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Synthesis of the first water-soluble C_2-symmetric bis(oxazolidinone) as a potential bifunctional chiral auxiliary

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Abstract

The first water-soluble C_2-symmetric bis(oxazolidinone) **1**, a potential bifunctional chiral auxiliary, has been synthesized via regioselective intramolecular cyclization of a biscarbamate. The sodium enolate derived from *N*,*N'*-di(phenylacetyl)bis(oxazolidinone) **7** reacts with methyl iodide with high facial selectivity (95:5). © 2000 Elsevier Science Ltd. All rights reserved.

It is often observed, as reviewed by Whitesell, that auxiliaries with C_2-symmetry elements perform in their capacity as stereochemical directors to provide higher levels of absolute stereochemical control compared to those totally lacking in symmetry.[1] Therefore, C_2-symmetrization of the non-symmetrical chiral auxiliaries is central in the development of chiral auxiliaries. Recently, to reduce the effective molecular mass (EMM) as far as possible within the limits of maintaining high stereocontrol, a series of C_2-symmetric imidazolidinones[2] and a cyclic sulfamide[3] have been synthesized. In spite of the high chiral induction abilities of chiral oxazolidin-2-ones as chiral auxiliaries, no C_2-symmetric versions have been reported yet.[4] Therefore, we decided to synthesize C_2-symmetric bis(oxazolidinone) **1** as a potential bifunctional chiral auxiliary. Bis(oxazolidinone) **1** has the following characteristic features: (a) each of the oxazolidinone rings could exhibit equivalent functions either sterically or stereoelectronically, and should act as an independent chiral-directing group; (b) C_2-symmetry of **1** could reduce the effective molecular mass (EMM = 86). Moreover, both enantiomers are available from inexpensive (D)- and (L)-tartaric acid.

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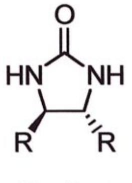

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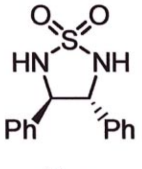

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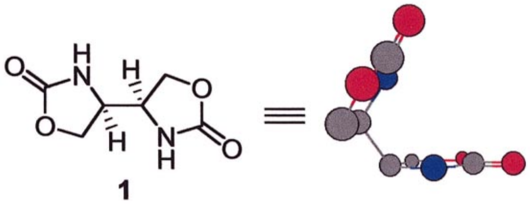

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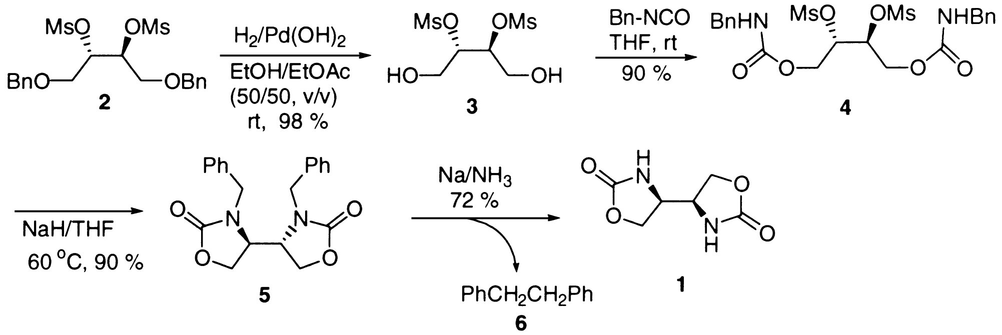
Recently, we and others have synthesized C_2-symmetric chiral bis(oxazolines),[5] bis(oxazines)[6] and bis(pyrrolinyl) or fused-bicyclic pyrrolinyl[7] via regioselective intramolecular cyclization of C_2-symmetric bis(amide) and bis(amine). It has also been reported that 2,3-epoxy alcohols react with isocyanates to provide the corresponding oxazolidinones.[8] Therefore, for the synthesis of the bis(oxazolidinone) **1**, the regioselective intramolecular cyclization reactions have been extended to the C_2-symmetric bis(carbamate) **4** which was synthesized from readily available dibenzyloxy dimesylate **2**[5a] as shown in Scheme 1. Debenzylation of **2** using $Pd(OH)_2/H_2$ afforded the debenzylated product **3** almost quantitatively. Subsequent reaction of **3** with benzyl isocyanate in THF afforded **4** (90%). When the bis(carbamate) **4** was treated with NaH, the ring closure occurred highly regioselectively to form bis(oxazolidinone) **5** in 90% yield.



Scheme 1.

For the debenzylation, N,N'-dibenzyl bis(oxazolidinone) **5** was subjected to Birch conditions (Na/NH_3). Unfortunately, all attempts to isolate the debenzylated product **1** from the organic phase failed. Instead, we could only isolate 1,2-diphenylethane **6**, which may be formed via intramolecular reductive homocoupling of the *N*-benzyl groups followed by debenzylation. Eventually, it was found that the bis(oxazolidinone) **1** is highly soluble in water. Thus, the desired bis(oxazolidinone) **1** could be isolated from the aqueous phase, i.e. after evaporation of water, the solid residue was extracted with Soxhlet using acetonitrile to give **1** in 72% yield. All spectral data including X-ray crystallographic analysis consistent with the structure of **1** (Fig. 1).[9] As shown in X-ray crystal structure of **1**, the two oxazolidinone rings formed a concave shape and the two nitrogen atoms are placed on opposite sides. Worthy of note is that the high water solubility of **1** may provide an additional advantage, i.e. easy separation, as with a solid supported auxiliary.[10]

As a preliminary application of this novel water-soluble C_2-symmetric bifunctional bis(oxazolidinone) **1**, auxiliary controlled diastereoselective methylation has been examined. The phenylacetyl units were successfully coupled to the auxiliary **1** according to the procedure reported by Prashad

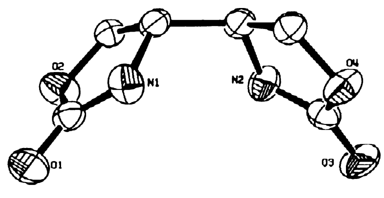
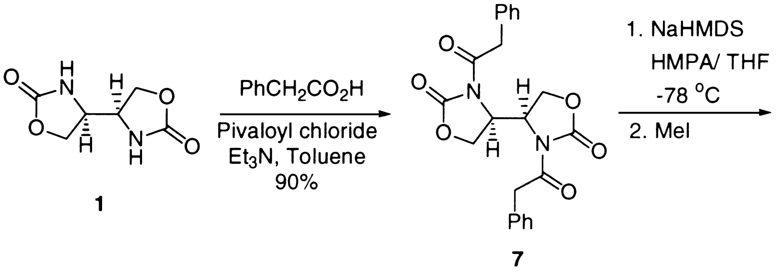
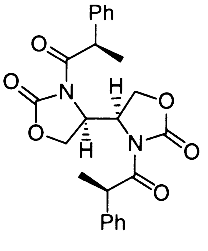


Figure 1. ORTEP diagram of compound **1**

et al., and afforded **7** in 90% yield.[11] For the diastereoselective methylation of **7**, to a solution of **7** in THF (0.1 M in THF) and HMPA (2/1,v/v) was slowly added 2.2 equivalents of $NaN(TMS)_2$ at –78°C followed by excess methyl iodide (5 equivalent) to give the methylated products in 78% yield. The distribution of the three possible diastereomers **8**, **9** and **10** was determined by ^{1}H NMR analysis. In ^{1}H NMR spectrum, the methyl proton signal of the major isomer **10** resonated at 1.52 ppm (d, $J=7.0$ Hz) and the two sets of methyl proton signals of the minor isomer **9** were detected at 1.48 and 1.32 ppm (d, $J=7.0$ Hz). The integration ratio of the major isomer **10** and minor isomer **9** is 10:1. If it is assumed that both alkylation steps proceeded with the same diastereoselectivity and the selectivity of one of the alkylation steps is X:1, the expected ratio of **8**:**9**:**10** should be $1{:}2X{:}X^2$. Calculation from the ratio of **9** and **10** resulted in a selectivity X of 20, consistent with a facial selectivity of 95:5. Hydrolysis of **10** afforded (*S*)-α-methylphenylacetic acid, and the bifunctional chiral auxiliary **1** can be recovered quantitatively from the aqueous phase by Soxhlet extraction using acetonitrile.





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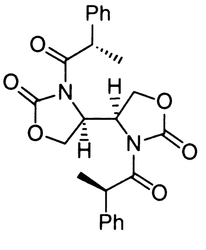

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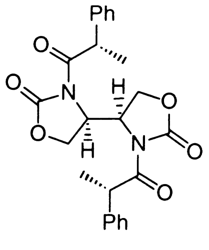

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In conclusion, we have synthesized a novel water-soluble C_2-symmetric bis(oxazolidinone) **1** via base induced regioselective intramolecular cyclization of bis(carbamate) **4**. The high diastereoselective methylation of **7** clearly indicates that each of the oxazolidinone rings could exhibit equivalent functions both sterically or stereoelectronically, and acts as an independent chiral-directing group. Moreover, the high water solubility of **1** allowed its easy separation from the product after cleavage of the *N*-acyl group. Studies on the extension of our bis(oxazolidinone) system to other asymmetric reactions are in progress.

Acknowledgements

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9. Data for **1**: mp 247–249°C; $[\alpha]_D^{25}$ −9.26 (c 1.02, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (bs, 2H), 4.35 (t, $J=8.9$ Hz, 2H), 4.06 (ABq, $J=4.6$ Hz, 2H), 3.86 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.79, 66.69, 54.72. The X-ray data were collected on an Enraf–Nonius CAD-4 automatic diffractometer with graphite-monochromated MoKα ($\lambda=0.71073$ Å) at 293(2) K. The structure was solved by the Patterson method (SHELXS-86) and was refined by full-matrix least-square technique. $C_6H_8N_2O_4$, M = 172.14, orthorhombic, $a=5.638(3)$, $b=5.649(2)$, $c=22.237(5)$ Å, space group = $P2_12_12_1$ (no.19), $V=708.2(5)$ Å^3, $Z=4$, $D_c=1.596$ g/cm^3, crystal size = 0.2×0.2×0.18 mm, $F(000)=360$, a total of 568 reflections in the range of $1.83° \leq \theta \leq 24.94°$ measured, the $\Delta\rho$max and $\Delta\rho$min are 0.288 and 0.265 e Å^{-3}, goodness-of-fit = 1.133, $I/\sigma(I) \geq 2.0$, $R=0.0537$.
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