



Synthesis and structural determination of new chiral auxiliaries derived from (–)- β -pinene

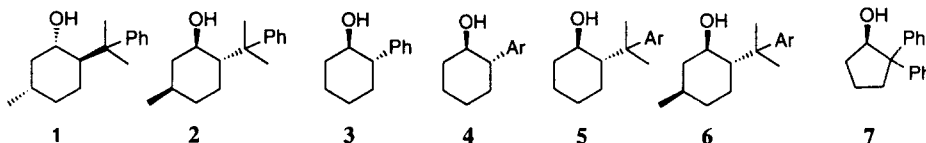
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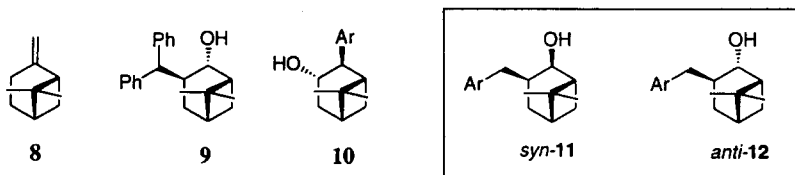
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Abstract: New chiral auxiliaries, alcohols *syn*-11a,e and *anti*-12a,e, were readily synthesized in a stereoselective manner from (–)- β -pinene. Their stereochemical determinations have been made on the basis of nOe experiments. © 1997 Elsevier Science Ltd. All rights reserved.

A survey of recent chemical literature reveals an explosion of interest in the development of new chiral auxiliaries to accomplish synthetic transformations with a high degree of asymmetric induction. The landmark in this field was reported by Corey in 1975 with the synthesis of (+)-8-phenylmenthol **1** from (–)-pulegone and its successful application to a highly diastereoselective Diels–Alder reaction of the corresponding acrylate.¹ Its enantiomer, (–)-8-phenylmenthol **2**,² firstly prepared by Oppolzer from naturally occurring (+)-pulegone, has become one of the most powerful and widely used chiral auxiliaries in organic synthesis. Among the numerous chiral auxiliaries reported during the past two decades, *trans*-2-phenylcyclohexanol **3**³ as well as *trans*-2-arylcyclohexanols **4**,⁴ *trans*-2-(1-methyl-1-arylethyl)cyclohexanols **5**⁵ and 2,2-diphenylcyclopentanol **7**^{4a,6} emerged as powerful simplified equivalents to (–)-8-phenylmenthol **2** or 8-arylmenthols **6**.⁷



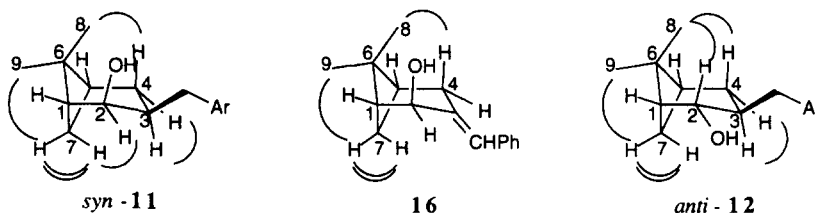
Although α -pinene-based chiral reagents are well known in asymmetric synthesis,⁸ somewhat surprisingly, the readily available (1*S*)-(–)- β -pinene **8** has been scarcely used in the elaboration of chiral auxiliaries, e.g. 3-(1,1-diphenylmethyl)nopinol **9**⁹ and 2-aryl-3-hydroxypinane **10**.¹⁰ The purpose of this paper is to report a practical synthesis of new alcohols, *syn*-**11** and *anti*-**12**, derived from natural (1*S*)-(–)- β -pinene **8**, in which the aromatic group is linked to the pinane nucleus through a one-carbon atom spacer. Some of these compounds are useful chiral auxiliaries, in particular in asymmetric Friedel–Crafts alkylations.¹¹



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LAH reduction (THF, 0°C) of ketones **15a,e** furnished *syn* alcohols **11a,e**. Alcohol **11a** has also been obtained starting from enone **14a**: LAH reduction led to allylic alcohol **16**, this was in turn subjected to catalytical hydrogenation (H₂, 10% Pd-C, AcOEt), giving stereoselectively *syn* alcohol **11a**. *Anti* alcohols **12a,c** were synthesized through sodium-isopropanol reduction (toluene, 110° C, 18 h) of ketones **15a,c** (de 100%).

Stereochemical assignments of alcohols **11a,e**, **12a,c** and **16** were made as above. Orientation of the hydroxy group was deduced from the nOe of the "endo" Me₈ with H₂ and H₄ in *anti* alcohols **12a,e**, and from the nOe of H₇_{endo} with H₂ and of "endo" Me₈ with H₄ in *syn* alcohols **11a,e** (Scheme 3).



Scheme 3.

We have reported herein, the highly stereoselective synthesis of new chiral alcohols derived from (1*S*)-(-)- β -pinene **8** and inexpensive reagents (O₂, H₂, LAH, Na). As (1*R*)-(+)- β -pinene *ent*-**8** can be efficiently prepared by isomerisation of (1*R*)-(+)- α -pinene,¹⁷ antipodal forms of these alcohols can be obtained following this protocol. We are now investigating various diastereoselective syntheses using these chiral auxiliaries. The results will be published in due course.

Acknowledgements

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 14. Spectroscopic data are given only for the derivatives bearing a benzyl group: **Enones**: **14a**: White solid, Mp 102°C (pentane: Et₂O 1:1); $[\alpha]_{\text{D}}^{20} -8.5$ (c=2.35, CHCl₃); IR (KBr): 3058, 2939, 1682, 1601 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ ppm: 0.98 (s, 3H₈); 1.41 (s, 3H₉); 1.55 (d, J=10.2 Hz, H_{7endo}); 2.41 (m, 1H₅) 2.66 (dt, J=10.2, 5.6 Hz, 1H_{7exo}) 2.75 (t, J=5.6 Hz, 1H₁); 3.11 (t, J=2.8 Hz, 2H₄); 7.4–7.9 (m, 5H_{arom.}); 8.08 (bs, 1H₁₀). ¹³C NMR (50 MHz, CDCl₃) δ ppm: 21.6 (CH₃); 26.1 (CH₃); 27.4 (CH₂); 30.8 (CH₂); 39.1 (CH); 40.8 (C); 55.8 (CH); 128.5 (CH); 128.8 (CH); 130.7 (CH); 132.6 (C); 135.6 (C) 203.4 (C). **14b**: White solid, Mp 75°C (pentane: Et₂O 3:1); $[\alpha]_{\text{D}}^{20} -72.2$ (c=1.44, EtOH_{abs}). **14c**: White solid, Mp 73°C (pentane); $[\alpha]_{\text{D}}^{20} -8.0$ (c=4.9, MeOH). **14d**: Pale yellow solid, Mp 114°C (Et₂O); $[\alpha]_{\text{D}}^{20} -8.5$ (c=2.35, CHCl₃). **14e**: Pale yellow solid, Mp 115°C (Et₂O); $[\alpha]_{\text{D}}^{20} -69.0$ (c=1.29, EtOH_{abs}). **Ketones**: **15a**: White solid, Mp 56°C (pentane); $[\alpha]_{\text{D}}^{20} -56.4$ (c=1.6, EtOH_{abs}); IR (KBr): 3068, 3032, 2950, 2872, 1708, 1602, 1453 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm: 0.77 (s, 3H₈); 1.33 (s, 3H₉); 1.58 (ddt, J=12.5, 7.9, 1.4 Hz, 1H_{4 β}); 1.68 (d, J=10.5 Hz, 1H_{7endo}); 2.06 (ddd, J=13.5, 10.2, 4.6 Hz, 1H_{4 α}); 2.21 (q, J=5.1 Hz, 1H₅); 2.42 (dd, J=13.8, 10.3 Hz, 1H₁₀); 2.44 (dt, J=10.5, 5.1 Hz, 1H_{7exo}); 2.64 (t, J=5.3 Hz, 1H₁); 2.84 (m, 1H₃); 3.55 (dd, J=13.8, 3.8 Hz, 1H₁₀); 7.18–7.30 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 21.9 (CH₃); 25.3 (CH₂); 26.2 (CH₃); 28.5 (CH₂); 35.3 (CH₂); 40.7 (CH); 42.9 (C); 44.1 (CH); 57.5 (CH); 125.9 (CH); 128.2 (CH); 128.8 (CH); 140.1 (C); 215.1 (C); E. A.: calc: C 84.16%, H 8.83%; found C 84.24%, H 8.96%. **15b**: Colorless oil; $[\alpha]_{\text{D}}^{20} -46.1$ (c=1.41, EtOH_{abs}). **15c**: White solid, Mp 60°C (pentane); $[\alpha]_{\text{D}}^{20} -67.4$ (c=1.9, EtOH_{abs}). **15d**: White solid, Mp 92°C (pentane); $[\alpha]_{\text{D}}^{20} -55.3$ (c=1.9, EtOH_{abs}). **15e**: White solid, Mp 69°C (pentane); $[\alpha]_{\text{D}}^{20} -27.4$ (c=1.9, EtOH_{abs}). **Syn alcohols**: **11a**: colorless oil; $[\alpha]_{\text{D}}^{20} -51.9$ (c=1.9, EtOH_{abs}); IR (neat): 3280, 3220, 3068, 2921 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm: 1.10 (s, 3H₈); 1.22 (s, 3H₉); 1.29 (d, J=10.0 Hz, 1H_{7endo}); 1.60 (1H_{OH}); 1.66 (dd, J=13.5, 9.3 Hz, 1H_{4 β}); 1.84 (ddd, J=13.5, 8.7, 4.9 Hz, 1H_{4 α}); 1.94 (q, J=5.4 Hz, 1H₅); 2.14 (dt, J=10.0, 4.9 Hz); 2.19 (q, J=4.9 Hz); 2.62 (m, 1H₃); 2.68 (dd, J=13.2, 8.0 Hz, 1H₁₀); 2.99 (dd, J=13.2, 7.7 Hz, 1H₁₀); 4.31 (dd, J=7.4, 4.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 23.0 (CH₃); 25.4 (CH₂); 27.7 (CH₃); 31.9 (CH₂); 34.8 (CH); 37.3 (CH₂); 38.7 (C); 41.3 (CH); 47.7 (CH); 74.2 (CH); 125.9 (CH); 128.5 (CH); 128.9 (CH); 141.6 (C). **11b**: White solid, Mp 47°C (pentane); $[\alpha]_{\text{D}}^{20} -25.3$ (c=1.7, EtOH_{abs}); **11c**: colorless oil; $[\alpha]_{\text{D}}^{20} -30.9$ (c=2.1, EtOH_{abs}); **11d**: white solid, Mp 112°C (pentane); $[\alpha]_{\text{D}}^{20} -54.0$ (c=1.45, EtOH_{abs}); **11e**: colorless oil; $[\alpha]_{\text{D}}^{20} -11.4$ (c=1.8, EtOH_{abs}); **Anti alcohols**: **12a**: White solid, Mp 110°C (Et₂O: pentane 1:1); $[\alpha]_{\text{D}}^{20} -42$ (c=2, EtOH_{abs}); IR (neat): 3152, 2926 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm: 0.78 (s, 3H₈); 1.23 (s, 3H₉); 1.41 (dd, J=13.4, 9.1 Hz, 1H_{4 β}); 1.55 (d, J=10.2 Hz, 1H_{7endo}); 1.59 (1H_{OH}); 1.83 (m, 1H_{4 α}); 1.89 (q, J=5.4 Hz, 1H₅); 1.95 (dt, J=5.4, 1.7 Hz, 1H₁); 2.05 (m, 2H_{7exo,3}); 2.67 (dd, J=13.1, 8.6 Hz, 1H₁₀); 2.97 (dd, J=13.1, 6.6 Hz, 1H₁₀); 3.90 (dd, J=6.9, 1.7 Hz, 1H₃); 7.19–7.32 (m, 5H) ¹³C NMR (100 MHz, CDCl₃) δ ppm: 19.8 (CH₃); 23.1 (CH₂); 26.7 (CH₃); 30.2 (CH₂); 40.4 (C); 40.6 (CH); 40.7 (CH₂); 40.8 (CH); 47.9 (CH); 75.0 (CH); 126.1 (CH); 128.5 (CH); 129.0 (CH); 140.9

(C). **12b**: White solid, Mp 112°C (pentane); $[\alpha]_{20}^D -51.6$ (c=1.5, EtOH_{abs}); **12c**: Colorless oil; $[\alpha]_{20}^D -57.3$ (c=1.5, EtOH_{abs}).

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