*Tetrahedron: Asymmetry* Vol. 2, No. 5, pp. 353-356, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

# New Chiral Auxiliaries Derived from β -Pinene : Their Use in the Asymmetric Reduction of β-Keto-Esters

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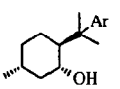
(*Received* 5 *April* 1991)

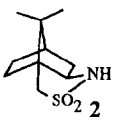
***Abstract** : 3-Ketobutyrates **6**, derived from chiral auxiliary alcohols **5** - themselves efficiently prepared from β-pinene **4** - were reduced with zinc borohydride, giving 3-hydroxybutyrates **7** with 2-70 % de, depending on the nature of aryl group in alcohols **5**.*

Owing to their great structural variety and their high availability, terpenes play an essential role as natural sources of chirality in asymmetric synthesis. Thus several important chiral auxiliaries are prepared from terpenes : (−)-8-arylmenthols **1** [1] from (*R*)-(+)-pulegone [*ent*-**1** from (*S*)-(−)-β-citronellol], *D*-(−)-2,10 camphor-sultam **2** [2] and *ent*-**2** from camphors.

Somewhat surprisingly, the readily available, inexpensive (1*R*)-(+)-α-pinene **3**, (1*S*)-(−)-α-pinene (*ent*-**3**), and (1*S*)-(−)-β-pinene **4** have been scarcely used to build chiral auxiliaries [3] (although numerous chiral reagents for the asymmetric hydroboration of alkenes [4] or the asymmetric reduction of carbonyl compounds [5] have been elaborated from these terpenes).



**1**



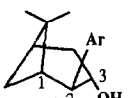
**2**


**3**

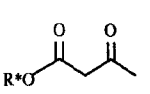

**4**

In connection with our efforts towards the synthesis of polyhydroxylated compounds of natural origin [6], we were in search of a general method for the construction of β-hydroxy-esters of defined stereochemistry. In this respect, reduction, by means of zinc borohydride, of chiral β-keto-esters appeared particularly attractive [7]. Indeed the zinc ion, which can accomodate bidentate ligands, should be chelated by the β-keto-ester moiety, thus blocking the *syn* conformation. On the other hand, the stereogenecity in the starting β-keto-ester can be located in the ester part, allowing the use of easily recyclable chiral auxiliary alcohols.

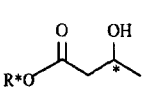
In this report we actually show that chiral 3-keto-butyrates **6**, derived from alcohols **5**, themselves, efficiently prepared from (1*S*)-(−)-β-pinene **4**, are easily reduced with zinc borohydride, giving the corresponding 3-hydroxy-butyrates **7** in high yields. If derivative **5a** (Ar = phenyl) gave only a minute diastereoselectivity (2 % de), satisfactory de (up to 70 %) were obtained, by replacing the phenyl ring in the precedent auxiliary with appropriate bulkier aromatic moieties (alcohols **5d**, **5e**, **5f**).



**5**

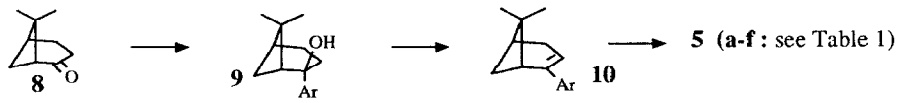


**6**



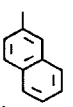
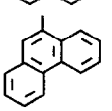
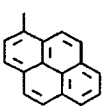
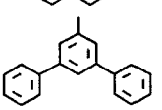
**7**

Chiral alcohols **5** were synthetized from (1*R*,5*S*)-(+)-nopinone **8**, itself obtained by ozonolysis of (−)-β-pinene **4** [8], in 3 steps, essentially according to the reaction sequence reported by Brown for the preparation of phenyl derivative **5a** [4b]. Nopinone was first transformed into tertiary alcohols **9** (ArLi, $Et_2O$, -78 °C, 65-70 % yield)[9] which were dehydrated into olefins **10** ($POCl_3$, pyridine, 0 °C then 18 h at 20 °C, 90-95 % yield). Hydroboration of the latter derivatives led finally to the desired auxiliaries **5** [10] ($BH_3$-$Me_2S$ complex, 12 h in refluxing $Et_2O$ then $H_2O_2$, NaOH 3 h at reflux, 65-75 % yield).

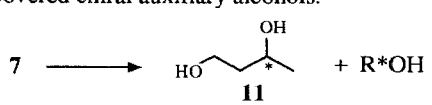



3-Keto-butyrates **6**, prepared from chiral alcohols **5** (ketene dimer, acetone, 3 h at 60 °C, 75-80 % yield) [11], were then reduced with zinc borohydride [12] into 3-hydroxy-butyrates **7** ($Et_2O$, -78 °C, 80-90 % yield). These were obtained as mixtures of diastereoisomers which were easily analyzed by $^1H$ NMR, by using Resolve-Al EuFOD as shift reagent [13]. The observed selectivities are presented in Table 1 (entries 1 to 6). Selectivity in the reduction of 3-keto-butyrate derived from (−)-8-phenylmenthol (**1**, Ar = $C_6H_5$) has also been determined for comparison (entry 7) [14].

**Table 1 : Reduction of chiral 3-keto-butyrates 6 with $Zn(BH_4)_2$**

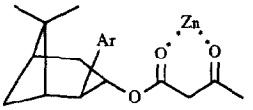
| | | 3-hydroxybutyrates 7 | |
|---|---|---|---|
| **entry** | **chiral auxiliary alcohols** | **config. at C-3 (major isomer)** | **de** |
| 1 | **5a**, Ar =  | *S* | 2 |
| 2 | **5b**, Ar =  | *S* | 2 |
| 3 | **5c**, Ar =  | *S* | 54 |
| 4 | **5d**, Ar =  | *S* | 70 |
| 5 | **5e**, Ar =  | *S* | 70 |
| 6 | **5f**, Ar =  | *S* | 70 |
| 7 | **1**, Ar =  | *R* | 40 [14] |

The absolute configuration at the newly created asymmetric center in β-hydroxy-esters 7 was determined by reduction (LAH, $Et_2O$, 20 °C) which led almost quantitatively to butane-1,3-diol **11**, of known configuration [15], along with the recovered chiral auxiliary alcohols.



**Discussion**

The selectivities observed in the reduction of chiral 3-keto-butyrates **6** with zinc borohydride may be reasonably interpreted, invoking that attack of the hydride ion took place preferentially on the less hindered side of zinc-chelated keto-ester **12**. Geometry of the most favorable conformer of **12** (Ar = phenyl), calculated by PCMODEL [16], is depicted in Fig. 1. An excellent agreement was obtained between the observed coupling constants in $^1$H NMR of this keto-ester and those calculated by the above program, providing thus an indication of the reliability of the present geometry.




**12**

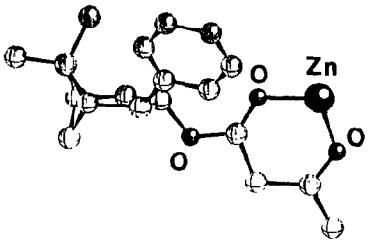



**Fig. 1**

Diastereoselectivities obtained with alcohols **5** may be easily rationalized on the basis of this geometry. Consider first the reduction of 3-keto-butyrate **6a** derived from alcohol **5a** (Ar = phenyl). It is clear, as shown in Fig. 2 -in which the arrows symbolize the attack of the hydride ion-, that the two diastereotopic π-faces of the electrophilic keto group are free of steric hindrance. As a matter of fact, alcohol **5a** furnished an insignificant de (Table 1,, entry 1). Compared to parent auxiliary **5a**, the pendent phenyl group in alcohol **5b** (Ar = β-naphthyl) is substituted at the *meta* and *para* positions by an additional fused aromatic ring. In corresponding β-keto-ester **6b**, this second nucleus should adopt the conformation of ring A of 9-phenanthryl derivative depicted in Fig. 3 (geometry optimized by PCMODEL) [16] - ***anti to the reaction site***. No increase of the steric hindrance is thus expected : indeed alcohol **5b** gave only a minute de (Table 1, entry 2). In alcohol **5c** (Ar = α-naphthyl) the second aromatic nucleus is fused with the pendent phenyl ring at the *ortho* and *meta* positions. Due to the presence of the *endo* bridgehead methyl group, this additional nucleus is pushed away from this bridge, adopting therefore the conformation of ring C of the 9-phenanthryl derivative depicted in Fig. 3 - ***syn to the reaction site*** - in the corresponding keto-ester **6c**. Consequently the *Si* π-face is significantly encumbered : a notable selectivity was thus obtained, leading predominandly to the *S* configuration at the newly created stereogenic center (Table 1, entry 3). The same kind of analysis can be applied to keto-esters **6** derived from alcohols **5d** (Ar = 9-phenanthryl, see Fig. 3) and **5e** (Ar = 1-pyrenyl) which possess both an α-naphthyl-type aromatic moiety, furnishing thus good stereoselectivity (Table 1, entries 4 and 5). In keto-ester **6f** derived from alcohol **5f** (Ar = 3,5-terphenyl), one of the two phenyl substituents at the *meta* positions of the central phenyl nucleus is necessarily *syn* to the *Si* π-face of the keto group. This face being thus notably sterically hindered, a good selectivity was observed (Table 1, entry 6).

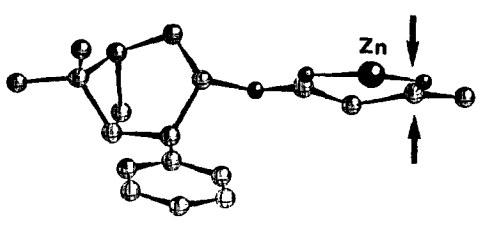



**Fig. 2**

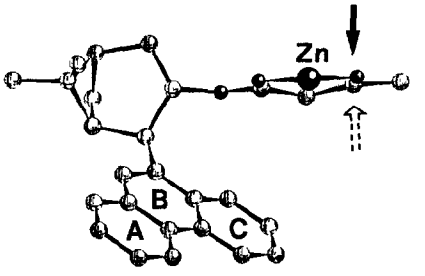



**Fig. 3**

*In this paper we have shown that alcohols* **5d-f** *proved to be notably more efficient chiral auxiliaries in the reduction of 3-keto-butyrates than the "standard" 8-phenyl-menthol* **1** *(*Ar = $C_6H_5$*)* (compare entries 4-6 to entry 7 in Table 1). Further applications of these promising chiral inducers are currently under investigation.

**References and Notes**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   (b) Brown, H.C. ; Weissman, S.A. ; Perumal, P.T. ; Dhokte, U.P. *J. Org. Chem.* **1990**, *55*, 1217-1223.
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7. Reduction of α-unsubstituted chiral β-keto-esters with $Zn(BH_4)_2$ : (a) Takano, S. ; Morimoto, M. ; Ogasawara, K. *Yakugaku Zasshi* **1983**, *103*, 1257-1263. (b) Taber, D.F. ; Deker, P.B. ; Gaul, M.D. *J. Am. Chem. Soc.* **1987**, *109*, 7488-7494.
8. Commercially available (1*S*)-(−)-β-pinene (**4**), $[\alpha]^{20}_D$ -21 (neat) 92 % ee, was used in the present study. (1*R*)-(+)-β-Pinene (*ent*-**4**) can be efficiently prepared by isomerization of (1*R*)-(+)-α-pinene (**3**) : Brown, H.C. ; Zaidlewicz, M. ; Bhat, K.S. *J. Org. Chem.* **1989**, *54*, 1764-1766.
9. The requisite aryllithiums were prepared from the corresponding bromides (nBuLi, $Et_2O$, 0 °C, 5 min). The aryl bromides used in the preparation of alcohols **5a-d** are commercially available. 1-Bromopyrene (precursor of alcohol **5e**) was prepared according to : Nonhebel, D.C. *J. Chem. Soc* **1963**, 1216-1220. 1-Bromo-3,5-terphenyl (precursor of alcohol **5f**) was prepared according to : Chi-Jen Frank Du ; Hart, H. ; Kwok-Keung Daniel Ng *J. Org. Chem.* **1986**, *51*, 3162-3165.
10. **5b** : solid, mp 105-106 °C (hexane), $[\alpha]^{20}_D$ +50 (c = 4.5, EtOH). **5c** : solid, mp 139-140 °C (hexane) $[\alpha]^{20}_D$ +62 (c = 6.0, EtOH). **5d** : solid, mp 130-131 °C (hexane), $[\alpha]^{20}_D$ +65 (c = 4.4, EtOH). **5e** : amorphous solid, $[\alpha]^{20}_D$ +48 (c = 3.7, EtOH). **5f** : amorphous solid, $[\alpha]^{20}_D$ +21 (c = 3.8, EtOH).
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12. Preparation of zinc borohydride : Gensler, W.J. ; Johnson, F.A. ; Sloan, A.D.B. *J. Am. Chem. Soc.* **1960**, *82*, 6074-6081.
13. Analysis of $^1H$ NMR spectrum (250 MHz, $CDCl_3$) of 3-hydroxy-butyrate **7f** (Ar = 9-phenanthryl) is given as an example : δ 1.10 (s, 3H) 1.15 (d, J = 6.3 Hz, 3H) 1.26 (s, 3H) 1.53 (d, J = 9.9 Hz, 1H) 1.92 (m, 1H) 2.15 (m, 1H) 2.30-2.57 (m, 3H) 2.71 (m, 1H) 2.85-3.03 (m, 2H) 4.06-4.25 (m, 2H) 6.16 (ddd, J = 4.8 Hz, J = 6.6 Hz, J = 9.2 Hz, 1H) 7.53-7.70 (m, 4H) 7.75 (s, 1H) 7.82 7.90 (m, 1H) 8.07-8.15 (m, 1H) 8.60-8.68 (m, 1H) 8.71-8.78 (m, 1H). Resonances attributed to H-2 and H-3 of the bicyclic system, and to H-10 of the aromatic moiety, centered at 4.22, 6.16, and 7.75 ppm, respectively, were well-differentiated in the two diastereoisomers, after addition of Resolve-Al EuFOD. The selectivity (85:15) was determined by integration of these signals and confirmed by optical rotation measurement on alcohol **11** [15], after derivatization (see Text).
14. Takano *et al* (ref 7a) reported that reduction of 8-phenylmenthyl 3-ketobutyrate with $Zn(BH_4)_2$ ($Et_2O$, -65 °C) gave 38 % de.
15. (*R*)-(−)-1,3-Butanediol, **11**, $[\alpha]^{20}_D$ -31 (c = 1, EtOH), is commercially available from Aldrich-Chimie.
16. For a recent analysis of bicyclo[3.1.1]heptane derivatives by using the PCMODEL program, see : Peterson, P.E. ; Grant, G. *J. Org. Chem.* **1991**, *56*, 16-20.