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An Efficient and Stereoselective Construction of the Core Structure of the Manzamines via an Intramolecular Michael Reaction.≠

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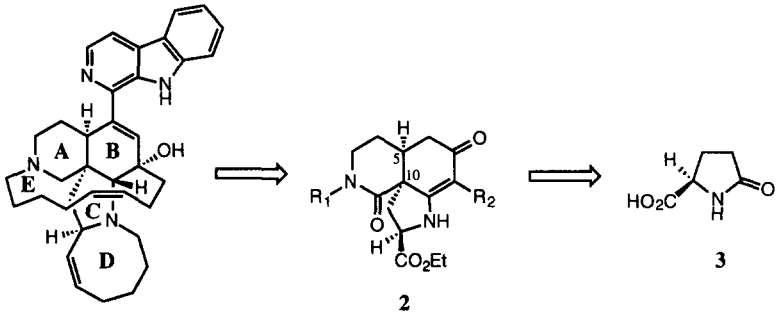
Abstract: *A strategically functionalized tricyclic subunit of the manzamines was efficiently synthesized with complete stereochemical control using a combination of an intramolecular Michael reaction of a pyroglutamic acid derivative and a hydrogenation.* © 1998 Elsevier Science Ltd. All rights reserved.

New members to the Manzamine alkaloid family continue to be isolated from marine sources.[1] This has prompted an interesting biogenetic theory.[2] These natural products have attracted considerable attention from the synthetic community due to their unique structural features and interesting biological activity. Recently, a variety of approaches to the core structure of Manzamine-A (**1**) have been reported, many of them featuring a Diels-Alder reaction.[3] In this Letter we wish to report a novel and efficient approach to the pyrrolo[*2,3-i*]isoquinoline subunit of the manzamines based on an intramolecular Michael reaction.



1 **2** **3**

Scheme 1

The tricyclic derivative **2** occupies a central position in our retrosynthetic analysis of **1.** This compound contains strategically placed functional groups for further elaboration (R_1 and R_2 are appropriately functionalized for formation of the E-ring) to the natural product. Further analysis led to identification of cheap pyroglutamic acid (**3**) as the enantiomerically pure starting material (Scheme 1). An intramolecular Michael reaction was envisaged for the formation of the strategic C_5-C_{10} bond in **2**.[4] It was thought that the requisite Michael substrate **6** could be synthesized via acylation of the enolate of **4** with an appropriately functionalized carbamoyl chloride. There is ample precedence for the regioselective enolization of pyroglutamic derivatives like **4** with complete retention of the stereochemical information of the ester bearing carbon.[5] Unfortunately, all attempts to react enolates of **4** with diethyl carbamoyl chloride which was used as a model were unsuccessful. Inspired by Ley's work[6] we devised a two-step method to synthesize **6** from **4** via **5** (Scheme 2). The lithium enolate of **4** could be quenched with commercially available ethylthio chloroformate in 79% yield after chromatographic purification. Treatment of a mixture of **5** and **9** with an equivalent of silver triflate in the presence of DIPEA as an acid scavenger gave the requisite **6**[7] in excellent yield. This highly successful tactic may find broader use in related transformations.

≠ *Dedicated to Professor U.K. Pandit on the occasion of his retirement from the University of Amsterdam.*

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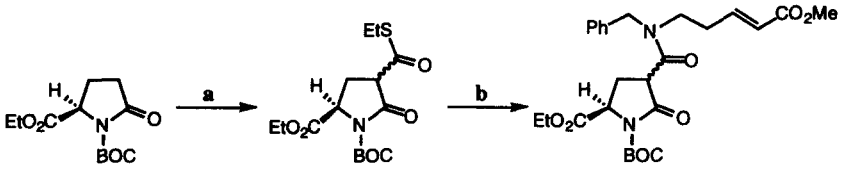
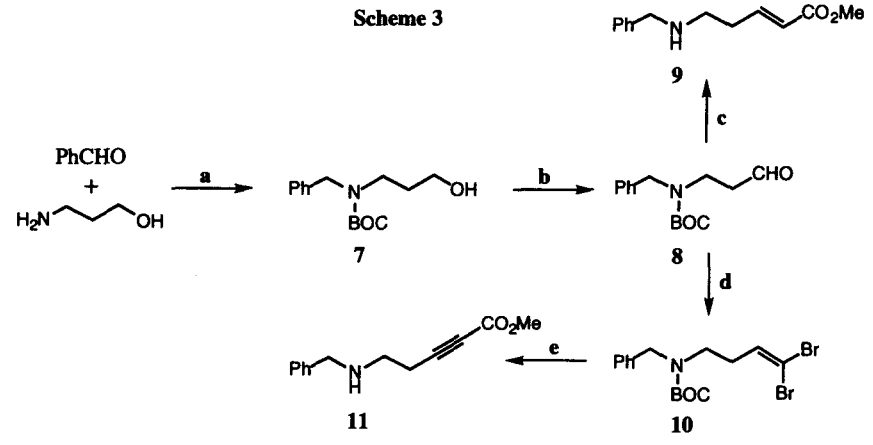
Scheme 2



(a) *i* 2eq LiHMDS, THF *ii* ClCOSEt; 79%. (b) **9**, AgOTf, DIPEA, MeCN; 91%.

The δ-amino ester **9** was synthesized according to Scheme 3.[8] BOC amino alcohol **7** was readily available via reductive amination of benzaldehyde with 3-amino-1-propanol followed by treatment with BOC_2O in 89% yield. Swern oxidation followed by a Wittig reaction and deprotection yielded **9** in 48% overall yield from **7**. This compound was immediately used for the preparation of **6** (Scheme 2).

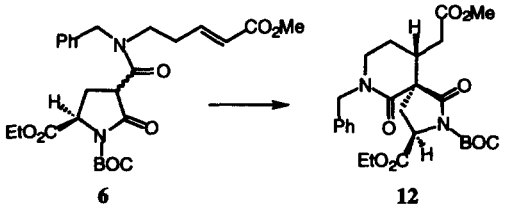
Scheme 3



(a) *i* H_2, Pd/C *ii* DMAP, BOC_2O; 89%. (b) Swern; quant. (c) *i* Ph_3PCHCO_2Me, CH_2Cl_2 *ii* TFA *iii* $NaHCO_3$; 48% overall from **7**. (d) CBr_4, Ph_3P; 81%. (e) *i* 2 eq n-BuLi, $ClCO_2Me$ *ii* TFA *iii* $NaHCO_3$; 68% overall from **10**.

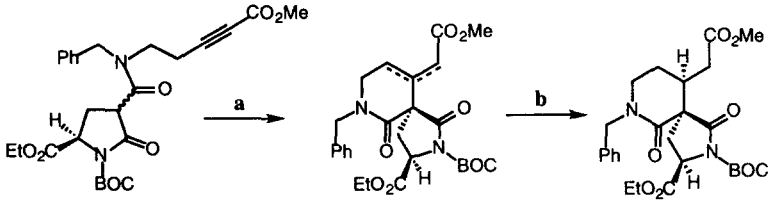
Heating **6**[7] in acetonitrile in the presence of excess DIPEA gave rise to a single product which was isolated in an unoptimized 72% yield (Scheme 4). Structure **12** was assigned to this product on the basis of its NMR spectra.[9] Although the stereoselective formation of **12** under these thermodynamically controlled conditions is notable, this compound contains the wrong stereochemistry at C_5 for further elaboration towards key tricyclic derivative **2**.

Scheme 4



An alternative, two-step, approach was more successful in securing the desired stereochemistry. Acetylenic amino ester **11** was readily prepared[10] from **8** using a standard Corey-Fuchs protocol[11] (Scheme 3). It proved advantageous to purify dibromo olefin **10** via SiO_2 chromatography (81% yield overall from **7**). After acylation of the corresponding lithium acetylide and deprotection with TFA **11** was obtained in 68% yield. Aminolysis of **5** with **11** yielded **13** in 95% yield. Cyclization of **13** occurred under identical conditions as described for **6** (*vide supra*). According to ^{1}H-NMR analysis of the crude reaction mixture three products were obtained in a ratio of 2.7/2.2/1.0. These were tentatively assigned as the *E*-α,β, *Z*-α,β and β,γ isomers of **14**, respectively. Upon hydrogenation in the presence of Pd/C all isomers yielded a single product, albeit at different rates[12] ! Detailed comparison of the NMR spectra of this product with those of **12** allowed its unambiguous structure assignment as the isomeric **15**.[9] NOE studies were particularly informative.[13] Thus, the transformation of **13** to the requisite **15** was achieved with complete stereocontrol in 85% yield.

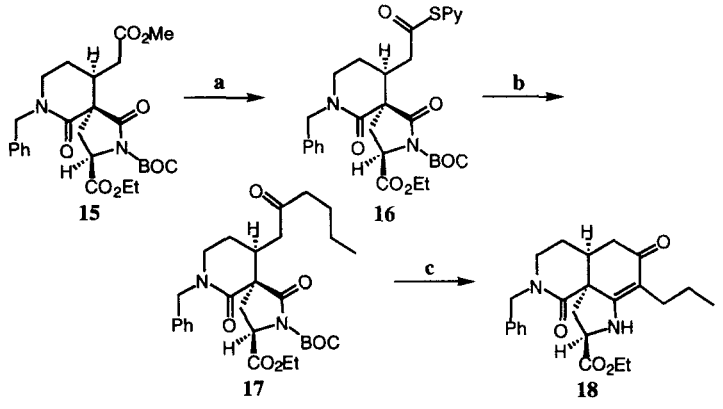
Scheme 5



(a) DIPEA, MeCN (b) H_2, Pd/C, MeOH; 85% overall from **13**

Various strategies for the annellation of the B-ring onto **15** were investigated. Selective manipulation of the lactam carbonyl functionality in **15** (e.g. intermolecular addition of organometallic reagents including reducing agents) was more difficult than anticipated probably due to steric hindrance at this site. Eventually, a Dieckman-type cyclization was found to be the method of choice. After selective hydrolysis of the methyl ester in **15**, pyridyl thiolester **16** could be prepared (Scheme 6). In a model study towards installation of a bridging chain to the piperidine nitrogen (ring E), **16** was allowed to react with butylmagnesium bromide yielding the expected **17** in 71% yield. Cyclization of **17** followed by treatment of the crude bicyclic intermediate with trifluoroacetic acid furnished the anticipated tricyclic vinylogous amide **18** in 60% yield.[14]

Scheme 6



(a) *i* LiOH, THF/H_2O *ii* PySSPy, Ph_3P, MeCN; 69%. (b) BuMgBr, THF; 71%.
(c) *i* KO^{t}Bu, THF *ii* TFA, CH_2Cl_2; 60% overall from **17**.

In summary, novel intramolecular Michael reactions were discovered in which the existing center of a pyroglutamate residue induces the formation of a new quaternary carbon of the spirocyclic product with complete stereocontrol. The Michael substrates are readily available from a protected pyroglutamic acid derivative via a novel and convergent two-step carbamoylation protocol. These methodologies in combination with a face selective hydrogenation allowed the practical preparation of a strategically functionalized pyrrolo[*2,3-i*]isoquinoline subunit of the manzamines in 9 steps and 19% overall yield.

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1. (a) Harrison, B.; Talapatra, S.; Lobkowsky, E.; Clardy, J.; Crews, P. *Tetrahedron Lett.*, **1996**, *37*, 9151-9154 and references cited therein. (b) Edrada, R.A.; Proksch, P.; Wray, V.; Witte, L.; Müller, W.E.G.; Van Soest, R.W.M. *J. Nat. Prod.*, **1996**, *59*, 1056-1060 and references cited therein. c) Tsuda, M.; Inaba, K.; Kawasaki, N.; Honma, K.; Kobayashi, J. *Tetrahedron*, **1996**, *52*, 2319-2324 and references cited therein.
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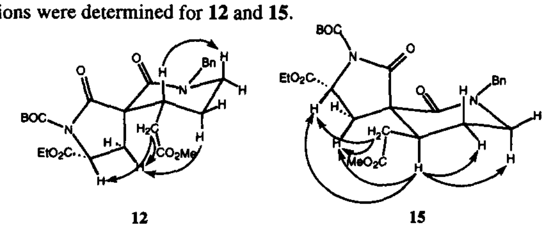
6. Ley, S.V.; Woodward, P.R. *Tetrahedron Lett.*, **1987**, *28*, 3019-3020.
7. According to ^{1}H-NMR compound **6** is a 4/1 mixture of trans and cis isomers, respectively, each present as a 1/1 mixture of amide rotamers.
8. We thank H. Bieräugel and U.K. Pandit of the University of Amsterdam (The Netherlands) for these unpublished observations.
9. For **12**: ^{1}H-NMR (400 MHz, CD_3CN) δ 7.41 (m, 2H), 7.36 (m, 1H), 7.29 (m, 2H), 4.66 (dd, J=10.1, J=4.5, 1H) , 4.56 (d, J=15.1, 1H), 4.45 (d, J=15.1, 1H), 4.20 (qd, J=7.2, J=1.3, 2H), 3.63 (s, 3H), 3.32 (ddd, J=12.6, J=11.9, J=5.3, 1H), 3.20 (ddd, J=12.6, J=6.0, J=3.0, 1H), 2.71 (dddd, J=11.5, J=9.6, J=4.5, J=2.8, 1H), 2.48 (dd, J=14.2, J=10.2, 1H), 2.34 (dd, J=14.2, J=4.5, 1H), 2.31 (dd, J=15.7, J=9.6, 1H), 2.22 (dd, J=15.7, J= 4.5, 1H), 1.98 (dtd, J=13.9, J=11.5, J=5.9, 1H), 1.57 (dddd, J=13.9, J=5.2, J=3.0, J=2.8, 1H), 1.47 (s, 9H), 1.23 (t, J=7.2, 3H). For **15**: ^{1}H-NMR (400 MHz, CD_3CN) δ 7.34 (m, 2H), 7.27 (m, 1H), 7.22 (m, 2H), 4.73 (d, J=15.0, 1H), 4.64 (dd, J=9.9, J=5.3, 1H), 4.30 (d, J=15.0, 1H), 4.19 (qd, J=7.1, J=2.0, 2H), 3.60 (s, 3H), 3.26 (m, 2H), 2.63 (dd, J=13.7, J=5.3, 1H), 2.58 (dd, J=16.1, J=4.5, 1H), 2.41 (om, 2H), 2.37 (dd, J=13.7, J=9.9, 1H), 2.19 (dd, J=16.1, J=9.0, 1H), 2.14 (om, 1H), 1.80 (ddd, J=13.7, J=3.9, J=3.4, 1H), 1.46 (s, 9H), 1.24 1.24 (t, J=7.1, 3H).
10. For an alternative preparation of **11**: Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc. Perkin Tr.I*, **1992**, 509-516.
11. Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.*, **1972**, 3769-3772.
12. It is of interest to note that the β,γ isomer was only hydrogenated at an acceptable rate in the presence of large excess of the 10% Pd/C catalyst (substrate/dry catalyst 2/1 w/w).
13. The following NOE interactions were determined for **12** and **15**.



12 **15**

14. ^{1}H-NMR (250 MHz, CD_2Cl_2) δ 7.38-7.28 (om, 3H), 7.22 (m, 2H), 5.86 (br s, 1H), 4.88 (d, J=14.6, 1H), 4.37 (dd, J=9.0, 1.2, 1H), 4.17 (m, J=7.1, 2H), 4.06 (d, J=14.6, 1H), 3.34 (ddd, J =2.6, 5.9, 1H), 3.24 (ddd, J =7.5, 5.2, 1.1, 1H), 2.93 (d, J=12.9, 1H), 2.4-1.9 (m, H), 1.74 (m, J=5.6, 1H), 1.40 (m, J=7.4, 2H), 1.27 (t, J=7.1, 3H), 0.92 (t, J=7.3, 3H); ^{13}C-NMR (62.9 Mhz, CD_2Cl_2) d 193.3, 171.1, 169.7, 164.4, 138.0, 129.1, 128.6, 128.0, 107.2, 61.9, 59.7, 51.9, 50.2, 43.9, 38.6, 38.4, 37.6, 26.1, 23.8, 22.1, 14.5, 14.4.