# SYNTHESIS OF AN OPTICALLY ACTIVE TRICYCLIC INTERMEDIATE FOR MANZAMINES#

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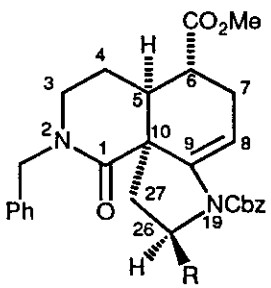
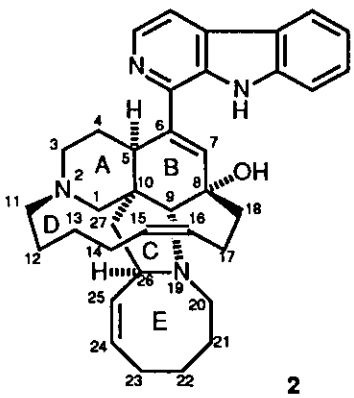
*ABSTRACT - L- Serine has been converted into a chiral pyrrolo[2,3-i]isoquinoline derivative which can serve as a potential intermediate for manzamines.*

In a recent communication we have presented a strategy for the synthesis of the tricyclic pyrrolo[2,3-i]-isoquinoline system (**1a**)[2], which represents the ABC substructure of the manzamine alkaloids[3] and, in addition, carries functional groups, which hold potential for the construction of the β-carboline and the thirteen-membered ring of our first synthetic target, namely, the alkaloid manzamine-A (**2**).




**1a** R = H

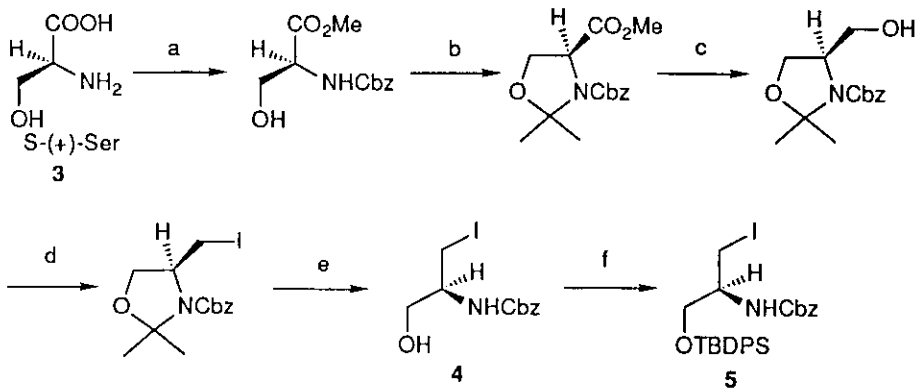
**1b** R = $CH_2OTBDPS$




**2**

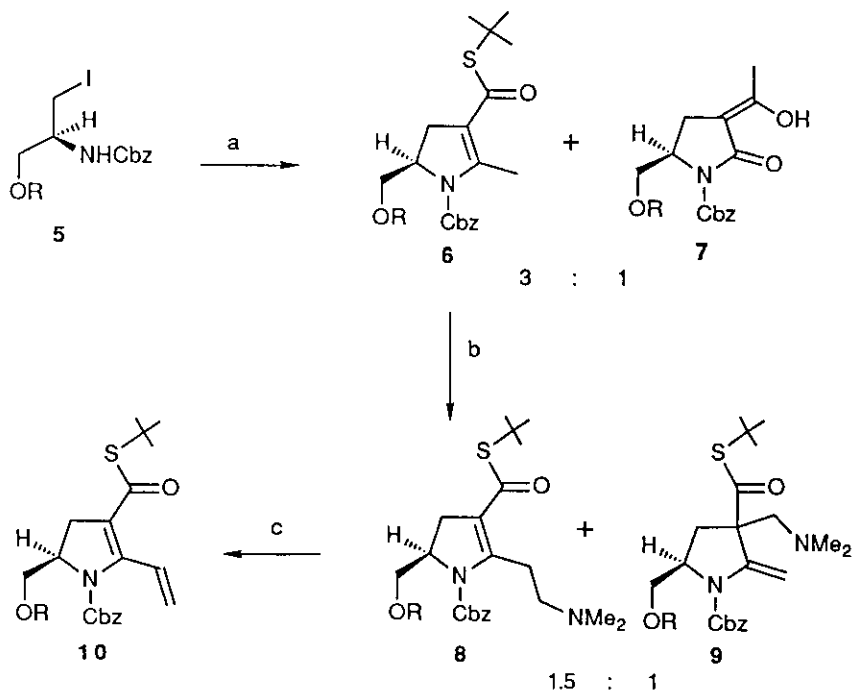
Another approach to the parent decahydropyrrolo[2,3-i]isoquinoline system has recently been reported by Hart.[4] In this communication we describe the application of our strategy for the preparation of optically active tricyclic intermediate **1b**. It should be emphasized at the outset that the **5S,10S,26R**

*# Dedicated to the memory of Professor Tetsuji Kametani; a dedicated and inspiring chemist and a good friend.*




(a) i $SOCl_2$, MeOH; ii CbzCl, $NaHCO_3$; 95 %. (b) dimethoxypropane, TsOH; 99 %.
(c) $Ca(BH_4)_2$, EtOH/THF; 99 %. (d) $Ph_3P$, $I_2$, imidazole; 85 %. (e) conc. HCl, acetone; 99 %.
(f) TBDPSCl, imidazole, DMF; 90 %.

**Scheme 1**



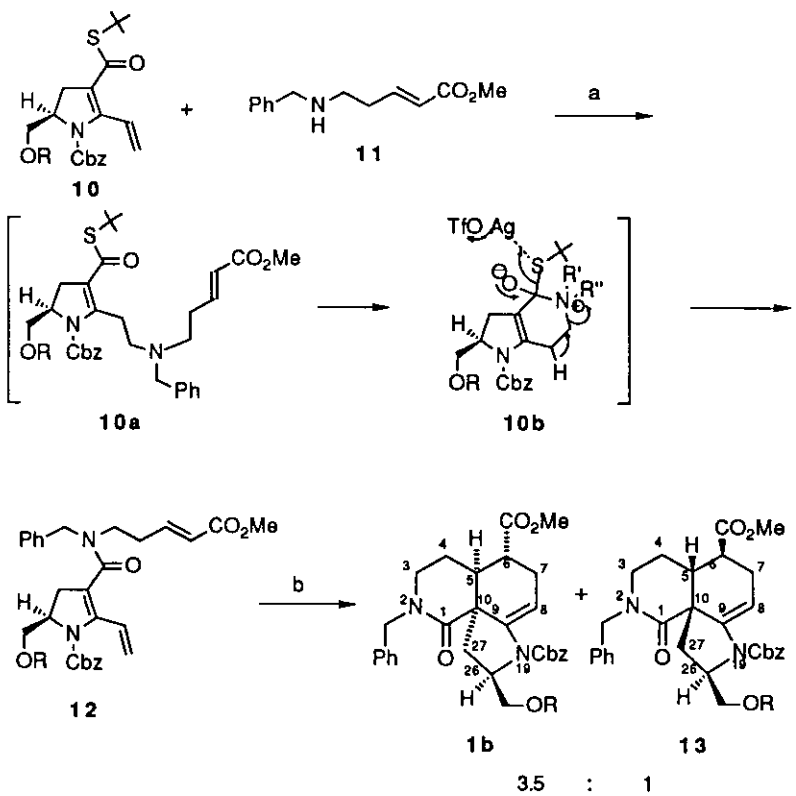

R = *tert.*-butyldiphenylsilyl

(a) i NaH, DME, *tert.*-butylacetothioacetate; ii TsOH, quinoline; 67 %. (b) i LiHMDS, THF, **6**; ii $CH_2{=}N(CH_3)_2^+$ $I^-$; 71 %. (c) i MeI, MeCN; ii DBU, $CH_2Cl_2$; 71 %.

**Scheme 2**

stereochemistry of **1b**[5] corresponds to that of the natural alkaloid (**2**) and moreover, the hydroxymethyl group attached at $C_{26}$ is ideally suited for the construction of the azocine ring E.

A retrosynthetic analysis of **1b**, along the lines described for **1a**, led to the requirement of optically pure iodide **5**. This compound was obtained in seven steps, starting from L-serine (**3**), in 71 % overall yield (**Scheme 1**).[6] The optical purity of intermediate **4** was demonstrated with the aid of (+)-Eu(hfc)$_3$ shift reagent. After alkylation of *tert*-butylacetothioacetate with **5** and cyclization of the resulting product mixture, the desired pyrroline thiolester **6** could be isolated together with the γ-lactam **7** (**Scheme 2**).After much experimentation it was found that for a high yield condensation of Eschenmoser's salt with the anion of **6** the use of lithium hexamethyldisilazide in tetrahydrofuran was crucial. In addition to the desired product **8**, α-alkylation product **9** was also formed. Transformation of **8** to the rather unstable **10** proceeded straightforward. This compound was immediately coupled with aminoester **11**[7] in the presence of silver triflate and diisopropylethylamine, yielding triene **12** in 69 %yield

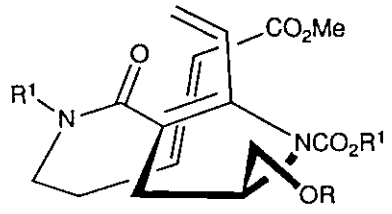



(a) AgOTf, DIPEA, MeCN; 69 %. (b) xylene, Δ, 2h; 90 %.

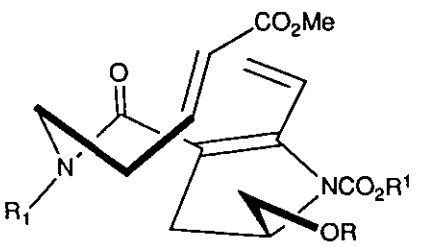
**Scheme 3**

(**Scheme 3**). This reaction proceeds via intermediates **10a** and **10b**. A Michael type addition product, corresponding to **10a**, has been isolated in high yield in the closely related coupling reaction of a model 2-pyrroline thiolester[2] and aminoester **11**. Subjection of this addition product to silver triflate yielded the expected amide coupling product. The fact that a corresponding aminolysis of thiolester **6**, lacking an activated vinyl group, under identical conditions did not lead to any reaction, further substantiates the proposed mechanism. Implications of this mechanism for the synthesis of **12** are being studied in our laboratory at the moment.

The intramolecular Diels-Alder reaction of **12** gave two diastereomeric products (3.5 : 1 ratio), to which structures **1b** and **13** have been assigned respectively, in 90 % combined yield. The diastereomeric transition states **A** and **B** can be envisaged for this reaction. As expected, the main and desired product (**1b**) is formed via the sterically more favourable transition state (**A**).




**A**




**B**

The gross structure elucidation of **1b** and **13** was facilitated by the corresponding data obtained for compound **1a**. The connectivities were clarified by COSY experiments. A clue for the distinction between **1b** and **13** is given by the chemical shifts of the protons attached to $C_{27}$. In compound **1b** $H_{27exo}$ and $H_{27endo}$ can be found at 1.61 and 2.64 ppm respectively, whereas in compound **13** these protons are observed at 1.97 and 2.23 ppm respectively. Steric repulsion between the silyloxymethylene group and the lactam carbonyl group in compound **1b** causes $H_{27endo}$ to move into the deshielding cone of the lactam carbonyl group and $H_{27exo}$ to move out of the shielding cone of the enecarbamate double bond, compared to the corresponding protons in compound **13**. In addition, the dihedral angle between $H_{27endo}$ and $H_{26}$ in compound **1b** becomes 90°, which causes the former to be found as a doublet (J = 13.2 Hz). In compound **13** $H_{27endo}$ is found as a doublet of a doublet (J = 12.4 and J = 7.2 Hz). The stereochemistry at $C_{26}$ in compound **1b** was also directly de-

duced from NOE experiments. Irradiation of $H_5$ at 1.95 ppm gave an enhancement for $H_7$ at 2.34 ppm and for $H_{27exo}$ at 1.61 ppm. Irradiation of $H_{27endo}$ at 2.64 ppm gave an enhancement for one of the protons of the silyloxymethylene group attached to $C_{26}$, found at 4.30 and 4.45 ppm. Conversely, irradiation of both methylene protons at 4.30 and 4.45 ppm gave only an enhancement for $H_{27endo}$ at 2.64 ppm.

Compound **1b** is suitably functionalized at the centres $N_2$, $C_8$; $C_6$; and $C_{26}$, $N_{19}$ for the construction of the remaining rings of manzamine-A. Work towards this end is currently in progress.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. Taken in part from the forthcoming doctorate thesis of Ir. K. M. J. Brands, University of Amsterdam.

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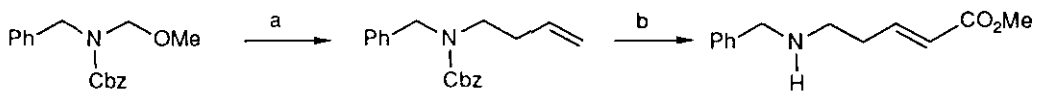
3. (a) R. Sakai, T. Higa, C. W. Jefford, and G. Bernardinelli, J. Am. Chem. Soc., **1986**, *108*, 6404; (b) R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford, and G. Bernardinelli, Tetrahedron Lett., **1987**, *28*, 5493; (c) T. Ichiba, R. Sakai, S. Kohmoto, G. Saucy, and T. Higa, ibid., **1988**, *29*, 3083; (d) H. Nakamura, S.Deng, J. Kobayashi, Y. Ohizumi, Y. Tomatake, T. Matsuzaki, and Y. Hirata, ibid., **1987**, *28*, 621.

4. D. J. Hart and J. A. Mckinney, Tetrahedron Lett., **1989**, *30*, 2611.

5. Manzamine-A numbering according to reference 3d.

6. All new compounds reported herein have spectral (250-MHz $^1$H nmr, ir and ms) data consistent with the assigned structures.

7. Synthesis of aminoester **11**, as reported in reference 2, has been slightly modified:




(a) allyltrimethylsilane, $BF_3.Et_2O$ ; quant. (b) i ozonolysis, ii Wittig reaction, iii deprotection ; 60%.

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