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# Total Synthesis of Zoanthamine Alkaloids, Part 2. Construction of the $C_1$–$C_5$, $C_6$–$C_{10}$, and $C_{11}$–$C_{24}$ Fragments of Zoanthamine

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This paper describes the construction of three key intermediates **11**, **15** and **23** for a projected total synthesis of the marine alkaloid zoanthamine. These building blocks, corresponding to the $C_1$–$C_5$, $C_6$–$C_{10}$, and $C_{11}$–$C_{24}$ fragments of the target molecule, are synthesised efficiently from (*R*)-γ-hydroxymethyl-γ-butyrolactone, methyl propiolate, and (*S*)-perillyl alcohol, respectively.

We have previously outlined[1] a convergent strategy for the enantioselective total synthesis of the marine alkaloid zoanthamine[2] (**1**) and its congeners. A key feature of our retrosynthetic analysis[1] is the use of an intramolecular Diels–Alder cycloaddition reaction to set up the carbotricyclic portion of the target, and model studies[1] based on this strategy were indeed encouraging. A slightly modified version of our original retrosynthetic analysis is shown below (Scheme 1) and calls for the preparation of the Diels–Alder precursor via transition-metal-mediated coupling of synthons **B** and **C**. In this paper we describe the preparation of materials corresponding to key retrosynthetic intermediates **A**, **B** and **C**, which represent the $C_1$–$C_5$, $C_6$–$C_{10}$, and $C_{11}$–$C_{24}$ portions of the target, respectively.

Zoanthamine displays interesting biological activity[2] but its mode of action is not yet understood, and part of our synthetic program involves preparation of simpler analogues for pharmacological testing. Further, since the absolute stereochemistry of the alkaloid is unknown,[2] it is important to develop a synthesis which allows access to either enantiomer of the target molecule. These considerations have guided the present work as well as our earlier synthetic studies.

## Results and discussion

*Synthesis of the $C_1$–$C_5$ fragment.* The starting material chosen was γ-hydroxymethyl-γ-butyrolactone, both enantiomers of which are commercially available. The (*R*)-antipode, incorporating the $C_2$-stereocentre of zoanthamine, was selected to match the absolute stereochemistry shown above for the target, and was converted into **2** by silylation and stereoselective alkylation according to published procedures[3a,b] for the enantiomer (Scheme 2).

Attempted reduction of **2** to diol **3** using $LiAlH_4$ resulted in extensive loss of the silyl protecting group, so the desired transformation was carried out by a two-stage process involving DIBAL (to give the lactol) followed by $NaBH_4$. Selective protection of the primary alcohol as the benzoate **4** and protection of the secondary hydroxy group as the MEM ether gave **5**. The silyl group was removed by fluoride to allow introduction of the $C_1$-nitrogen of zoanthamine, which was best accomplished by tosylation and then reaction with lithium azide. Basic hydrolysis of the benzoate ester, tosylation, and bromination yielded the desired fragment **11**, the overall yield being 32% based on the readily available **2**. After suitable manipulation of the azide group, the bromide of **11** will serve as the precursor to organometallic intermediate **A** shown in Scheme 1. (If necessary, alternative protected nitrogen functionality can be introduced[4] at the stage of **6**.)

*Synthesis of the $C_6$–$C_{10}$ fragment.* The key step in the construction of this intermediate was a lanthanide-catalyzed hetero Diels–Alder reaction (Scheme 3).

According to a known procedure, involving regioselective Pd-catalyzed hydrostannylation followed by DIBAL reduction,[5] methyl propiolate was converted into

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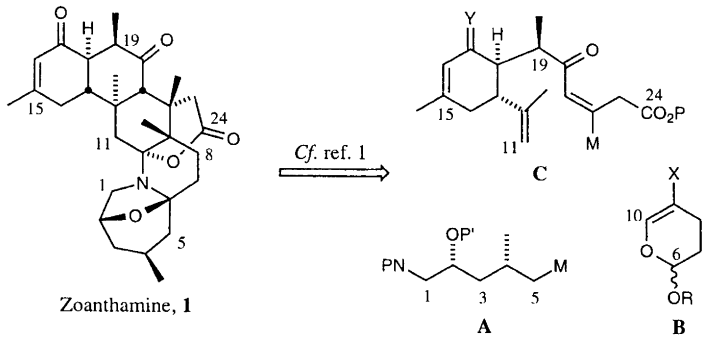
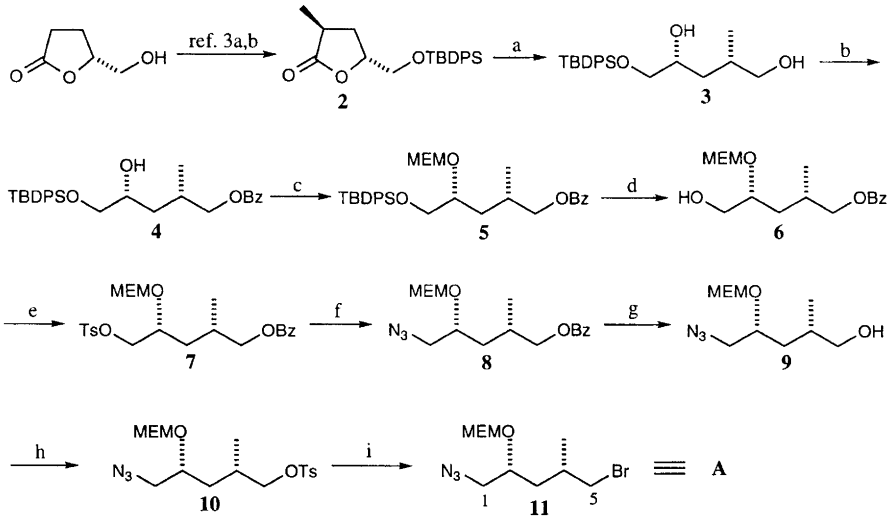
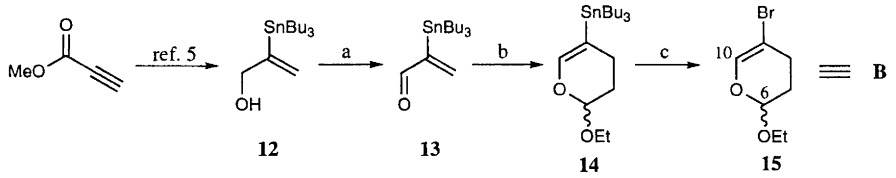



*Scheme 1.* Retrosynthetic analysis of zoanthamine. M = metal, e.g., $SnR_3$; P, P′ = protecting group; X = halide; Y = protected or latent carbonyl.



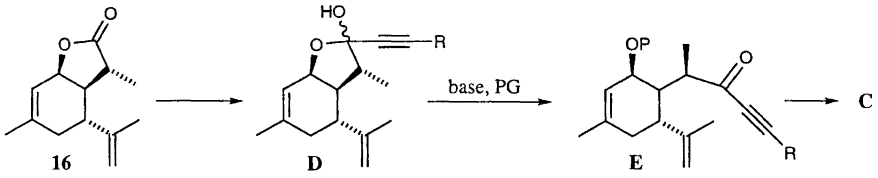

*Scheme 2.* TBDPS = $Si^tBuPh_2$; MEM = (2-methoxyethoxy)methyl. (a) i, DIBAL, $CH_2Cl_2$; ii, $NaBH_4$, EtOH, 86%. (b) BzCl, pyridine, $CH_2Cl_2$, 99%. (c) MEMCl, $^iPr_2NEt$, $CH_2Cl_2$, 95%. (d) $Bu_4NF$, THF, 100%. (e) TsCl, $NEt_3$, dimethylaminopyridine (DMAP), $CH_2Cl_2$, 73%. (f) $LiN_3$, DMF, 98%. (g) LiOH, THF, $H_2O$, 100%. (h) as for (e), 75%. (i) NaBr, DMF, 67%.




*Scheme 3.* (a) Tetrapropylammonium perruthenate (TPAP cat.), 4-methylmorpholine *N*-oxide, $CH_2Cl_2$, 85%. (b) Ethyl vinyl ether, Yb(fod)$_3$, 75%. (c) $Br_2$, 100% conversion (according to NMR spectroscopy).

the alcohol **12**. Oxidation by TPAP[6] gave aldehyde **13**, which was immediately subjected to a regioselective Yb-catalyzed cycloaddition[7] reaction with ethyl vinyl ether to yield the very sensitive dihydropyran **14**. Without delay, this material was treated with bromine to afford the desired coupling partner **15** corresponding to retrosynthetic intermediate **B** in Scheme 1. The overall yield of **15** was ca. 60% based on **12**. Compounds **13**–**15** are all very sensitive materials and are best handled and stored in solution; chromatographic purification is possible, but satisfactory elemental analyses could not be obtained. However, the structures could be assigned with confidence on the basis of high-field $^1H$ and $^{13}C$ NMR spectroscopy.

*Synthesis of the $C_{11}$–$C_{24}$ fragment.* The starting point was the bicyclic lactone **16** which we had earlier prepared[1] in diastereomerically and enantiomerically pure form via a highly efficient route based on the appropriate enantiomer of perillyl alcohol (both antipodes of which are commercially available). We envisioned that retrosynthetic intermediate **C** (Scheme 1) would derive from regio- and stereo-selective stannylcupration[8] of the corresponding acetylenic ketone, and our initial plan (Scheme 4) was to add an appropriate acetylide to **16** to give the lactol **D**, followed by base-induced capture of the open-chain tautomer by some protecting-group reagent. Intermediate **E** would then be subjected to stannylcupration.




*Scheme 4.* Proposed route to key intermediate **C**. PG = protecting group reagent.

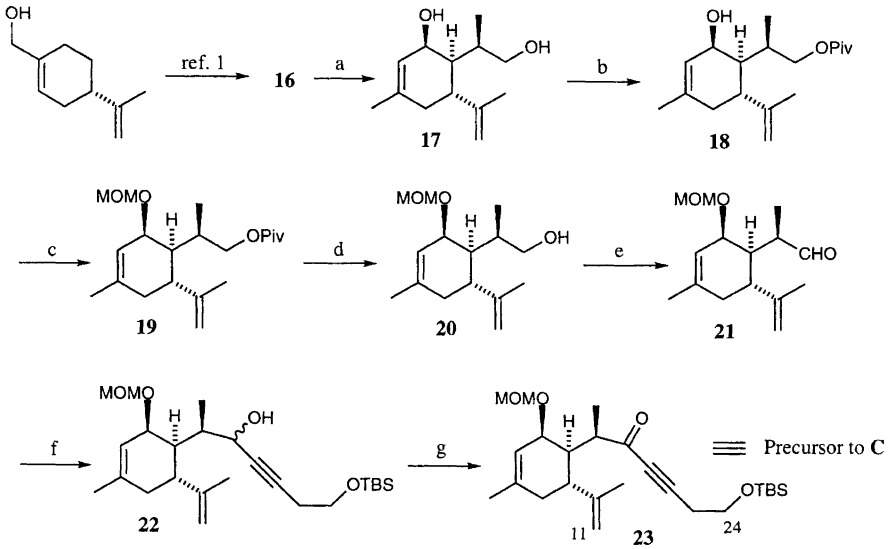
The addition of acetylides to **16** proceeded smoothly but unfortunately the second phase of the plan proved unworkable, despite many attempts under a variety of conditions. Presumably, this failure is due to kinetic factors, i.e., the anion of the open form of **D** recyclises faster than it is captured by external electrophiles. (In earlier model studies[1] an adduct akin to **D** could be oxidised smoothly to the corresponding diketone, but in the present case this was undesirable, since the presence of two α,β-unsaturated carbonyl groups would no doubt pose problems for the projected stannylcupration reaction.) We were thus forced to take the detour shown in Scheme 5.

Reduction of lactone **16** yielded diol **17**, the primary hydroxy group of which was protected selectively as the pivaloate ester **18**. Protection of the secondary hydroxy group as MOM ether **19**, reductive removal of the pivaloate, and TPAP oxidation provided aldehyde **21**. This was treated with the lithium acetylide derived from a silyl ether of 3-butyn-1-ol, followed by mild oxidation to provide acetylenic ketone **23**, which is the immediate precursor to intermediate **C** shown in Scheme 1. Although the sequence was lengthier than we had originally hoped, the overall yield of **23** was nevertheless 44% based on **16** (and 16% overall based on perillyl alcohol).

We have thus prepared building blocks which together correspond to the entire skeleton of zoanthamine (with the exception of the methyl groups on $C_9$ and $C_{22}$). Studies of the stannylcupration of **23**, subsequent Stille reaction[9] with **15**, and the key intramolecular Diels–Alder reaction are under way.

## Experimental

*General.* $^1H$ (300 or 400 MHz) and $^{13}C$ (75 or 100 MHz) NMR spectra were recorded on a Varian XL 300 or a Varian Unity 400 spectrometer ($CDCl_3$–TMS). Coupling constants, *J*, are given in Hz. IR spectra were obtained for thin films on a Perkin-Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks ($\nu_{max}/cm^{-1}$) are listed. Specific rotation values were measured at 25 °C on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed at the Analytical Department of the Research Institute for Pharmacy and Biochemistry, Prague, Czech Republic. Ether and tetrahydrofuran (THF) were distilled under nitrogen from Na–benzophenone. Dichloromethane, pyridine, triethylamine, and *N,N*-diisopropylethylamine were dried over calcium hydride and distilled under nitrogen. Dimethylformamide (DMF) was distilled at reduced pressure from calcium hydride. Silica gel for flash chromatography was purchased from Grace-Amicon.




*Scheme 5.* MOM = methoxymethyl; TBS = $Si^tBuMe_2$. (a) $LiAlH_4$, THF, 99%. (b) Pivaloyl chloride, pyridine, 84%. (c) MOMCl, $^iPr_2NEt$, $CH_2Cl_2$, 88%. (d) DIBAL, $CH_2Cl_2$, 99%. (e) Tetrapropylammonium perruthenate (TPAP cat.), 4-methylmorpholine *N*-oxide, $CH_2Cl_2$, 71%. (f) $LiCC(CH_2)_2OTBS$, THF, 99%. (g) $MnO_2$, $CH_2Cl_2$, 87%.

*Diol* **3**. Lactone[3c] **2** (0.51 g, 1.9 mmol) was dissolved with stirring under nitrogen in dry dichloromethane (50 ml) and the solution was cooled to −78 °C before addition of DIBAL (1 M in hexanes, 5.8 ml, 5.8 mmol). The resultant solution was stirred for 1 h at −78 °C. A 10% aqueous solution of Rochelle salt (5 ml) was added and the mixture stirred vigorously at ambient temperature for 2 h. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 5 ml). The combined organics were dried over $MgSO_4$, the solvent was evaporated *in vacuo* and the residue was dissolved in 99.5% ethanol (50 ml) and cooled to 0 °C. $NaBH_4$ (0.2 g, 5.8 mmol) was added in one portion and the mixture was stirred for 3 h. Acetic acid was added dropwise until gas evolution ceased. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and water. After separation, the aqueous phase was extracted three times with dichloromethane and the combined organics were dried over $MgSO_4$. Removal of the solvent gave a residue which was flash chromatographed using pentane–ether (50:50 to 25:75) to afford the product as a viscous oil (0.61 g, 86%). $[\alpha]_D$ −19.1 (*c* 0.68, $CH_2Cl_2$). $^1H$ NMR: δ 7.67–7.65 (4 H, m), 7.46–7.36 (6 H, m), 3.92–3.89 (1 H, m), 3.62 (1 H, dd, *J* 10, 4), 3.54–3.45 (3 H, m), 2.87 (1 H, br, –OH), 2.46 (1 H, br, –OH), 1.89–1.80 (1 H, m), 1.50–1.36 (2 H, m), 1.07 (9 H, s), 0.91 (3 H, d, *J* 7). $^{13}C$ NMR: δ 135.6, 133.1, 129.8, 127.8, 69.3, 68.0, 65.8, 36.4, 32.4, 26.9, 19.2, 16.9. IR ($CDCl_3$): 3332br. Anal. $C_{22}H_{32}O_3Si$: C, H.

*Benzoate* **4**. Diol **3** (3.7 g, 9.95 mmol) was dissolved in dry dichloromethane (10 ml) and the solution cooled with stirring under nitrogen to 0 °C. Pyridine (0.96 ml, 11.9 mmol) was added, followed by benzoyl chloride (1.26 ml, 10.9 mmol). The mixture was stirred for 6 h at 0 °C and then at room temperature for 16 h, before being washed with an aqueous solution of $CuSO_4$ (2 × 3 ml). The organic phase was dried over $MgSO_4$, the solvent was removed, and the residue purified by flash chromatography (pentane–ether 75:25) to give the benzoate as a viscous oil (4.7 g, 99%). $[\alpha]_D$ +4.64 (*c* 3.7, $CH_2Cl_2$). $^1H$ NMR: 8.19–8.14 (1 H, m), 8.04–8.00 (2 H, m), 7.68–7.62 (3 H, m), 7.58–7.50 (2 H, m), 7.45–7.34 (7 H, m), 4.22 (1 H, dd, *J* 11, 5), 4.16 (1 H, dd, *J* 11, 5), 3.92–3.82 (1 H, m), 3.65 (1 H, dd, *J* 10, 3), 3.49 (1 H, dd, *J* 10, 3), 2.60 (1 H, br s, –OH), 2.18–2.03 (1 H, m), 1.47–1.39 (2 H, m), 1.10–1.00 (9 H, s, overlapping 3 H, d, *J* 7). $^{13}C$ NMR: 166.6, 136.5, 135.5, 134.5, 132.8, 130.6, 129.8, 129.7, 129.5, 128.9, 128.3, 127.8, 127.7, 69.9, 69.2, 68.2, 36.5, 29.6, 26.7, 19.2, 17.8. IR ($CDCl_3$): 3524br, 1729. Anal. $C_{29}H_{36}O_4Si$: C, H.

*MEM ether* **5**. Compound **4** (0.73 g, 1.54 mmol) was dissolved with stirring under nitrogen in dry dichloromethane (20 ml) and the solution cooled to 0 °C. MEMCl (0.28 ml, 2.3 mmol) was added, followed by *N,N*-diisopropylethylamine (0.80 ml, 4.6 mmol). The resultant mixture was stirred for 16 h, water (5 ml) was added, and the phases were separated. The aqueous phase was back-extracted with dichloromethane (3 × 4 ml), the combined organics were dried over $MgSO_4$ and the solvent was removed to yield a residue which was flash chromatographed (pentane–ether gradient 90:10 to 75:25). There was obtained 0.83 g (95%) of the desired product as an oil. $[\alpha]_D$ +26.1 (*c* 1.33, $CH_2Cl_2$). $^1H$ NMR: 8.04–8.00 (2 H, m), 7.68–7.63 (3 H, m), 7.59–7.51 (3 H, m), 7.48–7.32 (7 H, m), 4.84 and 4.73 (2 H, AB, *J* 7, 2 H), 4.23 (1 H, dd, *J* 10, 5), 4.16 (1 H, dd, *J* 10, 5), 3.85–3.79 (2 H, m), 3.74–3.68 (3 H, m), 3.50–3.43 (2 H, m), 3.32 (3 H, s), 2.15–2.02 (1 H, m), 1.80–1.72 (2 H, m), 1.07–1.01 (9 H, s, overlapping 3 H, d, *J* 7). $^{13}C$ NMR: 166.5, 135.6, 133.4, 132.8, 130.4, 129.8, 129.7, 129.5, 128.4, 128.3, 127.7, 127.6, 95.1, 76.1, 71.6, 69.7, 67.1, 66.3, 59.0, 35.8, 29.4, 26.8, 19.2, 19.0. IR ($CDCl_3$): 1713. Anal. $C_{33}H_{44}O_6Si$: C, H.

*Alcohol* **6**. To a solution of **5** (0.38 g, 0.67 mmol) in dry THF (4 ml) was added a 1 M solution of tetrabutylammonium fluoride in THF (0.74 ml, 0.74 mmol). The resultant solution was stirred under nitrogen for 2 h, then ether (5 ml) and water (7 ml) were added. The separated aqueous phase was extracted with ether (2 × 5 ml) and the combined organics were washed with brine, dried over $MgSO_4$, and the solvents removed. Flash chromatography of the residue (pentane–ether 25:75) gave the pure product in essentially quantitative yield (0.22 g). $[\alpha]_D$ −24.2 (*c* 0.95, $CH_2Cl_2$). $^1H$ NMR: 8.03 (2 H, m), 7.60–7.52 (1 H, m), 7.46–7.42 (2 H, m), 4.84 and 4.77 (2 H, AB, *J* 7), 4.24 (1 H, ddd, *J* 11, 5, 1), 4.15 (1 H, ddd, *J* 11, 5, 1), 3.90–3.82 (1 H, m), 3.74–3.66 (3 H, m), 3.58–3.56 (2 H, m), 3.52–3.46 (1 H, m), 3.38 (3 H, s), 2.58 (1 H, br, –OH), 2.15–2.05 (1 H, m), 1.62–1.56 (2 H, m), 1.08 (3 H, d, *J* 7). $^{13}C$ NMR: 166.5, 132.9, 130.4, 129.5, 128.3, 95.8, 80.5, 71.6, 69.2, 67.5, 65.5, 59.0, 35.5, 29.5, 17.9. IR ($CDCl_3$): 3480br, 1714. Anal. $C_{17}H_{26}O_6$: C, H.

*Tosylate* **7**. Alcohol **6** (0.12 g, 0.37 mmol) was dissolved with stirring under nitrogen in dry dichloromethane (5 ml). The solution was cooled to 0 °C before addition of $NEt_3$ (0.10 ml, 0.74 mmol), *p*-TsCl (0.10 g, 0.48 mmol) and DMAP (0.01g, cat.). The mixture was stirred for 24 h, then poured into water and extracted with dichloromethane (3 × 4 ml). The combined organics were washed with brine, dried over $MgSO_4$, and the solvent was removed to give a residue which was taken up in the minimum amount of dichloromethane and filtered through a short plug of silica gel. Removal of the solvent gave 0.13 g (73%) of $^1H$ NMR spectroscopically pure product, which was used directly in the next step. $^1H$ NMR: 8.07–8.03 (2 H, m), 7.83–7.79 (2 H, m), 7.62–7.57 (1 H, m), 7.50–7.45 (2 H, m), 7.36–7.33 (2 H, m), 4.75 and 4.71 (2 H, AB, *J* 7), 4.23–4.04 (4 H, m), 3.96–3.90 (1 H, m), 3.70–3.66 (2 H, m), 3.53–3.50 (2 H, m), 3.37 (3 H, s), 2.46 (3 H, s), 2.10–2.01 (1 H, m),

1.72–1.64 (1 H, m), 1.60–1.52 (1 H, m), 1.07 (3 H, d, *J* 7). $^{13}$C NMR: 166.5, 144.9, 133.0, 132.9, 130.3, 129.8, 129.5, 128.4, 127.9, 95.0, 73.2, 71.6, 71.1, 68.9, 67.4, 59.0, 35.4, 29.3, 21.6, 17.8. IR ($CDCl_3$): 1714, 1275, 1177.

*Azide* **8**. The tosylate from above (0.13 g, 0.27 mmol) was dissolved with stirring under nitrogen in dry DMF (5 ml) and $LiN_3$ (0.024 g, 0.50 mmol) was added. The mixture was heated to 70 °C for 6 h, cooled to room temperature, poured into water (10 ml) and extracted with pentane–ether (3 × 5 ml). The combined organics were washed with brine (5 ml) then dried over $MgSO_4$, and the solvents were removed to give the pure product as an oil (0.093 g, 98%). $[\alpha]_D$ +7.42 (*c* 1.32, $CH_2Cl_2$). $^1$H NMR: 8.06–8.02 (2 H, m), 7.59–7.54 (1 H, m), 7.47–7.42 (2 H, m), 4.83 and 4.81 (2 H, AB, *J* 7), 4.23 (1 H, m), 4.18 (1 H, m), 3.91–3.84 (1 H, m), 3.80–3.70 (1 H, m), 3.55 (1 H, m), 3.48 (1 H, dd, *J* 13, 4), 3.38 (3 H, s), 3.31 (1 H, dd, *J* 13, 4), 2.12–2.03 (1 H, m), 1.74–1.56 (2 H, m), 1.08 (3 H, d, *J* 7). $^{13}$C NMR: 166.5, 132.9, 130.3, 129.5, 128.4, 95.0, 74.9, 71.7, 69.0, 67.4, 59.0, 54.5, 36.3, 29.5, 17.8. IR ($CDCl_3$): 2933, 2104, 1713. Anal. $C_{17}H_{25}N_3O_5$: C, H, N.

*Alcohol* **9**. Compound **8** (0.080 g, 0.23 mmol) was dissolved, with stirring under nitrogen, in dry THF (20 ml) before addition of water (20 ml) and LiOH (0.01 g, 0.34 mmol). The resultant mixture was stirred for 50 h, then water (10 ml) was added and the mixture was extracted with pentane–ether (50:50, 3 × 10 ml). The combined organics were washed with brine then dried over $MgSO_4$ and the solvents were removed to give a residue which was flash chromatographed (ether–pentane 25:75) to yield the alcohol as an oil (0.056 g, 100%). $[\alpha]_D$ +30.9 (*c* 0.33, $CH_2Cl_2$). $^1$H NMR: 4.85 and 4.78 (2 H, AB, *J* 7), 3.99–3.92 (1 H, m), 3.86–3.80 (1 H, m), 3.72–3.67 (1 H, m), 3.59–3.55 (2 H, m), 3.49 (1 H, m), 3.47 (1 H, m), 3.41 (1 H, dd, *J* 13, 6), 3.39 (3 H, s), 3.30 (1 H, dd, *J* 13, 6), 2.18 (1 H, br, –OH), 1.88–1.80 (1 H, m), 1.55 (2 H, m), 0.95 (3 H, d, *J* 7). $^{13}$C NMR: 95.1, 75.2, 71.8, 68.0, 67.5, 59.0, 54.7, 37.0, 32.0, 17.7. IR ($CDCl_3$): 3518br, 2103. Anal. $C_{10}H_{21}N_3O_4$: C, H, N.

*Tosylate* **10**. The alcohol from above (0.056 g, 0.23 mmol) was dissolved, with stirring under nitrogen in dry methylene chloride (5 ml) and the solution cooled to 0 °C before addition of DMAP (0.010 g, cat.), triethylamine (0.073 ml, 0.55 mmol) and *p*-TsCl (0.068 g, 0.36 mmol). The reaction mixture was stirred for 18 h at room temperature, then poured into water (5 ml). The aqueous phase was extracted with dichloromethane (3 × 4 ml) and the combined organics were washed with brine and dried over $MgSO_4$ before being filtered through a short plug of silica gel. Removal of the solvent gave material which was sufficiently pure to be used directly in the next step (0.072 g, 75%). $^1$H NMR: 7.78 and 7.35 (4 H, AA′BB′, $J_{AB}$ 8), 4.76 and 4.71 (2 H, AB, *J* 7), 3.91 (2 H, app. d, *J* 5), 3.76–3.64 (3 H, m), 3.53 (2 H, m) 3.38 (3 H, s), 3.36 (1 H, dd, *J* 13, 5), 3.21 (1 H, dd, *J* 13, 5), 2.46 (3 H, s), 1.98–1.91 (1 H, m), 1.53–1.48 (2 H, m), 0.95 (3 H, d, *J* 7). $^{13}$C NMR: 144.7, 129.8, 127.9, 95.1, 77.3, 74.7, 74.2, 71.7, 67.5, 59.0, 54.5, 35.6, 29.5, 21.6, 17.3.

*Bromide* **11**. The tosylate from above (0.072 g, 0.17 mmol) was dissolved with stirring under nitrogen in dry DMF (5 ml) and NaBr (0.030 g, 0.29 mmol) was added, and the mixture was stirred at 50 °C for 12 h before being poured into water (10 ml). Extraction with pentane–ether (50:50, 3 × 10 ml), drying over $MgSO_4$ and solvent removal gave a residue which was flash chromatographed (pentane–ether 90:10) to yield the desired product as an oil (0.034 g, 64%). $[\alpha]_D$ +22.2 (*c* 0.6, $CH_2Cl_2$). $^1$H NMR: 4.83 and 4.75 (2 H, AB, *J* 7), 3.82–3.76 (1 H, m), 3.76–3.72 (2 H, m), 3.58–3.54 (2 H, m), 3.44 (1 H, dd, *J* 13, 5), 3.41 (2 H, m), 3.39 (3 H, s), 3.28 (1 H, dd, *J* 13, 5), 2.02–1.93 (1 H, m), 1.70–1.57 (2 H, m), 1.06 (3 H, d, *J* 7). $^{13}$C NMR: 95.0, 74.5, 71.7, 67.5, 59.0, 54.5, 40.7, 37.6, 31.2, 19.5. IR ($CDCl_3$): 2931, 2104, 1040. Anal. $C_{10}H_{20}BrN_3O_3$: C, H, N.

*Aldehyde* **13**. Freshly activated and finely pulverised 4 Å molecular sieves (2 g) were slurried under nitrogen in dry dichloromethane (5 ml) and 4-methylmorpholine-*N*-oxide (0.04 g, 0.35 mmol) was added, followed by a solution of alcohol **12** (Ref. 5, 0.078 g, 0.22 mmol) in dichloromethane (0.5 ml). After 10 min, tetrapropylammonium perruthenate (TPAP, 0.004 g, 0.01 mmol) was added. The reaction mixture was stirred for 2 h at ambient temperature, during which time a dark green coloration developed. The reaction mixture was applied directly to a silica gel column and the product eluted with pentane–ether (95:5). There was obtained 0.10 g (85%) of the aldehyde as an oil. $^1$H NMR: 9.67 [1 H, s, with satellites: $J(^{117}SnH)$ 52, $J(^{119}SnH)$ 55], 6.85 [1 H, d, *J* 2, with satellites: $J(^{117}SnH)$ 102, $J(^{119}SnH)$ 108], 6.69 [1 H, d, *J* 2, with satellites: $J(^{117}SnH)$ 46, $J(^{119}SnH)$ 50], 1.60–1.15 (12 H, m), 1.10–0.76 (15 H, m). $^{13}$C NMR: 199.3, 156.4, 148.2, 28.9, 27.2, 13.7, 9.6. IR ($CDCl_3$): 1673. This material was not amenable to storage, and was used without delay in the next step.

*Dihydropyran* **14**. Yb(fod)$_3$ (0.02 g, 0.08 mmol) was dried *in vacuo* (6 h at 60 °C) before being added under nitrogen to freshly distilled ethyl vinyl ether (2.5 ml). The freshly prepared aldehyde from above (0.29 g, 0.84 mmol) was added and the resultant mixture stirred at 30 °C for 24 h. Volatile material was removed on a rotary evaporator and the residue was flash chromatographed on a short silica gel column (pentane containing 5% $NEt_3$). There was obtained 0.26 g (75%) of the cycloadduct as an oil. $^1$H NMR: 5.98 [1 H, app. t, *J* 2, with satellites: $J(^{117}SnH)$ 30, $J(^{119}SnH)$ 36], 4.96 (1 H, dd, *J* 5, 3), 3.86 and 3.58 (2 H, AB of $ABX_3$, $J_{AX}=J_{BX}$ 8), 2.21 (1 H, m), 2.01 (1 H, m), 1.84 (2 H, m), 1.72–1.20 (12 H, m), 0.95–0.80

(18 H, m). $^{13}C$ NMR: 143.3, 108.3, 96.9, 63.5, 29.2, 28.3, 27.3, 22.2, 15.3, 13.7, 9.0. IR ($CDCl_3$): 1604. The material could be stored under an inert atmosphere in the freezer for short periods, but no satisfactory elemental analysis was obtained.

*Bromide* **15**. Initial experiments were done in an NMR tube. Freshly prepared and purified compound **14** (0.010 g, 24 μmol) was dissolved in $CDCl_3$ (1 ml) in a dry NMR tube which had been flushed with nitrogen. A solution of $Br_2$ (0.004 g, 26 μmol) in carbon tetrachloride (0.2 ml) was added and the tube was shaken for 5 min, after which time the $^1H$ NMR spectrum indicated complete conversion of **14** into **15**. $^1H$ NMR: 6.62 (1 H, s), 4.96 (1 H, m), 3.91 and 3.60 (2 H, AB of $ABX_3$, $J_{AX} = J_{BX}$ 8), 2.17–2.09 (1 H, m), 2.06–1.98 (1 H, m), 1.86–1.79 (2 H, m), 0.92 (3 H, t, *J* 8). $^{13}C$ NMR: 141.7, 117.8, 98.6, 63.8, 29.0, 27.2, 15.9.

On a larger scale, the product could be purified as described for **14**; isolated yields were variable, due to decomposition, and no satisfactory elemental analysis could be obtained.

*Diol* **17**. Lactone **16** (ref. 1, 0.50 g, 2.43 mmol) was dissolved in dry THF (1 ml) and the solution added under nitrogen to a cooled (−78 °C) and stirred slurry of $LiAlH_4$ (0.06 g, 1.46 mmol) in THF (5 ml). The temperature was allowed to rise to −20 °C over 3 h, at which point no more lactone could be detected by TLC. The cooling bath was removed and water (2 ml) was added dropwise to the reaction flask, followed by ether (5 ml). The separated aqueous phase was extracted with ether (3 × 5 ml) and the combined organics were washed with brine, dried over $MgSO_4$ and evaporated to dryness. The diol was obtained pure as a crystalline solid (0.505 g, 99%) m.p. 105–107 °C. $[\alpha]_D$ −92 (*c* 0.59, $CH_2Cl_2$). $^1H$ NMR: 5.67 (1 H, d, *J* 6), 4.85 (1 H, s), 4.83 (1 H, s), 4.25 (1 H, s), 3.84 (1 H, dd, *J* 12, 2), 3.45 (1 H, dd, *J* 12, 5), 2.76 (1 H, m), 2.07 (1 H, ddd, *J* 17, 11, 1), 1.97 (1 H, dd, *J* 17, 6), 1.93–1.86 (1 H, m), 1.70 (6 H, 2 × s), 1.66 (1 H, m), 1.56 (1 H, m), 1.10 (3 H, d, *J* 6). $^{13}C$ NMR: 146.4, 138.8, 122.9, 113.7, 63.2, 62.2, 45.4, 40.2, 37.0, 34.3, 23.1, 18.0, 15.4. IR ($CDCl_3$): 3597br, 3404br. Anal. $C_{13}H_{22}O_2$: C, H.

*Pivaloate* **18**. The diol from above (0.16 g, 0.76 mmol) was dissolved with stirring under nitrogen in dry pyridine (10 ml) and the solution was cooled to 0 °C before addition of pivaloyl chloride (1.6 ml, 1.29 mmol). The reaction mixture was then stirred for 1 h at ambient temperature, then diluted with ether (10 ml) and extracted with an aqueous solution of $CuSO_4$ (6 × 4 ml). The organic phase was dried over $MgSO_4$ and the solvents removed to leave a residue which was flash chromatographed (ether–pentane 90 : 10) to give the pure product as an oil (0.19 g, 86%). $[\alpha]_D$ −86.1 (*c* 1.01, $CH_2Cl_2$). $^1H$ NMR: 5.62 (1 H, d, *J* 5), 4.87 (1 H, s), 4.86 (1 H, s), 4.28–4.26 (1 H, m), 4.25 (1 H, dd, *J* 11, 3), 4.12 (1 H, dd, *J* 11, 8), 2.68–2.59 (1 H, m), 2.12–1.99 (2 H, m), 1.94 (1 H, dd, *J* 18, 6), 1.71 (6 H, 2 × s), 1.59–1.54 (2 H, m) 1.20 (9 H, s), 1.11 (3 H, d, *J* 7). $^{13}C$ NMR: 178.5, 145.9, 138.3, 123.2, 113.6, 67.3, 64.6, 44.6, 40.1, 36.9, 33.2, 27.2, 26.5, 23.1, 18.2, 16.6. IR ($CDCl_3$): 3599br, 1715. Anal. $C_{18}H_{30}O_3$: C, H.

*MOM ether* **19**. Compound **18** (0.014 g, 0.047 mmol) was dissolved with stirring under nitrogen in dry dichloromethane (1 ml) and cooled to 0 °C before addition of *N,N*-diisopropylethylamine (0.04 ml, 0.25 mmol) and MOMCl (0.019 ml, 0.051 mmol). The resultant solution was stirred for 3 h, then water (5 ml) was added, and the separated aqueous phase was extracted with dichloromethane (3 × 5 ml). The combined organics were dried over $MgSO_4$ and the volatiles were removed to give the product (0.015 g, 88%) which was pure according to $^1H$ NMR spectroscopy. $[\alpha]_D$ −161.5 (*c* 0.54, $CH_2Cl_2$). $^1H$ NMR: 5.66 (1 H, d, *J* 5), 4.84 (1 H, s), 4.82 (1 H, br s), 4.76 and 4.60 (2 H, AB, *J* 7), 4.19 (1 H, dd, *J* 11, 3), 4.12 (1 H, m), 4.06 (1 H, dd, *J* 11, 10), 3.38 (3 H, s), 2.80–2.74 (1 H, m), 2.08–1.86 (1 H, m), 1.68 (6 H, 2 × s), 1.30–1.21 (1 H, m), 1.18 (9 H, s), 1.04 (3 H, d, *J* 7). $^{13}C$ NMR: 178.7, 146.2, 138.6, 121.2, 113.4, 94.9, 68.9, 67.7, 55.9, 43.7, 40.4, 38.7, 36.6, 33.5, 27.2, 23.2, 18.3, 16.8. IR ($CDCl_3$): 1715. Anal. $C_{20}H_{34}O_4$: C, H.

*Alcohol* **20**. Compound **19** (0.015 g, 0.044 mmol) was dissolved with stirring under nitrogen in dry dichloromethane (2 ml) and cooled to −78 °C before addition of DIBAL (1 M in hexanes, 0.11 ml, 0.11 mmol). After 30 min, TLC indicated complete reaction, an aqueous solution of Rochelle salt (2 ml) was added, and the resultant mixture was stirred at room temperature for 1 h. The separated aqueous phase was extracted with dichloromethane (2 × 2 ml) and the combined organics were washed with brine and dried over $MgSO_4$. Removal of solvent and flash chromatography (pentane–ether 50 : 50) yielded the desired product as an oil (0.011 g, 99%). $[\alpha]_D$ +172.3 (*c* 0.61, $CH_2Cl_2$). $^1H$ NMR: 5.67 (1 H, ddd, *J* 5, 2, 1), 4.85 (2 H, m), 4.82 and 4.60 (2 H, AB, *J* 7), 4.18 (1 H, m), 3.72–3.66 (1 H, m), 3.58–3.50 (1 H, m), 3.41 (3 H, s), 2.98 (1 H, dd, *J* 7, 5, –OH), 2.82–2.74 (1 H, ddd, *J* 12, 7, 3), 2.04 (1 H, m), 2.01 (1 H, m), 1.92–1.82 (1 H, m), 1.71 (3 H, s), 1.69 (3 H, s), 1.67 (1 H, m), 1.08 (3 H, d, *J* 7). $^{13}C$ NMR: 146.4, 139.4, 120.4, 113.4, 94.3, 68.8, 64.1, 56.1, 44.3, 40.7, 36.6, 35.6, 23.2, 18.3, 16.0. IR ($CDCl_3$): 3407br, 2360, 2241. Anal. $C_{15}H_{26}O_3$: C, H.

*Aldehyde* **21**. The alcohol from above (0.003 g, 11.8 μmol) was dissolved in dry dichloromethane (0.5 ml) and added under nitrogen to a stirred mixture of 4-methylmorpholine *N*-oxide (0.0021 g, 17 μmol) and pulverised 4 Å molecular sieves (0.16 g) in dry dichloromethane (0.5 ml). The resultant mixture was stirred for 10 min before addition of TPAP (0.0002 g, 0.6 μmol). After 15 min, reaction was complete according to TLC

analysis, and the reaction flask was charged with silica gel (0.5 g). The product was then eluted from the silica gel (pentane–ether 50:50) to yield the pure aldehyde as an oil (0.0021 g, 71%). $[\alpha]_D$ −221.4 (*c* 0.88, $CH_2Cl_2$). $^1H$ NMR: 9.83 (1 H, s), 5.65 (1 H, d, *J* 4), 4.92 (2 H, s), 4.59 and 4.44 (2 H, AB, *J* 8), 4.04 (1 H, m), 3.30 (3 H, s), 3.03 (1 H, m), 2.51–2.42 (1 H, m), 2.18–2.01 (2 H, m), 1.90 (1 H, dt, *J* 12, 4), 1.73 (3 H, br s), 1.55 (3 H, s), 1.10 (3 H, d, *J* 7). $^{13}C$ NMR: 202.9, 145.8, 139.0, 120.6, 114.4, 95.4, 69.1, 56.0, 45.1, 44.2, 41.0, 36.6, 23.3, 18.1, 12.2. IR ($CH_2Cl_2$) 1712. Anal. $C_{15}H_{24}O_3$: C, H.

*Ketone* **23**. The TBS ether[10] from 3-butyn-1-ol (0.090 g, 0.49 mmol) was dissolved, with stirring under nitrogen, in dry THF (0.5 ml) and cooled to −78 °C before addition of BuLi (1.47 M in hexanes, 0.32 ml, 0.47 mmol). The resultant solution was stirred for 1 h at −78 °C and a solution of the aldehyde from above (0.040 g, 0.16 mmol) in dry THF (0.5 ml) was added. After 2 h, the reaction temperature was brought to −20 °C and stirred for an additional 1 h. Water (3 ml) and pentane–ether (3 ml) were added and the phases separated. The aqueous phase was extracted with pentane–ether (2 × 5 ml) and the combined organics were dried over $MgSO_4$ and evaporated to dryness. The crude product consisted of a mixture of epimeric alcohols ($^1H$ NMR) and was used directly in the next step.

The crude product from above (0.070 g, 0.16 mmol) was dissolved, with stirring, in dry dichloromethane (2 ml) and activated[1] $MnO_2$ (0.14 g) was added. The mixture was stirred for 7 days at room temperature and then filtered through a plug of Celite. The solvent was removed to yield the pure ketone as an oil (0.060 g, 87% based on **21**). $[\alpha]_D$ −17 (*c* 0.80, $CH_2Cl_2$). $^1H$ NMR: 5.39 (1 H, br s), 4.86–4.83 (1 H, m), 4.71–4.69 (1 H, m), 4.48 and 4.47 (2 H, AB, *J* 7), 4.08–4.04 (1 H, m), 3.77 (2 H, t, *J* 7), 3.32 (3 H, s), 2.81–2.73 (1 H, m), 2.63 (1 H, m), 2.57 (2 H, t, *J* 7), 2.47–2.41 (1 H, m), 2.05 (1 H, dd, *J* 19, 5), 1.94 (1 H, dd, *J* 19, 5), 1.78 (3 H, s), 1.71 (3 H, s), 1.10 (3 H, d, *J* 7), 0.86 (9 H, s), 0.01 (6 H, 2 × s). $^{13}C$ NMR: 181.3, 146.2, 139.6, 120.6, 116.2, 95.1, 82.6, 79.3, 67.9, 65.1, 62.7, 56.7, 46.1, 44.5, 40.6, 36.8, 25.8, 23.2, 23.1, 18.8, 18.7, 15.9. IR ($CH_2Cl_2$): 1708. Anal. $C_{25}H_{42}O_4Si$: C, H.

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