A Useful Preparation of *O*-Protected α-Hydroxyketones of Defined Enantiomeric Purity from 2-Hydroxyalkanoic Esters

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α-Hydroxyketones (OH-protected) are prepared in high enantiomeric purity by reaction of chiral *O*-protected 2-hydroxyalkanoic esters with organolithium compounds in ether/pentane at −100 °C or by conversion of 2-hydroxyalkanoic esters into 2-hydroxy-*N*,*N*-dimethylalkanamides, *O*-protection of these amides, and reaction with organomagnesium bromides in tetrahydrofuran/ether at 5 °C.

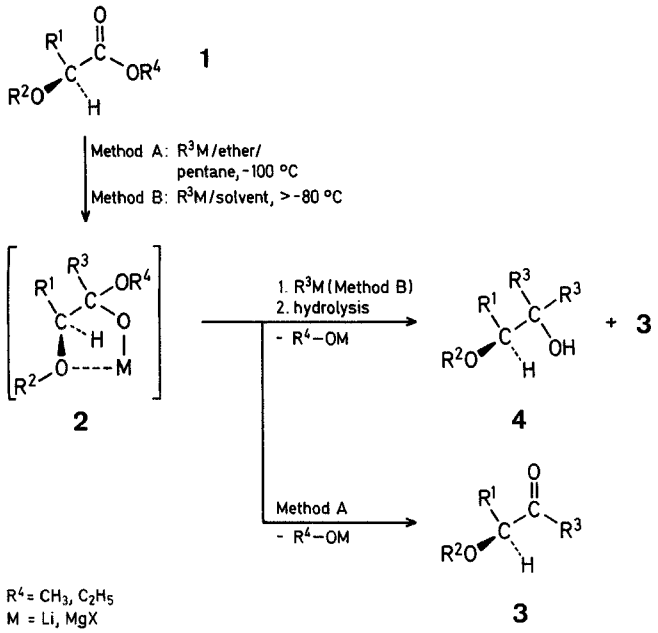
Chiral α-hydroxyketones are important building blocks for numerous synthetic purposes[1,2,3]. However, their preparation in high enantiomeric purity is not always easy. In connection with studies directed towards the synthesis of chiral pheromones, we needed a method for the synthesis of chiral α-hydroxyketones from optically pure 2-hydroxyalkanoic esters; we have previously described a synthesis of these esters[4].

The reaction of α-hydroxycarboxylic esters with organolithium compounds or with Grignard reagents is known to mainly afford tertiary alcohols[5]. Yet, some examples of ketone formation have been reported[6]; they are generally based on the use of a sufficiently basic medium to generate the enolate of the intermediate ketone and then avoid a further addition reaction. Another method used to obtain α-chloroketones involves the reaction of α,α-dichlorocarboxylic esters with methyllithium at low temperature[7]. We thought that it might be possible to apply such a reaction to α-hydroxycarboxylic esters.

Performance of the reaction of an *O*-protected 2-hydroxyalkanoic ester (**1**) with one molecular equivalent of an organometallic compounds without special regard to temperature control affords, after hydrolysis, a mixture of the ketone **3**, the mono-protected diol **4**, and the recovered ester **1**. By contrast, at low temperature (below −80 °C) the intermediate **2** is stable enough to preclude the *in situ* formation of the ketone **3** and thereby the subsequent addition of the orga-

nometallic compound to give the alcohol **4**. This stabilization of the intermediate **2** is probably due to chelation between the O-atoms and the metal cation.

Although the *O*-protected α-hydroxycarboxylic esters **1** are more reactive than simple esters, their reaction with Grignard reagents does not afford satisfactory results; this reaction proceeds only at − 50 °C and it yields a mixture of compounds **1**, **3**, and **4**, the temperature being not low enough to allow stabilization of the chelate **2**. The latter is also true for the reaction of esters **1** with organolithium reagents at − 50 °C; however, when the reaction is performed at − 100 °C in ether/pentane (the reaction with organolithium compounds is still possible at this temperature) and the mixture hydrolyzed after a maximum reaction time of 10 min it affords the nearly pure *O*-protected α-hydroxyketones **3**. The best results are obtained using protective groups which contain two *O*-atoms such as the methoxymethyl and the 2-methoxyethoxymethyl groups. The use of the *t*-butyldimethylsilyl group, which leads to sterical hindrance of the O-atom, results in the formation of a considerable percentage of alcohol **4** and an increased recovery of ester **1**.



In order to determine the enantiomeric purity of the *O*-protected hydroxyketones **3**, these compounds were reduced with sodium borohydride; the resultant diastereoisomeric mono-protected *vic*-diols were separated by medium pressure liquid chromatography and analyzed on a chiral capillary column according to the method of Ref.[8]. The percentage of the enantiomers thus determined was compared for each compound with the chromatogram of the mono-protected racemic diols obtained from the reduction of the *O*-protected α-hydroxyketones prepared from the corresponding racemic 2-hydroxyalkanoic esters. In some cases, the Mosher derivatives (i.e., the MTPA esters[12]) of the isolated diastereoisomeric mono-protected diols were also prepared and analyzed by H.P.L.C. to give the same results.

The yields given in Table 1 were obtained by using 1.1 equivalent of lithium compounds. If the protecting group is a poor chelating function (an alkylsilane for instance), it is possible to enhance the yields by adding a solvent such as tetramethylethylenediamine (TMEDA) which stabilizes the intermediate **2**. The enantiomeric excesses measured with such an additive were the same as previously observed.

Table 1. Preparation of *O*-Protected α-Hydroxyketones (**3**)

Type of Educt	Method	R^1	R^2	R^3	R^4	Yields [%]			e.e. of **3**	RR[a]
						Recovered **1** or **7**	Ketone **3**	Diol Derivative **4**		
1	A	CH_3	$H_3CO-CH_2-CH_2-O-CH_2-$	CH_3	C_2H_5	< 1	**3a** 70	3	> 95	< 0.05
1	A	CH_3	H_3CO-CH_2-	CH_3	C_2H_5	2	**3b** 49	14	56	0.02
1	A	CH_3	t-$C_4H_9(CH_3)_2Si-$	n-C_4H_9	C_2H_5	35	**3c** 29	20	> 97	0.02
1	A[b]	CH_3	t-$C_4H_9(CH_3)_2Si-$	n-C_4H_9	C_2H_5	4	**3c** 49	32	> 97	0.02
1	A	CH_3	H_3CO-CH_2-	n-C_4H_9	C_2H_5	25	**3d** 50	15	58	0.01
1	A	CH_3	$H_3CO-CH_2-CH_2-O-CH_2-$	n-C_4H_9	CH_3	< 1	**3e** 81	1	99	0.01
1	A	n-C_5H_{11}	$H_3CO-CH_2-CH_2-O-CH_2-$	n-C_4H_9	C_2H_5	7	**3f** 75	8	> 98	< 0.02
1	A		$-CH_2-O-C(CH_3)_2-$	CH_3	CH_3	2	**3g** 75	5	94	0.06
1	A		$-CH_2-O-C(CH_3)_2-$	n-C_4H_9	CH_3	3	**3h** 81	6	93	0.07
7	C		$-CH_2-O-C(CH_3)_2-$	CH_3	—	0	**3g** 77	5	> 98	< 0.02
7	C		$-CH_2-O-C(CH_3)_2-$	n-C_4H_9	—	0	**3h** 89	4	97	0.03
7	C		$-CH_2-O-C(CH_3)_2-$	$-C(CH_3)=CH_2$	—	0	**3i** 58	5	> 95	< 0.05
7	C	CH_3	$H_3CO-CH_2-CH_2-O-CH_2-$	n-C_4H_9	—	0	**3e** 80	0	> 99	< 0.01

[a] Racemization rate, defined as: $1 - \frac{\text{e.e.}\,\mathbf{3}}{\text{e.e.}\,\mathbf{1}}$.

[b] Reaction performed in ether/TMEDA 10/1.

Table 2. Physical Data of the *O*-Protected α-Hydroxycarboxylic Esters **1**

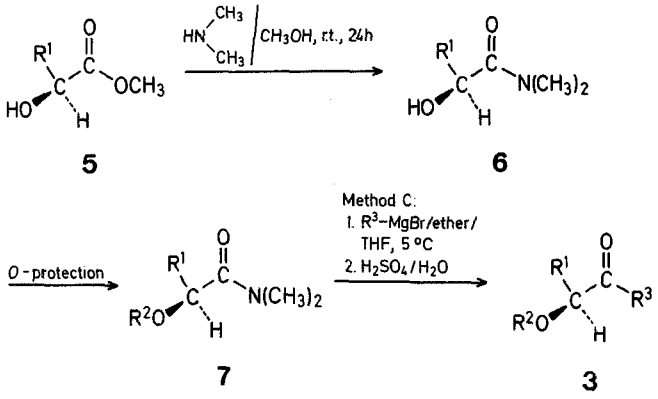
R^1	R^2	R^4	$[\alpha]_D^{20}$	I.R. (neat) ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ[ppm]
CH_3	$H_3CO—CH_2—$	C_2H_5	−78.2° (*c* 2.6, methanol)	1740	1.4 (m, 6H, $H_3C—CH—CO + O—CH_2—CH_3$); 3.35 (s, 3H, H_3CO); 4.25 (m, 3H, $CH—CO + O—CH_2—CH_3$); 4.65 (s, 2H, $O—CH_2—O$)
CH_3	$H_3CO—CH_2—CH_2—O—CH_2—$	C_2H_5	−56.7° (*c* 5.4, methanol)	1735	1.4 (m, 6H, $H_3C—CH—CO + O—CH_2—CH_3$); 3.3 (s, 3H, OCH_3); 3.65, 3.75 (2m, 4H, $O—CH_2—CH_2—O$); 4.2 (m, 3H, $CH—CO + CH_2—$); 4.8 (s, 2H, $O—CH_2—O$)
n-C_4H_9	$H_3CO—CH_2—CH_2—O—CH_2—$	C_2H_5	−22.9° (*c* 0.93, methanol)	1740	0.95 (t, 3H, CH_3); 1.3 [m, 9H, $(CH_2)_3 + CH_3$]; 1.75 (m, 2H, $CH_2—CH—CO$); 3.45 (s, 3H, OCH_3); 3.65, 3.75 (2m, 4H, $O—CH_2—CH_2—O$); 4.2 (m, 3H, $O—CH_2—CH_3 + CH_2—CH—CO$); 4.8 (s, 2H, $O—CH_2—O$)
CH_3	*t*-$C_4H_9(CH_3)_2Si—$	C_2H_5	−29.8° (*c* 1.8, CH_2Cl_2)	1735	0.8 [s, 9H, $(H_3C)_3C$]; 1.17 (t, 3H, $O—CH_2—CH_3$); 1.3 (d, 3H, *J* = 7.1 Hz, $H_3C—CH—CO$); 4.05 (q, 2H, $O—CH_2—CH_3$); 4.15 (q, 1H, *J* = 7.1 Hz, $H_3C—CH—CO$)

Table 3. Analytical and Physical Data of the *O*-Protected α-Hydroxyketones **3**

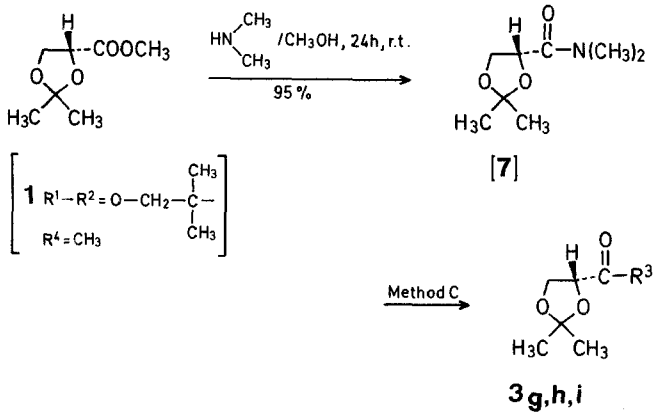
Compound	$[\alpha]_D^{20}$	Molecular Formula[a] or Lit. Data	I.R. (neat) $\nu_{C=O}$[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ[ppm]
3a	−15.2° (*c* 2.5, methanol)	$C_8H_{16}O_4$ (176.2)	1710	1.4 (d, 3H, *J* = 7 Hz, CH_3); 2.25 (s, 3H, $CO—CH_3$); 3.45 (s, 3H, OCH_3); 3.65, 3.75 (2m, 4H, $O—CH_2—CH_2—O$); 4.2 (q, 1H, *J* = 7 Hz, $H_3C—CH—CO$); 4.8 (s, 2H, $O—CH_2—O$)
3b	−43.6° (*c* 2.7, methanol)	$C_6H_{12}O_3$ (132.2)	1715	1.4 (d, 3H, *J* = 7 Hz, CH_3); 2.2 (s, 3H, $CO—CH_3$); 3.3 (s, 3H, OCH_3); 4.05 (q, 1H, *J* = 7 Hz, $H_3C—CH—CO$); 4.6 (s, 2H, $O—CH_2—O$)
3c	−3.8° (*c* 2.5, CH_2Cl_2)	$C_{13}H_{28}O_2Si$ (244.5)	1700	0.8 [s, 9H, $(H_3C)_3C$]; 1.2 (d, 3H, *J* = 8.3 Hz, $H_3C—CH—CO$); 1.25 (t, 3H, *J* = 7.8 Hz, $H_3C—CH_2$); 2.45 (t, 2H, *J* = 8.3 Hz, $CO—CH_2$); 4.05 (q, 1H, *J* = 7.8 Hz, $H_3C—CH—CO$)
3d	−29.1° (*c* 5.3, methanol)	$C_9H_{18}O_3$ (174.3)	1710	0.95 (t, 3H, *J* = 4.5 Hz, CH_3); 1.4 (m, 7H, $CH_2—CH_2—CH_3$); 2.55 (t, 2H, *J* = 6 Hz, $CO—CH_2$); 3.35 (s, 3H, H_3CO); 4.15 (q, 1H, *J* = 7 Hz, $H_3C—CH—CO$); 4.7 (s, 2H, $O—CH_2—O$)
3e	−16.1° (*c* 3.0, methanol)	$C_{11}H_{22}O_4$ (218.3)	1705	1.0 (t, 3H, *J* = 4.5 Hz, CH_3); 1.5 (m, 7H, $CH_2—CH_2—CH_3$); 2.5 (t, 2H, *J* = 6 Hz, $CO—CH_2$); 3.45 (s, 3H, H_3CO); 3.65, 3.75 (2m, 4H, $O—CH_2—CH_2—O$); 4.2 (q, 1H, *J* = 7 Hz, $H_3C—CH—CO$); 4.8 (s, 2H, $O—CH_2—O$
3f	−17.9° (*c* 0.95, methanol)	$C_{14}H_{28}O_4$ (260.4)	1710	0.95 (t, 6H, *J* = 4.5 Hz, $2CH_3$); 1.4 [m, 12H, $CO—CH_2—CH_2—CH_2—CH_3 + (CH_2)_4$]; 2.5 (t, 2H, *J* = 6 Hz, $CO—CH_2$); 3.45 (s, 3H, H_3CO); 3.65, 3.75 (2m, 4H, $O—CH_2—CH_2—O$); 4.0 (t, 1H, *J* = 7 Hz, $CH_2—CH—CO$); 4.8 (s, 2H, $O—CH_2—O$)
3g	+53.7° (*c* 1.0, benzene)	$[\alpha]_D^{23}$: +51.2° (*c* 2.11, benzene)[1]	1710	1.35, 1.45 [2s, 6H, $C(CH_3)_2$]; 2.2 (s, 3H, $CO—CH_3$); 4.1 (m, 3H, $CH_2—O + CH—CO$)
3h	+63.2° (*c* 2.2, CH_2Cl_2)	$C_{10}H_{18}O_3$ (186.3)	1715	0.88 (t, 3H, *J* = 7 Hz, CH_3); 1.3 (m, 4H, $CO—CH_2—CH_2—CH_2—CH_3$); 1.38, 1.45 [2s, 6H, $C(CH_3)_2$]; 2.55 (t, 2H, *J* = 8 Hz, $CO—CH_2$); 4.18 (m, 3H, $CH_2—O + CH—CO$)
3i	+3.7° (*c* 1.05, methanol)	$C_9H_{14}O_3$ (170.2)	1675; 1620 (C=C)	1.43 [s, 6H, $C(CH_3)_2$]; 1.88 (s, 3H, $C=C—CH_3$); 4.08 (m, 2H, $CH_2—O$); 4.8 (t, 1H, $CH—CO$); 5.8, 5.95 (2s, 2H, $C=CH_2$)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.25, H ±0.19.

In order to investigate the general applicability of the method, we also studied the reaction of α-hydroxy-*N,N*-dimethylcarboxamides with organomagnesium bromides since *N,N*-dialkylcarboxamides are known to react with Grignard reagents to give ketones in good yields[9]. The α-hydroxy-*N,N*-dimethylcarboxamides **(6)** were prepared from the corresponding α-hydroxycarboxylic esters **(5)** by reaction with anhydrous dimethylamine in methanol[10]. This reaction gives satisfactory results but it becomes slow when it is performed with *O*-protected α-hydroxycarboxamides **(7)** such as the *O*-(2-methoxyethoxymethyl) derivatives (30% yield after 8 days). We therefore prepared 2-hydroxy-*N,N*-dimethylpropanamide (**6**, $R^1 = CH_3$) from the unprotected methyl 2-hydroxypropanoate (**5**, $R^1 = CH_3$) and then converted the unprotected 2-hydroxy-*N,N*-dimethylpropanamide into the *O*-(2-methoxyethoxymethyl) derivative **7** ($R^1 = CH_3$, $R^2 = H_3CO—CH_2—CH_2—O—CH_2—$) which we submitted to the reaction with butylmagnesium bromide to give the desired *O*-protected α-hydroxyketone **3e** in 80% yield with an enantiomeric excess of > 99%.



In contrast to the *O*-(2-methoxyethoxymethyl) and similar derivatives of the α-hydroxy-*N,N*-dimethylcarboxamides **6**, the acetonide **6** [$R^1—R^2 = —CH_2—O—C(CH_3)_2—$] derived from 2,3-dihydroxy-*N,N*-dimethylpropanamide, i.e., 2,2-dimethyl-4-dimethylaminocarbonyl-1,3-dioxolane, can be obtained from methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate and dry dimethylamine in methanol in 95% yield; reaction of the amide with organomagnesium compounds in the above-described manner then affords the desired 4-acyl-2,2-dimethyl-1,3-dioxolanes **3g, h, i** which represent protected forms (acetonides) of alkyl 1,2-dihydroxyethyl ketones.



The yields and enantiomeric excesses of ketones **3 g** and **3 h** thus prepared are slightly higher than those obtained in the preparation of these ketones directly from methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate and organolithium reagents (Method A).

All reactions were performed under argon. Products were purified by flash chromatography (Kiesel gel 60 Merck 0.040–0.063 mm, or Florisil® 100–200 mesh, hexane/ethyl acetate). Enantiomeric excesses were measured by G.L.C. on a chiral capillary column (Chrompack XE60-*S*-valine-*S*-α-phenyl ethyl amide, 50 m) or by H.P.L.C. for Mosher derivatives (column: Zorbax Sil, 250 × 4.3 mm).

Racemic α-hydroxycarboxylic esters were prepared by acid alcoholysis of appropriate cyanohydrins and were *O*-protected by the usual procedures. Methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (the acetonide of methyl 2,3-dihydroxypropanoate) is commercially available (Fluka); it may be prepared from serine[11].

(2*S*)-2-(2-Methoxyethoxymethoxy)-*N,N*-dimethylpropanamide (7, $R^1 = CH_3$, $R^2 = H_3CO—CH_2—CH_2—O—CH_2—$); Typical Procedure:

(2S)-2-Hydroxy-N,N-*dimethylpropanamide* (**6**, $R^1 = CH_3$): A mixture of methyl 2-hydroxypropanoate (**5**, $R^1 = CH_3$; 0.521 g, 5 mmol), methanol (15 ml), and anhydrous dimethylamine (10 ml) is kept in a closed vessel at room temperature for 24 h. If the reaction is not complete (which may happen with some esters) the volatile materials are removed under vacuum and the reaction is repeated. The solvent is evaporated and the amide is purified by distillation in vacuo or by flash chromatography on Florisil®; yield: 0.474 g (81%); b.p. 105–166 °C/15 torr (Ref.[10], b.p. 78–79 °C/4 torr); $[\alpha]_D^{20}$: −1.2° (*c* 11, methanol).

I.R. (neat): $\nu_{C=O} = 1630\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.35$ (d, 3 H, $J = 6$ Hz, CH_3); 2.95 [s, 6 H, $N(CH_3)_2$]; 3.9 (s, 1 H, OH); 4.50 ppm (q, 1 H, $J = 6$ Hz, O—CH—CH_3).

(2S)-2-(2-Methoxyethoxymethoxy)-N,N-*dimethylpropanamide:* (2*S*)-2-Hydroxy-*N,N*-dimethylpropanamide (1.17 g, 10 mmol) is stirred for 12 h with methoxyethoxymethyl chloride (1.87 g, 15 mmol) and diisopropylamine (2 g, 15 mmol) in dichloromethane 820 ml). After acid hydrolysis (1 normal hydrochloric acid) and extraction with ether (5 × 10 ml), the product is distilled; yield: 1.64 g (80%); b.p. 148–150 °C/10 torr; $[\alpha]_D^{20}$: −70.5° (*c* 7.2, methanol).

$C_9H_{19}NO_4$	calc.	C 52.66	H 9.33	N 6.82
(205.25)	found	52.57	9.29	6.83

I.R. (neat): $\nu_{C=O} = 1640\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.40$ (d, 3 H, $J = 6$ Hz, CH_3); 2.95, 3.05 [2s, 6 H, $N(CH_3)_2$]; 3.45 (s, 3 H, OCH_3); 3.65, 3.75 (m, 4 H, O—CH_2—CH_2—O); 4.65 (q, 1 H, $J = 6$ Hz, H_3C—CH—CO); 4.80 ppm (s, 2 H, O—CH_2—O).

***(R)*-2,2-Dimethyl-4-dimethylaminocarbonyl-1,3-dioxolane:**

A mixture of methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (0.801 g, 5 mmol), methanol (15 ml), and anhydrous dimethylamine (10 ml) is kept in a closed vessel at room temperature for 24 h. The volatile materials are then removed under vacuum and the amide is purified by distillation in vacuo; yield: 0.820 g (95%); b.p. 100 °C/12 torr; $[\alpha]_D^{20}$: +1.2° (*c* 3.5, chloroform).

$C_8H_{15}NO_3$	calc.	C 55.47	H 8.73	N 8.09
(173.2)	found	55.57	8.77	8.15

I.R. (neat): $\nu_{C=O} = 1650\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.38$ [s, 6 H, $C(CH_3)_2$]; 2.88, 3.08 [2s, 6 H, $N(CH_3)_2$]; 4.18 (m, 2 H, CH_2—O); 4.63 ppm (t, 1 H, CH—CO).

***O*-Protected α-Hydroxyketones (3); General Procedures:**

Method A, from *O*-Protected 2-Hydroxyalkanoic Esters (*1*): An ~0.7 molar solution of the alkyllithium reagent (2.2 mmol) is added to a stirred solution of the ester **1** (2 mmol) in ether/pentane (1/1; 15 ml) at −100 °C. After 10 min, the mixture is hydrolyzed with concentrated ammonium chloride solution (2 ml) and extracted with

ether (3 × 5 ml). The extract is dried with magnesium sulfate and evaporated and the crude product **3** is purified by flash chromatography.

Method C, from *O*-Protected 2-Hydroxyalkanamides or 2,2-Dimethyl-4-dimethylaminocarbonyl-1,3-dioxolanes (**7**): The amide **7** (2 mmol) is dissolved in ether (7 ml) + tetrahydrofuran (3 ml) and an ~1 molar solution of the organomagnesium bromide (2.15 mmol) in ether is added with stirring at + 5°C. After 10 min, the mixture is hydrolyzed with 2 normal sulfuric acid (2 ml) and extracted with ether (3 × 5 ml). The organic extract is stirred with sodium carbonate (0.2 g) for 5 min and then dried with magnesium sulfate. The solvent is evaporated and the residual product **3** purified by flash chromatography.

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