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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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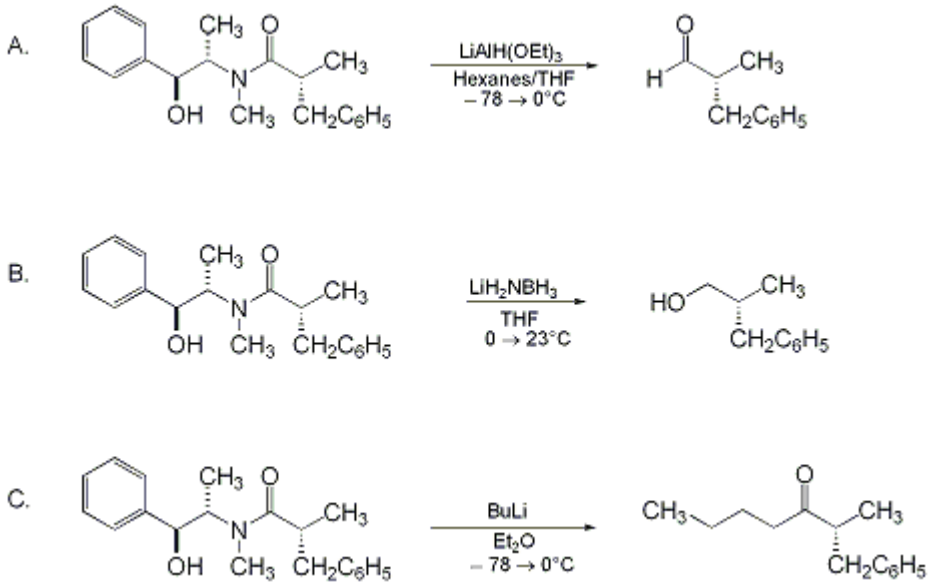
TRANSFORMATION OF PSEUDOEPHEDRINE AMIDES INTO HIGHLY ENANTIOMERICALLY ENRICHED ALDEHYDES, ALCOHOLS, AND KETONES



Submitted by Andrew G. Myers, Bryant H. Yang, and Hou Chen[1] .
Checked by William J. Smith, III and William R. Roush.

1. Procedure

A. (R)-α-Methylbenzenepropanal. A flame-dried, 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 2.95 g (73.9 mmol) of 95% lithium aluminum hydride (Note 1) under a nitrogen atmosphere. The flask is sealed with a rubber septum containing a needle adapter to an argon-filled balloon and is charged with 170 mL of hexanes (Note 2). The septum is removed and the flask is equipped with an oven-dried, 25-mL, pressure-equalizing addition funnel sealed with a rubber septum containing a needle adapter to an argon-filled balloon. The reaction flask is cooled to 0°C in an ice-water bath, the addition funnel is charged with 10.7 mL (109 mmol) of ethyl acetate (Note 3), and slow, dropwise addition of ethyl acetate is initiated and completed within 1.25 hr (Note 4). Upon completion of the addition, the addition funnel is removed, the reaction vessel is sealed with a rubber septum containing a needle adapter to an argon-filled balloon, and the reaction flask is cooled to −78°C in a dry ice-acetone bath. A solution of 10.0 g (32.1 mmol) of (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide (Note 5) in 110 mL of tetrahydrofuran (Note 6) is added to the cold suspension of lithium triethoxyaluminum hydride [2] [$LiAlH(OEt)_3$] via cannula over 5 min. Upon completion of the addition, the dry ice-acetone bath is removed and the reaction mixture is warmed to 0°C in an ice-water bath. During the course of warming, substantial gas evolution is observed and vented using a needle as necessary. The reaction mixture is stirred at 0°C for 1 hr, then transferred via a wide-bore cannula into a vigorously stirring solution of 400 mL of 1 N aqueous hydrochloric acid solution and 25 mL (325 mmol) of trifluoroacetic acid (Note 7) in an argon-purged, three-necked, 2-L, round-bottomed flask equipped with a mechanical stirrer and two rubber septa on the side-arms, one containing a needle adapter to an argon-filled balloon. A quantitative transfer is effected with 10 mL of tetrahydrofuran , and the biphasic hydrolysis mixture is stirred vigorously for 5 min at 23°C, then is poured into a 2-L separatory funnel containing 700 mL of 1 N aqueous hydrochloric acid solution (Note 8). After the layers are shaken vigorously, they are separated and the aqueous layer is further extracted with three 150-mL portions of ethyl acetate . The combined organic layers are extracted with 250 mL of saturated aqueous sodium bicarbonate solution with care to avoid excessive build-up of pressure in the separatory funnel. The aqueous phase is separated and extracted with 100 mL

of ethyl acetate (Note 9). This ethyl acetate extract is combined with the other organic extracts, and the resulting solution is dried over anhydrous sodium sulfate , filtered, and concentrated under reduced pressure (Note 10). The residue is purified by flash column chromatography (230-400 mesh silica gel, 270 g , packed with hexanes and eluted with 7.5% ethyl acetate-hexanes) to afford 3.64 g (76%) of (R)-α-methylbenzenepropanal as an oil (Note 11). The enantiomeric excess (ee) of this product is determined to be 95% (Note 12).

B. (R)-β-Methylbenzenepropanol . A flame-dried, 1-L, three-necked, round-bottomed flask equipped with a large, football-shaped, Teflon-coated magnetic stirring bar is sealed under argon with three rubber septa, one containing a needle adapter to an argon-filled balloon. One septum is removed briefly while the reaction flask is charged with 150 mL of tetrahydrofuran (Note 6), and the septum is replaced, sealing the flask. The flask is cooled to −78°C in a dry ice-acetone bath. Diisopropylamine (18.9 mL, 135 mmol, (Note 13)) and 53.5 mL (125 mmol) of a 2.34 M solution of butyllithium in hexanes (Note 14), respectively, are added to the reaction flask. The resulting yellow solution is stirred at −78°C for 10 min, then at 0°C (ice-water bath) for 5 min, and finally is cooled to −78°C. After 10 min, one of the rubber septa is removed, 4.41 g (129 mmol) of solid 90% borane-ammonia complex (Note 15) is added to the cold reaction solution in one portion, and the flask is sealed again with a rubber septum. The resulting suspension is warmed to 0°C and is stirred at that temperature for 20 min, during which time gas evolution is observed, and a sticky, white foam develops (Note 16). The suspension is warmed to 23°C in order to facilitate stirring and, after 20 min, the suspension of lithium amidotrihydroborate [3] is cooled to 0°C in an ice-water bath. After 10 min, a solution of 10.0 g (32.1 mmol) of (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide (Note 5) in 150 mL of tetrahydrofuran is added to the suspension of lithium amidotrihydroborate via cannula over 3 min (Note 17). A quantitative transfer is effected with 5 mL of tetrahydrofuran . The ice-water bath is removed, and the reaction mixture is stirred at 23°C for 50 min. The reaction mixture is cooled to 0°C, one of the septa is removed, and excess hydride is quenched by the cautious addition of 10-mL portions of 3 N aqueous hydrochloric acid solution (350 mL total) over 5 min (Note 18). The biphasic mixture is stirred at 23°C for 30 min, then poured into a 1-L separatory funnel. The aqueous layer is separated and extracted with three 150-mL portions of ether . The combined organic fractions are washed with 50 mL of 3 N aqueous hydrochloric acid solution followed by 50 mL of brine . The organic layer is dried over anhydrous magnesium sulfate , filtered, and concentrated under reduced pressure (Note 19). The residue is purified by flash column chromatography (230-400 mesh silica gel, 250 g , 43% ether-petroleum ether as eluent) to afford 4.35 g (90%) of analytically pure (R)-β-methylbenzenepropanol as a colorless oil (Note 20). The ee of this product is determined to be ≥95% (Note 21).

C. (R)-2-Methyl-1-phenyl-3-heptanone. A flame-dried, 500-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 10.0 g (32.1 mmol) of (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide (Note 5) and 50 mL of toluene (Note 22). This mixture is warmed with a heat gun until a clear solution is obtained. The solvent is removed under reduced pressure to afford a powdery white residue (Note 23). The flask is flushed with argon, charged with 250 mL of ether (Note 24), and then sealed with a rubber septum containing a needle adapter to an argon-filled balloon. The reaction flask is cooled to −78°C in a dry ice-acetone bath and 32.3 mL (77.2 mmol) of a 2.39 M solution of butyllithium in hexanes (Note 14) is added slowly via syringe over 5 min. The reaction mixture is stirred for 5 min at −78°C after which time the dry ice-acetone bath is removed and replaced with an ice-water bath. During the course of warming to 0°C, the reaction suspension clears to form a yellow solution. After 15 min at 0°C, 4.5 mL (32 mmol) of diisopropylamine (Note 13) is added to the reaction mixture to scavenge any excess butyllithium. After 15 min further stirring at 0°C, 100 mL of a solution of acetic acid (20% v/v) in ether is added as a final quench, producing a white flocculent precipitate. The mixture is transferred to a 1-L separatory funnel with 300 mL of water and 300 mL of ethyl acetate . After vigorous mixing, the phases are allowed to separate, giving two clear, colorless layers. The aqueous layer is separated and extracted with two 300-mL portions of dichloromethane . The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (230-400 mesh silica gel, 350 g , graded elution with 2 → 5% ethyl acetate-hexanes) yields 5.80 g (88%) of analytically pure (R)-2-methyl-1-phenyl-3-heptanone (Note 25), (Note 26). The ee of this product is determined to be ≥95% (Note 27), (Note 28).

2. Notes

1. Lithium aluminum hydride (95%) was obtained from Aldrich Chemical Company, Inc. , and was stored under an atmosphere of nitrogen.
2. Hexanes used in the preparation of $LiAlH(OEt)_3$ was distilled from calcium hydride under an atmosphere of nitrogen.
3. Ethyl acetate used in the preparation of $LiAlH(OEt)_3$ was distilled from calcium hydride under an atmosphere of argon.
4. Slow addition of ethyl acetate is crucial in order to achieve complete reaction in the reduction step. Rapid addition of ethyl acetate (≤5 min) results in incomplete reduction of the amide.
5. (1S,2S)-Pseudoephedrine-(R)-2-methylhydrocinnamamide was prepared as described in the preceding procedure.
6. Tetrahydrofuran was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen.
7. Trifluoroacetic acid was obtained from Mallinckrodt, Inc. , and was used without further purification.
8. This operation is necessary to hydrolyze the pseudoephedrine aminal which forms as a direct product of the reduction, in addition to the desired aldehyde. The use of the additional 700 mL of 1 N aqueous hydrochloric acid solution was found to be crucial for this hydrolysis reaction.
9. The pH of the aqueous phase following the addition of sodium bicarbonate is approximately 4. If the pH is less than 4, additional sodium bicarbonate should be added until the pH is 4 or slightly above. Small amounts of the pseudoephedrine aminal remain at this point, but are hydrolyzed during the rotary evaporation step.
10. Rotary evaporation was conducted at or below 30°C to prevent trifluoroacetic acid-induced decomposition of the aldehyde as well as its evaporative loss.
11. The product exhibits the following properties: $[\alpha]_D^{25}$ +13.3° (MeOH, *c* 0.46); ^{1}H NMR (300 MHz, C_6D_6) δ: 0.69 (d, 3 H, J = 6.9), 2.0-2.2 (m, 2 H), 2.72 (dd, 1 H, J = 13.2, 5.4), 6.8-7.1 (m, 5 H), 9.29 (d, 1 H, J = 1.2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.1, 36.5, 48.0, 126.3, 128.4, 128.9, 138.7, 204.3 ; IR (neat) cm^{-1}: 3028, 2971, 2932, 2814, 2716, 1723 (C=O), 1496, 1454, 742, 701 ; HRMS (EI) m/z 148.0890 [(M^+) calcd for $C_{10}H_{12}O$: 148.0888]. Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04, H, 8.16. Found: C, 80.98, H, 8.25.
12. The ee of this product was determined by oxidation[4] to the corresponding carboxylic acid (see following paragraph) followed by preparation and analysis of the corresponding (R)-α-methylbenzylamide.

A 25-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 26 mg (0.18 mmol) of (R)-α-methylbenzenepropanal , 4.0 mL of 2-methyl-2-propanol , 1.0 mL (2.0 mmol) of a 2.0 M solution of 2-methyl-2-butene in tetrahydrofuran (purchased from Aldrich Chemical Company, Inc., and used as received), and a solution of 0.17 g (1.9 mmol) of sodium chlorite (Aldrich Chemical Company, Inc.; 80% technical grade) and 0.20 g (1.4 mmol) of sodium dihydrogen phosphate monohydrate (Aldrich Chemical Company, Inc.) in 2.0 mL of water. The reaction flask is sealed with a rubber septum and the yellow, biphasic mixture is stirred vigorously at 23°C for 50 min, then partially concentrated by the removal of tetrahydrofuran, 2-methyl-2-butene, and 2-methyl-2-propanol on the rotary evaporator. The residue is transferred to a 125-mL separatory funnel with 50 mL of water and 0.5 mL of saturated aqueous sodium bicarbonate solution and the aqueous mixture is extracted with two 7-mL portions of 10% ethyl acetate-hexanes . The aqueous phase is acidified to pH 2 by the addition of 1.5 mL of 1 N aqueous hydrochloric acid solution, and the acidified solution is extracted with three 15-mL portions of ethyl acetate . The latter ethyl acetate extracts are combined, dried over anhydrous sodium sulfate , filtered, and concentrated under reduced pressure to afford 27 mg of crude (R)-α-methylbenzenepropanoic acid . The corresponding (R)-α-methylbenzylamide was prepared and analyzed by capillary gas chromatography as described in the following paragraph.

The following procedure describes the preparation and analysis of the (R)-α-methylbenzylamide of (R)-α-methylbenzenepropanoic acid. A flame-dried, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum is charged with 25 mg (0.15 mmol) of (R)-α-methylbenzenepropanoic acid , 31 mg (0.23 mmol) of 1-hydroxybenzotriazole hydrate , 44 mg (0.23 mmol) of 1-(3-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride , and 0.50 mL of anhydrous N,N-dimethylformamide . This mixture is stirred at 23°C for 10 min, then cooled to 0°C in an ice-water bath. To the cooled solution, 24 μL (0.19 mmol) of R-(+)-α-methylbenzylamine and 86 μL (0.62 mmol)

of triethylamine are added. Within 1 min, a fine white precipitate appears. The mixture is stirred for 1 hr at 0°C, then warmed to 23°C. After stirring for 20 hr at 23°C, the mixture is transferred to a 30-mL separatory funnel with 10 mL of dichloromethane . The product solution is extracted, sequentially, with four 10-mL portions of 1 N aqueous hydrochloric acid solution, 10 mL of saturated aqueous sodium bicarbonate solution, and 10 mL of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a white crystalline solid. The solid residue is dissolved in ethyl acetate for capillary gas chromatographic analysis. The analysis is carried out using a Chirasil-Val capillary column (25 m × 0.25 mm × 0.16 μm, Alltech, Inc.) under the following conditions: oven temp. 180°C, injector temp. 250°C, detector temp. 275°C. The following retention times are observed: 10.55 min (major diastereomer), 11.61 min (minor diastereomer). It should be noted that the retention times can vary greatly depending on the age and condition of the column. 1-Hydroxybenzotriazole hydrate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N,N-dimethylformamide and R-(+)-α-methylbenzylamine were purchased from Aldrich Chemical Company, Inc. and used without further purification. Triethylamine was purchased from Aldrich Chemical Company, Inc. and was distilled from calcium hydride under an atmosphere of nitrogen.

13. Diisopropylamine was obtained from Aldrich Chemical Company, Inc. , and distilled from calcium hydride under an atmosphere of nitrogen.

14. Butyllithium (2.5 M solution in hexanes) was purchased from Aldrich Chemical Company, Inc. , and titrated against diphenylacetic acid.[5]

15. Borane-ammonia complex (90%) was obtained from Aldrich Chemical Company, Inc. , and stored and transferred under nitrogen.

16. The foam is found to impede, but not prevent, magnetic stirring.

17. As the addition proceeds, the foam dissipates and stirring becomes increasingly more facile.

18. In addition to quenching excess hydride, the acidification and subsequent extraction steps remove pseudoephedrine and any tertiary amine reaction by-product; the latter is otherwise difficult to remove by column chromatography.

19. The residue contains (R)-β-methylbenzenepropanol and an alkoxy borane species that undergoes quantitative hydrolysis to (R)-β-methylbenzenepropanol during the subsequent chromatography step. As an alternative to flash column chromatography, the alkoxy borane species can be cleaved by treatment of the residue with 1 N aqueous sodium hydroxide solution.

20. The product exhibits the following properties: $[\alpha]_D^{25}$ +11.2° (benzene, *c* 4.2); ^{1}H NMR (300 MHz, C_6D_6) δ: 0.62 (t, 1 H, J = 5.2), 0.77 (d, 3 H, J = 6.7), 1.70 (m, 1 H), 2.22 (dd, 1 H, J = 13.3, 8.0), 2.62 (dd, 1 H, J = 13.3, 6.2), 3.15 (m, 2 H), 7.0-7.2 (m, 5 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4, 37.7, 39.6, 67.4, 125.7, 128.2, 129.0, 140.6 ; IR (neat) cm^{-1}: 3332 (OH), 3001, 2956, 2922, 2872, 1603, 1495, 1454, 1378, 1032, 986, 739, 700 ; HRMS (CI) m/z 148.0890 [$(M + NH_4^+)$. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.67; H, 9.05.

21. The ee of the alcohol was determined by analysis of the corresponding Mosher ester derivative[6] by high resolution ^{1}H NMR spectroscopy (400 MHz, C_6D_6). The preparation of the Mosher ester is described below.

A 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 40 mg (0.17 mmol) of (trifluoromethyl)phenylacetic acid . Dry benzene (2 mL) is added and the resulting solution is concentrated. The flask is sealed with a rubber septum containing a needle adapter to an argon-filled balloon and is charged with 1.0 mL of dichloromethane . To the resulting clear solution is added 19 μL (0.22 mmol) of oxalyl chloride and 2.0 μL (0.026 mmol) of anhydrous N,N-dimethylformamide . The latter addition causes bubbling, which persists for ~10 min. The mixture is stirred an additional 20 min at 23°C, then cooled to 0°C in an ice-water bath. The adapter to the argon-filled balloon is replaced with a needle leading to a source of vacuum and the flask is cautiously evacuated. After 30 min stirring under reduced pressure (0.5 mm) to remove dichloromethane and excess oxalyl chloride, the flask is flushed with argon. The resulting crude preparation of (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride is dissolved in 1.0 mL of dichloromethane , and the resulting clear solution is transferred via cannula to an ice-cooled, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum and containing a solution of 9.0 mg (0.060 mmol) of (R)-β-methylbenzenepropanol , 2.0 mg (0.016 mmol) of 4-dimethylaminopyridine , and 42 μL (0.30 mmol) of triethylamine in 0.5 mL of dichloromethane . The ice-water bath is removed, and the clear yellow reaction solution is stirred at 23°C for 24 hr. The reaction mixture is transferred to a 30-mL separatory funnel with 10 mL of dichloromethane , and the

solution is extracted, sequentially, with two 10-mL portions of saturated aqueous ammonium chloride solution, two 10-mL portions of saturated aqueous sodium bicarbonate solution, and 10 mL of water. The organic layer is dried over anhydrous sodium sulfate , filtered, and concentrated under reduced pressure to give a yellow oil. The residue is purified by passage through a Pasteur pipette half-filled with 230-400 mesh silica gel using 30% ethyl acetate-hexanes as the eluent. Care is taken to collect all fractions containing the Mosher ester. Concentration of these fractions under reduced pressure affords a clear, colorless oil that is analyzed by ^{1}H NMR spectroscopy (400 MHz, C_6D_6). Integration of a pair of doublets of doublets corresponding to the major diastereomer (3.97-4.04 ppm and 3.76-3.82 ppm) against those corresponding to the minor diastereomer (3.86-3.95 ppm) allows accurate determination of the ee of the original alcohol. (R)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, oxalyl chloride, 4-dimethylaminopyridine, and anhydrous N,N-dimethylformamide were obtained from Aldrich Chemical Company, Inc. , and were used without further purification. Benzene and dichloromethane used in the preparation of the Mosher ester were obtained from EM Science and were distilled from calcium hydride under a nitrogen atmosphere.

22. Toluene was purchased from EM Science and was distilled from calcium hydride under a nitrogen atmosphere.

23. This step is conducted to dry the amide, as well as to render it a fine powder.

24. Ether was purchased from EM Science and was distilled from sodium benzophenone ketyl under a nitrogen atmosphere.

25. This product exhibits the following properties: $[\alpha]_D^{25}$ −79.0° (benzene, *c* 2.1); ^{1}H NMR (300 MHz, C_6D_6) δ: 0.85 (t , 3 H, J = 7.3), 1.07 (d, 3 H, J = 6.9), 1.23 (sx, 2 H, J = 7.4), 1.45 (m, 2 H), 2.25 (dt, 1 H, J = 7.3, 16.9), 2.39 (dt, 1 H, J = 7.3, 16.9), 2.55 (dd, 1 H, J = 7.3, 13.2), 2.83 (sx, 1 H, J = 7.0), 2.97 (dd, 1 H, J = 7.1, 13.2), 7.20 (m, 5 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 16.5, 22.3, 25.6, 39.1, 41.7, 48.1, 126.2, 128.3, 128.9, 139.8, 214.4 ; IR (neat) cm^{-1}: 3028, 2959, 2932, 2873, 1947, 1878, 1805, 1712 (C=O), 1604, 1496, 1454, 1406, 1375, 1130, 1032, 992, 746, 700 ; HRMS (EI) m/z 204.1517 [$(M)^+$ calcd for $C_{14}H_{20}O$: 204.1514]. Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.14; H, 9.59.

26. The checkers also obtained 2-3% of (R)-3-butyl-2-methyl-1-phenylheptan-3-ol , resulting from addition of 2 equiv of butyllithium to the amide carbonyl. This by-product stains brightly on analytical TLC plates (phosphomolybdic acid or cerium molybdate stain) and has an R_f of 0.2 in 5% EtOAc-hexanes.

27. The ee of this product was determined by reduction to the corresponding alcohol with lithium aluminum hydride followed by preparation and analysis of the Mosher ester derivatives[6] by ^{1}H NMR spectroscopy (400 MHz, C_6D_6), as described in the following procedure.

A flame-dried, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 102 mg (0.50 mmol) of (R)-2-methyl-1-phenyl-3-heptanone and sealed with a rubber septum containing a needle adapter to an argon-filled balloon. The flask is charged with 1.0 mL of ether and cooled to 0°C whereupon 0.75 mL (0.75 mmol) of a solution of lithium aluminum hydride in ether (1.0 M) is added slowly via syringe. After stirring the reaction mixture for 15 min at 0°C, the septum is removed and 1 mL of water is added cautiously dropwise until gas evolution subsides. To the resulting cloudy mixture is added 2 mL of 15% w/v aqueous sodium hydroxide solution. This mixture is transferred to a 30-mL separatory funnel with 10 mL of water, and the resulting solution is extracted with three 10-mL portions of dichloromethane . The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. This crude preparation of diastereomeric alcohols (ca. 1:1 ratio) is used directly in the subsequent esterification step with the Mosher acid chloride, as described below.

A 0.3 M solution (0.50 mL, 0.15 mmol) of R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in dichloromethane is transferred via cannula to an ice-cooled, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and containing a solution of 10 mg (0.05 mmol) of the crude alcohol, 6 mg (0.05 mmol) of 4-dimethylaminopyridine , and 71 µL (0.51 mmol) of triethylamine in 1.0 mL of dichloromethane . The ice-water bath is removed, and the clear yellow reaction solution is stirred at 23°C for 24 hr. The reaction mixture is transferred to a 30-mL separatory funnel with 10 mL of dichloromethane , and the solution is extracted, sequentially, with two 10-mL portions of saturated aqueous ammonium chloride solution, two 10-mL portions of saturated aqueous sodium bicarbonate solution, and 10 mL of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. The residue is purified by passage through a Pasteur pipette half-filled with 230-400 mesh silica gel using 30% ethyl acetate-hexanes as the eluent.

Care is taken to collect all fractions containing the Mosher esters. Concentration of these fractions under reduced pressure affords a clear, colorless oil that is analyzed by ^{1}H NMR spectroscopy (400 MHz, C_6D_6). Integration of a pair of doublets of doublets corresponding to the major diastereomer pairs (2.67 ppm) against those corresponding to the minor diastereomer pairs (2.74 ppm) allows accurate determination of the ee of the original ketone. 1.0 M Lithium aluminum hydride solution in ether and 4-dimethylaminopyridine were obtained from Aldrich Chemical Company, Inc. , and were used without further purification. Dichloromethane used in the preparation of the Mosher ester was obtained from EM Science and was distilled from calcium hydride under a nitrogen atmosphere. (R)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride was prepared from (S)-(−)-α-methoxy-α-(trifluoromethyl) phenylacetic acid, as described in (Note 21).
28. The ee determined by the checkers was 97% ee.

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

These procedures illustrate the various methods used to transform pseudoephedrine amides into highly enantiomerically enriched aldehydes, alcohols, and ketones, and are applicable over a wide range of pseudoephedrine amide substrates.[7,8] Reduction of pseudoephedrine amides to the corresponding aldehydes is best achieved using Brown and Tsukamoto's lithium triethoxyaluminum hydride reagent,[2] whereas reduction to the corresponding primary alcohols is best achieved with a new reagent, lithium amidotrihydroborate (LAB).[3] In connection with the preceding procedure describing the synthesis and alkylation of pseudoephedrine amides, these methods provide access to a wide range of useful optically active synthetic intermediates in a highly practical manner.

References and Notes

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

(R)-α-Methylbenzenepropanal:
Benzenepropanal, α-methyl-, (R)- (9); (42307-59-5)

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

Ethyl acetate:
Acetic acid, ethyl ester (8,9); (141-78-6)

[1S(R),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N, 2-dimethylbenzene

propionamide:
(1S,2S)-Pseudoephedrine-(R)-2-methylhydrocinnamide:

Benzenepropanamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-N, α-dimethyl-,[1S-[1R(R),2R]]- (13); (159345-08-1); [1S-[1R(S),2R]]- (13); (159345-06-9)

Lithium triethoxyaluminum hydride:
Aluminate (1−), triethoxyhydro-, lithium (8);
Aluminate (1−), triethoxyhydro-, lithium, (I-4), (9); (17250-30-5)

Trifluoroacetic acid:
Acetic acid, trifluoro- (8,9); (76-05-1)

(R)-β-Methylbenzenepropanol:
Benzenepropanol, β-methyl-, (R)- (10); (77943-96-5)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Borane-ammonia complex: EXPLODES WHEN HEATED:
Borane, monoammoniate (8,9); (13774-81-7)

Lithium amidotrihydroborate:
Borate (1−), amidotrihydro-, lithium, (I-4)- (11); (99144-67-9)

(R)-2-Methyl-1-phenyl-3-heptanone:
3-Heptanone, 2-methyl-1-phenyl-, (R)- (13); (159213-12-4)

2-Methyl-2-propanol:
tert-Butyl alcohol (8);
2-Propanol, 2-methyl- (9); (75-65-0)

2-Methyl-2-butene:
2-Butene, 2-methyl- (8,9); (513-35-9)

Sodium dihydrogen phosphate:
Phosphoric acid, monosodium salt (8,9); (7558-80-7)

(R)-α-Methylbenzenepropanoic acid:
Benzenepropanoic acid, α-methyl-, (R)- (8); (14367-67-0)

1-Hydroxybenzotriazole hydrate:
1H-Benzotriazole, 1-hydroxy-, hydrate (12); (12333-53-9)

1-(3-Dimethylamino)propyl-3-ethylcarbodiimide hydrochloride:

Carbodiimide,

[3-(dimethylamino)propyl]ethyl-, monohydrochloride (8);
1,3-Propanediamine,

N'-(ethylcarbonimidoyl)-N,N-dimethyl-, monohydrochloride (9); (25952-53-8)

N,N-Dimethylformamide: CANCER SUSPECT AGENT:
Formamide, N,N-dimethyl- (8,9); (68-12-2)

(R)-(+)-α-Methylbenzylamine:
Benzylamine, α-methyl-, (R)-(+)- (8);

Benzenemethanamine, α-methyl-, (R)- (9); (3886-69-9)

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

(R)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid:
Hydratropic acid,
β,β,β-trifluoro-α-methoxy-, (+)- (9); (20445-31-2)

Benzene: CANCER SUSPECT AGENT: (8,9); (71-43-2)

Oxalyl chloride (8);
Ethanedioyldichloride (9); (79-37-8)

(S)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride:
Hydratropoyl chloride,
β,β,β-trifluoro-α-methoxy-, (+)- (8,9); (20445-33-4)

4-Dimethylaminopyridine: HIGHLY TOXIC:
Pyridine, 4-(dimethylamino)- (8);
4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

Phosphomolybdic acid:
Molybdophosphoric acid (9); (51429-74-4)

Cerium (III) molybdate:
Molybdic acid, cerium salt (9); (53986-44-0)

(S)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid:
Hydratropic acid,
β,β,β-trifluoro-α-methoxy-, (S)-(−)- (8);
Benzeneacetic acid,
α-methoxy-α-(trifluoromethyl)-, (S)- (9); (17257-71-5)