EPIMERIZATION OF ESTERS OF STEREOISOMERIC 8-ERGOLINECARBOXYLIC ACIDS ON CARBON $C_{(8)}$*

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Esters of 8β-ergolinecarboxylic acids, *I*—*XI*, exposed to strong bases, such as lithium diisopropylamide, in polar aprotic solvents gave enolates, which were decomposed by suitable proton donors to a mixture of epimers. This contained, apart from the starting 8β-esters, the corresponding 8α-esters, *Ia*—*IVa* and *VIa*—*XIa* (65—80%) and *Va* (about 16%). Exposure of 8α-ester *XIIa* to these conditions produced epimerization on $C_{(8)}$ (about 54%) and, to a small extent, isomerization on $C_{(10)}$, affording ester *I* (*c.* 1%) and *Ia* (*c.* 5%).

The recent finding[1,2] of high pharmacological efficacy of some derivatives of 8α-ergoline has prompted us to study epimerization on $C_{(8)}$ of (5*R*,8*R*,10*R*)-8-methoxycarbonyl-6-methylergoline (*I*, methyl ester of D-9,10-dihydrolysergic-I acid**), and analogous substituted esters, *II*—*XI*. This epimerization would make the mentioned 8α-ergolines readily accessible. A similar epimerization of an ester of the 8α-series, *viz.* (5*R*,8*S*,10*S*)-8-methoxycarbonyl-6-methylergoline (*XIIa*, methyl ester of D-9,10-dihydroisolysergic-II acid**) would open the way to ester *XII*, which is rather difficult to obtain.

(5*R*,8*S*,10*R*)-8-Methoxycarbonyl-6-methylergoline (*Ia*, methyl ester of D-9,10-dihydroisolysergic-I acid) has so far been prepared *via* peptide derivatives of (5*R*,8*S*,10*R*)-8-ergolinecarboxylic acid (*e.g. via* dihydroergotaminine-I (ref.[4])), or by selective hydrogenation of (5*R*,10*R*)-8-methoxycarbonyl-6-methyl-7,8-didehydroergoline[5]; either way is a multistep synthesis from the starting 8β-compound and gives a rather poor overall yield. As is known, derivatives of (5*R*,8*R*)-6-methyl-9,10-didehydro-8-ergolinecarboxylic acid (D-lysergic acid) readily undergo epimerization on $C_{(8)}$ by the action of alkaline agents in polar protic solvents even at room temperature[6]; the reaction is favourably influenced by the presence of a double bond at the 9,10-position of the molecule, which mediates conjugation of the enolate intermediate with the aromatic system of the indole part of the molecule[7]. As a result of saturation of this double bond, derivatives of the esters *I* and *Ia* fail to epimerize under the given con-

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** Nomenclature by Stoll and coworkers[3].

ditions[8]. Under more drastic conditions, such as the action of potassium tert-butoxide in tert-butanol at 80°C (ref.[9]), or potassium methoxide in methanol at 80°C (ref.[10]), or sodium hydride in boiling xylene[11], Bernardi and coworkers succeeded in epimerizing some esters and amides of 8-ergolinecarboxylic acids (*e.g. XIIa* to *XII*, equilibrium proportion 7 : 3).

TABLE I

Epimerization of ester *I* with sodium hydride[a]

Solvent	Temperature °C	Time[b] min	Content of *Ia* %
Toluene	25	360	28·0
Dimethylformamide	10	20	23·8
Dimethyl sulphoxide	10	20	16·1
Hexamethylphosphorictriamide	20	20	24·3
Tetrahydrofurane	20	80	30·2

[a] Four equivalents of NaH were used; samples were taken at 10 min intervals (ar 1 h intervals for toluene), brought into an excess of 2M-HCl at 0°C and pH of the solutions was brought to *c.* 8. Extracts in dichloromethane were dried ($MgSO_4$) and subjected to HPLC; [b] time of the reaction after which the content of *Ia* no longer increased.

TABLE II

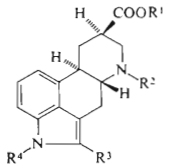
Contents of 8α- and 8β-epimers in the reaction mixture after epimerization of esters *I*—*XI*

Starting ester[a]	*I*	*II*	*III*	*IV*	*V*[b]	*VI*	*VII*	*VIII*	*IX*[c]	*X*	*XI*
Contents of epimers *Ia*—*XIa*, %	79·5	68·1	80·7	72·3	16·6	73·6	68·8	70·7	76·3	65·9	65·8
Temperature, °C	−20	−20	−20	−15	0	−10	−10	−20	−20	−20	−20
Time, min[d]	10	10	10	10	120	20	20	20	10	10	10

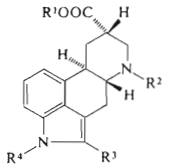
[a] Unless otherwise stated, the epimerization was conducted by method C in tetrahydrofurane with 4 equivalents of lithium diisopropylamide; samples were taken at 10 min intervals and worked up as given in Table I; [b] eight equivalents of the base were employed; [c] two equivalents of the base were employed; [d] time of the reaction after which the contents of the axial epimer *Ia*—*XIa* no longer increased.

In our study of epimerization of esters of 8-ergolinecarboxylic acids we first dealt with epimerization of the ester *I* on $C_{(8)}$ by sodium hydride as base in various media and at different temperatures. The results are given in Table I. In the use of polar aprotic solvents the epimerization of the ester *I* by sodium hydride proceeded at a higher rate, but the portion of the axial epimer *Ia* was not increased. Similar results were obtained even in the use of potassium tert-butoxide in the given solvents.

It seems likely that under the given conditions the reaction is thermodynamically controlled, with the two epimers attaining an equilibrium *via* an ester-enolate anion. In this equilibrium, which is not much affected by the base or solvent employed, the stabler[12] equatorial epimer *I* prevails (the ratio of $I : Ia \doteq 7 : 3$).



I – XI



Ia – XIa

$R^2 = CH_3$, $R^3 = R^4 = R^5 = H$
I, Ia, $R^1 = CH_3$
II, IIa, $R^1 = C_2H_5$
III, IIIa, $R^1 = -CH(CH_3)_2$
IV, IVa, $R^1 = -(CH_2)_3CH_3$

$R^1 = CH_3$, $R^3 = R^4 = R^5 = H$
V, Va, $R^2 = H$
VI, VIa, $R^2 = C_2H_5$
VII, VIIa, $R^2 = CH_2CH_2CH_3$
VIII, VIIIa, $R^2 = -CH_2CH{=}CH_2$

$R^1 = R^2 = CH_3$
IX, IXa, $R^3 = R^5 = H$, $R^4 = CH_3$
X, Xa, $R^3 = Br$, $R^4 = R^5 = H$
XI, XIa, $R^3 = R^4 = H$, $R^5 = OCH_3$

Molecular models reveal that the enolate that is common to the esters *I* and *Ia* is sterically more shielded from the β-side. The bulky solvated cation, forming an ionic pair[13] with the enolate anion, is probably coordinated on the sterically more accessible α-side of the plane enolate. Conversely, in hydrolysis of the enolate, *i.e.* a kinetically controlled irreversible reaction, the electrophilic attack by protons should be expected from the β-side (equatorial attack), leading to the desired axial epimer.

Using a described procedure[14] (the action of lithium diisopropylamide in tetrahydrofuran), we prepared lithium enolate of the ester *I*, which was decomposed *in situ* by a suitable source of protons (water alone or acidified with an organic or inorganic acid, a low-molecular-weight aliphatic alcohol). The axial epimer *Ia* indeed prevailed in the reaction mixture and its content did not much change (72 to

TABLE III

Esters of 8α- and 8β-ergolinecarboxylic acids

Compound	Yield, % (method)	M.p., °C solvent	$[\alpha]_D^{20}$ [a]	Formula (mol.mass)	Calculated/Found % C	% H	% N
II[b]	82 (*A*)	167—168 ethanol–water	— 99·8	$C_{18}H_{22}N_2O_2$ (298·4))	72·46 72·27	7·43 7·42	9·39 9·38
IIa[c]	52 (*C*)	159—161 ethanol–water	— 55·7	$C_{18}H_{22}N_2O_2$ (298·4)	72·46 72·19	7·43 7·40	9·39 9·38
III[d]	76 (*A*)	224—226 benzene	—109·3	$C_{19}H_{24}N_2O_2$ (312·4)	73·05 72·98	7·74 7·80	8·97 8·83
IIIa[e]	68 (*C*)	162—164 benzene–hexane	— 80·3	$C_{19}H_{24}N_2O_2$ (312·4)	73·05 73·06	7·74 7·79	8·97 8·83
IV[f]	57 (*A*)	169—172 benzene	—103·1	$C_{20}H_{26}N_2O_2$ (326·4)	73·59 73·52	8·03 8·04	8·58 8·45
IVa[g]	54 (*C*)	82—88 benzene–hexane	— 75·5	$C_{20}H_{26}B_2O_2$ (326·4)	73·59 73·24	8·03 8·06	8·58 8·53
VII[h]	73 (*B*)	203—205 benzene	— 82·1	$C_{19}H_{24}N_2O_2$ (312·4)	73·05 72·96	7·74 7·80	8·97 9·04
VIII[i]	80 (*B*)	143—146 hexane	—117·2	$C_{19}H_{22}N_2O_2$ (310·3)	73·55 73·53	7·15 7·45	9·03 9·04
IXa[j]	56 (*C*)	160—162 methanol–water	— 74·2	$C_{18}H_{22}N_2O_2$ (298·4)	72·46 72·60	7·43 7·61	9·39 9·32
Xa[k]	42 (*C*)	185—186 methanol–water	— 61·9	$C_{17}H_{19}BrN_2O_2$ (363·3)	56·21 55·99	5·27 5·36	7·71 7·62
XII[l]	41 (*C*)	169—170 methanol	75·4	$C_{17}H_{20}N_2O_2$ (284·4)	71·81 71·84	7·09 7·20	9·85 10·00

[a] Concentration 0·2, pyridine. [b] UV spectrum: λ_{max} (log ε) 291 (3·75), 281 (3·84), 223 (4·53) nm; IR spectrum: 3 340 (NH), 2 820 (NCH_3), 1 720 (ester) cm^{-1}; ^1H NMR spectrum: δ 8·15 (bs, 1 H, NH); 6·90—7·25 (m, 3 H, ArH); 6·85 (bs, 1 H, $C_{(2)}$—H); 4·22 (q, J = 7·0 Hz, 2 H, $COOCH_2$.CH_3); 2·50 (s, 3 H, NCH_3); 1·31 (t, J = 7·0 Hz, 3 H, $COOCH_2CH_3$). [c] UV spectrum: λ_{max} (log ε) 291 (3·63), 281 (3·72), 224 (4·43) nm; IR spectrum: 3 340 (NH), 2 820 (NCH_3), 1 720 (ester) cm^{-1}; ^1H NMR spectrum: δ 8·05 (bs, 1 H, NH); 6·90—7·30 (m, 3 H, ArH); 6·80 (bs, 1 H, $C_{(2)}$—H); 4·20 (q, 2 H, J = 7·0 Hz, $COOCH_2CH_3$); 2·48 (s, 3 H, NCH_3); 1·25 (t, J = 7·0 Hz, 3 H, $COOCH_2CH_3$). [d] UV spectrum: λ_{max} (log ε) 293 (3·77), 282·5 (3·85), 226 (4·51) nm; IR spectrum: 3 340 (NH), 2 825 (NCH_3), 1 710 (ester) cm^{-1}. [e] UV spectrum: λ_{max} (log ε) 293 (3·76), 282 (3·84), 225 (4·58) nm; IR spectrum: 3 300 (NH), 2 780 (NCH_3), 1 730 (ester) cm^{-1}; ^1H NMR spectrum: δ 8·00 (bs, 1 H, NH); 6·90—7·40 (m, 3 H, ArH); 6·82 (bs, 1 H, $C_{(2)}$—H); 5·10 (m, 1 H, $COOCH(CH_3)_2$; 2·40 (s, 3 H, NCH_3); 1·15 (q, J = 6·0 Hz, 6 H, $COOCH(CH_3)_2$). [f] UV spectrum: λ_{max} (log ε) 291 (3·75), 281 (3·84), 224 (4·52) nm; IR spectrum: 3 340 (NH), 2 820 (NCH_3), 1 720 (ester) cm^{-1}; ^1H NMR spectrum: δ 8·10 (bs, 1 H, NH); 6·85—7·20 (m, 3 H, ArH); 6·83

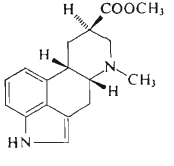
80%) by conducting the epimerization in a temperature range from −50 to 20°C. The same proportion of *I* and *Ia* was naturally obtained in epimerization of the 8α-ester *Ia*, conducted under the same conditions.

Use of non-polar solvents led to mixtures containing much less portions of the axial epimer (*e.g.* the conversion *I* → *Ia* in toluene was only 28%), whereas in tetrahydrofuran or 1,2-dimethoxyethane as much as 80% of the 8α-epimer was obtained. The addition of dipolar aprotic solvents[15] (dimethylformamide, hexamethylphosphorictriamide) or the use of other dialkylamides (lithium diethylamide, potassium diisopropylamide) did not increase the content of the axial epimer *Ia*.

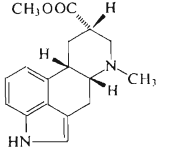
To ascertain the extent of applicability of this mode of epimerization we tried it with other esters of 8β-ergolinecarboxylic acid, *II*−*XI*.

As can be seen from Table II, replacement of the methyl group by a higher alkyl group (esters *II*−*IV*), as well as substitution at positions 1,2,6 and 10 (esters *VI*−*XI*) had no significant influence on the portion of the axial 8α-epimer, whose content after the epimerization ranged between 66 and 80%. An exception, was the 6-nor derivative *V*, where the corresponding N-anion, produced by deprotonization of the secondary amine at the 6-position of the molecule, markedly affected the possibility of formation and the stereochemistry of the ester-enolate anion. In this case an addition of hexamethylphosphorictriamide substantially raised the content of the axial epimer *Va* (from 16·6 to 40·3%). The properties of the newly prepared starting esters, *II*−*IV*, *VII*, *VIII*, and the epimerization products, *IIa*−*IVa*, *IXa*, *Xa*, are given in Table III; the properties of the esters *VIIa*, *VIIIa* see[1].

(bs, 1 H, $C_{(2)}$—H); 4·12 (t, J = 7·0 Hz, 2 H, $COOCH_2(CH_2)_2CH_3$); 2·48 (s, 3 H, NCH_3); 1·50 (m, 4 H, $COOCH_2CH_2CH_2CH_3$), 0·90 (t, 3 H, $COO(CH_2)_3CH_3$). [g] UV spectrum: λ_{max} (log ε) 291 (3·73), 281 (3·83), 224 (4·52) nm; IR spectrum: 3 350 (NH), 2 815 (NCH_3), 1 720 (ester) cm^{-1}; ^1H NMR spectrum: δ 7·98 (bs, 1 H, NH); 6·85—7·20 (m, 3 H, ArH); 6·80 (bs, 1 H, $C_{(2)}$—H); 4·15 (t, 2 H, J = 7·0 Hz, $COOCH_2(CH_2)_2CH_3$); 2·40 (s, 3 H, NCH_3); 1·50 (bm, 4 H, $COOCH_2CH_2CH_2CH_3$); 0·89 (t, 3 H, $COO(CH_2)_3CH_3$). [h] UV spectrum: λ_{max} (log ε) 289 (3·79), 279 (3·87), 221 (4·59) nm; IR spectrum: 3 370 (NH), 1 750 (ester) cm^{-1}; ^1H NMR spectrum: δ 8·00 (bs, 1 H, NH); 6·80—7·30 (m, 3 H,ArH); 6·82 (bs, 1 H, $C_{(2)}$—H); 3·70 (s, 3 H, $COOCH_3$); 0·88 (t, 3 H, $N(CH_2)_2CH_3$). [i] UV spectrum: λ_{max} (log ε) 290 (3·79), 279 (3·87), 222 (4·59) nm; IR spectrum: 3 360 (NH), 1 735 (ester) cm^{-1}; ^1H NMR spectrum: δ 8·00 (bs, 1 H, NH); 6·90—7·20 (m, 3 H, ArH); 6·85 (bs, 1 H, $C_{(2)}$—H); 5·90 (m, 1 H, $NCH_2CH{=}CH_2$); 5·22 (bd, J = 17·0 Hz, $NCH_2CH{=}CH\mathbf{H}$ *trans*); 5·18 (bd, J = 9·0 Hz, $NCH_2CH{=}C\mathbf{H}H$ *cis*); 3·70 (s, 3 H, $COOCH_3$); 3·50 (bm, 2 H, $NCH_2CH{=}CH_2$). [j] UV spectrum: λ_{max} (log ε) 299 (3·83), 290 (3·86), 225 (4·54) nm; IR spectrum: 2 790 (NCH_3), 1 720 (ester) cm^{-1}; ^1H NMR spectrum: δ 6·80—7·40 (m, 3 H, ArH); 6·69 (s, 1 H, $C_{(2)}$—H); 3·75 (s, 3 H, NCH_3); 3·70 (s, 3 H, $COOCH_3$); 2·40 (s, 3 H, NCH_3). [k] UV spectrum: λ_{max} (log ε) 291 (3·77), 281 (3·96), 276 (3·96), 225 (4·61) nm; IR spectrum: 3 220 (NH), 1 710 (ester) cm^{-1}; ^1H NMR spectrum: δ 7·98 (bs, 1 H, NH), 6·80—7·20 (m, 3 H, ArH), 3·70 (s, 3 H, $COOCH_3$), 2·40 (s, 3 H, NCH_3). [l] UV spectrum: λ_{max} (log ε) 290 (3·76), 279 (3·83), 223 (4·51) nm; IR spectrum: 3 240 (NH), 2 780(NCH_3), 1 720 (ester) cm^{-1}; ^1H NMR spectrum: δ 7·89 (bs, 1 H, NH); 6·85—7·30 (m, 3 H, ArH); 6·78 (bs, 1 H, $C_{(2)}$—H); 3·70 (s, 3 H, $COOCH_3$); 2·30 (s, 3 H, NCH_3).



XII



XIIa

(5*R*,8*R*,10*S*)-8-Methoxycarbonyl-6-methylergoline (*XII*, methyl ester of D-9,10-dihydrolysergic-II acid[3]) can also be prepared by this epimerization from the accessible 8-equatorial isomer *XIIa* ((5*R*,8*S*,10*S*)-8-methoxycarbonyl-6-methylergoline), although the situation is here complicated by the formation of their 10-isomers, whose proportions depend on the reaction time, the solvent and the base (Table IV). However, the reaction gives good yields of the 8β-isomer *XII*, thus being the first rewarding method for its preparation[16].

EXPERIMENTAL

The melting points were determined on the Kofler stage and are not corrected. The analytical samples were dried at a reduced pressure of 30 Pa and a temperature of 80—100°C. The specific optical rotations were determined in pyridine, employing a polarimeter Perkin–Elmer 141, and correspond to substances free of the crystal solvents. The ultraviolet spectra were measured with a spectrophotometer Unicam SP 8000, using 0·001% solutions in methanol. The infrared spectra

TABLE IV
Epimerization of ester *XIIa*

Base[a]	Solvent[b]	Temperature °C	Time min	Contents of isomers, %			
				I	*XII*	*Ia*	*XIIa*
LDA[c]	THF	−20	15	0·8	54·0	5·2	40·0
LDA[c]	THF/HMPT[d]	−20	5	1·2	54·5	6·3	38·0
LDA[c]	THF/HMPT[d]	−20	45	2·4	55·2	10·8	31·6
NaH	HMPT	10	30	0	29·1	0	70·9

[a] Four equivalents of the base were used; the mixture was worked up for HPLC as described in Table I; [b] THF tetrahydrofurane, HMPT hexamethylphosphoric triamide; [c] lithium diisopropylamide; [d] tetrahydrofurane with 4 equivalents of hexamethylphosphoric triamide.

in KBr pellets were recorded in an apparatus Perkin–Elmer 577. The ^{1}H NMR spectra were measured employing a spectrometer Tesla BSC 487 (80 MHz) and approx. 10% solutions in deuteriochloroform, with tetramethylsilane as internal standard; the values of σ are given in ppm. HPLC of the compounds prepared was performed in a chromatograph Varian 8500, equipped with a spectrophotometer Variscan 635, stop-flow dosing device, integrator CDS-111 and recorder A-25 (Varian AG, U.S.A.). Column: Micro Pak Si 5, 25 × 0·2 cm (Varian AG); mobil phase: dichloromethane–hexane–2-propanol–triethylamine (55 : 45 : 1 : 0·1); the flow rate was 60 ml/h, detection at 280 nm, sensitivity 0—0·5 AU. TLC was carried out on thin layers of silica gel Merck DC-Fertigplatte Kieselgel 60 F 254, using a system benzene–acetone–25% aqueous ammonia 30 : 20 : 0·1 (S-1), or on reflex foils of silica gel with a luminscent indicator (Silufol UV 254 Kavalier) in systems S—1, chloroform–ethanol–triethylamine 90 : 10 : 5, or benzene–dioxan–ethanol–triethylamine 50 : 40 : 10 : 5. The spots were detected under UV light at 254 nm or by spraying the plate with a 0·5% solution pf *p*-dimethylaminobenzaldehyde in cyclohexane, followed by exposing it to vapour of hydrogen chloride. Preparative TLC was conducted on silica gel plates Merck PSC Fergitplatte Kieselgel 60 KF 254. In column chromatography the compounds were separated on silica gel Merck Kieselgel 60 or Silpearl Kavalier in system S—1.

Esters *I—IV* and *IX* (Method *A*)

To 45 ml of an alcohol was added dropwise, under stirring and chilling to −10 to −20°C, 0·625 g (5·25 mmol) of thionyl chloride, then 5 mmol of the corresponding acid was added (1·35 g of (5*R*,8*R*,10*R*)-6-methyl-8-ergolinecarboxylic acid[17] for esters *I—IV*; 1·42 g of (5*R*,8*R*,10*R*)-1,6-dimethyl-8-ergolinecarboxylic acid[18] for ester *IX*) and the suspension was heated under a reflux condenser until the acid had dissolved (to the boil for 1·5 h with esters *I*, *II* and *IX*, for 23 h with *III*, and to 100°C for 1 h with *IV*). The alcohol was distilled off *in vacuo*, the remaining ester hydrochloride was taken into 80 ml of water, the solution was alkalinized with 1M-$NaHCO_3$ and the precipitated product was recrystallized. The physicochemical constants and the yields of the esters *I* (m.p. 185—187°C, $[\alpha]_D^{20} = -103°$, *c* 0·3, pyridine, yield 90%) and *IX* (m.p. 116—118°C, $[\alpha]_D^{20} = -105°$, *c* 0·3, pyridine, yield 81%) were consistent with the reported data[4,18]; for yields and physico-chemical properties of the esters *II—IV* see Table III.

(5*R*,8*R*,10*R*)-6-Alkyl-8-methoxycarbonylergolines *VI—VIII* (Method *B*)

(5*R*,8*R*,10*R*)-8-methoxycarbonylergoline[19] (*V*) was alkylated with an alkyl bromide (3 equivalents) in dimethylformamide, in the presence of anhydrous potassium carbonate (3 equivalents), by a described procedure[19]. The physico-chemical constants of the ester *VI* (m.p. 172—174°C, $[\alpha]_D^{20} = -76°$, *c* 0·2, pyridine) were consistent with the reported data[19]. For yields and physico-chemical properties of the new esters *VII* and *VIII* see Table III.

Preparation of Esters *Ia—XIa* and *XII* by Epimerization of Esters *I—XI* and *XIIa* (Method *C*)

To a solution of 0·04 mol of lithium diisopropylamide (prepared[20] from diisopropylamine (4·05g, 0·04 mol) and a 1·5M hexane solution of butyllithium (26·6 ml, 0·04 mol)) in 50 ml of tetrahydrofurane, under stirring and chilling to −20°C, was added dropwise a solution of 0·01 mol of the esters *I—IV*, *VI—VIII*, *X* (ref.[21]), *XI* (ref.[11]), *XIIa* (ref.[16]), or 0·005 mol of *V* (ref.[19]), or 0·02 mol of *IX* (ref.[18]), in a minimum amount of tetrahydrofurane. The mixture was stirred for 30 min at −20°C, then chilled to −50°C and neutralized with 10% aqueous acetic acid to *c.* pH 7. The volatile portions were removed *in vacuo* (water pump) at 40°C, the residue was stirred up in a saturated aqueous solution of sodium hydrogen carbonate and the product was extracted

into chloroform. The solvent was distilled off and the residue was resolved by column chromatography or preparative TLC, or HPLC (ester *Va*). The separated starting ester can be re-employed for the epimerization.

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