Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3845–3848

TETRAHEDRON: *ASYMMETRY*

The regio- and stereoselective oxyamination of pinenes and camphene

Sergio Pinheiro,[a,*] Sérgio F. Pedraza,[a] Florence M. C. Farias,[a] Angelo S. Gonçalves[b] and Paulo R. R. Costa[b]

[a]*Instituto de Química, GQO, Universidade Federal Fluminense, CEG, Centro, 24210-150 Niterói, RJ, Brazil*
[b]*Laboratório de Química Bioorgânica (LQB), Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, CCS, Ilha da Cidade Universitária, 21941-590 Rio de Janeiro, RJ, Brazil*

Received 26 July 2000; accepted 1 September 2000

Abstract

The osmium-induced vicinal oxyaminations of pinenes and camphene have been performed with high regio- and stereoselectivities. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantiomerically pure β-amino alcohols play important roles both in the treatment of a wide variety of human disorders[1] and as chiral auxiliaries and ligands in asymmetric synthesis.[2] In medicinal chemistry some examples include their uses as selective and active antagonists of the ionotropic glutamate receptor NMDA[3] and as effective β-adrenergic blockers in the treatment of heart disease.[4]

The *N*-sulfonamide derivatives of β-amino alcohols have been employed as chiral auxiliaries and ligands in aldol reactions,[5] in α-alkylations[6] and α-hydroxylations[7] of ester enolates, in conjugate addition to enoates,[8] in hydrogenation[9] and epoxidation[10] of *N*-tosyloxazolidines and in the alkylation of aldehydes.[11]

Some time ago Sharpless and co-workers described the one pot vicinal oxyaminations of olefins under stoichiometric[12] and osmium-catalyzed[13] conditions to reach β-amino alcohols and their *N*-tosyl derivatives in high regio- and diastereoselectivities. As part of our interest on the development of pinene-based β-amino alcohols,[14] herein we report the highly stereoselective osmium-induced vicinal oxyamination of α- and β-pinenes **1** and **2** and camphene **3** on useful scales.

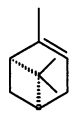
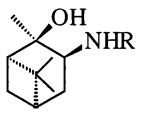
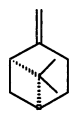
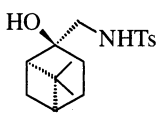
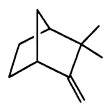
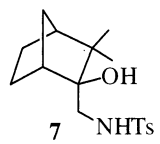
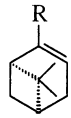
* Corresponding author. E-mail: spin@rmn.uff.br

0957-4166/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(00)00382-7

2. Results and discussion

The reaction of 36.7 mmol of (–)-α-pinene **1**[15] with a 10% excess of the imido osmium compound *t*-BuN=OsO_3[12] produced the β-amino alcohol **4**[16] in excellent regio- and stereoselectivity, with the attack occurring exclusively from the less hindered face of the olefin (Table 1, entry 1). The oxyamination of **1** carried out using catalytic OsO_4 in the presence of chloramine-T trihydrate[13] furnished the vicinal hydroxy *p*-toluenesulfonamide **5** in better yield (entry 2).[17,18] Similarly, when this protocol was applied to (–)-β-pinene **2** and to (–)-camphene **3**, the corresponding compounds **6** and **7** were obtained as single isomers (entries 3 and 4).[19,20] Interestingly, the osmium-catalyzed oxyamination of the functionalized pinene derivatives (–)-nopol **8a** and its benzyl ether **8b** failed to give the respective hydroxy *p*-toluenesulfonamides and complex mixtures of products were obtained. The (–)-phenylapopinene **8c** proved to be inert to the imido osmium compound *t*-BuN=OsO_3 (method A). Similarly a lack of reactivity was also observed in the osmium-catalyzed oxyamination (method B), as described for 1-phenylcyclohexene.[13b]

Table 1
Stereoselective osmium-induced oxyamination of **1**–**3**

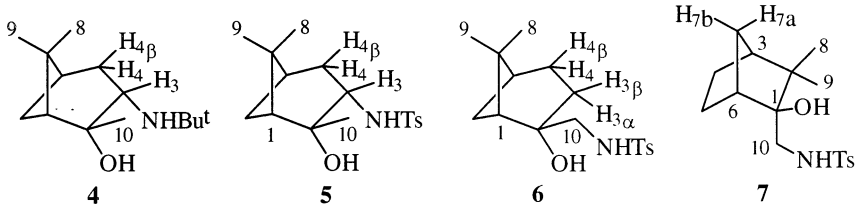
Entry	Olefin [a]	Method	Product [b]	% [c]
1	 **1**	A	 **4**: R = t-Bu **5**: R = Ts	60
2		B		80
3	 **2**	B	 **6**	88
4	 **3**	B	 **7**	79
5	 **8a**: R = CH_2CH_2OH **8b**: R = CH_2CH_2OBn **8c**: R = Ph	B	——	—

Method A: t-BuN=OsO_3 (1.1 eq.), pyridine, r.t., 15 h; **Method B**: OsO_4 (1 mol %), chloramine-T trihydrate (1.25 eq.), t-BuOH/ H_2O, reflux, 15 h then $NaBH_4$, r.t., 1 h. [a] All reactions were performed on a 36.7 mmol (5.0 g) scale; [b] Purified by flash chromatography on silica gel (20 % ethyl acetate in hexane as eluant). [c] Yields are for isolated, pure substances.

The oxyamination of the conformationally rigid (–)-α-pinene **1** using *t*-BuN=OsO_3 to give the amino alcohol **4** (entry 1) is noteworthy since hindered trisubstituted olefins react slower than the monosubstituted ones and give mainly the corresponding diols upon treatment with this imido osmium reagent.[12c] In fact, neither (–)-pinanediol nor the corresponding regio- and stereoisomeric amino alcohols related to **4** were detected by analysis of the crude ^1H and ^{13}C NMR spectra, since duplicities of signals were not observed. The osmium-catalyzed oxyamination of the trisubstituted olefin **1** (entry 2) was shown to be significantly faster than the reaction with 1-methyl-cyclohexene.[13b] Also, the spectral analyses of the reaction products using this catalytic procedure did not show the presence of regio- and stereoisomers of compounds **5**–**7**.

Stereochemical assignments of **4**–**7** were made on the basis of NOE NMR spectra at 300 MHz (Scheme 1). For compound **4**, starting from H_3 significant NOEs were observed with $H_{4\beta}$ (3.2%),

with H_8 (5.2%) and H_{10} (3.3%) and with the *t*-butyl group (8.1%). The hydrogen $H_{4\beta}$ showed NOE with H_8 (2.0%). In compound **5** the hydrogen H_3 exhibited NOE with $H_{4\beta}$ (5.3%), and with H_8 (11.5%) and H_{10} (4.2%). Also observed was a significant NOE of the hydrogen H_{10} with H_1 (4.7%). However, in compound **6** the NOE between H_1 and H_{10} was not observed, suggesting a preferred conformation in which the aromatic ring is *syn* periplanar to H_1. Indeed, H_1 showed a strong NOE with the aromatic hydrogens (11.3%). For compound **7**, H_{7a} exhibited significant NOE values with H_8 (3.4%) and H_{7b} (15.7%), while H_{10} showed NOE with H_9 (3.0%) but not with H_6.



Scheme 1.

In summary, the excellent regio- and stereoselectivities obtained for compounds **4**–**7** along with the transformations of the β-hydroxy sulfonamide moiety already described[13b] make the oxyamination of pinenes and camphene a very promising reaction to reach a variety of chiral β-amino alcohols and their *N*-tosyl derivatives in attractive scales. As (+)-β-pinene *ent*-**2** is efficiently prepared[21] by isomerization of (+)-α-pinene *ent*-**1** allied to the fact that this compound and (+)-camphene *ent*-**3** are commercially available, the antipodal forms of **4**–**7** can be obtained following this protocol. Studies aimed at the use of **4**–**7** and their enantiomers as chiral ligands and as intermediates in the synthesis of peptides are currently under investigation.

Acknowledgements

The authors thank PADCT-CNPq (National Council of Research of Brazil) for financial support and are indebted to Dr. Maria Cecília B. V. de Souza (UFF) for NMR spectra and to Dr. José O. Previatto (UFRJ) for optical rotation measurements. S.P. and P.R.R.C. are grateful to CNPq for individual research fellowships.

References

1. Grayson, M., Ed. *Kirk-Othmer Encycl. Chem. Technol.* **1982**, *17*, 311.
2. For reviews, see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994.
3. (a) Chenard, B. L.; Bordner, J.; Butler, T. W.; Chambers, L. K.; Collins, M. A.; Decosta, D. L.; Ducat, M. F.; Dumont, M. L.; Fox, C. B.; Mena, E. E.; Menniti, F. S.; Nielsen, J.; Pagnozzi, M. J.; Richter, K. E. G.; Ronau, R. T.; Shalaby, I. A.; Stemple, J. Z.; White, W. F. *J. Med. Chem.* **1995**, *38*, 3138. (b) Difabio, R.; Pietra, C.; Thomas, R. J.; Ziviani, L. *Biorg. Med. Chem. Lett.* **1995**, *5*, 551.
4. (a) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442. (b) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608. (c) Frishman, W. H. *New Engl. J. Med.* **1981**, *305*, 500. (d) Lefkowitz, R. J. *Ann. Rep. Med. Chem.* **1980**, *15*, 217.

5. (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (b) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527. (c) Xiang, Y.; Olivier, E.; Ouimet, N. *Tetrahedron Lett.* **1992**, *33*, 457. (d) Reetz, M. T.; Kükenhöhner, T.; Weinig, P. *Tetrahedron Lett.* **1986**, *27*, 5711. (e) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874.
6. (a) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60. (b) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. *Tetrahedron Lett.* **1983**, *24*, 3213. (c) Schmierer, G.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207.
7. Gamboni, R.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 615.
8. (a) Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 6047. (b) Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051.
9. Bernardi, A.; Carugo, O.; Pasquarello, A.; Sidjimov, A.; Poli, G. *Tetrahedron* **1991**, *47*, 7357.
10. Cardani, S.; Gennari, C.; Scolastico, C.; Villa, R. *Tetrahedron* **1989**, *45*, 7397.
11. Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1986**, 824.
12. (a) Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628. (b) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (c) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305.
13. (a) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544. (b) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177.
14. For pinene-based amino alcohols and *N*-tosyl derivatives, see: (a) Chrisman, W.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 2053 and references cited therein. (b) Goralski, C. T.; Chrisman, W.; Hasha, D. L.; Nicholson, L. W.; Rudolf, P. R.; Zackett, D.; Singaram, B. *Tetrahedron: Asymmetry* **1997**, *8*, 3863. (c) Evans, P. A.; Nelson, J. D.; Rheingold, A. L. *Tetrahedron Lett.* **1997**, *38*, 2235. (d) Masui, M.; Shioiri, T. *Tetrahedron* **1995**, *51*, 8363. (e) Cherng, Y.-J.; Fang, J.-M.; Lu, T.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 89. (f) Lu, T. J.; Liu, S. W. *J. Chin. Chem. Soc.* **1994**, *41*, 467.
15. (1*S*)-(−)-α-Pinene (81% e.e.), (1*S*)-(−)-β-pinene (97% e.e.), (−)-camphene, (1*R*)-(−)-nopol and (1*R*)-(−)-nopol benzyl ether were purchased from Aldrich Chem. Co.
16. White solid, mp 90–91°C, $[\alpha]_D^{27}$ −35.5 (*c* 1.1; $CHCl_3$); IR (KBr, cm^{-1}): 3290; 2964; 2921; 1481; 1465; 1374; 1220; 1177; 1124; 1087; 1018; 926. ^1H NMR (300 MHz, $CDCl_3$, ppm): 2.85 (dd, 9.9 Hz, 4.8 Hz, H3); 2.68–2.58 (m, H4β); 2.18–2.10 (m, H7β); 2.01 (t, 5.7 Hz, H1); 1.87–1.81 (m, H5); 1.31 (ddd, 13.8 Hz, 4.8 Hz, 3.0 Hz, H4α); 1.25 (s, H9); 1.21 (d, 10.2 Hz, H7α); 1.18 (s, H10); 1.12 (s, 3×CH_3); 0.97 (s, H8). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 71.4 (s, C2); 53.1 (d, C1); 50.8 (s, C); 50.7 (d, C3); 42.8 (t, C4); 40.4 (d, C5); 38.3 (s, C6); 30.6 (q, C10); 30.3 (q, 3×CH_3); 28.0 (t, C7); 27.7 (q, C9); 24.1 (q, C8).
17. Analytical and spectral data are in agreement with the literature. See Ref. 14d.
18. The removal of the tosyl group in compound **5** with Na–NH_3[13b] is expected to give (1*R*,2*R*,3*S*,5*R*)-3-amino-2-hydroxypinane, which is an effective chiral ligand for borane reductions of aryl ketones and α-oxoketoxime trityl ethers: (a) Masui, M.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 5195. (b) Masui, M.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 5199. (c) Masui, M.; Shioiri, T. *Synlett* **1997**, 273. (d) Masui, M.; Shioiri, T. *Synlett* **1996**, 49.
19. White solid, mp 123–125°C, $[\alpha]_D^{27}$ −3.0 (*c* 1.3; $CHCl_3$); IR (KBr, cm^{-1}): 3351; 3268; 3042; 2978; 2936; 2914; 1526; 1297; 1153; 1094; 913; 814. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.74 (d, 8.4 Hz, $H_{arom.}$); 7.30 (d, 8.4 Hz, $H_{arom.}$); 5.25 (t, 6.3 Hz, NH); 3.02 (dd, 12.3 Hz, 6.3 Hz, H10); 2.90 (dd, 12.3 Hz, 6.3 Hz, H10); 2.42 (s, CH_3); 2.24–2.15 (m, H7β); 2.01 (t, 6.0 Hz, H1); 1.96–1.91 (m, H5); 1.89–1.84 (m, H4β); 1.83–1.73 (m, H3); 1.70–1.63 (m, H4α); 1.61 (sl, OH); 1.34 (d, 10.2 Hz, H7α); 1.20 (s, C9); 0.89 (s, C8). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 143.2, 136.9, 129.6 and 126.9 ($C_{arom.}$); 76.0 (s, C2); 52.5 (t, C10); 49.5 (d, C1); 40.8 (d, C5); 38.1 (s, C6); 28.5 (t, C7); 27.1 (q, CH_3); 26.6 (t, C3); 24.6 (t, C4); 22.9 (q, C9); 21.4 (q, C8).
20. White solid, mp 126–128°C, $[\alpha]_D^{27}$ +14.1 (*c* 1.84; $CHCl_3$); IR (KBr, cm^{-1}): 3600–3360; 3290; 2962; 2883; 1619; 1473; 1458; 1322; 1311; 1154; 1085; 818. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.53 (d, 8.1 Hz, $H_{arom.}$); 7.32 (d, 8.1 Hz, $H_{arom.}$); 4.81–4.75 (m, NH); 3.14 (dd, 12.0 Hz, 7.5 Hz, H10); 2.85 (dd, 12.0 Hz, 4.4 Hz, H10); 2.45 (s, CH_3); 2.10 (dd, 4.6 Hz, 1.5 Hz, H6); 1.88 (d, 10.5 Hz, H7a); 1.77–1.74 (m, H3); 1.58 (sl, OH); 1.56–1.49 (m, H5); 1.42–1.35 (m, H5); 1.33–1.25 (m, H4); 1.15 (d, 10.5 Hz, H7b); 0.96 (s, H8); 0.90 (s, H9). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 143.2, 136.4, 129.6 and 127.0 ($C_{arom.}$); 81.3 (s, C1); 49.5 (d, C3); 47.7 (d, C6); 46.0 (t, C10); 43.9 (s, C2); 34.1 (t, C7); 24.8 (q, CH_3); 23.3 (t, C5); 22.7 (t, C4); 21.8 (q, C9); 21.4 (q, C8).
21. Brown, H. C.; Zaidlewicz, M.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1764.