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Remote, 1,5-*Anti* Stereoinduction in the Boron-Mediated Aldol Reactions of β-Oxygenated Methyl Ketones.

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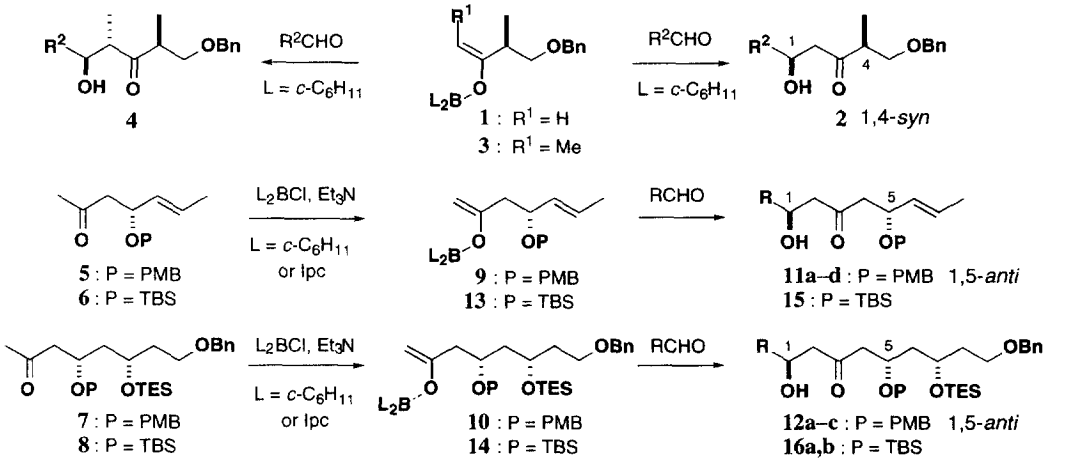
Abstract: High levels of 1,5-stereoinduction are obtained in the boron-mediated aldol reactions of β-oxygenated methyl ketones **5**, **7** and **8** with achiral aldehydes. The aldol products undergo stereoselective reductions, providing an efficient method of accessing a wide range of 1,3-polyols.

The use of boron enolates of ketones for asymmetric aldol reactions has become a powerful tool for the total synthesis of polyketide natural products, particularly those of propionate origin.[1-4] It has seen less use in the synthesis of polyacetate-derived systems due to the generally lower stereoselectivities observed in the aldol reactions of methyl *vs* ethyl ketones. Usually reagent control is required to obtain useful levels of asymmetric induction in the addition of unsubstituted boron enolates to achiral aldehydes.[2,3] A rare example of substrate control is observed with the chiral boron enolate **1** (**Scheme 1**), giving good levels of stereoinduction with aldehydes in favour of the 1,4-*syn* adduct **2**.[4a] Whereas excellent diastereoselectivities are obtained for the corresponding *E*-substituted enolate, as in **3** → **4**.[4]



Scheme 1

As part of studies towards the synthesis of the marine macrolide spongistatin 1,[5,6] we examined the aldol reactions of the four β-oxygenated chiral methyl ketones **5–8**. We now report that high levels of *substrate-based*, 1,5-stereocontrol can be achieved in the boron-mediated aldol reactions of the ketones **5** and **7**. In these two cases, where P = PMB, remote induction from the cyclohexyl boron enolates **9** and **10** gives, in addition to various aldehydes, the 1,5-*anti* adducts **11a–d** and **12a–c**. In situations where this substrate control is moderate, as in **8** where P = TBS, asymmetric induction[2,6] from isopinocampheyl (Ipc) ligands on boron in enolate **14** can be used to enhance selectivity for the 1,5-*anti* adducts **16a** and **16b**. The β-hydroxy ketones so obtained may then be reduced in a controlled fashion, leading to the efficient synthesis of a variety of long-chain 1,3-polyols.[7]

Initially, the aldol reactions of methyl ketones **5** and **7**, both containing a PMB-protected β-hydroxyl group, with several simple aldehydes were explored using $(c\text{-}C_6H_{11})_2BCl$ / Et_3N in Et_2O for enolisation.[4,8] As shown in **Scheme 1** and **Table 1** (entries 1–7),[9] these boron-mediated aldol reactions were found to proceed with an unexpectedly high degree of 1,5-stereoinduction – *anti* : *syn* = 85 : 15 to 98 : 2. The 1,5-induction obtained in these boron-mediated aldol reactions roughly correlates with the size of the aldehyde, where an increase in selectivity is observed on going from acetaldehyde to isobutyraldehyde (entries 1 *vs* 2, entries 5 *vs* 6). For entries 1 and 5–7, the chiral boron reagent (–)-Ipc_2BCl was employed in a matched sense with ketones **5** and **7** to further enhance the aldol diastereoselectivity for **11a** and **12a–c**.[2,6] In contrast, the corresponding lithium-mediated aldol reactions (LDA, THF, –78 °C) proceeded with essentially no selectivity to give authentic mixtures of diastereomers for comparison by ^1H and ^{13}C NMR spectroscopy.

Table 1: Aldol reactions of ketones **5–8** with RCHO using $(c\text{-}C_6H_{11})_2BCl/Et_3N$ and (–)-Ipc_2BCl/Et_3N.[a]

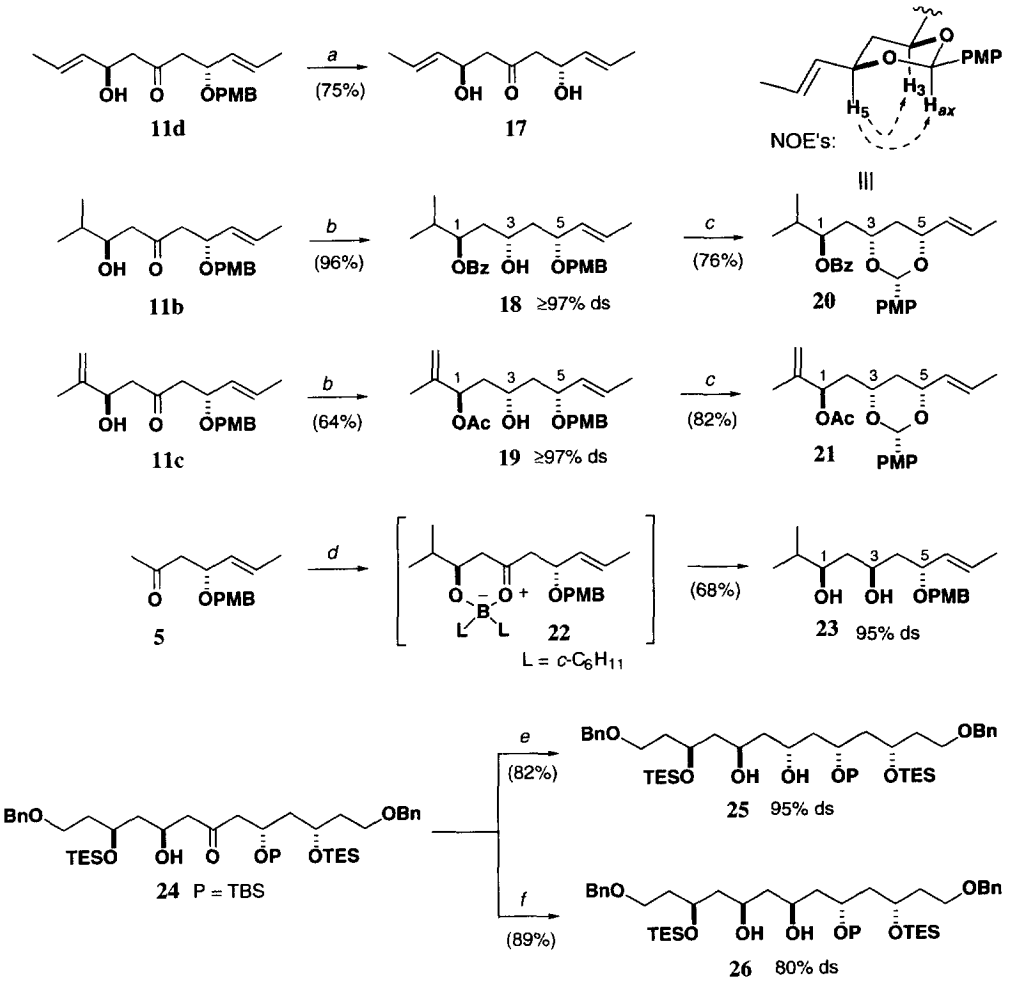
				$(c\text{-}C_6H_{11})_2BCl$		(–)-Ipc_2BCl	
entry	ketone[b]	R	adduct	*anti* : *syn*[c]	yield (%)[d]	*anti* : *syn*[c]	yield (%)[d]
1	**5**	Me	**11a**	93 : 7	80	95 : 5	87
2	**5**	^{i}Pr	**11b**	97 : 3	79	-	-
3	**5**	C(Me)=CH_2	**11c**	97 : 3	82	-	-
4	**5**	CH=CHMe	**11d**	98 : 2	80	-	-
5	**7**	Me	**12a**	85 : 15	78	92 : 8	83
6	**7**	^{i}Pr	**12b**	92 : 8	78	96 : 4	71
7	**7**	C(Me)=CH_2	**12c**	91 : 9	82	93 : 7	79
8	**6**	^{i}Pr	**15**	42 : 58	82	-	-
9	**8**	^{i}Pr	**16a**	77 : 23	80	95 : 5	84
10	**8**	C(Me)=CH_2	**16b**	71 : 29	80	90 : 10	80

[a]Reaction conditions: see note 10. [b](*R*)-**5** for entries 1 and 4, *rac*-**5** for entries 2 and 3, (*S,S*)-**7** for entries 5–7, *rac*-**6** for entry 8, (*S,S*)-**8** for entries 9 and 10. [c]Ratio determined by ^1H NMR analysis of the diastereomeric mixture of adducts. [d]Isolated yield of aldol adducts after chromatography.

To assist in determining the generality and origin of this surprising level of remote 1,5-asymmetric induction,[11] the aldol reactions of the corresponding methyl ketones **6** and **8** containing a β-*tert*-butyldimethylsiloxy group were investigated (entries 8, 9 and 10). The selectivities obtained with these chiral ketones were now uniformly low (42–77% ds), indicating that the nature of the protecting group on the β-oxygen is critical in determining the level of induction. These results are also consistent with the earlier findings of the Masamune group for some related boron aldol reactions,[3] where the substrate control was usually negligible. Note, however, that the lower selectivities obtained with ketone **8** could be boosted to synthetically useful levels (90–95% ds) in favour of **16a** and **16b**, again by using (–)-Ipc_2BCl (entries 9 and 10).[2,6,12]

These aldol products may be elaborated in several ways, which also enables their stereochemistry to be deduced. Some representative examples are shown in **Scheme 2**. In the case of ketone **11d**, simple deprotection of the PMB ether with DDQ generated the C_2-symmetric 1,5-diol **17**, $[\alpha]_D^{20}$ +40.4° (*c* 1.53, $CHCl_3$), as required by a 1,5-*anti* relationship. For **11b** and **11c**, Evans-Tishchenko reduction[13] with SmI_2 in the presence of benzaldehyde or acetaldehyde gave the alcohols **18** and **19** with ≥97% ds, respectively. These 1,3,5-polyoxygenated compounds have a 1,3-*anti*[14] and 3,5-*syn* arrangement with differentiation of the three oxygens. Treatment with DDQ under anhydrous conditions then gave the corresponding *para*-methoxybenzylidene acetals,[15] *i.e.* **18** → **20** and **19** → **21**. The *cis* stereochemistry around the acetal ring was

established by the observance of strong NOE's between the three *axial* protons, as required by the original 1,5-*anti* relationship between the hydroxyl and the *para*-methoxybenzyloxy substituents.



Scheme 2: (*a*) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 20 °C, 40 min; (*b*) SmI_2, PhCHO or MeCHO, THF, –20 °C, 2-4 h; (*c*) DDQ, 4 Å mol. sieves, CH_2Cl_2, 20 °C, 30 min.; (*d*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 5 min; ^iPrCHO, –78 → –20 °C, 5 h; $LiBH_4$, –78 °C, 90 min; NH_4Cl; H_2O_2, MeOH, NaOH; (*e*) $Me_4NBH(OAc)_3$, AcOH, MeCN, –20 → 0 °C, 18 h; (*f*) $Zn(BH_4)_2$, Et_2O, –20 °C, 90 min.

Other means are available for elaborating these aldol products to give long-chain 1,3-polyols,[7] as required for the synthesis of polyketides such as the polyene macrolides.[16] For example, the one-pot synthesis of *syn* 1,3-diols can be easily achieved by the *in situ* reduction of the intermediate dicyclohexylboron aldolates with $LiBH_4$,[17,18] as in **5** → **22** → **23** (95% ds). Other reduction methodology may also be successfully employed.[18] Thus the aldol product **24**[6] was reduced[19] with $Me_4NBH(OAc)_3$ to give the *anti* 1,3-diol **25** with 95% ds. In a complimentary fashion, a *syn* reduction[20] of **24** with $Zn(BH_4)_2$ gave its epimer **26** with 80% ds.

In conclusion, a series of highly selective methyl ketone aldol reactions are described, which, in conjunction with stereoselective reduction, enables 1,3,5-hydroxyl groups to be installed with defined

stereochemistry. As well as for spongistatin 1,[5,6] this methodology should be applicable to the synthesis of a wide variety of polyketide systems.[7,16] At present, the origin of the high level of 1,5-*anti* induction obtained with the boron enolates **9** and **10** is unclear. Preliminary modelling of the transition state using the Cambridge-Milano aldol force field[21] suggests that the enolate π-facial selectivity is critically dependent upon the nature of the β-alkoxy group and the ligands on boron. Studies are currently underway to determine the generality of the reaction and the scope for further manipulation of the aldol adducts.

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