Synthesis of (+)- and (−)-Homononactic Acid from (*S*)-1,2-Epoxybutane. Total Synthesis of Tetranactin by 'Reverse Coupe du Roi'

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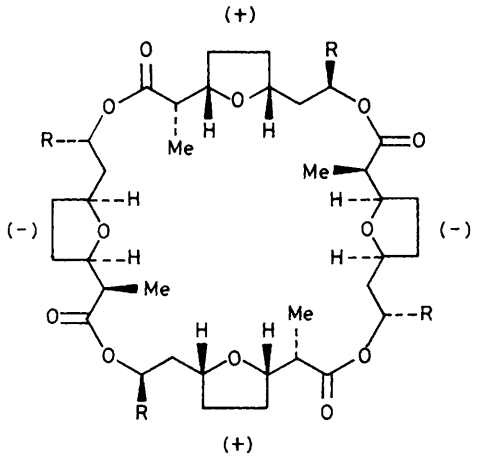
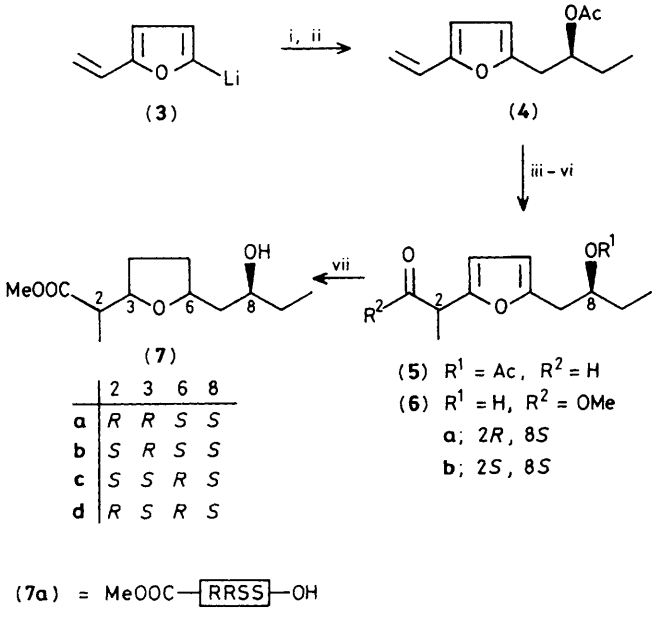
The synthesis of (+)- and (−)-homononactic acid was achieved in 6 steps and 4 steps respectively starting with the reaction of 2-lithium-5-vinylfuran and (*S*)-(−)-1,2-epoxybutane; both enantiomers were used in the construction of the achiral macrolide antibiotic tetranactin by esterification and subsequent lactonisation with the thiolester of 3-cyano-4,6-dimethyl-2-thiopyridone.

The parlour trick to divide an achiral object into homochiral halves is known in France as 'la coupe du roi.' By analogy 'the reverse coupe du roi' means the reconstruction of an achiral corpus from its two homochiral segments. This principle has been applied in organic synthesis as well.[1—3]

The nactins[3—5] are a group of macrotetrolides consisting of four hydroxy acids with alternating configuration linked to produce a 32-membered tetralactone ring with 16 asymmetric centres. Several homologues (R = Me, Et, Pr^i) have been isolated. Meso compounds with S_4 symmetry are nonactin (**1**; R = Me) and tetranactin (**2**; R = Et).[6] The latter contains two subunits of (−)-(2*R*,3*R*,6*S*,8*S*)-homononactic acid and two



Nonactin (**1**; R = Me)
Tetranactin (**2**; R = Et)

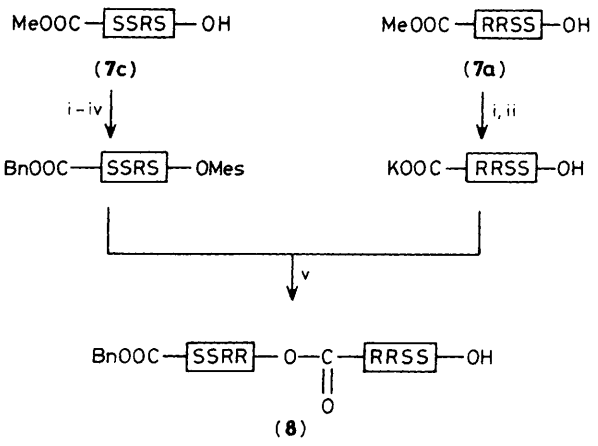


Scheme 1. i, (*S*)-(−)-1,2-Epoxybutane, THF, 4 h, 5 °C → room temp.; ii, AcCl, 30 min, −40 °C → room temp., 81% from (**3**); iii, 1 mol % $[Rh(cod)Cl]_2$, TPP, CO (100 atm)/H_2 (100 atm), 24 h, 70 °C, 90%; iv, $NaClO_2$, H_2N–SO_3H/Na_2HPO_4, pH 4, dioxane/H_2O, 30 min, room temp.; v, 2 M KOH/MeOH, 30 min, room temp.; vi, CH_2N_2, Et_2O, 2 min, room temp., 73% from (**5a,b**); vii, H_2, Rh/Al_2O_3 (5%), MeOH, 3 atm, 1.5 h, room temp., >90%. *Abbreviations:* THF = tetrahydrofuran, cod = cyclo-octa-1,5-diene, TPP = triphenylphosphine.

subunits of (+)-(2*S*,3*S*,6*R*,8*R*)-homononactic acid. Because the optically active starting material (*S*)-1,2-epoxybutane should be put into the homononactic acid synthesis at a late stage, we started with the readily accessible α-vinylfuran[7] whose side chain can be transformed easily into a propionic acid function (Scheme 1).

Metallation with *m*-tolyl-lithium† led to the formation of

† *m*-Tolyl-lithium formed cleanly the metallation product whereas n-butyl-lithium partially reacted to give the 1,6-addition product 2-hexyl-5-lithium-furan.



Scheme 2. i, 2 M KOH/MeOH, 30 min, room temp.; ii, $KHCO_3$, H_2O; iii, $PhCH_2Br$, DMF, 1 h, 50 °C, 82%; iv, $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, 1 h, 0 °C → room temp., 94%; v, DMSO, 16 h, 50 °C, 80%. *Abbreviations:* DMF = dimethylformamide, DMAP = 4-*N*,*N*-dimethylaminopyridine, DMSO = dimethyl sulphoxide.

the α-lithium derivative (**3**), which was reacted with (*S*)-1,2-epoxybutane[8] to give the alcohol whose acetyl derivative (**4**) formed the mixture of the two diastereoisomeric aldehydes (**5a,b**) in a completely regioselective but not stereoselective oxo-reaction.‡ Transformation to the diastereoisomeric esters (**6a,b**) and catalytic hydrogenation gave a mixture of four diastereoisomeric homononactic acid esters (**7a—d**). The two isomers (**7a**) [(−)-methyl homononactate] and (**7c**) were put into the following construction of tetranactin directly; the isomers (**7b**) and (**7d**) were rearranged by base into a mixture of (**7a**) + (**7b**) and (**7c**) + (**7d**) respectively and therefore could be used in the synthesis as well.

The diastereoisomer (**7c**) can be transformed into (+)-homononactic acid by a simple nucleophilic substitution and Walden inversion of its 8-methanesulphonate with potassium acetate. However this transformation was combined with the construction of the dimeric (+)-homononactyl-(−)-homononactate derivative (**8**) by the route to be streamlined as shown in Scheme 2.

Two molecules of this chiral diester could be dimerised by the thiolester method in only small yield to give the achiral tetranactin, but this combination could be performed smoothly by a two step procedure: two dimeric molecules (**8**) were combined to give the linear tetraester (**9**) (Scheme 3). Cyclization could be achieved in 51% yield using our method[9] with the thiolester of 3-cyano-4,6-dimethyl-2-thiopyridone.

Tetranactin was isolated and purified by medium pressure chromatography on LiChroprep Si 60 (pretreated with hydrochloric acid) and crystallized from n-hexane at −20 °C as large rhombs. The synthetic product was identical in every respect with the natural compound (^1H n.m.r., ^{13}C n.m.r., t.l.c., mass spectrometry, m.p.).

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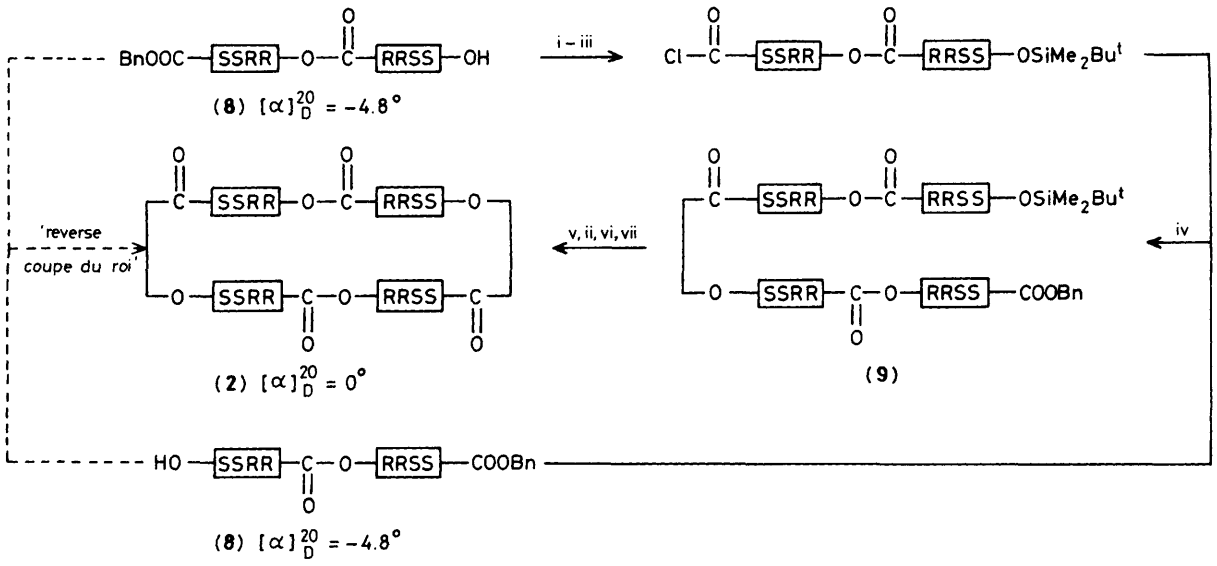
‡ Optical, induced hydroformylation using optically active phosphine ligands {diop, 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane; dipamp, *R*,*R*-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane} yielded only low optical rotations which decreased on standing at room temperature.



Scheme 3. i, Bu^{t}Me$_2$SiCl, imidazole, DMF, 1 h, 50 °C, 96%; ii, H_2, Pd/C (5%), THF, 1 h, room temp.; iii, $Me_2C{=}C(Cl)NMe_2$, CH_2Cl_2, 1.5 h, room temp.; iv, 4-pyrrolidinopyridine, CH_2Cl_2, 2 h, room temp., 83% from (**8**); v, 40% aq. HF, MeCN, 1 h, room temp., 94%; vi, bis-(3-cyano-4,6-dimethyl-2-pyridyl)disulphide, TPP, toluene, 1.5 h, 0 °C → room temp., 71%; vii, toluene-*p*-sulphonic acid, CH_2Cl_2, 4 h, reflux temp., high dilution conditions, 51%.

Tokyo, for a sample of tetranactin, the original ^{13}C n.m.r. spectrum and the h.p.l.c. data. This work was supported by the Fonds der Chemischen Industrie and BASF AG.

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