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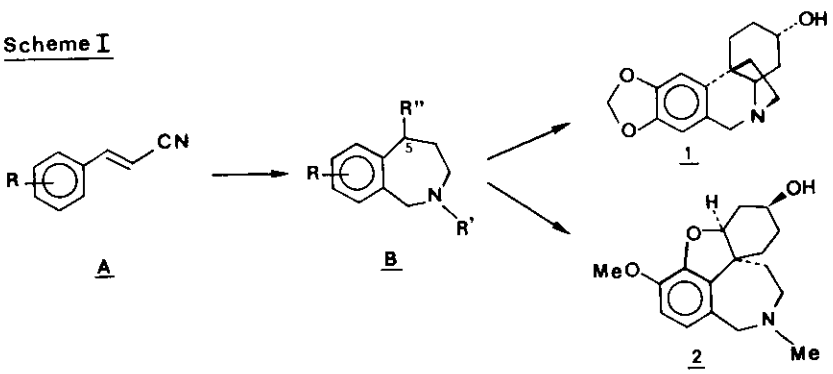
Abstract - The preparation of several 5-substituted 2,3,4,5-tetrahydro-1H-2-benzazepines of general structure B, versatile synthons for the total synthesis of Amaryllidaceae alkaloids, is described.

As part of our research program dealing with the synthesis of Amaryllidaceae alkaloids[1] we have recently completed the total synthesis of (±)-elwesine[2] (1) and (±)-lycoramine[3] (2), two representative members of the series, starting from common cinnamonitrile 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.

Scheme I

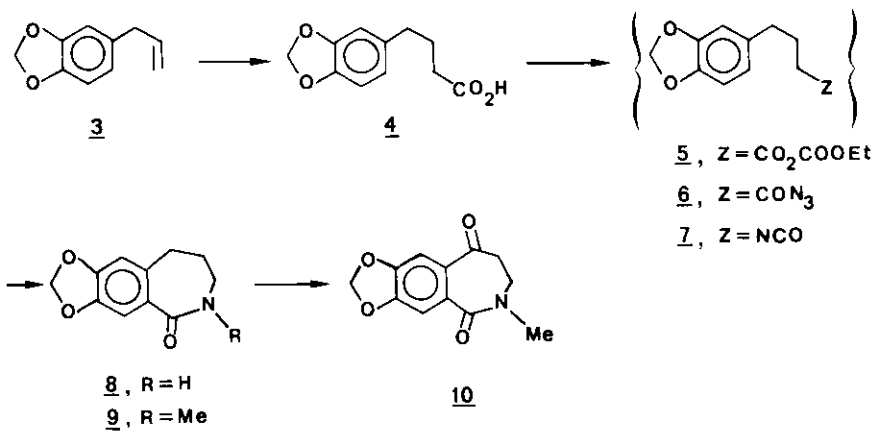


We now report two alternative methods for the preparation of tetrahydrobenzazepines[4] of general structure B. Our first approach to the synthesis of type-B compounds stems from the well-known[5] preparation of 4-arylbutanoic acids by carboxylation of the organometallic intermediate formed in the titanium tetrachloride-catalyzed Grignard transfer reaction between alkylmagnesium halides (ie., 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.[6] mp 67-69°C). Next, formation of the basic hydroazepine nucleus was

carried out under our usual conditions.[1a] Namely, initial treatment of acid 4 with ethyl chloroformate in the presence of triethylamine[7] (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 (ν_{max} 2270 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.[8]

Scheme II

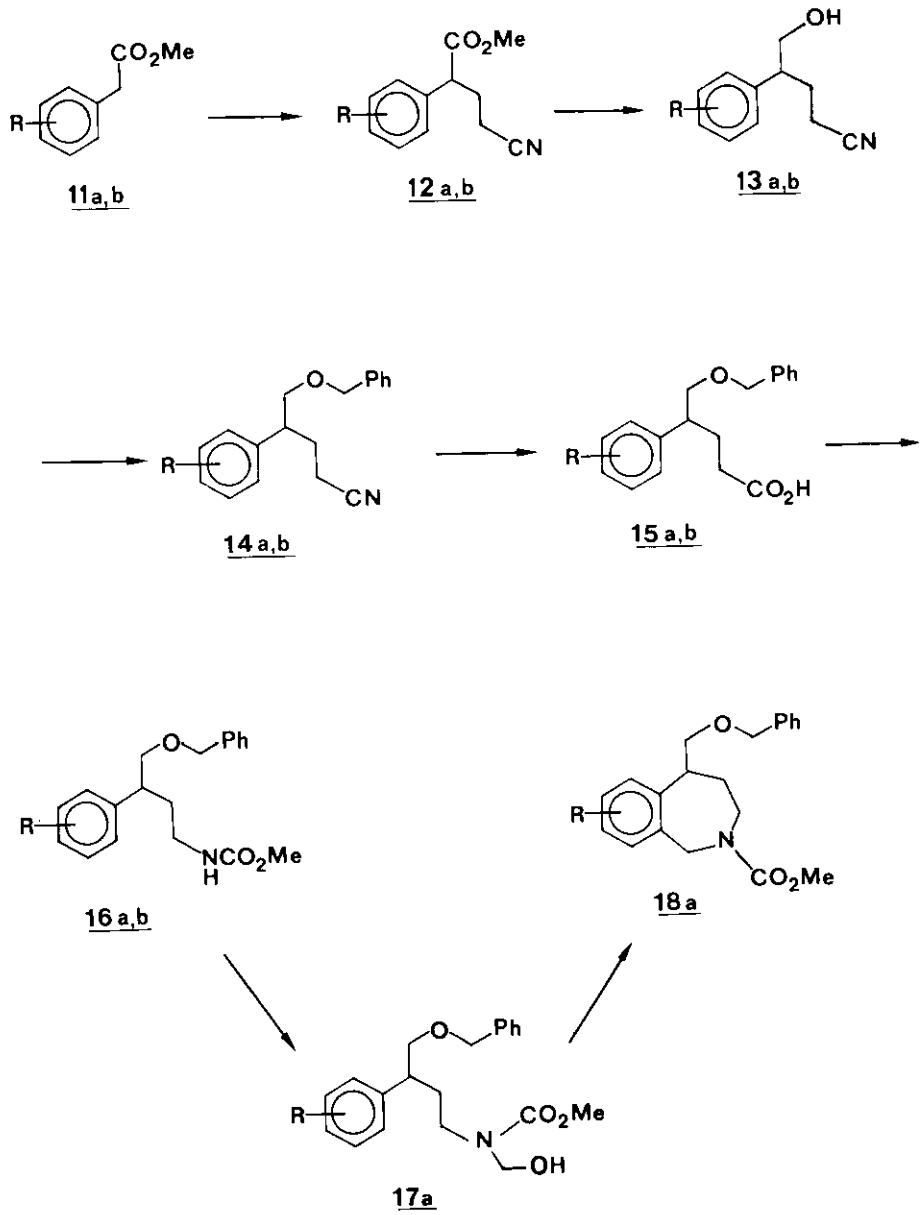


In order to introduce the necessary functional handle at the 5-position, we proceeded next to protect the nitrogen function. Straightforward N-alkylation with methyl iodide/sodium hydride in dry tetrahydrofuran (THF) afforded the N-methyllactam 9, mp 93-94°C (EtOAc-hex), in 96% yield. Photooxidation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

From our previous work[3] on the synthesis of the galanthamine-like Amaryllidaceae alkaloids,[10] it can be seen that hydrobenzazepinedione[11,12] 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[13] 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[14] 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



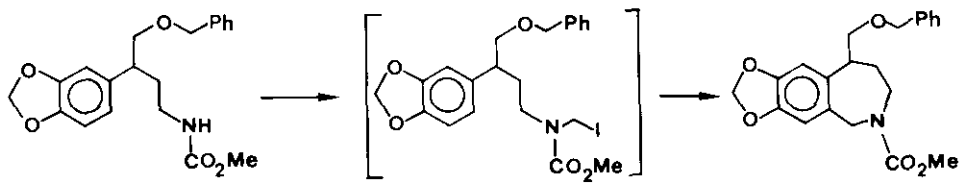
Series a, 3,4-$(OMe)_2$
b, 3,4-(OCH_2O)

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,[1a,7] 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.[15] Namely, hydroxymethylation of 16a (formaldehyde, 25% NaOH, dioxane, room temperature, 15h) proceeded uneventfuly in 92% yield. The ^{1}H-nmr spectrum ($CDCl_3$, 90 MHz) of the oily N-methylol derivative 17a showed a broad singlet (2H) at 4.70 ppm for the N-CH_2OH 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).[16] The overall yield of this sequence is 30.7%.

Alternatively, methyl 3,4-methylenedioxyphenylacetate[17] (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[18] at 5°C produces 18b[19] as a colorless oil in 82% yield.[20] The overall yield for this sequence is 29%.



16b 18b

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) ν_{max} 3020, 2960, 2880, 1710, 1600, 1525 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 7.32 (s, 5H, Ph), 6.70 (s, 2H, C_6-H and C_9-H), 4.53 (s, 2H, $-OCH_2Ph$), 4.35 (bs, 2H, C_1-H_2), 3.83 and 3.80 (s, 6H, 2xOCH_3), 3.61 (s, 3H, $-COOCH_3$), 3.68-3.53 (m, 3H, C_5-H and $-CH_2-OCH_2Ph$), 3.20 (m, 2H, C_3-H_2), 1.90 ppm (m, 2H, C_4-H_2).

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19. 18b: Colorless oil; ir (neat) ν_{max} 3030, 2950, 2890, 1700, 1250 cm^{-1}; ^{1}H-nmr (CCl_4) δ 7.17 (s, 5H, Ph), 6.50 (m, 2H, C_6-H and C_9-H), 5.70 (s, 2H, $-OCH_2O-$), 4.47 (s, 2H, $-OCH_2Ph$), 4.2 (bs, 2H, C_1-H_2), 3.53 (s, 3H, $-COOCH_3$), 3.67 - 3.2 (m, 3H, C_5-H and $-CH_2-OCH_2Ph$), 3.10 (m, 2H C_3-H_2), 1.7 ppm (m, 2H, C_4-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 α-amidoalkylation reaction.

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