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New developments in asymmetric Bradsher cycloadditions: use of chiral dienes

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Abstract

Several serinol derivatives have been prepared and condensed following the Zincke reaction with 2,7-naphthyridine. The resulting naphthyridinium salts were engaged in Bradsher cycloadditions with enol ethers and afforded tetracyclic adducts, potential synthetic precursors of manzamine A alkaloid.

Keywords: cycloaddition; alkaloid.

During the course of preliminary studies toward the total synthesis of cytotoxic alkaloid Manzamine A **1**,[1] we demonstrated[2,3] the synthetic utility of a Bradsher cycloaddition[4] strategy. An extension of this reaction to its asymmetric counter part has also been developed using chiral *Z*-enol ether as chiral dienophiles.[5,6] In the present communication, we describe our results in an alternative asymmetric Bradsher cycloaddition using chiral 2,7-naphthyridinium salts as chiral dienes.

These salts can be obtained by using the Zincke reaction, the way of choice for the preparation of pyridinium salts having a chiral carbon directly linked to nitrogen of a pyridine ring.[7] This reaction has also been used in our previous work for the preparation of achiral functionalised 2,7-naphthyridinium salt **3** obtained by condensation of serinol with 2,7-naphthyridine **2**. This salt **3**, after Bradsher cycloaddition, followed by olefin metathesis, led, respectively, to compounds **4** and **5**, intermediates in a synthetic approach of racemic manzamine A **1** (Scheme 1).[4] It was anticipated that the application of the Zincke reaction to chiral serinol derivatives as nucleophiles should give rise to chiral 2,7-naphthyridinium salts, which could be used in turn in asymmetric Bradsher cycloadditions.

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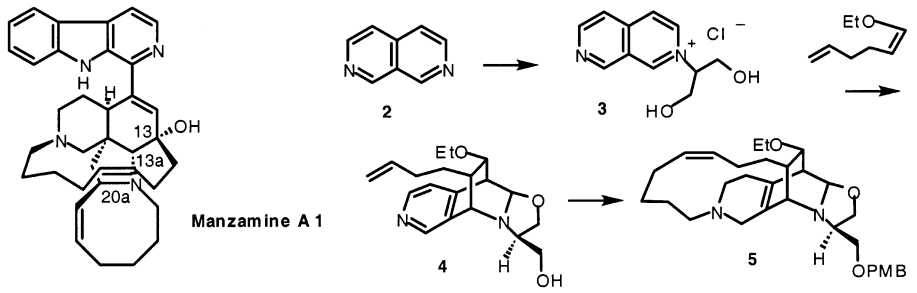
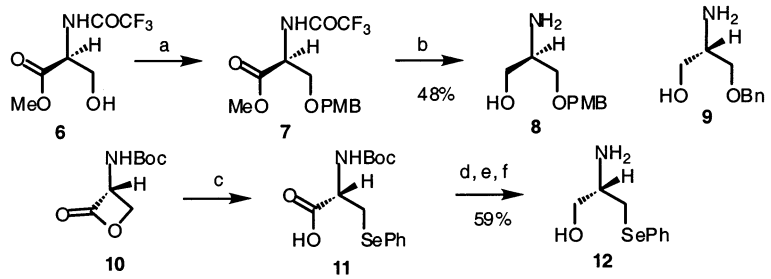


Scheme 1.

(*R*)-4-Methoxybenzyl serinol **8** was obtained in two steps after trichloroacetimidate alkylation, followed by $LiBH_4$ reduction of the acid functional group, in 48% overall yield, from the known methyl *N*-trifluoromethyl serinate **6**.[8] (*S*)-Benzyl serinol **9** was prepared in five steps from (*S*)-serine[9] following a described procedure (Scheme 2).[10]

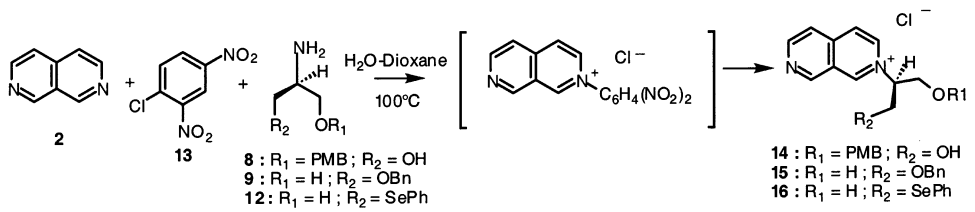


Scheme 2. (a) $Cl_3C(NH)OPMB$, TfOH (cat.), ether. (b) $LiBH_4$, EtOH/THF 1:1. (c) $(PhSe)_2$, Na, THF, HMPA. (d) CH_2N_2, Et_2O. (e) $LiAlH_4$, THF. (f) TFA, CH_2Cl_2.

In order to introduce at an early stage of the synthesis a selenoether functional group which could be used for a radical five-membered ring formation,[2] (*S*)-2-amino 3-phenylselanyl-propan-1-ol **12** was also prepared. Accordingly, β-lactone **10** was obtained following the Vederas synthesis[11] and subjected to a nucleophilic ring opening affording seleno amino acid **11**.[12] Amino acid **11** was then esterified with diazomethane and the resulting ester, after reduction with $LiAlH_4$ and cleavage of the *tert*-butyloxycarbonyl group in acidic medium, gave rise to the anticipated seleno ether derivative **12** in 59% overall yield (Scheme 2).

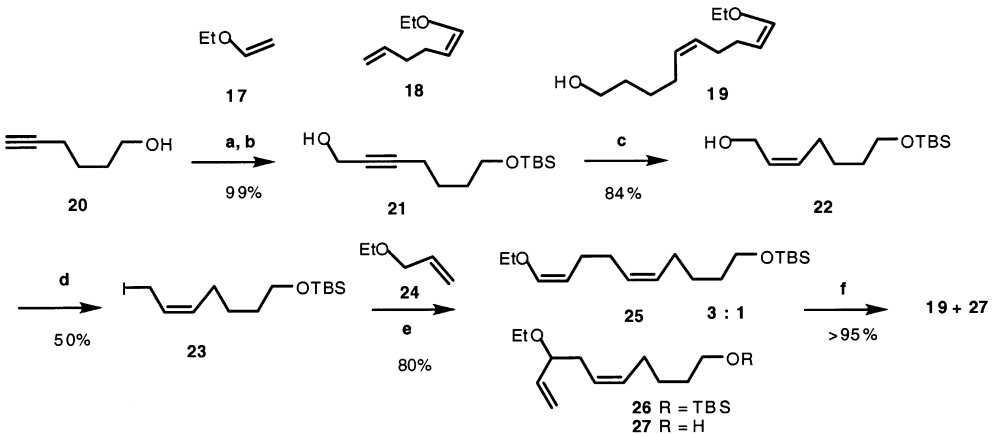
With serinol derivatives **8**, **9** and **12** in hand the study of the Zincke–Bradsher sequence of reactions was next addressed. Naphthyridinium salts **14**, **15** and **16** were prepared in a one-step procedure. Accordingly, naphthyridine **2**, 4-chloro 1,3-dinitrobenzene **13** and serinol derivatives **8**, **9** or **12** were heated at 100°C for 16 hours in a 4:1 mixture of water and dioxane affording, respectively, naphthyridinium salt intermediates **14**, **15** and **16** (Scheme 3). These salts which cannot be purified easily[13] and are always contaminated by serinol derivatives are used directly in the following Bradsher cycloaddition.

Three enol ethers were used as dienophiles in cycloadditions, ethylvinyl ether **17**, (1*Z*)-1-ethoxy hexa-1,5-diene **18**[3] and (9*Z*)-10-ethoxy-deca-5,9-dien-1-ol **19**. Enol ethers **18** and **19** were selected for further 13-membered ring elaboration either by metathesis[3] or by direct intramolec-



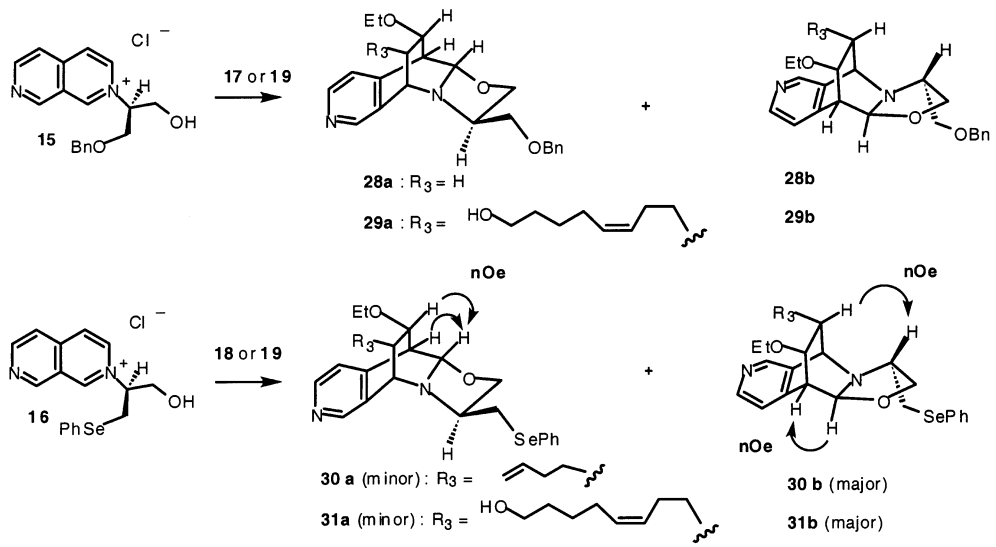
Scheme 3.

ular *N*-alkylation. Enol ether **19** was prepared in a six-step sequence as described in Scheme 4. Commercially available hex-5-yne-1-ol **20** was alkylated, after protection of the hydroxy group, with formaldehyde affording compound **21**. Lindlar selective reduction of the triple bond gave rise to the *Z* alcohol derivative **22**. Garegg type substitution afforded in moderate yield the corresponding iodide derivative **23**. Alkylation of **23** with the anion resulting from deprotonation of 3-ethoxy propene **24** was performed under transmetallation reaction conditions which generally increases both yield and γ-selectivity.[14] However a 1:3 mixture of α and γ regioisomers **25** and **26** was obtained in 80% yield. Deprotection gave rise to enol ether **19** and to its regioisomer **27**. This mixture of isomers was not purified at this stage, as far as enol ether **19** is the only product which is able to react as dienophile in the following Bradsher cycloaddition (Scheme 4).



Scheme 4. TBSCl, imid., DMF. (b) MeLi, CH_2O, THF. (c) Lindlar, quinoline, H_2. (d) PPh_3, I_2, imid, THF. (e) *sec*BuLi, $BaOTf_2$, THF, −78°C. (f) TBAF, THF.

The results of the Bradsher cycloadditions between naphthyridinium salts **14**, **15** and **16** and enol ethers **17**, **18** and **19** are summarised in Scheme 5 and in Table 1. Surprisingly, cycloaddition between naphthyridinium salts **14** and dienophile **18** (entry 1) afforded in low yield[15] an adduct which proved to be identical to racemic **4**. The possible mechanism of this racemisation will be discussed below. With naphthyridinium salt **15** (entries 2 and 3) yields were in the same range and the same lack of selectivity was observed, but two couples of isomeric adducts **28a**–**28b** and **29a**–**29b** were isolated.



Scheme 5.

Table 1

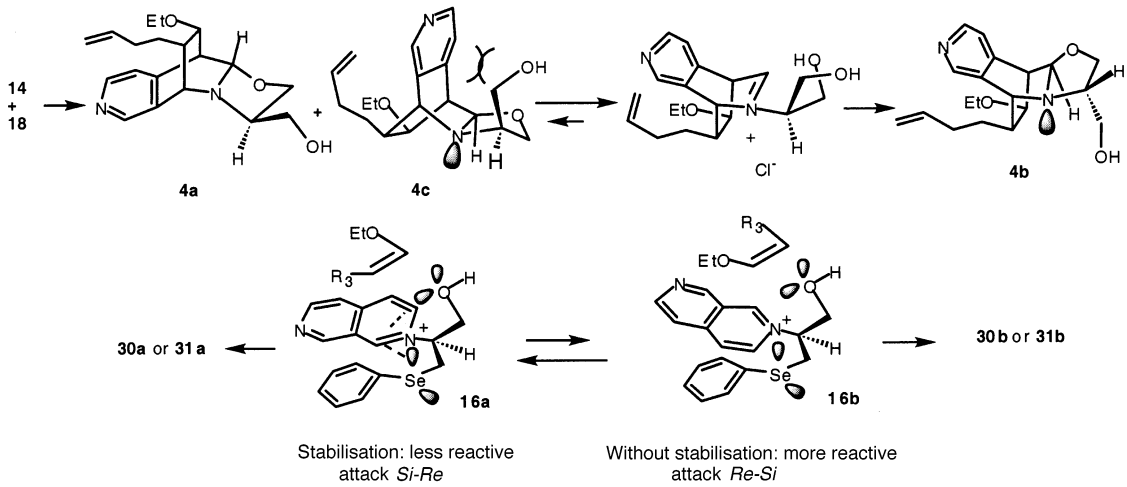
Entry	Diene	Dienophile	Solvants	Time	Adducts	Yield (%)	de (%)
1	**14**	**18**	*t*BuOH:H_2O = 2:1	3 days	(±)-**4**	15	0
2	**15**	**17**	H_2O	3 h 30	**28a** + **28b**	10	0
3	**15**	**19**	Dioxane:H_2O = 2:1	3 days	**29a** + **29b**	18	0
4	**16**	**18**	CH_2Cl_2:H_2O = 2:1 + SDS	6 h	**30a** + **30b**	21	70
5	**16**	**18**	THF:H_2O = 2:1	4 days	**31a** + **31b**	16	–
6	**16**	**19**	THF:H_2O = 2:1	3 days	**31a** + **31b**	46	72
7	**16**	**19**	CH_2Cl_2:H_2O = 2:1 + SDS	1 day	**31a** + **31b**	47	75
8	**16**	**19**	Dioxane:H_2O = 2:1	3 days	**31a** + **31b**	60	80

More interesting results were observed with naphthyridinium salt **16** (entries 4–8). The influence of the mixture of solvents is worthy of note. Rate acceleration was observed in a biphasic medium (CH_2Cl_2:H_2O) in the presence of SDS (entries 4 and 7), but better yield and selectivity were obtained in dioxane:H_2O with compound **19** as dienophile (entry 8). Enol ether **19** which presents an amphiphilic character[16] appeared to be the best dienophile during this study.

The structures of the adducts were established by chemical correlation[17] with the known adduct **4**[3] and by ^{1}H NMR NOE experiments, as indicated in Scheme 5.

The possible mechanism of racemisation leading to racemic compound **4** (entry 1) could be explained by two *Si–Re* and *Re–Si* cycloadditions between **14** and **18**, followed by a nucleophilic attack of the oxygen protected with PMB group with participation of the aromatic moiety on the iminium intermediate.[18] Hydrolysis of the new intermediate should give rise to two isomeric adducts **4a** and **4c**. Adduct **4c** would be disfavored by steric hindrance and ring opening of the

oxazolidine moiety could give rise to a more stable **4b** enantiomer of **4a** (Scheme 5).[19] With naphthyridinium salt **15**, oxygen is less nucleophile and the iminium intermediate is trapped by the free alcohol giving rise to the observed mixture of isomers **28a**–**28b** or **29a**–**29b**. The selectivity observed with naphthyridinium salt **16** (entries 4–8) could be the result of a stabilisation of the iminium in this salt by selenium and oxygen lone pairs of electrons in the conformation **16a** which should be less reactive. Conformational equilibrium could give rise to the more reactive conformation **16b** in which cycloaddition is favored leading to the major observed diastereoisomers **30b** or **31b** (Scheme 6).



Scheme 6.

The encouraging result obtained in Bradsher cycloaddition with nahthyridinium salt **16** and enol ether **19** allowed the control of the future asymmetric carbons 13 and 13a in manzamine A **1** by using the antipodal (*R*)-serine as starting material. However, in this case, the third asymmetric centre on carbon 20a should be reversed during a further stage of the synthesis.

Acknowledgements

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13. Purification by chromatography on silica gel induced a nucleophilic attack of the hydroxy group on C1 affording an unstable dihydronaphthyridine intermediate.
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15. Yields were calculated from 2,7-naphthyridine **2** for two steps: Zincke reaction and Bradsher cycloaddition.
16. Compound **25** in which the primary alcohol is silylated gave significantly lower yield in these cycloadditions.
17. Racemic **28a** was obtained by benzylation of the known corresponding adduct resulting from a cycloaddition between compounds **3** and **17**. Racemic adduct **4** was correlated in two steps with adduct **30a** (mesylation, nucleophilic displacement of the mesylate intermediate with $PhSe^-$).
18. Racemisation during salt **14** formation seems unlikely, see for other examples Ref. 7.
19. In the previous case[3] of naphthyridinium salt **3**, adduct **4** is the only product of the reaction. The same steric hindrance probably induced the nucleophilic attack of only the pro *R** primary alcohol on the iminium intermediate.