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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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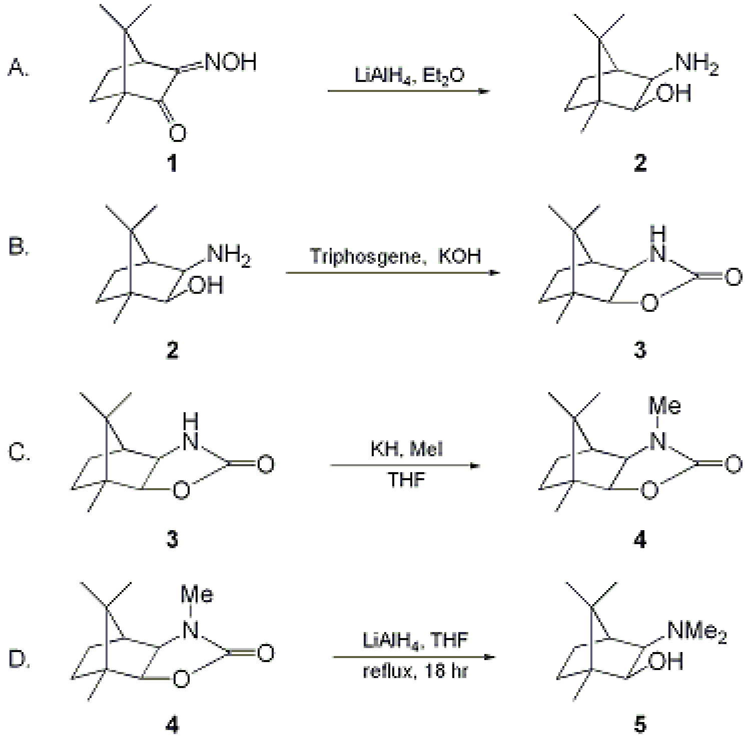
(2S)-(−)-3-exo-(DIMETHYLAMINO)ISOBORNEOL [(2S)-(−)-DAIB]

[Bicyclo[2.2.1]heptan-2-ol, 3-(dimethylamino)-1,7,7-trimethyl-, [1R-(exo,exo)]-]



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Checked by Christopher E. Neipp and Stephen F. Martin.

1. Procedure

A. (2S)-(−)-3-exo-Aminoisoborneol , **2**. All glassware for this step must be oven-dried prior to use. A 2-L, three-necked, round-bottomed flaskequipped with an efficient mechanical stirrer attached to a Teflon stirring blade, a thermometer, and a 1-L pressure-equalizing addition funnel connected to an argon inlet is flushed with argon and charged with 475 mL of dry diethyl ether (Note 1) and 5.12 g (0.14 mol) of lithium aluminum hydride Note 2. The addition funnel is charged with a solution of 8.46 g (0.047 mol) of (1R,4S)-(−)-camphorquinone monoxime (**1**) (Note 3) in 350 mL of dry ether. The reaction mixture is cooled to 0°C in an ice-water bath with stirring, and the solution of **1** is added slowly to the reaction mixture over 30 min (Note 4). After the addition is complete, the addition funnel is replaced with a reflux condenser connected to the argon inlet, and the reaction flask is removed from the cooling bath. The reaction mixture is stirred and heated at reflux for 1.5 hr and then cooled to 0°C in an ice-water bath. The reaction is quenched very carefully by dropwise addition of 75 mL of saturated aqueous sodium sulfate solution (Notes 5 and 6). The resulting white granular precipitate or slurry is removed by vacuum filtration through Celite, and the filter cake is washed with three portions of 75 mL of chloroform . The combined filtrate and washings are dried over sodium sulfate , filtered, and concentrated by rotary evaporation at 40°C to give 8.07 g of crude (2S)-(−)-3-exo-aminoisoborneol (**2**) as an off-white solid (Note 7). This material is suitable for the next reaction without purification.

B. (1R,2S,6R,7S)-1,10,10-Trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0]decane , **3**. A 500-mL, single-necked, round-bottomed flask equipped with a 250-mL pressure-equalizing dropping funnel and a magnetic stirring bar is charged with 8.06 g (0.048 mmol) of crude (2S)-(−)-3-exo-aminoisoborneol (**2**), 70 mL of toluene , and 55 mL (0.12 mol) of 12.5% aqueous potassium hydroxide solution. The reaction flask is cooled to 0°C in an ice-water bath, the dropping funnel is charged with a solution of 50 mL (0.095 mol) of triphosgene (1.9 M in toluene) (Note 8), and the triphosgene solution is slowly added over 40 min with vigorous stirring to the two-phase reaction mixture. After the reaction is complete, the reaction mixture is stirred at 0°C for 1 hr and diluted with 130 mL of ethyl acetate . The mixture is transferred to a 1-L separatory funnel, and the layers are separated. The organic layer is washed successively with 150 mL of saturated aqueous sodium bicarbonate solution (Note 9) and 150 mL of saturated sodium chloride solution. The organic layer is dried over magnesium sulfate , filtered, and concentrated by rotary evaporation to give 8.07 g of crude (1R,2S,6R,7S)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0]decane (**3**) as a waxy pale yellow solid that is suitable for further reaction without purification (Notes 10 and 11).

C. N-Methyl-(1R,2S,6R,7S)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0]decane , **4**. All glassware for this step must be oven-dried. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, a 125-mL pressure-equalizing addition funnel, and a rubber septum is flushed with argon and charged with 9.47 g (0.083 mol) of a 35% dispersion of potassium hydride (KH) in mineral oil (Note 12). The mineral oil is removed by introducing 85 mL of hexane with a syringe, gently stirring the mixture, allowing the potassium hydride to settle, and then withdrawing the liquid by syringe. The KH is washed twice using this procedure. The flask is further charged with 300 mL of dry tetrahydrofuran (THF), Note 13), and the dropping funnel is charged by syringe with a solution of 8.06 g (0.041 mol) of crude (1R,2S,3R,4S)-3-exo-amino-2-exo-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**3**) in 90 mL of dry THF. The magnetically stirred suspension of potassium hydride is cooled to 0°C, and the solution of **3** is added dropwise over a 10-min period. After the addition is complete, the mixture is stirred at 0°C for 20 min, and 13 mL (0.21 mol) of methyl iodide (Note 14) is introduced dropwise via syringe. The cooling bath is removed, and the reaction mixture is stirred at room temperature for 10 hr. The reaction is quenched by cautious addition of 15 mL of water, and the resulting mixture is transferred to a 1-L separatory funnel containing 125 mL of water. The layers are separated, and the aqueous layer is extracted three times with 100 mL of ethyl acetate . The combined organic extracts are washed with 300 mL of saturated sodium chloride solution, dried over magnesium sulfate , and concentrated by rotary evaporation to give crude **4.** Recrystallization of this material from 15 mL of cyclohexane provides brown crystals, which are dissolved in 15 mL ethyl acetate and decolorized with Norit SA3 (100 mesh) activated carbonat reflux. This solution is cooled to room temperature, and the Norit is removed by vacuum filtration through Celite. The filtrate is concentrated by rotary evaporation, and the resulting pale yellow crystals are recrystallized twice from 5 mL of cyclohexane to provide 2.77 g (32%) of N-methyl-(1R,2S,6R,7S)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0]decane (**4**) as colorless crystals, mp 124-125°C, $[\alpha]_D^{22}$ −39.6° (CH_2Cl_2, c 0.62) (Note 15).

D. (2S)-(−)-3-(−)-exo-(Dimethylamino)isoborneol, [(−)-DAIB] , **5**. *Caution! Since DAIB slowly decomposes in air , samples of DAIB should be stored under nitrogen or argon* . All glassware for this step must be oven-dried. A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser connected to an argon inlet, a magnetic stirring bar, a rubber septum, and a Teflon stopper, is flushed with argon and charged with 55 mL of dry THF and 5.20 g (0.075 mol) of lithium aluminum hydride (Note 4). The solution is cooled to 0°C in an ice-water bath, and a solution of 2.77 g (0.013 mol) of N-methyl-(1R,2S,6R,7S)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0]decane (**4**) in 35 mL of dry THF is introduced slowly with a cannula. After addition is complete, the flask is removed from the cooling bath, and the reaction mixture is heated at reflux for 18 hr. The reaction flask is cooled to 0°C in an ice-water bath, and the mixture is quenched by successive addition of 20 mL of ethyl acetate and 17 mL of saturated aqueous sodium sulfate solution (Notes 5 and 6). The white mixture is stirred at room temperature for 2 hr, and the resulting white granular precipitate or slurry is removed by vacuum filtration through Celite. The filter cake is washed with three 100-mL portions of ethyl acetate , and the combined filtrates are thoroughly dried over sodium sulfate , filtered, and concentrated by rotary evaporation to furnish crude **5** as an oil. Crude **5** is purified by bulb-to-bulb distillation to give 2.19 g (84%) of (2S)-(−)-3-exo-(dimethylamino)isoborneol, [(2S)-(−)-DAIB] (**5**) as a nearly colorless oil, bp 150°C (25 mm), $[\alpha]_D^{22}$ 36° (ethanol, c 4.65) (Notes 16, 17, and 18).

2. Notes

1. Anhydrous, analytical reagent grade diethyl ether was purchased from Mallinckrodt Inc. and was

used without additional drying.

2. Lithium aluminum hydride was purchased from Aldrich Chemical Company, Inc.
3. The oxime was prepared as described in *Org. Synth.* **2002**, *79*, 125.
4. *Caution! A large volume of gas is produced*.
5. This is an exothermic reaction and a large volume of gas is produced. Great care must be exercised at this stage to avoid adding the saturated aqueous sodium sulfate solution too rapidly.
6. In order to achieve efficient product recovery, it is important to add only sufficient saturated aqueous sodium sulfate solution to change the appearance of the reaction mixture from a gray slurry to a white slurry. At this point the white precipitate settles rapidly when stirring is stopped.
7. The spectral properties of (2S)-(−)-3-exo-aminoisoborneol (**2**) are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3 H), 0.79-1.03 (comp, 8 H), 1.35-1.42 (m, 1 H), 1.52 (d, 1 H, J = 4.6), 1.60-1.72 (m, 1 H), 2.4 (br s, 3 H), 3.02 (d, 1 H, J = 7.4), 3.34 (d, 1 H, J = 7.4) ; ^{13}C (125 MHz, $CDCl_3$) δ: 11.4, 21.2, 21.9, 26.9, 33.1, 46.6, 48.7, 53.4, 57.3, 79.0 ; IR ($CHCl_3$) cm^{-1}: 3279, 3019, 2957, 2884, 1478 ; mass spectrum (CI) m/z 170.1540 [$C_{10}H_{19}NO$ (M+1) requires 170.1545], 170 (base), 166, 152 .
8. Triphosgene (98%) was purchased from Aldrich Chemical Company, Inc.
9. Washing the organic layer with saturated sodium bicarbonate is accompanied by the vigorous evolution of large quantities of gas, so great care must be taken in this step to avoid loss of material.
10. This crude **3** can be purified by crystallization from a mixture of hexane and ethyl acetate to afford pure **3** as colorless crystals, mp 154-155°C (lit[2]. mp 156-158°C), $[\alpha]_D^{22}$ −48° (CH_2Cl_2, c 0.63).
11. The spectral properties of **3** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (s, 3 H), 1.01 (s, 3 H), 1.08 (s, 3 H), 1.45-1.74 (comp, 4 H), 1.84 (d, 1 H, J = 4.6), 3.75 (d, 1 H, J = 8.0), 4.37 (d, 1 H, J = 8.0 Hz), 5.83 (br s, 1 H) ; ^{13}C (75 MHz, $CDCl_3$) δ: 10.7, 19.3, 23.2, 24.7, 31.6, 46.3, 48.1, 48.6, 60.5, 88.3, 160.4 ; IR (CHCl3) cm^{-1}: 3470, 3268, 3019, 2962, 1746; mass spectrum (CI) m/z 196.1342 [$C_{11}H_{17}NO_2$ (M+1) requires 196.1338], 196 (base), 166, 89 .
12. Potassium hydride (35 wt. % dispersion in mineral oil) was purchased from Aldrich Chemical Company, Inc.
13. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under an atmosphere of argon immediately prior to use.
14. Methyl iodide was purchased from Aldrich Chemical Company, Inc.
15. The spectral properties of **4** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (s, 3 H), 0.90-1.06 (comp, 8 H), 1.49-1.57 (m, 1 H), 1.70-1.79 (m, 1 H), 1.96 (d, 1 H, J = 4.6), 2.82 (s, 3 H), 3.55 (d, 1 H, J = 8.1), 4.22 (d, 1 H, J = 8.1) ; ^{13}C (75 MHz, $CDCl_3$) δ: 10.5, 18.8, 23.1, 24.6, 29.2, 31.7, 45.3, 46.1 48.2, 65.9, 84.6, 158.3 ; IR ($CHCl_3$) cm^{-1}: 3009, 2960, 1741, 1482, 1435, 1407 ; mass spectrum (CI) m/z 210.1491 [$C_{12}H_{19}NO_2$ (M+1) requires 210.1494], 210 (base) .
16. The spectral properties of (2S)-(−)-exo-(dimethylamino)isoborneol , [(2S)-(−)-DAIB (**5**) are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.74 (s, 3 H), 0.90-0.98 (m, 5 H), 1.02 (s, 3 H), 1.32-1.43 (m, 1 H), 1.62-1.71 (m, 1 H), 1.92 (d, 1 H, J = 4.6) 2.21 (d, 1 H, J = 7.0), 2.26 (br s, 6 H), 3.41 (d, 1 H, J = 7.0) ; ^{13}C (75 MHz, $CDCl_3$) δ: 11.5, 20.7, 22.0, 27.8, 32.2, 46.3, 47.0, 49.0, 74.1, 78.7 (only ten carbon signals are observed at 25°C due to line broadening of one of the N-methyl signals); IR ($CHCl_3$) cm^{-1}: 3310, 2991, 2956, 2875, 2830, 2784, 1469 ; mass spectrum (CI) m/z 198.1860 [$C_{12}H_{23}NO$ (M+1) requires 198.1858], 198 (base) .
17. This material is enantiomerically pure, as confirmed by HPLC analysis of the 3,5-dinitrophenyl carbamate using a chiral stationary phase. The carbamate derivative of DAIB is prepared in the following manner: 3,5-Dinitrophenyl isocyanate (Sumika Chemical Analysis Service) and 5 mL of pyridine are added to a vigorously stirred solution of 10 mg (0.051 mmol) of DAIB (**5**) in 2 mL of toluene . After stirring for 30 min at 20°C, the reaction mixture is passed through 0.5 g of Merck 9385 silica gel, eluting with diethyl ether . The eluent is concentrated by rotary evaporation to give the crude N-3,5-dinitrophenyl carbamate . This material is analyzed by HPLC (Shimadzu LC-6A chromatograph equipped with a Rheodyne 7125 injector and a Shimadzu SPD-6A UV detector. A Sumitomo Chemical Co. Sumipax OA-4000 column is employed and the carbonate is eluted with a 99.5:0.5 mixture of hexane and isopropyl alcohol (flow rate, 1.0 mL/min; detection, 254 nm; tR, 23.7 min).The signal due to the minor R isomer could not be detected under the analysis conditions, and the ee of the sample is estimated to be at least 99.9%. (We are indebted to Professor Ryoji Noyori for this analysis.)
18. Toward the end of the distillation, a small amount of colored material begins to distill over, so the distillation must be stopped at this point.

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

The chiral β-dialkylamino alcohol DAIB serves as an efficient asymmetric catalyst for the addition of organozinc reagents to aldehydes.[3] The reaction of diethylzinc with benzaldehyde in the presence of 2 mol % of (2S)-(−)-DAIB to give (S)-1-phenyl-1-propanol in 89% ee is described in the procedure which follows.[4] DAIB exhibits the property of "chiral amplification," enabling the preparation of alcohols of high enantiomeric purity to be effected with catalyst of much lower enantiomeric purity.

Conversion of the keto ketoxime **1** to the exo-exo-amino alcohol **2** has been accomplished by hydrogenation over Adams' catalyst[5] and by reduction with lithium aluminum hydride.[6] Amino alcohol **2** has also been prepared from **1** by a two-stage process in which selective reduction of the ketone is carried out with sodium borohydride, and the resultant hydroxy oxime is reduced with lithium aluminum hydride [6] or by hydrogenation over Adams catalyst.[7]

Conversion of **2** to the highly crystalline oxazolidinone **3** with phosgene has been described by Thornton[7] who has employed this substance as a chiral auxiliary in asymmetric aldol reactions of its N-propionyl derivative. Kelly has also used an oxazoline derived from **3** as a chiral auxiliary in asymmetric alkylation of a glycolate enolate.[8] Oxazolidinone **3** has also been prepared from **2** with diethyl carbonate in the presence of potassium carbonate .[2] The conversion of **2** to the oxazolidinone **3** is accomplished using triphosgene in this procedure because of the high toxicity of phosgene.

N-Methylation of **3** and reduction of the crystalline oxazolidinone **4** with lithium aluminum hydride was found to give a superior yield of DAIB (**5**) and a more easily purified product than exhaustive methylation of **2** with methyl iodide and reduction of the quaternary methiodide with Super-Hydride.[9] Recently, a modified version of DAIB, 3-exo-morpholinoisoborneol (MIB), was prepared by Nugent that is crystalline and that is reported to give alcohols in high enantiomeric excess from the reaction of diethylzinc with aldehydes.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 635

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Appendix

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

(2S)-(−)-3-exo-(Dimethylamino)isoborneol: (2S)-(−)-DAIB:
Bicyclo[2.2.1]heptan-2-ol, 3-(dimethylamino)-1,7,7-trimethyl-, [1R-(exo,exo)]- (11); (103729-96-0)

(2S)-(−)-3-exo-Aminoisoborneol:
Bicyclo[2.2.1]heptan-2-ol, 3-amino-1,7,7-trimethyl-, (1R,2S,3R,4S)- (9); (41719-73-7)

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

(1R,4S0-(−)-Camphorquinone monoxime:
2,3-Bornanedione, 3-oxime (9);
Bicyclo[2.2.1]heptane-2,3-dione, 1,7,7-trimethyl-, 3-oxime (12); (663-17-2)

(1R,2S,6R,7S)-1,10,10-Trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0]decane:
4,7-Methanobenzoxazol-2(3H)-one, hexahydro-7,8,8-trimethyl-, [3aR-(3aα, 4β, 7β, 7aα)]- (12);
(131897-87-5)

Triphosgene:
Carbonic acid, bis(trichloromethyl) ester (8,9); (32315-10-9)

Potassium hydride (8,9); (7693-26-7)

Methyl iodide:
Methane, iodo- (8,9); (74-88-4)