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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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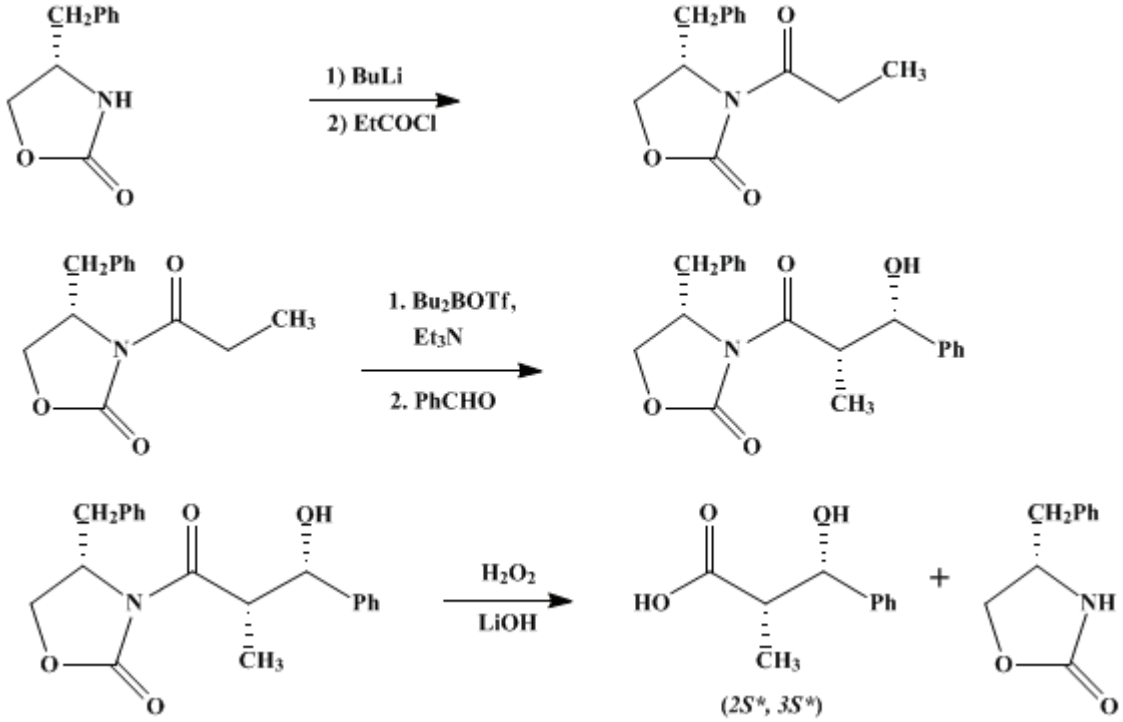
DIASTEREOSELECTIVE ALDOL CONDENSATION USING A CHIRAL OXAZOLIDINONE AUXILIARY: (2*S**,3*S**)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID

[Benzenepropanoic acid, β-hydroxy-α-methyl-, [*S*-(*R,*R**)]-]**



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1. Procedure

A. *(S)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone*. A dry, 500-mL flask equipped with a magnetic stirring bar is charged with 17.7 g (0.100 mol) of (*S*)-4-(phenylmethyl)-2-oxazolidinone,[2] capped with a rubber septum, and flushed with nitrogen. Anhydrous tetrahydrofuran, 300 mL (Note 1), is then added to the flask via cannula, and the resulting solution is cooled to −78°C in an acetone–dry ice bath. A solution of 68.3 mL (0.101 mol) of 1.47 *M* butyllithium in hexane (Note 2) is transferred via cannula first to a dry, septum-stoppered, 100-mL graduated cylinder with a ground-glass joint, and then to the reaction flask over a 10-min period. The solution may turn yellow and slightly cloudy. Freshly distilled propionyl chloride (9.6 mL, 0.11 mol, (Note 3) is added in one portion by syringe after completion of the addition of butyllithium. The resulting clear, nearly colorless solution is stirred for 30 min at −78°C, then allowed to warm to ambient temperature over a 30-min period. Excess propionyl chloride is quenched by the addition of 60 mL of saturated aqueous ammonium chloride. The bulk of the tetrahydrofuran and hexane is removed on a rotary evaporator (bath temp. ca. 25–30°C), and the resulting slurry is extracted with two 80-mL portions of dichloromethane. The combined organic extracts are washed with 75 mL of an aqueous 1 *M* sodium hydroxide solution and 75 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed by rotary evaporation, and the residue, a light-yellow oil, is placed in a refrigerator overnight to crystallize. The resulting crystalline solid is pulverized and triturated with a minimum quantity of cold hexane. After filtration and drying 21.2–22.3 g (91–96%) of the desired product is obtained as a colorless crystalline solid, mp 44–46°C (Note 4) and (Note 5).

B. *The boron aldol reaction*. Into a dry, 2-L flask equipped with a large magnetic stirring bar is introduced 21.2 g (0.091 mol) of the acylated oxazolidinone. The flask is sealed with a rubber septum and swept with nitrogen. The solid is dissolved in 200 mL of anhydrous dichloromethane (Note 6), which is introduced via syringe. A thermometer is inserted through the rubber septum, and the contents of the flask are cooled to 0°C with an ice bath. To this cooled solution is added via syringe 27 mL (0.107 mol) of dibutylboron triflate followed by 16.7 mL (0.120 mol) of triethylamine (Note 7) dropwise at such a rate as to keep the internal temperature below +3°C. The solution may turn slightly yellow or green during the dibutylboron triflate addition, and then to light yellow when triethylamine is added. The ice bath is then replaced with a dry ice–acetone bath (Note 8). When the internal temperature drops below −65°C, 10.3 mL (0.101 mol) of freshly distilled benzaldehyde is added over a 5-min period via syringe. The solution is stirred for 20 min in the dry ice–acetone bath, then for 1 hr at ice-bath temperature. The reaction mixture is quenched by the addition of 100 mL of a pH 7 aqueous phosphate buffer and 300 mL of methanol. To this cloudy solution is added by syringe 300 mL of 2 : 1 methanol–30% aqueous hydrogen peroxide at such a rate as to keep the internal temperature below +10° C. After the solution is stirred for an additional 1 hr, the volatile material is removed on a rotary evaporator at a bath temperature of 25–30°C. The resulting slurry is extracted with three 500-mL portions of diethyl ether. The combined organic extracts are washed with 500 mL of 5% aqueous sodium bicarbonate and 500 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, to afford 35–36 g of a white solid (Note 9). The unpurified aldol adduct has a diastereomeric purity of >97% as determined by gas chromatography (Note 10). The solid is recrystallized from ca. 500 mL of 1 : 2 ethyl acetate–hexane to yield 25.8 g (84%) of the desired aldol adduct, mp 92–93°C (Note 12). The mother liquor is purified by flash chromatography (column dimensions: 8 × 20 cm) with flash-grade silica gel (Note 13).[3] On elution with 25% ethyl acetate-hexane, an additional 2.8 g (9%) of diastereomerically pure material is obtained.

C. *Chiral auxiliary removal*. A 500-mL flask fitted with a magnetic stirring bar is charged with 8.48 g (0.025 mol) of the aldol adduct and 125 mL of 4 : 1 tetrahydrofuran–distilled water. The flask is sealed with a rubber septum, purged with nitrogen, and cooled to 0°C in an ice bath. To this solution is added via syringe 10.2 mL (0.100 mol) of 30% aqueous hydrogen peroxide (Note 14) over a 5-min period, followed by 0.96 g (0.040 mol) of lithium hydroxide in 50 mL of distilled water. Some gas evolves from the clear solution. After the solution is stirred for 1 hr, the septum is removed, and 12.6 g (0.100 mol) of sodium sulfite in 75 mL of distilled water is added. The bulk of the tetrahydrofuran is removed on a rotary evaporator at a bath temperature of 25–30°C, and the resulting mixture (pH 12–13) is extracted with three 100-mL portions of dichloromethane to remove the oxazolidinone auxiliary. The aqueous layer is cooled in an ice bath and acidified to pH 1 by the addition of an aqueous 6 *M* hydrochloric acid solution. The resulting cloudy solution containing the β-hydroxy acid is then extracted with five 100-mL portions of ethyl acetate. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated, affording 5.1 g of a white crystalline solid, which is dissolved in approximately 200 mL of an aqueous 5% sodium bicarbonate solution. This solution is extracted with two 100-mL portions of dichloromethane and then acidified and extracted with ethyl acetate as before. The combined dichloromethane extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 4.35 g (99%) of the oxazolidinone auxiliary as a white crystalline solid. This solid is recrystallized from 50 mL of 2 : 1 ethyl acetate–hexane to give 3.95 g (89%) of the recovered oxazolidinone as white crystals, mp 85–87°C. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 4.50 g (100%) of the desired hydroxy acid as a white crystalline solid, which is recrystallized from ca. 20 mL of carbon tetrachloride to give 4.00–4.03 g (89–90%) of pure (2S*,3S*)-3-hydroxy-3-hydroxy-3-phenyl-2-methylpropanoic acid, mp 89.5–90°C (Note 15).

2. Notes

1. Reagent-grade tetrahydrofuran was purchased from Fisher Scientific Company and either freshly distilled from sodium metal and benzophenone or dried at least 3 days over activated Linde 4A molecular sieves before use in Reaction A. It was used as received for reaction C.
2. Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc. and titrated prior to use.[4]
3. Propionyl chloride (d, 1.065) was obtained from Aldrich Chemical Company, Inc., and distilled prior

to use.
4. Trituration by the checkers gave 21.2–22.3 g (91–96%) of acylated product of somewhat higher purity: mp 45–46°C; $[\alpha]_D^{22}$ +99.5° (ethanol, *c* 1.01). Alternatively, the acylated oxazolidinone can be isolated by distillation (Kugelrohr, 125°C, 12 mm). Isolated yields were 97–99%.
5. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1}: 3030, 2980, 1780, 1705, 1455, 1385, 1245, 1210, 1080; ^1H NMR ($CDCl_3$) δ: 1.2 (t, 3 H, J = 7.2, CH_3), 2.8 (dd, 1 H, J = 13.3, 9.6, $CH_2C_6H_5$), 2.9 (m, 2 H, CH_2CH_3), 3.3 (dd, 1 H, J = 13.4, 3.3, $CH_2C_6H_5$), 4.1 (m, 2 H, $CHCH_2O$), 4.7 (m, 1 H, NCH), 7.1–7.5 (m, 5 H, ArH); $[\alpha]_D$ +92.9° (ethanol, *c* 1.01).
6. Dichloromethane was distilled from calcium hydride.
7. Dibutylboron triflate was prepared according to the method of Mukaiyama.[5] It is also available from Aldrich Chemical Company, Inc. as a solution in dichloromethane or diethyl ether, but results with this material are inconsistent. It should be used within 2 weeks of preparation or after redistillation. Triethylamine (Fisher Scientific Company) was distilled from calcium hydride immediately prior to use.
8. The entire reaction can be carried out at 0°C if desired. The ratio of diastereomers in the unpurified product mixture falls slightly to 97.6 : 0.2 : 2.2 (Note 10).
9. The checkers isolated a colorless viscous oil that crystallized on addition of 1 : 2 ethyl acetate–hexane. Care must be taken to avoid an excess of hexane, since oiling of the product can occur under these circumstances.
10. Diastereomer ratios were determined by gas chromatography. Since the aldol adduct undergoes retroaldol reaction on the column, it must be silylated prior to injection. Approximately 5 mg of the crude adduct is filtered through a short plug of silica gel to remove any trace metals. The material is taken up into 1–2 mL of dichloromethane in a 2-mL flask or small test tube. To this solution are added 4–5 drops of *N,N*-diethyl-1,1,1-trimethylsilylamine and a small crystal of 4-(*N,N*-dimethylamino) pyridine (Note 11). The solution is stirred for 2 hr and injected directly onto the column. (Column conditions: 30-m × 0.32-mm fused-silica column coated with DB 5, 14-psi hydrogen carrier gas, oven temperature 235°C.)
11. *N,N*-Diethyl-1,1,1-trimethylsilylamine and 4-(*N,N*-dimethylamino)pyridine were purchased from Aldrich Chemical Company, Inc.
12. The product has the following spectroscopic characteristics: IR (solution in dichloromethane) cm^{-1}: 3520, 3040, 2980, 1780, 1695, 1455, 1385, 1210, 1110; ^1H NMR ($CDCl_3$) δ: 1.2 (d, 3 H, J = 7.0, CH_3), 2.8 (dd, 1 H, J = 13.4, 9.5, 1 H $CH_2C_6H_5$), 3.1 (d, 1 H, J = 2.7, OH), 3.3 (dd, 1 H, J = 13.4, 3.4, $CH_2C_6H_5$), 4.1 (m, 3 H, $CHCH_2O$, $CHCH_3$), 4.6 (m, 1 H, NCH), 5.1 (m, 1 H, HOCH), 7.1–7.5 (m, 10 H, ArH); $[\alpha]_D$ +75.7° (dichloromethane, *c* 1.00).
13. Kieselgel 60 was purchased from EM Science, Cherry Hill, NJ, an affiliate of E. Merck, Darmstadt.
14. Hydrogen peroxide was obtained from Mallinckrodt, Inc.
15. The following spectroscopic characteristics were observed: IR (solution in dichloromethane) cm^{-1}: 3600, 3400–2300 broad hump, 3040, 3000, 1710, 1455, 1230; ^1H NMR ($CDCl_3$) δ: 1.2 (d, 3 H, J = 7.1, CH_3), 2.9 (m, 1 H, $CHCH_3$), 5.2 (d, 1 H, J = 3.9, C_6H_5CH), 7.2–7.4 (m, 5 H, ArH); $[\alpha]_D^{22}$ −26.4° (CH_2Cl_2, *c* 1.04). No epimerization was detected by NMR.

3. Discussion

This procedure demonstrates a particularly effective method for controlling the relative and absolute stereochemistry of the aldol reaction. It is quite general in scope.[6] Alkyl-, aryl, and α,β-unsaturated aldehydes all give good results. In addition to chiral propionates,[7] a range of related aldol reactions may be carried out. For example, the analogous aldol reactions of thioalkyl,[7] benzyloxy,[8] or haloacetate,[9] as well as succinate-[7] and crotonate-derived[10] carboximides, have been reported.

In addition to the high levels of asymmetric induction, two other attractive features of this sequence of reactions warrant comment. First, both acylation and hydrolysis of the chiral auxiliary are facile, high-yield reactions. Second, we have recently found that the lithium hydroperoxide hydrolysis protocol described in Part C is the method of choice for the *deacylation* process. This reagent exhibits remarkable regioselectivity for attack at the desired exocyclic acyl carbonyl moiety.[11]

References and Notes

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

silica gel

(2S*,3S*)-3-hydroxy-3-hydroxy-3-phenyl-2-methylpropanoic acid

(2S*,3S*)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID

Benzenepropanoic acid, β-hydroxy-α-methyl-, [S-(R*,R*)]-

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

propionyl chloride (79-03-8)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

lithium hydroxide (1310-65-2)

N,N-diethyl-1,1,1-trimethylsilylamine (996-50-9)

4-(N,N-dimethylamino)pyridine (1122-58-3)

dibutylboron triflate

lithium hydroperoxide

(S)-4-(Phenylmethyl)-2-oxazolidinone (90719-32-7)

(S)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (101711-78-8)