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Synthesis of Several Novel Optically Active Nitroxyl Radicals

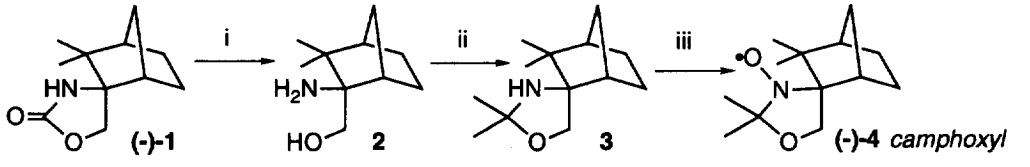
Rebecca Braslau,* Heiko Kuhn, Leland C. Burrill II, Kenneth Lanham and Chris J. Stenland

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

Abstract: Optically active nitroxyl radicals are prepared from enantiomerically pure bicyclic terpenoids. (-)-Camphoxyl radical **(-)-4** derived from commercially available oxazolidinone **(-)-1** and (+)-camphoxyl radical **(+)-4** derived from (-)-camphene are readily prepared, conformationally rigid, enantiomeric nitroxyl radicals. (-)-Camphorsulphonic acid is used to prepare two additional optically active nitroxyl radicals **9** and **12**.

Optically active nitroxyl radicals are of interest due to a variety of applications, including recent uses in the development of paramagnetic chiral liquid crystals[1] and as precursors to optically active oxidizing agents capable of kinetic resolution.[2] Herein we report the preparation of several new optically active nitroxyl radicals derived from inexpensive bicyclic terpenoid precursors: camphene or camphorsulfonic acid. Due to the availability of both (+) or (-) camphene, both enantiomers of the camphene-derived nitroxyl radical can be easily prepared.

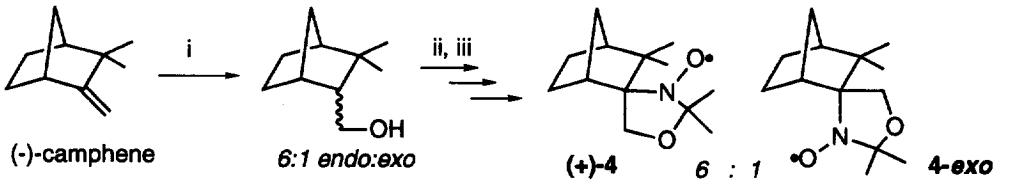
Persistent nitroxyl radicals[3] which can be isolated require both carbon atoms flanking the nitroxyl nitrogen atom to be fully substituted: α-hydrogens provide a route to decomposition via disproportionation. Thus a challenge in nitroxyl synthesis is to prepare appropriate precursors containing a neopentyl nitrogen atom. The commercially available optically active oxazolidinone **(-)-1** (ACROS) contains a neopentyl nitrogen, prepared by acyl nitrene insertion into the methine C-H bond of *endo*-camphenol. We recognized the availability of a doxyl radical precursor latent in this oxazolidinone structure. Thus hydrolysis of oxazolidinone **1** using sodium hydroxide in refluxing aqueous ethanol provided the β-amino alcohol **2**[4] in quantitative yield (Scheme 1). Acid catalyzed acetalization to form the oxazolidine **3** failed using acetone, but proceeded



Scheme 1 i. NaOH, aq. EtOH, reflux, 12h; ii. 2,2-dimethoxypropane, acetone, *p*TsOH, reflux, 4 days; iii. mCPBA, Et_2O, 0 °C to RT

smoothly using 2,2-dimethoxypropane to give a marginally stable material in 70% yield which was oxidized with *m*CPBA in 26% yield.[5] The resulting camphoxyl radical[6] **(-)-4** was isolated as an orange crystalline compound, and is stable for at least eleven months when stored in the freezer.

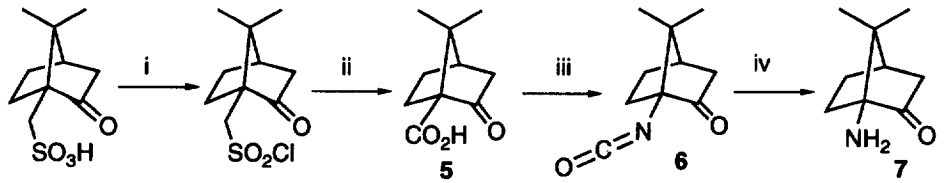
The enantiomeric nitroxyl radical **(+)-4** is derived from **(+)-1** which is prepared from (-)-camphene following the literature procedure.[7] In this preparation, the first step is a hydroboration of (-)-camphene resulting in a 6:1 *endo:exo* diastereomeric mixture (Scheme 2). This mixture is carried through to provide camphoxyl **(+)-4** (23% yield) and a minor nitroxyl diastereomer **4-exo** (3.6% yield) which are easily separated by column chromatography on silica gel (97:3 hex:EtOAc)



Scheme 2 i. BH_3.THF; KOH, HOOH; ii. See ref. 7 for preparation of **(+)-1**; iii. see **Scheme 1** i-iii

following oxidation. The enantiomeric nitroxyl radicals **(-)-4** and **(+)-4** are thus easily prepared, and are stable, isolable, easily stored compounds. Until now, most of the optically active nitroxyl radicals have been derived from chirons such as steroids or terpenes of a single enantiomeric series. The availability of optically pure **(-)-4** and **(+)-4** as either enantiomer provides new opportunities for probing and utilizing chiral recognition using stable, isolable nitroxyl radicals.

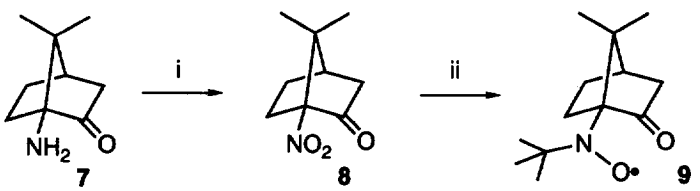
As an alternative inexpensive starting material, (1R)-(-)-10-camphorsulphonic acid was used to prepare two other novel optically active nitroxyl radicals. Conversion to the sulfonyl chloride with neat thionyl chloride followed by oxidation provided ketopinic acid[8] **5** (Scheme 3). The acyl



Scheme 3 i. $SOCl_2$, 79 °C; ii. $KMnO_4$, Na_2CO_3, water, 80 °C; iii. $ClCO_2Et$, Et_3N, acetone, water, NaN_3, 0 °C; iv. 0.08 N aq. HCl, 80 °C

azide was generated by treatment with ethyl chloroformate for 10 minutes at 0 °C followed by addition of aqueous sodium azide. A Curtius rearrangement occurs upon warming to room temperature to provide isocyanate[9] **6** as a white solid in 98% yield. Acidic hydrolysis of the isocyanate followed by addition of 10% aqueous sodium hydroxide and multiple ether extractions gave a poor yield of the key amino ketone **7**.[10] Recovery of the majority of the product was achieved only after further extraction of the aqueous phase with dichloromethane, to give a combined yield of 75%.

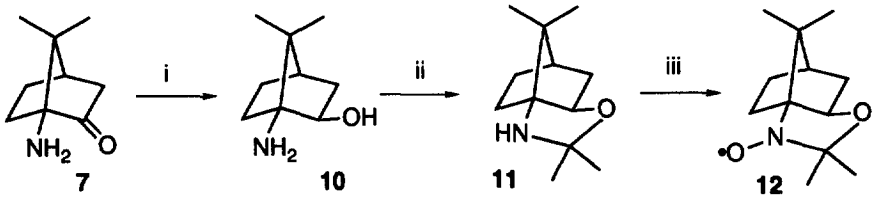
From this point the syntheses diverge; preparation of **9** utilizes a strategy developed by Rassat, which entails addition of a tertiary Grignard reagent to a nitro compound[11] (Scheme 4).



Scheme 4 i. $KMnO_4$, acetone, water, $MgSO_4$, RT; ii. *t* BuMgBr, Et_2O, 0 °C

Oxidation of amino ketone **7** with dioxirane generated *in situ* provided the nitro product **8** in 50% yield on small scale, but in only 25% yield on larger scale. A more satisfactory result was obtained by permanganate oxidation in the presence of magnesium sulfate,[12] providing the nitro compound in 67% yield as a white solid. Attempts to oxidize isocyanate **6** directly to nitro compound **8** with dioxirane prepared *in situ* failed. Addition of *t*-butylmagnesium bromide to **8** in diethyl ether gave nitroxyl radical **9** as a yellow-orange oil obtained by chromatography on silica gel followed by distillation at 125 °C at 0.1 mm Hg in 6% yield.[13]

Whereas the nitroxyl moiety in optically active **9** can rotate freely, a conformationally rigid analog was prepared in the form of doxyl radical **12** (Scheme 5). Reduction of the amino



7 **10** **11** **12**

Scheme 5 i. $NaBH_4$, MeOH, 0 °C; ii. 2,2-dimethoxypropane, *p*TsOH·H_2O, benzene, Dean-Stark reflux; iii. *m*CPBA, Et_2O, 0 °C

ketone **7** to amino alcohol **10**[14] by treatment with excess sodium borohydride in methanol at 0 °C provided the expected *exo* alcohol in nearly quantitative yield; *exo* approach of the reducing agent is sterically impeded by the proximal methyl group. Formation of oxazolidine **11** was achieved by reaction with 2,2-dimethoxypropane in refluxing benzene with catalytic *p*-toluenesulfonic acid and removal of methanol by means of a Dean-Stark trap containing 3 Å molecular sieves. The progress of the reaction was monitored by gas chromatography. After two days, the starting amino alcohol had been cleanly converted to oxazolidine **11**. However the product reconverted to the starting material within minutes upon exposure to air. It was found that the oxazolidine could be obtained cleanly by performing the aqueous work-up with chilled ether and chilled sodium hydroxide solution, and by storing the orange oil under nitrogen. Under these conditions, the oxazolidine was obtained in approximately 99% yield, and could be stored for at least several days at room temperature as long as it was protected from air. Oxidation to form doxyl radical **12** was carried out using commercial *m*-chloroperbenzoic acid (approximately 70-75%) in diethyl ether in 7% yield.[15] The ESR spectrum shows a clean triplet which persists for several days at room temperature when the sample is stored under nitrogen.

The syntheses presented herein detail the preparation of several novel optically active nitroxyl radicals. We are currently exploring additional avenues for the preparation of nitroxyl radicals of various structures from optically active starting materials.

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4. Novel compounds **2**, **4**, **8** and **11** have been fully characterized, including satisfactory HRMS or elemental analysis.
5. Experimental Procedure: **2** (184.2 mg, 1.1 mmol), *p*-TsOH·H_2O (21 mg, 0.1 mmol), and 2,2-dimethoxypropane (0.69 mL, 5.6 mmol) were refluxed in 3.8 mL of acetone for 4 days. Volatiles were removed *in vacuo*. Dilution with 20 mL of CH_2Cl_2, washing with 5 mL of sat. $NaHCO_3$ followed by 5 mL of brine and drying over $MgSO_4$ provided 165.1 mg of **3** as a clear oil (70% yield); ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.89 (d, 1H, J = 9.4 Hz), 3.70 (d, 1H, J = 9.4 Hz), 2.09 (m, 1H), 1.95-1.73 (m, 3H), 1.62-1.14 (m, 5H), 1.36 (s, 3H), 1.33 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H); ^{13}C-NMR (APT) (63 MHz, $CDCl_3$) δ 93.4 (s), 73.2 (s), 67.6 (t), 49.7 (d), 49.4 (d), 41.6 (s), 35.0 (t), 28.1 (q), 27.7 (q), 27.0 (q), 24.1 (t), 24.0 (q), 23.5 (t). This crude material was used directly in the next step: **3** (39.7 mg, 0.19 mmol) was dissolved in 0.20 mL Et_2O and cooled to 0 °C. A solution of *m*-CPBA (approx. 70%, 70.9 mg, 0.28 mmol) in 0.20 mL of Et_2O was added dropwise by cannula. The residues of peracid were washed into the reaction mixture with 2x0.20 mL of Et_2O. The reaction mixture was allowed to warm to RT overnight. Dilution with 10 mL of Et_2O, washing with 5 mL of sat. $NaHCO_3$ followed by 5 mL of water followed by 5 mL of brine, and drying over $MgSO_4$ provided 30.8 mg of an orange-yellow oil which was dissolved in a 6:1 pentane:Et_2O mixture and filtered through a 5-cm pipette-plug of neutral Alumina (Brockmann III) to give 11.2 mg of **(-)-4** as a crystalline orange solid (26% yield).
6. Nitroxyl Radicals **(-)-4**, **(+)-4**, **4-*exo***, **9**, and **12** all display clean triplets in the ESR, g=2.006, with coupling constants a_n = 15.0, 15.0, 13.7, 14.1 and 13.9 G respectively.
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8. Bartlett, P. D.; Knox, L. H. *Org. Synth. Coll. Vol. V*, 1973, 689-691. Note: ketopinic acid is now available from Aldrich.
9. Yan, T.-H.; Chu, V.-V.; Lin, T.-C.; Wu, C.-H.; Liu, L.-H. *Tetrahedron Lett.* **1991**, *32*, 4959-4962.
10. The amino ketone gave a negative Beilstein's test for the presence of the hydrochloride salt, however the melting point (197 °C) was identical to that of the salt reported by Beak: Beak, P.; Harris, B. R. *J. Am. Chem. Soc.* **1974**, *96*, 6363-6372.
11. For a discussion of this reaction and leading references, see: reference 3a, pp. 35-36.
12. Kornblum, N.; Clutter, R. J.; Jones, W. J. *J. Am. Chem. Soc.* **1956**, *78*, 4003-4004.
13. a. Such low yields seem to be inherent to this method: Brière, R.; Rassat, A. *Bull. Soc. Chim. Fr.* **1965**, 378-381; b. Based on the work of Bartoli, G.; Marcantoni, E.; Petrini, M. *J. Chem. Soc., Chem. Comm.* **1993**, 1373-1374, the use of cerium reagents on a similar substrate enhances the yields in this class of transformations (Wedeking, T., unpublished work from this lab).
14. Compound **10** has been previously prepared: Yan, T.-H.; Tan, C.-W.;Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613-2621.
15. The yield was determined by integration of the ESR signal of **12** relative to ESR spectra of standardized solutions of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO). The use of purified *m*CPBA (Fieser, L.F. and Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley: New York, 1967; p. 135) should provide a much cleaner and higher yielding reaction.

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