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Boron Mediated One-Pot Aldol-reduction Sequence:Enantio and Diastereoselective Synthesis of Typical Polyketide Fragments

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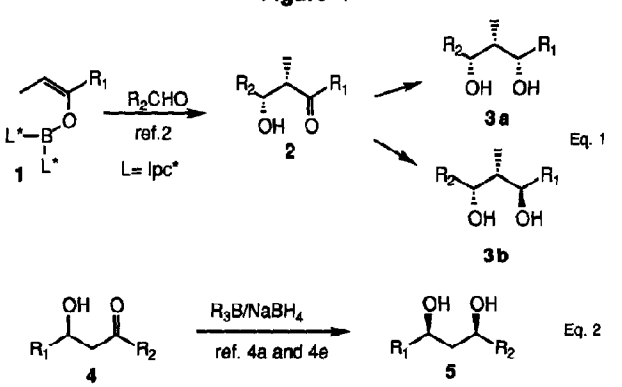
Summary: an aldol-reduction one-pot sequence allows *syn-syn* polyketide fragments such as **7** to be obtained enantio and diastereoselectively. Enol diisopinocampheylborinate is able to influence both the aldol and the subsequent reduction with $NaBH_4$, via a chelate chair like intermediate.

Boron-mediated reactions in organic synthesis represent some of the most powerful tools for enantio and diastereoselective reactions.[1] Two of them attracted our attention, since they could be relevant to the aldol like structure: boron mediated aldol condensation and reduction of β-hydroxy ketones.

The studies by Paterson[2] have clearly shown the way to build up, in enantio and diastereoselective fashion, the general *syn* aldol adduct **2** starting from the chiral boron enolate of type **1**: with the use of (+) or (-) diisopinocampheyl borinate (L = *Ipc) the e.e. of the final products reached up to 91% with d.e. up to 96% (see figure 1, eq.1). The isolated aldol adducts are often subsequently reduced to the *syn-syn* diastereoisomer **3a** or to the *syn-anti* diastereoisomer **3b** by recently developed methodologies, since these structures constitute important propionate subunits present in many natural polyketides.[3]

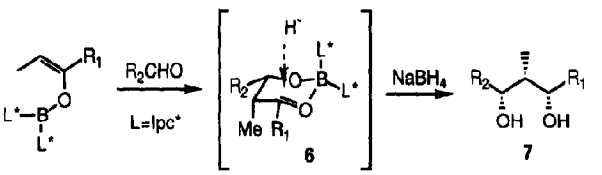
Among the recent methods[4] for the diastereoselective reduction of β-hydroxy ketones or ketoesters of type **4** to the corresponding *syn* 1,3 diols **5**, the use of boron chelating agents such as nBu_3B[4a] or Et_2BOMe[4e] has been successfully reported (figure 1, eq.2).

Figure 1



A one-pot aldol-reduction sequence[5] (see figure 2), with boron promoting the aldol reaction as enolborinate and then the subsequent reduction through the aldol chelate **6** (with a *syn* relationship between methyl and hydroxyl groups), would be a valuable tool for obtaining polypropionate structures like **7** with a *syn-syn* relationship of the three stereogenic centers.[6]

Figure 2



We have explored such an assumption using the enol diisopinocampheylborinates of several ethyl ketones[7], as illustrated in Table1, reacting them with methacrolein and (E)-crotonaldehyde which appeared to afford the highest enantio and diastereoselective aldol adducts.

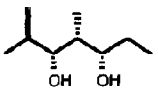
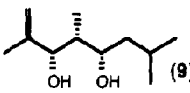
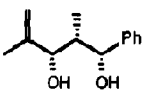
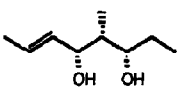
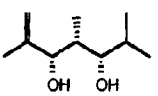
After the aldol reaction had gone to completion, $NaBH_4$ was added and, after the appropriate time and standard work up procedure, mixtures of diols were obtained. In order to assign the correct relative configuration within the 1,3 diols, and to separate the diastereomeric mixture, compounds **10** and **12** have been directly isolated: the other diols had to be derivatized as acetonides (compounds **8**, **11**) or p-methoxy benzylidenacetals (compound **9**)[8] and then separated. After deprotection, the major isomers were analyzed as their Mosher derivatives[9] to determine their enantiomeric excess.

The results are illustrated in Table 1, with five examples. In all the reported examples the *syn/syn* diastereoisomers **8-12** were the major products with fair to good diastereoselection . The use of a mild reducing agent such as $NaBH_4$ would also be valuable in presence of other reducible groups such as esters, instead of the reported use of $LiBH_4$.[5,10]

Typical experimental procedure: a (-)diisopinocampheylborane triflate solution (1,95 mmol , 1.9 M in hexane), prepared according to ref.2, was diluted with CH_2Cl_2 (8 mL) , under argon with stirring.The solution was cooled at -78°C and added of i-Pr_2NEt (3 mmol) and ketone (1.5 mmol). After 3h the aldehyde (2-4 mmol, freshly distilled) was added, and after 1h the solution was warmed at -20° C and left overnight. Then $NaBH_4$ (3 mmol) was added and left for a further 24 h. The reaction mixture was then quenched with acetic acid and neutralized with satd. Na_2CO_3. The mixture was then extracted with AcOEt (10 mL) and the organic layers were evaporated in vacuo. The residue was diluted with Et_2O (3 mL) and added of 3N NaOH (3 mL) and H_2O_2 30% (4 mL) . After stirring at room temp. for 4 h, the organic layer was separated and the aqueous layer, saturated with Na_2CO_3, was extracted with AcOEt (20 mL). The organic layers, washed with brine, were then dried over Na_2SO_4 and evaporated in vacuo. The yellow oil was purified by flash chromatography affording mixture of diols, which were analysed by ^{1}H-NMR for the determination of the diastereomeric excess or derivatized as acetonides (see above).

Table 1

Aldol-reduction reaction of enol (-)-diisopinocampheylborinates with aldehydes

Entry	ketone/aldehyde	Major stereoisomer	d.e. (%)[a]	e.e. (%)[a]	yield(%)[a]
1	EtCOEt/methacrolein	 (8)	88	92	56
2	$EtCOCH_2iPr$/methacrolein	 (9)	77	91	59
3	EtCOPh/methacrolein	 (10)	93	96	43
4	EtCOEt/crotonaldehyde	 (11)	75	88	52
5	EtCOiPr/methacrolein	 (12)	70	90	48

a) yields referred to the isolated major stereoisomers)

The fair overall yields of the isolated products reflect the complex diastereomeric mixture obtained in the double asymmetric induction, and need to be optimized, to avoid the problems during the borinate esters work up. The overall diastereomeric excess of the aldol condensation and of the subsequent reduction seems quite sensitive to the substrates used, as has already been noted.[6] The reported e.e.s are similar to those obtained in the related aldol condensations.[2] The bulky isopinocampheyl substituent on the chelating boron atom, can also be responsible for the results and studies are needed to better understand the role in different boron substitutents

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4. For different approaches to the *syn*-stereoselective reduction of β-hydroxy ketones see: a) Narasaka, K.; Pai, F.-C. *Tetrahedron*, **1984**, *40*, 2233-2238. b) Kathawala, F.G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M.J.; Stabler, R.S.; Widler, L. *Helv. Chim. Acta*, **1986**, *69*, 803-805. c) Kiyooka, S.; Kuroda, H.: Shimasaki, Y. *Tetrahedron Lett.*, **1986**, *27*, 3009-3112. d) Bonadies, F.; Di Fabio, R.; Gubbiotti, A.; Mecozzi, S.; Bonini, C. *ibidem*, **1987**, *28*, 703-706. e) Chen, K.M.; Gunderson, K.G.; Hartmann, G.E.; Prasad, K.; Repic, O.; Shapiro, M.J. *Chemistry Lett.*, **1987**, 1923-1926. f) Evans, D.A.; Hoveyda, A.H. *J. Org. Chem.*, **1990**, *555190-5192*.g) Bonini, C.; Bianco, A.; Di Fabio, R.; Mecozzi, S.; Proposito, S.; Righi, G. *Gazz. Chim. Ital.* **1991**, *121*, 75-80.
5. During our studies we have find out a single example of a related one-pot procedure toward the synthesis of polypropionate natural products (Paterson, I.; Channon, J.A. *Tetrahedron Lett.*, **1992**, *33*, 797-800; Paterson, I.; Perkins, M.V. *ibidem*, 801-804).In this case the aldol condensation of a chiral dicyclohexyl enolborinate with (E)-2-methyl-pentenal afforded an *anti-anti* isomer which was reduced "in situ", with $LiBH_4$, to the corresponding *anti-anti-syn* stereotetrad, with good diastereoselection.
6. The diastereoselective reduction of complex aldol adducts to the *syn* diols does not appear always straightforward: in a recent report (Evans, D.A., Ng., H.P.; Clark, J.S.; Rieger, D.L.*Tetrahedron*, **1992**, *48*, 2127-2142) the use of two of the most useful procedures with DIBAL (ref. 4c) and $Et_2BOMe/NaBH_4$ (ref.4e) resulted in *anti* diastereoselectivity for the former and decomposition for the latter; the optimal reagent ($Zn(BH_4)_2$) exhibited a fair (4:1) *syn* selectivity.
7. The use of simple methyl ketones was not verified since the optical purity of the aldol adducts appeared substantially lower than with the use of ethyl ketones (see ref. 2)
8. The mixture of diols was then functionalized as acetonides by standard procedure, analyzed by ^{1}H-NMR and ^{13}C-NMR experiments in order to assign the *syn* or *anti* 1,3 diols relative configuration (see : a) Evans, D.A., Rieger, R.L.; Gage, J.R. *Tetrahedron Lett.*, **1990**, *31*, 7099-7100.b) Rychnovsky, S.D.; Skalitzky, D.J. *ibidem*, **1990**, *31*, 945-948.
9. The corresponding Mosher derivatives, on the purified and deprotected diols, were prepared according to : Chen, T.H.; Nwe, K.T. *J. Org. Chem.*, **1992**, *57*, 6107-6111.The enantiomeric purity was checked by ^{1}H-NMR and GC/MS, in comparison with racemic compounds prepared following the previous procedure with the use of nBu_2BOTf.
10. The use of $LiBH_4$ on some substrates (entries 1, 3 and 4 in Table 1), did not give any appreciable improvement of the chemical yield and diastereoselectivity.
11. This work was partially supported by a MURST grant (40%) and C.N.R. Progetto Finalizzato"Chimica Fine e Secondaria"

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