

Kurzzmitteilungen/Short Communications

Cyclization of a Chiral α -(δ' -Benzyloxyalkyl)acrylate to a Novel Tetrahydrofuran DerivativeSiegfried E. Drewes*, Owen L. Njamela, and Gregory H. P. Roos ^{*)}Department of Chemistry, University of Natal,
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Key Words: Tetrahydrofurans / Acrylates, α -(δ' -hydroxyalkyl)- / Aldehydes, β -hydroxy-Methyl 3-hydroxy-2-(iodomethyl)-5-methyltetrahydrofuran-2-carboxylate (**4**) is synthesized from (3*S*)-3-(benzyloxy)butanal(**2**) via methyl 5-(benzyloxy)-3-hydroxy-2-methylenehexanoate (**3a**) as intermediate.

The reaction of methyl acrylate with aldehydes in the presence of DABCO (Baylis-Hillman reaction) provides convenient access to natural products containing the acrylate moiety and also opens a route to useful synthetic intermediates^{1,2}. The use of chiral β -hydroxy aldehydes represents a logical extension of the reaction and leads in this case to δ' -hydroxy acrylates. In this communication we report on one aspect of the synthetic utility of δ' -hydroxy acrylates, i.e. cyclization to a tetrahydrofuran derivative. Future work will be aimed at an examination of the generality of this pathway.

Obvious precursors for the requisite aldehydes (above) are chiral β -hydroxy esters which are readily accessible from β -oxo esters³ by microbial reduction. This method enjoys wide support, and recent advances include an improvement of optical yields and a procedure for the reversal of configuration⁴.

Using standard procedures we readily prepared ethyl (3*S*)-3-hydroxybutyrate (**1**) from ethyl acetoacetate. The hydroxy group required protection during initial reduction (LiAlH₄)⁵ of the ester followed by oxidation (Swern)⁶ to the requisite aldehyde **2**. Both the MOM group⁷ and the Bzl group⁸ were suitable for this purpose and did not result in significant racemization. Subsequent obser-

vations showed, however, that the MOM group was unsuitable for effecting cyclization to the title compound.

Reaction of the aldehyde **2** with methyl acrylate in the presence of DABCO afforded the α -(δ' -alkoxy- β' -hydroxyalkyl)acrylates **3a** and **3b** in 70% overall yield. The d.e. of **3a** was 51% (gas chromatography). Column-chromatographic separation afforded the predominant isomer with high d.e. By employing procedures similar to those developed by Bartlett⁹, compound **3a** was cyclized under thermodynamic-control conditions using the iodoetherification technique (I₂ in CH₃CN at 20°C for 20 h) to afford **4** in 66% yield. Stereochemical control was good and resulted predominantly in formation of one isomer (95% d.e.), m.p. 91–92°C. At this stage the cyclization behavior of the minor diastereomer **3b** has not been examined. It is also presently not known if the cyclization process is solvent-dependent.

The ether **4** is an interesting new tetrahydrofuran derivative bearing a striking likeness to the highly toxic muscarine¹⁰ (**5**) and possessing at the same time three stereogenic centers in a labile system. At present the configuration as depicted in **4** is speculative and derives from ¹H- and ¹³C-NMR correlations. An unambiguous assignment awaits the results from NOE and X-ray measurements.

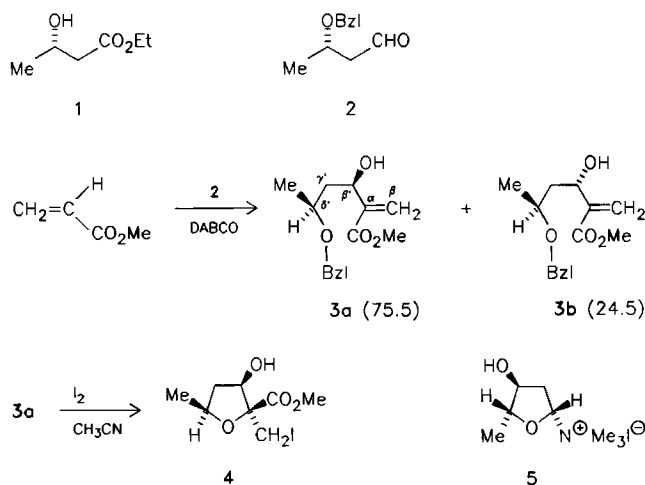
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Experimental

¹H and ¹³C NMR: Varian Gemini (200 MHz), TMS/CDCl₃ as internal standards. — Elemental analyses: Perkin-Elmer 240 B Elemental Analyser. — GC/MS: Hewlett-Packard 5890 gas chromatograph and 5988A spectrometer. — Specific rotations: Atago Polax-D Digital polarimeter.

Compounds **1** and **2** were prepared by published procedures³ using ethyl acetoacetate as starting material.

Methyl 5-(Benzyloxy)-3-hydroxy-2-methylenehexanoate (3a): To a solution of DABCO (0.17 g, 1.15 mmol) in methyl acrylate (1.58 g, 18.18 mmol), the aldehyde **2** (2.70 g, 15.15 mmol) was added and the mixture stirred for 7 d. The mixture was diluted with CHCl₃ (20 ml), washed with HCl (2 N, 10 ml), NaOH (2 N, 10 ml), and brine successively. The CHCl₃ solution was dried (MgSO₄), filtered, and concentrated to give a mixture of diastereomers; yield 2.80 g



*¹) With partial cooperation of G. H. P. R.

(70%) (51% d.e. by gas chromatography). Chromatographic separation [EtOAc/hexane (1:9)] afforded the major isomer **3a**. — $[\alpha]_D^{25} = +35.10$ ($c = 1.565$ in CDCl_3). — $^1\text{H NMR}$ (CDCl_3): $\delta = 1.22$ (d, $J = 6$ Hz, 3H, CHCH_3), 1.63–1.92 (poorly resolved d/d, 2H, OCHCH_2CHO), 3.69 (s, 3H, OCH_3), 3.81–3.95 (q/t, 2H, CHMe), 3.94 (s, 1H, OH), 4.68 (t, $J = 1.3$, 1H, CH_2CHOH), 5.94 and 6.23 (AB system, 2H, $\text{C}=\text{CH}_2$), 7.24–7.33 (m, 5H, aromatic H). — $^{13}\text{C NMR}$ (CDCl_3): $\delta = 19.56$ (CHCH_3), 43.91 (OCHCH_2CH), 51.78 (OCH_3), 70.08 (CHMe), 70.56 (CH_2Ph), 75.75 (CH_2CHOH), 125.01 ($=\text{CH}_2$), 128.13, 128.20, 128.86 (aromatic CH), 138.4 ($=\text{C}$), 142.88 (aromatic C), 167.03 ($\text{C}=\text{O}$). — MS (70 eV): m/z (%) = 205 (2) [$\text{M}^+ - \text{CO}_2\text{Me}$], 140 (17), 125 (22), 91 (100).

$\text{C}_{15}\text{H}_{20}\text{O}_4$ (264.3) Calcd. C 68.16 H 7.63
Found C 68.1 H 7.6

Methyl 3-Hydroxy-2-(iodomethyl)-5-methyltetrahydrofuran-2-carboxylate (4): To a solution of **3a** (0.30 g, 1.14 mmol) in anhydrous acetonitrile (10 ml), a solution of iodine (0.58 g, 2.27 mmol, 2 equiv.) in anhydrous acetonitrile (10 ml) was added. The mixture was stirred at room temperature for ca. 12 h. Solid NaHSO_3 was added until the mixture turned pale yellow. Water (10 ml) was added, and this was followed by extraction with ether (3 × 20 ml). The combined ether extracts were dried (MgSO_4) and concentrated to give a viscous material. The mixture (95% d.e. by gas chromatography) was purified by chromatography [EtOAc/hexane (1:9)] to give as major isomer the tetrahydrofuran **4** as colorless crystalline needles; yield 0.23 g (66%), m.p. 91–92°C (light petroleum ether). — $[\alpha]_D^{25} = +36.26$ ($c = 1.048$ in CHCl_3). — IR (KBr disc): $\tilde{\nu} = 1149.5$ cm^{-1} ($\text{C}-\text{O}-\text{C}$), 1746.5 ($\text{C}=\text{O}$). — $^1\text{H NMR}$ (CDCl_3): $\delta = 1.30$ (d, $J = 6$ Hz, 3H, CHCH_3), 1.89 (d/d/d, $J = 5.2/10.0/13.3$ Hz, 1H, 4-H^a), 2.18 (d/d/d, $J = 2.01/5.4/13.2$ Hz, 1H, 4-H^b), 2.49 (d, $J = 4.2$ Hz, 1H, OH), 3.51 (d/d, $J = 9.8/12.8$ Hz, 2H, CH_2I), 3.80 (s, 3H, OCH_3), 4.51 (m, 1H, CHMe), 4.75 (poorly resolved t, 1H,

CH_2CHOH). — $^{13}\text{C NMR}$ (CDCl_3): $\delta = 5.33$ (CH_2I), 21.14 (CHCH_3), 42.39 (CH_2CHOH), 59.99 (OCH_3), 76.63 (CHMe), 76.45 (CH_2CHOH), 89.08 (OCCH_2I), 172.64 ($\text{C}=\text{O}$). — MS (70 eV): m/z (%) = 241 (100) [$\text{M}^+ - \text{CO}_2\text{Me}$], 169 (35), 141 (13), 114 (52).

$\text{C}_8\text{H}_{13}\text{IO}_4$ (300.1) Calcd. C 32.02 H 4.37
Found C 32.04 H 4.16

CAS Registry Numbers

2: 99032-03-8 / **3a**: 129812-21-1 / **3b**: 129812-22-2 / **4**: 129832-99-1 / $\text{CH}_2=\text{CHCO}_2\text{Me}$: 96-33-3

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