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Synthesis of a Bifunctional 2,4-Dihydroxy Five-Carbon Synthon. Enantiomerically Pure Δ^2-Isoxazolines by Chromatographic Resolution

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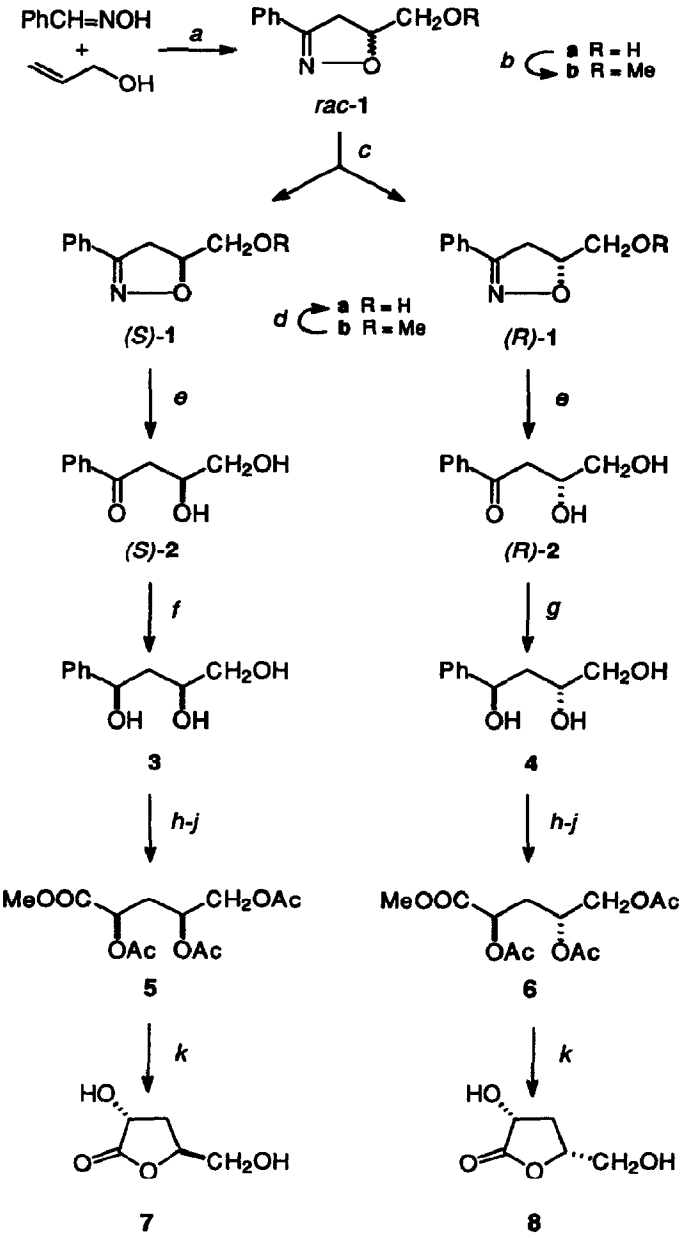
Abstract: Chromatography on cellulose triacetate allows the separation of *(R)*- and *(S)*-4,5-dihydro-3-phenyl-5-isoxazolemethanol in 100% ee. Reductive ring cleavage, diastereoselective reduction of the 3-hydroxy ketones thus obtained, and oxidation of the phenyl ring with RuO_4 leads to the synthesis of enantiomerically pure 2,4,5-trihydroxypentanoic acids virtually in all the possible configurations.

1,3-Diols are a relevant leitmotif in natural products therefore units with 1,3-hydroxy groups in the desired configuration and with suitable terminal functionalities can be of strategic importance for the synthesis of that kind of compound. Aim of the present research is a practical synthesis of such a unit with the two hydroxy groups in all the possible configurations.

It is known that the latent functionalities of isoxazolines (4,5-dihydroisoxazoles) allow access to a variety of acyclic derivatives, among them 1,3-diols, aminoalcohols, and hydroxyketones.[1] The synthesis of optically pure isoxazolines is thus object of much experimental study.[2,3] The 1,3-dipolar cycloaddition of nitrile oxides to dipolarophile chiral alkenes such as allyl derivatives,[2b] acrylate or crotonate derivatives,[2c-j] can exhibit good asymmetric induction[2f,h] but demands rather laborious synthesis of the alkene chirophor.

We have found that the enantiomers of isoxazoline *rac*-**1b** can be easily separated by chromatography on a preparative scale. Following the simple procedure described for flash chromatography,[4] we have utilized an usual column of glass packed with cellulose triacetate (CTA). This chiral stationary phase is commercially available and inexpensive; it can be used several times and recovered. 200 g of CTA (Merck; 15-25 μm particle size) allow the complete separation of the enantiomers of 1 g of *rac*-**1b**. The Figure, which shows the alike separation by analytical HPLC, displays an outstanding enantiomer separation factor: $\alpha = 3.6$.

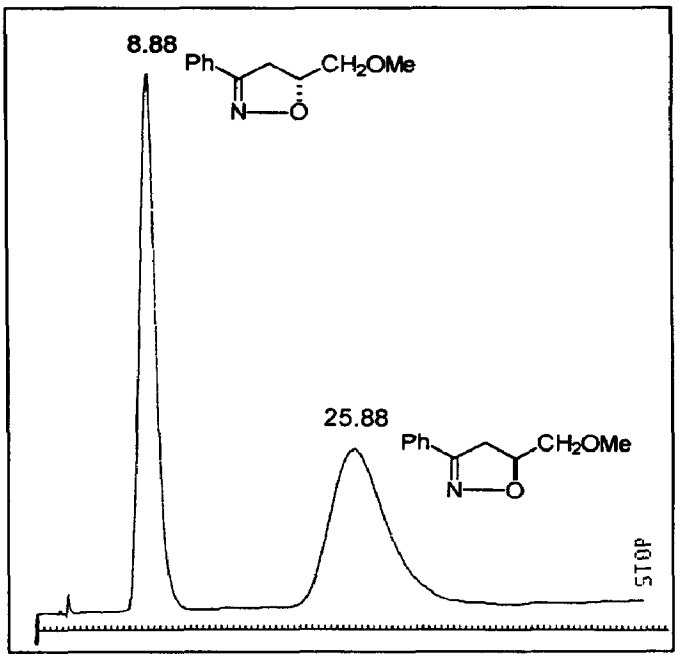
The sequence outlined in the Scheme shows the synthesis of the synthons **5** and **6** (and the virtual synthesis of their enantiomers): *rac*-**1a**, easily synthesized from benzaldehyde oxime, allyl alcohol and NaOCl, was methylated and the enantiomers separated as described; demethylation[5] with BBr_3 in CH_2Cl_2 led to the known compounds[2f, 2h, 2j] *(R)*-**1a** and *(S)*-**1a** in 100% ee. Curran has shown[6] that the aldehydes obtained from these alcohols by Swern oxidation, undergo diastereospecific addition of Grignard compounds thus allowing the introduction of a second chiral centre and chain elongation. Hydrogenolysis of the isoxazoline ring[7] with Raney Ni catalyst in $MeOH/H_2O/H_3BO_3$ gave the hydroxy ketones *(S)*-**2** and *(R)*-**2** in 74-80 % yield. 1,3-*Syn* diastereoselective reduction[8] of *(S)*-**2** with Et_2BOMe-$NaBH_4$ gave **3** in 90 % yield, no traces of the *anti* isomer could be detected; reduction of *(R)*-**2** with $Me_4NHB(OAc)_4$ in CH_3CN and CH_3COOH at -20 °C (ref. 9) gave **4** in 91 % yield in an *anti*/*syn* ratio 92/8; pure *anti*-isomer was obtained by crystallization. The former reactions, carried out in detail as described in the quoted references, are known to occur with complete retention of the configuration of the first chiral centre. Protection of triols **3** and **4** with Ac_2O-pyridine was followed by oxidation of the phenyl ring to carboxylic acid with RuO_4. This reaction required special attention: when performed as described[10] (CCl_4, CH_3CN, H_2O; catalytic amounts of $RuCl_3$; HIO_4 as the stoichiometric oxidant) some



SCHEME

Absolute configuration shown.

Reagent and conditions: *(a)* NaOCl; *(b)* MeI, NaH; *(c)* chromatography with CTA; *(d)* BBr_3 in CH_2Cl_2; *(e)* H_2, Raney Nickel, H_2O, MeOH, H_3BO_3; *(f)* Et_2BOMe, $NaBH_4$; *(g)* $Me_4NHB(OAc)_4$; *(h)* Ac_2O, pyridine; *(i)* $RuCl_3$, HIO_4; *(j)* CH_2N_2; *(k)* OH^- then H^+



Analytical HPLC of *rac*-**1b**

Analytical column: 240×4 mm. Chiral stationary phase: cellulose triacetate Merck (15-25 μm particle size). Eluent: hexane/ethanol/toluene 3/2/1. Flow rate: 0.9 ml/min. UV detection: λ 276 nm. An increase of toluene in the eluent mixture improves the resolution but makes difficult the UV detection. The column was packed with the same CTA used for the preparative column.
The preparative glass column (210×50 mm) was charged with 1g of *rac*-**1b** and eluted with hexane/ethanol/toluene 2/2/1 or with ethanol/toluene 4/1; with the latter solvent mixture the resolution is lower but the elution time shorter.

FIGURE

form of catalyst inactivation prevented the reaction from reaching completion. Best results were obtained using CH_2Cl_2 instead of CCl_4, a solution twice as diluted than reported, and using a slight excess of the oxidant HIO_4; most important, $RuCl_3$ was added in very small portions until the complete disappearance of the starting compounds; the free acid triacetate can be isolated but treatment of the crude of the reactions with CH_2N_2 allowed an easier isolation of esters **5** and **6** in 80-83% yield; the NMR spectrum of each compound showed no traces of diastereoisomer.

In order to confirm the absolute and relative stereochemistry of all compounds we treated **5** and **6** with a base then with acid: the known butanolides **7** and **8** were obtained in 80-85 % yield.[11] These compounds, and their enantiomers, are endogenous inductive agents to hunger and satiety in mammalians and have been previously synthesized.[12] The synthesis of one of these compounds, *ent*-**8**, is simple and straightforward as it is obtained in few steps from D-γ-*ribono*-1,4-lactone;[12d] the synthesis of the other three isomers appears more convenient with the method reported here.

Starting from a very readily available substrate the present procedure provides a convenient synthesis of C-5 blocks with two hydroxy groups in all the possible configurations and with two different terminal functionalities which can allow synthetically useful elaborations. Some features can be noted: phenyl ring, as synthetic equivalent of the carboxylic acid group, makes the compounds UV detectable with evident analitical advantages; the hydroxy groups are generated at distinct stages and can be protected in different way; compounds **1-4** are crystalline thus can be obtained in absolute chemical and optical purity.

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13. Selected spectroscopic data (**1b** and **3-6** are new compounds): (*R*)-**1a**: mp 79 °C (CCl_4); $[\alpha]_D$ - 185 (*c* 1.2, $CHCl_3$); lit.[2h] $[\alpha]_D$ -173. (*R*)-**1b**: mp 29 °C (hexane); $[\alpha]_D$ - 140 (*c* 1.1, $CHCl_3$). (*R*)-**2**: mp 70 °C (toluene); $[\alpha]_D$ 41.9 (*c* 1.8, $CHCl_3$)
3: mp 74 °C (isopropanol); $[\alpha]_D$ 58.3 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.76 (dt, 1, *J* = 14.5 and 3.0 Hz), 1.94 (dt, *J* = 14.5 and 9.9 Hz) 3.50 (dd, 1, *J* = 11.0 and 6.5 Hz), 3.64 (dd, *J* = 11.0 and 73.5 Hz), 4.05 (dddd, 1, *J* = 9.9, 6.5, 3.5 and 3.0), 4.99 (dd, 1, *J* = 9.9 and 3.0 Hz). ^{13}C NMR ($CDCl_3$) δ 41.46, 66.72, 72.28, 74.63, 125.66, 127.86, 128.62, 144.10.
4: mp 84 °C (EtOAc); $[\alpha]_D$ 56.4 (*c* 2.1, MeOH); ^1H NMR ($CDCl_3$) δ 1.86 (ddd, 1, *J* = 14.8, 7.7 and 3.5 Hz), 1.95 (ddd, 1, *J* = 14.8, 8.3 and 4.0 Hz), 3.55 (dd, 1, *J* = 11.1 and 7.1 Hz), 3.66 (dd, 1, *J* = 11.1 and 3.5 Hz), 3.98 (dddd, 1, *J* = 8.3, 7.1, 3.5 and 3.5 Hz), 5.08 (dd, 1, *J* = 8.0 and 4.0 Hz). ^{13}C NMR (CD_3OD) δ 43.54, 67.43, 69.95, 71.18, 126.42, 127.88, 129.05, 146.39.
5: $[\alpha]_D$ 3.70 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.05-2.26 (m, 2), 4.06 (dd, 1, *J* = 12.1 and 5.6 Hz), 4,29 (dd, 1, *J* = 12.1 and 3.7 Hz), 5.14 (t, 1, *J* = 8.4 Hz), 5.25 (m, 1).
6: $[\alpha]_D$ 17.0 (*c* 1.3, $CHCl_3$); ^1H NMR of the free acid triacetate ($CDCl_3$) δ 2.10 (m, 1), 2.28 (ddd, 1, *J* = 14.6, 10.3 and 3.3 Hz), 4.06 (dd, 1, *J* = 12.0 and 5.6 Hz), 4.31 (dd, 1, *J* = 12.0 and 3.7 Hz), 5.08 (dd, 1, *J* = 10.9 and 3.3 Hz), 5.23 (dddd, 1, *J* = 5.6, 5.15, 4.0 and 3.7 Hz).
7: $[\alpha]_D$ 49.2 (*c* 1.4, EtOH), lit.[12b] $[\alpha]_D$ 50.3; ^1H NMR (CD_3OD) δ 2.21 (dt, 1, 13.2 and 8.5 Hz), 2.48 (ddd, 1, *J* = 13.2, 8.5 and 3.0 Hz), 3.59 (dd, 1, *J* = 12.6 and 3.6 Hz), 3.77 (dd, 1, 12.6 and 2.8 Hz), 4.58 (t, 1, 8.4 Hz); 4.64 (dddd, 1, *J* = 8.5, 3.6, 3.0 and 2.8 Hz). See ref. 12b.
8: $[\alpha]_D$ -22.5 (*c* 1.5, MeOH), lit.[12b] $[\alpha]_D$ -22.2; ^1H NMR (CD_3OD) δ 1.98 (ddd, 1, *J* = 12.5, 10.5 and 10.5 Hz), 2.53 (ddd, 1, *J* = 12.5, 8.5 and 5.7 Hz), 3.58 (dd, 1, *J* = 12.5 and 5.0 Hz), 3.80 (dd, 1, *J* = 12.5 and 3.0 Hz), 4.46 (dddd, 1, *J* = 10.5, 5.7, 5.0 and 3.0 Hz), 4.55 (dd, 1, *J* = 10.5 and 8.5 Hz). See ref. 12d.

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