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X-Ray crystallographic evidence for a vinylogous anomeric effect in benzotriazole-substituted heterocycles

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Abstract—Structural evidence for the existence of a ‘vinylogous’ anomeric effect is presented for a series of 4*H*-4-benzotriazolyl-2,6-diarylpyrans **1a**,**b** and for their benzo-fused derivatives **2**–**5** and nitrogen analogue **6**. X-Ray crystal structure analyses reveal changes in the geometry of the central ring and exocyclic C–N bond, which are discussed in terms of an interaction of the benzotriazole fragment with a heteroatom through four bonds. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In cyclic systems, the classical anomeric effect[1] involves the geminal interaction of two heteroatoms. This effect is generally explained as being due to favorable overlap between the lone-pair orbital (n_o) of an endocyclic oxygen (or other heteroatom) with the antibonding σ^*_{CX} orbital of a geminal X-substituent. Such stereoelectronic interactions cause electronegative substituents X at C2 of tetrahydropyrans (Fig. 1a) to favor an axial orientation and also induce C–X* bond lengthening in such conformers. Extensive crystallographic data support the existence of such n_o–σ^*_{CX} delocalization by demonstrating that species with O–C–X_{axial} fragments have a shorter C–O bond and a longer C–X bond than those with an O–C–X_{eq} arrangement.[2]

As part of our ongoing studies centered around the use of benzotriazole as a synthetic auxiliary,[3] we have synthesized a number of 4-substituted pyrylium salts and their benzo-fused analogues.[4] Key intermediates in these syntheses were compounds such as **1**–**6** (Fig. 2), which undergo facile C–N

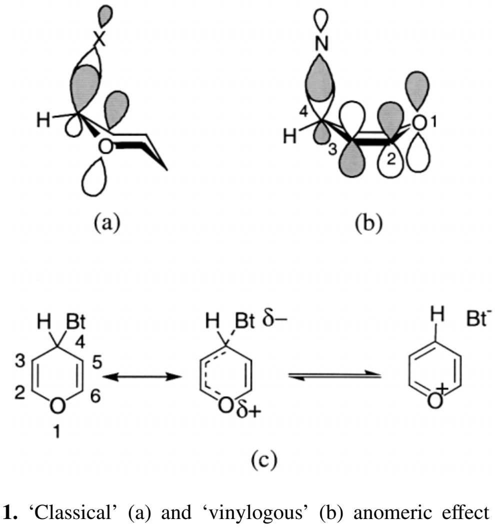

Figure 1. ‘Classical’ (a) and ‘vinylogous’ (b) anomeric effect in tetrahydropyran and pyran rings.

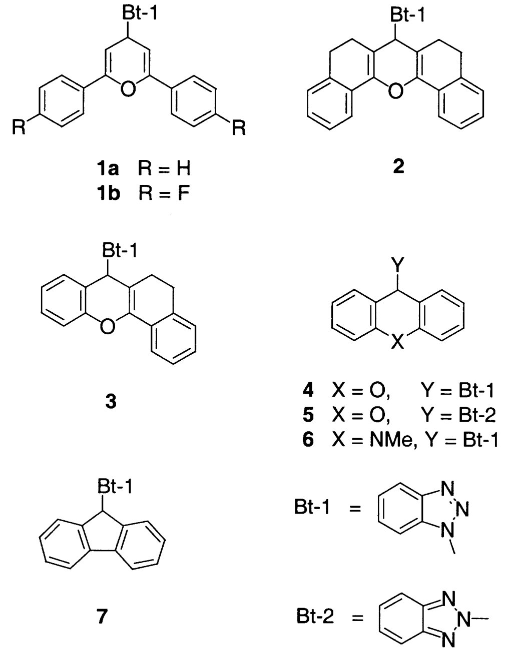

Figure 2. Studied benzotriazole-substituted heterocycles **1**–**6** and reference compound **7**.

Keywords: benzotriazole; X-ray crystallography; vinylogous anomeric effect.

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bond dissociation of the benzotriazole residue, similar to analogous dissociation shown by compounds containing a nitrogen atom geminal to a benzotriazole moiety.[5] We surmised that this C–N bond dissociation might be assisted by a stereoelectronic interaction (Fig. 1b) similar to that of the classical anomeric effect, but extending over four bonds. Such a 'vinylogous' anomeric effect would readily explain the facile loss of the benzotriazole moiety (Fig. 1c). In order to investigate this hypothesis experimentally, we have carried out accurate, low-temperature X-ray crystal structure determinations of compounds **1–6**, in search of structural evidence for such an interaction. We now present a detailed analysis of these structures, which we believe provides direct structural evidence for the existence of a 'vinylogous' anomeric effect, due to the interaction of a benzotriazole moiety with a heteroatom through four bonds.

2. Results

Accurate X-ray crystal structure determinations were performed on compounds **1–6**, as well as the model compound **7**. This model compound, which lacks the ring heteroatom and therefore cannot exhibit an anomeric effect, was selected as being the most appropriate synthetically accessible stable compound. Ideally, replacement of the oxygen atom of **1a** with a methylene group would provide a better model, but such benzotriazole-substituted 1,4-dihydrobenzenes are not stable. Compounds **1a** and **6**, each crystallize with two independent molecules in the asymmetric unit, which, in both cases, have almost identical geometries and conformations. Perspective views of each of the structures are shown in Figs. 3–10. The central rings of compounds **1–6** exist in non-planar boat conformations, with the two C=C double bonds located in one plane, and

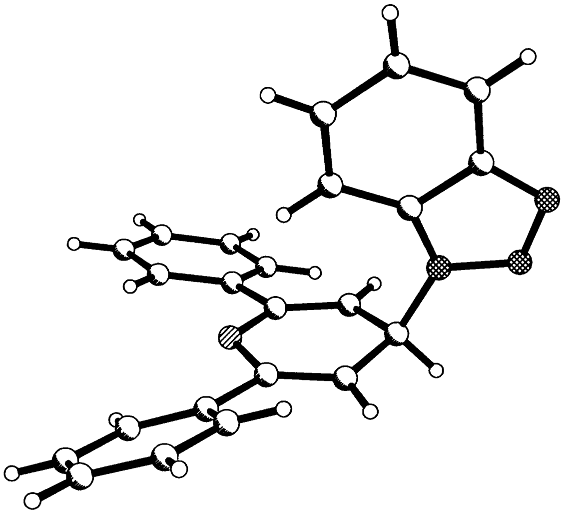

Figure 3. X-Ray structure of one of the two independent molecules of **1a**.

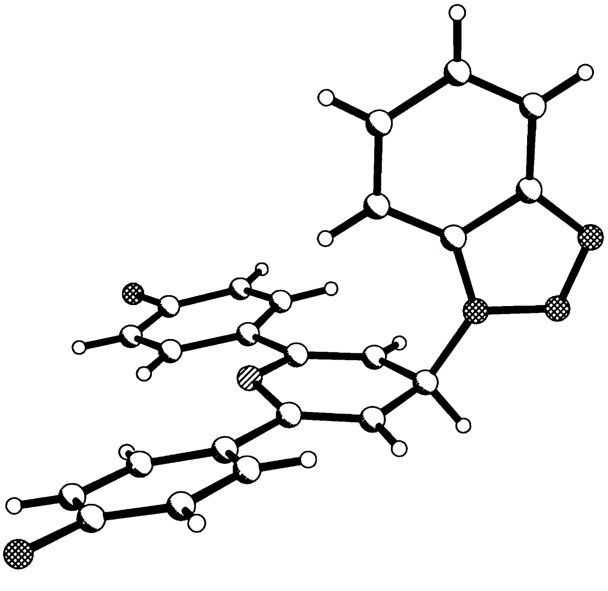

Figure 4. X-Ray structure of **1b**.

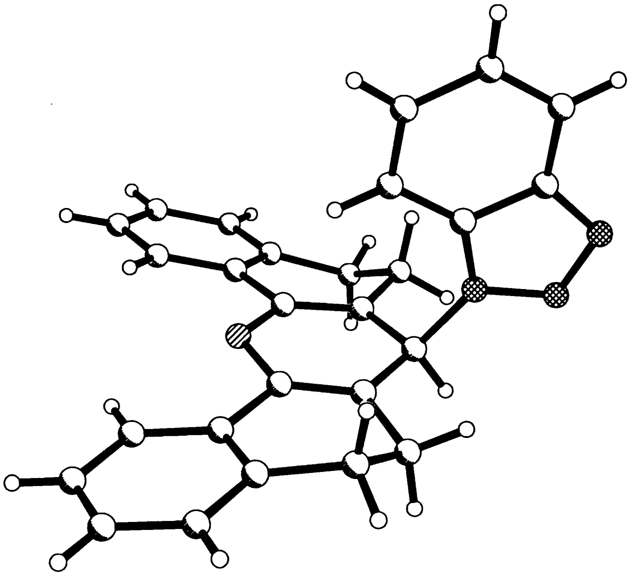

Figure 5. X-Ray structure of **2**.

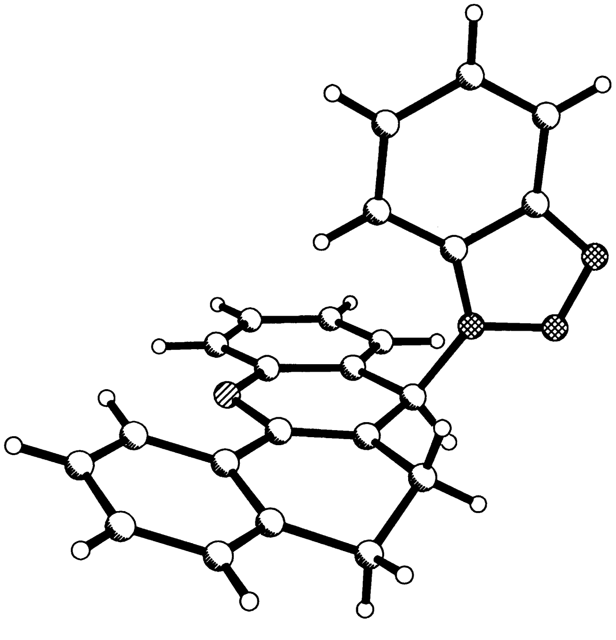

Figure 6. X-Ray structure of **3**.

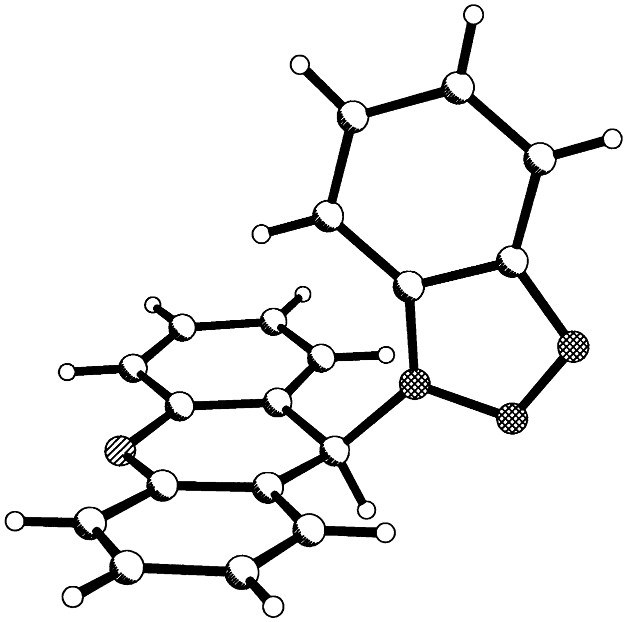

Figure 7. X-Ray structure of **4**.

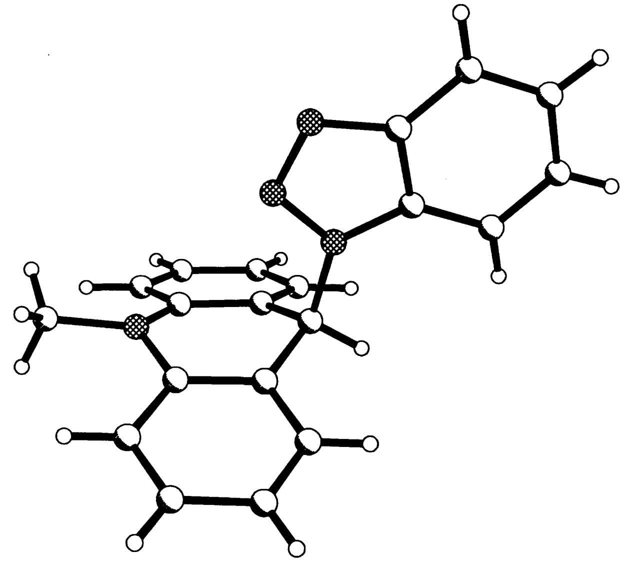

Figure 9. X-Ray structure of one of the two independent molecules of **6**.

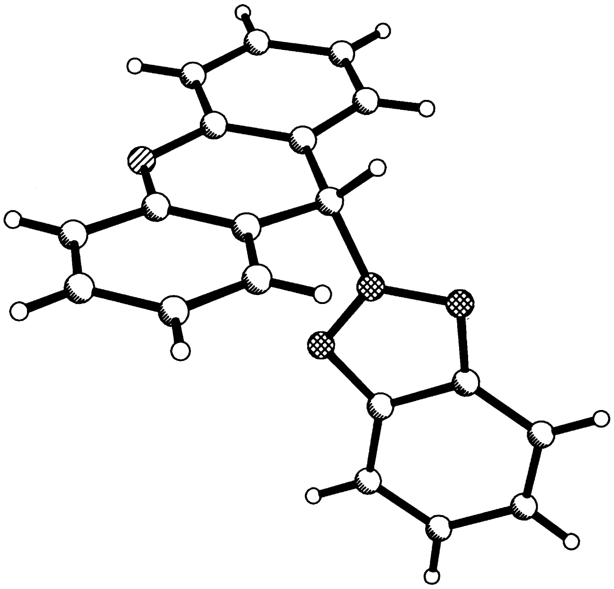

Figure 8. X-Ray structure of **5**.

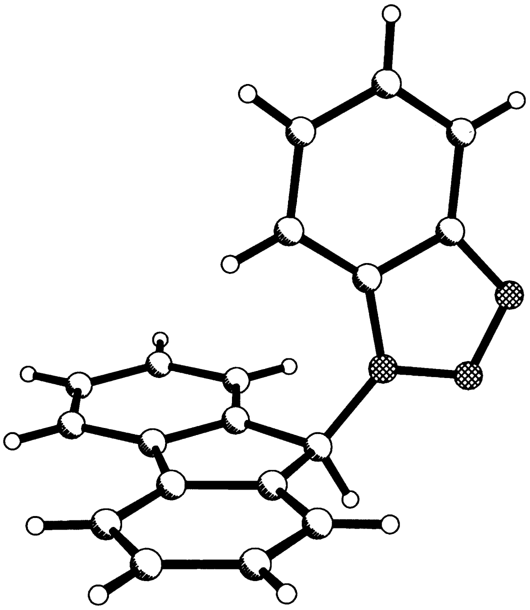

Figure 10. X-Ray structure of **7**.

the heteroatom and the sp^3-hybridized carbon atom lying above the plane of the C═C double bonds.

The two non-equivalent exocyclic bonds of the sp^3-hybridized carbon atom occupy pseudo-axial (flagpole) and pseudo-equatorial (bowsprit) positions. Importantly, the benzotriazole residue generally assumes the pseudo-axial position (except in compound **4**). Interestingly, in each of the structures of **1–6**, the plane of the benzotriazole ring almost exactly bisects the central pyran ring and does so with the fused benzo ring oriented towards the pyran ring in structures **1–4**, but with the triazole ring in this orientation in compound **6**. Pleasingly, the model compound **7** also has a similar orientation of the benzotriazole substituent.

3. Discussion

The existence of a 'vinylogous' anomeric effect, of the type shown in Fig. 1c, should manifest itself in the following ways: a lengthening of the C4–N bond, a shortening of the C3(5)– C4 bonds, an increase in the C3–C4–C5 bond angle and a decrease in the C2–C3–C4–N dihedral angle. Structural data relevant to such an analysis are collected in Table 1.

The C4–N bond length. Based on analogy with structural studies of the classical anomeric effect, this parameter should provide the most direct evidence for a 'vinylogous' anomeric effect. The C4–N bond length in compounds **1–6** is invariably greater than that in the model compound **7**

Table 1. X-Ray structural parameters for compounds **1**–**7**

	Bond length C4–N	Δ bond lengths C4–N[a]	Bond length C3–C4, C5–C4	Bond angle C3–C4–C5	Dihedral C2–C3–C4–N, C6–C5–C4–N	Dihedral X1–C2–C3–C4, X1–C6–C5–C4	Dihedral C6–X1–C2–C3, C2–X1–C6–C5	Bond length X1–C2, X1–C6	Bond length C2–C3, C6–C5
1a	1.484	0.026	1.495, 1.487	110.1	110.6, 113.7	7.2, 1.9	7.6, 2.9	1.383, 1.387	1.324, 1.325
1a′	1.484	0.026	1.496, 1.494	109.8	105.2, 105.2	4.1, 4.9	8.9, 8.6	1.391, 1.383	1.321, 1.323
1b	1.486	0.029	1.506, 1.495	110.0	113.1, 113.7	1.8, 1.9	7.2, 7.2	1.387, 1.398	1.331, 1.329
2	1.480	0.023	1.496, 1.499	111.9	118.4, 118.0	0.1, 0.3	6.6, 6.7	1.385, 1.380	1.338, 1.338
3	1.482	0.024	1.498, 1.503	112.0	115.7, 117.5	4.3, 1.1	6.2, 3.6	1.388, 1.388	1.332, 1.394
4	1.474	0.016	1.512, 1.516	111.7	134.1, 133.8	2.2, 0.1	8.2, 9.3	1.385, 1.377	1.385, 1.385
5	1.495	0.037	1.508, 1.501	112.0	110.4, 110.6	3.0, 1.7	7.2, 7.8	1.377, 1.378	1.389, 1.386
6	1.489	0.031	1.511, 1.502	111.0	93.8, 93.6	3.5, 5.0	24.3, 25.0	1.406, 1.403	1.401, 1.409
6′	1.494	0.036	1.506, 1.500	112.1	98.7, 98.1	2.8, 6.9	17.8, 19.8	1.415, 1.405	1.393, 1.401
7	1.458	0.0	1.521, 1.524	102.6	126.2, 127.9	–	–	–	1.401, 1.402

All e.s.d.s for bond lengths are ≤0.003 Å and bond angles ≤0.2°.

[a] Compared to **7**.

(Table 1). The use of **7** as the model compound is further justified by the fact that the observed C4–N bond length is identical to the mean value for the corresponding bond lengths in the seven compounds resulting from a search of the Cambridge Cystallographic Database for 1-substituted benzotriazoles attached to sp^3 carbons with no α- or vinylogous-heteroatom (excluding metal complexes). Importantly, the smallest bond elongation exists in compound **4**, which has the benzotriazole substituent in the pseudo-equatorial position, and therefore less favorably oriented for the orbital overlap required for stereoelectronic interaction. The other eight entries in Table 1 show an average bond elongation, compared to **7**, of 0.029(3) Å. This value is experimentally significant (ca. 10×e.s.d.) and comparable to values recorded for the classical anomeric effect,[1,2] despite the fact that this effect is operating over four, rather than two, bonds.

The C4–C3(5) bond lengths. For the interaction shown in Fig. 1c, one would expect an associated contraction of the C4–C3(5) bonds. Based on previous observations of the classical anomeric effect, one might expect the magnitude of this effect to be somewhat less. As shown in Table 1, all such bond lengths are indeed shorter than those in model compound **7**. Once again, the smallest contraction is experienced by compound **4**, with the other eight values averaging 0.023(3) Å (>7×e.s.d.) shorter than those in **7**. Thus, this parameter also supports our proposed hypothesis for a 'vinylogous' anomeric effect.

The C3–C4–C5 bond angle. The interaction depicted in Fig. 1c should also result in an increase in the sp^2 character of C4. As shown in Table 1, each of the values for compounds **1**–**6** show bond angles greater than the tetrahedral (sp^3) value. However, the statistical significance of these values is less convincing than the above parameters.

The C2(6)– C3(5)– C4–N dihedral angles. These parameters should also provide a test for the existence of our proposed effect, since orbital overlap between doubly occupied π-MOs and the antibonding σ^*_{CN} orbital will be maximized when the C4–N bond is coplanar with both the p-orbitals of the double bonds and the p-type lone pair of the heteroatom of the ring. Such an interaction should result in a decrease in these angles from a value of 125° for a strictly planar ring (as is the case in **7**). Once again, this is observed for all compounds, except for **4**, which exhibits an increased dihedral angle. The values for **1**–**3** and **5**–**7** are all significantly less than 125°, most notably for acridine **6**. The small values for **6** could result from the greater donation ability of a nitrogen atom compared to the oxygens in **1**–**5**.

Other parameters. Table 1 also includes the values for a number of other parameters that might also be expected to provide evidence for the proposed effect. Although individual values for these bond lengths and dihedral angles do provide such support, the effects are less definitive, as strict comparison between the different compounds is hindered by other structural changes within the molecules.

4. Conclusions

Analysis of X-ray crystallographic structural parameters in a series of 4*H*-4-benzotriazolyl-2,6-diarylpyrans **1a**,**b**, their benzo-fused derivatives **2**–**5** and *N*-methylacridine **6** has revealed internally consistent evidence for a stereoelectronic interaction between the ring heteroatom and the C4–N σ^* orbital. We believe that these results provide direct experimental evidence for the existence of a vinylogous counterpart of the classical anomeric effect. Further studies are underway of related systems containing other heteroatom substituents, in order to probe whether this is a general phenomenon.

5. Experimental

5.1. General

Compounds **1**, **2**,[4d] **3**,[4a] **4**,[4c] **5**, **6**,[6] **7**,[7] **8**[8] were prepared according to previously described procedures.

5.2. X-Ray crystallography

The crystal data, data collection and refinement parameters for the eight structures are listed in Table 2. Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized MoKα radiation (λ=0.71073 Å). The structures were solved by direct methods using SHELXS,[9] and refined on F^2, using all data, by full-matrix least-squares procedures with SHELXTL

Table 2. Crystal data, data collection and refinement parameters

	1a	**1b**	**2**	**3**	**4**	**5**	**6**	**7**
Formula	$C_{23}H_{17}N_3O$	$C_{23}H_{15}F_2N_3O$	$C_{27}H_{21}N_3O$	$C_{23}H_{17}N_3O$	$C_{19}H_{13}N_3O$	$C_{19}H_{13}N_3O$	$C_{20}H_{16}N_4$	$C_{19}H_{13}N_3$
M	351.4	387.4	403.5	351.4	299.3	299.3	312.4	283.3
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
a (Å)	10.619(1)	9.485(3)	20.060(1)	15.228(1)	8.884(1)	11.142(1)	11.540(6)	9.183(1)
b (Å)	10.847(1)	10.208(4)	11.074(1)	11.556(1)	12.453(2)	9.215(1)	11.607(6)	11.360(1)
c (Å)	17.756(1)	10.925(4)	18.618(1)	20.116(1)	13.124(2)	14.964(1)	13.232(7)	13.889(1)
α (°)	86.119(1)	102.844(5)	90	90	90	90	103.721(8)	90
β (°)	88.541(1)	113.253(4)	97.821(1)	99.671(1)	95.376(2)	109.530(1)	111.867(7)	97.502(1)
γ (°)	61.054(1)	99.383(5)	90	90	90	90	91.039(7)	90
V (Å^3)	1785.5(2)	909.7(6)	4097.4(4)	3492.7(2)	1445.5(4)	1488.1(2)	1586.8(14)	1436.5(2)
Space group	P-1	P-1	$C2/c$	$C2/c$	$P2_1/c$	$P2_1/c$	P-1	$P2_1/c$
Z	4	2	8	8	4	4	4	4
F(000)	736	400	1696	1472	624	624	656	592
D_x (g cm^{-3})	1.307	1.414	1.308	1.337	1.375	1.373	1.308	1.31
Dimensions (mm)	0.58×0.44×0.22	0.50×0.38×0.16	0.56×0.35×0.15	0.27×0.22×0.22	0.56×0.52×0.31	0.53×0.50×0.27	0.64×0.08×0.04	0.41×0.37×0.32
μ (mm^{-1})	0.082	0.103	0.081	0.084	0.088	0.088	0.080	0.079
Temperature (K)	150	158	296	140	158	158	163	158
$2\theta_{max}$ (°)	53	53	52	53	53	53	53	53
Unique data [R(int)]	5974 [0.0239]	3669 [0.0281]	2985 [0.0269]	3277 [0.0511]	2860 [0.0444]	2876 [0.0174]	6419 [0.0754]	2861 [0.0262]
No. with $I>2\sigma(I)$	5449	2568	2348	2274	2138	2434	3218	2300
Weighting (a/b)	0.0462/0.8485	0.0575/0	0.0703/1.55	0.0456/0	0.0582/0	0.0548/0.2605	0.0468/0	0.0616/0.0740
Parameters	487	262	280	244	208	208	435	199
wR (all data)	0.1370	0.0909	0.1381	0.1113	0.0945	0.0955	0.1117	0.0948
$R1$ [$I>2\sigma(I)$]	0.0572	0.0356	0.0517	0.0465	0.0353	0.0350	0.0487	0.0360

Version 5.10.[10] Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.2 times the isotropic equivalent of their carrier atoms and the torsional orientation of the CH_3 hydrogens in **6** deduced from circular Fourier syntheses. The functions minimized were $\sum w(F_o^2 - F_c^2)^2$, with $w = [\sigma^2(F_o) + (aP)^2 + bP]^{-1}$, where $P = [\max(F_o)^2 + 2F_c^2]/3$.

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References

1. (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer Verlag: Berlin, 1983. (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. (c) Juaristi, E.; Cuevas, G. *The Anomeric Effect*, CRC: Boca Raton, 1995.
2. (a) Allen, F. H.; Kirby, A. J. *J. Am. Chem. Soc.* **1984**, *106*, 6197. (b) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200. (c) Luger, P.; Kothe, G.; Paulsen, H. *Chem. Ber.* **1976**, *109*, 1850. (d) Cossé-Barbi, A.; Dubois, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 1503. (e) Cossé-Barbi, A.; Watson, D. G.; Dubois, J. E. *Tetrahedron Lett.* **1989**, *30*, 163. (f) Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715. (g) Kirby, A. J. *Adv. Phys. Org. Chem.* **1994**, *29*, 87. (h) Yokoyama, Y.; Ohashi, Y. *Bull. Chem. Soc. Jpn* **1999**, *72*, 2183. (i) Uehara, F.; Sato, M.; Kanedo, C.; Kurihara, H. *J. Org. Chem.* **1999**, *64*, 1436.
3. Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.
4. (a) Katritzky, A. R.; Czerney, P.; Levell, J. R. *J. Org. Chem.* **1997**, *62*, 8198. (b) Katritzky, A. R.; Denisenko, S. N.; Czerney, P. *Heterocycles* **1997**, *45*, 2413. (c) Katritzky, A. R.; Czerney, P.; Levell, J. R.; Du, W. *Eur. J. Org. Chem.* **1998**, 2623. (d) Katritzky, A. R.; Du, W.; Denisenko, S. N.; Czerney, P.; Steel, P. J. *J. Prakt. Chem.* **1999**, *341*, 152.
5. Katritzky, A. R.; Yannakopoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673.
6. Katritzky, A. R.; Denisenko, S. N.; Oniciu, D. C.; Ghiviriga, I. *J. Org. Chem.* **1998**, *63*, 3450.
7. Katritzky, A. R.; Yang, B. Unpublished work.
8. Katritzky, A. R.; Perumal, S.; Fan, W.-Q. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2059.
9. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
10. Sheldrick, G. M. SHELXTL: Bruker Analytical X-ray Systems, 1997.