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Application of olefin metathesis to the synthesis of ABE ring analogues of methyllycaconitine

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Abstract—The synthesis of four novel ABE ring analogues of methyllycaconitine (MLA) is reported, employing olefin metathesis as the key step for appending the seven-membered B ring onto an AE bicyclic ring system. This strategy allows the stereodivergent synthesis of ABE ring analogues in which the stereochemistry of the AB ring junction is well defined. The compounds are designed as ligands to study binding and function of the α7-nAChR.

Nicotinic acetylcholine receptor (nAChR) chemistry and biology is currently of enormous interest in the field of drug development.[1] The nAChRs are a large family of ligand gated ion channels located throughout the body in the central nervous system, peripheral nervous system and at the neuromuscular junction. The family contains numerous receptor subtypes consisting of pentameric arrays made up from a variety of distinct peptide subunits.[2] Due to the great multiplicity of nAChRs there is a pressing need for subtype selective agonists and antagonists to elucidate the biological roles of these receptors and to provide candidates for drug development.

The α7 subtype is amongst the most prevalent nAChR in the brain and has been implicated as playing a key role in conditions such as schizophrenia, Alzheimer's disease and epilepsy.[3] Very few compounds are known that bind with high affinity and selectivity to the α7 nAChR and these include the peptide toxins α-bungarotoxin,[4] α-conotoxin ImI[5] and the norditerpenoid alkaloid methyllycaconitine (MLA, **1**, Fig. 1).[6] MLA is the major toxic component of *Delphinium brownii*[7] and is a potent antagonist of the α7 nAChR in mammalian neuronal membranes. Furthermore, it exhibits very high selectivity for this subtype over other neuronal nAChRs. The combined qualities of high affinity binding, functional potency and subtype selectivity render MLA a prime lead for the development of new therapeutic agents targeting the α7 nAChR.

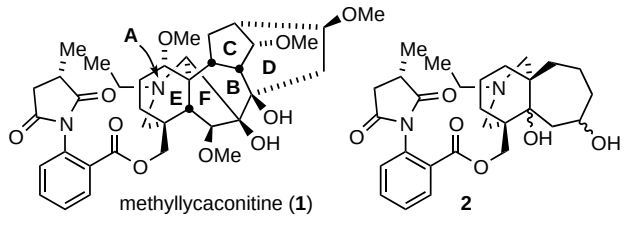

Figure 1. Methyllycaconitine (**1**) and tricyclic analogues **2**.

Structure activity studies on MLA have shown the *N*-substituted anthranilate ester moiety is an essential structural feature for pharmacological activity.[8] It has also been proposed that the tertiary amine and ester side-chain of MLA form an acylated homocholine pharmacophore at physiological pH that gives rise to the high affinity nicotinic acetylcholine receptor binding.

A number of approaches to the synthesis of small molecule analogues of MLA incorporating the putative pharmacophore have been reported, including the synthesis of E,[9] AE[10] and AEF[11] ring systems, some of which display significant biological activity.[9,12] In one of these studies[12a] the binding affinity of two diastereomeric ABE tricyclic analogues of MLA, **2** in competitive ligand binding assays on a rat brain membrane preparation, was reported. One of these diastereomers gave high affinity binding ($IC_{50}=478$ nM) which is amongst the highest reported to date for small molecule analogues of MLA. However, the relative stereochemistry of this diastereomer and hence structural features required for biological activity were not reported.

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We herein disclose the synthesis of four novel tricyclic analogues of MLA containing the key *N*-substituted anthranilate ester in which an additional six-membered ring (B ring) is appended to a 3-azabicyclo[3.3.1]nonane framework (the AE rings). These analogues will further probe structure activity relationships of MLA analogues such as **2** and firmly establish the stereochemical features required for high affinity binding. Our approach to the ABE tricyclic ring system was to apply the double Mannich cyclisation of a β-keto ester to afford the 3-azabicyclo[3.3.1]nonane AE-core ring system. Application of olefin metathesis to construct the seven-membered B-ring would then afford the ABE ring systems.

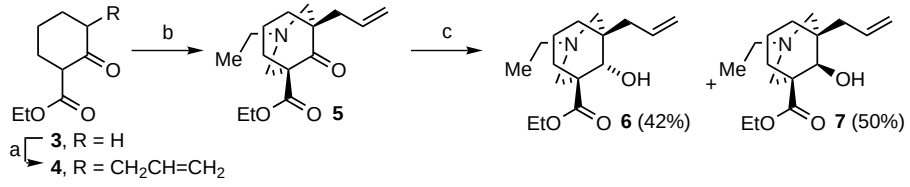
Synthesis of the analogue structures started from ethyl 2-cyclohexanonecarboxylate **3** (Scheme 1). Double deprotonation followed by allylation of the resulting dianion according to the procedure of Weiler[13] afforded the monoalkylated product **4**[14] in 93% yield. Subjecting this compound to the double Mannich cyclisation according to the method of Iwai[15] gave the bicyclo[3.3.1]nonane ring system **5**.[16] Sodium borohydride reduction of the resulting ketone then afforded a 1:1.2 mixture of the secondary alcohols **6** and **7** in 92% combined yield, which could be readily separated by flash column chromatography. Assignment of the relative stereochemistry of **6** and **7** was readily achieved by ^{1}H and ^{13}C NMR techniques.[17,18]

Both diastereomers of the secondary alcohols were independently elaborated to tricyclic ABE-ring systems to afford stereochemically divergent MLA analogues (Scheme 2). Allylation of **6** under standard conditions afforded diene **8** in 72% yield. Subjecting **8** to ring-closing metathesis[19] using Grubbs' catalyst **9**[20] afforded the seven-membered ether **10** in an excellent 90% yield. Reduction of the ester with lithium aluminium hydride smoothly afforded the primary alcohol **11** of known relative stereochemistry.

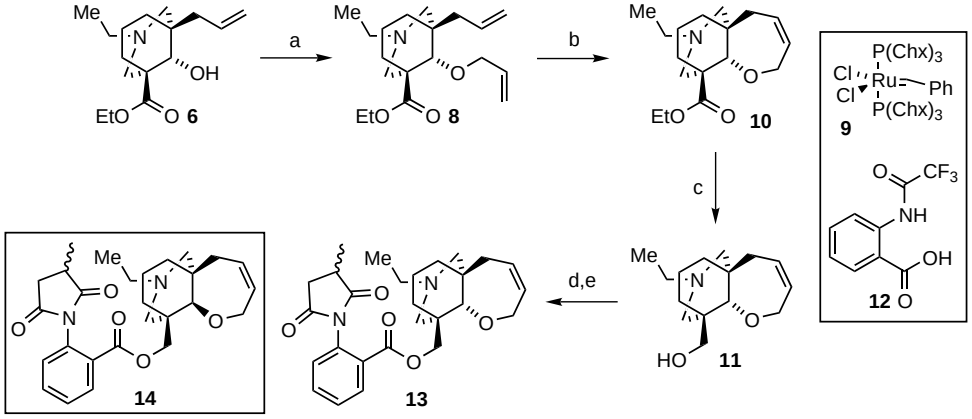
Introduction of the ester side-chain followed our recently developed two-step protocol. Formation of the anthranilate ester was achieved in good yield (62%) using *N*-(trifluoroacetyl)anthranilic acid **12**,[21] followed by fusion with methylsuccinic anhydride[22] to give the analogue **13** containing a seven-membered ether B-ring with the same *trans* AB ring fusion as present in MLA **1**. Application of the above five-step sequence to the diastereomeric secondary alcohol **7** proceeded in 26% overall yield to grant access to the analogue **14** containing *cis* AB ring fusion.

A second series of ABE-analogues containing a carbocyclic B-ring were afforded by a separate sequence starting from butenyl-substituted ketone **15**[23] (Scheme 3). Careful addition of 1.05 equiv. of allyl magnesium bromide to **15** afforded the allylated products **16** and **17** in 80% yield as a 2.2:1 ratio of diastereomers, which were separable by flash chromatography.

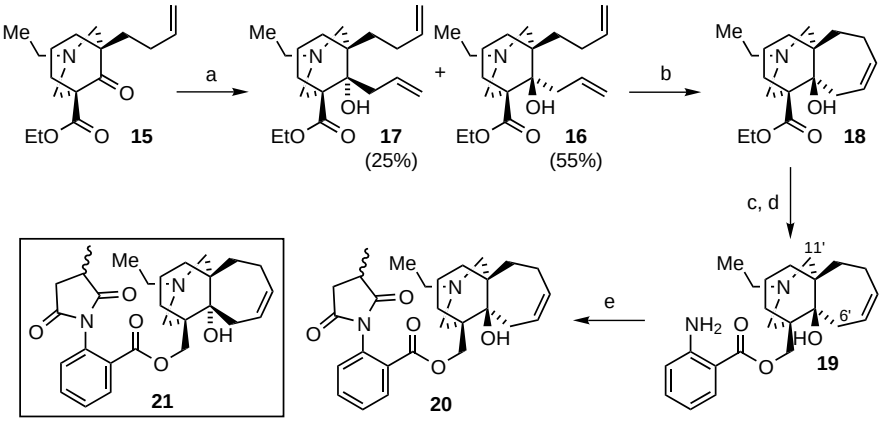
Ring-closing metathesis[19] of **16** afforded an excellent yield of the carbocyclic product **18** that was then reduced with lithium aluminium hydride (69%) to give the primary alcohol and esterified to afford **19** (78%).[21] The NOESY spectrum of ester **19** clearly displayed a strong reciprocal NOE between the C6′ and C11′ protons consistent with the *trans* AB ring junction. Reac-



Scheme 1. *Reagents and conditions*: (a) LDA, allyl bromide, THF, 0°C, 93%; (b) $EtNH_2$, CH_2O, EtOH, reflux, 47%; (c) $NaBH_4$, THF, H_2O, 0°C.



Scheme 2. *Reagents and conditions*: (a) NaH, allyl bromide, THF, rt, 72%; (b) **9**, rt, 90%; (c) $LiAlH_4$, THF, 0°C, 83%; (d) **12**, DCC, DMAP, CH_3CN, 40°C; then $NaBH_4$, EtOH, rt, 62%; (e) methylsuccinic anhydride, 125°C, 59%.



Scheme 3. *Reagents and conditions*: (a) allylmagnesium bromide, THF, 0°C; (b) **9**, rt, 99%; (c) $LiAlH_4$, THF, 0°C, 69%; (d) **12**, DCC, DMAP, CH_3CN, 40°C; then $NaBH_4$, EtOH, rt, 78%; (e) methylsuccinic anhydride, 125°C, 90%.

tion of **19** with methylsuccinic anhydride afforded analogue **20** in 90% yield exhibiting the *trans* AB ring fusion present in MLA **1**. Application of the same four-step synthesis to **17** afforded the diastereomeric tricyclic analogue **21** containing the *cis* AB ring fusion in 44% overall yield.

In summary, the synthesis of four stereochemically divergent ABE tricyclic analogues **13**, **14**, **20** and **21** of MLA has been reported using a double Mannich cyclisation followed by Grubbs' ring-closing metathesis to introduce the seven-membered B-ring. The evaluation of these compounds and intermediates at the α7 nAChR subtype for binding affinity in competitive ligand binding assays and functional potency against recombinant protein expressed in *Xenopus* oocytes is under investigation and will be reported elsewhere.

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