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ASYMMETRIZED *TRIS* (HYDROXYMETHYL)METHANE AS A HIGHLY STEREODIVERGENT CHIRAL BUILDING BLOCK: PREPARATION OF ALL FOUR STEREOISOMERS OF PROTECTED 2-HYDROXYMETHYL-1,3-BUTANEDIOL[1]

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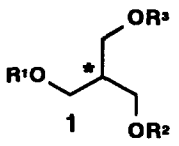
Summary : Monoacetate 3 is a synthetic equivalent of asymmetrized *tris* (hydroxymethyl)methane 1, which is a new chiral building block endowed with latent C_{3v} symmetry. Thanks to this property, starting from a single enantiomer 3, it is possible to get not only both (R) and (S) aldehydes 7, but also all the stereoisomers deriving from addition of a C-nucleophile to 7, just relying on a single diastereocontrol (double stereodivergency).

The two main problems often encountered in the asymmetric syntheses involving small chiral building blocks belonging to the "chirality pool" arise from the fact that: a) some of these units are actually easily available only in one enantiomeric form; b) during the creation of a new chiral centre it is not an easy task to find conditions allowing the synthesis of both possible diastereoisomers with high stereocontrol.[2]

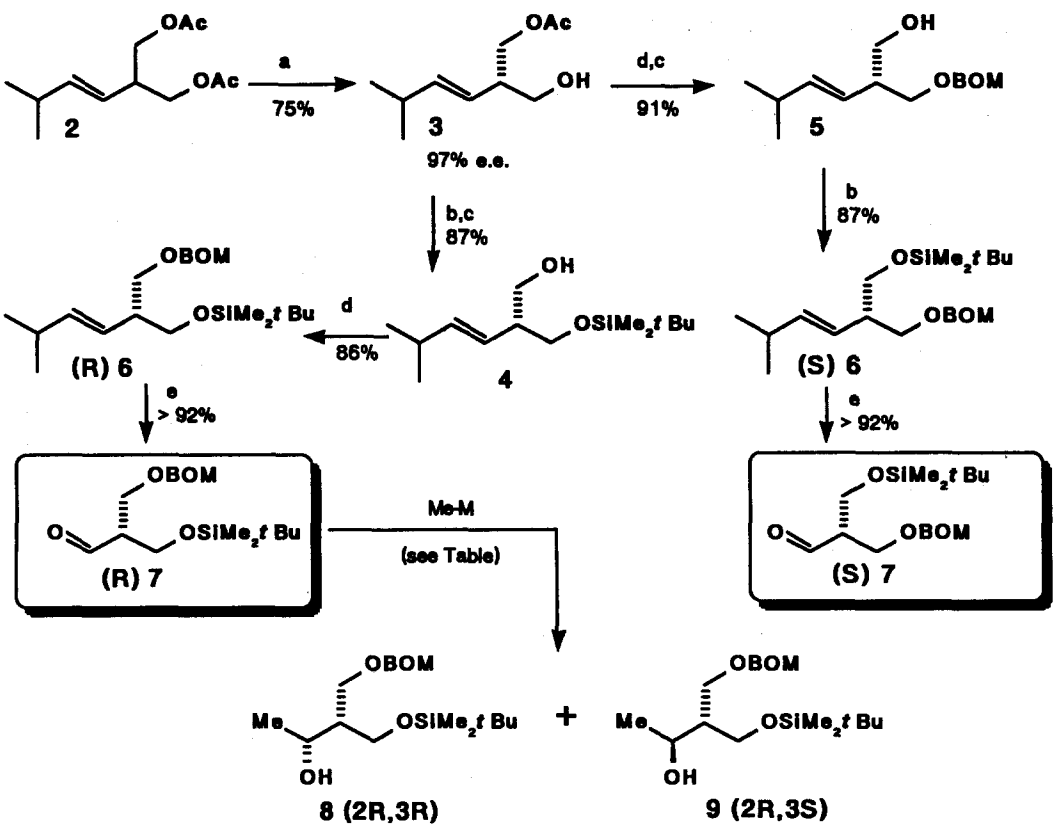


Here we wish to show how the new chiral C-4 building block 1 [asymmetrized *tris* (hydroxymethyl)methane (THYM*)], recently synthesized by us,[3] allows, thanks to its latent C_{3v} symmetry, the easy overcoming of both the above mentioned problems. As a first example of these properties, we report the fully stereodivergent[4] preparation of all possible stereoisomers of variously protected 2-hydroxymethyl-1,3-butanediols, starting from a single chiral precursor.

Scheme 1 describes the solution of the first problem: monoacetate 3, which is a synthetic equivalent of 1, and which is obtained in good yield and excellent enantioselectivity by pig pancreatic lipase catalysed monohydrolysis of diacetate 2,[3b] was converted by an equal number of steps, and in high yield, into both (R) and (S) aldehydes (7), simply by reversing the order of protective group introduction.[5]

We then examined the stereochemical course of condensation of methyl-metal compounds with these aldehydes.[6] It should be pointed out that 7 possesses two differently protected hydroxymethyl groups and that therefore chiral discrimination can rely only on the different nature of protecting groups. The results reported in the Table clearly indicate that, while conventional reagents like organolithium or organomagnesium derivatives show only modest levels of induction, excellent diastereoselection was achieved by employing lithium dimethylcuprate as nucleophile.[7] The high stereoselection is most likely ascribable to a chelated transition state, taking into account the known[8] propensity of dialkyl lithium cuprates for β-chelated transition states, and the low tendency of silyl ether to coordinate metal ions, both for electronic and steric reasons.[9] This is an example of protecting group directed diastereoselection.[10,11]

SCHEME 1



a) PPL, H_2O / iPr_2O 85:15, pH 7 (see ref. 4); b) $tBuMe_2SiCl$, DMF, Imidazole, R.T.; c) 0.1 N KOH in MeOH; d) $PhCH_2OCH_2Cl$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, R.T.; e) O_3, CH_2Cl_2/MeOH, -78°C; then Me_2S, R.T., 5h.

How can the other diastereoisomer be prepared efficiently? In the case of aldehyde 7, even if conditions avoiding chelation were employed, the Felkin open-chain model for asymmetric induction in the nucleophilic addition to carbonyl anticipates a low diastereoselection and still predicts 8 as the favoured product. However in this case we can benefit by the residual latent C_S symmetry still present in the right hand of 8, converting this adduct, by simple protecting group interchanges, *into* doubly protected triols of both diastereomeric series. This concept had been implemented as indicated in Scheme 2 and illustrated schematically in Scheme 3 . Thus we can conclude that monoacetate 3, which is a convenient synthetic equivalent of 1, is the first doubly stereodivergent building block,[4] since not only it can afford both aldehydes (R) and (S) 7 at will (enantiodivergency), but also, when these aldehydes are elongated with concurrent creation of a new chiral centre, a single type of stereocontrol is sufficient to give access to both possible epimers (diastereodivergency). As a consequence, all four stereoisomers of a given doubly protected 2-hydroxymethyl-1,3-butanediol are easily synthesized starting from the same chiral precursor (S) 3.

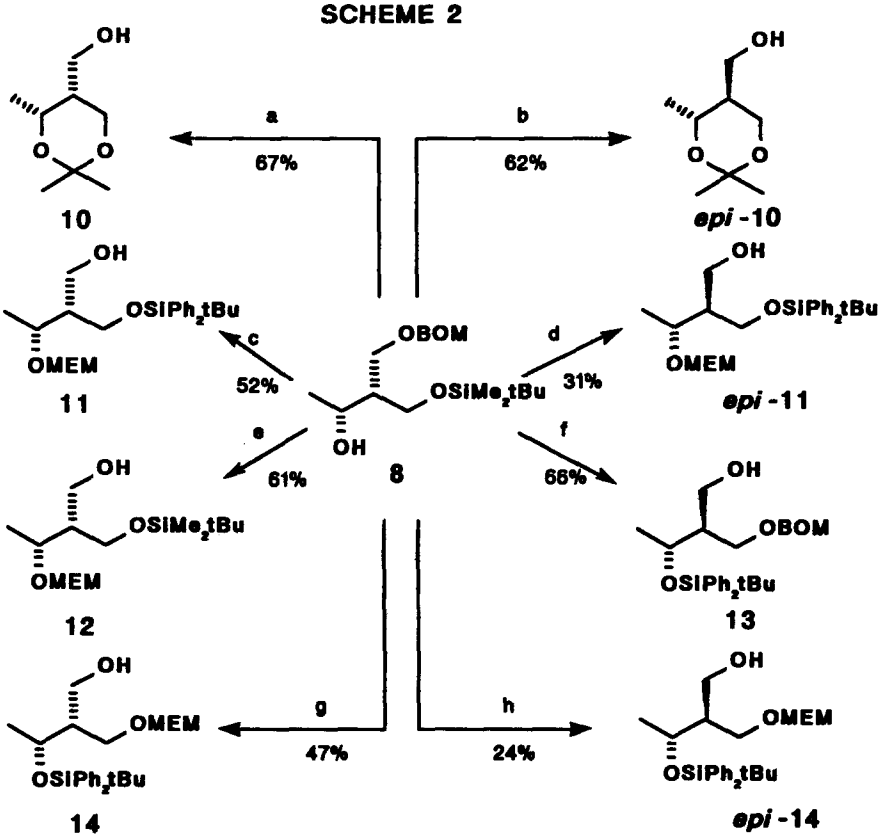
It should also be noted that compounds 11-14 still bear two protecting groups that can be

TABLE: Diastereoselection in methyl-metal additions to aldehyde (R) 7

Entry	Me-M	Solvent	Temperature	Yield[a]	8 : 9 ratio[b]
1	Me-Li	THF	-78°C	77%	54 : 46
2	Me-Li	Et_2O	-78°C	79%	52 : 48
3	Me-MgBr	Et_2O	-78°C→-20°C	55%	58 : 42
4	Me-MgI	Et_2O	-78°C→-20°C	69%	59 : 41
5	Me-MgCl	THF	-78°C→-20°C	61%	57 : 43
6	$MeCu{\cdot}MgBr_2$	Et_2O/ Me_2S	-78°C→-25°C	53%	82 : 18
7	Me_2CuLi	Et_2O	-78°C→-30°C	74%	95 : 5

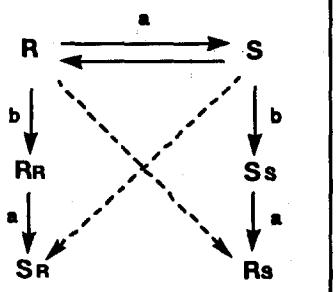
a) Isolated yields from 6 (2 steps); b) determined by ^1H n.m.r. of crude products in the presence of Yb(FOD)$_3$;

SCHEME 2



a) 1) *n*-$Bu_4NF{\cdot}3\ H_2O$, THF, R.T., 81%; 2) $H_2C{=}C(Me){-}OMe$, *p*-TSA, CH_2Cl_2, 0°C, 99%; 3)H_2, Pd-C, $CaCO_3$, EtOH, 84%. b) 1) H_2, Pd-C, $CaCO_3$, EtOH; then $H_2C{=}C(Me){-}OMe$, *p*-TSA, CH_2Cl_2, 0°C, 85%; 2) *n*-$Bu_4NF{\cdot}3\ H_2O$, THF, 0°C, 96%. c) 1) MEM-Cl, Et_3N, CH_3CN, reflux, 24 h, 73%; 2) *n*-$Bu_4NF{\cdot}3\ H_2O$, THF, 0°C, 95%; 3) Ph_2*t*-BuSiCl, imidazole, DMF, 24 h at R.T. + 8 h at 50°C, 86%; 4) H_2, Pd-C, EtOH, 87%; d) 1 and 2) see c; 3) Ph_2*t*-BuSiCl, imidazole, DMF, 18h, R.T., 91%; 4) pyridinium tosylate, EtOH, 60°C, 5h (ref. 12), 55%; e) 1) MEM-Cl, Et_3N, CH_3CN, reflux, 24 h, 73%; 2) H_2, Pd-C, $CaCO_3$, EtOH, 83%; f) 1) Ph_2*t*-BuSiCl, imidazole, DMF, 85°C, 10h, 88%; 2) pyridinium tosylate, EtOH, 60°C, 8h, 75%. g) 1 and 2) see f; 3) MEM-Cl, Et_3N, CH_3CN, reflux, 18h, 79%; 4) H_2, Pd-C, EtOH, 90%. h) 1) Ph_2*t*-BuSiCl, imidazole, DMF, 85°C, 10h, 88%; 2) H_2, Pd-C, $CaCO_3$, EtOH, 71%; 3) MEM-Cl, Et_3N, CH_3CN, reflux, 28h, 64%; 4) pyridinium tosylate, EtOH, 65°C, 4h, 61%.

SCHEME 3



a: protecting group interchange trick
b: chelation-controlled condensation

classified as "chelating" (MEM, BOM) or "non-chelating" (Me_2t BuSi-, Ph_2t BuSi-). In **11**, ***epi*-11**, and **12**, the "non-chelating" group is on the primary OH, while the "chelating" group is on the secondary one. The situation is reversed for **13**, **14** and ***epi*-14**. Therefore these compounds offer a complete range of options for further chelation-controlled condensations.

Utilization of this new C-4 chiral building block in the synthesis of biologically active compounds, as well as other applications of the double stereodivergency concept are in progress in our laboratory.

We wish to thank Chiara Ghiron for her enthusiastic collaboration in this work.

REFERENCES AND NOTES

1) Presented in part at the fifth IUPAC Symposium on Organometallic Chemistry directed towards Organic Synthesis, October 1-6, 1989, Firenze (Italy).
2) A straightforward solution to this problem can be given, whenever possible, by the double asymmetric synthesis (see Masamune S., Choy W., Petersen J.S., and Sita L.R., *Angew. Chem., Int. Ed. Engl.* , **1985**, *24* , 1).
3) a) Guanti G., Banfi L., and Narisano E., *Tetrahedron Lett.* , **1989**, *30* , 2697; b) Guanti G., Banfi L., and Narisano E., *Tetrahedron:Asymmetry* , in press.
4) "Stereodivergent", "enantiodivergent", or "diastereodivergent" synthesis means the stereoselective (enantioselective, diastereoselective) preparation of both possible stereoisomers (enantiomers, diastereoisomers) from a common stereoisomerically pure intermediate. These expressions have been previously used by other authors (representative examples: Bartlett P.A., Meadows J.D., and Ottow E., *J.Am.Chem.Soc.*, **1984**, *106* , 5304; Jefford C.W., Jaggi D., and Boukouvalas J., *Tetrahedron Lett.*, **1986**, *27* , 4011; Takano S., et al., *Chem. Lett.* , **1987**, 2017; *J. Chem. Soc., Chem. Commun.*, **1988**, 1538; cfr. also Trost B.M., Timko J.M., and Stanton J.L., *J. Chem. Soc., Chem. Commun.* , **1978**, 436 for the use of the complementary word "stereoconvergent"). We use the term "doubly stereodivergent building block" as a concise way to indicate a building block that can be elaborated twice in a stereodivergent manner. This property thus allows, in the present case, enantio- and diastereodivergency. To the best of our knowledge this represents the first example of this concept.
5) These aldehydes were not isolated, but used as such for further reaction; 92% was the yield of chromatographed alcohol after $NaBH_4$ reduction of (R) and (S) **7**.
6) For the sake of conciseness the addition of methyl-metal compounds listed in the Table and the transformations described in Scheme 2 are shown only starting from the (R) **7** aldehyde. However these reactions can be obviously carried out in the same way starting from (S) **7**.
7) Mosher ester analysis of compound **8**, obtained by Me_2CuLi addition, showed that its synthesis proceeded with negligible racemization.
8) Still W.C., and Schneider J.A., *Tetrahedron Lett.*, **1980**, *21* , 1035.
9) Frye S.V., Eliel E.L., and Cloux R., *J.Am.Chem.Soc.*, **1987**, *109* , 1862; Kahn S.D., Keck G.E., and Hehre W.J., *Tetrahedron Lett.*, **1987**, *28* , 279; Keck G.E., and Castellino S., *Tetrahedron Lett.*, **1987**, *28*, 281.
10) Representative examples: Nakata T., Tanaka T., and Oishi T., *Tetrahedron Lett.*, **1983**, *26* , 2653; Evans D.A., Morrissey M.M., and Dow R.L., *Tetrahedron Lett.*, **1985**, *26*, 6005; Reetz M.T., and Hullmann M., *J. Chem. Soc., Chem. Commun.*, **1986**, 1600; Hanamoto T., Katsuki T., and Yamaguchi M., *Tetrahedron Lett.*, **1987**, *28* , 6191;
11) The relative configuration of **8** was determined by ^1H n.m.r. of **10** and ***epi* -10**, showing a $J_{2,3}$ = 2.8 Hz. for **10** and = 9.7 Hz. for ***epi*-10**, in agreement, respectively, with *cis* and *trans* arrangements.
12) Prakash C., Saleh S., and Blair I.A., *Tetrahedron Lett.*, **1989**, *30* , 19.

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