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Efficient Formal Total Synthesis of the Erythrina Alkaloid (+)-Erysotramidine, Using a Domino Process

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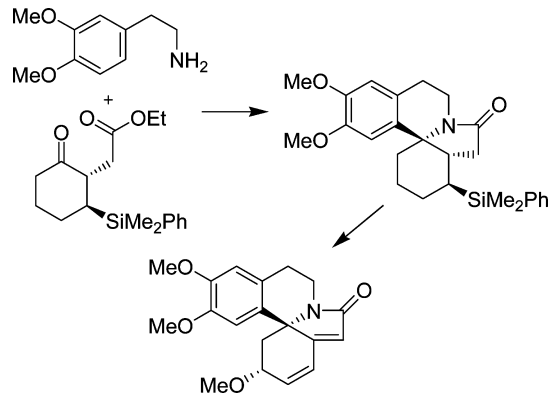
ABSTRACT



A domino process consisting of an amidation, spirocyclization, and formation of an iminium ion and electrophilic aromatic substitution of a phenylethylamine and a ketoester leads to the spirocyclic skeleton of (+)-erysotramidine, which can be further transformed into the natural alkaloid.

The erythrina alkaloids, **2** and **3**, containing the spirocyclic skeleton **1** comprise a widespread class of natural products which can be found in tropical and subtropical plants of the erythrina genus (Figure 1). They show a wide range of pharmacological effects, including sedative, hypotensive, anticonvulsive, CNS depressing, and curare-like properties.[1] Due to their biological activities and their interesting spirocyclic structure, several total syntheses of selected compounds of this family of natural products have been performed.[2] However, despite the great number of publications only a few syntheses lead to the enantiopure alkaloids.[2] Examples are the total synthesis of (+)-β-erythroidine (**2**) by Hatakeyama et al. in 2006 in 24 linear steps using a 2-fold ring-closing metathesis reaction[3]

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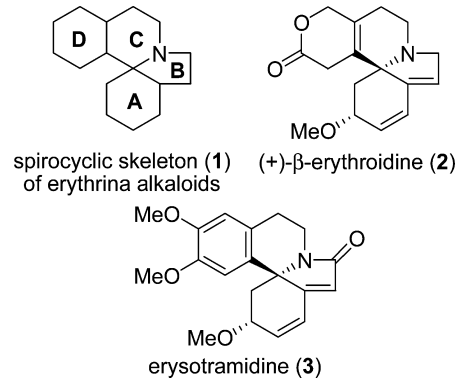


Figure 1. Erythrina alkaloids.

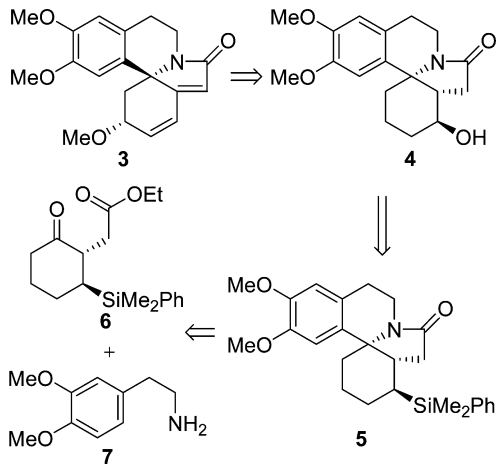
and of (+)-erysotramidine (**3**) by Simpkins et al. in 13 linear steps employing a chiral imine as intermediate.[4]

It was our goal to develop a shorter access to these alkaloids using a domino process.

Thus, the domino concept has proven to allow a highly efficient access to a wide variety of compounds with the advantage to meet the demand for an economically favorable and ecologically benign chemistry.[5,6]

Herein we describe a short and efficient synthesis of the alcohol **4**, which can be converted into (+)-erysotramidine (**3**) in four steps with a known procedure (Scheme 1).[4]

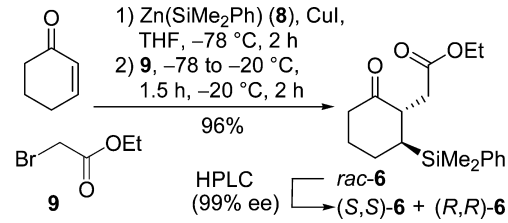
Scheme 1. Retrosynthesis of (+)-Erysotramidine (**3**) via the Alcohol **4**



The alcohol **4** can be traced back to the spirocyclic silane **5**, which can be further disconnected to the keto ester **6** and the amine **7**. Thus, according to our former investigations[7] treatment of a mixture of **6** and **7** with $AlMe_3$ in the presence of a catalytic amount of a Lewis acid should lead to **5** in a domino process consisting of an amidation, spirocyclization, formation of an iminium ion, and electrophilic aromatic substitution.

The necessary cyclohexanone derivative **6** was prepared by a conjugate addition of the silyl zincate **8**, developed by Oestreich,[8] to cyclohexenone in the presence of catalytic amounts of CuI (Scheme 2).

Scheme 2. Synthesis of (*S*,*S*)-**6** and (*R*,*R*)-**6**



The in situ generated enolate was then quenched with ethyl bromoacetate (**9**) to give the ketoester **6** in 96% yield as a single diastereomer with a 2,3-trans-orientation. So far we did not investigate an enantioselective conjugate addition, since *rac*-**7** could easily be resolved on a chiral stationary phase to give (*S*,*S*)-**6** and (*R*,*R*)-**6** with ≥99% ee. Reaction of the ketoester (*S*,*S*)-**6** with the phenylethylamine **7** with 2 equiv of $AlMe_3$ in the presence of 15 mol % of indium triflate followed by treatment with trifluoric acid led to a 4:1 mixture of the desired spirocyclic compounds **5** and **10** in 92% yield (Scheme 3). The two diastereomers could easily be separated by chromatography on silica gel. Since the absolute configuration of the enantiomeric cyclohexanone derivatives **6** was not known at the time of their usage, we also performed the domino reaction with (*R*,*R*)-**6** and compared the optical rotation of the alcohols obtained from **5** and its enantiomer with that of the known alcohol **4**. Moreover, the absolute confguration of **5** was determined by X-ray crystallography (Figure 2; see the Supporting Information for details).

As a mechanism for the domino process we presume that first an aluminum amide is formed by reaction of the amine **7** with $AlMe_3$, which then attacks the ester function exclusively to form an azaenolate. This reacts with the carbonyl moiety to give two isomeric enamines. Under treatment with TfOH the iminium ion **11** is obtained, which then undergoes an electrophilic aromatic substitution (Scheme 4).

Under the assumption that the presumed 2,3-trans-orientation at the cyclohexane moiety in the iminium ion **11** is

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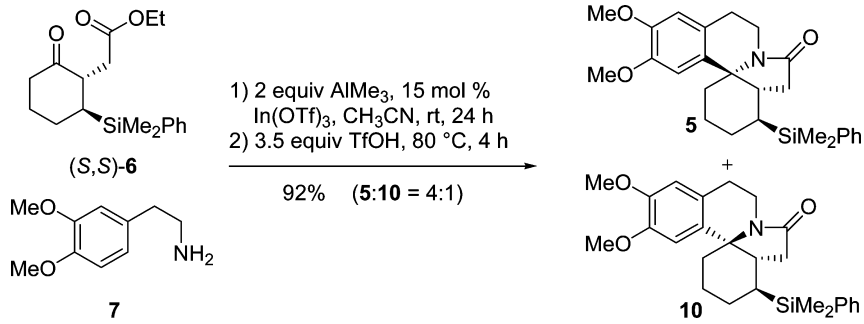
Scheme 3. Synthesis of **5** and **10**, Using a Domino Process



retained in the products, the formation of two diastereomers was expected.

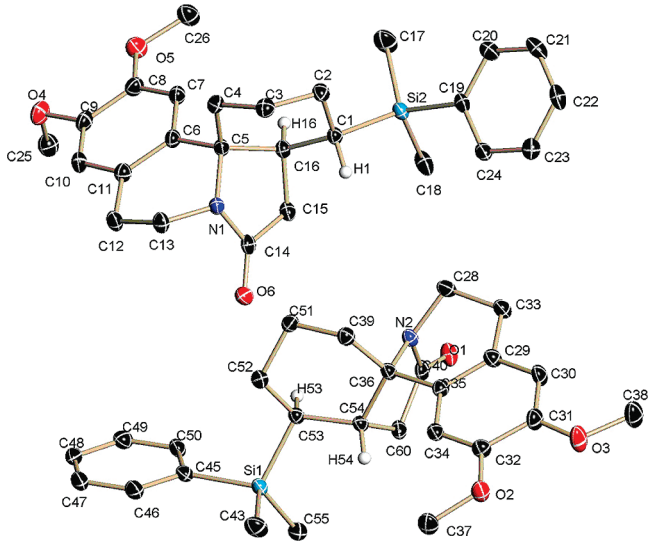
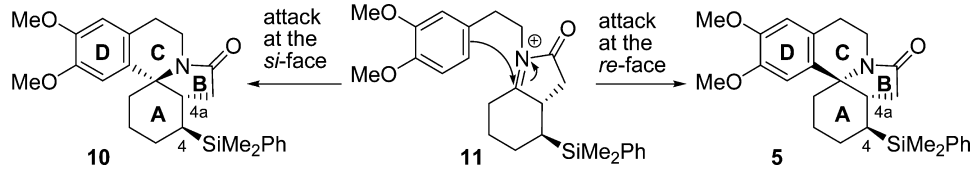


Figure 2. Structure of **5** showing the absolute configuration.

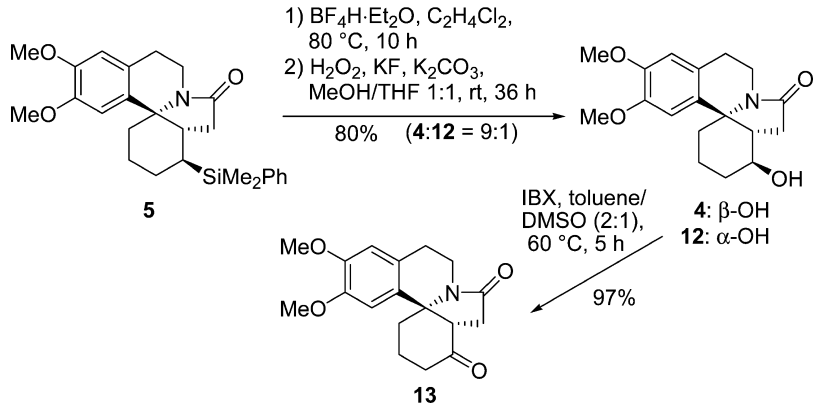
An attack from above, *anti* to the acetyl moiety (*re*-face), would lead to the cis-annelated compound **5**, which is the thermodynamically favored product (see also theoretical investigations in the Supporting Information) and the main product in the transformation (Scheme 4). The attack from below would give the thermodynamically disfavored trans-annelated compound **10**. However, we assume that the reaction proceeds under kinetic control since the difference of the ground state energies of **5** and **10** using a simplified model in the DFT calculations sums up to 29 kJ/mol, which is not in accordance with the ratio of **5** and **10** found in the experiment (for simplification, the $PhMe_2Si$ group was replaced by a Me_3Si group and the two methoxy groups were replaced by a methylenedioxo group).

As the final step for the synthesis of the alcohol **4** a Tamao−Fleming oxidation of the silane **5** was performed, using tetrafluoroboronic acid etherate at 80 °C under microwave irradiation, which is followed by oxidation of the formed fluorosilane with H_2O_2 in the presence of KF/$KHCO_3$ (Scheme 5). The reaction sequence led to a 9:1 mixture of the desired alcohol **4** and its epimer **12** in 80% yield, which could be separated by chromatography on silica gel. Performing the oxidation at a higher temperature such as 100 °C results in a slightly better yield of 83%, however, with loss of the stereointegrity of the stereogenic center at the silane moiety yielding **4** and **12** as a 1:1 mixture. Oxidation of the mixture of **4** and **12** with IBX gave the ketone **13** as a single compound, proving indeed **12** as an epimer of **4** with the opposite configuration at the carbon bearing the hydroxyl group (Scheme 5). We also performed the Tamao−Fleming oxidation of **10** to give two diastereomeric alcohols which have a different relative configuration as found in **4** and **12**, clearly showing that rings A and B in **10** are not cis-annelated. Since **4** is an intermediate in the synthesis of (+)-erysothramidine (**3**) by Simpkins et al.[4] its preparation constitutes a formal synthesis of **3** with a highly reduced number of steps.

Scheme 4. Intramolecular Electrophilic Aromatic Substitution of Iminium Ion **11** from the Two Diastereotopic Faces



Scheme 5. Tamao−Fleming Oxidation of the Silane **5**



In conclusion we have developed an effective synthesis of erysotramidine that employs two highly efficient multistep processes. With this modular approach applying different building blocks, access to a variety of analogous structures is possible.

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Supporting Information Available: Experimental procedures, spectral data, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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