organic compounds

Key tricyclic synthetic intermediates for the preparation of the sesquiterpenes *α*- and *β*-cedrene

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A completely novel and direct route towards the synthesis of the natural sesquiterpenes *α*-cedrene and *β*-cedrene delivered the compounds $(3\beta,3a\beta,7\beta)$-($\pm$)-6,6-ethylenedioxy-3,8,8-trimethyl-2,3,3a,4,5,6,7,8-octahydro-3a,7-methanoazulen-2-one, $C_{16}H_{22}O_3$, and $(3\beta,3a\beta,7\beta,8a\alpha)$-($\pm$)-6,6-ethylenedioxy-3,8,8-trimethyl-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,7-methanoazulen-2-one, $C_{16}H_{24}O_3$, at key stages of the preparative programme. Structural elucidation showed the latter compound to have added an H atom to the same face of the cyclopentenone ring as that occupied by the methyl substituent, and also allowed correct isomer identification for further reaction.

Comment

In order to extend and illustrate our endeavours to develop further the efficiency (Kennedy *et al.*, 2000; Ford *et al.*, 2000) and applicability (Donkervoort *et al.*, 1996) of the Khand cyclization reaction, we sought to utilize this annulation process strategically within the context of routes towards the naturally occurring sesquiterpenes *α*-cedrene, (I*a*), and *β*-cedrene, (I*b*). It was envisaged that use of these organo-cobalt-mediated methods would establish a direct and efficient pathway for the synthesis of the structurally demanding $[5.3.1.0^{1,5}]$ tricyclic carbon skeleton of this family of natural species.

The cyclization precursors (II*a*)/(II*b*), prepared as an inseparable 2:1 mixture of geometric isomers, were employed in the key intramolecular Khand cyclization, and the products (III*a*) and (III*b*) were isolated in an excellent optimum combined yield of 95% (Kerr *et al.*, 2001). Following separation, NMR spectroscopic studies could not fully identify each individual product with respect to the methyl group stereochemistry adjacent to the cyclopentenone carbonyl. Accordingly, the major component, (III*a*), was recrystallized and structural elucidation revealed the relative stereochemistry shown in Fig. 1. As this was not the required isomer, we were

able to concentrate our synthetic endeavours on the tricyclic species (III*b*), which was hydrogenated to give compound (IV), as shown in Fig. 2. The absolute configuration was not determined by our analysis and that shown is the relative configuration. In addition to showing the stereochemistry of the methyl group, the structure of (IV) also shows that the H atom introduced at the ring junction is *syn* to the methyl group. Pleasingly, this stereochemical outcome was that desired for the continuation of the total synthesis programme. The crystal structure analyses of compounds (III*a*) and (IV) are presented herein.

(I*a*)   (I*b*)

(i) 4.3 equivalents BuSMe, DCE, 356 K

(ii) H₂, 45 psi, 10% Pd/C.
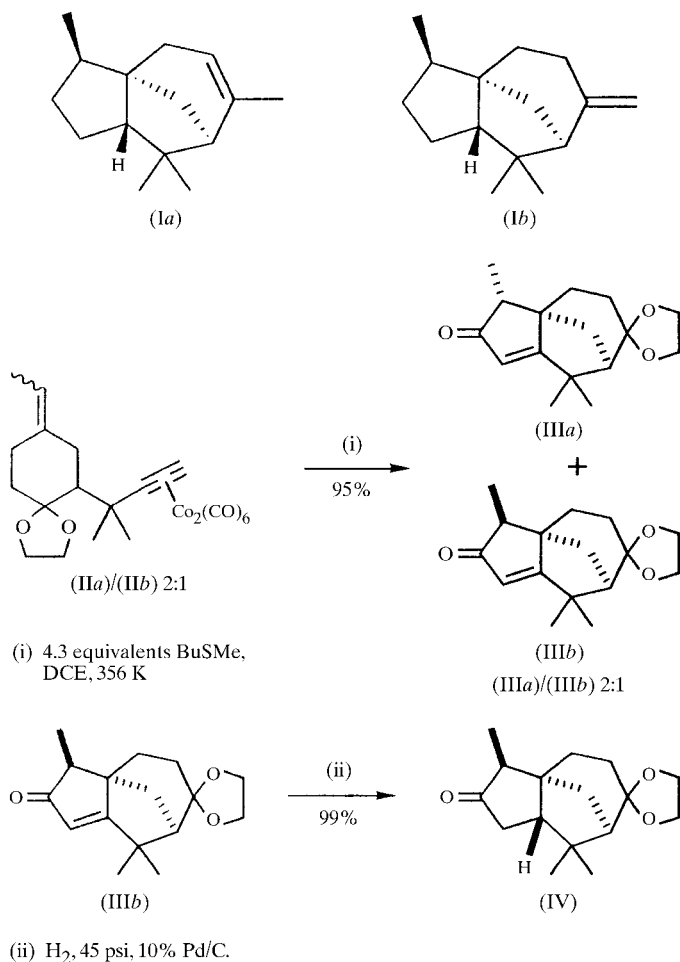
Both structures (III*a*) and (IV) are comprised of discrete molecules, with all intermolecular distances being equal to at least the sum of the van der Waals radii. Interestingly, (IV) crystallizes in the chiral space group $P2_1$, raising the possibility of resolving the racemic mechanical mixture of crystals by utilizing seeding techniques.

The main differences in geometry between the two compounds are, as expected, centred around the double bond found in (III*a*) but not (IV). Not only is this C2—C3 bond shorter in (III*a*), but conjugation to the carbonyl group also causes significant changes to the C1—C2 and C1=O1 distances [1.328 (3), 1.471 (3) and 1.221 (2) Å, respectively, for (III*a*), and 1.533 (2), 1.513 (3) and 1.210 (2) Å, respectively, for (IV)]. The presence of an sp^2-hybridized atom at C3 also

leads to a shortening of the C3—C4 and C3—C7 bonds. This shortening is more pronounced for C3—C4, which is within the cyclopentene ring, than it is for the aliphatic C3—C7 bond (see Tables 1 and 2). The bond lengths of the acetal group in (IIIa) are artificially shortened by a considerable degree of rotational motion (Fig. 1). A search of the Cambridge Structural Database (Release 5.21; Allen & Kennard, 1993) found no cedrane-based fragments with a double bond such as that in (IIIa). However, several saturated analogues of (IV) were found, though none with a similarly placed ketone functionality. These gave geometric parameters consistent with those found for (IV) (for typical examples, see Chen & Chang, 1996; Karlsson *et al.*, 1973; Khan *et al.*, 1985).

The conformation of the cedrene tricyclic skeleton is also affected by the introduction of an sp^2 atom at C3. Least changed is the C4/C9/C8/C12/C11/C10 six-membered ring, which adopts a chair conformation in both compounds. The planarity forced upon C2, C3, C4 and C7 in (IIIa) by the sp^2 atom C3 is not perfect, as C3 lies slightly above the plane of the other three atoms, but it still has a marked effect on the five-membered rings C1–C5 (ring *A*) and C3/C4/C9/C8/C7 (ring *B*). In (IIIa), there are two torsion angles around ring *A* that approach planarity [C1—C2—C3—C4 7.0 (3)° and C3—C2—C1—C5 6.5 (2)°], which means that atoms C4 and C5 are
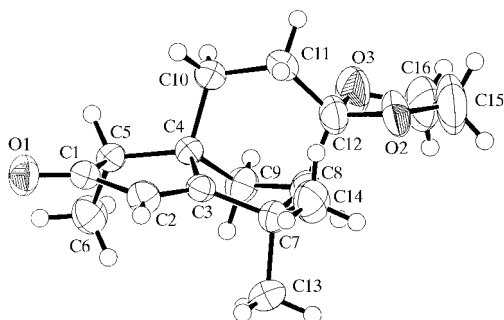
Figure 1
The molecular structure of (IIIa) with 50% probability displacement ellipsoids and H atoms drawn as small spheres of arbitrary size.

twisted furthest from the ring plane. The torsion angles about ring *A* in (IV) show both a greater overall deviation from planarity (Table 2) and that C1 and C2 are the atoms twisted furthest out of the plane. The torsion angles about ring *B* for the two structures show that for both (IIIa) and (IV) the C4—C3—C7—C8 angle is flattest, but only for (IIIa) does it truly approach planarity [4.2 (3) and 11.24 (16)°, respectively]. The flattened conformation of (IIIa) leaves the methyl groups of C13 and C14 staggered with respect to C2 [C2—C3—C7—C13 57.0 (3)°], whilst in (IV), the methyl group of C13 approaches an eclipsed position [16.4 (2)°]. The strain inherent in these fused-ring systems is shown by some large angular deviations from ideal geometry. Most notable are the widening of the C2—C3—C7 angles [to 135.2 (2) and 120.43 (15)° in (IIIa) and (IV), respectively], and of the C4—C5—C6 angle to 118.35 (15)° in (IV) and the C5—C4—C9 angle to 122.85 (18)° in (IIIa).
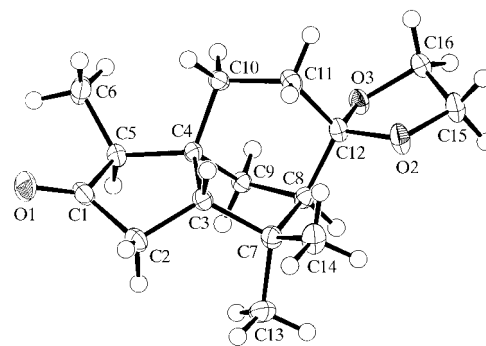
Figure 2
The molecular structure of (IV) with 50% probability displacement ellipsoids and H atoms drawn as small spheres of arbitrary size.

Experimental

The syntheses and spectroscopic characterizations of compounds (IIIa) and (IV) are described in detail by Kerr *et al.* (2001). Crystals of both compounds were grown by slow recrystallization from petroleum ether/diethyl ether mixtures at room temperature.

Compound (IIIa)

Crystal data

$C_{16}H_{22}O_3$	$D_x = 1.248$ Mg m^{-3}
$M_r = 262.34$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 21
$a = 6.0402$ (13) Å	reflections
$b = 31.423$ (4) Å	$\theta = 7.1–10.7°$
$c = 7.7111$ (13) Å	$\mu = 0.09$ mm^{-1}
$\beta = 107.469$ (15)°	$T = 295$ (2) K
$V = 1396.1$ (4) Å^3	Tabular, colourless
$Z = 4$	$0.50 \times 0.40 \times 0.15$ mm

Data collection

Rigaku AFC-7S diffractometer	$h = 0 \rightarrow 7$
$\omega/2\theta$ scans	$k = 0 \rightarrow 38$
2977 measured reflections	$l = -9 \rightarrow 9$
2721 independent reflections	3 standard reflections
1522 reflections with $I > 2\sigma(I)$	every 150 reflections
$R_{int} = 0.061$	intensity decay: 3.0%
$\theta_{max} = 26°$	

Table 1
Selected geometric parameters (Å, °) for (IIIa).

O1—C1	1.221 (2)	C2—C3	1.328 (3)
C1—C2	1.471 (3)	C3—C4	1.508 (3)
C1—C5	1.527 (3)	C3—C7	1.521 (3)
C2—C1—C5	108.22 (18)	C9—C4—C5	122.85 (18)
C2—C3—C7	135.2 (2)	C6—C5—C4	114.56 (18)
C5—C1—C2—C3	6.5 (2)	C3—C4—C5—C1	19.22 (19)
C1—C2—C3—C4	7.0 (3)	C4—C3—C7—C8	4.2 (2)
C7—C3—C4—C9	25.0 (2)	C3—C7—C8—C9	−31.8 (2)
C2—C3—C4—C5	−17.3 (2)	C3—C4—C9—C8	−43.9 (2)
C2—C1—C5—C4	−16.5 (2)	C7—C8—C9—C4	47.9 (2)

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Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.048$
$wR(F^2) = 0.142$
$S = 1.01$
2721 reflections
176 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0533P)^2 + 0.1589P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.18$ e Å^{-3}
$\Delta\rho_{min} = -0.15$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.017 (2)

Compound (IV)

Crystal data

$C_{16}H_{24}O_3$
$M_r = 264.35$
Monoclinic, $P2_1$
$a = 8.3280\ (3)$ Å
$b = 8.3930\ (3)$ Å
$c = 10.2120\ (4)$ Å
$\beta = 106.696\ (2)°$
$V = 683.70\ (4)$ Å^3
$Z = 2$

$D_x = 1.284$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 17 654 reflections
$\theta = 1.0-27.5°$
$\mu = 0.09$ mm^{-1}
$T = 150\ (2)$ K
Cut fragment, colourless
$0.50 \times 0.35 \times 0.10$ mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans to fill Ewald sphere
5455 measured reflections
1667 independent reflections
1579 reflections with $I > 2\sigma(I)$

$R_{int} = 0.030$
$\theta_{max} = 27.5°$
$h = -10 \rightarrow 10$
$k = -10 \rightarrow 10$
$l = -13 \rightarrow 13$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.080$
$S = 1.07$
1667 reflections
175 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0438P)^2 + 0.1142P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}

Table 2
Selected geometric parameters (Å, °) for (IV).

O1—C1	1.210 (2)	C3—C7	1.568 (2)
C1—C2	1.513 (3)	C3—C4	1.571 (2)
C1—C5	1.524 (2)	C4—C5	1.556 (2)
C2—C1—C5	108.38 (13)	C9—C4—C5	114.65 (13)
C2—C3—C7	120.43 (15)	C6—C5—C4	118.35 (15)
C5—C1—C2—C3	34.84 (18)	C3—C4—C5—C1	9.99 (18)
C1—C2—C3—C4	−27.19 (18)	C4—C3—C7—C8	11.24 (16)
C7—C3—C4—C9	18.98 (16)	C3—C7—C8—C9	−37.26 (16)
C2—C3—C4—C5	10.70 (18)	C3—C4—C9—C8	−42.31 (15)
C2—C1—C5—C4	−27.99 (18)	C7—C8—C9—C4	49.96 (16)

All H atoms were treated as riding, with C—H distances in the range 0.93–1.00 Å. For compound (IV), the Friedel equivalents were merged prior to the final refinement.

For compound (III*a*), data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1992); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). For compound (IV), data collection: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT* (Nonius, 1998); cell refinement: *DENZO* and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990). For both compounds, program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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