

TETRAHEDRON LETTERS

## 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. © 1998 Elsevier Science Ltd. All rights reserved.

The substituted 3-aminopropan-1-ol motif 1 occurs in many norditerpenoid alkaloid natural products found in higher plants,<sup>1,2</sup> and compounds containing this motif display diverse, important pharmacological activities at certain proteinaceous receptors.<sup>3</sup> 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*).<sup>1-3</sup> This group also contains the important (*S*-2-methylsuccinimido)benzoyl ester of lycoctonine, methyllycaconitine (MLA 4a),<sup>4-6</sup> one of the most potent and selective competitive antagonists of neuronal nicotinic acetylcholine receptors yet found (IC<sub>50</sub> = 7.6 nM).<sup>7-11</sup>

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.<sup>12</sup> 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,<sup>13</sup> in dioxane at 50 °C, in pyridine/ethanol or in xylene heated under reflux<sup>14</sup>). 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.<sup>15</sup>

0040-4039/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)01857-7 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.<sup>16</sup> 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).<sup>16</sup> Deprotection and rearrangement of crude allylic alcohol 11 gave the desired  $\alpha$ , $\beta$ -unsaturated aldehyde 12 (HgO, BF<sub>3</sub>.Et<sub>2</sub>O, 15% H<sub>2</sub>O-THF, reflux, 3 h, 50% yield from enone 10).<sup>16</sup> 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  $\alpha$ ,  $\beta$ -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<sub>4</sub>Cl, DMF-H<sub>2</sub>O, 100 °C, 80%).<sup>17</sup> 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 KtBuO 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<sub>4</sub>, LiAlH<sub>4</sub>/THF, NaBH<sub>3</sub>(OCOCF<sub>3</sub>), NaBH<sub>4</sub>/CoCl<sub>2</sub>, Et<sub>3</sub>O.BF<sub>4</sub>/EtOH/NaBH<sub>4</sub>). Axial alkyl nitriles are the most resistant and reluctant of the nitriles to undergo reduction.<sup>18</sup> We determined that vigorous conditions were necessary in order to reduce nitrile 6 to the corresponding amine 17 (LiAlH<sub>4</sub>, diglyme, 100 °C, 2 h). Reduction of nitrile 6 (LiAlH<sub>4</sub>) 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,Odiacetylation of (crude) amino alcohol 17 (Ac20, DMAP, Et2N, DCM, 25 °C, 16 h, 70%) was followed by amide reduction and concomitant ester deprotection (LiAlH<sub>4</sub>, 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<sub>2</sub>O-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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