$CDCl_3$) δ 23.00, 50.46, 61.77, 62.31, 70.23, 70.27, 71.30, 128.29, 128.31, 128.37, 128.52, 128.79, 128.96, 129.11, 129.37, 129.69, 129.78, 129.85, 133.08, 133.29, 133.39, 133.60, 144.81, 165.25, 165.51, 165.60, 166.00, 169.75. Anal. Calcd for $C_{37}H_{34}N_2O_{10}$ (666.683): C, 66.66; H, 5.14; N, 4.20. Found: C, 66.61; H, 5.16; N, 4.13.

2-Acetamido-2-deoxy-3:4,5:6-diisopropylidene-D-glucose Methyloxime (12). To a 250-mL round-bottom flask were added **5** (3.00 g, 13.56 mmol), methoxyamine hydrochloride (1.36 g, 16.27 mmol), and 60 mL of pyridine. The reaction was stirred for 12 h at which point the starting material was no longer visible by thin-layer chromatography (*n*-BuOH:AcOH:H_2O 5:3:2). The reaction was then concentrated by rotary evaporation, and toluene (3 × 100 mL) was used to azeotrope off any remaining pyridine to yield a clear syrup. To this reaction mixture were added 2,2-dimethoxypropane (100 mL) and *p*-toluenesulfonic acid (0.505 g, 0.2 equiv). The reaction mixture was refluxed for 5 h and allowed to cool to room temperature. Filtration followed by rotary evaporation gave a yellow syrup. This material was then dissolved in 150 mL of ethyl acetate and transfered to a 500-mL separatory funnel. The organic layer was washed twice with a brine solution (100 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. Purification by column chromatography on silica gel (2:1 hexanes:ethyl acetate) yielded **12** as a clear syrup (2.78 g, 62%): IR (NaCl) 3300, 2990, 2940, 2890, 1650, 1530, 1370, 1250, 1215, 1160, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (s, 6 H), 1.30 (s, 3 H), 1.37 (s, 3 H), 1.95 (s, 3 H), 3.60 (t, 1 H, *J* = 8.1 Hz), 3.75 (s, 3 H), 3.90 (dd, 1 H, *J* = 4.7, 8.5 Hz), 3.96 (m, 1 H), 4.06 (m, 1 H), 4.08 (dd, 1 H, *J* = 2.5, 5.2 Hz), 4.96 (ddd, 1 H, *J* = 2.6, 4.3, 9.2 Hz), 6.33, (d, 1 H, *J* = 9.2 Hz), 7.30 (d, 1 H, *J* = 4.3 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 23.04, 25.07, 26.33, 26.67, 26.68, 48.18, 61.59, 67.48, 76.63, 77.48, 79.80, 109.41, 109.91, 146.92, 169.40. Anal. Calcd for $C_{15}H_{26}N_2O_6$ (330.38): C, 54.53; H, 7.93; N, 8.48. Found: C, 54.46; H, 8.01; N, 8.39.

Procedure for the Ozonolysis of Oximes to Aldehydes. 2-Acetamido-2-deoxy-3,4,5,6-tetra-*O*-acetyl-*aldehydo*-D-mannose (16). To a 1-L Erlenmeyer flask were added **9** (3.00 g, 7.17 mmol) and 600 mL of CH_2Cl_2. The reaction was cooled to −78 °C, and ozone as bubbled through the reaction mixture for 1 h. The saturated ozone solution was allowed to stand for an additional 10 h, at which time the starting material was no longer visible by TLC (1:1 ethyl acetate:hexanes). Excess ozone was removed by purging the system with N_2. Dimethyl sulfide (6.0 mL, 81.6 mmol) was added to the reaction at −78 °C, and the reaction mixture was allowed to warm to room temperature (4 h). The reaction was transfered to a 1-L separatory funnel and washed twice with a brine–bicarbonate solution (1:1 v/v, 200 mL). The organic layer was dried over $NaSO_4$ and concentrated in vacuo to yield **16** as a colorless syrup (2.60 g, 93%, >95% purity). Compound **16** was unstable to silica gel and could not be further purified. The major impurity, DMSO, could be removed under high vacuum (48 h). IR (NaCl) 3350 (br), 2980, 1740, 1670, 1540, 1370, 1210, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 3 H), 2.04 (s, 6 H), 2.06 (s, 3 H), 2.13 (s, 3 H), 4.11 (dd, 1 H, *J* = 5.6, 12.6 Hz), 4.25 (dd, 1 H, *J* = 2.9, 12.6 Hz), 4.75 (d, 1 H, *J* = 5.5 Hz), 5.12 (ddd, 1 H, *J* = 2.9, 5.5, 8.0 Hz), 5.44 (dd, 1 H, *J* = 3.4, 5.5 Hz), 5.48 (dd, 1 H, *J* = 3.4, 7.7 Hz), 9.55 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.50, 20.65, 20.73, 20.76, 22.82, 58.38, 61.64, 68.48, 68.93, 69.82, 169.88, 170.16, 170.59, 196.10; mass spectrum (FAB^+) 390 (MH^+, 80%), 160 (base).

Compounds **13**, **14**, **15**, **17**, **18**, and **19** were prepared from their corresponding oximes according to the procedure described above. Spectral data for these compounds are provided below.[6,13]

2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-glucose (13): yield 87%; IR (NaCl) 3460, 2940, 1740, 1430, 1370, 1230, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.06 (s, 3 H), 2.07 (s, 6 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 4.10 (dd, 1 H, *J* = 5.5, 12.4 Hz), 4.28 (dd, 1 H, *J* = 3.2, 12.4 Hz), 5.13 (m, 1 H), 5.27 (d, *J* = 5.1 Hz), 5.50 (dd, 1 H, *J* = 3.6, 7.6 Hz), 5.5. (dd, 1 H, *J* = 3.6, 5.0 Hz), 9.52 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.22, 20.37, 20.42, 20.59, 20.67, 61.59, 68.10, 68.19, 68.33, 74.97, 169.25, 169.41, 169.59, 169.72, 170.53, 193.80.

2,3,4,5-Tetra-*O*-acetyl-*aldehydo*-D-arabinose (14): yield 90%; IR (NaCl) 3460, 2940, 1740, 1430, 1370, 1230, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 6 H), 2.09 (s, 3 H), 2.21 (s, 3 H), 4.19 (dd, 1 H, *J* = 4.5, 12.6 Hz), 4.32 (dd, 1 H, *J* = 2.6, 12.6 Hz), 5.27 (m, 1 H), 5.39 (d, 1 H, *J* = 2.1 Hz), 5.68 (dd, 1 H, *J* = 2.1, 9 Hz), 9.48 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.19, 20.36, 20.55, 20.59, 61.38, 67.13, 67.92, 75.77, 110.43, 169.41, 169.50, 169.78, 170.44, 193.79.

2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-mannose (15): yield 92%; IR (NaCl) 3520, 3030, 1775, 1765, 1470, 1460, 1390, 1240, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 2.03 (s, 3 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 2.16 (s, 3 H), 4.11 (dd, 1 H, *J* = 4.8, 12.6 Hz), 4.20 (dd, 1 H, *J* = 2.6, 12.6 Hz), 5.01 (dd, 1 H, *J* = 1.0, 7.8 Hz), 5.13 (ddd, 1 H, *J* = 2.6, 4.8, 9.0 Hz), 5.44 (dd, 1 H, *J* = 2.2, 9.0 Hz), 5.47 (dd, 1 H, *J* = 2.2, 7.7 Hz), 9.40 (d, 1 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.34, 20.44, 20.54, 20.60, 20.71, 61.71, 67.21, 67.47, 67.62, 74.14, 169.51, 169.58, 169.71, 169.82, 170.50, 195.19.

2-Acetamido-2-deoxy-3,4,5,6-tetra-*O*-benzoyl-*aldehydo*-D-mannose (17): yield 99%; IR (NaCl) 3360, 3060, 2960, 1720, 1670, 1520, 1315, 1260, 1180, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.00 (s, 3 H), 4.66 (dd, 1 H, *J* = 6.2, 12.4 Hz), 4.91 (dd, 1 H, *J* = 3.2, 12.3 Hz), 5.12 (dd, 1 H, *J* = 3.5, 6.9 Hz), 5.84 (m, 1 H), 6.03 (t, 1 H), 6.20 (t, 1 H, *J* = 5.7 Hz), 6.63 (d, 1 H, *J* = 6.6 Hz), 7.3–7.6 (7, 12 H), 7.85–8.05 (m, 8 H), 9.81 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.72, 59.80, 62.25, 70.22, 70.62, 71.11, 128.33, 128.38, 128.44, 128.65, 129.00, 129.33, 129.71, 129.76, 129.79, 129.85, 133.14, 133.41, 133.61, 133.85, 165.34, 165.42, 165.68, 166.02, 170.38, 195.48.

2-Acetamido-2-deoxy-3,4,5,6-tetra-*O*-acetyl-*aldehydo*-D-glucose (18): yield 85%; IR (NaCl) 3350 (br), 2980, 1740, 1670, 1540, 1370, 1210, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.11 (s, 3 H), 2.14 (s, 3 H), 4.10 (dd, 1 H, *J* = 4.9, 12.5 Hz), 4.23 (dd, 1 H, *J* = 3.0, 12.5 Hz), 4.88 (t, 1 H, *J* = 6.0 Hz), 5.16 (ddd, 1 H, *J* = 3.0, 5.0, 8.1 Hz), 5.38 (dd, 1 H, *J* = 3.1, 8.4 Hz), 5.71 (dd, 1 H, *J* = 3.1, 6.0 Hz), 6.25 (d, 1 H, *J* = 12 Hz), 9.67 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.27, 20.40, 20.51, 20.77, 22.67, 57.72, 60.16, 61.43, 67.92, 68.65, 169.19, 169.58, 169.82, 170.29, 170.98, 196.32.

2-Acetamido-2-deoxy-3:4,5:6-diisopropylidene-*aldehydo*-D-glucose (19): yield 90%; IR (NaCl) 3430, 3350, 1735, 1680, 1500, 1370, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32 (s, 3 H), 1.34 (s, 3 H), 1.36 (s, 3 H), 1.42 (s, 3 H), 2.08 (s, 3 H), 3.65 (t, 1 H, *J* = 8.1 Hz), 3.96 (dd, 1 H, *J* = 4.4, 8.7 Hz), 4.07 (ddd, 1 H, *J* = 4.4, 6.3, 8.0 Hz), 4.13 (dd, 1 H, *J* = 6.3, 8.7 Hz), 4.49 (dd, 1 H, 1.9, 8.0 Hz), 4.99 (dd, 1 H, *J* = 1.9, 9.0 Hz), 6.24 (d, 1 H, *J* = 8.8 Hz), 9.64 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.96, 25.01, 26.36, 26.65, 40.72, 58.24, 67.53, 76.68, 77.38, 109.91, 110.13, 170.13, 197.73.

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Registry No. 1, 50-99-7; 2, 10323-20-3; 3, 3458-28-4; 4, 3615-17-6; 5, 7512-17-6; 6, 91869-00-0; 7, 122408-27-9; 8, 122382-99-4; 9, 122383-00-0; 10, 122383-01-1; 11, 122383-02-2; 12, 122383-03-3; 13, 3891-59-6; 14, 3891-58-5; 15, 66888-27-5; 16, 122383-04-4; 17, 122383-05-5; 18, 53942-44-2; 19, 22595-97-7.

Restricted Rotation and Torsional Isomerism in Tamoxifen Derivatives

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Introduction. In recent years there has been an increased interest in the molecular structure of the anti-

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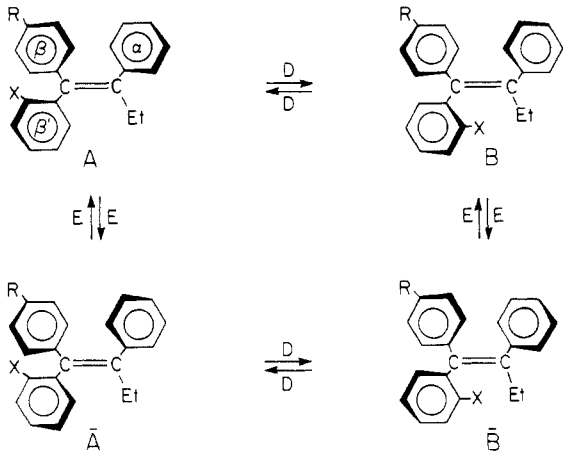
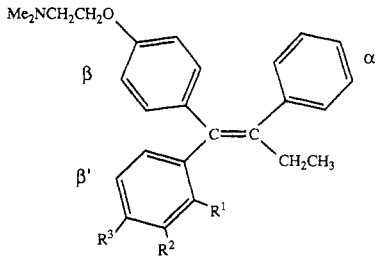


Figure 1. The four stereoisomeric forms of an ortho-substituted tamoxifen in the β'-ring (X = Et; R = $Me_2NCH_2CH_2O$–). Overbars on capital letters denote enantiomeric forms (e.g., A and $\bar{A}$ are enantiomers); diastereomerization and enantiomerization processes are indicated by D and E, respectively.

estrogenic drug *trans*-tamoxifen ((*Z*)-1-(*p*-(2-(dimethylamino)ethoxy)phenyl)-1,2-diphenylbut-1-ene, **1a**), its de-



1a, $R^1 = R^2 = R^3 = H$
1b, $R^1 = OH$, $R^2 = R^3 = H$
1c, $R^1 = R^3 = H$, $R^2 = OH$
1d, $R^1 = Me$, $R^2 = H$, $R^3 = OH$

rivatives, and related substituted triarylvinyl systems.[1] Since the binding of **1a** to the estrogen receptor is thought to be intimately associated with the topology of the molecule, several derivatives were studied by x-ray diffraction[2] to find a correlation between the binding ability to the receptor, the biological activity, and the conformation of the molecule. It is assumed that the solid-state conformation grossly reflects the preferred conformation in solution.[2] It has been found that the triarylvinyl moiety uniformly exists in a propeller conformation where the three rings are twisted in the same sense although to a different extent.[3] It has been argued that the dihedral angles of the propeller blades (rings) are related to the relative binding affinity (RBA) of the triarylvinyl system to estrogen receptors: the smaller the torsion angles, the lower the binding affinity.[4] Of special stereochemical interest are derivatives in which one of the rings is unsymmetrically substituted, e.g., at the ortho or meta position, by a "tag". Assuming fast interconversion between the different conformations of the ethyl and (dimethylamino)ethoxy groups and slow aryl rotation, the lower symmetry of the substituted ring results in the existence of four stereoisomeric forms. These forms (two pairs of enantiomers) can be viewed as differing in helicity (the sense of twist of the rings) and in the relative position of the tag substituent (above or below the mean double-bond plane).[5] The four stereoisomeric forms of a tamoxifen derivative substituted at the β' ring (the ring cis to the Et group) are schematically depicted in Figure 1: the two pairs of enantiomers are designated A and B, and an overbar designates an enantiomeric relation (e.g., A and $\bar{A}$ are enantiomers). In principle, the four stereoisomeric forms of a tagged tamoxifen should differ in their RBAs and in their biological activity. If the four forms could be separated and their relative RBAs measured separately, a better understanding of the geometric factors governing the binding of the tamoxifen to the receptor could be obtained.

Recent reports concerning the feasibility of the separation of stereoisomers of triarylvinyl derivatives are contradictory. In a work where the unsymmetrically substituted tamoxifens **1b–d** were crystallographically studied,[6] it was found that they exist in the crystal as a single enantiomeric pair. Empirical force field calculations of the interconversion barriers between only two stereoisomeric forms of **1b** and **1c** were reported. The mutual interconversion barriers were calculated as "higher than 999 kcal mol^{-1}"(!), and it was concluded that the stereoisomers are noninterconvertible.[6] However, such barriers to rotation must be wrong since barriers to rotation about a single bond *even 25-fold lower* are regarded as unusually high,[7] and these calculated barriers are at variance with experimental barriers for rotation around the C=C—Ar bonds in more crowded triarylvinyl compounds. In a more recent paper, MMP2 calculations were performed on **1b** and **1c** by driving the β' ring by 30° steps to test a possible correlation between cis ⇌ trans isomerization and the rotational barrier of the β' ring.[8] It was concluded that a substantial barrier to rotation exists, but the calculations indicated that the barrier for the enantiomerization process (see below) is lower than 10 kcal mol^{-1}.[9] Unfortunately, although these calculations disproved the claim that high rotational barriers separate the stereoisomers, two problems still remain: (a) Apparently both sets of calculations did not take into account the possible existence of four stereoisomeric forms (A, B, $\bar{A}$, and $\bar{B}$). (b) The two transition states, which involve an ideally coplanar arrangement of the β' ring and the double-bond plane with the tag pointing either to the Et substituent or to the β ring,

(1) See, for example: Jordan, V. C. *Pharmacol. Rev.* **1984**, *36*, 245, and references therein.
(2) For example: (a) Kilbourn, B. T.; Owston, P. G. *J. Chem. Soc. B* **1970**, 1. (b) Precigoux, P. G.; Courseille, C.; Geoffre, S.; Hospital, M. *Acta Crystallogr., Sect. B* **1979**, *35*, 3070. (c) Hunter, D. H.; Payne, N. C.; Rahman, A.; Richardson, J. F.; Ponce, Y. Z. *Can. J. Chem.* **1983**, *61*, 421. (d) Shani, J.; Gazit, A.; Livshitz, T.; Biran, S. *J. Med. Chem.* **1985**, *28*, 1504. (e) McCague, R.; Kuroda, R.; Leclerq, G.; Stoessel, S. *Ibid.* **1986**, *29*, 2053.
(3) We concluded from analysis of crystal data of triarylvinyl compounds that the propeller conformation represents the minimum energy conformation for the 1,1-di-, tri-, and tetraarylvinyl moieties (Kaftory, M; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1701. Kaftory, M.; Nugiel, D. A.; Biali, S. E.; Rappoport, Z. *Ibid.*, in press).
(4) This is corroborated by using triarylvinyl systems with geometrical constrains as described in ref 2e.
(5) The number of stereoisomers for different substitution patterns of a triarylvinyl propeller was previously tabulated: Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1984**, *106*, 477.
(6) Kuroda, R.; Cutbush, S.; Neidle, S.; Leung, O.-T. *J. Med. Chem.* **1985**, *28*, 1497. In figures 7 and 8 of this paper the contours of 1 kcal mol^{-1} around the stable conformers are rather spread, and it is difficult to imagine how this is consistent with the >999 kcal mol^{-1} barrier.
(7) Rotational barriers around C–C bonds are usually in the 3–28 kcal mol^{-1} range, and values larger than 40 kcal mol^{-1} are rare. For an extensive source of C–C rotational barriers determined by NMR see: Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH Publishers: Deerfield Beach, FL, 1985. One of the largest rotational barriers around a C–C bond was reported in dicarbomethoxy-9,9′-bitriptycyl for which a lower limit of $\Delta G_c^* > 55$ kcal mol^{-1} was experimentally obtained. See: Schwarz, L. H.; Koukotas, C.; Kukkola, P.; Yu, C. S. *J. Org. Chem.* **1986**, *51*, 995. Schwarz, L. H.; Koukotas, C. *J. Am. Chem. Soc.* **1977**, *99*, 7710.
(8) Duax, W. L.; Griffin, J. F. *J. Steroid Biochem.* **1987**, *27*, 271.
(9) Surprisingly, no reference was made to the calculated >999 kcal mol^{-1} barrier.

were calculated as having identical energy.[10] These results prompted us to reanalyze the internal rotation of tamoxifen analogues in terms of flip mechanisms (see below).

Rotational Barriers in Triarylvinyl Propellers. Molecular propellers usually display correlated rotation (leading to helicity reversal), which is usually analyzed in terms of flip mechanisms.[11,12] In these mechanisms as applied to vinyl propellers the ring that "flips" passes through the normal to the double-bond plane, whereas the nonflipping rings rotate concurrently in the opposite direction and pass through the double-bond plane. Depending on the number of flipping rings, these mechanisms are dubbed zero-, one-, two-, or three-ring flip.[13] For the case of the tamoxifen derivatives **1b** or **1c**, a flip process that can interconvert the diastereomers A and B or $\bar{A}$ and $\bar{B}$ (i.e., a diastereomerization process, D in Figure 1) is the three-ring flip. For the enantiomerization process (E in Figure 1) that interconverts A and $\bar{A}$ or B and $\bar{B}$, the tagged ring must pass through the double-bond plane (for example, via an [α,β] two-ring flip). Two diastereomeric transition states can be envisioned for this process, since the tag can point either to the β ring or to the Et group.

The highest barrier for a three-ring flip process of a triarylvinyl compound reported to date is 20.5 kcal mol^{-1} in the sterically hindered trimesitylethylene (**2**).[14] Since

$$\underset{\mathbf{2}}{Mes_2C{=}CHMes}$$

$$\underset{\mathbf{3}}{Mes_2C{=}C(OAc)(2,4,6\text{-}Me_3\text{-}3\text{-}MeOC_6H)}$$

$$Mes = 2,4,6\text{-}Me_3C_6H_2$$

2 rapidly enantiomerizes at room temperature via a lower energy (16.8 kcal mol^{-1}) [α,β] two-ring flip, its resolution is precluded at room temperature. It is therefore highly unlikely that the barrier for helicity reversal (diastereomerization) process for **1b** or **1c** will be higher than 23–25 kcal mol^{-1}, which is the barrier required for the separation of isomers at room temperature. Indeed, if the rotational barrier is mainly determined by the mutual steric interactions in the transition state, these rotational barriers for **1b** and **1c** should be lower than 20.5 kcal mol^{-1}. The NMR evidence is in full agreement with this conclusion: for a frozen propeller conformation of **1a** the two CH_2 protons of the Et group are diastereotopic and, precluding accidental isochrony, are therefore anisochronous. However, the NMR spectrum of **1a** does not display diastereotopic protons, therefore indicating that the enantiomerization of the molecule in solution is rapid on the NMR time scale. Moreover, the report that cooling a sample to 198 K had no effect on the appearance of the spectrum[2e] indicates an even lower enantiomerization barrier.[9]

Less information is available concerning the E process, which requires the passage of the tagged ring through the double-bond plane with concomitant helicity reversal. We have shown earlier that the barrier for this process for compound **3** is 22.2 kcal mol^{-1} and isolated its residual enantiomers.[15] The barrier for the D process of **3** is 19.0 kcal mol^{-1}. Although the steric requirements of the 3-methoxy-2,4,6-trimethylphenyl ring in **3** are larger than for the unsubstituted phenyl ring in **1**, and this should render highly unlikely the existence of a >22 kcal mol^{-1} barrier, it could be argued that the different relative positions of the rings and the different substituents cis to them raise the barrier for **1** to the calculated high value. We therefore decided to estimate the rotational barriers by molecular mechanics (MM2(85) force field) calculations.[16]

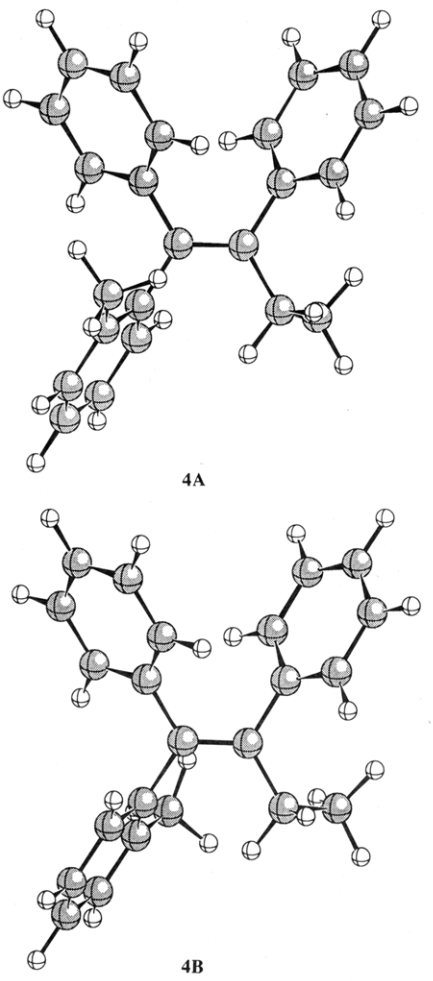
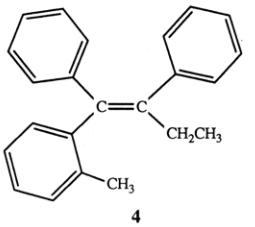


Figure 2. Calculated structures for the two diastereomeric forms of **4** (**4A** and **4B**).

Molecular Mechanics Calculations. To reduce the computation time, we chose **4** with the unsymmetrical



4

β'-tolyl ring as a model compound for **1d**, since the para substituents in the β and β' rings in **1** should have only a minor effect on the rotational barriers.

In the calculations the crystallographic conformation of the ethyl group ((−)-anticlinal, C_{sp^3}—C_{sp^3}—C=C torsional

(10) Cf. Figure 10 in ref 8.

(11) (a) Kurland, R. J.; Schuster, I. I.; Colter, A. K. *J. Am. Chem. Soc.* **1965**, *87*, 2279. (b) Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 1535. (c) Mislow, K. *Acc. Chem. Res.* **1976**, *9*, 26.

(12) For a recent review on correlated rotation in molecular propellers see: Willem, R.; Gielen, M.; Hoogzand, C.; Pepermans, H. In *Advances in Dynamic Stereochemistry*; Gielen, M., Ed.; Freund: London, 1985; p 207.

(13) For a schematic representation of the ideal transition states of the flip mechanisms see Figure 3 in ref 5.

(14) Biali, S. E.; Rappoport, Z. *J. Org. Chem.* **1986**, *51*, 2245.

(15) Biali, S. E.; Rappoport, Z.; Mannschreck, A.; Pustet, N. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 199.

(16) Allinger, N. L. *QCPE MM2(85)*. See also: Sprague, J. T.; Tai, J. C.; Yuh, Y. H.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 1051.

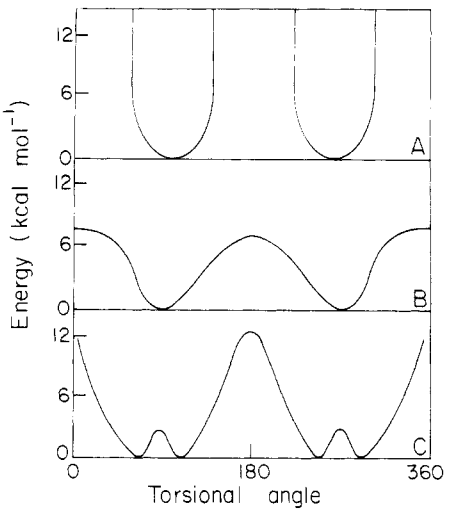


Figure 3. Qualitative calculated potential energy diagrams as a function of the (β')C_x—C_{ipso}—C=C torsional angle for unsymmetrical substituted tamoxifen derivatives. A: adapted from Figure 6 of ref 6; two noninterconvertible stereoisomers. B: adapted from Figure 10 of ref 8; two interconvertible forms. C: present work; four interconvertible forms at room temperature.

angle of 120°) was chosen for the starting geometry. The conformations of the two diastereomeric forms of **4** (corresponding to Ā and B̄ in Figure 1) were first calculated.[17] The energy-minimized structures **4A** and **4B** have similar steric energies and similar torsional aryl—C=C angles (73°, 47°, and 49° (**4A**) and 71°, 47°, and 50° (**4B**) for the β', β, and α rings, respectively) and bond lengths and angles (Figure 2). In both calculated conformations, the ethylenic double bond is slightly twisted (i.e., the *trans*-C_{Ar}—C=C—C_{Ar} angles are 173.3° and 173.7° for **4A** and **4B**, respectively). The ethyl groups are oriented in a (-)-anticlinal conformation (C_{sp^3}—C_{sp^3}—C=C angles of -131° (**4A**) and -118° (**4B**)).

In general, the calculated structural parameters of **4A** and **4B** are close to the experimental (X-ray) values of **1d**:[6,8] e.g., the experimental torsional angles for **1d** are 67.9°, 43.1°, and 59.6°. The calculated ethylenic C=C bond length is 1.356 Å, which compares with the experimental value of 1.351 Å for **1d**. The calculated =C—Ar bond lengths are in the 1.489-1.500-Å region, while the C—C=C and C—C(=)—C bond angles are in the 115-122° region.

To estimate the barriers for the D and E processes, the *o*-tolyl ring was first driven in either a clockwise or a counterclockwise direction by increments in its torsional angle of 10°. After the high-energy regions were located, the calculations were repeated using 2° steps to locate the transition states. Although only this tagged ring was driven, in each case the two other rings followed and the overall processes calculated resulted in helicity reversal. The calculated barriers were 13 kcal mol^{-1} for the enantiomerization process **4A** ⇌ **4Ā** (or **4B** ⇌ **4B̄**) occurring via an [α,β] two-ring flip in which the methyl group on the β' ring points to the β ring in the transition state[18] and 3 kcal mol^{-1} for the diastereomerization **4A** → **4B** (or **4B̄** → **4Ā**), which occurs via a three-ring flip. As expected, these values are lower, and their difference is larger than the corresponding values observed for the two- and three-ring flips for the apparently more crowded **2** and **3**.[14,15] In conclusion, in contrast to the earlier calculations, which dealt only with a two-minima potential energy surface and gave either very high barriers for aryl rotation[6] or a low barrier for the two-ring flip and no barrier for the three-ring flip,[10] our calculations show a four-minima surface with two low barriers of different magnitude. A schematic comparison of the three calculations is given in Figure 3.

RBA of Tamoxifen Derivatives. The crystal structures of **1b** and **1c** showed the hydroxy group as being respectively "above" and "below" the double-bond plane. Differences in the RBAs were ascribed to these differences, and it was suggested that substituents "below" the double-bond plane reinforce the binding. However, if the barriers for interconversion of stereoisomers in solution are indeed of the order of magnitude calculated in the present work, this conclusion cannot hold without additional support. Only if the dissolution of a crystal of a single diastereomer is followed by an irreversible binding that is faster than stereoisomer interconversion will the above conclusion be correct. Since the low rotational barriers of **1b-d** result in rapid diastereomerizations and enantiomerizations in solution, the previous conclusions are probably incorrect. More likely, the different RBAs are the result of the nature and the position of the substituents on the β' ring and not due to a different frozen orientation of the substituent above or below the double-bond plane.

Conclusions. The calculated barriers for the D and E processes of substituted tamoxifens are relatively low. In contrast with a previous conclusion, the low rotational barriers should preclude the isolation of the four diastereomeric forms of a "tagged" tamoxifen derivative at room temperature, at least when the substituents are not extremely bulky.

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(17) All calculations were done using the NPLANE=1 (nonplanar option) of the MM2(85) program.

(18) The transition state of the enantiomerization process involving an [α,β] two-ring flip in which the methyl or the *o*-tolyl ring points to the ethyl group was calculated as having higher energy than the aforementioned enantiomerization process.

A General Route to 3-Functionalized 3-Norcephalosporins

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Modifications of natural cephalosporins (i.e. **1**) by chemical manipulation at C-3 have yielded biologically important derivatives.[1] More specifically, the class of 3-norcephalosporins, i.e. cephalosporins bearing substituents other than carbon at C-3, although still relatively unexplored, has already afforded several useful antibacterials, including the powerful broad-spectrum antibiotics cefaclor,[2] **2**, cefroxadine,[3] ceftizoxime,[4] and others.[1,5] The lack of a convenient general route to 3-norcephalosporins may have delayed progress in this area.

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