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Protecting Group Controlled Diastereoselective Reduction of Diprotected α,α-*Bis*(hydroxymethyl)ketones Derived from THYM*, using the DIBALH / $MgBr_2$ System

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Abstract: The reduction of diprotected α,α-*bis*(hydroxymethyl)ketones **5**, derived from the novel chiral building blocks THYM* **1** and BHYMA* **2** has been realized with good to excellent stereoselectivity (from 85:15 to 97:3), through a appropriate choice of the two protecting groups and by employing the combination of DIBALH and $MgBr_2 \cdot Et_2O$.

We have recently reported the chemoenzymatic preparation in both enantiomeric forms of the new branched chiral building blocks **1** and **2**, corresponding to *tris*(hydroxymethyl)methane (THYM*) and *bis*(hydroxymethyl)acetaldehyde (BHYMA*).[1] We have also previously demonstrated the possibility to convert diastereoselectively aldehydes **2** into secondary alcohols like **3** through "protecting group controlled" addition of various C-nucleophiles.[2] The good to excellent stereoselectivity of these additions was based on the intervention of a cyclic chelated transition state and on the different coordinating capabilities of the two β-oxygens, whose Lewis basicity was suitably modulated by the choice of protecting groups. Although the synthetic equivalence of the two protected CH_2OR groups in **3** allows easy inversion of the original asymmetric centre through protecting group interchange (diastereodivergency),[2a] we thought that a more direct access to the diastereomeric series represented by **4** would have been useful.

In this communication we report the fulfilment of this goal through "protecting group controlled" stereoselective reduction of ketones **5**, which were easily prepared in three steps from alcohols **1**.[3,4] It is worth noting that in these ketones the two synthetically equivalent hydroxymethyl groups are protected with a "chelating" group,[6] like the *p*-methoxybenzyloxymethyl ether (PMBOM),[5] and with a "non-chelating" protecting group,[6] like a silyl ether.[2] Under reduction conditions which favour a cyclic chelated transition state, isomers **4** were therefore expected to be favoured. Unfortunately, a careful literature search showed only one case of highly

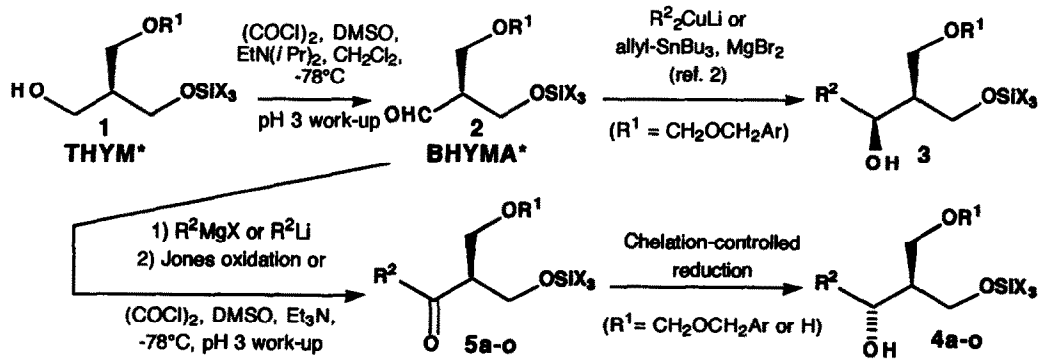
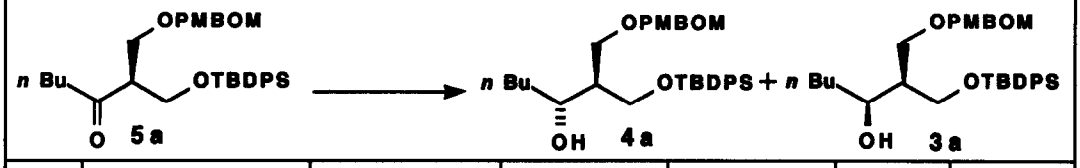


Table 1: Stereoselective reduction of ketone **5a**.[a]



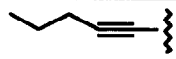
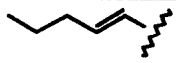
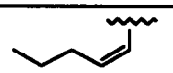
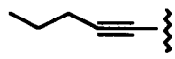
Entry	Reducing Agent	Additive	Solvent	Temperature	Yield[b]	4a : 3a[c]
1	$NaBH_4$	none	MeOH	-78°C → 0°C	90%	50 : 50
2	L-Selectride™	none	THF	-65°C	75%	49 : 51
3	$Zn(BH_4)_2$	none	Et_2O	0°C	82%	69 : 31
4	$LiAlH(OtBu)_3$	none	Et_2O	-78°C → 20°C	77%	56 : 44
5	DIBALH	none	Et_2O	-78°C	74%	51 : 49
6	$LiAlH(OtBu)_3$	$Ti(OiPr)_4$	Et_2O	20°C	90%	44 : 56
7	$LiAlH(OtBu)_3$	Et_2AlCl	Et_2O	-78°C → 20°C	79%	55 : 45
8	$LiAlH(OtBu)_3$	CuI	Et_2O	20°C	82%	59 : 41
9	$LiAlH(OtBu)_3$	LiI	Et_2O	-78°C → 0°C	80%	65 : 35
10	$LiAlH(OtBu)_3$	ZnI_2	Et_2O	-78°C → -40°C	82%	76 : 24
11	$LiAlH(OtBu)_3$	$MgI_2 \cdot Et_2O$	Et_2O	-78°C → 0°C	75%	69 : 31
12	$LiAlH(OtBu)_3$	$MgBr_2 \cdot Et_2O$	Et_2O	-78°C → -20°C	80%	77 : 23
13	DIBALH	$Ti(OiPr)_4$	Et_2O	20°C	65%	47 : 53
14	DIBALH	$Ti(OiPr)_3Cl$	Et_2O	20°C	79%	52 : 48
15	DIBALH	Et_2AlCl	Et_2O	-78°C	82%	54 : 46
16	DIBALH	CdI_2	Et_2O	-78°C → 0°C	79%	60 : 40
17	DIBALH	$CdCl_2$	Et_2O	-78°C	88%	60 : 40
18	DIBALH	ZnI_2	Et_2O	-78°C	50%	67 : 33
19	DIBALH	$Mg(CF_3COO)_2$	Et_2O	20°C	70%	52 : 48
20	DIBALH[d]	$MgBr_2 \cdot Et_2O$	Et_2O[e]	-78°C	**94%**	**91 : 9**
21	$Zn(BH_4)_2$	$MgBr_2 \cdot Et_2O$	Et_2O	-35°C → -25°C	75%	57 : 43
22	$LiAlH_4$	$MgBr_2 \cdot Et_2O$	Et_2O	-78°C	61%	54 : 46
23	$LiBEt_3H$	$MgBr_2 \cdot Et_2O$	Et_2O	-78°C	96%	62 : 38

[a] TBDPS= *t*-Butyldiphenylsilyl. PMBOM= *p*-methoxybenzyloxymethyl. [b] Yields not optimized, except for reaction of entry 20. [c] Determined by HPLC or by ^1H n.m.r. of crude products (by integration of O*H* signals).[d] 1.0M DIBALH in toluene or in CH_2Cl_2 was used. [e] Et_2O was found to be superior to other solvents, like THF, toluene, CH_2Cl_2, for this reaction.

stereoselective (chelation-controlled) reduction of protected β-hydroxyketones having a chiral centre in α.[7,8] Moreover, that methodology, which makes use of ethereal $Zn(BH_4)_2$, seemed to afford good results only in the case of aromatic or α,β-unsaturated ketones.[7a]

Nevertheless, we decided to explore this possibility, employing ketone **5a** as typical substrate. The results are shown in Table 1. Entries 1-5 indicate that the use of various reducing agents (including $Zn(BH_4)_2$) in the absence of additives brings about unsatisfactory stereoselectivities. Thus, in the attempt to block ketone **5a** in a cyclic chelated structure, we precomplexed it with a Lewis acid, and treated this mixture with a representative basic hydride ($LiAl(OtBu)_3H$, entries 6-12) or with a typical acidic hydride (DIBALH, entries 13-20). In both cases $MgBr_2 \cdot Et_2O$ turned out to be the best additive, but the best result was obtained in conjunction with DIBALH, giving in excellent yield a 91:9 diastereomeric ratio (entry 20). Also other basic hydrides, in combination with $MgBr_2 \cdot Et_2O$, gave worse results, as compared to DIBALH (entries 21-23).

Table 2. Reduction of various ketones **5** (see Scheme)[a]

					$Zn(BH_4)_2$[b]		DIBALH / $MgBr_2$[c]	
Entry	Ketone	R^1	R^2	R^3	Yield[d]	**4** : **3**[e]	Yield[d]	**4** : **3**[e]
1	**5a**	*n*Bu	PMBOM	TBDPS	82%	69 : 31	94%	**91** : 9
2	**5b**	*n*Bu	PMBOM	TBDMS	not det.	not det.	86%	**85** : 15
3	**5c**	*n*Bu	PMBOM	TIS	not det.	not det.	79%	**83** : 17
4	**5d**	*n*Bu	MPM	TBDPS	not det.	not det.	70%	**80** : 20
5	**5e**	Allyl	PMBOM	TBDPS	83%	**82** : 18	71%	**84** : 16
6	**5f**	Allyl	PMBOM	TIS	not det.	not det.	91%	**90** : 10
7	**5g**	*i*Pr	PMBOM	TBDPS	80%	73 : 27	82%	**85** : 15
8	**5h**	Ph	PMBOM	TBDPS	74%	**96** : 4	86%	**96** : 4
9	**5i**	CH_2=CH-	PMBOM	TBDPS	80%	**88** : 12	62%	**87** : 13
10	**5j**	CH_2=C(Me)-	PMBOM	TBDPS	81%	**94** : 6	90%	**97** : 3
11	**5k**		PMBOM	TBDPS	53%	55 : 45	90%	60 :40
12	**5l**		PMBOM	TBDPS	79%	**81** : 19	79%	**94** : 6
13	**5m**		PMBOM	TBDPS	75%	**80** : 20	80%	**93** : 7
14	**5n**	*n*Bu	H	TBDPS	86%	77 : 23	79%	**85** : 15
15	**5o**		H	TBDPS	91%	52 : 48	60%	67 : 33

[a] TBDPS= *t*-Butyldiphenylsilyl. PMBOM= *p*-methoxybenzyloxymethyl. [b] Reactions carried out in Et_2O at 0°C. [c] Typical Procedure: A solution of ketone (1 mmol.) in dry Et_2O (20 mL) was treated with 4Å powdered molecular sieves (100 mg), stirred at r.t. for 15 min, cooled to -78°C, and treated with $MgBr_2 \cdot Et_2O$ (5 mmol). The temperature was allowed to rise to -50°C during 30 min. The mixture was recooled to -78°C and DIBALH (1.0 M in toluene, 2 mmol) was added. After reaction completion (usually 15 min), the mixture was quenched with aqueous NH_4Cl and aqueous Na,K tartrate. Extraction with Et_2O gave the crude products, which were then purified by silica gel chromatography. In the case of entries 8-13 and 15, after addition of $MgBr_2$, the temperature was raised to -25°C during 1h. [d] Isolated yields of both stereoisomers. [e] Determined by HPLC or by ^1H n.m.r. of crude products (by integration of O*H* signals). [f] Reduction of ketones **5n-o** were also carried out with the system Et_2BOMe, $NaBH_4$, THF-MeOH (ref. 8a) giving 91% yield (**4** : **3** ratio= 89:11) for **5n** and 69% yield (**4** : **3** ratio= 65:35) for **5o**.

In order to determine the generality of this new methodology, we reduced with DIBALH-$MgBr_2$ a series of ketones **5** characterized by different protecting groups (Table 2, entries 1-4), or by various R^2 groups (entries 5-13).[9] For comparison we also reduced the same ketones with $Zn(BH_4)_2$. With regard to the protecting groups, we have found that a noticeable decrease of induction took place on passing from an acetal "chelating" protecting group (PMBOM) to the *p*-methoxybenzyl (MPM) ether (entries 1 and 4). On the other hand, among the silyl ethers, the *t*BuPh$_2$Si (TBDPS) turned out to be the best.

As for R^2 group, the results collected by us show that, with the surprising exception of propargyl ketone **5k**, all ketones were reduced with good to excellent asymmetric induction. The higher ratios were achieved for conjugated enones (entries 9,10,12,13) or aromatic ketone **5h** (entry 8). The importance of α,β-unsaturation was even more striking for $Zn(BH_4)_2$: in this case only phenyl ketone and 2,3-enones gave acceptable inductions. This finding is in line with the results of Oishi,[7a] concerning the reduction of α-methyl-β-alkoxyketones. Once again, acetylenic ketone **5k** was reduced with poor selectivity. Anyway, the combination of DIBALH and $MgBr_2$ seems to give in general superior results, compared to $Zn(BH_4)_2$. This is especially true for unconjugated compounds.

The last two entries of Table 2 show the reduction of two partially protected ketones. For R^2= *n*Bu the

good induction with DIBALH-$MgBr_2$ is in part maintained. In this case, however, a better result was realized by using the system Et_2BOMe-$NaBH_4$ (note f).[8a] For R^2= pentinyl all three methods furnished low induction.

In conclusion we have demonstrated that DIBALH reduction of $MgBr_2$ precomplexed diprotected α,α-*bis*(hydroxymethyl)ketones bearing two protecing groups of different nature (that is "chelating" or "non-chelating") represents a general stereoselective method for a wide range of substituents at the carbonyl, the only one exception being alkynones. Extension of this methodology to other protected α-substituted-β-hydroxyketones is in progress.[10]

We wish to thank Miss Giovanna Schmid for her precious collaboration and CNR (Progetto Finalizzato Chimica Fine) and M.U.R.S.T. for financial assistance.

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1. Guanti, G.; Banfi, L.; Narisano, E. *J. Org. Chem.* **1992**, *57*, 1540-1554.
2. **a)** Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1990**, *31*, 6421-6424. **b)** Guanti, G.; Banfi, L.; Ghiron, C.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 267-270. **c)** Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 6939-6942. **d)** Guanti, G.; Banfi, L.; Narisano, E.; Zannetti, M.T. *J. Org. Chem.* **1993**, *58*, 1508-1514; **e)** Banfi, L.; Guanti, G.; Narisano, E. *Tetrahedron* , submitted for publication.
3. Aldehydes **2** used in this work were prepared by modified Swern conditions, 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°C→-40°C, neutral work-up) led to variable degrees of racemization, especially for SiX_3 = Me_2tBuSi (ref. 2e). The overall yields of ketones **5a-k** from **1** were in the range 50-70%. Compound **5l** was obtained through addition of (*E*) 1-pentenyl(di*iso*butyl)alane to **2**, followed by Swern oxidation. Compound **5m** was prepared through reduction (H_2, Pd-Lindlar, 2,6-lutidine, AcOEt) of **5k** (this reduction afforded a 87:13 *Z* : *E* ratio, but the two isomers **5m** and **5l** could be separated by chromatography). **5n** and **5o** were prepared from **5a** and **5k** by reaction with DDQ[5] (83% and 93% yield respectively). Details on the preparation of all compounds quoted in this communication will be reported in a forthcoming full paper.
4. The absence of racemization during preparation of ketones **5a-m** as well as during DIBALH-$MgBr_2$ reduction was checked through Mosher's ester analysis (^1H n.m.r.) of the main diastereoisomers **4a-m**.
5. Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1987**, *28*, 5125-5128.
6. We call "chelating" protecting group a p.g. which favours cohordination 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 coordination of a Lewis acid.
7. **a)** Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411-1415. There were also very few reports on reduction of unprotected β-hydroxyketones controlled by the α chiral centre: see ref. 7a and **b)** Suzuki, K.; Shimazaki, M.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1986**, *27*, 6233-6236.
8. On the contrary, several reports deal with reductions of protected or unprotected 3-hydroxyketones, controlled by the chiral centre in β. See for example: **a)** Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155-158. **b)** Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233-2238. **c)** Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578. **d)** Bonini, C.; Bianco, A.; Di Fabio, R.; Mecozzi, S.; Proposito, A.; Righi, G. *Gazz. Chim. Ital.* **1991**, *121*, 75-80. **e)** Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans 1* **1990**, 1809-1812. **f)** Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190-5192 and references therein.
9. The relative configuration of all reduction products was established through conversion into O,O-*iso*propylidene derivatives and by ^1H and ^{13}C nmr analysis on them.
10. The combination $MgBr_2$•Et_2O and DIBALH had been previously used for the regioselective reduction of dimethyl O-benzylmalate: Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417-420.

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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 asymmetrized *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 cohordinate 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, $MgBr_2 \cdot Et_2O$ catalyzed allylation of aldehydes **3a-c**[4] with allyltributyltin furnished the expected

Scheme 1

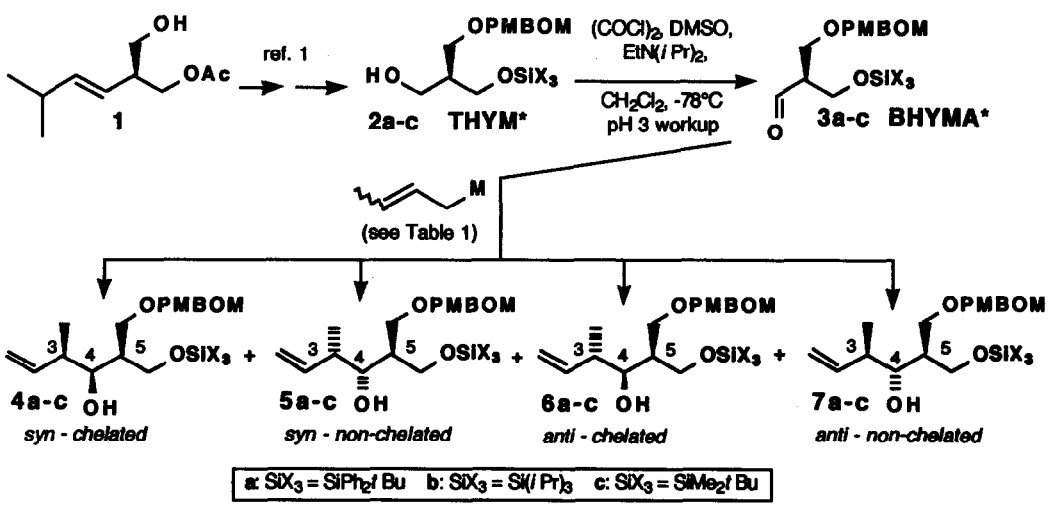


Table 1. Crotylation of aldehydes **3a-c**

Entry	SiX_3	Conditions	Yield[a]	**4** : **5** : **6** : **7**[b]
1	$SiPh_2tBu$	Crotyl-Sn(*n*Bu)$_3$, $MgBr_2$[c]	80%	**8**8 : 3 : 8 : 1
2	$Si(iPr)_3$	Crotyl-Sn(*n*Bu)$_3$, $MgBr_2$[c]	85%	**86** : 4 : 7 : 3
3	$SiMe_2tBu$	Crotyl-Sn(*n*Bu)$_3$, $MgBr_2$[c]	81%	**87** : 4 : 7 : 2
4	$SiPh_2tBu$	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 CH_2Cl_2, using 2.5 eq. $MgBr_2 \cdot Et_2O$ and 2 eq. crotylstannane (see note 9), at -78°C → -20°C. [d] see ref. 17.

chelation-controlled products[5] with diastereoselectivities ranging from 85:15 to 87:13.[2c,d]

We have now studied the $MgBr_2$ catalyzed condensation of **3a-c**[6] with crotyltributyltin[9] (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 reported[12] that the *internal asymmetric induction* in the crotylation of aldehydes is dependent on the Lewis acid utilized, $MgBr_2 \cdot Et_2O$ and $BF_3 \cdot Et_2O$ being the best. In both cases the 3,4-*syn* isomers were favoured. Moreover $MgBr_2 \cdot Et_2O$ was already found by us to be well suited for chelation-controlled allylation of **3**.[2c-d,13] Thus we chose $MgBr_2 \cdot Et_2O$ 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-controlled[5] 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*-methoxybenzyl[14] 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 reagent[17] 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

Scheme 2

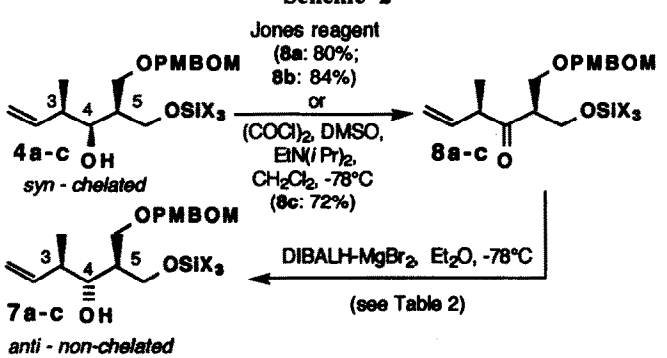
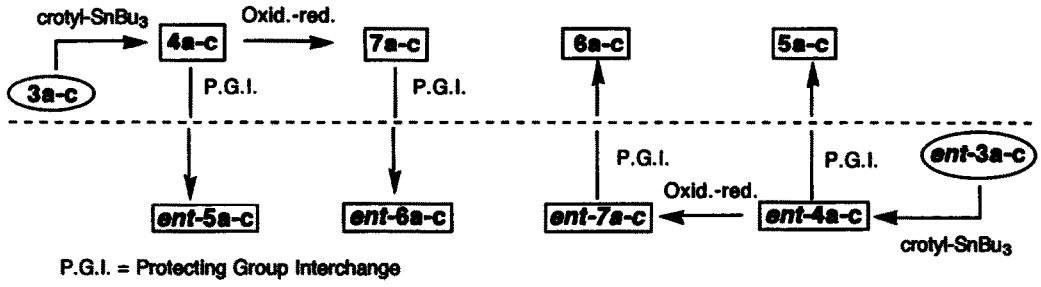


Table 2. Reduction of ketones **8a-c** with DIBALH-$MgBr_2$[a]

Entry	SiX_3	Yield[b]	**4** : **7**[c]
1	$SiPh_2tBu$	87%	14 : **86**
2	$Si(iPr)_3$	93%	19 : **81**
3	$SiMe_2tBu$	87%	18 : **82**

[a] Reactions performed at -78°C in Et_2O, precomplexing the ketone with $MgBr_2$ (5 eq.) and then treating it with DIBALH (2 eq.), as described in ref. 7. [b] Isolated yields. [c] Determined by ^1H and ^{13}C 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 $MgBr_2 \cdot Et_2O$.[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 $MgBr_2 \cdot Et_2O$, 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 he 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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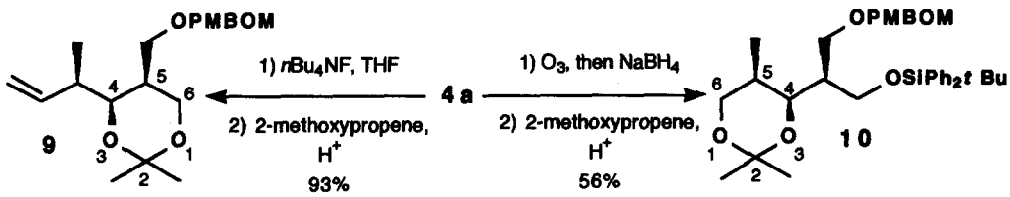
3. We call "chelating" protecting group a p.g. which favours cohordination of a suitable Lewis acid by the oxygen (and thus the formation of a cyclic chelated transition state), while with "non-chelating" protecting group we indicate a p.g. which depresses the Lewis basicity of oxygen, thus disfavouring cohordination of a Lewis acid.
4. PMBOM = *p*-methoxybenzyloxymethyl. See Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1987**, *28*, 5125-5128.
5. 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 yieds were somewhat higher (and reproducibility better) than using aldehydes directly obtained from ozonolysis reaction (ref. 2d). Use of ordinary Swern conditions (Et_3N, -78°C→-40°C, neutral work-up) led to variable degrees of racemization, especially for SiX_3 = Me_2t BuSi (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$$Bu_3SnH$ 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* acetonides **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**.



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13. On the contrary BF_3•Et_2O was discarded because it is not able to give cyclic chelated transition states.
14. The analogous of alcohol **2a** (SiX_3 = Ph_2t BuSi) where the PMBOM group was replaced by a MPM (*p*-methoxybenzyl) group was prepared from **1** by this reaction sequence: 1) *p*-$MeOC_6H_4CH_2OC(=NH)CCl_3$, CSA, CH_2Cl_2, r.t. (ref. 15); 2) KOH, MeOH, 84% (2 steps); 3) Ph_2tBuSiCl, DMF, imidazole, r.t., 90%; 4) O_3, -78°C, MeOH-CH_2Cl_2, then $NaBH_4$, -78°C→0°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. ≥ 95%.
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Synthesis and Assignment of the Relative Stereochemistry of a Putative Biosynthetic Precursor of Tabtoxinine β-Lactam.

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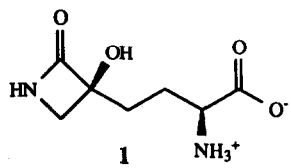
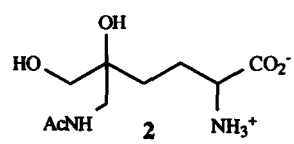
Abstract: The synthesis and assignment of the relative stereochemistry of a recently isolated amino acid is reported. This synthesis utilises the S_H2' coupling of an allylic stannane to a protected β-iodoalanine.

We have been interested in tabtoxinine β-lactam **1**,[1] the causative agent of wildfire disease in tobacco plants, and related compounds for some time.[2] Consequently our attention was drawn to a recent report by Durbin *et al.* on the isolation of a putative biosynthetic intermediate **2**[3] from a genetically blocked mutant of *Pseudomonas syringae* pv. *tabaci*, Fig. 1.



1

Tabtoxinine β-lactam

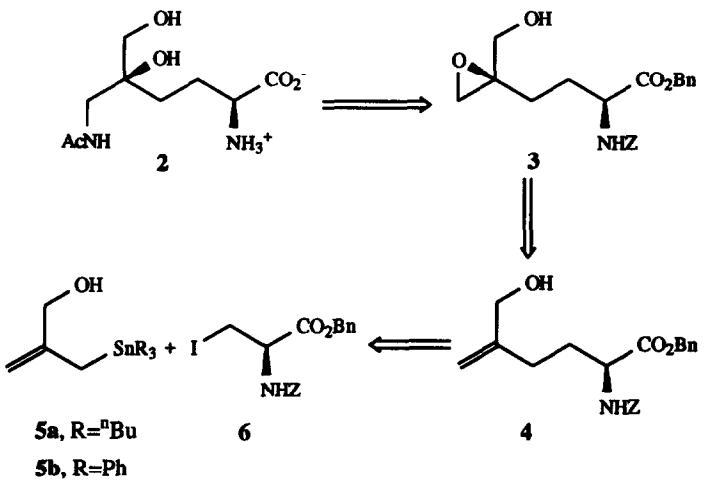


2

Fig. 1

The molecular formula and connectivity of **2** were established by a combination of ^1H and ^{13}C nmr and mass spectrometric methods. We felt that synthesis of **2** would be able to confirm the proposed structure and establish the stereochemistry. By comparison to tabtoxinine-ß-lactam it would appear that the stereochemistry of **2** is most likely to be as shown in Scheme 1.

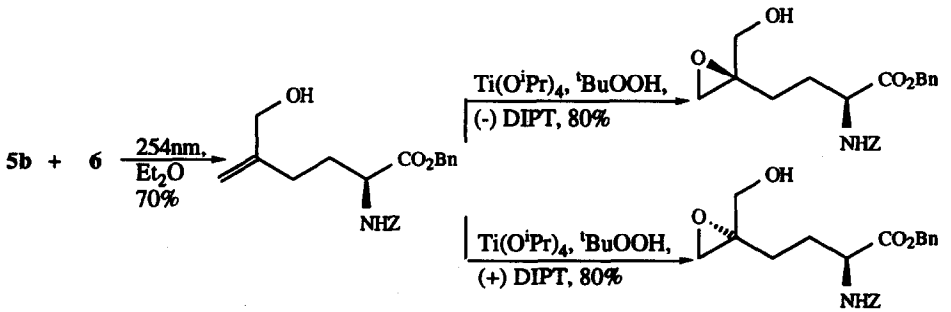
For preference, however, the synthetic route should allow preparation of any desired stereoisomer. It appeared that the most direct approach to the acetamido-diol fragment would be from epoxyalcohol **3**, which in turn could be established in either epimeric form *via* a Sharpless asymmetric epoxidation.[4] It was anticipated that the required δ-alkenyl amino acid **4** could be made using our previously reported radical coupling methodology, as the required stannane **5** had the necessary degeneracy to rearrangement under radical conditions.[5]



Scheme 1

Initially we prepared the stannane **5a** in 43% yield using a procedure adapted from Trost *et al.* for the trimethylsilyl analogue.[6] This compound proved difficult to purify, requiring the use of base washed silica,[7] and in addition was found to undergo slow decomposition on storage. Since it is known that simple allyltriphenylstannanes are frequently crystalline,[8] we next prepared **5b** in an analogous manner in 58% yield. This was found to be a white crystalline solid (m.p. 81°C) and stable to storage for several months at room temperature. Additionally it was found to be more stable towards protodestannylation than **5a**, permitting chromatography on flash silica.[9] The diprotected iodoalanine **6** was prepared by known methods.[10]

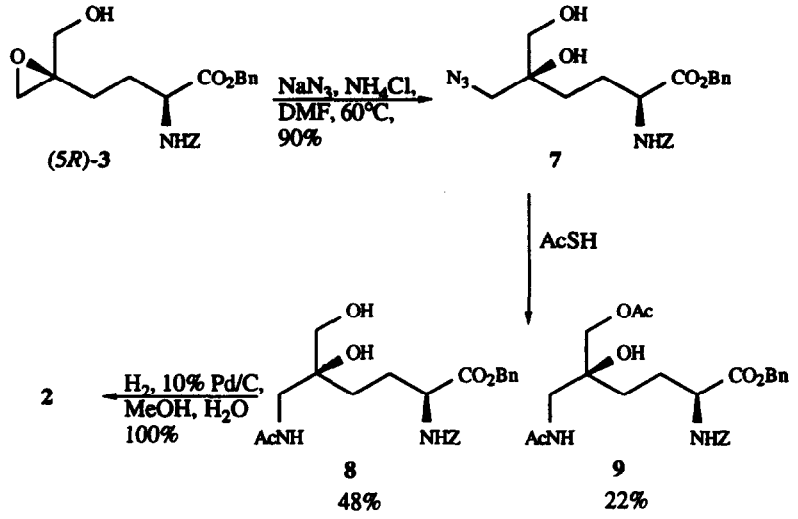
The radical coupling reaction could be initiated thermally using AIBN but the best yield[11] (70%) was obtained by irradiation of a 3:1 mixture of **5b** and **6** in ether with a medium pressure Hg lamp. Subsequent Sharpless epoxidation with either enantiomer of diisopropyl tartrate (DIPT) proceeded smoothly in 80% yield to give the corresponding epoxides, diastereomerically pure in each case as judged by 500 MHz ^{1}H nmr, (Scheme 2).



Scheme 2

Optimised conditions for introduction of the azido group were found to be $NaN_3/NH_4Cl/DMF/60°C$, affording the crude azide **7** in 90% yield as a single regioisomer. We were not able to prepare an analytically pure sample and so the material was carried through to the next step directly. Any possibility that a Payne rearrangement had accompanied epoxide opening was ruled out by comparison of the ^{13}C nmr spectra of the diastereomeric azides : two clearly resolved signals for the CH_2N_3 carbon were seen in a mixed sample.

Reductive acetylation of the azide **7** to acetamide **8** was achieved directly in 48% yield by treatment with neat thiolacetic acid[12] for 2 days,with 22% of diacetyl compound **9** being isolated. Shorter reaction times reduced the amount of desired product, however. Hydrogenation over 10% Pd/C in MeOH/H_2O gave the amino acid in quantitative yield as a fluffy white powder (Scheme 3).



Scheme 3

The (5*R*) diastereomer of **2** was also synthesised, from the corresponding (5*S*) epoxide, and comparison of the ^1H nmr (500MHz) of the two diastereomeric amino acids revealed a difference in the resonances associated with the γ-CH_2 protons, Fig. 2. This was sufficient to allow assignment of the relative stereochemistry of the natural product as shown in Scheme 1. In the absence of optical data it was not possible to assign the absolute stereochemistry, although on biosynthetic grounds it is highly likely to be as shown.

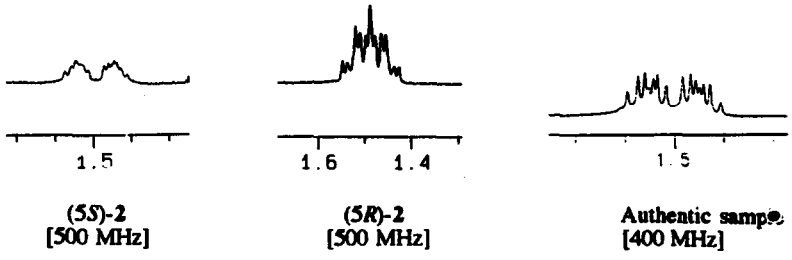


Fig. 2

In summary we have described a short asymmetric synthesis of a recently isolated amino acid, and in so doing have confirmed the proposed connectivity and assigned its relative stereochemistry.

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Synthesis of a 1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline from a Quinoline

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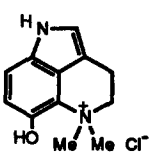
Key Words: Damirones; batzellines; isobatzellines; dehydrobufotenine; 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline.

Abstract: 6-Methoxy-4-methylquinoline has been converted into 8-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline.

	R^1	R^2
damirone B	H	H
batzelline C	Cl	Me

isobatzelline C



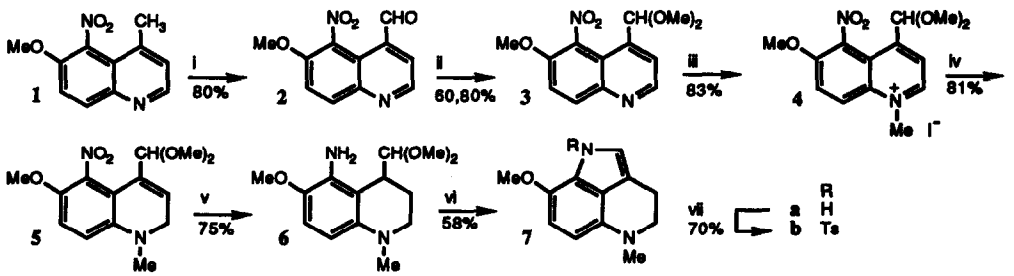
dehydrobufotenine chloride

The 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system was first recognised as a component of a natural product when the structure of the toad poison, dehydrobufotenine was elucidated.[1] Much more recently, several marine alkaloids[2] such as the tricyclic batzellines,[3] isobatzellines,[4] and damirones,[5] (the simplest example from each of these groups is shown above) and more complex molecules such as the discorhabdines,[6] and prianosines[7] have been described which are also based on a 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus.

In *all* synthetic work so far described, relating to these natural products, including preparations of the unsubstituted-[8,9] and 1-methyl-[10] tricyclic system, of *O*-methylnordehydrobufotenine,[11] of dehydrobufotenine itself[12], and then later of batzelline C and isobatzelline C,[13] discorhabdin C,[14] and damirones A and B,[15] the tricyclic heterocycle has been constructed *from an indole, i.e.* by forming the six-membered nitrogen-containing ring as a late step, by cyclisation either of a 4-aminoindole carrying a two-carbon chain at its C-3,[8-14] or of a tryptamine quinone.[15]

We have taken a different approach to the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline system and describe here how a quinoline can be utilised as starting point. 6-Methoxy-4-methyl-5-nitroquinoline,[16] **1**, was oxidised to the 4-aldehyde, **2** using Vismara's method.[17] Although the aldehyde could be converted into an acetal with ethane-1,2-diol, problems arose at a later stage when too vigorous conditions were required for its removal, so the dimethyl acetal, **3**, was prepared and carried forward. Quaternisation (→ **4**) then borohydride reduction produced the 1,2-dihydroquinoline, **5** which on subjection to catalytic hydrogenation was reduced at the C-C double bond *and* the nitro group, producing acetal-amine, **6**.

The completion of the synthesis required removal of the acetal protection – it was at this stage that acid hydrolysis of the ethane-1,2-diol acetal proved to require too vigorous conditions – however the dimethyl acetal



Reagents: i, I_2, *t*-BuI, $FeCl_2$, TFA, DMSO, 80°C; ii, $HC(OMe)_3$/MeOH/reflux or dry HCl/MeOH/reflux; iii, MeI/MeCN/50°C; iv, $NaBH_4$/MeOH/20°C; v, H_2/Pt-C/20°C; vi, aq. 1N HCl/THF/40°C/24 h or *p*-TsOH/THF/reflux/3 h; vii, $TsCl/CH_2Cl_2/Bu_4N^+ HO^-$.

could be hydrolysed, with ring closure to indole **7a** under mild conditions. Characterisation of 'purified' **7a** proved difficult, for although a perfectly satisfactory ^1H NMR spectrum[18] could be obtained on the 'crude' product, after chromatography, material was obtained which though homogenous by the usual criteria, and giving a mass spectrum consistent with structure **7a**, yet would give no ^1H NMR signals; this observation was reproducible. Conversion to the *N*-tosyl derivative, **7b**, gave material which gave entirely consistent spectroscopic data.[19]

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18 Amorphous gum, δ_H ($CDCl_3$) 2.96 (3H, s), 3.09 (2H, t, J 5.5 Hz), 3.27 (2H, t, J 5.5 Hz), 3.93 (3H, s), 6.14 (1H, d, J 8.0 Hz), 6.75 (1H, d, J 8.0 Hz), 6.77 (1H, s), and 8.05 (1H, bs).
19 Amorphous solid, δ_H ($CDCl_3$) 2.37 (3H, s), 2.88 (3H, s), 3.00 (2H, t, J 6.0 Hz), 3.20 (2H, t, J 6.0 Hz), 3.71 (3H, s), 6.28 (1H, d, J 8.3 Hz), 6.62 (1H, d, J. 8.3 Hz), 7.23 (2H, d, J 8.3 Hz), 7.34 (1H, s), 7.79 (2H, d, J 8.3 Hz).

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