Erythrina Alkaloids

A Highly Efficient Synthesis of the Erythrina and B-Homoerythrina Skeleton by an $AlMe_3$-Mediated Domino Reaction**

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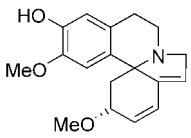
Dedicated to Professor Armin de Meijere on the occasion of his 65th birthday

The development of efficient and environmentally acceptable synthetic methods is an important task of modern chemistry. In this context the domino concept has proved to be very successful.[1] In domino reactions bonds and new functionalities are constructed, which, in turn, react further in subsequent steps under identical conditions to form new bonds and functionalities. The larger the number of bonds formed and the higher the complexity of the product is the greater is the quality of a domino reaction. A plethora of two-step domino reactions have been reported, but three-step transformations are the exception. Here we describe a novel domino reaction for the construction of three bonds in sequential steps that allows efficient access to the skeleton of the erythrina and B-homoerythrina alkaloids.

The erythrina alkaloids[2] such as erysodine (**1**) are a widespread, structurally interesting class of natural products with extensive biological activity.[3] Many compounds of this family exhibit curare-like activity as well as hypotensive, sedative, and CNS depressant properties.[4]



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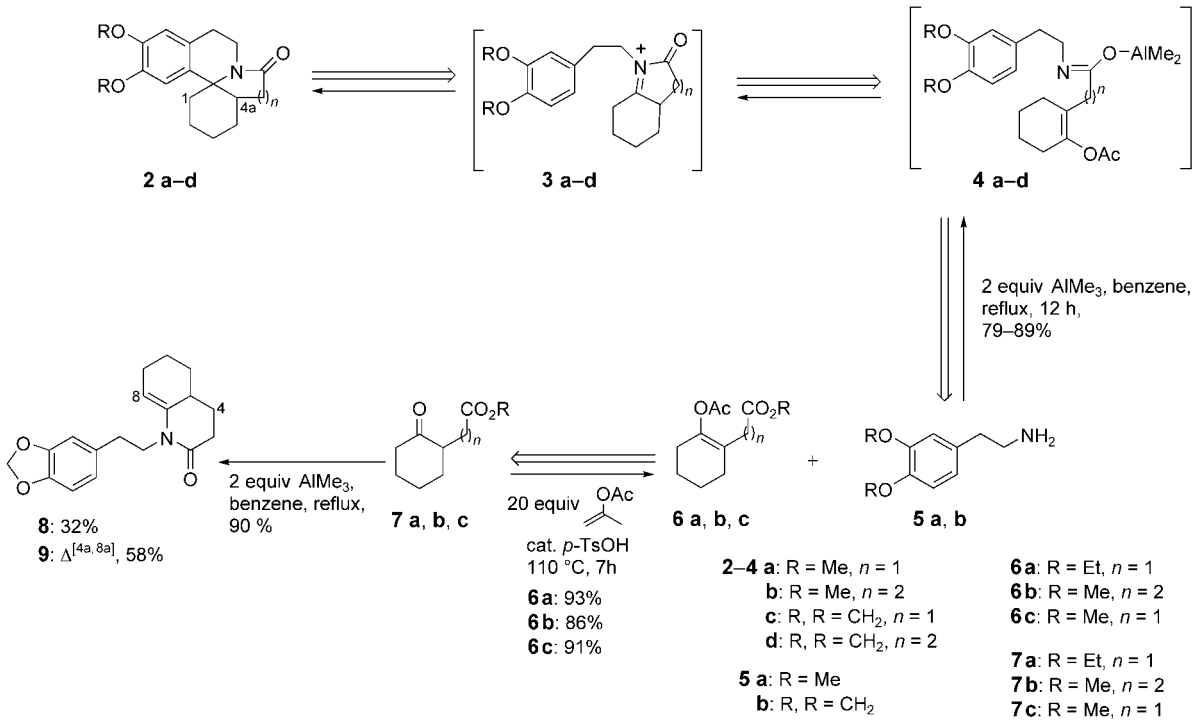
The retrosynthesis of the skeleton of the erythrina and B-homoerythrina alkaloids **2a** and **2b** within the context of the domino concept leads to the amine **5a** and the cyclohexene derivatives **6a** and **6b** via the *N*-acyliminium ions **3a** and **3b** and the metalated amides **4a** and **4b** (Scheme 1). The intermediate *N*-acyliminium ions **3** could be formed by an intramolecular addition of an aluminum complex of the primary carboxamide[5] to the enol acetate moiety in **4** with subsequent elimination of acetic acid. The aluminum complex might be accessible in situ by reaction of the primary amine **5** with the ester function of the enol acetate **6**.



Scheme 1. Retrosynthesis and synthesis of the erythrina and B-homoerythrina skeleton **2** as well as the enamines **8** and **9**.

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The enol acetates **6a** and **6b** were readily obtained in 86 and 93% yield, respectively, by reaction of the known ketones[6] **7a** and **7b** with isoprenyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid. For the synthesis of **2a** and **2c**, the amines **5a** and **5b**, respectively, were each treated with trimethylaluminum in benzene, stirred for one hour at 20°C, and after the addition of **6a** heated under reflux for five hours.[7] After workup **2a**[8] and **2c** were isolated in 79 and 82% yield, respectively. In an analogous

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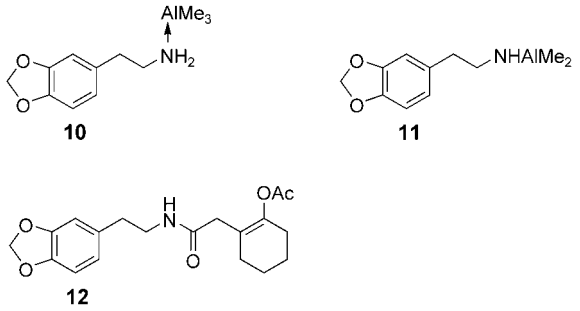
manner the homoerythrina alkaloids **2b**[9] and **2d** were obtained in 89% and 85% yield, respectively, by the reaction of **5a** and **5b** with **6b** in the presence of trimethylaluminum. In the reaction of the keto esters **7a** and **7b** with the amines **5a** and **5b** and trimethylaluminum, no cyclization to the erythrina and homoerythrina skeleton occurred, but instead as in the transformation of **5b** and **7b**, the enamines **8** and **9** were obtained in 32 and 58% yield, respectively.

On-line NMR investigations during the reaction of a mixture of **5b**, **6c**, and $AlMe_3$ show that at 20°C the Lewis acid/Lewis base complex **10** is formed from **5b** with $AlMe_3$ (Scheme 2); the ester function of **6c** is not attacked. In



10 **11** **12**

Scheme 2. Addition complexes **10** and **11** of the amine **5a** with trimethylaluminum and the carboxamide **12**.

contrast, in the reaction of **6c** with $AlMe_3$ without the addition of the amine **5b** a transformation of the ester function of **6c** is observed even at 20°C. Heating the mixture of **5b**, **6c**, and $AlMe_3$ to 70°C leads to the formation of **11** together with the evolution of methane (Scheme 2), **11** then reacts rapidly with the ester group of **6c**. Among the products isolated on working up the reaction mixture after one hour is the carboxamide **12** (Scheme 2), which, however, on reaction with $AlMe_3$ does not lead to the desired product. Thus, we conclude that in the domino reaction the free carboxamide **12** is not generated but rather a metalated species (e.g. **4**), which, however, is not formed by the reaction of **12** with $AlMe_3$.

The formation of the iminium ion **3** from **4** also appears to be a very fast reaction. Thus, in the ^1H NMR spectrum of the reaction mixture a singlet at $\delta = 1.13$ ppm, which can be assigned to a R_2AlOAc group, is found after just a few minutes in place of the signal at $\delta = 1.76$ ppm for the CH_3 moiety of the enol acetate group of **6c**. The rate-determining step of the domino process is probably the electrophilic substitution of the arene by the iminium ion **3**.

The domino reaction presented here in which three sequential bonds are formed in one reaction process allows the efficient construction of the erythrina and B-homoerythrina alkaloid skeleton in good yields. The required substrates are readily accessible and may be varied in many ways. This method should therefore be of interest in drug research.

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[7] General method for the $AlMe_3$-mediated domino reaction: One equivalent of a 0.14 M solution of amine **5** in benzene was treated with two equivalents of a 1.36 M $AlMe_3$ solution in benzene at 0°C and stirred for 1 h at room temperature. After the addition of one equivalent of a 0.14 M solution of the enol acetate **6** in benzene, the mixture was heated at 80°C for 5 h in a pre-heated oil bath. At 0°C 2 N HCl (5 mL mmol^{-1}) was then added and the mixture was stirred for 30 min at this temperature. After phase separation, the aqueous phase was extracted four times with ethyl acetate (10 mL mmol^{-1}), the combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuum. The crude product was

purified by column chromatography on silica (petroleum ether/ethyl acetate = 1:1).

[8] **2a**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 6.83$ (s, 1H; 13-H), 6.54 (s, 1H; 10-H), 4.11 (ddd, $J = 13.2, 7.0, 3.2$ Hz, 1H; 8-H_{eq}), 3.83 (s, 3H; OMe at C-12), 3.77 (s, 3H; OMe at C-11), 3.18 (ddd, 1H; $J = 13.2, 9.8, 5.2$ Hz, 8-H_{ax}), 2.93 (ddd, 1H; $J = 16.4, 9.8, 7.0$ Hz, 9-H_{eq}), 2.63 (ddd, 1H; $J = 16.4, 5.2, 3.2$ Hz, 9-H_{ax}), 2.60–2.52 (m, 1H; 4a-H), 2.36 (s, 1H; 5-H_a), 2.33 (d, 1H; $J = 1.2$ Hz, 5-H_b), 2.16–1.92 (m, 1H; 1-H_a), 1.93–1.80 (m, 2H; 4-H_2), 1.80–1.71 (m, 1H; 1-H_b), 1.74–1.60 (m, 2H; 2-H), 1.60–1.48 ppm (m, 2H; 3-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 174.9$ (C-6), 147.6 (C-12), 147.1 (C-11), 134.7 (C-13a), 125.6 (C-9a), 111.7 (C-10), 108.0 (C-13), 62.09 (C-13b), 55.99 (OMe at C-11), 55.67 (OMe at C-12), 37.51 (C4a), 36.46 (C-8), 35.74 (C-5), 34.67 (C-4), 27.02 (C-1, C-9), 20.63 (C-2), 20.20 ppm (C-3).

[9] **2b**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 6.70$ (s, 1H; 14-H), 6.58 (s, 1H; 11-H), 4.79 (m_c, 1H; 9-H_a) 3.96 (s, 3H; OMe at C-12), 3.87 (s, 3H; OMe at C-13), 3.35–3.08 (m, 2H; 9-H_b 10-H_a), 2.78–2.42 (m, 3H; 4a-H, 6-H, 10-H_b), 2.38–2.20 (m, 2H; 5-H), 1.98–1.72 (m, 3H; 1-H, 2-H_a), 1.71–1.42 ppm (m, 6H; 6-H, 4-H, 2-H_b, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 172.16$ (C-7), 147.4 (C-12), 146.9 (C-13), 135.4 (C-14a), 126.84 (C-10a), 112.2 (C-14), 105.9 (C-11), 61.27 (C-14b), 55.96 (OMe at C-12), 55.43 (OMe at C-13), 40.47 (C-6), 35.75 (C-4a), 34.91 (C-9), 28.38 (C-5), 26.62 (C-10), 25.77 (C-4), 25.56 (C-1), 22.19 (C-2), 21.35 ppm (C-3).

