Application of a Double Mannich Reaction Using *Bis*(aminol) Ethers in the Synthesis of AE Ring Analogues of Methyl Lycaconitine

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Abstract: An efficient method for the construction of azabicyclo[3.3.1]nonanes and azabicyclo[3.2.1]octanes is reported via double Mannich reaction of cyclic ketoesters with *bis*(aminol) ethers. This method is applied to the synthesis of AE ring analogues of methyl lycaconitine.

Key words: Mannich reaction, aminoalkylation, *bis*(aminol) ethers, methyl lycaconitine, alkaloids

The Mannich reaction provides a versatile method for the preparation of β-aminoketones, esters, and alcohols which are key synthetic intermediates for the construction of nitrogen containing natural products.[1] The inter- and intramolecular version of the Mannich reaction provides a powerful method for the preparation of azacyclic products from acyclic precursors and has formed the crucial step in a number of syntheses of alkaloids.[2]

Our work[3] in this area has focused on the synthesis of analogues of the alkaloid methyl lycaconitine (MLA, **1**)[4] using a double Mannich reaction to form the azabicyclo[3.3.1]nonane AE ring system (Figure 1). The main disadvantage of our approach, also experienced by others,[5] was the low yield of the azabicyclo[3.3.1]nonane obtained using the classical Mannich reaction involving heating ethyl 2-oxocyclohexanecarboxylate with aqueous ethylamine and aqueous formaldehyde.

Prompted by the report by Heaney and Papageorgiou[6] on the use of *bis*(aminol) ethers derived from primary amines as *bis*-aminoalkylating agents for use in the synthesis of tertiary amines, we herein describe the *bis*-aminoalkylation of cyclic β-ketoesters using *bis*(aminol) ethers as an efficient entry to azabicyclo[3.3.1]nonanes and azabicyclo[3.2.1]octanes.

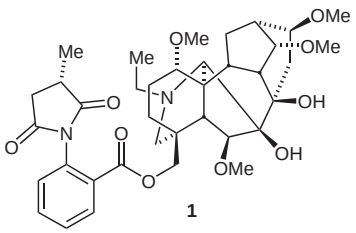

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Figure 1 Methyl lycaconitine (MLA, **1**).

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A general method for the preparation of *bis*(aminol) ethers consists of the reaction of one equivalent of amine with two equivalents of paraformaldehyde and one equivalent of potassium carbonate in the presence of excess alcohol, followed by vacuum distillation.[7] Previous studies by Heaney[6] on Mannich reactions of *bis*(aminol) ethers with aromatic nucleophiles provided a number of acidic reagents suitable for activation, including acetyl chloride, trifluoroacetic anhydride, sulfur dioxide and titanium tetrachloride. In these cases both secondary and tertiary amines were isolated as products. Higher yields of secondary amines were obtained using hydrogen chloride in diethyl ether, whereas chlorosilane derivatives promoted the formation of tertiary amines.

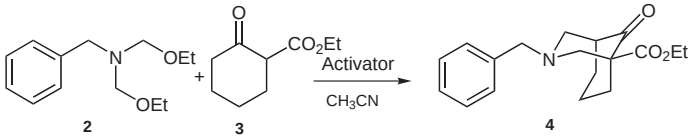
In order to establish a procedure for the double Mannich reaction of *bis*(aminol) ethers with cyclic β-ketoesters to afford bicyclic tertiary amines, the reaction of *N*,*N*-*bis*(ethoxymethyl)benzylamine (**2**)[6] with ethyl 2-oxocyclohexanecarboxylate (**3**) using several different Lewis acids as activators was investigated (Table 1). No reaction was observed using trimethylsilyl derivatives as promotors, and only poor yields of the azabicyclic product were obtained with scandium triflate, aluminium trichloride and titanium tetrachloride as activators. Superior results were achieved using methyltrichlorosilane as the activating reagent. The azabicyclic adduct **4** was isolated in 75% yield by treatment of **3** with two equivalents of *bis*(aminol) ether **2** and two equivalents of methyltrichlorosilane in acetonitrile.

A variety of N-substituted 3-azabicyclo[3.3.1]nonane derivatives was then prepared by adopting these optimized conditions.[8] The use of *bis*(aminol) ethers **5**–**11** afforded the corresponding azabicyclic products **12** to **18** in good yields (75–99%) after purification by flash chromatography (Table 2).

The double Mannich reaction was also applied to the synthesis of smaller N-substituted 3-azabicyclo-[3.2.1.]octane derivatives (Table 3). In this case, the bicyclic products **20**–**27** were isolated in an average yield of 80–90%.

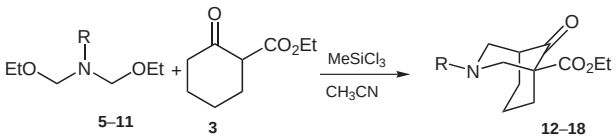
The formation of azabicyclic ring systems containing two quaternary centers at the points of ring fusion was also investigated. The allyl substituted cyclohexanone and cyclopentanone derivatives **28**[10,11] and **29**[10,12] were converted into the corresponding bicyclic amines in good yield (Table 4). In the case of the cyclohexanone pre-

Table 1 Optimization of the Double Mannich Reaction



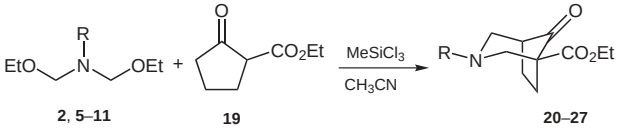
Entry	Activator	Equiv of Activator	Equiv of **2**	Yield of **4** (%)
1	Me_3SiCl	1.1	1.1	–
2	Me_3SiOTf	1.1	1.1	–
3	$Sc(OTf)_3$	0.1	1.1	7
4	$AlCl_3$	1.1	1.1	19
5	$TiCl_4$	0.25	1.1	22
6	$MeSiCl_3$	1.0	1.1	66
7	$MeSiCl_3$	2.0	1.1	64
8	$MeSiCl_3$	2.0	2.0	75
9	$MeSiCl_3$	4.0	4.0	53

Table 2 Application of the Double Mannich Reaction to the Synthesis of 3-Azabicyclo[3.3.1]nonane Derivatives



Entry	*Bis*(aminol) ether	R	Product	Yield (%)
1	**5**[6]	Ethyl	**12**[5]	92
2	**6**[6]	*i*-Propyl	**13**	75
3	**7**[6]	*n*-Butyl	**14**	>99
4	**8**	*tert*-Butyl	**15**	>99
5	**9**	Cyclohexyl	**16**	92
6	**10**[9]	2-Phenylethyl	**17**	>99
7	**11**	3-Phenylpropyl	**18**	>99

Table 3 Application of the Double Mannich Reaction to the Synthesis of 3-Azabicyclo[3.2.1]octane Derivatives



Entry	*Bis*(aminol) ether	R	Product	Yield (%)
1	**5**	Ethyl	**20**	56
2	**6**	*i*-Propyl	**21**	81
3	**7**	*n*-Butyl	**22**	97
4	**8**	*tert*-Butyl	**23**	89
5	**9**	Cyclohexyl	**24**	83
6	**2**	Benzyl	**25**	83
7	**10**	2-Phenylethyl	**26**	81
8	**11**	3-Phenylpropyl	**27**	84

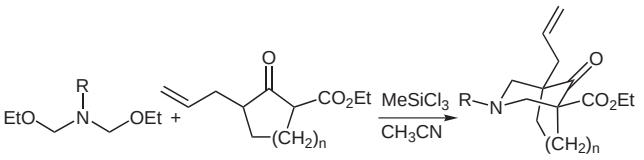
cursor, the allyl derivative **28** gave ca. 20% lower yields of the bicyclic products **30** and **31** than the unsubstituted analogues **4** and **18**. In contrast, the yield of the allylated bicyclic product **32** derived from cyclopentanone precursor **29** was increased by ca. 20% compared to **20**.

The double Mannich reaction described above was then applied to the synthesis of AE ring analogues of methyl lycaconitine by attaching the N-substituted anthranilate ester pharmacophore to the azabicyclic AE ring system.

Inhibition studies on the nicotine-stimulated catecholamine release by nicotinic antagonists have shown that analogues of methyl lycaconitine, in which the *N*-ethyl group was replaced by a 3-phenylpropyl group, are more efficient than the corresponding *N*-ethyl substituted compounds.[13] Therefore, the *N*-(3-phenylpropyl) substituted bicyclic compound **18** was chosen as a starting material for further elaboration to append the N-substituted anthranilate pharmacophore.

Reduction of **18** with lithium aluminum hydride in THF gave the corresponding diol as a mixture of diastereomers **33a** and **33b**, which could be separated by flash chromatography (Scheme 1). The stereoisomers were formed in an overall yield of 65% in a ratio of **33a**:**33b** = 3.2:1, favoring the diastereomer containing the equatorial hydroxy group. Evidence for this stereochemistry was obtained by

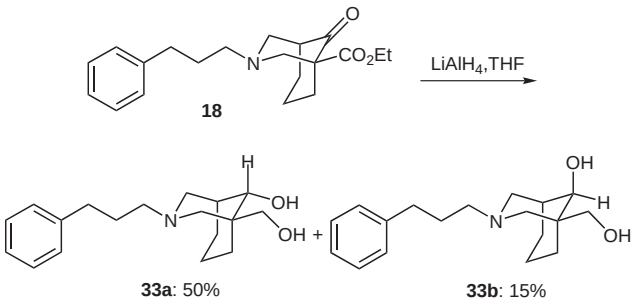
Table 4 Application of the Double Mannich Reaction to the Synthesis of Allyl-Substituted 3-Azabicyclic Compounds



2, **5**–**11** **28**: n = 2 **29**: n = 1 **30**–**32**

Entry	Starting material	*Bis*(aminol) ether	R	Product	Yield (%)
1	**28**	**2**	Benzyl	**30** (n = 2)	58
2	**28**	**11**	3-Phenylpropyl	**31** (n = 2)	77
3	**29**	**5**	Ethyl	**32** (n = 1)	75

^{1}H NMR-NOESY experiments showing NOE enhancements between 9-H and 4-H in the case of diastereomer **33a**, whereas NOE enhancements between 9-H and 6-H as well as 8-H were observed for the other diastereomer **33b** (Figure 2).



Scheme 1

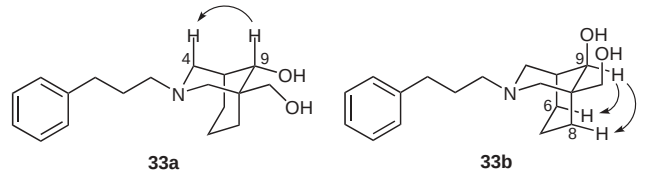
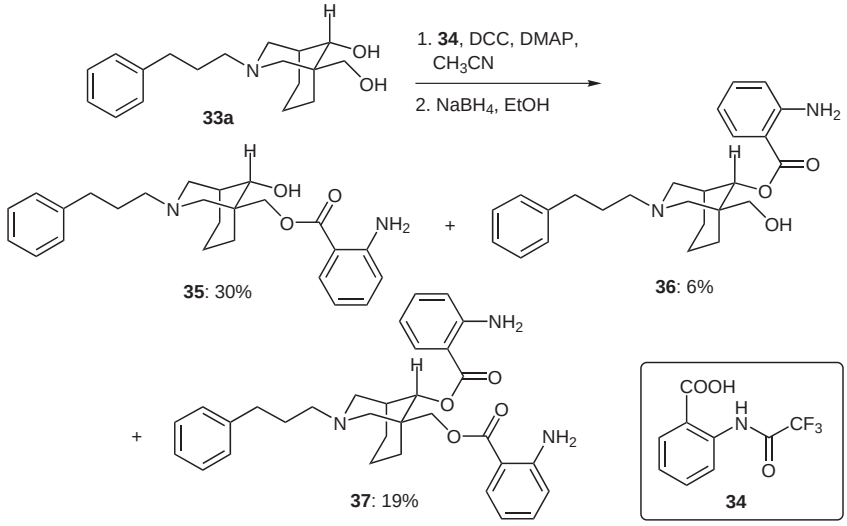


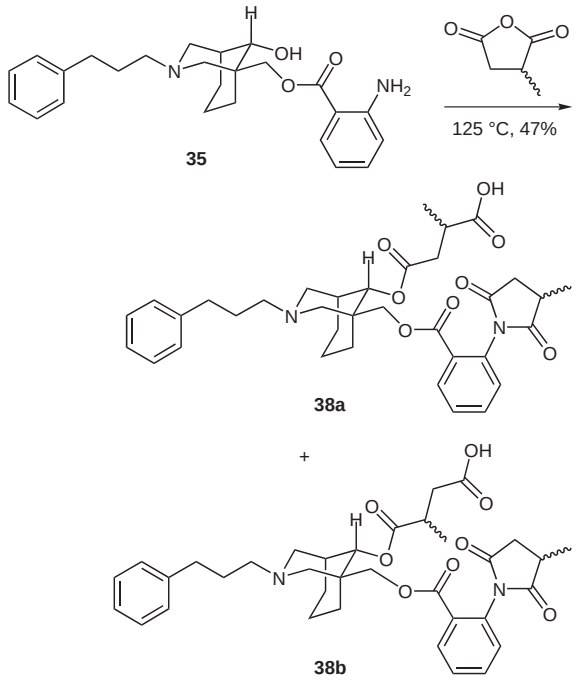
Figure 2 NOE effects observed for the diastereomers **33a** and **33b**. In case of compound **33a**, no interactions were detected between 9-H and 6-H or 8-H, while compound **33b** showed no NOE between 9-H and 4-H.

The ester side chain was then introduced by condensing diol **33a** with one equivalent of *N*-(trifluoroacetyl)anthranilic acid (**34**),[14] followed by reductive cleavage of the N-protecting group.[15] The condensation was carried out under Steglich conditions,[16] with the reaction occurring predominantly at the primary hydroxy function (Scheme 2). After deprotection with sodium borohydride and subsequent flash chromatography, the corresponding ester **35** was isolated in 30% yield (over two steps). However, the regioisomeric ester **36**, derived from the secondary alcohol, also formed as a by-product in 6% yield together with diester **37** in 19% yield.

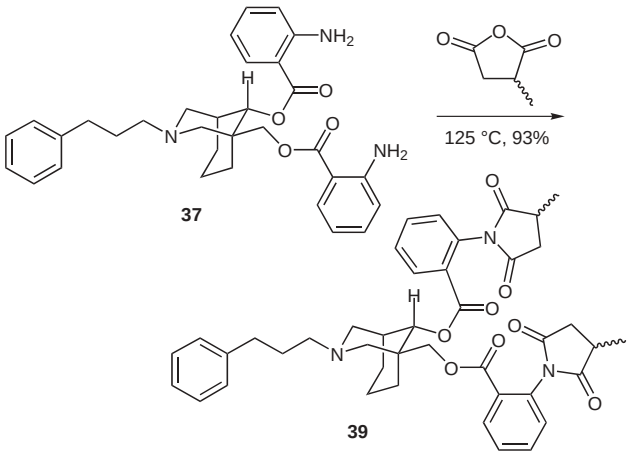
Recent structure-activity studies have established that the methyl group of the succinimido moiety is crucial for the binding affinity of MLA analogues, although a change in the absolute configuration of this methyl group has no significant effect.[17] In the final step, amine **35** was reacted with racemic methylsuccinic anhydride at 125 °C.[18] Under these conditions, the methylsuccinic imide was formed, but excess reagent also reacted with the secondary hydroxy group to produce the corresponding esters **38a** and **38b** (Scheme 3). After purification by flash chromatography, an inseparable mixture of the regioisomers **38a** and **38b** was obtained in 47% yield. The same reaction conditions were applied to the fusion of diester **37**



Scheme 2



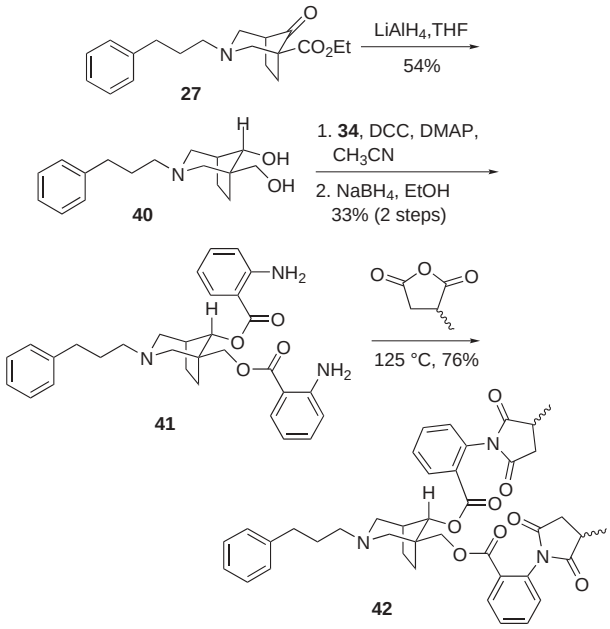
Scheme 3



Scheme 4

with methylsuccinic anhydride, resulting in the formation of MLA analogue **39**. This compound, which contains two pharmacophoric units as well as the azabicyclic MLA core structure, was isolated in 93% yield after flash chromatography (Scheme 4).

The same reaction sequence was performed with 3-azabicyclo[3.2.1]octane derivative **27** as the starting material (Scheme 5). In this case, the reduction with lithium aluminum hydride proceeded diastereoselectively to afford diol **40** as the only product in 54% yield. Compound **40** was then condensed with two equivalents of *N*-(trifluoroacetyl)anthranilic acid **34**, and the diester **41** was isolated in a yield of 33% (over two steps) after reductive N-deprotection. Finally, the diester **41** was converted into the methylsuccinic *bis*imide **42** in 76% yield.



Scheme 5

In conclusion, the double Mannich reaction using preformed *bis*(aminol) ethers provides a powerful tool for the synthesis of azabicyclic N-substituted ring systems in high yields. The use of mild reaction conditions involving activation of the *bis*(aminol) ethers with methyltrichlorosilane at room temperature affords significantly improved yields compared to conventional aminomethylation protocols involving heating a primary amine with formaldehyde. By applying this new methodology, the AE ring analogues **39** and **42** of methyl lycaconitine have been synthesized. They are currently undergoing evaluation as α7 selective nicotinic acetylcholine receptor antagonists.

Acknowledgment

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(8) **General Procedure for the Preparation of the Azabicyclic Compounds 4, 12–18, 20–27, and 30–32 by Double Mannich Reaction:** To a mixture of β-ketoester (100 mg, 1 equiv) and *N,N-bis*(ethoxymethyl)amine (2 equiv) in MeCN (2 mL) was added $MeSiCl_3$ (2 equiv). The reaction mixture was stirred for 20 h at r.t., then quenched with aq $NaHCO_3$ (20 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc–hexane). All products were characterized by ^1H NMR and ^{13}C NMR spectroscopy and mass spectrometry.
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