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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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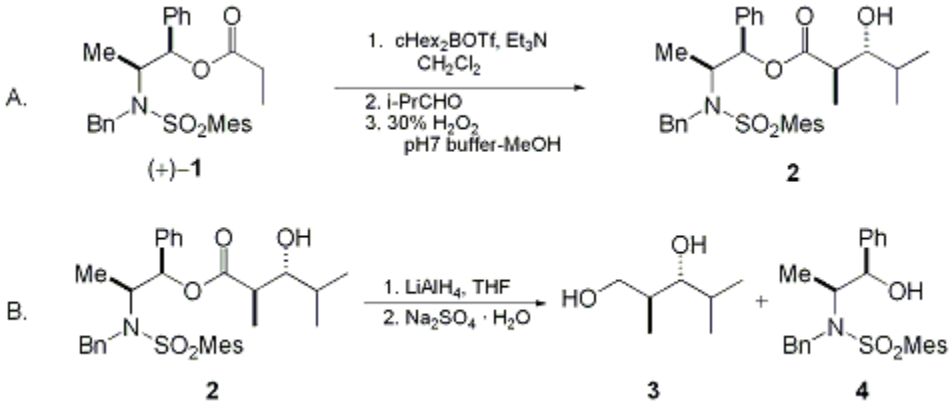
# ANTI-SELECTIVE BORON-MEDIATED ASYMMETRIC ALDOL REACTION OF CARBOXYLIC ESTERS: SYNTHESIS OF (2S, 3R)-2,4-DIMETHYL-1,3-PENTANEDIOL

**[ 1,3-Pentanediol, 2,4-dimethyl-, [S-(R*,S*)- ]**




Submitted by Atsushi Abiko[1]
Checked by Eric M. Flamme and William R. Roush.

## 1. Procedure

*A. (1'R)-Phenyl-(2'S)-[(phenylmethyl)[(2,4,6-trimethylphenyl)sulfonyl]amino]-propyl (3R)-hydroxy-(2R),4-dimethylpentanoate* .[2] An oven-dried, 500-mL, round-bottomed flask is charged with (1R, 2S)-(+)-**1** (4.80 g, 10 mmol) (Note 1) and dichloromethane (50 mL) (Note 2) under nitrogen. To this solution is added triethylamine (3.40 mL, 24 mmol) (Note 2) via syringe. The solution is cooled to −78° C and a solution of dicyclohexylboron triflate (1.0 M in hexane, 22 mL, 22 mmol) (Note 3) is added dropwise over 20 min. The resulting solution is stirred at −78°C for 30 min. To the −78°C enolate solution is then added isobutyraldehyde (1.08 mL, 12 mmol, freshly distilled) dropwise. The reaction mixture is stirred for 30 min at −78°C and allowed to warm to room temperature over 1 hr, then quenched by the addition of pH 7 buffer solution (40 mL). The mixture is diluted with methanol (MeOH, 200 ml) and 30% hydrogen peroxide (20 mL) is added carefully (Note 4). The mixture is stirred vigorously overnight and then concentrated on a rotary evaporator. The residue is partitioned between water (100 mL) and dichloromethane (200 mL). The aqueous layer is extracted with dichloromethane (150 mL × 2). The combined organic extracts are washed with water (100 mL × 3) and dried with anhydrous sodium sulfate . The solids are removed by flitration, and the organic layer is concentrated. The residue (Notes 5, 6) is crystallized from 80% hexane-20% ethyl acetate (EtOAc, 80 mL) to afford (+)-**2** (4.1 g, 74%) with a diastereomeric purity of 24 : 1 (Note 7). The mother liquors are concentated using a rotary evaporator, and the residue is diluted with mesitylene (50 mL). This mixture is distilled at ≈60°C (0.1 mm) to remove cyclohexanol . The resulting material is purified by chromatography over silica gel (30 g) (Note 2) using a 9 : 1 : 1 mixture of hexane, ethyl acetate and dichloromethane (Note 8) to give isomerically pure (+)-**2** (0.8 g, 14%) (Note 9). If desired, the material from the first crystallization may also be purified by silica gel chromatography to give diastereomerically pure product (Note 10).

*B. (2S, 3R)-2,4-Dimethyl-1,3-pentanediol* ***3*** . To a stirred solution of (+)-**2** (2.75 g, 5 mmol, 96 : 4 isomeric purity) in tetrahydrofuran (THF) (50 mL) is added lithium aluminum hydride (0.19 g, 5 mmol) at 0°C. The reaction mixture is stirred at room temperature for 1 hr and quenched by the careful addition of sodium sulfate decahydrate (5 g). The mixture is stirred vigorously for 30 min and filtered. The filtrate is concentrated, dissolved in 75 mL of a 1:1 mixture of hexane and dichloromethane . This solution is dried over sodium sulfate, filtered and concentrated under reduced pressure. Trituration of

the resulting oil with hexane (50 ml) results in the precipitation of auxiliary alcohol **4** (1.6-1.8 g) which is recovered by filtration (Note 11). The residue is separated by chromatography over silica gel (40 g) (Note 2) with hexane and ethyl acetate (3:1-1:1) to afford additional **4** (0.2-0.4 g, Note 12) and **3** (0.60 g, 92%) (Notes 13, 14).

## 2. Notes

1. (1R,2S)-(+)- **1** was prepared according to the accompanying procedure (Abiko, A. *Org. Synth*. **2002**, *79*, 109).
2. Dichloromethane and triethylamine were distilled from calcium hydride before use. Silica gel 60, 0.040-0.063 mm (Merck) was used for column choromatography. Lithium aluminum hydride (95%, powder) was obtained from Aldrich Chemical Co., Inc.
3. A stock solution (1 M) of dicyclohexylboron trifluromethanesulfonate was prepared according to the accompanying procedure (Abiko, A. *Org. Synth*. **2002**, *79*, 103). Two equivalents of the boron triflate are necessary for complete enolization of the ester. When one equivalent is used, the enolization proceeds only to 50% conversion.
4. Addition of hydrogen peroxide may cause a vigorous exothermic reaction.
5. The reaction may be monitored by TLC using a solvent mixture of 90% hexanes and 10% ethyl acetate . Starting material **1** has an $R_f$ = 0.37 and the product **2** has an $R_f$ = 0.25. Both spots were visualized by UV detection. It is possible to visualize the minor diastereoisomer by using a dilute TLC sample and a solvent system of 85% hexanes and 15% ethyl acetate . Under these conditions product **2** has an $R_f$ = 0.32 and the minor aldol diastereoisomer has an $R_f$ = 0.27.
6. HPLC analysis [21 mm Dynamax-60A column (Si 83-111-C), 78% hexanes-22% ethyl acetate , 10 ml/min flow rate, UV detection; retention time for **1** = 14 min; retention time for **2** = 16.5 min; retention time for minor aldol diastereoisomer = 17.9 min] of the crude reaction product showed that the residue contained 10-15% of the starting ester and that the two anti aldol products were obtained in 96 : 4 ratio. The submitter found the product ratio to be 97 : 3 by HPLC analysis, with less than 3% of the starting ester remaining.
7. Attempts to further purify this material by additional recrystallizations were unsuccessful. The submitter indicated that diastereomerically pure **2** could be obtained by additional recrystallizations from 85 : 15 hexanes-ethyl acetate , but the checkers were unable to achieve this result. However, the two aldol diastereomers can be separated chromatographically, as described in the body of the procedure.
8. The submitter performed this chromatography step using a 5 : 1 mixture of hexane and ethyl acetate . However, the checkers found that the mother liquors did not dissolve in this solvent mixture, and added dichloromethane to the chromatography mixture to solve this problem.
9. The physical and spectral data of (+)-**2** are as follows: mp 142-142.5°C, $[\alpha]_D^{23}$ 19.7° (c 2.05, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ: 0.90 (d, 3H, J = 6.7), 0.95 (d, 3H, J = 6.8), 1.10 (d, 3H, J = 7.2), 1.17 (d, 3H, J = 7.0), 1.73, (m, 1H), 2.28 (s, 3H), 2.37 (br s, 1H, OH), 2.49 (s, 6H), 2.62 (dq, 1H, J = 7.1, 7.2), 3.41 (br, 1H), 4.11 (dq, 1H, J = 4.4, 7.0), 4.55 (1H, A of ABq, $J_{AB}$ = 16.5), 4.79 (1H, B of ABq, $J_{AB}$ = 16.5), 5.82 (d, 1H, J = 4.4), 6.82-6.86 (m, 2H), 6.87 (s, 2H), 7.12-7.33 (m, 8H) ; $^{13}$C NMR ($CDCl_3$) δ: 13.4, 14.2, 15.5, 19.8, 20.7, 22.8, 30.0, 42.9, 48.1, 56.7, 77.6, 78.1, 125.8, 127.0, 127.6, 127.8, 128.2, 128.3, 132.0, 133.3, 138.1, 138.5, 140.1, 142.4, 174.8 . Anal. Calcd for $C_{32}H_{41}NO_5S$: C, 69.66; H, 7.49; N, 2.54. Found: C, 69.84; H, 7.62; N, 2.53.
10. In one run (5.0-mmol scale), the checkers obtained a crude product that contained ca. 40% of recovered **1**. Attempts to purify the aldol product from this mixture by using the described crystallization procedure was unsuccessful. Accordingly, the crude product (2.36 g) was purified by flash chromatography on 170 g of silica gel using 1000 ml of a 9 : 1 : 1 mixture of hexane, ethyl acetate and methylene chloride . This provided 0.72 g of starting ester **1**, 1.39 g of pure aldol **2**, and 0.259 g of mixed fractions containing **2** and the minor aldol diastereoisomer (4 : 1 by 1H NMR analysis).
11. If the auxiliary does not precipitate during the trituration step, the solution is not sufficiently dry or may contain too much dichloromethane . Under these circumstances, the solution should be concentrated, redried with sodium sulfate, and the trituration procedure repeated. The checkers also found that trituration is best performed by spinning the flask on a rotary evaporator (at atmospheric pressure) for several minutes. Swirling the flask by hand was not always successful.
12. The checkers found that small amounts of ester **2** (2-7%) remained unreacted, even when 1.1 equiv of lithium aluminum hydride was used for the reduction. Progress of the reduction can be monitored by

TLC ( 70% hexane, 30% ethyl acetate ): **2**, $R_f$ = 0.75; **3**, Rf = 0.2; **4**, $R_f$ = 0.75. Because **2** and **4** co-elute under the chromatography conditions, auxiliary **4** recovered by chromatography is not pure.
13. The submitter and checkers have successfully performed this procedure on double the reaction scale [10 mmol of (+)-**2**], and obtained the product in 92% yield.
14. The spectroscopic properties of product (2S, 3R)-**3** are as follows: $[\alpha]_D^{23}$ 19.6° (c 0.57, $CHCl_3$), lit.[2] 19.6° (c 0.75, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ: 0.78 (d, 3 H, J = 7), 0.81 (d, 3 H, J = 6.6), 0.87 (d, 3 H, J = 7.0), 1.73 (m, 2H), 3.24(dd, 1 H, J = 3.4, 8.0), 3.53 (1 H, B of ABX, $J_{AB}$ =10.8, $J_{BX}$ = 7), 3.65 (1 H, A of ABX, $J_{AB}$ = 10.8, $J_{AX}$ = 3.7), 3.70 (br s, 2 H, OH) ; $^{13}$C NMR ($CDCl_3$) δ: 14.0, 15.2, 20.0, 30.5, 37.2, 68.0, 81.8 ; Anal. Calcd for $C_7H_{16}O_2$: C, 63.60; H, 12.20. Found: C, 63.42; H, 12.01.

## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

Several methods for the anti-selective, asymmetric aldol reaction[3] recorded in the literature include (i) the use of boron, titanium, or tin(II) enolate carrying chiral ligands,[4] (ii) Lewis acid-catalyzed aldol reactions of a metal enolate of chiral carbonyl compounds,[5] and (iii) the use of the metal enolate derived from a chiral carbonyl compound.[6] Although many of these methods provide anti-aldols with high enantioselectivities, these methods are not as convenient or widely applicable as the method reported here, because of problems associated with the availability of reagents, the generality of reactions, or the required reaction conditions.

The present procedure is based on the original report by the author and co-workers,[7] and utilizes the characteristic features of the boron-mediated aldol reaction of carboxylic esters, represented by the ability to produce either anti- or syn-aldols under the specified reaction conditions.[8] The reliability and practicality of the boron- mediated aldol reaction have been demonstrated by many examples.[9] Both enantiomers of the chiral auxiliary alcohol in this procedure are prepared from readily available (−)- or (+)-norephedrine in three easy steps in high overall yield.[10] The auxiliary alcohol could be recovered in nearly quantitative yield (and reused) with the transformation of the aldol products to chiral diols or other derivatives. The stoichiometry of the boron triflate required for the enolization of carboxylic esters was determined empirically. The present procedure is applicable to a wide range of aldehydes with high selectivity (both syn:anti and diastereofacial selectivity of anti isomer); see the following Table.[7] An application to a natural product synthesis has been reported.[11]

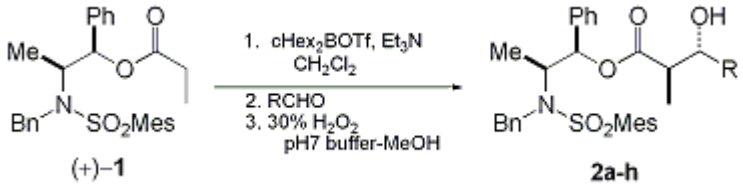
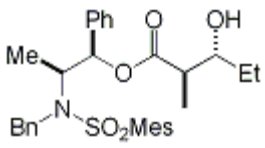
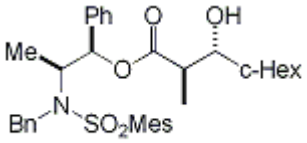
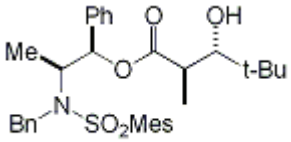
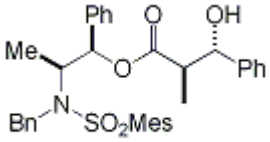
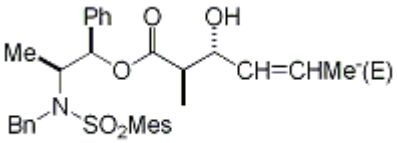
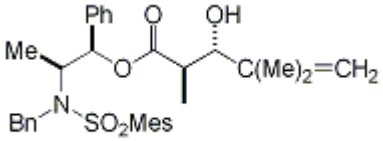
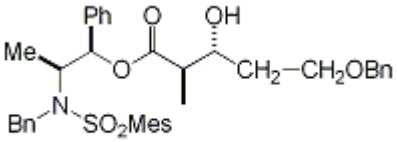
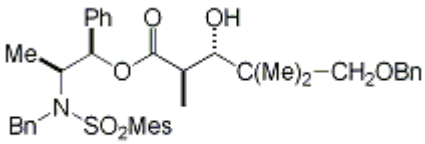



Table Boron-Mediated Asymmetric Aldol Reactions

| Aldehyde, R- | yield (%)[a] | ds for anti[a] | product | mp (°C); $[\alpha]_D$ in $CHCl_3$ |
|---|---|---|---|---|
| Et-   **2a-h** | 90 | 96:4 | **2a** | 128-129; 16.2° (c 1.52) |
| c-Hex- | | | | |

| | | | | | |
|---|---|---|---|---|---|
|  **2a-h** tert-Bu- | 91 | 95:5 | **2b** | glass; 21.7° (c 2.40) |
|  **2a-h** Ph- | 96 | 99:1 | **2c** | 185-186; 22.1° (c 1.70) |
|  **2a-h** (E)-MeCH=CH- | 93 | 95:5 | **2d** | glass; 18.9° (c 1.70) |
|  **2a-h** $CH_2$=C(Me)- | 96 | 98:2 | **2e** | glass; 24.8° (c 1.25) |
|  **2a-h** $BnOCH_2CH_2$- | 97 | 96:4 | **2f** | 97-98; 19.7° (c 1.32) |
|  **2a-h** $BnOCH_2C(Me)_2$- | 94 | 95:5 | **2g** | glass; 16.2° (c 1.30) |
|  **2a-h** | 98 | 96:4 | **2h** | 109-110; 16.2° (c 1.30) |

[a] Yield and isomer ratio by HPLC. Syn isomers <2%.

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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1'R)-Phenyl-(2'S)-[(phenylmethyl)[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl (3R)-hydroxy-(2R), 4-dimethylpentanoate:
Pentanoic acid, 3-hydroxy-2,4-dimethyl-1-phenyl-2-[(phenylmethyl)[(2,4,6-trimethylphenyl)sulfonyl] amino]propyl ester, [2R-[1(1R*, 2S*)2R*,3R*]]- (14); (187324-70-5)

2(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propyl propionate :
Benzenesulfonamide, 2,4,6-trimethyl-N-[1-methyl-2-(1-oxopropoxy)-2-phenylethyl]-N-(phenylmethyl)-, [R-(R*,S*)]- (14); (187324-66-9)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)

Dicyclohexylboron trifluoromethanesulfonate:
Methanesulfonic acid, trifluoro-, anhydride with
dicyclohexylborinic acid (13); (145412-54-0)

Isobutyraldehyde (8);
Propanal, 2-methyl- (9); (78-84-2)

Hydrogen peroxide (8,9); (7722-84-1)

(2S,3R)-2,4-Dimethyl-1,3-pentanediol:
1,3-Pentanediol, 2,4-dimethyl-, [S-(R*,S*)]- (12); (129262-73-3)

Lithium aluminum hydride:
Aluminate (1−), tetrahydro-, lithium (8);
Aluminate (1−), tetrahydro-, lithium, (T-4) (9); (16853-85-3)