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An Improved Synthesis of 1α-Hydroxy-7-dehydrocholesterol Derivatives

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The effect of protective groups on the allylic bromination and the subsequent dehydrobromination of cholesterol and 1α-hydroxycholesterol derivatives was investigated. 1α-Hydroxy-7-dehydrocholesterol derivatives were selectively obtained in high yield by using alkoxycarbonyl groups as protective groups.

Keywords——1α-hydroxy-7-dehydrocholesterol derivative; allylic bromination; dehydrobromination; protective group effect

Since the isolation and identification of vitamin D_3 metabolites, a number of reports on the synthesis of vitamin D_3 metabolites and analogues have been published.[2] In general, the preparative approaches to these compounds require the conversion of the corresponding cholesterol derivatives such as (I) to the 7-dehydrocholesterol derivatives (III), as shown in Chart 1. Such a transformation was first described by Ziegler.[3] However, treatment of a cholesterol derivative (I) with *N*-bromosuccinimide affords the 7-bromocholesterol derivative (II) as an epimeric mixture at C-7 and the subsequent dehydrobromination leads to the 7-dehydrocholesterol derivative (III) along with a substantial quantity of the undesired 4,6-diene isomer (IV). Thus, the yield of these steps is generally low and the separation and purification of the 5,7-diene isomer (III) are very difficult. To solve this problem, other types

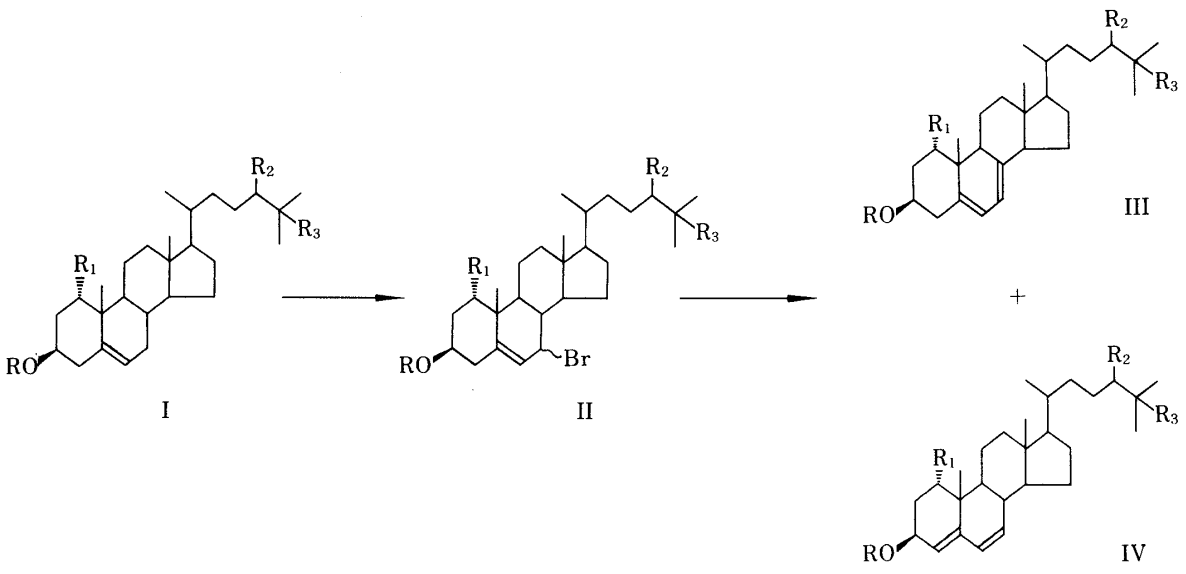

Chart 1

TABLE I. Preparation of Cholesterol Derivatives (Ia—m)

Compd.	R	R_1	R_2	R_3	Yield (%)	mp[c] (°C)	IR $\nu_{max}^{CCl_4}$ (cm^{-1})
Ia	CH_3CO	H	H	H	75[a]	116.5—117	1723
Ib	$(CH_3)_3CCO$	H	H	H	69[a]	163.5—164	1712
Ic	$CH_3(CH_2)_4CO$	H	H	H	66[a]	86—89	1720
Id	$C_6H_5CH_2OCO$	H	H	H	55[a]	104—106	1733
Ie	C_2H_5OCO	H	H	H	77[a]	83—83.5	1735
If	CH_3CO	CH_3CO_2	H	H	79[b]	93—94	1738
Ig	$(CH_3)_3CCO$	$(CH_3)_3CCO_2$	H	H	85[a]	132.5—133	1725
Ih	$CH_3(CH_2)_4CO$	$CH_3(CH_2)_4CO_2$	H	H	81[b]	—	1732
Ii	$C_6H_5CH_2OCO$	$C_6H_5CH_2OCO_2$	H	H	77[a]	157—158	1743
Ij	C_2H_5OCO	$C_2H_5OCO_2$	H	H	93[b]	113.5—114	1744
Ik	C_2H_5OCO	$C_2H_5OCO_2$	$(24R)C_2H_5OCO_2$	H	68[a]	101—103	1730
Il	C_2H_5OCO	$C_2H_5OCO_2$	$(24S)C_2H_5OCO_2$	H	80[a]	114—115	1735
Im	C_2H_5OCO	$C_2H_5OCO_2$	H	OH	65[b]	129—130.5	1740

a) Yields of products isolated by recrystallization are given.
b) Yields of products isolated by chromatography are given.
c) Uncorrected melting points are given.

TABLE II. Yields of 5,7-Diene Isomers (III) and Ratios of Isomers (III/IV)

Starting materials Ia—m	% yields[a] of III	Ratios[a] of III/IV
Ia	60.5	2.2
Ib	39.0	2.0
Ic	44.1	2.4
Id	56.7	2.8
Ie	52.8	2.4
If	57.5	2.9
Ig	35.1	1.7
Ih	49.5	2.0
Ii	57.8	4.1
Ij	78.8	5.3
Ik	80.2	4.6
Il	78.2	4.8
Im	79.7	5.5

a) Yields and ratios estimated by UV spectrum are given.

of elimination reaction[4-6] and a number of valuable and interesting modifications of Ziegler's process[7,8] have been described. The reported modifications have been focussed mainly on the combinations of bases and solvents, and little is known about the effect of protective groups.[8] In this work, the effect of protective groups on the bromination-dehydrobromination steps was investigated.

The starting materials (Ia—m) were prepared from variously substituted cholesterol derivatives. The yields, melting points and infrared spectral data are listed in Table I.

These compounds (Ia—m) were brominated with 1,3-dibromo-5,5-dimethylhydantoin and subsequently dehydrobrominated with *sym*-collidine. The ultraviolet (UV) absorption spectra of crude products were measured and the ratios of 5,7-diene isomers (III) to 4,6-diene isomers (IV) and the yields of 5,7-diene isomers (III) were calculated from the maximum absorbance of each isomer. The results are listed in Table II.

In the case of cholesterol derivatives (Ia—e), no effect of protective groups could be found. Thus, the ratios of isomers (III/IV) were almost the same. On the other hand, in the case of 1α-hydroxycholesterol derivatives (If—j), both the ratios of isomers (III/IV) and the yields of 5,7-diene isomers (III) varied considerably depending on the protective groups. When bulky protective groups were used (Ig, h), the yields of 5,7-diene isomers (IIIg, h) decreased, as in the case of the cholesterol derivatives (Ib, c), but when alkoxycarbonyl groups were used as protective groups (Ii, j), the ratios of isomers (III/IV) and the yields of 5,7-diene isomers (IIIi, j) increased remarkably. The ethoxycarbonyl group seemed to be the most effective. To confirm the utility of this group, 1α,24(*R*)-dihydroxycholesterol, 1α,24(*S*)-dihydroxycholesterol and 1α,25-dihydroxycholesterol were protected with the ethoxycarbonyl group, and the ratios of isomers (III/IV) and the yields of 5,7-diene isomers (IIIk—m) were measured. In these cases, similar results were obtained, as shown in Table II (Ik—m).

It is interesting that the protective groups at the 1α-position affect the ratios of isomers (III/IV) and the yields of 5,7-diene isomers (III). 1α-Hydroxy-7-dehydrocholesterol derivatives protected with alkoxycarbonyl groups, especially the ethoxycarbonyl group, were obtained in high yield and, furthermore, were easily separated and purified by a single recrystallization. This method is quite general and has been applied to a variety of 1α-hydroxycholesterol derivatives relevant to the synthesis of biologically active vitamin D_3 metabolites and analogues.

Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a Shimadzu IR-27 G spectrometer, UV absorption spectra on a Hitachi ESP-3T spectrometer, and nuclear magnetic resonance (NMR) spectra on a JEOL JNM-MH-100 (100 MHz) spectrometer (with tetramethylsilane as an internal standard). Column chromatography was carried out on Merck Silica-gel 60 (230—400 mesh).

Typical Procedure for the Allylic Bromination and the Subsequent Dehydrobromination of Cholesterol Derivatives (Ia—m)——A solution of I (5 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (3 mmol) in dry hexane (50 ml) was refluxed for 15 min. The reaction mixture was cooled and filtered. The filtrate was concentrated under reduced pressure. The residue in xylene was added dropwise to a refluxing solution of *sym*-collidine (12.5 ml) and xylene (16.5 ml). After 20 min, the reaction mixture was cooled, filtered and evaporated to dryness. The product was dissolved in ethyl acetate (100 ml) and washed with 1 N HCl, sat. $NaHCO_3$ solution and brine, then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The UV spectra of the crude product were measured in Et_2O as a solvent. The UV spectra showed λ_{max} 232, 241, 254.4 (shoulder), 260 (shoulder), 271, 281 and 293. By calculation based on the absorbance at λ_{max} 281, the reaction yield of the 5,7-diene isomer (III) was determined. On the other hand, from the ratio of absorbance at λ_{max} 281 and 241, the yield ratio of 5,7-diene isomer (III) to 4,6-diene isomer (IV) was calculated. These products were separated and purified by column chromatography and/or recrystallization. The ratios of isomers (III/IV) and the yields of 5,7-diene isomers (III) are listed in Table II.

1α,3β-Diethoxycarbonyloxycholesta-5,7-diene (IIIj)——This was prepared from Ij. A single recrystallization gave pure IIIj as colorless crystals in 62.5% yield, mp 140.5—142 °C (from MeOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1370, 1465, 1740, 2860 and 2950. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 0.62 (3H, s, CH_3), 0.86 (6H, d, $2\times CH_3$), 1.31 (6H, t, $J=7$ Hz, $2\times CH_3$), 4.20 (4H, q, $J=7$ Hz, $2\times CH_2$), 4.86 (2H, br, C(1)–H, C(3)–H), 5.37 and 5.67 (2H, br, C(6)–H, C(7)–H). UV λ_{max}^{EtOH} nm (ε): 262 (shoulder, 7580), 271 (10800), 281 (11530) and 293 (6760). UV $\lambda_{max}^{Et_2O}$ nm (ε): 262 (shoulder, 8910), 271 (12360), 281 (13010) and 293 (7710).

References and Notes

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