Selective Reduction of the 7(8)-Double Bond in Ergosterol

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Reduction of ergosterol alkoxide derivatives with lithium metal gives better yields of the 7(8)-reduced product brassicasterol than previous procedures; the mixed products of the reduction are easily converted into ergosta-2,22-dien-6-one, a convenient intermediate for brassinolide synthesis.

Brassinolide (**1**) is an interesting plant growth-promoting steroid.[1] Related compounds with modified side chains have also shown biological activity.[2—6] We considered that the abundantly available ergosterol (**2**) would provide a convenient starting material. There are two challenges in this approach. The first is the selective reduction of the 7(8)-double bond of (**2**); the second is the inversion of configuration of the C-24-methyl group and the introduction of hydroxy groups with the correct configuration at C-22 and C-23. Recent syntheses[7—11] use 6-keto-2(3)-olefins like (**3**) as intermediates. So far no one has converted ergosterol into brassinolide without removing and replacing the side chain.

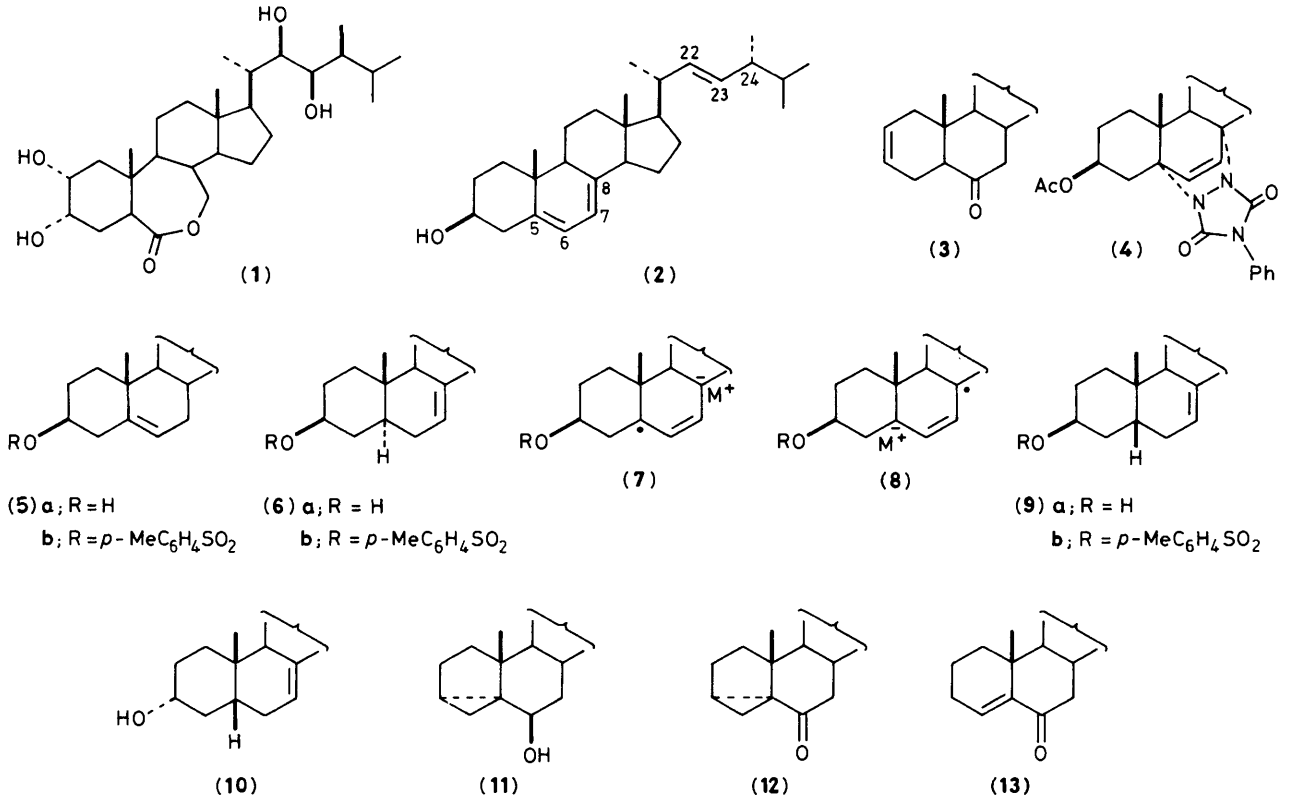

Table 1

Ergosterol hydroxy substituent	Metal	Conditions: Solvent[d]	Conditions: Proton Source[d]	Conditions: Temp./°C	Yields (%)[a]: (5a)	Yields (%)[a]: (6a)
H	Li[b]	$EtNH_2$	—	19	50	45
PhCO	Li[b]	$EtNH_2$	—	19	60	35
Bu^tMe_2Si	Li[b]	$EtNH_2$	—	19	25	70
$MeOCH_2$	Li[b]	$EtNH_2$	—	19	30	45
H	Na	Bu^tOH–THF	—	30	Trace	96
K	K[c]	HMPA–THF	TMP[d]	0	23	72
Li	Li[c]	HMPA–THF	Bu^tOH	0	55	40
Li	Li[c]	HMPA–THF	Pr^iOH	18	64	31
Li	Li[c]	HMPA–THF	Me_2NH	0	71	24
Li	Li[c]	HMPA–THF	TMP[d]	0	76	20
Li	Li[c]	HMPA–THF	TMP[d]	40	72	23
Li	Li[c]	HMPA–THF	TMP[d]	−40	69	26

[a] Ratios were determined by the 18-methyl n.m.r. integrals: (**5a**), δ 0.696; (**6a**), δ 0.551; (**9a**), δ 0.562. [b] Lithium (100 mg/mmol of substrate) was added to ethylamine (20 ml/mmol) to give a deep blue colour. The substrate was added as a solid under argon. The reduction was complete after 30 min as indicated by t.l.c. The solution was neutralised with saturated NH_4Cl and extracted with methylene chloride. [c] Lithium (40 mg/mmol substrate) was added to a solution of the substrate in HMPA (5 ml/mmol) and THF (10 ml/mmol) under argon at the given temperature. Anions were generated by prior addition of Bu^nLi or KH (1 equiv.). A proton source (3 mmol/mmol substrate) was added immediately after the lithium. The reductions were complete shortly after the appearance of a deep blue colour (15 min to 2 h). [d] THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; TMP = 2,2,6,6-tetramethylpiperidine.

Electron-transfer reduction of steroidal-5,7-dienes in alcoholic solvents is a good source of 7(8)-olefins.[12,13] However, in a recent report[14] on the reduction of the triazoline adduct (**4**) of ergosterol acetate by lithium in ethylamine the isomers (**5a**) and (**6a**) were formed in 40 and 27% yields respectively.

Electron-transfer reduction of ergosterol and its derivatives should furnish, if tight ion pairs are admitted,[15,16] two radical anions (**7**) and (**8**) (M = Li, Na, K, *etc.*). It seemed to us that the concentration of (**7**) would be greater the greater the negative charge at C-3. Thus the anion (**7**, RO = O^-) should give the maximum chance of protonation at C-8 followed by, after the second electron transfer, protonation at C-7, even though C-5 is less hindered than C-8. In each case the more remote carbon atom would bear the tight ion pair and be preferentially protonated.

The results reported in Table 1 support this simple theoretical treatment. Thus the alcohol (**2**), its benzoate, and the preformed lithium salt all give a preponderance of brassicasterol (**5a**) on reduction with lithium metal. In contrast the methoxymethyl and t-butyldimethylsilyl ethers, groups

which are not reductively removed by lithium metal, afford α-dihydroergosterol (**6a**) as the major product. Sodium and potassium, which form loose ion pairs, give mainly (**6a**) also. *In all cases except* the methoxymethyl ether all the starting material was reduced.

In all experiments, traces of β-face protonation of (**8**) were also observed. 5β-Ergosta-7,22-dien-3β-ol (**9a**) {m.p. 123 °C (EtOAc), $[\alpha]_D^{22}$ + 19° (*c* = 1.2, $CHCl_3$), benzoate m.p. 113 °C (acetone), $[\alpha]_D^{28}$ + 42° (*c* = 1.0, $CHCl_3$)} was identified by oxidation to the ketone and reduction to the known 5β-ergosta-7,22-dien-3α-ol (**10**)[17] identical with an authentic specimen.

It was normally found convenient to tosylate the entire mixture of (**5a**), (**6a**), and (**9a**) to furnish (**5b**), (**6b**), and (**9b**) and then carry out the solvolysis[18] leading to the readily separable steroid (**11**).[19] In a typical procedure, 9.19 g of a 1.1 : 1.0 mixture of (**5a**) and (**6a**) yielded 4.63 g of (**11**). Oxidation to (**12**) was accomplished quantitatively using pyridinium dichromate[20] in methylene chloride. Rearrangement of the cyclopropyl ketone (**12**) to the isomeric 2-ene product (**3**) (89%) was accomplished with a catalytic amount of camphorsulphonic acid in sulpholane[21] at 170 °C. A small amount (10%) of the isomer (**13**) was also obtained.†

This synthesis of brassicasterol directly from ergosterol is convenient for further transformations as described. If pure brassicasterol is needed our original synthesis[22] still remains competitive.

The appropriate modifications of the ergosterol side chain are now in hand.

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† All new compounds gave correct microanalytical and spectral data.

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