Enantiopure *Cis*-2,5-Disubstituted-2,5-Dihydropyrroles from D-Glycal-Derived Vinyl Aziridines[†]

Valeria Di Bussolo,[‡]* Ileana Frau,[‡] Stefano Crotti,[‡§] Gloria Uccello-Barretta,[¶] Federica Balzano,[¶] Mauro Pineschi[‡] and Paolo Crotti[‡]*

Dipartimento di Farmacia, Via Bonanno 33 and Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, Università di Pisa, 56126 Pisa, Italy

paolo.crotti@farm.unipi.it

ABSTRACT

Z = OMe, Ph; R = CH(CO₂Me)₂ , CH(COPh)₂ , CH₂COPh
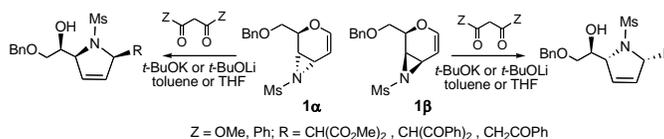
Upon treatment with the K- and Li-enolates of a methylene active compound, such as dimethyl malonate and dibenzoylmethane, D-allal- and D-galactal-derived vinyl *N*-mesyl aziridines are stereoselectively transformed, in a unique step, into diastereoisomeric, highly functionalized, enantiopure *cis* 2,5-disubstituted-*N*-mesyl-2,5-dihydropyrroles.

Multisubstitued chiral 2,5-dihydropyrrole scaffolds are present in several pharmaceuticals and biologically active natural products[1] and constitute a versatile synthon in organic synthesis, particularly in medicinal chemistry and alkaloid synthesis.[2] As a consequence, procedures for the construction of chiral 2,5-dihydropyrrole derivatives bearing functionalized substituents have received growing interest and great effort has been made in order to attain these compounds by asymmetric synthesis. In particular, all four 2,5-disubstituted-2,5-dihydropyrrole stereoisomers were stereoselectively prepared by Trost by a double application of the asymmetric allylic alkylation (AAA) to suitable amino derivatives;[3a] enantiopure 2-alkyl-substituted-2,5-dihydropyrroles were prepared by RCM of *N*-allyl-β-amino-α-methylene esters;[3b,c] and multisubstituted chiral 2,5-dihydropyrroles were obtained by cascade iminium/enamine metal cooperative catalysis[3d] and by phosphine-catalyzed [3+2] cycloaddition of allenoates with imines[3e,f] whereas *cis*- or *trans*-2,5-

[†] Dedicated to the memory of Charles H. DePuy, Professor Emeritus at the University of Colorado Boulder, recognized researcher of great value, excellent person and dear friend.
[‡] Dipartimento di Farmacia.
[¶] Dipartimento di Chimica e Chimica Industriale.
[§] Present address: Novartis Vaccines & Diagnostics, Siena (Italy).
(1) (a) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843-5845. (b) Mack, H.; Baucke, D.; Hornberger, W.; Lange, U. E. W.; Seitz, W.; Hoeffken, H. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2641-2647. (c) Lange, U. E. W.; Baucke, D.; Hornberger, W.; Mack, H.; Seitz, W.; Hoeffken, H. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2648-2653. (d) Krishna, M. C.; DeGraff, W.; Hankovszky, O. H.; Sar, C. P.; Kalai, T.; Jeko, J.; Russo, A.; Mitchell, J. B.; Hideg, K.. *J. Med. Chem.* **1998**, *41*, 3477-3492.
(2) (a) Fattorusso, E.; Taglialatela-Scafati, O., Modern Alkaloids: Structure, Isolation, Synthesis and Biology, Wiley-VCH Verlag GmbH &Co. KGaA, Weinheim, 2008. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron* **1991**, *47*, 2087-2096.

(3) (a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607-6620. (b) Ishikawa, A.; Noguchi, F.; Kamimura, A. *J. Org. Chem.* **2010**, *75*, 3578-3586. (c) Sun, W.; Ma, X.; Hong, L.; Wang, R. *J. Org. Chem.* **2011**, *76*, 7826-7833. (d) Sun, W.; Zhu, G.; Hong, L.; Wang, R. *Chem. Eur. J.* **2011**, *17*, 13958-13962. (e) Pinto, N.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, 146-151. (f) Fang, Y.-Q., Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660-5661. (g) Viso, A.; de la Pradilla, R. F.; Ureña, M.; Bates, H.R.; Águila, M. A.; Colomer. I. *J. Org. Chem.* **2012**, *77*, 525-542.

disubstituted-3-sulfinyl-2,5-dihydropyrroles were obtained from a common sulfinamide intermediate.[3g] In spite of the several procedures described,[3,4] the difficulty in some cases associated with the preparation of the necessary substrate and the need for 2,5-dihydropyrrole systems suitable for further elaborations make the development of alternative methodologies leading to enantiopure, multifunctionalized 2,5-disubstituted-2,5-dihydropyrroles valuable for organic and medicinal chemistry.

As an extension of our interest in heterocyclic compounds and in the synthesis of compounds with potential biological activity, we saw the possibility to construct 2,5-disubstituted-2,5-dihydropyrroles starting from N-mesyl aziridines **1α** and **1β**,[5] through an opening-closing process with contemporary ring contraction of a corresponding, appropriate addition product. Three points were necessary for such a rearrangement process to occur: *a)* the use of a *C*-nucleophile characterized by the presence of two C-H bonds with a consistent acidity, as an active methylene compound, *b)* the formation of a corresponding *syn-* and/or *anti-1,4-addition product* and *c)* the presence in the reaction intermediate of a sufficiently acid N-H bond, *e.g.* MsN-H.

In order to check the validity of the new approach to 2,5-dihydropyrroles, initially we examined the reaction of N-mesyl aziridines **1α** and **1β** with metal enolates of dimethyl malonate, as the active methylene compound.

Aziridines **1α**[5a] and **1β**[5b] can be generated only *in situ* by base-catalyzed cyclization (*t*-BuOK, 1.1-1.3 equiv) of the corresponding stable precursor, the *trans N,O*-dimesylate **2α** and **2β**, respectively (Scheme 1) and immediately left to react with the appropriate nucleophile (2.5-3 equiv) in a non-nucleophilic solvent (*protocol B*).[5] *Trans N,O*-dimesylates **2α**[5a] and **2β**[5b] were prepared, as previously described, starting from vinyl epoxides **3β** and **3α** of

Scheme 1. Precursors of N-Mesyl-Aziridines **1α** and **1β**.

opposite configuration, respectively, on their own obtained from tri-*O*-acetyl-D-glucal (**4**),[6] the simple chiral source of the synthetic process (Scheme 1).

Under *protocol B* reaction conditions, the reaction of N-mesyl aziridine **1α** with the K-enolate of dimethyl malonate (by *t*-BuOK, 2.5 equiv) in dry toluene, afforded a crude reaction product consisting of the highly functionalized (2R,5S,6S)-2-(dimethoxycarbonylmethyl)-5-(2-benzyloxy-1-hydroxy-ethyl)-N-mesyl-2,5-dihydropyrrole [(+)-**5**, 32%], as expected, in a mixture with the *anti-1,2-addition product*, the *trans* 4-(N-mesylamino-)-3-(dimethoxycarbonyl-methyl)-D-glucal derivative (−)-**6** (68%) which were separated by SiO₂ flash chromatography (Scheme 2).[7]

Scheme 2. Reaction of aziridine **1α** with the K- and Li-enolates of Dimethyl Malonate.

	(+)-**5**	(−)-**6**
1) K-enolate (2.5 equiv, *t*-BuOK)	32%	68%
2) Li-enolate (3.0 equiv, LiH)	74%	26%
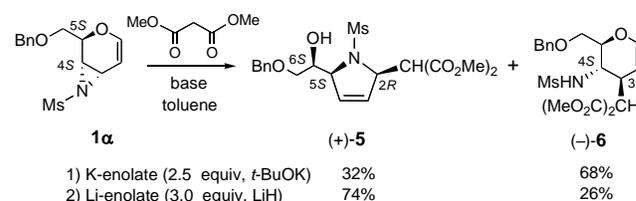
Since we thought that 2,5-dihydropyrrole derivative (+)-**5** derived from the corresponding *syn-* **7α** and/or *anti-1,4-addition product* **7β** (Scheme 3), if the amount of these 1,4-adducts could be increased also the amount of the rearranged product would have been reasonably and correspondently increased in the final crude reaction mixture. In this sense, we had previously demonstrated that in the reactions of glycal-derived aziridines **1α** and **1β**[5,8] with other nucleophiles, the corresponding *syn-1,4-addition product/ anti-1,2-addition product* ratio could be increased by favoring the occurrence of a coordination between the nucleophile and the aziridine nitrogen.[9] For this reason, we repeated the reaction of aziridine **1α** with the Li-enolate of dimethyl malonate (generated by LiH, 3.0 equiv, toluene) in order to have in the reaction mixture a cation, as Li⁺, more coordinating than the previously used K⁺ (from *t*-BuOK). Actually, under these modified reaction conditions, 2,5-dihydropyrrole (+)-**5** turned out to be the main reaction product (74%) accompanied by a reduced amount of *anti-1,2-addition product* (−)-**6** (26%), as desired (Scheme 2).

(4) See also: (a) Shi, F.; Xing, G.-J.; Tan, W.; Zhu, R.-Y.; Tu, S. *Org. Biomol. Chem.* **2013**, *11*, 1482-1489, and references therein. (b) Mitasev, B.; Brummond, K. M. *Synlett* **2006**, 3100-3104. (c) Linsay, k. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731-734.

(5) (a) Di Bussolo, V; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299-1302. (b) Di Bussolo, V; Favero, L.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2006**, *71*, 1696-1699.

(6) (a) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383-7386. (b) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 8702-8708.

(7) The structure of compounds **5** and **6** and configuration at C(3) in **6** and at C(2) carbon in **5** were determined by examination of their ¹H and ¹³C NMR spectra and by appropriate NOE experiments which also confirmed that the configuration at C(4) and C(5) carbons in **6** and **5**, respectively, corresponds to that at C(4) carbon of the starting aziridine **1α**.

(8) Di Bussolo, V.; Frau, I.; Pineschi, M.; Crotti, P. *Synthesis* **2012**, *44*, 2863-2871.

(9) The same behavior had been observed also with epoxides **3α** and **3β** (ref. 6).

The formation of 2,5-dihydropyrrole (+)-**5** indifferently starts from *syn*- **7α** and/or *anti-1,4-addition product* **7β** (primary reaction products) by base-catalyzed deprotonation (a small excess of base is present in the reaction mixture) of the residual acid C-H bond of the (dimethoxycarbonyl)-methyl group generating the corresponding enolate species **8** (Scheme 3). Subsequent E1cb-type elimination, with an intramolecular alcoholate species acting as the leaving group, leads to formation of the intermediate α,β-γ,δ-unsaturated ester system **9**. Acid-base equilibration between the alcoholate and the acid MsN-H group present in **9** leads to the new species **10** bearing the hydroxy group and the weaker base MsN⁻. Intramolecular nucleophilic attack by the MsN⁻ group, in a conjugate fashion, to the α,β-unsaturated system through the folded conformer **10b** leads to the regio- and stereoselective formation of *cis*-2,5-disubstituted-2,5-dihydropyrrole (+)-**5**. Actually, in **10b** the conjugate system assumes an *s*-cis conformation in order to form a hydrogen bond between the carbonyl oxygen and the secondary hydroxy functionality. This makes the nucleophilic MsN⁻ appropriately disposed for a favored, completely facial selective attack on the *Re* face of the α,β-conjugated system, with consequent complete *cis*-steroselectivity. (Scheme 3).

Scheme 3. Rationalization of the formation of 2,5-Dihydropyrrole (+)-**5** from aziridine **1α**.
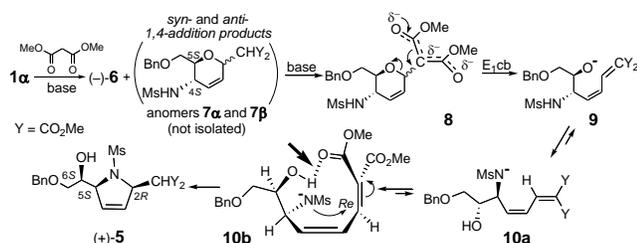
When the same reaction was repeated, under the same reaction conditions (dimethylmalonate/*t*-BuOK, 2.5 equiv, toluene), with the diastereoisomeric aziridine **1β** (Scheme 4), the corresponding *anti-1,2-addition product*,

Scheme 4. Reaction of aziridine **1β** with the K- and Li-enolates of Dimethyl Malonate.

	(+)-11	**(+)-12**
1) K-enolate (2.5 equiv, *t*-BuOK)	7%	93%
2) Li-enolate (3.0 equiv, LiH)	15%	85%
3) Li-enolate (3.0 equiv, *t*-BuOLi)	41%	59%
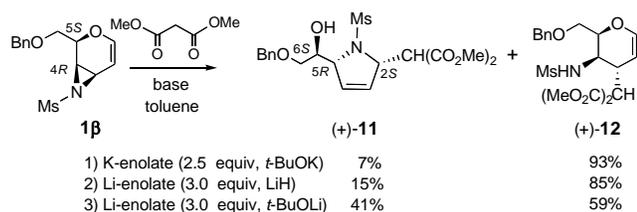
the *trans* 4-(*N*-mesylamino)-3-(dimethoxycarbonylmethyl)-D-gulal derivative (+)-**12** was practically the only reaction product, accompanied by only a small amount (7%) of a rearranged product which turned out to be (2S,5R,6S)-2-(dimethoxycarbonylmethyl)-5-(2-benzylozy-1-hydroxy-ethyl)-*N*-mesyl-2,5-dihydropyrrole (+)-**11**, a distereoisomer of (+)-**5**. As expected, by changing the base from *t*-BuOK to LiH and finally to *t*-BuOLi, the amount of the 2,5-dihydropyrrole (+)-**11** increased to 15 and 41%, respectively (Scheme 4).

Also in this case, 2,5-dihydropyrrole (+)-**11** reasonably derives from both the corresponding *syn*- and/or *anti-1,4-addition product* **13α** and **13β** (Scheme 5) which, as with **7α** and **7β** from aziridine **1α**, are not found in the crude product, due to their evidently rapid rearrangement. In this case, intramolecular nucleophilic attack selectively occurs at the *Si* face of the intermediate α,β-conjugated system, as shown in **14b** (Scheme 5).

Scheme 5. Rationalization of the formation of 2,5-Dihydropyrrole (+)-**11** from aziridine **1β**.
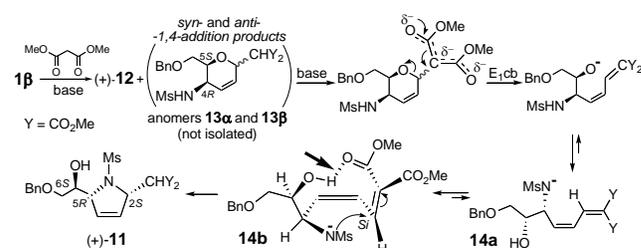
Necessarily having the same (S)-configuration at C(6) of the (1-hydroxy-2-benzyloxyethyl)- side chain, the diastereoisomeric relationship between 2,5-dihydropyrroles (+)-**11** from **1β** and (+)-**5** from **1α** is due to the opposite configuration at C(4) in the starting aziridine and, as a consequence, at C(4) in the corresponding *1,4-addition products* (Schemes 2-5). This determines an opposite configuration at the C(5) carbon of the corresponding 2,5-dihydropyrrole and the occurence of a completely *Re*- and *Si*-face-selective conjugate addition by the internal nucleophile (intermediates **10b** from **1α** and **14b** from **1β**, Schemes 3 and 5), respectively and, consequently, an opposite configuration at C(2) carbon in 2,5-dihydropyrroles (+)-**5** and (+)-**11**.

To check the scope of this new protocol for the construction of highly functionalized 2,5-disubstituted-2,5-dihydropyrroles, dibenzoyl methane K-enolate [from CH₂(PhCO)₂ and *t*-BuOK (2.5 equiv) in dry toluene (*protocol B*)] was taken as an appropriate *C*-nucleophile for the rearrangement reaction to occur and, initially, we checked this further possibility with aziridine **1α**. A clean reaction occurred leading to a crude reaction product consisting of (2R,5S,6S)-2-(dibenzoylmethyl)-5-(2-benzylozy-1-hydroxy-ethyl)-*N*-mesyl-2,5-dihydropyrrole [(+)-**15**, 42%] in a mixture with the corresponding *anti-1,2-*

addition product, the *trans* 4-(*N*-mesylamino)-3-(dibenzoylmethyl)-D-glucal-derivative (–)-**16** (42%) and a small amount of an *anti-1,4-addition product*, the β-*C*-glycoside **17β** (16%) which were separated by SiO$_2$ flash chromatography (Scheme 6). When dry THF was used as the solvent, an increased amount of the rearranged product (+)-**15** (60%) was obtained, accompanied only by the *anti-1,2-addition product* (–)-**16** (40%). More interestingly, and superior to any reasonable expectation, was the result obtained when the corresponding Li-enolate (3 equiv, by *t*-BuOLi) was used under a partially modified protocol.[10] Under the new conditions, the 2-(dibenzoylmethyl)-substituted dihydropyrrole (+)-**15** (66%) and the corresponding 2-(benzoylmethyl)-derivative (+)-**18** (34%) were the only reaction products (Scheme 6).[11] No trace of *anti-1,2-addition product* (–)-**16** was found.

Scheme 6. Reaction of aziridine **1α** with the K- and Li-enolates of Dibenzoylmethane.
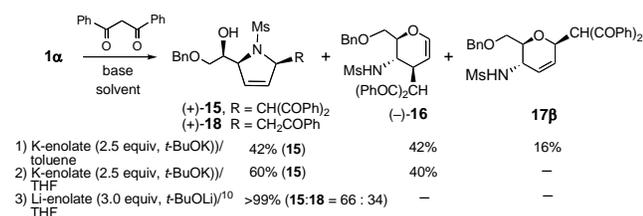
Treatment of β-*C*-glycoside **17β**, the *anti-1,4-addition product* from the reaction of aziridine **1α** (entry 1, Scheme 6), with *t*-BuOK/toluene afforded, after 24 h at rt, the same 2,5-dihydropyrrole (+)-**15** already present in the crude reaction mixture (Schemes 6 and 7). This result confirmed the validity of the proposed mechanism of formation of 2,5-dihydropyrroles by our protocol (Schemes 3 and 5).

Scheme 7. The treatment of β-*C*-Glycoside **17β** with *t*-BuOK.
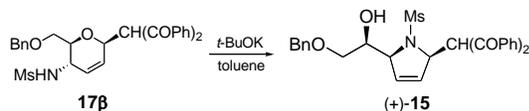
In the course of this control reaction, we found that if the 2,5-dihydropyrrole (+)-**15** was left in contact with the base (*t*-BuOK, 50% molar excess, toluene) for 48 h at rt, a haloform-like reaction occurred, with formation of the corresponding 2,5-dihydropyrrole (+)-**18** in which the 2-(dibenzoylmethyl)-substitution of (+)-**15** was transformed into the simpler 2-(benzoylmethyl)-group (a mono-debenzoylation reaction had occurred, Scheme 8). The same transformation was observed also with the isomeric *anti-1,2-addition product* (–)-**16**, with the obtainment of the corresponding 3-(benzoylmethyl)-derivative (–)-**19** (Scheme 8).

Scheme 8. The transformation of compounds (+)-**15** and (-)-**16** into the corresponding mono-debenzoylated (+)-**18** and (-)-**19**.
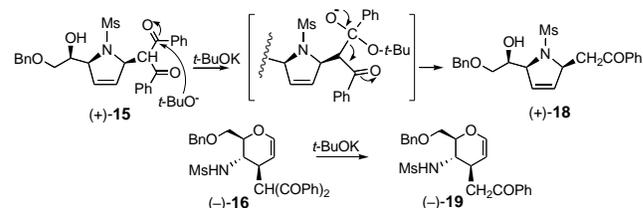
Addition of the K-enolate of dibenzoyl methane (1.5 equiv) to the diastereoisomeric *N*-mesyl aziridine **1β** afforded only the corresponding *anti-1,2-addition product*, the *trans* 4-(*N*-mesylamino)-3-(dibenzoylmethyl)-D-gulal derivative (+)-**20**[12] and no dihydropyrroles were observed (Scheme 9). However, when the addition reaction was repeated with the corresponding, more coordinating Li-enolate (3 equiv, by *t*-BuOLi),[10] the *anti-1,2-adduct* (–)-**21** (58%) was accompanied by a consistent amount of 2,5-dihydropyrrole derivative (–)-(**23**) (42%). To note that under these conditions, both reaction products **21** and **23** bear the simplified 2-(benzoylmethyl)-substitution.[13]

Scheme 9. Reaction of aziridine **1β** with the K- and Li-enolates of Dibenzoylmethane.
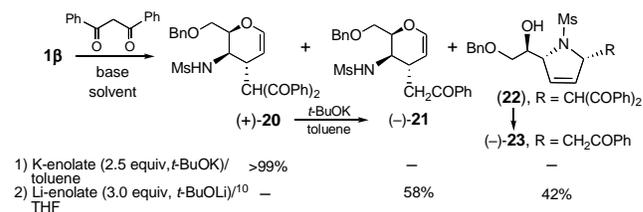
In conclusion, enantiopure *cis*-2,5-disubstituted-*N*-mesyl-2,5-dihydropyrroles (+)-**5**, (+)-**11**, (+)-**15**, (+)-**18** and (–)-**23** have been obtained, in a unique and completely

(10) Under the new protocol, *t*-BuOLi (3 equiv) was used only for the preventive generation of the Li-enolate of dibenzoylmethane, whereas aziridine **1α** (or **1β**) was formed in situ by cyclization of *trans N,O*-dimesylate **2α** (or **2β**) by *t*-BuOK (1.5 equiv, see Supporting Information).

(11) For the formation of (+)-**18**, see Scheme 8 and the related discussion.

(12) The treatment with *t*-BuOK transformed compound (+)-**20** into corresponding 2-(benzoylmethyl)-derivative (-)-**21** (Scheme 9).

(13) On the basis of the experimental evidence obtained for **20/21** (ref. 12) and by a reasonable extension to **23** of what previously found for **18** (Scheme 8), the (benzoylmethyl)-substituted reaction products **21** and **23** derive from the corresponding (dibenzoylmethyl)-substituted derivatives **20** and **22** (the primary reaction products) which were not isolated due to their, evidently fast, monodebenzoylation process under the alkaline reaction conditions (entry 2, Scheme 9).

stereoselective fashion, by addition of metal enolates of β-dicarbonyl compounds (*C*-nucleophiles) to glycal-derived vinyl *N*-mesyl aziridines **1α** and **1β**. A reaction mechanism involving a base-catalyzed rearrangement of the corresponding *1,4-addition products,* with ring contraction, is congruent with the experimental evidence obtained. The presence of two highly functionalized side chains and of the endocyclic double bond, make the obtained 2,5-disubstituted-2,5-dihydropyrroles particularly useful for further elaboration on the route to alkaloids and furanosidic azasugars.

Supporting Information Available. Experimental details, spectral and analytical data for all reaction products, This material is available free of charge via the Internet at http//:www.acs.pubs.org.