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A Direct Connection of a Tricyclic Analog of Methyllycaconitine with 2-Methylsuccinimidobenzoic Acid

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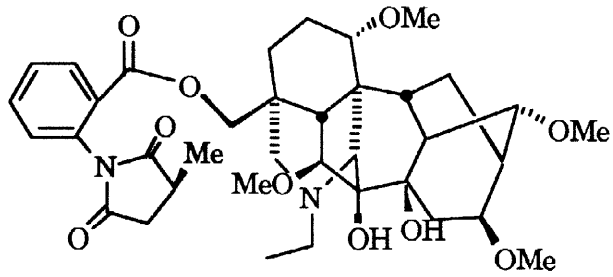
Abstract: An efficient procedure for attaching the methylsuccinimidobenzoate ester unit to an ABE ring segment of methyllycaconitine is described.

Methyllycaconitine (**1**) is an alkaloid which was isolated from *Delphinium brownii* Rydberg in 1938.[1] Recently, Blagbrough and coworkers have defined the absolute stereochemistry of the stereogenic center bearing the methyl group in the aryl ester unit.[2] This novel alkaloid contains a hexacyclic structure with a methylsuccinimido benzoate ester attached to the neopentyl alcohol. Methyllycaconitine has been shown to be a potent inhibitor of α-bungarotoxin binding to housefly heads (K_{inh}=2.5 x 10^{10} M) and is used as a selective probe for neuronal α-bungarotoxin binding sites.[3] Methyllycaconitine inhibited acetylcholine- and anatoxin-



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induced whole-cell currents in cultured fetal rat hippocampal neurons at picomolar concentrations. This antagonism was specific, concentration dependent, reversible, and voltage independent.[4] Furthermore, methyllycaconitine inhibited ^{125}I-α-bungarotoxin binding to adult rat hippocampal membranes, protected against the α-bungarotoxin-induced pseudoirreversible blockade of nicotinic currents, and shifted the concentration-response curve of acetylcholine to the right in fetal rat hippocampal neurons, suggesting a possible competitive mode of action for this toxin.[3] Remarkably low concentrations of methyllycaconitine (1-1000 fM) decreased the frequency of anatoxin-induced single-channel openings, with no detectable decrease in the mean channel open time.[4] Thus, methyllycaconitine, (**1**), appears to be extremely useful for the characterization of the α-bungarotoxin-sensitive subclass of neuronal nicotinic receptors, which has previously eluded functional demonstration.[4]

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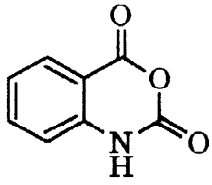
A few synthetic approaches to fragments of the methyllycaconitine skeleton have been reported.[5-7] Recently, a useful two-pot procedure for the appendage of the ortho-methylsuccinimidobenzoate group has been reported by Blagbrough and coworkers.[8] Limited structure-activity data indicates that both the benzoate group and the N-ethyl group are important for biological activity.[9] In order to better understand the remarkable biological activity of this compound, we generated a key subunit of **1** and developed an efficient procedure for the introduction of the benzoate ester. We describe herein a direct connection which should be widely applicable.

The three-step procedure developed by Blagbrough and coworkers was applied to lycoctonine. The first step, acylation with **2**, afforded the amino ester in 21% yield. The remaining two steps, acylation of the aromatic amino group and cyclization to the succinimide, afforded **1** in approximately 10% yield over three steps. Nevertheless, this work constituted the first route for the conversion of lycoctonine into **1**. The same two-pot procedure, when conducted with small molecule analogs, provided the acylated product in overall yields of approximately 35%.



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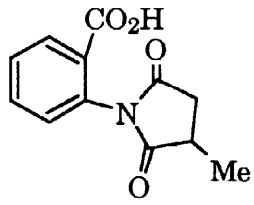

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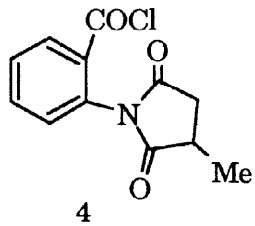

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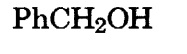
As an alternative, we sought to connect a preformed imide acid directly to the primary alcohol. Imide acid **3** was readily prepared by the procedure of Kumar.[10] The reaction of **3** with benzyl alcohol (**5**) in the presence of dicyclohexylcarbodiimide (DCC) did not afford the desired product.. The imide acid was not recovered in this reaction. The use of the Mitsunobu protocol (DEAD, Ph_3P) also failed to produce the desired benzyl ester. Apparently, one of the imide carbonyl groups was reacting with the activated acid much faster than the desired intermolecular esterification. However, generation of the acid chloride **4** using the sodium salt of acid **3** and oxalyl chloride at 0 °C gave the acid chloride which, without isolation, was reacted with benzyl alcohol and triethylamine to afford the benzyl ester **6** in 95% isolated yield. Similarly, the reaction of acid chloride **4** with cyclohexylethanol **7** produced ester **8** in 97% yield. The reaction of 3-hydroxymethylpyridine (**9**) furnished ester **10** in 93% yield.



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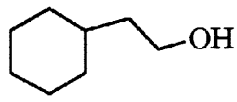

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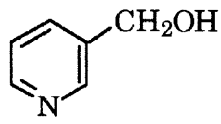

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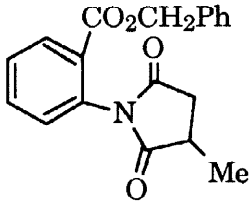

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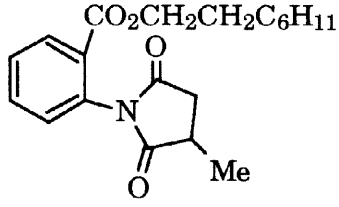

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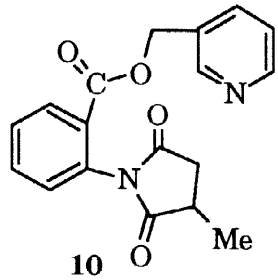

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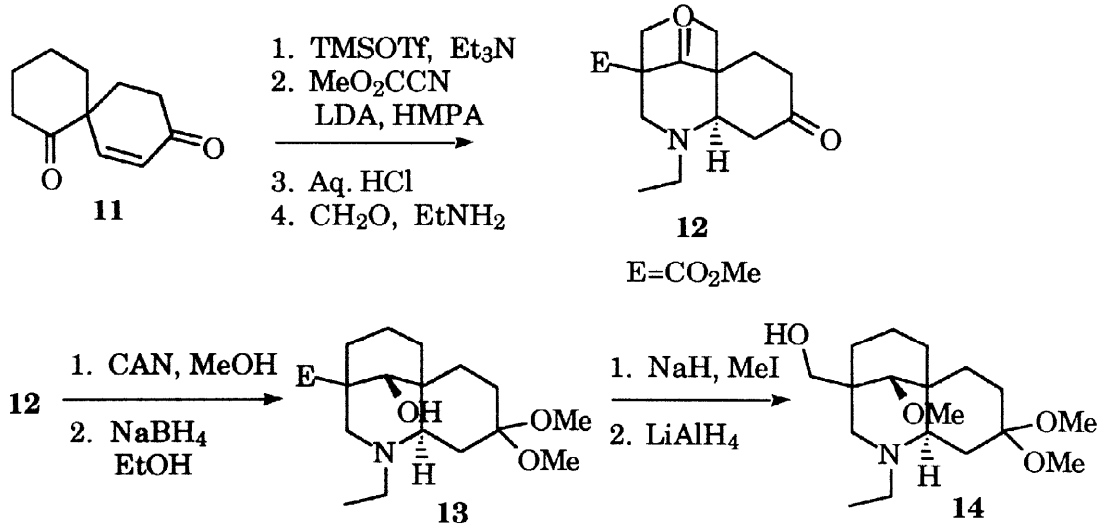
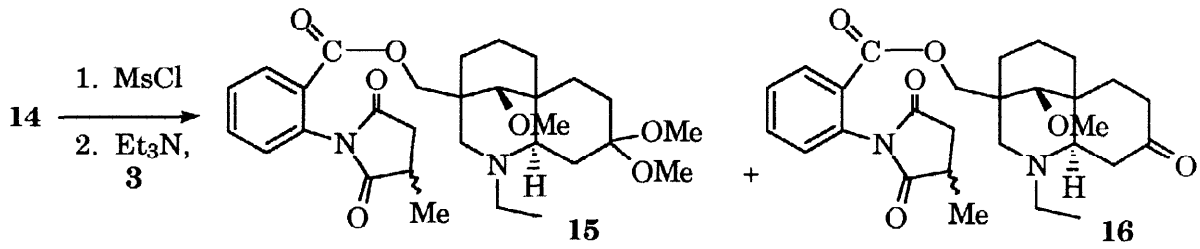
The tricyclic intermediate which incorporates the fuctionality of the ABE rings of **1** was constructed as shown in Scheme 1. The route began with known[11] spirocyclic diketone **11** which has been made in three steps from cyclohexanone. Although selective enolate formation was not possible, the enol silyl ether of the unsaturated ketone could be prepared in quantitative yield by the reaction of **11** with trimethylsilyltriflate and triethylamine at 0 °C in ether. Carbomethoxylation of the saturated ketone using the method of Mander (LDA, HMPA, $CNCO_2Me$)[12] followed by acidic workup to hydrolyze the enol silyl ether (aq. HCl) afforded a beta-keto ester in 86% yield. Mannich reaction of the resulting beta-keto ester provided amino ketone **12** in yields ranging from 65-85%. This structure was confirmed by an x-ray structure determination. Selective ketalization using ceric ammonium nitrate (0.1 eq CAN, MeOH, 30 min) furnished a ketal ketone in 100% yield. The use of ceric ammonium nitrate for ketalization is unusual. This selective and very reproducible ketalization reaction was discovered unexpectedly in the course of an unsuccessful oxidative alkylation of **12**. Reduction of the ketone with sodium borohydride in ethanol at 0 °C afforded the alcohol **13** in quantitative yield. Methylation with methyl iodide and sodium hydride in THF at 25 °C proceeded cleanly without quaternization of the tertiary amine. Hydride reduction of the ester (LAH, THF, 0 °C) provided alcohol **14** in 90-95% yield.

Scheme 1



The reaction of alcohol **14** with the in situ generated acid chloride **4** did not produce ester **15**, possibly a result of the greater steric hindrance of this neopentyl alcohol. This result forced us to evaluate a different approach. Much of the difficulty with handling acid **3** or acid chloride **4** stemmed from the electrophilic acyl group. Another option would be to employ the carboxylate anion of **3** in a S_N2 substitution of an activated alcohol derivative. The tosylate of **14** was easily prepared by treatment of **14** with p-toluenesulfonyl chloride and pyridine. Unfortunately, the reaction of the resulting tosylate with triethylamine and **3** in acetonitrile returned the starting tosylate. The mesylate was then prepared from the reaction of **14** with mesyl chloride and triethylamine in THF at 0 °C. Fortunately, the reaction of this mesylate with acid **3** and triethylamine in anhydrous THF at ambient temperature over three hours afforded a 1:1 mixture of ketal ester **15** and the keto ester **16** in a combined yield of 95%.[13] Similarly the mesylate derived from pyridinol **9** reacted with acid **3** and Et_3N to afford ester **10** in 67% yield.[13]



This research offers a convenient alternative for the introduction of the methylsuccinimidobenzoate ester side chain onto small molecule analogs of methyllycaconitine. The yields of the coupling step are excellent and will permit the synthesis of quantities of compounds for structure-activity studies. The results of biological testing of compounds **10**, **15** and **16** will be reported in due course.

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13. Procedure: To a solution of 1 equiv. of an alcohol in dry THF at 0 °C was added 1.2 equiv. of MsCl, followed by 2.0 equiv. of triethylamine. The mixture was allowed to stir to rt. A solution of 2.0 equiv. of the acid in dry THF was added and stirred to rt. After the addition of CH_2Cl_2 the organic layer was washed with saturated NaCl solution and dried over $CaCl_2$.
Data for **15**: NMR ($CDCl_3$) δ 0.99 (t, J=6 Hz, 3H), 1.3-2.0 (m, 10 H), 2.23-2.30 (m, 1 H), 2.30-2.55 (m, 3 H), 2.60-2.80 (m, 3 H), 3.43 (bs, 1 H), 3.02 (s, 6 H), 3.46 (s, 3 H), 3.91 (d, J=9 Hz, 1 H), 4.13 (d, J=9 Hz, 1 H), 7.21 (bs, 1 H), 7.44 (bs, 1 H), 7.59 (bs, 1 H), 8.1 (bs, 1 H). CMR ($CDCl_3$) δ 12.8, 16.3, 20.5, 34.0, 35.2, 36.6, 36.8, 37.0, 37.2, 38.1, 39.1, 41.0, 41.3, 47.2, 48.2, 61.5, 63.2, 73.8, 89.0, 129.3, 132.3, 132.4, 132.7, 132.9, 133.0, 176.8, 180.2, 180.9.