SYNTHESIS OF AN OPTICALLY ACTIVE TRICYCLIC INTERMEDIATE FOR MANZAMINES#

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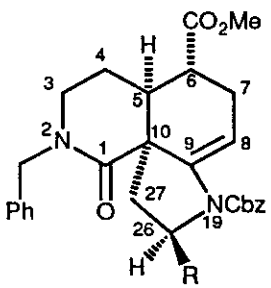
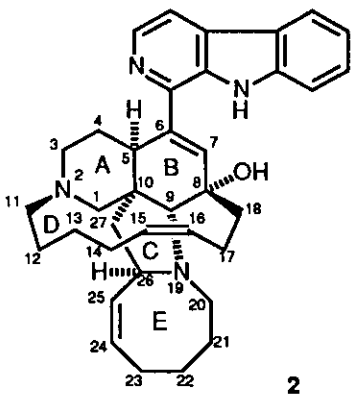
ABSTRACT - L- Serine has been converted into a chiral pyrrolo[2,3-i]isoquinoline derivative which can serve as a potential intermediate for manzamines.

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

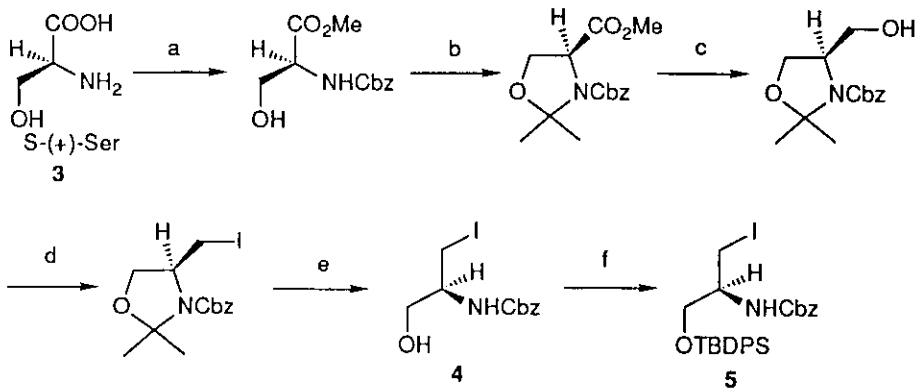
1b R = $CH_2OTBDPS$



2

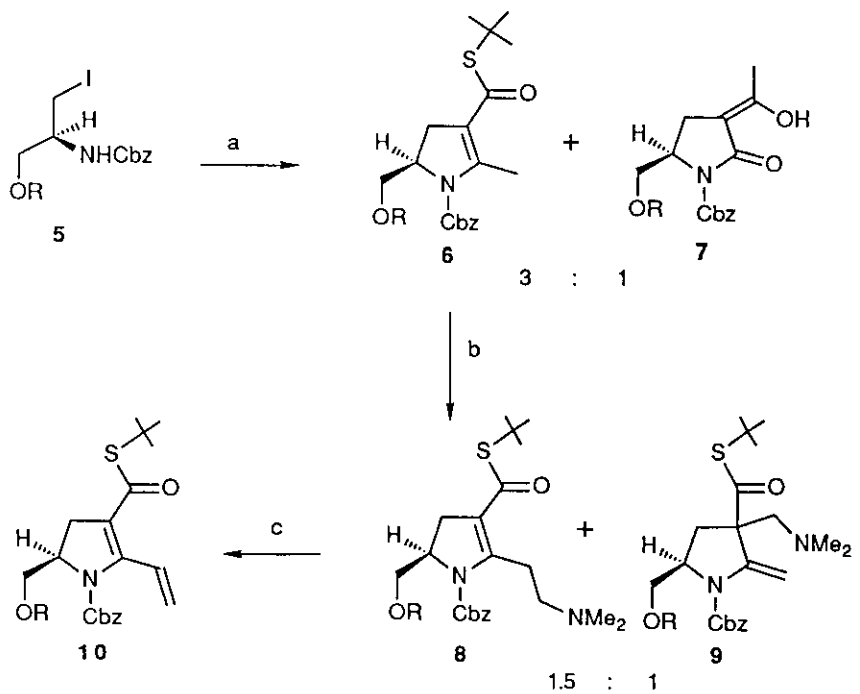
Another approach to the parent decahydropyrrolo[2,3-i]isoquinoline system has recently been reported by Hart.[4] In this communication we describe the application of our strategy for the preparation of optically active tricyclic intermediate **1b**. It should be emphasized at the outset that the **5S,10S,26R**

 # 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



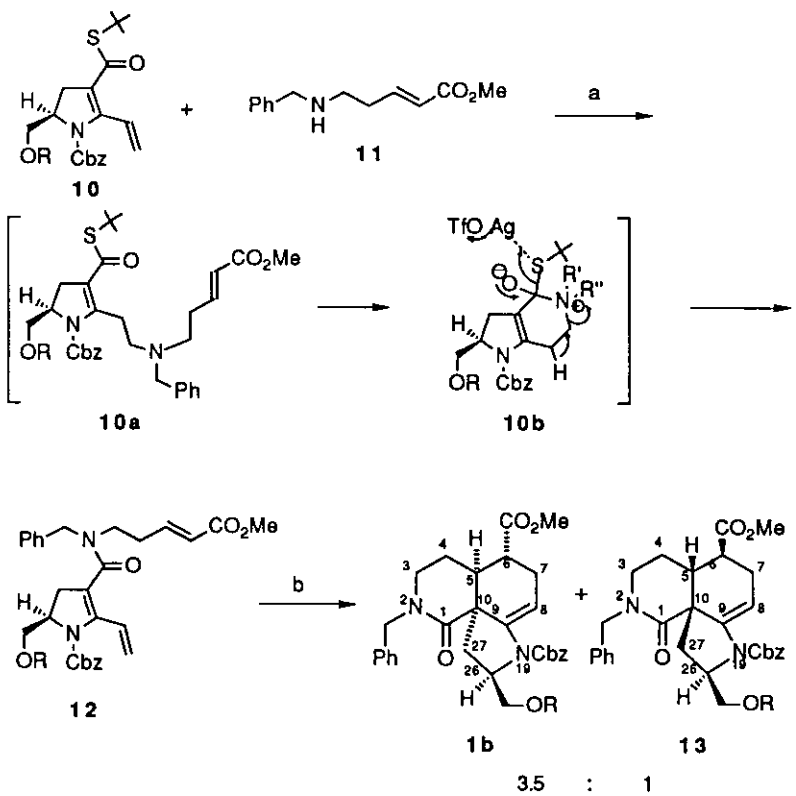
R = *tert.*-butyldiphenylsilyl

(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

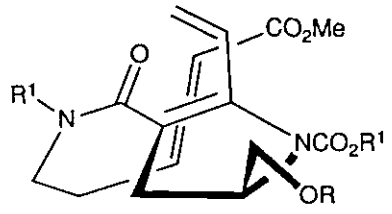


(a) AgOTf, DIPEA, MeCN; 69 %. (b) xylene, Δ, 2h; 90 %.

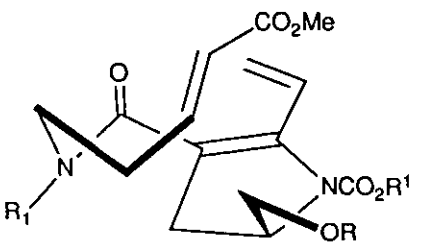
Scheme 3

(**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

This work was carried out under auspices of the Netherlands Foundation for Chemical Research (SON) with financial support from the Netherlands Organisation of Scientific Research (NWO). We are indebted to Dr. H.Hiemstra for helpful discussions.

REFERENCES AND NOTES

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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.

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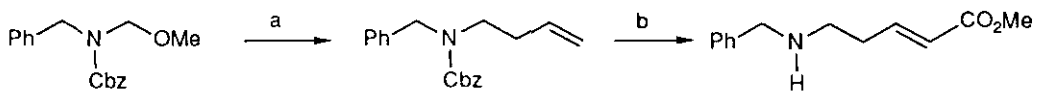
5. Manzamine-A numbering according to reference 3d.

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%.

Received, 17th July, 1989