Tetrahedron 68 (2012) 7598–7604

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The total synthesis of (−)-aplysin via a lithiation–borylation–propenylation sequence

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ARTICLE INFO

Article history:
Received 21 March 2012
Received in revised form 4 May 2012
Accepted 22 May 2012
Available online 28 May 2012

This paper is dedicated to Professor Manfred Reetz, one of the most creative academics of his generation and a pretty good tennis player too, on the occasion of the Tetrahedron Prize. Many congratulations

Keywords:
Lithiation–borylation
Quaternary stereocenter
Aplysin
Total synthesis
Sesquiterpene

ABSTRACT

A concise, highly enantioselective synthesis of sesquiterpene natural products (−)-debromoaplysin and (−)-aplysin has been completed. The key steps included lithiation–borylation of a secondary benzylic carbamate to give a tertiary boronic ester followed by propenylation which installed the quaternary stereocenter with complete enantioselectivity. Subsequent RCM followed by deprotection and in situ cyclization led to debromoaplysin with good diastereoselectivity from which the target compound was prepared in just eight overall steps.

1. Introduction

Over the last 50 years, marine mollusc species *aplysia* and the red algal species *laurencia* have provided a wealth of sesquiterpenoid natural products.[1] These marine molluscs are known to feed almost exclusively on the *laurencia* algae and sequester compounds exhibiting antifeedant properties to protect themselves from predation.[2] A number of these sesquiterpenes can be grouped together due to structural similarities, such as aplysin (**1**) and debromoaplysin[3] (**2**); laurinterol[4] (**3**) and debromolaurinterol[5] (**4**); filiformin[6] (**5**) and debromofiliformin[7] (**6**); 3,7-dihydroxy-dihydrolaurene[8] (**7**); laurequinone[9] (**8**); allolaurinterol[6] (**9**); 7-hydroxylaurene[7] (**10**); carabical[10] (**11**) and laurol[11] (**12**). All of these contain a cyclopentane ring with a benzylic quaternary stereogenic centre and an array of methyl substitutions with varying stereochemistry. The aromatic ring in each case shows the same *p*-methyl, *o*-hydroxy substitution relative to the quaternary centre (Fig. 1). There have been numerous syntheses of *aplysia* and *laurencia* sesquiterpenes; of these, aplysin (**1**) has attracted the most attention with four published enantioselective routes to date.[12]

Ronald and co-workers in 1980[13] were the first to report a synthesis of enantioenriched (−)-aplysin, but their synthesis used an (isopinocamphenyloxy) methyl ether for simultaneous phenolic hydroxyl protection and diastereomeric resolution, so did not constitute an asymmetric synthesis.

The first enantioselective synthesis in 1992 by Takano[12a] used a Fisher indolisation of a chiral cyclopentanone starting material to introduce the quaternary stereocenter. Fukumoto's synthesis in 1994[12b] used a tandem Katsuki-Sharpless asymmetric epoxidation of 2-aryl-2-cyclopropylidene ethanols and Yoshida's synthesis in 2010[12c] used an Eschenmoser/Claisen rearrangement of an enantioenriched allylic alcohol to introduce the quaternary stereocenter.

Whilst these syntheses use some elegant methodology to introduce the quaternary stereocenter, they are relatively long and require a number of functional group interconversions. Srikrishna's synthesis in 2001[12d] is the shortest to date, with only ten steps and employing a Claisen rearrangement to introduce the quaternary stereocenter. However, it suffers from low diastereoselectivity in the key step (5:1:2 ratio of the required diastereomer, the minor diastereomer and an unwanted side product).

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doi:10.1016/j.tet.2012.05.095

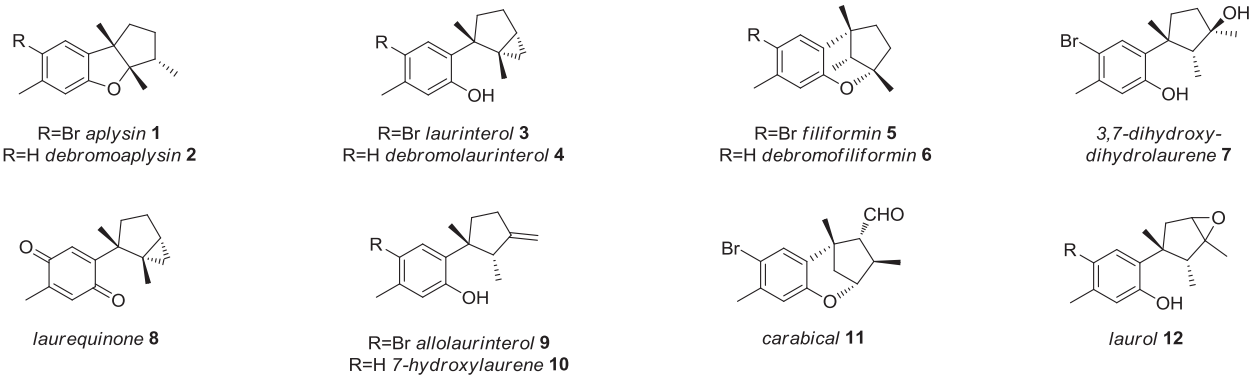
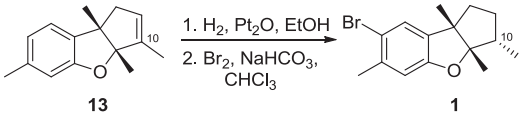


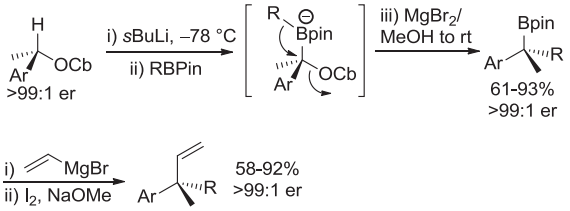
Fig. 1. Natural products derived from *aplysia* and *laurencia*.

All syntheses reported to date converge at intermediate **13**, completing the synthesis with a highly face-selective reduction using Adam's catalyst and finally bromination (Scheme 1).



Scheme 1. Previous completion of aplysin.

Recently, we reported a method for the preparation of highly enantioenriched tertiary boronic esters through a lithiation–borylation reaction of secondary aryl carbamates with pinacol boronic esters.[14] We then demonstrated the homologation of these tertiary boronic esters to give quaternary stereocenters in high yields and with complete stereoretention (Scheme 2).[15] We envisaged that our methodology could be applied to the synthesis of aplysin, which contains a quaternary stereogenic centre, by a concise route.



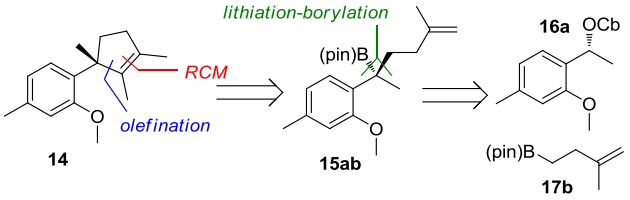
Scheme 2. Lithiation–borylation–vinylation sequence for preparation of quaternary stereocenters.

The key structural features of aplysin, including the quaternary stereocenter, are common to a range of sesquiterpene natural products. In our synthesis, we sought not only to devise a concise and highly stereoselective synthesis of aplysin, but to devise a route that would enable access to a host of natural products in just a few transformations from elaboration of a common precursor. We decided upon core structure **14** as the key common precursor and so made it our initial target.

Retrosynthetic analysis of **14** took us back to tertiary boronic ester **15ab** via olefination and ring-closing metathesis (Scheme 3). The boronic ester in turn could be derived from enantioenriched carbamate **16a** and boronic ester **17b** via lithiation–borylation.

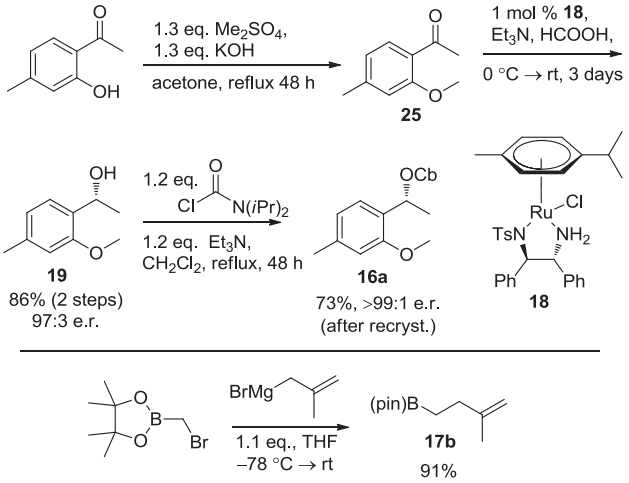
2. Results and discussion

The synthesis of the core structure **14** began with the preparation of tertiary boronic ester **15ab**. Carbamate **16a** was synthesized



Scheme 3. Retrosynthetic analysis of core structure **14**.

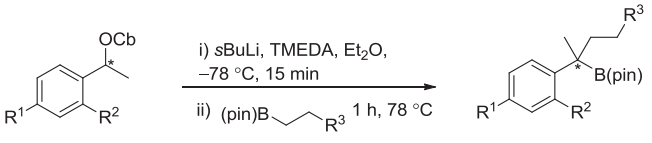
in three facile steps (Scheme 4). After protection of the phenol of 2′-hydroxy-4′-methylacetophenone as the methyl ether, Noyori reduction[16] with RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (**18**) gave alcohol **19** in 97:3 er. Simple carbamoylation completed the carbamate synthesis with the same high er. Furthermore, recrystallization from pentane enabled enantioenrichment to >99:1 er without significant loss of yield. Primary boronic ester **17b** was prepared in one step from bromomethylboronic acid pinacol ester and 2-methylallyl Grignard in 91% yield.



Scheme 4. Preparation of carbamate **16a** and boronic ester **17b**.

With carbamate **16a** and boronic ester **17b** in hand, we were now ready to test the lithiation–borylation step. As had been found previously with carbamates with an *ortho*-methoxy substituent,[14b] use of TMEDA was essential to achieve clean lithiation. The first attempt at the lithiation–borylation led to **15ab** in 47% yield (Table 1, entry 1). Initially, the reason for the moderate yield was not clear and so we investigated the steps in the reaction, individually. Lithiation of carbamate **16a** with ^{s}BuLi in Et_2O at −78 °C over a range of times, followed by addition of deuterated methanol

Table 1
Investigation into lithiation–borylation step



16a R^1=Me, R^2=OMe
16b R^1=R^2=H
17a R^3=Et
17b R^3=$C(CH_3)CH_2$

15aa R^1=Me, R^2=OMe, R^3=Et
15bb R^1=R^2=H, R^3=$C(CH_3)CH_2$
15ab R^1=Me, R^2=OMe, R^3=$C(CH_3)CH_2$

Entry	Carbamate	1° Boronic ester	3° Boronic ester	Yield %	er
1	**16a**	**17b**	**15ab**	47	>99:1
2	**16a**	**17b**	**15ab**	46[a]	nd
3	**16a**	**17a**	**15aa**	76	nd
4	**16b**	**17b**	**15bb**	45	>99:1

[a] Boronic ester (2 equiv) **17b** used.

showed that full lithiation was achieved after 15 min (100% D incorporation observed by ^{1}H NMR). Monitoring of the reaction by ^{11}B NMR showed that after 2 h at room temperature there was no boron-ate complex remaining, indicating that this time was sufficient for the 1,2-metallate rearrangement to occur. However, significant quantities of carbamate starting material (~15–20%) were recovered from the reaction despite using an excess of boronic ester **17** [1.5 or 2 equiv (entries 1, 2)]. As the lithiation was shown to be complete, this suggests some reversibility of the boron-ate complex.

We decided to examine the effect on yield of the structure of the boronic ester and carbamate groups independently. When using carbamate **16a** with a simple alkyl boronic ester, butyl boronic acid pinacol ester **17a**, the reaction proceeded smoothly to give tertiary boronic ester **15aa** in a considerably improved 76% yield (entry 3). When using carbamate **16b**, with no aromatic substituents and alkenyl boronic ester **17b** a similarly low yield of **15bb** was obtained to that obtained with carbamate **16a** (entry 4). This indicated that the low yield observed was due to the structure of the boronic ester.

We have previously observed that when alkenes are present in the boron-ate complex, e.g., **A** (Fig. 2), 1,2-migration can be severely retarded.[17] This was attributed to co-ordination of lithium to the double bond.[18] Similar co-ordination, e.g., **B** (Fig. 2), may be responsible here for the lower yields observed. Despite the moderate yield, the tertiary boronic ester **15ab** was obtained in excellent er, without any loss of stereochemical information from the carbamate starting material, and the reaction was easily scaled up to 10 mmol with equally good result.

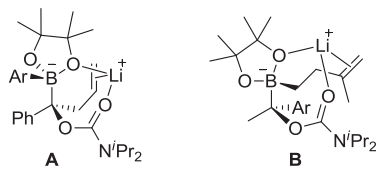
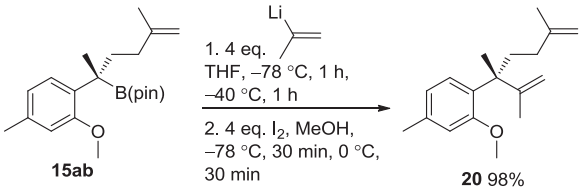


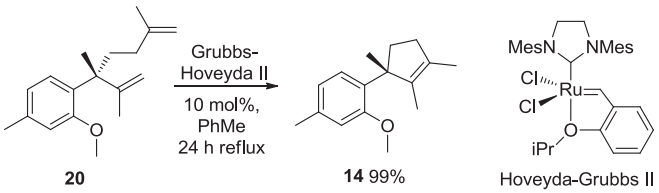
Fig. 2. Possible co-ordination of lithium to double bonds in boron-ate complexes.

The next step was to convert the tertiary boronic ester into an all-carbon quaternary stereocenter using the methodology previously developed within the Aggarwal group.[15] Tertiary boronic ester **15ab**, however, is particularly hindered due to the *o*-methoxy substituent and the olefination step represented a propenylation (rather than the previously reported vinylation) with a hindered organolithium, both of which had hitherto not been tested. With these two points in mind the olefination was approached with caution. Unsurprisingly, use of 2-propenyl magnesium bromide was ineffective in forming any boron-ate complex intermediate (monitored by ^{11}B NMR). Changing to the more reactive organolithium afforded some product but incomplete conversion from the starting boronic ester (2:1 SM:P observed by ^{1}H NMR). Previously, in formation of boron-ate complexes in hindered systems, it was found that raising the temperature of the bath to −40 °C was required to effect full ate complex formation.[19] Pleasingly, we found that upon reacting the organolithium with the tertiary boronic ester for 1 h at −78 °C followed by 1 h at −40 °C, followed by addition of iodine in MeOH and warming to room temperature, bis olefin **20** was isolated in quantitative yield and >99:1 er with complete retention of stereochemistry from the boronic ester starting material (Scheme 5).



Scheme 5. Propenylation of tertiary boronic ester **15ab**.

The final step to form the key core intermediate **14** was ring closing metathesis (RCM). However, steric hindrance also posed a potential problem in this step due to the 1,1-disubstitution of both olefins in **20**, which would require formation of a tetrasubstituted alkene adjacent to a quaternary centre. Tetrasubstituted olefins are known to be difficult to form, although there are examples in the literature using both molybdenum[20] and ruthenium[21] based catalysts. Similarly, formation of olefins adjacent to quaternary stereocenters has been shown to be difficult. For example, both Trost[22] and Thomas[23] have independently reported being unable to form a disubstituted double bond with an adjacent quaternary stereocenter in the attempted syntheses of the macrocycle bryostatin 1. The RCM proposed in our strategy stands out as an especially difficult case as it would encounter both of these obstacles. Indeed, only one example of a RCM with this scaffold existed in the literature,[24] which utilized 1.3 mol % Grubbs II catalyst in refluxing toluene for 12 h. Application of these conditions to **20**, however gave no reaction. Increasing the catalyst loading to 10 mol % allowed partial conversion to the product, but neither extending the reaction time nor adding the catalyst portionwise effected any change. Alternative catalysts were therefore examined. Pleasingly, it was found that 10 mol % of Hoveyda–Grubbs II, in refluxing toluene for 24 h was successful in forming the desired tetrasubstituted olefin **14**, in quantitative yield (Scheme 6). With the core structure in hand, our task fell to the elaboration to sesquiterpene natural products.

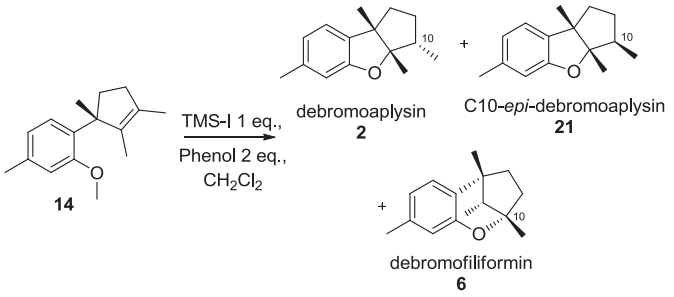


Scheme 6. Ring closing metathesis to give core structure **14**.

We thought that deprotection of the methyl ether of **14** could lead, under acidic conditions, to spontaneous cyclization upon water work-up to give debromoaplysin **2**. BBr_3 is commonly used to deprotect methyl ethers in this series of natural products,[12a,25]

however with our substrate only decomposition products were obtained. Use of TMS-I was more successful and led to a mixture of products in a 7:2:1 ratio of debromoaplysin (**2**), C10-*epi*-debromoaplysin (**21**) and debromofiliformin (**6**), respectively (Table 2, entry 1). We supposed that during the reaction the methyl ether was cleaved to give the silyl ether and MeI, and subsequent cyclization occurred upon aqueous work-up. Debromoaplysin (**2**) is the result of protonation on the less hindered face and the C10-epimer (**21**) on the more hindered face, which accounts for the preference observed. Debromofiliformin is the result of a 6-*endo-trig* cyclization, rather than a 5-*exo-trig* again with protonation on the less hindered face.

Table 2
Optimization of deprotection–cyclization step



Entry	Phenol[a]	Temp, °C	**2**[b]	**21**[b]	**6**[b]
1	None	rt	70	20	10
2	**22**	rt	50	10	40
3	**23**	rt	60	5	35
4	**24**	rt	65	5	30
5	**24**	−40	80	15	5
6	**24**	−78	80	15	5
7	**24**[c]	−78	80	15	5

[a] Phenol (2 equiv).
[b] Ratio determined by NMR to nearest 5%.
[c] Phenol and TMS-I premixed.

With this promising result we sought further improvements. Lowering the temperature of reaction mixture to 0 °C gave similar results. We then considered the use of hindered phenols (Fig. 3) to promote delivery of a proton to the less hindered face. With the use of *o*-cresol (**22**) we saw a marked improvement in dr (entry 2), which continued to improve as we moved to more hindered phenols **23** (entry 3) and **24** (entry 4) supporting our theory. Unfortunately, this also resulted in a significant increase in the formation of debromofiliformin **6**. Lowering the temperature of the reaction to −40 °C and −78 °C was successful in significantly reducing the formation of debromofiliformin **6** at a slight cost in the dr, but overall provided optimum conversion to the desired product debromoaplysin **2**.

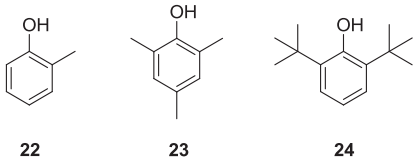
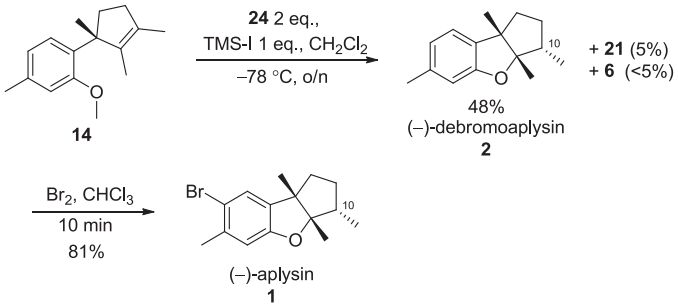


Fig. 3. Phenol additives used in the cyclization of **14**.

We found these results to be reproducible on larger scales, and after separation of both side products by flash column chromatography we were able to obtain a 48% isolated yield of pure (−)-debromoaplysin (Scheme 7). Bromination using bromine in chloroform gave (−)-aplysin **1** in 81% yield, which was identical in all respects to the natural product. This completed the total synthesis of (−)-aplysin in just eight steps, and 12% overall yield.



Scheme 7. Completion of (−)-aplysin.

3. Conclusion

A highly concise, novel route to (−)-debromoaplysin and (−)-aplysin has been completed with excellent enantioselectivity and good diastereoselectivity in the cyclization step. Complete stereocontrol was observed in the lithiation–borylation and propenylation steps leading to the all carbon quaternary stereocenter of (−)-aplysin in >99% er. Application of this method towards the synthesis of other *aplysia* and *laurencia* sesquiterpenes is underway.

4. Experimental

4.1. General

All required fine chemicals were used directly without purification unless mentioned. Compounds lacking experimental details were prepared according to the literature as cited and are in agreement with published spectra. All air- and water-sensitive reactions were carried out in flame-dried glassware under argon atmosphere using standard Schlenk manifold technique. ^{1}H- and ^{13}C-Nuclear Magnetic Resonance (NMR) spectra were acquired at various field strengths as indicated, and were referenced to $CHCl_3$ (7.27 and 77.0 ppm for ^{1}H and ^{13}C, respectively) or TMS (0.00 ppm for ^{1}H and ^{13}C). ^{1}H NMR coupling constants are reported in hertz and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, qi=quintet, sx=sextet, sp=septet, m=multiplet, dd=doublet of doublet, etc.) and integration. ^{11}B NMR spectra were recorded with complete proton decoupling using $BF_3{\cdot}Et_2O$ (0.0 ppm) as an external standard. High resolution mass spectra were recorded using Electronic Ionization (EI), Electron Spray Ionization (ESI) or Chemical Ionization (CI). For CI, methane was used. Infrared spectra were obtained using a Perkin Elmer Spectrum One FT-IR spectrometer, reporting as ATR plates (solids) or films (oils) irradiating over the range 4000 cm^{-1} and 600 cm^{-1}. Optical rotations were obtained on a Perkin–Elmer 241 MC polarimeter. Analytical TLC: aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F_{254}. Compounds were visualized by exposure to UV-light or by dipping the plates in a 5% solution of $[MoO_3]_{12}[PO_4H_3]$ in EtOH followed by heating. Flash column chromatography was performed using Merck Silica Gel 60 (40–63 μm). All mixed solvent eluents are reported as v/v solutions. Melting points were determined with a Boetius hot stage apparatus and were not corrected. Chiral HPLC separations were done using an Agilent 1100 series normal phase high performance liquid chromatography unit using HP Chemstation software, on Chiralpak IA (250×4.6 mm) with Chiralpak IA Guard Cartridge (10×4 mm), Chiralpak IB (250×4.6 mm) with Chiralpak IB Guard Cartridge (10×4 mm) or Chiralpak IC (250×4.6 mm) with

Chiralpak IC Guard Cartridge (10×4 mm) columns and monitored by DAD (Diode Array Detector). Solvents were purified by standard methods.[26] TMEDA was distilled over CaH_2. ^{s}BuLi was purchased from Acros. The molarity of organolithium solutions was determined by titration using salicylaldehyde phenylhydrazone as indicator.[27]

4.1.1. 2′-Methoxy-4′-methyl acetophenone ***25***. KOH (4.85 g, 86 mmol, 1.3 equiv) and dimethyl sulfate (8.21 mL, 86.6 mmol, 1.3 equiv) were added to a solution of 2′-hydroxy 4′-methylacetophenone (9.26 mL, 66.6 mmol, 1 equiv) in anhydrous acetone (140 mL) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue dissolved in EtOAc (400 mL) and washed with water (400 mL) and brine (400 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo giving the crude product as a colourless oil. This oil was purified by flash column chromatography (15:85 EtOAc/petroleum ether) to give *methyl ether* **25** (10.3 g, 95%) as white needles, mp 36–38 °C from hexane (lit.[28] 37–38 °C); R_f (15% EtOAc/petroleum ether) 0.22; δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s), 2.60 (3H, s), 3.90 (3H, s), 6.77 (1H, s), 6.81 (1H, d, J=7.9 Hz), 7.68 (1H, d, J=7.9 Hz); δ_C (100 MHz, $CDCl_3$) 21.8 (CH_3), 31.8 (CH_3), 55.4 (CH_3), 112.2 (CH), 121.3 (CH), 125.4 (C), 130.5 (CH), 144.8 (C), 159.1 (C), 199.1 (C). Data were consistent with those previously reported.[28]

*4.1.2. (R)-(+)-1-(2′-Methoxy-4′-methylphenyl)ethanol (+)-****19***. Formic acid (11.64 mL, 290 mmol, 5.4 equiv) was added to triethylamine (17.4 mL, 116 mmol, 2.1 equiv) at 0 °C, and then warmed to room temperature. 2′-Hydroxy 4′-methylacetophenone **25** (8.89 g, 54 mmol, 1 equiv) and (*S*)-RuCl[(1*R*,2*R*)-*p*-TsNCH (C_6H_5)NH_2](η^6-*p*-cymene) (344 mg, 0.54 mmol, 0.01 equiv) were added and the mixture stirred for 96 h whilst bubbling N_2 through the reaction mixture via a needle. The reaction mixture was quenched with water (250 mL), and the organic layer separated. The aqueous phase was washed with EtOAc (3×250 mL), the organic phases were combined, dried over $MgSO_4$, filtered and concentrated to give the crude product as a black oil. The oil was purified by flash column chromatography (1:9 EtOAc/petroleum ether) to give *alcohol* (+)-**19** as a colourless oil (91%, 8.18 g, 97:3 er); [found: C, 72.16; H, 8.70. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%]; R_f (25% EtOAc/petroleum ether) 0.33; $[\alpha]_D^{20}$ +20 (*c* 0.98, $CHCl_3$); ν_{max} (liquid film) 3383, 2969, 2927, 1613, 1256, 1081, 1038, 813 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.51 (3H, d, J=6.6 Hz); 2.36 (3H, s), 2.62 (1H, br d, J=4.5 Hz), 3.86 (3H, s), 5.07 (1H, qd, J=6.6, 4.5 Hz), 6.71 (1H, s), 6.78 (1H, d, J=7.6 Hz), 7.22 (1H, d, J=7.6 Hz); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 22.8 (CH_3), 55.2 (CH_3), 66.4 (CH), 111.4 (CH), 121.3 (CH), 126.0 (C), 130.4 (CH), 138.3 (C), 156.5 (C); *m*/*z* (CI) 177 (5), 166 (15, M^+), 151 (40), 149 (100), 135 (20), 123 (30%); HRMS (CI): M^+, found 166.0991. $C_{10}H_{14}O_2$ requires 166.0994.

*4.1.3. (R)-1-(2-Methoxy-4-methylphenyl)ethyl diisopropyl-carbamate (−)-****16a***. (*R*)-(+)-1-(2′-Methoxy-4′-methylphenyl)ethanol (+)-**19** (8.00 g, 48 mmol, 1 equiv) was added to a solution of *N*,*N*-diisopropylcarbamoyl chloride (9.48 g, 57.6 mmol, 1.2 equiv) and triethylamine (8.08 mL, 57.6 mmol, 1.2 equiv) in dichloromethane (100 mL), and heated to reflux for 48 h. The reaction mixture was cooled to room temperature and water (250 mL) was added. The organic phase was separated and the aqueous phase extracted with dichloromethane (3×250 mL), the organic phases were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product as a yellow oil. Purification by column chromatography (1:9 EtOAc/petroleum ether) gave *carbamate* (−)-**16** as colourless cubes (11.93 g, 81%, 97:3 er; >99:1 recryst from pentane 90%); mp 52–53 °C from pentane; R_f (10% EtOAc/petroleum ether) 0.23; $[\alpha]_D^{20}$ −20 (*c* 1, $CHCl_3$); ν_{max} (ATR plate) 2969, 2933, 1683, 1285, 1065, 1045, 810 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.24 (12H, br s), 1.50 (3H, d, J=6.5 Hz), 2.35 (3H, s), 3.82 (3H, s), 3.84–4.20 (2H, br m), 6.16 (1H, q, J=6.5 Hz), 6.69 (1H, s), 6.77 (1H, d, J=7.8 Hz), 7.24 (1H, d, J=7.8 Hz); δ_C (100 MHz, $CDCl_3$) 21.1 (br, 4× CH_3); 21.5 (CH_3), 21.9 (CH_3), 45.7 (br, 2× CH), 55.3 (CH_3), 67.8 (CH), 111.4 (CH), 121.0 (CH), 125.9 (C), 128.7 (CH), 138.1 (C), 155.1 (C), 155.8 (C); *m*/*z* (CI) 395 (5), 379 (10), 351 (5), 294 (20), 293 (35, M^+), 292 (40), 249 (25), 234 (40), 149 (100), 102 (25%); HRMS (CI): M^+, found 293.1997. $C_{17}H_{27}NO_3$ requires 293.1991.

4.1.4. 4,4,5,5-Tetramethyl-2-(3-methylbut-3-enyl)-1,3,2-dioxaborolane ***17b***. 2-Methylallylmagnesium chloride (0.5 M in THF, 98 mL, 49 mmol, 1.1 equiv) was added dropwise to a solution of bromomethylboronic acid pinacol ester (9.78 g, 44.3 mmol, 1 equiv) in THF (90 mL) at −78 °C over 0.5 h. The reaction mixture was allowed to warm to room temperature over night, after which the reaction was quenched with water (150 mL). The organic layer was separated and the aqueous layer washed with EtOAc (3×150 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo affording *boronic ester* **17b** as a colourless oil (8.1 g, 91%), which was used without further purification; R_f (10% EtOAc/petroleum ether) 0.35; δ_H (400 MHz, $CDCl_3$) 0.93 (2H, t, J=7.9 Hz, CH_2), 1.25 (12H, s, CH_3), 1.72 (3H, s, CH_3), 2.12 (2H, t, J=7.9 Hz, CH_2), 4.67 (2H, br s, CH_2); δ_C (100.6 MHz, $CDCl_3$), 22.6 (CH_3), 24.9 (4× CH_3), 31.8 (CH_2), 83.1 (2× C), 108.5 (CH_2), 147.9 (C); δ_B (128 MHz, $CDCl_3$) 34.0. Data were consistent with those previously reported.[29]

*4.1.5. (R)-2-(2-(2-Methoxy-4-methylphenyl)-5-methylhex-5-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (+)-****15ab***. ^{s}BuLi (1.16 M in hexane; 11.2 mL, 13 mmol, 1.3 equiv) was added dropwise to a solution of carbamate (−)-**16a** (2.94 g, 10 mmol, 1 equiv, >99:1 er) and TMEDA (2 mL, 15 mmol, 1.5 equiv) in Et_2O (45 mL) at −78 °C. The reaction was stirred for 15 min after which boronic ester **17b** (2.94 g, 15 mmol, 1.5 equiv) was added dropwise at −78 °C. The solution was stirred at −78 °C for 1 h, after which $MgBr_2$ (1.0 M in MeOH; 17 mL, 17 mmol, 1.7 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature over night. The reaction mixture was concentrated in vacuo and the residue dissolved in Et_2O (300 mL) to which water (300 mL) was added and the organic phase separated. The aqueous phase was extracted with Et_2O (2×300 mL), the organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo giving an oil, which was purified by column chromatography (Gradient: 5:95 to 7:93 EtOAc/pentane) to give *boronic ester* (+)-**15ab** as white needles (1.61 g, 47%, >99:1 er); mp 63–65 °C; [found: C, 73.59; H, 9.93. $C_{21}H_{34}O_3B$ requires C, 73.26; H, 9.66%]; R_f (5% EtOAc/petroleum ether) 0.17; $[\alpha]_D^{20}$ +38 (*c* 1, $CHCl_3$); ν_{max} (ATR plate) 3031, 2974, 2933, 1611, 1577, 1503, 1146, 810 cm^{-1}; δ_H (400 MHz, $CDC1_3$), 1.24 (6H, s), 1.25 (6H, s), 1.26 (3H, s), 1.68 (3H, s), 1.69–1.84 (2H, m), 1.90–2.02 (2H, m), 2.32 (3H, s), 3.79 (3H, s), 4.63 (2H, s), 6.64 (1H, s), 6.74 (1H, d, J=7.8 Hz), 7.07 (1H, d, J=7.8 Hz); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 22.7 (CH_3), 24.9 (2× CH_3), 24.9 (2× CH_3), 32.9 (CH_2), 34.7 (CH_2), 54.7 (CH_3), 82.7 (2× C), 109.0 (CH_2), 110.9 (CH), 121.2 (CH), 126.2 (CH), 132.8 (C), 135.9 (C), 147.3 (C), 156.4 (C); δ_B (128 MHz; $CDCl_3$) 34.1; *m*/*z* (CI) 345 (25, MH^+), 329 (20), 245 (100%); HRMS (CI): M+H, found 345.2609. $C_{21}H_{34}O_3B$ requires 345.2601.

*4.1.6. (R)-2-Methoxy-4-methyl-1-(2,3,6-trimethylhepta-1,6-dien-3-yl)benzene (+)-****20***. ^{t}BuLi (14.6 mL, 23.3 mmol, 8 equiv) was added dropwise to a solution of 2-bromoprop-1-ene (1.02 mL, 11.6 mmol, 4 equiv) in THF (25 mL) at −78 °C for 30 min. Boronic ester (+)-**15ab** (1.00 g, 2.91 mmol, 1 equiv >99:1 er) in THF (12 mL) was added dropwise at −78 °C and the reaction mixture stirred for 1 h, then warmed to −40 °C for a further hour. The mixture was cooled to −78 °C prior to dropwise addition of iodine (2.95 g, 11.6 mmol, 4 equiv) in MeOH (46 mL), which was stirred at −78 °C for 0.5 h, followed by warming to 0 °C for a further 0.5 h. The reaction mixture was warmed to room temperature and $Na_2S_2O_3$ (100 mL,

5% w/v aqueous) was added and the resultant biphasic mixture was stirred for a 1 h. The organic phase was separated and the aqueous phase washed with Et_2O (3×125 mL). The combined organic phases were dried over $MgSO_4$ and solvent removed in vacuo and purified by column chromatography (pentane) to give *diene* (+)-**20** as a colourless oil (0.73 g, 98%, >99:1 er); [found: C, 83.48; H, 10.38. $C_{18}H_{26}O$ requires C, 83.67; H, 10.14%]; R_f (100% petroleum ether) 0.19; $[\alpha]_D^{20}$ +41 (*c* 1, $CHCl_3$); ν_{max} (liquid film) 3072, 2968, 2925, 1638, 1575, 1501, 805 cm^{-1}; δ_H (400 MHz $CDCl_3$) 1.42 (3H, s, 8-CH_3), 1.55 (3H, d, *J*=1.0 Hz), 1.57–1.66 (1H, m), 1.71 (3H, s), 1.76–1.90 (2H, m), 2.31–2.40 (1H, m), 2.34 (3H, s), 3.73 (3H, s), 4.67 (2H, d, *J*=1.0 Hz), 4.75 (1H, d, *J*=1.0 Hz), 4.81 (1H, quin., *J*=1.0 Hz) 6.66 (1H, s), 6.73 (1H, d, *J*=7.8 Hz), 7.12 (1H, d, *J*=7.8 Hz); δ_C (100 MHz, $CDCl_3$) 20.8 (CH_3); 21.2 (CH_3), 22.7 (CH_3), 24.9 (CH_3), 33.4 (CH_2), 36.1 (CH_2), 45.8 (C), 55.1 (CH_3), 108.4 (CH_2), 109.1 (CH_2), 112.7 (CH), 120.7 (CH), 127.8 (CH), 132.3 (C), 137.0 (C), 147.2 (C), 152.6 (C), 158.2 (C); *m*/*z* (CI) 258 (5, M^+), 149 (40), 137 (30), 61 (100%); HRMS (CI): M+H, found 259.2061. $C_{18}H_{26}O$ requires 259.2062.

*4.1.7. (R)-2-Methoxy-4-methyl-1-(1,2,3-trimethylcyclopent-2-enyl) benzene (−)-**14**.* Hoveyda–Grubbs second generation alkene metathesis catalyst (0.144 g, 0.23 mmol) was added to a solution of (+)-**20** (0.600 g, 2.3 mmol, >99:1 er) in toluene (23 mL) and was heated to reflux for 24 h. The reaction mixture was filtered through a plug of silica, which was washed with 5% EtOAc/pentane. The filtrate was concentrated in vacuo giving the *cyclopentene* −**14** as an oil, which solidified on standing (0.525 g, 99%); mp 37–39 °C; [found: C, 83.85; H, 9.98. $C_{16}H_{22}O$ requires C, 83.43; H, 9.63%]; R_f (2% EtOAc/petroleum ether) 0.31; $[\alpha]_D^{20}$ −7 (*c* 1, $CHCl_3$); ν_{max} (ATR plate) 2960, 2915, 2859, 2836, 1610, 1574, 1500, 1255, 809 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.43 (3H, s), 1.50 (3H, d, *J*=1.0 Hz), 1.69 (3H, d, *J*=1.0 Hz), 1.70–1.76 (1H, m), 2.12–2.18 (2H, m), 2.23 (1H, ddd, *J*=12.4, 6.8, 5.0 Hz), 2.31 (3H, s), 3.77 (3H, s), 6.65 (1H, d, *J*=7.8 Hz), 6.68 (1H, s), 6.89 (1H, d, *J*=7.8 Hz); δ_C (100 MHz, $CDCl_3$) 11.1 (CH_3), 14.4 (CH_3), 21.2 (CH_3), 25.3 (CH_3), 35.9 (CH_2), 38.5 (CH_2), 53.9 (C), 55.2 (CH_3), 112.6 (CH), 120.4 (CH), 127.7 (CH), 131.7 (C), 133.3 (C), 136.7 (C), 136.7 (C), 158.3 (C); *m*/*z* (CI) 230 (30, M^+), 215 (100%); HRMS (CI): M^+, found 230.1677. $C_{16}H_{22}O$ requires 230.1671.

*4.1.8. (−)-Debromoaplysin (−)-**2**.* Trimethylsilyl iodide (0.07 mL, 0.47 mmol, 1 equiv) was added dropwise to a solution of (−)-**14** (0.100 g, 0.43 mmol, 1 equiv) and 2,6-di*tert*-butylphenol (179 mg, 0.87 mmol, 2 equiv) in CH_2Cl_2 (4 mL) at −78 °C and stirred at this temperature for 24 h before dropwise addition of aqueous ammonia (10 mL 17.5% w/v NH_3/H_2O). The reaction mixture was warmed to room temperature and the organic layer separated, the aqueous layer was washed with dichloromethane (3×10 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated to give the crude product as a yellow oil. The crude oil as purified by column chromatography (5% toluene/pentane), to give debromoaplysin (−)-**2** as a colourless oil (0.045 g, 48%); R_f (5% toluene/pentane) 0.25; $[\alpha]_D^{20}$ −62 (*c* 1.27, $CHCl_3$) lit.: $[\alpha]_D^{21}$ −68 (*c not quoted*, $CHCl_3$);[13] $[\alpha]_D^{25}$ −53 (*c* 0.15, $CHCl_3$);[30] $[\alpha]_D^{29}$ −66.5 (*c* 0.72, $CHCl_3$);[12a] $[\alpha]_D^{25}$ −61.8 (*c* 0.16, $CHCl_3$);[12b] ν_{max} (liquid film) 2954, 2928, 2865, 1619, 1593, 1499, 1280, 1122, 1008, 948, 801 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15–1.24 (1H, m), 1.15 (3H, d, *J*=6.8 Hz), 1.32 (3H, s), 1.35 (3H, s), 1.56–1.67 (2H, m), 1.79 (1H, m), 1.88 (1H, dd, *J*=11.2, 6.1 Hz), 2.31 (3H, s), 6.55 (1H, s), 6.67 (1H, d, *J*=7.3 Hz), 6.94 (1H, d, *J*=7.3 Hz); δ_C (100 MHz, $CDCl_3$) 13.1, 20.0, 23.5, 31.2, 42.6, 46.1, 54.0, 98.9, 109.3, 120.68, 122.6, 133.4, 137.8, 158.9; *m*/*z* (CI) 216 (20, M^+), 201 (80%); HRMS (CI): M^+, found 216.1515. $C_{15}H_{20}O$ requires 216.1514.

*4.1.9. (−)-Aplysin (−)-**1**.* Bromine (0.97 mL, 0.1 M in $CHCl_3$, 0.097 mmol, 1.5 equiv) was added dropwise to a vigorously stirred solution of (−)-**2** (14 mg, 0.065 mmol, 1 equiv) in $CHCl_3$ (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 min, after which all solvent was removed to give a light brown oil. The oil was filtered through a short plug of silica to give aplysin (−)-**1** (0.0156 g, 81%) as fine white needles; mp 84–85 °C (lit.[3] 85–86 °C); R_f (1:1 CH_2Cl_2/hexane) 0.6; $[\alpha]_D^{22}$ −80 (*c* 1, $CHCl_3$) lit.: $[\alpha]_D^{21}$ −84.2 (*c* 0.31, $CHCl_3$);[13] $[\alpha]_D^{32}$ −83.5 (*c* 0.31, $CHCl_3$);[12a] $[\alpha]_D^{25}$ −83.2 (*c* 0.15, $CHCl_3$);[12b] δ_H (500 MHz, $CDCl_3$) 1.11 (3H, d, *J*=6.9 Hz), 1.15 (1H, s), 1.29 (3H, s), 1.32 (3H, s), 1.57–1.67 (2H, m), 1.72–1.82 (1H, m), 1.87 (1H, s), 2.32 (3H, s), 6.60 (1H, s), 7.15 (1H, s); δ_C (100 MHz, $CDCl_3$) 13.1 (CH_3), 19.9 (CH_3), 23.2 (CH_3), 23.4 (CH_3), 31.2 (CH_2), 42.5 (CH_2), 46.0 (CH), 54.3 (C), 99.8 (C), 110.9 (CH), 114.0 (C), 126.5 (CH), 136.2 (C), 136.9 (C), 158.2 (C); HRMS (APCI): M+H, found 295.0691. $C_{15}H_{20}OBr$ requires 295.0692.

Acknowledgements

We thank EPSRC and the European Research Council (ERC) in the context of the European Community's Seventh Framework Programme (FP7/2007–2013, ERC grant no. 246785) for financial support. VKA thanks EPSRC for a Senior Research Fellowship. C.J.F. thanks the EPSRC and GSK for funding. We thank Inochem-Frontier Scientific for generous donation of boronic acids and boronic esters.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.095.

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