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General and Efficient Strategy for Erythrinan and Homoerythrinan Alkaloids: Syntheses of (±)-3-Demethoxyerythratidinone and (±)-Erysotramidine

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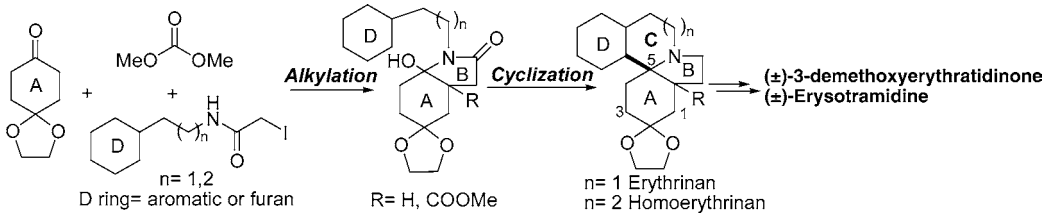
ABSTRACT



A general and efficient strategy to both aromatic-type and nonaromatic-type erythrinan and homoerythrinan alkaloids has been developed. This approach involves a key two-step sequence, an alkylation of a ketone with various N-substituted iodoacetamides followed by a *N*-acyliminium ion promoted intramolecular cyclization, and represents one of the shortest routes to erythrinan and homoerythrinan alkaloids. As the application, the formal total synthesis of (±)-3-demethoxyerythratidinone and the total synthesis of (±)-erysotramidine have been achieved, respectively.

The erythrinan and homoerythrinan alkaloids, which possess 6-5-6-*n*-membered and 6-5-7-*n*-membered (A-B-C-D) tetracyclic systems, respectively, constitute a large class of structurally diverse natural products existing widely in tropical and subtropical regions. Members of the erythrinan and homoerythrinan family, as exemplified in Figure 1, display curarelike and hypnotic activity, and a variety of pharmacological effects are associated with the erythrinane skeleton, including sedative, hypotensive, neuromuscular blocking, and CNS activity.[1] Each of these alkaloid groups is conveniently subdivided into two groups according to the structural features of their D-rings:[2] those whose D-rings are aromatic (e.g., 3-demethoxyerythratidinone **1**, erysotramidine **2**, and schelhammerine **4**) and those whose D-rings are nonaromatic (e.g., cocculolidine **3**, phellibiline **5**, and selaginaidine **6**).[3]

Because of their intriguing tetracyclic structures, wide range of biological activities, and being a proving ground for new strategies and synthetic methods, these two groups of alkaloids have been attracting considerable attention over the years. In general, recent strategies for building up the

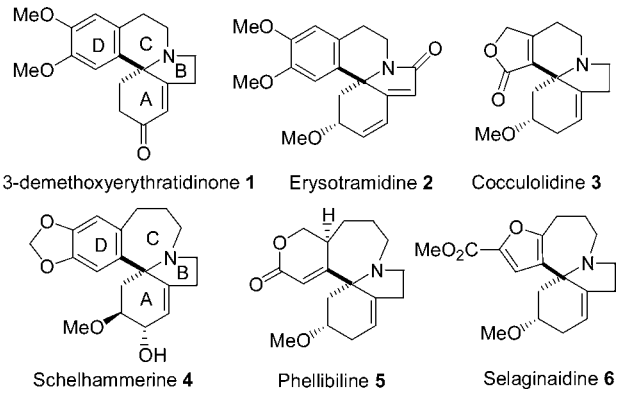


Figure 1. Representative erythrinan and homoerythrinan alkaloids.

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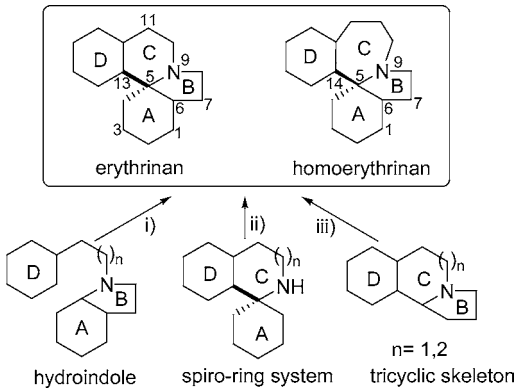
Scheme 1. Methods for the Construction of the Erythrinan and Homoerythrinan Ring System

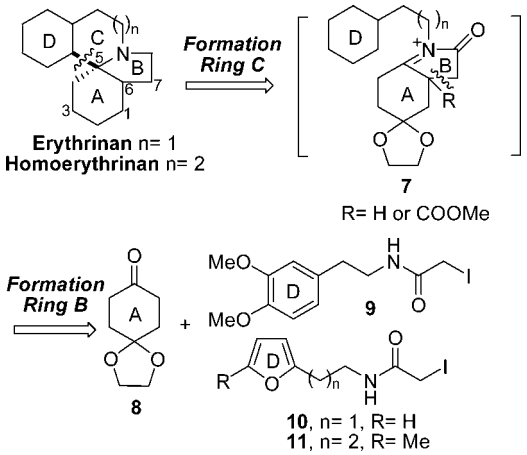


erythrinan and homoerythrinan ring system can be classified into three types (as shown in Scheme 1): (i) formation of ring C with the C-5 quaternary center being constructed by intramolecular cyclization of hydroindole;[4] (ii) formation of ring B from the C-5 spiro-ring system;[5] (iii) formation of ring A by introduction of a four-carbon unit into the tricyclic skeleton.[6] Despite the availability of some synthetic methods for erythrinan and homoerythrinan alkaloids, even more efficient and general approaches to these two groups of alkaloids are still desirable in light of the potential pharmaceutical needs.

We describe herein a highly efficient route to the basic tetracyclic system of the above two alkaloids types and its application to the syntheses of (±)-3-demethoxyerythratidinone **1** and (±)-erysotramidine **2**.

As shown in Scheme 2, our retrosynthetic considerations on the basic tetracyclic skeleton of erythrinan and homo-

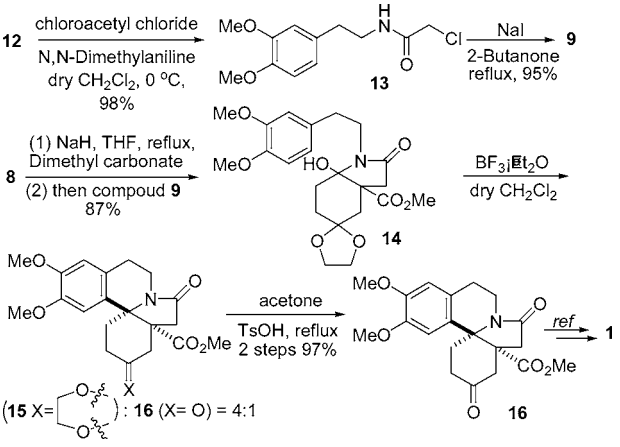
Scheme 2. Retrosynthetic Analysis of Erythrinan and Homoerythrinan Alkaloids



erythrinan were focused on the efficient establishment of ring C and B. We envisioned that ring C of both of these types of alkaloids could be available through a *N*-acyliminium ion[7] promoted intramolecur cyclization of intermediate **7**, and ring B of them could be easily achieved by means of alkylation of an enol ether of **8** with various N-substituted iodoacetamides **9**−**11**.

Initially, we selected (±)-3-demethoxyerythratidinone **1** possessing the basic structural element of interest as an optimal target to test our strategy. As shown in Scheme 3,

Scheme 3. Formal Total Synthesis of (±)-3-Demethoxyerythratidinone **1**



the synthesis commenced from β-(3,4-dimethoxy)phenethylamine **12**, which was converted to **9** in 93% overall yield via two steps involving acylation with chloroacetyl chloride and iodation of the corresponding amide with NaI in 2-butanone.[8] In turn, refluxing ketone **8** in dry THF in the presence of NaH and dimethyl carbonate led to the thermo-

(1) (a) Tanaka, H.; Tanaka, T.; Etoh, H.; Goto, S.; Terada, Y. *Heterocycles* **1999**, *51*, 2759−2764. (b) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, pp 1−98.

(2) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Vol. 48, pp 249−337.

(3) Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2001**, *42*, 8003.

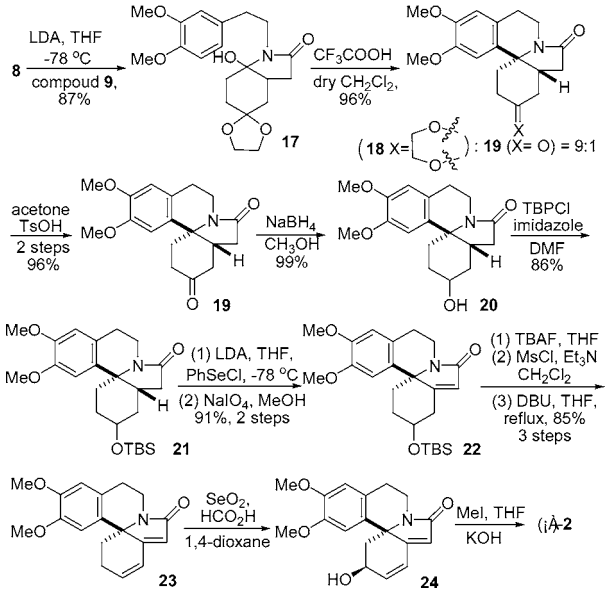
(4) (a) Wang, Q.; Padwa, A. *Org. Lett.* **2006**, *8*, 601. (b) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185. (c) Cassidy, M. P.; Özdemir, A. D.; Padwa, A. *Org. Lett.* **2005**, *7*, 1339. (d) Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067. (e) Belleau, B. *J. Am. Chem. Soc.* **1953**, *75*, 5765. (f) Mondon, A.; Hansen, K. F. *Tetrahedron Lett.* **1960**, 5. (g) Ishibashi, H.; Sato, T.; Takahashi, M.; Hayashi, M.; Ikeda, M. *Heterocycles* **1988**, *27*, 2787. (h) Tsuda, Y.; Hosoi, S.; Ishida, K.; Sangai, M. *Chem. Pharm. Bull.* **1994**, *42*, 204. (i) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995. (j) Rigby, J. H.; Deur, C.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 6887. (k) Toyao, A.; Chikaoka, S.; Takeda, Y.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Tetrahedron Lett.* **2001**, *42*, 1729. (l) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135. (m) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (n) Toda, J.; Niimura, Y.; Takeda, K.; Sano, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 906. (o) Jousse, C.; Demaële, D. *Eur. J. Org. Chem.* **1999**, 909 and references therein. (p) Parsons, A. F.; Williams, D. A. *Tetrahedron* **2000**, *56*, 7217.

(5) (a) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917. (b) Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem.* **1987**, *52*, 1478. (c) Irie, H.; Shibata, K.; Matsuno, K.; Zhang, Y. *Heterocycles* **1989**, *29*, 1033. (d) Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2001**, *42*, 8003 and references therein.

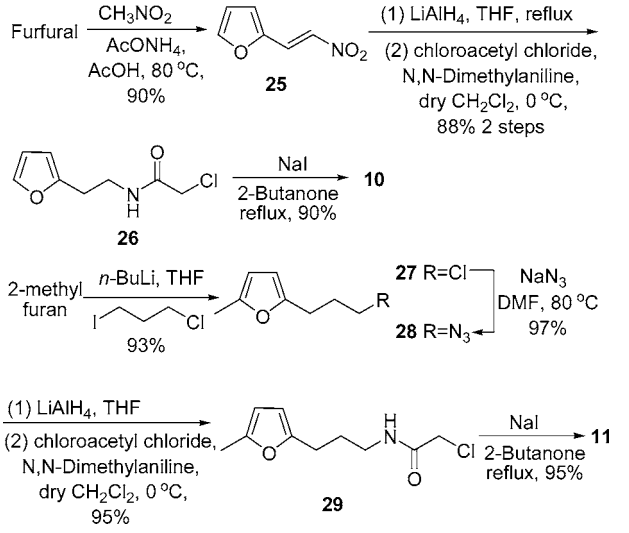
(6) (a) Wasserman, H. H.; Amici, R. M. *J. Org. Chem.* **1989**, *54*, 5843. (b) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. (c) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497 and references therein.

(7) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

Scheme 4. Total Synthesis of (±)-Erysotramidine **2**



Scheme 5. Synthesis of **10** and **11**



dynamic sodium enolates of the corresponding β-keto ester, which was quenched with compound **9**. Then, the desired *N*-arylethylhydroindole **14** with a quaternary carbon center located at the bridgehead as a single diastereoisomer[9,10] was obtained in 87% yield. With **14** in hand, the key *N*-acyliminium ion[7] promoted intramolecur cyclization was then investigated. As expected, after subjection of **14** to $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 at room temperature for 1 h, a mixture of **15** and **16** with a ratio of 4:1 was obtained, wherein the cleavage of the acetal group partly took place in the acid conditions. Deprotection of the acetal group of **15** with *p*-toluenesulfonic acid (TsOH) in acetone yielded **16**, which is the known advanced intermediate for the synthesis of **1**, and its spectral properties were in agreement with those previously reported.[4a] As far as we are aware, this two-step sequence, alkylation (formation of ring B) followed by intramolecular cyclization (formation of ring C), represents one of the shortest routes to an erythrinan derivative.

The successful formal total synthesis of (±)-3-demethoxyerythratidinone **1** encouraged us to apply and expand the strategy above to another more complex (±)-erysotramidine **2** which contains an $\alpha,\beta,\gamma,\delta$-unsaturated diene amide located at the AB ring. As shown in Scheme 4, our synthesis is started from the identical ketone **8**. Reaction of the lithium enolates of ketone **8** with **9** at −78 °C for 1 h gave the alkylation product **17** in 87% yield as a single diastereoisomer.[10] As the cyclization precursor, **17** was smoothly converted to the cis-fused tetracyclic erythrina **19** via "Mondon-type" *N*-acyliminium ion cyclization.[7] Reduction of **19** with $NaBH_4$ obtained alcohol **20** as a 10:1 mixture of diastereoisomers in 99% combined yield without isolation. The secondary hydroxyl of **20** was readily protected as its TBS ether **21**. Oxidative elimination of the corresponding phenylselenylation product of **21** with $NaIO_4$ resulted in the desired unsaturated amide **22**. Then, $\alpha,\beta,\gamma,\delta$-unsaturated diene amide **23**, which is the known intermediate for the synthesis of **2**,[4d] was achieved from **22** in 85% overall yield via three steps involving transformation of the protecting group and DBU promoted thermodynamic elimination. Finally, the total synthesis of **2** was accomplished according to the reported sequence through stereoselective allylic oxidation and the final methylation.[4d]

Having successfully synthesized two aromatic erythrinan alkaloids, (±)-3-demethoxyerythratidinone **1** and (±)-erysotramidine **2**, we turned our attention to the unaromatic-type (homo) erythrinan, whose D rings are unsaturated lactone or furan (e.g., cocculolidine **3**, phellibiline **5**, and selaginaidine **6**). We envisioned that the unsaturated lactone-type (homo) erythrinan could be available from the corresponding furan-type (homo) erythrinan according to the Tsuda protocol.[2] Accordingly, the following work was focused on the efficient construction of the furan-type (homo) erythrinan.

As shown in Scheme 5, compound **10** was achieved from furfural in 71% overall yield by the following sequence: (1) Henry reaction/dehydration, (2) reduction/acylation, and (3) iodation of the corresponding amide with NaI. Treatment of 2-methyl furan with *n*-BuLi and 1-chloro-3-iodopropane afforded **27** which was transformed into **28** with NaN_3 in dry DMF. **11** was prepared from **28** using a procedure similar to that for the installation of **9** and **10** (see details in Supporting Information).

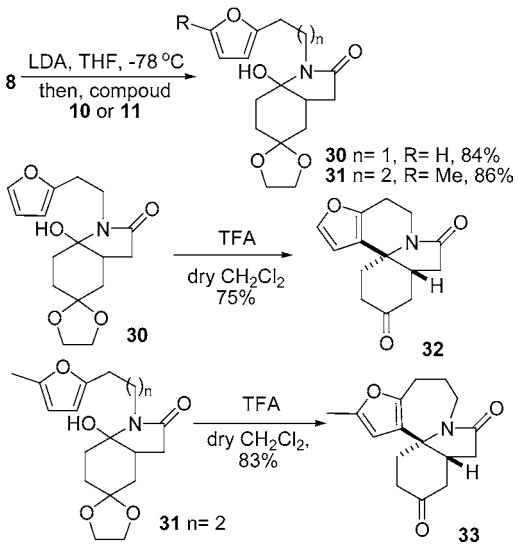
With the necessary components, N-substituted iodoacetamide **10** and **11**, in hand, we executed the alkylation and intramolecular cyclization. According to the same strategy

(8) (a) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106. (b) Dufour, M.; Gramain, J. C.; Husson, H. P.; Sinibaldi, M. E.; Troin, Y. *J. Org. Chem.* **1990**, *55*, 5483.

(9) *N*-Arylethylhydroindole **14** can also be prepared directly from β-keto ester and N-substituted iodoacetamide **9** (see details in Supporting Information).

(10) *N*-Arylethylhydroindole as only one single isomer was isolated in this transformation, and its relative configuration was not further confirmed because it was eliminated in the next step, *N*-acyliminium ion promoted intramolecur cyclization.

Scheme 6. Synthesis of Furan-Type Erythrinan **32** and Homoerythrinan **33**



as that of Scheme 4, the desired intermediates **30** and **31** can be easily obtained by the alkylation of the lithium enolate ketone **8** with **10** and **11** in 84% and 86% yield, respectively (as shown in Scheme 6).[10] In a manner similar to that previously used, compounds **30** and **31** were converted to cis-fused furan-type erythrinan **32**[2,11] and homoerythrinan **33** through Mondon-type cyclization[7] in the presence of TFA.[12] Thus, we uneventfully constructed the seven-membered C ring of compound **33** containing the similar tetracyclic furan-type skeleton with selaginaidine **6**. Because construction[13] of the homoerythrinan ring sytem is far more difficult than that of the erythrinan ring system, our further studies will focus on related homoerythrinan alkaloids and the total synthesis of **6** using a similar strategy.

In summary, we have developed a general and efficient strategy for both aromatic-type and nonaromatic-type (homo) erythrinan alkaloids. The total syntheses of (±)-3-demethoxy-erythratidinone **1** and (±)-erysotramidine **2** have been achieved. Application of this methodology to other kinds of more complex alkaloids is currently under investigation in our group.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Cis-fused furan-type erythrinan **32** has been used for the construction of the β-erythroidine skeleton as a key intermediate. See: (a) Isobe, K.; Mohri, K.; Itoh, Y.; Toyokawa, Y.; Takeda, N.; Taga, J.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2618. (b) Sano, T.; Toda, J.; Yamamoto, R.; Shoda, M.; Isobe, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2663.

(12) (a) Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, *28*, 2495. (b) Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; Mcmills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6419 and references therein.

(13) (a) Ishibashi, H.; Harada, S.; Sato, K.; Ikeda, M.; Akai, S.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5278. (b) Tsuda, Y.; Sakai, Y.; Nakai, A.; Kaneko, M.; Ishiguro, Y.; Isobe, J.; Taga, J.; Sano, T. *Chem. Pharm. Bull.* **1990**, *38*, 1462. (c) Tsuda, Y.; Ohshima, T.; Sano, T.; Toda, J. *Heterocycles* **1982**, *19*, 2053. (d) Tanaka, H.; Tamura, M.; Shibata, M.; Ito, K. *Chem. Pharm. Bull.* **1986**, *34*, 24.