

APPROACHES TO THE TOTAL SYNTHESIS OF AMARYLLIDACEAE ALKALOIDS. ALTERNATIVE PREPARATIONS OF 5-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-2-BENZAZEPINES

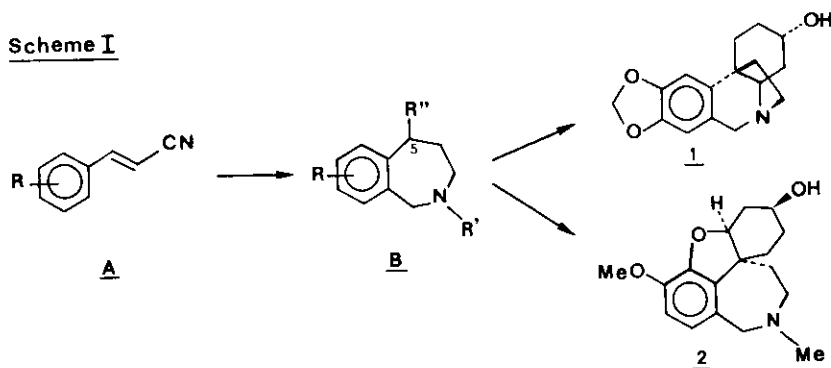
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**Abstract** - The preparation of several 5-substituted 2,3,4,5-tetrahydro-1H-2-benzazepines of general structure **B**, versatile synthons for the total synthesis of Amaryllidaceae alkaloids, is described.

As part of our research program dealing with the synthesis of Amaryllidaceae alkaloids<sup>1</sup> we have recently completed the total synthesis of ( $\pm$ )-elwesine<sup>2</sup> (**1**) and ( $\pm$ )-lycoramine<sup>3</sup> (**2**), two representative members of the series, starting from common cinnamitrile precursors **A** (Scheme I). Along the lines of our synthetic strategy, a second common target was soon envisaged, namely, the 5-substituted 2,3,4,5-tetrahydro-1H-2-benzazepine **B**.

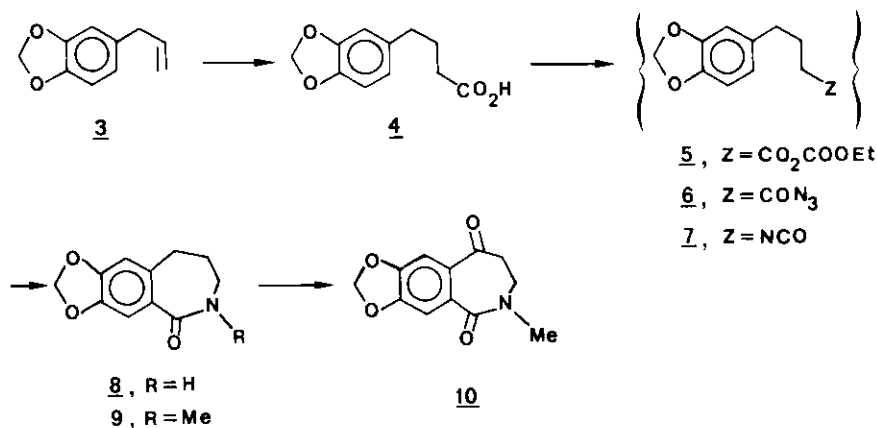


We now report two alternative methods for the preparation of tetrahydrobenzazepines<sup>4</sup> of general structure **B**. Our first approach to the synthesis of type-B compounds stems from the well-known<sup>5</sup> preparation of 4-arylbutanoic acids by carboxylation of the organometallic intermediate formed in the titanium tetrachloride-catalyzed Grignard transfer reaction between alkylmagnesium halides (i.e., *n*-propylmagnesium bromide) and the appropriate terminal olefins.

In this manner, safrole (**3**), readily generates in 63% yield the 4-(3,4-methylenedioxyphenyl)butanoic acid (**4**), mp 67-69°C (lit.<sup>6</sup> mp 67-69°C). Next, formation of the basic hydroazepine nucleus was

carried out under our usual conditions.<sup>1a</sup> Namely, initial treatment of acid 4 with ethyl chloroformate in the presence of triethylamine<sup>7</sup> (Scheme II) furnished the mixed anhydride 5, which without isolation was allowed to react with sodium azide in wet acetone. The resulting (crude) acyl azide 6 was then heated to reflux in toluene for 2.5 h to yield isocyanate 7 ( $\nu_{\max}$  2270  $\text{cm}^{-1}$ ). Finally, treatment of 7 with neat polyphosphoric acid (PPA) at room temperature produced the highly crystalline seven-membered ring lactam 8, mp 127-129°C (EtOAc-hex), in 52% overall yield.<sup>8</sup>

**Scheme II**

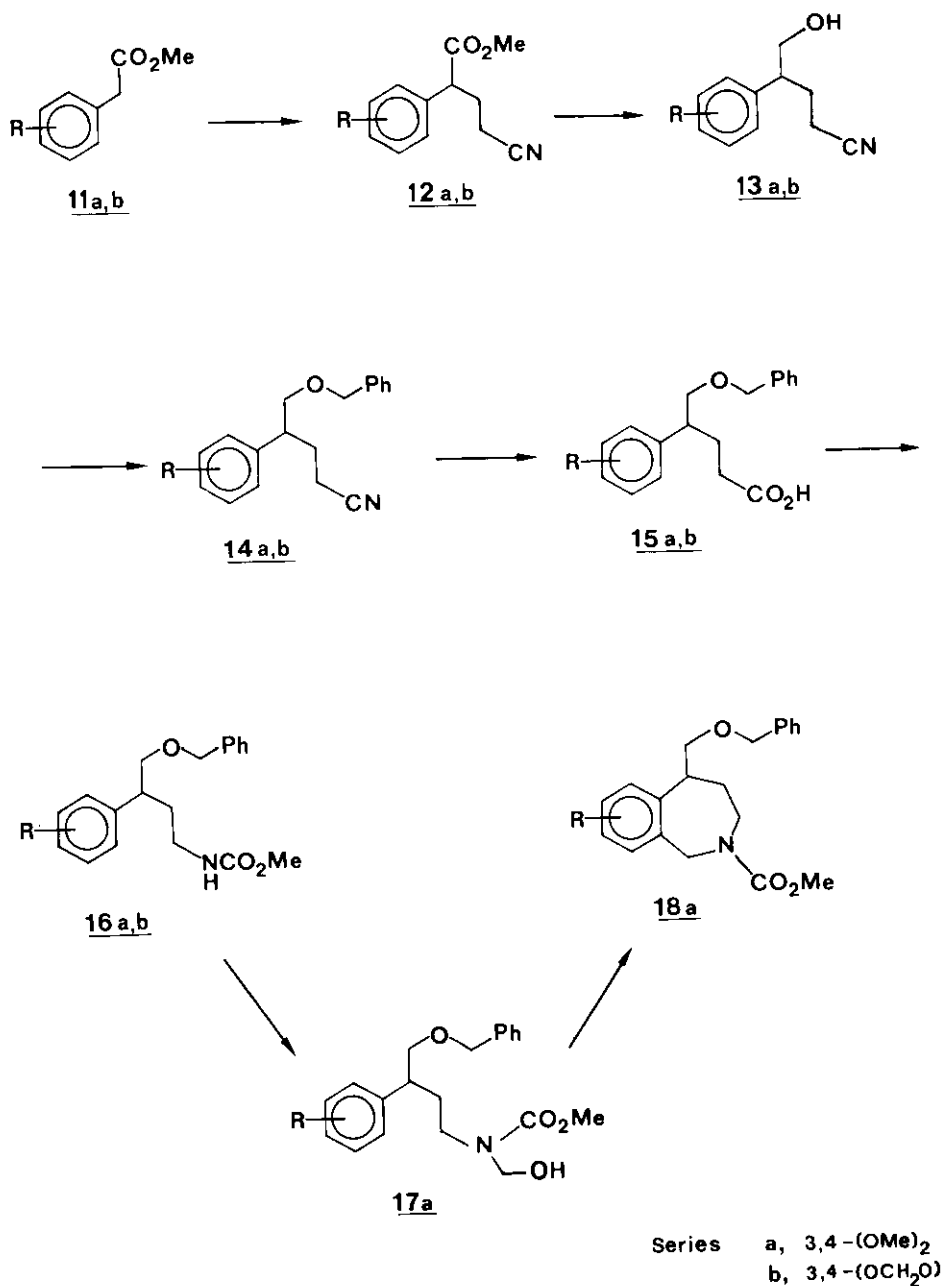


In order to introduce the necessary functional handle at the 5-position, we proceeded next to protect the nitrogen function. Straightforward N-alkylation with methyl iodide/sodium hydride in dry tetrahydrofuran (THF) afforded the N-methyl lactam 9, mp 93-94°C (EtOAc-hex), in 96% yield. Photooxidation of 9 in the presence of N-bromosuccinimide (NBS) and anhydrous calcium carbonate<sup>9</sup> furnished the desired 5-oxo derivative 10, mp 133-135°C (EtOAc-hex), in 89% yield. (Scheme II).

From our previous work<sup>3</sup> on the synthesis of the galanthamine-like *Amaryllidaceae* alkaloids,<sup>10</sup> it can be seen that hydrobenzazepinedione<sup>11,12</sup> 10 is in fact a versatile and now readily available advanced intermediate.

On the other hand, the readily available alkyl aryl acetates are amenable substrates for the elaboration of various type-B hydrobenzazepines. The series has been elaborated with both the methyl 3,4-dimethoxy-(11a) and 3,4-methylenedioxyphenylacetates (11b). Thus, reaction of ester 11a<sup>13</sup> with acrylonitrile under Triton B catalysis affords (Scheme III) cyanoester 12a, mp 63-64°C (EtOAc-hex), in 72% yield. The ester grouping was chemospecifically<sup>14</sup> reduced to the primary alcohol 13a (92% yield) by using a small excess of lithium borohydride in THF at room temperature, followed by protection as the corresponding benzyl ether (84%; benzyl chloride/NaH in a 9:1 mixture of THF-dimethylformamide).

Scheme III

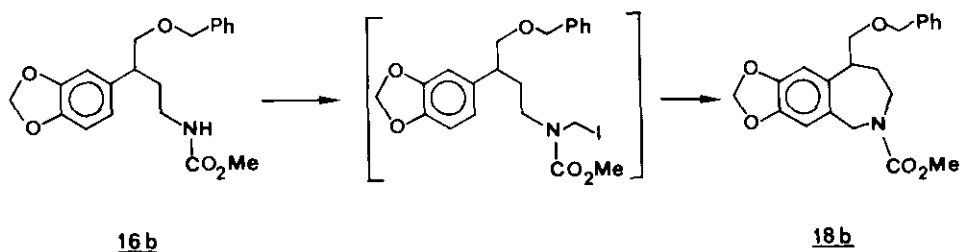


Next, basic hydrolysis (40% NaOH in refluxing ethanol) of the nitrile grouping produced the oily acid 15a in 81% yield. Transformation of the latter into urethane 16a was carried out as before by means of a one-pot Curtius rearrangement,<sup>1a,7</sup> with final methanolysis of the resulting (crude) isocyanate. The expected urethane 16a was isolated as a thick colorless oil in 74% yield.

Finally, the missing one-carbon unit was introduced *via* a modified two-step Tscherniac-Einhorn reaction.<sup>15</sup> Namely, hydroxymethylation of 16a (formaldehyde, 25% NaOH, dioxane, room temperature, 15h) proceeded uneventfully in 92% yield. The <sup>1</sup>H-nmr spectrum (CDCl<sub>3</sub>, 90 MHz) of the oily N-methyl-ol derivative 17a showed a broad singlet (2H) at 4.70 ppm for the N-CH<sub>2</sub>OH grouping. The formation of the desired complete hydrobenzazepine skeleton of 18a was carried out next, in nearly quantitative yield, by simply heating 17a with a catalytic amount of *p*-toluenesulfonic acid in benzene (Dean-Stark trap).<sup>16</sup> The overall yield of this sequence is 30.7%.

Alternatively, methyl 3,4-methylenedioxyphenylacetate<sup>17</sup> (11b) was reacted with acrylonitrile to produce the oily cyano ester 12b in 74% yield. As before, lithium borohydride reduction to 13b (94%), followed by benzyl ether formation (77%) afforded nitrile 14b as a colorless oil. Basic hydrolysis (40% NaOH, EtOH, reflux, 8h) furnished acid 15b, mp 103-105°C (EtOAc-hex), in 88% yield after column chromatography on silica gel. Curtius rearrangement, followed by methanolysis of the intermediate isocyanate gave urethane 16b, as a thick colorless oil, in 75% overall yield.

Finally, the desired hydrobenzazepine 18b was prepared by a modification of our original cyclization conditions. Namely, direct treatment of 16b with excess chloromethyl methyl ether (as the one-carbon source) and 57% hydriodic acid in glacial acetic acid<sup>18</sup> at 5°C produces 18b<sup>19</sup> as a colorless oil in 82% yield.<sup>20</sup> The overall yield for this sequence is 29%.



Full account of this work and its application in the total synthesis of other Amaryllidaceae alkaloids will be reported elsewhere.

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16. 18a: Colorless oil; ir (neat)  $\nu_{\max}$  3020, 2960, 2880, 1710, 1600, 1525  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ )  $\delta$  7.32 (s, 5H, Ph), 6.70 (s, 2H,  $\text{C}_6\text{-H}$  and  $\text{C}_9\text{-H}$ ), 4.53 (s, 2H,  $-\text{OCH}_2\text{Ph}$ ), 4.35 (bs, 2H,  $\text{C}_1\text{-H}_2$ ), 3.83 and 3.80 (s, 6H,  $2 \times \text{OCH}_3$ ), 3.61 (s, 3H,  $-\text{COOCH}_3$ ), 3.68-3.53 (m, 3H,  $\text{C}_5\text{-H}$  and  $-\text{CH}_2\text{-OCH}_2\text{Ph}$ ), 3.20 (m, 2H,  $\text{C}_3\text{-H}_2$ ), 1.90 ppm (m, 2H,  $\text{C}_4\text{-H}_2$ ).
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19. 18b: Colorless oil; ir (neat)  $\nu_{\max}$  3030, 2950, 2890, 1700, 1250  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  ( $\text{CCl}_4$ )  $\delta$  7.17 (s, 5H, Ph), 6.50 (m, 2H,  $\text{C}_6\text{-H}$  and  $\text{C}_9\text{-H}$ ), 5.70 (s, 2H,  $-\text{OCH}_2\text{O}-$ ), 4.47 (s, 2H,  $-\text{OCH}_2\text{Ph}$ ), 4.2 (bs, 2H,  $\text{C}_1\text{-H}_2$ ), 3.53 (s, 3H,  $-\text{COOCH}_3$ ), 3.67 - 3.2 (m, 3H,  $\text{C}_5\text{-H}$  and  $-\text{CH}_2\text{-OCH}_2\text{Ph}$ ), 3.10 (m, 2H  $\text{C}_3\text{-H}_2$ ), 1.7 ppm (m, 2H,  $\text{C}_4\text{-H}_2$ ).
20. A few practical limitations of this reaction have been found. It works best for acid-stable protected derivatives of the primary hydroxyl group (ie., acetates, alkyl ethers), but fails completely for the free hydroxyl compound or for acid-labile protecting groups (ie., THP ethers). Otherwise, it constitutes a viable alternative to the two-step Tscherniac-Einhorn  $\alpha$ -amidoalkylation reaction.

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