Enantiomerically enriched *vic*-amino alcohols from 2-iminobornanes[†]

Michael D. Squire,[a] Amanda Burwell,[b] Gregory M. Ferrence[b] and Shawn R. Hitchcock[a],*

[a]*Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA*
[b]*Department of Chemistry, Structure Determination Laboratory, Illinois State University, Normal, IL 61790-4160, USA*

Abstract—Enantiomerically enriched *vic*-amino alcohols derived from D-camphor have been synthesized by condensation of the highly electrophilic *N*-nitroimine of D-camphor with ethanolamine, (*R*)-phenylglycinol and (1*R*,2*S*)-norephedrine to afford imines **8a**–**c**. The iminobornanes were reduced with lithium aluminum hydride to afford the corresponding amines in good yield (78–88%). The stereochemistry of the reduction was confirmed by X-ray crystallographic studies of the *N*-nitrosated norephedrine–camphor derivative **12**. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The need for enantiomerically pure materials has steadily increased over the past several decades, especially in the pharmaceutical market because of regulations concerning the efficacy of chiral drugs.[1] In answer to the escalating demand for chiral, non-racemic materials, a variety of catalytic, asymmetric methods have been developed that are capable of producing enantiomerically enriched compounds. Among these methods are catalytic asymmetric reductions of prochiral ketones[2] and asymmetric 1,2-addition of organozinc reagents to aldehydes.[3a–c,e] A central theme to these synthetic transformations is the use of amino alcohols that are most often derived from the chiral pool (α-amino acids, terpenes, alkaloids, etc.).[4] In particular, many research groups have pursued the use of D-camphor as a template for creating diverse *vic*-amino alcohols for the purpose of application in asymmetric synthesis (Chart 1).[3]

In conjunction with our program focused on the study of 1,3,4-oxadiazinan-2-ones,[5] we became interested in developing syntheses of *vic*-amino alcohols. Herein, we report on the synthesis of chiral, non-racemic *vic*-amino alcohols derived from D-camphor.

2. Results and discussion

The *vic*-amino alcohols that we envisioned preparing involved a synthetic pathway that would require the formation of an iminobornane from D-camphor and subsequent reduction. In our initial experimentation we attempted to condense D-camphor **7** with (1*R*,2*S*)-norephedrine under reflux conditions in dichloroethane (Scheme 1). After 100 h, we obtained the desired imine **8** in 12% yield after column chromatography. At this
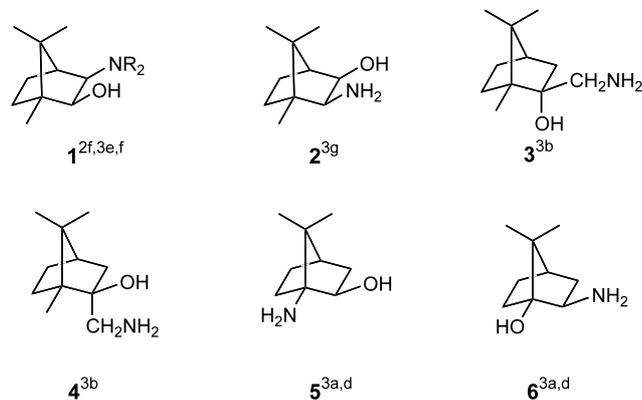
Chart 1.
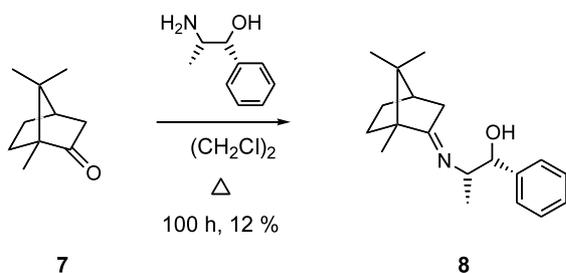
Scheme 1.

point, we decided to pursue a more effective route to the iminobornane. Several research groups have developed methods for circumventing the relatively low electrophilicity of camphor via modification of carbonyl by introduction of the *N*-nitroimine functionality.[6] *N*-Nitroimines are considerably more reactive than their ketone counterparts and probably react as Michael acceptors with the concomitant evolution of nitrous oxide.[6c]

The *N*-nitroimine of D-camphor was thus prepared as described in the literature (Scheme 2).[6c] This process was straightforward and could be conducted on multi-gram scales (25–100 g). With the *N*-nitroimine in hand, we pursued the condensation reaction with a variety of *vic*-amino alcohols including ethanolamine, (1*R*,2*S*)-norephedrine and (*R*)-phenylglycinol.[7,8] The formation of the camphor based imines **8a–c** proceeded in high yield (78–88%).[9] Numerous attempts were made to condense the *N*-nitroimine with 2-amino-2-methyl-1-propanol. Unfortunately, the imine product was not observed; only an unidentified by-product was produced in low yield. The failure to achieve complete condensation to afford the desired imine is most likely due to the steric environment near the nitrogen.[10] The stereochemistry of the isolated imines **8a–c** was not determined although ^{1}H and ^{13}C NMR spectroscopy suggested that there was a single isomer in each case.

Danks and co-workers[10] were able to successfully reduce camphor imines derived from α-substituted benzylamines using sodium borohydride in ethanol. In a similar fashion, imines **8a–c** were subjected to sodium borohydride reduction in an attempt to acquire amines **11a–c**. This process failed to generate the desired *vic*-amino alcohols in acceptable yield and purity. We then opted to use lithium aluminum hydride in THF at reflux to perform the transformation. The LAH reduction proceeded cleanly to afford the corresponding amines in high yield and purity after column chromatography (78–88%). The addition of hydride to the *endo*-face of the iminobornane system was expected to be the dominant reaction pathway although there have been observations of the *exo*-addition of hydride to camphor imines.[10a,11] To confirm this stereochemical assignment, the norephedrine based *vic*-amino alcohol **11c** was converted to its corresponding *N*-nitrosamine[12] which was subjected to X-ray crystallographic studies (Scheme 3, Table 1). The X-ray crystal structure (Fig. 1)[13] confirmed that hydride added to the *endo*-face to give the 2-*exo*-amino product.

3. Conclusion

Diastereomerically pure *vic*-amino alcohols have been prepared by reaction of the *N*-nitroimine of D-camphor with ethanolamine, (1*R*,2*S*)-norephedrine and (*R*)-phenylglycinol to yield iminobornanes **8a–c** which were reduced by lithium aluminum hydride to afford the

Scheme 3.

a: R^1 = H, R^2 = H, R^3 = H, R^4 = H (ethanolamine)
b: R^1 = H, R^2 = Ph, R^3 = H, R^4 = H (phenylglycinol)
c: R^1 = CH$_3$, R^2 = H, R^3 = H, R^4 = Ph (norephedrine)
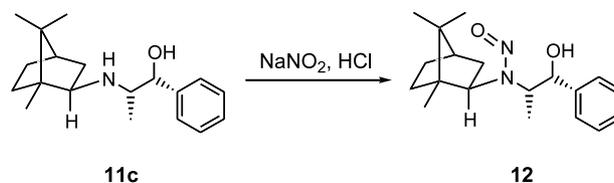
Scheme 2.

Table 1. Summary of data collection, solution and refinement parameters

Molecular formula	$C_{19}H_{28}N_2O_2$
F_w (g/mol)	315.4
Crystal dimensions (mm)	$0.39 \times 0.18 \times 0.29$
Color, shape	beige plate
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell parameters	
a (Å)	8.7419(15)
b (Å)	10.119(2)
c (Å)	20.887(3)
V (Å^3)	1847.66(6)
Z	4
D_{calcd} (g cm^{-3})	1.13
μ (cm^{-1})	0.73
Diffractometer	Brüker-Nonius CAD4/MACH3/Scintillation
Wavelength (λ, Å)	0.71073
Temperature (K)	298
θ Range	2.0–25.9
$F(000)$	683.9
Reflections collected	4021 ($0 \leq h \leq 10$, $0 \leq k \leq 12$, $-25 \leq l \leq 25$)
Independent reflections	3579
Reflections observed	2722 ($I > 25(I)$)
R indices observed (all data)	0.037 (0.064)
wR_2 observed (all data)	0.092 (0.102)
Parameters (restraints)	209 (0)
Extinction coefficient	None
Goodness-of-fit	1.043
Shift/e.s.d. max (mean)	0.000 (0.000)
Largest difference peak and hole (e Å^{-3})	0.110 and -0.156

corresponding amines **11a**–**c** in good overall yield (60–77%). The stereochemistry of the reduction was confirmed to have given the 2-*exo*-amine product by X-ray crystallographic studies of the *N*-nitrosated norephedrine–camphor derivative **12**. Research is underway for the preparation of novel [1,3,4]oxadiazinan-2-ones from the *vic*-amino alcohols **11a**–**c**.

4. Experimental

4.1. Crystal structure determination

A beige plate of approximate dimensions 0.39×0.18×0.29 mm was mounted on a glass fiber with Superglue and transferred to a Brüker-Nonius CAD4/Mach3 diffractometer. The X-ray diffraction data were collected at room temperature using Mo Kα radiation. Data collection and cell refinement was performed using CAD4 Express.[14] Data reduction was carried out using XCAD4.[15] The unit cell parameters were obtained from a least-squares refinement of 25 centered reflections. The systematic absences indicated the space group $P2_12_12_1$ (no. 19).[16] The *N*-nitrosamine derivative **12** was found to crystallize in the orthorhombic crystal system with the following unit cell parameters: $a = 8.7419(15)$, $b = 10.119(2)$, $c = 20.887(3)$ Å, $V = 1847.66(6)$ Å^3, $Z = 4$. A total of 4021 reflections were collected, of which 3579 were unique, and 2722 were observed $F_o^2 > 2\sigma(F_o^2)$. The

data were corrected for absorption through the use of empirical psi-scans.[17]

Solution and data analysis was performed using the WinGX software package.[18] The structure of **1** was solved using the direct method program SIR-92 and the refinement was completed using the program SHELXL-97.[19] Hydrogen atoms were assigned positions based on the geometries of their attached carbon atoms, and were given thermal parameters of 20% greater than those of the attached atoms. Full-matrix least-squares refinement on F^2 led to convergence with $R_1 = 0.032$ and $wR_2 = 0.084$ for 2404 data with $F_o^2 > 2\sigma(F_o^2)$. A final difference Fourier synthesis showed features in the range of +0.100 to -0.178 e Å^{-3}.

4.2. General remarks

Tetrahydrofuran (THF) was distilled from a potassium/sodium alloy containing benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Flash chromatography was conducted with silica gel (32–63 mesh). All ^{1}H and ^{13}C NMR spectra were recorded at 25°C on a Varian spectrometer in $CDCl_3$ operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}). Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Elemental analyses were conducted by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign.

4.3. General procedures for the formation of imines 8

In a round-bottomed flask containing a minimal amount of pre-dried 4 Å molecular sieves, *N*-nitroimino-D-bornane (3.30 g, 16.8 mmol) was dissolved in 1,2-dichloroethane (15 mL). To the resulting solution was added primary amine (15.3 mmol) and the reaction was heated under reflux for 24 h under a nitrogen atmosphere. The reaction was then gravity filtered and the filtrate was washed with chloroform (30 mL). The resulting solution was extracted with a saturated aqueous solution of $NaHCO_3$ (3×50 mL). The organic layer was washed with a saturated aqueous solution of brine (50 mL) and dried over $MgSO_4$. The solvents were removed by rotary evaporation and crude product was purified by column chromatography (EtOAc/hexanes, 1:4). The reported yields reflect chromatographically pure material.

4.3.1. (1*R*,2*R*)-2-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylideneamino)ethanol, 8a. Note: *This reaction preparation is initially exothermic with the release of nitrous oxide gas.* 78% yield as colorless crystals; mp 65–66°C (hexanes); [α]$_D$ = −27.1 (*c* 1, MeOH); ^{1}H NMR: δ 0.75 (s, 3H), 0.93 (s, 3H), 0.97 (s, 3H), 1.21 (ddd, $J = 17.6, 9.6, 4.0$ Hz, 1H), 1.35 (ddd, $J = 18.0, 9.6, 4.4$ Hz, 1H), 1.68 (td, $J = 12.4, 4.4$ Hz, 1H), 1.81–1.89 (m, 2H), 2.35 (dt, $J = 17.2, 3.2$ Hz, 1H), 2.89 (s, 1H), 3.3 (m, 2H), 3.80 (m,
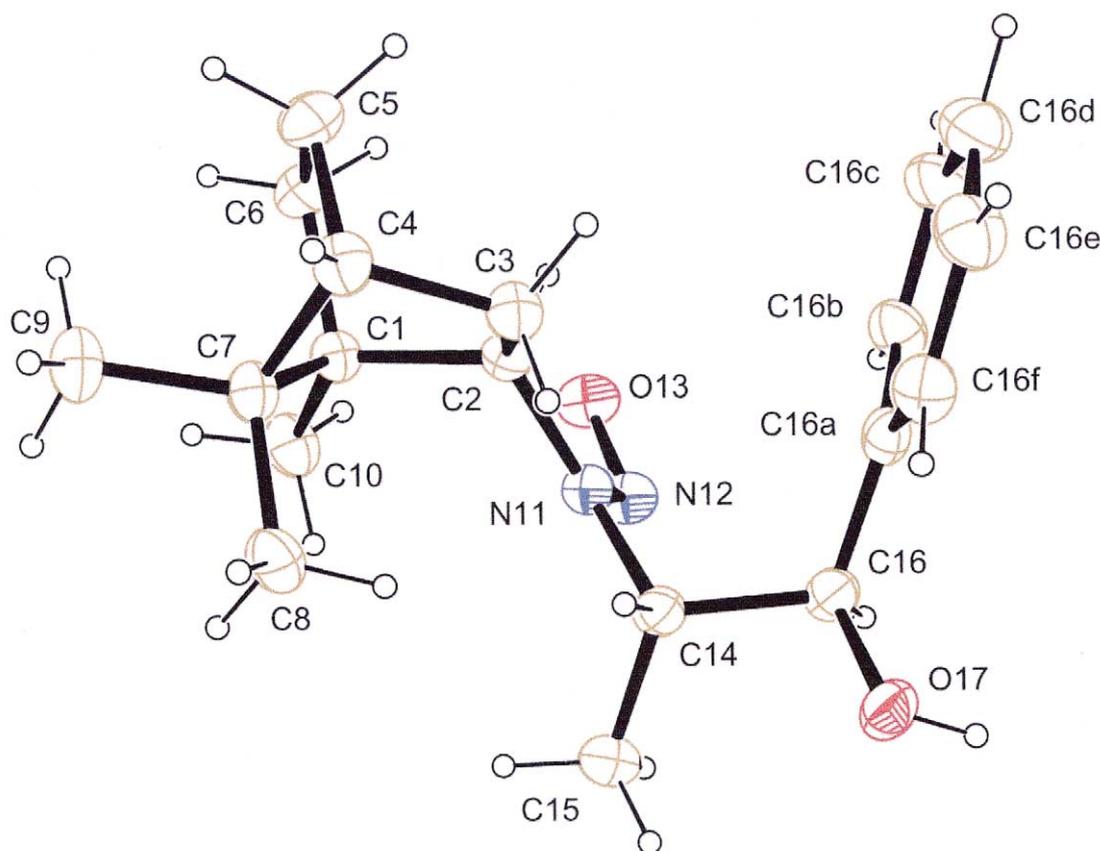
Figure 1. ORTEP of *N*-nitrosamine **12** with 20% probability ellipsoids.

2H); ^{13}C NMR (CDCl$_3$): δ 11.3, 18.9, 19.5, 27.4, 32.1, 36.1, 43.8, 47.2, 53.5, 53.9, 62.3, 184.6; IR (Nujol): 3147, 2926, 1681, 1076 cm^{-1}. Anal. calcd for C$_{12}$H$_{21}$NO: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.50; H, 10.97; N, 7.28%.

4.3.2. (1*R*,1′*R*,4′*R*)-2-Phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)ethanol, 8b. 83% yield as colorless crystals; mp 72–73°C (hexanes); [α]$_D$ = −94.1 (*c* 1, MeOH); ^{1}H NMR (CDCl$_3$): δ 0.79 (s, 3H), 0.92 (s, 3H), 0.93–0.99 (m, 1H), 1.043 (s, 3H), 1.27 (ddd, *J* = 18.0, 9.6, 4.4 Hz, 1H), 1.64 (td, *J* = 12.0, 4.4 Hz, 1H), 1.71–1.79 (m, 1H), 1.87 (t, *J* = 4.2 Hz, 1H), 2.45 (dt, *J* = 17.2, 3.2 Hz, 1H), 2.78 (s, 1H), 3.73–3.84 (m, 2H), 4.38 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.19–7.28 (m, 5H); ^{13}C NMR (CDCl$_3$): δ 11.4, 18.8, 19.6, 27.1, 31.8, 36.1, 43.8, 46.7, 54.2, 65.7, 68.3, 126.8, 127.1, 128.2, 141.2, 185.6; IR (Nujol): 3254; 3022; 1601; 1053 cm^{-1}. Anal. calcd for C$_{18}$H$_{25}$NO: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.80; H, 9.29; N, 5.45%.

4.3.3. (1*R*,1′*R*,2*S*,4′*R*)-1-Phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)propan-1-ol, 8c. 88% yield as colorless crystals; mp 84–85°C (hexanes); [α]$_D$ = −2.9 (*c* 1, MeOH); ^{1}H NMR (CDCl$_3$): δ 0.70 (s, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.98–1.08 (m, 2H), 1.53 (td, *J* = 12.8, 3.6 Hz, 1H), 1.67–1.78 (m, 1H), 1.83 (t, *J* = 4.4 Hz, 1H), 2.2 (dt, *J* = 16.4, 4.0 Hz, 1H), 3.51 (quintet, *J* = 6.4 Hz, 1H), 3.63 (s, 1H), 4.64 (d, *J* = 5.2 Hz, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR (CDCl$_3$):

δ 11.5, 15.0, 18.9, 19.3, 27.3, 31.8, 35.3, 43.6, 46.8, 53.4, 62.1, 76.7, 126.4, 126.9, 127.8, 142.1, 180.7; IR (KBr): 3200, 2868, 1668, 1043 cm^{-1}. Anal. calcd for C$_{19}$H$_{27}$NO: C, 79.95; H, 9.54; N, 4.91. Found: C, 79.88; H, 9.69; N, 5.12%.

4.4. General procedures for the formation of secondary amines 11

In a flame dried three-necked, round-bottomed flask, lithium aluminum hydride 0.946 g (24.9 mmol) was suspended in THF (50 mL) and heated to reflux. A solution of the imine (1.622 g, 8.305 mmol) in THF (17 mL) was added to the reaction flask via a pressure equilibrating addition funnel and was allowed to reflux for 24 h under a nitrogen atmosphere. The solution was then cooled to 0°C and quenched by dropwise addition of water (100 mL). The organic layer was washed with NaOH (6 M, 3×100 mL), then treated with saturated aqueous solution of NaCl (100 mL), and dried over MgSO$_4$. The solvents were removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc/hexanes, 1:4). The reported yields reflect chromatographically pure material.

4.4.1. (1*R*,2′*S*,4*R*)-2-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylamino)ethanol, 11a. 78% yield as colorless crystals; mp 48–49°C (hexanes); [α]$_D$ = −80.1 (*c* 1, MeOH); ^{1}H NMR: δ 0.82 (s, 3H), 0.89 (s, 3H), 1.00 (s, 3H), 1.06–1.08 (m, 2H), 1.50–1.71 (m, 5H), 1.90 (bs, 1H),

2.54 (dd, $J = 7.6$, 5.2 Hz, 1H), 2.67–2.76 (m, 2H), 3.57 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR: δ 12.1, 20.5, 20.5, 27.2, 36.9, 39.1, 45.0, 46.6, 48.4, 49.8, 61.0, 66.4; IR (Nujol): 3320, 3176, 1067 cm^{-1}. Anal. calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.80; H, 11.89; N, 7.25%.

4.4.2. (1*R*,1′*R*,2′*S*,4′*R*)-2-Phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamino)ethanol, 11b.

82% yield as colorless crystals; mp 76–77°C (hexanes); $[\alpha]_D = -26.0$ (*c* 1, MeOH); ^{1}H NMR: δ 0.56 (dd, $J = 12.8$, 4.4 Hz, 1H), 0.78 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 1.09 (ddd, $J = 9.2$ Hz, 4.4 Hz, 4.4 Hz, 1H), 1.27–1.35 (m, 1H), 1.51 (t, $J = 4.4$ Hz, 1H), 1.63–1.72 (m, 1H), 1.76–1.82 (m, 1H), 1.97–2.05 (m, 1H), 2.83 (ddd, $J = 10.0$, 4.4, 1.6 Hz, 1H), 3.47 (dd, $J = 10.4$, 8.4 Hz, 1H), 3.67 (dd, $J = 10.4$, 4.4 Hz, 1H), 3.75 (dd, $J = 8.0$, 4.4 Hz, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR: δ 14.3, 18.5, 19.8, 27.3, 28.4, 39.5, 45.1, 17.9, 49.3, 61.7, 64.7, 65.9, 127.0, 127.4, 128.5, 142.3; IR (Nujol): 3285, 3155, 3060, 3025, 1042 cm^{-1}. Anal. calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.11; H, 10.04; N, 5.31%.

4.4.3. (1*R*,1′*R*,2*S*,2′*S*,4′*R*)-1-Phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamino)propan-1-ol, 11c.

88% yield as colorless crystals; mp 47–48°C (hexanes); $[\alpha]_D = -31.3$ (*c* 1, MeOH); ^{1}H NMR: δ 0.77 (d, $J = 6.8$ Hz, 3H), 0.84 (s, 3H), 0.93 (s, 3H), 0.94 (s, 3H), 1.09 (*AB* spin system, $J = 18.8$, 8.4 Hz, 2H), 1.50–1.59 (m, 2H), 1.68–1.73 (m, 2H), 1.81 (dd, $J = 12.8$, 8.8 Hz, 1H), 2.63 (dd, $J = 8.4$, 4.4 Hz, 1H), 2.94 (dq, $J = 6.8$, 4.0 Hz, 1H), 4.017 (bs, 1H), 4.68 (d, $J = 4.4$ Hz, 1H), 7.21–7.45 (m, 5H); ^{13}C NMR: δ 12.7, 16.1, 20.5, 20.6, 27.2, 37.0, 41.1, 45.1, 16.7, 48.4, 57.5, 64.0, 72.5, 126.0, 126.8, 127.9, 141.4; IR (KBr): 3416; 3062, 3028 cm^{-1}. Anal. calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.40; H, 10.07; N, 5.08%.

4.4.4. (1*R*,1′*R*,2*S*,2′*S*,4′*R*)-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-*N*-nitrosoamino)-1-phenylpropan-1-ol, 12.

Amine **11c** (11.8 g, 41.1 mmol) was dissolved in THF (18 mL) and to this solution was added sodium nitrite (3.12 g, 45.2 mmol) followed by the cautious addition of an aqueous solution of HCl (2.74 M, 17.3 mL, 47.3 mmol). The reaction was stirred overnight and was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (100 mL). The *N*-nitrosamine product was extracted from this mixture by the use of ethyl acetate (2×100 mL). The combined organic layers were treated with a saturated aqueous solution of brine (100 mL), dried (MgSO$_4$) and the solvent was removed by rotary evaporation to afford the title compound as yellow crystals in nearly quantitative yield. A small sample was recrystallized from pure hexanes for characterization: mp 118.5–120°C (hexanes); $[\alpha]_D = +180$ (*c* 5, MeOH); ^{1}H NMR: δ 0.54–0.59 (m, 1H), 0.55 (s, 3H), 0.73 (s, 3H), 0.76 (s, 3H), 0.99–1.05 (m, 1H), 1.45–1.50 (m, 1H), 1.56–1.68 (m, 2H), 1.70 (d, $J = 6.8$ Hz, 3H), 2.59 (d, $J = 2.4$ Hz, 1H), 4.25–4.37 (m, 3H), 5.05 (dd, $J = 6.0$, 2.0 Hz, 1H), 7.24–7.36 (m, 5H); ^{13}C NMR: δ 10.2, 11.5, 13.0, 17.9, 20.2, 20.3, 26.3, 31.8, 35.9, 38.5, 44.4, 46.3, 52.5, 59.9, 63.1, 78.1, 126.3, 127.8, 128.2, 141.3; IR (KBr): 3356, 3066, 1420, 1361, 1081, 757, 704 cm^{-1}. Anal. calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.15; H, 9.13; N, 8.94%.

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enantiomeric purity of the synthesized (*R*)-(−)-phenylgly-cinol was determined to be at least 95% ee based on a comparison of the optical activity of the sample $\{[\alpha]_D = -31.3$ (*c* 0.71, 1N HCl)$\}$ and the literature value of $[\alpha]_D = -31.7$ (*c* 0.76, 1N HCl) from Aldrich Chemical Co.

8. For examples of (*R*)-(−)-phenylglycinol as a chiral auxil-iary, see: (a) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413; (b) Santes, V.; Gómez, E.; Zárate, V.; Santillan, R.; Farfán, N.; Rojas-Lima, S. *Tetrahedron: Asymmetry* **2001**, *12*, 241; (c) Roussi, F.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1998**, *39*, 8081.

9. ^{13}C NMR and IR spectroscopy established that the iso-lated material was indeed the imine; ^{13}C NMR spectrum: $\delta_{avg}(imine) = 183.6$ ppm; IR spectrum: $\nu_{avg}(imine) = 1650$ cm^{-1}). There was no direct evidence for the presence of the oxazolidine, the product of cyclization of the imine with the appendant alcohol moiety. In addition there was no observable equilibration between the imine or the putative oxazolidine based on the detection limits of the ^{1}H NMR spectra.

10. (a) Bolton, R.; Danks, T. N.; Paul, J. M. *Tetrahedron Lett.* **1994**, *35*, 3411; (b) Danks and co-workers noted that sterically hindered amines either require long reac-tion times to react with camphor in the presence of anhydrous ZnCl$_2$ or fail to yield any product in signifi-cant amounts.

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12. *Caution*: Many *N*-nitrosamines are known to have car-cinogenic activity. See: (a) *Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry*; Loeppky, R. N.; Michejda, C. J., Eds.; ACS Symposium Series 553, 1994; (b) Linjinsky, W.; Reuber, M. D.; Saavedra, J. E.; Singer, G. M. *J. Natl. Cancer Inst.* **1983**, *70*, 959.

13. Crystallographic data (excluding structure factors) for structure **12** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The atomic coordinates and equivalent isotropic displacement coefficients are included in the deposited material (CCDC 190337) as are a complete list of bond distances and angles. Copies of available material can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (Fax:+44-1223-336033 or e-mail: deposit@ccdc.am.ac.uk).

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