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New Camphor Derivatives for Enantioselective Syntheses

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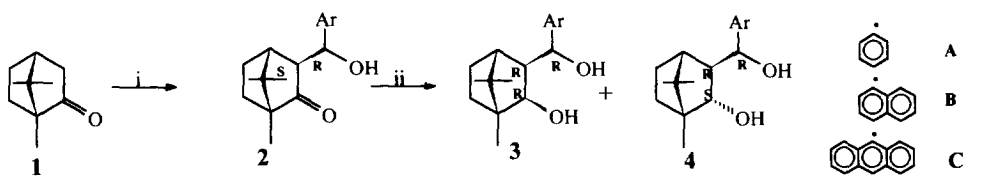
***Abstract**: New 1,3 diols **3a→3c** were efficiently prepared in the enantiopure form in 50-68% yield (2 steps), from the available 1-(R)-(+)-camphor **1**.* Copyright © 1996 Elsevier Science Ltd

The readily available 1-(R)-(+)-camphor **1** and its derivatives have been successfully employed as chiral auxiliaries in numerous systems in the field of asymmetric synthesis.[1]

In connection with our efforts towards the synthesis of inexpensive chiral promoters,[2,3] we decided to investigate a very simple and efficient route for the preparation of new optically active 1,3-diols.[4]

In this report we describe a synthesis for the (1R,2R,3R,3'R,4R)-3-(phenylhydroxymethyl)-1,7,7-bicyclo-[2.2.1]-heptan-2-ol **3A** and its analogs **3B** and **3C** by stereoselective aldol reaction between **1** and the appropriate aromatic moieties, and stereoselective reduction of the resulting aldol adducts **2A-C**.The route employed for the preparation of diols **3A→3C** is outlined in scheme 1 and summarized in the table.



Scheme 1

Scheme 1: i) 1- 1.5 Eq LDA, THF, -78°C, 90 min; 2- ArCHO, THF, -78°C, 1h; 3- NH_4Cl (solution), -78°C. ii) $NaBH_4$, THF, H_2O, 0°C, 6h.

Table

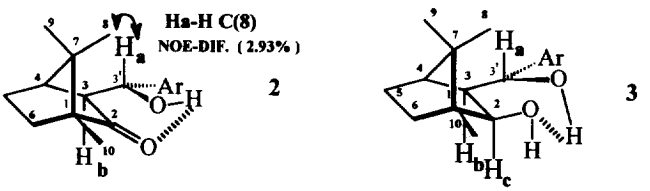
entry	ArCHO	2, yield (%)[a]	2, de (%)[b]	2, $[\alpha]_D^{20}$ [a,d]	3/4[b,e]	3,yield(%)[f]	$[\alpha]_D^{20}$ [f]
1	Ar= **A**	77	88(≥99)[c]	+35.8	5.3	64	+65.4
2	Ar= **B**	64	80	+33.0	11.5	92	+79.6
3	Ar= **C**	83	96	+24.5	5.3	82	+49.5

Table: a- After purification by chromatography; b- Before purification; c- After recrystallization in Hexane; d- $[\alpha]_D^{20}$, C=1 in $CHCl_3$; e- Evaluated by its weight after separations and NMR ^1H analysis

before separations. f- After separation by chromatography (entry 1 and 2) or crystallization in hexane (entry 3) (diastereoisomerically and enantiomerically pure products).

The configuration **S** at the C(3) position of **2C** was determined by NOE-DIFF experiments[5] . The results are in agreement with the Albizati's prior reports, for analog **2A**[6]. The relative configuration for C(2)/C(3) in **3** was determined by analysis of the coupling constants between Hb/Hc ($J_{HbHc} \cong 8Hz$, $\omega = 0°$, cis) and the configuration **R** at the C(3') position, was determined by the magnitude of the coupling constants between Ha/Hb in **2** ($J_{HaHb} \cong 11Hz$, $\omega \cong 180°$) and **3** ($J_{HaHb} \cong 10Hz$, $\omega \cong 180°$), Figure 1.

Figure 1



The diastereoselectivities obtained in the aldol reaction may be rationalized in terms of the favourable chelated transition state outlined in Figure 2 (Zimmerman -Traxler model [7]). On the other hand, the selectivities observed in the reduction with sodium borohydride may be reasonably interpreted, invoking the attack of the hydride ion took place preferentially on the less hindered side of aldols **2A-2C** (Figure 3).

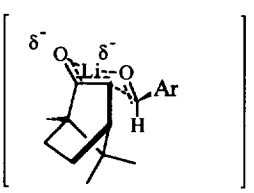


Figure 2

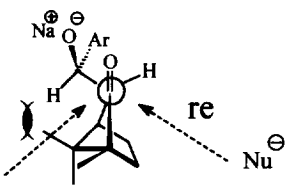


Figure 3

The very bulky aromatic moiety in **3C** (Ar=9-anthryl) is very important in some aspects: 1- It is prepared in the best yield; 2- The Diol **3C** is easily cristallized; 3- The preparation of **3C** in enantiopure form acheived by crystallization in hexane, separation by chromatography was not necessary. In fact, we believe that this very bulky aromatic substituent will also be important for good facial selection in asymmetric

reactions.[2,8] The synthesis at multi-gram quantities have been carried out and the exploration of **3A-C** in the enantioselective reductions of ketones by chiral modifications of Lithium aluminium hidride [4] are under investigation .

Experimental Procedures

General Procedure for 2A-2C: To a solution of LDA (51.8 mmol in 22 mL of dry THF and 37mL of hexane) at -78° C under argon, a solution of **1** (33mmol, 5.0g, in 22mL of dry THF) was slowly added (10min). The reaction mixture was stirred for 90 min ,then a solution of aldehyde (33mmol in 22mL of THF) was added and the resulting mixture was stirred for 60min. When completed (monitorated by TLC, hexane:ethyl acetate 9:1),the reaction was quenched whith 100 mL of saturated ammonium chloride and it was allowed to warm to room temperature. The mixture was concentrated at reduced pressure and 200mL of dichloromethane were added. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated at reduced pressure. The resulting solid was used without futher purification [9]

General Procedure for 3A-3C: To a solution of **2A-2C** (1.2 mmol in 15mL of THF) at 0 ° C, sodium borohydride (252 mg , 6.6mmol) was slowly added (3 min . The reaction mixture was stirred for 6 h at 0°C (monitorated by TLC, hexane: ethyl acetate 4:1) . When completed, it was allowed to warm at room temperature and quenched with 1 mL of saturated ammonium chloride (slowly!). The mixture was concentrated at reduced pressure and 50mL of dichloromethane were added. The organic layer was washed with brine (3x25mL), dried over magnesium sulfate, filtered and concentrated at reduced pressure.The resulting solid was purified by *flash* chromatography (hexane: ethyl acetate 9:1,then 1:5, silica gel /product 100:1)[9]

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References and notes

1. Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

2. Vasconcellos, M.L.; d'Angelo, J.; Desmaele, D.; Costa, P.R.R.; Potin, D. *Tetrahedron:Asymmetry* **1991**, *2*, 353.

3. Cabral, L.M.; Costa, P.R.R.; Vasconcellos, M.L.A.A.; Barreiro, E.J.; and Castro, R.N. *Synthetic Comm.* **1996**,*000 ,in press.*

4. a- Cherng, Y.; Fang, J.; Lu, T. *Tetrahedron:Asymmetry* **1995**, *6*, 89; b- Wallace, R.H.; Lu, Y.; Liu, J.; Atwood, J.L.; *Synlett* **1992**, 992. c- For a recent review of applications to Binaphtol, see: Rosini, C.; Franzini, L.; Rafaelli, A.; Salvadori, P *Synthesis* **1992**, 503.

5. The NOE-DIFF experiments were made for Dr. J. Mahuteau (F.F.-Châtenay-Malabry-France, 400MHz), in conciliation with Dr. E. Rangel (I.M.E. - Brazil).

6. Vaillancourt, V.; Agharahimi, M.R.; Sundran, V.N.; Richou, O.; Faulkner, D.J.; Albizati, K..F. *J. Org. Chem.* **1991**, *56*, 378.

7. Zimmerman, H.E.; Traxer, M.D. *J.Am.Chem.Soc.***1957**,*79*,1920

8. a- d'Angelo, J.; Maddaluno, J. *J.Am. Chem. Soc.* **1986**, *108*, 8112; b- Potin, D.; Dumas, F., d'Angelo, J. Ibid. **1990**, *122*, 3483.

9. **2c**, mp= 156-158°C; $[\alpha]_D^{20}$ = +24.5 (c=1.02, $CDCl_3$); NMR ^1H (400MHz, $CDCl_3$) δ 0.79(s, 3H); 0.94-0.99(m, 1H); 1.00(s, 3H); 1.19(s, 3H), 1.24 (d, 1H, J=3.32Hz); 1.56-1.63(m, 3H); 3.26(d, 1H, J=9.97); 4.80(sl, 1H, OH); 6.52(d, 1H, J=9.97Hz); 7.43-8.44(m, 9H). NMR^{13}C (50MHz, $CDCl_3$): δ 9.10(CH_3); 10.00(CH_3); 21.74(CH_3); 28.85(CH_2); 29.26(CH_2); 25.46(CH); 46.70(C); 58.05(C); 58.84(CH); 71.47(CH); 124.56 (2CH); 125.65(CH); 128.69(2CH); 129.32(4CH); 129.81(3C); 131.41(2C); 223.51(C); MS m/z 358 (2%, M^+); 349(6%, M^+-H_2O); **3c**, mp= Decomposition; $[\alpha]_D^{20}$ = +49.5(C=1.05, $CHCl_3$); NMR^{1}H (400MHz, $CDCl_3$), δ 0.50-0.56(m, 1H); 0.66(s, 3H); 0.90(d, 1H, J=3.59Hz); 1.02(s, 3H); 1.05-1.09(m, 1H); 1.24-1.36(m, 1H); 1.36-1..42(m, 1H); 1.52(s, 3H); 3.02(sl, 1H, OH); 3.09(dd, 1H, J=11.49, J=7.74); 4.17(d, 1H, J=7.69); 6.66(d, 1H, J=11.65); 7.43-9.26(m, 9H); NMR^{13}C (50MHz, $CDCl_3$), δ 11.55(CH_3); 21.97(CH_3); 22.20(CH_3); 30.14(CH_2); 33.00(CH_2); 46.80(2C); 446.98(CH); 55.58(CH); 71.35(CH); 82.79(CH); 124.06(CH); 124.56(CH); 124.83(2CH); 125.79(CH); 127.38(CH); 128.46(CH); 129.31(2CH); 131.1092c); 132.39(2c). MS m/z 360 (4%, M^+); 342 (57%, M^+ - H_2O).

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