# New Route to (+)-(20*R*)-De-*AB*-cholesta-8(14),22-dien-9-one and (+)-(20*S*)-De-*AB*-isocholesta-8(14),22-dien-9-one from (*S*)- and (*R*)-2,3-*O*-Isopropylideneglyceraldehyde

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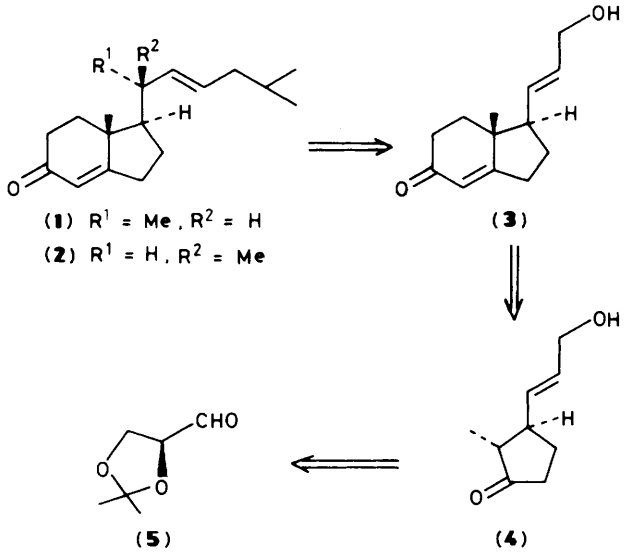
The optically active (+)-(20*R*)-de-*AB*-cholesta-8(14),22-dien-9-one (**1**) and (+)-(20*S*)-de-*AB*-isocholesta-8(14),22-dien-9-one (**2**) have been synthesised *via* stereo- and regio-selective Michael addition to the (3*S*)-methylcyclopentanone (**4**) derived from (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**5**) and its (*R*)-isomer; the methyl group at $C_{20}$ in (**1**) and (**2**) was introduced by Claisen rearrangement of the allyl vinyl ether (**12**) followed by decarbonylation of the resulting homoaldehydes (**13**) and (**14**), respectively.

The discovery of biologically important steroids possessing a modified side chain such as ecdysone, brassinolide, and metabolites of vitamin D has raised interest in the development of effective synthetic methods for the steroids. The enantioselective construction of the *CD* ring containing a requisite functional group at $C_{17}$ (steroidal numbering)[1] which could be transformed into various types of side chain is also useful in the synthesis of steroids.

In our continuing efforts toward the synthesis of the biologically active natural products using a chiral starting




Scheme 1

material, we have developed synthetic methods to optically active (20*R*)-de-*AB*-cholesta-8(14),22-dien-9-one (**1**)[3] and (20*S*)-de-*AB*-isocholesta-8(14),22-dien-9-one (**2**)[3] as synthetic precursors for metabolites of vitamin D and severed (20*S*)-sterols,[4] both possessing interesting biological activity.[5]

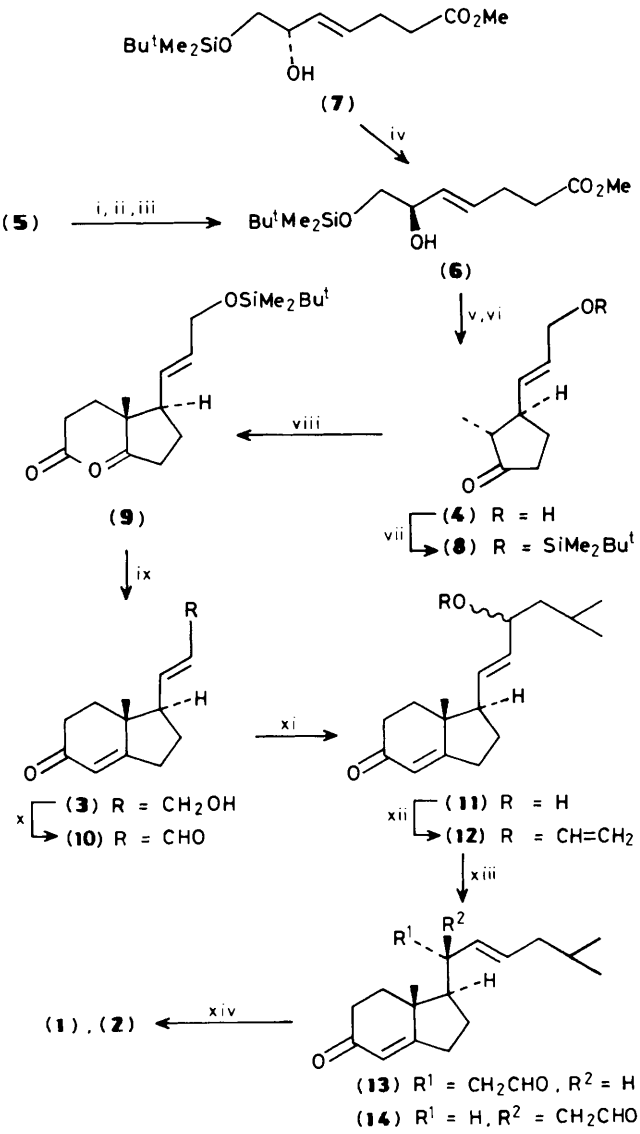
The retrosynthetic plan is outlined in Scheme 1. A stereo- and regio-selective Michael addition[2] to the (3*S*)-methylcyclopentanone (**4**), easily formed from (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**5**), followed by intramolecular aldol condensation provides the *CD* ring (**3**), possessing both the requisite stereochemistry and functional group for further elaboration of the side chain at $C_{17}$. Introduction of the isobutyl group to the corresponding aldehyde of (**3**) followed by combination of Claisen rearrangement and decarbonylation provides the desired compounds (**1**) and (**2**).

The first target compound (**4**) {$[\alpha]_D^{25}$ −81.3° (*c* 0.209, $CHCl_3$)} was synthesised in 7 steps in 48.1% overall yield from (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**5**)[6] prepared from L-ascorbic acid *via* the compound (**6**) {$[\alpha]_D^{25}$ −10.5° (*c* 1.01, $CHCl_3$)}[2] which was also obtained in 42.7% yield from the inversion of the hydroxy group in the known monoprotected allyl alcohol (**7**)[2] by Mitsunobu reaction and subsequent hydrolysis of the resulting benzoate.

The formation of the *trans*-angularly methylated *CD* ring was achieved through stereo- and regio-selective Michael addition and subsequent intramolecular aldol condensation. Michael addition of the lithium enolate generated from the protected compound (**8**) {$[\alpha]_D^{27}$ −46.6° (*c* 1.52, $CHCl_3$)} *via* silyl enol ether[7] (trimethylsilyl iodide, hexamethyldisilazane in dichloromethane) with α-silylated vinyl ketone[8] provided the diketone (**9**)†{$[\alpha]_D^{21}$ −22.9° (*c* 0.367, $CHCl_3$)} in 76.7% overall yield. Treatment of (**9**) with base[9] (0.5 M KOH in 90% ethanol, 80 °C for 2 h) resulted in cyclisation and simultaneous deprotection of the t-butyldimethylsilyl group to give the desired enone (**3**) {$[\alpha]_D^{21}$ +41.3° (*c* 0.184, $CHCl_3$)} in 93.3% yield.

Introduction of the methyl group to $C_{20}$ (steroidal numbering) and further elaboration of the side chain were carried out in the following way. Grignard reaction of the aldehyde (**10**) {$[\alpha]_D^{22}$ +54.3° (*c* 0.199, $CHCl_3$)} obtained in 89.8% yield by

† The trimethylsilyl group was deprotected in the purification through silica gel column chromatography.




**Scheme 2.** *Reagents and conditions*: i, vinylmagnesium bromide, $CH_2Cl_2$, 0 °C, 80.3%; ii, $MeC(OMe)_3$, cat. propionic acid, xylene, 140 °C, 85.0%; iii, 10% $H_2SO_4$, MeOH, room temp. (r.t.); $Bu^tMe_2SiCl$, 4-*N*,*N*-dimethylaminopyridine (4-DMAP), $CH_2Cl_2$, −10 °C, 78.6%; iv, $EtO_2CN{=}NCO_2Et$ (1.5 equiv.), $Ph_3P$ (1.5 equiv.), $PhCO_2H$ (1 equiv.), tetrahydrofuran (THF), r.t.; $K_2CO_3$, MeOH; v, $EtC(OMe)_3$, cat. propionic acid, xylene, 150 °C, 98.8%; vi, $LiN(SiMe_3)_2$, dry THF, −78 °C; $MgCl_2{\cdot}6H_2O$, $Me_2SO$, 140 °C, 90.7%; vii, $Bu^tMe_2SiCl$, 4-DMAP, $CH_2Cl_2$, r.t., 80.0%; viii, $Me_3SiI$ (3 equiv.), $HN(SiMe_3)_2$ (3.6 equiv.), dry $CH_2Cl_2$, r.t.; MeLi (1.5 equiv.) in $Et_2O$, dry THF, −50 °C r.t.; 2-trimethylsilyl-1-buten-3-one (3 equiv.), −78 °C, 76.7%; ix, 0.5% KOH in 90% EtOH, 80 °C, 93.3%; x, $(COCl)_2$, $Me_2SO$, $Et_3N$, $CH_2Cl_2$, 89.8%; xi, isobutylmagnesium chloride (1.2 equiv.), $CH_2Cl_2$, −40 °C, 81.4%; xii, ethyl vinyl ether, $Hg(OAc)_2$ reflux, and then cat. AcOH, r.t.; xiii, collidine, 150 °C; xiv, $(Ph_3P)_3RhCl$, benzene, reflux.

Swern oxidation[10] of (**3**), with isobutylmagnesium chloride afforded the allyl alcohol (**11**) {$[\alpha]_D^{27}$ +36.5° (*c* 1.26, $CHCl_3$)} as an inseparable mixture of diastereoisomers at $C_{22}$ (steroidal numbering) in 81.4% yield. After preparing the vinyl ether[3,11] of (**11**), Claisen rearrangement of the resulting compound (**12**) provided the separable aldehyde (**13**) and (**14**) in 14.5 and 19.0% yield, respectively, along with the starting material (**11**) (27.5%). Decarbonylation[3,12] of (**13**) with chlorotris(tri-

phenylphosphine)rhodium in refluxing benzene produced (+)-(20*R*)-de-*AB*-cholesta-8(14),22-dien-9-one (**1**) {$[\alpha]_D^{25}$ +28.2° (*c* 0.0425, $CHCl_3$); found: $M^+$, 260.2148, $C_{18}H_{28}O$ requires $M^+$, 260.2139} in 50.1% yield. The same treatment of the $C_{20}$ epimer (**14**) gave (+)-(20*S*)-de-*AB*-isocholesta-8(14),22-dien-9-one (**2**) {$[\alpha]_D^{25}$ +74.3° (*c* 0.055, $CHCl_3$); found: $M^+$, 260.2139, $C_{18}H_{28}O$ requires $M^+$, 260.2139} in 88.8% yield. Both products of (**1**) and (**2**) had i.r. and n.m.r. spectra‡ identical with published physical data.[3]

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‡ The $C_{20}$ α-methyl resonances are 0.06 p.p.m. higher field in the $^1H$ n.m.r. spectrum than $C_{20}$ β-methyl. Compound (**4**): $^1H$ n.m.r. ($CDCl_3$, 400 MHz) δ 0.88 (6 H, d, *J* 6.6 Hz, $CMe_2$), 1.06 (3 H, d, *J* 6.6 Hz, Me), 1.11 (3 H, s, Me), 5.25 (1 H, dd, *J* 15.4, 8.3 Hz, CC*H*=CH), 5.33—5.41 (1 H, m, CCH=C*H*), 5.73 (1 H, s, enone); i.r. ($CHCl_3$) $\nu_{max}$ 1653 $cm^{-1}$ (enone); $R_F$ = 0.45 (hexane–EtOAc = 4:1, v/v). Compound (**5**): $^1H$ n.m.r. ($CDCl_3$, 400 MHz) δ 0.88 (6 H, d, *J* 6.6 Hz, $CMe_2$), 1.00 (3 H, d, *J* 6.8 Hz, Me), 1.08 (3 H, s, Me), 5.23 (1 H, dd, *J* 15.3, 9.2 Hz, CC*H*=CH), 5.35—5.42 (1 H, m, CCH=C*H*), 5.72 (1 H, s, enone); i.r. ($CHCl_3$) $\nu_{max}$ 1653 $cm^{-1}$ (enone); $R_F$ = 0.48 (hexane–EtOAc = 4:1, v/v).