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Zincke-Bradsher Convergent Strategy for the Synthesis of the ABE tricyclic Core of Manzamine A.

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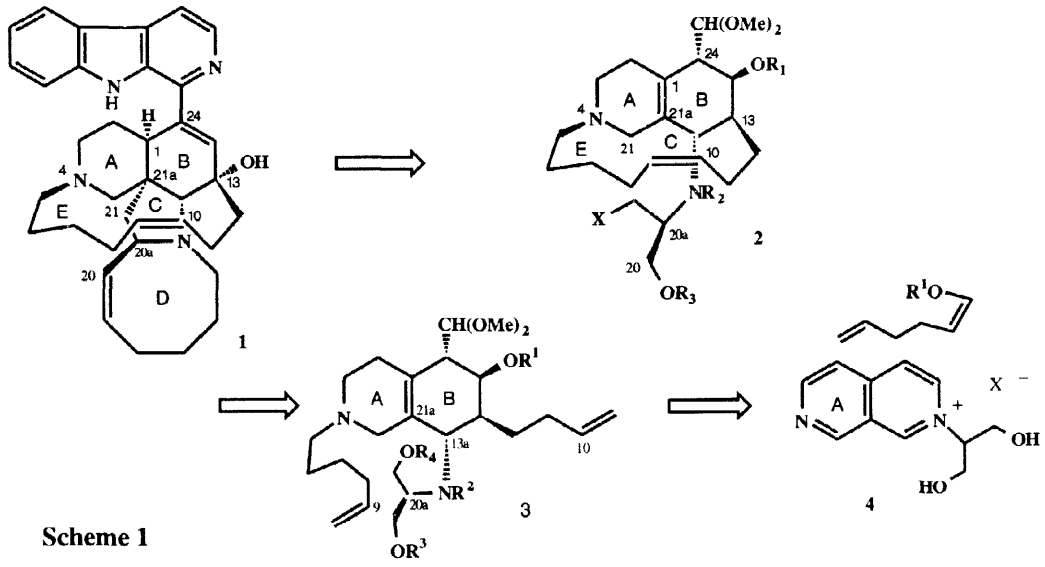
Abstract: The ABE tricyclic core of Manzamine A **1** has been synthetized in six steps, in 18% overall yield from 2,7-naphthyridine using a Zincke-Bradsher reaction and an olefin metathesis.

Manzamine alkaloids[1] are a new family of natural products extracted from various species of sponges. Owing to their cytotoxic activity and original framework, these alkaloids and particuliarly Manzamine A **1** became in the last few years the target of a number of synthetic approaches[2].

A retrosynthetic analysis shown in scheme 1, led us to consider that a strategy using a Bradsher cycloaddition[3] could lead to a highly convergent stereoselective synthesis of Manzamine A **1**. In previous communications, we have described the synthesis of a model of the ABC tricyclic core of Manzamine A **1**[4] as well as the development of an asymmetric Bradsher cycloaddition[5] using 2,7-naphthyridine as starting material. However, the final radical cyclisation forming the five membered ring gave rise to a 1:1 mixture of *cis* and *trans* isomers at the AB ring junction.



Scheme 1

To overcome this lack of stereoselectivity, we decided to use an other tactic in which the thirteen membered ring E would be formed in **2** before the five membered ring C in order to hinder the β-face of the molecule and to increase the stereoselectivity of the C ring closure. The naphthyridinium salt **4** bearing two appendages for future five and eight membered rings cyclisations was selected as starting material.

Preparation of naphthyridinium salt **4** by direct alkylation despite several examples[6] in the literature proved to be frustrating. 2-Chloro and 2-iodo-1,3-propanediol or their protected counterpart

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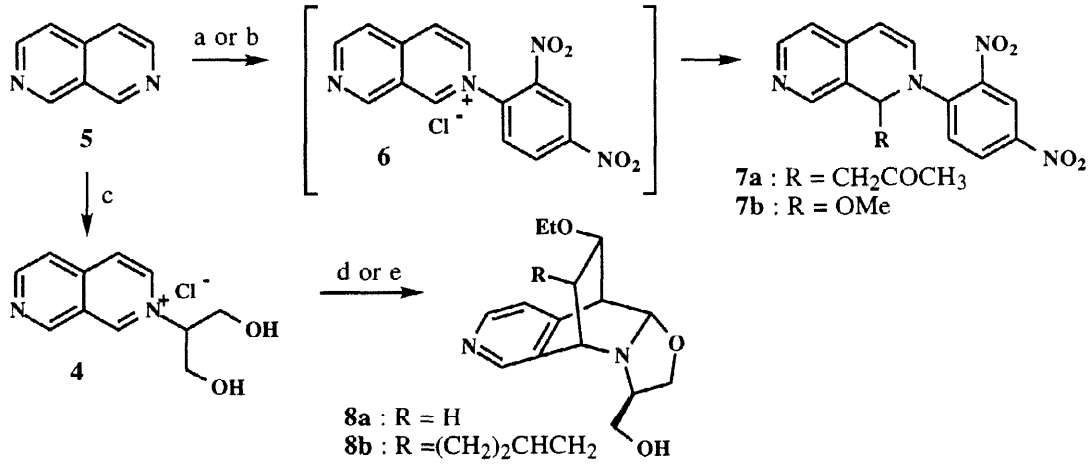
(dioxane or diacetate) were unreactive in the presence of 2,7-naphthyridine **5** under a number of conditions including high pressure (CH_2Cl_2, 15 kbar, 65°C, 7d). The Zincke reaction[7], which is in fact an addition-tautomerism-elimination sequence of reactions, allowed to circumvent this problem. Thus 2,7-naphthyridine **5** was treated with 1-chloro-2,4-dinitrobenzene to prepare the Zincke salt **6**. However, classical preparation of salt **6** gave rise in low yields to side products **7a** or **7b** resulting respectively from solvents (acetone or methanol) nucleophilic attack on naphthyridinium salt **6**[8] (scheme 2).

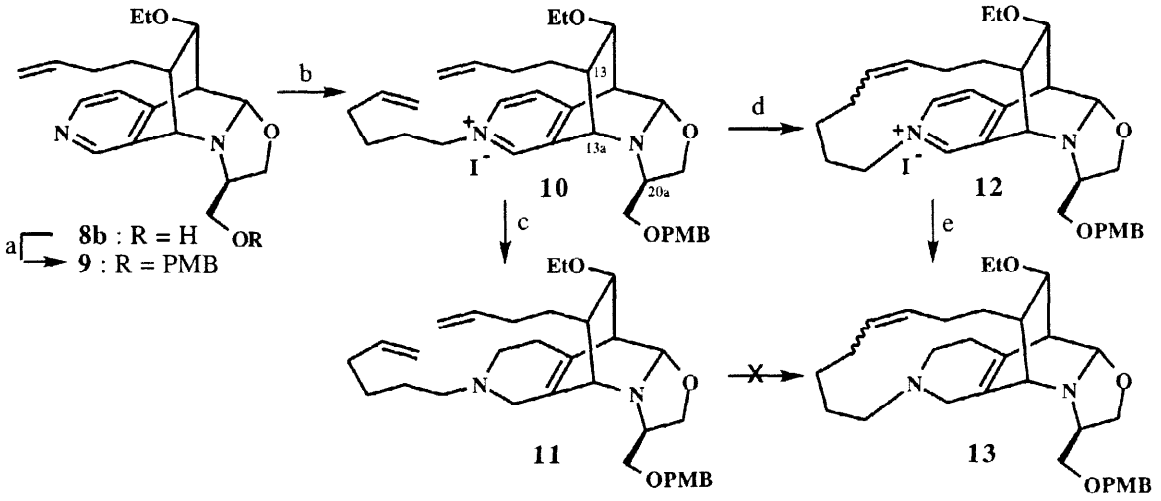
Following these observations, we took advantage of the high reactivity of naphthyridinium salt **6**. Thus, naphthyridine **5** was refluxed in butanol in the presence of both 1-chloro-2,4-dinitrobenzene, as electrophile and 2-amino-1,3-propanediol, as nucleophile to afford naphthyridinium salt intermediate **4**. This compound was directly subjected to a Bradsher cycloaddition in water with ethylvivnylether as dienophile and afforded adduct **8a** in 20% overall yield from **5**. Higher yield (33%) was observed when the whole sequence was conducted in water[9]. In the presence of (*Z*)-1-ethoxy-1,5-hexadiene **9**[10], best results were obtained when the Zincke reaction was performed in water as above, and the Bradsher cycloaddition in water/THF 8:2. Under these conditions adduct **8b** was obtained in 25% overall yield from 2,7-naphthyridine **5** (Scheme 2). Tandem Zincke-Bradsher reaction without isolation of salt intermediate **4** was also studied. Under this condition, adduct **8b** was formed in 15% overall yield. Relative configurations of the six asymmetric centers in adduct **8b** was deduced from nOe experiments and confirmed by an X-ray analysis[11].



Scheme 2 : a) 1-chloro-2,4-dinitrobenzene, 2eq., acetone, rfx, 3h, **7a** (10%). b) 1-chloro-2,4-dinitrobenzene, 2eq., CH_2Cl_2, chromatography SiO_2, CH_2Cl_2/MeOH 95:5, **7b** (25%). c) 1-chloro-2,4-dinitrobenzène, 2eq., 2-amino-1,3-propanediol, 2eq., H_2O, rfx, 16h. d) $EtOCHCH_2$, 10eq., $CaCO_3$, 2eq., H_2O, 20°C, 3h, **8a** (33% from **5**). e) (*Z*)-$EtOCHCH(CH_2)_2CHCH_2$, 10eq. (see ref 10), $CaCO_3$, 2eq., H_2O/THF 8:2, 20°C, 3d, **8b** (25% from **5**).

With compound **8b** in hand, we next examined the possibility of thirteen membered ring elaboration.The primary alcohol was first protected as *p*-methoxybenzylether **9**. Alkylation of **9** with 6-iodo-1-hexene afforded nearly quantitatively pyridinium salt **10** (Scheme 3). This particular chemoselectivity is due to the presence of the *p*-methoxybenzyl group which protect oxazolidine nitrogen from electrophilic attack.[12] This selective alkylation both avoids oxazoline ring opening and subsequent secondary nitrogen protection and allows to take advantage of the template effect due to the presence of a [2,2,2] bicyclic framework. The presence of this additional bridge should favor the anticipated metathesis with the requisite orientation of side chain at C13. Pyridinium salt **10** was in turn reduced under classical conditions to tetrahydropyridine **11**. As previously observed[4], poor yield and reproductibility were obtained for this step

(30-50%). Moreover, tetrahydropyridine **11** proved to be unreactive in the presence of Grubbs catalyst[13]. It is already known that this catalyst is highly sensitive to polar groups and especially to amino groups[14]. For this reason the thirteen membred ring of Manzamine A has already been prepared by Pandit[2j] using a bis lactam as precursor. All these considerations led us to test metathesis cyclisation on pyridinium salt **10**. After 2 days at 60°C in benzene in the presence of Grubbs catalyst (10% molar equiv.), a new product corresponding to the pentacyclic pyridinium salt **12** was obtained in nearly quantitative yield. Careful 400MHz ^{1}H NMR double irradiations showed that this compound was constituted by a 7:3 unseparable mixture of *Z* and *E* isomers[15]. Sodium borohydride reduction of pyridinium salts **12** afforded in 80% yield the anticipated terahydropyridine derivatives **13**. This compound which contains the appendages for further five and eight membered rings elaboration was obtained in 18% overall yield from 2,7-naphthyridine **5**.



Scheme 3 : a) NaH, 4eq., PMBCl, 3eq., THF/DMF 8:2, 20°C, 6h, **9** (90%). b) $I(CH_2)_4CHCH_2$, 1,1eq., MeCN, rfx, 6h, **10** (>95%). c) $NaBH_4$, 1eq., MeOH/THF 6:4, 0°C, 1h, **11** (50%). d) $Cl_2(PCy_3)_3RuCHCHCPh_2$, 0,1eq., C_6H_6, 60°C, 2d, **12** (>95%). e) $NaBH_4$, 2eq., MeOH/THF 1:1, 0°C, 1h, **13** (80%).

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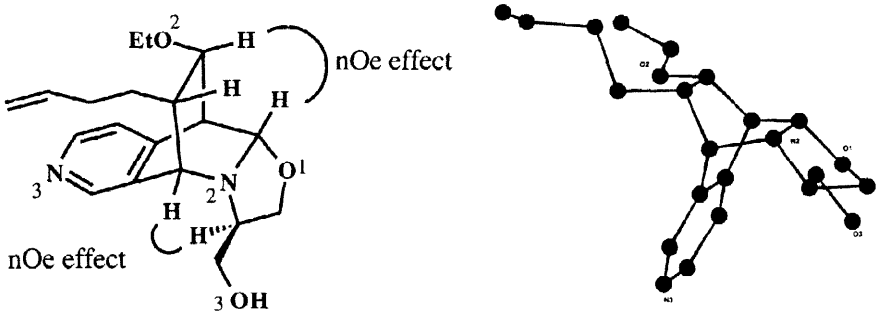
8) Compounds **7a** and **7b** were obtained in low yields with unidentified secondary compounds. These side reactions which are due to the particular reactivity of 2,7-naphthyridinium salts were not observed with isoquinoleinium salt.

9) For a recent review concerning the water promoted organic reactions, see: Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis*, **1994**, 741-760.

10) 1-ethoxy-1,5-hexadiene was prepared by alkylation of allylethylether with allyl bromide (*sec*-BuLi, THF/HMPA, -78°C), according to : Clark-Still, W.; MacDonald, T.L. *J. Org. Chem.* **1976**, *41*, 3620-3622. This reaction afforded a mixture of two regioisomers : the title compound and 3-ethoxy-1,5-hexadiene (7:3). This latter compound bearing no enol ether was unreactive in the Bradsher cycloaddition. For this reason, the crude mixture of isomers was used in the cycloaddition whithout further purification. Accordingly, **5** (3.84 mmol), 2-amino-1,3-propanediol (7.69 mmol) and 1-chloro-2,4-dinitrobenzene (7.69 mmol) in water (5mL) was refluxed for 16 hours under vigourous stirring. After extraction with CH_2Cl_2, the aqueous layer was concentrated under vacuum. The resulting crude salt **4** in solution in a mixture of water/THF 8:2 (5mL) was stirred vigourously for 3 days in the presence of a mixture of 1-ethoxy-1,5-hexadiene (mixture with isomeric compound, 38.4 mmol), and $CaCO_3$ (7.69 mmol). After dilution with water, extraction with $CHCl_3$ and usual work up, the crude residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5) affording pure **8b** (0.28g, 25% from **5**).

11)



Crystallographic data for **8b** : $C_{19}H_{29}N_2O_3$, crystal size 0.1×0.1×0.5 mm, monoclinic, space group P 21/c, a = 15.338 Å, b = 7.083 Å, c = 18.443 Å, V = 1829 Å^3, Z = 4, D_{cal} = 1.10 mg.m^3, R = 10.357, ϖR = 10.857, for 650 observed reflections. Intensity data were collected on a ENRAF-NONIUS CAD-4 diffractometer.

12) In contrast to our previous study (ref. 4), compound **9** was also unreactive in the presence of BrCN.

13) a) For a review concerning carbon-carbon coupling by metathesis see: a) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2037-2056. b) Schmalz, H.-G. *Angew. Chem. Int. Ed.* **1995**, *34*, 1833-1836. c) For previous uses of metathesis in Manzamine A synthetic approaches, see references 2j and 2k.

14) For molybdenum catalyst efficient for nitrogen ring closure, see: Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324-7325.

15) ^{1}H NMR of **12** ($CDCl_3$, 400MHz) is charaterized by the presence of two broad multiplets at 5.46 and 5.32 ppm. The latter signal after decoupling experiment is transformed in a broad singlet. ^{13}C NMR is charaterized by the presence of four signals at 128.4, 128.1, 126.0 and 125.4.