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The (–)-Menthyl Ester Group as a Chiral Auxiliary in Electrophilic Glycine Derivatives

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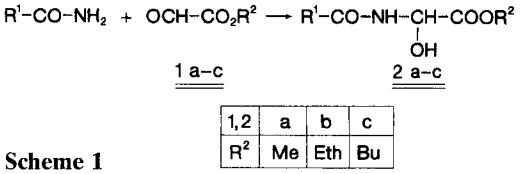
In the course of our studies on α-amidoalkylation reactions with glycine cation equivalents [1] it was of interest to examine more closely compounds containing a chiral auxiliary [2]. Using this approach it may be possible to synthesize enantiomerically pure α-amino acids.

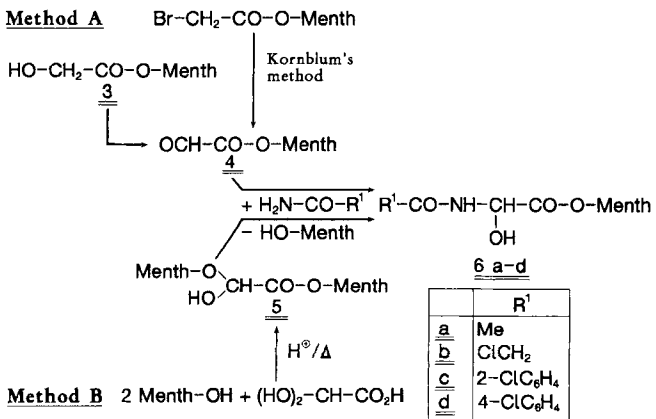
The efficient reaction between the well accessible alkyl glyoxylates **1a–c** and carbonamides which forms the addition products **2a–c** (Schema 1) has been well described [3]. The more costly and laborious preparation of **4** has previously been published by Kornblum [4]. The formation of the analogous adducts **6** of (–)-mentyl glyoxylate **4** which proved much more complicated, is described in the present paper.



1,2	a	b	c
R^2	Me	Eth	Bu

Scheme 1

Using a modified Swern-oxidation [5] of (–)-menthyl glycolate **3** with phosphorus pentoxide for activation of dimethyl sulfoxide instead of oxalyl chloride [6], we succeeded in producing **4** in good yield (71 %) (Scheme 2).



	R^1
a	Me
b	$ClCH_2$
c	2-ClC_6H_4
d	4-ClC_6H_4

Scheme 2

Crystalline menthyl hemiacetal **5** was prepared by the sulfuric acid catalyzed reaction of melted glyoxylic acid hydrate and one part of (–)-menthol. This compound **5** was suitable for synthesizing the products **6a–d** with high efficiency.

The 400 MHz ^{1}H-n.m.r. spectrum of **5** (C_6D_6) exhibited a 3:1 ratio of two hydroxy doublets (δ = 3.95, 3.75) and of two methin doublets (δ = 5.05, 5.19) suggesting a 3:1 mixture of diastereomers was present. As the ^{1}H-n.m.r. analysis of the related products **6a–d** did not show any diastereomeric excess, an elimination-addition mechanism seems obvious.

In contrast to **6a–c**, one pure isomer from **6d** could by separated by fractionated crystallization.

Experimental

M.ps. are uncorrected. IR spectra (KBr, NaCl) are reported in cm^{-1}. N.m.r. spectra are recorded at 250 and 400 MHz. Chemical shifts are given in δ (ppm) downfield from TMS. Centrifugal chromatography (chrom.) was carried out by Chromatotron Model 8924, Harrison Research, USA; eluent (CH_2Cl_2/ethyl acetate [5:2]).

(–)-Menthyl glycolate **(3)** *[7]*

The mixture of 15.63 g (100 mmol) of (–)-menthol, 7.60 g (100 mmol) of glycolic acid and a trace of p-toluenesulfonic acid in 100 ml of toluene was refluxed in a Dean-Stark separator until the calculated amount of H_2O had collected. The residue of the filtered and concentrated (in vacuo) solution of the product, was dissolved in 50 ml of CH_2Cl_2. After washing with a saturated solution of $NaHCO_3$ (2×15 ml), drying over Na_2SO_4 and evaporating in vacuo, the remaining viscous oil was purified from unreacted menthol by vacuum sublimation (2h, 100 °C, 15 Torr) and solidified under 10 ml of light petroleum (40–60 °C).

Recrystallization from cyclohexane yielded 18.2 g (85 %); m.p. 83–83.5 °C(lit. m.p. 87.5 °C), IR: 3480 br. (OH), 1740 (CO-O). ^{1}H-n.m.r. (DMSO-d_6): 0.50–2.00 (m, 18H, CH_3, CH_2, CH, menthyl), 4.00 (d, 2H, CH_2), 4.65 (m, 1H, CH, menthyl), 5.30 (dd, 1H, OH).

Optical activity $[\alpha]_D^{20}$: −73.5° ± 0.18 (c=5; benzene) (lit. [7]: $[\alpha]_D^{20}$: −73.30; c=5; benzene)
Anal. calcd. for $C_{12}H_{22}O_3$: C 67.26 H 10.35
(214.30) Found: C 67.03 H 10.11

(−)-Menthyl glyoxylate **(4)** *from* **3**

1.42 g (10 mmol) dry P_2O_5 and 0.78 g (10 mmol) DMSO were alternately added over 10 min under vigorous stirring to a solution of 1.10 g (5 mmol) **3** in 45 ml of absolute CH_2Cl_2 in an ice cooled three necked flask (N_2 atmosphere). After removal from the ice bath and continous stirring the mixture was allowed to warm to r.t. until the starting material was completely converted as assessed by TLC analysis. After cooling again to 0 °C 1.80 g (17.5 mmol) of triethylamine (NEt_3) were added within 1 min into the suspension which changed into a clear solution. After 30 min without cooling, the reaction was quenched by addition of diluted HCl (10 %) adjusting the pH to 1. The mixture was poured into 30 ml of H_2O, the organic layer was washed with brine, dried over $MgSO_4$, concentrated in vacuo. Distillation of the residue recovered 0.75 g (71 %) of **4**, b.p. $_{0,1}$ 75–76 °C(lit. [4] b.p. $_{0,4}$ 95–96 °C).
IR (Hemihydrate): 3450 br. (OH), 1750 br. (CO–O).
^{1}H-n.m.r. ($CDCl_3$): 0.5–200 (m, 18H, menthyl), 4.75 (m, 1H, CH).
$[\alpha]_D^{20}$: −96,8° ± 0.31 (c=2.03, CH_2Cl_2).
Hydrate of **4**: m.p. 83–84 °C (ethylacetate) (lit. [4b]: 84–86 °C).
IR: 3430, 3360 (2×OH), 1740 (CO–O).
^{1}H-n.m.r. (DMSO): 0.50–2.00 (m, 18H, menthyl), 4.65 (m, 1H, CH, menthyl), 5.00 (s, 1H, CH), 6.55 br. (s, 2H, 2OH).

(−)-Menthyl glyoxylate-(−)-menthyl-hemiacetal **(5)**

7.81 g (50 mmol) (−)-menthol and 4.60 g (50 mmol) glyoxylic acid monohydrate were melted at 100 °C (oil bath) and stirred for 90 min catalysed by 10 drops of concentrated. H_2SO_4. The solution of the cooled mixture in 50 ml of ethyl acetate was washed with H_2O, sat. solution of $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and evaporated in vacuo. The remaining yellowish, viscous oil was then subjected to vacuum at 100 °C/13 Torr for 60–90 min (to remove unreacted (−)-menthol) produced **5** as a solid compound, ready for use.
Yield: 6.6 g (71 %); m.p. 81–82 °C.
IR: 3450 br. (OH), 1735 (CO–O).
^{1}H-n.m.r. (C_6D_6) Epimer I+II: 0.55–2.50 (m, 76H, 4 menthyl). Epimer I (dominating): 3.37 (m, 1H, menth-CH–O, hemiacetal), 3.95 (d, 1H, OH), 4.90 (m, 1H, menth-CH–O; ester), 5.05 (d, 1H, CH–CO).
Epimer II. 3.75 (d, 1H, OH). 5.19 (d, 1H, CH–OH).
$[\alpha]_D^{20}$: −86.63° ± 0.27 (c=1.88; CH_2Cl_2).
Anal. calcd. for $C_{22}H_{40}O_4$: C 71.70 H 10.94
(368.55) Found: C 71.79 H 11.06

(−)-Menthyl-2-acylamino-2-hydroxy-acetates **(6a–d)**

Refluxing either 10 mmol of the respective carbonamide and of **5** (method B) or of **4** (method A) in 25 ml of ethyl acetate for 90 min yielded after addition of 10 ml of light petroleum the following crystalline compounds as 1:1 mixtures of diastereomers:
6a: R^1=Me, m.p. 133–134 °C (ethyl acetate),
IR: 3420–3260 br. (OH, NH), 1745 (CO–O), 1665 (CON).
^{1}H-n.m.r. ($CDCl_3$): 0.70–1.98 (m, 18H, CH_3, CH_2, CH, menthyl), 2.05 (s, 3H, CH_3), 4.75 (m, 2H, CH, menthyl, OH), 5.60 (m, 1H, CH–CO), 7.05 (d, 1H, NH).
Anal. calcd. for $C_{14}H_{25}NO_4$: C 61.97 H 9.29 N 5.16
(271.35) Found: C 61.92 H 9.12 N 5.14

6b: R^1=$ClCH_2$, m.p. 138–139 °C (ethyl acetate),
IR: 3400–3240 br. (OH, NH), 1745 (CO–O), 1680 (CON).
^{1}H-n.m.r: 0.72–2.14 (m, 18H, CH_3, CH_2, CH, menthyl), 4.09 (s, 2H, CH_2–CO), 4.37 br. (m, 1H, OH), 4.80 (m, CH, menthyl), 5.60 (dd, 1H, CH–CO), 7.71 (m, 1H, NH).
Anal. calcd. for $C_{14}H_{24}NClO_4$: C 54.99 H 7.91 Cl 11.59 N 4.58
(305.80) Found: C 54.93 H 7.84 Cl 11.54 N 4.72

6c: R^1=4-ClC_6H_4, m.p. 153–154 °C (chrom.),
IR: 3400 br. (OH), 3360 br. (NH), 1750 (CO–O), 1650 (CON).
^{1}H-n.m.r: 0.70–2.15 (m, 18H, CH_3, CH_2, CH, menthyl), 4.20 (m, 1H, OH), 4.85 (m, 1H, CH, menthyl), 5.75 (m, 1H, CH–CO), 7.35 (m, 1H, NH), 7.40–7.80 (dd, 4H, aromat.)
Anal. calcd. for $C_{19}H_{26}ClNO_4$: C 62.04 H 7.12 Cl 9.64 N 3.81
(367.87) Found: C 61.78 H 7.10 Cl 9.50 N 3.61

6d: R^1=2-ClC_6H_4, pure diastereomer m.p. 130.5–131 °C (fract. cryst. ethyl acetate),
IR: 3420 (OH), 3320 (NH), 1740 (CO–O), 1650 (CON).
^{1}H-n.m.r: 0.70-2.15 (m, 18H, CH_3, CH_2, CH, menthyl), 4.40 (d, 1H, OH), 4.83 (m, 1H, CH, menthyl), 5.78 (dd, 1H, CH–CO), 7.28–7.48 (m, 2H, aromat.), 7.65 (d, 1H, NH), 7.75 (d, 2H, aromat.). $[\alpha]_D^{20}$ −64.2 °C ± 0.31 (c=2; $CHCl_3$)
Anal. calcd. for $C_{19}H_{26}ClNO_4$: C 62.04 H 7.12 Cl 9.64 N 3.81
(367.87) Found: C 62.12 H 7.28 Cl 9.67 N 3.78

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