Polyhydroxylated Chiral Building Block by Enzymatic Desymmetrization of Meso 1,3 Syn Diols

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Summary: A new seven-carbon polyhydroxylated chiral synthon is obtained, as single enantiomer, in nearly quantitative yield by enzymatic desymmetrization of the appropriate meso compound. *Pseudomonas fluorescens* shows an high degree of enantiotopic discrimination in a particularly complex molecule possessing a 1,3 syn diol structure; likewise, this chiral synthon has been easily transformed into a known compactin analogue.

Optically active functionalized diols and polyols of defined stereochemistry are valuable synthetic intermediates. Among them the 1,3 polyols or skipped polyols are of strategic importance in the synthesis of many natural products such as mevinic acids[1] and polyene macrolide antibiotics.[2] Many synthetic methodologies leading to skipped polyols have been developed, employing chiral starting material obtained by both chemical and biocatalytic transformations.[3]

To this end we have recently developed[4] a biocatalytic lactonization of 3,5-*syn*-dihydroxy esters of type 1 (see Figure 1) by means of porcine pancreatic lipase (PPL) in organic solvent (ether). This key step was used for the synthesis of optically active 3-hydroxy, 5-substituted δ-lactones of type **2** as mevinic acid analogs[4] or naturally occurring δ-lactones.[5] Although the optical purity of the obtained compounds (ee from 86 to 98%) was highly valued, the theoretical yield of the chiral lactones is 50% (racemic resolution): in practice it was considerably lower because, in order to avoid the competitive reaction of the unwanted enantiomer, the reaction must be stopped at a low conversion stage (30–40%).

This problem could be solved, in principle, if the substrate is a meso of prochiral compound (i.e., a meso compound of type **3**). In this case a suitable enzymatic specificity to discriminate between the two enantiotopic groups (R or R') would lead to an extremely useful seven-membered chiral polyhydroxylated synthon like **4** or **4'** which possess a syn relationship between the 1,3 diol and different substituents (X) to be properly elaborated.

Our first designed model, possessing a 1,3 syn diol system, was the polyhydroxylated compound **9** and its diacetyl derivative **10** (Scheme I), where we determined a possible enzyme discrimination between the two primary hydroxyl groups. In designing such a model the choice of

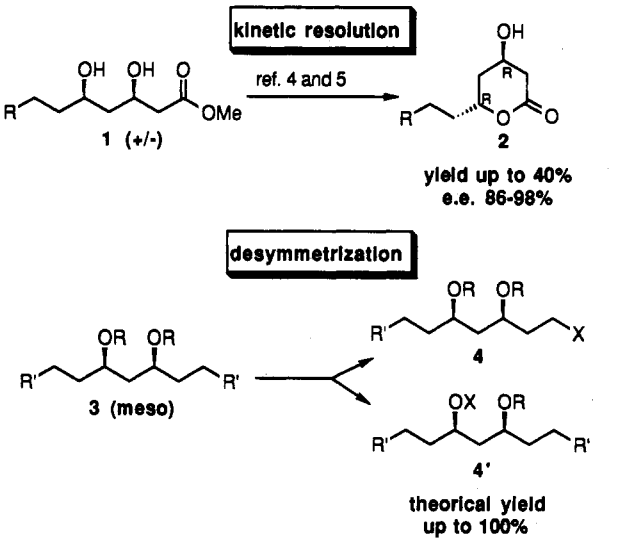
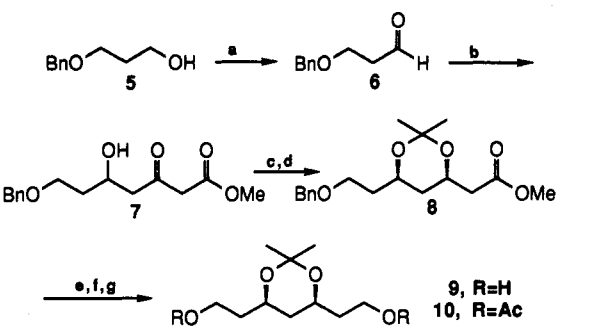


Figure 1.

Scheme I[a]



[a] (a) PCC, 78%; (b) CH_3COCH_2COOMe, NaH, nBuLi, 0 °C, 38%; (c) Et_3B/MeOH, $NaBH_4$, in THF, 66%; (d) $(CH_3)_2C(OCH_3)_2$, TsOH, 95%; (e) $LiAlH_4$, THF, 95%; (f) Pd/C, H_2, 85%; (g) Ac_2O, Py, 98%.

the protection of the 1,3 diol as acetonide was quite crucial; we expected that a sufficiently rigid conformation of the six-membered ring would be helpful for the enzymatic reaction. We were also aware that, in our designed substrate, the two carbons' distance between the enantiotopic groups (OR) and the chiral centers would be a possible drawback to a high enantiotopic discrimination. In fact, so far, the use of enzymes (i.e., hydrolases or esterases) in similar oxygenated compounds has been successfully employed only in simpler substrates.[6]

The preparation of the substrates **9** and **10** was achieved as shown in Scheme I. The aldol condensation between aldehyde **6** and methyl acetoacetate and the subsequent

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(1) For a recent paper see: Brower, P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2279–2282 and references cited therein.

(2) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984, 351–552.

(3) For a recent review see: Oishi, T.; Nakata, T. *Synthesis* **1990**, 635–645.

(4) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050–4052.

(5) Bonini, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron Asymmetry* **1992**, *3*, 29–32.

(6) For related building blocks based on 1,3 syn diol polyols prepared by enzymatic hydrolysis see: (a) Xie, Z.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1650–1652. (b) Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 736–738. For a recent review on the preparation of useful synthons by enzymes see: Xie, Z. *Tetrahedron Asymmetry* **1991**, *2*, 733–750 and references cited therein.

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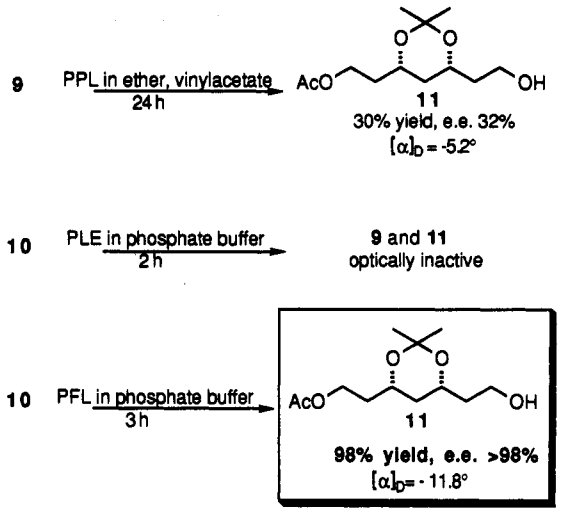
Scheme II



diastereoselective reduction[7] of the aldol 7 to the syn 1,3 diol still requires improvement, while the protection as acetonide proceeded quantitatively to compound 8. The subsequent reduction of the carbomethoxy group and the debenzylation reaction, although particular care was required,[8] resulted smoothly in the meso compound 9 and, after acetylation, in compound 10.

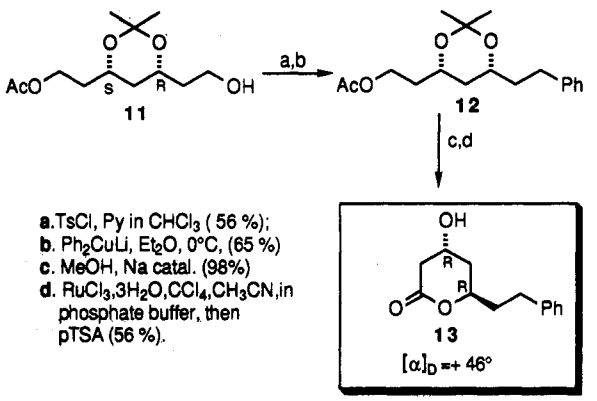
With our substrates in hand we have utilized some commercially available enzymes such as porcine pancreatic lipase (PPL), pig liver esterase (PLE), and *Pseudomonas fluorescens* lipase (PFL).[9]

As shown in Scheme II, compound 9 was first submitted to a biocatalytic transesterification in organic solvent with PPL in ether and vinyl acetate.[10] The slow reaction, stopped after 24 h, afforded, with fair yield and some diacetyl product, the optically active monoacetyl derivative 11 whose enantiomeric excess was measured to be 32%.[11]

Then we examined the enzymatic hydrolysis of compound 10, with PLE in phosphate buffer solution;[12] monoacetylated product 11 in low yield was isolated (together with some deacetylated compound 9) which did not show any optical activity.

Finally, 10 was submitted (on a 1-g scale)[13] to PFL in phosphate buffer solution affording, after 5 h, a single

Scheme III



product in a nearly quantitative yield (98%). The product was shown to be the previously isolated enantiomer 11 (with a superior value of optical rotation) but optically pure (ee >98%).

In order to determine the absolute configuration and to show a first utilization of this new chiral synthon, compound 11 was easily transformed into the (3*R*,5*R*) lactone 13, which is a well-known compactin analog (see Scheme III).[14] This transformation was accomplished first by introducing the phenyl substituent, affording compound 12, and then by deacetylation and subsequent oxidation[15] and lactonization to 13. Then the absolute configuration of 13 was established (by the sign of the optical rotation, $[\alpha]_D = +46°$)[14] to be 3*R*,5*R*; thus, the absolute configuration of compound 11 must be 3*S*,5*R*.

Noteworthy is the possibility, by differently utilizing the two primary hydroxyl groups by standard protection–deprotection chemistry, to prepare compounds of opposite absolute configuration. Furthermore, the direct coupling of the tosyl derivative with any different organocuprate reagent would allow the preparation of all kinds of 3,5-*syn*-dihydroxy compounds in an optically active form.

In conclusion, these reported results clearly indicate a somewhat surprisingly but welcome ability of the enzyme (PFL) to accomplish a previously unreported desymmetrization of polyhydroxylated compounds: this result prompts us to explore other enzymes in order to obtain the other enantiomer. The obtention of a complex chiral building block as compound 11 is intended to be further utilized for the synthesis of 1,3 skipped polyols and related natural products. Quite interesting will be also the investigation of the enantiotopic discrimination by enzymes on more complex polyhydroxylated molecules in meso form; some of those have been already desymmetrized by chemical methods.[16]

Supplementary Material Available: Experimental procedures and ^1H and ^{13}C NMR spectra (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Chen, K. M.; Gunderson, K. G.; Hartmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926.

(8) The acetonide protective group was shown to be highly sensitive to acid traces, with subsequent deprotection and/or rearrangement. To avoid such problems silica gel chromatography ($CHCl_3$/MeOH as eluent) was carried out with the use of $CHCl_3$ passed through a basic alumina column before use. Related to this the benzylation step, leading to compound 9, was shown to be unsuccessful with other commonly used methods (i.e., cyclohexene in EtOH) and must be carried out as described in order to avoid the acetal rearrangement.

(9) Pig liver esterase (PLE EC 3.1.1.1 of type I) and crude porcine pancreatic lipase (PPL EC 3.1.1.2 of type II) were obtained from Sigma Chemical Co. *Pseudomonas fluorescens* lipase (PFL EC 3.1.1.2) was purchased from Fluka.

(10) The classical procedure described by Klibanov was employed; see: Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114–118 and references therein.

(11) The enantiomeric excess was easily determined by ^1H-NMR (200-MHz) analysis with the use of Eu(hfc)$_3$. The angular geminal methyls of acetonide show a large splitting in the chemical shift values, and the integration area can be easily calculated.

(12) See ref 13 for a related procedure.

(13) Compound 10 (1 g, 34.6 mmol) was suspended in a 0.2 M phosphate buffer solution (60 mL, pH = 7). Then PFL (238 mg) was added, and the pH was kept at 7 by adding 1 M NaOH solution with an automatic pH starter. The reaction can be easily monitored by TLC. After 5 h the reaction was stopped with addition of AcOEt. The aqueous solution was repeatedly extracted with AcOEt, and the collected organic layers were evaporated in vacuo affording a crude mixture. After silica gel chromatography, optically active compound 11 (0.9 g, 98%) was collected as the only isolated product, $[\alpha]_D = -11.8°$, $c = 3.9\%$ in $CHCl_3$.

(14) See refs 4 and 6b and: (a) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101–2104. (b) Bonadies, F.; Di Fabio, R.; Gubbiotti, A.; Mecozzi, S.; Bonini, C. *Ibid.* **1987**, *28*, 703–707. (c) Roth, D. D.; Roark, W. H. *Ibid.* **1988**, *29*, 1255–1258. (d) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161–5169.

(15) The following modified procedure of the original one (Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938) was used in order to avoid the deprotection of the diol: Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4413–4420.

(16) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090–1091 and references cited therein.

(17) This work was partially supported by C.N.R. "Progetto Chimica Fine e Secondaria" and by a MURST grant. The authors thank Mr. Marchianò for technical assistance.