# THE DOUBLE-MESO TRICK

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Abstract : Lipase-catalyzed acetylation of a twice-prochirally shaped tetraol, 1, gave a mixture of diastereomeric diacetates from which an optically pure derivative belonging to the C_2-symmetry group could be isolated.

Optically active diols and derivatives hold a significant position in todays synthetic studies, especially where natural product chemistry is concerned. Among the numerous and still valuable preparative methods which have been devised accordingly, lipase-catalyzed esterification procedures have dramatically gained in popularity[1].

When dealing with such enzymatic processes a high level of stereoselectivity often results from the use of substrates having a plane of symmetry (scheme).


meso approach
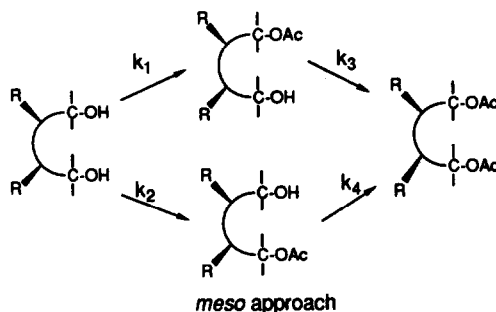
In this *meso* pathway, an improvement of the e.e. can be secured, provided the process displays some selectivity - i.e. $k_1 > k_2$; $k_4 > k_3$ - using the so-called *meso trick*[2]. Further acylation of the monoacetate mixture will consume the minor component more rapidly, hence perfecting the optical purity of the monoacetate without affecting the yield detrimentally. After separation, the diacetate can be converted back to the starting diol by full saponification. Therefore, the yield in chiral material is theoritically quantitative.

In a different context (Sharpless epoxidation of allylic diols), a similar concept of e.e. amplification has been expressed by Hoye[3] : bis-asymmetric reaction of a C_{2v} substrate, in which two identical prochiral reacting centers are linked so that a third element of symmetry -i.e. a C_2 axis - results, should occur with an enantioselectivity better than that observed (or supposed to be observed) in the corresponding mono-reaction.

During a project aimed at synthesizing spiramycin[4], we needed to prepare the chiral sulfide shown. It appeared that utilization of the tetraol 1 as starting material would provide the opportunity to extend Hoye's concept to enzyme-catalyzed esterification processes.

S₁,S₂ = aminosugars   1
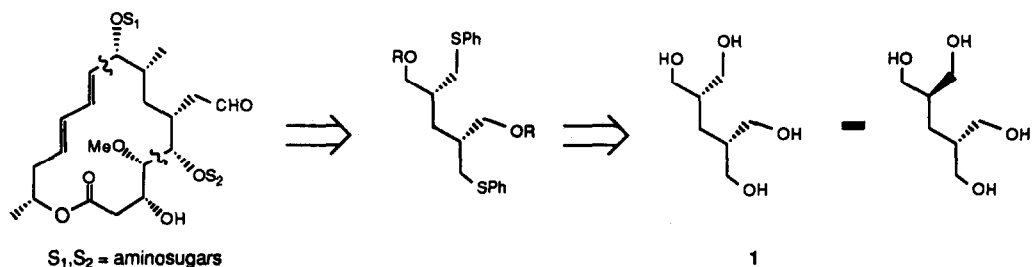
Let us suppose that any enzyme involved in biochemical acetylation of 1 will show the same *pro-R* (or *pro-S*) stereoselectivity when acting on each prochiral 1,3-propanediol terminus. It then appears that the diacetate formed on bis-acylation would belong to the C_2-symmetry group. Furthermore, in cases where this stereoselectivity would be only partial in the first step the conversion of the incipient monoacetate into the diacetate should benefit from the advantages displayed by the *meso* approach: the minor monoacetate would preferentially give the *meso* diacetate whereas the major one would form mainly the *R,R* (or the *S,S*) isomer[5]. The yield in *R,R* (or *S,S*) diacetate would stand to be high since any by-products will give back 1 upon saponification. The same reasoning applies to the reverse reaction.
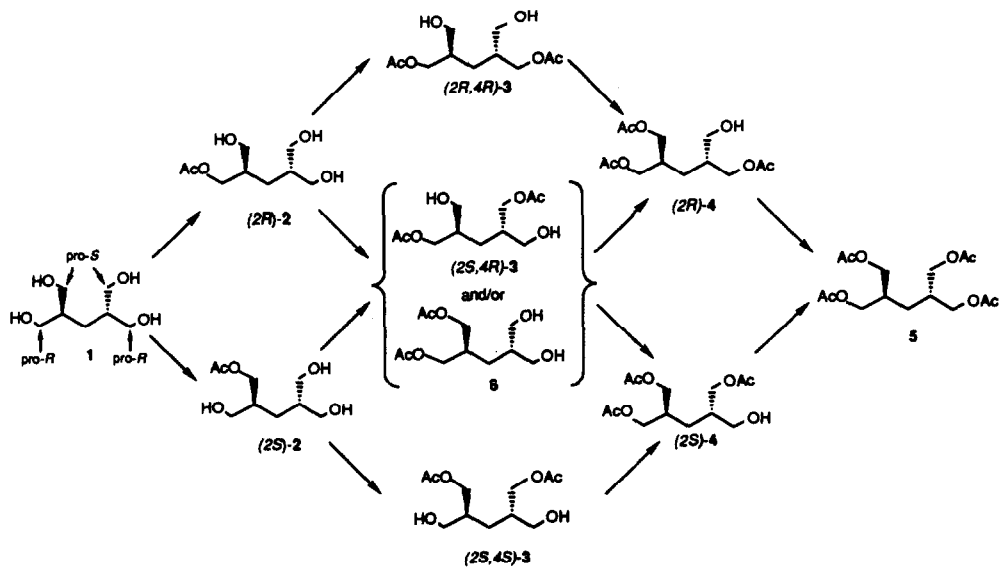

Condensation of diethyl malonate with formaldehyde[6], followed by LiAlH₄ reduction in THF (50°, 20h) gave the cristalline tetraol 1 (m.p. 130°C), which was eventually transformed into a tetraacetate 5 (Bp$_{0.9}$ 86-88°C).

Submitting 5 to hydrolytic conditions (PFL, pH7 phosphate buffer) proved very disappointing. A very slow reaction ensured less than 10% conversion after 1 month, giving the triacetate 4 (26% ; $[\alpha]_D$ -1, c=5.6) and a diacetate (41%; $[\alpha]_D$ 0), which proved to be 6 by quantitative trans-acetalisation with the dimethyl acetal of benzaldehyde under mild conditions (pyridinium tosylate, CH₂Cl₂, 10-20°). The

formation of 6, as well as the lack of selectivity, could be due to competitive chemically-induced scrambling of acetyl groups in 3.

Indeed, a more rewarding result was obtained reacting 1 under Maillard's conditions[7] (PFL, vinyl acetate in excess, THF). The TLC showed only the formation of a diacetate and the reaction was stopped as soon as some triacetate was detected (2 weeks). Chromatography (silica gel; ether/CH_2Cl_2) afforded a small amount of triacetate 4 (12%; $[\alpha]_D$ +10, c=0.8), then the diacetates 3 (78%; $[\alpha]_D$ +12, c=4.8). ^{13}C NMR spectrum of 3 clearly showed the presence of two isomeric compounds but no signal corresponding to 6. All attempts to fractionate 3 failed. This diacetate fraction was then treated with PhSSPh/PBu_3 (2 eq., 82%). To our delight, the resulting bis-sulfide mixture displayed two spots on TLC plates (1% AcOEt in hexane, several elutions) and a perfect separation was achieved on thick layer of silica gel, giving two fractions : a minor component (10%) with $[\alpha]_D$ 0 and a major component (90%) with $[\alpha]_D$ +13 (c=3.4)[8].

Both absolute configuration and optical purity were established by treating the major sulfide, which proved *vide infra* to be (2S,4S)-7, with Raney-Nickel in ethanol, then with K_2CO_3 in methanol. The resulting diol was (2S,4S)-2,4-dimethyl-1,5-pentanediol, 8, with $[\alpha]_D$ -37, c=2.4 in MeOH (litt[9] : $[\alpha]_D$ -34 ; c=2.4 in MeOH). Our product was therefore enantiomerically pure and the selectivity of PFL is accordingly *pro-R*. The main results are summarized below. Alternatively, silylation of acetates 3 (DPTBSCl, imidazole, DMF, 2 eq., 97%), followed by a mild hydrolysis (K_2CO_3, MeOH, -10°), then treatment with PhSSPh as above gave a sulfide. Deprotection (aqueous HF, pyridine, CH_3CN), followed by acetylation (Ac_2O, DMAP, CH_2Cl_2) furnished, after separation, (2R,4R)-7 ($[\alpha]_D$ -11; c=4).
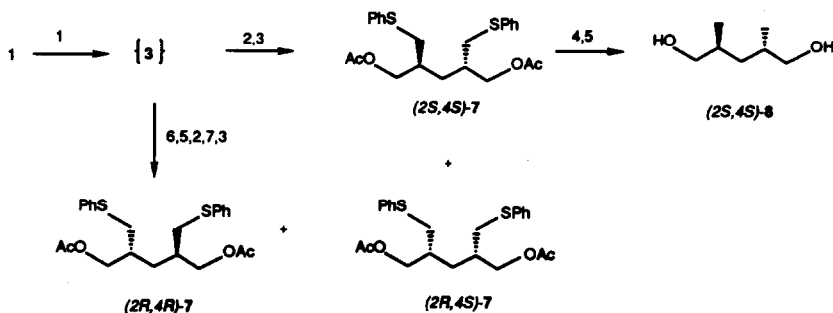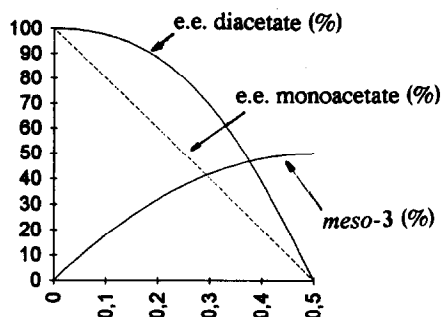

1: PFL, vinyl acetate; 2: PhSSPh/PBu_3, CH_2Cl_2; 3: Flash-chromatography (SiO_2,CH_2Cl_2/ether);
4: Ni-Raney, EtOH; 5: K_2CO_3, MeOH; 6: DPTBSCl, DMF, imidazole; 7: Ac_2O, DMAP, CH_2Cl_2

In conclusion, the first clear-cut experiment in which a *meso* polyol has been converted into an optically active diacetate belonging to the C_2-symmetry group has been provided. The potential of the method has been illustrated by preparing, from diethyl malonate and formaldehyde, a chiral synthon useful for our synthetic task. It is worth mentioning that obtaining an optically active derivative of 2,4-dimethyl-pentane bearing a substituent on each terminal methyl group in one step is unprecedented.

Since the efficiency of the present method required *inter alia* a separation of the eventually formed *meso/d* or *l* mixture, some limitations may result. For instance, acetylation of 2,6-bis-(hydroxymethyl)-1,7-heptanediol gave indeed an optically active diacetate ($[\alpha]_D$ +8, c=5); all attempts in separating both the diastereomeric diacetates or the corresponding sulfides have failed so far. Nevertheless, it has to be realized that this strategy could be applied to any chemical or biochemical processes showing some stereospecificity, using any twice-*meso*-shaped substrate. For instance, enzyme-mediated bis-hydroxylation of 2,4-dimethyl-pentane itself should provide a rather straightforward access to 8. Such further applications are currently under investigation.

REFERENCES AND NOTES

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3- Hoye T.R., and Suhadolnik J.C., *J. Am. Chem. Soc.*, 1985, *107*, 5312-5313. See also : Aggarwal V.K., Evans G., Moya E., and Dowden J., *J. Org. Chem.*, 1992, *57*, 6390-6391, and references therein.

4- a) Nakajima N., Uoto K., Yonemitsu O., and Hata T., *Chem. Pharm. Bull.*, 1991, *39*, 64-74, and references therein; b) we thank Dr. D. Michelet (Rhône-Poulenc), Drs M. Barreau and J.M. Paris (Rhône-Poulenc-Rorer) for their interest.

5- The magnitude of this amplification can easily been derived in considering a stoechiometric conversion of 1 into 3. Supposing that one mole of 1 would give (1-x) mole of *(2R)*-2 in the first step with $0<x<0.5$ (e.e = $1-2x$) and that the selectivity will be the same in the second step, the ratio of diacetates- i.e. $[(2R,4R)$-3]/[(2S,4R)-3]/[(2S,4S)-3]$- will be : $(1-x)^2/2x(1-x)/x^2$, respectively. It follows that e.e. = $(1-2x):(1-2x+2x^2)$, which is greater than $(1-2x)$ for $0<x<0.5$. This clearly appears plotting e.e. versus x, as shown. It then occurs that, *providing the diastereomeric diacetates be separated*, the optical purity will be better than expected from the intrinsic stereoselectivity.

6- Welch K., *J. Chem. Soc.*, 1931, 673-674; a few drops of 1N sodium ethoxide in ethanol were used instead of KOH, as described.

7- Degueil-Castaing M., De Jeso B., Drouillard S., and Maillard B., *Tetrahedron Lett.*, 1987, *28*, 953-954; a mixture of tetraol 1 (328 mg, 2 mmol), *Pseudomonas fluorescens* lipase (SAM II from Fluka ; 20 mg), freshly distilled vinyl acetate stabilized by adding one crystal of 2,6-di-*t*-butyl-*para*cresol (2.6 ml, 28 mmol), in THF (5 ml) was rapidly stirred at room t. in a flask filled with argon. After 2 weeks, the suspension was diluted with ether then filtered on celite. Evaporation, followed by flash-chromatography on silica gel (CH_2Cl_2/ether) afforded: 1- the triacetate (50 mg); 2- the diacetate (270 mg); 3- the unreacted 1 (60 mg). Washing the celite cake with MeOH gave some more unreacted 1 (40 mg). In one instance, a lower selectivity (*d-l/meso* ratio= 7:3; $[\alpha]_D$ +9), for 3 was observed using enzyme from a different batch. Except otherwise stated, α_D have been recorded in CH_2Cl_2. DPTBSCl refers to diphenyl-*t*-butylsilyl chloride.

8- Selected ^{13}C NMR data (CDCl$_3$, 50MHz): (2R,4R)-3: 20.930, 26.630, 37.678, 62.519, 64.761, 171.741; (2R,4S)-3: 20.930, 26.128, 37.765, 62.268, 64.834, 171.741; *(2S,4S)-7*: 20.9, 21.1, 31.99, 35.15, 37.06, 65.62, 129.86, 130.44, 132.44, 136.57, 170.92; *(2S,4R)-7*: 20.9, 21.10, 32.06, 35.29, 36.75, 65.72, 129.84, 130.45, 132.40, 136.54, 170.92; 8: 16.48, 32.94, 36.82, 68.91.

9- Marshall J.A., Shearer B.G., and Crooks S. L., *J. Org. Chem.*, 1987, *52*, 1236-1245.