Pergamon

Tetrahedron Letters, Vol. 35, No. 5, pp. 691-694, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0321-4

A NOVEL APPROACH TO THE ASYMMETRIC SYNTHESIS OF MANZAMINE A. CONSTRUCTION OF THE TETRACYCLIC ABCE RING SYSTEM

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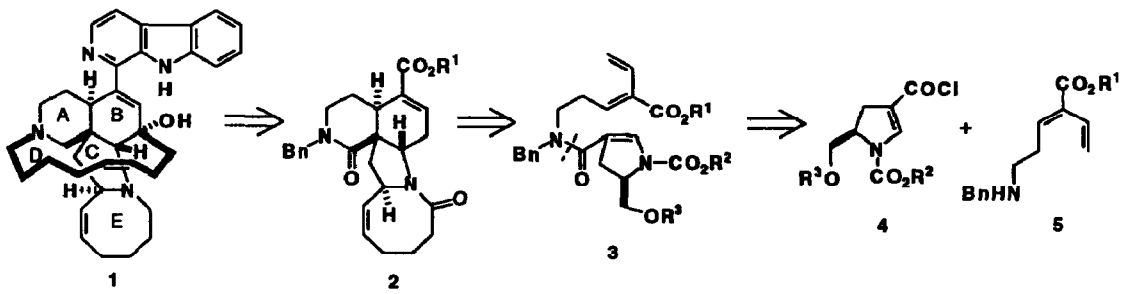
Abstract. The enantiomerically pure tetracyclic ABCE subunit of manzamine A has been constructed by an intramolecular Diels-Alder reaction of the vinylogous imide **13** to give the ABC tricyclic core **14**; elaboration of **14** into **16** followed by a novel olefin metathesis reaction to form the azocine ring then delivered the tetracycle **17**.

Manzamine A (**1**) is a novel antitumor alkaloid that was isolated from marine sponges of the genera *Haliclona* and *Pellina*, which are found off the coast of Okinawa.[1] The combination of its complex and unusual structure and its exciting biological activity has elicited the interest of a number of synthetic groups around the world.[2] To this point, most of these efforts have been on the design of entries to the tricyclic ABC ring subunit, but there have recently been three reports of successful approaches to the ABCE tetracyclic subunit.[3]

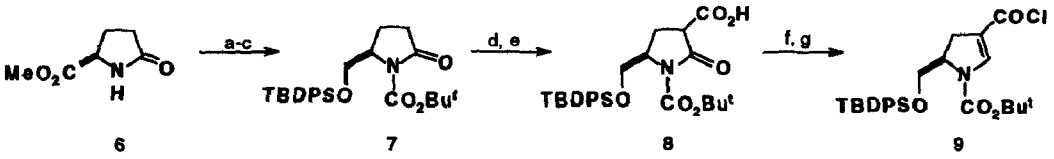
In our previous work, we established the viability of inducing intramolecular [4+2] cycloadditions using vinylogous imides as the dienophilic partner and the application of such a process to the facile synthesis of the tricyclic ABC ring core of manzamine A in racemic form.[4] We now wish to disclose the asymmetric synthesis of **2**, which comprises the tetracyclic ABCE ring system of manzamine A according to the general pathway outlined in Scheme 1. The tetracyclic intermediate **2** contains four of the five chiral centers present in manzamine A as well as an α,β-unsaturated ester moiety at C(6), which provides a critical functional handle for the introduction of the β-carboline ring in the target alkaloid. We envisioned that **2** would be accessible from **3** by a sequence involving an intramolecular Diels-Alder reaction followed by annelation of the E ring, which might be achieved by a variety of tactics. The stereochemistry of the cycloaddition would be directed by the geometry of the internal double bond of the diene in **5**, which would ensure the formation of the requisite *cis*-AB ring fusion,[5] and the stereocenter on the dienophilic subunit, which would direct the diene from the less hindered face. We reasoned that the Diels-Alder substrate **3** could be readily accessed by construction of an amide bond to unite the dienophile **4** and the diene **5**.

Scheme 1



Given the strategy depicted in Scheme 1, the first task before us was the asymmetric synthesis of the dienophilic partner **9**. This was realized in a relatively straightforward sequence of reactions that commenced with methyl pyro-D-glutamate **6** (Scheme 2). Refunctionalization of **6** by standard procedures led to **7**, which was then converted into **9** by acylation, reduction, dehydration, and acid chloride formation.

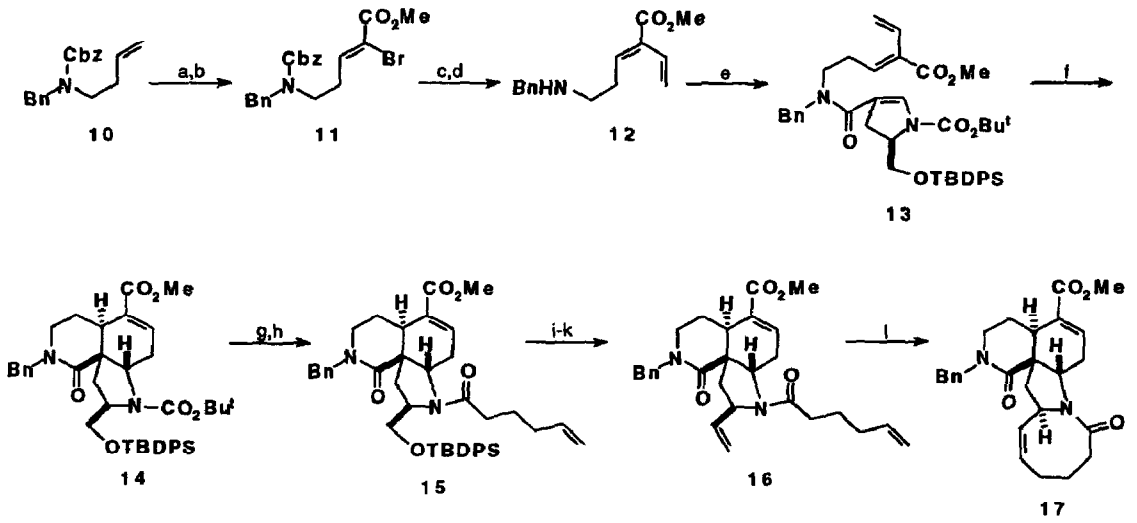
Scheme 2



(a) $LiBH_4$, THF, RT, 2 h; 80%. (b) TBDPS-Cl, imidazole, DMF, RT, 12 h; 95%.
(c) $(Boc)_2O$, CH_2Cl_2, Et_3N, DMAP, RT, 12 h; 94%. (d) LHMDS; BnOCOCl, THF, -78 °C, 2 h; 93%.
(e) H_2, 10% Pd/C, EtOAc, RT, 8 h; 90%. (f) $NaBH_4$, HCl, EtOH, -10 °C, 1 h; 84%.
(g) $(COCl)_2$, CH_2Cl_2, RT, 2 h, 100%.

The preparation of the diene **12** featured a stereoselective Wittig reaction to prepare the vinyl bromide **11**, which was then subjected to a Stille coupling to construct the diene moiety; removal of the nitrogen protecting group delivered **12** (Scheme 3). The dienophilic and dienic partners were then conjoined by amide bond formation to give the **13**, the substrate for the intramolecular Diels-Alder reaction.[6] The cyclization of **13** to give the tricyclic

Scheme 3



(a) O_3, CH_2Cl_2, -78 °C, 1 h; Zn, HOAc, -78 °C to RT, 4 h; 93%. (b) $Ph_3P{=}CBrCO_2Me$, THF, RT, 12 h; 92%.
(c) $Pd(PPh_3)_4$, $CH_2{=}CHSnBu_3$, toluene, 100 °C, 4 h; 82%. (d) TMS-I, CH_2Cl_2, 0 °C, 1 h; 77%.
(e) **9**, Et_3N, CH_2Cl_2, 0 °C, 2 h; 90%. (f) 160 °C (bath temp), 48 h, toluene; 74%. (g) TMS-I, 0 °C, 1 h; 65%.
(h) C_6H_9COCl, CH_2Cl_2, Et_3N, 12 h; 70%. (i) HF/Py, CH_2Cl_2, 0 °C; 90%. (j) DMSO, i-Pr_2NEt, $(COCl)_2$, 12 h; 80%.
(k) $Ph_3P{=}CH_2$, THF, 0 °C to RT, 12 h; 75%. (l) $Mo(CHCMe_2Ph)[N\text{-}2,6\text{-}(i\text{-}Pr)_2C_6H_3][OCMe(CF_3)_2]_2$, PhH, 50 °C, 4 h, 63%.

intermediate **14** proceeded under relatively mild conditions without the intervention of any 1,5-H shifts that would have isomerized the diene component and provided isomeric cycloadducts. The structural assignment of **14** is based upon careful NMR analysis, including COSY and NOE experiments, and comparisons of its NMR spectra with those of a number of related tricyclic substances, a number of which have been unequivocally characterized by X-ray analysis. The carbomethoxy group on the dienic array facilitated this cyclization relative to the unsubstituted case, a result that suggests that the dienophile is participating as the electron rich component of an inverse demand Diels-Alder reaction.[4] Further experiments to examine more precisely the nature of the Diels-Alder reactions of vinylogous imides are in progress.

Having completed the stereoselective assembly of the tricyclic ABC ring core **14** in optically pure form, it remained to address the equally important issue of annelating the eight-membered azocine E ring. The methodology for such constructions is limited, and we considered the obvious possibilities involving intramolecular Wittig or reductive coupling reactions. However, the opportunity for developing new chemisty using such tactics seemed minimal, and we were attracted to a recent report by Grubbs who described a novel route to monocyclic amines and lactams (5- to 7-membered rings) via an olefin metathesis.[7] We conducted several preliminary experiments to establish the feasibility of forming azocines and other fused heterocyclic systems by metathesis of simple dienes containing nitrogen in the chain linking the two olefinic subunits.[8] Since these investigations were highly successful, we converted **14** into the more complex substrate **16** in five simple operations as shown (Scheme 3) to establish whether such metatheses could be conducted on more highly functionalized substrates resulting in forming the E ring of manzamine A. In the event cyclization of **16** in the presence of the Grubbs catalyst delivered the tetracyclic product **17** in good yield.[9]

In summary, the key tetracyclic intermediate **17**, which contains the ABCE ring system of manzamine A has been prepared in optically pure form. Significantly, **17** is endowed with functionality that is well suited for subsequent elaboration into the natural product, and we are exploring a variety of possible tactics to achieve this goal.

Acknowledgment. We thank the National Institutes of Health (GM 25439) and The Robert A. Welch Foundation for their generous support of this research. We also thank Dr. R. H. Grubbs (California Institute of Technology) and Dr. G. C. Fu for providing generous quantities of the molybdenum catalyst for the olefin metathesis.

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9. Selected data for compound **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.19 (comp, 5 H, (Ar)), 7.08 (dd, J = 6.9, 2.5 Hz, 1 H), 5.65 (ddt, J = 11.8, 1.6, 8.1 Hz, 1 H), 5.53 (ddd, J = 11.9, 3.8, 1.4 Hz, 1 H), 4.72 (d, J = 14.6 Hz, 1 H), 4.67 (dd, J = 4.9, 1.4 Hz, 1 H), 4.51 (m, 1 H), 4.45 (d, J = 14.6 Hz, 1 H), 3.74 (s, 3 H), 3.29 (t, J = 6.0 Hz, 1 H), 3.17 (m, 2 H), 2.95 (t, J = 6.0 Hz, 1 H), 2.64 (dt, J = 5.6, 12.3 Hz, 1 H), 2.54-2.48 (comp, 2 H), 2.41 (dd, J = 12.7, 9.9 Hz, 1 H), 2.23-2.18 (comp, 2 H), 2.02 (m, 1 H), 1.88 (comp, 3 H), 1.63 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 173.5, 172.1, 166.5, 139.8, 136.9, 132.0, 131.4, 128.7, 128.0, 127.5 126.0, 61.02, 59.3, 51.8, 50.8, 49.9, 44.9, 44.0, 36.7, 33.7, 27.7, 24.8, 24.5, 23.4; IR (neat) 3017, 2949, 1707, 1632, 1435, 1349, 1248 cm^{-1}; mass spectrum (CI) *m/e* calc'd for $C_{26}H_{30}N_2O_4(M^+)$: 434.2206, found 434.2207; 312, 296, 198, 177, 162, 149, 134, 120, 109(base). Irradiation of H_5 at 2.95 ppm gave 5.1% enhancement for H_{26} at 4.51 ppm.

(*Received in USA* 29 *September* 1993; *revised* 16 *November* 1993; *accepted* 23 *November* 1993)