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STRUCTURE AND STEREOCHEMISTRY OF ZEXBREVIN, A 3 (2H) FURANONE GERMACRANOLIDE*

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Abstract—Formulation of zexbrevin as 1 is based mainly on analysis of the NMR spectra† of zexbrevin (1) and of the ketone 8 (Tables I and II).

CONTINUING our studies of the sesquiterpenoid constituents of members of the *compositae* family we have isolated from the aereal part of the Schrub *Zexmenia brevifolia* a new germacranolide for which we have proposed the name zexbrevin and formulated as 1 based on the following evidence.

Zexbrevin $C_{19}H_{22}O_6$ m.p. 217–218°, $[\alpha]_D$ + 41°, contains a γ-lactone conjugated with an exocyclic methylene group as indicated by its IR bands (1760 and 1639 cm^{-1}) and the characteristic NMR doublets[1] at 5·68 (J = 3 Hz) and 6·30 ppm (J = 3·5 Hz). Zexbrevin contains a methacrylic ester as shown by the IR band at 1710 cm^{-1} and the signals in the NMR spectrum at 1·82 ppm (3H, doublet of doublets J_{cx_3} = 1·5 Hz, J_{dx_3} = 1·0 Hz) due to its vinylic Me group, the terminal double bond of the ester is shown in the NMR spectrum as two complex signals, both resulting of the overlapping of two quartets, Hc appeared as five peaks centred at 5·95 ppm with relative intensities 1, 4, 6, 4, 1 and Hd as six peaks centred at 5·57 ppm with relative intensities 1, 3, 4, 4, 3, 1. In the mass spectrum of zexbrevin the parent peak appeared at *m/e* 69 ($CH_2{=}C[CH_3]{-}\overset{+}{C}{\equiv}O$) giving further support to the presence of the methacrylic ester.

The two remaining O atoms in zexbrevin are present as part of a 3 (2H) foranone[2, 3] as indicated by the characteristic IR bands at 1690 cm^{-1} (keto group) and at 1590 cm^{-1} (strong band due to the enolic double bond).

The UV spectrum of zexbrevin confirms the presence of the 3 (2H) furanone (λ max 259 mμ; ε, 11,255); the lactone and the methacrylic ester are shown by an additional maximum in the UV spectrum (λ max 210 mμ; ε, 18,600).

The oxygen bridge of the dihydrofuranone lies between positions C-3 and C-10 of the germacranolide, as represented in partial formula A. The Me group at C-10 appeared in the NMR spectrum as a singlet at 1·38 ppm (3H). The signal which appeared at about 4 ppm in zexbrevin and its derivatives is attributed to the lactone closure since it did not change its position after saponification. Whereas the signal appearing at lower field (5·14 ppm in 1) moved upfield in the desmethacryl derivatives

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† The NMR spectra were run on a Varian A-60A and a Varian HA-100 spectrometers. The spin decoupling experiments were carried out with an audio oscillator Hewlett-Packard, Model 200 CD and 200 AB.

(see later) and may be assigned to the hydrogen located at the carbon bearing the ester group.

The ester group and the C-7 hydrogen must be at vicinal positions as shown by spin-decoupling experiments (Fig. 1) when H-7 was irradiated at 3 ppm the doublet of doublet of doublet at 5·14 ppm (ester attachment) collapsed to a doublet of doublets

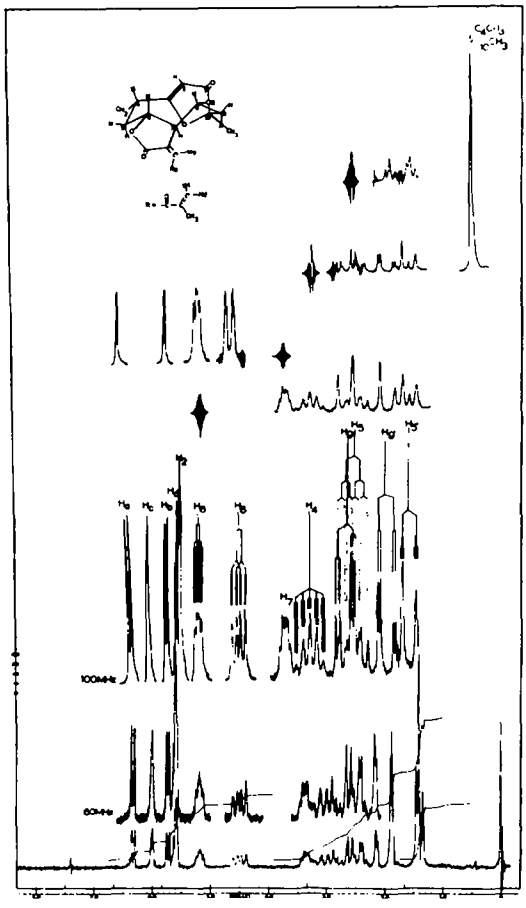
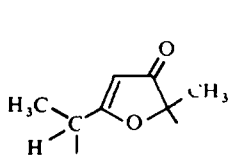
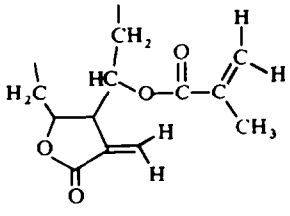


FIG 1.

and the doublet of doublet of doublet at 4·45 ppm (lactone closure) was transformed into a doublet of doublets simultaneously, thus permitting us to write partial formula B.



A



B

The ester group of zexbrevin must be placed at C-8 since its neighbouring methylene group (C-9) showed eight signals as an ABX pattern (C-5 methylene give 16 signals) which on irradiation at 5·14 ppm (H-8) is simplified to four signals as an AB pattern. These experiments permit us to locate the ester group at C-8 and the lactone closure at C-6 as depicted in formula 1.

Hydrogenation of zexbrevin (1) with paladium on charcoal afforded tetrahydrozexbrevin (**2**) which still contains the 3 (2H) furanone as indicated by the IR bands at 1705 and 1600 cm^{-1}, the UV absorption at 260 mμ (ε, 12,450) and the NMR signal at 5·56 ppm for the vinylic proton at C-2; H-8 is shown by a doublet of doublet of doublet centred at 5·1 ppm and the lactone closure showed a signal of similar multiplicity at 4·58 ppm.

The C-2 double bond of tetrahydrozexbrevin was saturated catalytically with platinum oxide in acetic acid, giving rise to hexahydrozexbrevin (**3**).

A sodiumborohydride reduction of compound **2** produced octahydrozexbrevin (**4**) in which both the C-1 carbonyl group and the C-2 double bond have been reduced. The latter was also obtained from hexahydrozexbrevin (**3**) by sodiumborohydride reduction.

Hexahydrozexbrevin (**3**) afforded on basic hydrolisis the free compound (**6**) which did not show the signal due to the ester attachment, instead it showed a complex signal at 4·22 ppm which includes the lactone and ester closures, a milder basic treatment of **3** resulted in a mixture of the alcohol (**6**) and 11 epihexahydrozexbrevin (**7**). In the above experiments we did not find evidence of another free compound (lactone reoriented to C-8).

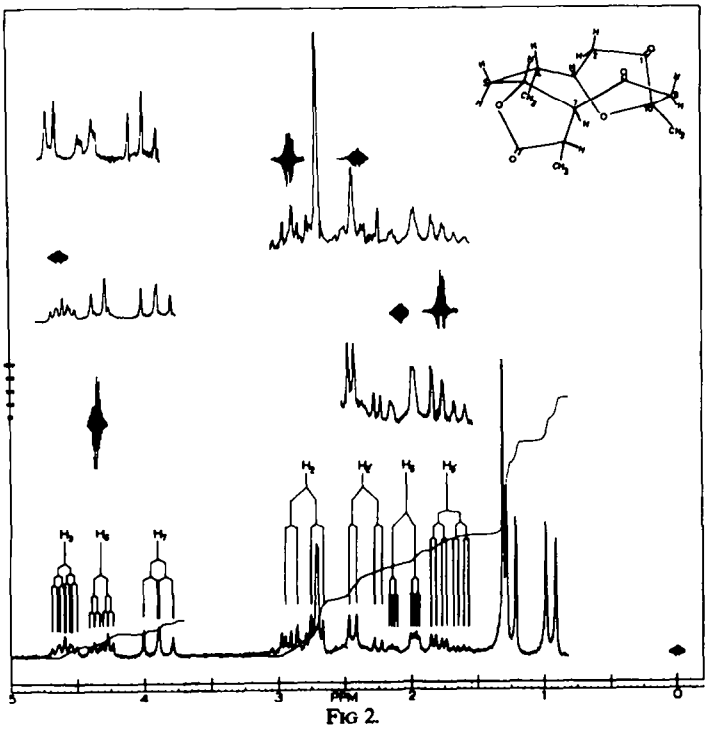


FIG 2.

A chromic acid oxidation of desmethacryl-11-epihexahydrozexbrevin (**6**) afforded the ketone **8**. A detailed first order analysis of the NMR spectrum of **8** (Fig. 2) was possible due to the relatively large difference in chemical shifts of the vicinal protons. This, combined with spin decoupling experiments (double and triple irradiations) provided enough evidence for establishing the constitution and stereochemistry of this ketone as depicted in **8**.

The hydrogen on the C atom bearing the lactone produced an octuplet at 4·5 ppm due to interaction with H-7 (3·9 ppm) and with both protons at C-5 (16 signals as an ABMX pattern centred at 1·7 ppm), the multiplicity observed for the protons at C-5 is only possible with the lactone group closed to C-6. If the lactone group would be oriented to C-8 there would be no methylene group in the molecule which could show 16 signals. In order to establish the stereochemistry of **8** we assume that the side chain at C-7 is β oriented as in all the sesqueterpene lactones already reported.[4, 5] This is supported by the fact that H-7 is close to the heterocyclic oxygen of the furan ring

TABLE 1. NMR SPECTRUM OF ZEXBREVIN 1

Chemical shifts (ppm)	Multiplicity	Coupling constants (Hz)		Dihedral angles[a]	
H-2 = 5·54	d	$J_{2,4}$[b]	1·2	20	
H-4 = 3·04	m	$J_{4,5}$	7	4,5	68 or 107
		$J_{4,5'}$	1·4	4,5′	33 or 131
		J_{4,CH_3}	7		
H-5 = 2·60	d,d,d	$J_{5,5'}$	14·5		
H-5′ = 2·06	d,d,d				
H-6 = 4·45	d,d,d	$J_{6,5}$	9	6,5	18 or 138
		$J_{6,5'}$	1	6,5′	70 or 105
H-7 = 3·30	m	$J_{6,7}$	5	6,7	45 or 124
H_a = 6·30	d	$J_{a,7}$	3·5[b]		
H_b = 6·30	d	$J_{b,7}$	3[b]		
		$J_{7,8}$	1	7,8	71 or 105
H-8 = 5·14	d,d,d	$J_{8,9}$	4·5		48 or 22
		$J_{8,9}$	2·5	8,9′	60 or 113
H-9 = 2·67	d,d	$J_{9,9'}$	15·5		
H-9′ = 2·27	d,d				
C_{10}-CH_3 = 1·38	s				
C_4-CH_3 = 1·34	d				

[a] For each J value Karplus equation calculates two possible dihedral angles. Angles underlined are those more compatible with the Dreiding model of the molecule.

[b] Allylic coupling.

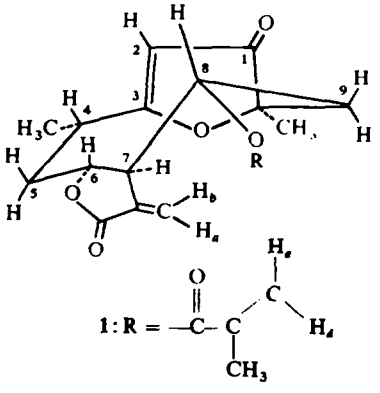
since it produces a signal at an abnormally low chemical shift value (3·9 ppm d,d; J = 11 Hz). This proximity requires an α oriented C-7 hydrogen, as shown by a Dreiding model of the ketone **8**.

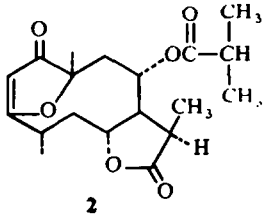
The large J values for the interactions of H-7 with its vicinal hydrogens (H-6, H-7; J = 10 Hz; H-7, H-11; J = 11 Hz) established in accord with Karplus equation[6] (Table 1) the configuration for H-6 and H-11 as shown in **8**.

The Me group at C-10 must be α oriented in order to permit the proximity of the ethereal oxygen to H-7.

The stereochemistry deduced for the asymmetric centres C-6, C-7 and C-10 for the ketone **8** may be extended to zexbrevin (**1**) in which it only remains to determine the configuration at C-4 and C-8.

The configuration of the oxygen function at C-8 was found to be α by the application of Horeau's method[6–9] to the free compound (**6**). The Me group at C-4 is probably α oriented since the allylic coupling constant between H-4 and H-2 in zexbrevin (**1**) is 1·2 Hz; this small J value requires an angle between H-4 and C-2 double bond of about 20–30°.[10, 11] A larger J value would be expected for a β oriented C-4 Me group. Hence the structure and the more probable stereochemistry for zexbrevin must be as depicted in formula I.





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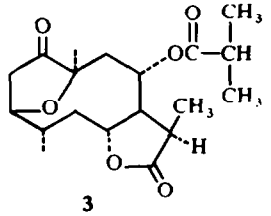

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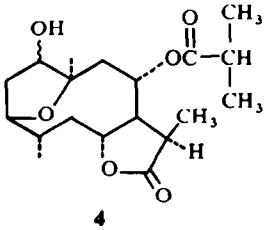

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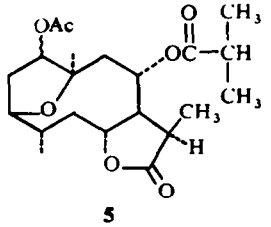

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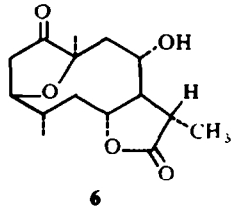

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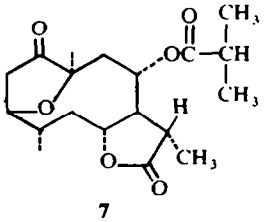

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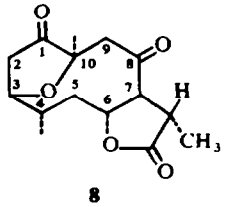

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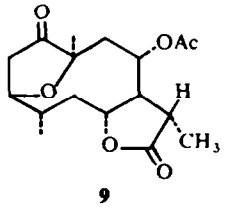

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TABLE 2. NMR SPECTRUM OF KETONE 8

Chemical shifts in δ values (ppm)	Multiplicity	Coupling constants (Hz)		Dihedral angles	
H-2 = 2·77	d,d	$J_{2,3}$	9·3	16	139
		$J_{2,2'}$	19		
H-2′ = 2·4	d,d	$J_{3,2'}$	5·5	42	126
H-3 = 4·59	d,d,d	$J_{3,4}$	4·0	51	120
		$J_{4,5'}$	8	26	135
H-4 = 2·9	m	$J_{4,5}$	2	65	110
		J_{4,CH_3}	7		
H-5 = 2·02	d,d,d	$J_{5,6}$	3·5	54	118
		$J_{5,5'}$	17		
H-5′ = 1·75		$J_{5',6}$	3·5	54	118
H-6 = 4·33	d,d,d	$J_{6,7}$	10	0	142
H-7 = 3·9	d,d	$J_{7,11}$	11		146
H-9,9′ = 2·7	s				
C_4-CH_3 = 1·24	d	J	7		
C_{10}-CH_3 = 1·3	s				
C_{11}-CH_3 = 0·95	d	J	7		

EXPERIMENTAL*

Isolation of zexbrevin. Zexmenia brevifolia† dried and ground (9·4 Kg) was extracted twice with EtOH (10 l) under reflux for 8 hr. The combined extracts were concentrated to 12 l. and treated with lead acetate soln until no precipitation was observed, the suspension was left at room temp overnight, filtered and concentrated to half its volume and extracted with $CHCl_3$. The extract was evaporated to dryness, the residue (120 g) was dissolved in a mixture of benzene–hexane 4:1 and chromatographed on 1·5 Kg alumina Alcoa F-20. Zexbrevin crystallized in the fractions eluted with benzene containing 15% hexane, a recrystallization from acetone–ether afforded 14·8 g, m.p. 211–214°, a recrystallization from acetone isopropyl–ether raised the m.p. to 217–218°, $[\alpha]^{27}_{CHCl_3}$ +41° (*c*, 1·02), λ_{max} 210, 259 mμ; ε, 18,600 and 11,255, respectively; ν_{max} 1760, 1710, 1690, 1625, 1630 and 1585 cm^{-1}. (Found: C, 65·87; H, 6·41; O, 27·82. Calc. for $C_{19}H_{22}O_6$: C, 65·88; H, 6·40; O, 27·72%).

Tetrahydrozexbrevin (2). A soln of zexbrevin (2·75 g) in MeOH (100 ml) was hydrogenated with Pd/C (300 mg) until the H_2 uptake ceased, the catalyst was filtered off and the soln concentrated, the substance crystallized on addition of isopropyl-ether affording 1·6 mg tetrahydrozexbrevin m.p. 156–157°, λ_{max} 260 mμ; (ε, 12,499); ν_{max} 1770, 1735, 1705 and 1600 cm^{-1}; NMR δ; 4·6 (H-6), 5·1 (H-8), 5·58 (H-2). (Found: C, 65·29; H, 7·35; O, 27·42. Calc. for $C_{19}H_{26}O_6$: C, 65·12; H, 7·48; O, 27·40%).

Hexahydrozexbrevin (3) *and octahydrozexbrevin* (4). A soln of zexbrevin (2 g) in AcOH (50 ml) containing 3 drops perchloric acid was hydrogenated until the uptake of H_2 ceased. The catalyst was filtered off and the soln was treated with solid Na_2CO_3 (2 g) and concentrated in vacuo to a reduced volume.

Hexahydrozexbrevin (1·5 g) m.p. 120–125° crystallized on addition of water. A recrystallization from acetone-isopropyl ether raised the m.p. to 125–127°; ν_{max} 1755, 1725 cm^{-1}; NMR 100 mHz: δ H-8, 4·95 (1H d,d,d; J = 1·3, 3·5 and 4·8 Hz), H-6, 4·33 (1H d,d,d; J = 4, 5 and 8·5 Hz); H-3, 3·83 (1H d,t; J = 7·5

* All m.ps were carried out in a Fisher Jones m.p. apparatus and are uncorrected. Analyses were determined by Dr. Franz Pascher, Bonn, W. Germany.

† We are grateful to Dr. A. Gómez Pompa from the Botanical Department of the Universidad Autónoma de México for the identification of this plant.

and 2·5 Hz); H-7, 3·02 (1H d,d,d; J = 1·3, 4 and 9 Hz). (Found: C, 64·81; H, 8·09; O, 27·16. Calc. for $C_{19}H_{28}O_6$: C, 64·75; H, 8·01; O, 27·24%).

The mother liquors were chromatographed affording an additional crop of 50 mg hexahydrozexbrevin and 40 mg octahydrozexbrevin m.p. 175–177°, a recrystallization from acetone-isopropyl ether raised the m.p. to 180–182°; ν_{max} 3625, 1760, 1725 cm^{-1}. (Found: C, 64·30; H, 8·63; O, 27·38. Calc. for $C_{19}H_{30}O_6$: C, 64·30; H, 8·53; O, 27·09%).

Octahydrozexbrevin (**4**) *obtained by* $NaBH_4$ *reduction of tetrahydrozexbrevin* (**2**). A cold soln of **2** (600 mg) in MeOH (15 ml) was mixed with a cold soln of $NaBH_4$ (600 mg) in MeOH (15 ml). The reaction mixture was kept at 5° for 5 min and then for 10 min at room temp. It was acidified with AcOH and extracted with $CHCl_3$. The solvent was eliminated by evaporation and the substance crystallized from isopropyl ether, yielding 280 mg m.p. 180–182° of octahydrozexbrevin (**4**).

Octahydrozexbrevin (**4**) *obtained by* $NaBH_4$ *reduction of hexahydrozexbrevin* (**3**). A reduction of **3** with $NaBH_4$ in the same conditions as the preceding experiment gave rise to 25 mg of **4**.

Desmethacrylhexahydrozexbrevin (**6**). A soln of **3** (500 mg) in MeOH (10 ml) was treated with K_2CO_3 (500 mg) in water (500 ml) for 8 hr at room temp, extracted with $CHCl_3$. The organic layer was washed, dried and evaporated, the residue crystallized from acetone-isopropyl ether yielding 175 mg of **6**, m.p. 208–210°; NMR (60 MHz): δ 0·8 (3H d; J = 7 Hz); 1·2 (3H d; J = 7 Hz); 3·2 (1H ddd, J = 8·5, 11·5, 12 Hz) (H-7), a complex signal at 4·22 includes H-8, H-4 and H-6; ν_{max} 3610, 1760 cm^{-1}. (Found: C, 63·52; H, 7·95; O, 28·23. Calc. for $C_{15}H_{22}O_5$: C, 63·81; H, 7·86; O, 28·33%).

The same substance was obtained treating VI with MeONa.

11-*Epihexahydrozexbrevin* VII. A soln of **3** (200 mg) in MeOH (10 ml) was treated with $KHCO_3$ (200 mg) in water (10 ml) and kept at room temp for 48 hr. The reaction mixture was extracted with $CHCl_3$, dried and taken to dryness leaving 175 mg of residue which was separated in 3 components by TLC in silica, using a mixture of benzene–EtOAc 1:1.

11-Epihexahydrozexbrevin was the less polar, the next was recovered product and the more polar was the free compound **6**.

Compound VII was recrystallized from acetone–hexane yielding white crystals m.p. 153–154°. (Found: C, 64·84; H, 8·26; O, 27·18. Calc. for $C_{19}H_{28}O_6$: C, 64·75; H, 8·01; O, 27·24%).

Octahydrozexbrevin acetate (**5**). Acetylation of **5** with pyridine Ac_2O for 48 hr at room temp afforded the oily acetate (**5**), ν_{max} 1760, 1740 cm^{-1} (acetate and ester).

Acetylation of desmethacrylhexahydrozexbrevin. Acetylation of **6** (80 mg) with pyridine–Ac_2O for 22 hr at room temp afforded 50 mg of **9**, m.p. 198–200° (from acetone–isopropyl ether); ν_{max} 1760 (broad band which includes a γ-lactone, an acetate and a cyclopentanone). (Found: C, 63·01; H, 7·33; O, 29·47. Calc. for $C_{17}H_{24}O_6$: C, 62·95; H, 7·46; O, 29·59%).

Dehydrodesmethacrylhexahydrozexbrevin (**8**). A soln of 130 mg of **6** in acetone (5 ml) was treated with 8N CrO_3 until the persistence of orange colour. Kept 2·5 hr at room temp, diluted with water and extracted with $CHCl_3$. The organic layer was washed, dried and concentrated yielding 95 mg of **8**, m.p. 105–106°, a recrystallization from acetone–ether raised the m.p. to 117–118°; ν_{max} 1775 (γ-lactone), 1755 (cyclopentanone) and 1710 cm^{-1} (Ketone on 9 membered ring). (Found: C, 63·98; H, 7·19; O, 28·61. Calc. for $C_{15}H_{20}O_5$: C, 64·27; H, 7·19; O, 28·54%).

Determination of the absolute configuration of the alcohol at C-8 *in zexbrevin* (**1**). The method of Horeau[7] was applied using the work up procedures outlined for similar compounds.[8, 9] A soln of 145·4 mg α-phenylbutyric anhydride in 3 ml dry pyridine was allowed to stand overnight at room temp and worked up as described.[8, 9] There was recovered 60 mg of the ester of **6**, 105 mg of α-phenylbutyric acid $[\alpha]_D^{27}$ −12° corresponding to an optical yield of 53·5%.

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