Tetrahedron Vol. 47, No. 43, pp. 9097-9102, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Synthesis of Substituted cis-Bicyclo[3.3.0]octane-1-carbonyl Derivatives by Stereospecific Rearrangement of 1-Chloro- 9-hydroxybicyclo [3.3.1]nonanes

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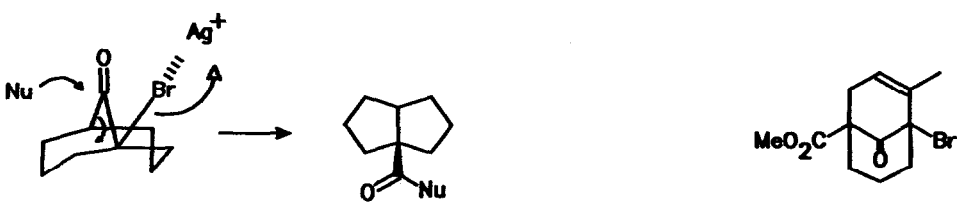
(*Received in UK* 11 *June* 1991)

Abstract: Substituted *cis*-1-formyl (or acetyl) bicyclo[3.3.0]octanes are stereospecifically obtained in high yield by a base-catalyzed rearrangement of readily accessible substituted 1-chloro-9-hydroxy (or acetoxy) bicyclo[3.3.1] nonanes.

Cis-Bicyclo [3.3.0] octanes (diquinanes or pentalanes) occur as important mojeties in natural bioactive polyquinanes.[1] Moreover, substituted diquinanes with well defined stereochemistry have been used as building blocks in the total synthesis of linear and angular triquinanes[2] and, therefore, several synthetic approaches to the bicyclo[3.3.0]octane system have been described.[2,3] We report here a new general approach based on a base-catalyzed rearrangement of functionalized 1-chloro-9-hydroxy (or acetoxy) bicyclo[3.3.1]nonanes.

Substituted bicyclo[3.3.1]nonanes are readily prepared in regio and stereoselective way[4] and undergo skeletal rearrangement[5] strongly driven by the position of the leaving groups[5]. Namely, if a negatively charged oxygen is bonded to C9 and a leaving group is present at the bridgehead position, this latter can undergo, under the appropriate conditions, intramolecular nucleophilic displacement by the antiperiplanar C5-C9 bond leading to bicyclo[3.3.0]octane derivatives 2.

Scheme 1

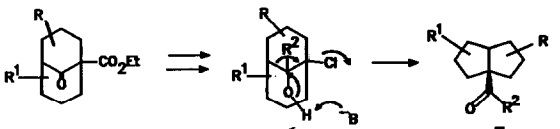


1 2 3

Such a behaviour was firstly reported by Cope for the bromoketone **1** when treated with strongly basic nucleophiles[6a] or mild nucleophiles but under Lewis acid catalysis,[6b] and explained in terms of the "push-pull" mechanism reported in Scheme 1. Very recently, while we were writing this work, similar results were reported for the bicyclononanic bromoketone **3** under the action of lithium enolates.[7]

Under these grounds, we felt that the conversion of easily accessible substituted 1-carboethoxy bicyclo [3.3.1] nonan-9-ones **4** (Scheme 2) to the corresponding 1-chloro-9-hydroxy derivatives **6** could result in substrates where the presence of the easily polarizable O-H bond should activate the rearrangement to substituted *cis*-bicyclo[3.3.0]octane-1-carbonyl derivatives **7** by the action of mild bases and without the aid of Lewis catalysis.

Scheme 2



4 **6** **7**

Thus, in order to verify this hypothesis, we prepared the chloroderivatives **6a-e** and reacted them with KOH/EtOH. Chloroderivatives **6a-e** were easily prepared, as depicted in Scheme 3, starting from the known bicyclononanic ketoesters **4a**,[8] **4c-d**,[9] and **4e**[10] by a routinary sequence. Thus, hydrolysis of esters **4a-e** followed by $NaBH_4$ reduction (or Grignard methylation[11] and subsequent hydrolysis in the case of compound **5b**) gave the hydroxyacids **5a-e** which, after protection as acetates of the secondary hydroxy groups, were chlorodecarboxylated[12] to afford the 1-chloro-9-acethoxy (or hydroxy) derivatives **6a-e** in good yields. Compounds **5c-e** and **6c-e** are epimeric mixtures at C_9, but no attempts were made to separate the epimers because their rearrangements were expected to be irrespective of the stereochemistry at C_9.

Stereochemistry at C_4 in compounds **5c,d** and **6c,d** was assigned on the basis of their ^{1}H-NMR spectra. Thus, compound **5c** shows a *trans*-diaxial coupling constant ($J = 9.77$ Hz) for the proton at C_4 and, consequently, the acetoxy group at the same carbon must be in the *endo* equatorial configuration. On the contrary, the proton at C_4 in compound **5d** is equatorial and appears as a broad singlet. The same patterns are observable for the chloroderivatives **6c** and **6d**, respectively.

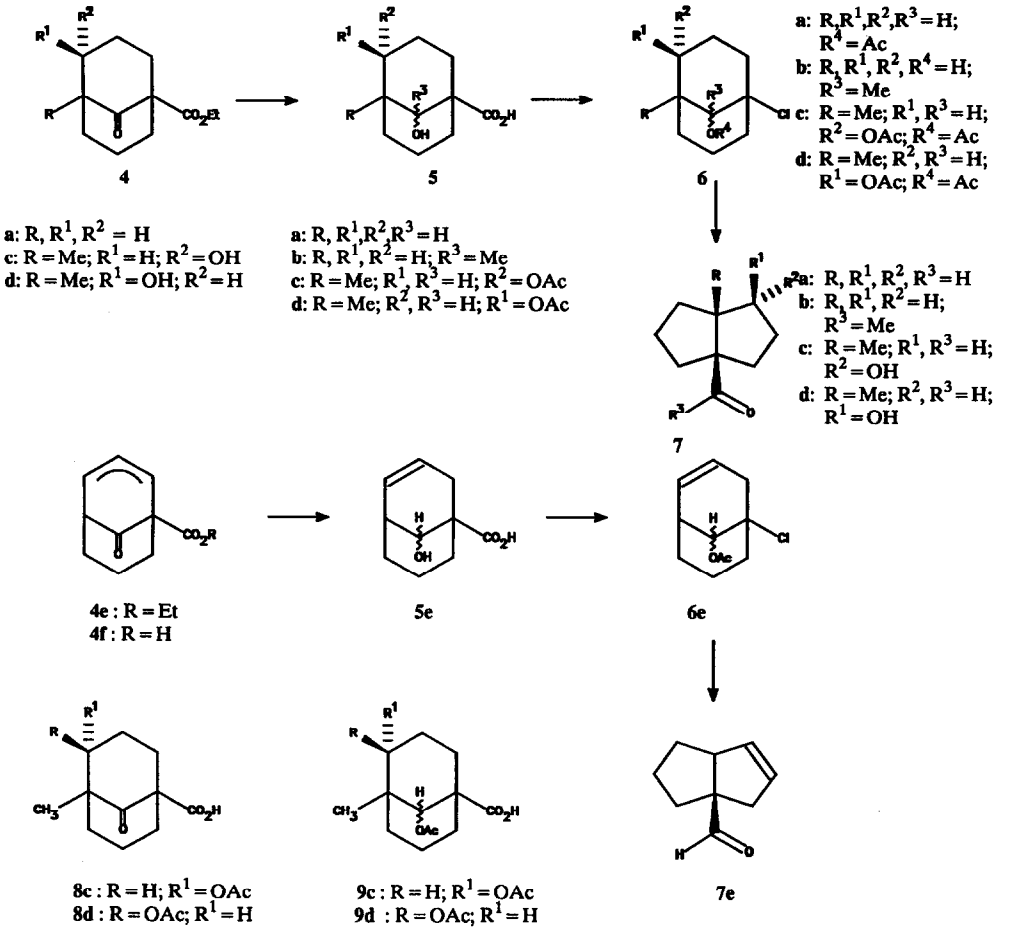
Reactions of the chloroderivatives **6a-e** with 5% ethanolic KOH occurred smoothly at room temperature and gave the expected *cis*-pentalanic derivatives **7a-e** with complete retention of both stereo and regiochemistry present in the parent compounds and isolated yields ranging from 78% to 87%.

All pentalanic aldehydes showed to be unstable and, in the case of compounds **7c** and **7d**, yields were strongly affected by the reaction time. Short reaction times resulted in a mixture of the rearranged product (**7c** or **7d**, respectively) together with unrearranged but partially deacetylated chloroderivatives. On the contrary, prolonged reaction times gave rise to other products, not further investigated, with consumption of **7c** or **7d**.

Spectroscopic properties of compounds **7a-e** are consistent with the reported structures. In particular, *cis*-junction for all pentalanes **7a-e** follows from the downfield chemical shifts observed for the respective protons (or methyl groups) at C_5, while the configurations at C_4 in compounds **7c** and **7d** were assigned by coupling ^{1}H-NMR spectra and force field calculations (Alchemy^R, Tripos Associated^{TM}). Thus, the methyl group at C_5 in the 4-*endo*-hydroxyderivative **7c** shows a lower chemical shift if compared with the same group in the 4-*exo*-hydroxy derivative **7d** and the observed coupling constants for the *exo*-proton at C_4 in **7c** (10.00 and 5.90 Hz) are in good agreement with the calculated dihedral angles (146.2° and 24.7°). Coherently, the *endo*-proton at C_4 in **7d** shows smaller coupling constants (3.90 and 3.30 Hz) in agreement with calculated dihedral angles of 93.7° and 26.3°.

These results, in view of the easy and stereoselective access to highly substituted 1-carboxybicyclo[3.3.1]nonan-9-ones and their easy conversion to the corresponding 1-chloro-9-hydroxy deriva-

Scheme 3



tives, constitute a versatile and stereospecific route to substituted *cis*-bicyclo[3.3.0]octane-1-carbonyl derivatives. Moreover, the mildness of the reaction conditions makes the rearrangement compatible with substrates carrying functional groups affected by strong nucleophiles.

EXPERIMENTAL

General procedures. M.ps are uncorrected. 1H-NMR and 13C-NMR were recorded in CDCl3 with either VARIAN XL-300 or VARIAN "Gemini" 200 MHz instruments, while IR spectra were obtained with a P.E. 257 instrument. MS spectra were recorded by HP5971A/MS detector coupled with HP 5890 Gaschromatograph.

Dry Na_2SO_4 was always used in drying organic extracts. Washed silica gel refers to SiO_2 suspended overnight in 2N HCl, filtered, washed with warm H_2O until neutrality and activated at 120°C overnight.

Unless otherwise stated, alkalyne hydrolyses were carried out by refluxing 0.4M solution of the appropriate substrate in 5% aqueous KOH for 2h, followed by acidification at pH 3, addition of brine and extraction with Et_2O.

$NaBH_4$ reductions were carried out by adding 2.5 equivalents of the reagent to a 0.6M solution of the appropriate substrate in dry isopropanol and stirring at room temp. overnight. At the end, the solution was neutralized with 0.2M HCl and the alcoholic phase removed under reduced pressure. The resulting mixture was acidified at pH 3, additionated with brine and extracted several times with AcOEt.

Chlorodecarboxylations were carried out, according to literature[12], *by treating 0.6M solutions of the appropriate substrate* in DMF/AcOH (5:1) with a 6 molar excess of NCS.

All rearrangements were carried out by stirring 0.2M solutions of the appropriate chloroderivative in 5% KOH in EtOH at room temperature for 2-4h. At the end, brine (2 volumes) was added followed by neutralization with AcOH and extraction with hexane. Solvent was removed through Vigreux distillation.

9-Hydroxybicyclo[3.3.1]nonane-1-carboxylic acid (5a). *Bicyclo[3.3.1]nonan-9-one-1-carboxylic acid*[8] **(4.76g),** *obtained by* alkalyne hydrolysis of ester **4a**[8], was reduced with $NaBH_4$. Evaporation of the dried organic phase afforded **5a** (4.57g, 95%), m.p. 121-124°C (lit. 122-123°C).[13]

9-Acetoxy-1-chlorobicyclo[3.3.1]nonane (6a). Hydroxy acid **5a** (4.50g) was acetylated to give the acetylderivative (5.36g, 97%), m.p. 133-134°C (lit. 130-131°C).[13] This latter (5.00g) was chlorodecarboxylated without further purification to give an oil *evaporatively distilled (90°C/1mmHg) to afford* **6a** *(4.15g, 87%); IR* (CCl_4) ν_{max} 2960, 2860, 1750 cm^{-1}; ^{1}H-NMR: δ 5.03 (d, J = 3.90Hz, 1H; C9H), 2.15 (s, 3H; Ac), 2.50-1.40 (m, 13H); MS m/z (% rel. int.): 216, 218 (isotopic pair, M^+, not detected), 181(7), 122(100), 121(26).

Cis-**1-formylbicyclo[3.3.0]octane (7a).** Chloroderivative **6a** (3.00g) was rearranged as usual. Afted 2h, workup and solvent removal (Vigreux distillation) left a crude product evaporatively distilled (125°C/25mmHg) to give **7a** (1.50g, 78%); IR (CCl_4)ν_{max} 2980, 2930, 2860, 2740, 1730 cm^{-1}; ^{1}H-NMR: δ 7.98 (s, 1H; CHO), 2.67 (dddd, J_s = 7.54, 7.54, 5.54, 5.54 Hz, 1H; C5H), 2.20-1.00 (m, 12H); ^{13}C-NMR: δ 185.64 (CO), 59.71 (C_1), 49.71 (C_5), 38.18 (2C), 34.07 (2C), 26.30 (2C); MS m/z (% rel. int.): 138 (M^+, 0.3), 108(100), 97(87), 80(82). Found: C, 78.21; H, 10.12. Calc. for $C_9H_{14}O$: C, 78.26; H, 10.14.

9-Hydroxy-9-methylbicyclo[3.3.1]nonane-1-carboxylic acid (5b). Two equivalents of a titolated solution of MeMgI in Et_2O were added dropwise under stirring and N_2 stream to a cold solution (0°C) of ketoester **4a**[8] (3.7g) in Et_2O (170ml). After 1h stirring, the mixture was acidified with 0.5M HCl and brine and extracted with Et_2O. The separated organic phase was washed with brine, dried and evaporated to give a crude mixture (3.85g). A sample (0.10g) was adsorbed on Silica (100g) and eluted (light petroleum/AcOEt, 9:1) to afford *1-carboethoxy-9-methylbicyclo[3.3.1]nonan-9-ol* as an oil; b.p. 105°C/0.1mmHg; IR (CCl_4) ν_{max} 3580, 2980, 2890, 1740 cm^{-1}; ^{1}H-NMR: δ 4.04 (q, J = 7.0Hz, 2H;CO_2Et), 3.62 (s, 1H; OH), 1.25 (s, 3H; C9-CH_3), 1.20 (t, J = 7.0Hz; CO_2Et), 2.50-1.00 (m, 13H); MS m/z (% rel. int.): 226 (M^+, 57), 211(23) 208(23), 182(23), 180(51), 152(100). The above crude hydroxyester (3.70g) was hydrolized by refluxing with 10% KOH in 2:1 H_2O/EtOH (70ml) for 2h. Ethanol was removed under reduced pressure, the resulting mixture washed with Et_2O and acidified at pH 3. Filtration gave chrystalline **5b** (3.05g, 94%); m.p. 150-157 (dec.); IR ($CHCl_3$) ν_{max} 3600-2700, 2990, 2880, 1740, 1710 cm^{-1};^{1}H-NMR: δ 7.60-7.00 (br s, 2H; CO_2H, OH), 1.36 (s, 3H; C9-CH_3), 2.50-1.50 (m, 13H); MS m/z (% rel. int.): 198(M^+,48), 180(39), 165(21), 152(100), 137(36), 109(71).

Cis-**1-Acethylbicyclo[3.3.0]octane (7b).** Hydroxyacid **5b** (2.5g) was chlorodecarboxylated to give the corresponding 1-chloroderivative **6b** (M^+ = 190, 188 as isotopic pair *via* GC-MS) contaminated by **7b** (30% *via* GC). Attempts to purify **6b** were unsuccesfull and the crude mixture (2.35g) was directly rearranged as usual to afford **7b** (1.60g, 81% referred to **5b**); b.p. 135°C/25mmHg; IR ($CHCl_3$)ν_{max} 2950, 2860, 1710 cm^{-1}; ^{1}H-NMR: δ 2.71 (dddd, J_s = 8.30, 8.30, 4.99, 4.99 Hz, 1H; C5H), 2.15 (s, 3H; $COCH_3$), 2.20-1.20 (m, 12H); ^{13}C-NMR: δ 212.04 (CO), 67.39 (C_1), 46.09 (C_5), 37.42 (2C), 34.29 (2C), 26.01 (2C), 25.92 (CH_3); MS m/z (% rel. int.): 152 (M^+, 8), 137(25), 111(25), 109(66), 67(100). Found: C, 78.89; H, 10.54. Calc. for $C_{10}H_{16}O$: C, 78.95; H, 10.53.

4-*endo*-Acetoxy-5-methylbicyclo[3.3.1]nonan-9-one-1-carboxylic acid (8c) and 4-*exo* epimer (8d). Alkalyne hydrolysis of **4c,d**[9] (6.10g) afforded the corresponding carboxylic acids (5.4g) as an epimeric mixture at C_4. Acetylation of the latter mixture gave crude acetylderivatives (6.40g) which were resolved on washed silica (1.3Kg) by eluting with light petroleum/AcOEt (8:2). First fractions gave **8c** (4.1g, 63% referred to **4c,d**); m.p. 169-170°C; IR ($CHCl_3$) ν_{max} 3600-2400, 2940, 2860, 1740 cm^{-1}; ^{1}H-NMR: δ 9.20-8.40 (br s, 1H; CO_2H), 4.84 (dd, J_s = 9.60, 7.20 Hz, 1H; C_4H), 2.12 (s, 3H; $COCH_3$), 1.04 (s, 3H; C_5-CCH_3), 2.60-1.00 (m, 10H); MS m/z (% rel. int.): 254 (M^+, 4), 195(20), 157(68), 151(80), 139(48), 125(100). Further elution afforded **8d** (1.9g, 29% referred to **4c,d**); m.p. 149-150°C; IR ($CHCl_3$) ν_{max} 3600-2400, 2940, 2870, 1740 cm^{-1}; ^{1}H-NMR: δ 9.30-8.70 (br s, 1H; CO_2H), 5.20 (dd, J_s = 2.40, 2.40 Hz, 1H; C_4H), 2.05 (s, 3H; $COCH_3$), 1.03 (s, 3H; C_5-CH_3), 2.70-1.00 (m, 10H); MS m/z (% rel. int.): 254 (M^+, not detected), 210(42), 195(28), 157(66), 150(95), 139(42), 125(100).

4-*endo*-Acetoxy-9-hydroxy-5-methylbicyclo[3.3.1]nonane-1-carboxylic acid (5c). Usual $NaBH_4$ reduction of **8c** (4.00g) gave **5c** (3.71g, 93%) as a 9-*syn*/*anti* mixture (1:2 *via* ^{1}H-NMR); m.p. 173-177°C; IR ($CHCl_3$) ν_{max} 3700-2400, 1730, 1695 cm^{-1}; ^{1}H-NMR: δ 5.16 (dd, J_s = 9.77, 7.59 Hz, 0.3H; *syn* C_4H), 4.86 (br s, 1H; OH), 4.69 (dd, J_s = 9.62, 7.23 Hz; 0.7H, *anti* C_4), 3.82 (s, 0.3H; *syn* C9H), 3.64 (s, 0.7H; *anti* C9H), 2.19, 2.17 (2s, 3H; $COCH_3$), 1.00-0.96 (2s, 3H; C_5-CH_3), 2.40-0.80 (m, 10H); MS m/z (% rel. int.): 256 (M^+, 3), 197(90), 179(70), 152(51), 151(61), 134(100).

4-*exo*-Acetoxy-9-hydroxy-5-methylbicyclo[3.3.1]nonane-1-carboxylic acid (5c). Usual $NaBH_4$ reduction of **8d** (1.80g) gave **5d** (1.67g, 92%) as a 9-*syn*/*anti* mixture (1:2 *via* ^{1}H-NMR); m.p. 110-115°C; IR ($CHCl_3$) ν_{max} 3700-2400, 1730 cm^{-1}; ^{1}H-NMR: d 4.92 (dd, J_s = 3.00, 0.30 Hz, 0.3H; *syn* C_4H), 4.87 (dd, J_s = 3.90, 1.50 Hz, 0.7H; *anti* C_4H), 4.14 (s, 0.7H; *anti* C9H), 2.11-2,07 (2s, 3H; $COCH_3$), 1.08-0.98 (2s, 3H; C_5-CH_3), 2.30-0.80 (M, 10H); MS m/z (% rel. int.): 256 (M^+, not detected), 212(74), 197(41), 181(100), 167(77), 149(93).

4-*endo*-9-Diacetoxy-1-chloro-5-methylbicyclo[3.3.1]nonane (6c). Usual acetylation of **5c** (3.60g) gave *4-endo-9-diacetoxy derivative* **9c** (3.98g, 95%) as a 9-*syn*/*anti* mixture (1:2); IR ($CHCl_3$) ν_{max} 3600-2400, 1740, 1710 cm^{-1}; ^{1}H-NMR: δ 5.29 (s, 0.3H; *syn* C9H), 5.14 (s, 0.7H; *anti* C9H), 4.99 (dd, J_s = 10.50, 7.35 Hz, 0.3H; *syn* C_4H), 4.82 (dd, J_s = 10.80, 6.45 Hz, 0.7H; *anti*C_4H), 2.08-2.06 (2s, 3H; $COCH_3$), 0.86-0.81 (2s, 3H; C_5-CH_3), 2.50-0.70 (m, 10H); MS m/z (% rel. int.): 298 (M^+, 8), 255(37), 196(37), 178(62),

167(41), 149(100), 133(75). The above crude product (3.50g) was chlorodecarboxylated to give **6c** (2.90g, 86%) as 9-*syn/anti* mixture (1:2) not further purified to avoid decomposition; IR ($CHCl_3$) ν_{max} 2970, 2880, 1740, 1735 cm^{-1}; ^{1}H-NMR: δ 5.11 (s, 0.3H; *syn* C_9H), 5.02 (dd, J_s = 11.35, 8.10 Hz, 0.3H; *syn* C_4H). 4.99 (s, 0.7H; *anti* C_9H), 4.80 (dd, J_s = 11.10, 7.50 Hz, 0.3H; *anti* C_4H), 2.17-2.07 (2s, 3H; $COCH_3$), 0.88-0.84 (2s, 3H; C_5-CH_3), 2.40-1.00 (m, 10H); MS m/z (% rel. int.): 290. 288 (M^+, isotopic pair, not detected), 230(1), 188(2), 186(5), 151(8), 133(30), 43(100).

4-*exo*-9-Diacetoxy-1-chloro-5-methylbicyclo[3.3.1]nonane (6d). Usual acetylation of **5d** (1.50g) gave *4-exo-9-diacetoxy derivative* **9d** (1.70g, 97%) as a 9-*syn/anti* mixture (1:2); IR ($CHCl_3$) ν_{max} 3700-2400, 2970, 1740, 1730 cm^{-1}; ^{1}H-NMR: δ 5.58 (s, 0.7H; *anti* C-9H), 5.19 (s, 0.3H; *syn* C_9H), 4.91 (br s, J_s = 2.1 Hz, 0.7H; *anti* C_4H), 4.79 (br s, J_s = 3.30 Hz, 0.3H; *syn* C_4H), 2.11, 2.06, 2.05, 2.04 (4s, 6H; $2COCH_3$), 0.89, 0.84 (2s, 3H; C_5-CH_3), 2.40-0.80 (m, 10H); MS m/z (% rel. int.): 298 (M^+, not detected), 280(40), 220(22), 196(40), 179(25), 168(58), 150(100). The above crude product (1.50g) was chlorodecarboxylated to afford **6d** (1.20g, 81%, 1:2 *syn/anti* mixture) not further purified; IR ($CHCl_3$) ν_{max} 2940, 2860, 1750, 1745 cm^{-1}; ^{1}H-NMR: δ 5.38 (s, 0.7H; *anti* C_9H), 4.94 (s, 0.3H; *syn* C_9H), 4.83 (br s, 0.7H; *anti* C_4H), 4.72 (br s, 0.3H; *syn* C-4H), 2.10, 2.09, 2.09, 2.05, 2.00 (4s, 6H, $2COCH_3$), 0.86, 0.81 (2s, 3H; C_5-CH_3), 2.50-0.70 (m, 10H); MS m/z (% rel. int.): 290, 288 (M^+, isotopic pair, not detected), 253(15), 228(57), 186(42), 151(43), 133(36), 43(100).

1β-Formyl-4α-hydroxy-5β-methylbicyclo[3.3.0]octane (7c). Rearrangement of **6c** (2.0g) was carried out as usual and the reation progress was monitored by GC. After 3.5h, the workup gave a crude mixture (1.10g) which was adsorbed on SiO_2 (100g) and eluted with light petroleum/Et_2O (7:3) to give **7c** (1.00g, 87%) as an unstable low melting solid; IR ($CHCl_3$) ν_{max} 3610, 2940, 2880, 2730, 1715 cm^{-1}; ^{1}H-NMR: δ 9.50 (s, 1H; CHO), 3.72 (ss, J_s = 10.00, 5.90 Hz, 1H; C_4H), 2.60 (br s, 1H; OH), 1.01 (s, 3H; C_5-CH_3), 2.30-0.80 (m, 10H); ^{13}C-NMR: δ 205.85 (CHO), 81.59 (C_4), 64.14 (C_1), 58,12 (C_5), 36.86, 35.88, 32.39, 28.55, 26.35, 23.20 (CH_3); MS m/z (% rel. int.): 168 (M^+, 2), 150(18), 124(12), 121(14), 111(23), 107(18), 95(100). Found: C, 71.48; H, 9.53. Calc. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52.

1β-Formyl-4β-hydroxy-5β-methylbicyclo[3.3.0]octane (7d). Chloroderivative **6d** (1.00g) was rearranged by following the reaction progress *via* GC. After 3h, the workup left 0.57g of a crude mixture. Column chromatography allowed the isolation of **7d** (0.51g, 88%) as an unstable low melting solid; IR ($CHCl_3$) ν_{max} 3610, 2960, 2880, 2730, 1720 cm^{-1}; ^{1}H-NMR: δ 9.60 (s, 1H; CHO), 3.87 (dd, J_s = 3.90, 3.30 Hz, 1H; C_4H), 1.10 (s, 3H, C_5-CH_3), 2.50-0.80 (m, 11H); ^{13}C-NMR: δ 206.48 (CO), 80.88 (C_4), 65.82 (C_1), 58.42 (C_5), 40.65, 35.04, 33.38, 31.46, 24.58, 18.38 (CH_3); MS m/z (% rel. int.): 168 (M^+, 0.1), 166(17), 138(52), 120(71), 95(100). Found: C, 71.46; H, 9.50. Calc. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52.

9-Hydroxybicyclo[3.3.1]non-3-en-1-carboxylic acid (5c). Ketoester **4e** (4.50g, mixture of regioisomers)[8,10] was hydrolized and the obtained mixture of ketoacids[8] was separated by column chromatography on washed silica (1:100) by eluting with light petroleum/AcOEt (9:1). First fractions gave bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid **4f** (1.40g), m.p. 137.5-138°C; IR ($CHCl_3$) ν_{max} 3700-2400, 2960, 1760, 1710 cm^{-1}; ^{1}H-NMR: δ 11.72 (br s, 1H; CO_2H), 5.89 (dddd, J_s = 9.69, 3.58, 3.38, 0.5 Hz, 1H; C_4H), 3.17 (ddd, J_s = 18.96, 3.38, 2.12 Hz, 1H; C_2Ha), 2.93 (dddd, J_s = 5.94, 3.25, 3.25, 0.5 Hz, 1H, C_5H), 2.62 (ddd, J_s = 18.96, 3.58, 1.50 Hz, 1H; C_2Hb), 2.30-1.40 (m, 6H).

Usual $NaBH_4$ reduction of **4f** (1.00g) afforded an 1:3 *syn/anti* mixture of **5e** (0.97g, 96%); IR ($CHCl_3$)ν_{max} 3615, 3600-2300, 2960, 1740, 1650 cm^{-1}; ^{1}H-NMR: δ 6.94 (br s, 2H; CO_2H), 5.97 (ddd, J_s = 9.77, 3.55, 3.20 Hz, 0.25H, *syn* C_3H), 5.76 (ddd, J_s = 9.76, 3.31, 3.17 Hz, 0.75H, *anti* C_3H), 5.64-5.48 (m, 1H, *anti* + *syn* C_4H), 4.16 (d, J = 3.30 Hz, 0.75H, *anti* C_9H), 4.05 (d, J = 2.33 Hz, 0.25H, *syn* C_9H), 2.80-1.20 (m, 9H), MS m/z (% rel. int.): 182 (M^+, 3), 164(53), 120(100), 91(34).

9-Acethoxy-1-chlorobicyclo[3.3.1]non-ene (6e). Methylation of **5e** (0.90g) gave the acethoxyderivative (1.08g, 98%, 1:3 *syn/anti* misture); IR ($CHCl_3$)ν_{max} 3600-2400; 2940, 1820, 1730, 1710 cm^{-1}; ^{1}H-NMR: δ 9.70 (br s, 1H, CO-2H), 5.94 (ddd, J_s = 10.10, 3.70, 3.20 Hz, 0.25H, *syn* C_3H), 5.80 (ddd, J_s = 9.70, 3.40, 3.30 Hz, 0.75H, *anti* C_3H), 5.59 (dddd, J_s = 9.70, 6.70, 1.90, 1.90 Hz, 0.75H, *anti* C_4H), 5.45 (dddd, J_s = 10.10, 6.00, 2.00, 2.00 Hz, 0.25H, *syn* C_4H), 5.30 (d, J = 3.90 Hz, 0.75H, *anti* C_9H), 5.20 (d, J = 2.10 Hz, 0.25H, *syn* C_9H), 2.80-2.50 (m, 2H, C_2H_2), 2.07 (s, 2..25H, *anti* $COCH_3$), 1.99 (s, 0.75H, *syn* COCH-3), 2.40-1.20 (m, 7H); MS m/z (% rel. int.): 224 (M^+,1), 164(66), 135(15), 1119(100), 91(40). The latter crude compound (1.00g) was chlorodecarboxylated to afford **6e** (0.81g, 85%) as 1:3 *syn/anti* mixture not further purified; IR ($CHCl_3$) ν_{max} 3040, 2940, 1750 cm^{-1}; ^{1}H-NMR: d 5.79 (dddd, J_s = 10.25, 4.85, 2.80, 1.00 Hz, 0.25H; *syn* C_4H), 5.70 (dddd, J_s = 9.44, 4.20, 3.90 Hz, 0.75H; *anti* C_3H), 5.42 (ddd, J_s = 10.25, 3.60, 3.40 Hz, 0.25H; *syn* C_9H), 3.00-2.64 (m, 2H; C_2H_2), 2.15 (s, 2.25H; *anti* $COCH_3$), 2.09 (s, 0.75H; *syn* $COCH_3$), 2.60-1.20 (m, 7H); MS m/z (% rel. int.): 216, 214 (M^+, isotopic pair, 5), 188(45), 153(80), 152(50), 149(100).

***cis*-1-Formylbicyclo[3.3.0]ott-3-ene (7e).** Rearrangement of chloroderivative **6e** (0.75g) gave **7e** (0.35g, 79%) as an unstable oil. An analytical sample was obtaine by bulb-to-bulb distillation (100°C/30mmHg); IR ($CHCl_3$) ν_{max} 2950, 2730, 1690, 1640 cm^{-1}; ^{1}H-NMR: δ 9.61 (s, 1H; CHO), 5.59 (dddd, J_s = 6.94, 5.62, 3.85, 2.10 Hz, 1H; C_3H), 5.47 (dddd, J_s = 5.62, 4.23, 2.33, 2.20 Hx, 1H; C_4H), 3.51 (m, 1H; C_5H), 3.08 (ddd, J_s = 17.25, 3.85, 2.20 Hz, 1H; C_2H_b), 2.33 (ddd, J_s = 17.25, 6.94, 2.33 Hz, 1H; C_2H_a), 2.25-1.40 (m, 6H); ^{13}C-NMR: δ 203.26 (CO), 132.57 (C_3) 129.14 (C_4), 62.61 (C_1), 54.16 (C_5), 40.73, 35.79, 32,41, 25.55; MS m/z (% rel. int.): 136 (M^+,1), 122(4), 107(1), 94(56), 79(100). Found: C, 79.37; H, 8.80. Calc. for $C_9H_{12}O$: C, 79.41; H, 8.82.

Acknowledgement. We are indebted to the Italian Board of Education (MPI) and the "Progetto Finalizzato Chimica Fine e Secondaria II", C.N.R., Rome for financial support.

REFERENCES

1. See, for example: Burkolder, P.R.; Burkolder, L.M. *Science*, **1958**, *127*, 1174; Takeuchi, T.; Takahashi, S.; Inuma, H.; Umezawa, H. *J. Antibiotics*, **1971**, *24*, 631; Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.*, **1972**, 4609; Danishesfky, S.; Zamboni, R. *J. Am. Chem. Soc.*, **1980**, *102*, 2097; Trost, B.; Curran, D.P. *J. Am. Chem. Soc.*, **1981**, *103*, 7380; Dawson, B.A.; Ghosh, A.K.; Jurvilina J.N., Ragauskas, A.J.; Stothers, J.B. *Can. J. Chem.*, **1984**, *62*, 2521; Groweiss, A.;Fenical, W.; Clardy J., Cunheng, H. *Tetrahedron Lett.*, **1985**, *26*, 2379.

2. Paquette, L.A. *Topics in Current Chemistry*, Springer, Berlin, V.79, 1979; Paquette, L.A. *ibidem*, V.119, **1984**; Sternbach, D.D. *Strategies and Tactics in Organic Synthesis*, T.Lindberg Ed., Academic Press, London, *V.2*, **1989**, 415; Roberts, J.S.; Bryson, J. *Nat. Product. Chem.*, **1984**, *1*, 131; J.S. Roberts, *ibidem*, **1985**, *2*, 125.

3. See, for example: Callant, P.; De Wilde, H.; Vandewalle, M.; *Tetrahedron*, **1981**, *37*, 2084; b) Kramer G.W.; Brown, H.C. *J. Org. Chem.*, **1977**, *42*, 2832; Demuth M., Schaffner K. *Angew. Chem. Int. Ed.*, **1982**, *21*, 820; Magnus, B.; Exon, C.; Roberson, A. *Tetrahedron*, **1985**, *41*, 5861.

4. Peters, J.A. *Synthesis*, **1979**, 321; Momose, T.; Itooka, T.; Nishi, T.; Ukimoto, M.; Ohnishi, K.; Muraoka, O. *Tetrahedron*, **1987**, *43*,3713.

5. Balata, F.; Dello Jacono, A.R.; Gambacorta, A. *J. Org. Chem.*, **1983**, *48*, 566; Alessandri P., De Angelis F.; Gambacorta, A. *Tetrahedron*, **1985**, *41*, 2831; Botta , M.; Castelli S.,Gambacorta A., *ibidem*, **1988**, *44*, 2913.

6. a) Cope, A.C.; Graham, E.S. *J. Am. Chem. Soc.*, **1951**, *73*, 4702; b) Cope A.C., Graham , E.S.; Marshall, D.J. *ibidem*, **1954**, *76*, 6159.

7. Kraus, G.A.; Jianmin Shi *J. Org. Chem.*, **1990**, *55*, 5423.

8. Cope, A.C.; Synerholm, M.E. *J. Am. Chem. Soc.*, **1950**, *72*, 5228.

9. Martin, J.; Parker, W.; Raphael, R.A.; Jhaveri, D.B.*Tetrahedron*, **1962**, *18*, 55.

10. Colvin, E.W.; Parker, W. *J. Org. Soc.*, **1965**, 5764.

11. Cianetti, C.; Di Maio, G.; Pignatelli, V.; Tagliatesta, P.; Vecchi, E.; Zeuli, E. *Tetrahedron*, **1983**, *39*, 657.

12. Becker, K.B.; Geisel, M.; Grob, C.A.; Kuhnen, F. *Synthesis*, **1973**, 493.

13. Casanovas, C.P. *Rev. Real Acad. Ciencias*, Madrid, **1968**, *62*, 413.