Synthetic Application of Sequential Palladium-Catalyzed Allylic Acetate Alkylation and Michael Addition Carbocyclization: Synthesis of (±)-Dihydroerythramine

Céline Jousse-Karinthi,[a] Claude Riche,[b] Angèle Chiaroni,[b] and Didier Desmaële*[a]

Keywords: Alkaloids / Annulation / Michael additions / Nitrogen heterocycles

A new synthetic route to aromatic *Erythrina* alkaloids is reported. (Nitromethyl)arene **3** underwent a palladium-catalyzed annulation reaction with allylic acetate **11** to provide nitro esters **12a** and **12b** by an (η^3-allyl)palladium complex alkylation/Michael addition domino sequence. Reduction of the nitro group of **12a**, followed by cyclization of the resulting amino group on the acetate appendage, afforded the bicyclic lactam **29**. Two-carbon elongation at the nitrogen atom of **29** by hetero Michael addition of vinyl phenyl sulfoxide, followed by Pummerer-type cyclization, gave *cis*-11-phenylthioerythrinan-8-one (**32a**, **32b**) along with the rearranged lactam **34**. Reductive desulfurization at C-11, and oxidative cleavage of the C-3 exocyclic double bond afforded the 15,16-(methylenedioxy)erythrinan-3,8-dione (**42**). Reduction of the C-3 carbonyl group and methylation of the resulting alcohol afforded hexahydrocrystamidine (**44**), which was further reduced by aluminum hydride to give (±)-dihydroerythramine (**9**).

Introduction

The *Erythrina* alkaloids are a widely distributed family of structurally interesting and biologically active natural products.[1] Aromatic *Erythrina* alkaloids, exemplified by erythramine (**2**), have the basic skeleton **1**, characteristically possessing a tetrahydroisoquinoline system (C and D rings) fused to a perhydroindole subunit (A and B rings), sharing a common nitrogen atom and a spiro carbon center. Most *Erythrina* alkaloids possess curare-like activity, due to nicotinic cholinergic receptor-blocking properties. Their pharmacological application, however, has been impeded by poor selectivity between the different cholinergic sites, inducing a large array of physiological responses.[2] The considerable synthetic attention received by *Erythrina* alkaloids is most probably due to their polycondensed carbon framework, which constitutes an ideal testing ground for new ring-forming methodologies. Following the early pioneering studies by Belleau,[3] Mondon et al.,[4] and Prelog et al,[5] numerous synthetic approaches for construction of the *Erythrina* ring system have been developed[6–9](Figure 1).

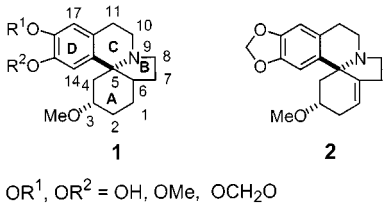


Figure 1. Structure and numbering system of the erythrinane skeleton, and structure of erythramine

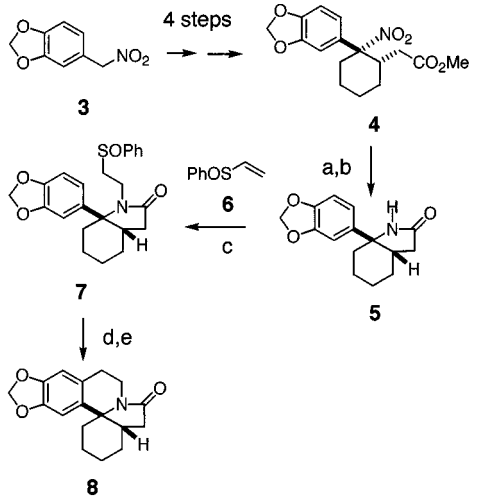
We recently described an efficient route to the tetracyclic lactam **8**, possessing a full erythrinane carbon framework.[10a] The most notable feature of our strategy was the elaboration of the C ring from the ABD subunit **5**, through hetero-Michael addition of vinyl phenyl sulfoxide **6**, followed by Pummerer-type cyclization of the resulting sulfoxide **7**. Lactam **5**, bearing the required angular aryl group, was obtained from nitro ester **4** by reduction of the nitro group, followed by five-membered annulation involving nucleophilic attack of the amino group thus formed on the acetate appendage. Nitro ester **4** had been prepared by a four-step sequence from (nitromethyl)arene **3** (Scheme 1).

In order to extend this strategy to the synthesis of naturally occurring *Erythrina* alkaloids, the introduction of the alkoxy residue at C-3 needs to be addressed. In this context, we have recently reported a new annulation reaction involving an (η^3-allyl)palladium complex alkylation/Michael addition domino sequence, designed to prepare nitro ester **12** from (nitromethyl)arene **3** and allylic acetate **11**.[11] This sequential reaction opened up a one-step route to an erythrinane AD subunit, in which the future methoxy group at C-3 might easily be derived from the exocyclic double bond (Scheme 2).

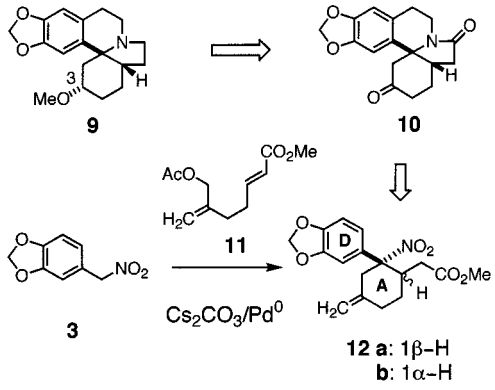
In this paper we wish to give a full account of the synthesis of the nitro ester **12** by applying this domino carbocyclization reaction, and describe the successful conversion of **12** into 15,16-methylenedioxyerythrinan-3,8-dione (**10**), from which most *Erythrina* alkaloids should be derivable. As an illustration, the pivotal lactam **10** was further converted into (±)-dihydroerythramine (**9**).[12]

[a] Unité de Chimie Organique Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris Sud,
5 rue J.-B. Clément, 92296 Châtenay-Malabry, France
Fax: (internat.) + 33-1/46835752
E-mail: didier.desmaele@cep.u-psud.fr
[b] Institut de Chimie des Substances Naturelles, CNRS,
Avenue de la Terrasse, 91198 Gif sur Yvette, France

  1434–193X/01/1019–3631 $ 17.50+.50/0



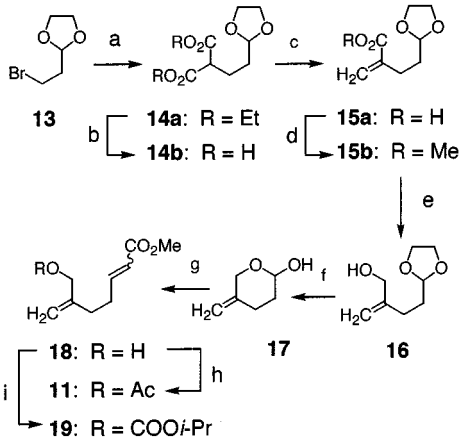
Scheme 1. Synthesis of the 15,16-methylenedioxy-*cis*-erythrinan-8-one **8**; reagents and conditions: (a) Raney nickel, H_2, MeOH, 20 °C, 16 h; (b) toluene, reflux, 2 h (42% from **4**); (c) *i*: NaHMDS, THF, 0 °C, *ii*: **6**, HMPA, 20 °C, 5 h (58%); (d) *i*: Ac_2O, reflux, 1 h, *ii*: $SnCl_4$, CH_2Cl_2, 15 min, 0 °C (56%); (e) *n*Bu_3SnH, AIBN cat., toluene reflux, 30 min (75%)



Scheme 2. Retrosynthetic analysis of C-3-functionalized erythrinane, and synthesis of the A-ring synthon **11** from (nitromethyl)arene **3** by the (η^3-allyl)palladium complex alkylation/Michael addition domino sequence

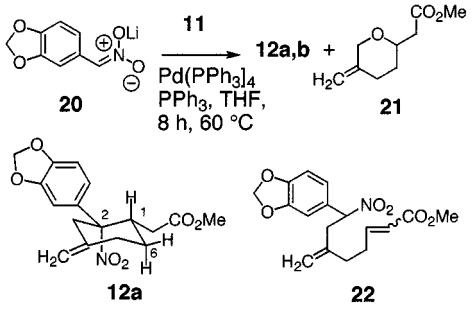
Results and Discussion

The requisite acetoxy ester **11** was prepared by a variant on our initial procedure, allowing a more effective synthetic route on multigram scales.[11] Commercially available bromo ketal **13** was treated with diethyl malonate in the presence of sodium ethoxide according to the procedure of Sakai et al.[13] to afford adduct **14a** in 71% yield. Saponification of both ester groups of compound **14a** with potassium hydroxide gave diacid **14b** in 93% yield. Upon decarboxylative Mannich reaction using formalin and dimethylamine,[14] diacid **14b** provided the unsaturated acid **15a**, which was then treated with *N*,*N*-dimethylformamide dimethyl acetal to give ester **15b** in 61% overall yield. Selective 1,2-reduction of the unsaturated ester group in **15b** was achieved using DIBAH.[15] Hydrolysis of the ketal group of **16** afforded the sensitive hemiketal **17**, which was treated with methyl (triphenylphosphoranylidene)acetate, and then acetylated to provide the desired unsaturated ester **11** as a 4:1 mixture of (*E*) and (*Z*) isomers in 74% overall yield from **16** (Scheme 3).



Scheme 3. Synthetic route to the allylic acetate **11**; reagents and conditions: (a) $EtO_2CCH_2CO_2Et$, EtONa, EtOH, 80 °C, 3 h (71%); (b) KOH, EtOH, 20 °C, 12 h (93%); (c) formalin 40%, Me_2NH, DMSO, 100 °C, 2 h (70%); (d) $Me_2NCH(OMe)_2$, toluene 110 °C, 1 h (87%); (e) DIBAH, CH_2Cl_2, −78 °C; 1 h (72%); (f) HCl 2 N, THF, 20 °C, 6 h; (g) 2 equiv. $Ph_3P{=}CHCO_2Me$, THF, 20 °C, 24 h (77% from **16**); (h) Ac_2O, CH_2Cl_2, Et_3N, DMAP, 20 °C, 30 min (97%); (i) *i*PrOCOCl, CH_2Cl_2, py, 20 °C, 8 h (88%)

(Nitromethyl)arene **3**[16] was initially condensed with allylic acetate **11** [(*E*)/(*Z*) = 4:1] using the lithium nitronate **20**, preformed from **3** by treatment with lithium methoxide in methanol (Scheme 4).[11] Thus, treatment of **20** with 1.1 equiv. of acetate **11** in THF in the presence of 3 mol-% of tetrakis(triphenylphosphane)palladium and 6 mol-% of triphenylphosphane as catalyst provided nitro esters **12a** and **12b** as a ca. 2:1 mixture of diastereomers in 56% yield, along with 10% of tetrahydropyran **21**. The last product presumably arose from deacetylation of acetate **11** by a small amount of lithium methoxide contaminating the nitronate **20**, followed by intramolecular hetero Michael type addition of the resulting alkoxide on the unsaturated ester moiety.[17] If a more hindered base such as lithium *tert*-butoxide was used to prepare the lithium nitronate **20**, the tetrahydropyran **21** was no longer detectable; the yield of nitro esters **12** was found to have decreased slightly, however. A more satisfactory result was obtained when Cs_2CO_3



Scheme 4. Condensation of lithium nitronate **20** with allylic acetate **11**, and relative configuration of nitro ester **12a**

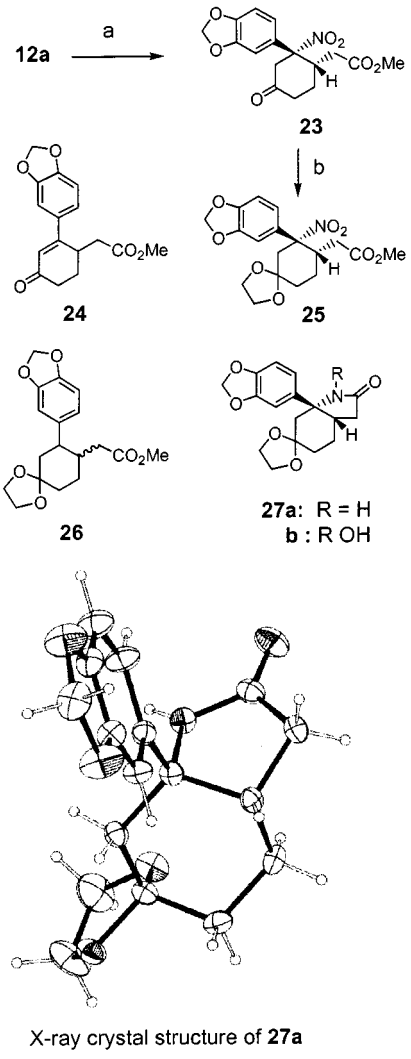
was used as a base. Thus, condensation of (nitromethyl)arene **3** with acetate **11** [2 equiv. of Cs_2CO_3, 3 mol-% of Pd$(PPh_3)_4$, 6 mol-% of PPh_3, 8 h in refluxing THF] gave rise to a 4:1 mixture of nitro esters **12a** and **12b** in a 79% combined yield. The use of DMF as a solvent gave **12a** and **12b** in a similar yield, but with a reduced stereoselectivity (**12a**/**12b** = 2:1). Interestingly, when the reaction was conducted using pure (*Z*)-**11**, the adducts **12a** and **12b** were obtained in 80% yield with the same 4:1 ratio of stereoisomers. Attempts at using allylic carbonate **19** as the electrophilic partner without additional base[18] afforded only the monoalkylated compound **22**, in 83% yield. The annulating process could be restored by addition of lithium *tert*-butoxide to the reaction mixture to induce the Michael addition. Nevertheless, since neither the yield nor the selectivity was improved, the former method was preferred.

The relative stereochemistry of **12a** was assigned by ^1H NMR, by means of NOE and decoupling experiments. The coupling constants between 1-H (δ = 2.98) and the two vicinal 6-H protons (δ = 1.55 and 1.85) were obtained after having simplified the signals by irradiation of the methylene group of the acetate appendage. These values [*J*(1-H/6ax-H) = 10.0 Hz and *J*(1-H/6eq-H) = 3.7 Hz] are in agreement with an axial orientation for 1-H. Furthermore, the *syn* arrangement of the aromatic nucleus respective to the 1-H proton was deduced from an 8% enhancement of the aromatic proton signal when 1-H was irradiated.

Since the stereochemistry of the nitro esters **12** is set in the Michael addition step, a possible equilibration of the adducts was suspected. However, when pure nitro esters **12a** and **12b** were subjected to the same reaction conditions, no isomerization was detected, indicating that the products probably arose from kinetic control in the Michael addition step (Scheme 5). We believe that the preferential formation of nitro ester **12a** results from an approach in which both the nitronate and the unsaturated ester appendage were chelated by the cesium cation.[19] Indeed, when the nitro ester **22** was cyclized by using a base with a nonchelating counterion such as nBu_4NF, an equimolar mixture of the two diastereomers **12a** and **12b** was obtained in 79% yield, demonstrating the lack of stereochemical preference when no chelating cation is present in the reaction medium (Scheme 4).

With the advanced AD subunit **12a** in hand, formation of ring B was next investigated. Since the reduction of the nitro group might be thwarted by competitive reduction of the exocyclic double bond at C-3, we decided to perform its oxidative cleavage first. To this end, Lemieux-Johnson oxidation[20] of **12a** gave ketone **23**. However, attempts to purify this compound by chromatography on silica gel promoted β-elimination of nitrous acid, resulting in enone **24**. In view of the sensitivity of **23** to acid, the protection of the ketone function was carried out using Noyori's method.[21] Thus, treatment of crude **23** with bis(trimethylsilyloxy)ethane in the presence of TMSOTf provided ketal **25** in 58% overall yield from **12a**.

The reduction of the nitro group turned out to be much more difficult than expected, due to steric hindrance and



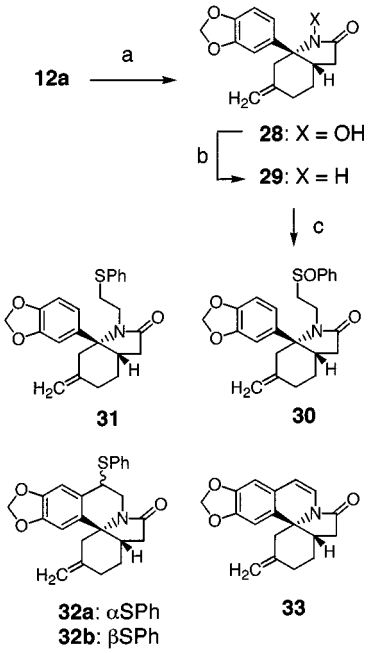
Scheme 5. Oxidative cleavage of the C-3 methylene group and cyclization of the B ring, and X-ray crystal structure of lactam **27a**; reagents and conditions: (a) OsO_4 cat., $NaIO_4$, THF, *t*BuOH, H_2O, 20 °C, 2 h; (b) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, 0 °C (58% overall from **12a**)

competitive hydrogenolysis.[22] Raney nickel reduction of **25**, which had successfully been used to reduce the model compound **4**,[10a] unexpectedly gave lactam **27a** in only 15% yield, the major product being the "denitrated" ester **26**. Upon attempted catalytic hydrogenation using Rh/C or PtO_2, the nitro ester **25** was recovered unchanged, whereas Pd/C gave only hydrogenolysis product **26**. Conventional nickel boride[23] or aluminum amalgam[24] afforded complex mixtures. Treatment of nitro ester **25** with Zn/NH_4Cl[25]provided hydroxamic acid **27b**, albeit with a low mass balance. Since the spectroscopic data of the latter compound were very close to those of lactam **27a**, the structural assignment of **27a** was confirmed by X-ray diffraction analysis, unambiguously establishing the presence of the lactam function, and corroborating the *cis* AB-ring junction (Scheme 5).[26]

In response to these obstacles, the oxidative cleavage of the double bond was postponed until the elaboration of the tetracyclic system. Thus, treatment of nitro ester **12a** with

zinc dust and ammonium chloride in refluxing methanol provided hydroxamic acid **28**, along with a small amount of lactam **29**. This crude mixture was reduced further with a buffered solution of $TiCl_3$[27] to give lactam **29** in 55% overall yield. It is worthy of note that lactam ring-closure is spontaneous in this case, in contrast with our previous findings using the model compound **5**,[10] and did not require any thermal activation.

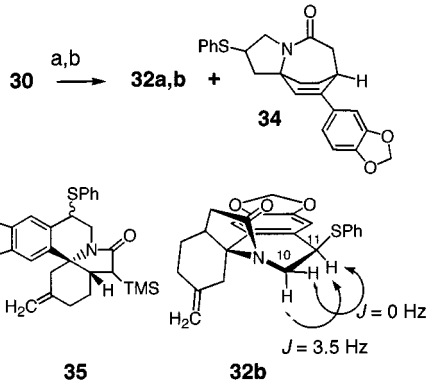
The two-carbon elongation at the nitrogen atom of lactam **29** was next investigated. We were pleased to find that addition of phenyl vinyl sulfoxide (**6**) to the sodium anion of lactam **29** (NaHMDS, THF, −78 °C) provided the desired Michael adduct **30** in 85% yield. The crucial cyclization of the C ring of the erythrinane core was then checked. Although previous investigations[10a][10b] had set precedents for the Pummerer cyclization of sulfoxides of type **30**, the ease of this transformation was by no means certain, since the double bond might compete with the aromatic ring for attack at the sulfenium site. Supporting evidence for this assumption was quickly obtained, since sequential treatment of **30** with acetic anhydride and $SnCl_4$ inflicted extensive damage on the molecule. On the other hand, treatment of sulfoxide **30** with trifluoroacetic anhydride (TFAA) (CH_2Cl_2, −78 to 20 °C) produced a mixture of thioethers **32a** (21%) and **32b** (10%), olefin **33** (29%), and uncyclized thioether **31** (25%)[28] (Scheme 6).



Scheme 6. Elaboration of ring B of nitro ester **12a** and attempts at forming the C ring through Pummerer-type reaction; reagents and conditions: (a) Zn, NH_4Cl, MeOH, reflux, 4 h; (b) 17% aq. $TiCl_3$, AcONa, 20 °C, 3 h; (c) *i*: NaHMDS, THF, 0 °C, 15 min, *ii*: H_2C=CHSOPh (**6**), − 78 °C to 20 °C, 12 h

A more satisfactory result was obtained by treatment of sulfoxide **30** with TMSOTf in the presence of iPr_2NEt.[29] Since a substantial amount of the *C*-silylated lactam **35** was formed during the Pummerer cyclization, the crude product was directly subjected to desilylation with nBu_4NF. This method provided a 1:2 mixture of thioethers **32a** and **32b** in a 54% combined yield, along with the "rearranged" lactam **34** (14%).

The β-stereochemical orientation of the phenylthio group in **32b** was inferred from ^1H NMR spectroscopy. The methine hydrogen atom at C-11 (δ = 4.16) occurs as a doublet, with a coupling constant only with the vicinal 10-Hα [*J*(11-H/10α-H) = 3.5 Hz, *J*(11-H/10β-H) = 0 Hz]. These data are consistent with a β configuration for the phenylthio group, pseudoaxially disposed on a half-chair (Scheme 7). In contrast, the 11-H proton (δ = 4.34) in the **32a** isomer exhibits two large coupling constants (*J* = 10.7 and 7.4 Hz) with the vicinal 10α-H (δ = 3.15) and 10β-H (δ = 4.77) protons, respectively.

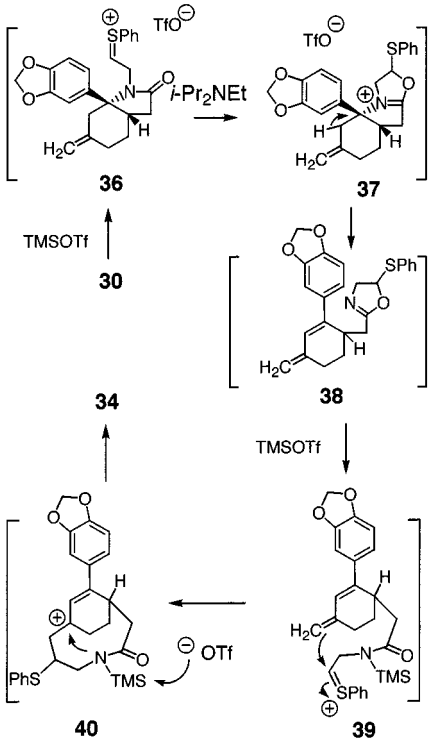


Scheme 7. Pummerer reaction of sulfoxide **30**; reagents and conditions: (a) TMSOTf, iPr_2NEt, CH_2Cl_2; (b) nBu_4NF, THF

The structure of compound **34** eluded us for quite some time. Examination of the NMR and IR spectra revealed that **34** is an isomer of lactam **32**. The ^1H NMR spectrum shows a monosubstituted methylenedioxyphenyl group, a phenylthio ether group, and a sharp doublet (at δ = 6.23, *J* = 1.4 Hz) corresponding to an isolated olefinic proton. The structure was eventually solved with the use of HMQC and HMBC experiments, allowing complete assignment of the C−C and C−H connectivities. These data clearly indicate that the methine atom bearing the phenylthio group is flanked by two methylene groups. From this information, we were able to attribute the hitherto unknown 5-azatricyclo[6.2.2.$0^{1,5}$]dodecane ring system to lactam **34** (Scheme 7).

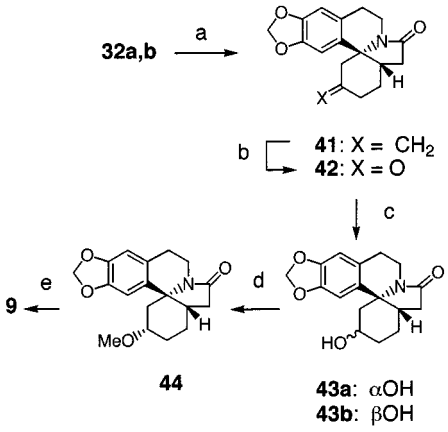
Formation of the lactam **34** could be tentatively explained by invoking the mechanism depicted in Scheme 8. Initial reaction of the sulfoxide group of **30** with TMSOTf gave thionium ion **36**. Intramolecular attack by the lactam oxygen atom on the cationic center of **36** should provide dihydroazolium ion **37**,[30] which undergoes an easy β elimination, giving rise to the diene **38**. Further reaction of the oxazoline moiety with TMSOTf induces ring fragmentation, with the formation of the sulfenium ion **39**. Attack on this species by the exocyclic double bond then affords the stabilized cation **40**, which finally cyclizes to the tricyclic lactam **34** (Scheme 8).

Upon treatment with tri-*n*-butyltin hydride and 2,2′-azobis(isobutyronitrile) in refluxing toluene, the above mixture of lactams **32a** and **32b** was smoothly converted into the



Scheme 8. Hypothetical mechanism for the formation of tricyclic lactam **34**

desired 3-methyleneerythrinan-8-one (**41**) in 75% yield. Having completed the elaboration of the erythrinane system, our attention turned to functionalization of the A ring. To this end, oxidative cleavage of the exocyclic double bond was first undertaken. In the event, Lemieux–Johnson oxidation[20] of **41** gave ketone **42** in 62% yield. Luche reduction of the carbonyl group at C-3 according to the procedure of Tsuda et al.[31] afforded a 3:1 mixture of epimeric alcohols **43a** and **43b** in 90% yield. After chromatographic separation, methylation of the hydroxy group of **43a** provided hexahydrocrytamidine (**44**)[32] in 95% yield. Finally,



Scheme 9. Functionalization of the A ring; reagents and conditions: (a) nBu$_3$SnH, AIBN, refluxing toluene 2 h (75%); (b) OsO_4, $NaIO_4$, THF, H_2O, MeOH (62%); (c) $NaBH_4$, $CeCl_3$, MeOH (90%); (d) NaH, nBu$_4$NHSO$_4$, MeI, THF (95%); (e) AlH_3, THF, Et_2O, 2 h, 20 °C (78%)

reduction of the carbonyl group of **44** with AlH_3[33] gave (±)-dihydroerythramine (**9**)[12] in 78% yield (Scheme 9).

Conclusion

In summary, (±)-dihydroerythramine (**9**) has been synthesized from (nitromethyl)arene **3** by a linear sequence of 10 chemical operations, with an overall yield of 4.9%. A sequential palladium-catalyzed annulation reaction was used to assemble the AD subunit **12a** rapidly. Completion of the construction of the erythrinane skeleton was achieved by elaboration of the C ring through Pummerer-type cyclization, followed by introduction of the methoxy group at C-3. This tandem intermolecular alkylation/intramolecular Michael addition is particularly attractive, as two carbon–carbon bonds and two stereocenters are formed in a single step. Further applications of this method are currently under investigation in our laboratory.

Experimental Section

General: Melting points: Büchi capillary tube melting point apparatus, values uncorrected. – IR spectra: Perkin–Elmer 841 spectrometer; neat films between NaCl plates or KBr pellets. Only significant absorptions are listed. – The ^{1}H and ^{13}C NMR spectra were recorded with 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, respectively) spectrometers. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in the ^{13}C NMR spectra is based on the *J*-modulated spin-echo sequence. – Mass spectra were recorded with a Hewlett Packard G 1019 A (70 eV). – Analytical thin layer chromatography was performed on Merck $60F_{254}$ silica gel precoated glass plates (0.25 mm layer). – Column chromatography was performed on Merck 60 silica gel (230–400 mesh ASTM). – Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methanol and ethanol were dried with magnesium and distilled. Benzene, toluene, DMF, and CH_2Cl_2 were distilled from calcium hydride under nitrogen. – All reactions involving air- or water-sensitive compounds were routinely conducted in glassware that had been flame-dried under positive nitrogen pressure. – 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 were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

2-[2-(1,3-Dioxolan-2-yl)ethyl]propanedioic Acid (14b): Diester **14a**[13] (24.0 g, 92.2 mmol) in 95% ethanol (50 mL) was added to a solution of KOH (15.0 g, 0.268 mol) in 95% ethanol (200 mL). The reaction mixture was stirred at 20 °C for 12 h and concentrated under reduced pressure. The viscous residue was cooled to 0 °C and acidified to pH = 3 with 6 N hydrochloric acid. The mixture was then concentrated to dryness under vacuum while keeping the temperature below 30 °C. The residue was taken into methanol and filtered. The solid was thoroughly washed with methanol, and the filtrate was concentrated to give 17.5 g of diacid **14b** (93%); colorless crystals, m.p. 94–96 °C (MeOH). – IR (neat): $\tilde{\nu}$ = 3200–2550 cm^{-1} (OH), 1697 (C=O), 1400, 1251. – ^{1}H NMR ([D$_6$]acetone, 200 MHz): δ = 1.63–1.85 [m, 2 H, H_2CCH(OCH$_2$)$_2$], 1.90–2.10 [m, 2 H, H_2CCH$_2$CH(OCH$_2$)$_2$], 3.44 (t, J = 7.4 Hz, 1 H, HO$_2$CCH-

CO_2H), 3.75−3.95 (m, 4 H, OCH_2CH_2O), 4.83 [t, J = 4.5 Hz, 1 H, $CH(OCH_2)_2$], 5.20−6.10 (broad, 2 H, O*H*). − ^{13}C NMR ([D$_6$]-acetone, 50 MHz): δ = 24.0 [$H_2CCH_2CH(OCH_2)_2$], 32.1 [$H_2CCH(OCH_2)_2$], 51.7 (HO_2CCHCO_2H), 65.5 (2 CH_2, OCH_2-CH_2O), 104.5 [$CH(OCH_2)_2$], 171.2 (2 *C*O). − $C_8H_{12}O_6$ (204.2): calcd. C 47.06, H 5.92; found C 47.11, H 5.87.

2-[2-(1,3-Dioxolan-2-yl)ethyl]propenoic Acid (15a): Aqueous formaldehyde (37%, 21 mL, 280 mmol), aqueous dimethylamine (40%, 8.5 mL, 68 mmol), and a drop of piperidine were added to a solution of diacid **14b** (14.0 g, 68.6 mmol) in DMSO (150 mL). The reaction mixture was heated at 100 °C for 2 h. After cooling to 0 °C, the solution was acidified to pH = 3 with 1 N hydrochloric acid. The mixture was extracted with ether, dried, and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 4:1) gave 8.2 g of acid **15a** (70%); colorless crystals, m.p. 56−58 °C (MeOH). − IR (neat): $\tilde{\nu}$ = 3720−2400 cm^{-1} (OH), 1676 (CO), 1628 (C=C), 1442, 1415. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.81−1.95 [m, 2 H, $H_2CCH(OCH_2)_2$], 2.45 [t, J = 8.5 Hz, 2 H, $H_2CCH_2CH(OCH_2)_2$], 3.78−4.02 (m, 4 H, OCH_2CH_2O) 4.91 [t, J = 4.8 Hz, 1 H $CH(OCH_2)_2$], 5.70 (s, 1 H, *H*C=C), 6.30 (s, 1 H, *H*C=C). − ^{13}C NMR ([D$_6$]acetone, 50 MHz): δ = 27.0 [$H_2CCH(OCH_2)_2$], 33.4 [$H_2CCH_2CH(OCH_2)_2$], 65.4 (2 CH_2, OCH_2CH_2O), 104.4 [$CH(OCH_2)_2$], 125.6 (H_2C=C), 141.3 (H_2C=*C*), 168.9 (*C*O). − $C_8H_{12}O_4$ (172.1): calcd. C 55.81, H 7.02; found C 55.62, H 6.93.

Methyl 2-[2-(1,3-Dioxolan-2-yl)ethyl]propenoate (15b): *N*,*N*-Dimethylformamide dimethylacetal (8.3 g, 69.6 mmol) was added to a solution of acid **15a** (8.0 g, 46.5 mmol) in toluene (100 mL). After stirring for 1 h at reflux, the mixture was concentrated under reduced pressure. Chromatographic purification on silica gel (hexane/ethyl acetate/Et_3N, 4:1:0.002) gave 7.5 g of ester **15b** (87%); colorless oil. − IR (neat): $\tilde{\nu}$ = 1725 cm^{-1} (CO), 1633 (C=C), 1440, 1411, 1311. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.70−1.82 [m, 2 H, $H_2CCH(OCH_2)_2$], 2.38 [t, J = 8.5 Hz, 2 H, $H_2CCH_2CH(OCH_2)_2$], 3.68 (s, 3 H, OCH_3), 3.70−3.93 (m, 4 H, OCH_2CH_2O), 4.81 [t, J = 4.8 Hz, 1 H, $CH(OCH_2)_2$], 5.45 (s, 1 H, H_2C=C), 6.08 (s, 1 H, H_2C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 26.2 [$H_2CCH_2CH(OCH_2)_2$], 32.3 [$H_2CCH(OCH_2)_2$], 51.6 (OCH_3), 64.7 (2 CH_2, OCH_2CH_2O), 103.6 [$CH(OCH_2)_2$], 124.7 (H_2C=C), 139.8 (H_2C=*C*), 167.2 (*C*O). − $C_9H_{14}O_4$ (186.2): calcd. C 58.05, H 7.58; found C 57.90, H 7.55.

2-[2-(1,3-Dioxolan-2-yl)ethyl]prop-2-en-1-ol (16): A toluene solution of DIBAH (1 M, 8.4 mL, 84 mmol) was added dropwise to a cold solution (−78 °C) of ester **15b** (7.5 g, 40.2 mmol) in THF (70 mL). The mixture was stirred for 1 h at −78 °C, and 5 mL of ethyl acetate was then carefully added. The clear solution was poured into an aqueous solution of potassium sodium tartrate (100 mL) and the resulting mixture was stirred for 12 h at 20 °C. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate/Et_3N, 4:1:0.002) provided alcohol **16** (4.6 g, 72%); colorless oil b.p. 79−80 °C/0.5 Torr. − IR (neat): $\tilde{\nu}$ = 3680−3150 cm^{-1} (OH), 1657 (C=C), 1446, 1412, 1139. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.68−1.78 [m, 2H, $H_2CCH(OCH_2)_2$], 2.09 [t, J = 7.3 Hz, 2 H, $H_2CCH_2CH(OCH_2)_2$], 2.80 (m, 1 H, O*H*), 3.71−4.00 (m, 4 H, OCH_2CH_2O), 3.95 (s, 2 H, $HOCH_2$), 4.78 [m, 2 H, H_2C=C and $CH(OCH_2)_2$], 4.94 (s, 1 H, H_2C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 26.5 [$H_2CCH_2CH(OCH_2)_2$], 31.5 [$HH_2CCH(OCH_2)_2$], 64.3 (2 CH_2, OCH_2CH_2O), 64.8 ($HOCH_2$), 103.6 [$CH(OCH_2)_2$], 108.6 (H_2C=C), 147.8 (H_2C=*C*).

Methyl (*Z*)- and (*E*)-6-(Hydroxymethyl)hepta-2,6-dienoate (18): Aqueous HCl (2 N, 30 mL, 60 mmol) was added to a solution of alcohol **16** (4.3 g, 27.2 mmol) in THF (60 mL). After the mixture had been stirred for 5 h at 20 °C, the pH was brought to 10 with solid $NaHCO_3$. Evaporation of the THF afforded a residue that was extracted thoroughly with CH_2Cl_2. The organic layers were dried and concentrated under reduced pressure to leave hemiketal **17** as a pale yellow oil. The crude hemiketal was taken into CH_2Cl_2 (50 mL) and methyl (triphenylphosphoranylidene)acetate (17.0 g, 50.9 mmol) was added portionwise. The reaction mixture was stirred at 20 °C for 16 h. The solvent was removed under reduced pressure and the residue was taken into a mixture of ether/pentane (1:1, 100 mL) and filtered. The filtrate was concentrated in vacuo to leave a colorless oil. Chromatographic separation on silica gel (cyclohexane/ethyl acetate, 4:1) first afforded 0.70 g of unsaturated ester (*Z*)-**18** (15%), R_f = 0.57; colorless oil. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.79 (m, 1 H, O*H*), 2.24 (t, J = 7.6 Hz, 2 H, H_2CCH_2CH=$CHCO_2Me$), 2.75−2.90 (m, 2 H, H_2CCH=$CHCO_2Me$), 3.71 (s, 3 H, OCH_3), 4.10 (s, 2 H, $HOCH_2$), 4.89 (s, 1 H, H_2C=C), 5.07 (s, 1 H, H_2C=C), 5.80 (dt, J = 12.1, 0.4 Hz, 1 H, HC=$CHCO_2CH_3$), 6.25 (td, J = 12.1, 6.7 Hz, 1 H, *H*C=$CHCO_2CH_3$). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.1 (CH_2), 32.1 (CH_2), 51.1 (OCH_3), 65.8 ($HOCH_2$), 110.4 (H_2C=C), 119.8 (HC=$CHCO_2CH_3$), 147.7 (H_2C=*C*), 149.7 (H*C*=$CHCO_2CH_3$), 166.9 (*C*O). − Further elution gave 2.86 g of (*E*)-**18** (62%), R_f = 0.48; colorless oil. − IR (neat): $\tilde{\nu}$ = 3590−3160 cm^{-1} (OH), 1720 (C=O), 1655 (C=C), 1436, 1272, 1200. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.24 (t, J = 7.6 Hz, 2 H, H_2CCH_2CH=$CHCO_2Me$), 2.30−2.40 (m, 2 H, H_2CCH=$CHCO_2Me$), 3.33 (m, 1 H, O*H*), 3.69 (s, 3 H, OCH_3), 4.04 (s, 2 H, $HOCH_2$), 4.86 (s, 1 H, H_2C=C), 5.05 (s, 1 H, H_2C=C), 5.71 (dt, J = 16.8, 0.4 Hz, 1 H, HC=$CHCO_2CH_3$), 6.84 (td, J = 16.8, 5.7 Hz, 1 H, *H*C=$CHCO_2CH_3$). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 29.9 (CH_2), 30.7 (CH_2), 51.3 (OCH_3), 65.3 ($HOCH_2$), 109.8 (H_2C=C), 120.9 (HC=$CHCO_2CH_3$), 147.1 (C, H_2C=*C*), 148.5 (H*C*=$CHCO_2CH_3$), 166.9 (*C*O).

Methyl (*E*)-6-Acetoxymethylhepta-2,6-dienoate (11): A solution of alcohol (*E*)-**18** (1.50 g, 8.8 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. Triethylamine (1.8 g, 17.8 mmol), DMAP (20 mg), and acetic anhydride (1.35 g, 13.2 mmol) were added sequentially. After this had stirred for 1 h at 20 °C, 1 N HCl was added. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2. After drying, the combined organic layers were concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give 1.81 g of acetate (*E*)-**11** (97%); colorless oil, b.p. 60−65 °C/0.5 mm. − IR (neat): $\tilde{\nu}$ = 1745 cm^{-1} (C=O), 1731 (C=O), 1657 (C=C), 1440, 1376. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.00 (s, 3 H, CH_3CO), 2.14 (t, J = 7.6 Hz, 2 H, H_2CCH_2CH=$CHCO_2Me$), 2.30−2.35 (m, 2 H, H_2CCH=$CHCO_2Me$), 3.63 (s, 3 H, OCH_3), 4.43 (s, 2 H, $AcOCH_2$), 4.88 (s, 1 H, H_2C=C), 5.00 (s, 1 H, H_2C=C), 5.77 (dt, J = 15.4, 2.8 Hz, 1 H, HC=$CHCO_2CH_3$), 6.88 (td, J = 15.4, 6.5 Hz, 1 H, *H*C=$CHCO_2CH_3$). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.8 (CH_3CO_2), 30.0 (CH_2CH=$CHCO_2Me$), 31.3 (CH_2CH_2CH=$CHCO_2Me$), 51.2 (OCH_3), 65.2 ($AcOCH_2$), 113.3 (H_2C=C), 121.4 (HC=$CHCO_2CH_3$), 142.3 (C, H_2C=*C*), 147.9 (H*C*=$CHCO_2CH_3$), 166.7 (CO_2CH_3), 170.4 (CH_3COO). − $C_{11}H_{16}O_4$ (212.2): calcd. C 62.25, H 7.60; found C 62.19, H 7.64.

Methyl *cis*- and *trans*-[2-(1,3-Benzodioxol-5-yl)-4-methylene-2-nitrocyclohexyl]acetate (12a and 12b): Cesium carbonate (1.8 g, 5.5 mmol) was added to a solution of (nitromethyl)arene **3** (500 mg, 2.76 mmol), allylic acetate **11** [4:1 (*E*)/(*Z*) mixture, 670 mg,

3.15 mmol], triphenylphosphane (52 mg, 0.2 mmol), and tetrakis-(triphenylphosphane)palladium (120 mg, 0.10 mmol) in THF (15 mL). The mixture was carefully degassed by means of two freeze-pump-thaw cycles and stirred at 50 °C for 8 h. Aqueous oxalic acid was then added, and the mixture was extracted with ether. The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate, 4:1) afforded adducts **12a** (582 mg, 63%, R_f = 0.42) and **12b** (145 mg, 16%, R_f = 0.36).

Compound 12a: Colorless crystals, m.p. 85−86 °C (MeOH). − IR (neat): $\tilde{\nu}$ = 1725 (CO) cm^{-1}, 1658 (C=C), 1539 (NO_2), 1493, 1439, 1250, 1034, and 927 (OCH_2O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.55 (m, 1 H, 6-H_{ax}), 1.85 (ddt, J = 13.7, 4.9, 3.7 Hz, H 6-H_{eq}), 2.20 (m, 1 H, 5-H_{ax}), 2.34 (dt, J = 14.2, 4.9 Hz, 1 H, 5-H_{eq}), 2.48 (dd, J = 17.0, 2.3 Hz, 1 H, H_2CCO_2Me), 2.66 (dd J = 17.0, 10.0 Hz, 1 H, H_2CCO_2Me), 2.85 (d, J = 14.5 Hz, 1 H, 3-H_{ax}), 2.98 (dddd, J = 10.0, 9.8, 3.7, 2.3 Hz, HCCH$_2$CO$_2$Me), 3.19 (d, J = 14.2 Hz, 1 H, 3-H_{eq}), 3.65 (s, 3 H, OCH_3), 4.83 (d, J = 2.0 Hz, 1 H, H_2C=C), 4.86 (d, J = 2.0 Hz, 1 H, H_2C=C), 5.97 (s, 2 H, OCH_2O), 6.70−6.79 (m, 3 H, 4′-H, 6′-H, 7′-H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.5 (CH_2, C-6), 32.1(CH_2, C-5), 34.9 (CH_2CO_2Me), 41.2 (CHCH$_2$CO$_2$Me), 44.7 (CH_2, C-3), 51.6 (OCH_3), 98.2 (ArCNO$_2$), 101.5 (OCH_2O), 106.0 (CH, C-4′), 108.2 (CH, C-7′), 112.0 (H_2C=C), 119.1 (CH, C-6′), 131.7 (C, C-5′), 141.7 (H_2C=C), 147.6 (C, C-3′a or C-7′a), 148.2 (C, C-3′a or C-7′a), 172.9 (CO). − $C_{17}H_{19}NO_6$ (333.3): calcd. C 61.25, H 5.75, N 4.20; found C 61.17, H 5.82, N 4.09.

Compound 12b: Colorless crystals, m.p. 111−112 °C (MeOH). − IR (KBr): $\tilde{\nu}$ = 1730 (CO) cm^{-1}, 1657 (C=C), 1536 (NO_2), 1505, 1493, 1439, 1039, and 934 (OCH_2O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.66−1.85 (m. 2 H, 6-H), 2.03 (dd, J = 15.7, 3.0 Hz, 1 H, H_2CCO_2Me), 2.15−2.25 (m, 2 H, 5-H), 2.32 (dd, J = 15.7, 11.2 Hz, 1 H, H_2CCO_2Me), 2.67 (d, J = 14.2 Hz, 1 H, 3-H_{ax}), 3.52 (dd, J = 14.2, 1.7 Hz, 1 H, 3-H_{eq}), 3.63 (s, 3 H, OCH_3), 3.65 (m, 1 H, HCCH$_2$CO$_2$Me), 4.88 (br. s, 2 H, H_2C=C), 5.98 (s, 2 H, OCH_2O), 6.78 (d, J = 8.6 Hz, 1 H, 7′-H), 6.98 (m, 2 H, 2′-H, 6′-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.2 (CH_2, C-6), 28.1 (CH_2, C-5), 33.8 (CH_2CO_2Me), 37.4 (CHCH$_2$CO$_2$Me), 37.7 (CH_2, C-3), 51.9 (OCH_3), 96.5 (ArCNO$_2$), 101.6 (OCH_2O), 106.1 (CH, C-4′), 108.4 (CH, C-7′), 113.4 (H_2C=C), 119.2 (CH, C-6′), 131.5 (C, C-5′), 141.5 (H_2C=C), 148.5 (2 C, C-3′a and C-7′a), 172.0 (CO). − $C_{17}H_{19}NO_6$ (333.3): calcd. C 61.25, H 5.75, N 4.20; found C 61.17, H 5.86, N 4.21.

Methyl *cis*-2-[(1,3-Benzodioxol-5-yl)-4-(1,3-dioxolan-2-yl)-2-nitrocyclohexyl]acetate (25): A solution of OsO_4 in *tert*-butyl alcohol (2.5 g/L, 30 mL, 0.3 mmol) and sodium metaperiodate (3.20 g, 15 mmol) were added to a solution of nitro ester **12a** (1.0 g, 3.0 mmol) in THF (80 mL) and water (20 mL). After this had stirred at room temperature for 2 h, brine was added and the mixture was extracted with ethyl acetate. The organic layer was dried and concentrated to leave 690 mg (69%) of ketone **23** as a pale yellow oil. Crude **23** (690 mg, 2.54 mmol) was taken into anhydrous CH_2Cl_2 (20 mL), 1,2-bis(trimethysilyloxy)ethane (850 mg, 3.14 mmol) was added, and the solution was cooled to −78 °C. TMSOTf (120 mg, 0.54 mmol) was added dropwise and the mixture was stirred at −78 °C. After 1 h, the mixture was allowed to warm to 0 °C and kept at this temperature for a further hour. The reaction was quenched with pyridine (100 mg, 1.26 mmol) and poured into brine. The organic layer was separated, and the aqueous phase extracted with CH_2Cl_2. After drying, the combined organic layers were concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate/Et_3N, 2:1:0.005) to give 672 mg of acetal **25** (59% from nitro ester **12a**); colorless crystals, m.p. 144−146 °C (MeOH). − IR (neat): $\tilde{\nu}$ = 1723 cm^{-1} (CO), 1542 (NO_2), 1492, 1439, 1246, 1038, and 928 (OCH_2O). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.74−2.00 (m, 4 H, 5-H, 6-H), 2.32 (d, J = 13.9 Hz, 1 H, 3-H), 2.35 (dd, J = 17.0, 1.3 Hz, 1 H, H_2CCO_2Me), 2.53 (m, 1 H, HCCH$_2$CO$_2$Me), 2.81 (dd, J = 17.0, 8.9 Hz, 1 H, H_2CCO_2Me), 2.98 (d, J = 13.9 Hz, 1 H, 3-H), 3.59 (s, 3 H, OCH_3), 3.79−4.00 (m, 4 H, OCH_2CH_2O), 5.97 (s, 2 H, OCH_2O), 6.55−6.65 (m, 2 H, 4′-H, 7′-H), 6.75 (d, J = 7.8 Hz, 1 H, 6′-H). − ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 25.5 (CH_2, C-6), 34.5 (CH_2, C-5), 34.9 (CH_2CO_2Me), 42.5 (CHCH$_2$CO$_2$Me), 43.2 (CH_2, C-3), 51.5 (OCH_3), 64.2 (OCH_2CH$_2$O), 64.3 (OCH$_2$$CH_2$O), 97.2 (Ar$CNO_2$), 101.5 (O$CH_2$O), 105.9 (CH, C-4′), 106.8 [C(OCH$_2$)$_2$], 108.1 (CH, C-7′), 118.7 (CH, C-6′), 132.2 (C, C-5′), 147.4 (C, C-3′a or C-7′a), 148.1 (C, C-3′a or C-7′a), 173.0 (CO). − $C_{18}H_{21}NO_8$ (379.3): calcd. C 56.99, H 5.58, N 3.69; found C 56.92, H 5.55, N 3.62.

***cis*-7a-(1,3-Benzodioxol-5-yl)-6-(1,3-dioxolan-2-yl)-3a,4,5,6,7,7a-hexahydro-2-indolinone (27a):** A solution of nitro ester **25** (443 mg, 1.16 mmol) in ethyl acetate (5 mL) was added to a suspension of Raney nickel (ca. 2 g) in methanol (20 mL). The mixture was subjected to hydrogenation at 6 bars for 16 h. The reaction mixture was filtered through Celite, and concentrated in vacuo. The crude oil was taken up into toluene (20 mL), and the resulting solution was heated at reflux for 2 h. After concentration under reduced pressure, chromatographic purification on silica gel (ethyl acetate) afforded 140 mg of ester **26** as a colorless oil (40%), and further elution (ethyl acetate/MeOH, 98:2) provided lactam **27a** (66 mg, 15%) as colorless crystals. − IR (neat): $\tilde{\nu}$ = 3280 cm^{-1} (NH), 1693 (C=O), 1487, 1494, 1436, 1240, 1031, and 923 (OCH_2O). − ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.45−1.57 (m, 1 H, 4-H_{ax}), 1.58 (d, J = 15.7 Hz, 3-H), 1.61−1.63 (m, 1 H, 5-H), 1.70−1.80 (m, 2 H, 4-H_{eq}, 5-H_{eq}), 1.79 (d, J = 14.7 Hz, 1 H, 7-H_{eq}), 1.90 (dd, J = 14.7 Hz, 1 H, 7-H_{ax}), 1.96 (dd, J = 15.7, 5.9 Hz, 1 H, 3-H), 2.42 (m, 1 H, 3a-H), 3.77 (m, 2 H, OCH$_2$CH_2O), 3.88 (m, 2 H, OCH_2CH$_2$O), 5.98 (s, 2 H, OCH_2O), 6.82 (d, J = 8.1 Hz, 1 H, 7′-H), 6.87 (dd, J = 8.1, 1.4 Hz, 1 H, 6′-H), 7.04 (d, J = 1.4 Hz, 1 H, 4′-H), 8.12 (s, 1 H, NH). − ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 26.8 (CH_2, C-4), 31.9 (CH_2, C-5), 37.4 (CH_2CONH), 39.0 (CHCH$_2$CONH), 43.3 (CH_2, C-7), 63.1 (OCH$_2$CH$_2$O), 63.9 (OCH$_2$-CH_2O), 64.8 (ArCNHCO), 101.1 (OCH_2O), 106.5 (CH, C-4′), 107.1 [C(OCH$_2$)$_2$], 107.6 (CH, C-7′), 118.4 (CH, C-6′), 141.6 (C, C-5′), 145.4 (C, C-7′a), 147.4 (C, C-3′a), 175.0 (CO). − MS (CI, CH_4): m/z (relative intensity): 318 (100) [$M^{\cdot+}$+1], 300 (9), 255 (14), 216 (15), 99 (21).

Crystal Data for Lactam 27a: $C_{17}H_{19}NO_5$, M_w = 317.33, colorless crystal of 0.2 × 0.1 × 0.008 mm, monoclinic, space group $P2_1/n$, Z = 4, a = 10.329(2), b = 7.805 (3), c = 18.707(4) Å, β = 94.00(2)°, V = 1504.5(7) Å^3, $d_{calcd.}$ = 1.401 gcm^{-3}, F(000) = 672, λ(Mo-K_α) = 0.71070 Å, μ = 0.104 mm^{-1}, Nonius Kappa CCD diffractometer, θ range: 2.18−27.24°, 4372 collected reflections, 2803 unique (R_{int} = 0.0401), 1762 observed [$I > 2\sigma(I)$]. The structure was refined by full-matrix least squares with SHELXL-93, R = 0.0885 for 1762 observed reflections, wR_2 = 0.3121 for 2803 unique reflections, goodness of fit = 1.085, residual electron density −0.294/0.384 e·Å^{-3}. Atoms C12 and C13 of the methylenedioxy ring are disordered. The major position (82%) is represented in the figure (Scheme 5).

***cis*-7a-(1,3-Benzodioxol-5-yl)-6-methylene-3a,4,5,6,7,7a-hexahydro-2-indolinone (29):** Nitro ester **12a** (500 mg, 1.5 mmol) was heated in methanol until complete dissolution. Ammonium chloride (1.20 g,

22.6 mmol) and zinc powder (1.40 g, 21.4 mmol) were added sequentially. After having been stirred at reflux for 4 h, the hot reaction mixture was filtered through a pad of Celite in a sintered glass funnel. The solid was repeatedly washed with methanol, and the filtrate was concentrated. The residue was taken up into water and the mixture extracted with CH_2Cl_2. After drying, the combined organic layers were concentrated. The oily residue was taken into THF (15 mL), and sodium acetate (430 mg, 5.24 mmol) was added, followed by titanium trichloride (17% aqueous solution, 5.2 g, 5.7 mmol). The mixture was degassed through two freeze-pump-thaw cycles and the resulting dark blue solution was stirred for 3 h at 20 °C. Aqueous potassium sodium tartrate (5 mL) was then added, and the mixture was stirred for 1 h at 20 °C. The mixture was extracted with ether. The organic layers were dried and concentrated under reduced pressure. Chromatography on silica gel (ethyl acetate) gave lactam **29** (225 mg, 55%); colorless crystals, m.p. 168−170 °C (MeOH). − IR (KBr): $\tilde{\nu}$ = 3650−3200 cm^{-1} (NH), 1696 (C=O), 1668 (C=C), 1505, 1493, 1478, 1434, 1401, 1037 and 928 (OCH_2O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.55−1.65 (m, 1 H, 4-H), 1.85−1.95 (m, 1 H, 4-H), 2.10 (dd, *J* = 16.3, 5.2 Hz, 1 H, C*H*CON), 2.24−2.32 (m, 1 H, 5-H), 2.40 (m, 2 H, 5-H, C*H*CON), 2.45 (d, *J* = 14.4 Hz, 1 H, 7-H), 2.50−2.55 (m, 1 H, C*H*CH_2CONH), 2.75 (d, *J* = 14.4 Hz, 1 H, 7-H), 4.81 (s, 1 H, H_2C=C), 4.88 (s, 1 H, H_2C=C), 5.96 (s, 2 H, OCH_2O), 6.62 (s, NH), 6.77 (d, *J* = 7.8 Hz, 1 H, 7′-H), 6.90 (dd, *J* = 7.8, 1.0 Hz, 1 H, 6′-H), 6.92 (d, *J* = 10.0 Hz, 1 H, 4′-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.7 (CH_2, C-4), 29.9 (CH_2, C-5), 36.5 (*C*H_2CONH), 42.1 (*C*HCH_2CONH), 44.7 (CH_2, C-7), 65.1 (Ar*C*NHCO), 101.2 (O*C*H_2O), 106.1 (CH, C-4′), 107.9 (CH, C-7′), 110.9 (H_2C=C), 118.2 (CH, C-6′), 140.4 (C, C-5′), 143.3 (H_2C=*C*), 146.6 (C-3′a or C-7′a), 147.9 (C, C-7′a or C-3′a), 177.3 (*C*O). − $C_{16}H_{17}O_3N$ (271.3): calcd. C 70.83, H 6.32, N 5.16; found C 70.52, H 6.27, N 5.14.

***cis*-7a-(1,3-Benzodioxol-5-yl)-6-methylene-1-[2-(phenylsulfinyl)-ethyl]-3a,4,5,6,7,7a-hexahydro-2-indolinone (30):** A THF solution of sodium bis(trimethylsilyl)amide (2 M, 0.49 mL, 0.50 mmol) was added dropwise to an ice-cooled solution of lactam **29** (220 mg, 0.81 mmol) in THF (5 mL). The pale yellow solution was stirred at 0 °C for 15 min and then cooled to −78 °C. Phenyl vinyl sulfoxide (155 mg, 0.89 mmol) was then added and the resulting mixture was stirred for 15 min. The temperature was gradually raised to 20 °C. After stirring for 12 h, 1 N HCl was added, and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate, 1:1) afforded 292 mg of **30** (85%) as a 1:1 mixture of stereoisomers; amorphous solid. − IR (neat): $\tilde{\nu}$ = 1688 cm^{-1} (CO), 1661 (C=C), 1504, 1488, 1444, 1239, 1038, (S=O), 1037 and 928 (OCH_2O). − ^1H NMR ($CDCl_3$, 400 MHz), the stereogenic sulfur atom induced a splitting of most signals: δ = 1.45−1.53 (m, 1 H, 4-H), 1.60−1.75 (m, 1 H, 4-H), 2.15−2.35 (m, 3 H, 5-H, 3-H), 2.40−2.50 (m, 2.5 H, 3-H, 3a-H, $^1/_2$ 7-H), 2.55 (d, *J* = 15.0 Hz, 0.5 H, 7-H), 2.85−3.00 (m, 1.5 H, $^1/_2$ 7-H, NCH_2CH_2SOPh), 3.00 (d, *J* = 15.0 Hz, 0.5 H, 7-H), 3.20−3.40 (m, 2.5 H, NCH_2CH_2SOPh, $^3/_2$ NCH_2CH_2SOPh), 3.65−3.75 (m, 0.5 H, $^1/_2$ NCH_2CH_2SOPh), 4.88, 4.90, 4.94, and 4.96 (4 s, 2 H, H_2C=C), 5.95 and 5.96 (2 s, 2 H, OCH_2O), 6.75 (m, 3 H, 4′-H, 6′-H, 7′-H), 7.45−7.57 (m, 5 H, C_6H_5SO). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.1 (CH_2, C-4), 28.7 (CH_2, C-5), 34.9 (CH_2, C-3), 34.3 and 35.6 (NCH_2CH_2SOPh), 40.3 (CH_2, C-7), 41.6 and 41.8 (C-3a), 53.0 and 54.7 (NCH_2CH_2SOPh), 69.5 and 69.6 (C, C-7a), 101.3 (O*C*H_2O), 106.8 (CH, C-4′), 107.0 (CH, C-7′), 111.6 (H_2C=C), 119.8 (CH, C-6′), 123.8 (2 CH, C-2'', C-6"), 129.1 (2 CH, C-3'', C-5"), 130.9 (CH, C-4"), 137.5 (C, C-5′), 142.9 (C, C-1"), 143.4 (H_2C=*C*), 146.9 (C-7′a or C-3′a), 148.0 (C-3′a or C-7′a), 175.6 (*C*O).

3-Methylene-15,16-methylenedioxy-11β-phenylthio-*cis*-erythrinan-8-one (32b), 3-Methylene-15,16-methylenedioxy-11α-phenylthio-*cis*-erythrinan-8-one (32a), and 9-Benzo[1,3]dioxol-5-yl-3-phenylsulfanyl-5-azatricyclo[6.2.2.0^{1,5}]dodec-9-en-6-one (34): Trimethylsilyl trifluoromethanesulfonate (122 mg, 0.55 mmol) and *N*,*N*-diisopropylethylamine (71 mg, 0.55 mmol) were added dropwise to a solution of sulfoxide **30** (100 mg, 0.24 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was concentrated under reduced pressure, and the residue was taken up into CH_2Cl_2 (5.0 mL). After stirring for 45 min, aqueous sodium bicarbonate was added, and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated under reduced pressure. The oily residue was taken into THF (2 mL), and tetrabutylammonium fluoride (1 M in THF, 0.4 mL, 0.4 mmol) was added. The reaction mixture was stirred at 20 °C for 3 h and quenched with aqueous oxalic acid. The mixture was extracted with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. Chromatographic purification on silica gel (cyclohexane/ethyl acetate, 1:1) afforded 52 mg (54%) of a 1:2 mixture of thioethers **32a** and **32b**, R_f = 0.39, as an amorphous solid. Further elution provided 13 mg of lactam **34** (14%, R_f = 0.19), as a viscous, colorless oil.

Compound 32b: IR (neat): $\tilde{\nu}$ = 1685 cm^{-1} (CO), 1660 (C=C), 1503, 1481, 1035, and 932 (OCH_2O). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.63−1.95 (m, 2 H, 1-H), 2.00−2.64 (m, 7 H, 2-H, 4-H, 6-H, 7-H), 3.13 (dd, *J* = 13.9, 3.5 Hz, 1 H, 10-Hα), 4.16 (d, *J* = 3.5 Hz, 1 H, *H*CSPh), 4.33 (d, *J* = 13.9 Hz, 1 H, 10-Hβ), 4.67 (s, 1 H, H_2C=C), 4.88 (s, 1 H, H_2C=C), 5.95 (s, 2 H, OCH_2O), 6.84 (s, 1 H, 17-H), 6.90 (s, 1 H, 14-H), 7.21−7.40 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.61 (m, 2 H, 2′-H, 6′-H). − $C_{24}H_{23}NO_3S$ (405.5): calcd. C 71.08, H 5.71, N 3.45; found C 70.96, H 5.71, N 3.36.

Compound 34: IR (neat): $\tilde{\nu}$ = 1687 cm^{-1} (CO), 1617 (C=C), 1503, 1487, 1438, 1400, 1036, and 928 (OCH_2O) − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.80−1.94 (m, 2 H, 11-H, 12-H), 1.93−2.03 (m, 1 H, 11-H), 2.07 (dd, *J* = 12.9, 10.7 Hz, 1 H, 2-H), 2.37 (m, 1 H, 12-H), 2.50 (ddd, *J* = 12.9, 6.4, 1.5 Hz, 1 H, 2-H), 2.67 (m. 2 H, H_2CCON), 3.05 (m, 1 H, *H*CCH_2CON), 3.35 (dd, *J* = 12.2, 9.0 Hz, 1 H, CONCH_2), 3.71 (ddt, *J* = 10.7, 9.0, 6.4 Hz, 1 H, *H*CSPh), 4.21 (ddd, *J* = 12.2, 6.4, 1.2 Hz, 1 H, CONCH_2), 5.96 (s, 2 H, OCH_2O), 6.23 (d, *J* = 1.4 Hz, 1 H, *H*C=C), 6.77 (d, *J* = 8.2 Hz, 1 H, 7′-H), 6.83−6.87 (m, 2 H, 4′-H, 6′-H), 7.26−7.33 (m, 3 H, 2′-H, 4′-H, 6′-H), 7.42−7.46 (m, 2 H, 3′-H, 5′-H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 25.4 (CH_2, C-11), 33.4 (H*C*CH_2CON), 35.7 (CH_2, C-12), 41.2 (*C*H_2CON), 41.7 (H*C*SPh), 46.6 (CH_2, C-2), 53.1 (OCN*C*H_2), 60.3 (C, C-1), 101.2 (O*C*H_2O), 105.7 (CH, C-4′), 108.3 (CH, C-7′), 118.9 (CH, C-6′), 127.5 (C, C-4"), 129.2 (2 CH, C-2'', C-6"), 130.6 (H*C*=CAr), 132.0 (2 CH, C-3'', C-5"), 132.9 (C, C-5′), 133.5 (C, C-1"), 146.1 (HC=*C*Ar), 146.9 (C, C-7′a or C-3′a), 148.5 (C, C-3′a or C-7′a), 169.1 (*C*O)

3-Methylene-15,16-methylenedioxy-*cis*-erythrinan-8-one (41): Tri-*n*-butyltin hydride (250 mg, 0.86 mmol) and a few crystals of 2,2′-azobis(isobutyronitrile) were added to a solution of thioethers **32a** and **32b** (100 mg, 0.24 mmol) in toluene (6 mL). The solution was degassed through two freeze-pump-thaw cycles, and stirred at 110 °C for 2 h. After cooling, the mixture was concentrated under reduced pressure, and the residue directly purified by chromatography over silica gel, (cyclohexane/ethyl acetate, 1:1) to give 55 mg of lactam **41** (75%); colorless oil. − IR (KBr): $\tilde{\nu}$ = 1682−1650 cm^{-1} (C=O, C=C), 1503, 1484, 1230, 1035, and 933 (OCH_2O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.85 (dq, *J* = 15.2,

3.7 Hz, 1 H, 1-H_{eq}), 2.15 (m, 1 H, 1-H_{ax}), 2.40−2.45 (m, 4 H, 2-H, 7-H), 2.47 (d, J = 13.9 Hz, 1 H, 4-H_{ax}), 2.50−2.57 (m, 1 H, 6-H), 2.60 (d, J = 13.9 Hz, 1 H, 4-H_{eq}), 2.62 (ddd, J = 15.6, 4.5, 2.0 Hz, 1 H, 11-Hα), 2.90 (ddd, J = 15.6, 12.0, 6.5 Hz, 1 H, 11-Hβ), 3.03 (ddd, J = 13.0, 12.0, 4.5 Hz, 1 H, 10-H), 4.23 (ddd, J = 13.0, 6.5, 2.0 Hz, 1 H, H-10), 4.70 [dd, J = 2.7, 1.3 Hz, 1 H, (*E*)-H_2C=C], 4.87 [s, 1 H, (*Z*)-H_2C=C], 5.92 (d, J = 1.5 Hz, 1 H, OCH_2O), 5.91 (d, J = 1.5 Hz, 1 H, OCH_2O), 6.54 (s, 1 H, 17-H), 6.84 (s, 1 H, 14-H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 25.8 (CH_2, C-1), 27.7 (CH_2, C-2), 28.6 (H_2CCH_2NCO), 34.3 (H_2CCH_2NCO), 35.7 ($HCCH_2CON$), 38.6 ($NCOCH_2CH$), 44.3 (CH_2, C-4), 64.2 (C, C-5), 100.9 (OCH_2O), 105.2 (CH, C-17), 108.9 (CH, C-14), 112.0 (H_2C=C), 126.2 (C, C-13), 135.4 (C, C-12), 142.2 (H_2C=C), 146.1 (2 C, C-15, C-16), 172.6 (*C*O). − MS (EI): *m*/*z* (relative intensity): 297 (14) [$M^{\cdot+}$], 242 (100), 231 (6), 230 (6), 200 (6), 115 (16).

15,16-Methylenedioxy-*cis*-erythrinane-3,8-dione (42): A solution of OsO_4 in *tert*-butyl alcohol (2.5 g/L, 6 mL, 3.0 mmol) and sodium metaperiodate (570 mg, 2.0 mmol) were added sequentially to a solution of lactam **41** (160 mg, 0.50 mmol) in THF (15 mL) and water (5 mL). After stirring at room temperature for 2 h, brine was added and the mixture was extracted with ethyl acetate. The organic layer was dried and concentrated to leave a yellow oil, which was purified by column chromatography on silica gel (ethyl acetate) to give 100 mg of oxo lactam **42** (62%), colorless oil. − IR (KBr): $\tilde{\nu}$ = 1713 cm^{-1}, (C=O), 1675 (NC=O), 1484, 1408, 1034 and 932 (OCH_2O). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.04 (m, 1 H, 1-H), 2.20−3.12 (m, 11 H, 1-H, 2-H, 4-H, 6-H, 7-H, 11-H), 4.23 (m, 1 H, 10-H), 5.94 (s, 2 H, OCH_2O), 6.53 (s, 1 H, 17-H), 6.62 (s, 1 H, 14-H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 26.7 (CH_2, C-1), 27.4 (H_2CCH_2NCO), 34.0 (CH_2), 34.8 (CH_2), 36.0 (CH_2), 37.0 (CH, $HCCH_2CON$), 50.4 (CH_2, C-4), 65.1 (C, C-5), 101.2 (OCH_2O), 104.4 (CH, C-14), 109.1 (CH, C-17), 127.0 (C, C-12), 134.6 (C, C-13), 147.1 (2C, C-15, C-16), 173.5 (N*C*O), 208.2 (*C*O). − HRMS (EI): calcd. for $C_{17}H_{17}NO_4$ 299.1164, found 299.1157.

3α-Hydroxy-15,16-methylenedioxy-*cis*-erythrinan-8-one (43a) and 3β-Hydroxy-15,16-methylenedioxy-*cis*-erythrinan-8-one (43b): Cerium trichloride hexahydrate (79 mg, 0.21 mmol) was added to a solution of ketone **42** (32 mg, 0.107 mmol) in methanol (2 mL). After stirring for 30 min, the mixture was cooled to 0 °C, and sodium borohydride (10 mg, 0.26 mmol) was added in one portion. The reaction mixture was stirred for 20 min and water was added. The mixture was extracted with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/EtOH, 95:5) afforded 22 mg of an α-alcohol **43a** (R_f = 0.46, 68%) and 7 mg of a β-alcohol **43b** (R_f = 0.37, 22%).

Compound 43a: Gum. − IR (neat): $\tilde{\nu}$ = 3500−3300 cm^{-1} (OH), 1653 (C=O), 1504, 1485, 1447, 1034, and 930 (OCH_2O). − ^{1}H NMR ([D_6]benzene, 400 MHz): δ = 1.20−1.40 (m, 3 H, 1-H_{ax}, 1-H_{eq}, 2-H_{eq}), 1.35 (dd, J = 13.1, 10.0 Hz, 1 H, 4-H_{ax}), 1.46−1.54 (m, 1 H, 2-H), 1.86 (dd, J = 13.1, 3.2 Hz, 1 H, 4-H_{eq}), 1.85−1.93 (m, 1 H, 6-H), 2.02 (dd, J = 16.2, 8.4 Hz, 1 H, 7-H), 2.10 (dd, J = 16.2, 5.5 Hz, 1 H, 1 H, 7-H), 2.18 (dt, J = 16.1, 5.5 Hz, 1 H, 11-Hα), 2.44 (ddd, J = 16.1, 8.4, 6.9 Hz, 1 H, 11-Hβ), 3.02 (ddd, J = 12.9, 8.4, 5.5 Hz, 1 H, 10-Hα), 3.46 (m, 1 H, 3-H), 3.87 (ddd, J = 12.9, 6.9, 5.5 Hz, 1 H, 10-Hβ), 5.36 (s, 2 H, OCH_2O), 6.29 (s, 1 H, 17-H), 6.57 (s, 1 H, 14-H). − ^{13}C NMR ([D_6]benzene, 100 MHz): δ = 24.6 (CH_2, C-1), 27.9 (CH_2, C-11), 30.0 (CH_2, C-2), 35.3 (CH_2, C-10), 36.0 (CH_2, C-7), 37.6 (CH, $HCCH_2CON$), 45.0 (CH_2, C-4), 63.2 (C, C-5), 65.9 (CH, C-3), 101.9 (OCH_2O), 105.2 (CH, C-14), 109.5 (CH, C-17), 127.6 (C, C-12), 134.6 (C, C-13), 146.2 (C, C-15 or C-16), 146.7 (C, C-15 or C-16),171.7 (*C*O).

(±)-Hexahydrocrystamidine (44): Sodium hydride (60% in mineral oil, 80 mg, 2.0 mmol) was added to an ice-cooled solution of alcohol **43a** (12 mg, 0.04 mmol) in THF (2 mL) containing a catalytic amount of imidazole, and the mixture was refluxed for 30 min. After cooling to 20 °C, nBu_4NHSO_4 (20 mg, 0.06 mmol) and iodomethane (1.60 g, 11.2 mmol) were added, and the resulting mixture was stirred for 2 h at 20 °C and 30 min at reflux. After cooling, 3 N HCl was added and the mixture was extracted with chloroform. The organic phase was dried and concentrated. The crude product was purified by silica gel chromatography (ethyl acetate/methanol, 95:5) to give 12 mg of lactam **44** (95%) as a colorless gum. − IR (neat): $\tilde{\nu}$ = 1665 (C=O), 1504, 1485, 1441, 1241, 1031, and 928 (OCH_2O). − ^{1}H NMR ([D_6]benzene, 400 MHz): δ = 1.15−1.40 (m, 3 H, 1-H_{ax}, 1-H_{eq}, 2-H_{eq}), 1.48 (dd, J = 13.3, 10.1 Hz, 1 H, 4-H_{ax}), 1.55−1.60 (m, 1 H, 2-H_{ax}), 1.91−2.00 (m, 1 H, 6-H), 2.00−2.15 (m, 3 H, 7-H, 4-H_{eq}), 2.17 (dt, J = 16.1, 5.5 Hz, 1 H, 11-Hα), 2.44 (ddd, J = 16.1, 8.4, 6.9 Hz, 1 H, 11-Hβ), 2.93 (s, 3 H, OCH_3), 2.95−3.08 (m, 2 H, 3-H, 10-Hα), 3.94 (ddd, J = 12.9, 6.9, 5.5 Hz, 1 H, 10-Hβ), 5.36 (m, 2 H, OCH_2O), 6.28 (s, 1 H, 17-H), 6.64 (s, 1 H, 14-H). − ^{13}C NMR ([D_6]benzene, 100 MHz): δ = 24.6 (CH_2, C-1), 26.1 (CH_2, C-2), 28.1 (CH_2, C-11), 35.2 (CH_2, C-10), 35.8 (CH_2, C-7), 38.0 (CH, $HCCH_2CON$), 42.0 (CH_2, C-4), 55.4 (OCH_3), 63.2 (C, C-5), 75.0 (CH, C-3), 101.0 (OCH_2O), 105.1 (CH, C-14), 109.6 (CH, C-17), 127.6 (C, C-12), 136.7 (C, C-13), 146.5 (2 C, C-15, C-16), 170.6 (*C*O).

(±)-Dihydroerythramine (9): A solution of hexahydrocrystamidine (**44**) (14 mg, 0.046 mmol) in THF was treated with an ethereal solution of aluminum hydride (2 mL, 1.2 mmol) for 2 h at 20 °C. Aqueous ammonia was cautiously added and the resulting mixture was extracted with chloroform to leave 10.5 mg of (±)-dihydroerythramine (**9**) (78%); colorless gum. − IR (neat): $\tilde{\nu}$ = 1503, 1482, 1373, 1231, 1092, 1038, and 932 (OCH_2O). − ^{1}H NMR ([D_6]benzene, 400 MHz): δ = 1.35−1.46 (m, 1 H, 7-H), 1.45−1.54 (m, 1 H, 1-H), 1.55−1.65 (m, 3 H, 7-H, 2-H), 1.70−1.76 (m, 1 H, 1-H), 1.77 (dd, J = 13.8, 4.3 Hz, 1 H, 4-H), 1.93 (dd, J = 13.8, 8.0 Hz, 1 H, 4-H), 2.09 (quint, J = 6.9 Hz, 1 H, H-6), 2.22−2.29 (m, 1 H, 11-H), 2.60−2.73 (m, 3 H, 11-H, 10-H, 8-H), 2.79−2.83 (m, 1 H, 8-H), 3.06 (s, 3 H, O*Me*), 3.04−3.12 (m, 1 H, 10-H), 3.24 (m, 1 H, 3-H), 5.38 (m, 2 H, OCH_2O), 6.46 (s, 1 H, H-17), 6.79 (s, 1 H, H-14). − ^{13}C NMR ([D_6]benzene, 100 MHz): δ = 25.8 (CH_2, C-11), 25.9 (CH_2, C-1), 27.9 (CH_2, C-2), 29.1 (CH_2, C-7), 39.4 (CH_2, C-4), 43.1 (CH_2, C-10), 43.2, (CH, C-6), 48.8 (CH_2, C-8), 55.5 (OCH_3), 64.0 (C, C-5), 75.9 (CH, C-3), 100.6 (OCH_2O), 106.2 (CH, C-14), 109.1 (CH, C-17), 129.1 (C, C-12), 138.3 (C, C-13), 143.3 (C, C-15 or C-16), 145.9 (C, C-15 or C-16). − Picrate derivative, m.p. 198 °C (MeOH). − $C_{24}H_{26}N_4O_{10}$ (530.5): calcd. C 54.34, H 4.94, N 10.56; found C 54.03, H 5.22, N 10.29.

Acknowledgments

We gratefully acknowledge Dr. J. Mahuteau and Dr. M. Ourevitch for the 2D NMR and NOE experiments, and Mrs. S. Mairesse-Lebrun for the elemental analyses.

[1] For recent reviews see: [1a] A. S. Chawla, V. K. Kapoor, in: *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Pergamon, Oxford, **1993**, vol. 9, p. 86−153. − [1b] Y. Tsuda, T. Sano, in: *The Alkaloids* (Ed.: G. A. Cordell), Academic Press, San Diego, **1996**, vol. 48, p. 249−337.

[2] [2a] S. Ghosal, S. K. Dutta, S. K. Bhattacharya, *J. Pharm. Sci.* **1972**, *61*, 1274−1277. − [2b] M. Williams, J. L. Robinson, *J.*

Neurosci. **1984**, *4*, 2906−2911. − [2c] M. W. Decker, M. J. Anderson, J. D. Brioni, D L. Donnelly-Roberts, C. H. Kang, A. B. O'Neill, M. Piattoni-Kaplan, S. Swanson, J. P. Sullivan, *Eur. J. Pharmacol.* **1995**, *280*, 79−89.

[3] B. Belleau, *J. Am. Chem. Soc.* **1953**, *75*, 5765−5766.

[4] [4a] A. Mondon, *Angew. Chem.* **1956**, *68*, 578. − [4b] A. Mondon, G. Hasselmeyer, J. Zander, *Chem. Ber.* **1959**, *92*, 2543−2552. − [4c] A. Mondon, K. F. Hansen, *Tetrahedron Lett.* **1960**, 5−8.[4d] A. Mondon, H. J. Nestler, *Angew. Chem. Int. Ed. Engl.* **1964**, *68*, 588.

[5] [5a] V. Prelog, *Angew. Chem.* **1957**, *69*, 33−39. − [5b] V. Prelog, A. Langemann, O. Rodig, M. Ternbah, *Helv. Chim. Acta* **1959**, *42*, 1301−1310.

[6] For further examples featuring the formation of the C-5−C-15 bond see: [6a] M. Haruna, K. Ito, *J. Chem. Soc., Chem. Commun.* **1976**, 345−346. − [6b] H. Ishibashi, K. Sato, M. Ikeda, M. Maeda, S. Akai, Y. Tamura, *J. Chem. Soc., Perkin Trans. 1* **1985**, 605−609. − [6c] H. Ishibashi, T. Sato, M. Takahasi, M. Hayashi, M. Ikeda, *Heterocycles* **1988**, *27*, 2787−2790. − [6d] J. H. Rigby, M. Qabar, *J. Am. Chem. Soc.* **1991**, *113*, 8975−8976. − [6e] A. Padwa, R. Hennig, C. O. Kappe, T. S. Reger, *J. Org. Chem.* **1998**, *63*, 1144−1155. − [6f] J. Cassayre, B. Quiclet-Sire, J.-B. Saunier, S. Z. Zard, *Tetrahedron Lett.* **1998**, *39*, 8995−8998. − [6g] J. H. Rigby, C. Deur, M. J. Heeg, *Tetrahedron Lett.* **1999**, *40*, 6887−6890. − [6h] A. Padwa, A. G. Waterson, *J. Org. Chem.* **2000**, *65*, 235−244.[6i] A. Toyao, S. Chikaoka, Y. Takeda, O. Tamura, O. Muraoka, G. Tanabe, H. Ishibashi, *Tetrahedron Lett.* **2001**, *42*, 1729−1732.

[7] For A ring annulation onto a benzoindolizidine subunit see: [7a] R. V. Stevens, M. Wentland, *J. Chem. Soc., Chem. Commun.* **1968**, 1104−1105. − [7b] T. Sano, J. Toda, N. Kashiwaba, Y. Tsuda, Y. Iitaka, *Heterocycles* **1981**, *16*, 1151−1156. − [7c] T. Sano, J. Toda, Y. Tsuda, *Heterocycles* **1982**, *18*, 229−232. − [7d] H. H. Wasserman, R. M. Amici, *J. Org. Chem.* **1989**, *54*, 5843−5844. − [7e] Y. Tsuda, S. Hosoi, N. Katagiri, C. Kaneko, T. Sano, *Heterocycles* **1992**, *33*, 497−502. − [7f] S. Hosoi, M. Nagao, Y. Tsuda, K. Isobe, T. Sano, T. Ohta, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1505−1511.

[8] For B ring formation starting from a C-5 spiro-isoquinoline system see: [8a] S. J. Danishefsky, J. S. Panek, *J. Am. Chem. Soc.* **1987**, *109*, 917−918. − [8b] C.-T. Chou, J. S. Swenton, *J. Am. Chem. Soc.* **1987**, *109*, 6898−6899. − [8c] R. Ahmed-Schofield, P. S. Mariano, *J. Org. Chem.* **1987**, *52*, 1478−1482. − [8d] H. Irie, K. Shibata, K. Matsuno, Y. Zhang, *Heterocycles* **1989**, *29*, 1033−1035. For annulation of the AB subunit onto an isoquinoline system see: [8e] M. Westling, R. Smith, T. Livinghouse, *J. Org. Chem.* **1986**, *51*, 1160−1161.

[9] For biomimetic approches: [9a] J. E. Gervay, F. McCapra, T. Money, G. M. Sharma, A. I. Scott, *J. Chem. Soc., Chem. Commun.* **1966**, 142−143. − [9b] A. Mondon, M. Ehrhardt, *Tetrahedron Lett.* **1966**, 2557−2568. − [9c] H. Tanaka, M. Shibata, K. Ito, *Chem. Pharm. Bull.* **1984**, *32*, 1578−1582.

[10] [10a] C. Jousse, D. Desmaële, *Eur. J. Org. Chem.* **1999**, 909−915. − For a similar cyclization of the C ring by Pummerer-type reaction see: [10b] J. Toda, Y. Nimura, K. Takeda, T. Sano, Y. Tsuda, *Chem. Pharm. Bull.* **1998**, *46*, 906−912.

[11] C. Jousse, D. Mainguy, D. Desmaële, *Tetrahedron Lett.* **1998**, *38*, 1349−1352.

[12] [12a] V. Prelog, K. Wiesner, H. G. Khorana, G. W. Kenner, *Helv. Chim. Acta* **1949**, *32*, 453−461.[12b] K. Ito, H. Furukawa, H. Tanaka, *J. Chem. Soc., Chem. Commun.* **1970**, 1076−1077.

[13] E. Yamanaka, M. Narushima, K. Inukai, S.-i. Sakai, *Chem. Pharm. Bull.* **1986**, *34*, 77−81.

[14] O. P. Vig, B. Vig, R. K. Khertarpal, R. C. Anand, *Indian J. Chem.* **1969**, *7*, 450−452.

[15] Attempts to reduce the ester function using LAH as described in ref.[14] gave an inseparable mixture of 1,2- and 1,4-reduced alcohols.

[16] N. Kornblum, W. M. Weaver, *J. Am. Chem. Soc.* **1958**, *80*, 4333−4337.

[17] R. A. Bunce, M. J. Bennett, *Synth. Commun.* **1993**, *23*, 1009−1020.

[18] J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura, *Tetrahedron Lett.* **1982**, *23*, 4809−4812.

[19] M.-A. Le Dréau, D. Desmaële, F. Dumas, J. d'Angelo, *J. Org. Chem.* **1993**, *58*, 2933−2935.

[20] R. Pappo, D. S. Allen Jr, R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478−479.

[21] T. Sunoda, M. Susuki, R. Noyori, *Tetrahedron Lett.* **1980**, *21*, 1357−1358.

[22] C. D. Weis, G. R. Newkome, *Synthesis* **1995**, 1053−1065.

[23] J. O. Osby, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 6413−6416.

[24] A. Calder, A. R. Forrester, S. P. Hepburn, *Org. Synth., Coll. Vol.* **1988**, vol. VI, p. 803−806.

[25] [25a] T.-L. Ho, *Synth. Commun.* **1980**, *10*, 469−472. − [25b] R. M. Allen, G. W. Kirby, D. J. McDougall, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1143−1147.

[26] Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with deposition number CCDC-154481. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[27] P. G. Mattingly, M. J. Miller, *J. Org. Chem.* **1980**, *45*, 410−415.

[28] Although the mechanism is still under debate, the reduction of phenyl sulfoxide to phenyl thioether upon treatment with TFAA has been reported previously: K. Cardwell, B. Hewitt, P. Magnus, *Tetrahedron Lett.* **1987**, *28*, 3303−3306.

[29] T. Kaneko, *J. Am. Chem. Soc.* **1985**, *107*, 5490−5492.

[30] The interception of a thionium ion intermediate by an adjacent amido carbonyl group has been reported previously: [30a] A. Padwa, C. O. Kappe, T. S. Reger, *J. Org. Chem.* **1996**, *61*, 6166−6174. − [30b] J. T. Kuethe, A. Padwa, *J. Org. Chem.* **1997**, *62*, 774−775.

[31] Y. Tsuda, M. Murata, S. Hosoi, M. Ikeda, T. Sano, *Chem. Pharm. Bull.* **1996**, *44*, 515−524.

[32] K. Ito, M. Haruna, Y. Jinno, H. Furukawa, *Chem. Pharm. Bull.* **1976**, *24*, 52−55.

[33] A. E. Finholt, A. C. Bond, Jr, H. I. Schlessinger, *J. Am. Chem. Soc.* **1947**, *69*, 1199−1203.

Received March 30, 2001
[O01151]