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A Convenient Preparation of Elements of the Stereotriade

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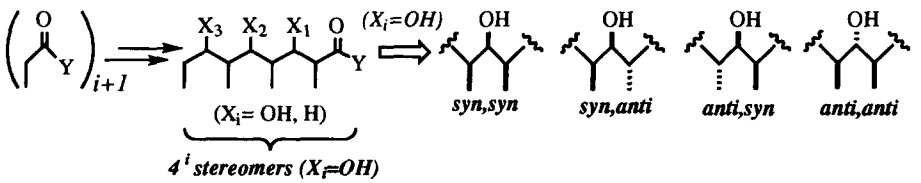
Abstract: *Enzyme-catalysed acetylation of either* syn,syn- or anti,anti-*2,4-dimethyl-1,3,5-pentane triol, easily obtained from a mixture of diastereomeric 3-hydroxy-2,4-dimethylglutaric acids, proceeds stereoselectively with preferential attack of the hydromethyl group linked to the* R *carbon atom of the starting triol, hence providing synthons useful for preparing compounds of the polypropionic pool.*

Due to their useful antibiotic properties, metabolites produced by *Streptomyces* species, especially those of the macrolide type, have strongly attracted the interest of synthetic chemists over the last three decades, with the result of both an impetuous development of synthetic methodologies -*e.g.* asymmetric aldol condensations- and the achievement of numerous clever total syntheses.[1]

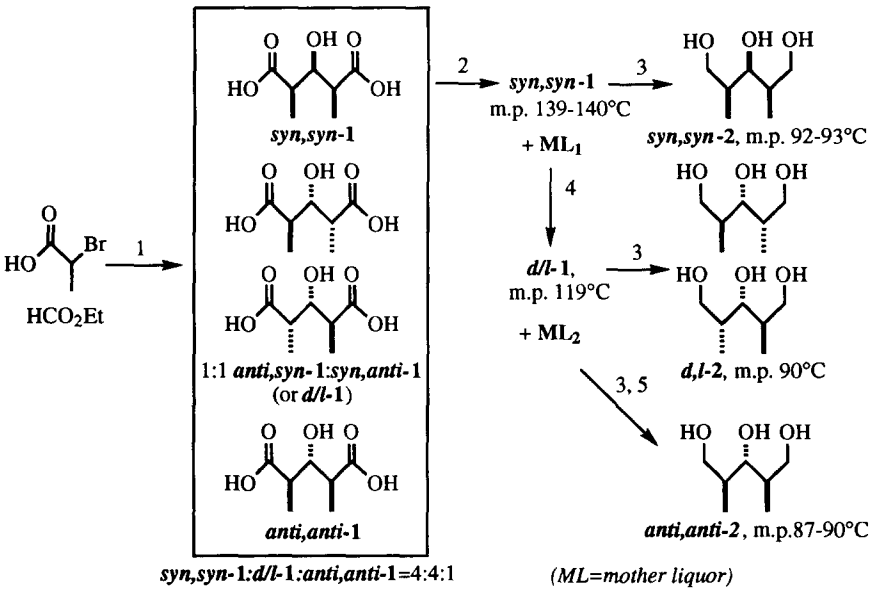
Important fragments of the carbon framework of these products result biogenetically from repeated Claisen-like condensation of propionyl-CoA units and subsequent reductions, with the consequence, as shown, of the possible generation of an exponential number of stereochemical combinations.



Much of the strategies adopted for synthesizing such compounds are also linear, starting with a synthon which is then stereoselectively homologated. As pointed out earlier by Hoffmann,[2a] the search of more convergent approaches is, accordingly, of interest.

Fictitious disconnection of these structures leads in much cases to the identification of at least one of the four units shown, commonly designated as "elements of the stereotriade". Stereoselective preparation of related synthons, equipped at both ends with a functionality allowing an easy appendage to the missing carbon atoms paved indeed the way for rapid syntheses of various propionic derivatives.[2] A practical access to adequately-functionalized elements of the stereotriade having the *syn,syn*- and the *anti,anti*-stereochemistry, respectively, is presented herein.

Reformatsky condensation of ethyl 2-bromo-propionate with ethyl formate under improved conditions[3d] (82-87% on a 0.5-1 mol scale), followed by saponification afforded, as outlined below, an approximately 4:4:1 mixture of the diastereomeric 2,4-dimethyl-3-hydroxy-glutaric acids from which the pure *syn,syn* (or *syn,meso*) isomer was isolated by crystallisation (32-38%).[3] Subsequent esterification with diazomethane, followed by LAH reduction of the corresponding dimethyl ester then gave pure ***syn,syn*-2** (81%).[3f]

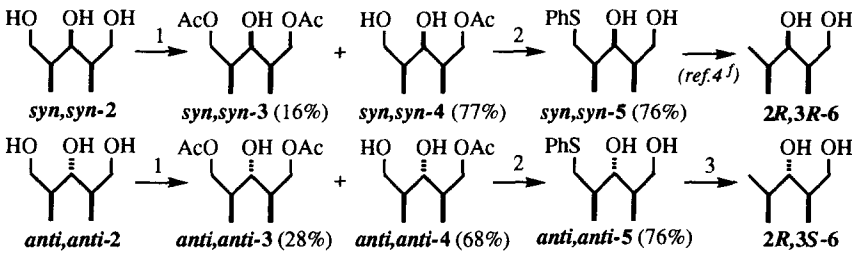


Reagents and conditions: 1- *i*) Zn (2.4 eq.), Me_3SiCl (0.16 eq.), THF; r.t., 2 hours; *ii*) 1.7 N aqueous NaOH; 90°C, 3 hours, then 6N aqueous HCl; 2- crystallisation from ether (according to ref. 3a); 3- *i*) CH_2N_2 (excess), ether; *ii*) LAH (2 eq.), THF; r.t., 3 hours; 4- crystallisation from diisopropyl ether; 5- flash-chromatography (60H silica gel; CH_2Cl_2:hexane, then MeOH:CH_2Cl_2).

By evaporating the solvents, the mother liquor of this first crystallisation -*i.e.* **ML_1**- afforded a pasty residue, which, when taken up in diisopropyl ether, deposited crystals of the racemic mixture of ***anti,syn*-1** and ***syn,anti*-1** (***d/l*-1**; 40%). Esterification and reduction as above then gave the pure *d/l* triol. Attempts to crystallise the main constituent -*i.e.* ***anti,anti*-1** (or ***anti,meso*-1**) from the residue obtained by evaporating to dryness the last mother liquor (*i.e.* **ML-2**) proved disappointing. Fortunately, reduction of this residue afforded a mixture of triols from which pure ***anti,anti*-2** could be isolated easily by chromatography (9%, overall).[4]

The *meso* triols -*i.e.* ***syn,syn*-2** and ***anti,anti*-2**- were then individually submitted to *Pseudomonas fluorescens* lipase-catalysed acetylation in conditions previously described,[5] the reaction being stopped as soon as the starting triol disappeared (TLC). The formed bis-acetates **3** were easily separated from the monoacetates - *i.e.* ***syn,syn*-4** and ***anti,anti*-4**, respectively- by chromatography (ether:CH_2Cl_2).

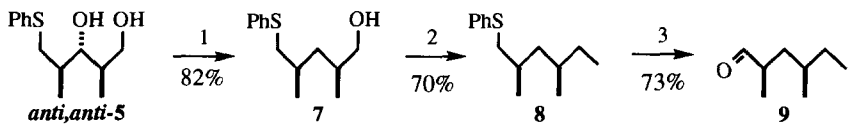
For sake of structure determination and with the aim of generating, from these monoacetates, chirons well-equipped for further utilisation (*vide supra*), both ***syn,syn*-4** and ***anti,anti*-4** were converted into the sulfides ***syn,syn*-5** and ***anti,anti*-5**, respectively, as outlined below.



Reagents and conditions: 1- PFL, vinyl acetate, THF (see ref. 5); r.t., 6 days; 2- *i*) flash-chromatography (silica gel; CH_2Cl_2:ether); *ii*) tosyl chloride (1 eq.), pyridine (4 eq.); 4°C, 16 hours; *iii*) NaI (3 eq.), acetone; r.t., 4 hours; *iv*) PhSNa (1.1 eq.), EtOH; r.t., 5 hours, then K_2CO_3 (0.2 eq.); r.t., 1 hour; 3- Ni-R, EtOH; r.t., 3 hours.

The sulfide ***syn,syn*-5** thus obtained proved to have the depicted 2*R*,3*S*,4*R* stereochemistry by identifying with an authentic sample. Desulfuration of ***anti,anti*-5** furnished the known diol **2*R*,3*S*-6**. The absolute configuration of ***anti,anti*-5** is, accordingly, 2*R*,3*R*,4*R*.[6] The enantiomeric purity of these sulfides was high (e.e.>94%), as estimated by ^1H NMR in presence of Eu(hfc)$_3$.[7]

The synthetic usefulness of ***syn,syn*-5** has already been demonstrated.[3f] That of its *anti* isomer was tested by converting, as shown, ***anti,anti*-5** into the sulfide **7**. **7** was then homologated into **8**, which furnished the aldehyde **9**, an intermediate in the synthesis of bourgeanic acid.[8]



Reagents and conditions: 1- *i*) TBDMSCl (1 eq.), imidazole (2 eq.), DMF; r.t., overnight; *ii*) Tosyl chloride (I eq.), pyridine (5 eq.); r.t., 2 days; *iii*) 1.5N HF (1eq.), pyridine (1 eq.), CH_3CN; r.t., 4 hours; *iv*) LAH (1 eq.), THF; r.t., 2 hours; 2- *i*) PPh_3 (1.1 eq.), I_2 (1.1 eq.), imidazole (1.1 eq.), 3:1 ether:acetonitrile; r.t., 2 hours; *ii*) MeMgBr (3M in ether; 1.3 eq.), Li_2CuCl_4 (0.13 eq.),THF; -78°C to r.t., 16 hours; 3- *i*) $NaIO_4$ (1 eq.), 1:1 acetone:H_2O; 0°C, 2 hours; *ii*) AcONa (2 eq.), Ac_2O; 110°C, 7 hours; *iii*) K_2CO_3 (1 eq.), MeOH; 10°C, 1 hour.

Attempted kinetic resolution of the *d,l* triol mixture by using the same enzymatic process proved to be inefficient, giving a diol and a diacetate having both a low enantiomeric purity (e.e.<40%). Though the problem of separating the *anti,syn* triol from its *syn,anti* enantiomer has obviously still to be addressed, it appears that the methodology presented herein allows to prepare conveniently two synthons useful for synthesizing products of the polypropionic pool.

References and Notes

1- a) Paterson, I.; Mansuri, M. *Tetrahedron* **1985**, *41*, 3569-3624; b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry* **1982**, *13*, 1-115; c) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem. Inter. Ed.* **1985**, *24*, 7-76.

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3- a) Reformatsky, S. *Chem. Ber.* **1895**, 3662-3665; b) Gerzon, K.; Flynn, E. H.; Sigal, M. V.; Wiley, P. F.; Monaham, R.; Quarck, U. C. *J. Am. Chem. Soc.* **1956**, *78*, 6396-6408; c) Mohr, P.; Tamm. C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501-2511; d) Gawronski, J. K. *Tetrahedron Lett.* **1984**, *25*, 2605-2608; e) Homes, D. S.; Sherringham, J. A.; Dyer, V. C.; Russell, S. T.; Robinson, J. A. *Helv. Chim. Acta* **1990**, *73*, 239-259; f) Adjé, N.; Breuilles, P; Uguen, D. *Tetrahedron Lett.* **1992**, *33*, 2151-2154.

4- ^{13}C NMR data (50MHz, D_2O): *i)* ***syn,syn*-1**: 13.2, 44.8, 74.6, 180.5; *ii)* ***d/l*-1**: 10.9, 15.4, 43.5, 45.5, 75.1, 180.7, 181; *iii)* ***anti,anti*-1**: 15.4, 44.7, 76.6, 180.6; *iv)* ***syn,syn*-2**: 13.2, 39.3, 66.5, 74.9; *v)* ***d/l*-2**: 10.6, 15, 38.5, 39.7, 66.5, 66.9, 74.8; *vi)* ***anti,anti*-2**: 15.9, 39.1, 65.6, 78.5. Rf (silica gel; 9:1 $CHCl_3$:MeOH): *i)* ***syn,syn*-2**: 0.25; *ii)* ***d/l*-2**: 0.35; *iii)* ***anti,anti*-2**: 0.4. The triol ***anti,anti*-2** can also be obtained by 9-BBN hydroboration of 2,4-dimethyl-1,4-pentadiene-3-ol (Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A *J. Org. Chem.* **1992**, *57*, 1637-1639).

5- Breuilles, P.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4205-4208.

6- Selected data: *i)* ***syn,syn*-4**: m.p. 61°C; $[\alpha]_D$ +7 (c=5, CH_2Cl_2); C, H (%): 56.8, 9.5 (calc.: 56.9, 9.5); ^{13}C NMR (50MHz, $CDCl_3$): 10.9, 12.7, 20.8, 35.4, 37.5, 65.7, 67, 73.4, 171.6; *ii)* ***anti,anti*-4**: oil; $[\alpha]_D$ +26 (c=4, CH_2Cl_2); C, H (%): 56.6, 9.3 (calc.: 56.9, 9.5); ^{13}C NMR (50MHz, $CDCl_3$): 14.2, 14.8, 20.9, 35.5, 36.4, 66, 66.6, 78.9, 171.6; *iii)* (2*R*,3*S*,4*R*)-2,4-dimethyl-5-phenylthio-1,3-pentane diol, ***syn,syn*-5**: m.p. and mixed m.p. 65°C; lit.:[3f] m.p. 65°C; $[\alpha]_D$ -20 (c=6, CH_2Cl_2); lit.:[3f] $[\alpha]_D$ -20 (c=6, CH_2Cl_2); *iv)* (2*R*,3*R*,4*R*)-2,4-dimethyl-5-phenylthio-1,3-pentane diol, ***anti,anti*-5**: oil; $[\alpha]_D$ -65 (c=2, CH_2Cl_2); C, H (%): 64.8, 8.1 (calc.: 65, 8.4); ^{13}C NMR (50MHz, $CDCl_3$): 14.3, 17, 35.9, 36.1, 36.5, 67.2, 81, 126, 129, 129.2, 137.1; *v)* **2*R*,3*S*-6**: m.p. 38°C; $[\alpha]_D$ -21 (c=0.7, CH_2Cl_2 or $CHCl_3$); lit.: $[\alpha]_D$ −20.7 (c=3.8, $CHCl_3$) (Masamune, S.; Sato, T.; Kim, M.; Willmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281); ^{13}C NMR: 13.4, 14.5, 19.3, 29.6, 36.7, 67.6, 81.6. All the $[\alpha]_D$ values reported herein have been recorded at 21°C. *Candida cylindracea* lipase-catalysed acetylation of the 3-O-TBDMS derivative of ***anti,anti*-2** has been shown to occur exclusively on the pro-*S* branch (Chenevert, R.; Couchesne, L. *Tetrahedron Asym.* **1995**, *6*, 2093-2096).

7- In ^1H NMR (250MHz, $CDCl_3$), the signal (*i.e.* a doublet) displayed by the methyl group closed to the hydroxymethyl residue of either (±)-***syn,syn*-5** or (±)-***anti,anti*-5**, prepared independently, is splitted into two well-resolved doublets by adding $Eu(hfc)_3$ (≥0.2 eq.) to the NMR tube. Performing the same shift experiment with the optically active sulfides **5** described herein revealed the presence of only trace amount of the corresponding enantiomer (less than 3% by integration). Hence, the e.e. are better than 94%.

8- (2*S*,4*R*)-2,4-dimethyl-5-phenylthio-1-pentanol, **7**: $[\alpha]_D$ -16 (c=3, CH_2Cl_2); ^{13}C NMR (50MHz, $CDCl_3$): 17.4, 20.4, 30.6, 33.3, 40.2, 41.1, 68, 125.8, 128.9, 129.1, 137.3; (2*R*,4*R*)-2,4-dimethyl-1-phenylthio-hexane, **8**: $[\alpha]_D$ -21 (c=2, CH_2Cl_2); ^{13}C NMR (50MHz, $CDCl_3$): 11.2, 19.8, 20.2, 29.1, 30.6, 31.7, 41.3, 43.9, 125.6, 128.9, 129, 137.8; **9-DNPH**: m.p. 109-112°C (lit.: m.p. 112-113°C (White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347-335)).

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