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# Studies on the Substituted 3-Aminopropan-1-ol Motif of Lycoctonine Class Norditerpenoid Alkaloids: A Novel Route to 3-Hydroxymethylcyclohex-2-enone

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***Abstract***: Pursuing our interest in methyllycaconitine (MLA), we have designed a synthetic route to substituted ring-A of lycoctonine class norditerpenoid alkaloids. A novel synthesis of 3-hydroxymethylcyclohex-2-enone has been achieved starting from cyclohex-2-enone. Key reactions are: 1,2-addition of 1,3-dithiane followed by allylic rearrangement, 1,4-hydrocyanation, Wittig reaction and conversion into the substituted *N*-ethyl-3-aminopropan-1-ol motif of these neopentyl-like alcohols.



The substituted 3-aminopropan-1-ol motif **1** occurs in many norditerpenoid alkaloid natural products found in higher plants,[1,2] and compounds containing this motif display diverse, important pharmacological activities at certain proteinaceous receptors.[3] Typical of these biologically important amines are methyl ether **2** which occurs in aconitine, a potent neurotoxin present in garden *Aconitum* (death's head, monk's bane) and a modulator of voltage-sensitive sodium channels, neopentyl-like alcohol **3** found in lycoctonine and its corresponding substituted aromatic ester **4** found *inter alia* in lycaconitine and nappaconitine (in garden *Delphinium* and *Consolida*).[1-3] This group also contains the important (*S*-2-methylsuccinimido)benzoyl ester of lycoctonine, methyllycaconitine (MLA **4a**),[4-6] one of the most potent and selective competitive antagonists of neuronal nicotinic acetylcholine receptors yet found ($IC_{50}$ = 7.6 nM).[7-11]

We required substituted cyclohexane carboxaldehyde **5** as a key early intermediate for the synthesis of these and related biologically active natural products, and we reasoned that methyl vinyl ether **6** was a convenient precursor which could be obtained by a Wittig olefination reaction on ketone **7** resulting from a 1,4-conjugate addition of cyanide to 3-substituted cyclohex-2-enone **8**.[12] We therefore attempted the allylic hydroxylation of 3-methylcyclohex-2-enone **9**, but we were not able to obtain **8** under a variety of selenium dioxide based conditions (with *t*-butylhydroperoxide and silica,[13] in dioxane at 50 °C, in pyridine/ethanol or in xylene heated under reflux[14]). A practical approach to 3-hydroxymethylcyclohex-2-enone **8** is not trivial and requires a solution of the "hydroxymethylene problem" as exemplified by Heathcock *et al.* in their synthesis of vernolepin from 3-methoxycyclohex-2-enone by a Wittig olefination reaction, epoxidation, and then rearrangement of the oxirane-alkenyl methyl ether.[15]

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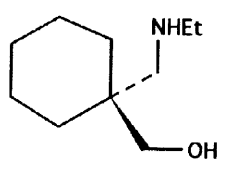
In this *Letter*, we report a novel, practical route to 3-hydroxymethylcyclohex-2-enone **8**[12,15] by the 1,2-addition of 1,3-dithiane to cyclohex-2-enone **10** and a subsequent allylic alcohol rearrangement of the adduct **11**.[16] Thus, 1,2-addition of the anion derived from 1,3-dithiane to cyclohex-2-enone **10** afforded tertiary allylic alcohol **11** (*n*BuLi, anhydrous THF, -78 to 0 °C, 18 h).[16] Deprotection and rearrangement of crude allylic alcohol **11** gave the desired α,β-unsaturated aldehyde **12** (HgO, $BF_3.Et_2O$, 15% $H_2O$-THF, reflux, 3 h, 50% yield from enone **10**).[16] DiBAlH reduction of aldehyde **12** to yield diol **13** (62%) was unexpectedly accompanied by significant quantities of 3-hydroxymethylcyclohex-2-enone **8** (5-28%). A Meerwein-Pondorf-Verley (MVP) reduction mechanism may account for the formation of enone **8** and some support for such an intermolecular hydride transfer comes from experiments under more classical MVP conditions with aluminium 2-propoxide in propan-2-ol which gave diol **13** (31%) and enone **8** (5%). A mechanism based on hydride transfer, probably involving a Tischenko-type reaction, is likely although enolisation of the aluminium alkoxide cannot be entirely ruled out. Unfortunately, we were unable to favour the formation of enone **8** to the significant detriment of diol **13**.

This novel nett rearrangement of **12** to **8** was confirmed by a more efficient, selective reduction of aldehyde **12** to allylic diol **13** using hindered borane 9-BBN (anhydrous THF, 0 to 25 °C, 88%), then selective protection of the primary alcohol as its corresponding trityl ether **14** (1.1 equiv. TrCl, 10% DMAP-pyridine, 40 °C, 18 h, 60%), and oxidation of secondary alcohol **14** to α,β-unsaturated ketone **15** (PDC, DCM, 25 °C, 18 h, 90%). 1,4-Conjugate Michael addition of cyanide to enone **15** gave keto-nitrile **16** (KCN, $NH_4Cl$, DMF-$H_2O$, 100 °C, 80%).[17] Although Wittig olefination of keto-nitrile **16** was possible (61%), despite the steric bulk of the trityl protecting group and with no detectable 1,2-elimination of cyanide, reduction of the nitrile functional group was not practical. Therefore, we removed the trityl protection prior to the Wittig reaction, efficiently achieved in acetic acid (80% AcOH, 17 h, 55 °C, 63%) to afford neopentyl-like alcohol **7** which was subjected to a Wittig olefination procedure using commercially available triphenylphosphonium chloride salt and K*t*BuO in anhydrous THF to give enol ether **6** (70%). Attempts to reduce the axial cyano functional group of **6**, to neopentyl-like amine **17**, were completely unsuccessful under a range of conditions using a variety of reducing agents (DiBAlH/NaF/EtI/$NaBH_4$, $LiAlH_4$/THF, $NaBH_3(OCOCF_3)$, $NaBH_4/CoCl_2$, $Et_3O.BF_4$/EtOH/$NaBH_4$). Axial alkyl nitriles are the most resistant and reluctant of the nitriles to undergo reduction.[18] We determined that vigorous conditions were necessary in order to reduce nitrile **6** to the corresponding amine **17** ($LiAlH_4$, diglyme, 100 °C, 2 h). Reduction of nitrile **6** ($LiAlH_4$) also afforded aldehyde **18** on work-up, presumably from hydrolysis of the intermediate imine (70%) *N*-Ethyl functionality was then conveniently introduced in two steps: *N,O*-diacetylation of (crude) amino alcohol **17** ($Ac_2O$, DMAP, $Et_3N$, DCM, 25 °C, 16 h, 70%) was followed by amide reduction and concomitant ester deprotection ($LiAlH_4$, THF, 60 °C, 16 h) to afford secondary amine **19**. Acid catalysed hydrolysis of crude enol ether **19** (5 drops aq. 6 N HCl, 1:4 $H_2O$-THF, 25 °C, 4 h) yielded the desired aldehyde-substituted 3-aminopropan-1-ol **5** (37% for reduction and deprotection steps). Thus, practical synthetic routes to enone **8** and substituted 3-aminopropan-1-ol **5** have been achieved.

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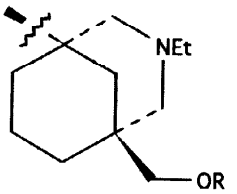
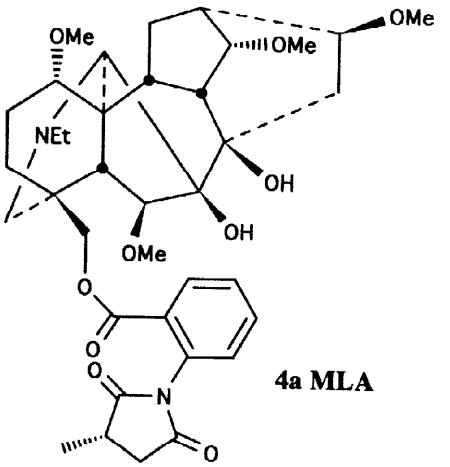
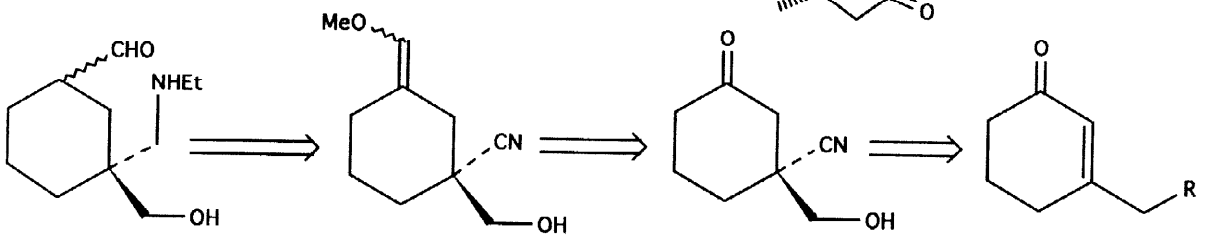



**2 R = Me**
**3 R = H**
**4 R = COPh**

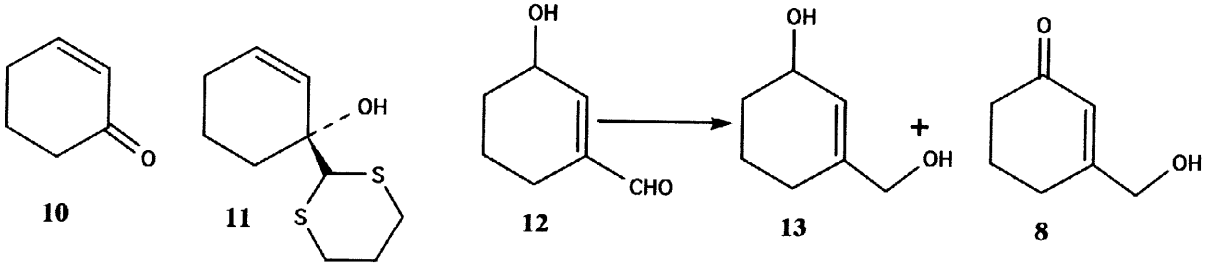



**4a MLA**

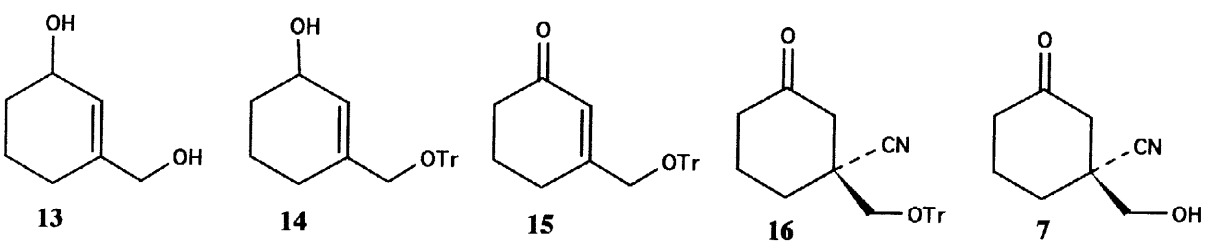



**5** **6** **7**

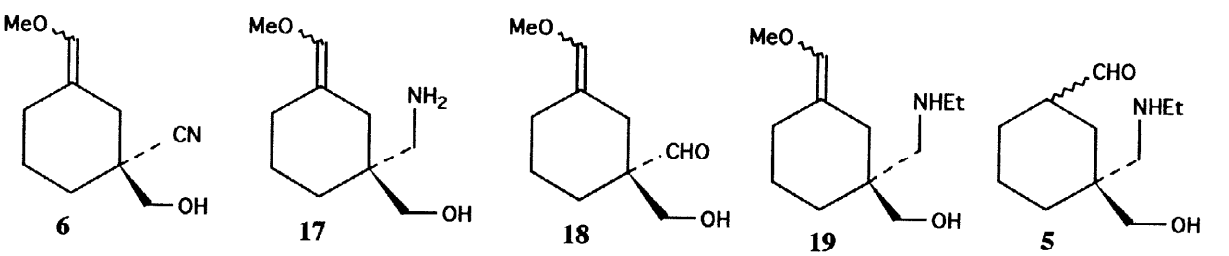
**8 R = OH**
**9 R = H**




**10** **11** **12** **13** **8**




**13** **14** **15** **16** **7**




**6** **17** **18** **19** **5**

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