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THE SYNTHESIS OF SUBSTITUTED 3-OXABICYCLO [3:3:1]NONANES AND 3-OXABICYCLO-[3.3.1]NON-6-ENES

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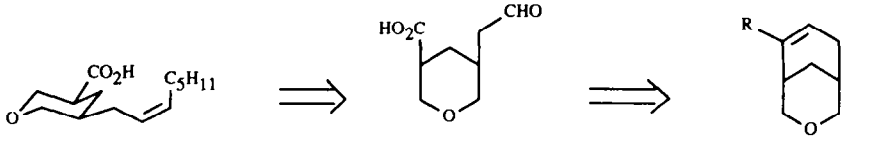
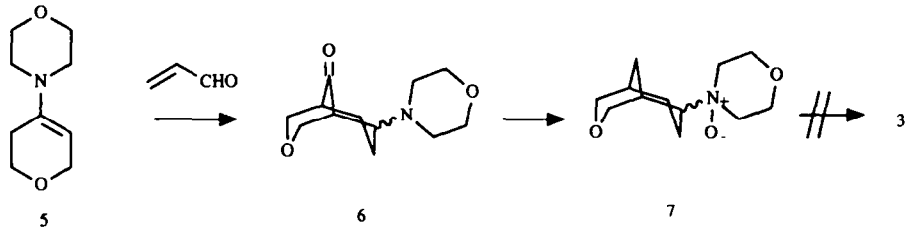
Abstract. *A variant of the enamine-mediated route to 2-amino substituted bicyclo[3.3.1]nones has been developed for the synthesis of 3-oxabicyclo[3.3.1]nonanes and 3-oxabicyclo[3.3.1]non-6-enes.*

3-Alkenyl-5-carboxytetrahydropyrans such as (1) were required as potential transition state surrogates for lipoxygenase enzymes. A concise entry via carboxyaldehyde (2) was apparent, with (2) being derived from 3-oxabicyclo[3.3.1]non-6-enes such as (3) and (4). To our surprise, simple systems such as (3) and (4) are unknown, although there is ample precedent for the saturated 3-oxabicyclo[3.3.1]nonanes.[1]



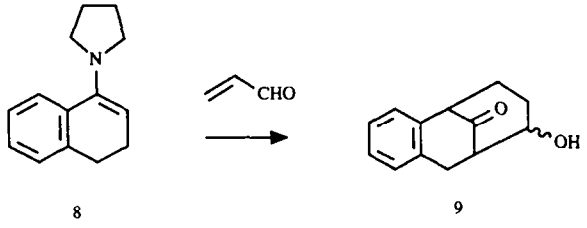
1 2 3, R=H 4, R=OSiR$^1_3$

Initial studies involved reaction of the morpholino enamine (5) with acrolein, giving the 6-morpholino 3-oxabicyclo[3.3.1]nonan-9-one (6) as a mixture of *exo* and *endo* isomers (70:30) as determined by NMR spectroscopy and GLC analysis. This compares with results from the corresponding carbacyclic systems formed under thermodynamic control.[2,3] The 9-oxo group was reduced to the methylene group by the Huang-Minlon procedure,[4] and the morpholino group oxidized to the N-oxides(7) (72%) as a 9:1 exo/endo mixture. Pyrolysis of the N-oxides (7)[5] was complex. Other milder elimination methods, e.g. THF-molecular sieves[6] and DMSO-molecular sieves[6] were similarly unsuccessful. A different strategem was therefore necessary.

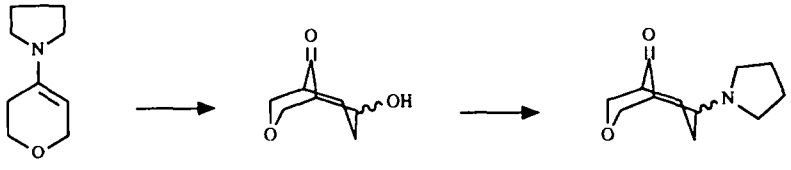


5 6 7

It had earlier been discovered that carbacyclic enamines of general structure (8) could be reacted under specific conditions with acrolein to give bicyclic ketoalcohols (9).[7] We therefore adopted this procedure and prepared a mixture (1:1) of *endo*- and *exo*- isomers (11) and (12) in 57% yield by treatment of the enamine (10) with acrolean and then addition of dilute HCl. Also obtained as by-products were the *endo*- and *exo* isomers (13). The stereochemistries of (11) and (12) were rigorously assigned by NMR spectroscopy, from which the *exo*- and *endo*- methine protons of the secondary alcohols appeared at δ 4.11 and δ 4.6 respectively,[7] and ^4J coupling was observed only for the *exo*- isomer, in accordance with earlier studies in the carbacyclic series.[7]



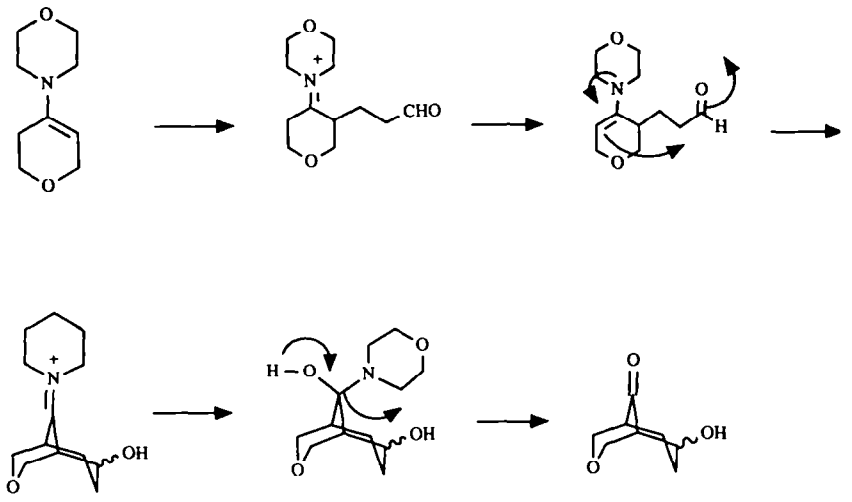
8 9



10 11, endo 12, exo 13

Previous mechanisms describing the formation of carbacyclic variants of (13) do not account for the formation of ketoalcohols (9), (11) and (12).[8] It is therefore postulated that, under our reaction conditions, a possible pathway to (11) and (12) is as shown in the Scheme.

Acid catalysed dehydrations of (11) and (12) were complex, possibly because of carbocationic rearrangements. Phosphorus oxychloride gave the *endo*- and *exo*- chlorobicyclics (14) and (15) together

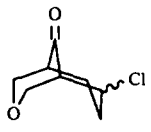


Scheme

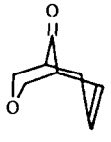
with a low yield of the alkene (16).

Mesylation of the mixture of alcohols gave isomers (17) and (18) which, when heated with collidine under reflux afforded the alkene (16) in 37% overall yield. Bromination (LiBr-acetone) of the mesylates and elimination (Li_2CO_3-LiBr-DMF)[9] furnished the alkene in 37% overall yield from the alcohols.

The best method, however, was elimination from the *endo*- and *exo*- mixture of nitrooxybicyclics (19) and (20) which probably proceeds by a *syn* pathway. This gave an overall yield from the mixture of alcohols of 54%.



14, endo
15, exo



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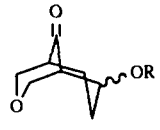
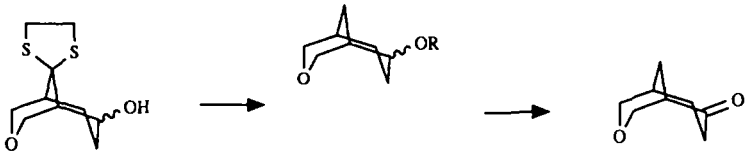


17, endo, R=Mes
18, exo, R=Mes
19, endo, R=ONO_2
20, exo, R=ONO_2

The synthesis of 3-oxabicyclo[3.3.1]nonan-6-one (25) was achieved by conversion of (11) and (12) to the dithiolanes (21) and (22). Treatment of (25) with Raney nickel gave the bicyclic hydroxyethers (23) and (24), which were separated by chromatography. (Non-aqueous work-up was necessary because of high water solubility). Oxidation (PCC)[10] gave the bicyclic ketoether (25) (70%).

The target alkene (3) was now obtained in several different ways. Firstly, Huang-Minlon reduction of (16) gave (3) in very low yield, due to the harsh conditions. Secondly, mesylates (26) and (27) underwent elimination (DBU) to give (3) (39%). Thirdly, ketoether (25) was treated with chlorotrimethyl silane and zinc,[11] affording the desired alkene in 41% yield.

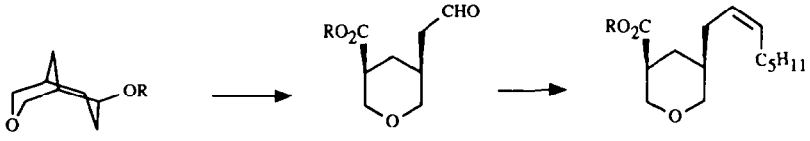
Ketoether (25) was coverted[12] into the enol trimethylsilane (28) (56%), and the enol *tert*-butyldimethylsilane (29)[13] (95%). Ozonolysis gave the carboxyaldehyde (2), and the protected variant (30) respectively in good yields. The COSY spectrum of (2) was in accord with *syn*-3,5-substitution of the tetrahydropyran ring.



21, endo
22, exo

23, R=H, endo
24, R=H, exo
26, R=Mes, endo
27, R=Mes, exo

25



28, R=$SiMe_3$
29, R=Si^tBuMe_2

2, R=H
30, R=Si^tBuMe_2

1

To illustrate the applications of such tetrahydropyrans in the synthesis of leukotriene mimetics, carboxyaldehyde (2) was reacted with n-hexyltriphenyl phosphonium bromide, giving the *cis*- alkene (1). We have therefore demonstrated that the new 3-oxabicyclo [3.3.1] non-6-ene(3) is a potentially versatile precursor of 3,5-disubstituted tetrahydropyrans.

Acknowledgments

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EXPERIMENTAL

6-Morpholino 3-oxabicyclo[3.3.1]nonan-9-one (6)

Acrolein (0.54g, 0.65ml) was added over 30min to a solution of (129) (1.64g, 9.8mmol)in benzene (30ml), maintained at 0°. Stirring of the cold solution was continued for an additional 1hr, after which the mixture was heated at reflux for 3 hrs. The benzene was evaporated and the product collected by distillation on the Kugelrohr (b.p. 120°, 0.15mm Hg) to yield 1.62g (74%) of a pale yellow oil as a mixture of exo and endo isomers [G.C. (71.29) OV column 175°]; υ_{max} (thin film) 1717cm^{-1} (71:29);, δ_H ($CDCl_3$) 4.2-3.6 (m, 8H, C<u>H</u>$_2$OC<u>H</u>$_2$, C<u>H</u>$_2$OC<u>H</u>$_2$), 2.85 (m, 1H, C<u>H</u>-N), 2.5 (m, 4H, CH_2NOH_2), 2.3-1.8 (m, 6H); *m/z* (70eV E.I.) 225 (M^+), 126 (100%). Found: C, 64.12, H, 8.43 N. 6.32. $C_{12}H_{19}NO_3$ requires C, 63.98, H, 8.50, N, 6.22%

6-Morpholino 3-oxabicyclo[3.3.1]nonane N-oxide (7)

Enamine (6) (0.5g, 2.2mmol) was refluxed with 0.36ml hydrazine (99-100%) and potassium hydroxide (0.42g) in triethylene glycol (5ml) for 1.5hrs. Then the mixture was distilled until a temperature of 190° was reached. The residue was then refluxed for 3 hrs. The residue and distillate were combined and diluted with H_2O (10ml), extracted with ether (3x20ml), washed with brine (2x30ml), dried ($MgSO_4$), solvent evaporated and product distilled on the Kugelrohr (120°, 0.3mmHg) to yield 0.33g (72%) of a pale green oil, which was a mixture of exo and endo isomers. [G.C. (91:9), OV column, 175°]. . δ_H ($CDCl_3$) 4.2-3.6 (m, 8H, C<u>H</u>$_2$OC<u>H</u>$_2$, C<u>H</u>$_2$OC<u>H</u>$_2$), 2.85 (m, 1H, C<u>H</u>-N), 2.5 (m, 4H, C<u>H</u>$_2$-N-C<u>H</u>$_2$), 2.3-1.6 (m, 8H). <u>M/Z</u> (70ev E.I.) 211 (M^+), 126 (100%), 100,87.Found: C, 67.90, H, 10.01, N, 6.59, $C_{12}H_{21}NO_2$ requires C, 68.21, H, 10.02, N, 6.63%

To a solution of the exo and endo isomers (150mg, 0.7mmol), ethanol (1.5ml), methanol (1.5ml) was added 30% H_2O_2 (1ml). The resulting solution was heated at 70-72° for 36 hours. The excess H_2O_2 was decomposed by stirring the solution for 8 hours in the presence of platinum black, filtered and evaporated to give a colourless viscous syrup. This was dried at 80° (1mm) to give a colourless crystalline solid. <u>M/Z</u> (70ev E.I.) 227 (M^+).

Endo and exo 6-hydroxy 3-oxabicyclo[3.3.1]nonane-9-one (11) and (12)

Enamine (10) (4.39g, 0.029mol) was dissolved in THF (75ml) and purged with N_2. The solution was stirred in an N_2 atmosphere and cooled to below 10°, H_2O (0.8ml) added, followed immediately by acrolein (2.9ml, 0.044mol) dropwise. The reaction was stirred at room temperature for 2hr, after which dilute HCl was added until pH 1-2 was reached. The reaction was then stirred for 30min, after which ether was added and stirring continued for 10min. The solution was allowed to settle for 10-15min, after which the aqueous layer was run off. The aqueous layer was extracted with ether (3x50ml). The organic layer was washed with H_2O (1x50ml), brine (1x50ml). Each of these washes was back extracted with the ether extracts used for the main aqueous. Ether extracts wre combined, dried ($MgSO_4$), the solvent evaporated to yield 2.6g (57%) of 6-hydroxy 3-oxabicyclo[3:3:1]nonane-9-one as a mixture of exo and endo isomers. [G.C. (1:1) OV column 175°C]. The isomers were separated on a Chromatotron (PE/EA, 2:1). Endo isomer (11) eluted first

as a colourless oil *Endo isomer*: υ_{max} ($CHCl_3$) 3460, 3450 (-OH), 1720 (C=O), 1080cm^{-1}; δ_H ($CDCl_3$) 4.6 (septet, 1H, C<u>H</u>OH), 4.27 (dt, 1H, $J_{2e\text{-}2a}$ = 11.28Hz, J_2 = 1.6Hz), 4.18 (dt, 1H, $J_{4e\text{-}4a}$ = 11.72Hz, J_2 = 1.5Hz), 3.88 (dt, 1H, $J_{2a\text{-}2e}$ = 11.28Hz, J_2 = 2.1Hz), 3.83 (dd, 1H, $J_{4a\text{-}4e}$ = 11.72Hz, J_2 = 2.8Hz), 2.75 (m, 1H), 2.48 (octet, 1H), 2.375 (m, 2H), 2.10 (m, 1H), 1.74 (m, 1H), 1.72 (m, 1H, -O<u>H</u>). δ_C ($CDCl_3$) 212.65 (s, C-9), 74.96 (d, C-6), 74.48 (t, C-2), 68.70 (t, C-4), 57.41 (d, C-5), 48.46 (d, C-1), 30.44 (t, C-7), 27.246 (t, C-8). M/Z (70ev. E.I.) 156 (M^+), 138, 111, 97, 83, 71, 55, 54, 41, 28, 27. M^+ 156.0781 calculated for $C_8H_{12}O_3$ 156.0786.

Exo isomer (12) was obtained after further elution as colourless crystals. m.p. 184.5-185°. υ_{max} ($CHCl_3$) 3460, 3450 (-OH), 1720 (C=O), 1080cm^{-1}; δ_H ($CDCl_3$) 4.6 (dt, 1H, $J_{4e\text{-}4a}$ = 11.56Hz, J_2 = 1.48Hz), 4.2 (dt, 1H, $J_{2e\text{-}2a}$ = 11.32Hz, J_2 = 1.6Hz), 4.11 (m, 1H, C<u>H</u>OH), 3.91 (dt, 1H, $J_{2a\text{-}2e}$ = 11.32Hz), 3.73 (dq, 1H, $J_{4a\text{-}4e}$ = 11.56Hz, J_2 = 2.4Hz, J_3 = 1.1Hz), 2.57-2.45 (m, 2H), 2.35 (septet, 1H), 2.11 (m, 1H), 2.02 (m, 1H), 1.83-1.79 (m, 2H). δ_C ($CDCl_3$) 214.11 (s, C-9), 76.53 (d, C-6), 75.67 (t, C-2), 70.94 (t, C-4), 57.38 (d, C-5), 49.87 (d, C-1), 29.22 (t, C-7 and 8). <u>M/Z</u> (70ev E.I.) 156 (M^+), 138, 111, 97, 83, 71, 55, 54, 41, 28, 27 M^+ 156.0785 calculated for $C_8H_{12}O_3$ 156.0786.

The acidic aqueous layer was basified, extracted with ether (3x30ml), washed with H_2O (30ml), brine (30ml) to yield 0.84g of a gum which was filtered through silica gel to yield 0.15g of *6-pyrrolidinyl 3-oxabicyclo[3.3.1]nonan-9-one (13)* as a mixture of exo and endo isomers. υ_{max} (thin film) 1726cm^{-1} (C=O), δ_H ($CDCl_3$) 4.2-3.7 (m, 4H, C<u>H</u>$_2$-O-C<u>H</u>$_2$), 2.9 (m, 1H), 2.5 (m, 4H, CH_2-NCH_2) 2.3-1.6 (m, 10H). <u>M/Z</u> (70ev. E.I.) 209 (M^+), 126 (100%).

Reaction of endo and exo 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-one (11) and (12) with phosphorus oxychloride and pyridine

A solution of (11) and (12) (200mg, 1.3mmol) in dry benzene (2ml) was added to a stirred solution of phosphorus oxychloride (0.18ml, 1.9mmol) and pyridine (1.54ml. 1.9mmol) in dry benzene under N_2 at room temperature overnight. The reaction mixture was quenched with H_2O (10ml), washed with sat. aqueous $CuSO_4$, brine, and dried ($MgSO_4$) and evaporated to yield 180mg of a yellow oil. Column chromatography (PE/EA, 5:1) yielded 40mg of a waxy solid, *3-oxabicyclo[3.3.1]non-6-en-9-one* (16); υ_{max} (CH_2Cl_2) 3031, 1728 1648cm^{-1}; δ_H ($CDCl_3$) 6.01 (dt, 1H, J_1 = 9.5Hz, J_2 = 3.3Hz, = C<u>H</u> (C-6)), 5.7 (qt, 1H, J_1 = 9.5Hz, J_2 = 6Hz, J_3 = 1.9Hz, = C<u>H</u> (C-7)), 4.15 (dt, 1H, $J_{4e=4a}$ = 11.2Hz, J_2 = 1.8Hz), 3.94 (dt, 1H, $J_{2e\text{-}2a}$ = 10.8Hz, J_2 = 1.83Hz), 3.79 (dd, 1H, $J_{4a\text{-}4e}$ = 11.2Hz, J_2 = 1.46Hz), 3.71 (dd, 1H, $J_{2a\text{-}2e}$ = 10.8Hz, J_2 = 1.83Hz), 2.81 (m, 3H, C<u>H</u>$_2$-CH=CH and =CH-C<u>H</u> (bridgehead)), 2.54 (m, 1H, bridgehead). δ_C ($CDCl_3$) 210.58 (s, C-9), 131.01 (d, C-6), 125.08 (d, C-7), 76.81 (t, C-4), 72.25 (t, C-2), 50.16 (d, C-5), 48.45 (d, C-1), 36.58 (t, C-8). <u>M/Z</u> (70ev. E.I.) 138 (M^+, 100%), 108, 79; <u>M/Z</u> 138.0673, calculated for $C_8H_{10}O_2$ 138.0679; 60mg of *endo 6-chloro 3-oxabicyclo[3.3.1]nonan-9-one* (14); υ_{max} ($CHCl_3$) 1720cm^{-1} (C=O); δ_H ($CDCl_3$) 4.82 (sextet, 1H, C<u>H</u>Cl), 4.28 (dt, 1H, J_{gem} = 11.5Hz, J_2 =1.5Hz), 4.24 (dt, 1H, J_{gem} = 12Hz, J_2 = 1.5Hz), 3.90 (dt, 1H, J_{gem} = 11.5Hz, J_2 = 2.2Hz), 3.86 (dd, 1H, J_{gem} = 12Hz, J_2 = 2.75Hz), 3.08 (m, 1H), 2.7 (m, 1H), 2.44 (m, 1H), 2.15 (m, 2H), 2.0 (m, 1H); δ_C ($CDCl_3$) 210.12 (s, C-9), 76.69 (t, C-2), 74.42 (t, C-4), 61.92 (d, C-6), 56.87 (d, C-5), 49.44 (d, C-1), 28.56 (t, C-7), 27.73 (t, C-8); <u>M/Z</u> (70 ev. E.I.) 176/174 (M^+), 139, 109, 81, 67, 55 (100). Found: C, 54.91; H, 6.42. $C_8H_{11}ClO_2$ requires C, 55.02; H, 6.35%; 60mg of *exo*

6-chloro 3-oxabicyclo[3.3.1]nonan-9-one (15); υ_{max} ($CHCl_3$) 1720cm^{-1} (C=O), δ_H ($CDCl_3$) 4.73 (dt, 1H, J_{gem} = 12Hz), J_2 = 1.5Hz, 4.35 (m, 1H, C<u>H</u>Cl), 4.23 (dt, 1H, J_{gem} = 11.36Hz, J_2 = 1.6Hz), 3.92 (dt, 1H, J_{gem} = 12Hz, J_2 = 2.2Hz), 3.79 (dt, 1H, J_{gem} = 11.9Hz), 2.88 (m, 1H), 2.64 (m, 1H), 2.4 (m, 1H), 2.2 (m, 2H), 1.9 (m, 1H); δ_C ($CDCl_3$) 210.16 (s, C-9), 76.65 (t, C-2), 72.76 (t, C-4), 64.92 (d, C-6), 57.88 (d, C-5), 48.81 (d, C-1), 32.15 (t, C-7), 29.77 (t, C-8). <u>M/Z</u> (70ev. E.I.) 176/174 (M^+), 138 (100), 109, 81, 55. Found: C, 55.12; H, 6.29, $C_8H_{11}ClO_2$ requires C, 55.02; H, 6.35%.

6-Methanesulphonyloxy 3-oxabicyclo[3.3.1]nonan-9-ones (17) and (18).

To a stirred solution of (11) and (12) (200mg, 1.3mmol), Et_3N (0.26ml, 1.8mmol) in dry DCM (5ml) at O° was added dropwise over 15min a solution of methane sulphonylchloride (0.12ml, 1.6mmol) in dry DCM (2ml). The resulting solution was stirred for 2hr at O°. The reaction was quenced with H_2O. The organic phase was separated, washed with 2MHCL, brine and dried ($MgSO_4$). Evaporation of solvent gave 310mg of a yellow oil, which was chromatographed (PE/EA, 3:1) to give the mesylates as a waxy solid (260mg, 86%) as amixture of exo and endo isomers (1:1); υ_{max} ($CHCl_3$) 1720cm^{-1}; δ_H ($CDCl_3$) 5.2 (m, 1H, C<u>H</u>OMs (eqH)), 4.3 (m, 1H, CHOMs (axH)), 4.1-3.6 (m, 4H, C<u>H</u>$_2$-O-C<u>H</u>$_2$), 3.0 (s, 3H, -$SO_2C\underline{H}_3$), 2.7 (m, 1H), 2.4 (m, 2H), 2.2-1.8 (m, 4H). <u>M/Z</u> (70ev. E.I.) 234 (M^+), 138 (100%), 109, 79, 55 (100%). M^+ (E.I.) 234.0556, calculated for $C_9H_{14}O_5S$ 234.0561.

The mixture was refluxed in collidine (1ml) for 15min., partitioned between ethyl acetate and dilute HCl. The organic layer was dried ($MgSO_4$), and chromatographed to give the alkene (16) (42%).

Elimination from endo- and exo- 6-bromo 3-oxabicyclo[3.3.1]nonan-9-one

Mesylates (17) and (18) (1.9g, 8.1mmol) and lithium bromide (1.7g, 19.4mmol) were heated under reflux in analar acetone (30ml) for 48hr. The suspension was concentrated, then diluted with ether, washed with H_2O, brine and dried ($MgSO_4$) and evaporated to give 1.28g of a brown oil, passed through a column of Florisil to yield 1.14g (64%) of a yellow oil as a mixture of exo and endo isomers; υ_{max} (film) 1710cm^{-1} (C=O); δ_H ($CDCl_3$) 4.91 (sextet, 1H, C<u>H</u>Br, equatorial), 4.75 (dt, 1H, C<u>H</u>$_2$O), 4.45 (m, 1H, C<u>H</u>Br, axial), 4.31-4.22 (m, 3H, C<u>H</u>$_2$O) 4.0-3.8 (m, 4H, C<u>H</u>$_2$O), 3.21-2.95 (m, 2H), 2.8 (m, 1H), 2.7 (m, 1H), 2.45 (m, 3H), 2.3-1.9 (m, 3H). <u>M/Z</u> (70ev. E.I.) 221/219 (M^+), 139 (100), 109, 81, 55. Found: C, 43.95; H, 5.13, $C_8H_{11}BrO_2$ requires C, 43.86; H, 5.06%. The bromoketones (700mg, 4mmol), LiBr (1.04g, 12mmol), and Li_2CO_3 (890mg, 12mmol) were dissolved in dry DMF (10ml) under an N_2 atmosphere. The solution was stirred at 150° for 5hr, then poured into H_2O (30ml), extracted with ether (3x20ml), washed with brine and dried (Na_2SO_4) and evaporated to yield 600mgs of a yellow oil. Flash chromatography (PE/EA, 5:1) yielded 370mg (67%) of (16) as a waxy colourless solid.

6-Nitrooxy 3-oxabicyclo[3.3.1]nonan-9-one (19) and (20)

Fuming HNO_3 (19.1ml) was added to acetic anhydride (39ml) whilst cooled at -25°, and stirred for 10min, after which (11) and (12) (2.3g, 14.7mmol) in acetic anhydride (2ml) were added dropwise, stirred for 2hr (followed by TLC) and then poured into H_2O and stirred overnight (to decompose acetic anhydride), extracted with ether (3x30ml), washed with brine, dried (Na_2SO_4) and evaporated to yield an orange oil.

Chromatography (PE/EA, 4:1) yielded 2.8g (78%) of colourless crystals as a mixture of exo and endo isomers, (recrystallised from PE/EA), m.p. 65.9-67.0°; υ_{max} (CH_2Cl_2) 1735 (C=O), 1629 1219cm^{-1}; δ_H ($CDCl_3$) 5.62 (m, 1H, C<u>H</u>ONO$_2$, equatorial), 5.25 (m, 1H, C<u>H</u>ONO$_2$, axial), 4.28 (m, 4H, C<u>H$_2$</u>OC<u>H$_2$</u>), 3.94 (m, 4H, C<u>H$_2$</u>OC<u>H$_2$</u>), 2.8 (m, 4H), 2.5-1.8 (m, 8H); Found: C, 47.71, H, 5.55, N, 6.82. $C_8H_{11}NO_5$ requires C, 47.76, H, 5.51, N, 6.96%.

6-Oxo 3-oxabicyclo[3.3.1]non-6-ene (16) by nitrate elimination

Nitrooxy isomers (19) and (20) (1g, 5mmol), LiCl (0.55g, 13mmol) and Li_2CO_3 (0.5g, 6.8mmol) were dissolved in N-methyl pyrrolidone (5ml) under an N_2 atmosphere. Using an oil bath, the temperature was slowly raised to 85° and then heated at this temperature for 2 hr, cooled, poured onto H_2O, and extracted with ether (3x20ml), washed with brine, dried ($NaSO_4$) and azeotroped with CCl_4 (3x25ml) to yield 1.2g of a brown oil. Flash chromatography (PE/EA, 5:1) yielded 480mg of (16) (70%).

Ethylenethioacetals (21) and (22) of 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-ones (11) and (12)

To a solution of (11) and (12) (9.5g, 0.061mol) and ethanedithiol (9.5ml, 0.09mol) at 0^0 under N_2 atmosphere in dry DCM (20ml) was added $BF_3.Et_2O$ (1.9ml, 0.012mol) dropwise. The reaction mixture was stirred for 20min, warmed to room temperature and stirred an additional 2hr. The solvent was evaporated *in vacuo* and the residue chromatographed (dry column "flash" chromatography, PE/EA, 10:1) to yield 12.2g (86%) of a colourless oil comprising a mixture of exo and endo isomers; δ_H ($CDCl_3$) 4.18 (m, 1H), 4.17-4.06 (m, 2H), 3.95 (m, 1H), 3.87 (m, 1H), 3.88 (dd, 1H), 3.35-3.13 (m, 4H, -S-C<u>H$_2$</u>-C<u>H$_2$</u>-S), 2.47 (m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 2.05 (m, 1H), 1.91 (m, 2H), 1.72 (m, 1H). <u>M/Z</u> (70ev. E.I.) 232 (M^+), 214 (100%), 131, 105. Found: C, 5.174, H, 6.91. $C_{10}H_{18}O_2S_2$ requires C, 51.69, H, 6.94%.

Endo and exo 6-hydroxy 3-oxabicyclo[3.3.1]nonane (23) and (24)

Raney nickel (W-2), (50% slurry in H_2O (pH-10)) was washed with H_2O until neutral, then 95% ethanol (3x50ml), and absolute ethanol (3x50ml). Raney nickel (7g) was suspended in absolute ethanol (30ml) The mixture of (21) and (22) (1g, 4.3mmol) in absolute ethanol (5ml) was added and the resulting solution refluxed for 30min. The solution was filtered and passed through a small plug of Florisil to yield 460mg (76%) as a colourless oil, which was a mixture of exo and endo isomers in an approximately 1:1 ratio. Separation was achieved by flash chromatography (PE/EA, 4:1). The endo isomer eluted first, followed by the exo isomer, as colourless oils.

Endo isomer: υ_{max} ($CHCl_3$) 3460, 3450 (-OH), 1080cm^{-1}; δ_H ($CDCl_3$) 4.09 (m, 1H, C<u>H</u>OH), 3.88 (dt, 1H, J_{gem} = 11Hz), J_2 = 2Hz), 3.83 (dt, 1H, J_{gem} = 11.5Hz), J_2 = 2Hz), 3.74 (dt, 1H, J_{gem} = 11Hz, J_2 = 2Hz), 3.71 (dd, 1H, J_{gem} = 11.5Hz, 2.6Hz), 2.49 (m, 1H), 2.13 (m, 1H), 1.8 (m, 1H), 1.7 (m, 2H), 1.6 (m, 3H), 1.4 (m, 1H, CHO<u>H</u>), δ_C ($CDCl_3$) 73.38 (t, C-2), 70.58 (d, C-6), 69.56 (t, C-4), 36.33 (d, C-5) 31.14 (t, C-9) 30.91 (t, C-7), 29.34 (d, C-1) 28.33 (t, C-8); <u>M/Z</u> (70ev. E.I.) 142 (M^+), 124, 92, 79, 67, 55, 41. Found: C, 67.72; H, 9.89. $C_8H_{14}O_2$ requires C, 67.67%, H, 9.93%.

Exo isomer: υ_{max} ($CDCl_3$) 3460, 3450 (-OH), 1080cm^{-1}; δ_H ($CDCl_3$) 4.19 (dt, 1H, J_{gem} = 11.8Hz, J_2 = 1.5Hz), 3.98 (m, 1H, C<u>H</u>OH), 3.85 (dt, 1H, J_{gem} = 11Hz, J_2 = 2Hz), 3.71 (dt, 1H, J_{gem} = 11Hz, J_2 = 2.15Hz), 3.6 (dq, 1H, J_{gem} = 11.8Hz, J_2 = 2.3Hz, J_3 = 1.15Hz), 2.45 (m, 1H), 2.18 (m, 1H), 1.9 (m, 2H), 1.7 (m, 1H),

1.6 (m, 2H), 1.5 (bs, 1H, CHOH). δ_C ($CDCl_3$) 73.04 (t, C-2), 72.91 (d, C-6), 66.48 (t, C-4), 36.14 (d, C-5), 31.76 (t, C-9), 30.32 (t, C-7), 29.39 (t, C-8), 28.55 (d, C-1). M/Z (70ev. E.I.) 142 (M^+), 124, 92, 79, 67, 55, 41. Found: C, 67.73; H, 9.91. $C_8H_{14}O_2$ requires C, 67.67%, H, 9.93%.

3-Oxabicyclo[3.3.1]nonan-6-one (25)

Pyridinium chlorochromate (910mg, 4.2mmol) was suspended in DCM (5ml) and (23) and (24) (400mg, 2.8mmol) in DCM (2ml) were rapidly added at R.T. The solution became briefly homogeneous before depositing black insoluble reduced reagent. After 1-2hr the oxidation, as followed by t.l.c, was complete. The black reaction mixture was diluted with 5 volumnes of anhydrous ether, the solvent decanted and the black solid washed twice with ether. Product was isolated by filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure to yield 310mg (79%) of a colourless wax oil/solid; υ_{max} ($CHCl_3$) 1705cm^{-1} (C=O); δ_H ($CDCl_3$) 4.03 (d, 1H, J_{gem} = 11.2Hz), 3.91 (dt, 1H, J_{gem} = 11.4Hz, J_2 = 2.2Hz), 3.84 (dt, 1H, J_{gem} = 11.4Hz, J_2 = 2.2Hz), 3.72 (dd, 1H, J_{gem} = 11.4Hz), J_2 = 2.2Hz), 2.85 (m, 1H), 2.55 (m, 2H), 2.2-1.95 (m, 5H); δ_C ($CDCl_3$) 213.86 (s, C-6), 73.84 (t, C-2), 69.40 (t, C-4), 47.18 (d, C-5), 40.57 (t, C-7), 31.76 (t, C-9), 29.72 (t, C-8), 28.63 (d, C-1). M/Z (iBuH. C.I.) 141 (M+1), 95, 81. Found: C, 68.16; H, 8.72. $C_8H_{12}O_2$ requires: C, 68.55; H, 8.63%.

3-Oxabicyclo[3.3.1]non-6-ene (3) Method A

To a solution of (16) (200mg, 1.5mmol), KOH (200mg) in diethylene glycol (5ml) was added 0l2ml of 98% hydrazine hydrate. After refluxing for 1hr, the apparatus was set up for a distillation, and distilled until the temperature had reached 195°-200°, then refluxing was continued for 3hrs. Distillate and residue were combined and poured into ice/H_2O, acidified and then extracted with ether, washed with brine, dried ($MgSO_4$) and evaporated to yield 130mg of a yellow oil. Chromatography (medium presure, PE/EA 5:1) yielded 23mg of (3) (12%) as a colourless oil; υ_{max} ($CHCl_3$) 3030 1640cm^{-1}; δ_H ($CDCl_3$) 5.9 (m, 1H, =CH), 5.6 (m, 1H, =CH), 4.05-3.6 (m, 4H, CH_2OCH_2), 2.45 (m, 1H), 2.3 (m, 2H), 1.95 (m, 3H). M/Z (70ev E.I.) 124 (M^+), 93, 92, 67. M^+ 124.0879 (M, 100%, calculated for $C_8H_{12}O$, 124.0887).

3-Oxabicyclo[3.3.1]non-6-ene (3) Method B

Mesylates (26) and (27) (110mg, 0.5mmol) were dissolved in freshly distilled DBU (0.25ml, 1.6mmol) under an N_2 atmosphere, and the solution heated at 70° for 2hr. The solution was cooled and diluted with DCM (10ml), washed with H_2O (10ml), NH_4SO_4 (10ml) and H_2O (10ml), dried (Na_2SO_4) and evaporated. The residue was dissolved in ether and passed down a column of Florisil to yield 24mg (39%) of (3) as a colourless oil.

3-Oxabicyclo[3.3.1]non-6-ene (28) Method C

A solution of (25) (100mg, 0.72mmol) in anhydrous ether (1ml) was added to a rapidly stirred suspension of zinc (dust) (480mg, 7.2mmol) and chlorotrimethylsilane (400mg, 3.6mmol) in anydrous ether (10ml), then placed in a temperature controlled oil bath (40°) for 72hr. The solution was cooled, filtered and the etheral solution washed with $NaHCO_3$ (aq) and dried (Na_2SO_4) to yield 60mg of (3) as a slightly yellow oil. Chromatography (medium pressure, PE/EA, 5:1) yielded 37mg of (3) (41%) as a colourless oil.

6-(Trimethylsiloxy)-3-oxabicylo[3.3.1]non-7-ene (28)

A solution of (25) (540mg, 3.9mmol) in dry DMF (6ml) and triethylamine (1.3ml, 9.4mmol) was treated with chlorotrimethylsilane (0.6ml, 4.7mmol) and the resulting slurry refluxed for 20hr. The cooled mixture was diluted with pentane and washed with cold 5% sodium bicarbonate and H_2O. The pentane was dried and evaporated to yield 550mgs of a yellow oil. Distillation on a Kugelrohr (0.1mm/90°) gave 460mg (56%) of a colourless oil. υ_{max} ($CHCl_3$) 1650cm^{-1} (C=CSt). δ_H ($CDCl_3$) 4.8 (t, 1H, =C<u>H</u>, J=3Hz), 3.8-3.4 (m, 4H), 2.5 (m, 1H), 2.1 (m, 2H), 1.8 (m, 3H), 0.15 (s, 9H, $SiMe_3$), <u>M/Z</u> (70ev E.I.) 21 (M^+), 105, 75, 73, 59. M^+ (E.I.) 212.1245, calculated for $C_{11}H_{20}O_2Si$, 212.1232).

6-(t-Butyldimethylsiloxy)-3-oxabicylo[3.3.1]non-7-ene (29)

TBDMS triflate (1.3mls, 7.4mmol) was added to a solution of (25) 0.5g, 3.7mmol) and 2,6-lutidine (0.63mls, 0.056moles) in DCM (5ml) in a N_2 atmosphere. The reaction was monitored by t.l.c. (alumina) and when complete, diluted with DCM (10mls), washed with cold sodium bicarbonate (1x10ml), $CuSO_4$ (aq) (1x10ml). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*, the residue taken up in dry ether, separated from insoluble material and evaporated to yield 1.1h. of an oil, chromatography on neutral alumina using 5% ether in petroleum ether (30-40°) containing 1 drop of pyridine gave 890mgs (95%) of a colourless oil; υ_{max} (thin film) 1660cm^{-1} δ_H ($CDCl_3$) 5.0 (t, 1H, =C<u>H</u>, J=2Hz), 3.81 (d, 1H, J_{gem} = 10.8Hz), 3.75 (d, 1H, J_{gem} = 10.6Hz), 3.65 (d, 1H, J_{gem} = 11Hz), 3.45 (dd, 1H, J_{gem} = 10.6Hz, J_2 = 1.84Hz). 2.4 (dd, 1H), 2.10-2.00 (m, H) 1.9 (m, 3H), 0.95 (s, 9H, Si(t<u>Bu</u>)), 0.15 (s, 6H, Si(<u>Me</u>$_2$)); δ_C ($CDCl_3$) 155.01 (s, C-6), 108.96 (d, C-7), 79.69 (t, C-4), 72.52 (t, C-2), 41.42 (d, C-5), 34.36 (t, C-8), 34.23 (t, C-9), 34.21 (s, -<u>C</u>(CH_3)$_3$), 32.77 (d, C-1), 30.24 (q, (C<u>H</u>$_3$)$_3$), -4.67 (q, Si-(C<u>H</u>$_3$)$_2$); <u>M/Z</u> (70ev E.I.) 254 (M^+), 197, 105, 75, 73, 59. M^+ (E.I.) 254.1697, calculated for $C_{14}H_{26}O_2Si$, 254.1700).

3-Carboxy-5-formylmethyltetrahydropyran (2). Method A.

Trimethylsilylenolate (28) (450mg, 21mmol) was dissolved in methanol (15ml), and DCM (12ml) and was cooled to -78°. Ozone was passed through until starch-iodine paper indicated the presence of excess oxidant. On completion, the reaction mixture was treated with dimethyl sulphide (0.5ml) and allowed to warm to room temperature. Solvent was evaporated to yield 340mg (94%) of a colourless oil. Chromotography (medium pressure) (PE/EA, 1:1 + 1% formic acid) gave a white solid (290mg, 81%).

3-Carboxy-5-formylmethyltetrahydropyran (2). Method B

Tert-butyldimethylsilylenolate (29) (440mg, 15mmol) was stirred in acetic acid (3ml), H_2O (1ml) and THF (1ml) for 20hr at 25°. The THF was evaporated and the residue dissolved in ether and stirred vigorously for an hour, washed with brine and then the brine back-extracted with ether. The organic extracts were dried (Na_2SO_4) and evaporated to yield 280mg of a slightly yellow oil. Chromatography (medium pressure) (PE/EA, 1:1 + 1% formic acid) gave (2) as a white solid (210mg, 81%), m.p. 127-128°. υ_{max} ($CHCl_3$) 3500-3000 (broad) (COOH), 1700cm^{-1} (C=O); δ_H ($CDCl_3$) 9.9 (m, 1H, C<u>H</u>O, aldehyde), 9.0 (br. s, 1H, COO<u>H</u>), 4.19 (m, 1H, C-2, Heq), 3.94 (m, 1H, C-6, Heq), 3.35 (m, 1H, C-2, Hax), 3.05 (m, 1H, C-6, Hax), 2.75 (m, 1H, C<u>H</u>-COOH (bridgehead), 2.35 (m, 1H, C<u>H</u>CH$_2$CHO 2.31 (m, 2H, CHC<u>H</u>$_2$CHO),

1.4 (q, 2H, $CHC\underline{H}_2CH$). M/Z (iBuH C.I.) 171 (M^+ (100), 153, 129, 111; Found C, 55.76, H, 7.12. $C_8H_{12}O_4$ requires C, 55.81, H, 7.02%. This product was identical to that formed by Method A.

3-Carboxy-5-(cis-2-octenyl) tetrahydropyran (1)

n-Hexyltriphenyl phosphonium bromide (200mg, 0.5mmol) was suspended in anhydrous THF (5ml) under N_2 and cooled to -78°. nBuLi (0.36ml, 0.5mmol, 1.6M) was added dropwise and the resulting orange solution was warmed to -20° and stirred for 30mins. The suspensin was recooled to -78° and anhydrous HMPA (1.2ml, 15 equivalents based on phosphonium salt) was added followed by (2) (40mg, 0.23mmol) in anhydrous THF (2ml) via a cannula and stirred for 1hr then allowed to warm to O°, quenched with ether, evaporated and the residue dissolved in ether, acidified with dil HCl (aq), extracted with ether (3x20ml), dried (Na_2SO_4) and evaporated. The residue was dissolved in pentane and solid filtered off. The pentane was evaporated to yield a colourless oil, which was chromatographed (medium pressure) (PE/EA, 1:1 + 1% formic acid) to yield 41mg (73%) of a colourless wax. υ_{max} ($CHCl_3$) 3500-3150 (-COOH), 3020, 1700cm^{-1} (C=O); δ_H ($CDCl_3$) 10.54 (br. s, 1H, COO<u>H</u>), 5.34 (m, 1H, C<u>H</u>=), 4.15 (m, 1H, $C\underline{H}_2O$), 3.93 (m, 1H, $C\underline{H}_2O$), 3.35 (t, 1H, J_1 = 11.2Hz $C\underline{H}_2O$), 2.96 (t, 1H, J_1 = 11.2Hz, $C\underline{H}_2O$), 2.66 (m, 1H, C<u>H</u>COOH), 2.2 (m, 1H), 1.97 (m, 3H), 1.69 (m, 1H), 1.26 (m, 8H), 0.88 (t, 3H, J_1 = 6.5Hz, $C\underline{H}_3$); M/Z (70ev. E.I.) 240 (M^+), 150, 141, 128, 107, 94, 81, 79, 67, 55, 41. M^+ 240.1729, calculated for $C_{14}H_{24}O_3$, 240.1725.

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