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ENZYMES AS SELECTIVE REAGENTS IN ORGANIC SYNTHESIS: ENANTIOSELECTIVE PREPARATION OF "ASYMMETRIZED *tris* (HYDROXYMETHYL)METHANE"

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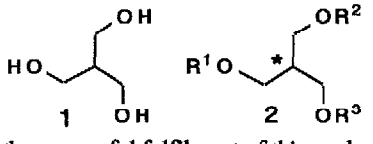
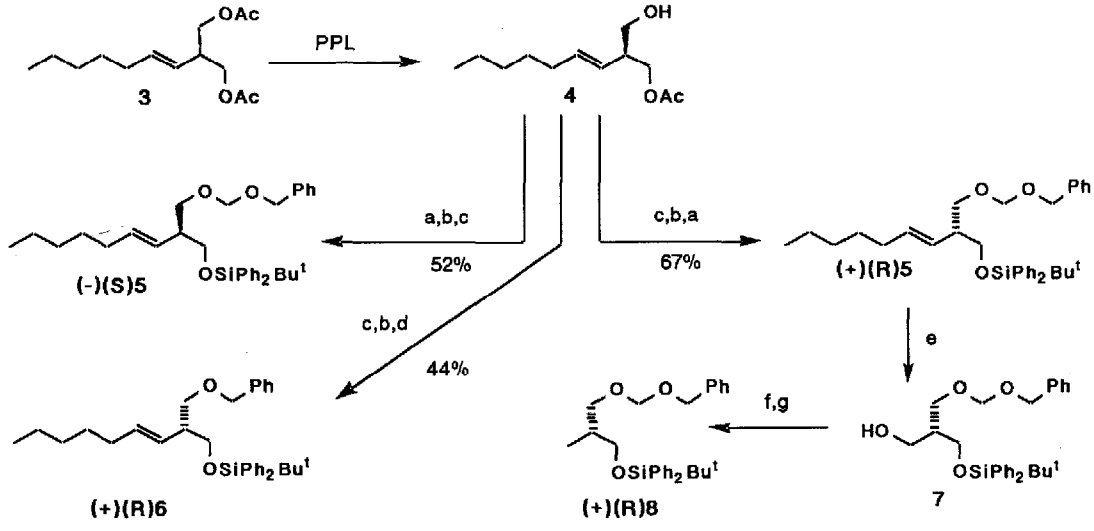
Summary : A new C-4 chiral building block, that is a *tris* (hydroxymethyl)methane derivative where the three equivalent hydroxymethyl groups have been differentiated [(THYM)*], was prepared with excellent enantioselection, through PPL catalysed monohydrolysis of prochiral diacetate 3.

In the course of a research program directed toward the preparation of new "chiral building blocks" through enzyme-catalysed reactions,[1] we were attracted by the structure of the fairly symmetric *tris* (hydroxymethyl)methane (THYM) 1. Since a primary alcohol is probably the most synthetically useful moiety, allowing a variety of functional group interchanges as well as C-C bond forming reactions, 1 can be regarded as a useful starting material for nearly all molecules possessing a tertiary carbon centre. In order to make this centre chiral it is necessary to distinguish the three equivalent hydroxymethyl groups or, in other words, to prepare an "asymmetrized *tris* (hydroxymethyl)-methane" (THYM)*, like for example 2 where $R^1 \neq R^2 \neq R^3$. In this communication we wish to report the successful fulfilment of this goal, using an enantioselective enzyme catalysed hydrolysis as key step.



A first possibility to accomplish our purpose is the hydrolysis of diacetates 2 ($R^1 = R^2 = OAc$; R^3 = various protecting groups). However, although this approach is simplest in principle, we experienced some difficulties and have not yet been able to achieve successful results.[2]



a) $ClCH_2OBzl$, iPr_2EtN, CH_2Cl_2; b) KOH/MeOH; c) $ClSiPh_2tBu$, imidazole, DMF; d) BzlBr, NaH, DMF; e) 1. O_3; 2. Me_2S; 3. $NaBH_4$, 60%; f) TsCl, Et_3N, DMAP, CH_2Cl_2; g) $NaBH_4$, DMSO, 60°C, 52% from 20.

Table: Enzymatic hydrolysis of diacetate 3 to monoacetate 4

Entry	Solvent	Yield	$[\alpha]_D$[a]	e.e.	Configuration
1	H_2O[b]	49%	-17.3°	84%[c] (76%)[d]	S
2	H_2O[b]/THF 85:15	62%	-18.6°	85%[c] (82%)[d]	S
3	H_2O[b]/*t*BuOH 90:10	59%	-19.3°	93%[c] (89%)[d]	S
4	H_2O[b]/*i*Pr_2O 85:15	63%	-21.8°	96%[c]	S

a) c 2, $CHCl_3$; **b**) 0.05 M phosphate buffer (pH=7); **c**) Determined at ^1H n.m.r. in the presence of $Eu(hfc)_3$, by integration of $CH_3C{=}O$ signals; **d**) Calculated from the $[\alpha]_D$, by comparison with that of entry 4;

Since a disubstituted double bond can be easily ozonolysed and thus regarded as synthetically equivalent of an aldehyde or of a primary alcohol, we envisioned an alternative approach involving a 2-alken-1-yl-1,3-propanediol diacetate like 3 as intermediate. Moreover a careful examination of the scarce literature data[3] on the enzymatic hydrolysis of 2-substituted 1,3-diacetoxypropanes suggested that, at least in the case of PPL, the presence of a II system near the prochiral centre seems to have a beneficial effect on the enantioselectivity.[4,5] **3** was synthesized in three steps from inexpensive starting materials,[6] and hydrolysed in the presence of pig pancreatic lipase (PPL).[7] Although a satisfactory result, both with regard to chemical yield and enantioselectivity (see Table), was obtained using water as reaction medium (entry 1), we found a clear improvement of both yield and e.e. by carrying out the reaction in the presence of cosolvents like *t*-BuOH, THF, and di*iso* propylether.[8] Under the best conditions (entry 4), we obtained **4** in 63% yield and 96% e.e.! The optically active monoacetate **4** was then transformed into some representative "asymmetrized *tris*(hydroxymethyl)methane equivalents", as depicted in the Scheme. It is worth noting that both (-) and (+) **5** have been synthesized from the common precursor **4** simply by inverting the order of introduction of protective groups. A great advantage of **4** is indeed the interchangeability of the three masked hydroxymethyl groups. Ozonolysis of (+) **5**, followed by $NaBH_4$ reduction gave the alcohol **7**. Its absolute configuration was unambiguously established as (R), through conversion into (R) **8**, which had the same $[\alpha]_D$ of an authentic sample prepared from commercially available (S)(+) methyl 3-hydroxy-2-methyl-propanoate ($[\alpha]_D$ (c 1, $CHCl_3$)= + 6.0° and + 5.96° respectively). This rotatory power shows also that the protection-deprotection steps used in this Scheme are not racemizing, at least within the limits of $[\alpha]_D$ accuracy.

In conclusion, the here reported method allows an easy preparation of variously protected "asymmetrized *tris* (hydroxymethyl)methane equivalents" whose utility as chiral building blocks is potentially wide. Synthetic applications are in progress.[9]

REFERENCES AND NOTES

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2) Details on preparation of these diacetates and on their enzymatic hydrolyses will be reported in a forthcoming full paper.

3) a) Y.F. Wang, C.J. Sih, *Tetrahedron Lett.*, 4999 (1984); b) G.M. Ramos Tombo, H. P. Schaer, X. Fernandez I Busquets, and O. Ghisalba, *Tetrahedron Lett.*, 5707 (1986); c) D. Breitgoff, K. Laumen, and M.P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1523 (1986); d) V. Kerscher, W. Kreiser, *Tetrahedron Lett.*, 531 (1987); e) M. Eberli, M. Egli, and D. Seebach, *Helv. Chim. Acta, 71*, 1 (1988); f) Y.F. Wang, C.H. Wong, *J.Org.Chem., 53*, 3127 (1988).

4) For example 1,3-diacetoxy-2-phenyl-propane gave >95% e.e. while 1,3-diacetoxy-2-cyclohexyl-propane afforded only 60% e.e. (ref. 3b).

5) After completion of this work, a report appeared where the importance of a double bond near the prochiral centre in a PLE catalysed reaction is noted: M. Nakada, S. Kobayashi, M. Ohno, S.Iwasaki, and S. Okuda, *Tetrahedron Lett.*, 3951 (1988).

6) Preparation of **3**: 1) diethyl malonate, heptaldehyde, piperidinium acetate; 2) a) LDA, THF, HMPA; b) H_2O, 77%; 3) a) $LiAlH_4$, Et_2O; b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 83%.

7) Crude PPL, purchased from Sigma (code L 3126). All enzymatic reactions were carried out at pH 7 and at a temperature of 22°C in buffered media (0.025-0.1 M phosphate buffer), maintaining the pH constant by addition of 1N NaOH from an automati burette and working out the reaction after consumption of 1 equivalent of base.

8) The use of THF and di*iso* propylether as cosolvents in PPL catalysed reactions was already reported (ref. 3c and 3d); *t*BuOH w shown by us to improve dramatically the selectivity in a PLE catalysed hydrolysis (ref. 1c).

9) We wish to thank the Ministero della Pubblica Istruzione, the C.N.R., and the European Economic Community (Stimulation Action) for funding, and miss Cristina Soncini for her appreciated assistance.

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