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Bicyclo[3.3.1]nonane Approach to Triquinanes. Formal Synthesis of (+/-)$\Delta^{9(12)}$Capnellene and (+/-)$\Delta^{9(12)}$Capnellene-8β-10α-diol

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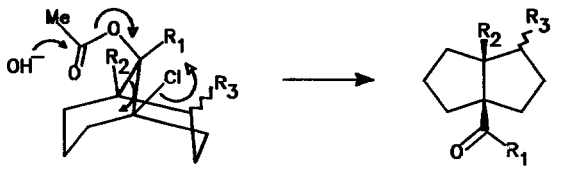
Abstract. A new synthetic strategy for natural triquinanes is presented as a model study. Stereospecific rearrangement of the ready accessible bicyclo[3.3.1] nonanic acetoxychloride **6** gave the *cis*-pentalanic hydroxyaldehyde **5**, which has been converted into the ketone **4** already reported as a key intermediate in some syntheses of the title capnellenes.

Natural triquinanes constitute an interesting synthetic target because of their structural features and biological activities.[1] Most of the synthetic strategies involve the chemical elaboration of functionalized *cis*-bicyclo[3.3.0]octanes (or pentalanes) as a key step.[2]

Under these grounds, we have previously reported[3] a new high yielding route for the regio and stereospecific synthesis of substituted *cis*-bicyclo[3.3.0]octane-1-carbonyl derivatives **2** by base-catalyzed rearrangement of readily accessible substituted 1-chloro-9-acetoxy-bicyclo[3.3.1]nonanes **1** (Scheme 1).

The rearrangement takes place through the intramolecular nucleophilic displacement of the chlorine

SCHEME 1



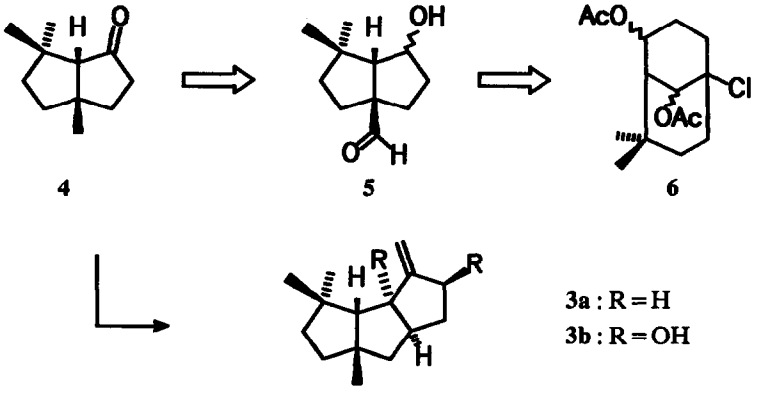
1 **2**

ion by the antiperiplanar C5-C9 bond and is activated by the negatively charged oxygen at the C9 position.

In order to apply the above methodology to the total synthesis of natural bioactive triquinanes, we have studied, as a model, the synthesis of the pentalanic trimethylketone **4**, which has been used as a key

intermediate in the total synthesis of both (+/-)$\Delta^{9(12)}$capnellene **3a**[2b,c] and (+/-)$\Delta^{9(12)}$capnellene-8β-10α-diol **3b**.[2d] Therefore, our report constitutes a formal synthesis of both capnellenes **3a** and **3b**.

SCHEME 2



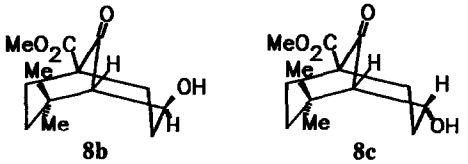
Retrosynthetic analysis (Scheme 2) showed that ketone **4** could be obtained by chemical elaboration of the pentalanic hydroxyaldehyde **5**, which, in turn, could be the only product of the above described rearrangement of the bicyclononanic chloride **6**.

Thus, following the Scheme 3, we prepared the precursor **6**. Enone **7a**[4] was hydrogenated to the corresponding saturated ketone. Carbomethoxylation [5] of this, due to the steric hindrance of the *gem*-dimethyl group at C_3, gave the ketoester **7b** as the only regioisomer. Subsequent Michael alkylation with acrolein afforded the aldehyde **8a** which was subjected to intramolecular aldol condensation to give the 4-*exo*-bicyclononanic ketol **8b** in moderate yield . However, the isolated **8b** underwent spontaneous retro-aldol opening and this accounted for the observed low conversion.

The stereochemistry at C_4 in **8b** followed from the observation of small coupling constants for the equatorial proton at C_4 in the ^{1}H-NMR spectrum (see Experimental).

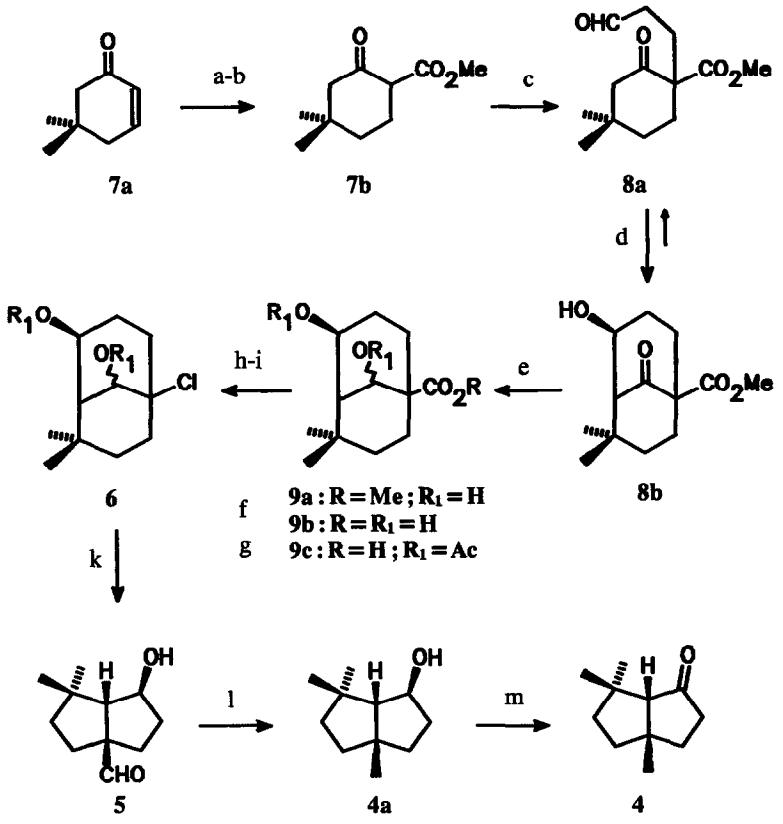
Formation of the *exo*-alcohol **8b** with such a high stereospecificity is quite unusual for an equilibrium process like the intramolecular aldol condensation leading to bicyclononanic ketols, where the usually more stable *endo* (equatorial)-alcohols predominate.[6] Moreover, spontaneous retro-aldol opening has never been reported for these systems, to the best of our knowledge.

However, these results can again be explained as a consequence of the presence of the *gem*-dimethyl group both in the precursor **8a** and in the product **8b**. In the latter compound, the more populated chair-chair conformation[7] shows the 6-*endo*-methyl group coplanar with the 4-*endo*-substituent . Such a negative eclypsing effect operates both in the final products and in the transition states, so that the 4-*exo* configuration **8b** should be preferred with respect to the 4-*endo* one **8c**.



Force field calculations [8] are in agreement with this hypothesis and show **8b** about 1 Kcal/mole more stable than **8c**. Under this point of view, the observed retro-aldol opening could be explained as a consequence of steric relief.

SCHEME 3



a: H_2/Pd, AcOEt, 99%; b: $(MeO)_2CO$/NaH, PhH, reflux, 90%; c: acrolein, MeONa / MeOH, -60°, 97%; d: MeONa / MeOH, 0°, 62%; e: $NaBH_4$, MeOH, r.t., 95%; f: NaOH / EtOH, r.t., 90%; g: Ac_2O / Py, reflux, 97%; h: $(COCl_2)$ / DMF, PhH, r.t.; i: Barton's chlorodecarboxylation;[9] k : 5% NaOH / EtOH, r.t., 84%; l: $(NH_2)_2$ / $(HOCH_2CH_2)O$, 180°, 88%; m: PDC, CH_2Cl_2, r.t., 98%.

In order to overcome the above problems, the isolated ketol **8b** was immediately reduced to the stable corresponding 2,9-diol **9a** (epimeric mixture at C_9), and the recovered aldehyde was recycled twice to give **9a** in 95% overall yield from **8a**. No attempts were made to isolate the epimers at C_9 since the planned rearrangement is irrespective of the stereochemistry at C_9.

Basic hydrolysis of **9a**, followed by protection of the hydroxy groups as acetates, gave the acid **9c** which was converted into the desired pentalanic hydroxyaldehyde **5** through a sequence of one-pot

reactions. Thus, acid **9c** was converted into the corresponding acid chloride and chlorodecarboxylated by the Barton's procedure[9] to afford the chloride **6** which was directly rearranged under the usual conditions[3] to give the 1β-formyl-4β-hydroxy-6,6- dimethyl-*cis*-bicyclo[3.3.0]octane **5** in 84% yield with respect to the acid **9c**.

Chemical elaboration of **5** to the target ketone **4**[2b-d] involved Wolff-Kishner reduction of the formyl group to the alcohol **4a** and subsequent PDC oxidation.

The present model study, in view of the ready and stereospecific access to highly substituted bicyclo[3.3.1]nonanic precursors[10] and the mildness and stereospecificity of the key rearrangement,[3] constitutes a suitable alternative approach to natural triquinanes.

EXPERIMENTAL

General procedures. Unless otherwise stated, ^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ with either Varian XL-300 or Varian "Gemini" 200 MHz instruments, while IR spectra were recorded in CCl_4 with a Shimadzu IR-470 instrument. MS spectra were recorded by HP5971A/MS detector coupled with HP5890 gaschromatograph.

Dry Na_2SO_4 was always used in drying organic extracts. Column chromatographies, unless otherwise stated, were carried out on silica gel (1:100 ratio) by eluting with light petroleum (40-70°)/ EtOAc mixtures.

2-Carbomethoxy-5,5-dimethylcyclohexanone(**7b**).Enone **7a**[4] (13.90g, 0.112 moles) was hydrogenated in AcOEt (150 ml) with Pd/C (1.5 g) as a catalyst. After filtration, solvent removal left 3,3-dimethyl-cyclohexanone (13.96g, 0.111 moles, 99%) which was added to a refluxing mixture of dimethylcarbonate (18.7 ml, 0.208 moles) and NaH (7.48g, 0.312 moles) in benzene (140ml). After 3 hrs reflux, the mixture was cooled, neutralized with iced AcOH/H_2O (1:3, 100ml), extracted with Et_2O, washed with brine and dried. Solvent removal left **7b** (18.38g, 99.9 mmoles, 90%); IR ν_{max} 3620, 2950, 1744, 1715, 1655, 1615 cm^{-1}; ^{1}H-NMR: δ 12.010(s,1H, enolic H), 3.710(s, 3H, OMe), 2.200(t, J = 6.50Hz, 2H, $2H_3$), 2.005(brs, 2H, $2H_6$), 1.328(t, J = 6.50Hz, 2H, $2H_4$), 0.910(s, 6H,2Me); MS *m/z*(%rel.int.): 184 (M^+, 69), 169(39), 156(33), 152(100), 137(47), 83(97).

3-(1-Carbomethoxy-2-oxo-4,4-dimethylcyclohexyl) propanale (**8a**). Ketoester **7b** (14.41g,78 mmoles) and acrolein (5.8 ml, 87 mmoles) were dropwise added in mixture to a cold (-60°) stirred solution of MeONa (0.659g, 12 mmoles) in MeOH (130 ml) under argon and stirring was prolonged for 4 hrs. After quenching with AcOH and solvent removal, the residue was dissolved in Et_2O, washed with brine, dried, evaporated and purified by flash-chromatography to afford **8a** (18.193g, 76 mmoles, 97%); IR ν_{max} 2960, 2820, 1738, 1720, 1713 cm^{-1}; ^{1}H-NMR: δ 9.703(brs, 1H, CHO), 3.698 (s, 3H, OMe), 2.65-1.10 (m, 10H,), 0.991 (s, 3H, C_5-Me), 0.836 (s, 3H, C_5-Me); MS *m/z*(%rel.int.): 240(M^+, 1), 184(100), 156(15), 152(32), 111(26).

1-Carbomethoxy-4-exo-hydroxy-6,6-dimethylbicyclo[3.3.1] nonan-9-one (**8b**) . A solution of the aldehyde **8a** (13.270g, 55.3 mmoles) in MeOH (30 ml) was added dropwise to a stirred cold (0°) solution of MeONa (24.8 g, 0.46 moles) in dry MeOH (670 ml) and the mixture was left at 0° for 24 hrs. After neutralization with HCl conc. and solvent removal under reduced pressure, the residue was suspended in Et_2O, washed with brine, dried and evaporated. Flash- chromatography gave unreacted **8a** (4.95 g, recycled twice) and **8b** (8.25g, 34 mmoles, 62%); IR ν_{max} 3610, 3445, 2965, 1738, 1714 cm^{-1}; ^{1}H-NMR: δ 4.413 (ddd, J_s = 3.78, 3.62, 3.20 Hz, 1H, $H_{4\alpha}$), 3.725 (s, 3H, OMe), 2.800 (dddd, J_s = 13.90, 11.63, 6.68, 2.00Hz, 1H,$H_{2\beta}$), 2.568 (dddd, J_s = 19.35, 6.78, 6.78, 2.00Hz, 1H, $H_{8\beta}$), 2.247 (dddd, J_s = 14.74, 11.63, 6.20, 3.78, Hz, 1H, $H_{3\alpha}$), 2.20-2.35 (brs, 1H, OH), 2.135 (ddd, J_s = 3.20, 1.15, 1.05 Hz, 1H, H_5), 2.058 (ddd, J_s = 14.40, 6.78, 0.0 Hz,

1H, $H_{7\alpha}$), 1.98-1.82 (m, 2H, $H_{2\alpha}$ + $H_{8\alpha}$), 1.712 (ddddd, J_s = 14.74, 6.68, 3.62, 3.47, 1.05 Hz, 1H, $H_{3\beta}$), 1.363 (dddd, J_s = 14.40, 10.24, 6.78, 1.14 Hz, 1H, $H_{7\beta}$), 1.070 (s, 3H, C_6-αMe), 0.945 (s, 3H, C_6-βMe); ^{13}C-NMR: δ 212.784(C_9), 173.173 (CO_2Me), 72.670 (C_4), 65.819 (OMe), 57.372 (C_1), 52.280 (C_5), 38.784 (C_6), 32.472, 31.103, 28.189 (2C), 27.975 (Me), 27.832 (Me); MS *m/z*(% rel.int.): 240 (M^+, 12), 225 (26), 193 (24), 184 (97), 169 (100).

1-Carbomethoxy-exo-4,9-dihydroxy-6,6-dimethylbicyclo [3.3.1] nonane (**9a**). Ketol **8b** (8.246 g, 34.4 mmoles) was treated with $NaBH_4$ (1.031 g, 27 mmoles) in MeOH (1 l) at r.t.. After neutralization with 2N HCl and solvent removal under reduced pressure, the residue was suspended in Et_2O, washed with brine, dried and evaporated to give **9a** (7.908 g, 32.7 mmoles, 95%) as *anti/syn* (3:1) mixture at C_9; IRν_{max} 3610, 3540, 2940, 1706 cm^{-1}; ^{1}H-NMR: δ 4.678 (d,J = 2.22Hz, 0.7H, *anti* H_9), 4.538 (brs, 0.3H, *syn* H_9, 4.333 (m, 0.3H, *syn* H_4), 4.271 (m, 0.7H, *anti* H_4), 3.672 and 3.644 (2s, 3H, OMe), 3.642 (brs, 2H, 2OH), 2.30-1.30 (m, 11H), 1.240 (brs, 3H, C_5-Me), 0.906 (brs, 3H, C_5-Me); Ms *m/z*(%rel. int.): 242(M^+, not detected), 224(12), 165(8), 156(14), 153(100), 147(9).

Exo-4,9-dihydroxy-6,6-dimethylbicyclo[3.3.1]nonane-1-carboxylic acid (**9b**). Diol **9a** (6.347 g, 26.2 mmoles) was dissolved in 10% NaOH/ EtOH (100ml) and stirred at r.t. for 4 hrs. After neutralization (2N HCl) and solvent removal under reduced pressure, the crude residue was suspended in 2N HCl, saturated with NaCl and extracted with AcOEt. Drying and solvent removal left **9b** (5.674 g, 24.9 mmoles, 95%) as *anti/syn* mixture at C_9; IR($CHCl_3$)ν_{max} 3690, 3510-2400, 1720, 1687 cm^{-1}; ^{1}H-NMR(d_6-DMSO): δ 4.355 (d, J = 3.15, 0.3H, *syn*H_9), 4.158 (d, J = 2.56, 0.7H, *anti* H_9), 3.980 (brs, 0.3H, *syn*H_4), 3.915 (brs, 0.7H, *anti*H_4), 3.477(brs,3H, 3OH), 2.30-1.20 (m, 9H), 1.126 (s, 3H, C_6-Me), 0.997 (s, 3H, C_6-Me).

Exo-4,9-diacetoxy-6,6-dimethylbicyclo[3.3.1]nonane-1-carboxylic acid (**9c**). Acid **9b** (5.00 g, 21.9 mmoles) and Ac_2O (18 ml) in dry pyridine (50 ml) were refluxed for 4 hrs. Methanol was added and the mixture was evaporated under reduced pressure. The residue was dissolved in Et_2O, washed with 2N H_2SO_4, brine and dried. Solvent removal gave **9c** (6.614 g, 21.2 mmoles, 97%) as *anti/syn* mixture; IRν_{max} 3500-2400, 2960, 1735, 1700 cm^{-1}; ^{1}H-NMR: δ 9.250 (brs, 1H, CO_2H), 5.551 (d, J = 2.18 Hz, 0.7H, *anti* H_9), 5.482 (m, 0.3H, *syn* H_9), 5.294 (m, 0.3H, *syn* H_4), 5.221 (m, 0.7H, *anti* H_4), 2.40-1.10 (m, 9H), 2.050 (s, 3H, COMe), 1.924 (s, 3H, COMe), 1.149 (s, 3H, C_6-Me), 0.960 (s, 3H, C_6-Me); MS *m/z*(%rel.int.): 312(M^+, not detected), 252(4), 234(14), 210(40), 192(95), 165(53), 164(100), 149(23), 147(85).

1β−Formyl-4β-hydroxy-6,6-dimethyl-cis-bicyclo [3.3.0] octane (**5**). Acid **9c** (4.784 g, 15.3 mmoles) and oxalyl chloride (1.946 g, 15.3 mmoles) were stirred in dry benzene (70 ml) containing few drops of DMF for 1h. Cooling at -20^0 and subsequent slow heating at r.t. allowed the DMF layer to separate from the benzenic one. Benzene evaporation gave the crude acyl chloride (5.1 g) which was directly chlorodecarboxylated[9] by dropwise addition to a refluxing CCl_4 suspension (40 ml) of N-hydroxypyridine-2-thione sodium salt (2.51 g, 16.8 mmoles) and a catalytic amount of DMAP under N_2 stream. After 1 h reflux, the cooled mixture was washed with water, dried and evaporated to give a crude mixture (8.40 g) containing the *4,9-diacethoxy-1-chloro-6,6-dimethyl bicyclo[3.3.1]nonane* **6** (MS *m/z*(%rel.int): 302-304[M^+, isotopic pair, not detected), 242-244(6), 199-201(34), 182-184(92), 164(97), 147(100)] which was directly rearranged without further purification. The crude mixture was poured into 5%KOH/ EtOH (80 ml) and stirred at r.t. for 2 hrs. After neutralization with 2N HCl, brine was added and the mixture was extracted with Et_2O, dried and evaporated to afford a residue (4.6 g) which was adsorbed on SiO_2 and eluted (CH_2Cl_2/ Et_2O, 8:2) to give **5** (2.339 g, 15.3 mmoles, 84% with respect to **9c**); IR ν_{max} 3620, 3415, 2960, 1720, 1690 cm^{-1}; ^{1}H-NMR :δ 9.558 (s, 1H, CHO), 4.064 (ddd, J_s = 7.39, 5.49, 5.36 Hz, 1H, $H_{4\alpha}$), 1.098 (d, J = 5.36 Hz, 1H, $H_{5\beta}$), 2.40-1.20 (m, 9H), 1.078 (s, 3H, C_6-βMe), 0.910 (s, 3H, C_6-αMe); ^{13}C-NMR: δ 203.879 (CHO), 75.852 (C_4), 64.312 (C_5), 40.863 (C_1), 39.726, 35.472, 31.530, 29.483 (C_6), 28.875 (Me), 23.834 (Me); MS *m/z*(%rel. int.): 182 (M^+, 0.3), 164 (12), 138 (29), 123 (28), 121 (30), 108 (53), 93 (33), 80 (100). Found: C, 72.49; H, 9.90. Calc. for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89.

2β-Hydroxy-5β,8,8-trimethyl-cis-bicyclo[3.3.0]octane (**4a**) . Hydroxyaldehyde **5** (1.838 g, 10.1 mmoles) was dissolved in diethyleneglycol (12 ml) and poured in a bulb-to-bulb distillation apparatus. KOH (1.93 g, 34.4 mmoles) and hydrazine monohydrate (1.52 g, 30.4 mmoles) were added and the mixture was heated at 180 while collecting the distillate. At the end, the distillate was dissolved in Et_2O, washed with brine, dried and evaporated to leave **4a** (1.493 g, 8.9 mmoles, 88%). A small sample was evaporatively distilled (120°/20mm) for analytical purposes; IR ν_{max} 3620, 2955, 2870, 1454, 1062 cm^{-1}; ^{1}H-NMR: δ 3.917 (dddd, J_s = 7.49, 6.69, 6.45, 0.51 Hz, 1H, $H_{2\alpha}$), 1.90-1.72 (m, 1H, $H_{1\beta}$), 1.65-1.25 (m, 9H), 1.195 (s, 3H, Me), 1.039 (s, 3H, Me), 0.975 (s, 3H, Me); ^{13}C-NMR: δ 76.927 (C_2), 68.799 (C_1), 49.567 (C_5), 40.534 (C_8), 39.985, 39.170, 38.093, 34.773, 31.228 (Me), 29.469 (Me), 24.289 (Me); MS *m/z*(%rel.int.): 168 (M^+, 1.6), 153 (35), 135 (19), 111 (64), 110 (43), 109 (85), 95 (57), 81 (100).

5β,8,8-Trimethyl-cis-bicyclo[3.3.0]octan-2-one (**4**). Alcohol **4a** (1.2 g, 7.1 mmoles) in CH_2Cl_2 (1,5 ml) was added to a suspension of PDC (4.15 g, 11.0 mmoles) in CH_2Cl_2 (15 ml) at r.t. and stirred for 2 hrs. Et_2O (5 ml) was added and the liquid phase separated, while the gummy residue was triturated with Et_2O. The collected ethereal phases were filtered through Celite and evaporated to leave **4** (1.162 g, 7.0 mmoles, 98%); IR ν_{max} 2955, 2855, 1707, 1256 cm^{-1}; ^{1}H-NMR: δ 2.297 (ddd, J_s = 7.85, 0.92, 0.79 Hz, 1H, $H_{3\alpha}$), 2.257 (ddd, J_s = 7.85, 0.85, 0.0 Hz, 1H, $H_{3\beta}$), 1.679 (s, 1H, H_1), 1.92-1.50 (m, 6H), 1.196 (s, 3H, Me), 1.110 (s, 3H, Me), 0.942 (s, 3H, Me); ^{13}C-NMR: 222.163 (C_2), 69.454 (C_1), 49.233 (C_5), 44.164 (C_8), 42.264, 39.532 (2C), 34.823, 31.641 (Me), 28.780 (Me), 25.583 (Me); MS *m/z*(%rel.int.): 166 (M^+, 10), 109 (12), 97 (100), 95 (23).

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