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TETRAHEDRON

A New Asymmetric Approach Toward 5-Substituted Pyrrolidin-2-one Derivatives

Giovanni Poli,* Simone Ciofi Baffoni, Giuliano Giambastiani, Gianna Reginato

Centro CNR per la Struttura e la Reattività degli Eterocicli e loro Applicazioni, Dipartimento di Chimica Organica dell'Università di Firenze, Via G. Capponi 9, I-50121, Firenze, Italy

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Abstract: The condensation between a chiral 2-silyloxypyrrole and either achiral or chiral formyl cation equivalents has been studied. The methodology has allowed to build-up 5-substituted pyrrolidin-2-one derivatives with a stereocontrol from good to excellent. The chiral auxiliary located on the silyloxypyrrole showed an intrinsic good level of diastereoface discrimination at C-5. However, the use of a 2-methoxy-3-tosyl-oxazolidine as chiral formylating agent allowed a total stereocontrol in the condensation. A rationale for the observed stereochemical outcome is presented. The stereoselective manipulation of these adducts provided new potentially interesting pyroglutamic aldehyde and prolinal derivatives, whereas treatment with $TiCl_4$ triggered unexpectedly a Pomeranz-Fritsch type intramolecular condensation affording a benzocondensated indolizidinone. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Oxazolidines, Pyrrolidinones, Indolizidines

INTRODUCTION

5-Membered aza-heterocycles are compounds of great biological and pharmacological interest. Thus, for example, several pyrrolidones are potent neuroactive compounds capable of interacting with pyroglutammate receptors [1-11], whereas many hydroxylated pyrrolidines, pyrrolizidines, and indolizidines are quite popular for their glycosidase inhibitory activities [12-15]. Although most of the syntheses of such compounds have been accomplished via chemical modifications of molecules of the *chiral pool* [16-23], approaches featuring more versatile *de novo* stereoselective constructions of the five membered ring have been so far less studied [24-26] and new asymmetric routes are certainly highly desirable.

In this context, reports on the generation of anionic positions at C-5 of a pyrrolidine derivative are not abundant. Thus, for example, metallation α to a pyrrolidine nitrogen can be obtained only with very strong bases and in the presence of suitable and strategically positioned functional groups [27-29].

In 1984 Ricci and coworkers reported the use of 1-methyl-2-trimethylsilyloxy-pyrrole **1** to build-up C-5 substituted pyrrolidinone derivatives [30]. More recently, Casiraghi's group has elegantly exploited the analog 1-

* Prof. Giovanni Poli E-mail: poli@risc1.chimorg.unifi.it fax: 0039-(55)-2476964

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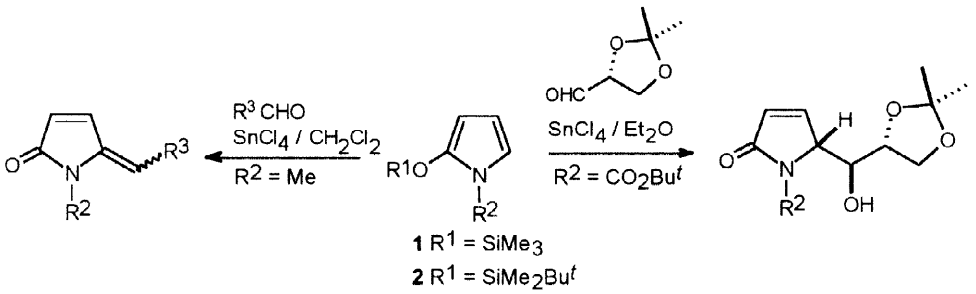
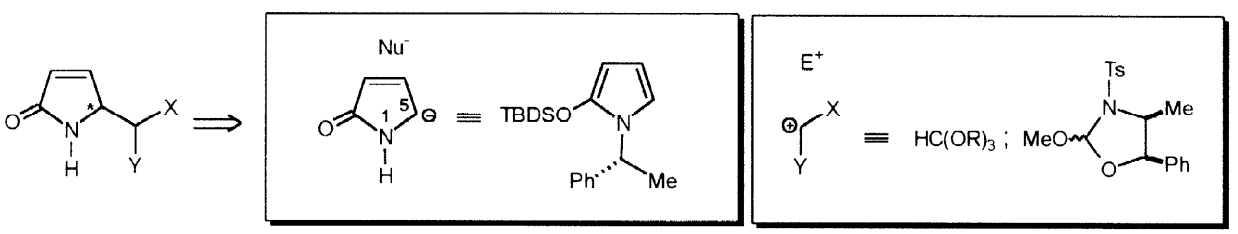
t-butoxycarbonyl-2-dimethyl-*tert*-butylsilyloxy-pyrrole **2** which reacted with glyceraldehyde acetonide and other related aldehydes with excellent diastereoselection (Scheme 1) [31-38].



Scheme 1

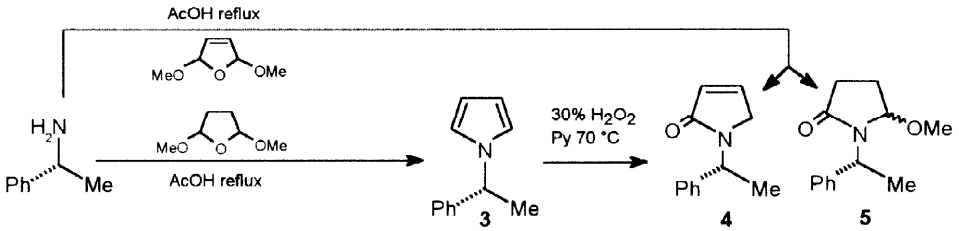
RESULTS AND DISCUSSION

Preparation of the chiral silyloxypyrrole. Given these precedents, we decided to develop a chiral analog of the 1,5-dihydro-pyrrol-2-one-5-anion equivalent (Nu^-) and study its behavior with achiral and chiral electrophilic C-1 synthons (E^+). The present paper shows a full account of our recent efforts on this subject using a α-methyl-benzylamine-derived 2-silyloxypyrrole as the nucleophile and trialkyl orthoformates or a nor-ephedrine-derived 2-methoxy-oxazolidine [39] as electrophiles (Scheme 2).



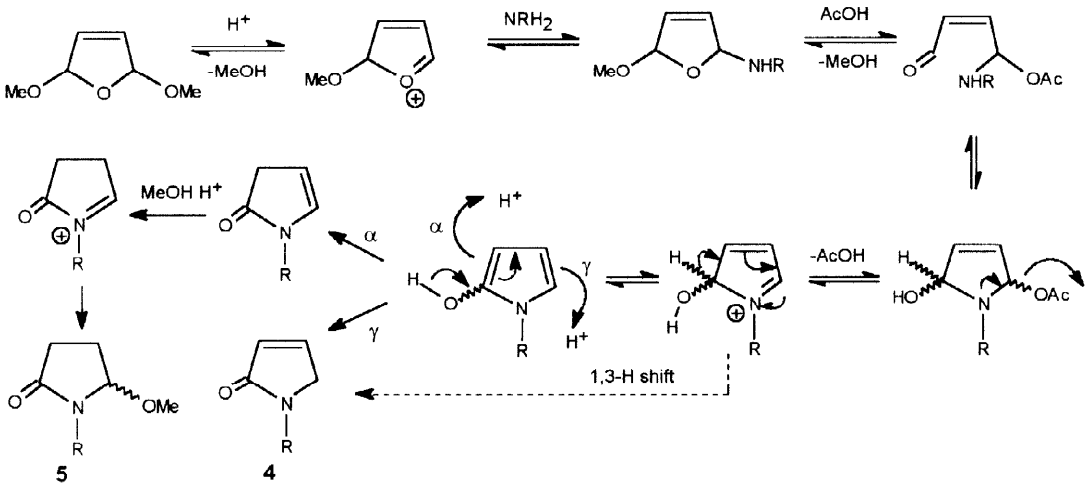
Scheme 2

Following a protocol analogous to that reported in the literature for the preparation of **1** and **2**, the known [40, 41] chiral pyrrole **3** was first secured via Paal-Knorr type condensation between (*R*)-(+)-α-methyl-benzylamine and 2,5-dimethoxy-tetrahydrofurane in AcOH. The subsequent treatment with 30% hydrogen peroxide [42] in pyridine gave the desired Δ^3-pyrrolin-2-one **4**. Although this oxidation gave sometimes acceptable yields, serious reproducibility problems were often encountered when performing the reaction on multigram scale. Such a drawback led us to the search for an alternative route. After some trials we eventually found that the condensation of (*R*)-(+)-α-methyl-benzylamine with 2,5-dimethoxy-2,5-dihydrofurane in AcOH, according to a modification of a procedure by Royer [25], gave directly **4** accompanied by the 5-methoxy pyrrolidin-2-one **5** as a 80 : 20 diastereomeric mixture (Scheme 3).



Scheme 3

Although a 1,3-hydride shift has been postulated to justify the formation of the conjugated pyrrolinone [25, 43-44], we believe that the mixture of **4** and **5** might be the result of a competitive α- and γ-tautomerization of the transient 2-hydroxypyrrole. The acidic conditions of the condensation might be responsible for the N-acyliminium mediated formation of the 5-methoxy pyrrolidin-2-one **5** (Scheme 4).



Scheme 4

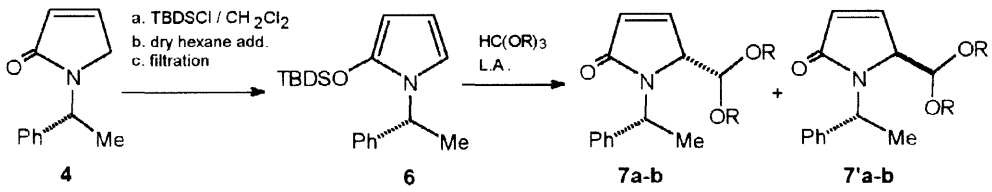
Treatment of **4** with *t*-BuMe$_2$SiCl and *i*-Pr$_2$EtN in CH$_2$Cl$_2$ gave the desired 2-silyloxy derivative **6**[†] the isolation of which proved to be rather troublesome. After some experimentation it was eventually found that addition of dry hexane to the reaction mixture caused quantitative precipitation of *i*-Pr$_2$EtN·HCl which could be filtered-off under nitrogen atmosphere. Careful solvent evaporation of the filtrate gave **6** as a highly moisture sensitive oil. Following the same protocol the antipode **ent-6** was analogously obtained starting from of (*S*)-(-)-α-methyl-benzylamine.

Condensation between the silyloxypyrrol 6 and electrophilic C-1 synthons. Simple stereoselection. The Lewis acid mediated condensations between **6** and orthoformates [45] was tested next.

DBU, lutidine and NEt$_3$ as bases in the silylation gave poorer or negligible yields of 7.

The reaction was briefly studied varying the amount and the nature of the Lewis acid, as well as of the orthoformate (Table 1). $BF_3{\cdot}Et_2O$ soon revealed to be the promoter of choice, giving the expected adducts **7a/7a'** and **7b/7b'** in 88 :12 ratio as an unseparable mixture (exp. 4). Further experiments indicated that catalytic amounts of $BF_3{\cdot}Et_2O$ were not effective (compare exp.4 and 5), and the diastereoselectivity was not affected by the nature of the orthoformate (compare exp. 4 and 7).

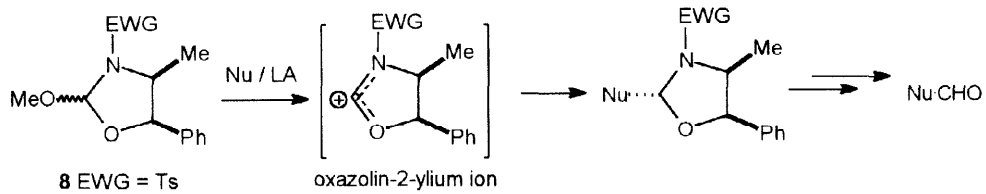
Table 1: Formation of the silyloxypyrrole **6** and its condensation with orthoformates.



Exp	L.A.	**6**./ L.A./ $HC(OR)_3$	$HC(OR)_3$	T (C°)	time (h)	yield (%)	**7a-b : 7'a-b**
1	$CF_3SO_3SiMe_3$	1.0 : 0.05 : 2.0	$HC(OMe)_3$	-78	1	-	
2	$CF_3SO_3SiMe_3$	1.0 : 2.0 : 2.0	$HC(OMe)_3$	-78	1	14	
3	$CF_3SO_3SiMe_3$	1.0 : 2.0 : 2.0	$HC(OMe)_3$	0	4	15	
4	$BF_3{\cdot}Et_2O$	1.0 : 2.0 : 2.0	$HC(OMe)_3$	-78	1	66	88 : 12
5	$BF_3{\cdot}Et_2O$	1.0 : 0.05 : 2.0	$HC(OMe)_3$	-78	1	-	
6	$SbCl_5$	1.0 : 2.0 : 2.0	$HC(OMe)_3$	-78	1	-	
7	$BF_3{\cdot}Et_2O$	1.0 : 2.0 : 2.0	$HC(OEt)_3$	-78	1	62	88 : 12

a: R = Me; **b**: R = Et

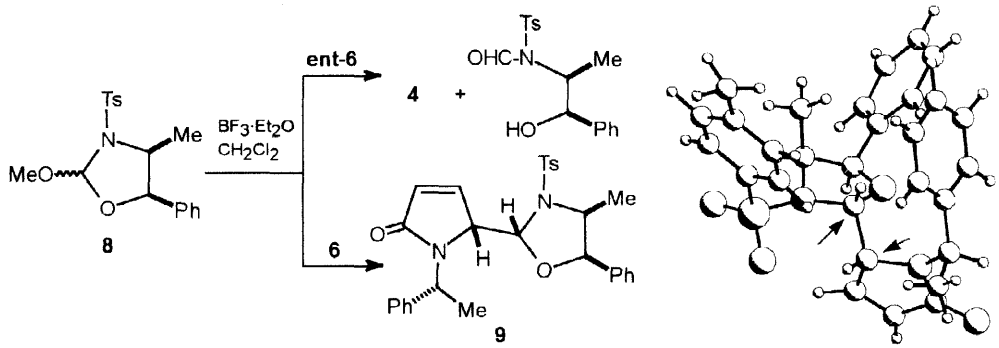
Double Stereoselection. The behavior of **6** and of its enantiomer **ent-6** was next studied in double stereoselection using the norephedrine derived 2-methoxy-3-tosyl oxazolidine **8**.[8] This heterocycle, and other related chiral formylating agents, have been the object of study by us and others. In fact, in the presence of Lewis acids, they readily generate cationic intermediates [46-50], which can be stereoselectively intercepted by carbon based nucleophiles such as silylenolethers and silylketeneacetals [51-55], enamines [56], allylstannanes [57], α- and γ-allylstannanes [58], and trimethylsilylcyanide [59-61]. The condensations are usually highly diastereoselective, the stereochemical outcome depending on the nature of the nucleophile (Scheme 5).



Scheme 5

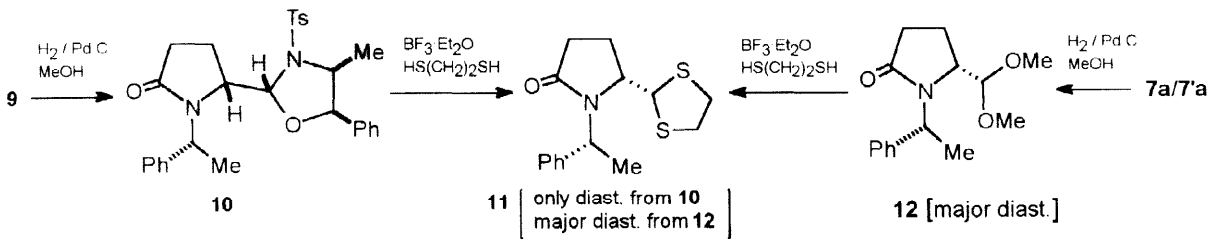
In the event, the $BF_3{\cdot}Et_2O$ promoted condensation between **ent-6** and the oxazolidine **8** gave back only hydrolyzed material. On the other hand, we were pleased to find that *the corresponding condensation between the antipodal silyl-derivative* **6** *and* **8** *gave the adduct* **9** *as the only diastereoisomer*. The X-ray analysis of **9** unequivocally established the *R* absolute configuration of the two newly created stereocenters (Scheme 6).[‡]

Left: Lewis acid mediated condensation between oxazolidine **8** and **6** or **ent-6**. Right: X-ray crystal structure of **9**.



Scheme 6

The adducts **7a/7'a** and **9** were then correlated as described in Scheme 7. Standard hydrogenation of **9** gave the corresponding pyrrolidinone **10**, which was submitted to $BF_3{\cdot}Et_2O$ mediated *trans*-thioacetalisation with 1,2-ethaneditiol to give the dithiolane **11** as the only diastereoisomer. Since the same hydrogenation / thioacetalisation sequence, when applied to **7a/7'a**, gave **11** as the major diastereomer, it appears that the intrinsic induction of the silyloxy derivative **6** favors addition from the C-5/Si face, thereby generating an *R* configurated stereocenter (Scheme 8, left). Such a stereochemical result may be understood assuming that, for allylic strain reasons [62], the reactive conformation of **6** favors eclipsing of the benzylic hydrogen atom with the plane of the pyrrole ring. As a result, addition of the cationic reagents away from the bulky aromatic ring will be preferred → *Requirement 1*.

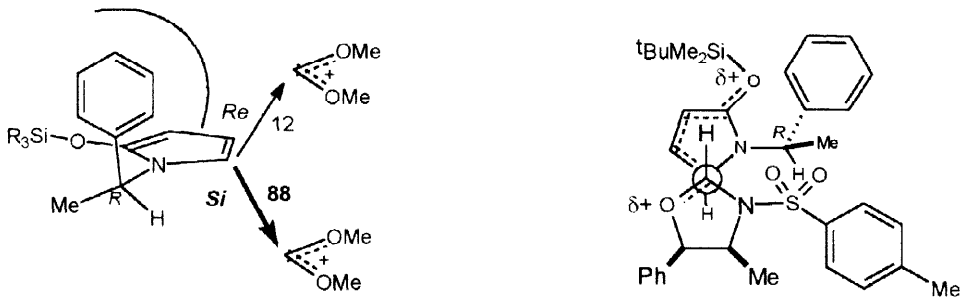


Scheme 7

‡ 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^3, Z = 4, Dcalc = 1.319 g·cm^{-3}, λ = 1.54184 Å (graphite monochromated), μ (Cu Kα) = 1.406 mm^{-1} 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 Center.

On the other hand, the known steric and stereoelectronic demands associated with the cationic intermediate derived from **8** favor a transition state having the following features: a) transient formation of an oxazolin-2-ylium ion, mainly stabilized by the oxygen atom, allowing exclusive approach of the nucleophile from the more available *Re* face → *Requirement 2*. b) staggered approach of the reacting partners where the hydrogen atom on C-5 of the nucleophile occupies the position between the oxazolidine ring heteroatoms, and the reacting π-bonds are disposed so as to allow maximal charge separation [63] → *Requirement 3* (Scheme 8, right).

Left: possible approaches in the condensation between the silyloxypyrrol **6** and achiral orthoformates. Right: proposed transition state in the condensation between **6** and the oxazolin-2-ylium ion intermediate derived from **8**.



Scheme 8

The possible competing transition states involved in the matching and mis-matching pairs, **6/8** and **ent-6/8** respectively, may thus be described as shown in Figure 1. Worthy of note, only approach C, leading to the observed diastereoisomer, fulfills at the same time all the above mentioned requirements. On the other hand, it turns out that the transition states associated to the *mis*-matched pair are so unfavorable that the condensation does not take place at all.

Stereochemical models in the $BF_3{\cdot}Et_2O$ promoted addition of **6** and **ent-6** to **8**.

Mode	Nu/El Topicity	*Req. 1*	*Req. 2*	*Req. 3*
A	*Re-Re*	-	+	-
B	*Si-Si*	+	-	-
C	***Si-Re***	+	+	+
D	*Re-Si*	-	-	+
E	*Si-Re*	-	+	+
F	*Re-Si*	+	-	+
G	*Re-Re*	+	+	-
H	*Si-Si*	-	-	-

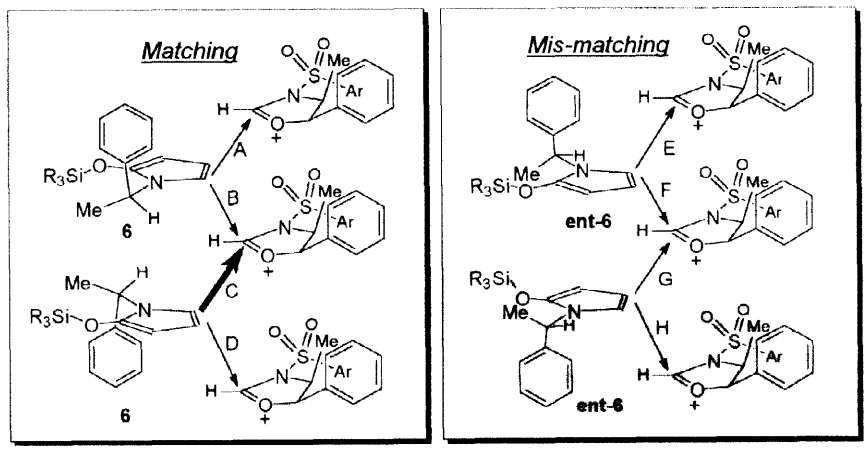
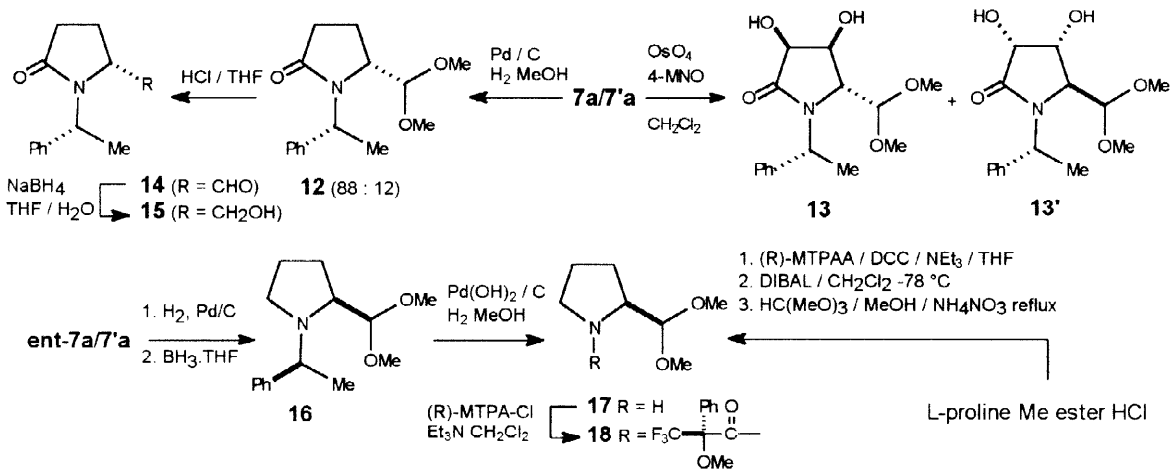


Figure 1

Further transformations of the adducts. In order to establish the usefulness of the new method some functional group manipulations of **7a/7'a** and **ent-7a/7'a** were studied next (Scheme 9). *Catalytic "anhydrous" osmylation* [64] of these adducts gave the expected dihydroxylated diastereoisomeric diols **13/13'** as a 88 :12 mixture. This result indicates that the osmylation took place with total stereoselectivity on both the diastereoisomers. Although we did not attempt to find spectroscopic evidence for the stereochemistry of the dihydroxylated structure, the well known behavior of OsO_4 with stereogenic alkenes [65] suggests the complete *anti* addition of this reagent with respect to the allylic dimethoxymethyl substituent, a significant result in view of the biological interest of hydroxylated pyrrolidines. Treatment of the pyrrolidone **12** with aqueous HCl afforded the aldehyde **14** without detectable racemization. The subsequent reduction with $NaBH_4$ in THF gave the alcohol **15**. Curiously, the same reduction did not take place when performed in MeOH. This result suggests that in the latter solvent hemiacetal formation prevents the reduction. Treatment of **ent-12**[§] with $NaBH_4/I_2$ [66], or BH_3·THF [67, 68] gave the pyrrolidine **16**, which could be released from the minor diastereoisomer during the chromatographic stage. Subsequent hydrogenolysis with $Pd(OH)_2/C$ cleaved the chirophoric group giving the secondary amine **17**. Since this amine turned out to be rather unstable, its was immediately converted into its corresponding (*R*)-Mosher amide **18**. Definitive proof of the absolute stereochemistry and enantiomeric purity of the product came from the independent preparation of a genuine sample of **18** from *L*-proline methyl ester and (*R*)-Mosher acid, which appeared to be indistinguishable from the specimen derived from (S)-(-)-α-methyl-benzylamine (Scheme 9).[**]

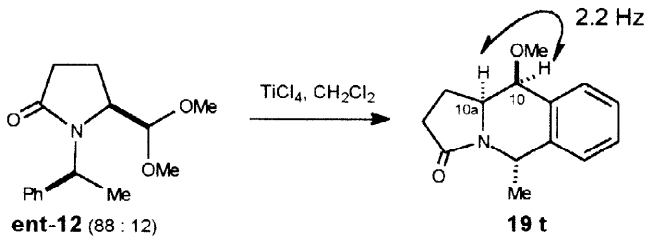


Scheme 9

[§] **Ent-12** was obtained starting from (*S*)-(-)-α-methyl-benzylamine following the same procedure as used for antipode **12.**

[**] Experimental procedures and characterization data for the synthesis of **18** from L-proline methyl ester can be requested from the authors.

Last but not least, an intriguing reactivity was observed when attempting the Lewis acid promoted addition of the *t*-butyldimethylsilyl ketene acetal of methyl propionate to **ent-12** [69-70]. In fact, treatment of **ent-12** with $TiCl_4$ triggered a Pomeranz-Fritsch [71-75] type condensation of the phenyl ring onto the acetal carbon affording unexpectedly the benzocondensated hexahydroindolizinone **19 t** (Scheme 10).



ent-12 (88 : 12) **19 t**

Scheme 10

Worthy of note, the reaction is totally stereoselective. The stereochemistry of the newly created stereocenter was inferred as follows. Molecular mechanics calculations were performed with MacroModel 5.5 [76] on the two C-10 epimeric compounds **19t** and **19c**, using its MM2 force field [77] and the implicit chloroform GB/SA solvation model [78]. Random variation of the torsional space of each molecule with the usage-directed Monte Carlo conformational search [79][††] located six low-energy conformers for each molecule, the energy difference between the two global minima being 6.3 kJ/mol (1.5 kcal/mol) in favor of the *trans* isomer. Computation of the $J_{10\text{-}10a}$ coupling constants (Boltzmann averaged at 300 K) by application of the Altona equation [81] on the minima of the conformational analysis gave 1.8 Hz and 7.6 Hz for the *trans* and *cis* isomers, respectively. Comparison of these values with the experimentally observed vicinal coupling constant $J_{10\text{-}10a}$ indicated that our structure was **19 t** (figure 2).

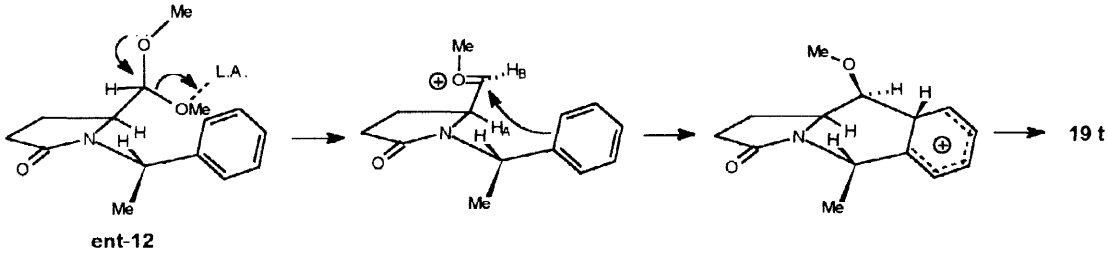
Figure 2. Structures and energies of the global minima found for **19 t** and **19 c**, and Boltzmann averaged $J_{10\text{-}10a}$.

19 t **19 c**

	extim. $J_{10\text{-}10a}$ (global min.)	extim. $J_{10\text{-}10a}$ (mediated)	E (kj/mol)
19 t	1.8 Hz	1.8 Hz	-77.59
19c	9.4 Hz	7.6 Hz	-71.33

[††] For each search, 5000 starting structures were generated and minimized using the truncated Newton-Raphson method [80] implemented in MacroModel. Duplicate conformations and those with an energy greater than 50 kJ/mol (12 kcal/mol) above the global minimum were discarded.

Although an adequate understanding of the stereochemistry has to wait for more detailed studies, we can anticipate that the high selectivity is likely to depend on the conformation of the transient oxocarbenium ion, which is intramolecularly intercepted by the phenyl ring (scheme 11).‡‡



Scheme 11

Of course, in this instance the use of a benzylic-type group as a removable chiral auxiliary is precluded. Nevertheless, this novel reactivity opens-up a new stereoselective access to the benzocondensated hexahydroindolizine framework, an interesting result in view of the structure of the phenantroindolizidine alkaloids [82], Tylophorine **20** [83], Antofine **21** [83, 84], Tylophorinidine **22** [85], and Tylophorinine **23** [86] belong to this family. Interestingly, some of them posses pharmacological activities and are known to bind a variety of DNA nucleosides and nucleotides, and also interacted with DNA.

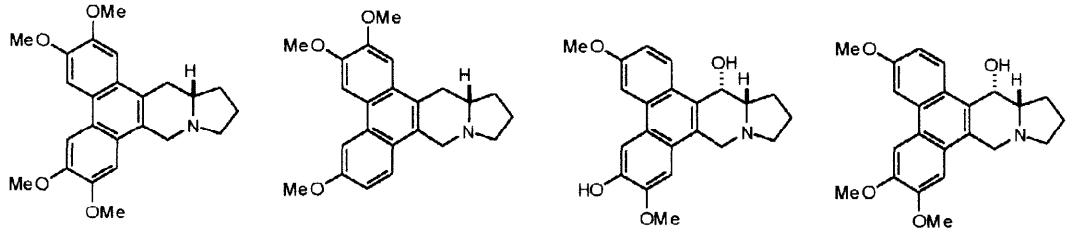


Figure 2

Conclusion. In the present work we have developed the first chiral synthetic equivalent of 1,5-dihydro-2-pyrrolidone 5-anion using a low cost chiral auxiliary, commercially available in both the enantiomeric forms. Its Lewis acid promoted condensation with trimethyl or triethyl orthoformate took place with moderate (88:12) diastereoselectivity giving pyroglutamic acetal derivatives. The concomitant usage of a nor-ephedrine derived electrophilic C-1 reagent allowed a totally diastereoselective condensation. The synthetic manipulation of the acetal adducts led to the asymmetric synthesis of pyroglutammic aldehyde and prolinal derivatives. During these studies it was also unexpectedly discovered that treatment of the acetal adducts with $TiCl_4$ triggered an intramolecular Pomeranz-Fritsch condensation that gave a benzocondensated indolizidinone. More detailed studies on such interesting reactivity are planned for the future.

‡‡ It is tempting to speculate that the conformation of the oxocarbenium intermediate showing H_A/H_B eclipsing might benefit of an extra stabilization by the nitrogen atom.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C-NMR spectra were obtained with a Varian-Gemini or a Bruker DRX 500 or a VXR 300 working in FT, using the residual peak of the deuterated solvent as the internal standard, recorded in $CDCl_3$ as indicated, at 200, 500 and 50.3 MHz, respectively (the usual abbreviation are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The positive chemical shift values are given in ppm and the coupling constants in Hz. Thin-layer chromatography (TLC) was carried out using Merck 60 F_{254} precoated silica gel. Flash chromatography was carried out with ICN-Silica 32-63, 60Å. Solvents were dried with standard procedures and reactions requiring anhydrous conditions were performed under a positive nitrogen atmosphere. Final product solutions were dried over Na_2SO_4, filtered and evaporated under reduced pressure on a rotary evaporator.

(1'*R*)-1-(1'-phenyl-ethyl)-1H-pyrrole 3. To a solution of (*R*)-α-methyl-benzylamine (1.06 ml, 8.26 mmol) in acetic acid (1.65 ml), 2,5-dimethoxytetrahydrofuran (1.07 ml, 8.26 mmol) was dropwise added with stirring at room temperature. The resulting mixture was heated at reflux for 90 min, then acetic acid was removed in vacuo. The product was dissolved in Et_2O (5 ml) and washed with water, 0.1M NaOH, 0.05M HCl, then dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was bulb-to-bulb distilled (116-117°C, 7 mmHg), to give a colourless liquid (1.222g, 84%). $[\alpha]_D^{25}$ = -14.4 ($CHCl_3$; c = 1.25); ^{1}H-NMR ($CDCl_3$) δ: 1.88 (d, 3H, J = 7.0 Hz); 5.33 (q, 1H, J = 7.0 Hz); 6.25 (t, 2H, J = 2.0 Hz); 6.81 (t, 2H, J = 2.0 Hz); 7.12-7.4 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ: 23.45; 59.40; 109.41; 120.81; 127.17; 128.75; 129.95; 144.92; m/z (%): 171 (M^+, 24); 104 (100); 91 (100); 77 (45); 67 (52).

(1'*R*)-1-(1'-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one 4 (from 3). To a solution of **3** (2g, 11.70 mmol) in pyridine (5.3 ml), H_2O_2 (5.8 ml, 175.50 mmol) was added with stirring at 70°C. After 24 h the resulting solution was cooled at room temperature and further stirred for 7 d. The product obtained was extracted in CH_2Cl_2, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was subjected to column chromatography, 8:2 v/v AcOEt - petroleum ether, to afford the product **4** as an oil (0.476 g, 22%, 37% considering the recovered pyrrole). $[\alpha]_D^{21}$ = +92.25 (c= 1.11, $CHCl_3$); m/z (%): 187 (M^+,100); 105 (92); 77 (92); IR ($CHCl_3$) ν: 3003; 2940; 1680 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ = 17.72; 48.65; 48.92; 126.94; 127.50; 127.96; 128.65; 140.99; 142.82; 171.07; ^{1}H-NMR ($CDCl_3$) δ: 1.59 (d, 3H, J = 7.0 Hz); 3.78 (*AB part of ABMX system*, 2H); 5.57 (q, 1H, J = 7.0 Hz); 6.17 (dt, 1H, J = 6.0 Hz, J = 2.0 Hz); 6.96 (dt, 1H, J = 6.0 Hz, J = 2.0 Hz); 7.18-7.36 (m, 5H); Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.01; H, 7.21; N, 7.47.

(1'*R*)-1-(1'-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one 4, and **(1'*R*, 5*R*)-** and **(1'*R*, 5*S*)-5-methoxy-1-(1'-phenyl-ethyl)-pyrrolidin-2-one 5** (from 2,5-dimethoxy-2,5-dihydrofurane)**.** To a solution of (*R*)-(+)-α-methyl-benzylamine (0.53 ml, 4.13 mmol) in acetic acid (0.2 ml), 2,5-dimethoxy-2,5-dihydrofurane (0.5 ml, 4.13 mmol) was added dropwise with stirring at room temperature. The resulting mixture was heated at reflux for 3 h, and then cooled to room temperature. The product was treated with water and submitted to standard extractive work-up with CH_2Cl_2. The collected organic phases were dried and the solvent was removed in vacuo. The crude material was distilled (T 200°C/1.0*10^{-2}mmHg), to give a black thick oil that was chromatographed on silica gel 8:2 v/v AcOEt - petroleum ether. **5** was the first compound eluted as unseparable diastereomeric mixture (63 mg, 7%), **4** was the second compound eluted (178 mg, 23%). **5**: *Major diastereoisomer* ^{1}H-NMR ($CDCl_3$) δ: 1.61 (d, 3H, J = 7.0 Hz); 1.83-1.96 (m, 2H); 2.24-2.39 (m, 1H); 2.51-2.67 (m, 1H); 3.14 (s, 3H); 4.46 (m, 1H); 5.36 (q, 1H, J = 7.0 Hz); 7.25-7.40 (m, 5H); *Minor diastereoisomer (only discerned signals)*: ^{1}H-

NMR ($CDCl_3$) δ: 1.65 (d, 3H, J = 7.0 Hz); 2.92 (s, 3H); 5.04 (m, 1H); 5.14 (q, 1H, J = 7.0 Hz); 7.25-7.45 (m, 5H). *For the spectroscopic data of* **4** *see the preceding preparation of the same compound.*

(1'*R*)-1-(1'-phenyl-ethyl)-2-*tert*-butyldimethylsilyloxy-1*H*-pyrrole 6. To a solution of **4** (75 mg, 0.401 mmol) in dry CH_2Cl_2 (0.300 ml), diisopropyl-ethyl-amine (0.209 ml, 1.203 mmol) and *tert*-butyldimethylsilyl-chloride (0.182 g, 1.205 mmol), were added with stirring, under nitrogen atmosphere. After 40 min stirring, dry petroleum ether (10 ml) was added, then the solution was filtered through a Celite plug and evaporated under reduced pressure to give 115 mg of pure **6** (95%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 3H); 0.23 (s, 3H); 0.91 (s, 9H); 1.78 (d, 3H, J =7.0 Hz); 5.29 (dd, 1H, J = 4.0 Hz, J= 2.0 Hz); 5.42 (q, 1H, J = 7.0 Hz); 6.03 (t, 1H, J = 4.0 Hz); 6.38 (dd, 1H, J= 4.0 Hz, J = 2.0 Hz); 7.01-7.39 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ: -4.68; -4.30; 18.45; 22.14; 26.06; 52.97; 87.89; 105.36; 109.56; 126.34; 127.38; 128.87; 129.14; 144.41; m/z (%): 301 (M^+, 6); 149 (32); 105 (100); 73 (45).

(1'*R*, 5*R*)- and **(1'*R*, 5*S*)-5-dimethoxymethyl-1-(1'-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one 7a** and **7'a** and **(1'*R*, 5*R*)-** and **(1'*R*, 5*S*)-5-diethoxy-1-(1'-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one 7b** and **7'b. (General Procedure):** To a solution of **6** (0.5 g, 1.66 mmol) in dry CH_2Cl_2 (11 ml) at room temperature, the appropriate orthoformate (3.32 mmol) was added with stirring, under nitrogen atmosphere. The resulting mixture was then cooled at -78 °C and $BF_3{\cdot}Et_2O$ (0.410 ml, 3.32 mmol) was dropwise added. After 1 h the mixture was treated with saturated aqueous $NaHCO_3$ (15 ml) and submitted to standard extractive work-up with Et_2O. The collected organic layers were dried and evaporated in vacuo. Flash chromatography, 7:3 v/v AcOEt - petroleum ether, afforded the pure products **7a** and **7'a** (0.286 g, 66%), and **7b** and **7'b** (0.297 g, 62%) as unseparable diastereomeric mixtures. **7a** and **7'a**: *Major diastereoisomer* ^{1}H-NMR ($CDCl_3$) δ: 1.67 (d, 3H, J = 7.0 Hz); 3.05 (s, 3H); 3.06 (s, 3H); 3.74 (d, 1H, J = 5.0 Hz); 4.25-4.28 (m, 1H); 5.52 (q, 1H, J = 7.0 Hz); 6.23 (dt, 1H, J = 6.0 Hz, J = 1.3 Hz); 7.0 (d, 1H, J = 6.0 Hz); 7.15-7.36 (m, 5H). *Minor diastereoisomer (only discerned signals)* ^{1}H-NMR ($CDCl_3$) δ: 3.19 (s, 1H); 3.32 (s, 1H); 3.92 (m,1H); 4.21 (d, 1H, J = 5.0 Hz); 5.40 (q, 1H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$): 17.54; 50.11; 56.21; 56.66; 64.43; 105.05; 127.47; 127.52; 128.72; 128.8; 142.44; 145.01; 173.16; m/z (%): 229 (M^+-MeOH, 2.3); 201 (10); 105 (45); 96 (5); 75 (100); Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.99; H, 7.44; N, 5.43. **7b** and **7'b**: *Major diastereoisomer* ^{1}H-NMR ($CDCl_3$) δ: 0.98 (t, 3H, J = 7.0 Hz); 1.06 (t, 3H, J = 7.0 Hz); 1.50 (d, 3H, J = 7.0 Hz); 3.08 (m, 2H); 3.63 (m, 2H); 3.91 (d, 1H, J = 5.0 Hz); 4.26 (m, 1H); 5.43 (q, 1H, J = 7.0 Hz); 6.17 (d, 1H, J = 6.0 Hz); 7.04 (d, 1H, J = 6.0 Hz); 7.17-7.37 (m, 5H). *Minor diastereoisomer (only discerned signals)* ^{1}H-NMR ($CDCl_3$) δ: 1.7 (d, 3H, J = 7.0 Hz); 4.39 (d, 1H, J = 5.0 Hz). ^{13}C-NMR ($CDCl_3$) (*selected data*): 12.55; 15.63; 17.85; 19.12; 64.72; 65.29; 127.5; 127.6; 128.76; 142.31; 145.34; m/z (%): 243 (M^+-EtOH, 14); 234 (14); 188 (8); 105 (75); 75 (100). (Starting from (-)-(S)-α-methylbenzylamine the antipodal pair **7a/7'a** was analogously obtained).

(1'*R*, 5*R*)- and **(1'*R*, 5*S*)-5-dimethoxymethyl-1-(1'-phenyl-ethyl)-pyrrolidin-2-one 12.** To a suspension of 10% Pd/C (4 mg) in MeOH (3 ml) a solution of **7a** and **7'a** (90 mg, 0.346 mmol) in MeOH (4 ml) was added under nitrogen atmosphere. Hydrogen atmosphere was then introduced by means of a three ways tap and vigorous stirring was started. After 2 h the reaction was filtered through a Celite plug and evaporated to give 90 mg (> 95%) of pure **12** (d.r. 88 / 12). *Major diastereoisomer* ^{1}H-NMR ($CDCl_3$) δ: 1.63 (d, 3H, J = 7.0 Hz); 1.68-2.66 (m, 4H); 2.93 (s, 3H); 3.17 (s, 3H); 3.41 (d, 1H, J = 2.2 Hz); 3.74 (dt, 1H, J = 2.2 Hz, J = 8.8 Hz); 5.52 (q, 1H, J = 7.0 Hz); 7.22-7.43 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 16.57; 20.03; 31.55; 49.82; 56.95; 57.15; 58.39; 106.16; 127.96; 128.91; 129.03; 142.19; 177.07; m/z (%): 243 (14); 234 (14); 188 (8); 105 (75); 75 (100); IR ($CHCl_3$) ν: 2998; 2939; 1666 cm^{-1}; $[\alpha]_D^{17}$ +147.5 (c 1.12, $CHCl_3$); *Minor diastereoisomer (only discerned signals)*: ^{1}H-NMR ($CDCl_3$) δ: 1.53 (d, 3H, J = 7.0 Hz); 3.26 (s, 3H); 3.38 (s, 3H); 3.47 (d, 1H, J =

2.6 Hz); 4.24 (d, 1H, J = 2.6 Hz); 5.39 (q, 1H, J = 7.0 Hz). (Starting from (S)-(-)-α-methylbenzylamine the antipodal **ent-12** was analogously obtained).

(1''*R*, 2'*R*, 4'*S*, 5,5'*R*)-5-[4'-methyl-5'-phenyl-3'-(toluene-4'''-sulfonyl)-oxazolidine-2'-yl]-1-(1''-phenyl-ethyl)-pyrrol-2-one 9. To a solution of **6** (200 mg, 0.664 mmol) in dry CH_2Cl_2 (5 ml) at room temperature, the oxazolidine (461 mg, 1.33 mmol) was added with stirring under nitrogen atmosphere. The resulting mixture was then cooled at -78 °C and $BF_3{\cdot}Et_2O$ (0.168 ml, 1.33 mmol) was dropwise added. After 1 h the mixture was left to 0 °C and further stirred for 2 h. The solution was then treated with saturated aqueous $NaHCO_3$ (15 ml) and submitted to standard extractive work-up with Et_2O. The collected organic layers were dried and evaporated in vacuo. Flash chromatography of the crude material, 3:7 v/v AcOEt - petroleum ether, afforded pure **9** (206 mg, 65%). ^{1}H-NMR ($CDCl_3$) δ: 0.46 (d, 3H, J = 6.0 Hz); 1.77 (d, 3H, J = 7.0 Hz); 2.46 (s, 3H); 4.17-4.2 (m, 1H); 4.89 (m, 2H); 5.05 (d, 1H, J = 1.5 Hz); 5.66 (q, 1H, J = 7.0 Hz); 6.23 (dd, 1H, J = 6.0 Hz, J = 1.5 Hz); 7.10 (dd, 1H, J = 6.0 Hz, J = 2.6 Hz); 7.2-7.68 (m, 14H); ^{13}C-NMR ($CDCl_3$) (*Selected data*) 14.03; 17.76; 22.11; 49.55; 60.19; 65.74; 82.90; 86.21; 126.34; 127.70; 127.87; 128.12; 128.43; 128.67; 128.72; 130.18; 130.38; 135.67; 138.22; 141.44; 142.81; 172.52; m/z (%): 316 (63); 288 (45); 155 (23); 105 (85); 91 (100); 77 (19); IR ($CHCl_3$) ν: 3004; 2930; 1677 cm^{-1}; Anal. Calcd. for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.43; H, 6.21; N, 5.71.

(1''*R*, 2'*R*, 4'*S*, 5,5'*R*)-5-[4'-methyl-5'-phenyl-3'-(toluene-4'''-sulfonyl)-oxazolidine-2'-yl]-1-(1''-phenyl-ethyl)-pyrrolidin-2-one 10. To a suspension of 10% Pd/C (6.3 mg) in MeOH (30 ml) a solution of **9** (300 mg, 0.598 mmol) in MeOH (30 ml) was added under nitrogen atmosphere. Hydrogen atmosphere was then introduced by means of a three ways tap and vigorous stirring was started. After 2 h the reaction was filtered through a Celite plug and evaporated to give 270 mg (90%) of **10**. ^{1}H-NMR ($CDCl_3$) δ: 0.53 (d, 3H, J = 7.0 Hz); 1.71 (d, 3H, J = 7.0 Hz); 1.99-2.66 (m, 4H); 2.46 (s, 3H); 4.25-4.39 (m, 2H); 4.59 (s, 1H); 5.16 (d, 1H, J = 5.0 Hz); 5.68 (q, 1H, J = 7.0 Hz); 6.88-7.63 (m, 14H); ^{13}C-NMR ($CDCl_3$) δ: 13.66; 16.48; 19.98; 30.20; 31.17; 49.17; 59.06; 61.0; 82.88; 87.71; 126.47; 127.65; 127.85; 127.96; 128.41; 128.65; 128.80; 130.23; 136.49; 138.51; 142.14; 144.48; 176.51; Anal. Calcd. for $C_{29}H_{32}N_2O_4S$: C, 69.02; H, 6.39; N, 5.55. Found: C, 69.13; H, 6.44; N, 5.63.

(1'*R*, 5*R*)-5-[1,3]-dithiolan-2-yl-1-(1'-phenyl-ethyl)-pyrrolidin-2-one 11. To a solution of **10** (320 mg, 0.63 mmol) in dry CH_2Cl_2 (7 ml), 1,2-ethanedithiol (0.53 ml, 6.30 mmol) and $BF_3{\cdot}Et_2O$ (0.310 ml, 2.52 mmol) were added portionwise over 2 d, under nitrogen atmosphere. After this period a saturated aqueous solution of phosphate buffer (5ml) (pH=7.2) was added, and the organic phase was extracted with Et_2O. The collected organic phases were dried and the solvent was removed in vacuo. Flash chromatography of the crude product, 6:4 v/v AcOEt - petroleum ether, afforded pure dithioacetal **11** (129 mg, 70%). ^{1}H-NMR ($CDCl_3$) δ: 1.66 (d, 3H, J = 7.0 Hz); 1.99-2.14 (m, 2H); 2.27-2.42 (m, 2H); 2.65-2.83 (m, 2H); 3.01-3.16 (m, 2H); 3.98-4.05 (m, 1H); 4.32 (d, 1H, J = 2.6 Hz); 5.46 (q, 1H, J = 7.0 Hz); 7.26-7.42 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ: 16.52; 20.89; 31.48; 39.47; 39.90; 49.95; 56.70; 61.01; 127.74; 128.00; 128.05; 129.05; 176.6; IR ($CHCl_3$) ν: 3001; 2935; 1670; 1409; 1278 cm^{-1}. The same thioacetalization when applied to the pyrrolidone **12**, gave dithiolan **11** as the same major diastereoisomer.

(1'*S*, 2*S*)-2-dimethoxymethyl-1-(1'-phenyl-ethyl)-pyrrolidine 16. To a solution of **ent-12** (870 mg, 3.31 mmol) in dry THF (33 ml), $BH_3{\cdot}THF$ (5.70 ml, 5.95 mmol) was added dropwise with stirring under nitrogen atmosphere. The mixture was brought to reflux for 40 min, then cooled to room temperature and evaporated in vacuo. Treatment of the product dissolved in Et_2O (30 ml) with TMEDA (0.25 ml, 1.65 mmol) produced a

white suspension which was centrifuged and the white solid washed three time with Et_2O (40 ml). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography ,AcOEt, to afford the pure pyrrolidine **16** (716 mg, 87%). $[\alpha]_D^{22}$ -35.78 (c 1.04, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.46 (d, 3H, J = 7.0 Hz); 1.52-1.90 (m, 4H); 2.32-2.44 (m, 1H); 2.85-3.02 (m, 2H); 3.46 (s, 3H); 3.51 (s, 3H); 3.96 (q, 1H, J = 7.0 Hz); 4.19 (d, 1H, J = 4.4 Hz); 7.4-7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$) (*Selected data*) δ: 20.12; 22.47; 24.74; 26.84; 51.17; 56.64; 61.87; 62.49; 109.19; 127.25; 128.51; 128.58; m/z (%): 218 (3); 174 (71); 144 (3); 114 (17); 105 (100); 77 (26); 70 (88); Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.35; H, 9.41; N, 5.51.

(1'*R*, 2*R*)- and **(1'*R*, 2*S*)-5-oxo-1-(1'-phenyl-ethyl)-pyrrolidin-2-carbaldehyde 14.** To a solution of **12** (50 mg, 0.19 mmol) in THF (1.5 ml) and H_2O (0.5 ml), 1M HCl (0.018 ml, 0.57 mmol) was added with stirring at room temperature and the resulting mixture was heated at 50°C for 1 d. Then, the reaction was cooled at room temperature and further stirred for 12 h. After addition of H_2O (1 ml), the mixture was extracted with Et_2O and the collected organic layers were dried and evaporated in vacuo. Flash chromatography, AcOEt, afforded the pure aldehyde **14** (30 mg, 73%). *Major diastereoisomer* ^{1}H-NMR ($CDCl_3$) δ: 1.57 (d, 3H, J = 7.0 Hz); 1.83-2.56 (m, 4H); 4.01-4.13 (m, 1H); 5.58 (q, 1H, J = 7.0 Hz); 7.28-7.36 (m, 5H); 8.62 (d, 1H, J = 4.0 Hz); IR ($CHCl_3$) ν: 3047; 2933; 1686 cm^{-1}; *Minor diastereoisomer (only discerned signals)*: ^{1}H-NMR ($CDCl_3$) δ: 1.52 (d, 3H, J = 7.0 Hz); 2.93-3.77 (m, 4H); 9.64 (d, 1H, J = 4.0 Hz); m/z (%): 188 (M^+-CHO, 14); 105 (100).

(1'*R*, 5*R*)- and **(1'*R*, 5*S*)-5-hydroxymethyl-1-(1'-phenyl-ethyl)-pyrrolidin-2-one 15.** To a solution of **14** (230 mg, 1.06 mmol), in THF (9 ml) and H_2O (3 ml), $NaBH_4$ (403 mg, 10.60 mmol) was added with stirring at 0°C. After 1h the reaction mixture was treated with saturated aqueous NH_4Cl, and submitted to standard extractive work-up with Et_2O. The collected organic phases were dried and the solvent was removed in vacuo. Flash chromatography of the crude product, AcOEt, gave the pure alcohol **15** (160 mg, 70%). *Major diastereoisomer* ^{1}H-NMR ($CDCl_3$ + D_2O) δ: 1.62 (d, 3H, J = 7.0 Hz); 1.91-2.67 (m, 4H); 3.12-3.16 (m, 2H); 3.75-3.83 (m, 1H); 5.61 (q, 1H, J = 7.0 Hz); 7.24-7.46 (m, 5H); *Minor diastereoisomer (only discerned signals)*: ^{1}H-NMR ($CDCl_3$) δ: 1.63 (d, 3H, J = 7.0 Hz); 3.25-3.4 (m, 1H); 5.39 (q, 1H, J = 7.0 Hz); m/z (%): 219 (M^+, 1.6); 188 (10); 115 (3); 105 (96); 91 (38); 84 (100);

(1'*R*, 3*S*, 4*S*, 5*R*)- and **(1'*R*, 3*R*, 4*R*, 5*S*)-3,4-dihydroxy-5-dimethoxymethyl-1-(1'-phenyl-ethyl)-pyrrolidin-2-one 13** and **13'.** To a solution of **7a** and **7'a** (100 mg, 0.383 mmol), in dry CH_2Cl_2 (8 ml), 4-methylmorpholine-*N*-oxide (68 mg, 0.578 mmol) and $OsCl_3$ (11 mg, 0.039 mmol), were added with stirring at room temperature. The resulting mixture was stirred for 4 h, then the solvent was removed under reduced pressure on a rotary evaporator. Flash chromatography of the crude product, 9:1 v/v AcOEt - petroleum ether, afforded the pure diol **13** and **13'** (34 mg, 30% - not optimized -). ^{1}H-NMR ($CDCl_3$+D_2O) δ: 1.62 (d, 3H, J = 7.0 Hz); 2.96 (s, 3H); 3.15 (d, 1H, J = 4.0 Hz); 3.20 (s, 3H); 3.69 (d, 1H, J = 4.0 Hz); 4.44 (d, 1H, J = 6.0 Hz); 4.53 (d, 1H, J = 6.0 Hz); 5.51 (q, 1H, J = 7.0 Hz); 7.28-7.44 (m, 5H); ^{13}C-NMR ($CDCl_3$) (*Selected data*) δ: 15.83; 30.20; 32.42; 50.58; 64.25; 67.62; 104.85; 128.09; 128.51; 129.16; 140.93; m/z (%): 296 (3); 235 (4); 149 (22); 105 (64); 75 (100).

(2*S*)-2-dimethoxymethyl-pirrolidine 17 and **(2'*R*, 2*S*)-1-(2-dimethoxymethyl-pyrrolidin-1'-yl)-3-3-3-trifluoro-2-methoxy-2-phenyl-propan-1-one 18.** To a suspension of 10% $Pd(OH)_2/C$ (31 mg) in MeOH (20 ml) a solution of compound **16** (540 mg, 2.17 mmol) in MeOH (20 ml) was added under nitrogen atmosphere. Hydrogen atmosphere was then introduced by means of a three ways tap and vigorous stirring was started. After 12 h stirring the reaction was filtered through a Celite plug and 1N HCl was added. The solution was then

washed with Et_2O, treated with 2N NaOH, and the separated aqueous phase extracted with Et_2O. The collected organic layers were dried and evaporated in vacuo to afford the unstable pirrolidine **17** as an oil. To the crude **17**, in dry CH_2Cl_2 (30 ml), under nitrogen atmosphere, NEt_3 (0.33 ml, 2.35 mmol) and (*R*)-(-)-α-methoxy-α-trifluoro-methyl-phenylacetyl-chloride (0.41 ml, 2.17 mmol), were added with stirring at room temperature. The resulting mixture was stirred for 1 d, then some drops of 1N HCl, were added and the reaction mixture was submitted to standard extractive work-up with AcOEt. The collected organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated in vacuo. Flash chromatography of the crude product, 1:1 v/v AcOEt - petroleum ether, afforded the pure amide **18** (251 mg, 32%). **17** (crude): ^{1}H-NMR δ: 1.65-1.93 (m, 6H); 2.85 (m, 1H); 3.37 (s, 3H); 3.4 (s, 3H); 4.16 (d,1H, J = 8.0 Hz); m/z (%): 145 (M^+, 12); 115 (7); 57 (12). **18:** ^{1}H-NMR ($CDCl_3$) δ: 1.50-1.83 (m, 4H); 1.92-2.10 (m, 1H); 2.32-2.43 (m, 1H); 3.42 (s, 3H); 3.54 (s, 3H); 3.64 (bs, 3H); 4.35 (m, 1H); 4.96 (d, 1H, J = 2.5 Hz); 7.34-7.56 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ: 22.72; 25.18; 46.96; 47.23; 55.30; 56.84; 57.06; 59.81; 65.47; 104.29; 127.14; 127.96; 129.18; 133.62; 164.41; $[\alpha]_D^{20}$ +60.1 (c 0.94, $CHCl_3$); m/z (%): 361 (M^+, 2); 330 (4); 286 (10); 189 (100); 105 (26); 75 (71); IR ($CHCl_3$) ν: 2929; 2855; 1642 cm^{-1}; Anal. Calcd. for $C_{17}H_{22}F_3NO_4$: C, 56.50; H, 6.14; N, 3.88. Found: C, 56.62; H, 6.16; N, 3.96.

(5*S*, 10*S*, 10a*S*)-10-methoxy-5-methyl-2,5,10,10a-tetrahydro-1H-pyrrolo-[1,2-b]-isoquinolin-3-one 19 t. To a solution of **ent-12** (640 mg, 2.4 mmol) in dry CH_2Cl_2 (24 ml), at -78°C, $TiCl_4$ (1.45 g, 7.2 mmol) was added, under nitrogen atmosphere. After 30 min stirring a saturated aqueous solution of $NaHCO_3$ was added and the organic phase was extracted with Et_2O. The collected organic layers were dried and solvent was evaporated under reduced pressure. Flash chromatography of the crude product, 8:2 v/v AcOEt - petroleum ether, afforded the pure tricyclic compound **19 t** (384 mg, 69%). ^{1}H-NMR ($CDCl_3$, 500MHz) δ: 1.44 (d, 3H, J = 7.0 Hz); 2.18-2.57 (m, 4H); 3.22 (s, 3H); 4.04 (dt, 1H, J = 8.8 Hz, J = 2.2 Hz); 4.09 (d, 1H, J = 2.2 Hz); 5.22 (q, 1H, J = 7.0 Hz); 7.18-7.37 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ: 20.61; 22.00; 31.28; 47.47; 55.77; 56.55; 78.70; 126.50; 127.89; 129.52; 130.94; 132.11; m/z (%): 232 (M^++1, 20); 216 (28); 184 (30); 148 (100); 133 (86); 116 (43); 77(34); IR ($CHCl_3$) ν: 3005; 2990; 2930; 2823; 1666 cm^{-1}; $[\alpha]_D^{20}$ +93.7 (c 0.525, $CHCl_3$); Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.43; N, 5.95.

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