Asymmetrized Tris(hydroxymethyl)methane and Related Synthons: Enantioselective Preparation and Synthetic Applications

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Asymmetrized *tris*(hydroxymethyl)methane (THYM*) is a new chiral building block easily accessible in both enantiomeric forms by a chemoenzymatic methodology. The presence of three synthetically equivalent masked hydroxymethyl groups and a high degree of latent symmetry (C_{3v}) makes this synthon very versatile in synthetic applications. This review describes its preparation and a series of elaborations (with particular enphasis on the diastereoselective generation of additional chiral centers) leading to advanced intermediated for the preparation of biologically active compounds.

1. Introduction

Small enantiomerically pure chiral molecules derived from natural substances are widely used as starting material for the construction of biologically active compounds.[1] However, the number and availability of these chiral units is limited and thus many efforts are currently devoted toward the enlargement of the "chirality pool", synthesizing new chiral building blocks through asymmetric synthesis either using non-biological or biological methods.

In this context in late 1987 we were attracted by the fairly symmetrical structure of *tris*(hydroxymethyl)methane **1** ($R^1 = R^2 = R^3 = H$) and reasoned that, if one could distinguish the three equivalent hydroxymethyl groups, a new highly versatile chiral building block ["asymmetrized *tris*-(hydroxymethyl)methane" (THYM*)] would have been available. The usefulness of this unit is that in principle, any chiral C-branched molecule could be synthesized from it,

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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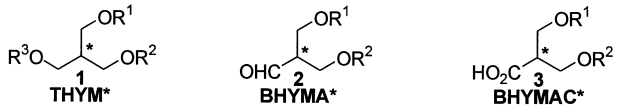
since in **1** the three masked CH_2OH groups can be manipulated indipendently in a variety of ways. Moreover **1** possesses a latent C_{3v} symmetry (a C_3 axis and three vertical planes), a fact which imparts to this molecule a high stereochemical flexibility, as it will be pointed out later.

THYM* can be synthetically related to any molecule deriving from oxidation of one of the three side arms giving rise to an aldehyde [*bis*(hydroxymethyl)acetaldehyde BHYMA* (**2**)] or a carboxylic acid derivative [for example *bis*(hydroxymethyl)acetic acid BHYMAC* (**3**)]. These synthons can be very useful as well, in view of possible elaborations of the oxidized arm.

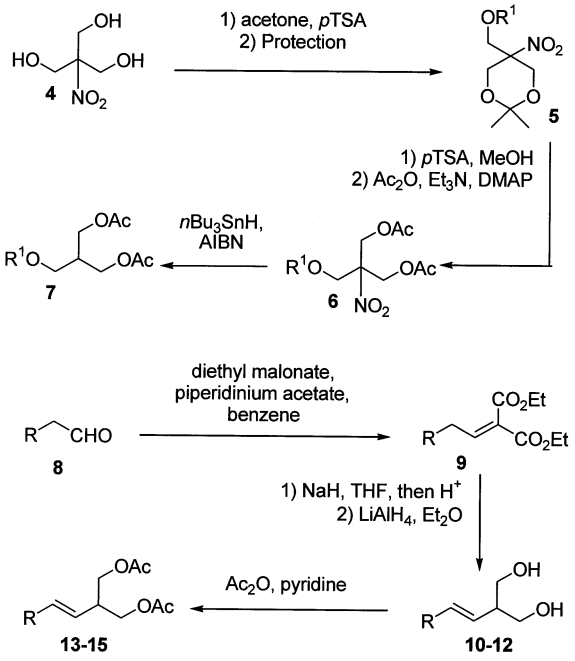
Scheme 1



2. Preparation

Enantioselective preparation of these chiral building blocks was first attempted through enzymatic asymmetrization of suitable diols or diacetates like **7**, **10−12** or **13−15**. The required starting materials have been prepared as shown in Scheme 2.[2]

Scheme 2



Enzyme catalysed monohydrolysis of a series of prochiral diacetates **7** to give compounds **16** (Scheme 3) was however unsatisfactory, since the desired monoacetates were obtained only in poor yield and with very low asymmetric induction.[2] On the contrary very high *ee*s were realized by submitting a series of 2-(*E*)-alkenyl 1,3-diacetoxypropanes **13−15** to pig pancreatic lipase (PPL) mediated monohydrolysis to give (*S*) monoacetates **17−19** (Table 1). The synthetic equivalence of these monoacetates with THYM* **1** or BHYMA* **2** is secured by the possibility of breaking the double bond by ozonolysis to give, depending on the conditions of reductive work-up, either a formyl or a hydroxymethyl group. Hydrolysis of diacetates **13−15** was optimized adding various cosolvents to the aqueous medium, and varying the R group. The best conditions were achieved using the branched substrate **15** and in the presence of 15% of diisopropyl ether (entry 5).[2][3][4]

Scheme 3

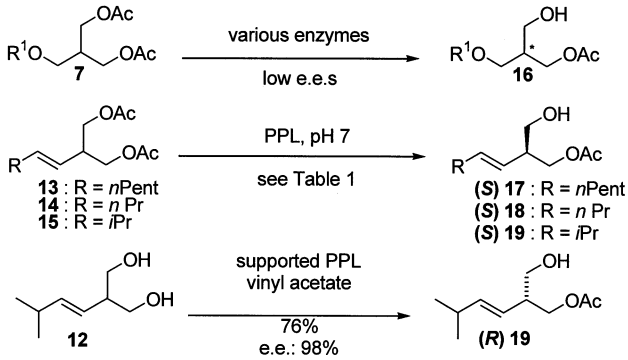


Table 1. Results of enzymatic hydrolysis of diacetates **13−15**

Entry	R	Solvent	Yield	*ee*
1	*n*Pent	H_2O	49%	84%
2	*n*Pent	H_2O/*t*BuOH, 90:10	59%	93%
3	*n*Pent	H_2O/*i*Pr_2O, 85:15	63%	95%
4	*n*Pr	H_2O/*i*Pr_2O, 85:15	46%	94%
5	*i*Pr	H_2O/*i*Pr_2O, 85:15	**75%**	**97%**

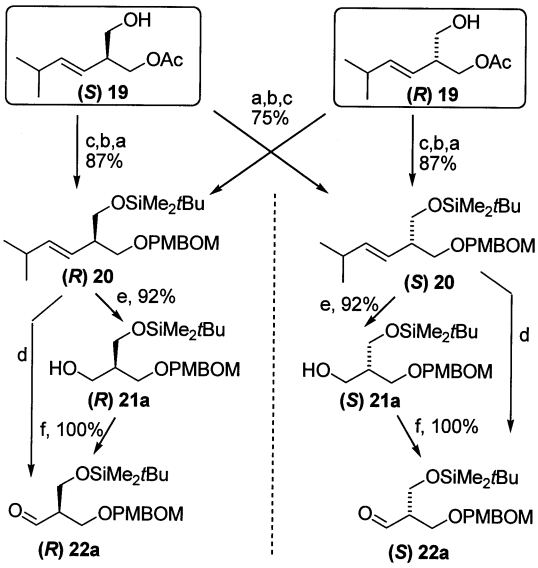
The high asymmetric induction achieved was in part due to the presence of the (*E*) double bond. A comparative study has indeed demonstrated that when the double bond was saturated, the *ee* dropped significantly to 70−72%. Interestingly, while the presence of a triple bond maintained an acceptable level of enantioselection (82−88% *ee*), when the configuration of double bond was changed to (*Z*), a surprising reversal of enantioselectivity, leading to the (*R*) enantiomer, albeit in modest *ee*,[2][4] was observed. These results have been tentatively rationalized with an empirical model of PPL active site (for other empirical models of PPL active site see refs.[5][6]).

In order to gain access to the (*R*) enantiomer of monoacetate **19**, we have also studied the enzyme catalyzed acetylation of diol **12** (Scheme 2). By using crude PPL under usual conditions (a moderate excess of vinyl acetate in solvents like CH_2Cl_2), the reactions were sluggish and the *ee* unsatisfactory, probably because of equilibration processes. On the other hand, different lipases showed unsatisfactory levels of asymmetric induction. Thus we turned back to PPL and, after a deep study, discovered that the reaction rate could be dramatically increased by supporting the crude PPL on celite, and using vinyl acetate as solvent. Under the optimized conditions, (*R*)-**19** could be prepared in excellent *ee* (98%) by using a quantity of enzyme even smaller than the one needed for the monohydrolysis of **15**.[7][8] It is worth noting that both prochiral precursors **12**

and **15** are easily available in 55% and 54% overall yield from isovaleraldehyde (Scheme 2) and that all the intermediates and final products are easily purified by distillation or crystallization.

Monoacetates **19** were converted by a four step sequence into a series of asymmetrized tris(hydroxymethyl)methanes (THYM*) (**21**), or of asymmetrized bi(hydroxymethyl)acetaldehydes (BHYMA*) (**22**). Scheme 4 shows, as an example, the preparation of **21a** and **22a**.[2][9][10] It should be stressed that both enantiomers of a given THYM* or of a given BHYMA* are accessible in similar yield and with the same number of steps starting from a given enantiomer of **19**, simply by reversing the order of protecting group introduction. This property (*enantiodivergency*)[11] is typical of all the building blocks possessing a latent plane of symmetry, and in our case adds further stereochemical flexibility. The last step in preparation of aldehydes **22** involved ozonolysis of the double bond. In some cases reductive work-up with Me_2S afforded directly the desired aldehydes pure enough to be used as such, without isolation, for further reactions. However, in other cases (especially when the Me_2tBuSi group was present), more reproducible results were achieved by work-up with $NaBH_4$, followed by quantitative oxidation of the resulting primary alcohol (a THYM* equivalent) under modified Swern conditions.[9] It is worth noting that usual Swern conditions led to varaiable degrees of racemization.

Scheme 4

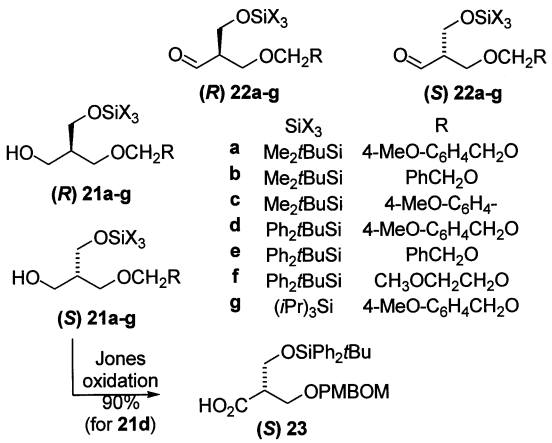


a) PMBOM−Cl, EtN(*i*Pr)$_2$, CH_2Cl_2. b) KOH, MeOH. c) $tBuMe_2SiCl$, imidazole, DMF. d) O_3, CH_2Cl_2−MeOH, then Me_2S. e) O_3, CH_2Cl_2, MeOH, then $NaBH_4$. f) $(COCl)_2$, DMSO, EtN(*i*Pr)$_2$, CH_2Cl_2, −78°C; PMBOM = 4-$MeOC_6H_4CH_2OCH_2$.

By a similar strategy we have also prepared all the THYM* and BHYMA* derivatives depicted in Scheme 5.

Monoacetates (*S*)- or (*R*)-**19** have also been converted into the asymmetrized *bis*(hydroxymethyl) acetic acids (BHYMAC*) **23**, by oxidation of THYM* derivative **21d**.[12] The oxidation proceeded without any racemization.

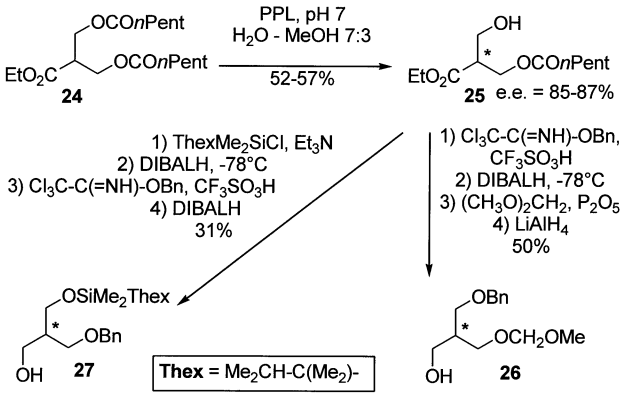
Scheme 5



Although asymmetrization of diol **12** or of diacetate **15** mediated by PPL appears to be the best procedure for the synthesis of these building blocks, other alternative methods have been reported.

Scheme 6 shows an alternative chemoenzymatic approach through PPL catalysed monohydrolysis of dicaproate of ethyl *bis*(hydroxymethyl)acetate (**24**).[5] After optimization of the reaction by using various enzymes and solvent mixtures, under the best conditions (once again realized with PPL), an *ee* of 85−87% was obtained. Monocaproate **25**, whose absolute configuration was not determined, was converted in four steps into THYM* equivalents **26** and **27**. In both cases a certain amount of racemization was observed. Racemization could in principle take place either via ester enolization or by acid or base-catalysed migration of caproyl group from one OH to the other.

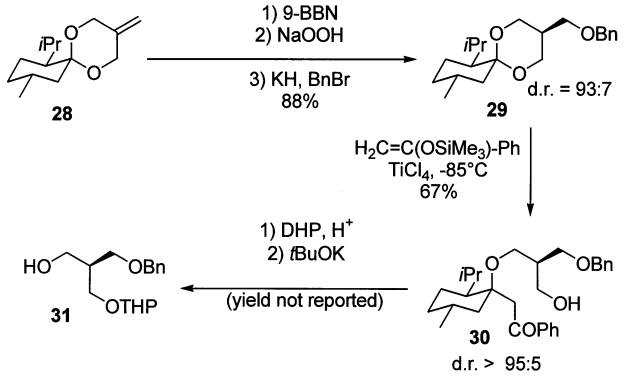
Scheme 6



A non-biological preparation of THYM* derivatives has been reported by Oku and Harada[13][14] (Scheme 7) and is based on two successive diastereoselective reactions starting from ketal **28**, in turn prepared from *l*-menthone. The first asymmetric transformation is the stereoselective hydroboration of the double bond to give, after protection, compound **29**. $TiCl_4$ mediated cleavage of the acetal by a silyl enol ether turned out to be highly stereoselective affording

30, which was converted in two steps into THYM* derivative **31**.

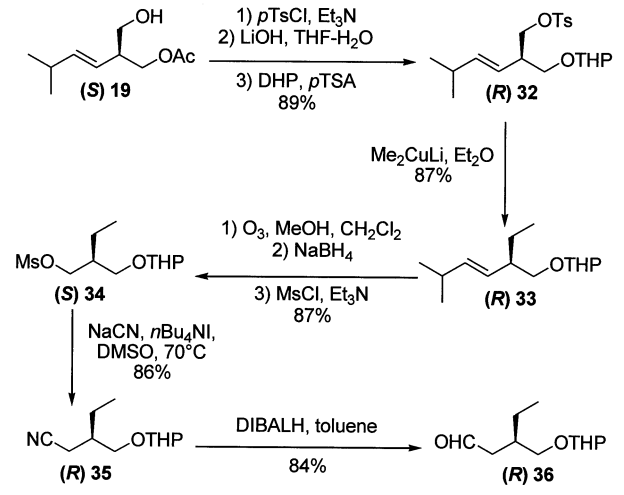
Scheme 7



3. Elaborations not Involving Creation of Additional Stereocenters

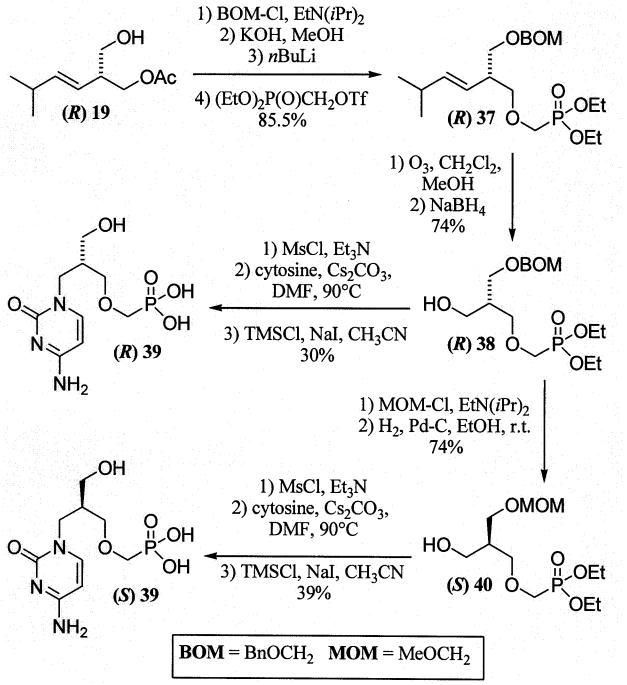
Each of the three side arms in THYM* equivalents can be elaborated indipendently to give various types of chain extension. For example, after conversion of an OH into a good leaving group, nucleopilic substitutions, either with carbon or heteroatomic nucleophiles, can be realized. An example of this strategy is given in Scheme 8, where two substitution reactions have been utilized in the synthesis of (*R*)-**36**, representing the upper fragment of natural toxin Talaromycin A.[15] A simple alkyl group (in this case a methyl) was introduced by coupling a lithium dialkyl cuprate with tosylate **32**, while, in order to obtain a homologated functionalized compound, the classical replacement of mesylate **34** with cyanide was employed. All the steps proceeded in high yield.

Scheme 8



Another example is depicted in Scheme 9, which illustrates the enantiodivergent[11] preparation, starting from a single enantiomer of monoacetate **19**, of both enantiomers of the "open-chain" nucleotide analogue **39**.[16] These compounds are interesting as potential antiviral agents. They are indeed homologues of (*S*)-1-[3′-hydroxy-2′-(phosphonomethoxy)propyl]cytosine [HMPC], which showed an antiviral activity against a wide range of DNA viruses, superior in some respect to that of acyclovir. The synthesis was achieved by introduction of the phosphonomethyl moiety on the oxygen of one arm, followed by substitution of the OH of a second arm with cytosine. The obtainment of (*S*) enantiomer [which could be also realized starting from (*S*)-**19**] was achieved by inversion of the stereogenic centre of **38** through a protecting group interchange. A crucial step of these syntheses was represented by the final removal of BOM or MOM protecting groups. This was eventually performed, with simultaneous hydrolysis of the phosphonic ester, by treatment with in situ generated trimethylsilyl iodide.

Scheme 9



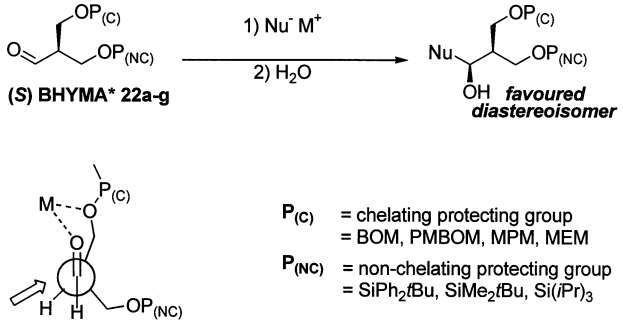
The syntheses shown in Schemes 8 and 9 already put in evidence the remarkble flexibility of these building blocks. Indeed there are in principle 36 different ways to convert a given enantiomer of **19** into **36** or **39**, half of them leading to the (*S*), and half to the (*R*) antipodes. This descends from the synthetic equivalence of the three side arms. So one can think of trasforming any of them into any of the functions present in the final products (leading to 6 different choices). Moreover one can choose at will the order of introduction of the three substituents (6 different possibilities). Although it is obvious that some of these theoretical routes suffer from being too long and from requiring extensive use of protecting groups, it is still possible to design several alternative logical synthetic schemes, from which to pick out the most efficient one.

4. Elaborations Through Diastereoselective Additions To BHYMA* Derivatives

Interesting synthetic applications have been realized through addition of carbon nucleophiles to asymmetrized

bis(hydroxymethyl)acetaldehydes BHYMA* **22a−g**. In this case at least one new stereogenic center is created, and thus diastereoselection becomes an important issue. It is important to note that in **22a−g** the two synthetically equivalent masked hydroxymethyl groups are differentiated only by the protections. Therefore, in order to achieve high levels of diastereoselection in additions to BHYMA* it is necessary to magnify the differences between them. An approach based only on steric biases was expected to be unsatisfactory, because the first point of difference is too far away from the stereogenic centre. On the other hand, it was reasoned that "chelation controlled" additions would have been ideal in this case, given the possibility to increase or depress the coordinating ability of ethereal oxygen through judicious choice of the protecting group. If we call $P_{(C)}$ a group that favours, and $P_{(NC)}$ a group that depresses chelation, the preferential formation of the diastereoisomer indicated in Scheme 10 can be predicted. Silyl ethers have been thus far employed by us as "non-chelating" protecting groups: it is actually well known that in such ethers the oxygen tendency of coordinating Lewis acids is sensibly lower than in the corresponding alkyl ethers.[17][18] On the other hand, alkoxymethyl ethers or *p*-methoxybenzyl ether were employed as "chelating protecting groups".

Scheme 10



Since the control over the configuration of the newly created stereogenic centre is only due to the different nature of protecting groups, we can speak of an *exclusively protecting group controlled asymmetric synthesis (EPGCS)*. Implementation of this strategy is shown in Table 2. While the use of more conventional nucleophiles like organolithium or Grignard reagents led to poor stereoselection (entries 1, 2, 10), good to excellent inductions have been achieved in the condensation of BHYMA* equivalents with dialkyllithium cuprates (entries 4−7). The allylation reaction was also particularly investigated because of its high utility being synthetically equivalent to an aldol or an homoaldol reaction, depending on the subsequent double bond functionalization (ozonolysis or hydroboration-oxidation). In this case the best conditions for achieving good chelation control made use of allyltri-*n*-butyltin under the catalysis of $MgBr_2$ (entries 11−17). It is noteworthy that in both cases the diastereoselection seems to depend very little on variation in the chelating or non-chelating protecting group, provided that the former is an acetal or a benzyl ether, and the latter is a silyl ether.

Obviously these chelation-controlled additions can lead, with good stereoselection, only to one of the two possible diastereoisomers. While with building blocks characterized only by a latent C_s symmetry this fact constitutes a serious drawback, in the present case, the higher degree of latent symmetry (C_{3v} instead than C_s) allows to overcome the problem. Since the original stereogenic centre bears two synthetically equivalent protected hydroxymethyl groups, its configuration remains indeed flexible and can be varied at will with simple protecting group introduction-deblocking steps. This concept is esemplified by the transformations shown in Scheme 11.[11][21][22] Two epimers **a** and **b** with the same constitutional formula were prepared starting from a common diastereomerically pure precursor. In other words a single type of stereocontrol is sufficient to give access to both possible epimers. This property has been defined as *diastereodivergency*.[11] Since also both enantiomers of starting BHYMA* are *enantiodivergently* accessible, all four stereoisomers of a given protected 2-hydroxymethyl-1,3-alkanediol can be prepared (*double stereodivergency*)[11] starting from a single enantiomer of monoacetate **19**.

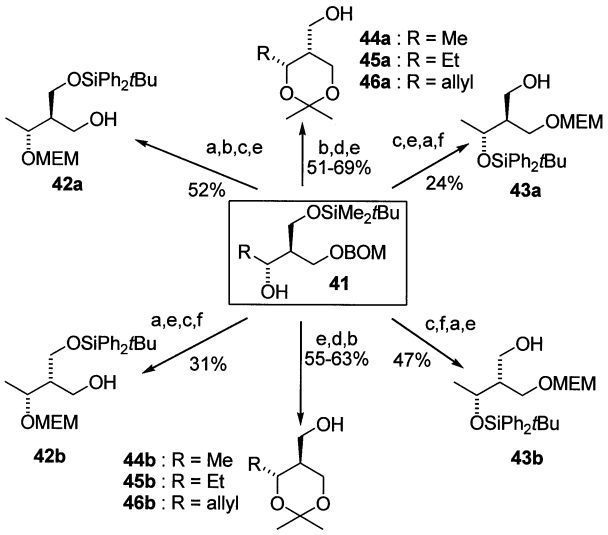
Another way to prepare the diastereoisomers not directly obtainable from chelation-controlled nucleophilic additions to BHYMA* lies in the chelation-controlled reduction of ketones of general formula **47** (Scheme 12). In this case a cyclic chelated transition state would predict the opposite diastereoisomer than that obtained in chelation controlled additions to BHYMA*. Thus, a series of ketones **47** was prepared, generally through addition of organolithium reagents to BHYMA* followed by reoxidation under Swern or Jones conditions. After a thorough examination of various reducing agents as well as combinations of reducing agents with Lewis acids, the best conditions for these reductions were found to involve the addition of diisobutylaluminium hydride at −78°C to a preformed mixture of substrate and $MgBr_2{\cdot}Et_2O$ (Table 3). In this way good diastereomeric ratios, between 83:17 and 97:3, have been obtained.[24] The type of R group in the ketone was important in determining the level of diastereoselection. Best results were observed when the ketone was conjugated with a double bond or aromatic (entries 15−19). On the other hand when the ketone was conjugated with a triple bond, the asymmetric induction, for reasons not yet understood, was unsatisfactory (entry 20). It is worth noting that zinc borohydride, which afforded good results in the reduction of phenyl (1-alkoxy-2-propyl) ketone (the analogous of **47** with a methyl instead than a silyloxymethyl group),[25] gave in the case of non-conjugated ketones, only modest induction. High induction in $Zn(BH_4)_2$ reduction was on the contrary observed only when the ketone was α,β-unsaturated or aromatic. Diastereoselectivities obtained with DIBALH − $MgBr_2$ remained, however, superior. The influence of protecting group was in this case greater than in the previously described additions to BHYMA* (Table 2). For example the use of MEM as "chelating" group led to unsatisfactory results (entry 10). The utility of these reductions lies

Table 2. Chelation-controlled addition of C-nucleophiles to BHYMA* **22a−g**

Entry	$P_{(C)}$[a]	$P_{(NC)}$	Reagents/conditions	Yield	Diast. ratio[b]	Ref.
1	BOM	Me_2tBuSi	$MeLi/Et_2O$	79%	52:48	11
2	BOM	Me_2tBuSi	$MeMgBr/Et_2O$	55%	58:42	11
3	BOM	Me_2tBuSi	$MeCu{\cdot}MgBr_2/Et_2O$-Me_2S	53%	82:18	11
4	BOM	$SiMe_2tBu$	Me_2CuLi/Et_2O	74%	**95:5**	11
5	PMBOM	$SiMe_2tBu$	Me_2CuLi/Et_2O	84%	**95:5**	9
6	PMBOM	$SiPh_2tBu$	Me_2CuLi/Et_2O	90%	**96:4**	20
7	MEM	$SiPh_2tBu$	Me_2CuLi/Et_2O	65%	**95:5**	19
8	BOM	$SiMe_2tBu$	Et_2CuLi/Et_2O	87%	**93:7**	21
9	BOM	$SiMe_2tBu$	nBu_2CuLi/Et_2O	93%	**87:13**	21
10	PMBOM	$SiMe_2tBu$	Allyl-MgBr	51%	51:49	22
11	BOM	$SiMe_2tBu$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	70%	**83:17**	22, 15
12	PMBOM	$SiMe_2tBu$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	85%	**86:14**	19
13	BOM	$SiPh_2tBu$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	92%	**87:13**	22, 15
14	PMBOM	$SiPh_2tBu$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	91%	**91:9**	22, 15
15	MPM	$SiPh_2tBu$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	66%	**86:14**	23
16	MEM	$SiPh_2tBu$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	89%	**89:11**	19
17	PMBOM	$Si(iPr)_3$	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2	76%	**85:15**	22, 15

[a] BOM = benzyloxymethyl; PMBOM = *p*-methoxybenzyloxymethyl; MPM = *p*-methoxybenzyl; MEM = methoxyethoxymethyl. − [b] The major stereoisomer was always the one depicted in Scheme 10.

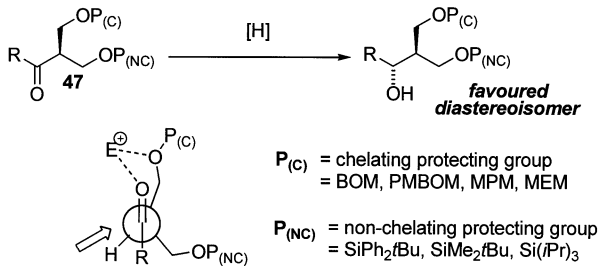
Scheme 11



a) MEM−Cl, Et_3N, CH_3CN; b) $nBu_4NF{\cdot}3H_2O$. c) $Ph_2tBuSiCl$, imidazole, DMF. d) $H_2C{=}C(Me){-}OMe$, H^+. e) H_2, Pd−C, $CaCO_3$. f) pyridinium *p*-toluenesulfonate, EtOH.

not only in being a method for the obtainment of the epimers of compounds gained by direct addition, but also in allowing the synthesis of adducts not achievable with good stereoselection by chelation controlled additions, like those of entries 15−19.

Scheme 12



Some of the products of chelation-controlled nucleophilic additions of alkyl or allyl groups to BHYMA* (or the diastereoisomers prepared by chelation-controlled reduction of the corresponding ketones) have been employed in the synthesis of biological active substances, or fragments of them. For the synthesis of a fragment of Tylonolide, the aglicone of antibiotic Tylosine, alcohol **48**, prepared by reaction of the appropriate BHYMA* with Et_2CuLi, was transformed through protecting group manipulations, into alcohols **49** and **50**, which, upon further elongation via a Wittig condensation, afforded respectively allylic alcohols **51** and **52** (Scheme 13).[20] The transformation of these intermediates, both corresponding to the $C_{11}-C_{17}$ fragment, into the natural product had been already previously reported. While the synthesis of **49** posed no special problems, the preparation of **50** required a regioselective deblocking of $tBuMe_2Si$ protected primary alcohol in the presence of a secondary alcohol protected in the same way.

Another regioselective silyl ether deblocking was required in the synthesis of β-lactam **56**,[9] an intermediate for Thienamycin and its derivatives (Scheme 14). In this case the efficient selective deprotection of *t*-butyldimethylsilyl ether in the presence of a triisopropylsilyl ether was carried out by an original methodology, which makes use of *p*-toluenesulfonic acid in dry isopropyl alcohol. In this way it was possible to selectively unmask the silyl-protected hydroxymethyl group, which was then oxidized and converted to the β-lactam **55** by a biomimetic β-hydroxyhydroxamate cyclization.[26] Finally, reductive removal of *N*-benzyloxy group gave the target compound **56**.

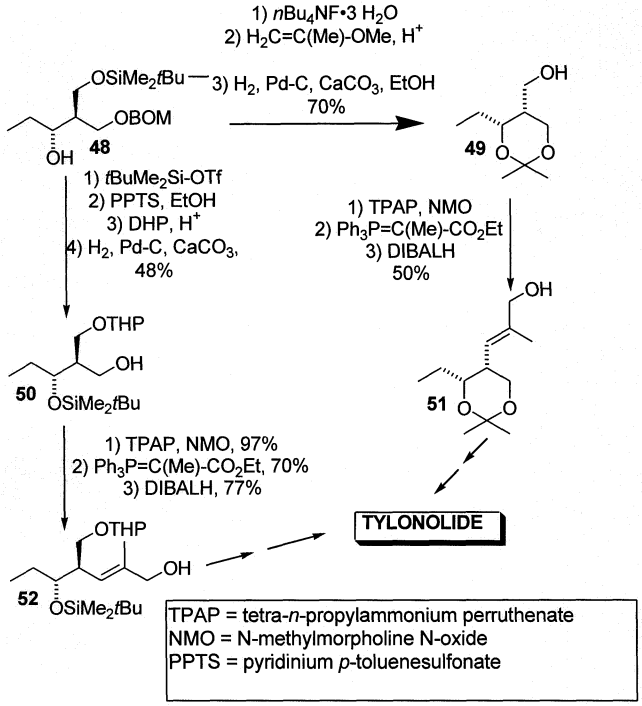
The product of allyl addition **57** was converted, with standard methods, into phosphorane **59**,[15] which represents the lower fragment of Talaromycin A and has been already transformed into the natural product (Scheme 15). This synthesis represents an example of synthetic equivalence between the nucleophilic allylation and an aldol addition by acetaldehyde. Since the top fragment of this natural toxin was also prepared by us starting from a THYM*

Table 3. Chelation-controlled reduction of ketones **47**

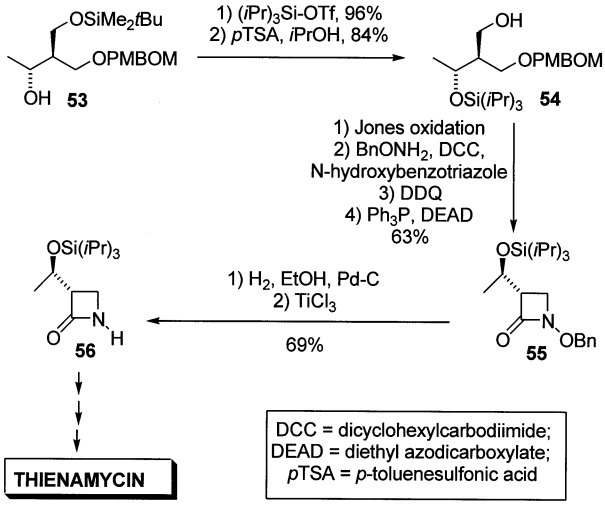
Entry	R	$P_{(C)}$[a]	$P_{(NC)}$	Reducing agent	Additive	Yield	Diast. ratio[b]	Ref.
1	*n*Bu	PMBOM	$SiPh_2tBu$	$NaBH_4$	none	90%	50:50	24
2	*n*Bu	PMBOM	$SiPh_2tBu$	$Zn(BH_4)_2$	none	90%	63:37	24
3	*n*Bu	PMBOM	$SiPh_2tBu$	$LiAlH(OtBu)_3$	none	77%	56:44	24
4	*n*Bu	PMBOM	$SiPh_2tBu$	DIBALH	none	74%	51:49	24
5	*n*Bu	PMBOM	$SiPh_2tBu$	$LiAlH(OtBu)_3$	$MgBr_2$	80%	77:23	24
6	*n*Bu	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	94%	91:9	24
7	*n*Bu	PMBOM	$SiMe_2tBu$	DIBALH	$MgBr_2$	86%	85:15	24
8	*n*Bu	PMBOM	$Si(iPr)_3$	DIBALH	$MgBr_2$	79%	83:17	24
9	*n*Bu	MPM	$SiPh_2tBu$	DIBALH	$MgBr_2$	70%	80:20	24
10	*n*Bu	MEM	$SiPh_2tBu$	DIBALH	$MgBr_2$	84%	75:25	19
11	Allyl	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	90%	84:16	19
12	Allyl	PMBOM	$SiMe_2tBu$	DIBALH	$MgBr_2$	88%	87:13	19
13	Allyl	PMBOM	$Si(iPr)_3$	DIBALH	$MgBr_2$	91%	90:10	24
14	*i*Pr	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	82%	85:15	24
15	Ph	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	86%	96:4	24
16	CH_2=CH-	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	62%	87:13	24
17	CH_2=C(CH_3)-	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	90%	93:7	24
18	(*E*)-nC_3H_7-CH=CH-	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	79%	94:6	24
19	(*Z*)-nC_3H_7-CH=CH-	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	80%	93:7	24
20	nC_3H_7-C≡C-	PMBOM	$SiPh_2tBu$	DIBALH	$MgBr_2$	90%	60:40	24

[a] PMBOM = *p*-methoxybenzyloxymethyl; MPM = *p*-methoxybenzyl; MEM = methoxyethoxymethyl. – [b] The major stereoisomer was always the one depicted in Scheme 12.

Scheme 13



Scheme 14

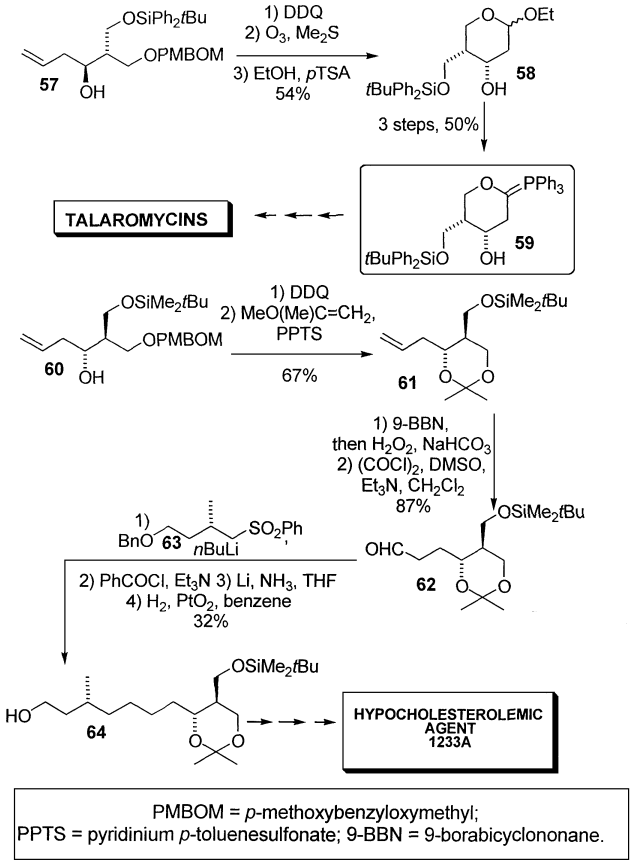


equivalent (Scheme 8) we have thus developed a new convergent synthesis of Talaromycin using a single building block. This further demonstrates its high synthetic versatility.

In another application we took instead advantage of the equivalence between the allylation and a homoaldol reaction.[10] Thus the allylated compound **60**, after conversion into the isopropylidene derivative **61**, was hydroborated and oxidized to the aldehyde **62**. It was then coupled with enantiomerically pure sulfone **63** (prepared from a different building block, namely 3-hydroxy-2-methyl propanoate)[27] to give **64** which is a key intermediate for the synthesis of hypocholesterolemic agent 1233A.

The addition of crotyl-metal compounds to BHYMA* aldehydes represents a more complicated case from a stereochemical point of view. In the course of the reaction two new chiral centers are formed and thus 4 possible diastereoisomers are in principle possible (Scheme 16). The problem of "induced diastereoselectivity", already present in the examples reported above in tables 2,3, is here accompanied by the "simple diastereoselectivity" issue. Once again the $MgBr_2$ mediated condensation of allylstannanes with BHYMA* gave good results (Table 4).[28] The "induced diastereoselectivity" (ranging from 93:7 to 96:4) was indeed considerably better than the one achieved in the condensation with unsubstituted allylstannanes (Table 2).

Scheme 15



Moreover a high degree of "simple diastereoselectivity" (ca. 9:1) was realized. The latter result was in line with the previously reported finding with other aldehydes.[29] As a consequence, a single stereoisomer, among the four possible, could be obtained in 86−88% diastereoselectivity.

Table 4. Chelation-controlled addition of crotylstannane to BHYMA* **22**

Entry	SiX_3	Yield	Diastereoisomeric ratio **65**:**66**:**67**:**68**
1	Ph_2tBuSi	80%	**88**:3:8:1
2	Me_2tBuSi	81%	**87**:4:7:2
3	$(iPr)_3Si$	85%	**86**:4:7:3

Although we were unable to find conditions for the efficient access to the other three diastereoisomers by direct crotylation of BHYMA*, we developed indirect mehods for obtaining all of them taking advantage of: (a) The chelation controlled reduction[28] of ketones **69**, derived by oxidation of the major stereoisomers **65** (Table 5) and (b) the inversion of configuration of the original chiral centre by simple protecting group interchange on the two CH_2OR arms, taking advantage of the stereochemical properties of these building blocks, in particular of their "diastereodivergency" (see Scheme 16).

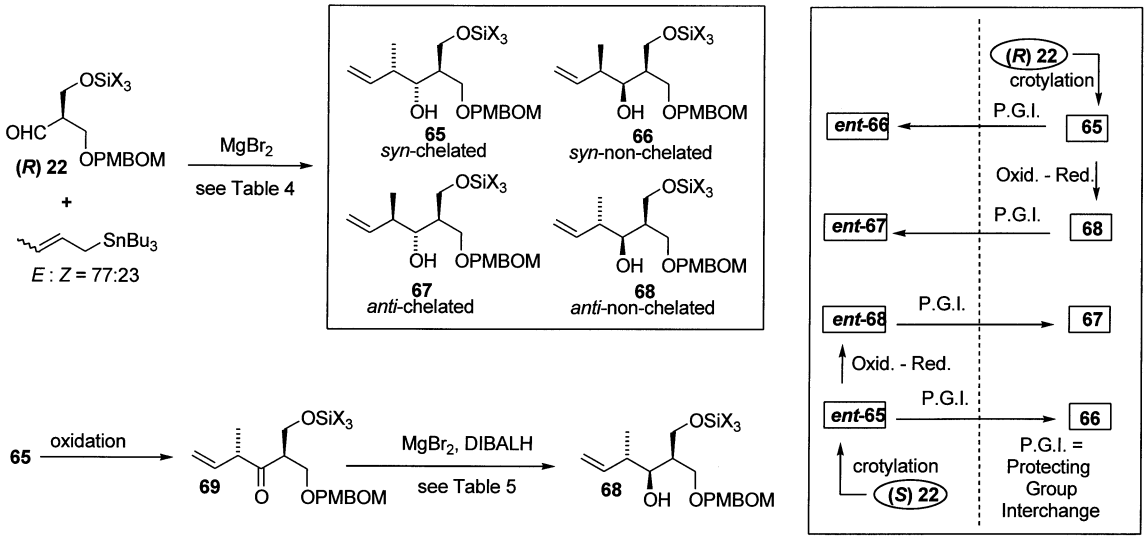
Finally, since both enantiomers of a given BHYMA* are equally well accessible, as already pointed out above, we can say that all the eight stereoisomers of crotyl derivatives like **65**−**68** are at hand, relying on two alternative "protecting group controlled" asymmetric transformations (direct nucleophilic crotylation and ketone reduction).

Table 5. Chelation-controlled reduction of ketones **69**

Entry	SiX_3	Yield	Diastereoisomeric ratio **68**:**65**
1	Ph_2tBuSi	87%	**86**:14
2	Me_2tBuSi	87%	**82**:18
3	$(iPr)_3Si$	93%	**81**:19

All the elaboration through nucleophilic additions of aldehydes BHYMA* thus far described involved only elongation of one of the three synthetically equivalent side-

Scheme 16



arms. Thus, after the first addition, two more protected CH_2OH groups remain at hand for further elaborations. In order to check the stereochemical consequence of a double addition to two different arms, we have recently studied the stereodivergent preparation of all the 8 possible stereoisomers of triols **71** (Scheme 17).[19] It is interesting to note that, thanks to the high latent symmetry of THYM* and BHYMA*, and to the complementarity of chelation-controlled additions and reductions, there are in principle at least 64 different ways for going from **22** to **71**, 8 for every single stereoisomer. In order to understand which of these routes were stereochemically more efficient, we examined the addition of C-nucleophiles to aldehydes **72**, **74**, **76**, **78** (Scheme 17 and Table 6) or the reduction of corresponding ketones **80**−**87** (Scheme 18 and Table 7).

Scheme 17

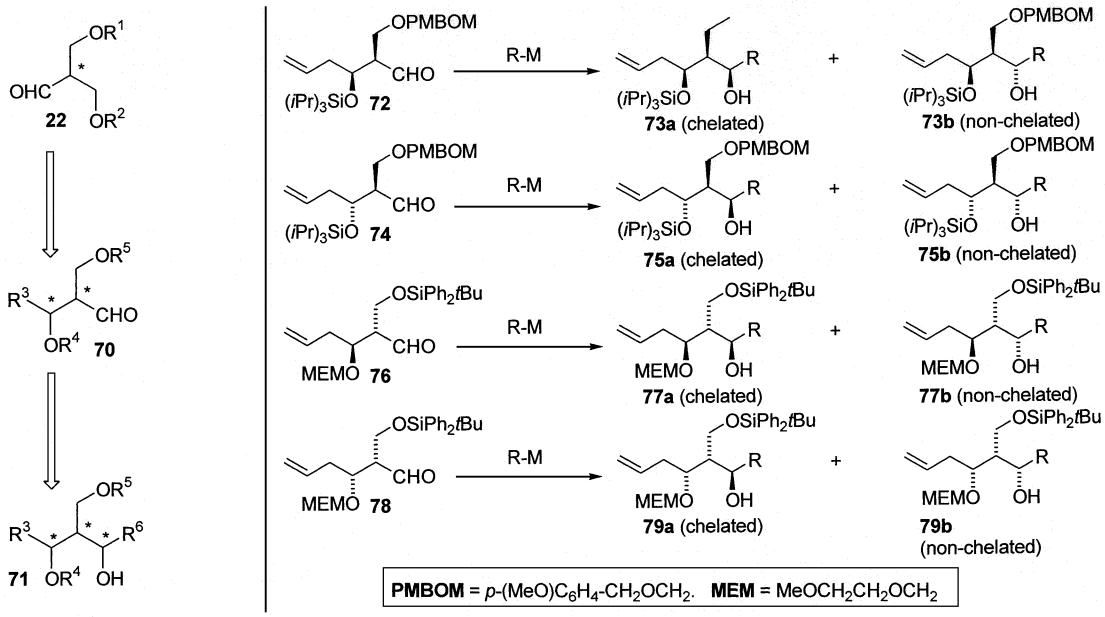


Table 6. Chelation-controlled additions of C-nucleophiles to aldehydes **72**, **74**, **76**, **78**

Entry	Aldehyde	R	Reagent/Conditions	Yield	**a** (chelated):**b** (non-chelated)
1	**67**	Me	Me_2CuLi	79%	**> 97:3**
2	**67**	Allyl	Allyl-$SnBu_3/MgBr_2$	97%	**95:5**
3	**69**	Me	Me_2CuLi	85%	**> 97:3**
4	**69**	Allyl	Allyl-$SnBu_3/MgBr_2$	86%	**87:13**
5	**71**	Me	Me_2CuLi	85%	45:55
6	**71**	Allyl	Allyl-$SnBu_3/MgBr_2$	86%	**92:8**
7	**73**	Me	Me_2CuLi	56%	**> 97:3**
8	**73**	Allyl	Allyl-$SnBu_3/MgBr_2$	91%	**95:5**

The model for the asymmetric induction previously shown in Schemes 10 and 12 are here complicated by the presence of an additional chiral centre in β-position. The results collected by us indicate that, when the "chelating" protecting group (PMBOM, MEM) is placed on the primary alcohol, the influence of the oxygen bearing stereogenic centre, which is not part of the the ring formed by chelation (see Schemes 10 and 12) is negligible, and the diastereoselection is nearly exclusively controlled by the original stereogenic centre (entries 1−4 of both tables). The observed general improvement in diastereoselectivity, as compared with the examples reported in Tables 2 and 3, is probably related only to the increased bulkiness of "non-chelating" substituent.

On the other hand, when the "chelating" protecting group is on the secondary alcohol, the oxygen bearing stereogenic centre is included in the ring formed by chelation, and its influence is greater. The control of diastereoselection is thus in this case in the hands of both stereogenic centers. For aldehydes **78**, the two controls are "matched", resulting in high induction (entries 7, 8 of Table 6), while for **76** they are "mismatched", and the stereoselectivity depends heavily on the nucleophile employed (entries 5, 6). On the contrary, in regard to ketones, unsatisfactory results were obtained for all the four derivatives **84**−**87** where the "chelating" protecting group is placed on the secondary alcohols. In this case the problem is probably due to a lesser coordination of $MgBr_2$ by the MEM group caused by the greater bulkyness of the secondary ether or to the particular nature of this protecting group (possessing three oxygens instead of two as in BOM or PMBOM).

Anyway, even if not all the reactions studied proceeded with good stereoselectivity, at least an efficient pathway for each of the four diastereoisomers of **71** (R^3 = R^6 = allyl, or R^3 = Me, R^6 = allyl) was disclosed. Actually, although for example neither **77a** (R = Me)(entry 5 of Table 6) nor **77b** (R = Me or allyl) (entries 5, 6 of Table 7) seem to be stereoselectively available, they have the same relative configuration of **75b** and **75a** respectively, from which they differ only for the protecting groups and for the absolute configuration of all stereocenters. Thus analogues of **77a** and

Scheme 18

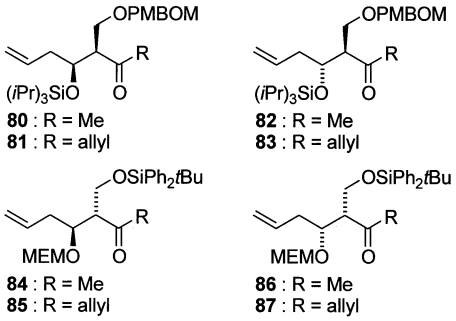


Table 7. Chelation-controlled reductions of ketones **80**−**87**

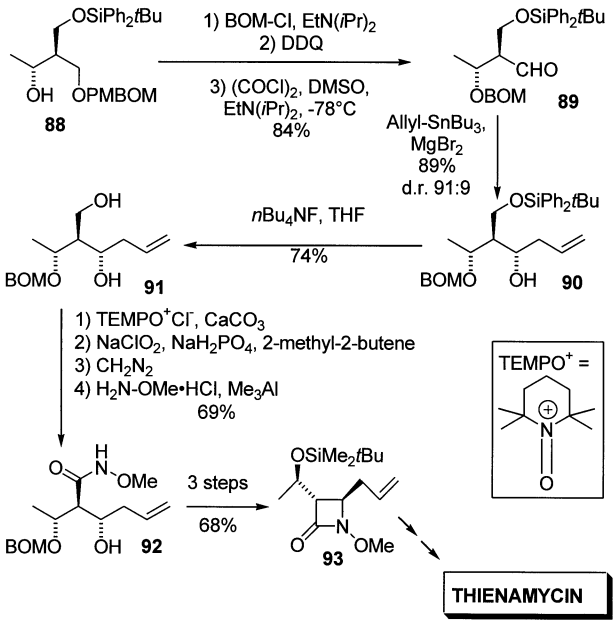
Entry	Ketone	R	Products	Yield	**a** (non-chelated):**b** (chelated)
1	**80**	Me	**73a,b**	93%	**< 5:95**
2	**81**	Allyl	**73a,b**	79%	**< 5:95**
3	**82**	Me	**75a,b**	87%	**16:84**
4	**83**	Allyl	**75a,b**	69%	**20:80**
5	**84**	Me	**77a,b**	76%	60:40
6	**85**	Allyl	**77a,b**	86%	27:73
7	**86**	Me	**79a,b**	60%	43:57
8	**87**	Allyl	**79a,b**	84%	38:62

77b can be prepared respectively by reduction of *ent*-**82** and *ent*-**83** or by addition to *ent*-**74**. Moreover, **79b**, another stereoisomer which does not seem to be directly available (entries 7, 8 of Table 7) has the same relative configuration of **73a**. Thus, given the availability of both enantiomers of a given BHYMA*, all 8 stereoisomers of protected triols **71** are at hand.

Protected triols of general formula **71** can be employed in several synthetic application. For example compounds of this type (prepared in a different way, starting from another chiral building block) have been recently used by Seebach in the preparation of chiral dendrimers.[30]

On the other hand, we have reported the stereoselective synthesis of β-lactam **93**, which is a known intermediate for the synthesis of the broad-spectrum antibiotic Thienamycin (Scheme 19).[20] This intermediate can be retrosynthetically connected, by functional group transformations, to protected triols **90** or **91**. As stated above, there are 8 possible routes for their preparation. Among them we chose the one which was predicted to be most efficient in term of lower number of step and of global stereoselectivity, on the basis of the previous general study. Alcohol **88** was indeed obtained in high diastereomeric ratio (96:4, see Table 2, entry 6) by the usual addition of Me_2CuLi addition to BHYMA*. After transformation into aldehyde **89**, the second nucleophilic addition proceeded with high diastereoselection (91:9) as well, furnishing **90**, which has the correct absolute and relative configuration for Thienamycin synthesis. The key step in the subsequent conversion into **93** was the regioselective oxidation of diol **91**, achieved with a two-step procedure: stoichiometric $TEMPO^+$ oxidizes regioselectively only the primary alcohol to an aldehyde which is then further oxidized in situ by the action of $NaClO_2$.

Scheme 19



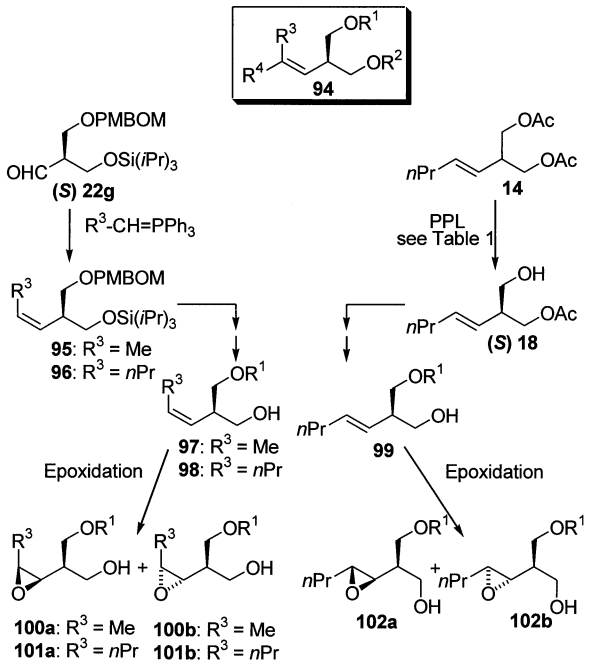
5. Elaborations through Olefination Followed by Electrophilic Additions

Asymmetrized 2-alkenyl-1,3-propanediols of general formula **94** are potentially useful chiral building blocks. They can indeed be manipulated in various ways through electrophilic additions to the double bond. Their efficient preparation in high *ee* was realized by us by two strategies, both starting from THYM* equivalents (Scheme 20). The first one, depicted on the left, takes advantage of a completely stereoselective Wittig olefination of BHYMA*. The second one, shown on the right, uses directly the (*E*) monoacetate **18** obtained, as already described, through PPL catalysed monohydrolysis. The two methodologies are complementary, since the first one is suited for (*Z*) isomers, while the second one works well only for (*E*) diacetates. Protecting group interchange reactions led easily to a series of variously protected alkenes **97**−**99**.[31][32]

Among the several possible elaborations of the double bond in alkenes **97**−**99** we studied deeply only the epoxidation.[31][32] The results, shown in Table 8, indicate that only poor stereoselectivities can be achieved starting from the (*E*) isomer. On the contrary, at least when one of the two hydroxymethyl groups is unprotected, very high asymmetric induction was gained starting from the (*Z*) derivatives **97** and **98** and using the system *t*BuOOH/$VO(acac)_2$. This outcome has been explained by postulating a cyclic transition state derived by bonding of the free hydroxyl with the catalyst.

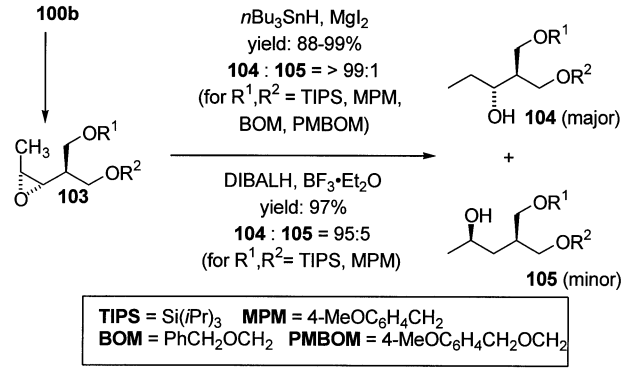
Having in hand a stereoselective route to epoxides **100b**−**101b** we then explored their nucleophilic ring opening, with an eye to the regioselectivity of the process. It is

Scheme 20



for the obtainment of regioisomers **105**, deriving from attack of reducing agent at the carbon α to the branching.

Scheme 21



Opening of the epoxide with halides furnishes halohydrins, which are useful intermediates in organic synthesis (Scheme 22).[35] Also in this case the major regioisomer was in all cases **107**, resulting from β-attack. The ideal conditions depended heavily on the protecting groups present in starting epoxide **106** (Table 9). For example Et_2AlCl alone worked well only when no benzyl or acetal protections were present (entry 3). In the other cases (entries 1,

Table 8. Stereoselective epoxidation of alkenes **97**−**99**[a]

Entry	Alkene	Configuration	R^1	Reagents	Yield	**a**:**b**
1	**99**	*E*	Ac	MCPBA	84%	6:54
2	**99**	*E*	Ac	*t*BuOOH, $VO(acac)_2$	58%	50:50
3	**99**	*E*	$SiMe_2tBu$	MCPBA	77%	43:57
4	**99**	*E*	$SiMe_2tBu$	*t*BuOOH, $VO(acac)_2$	96%	32:68
5	**98**	*Z*	$SiMe_2tBu$	MCPBA	79%	30:70
6	**98**	*Z*	$SiMe_2tBu$	*t*BuOOH, $VO(acac)_2$	63%	**< 5:95**
7	**98**	*Z*	$SiPh_2tBu$	*t*BuOOH, $VO(acac)_2$	57%	**< 5:95**
8	**98**	*Z*	$Si(iPr)_3$	*t*BuOOH, $VO(acac)_2$	61%	**< 5:95**
9	**98**	*Z*	Bn	*t*BuOOH, $VO(acac)_2$	56%	**< 5:95**
10	**98**	*Z*	PMBOM	*t*BuOOH, $VO(acac)_2$	74%	**< 5:95**
11	**97**	*Z*	$Si(iPr)_3$	*t*BuOOH, $VO(acac)_2$	98%	**< 5:95**
12	**97**	*Z*	PMBOM	*t*BuOOH, $VO(acac)_2$	90%	**5:95**

[a] PMBOM = *p*-methoxybenzyloxymethyl; Bn = benzyl; MCPBA = *meta*-chloroperbenzoic acid; Acac = acetylacetonate.

worth noting that the two epoxidic carbons are both secondary, and thus their differentiation is not an easy task.

The first reaction examined was the reductive opening (Scheme 21). When the attack of the reducing agent takes place at the carbon more distant from to the branching, this reaction furnishes adducts (e.g. **104**) structurally similar to those achievable by stereoselective nucleophilic addition to BHYMA*. After a deep investigation,[33] on varying the protecting groups and the reagents, we eventually found two methods yielding the regioisomers **104** in excellent regioselectivity, that is the combination of DIBALH and BF_3•Et_2O, and the system MgI_2-nBu_3SnH.[34] The latter method proceeds through an intermediate iodohydrin, that can be also isolated in the absence of tributyltin hydride. Since MgI_2 is a mild Lewis acid, this procedure is equally well suited for silylated or acetal-type protecting groups. On the contrary the first method is limited only to benzyl or silyl protections. We could not find instead valid methods

2), a combination of dialkylammonium chloride and a Lewis acid gave best results. A similar method was used for the introduction of bromine ion (entry 5) although, in the case of TIPS-MPM diprotected epoxide, $MgBr_2$ worked better. Finally MgI_2 was, as already noted above, the choice reagent for iodohydrin synthesis.

Particularly useful from a synthetic point of view is the opening of oxiranes **106** with carbon nucleophiles. Representative data collected by us are reported in Table 10.[35][36]

While lower order cuprates resulted totally unreactive toward these epoxides, satisfactory yield accompanied by high levels of regioselection were achieved by using "higher order" cuprates, especially in the presence of BF_3·Et_2O as Lewis acidic additive. The use of "higher order" methyl cuprate, however, furnished low yield, because of competitive epoxide reduction to give alkene products. Opening

Scheme 22

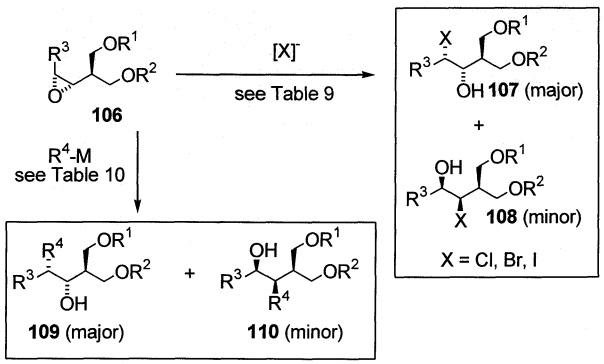


Table 9. Regioselective opening of epoxides **106** with halides[a]

Entry	R^2	R^3	X	Reagent/Conditions	Yield	**107**:**108**
1	TIPS	MPM	Cl	$Et_2NH{\cdot}HCl$, Et_2AlCl	86%	93:7
2	TIPS	H	Cl	$Et_2NH{\cdot}HCl$, $(iPrO)_4Ti$	71%	> 99:1
3	TIPS	Ac	Cl	Et_2AlCl	75%	99:1
4	TIPS	MPM	Br	$MgBr_2$	66%	90:10
5	TIPS	H	Br	$Et_2NH{\cdot}HBr$, $(iPrO)_4Ti$	88%	> 99:1
6	PMBOM	BOM	I	MgI_2	93%	92:8
7	TIPS	MPM	I	MgI_2	99%	> 99:1

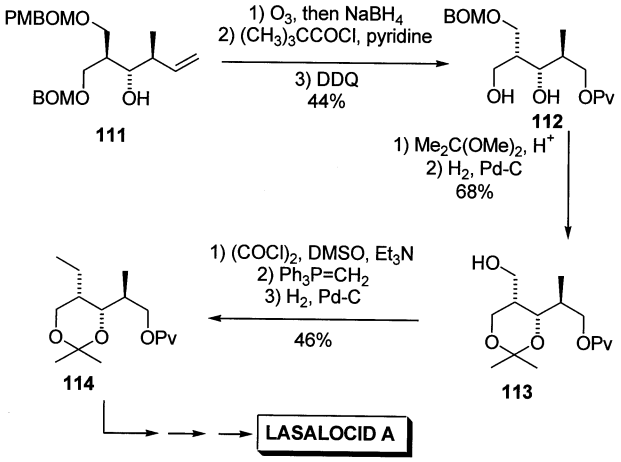
[a] TIPS = $Si(iPr)_3$; MPM = 4-$MeOC_6H_4CH_2$; PMBOM = 4-Me-$OC_6H_4CH_2OCH_2$; BOM = $PhCH_2OCH_2$.

with cyanide (entries 5 and 6) proceeded smoothly employing LiCN in tetrahydrofuran.

The products of entries 3 and 4 are particularly useful. They are indeed synthetic equivalents of the crotylation adducts of BHYMA* (see Scheme 16), and can be viewed as synthetic intermediates for polypropionate natural products, in particular those possessing a side-chain different from methyl. This unusual side-chain (for example a COOH in Streptovaricin, or an ethyl group in the Lasalocid family) can be actually constructed from one of the two residual CH_2OH groups of our synthons. Since the compounds obtained by the here described method have an *anti* relative configuration at C-3 and C-4, the protocol olefination-epoxidation-cuprate opening is in some way complementary with direct crotylation of BHYMA*, which allowed an easier access to C-3/C-4 *syn* isomers.

As a first application, we recently reported the synthesis of a fragment of polyether antibiotic Lasalocid A (Scheme 23).[36] For this purpose, the adduct **111** was converted, by protecting group interchange reactions, into the isopropylidene derivative **113**, taking advantage of the orthogonality of BOM and PMBOM protections. The transformation of CH_2OH into ethyl was first attempted by conversion into the corresponding tosylate and coupling with Me_2CuLi. Surprisingly, although this strategy has previously proved very efficient in the synthesis of Talaromycin A (Scheme 8) in this case it failed to give any of the desired product **114**. This problem was overcome by a three step sequence involving Wittig methylenation of the aldehyde corresponding to **113**, followed by hydrogenation. **114** is a known intermediate for the synthesis of the natural product.

Scheme 23



6. Elaborations Through Stereospecific Degradations

In all the elaborations of THYM* previously described, the intermediates obtained maintained the branching typical of these building blocks. However, if stereospecific degradation of one of the three synthetically equivalent CH_2OH groups were possible, THYM* could be also be a precursor of a myriad of unbranched chiral building blocks.

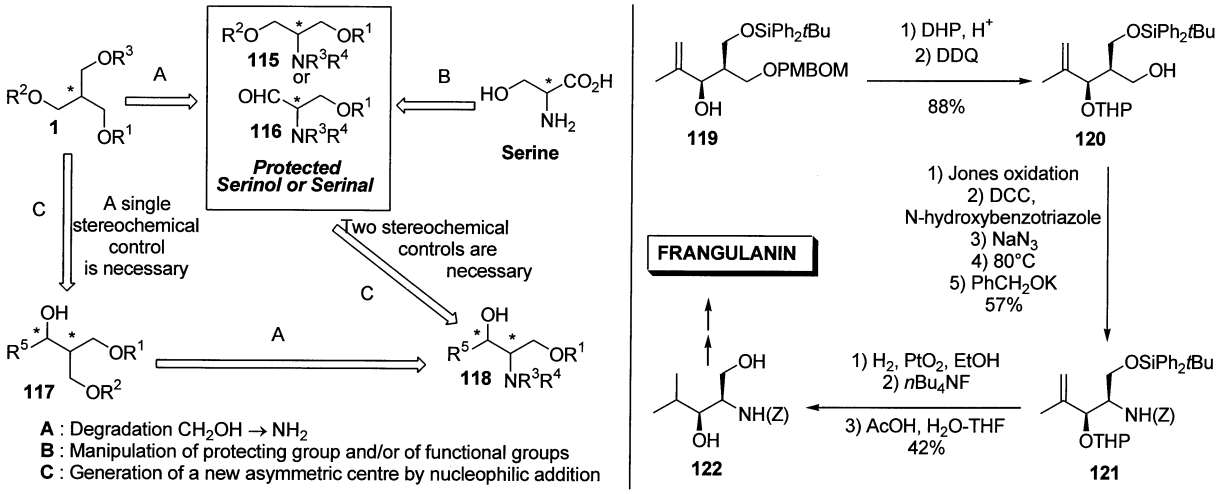
As an example of this concept, we recently reported the stereospecific Curtius degradation of synthons derived from

Table 10. Regioselective opening of epoxides **106** with C-nucleophiles[a]

Entry	R^3	R^1	R^2	R^4	Reagent	Additive	Yield	**109**:**110**	Ref.
1	Me	PMBOM	BOM	*n*Bu	$nBu_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	69%	94:6	35
2	Me	TIPS	MPM	*n*Bu	$nBu_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	72%	93:7	35
3	Me	PMBOM	BOM	CH_2=CH-	$(CH_2{=}CH)_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	84%	94:6	36
4	Me	TIPS	MPM	CH_2=CH-	$(CH_2{=}CH)_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	75%	90:10	36
5	Me	PMBOM	BOM	CN	LiCN	none	63%	> 99:1	35
6	Me	TIPS	MPM	CN	LiCN	none	65%	> 99:1	35
7	*n*Pr	PMBOM	BOM	*n*Bu	$nBu_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	57%	> 99:1	35
8	*n*Pr	TIPS	MPM	*n*Bu	$nBu_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	52%	> 99:1	35
9	*n*Bu	PMBOM	BOM	*n*Pr	$nPr_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	52%	> 99:1	35
10	*n*Bu	TIPS	MPM	*n*Pr	$nPr_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	49%	> 99:1	35

[a] TIPS = $Si(iPr)_3$; MPM = 4-$MeOC_6H_4CH_2$; PMBOM = 4-$MeOC_6H_4CH_2OCH_2$; BOM = $PhCH_2OCH_2$.

Scheme 24



THYM*, as a new, highly stereodivergent route for aminodiols.[12] As shown in Scheme 24, the aminodiols of general formula **118** can be reached from **1** by two different strategies: (a) Stereospecific degradation of a side-arm of **1** to give an amino group, followed by diastereoselective additions to the resulting serinal **116**, or (b) diastereoselective addition to BHYMA* derived from THYM* followed by stereospecific degradation.

The first strategy does not present particular advantages over the one starting from the two enantiomers of serine, which are commercially available. On the other hand the second methodology presents the advantage of a higher degree of stereodivergency. Actually, as already pointed out before, both diastereoisomers of a given protected triol of general formula **117** are available with a single stereochemical control, by exploiting the latent C_{3v} symmetry of THYM*. On the contrary, starting from **116**, which has only a latent C_S symmetry, different conditions for the obtainment of both diastereoisomers must be established.

An implementation of this concept is given by the synthesis of protected aminodiol **122**, which is a known intermediate in the synthesis of alkaloid Frangulanin.[12]

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