Diastereoselective cyclopropanation of α,β-unsaturated acetals of a novel camphor-derived chiral auxiliary

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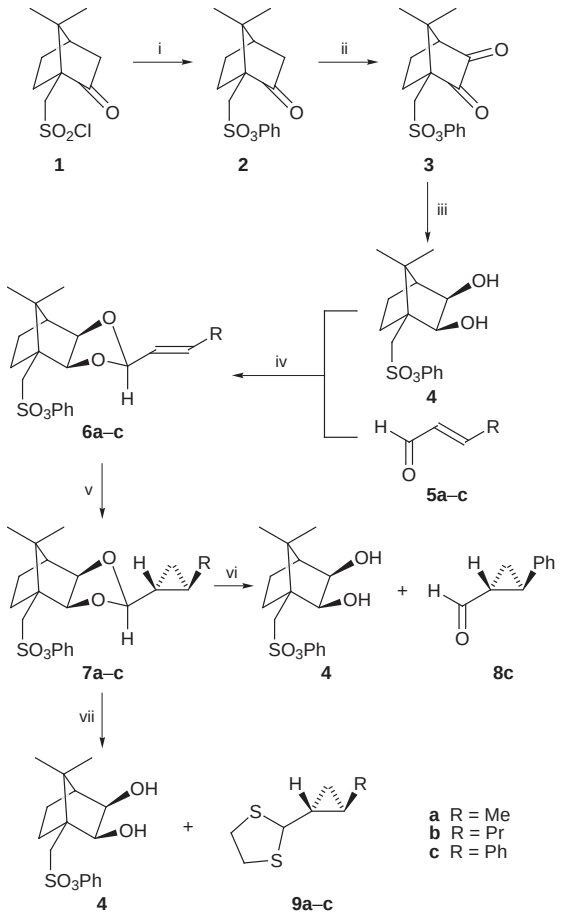
Reaction of selected α,β-unsaturated aldehydes with phenyl 2,3-dihydroxybornane-10-sulfonate affords acetals which undergo diastereoselective (>99% de) Simmons-Smith cyclopropanation.

The cyclopropyl group occurs in various natural products[1] and, due to its inherent ring strain, finds use as a structural intermediate in synthesis.[2] Barrett and Kasdorf,[3] for example, have exploited the Charette methodology[4] in tandem asymmetric cyclopropanation reactions in the synthesis of a nucleoside containing five cyclopropane units. The Simmons-Smith reaction[5] is commonly used to construct cyclopropane derivatives, and asymmetric applications involving the use of chiral acetals[6] and ketals[7] have been described. We have recently reported[8] moderate diastereoselectivity (40–70% d.e.) in the Simmons-Smith cyclopropanation of α,β-unsaturated acetals, using bornane-2,3-diol as a chiral auxiliary. Increasing steric demand at C-10 of the bornane skeleton was expected to enhance diastereofacial selectivity, and here we report the synthesis and use of phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate **4** as a highly efficient chiral auxiliary for the asymmetric cyclopropanation of α,β-unsaturated acetal derivatives.



Scheme 1 *Reagents and conditions*: i, PhOH, pyridine; ii, H_2SeO_3, dioxane; iii, $NaBH_4$, MeOH; iv, TsOH, $MgSO_4$, benzene; v, Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C; vi, (for R = Ph) TsOH, THF–H_2O, reflux, 72 h; vii, $HSCH_2CH_2SH$, TsOH, CH_2Cl_2.

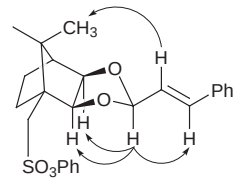


Fig. 1 NOE interactions observed in the NOESY spectrum of the acetal **6c**.

Treatment of (+)-camphor-10-sulfonyl chloride **1** with phenol in pyridine at 0 °C afforded the phenyl ester **2** in 81% yield (Scheme 1), the corresponding camphorquinone **3**† being obtained by subsequent selenous acid (H_2SeO_3) oxidation. Reduction of the diketone **3** with $NaBH_4$ gave the required diol **4**, which was unambiguously characterised by elemental (HRMS) and spectroscopic analysis.‡

Following the procedure developed for the synthesis of bornane-2,3-diol acetals,[8] the diol **4** was condensed with the α,β-unsaturated aldehydes **5a–c** to give the corresponding acetals **6a–c** in 64–74% yield. ^1H and ^{13}C NMR analyses indicated the formation of a single diastereomeric acetal in each case. The presence of heteroatoms and bulky substituents is known to inhibit pseudorotation in 1,3-dioxolane rings[9] and, in the systems studied here, fusion to the rigid bicyclic bornane skeleton is likely to lock the 1,3-dioxolane ring into an envelope conformation. Steric factors are expected to favour formation of the *exo*-acetals—an expectation supported by the NOE interactions observed for the cinnamaldehyde acetal **6c** (Fig. 1) and confirmed by single crystal X-ray analysis of this compound (Fig. 2).§

The Simmons-Smith organozinc reagent exhibits high affinity for ethereal oxygen, and transition state steric demands are considered to be significant.[10] Computer modelling¶ (Fig. 3) clearly indicates the capacity of the phenyl sulfonate moiety to hinder access to the 'front' face of the unsaturated acetals **6a–c**, and initial coordination of the organozinc reagent to the less

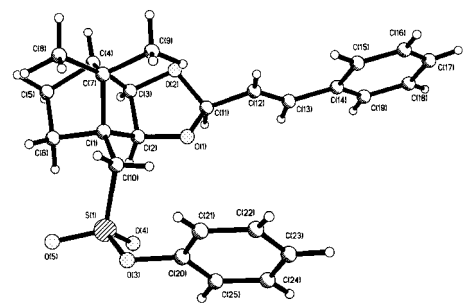


Fig. 2 X-Ray crystal structure of the acetal **6c** at 173 K, showing the crystallographic numbering.

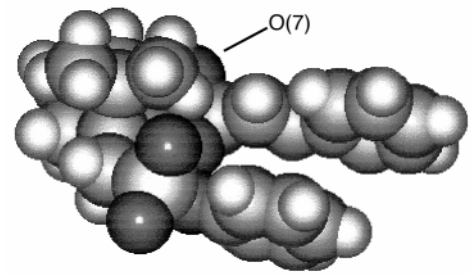


Fig. 3 Computer-modelled space-filling structure of a rotamer of the acetal **6c**, in which the phenyl sulfonate moiety effectively blocks access to one face of the double bond.

hindered acetal oxygen O(7) is predicted to precede methylene delivery from the 'back'.

Cyclopropanation of the acetals **6a–c** was effected by their dropwise addition (as solutions in dry CH_2Cl_2) to a cold, vigorously stirred mixture of Et_2Zn and CH_2I_2 in CH_2Cl_2.[8] Work-up and preparative layer chromatography afforded the cyclopropyl derivatives **7a–c** in good material yield (76–95%) and with complete diastereoselectivity (> 99% de).‖ Confirmation of the predicted stereochemical bias was achieved by hydrolysis of acetal **7c** to afford the known[11] laevorotatory (1*R*, 2*R*)-aldehyde **8c**;** the remarkable resistance of the acetal **7c** to acidic hydrolysis under various conditions is attributed to steric crowding. Release of the chiral auxiliary **4** (in 83–87% yield) from the cyclopropyl derivatives **7a–c** was finally achieved by transthioacetalisation,[12] the corresponding dithiolanes **9a–c** being isolated in 87–92% yield.††

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Notes and references

† *Selected data* for **3**: yellow crystals, 48%, mp 78–82 °C (Found: M^+ 322.0846. $C_{16}H_{18}O_5S$ requires *M*, 322.0875).

‡ *Selected data* for **4**: 51%, mp 126–130 °C (from CCl_4) (Found: M^+ 326.1194. $C_{16}H_{22}O_5S$ requires *M*, 326.1188); υ_{max}(KBr)/cm^{-1} 3300 (OH) and 1370 and 1150 (SO_2O); δ_H (400 MHz; $CDCl_3$) 0.84 and 1.14 (6H, 2 × s, 8- and 9-Me), 1.08, 1.49 and 1.76 (4H, 3 × m, 5-CH_2 and 6-CH_2), 1.86 (1H, d, 4-H), 3.05 and 3.21 (2H, 2 × m, 2- and 3-OH), 3.46 (2H, dd, 10-CH_2), 3.88 and 4.16 (2H, 2 × m, 2- and 3-H) and 7.27–7.43 (5H, m, Ar-H); δ_C(100 MHz; $CDCl_3$) 20.8 and 21.9 (C-8 and C-9), 23.7 and 29.4 (C-5 and C-6), 49.1 and 49.4 (C-1 and C-7), 49.8 (C-10), 50.4(C-4), 75.7 and 76.1 (C-2 and C-3) and 122.0, 127.3, 130.0 and 149.1 (Ar-C); *m/z* 308 (**M**−H_2O, 0.001%) and 94 (100).

§ *Crystal data* for **6c**: $C_{25}H_{28}O_5S$, M = 440.53; crystal size 0.36 × 0.18 × 0.08 mm, orthorhombic, space group $P2_12_12_1$; a = 6.8183(4), b = 13.0928(8), c = 25.198(2) Å, V = 2249(2) Å^3, Z = 4, F(000) = 936, D_c = 1.301 g cm^{-3}, μ = 0.178 mm^{-1}. Data collection (Siemens SMART CCD diffractometer; graphite-monochromated Mo-Kα radiation, λ = 0.71070 Å, T = 173 K), ω–2θ scans, 1.62 < θ < 28.26°, 13981 reflections collected (−9 ⩽ h ⩽7, −17 ⩽ k ⩽ 17, −26 ⩽ l ⩽17), 5049 unique with $I > 2\sigma(I)$. Hydrogen atoms were placed in calculated positions and the structure was solved by direct methods using SHELXTL (ref. 13); full-matrix least-squares refinement converged at R_1 = 0.810, wR_2 = 0.1713, GOF = 1.133. Max., min. peaks in final difference map = 0.221, −0.253 e Å^{-1}. CCDC 182/1049.

¶ Using the computer modelling software package, HYPERCHEM®.

‖ As evidenced by both ^{1}H and ^{13}C NMR spectroscopy.

** A solution of the acetal **7c** and PTSA (2 equiv.) in THF–H_2O (5:1) was boiled under reflux for 72 h to afford the aldehyde **8c** (10%), $[\alpha]_D^{26}$ −324 (*c* 0.333, $CHCl_3$), corresponding to (−)-(1*R*,2*R*)-2-phenylcyclopropanecarbaldehyde {$[\alpha]$ −340 (*c* 0.363, $CHCl_3$)} (ref. 11).

†† The cyclopropyl dithiolanes **9a–c** (87–92%) and the diol **4** (83–87%) were obtained from the acetals **7a–c**, following a method described by Caballero *et al*. (ref. 12) and gave satisfactory elemental (HRMS) and spectroscopic analyses. Optical rotation data for the dithiolanes are as follows: **9a**: $[\alpha]_D^{26}$ −35.2 (*c* 0.774, $CHCl_3$); **96**: $[\alpha]_D^{26}$ −18.9 (*c* 2.144, $CHCl_3$); **9c** $[\alpha]_D^{26}$ −88.4 (*c* 1.300, $CHCl_3$).

1 See, for example, A. Mori, I. Arai, H. Yamamoto, H. Nakai and Y. Arai, *Tetrahedron*, 1986, **42**, 6447; A. G. M. Barrett, K. Kasdorf, A. J. P. White and D. J. Williams, *J. Chem. Soc., Chem. Commun*., 1995, 649.
2 H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev*., 1989, **89**, 165.
3 A. G. M. Barrett and K. Kasdorf, *Chem. Commun*., 1996, 325.
4 A. B. Charette and H. Juteau, *J. Am. Chem. Soc*., 1994, **116**, 2651.
5 H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc*., 1958, **80**, 5323.
6 I. Arai, A. Mori and H. Yamamoto, *J. Am. Chem. Soc*., 1985, **107**, 8254; J. Kang, G. J. Lim, S. K. Yoon and M. Y. Kim, *J. Org. Chem*., 1995, **60**, 564.
7 E. A. Mash, S. K. Math and C. J. Flann, *Tetrahedron*, 1989, **45**, 4945.
8 P. T. Kaye and W. E. Molema, *Synth. Commun.*, in press.
9 W. E. Willy, G. Binsch and E. L. Eliel, *J. Am. Chem. Soc*., 1970, **92**, 5394.
10 T. L. Cairns, H. E. Simmons and S. A. Vladuchick, *Org. React*., 1972, **20**, 1.
11 H. Abdallah, R. Cree and R. Carrie, *Tetrahedron Lett*., 1982, **23**, 503.
12 M. Caballero, M. Garcia-Valverde, R. Pedrosa and M. Vicente, *Tetrahedron*: *Asymmetry*, 1996, **7**, 219.
13 G. M. Sheldrick, SHELXTL Ver. 5.03, 1996, Institut für Anorg. Chemie, Göttingen.

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