Highly Efficient Domino Reaction for the Synthesis of the Erythrina and B-Homoerythrina Alkaloid Skeleton

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Abstract: A Lewis acid catalyzed domino–amidation–spirocyclization reaction is described which provides the spirocyclic core of the erythrina and B-homoerythrina alkaloids, forming three bonds in one process.

Key words: domino reactions, erythrina alkaloids, spiro compounds, Lewis acids, indolizidine, lactams

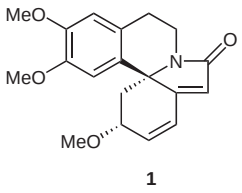

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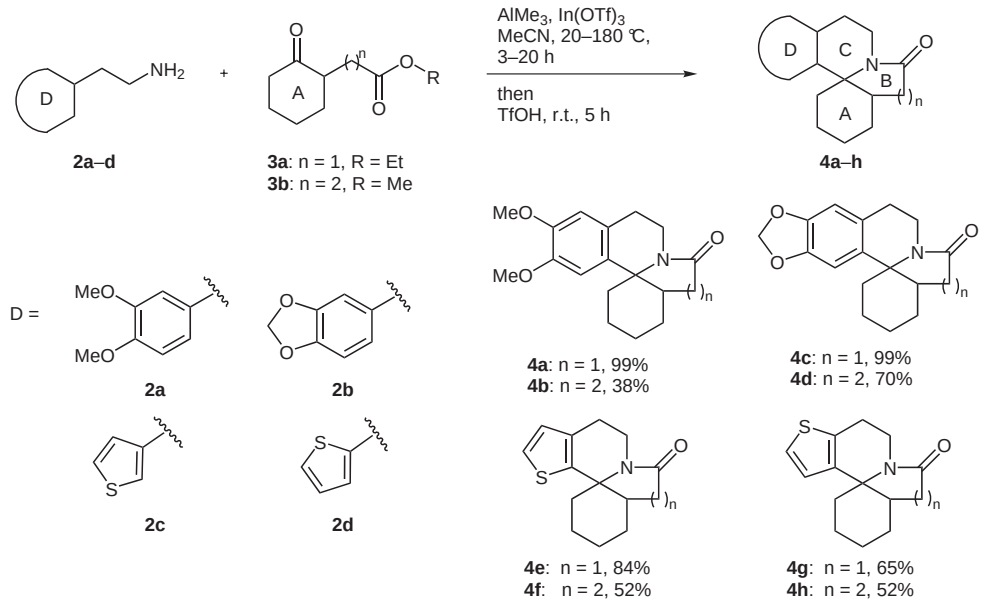
Figure 1 Erysotramidine (**1**)

Ecological and economical aspects are increasingly important in modern synthetic chemistry. The domino concept has proven to be very successful in this context.[1] A domino reaction is a transformation of two or more bond-forming reactions – that in an ideal procedure proceeds under identical reaction conditions – in which the latter transformations take place at the functionalities obtained in the former steps.[1] Here we describe a domino process which allows us to build up the erythrina and B-homoerythrina skeleton in one process starting from readily available substrates. The erythrina alkaloids are a widely spread class of natural products that can be found in tropical and subtropical *Febaceae* plants of the erythrina genus.[2] Numerous alkaloids of this family, such as erysotramidine (**1**, Figure 1), have been isolated which show pronounced biological activity,[3] e.g. curare-like properties as well as hypotensive, sedative, anticonvulsive, and CNS-depressive properties.[4] Some members of this alkaloid family have already been synthesized.[5]

The characteristic tetracyclic aza-spiro structure **4a**–**d** of the erythrina and homoerythrina alkaloids was formed by a Lewis acid catalyzed domino reaction of primary arylethylamines **2a**,**b** and an oxocarboxylate **3** in the presence of $AlMe_3$; three bonds are formed succeedingly in this process (Figure 1, Table 1). Similarly, also heteroanalogous compounds **4e**–**h** can be formed using heteroarylethylamines as **2c**,**d**.



Scheme 1 Lewis acid mediated domino reactions

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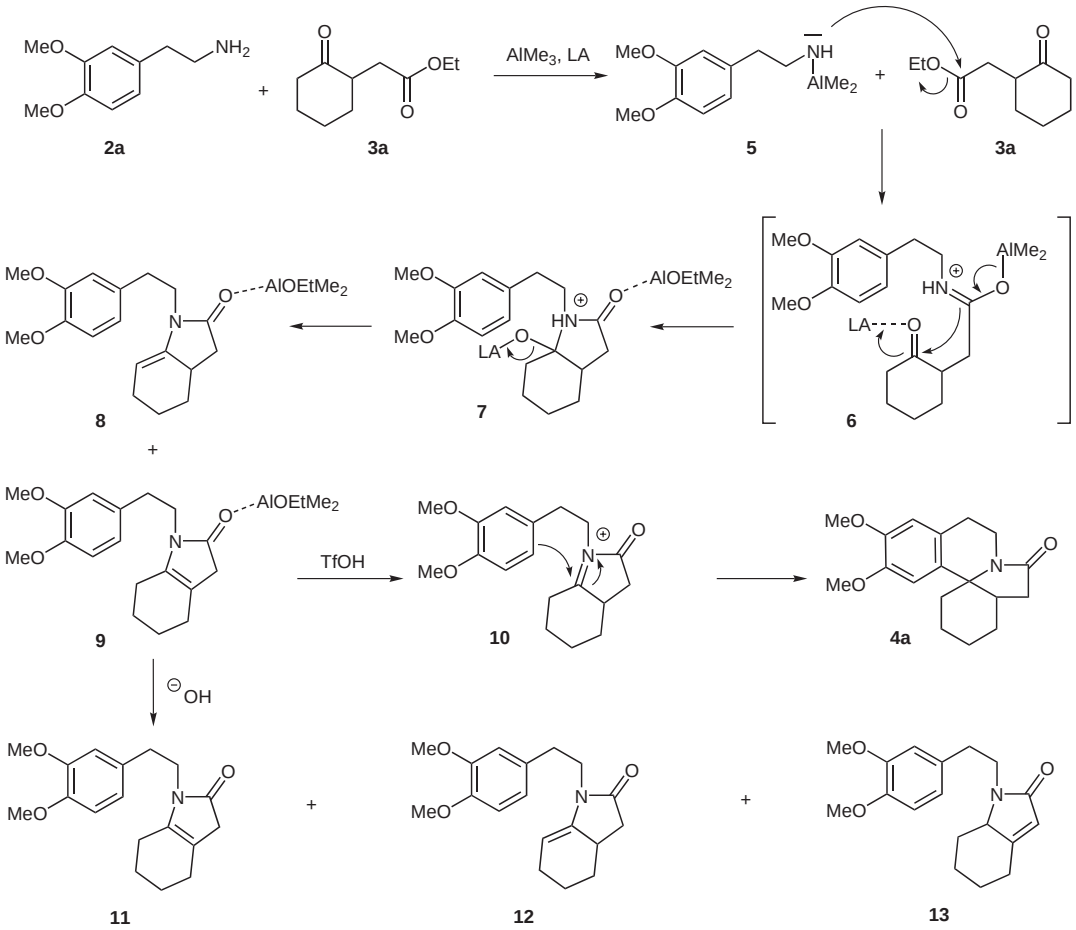

Scheme 2 Proposed mechanism of the domino reaction

As an example, the reaction of **2a** and **2b** with **3a** using two equivalents of $AlMe_3$ and 4 mol% to 25 mol% of indium triflate [$In(OTf)_3$] at room temperature for 17 hours followed by treatment of the reaction mixture with trifluoromethanesulfonic acid (TfOH) for 5 hours gave **4a** and **4c**, respectively, in 99% yield (Scheme 1, Table 1, entries 1 and 3). Similarly, transformation of **2b**–**d** and **3b** as well as **2a**–**d** and **3b** led to **4b** and **4d**–**4h** in 38–84% yield employing the reaction conditions shown in Table 1 (entries 2 and 4–8). The yields of the reaction leading to the homoerythrina skeleton are always somehow lower. Interestingly, the reaction also works using the 2- and 3-thienylethylamines **2c** and **2d**; however, again with lower yields than in the case of **2a**.

The mechanistic details of the domino process are not yet fully understood. Online NMR investigations[7] and isolated intermediates let us propose the following mode of action (Scheme 2). Treatment of the amine **2a** with $AlMe_3$ and **3a** in the presence of catalytic amounts of $In(OTf)_3$ gives the corresponding aluminum amide **5** which attacks the ester **3a** forming the aluminum aza-enolate **6**. An attack of the aluminum amide **5** onto the keto instead of the ester functionality in **3a** has not been observed, which corresponds well to the high oxophilicity of the aluminum species. Subsequent intramolecular attack at the keto functionality under Lewis acid catalysis leads to the formation of the enamines **8** and **9**, indicated by the corresponding lactam species **11**–**13** formed if the reaction is quenched with base at this stage. Addition of TfOH to the reaction mixture results in the formation of the iminium ion **10**, which undergoes a ring closure upon intramolecu-

Table 1 Results of the Domino Reactions

Entry	Amine	Ester	Temp (°C)	Time (h)	$In(OTf)_3$	Product	Yield (%)
1	**2a**	**3a**	25	17	5	**4a**	99
2	**2a**	**3b**	100	3	4	**4b**	38
3	**2b**	**3a**	25	17	25	**4c**	99
4	**2b**	**3b**	160	12	25	**4d**	70
5	**2c**	**3a**	25	13	17	**4e**	84
6	**2c**	**3b**	100	12	5	**4f**	52
7	**2d**	**3a**	100	3	5	**4g**	65
8	**2d**	**3b**	180	3	5	**4h**	52

[a] Amine (**2**, 1.00 equiv), $AlMe_3$ (2.00 equiv, 2 M, in toluene), keto ester (**3**, 1.00 equiv), MeCN (0.5 mL/equiv), time, temp, then TfOH (3.50 equiv), r.t., 5 h.[6]

lar electrophilic attack at the aromatic ring to give the spirocyclic product **4a**.

The described process is much more convenient than the reaction of the enol acetate of the keto esters **3a** or **3b**[7] since it saves one step and gives better yields. We have investigated the use of other acids for the C-ring closure; however, TfOH was the only reagent which allowed the cyclization. It should be pointed out that the aryl ethyl amines **2a** and **2b** with **3a** gave similar results, though the electron density of the aromatic moiety of the two substrates, being important for the electrophilic aromatic substitution, is different. Thus, in the case of the methylenedioxy-substituted compound the electron density should be lower due to a reduced overlap of the nonbonding electron pairs at the oxygen atoms of the 1,3-dioxy moiety and the π-system of the aromatic ring due to an anomeric effect. However, acyl iminium ions as **10** are highly reactive species that this difference of electron density does not affect the transformation in this case.

The presented domino reaction with the formation of three bonds is a highly efficient process, which allows the synthesis of the erythrina and B-homoerythrina alkaloid skeletons in up to 99% yield.

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(6) **General Procedure**
To a stirred solution of amine **2** (1.00 equiv) in MeCN (0.5 mL/mmol) was added dropwise at 0 °C $AlMe_3$ (2.00 M in toluene, 2.00 equiv), then $In(OTf)_3$ (4–25 mol%) and the ester **3** (1.00 equiv), and stirring was continued for 3–17 h at r.t. or the mixture was heated to 100–180 °C under microwave irradiation. The reaction mixture was cooled to 0 °C, TfOH (3.5 equiv) was added dropwise and stirring was continued for 5 h at r.t. Subsequently, the mixture was quenched by addition of sat. aq $NaHCO_3$ at 0 °C with stirring for 20 min. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography to yield 38–99% of the spirocycle **4**.
Compound **4a**: ^{1}H NMR (300 MHz, DMSO): δ = 1.35–1.60 (m, 5 H, 3-H_2, 2-H_2, 1-H_a), 1.75–1.82 (m, 2 H, 4-H_2), 1.95–1.99 (m, 1 H, 1-H_b), 2.12 (m_c, 2 H, 7-H_2), 2.54–2.60 (m, 1 H, 6-H), 2.63 (ddd, *J* = 3.0, 6.0, 16.5 Hz, 1 H, 11-H_a), 2.80 (ddd, *J* = 7.4, 10.0, 16.5 Hz, 1 H, 11-H_b), 3.15 (ddd, *J* = 6.0, 10.0, 13.2 Hz, 1 H, 10-H_a), 3.71 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.86 (ddd, *J* = 3.0, 7.4, 13.2 Hz, 1 H, 10-H_b), 6.67 (s, 1 H, 17-H), 6.91 (s, 1 H, 14-H). ^{13}C NMR (300 MHz, DMSO): δ = 20.06 (C-2), 20.57 (C-3), 26.14 (C-11), 27.17 (C-1), 34.26 (C-10), 35.01 (C-4), 36.29 (C-7), 36.67 (C-6), 55.42 (OCH_3), 55.74 (OCH_3), 61.75 (C-5), 108.7 (C-14), 112.5 (C-17), 125.5 (C-12), 134.7 (C-13), 147.0 (C-16), 147.5 (C-15), 173.6 (C-8).
Compound **4b**: ^{1}H NMR (300 MHz, DMSO): δ = 1.18–1.42 (m, 2 H, 11-H_a, 13*-H_a), 1.42–1.69 (m, 5 H, 2-H_2, 12*-H_2, 13*-H_b), 1.69–1.82 (m, 2 H, 1-H_2), 2.05 (dd, *J* = 18.5, 6.2 Hz, 1 H, 14-H_a), 2.18–2.26 (m, 1 H, 11-H_b), 2.33–2.47 (m, 1 H, 14-H_b), 2.52 (d, *J* = 5.9 Hz, 1 H, 6-H_a), 2.63 (m_c, 1 H, 14a-H), 2.84–2.99 (m, 1 H, 6-H_b), 3.19 (td, *J* = 12.3, 5.9 Hz, 1 H, 5-H_a), 3.70 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.53 (dd, *J* = 13.2, 7.5 Hz, 1 H, 5-H_b), 6.62 (s, 1 H, 7-H), 6.82 (s, 1 H, 10-H). ^{13}C NMR (300 MHz, DMSO): δ = 21.42 (C-13*), 22.15 (C-12*), 25.07 (C-1), 25.60 (C-2), 26.06 (C-6), 28.14 (C-14), 34.48 (C-5), 34.77 (C-14a), 39.58 (C-11), 55.32 (OCH_3), 55.89 (OCH_3), 60.99 (C-10b), 107.2 (C-10), 112.9 (C-7), 126.5 (C-6a), 135.8 (C-10a), 146.9 (C-9), 147.4 (C-8), 171.0 (C-3).
Compound **4c**: ^{1}H NMR (300 MHz, DMSO): δ = 1.28–1.48 (m, 3 H, 3-H_2, 1-H_a), 1.49–1.58 (m, 2 H, 2-H_2), 1.71–1.75 (m, 1 H, 4-H_a), 1.78–1.83 (m, 1 H, 4-H_b), 1.91–1.99, (m, 1 H, 1-H_b), 2.09–2.14 (m, 2 H, 7-H_2), 2.49–2.54 (m, 1 H, 6-H), 2.59–2.67 (m, 1 H, 11-H_a), 2.73–2.87 (m, 1 H, 11-H_b), 3.11–3.21 (m, 1 H, 10-H_a), 3.78–3.85 (m, 1 H, 10-H_b), 5.94 (s, 2 H, 18-H_2), 6.65 (s, 1 H, 17-H), 6.97 (s, 1 H, 14-H). ^{13}C NMR (300 MHz, DMSO): δ = 19.90 (C-2), 20.49 (C-3), 26.58 (C-11), 27.02 (C-1), 34.25 (C-10), 35.01 (C-4), 36.22 (C-7), 36.71 (C-6), 62.13 (C-5), 100.7 (C-18), 104.9 (C-14), 108.7 (C-17), 126.8 (C-12), 135.9 (C-13), 145.6 (C-16), 145.7 (C-15), 173.6 (C-8).
Compound **4d**: ^{1}H NMR (300 MHz, DMSO): δ = 1.20–1.35 (m, 2 H, 11-H_a, 13*-H_a), 1.35–1.52 (m, 2 H, 1-H_2), 1.50–1.80 (m, 5 H, 2-H_2, 12*-H_2, 13*-H_b), 2.04 (dd, *J* = 18.6, 6.6 Hz, 1 H, 14-H_a), 2.18–2.25 (m, 1 H, 11-H_b), 2.32–2.44 (m, 1 H, 14-H_b), 2.55–2.70 (m, 2 H, 6-H_a, 14a-H), 2.80–2.92 (m, 1 H, 6-

H_b), 3.14 (td, *J* = 11.9, 5.8 Hz, 1 H, 5-H_a), 4.52 (dd, *J* = 13.7, 7.4 Hz, 1 H, 5-H_b), 5.96 (s, 2 H, OCH_2O), 6.61 (s, 1 H, 7-H), 6.92 (s, 1-H, 10-H).^{13}C NMR (300 MHz, DMSO): δ = 21.36 (C-13*), 22.07 (C-12*), 25.05 (C-1), 25.56 (C-2), 26.53 (C-6), 28.10 (C-14), 34.22 (C-5), 34.83 (C-14a), 39.62 (C-11), 61.12 (C-10b), 100.5 (OCH_2O), 103.3 (C-10), 109.1 (C-7), 127.6 (C-6a), 137.0 (C-10a), 145.4 (C-9), 145.5 (C-8), 170.8 (C-3).

Compound **4e**: ^{1}H NMR (300 MHz, DMSO): δ = 1.48–1.64 (m, 6 H, 11-H_a, 10-H_2, 9-H_2, 8-H_a), 1.82–1.87 (m, 1 H, 11-H_b), 1.94–1.99 (m, 1 H, 8-H_b), 2.10–2.19 (m, 2 H, 4-H_a, 8a-H), 2.39–2.48 (m, 1 H, 4-H_b), 2.48–2.74 (m, 2 H, 12-H_2), 2.96 (td, *J* = 12.3, 6.7 Hz, 1 H, 5-H_a), 4.00–4.11 (qd, 1 H, *J* = 6.5, 1.3 Hz, 5-H_b), 6.85 (d, *J* = 5.4 Hz, 1 H, 3-H), 7.35 (d, *J* = 5.4 Hz, 1 H, 2-H). ^{13}C NMR (300 MHz, DMSO): δ = 19.57 (C-10), 21.00 (C-9), 24.46 (C-11), 25.10 (C-12), 33.16 (C-5), 34.43 (C-8), 34.54 (C-4), 40.33 (C-8a), 61.03 (C-12a), 122.9 (C-2), 126.9 (C-3), 132.4 (C-12b), 139.2 (C-3a), 171.0 (C-7).

Compound **4f**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35–1.61 (m, 4 H, 12-H_a, 13-H_2, 12-H_b), 1.61–1.80 (m, 4 H, 10-H_2, 9-H_a, 11-H_a), 1.84–1.94 (m, 2 H, 11-H_b), 2.03–2.09 (m, 1 H, 9a-H), 2.11–2.25 (m, 2 H, 8-H_a, 9-H_b), 2.37–2.49 (m, 1 H, 8-H_b), 2.53 (ddd, *J* = 1.0, 5.3, 16.5 Hz, 1 H, 4-H_a), 2.70 (ddd, *J* = 6.8, 11.7, 16.5 Hz, 1 H, 4-H_b), 3.16 (ddd, *J* = 5.3, 11.7, 13.3 Hz, 1 H, 5-H_a), 4.58 (ddd, *J* = 1.0, 6.8, 13.3 Hz, 1 H, 5-H_b), 6.80 (d, *J* = 5.0 Hz, 1 H, 3-H), 7.34 (d, *J* = 5.0 Hz, 1 H, 2-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.69 (C-12), 22.77 (C-10), 23.10 (C-13), 24.30 (C-4), 26.82 (C-11), 29.68 (C-8), 34.88 (C-5), 38.20 (C-9), 39.34 (C-9a), 61.27 (C-13a), 122.8 (C-2), 127.3 (C-3), 134.3 (C-3a), 142.1 (C-13b), 170.2 (C-7).

Compound **4g**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.46–1.68 (m, 6 H, 5-H_2, 6-H_2, 7-H_a, 4-H_a), 1.85–2.99 (m, 2 H, 7-H_b, 4-H_b), 2.14 (dd, *J* = 6.9, 14.0 Hz, 8-H_a), 2.21–2.29 (m, 1 H, 7a-H), 2.35 (ddd, *J* = 0.8, 8.9, 14.0 Hz, 1 H, 8-H_b), 2.70–2.86 (m, 2 H, 12-H_2), 3.01–3.11 (m, 1 H, 11-H_a), 4.09–4.16 (m, 1 H, 11-H_b), 7.18 (d, *J* = 5.3 Hz, 1 H, 3-H), 7.35 (d, *J* = 5.3 Hz, 1 H, 2-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.95 (C-5), 20.23 (C-6), 23.88 (C-12), 24.97 (C-7), 33.45 (C-11), 34.12 (C-4), 35.08 (C-8), 37.68 (C-7a), 61.10 (C-3b), 123.4 (C-2), 124.3 (C-3), 132.3 (C-12a), 140.8 (C-3a), 171.9 (C-9).

Compound **4h**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.21–1.38 (m, 1 H, 4-H_a), 1.38–1.55 (m, 4 H, 4-H_b, 8-H_2, 6-H_a), 1.55–1.68 (m, 2 H, 5-H_2), 1.68–1.78 (m, 2 H, 7-H_2), 2.09 (m_c, 1 H, 9-H_a), 2.17–2.24 (m, 1 H, 6-H_b), 2.37–2.47 (m, 2 H, 7a-H, 9-H_b), 2.63 (dd, *J* = 5.3, 16.2 Hz, 1 H, 13-H_a), 2.90 (ddd, *J* = 6.9, 11.7, 16.2 Hz, 1 H, 13-H_b), 3.23 (ddd, *J* = 5.3, 11.7, 13.2 Hz, 1 H, 12-H_a), 4.58 (dd, *J* = 6.9, 13.2 Hz, 1 H, 12-H_b), 7.00 (d, *J* = 5.4 Hz, 1 H, 3-H), 7.27 (d, *J* = 5.4 Hz, 1 H, 2-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.35 (C-4), 22.78 (C-8), 23.06 (C-13), 24.69 (C-7), 25.76 (C-5), 28.67 (C-9), 35.06 (C-12), 36.46 (C-7a), 38.31 (C-6), 61.42 (C-3b), 122.7 (C-3), 123.2 (C-2), 134.1 (C-13a), 143.21 (C-3a), 171.3 (C-10).

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