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# A Synthetic Approach to the Zoanthamine Alkaloids

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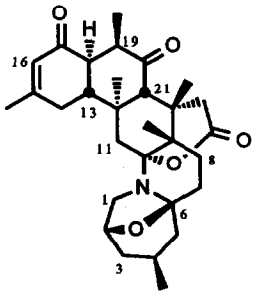
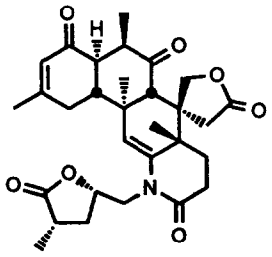
***Abstract:*** *A synthetic approach to the marine alkaloid Zoanthamine is outlined. Starting with (-)-perillyl alcohol, the C-11 to C-20 fragment* ***9b*** *has been synthesized in 12 operations and >30% overall yield. Model studies for a proposed intramolecular Diels-Alder strategy are also described.*

Zoanthamine (**1**) is the first member[1a] of a new class of alkaloids[1b-d] isolated from an unidentified marine zoanthid of the genus *Zoanthus* found on the coast of India. The structure of zoanthamine was elucidated[1a,b] via a combination of NMR spectroscopic methods and X-ray crystallography, but the absolute configuration remains unknown, as does the biosynthetic origin of this intriguing molecule. Zoanthamine and its congeners (e.g. zoanthamide and 28-deoxyzoanthenamine) were isolated in an attempt to determine the structures of inflammatory agents produced by the zoanthid, but the alkaloids were actually found[1b,c] to inhibit phorbol myristate acetate induced inflammation of the mouse ear; as far as we are aware, the mode of biological action has not yet been defined in detail.



Zoanthamine, 1



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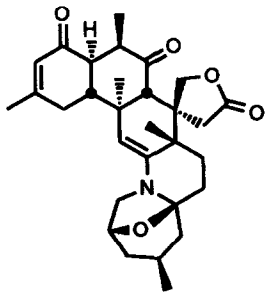
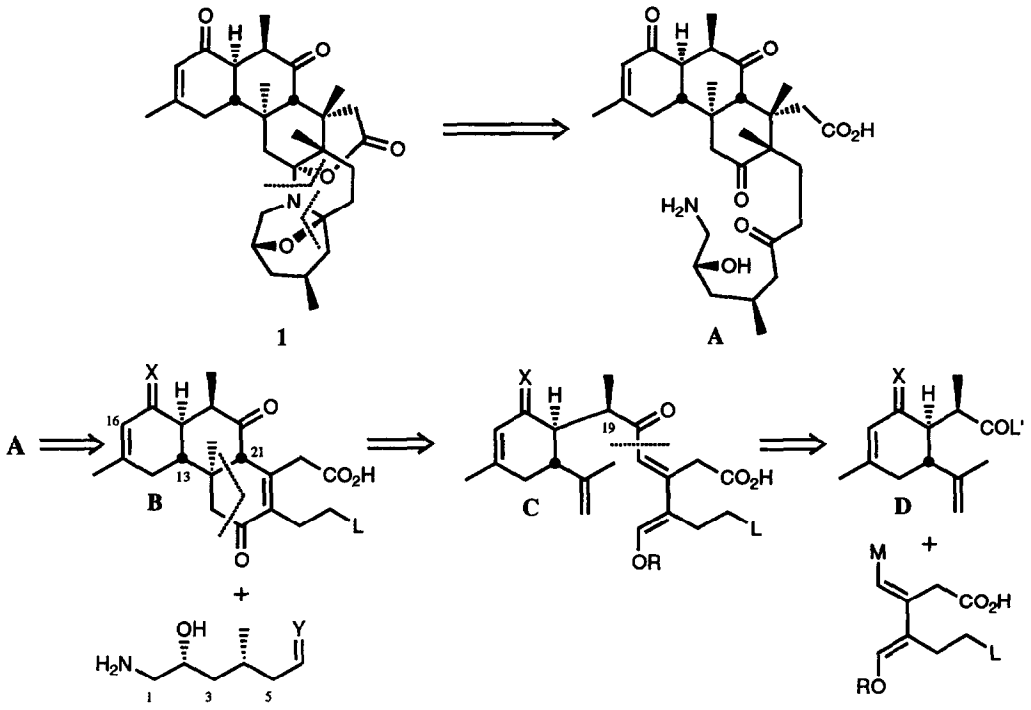


28-Deoxyzoanthenamine

These interesting biosynthetic and pharmacological issues combined with stereochemically complex molecular structures make this family of compounds attractive targets for synthesis. Our goal was thus development of a stereocontrolled synthetic route which would: *(i)* be flexible enough to provide access to several members of the alkaloid class, *(ii)* allow the preparation of simpler analogues for biological testing, in order to define the pharmacophore, and *(iii)* permit the assignment of absolute stereochemistry via direct comparison with the natural product itself or materials derived therefrom. In this paper we present our synthetic plan and some results relating to the C-9 to C-22 portion of zoanthamine. The retrosynthetic analysis is shown in Scheme 1.

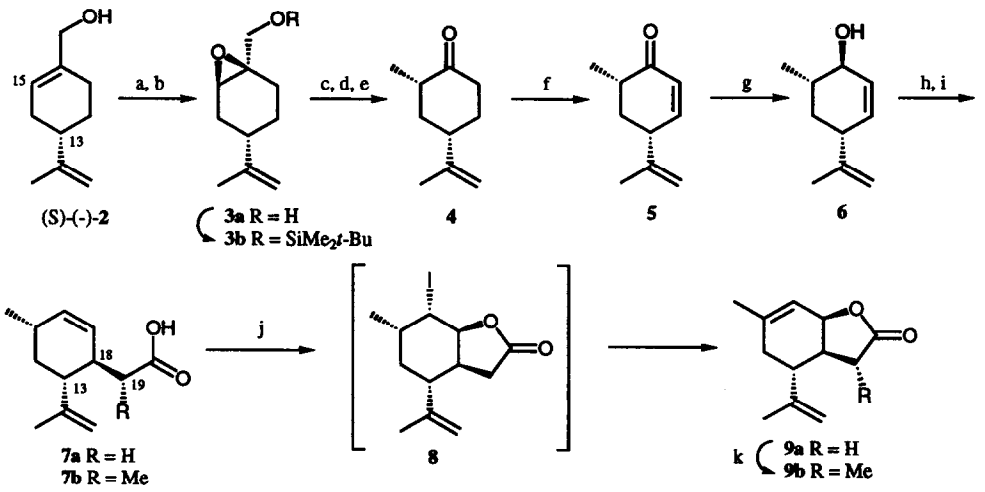



Scheme 1. Retrosynthetic analysis of Zoanthamine. (X = protected carbonyl; Y = umpoled carbonyl; L and L' = potential leaving group; M = metal).

Simultaneous disconnection of the four carbon-heteroatom bonds indicated above unravels the "lower" portion of the target, to give structure **A**[2]. Further retrosynthetic analysis (Scheme 1) defines a convergent route to **A**, the "upper" portion of zoanthamine being embedded in key intermediates **B**, **C** and **D**.

Thus, with the C-17 carbonyl (zoanthamine numbering) of **B** protected, the vicinal methyls on C-22 and C-9 of the target would be introduced by a conjugate addition-enolate trapping sequence on the less-hindered (β) face of the enone. (Inspection of molecular models suggests that nucleophilic attack on the α face is hindered by the axial methyl on C-12). Intermediate **B** is itself projected to arise from **D** via intramolecular Diels-Alder reaction of **C**, the cycloaddition process setting up the stereochemistry at both C-12 and C-21, with one of the controlling factors being the stereochemistry at C-19.

Our synthetic route to an intermediate of type **D** is described in Scheme 2, salient features being a Sharpless asymmetric epoxidation (**2** → **3a**), the stereoselective reduction of an enone (**5** → **6**), a [3,3] sigmatropic rearrangement (**6** → **7a**), and a "one-pot" iodolactonization-elimination sequence (**7a** → **9a**).




Scheme 2. (a) 0.1 eq. $Ti(OiPr)_4$, 0.12 eq. (-) diethyltartrate, 1.5 eq. TBHP, 4 Å mol. sieves, $CH_2Cl_2$, 85%, >99% *de*. (b) *t*-BDMSCl, $Et_3N$, DMAP, $CH_2Cl_2$, 95%. (c) 2eq. $LiMe_2Cu$, $Et_2O$, 97%. (d) HCl, MeOH, 98%. (e) 1.2 eq. $Pb(OAc)_4$, benzene, 92%. (f) *i.* 1.2 eq. LDA, THF. then 1.2 eq. PhSeBr. *ii.* $H_2O_2$, pyridine, 85%. (g) $LiAlH_4$, $Et_2O$, -78°C, 96%, 96% *de*. (h) 10 eq. triethyl orthoacetate, cat. 2,4-dinitrophenol, toluene, 120°C, 85%. (i) LiOH, THF, $H_2O$, 95%. (j) for **7a**: 2 eq. $I_2$, 1.5 eq. DBU, $CH_3CN$, 70 °C, 84%. (k) 1.1 eq. LDA, 1.2 eq. MeI, 94 %, > 99% *de*.

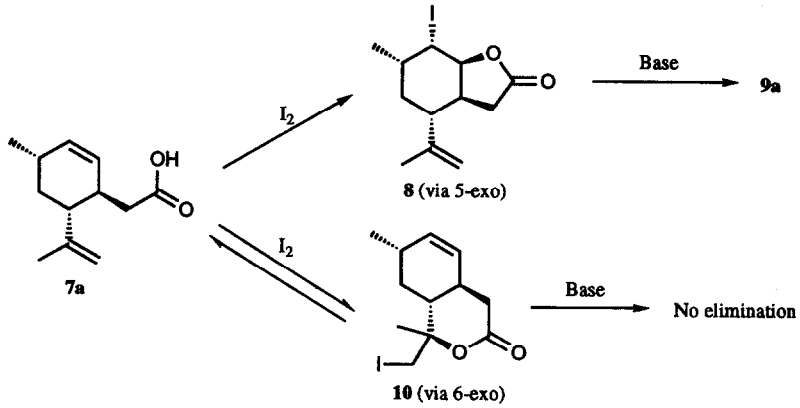
The starting material chosen[3] was perillyl alcohol (**2**, both enantiomers of which are commercially available) which provides the C-13 stereochemistry of the target. The cheaper (*S*)-enantiomer was selected in order to conform with the absolute stereochemistry depicted in Scheme 1. The catalytic version[4] of the Sharpless asymmetric epoxidation reaction provided alcohol **3a** as a single diastereomer[5] which was converted to silyl ether **3b**. The methyl group on C-15 of the target was then introduced by regioselective ring-opening of **3b** with lithium dimethylcuprate. (Attempts to ring-open **3a** directly gave a mixture of products, presumably due to a competing Payne-type rearrangement[6] of the epoxy alcohol with the lithium cation acting as a Lewis acid). The product of the cuprate reaction was exposed to dilute hydrochloric acid to remove the silyl group, and the resultant 1,2-diol was cleaved by lead tetraacetate to give ketone **4**. The kinetic enolate of this ketone was generated and then trapped with phenylselenyl bromide to give a diastereomeric mixture of two phenylselenides, both of which yielded enone **5** after a standard oxidation-elimination[7] sequence.

Although the stereochemistry at the $sp^3$ α-carbon of **5** is eventually lost, we reasoned it would nevertheless be of importance for the success of subsequent operations (conversion of **7a** to **9a** via **8**, as discussed below). The next crucial step was the stereoselective reduction of the enone to obtain the allylic alcohol **6**, the stereochemistry of which was to be used to control formation of the C-18 (and possibly also the C-19) centre of the target via [3,3] sigmatropic rearrangements of suitable derivatives of **6**. Reduction of **5** by lithium aluminum hydride in diethyl ether at low temperature smoothly yielded a

separable 98:2 mixture of diastereomers, the major component being the desired **6**, which is the product of pseudoaxial attack by hydride[8]. (We have not investigated whether changing the absolute configuration at the α-carbon of the substrate has any effect on the stereochemical outcome of the reduction).

In principle, the Ireland-Claisen[9a,b] rearrangement could be used to generate **7b** from a silyl ketene acetal derived from the propionate ester of **6**, thus setting up both the C-18 and C-19 centres of the target in one operation. However, an analysis of the possible transition states for the reaction reveals that the cyclohexenyl ring is likely to always adopt a boat conformation[9c] since the corresponding chair would be destabilized by a severe 1,3-diaxial interaction between the methyl and isoprenyl substituents. Formation of the desired stereochemistry for C-19 would then require either *(a)* another boat for reaction of the (*Z*)-silyl ketene acetal or *(b)* a chair for the (*E*)-isomer. The former combination is unlikely, and realization of the latter was hampered by our inability to cleanly generate the (*E*)-enolate species. At best, chemical yields were modest (40-50%), as was diastereoselectivity for the side-chain stereocentre of **7b** (ca. 5:1).

Our attention then turned to a stereochemically simpler variation on the Claisen theme in the form of the Johnson rearrangement[10] of the orthoacetate derived from **6**. Thus, acid-catalyzed reaction of the allylic alcohol with excess triethyl orthoacetate at *ca.* 120°C, with continuous removal of ethanol by distillation, smoothly yielded the ethyl ester of **7a**. The desired carboxylic acid, having the correct stereochemistry for C-18 of zoanthamine, was obtained by basic hydrolysis. Acid **7a** was then used to introduce the C-17 oxygen and the C-15/C-16 unsaturation of the target via an iodolactonization-elimination sequence which furnished lactone **9a**. As shown in Scheme 3, iodolactonization[11] of **7a** is complicated by the possibility of two competing reactions (5-exo *vs.* 6-exo).



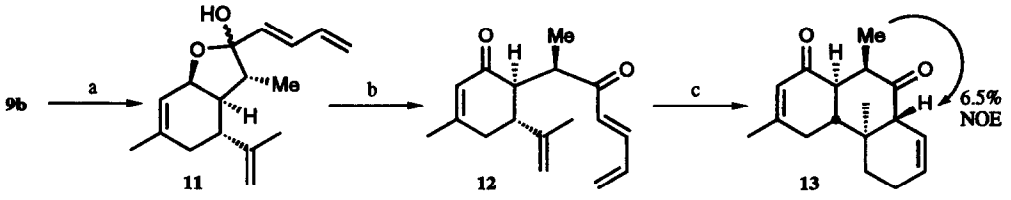

Scheme 3. (5-exo) vs. (6-exo) iodolactonization of **7a**.

Initially, the reaction was carried out in acetonitrile solution at room temperature and did indeed yield a mixture of the 5- and 6-membered iodolactones **8** and **10**, respectively (60:40 ratio). However, since the reaction is reversible, and since the desired 5-membered lactone is the thermodynamically more stable of the two, we were able to obtain an equilibrium mixture containing more than 95% of **8** by heating the original product mixture with a further portion of iodine in acetonitrile at 70°C. This observation prompted us to attempt the "one-pot" conversion of **7a** to **9a** by carrying out the

iodolactonization in the presence of a suitable base: lactone **10** cannot eliminate HI, while elimination from **8** was expected to be particularly facile due to the trans-diaxial relationship of iodine and the β-hydrogen. This favourable stereochemical situation is a consequence not only of the mechanism of the iodolactonization process but also of the absolute stereochemistry at the methyl-substituted centre which was introduced early on in the sequence. For the elimination, the base of choice was DBU and the one-pot procedure (acetonitrile, 70°C) yielded **9a** as a crystalline solid in 84% yield.

Introduction of the methyl group corresponding to that on C-19 in the target was accomplished (Scheme 2) by stereoselective alkylation of the lactone enolate at low temperature (LDA, MeI, THF). This furnished crystalline **9b** as a single diastereomer, the (desired) stereochemistry at the newly-formed centre being that expected from alkylation on the less-hindered face of the fused bicyclic system. Diastereomerically pure lactone **9b**, which corresponds to retrosynthetic intermediate **D** in Scheme 1, is thus available in multigram quantities from commercially available perillyl alcohol via 12 synthetic operations and in a respectable 35% overall yield; only one protective group was required.

To test the viability of the proposed intramolecular Diels-Alder strategy (**C** → **B** in Scheme 1) we have carried out the model study shown in Scheme 4.




Scheme 4. (a) (*E*)-1-Lithio-1,3-butadiene, THF, -78°C, 81%. (b) $MnO_2$, $CH_2Cl_2$, RT, 76%. (c) Δ, toluene-$d_8$, quantitative conversion.

Lactone **9b** was reacted with (*E*)-1-lithio-1,3-butadiene[12] at low temperature to give **11** as a diastereomeric mixture of lactols. The lactols were then exposed to freshly prepared[13] manganese dioxide which produced diketone **12** as a single diastereomer (according to high-field NMR spectroscopy) thus suggesting that no epimerization had occurred during the sequence. The desired intramolecular Diels-Alder reaction was then observed to occur upon prolonged heating of an NMR sample of **12** in deuterated toluene (115°C, $t_{1/2}$ *ca.* 22hr) with smooth formation of a single cycloadduct. The product is assigned the structure and stereochemistry shown for **13** on the basis of NOE studies (see Scheme 4) and we thus conclude that the cycloaddition does indeed give the stereochemistry required for zoanthamine. This gratifying result was not entirely unexpected, since inspection of molecular models had suggested that, in the transition state leading to **13**, the chain linking the diene and dienophile adopts a chair-like conformation (axial methyl on C-19), the carbonyl group is twisted slightly out of the plane of the diene unit, and non-bonded interactions are minimized. We are currently engaged on the preparation and installation of the more elaborate diene unit and the chiral C-1 to C-6 moiety depicted in Scheme 1.

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## EXPERIMENTAL

*General remarks.* $^1H$ (300 MHz) and $^{13}C$ (75 MHz) NMR spectra were recorded on a Varian XL 300 spectrometer ($CDCl_3$/TMS). IR spectra were obtained on a Perkin-Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. Specific rotation values were measured at 25°C on a Perkin-Elmer 241 polarimeter. Mass spectra were run on a Finnigan MAT INCOS 50 instrument. Elemental analyses were performed by Analytische Laboratorien, Gummersbach, Germany. Ether and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone. Benzene, methylene chloride, pyridine and triethylamine were dried over calcium hydride and distilled under nitrogen. Merck silica gel 60 (230-400 mesh) was used for flash chromatography.

*Epoxy alcohol* **3a**. Finely-ground activated 4Å molecular sieves (7.5 g) were slurried in $CH_2Cl_2$ (600 mL) under nitrogen and the stirred mixture was cooled to -20°C. $Ti(O^iPr)_4$ (5.6 g, 19.7 mmol), (-)-diethyl tartrate (4.87 g, 23.6 mmol) and (*S*)-(-)-perillyl alcohol (30.0 g, 197 mmol) were added and the mixture was stirred at -20°C before addition of $^t$BuOOH (79 mL of a 3.8M toluene solution, 300 mmol). The mixture was stirred overnight at -20°C, water (72 mL) was added and the mixture was allowed to reach room temperature. The organic phase was separated and the aqueous phase back-extracted with ether (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, and the solvents evaporated to leave a residue which was purified by flash chromatography (ether/pentane, 50/50) to yield the product as an oil (28.1 g, 85%). $^1H$ NMR: δ 4.73 (m, 1H), 4.68 (m, 1H), 3.67 (dd, *J*=12, 4.5 Hz, 1H), 3.58 (dd, *J*=12, 9, 1H), 3.36 (app. t, *J*=2, 1H), 2.23-2.12 (m, 2H), 1.89-1.79 (m, 3H), 1.70 (br s, 3H), 1.68-1.57 (m, 2H), 1.20 (dd, *J*=9, 4.5, 1H). $^{13}C$ NMR: δ 148.7, 109.2, 64.1, 59.9, 56.7, 36.9, 30.3, 25.9, 24.8, 20.9. IR: 3423, 3081, 2934, 1725 $cm^{-1}$. (*Cf.* spectral data in ref. 5). $[\alpha]_D$ -35.5° (*c*=1.35, $CH_2Cl_2$). Anal. Calc. for $C_{10}H_{16}O_2$: C, 71.38%; H, 9.59. Found: C, 71.14; H, 9.48.

*Epoxide* **3b**. $^t$Butyldimethylsilyl chloride (36.5 g, 242 mmol), triethylamine (24.5 g, 242 mmol) and 4-dimethylaminopyridine (2.69 g, 22 mmol) were dissolved with stirring under nitrogen in $CH_2Cl_2$ (400 mL) and the solution was cooled to 0°C. A solution of **3a** (37.0 g, 220 mmol) in $CH_2Cl_2$ (5 mL) was added and the resultant mixture stirred for 2 h. Water (200 mL) was added, the organic phase was separated, and the aqueous phase extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Flash chromatography (10% ether in pentane) gave **3b** as an oil (58.9 g, 95%). $^1H$ NMR: 4.72 (s, 1H), 4.67 (s, 1H), 3.59 (AB, *J*=11.5, 2H), 3.18 (br s, 1H), 2.20-2.09 (m, 2H), 2.03 (ddd, *J*=16, 6, 3.5, 1H), 1.80-1.59 (m, 2H), 1.69 (s, 3H), 1.22-1.12 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}C$ NMR: 149.0, 109.0, 67.1, 59.9, 57.7, 36.8, 30.6, 26.1, 25.9, 24.4, 21.0, 11.4, 5.27, 5.32. IR: 2929, 2857,2253, 1100. $[\alpha]_D$ -24.0° (*c*=1.25, $CH_2Cl_2$). Anal. Calc. for $C_{16}H_{30}O_2Si$: C, 68.03%; H, 10.72. Found: C, 68.12; H, 10.63.

*Ketone* **4**. (i) CuI (71.5 g, 375 mmol) was slurried under nitrogen in ether (94 mL) and the stirred mixture was cooled to -40°C. MeLi (470 mL of a 1.6M solution in ether, 752 mmol) was added over 15 min to produce a clear solution of the cuprate reagent. The flask was then cooled to -78°C before dropwise addition of a solution of epoxide **3b** (53.0 g, 187 mmol) in ether (20 mL). The reaction mixture was allowed to reach room temperature over 36 h, and water (13.5 mL) was added carefully over 3 h to give a clear supernatant and a grey precipitate which was removed by filtration. The organic phase was dried over $MgSO_4$ and the solvents were evaporated to give a residue which was purified by flash chromatography (5% ether in pentane). There was obtained 54.05 g (97%) of the ring-opened product as

an oil. $^1$H NMR: 4.71 (br s, 2H), 3.61 (AB, *J*=10, 2H), 2.80 (s, 1H), 2.06 (m, 2H), 1.88-1.65 (m, 4H), 1.75 (s, 3H), 1.40-1.01 (m, 4H), 0.99 (d, *J*=7, 3H), 0.95 (s,9H), 0.10 (s, 6H). $^{13}$C NMR: 149.8, 108.3, 73.2, 62.3, 44.8, 39.9, 36.9, 36.1, 28.8, 25.8, 21.1, 15.4, -5.4, -5.5. IR: 2930, 1088. $[\alpha]_D$ +8.12° (*c*=1.01, $CH_2Cl_2$). Anal. Calc. for $C_{17}H_{34}O_2Si$: C, 68.40%; H, 11.49. Found: C, 68.19; H, 11.37.

(ii) The product from the previous step (50.2 g, 168 mmol) was dissolved with stirring in methanol (600 mL) and conc. HCl (2 mL) was added. The mixture was stirred for 2 h and then evaporated to dryness *in vacuo*. Flash chromatography of the residue (10% ether in pentane) gave the 1,2-diol (30.29 g, 98%) as a crystalline solid, m.p. 108-110°C. $^1$H NMR: 4.69 (br s, 2H), 3.65 (AB, *J*=10.2, 2H), 2.19-2.14 (m, 1H), 2.07-2.00 (m, 1H), 1.79-1.66 (m, 3H), 1.72 (s, 3H), 1.36-1.24 (m, 2H), 1.18-1.09 (m, 1H), 0.97 (d, *J*=7.3, 3H). $^{13}$C NMR: 149.4, 108.6, 74.2, 61.9, 44.9, 41.3, 37.1, 35.8, 28.9, 20.9, 15.1. IR: 3288, 2923, 2853, 1461, 1376. $[\alpha]_D$ +44.2° (*c*=0.95, $CH_2Cl_2$). Anal. Calc. for $C_{11}H_{20}O_2$: C, 71.68%; H, 10.94. Found: C: 71.47; H, 10.77.

(iii) The 1,2-diol from the previous step (21.6 g, 117 mmol) was dissolved with stirring in benzene (500 mL) and $Pb(OAc)_4$ (62.4 g, 141 mmol) was added in portions. The resultant mixture was stirred for 2 h at room temperature, then washed with water (2 x 250 mL) and brine (50 mL). The solvent was removed to yield a residue which was purified by flash chromatography (10% ether in pentane). There was obtained 16.36 g (92%) of the ketone **4** as an oil. $^1$H NMR: 4.75 (br s, 2H), 2.55-2.38 (m, 4H), 2.15-2.05 (m, 2H), 1.75 (s, 3H), 1.75-1.56 (m, 1H), 1.39 (q, *J*=13, 1H), 1.03 (d, *J*=6.6, 3H). $^{13}$C NMR: 212.9, 148.1, 109.5, 44.5, 44.3, 41.2, 40.9, 32.5, 20.9, 14.5. IR: 2966, 2931, 2865, 1712. MS: *m/e* 152 ($M^+$, 40%). (*Cf.* spectral data in ref. 3). $[\alpha]_D$ +1.76° (*c*=5.21, EtOH). Lit.[3] for *ent*-**4**: -5.5° (neat).

*Enone* **5**. (i) Ketone **4** (16.8 g, 111 mmol) was dissolved in THF (400 mL) and cooled with stirring under nitrogen to -78°C. A freshly prepared 1M solution of LDA in THF (132.6 mL, 132.6 mmol) was added via syringe and the resultant mixture was stirred for 10 min before addition of phenylselenyl bromide (31.2 g, 132.6 mmol). (It was important to add the PhSeBr in one portion, as rapidly as possible). After 10 min, water (5 mL) was added and the reaction mixture was allowed to reach room temperature. The organics were washed with water (2 x 10 mL), dried over $MgSO_4$, and the solvent was evaporated to give a residue which was purified by flash chromatography (5% ether in pentane). The two possible diastereomers of the α-phenylselenyl ketone were obtained pure in a total yield of 93% (31.69 g, ratio 2:1). $^1$H NMR (major isomer, equatorial SePh): 7.55 (m, 2H), 7.30 (m, 3H), 4.70 (s, 1H), 4.69 (s, 1H), 4.19 (ddd, *J*=12, 4.8, 0.9, 1H), 2.65-2.57 (m, 1H), 2.55-2.41 (m, 1H), 2.35-2.24 (m, 1H), 2.17-2.11 (m, 1H), 1.90 (q, *J*=12, 1H), 1.68 (s, 3H), 1.45 (q, *J*=12, 1H), 1.09 (d, *J*=6.8, 3H); (minor isomer, axial SePh): 7.55 (m, 2H), 7.28 (m, 3H), 4.77 (s, 1H), 4.73 (s, 1H), 3.90 (m, $W_{1/2}$= 6 Hz, 1H), 3.38-3.32 (m, 1H), 2.80-2.65 (m, 1H), 2.40-2.31 (m, 1H), 2.22-2.04 (m, 2H), 1.78 (s, 3H), 1.39 (q, *J*=12, 1H), 1.05 (d, *J*=6.5, 3H). Normally, a mixture of the isomers was taken on to the next step.

(ii) A mixture of the ketones from the previous step (7.0 g, 22.8 mmol) was dissolved with stirring in $CH_2Cl_2$ (130 mL) containing pyridine (3.7 mL). Hydrogen peroxide (5.3 mL of 30% aqueous solution) was added and the resultant mixture was stirred for 4 h before being washed with water (3 x 5 mL). The aqueous phases were back-extracted with $CH_2Cl_2$ (5 mL) and the combined organics were dried ($MgSO_4$) before being stripped down to give a residue which was purified by flash chromatography (5% ether in pentane). The enone **5** was obtained as an oil (3.11 g, 91%). $^1$H NMR: 6.81 (dt, *J*=10.2, 2, 1H), 6.02 (dd, *J*=10.2, 3.6, 1H), 4.86 (m, 1H), 4.80 (br s, 1H), 3.25 (m, 1H), 2.50-2.35 (m, 1H), 2.20-2.05 (m, 1H), 1.80 (s, 3H), 1.75-1.60 (m, 1H), 1.15 (d, *J*=7.3, 3H). $^{13}$C NMR: 201.8, 152.4, 146.7, 129.4, 111.8,

45.1, 41.6, 37.5, 20.7, 14.9. IR: 2967, 2934, 2864, 1681. MS: *m/e* 150 ($M^+$, 72%). (*Cf.* spectral data in ref. 3). $[\alpha]_D$ +91.3° (*c*=1.72, $CH_2Cl_2$). Lit.[3] for *ent*-**5**: -84° (neat).

*Allylic alcohol* **6**. Lithium aluminum hydride (1.7 g, 46 mmol) was slurried in ether (100 mL) and the mixture cooled with stirring under nitrogen to -78°C. A solution of **5** (6.9 g, 46 mmol) in ether (2 mL) was added dropwise over 15 min and the reaction mixture was stirred for 3 h at -78°C. The flask was allowed to reach room temperature, water (1.75 mL) was added carefully and the mixture was stirred for 30 min. 2M NaOH (1.75 mL) was then added, followed by water (1.75 mL). The separated organic phase was dried ($MgSO_4$) and the solvent removed to give a residue (7.01 g) consisting of a 98:2 mixture of epimeric alcohols ($^1H$ NMR spectroscopic analysis). Careful flash chromatography (5% ether in pentane) yielded pure **6** as an oil (6.57g, 94%). $^1H$ NMR: 5.70 (m, $J_{cis}$= 10.2, 1H), 5.63 (m, $J_{cis}$= 10.2, 1H), 4.74 (s, 2H), 3.81 (m, $J_{ax,ax}$= 9, C*H*OH), 2.92-2.83 (m, 1H), 1.84-1.75 (m, 1H), 1.69 (s, 3H), 1.63-1.50 (m, 1H), 1.49 (br s, O*H*), 1.24 (q, *J*=12, 1H), 1.10 (d, *J*=7.4, 3H). IR: 3361, 3075, 3024, 1643. MS: *m/e* 152 ($M^+$, 19%). (*Cf.* spectral data in ref. 3). $[\alpha]_D$ +121.9° (*c*=1.80, $CH_2Cl_2$). Lit.[3] for *ent*-**6**: -169° (neat). In the $^1H$ NMR spectrum of the minor epimer, the C*H*OH gives a signal at δ 3.90 with $J_{eq,ax}$= 4.2 Hz.

*Carboxylic acid* **7a**. (i) Compound **6** (5.0 g, 33 mmol), triethyl orthoacetate (37.0 g, 230 mmol) and 2,4-dinitrophenol (0.48 g, 2.6 mmol) were dissolved in toluene (50 mL) and the mixture was heated at 120°C for 30 h with continuous removal of ethanol by distillation. (The toluene was replenished as necessary). The volatiles were then removed *in vacuo* and the residue was purified by flash chromatography (5% ether in pentane) to give the ethyl ester of **7a**. (6.23 g, 85%). $^1H$ NMR: 5.53 (app. s, 2H), 4.76 (s, 1H), 4.75 (s, 1H), 4.11 (q, *J*=7.5, 2H), 2.62-2.44 (m, 2H), 2.30-2.15 (m, 1H), 2.07-1.96 (m, 2H), 1.80-1.68 (m, 1H), 1.69 (s, 3H), 1.25 (t, *J*=7.5, 3H overlapping q *J*=11, 1H), 0.97 (d, *J*=7.5, 3H). $^{13}C$ NMR: 173.1, 147.6, 133.7, 128.8, 111.7, 60.2, 40.6, 38.6, 37.7, 35.1, 31.3, 21.6, 18.8, 14.2. IR: 3072, 3015, 2956, 2924, 1736. $[\alpha]_D$ -17.1° (*c*=0.83, $CH_2Cl_2$). Anal. Calc. for $C_{14}H_{22}O_2$: C, 75.62%; H, 9.98. Found: C, 75.39; H, 9.89.

(ii) The ester from the previous step (4.88 g, 22 mmol) was dissolved with stirring in dry THF (20 mL) and a 1M aqueous solution of LiOH (55 ml) was added. The mixture was stirred overnight at room temperature, cooled to 0°C, and acidified by addition of 10% aqueous HCl. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organics were dried over $MgSO_4$. Removal of the solvent gave acid **7a** as a viscous oil which was NMR spectroscopically pure and was used directly in the next step. The yield was 4.05 g (95%). $^1H$ NMR: 5.58 (AB, *J*=8.7, 2H), 4.79 (s, 1H), 4.76 (s, 1H), 2.61-2.50 (m, 2H), 2.32-2.18 (m, 1H), 2.10-1.97 (m, 2H), 1.77-1.71 (m, 1H), 1.67 (s, 3H), 1.23 (q, *J*=11.9, 1H), 0.98 (d, *J*=7.3, 3H). $^{13}C$ NMR: 182.0, 147.2, 134.0, 128.3, 112.0, 48.5, 38.2, 37.6, 34.9, 31.4, 21.6, 18.8. IR: 3400-2500 (br), 1708 (br). $[\alpha]_D$ -189.2° (*c*=1.54, $CH_2Cl_2$). Anal. Calc. for $C_{12}H_{18}O_2$: C, 74.18%; H, 9.35. Found: C, 74.11; H, 9.29.

*Lactone* **9a**. Carboxylic acid **7a** (3.5 g, 18 mmol), iodine (9.1 g, 36 mmol) and DBU (5.5 g, 36 mmol) were dissolved in acetonitrile (230 mL) and stirred under nitrogen for 2h at 70°C. A 50/50 ether/pentane mixture (10 mL) was added to the cooled reaction mixture and the resultant solution was washed with water (3 x 100 mL) and with brine (50 mL) before drying of the organic phase ($MgSO_4$) and removal of the solvents. Flash chromatography of the residue (45% ether in pentane) yielded the unsaturated lactone **9a** (2.90 g, 84%) as a crystalline solid, m.p. 111-112°C. $^1H$ NMR: 5.67 (br s, 1H), 4.89 (m, 1H), 4.84 (app. t, *J*=4.5, 1H), 4.80 (s, 1H), 2.68 (dd, *J*=17,6, 1H), 2.48 (d, *J*=17, 1H), 2.44-2.35 (m, 1H), 2.20-2.10 (m, 1H), 2.06-1.96 (m, 2H), 1.80 (s, 3H), 1.68 (s, 3H). $^{13}C$ NMR: 176.4, 144.6, 143.0,

116.7, 113.8, 76.4, 42.6, 35.9, 34.5, 34.3, 23.7, 19.1. IR: 2978, 2872, 1765. $[\alpha]_D$ -9.38° (*c*=0.32, $CH_2Cl_2$). Anal. Calc. for $C_{12}H_{16}O_2$: C, 74.97%; H, 8.46. Found: C, 75.02; H, 8.53.

*Lactone* **9b**. The product from the previous step (2.42 g, 12.6 mmol) was dissolved with stirring under nitrogen in THF (20 mL) and the solution was cooled to -78°C. A 1M solution of LDA in THF (13.9 mL, 13.9 mmol) was added and the resultant solution was stirred for 15 min before dropwise addition of methyl iodide (2.13 g, 15 mmol). The reaction mixture was stirred for 30 min at -78°C, then water (10 ml) was added and the mixture was allowed to reach room temperature. The aqueous phase was extracted with ether (3 x 5 mL) and the combined organics were washed with brine, dried, and the solvents were removed to give a residue which was purified by flash chromatography (45% ether in pentane). Diastereomerically pure lactone **9b** (2.26 g, 87%) was obtained as a crystalline solid, m.p. 122-123°C. $^1$H NMR: 5.64 (br s, 1H), 4.94 (m, 1H), 4.89 (m, 1H), 4.77 (s, 1H), 2.54 (qd, *J*=7,2.5, 1H), 2.20 (ddd, *J*=10.5,9.5,5.5, 1H), 2.10 (ddd, *J*=10.5,6,2.5, 1H), 2.02-1.96 (m, 2H), 1.79 (s, 3H), 1.70 (s, 3H), 1.32 (d, *J*=7, 3H). $^{13}$C NMR: 179.6, 145.0, 142.1, 117.0, 113.2, 75.1, 43.3, 42.3, 40.2, 34.0, 23.6, 19.8, 15.5. IR: 1756. $[\alpha]_D$ +3.92° (*c*=1.53, $CH_2Cl_2$). Anal. Calc. for $C_{13}H_{18}O_2$: C, 75.69%; H, 8.79. Found: C, 75.61; H, 8.88.

*Diketone* **12**. (i) A solution of (*E*)-1-lithio-1,3-butadiene in THF (10 mL) was prepared[12] from (*E*)-1,3-butadienyl(tributyl)stannane[14] (0.960 g, 2.8 mmol) and BuLi (1.7 mL of 1.6M in hexanes, 2.72 mmol) and the solution was cooled under nitrogen to -78°C before addition of a solution of **9b** (0.454 g, 2.4 mmol) in THF (2 mL). After 30 min at -78°C the reaction was quenched by addition of water (2 mL), the organics were dried over $MgSO_4$, and the volatiles were removed *in vacuo*. Flash chromatography of the residue (10% ether in pentane) gave an epimeric mixture of lactols **11** ($^1$H NMR analysis) which was used directly in the next step. Yield: 0.505 g, 81%.

(ii) The mixture of lactols from the previous step (0.130 g, 0.5 mmol) was dissolved with stirring under nitrogen in $CH_2Cl_2$ (20 mL) and freshly prepared manganese dioxide[13] (5 g) was added and the resultant mixture stirred vigorously at room temperature for 8 h. The mixture was filtered through Celite, the filter-cake was washed with fresh $CH_2Cl_2$, and the combined filtrate and washings were evaporated to dryness. The residue was purified by flash chromatography (10% ether in pentane) which yielded **12** as an oil (0.098 g, 76%). This material was characterized only by $^1$H NMR spectroscopy: 7.14 (dd, *J*=15,11, 1H), 6.44 (ddd, *J*=17,11,10.2, 1H), 6.35 (d, *J*=15, 1H), 5.92 (br s, 1H), 5.62 (d, *J*=17, 1H), 5.50 (d, *J*=10.2, 1H), 4.79 (br s, 2H), 3.24 (qd, *J*=7.5,2.5, 1H), 2.93 (td, *J*=11.5,4.9, 1H), 2.64 (dd, *J*=11.5,2.5, 1H), 2.41 (br dd, *J*=18,11.5, 1H), 2.20 (dd, *J*=18,4.9,1H), 1.94 (s, 3H), 1.65 (s, 3H), 1.30 (d, *J*=7.5, 3H).

*Intramolecular Diels-Alder reaction of* **12**. A sample of **12** (*ca.* 10 mg) in toluene-$d_8$ was sealed in an NMR tube which was placed in an oil bath at 115°C. The progress of the reaction was monitored periodically by $^1$H NMR spectroscopy, reaction being complete after *ca.* 48 h. The cycloadduct **13** was not isolated, but characterized by $^1$H NMR spectroscopy (toluene-$d_8$, $\delta_{Me}$= 2.09): 6.13 (m, $J_{cis}$= 10, 1H), 5.75 (br s, 1H), 5.59 (m, $J_{cis}$= 10, 1H), 3.26 (m, 2H), 2.89 (m, 1H), 1.91 (m, 2H), 1.63 (m, 2H), 1.48 (s, 3H), 1.42 (m, 1H), 1.21 (m, 1H), 1.04 (d, *J*=7.3, 3H), 0.95 (m, 1H), 0.42 (s, 3H). The assignment of stereochemistry was made on the basis of an NOE experiment: irradiation of the methyl doublet at δ 1.04 (C-19 methyl, zoanthamine numbering) caused a 6% increase in the signal at 2.89 (C-21, see also Scheme 4).

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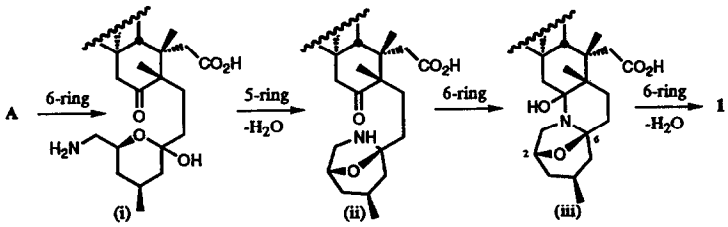
2. Synthetically, **A** (or a suitable derivative thereof) under acidic conditions could be expected to furnish the zoanthamine skeleton via intermediates (i), (ii) and (iii).




The proposed construction thus involves formation of "easy" ring sizes (6- or 5-membered) and relies, *inter alia*, on the stereochemistry at C-2 to set up that at C-6.
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14. See ref. 12 and: Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Synthesis* **1993**, 943. We thank Prof. Fraser-Reid for a preprint.


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