

Asymmetric Synthesis of All 8 Stereoisomers of α -Methyl Homoallylic Alcohols Derived by Crotyl Addition onto *Bis*(hydroxymethyl)acetaldehydes (BHYMA*)

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Abstract: The asymmetric synthesis of epimeric α -methyl homoallylic alcohols **4** and **7** has been realized respectively through chelation-controlled addition of crotyltributyltin to asymmetricized *bis*(hydroxymethyl)acetaldehydes (BHYMA*) **3**, and *via* chelation-controlled reduction of ketones **8**. Due to the stereochemical flexibility of the C-5 chiral centre and to the enantiodivergent preparation of both enantiomers of **3**, all 8 isomers of these crotylation products become accessible, starting from an unique precursor **1**.

We have recently developed a chemoenzymatic methodology for the preparation, in 96-97% e.e., of (*S*) monoacetate **1**, which was enantiodivergently converted by us through the same number of steps into both enantiomeric forms of chiral building blocks like *tris*(hydroxymethyl)methanes (THYM*) **2** and *bis*(hydroxymethyl)acetaldehydes (BHYMA*) **3**.¹ We have also demonstrated the possibility of performing diastereoselective nucleophilic additions to **3**, through chelation-controlled reactions.² The expedient for obtaining good asymmetric induction laid on a) the differentiation of the two protected hydroxymethyl groups in **3**, by employing protecting groups of different nature (that is a "non-chelating" group,³ like a silyl ether, which has low tendency to coordinate a suitable Lewis acid or a metal, and a "chelating"³ group, usually represented by an alkoxyalkyl ether); b) The employment of reaction conditions which favoured a cyclic chelated transition state. In particular, MgBr₂·Et₂O catalyzed allylation of aldehydes **3a-c**⁴ with allyltributyltin furnished the expected

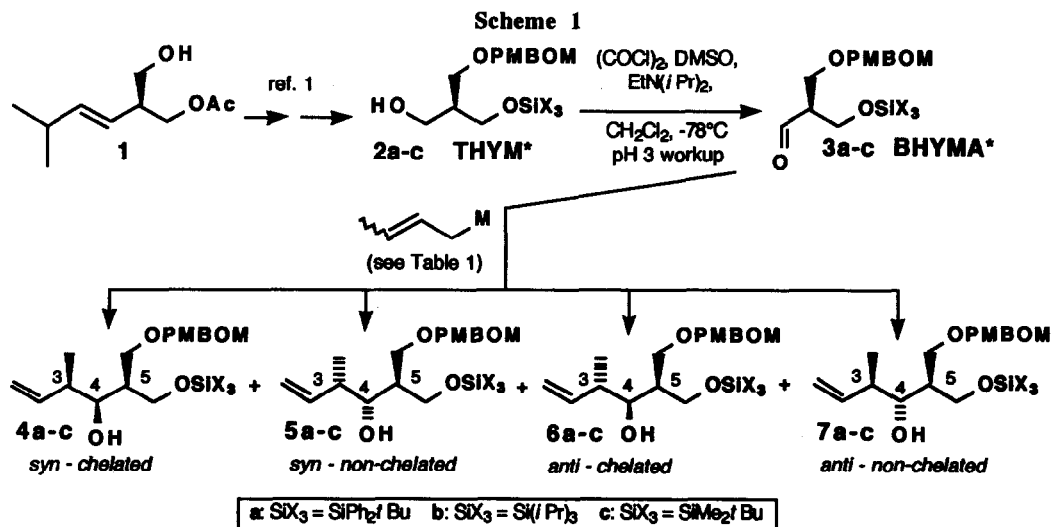


Table 1. Crotylation of aldehydes 3a-c

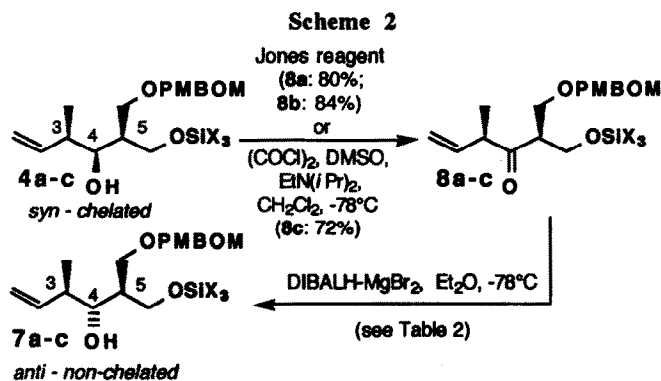
Entry	SiX ₃	Conditions	Yield ^a	4 : 5 : 6 : 7 ^b
1	SiPh ₂ tBu	Crotyl-Sn(<i>n</i> Bu) ₃ , MgBr ₂ ^c	80%	88 : 3 : 8 : 1
2	Si(<i>i</i> Pr) ₃	Crotyl-Sn(<i>n</i> Bu) ₃ , MgBr ₂ ^c	85%	86 : 4 : 7 : 3
3	SiMe ₂ tBu	Crotyl-Sn(<i>n</i> Bu) ₃ , MgBr ₂ ^c	81%	87 : 4 : 7 : 2
4	SiPh ₂ tBu	Crotyl-Br, CrCl ₂ ^d	30%	9 : 6 : 41 : 44

^a Isolated yields of all diastereoisomers, starting from alcohol 2. ^b Determined by HPLC and ¹H n.m.r. ^c Reactions carried out in CH₂Cl₂, using 2.5 eq. MgBr₂•Et₂O and 2 eq. crotylstannane (see note 9), at -78°C → -20°C. ^d see ref. 17.

chelation-controlled products⁵ with diastereoselectivities ranging from 85:15 to 87:13.^{2c,d}

We have now studied the MgBr₂ catalyzed condensation of 3a-c⁶ with crotyltributyltin⁹ (Table 1, entries 1-3).¹⁰ In this case two new stereogenic centers are generated during the condensation and thus the problem of *relative asymmetric induction*,¹¹ already present in the case of unsubstituted allylstannane, is here accompanied by the problem of *internal asymmetric induction*.¹¹ It has been reported¹² that the *internal asymmetric induction* in the crotylation of aldehydes is dependent on the Lewis acid utilized, MgBr₂•Et₂O and BF₃•Et₂O being the best. In both cases the 3,4-*syn* isomers were favoured. Moreover MgBr₂•Et₂O was already found by us to be well suited for chelation-controlled allylation of 3.^{2c-d,13} Thus we chose MgBr₂•Et₂O as the catalyst. The data of entries 1-3 show that a good *internal asymmetric induction* (with a global 3,4-*syn* : 3,4-*anti* ratio up to 91:9) was accompanied by an excellent *relative asymmetric induction* affording chelation-controlled⁵ products in up to 96:4 ratio. This *relative induction* was remarkably higher than that realized in the corresponding reactions with allyltributyltin.^{2c,d} It is important to stress that the use of the *p*-methoxybenzyl¹⁴ instead of the PMBOM as "chelating"³ protecting group brings about a remarkable decrease of both *internal* and *relative asymmetric induction* (the ratio 4 : 5 : 6 : 7 was = 77 : 6 : 15 : 2. Yield= 50%). This result is in line with the result reported by Boeckmann,¹⁶ who found an increase of overall selectivity by using an acetal protecting group (methoxymethyl ether, MOM) instead than the benzyl ether.¹¹ On the contrary, the type of silyl protecting group seems to have little influence. In conclusion, 3,4-*syn*-chelated diastereoisomers 4a-c could be obtained in 86-88% overall diastereoselectivity. Attempts to find a direct entry also for 3,4-*anti* diastereoisomers 6 or 7 have been unsuccessful. Actually, the reaction with Hiyama's crotylchromium reagent¹⁷ afforded, as expected, preferentially 3,4-*anti* compounds, but the *relative induction* was very low (entry 4).

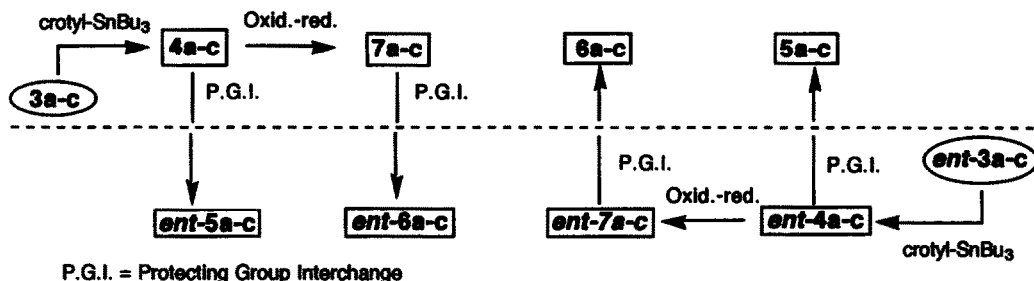
Thus, in order to find an access to other stereoisomers of 4a-c, we exploited a less direct way (Scheme 2), involving oxidation of the main diastereoisomers 4a-c to the corresponding ketones 8a-c followed by "chelation-controlled"⁵ reduction. In this case, being the hydride the entering nucleophile, the opposite 4,5 *relative stereochemistry* had to be expected, leading to compounds 7a-c as major products. This reduction was

Table 2. Reduction of ketones 8a-c with DIBALH-MgBr₂^a

Entry	SiX ₃	Yield ^b	4 : 7 ^c
1	SiPh ₂ tBu	87%	14 : 86
2	Si(<i>i</i> Pr) ₃	93%	19 : 81
3	SiMe ₂ tBu	87%	18 : 82

^a Reactions performed at -78°C in Et₂O, precomplexing the ketone with MgBr₂ (5 eq.) and then treating it with DIBALH (2 eq.), as described in ref. 7. ^b Isolated yields. ^c Determined by ¹H and ¹³C n.m.r.

Scheme 3



carried out using our newly developed methodology, that involves DIBALH reduction of diprotected α,α -bis(hydroxymethyl)ketones precomplexed with $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$.⁷ The results, listed in Table 2, show that, especially for **8a**, the stereoselectivity was good, in line with our previous findings on related substrates.⁷

Therefore, by employing the same Lewis acid, that is $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, for blocking the transition state conformation in a cyclic chelated transition state, and using respectively the crotyltin addition to aldehydes **3** or the DIBALH reduction of crotylketones **8**, both epimers **4a-c** and **7a-c** have been synthesized in a diastereodivergent manner.¹⁸

Although the access to the remaining two diastereoisomers seems to be not easy, it should be stressed that the configuration of C-5 asymmetric centre can be still determined at will by simple protecting group interchange (P.G.I.), since the two protected hydroxymethyl groups are synthetically equivalent and distinguished exclusively by the protecting groups. This flexibility of the original chiral centre (in this case C-5) descends from the high latent symmetry (C_{3v}) of THYM* **2,2a** and was previously utilized by us for other diastereodivergent preparations.^{2a-c,20} Coupled with the above stated possibility of synthesizing both enantiomers of **2** and **3**, this flexibility should allow the obtainment of stereoisomers like **5** and **6**, which cannot be directly obtained in good stereoselectivity through crotyltin addition or through reduction, starting from **3** (Scheme 3). For example, **5a** and **6a** can be prepared, by protecting group interchange, respectively from the enantiomer of **4a** and from *ent*-**7a**, in turn obtained from *ent*-**3a** by crotyl addition. Thus we should be able to prepare all 8 possible stereoisomers of the constitutional formula common to **4-7a-c**, starting from the common precursor **1**, relying on chelation controlled addition and on chelation controlled reduction.

Application of these adducts in the field of biologically active substances is in progress.

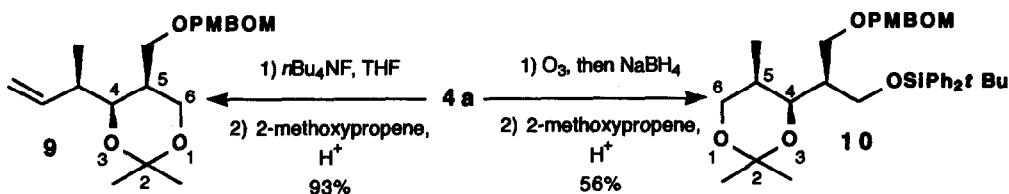
We wish to thank CNR (Progetto Finalizzato Chimica Fine) and M.U.R.S.T. for financial assistance.

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- We call "chelating" protecting group a p.g. which favours cooordination of a suitable Lewis acid by the oxygen (and thus the formation of a cyclic chelated transition state), while with "non-chelating" protecting group we indicate a p.g. which depresses the Lewis basicity of oxygen, thus disfavouring cooordination of a Lewis acid.
- PMBOM = *p*-methoxybenzyloxymethyl. See Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1987**, *28*, 5125-5128.
- As chelation-controlled products, we mean the diastereoisomers deriving from a cyclic chelated transition state involving the carbonyl and one of the PMBOM oxygens, under the reasonable hypothesis that attack

then takes place from the less encumbered side.

6. Although, for the sake of clarity, only one enantiomer is shown in the Scheme, both (*R*) and (*S*) **2a-c** have been utilized. Aldehydes **3a-c** used in this work were prepared by modified Swern conditions (ref. 7,8), because overall yields were somewhat higher (and reproducibility better) than using aldehydes directly obtained from ozonolysis reaction (ref. 2d). Use of ordinary Swern conditions (Et_3N , $-78^\circ\text{C} \rightarrow -40^\circ\text{C}$, neutral work-up) led to variable degrees of racemization, especially for $\text{SiX}_3 = \text{Me}_2\text{tBuSi}$ (ref. 8).
7. Guanti, G.; Banfi, L.; Riva, R.; Zannetti, M. T., accompanying communication.
8. Banfi, L.; Guanti, G.; Narisano, E. *Tetrahedron*, submitted for publication.
9. Prepared by reaction of 1 eq. LDA with 1 eq. $n\text{Bu}_3\text{SnH}$ and 1 eq. of (*E*) crotyl chloride in THF at 0°C . We thank prof. Giovanni Poli (Dipartimento di Chimica Organica "Hugo Schiff", Università di Firenze) for sending us a recipe for this synthesis.
10. The relative configuration of products **4-7a** was established in this way: **4a** was converted into *cis* acetones **9** and **10**, whose relative configuration was established through ^1H n.m.r. (**9**: $J_{4,5} = 2.5$, $J_{5,6} = 1.7$ and 2.6 Hz.; **10**: $J_{4,5} = 3.0$, $J_{5,6} = 1.4$ and 2.0 Hz.). The configuration of **7a** was related to that of **4a** through the oxidation-reduction sequence, and was confirmed by its conversion into the C-4 epimer of **10**. Of the remaining two isomers, **6a** was assigned as 3,4-*anti* since it was formed in higher amount (Table 1, entry 4) in the condensation with chromium reagent, which is known to afford mainly *anti* compounds (ref.17). The relative configurations of **4-7b-c** was assigned on the basis of tlc and n.m.r. analogies with **4-7a**.



11. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3-72.
12. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883-1886.
13. On the contrary $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was discarded because it is not able to give cyclic chelated transition states.
14. The analogous of alcohol **2a** ($\text{SiX}_3 = \text{Ph}_2\text{tBuSi}$) where the PMBOM group was replaced by a MPM (*p*-methoxybenzyl) group was prepared from **1** by this reaction sequence: 1) *p*- $\text{MeOC}_6\text{H}_4\text{CH}_2\text{OC}(=\text{NH})\text{CCl}_3$, CSA, CH_2Cl_2 , r.t. (ref. 15); 2) KOH, MeOH, 84% (2 steps); 3) $\text{Ph}_2\text{tBuSiCl}$, DMF, imidazole, r.t., 90%; 4) O_3 , -78°C , MeOH- CH_2Cl_2 , then NaBH_4 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 71%. The overall sequence was found to be non-racemizing. The preparation of the corresponding benzyl ether, on the contrary, turned out to be difficult, due to low yield in the benzylation of **1**.
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18. The optical purity of alcohols **4a-c** and **7a-c** was checked by ^1H n.m.r. analysis of the corresponding Mosher's ester [prepared through reaction with (*R*) and (*S*) (methoxy)(phenyl)(trifluoromethyl)acetyl chlorides (ref. 19)]. This analysis indicated an e.e. $\geq 95\%$.
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