Highly Regio- and Stereo-selective Diels–Alder Reactions of 5-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone

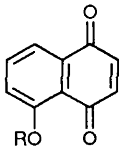
Brian Beagley, Anthony D. M. Curtis, Robin G. Pritchard and Richard J. Stoodley*

Department of Chemistry, UMIST, PO Box 88, Manchester M60 1QD, UK

The title compound **1b** reacts with cyclopentadiene to give a single cycloadduct, assigned the stereostructure **6a** by X-ray crystallography; single cycloadducts, *i.e.* **4c** and **d**, also arise in the corresponding reactions involving the dienes **2b** and **c**.

Diel–Alder cycloadducts of juglone **1a** and its derivatives are of value in the synthesis of quinonoid natural products and their relatives. Not surprisingly, therefore, much attention has been devoted to controlling the regio- and stereo-chemical outcome of such reactions.

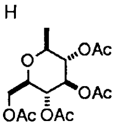
The observations of Trost and his coworkers, that the regiochemistry of the cycloaddition of juglone **1a** with the diene **2a** is markedly improved in the presence of boron trifluoride [from a 2 : 1 mixture to a > 20 : 1 mixture of the (±)-cycloadducts **3a** and **4a**],[1] has played an important role in



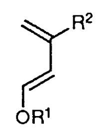
1

a; R = H

b; R =



c; R = Me

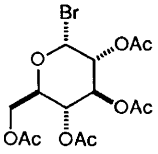


2

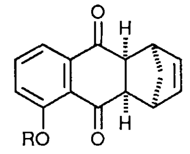
a; R^1 = Ac, R^2 = H

b; R^1 = Me, R^2 = $OSiMe_3$

c; R^1 = $SiMe_3$, R^2 = Me

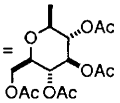


5

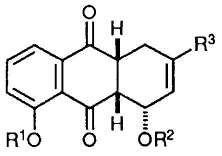


6

a; R =

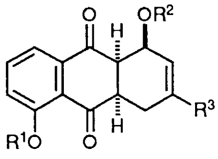


b; R = H



3

a; R^1 = R^3 = H, R^2 = Ac

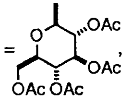


4

a; R^1 = R^3 = H, R^2 = Ac

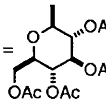
b; R^1 = R^2 = Me, R^3 = $OSiMe_3$

c; R^1 =

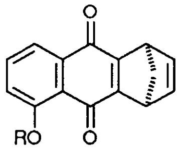


, R^2 = Me, R^3 = $OSiMe_3$

d; R^1 =

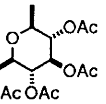


, R^2 = $SiMe_3$, R^3 = Me

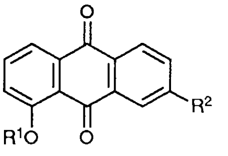


7

a; R =

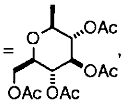


b; R = H



8

a; R^1 =



, R^2 = OH

b; R^1 = H, R^2 = OH

c; R^1 = H, R^2 = Me

the two strategies that have been successfully developed to derive cycloadducts of type **3** and their enantiomers/diastereoisomers.

One strategy, established by Trost[2] and ourselves,[3] makes use of enantiopure dienes and achiral Lewis acids to generate cycloadducts of type **3** and their diastereoisomers. The other strategy, progressed by the groups of Kelly[4] and Yamamoto,[5] employs enantiopure boron-based Lewis acid complexes of juglone **1a** (produced *in situ*) and achiral dienes to generate cycloadducts of type **3** and their enantiomers.†

We now report a third strategy, involving the use of juglone derivatives of type (**1**; R = a detachable enantiopure ligand), which is remarkably effective for the synthesis of cycloadducts of type **4**.

Prompted by our finding that dienes of type (**2**; R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) display a notable diastereofacial reactivity towards cyclic dienophiles,[6,7] we decided to investigate the dienophilic reactivity of the juglone glycoside **1b**.‡ Initially, the last-cited compound, m.p. 148 °C, $[\alpha]^{20}_D$ −80° (1.5% in $CHCl_3$) was prepared (78% yield after recrystallisation) by treating a mixture of juglone **1a** and the acetobromoglucose **5**[8] in quinoline with silver(I) oxide.§ However, the reaction was somewhat capricious and better, and reproducible, results (82% yield) were obtained by using acetonitrile as the solvent and subjecting the mixture to sonication.¶

Compound **1b** reacted with cyclopentadiene in benzene to give a single cycloadduct (83% yield after recrystallisation), m.p. 152–154 °C, $[\alpha]^{20}_D$ −114° (0.5% in $CHCl_3$) assigned the stereostructure **6a** by X-ray crystallography.‖ Clearly, the diene had added in an *endo*-selective manner to the 'top' face of the alkene moiety of compound **1b**.

Acidic hydrolysis of the glycoside **6a** afforded the aglycone **6b** in a somewhat impure state. However, the dehydroderivative **7a** (obtained in 72% yield after chromatography and crystallisation by treatment of compound **6a** with Et_3N in CH_2Cl_2 under O_2), m.p. 188 °C (decomp.), $[\alpha]^{20}_D$ −72° (0.3% in $CHCl_3$), reacted with hot ethanolic hydrochloric acid to give the quinone **7b** (92% yield after crystallisation), m.p. 150 °C, $[\alpha]^{20}_D$ +20° (0.2% in $CHCl_3$).

Based upon the aforementioned stereochemical result and the finding of Boeckman and his coworkers, that the dienophile **1c** and the diene **2b** react to give only the (±)-cycloadduct **4b**,[9] we hoped that the cycloadduct **4c** would be produced in the Diels–Alder reaction of compounds **1b** and **2b**. Gratifyingly, a single cycloadduct (92% yield after

---

† Stoichiometric amounts of the Lewis acids are required. However, bovine serum albumin has been shown to catalyse the Diels–Alder reaction of juglone **1a** and 1-methoxycyclohexa-1,3-diene to give a 2.5 : 1 mixture of cycloadducts; the major cycloadduct possessed an enantiomeric excess of 38% (S. Colonna, A. Manfredi and R. Annunziata, *Tetrahedron Lett.*, 1988, **29**, 3347).

‡ Previous attempts to prepare this compound were unsuccessful (N. F. Hayes and R. H. Thomson, *J. Chem. Soc.*, 1954, 904).

§ Similar conditions were used by Müller to effect the glycosidation of hydroxyanthraquinones (A. Müller, *Chem. Ber.*, 1929, **62**, 2793).

¶ We thank Dr A. Whiting for suggesting these conditions.

‖ *Crystal data*: $C_{29}H_{28}O_{12}$, M = 568.5, a = 6.270(3), b = 19.811(9), c = 23.162(6) Å, U = 2877 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.31 g cm^{-3}, μ(Mo-Kα) = 0.64 cm^{-1}. An Enraf-Nonius CAD-4 diffractometer employing graphite monochromated Mo-Kα radiation (λ = 0.71069 Å) in the ω-2θ scan mode, was used to record 4023 reflections ($0 < \theta < 25°$). Lorentz-polarisation corrections were applied but absorption effects were ignored. The structure was solved by direct methods (P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M. M. Woolfson, MULTAN-80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data, Universities of York, England, and Louvain-la-Neuve, Belgium, 1980) and refined by block-matrix least-squares procedures (G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, 1976) to final residuals of R = 0.043 and R_w = 0.041 {w = 1.603/[$\sigma^2(F_o)$ + $0.002F_o^2$]} for 2965 observed reflections with $F_o \geq 3\sigma(F)_o$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Data Centre. See Notice to Authors, Issue No. 1.

crystallisation), m.p. 182–183 °C (decomp.), $[\alpha]^{20}_D$ +51° (2.2% in $CHCl_3$) emerged when the reaction was conducted in benzene. It reacted with a few drops of hydrochloric acid (conc.) in chloroform to give the anthraquinone **8a** (93% yield after recrystallisation), m.p. 150 °C, $[\alpha]^{20}_D$ −60° (1% in $CHCl_3$), which when heated in ethanolic hydrochloric acid afforded compound **8b** (90% after recrystallisation), m.p. 292 °C (lit.,[10] 293–294 °C).** We, therefore, assign the structure **4c** to the cycloadduct.

The diene **2c** reacted with the dienophile **1b** in benzene to give the cycloadduct **4d** (93% yield after recrystallisation), m.p. 158 °C, $[\alpha]^{20}_D$ +75° (0.1% in $CHCl_3$). In accord with its assigned regiostructure, compound **4d** was converted into the anthraquinone **8c** (77% yield after recrystallisation), m.p. 180 °C (lit.,[11] 183–184 °C),†† under acidic conditions (conc. HCl–$CHCl_3$; HCl–EtOH).

In addition to their synthetic value, the aforementioned results are of considerable mechanistic interest. Clearly, the sugar is exerting a remarkable stereodirecting effect (a 1,6-relationship exists between the closest stereogenic and reacting centres). The results are not consistent with the model which we have developed[7] to explain the diastereofacial reactivity of dienes of types (**2**; R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) towards dienophiles.

We thank the SERC for a research studentship (to A. D. M. C.).

Received, 24th September 1990; Com 0/04311G

References

1 B. M. Trost, J. Ippen and W. C. Vladuchick, *J. Am. Chem. Soc.*, 1977, **99**, 8116; B. M. Trost, C. G. Caldwell, E. Murayama and D. Heissler, *J. Org. Chem.*, 1983, **48**, 3252.
2 B. M. Trost, D. O'Krongly and J. L Belletire, *J. Am. Chem. Soc.*, 1980, **102**, 7595.
3 D. S. Larsen and R. J. Stoodley, *Tetrahedron*, 1990, **46**, 4711.
4 T. R. Kelly, A. Whiting and N. S. Chandrakumar, *J. Am. Chem. Soc.*, 1986, **108**, 3510.
5 K. Muroka, M. Sakurai, J. Fujiwara and H. Yamamoto, *Tetrahedron Lett.*, 1986, **27**, 4895.
6 R. C. Gupta, P. A. Harland and R. J. Stoodley, *Tetrahedron*, 1984, **40**, 4657; R. C. Gupta, C. M. Raynor, R. J. Stoodley, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1773.
7 R. C. Gupta, D. S. Larsen, R. J. Stoodley, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1989, 739; D. S. Larsen and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1841.
8 R. U. Lemieux, in *Methods in Carbohydrate Chemistry*, eds. R. L. Whistler and M. L. Wolfrom, Academic Press, New York, 1963, vol. 2, p. 221; D. S. Larsen and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1841.
9 R. K. Boeckman, Jr., T. M. Dolak and K. O. Culos, *J. Am. Chem. Soc.*, 1978, **100**, 7098.
10 M. M. Shemiakin, M. H. Kolosov, U. A. Arbuzov, M. G. Karapemian, E. C. Chaman and A. A. Anishenko, *Zh. Org. Khim.*, 1959, **29**, 1831.
11 R. C. Gupta, D. A. Jackson and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1982, 929.

** The regioisomeric anthraquinone is reported[9] to have an m.p. of 272–275 °C.

†† The regioisomeric anthraquinone is reported to have an m.p. of 147 °C (P. C. Mitter and A. K. Sarkar, *J. Indian Chem. Soc.*, 1930, **2**, 619).