SYNTHESIS OF 8,14-SECOSTEROIDS FROM (*S*)-(+)-CARVONE

Anna I. KOTYATKINA[a1], Vladimir N. ZHABINSKII[a2], Vladimir A. KHRIPACH[a3,*] and Aede de GROOT[b]

[a] *Institute of Bioorganic Chemistry, National Academy of Sciences, Kuprevich str. 5/2, 220141 Minsk, Belarus; e-mail:* [1] *steroids@ns.iboch.ac.by,* [2] *vz@ns.iboch.ac.by,* [3] *khripach@ns.iboch.ac.by*

[b] *Wageningen University and Research Center, Dreijenplein 8, 6703 HB Wageningen, The Netherlands; e-mail: aede.degroot@bio.oc.wau.nl*

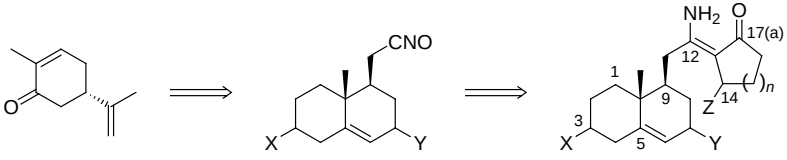
Received November 23, 1999
Accepted March 24, 2000

A total synthesis of functionalised 8,14-seco steroids with five- and six-membered D rings is described. The synthesis is based on the transformation of (*S*)-carvone into a steroidal AB ring moiety with a side chain at C-9 that allowed the creation of a nitrile oxide at this position. The nitrile oxides were coupled with cyclic enones or enol derivatives of 1,3-diketones, and reductive cleavage of the obtained cycloadducts gave the desired products. The formation of a twelve-membered ring compound was observed in cycloaddition of one of the nitrile oxides with cyclopentenone as the result of an intramolecular ene-reaction followed by retroaldol reaction.

Key words: Steroids; Secosteroids; Isoxazoles; Isoxazolines; Nitrile oxides; Carvone; Terpenoids; Total synthesis.

Total synthesis of steroids has been a subject of interest for a long time[1–4]. First of all, this gives a possibility to get access to steroids with unusual skeletons. Second, functional groups can be introduced to many positions that are difficult to functionalise starting from natural skeletons. Secosteroids are good examples[5–10] of and total synthesis is often the method of choice for their preparation[11–14]. The total synthesis of homochiral products creates an extra problem. We would like to report on an enantioselective approach to 8,14-secosteroids **3** starting from (*S*)-(+)-carvone[15] (**1**) *via* AB ring moiety (**2**) (Scheme 1). Chiral cyclohexenone derivatives are known to be used for the preparation of similar AB rings fragments[16,17]. Coupling of **2** with D ring moiety was achieved using the dipolar cycloaddition[18] of the nitrile oxide group with cyclopentane and cyclohexane derivatives. This approach allows not only to combine the AB and D moieties, but also to in-

troduce additional functional groups at C-12, C-14, and C-17, the positions that are often functionalised in the molecules occurring in nature.



(*S*)-carvone **1** **2** **3**

SCHEME 1

EXPERIMENTAL

Infrared spectra (wavenumbers in cm^{-1}) were recorded on a UR-20 spectrometer. ^1H NMR spectra were measured on a Bruker AC-200 in $CDCl_3$ solutions with tetramethylsilane as internal standard for ^1H (200 MHz) and ^{13}C (50 MHz) spectra. Chemical shifts are reported in ppm (δ-scale) and coupling constants (*J*) are in Hz. Mass spectra were recorded on a GC-MS HP5890 spectrometer with mass-selective detector HP5970B (energy of ionising electrons 70 eV). Column chromatography was performed on Merck silica gel 60. Reactions were monitored by TLC silica gel plates (Merck Kieselgel $60F_{254}$) and visualisation of the compounds was accomplished by UV light, and/or spraying with an acidic anis aldehyde solution.

(1*R*,8a*R*)-6,6-Ethylenedioxy-3-isopropylidene-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetonitrile (**5**)

To a solution of nitrile[19] **4** (0.20 g, 0.8 mmol) in diethyleneglycol (4 ml), KOH (0.18 g, 3.2 mmol) was added and the mixture was heated at 140 °C for 1.5 h. Then it was diluted with water, extracted with ether, and the extract was dried and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 1) to give nitrile **5** (0.19 g; 95%), m.p. 139–141 °C (hexane–ether). ^1H NMR: 1.00 s, 3 H (Me-8a); 1.76 s, 3 H and 1.78 s, 3 H ($=CMe_2$); 3.96 brs, 4 H ($-OCH_2-CH_2O-$); 6.18 s, 1 H (H-4). ^{13}C NMR: 17.0 q, 18.7 t, 19.7 q, 20.7 q, 28.6 t, 31.0 t, 35.8 t, 36.6 s, 41.8 t, 42.8 d, 64.4 t, 64.5 t, 109.0 s, 119.7 s, 122.9 d, 125.5 s, 127.1 s, 138.2 s. IR (KBr): 2 245, 1 650, 1 630, 1 450, 1 380, 1 120, 1 110.

(1*R*,8a*R*)-6,6-(Ethylenedioxy)-8a-methyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetonitrile (**6**)

A mixture of the compound **5** (0.70 g, 2.43 mol) and $NaHCO_3$ (0.5 g) in MeOH (40 ml) and $CHCl_3$ (40 ml) was ozonised at –75 °C. After the reaction was complete, argon was passed through the reaction mixture and then dimethyl sulfide (7 ml) was added. The temperature was allowed to rise to ambient, then the solvent was evaporated, and the residue was chromatographed on silica gel (hexane–EtOAc 1 : 3) to give the enone **6** (0.38 g; 60%), m.p. 173–175 °C (hexane–EtOAc). ^1H NMR: 1.16 s, 3 H (Me-8a); 3.97 m, 4 H ($-OCH_2-CH_2O-$); 5.82 s, 1 H (H-4). EI MS, *m*/*z* (%): 261 (2, M), 207 (1), 193 (4), 149 (2), 121 (1), 105 (2), 100 (7), 99 (100), 91 (6), 79 (5), 77 (6), 55 (15).

(1*S*,8a*R*)-6,6-(Ethylenedioxy)-3α-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (**7a**)

To a stirred solution of nitrile **4** (1.0 g, 3.5 mmol) in dry toluene (30 ml), a 1 M solution of diisobutylaluminium hydride in toluene (5.4 ml) was added dropwise at –78 °C. Stirring was continued for 10 min, then 1 drop of water was added, and the temperature was allowed to rise to ambient. The mixture was treated with 5% oxalic acid, dried, and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 10 : 1) to afford the aldehyde **7a** (0.75 g; 75%), m.p. 102–104 °C (hexane–ether). ^{1}H NMR: 0.98 s, 3 H (Me-8a); 1.76 s, 3 H (-C(=CH$_2$)C**H**$_3$); 3.96 brs, 4 H (-OCH$_2$CH$_2$O-); 4.78 s, 1 H and 4.90 s, 1 H (=CH$_2$); 5.31 d, 1 H, *J* = 5.4 (H-4); 9.64 brs, 1 H (CHO). IR (KBr): 1 730, 1 660, 1 450, 1 420, 1 370, 1 110.

(1*R*,8a*R*)-3β-(*tert*-Butyldimethylsilyloxy)-6,6-(ethylenedioxy)-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetaldehyde (**7b**)

To a stirred solution of the enone **6** (0.40 g, 1.5 mmol) in EtOAc (6 ml) and EtOH (1.5 ml), $NaBH_4$ (60 mg, 1.5 mmol) was added in small portions at 0 °C. Stirring was continued for 10 min and then the excess of $NaBH_4$ was decomposed by addition of 5% acetic acid. The mixture was extracted with $CHCl_3$ and the extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 4) to give (1*R*,8a*R*)-6,6-(ethylenedioxy)-3β-hydroxy-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetonitrile (0.36 g; 90%) as an oil. ^{1}H NMR: 1.02 s, 3 H (Me-8a); 3.97 brs, 4 H (-OCH$_2$-CH$_2$O-); 4.36 m, 1 H (H-3); 5.40 brs, 1 H (H-4). IR (KBr): 3 510, 2 230, 1 610, 1 460, 1 300. This product was converted into its *tert*-butyldimethylsilyl derivative without further purification.

To a solution of the obtained alcohol (0.70 g, 2.7 mmol) in DMF (2.5 ml), imidazole (0.55 g, 8.1 mol) and *tert*-butyldimethylsilyl chloride (557 mg, 3.7 mmol) were added. The mixture was stirred at room temperature for 2 h, treated with water (10 ml), and extracted with $CHCl_3$. The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 4) to give (1*R*,8a*R*)-6,6-(ethylenedioxy)-3β-(*tert*-butyldimethylsilyloxy)-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetonitrile (0.95 g; 94%) as an oil. ^{1}H NMR: 0.10 s, 6 H (SiMe$_2$); 0.90 s, 9 H (SiCMe$_3$); 1.04 s, 3 H (Me-8a); 3.97 m, 4 H (-OCH$_2$-CH$_2$O-); 4.36 m, 1 H (H-3); 5.32 d, 1 H, *J* = 1.5 (H-4). IR (KBr): 3 500, 2 230, 1 610, 1 420, 1 370, 1 300.

The obtained nitrile was transformed into the title compound **7b** as described for the aldehyde **7a** in 68% yield, m.p. 118–120 °C (hexane–ether). ^{1}H NMR: 0.04 s and 0.06 s, 6 H (SiMe$_2$); 0.90 s, 9 H (SiCMe$_3$); 1.04 s, 3 H (Me-8a); 3.98 m, 4 H (-OCH$_2$-CH$_2$O-); 4.36 m, 1 H (H-3); 5.30 brs, 1 H (H-4); 9.78 m, 1 H (CHO). IR (KBr): 1 730, 1 600, 1 460, 1 370, 1 310.

(1*R*,3*S*,8a*R*)-6,6-(Ethylenedioxy)-3α-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetaldehyde Oxime (**8a**)

To a solution of aldehyde **7a** (0.53 g, 1.83 mmol) in pyridine (2 ml), hydroxylamine hydrochloride (0.382 g, 5.49 mmol) was added. The mixture was kept at room temperature for 1.5 h, diluted with water, and extracted with ether. The organic layer was dried and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 1) to afford a mixture of (*Z*)- and (*E*)-oximes **8a** (0.54 g; 96%), m.p. 93–95 °C (hexane–ether). ^{1}H NMR: 0.97 s and 1.00 s, 3 H (Me-8a); 1.74 s and 1.76 s, 3 H (-C(=CH$_2$)C**H**$_3$); 3.96 brs, 4 H (-OCH$_2$-CH$_2$O-);

4.84 brs, 1 H and 4.96 brs, 1 H (=CH_2); 5.26 d, 1 H, *J* = 4.8 (H-4); 6.64 t, 0.5 H, *J* = 5.4 and 7.30 m, 0.5 H (C**H**=NOH); 8.40 brs, 1 H (CH=NO**H**). IR (KBr): 3 500, 1 620, 1 420, 1 410, 1 360, 1 110. EI MS, *m*/*z* (%): 277 (3), 276 (14), 247 (3), 214 (2), 185 (2), 157 (2), 143 (5), 133 (3), 105 (10), 100 (21), 99 (100), 91 (13), 55 (35).

(1*R*,8a*R*)-3β-(*tert*-Butyldimethylsilyloxy)-6,6-(ethylenedioxy)-3-isopropylidene-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-acetaldehyde Oxime (**8b**)

Title compound **8b** was prepared from **7b** by the procedure described for the oxime **8a** and obtained in 96% as an oil. ^{1}H NMR: 0.08 s, 6 H ($SiMe_2$); 0.91 s, 9 H ($SiCMe_3$); 1.06 s and 1.08 s, 3 H (Me-8a); 3.96 m, 4 H (-OCH_2-CH_2O-); 4.32 m, 1 H (H-3); 5.32 brs, 1 H (H-4); 6.83 t, 0.5 H, *J* = 6.0 and 7.40 dd, 0.5 H, *J* = 8.4, 6.6 (C**H**=NOH); 8.06 brs, 0.5 H (CH=NO**H**). IR (KBr): 1 610, 1 460, 1 370, 1 310.

3,3-(Ethylenedioxy)-4′,5′-dihydro[1′,2′]oxazolo[3′,4′,5′:12,13,17a]-7α-isopropenyl-8,14-seco-17a-homo-18-norandrost-5-en-14-one (**10**)

To a stirred suspension of *N*-chlorosuccinimide (110 mg, 0.82 mmol) and a catalytic amount of pyridine in chloroform (1 ml), a solution of the oxime **8a** (100 mg, 0.32 mmol) in chloroform (3 ml) was added. Stirring was continued at room temperature for 1 h, and then a solution of cyclohex-2-en-1-one (460 mg, 4.8 mmol) and triethylamine (0.10 ml, 0.82 mol) in chloroform (1 ml) was added dropwise in 4 h. The mixture was left overnight, diluted with water, and extracted with ether. The extract was dried and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 1) to give the isoxazoline **10** as a mixture of diastereomers (64.5 mg; 50%), m.p. 145–147 °C (hexane–EtOAc). ^{1}H NMR: 1.00 s and 1.04 s, 3 H (3 × 19-H); 1.62 s, 3 H (-C(=CH_2)C**H**$_3$); 3.52 m, 1 H (H-17a); 3.92 brs, 4 H (-OCH_2-CH_2O-); 4.76 brs, 1 H and 4.88 brs, 1 H (=CH_2); 5.30 m, 2 H (H-6 and H-13). IR (KBr): 1 745, 1 490, 1 370, 1 100.

1,3-Dipolar Cycloaddition of Nitrile Oxide **9a** with Cyclopent-2-en-1-one

To a stirred solution of the oxime **8a** (270 mg, 0.88 mmol) and a catalytic amount of pyridine in chloroform (8 ml), *N*-chlorosuccinimide (585 mg, 4.4. mmol) and cyclopent-2-en-1-one (480 mg, 5.85 mmol) were added. Then a solution of triethylamine (0.66 ml, 4.4 mmol) in chloroform (3 ml) was added during 5 h. The mixture was kept at room temperature overnight, diluted with water, and extracted with ether. The extract was dried and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 1) to give the compound **15** as a mixture of diastereomers (120 mg; 35%), m.p. 141–143 °C (hexane–EtOAc). ^{1}H NMR: 1.00 s, 3 H (3 × 19-H); 2.90 m, 2 H (2 × H-13); 3.50 m and 3.86 m, 1 H (H-14); 3.92 brs, 4 H (-OCH_2-CH_2O-); 5.04 brs, 1 H (H-6); 5.20–5.40 m, 2 H (=CH_2). IR (KBr): 1 700, 1 670, 1 610, 1 430, 1 370. One of the diastereomers of **15** was isolated as a separate compound. Its ^{13}C NMR: 16.9 q, 25.9 t, 27.1 t, 28.4 t, 29.6 t, 31.0 t, 35.4 t, 38.1 s, 39.3 t, 39.4 d, 41.5 t, 41.7 t, 61.7 d, 64.1 t, 64.2 t, 83.5 d, 109.1 s, 117.6 t, 124.0 d, 141.6 s, 146.8 s, 153.9 s, 210.7 s.

12-Amino-3,3-(ethylenedioxy)-7α-isopropenyl-8,14-seco-17a-homo-18-norandrost-5,12-dien-17a-one (**11**)

The title compound was prepared in 63% yield from the isoxazoline **10** by the procedure described for preparation of compound **16** and obtained as an oil. ^{1}H NMR: 1.02 s, 3 H (3 × 19-H); 1.70 s, 3 H (-C(=CH_2)C**H**$_3$); 3.90 brs, 4 H (-OCH_2CH_2O-); 4.72 s, 1 H and 4.86 brs, 1 H (=CH_2); 5.26 d, 1 H, *J* = 4.5 (H-6). ^{13}C NMR: 17.5 q, 21.2 t, 22.1 q, 25.7 t, 26.4 t, 31.0 t, 36.6 t, 37.5 t, 38.2 s, 38.9 t, 39.7 t, 40.8 d, 41.71 d, 41.75 t, 64.2 t, 64.3 t, 109.3 s, 110.0 s, 113.0 t, 124.8 d, 141.0 s, 147.3 s, 178.0 s, 200.5 s. IR (KBr): 3 400, 1 650, 1 610, 1 420, 1 400, 1 220, 1 110.

3,3-(Ethylenedioxy)-4′,5′-dihydro[1′,2′]oxazolo[3′,4′,5′:12,13,17]-7α-isopropenyl-8,14-seco-18-norandrost-5-en-14-one (**12**)

To a stirred mixture of *N*-chlorosuccinimide (59 mg, 0.44 mmol), 1 drop of pyridine and a chloroform (1 ml) solution of the oxime **8a** (120 mg, 0.40 mmol) were added. Stirring was continued for 1 h, and then a solution of cyclopent-2-en-1-one (480 mg, 5.85 mmol) and triethylamine (0.06 ml, 0.44 mmol) in chloroform (1 ml) was added slowly. The mixture was left standing overnight at room temperature, diluted with water, and extracted with ether. The extract was dried and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 1 : 1) to give the isoxazoline **12** as a mixture of diastereomers (85 mg; 56%), m.p. 121–123 °C (hexane–EtOAc). IR (KBr): 1 750, 1 470, 1 370, 1 100. One of the diastereomers of **12** was isolated as individual compound. Its ^{1}H NMR: 1.00 s, 3 H (3 × 19-H); 1.70 s, 3 H (-C(=CH_2)C**H**$_3$); 3.56 d, 1 H, *J* = 10 (H-17); 3.96 m, 4 H (-OCH_2-CH_2O-); 4.76 s, 1 H and 4.86 s, 1 H (=CH_2); 5.22–5.36 m, 2 H (H-6 and H-13). ^{13}C NMR: 17.8 q, 22.8 q, 26.4 t, 27.0 t, 29.0 t, 31.7 t, 36.0 t, 36.4 t, 38.0 s, 38.4 d, 42.3 t, 42.3 d, 62.0 d, 64.9 t, 65.0 t, 84.5 d, 110.0 s, 113.4 t, 125.6 d, 141.5 s, 148.0 s, 155.5 s, 211.3 s. EI MS, *m*/*z* (%): 331 (1), 287 (4), 253 (2), 145 (2), 133 (2), 115 (2), 100 (6), 99 (100), 91 (6),77 (3), 55 (11).

12-Amino-3,3-(ethylenedioxy)-7α-isopropenyl-8,14-seco-18-norandrosta-5,12-dien-17a-one (**16**)

A mixture of isoxazoline **12** (80 mg, 0.22 mmol), boric acid (68 mg, 1.1 mmol), and Raney nickel in ethanol (5 ml) was vigorously stirred under hydrogen at room temperature for 24 h. The usual work-up gave the enamino ketone **16** (56 mg; 60%), m.p. 208–210 °C (hexane–EtOAc). ^{1}H NMR: 1.02 s, 3 H (3 × 19-H); 1.70 s, 3 H (-C(=CH_2)C**H**$_3$); 3.96 m, 4 H (-OCH_2CH_2O-); 4.76 s, 1 H and 4.86 brs, 1 H (=CH_2); 5.26 d, *J* = 4.5 (6-H); 9.23 brs, 1 H (NH_2). ^{13}C NMR: 17.9 q, 21.3 t, 22.8 q, 27.1 t, 28.1 t, 31.8 t, 35.1 t, 36.6 t, 38.0 s, 39.6 d, 39.7 t, 41.6 d, 42.3 t, 64.9 t, 65.0 t, 104.7 s, 109.9 s, 113.3 t, 125.9 d, 141.0 s, 148.1 s, 159.5 s, 208.7 s. IR spectrum (KBr): 3 400, 1 690, 1 610, 1 420, 1 400, 1 220, 1 110.

3,3-(Ethylenedioxy)-[1′,2′]oxazolo[3′,4′,5′:12,13,17a]-7α-isopropenyl-8,14-seco-17a-homo-18-norandrost-5-en-14-one (**17a**)

The title compound was prepared in 63% yield from the oxime **8a** and 3-morpholinocyclohex-2-en-1-one by the procedure described for preparation of compound **12**, m.p. 161–163 °C (hexane–EtOAc). ^{1}H NMR: 1.06 s, 3 H (3 × 19-H); 1.58 s, 3 H (CH(=CH_2)C**H**$_3$);

2.90–3.18 m, 2 H (15-H and 17-H); 3.94 brs, 4 H (-OCH_2-CH_2O-); 4.62 s, 1 H and 4.72 s, 1 H (=CH_2); 5.25 d, 1 H, *J* = 4.5 (6-H). ^{13}C NMR: 17.2 q, 21.8 q, 22.4 t, 23.2 t, 25.7 t, 26.5 t, 31.0 t, 35.5 t, 37.5 s, 38.0 t, 39.1 d, 41.7 d, 41.8 d, 64.2 t, 64.2 t, 109.4 s, 112.3 t, 114.6 s, 125.0 d, 140.7 s, 147.2 s, 161.0 s, 180.9 s, 192.5 s. IR (KBr): 1 690, 1 610, 1 470, 1 110. EI MS, *m*/*z* (%): 228 (2), 169 (1), 161 (1), 131 (1), 119 (1), 105 (2), 100 (6), 99 (100), 91 (4), 55 (20).

3,3-(Ethylenedioxy)-[1′,2′]oxazolo[3′,4′,5′:12,13,17a]-7β-(*tert*-butyldimethylsilyloxy)-8,14-seco-17a-homo-18-norandrost-5-en-14-one (**17b**)

The title compound was prepared in 54% yield from the oxime **8b** and 3-morpholinocyclohex-2-en-1-one by the procedure described for preparation of compound **12**, m.p. 184–186 °C (hexane–EtOAc). ^{1}H NMR: 0.06 s, 6 H ($SiMe_2$); 0.95 s, 9 H ($SiCMe_3$); 1.10 s, 3 H (3 × 19-H); 3.96 m, 4 H (-OCH_2-CH_2O-); 4.20 m, 1 H (H-7); 5.30 brs, 1 H (H-6). ^{13}C NMR: –4.5 q, –4.4 q, 17.5 q, 18.3 s, 22.4 t, 23.2 t, 26.0 q, 26.0 q, 26.0 q, 31.0 t, 33.4 t, 35.5 t, 37.5 s, 38.0 t, 41.6 t, 42.3 d, 64.3 t, 64.4 t, 68.5 d, 109.4 s, 114.7 s, 128.1 d, 141.4 d, 160.6 s, 181.1 s, 192.7 s. IR (KBr): 1 690, 1 610, 1 470, 1 180. EI MS, *m*/*z* (%): 488 (2, M + 1), 487 (4, [M^+]), 430 (13), 355 (23), 340 (68), 324 (15), 310 (23), 296 (42), 278 (12), 254 (9), 205 (12), 184 (10), 161 (26), 153 (18), 115 (16), 99 (100), 75 (32), 55 (41).

12-Amino-3,3-(ethylenedioxy)-7α-isopropenyl-8,14-seco-17a-homo-18-norandrosta-5,12-diene-14,17a-dione (**18a**)

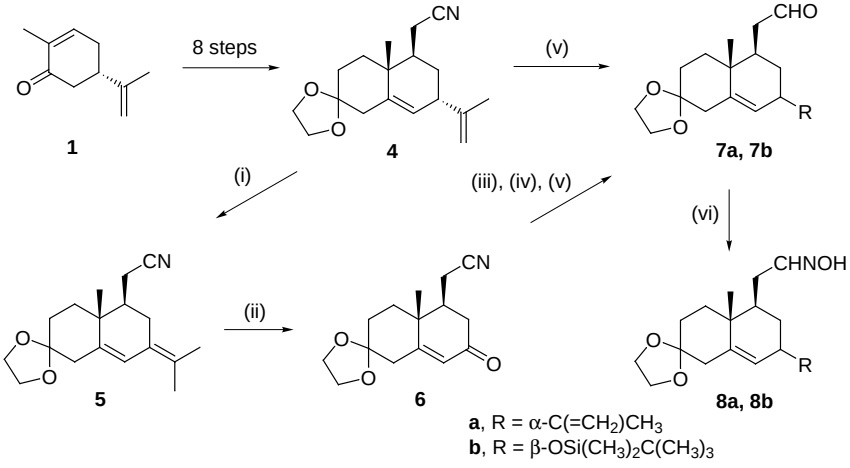
A mixture of the isoxazole **17a** (100 mg, 0.26 mmol) and Raney nickel in ethanol (5 ml) was stirred under hydrogen at room temperature for 24 h. Then the catalyst was filtered off, the residue was evaporated and chromatographed on silica gel (hexane–EtOAc 1 : 1) to give the enamino diketone **18a** (60 mg; 62%), m.p. 205–207 °C (hexane–EtOAc). ^{1}H NMR: 1.04 s, 3 H (3 × 19-H); 1.72 s, 3 H (-C(=CH_2)C**H**$_3$); 3.90 brs, 4 H (-CH_2CH_2-); 4.74 s, 1 H and 4.82 s, 1 H (=CH_2); 5.30 d, 1 H, *J* = 4.5 (6-H); 6.50 brs, 1 H and 12.0 brs, 1 H (NH_2). ^{13}C NMR: 18.4 q, 20.6 t, 23.0 q, 28.2 t, 29.0 t, 32.0 t, 36.3 t, 38.4 s, 40.0 d, 41.0 d, 41.6 t, 42.7 t, 64.2 t, 64.8 t, 102.3 s, 109.3 s, 113.0 t, 126.3 d, 141.7 s, 149.2 s, 160.4 s, 195.6 s, 202.2 s. IR (KBr): 3 400, 1 650, 1 610, 1 420, 1 400, 1 220, 1 110. EI MS, *m*/*z* (%): 399 (1, M + 1), 246 (8), 231 (4), 179 (5), 162 (6), 153 (7), 125 (3), 100 (6), 99 (100), 91 (5), 86 (3), 55 (26).

12-Amino-3,3-(ethylenedioxy)-7β-(*tert*-butyldimethylsilyloxy)-8,14-seco-17a-homo-18-norandrosta-5,12-diene-14,17a-dione (**18b**)

The title compound was prepared from isoxazole **17b** in 80% yield by the procedure described above, m.p. 165–167 °C (hexane–EtOAc). ^{1}H NMR: 0.02 s, 6 H ($SiMe_2$); 0.88 s, 9 H ($SiCMe_3$); 1.08 s, 3 H (3 × 19-H); 3.96 brs, 4 H (-OCH_2-CH_2O-); 4.22 m, 1 H (7-H); 5.30 brs, 1 H (6-H); 6.64 brs, 1 H and 12.42 brs, 1 H (NH_2). ^{13}C NMR: –4.5 q, –4.4 q, 17.8 q, 18.3 s, 19.1 t, 26.0 q, 26.0 q, 26.0 q, 30.9 t, 33.2 t, 35.6 t, 37.6 s, 38.2 t, 39.0 t, 39.7 t, 42.7 t, 42.4 d, 64.3 t, 64.5 t, 68.6 d, 108.5 s, 109.3 s, 127.9 d, 141.5 s, 177.3 s, 196.7 s, 200.8 s. IR (KBr): 3 400, 1 690, 1 620, 1 560, 1 210.

RESULTS AND DISCUSSION

Conjugate addition of cyanide to (*S*)-carvone followed by Robinson annulation provides an effective method for stereoselective preparation of functionalised decalins **2** with the required stereochemistry[19] at C-9 and C-10. Two types of decalin oximes **8**, with different substituents R, were investigated for the generation of the corresponding nitrile oxides. Decalin oxime **8a** was prepared *via* nitrile[19] **4** and aldehyde **7** (Scheme 2). Transformation of the isopropenyl group allowed to indroduce various functional groups at C-7. Isomerisation of **4** under alkaline conditions led to the isopropylidene derivative **5**, and its ozonolysis gave the enone **6**. Attempts

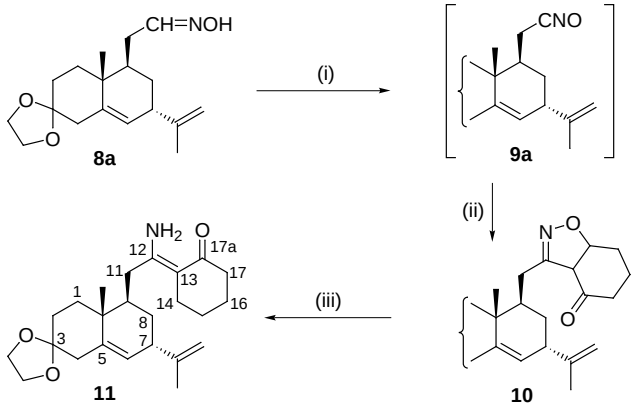


(i) KOH, diethylene glycol, 140 °C, 95%; (ii) O_3, MeOH–$CHCl_3$, –75 °C, 60%; (iii) $NaBH_4$, EtOAc–EtOH, 0 °C, 90%; (iv) TBDMSCl, imidazole, DMF, r.t., 94%; (v) DIBAH, $PhCH_3$, –78 °C, 68–75%; (vi) NH_2OH·HCl, Py, r.t., 96%

SCHEME 2

to reduce both the enone and the nitrile in **6** simultaneously with DIBAH failed, only a complex mixture of compounds was obtained. The desired aldehyde **7b** was prepared by reduction of the enone with $NaBH_4$, protection of the C-7 hydroxy group as *tert*-butyldimethylsilyl ether and subsequent reduction of the nitrile group with DIBAH. Both the (*Z*)- and (*E*)-oximes **8** were formed in the next stage on reaction with NH_2OH. That was obvious as confirmed by the ^{1}H NMR spectrum, which showed two triplets (J = 5) at δ 7.30 and 8.40 of the C**H**=NOH protons. Both isomers of the oximes **8** were suitable for generation of the corresponding nitrile oxides.

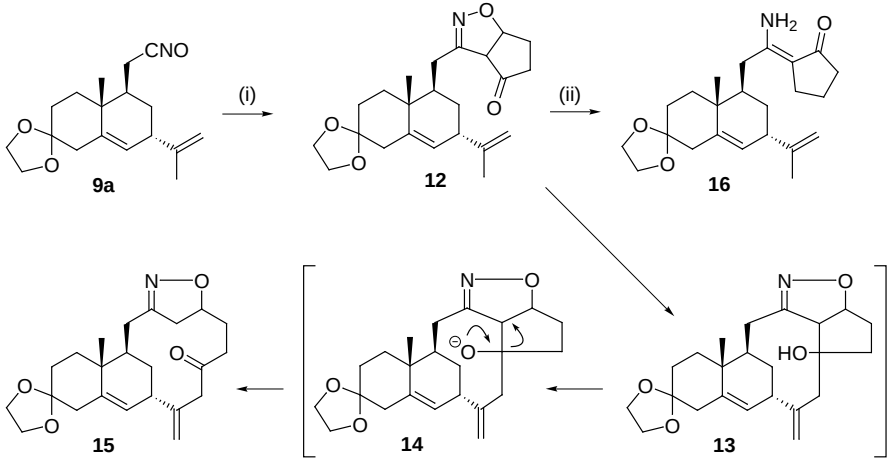
The 1,3-dipolar cycloaddition of nitrile oxide **9** to a cyclohexenone led to a diastereomeric mixture (1 : 1) of isoxazolines **10** (Scheme 3). A reductive opening of the isoxazoline ring afforded the enamino ketone **11**.



(i) NCS, $CHCl_3$, Et_3N, r.t.; (ii) cyclohex-2-en-1-one, 50% from **8a**; (iii) H_2, Raney-Ni, EtOH, r.t., 63%

SCHEME 3

It is noteworthy that our first attempts to carry out the cycloaddition of **9a** with cyclopentenone led to the isolation of a new type of product (Scheme 4). The macrocycle **15**, containing a twelve-membered ring, was obtained as the main product of the reaction in 35% yield. Its formation



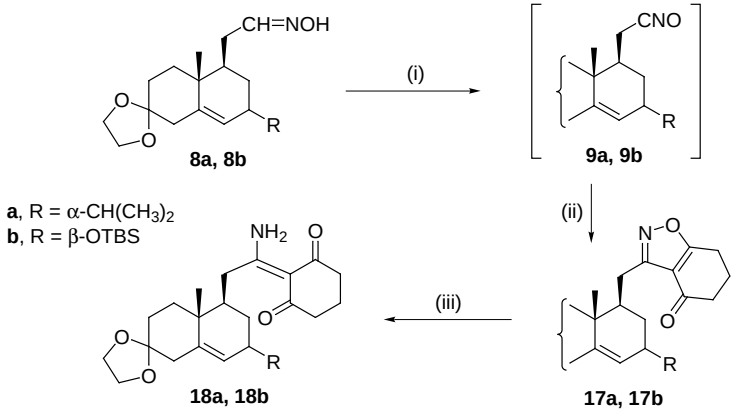
(i) cyclopent-2-en-1-one, 56%; (ii) H_2, Raney-Ni, EtOH, r.t., 80%

SCHEME 4

could be explained by an initial intramolecular ene-reaction to the intermediate homoallylic alcohol **13**. This ene-reaction proved to be feasible because of the steric proximity of the isopropenyl group and the C-14 carbonyl group. The intermediate **13** was unstable under the reaction conditions and was deprotonated to **14**, which gave **15** by retroaldol reaction.

It was possible to prevent the formation of **15** by diminishing an excess of Et_3N and NCS from 5 to 1.1 equivalent. The desired isoxazoline **12** now could be isolated in 56% yield as a mixture of diastereomers, one of which being separated by crystallisation. Reductive ring opening of the isoxazoline gave the enamino ketone **16**.

Compounds **17a** and **17b**, containing an isoxazole heterocycle could be prepared by the reaction of the nitrile oxide **9a** and **9b** with cyclohexane-1,3-dione[20]. However, better results were obtained when the corresponding morpholino derivative was used. The 1,3-dipolar cycloaddition of the nitrile oxides **9a** and **9b** to 3-morpholinocyclohex-2-en-1-one gave the isoxazoles **17a** and **17b** (Scheme 5).



(i) NCS, $CHCl_3$, Et_3N, r.t.; (ii) 3-morpholinocyclohexen-2-en-1-one, r.t., 54–63%; (iii) H_2, Raney-Ni, EtOH, r.t., 62–80%

SCHEME 5

The realisation of the latent functionality of the heterocycle was again effected *via* Raney nickel hydrogenolysis to give the corresponding enamino diketones[21] **18a** and **18b**. The exo methylene group in **17a** was stable under these conditions.

REFERENCES

1. Taub D.: *Nat. Prod. Rep*. **1982**, 1.
2. Zeelen F. J., Groen M. B.: *Rec. Trav. Chim. Pays-Bas*. **1986**, *105*, 465.
3. Zeelen F. J.: *Nat. Prod. Rep*. **1994**, 607.
4. Bijoy P., Naik R. G., Shivakumar U., Subba R. G.: J. Indian Inst. Sci. **1994**, 74, 519; Chem. Abstr. **1995**, *122*, 314907.
5. Rami R. M. V., Kay H. M., John F. D.: *J. Nat. Prod.* **1997**, *60*, 41.
6. Qing L., John F. D.: *J. Nat. Prod.* **1997**, *60*, 195.
7. Akemi U., Noboru S., Megumi E., Shigenobu R.: *J. Nat. Prod.* **1997**, *60*, 296.
8. Koljak R., Pehk T., Jaerving I., Liiv M., Loop A., Varvas K., Vahemets A., Lille U., Samel N.: *Tetrahedron Lett.* **1993**, *34*, 1985.
9. Li H., Matsunaga S., Fusetani N.: *Experientia* **1994**, *50*, 771.
10. Modaio A., Notaro G., Minor S. D.: *J. Nat. Prod*. **1990**, *53*, 565.
11. Kerr R. G., Rodrigues L. C., Kellman J.: *Tetrahedron Lett.* **1996**, *46*, 8301.
12. Pejanovic W. M., Petrovic J. A., Csanadi J. J., Stankovic S. M., Miljkovic D. A.: *Tetrahedron* **1995**, *51*, 13379.
13. Adinolfi R., Migiuolo A., Sica D.: *J. Nat. Prod*. **1994**, *57*, 1220.
14. Hernandes R., Velazquez S. M., Suarez E.: *Tetrahedron Lett.* **1996**, *37*, 6409.
15. Rejean R., Deslongchamps P.: *Can. J. Chem*. **1992**, *70*, 1939.
16. Jansen B. J., Kreuger J. A., de Groot A.: *J. Org. Chem*. **1988**, *53*, 855.
17. Ruel R., Deslongchamps P.: *Can. J. Chem*. **1992**, *70*, 1939.
18. Torsell K. B. G.: *Nitrile Oxides, Nitrones and Nitronates*. VCH Verlagsgeselschaft, Weinheim 1988.
19. Verstegen-Haaksma A. A., Swarts H. J., Jansen B. J. M., de Groot A.: *Tetrahedron* **1994**, *50*, 10073.
20. Akhrem A. A., Lakhvich F. A., Khripach V. A., Pozdeyev A. G.: *Synthesis* **1971**, 43.
21. Akhrem A. A., Lakhvich F. A., Khripach V. A., Petrusevich I. I.: *Khim. Geterotsikl. Soedin*. **1975**, *7*, 891.