# Aromatic Claisen Rearrangements in Carbohydrates: Stereocontrol of Rearrangement Rates in Unsaturated Sugar Substrates†

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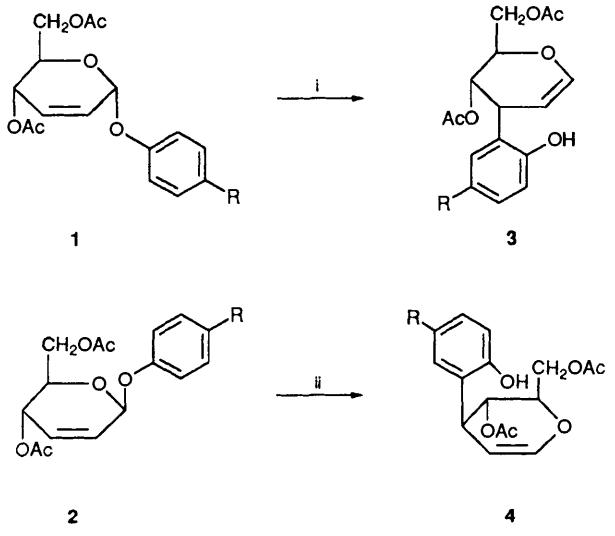
A remarkable difference is observed in the rates of [3,3]-sigmatropic rearrangement of aryl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosides **1** and **2**; the slower reactivity of the α-isomers is consistent with AM1 calculated transition state energetics of model systems.

The stereochemical reliability of the Claisen rearrangement[1] makes it an attractive methodology in carbohydrate synthesis. Numerous applications of the aliphatic Claisen rearrangement as well as the Ireland ester enolate and Eschenmoser variants have been reported.[2-6] As part of our efforts towards the synthesis of aflatoxins,[7] a class of naturally occurring mycotoxins, we now report the first examples of *aromatic* Claisen rearrangement in 2,3-unsaturated sugars. The study reveals a counter-intuitive dependence of ease of rearrangement on the stereochemistry of the migrating group. The factors contributing to the observed reactivity trends are unravelled using AM1 calculations.

A series of α- and β-isomeric aryl 4,6-di-*O*-acetyl-2,3-dideoxy-hex-2-enopyranosides **1** and **2**, prepared following literature procedures,[8] were subjected to thermal Claisen rearrangement by refluxing in *N,N*-diethylaniline. The substrates undergo [3,3]-sigmatropic shift stereospecifically, resulting in 4,6-di-*O*-acetyl-3-*C*-aryl-3-deoxyglycals **3** and **4** (Scheme 1). The stereochemistry at C-3 in the products was confirmed by $^1$H NMR.[10,‡]




**Scheme 1** *Reagents and conditions:* i, *N,N*-diethylaniline, reflux, 35 h; ii, *N,N*-diethylaniline, reflux, 0.5 h

The α-isomers **1a–d** rearrange sluggishly, with less than 65% conversion even after refluxing for 35 h (Table 1). The percentage conversions of **1b** to **3b**, as estimated from the ratios of NMR intensities of the anomeric protons of **1b** and **3b** in the crude reaction mixtures at different time intervals, were 27, 42, 55 and 67 at 10, 15, 25 and 35 h of reaction time, respectively, leading to a half-life of about 20 h. Under identical conditions, the β-isomers **2a–d** were found to rearrange with great ease requiring only 0.5 h for conversion to **4a–d** in high yields (Table 1).

Formation of a cyclic six-membered Claisen transition state should be facile if the migrating unit is in the axial position. For example, Ferrier *et al.*[2] have shown that the *erythro*-pyranoside, **5**, rearranges slowly (3.5 h at 185 °C) compared to the related *threo*-vinyl ether, **6** (0.5 h) (see Fig. 1). Migration of a quasi-axial group is consistently more facile in the rearrangements of azides and thiocyanates too.[11] Hence, the low reactivity of **1**, with the OAr group in the axial position to take advantage of anomeric stabilisation,[10] is surprising. The possible role of electronic effects is also intriguing. Curran *et al.*, from their study of selective mono-Claisen rearrangement in carbohydrate glycals, have proposed a vinylogous anomeric effect[3,11] (**7**) due to the oxygen lone pair across a vinylic unit which aids the bond breaking process in the Claisen transition state. A similar, perhaps more effective, interaction should operate in the transition structure of the rearrangement of **1**.

AM1 calculations[12,§] on the minima and Claisen transition structures for the model substrates **8** and **9** provide a rationale for the unprecedented rate reversal in **1** and **2**. The OAr unit is calculated to be axial in the preferred conformations of both α- and β-isomers. The preferred minimum energy structures (hessian = 0) for the α- and β-isomers correspond to the $^0H_5$ (**8a**) and $^5H_0$ (**9b**) conformers, respectively (see Fig. 1). Interestingly, the $^0H_5$ conformer **9a** for the β-isomer is 2.5 kcal mol$^{-1}$ less stable than **9b**. Anomeric stabilisation involving the axial OAr group is evidently effective even in the β-isomer and overcomes the steric predilections of the pseudo-axial alkyl groups. The predicted preference for the $^5H_0$ form is consistent with the $^1$H NMR coupling constants of **2**.¶ Since the OAr group is ideally poised for migration in the axial position in both the α- and β-isomers, ground state conformations cannot be held responsible for the observed rate differences.

Generally, in Claisen transition structures, the six-membered

† Non-S.I. unit employed: 1 cal = 4.18 J.

‡ All compounds were thoroughly characterised by spectral and high resolution mass spectral or analytical data. In **3**, 4-H resonates at δ 5.35 as a doublet of doublets with $J$ = 7.1 (4-H–5-H diaxial coupling) and 5.6 Hz (4-H–3-H axial–equatorial coupling). In **4**, 4-H resonates as a triplet with $J$ = 6.84 Hz (two diaxial couplings with 3-H and 5-H, taking into account the ring flattening due to the double bond).

§ AM1 calculated geometries and heats of formation have been deposited under the Supplementary Publication Scheme. For details of the scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1. [Suppl. Publ. No. 57020 (7 pp.)].

¶ There is no coupling between 4-H and 5-H in **2b** (4-H appears as a singlet at δ 5.12), whereas in **1**, 4-H appears at δ 5.34 as a doublet with $J$ = 10.2 Hz (diaxial coupling with 5-H).

**Table 1** Isolated yields (%) of Claisen rearrangement products

| | α-Substrate[a] | | | β-Substrate[b] | | |
|---|---|---|---|---|---|---|
| R | Reactant | Product | Yield | Reactant | Product | Yield |
| H | **1a** | **3a** | 55 | **2a** | **4a** | 78 |
| Me | **1b** | **3b** | 63 | **2b** | **4b** | 83 |
| OMe | **1c** | **3c** | 60 | **2c** | **4c** | 80 |
| Cl | **1d** | **3d** | 60 | **2d** | **4d** | 75 |

[a] After 35 h; 10–12% of cleaved parent phenol was also obtained in these cases. [b] After 0.5 h.

**Table 2** AM1 heats of formation and activation enthalpies for Claisen rearrangement in **8** and **9**

| | | | Transition state conformation | | | |
|---|---|---|---|---|---|---|
| Molecule | Reactant conformation | $\Delta_fH°$/kcal mol$^{-1}$ | Pyranose ring | [3,3]-Moiety | $\Delta_fH°$/kcal mol$^{-1}$ | $E_a$/kcal mol$^{-1}$ |
| **8** | $^0H_5$ | −52.8 | $^0H_5$ | Chair | 1.9 | 54.7 |
| | | | $^0H_5$ | Boat | 2.1 | 54.9 |
| **9** | $^5H_0$[a] | −51.7 | $^{2,5}B$ | Chair | −1.0 | 50.7 |
| | | | $^{2,5}B$ | Boat | 2.7 | 54.4 |

[a] The heat of formation of the $^0H_5$ conformer is −49.2 kcal mol$^{-1}$.

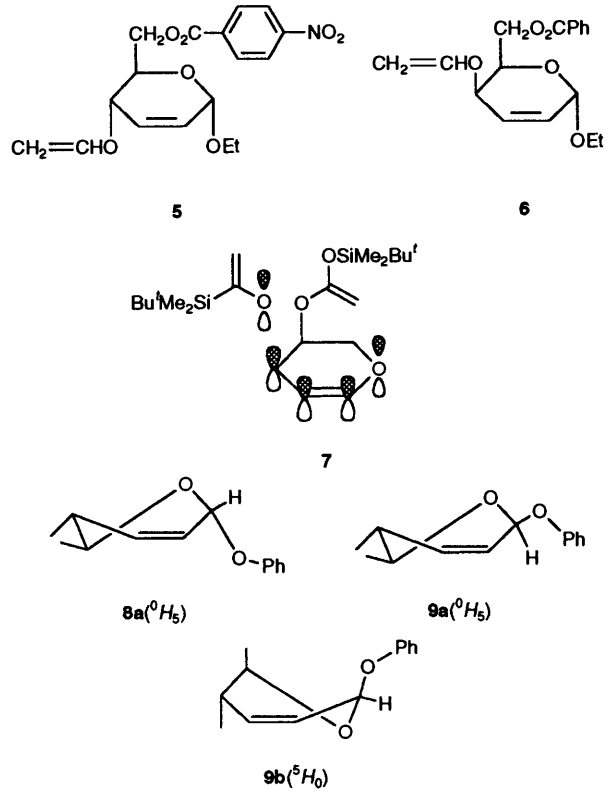



**Fig. 1**

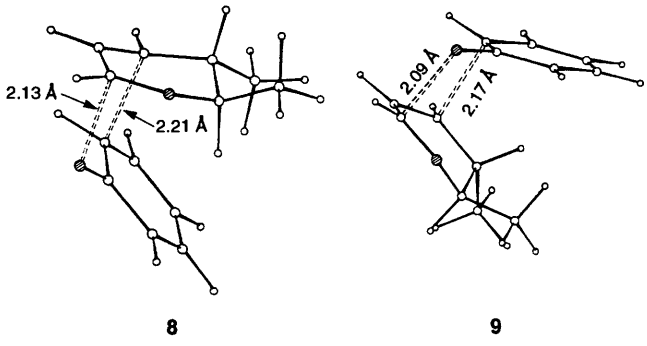



**Fig. 2** Preferred AM1 transition state structures for Claisen rearrangement in **8** and **9**

sigmatropic moiety prefers a chair conformation over a boat by 6–10 kcal mol$^{-1}$,[12] although in some highly encumbered substrates, the boat form has been proposed.[1,4] The computed transition state geometry (hessian = 1) for Claisen rearrangement in the α-isomer (Fig. 2) is characterised by chair conformations for the six-atom Claisen unit as well as for the unsaturated sugar ring. The calculated activation barrier in **8** (Table 2) is quite large, suggesting strong repulsive interactions between the migrating group and the underlying ring.

The optimised transition state structure for the rearrangement of the β-isomer also has the sigmatropic unit in the chair conformation but the sugar ring is found to adopt the $^{2,5}B$ form (Fig. 2). Formation of a cyclic transition state is evidently not possible from the $^0H_5$ sugar conformation with the migrating unit in the equatorial position. The alternative $^5H_0$ form would involve large repulsions between the migrating group and the pseudo-axial substituent at C-5. By distorting the pyranose ring to a $^{2,5}B$ conformation, the OAr unit continues to be ideally placed for migration, while the repulsive substituents are moved away. The boat geometry for the sugar ring also does not suffer from the usual unfavourable interactions characteristic of this conformation. The presence of three near-trigonal carbon atoms and an oxygen in the ring would reduce flagpole interactions and torsional strain. Due to the boat conformation of the pyran ring in the transition state, the repulsions between the migrating unit and substituents in the underlying ring are reduced. Hence, the $^{2,5}B$ transition structure of the β-isomer is more stable than the preferred $^0H_5$ structure of the α-isomer. The activation barrier for the rearrangement of **9** is 4 kcal mol$^{-1}$ smaller than that compound for **8** (Table 2), precisely following the trend noted experimentally for **1** and **2**.

The energies of alternative transition structures in which the sigmatropic moiety adopts a boat conformation confirm the steric interpretation. The corresponding structures are less stable than the chair forms, but the unfavourable contacts between the sigmatropic unit and the substituents on the sugar ring are avoided. Hence, these forms have similar energies for the α- and β-isomers (Table 2). The energy difference between the lower energy chair transition states of the α- and β-isomers can therefore be attributed to differential steric interactions involving the migrating unit and the sugar ring.

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## References

1 For a recent review, see P. Wipf in *Comprehensive Organic Synthesis*, vol. 5, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon Press, 1991, pp. 827–874.
2 (*a*) R. J. Ferrier and N. Vethaviyasar, *J. Chem. Soc.*, 1973, 1791; (*b*) A. Raadt and R. J. Ferrier, *Carbohyd. Res.*, 1991, **216**, 93.
3 (*a*) D. P. Curran and Y.-G. Suh, *Carbohyd. Res.*, 1987, **171**, 161; (*b*) D. P. Curran and Y.-G. Suh, *Tetrahedron Lett.*, 1984, **25**, 4179; (*c*) D. P. Curran, *Tetrahedron Lett.*, 1982, **23**, 4309.
4 (*a*) R. E. Ireland, C. S. Wilcox, S. Thaisrivongs and N. R. Vanier, *Can. J. Chem.*, 1979, **57**, 1743; (*b*) R. E. Ireland, S. Thaisrivongs and C. S. Wilcox, *J. Am. Chem. Soc.*, 1980, **102**, 1155; (*c*) R. E. Ireland and J. P. Vevert, *Can. J. Chem.*, 1981, **59**, 572; (*d*) R. E. Ireland, P. G. M. Wutz and B. Ernst, *J. Am. Chem. Soc.*, 1981, **103**, 3205; (*e*) R. E. Ireland and J. P. Daub, *J. Org. Chem.*, 1981, **46**, 479; (*f*) R. E. Ireland, R. C. Anderson, R. Badoub, B. J. Fitzsimmons, G. McGarvey, S. Thaisrivongs and C. S. Wilcox, *J. Am. Chem. Soc.*, 1983, **105**, 1988; (*g*) R. E. Ireland, D. W. Noebeck, G. S. Mandel and N. S. Mandel, *J. Am. Chem. Soc.*, 1985, **107**, 3285.
5 (*a*) D. B. Tulshian and B. Fraser-Reid, *J. Org. Chem.*, 1984, **49**, 518; (*b*) D. B. Tulshian, R. Tsang and B. Fraser-Reid, *J. Org. Chem.*, 1984, **49**, 2347; (*c*) B. Fraser-Reid, D. B. Tulshian, R. Tsang, D. Lowe and V. G. S. Box, *Tetrahedron Lett.*, 1984, **25**, 4579; (*d*) B. Fraser-Reid, R. D. Dawe and D. B. Tulshian, *Can. J. Chem.*, 1979, **57**, 1746.
6 (*a*) K. Tadano, Y. Idokagi, H. Yamada and T. Suami, *J. Org. Chem.*, 1987, **52**, 1201; (*b*) S. D. Burke, D. M. Armistead, F. J. Schoenen and J. M. Fevig, *Tetrahedron*, 1986, **42**, 2787; (*c*) S. D. Burke, D. M. Armistead and F. J. Schoenen, *J. Org. Chem.*, 1984, **49**, 4320; (*d*) P. Rollin, V. V. Bencomo and P. Sinay, *J. Org. Chem.*, 1984, 134; (*e*) L. Cottier, G. Remy and G. Descotes, *Synthesis*, 1979, 711; (*f*) K. Heyns and R. Hohlweg, *Chem. Ber.*, 1978, **111**, 1632.
7 (*a*) R. A. Coulombe, Jr., *Mycotoxins Phytoalexins*, ed. R. P. Sharma and D. K. Salunke, CRC Publishers, Boca Raton, 1991, pp. 1003–1043; (*b*) G. E. Wood, pp. 145–164; (*c*) G. A. Kraus, B. E. Johnston and J. M. Applegate, *J. Org. Chem.*, 1991, **56**, 5688.
8 (*a*) N. G. Ramesh and K. K. Balasubramanian, *Tetrahedron Lett.*, 1992, **33**, 3061; (*b*) M. Brakta, P. Lhoste and D. Sinou, *J. Org. Chem.*, 1989, **54**, 1890.
9 R. J. Ferrier and N. Vethaviyasar, *J. Chem. Soc. C*, 1971, 1907.
10 A. J. Kirby, *The Anomeric and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Weinheim, 1983.
11 The term 'vinylogous anomeric effect' was first introduced in S. E. Denmark and M. S. Dappen, *J. Org. Chem.*, 1984, **49**, 798.
12 M. J. S. Dewar, E. G. Zoebisch, E. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902. For successful applications to aliphatic Claisen rearrangements, see M. J. S. Dewar and C. Jie, *J. Am. Chem. Soc.*, 1989, **111**, 511.

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