Novel Synthesis of Substituted *cis*-Bicyclo[3.3.0]octanes *via* Palladium-catalysed Cyclisation and Subsequent Baeyer–Villiger Ring Cleavage

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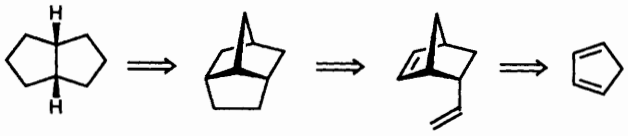
The formal transformation of cyclopentadiene to *cis*-bicyclo[3.3.0]octanes *via endo*-5-vinyl-2-norbornene involving two different oxidation reactions, such as Pd-catalysed cyclisation and Baeyer–Villiger (BV) ring opening is described.

Bicyclo[3.3.0]octanes (quinanes) and higher homologues such as bicyclo[4.3.0]octanes (indanes) are basic structure frameworks in numerous natural products including those with important biological properties.[1,2] They are also a part of interesting polycyclic hydrocarbons, *e.g.* dodecahedrane.[3] Stereospecific functionalisation of cyclic molecules can be achieved *via* cyclisation or cycloaddition to bridged bicyclic molecules followed by reopening of the bicyclic system.[4] We now report such regio- and stereo-specific formations of di- or tri-substituted diquinanes involving palladium-catalysed cyclisation of a suitable 1,5-diene and Baeyer–Villiger (BV) oxidative ring cleavage of the resulting substituted brendane[5] skeleton, according to the retrosynthetic outline shown in Scheme 1.

The *endo* isomer of 5-vinyl-2-norbornene **1**,† one of the Diels–Alder adducts of cyclopentadiene and butadiene, is readily cyclised to *exo*-2-acetoxy-*exo*/*endo*-5-chlorobrendane **2** and **3** with palladium(II)–copper(II) catalysis.[6] The original reaction can be considerably improved by reducing the amount of $CuCl_2$ and working under conditions with molecular oxygen as co-oxidant. The chloride is furnished by

† Commercially available from Aldrich as *exo*:*endo* mixture (3:7).

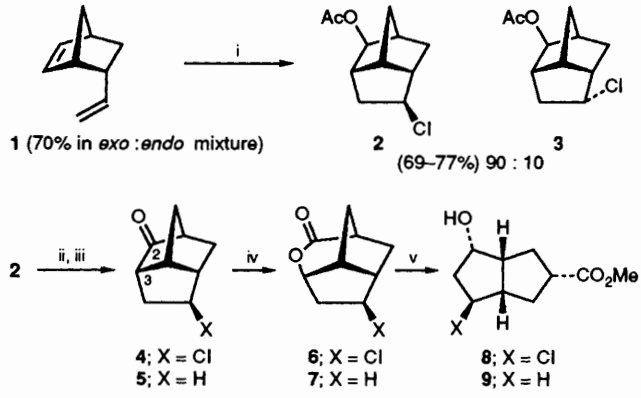


Scheme 1

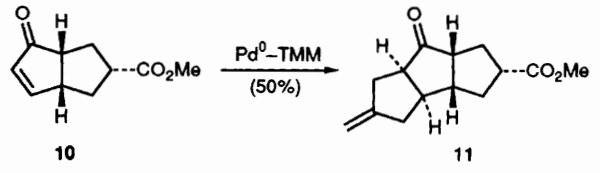
additional LiCl. Under these conditions the *exo,exo* isomer **2** (diastereoisomeric ratio 9:1, yield 69–77% with respect to *endo*-**1**) is highly predominant and the formation of (non-cyclised) chlorinated byproducts is considerably reduced.

The BV lactonisation[7] enables the cleavage of C–C bonds next to a carbonyl group. The Pd-catalysed oxidation of **1** directs an oxygen function at C-2 of the norbornane ring which should allow the BV bond cleavage of the subsequent ketones **4** and **5** to take place at the bridged part of the molecule that leads to *cis*-bicyclo[3.3.0]octanes.

When ketones **4** and **5**, which are readily obtained by standard procedures in high yields‡§ (Scheme 2) are submitted to conditions of peroxide oxidation[8–10] smooth transformation to tricyclic lactones **6**‡ (77%) and **7** (89%) takes place, respectively. The best results have been obtained with Oxone[10] as an oxidant¶ together with wet alumina.‖ The lactone cleavage to **8** (78%) or **9** (79%) is best performed by acidic methanolysis (BF_3–Et_2O,MeOH). It should be noted that the peroxide oxidation exclusively breaks the C-2–C-3 bond close to the 'ethano' bridge[11] thus giving rise (after hydrolysis of the lactones) to tri- or di-substituted diquinanes with complete control of all 4 or 5 stereogenic centres. This regioselectivity is in contrast to that observed in the BV ring



Scheme 2 *Reagents and conditions*: i, $PdCl_2$ (0.02 equiv.), $CuCl_2$ (0.2 equiv.) LiCl, O_2, HOAc, 80 °C, 36 h; formation of **8** ii, K_2CO_3, MeOH, 25 °C, 3 h, (93%); iii, $K_2Cr_2O_7$, H_2SO_4, H_2O, 3 h, (75%); iv, $KHSO_5$, wet alumina, CH_2Cl_2, reflux, 3.5 days, (77%); v, MeOH, BF_3–Et_2O, 25 °C, 1 h, (78%); formation of **9** ii, Bu_3SnH, azoisobutyronitrile, 25 °C, 3 h, hydrolysis, (82%); then as above iii, (75%); iv, (89%); v, (79%)



Scheme 3 *Reagents and conditions*: $Pd(OAc)_2$ (0.05 equiv.), $P(OPr^i)_3$ (0.35 equiv.), 2-[(trimethylsilyl)methyl]prop-2-en-1-yl acetate (1 equiv.), toluene reflux, 24 h (50%)

‡ NMR spectra of **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (tt, $J_1 = J_2 = 5$, $J_3 = J_4 = 1.2$ Hz, 1H, H_4), 4.17 (dt, J_1 2.1, $J_2 = J_3 = 6.8$ Hz, 1H, 6-*endo*-H), 3.01 (q, J 5.5 Hz, 1H, 8-H), 2.87 (ddm, J_1 7, J_2 4 Hz, 1H, 1-H), 2.82 (m, W/2 12.4 Hz, 1H, 7-H), 2.65 (ddm, part of an AB, J_1 15.6, J_2 7.2 Hz, 1H, 5-*endo*-H), 2.27 (ddd, J_1 14.4, J_2 11.3, J_3 6.7 Hz, 1H, 10-*exo*-H and ddd J_1 15.5, J_2 6.5, J_3 5 Hz, 1H, 5-*exo*-H), 2.06 (br d, part of an AB, J 12.7 Hz, 1H, 9-*syn*-H), 1.78 (dt, part of an AB, J_1 12.4, $J_2 = J_3 = 4.4$ Hz, 1H, 9-*anti*-H), 1.64 (dt, part of an AB, J_1 14.6, $J_2 = J_3 = 2.3$ Hz, 1H, 10-*endo*-H). ^{13} NMR (100.6 MHz, $CDCl_3$) δ 174.1 (CO), 84.0 (C-4), 63.7 (C-6), 51.3 (C-7), 46.7 (C-5), 44.0 (C-8), 41.8 (C-1), 36.4 (C-10), 29.8 (C-9).

8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (dt, J_1 5.9, $J_2 = J_3 = 7.6$ Hz, 1H, 2-H), 4.06 (m, W/2 12.4 Hz, 1H, 4-H), 3.64 (s, 3H, Me), 2.63–2.84 (m, 3H, left part 1-H, middle part 7-H, right part 5-H), 2.22–2.31 (m, 1H, 6-H), 2.12–2.22 (m, 2H, 2 × 3-H), 1.87–1.92 (m, 2H, 2 × 8-H), 1.45 (ddd, 1H, J_1 9, J_2 11, J_3 12.9 Hz, 6-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.7 (CO), 72.0 (C-2), 63.2 (C-4), 54.0 (C-7), 51.9 (Me), 45.9 (C-1), 45.6 (C-5), 43.1 (C-3), 36.4 (C-6), 29.7 (C-8).

11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (dm, J_1 13.5 Hz, 2H, $=CH_2$), 3.59 (s, 3H, Me), 2.4–2.85 (m, 8H), 2.17–2.28 (m, 2H), 1.88–1.98 (m, 2H), 1.51 (dt, J_1 13, $J_2 = J_3 = 10.4$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 223.3 (CO), 175.1 (CO-ester), 150.1 (C-5), 106.7 (C-12), 51.8 (Me), 51.0, 50.7, 46.6, 45.1, 43.9 (5 × CH), 40.2, 37.0, 35.6, 32.3 (4 × CH_2).

§ All new compounds have been characterised by elemental analysis, ^{1}H and ^{13}C NMR (COSY and NOE experiments).

¶ Oxidation with *m*-chloroperbenzoic acid in methylene chloride[8] or H_2O_2–CF_3CO_2H[9] leads to slightly lower yields (60–66%) for **6** and **7**.

‖ Preparation of **6**: 'wet alumina A' (type I, 10 g) is prepared by shaking Al_2O_3 vigorously with distilled water (2 g). Under an argon atmosphere *exo*-5-chlorobrendan-2-one **4** (511 mg, 3 mmol) is dissolved in dichloromethane (20 ml) and wet 'alumina A' (3.7 g) is added together with Oxone (3.8 g, 6 mmol). Every 20 h additional Oxone (3 × 1.9 g) is added, the mixture is refluxed for 3½ d. The mixture is filtered, the solid residues rinsed with CH_2Cl_2 and the CH_2Cl_2 solution concentrated *in vacuo*. After purification by flash chromatography with CH_2Cl_2 as eluent 432 mg of **6** (77%) was obtained.

opening of norcamphor, however, known in the more sterically crowded camphor *via endo* attack.[11] There should be a huge preference for *exo* attack of oxidant on the C=O in **4** and **5**, and the migration in the opposite direction from that previously observed might be a consequence of restricted conformations in the brendane BV intermediate. The stereochemistry of **6** and **7** is evident from the NMR spectra,‡[12] but also from a first useful transformation of *endo*-2-hydroxy-*exo*-4-chloro-7=methoxycarbonyl-*cis*-bicyclo[3.3.0]octane **8**. The oxidation of the secondary alcoholic group with Cr^{VI} (pyridinium chlorochromate, Celite, NaOAc, CH_2Cl_2, room temp., 79%) leads directly to enone **10**. This transformation demonstrates unambiguously that the OH function in the BV product, percursor of the enone carbonyl, has been formed in the Cl substituted five-membered ring. It also demonstrates the usefulness of diquinane **8** for the synthesis of more complex quinanes since triquinane **11**, the next higher tricyclopentanoid, is easily accessible with palladium catalysed trimethylenemethane (TMM) methodology[13] (Scheme 3). The *cis*:*anti*:*cis* stereochemistry, usually observed when a new cyclopentane ring is added to the unhindered face of the folded *cis*-diquinane,[1] is assigned from the ^{13}C NMR spectra.[12] The signals of $CHCO_2Me$ (δ 51.0) and both neighbouring CH_2 groups (δ 32.3 and 35.6) remain nearly unaffected by the new *exo*-methylenecyclopentane ring with respect to enone **10** or the more closely related alcohol **8**.

The construction of diquinanes remains a challenging topic[1,4] and the synthetic approach presented here should become a useful addition not only because it is simple and straightforward but also by the fact that all steps are stereospecific and completely compatible with the synthesis and transformation of optically active substances.

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