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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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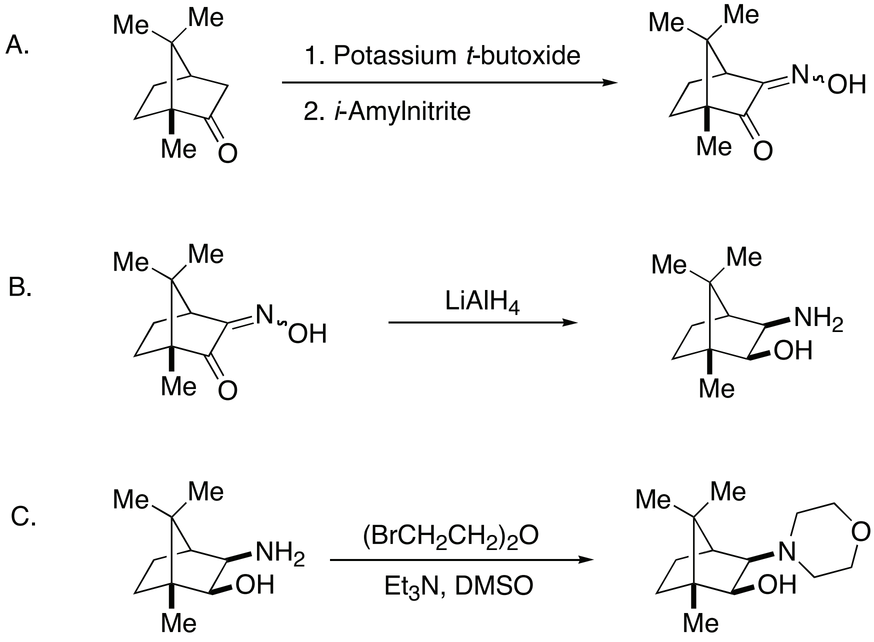
(2*S*)-(–)-3-exo-(MORPHOLINO)ISOBORNEOL [(–)-MIB] ([1*R*-(exo,exo)]-1,7,7-Trimethyl-3-morpholin-4-yl-bicyclo[2.2.1] heptan-2-ol)



Submitted by Young K. Chen,[1] Sang-Jin Jeon,[1] Patrick J. Walsh,[1] and William A. Nugent.[2]
Checked by Christopher Kendall and Peter Wipf.
Discussion Addendum *Org. Synth.* **2013**, *90*, 25

1. Procedure

A. Camphorquinone oxime. A flame-dried 1-L three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer and septum is charged with potassium *t*-butoxide (46.0 g, 410 mmol) (Note 1). The contents of the flask are thoroughly purged with a stream of N_2 exhausted through an oil bubbler. After 15 min, 500 mL of Et_2O (Note 2) is added *via* cannula and the flask is submerged in a cold bath cooled to -30 °C (Note 3). A second 250-mL round-bottom flask is charged with (*R*)-Camphor (50.0 g, 328 mmol) (Note 4) and 100 mL of Et_2O. The resulting clear solution is added *via* cannula into the first flask over 10 min while keeping the internal temperature below -30 °C. The second flask is thoroughly rinsed with 20 mL of Et_2O, which is also transferred into the first flask. The cooling bath is removed and the reaction mixture is allowed to warm to room temperature. After stirring at room temperature for 30 min, the reaction mixture is cooled to -30 °C. Isoamyl nitrite (55.0 mL, 409 mmol) (Note 5) is added by syringe over 20 min while keeping the internal temperature below -30 °C. An orange to red color appears during the addition of isoamyl nitrite. The reaction mixture is allowed to warm to room temperature and is stirred for 16 h at ambient temperature under a N_2 atmosphere. The solution is extracted with water (3 x 150 mL), and the combined aqueous layers (approximately 450 mL) are cooled in an ice bath with magnetic stirring. The pH is adjusted to 4 by dropwise addition of approximately 30 mL of conc. HCl. After the pH is adjusted, an off-white solid precipitates from solution. The biphasic mixture is extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers are washed successively with 50 mL of saturated $NaHCO_3$, 50 mL of water, 50 mL of brine, and then dried over anhydrous $MgSO_4$. The solvent is removed *in vacuo* to afford 52.8 g (89%) of the title compound. The solid is a 10/90 mixture of *syn*- and *anti*-camphorquinone oximes (Note 6). This material is suitable for the next reaction without further purification.

B. (2S)-(-)-3-exo-Aminoisoborneol. A 250-mL two-necked, round-bottomed flask is charged with camphorquinone oximes (12.1 g, 66.8 mmol). The flask is fitted with a condenser and a septum, and is thoroughly purged with a steady stream of N_2. After 15 min, the N_2 flow is reduced to a slow bleed and 30 mL of anhydrous THF (Note 2) is added via syringe. The homogeneous solution is cooled in an ice bath to 0 °C. A 1.0 M solution of $LiAlH_4$ in THF (100 mL, 100 mmol) (Note 7) is slowly transferred *via* cannula to the mixture over 30 min (Note 8). After vigorous H_2 gas evolution ceased, the reaction mixture is allowed to warm to ambient temperature and then heated at reflux for 30 min. The solution is cooled to room temperature, diluted with 65 mL of Et_2O, cooled to 0 °C and quenched by the successive dropwise addition of 3.8 mL of water, 3.8 mL of 10% NaOH solution, and 11.4 mL of water (Note 9). The colorless precipitate was vacuum filtered through Celite, and the filter cake was washed with THF (3 x 20 mL) (Note 10). The combined filtrate was concentrated to give 10.4 g (92%) of a waxy solid. This material was used in the next step without further purification.

C. (2S)-(-)-exo-(Morpholino)isoborneol. To a 150-mL round-bottomed flask charged with (*2S*)-(-)-3-*exo*-aminoisoborneol (6.53 g, 38.6 mmol) is added 40 mL of reagent grade DMSO followed by Et_3N (16.3 mL, 117 mmol) (Note 11). Bis(2-bromoethyl) ether (6.50 mL, 46.5 mmol) (Note 11) in 30 mL of DMSO is added dropwise over 10 min and the reaction mixture is stirred at ambient temperature under N_2 for 72 h. The solution is poured into 400 mL of water, and the aqueous mixture is extracted with Et_2O (3 x 150 mL). The combined organic layers are washed successively with 100 mL of water, 50 mL of brine and then dried over anhydrous $MgSO_4$. The solvent is removed *in vacuo* and the residue is purified by flash column chromatography (Notes 12, 13 and 14) to give 5.23 g (57%) of (-)-MIB as a colorless solid.

2. Notes

1. Potassium *t*-butoxide was purchased from Acros and used under a stream of N_2.

2. Et_2O and THF were purchased from Fisher and dried by passage through an activated alumina column under N_2.

3. The reaction was successfully performed at temperatures ranging from –30 °C to –50 °C.

4. (1*R*)-(+)-Camphor 98%, was purchased from Aldrich Chemical. The optical purity of (1*R*)-(+)-Camphor varies with the natural source. For analysis of the optical purity of commercial (+)- and (–)-camphor see: Armstrong, D. W.; Lee, J. T.; Chang, L. W. *Tetrahedron: Asymmetry* **1998**, *9*, 2043.

5. Isoamyl nitrite was purchased form Aldrich Chemical Company, Inc. Because of the appalling odor of the reagent, it was used without prior distillation.

6. *Anti*-(1*S*)-(–)-camphorquinone 3-oxime ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.70-8.80 (br, 1 H, N-OH), 3.25 (d, *J* = 4.3, 1 H), 2.08-2.00 (m, 1 H), 1.83-1.74 (m, 1 H), 1.62-1.52 (m, 2 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 0.89 (s, 3 H) ppm; ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 204.5, 160.1, 58.8, 47.1, 45.3, 31.1, 24.2, 21.1, 18.0, 9.3, 18.0 ppm. *Syn*-(1*S*)-(–)-camphorquinone 3-oxime ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.70-8.80 (br, 1 H, N-OH), 2.70 (d, *J* = 4.2, 1 H), 2.14-2.08 (m, 1 H), 1.83-1.74 (m, 1 H), 1.66-1.55 (m, 2 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.93 (s, 3 H) ppm; ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 205.3, 156.6, 60.0, 50.0, 47.4, 30.4, 25.4, 21.0, 18.4, 8.8 ppm.[3,4a]

7. 1.0 M $LiAlH4$ in THF was purchased from Aldrich. The yields and diastereoselectivity were much higher when homogeneous solutions of $LiAlH4$ were used instead of the powder form.

8. H_2 gas evolution was vigorous at the beginning of the addition.

9. Addition of the initial 3.8 mL of water is accompanied by vigorous generation of H_2 and is very exothermic.

10. The best product recovery was accomplished when the filter cake was washed with THF. For spectral properties see reference 4b.

11. Bis(2-bromoethyl) ether (technical grade, 90% purity) was purchased from Aldrich. Reagent grade DMSO was purchased from Fisher. (Note revised 3/2017).

12. ~200 g of silica, 10% to 15% EtOAc in hexanes. TLC in 20% EtOAc in hexanes; R_f 0.25; Stained brown in I_2 Chamber.

13. Recrystallization is also possible from hexanes 4 mL/g at –30 °C.[5]

14. Characterization data for (2S)-(–)-exo-(morpholino)isoborneol: $[\alpha]^{20}D$ = -6.9 (c = 1.0, MeOH); mp = 65-66 °C (hexane); ^1H NMR (400 MHz, C_6D_6) δ: 3.91 (s, 1 H), 3.43 (d, 1 H, J = 7.1 Hz), 3.40 (bs, 4 H), 2.30 (bs, 2 H), 2.10 (bs, 2 H), 2.07 (d, 1 H, J = 7.1 Hz), 1.66 (d, 1 H, J = 4.7 Hz), 1.51 (tt, 1 H, J = 12.0, 4.6 Hz), 1.35 (td, 1 H, J = 12.2, 3.6), 1.13 (s, 3 H), 1.02 (s, 3 H), 0.92-0.82 (m, 1 H), 0.77-0.70 (m, 1 H), 0.68 (s, 3 H); $^{13}C\{^1H\}$ NMR (76 MHz, C_6D_6, d_1 = 5 sec) δ 79.6, 74.0, 67.4, 50.1, 47.2, 46.0, 33.2, 28.6, 22.8, 21.7, 12.4; IR (KBr) 3460, 3367, 1478, 1448, 1396, 1360, 1284, 1261, 1202, and 1200 cm^{-1}; EIMS m/z 239 (M^+, 13), 154 (100); HRMS (EI) m/z calcd for $C_{14}H_{25}NO_3$: 239.1885, found 239.1889. Enantiomeric excess was determined as followed: To a screw cap vial (1 dram) charged with (–)-MIB (24 mg, 0.1 mmol) was added dichloromethane (1 mL), followed by Et_3N (17 µL, 0.12 mmol), and DMAP (~2 mg). p-Bromobenzoyl chloride (22 mg, 0.1 mmol) was added to the clear solution and stirred for 10 min. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (5% ethyl acetate in hexanes). HPLC analysis of the resultant p-bromobenzyl ester established the enantiomeric excess as 96.0% ee (Chiralcel OD column, flow 1 mL/min, 254 nm, 2% isopropanol in hexanes; minor isomer 4.6 min, and major isomer 5.3 min).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(–)-MIB has been shown to be an excellent chiral ligand in the asymmetric alkylation of aldehydes. In comparison, MIB was equal or better than DAIB in Et_2Zn addition to aromatic aldehydes with ee's > 95. Highly enantioselective Et_2Zn additions to alkyl substituted aldehydes are also possible with (–)-MIB.[5] Remarkably, the generation of (*S*)-1-phenylpropan-1-ol with 90% ee can be achieved when MIB of only 10% ee was used in the Et_2Zn addition with benzaldehyde. This result shows a large positive non-linear effect that parallels DAIB.[6] Recently, MIB has been shown to be equally effective with DAIB in the alkenylzinc addition to aldehydes pioneered by Oppolzer.[7] A number of terminal alkynes with various substituents were used in the study. Using MIB in this reaction constitutes a powerful and practical method to access both enantiomers of allylic alcohols in high optical purity.[8] Furthermore, it has recently been shown that MIB can be used in a one-pot tandem asymmetric addition/diastereoselective epoxidation sequence to generate epoxy alcohols with up to three stereocenters and the asymmetric addition/diastereoselective cyclopropanation with up to four stereogenic centers with high enantio- and diastereoselectivity.[9]

The distinct advantage of MIB is its ease of preparation. Gram quantities of both enantiomers of MIB can be made in only three steps and one purification, while the most efficient synthesis of (–)-DAIB was achieved in six steps and involved a low yielding and laborious purification step to remove the undesired diastereomer.[4] Furthermore, MIB is a crystalline solid and can be stored for months in the presence of air without noticeable decomposition.[5]

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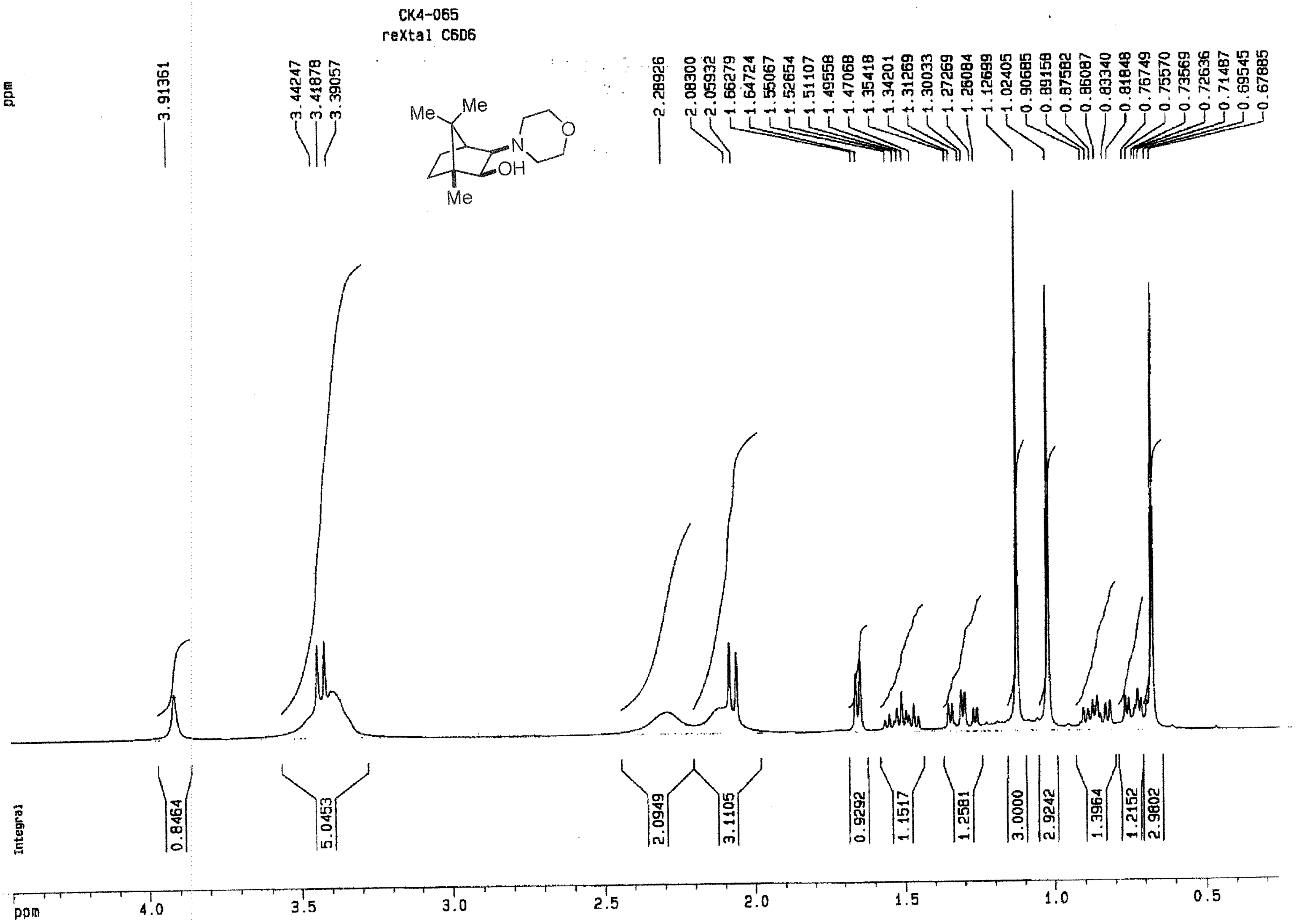
Appendix
Chemical Abstracts Nomenclature (Registry Number)

anti-(1*R*)-(1)-Camphorquinone 3-oxime: 1,7,7-Trimethyl-bicyclo[2.2.1]heptane-2,3-dione 3-oxime; (31571-14-9)
(1*R*)-(+)-Camphor: 1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one; (464-49-3)
(2*S*)-(–)-3-exo-Aminoisoborneol: 3-Amino-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol; (417199-73-7)
Bis(2-bromoethyl) ether: Ethane, 1,1'-oxybis[2-bromo-; (5414-19-7)
Lithium aluminum hydride; (16863-85-3)
Isoamyl nitrite: isopentyl nitrite; (110-46-3)
Potassium *tert*-butoxide; (865-47-4)
Triethylamine: Ethanamine, *N,N*-diethyl-; (121-44-8)


CK4-065
reXtal C6D6

Note 14