Unique Solvent-Dependent Atropisomerism of a Novel Cytotoxic Naphthoxanthene Antibiotic FD-594†

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The absolute stereochemistry of FD-594 **1**, a new cytotoxic antibiotic, was determined by X-ray diffraction, and its conformation was studied by CD and NMR spectroscopy. The aglycon part of **1** was found to have (3*R*,6*S*,7*S*) configuration. Particularly interesting was the solvent-dependent atropisomerism of **1** and related compounds. The CD spectra of **1** exhibited in two solvent systems almost opposite mirror-image curves depending on the solvent. While a large negative Cotton effect ($\Delta\epsilon = -33.9$, 279 nm) was observed in $CHCl_3$, a similar positive Cotton effect ($\Delta\epsilon = 38.9$, 279 nm) appeared in methanol most probably due to dramatic conformational changes. Similar chiroptical reversal was observed in aglycon **2** and aglycon methyl ether **4**. These results can be best described in terms of solvent-dependent atropisomerism. This constitutes the first observation of solvent-dependent atropisomerism of a natural product. The crucial factor that perturbs the stable conformation in different solvents is discussed on the basis of molecular mechanics calculations.

Introduction

A multinuclear or polyaromatic organic molecule generally constitutes a rather rigid structure, which allows little conformational mobility. Irrespective of this general trend, however, nature occasionally creates intriguing molecules, in which atropisomerism can be observed. Streptovaricins, a classical group of ansamycin antibiotics, were the very first molecules of this class.[1] Several plant metabolites such as lignans and flavonoids and other natural products were also reported to exist in an atropisomeric state due to axial dissymmetry.[2]

A new cytotoxic antibiotic FD-594 (**1**) was isolated from *Streptomyces* sp. TA-0256, having moderate activities against several tumor cell lines as well as antibacterial activities against some Gram-positive bacteria.[3] We have recently elucidated the structure of **1** to have a glycosylated pyrano[4′,3′:6,7]naphtho[1,2-*b*]xanthene skeleton by spectroscopic means as shown in Figure 1.[4] The structure of **1** is related to a series of antibiotics, including pradimicins[5] and benanomicins,[6] and is quite similar to MS901809[7] and BE-13973X.[8] However, the stereochemistry of the latter two antibiotics has not been elucidated to date. While the chromophore of **1** is related to that of pradimicins, which are unique in that they form aggregates for exerting biological activity,[9] the site of glycosidation and the presence of a nitrogen functionality are completely different, which may be major reasons for their different biological activities.

The stereochemistry of the sugar moieties of **1** was determined by degradation experiments.[4] However, the absolute configuration of the aglycon part still remained to be clarified. During the chemical and biochemical studies of **1**, we became aware of an intriguing stereo-

† This paper is dedicated to Professor Kenneth L. Rinehart on the occasion of his 70th birthday.

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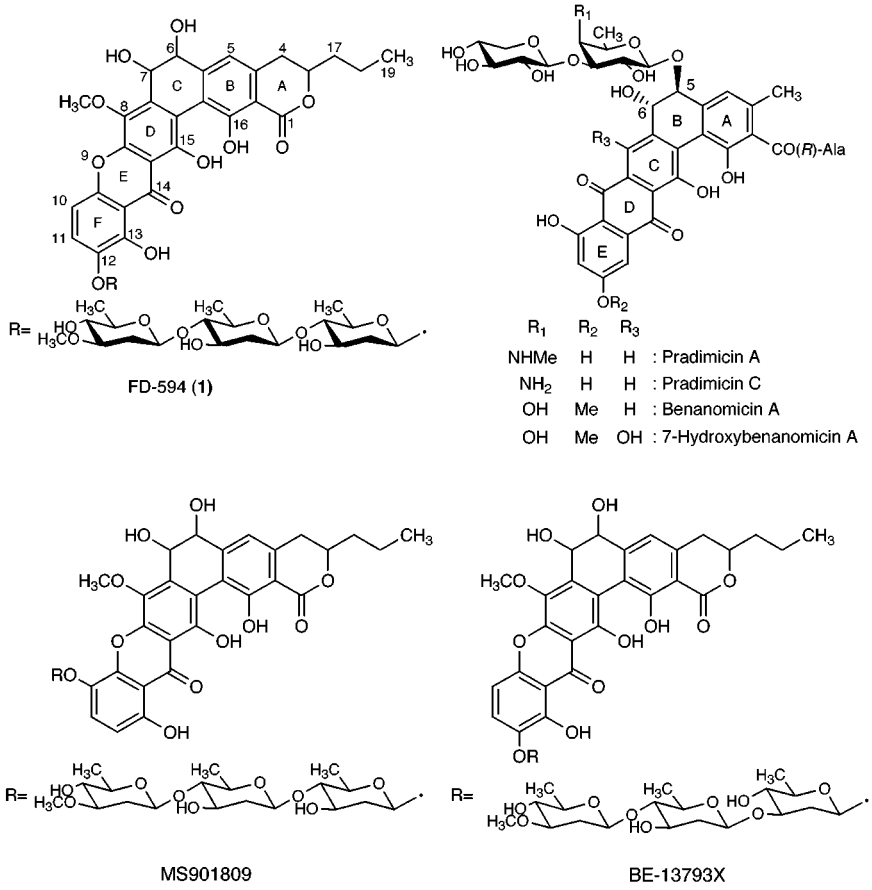


Figure 1. Structures of FD-594, pradimicins, benanomicins, MS901809, and BE-13973X.

chemical alteration of **1** and its derivatives. In this paper, we describe the absolute stereochemistry of **1** and the experimental and computational studies of the unique behavior of **1**, i.e., solvent-dependent atropisomerism.

Results and Discussion

The absolute stereochemistry at the B-ring of pradimicins was determined by means of ^{1}H NMR and CD spectroscopy.[5b] Konishi et al. reported that pradimicin and its derivatives exhibited a coupling constant of ca. 10 Hz between H-5 and H-6 in ^{1}H NMR spectra and showed negative first ($\Delta\epsilon = -30.6$, 225.4 nm) and positive second Cotton ($\Delta\epsilon = 16.14$, 205.8 nm) effects in the CD spectrum. From these results, it was concluded that pradimicins have (5*S*,6*S*)-configurations at the B-ring. This methodology seemed initially to be applicable to the determination of the absolute stereochemistry at the 6- and 7-positions of **1**, but this was not the case.

We had been aware from the early stage of the structural studies of **1** that the significant structural alteration of **1** took place depending on the experimental conditions of NMR spectroscopy; that is, several signals in the ^{13}C NMR spectrum were heavily broadened and were even diminished in various solvents probably due to slow conformational change.[4] In addition, the ^{1}H−^{1}H coupling constant of the crucial proton signals ($^3J_{\text{H-6,H-7}}$) varied depending on the solvent, e.g., 3.2 Hz in pyridine-d_5 and 9.3 Hz in $CDCl_3$. The latter coupling constant most likely suggested that the protons at 6- and 7-positions are diaxially oriented in a $CDCl_3$ solution. Furthermore, curious to us was the fact that the sign and value of optical rotation of the aglycon **2**,[4] which was derived from acid hydrolysis of **1**, was alternated again by changing the solvent; **2**: $[\alpha]_D$ −296° ($c = 0.66$, $CHCl_3$) and +493° ($c = 0.66$, methanol).

On the basis of these interesting observations, the CD spectra of **1** were measured with $CHCl_3$ and methanol solvents to analyze the chiroptical properties. The UV and CD spectra of **1** in $CHCl_3$ and in methanol are shown in Figure 2. The CD curves of **1** exhibited almost opposite signs depending on the solvent. While a large negative Cotton effect ($\Delta\epsilon = -33.9$, 279 nm) was observed in $CHCl_3$, a large positive Cotton effect ($\Delta\epsilon = 38.9$, 279 nm) appeared in methanol. To determine the absolute stereochemistry of **1** from these CD spectra, it was necessary to know the direction and position of the exciton transition moments in the molecule. Qualitatively, the UV bands at 276 and 233 nm, as also shown in Figure 2, may be ascribed to the intrachromophoric charge transfer and the long axis polarized transitions of the benzophenone (DEF rings) and benzoyl chromophores (AB rings) in **1**, respectively. However, it is rather difficult to assign the spatial arrangements of the exciton dipoles of these highly substituted chromophores, so that it is not easy to deduce the absolute stereochemistry of such a complex system by simple application of the CD exciton chirality method. But, the chiroptical reversal apparently indicates that **1** exists in a conformation having opposite orientation of the exciton dipoles depending on the solvent. This can be best described by solvent-dependent atropisomerism.

To obtain further insight into the interesting chiroptical properties of **1**, we studied the ^{1}H NMR and CD spectra of the derivatives of **1**, including the aglycon **2**,

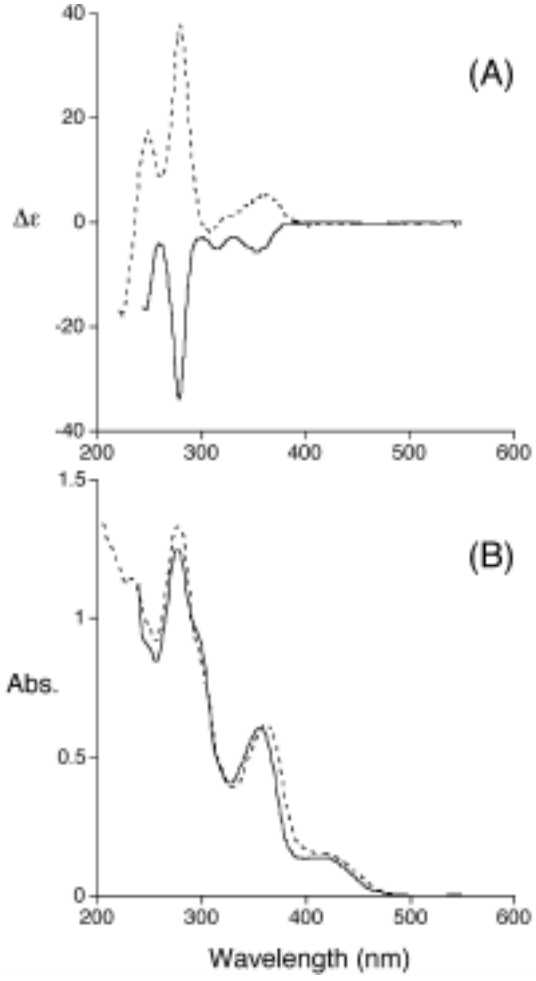


Figure 2. CD (A) and UV (B) spectra of FD-594 (**1**). The solid and dashed lines are plots of the spectra in $CHCl_3$ and in methanol, respectively.

an octaacetate **3**, an aglycon methyl ether **4**, and an acetonide derivative **5**. Derivatization of **1** into **2** and **3** were already reported in our previous paper,[4] and the compounds **4** and **5** were synthesized from **2** in the present study as shown in Scheme 1. The acetonide derivative **5** was synthesized as a conformationally fixed derivative. The CD spectra of **2**−**5** in $CHCl_3$ and methanol are shown in Figure 3, and the results of the CD spectra and the NMR coupling constants ($^3J_{H\text{-}6,H\text{-}7}$) of **2**−**5**, together with data for **1**, are summarized in Table 1. Interestingly, the aglycon **2** and the aglycon methyl ether **4** showed the same behavior of solvent-dependent atropisomerism as **1**, while the acetonide derivative **5** exhibited, as expected, almost the same CD curves with a large

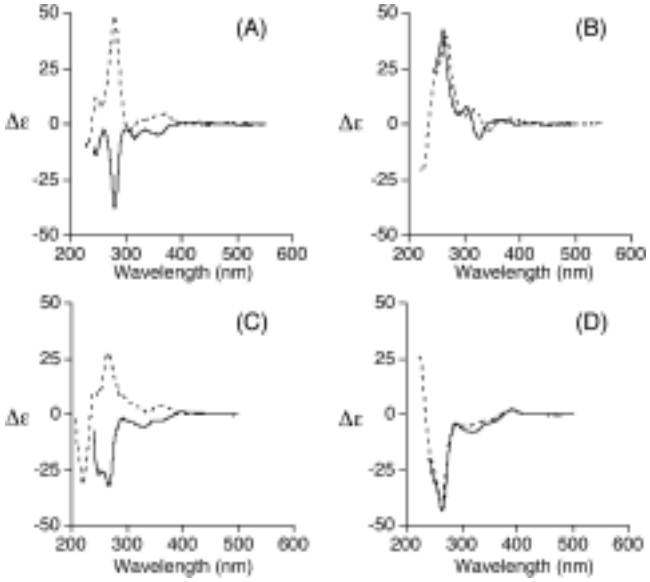


Figure 3. CD spectra of (A) the aglycon of FD-594 **2**, (B) octaacetate **3**, (C) methyl ether **4**, and (D) acetonide **5**. The solid and dashed lines are plots of the CD spectra in $CHCl_3$ and in methanol, respectively.

negative Cotton at 265 nm in both solvents. The acetonide **5** must exist in a conformation having two equatorial substituents at 6- and 7-positions, which was clearly verified by the coupling constants of $^3J_{H\text{-}6,H\text{-}7}$ (ca. 10 Hz). In contrast, the octaacetate **3** displayed only a large positive Cotton effect at ca. 265 nm in both $CHCl_3$ and methanol. By taking into account of the coupling constants between 6- and 7-H of **3** in both solvents, it appears that **3** exists in a single conformation with diaxial substituents at the 6- and 7-positions irrespective to the difference of the solvent. These results strongly suggest that the presence of the hydroxy groups at the 6- and 7-positions is an important factor for this solvent-dependent atropisomerism.

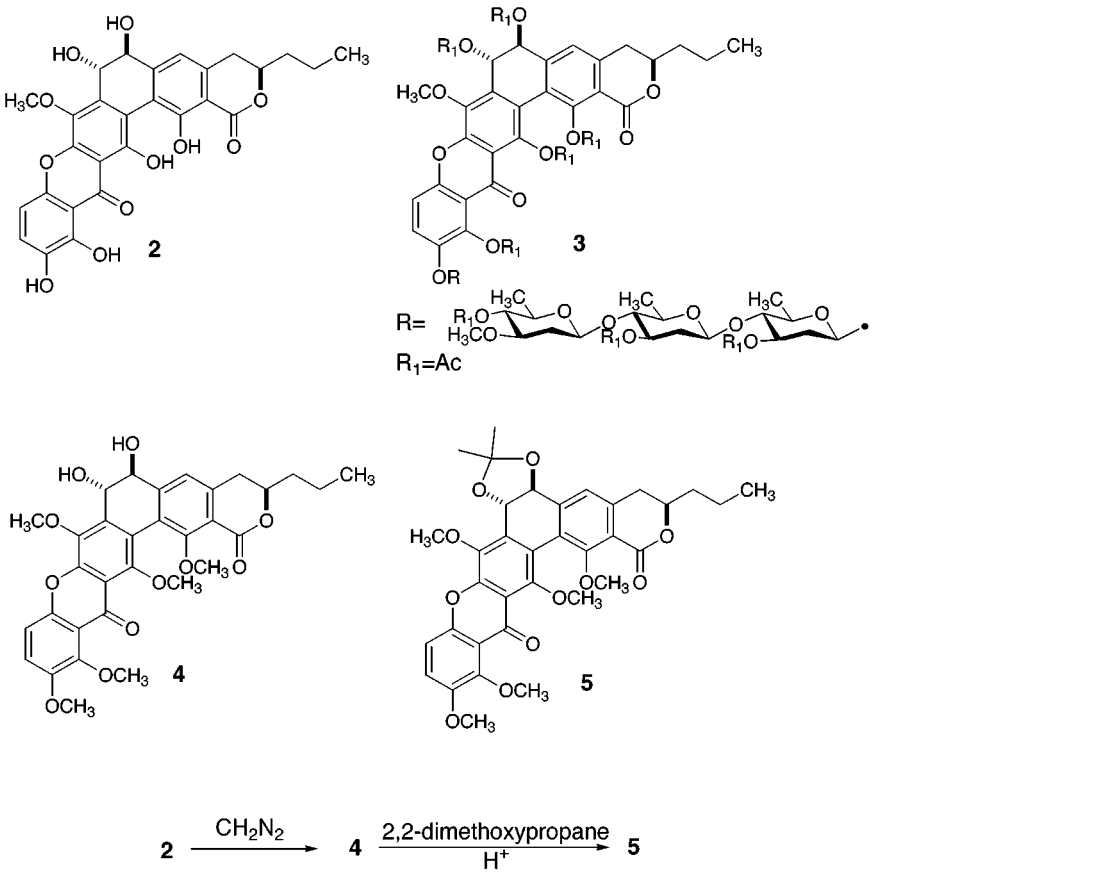
To determine the absolute stereochemistry of **1** and to get more insight into the conformational perspective of these compounds, X-ray crystallographic analysis was undertaken. Fortunately, the octaacetate **3** formed suitable prism-like crystals for X-ray analysis by recrystallization from $CHCl_3$−methanol (Figure 4). The absolute stereochemistry of the aglycon part of **1** was unambiguously determined to be 3*R*, 6*S*, and 7*S* as shown in Figure 5 based simply on the absolute structure of D-sugars.[4] Furthermore, the solid state conformation of **3** turned out to have two axial substituents at the 6- and 7-positions and a positive helicity of the axis between the planes of ring B and ring D. Since **3** exists in a single conformation

Table 1. CD and ^{1}H NMR Data of 1−5

compound	solvent	Δε (nm)	$^3J_{H\text{-}6,H\text{-}7}$ (Hz)[a]
FD-594 (**1**)	$CHCl_3$	−33.9 (279), −5.1 (315), −5.5 (353), 0.5 (422)	9.3
	methanol	−18.4 (224), +17.6 (248), +38.9 (279), −2.7 (308), +5.0 (362), −0.8 (409)	nd[b,c]
2	$CHCl_3$	−14.3 (247), −38.2 (280), −6.3 (317), −4.3 (357)	9.2
	methanol	+12.4 (247), +47.5 (280), −2.7 (307), +4.4 (366)	3.6
3	$CHCl_3$	+41.7 (261), +4.0 (304), −3.2 (327), +0.8 (362)	3.4
	methanol	+39.6 (267), +3.3 (306), −1.5 (335), +1.4 (375)	3.4
4	$CHCl_3$	−27.4 (249), −32.1 (267), −6.2 (331), −3.1 (359), +0.8 (397)	nd[b]
	methanol	−31.5 (221), +10.0 (242), +27.8 (265), +3.0 (361), −0.9 (398)	nd[b]
5	$CHCl_3$	−42.8 (265), −8.2 (320), +1.1 (389)	10.0
	methanol	−40.9 (266), −6.0 (315), +1.4 (388)	9.9

[a] Measured in the corresponding deuterated solvent. [b] Not determined due to signal broadening or overlapping. [c] 3.2 Hz in pyridine-d_5, 5.3 Hz in DMSO-d_6.

Scheme 1



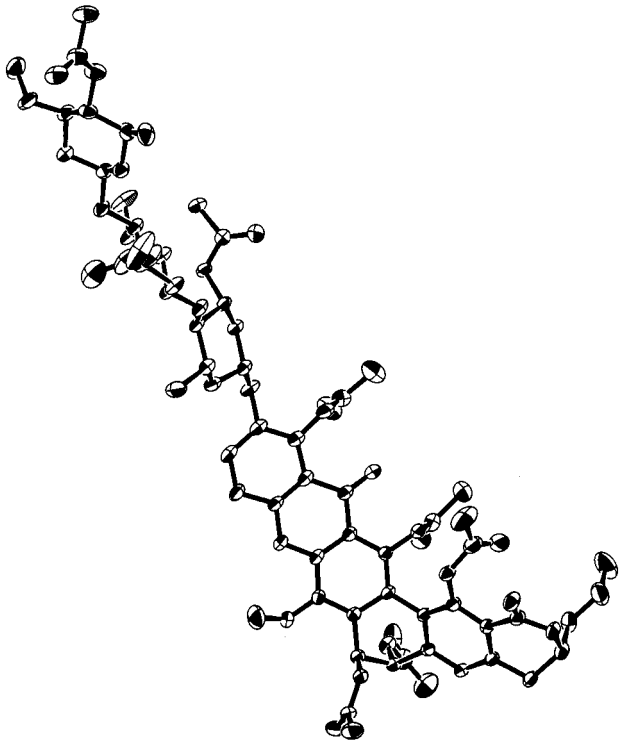


Figure 4. ORTEP drawing of **3** (thermal ellipsoids 25% probability level). H atoms have been omitted for clarity.

in solution with diaxial substituents at 6- and 7-positions, the solution conformation of **3** appeared to coincide with its solid state conformation. These results secured the conformational arguments of a series of these compounds.

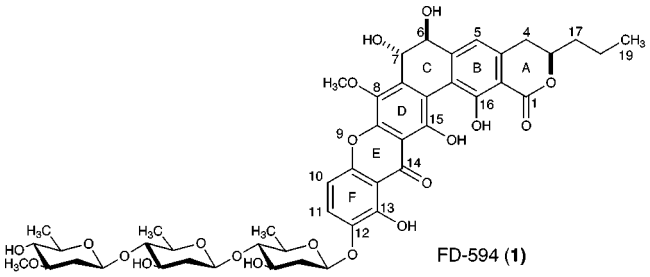


Figure 5. Stereostructure of FD-594 (**1**).

A large positive or negative Cotton effect around 270 nm reflects the helicity of the planes of ring B and ring D as in the case of the pradimicin group antibiotics. It appears, therefore, that a positive Cotton effect around 270 nm implies positive helicity of the biphenyl bond. The solvent-dependent atropisomerism of **1** can now be shown as Figure 6.

An important question arises regarding what factor(s) dictates the differentiation of a stable conformation when the solvent system is varied. Molecular modeling approaches have been frequently used to determine the lower energy conformations of a studied molecule. We took advantage of recent advances in molecular modeling techniques to evaluate this type of conformational equilibrium in addition to the results described above. Conformational searches and energy minimizations of **2**, **4**, and **6** were performed using the MM2 force field[10] in Macromodel version 5.5.[11] Compound **6** was employed as a model of the octaacetate **3**. All calculations were

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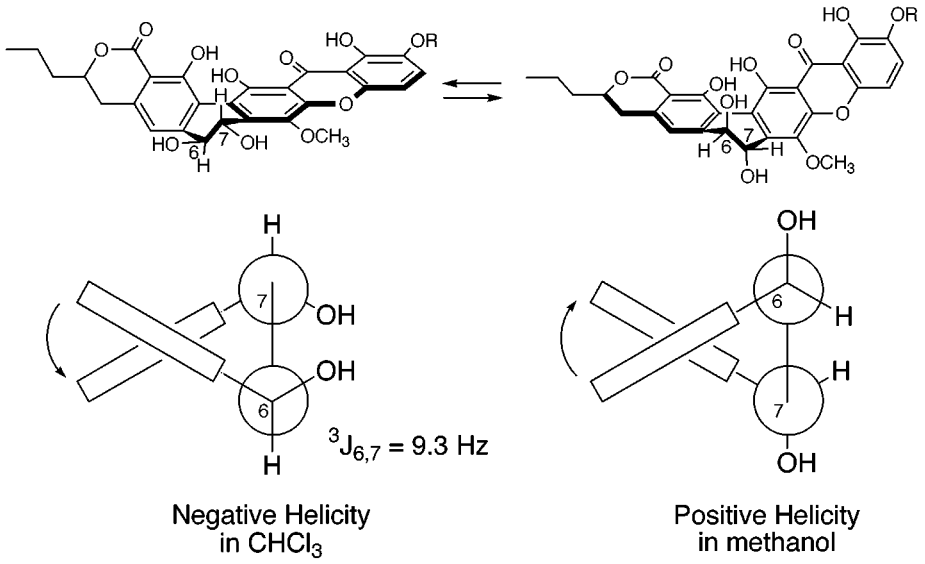
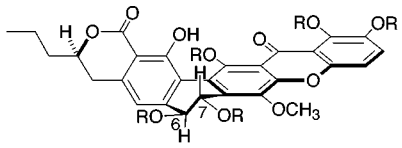
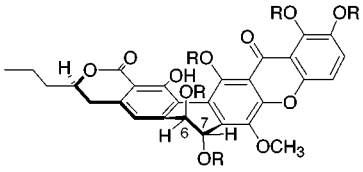
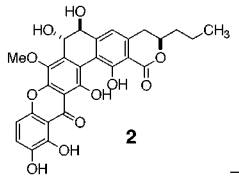
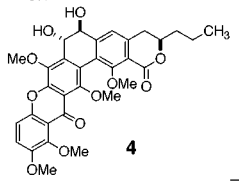
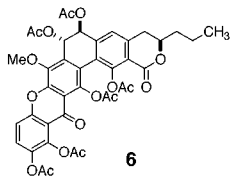


Figure 6. Solvent-dependent atropisomerism of **1**.

Table 2. Calculated Relative Steric Energies of 2, 4, and 6 in $CHCl_3$ and H_2O

			
 **2**	in $CHCl_3$	ΔSE= 0 kcal/mol	ΔSE = +2.24 kcal/mol
	in H_2O	ΔSE = +1.95 kcal/mol	ΔSE = 0 kcal/mol
 **4**	in $CHCl_3$	ΔSE = 0 kcal/mol	ΔSE = +1.17 kcal/mol
	in H_2O	ΔSE = +1.70 kcal/mol	ΔSE = 0 kcal/mol
 **6**	in $CHCl_3$	ΔSE = +4.33 kcal/mol	ΔSE = 0 kcal/mol
	in H_2O	ΔSE = +4.28 kcal/mol	ΔSE = 0 kcal/mol

performed using the implicit water or $CHCl_3$ GB/SA solvation model of Still et al.[12] Conformational searches were performed using the Monte Carlo method of Goodman and Still.[13]

The lowest energy structures and their relative steric energies (ΔSE) in each solvent system for **2**, **4**, and **6** are summarized in Table 2. The most stable conformations of **2** and **4** in $CHCl_3$ were calculated to have the negative helicity of the axis between the planes of ring B and ring D and the equatorial-like orientation of the two hydroxyl groups at the 6- and 7-positions, while in H_2O, the most stable conformations of **2** and **4** were estimated to have positive helicity and diaxially oriented hydroxy groups. Furthermore, the octaacetate model **6** was shown to prefer a single conformation with positive helicity in both solvent systems. The calculated results were consistent with the conformations deduced from the experimental data and further confirmed the solvent-dependent atropisomerism of **1**, **2**, and **4**.

(11) Macromodel Ver 5.5: Department of Chemistry, Columbia University, New York, 10027. See: Mohamadi, F.; Richard, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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These results probably indicate that important factors for these dramatic conformational changes include the intramolecular hydrogen bonding between the two hydroxy groups and the steric repulsion of the gauche-oriented two substituents at the 6- and 7-positions. In a less-polar solvent such as $CHCl_3$, the intramolecular hydrogen bonding effect seems to be superior to the steric effect, thereby leading to the conformation possessing the diequatorial hydroxy groups. In contrast, a more polar or protic solvent such as methanol or pyridine may break up the hydrogen bonding, and accordingly the steric repulsion of the gauche substituents as a whole bulk becomes predominant and leads to this type of conformational change. As for the peracetate derivative, the orientation of the *trans*-diaxial substituents is constantly favored by the steric effect between two acetate groups.

Similar solvent-dependent changes in CD spectra were previously reported for 9,10-dihydroxy-9,10-dihydrophenanthrene and its derivatives by Armstrong et al.,[14] who pointed out the importance of the intramolecular hydrogen bonding. However, to our knowledge, the present study represents the first example of naturally occurring compound showing the solvent-dependent atropisomerism.

In summary, during the studies on the absolute stereochemistry of FD-594 **1**, a new cytotoxic antibiotic, we observed the solvent-dependent atropisomerism of FD-594 and its related compounds.

Experimental Section

General. ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. ^1H and ^{13}C NMR chemical shifts were reported in δ values based on internal TMS ($\delta_H = 0$) or the solvent signal ($CDCl_3$ $\delta_C = 77.0$) as reference. Coupling constants (J) are reported in hertz. Column chromatography was carried out with Kieselgel 60 (70−230 mesh, Merck).

Methylation of the FD-594 Aglycon 2. To a solution of the FD-594 aglycon **2**[3] (32 mg) in methanol (1 mL) was added an excess amount of ethereal diazomethane. The mixture was allowed to stand at room-temperature overnight, and then the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography ($CHCl_3$−methanol, 15:1 to 8:1) to give 18 mg of **4**; $[\alpha]^{22}_D$: −171° (*c* 0.59, $CHCl_3$); UV ($CHCl_3$) λ_{max} (ϵ) 375 (4200), 329 (9400), 275 (31900) nm; IR ($CHCl_3$): 3573, 1716, 1666, 1481 cm^{-1}; HR-FABMS calcd for $C_{32}H_{33}O_{11}$ *m/z*: 593.2023, found 593.2052; ^1H NMR ($CDCl_3$) δ 7.34 (2H, m), 7.24 (1H, d, $J = 9.0$), 5.59 (1H, br), 5.35 (1H, br), 4.64 (2H, s), 4.49 (1H, br), 4.08 (3H, s), 4.03 (3H, s), 3.94 (3H, s), 3.84 (3H, s), 3.69 (3H, s), 2.96 (2H, m), 1.5−1.9 (3H, m), 1.26 (1H, m), 1.00 (3H, t, $J = 7.3$); ^{13}C NMR ($CDCl_3$) δ 175.1, 162.7, 159.6, 154.4, 149.6 (2C), 148.7, 143.3, 142.1, 141.7, 140.3, 135.0, 121.5, 119.5, 118.3, 117.8, 117.4, 116.8, 116.7, 112.4, 77.0, 74.1, 73.4, 62.8, 62.6, 62.3, 61.8, 57.1, 36.7, 34.6, 18.2, 13.9.

Acetonide Formation of 4. A solution of **4** (10 mg), 2,2-dimethoxypropane (33 mg), and *p*-toluenesulfonic acid (0.2 mg) in benzene (2 mL) was refluxed for 1 h. Saturated aqueous $NaHCO_3$ was added to the mixture, and the mixture was extracted with $CHCl_3$. The organic layer was washed twice with water, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel column chromatography ($CHCl_3$−methanol, 30:1 to 25:1) to give 4.9 mg of **5**; $[\alpha]^{22}_D$: −273° (*c* 0.49, $CHCl_3$); UV (methanol) λ_{max} (ϵ) 274 (50800), 221 (34500) nm; IR ($CHCl_3$) 1718, 1664, 1481, 1469 cm^{-1}; HR-FABMS calcd for $C_{35}H_{37}O_{11}$ *m/z*: 633.2336, found 633.2307; ^1H NMR ($CDCl_3$) δ 7.33 (1H, d, $J = 9.1$), 7.29 (1H, d, $J = 9.1$), 7.10 (1H, s), 4.62 (1H, dd, $J = 1.0, 10.0$), 4.58 (1H, d, $J = 10.0$), 4.50 (1H, m), 4.04 (3H, s), 4.01 (3H, s), 3.94 (3H, s), 3.81 (3H, s), 3.71 (3H, s), 2.99 (1H, d, $J = 16.5$ Hz), 2.90 (1H, dd, $J = 3.5, 16.5$), 1.88 (1H, m), 1.5−1.8 (3H, m), 1.63 (3H, s), 1.62 (3H, s), 1.00 (3H, t, $J = 7.3$); ^{13}C NMR ($CDCl_3$) δ 175.5, 162.4, 160.3, 154.3, 150.9, 149.9, 149.5, 148.6, 142.5, 141.7, 139.5, 133.9, 122.3, 119.5, 118.5, 118.0, 117.9, 116.7, 115.1, 114.9, 112.6, 79.8, 79.5, 77.0, 62.7, 62.6, 62.4, 61.9, 57.2, 36.8, 34.5, 27.2 (2C), 18.2, 13.9.

X-ray Crystallography. Diffraction data were collected by four-circle diffractometer using graphite monochromated Cu Kα radiation. Intensities were corrected for the Lorentz and polarization, crystal decay, and absorption (ψ-scan). The structure was solved by direct methods and refined by full matrix least squares using all intensities. Non-hydrogen atoms were refined using anisotropic models. Hydrogen atoms were located in calculated positions and refined using riding models.

Molecular Modeling. Conformational searches and energy minimizations were performed using Macromodel version 5.5.[11] The MM2 force field[10] implemented in Macromodel was used. All calculations were performed using the implicit water or $CHCl_3$ GB/SA solvation model of Still et al.[12] Conformational searches were performed using the Monte Carlo method of Goodman and Still.[13] For each search, 5000 starting structures were generated and minimized to an energy convergence of 0.05 (kJ/mol)/Å-mol using the full matrix Newton−Raphson method implemented in Macromodel. Duplicated structures and those greater than 50 kJ/mol above the global minimum were discarded.

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Supporting Information Available: X-ray crystallographic data of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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