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Preparation of Optically Active (*S*)-2-(Benzyloxy)propanal*

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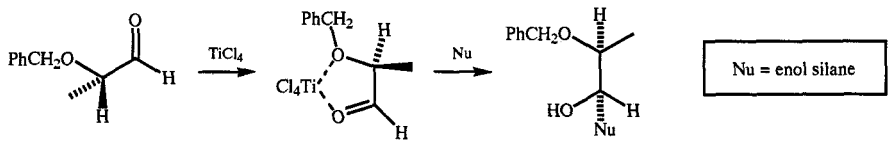
Abstract

A convenient and large scale amenable preparation of optically active ethyl (*S*)-2-(benzyloxy)propionate (5) from ethyl (*S*)-lactate (4), and the conversion of the ester (5) by two alternative methods into (*S*)-2-(benzyloxy)propanal (1) are described.

The report by Reetz and coworkers[1] in 1983 that (*S*)-2-(benzyloxy)propanal (1) underwent reaction in a highly stereoselective manner with a variety of enol silanes via an octahedral complex (Scheme 1), and the fact that this aldehyde is readily available in optically pure form from inexpensive starting materials have attracted considerable interest in the use of (1) as a synthon for stereocontrolled organic reactions.[2–7] Indeed, the stereocontrol achievable with this aldehyde, and its application in the field of natural product synthesis have been elegantly demonstrated on several occasions.[8–11]



(1) (2) (3)

Scheme 1. Stereochemical outcome of a chelation-controlled nucleophilic addition to the aldehyde (1).

* (*S*)-2-(Benzyloxy)propanal is also known by the trivial name of (*S*)-*O*-benzyllactaldehyde.

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It is perhaps then not surprising that several procedures for the preparation of this useful aldehyde, in both optically active and racemic forms, have been published.[11–19] A review of these procedures reveals that the methods most frequently used to obtain the aldehyde (1) employ ethyl (*S*)-2-(benzyloxy)propionate (5).* This ester is generally obtained in optically pure form by *O*-benzylation of commercially available ethyl (*S*)-lactate (4) with silver(I) oxide according to the method described by Mislow *et al.*[20] Whilst this method is high yielding and does not result in epimerization of the desired ester it is, however, somewhat inconvenient to use in that purification of the crude product is effected by chromatography.[21] Consequently the silver(I) oxide promoted *O*-benzylation of ethyl (*S*)-lactate (4) is not amenable to large scale preparation of ethyl (*S*)-2-(benzyloxy)propionate (5). We report here a method that is both convenient and amenable to large scale preparation of optically active ethyl (*S*)-2-(benzyloxy)propionate (5) by *O*-benzylation of ethyl (*S*)-lactate (4) with benzyl bromide–sodium hydride, and compare two alternative methods for its conversion into (*S*)-2-(benzyloxy)propanal (1).

O-Benzylation of ethyl (*S*)-lactate (4) (Scheme 2) with sodium hydride and benzyl bromide in tetrahydrofuran/*N*,*N*-dimethylformamide (thf/dmf) afforded the ester (5) in 88% yield, and $[\alpha]_D$ −88·2° (*c*, 10 in $CHCl_3$) was recorded. The optical purity of (5) was determined with the chiral shift reagent $Eu(hfc)_3$, and on this basis an e.e. of greater than 98% was assigned to the ester (5). These results are in contrast to the report that *O*-benzylation of ethyl (*S*)-lactate with sodium hydride–benzyl bromide results in considerable racemization[6] of the ester (5) and proceeds in low yield.[22]

O-Benzylation of ethyl (*S*)-lactate (4) was also performed according to the method described by Mislow *et al.*[20] for the purpose of comparing the optical rotations of the ester (5) obtained by the two alternative procedures. Thus, treatment of ethyl (*S*)-lactate (4) with silver(I) oxide–benzyl bromide gave a crude product, which was shown by ^1H n.m.r. spectroscopy to contain 20 mole % of dibenzyl ether.[21] Distillation of the crude product through a spinning band column effected separation of the two components and provided the ester (5) with $[\alpha]_D$ −87·7° (*c*, 6·0 in $CHCl_3$), which compares favourably with that of

* This compound is also known by the trivial name of ethyl (*S*)-*O*-benzyllactate.

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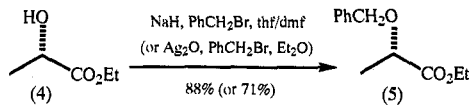
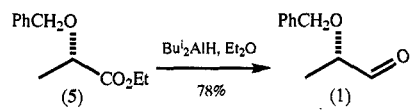
the ester (5), $[\alpha]_D$ $-88\cdot2°$ (c, 10 in $CHCl_3$), obtained by our procedure. It is interesting to compare the optical rotation of our samples of the ester (5) obtained by both methods with that reported by Cue and Moore,[23] $[\alpha]_D$ $-83\cdot3°$ (c, $1\cdot13$ in $CHCl_3$), a value which is the highest reported for this compound.

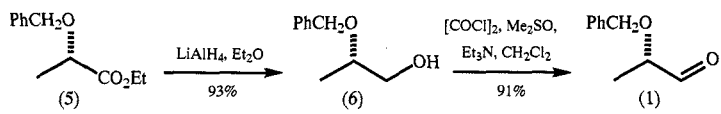


Scheme 2



Scheme 3

The first procedure examined for the conversion of the ester (5) into the aldehyde (1) was by partial reduction of the ester with diisobutylaluminium hydride (Bu^i_2AlH). Schlessinger and Graves[9] have obtained the aldehyde (1) (described as an unstable compound) by reduction of the ester (5) with $1\cdot2$ equiv. of (Bu^i_2AlH) in dichloromethane. In our hands, reduction of the ester under these conditions gave the aldehyde (1) as a stable, distillable oil, which on the basis of a gas chromatographic analysis was found to contain 5% of the ester (5) and 1% of 2-(benzyloxy)propan-1-ol (6). Increasing or decreasing the reaction time gave varying amounts of all three compounds. On the other hand, using 1 equiv. of (Bu^i_2AlH) gave mixtures containing up to 20% of the reactant (5). However, the aldehyde (1) was obtained in a chemically pure state (gas chromatography) by this method when the reduction was performed in the more Lewis acid coordinating solvent ether rather than dichloromethane (Scheme 3). The aldehyde obtained in this manner had $[\alpha]_D$ $-49\cdot6°$ (c, $6\cdot2$ in $CHCl_3$). It should be noted that the aldehyde (1), and its (R) antipode have been described by Baker and Hawkins[16] as compounds that hydrate (or alcoholate) rapidly upon exposure to moisture, or solvent that contained traces of moisture (or alcohol). This was noted by the authors to cause considerable difficulty in obtaining reproducible optical rotations for these compounds. We found that a reproducible optical rotation for the aldehyde (1) could be obtained by using dry chloroform which had been passed through neutral alumina, rather than the reported method of allowing the aldehyde to stand for at least 6 h in 95:5 ethanol/water before measuring its optical rotation.[16]



Scheme 4

The alternative procedure used to prepare the aldehyde (1) was by Swern oxidation of the alcohol (6) (Scheme 4), and was preferred to the diisobutylaluminium hydride method because the product consistently gave higher optical rotations. Reduction of the ester (5) with lithium aluminium hydride gave (S)-2-(benzyloxy)propan-1-ol (6). Swern oxidation of the primary alcohol by using a modification of the published methods[6,12] provided the crude aldehyde (1), which was purified by distillation after ensuring trace amounts of triethylammonium chloride were removed by

[23] Cue, B. W., and Moore, B. S., U.S. Pat. 4412958 (1983) (*Chem. Abstr.*, 1983, **99**, 121997h).

trituration with pentane, and gave $[\alpha]_D$ −53·8° (*c*, 6·6 in $CHCl_3$). The optical purity of the aldehyde could not be assayed from its Eu(hfc)$_3$-complexed ^1H n.m.r. spectrum because the signals were far too broad for an accurate analysis. The optical purity of (1) was indirectly established by reducing a specimen with lithium aluminium hydride in ether to the corresponding alcohol, which was then assayed by ^1H n.m.r. spectroscopy after addition of Eu(hfc)$_3$. Thus, when 7·5 mole % of Eu(hfc)$_3$ was added to a 10% solution of the alcohol (6) with an e.e. of 60% in HCl-free (D)chloroform the n.m.r. signal of the methyl protons for the (*S*) antipode occurred at 1·88 ppm and that for the (*R*) antipode occurred at 1·99 ppm. When this protocol was applied to the aldehyde (1) with $[\alpha]_D$ −53·8° (*c*, 6·6 in $CHCl_3$), the n.m.r. signal of the methyl protons of the enantiomeric material was not detected.

Experimental

Optical rotations were measured in 1-dm cells of 1 ml capacity. Chloroform, when used as a solvent for optical rotation determinations, was filtered through neutral alumina immediately prior to use. ^1H n.m.r. spectra were measured in (D)chloroform on a Bruker AM-300 instrument (300 MHz). Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. These data are reported as follows: chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet; br, broad), coupling constant (Hz), relative area, assignment.

Ethyl (*S*)-2-(Benzyloxy)propionate (5)

Procedure A: *With Sodium Hydride–Benzyl Bromide*

Ethyl (*S*)-lactate (4), $[\alpha]_D$ −10·8° (l = 1, neat) (23·6 g, 0·20 mol), was added dropwise to a stirred mixture of benzyl bromide (36·0 g, 0·21 mol), sodium hydride (4·8 g, 0·20 mol), dry tetrahydrofuran (150 ml) and *N*,*N*-dimethylformamide (100 ml) cooled to −20°C (bath). After 30 min, the reaction mixture was allowed to warm to room temperature over 30 min, and then heated in an oil bath at 50°C (bath) for 30 min. The resulting mixture was poured into a mixture of water (500 ml) and petrol (300 ml). The organic layer was separated and the aqueous phase was extracted with a 1:1 mixture of ether and petrol (2×100 ml). The organic layer and extracts were combined and washed with water (2×100 ml), brine (200 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a yellow oil, which was distilled to give ethyl (*S*)-2-(benzyloxy)propionate (5) as a colourless oil (36·6 g, 88%, b.p. 90–96°C/0·5 mm, $[\alpha]_D$ −88·2° [*c*, 10 in $CHCl_3$]; lit.[20] b.p. 105·5–106°C/1·5 mm, lit.[23] $[\alpha]_D$ −83·3° [*c*, 1·13 in $CHCl_3$]). ^1H n.m.r. δ 1·30, d, J 7·1 Hz, 3H, OCH_2CH_3; 1·44, d, J 6·7 Hz, 3H, CH_3CH; 4·05, q, J 6·7 Hz, 1H, H2; 4·22, m, 2H, OCH_2CH_3; 4·55, A part of an AB pattern, J 12·0 Hz, 1H, PhCHH; 4·69, B part of an AB pattern, J 12·0 Hz, 1H, PhCHH; 7·34, m, 5H, ArH. The ^1H n.m.r. spectrum was identical with that reported.[19]

Procedure B: *With Silver(I) Oxide–Benzyl Bromide*

O-Benzylation of ethyl (*S*)-lactate (5), $[\alpha]_D$ −10·8° (l = 1, neat), was carried out by the method of Knowles *et al.*[21] except that the crude ester was purified by distillation through a spinning band column rather than by chromatography. This afforded ethyl (*S*)-2-(benzyloxy)propionate (5) in 71% yield (b.p. 110–111°C/11 mm, $[\alpha]_D$ −87·7° [*c*, 6·0 in $CHCl_3$]; lit.[20] b.p. 105·5–106°C/1·5 mm, lit.[23] $[\alpha]_D$ −83·3° [*c*, 1·13 in $CHCl_3$]). The ^1H n.m.r. spectrum was identical with that described above.

(*S*)-2-(Benzyloxy)propan-1-ol (6)

Ethyl (*S*)-2-(benzyloxy)propionate (5), $[\alpha]_D$ −88·2° (*c*, 10 in $CHCl_3$), was reduced with lithium aluminium hydride according to the method of Takai and Heathcock,[6] except that the crude product was purified by distillation only. This gave (*S*)-2-(benzyloxy)propan-1-ol (6) as a colourless oil (93%, b.p. 90–93°C/0·5 mm, $[\alpha]_D$ +46·3° [*c*, 7·5 in $CHCl_3$]; lit.[6] b.p.

95°C/1 mm, $[\alpha]_D$ +45·86° [*c*, 6·4 in $CHCl_3$]). ^1H n.m.r. δ 1·16, d, *J* 6·2 Hz, 3H, CH_3CH; 2·39, br s, 1H, OH; 3·48, m, 1H, CHHOH; 3·57, m, 1H, CHHOH; 3·64, m, 1H, CH_3CH; 4·47, A part of an AB pattern, *J* 11·6 Hz, 1H, PhCHH; 4·63, B part of an AB pattern, *J* 11·6 Hz, 1H, PhCHH; 7·34, m, 5H, ArH. The ^1H n.m.r. spectrum was consistent with that reported.[6]

(*S*)-2-(Benzyloxy)propanal (1)

Procedure A: *Reduction of Ethyl* (S)-*2-(Benzyloxy)propionate (5) with* Bu^i_2AlH

A solution of diisobutylaluminium hydride in hexane (2·0 M, 8·4 ml, 16·8 mmol) was added dropwise to a stirred solution of the ester (5) (2·6 g, 12·7 mmol, $[\alpha]_D$ −88·2°[*c*, 10 in $CHCl_3$]) in dry ether (30 ml) cooled to −78°C (bath). After 2·5 h, a saturated aqueous solution of sodium sulfate (20 ml) was added and the mixture was allowed to warm to room temperature, and then filtered through a pad of Celite. The filter cake was thoroughly washed with ether, and the filtrate and washings were combined and washed with water (3×100 ml), saturated aqueous sodium bicarbonate (100 ml), brine (100 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residual oil, which was distilled under reduced pressure to give (*S*)-2-(benzyloxy)propanal (1) as a colourless oil (1·6 g, 78%, b.p. 150°C/0·1 mm (Kugelrohr), $[\alpha]_D$ −49·6° [*c*, 6·2 in $CHCl_3$]; lit.[12] b.p. 100°C/0·1 mm (bulb to bulb), $[\alpha]_D$ −65·85° [neat], lit.[6] $[\alpha]_D$ −52·2° [*c*, 6·6 in $CHCl_3$]). ^1H n.m.r. δ 1·32, d, *J* 7·0 Hz, 3H, CH_3CH; 3·88, dq, *J* 7·0, 1·8 Hz, 1H, CH_3CH; 4·57, A part of an AB pattern, *J* 11·8 Hz, 1H, PhCHH; 4·67, B part of an AB pattern, *J* 11·8 Hz, 1H, PhCHH; 7·34, m, 5H, ArH; 9·66, d, *J* 1·8 Hz, 1H, CHO. The ^1H n.m.r. spectrum was identical with that reported.[12]

Procedure B: *Swern Oxidation of* (S)-*2-(Benzyloxy)propan-1-ol (6)*

A solution of oxalyl chloride (3·4 g, 26·8 mmol) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of dimethyl sulfoxide (3·2 g, 41·0 mmol) in dichloromethane (75 ml) cooled to −78°C (bath). After 10 min, a solution of the alcohol (6) (3·3 g, 20·1 mmol, $[\alpha]_D$ +46·3° [*c*, 7·5 in $CHCl_3$]) in dichloromethane (10 ml) was added dropwise and the resulting mixture was stirred at −78°C for 15 min. A solution of triethylamine (5·2 g, 51·4 mmol) in dichloromethane (10 ml) was then added dropwise and the resulting suspension was stirred at −78°C for 30 min. The cooling bath was removed and the mixture was allowed to warm to 0°C, then poured into a mixture of water (200 ml) and dichloromethane (100 ml). The organic layer was separated and washed with water (2×100 ml), brine (100 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil, which was triturated with pentane, and then filtered through a pad of Celite. Evaporation of the solvent under reduced pressure, and distillation of the residue gave (*S*)-2-(benzyloxy)propanal (1) as a faint yellow oil (3·0 g, 91%, b.p. 150°C/0·1 mm (Kugelrohr), $[\alpha]_D$ −53·8° [*c*, 6·6 in $CHCl_3$]; lit.[12] b.p. 100°C/0·1 mm (bulb to bulb), $[\alpha]_D$ −65·85° [neat], lit.[6] $[\alpha]_D$ −52·2° [*c*, 6·6 in $CHCl_3$]). The ^1H n.m.r. spectrum was identical with that described above.

Acknowledgment

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