (2H, m), 2.48 (1H, dd, J = 13.3, 8.3 Hz), 3.68 (1H, m), 3.71 (3H, s), 5.00 (1H, m), 5.13 (1H, m), 5.51 (1H, m), 7.70−6.62 (17H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ 36.8, 54.2, 57.7, 71.1, 71.6, 112.7, 114.1, 118.9, 124.5, 125.0, 125.3, 126.2, 126.7, 126.8, 127.3, 127.3, 127.4, 129.4, 130.0, 138.7, 139.3, 139.6, 144.3, 148.0, 149.0, 156.9. Anal. Calcd for $C_{31}H_{29}NO_2$: C, 83.19; H, 6.53; N, 3.13. Found: C, 83.25; H, 6.30; N, 3.34.

(3*S*,4*R*)-4-(*N*-9-phenylfluoren-9-yl)amino-3-acetoxy-5-(*p*-methoxyphenyl)-1-pentene (9). To a solution of enantiomerically pure **7a** (1.5 g, 3.35 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.93 mL, 6.71 mmol), 4-(dimethylamino)pyridine (DMAP, 0.1 g), and acetic anhydrous (0.47 mL, 5.03 mmol). The mixture was stirred for 2 h at room temperature and quenched by satd $NaHCO_3$ (30 mL). The resulting mixture was extracted with CH_2Cl_2 (10 mL × 3), and the extract was washed with brine and dried over Na_2SO_4. The organic layer was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 8/1) to give compound **9** (1.6 g, 98%) as a solid: mp 44 °C; $[\alpha]_D$ +1.42 (*c* 1.0, $CHCl_3$); IR (KBr) 3327, 3063, 2934, 1737 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 2.00 (3H, s), 2.45 (3H, m), 4.80 (1H, m), 4.85 (1H, m), 5.08 (1H, d, J = 10.6 Hz), 5.63 (1H, m), 7.70 ~ 6.69 (17H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ 17.9, 21.7, 37.7, 55.6, 58.6, 73.2, 77.1, 114.0, 117.8, 120.0, 120.2, 126.0, 126.5, 126.6, 127.5, 128.1, 128.4, 128.6, 128.8, 130.7, 131.6, 134.4, 140.7, 140.8, 146.0, 149.6, 150.0, 158.4, 170.4. Anal. Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 81.08; H, 6.52; N, 3.01.

(2*R*,3*R*,4*R*)-4-(*N*-9-Phenylfluoren-9-yl)-3-acetoxy-4-iodo-2-(*p*-methoxybenzyl)pyrrolidine (10). To a solution of **9** (1.6 g, 3.26 mmol) in biphasic solvent (satd $NaHCO_3$/THF/Et_2O = 2/1/1, 10 mL) was added iodine (2.0 g) at room temperature. After being stirred for 36 h, the reaction mixture was quenched by addition of 0.1 M $Na_2S_2O_3$ solution and extracted with EtOAc (12 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was chromatographed on silica gel (hexane/EtOAc = 16/1) to give pyrrolidine **10** (1.81 g, 90%) as a solid: mp 63 °C; $[\alpha]_D$ −56.28 (*c* 1.0, $CHCl_3$); IR (KBr) 3068, 2940, 1726 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 1.62 (3H, s), 2.37 (1H, dd, J = 13.7, 4.0 Hz), 2.44 (1H, m), 2.67 (1H, dd, J = 13.7, 9.6 Hz), 2.74 (1H, m), 3.00 (1H, m), 3.28 (1H, m), 3.72 (3H, s), 4.56 (1H, t, J = 5.1 Hz), 7.75 ~ 6.71 (17H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ 13.2, 20.5, 39.4, 55.2, 64.3, 65.8, 73.4, 75.8, 113.6, 119.9, 120.1, 126.8, 127.1, 127.2, 127.9, 128.1, 128.2, 128.8, 128.9, 129.6, 130.2, 140.3, 140.8, 141.4, 145.6, 146.0,

158.0, 169.6. Anal. Calcd for $C_{33}H_{30}NO_3I$: C, 64.40; H, 4.91; N, 2.28. Found: C, 64.51; H, 5.03; N, 2.35.

(2*R*,3*R*,4*R*)-(*N*-9-Phenylfluoren-9-yl)-4-*O*-benzoylanisomycin (11). Iodoacetate **10** (0.9 g, 1.46 mmol) and silver benzoate (0.67 g, 2.95 mmol) were refluxed in dried toluene (6 mL) for 12 h. The mixture was filtered and evaporated. The residue was chromatographed on silica gel (hexane/EtOAc = 8/1) to give compound **11** (0.82 g, 92%): $[\alpha]_D$ + 64.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3063, 2924, 1752, 1722 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.62 (3H, s), 2.47 (1H, dd, *J* = 13.4, 3.9 Hz), 2.64 (1H, m), 2.80 (1H, dd, *J* = 10.3, 3.2 Hz), 3.41 (1H, dd, *J* = 12.0, 3.6 Hz), 3.73 (3H, s), 3.80 (1H, dd, *J* = 12.0, 6.2 Hz), 5.00 (1H, m), 5.29 (1H, m), 8.13 ~ 6.54 (22H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.7, 39.4, 53.5, 55.1, 65.7, 76.1, 77.7, 79.6, 113.6, 119.9, 120.1, 126.7, 127.0, 127.3, 127.4, 127.7, 128.4, 128.5, 129.7, 129.8, 130.2, 130.6, 133.3, 139.7, 141.3, 142.9, 147.2, 148.6, 157.8, 165.7, 169.4. Anal. Calcd for $C_{40}H_{35}NO_5$: C, 78.80; H, 5.79; N, 2.30. Found: C, 78.91; H, 5.83; N, 2.38.

(2*R*,3*R*,4*R*)-(*N*-9-Phenylfluoren-9-yl)deacetylanisomycin (12). To a suspended $LiAlH_4$ (0.11 g, 2.70 mmol) solution in dried THF (6 mL) was added compound **11** (0.82 g, 1.34 mmol) in THF (4 mL) and the mixture stirred for 30 min at 0 °C. The reaction mixture was quenched with water (0.4 mL), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc = 2/1) to give compound **12** (0.58 g, 94%) as a solid: mp 93 °C; $[\alpha]_D$ +111.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3301, 3063, 2924 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 0.75 (1H, OH), 1.99 (1H, OH), 2.28 (1H, dd, *J* = 12.3, 2.8 Hz), 2.46 (2H, m), 3.26 (1H, dd, *J* = 11.2, 3.8 Hz), 3.44 (1H, dd, *J* = 11.2, 5.7 Hz), 3.72 (3H, s), 3.75 (1H, m), 4.01 (1H, m), 6.70 ~ 6.54 (4H, m), 7.60−7.24 (13H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 39.9, 54.9, 55.2, 68.8, 76.1, 76.4, 77.2, 81.1, 113.9, 119.9, 120.1, 127.1, 127.3, 127.5, 127.8, 128.4, 128.5, 128.8, 130.3, 131.2, 139.6, 141.4, 143.0, 146.9, 148.7, 157.8. Anal. Calcd for $C_{31}H_{29}NO_3$: C, 80.32; H, 6.31; N, 3.02. Found: C, 80.43; H, 6.46; N, 3.09.

(2*R*,3*R*,4*R*)-Deacetylanisomycin (3). *N*-Protected compound **12** (0.58 g, 1.25 mmol) was hydrogenated with Pd/C in EtOAc (6 mL) at room temperature for 6 h. The reaction mixture was filtered and evaporated. The residue was dissolved in MeOH (10 mL) and mixed with Dowex 50W-X8 (2 g). The mixture was filtered and then was washed MeOH. The remaining residue was diluted with 3 N NH_4OH solution. The solution was evaporated and then coevaporated with toluene to give compound **3** (0.25 g, 89%) as a solid: mp 120 °C; $[\alpha]_D$ + 20 (*c* 1.0, MeOH); IR (KBr) 3314, 2924 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 2.76 (1H, dd, *J* = 13.7, 8.1 Hz), 2.94 (2H, m), 3.12 (2H, m), 3.77 (3H, s), 3.79 (1H, m), 4.05 (1H, m), 6.87 (2H, d, *J* = 8.5 Hz), 7.20 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 37.9, 51.4, 54.2, 66.9, 77.3, 80.9, 113.2, 113.6, 129.7, 130.3, 158.4; MS-EI *m/z* 223 (M^+), 144, 121, 102; HRMS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1201.

(2*R*,3*R*,4*S*)-(*N*-9-Phenylfluoren-9-yl)deacetylanisomycin (14). A suspension of 3-acetyl-4-iodopyrrolidine **10** (0.9 g, 1.46 mmol) and silver tetrafluoroborate (0.71 g, 3.67 mmol) in toluene/water (9/1, 8 mL) was stirred at room temperature for 12 h. The reaction mixture was quenched with MeOH (20 mL) and satd NaCl (0.7 mL), filtered, and evaporated. The residue was reduced with $LiAlH_4$ (0.12 g, 3.0 mmol) in THF (10 mL) at 0 °C and quenched with water (0.5 mL). The mixture was filtered and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc = 2/1) to give *N*-protected compound **14** (0.49 g, 73%) as a solid: mp 95 °C; $[\alpha]_D$ +116.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3298, 3011, 2950 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 0.80 (1H, OH), 2.03 (1H, OH), 2.27 (1H, dd, *J* = 12.3, 2.9 Hz), 2.46 (2H, m), 3.25 (1H, dd, *J* = 11.1, 3.9 Hz), 3.44 (1H, dd, *J* = 11.2, 5.7 Hz), 3.72 (3H, s), 3.74 (1H, m), 4.01 (1H, m), 6.71−6.54 (4H, m), 7.57−7.24 (13H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 39.8, 54.8, 55.2, 68.8, 76.1, 76.4, 77.2, 81.1, 113.8, 119.9, 120.1, 126.3, 127.1, 127.3, 127.5, 127.8, 128.4, 128.5, 128.7, 130.0, 131.2, 139.6, 141.4, 143.0, 146.9, 148.7, 157.8. Anal. Calcd for $C_{31}H_{29}NO_3$: C, 80.32; H, 6.31; N, 3.02. Found; C, 80.45; H, 6.48; N, 3.11.

(2*R*,3*R*,4*S*)-Deacetylanisomycin (4). Compound **14** (0.49 g, 1.06 mmol) was hydrogenated with Pd/C in EtOAc (6 mL) at room temperature for 6 h. The reaction mixture was filtered and evaporated. The residue was dissolved in MeOH (10 mL) and mixed with Dowex 50W-X8 (2 g). The mixture was filtered and then was washed MeOH. The remaining residue was diluted with 3 N NH_4OH solution. The solution was evaporated and then coevaporated with toluene to give compound **3** (0.22 g, 93%): $[\alpha]_D$ +26.8 (*c* 0.53, MeOH); IR (KBr) 3295, 3032, 2950 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 2.94 (1H, dd, *J* = 14.0, 8.2 Hz), 3.13 (2H, m), 3.46 (1H, m), 3.79 (3H, s), 3.94 (1H, m), 4.15 (1H, m), 6.91 (2H, d, *J* = 8.6 Hz), 7.23 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 36.6, 51.1, 54.3, 67.8, 75.9, 79.0, 113.8, 128.9, 129.7, 158.8; MS-EI *m/z* 223 (M^+), 144, 121, 102; HRMS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1205.

(2*R*,3*R*,4*R*)-(*N*-9-Phenylfluoren-9-yl)anisomycin (15). A suspension of iodoacetate **10** (0.9 g, 1.46 mmol) and silver trifluoroacetate (0.65 g, 2.95 mmol) in dried toluene (6 mL) was refluxed for 6 h. The mixture was quenched with satd $NaHCO_3$ (10 mL) and extracted with EtOAc (5 mL × 3). The extract was washed with brine and dried over Na_2SO_4. The organic layer was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc = 6/1) to give compound **15** (0.62 g, 84%): $[\alpha]_D$ + 25.1 (*c* 1.0, $CHCl_3$); IR (KBr) 3321, 3068, 2980, 1746 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.70 (3H, s), 2.38 (2H, m), 2.94 (1H, OH), 3.26 (1H, dd, *J* = 11.0, 5.6 Hz), 3.49 (1H, dd, *J* = 11.0, 6.7 Hz), 3.73 (3H, s), 4.10 (1H, m), 4.49 (1H, t, *J* = 2.2 Hz), 6.69−6.54 (4H, m), 7.78−7.24 (13H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.8, 38.2, 54.1, 55.1, 65.3, 75.6, 76.2, 77.2, 85.6, 113.6, 120.0, 126.4, 126.9, 127.0, 127.2, 127.4, 127.6, 128.3, 128.4, 130.1, 130.7, 140.1, 140.8, 143.4, 147.5, 148.4, 157.8, 171.7. Anal. Calcd for $C_{33}H_{31}NO_4$: C, 78.39; H, 6.18; N, 2.77. Found; C, 78.48; H, 6.24; N, 2.82.

(2*R*,3*R*,4*R*)-Anisomycin (2). *N*-Protected anisomycin **15** (0.62 g, 1.23 mmol) was hydrogenated with Pd/C in EtOAc (5 mL) at room temperature for 6 h. The reaction mixture was filtered and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 8/1) to give anisomycin **2** (0.29 g, 91%) as a solid: $[\alpha]_D$ −15.4 (*c* 1.0, MeOH); IR (KBr) 3321, 2991, 1752 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.81 (3H, s), 2.68 (1H, dd, *J* = 13.7, 7.9 Hz), 2.80 (3H, m), 3.04 (1H, m), 3.62 (3H, s), 3.96 (1H, m), 4.63 (1H, m), 6.71 (2H, d, *J* = 8.5 Hz), 7.01 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 19.4, 38.1, 52.1, 54.3, 65.1, 75.9, 83.8, 113.6, 129.7, 130.2, 158.4, 170.7; MS-EI *m/z* 265 (M^+), 144, 121, 102; HRMS calcd for $C_{14}H_{19}NO_4$ 265.1314, found 265.1305.

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Supporting Information Available: General procedures, product characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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