A Photochemical Route for Erythrane Ring Construction

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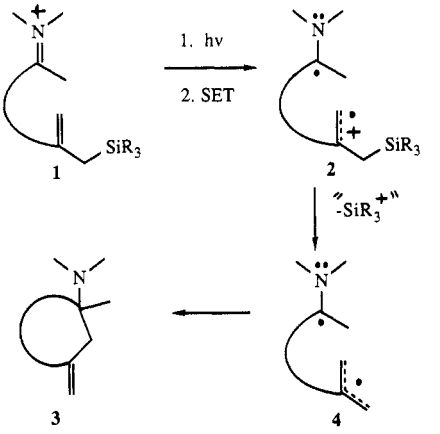
A novel strategy for synthesis of members of the erythrina alkaloid family is described. The route features an electron-transfer-induced, photocyclization process which is used to construct the spirocyclic tricyclic framework of these substances. The tricyclic intermediate **15**, generated (60%) by irradiation of the corresponding (silylalkenyl)-3,4-dihydroisoquinolinium perchlorate **14**, is transformed to the tetracyclic dione **17** or ketone **26** by use of respective Claisen and alkylation–cyclization processes. The methodology is demonstrated by its application to the synthesis of the known 15,16-dimethoxy-*cis*-erythrinan **27**.

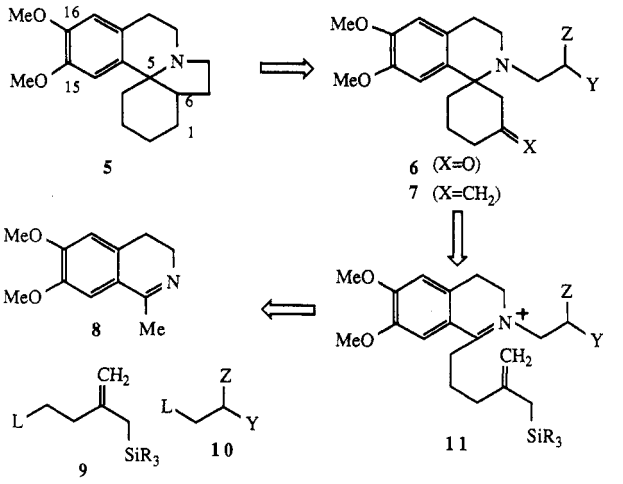
In previous reports,[1,2] we have described the electron-transfer photochemistry of the iminium salt–allylsilane and –benzylsilane systems. In addition, we have shown how intramolecular reactions of these systems which proceed via the intermediacy of 1,*n*-diradicals serve as reasonably efficient methods for N-heterocyclic and carbocyclic ring construction.[3] An example of how this process can be applied to carbocyclic ring synthesis is outlined in Scheme I. Thus, irradiation of an appropriately substituted, *C*-(silylalkenyl)–iminium salt **1** would lead to generation of the corresponding nitrogen-substituted carbocycle **3** via a mechanistic pathway involving excited-state electron transfer, cation diradical **2** desilylation, and 1,*n*-diradical **4** cyclization.

The reasonably high efficiencies of intramolecular processes following sequential electron-transfer–desilylation pathways along with their unique structural and functional outcome suggested that methodology based upon this chemistry would find applications in the area of alkaloid synthesis.[3] As part of a program designed to explore this feature, we have recently investigated a novel erythrina alkaloid synthetic strategy that is based upon electron-transfer photochemical methods for formation of the key spirocyclic skeleton of members of this family of compounds.[4] The general strategy incorporating this methodology and targeted at the 15,16-dimethoxyerythrinanes is outlined in Scheme II. We anticipated that construction of the substituted (silylalkenyl)dihydroisoquinolinium perchlorate **11** would be readily accomplished by C-alkylation of the 1-methyldihydroisoquinoline **8** anion with an appropriate silylalkenyl substrate **9** followed by N-alkylation with a two-carbon unit (**10**). Photocyclization to produce the spirocyclic center in **7** would then be followed by pyrrolidine D-ring installation. The enolate of the C-1 ketone **6** would be used for this purpose.

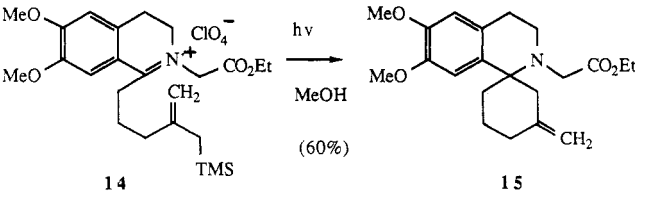
Scheme I



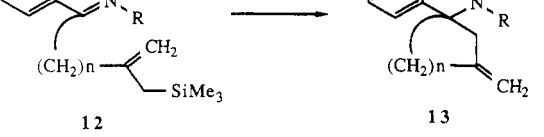
Scheme II



Scheme III



In recent efforts, we have investigated the photochemistry of a series of 1-(silylalkenyl)-3,4-dihydroisoquinolinium perchlorates **12**.[3c] These model studies



(1) Ohga, K. Mariano, P. S. *J. Am. Chem. Soc.* **1982**, *104*, 617. Ohga, K.; Yoon, U. C.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 213.

(2) Lan, A.; Quillen, S. L.; Heuckeroth, R. O.; Mariano, P. S. *J. Am. Chem. Soc.* **1984**, *106*, 6439.

(3) (a) Chiu, F. T.; Ullrich, J. W.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 228. (b) Ho, G. D.; Lan, A.; Mariano, P. S. *Tetrahedron Lett.* **1985**, *26*, 5867. (c) Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem.* **1985**, *50*, 5667.

(4) (a) For general review of erythrina alkaloid synthetic approaches, see: Manske, R. H. F. *Alkaloids*; Academic Press: New York, 1967; Vol. X, Chapter 12, p 483. Reference 4a, 1960, Vol. VII, Chapter 11, p 201. Reference 4a, 1960, Vol. II, Chapter 14, p 499. (b) Several more recent synthetic approaches are described: Haruna, M.; Ito, K. *J. Chem. Soc., Chem. Commun.* **1976**, 345. Mondon, A.; Nestler, N. *J. Angew. Chem.* **1964**, *76*, 651. Tsuda, Y.; Sakai, Y.; Kaneko, M.; Akiyama, K. *Heterocycles* **1981**, *16*, 921. Ito, K.; Suzuki, F.; Haruna, M. *J. Chem. Soc., Chem. Commun.* **1978**, 733. Sano T.; Toda, J.; Tsuda, Y. *Heterocycles* **1982**, *18*, 229. Sano, T.; Toda, J.; Kashiwaba, K.; Tsuda, Y.; Iitaka, Y. *Heterocycles* **1981**, *16*, 1151.

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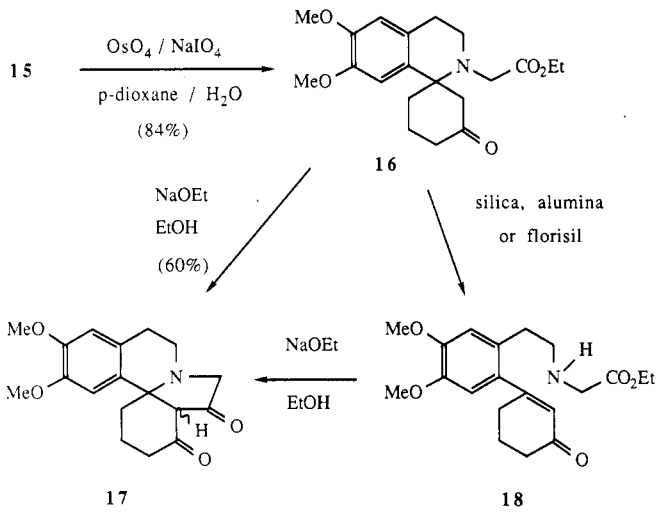
Scheme IV

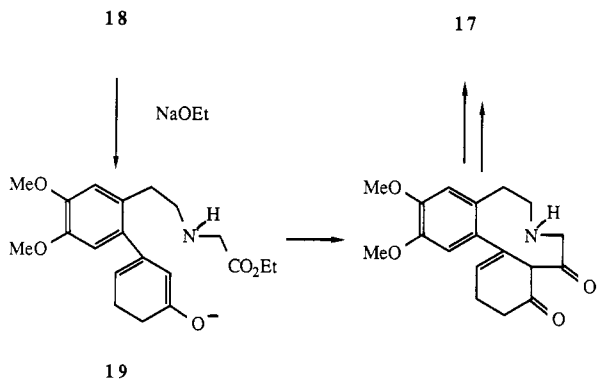


demonstrated that formation of the spirocyclic products **13** occurs upon irradiation of these salts in variable yields which depend upon the nature of the nitrogen substituents, alkenyl side-chain length, and medium polarity. In this publication, we describe the results of continuing investigations in this area which shown that the strategy outlined in Scheme II serves as the basis for a reasonably efficient method for construction of the erythrina alkaloid tetracyclic skeleton.

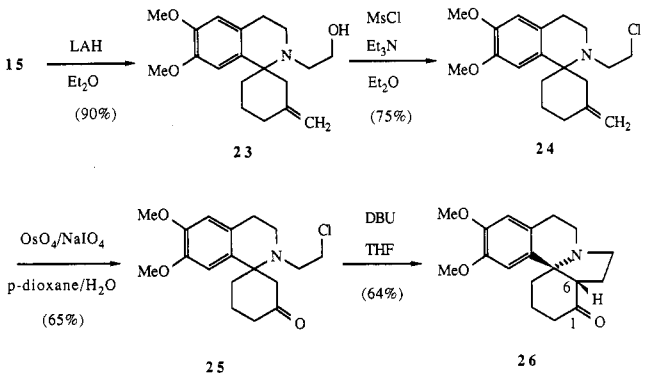
The key tricylcic intermediate **15** employed in this synthetic approach to the dimethoxyerythrinan skeleton was prepared by a route described earlier[3c] involving photospirocyclization of the (silylalkenyl)dihydroisoquinolinium perchlorate **14** (Scheme III). The photocyclization reaction is conducted by irradiation of **14** at wavelengths greater than 310 nm (flint glass filter) in methanol. Isolation of the tricyclic product **15** is by silica gel chromatography. The yield of this process is 60% even when the photoreactions are conducted on modestly large (ca. 1.0 g) scales.[5]

Three closely related approaches for pyrrolidine D-ring formation starting with the spirocyclic amino ester **15** have been investigated. The first methodology involves Claisen cyclization of the keto ester **16** (Scheme IV). Liberation of the C-1 ketone function was accomplished by oxidative cleavage of the exocyclic methylene function of **15**. The keto ester **16** obtained by this procedure is a reasonably unstable substance which undergoes elimination to produce the enone **18** when subjected to a variety of chromatographic purification conditions. However, this material of ca. 90% purity can be used without purification. Treatment of **16** with sodium ethoxide in ethanol induces Claisen cyclization to produce the tetracyclic β-diketone **17**. Interestingly, this substance, which has the erythrinan skeleton in place, exists in deuteriochloroform solution in its diketone rather than enolic form and as an ca. 1:1 mixture of cis and trans, CD-hydroindole ring stereoisomers. Moreover, the diketone **17** can be generated starting with the enone **18** by treatment with sodium ethoxide. This suggests that enone **18** exists in equilibrium with the tricyclic form **16** under basic conditions or that **18** undergoes direct conversion to **17** by a pathway involving intramolecular α-acylation of the dienolate anion **19** followed by π-bond migration and Michael addition of the internal amine (Scheme V).

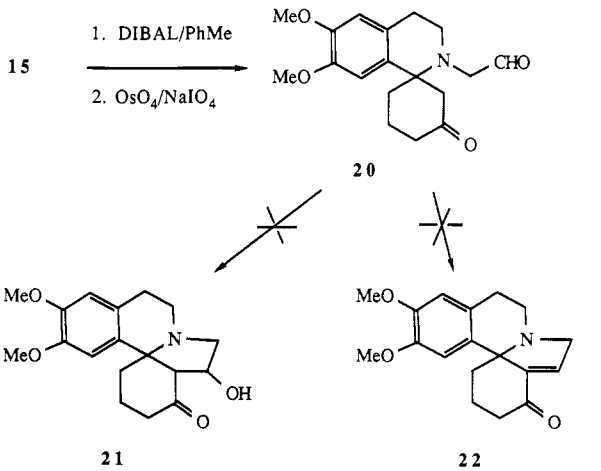
Scheme V



Scheme VI



An alternative methodology based upon Aldol cyclization of the keto aldehyde **20** proved unsuccessful. Thus, **20** can be produced from **15** by DIBAL reduction and oxidative cleavage. However, it does not undergo cyclization to generate the hydroxy ketone **21** or tetracyclic enone **22** when subjected to basic (KO-*t*-Bu/HO-*t*-Bu) conditions normally used for intramolecular Aldol processes.

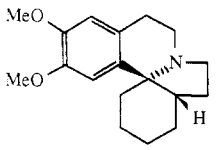


Pyrrolidine D-ring formation can be achieved through intramolecular alkylation of the C-1 ketone enolate. The chloro ketone **25** required for this purpose is produced starting with the tricyclic amino ester **15** by the sequence outlined in Scheme VI). Reduction (LAH) of **15** generates the corresponding alcohol **23** which is transformed to the chloro compound **24** directly by treatment with methanesulfonyl chloride and triethylamine. This unusual process is most probably the result of a facile chloride displacement of the intermediate mesylate assisted by the β-amine function. Oxidative cleavage then liberates the C-1 ketone function in **25**. Cyclization to introduce the pyrrolidine D ring is conveniently performed by use of

(5) In principle, this process can be run on an even larger scale than this. This photoreaction also produces a minor tetracyclic product described previouisly[3c] which requires that separation be performed to obtain the desired tricyclic product in pure form.

DBU. This furnishes the tetracyclic ketone **26** as a single diastereomer which has been identified as having the *cis*-erythrinone stereochemistry shown on the basis of characteristic ^{1}H NMR spectroscopic data and its transformation to the known 15,16-dimethoxy-*cis*-erythrinane **27**[6] as described below.

Information about the stereochemistry of **26** initially derived from a comparison of the aromatic proton region of the ^{1}H NMR spectra of **26** with those of other *cis*- and *trans*-15,16-dimethoxyerythrinanes. Particularly informative was the close match for the arene proton (H-14 and H-17) chemical shifts in **26** (6.58 and 6.51 ppm) and 15,16-dimethoxy-*cis*-erythrinan (**27**) (6.71 and 6.51 ppm)



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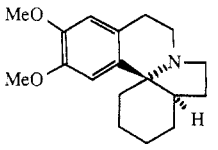

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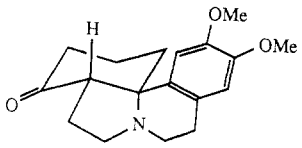
as compared to those for the corresponding trans isomer (**28**) (6.63 and 7.18 ppm).[6] In addition, the conditions under which the tetracyclic ketone **26** is produced should cause epimerization at the α-carbonyl C-6 center. Molecular mechanics calculations[7] on the epimeric ketones **26** and **29** indicate in a convincing fashion that the cis isomer **26** is more stable by 3.5 kcal/mol. This large difference can be easily rationalized on the basis of the normal energetic preferences for cis rather than trans hydroindole ring systems found in the respective stereoisomers **26** and **29**. More importantly, a sterically unfavorable 1,3-diaxial interaction exists in **29** as a result of the axially oriented hydroisoquinoline aromatic ring.



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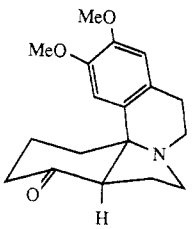

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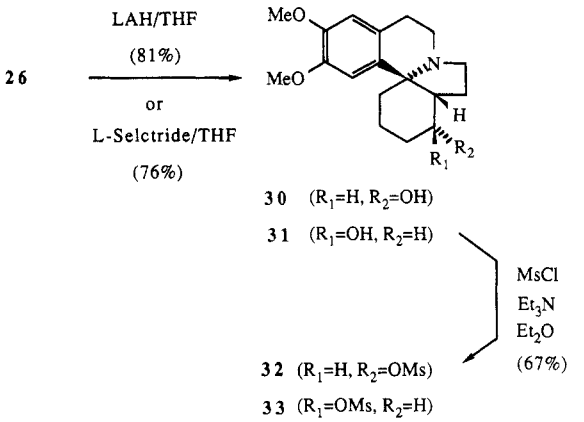
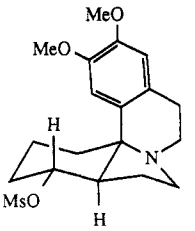
An unambiguous stereochemical assignment along with a confirmation of the utility of the synthetic strategy were both accomplished by transformation of the tetracyclic ketone **26** to the known,[6] 15,16-dimethoxy-*cis*-erythrinan. Thus, reduction of **26** with $LiAlH_4$ provided the alcohols **30** and **31** as a 2.3:1 mixture of the respective diastereomers. The major isomer formed in this process is assigned the α-hydroxyl stereochemistry depicted in **30** since this is the expected result hydride delivery from the least sterically encumbered face of the carbonyl function of **26**. Consistent with this is the observation that reaction of **26** with the more bulky reducing agent, L-Selectride (Aldrich), provides the α-alcohol **30** exclusively. These stereochemical assignments to **30** and **31** were confirmed by ^{1}H NMR analysis of the methanesulfonate esters **32** and **33**, derived by treatment with methanesulfonyl chloride. The methine hydrogens at C-1 in **32** and **33** appear at 5.34 ppm (dt, 8.4 and 5.8 Hz) and 4.79 ppm (td, 9.2 and 5.9 Hz), respectively. These data are in accord with the relative stereochemical assignments made and the existence of the esters in the





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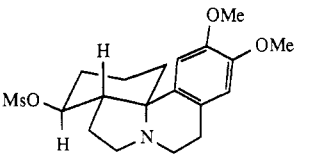

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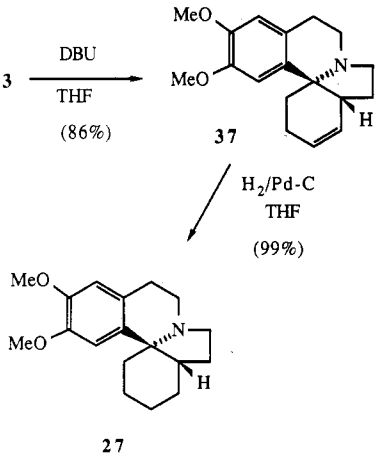
respective conformations **34** and **35** depicted below. Accordingly, the greater downfield shift of the methine H-1 hydrogen in the spectrum of **32** is a result of its existence in the deshielding region of the axial aryl grouping. In addition, the deviation of the observed coupling constants from those normally expected for vicinally related cyclohexane ring protons suggests that both isomers have slightly distorted six-membered C rings.

Attempts to transform the methanesulfonates **32** and **33** directly to the corresponding erythrinan **27** by $LiAlH_4$ reduction were unsuccessful. In each case, the reaction led to regeneration of the respective alcohol **30** or **31** with complete retention of configuration at the C-1 centers. These results while unanticipated are not without precedent since it has been reported that sterically crowded sulfonate esters often undergo hydride reduction via cleavage of the oxygen–sulfur bond.[8]

An alternate route to the erythrinan **26** was then developed. Elimination of the methanesulfonates **32** and **33** by treatment with DBU gave a single olefin characterized as the erythrin-2-ene **37**.[9] Catalytic hydrogenation of **37** produced the reduced material, 15,16-dimethoxy-*cis*-erythrinan (**27**) having identical spectroscopic properties with those obtained on a sample of this substance prepared earlier by a different route and kindly supplied to us by Professor Albert Mondon. Importantly, the ^{1}H NMR spectroscopic data for **27** are markedly different from those reported for the corresponding trans isomer **28**, thus, confirming the *CD-cis*-indolizidine stereochemical assignments made to the tetracyclic ketone **26** and other intermediates in the synthetic pathway.

In summary, the strategy outlined in Scheme II based upon an electron-transfer-induced spirocyclization methodology appears to represent a novel method for constructing the tetracyclic skeleton common to members of

(6) Mondon, A.; Seidel, P. R. *Chem. Ber.* **1971**, *104*, 2937.
(7) (a) Calculations were performed by using the Allinger MMP2 molecular mechanics program.[7b] The calculated heats of formation of **26** and **29** are 68.5 kcal/mol and 72.0 kcal/mol, respectively. (b) Allinger, N. L.; Flanogan, H. L. *J. Comput. Chem.* **1983**, *4*, 399.
(8) Strating, J.; Bache, H. J. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 638.
(9) Mondon, A.; Zander, J.; Menz, H. U. *Liebigs Ann. Chem.* **1963**, *667*, 126.



the erythrina alkaloid family. In addition, the ability to incorporate functionality in the C and D ring systems suggests that this strategy might be applicable for generation of more highly functionalized substances in this class of alkaloids.

Experimental Section

General Procedures. ^1H NMR spectra were recorded on $CDCl_3$ solutions by using Varian EM-360 or IMB WP-200 (FT) spectrometers. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. For compounds containing trimethylsilyl groupings, $CHCl_3$ was employed as an internal standard. ^{13}C NMR spectra were recorded on $CDCl_3$ solutions with the IBM WP-200 spectrometer. Chemical shifts are recorded in ppm relative to tetramethylsilane or $CHCl_3$ as internal standards. Multiplicities (q, CH_3; t, CH_2; d, CH; s, C) are assigned on the basis on INEPT results. Infrared spectra were taken on a Perkin-Elmer spectrometer. A GCA McPherson EU-700-56 spectrometer was used to record ultraviolet spectra. Drying of organic layers obtained by workup of reaction mixtures was by treatment with anhydrous sodium sulfate. Column chromatography was performed with either Florisil (100–200 mesh) or silica gel (220–400 mesh) as absorbent. All reactions were carried out under a N_2 atmosphere. Mass spectrometric analysis was accomplished by using a low resolution Hitachi RMU-6E and a high resolution VG-7700 instrument. Yields and spectroscopic data are reported on materials of >95% purity (by ^1H and ^{13}C NMR). All materials identified below were oils.

Tricyclic Keto Ester 16 and Enone 18. A solution of the tricyclic photoproduct **15**[3c] (124 mg, 0.35 mmol) and osmium tetraoxide (10 mg, 0.039 mmol) in 2 mL of dioxane and 2 mL of water was stirred at 25 °C for 20 min. Sodium periodate (240 mg, 1.12 mmol) was next added slowly over a 30-min period. This mixture was then stirred at 25 °C for 3 h by which time the initially dark reaction mixture changed to pale yellow in color. Ether was then added and the product mixture washed with saturated sodium bicarbonate solution. The ethereal extracts were dried over sodium sulfate and concentrated in vacuo, yielding 105 mg (84%) of the desired ketone **16**: ^1H NMR δ 1.20 (t, 3 H, OCH_2CH_3), 1.73–3.39 (m, 14 H), 3.86 (s, 6 H, C-6- and C-7-OCH_3), 4.11 (q, 2 H, OCH_2CH_3), 6.54 (s, 1 H, C-5-CH), 6.58 (s, 1 H, C-8-CH); ^{13}C NMR 14.2 (q, OCH_2CH_3), 20.7 (t, C-5′), 21.7 (t, C-6′), 36.1 (t, C-4), 40.3 (t, C-4′), 41.7 (t, C-3), 49.3 (t, CH_2CO_2Et), 51.6 (t, C-1′), 55.9 (q, C-7-OCH_3), 56.3 (q, C-6-OCH_3), 60.5 (t, $CO_2CH_2CH_3$), 62.5 (s, C-1), 109.0 (d, C-5), 112.5 (d, C-8), 126.0 (s, c-9), 132.5 (s, C-10), 147.5 (s, C-78), 148.1 (s, C-6), 171.4 (s, CO_2Et), 209.6 ppm (s, carbonyl); IR ($CHCl_3$) 3020, 1720, 1610, 1515, 1210 cm^{-1}.

Attempt to purify spirocyclic ketone **16** by column chromatography (Florisil and alumina) resulted in its rearrangement to cyclohexenone **18**: ^1H NMR δ 1.29 (t, 3 H, OCH_2CH_3), 1.92 (s, 1 H, NH), 2.18 (m, 2 H, β-CH_2 of cyclohexenone), 2.50 (t, 2 H, α-CH_2 of cyclohexenone), 2.59 (t, 2 H, $ArCH_2$), 2.68–2.88 (m, 4 H, δ-CH_2 of cyclohexenone and $ArCH_2CH_2$), 3.40 (s, 2 H, $CH_2CO_2CH2CH_3$), 3.88 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.17 (q, 2 H, OCH_2CH_3), 6.00 (s, 1 H, vinyl CH), 6.58 (s, 1 H), 6.77 (s, 1 H); ^{13}C NMR 14.0 (q, CH_3), 23.0 (t, β-CH_2 of cyclohexenone), 31.8 (t, $ArCH_2$), 33.2 (t, α-CH_2 of cyclohexenone), 37.0 (t, δ-CH_2 of cyclohexenone), 50.5 (t, $ArCH_2CH_2$), 50.6 (t, CH_2CO_2Et), 55.7 (m, OCH_3's), 60.5 (t, $CO_2CH_2CH_3$), 110.5 and 112.7 (m, Ar CH), 128.1 and 133.0 (s's, Ar C's), 128.8 (s, vinyl CH), 147.1 and 148.8 (s's, Ar C's), 163.0 (s, vinyl), 172.0 (s, $CO_2CH_2CH_3$), 199.1 ppm (s, carbonyl C); IR ($CHCl_3$) 2940, 1730, 1660 cm^{-1}; mass spectrum, *m/e* (rel intensity) 361 (M^+, 40), 360, M^+ – H, 15), 318 (40), 288 (50), 247 (50), 246 (100), 218 (60); high resolution mass spectrum, *m/e* 361.1854 ($C_{20}H_{27}NO_5$ requires 361.1867).

15,16-Dimethoxyerythrinan-1,7-dione (17). An ethanol solution of sodium ethoxide (0.32 mL of a 1.06 M solution, 0.34 mmol) was added to a 0 °C solution of keto ester **16** (109 mg, 0.30 mmol) in 10 mL of ethanol. This mixture was stirred at 0 °C for 4 h. Ice water was added to the reaction mixture which was extracted with ether. The aqueous layer was acidified with a 10% H_3PO_4 until the pH was 7. The product was extracted with $CHCl_3$. Drying and concentration in vacuo yielded 57 mg (60%) of isomeric mixture of 5,6-cis- and 5,6-trans diketones **17**: ^1H NMR of mixture δ 1.88–3.52 (m, 11 H), 3.567–3.84 (m, 8 H), 6.44–6.62 (q, 4 H); ^{13}C NMR cis isomer 20.1 (t, C-3), 21.0 (t, C-4), 33.6 (t, C-11), 39.4 (t, C-2), 40.0 (t, C-10), 55.1 (t, C-8), 55.8 (q, C-15-OCH_3), 56.1 (q, C-16-OCH_3), 66.8 (s, C-5), 68.0 (d, C-6), 109.5 (d, C-17), 112.0 (d, C-14), 125.3 (s, C-12), 130.5 (s, C-13), 147.90 (s, C-15), 148.3 (s, C-16), 203.6 (s, C-1), 205.9 ppm (s, C-7); trans isomer 17.9 (t, C-3), 22.5 (t, C-4), 29.6 (t, C-11), 35.6 (t, C-2), 42.1 (t, C-10), 55.1 (t, C-8), 55.8 (q, C-15-OCH_3), 56.1 (q, C-16-OCH_3), 66.8 (s, C-1), 68.0 (d, C-6), 111.7 (d, C-17), 112.3 (d, C-14), 125.3 (s, C-12), 130.2 (s, C-13), 146.9 (s, C-15), 148.3 (s, C-16), 203.6 (s, C-1), 205.9 ppm (s, C-7); IR ($CHCl_3$) 3000, 2940, 1760, 1690, 1600–1640, 1510, 1460, 1200–1250 cm^{-1}; mass spectrum, *m/e* (rel intensity) 315 (M^+, 45), 300 (10), 287 (25), 272 (50), 174 (85), 160 (100); high resolution mass spectrum, *m/e* 315.1343 ($C_{18}H_{21}NO_4$ requires 315.1426).

Tricyclic Olefin Alcohol 23. A solution of the tricyclic keto ester **15** (257 mg, 0.72 mmol) in 50 mL of ether was added to a solution of $LiAlH_4$ (54 mg, 1.42 mmol) in 100 mL of ether at 0 °C. After addition, the reaction mixture was stirred at 25 °C for 1 h, cooled to 0 °C, and quenched with aqueous Na_2SO_4. Filtration of the formed crystalline precipitate through celite gave an etheral filtrate which was washed with water, aqueous NaCl, and dried. Concentration in vacuo yielded 206 mg (91%) of the desired alcohol **23**: ^1H NMR δ 1.64–2.74 (m, 12 H), 3.16 (t, 2 H, C-3 CH_2), 3.62 (t, 2 H, CH_2OH), 3.82 (s, 6 H, OCH_3), 4.70–4.82 (d, 2 H, vinyl), 6.55 (s, 1 H, C-5 CH), 6.84 (s, 1 H, C-8 CH); ^{13}C NMR 21.9 (m, C-5′ and C-6′), 34.0 (t, C-4), 36.1 (t, CH_2CH_2OH), 38.2 (t, C-4′), 44.7 (t, C-3), 45.4 (t, C-1′), 55.7 (q, C-7 -OCH_3), 55.9 (t, C-6 -OCH_3), 58.3 (t, CH_2OH), 59.1 (s, C-1), 108.8 (d, C-5), 109.6 (t, vinyl CH_2), 111.8 (d, C-8), 126.0 (s, C-9), 134.8 (s, C-10), 146.3 (s, vinyl C), 147.0 (s, C-7), 147.4 ppm (s, C-6); IR ($CHCl_3$) 3220–3800, 3000, 2940, 1610, 1510, 1220 cm^{-1}; mass spectrum, *m/e* (rel intensity) 317 (M^+, 35), 316 (20), 302 (10), 262 (100), 174 (50), 160 (70); high resolution mass spectrum, *m/e* 317.1980 ($C_{19}H_{27}NO_3$ requires 317.1991).

Tricyclic Chloride 24. Triethylamine (123 mg, 1.22 mmol) and methanesulfonyl chloride (138 mg, 1.20 mmol) was added to a 25 °C solution of alcohol **23** (263 mg, 0.83 mmol) in 50 mL of ether. This mixture was stirred at 25 °C for 16 h, poured into water, and extracted with ether. The ether extracts were dried, concentrated in vacuo, and subjected to purification on flash silica column chromatography (100% $CHCl_3$) to yield 209 mg (57%) of the desired chloride **24**: ^1H NMR δ 1.51–3.47 (m, 14 H), 3.51–3.78 (t, 2 H, CH_2Cl), 3.83 (s, 6 H, C-6- and C-7-OCH_3), 4.71–4.81 (d, 2 H, vinyl CH_2), 6.56 (s, 1 H, C-5-CH), 6.87 (s, 1 H, C-8-CH); ^{13}C NMR 22.2 (t, C-5′), 22.6 (t, C-6′), 34.2 (t, C-4), 36.6 (t, C-4′), 41.3 (t, CH_2CH_2Cl), 43.0 (t, CH_2Cl), 44.5 (t, C-3), 49.0 (t, C-1′), 55.9 (q, C-7-OCH_3), 56.2 (q, C-6-OCH_3), 59.9 (s, C-1), 109.1 (d, C-5), 109.2 (t, vinyl CH_2), 112.4 (d, C-8), 126.3 (s, C-9), 135.3 (s, C-10), 147.0 (d, vinyl and C-7, 147.5 ppm (s, C-6); IR ($CHCl_3$) 3000, 2940, 1510, 1200 cm^{-1}; mass spectrum, *m/e* (rel intensity) 337 (M^+ + 2, 7), 335 (M^+, 21), 334 (14), 280 (100), 272 (13); high resolution mass spectrum, *m/e* 335.1642 ($C_{19}H_{26}NO_2Cl$ requires 335.1645).

Tricyclic Chloro Ketone 25. A solution of the chloride **24** (200 mg, 0.657 mmol) and osmium tetraoxide (0.31 mL of a 4% by wt solution in water, 12 mg, 0.47 mmol) in 6 mL of dioxane and 2 mL of water was stirred at 25 °C for 20 min. Sodium periodate (295 mg, 1.38 mmol) was next added slowly over a 0.5-h

period. This mixture was then stirred at 25 °C for 2 h 15 min, by which time the initially dark reaction changed to pale yellow in color. Water was then added and the product mixture extracted with ether. The ethereal extracts were dried and concentrated in vacuo, yielding 145 mg (65%) of the desired chloro ketone **25**: ^{1}H NMR δ 2.02–2.82 (m, H), 3.18 (t, 2 H, C-3-CH_2), 3.48 (t, 2 H, CH_2Cl), 2.83 (s, 6 H, C-6 and C-7-OCH_3), 6.56 (s, 1 H, C-5-CH), 6.62 (s, 1 H, C-8-CH); ^{13}C NMR 20.7 (t, C-5′), 21.9 (t, C-6′), 36.1 (t, C-4), 40.4 (t, C-4′), 40.9 (t, CH_2CH_2Cl), 42.4 (t, CH_2Cl), 48.6 (t, C-3), 51.4 (t, C-1′), 55.9 (q, C-7-OCH_3), 56.3 (q, C-6-OCH_3), 62.8 (s, C-1), 108.8 (d, C-5), 112.6 (d, C-8), 126.0 (s, C-9), 132.9 (s, C-10), 147.5 (s, C-7), 148.1 (s, C-6), 209.9 (s, carbonyl); IR ($CHCl_3$) 2940, 1705, 1505, 1460, 1250 cm^{-1}; mass spectrum, *m/e* (rel intensity) 339 (M^+ + 2, 4), 337 (M^+, 12), 322 (6), 309 (10), 302 (100); high resolution mass spectrum, *m/e* 337.1436 ($C_{18}H_{24}NO_3Cl$ requires 337.1445).

15,16-Dimethoxy-*cis*-erythrinan-1-one (26). Diazobicycloundecene (254 mg, 1.67 mmol) was added to a solution of chloro ketone **25** (287 mg, 0.850 mmol) in 15 mL of anhydrous THF. This mixture was warmed to 60 °C, stirred for 4 h, poured into water, and extracted with ether. The ethereal extracts were dried, concentrated in vacuo, and subjected to Florisil column chromatography (100% $CHCl_3$ to 3% MeOH in $CHCl_3$) to yield 163 mg (64%) of the desired ketone **26**: ^{1}H NMR δ 1.48–3.17 (m, 15 H), 3.83 (d, 6 H), 6.51 (s, 1 H), 6.58 (s, 1 H); ^{13}C NMR 20.7 (t, C-3), 21.5 (t, C-4), 32.7 (t, C-7), 35.6 (t, C-11), 40.1 (t, C-2), 40.9 (t, C-8), 47.1 (t, C-10), 55.9 (q, C-15-OCH_3), 56.3 (q, C-16-OCH_3), 57.7 (d, C-6), 109.5 (d, C-17), 112.0 (d, C-14), 126.4 (s, C-12), 133.8 (s, C-13), 147.8 (s's, C-15 and C-16), 211.3 ppm (s, C-1); IR ($CHCl_3$) 2940, 1705, 1605, 1505, 1460, 1250, 1130 cm^{-1}; mass spectrum, *m/e* (rel intensity) 301 (M^+, 30), 270 (15), 258 (15), 231 (70), 166 (65), 126 (100), 113 (100); high resolution mass spectrum, *m/e* 301.1704 ($C_{18}H_{23}NO_3$ requires 301.1678).

15,16-Dimethoxy-*cis*-erythrinan-1-ols 30 and 31. A solution of tetracyclic ketone **26** (60 mg, 0.20 mmol) in 15 mL of anhydrous THF was added to a solution of $LiAlH_4$ (15 mg, 0.40 mmol) in 15 mL of anhydrous THF at 0 °C. After addition, the reaction mixture was stirred at 25 °C for 2 h, cooled to 0 °C, and quenched with aqueous Na_2SO_4. Filtration (with ether) of the formed crystalline precipitate through Celite gave a filtrate which was washed with water and dried. Concentration in vacuo yielded 49 mg (81%) of the desired alcohols **30** and **31** in a 3.2:1 ratio (by NMR): ^{1}H NMR δ 1.24–3.29 (m, 15 H), 3.73 (t, 1 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 6.48 (s, 1 H), 5.58 and 6.67 (two s, 1 H); ^{13}C NMR isomer **30** 14.8 (t, C-8), 20.7 (t, C-4), 24.2 (t, C-7), 32.5 (t, C-2), 35.2 (C-11), 38.7 (t, C-8), 45.6 (d, C-6), 46.9 (t, C-10), 55.7 (q, C-15-OCH_3), 56.2 (q, C-16-OCH_3), 64.7 (s, C-5), 70.2 (d, C-1), 108.5 (d, C-17), 111.9 (d, C-14), 125.2 (s, C-12), 133.8 (s, C-13), 147.6 ppm (s's C-15 and C-16); isomer **31** 14.8 (t, C-3), 20.1 (t, C-4), 25.1 (t, C-7), 34.8 (t, C-2), 35.6 (t, C-11), 40.1 (t, C-8), 46.1 (t, C-10), 52.2 (d, C-6), 55.7 (q, C-15-OCH_3), 56.2 (q, C-16-OCH_3), 66.4 (s, C-5), 71.1 (d, C-1), 109.1 (d, C-17), 111.6 (d, C-14), 126.7 (s, C-12), 134.5 (s, C-13), 147.5 ppm (s's, C-15 and C-16); IR ($CHCl_3$) 3100–3500, 1605, 1505, 1460, 1250, 1120 cm^{-1}; mass spectrum, *m/e* (rel intensity) 303 (M^+ – H, 100), 285 ($M^+ - H_2O$, 60), 259 (95), 232 (70), 231 (65); high resolution mass spectrum, *m/e* 303.1840 ($C_{18}H_{25}NO_3$ requires 303.1834).

15,16-Dimethoxy-*cis*-erythrinan-1-ol (30). A solution of L-Selectride (0.5 mL of 1.0 M solution) and the erythrinanone **26** (25 mg, 0.083 mmol) in 4 mL of THF was stirred at 25 °C for 14 h, pured into water, and extracted with ether. The ethereal extracts were dried and concentrated in vacuo, giving a residue which was subjected to Florisil column chromatography (2.5% MeOH–$CHCl_3$), yielding 19 mg (76%) of the pure erythrinan-5-ol **30**: ^{1}H NMR δ 6.57 (s, 1 H, Ar), 6.48 (s, 1 H, Ar), 3.89 (n, 1 H, H-4), 8.84 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 2.9–3.3 (m, 3 H), 2.75 (dt, 1H, H-8), 2.40 (m, 2 H, H-11), 1.3–2.2 (m, 9 H).

15,16-Dimethoxy-*cis*-erythrinan-1-yl Methanesulfonate (32 and 33). To a 25 °C solution of 1-hydroxy-15,16-dimethoxyerythrinans **30** and **31** (45 mg, 0.149 mmol) in 5 mL of ether and 5 mL of THF was added triethylamine (20 mg, 0.201 mmol) and methanesulfonyl chloride (23 mg, 0.201 mmol). The resulting mixture was stirred for 2 h 15 min, poured into water, and extracted with ether. The ethereal extracts were dried and concentrated in vacuo, giving a residue which was purified by flash column chromatography (silica gel–100% $CHCl_3$ to 4% MeOH in $CHCl_3$) to afford 13 mg of isomer **33** (23%) and 25 mg of isomer **32** (44%). Spectroscopic data for mesylate **33**: ^{1}H NMR δ 1.38–3.17 (m, 18 H including CH_3 of mesylate), 3.83–3.85 (d, 6 H), 4.73–4.85 (m, 1 H), 6.49 (s, 1 H), 6.61 (s, 1 H); ^{13}C NMR 19.6 (t, C-3), 20.7 (t, C-4), 24.9 (t, C-7), 32.3 (t, C-2), 34.9 (t, C-11), 38.8 (q, CH_3), 40.0 (t, C-8), 45.9 (t, C-10), 49.5 (d, C-6), 55.9 (q, C-15-OCH_3), 56.3 (q, C-16-OCH_3), 67.0 (s, C-5), 83.5 (d, C-1), 108.8 (d, C-17), 111.9 (d, C-14), 126.7 (s, C-12), 133.3 (s, C-13), 147.9 ppm (s, C-15 and C-16); IR ($CHCl_3$) 2940, 1510, 1465, 1360, 1240, 1175 cm^{-1}; mass spectrum, *m/e* (rel intensity) 381 (2), 286 (80), 285 (100), 271 (75), 270 (90), 242 (50); high resolution mass spectrum, *m/e* 381.1619 ($C_{19}H_{27}NO_5S$ requires 381.1610).

Spectroscopic data for mesylate **32**: ^{1}H NMR δ 1.48–3.16 (m, 18 H including CH_3 of mesylate), 3.84 (d, 6 H), 5.29–5.39 (m, 1 H), 6.50 (s, 1 H), 6.64 (s, 1 H); ^{13}C NMR 17.0 (t, C-3), 22.8 (t, C-4), 24.2 (t, C-7), 25.3 (t, C-2), 32.8 (t, C-11), 39.1 (q, CH_3), 42.0 (t, C-8), 48.6 (d, C-6), 48.7 (t, C-10), 55.9 (q, C-15-$OCDH_3$), 56.3 (q, C-16-OCH_3), 64.9 (s, C-5), 81.0 (d, C-1), 109.6 (d, C-17), 111.8 (d, C-14), 126.3 (s, C-12), 135.6 (s, C-13), 147.7 (s, C-15), 147.9 ppm (s, C-16); IR ($CHCl_3$) 2940, 1510, 1465, 1360, 1240, 1157 cm^{-1}; mass spectrum, *m/e* (rel intensity) 381 (1), 286 (37), 285 (75), 271 (19), 270 (100), 242 (13); high resolution mass spectrum, *m/e* 381.1624 ($C_{19}H_{27}NO_5S$ requires 381.1610).

15,16-Dimethoxy-*cis*-erythrin-2-ene (37). A solution of the methanesulfonates **32** and **33** (31 mg, 0.081 mmol) and DBU (54 mg, 0.86 mmol) in 7 mL of THF was stirred at 80 °C for 36 h, poured into water, and extracted with ether. The ethereal extracts were dried and concentrated in vacuo, giving 20 mg (86%) of pure erythrinene **37**: ^{1}H NMR δ 1.62–2.35 (m, 6 H), 2.73–3.69 (m, 6 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 5.83 (s, 2 H), 6.58 (s, 1 H), 6.71 (s, 1 H); ^{13}C NMR 22.4 (t, C-4), 24.7 (t, C-3), 30.5 (t, C-7), 33.7 (t, C-11), 44.9 (t, C-8), 45.2 (d, C-6), 50.3 (t, C-10), 55.8 (q, C-15-OCH_3), 56.0 (q, C-16-OCH_3), 63.3 (s, C-5), 109.4 (d, C-17), 111.0 (d, C-14), 126.8 (d, C-2), 127.2 (s, C-12), 130.7 (d, C-1), 134.7 (s, C-13), 147.1 (s, C-15), 147.3 (s, C-16); IR ($CHCl_3$) 2940, 1610, 1510, 1460, 1250 cm^{-1}; mass spectrum, *m/e* (rel intensity) 285 (90), 284 (50), 270 (100); high resolution mass spectrum, *m/e* 285.1726 ($C_{18}H_{23}NO_2$ requires 285.1728).

15,16-Dimethoxy-*cis*-erythrinan (27). A solution of the erythrinene **37** (15 mg, 0.052 mmol) in 3 mL of THF containing 10% Pd/C (10 mg) suspended was stirred under a hydrogen atmosphere (1 atm) at 25 °C for 12 h. Filtration gave a filtrate which was concentrated in vacuo to yield 15 mg (99%) of the erythrinan **27** which had spectroscopic properties (IR, ^{1}H NMR, MS) that matched those previously reported:[6] ^{13}C NMR (not previously reported) 21.4 (C-2, C-3), 25.0 (C-1), 28.6 (C-7), 28.9 (C-4), 35.7 (C-11), 40.4 (C-10), 43.6 (C-6), 46.3 (t, C-8), 55.7 (OCH_3), 56.1 (OCH_3), 63.3 (C-5), 109.0 (C-17), 111.2 (C-14), 147.1 and 147.3 ppm (C-15 and C-16).

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