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

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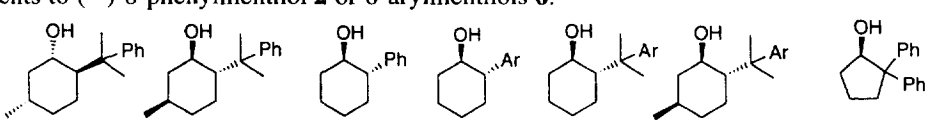
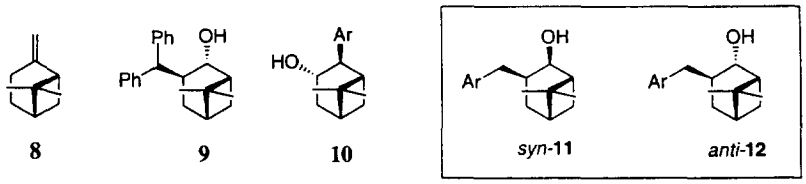
Abstract: New chiral auxiliaries, alcohols *syn*-**11a,e** and *anti*-**12a,e**, were readily synthesized in a stereoselective manner from (−)-β-pinene. Their stereochemical determinations have been made on the basis of nOe experiments. © 1997 Elsevier Science Ltd. All rights reserved.

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]



1 **2** **3** **4** **5** **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 auxiliairies, 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]



8 **9** **10** *syn*-**11** *anti*-**12**

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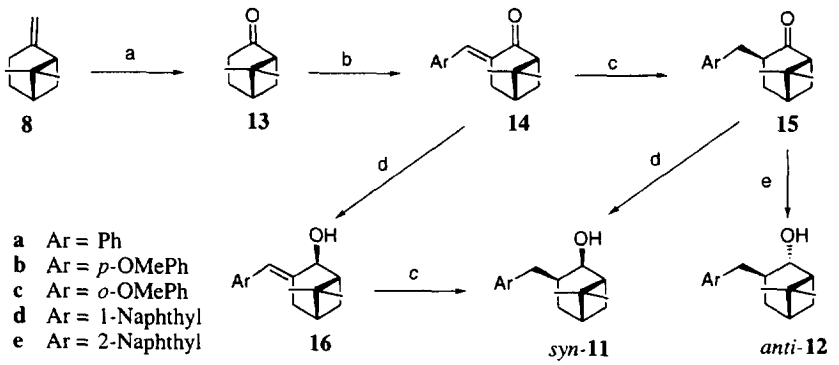
Indeed, such one-carbon atom spacer in cyclohexane-based chiral auxiliaries has been demonstrated to have a crucial importance in the Michael addition of diphenylmethaneamine to stereogenic crotonates.[5d]

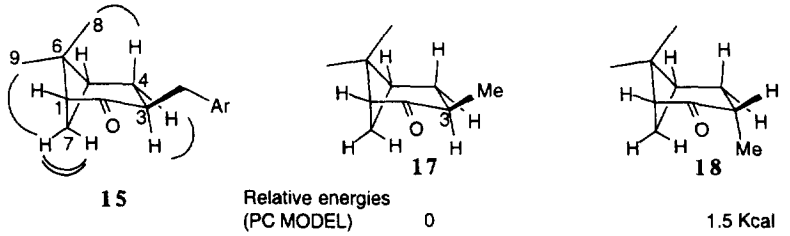
Alcohols *syn*-**11a,e** and *anti*-**12a,c** were synthesized according to Scheme 1. (−)-β-Pinene **8**[12] was treated with ozone at −78°C, then with Me_2S to provide pure (+)-nopinone **13**,[13] ($[\alpha]^{20}_D$ +17.6 (neat), 92% ee). Nopinone **13** was allowed to react with aromatic aldehydes in aqueous potassium hydroxide leading to the corresponding *E*-enones **14a,e**.[14]



(a) O_3, CH_2CL_2 / MeOH, -78 °C then Me_2S, -78 °C to RT, 18 h, 86 % yield.(b) 1 eq. ArCHO, 10 % KOH, 100 °C, 24 h, 70-95 % yield. (c) H_2, 10 % Pd-C, AcOEt, 85-98 % yield. (d) $LiAlH_4$, THF, 0 °C to RT, 30 min, 98 %. (e) Na, *i* PrOH, toluene, 110 °C, 18 h, 60-88 % yield (**12a,c**) or $CeCl_3$, MeOH, RT, 18h then $NaBH_4$, RT, 30 min, (**12d,e**).

Scheme 1.

Catalytical hydrogenation (H_2, 10% Pd–C, AcOEt) of enones **14a,e** afforded stereoselectively ketones **15a,e** (^{13}C NMR analysis of the isolated products indicated that only one epimer was formed). Assigments of all the hydrogen and carbon atoms were made on the basis of 1D and 2D experiments, DQF COSY, $^1H - ^{13}C$ direct and long range correlations (HMQC and HMBC) and decoupling studies (400 MHz), starting from H_{7endo}.[15] In this study, this hydrogen atom was always observed as a doublet [J=10 Hz (geminal coupling with H_{7exo}), the approximate zero coupling to the bridgehead hydrogen H_1 is attributed to the magnitude of the dihedral angle, 90°], and generally appears as one of the most upfield hydrogens, sometimes in the methyl region of the NMR spectra. Stereochemical assignments of ketones **15a,e** were made on the basis of nOe experiments, starting again from H_{7endo} (Scheme 2). Strong nOe (11–27%) with H_{7exo} and significant nOe of H_{7exo} with one methyl signal were observed, allowing the assignment of Me_9 and therefore the "endo" Me_8. This Me_8 has significant nOe (2–7%) with $H_{4\beta}$, and $H_{4\alpha}$ has significant nOe with H_3. This implies a *syn* relationship between the methylene-aryl appendage and the gem-dimethylene bridge of the pinane nucleus.

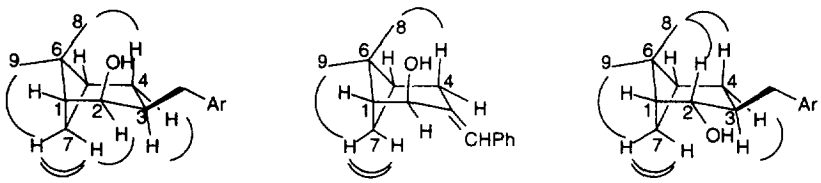


Scheme 2.

When subjected to equilibrating conditions (5% KOH, MeOH, RT, 48 h), these ketones **15** were found unchanged. This observation is in agreement with the thermodynamic *syn* arrangement of the related 3-methyl-pinan-2-one **17**. This "*syn*" ketone **17** lies approximatively 1.5 kcal lower in energy than the corresponding "*anti*" ketone **18** (PC MODEL) (Scheme 2).[16]

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 (H_2, 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" Me_8 with H_2 and H_4 in *anti* alcohols **12a,e**, and from the nOe of H_{7endo} with H_2 and of "endo" Me_8 with H_4 in *syn* alcohols **11a,e** (Scheme 3).



syn - **11** **16** *anti* - **12**

Scheme 3.

We have reported herein, the highly stereoselective synthesis of new chiral alcohols derived from (1*S*)-(−)-β-pinene **8** and inexpensive reagents (O_2, H_2, 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.

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13. Nopinone of high enantiomeric purity: Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217. Kozmina, N.; Paquette, L. A. *Synth. Comm.* **1996**, *26*, 2027–2030.
14. Spectroscopic data are given only for the derivatives bearing a benzyl group: ***Enones*: 14a**: White solid, Mp 102°C (pentane: Et_2O 1:1); $[\alpha]^D_{20}$ −8.5 (c=2.35, $CHCl_3$); IR (KBr): 3058, 2939, 1682, 1601 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 0.98 (s, $3H_8$); 1.41 (s, $3H_9$); 1.55 (d, J=10.2 Hz, H_{7endo}); 2.41 (m, $1H_5$) 2.66 (dt, J=10.2, 5.6 Hz, $1H_{7exo}$) 2.75 (t, J=5.6 Hz, $1H_1$); 3.11 (t, J=2.8 Hz, $2H_4$); 7.4–7.9 (m, $5H_{arom.}$); 8.08 (bs, $1H_{10}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 21.6 (CH_3); 26.1 (CH_3); 27.4 (CH_2); 30.8 (CH_2); 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: Et_2O 3:1); $[\alpha]^D_{20}$ −72.2 (c=1.44, $EtOH_{abs}$). **14c**: White solid, Mp 73°C (pentane); $[\alpha]^D_{20}$ −8.0 (c=4.9, MeOH). **14d**: Pale yellow solid, Mp 114°C (Et_2O); $[\alpha]^D_{20}$ −8.5 (c=2.35, $CHCl_3$). **14e**: Pale yellow solid, Mp 115°C (Et_2O); $[\alpha]^D_{20}$ −69.0 (c=1.29, $EtOH_{abs}$). ***Ketones*: 15a**: White solid, Mp 56°C (pentane); $[\alpha]^D_{20}$ −56.4 (c=1.6, $EtOH_{abs}$); IR (KBr): 3068, 3032, 2950, 2872, 1708, 1602, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.77 (s, $3H_8$); 1.33 (s, $3H_9$); 1.58 (ddt, J=12.5, 7.9, 1.4 Hz, $1H_{4\beta}$); 1.68 (d, J=10.5 Hz, $1H_{7endo}$); 2.06 (ddd, J=13.5, 10.2, 4.6 Hz, $1H_{4\alpha}$); 2.21 (q, J=5.1 Hz, $1H_5$); 2.42 (dd, J=13.8, 10.3 Hz, $1H_{10}$); 2.44 (dt, J=10.5, 5.1 Hz, $1H_{7exo}$); 2.64 (t, J=5.3 Hz, $1H_1$); 2.84 (m, $1H_3$); 3.55 (dd, J=13.8, 3.8 Hz, $1H_{10}$); 7.18–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.9 (CH_3); 25.3 (CH_2); 26.2 (CH_3); 28.5 (CH_2); 35.3 (CH_2); 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; $[\alpha]^D_{20}$ −46.1 (c=1.41, $EtOH_{abs}$). **15c**: White solid, Mp 60°C (pentane); $[\alpha]^D_{20}$ −67.4 (c=1.9, $EtOH_{abs}$). **15d**: White solid, Mp 92°C (pentane); $[\alpha]^D_{20}$ −55.3 (c=1.9, $EtOH_{abs}$). **15e**: White solid, Mp 69°C (pentane); $[\alpha]^D_{20}$ −27.4 (c=1.9, $EtOH_{abs}$). ***Syn alcohols*: 11a**: colorless oil; $[\alpha]^D_{20}$ −51.9 (c=1.9, $EtOH_{abs}$); IR (neat): 3280, 3220, 3068, 2921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.10 (s, $3H_8$); 1.22 (s, $3H_9$); 1.29 (d, J=10.0 Hz, $1H_{7endo}$); 1.60 ($1H_{OH}$); 1.66 (dd, J=13.5, 9.3 Hz, $1H_{4\beta}$); 1.84 (ddd, J=13.5, 8.7, 4.9 Hz, $1H_{4\alpha}$); 1.94 (q, J=5.4 Hz, $1H_5$); 2.14 (dt, J=10.0, 4.9 Hz); 2.19 (q, J=4.9 Hz); 2.62 (m, $1H_3$); 2.68 (dd, J=13.2, 8.0 Hz, $1H_{10}$); 2.99 (dd, J=13.2, 7.7 Hz, $1H_{10}$); 4.31 (dd, J=7.4, 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 23.0 (CH_3); 25.4 (CH_2); 27.7 (CH_3); 31.9 (CH_2); 34.8 (CH); 37.3 (CH_2); 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); $[\alpha]^D_{20}$ −25.3 (c=1.7, $EtOH_{abs}$); **11c**: colorless oil; $[\alpha]^D_{20}$ −30.9 (c=2.1, $EtOH_{abs}$); **11d**: white solid, Mp 112°C (pentane); $[\alpha]^D_{20}$ −54.0 (c=1.45, $EtOH_{abs}$); **11e**: colorless oil; $[\alpha]^D_{20}$ −11.4 (c=1.8, $EtOH_{abs}$); ***Anti alcohols*: 12a**: White solid, Mp 110°C (Et_2O:pentane 1:1); $[\alpha]^D_{20}$ −42 (c=2, $EtOH_{abs}$); IR (neat): 3152, 2926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.78 (s, $3H_8$); 1.23 (s, $3H_9$); 1.41 (dd, J=13.4, 9.1 Hz, $1H_{4\beta}$); 1.55 (d, J=10.2 Hz, $1H_{7endo}$); 1.59 ($1H_{OH}$); 1.83 (m, $1H_{4\alpha}$);1.89 (q, J=5.4 Hz, $1H_5$); 1.95 (dt, J=5.4, 1.7 Hz, $1H_1$); 2.05 (m, $2H_{7exo,3}$); 2.67 (dd, J=13.1, 8.6 Hz, $1H_{10}$); 2.97 (dd, J=13.1, 6.6 Hz, $1H_{10}$); 3.90 (dd, J=6.9, 1.7 Hz, $1H_3$); 7.19–7.32 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.8 (CH_3); 23.1 (CH_2); 26.7 (CH_3); 30.2 (CH_2); 40.4 (C); 40.6 (CH); 40.7 (CH_2); 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); $[\alpha]^{D}_{20}$ −51.6 (c=1.5, $EtOH_{abs}$); **12c**: Colorless oil; $[\alpha]^{D}_{20}$ −57.3 (c=1.5, $EtOH_{abs}$).

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