# Formal Desymmetrization by a "Mitsunobu Trick" − Enantiomerically Pure *cis*-3,4-Dihydroxypyrroline *N*-Oxides for the Enantiodivergent Synthesis of Trihydroxyindolizidines

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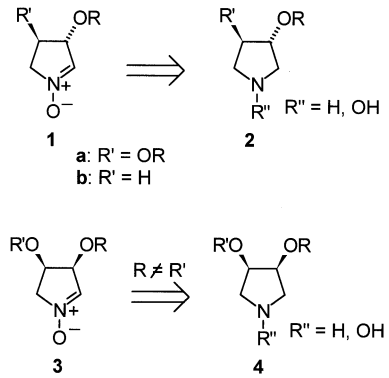
A protocol is presented for a completely enantioselective formal desymmetrization of $\mathbf{C_s}$-symmetric diols by monoprotection of the corresponding enantiopure $\mathbf{C_2}$ diols, followed by an inversion of configuration by a Mitsunobu reaction ("Mitsunobu trick"). Its application to the unprecedented synthesis of enantiopure *cis*-3,4-dihydroxypyrroline *N*-oxides, employed in the enantiodivergent synthesis of two selectively protected 1,2,7-trihydroxyindolizidines, is also reported.

A route of easy access to enantiopure hydroxypyrroline *N*-oxides **1** (Scheme 1), together with their straightforward application to the synthesis of polyhydroxy indolizidine[1] and pyrrolizidine[2] alkaloids and their unnatural congeners, was recently reported.

Scheme 1. Retrosynthetic analysis for monohydroxy- and *trans*- and *cis*-dihydroxypyrroline *N*-oxides




The simple synthetic sequence to produce nitrones **1** in excellent yields has as a starting point materials such as tartaric (**1a**) and malic (**1b**) acid (in both enantiomeric forms), which are available from the chiral pool. The key step of the synthesis is represented by the final oxidation step of an enantiomerically pure pyrrolidine or *N*-hydroxypyrrolidine **2** (Scheme 1).[1][2][3] To extend this process to the synthesis of the related indolizidines, or pyrrolizidines bearing the *cis*-hydroxy substitution pattern, an appropriate nitrone (**3**) was necessary. It was clear that, in order to obtain enantiopure materials, the goal to pursue was the differentiation of the two protected hydroxy groups in **4** (Scheme 1). In this communication we present the successful solution to this problem, together with the first synthesis of optically pure nitrones **3**,[4] based on a general strategy which might present an alternative to the desymmetrization of *meso*-diols. This process is generally accomplished by the selective derivatization of a single hydroxy group in the $\mathbf{C_s}$-symmetric diols by means of enzymatic catalysis ("*meso* trick").[5][6] We now propose a route of access to the same selectively protected enantiopure *cis*-diols by means of a Mitsunobu reaction,[7] which inverts the configuration of one stereogenic centre in a $\mathbf{C_2}$-symmetric diol ("Mitsunobu trick").

Monoprotection of the *trans*-3,4-dihydroxypyrrolidine **5**,[8] readily available from L-tartaric acid, with MEM chloride was achieved in good yield. This is an excellent result when one considers the possibility of recycling the unprotected and the diprotected (30%) side products. Inversion of configuration at the stereogenic centre bearing the unprotected hydroxy group was then carried out under standard Mitsunobu conditions, using DEAD, $PPh_3$, and benzoic acid at room temperature (Scheme 2). Benzoate **7** was isolated in a yield of 76% and its stereochemical integrity was verified by spectroscopic analysis. The 3-H,4-H proton coupling constant unequivocally attests to the *cis* relationship acquired in the course of the reaction.

The new method of formal desymmetrization of *cis*-diols seems to hold claim to a wider scope of application. As an example, the monoprotected ditosylate **8**, prepared from the corresponding $\mathbf{C_2}$-symmetric threitol, also gave the optically pure *cis*-protected erythritol **9**, in good yield, under the same conditions (Scheme 2).

The "Mitsunobu trick" represents, therefore, a new and useful strategy for the chiral discrimination of $\mathbf{C_s}$-symmetric diols by inversion of the configuration of one stereocentre in the corresponding $\mathbf{C_2}$-symmetric diols, which then represent chiral synthetic equivalents of the *meso*-diols

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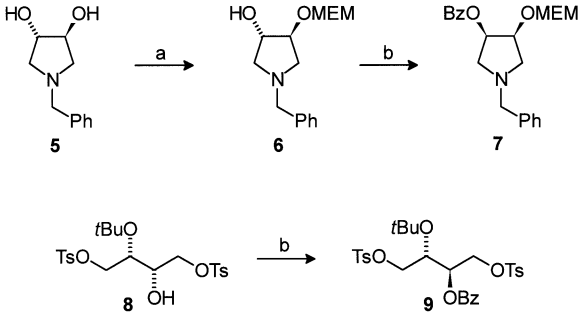
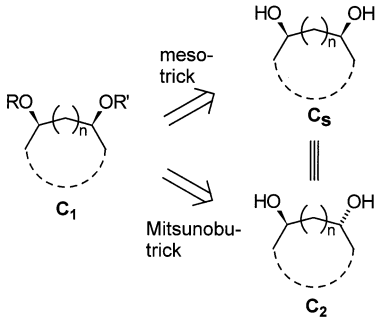
Scheme 2. Synthesis of desymmetrized $C_s$ diols by the "Mitsunobu trick




(a) NaH (1.2 equiv.), MEMCl (1.2 equiv.), THF, 0°C, 75 min, 61%; (b) $PPh_3$ (1.5 equiv.), PhCOOH (1.5 equiv.), DEAD (1.5 equiv.), THF, 0°C to room temp., 24 h, 76% of **7**, 87% of **9**.

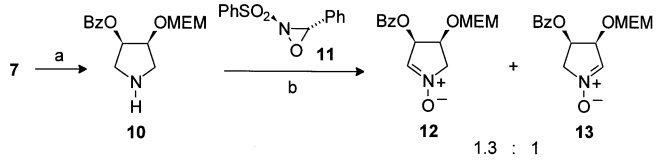
(Scheme 3). This alternative to the "*meso* trick" sounds particularly attractive when, as in the present case, where tartaric acids are considered, the $C_2$-symmetric diols are both much more easily available and cheaper than their *meso* counterparts. The latter example in Scheme 2 is particularly outstanding, since only a few *meso* derivatives of acyclic vicinal diols have been asymmetrized successfully by the use of enzymes.[5]

Scheme 3. Synthetic equivalence of a $C_2$ diol with a $C_s$ diol by the "Mitsunobu trick"




In order to achieve our final target, the debenzylation of **7** by hydrogenation with Pd on carbon at ambient pressure, to afford the optically pure pyrrolidine **10** (quantitatively and ready for the oxidation), was carried out (Scheme 4).

Scheme 4. Synthesis of protected *cis*-dihydroxypyrroline *N*-oxides **12** and **13**

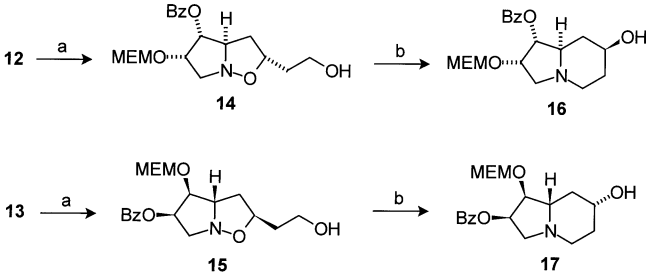



(a) $H_2$ (1 atm), $Pd(OH)_2/C$, $CH_3OH$, room temp., 21 h, 100%; (b) **11** (2 equiv.), $CHCl_3$, 0°C, 20 min, room temp., 40 min, 59%.

This process proved to be much more difficult than expected; the most common methods of oxidation,[9] used recently by us and others on analogous *trans*- or mono-substituted substrates, failed, generally giving complex reaction mixtures. More selective and mild oxidants also failed.[10] The oxidation was only achieved by using *N*-benzenesulfonyl-*C*-phenyloxaziridine **11**,[11] already used by Wightman in his synthesis of a racemic nitrone **3**.[2a] The regioisomeric nitrones **12** and **13** were obtained in a good yield, but with poor regioselectivity (1.3:1). This is in contrast to our previous observation of the use of a BzO group to induce regioselective oxidation on the β-carbon atom in cyclic hydroxylamines.[3d] However, the result might be ascribed to a different mechanism for the oxidation of amines with respect to hydroxylamines. The two nitrones were clearly identified from the HCOBz and HCOMEM proton resonances, which are more differentiated in the major compound **12** than in **13** ($\delta$ = 6.03 and 4.75, versus $\delta$ = 5.74 and 5.07, respectively). Flash chromatography was efficient in separating the two nitrones which could be then be completely analyzed. The oxidation therefore allowed simultaneous access to protected *cis*-dihydroxynitrones of both configurations.

The application of the nitrones **12** and **13** to the synthesis of selectively protected enantiomeric 1,2,7-trihydroxyindolizidines[1b][1c] illustrates the potential of the enantiopure cyclic nitrones obtained as useful chiral building blocks (Scheme 5). Cycloadditions of both nitrones to but-3-en-1-ol gave, in each case, a 7:1 mixture of *exo*/*endo* cycloadducts derived by the approach of dipolarophile *anti* to the substituents on the nitrones.[1][2] The major cycloadducts **14** and **15** were separated and converted into the indolizidinols **16** and **17** by a sequential mesylation/hydrogenation procedure.[1c][1e][2a][12] These compounds are useful intermediates for further transformations, presenting an orthogonal protection pattern of the three hydroxy functionalities. The overall process represents an enantiodivergent synthesis of the two trihydroxyindolizidines starting from the common precursor **7**, derived in turn from L-tartaric acid.

Scheme 5. Enantiodivergent synthesis of selectively protected trihydroxyindolizidines **16** and **17**




(a) But-3-en-1-ol, benzene, 60°C, 43 h, 92% of **14**, 97% of **15**; (b) i. $NEt_3$ (1.5 equiv.), MsCl (1.1 equiv.), $CH_2Cl_2$, 0°C; ii. $H_2$ (50 ψ), 10% Pd/C, $CH_3OH$, room temp., 12 h, 75% of **16**, 57% of **17**.

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## Experimental Section

*General Procedure for the Mitsunobu Reaction:* A solution of the monoprotected diol (**6** or **8**, 1−2 mmol) in THF (10−15 ml) was added to $PPh_3$ (1.5 equiv.) and benzoic acid (1.5 equiv.). The solution was cooled to 0−5°C with an ice bath and DEAD (1.5 equiv.) was added dropwise whilst stirring. The resulting yellow solution was left at room temp. for 24 h. The solution was diluted with 30 ml of diethyl ether and washed with 10% $NaHCO_3$ (2 × 10 ml) and brine. The organic phase was dried with $Na_2SO_4$ and concentrated to afford a crude reaction mixture, which was then purified by flash column chromatography on silica gel.

*Pyrrolidine* **7**: Yield: 76%. − $R_f$ ($Et_2O$) = 0.53. − $[\alpha]_D^{20}$ = −4.1 (*c* = 1.82 in $CH_2Cl_2$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3032 (CH) $cm^{-1}$, 2932 (CH), 1741 (C=O), 1275 (C−O), 1120 (C−O). − $^1H$ NMR ($CDCl_3$): δ = 2.72 (dd, *J* = 9.5, 6.2 Hz, 1 H, *H*CHN), 2.80 (dd, *J* = 10.6, 4.7 Hz, 1 H, *H*CHN), 3.11 (dd, *J* = 9.5, 6.2 Hz, 1 H, *H*CHN), 3.23 (dd, *J* = 10.8, 6.6 Hz, 1 H, *H*CHN), 3.32 (s, 3 H, *Me*O), 3.42−3.69 (m, 4 H, $OCH_2CH_2O$), 3.73 (s, 2 H, $NCH_2Ph$), 4.43 (q, *J* = 6.2 Hz, 1 H, C*H*OMEM), 4.65 (d, *J* = 7.0 Hz, 1 H, O*H*CHO), 4.73 (d, *J* = 7.0 Hz, 1 H, O*H*CHO), 5.42 (dd, *J* = 11.2, 6.2 Hz, 1 H, C*H*OC=O), 7.23−7.60 (m, 8 H, aromatic H), 8.03−8.10 (m, 2 H, aromatic H). − $^{13}C$ NMR ($CDCl_3$): δ = 57.6 (t, N−*C*$H_2$), 58.1 (t, N*C*$H_2$), 59.5 (q, *Me*), 60.9 (t, N*C*$H_2$Ph), 67.6 (t, $OCH_2CH_2O$), 72.1 (t, $OCH_2CH_2O$), 73.0 (d, *C*HOMEM), 75.2 (d, *C*HOC=O), 95.8 (t, $OCH_2O$), 127.3 (d, aromatic C), 128.4 (d, aromatic C), 128.9 (d, aromatic C), 129.7 (d, aromatic C), 130.1 (s, aromatic C), 133.0 (d, aromatic C), 138.0 (s, aromatic C), 166.1 (s, C=O). − MS (70 eV); *m/z* (%): 385 (3) [$M^+$], 204 (27), 159 (92), 158 (100), 105 (90), 91 (100), 77 (80). − $C_{22}H_{27}NO_5$ (385): calcd. C 68.57, H 7.01, N 3.64; found C 68.90, H 7.17, N 3.31.

*Ditosylate* **9**: Yield: 87%. − $R_f$ (petroleum ether/$Et_2O$, 2:1) = 0.38. − $[\alpha]_D^{20}$= +8.3 (*c* = 0.41 in $CHCl_3$). − $^1H$ NMR ($CDCl_3$): δ = 1.14 (s, 9 H, O*tBu*), 2.32 (s, 3 H, *Me*Ar), 2.34 (s, 3 H, *Me*Ar), 4.08 (m, 3 H, C*H*$_2$O + C*H*O*t*Bu), 4.30 (m, 2 H, C*H*$_2$O), 5.1 (q, *J* = 4.0 Hz, 1 H, C*H*OC=O), 7.08−7.86 (m, 13 H, aromatic H). − $^{13}C$ NMR ($CDCl_3$): δ = 21.6 (q, *tBu*), 28.2 (q, 2 × Me), 67.1 (t, *C*$H_2$O), 67.7 (d, *C*HO), 69.3 (t, *C*$H_2$O), 71.1 (d, *C*HO), 75.8 (s, *C*$Me_3$), 127.8 (d, aromatic C), 127.9 (d, aromatic C), 128.3 (d, aromatic C), 129.2 (s, aromatic C), 129.7 (d, aromatic C), 129.8 (d, aromatic C), 130.0 (d, aromatic C), 132.4 (s, aromatic C), 133.3 (d, aromatic C), 144.9 (s, aromatic C), 164.9 (s, C=O). − $C_{29}H_{34}O_8S_2$ (574.7): calcd. C 58.98, H 5.76; found C 58.67, H 5.75.

*Pyrroline N-Oxides* **12** *and* **13**: A solution of pyrrolidine **10** (570 mg, 1.93 mmol) in $CHCl_3$ (28 ml), cooled at 0°C with an ice bath, was added to oxaziridine **11** (1.00 g, 3.86 mmol). The solution was stirred at 0°C for 20 min, then at room temp. for 40 min. The resulting suspension was filtered and the solution concentrated to afford a crude reaction mixture which was then purified by flash column chromatography to afford the nitrones **12** (202 mg, 34%) and **13** (150 mg, 25%).

**12**: $R_f$ (AcOEt/MeOH, 15:1) = 0.34. − M.p. 78−79°C; $[\alpha]_D^{20}$ = −80.0 (*c* = 0.31 in methanol). − IR ($CHCl_3$): $\tilde{\nu}$ = 2897 $cm^{-1}$, 1722 (C=O), 1574 (C=N), 1262 (C−O), 1094 (C−O). − $^1H$ NMR ($CDCl_3$): δ = 3.35 (s, 3 H, O*Me*), 3.74−3.45 (m, 4 H, $OCH_2CH_2O$), 4.18 (d, *J* = 6.22 Hz, 2 H, N*C*$H_2$), 4.69 (d, *J* = 7.4 Hz, 1 H, O*H*CHO), 4.78 (d, *J* = 7.4 Hz, 1 H, OHC*H*O), 4.75 (m, 1 H, C*H*-OMEM), 6.03 (d, *J* = 5.2 Hz, 1 H, C*H*OC=O), 7.08 (s, 1 H, N=C*H*), 7.64−7.42 (m, 3 H, aromatic H), 8.04 (m, 2 H, aromatic H). − $^{13}C$ NMR ($CDCl_3$): δ = 59.0 (q, O*Me*), 66.2 (t, N*C*$H_2$), 67.7 (t, $OCH_2CH_2O$), 70.6 (d, *C*HOMEM), 71.5 (t, $OCH_2CH_2O$), 72.9 (d, *C*HOC=O), 95.6 (t, $OCH_2O$), 128.6 (d, aromatic C), 129.9 (d, aromatic C), 131.5 (d, N=*C*H), 133.7 (aromatic C), *ipso*-carbon signal not detected, 166.0 (s, C=O). − MS (70 eV); *m/z* (%): 204 (3) [$M^+$ − PhCO], 203 (3), 105 (62), 104 (74), 89 (48), 58 (100). − $C_{15}H_{19}NO_6$ (309.3): calcd. C 58.25, H 6.19, N 4.53; found C 58.57, H 6.45, N 4.19.

**13**: $R_f$ (AcOEt/MeOH, 15:1) = 0.22. − M.p. 93−94°C; $[\alpha]_D^{20}$ = +100.7 (*c* = 0.30 in methanol). − IR ($CHCl_3$): $\tilde{\nu}$ = 2932 (CH) $cm^{-1}$, 1724 (C=O), 1584 (C=N), 1266 (C−O) 1113 (C−O). − $^1H$ NMR ($CDCl_3$): δ = 3.36 (s, 3 H, O*Me*), 3.80−3.46 (m, 4 H, $OCH_2CH_2O$), 4.25 (d, *J* = 5.1 Hz, 2 H, N*C*$H_2$), 4.66 (d, *J* = 7.0 Hz, 1 H, OHC*H*O), 4.77 (d, *J* = 7.0 Hz, 1 H, OHC*H*O), 5.07 (dd, *J* = 6.0, 1.0 Hz, 1 H, C*H*OMEM), 5.74 (q, *J* = 6.0 Hz, 1 H, C*H*OC=O), 7.08 (d, *J* = 1.8 Hz, 1 H, N=C*H*), 7.64−7.42 (m, 3 H, aromatic H), 8.04 (m, 2 H, aromatic H). − $^{13}C$ NMR ($CDCl_3$): δ = 59.0 (q, O*Me*), 65.3 (t, N*C*$H_2$), 67.4 (d, CHOMEM), 68.2 (t, $OCH_2CH_2O$), 71.5 (t, $OCH_2CH_2O$), 76.1 (d, *C*HOC=O), 95.9 (t, $OCH_2O$), 97.1 (d, N=*C*H), 128.6 (d, aromatic C), 129.8 (d, aromatic C), 133.7 (d, aromatic C), *ipso*-carbon signal not detected, 166.0 (s, C=O). − MS (70 eV); *m/z* (%): 309 (0.2) [$M^+$], 204 (1), 203 (14), 105 (100), 89 (45), 77 (43), 59 (56). − $C_{15}H_{19}NO_6$ (309.3): calcd. C 58.25, H 6.19, N 4.53; found C 57.91, H 6.19, N 4.20.


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