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Crystallographic Analysis and Structural Revision of a Spiroterpenoid Rearrangement Product

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ABSTRACT

Single crystal X-ray analysis of a spiroterpenoid rearrangement product has revealed that its structure is, in fact, isomeric with the structure proposed previously – an observation that has significant mechanistic implications.

KEYWORDS

Spiroterpenoid, rearrangement, X-ray crystallography, camphor derivative.

Various derivatives of D-(+)-camphor, a readily available, optically pure natural product, have been developed for use as chiral auxiliaries in asymmetric synthesis.[1] As part of an ongoing investigation, we have reported diastereoselective reactions of camphor-derived silyl enol ethers,[2] acetals[3] and carboxylic esters.[4]

In an attempt to prepare novel silylated camphor derivatives for use as chiral auxiliaries,[5] the tosylate **3** (Scheme 1) was identified as a potential precursor, the intention being to displace the tosyl moiety by a silyllithium reagent to afford the desired silylated derivative. However, when the alcohol **2** was treated with butyllithium at 0°C, followed by *p*-toluenesulfonyl chloride in refluxing tetrahydrofuran, the spirocamphene **6** was obtained in 64% yield.[5] When the reaction with *p*-toluenesulfonyl chloride was conducted at room temperature, an isomeric product, initially identified as the spiropinene derivative **8**, was isolated in 66% yield.[5] Formation of the products was

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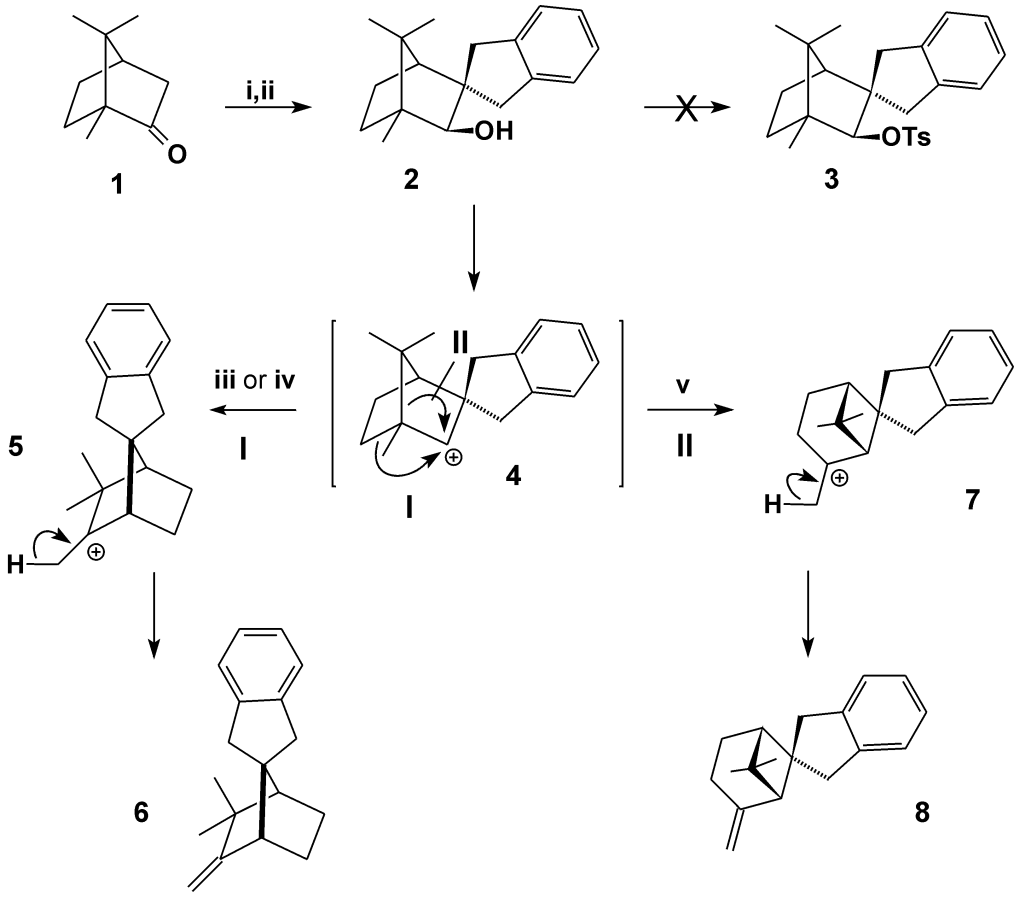


Scheme 1
Reagents and conditions: **i**, 2 eq. NaH, toluene, then α,α′-dichloro-*o*-xylene, reflux; **ii**, $LiAlH_4$, Et_2O, 0°C; **iii**, $SOCl_2$, pyridine, r.t., 4h; **iv**, *n*-BuLi, THF, 0°C, then *p*-TsCl, reflux; **v**, *n*-BuLi, THF, 0°C, then *p*-TsCl, r.t.

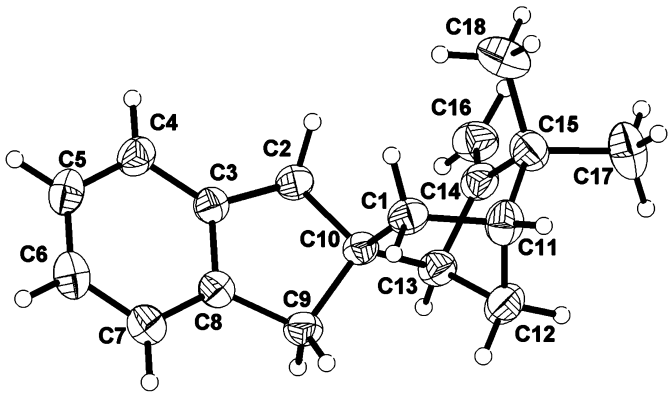
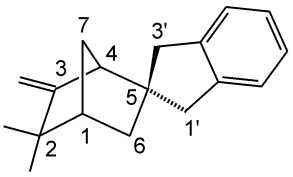


Figure 1 X-ray crystal structure of compound **9** (one enantiomer), showing the crystallographic numbering (50% probability ellipsoids).

rationalized in terms of rearrangement of a common, secondary carbocation intermediate **4** to give the corresponding tertiary carbocations **5** and **7** (*via* Paths **I** and **II**, respectively), subsequent deprotonation affording the spiroterpenoids **6** and **8**. The structural assignments appeared to be consistent with the high-resolution MS and the one- and two-dimensional NMR data.

The rearrangement products were originally isolated as oils, but the compound initially identified as the spiropinene **8** slowly crystallized.[5] In subsequent preparations, undertaken as part of a detailed mechanistic/computational study, both products were obtained as crystalline products, the former (**6**) with a very low melting point (24°C).[6] Single crystal X-ray analysis of the second product indicated that its structure (Fig. 1) did not correspond to the pinene derivative **8**, but rather to the isomeric camphene system, spiro[camphene-5,2′-indan] **9**.[7] Moreover, careful examination of the asymmetric unit (Fig. 2) revealed the presence of a *pair of enantiomers*.



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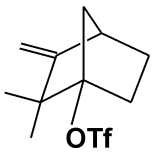

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Since our synthesis begins with optically active D-(+)-camphor **1**,[8] the formation of a *racemic compound*[9] clearly requires a different mechanistic sequence to that presumed in Scheme 1 – one which, effectively, permits inversion of configuration at both stereogenic centres (C-1 and C-4). Martinez *et al.*[10] have proposed a mechanism for the formation of somewhat analogous racemic products (including the triflate **10**) from D-(+)-camphor. A similar process may well be involved in the rearrangements that we have observed, and the mechanistic sequence is currently being examined.[11]

The observed optical activity cited,[5] for what was initially believed to be compound **8**, could be attributed, in principle, to *either* the presence of chiral contaminants *or* an *excess* of *one* enantiomeric product in the isolated material. Polarimetric analysis of the chromatographically pure oil [isolated in a subsequent reaction;[6] ($[\alpha]_D^{34}$ + 18.7°, $CHCl_3$)] supports the latter explanation. Interestingly, however, a solution of crystals precipitated from this oil also exhibited optical activity ($[\alpha]_D^{29}$ + 12.2°, $CHCl_3$), implying crystallization of *both* racemic *and* enantiomerically pure compounds. It thus seems that the fortuitous selection of a single crystal of the racemic compound for X-ray analysis has exposed the latent mechanistic complexity.

Experimental

NMR spectra were obtained from $CDCl_3$ solutions on a Bruker Avance 400MHz NMR spectrometer and are referenced using the solvent signals (δ_H 7.25 and δ_C 77.0 ppm). Signal assignments for the revised structure **9** are detailed below; the other analytical data for this product are as reported previously.[5]

(±)-Spiro[camphene-5,2′-indan] **9** (76%),[12] mp 68-70°C (lit.[5] 60–63°C); δ_H(400MHz; $CDCl_3$); 1.09 and 1.10 (6H, 2 × s, 2 × Me), 1.54–1.63 and 1.74–1.82 (4H, series of multiplets, 6- and 7-CH_2), 1.90 (1H, m, 1-H), 2.34 (1H, br s, 4-H), 2.68 and 3.08 (2H, 2 × d, *J* 15.9 Hz, Ar-CH_2), 2.82 and 2.95 (2H, 2 × d, *J* 15.6 Hz, Ar-CH_2), 4.73 (2H, 2 × s, C=CH_2), 7.08–7.17 (4H, complex of multiplets, Ar-H); δ_C(100 MHz; $CDCl_3$); 25.1 and 30.1 (2 × Me), 41.4 (C-2), 43.4 and 49.2 (2 × Ar-CH_2), 48.6 (C-1), 49.3 (C-5), 56.7 (C-4), 103.4 (C=CH_2), 124.15, 124.18, 125.9, 126.0, 142.9 and 143.6 (Ar-C) and 161.8 (C-3).

X-Ray data for compound **9**

Crystal size 0.05 × 0.11 × 0.3 mm^3; monoclinic, space group $P2_1/c$; a = 18.641 (4), b = 6.1420 (12), c = 12.756 (3) Å, β = 108.53 (3)°, V = 1384.7 (5) $Å^3$, Z = 4, $F(000)$ = 520, D_c = 1.143 mg cm^{-3}, μ = 0.064 mm^{-1}. Data collection with graphite-monochromated Mo-K_α radiation, λ = 0.71073 Å, T = 193 K, θ range 3.20 to 27.47°, 5859 reflections collected ($-24 \le h \le 23$, $-7 \le k \le 7$, $-16 \le l \le 16$), 3144 unique with $I > 2\sigma(I)$ on a Nonius Kappa CCD (University of Cape Town). Hydrogen atoms were placed in calculated

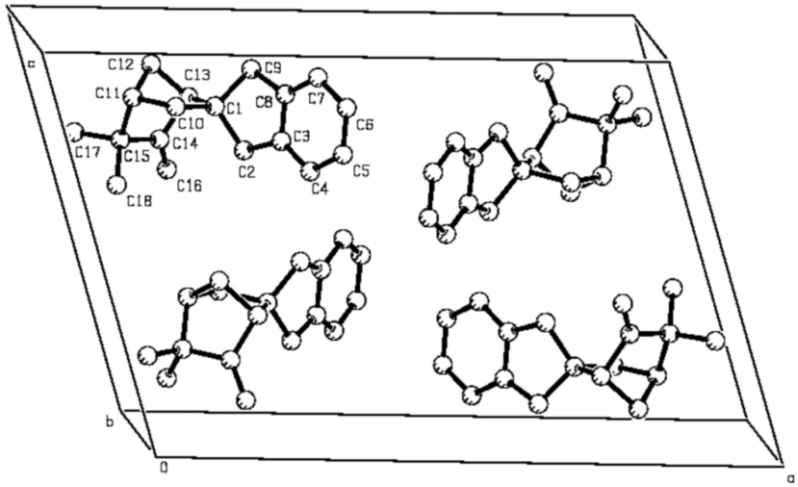

Figure 2 Diagram of the unit cell showing two enantiomer pairs of **9**.

Table 1 Bond lengths [Å] and angles [degrees] for compound **9**.

C(3)-C(4)	1.388(2)	C(7)-C(8)-C(9)	129.97(14)
C(3)-C(8)	1.390(2)	C(3)-C(2)-C(1)	103.99(11)
C(3)-C(2)	1.504(2)	C(2)-C(1)-C(13)	114.73(12)
C(8)-C(7)	1.393(2)	C(2)-C(1)-C(9)	102.49(12)
C(8)-C(9)	1.508(2)	C(13)-C(1)-C(9)	113.79(12)
C(2)-C(1)	1.544(2)	C(2)-C(1)-C(10)	113.21(12)
C(1)-C(13)	1.545(2)	C(13)-C(1)-C(10)	102.01(12)
C(1)-C(9)	1.553(2)	C(9)-C(1)-C(10)	111.00(12)
C(1)-C(10)	1.565(2)	C(16)-C(14)-C(15)	126.14(15)
C(14)-C(16)	1.317(2)	C(16)-C(14)-C(13)	126.69(15)
C(14)-C(15)	1.520(2)	C(15)-C(14)-C(13)	107.15(13)
C(14)-C(13)	1.527(2)	C(11)-C(10)-C(1)	104.12(12)
C(10)-C(11)	1.526(2)	C(5)-C(6)-C(7)	120.73(15)
C(6)-C(5)	1.381(2)	C(8)-C(9)-C(1)	103.27(11)
C(6)-C(7)	1.390(2)	C(6)-C(7)-C(8)	119.06(15)
C(13)-C(12)	1.540(2)	C(14)-C(13)-C(12)	100.58(13)
C(4)-C(5)	1.389(2)	C(14)-C(13)-C(1)	107.57(12)
C(15)-C(17)	1.539(2)	C(12)-C(13)-C(1)	100.63(12)
C(15)-C(18)	1.545(2)	C(3)-C(4)-C(5)	119.14(15)
C(15)-C(11)	1.562(2)	C(14)-C(15)-C(17)	111.08(15)
C(12)-C(11)	1.530(2)	C(14)-C(15)-C(18)	113.27(14)
		C(17)-C(15)-C(18)	107.74(15)
C(4)-C(3)-C(8)	120.61(14)	C(14)-C(15)-C(11)	100.55(13)
C(4)-C(3)-C(2)	129.54(13)	C(17)-C(15)-C(11)	110.47(14)
C(8)-C(3)-C(2)	109.85(13)	C(18)-C(15)-C(11)	113.68(15)
C(3)-C(8)-C(7)	120.04(14)	C(6)-C(5)-C(4)	120.41(15)
C(3)-C(8)-C(9)	109.97(13)	C(11)-C(12)-C(13)	94.78(12)
		C(10)-C(11)-C(12)	100.75(13)
		C(10)-C(11)-C(15)	110.12(13)

positions and the structure was solved by direct methods using SHELX-97;[13] full-matrix least-squares refinement converged at $R_1 = 0.0519$, wR2 = 0.1227, GOF = 1.038. Selected bond lengths and angles are listed in Table 1. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 198720. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK, fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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