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Total synthesis of the marine sponge metabolites (+)-rottnestol, (+)-raspailol A and (+)-raspailol B †

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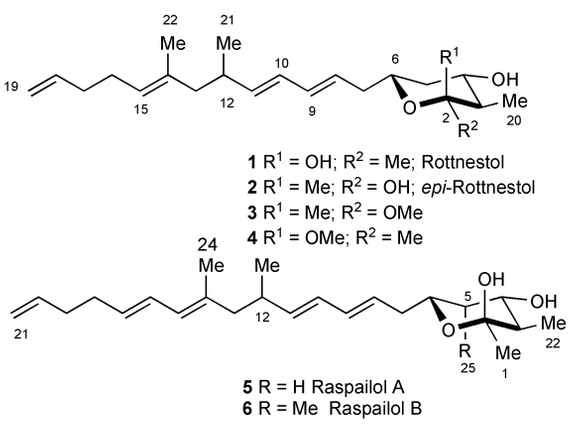
The asymmetric syntheses of (+)-rottnestol (**1**) and the related marine sponge metabolites (+)-raspailols A (**5**) and B (**6**) are described. The key step in each of these sequences was a Stille coupling to form the C9–C10 sp^2–sp^2 bond and connect the polyene sidechains to the appropriate optically active tetrahydropyran core. For rottnestol (**1**), both C12 epimers were synthesised by a coupling between stannane **7** and (*R*)- or (*S*)-**8** followed by acid hydrolysis which allowed for the assignment of the absolute configuration at the remote C12 stereocentre as *R* upon comparison of chiroptical data of the synthetic material with that reported for the natural product. In accord with this, (12*R*)-raspailol A (**5**) was synthesised from stannane **7** and sidechain **9** and this compound also compared well with the data for natural material including sign and absolute value of the specific rotation. Finally, the same C12 epimer of raspailol B (**6**) was secured *via* a union between stannane **10** and iodide **9** and this also possessed a similar rotation to that described for the natural product. Thus, all three compounds appear to possess the (12*R*) configuration, while that of the core tetrahydropyran ring is the same as proposed originally.

Introduction

Rottnestol (**1**) is a naturally occurring hemiketal isolated from the sponge *Haliclona* sp., collected in the waters around Rottnest Island off the coast of Western Australia.[1] Small amounts of *epi*-rottnestol (**2**), as well as the corresponding methyl ketal **3** were also isolated from the methanolic extracts; however the structure originally assigned for the latter compound may be in error as the methoxy group should be in an axial orientation owing to the anomeric effect and therefore rottnestol methyl ketal is probably the C2 epimer **4**. The structure of rottnestol (**1**) was deduced by a combination of ^{1}H, ^{13}C, COSY, HMBC and HMQC NMR experiments. The absolute configuration of the pyran ring was assigned as 2*S*,3*R*,4*S*,6*R* in accordance with the absolute stereochemistry reported for the structurally related raspailols A (**5**) and B (**6**), which were isolated from the sponge genus *Raspailia* sp. collected in the reefs of Palau, Western Caroline Islands.[2] The absolute stereochemistry at the C12 asymmetric centre in **1**, **5** and **6** could not be determined from the data at hand and there was insufficient material available to conduct any degradation studies. Neither rottnestol (**1**) nor the raspailols A (**5**) and B (**6**) fall within an established chemotaxonomic group and are of interest because they may represent a new one. In the past, such novel natural products have been instrumental in the study and understanding of biochemical pathways *in vivo* and *in vitro*. Both **5** and **6** have been found to possess mild antibiotic activity, in particular against *Bacillus subtilis*,[2] but no such activity has been demonstrated by rottnestol (**1**).[1] All three compounds are interesting synthetic targets due to the fact that the stereochemistry of the C12 stereogenic center was not determined. Several recent reports demonstrate that total synthesis remains an important technique for the structural determination of complex natural products.[3–5] Computing techniques which allow for molar rotation calculations are improving and this method, in conjunction with synthesis, can also be a powerful tool for the determination of absolute configuration.[6–8] We embarked on an asymmetric synthesis of **1**, **5** and **6** in order to determine their absolute configuration and in this article, we report the full details of the total synthesis of (+)-rottnestol (**1**)[9] as well as the first total synthesis of (+)-raspailols A (**5**) and B (**6**) that allowed for the assignment of the absolute configurations of all these compounds.



Results and discussion

Retrosynthetic analysis

We began with the synthesis of the slightly simpler target rottnestol (**1**). It is not unreasonable to suggest that both **1** and the raspailols **5** and **6** possess the same absolute configuration at C12 so we would first target both diastereoisomers of **1** and then one C12 epimer each of **5** and **6**. It was envisaged that both the C12 epimers of **1** could be produced by a sp^2–sp^2 Stille coupling[10,11] between the tetrahydropyran fragment **7** and the *R* or *S* enantiomer of vinyl iodide **8** followed by acetal hydrolysis (Scheme 1). We chose the Stille coupling to form the C9–C10 bond due to the tolerance of acid sensitive functional groups to the coupling conditions.[11] At the onset, we surmised that the NMR spectra of (12*R*)- or (12*S*)-isomers would be indistinguishable owing to the number of atoms separating the stereochemical elements in the pyran core and the C12 stereogenic center. Therefore, the absolute configuration at C12 could possibly only be determined by comparison of the chiroptical properties of the synthetic and natural material.

† Taken in part from the PhD thesis of I. R. Czuba, *The University of Melbourne*, 2002.

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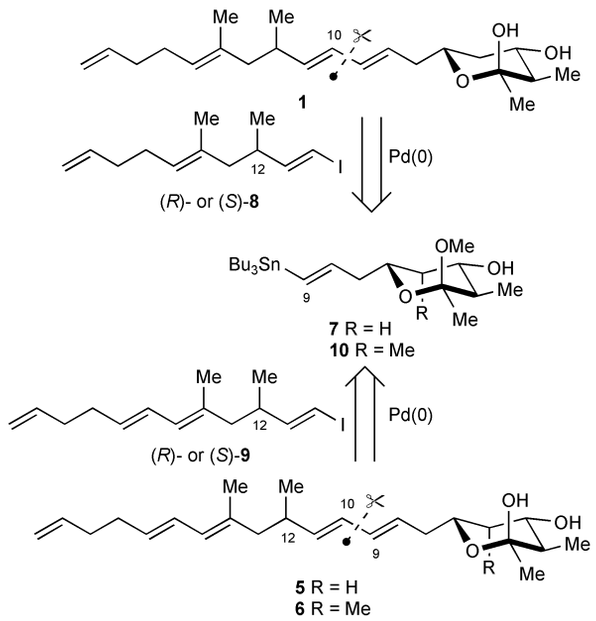


Scheme 1 Retrosynthetic analysis of rottnestol (**1**) and raspailols A (**5**) and B (**6**).

Similarly, raspailol A (**5**) could be obtained from a coupling between the same tetrahydropyran core **7** and the vinyl iodide (*R* or *S*)-**9**. For the synthesis of raspailol B (**6**), the more substituted core **10** is required. Coupling with the same iodide **9** then provides compound **6**.

Total synthesis of (+)-rottnestol (1)

A first generation synthesis of the optically active rottnestol sidechain **8** involving a resolution step[12] is depicted in Scheme 2. Addition of 3-butenylmagnesium bromide to methacrolein provided the known racemic alcohol **11**[13] which was acylated to give the propionyl ester **12**. Ireland–Claisen rearrangement[14,15] of **12** using LDA as base with TBSCl followed by hydrolysis of the resultant ester gave racemic acid **13** in good yield. The use of TMSCl as silylating agent gave large amounts of C-silylated product which was inseparable from the desired compound. Acid **13** was then converted into the diastereoisomeric mandelate esters[12] **14** (R_t 16.39 min) and **15** (R_t 17.30 min) which were cleanly separated by semi-preparative HPLC. Reduction of each ester gave the corresponding alcohols (*R*)- and (*S*)-**16**. We found this method provided **16** in higher optical purity than conducting the [3,3]-rearrangement on optically pure ester **12** since complete control of the enolate geometry, which is critical to total transfer of asymmetry, was difficult.[16,17] The determination of the absolute configurations of each enantiomer of alcohol **16** initially relied on NMR analysis of the derived Mosher esters **18** and **19** (Fig. 1). Yasuhara and co-workers reported that the signals for the C1 methylene protons in the ^{1}H NMR spectra for diastereoisomeric Mosher ester derivatives of chiral α-methyl substituted primary alcohols appear as characteristic multiplets.[18] For the (*S*,*R*)-diastereoisomer, the methylene protons each appear as a doublet of doublets while for the (*S*,*S*)-isomer, the same protons resonate as one doublet. This was in accord with the ^{1}H NMR spectra of the Mosher esters **18** and **19** derived from (*R*)- and (*S*)-**16**, respectively, as shown in Fig. 1.

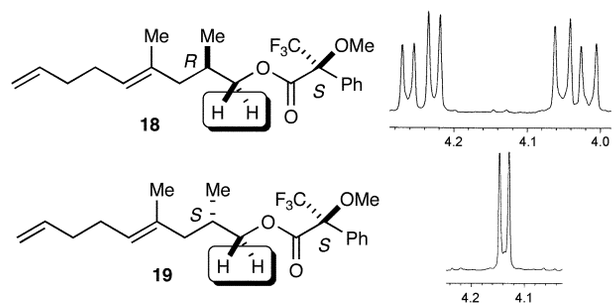
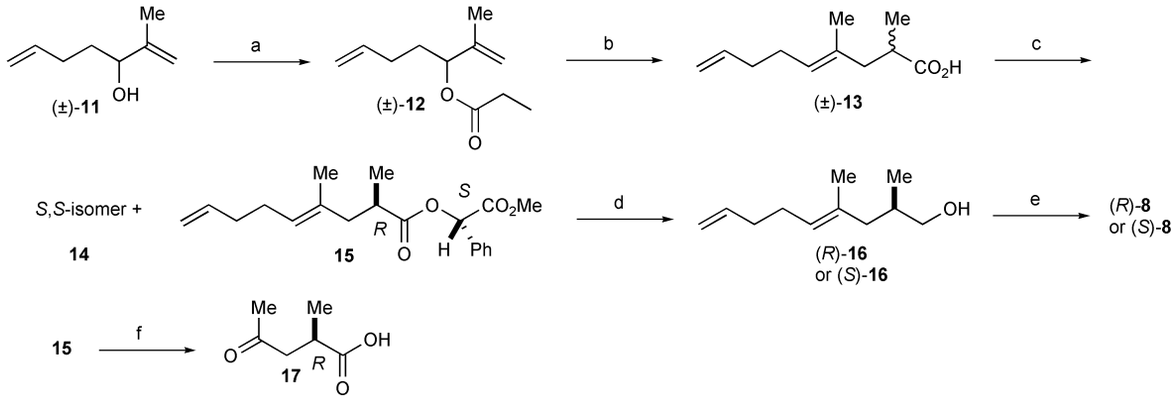


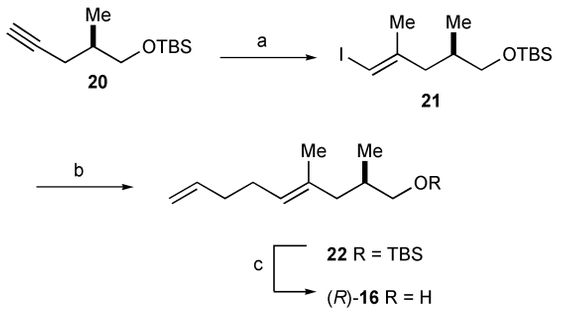
Fig. 1 Methylene region of ^{1}H NMR spectra of Mosher esters **18** and **19**.

Conclusive evidence for the absolute configuration of (*R*)-**16** arose from the degradation of its precursor mandelate ester **15** into (*R*)-4-oxo-2-methylpentanoic acid **17**.[19] Ozonolysis and hydrolysis of ester **15** gave the known (*R*)-γ-acid **17**,[19] the optical rotation of which compared well with literature values [Synthetic **17**: $[a]_D$ +30.2 (*c* 0.63, $CHCl_3$); $[a]_D$ +9.5 (*c* 0.29, AcOH); lit.[20] for (*S*) enantiomer 98%ee: $[a]_D$ −21.1 (*c* 0.80, $CHCl_3$); lit.[19] for (*R*) enantiomer: $[a]_D$ +21.8 (*c* 1.19, AcOH)]. The required rottnestol sidechains (*R*)- or (*S*)-**8** were then synthesised from (*R*)- or (*S*)-**16** by oxidation[21] and vinyliodination using Takai's procedure[22] in solvent mixture of THF–dioxane (1 : 6).[23]

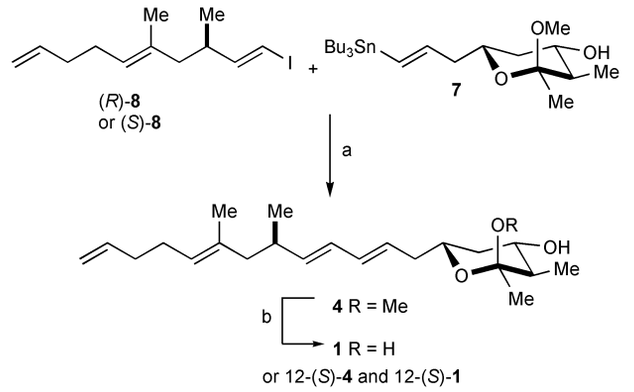
The tedious HPLC separation of the esters **14** and **15** inspired us to seek a more direct enantiospecific synthesis of the sidechain **8**. The known alkyne **20**[24] (synthesized from commercially available methyl (*S*)-(−)-3-hydroxy-2-methylpropionate)[25] was converted into a vinyl iodide by carboalumination[26] followed by iodine quench to provide iodide **21** (Scheme 3).[27] As it turned out, intermediate **21** was also utilised in the synthesis of the raspailol sidechain (see below). A Negishi coupling[28] between the zincate derived from 3-butenylmagnesium bromide and iodide **21** proceeded smoothly to give diene **22**. Desilylation then provided (*R*)-alcohol **16** which was identical to the compound prepared by the resolution route above. Alternatively, alcohol (*S*)-**16** could be



Scheme 2 *Reagents and conditions:* (a) Propionyl chloride, pyridine, DMAP, 91%; (b) LDA, TBSCl, HMPA, THF, −78 °C, then aq. NaOH; (c) (*S*)-mandelic acid, DCC, DMAP, 86%; (d) $LiAlH_4$, Et_2O, 74%; (e) (i) Dess–Martin periodinane, CH_2Cl_2, 1 h, rt; (ii) $CrCl_2$, CHI_3, THF–dioxane 1 : 6, 5 h, rt, 71% for 2 steps; (f) (i) O_3, Me_2S, CH_2Cl_2–MeOH, −78 °C; (ii) LiOH, aq. THF, 4 h, 15%.



Scheme 3 *Reagents and conditions:* (a) (i) $AlMe_3$, Cp_2ZrCl_2 $ClCH_2CH_2Cl$, 1 h, rt; (ii) I_2, THF, 82%; (b) (i) 3-Butenylmagnesium bromide, $ZnCl_2$, THF, 0 °C; (ii) cat. $Pd(PPh_3)_4$ then iodide **21**, 54%; (c) TBAF, THF, 58%.



Scheme 5 *Reagents and conditions:* (a) 15 mol% $Pd(MeCN)_2Cl_2$, DMF, *i*-Pr_2NEt (2.4 eq.), rt, 21.5 h, 57–62%; (b) 5% aq.HCl, THF, 0 °C, 35 min, 55–63%.

obtained in the same manner starting with (*R*)-(+)-3-hydroxy-2-methylpropionate. Although this route to optically pure (*R*)-**16** was slightly longer, it was more effectively conducted on a large scale and the HPLC separation could be avoided.

The synthesis of the core tetrahydropyran fragment **7** began with the known aldehyde **23**, available in four steps from (*S*)-malic acid.[29] Brown crotylmetallation[30] of **23** gave adduct **24** in good yield and high diastereoselectivity and protection as the TBDPS ether afforded **25** Scheme 4. Wacker oxidation[31] of alkene **25** proceeded smoothly under standard conditions to provide ketone **26** in excellent yield and subsequent cyclisation to the tetrahydropyran **27** was achieved by treatment of **26** with 20 mol% CSA in methanol.

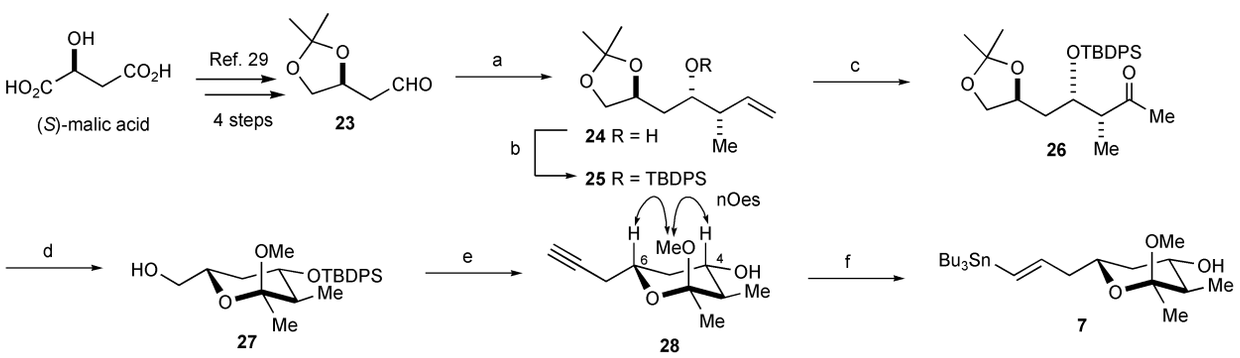
Introduction of the 2 carbon unit for elaboration to the vinyl stannane proved quite challenging. Studies on acetylide anion substitution of the iodide or mesylate derived from **27** proved fruitless. Eventually, we found that substitution of the sensitive triflate derived from **27** with lithium trimethylsilylacetylide[9,32] in the presence of HMPA followed by global desilylation gave alkyne **28** in good overall yield. The presumed preferred axial orientation of the methoxy group in **28** (and precursor **27**) was confirmed by a NOESY spectrum which revealed NOEs between the axial protons H6 and H4 and the OMe group as shown. Radical hydrostannylation[33] of **28** then gave the desired tetrahydropyran fragment **7**.

The key Stille coupling reaction between **7** and iodide (*R*)- or (*S*)-**8** was then investigated. Initially, we found that Pd(0) based catalysts such as Pd_2dba_3 in the presence of various ligands[34] resulted in no desired product and substantial iodine–tin exchange[35] to afford the vinyl iodide derived from stannane **7** Scheme 5. Pd(II) catalysts also failed initially, causing consumption of the stannane *via* an unproductive pathway. The addition of amine base, however, resulted in a substantial improvement and provided coupled products (12*R*)-rottnestol methyl ketal **4** or the corresponding (12*S*)-epimer in good yield. Both these compounds had identical NMR spectra which compared well with the methyl ketal derived from natural rottnestol.[1] Therefore, it appears that the structure originally proposed for rottnestol methyl ketal (**3**) is in error. The methoxy group should be in the axial orientation as depicted in compound **4**. Final acetal hydrolysis gave the (12*R*) and (12*S*)-isomers of **1** both of which again had identical spectra to natural **1** (see Table 1). Comparison of the specific rotations of each [(12*R*)-**1**: $[\alpha]_D$ +58.4 (*c* 0.18, CH_2Cl_2); (12*S*)-**1**: $[\alpha]_D$ +33.9 (*c* 0.35, CH_2Cl_2)] with that reported for natural rottnestol (**1**)[1] [$[\alpha]_D$ +67.4 (*c* 0.43, CH_2Cl_2)] led to the conclusion that the absolute configuration at C12 is *R* in the natural product.[9]

Total synthesis of (+)-raspailol A (5)

We then targeted the (12*R*)-epimer of raspailol A (**5**) since the related rottnestol (**1**) was shown to possess this absolute configuration. Furthermore, calculations also supported the assignment of the *R* configuration at C12 [For **5** theoretical $[\alpha]_D$ +57 (*c* 1.0, CH_2Cl_2) lit.[2] $[\alpha]_D$ +62 (*c* 0.46, C_6D_6)].[6,7,36] Our route to (12*R*)-raspailol A (**5**) began with the synthesis of the raspailol sidechain **9** as outlined in Scheme 6. The known stannane **29**[37] (4 : 1 *E* : *Z* mixture) was coupled with the iodide **21** to afford the diene **30** as the major product. Originally, we investigated coupling vinyl iodide **21** (and the primary alcohol derived from desilylation of **21**) with the analogue of **29** that possessed the requisite terminal double bond but the synthesis of this stannane was low yielding and difficult to scale up. Furthermore, several attempted couplings failed to give the desired triene in good yield. The alcohol **29** served as a convenient precursor to the terminal alkene and was easily prepared in one step from commercially available 4-butynol. Oxidation of **30** followed by Wittig extension gave triene **31** which upon treatment with TBAF provided alcohol **32**. The vinyl iodide **9** was then secured by oxidation and vinyliodidination as for the rottnestol sidechain.

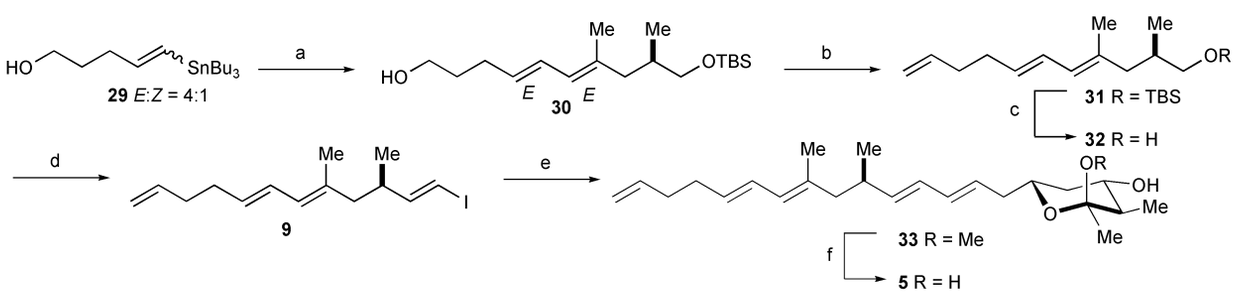
Stille coupling[11] between iodide **9** and stannane **7** proceeded smoothly to provide raspailol A methyl ketal (**33**) in good yield.



Scheme 4 *Reagents and conditions:* (a) (+)-Ipc_2B-(*Z*)-crotyl, THF, −78 °C, then NaOH, H_2O_2, 76%; (b) TBDPSCl, imidazole, DMF, 40 °C, 72 h, 85%; (c) 20 mol% $PdCl_2$, 1.1 eq. CuCl, O_2, aq. DMF, 50 °C, 85%; (d) 20 mol% CSA, MeOH, rt, 3 h, 72%; (e) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (ii) LiCCTMS, THF–HMPA, −78–0 °C; (iii) TBAF, THF, rt, 71% for 3 steps; (f) Bu_3SnH, cat. AIBN, benzene, reflux, 2 h, 54%.

Table 1 Comparison of NMR data for natural and synthetic rottnestol (**1**)

Position	δ_C (C_6D_6)		δ_H (C_6D_6)	
	Natural[1] 125 MHz	Synthetic 100 MHz	Natural[1] 500 MHz (m, *J* Hz)	Synthetic 300 MHz (m, *J* Hz)
1	28.2	28.2	1.18 (s)	1.18 (s)
2	98.9	98.9	—	—
3	47.2	47.2	1.25 (dq, 10.8, 6.3)	1.24 (m)
4	69.7	69.7	3.58 (dddd, 12.2, 10.8, 5.4, 4.4)	3.57 (ddd, 10.8, 9.6, 4.8)
5	41.3	41.3	1.14 (q, 12.2)	1.13–1.19 (m)
			1.71 (ddd, 12.2, 4.4, 2.5)	1.71 (ddd, 12.4, 4.4, 2.0)
6	68.3	68.3	3.84 (dtd, 12.2, 6.4, 2.5)	3.83 (dddd, 12.0, 6.4, 6.0, 2.8)
7	39.7	39.7	2.18 (br ddd, 13.7, 7.3, 6.4)	2.19 (ddd, 14.0, 7.2, 6.8)
			2.36 (br ddd, 13.7, 7.3, 6.4)	2.34 (ddd, 13.6, 6.8, 6.4)
8	128.4	128.4	5.69 (dt, 14.7, 7.3)	5.69 (dt, 14.0, 7.2)
9	133.2	133.2	6.12 (dddd, 14.7, 10.2, 1.5, 1.0)	6.06–6.17 (m)
10	128.9	128.9	6.10 (ddd, 14.7, 10.2, 1.0)	6.06–6.17 (m)
11	138.8	138.75	5.54 (dd, 14.7, 7.8)	5.54 (dd, 14.0, 7.2)
12	35.0	35.0	2.32 (m)	2.34 (sept, 5.1)
13	47.9	47.9	1.92 (dd, 13.2, 7.9)	1.92 (dd, 13.2, 7.6)
			2.07 (m)	2.02–2.12 (m)
14	133.8	133.8	—	—
15	126.2	126.2	5.16 (br t, 6.8)	5.17 (br t)
16	27.8	27.8	2.07 (m)	2.04–2.06 (m)
17	34.4	34.3	2.07 (m)	2.04–2.06 (m)
18	138.8	138.82	5.79 (ddt, 17.1, 10.2, 6.8)	5.80 (ddt, 17.2, 10.4, 7.2)
19	114.8	114.8	4.98 (ddd, 10.2, 2.5, 1.4)	4.99 (d, 10.0)
			5.04 (ddd, 17.1, 2.5, 1.5)	5.04 (dd, 16.8, 1.6)
20	12.3	12.3	1.12 (d, 6.3)	1.12 (d, 6.4)
21	20.1	20.1	0.97 (d, 6.9)	0.98 (d, 6.8)
22	16.0	16.1	1.50 (s)	1.50 (s)



Scheme 6 *Reagents and conditions:* (a) Iodide **21**, $Pd(MeCN)_2Cl_2$, *i*-Pr_2NEt, DMF, 40 °C, 54%; (b) (i) Dess–Martin periodinane, CH_2Cl_2, rt; (ii) $Ph_3P{=}CH_2$, THF, 0 °C, 68%; (c) TBAF, THF, rt, 2.5 h, 95%; (d) (i) Dess–Martin periodinane, CH_2Cl_2, rt; (ii) $CrCl_2$, CHI_3, THF–dioxane 1 : 6, rt, 17 h, 58%; (e) Stannane **7**, 15 mol% $Pd(MeCN)_2Cl_2$, DMF, *i*-Pr_2NEt (2.4 eq.), rt, 21.5 h, 57%; (f) 5% aq.HCl, THF, 0 °C, 30 min, 65%.

Hydrolysis then afforded raspailol A (**5**) which was identical to the data reported for natural material[2] (see Table 2) in all respects including the sign and value of specific rotation [Synthetic **5**: $[a]_D$ +78.4 (*c* 0.42, C_6D_6); Natural **5**:[2] $[a]_D$ +62 (*c* 0.46, C_6D_6)]. This again allowed for the C12 stereochemistry to be assigned as *R* while the configuration of the tetrahydropyran core is identical to rottnestol (**1**).

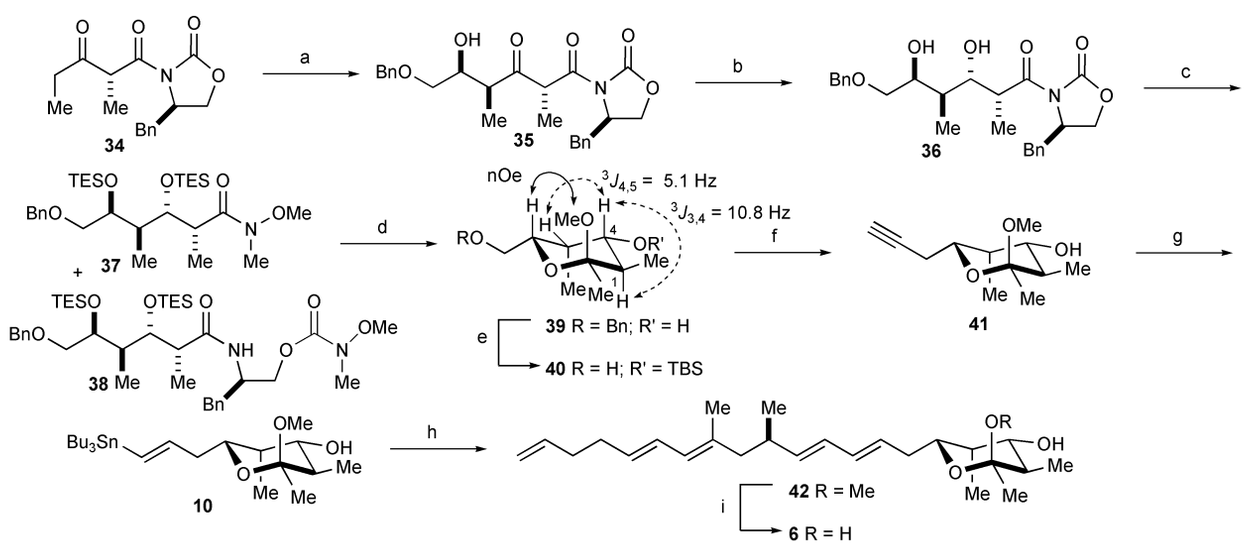
Total synthesis of (+)-raspailol B (6)

The final target raspailol B (**6**) was synthesised as outlined in Scheme 7. The stereochemistry of the more highly substituted core was set first by a tin mediated substrate controlled Evans aldol reaction between the β-ketoimide **34**[38,39] and benzyloxyacetaldehyde. This afforded the adduct **35** in excellent yield and high ds. Directed *anti* reduction[40] then gave diol **36** again with high selectivity for the desired *syn-anti-syn*-diastereoisomer. Conversion of the diol **36** into the Weinreb amide proved troublesome.[41,42] Treatment of imide **36** with $AlMe_3$ and *N*,*O*-dimethylhydroxylamine hydrochloride[42] at 0 °C resulted in the formation of a substantial amount of the amide resulting from ring opening at the *endo* carbonyl group[43] along with the desired amide. Careful control of the temperature (−20 °C) and time provided optimum yields and conversion of the crude mixture into the bis-TES ethers allowed for the isolation of pure bis-TES ether **37** along with a small amount of undesired amide **38**. This allowed for the synthesis of **37** without recourse to alternative Lewis acids.[44] Treatment of amide **37** with methyl magnesium chloride followed by desilylation and cyclisation of the crude ketone product with PPTS in methanol gave tetrahydropyran **39** in excellent overall yield. Protection of the secondary alcohol as the TBS ether and hydrogenolysis of the primary benzyl group afforded alcohol **40**. The stereochemistry of **40** followed from NMR analysis; in particular, the coupling constants between H3–H4 and H4–H5 indicated an ax-ax-eq arrangement of H3–5 while an NOE was observed between H6 and the axial OMe group. Two carbon homologation[9,32] as described for the rottnestol pyran fragment above gave the alkyne **41** which was converted into stannane **10** under standard conditions.[33] Stille coupling[11] between **10** and sidechain **9** gave raspailol B methyl ketal (**42**) which upon acid treatment gave raspailol B (**6**). The data of the synthetic material compared well with the literature values[2] (see Table 3) including the optical rotation [Synthetic **6**: $[a]_D$ +108 (*c* 0.045, C_6D_6); Natural **6**:[2] $[a]_D$ +111 (*c* 0.14, C_6D_6)]. This confirms the absolute configuration at C12 in all three natural products is *R*.

In conclusion, we have achieved the first total synthesis of (+)-rottnestol (**1**) and the related raspailols A (**5**) and B (**6**) using a convergent Stille coupling reaction to construct the C9–C10 bond. This allowed for the assignment of the absolute configurations of all these natural products.

Table 2 Comparison of NMR data for natural and synthetic raspailol A (**5**)

Position	δ_C (C_6D_6)		δ_H (C_6D_6)	
	Natural[2] 125 MHz	Synthetic 100 MHz	Natural[2] 500 MHz (m, *J* Hz)	Synthetic 400 MHz (m, *J* Hz)
1	28.2	28.2	1.17 (s)	1.18 (s)
2	98.9	98.9	—	—
3	47.2	47.2	1.25 (dq, 10, 7)	1.26 (m)
4	69.7	69.7	3.57 (ddt, 11, 10, 5)	3.57 (ddd, 10.8, 10.4, 4.4)
5	41.3	41.3	1.13 (dt, 12, 11)	1.05–1.15 (m)
			1.69 (ddd, 12, 5, 2)	1.69 (m)
6	68.2	68.3	3.82 (dtd, 11, 7, 2)	3.82 (m)
7	39.7	39.7	2.16 (br dt, 14, 7)	1.97–2.18 (m)
			2.34 (br dt, 14, 7)	2.29–2.39 (m)
8	128.6	128.6	5.68 (br dt, 14, 7)	5.67–5.82 (m)
9	133.2	133.2	6.12 (m)	6.07–6.14 (m)
10	129.0	128.9	6.08 (m)	6.07–6.14 (m)
11	138.5	138.5	5.54 (br dd, 14, 7)	5.50–5.61 (m)
12	35.1	35.2	2.34 (sept, 7)	2.29–2.39 (m)
13	48.0	48.0	1.95 (br dd, 15, 7)	1.93 (dd, 13.2, 7.6)
			2.10 (m)	1.97–2.18 (m)
14	134.5	134.5	—	—
15	127.3	127.3	5.91 (br d, 11)	5.93 (d, 10.8)
16	127.6	127.6	6.31 (ddt, 15, 11, 2)	6.33 (dd, 14.8, 10.8)
17	131.8	131.7	5.56 (br dt, 15, 7)	5.50–5.61 (m)
18	32.7	32.7	2.10 (m)	1.97–2.18 (m)
19	34.1	34.1	2.05 (m)	1.97–2.18 (m)
20	138.4	138.4	5.75 (ddt, 17, 11, 7)	5.67–5.82 (m)
21	114.9	114.9	4.97 (d, 11)	4.95 (d, 10.4)
			5.01 (d, 17)	4.98 (d, 17.2)
22	12.2	12.3	1.12 (d, 7)	1.11 (d, 6.8)
23	20.1	20.1	0.96 (d, 7)	0.94 (d, 6.4)
24	16.5	16.6	1.62 (br s)	1.60 (s)



Scheme 7 *Reagents and conditions:* (a) $Sn(OTf)_2$, NEt_3, benzyloxyacetaldehyde, CH_2Cl_2, −78 °C, 77%; (b) $Me_4NBH(OAc)_3$, MeCN–AcOH, −40–0 °C, 91%; (c) (i) $AlMe_3$, MeNH(OMe)HCl, −20 °C, 16 h; (ii) TESCl, imidazole, DMF, 59% **37**; 10% **38** for 2 steps; (d) (i) MeMgCl, rt, 3 h; (ii) 20 mol% PPTS, MeOH–CH_2Cl_2 1 : 3, rt, 3 h, 91%; (e) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 2 h (ii) 50 psi H_2, $Pd(OH)_2$/C, MeOH, 48 h, 74% for 2 steps; (f) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C (ii) LiCCTMS, THF–HMPA, −78–0 °C (iii) TBAF, THF, rt, 66% for 3 steps; (g) Bu_3SnH, cat. AIBN, benzene, reflux, 2 h, 70%; (h) Iodide **9**, 15 mol% $Pd(MeCN)_2Cl_2$, DMF, *i*-Pr_2NEt (7.0 eq.), rt, 24 h, 58%; (i) 5% aq.HCl, THF, 0 °C, 4 h, 93%.

Experimental

General

Optical rotations were recorded in a 10 cm microcell and are given in 10^{-1} deg cm^2 g^{-1}. Low resolution mass spectra (electrospray ionisation, ESI) and high resolution mass spectra (HRMS) electrospray ionisation (ESI) were run at Monash University, Clayton, Victoria. Proton nuclear magnetic resonance (^{1}H NMR, 300 and 400 MHz) and proton decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR, 75.5 and 100 MHz) were recorded for deuteriochloroform solutions with residual chloroform as internal standard unless otherwise stated. Microanalyses were carried out by the Campbell Microanalytical Laboratory at the University of Otago, Dunedin, New Zealand. Analytical thin layer chromatography (TLC) was conducted on aluminium backed 2 mm thick silica gel GF_{254}. Compounds were visualised with solutions of 20% w/w phosphomolybdic acid in ethanol, 20% w/w potassium permanganate in water or under UV (365 nm). Preparative HPLC was conducted on a 10 mm × 250 column (spherex 5 silica, 5 μm, flow rate: 2 mL min^{-1}, RI detection). Anhydrous THF and diethyl ether were distilled from sodium benzophenone ketyl and sodium metal under a nitrogen atmosphere. Petrol refers to the fraction boiling at 40–60 °C. All other commercial reagents were used as received. All air and moisture sensitive reactions were performed in glassware that was either flame dried under an atmosphere of dry argon or oven dried at 150 °C.

Table 3 Comparison of NMR data for natural and synthetic raspailol B (**6**)

Position	δ_C (C_6D_6)		δ_H (C_6D_6)	
	Natural[2] 125 MHz	Synthetic 100 MHz	Natural[2] 500 MHz (m, *J* Hz)	Synthetic 400 MHz (m, *J* Hz)
1	28.1	28.1	1.14 (s)	1.15 (s)
2	98.6	98.6	—	—
3	40.4	40.3	1.50 (dq, 10, 7)	1.50 (dq, 11, 6)
4	72.6	72.6	3.62 (dt, 11, 5)	3.63 (dd, 11, 5)
5	38.4	38.4	1.62 (m)	1.62 (m)
6	70.8	70.8	3.94 (td, 7, 2)	3.94 (td, 7, 2)
7	36.3	36.3	2.40 (br dt, 14, 7) 2.13 (br dt, 14, 7)	2.10 (m)
8	128.8	128.7	5.59 (br dt, 14, 7)	5.57 (m)
9	133.0	133.0	6.14 (m)	6.12 (m)
10	129.0	128.9	6.10 (m)	6.12 (m)
11	138.5	138.4	5.55 (br dd, 14, 7)	5.57 (m)
12	35.1	35.2	2.35 (sept, 7)	2.38 (sept, 7)
13	48.0	48.0	2.10 (m) 1.96 (br dd, 15, 7)	2.10 (m) 1.96 (dd, 13,8)
14	134.5	134.5	—	—
15	127.3	127.3	5.92 (br d, 11)	5.92 (d, 11)
16	127.6	127.5	6.31 (ddt, 15, 11, 2)	6.31 (dd, 15, 11)
17	131.8	131.8	5.56 (m)	5.57 (m)
18	32.7	32.7	2.10 (m)	2.10 (m)
19	34.1	34.1	2.05 (m)	2.10 (m)
20	138.4	138.4	5.75 (ddt, 17, 11, 7)	5.75 (ddt, 17, 10, 6)
21	114.9	114.9	5.01 (d, 17) 4.97 (d, 11)	5.00 (d, 18) 4.97 (d, 10)
22	12.4	12.4	1.07 (d, 7)	1.07 (d, 6)
23	20.1	20.1	0.97 (d, 7)	0.97 (d, 6)
24	16.6	16.6	1.62 (br s)	1.62 (s)
25	4.7	4.7	0.89 (d, 7)	0.90 (d, 7)

(±)-2-Methylhepta-1,6-dien-3-yl propanoate 12

To a solution of the alcohol (±)-**11**[13] (3.0 g, 24 mmol), pyridine (3.7 mL, 45 mmol) and DMAP (290 mg, 2.38 mmol) in anhydrous CH_2Cl_2 (70 mL) at 0 °C was added dropwise, freshly distilled propionyl chloride (2.5 mL, 28.5 mmol). After stirring for 1 h at 0 °C, saturated aqueous NH_4Cl was added and the reaction mixture was extracted with Et_2O (2×). The combined organic fractions were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, dried and the solvent removed under reduced pressure. Purification of the crude product by flash filtration through silica gel with 5% EtOAc–petrol as solvent afforded the ester **12** (3.93 g, 91%) as a colourless oil: (Found: C, 72.25; H, 9.85; $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%); ν_{max} (thin film) 3080, 2978, 1734, 1652, 1456, 1272, 1179, 1082, 908 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.14 (t, *J* = 7.5 Hz, 3H), 1.62–1.82 (m, 2H), 1.71 (s, 3H), 1.98–2.09 (m, 2H), 2.34 (q, *J* = 7.5 Hz, 2H), 4.86–5.06 (m, 4H), 5.18 (t, *J* = 6.9 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) 9.1, 18.0, 27.7, 29.5, 31.8, 76.4, 112.5, 114.9, 137.5, 143.1, 173.5; *m*/*z* (ESI) 205 ($[M + Na]^+$, 36%), 163 (33), 159 (100).

(±)-(4*E*)-2,4-Dimethylnona-4,8-dienoic acid 13

To a solution of *i*-Pr_2NH (4.0 mL, 30.5 mmol) in dry THF (38 mL) at 0 °C under an argon atmosphere was added a solution of *n*-BuLi in hexanes (10.4 mL, 2.5 M, 26.0 mmol). The solution was cooled to −78 °C and a 1 : 1 mixture of HMPA (29 mL) and anhydrous THF (29 mL) was added dropwise over 10 min. After stirring for 5 min, a solution of the ester **12** (2.62 g, 14.4 mmol) in THF (22.5 mL) was added dropwise by cannula followed by TBSCl (4.0 g, 27 mmol) in THF (13.3 mL). The reaction mixture was stirred at −78 °C for 20 min and then allowed to warm to rt and stirred for 3 h. The reaction mixture was diluted with petrol and washed with 10% aqueous HCl, water, brine and the solvent was evaporated. The residue was dissolved in THF (105 mL), 10% aqueous HCl was added and the mixture was vigorously stirred for 1 h and then extracted with Et_2O. The organic layer was washed with water and brine, dried and the residue remaining on removal of the solvent was dissolved in 1 M KOH. The aqueous layer was washed with Et_2O (2×), then cooled to 0 °C and acidified with concentrated aqueous HCl and extracted with EtOAc. The organic phase was washed with water, brine, dried and concentrated to give the acid **12** (2.22 g, 85%) as a pale yellow oil which was used without further purification. A small sample was distilled (bp 100 °C, 30 mmHg) under reduced pressure for analysis: (Found: C, 72.55; H, 10.05; $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%); ν_{max} (thin film) 2978, 1698, 1640, 1294, 1241, 1123, 911, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.12 (d, *J* = 6.6 Hz, 3H), 1.60 (s, 3H), 2.02–2.10 (m, 1H), 2.05–2.11 (m, 4H), 2.41 (dd, *J* = 13.2, 6.6 Hz, 1H), 2.63 (sext, 1H, *J* = 6.9 Hz), 4.94 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.19 (br t, *J* = 6.0 Hz, 1H), 5.80 (ddt, *J* = 16.8, 10.5, 6.6 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) 15.7, 16.3, 27.4, 33.8, 37.9, 43.6, 114.5, 126.8, 132.1, 138.4, 138.3; *m*/*z* (ESI) 182 (M^+, 13%), 181 ($[M - H]^+$, 100).

(1*S*)-Methyl 1-phenylethanoate (2*S*,4*E*)-14 and (1*S*)-(methoxycarbonyl)phenylmethyl (2*R*,4*E*)-2,4-dimethyl-4,8-nonadienoate 15

To a stirred solution of the racemic acid **12** (215 mg, 1.18 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C was added methyl (*S*)-(+)-mandelate (197 mg, 1.18 mmol), DMAP (14.4 mg, 0.11 mmol) and DCC (268 mg, 1.30 mmol). The reaction mixture was then allowed to stir for 10 min at 0 °C and at rt for 2.5 h. Petrol was added and the reaction mixture was filtered through Celite. The filtrate was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water, brine, dried and concentrated. Purification of the crude product by flash chromatography using 5% EtOAc–petrol as eluent followed by HPLC separation of the diastereoisomers on a semi-preparative column (spherex 5 μm silica, 10 mm × 250 mm) using 5% EtOAc–petrol as eluent (2 mL min^{-1}) provided the (*S*,*S*)-diastereoisomer **14** (R_t = 16.39 min) (168 mg, 43%) and the (*S*,*R*)-isomer **15** (167 mg, 43%) (R_t = 17.30 min) as colourless oils.

Data for (*S*,*S*)-isomer **14**: $[a]_D^{23}$ +86.9 (*c* 1.01, $CHCl_3$) (Found: C, 73.0; H, 7.8; $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.95%); ν_{max} (thin film) 3068, 2976, 1740, 1640, 1272, 1158 cm^{-1}; δ_H (300 MHz,

$CDCl_3$) 1.15 (d, J = 6.9 Hz, 3H), 1.61 (s, 3H), 2.01–2.12 (m, 5H), 2.53 (dd, J = 13.2, 6.0 Hz, 1H), 2.76 (sext, J = 6.6 Hz, 1H), 3.71 (s, 3H), 4.94 (dd, J = 10.2, 1.8 Hz, 1H), 5.00 (dd, J = 17.1, 1.8 Hz, 1H), 5.17 (br t, J = 6.9 Hz, 1H), 5.73–5.86 (m, 1H), 5.92 (s, 1H), 7.36–7.41 (m, 3H), 7.44–7.49 (m, 2H); δ_C (75.5 MHz, $CDCl_3$) 15.6, 16.1, 27.3, 33.7, 37.6, 43.4, 52.4, 74.1, 114.4, 126.7, 127.5, 128.7, 129.0, 132.0, 134.0, 138.4, 169.2, 175.6; *m*/*z* (ESI) 353 ([M + Na]$^+$, 58%), 348 ([M + H_2O]$^+$, 100), 331 ([M + H]$^+$, 27).

Data for (*S,R*)-isomer **15**: $[\alpha]_D^{23}$ +90.4 (*c* 1.01, $CHCl_3$) (Found C, 72.65; H, 7.9; $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.95%); ν_{max} (thin film) 3068, 2976, 1740, 1640, 1272, 1158 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.19 (d, J = 7.2 Hz, 3H), 1.56 (s, 3H), 1.98–2.03 (m, 4H), 2.08 (dd, J = 13.8, 7.8 Hz, 1H), 2.43 (dd, J = 13.8, 7.2 Hz, 1H), 2.78 (sext, J = 6.6 Hz, 1H), 3.72 (s, 3H), 4.92 (dd, J = 10.5, 1.5 Hz, 1H), 4.97 (dd, J = 17.4, 1.5 Hz, 1H), 5.16 (br t, 1H), 5.77 (m, 1H), 5.91 (s 1H), 7.36–7.41 (m, 3H), 7.45–7.48 (m, 2H); δ_C (75.5 MHz, $CDCl_3$) 15.7, 16.4, 27.3, 33.7, 37.5, 43.5, 52.4, 74.0, 114.4, 126.6, 127.5, 128.7, 129.0, 132.1, 133.9, 138.4, 169.3, 175.8. MS (ESI) *m*/*z* 353 ([M + Na]$^+$, 90%), 348 ([M + H_2O]$^+$, 100), 331 ([M + H]$^+$, 37).

(2*S*,4*E*)- (*S*)-16 and (2*R*,4*E*)-2,4-Dimethylnona-4,8-dien-1-ol (*R*)-16

To a suspension of $LiAlH_4$ (57 mg, 1.5 mmol) in dry Et_2O (3.4 mL) at 0 °C was added dropwise a solution of the (*S,R*)-mandelate ester **15** (50 mg, 0.15 mmol) in dry Et_2O (3.4 mL). The reaction mixture was then allowed to stir at rt for 10 min after which time it was cooled to 0 °C and quenched with water and 5 M NaOH was added until coagulation ceased. The suspension was filtered through Celite and the filtrate was concentrated. Purification of the residue by flash chromatography on silica gel using 15% EtOAc–petrol as eluent gave the alcohol (*R*)-**16** (24 mg, 93%) as a pale yellow oil: $[\alpha]_D^{26}$ −6.6 (*c* 1.03, $CHCl_3$) (Found: C, 78.3; H, 11.75; $C_{11}H_{20}O$ requires C, 78.5; H, 12.0%); ν_{max} (thin film) 3346, 3077, 2922, 1640, 1383, 1038 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.86 (d, J = 6.3 Hz, 3H), 1.60 (s, 3H), 1.78–1.89 (m, 2H), 2.02–2.11 (m, 5H), 3.42 (dd, J = 10.5, 5.7 Hz, 1H), 3.49 (dd, J = 10.5, 5.4 Hz, 1H), 4.95 (dd, J = 10.2, 1.5 Hz, 1H), 5.01 (dd, J = 17.1, 1.5 Hz, 1H), 5.17 (br t, 1H), 5.81 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) 15.9, 16.5, 27.3, 33.5, 33.8, 44.1, 68.2, 114.4, 125.6, 134.0, 138.5; *m*/*z* (ESI) 191 ([M + Na]$^+$, 100%).

Reduction of the (*S,S*)-mandelate ester **14** (312 mg, 0.95 mmol) in the same manner as described for the alcohol (*R*)-**16** above provided (*S*)-**16** (150 mg, 94%) as a pale yellow oil: $[\alpha]_D^{26}$ +6.5 (*c* 1.03, $CHCl_3$).

(2*S*,2*S*′,4*E*)- 18 and (2*R*,2*S*′,4*E*)-2,4-Dimethyl-4,8-nonadienyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate 19

To a stirred solution of the alcohol (*S*)-**16** (23.6 mg, 140 μmol) in dry CH_2Cl_2 (4 mL) at 0 °C was added (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (65.4 mg, 279 μmol), DMAP (2 mg, 16.4 μmol) and DCC (57.6 mg, 279 μmol). The reaction mixture was allowed to stir for 10 min at 0 °C and then at rt for 1 h after which time petrol was added and the reaction mixture was filtered through Celite. The filtrate was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water, brine, dried and concentrated. Purification of the crude product by chromatography on silica gel using 10% EtOAc–petrol as eluent gave the (*S,S*)-Mosher ester **18** (48 mg, 90%) as a colourless oil (de: 98.2% by ^{1}H NMR): $[\alpha]_D^{25}$ −29.6 (*c* 1.03, $CHCl_3$); ν_{max} (thin film) 3068, 2931, 2851, 1750, 1641, 1498, 1273, 1170, 1024, 719 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.86 (d, J = 6.8 Hz, 3H), 1.56 (s, 3H), 1.82 (m, 1H), 1.98–2.05 (m, 2H), 2.07–2.09 (m, 4H), 3.55 (s, 3H), 4.03 (dd, J = 10.8, 6.4 Hz, 1H), 4.24 (dd, J = 10.8, 4.8 Hz, 1H), 4.95 (dd, J = 10.4, 2.0 Hz, 1H), 5.00 (dd, J = 17.2, 1.2 Hz, 1H), 5.11 (br t, 1H), 5.80 (m, 1H), 7.39–7.43 (m, 3H), 7.50–7.54 (m, 2H); δ_C (75.5 MHz, $CDCl_3$) 15.8, 16.7, 27.4, 30.4, 33.8, 43.6, 55.4, 70.8, 114.6, 121.4, 125.3, 126.5, 127.4, 128.4, 129.6, 132.3, 132.6, 138.5, 166.6; HRMS (ESI): Calcd for $C_{21}H_{27}F_3O_3M^+$ 407.1810, found 407.1808. The alcohol (*R*)-**16** (23.4 mg, 139 μmol) was converted into the ester in an analogous manner to that described above to afford the (*S,R*)-Mosher ester **19** (47.5 mg, 89%), also as a colourless oil (de: 92.7% by ^{1}H NMR): $[\alpha]_D^{25}$ −46.0 (*c* 1.02, $CHCl_3$); ν_{max} (thin film) 3074, 2924, 2849, 1750, 1641, 1498, 1273, 1170, 1024, 719 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (d, J = 6.4 Hz, 3H), 1.55 (s, 3H), 1.80 (m, 1H), 1.98–2.04 (m, 2H), 2.07–2.08 (m, 4H), 3.55 (s, 3H), 4.14 (d, J = 5.2 Hz, 2H), 4.95, (dd, J = 10.0, 1.6 Hz, 1H), 5.01 (dd, J = 16.8, 1.6 Hz, 1H), 5.08 (br t, 1H), 5.75–5.85 (m, 1H), 7.39–7.43 (m, 3H), 7.51–7.54 (m, 2H); δ_C (75.5 MHz, $CDCl_3$) 15.8, 16.7, 27.4, 30.4, 33.8, 43.5, 55.4, 70.8, 114.5, 121.4, 125.3, 126.5, 127.3, 128.4, 129.6, 132.4, 132.6, 138.5, 166.6; HRMS (ESI): Calcd for $C_{21}H_{27}F_3O_3Na$ [M + Na]$^+$ 407.1810, found 407.1808.

(2*R*)-2-Methyl-4-oxopentanoic acid 17

Ozone gas was bubbled into a solution of the (*S,R*)-mandelate ester **15** (213 mg, 0.648 mmol) in dry CH_2Cl_2 (14 mL) and MeOH (502 μL) at −78 °C until the solution turned blue. Dimethyl sulfide (240 μL, 3.27 mmol) was then added at −78 °C and the solution was stirred at rt for 4 h. Water and EtOAc were added and the aqueous phase was further extracted with EtOAc. The combined organic fractions were washed with water, brine, dried and concentrated. The residue was dissolved in THF (4.9 mL) and water (4.9 mL) and treated with lithium hydroxide monohydrate (172 mg, 4.1 mmol) at 30 °C for 4 h. The solvent was removed under reduced pressure and the residue was acidified with 10% aqueous HCl and extracted into EtOAc (3×). The combined organic fractions were washed with water, brine, dried and concentrated. Purification of the crude acid by column chromatography using 40% EtOAc–petrol as eluent afforded the acid **17**[19] (12.7 mg, 15%) as a colourless oil: $[\alpha]_D^{20}$ +9.5 (*c* 0.29, AcOH), lit.,[19] $[\alpha]_D^{25}$ +21.8 (*c* 1.19, AcOH); $[\alpha]_D^{21}$ +30.2 (*c* 0.63, $CHCl_3$), lit.,[20] or (*S*)-enantiomer $[\alpha]_D^{25}$ −21.1 (*c* 0.80, $CHCl_3$, 98% ee); δ_H (300 MHz, $CDCl_3$) 1.21 (d, J = 7.2 Hz, 3H), 2.16 (s, 3H), 2.49 (dd, J = 16.8, 4.5 Hz, 1H), 2.88–3.20 (m, 1H), 2.90 (dd, J = 17.7, 8.1 Hz, 1H).

(8*R*,5*E*)-9-(*tert*-Butyldimethylsiloxy)-6,8-dimethylnona-1,5-diene 22

A solution of 1-bromo-3-butene (0.5 g, 3.7 mmol) in anhydrous THF (6.7 mL) was added dropwise *via* cannula to flame-dried magnesium turnings (122 mg, 5.02 mmol) under argon. The reaction mixture was stirred for 30 min and the resultant Grignard reagent (2 mL) was added dropwise *via* syringe to a solution of anhydrous zinc(II) chloride in dry THF (7.4 mL) at 0 °C. The resultant mixture was allowed to stir at 0 °C for 30 min after which time a solution of the vinyl iodide **21** (100 mg, 0.28 mmol) and tetrakis(triphenylphosphine)palladium(0) (32.6 mg, 28.2 μmol) in dry THF (3.6 mL) was added *via* cannula. The resultant solution was stirred at 0 °C for 10 min and then allowed to stir overnight at rt. The reaction was quenched by the addition of saturated aqueous NH_4Cl and then worked up in the usual manner and the residue was purified by flash chromatography using petrol as eluent to afford the diene **22** (43 mg, 54%) as a colourless oil: $[\alpha]_D^{18}$ −0.2 (*c* 1.04, $CHCl_3$); ν_{max} (thin film) 3080, 2931, 1642, 1470, 1255, 1090, 839, 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 (s, 6H), 0.81 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 1.58 (s, 3H), 1.66 (dd, J = 12.0, 8.4 Hz, 1H), 1.75 (m, 1H), 2.08–2.14 (m, 5H), 3.34 (dd, J = 9.9, 6.6 Hz, 1H), 3.43 (dd, J = 9.6, 5.4 Hz, 1H), 4.95 (dd, J = 9.9, 2.4 Hz, 1H), 5.01 (dd, J = 17.1, 1.8 Hz, 1H), 5.11 (br t, 1H), 5.83 (m, 1H); δ_C (75.5 MHz, $CDCl_3$) −5.3, 16.0, 16.5, 18.4, 26.0, 27.5, 33.7, 34.0, 43.8, 68.2, 114.4, 125.3, 134.0, 138.7; HRMS (ESI): Calcd for $C_{17}H_{34}OSiNa$ [M + Na]$^+$ 305.2277, found 305.2271.

(2*R*,4*E*)-2,4-Dimethylnona-4,8-dien-1-ol (*R*)-16

A solution of the ether **22** (35 mg, 0.124 mmol) in THF (1 mL) was treated with TBAF (59 mg, 0.187 mmol) overnight. Water was added and the reaction mixture was extracted with Et_2O. The usual workup and purification of the crude product by flash chromatography using 15% EtOAc–petrol as eluent gave (*R*)-**16** (12 mg, 58%) as a colourless oil, the spectroscopic data for which was identical to the alcohol obtained by the earlier resolution route: $[\alpha]_D^{17}$ +8.0 (*c* 0.47, $CHCl_3$).

(3*R*,1*E*,5*E*)- (*R*)-8 and (3*S*,1*E*,5*E*)-1-Iodo-3,5-dimethyl-1,5,9-decatriene (*S*)-8

To a solution of the alcohol (*R*)-**16** (100 mg, 0.59 mmol) in anhydrous CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (378 mg, 0.89 mmol). After stirring at rt for 30 min, Et_2O and a 1 : 1 v/v mixture of saturated aqueous $NaHCO_3$ and 1.5 M $Na_2S_2O_3$ was added and the reaction mixture was vigorously stirred until the layers cleared. The organic layer was washed with the 1 : 1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M $Na_2S_2O_3$ then saturated aqueous $NaHCO_3$, water, brine, dried and the solvent removed under reduced pressure. The crude aldehyde (98.8 mg, 0.594 mmol) and iodoform (433 mg, 1.1 mmol) were dissolved in anhydrous dioxane (10.3 mL) and added dropwise to a vigorously stirred slurry of flame-dried chromium(II) chloride (546 mg, 4.44 mmol) in anhydrous THF (1.7 mL) under an argon atmosphere. The resulting brown suspension was stirred at rt for 17 h and was then diluted with Et_2O and water and the aqueous fraction was saturated with NaCl and further extracted with Et_2O. The combined organic fractions were washed with brine, dried and concentrated. The crude vinyl iodide was dissolved in Et_2O (12 mL) and treated with TBAF (1.26 g, 4.0 mmol) in THF (4 mL) for 10 min. The solvent was removed under reduced pressure and the residue filtered through a plug of silica gel using Et_2O as eluent. The crude product was purified by flash chromatography using petrol as eluent to give the vinyl iodide (*R*)-**8** (122 mg, 71%) as an orange oil: $[\alpha]_D^{23}$ −9.4 (*c* 1.03, $CHCl_3$) (Found: C, 49.4; H, 6.5; $C_{12}H_{19}I$ requires C, 49.65; H, 6.6%); ν_{max} (thin film) 3076, 2922, 1641, 1219, 912 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.95 (d, *J* = 6.6 Hz, 3H), 1.56 (s, 3H), 1.90 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.02 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.08–2.10 (m, 4H), 2.35 (m, 1H), 4.96 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.02 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.12 (br s, 1H), 5.81 (m, 1H), 5.93 (d, *J* = 14.4 Hz, 1H), 6.41 (dd, *J* = 14.4, 7.2 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) 16.0, 19.0, 27.4, 33.9, 38.7, 46.6, 73.0, 114.5, 126.5, 132.8, 138.6, 151.9; *m*/*z* (GCMS) 290 (M^+, 0.5%), 181 (100), 67 (98).

The (*S*)-vinyl iodide (*S*)-**8** (118 mg, 60%) was prepared from the alcohol (*S*)-**16** according to the procedure described above. The spectroscopic data for the (*S*)-**8** was identical to that quoted for (*R*)-**8**: $[\alpha]_D^{22}$ +12.6 (*c* 1.01, $CHCl_3$).

(4*S*)-4-[(2*S*,3*S*)-2-Hydroxy-3-methyl-4-pentenyl]-2,2-dimethyl-1,3-dioxolane 24

To a mixture of potassium *tert*-butoxide (1.75 g, 15.6 mmol) and *cis*-2-butene (1.80 mL) in freshly distilled THF (17 mL) at −78 °C was added dropwise a solution of *n*-BuLi in hexanes (7.1 mL, 2.2 M, 15.6 mmol). The reaction mixture was then warmed to 0 °C for 5 min, recooled to −78 °C and a solution of (+)-β-methoxydiisopinocampheylborane[30] (4.92 g, 15.6 mmol) in THF (18.6 mL) was added dropwise *via* cannula. The clear reaction mixture was stirred at −78 °C for 30 min and then boron trifluoride diethyl etherate (2.55 mL, 20.2 mmol) was added dropwise followed by a solution of the aldehyde **23**[29] (1.50 g, 10.4 mmol) in THF (17 mL). The resultant mixture was stirred at −78 °C for a further 2 h after which time 1 M NaOH (42 mL) and 30% H_2O_2 (8.5 mL) were added at 0 °C and the mixture was stirred at rt overnight. Most of the solvent was removed under reduced pressure and the residue partitioned between water and Et_2O. The organic layer was washed with water, brine, dried and concentrated. Purification by column chromatography using 15–20% EtOAc–petrol as eluent afforded the alcohol **24** (1.59 g, 76%) as a pale yellow oil: $[\alpha]_D^{18}$ −23.5 (*c* 1.01, $CHCl_3$); (Found: C, 65.7; H, 9.95; $C_{11}H_{20}O_3$ requires C, 65.95; H, 10.05%); ν_{max} (thin film) 3457, 3078, 2984, 1371, 1159, 1060 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.05 (d, *J* = 6.9 Hz, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.62 (ddd, *J* = 14.4, 9.6, 4.8 Hz, 1H), 1.77 (ddd, *J* = 14.4, 7.2, 2.4 Hz, 1H), 2.28 (sext, *J* = 6.9 Hz, 1H), 3.56 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.70 (ddd, *J* = 12.0, 5.7, 2.1 Hz, 1H), 4.07 (dd, *J* = 7.8, 6.0 Hz, 1H), 4.32 (quint, *J* = 7.2 Hz, 1H), 5.07 (d, *J* = 11.4 Hz, 1H), 5.08 (d, *J* = 16.2 Hz, 1H), 5.75 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) 14.8, 25.6, 26.9, 37.2, 44.0, 69.5, 71.7, 73.8, 108.6, 115.4, 140.5; *m*/*z* (ESI) 201 ($[M + H]^+$, 100%).

(4*S*)-4-[(2*S*,3*S*)-2-(*tert*-Butyldiphenylsiloxy)-3-methyl-4-pentenyl]-2,2-dimethyl-1,3-dioxolane 25

To a solution of the alcohol **24** (1.30 g, 6.49 mmol), DMAP (82.1 mg, 0.672 mmol) and imidazole (1.15 g, 16.9 mmol) in dry DMF (15.5 mL) was added TBDPSCl (3.53 mL 13.5 mmol). The reaction mixture was then warmed to 40 °C and stirred under an argon atmosphere for 24 h after which time a further portion of imidazole (0.58 g, 8.45 mmol) and TBDPSCl (1.77 mL, 6.75 mmol) were added. Stirring was then continued at 40 °C for a further 48 h. The usual workup and purification of the crude product by column chromatography using 10% EtOAc–petrol as eluent gave the ether **25** as a colourless oil (2.61 mg, 92%): $[\alpha]_D^{19}$ −31.3 (*c* 1.01, $CHCl_3$) (Found: C, 73.8; H, 8.65; $C_{27}H_{38}O_3Si$ requires C, 73.9; H, 8.75%); ν_{max} (thin film) 3072, 2933, 1640, 1590, 1111, 1061 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.17 (s, 3H), 1.28 (s, 3H), 1.50 (ddd, *J* = 14.1, 8.1, 4.5 Hz, 1H), 1.62 (ddd, *J* = 13.8, 8.4, 4.5 Hz, 1H), 2.31 (m, 1H), 3.21 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.80 (dd, *J* = 7.8, 5.7 Hz, 1H), 3.93 (m, 1H), 4.02 (m, 1H), 4.90–5.05 (m, 2H), 5.99 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H), 7.33–7.45 (m, 6H), 7.67–7.72 (m, 4H); δ_C (75.5 MHz, $CDCl_3$) 14.1, 19.6, 25.7, 26.9, 27.1, 37.2, 42.3, 69.6, 72.9, 74.7, 108.5, 114.4, 127.4, 127.5, 129.5, 129.6, 134.2, 134.5, 136.0, 136.1, 140.3; *m*/*z* (ESI) 461 ($[M + Na]^+$, 100%), 462 (42).

(4*S*)-4-[(2*S*,3*S*)-2-(*tert*-Butyldiphenylsiloxy)-3-methyl-4-oxopentyl]-2,2-dimethyl-1,3-dioxolane 26

A suspension of palladium(II) chloride (27.4 mg, 0.155 mmol) and copper(I) chloride (84 mg, 0.85 mmol) in water (537 μL) and DMF (3.8 mL) was stirred at rt for 2 h under an oxygen atmosphere. A solution of the alkene **25** (339 mg, 0.77 mmol) in water (537 μL) and DMF (4.26 mL) was then added slowly by cannula and the resultant solution was warmed to 50 °C and stirred for 23 h. The mixture was diluted with Et_2O, cold 5% aqueous HCl was added and the organic layer was washed with saturated aqueous $NaHCO_3$. Purification of the crude product by flash chromatography using 10% EtOAc–petrol as eluent afforded the ketone **26** (297 mg, 85%) as a yellow oil: $[\alpha]_D^{18}$ −16.2 (*c* 0.39, $CHCl_3$) (Found: C, 71.15; H, 8.65; $C_{27}H_{38}O_4Si$ requires C, 71.30; H, 8.40%); ν_{max} (thin film) 2933, 1713, 1111, 1059 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.03 (s, 9H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.27 (s, 3H), 1.54 (ddd, *J* = 14.4, 6.4, 4.0 Hz, 1H), 1.72 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 2.06 (s, 3H), 2.63 (dq, *J* = 6.8, 2.8 Hz, 1H), 3.12 (dd, *J* = 8.0, 7.6 Hz, 1H), 3.73 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.86 (m, 1H), 4.25 (ddd, *J* = 6.4, 3.2 Hz, 1H), 7.36–7.47 (m, 6H), 7.66–7.71 (m, 4H); δ_C (100 MHz, $CDCl_3$) 10.4, 19.5, 25.7, 26.8, 29.8, 38.4, 52.0, 69.3, 72.5, 72.7, 77.2, 108.8, 127.5, 127.7, 129.7, 129.9, 133.3, 134.2, 135.9, 136.0, 210.6; *m*/*z* (ESI) 477 ($[M + Na]^+$, 100%), 397 ($[M-{}^tBu]^+$, 38).

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-4-(*tert*-butyldiphenylsiloxy)-6-hydroxymethyl-2-methoxy-2,3-dimethyl-2*H*-pyran 27

To a stirred solution of the ketone **26** (164 mg, 0.36 mmol) in dry MeOH (5.2 mL) was added (±)-camphorsulfonic acid (16.7 mg, 0.072 mmol). The reaction mixture was stirred at rt for 1 h then quenched with saturated aqueous $NaHCO_3$. The product was isolated by extraction with EtOAc and the combined organic fractions were washed with saturated aqueous $NaHCO_3$, water and brine. Purification of the crude product by column chromatography using 20% EtOAc–petrol as eluent gave the pyran **27** (111 mg, 72%) as a colourless gum: $[\alpha]_D^{19}$ +81.3 (*c* 0.71, $CHCl_3$) (Found: C, 69.75; H, 8.25; $C_{25}H_{36}O_4Si$ requires C, 70.05; H, 8.45%); ν_{max} (thin film) 3441, 2942, 2857, 1377, 1111, 1060 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 3H), 1.40 (ddd, *J* = 10.4, 4.8, 2.4 Hz, 1H), 1.57–1.62 (m, 1H), 1.60 (dq, *J* = 9.6, 7.2 Hz, 1H), 1.87 (br t, *J* = 5.1 Hz, 1H), 3.06 (s, 3H), 3.35–3.42 (m, 3H), 3.88 (ddd, *J* = 10.4, 10.4, 4.8 Hz, 1H), 7.34–7.44 (m, 6H), 7.66–7.70 (m, 4H); δ_C (75.5 MHz, $CDCl_3$) 12.6, 19.4, 21.8, 27.0, 36.7, 47.5, 48.5, 65.7, 68.7, 71.5, 101.8, 127.4, 127.5, 129.4, 129.5, 134.1, 134.9, 135.9, 136.0; *m*/*z* (ESI) 451 ($[M + Na]^+$, 100%), 397 ($[M - OMe]^+$, 13).

(2*S*,3*R*,4*S*,6R)-Tetrahydro-2-methoxy-2,3-dimethyl-6-(2-propynyl)-2*H*-pyran-4-ol 28

To a stirred solution of the pyran **27** (981 mg, 2.29 mmol) in dry CH_2Cl_2 (22.7 mL) at −78 °C was added 2,6-lutidine (1.34 mL, 11.5 mmol) and Tf_2O (753 μL, 4.48 mmol). After stirring at −78 °C for 30 min, saturated aqueous $NaHCO_3$ was added and the pale yellow reaction mixture was stirred at rt for 1 h. The product was isolated by extraction with Et_2O and the organic fraction was washed with saturated aqueous $NaHCO_3$, water, saturated aqueous $CuSO_4$, water, brine, dried and concentrated. A solution of the crude triflate in anhydrous THF (19.5 mL) was added dropwise *via* cannula to a solution of lithium trimethylsilylacetylide [from trimethylsilylacetylene (1.63 mL, 11.5 mmol) and *n*-BuLi in hexanes (4.9 mL, 2.5 M, 12.3 mmol)] in dry THF (19.5 mL) and HMPA (4.4 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h then saturated aqueous NH_4Cl was added and the mixture was then extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and the solvent removed under reduced pressure to provide the crude TMS acetylide which was subsequently dissolved in THF (34.5 mL) and treated with TBAF (1.97 g, 7.53 mmol) overnight. Water was added and the reaction mixture was extracted with EtOAc. The organic fraction was washed with water, brine, dried and concentrated. Purification of the crude product by flash chromatography using 20% EtOAc–petrol as eluent gave the acetylene **28** (330 mg, 73%) as an oil: $[\alpha]_D^{24}$ +110.9 (*c* 0.71, CH_2Cl_2) (Found: C, 66.60; H, 9.00; $C_{11}H_{18}O_3$ requires C, 66.65; H, 9.15%); ν_{max} (thin film) 3406, 2945, 2120, 1379, 1168, 1045, 840 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.06 (d, *J* = 6.9 Hz), 1.29 (m, 1H), 1.31 (s, 3H), 1.41 (m, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 2.12 (ddd, *J* = 12.3, 4.8, 2.1 Hz, 1H), 2.32 (ddd, *J* = 16.5, 6.9, 2.7 Hz, 1H), 2.44 (ddd, *J* = 16.5, 6.3, 2.7 Hz, 1H), 3.17 (s, 3H), 3.37–3.75 (m, 2H); δ_C (100 MHz, $CDCl_3$) 11.7, 21.6, 25.5, 39.9, 47.6, 47.8, 66.7, 69.5, 70.0, 80.8, 101.7; *m*/*z* (ESI) 221 ($[M + Na]^+$, 100%).

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2-methoxy-2,3-dimethyl-6-[(2*E*)-3-tributylstannyl-2-propenyl]-2*H*-pyran-4-ol 7

A solution of the acetylene **28** (159 mg, 0.81 mmol) and freshly prepared Bu_3SnH (281 μL, 1.04 mmol) in dry benzene (8 mL) was heated at reflux and AIBN (13.2 mg, 80 μmol) was added. After 40 min at reflux a further portion of Bu_3SnH (140 μL, 0.52 mmol) was added and the reaction was heated a further 5 min. The solvent was then removed under reduced pressure and the residue purified on silica gel using 1% NEt_3–10% EtOAc–petrol as eluent to provide the (*E*)-vinylstannane **7** (268 mg, 68%) as a clear gum: $[\alpha]_D^{20}$ +59.3 (*c* 1.03, CH_2Cl_2); ν_{max} (thin film) 3435, 2956, 2853, 1641, 1049 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.94 (t, *J* = 6.9 Hz, 9H), 0.95–1.01 (m, 6H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.24 (s, 3H), 1.38 (sext, *J* = 7.2 Hz, 6H), 1.56–1.64 (m, 2H), 1.61 (quint, *J* = 7.5 Hz, 6H), 1.76 (ddd, *J* = 12.0, 4.5, 2.1 Hz, 1H), 2.29 (m, 1H), 2.50 (m, 1H), 3.09 (s, 3H), 3.57–3.70 (m, 2H), 5.75–5.97 (m, 2H); δ_C (75.5 MHz, C_6D_6) 9.7, 12.1, 13.9, 21.9, 27.7, 29.6, 41.3, 44.9, 47.4, 48.6, 68.4, 69.6, 101.6, 130.3, 146.3; HRMS (ESI): Calcd for $C_{23}H_{46}O_3SnNa$ $[M + Na]^+$ 511.2367, found 511.2383.

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2-methoxy-2,3-dimethyl-6-[(12*R*,2*E*,4*E*,8*E*)-6,8-dimethyl-2,4,8,12-tridecatetraenyl]-2*H*-pyran-4-ol. Rottnestol methyl ketal (12*R*)-(4)

To a freeze–thaw degassed (3×) solution of the (*R*)-vinyl iodide (*R*)-**8** (18.2 mg, 62.8 μmol), stannane **7** (42 mg, 81.7 μmol) and *i*-Pr_2NEt (34 μL, 0.195 mmol) in dry DMF (570 μL) was added bis(acetonitrile)palladium(II) chloride (2.6 mg, 10.0 μmol). The reaction mixture was stirred in the absence of light at rt for 21.5 h and then diluted with water and extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and concentrated. Purification of the crude product by column chromatography using 10–15% EtOAc–petrol as eluent provided rottnestol methyl ketal (12*R*)-**4** (14 mg, 62%) as a colourless gum. $[\alpha]_D^{22}$ +89.7 (*c* 0.41, CH_2Cl_2); ν_{max} (thin film) 3400, 3078, 2919, 1641, 1047 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.97 (d, *J* = 6.9 Hz, 3H, H21), 1.11–1.18 (m, 1H, H5), 1.15 (d, *J* = 6.6 Hz, 3H, H20), 1.22 (s, 3H, H1), 1.31 (m, 1H, H3), 1.50 (s, 3H, H22), 1.70 (ddd, *J* = 12.0, 4.8, 2.1 Hz, 1H, H5), 1.91 (dd, *J* = 13.2, 7.8 Hz, 1H, H13), 1.98–2.09 (m, 1H, H13), 2.02–2.06 (m, 4H, H16, H17), 2.17 (m, 1H, H7), 2.27–2.39 (m, 2H, H7, H12), 3.01 (s, 3H, H23), 3.52 (dddd, *J* = 12.3, 6.6, 6.3, 2.4 Hz, 1H, H6), 3.62 (m, 1H, H4), 4.99 (d, *J* = 9.9 Hz, 1H, H19), 5.04 (d, *J* = 16.7 Hz, 1H, H19), 5.16 (br t, 1H, H15), 5.53 (dd, *J* = 14.4, 7.2 Hz, 1H, H11), 5.69 (dt, *J* = 14.4, 7.5 Hz, 1H, H8), 5.78 (m, 1H, H18), 6.04–6.17 (m, 2H, H9, H10); δ_C (100 MHz, C_6D_6) 12.0, 16.1, 20.1, 21.9, 27.8, 34.3, 35.0, 39.6, 41.1, 47.4, 47.9, 48.6, 68.5, 69.6, 101.6, 114.7, 126.2, 127.6, 128.8, 133.3, 133.8, 138.7, 138.8; HRMS (ESI): Calcd for $C_{23}H_{38}O_3Na$ $[M + Na]^+$ 385.2719, found 385.2713.

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2,3-dimethyl-6-[(12*R*,2*E*,4*E*,8*E*)-6,8-dimethyl-2,4,8,12-tridecatetraenyl]-2*H*-pyran-2,4-diol. Rottnestol (1)

To a solution of rottnestol methyl ketal (12*R*)-**4** (8.0 mg, 22.0 μmol) in THF (670 μL) at 0 °C was added 5% aqueous HCl (135 μL). After stirring at 0 °C for 35 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and the solvent removed under reduced pressure. The crude product was purified by column chromatography using 25–30% EtOAc–petrol as eluent to afford rottnestol (12*R*)-**1** (4.2 mg, 55%) as a pale yellow gum (See Table 1 for NMR data): $[\alpha]_D^{21}$ +58.4 (*c* 0.18, CH_2Cl_2), lit.,[1] $[\alpha]_D$ +67.4 (*c* 0.43, CH_2Cl_2); ν_{max} (thin film) 3402, 2930, 1648, 1388, 1084, 1024 cm^{-1}; MS (ESI) *m*/*z* 371 ($[M + Na]^+$, 100%); HRMS (ESI): Calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2564, found 371.2551.

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2-methoxy-2,3-dimethyl-6-[(12*S*,2*E*,4*E*,8*E*)-6,8-dimethyl-2,4,8,12-tridecatetraenyl]-2*H*-pyran-4-ol. 12-*epi*-Rottnestol methyl ketal (12*S*)-(4)

To a freeze–thaw degassed (3×) solution of the (*S*)-vinyl iodide (*S*)-**8** (31 mg, 0.11 mmol), stannane **7** (67 mg, 0.137 mmol) and *i*-Pr_2NEt (57 μL, 0.327 mmol) in dry DMF (1.0 mL) was added bis(acetonitrile)palladium(II) chloride (3.5 mg, 13.0 μmol). The reaction mixture was stirred in the absence of light at rt for 48 h

and then diluted with water and extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and concentrated. Purification of the crude product by column chromatography using 20% EtOAc–petrol provided 12-*epi*-rottnestol methyl ketal (12*S*)-**4** (21.8 mg, 57%) as a colourless gum. The spectroscopic data for (12*S*)-rottnestol methyl ketal was identical to that quoted for the (12*R*) compound: $[\alpha]_D^{21}$ +74.4 (*c* 0.76, CH_2Cl_2); HRMS (ESI): Calcd for $C_{23}H_{38}O_3Na$ $[M + Na]^+$ 385.2719, found 385.2717.

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2,3-dimethyl-6-[(12*S*,2E,4*E*,8*E*)-6,8-dimethyl-2,4,8,12-tridecatetraenyl]-2*H*-pyran-2,4-diol. 12-*epi*-Rottnestol (12*S*)-(1)

To a solution of 12-*epi*-rottnestol methyl ketal (12*S*)-**4** (11.9 mg, 32.8 μmol) in THF (1.0 mL) at 0 °C was added 5% aqueous HCl (150 μL). After stirring at 0 °C for 35 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and the solvent removed under reduced pressure. The crude product was purified by column chromatography using 15–30% EtOAc–petrol as eluent to afford 12*epi*-rottnestol (12*S*)-**1** (7.2 mg, 63%) as a colourless gum. The spectroscopic data for 12-*epi*-rottnestol was identical to that quoted for the (12*R*) isomer: $[\alpha]_D^{24}$ +33.9 (*c* 0.35, CH_2Cl_2); HRMS (ESI): Calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2564, found 371.2547.

(9*R*,4*E*,6*E*)-10-(*tert*-Butyldimethylsiloxy)-7,9-dimethyldeca-4,5-dien-1-ol 30

To a freeze–thaw degassed (3×) solution of the (*E*)-vinyl iodide (*R*)-**21** (50 mg, 0.14 mmol), stannane **29**[37] (74 mg, 0.197 mmol) and *i*-Pr_2NEt (52 μL, 0.30 mmol) in dry DMF (2 mL) was added bis(acetonitrile)palladium(II) chloride (5.2 mg, 20 μmol) and the reaction mixture was freeze–thaw degassed again. The resultant black mixture was then stirred at 40 °C in the absence of light for 11.5 h after which time water and Et_2O were added. The organic fraction was washed with water, brine, dried and concentrated. The residue was purified on silica gel (treated with 1% NEt_3–10% EtOAc–petrol) using 10% EtOAc–petrol as eluent to afford the conjugated diene **30** (24 mg, 54%) as a clear oil: $[\alpha]_D^{19}$ +5.4 (*c* 0.98, CH_2Cl_2); ν_{max} (thin film) 3347, 2930, 1620, 1256, 1091 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 (s, 6H), 0.82 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 1.63–1.83 (m, 4H), 1.71 (s, 3H), 2.16–2.23 (m, 3H), 3.34–3.44 (m, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 5.56 (dt, *J* = 15.0, 7.2 Hz, 1H), 5.77 (d, *J* = 10.8 Hz, 1H), 6.23 (dd, *J* = 15.3, 10.8 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) −5.4, 16.5, 18.3, 25.9, 29.2, 32.4, 34.0, 43.8, 62.4, 68.0, 125.9, 127.2, 131.1, 135.3; HRMS (ESI): Calcd for $C_{18}H_{36}O_2SiNa$ $[M + Na]^+$ 335.2382, found 335.2382.

(10*R*,5*E*,7*E*)-11-(*tert*-Butyldimethylsiloxy)-8,10-dimethylundeca-1,5,7-triene 31

To a stirred solution of the alcohol **30** (50 mg, 0.16 mmol) and pyridine (100 μL, 1.24 mmol) in anhydrous CH_2Cl_2 (2.7 mL) was added Dess–Martin periodinane (103 mg, 0.24 mmol). After stirring at rt for 30 min, Et_2O and a 1 : 1 v/v mixture of saturated aqueous $NaHCO_3$ and 1.5 M $Na_2S_2O_3$ were added and the reaction mixture was vigorously stirred until the layers cleared. The organic layer was washed with the 1 : 1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M $Na_2S_2O_3$ then saturated aqueous $NaHCO_3$, water, saturated aqueous $CuSO_4$, brine, dried and the solvent removed under reduced pressure to give the aldehyde which was used immediately in the next reaction. To a suspension of methyltriphenylphosphonium bromide (230 mg, 0.64 mmol) in anhydrous THF (1 mL) at 0 °C was added dropwise ^{n}BuLi in hexanes (400 μL, 2.2 M, 0.88 mmol). The resulting yellow solution was stirred at rt for 5 min then recooled to 0 °C and a solution of the aldehyde (49 mg, 0.16 mmol) in dry THF (2 mL) was added slowly *via* cannula. The reaction mixture was stirred at 0 °C for 1 h in the absence of light and Et_2O and water were added and the aqueous phase was extracted with Et_2O. The combined organic fractions were washed with brine, dried and the solvent removed under reduced pressure. Purification of the crude product on silica gel (treated with 1% NEt_3–petrol) using petrol as eluent afforded the triene **31** (33.6 mg, 68%) as a colourless oil: $[\alpha]_D^{21}$ +5.5 (*c* 1.04, CH_2Cl_2); ν_{max} (thin film) 2929, 1642, 1090 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.05 (s, 6H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.99 (s, 9H), 1.71 (s, 3H), 1.74–1.85 (m, 2H), 2.03–2.18 (m, 4H), 2.27 (m, 1H), 3.33–3.43 (m, 2H), 4.97 (d, *J* = 9.0 Hz, 1H), 5.01 (d, *J* = 15.3 Hz, 1H), 5.57 (dt, *J* = 14.7, 6.6 Hz, 1H), 5.76 (ddt, *J* = 16.8, 10.2, 6.3 Hz, 1H), 5.96 (d, *J* = 10.8 Hz, 1H), 6.34 (dd, *J* = 15.3, 10.8 Hz, 1H); δ_C (75.5 MHz, C_6D_6) −5.24, 16.5, 16.9, 18.5, 26.2, 32.8, 34.2, 34.4, 44.3, 68.1, 114.9, 127.1, 128.8, 131.5, 134.8, 138.4; HRMS (ESI): Calcd for $C_{19}H_{36}OsiNa$ $[M + Na]^+$ 331.2433, found 331.2428.

(2*R*,4*E*,6*E*)-2,4-Dimethylundeca-4,6,10-trien-1-ol 32

To a solution of the ether **31** (70 mg, 0.23 mmol) in anhydrous THF (2.4 mL) was added TBAF (176 mg, 0.558 mmol) and the resultant solution was stirred at rt for 2.5 h. Water and Et_2O were added and the aqueous layer was further extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and the solvent removed under reduced pressure. Purification of the crude product by flash chromatography using 15% EtOAc–petrol as eluent afforded the alcohol **32** (42 mg, 95%) as a clear oil: $[\alpha]_D^{22}$ +4.1 (*c* 1.21, CH_2Cl_2); ν_{max} (thin film) 3354, 3078, 3021, 2922, 1641, 1450, 1038, 964, 912 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.80 (d, *J* = 6.3 Hz, 3H), 1.61 (s, 3H), 1.60–1.71 (m, 1H), 1.67 (d, *J* = 6.9 Hz, 1H), 1.74 (d, *J* = 8.4 Hz, 1H), 2.05–2.14 (m, 4H), 3.11–3.27 (m, 2H), 4.97 (d, *J* = 9.3 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 5.56 (dt, *J* = 15.0, 6.6 Hz, 1H), 5.76 (ddt, *J* = 17.1, 10.5, 6.3 Hz, 1H), 5.89 (d, *J* = 10.8 Hz, 1H), 6.32 (dd, *J* = 15.3, 10.8 Hz, 1H); δ_C (75.5 MHz, C_6D_6) 16.5, 16.7, 32.7, 34.2, 34.3, 44.4, 67.9, 115.9, 127.0, 127.5, 131.6, 134.9, 138.4; HRMS (ESI): Calcd for $C_{13}H_{22}ONa$ $[M + Na]^+$ 194.1671, found 194.1669.

(3*R*,1*E*,5*E*,7*E*)-1-Iodo-3,5-dimethyldodeca-1,5,7,11-tetraene 9

To a stirred solution of the alcohol **32** (33 mg, 0.17 mmol) and pyridine (110 μL, 1.36 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added Dess–Martin periodinane (101 mg, 0.24 mmol). After stirring at rt for 1 h, Et_2O and a 1 : 1 v/v mixture of saturated aqueous $NaHCO_3$ and 1.5 M $Na_2S_2O_3$ were added and the reaction mixture was vigorously stirred until the layers cleared. The organic layer was washed with the 1 : 1 mixture of saturated aqueous $NaHCO_3$ and 1.5 M $Na_2S_2O_3$ then saturated aqueous $NaHCO_3$, water, saturated aqueous $CuSO_4$, brine, dried and the solvent removed under reduced pressure. The crude aldehyde (32 mg, 0.17 mmol) and iodoform (134 mg, 0.34 mmol) were dissolved in anhydrous dioxane (4.5 mL) and added dropwise to a vigorously stirred slurry of flame-dried chromium(II) chloride (167 mg, 1.36 mmol) in anhydrous THF (0.8 mL) under an argon atmosphere. The resulting brown suspension was stirred at rt for 4 h and was then diluted with Et_2O and water. The aqueous fraction was saturated with NaCl and further extracted with Et_2O. The combined organic fractions were washed with brine, dried and concentrated and the crude vinyl iodide was dissolved in Et_2O (3.4 mL) and treated with TBAF (268 mg, 0.85 mmol) in THF (1.2 mL) for 30 min. The solvent was removed under reduced pressure and the residue filtered through a plug of silica gel using Et_2O as eluent. The crude product was purified by flash chromatography on silica gel (treated with 1% NEt_3–petrol) using petrol as eluent to give the vinyl iodide **9** (32 mg, 58%) as a colourless oil: $[\alpha]_D^{16}$ +14.4 (*c* 0.87, CH_2Cl_2); ν_{max} (thin film) 3075, 3020, 2924, 1641, 1453, 964, 949, 911 cm^{-1}; δ_H (300 MHz, $CDCl_3$)

0.95 (d, J = 6.9 Hz, 3H), 1.70 (s, 3H), 1.94 (dd, J = 13.5, 7.8 Hz, 1H), 2.38 (m, 1H), 2.04–2.30 (m, 5H), 4.97 (d, J = 10.8 Hz, 1H), 5.03 (dd, J = 17.4, 1.2 Hz, 1H), 5.60 (dt, J = 15.0, 6.3 Hz, 1H), 5.72–5.90 (m, 1H), 5.76 (d, J = 11.1 Hz, 1H), 5.87 (d, J = 14.4 Hz, 1H), 6.24 (dd, J = 15.3, 10.8 Hz, 1H), 6.44 (dd, J = 14.4, 7.8 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$) 16.5, 18.9, 32.3, 33.7, 38.8, 46.7, 73.4, 114.7, 126.8, 127.0, 132.1, 133.7, 138.3, 151.7; HRMS (ESI): Calcd for $C_{14}H_{21}INa$ $[M + Na]^+$ 316.0688, found 316.0678.

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2-methoxy-2,3-dimethyl-6-[(12*R*,2*E*,4*E*,8*E*,10*E*)-6,8-dimethyl-2,4,8,10,14-pentadecapentaenyl]-2*H*-pyran-4-ol. Raspailol A methyl ketal (33)

To a freeze–thaw degassed (3×) solution of the (*R*)-vinyl iodide (*R*)-**9** (36 mg, 0.11 mmol), stannane **7** (73 mg, 0.15 mmol) and *i*-Pr_2NEt (62 μL, 0.356 mmol) in dry DMF (1.1 mL) was added bis(acetonitrile)palladium(II) chloride (4.7 mg, 18.0 μmol). The reaction mixture was stirred in the absence of light at rt overnight after which time a further portion of palladium catalyst (1.0 mg, 3.85 μmol) was added. The mixture was stirred for a further 4 h and then diluted with water and extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and concentrated. Purification of the crude product by column chromatography on silica gel (treated with 1% NEt_3–10% EtOAc–petrol) using 10–15% EtOAc–petrol as eluent provided raspailol A methyl ketal (**33**) (25 mg, 57%) as a colourless oil: $[\alpha]_D^{22}$ +94.5 (*c* 1.23, CH_2Cl_2); ν_{max} (thin film) 3432, 3023, 2924, 1642, 1378, 1048 cm^{-1}; δ_H (400 MHz, C_6D_6) 0.97 (d, J = 6.4 Hz, 3H, H23), 1.17 (d, J = 6.8 Hz, 3H, H22), 1.24 (s, 3H, H1), 1.28–1.39 (m, 2H, H3, H5), 1.64 (s, 3H, H24), 1.72 (m, 1H, H5), 1.96 (dd, J = 13.6, 8.0 Hz, 1H, H13), 2.04–2.20 (m, 6H, H7, H13, H18, H19), 2.32–2.39 (m, 2H, H7, H12), 3.02 (s, 3H, H25), 3.53 (m, 1H, H4), 3.65 (ddd, J = 10.4, 10.4, 4.4 Hz, 1H, H6). 4.99 (d, J = 10.4 Hz, 1H, H21), 5.03 (d, J = 17.2 Hz, 1H, H21), 5.48–5.58 (m, 2H, H11, H17), 5.63–5.78 (m, 2H, H8, H20), 5.89 (d, J = 10.4 Hz, 1H, H15), 6.00–6.11 (m, 2H, H9, H20), 6.24–6.33 (m, 1H, H16); δ_C (75.5 MHz, C_6D_6) 12.4, 17.0, 20.4, 22.3, 33.1, 34.5, 35.5, 39.9, 41.5, 47.7, 48.4, 49.0, 68.9, 69.9, 102.0, 115.3, 127.7, 127.9, 128.8, 129.3, 132.1, 133.7, 134.9, 138.8, 139.9; HRMS (FAB): Calcd for $C_{25}H_{40}O_3Na$ $[M + Na]^+$ 411.2875, found 411.2875.

(2*S*,3*R*,4*S*,6*R*)-Tetrahydro-2,3-dimethyl-6-[(12*R*,2*E*,4*E*,8*E*,-10*E*)-6,8-dimethyl-2,4,8,10,14-pentadecapentaenyl]-2*H*-pyran-4-ol. Raspailol A (5)

To a solution of raspailol A methyl ketal (**33**) (22.7 mg, 58.0 μmol) in THF (1.8 mL) at 0 °C was added 5% aqueous HCl (360 μL). After stirring at 0 °C for 30 min the reaction mixture was stirred at rt for 5 min and was then quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic fractions were washed with water, brine, dried and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (treated with 1% NEt_3–30% EtOAc–petrol) using 30% EtOAc–petrol as eluent to afford raspailol A (**5**) (14.3 mg, 65%) as a colourless gum (See Table 2 for NMR data): $[\alpha]_D^{23}$ +78.4 (*c* 0.42, C_6H_6), lit.,[2] $[\alpha]_D$ +62.0 (*c* 0.46, C_6H_6); ν_{max} (thin film) 3404, 2923, 1641, 1381, 1159, 1077 cm^{-1}; HRMS (FAB): Calcd for $C_{24}H_{38}O_3Na$ $[M + Na]^+$ 397.2719, found 397.2721.

[[3-(2*R*,4*S*,5*S*),4*R*]-3-(6-Benzyloxy-5-hydroxy-2,4-dimethyl-1,3-dioxohexyl)-4-(phenylmethyl)]-2-oxazolidinone 35

A suspension of tin triflate (2.79 g, 6.69 mmol) in anhydrous CH_2Cl_2 (11.0 mL) was treated with NEt_3 (933 μL, 6.69 mmol). The mixture was immediately cooled to −20 °C and the β-keto imide **34**[38] (1.76 g, 6.08 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise. The reaction mixture was stirred for 1 h at −20 °C, cooled to −78 °C and a solution of benzyloxyacetaldehyde (1.10 g, 7.33 mmol) in CH_2Cl_2 (5.0 mL) was cannulated to the reaction. The reaction mixture was stirred at −78 °C for 90 min and cannulated into a 1 : 1 mixture of CH_2Cl_2 : 1 M $NaHSO_4$ (400 mL) at 0 °C. The biphasic mixture was stirred for 10 min at 0 °C and diluted with additional CH_2Cl_2 : 1 M $NaHSO_4$. The organic phase was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the crude alcohol which was purified by column chromatography using 30%EtOAc–petrol as eluent to afford the alcohol **35** (2.06 g, 77%) as a colourless oil: $[\alpha]_D^{15}$ −64.2 (*c* 1.01, CH_2Cl_2); ν_{max} (thin film) 3527, 2985, 1782, 1360, 1114 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.24 (d, J = 7.2 Hz, 3H), 1.45 (d, J = 7.2 Hz, 3H), 2.73 (br s, 1H), 2.77 (dd, J = 13.2, 9.2 Hz, 1H), 3.02 (m, 1H), 3.26 (dd, J = 13.5, 3.3 Hz, 1H), 3.46 (m, 2H), 4.16 (m, 2H), 4.13–4.22 (m, 3H), 4.51 (d, J = 3.9 Hz, 2H), 4.72 (m, 1H), 4.88 (q, J = 7.2 Hz, 1H), 7.18–7.35 (m, 10H); δ_C (75.5 MHz, $CDCl_3$) 11.7, 12.7, 37.7, 46.3, 51.9, 55.1, 66.2, 70.5, 71.2, 73.2, 127.2, 127.7, 128.3, 128.8, 129.3, 134.9, 137.6, 153.3, 170.5, 210.3; HRMS (ESI): Calcd for $C_{25}H_{29}NO_6Na$ $[M + Na]^+$ 462.1893, found 462.1898.

[[3-(2*R*,3*S*,4*R*,5*S*),4*R*]-3-(6-Benzyloxy-3,5-dihydroxy-2,4-dimethyl-1-oxohexyl)-4-(phenylmethyl)]-2-oxazolidinone 36

A solution of $Me_4NBH(OAc)_3$[40] (4.61 g, 17.53 mmol) in anhydrous acetonitrile (20 mL) and freshly distilled glacial acetic acid (20 mL) was cooled to −40 °C. The ketal **35** (1.93 g, 4.38 mmol) in acetonitrile (35 mL) was added *via* cannula and the reaction was stirred for 1 h, warmed to 0 °C and stirred for an additional 1 h. The reaction mixture was warmed to room temperature, stirred for 1 h and cannulated to a stirring biphasic mixture of CH_2Cl_2 (415 mL) and saturated aqueous $NaHCO_3$ (275 mL). The organic phase was extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. The crude oil was purified by column chromatography with 40%EtOAc–petrol as eluent to yield the diol **36** (1.76 g, 91%) as a pale yellow gum: $[\alpha]_D^{17}$ −44.3 (*c* 1.02, CH_2Cl_2); (Found: C, 68.0; H, 7.3; N, 3.3; $C_{25}H_{31}NO_6$ requires C, 68.0; H, 7.1; N, 3.15%); ν_{max} (thin film) 3450, 1692, 1388 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (d, J = 6.9 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.85 (m, 1H), 2.75 (dd, J = 13.5, 9.6 Hz, 1H), 3.04 (d, J = 3.9 Hz, 1H), 3.23 (dd, J = 13.5, 3.3 Hz, 1H), 3.52–3.55 (m, 2H), 3.75 (d, J = 3.3 Hz, 1H), 3.91–3.98 (m, 2H), 4.10–4.20 (m, 3H), 4.54 (d, J = 5.7 Hz, 2H), 4.64 (m, 1H), 7.17–7.33 (m, 10H); δ_C (75.5 MHz, $CDCl_3$) 10.2, 11.0, 14.0, 20.9, 37.1, 37.5, 39.9, 55.1, 60.2, 66.0, 70.9, 72.2, 73.1, 73.5, 127.2, 127.4, 127.5, 127.6, 128.2, 128.3, 128.8, 129.3, 135.0, 137.9, 152.8, 176.9; HRMS (ESI): Calcd for $C_{25}H_{31}NO_6Na$ $[M + Na]^+$ 464.2049, found 464.2046.

(2*R*,3*S*,4*R*,5*S*)-6-Benzyloxy-2,4-dimethyl-3,5-bis(triethylsilyloxy)-*N*-methoxy-*N*-methylhexanamide 37

A suspension of *N,O*-dimethylhydroxyamine hydrochloride (796 mg, 8.16 mmol) in CH_2Cl_2 (30 mL) was treated at 0 °C with $AlMe_3$ (2 M in toluene, 4.1 mL, 8.16 mmol). When methane gas had ceased to bubble from the vessel it was warmed to room temperature and stirred for 30 min. The reaction was then cooled to −45 °C and a solution of the diol **36** (600 mg, 1.36 mmol) in CH_2Cl_2 (16 mL) was cannulated to the reaction vessel. The yellow solution was stirred at −45 °C for five hours and quenched with 0.5 M potassium tartrate. The mixture was stirred for two hours until the aqueous layer became clear and the biphasic mixture was filtered through Celite. The organic phase was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude Weinreb amide. A solution of the crude amide (360 mg, 1.11 mmol) in DMF (8 mL) was treated with imidazole (226 mg, 3.32 mmol) and TESCl (464 μL, 2.77 mmol) at rt. The reaction mixture was stirred overnight and diluted with water and Et_2O. The organic layer was extracted with Et_2O and the combined organic

extracts were washed with saturated aqueous $NaHCO_3$, water, brine and dried over $MgSO_4$. The crude residue was purified by column chromatography using 10% EtOAc–petrol as eluent to yield the bis-protected amide **37** (445 mg, 59% for 2 steps): $[\alpha]_D^{16}$ +8.2 (*c* 1.00, CH_2Cl_2) (Found: C, 62.8; H, 10.1; N, 2.6; $C_{29}H_{55}NO_5Si_2$ requires C, 62.9; H, 10.0; N, 2.55%); ν_{max} (thin film) 3453, 2912, 1665, 1458, 1004 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.53–0.65 (m, 12H), 0.89–0.99 (m, 21H), 1.12 (d, 3H, *J* = 6.9 Hz), 1.86 (m, 1H), 3.03 (m, 1H), 3.12 (s, 3H), 3.48 (m, 2H), 3.65 (s, 3H), 3.69 (m, 1H), 4.05 (dd, *J* = 6.3, 4.8 Hz, 1H), 4.51 (AB quartet, *J* = 12 Hz, 2H), 7.26–7.33 (m, 10H); δ_C (75.5 MHz, $CDCl_3$) 5.2, 5.3, 7.0, 7.1, 11.6, 14.0, 32.1, 38.0, 42.3, 61.1, 72.5, 73.2, 73.5, 74.0, 127.3, 127.7, 128.1, 138.5, 176.6; HRMS (ESI): Calcd for $C_{29}H_{55}NO_5Si_2Na$ $[M + Na]^+$ 576.3516, found 576.3504. Further elution gave the amide bi-product **38** (99 mg, 10% for 2 steps): $[\alpha]_D^{14}$ +0.0 (*c* 1.03, CH_2Cl_2) (Found: C, 64.15; H, 9.15; N, 3.9; $C_{29}H_{55}NO_5Si_2$ requires C, 64.05; H, 9.1; N, 3.85%); ν_{max} (thin film) 3400, 2912, 1674, 1051, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.61 (q, *J* = 7.8 Hz, 12H), 0.92 (m, 24H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.86 (m, 1H), 2.47 (quint, *J* = 6.9 Hz, 1H), 2.68 (dd, *J* = 13.8, 8.1 Hz, 1H), 2.77 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.12 (s, 3H) 3.46 (dd, *J* = 3.9, 9.9 Hz, 1H), 3.59 (dd, *J* = 4.8, 10.0 Hz, 1H) 3.68 (s, 3H), 3.81 (q, *J* = 4.8 Hz, 1H), 3.96 (m, 3H), 4.05 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.36 (m, 1H) 6.19 (d, 1H), 7.17–7.34 (m, 10H, ArH); δ_C (75.5 MHz, $CDCl_3$) 5.1, 5.3, 6.9, 7.0, 13.1, 13.8, 35.5, 37.2, 41.1, 45.1, 49.4, 61.5, 65.9, 72.9, 73.2, 73.5, 75.9, 126.5, 127.5, 127.7, 128.2, 128.4, 129.1, 137.1, 138.1, 156.8, 174.6; HRMS (ESI): Calcd for $C_{29}H_{55}NO_5Si_2Na$ $[M + Na]^+$ 753.4306, found 753.4328.

(2*S*,3*R*,4*S*,5*R*,6*S*)-Tetrahydro-6-benzyloxymethyl-2-methoxy-2,3,5-trimethyl-2*H*-pyran-4-ol 39

A solution of the bis-protected Weinreb amide **37** (221 mg, 0.40 mmol) in anhydrous THF (6 mL) was cooled to 0 °C. The amide was treated with MeMgCl in hexanes (0.80 mL, 3.0 M, 2.39 mmol) and stirred for 3 h at rt. The reaction vessel was cooled to 0 °C and quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was extracted with Et_2O and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, brine and dried over $MgSO_4$ to afford the ketone (198 mg, 0.39 mmol) which was dissolved in a 3 : 1 mixture of CH_2Cl_2 (8.1 mL) : MeOH (2.7 mL) and treated with PPTS (20 mg, 0.078 mmol) and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The organic layer was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water, brine and dried over $MgSO_4$. Purification by column chromatography with 10% EtOAc–petrol as eluent afforded the tetrahydropyran **39** (106 mg, 91% for 2 steps) as a pale yellow oil: $[\alpha]_D^{16}$ +100.0 (*c* 0.96, CH_2Cl_2) (Found: C, 69.6; H, 9.05; $C_{17}H_{26}O_4$ requires C, 69.35; H, 8.9%); ν_{max} (thin film) 3428, 2918, 1074 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81 (d, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 6.8 Hz), 1.29 (s, 3H), 1.56–1.64 (dq, *J* = 10.8, 6.8 Hz, 1H), 1.94–1.97 (m, 1H), 3.15 (s, 3H), 3.42 (dd, *J* = 5.6, 10 Hz, 1H), 3.53 (dd, *J* = 7.2, 9.6 Hz, 1H), 3.77 (dd, *J* = 5.2, 10.8 Hz, 1H), 3.89 (dt, *J* = 6.2, 2 Hz, 1H), 4.46–4.61 (AB quartet, *J* = 12 Hz, 2H), 7.26–7.31 (m, 10H); δ_C (100 MHz, $CDCl_3$) 4.9, 11.8, 21.5, 36.2, 41.4, 47.6, 69.7, 71.0, 72.2, 73.3, 101.2, 127.4, 127.5, 128.3, 138.3; HRMS (ESI): Calcd for $C_{17}H_{26}O_4Na$ $[M + Na]^+$ 317.1729, found 317.1721.

(2*S*,3*R*,4*S*,5*R*,6*S*)-Tetrahydro-4-(*tert*-butyldimethylsiloxy)-6-hydroxymethyl-2-methoxy-1,3,5-trimethyl-2*H*-pyran 40

A solution of the alcohol **39** (205 mg, 0.70 mmol) in CH_2Cl_2 (15 mL) was treated with 2,6-lutidine (162 μL, 1.39 mmol) and TBSOTf (240 μL, 1.05 mmol) at rt. The reaction mixture was stirred for 2.5 h and upon completion the reaction was diluted with Et_2O and water. The organic phase was extracted Et_2O, washed with saturated aqueous $NaHCO_3$, water, brine and dried over $MgSO_4$. The crude product was purified by column chromatography, eluting with 2.5–5% EtOAc–petrol to yield the silylated tetrahydropyran. To a solution of this silyl ether (142 mg, 0.35 mmol) in MeOH (15 mL) was added 10% $Pd(OH)_2$/C (49 mg, 0.070 mmol) and the reaction was agitated under 50 psi of hydrogen gas for 12 h. The suspension was filtered though Celite and the solvent was removed under reduced pressure. Purification by column chromatography using 10% EtOAc–petrol as eluent afforded the alcohol **40** (103 mg, 74%) as a yellow film: $[\alpha]_D^{15}$ +131.3 (*c* 1.02, CH_2Cl_2); ν_{max} (thin film) 3315, 2886 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 (d, *J* = 6.6 Hz, 6H), 0.83 (d, 3H, *J* = 7.2 Hz), 0.87 (s, 9H), 0.92 (d, 3H, *J* = 6.9 Hz), 1.29 (s, 3H), 1.63 (dq, *J* = 10.8, 6.8 Hz, 1H), 1.76 (m, 1H), 2.18 (br s, 1H), 3.15 (s, 3H), 3.47 (d, *J* = 9.0 Hz, 1H), 3.66–3.77 (m, 3H); δ_C (75.5 MHz, $CDCl_3$) −4.8, −4.3, 5.4, 12.4, 18.0, 21.6, 25.8, 36.9, 41.7, 47.5, 64.1, 71.6, 72.6, 101.5; HRMS (ESI): Calcd for $C_{16}H_{34}O_4SiNa$ $[M + Na]^+$ 341.2124, found 341.2118.

(2*S*,3*R*,4*S*,5*R*,6*R*)-Tetrahydro-2-methoxy-2,3,5-trimethyl-6-prop-2-ynyl-2*H*-pyran-4-ol 41

A solution of the pyran **40** (145 mg, 0.46 mmol) in CH_2Cl_2 (4.0 mL) was cooled to −78 °C and treated with 2,6-lutidine (265 μL, 2.28 mmol) and Tf_2O (153 μL, 0.91 mmol). The reaction was stirred at −78 °C for 45 min, quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic phase was extracted with ether, washed with saturated aqueous $NaHCO_3$, water, saturated aqueous $CuSO_4$, water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure in an ice bath to prevent decomposition and the crude triflate was obtained as an orange oil. The crude triflate (205 mg, 0.455 mmol) in anhydrous THF (3.0 mL) was added dropwise *via* cannula to a solution of lithium trimethylsilylacetylide [from trimethylsilylacetylene (322 μL, 2.28 mmol) and *n*-BuLi in hexanes (986 μL, 2.4 M, 2.38 mmol)] in dry THF (3.0 mL) and HMPA (792 μL, 4.55 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was extracted with Et_2O and the combined organic fractions were washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude acetylene as a yellow oil (182 mg, 0.46 mmol) which was dissolved in DMF (8.0 mL) and treated with TBAF (575 mg, 1.82 mmol) at rt for 2 days. Water and Et_2O were added and the organic phase was extracted with Et_2O. The combined organic fractions were washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude alkyne was purified by column chromatography using 15%EtOAc–petrol as eluent to afford the alkyne **41** (64 mg, 66% for 3 steps) as a white crystalline solid: $[\alpha]_D^{17}$ +133.9 (*c* 0.67, CH_2Cl_2); ν_{max} (thin film) 3369, 2944 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (d, 3H, *J* = 7.2 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 1.31 (s, 3H), 1.49 (br s, 1H), 1.62 (m, 1H), 1.97 (t, 1H, *J* = 2.7 Hz), 2.08 (m, 1H), 2.25–2.34 (ddd, *J* = 2.7, 7.7, 16.7 Hz, 1H), 2.40–2.49 (ddd, *J* = 2.7, 7.3, 16.5 Hz, 1H), 3.18 (s, 3H), 3.78–3.84 (m, 2H); δ_C (75.5 MHz, $CDCl_3$) 4.3, 11.8, 21.5, 22.2, 37.1, 41.1, 47.7, 69.2, 69.5, 72.2, 81.0, 101.4; HRMS (ESI): Calcd for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ 235.1310, found 235.1309.

(2*S*,3*R*,4*S*,5*R*,6*R*)-Tetrahydro-2-methoxy-2,3,5-trimethyl-6-[3-(tributylstannanyl)allyl]-2*H*-pyran-4-ol 10

A solution of the alkyne **41** (45 mg, 0.21 mmol) in anhydrous benzene (3.0 mL) was treated with Bu_3SnH (80 μL, 0.30 mmol) and AIBN (3.5 mg, 0.021 mmol). The reaction mixture was refluxed for 2 h and additional Bu_3SnH (40 μL, 0.15 mmol) and AIBN (1.8 mg, 0.0085 mmol) were added and the reaction was refluxed for another 2 h. The benzene was removed under reduced pressure and the crude stannane was purified immediately by column chromatography using 1%NEt_3–petrol as eluent to afford the stannane **10** (75 mg, 70%) as a colourless

oil: $[\alpha]_D^{22}$ +53.7 (*c* 0.37, CH_2Cl_2); ν_{max} (thin film) 3436, 2926, 1463, 1068 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.91–0.99 (m, 18H), 1.10 (d, 3H, *J* = 6.9 Hz), 1.21 (s, 3H), 1.38 (sext, *J* = 7.5 Hz, 6H), 1.60 (quint, *J* = 7.8 Hz, 6H), 1.68–1.72 (m, 2H), 2.20 (m, 1H), 2.60 (m, 1H), 3.12 (s, 3H), 3.70–3.76 (m, 2H), 6.10–6.20 (m, 2H); δ_C (75.5 MHz, C_6D_6) 5.0, 9.7, 10.6, 12.2, 14.0, 21.7, 27.7, 29.6, 38.8, 41.7, 47.5, 70.9, 72.4, 101.4, 130.1, 146.8; HRMS (ESI): Calcd for $C_{24}H_{48}O_3SnNa$ $[M + Na]^+$ 527.2523, found 527.2522.

(2*S*,3*R*,4*S*,5*R*,6*R*)-Tetrahydro-6-[(12*R*,2*E*,4*E*,8*E*,10*E*)-6,8-dimethyl-2,4,8,10,14-pentadecapentaenyl]-2,3,5-trimethyl-2*H*-pyran-2,4-diol. Raspailol B methyl ketal (42)

To a freeze–thaw degassed (×3) solution of the vinyl iodide **9** (23 mg, 0.073 mmol) and stannane **10** (70 mg, 0.14 mmol) in DMF (2.7 mL) and *i*-Pr_2NEt (89 μL, 0.51 mmol) was added bis(acetonitrile)palladium(II) chloride (1.9 mg, 0.0073 mmol). The reaction was stirred at rt, in the absence of light overnight. Additional catalyst (1 mg, 0.0036 mmol) was added and the reaction was stirred for a further 4 h and diluted with water and Et_2O. The organic layer was extracted with Et_2O and the combined organic extracts were washed with water, brine and dried over $MgSO_4$. The crude residue was purified by column chromatography with 10%EtOAc–petrol as eluent to afford raspailol B methyl ketal (**42**) (17 mg, 58%): $[\alpha]_D^{23}$ +126.7 (*c* 0.48, CH_2Cl_2); ν_{max} (thin film) 3430, 2922, 1727, 1459, 1065 cm^{-1}; δ_H (400 MHz, C_6D_6) 0.91 (d, *J* = 7.2 Hz, 3H, H25), 0.96 (d, *J* = 6.4 Hz, 3H, H23), 1.09 (d, *J* = 6.8 Hz, 3H, H22), 1.19 (s, 3H, H1), 1.56 (dq, *J* = 10.8, 6.7 Hz, 1H, H3), 1.62 (m, 1H, H5), 1.62 (s, 3H, H24), 1.95 (dd, *J* = 13.2, 7.6 Hz, 1H, H13), 2.08 (m, 6H, H7, H13, H18, H19), 2.37 (m, 2H, H7, H17), 3.03 (s, 3H, H26), 3.62 (td, *J* = 7.0, 2.0Hz, 1H, H4), 3.67 (dd, *J* = 10.8, 8.4Hz, 1H, H6), 4.97 (d, *J* = 11.2 Hz, 1H, H21), 5.00 (d, *J* = 17.6Hz, 1H, H21), 5.56 (m, 3H, H8, H11, H17), 5.75 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H, H20), 5.90 (d, *J* = 10.8 Hz, 1H, H15), 6.10 (m, 2H, H9, H10), 6.32 (dd, *J* = 15.0, 10.8 Hz, 1H, H16); δ_C (100 MHz, C_6D_6) 4.9, 12.2, 16.6, 20.1, 21.7, 32.7, 34.1, 35.2, 36.2, 38.4, 41.7, 47.4, 48.0, 71.1, 77.4, 101.4, 114.9, 127.3, 127.5, 128.7, 128.9, 131.8, 133.1, 134.5, 138.4, 138.5; HRMS (ESI): Calcd for $C_{26}H_{42}O_3Na$ $[M + Na]^+$ 425.3032, found 425.3060.

(2*S*,3*R*,4*S*,5*R*,6*R*)-Tetrahydro-6-[(12*R*,2*E*,4*E*,8*E*,10*E*)-6,8-Dimethyl-2,4,8,10,14-pentadecapentaenyl]-2,3,5-trimethyl-2*H*-pyran-2,4-diol. Raspailol B (6)

The methyl ketal (**42**) (9 mg, 0.022 mmol) in THF (2.5 mL) was treated at 0 °C with 5% aqueous HCl (140 μL) for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic phase was extracted with Et_2O and the combined organic extracts were washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude natural product was purified by column chromatography. Elution with 20% EtOAc–petrol afforded raspailol B (**6**) (8.0 mg, 93%) as a colourless oil (See Table 3 for NMR data): $[\alpha]_D^{22}$+114.7 (*c* 0.34, CH_2Cl_2); $[\alpha]_D^{23}$ +108.0 (*c* 0.045, C_6H_6); lit.,[2] $[\alpha]_D$ +111 (*c* 0.14, C_6D_6); ν_{max} (thin film) 3422, 2920, 1457, 1381, 1087, 990 cm^{-1}; HRMS (ESI): Calcd for $C_{25}H_{40}O_3Na$ $[M + Na]^+$ 411.2875, found 411.2884.

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