

## A New Asymmetric Approach Towards 2-Pyrrolidinones and Pyrrolidines: Simple *Versus* Double Stereodifferentiation

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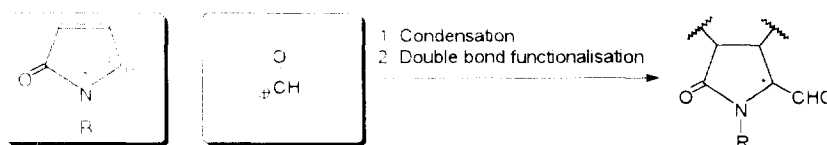
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**Abstract** The condensation of a chiral 2-silyloxypyrrole derivative with achiral and chiral formyl cation equivalents has been studied for the first time. The methodology allows to build-up pyroglutamic aldehydes and proline systems with a stereocontrol from good to excellent. Whereas the chiral auxiliary residing on the pyrrole system shows an intrinsic good level of diastereoface discrimination at C-5, the combined use of a 2-methoxy-3-tosyl-oxazolidine as a chiral formylating agent allows a total stereocontrol of the condensation. A rationale for the observed stereochemical outcome is presented.

2-Pyrrolidinone and pyrrolidine derivatives are compounds of utmost biological and pharmacological interest. Thus, for example, several molecules belonging to the former class are potent neuroactive compounds owing to their interaction with pyroglutamate receptors,<sup>1</sup> whereas many hydroxylated pyrrolidines are quite popular for their glycosidase inhibitory activities.<sup>2</sup> Although most of the syntheses of such compounds have been accomplished starting from the naturally occurring pyroglutamic acid,<sup>3</sup> approaches featuring more versatile *de novo* stereoselective constructions of the five membered ring<sup>4</sup> have been so far less studied and new asymmetric routes are certainly highly desirable.

In this context, the use of 1-methyl-2-trimethylsilyloxy-pyrrole to build-up C-5 substituted pyrrolidinone derivatives, was first reported in 1984 by Ricci and coworkers.<sup>5</sup> More recently, Casiraghi's group<sup>6</sup> has smartly exploited 1-*tert*-butoxycarbonyl-2-dimethyl-*tert*-butylsilyloxy-pyrrole (TBSOP) which reacted with glyceraldehyde acetonide and other related aldehydes with excellent diastereoselection. Given these interesting precedents, we were intrigued by the possibility of developing a chiral silyloxy nucleophile and studying it in double stereoselection.

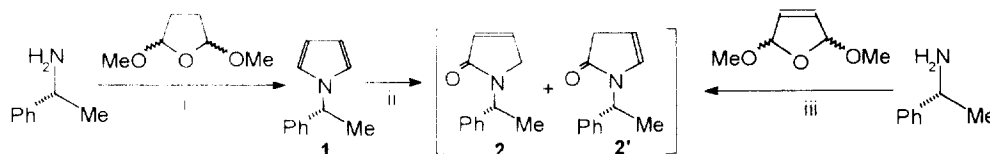
In the present communication we wish to disclose our recent efforts in the development of a new  $\alpha$ -methyl-benzylamine-derived 2-silyloxypyrrole as a chiral 1,5-dihydro-pyrrol-2-one-5-anion equivalent and its formylation at C-5 with achiral and chiral C=O electrophiles (Scheme 1).



Scheme 1

Accordingly, Paal-Knorr type condensation between (*R*)-(+)- $\alpha$ -methyl-benzylamine and 2,5-dimethoxytetrahydrofuran in AcOH gave the known pyrrole 1, which was submitted to 30% hydrogen peroxide oxidation<sup>8</sup> in pyridine, to give the corresponding  $\Delta^1$ - and  $\Delta^2$ -pyrrolin-2-ones 2 and 2' as an 88:12 mixture.<sup>9</sup> Although the oxidation reaction gave good

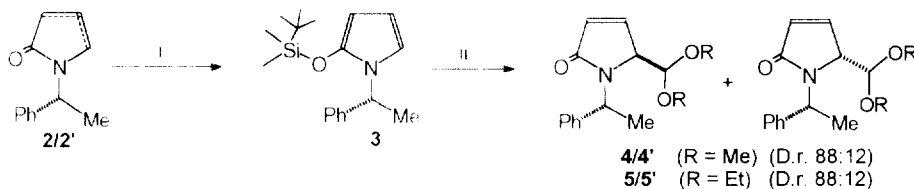
yields of the desired 2-pyrrolinones, serious reproducibility problems were often encountered when performing the reaction on multigram scale. This led us to search for a better route to **2/2'**. After some trials we eventually found that condensation of (*R*)-(+)- $\alpha$ -methyl-benzylamine with 2,5-dimethoxy-2,5-dihydrofuran in AcOH, according to a modification of a procedure by Royer,<sup>4b</sup> gave directly **2/2'** in a good and reproducible yield (Scheme 2).



Scheme 2

Reagents i) AcOH, reflux, 87% ; ii) 30% H<sub>2</sub>O<sub>2</sub>, pyridine, 70°C, 7d, 53% (70% considering recovered starting material) ; iii) AcOH, reflux, 60%.

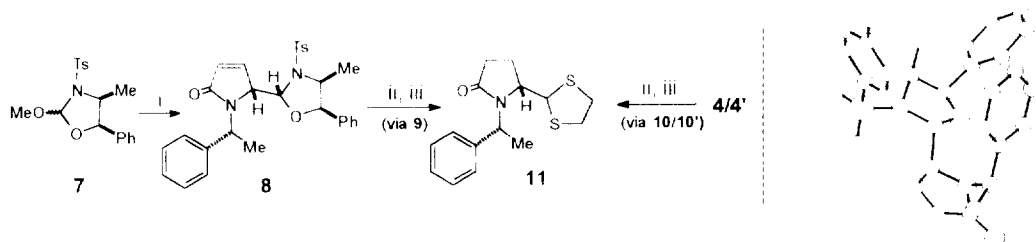
Treatment of **2/2'** with *t*-BuMe<sub>2</sub>SiCl and *i*-Pr<sub>2</sub>EtN in CH<sub>2</sub>Cl<sub>2</sub> gave the highly moisture sensitive 2-silyloxy derivative **3**<sup>10</sup> which was next tested in Lewis acid mediated condensations. Addition of BF<sub>3</sub>·OEt<sub>2</sub> to a mixture of **3** and trimethyl orthoformate, at -78°C, gave the desired adducts **4** and **4'** as an 88:12 mixture of unseparable diastereomers. When triethyl orthoformate was used instead of the trimethyl derivative the pair **5/5'** was analogously obtained with identical selectivity (Scheme 3).<sup>11</sup>



Scheme 3

Reagents i) *t*-BuMe<sub>2</sub>SiCl, *i*-Pr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, 84°C ; ii) HC(OR)<sub>3</sub> (R = Me or Et), BF<sub>3</sub>·OEt<sub>2</sub> (2.0 mol equiv.), CH<sub>2</sub>Cl<sub>2</sub> -78°C (R = Me, 66%, R = Et 62%)<sup>11</sup>

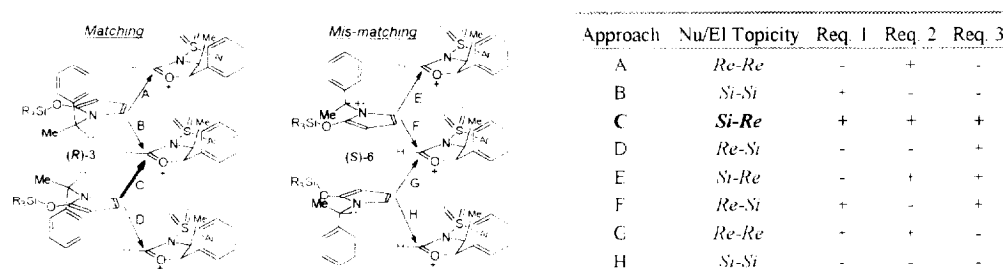
The behaviour of (*R*)-**3** and of its enantiomer (*S*)-**6**<sup>12</sup> was next tested in double stereoselection using the norephedrine derived 2-methoxy-3-tosyl oxazolidine **7**<sup>13</sup> as a formylmium equivalent. In the event, the BF<sub>3</sub>·OEt<sub>2</sub> promoted condensation between **4** and **6** gave rise only to hydrolysed material. On the other hand, we were pleased to find that the corresponding condensation with the antipode **3** gave the adduct **8** as the only new product. X-ray analysis of this compound unequivocally established the *R* absolute configuration of the two newly created stereocentres.<sup>14</sup> For correlation purposes the adducts **8** and **4/4'** were then transformed as described in Scheme 4. Standard hydrogenation of **8** gave the corresponding pyrrolidinone **9**, which was submitted to BF<sub>3</sub>·OEt<sub>2</sub> mediated *trans*-thioacetalisation with 1,2-ethanedithiol to give the dithiolane **11** as the only diastereoisomer.



Scheme 4

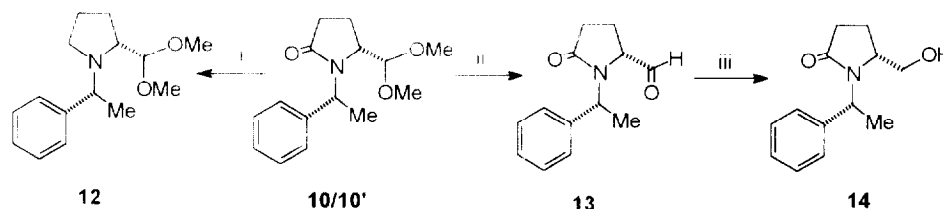
Left side: Reagents i) **3**, BF<sub>3</sub>·OEt<sub>2</sub> (2.0 mol equiv.), CH<sub>2</sub>Cl<sub>2</sub> -78°C, 65% ; ii) H<sub>2</sub>, Pd/C, MeOH, 95% from **8**, 99% from **4/4'** ; iii) HSCH<sub>2</sub>CH<sub>2</sub>SH, BF<sub>3</sub>·OEt<sub>2</sub>, 70% from **9**, 62% from **10/10'**. Right side: X-ray crystal structure of **8**.

Since the same hydrogenation / thioacetalisation sequence, when applied to **4/4'**, gave **11** as the major diastereomer, it appears that the intrinsic induction of the silyloxy derivative (**R**)-**3** favours addition from the C-5/Si face, thereby generating an *R* configured stereocentre (requirement 1). On the other hand, the known steric and stereoelectronic demands associated with the oxazolium species derived from **7**<sup>13</sup> favour a transition state having the following features: a) Transient formation of an oxazolium cation, mainly stabilised by the oxygen atom, allowing exclusive approach of the nucleophile from the *Re* face (requirement 2). b) Staggered approach of the reacting partners where the small hydrogen atom on C-5 of the nucleophile occupies the position between the oxazolidine ring heteroatoms and the reacting  $\pi$ -bonds are disposed so as to allow maximal charge separation (requirement 3).<sup>15</sup> It thus follows that the possible competing transition states involved in the matching and mis-matching pairs, **3/7** and **6/7** respectively, may be described as shown in the Figure. Worthy of note, only approach C, leading to the observed diastereoisomer, fulfils at the same time all the above mentioned requirements. On the other hand, it turns out that the transitions states associated to the mis-matched pair are so unfavourable that the condensation does not take place.



**Figure** Stereochemical models for the competing transition states of the matching (**3/7**) and mis-matching (**6/7**) pairs. Key: "+" = fulfilled requirement; "-" = unfulfilled requirement

In order to test the scope of the present methodology some preliminary experiments of functional group modification have also been performed. Thus, treatment of the pyrrolidinone **10/10'** with  $\text{NaBH}_4$  /  $\text{I}_2$ <sup>16</sup> smoothly gave the pyrrolidine derivative **12**. On the other hand, aqueous acidic hydrolysis of the same compound afforded the corresponding aldehyde **13** without detectable racemisation. Treatment of **13** with  $\text{NaBH}_4$  in THF gave the alcohol **14**.<sup>17</sup>



**Scheme 5**

Reagents: i)  $\text{NaBH}_4$ , 1), THF, reflux, 60%, ii) 37%  $\text{HCl}$ , THF, 50°C, 73%, iii)  $\text{NaBH}_4$ , THF/ $\text{H}_2\text{O}$  3/1, 70%.

In summary, in the present communication we have developed a new chiral 1,5-dihydro-pyrrol-2-one-5-anion equivalent which has been studied in formylation at C-5 with achiral (orthoformates) and chiral (2-methoxy-3-tosyl-oxazolidines) C-1 electrophiles. This methodology enabled the construction of 5-substituted 2-pyrrolidinone and pyrrolidine systems with good to excellent diastereocontrol. We are presently focusing our work on the cleavage and the possible modifications of the auxiliary moiety in order to achieve higher diastereoselections even with achiral electrophiles.

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- All new compounds exhibited spectroscopic (IR,  $^1\text{H}$  and  $^{13}\text{C}$ ) and analytical data in accord with the assigned structure.
- Attempted silica-gel or alumina chromatographic purification of **3** constantly gave back the hydrolysed starting material.
- These conditions are the optimal ones so far obtained. Other Lewis acids such as  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{CF}_3\text{SO}_2\text{SiMe}_3$ ,  $\text{SbCl}_5$ , and other molar ratios gave less satisfactory results or no reactivity at all. Interestingly, the reaction did not work in the presence of catalytic amounts of  $\text{BF}_3 \cdot \text{OEt}_2$ .
- (**S**)-**6** was obtained starting from of (+)-(-)- $\alpha$ -methyl-benzylamine following the same procedure as used for antipode **3**.
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- The crystal data for **8** are as follow: orthorhombic,  $P2_12_12_1$  with  $a = 8.935(1)$ ,  $b = 14.348(1)$ ,  $c = 19.689(1)$  Å,  $V = 2530.4(1)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_{\text{calc}} = 1.319$  g cm<sup>-3</sup>,  $\lambda = 1.54184$  Å (graphite monochromated),  $\mu$  (Cu K $\alpha$ ) = 1.406 mm<sup>-1</sup> by Enraf-Nonius CAD-4 diffractometer. Final R value was 0.038 for 2655 reflections. Atomic coordinates and e.s.d.'s have been deposited at the Cambridge Crystallographic Data Centre.
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- Curiously, the same reduction did not take place when performed in MeOH. This result suggests the quantitative involvement of the hemiacetal derivative of the highly electrophilic aldehyde **13** in the presence of this solvent.

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