A New Approach to Erythrinanes through Pummerer-Type Cyclization

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A successful new strategy for the synthesis of erythrinanes is reported. (Nitromethyl)arene derivative **16** was condensed with aldehyde **17** to give nitro aldol **19**. After removal of the hydroxy group, the subunits **26a**,**b**, containing the erythrinane rings A and D, were formed by intramolecular Michael addition. Reduction of the nitro function, followed by cyclization of the resulting amino group with the appended acetate group afforded the bicyclic lactams **29a**,**b**, bearing an angular aryl group. Two-carbon elongation at the nitrogen atoms of **29a** and **29b** by means of hetero Michael addition of methyl phenyl sulfoxide, followed by Pummerer-type cyclization, gave *cis*- and *trans*-11-phenylthio-erythrinan-8-ones **35a** and **35b**, respectively. Reductive desulfurization at C-11 furnished the desired erythrinan-8-ones **39a** and **39b** in 8 steps from **16**.

Introduction

Numerous synthetic approaches have been developed for the construction of *Erythrina* alkaloids, and these compounds are still considered as attractive targets for total synthesis.[1] Though some of them display interesting curare-like pharmacological activity,[2] the main driving force for these synthetic studies remains their polycondensed framework, which constitutes an ideal testing ground for new ring-forming methodologies. Aromatic *Erythrina* alkaloids have in common the basic skeleton **1**, characteristically possessing a tetrahydroisoquinoline system (C and D rings) and a hydroindole subunit (A and B rings), which share a common nitrogen atom and a spiro carbon center. The majority of these compounds, as exemplified by erythramine **2**, bear an alkoxy residue at C3, and one or two double bonds in rings A and/or B.

Most of the hitherto reported syntheses rely on a small number of strategies. Following the early pioneering studies of Belleau[3] and Mondon,[4] many synthetic approaches have been based on the interception of a C5-centered iminium ion by the aromatic nucleus, as in intermediate **3**.[5] Formation of the tetracyclic system by annulation of the A ring onto the benzoindolizidine subunit **4** has been widely explored by Prelog,[6a] Stevens,[6b] and Tsuda.[7] Wasserman took advantage of a similar tricyclic intermediate, and built the A ring by an intramolecular aldol reaction of diketone **5**.[8] More recently, various strategies have been explored in which the erythrinane skeleton is completed by B-ring formation, starting from a C5 spiro-isoquinoline system such as **7**[9] or **8**.[10] Finally, several very efficient syntheses have been based on oxidative phenolic coupling of the bis-(arylethyl)amine subunit **6**, in accordance with the biosynthetic hypothesis[11] (Figure 1).

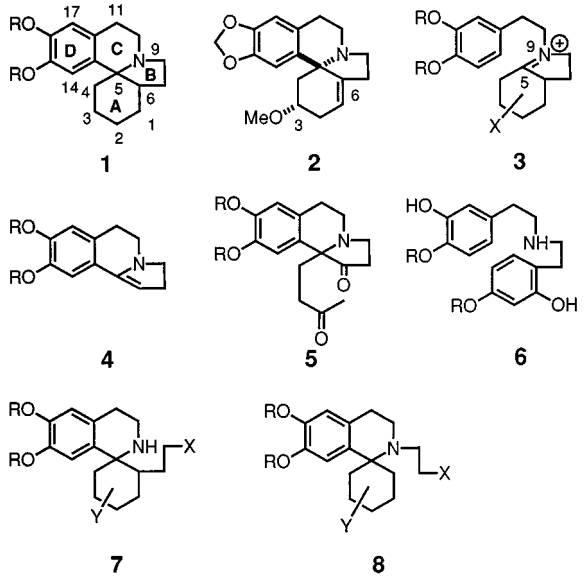

Figure 1. Principal synthetic approaches for the construction of *Erythrina* alkaloids; OR = OMe, OCH_2O

Results and Discussion

Although the aforementioned multitude of synthetic studies have led to straightforward syntheses of the erythrinane carbon core, few of them allow an efficient introduction of the C3 oxygen functionality. In our search for a new strategy facilitating this, we speculated that the tetracyclic framework might conceivably be constructed by formation of the C11−C12 bond through electrophilic cyclization of the aryl-substituted hexahydroindolinone **11a**. The Pummerer reaction seemed to be particularly well suited for executing this plan, since the resulting C11 thioether **10a** might easily be reduced to give erythrinan-8-one **9a**. Sulfoxide **11a** could formally be obtained by two-carbon elongation at the nitrogen atom of lactam **12a** by means of hetero Michael addition of phenyl vinyl sulfoxide. This synthetic scheme required efficient access to substituted lactam **12** bearing an angular aryl group. In this regard, nitro ester

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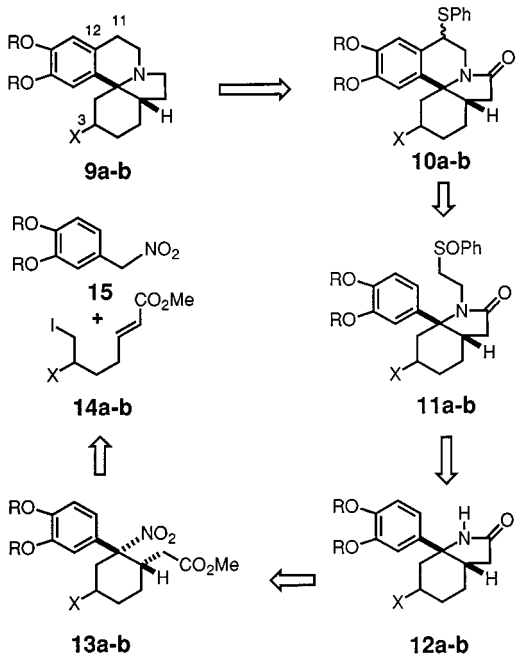
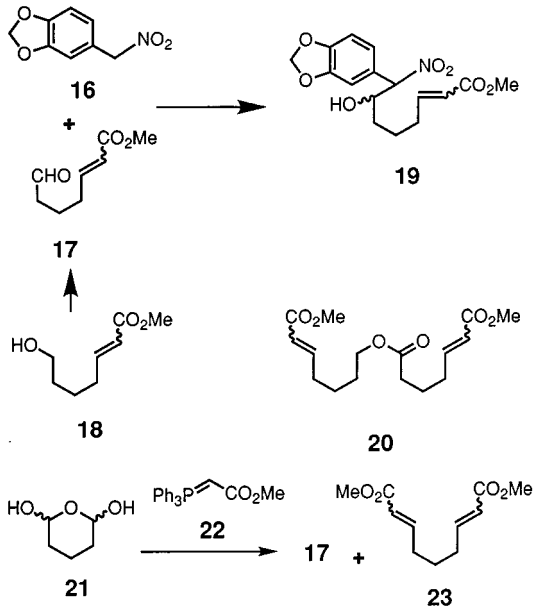
13a appeared to be an attractive building block, since reduction of the nitro group could be expected to be accompanied by nucleophilic attack of the thus formed amino group on the appended acetate group, thereby providing the desired ABD subunit. We anticipated that **13a** might be obtained from an (nitromethyl)arene compound of type **15**, having 2-fold nucleophilic capability, taking advantage of our previously reported one-pot annulation reaction of methylene-active compounds with ω-halo-unsaturated esters such as **14a**.[12] To establish the viability of this plan, we decided to test it within the restricted case of the C3-unfunctionalized erythrinane skeleton **9b**. In this paper, we report the successful outcome of this strategy [**15** → **13b** → **9b**], which opens the way to the synthesis of more complex naturally occurring *Erythrina* alkaloids (Scheme 1).



Scheme 1. Retrosynthetic analysis of erythrinane ring system **9**; OR = OMe, OCH_2O; a: X = OP (P = protecting group); b: X = H

Our *tandem* annulation reaction has been shown to involve initial alkylation of the nucleophile, followed by intramolecular Michael addition, thereby efficiently producing 2-(cyclohexyl)acetic acid derivatives. Although the sequential annulation process worked quite well using a variety of nucleophilic substrates, attempted assembly of nitro ester **13b** in this way, by condensation of (nitromethyl)arene **16**[13] with iodo ester **14b**, met with failure. We suspected that this failure of the *tandem* process was related to the alkylation step, given the known reluctance of such derivatives to give *C*-alkylated products with alkyl halides.[14] Assuming the intramolecular Michael reaction to be operative in building the six-membered ring, an alternative procedure was thus devised in which the first C−C bond was formed by nitro aldol reaction between (nitromethyl)arene **16** and aldehyde **17**. The latter material was initially prepared by oxidation of alcohol **18**, which is readily available from δ-valerolactone according to the procedure of Takacs.[15] PDC oxidation of **18** gave the desired aldehyde **17** in 55% yield, along with 15% of the dimeric ester **20**. Since undesirable side reactions interfered with most common oxidation procedures examined (Swern, Moffatt, PDC, PCC/Al_2O_3, etc.), a more convenient protocol was sought. Thus, addition of 1 equiv. of methyl (triphenylphosphoranylidene)acetate (**22**) to an aqueous solution of 3 equiv. of glutaraldehyde (**21**)[16] provided the desired aldehyde **17** (*E*/*Z* = 2.5:1) in one step in 60% yield, accompanied by diester **23** (ca. 20%), which could easily be separated by chromatography on silica gel (Scheme 2).

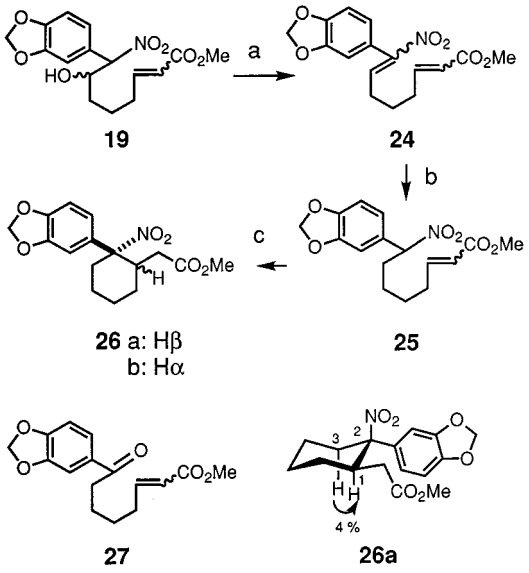


Scheme 2. Synthesis of aldehyde **17** and nitro aldol condensation with (nitromethyl)arene **16**

Once a practicable synthesis of aldehyde **17** had been established, we turned our attention toward the elaboration of the AD subunit **26**. Attempted condensation of (nitromethyl)arene **16** with aldehyde **17** in the liquid phase, using standard bases (MeONa, *t*BuOK, NaH, Triton B in MeOH, Et_3N in DMSO[17]) as catalysts ultimately proved fruitless. On the other hand, reaction on a solid support such as basic alumina[18] or Amberlyst® A-21[19] was found to be much more efficient, giving nitro aldol **19** in yields of 55% and 74%, respectively. Although only one stereoisomer was apparently formed in this reaction, no attempt was made to elucidate its relative stereochemistry since the hydroxy group is removed in the ensuing steps. Tosylation or mesylation of **19**, followed by base-induced elimination, gave intractable mixtures. Dehydration of **19** using DCC/CuCl according to the Seebach procedure[20] proved more efficient, giving nitro alkene **24** as a mixture of geometric isomers (47%). However, the reaction was slow and barely reached completion on a large scale. Eventually, it was found that treatment of **19** with Burgess′ inner salt[21] in refluxing benzene cleanly afforded **24** in 70% yield. Chemoselective reduction of the double bond at C7−C8 of nitro olefin **24** with $NaBH_3CN/AcOH$[22] smoothly gave the reduced nitro ester **25** (88% yield). Next, the crucial formation of the A ring by intramolecular addition was investi-

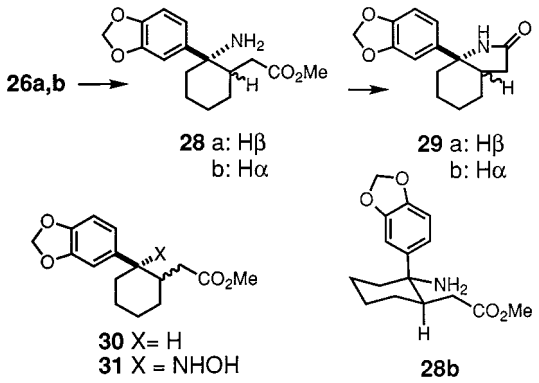
gated. Most standard reagents used for conjugate addition reactions of nitro compounds (MeONa/MeOH, Cs_2CO_3/DMF,[12b] nBu_3P/CH_3CN,[23] KOH/toluene/aza-crown ether,[24] Amberlyst® A-27[25], etc.) left the starting material **25** unchanged or induced its decomposition. However, by treatment with diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile[26] the desired Michael adduct **26a** was obtained in 45% yield, along with ketone **27**. The formation of the latter product was most likely due to competitive oxidation of the nitronate anion, which could be minimized by rigorous exclusion of oxygen.[27] The relative stereochemistry of **26a** was unambiguously determined by NOE experiments, which showed a 4% signal enhancement at axial proton 3-H when 1-H was irradiated. After extensive experimentation, it was found that replacement of DBU by nBu_4NF[28] gave adducts **26a** and **26b** as a 1:1 mixture of isomers in a combined yield of 68%, in a more reproducible manner. The stereochemical outcome of the key Michael addition has been demonstrated to be the result of kinetic control since separated isomers were recovered unchanged when re-exposed to the reaction conditions (Scheme 3).

It is worthy to note that, as most *Erythrina* alkaloids possess an sp^2-carbon atom at C-6, *both isomeric nitro esters* **26a** *and* **26b** *can be used to complete the synthetic scheme.*



Scheme 3. Synthesis of the AD subunit **26** by means of intramolecular Michael addition; reagents and conditions: (a) $EtO_2CN^-SO_2N^+Et_3$, ΔT, benzene, 15 min; (b) $NaBH_3CN$, AcOH, MeOH; (c) nBu_4NF, THF, 20°C, 18 h

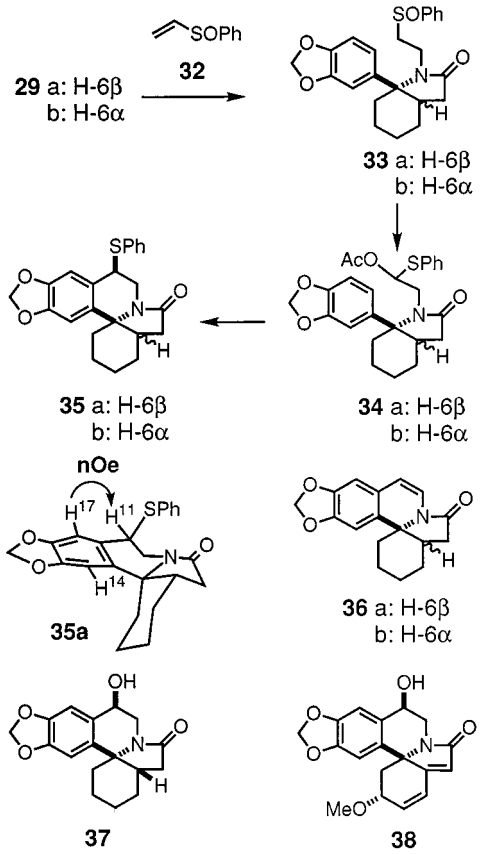
Reduction of the nitro group turned out to be much more difficult than expected, due to both steric hindrance and competitive hydrogenolysis.[29] Catalytic hydrogenation using Pd/C gave a large amount of the "denitrated" ester **30**, whereas attempted reduction using Zn/HCl/*t*BuOH[30] stopped at the hydroxylamine stage **31**. Eventually, we found that Raney nickel reduction of the two isomers gave amino esters **28a** and **28b**, respectively, in moderate yield and with only a trace amount of **30**. Contrary to our expectations, the lactam ring closure was not spontaneous but required thermal activation. Isomer **28a** cyclized upon refluxing in toluene for 1 h, yielding the *cis*-lactam **29a** in 42% overall yield based on **26a**. In contrast, isomer **28b**, bearing an axially appended acetate group, required prolonged refluxing in mesitylene in the presence of Amberlite® IR-45(OH) as catalyst to achieve cyclization to the corresponding *trans*-lactam **29b** (35% overall yield based on **26b**). These more drastic conditions reflect the fact that the aryl substituent has to occupy an axial position in amino ester **28b** (as depicted in Scheme 4) in order to allow cyclization. Molecular mechanics calculations[31] have revealed this conformer to be 3.5 kcal mol^{-1} less stable than the conformer having the aryl group in an equatorial position.



Scheme 4. Synthesis of the ABD subunit **29a**,**b** through B-ring cyclization

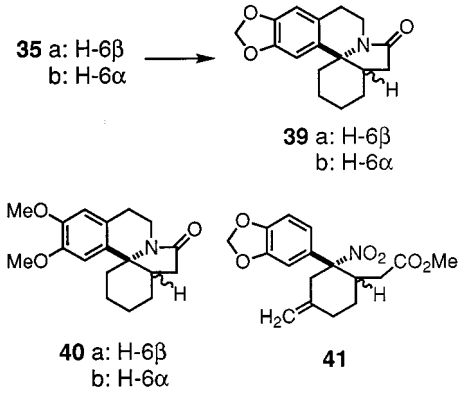
Next, the two-carbon elongation at the nitrogen atoms of lactams **29a** and **29b** was investigated. The most direct route to our target **33** appeared to be the hetero Michael addition of the lactam anion to phenyl vinyl sulfoxide (**32**). Although unsaturated sulfoxides have readily been used as Michael acceptors with amines, to the best of our knowledge intermolecular addition of amides or lactams has not previously been reported.[32] In the event, when the sodium salt of **29a** (NaHMDS, THF, −78°C) was treated with an excess of phenyl vinyl sulfoxide (**32**) in a THF/HMPA mixture, the desired Michael adduct **33a** was obtained in 55% yield along with some recovered starting material **29a**. All attempts to improve this yield by using other bases (LDA, NaH, KH, Triton B in MeOH, aqueous KOH under phase-transfer conditions) were unsuccessful. Clearly, the moderate yield was most likely due to steric hindrance of the lactam anion, coupled with the poor Michael acceptor ability of phenyl vinyl sulfoxide (**32**). The crucial cyclization of the C ring of the erythrinane carbon core was then investigated. Treatment of sulfoxide **33a** with trifluoroacetic anhydride[33] in dichloromethane (−78°C to 20°C) produced a mixture of cyclized compounds **35a**, **36a**, and **37**. Formation of the major component **37** (40%) has been tentatively rationalized, invoking the solvolysis of the initially formed thioether **35a** by traces of water present in the reaction medium. The β configuration of the hydroxy group was deduced on the basis of the ^{1}H-NMR spectrum, in which the 11-H gives rise to a triplet with a small coupling constant (δ = 4.60, J = 2.7 Hz). Interestingly, compound **37** displays the same stereochemistry at C11 as hydroxy-substituted *Erythrina* al-

kaloids such as 8-oxoerythrinine (**38**) (11-H: δ = 4.84, *J* = 5 Hz).[34] A more satisfactory result was obtained by a two-step procedure involving initial treatment of **33a** with acetic anhydride under reflux followed by Lewis acid induced cyclization ($SnCl_4$, CH_2Cl_2, 0°C) of the intermediate α-acetoxy thioether **34a**. This protocol furnished the desired 11-phenylthioerythrinan-8-one **35a** in 56% yield, accompanied by some olefin **36a** (15%). Support for the β-stereochemical assignment of the phenythio group in **35a** was provided by ^{1}H-NMR spectroscopy. The methine hydrogen atom 11-H (δ = 4.21) shows two small couplings (*J* = 3.4 and 1.1 Hz) with vicinal 10α-H (δ = 3.22) and 10β-H (δ = 4.33), respectively. These data are consistent with a pseudoequatorial conformation of 11α-H, which is further supported by the observation of a strong nuclear Overhauser enhancement between the aromatic 17-H and the 11-H proton (Scheme 5).



Scheme 5. C-ring cyclization through intramolecular Pummerer-type reaction

Attempted desulfurization of thioether **35a** with Raney nickel was unsuccessful. However, upon treatment with tri-*n*-butyltin hydride and 2,2′-azobis(isobutyronitrile) in refluxing toluene, **35a** was smoothly converted into the desired *cis*-8-erythrinanone **39a**, previously reported by Mondon[4b] (75% yield). Similarly, *trans*-lactam **29b** was transformed into sulfoxide **33b** (58%), which was cyclized by means of the Pummerer reaction to give thioether **35b** along with some olefin **36b**. Desulfurization of **35b** as described above gave *trans*-erythrinan-8-one **39b** in 30% overall yield (Scheme 6). Although no NMR data have previously been reported for lactams **39a**,**b**, the chemical shifts of the aromatic protons 14-H and 17-H of our samples closely match the reported values for the 15,16-dimethoxyerythrinan-8-ones (**40a**,**b**).[35] Since the chemical shift of these two protons has been demonstrated to be a valuable probe in determining the stereochemistry of erythrinanes, this result further confirmed our initial assignment.



Scheme 6. Completion of the synthesis of the erythrinane skeleton

Conclusion

In summary, we have developed a new strategy for constructing the erythrinane carbon framework from the (nitromethyl)arene derivative **16**, the key steps of which are intramolecular Michael addition of nitro ester **25** to establish the subunit **26a**,**b** containing the erythrinane rings A and D, and Pummerer-based cyclization of the C ring. In order to extend the present strategy to the synthesis of *Erythrina* alkaloids, the introduction of the alkoxy residue at C-3 had to be addressed. The failure of the domino process [**16** + **14b** → **26**] was somewhat frustrating, forcing us to adopt a lengthy four-step sequence to obtain the cyclized nitro ester **26a**. However, we have recently been able to adapt the domino sequence, replacing the S_N2 process by an alkylation reaction of an (η^3-allyl)palladium complex.[12c] This new sequential reaction opens a one-step route to the erythrinane AD subunit **41**, in which the eventual C3 methoxy group might easily be derived from the exocyclic double bond. Application of the present strategy, starting from nitro ester **41**, to the preparation of naturally occurring *Erythrina* alkaloids such as erythramine **2** is currently in progress in our laboratory, and our results will be reported in due course.

Experimental Section

General: Melting points: Büchi capillary tube melting point apparatus, uncorrected. − IR spectra: Perkin−Elmer 841 spectrometer; neat films between NaCl plates or KBr pellets. Only significant absorptions are listed. − ^{1}H- and ^{13}C-NMR spectra: Bruker AC 200 P (200 MHz and 50 MHz for ^{1}H and ^{13}C, respectively) or Bruker ARX 400 (400 MHz and 100 MHz for ^{1}H and ^{13}C, respec-

tively) spectrometers. Methyl, methylene, methine, and quaternary carbon nuclei were identified in the ^{13}C-NMR spectra on the basis of *J*-modulated spin-echo sequences. − Analytical thin-layer chromatography: precoated Merck silica gel $60F_{254}$ glass plates (0.25 mm layer). − Liquid chromatography separations: Merck silica gel 60 (230−400 mesh ASTM). − Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methanol was dried with magnesium and distilled prior to use. Benzene, toluene, DMF, HMPA, and CH_2Cl_2 were distilled from calcium hydride under nitrogen. − All reactions involving air- or moisture-sensitive compounds were routinely conducted in glassware that had been flame-dried under a positive pressure of nitrogen. Organic layers were dried with anhydrous $MgSO_4$. − The boiling points refer to oil-bath temperatures. − Chemicals obtained from commercial suppliers were used without further purification. − Elemental analyses: Service de Microanalyse, Centre d′Etudes Pharmaceutiques, Châtenay-Malabry, France; Perkin−Elmer 2400 analyzer.

Methyl 7-Oxo-2-heptenoate (17): To a 50% aqueous solution of glutaraldehyde (7.2 g, 36 mmol) in THF (15 mL), 4.0 g of methyl (triphenylphosphoranylidene)acetate (12 mmol) was added portionwise. The reaction mixture was stirred at 20°C for 12 h, and then water was added. The mixture was extracted with diethyl ether, and the combined extracts were dried and concentrated under reduced pressure. The residue was taken up in a mixture of diethyl ether/pentane (1:1, 100 mL) and this solution was filtered. The filtrate was concentrated in vacuo to leave a colorless oil. Chromatographic separation on silica gel (cyclohexane/ethyl acetate, 4:1) afforded 1.12 g of aldehyde **17** (60%); colorless oil, b.p. 80−85°C/0.5 Torr. − IR (neat): $\tilde{\nu}$ = 2843 cm^{-1} (HCO), 1723 (C=O), 1657 (C=C), 1435. − ^1H NMR ($CDCl_3$, 200 MHz); the spectrum revealed the presence of *E*/*Z* isomers in a 2:1 ratio, only the *E* isomer is described: δ = 1.60 (quint, *J* = 7.4 Hz, 2 H, 5-H), 2.05 (tdd, *J* = 7.4, 6.9, 1.4 Hz, 2 H, 4-H), 2.30 (td, *J* = 7.0, 1.4 Hz, 2 H, 6-H), 3.50 (s, 3 H, OCH_3), 5.65 (dt, *J* = 15.6, 1.5 Hz, 1 H, HC=C*H*CO_2CH_3), 6.71 (td, *J* = 15.6, 6.9 Hz, 1 H, *H*C=$CHCO_2CH_3$), 9.70 (td, *J* = 1.4, 0.7 Hz, 1 H, *H*CO). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.9 (C-5), 30.8 (C-4), 42.4 (C-6), 50.8 (O*C*H_3), 121.3 (HC=*C*HCO_2CH_3), 147.5 (H*C*=$CHCO_2CH_3$), 166.1 (O*C*=O), 201.1 (H*C*=O).

Methyl 8-(1,3-Benzodioxol-5-yl)-7-hydroxy-8-nitro-2-octenoate (19): To a solution of (nitromethyl)arene **16** (0.87 g, 4.8 mmol) and aldehyde **17** (0.75 g, 4.8 mmol) in diethyl ether (10 mL) was added Amberlyst® A-21 (3 g). The solvent was evaporated under reduced pressure and the solid mixture obtained was left to stand at 20°C for 12 h. Ethyl acetate was then added and the mixture was filtered through a plug of Celite. The solid was thoroughly washed with ethyl acetate, and the filtrate was concentrated in vacuo. Chromatography of the residue on silica gel (cyclohexane/ethyl acetate, 2:1) afforded 1.20 g of nitro aldol **19** (74%); yellow oil. − IR (neat): $\tilde{\nu}$ = 3468 cm^{-1} (OH), 1721 (CO), 1657 (C=C), 1610 (C=C aromatic), 1552 (NO_2), 1493, 1446. − ^1H NMR ($CDCl_3$, 200 MHz); only the major *E* isomer is described: δ = 1.15−1.75 (m, 4 H, 5-H and 6-H), 2.00−2.25 (m, 2 H, 4-H), 3.50 (m, 1 H, O*H*), 3.68 (s, 3 H, OCH_3), 4.46 (m, 1 H, 7-H), 5.19 (d, 1 H, *J* = 9.6 Hz, 8-H), 5.72 (dt, *J* = 15.6, 1.6 Hz, 1 H, HC=C*H*CO_2CH_3), 5.93 (s, 2 H, OCH_2O), 6.68−6.95 (m, 4 H, *H*C=$CHCO_2CH_3$ and aromatic H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.4 (C-5), 31.5 (C-4 and C-6), 51.5 (O*C*H_3), 72.1 (C-7), 96.4 (Ar*C*HNO_2), 101.7 (O*C*H_2O), 107.6 (C-2′), 108.7 (C-5′), 121.3 (C-6′), 122.7 (HC=*C*HCO_2CH_3), 125.5 (C-1′), 148.3 (C-4′), 148.4 (H*C*=$CHCO_2CH_3$), 149.1 (C-3′), 167.0 (*C*O). − $C_{16}H_{19}NO_7$ (337.3): calcd. C 56.97, H 5.78, N 4.15; found C 56.75, H 5.73, N 4.06.

Methyl 8-(1,3-Benzodioxol-5-yl)-8-nitro-2,7-octadienoate (24): A solution of nitro aldol **19** (100 mg, 0.29 mmol) and Burgess′ salt (0.14 g, 0.6 mmol) in benzene (3 mL) was heated under reflux for 15 min. After cooling, the mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate, 4:1) to give 65 mg of nitro alkene **24** (70%); yellow oil. − IR (neat): $\tilde{\nu}$ = 2955 cm^{-1}, 1722 (C=O), 1659 (C=C), 1609 (C=C aromatic), 1520 (NO_2), 1489, 1438, 1328. − ^1H NMR ($CDCl_3$, 200 MHz); the presence of 4 stereomers complicates the spectrum, only the major isomer is described: δ = 1.50−1.65 (m, 2 H, 5-H), 2.05−2.24 (m, 4 H, 4-H and 6-H), 3.65 (s, 3 H, OCH_3), 5.67 (dt, *J* = 15.6, 1.5 Hz, 1 H, HC=C*H*CO_2CH_3), 6.02 (s, 2 H, OCH_2O), 6.69−6.89 (m, 4 H, *H*C=$CHCO_2CH_3$ and aromatic H), 7.30 (t, 1 H, *J* = 9.1 Hz, *H*C=CNO_2). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 26.5 (CH_2), 27.6 (CH_2), 31.0 (CH_2), 51.3 (O*C*H_3), 101.5 (O*C*H_2O), 108.2 (C-5′), 110.2 (C-2′), 121.7 (HC=*C*HCO_2CH_3), 122.6 (C-1′), 124.3 (C-6′), 137.1 [H*C*=C(NO_2)Ar], 147.5 (H*C*=$CHCO_2CH_3$), 147.6 [C=*C*(NO_2)Ar], 148.6 (C-3′), 151.2 (C-4′), 166.6 (*C*O).

Methyl 8-(1,3-Benzodioxol-5-yl)-8-nitro-2-octenoate (25): To a solution of nitro alkene **24** (1.2 g, 3.8 mmol) in anhydrous methanol (5 mL) was added a crystal of bromocresol green and 0.45 g (7.12 mmol) of sodium cyanotrihydroborate. Acetic acid was then added dropwise until the blue color just faded. After stirring at 20°C for 1 h, the resulting yellow solution was quenched with water and extracted with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica gel (hexane/ethyl acetate, 4:1) gave 1.07 g of nitro ester **25** (88%); yellow oil. − IR (neat): $\tilde{\nu}$ = 2938 cm^{-1}, 1722 (C=O), 1658 (C=C), 1613 (C=C aromatic), 1548 (NO_2), 1503, 1492, 1446. − ^1H NMR ($CDCl_3$, 200 MHz); only the major *E* isomer is described: δ = 1.30−1.60 (m, 4 H, 5-H and 6-H), 2.03−2.43 (m, 4 H, 4-H and 7-H), 3.71 (s, 3 H, OCH_3), 5.32 (dd, 1 H, *J* = 8.3, 6.7 Hz, 8-H), 5.77 (dt, *J* = 15.6, 1.7 Hz, 1 H, HC=C*H*CO_2CH_3), 5.98 (s, 2 H, OCH_2O), 6.77 (d, *J* = 7.9 Hz, 1 H, 5′-H), 6.85−6.96 (m, 3 H, *H*C=$CHCO_2CH_3$, C-2′ and C-6′). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 25.3 (CH_2), 26.9 (CH_2), 31.3 (CH_2), 33.9 (CH_2), 50.9 (O*C*H_3), 90.6 (*C*HNO_2), 101.3 (O*C*H_2O), 107.2 (C-2′ or C-5′), 107.9 (C-2′ or C-5′), 120.9 (C-6′), 121.4 (HC=*C*HCO_2Me), 127.8 (C-1′), 147.8 (C-3′ or C-4′), 148.2 (H*C*=$CHCO_2$Me), 148.9 (C-3′ or C-4′), 166.5 (*C*O). − $C_{16}H_{19}NO_6$ (321.3): calcd. C 59.80, H 5.96, N 4.35; found C 59.92, H 5.98, N 4.39.

***trans*- and *cis*-Methyl [2-(1,3-Benzodioxol-5-yl)-2-nitrocyclohexyl]-acetate (26a and 26b):** To a solution of nitro ester **25** (0.48 g, 1.49 mmol) in THF (5 mL) was added a 1 M THF solution of *n*Bu_4NF (2.16 mL, 2.16 mmol) and a few crystals of hydroquinone. The resulting mixture was carefully degassed by means of two freeze-pump-thaw cycles and then stirred at 20°C for 15 h. Aqueous oxalic acid was then added and the mixture was extracted with diethyl ether. The combined organic phases were dried and concentrated under reduced pressure. Chromatography of the residue on silica gel (cyclohexane/ethyl acetate, 9:1 then 4:1) afforded 162 mg of **26a** (34%), R_f = 0.69; colorless crystals, m.p. 90−91°C (Et_2O). − IR (KBr): $\tilde{\nu}$ = 2956 cm^{-1}, 1732 (CO), 1611 (C=C aromatic), 1540 (NO_2), 1492, 1359, 1177. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40−1.57 (m, 3 H, 5-H_{ax}, 4-H_{ax}, 6-H_{ax}), 1.60−1.72 (m, 2 H, 4-H_{eq}, 5-H_{eq}), 1.77 (m, 1 H, 6-H_{eq}), 2.12 (m, 1 H, 3-H_{ax}), 2.45 (dd, *J* = 16.7, 2.3 Hz, 1 H, *H*CCO_2Me), 2.59 (m, 1 H, 3-H_{eq}), 2.65 (dd *J* = 16.7, 9.7 Hz, 1 H, *H*CCO_2Me), 2.89 (m, 1 H, 1-H), 3.65 (s, 3 H, OCH_3), 5.98 (s, 2 H, OCH_2O), 6.66−6.80 (m, 3 H, aromatic H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.7 (C-4 or C-5), 23.7 (C-4 or C-5), 28.0 (C-6), 35.5 (*C*H_2CO_2Me), 36.8 (C-3), 41.3 (C-1),

51.7 (O*C*H$_3$), 97.6 (Ar*C*NO$_2$), 101.6 (O*C*H$_2$O), 106.1 (C-2′), 108.4 (C-5′), 119.0 (C-6′), 132.5 (C-1′), 147.5 (C-3′ or C-4′), 148.2 (C-3′ or C-4′), 173.2 (*C*O). − MS (70 eV); *m*/*z* (%): 292 (95) [M$^+$ − 29], 275 (100) [M$^+$ − 46 (NO$_2$)], 243 (5), 200 (5). − $C_{16}H_{19}NO_6$ (321.3): calcd. C 59.80, H 5.96, N 4.35; found C 59.62, H 5.99, N 4.26. − Further elution (cyclohexane/ethyl acetate, 4:1) gave 160 mg of **26b** (34%), R_f = 0.62; colorless crystals, m.p. 115−116°C (MeOH). − IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1}, 1731 (CO), 1611 (C=C aromatic), 1533 (NO$_2$), 1505, 1494, 1453, 1441, 1359. − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.29 (m, 1 H, 4-H$_{ax}$), 1.36−1.43 (m, 1 H, 5-H$_{ax}$), 1.48−1.53 (m, 1 H, 5-H$_{eq}$), 1.65−1.70 (m, 2 H, 6-H), 1.80−1.91 (m, 3 H, *H*$_2$CCO$_2$Me, 3-H$_{ax}$ and 4-H$_{eq}$), 2.25 (dd, *J* = 15.7, 11.1 Hz, 1 H, *H*$_2$CCO$_2$Me), 2.94 (br. d, *J* = 13.3 Hz, 1 H, 3-H$_{eq}$), 3.59 (s, 3 H, OC*H*$_3$), 3.64 (m, 1 H, 1-H), 5.94 (s, 2 H, OC*H*$_2$O), 6.75 (d, *J* = 8.1 Hz, 1 H, 5′-H), 6.95 (dd, *J* = 8.1, 1.8 Hz, 1 H, 6′-H), 6.97 (d, 1 H, *J* = 1.8 Hz, 2′-H). − ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 18.4 (C-5), 22.3 (C-4), 25.8 (C-6), 28.4 (C-3), 33.8 (H$_2$*C*CO$_2$Me), 37.4 (C-1), 51.8 (O*C*H$_3$), 95.1 (Ar*C*NO$_2$), 101.6 (O*C*H$_2$O), 106.0 (C-2′), 108.3 (C-5′), 119.5 (C-6′), 132.2 (C-1′), 148.4 (C-3′ and C-4′), 173.2 (*C*O). − $C_{16}H_{19}NO_6$ (321.3): calcd. C 59.80, H 5.96, N 4.35; found C 59.89, H 6.05, N 4.31.

***cis*-7a-(1,3-Benzodioxol-5-yl)-3a,4,5,6,7,7a-hexahydro-2-indolinone (29a):** To a suspension of Raney nickel (ca. 2 g) in methanol (4 mL) was added a solution of nitro ester **26a** (430 mg, 1.34 mmol) in DMF (1 mL). The mixture was subjected to hydrogenation at 6 bar for 16 h, then filtered through Celite, and the filtrate was concentrated in vacuo. The crude amino ester **28a** was taken up in toluene (10 mL), and the resulting solution was heated under reflux for 2 h. After concentration under reduced pressure, chromatographic purification of the residue on silica gel (ethyl acetate) afforded 145 mg of lactam **29a** (42% overall yield from **26a**); colorless crystals, m.p. 167−168°C (MeOH). − IR (KBr): $\tilde{\nu}$ = 3192 cm^{-1} (NH), 3081 (NH), 1691 (C=O), 1509, 1494, 1479, 1427. − ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 1.30−1.90 (m, 8 H), 1.90 (dd, *J* = 16.0, 2.2 Hz, 1 H, 3β-H), 2.43 (dd, *J* = 16.0, 6.4 Hz, 1 H, 3α-H), 2.50 (m, 1 H, 3a-H), 5.93 (s, 2 H, OC*H*$_2$O), 6.63 (d, *J* = 8.8 Hz, 1 H, 5′-H), 6.80 (dd, *J* = 8.8, 1.8 Hz, 1 H, 6′-H), 6.79 (d, *J* = 1.8 Hz, 1 H, 2′-H), 7.22 (s, 1 H, NH). − ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 21.6 (C-5 or C-6), 23.2 (C-5 or C-6), 28.7 (C-4), 36.8 (C-3), 38.0 (C-7), 41.5 (C-3a), 64.1 (C-7a), 101.2 (O*C*H$_2$O), 106.3 (C-2′), 107.8 (C-5′), 118.4 (C-6′), 140.7 (C-1′), 146.4 (C-3′), 147.8 (C-4′), 178.8 (*C*O). − MS (70 eV); *m*/*z* (%): 259 (20) [M$^+$], 216 (100), 202 (18), 186 (6), 174 (5), 158 (5), 148 (28). − $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.56, H 6.54, N 5.76.

***trans*-7a-(1,3-Benzodioxol-5-yl)-3a,4,5,6,7,7a-hexahydro-2-indolinone (29b):** Raney nickel reduction of *trans*-nitro ester **26b** (1.0 g, 3.11 mmol) as described above furnished the corresponding *trans*-amino ester **28b**. The crude product was taken up in mesitylene, Amberlite IR-45(OH) (50 mg) was added, and the resulting mixture was heated at 160°C for 8 h. The mixture was then filtered and concentrated under reduced pressure. Chromatographic purification of the residue on silica gel (ethyl acetate) gave 282 mg of pure *trans*-lactam **29b** (35% overall yield from **26b**); colorless crystals, m.p. 159−160°C (Et$_2$O). − IR (KBr): $\tilde{\nu}$ = 3076 and 2973 cm^{-1} (NH), 1701 (C=O), 1502, 1488, 1235. − ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 0.90−2.10 (m, 7 H), 2.10−2.55 (m, 4 H), 5.82 (s, 2 H, OC*H*$_2$O), 6.61 (d, *J* = 7.0 Hz, 1 H, 5′-H), 6.80 (dd, *J* = 7.0, 2.0 Hz, 1 H, 6′-H), 6.83 (d, *J* = 2.0 Hz, 1 H, 2′-H), 7.68 (s, 1 H, NH). − ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 22.0 (C-5), 24.1 (C-6), 26.7 (C-4), 36.3 (C-3), 39.1 (C-7), 48.2 (C-3a), 63.5 (C-7a), 101.0 (O*C*H$_2$O), 107.9 (C-2′ or C-5′), 108.0 (C-2′ or C-5′), 120.4 (C-6′), 136.5 (C-1′), 145.9 (C-3′ or C-4′), 147.7 (C-3′ or C-4′), 178.4 (*C*O).

***cis*-7a-(1,3-Benzodioxol-5-yl)-1-[2-(phenylsulfinyl)ethyl]-3a,4,5,6,7,7a-hexahydro-2-indolinone (33a):** To an ice-cooled solution of lactam **29a** (110 mg, 0.42 mmol) in THF (2 mL), a THF solution of sodium bis(trimethylsilyl)amide (2 M, 0.25 mL, 0.50 mmol) was added dropwise. The resulting pale-yellow solution was stirred at 0°C for 10 min and then cooled to −78°C. Phenyl vinyl sulfoxide (100 mg, 0.65 mmol) was then added and the resulting mixture was stirred for 15 min. The temperature was gradually raised to 20°C and then HMPA (0.5 mL) was added. After stirring for 2 h, a second portion of phenyl vinyl sulfoxide (100 mg, 0.65 mmol) was added, and the reaction mixture was stirred for a further 3 h. Then, 1 N HCl was added, and the mixture was extracted with ethyl acetate. The combined organic phases were dried and concentrated under reduced pressure. Chromatography of the residue on silica gel (cyclohexane/ethyl acetate, 1:1) afforded 100 mg of **33a** (58%) as a 1:1 mixture of stereoisomers; amorphous solid. − IR (neat): $\tilde{\nu}$ = 2935 cm^{-1}, 1683 (CO), 1504, 1488, 1444, 1398, 1238, 1039 (S=O). − ^{1}H NMR (CDCl$_3$, 400 MHz); the stereogenic sulfur atom induced a splitting of most signals: δ = 1.40−1.75 (m, 7 H, 4-H, 5-H, 6-H, 7-H$_{eq}$), 2.10−2.40 (m, 3 H, 7-H$_{ax}$, 3-H), 2.50 (m, 1 H, 3a-H), 2.80 (m, 1 H, NCH$_2$C*H*$_2$SOPh), 3.00−3.30 (m, 2 H, NC*H*$_2$CH$_2$SOPh and NCH$_2$C*H*$_2$SOPh), 3.20 and 3.50 (2 m, 1 H, NC*H*$_2$CH$_2$SOPh), 5.93 and 5.95 (2 s, 2 H, OC*H*$_2$O), 6.72−6.77 (m, 3 H, 2′-H, 5′-H and 6′-H), 7.45−7.57 (m, 5 H, C$_6$*H*$_5$SO). − ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 20.8 (C-5), 22.4 (C-6), 25.7 (C-4), 31.8 (C-7), 34.4 and 35.2 (N*C*H$_2$CH$_2$SOPh), 35.0 (C-3), 41.6 and 41.8 (C-3a), 54.0 and 55.0 (NCH$_2$*C*H$_2$SOPh), 67.6 (C-7a), 101.2 (O*C*H$_2$O), 107.4 (C-2′), 107.9 (C-5′), 120.4 (C-6′), 123.8 and 123.9 (C-2″), 129.1 (C-3″), 130.8 (C-4″), 135.7 (C-1′), 142.8 and 143.0 (C-1″), 147.0 (C-3′ or C-4′), 148.1 (C-3′ or C-4′), 175.8 (*C*O). − MS (70 eV); *m*/*z* (%): 411 (2) [M$^+$], 394 (62), 390 (4), 360 (2), 301 (10), 286 (73), 284 (100), 126 (12).

15,16-Methylenedioxy-11β-phenylthio-*cis*-erythrinan-8-one (35a) and 15,16-Methylenedioxy-10,11-dehydro-*cis*-erythrinan-8-one (36a): A solution of sulfoxide **33a** (126 mg, 0.3 mmol) in acetic anhydride (5.0 mL) was heated under reflux for 1 h. The reaction mixture was then concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 (5.0 mL). The resulting solution was cooled to 0°C, whereupon a 1 M CH_2Cl_2 solution of $SnCl_4$ (0.33 mL, 0.33 mmol) was added dropwise. After stirring for 15 min, aqueous sodium hydrogen carbonate solution was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated under reduced pressure. Chromatographic purification of the residue on silica gel (cyclohexane/ethyl acetate, 1:1) afforded 13.0 mg (15%) of olefin **36a**; colorless crystals, m.p. 179−180°C (EtOH). − IR (neat): $\tilde{\nu}$ = 2937 cm^{-1}, 1695 (CO), 1634 (C=C), 1500, 1484, 1445. − ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 1.10−1.60 (m, 4 H), 1.70−2.25 (m, 4 H), 2.45 (dd, *J* = 16.8, 9.8 Hz, 1 H, 7-H), 2.56 (dd, *J* = 16.8, 11.4 Hz, 1 H, 7-H), 2.80 (m, 1 H), 5.86 (d, *J* = 7.6 Hz, 1 H, 10-H), 5.94 (s, 2 H, OC*H*$_2$O), 6.60 (s, 1 H, 17-H), 6.80 (d, *J* = 7.6 Hz, 1 H, 11-H), 6.92 (s, 1 H, 14-H). − ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 19.6 (C-2), 20.7 (C-3), 26.5 (C-1), 34.9 (C-4 or C-7), 35.1 (C-4 or C-7), 37.7 (C-6), 62.0 (C-5), 101.1 (O*C*H$_2$O), 105.4 (C-17), 106.2 (C-14), 111.3 (C-11), 119.3 (C-10), 125.0 (C-12), 131.3 (C-13), 146.5 (C-15 and C-16), 170.6 (*C*O). − Further elution gave 68 mg of **35a** (56%); colorless crystals, m.p. 153°C (EtOH). − IR (KBr): $\tilde{\nu}$ = 1689 cm^{-1} (C=O), 1503, 1486, 1451, 1238. − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.50−1.70 (m, 4 H, 2-H$_{ax}$, 3-H, 4-H$_{ax}$), 1.70−1.85 (m, 2 H, 1-H$_{ax}$, 2-H$_{eq}$), 1.87 (m, 1 H, 4-H$_{eq}$), 2.05 (m, 1 H, 1-H$_{eq}$), 2.38 (m, 1 H, 6-H), 2.47 (m, 2 H, 7-H), 3.22 (dd, *J* = 13.9, 3.4 Hz, 1 H, 10α-H), 4.21 (dd, *J* = 3.4, 1.1 Hz, 1 H, 11α-H), 4.33 (dd, *J* = 13.9, 1.1 Hz, 1 H, 10β-H), 5.97 (s, 2 H, OC*H*$_2$O), 6.90 (s, 1 H, 17-H), 6.94 (s, 1

H, 14-H), 7.30 (m, 3 H, 3′-H, 4′-H and 5′-H), 7.60 (m, 2 H, 2′-H and 6′-H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.8 (C-2), 19.2 (C-3), 24.8 (C-1), 35.5 (C-4 and C-7), 37.7 (C-6), 38.3 (C-10), 48.8 (C-11), 61.1 (C-5), 101.2 (O*C*H$_2$O), 104.6 (C-17), 110.5 (C-14), 125.0 (C-12 or C-13), 128.3 (C-4′), 128.9 (C-3′ and C-5′), 133.7 (C-12 or C-13), 134.8 (C-2′ and C-6′), 137.2 (C-1′), 146.3 (C-15 or C-16), 147.4 (C-15 or C-16), 172.6 (*C*O). – MS (70 eV); *m*/*z* (%): 393 (2) [M$^+$], 284 (100) [M$^+$ – SPh], 240 (11), 226 (10), 200 (10), 198 (10), 110 (22) [PhSH].

15,16-Methylenedioxy-*cis*-erythrinan-8-one (39a): To a solution of thioether **35a** (36.4 mg, 0.09 mmol) in toluene (2 mL) was added tri-*n*-butyltin hydride (52 mg, 0.18 mmol) and a few crystals of 2,2′-azobis(isobutyronitrile). The solution was degassed by means of two freeze-pump-thaw cycles, and then stirred at 100°C for 30 min. After cooling, the mixture was concentrated under reduced pressure and the residue was directly purified by chromatography on silica gel (cyclohexane/ethyl acetate, 1:1) to give 20 mg of lactam **39a** (75%); colorless oil. – IR (KBr): $\tilde{\nu}$ = 1679 cm^{-1} (C=O), 1483, 1442, 1417, 1372, 1237. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.50–1.54 (m, 2 H, 3-H), 1.57–1.71 (m, 3 H, 2-H and 1-H$_{ax}$), 1.80–1.83 (m, 2 H, 4-H), 1.98–2.05 (m, 1 H, 1-H$_{eq}$), 2.28 (ddd, *J* = 16.6, 8.1, 0.8 Hz, 1 H, 7-H), 2.34 (dd, *J* = 16.6, 8.0 Hz, 1 H, 7-H), 2.53 (dddd, *J* = 8.1, 8.0, 5.7, 5.1 Hz, 1 H, 6-H), 2.66 (ddd, *J* = 16.4, 5.8, 3.7 Hz, 1 H, 11α-H), 2.93 (dddd, *J* = 16.4, 9.7, 7.1, 0.8 Hz, 1 H, 11β-H), 3.21 (dddd, *J* = 13.2, 9.7, 5.8, 0.8 Hz, 1 H, 10α-H), 4.01 (dddd, *J* = 13.2, 7.1, 3.7, 0.8 Hz, 1 H, 10β-H), 5.91 (s, 2 H, OC*H*$_2$O), 6.55 (s, 1 H, 17-H), 6.86 (s, 1 H, 14-H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.1 (C-3), 20.7 (C-2), 27.0 (C-1), 27.6 (C-11), 34.9 (C-10), 35.9 (C-4), 36.5 (C-7), 37.7 (C-6), 62.6 (C-5), 100.9 (O*C*H$_2$O), 104.9 (C-17), 109.0 (C-14), 126.9 (C-12), 136.0 (C-13), 146.1 (C-15 or C-16), 146.3 (C-15 or C-16), 174.2 (*C*O). – MS (ESI); *m*/*z* (%): 286 (27) [M$^+$ + 1], 268 (3), 258 (6), 149 (100), 119 (15), 91 (10).

15,16-Methylenedioxy-*trans*-erythrinan-8-one (39b): According to a similar protocol as that described above, starting from *trans*-lactam **33b**, **39b** was obtained in 30% overall yield. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.60–1.75 (m, 2 H), 1.87–1.93 (m, 1 H), 2.00–2.20 (m, 6 H), 2.20–2.27 (m, 2 H, 7-H), 2.78 (ddd, *J* = 14.8, 8.0, 5.8 Hz, 1 H, 11-H), 2.98 (dddd, *J* = 14.8, 8.7, 6.0, 0.5 Hz, 1 H, 11-H), 3.29 (dddd, *J* = 14.5, 8.0, 6.0, 0.5 Hz, 1 H, 10-H), 4.08 (ddd, *J* = 14.5, 8.7, 5.8 Hz, 1 H, 10-H), 5.92 (s, 2 H, OC*H*$_2$O), 6.61 (s, 1 H, 17-H), 7.17 (s, 1 H, 14-H).

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