



## Highly Selective Chirally Templated Isomünchnone Cycloadditions of Achiral Aldehydes: Synthesis of an Enantiopure $\alpha,\beta$ -Dihydroxyacid.

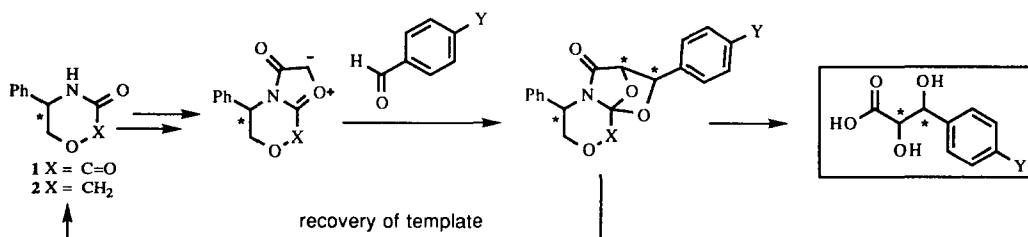
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**Abstract:** Additions of *p*-nitro- and *p*-methoxybenzaldehyde to isomünchnone derivatives of (5*S*)-phenyloxazin-3-one and -2,3-dione led to corresponding adducts (3,4, 6) with excellent diastereofacial- and *exo*-selectivity. Hydrolysis and subsequent cleavage of adduct 3 permitted recovery of the original template and furnished dihydroxyacid 9 that was transformed into the known ethyl ester 10. Comparison of its optical rotation with the literature value confirmed its high optical purity.

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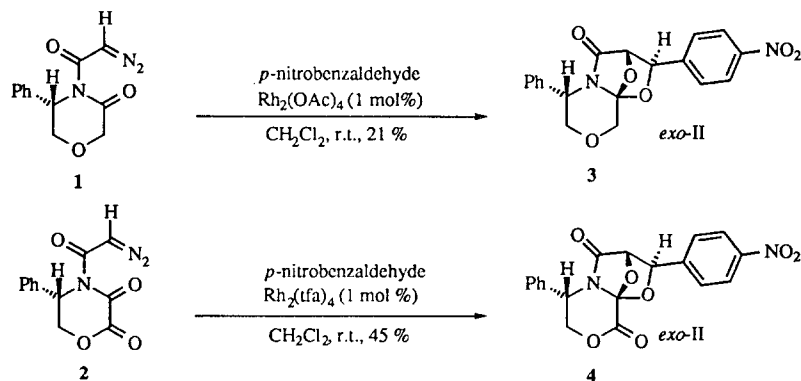
In previous papers<sup>1</sup> we had described a methodology for introducing chiral auxiliaries in isomünchnone cycloadditions of carbon-carbon dipolarophiles. The results obtained encouraged us to investigate the feasibility of a route for the preparation of enantiopure  $\alpha,\beta$ -dihydroxyacids from achiral aromatic aldehydes by application of our chirally templated cycloaddition mode. Optically active 1,2-diol units are often observed as key structures of natural products such as macrolides, polyether antibiotics and carbohydrates. Aromatic  $\alpha,\beta$ -dihydroxy acids in particular are e.g. used in the synthesis of chloramphenicol (broad spectrum antibiotic)<sup>2</sup>, diltiazem (calcium channel blocker),<sup>3</sup> macrocyclic antitumor drugs,<sup>4</sup>  $\beta$ -lactams,<sup>5</sup> and the taxol side chain.<sup>6</sup> Our target was to investigate isomünchnone cycloadditions with chiral diazoimides derived from (5*R*)- and (5*S*)-phenyloxazin-3-one and -2,3-dione and aldehydes.<sup>7</sup> Such cycloadducts should be capable of furnishing enantiopure  $\alpha,\beta$ -dihydroxyacids while regenerating the template (Scheme 1).



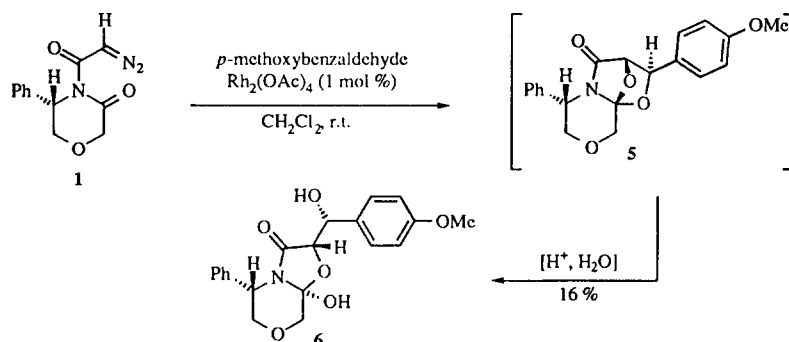
Scheme 1

The  $\alpha$ -diazocompounds were transformed into isomünchnones using rhodium(II) acetate or -trifluoroacetate (1 mol %) in the presence of aldehyde (Scheme 2, 3). Gratifyingly all cycloadditions with *p*-nitro- and *p*-methoxybenzaldehyde proceeded with high diastereofacial- and high *exo*-selectivity though in comparatively

moderate yields. The observed high regioselectivity is in accordance with other carbonyl ylide additions to aldehydes,<sup>7</sup> although the exclusive approach from the  $\beta$ -face of the molecule is not fully understood but the *exo*-control agrees with earlier observations where steric hinderance precludes an *endo*-approach.<sup>8</sup> The lower yield for aldehyde cycloadditions might be explained by higher LUMO energy levels for aldehyde dipolarophiles compared to alkene and alkyne derivatives resulting in a bigger energy gap between HOMO of the dipole and LUMO of the dipolarophile (in a HOMO controlled reaction).<sup>9</sup>



Scheme 2



Scheme 3

Isolation of the partly hydrolysed adduct in case of the addition of the isomünchnone derived from diazocompound 3 to anisaldehyde (Scheme 3) is presumably a reflection of the higher electrophilicity of the acetal oxygen due to the electron donating *p*-methoxy substituent compared to the strongly withdrawing effect. The stereochemistries of the cycloadducts (3,4,6)<sup>10</sup> were assigned by evaluation of the NOE-data and comparison of  $^1\text{H}$ -NMR data with those of compounds 3 and 6 whose structures were verified by single X-ray crystal structures (Figure 1).<sup>11</sup>

In order to investigate access to  $\alpha,\beta$ -dihydroxyacids<sup>12</sup> from the aldehyde adducts, cycloadduct 3 was subjected to initial mild acid ketal hydrolysis followed by treatment with lithium hydroperoxide according to a method by Evans<sup>13</sup> to cleave the exocyclic amide selectively. Extraction of the basic reaction mixture with dichloromethane afforded the template in a yield of 79%  $\{[\alpha]_{\text{D}}^{23} +89.4$  ( $c=0.8$ ,  $\text{CHCl}_3$ ); starting material  $[\alpha]_{\text{D}}^{23} +90.3$  ( $c=1.02$ ,  $\text{CHCl}_3$ )}.

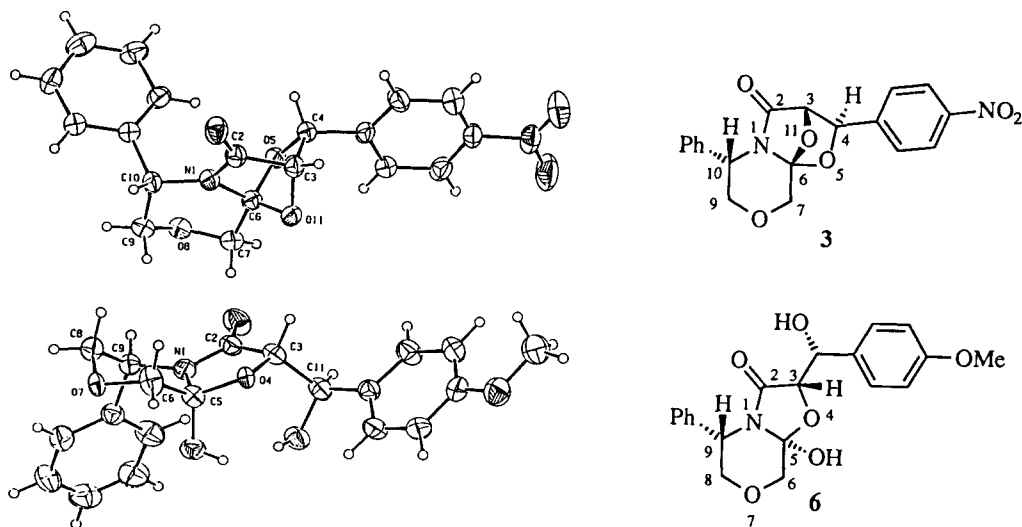
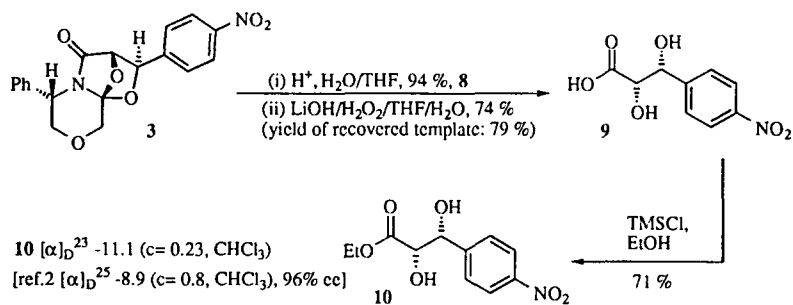


Figure 1

Acidification of the aqueous layer, followed by extraction with ethyl acetate led to the crude  $\alpha,\beta$ -dihydroxyacid **9** in a yield of 74 % which was immediately treated with  $\text{Me}_3\text{SiCl}/\text{EtOH}$ <sup>14</sup> to furnish the known ethyl ester **10** in 53 % overall yield (from diol **8**).<sup>2</sup> Our value of  $-11.1$  compared to the literature value of  $-8.9$  for material with quoted ee of 96 %<sup>2</sup> coupled with the lack of racemisation of recovered template confirmed the high optical purity of the compound obtained *via* the isomünchnone cycloaddition route.



Scheme 4

In conclusion we have presented a method with potential for preparation of enantiopure  $\alpha,\beta$ -dihydroxyacids from achiral aldehydes using a novel chirally templated highly selective isomünchnone cycloaddition procedure in which the original chiral template may be recovered.

### Acknowledgements

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## References and Notes

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10. All novel compounds described had structures in accordance with their spectroscopic data. Selected spectroscopic data: (3) m.p. 149-152 °C; C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>6</sub> requires 369.1086, found MH<sup>+</sup> 369.1078;  $\nu_{\max}$  (KBr disc) 2981-2926, 1738, 1519, 1347, 1004, 973, 897 and 707 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.37-7.28 (m, 9H, Ph and *p*-NO<sub>2</sub>Ph), 4.90 (t, J<sub>9Ha,10</sub> = J<sub>9Hb,10</sub> = 4.0 Hz, 1H, 10-H), 4.87 (s, 1H, 3-H), 4.75 (s, 1H, 4-H), 4.62 (d, J<sub>AB</sub> = 12.8 Hz, 1H, 7-Ha or 7-Hb), 4.35 (d, J<sub>AB</sub> = 12.7 Hz, 1H, 7-Ha or 7-Hb), 4.13 (dd, J<sub>AB</sub> = 12.1, J = 4.8 Hz, 1H, 9-Ha or 9-Hb), 4.06 (dd, J<sub>AB</sub> = 12.1, J = 3.7 Hz, 1H, 9-Ha or 9-Hb);  $\delta_{\text{C}}$  (100.4 MHz, CDCl<sub>3</sub>) 169.7 (C-2), 148.1 (2C, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), 144.2 (2C, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), 138.0 (ipso C, Ph), 128.8, 128.2, 127.3, 127.2, 123.8 (Ph), 109.5 (C-6), 83.1 (C-3), 74.3 (C-4), 70.9 (C-7), 66.9 (C-9), 52.2 (C-10); [ $\alpha$ ]<sub>D</sub><sup>24</sup> -52.6 (c = 1.13, CHCl<sub>3</sub>); (10) m.p. 137-139 °C, Lit.<sup>2</sup> 139 °C;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.24 (d, J = 8.8 Hz, 2H, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), 7.60 (d, J = 8.8 Hz, 2H, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), 5.14 (dd, J<sub>2,3</sub> = 2.5, J<sub>3,OH</sub> = 7.7 Hz, 1H, 3-H), 4.38 (dd, J<sub>2,3</sub> = 2.6 Hz, J<sub>2,OH</sub> = 5.2 Hz, 1H, 2-H), 4.32 (q, J = 7.0 Hz, 2H, CH<sub>2</sub>), 3.19 (d, J<sub>2,OH</sub> = 5.2 Hz, 1H, OH), 2.86 (d, J<sub>3,OH</sub> = 7.7 Hz, 1H, OH), 1.32 (t, J = 7.0 Hz, 3H, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100.4 MHz, CDCl<sub>3</sub>) 172.1 (C-1), 147.7, 147.3 (2 x ipso C, C<sub>6</sub>H<sub>4</sub>), 127.3, 123.6 (C<sub>6</sub>H<sub>4</sub>), 74.1 (C-2 or C-3), 73.6 (C-2 or C-3), 62.7 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>); [ $\alpha$ ]<sub>D</sub><sup>23</sup> -11.1 (c = 0.23, CHCl<sub>3</sub>), ref. 2 96 % ee, [ $\alpha$ ]<sub>D</sub><sup>25</sup> -8.9 (c = 0.8, CHCl<sub>3</sub>).
11. Crystal data (3), C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>, M = 368.3, orthorhombic, spacegroup P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, a = 7.882 (7), b = 9.636 (9), c = 23.11 (2) Å, U = 1755 Å<sup>3</sup>, z = 4, dc = 1.394 Mgm<sup>-3</sup>, 5165 reflections collected, 3203 independent R<sub>9int</sub> 0.032. Crystal data (6), C<sub>22</sub>H<sub>21</sub>NO<sub>4</sub>, M = 363.4, orthorhombic, spacegroup P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, a = 5.494 (7), b = 13.908 (11), c = 23.731 (22) Å, U = 1813 Å<sup>3</sup>, Z = 4, dc = 1.331 Mgm<sup>-3</sup>, F(000) = 768, 5407 reflections collected, 3236 independent reflections R (int) = 0.035. Data for both crystals were collected with Moka radiation ( $\lambda$  = 0.71073 Å) using the MARresearch Image Plate System. The crystals were positioned at 70 mm from the Image Plate. 95 frames were collected at 2° intervals with a counting time of 2 mins. Data analysis was carried out with the XDS program. The two structures were solved using direct methods with the Shelx86 program. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. Both structures were refined on F<sup>2</sup> with Shelxl. Final R factors for data with I > 2s(I) were 0.0897 for 6 and 0.0620 for 3. Crystal Data for both structures have been deposited at the Cambridge Crystallographic Data Centre.
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