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Total synthesis of pteridic acids A and B

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Abstract

A convergent synthesis of pteridic acids A and B, epimeric spiroacetal polyketides with potent plant growth promoter properties, is described. The use of boron aldol methodology efficiently achieved the stereocontrolled construction of advanced C1–C11 and C12–C16 subunits, which were coupled to generate a linear (*Z*)-enone precursor that underwent spiroacetalization with HF·pyridine, providing pteridic acids A and B after saponification.

Keywords: Spiroacetal; Natural products; Aldol reaction; Plant growth promoter

1. Introduction

The spiroacetal motif is a feature common to a vast array of naturally occurring substances, including those of marine, plant and bacterial origin, which often display impressive biological profiles.[1] Spiroacetal-containing natural products therefore provide an attractive target for total synthesis, both in terms of the inherent complexity associated with efficient construction of the spiroacetal moiety, and also in terms of the wide-ranging and potent biological activities often associated with this important scaffold. Within this laboratory, synthetic endeavours directed towards accessing such molecular frameworks have recently encompassed a range of challenging polyketide targets, including spongistatin 1/altohyrtin A (**1**),[2] siphonarin B (**2**),[3] spirangien A (**3**)[4] and spirastrellolide A (**4**)[5] (Fig. 1).

Pteridic acids A and B (**5** and **6**, Fig. 2) are also spiroacetal-containing polyketides, isolated by Igarashi et al.[6] from a fermentation broth of *Streptomyces hygroscopicus* TP-A0451 (obtained from the stems of the bracken *Pteridium aquilinium*). Preliminary biological testing indicated that the pteridic acids have potent plant growth promoter properties, inducing the formation of adventitious roots in kidney beans at exceptionally low concentrations.

Structurally, the pteridic acids differ only in being epimeric at the C11-acetal centre. They comprise a highly substituted [6,6]-spiroacetal scaffold featuring seven stereocentres, and an unsaturated side chain appended at C7, which incorporates a further stereocentre and a carboxylic acid terminus. The spiroacetal unit of pteridic acid A benefits from stabilization by a double anomeric effect, offset by pseudo-axial ethyl and methyl groups at C14 and C15, respectively, while pteridic acid B, which exhibits only a single anomeric effect, profits energetically from pseudo-equatorial alkyl substituents at C14 and C15. Molecular modelling (MacroModel, MM2) reveals the global minima of the epimeric spiroacetals to be of similar energy, possibly accounting for their natural coexistence as microbial secondary metabolites.

In 2005, Nakahata and Kuwahara reported the first total synthesis of (+)-pteridic acid A, accompanied by the reassignment of the configuration of the methyl-bearing C10 stereocentre relative to that indicated previously.[7a] Subsequent work also allowed completion of a total synthesis of (−)-pteridic acid B using a late-stage $MgBr_2$-mediated spiroacetal isomerization.[7b] Herein, we report an expedient total synthesis of these interesting microbial polyketide metabolites, which utilizes our versatile boron aldol methodology to install much of the required stereochemistry, and employs a late-stage

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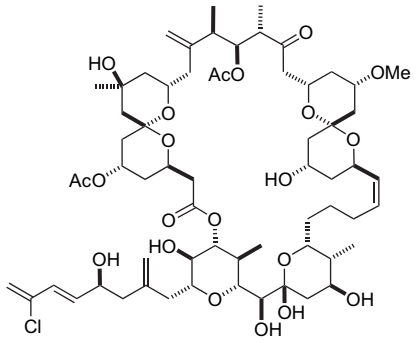
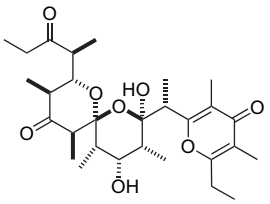
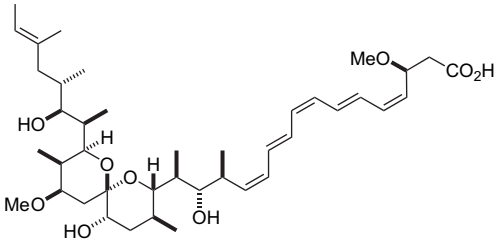


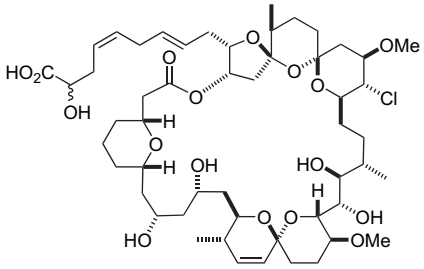
1: Spongistatin 1 (Altohyrtin A)



2: Siphonarin B

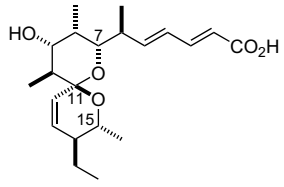


3: Spirangien A

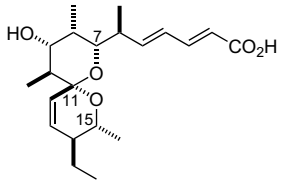


4: Spirastrellolide A

Figure 1. Structures of spiroacetal-containing polyketide natural products.



5: Pteridic Acid A



6: Pteridic Acid B

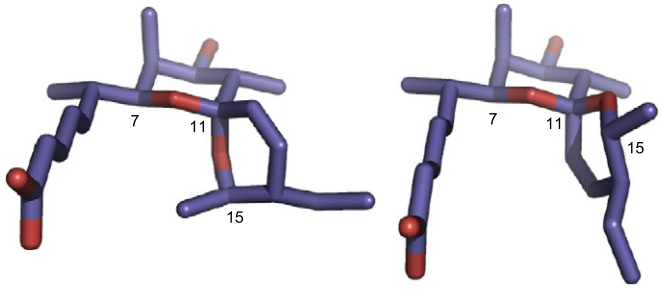
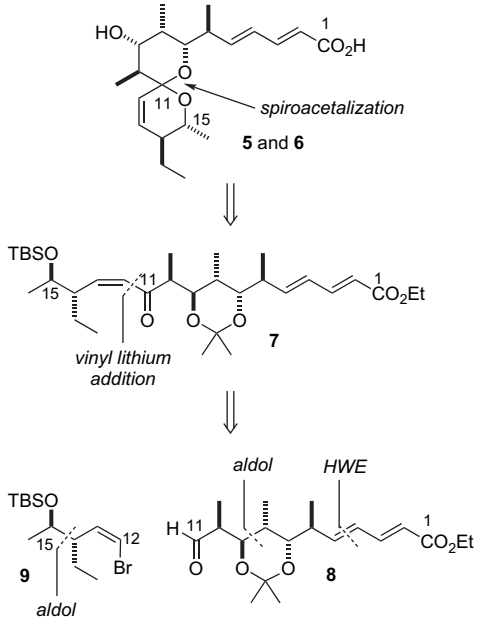


Figure 2. Structures of pteridic acids A and B with calculated minimum energy conformations.



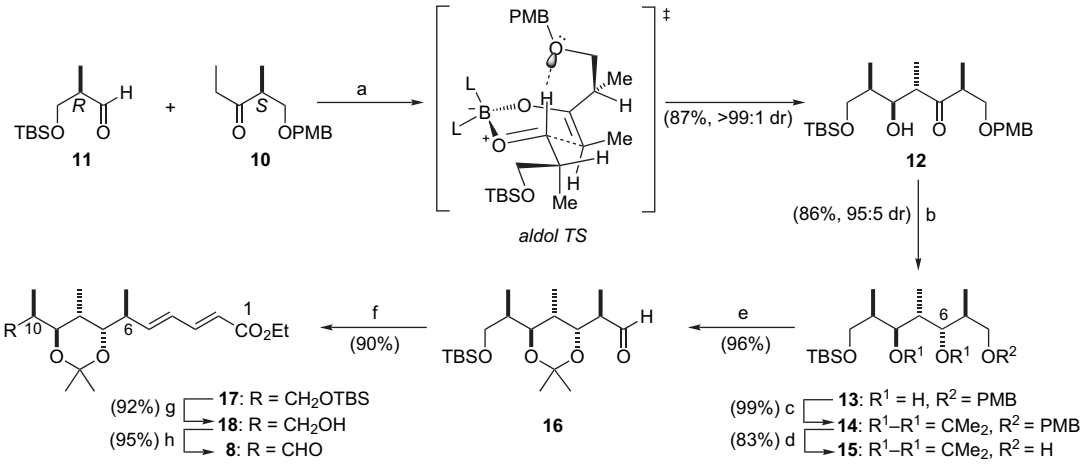
Scheme 1. Retrosynthetic analysis of the pteridic acids leading to key building blocks **8** and **9**.

spiroacetalization to obtain both pteridic acids A and B from a fully elaborated linear precursor.

2. Results and discussion

In our synthetic plan (Scheme 1), the (*Z*)-enone **7** was envisaged to function as a suitable acyclic precursor to the pteridic acids and might arise, in turn, from coupling of the C1–C11 aldehyde **8** with the C12–C16 vinyl bromide **9**. These two subunits should be accessible with a high level of stereocontrol using aldol methodology developed in our laboratory.

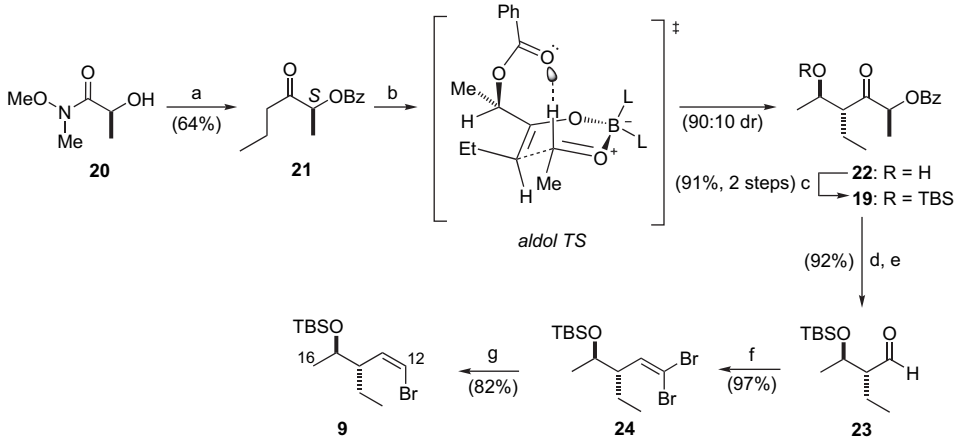
As shown in Scheme 2, formation of the C1–C11 aldehyde **8** began with a boron-mediated *anti* aldol reaction to rapidly establish the required C6–C10 stereopentad.[8] Formation of the (*E*)-enolate of the Roche ester derived ethyl ketone (*S*)-**10**,[9] upon treatment with *c*-Hex_2BCl/Et_3N, was followed by addition of the α-chiral aldehyde (*R*)-**11**.[10] The expected *anti*,-*anti* aldol adduct **12** was generated in 87% yield with excellent selectivity (>99:1 dr) in this matched situation.[11] The high level of enolate π-facial selectivity is governed by the formation of a stabilizing formyl hydrogen bond with the oxygen of



Scheme 2. (a) *c*-Hex_2BCl, Et_3N, Et_2O, −78→0 °C; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN, −30 °C; (c) 2,2,-dimethoxypropane, PPTS, rt; (d) H_2, $Pd(OH)_2$, EtOAc, rt; (e) DMP, $NaHCO_3$, CH_2Cl_2, rt; (f) $(EtO)_2P(O)CH_2(CH)_2CO_2Et$, LiHMDS, THF, −78 °C; (g) TBAF, THF, 0 °C→rt; (h) DMP, $NaHCO_3$, CH_2Cl_2, rt.

the PMB ether in the bicyclic aldol transition state shown, acting in unison with the minimization of allylic strain between the α-stereocentre of the enolate and the methyl substituent.[12] This stereoinduction from the boron enolate is further enhanced by the conformational preference of the aldehyde α-stereocentre, which in the case of (*E*)-boron enolate aldol reactions is matched/reinforced for the formal Felkin–Anh adduct, which avoids *syn*-pentane interactions between the aldehyde substituents and the enolate methyl group.[13] Installation of the remaining C7 stereocentre was achieved using an Evans–Saksena hydroxyl-directed reduction.[14] Thus, treatment of **12** with $Me_4NBH(OAc)_3$ in MeCN/AcOH (3:1) provided the corresponding 1,3-*anti* diol **13** in 87% yield and 95:5 dr, which was then converted into the acetonide **14** by $(MeO)_2CMe_2$ in the presence of catalytic acid (PPTS). Hydrogenolysis of the PMB ether (H_2, $Pd(OH)_2$), followed by oxidation of the resulting alcohol **15** using Dess–Martin periodinane (DMP),[15] led smoothly to the corresponding aldehyde **16**. With the correctly configured aldehyde **16** in hand, elaboration of the diene side chain of the pteridic acids was undertaken via a Horner–Wadsworth–Emmons olefination. A high degree of selectivity for the desired (*E*,*E*)-diene **17** (>95:5) was achieved using triethyl-4-phosphonocrotonate with LiHMDS as base. Finally, TBAF-mediated cleavage of the TBS ether, followed by Dess–Martin oxidation of the resulting alcohol **18** to give the aldehyde **8** (79%, 3 steps), completed the efficient stereocontrolled construction of the C1–C11 subunit.

Synthesis of the C12–C16 vinyl bromide coupling partner **9** commenced with preparation of the ketone **19** via a second *anti*-selective boron aldol reaction, this time using our lactate-based methodology (Scheme 3).[16] Based on our standard procedure, the Weinreb amide **20**[16a] derived from ethyl (*S*)-lactate was treated with *n*-PrMgCl followed by benzoylation to give the propyl ketone (*S*)-**21**. Enolization of **21** with *c*-Hex_2BCl/Me_2NEt, followed by addition of acetaldehyde at −85 °C, generated the desired *anti* adduct **22** (90:10 dr).[17] Again the enolate π-facial selectivity is presumably governed by the formation of a stabilizing formyl hydrogen bond, now involving the carbonyl oxygen of the benzoate, in the bicyclic aldol transition state shown, along with minimization of allylic strain between the α-stereocentre of the enolate and the ethyl substituent.[12,16a] From here, TBS ether formation to give the β-siloxy

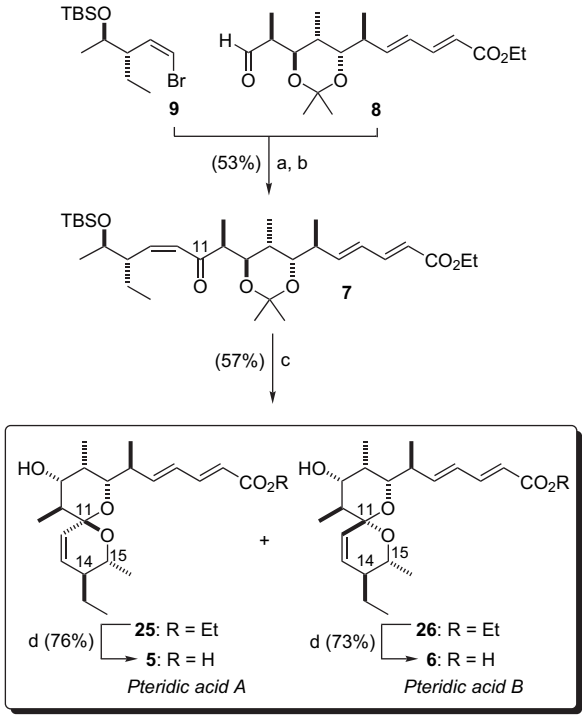


Scheme 3. (a) *n*-PrMgCl, THF, 0 °C→rt, $(PhCO)_2O$, DMAP, *i*-Pr_2NEt, THF; (b) *c*-Hex_2BCl, Me_2NEt, Et_2O, −78→0 °C; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt; (d) $NaBH_4$, MeOH, K_2CO_3, rt; (e) $NaIO_4$, MeOH, pH 7 buffer, rt; (f) CBr_4, PPh_3, Et_3N, CH_2Cl_2, −55 °C; (g) $Pd(PPh_3)_4$, Bu_3SnH, C_6H_6, rt.

ketone **19** was followed by a one-pot $NaBH_4$ reduction/ester solvolysis, then cleavage of the resulting glycol with $NaIO_4$, to generate aldehyde **23** in 92% overall yield. Treatment of **23** with CBr_4 and PPh_3 converted the aldehyde into the corresponding vinyl dibromide **24**,[18] the less hindered bromide of which was selectively reduced ($Pd(PPh_3)_4$, Bu_3SnH)[19] to provide the necessary (*Z*)-alkenyl bromide **9** and complete the efficient preparation of the C12–C16 subunit.

At this point, the development of suitable reaction conditions for the coupling of **8** and **9** was investigated (Scheme 4). Gratifyingly, generation of the corresponding (*Z*)-alkenyl lithium species, via treatment of the bromide **9** with *tert*-butyl lithium in Et_2O at −78 °C, followed by addition of the aldehyde **8**, generated two epimeric alcohol adducts, which were subjected directly to Dess–Martin oxidation to give the (*Z*)-enone **7** in 53% overall yield. With the desired linear precursor **7** in hand, our envisaged endgame required a suitable acid treatment to cleave the TBS ether and acetonide groups, thereby inducing spiroacetalization of the resulting triol with the C11 ketone. However, our concerns over the intervention of competing undesired reaction pathways proved to be justified, as exposure of **7** to a range of acidic conditions (e.g., CSA, HCl, PPTS, TFA, H_2SiF_6, etc.) led to intractable complex mixtures of products. We reasoned that possible side-reactions, including hetero-Michael additions to the enone or dienoate, or acid-mediated eliminations, might be avoided by a selective cleavage of the TBS ether of **7** to generate a mixture of hemiacetal products that could subsequently be converted into the desired spiroacetals via acetonide cleavage. In the event, treatment of **7** with HF·pyridine in THF induced deprotection of the TBS ether. Fortuitously, cleavage of the acetonide was also observed, followed by in situ cyclization to give both spiroacetal epimers **25** and **26** (ca. 1:1 mixture). Unfortunately, the yield for this reaction was unacceptably low (20%) and proved unreliable upon scale-up. Detailed ^1H NMR analysis of the by-products revealed that significant dehydration had occurred and, as such, water was added as a co-solvent in the reaction. Pleasingly, treatment of **7** with HF·pyridine in THF/H_2O (10:1) again generated **25** and **26** as a roughly equimolar mixture, but in an improved yield (57%). These compounds were readily separable by chromatography and could be assigned by comparison of the ^1H NMR spectra with those of the natural acids. Specifically, the double anomeric effect stabilization experienced by pteridic acid A ethyl ester **25**, which places the C14 ethyl and C15 methyl substituents in pseudo-axial positions (cf. Fig. 2), is evidenced by a small H14–H15 coupling constant ($J_{14-15}\leq$ 1 Hz). In contrast, pteridic acid B ethyl ester **26**, with the epimeric C11 configuration, benefits from a bis-equatorial arrangement of these substituents, resulting in a correspondingly large coupling constant (J_{14-15}=9.9 Hz) between the two (axial) protons.

At this stage, all that remained was saponification of the esters to produce the corresponding acids, avoiding any potential equilibration at the C11-acetal centre. Separate treatment of the epimeric ethyl esters with KOH in EtOH generated pteridic acids A (**25**→**5**, 76%) and B (**26**→**6**, 73%). The spectroscopic data obtained (^1H, ^{13}C NMR, MS, IR) and the specific rotation, $[\alpha]_D^{20}$ +20.7 (*c* 0.07, $CHCl_3$) cf. +22.3 (*c* 1.0, $CHCl_3$) for **5** and $[\alpha]_D^{20}$ −21.8 (*c* 0.22, $CHCl_3$) cf. −20.8 (*c* 0.68, $CHCl_3$) for **6**, correlated fully with that reported previously for pteridic acids A and B.[6,7]



Scheme 4. (a) ^{t}BuLi, Et_2O, −78 °C, **8**, −78 °C; (b) DMP, $NaHCO_3$, CH_2Cl_2, rt; (c) HF·pyridine, THF/H_2O (10:1), 0 °C→rt; (d) KOH (aq), EtOH, rt.

3. Conclusions

In conclusion, we have developed an expedient synthetic route to pteridic acids A and B that proceeds in a combined 10.6% yield over 12 steps from ketone **10**. Key features are the use of our versatile boron aldol methodology to configure the majority of the stereocentres, with both C11-epimers being generated via a late-stage spiroacetalization reaction.

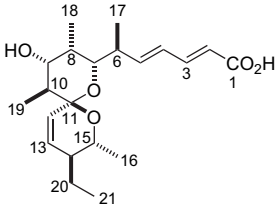
4. Experimental

4.1. Molecular modelling

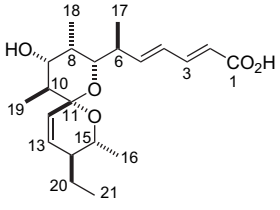
Molecular modelling was performed using Macromodel (Version 8.0). To thoroughly probe the conformational potential surface, a 10,000 step Monte Carlo Multiple Minimum search was performed using the MM2 force field in conjunction with the generalized Born/surface area (GB/SA) chloroform solvent model.

4.2. Compound numbering

The numbering system introduced by Igarashi has been adopted.[6]



5: Pteridic Acid A



6: Pteridic Acid B

4.3. Experimental section

4.3.1. Ketone **12**

To a stirred solution of dicyclohexylboron chloride (278 μL, 1.31 mmol) in dry Et_2O (2 mL) at −78 °C was added Et_3N (226 μL, 1.62 mmol). Ketone **10**[9] (297 mg, 1.25 mmol) in Et_2O (2 mL) was added via cannula and the reaction mixture allowed to warm to 0 °C over 1 h before recooling to −78 °C. A solution of aldehyde **11**[10] (278 mg, 1.37 mmol) in Et_2O (3 mL) was added via cannula and the resulting solution was stirred for a further 3 h before placing in the freezer overnight (−20 °C). MeOH (2 mL) and pH 7 buffer (2 mL) were then added dropwise, followed by H_2O_2 (1 mL, 30%). The mixture was stirred vigorously at rt for 1 h and the phases separated. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:6 Et_2O/pet. ether) afforded ketone **12** (525 mg, 87%, >99:1 dr) as a colourless oil. R_f 0.29 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ +15.5 (*c* 1.55, $CHCl_3$); IR (neat) 3483, 2956, 2934, 2882, 2858, 1712, 1613, 1587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (2H, d, *J*=8.6 Hz, PhH_a), 6.86 (2H, d, *J*=8.6 Hz, PhH_b), 4.44 (1H, d, *J*=11.7 Hz, $CH_{2a}Ph$), 4.39 (1H, d, *J*=11.7 Hz, $CH_{2b}Ph$), 4.01 (1H, dt, *J*=9.4, 2.3 Hz, H9), 3.80 (3H, s, OMe), 3.71 (1H, dd, *J*=9.8, 4.3 Hz, $H11_a$), 3.67 (1H, dd, *J*=9.8, 5.3 Hz, $H11_b$), 3.64 (1H, dd, *J*=8.7, 8 Hz, $H5_a$), 3.43 (1H, dd, *J*=9, 5.1 Hz, $H5_b$), 3.12 (1H, d, *J*=2.5 Hz, 9-OH), 3.09−3.04 (1H, m, H6), 2.84 (1H, dq, *J*=9.4, 7.1 Hz, H8), 1.75−1.69 (1H, m, H10), 1.06 (3H, d, *J*=7.0 Hz, Me17), 0.93 (3H, d, *J*=7.0 Hz, Me18), 0.91 (3H, d, *J*=7.0 Hz, Me19), 0.89 (9H, s, Si*t*Bu), 0.06 (3H, s, SiMe), 0.05 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 159.2, 130.1, 129.2, 113.8, 75.1, 73.0, 72.2, 68.0, 55.3, 49.5, 46.2, 36.0, 25.9, 18.3, 13.5, 13.0, 9.2, −5.5, −5.5; HRMS (ES^+) calcd for $C_{24}H_{43}O_5Si$ ($[M+H]^+$): 439.2874, found: 439.2877.

4.3.2. Diol **13**

A solution of tetramethylammonium triacetoxyborohydride (90 mg, 0.34 mmol) in MeCN (6.5 mL) and AcOH (2.5 mL) was stirred at rt for 1 h. The mixture was cooled to −40 °C and a solution of ketone **12** (30 mg, 0.07 mmol) in MeCN (10 mL) added via cannula. The resulting solution was stirred at −40 °C for 1 h and then stirred at −30 °C overnight. The reaction was quenched by the addition of satd aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). Satd aqueous sodium potassium tartrate (10 mL) was added and the mixture stirred vigorously for 1 h. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (1:3 Et_2O/pet. ether) afforded diol **13** (26 mg, 87%, 95:5 dr) as a colourless oil. R_f 0.13 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ +17.2 (*c* 1.47, $CHCl_3$); IR (neat) 3446, 2958, 2930, 2858, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.5 Hz, PhH_a), 6.87 (2H, d, *J*=8.6 Hz, PhH_b), 4.48 (1H, d, *J*=11.4 Hz, $CH_{2a}Ph$), 4.43 (1H, d, *J*=11.4 Hz, $CH_{2b}Ph$), 3.93 (1H, d, *J*=9.5 Hz, H7), 3.84−3.80 (2H, m, H9 and 7-OH), 3.80 (3H, s, OMe), 3.79 (1H, obs. dd, *J*=9.7, 3.6 Hz, $H11_a$), 3.70 (1H, dd, *J*=9.7, 3.8 Hz, $H11_b$), 3.57 (1H, dd, *J*=9, 4.4 Hz, $H5_a$), 3.52 (1H, t, *J*=8.8 Hz, $H5_b$), 3.52−3.50 (1H, obs. s, 9-OH), 2.04−1.93 (1H, m, H6), 1.80−1.73 (1H, m, H10), 1.69 (1H, quint, *J*=6.9, 3.7 Hz, H8), 0.99 (3H, d, *J*=7.0 Hz, Me19), 0.89 (9H, s, Si*t*Bu), 0.84 (3H, d, *J*=6.9 Hz, Me18), 0.79 (3H, d, *J*=6.9 Hz, Me17), 0.06 (6H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 129.8, 129.4, 113.9, 75.8, 75.4, 73.2, 69.0, 55.3, 37.3, 36.4, 36.0, 25.9, 18.2, 13.1, 9.9, 9.2, −5.5, −5.6; HRMS (ES^+) calcd for $C_{24}H_{45}O_5Si$ ($[M+H]^+$): 441.3031, found: 441.3032.

4.3.3. Acetonide **14**

To a stirred solution of diol **13** (73 mg, 0.17 mmol) in 2,2-dimethoxypropane (2 mL) at rt was added PPTS (30 mg, 0.12 mmol). The resulting solution was stirred at rt for 16 h before quenching by the addition of satd aqueous $NaHCO_3$ (2 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×2 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo, and flash chromatography (1:1 Et_2O/pet. ether) afforded acetonide **14** (80 mg, 99%) as a colourless oil. R_f 0.71 (1:1 Et_2O/pet. ether); $[\alpha]_D^{20}$ −8.5 (*c* 2.27, $CHCl_3$); IR (neat) 2956, 2932, 2857, 1614, 1587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J*=8.5 Hz, PhH_a), 6.88 (2H, d, *J*=8.6 Hz, PhH_b), 4.41 (2H, app. s, CH_2Ph), 3.80 (3H, s, OMe), 3.57 (1H, dd, *J*=11.0, 4.2 Hz, H9), 3.55 (1H, dd, *J*=8.5, 3.0 Hz, $H11_a$), 3.51 (1H, dd, *J*=9.4, 7.8 Hz, $H5_a$), 3.45−3.41 (2H, m, $H5_b$ and H7), 3.38 (1H, dd, *J*=8.7, 6.5 Hz, $H11_b$), 1.84 (2H, m, H8 and H10), 1.70−1.62 (1H, m, H6), 1.29 (3H, s, Me), 1.25 (3H, s, Me), 0.95 (3H, d, *J*=6.7 Hz, Me18), 0.89 (9H, s, Si*t*Bu), 0.87 (3H, d, *J*=6.9 Hz, Me17), 0.85 (3H, d, *J*=6.7 Hz, Me19), 0.04 (3H, s, SiMe), 0.04 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 131.1, 129.1, 113.7, 100.4, 73.9, 72.8, 72.4, 70.4, 65.0, 55.3, 39.3, 35.0, 33.8, 25.9, 25.0, 23.6, 18.2, 13.5, 11.6, 10.8, −5.4, −5.4; HRMS (ES^+) calcd for $C_{27}H_{49}O_5Si$ ($[M+H]^+$): 481.3344, found: 481.3350.

4.3.4. Alcohol **15**

To a solution of acetonide **14** (53 mg, 0.11 mmol) in EtOAc (2 mL) at rt was added $Pd(OH)_2$ (20 wt % on carbon, 15 mg, 0.11 mmol). The resulting suspension was stirred for 5 min before being evacuated/filled with H_2 gas five times and then left under a positive pressure of H_2 for 2.5 h. The mixture was filtered through a thin layer of Celite, eluting with Et_2O (3×10 mL) and the filtrate then concentrated in vacuo. Flash chromatography (1:9 Et_2O/pet. ether → 100% Et_2O) afforded alcohol **15** (33 mg, 83%) as a colourless oil. R_f 0.19 (1:9 Et_2O/pet. ether); $[\alpha]_D^{20}$ +10.4 (*c* 1.64, $CHCl_3$); IR (neat)

2957, 2929, 2858, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.61 (1H, dd, J=10.4, 4.1 Hz, H7), 3.58 (1H, dd, J=9.6, 8.4 Hz, $H5_a$), 3.52 (1H, td, J=9.9, 3.1 Hz, $H5_b$), 3.47 (1H, dd, J=9.7, 2.7 Hz, $H11_a$), 3.46 (1H, dd, J=7.8, 2.8 Hz, H9), 3.43 (1H, dd, J=9.6, 5.6 Hz, $H11_b$), 3.27 (1H, d, J=9.2 Hz, 5-OH), 1.95–1.87 (1H, m, H6), 1.87–1.81 (1H, m, H8), 1.70–1.63 (1H, m, H10), 1.35 (3H, s, Me), 1.30 (3H, s, Me), 0.89 (9H, s, Si^{t}Bu), 0.87 (3H, d, J=6.8 Hz, Me18), 0.87 (3H, d, J=6.8 Hz, Me19), 0.77 (3H, d, J=6.8 Hz, Me17), 0.03 (3H, s, SiMe), 0.03 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.6, 76.3, 73.5, 69.2, 64.8, 39.2, 35.2, 35.0, 25.9, 25.2, 23.6, 18.2, 12.7, 11.7, 10.6, −5.4, −5.4; HRMS (ES^+) calcd for $C_{19}H_{41}O_4Si$ ($[M+H]^+$): 361.2769, found: 361.2764.

4.3.5. Aldehyde **16**

To a stirred solution of alcohol **15** (137 mg, 0.38 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added $NaHCO_3$ (48 mg, 0.57 mmol) followed by Dess–Martin periodinane (242 mg, 0.57 mmol). The resultant mixture was stirred at rt for 1 h, before being quenched with satd aqueous $NaHCO_3$ (6 mL) and sodium thiosulfate (6 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:49→1:19 Et_2O/pet. ether) afforded aldehyde **16** (146 mg, 96%) as a colourless oil. R_f 0.41 (1:9 Et_2O/hexane); $[\alpha]_D^{20}$ −28.9 (*c* 1.49, $CHCl_3$); IR (neat) 2957, 2933, 2859, 1733, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.69 (1H, d, J=3.0 Hz, H5), 3.90 (1H, dd, J=10.9, 4.4 Hz, H7), 3.53–3.48 (2H, m, H9 and $H11_a$), 3.45 (1H, dd, J=9.8, 5.5 Hz, $H11_b$), 2.53–2.45 (1H, m, H6), 1.93–1.86 (1H, m, H8), 1.72–1.64 (1H, m, H10), 1.29 (3H, s, Me), 1.27 (3H, s, Me), 0.98 (3H, d, J=6.9 Hz, Me17), 0.89 (9H, s, Si^{t}Bu), 0.88 (3H, d, J=6.1 Hz, Me19), 0.88 (3H, d, J=7.0 Hz, Me18), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 100.7, 73.5, 70.5, 64.8, 46.0, 39.2, 34.7, 25.9, 25.0, 23.4, 18.2, 11.7, 10.7, 10.1, −5.4, −5.5; HRMS (ES^+) calcd for $C_{19}H_{39}O_4Si$ ($[M+H]^+$): 359.2612, found: 359.2614.

4.3.6. Dienoate **17**

To a solution of triethyl-4-phosphonocrotonate (254 mg, 1.01 mmol) in THF (4 mL) at −78 °C was added LiHMDS (0.97 mL, 1 M in THF, 0.97 mmol) and the resultant solution stirred for 10 min. A solution of aldehyde **14** (146 mg, 0.41 mmol) in THF (2 mL) was then added slowly via cannula and the reaction mixture allowed to warm to −25 °C and stirred for 1.5 h. The reaction was then allowed to warm to rt and quenched by the addition of satd aqueous NH_4Cl (6 mL). The aqueous phase was extracted with Et_2O (3×7 mL) and the combined organic phases dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:19 Et_2O/pet. ether) afforded dienoate **17** (167 mg, 90%) as a colourless oil. R_f 0.28 (1:19 Et_2O/pet. ether); $[\alpha]_D^{20}$ −5.2 (*c* 1.70, $CHCl_3$); IR (neat) 2959, 2935, 2858, 1717, 1643, 1618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (1H, obs. dd, J=15.3, 10.3 Hz, H3), 6.21 (1H, dd, J=15.4, 10.3 Hz, H4), 6.14 (1H, dd, J=15.4, 6.8 Hz, H5), 5.79 (1H, d, J=15.4 Hz, H2), 4.20 (2H, q, J=7.1 Hz, CO_2CH_2Me), 3.50 (1H, dd, J=9.5, 7.9 Hz, $H11_a$), 3.47–3.41 (3H, m, H7, H9 and $H11_b$), 2.44–2.36 (1H, m, H6), 1.92–1.84 (1H, m, H8), 1.70–1.62 (1H, m, H10), 1.29 (3H, t, J=7.1 Hz, CO_2CH_2Me), 1.28 (3H, s, Me), 1.23 (3H, s, Me), 0.98 (3H, d, J=6.7 Hz, Me17), 0.89 (9H, s, Si^{t}Bu), 0.87 (3H, d, J=7.1 Hz, Me19), 0.86 (3H, d, J=6.8 Hz, Me18), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 147.9, 145.3, 127.5, 119.3, 100.6, 73.7, 73.2, 64.9, 60.1, 39.3, 36.8, 35.2, 25.9, 24.9, 23.6, 18.2, 15.8, 14.3, 11.7, 10.7, −5.4, −5.4; HRMS (EI) calcd for $C_{25}H_{46}O_5Si$ ($[M]^+$): 454.3109, found: 454.3107.

4.3.7. Alcohol **18**

To a stirred solution of dienoate **17** (630 mg, 1.39 mmol) in THF (15 mL) at 0 °C was added tetrabutylammonium flouride (1.66 mL, 1 M in THF, 1.66 mmol) dropwise. The resulting solution was stirred at rt for 3 h before quenching by the addition of satd aqueous NH_4Cl (15 mL). The resultant biphasic mixture was stirred vigorously before concentration in vacuo. The remaining aqueous phase was extracted with Et_2O (4×15 mL) and the combined organic phases dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:2 Et_2O/pet. ether) afforded alcohol **18** (435 mg, 92%) as a colourless oil. R_f 0.17 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ +14.1 (*c* 1.21, $CHCl_3$); IR (neat) 3467, 2982, 2936, 2878, 1713, 1642, 1618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (1H, obs. dd, J=15.3, 10.5 Hz, H3), 6.21 (1H, dd, J=15.4, 10.6 Hz, H4), 6.13 (1H, dd, J=15.4, 7 Hz, H5), 5.80 (1H, d, J=15.4 Hz, H2), 4.20 (2H, q, J=7.1 Hz, CO_2CH_2Me), 3.68–3.62 (2H, m, H11), 3.51 (1H, dd, J=7.3, 2.8 Hz, H9), 3.47 (1H, dd, J=10.3, 4.1 Hz, H7), 2.44–2.36 (1H, m, J=10.6, 6.8 Hz, H6), 2.34–2.30 (1H, m, 11-OH), 1.98–1.90 (1H, m, H8), 1.88–1.80 (1H, m, H10), 1.32 (3H, s, Me), 1.29 (2H, t, J=7.1 Hz, CO_2CH_2Me), 1.26 (3H, s, Me), 0.99 (3H, d, J=6.8 Hz, Me17), 0.97 (3H, d, J=7.1 Hz, Me19), 0.90 (3H, d, J=6.7 Hz, Me18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 147.3, 145.1, 127.7, 119.5, 100.8, 77.4, 73.2, 66.9, 60.2, 37.8, 36.7, 34.4, 25.0, 23.5, 15.7, 14.3, 12.2, 10.7; HRMS (ES^+) calcd for $C_{19}H_{33}O_5$ ($[M+H]^+$): 341.2323, found: 341.2321.

4.3.8. Aldehyde **8**

To a stirred solution of alcohol **18** (68 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added $NaHCO_3$ (22 mg, 0.26 mmol) followed by Dess–Martin periodinane (106 mg, 0.25 mmol). The resultant mixture was stirred at rt for 1 h, before being quenched with satd aqueous $NaHCO_3$ (3 mL) and sodium thiosulfate (3 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3×7 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:6→1:1 Et_2O/pet. ether) afforded aldehyde **8** (64 mg, 95%) as a yellow oil. R_f 0.38 (1:1 Et_2O/pet. ether); $[\alpha]_D^{20}$ +37.6 (*c* 2.03, $CHCl_3$); IR (neat) 2983, 2938, 2878, 1712, 1642, 1618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.70 (1H, d, J=0.9 Hz, H11), 7.25 (1H, dd, J=15.3, 10.6 Hz, H3), 6.21 (1H, dd, J=15.4, 10.6 Hz, H4), 6.12 (1H, dd, J=15.4, 7.1 Hz, H5), 5.80 (1H, d,

J=15.4 Hz, H2), 4.19 (2H, q, J=7.1 Hz, CO_2CH_2Me), 3.76 (1H, dd, J=7.4, 3.4 Hz, H9), 3.48 (1H, dd, J=10.3, 4.3 Hz, H7), 2.44–2.40 (2H, m, H6 and H10), 1.95 (1H, qnd, J=7, 2.6 Hz, H8), 1.30 (3H, s, Me), 1.29 (3H, t, J=7.1 Hz, CO_2CH_2Me), 1.24 (3H, s, Me), 1.15 (3H, d, J=7.0 Hz, Me19), 0.98 (3H, d, J=6.8 Hz, Me17), 0.93 (3H, d, J=6.7 Hz, Me18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 167.3, 147.1, 145.1, 127.8, 119.6, 101.1, 73.9, 72.9, 60.2, 49.0, 36.7, 34.8, 24.6, 23.4, 15.7, 14.3, 12.0, 8.0; HRMS (EI) calcd for $C_{19}H_{30}O_5$ ($[M]^+$): 339.2166, found: 339.2167.

4.3.9. Ketone **21**

To a stirred solution of Weinreb amide **20**[16a] (1.27 g, 9.52 mmol) in THF (20 mL) at 0 °C was added *n*-PrMgCl (14.3 mL, 2 M in Et_2O, 28.6 mmol) dropwise. The resulting solution was stirred at 0 °C for 2 h, allowed to warm to rt and stirred for a further 1.5 h. The reaction was quenched by the addition of satd aqueous NH_4Cl (20 mL) and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the combined organic phases dried ($MgSO_4$) were concentrated in vacuo to afford a colourless oil, which was then taken up in THF (20 mL). Benzoic anhydride (3.23 g, 14.3 mmol) and 4-dimethylaminopyridine (47 mg, 0.38 mmol) were added at rt, followed by the dropwise addition of diisopropylethylamine (2.15 mL, 15.3 mmol). The mixture was stirred at rt for 16 h before the dropwise addition of dimethylethylenediamine (1.15 mL, 10.5 mmol). Stirring was continued for a further 1.5 h before the addition of water (15 mL). The phases were separated and the aqueous phase extracted with Et_2O (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:9 Et_2O/hexane) afforded ketone **21** (1.34 g, 64%) as a colourless oil. R_f 0.19 (1:9 Et_2O/hexane); spectroscopic data identical to that reported for *ent*-**21**.[16b]

4.3.10. Ketone **22**

To a solution of dicyclohexylboron chloride (4.2 mL, 19.8 mmol) in Et_2O (50 mL) at −78 °C was added dimethylethylamine (2.57 mL, 23.7 mmol). The resulting solution was stirred for 15 min and a solution of ketone **20** (2.91 g, 13.2 mmol) in Et_2O (10 mL) then added dropwise via cannula. After allowing to warm to 0 °C and stirring for 1.25 h, the reaction mixture was cooled to −85 °C and freshly distilled acetaldehyde (2.22 mL, 39.4 mmol) was added. The resultant slurry was stirred for 1 h at −85 °C, 1.7 h at −78 °C, and then placed in the freezer (−20 °C) overnight. After warming to 0 °C, MeOH (15 mL) and pH 7 buffer (15 mL) were added, followed by the dropwise addition of H_2O_2 (15 mL, 30%). The resultant biphasic mixture was stirred vigorously at rt for 1 h before the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with satd aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:2 Et_2O/pet. ether) afforded **22** as a white solid. R_f 0.13 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ +48.4 (c 1.74, $CHCl_3$); IR (neat) 3311, 2968, 2939, 1730, 1717, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (2H, d, J=7.5 Hz, o-PhH), 7.58 (1H, t, J=7.4 Hz, p-PhH), 7.46 (2H, t, J=7.7 Hz, m-PhH), 5.48 (1H, q, J=7.1 Hz, CHMeOBz), 4.02 (1H, dq, J=6.5, 6.3 Hz, H15), 2.84 (1H, dd, J=12.9, 6.5 Hz, H14), 2.45 (1H, d, J=6.9 Hz, 15-OH), 1.83–1.71 (2H, m, H20), 1.57 (3H, d, J=7.1 Hz, CHMeOBz), 1.23 (3H, d, J=6.4 Hz, Me16), 1.00 (3H, t, J=7.5 Hz, Me21); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 165.8, 133.3, 129.8, 129.5, 128.5, 75.3, 67.9, 55.9, 22.4, 21.6, 15.8, 11.5; HRMS (ES^+) calcd for $C_{15}H_{21}O_4$ ($[M+H]^+$): 265.1434, found: 265.1436.

4.3.11. Silyl ether **19**

To a stirred solution of ketone **22** in DMF (15 mL) at 0 °C was added *tert*-butyldimethylchlorosilane (7.22 g, 47.9 mmol), followed by imidazole (6.28 g, 88.3 mmol) and DMAP (373 mg, 3.05 mmol). The reaction mixture was allowed to warm to rt and stirred for 3 h before the addition of water (30 mL). The phases were then separated and the aqueous phase extracted with CH_2Cl_2 (4×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:9 Et_2O/pet. ether) afforded silyl ether **19** (4.57 g, 91%) as a colourless oil. R_f 0.23 (1:19 Et_2O/pet. ether); $[\alpha]_D^{20}$ −7.6 (c 1.69, $CHCl_3$); IR (neat) 2959, 2932, 2885, 2858, 1721, 1603 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (2H, d, J=7.1 Hz, o-PhH), 7.58 (1H, t, J=7.4 Hz, p-PhH), 7.46 (2H, t, J=7.8 Hz, m-PhH), 5.47 (1H, q, J=6.9 Hz, CHMeOBz), 4.02 (1H, app. dq, J=8.1, 6.1 Hz, H15), 2.84 (1H, td, J=8.8, 3.8 Hz, H14), 1.70–1.61 (1H, m, $H20_a$), 1.61–1.52 (1H, m, $H20_b$), 1.51 (3H, d, J=6.9 Hz, CHMeOBz), 1.16 (3H, d, J=6.1 Hz, Me16), 0.93 (3H, t, J=7.5 Hz, Me21), 0.84 (9H, s, Si^{t}Bu), 0.03 (3H, s, SiMe), −0.03 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4, 165.6, 133.1, 129.9, 129.8, 128.4, 75.9, 69.9, 57.1, 25.8, 22.0, 21.7, 17.9, 15.2, 11.6, −4.7, −4.8; HRMS (ES^+) calcd for $C_{21}H_{35}O_4Si$ ($[M+H]^+$): 379.2299, found: 379.2303.

4.3.12. Aldehyde **23**

To a stirred solution of silyl ether **19** (2.74 g, 7.23 mmol) in MeOH (23 mL) at rt was added sodium borohydride (549 mg, 14.5 mmol) and the resulting mixture was stirred for 30 min. After cooling to 0 °C, potassium carbonate (4.00 g, 28.9 mmol) was added and the mixture was allowed to warm to rt and stirred for a further 6 h. Water (15 mL) and pH 7 buffer (15 mL) were added and the biphasic mixture extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Residual methyl benzoate was removed by flash chromatography (1:4 → 100% Et_2O/pet. ether) to give a colourless oil, which was dissolved in MeOH (84 mL) and pH 7 buffer (15 mL). Sodium periodate (5.19 g, 24.2 mmol) was added and the resultant slurry stirred at rt for 3 h before water (60 mL) was added. The resultant biphasic mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phases were then dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:4 Et_2O/pet. ether) afforded aldehyde **23** (1.53 g, 92%) as a yellow oil. R_f 0.66 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ −17.7 (c 2.05, $CHCl_3$); IR (neat) 2959, 2932, 2883, 2859, 1727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (1H, d, J=3.8 Hz, H13), 4.07 (1H, qd, J=6.1,

5.1 Hz, H15), 2.12–2.06 (1H, m, H14), 1.78–1.68 (1H, m, $H20_a$), 1.57–1.50 (1H, m, $H20_b$), 1.21 (3H, d, J=6.3 Hz, Me16), 0.91 (3H, t, J=7.5 Hz, Me21), 0.87 (9H, s, Si^{t}Bu), 0.06 (3H, s, SiMe), 0.06 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5, 68.9, 61.1, 25.7, 22.3, 19.5, 17.9, 11.8, −4.2, −5.0; HRMS (ES^+) calcd for $C_{12}H_{27}O_2Si$ ($[M+H]^+$): 231.1775, found: 231.1774.

4.3.13. Vinyl dibromide **24**

To a solution of CBr_4 (493 mg, 1.48 mmol) [dried by stirring under vacuum (1 mmHg) at rt for 1.5 h] in CH_2Cl_2 (2 mL) at 0 °C was added a solution of triphenylphosphine (771 mg, 2.94 mmol) in CH_2Cl_2 (2.3 mL). The resultant solution was stirred for 5 min and triethylamine (100 μL, 0.74 mmol) was added dropwise. After cooling to −55 °C, a solution of aldehyde **23** (171 mg, 0.74 mmol) in CH_2Cl_2 (1.7 mL) was added via cannula. The reaction mixture was stirred for 2.5 h, before being warmed to 0 °C and quenched with satd aqueous $NaHCO_3$ (6 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (pet. ether) afforded vinyl dibromide **24** (279 mg, 97%) as a colourless oil. R_f 0.50 (pet. ether); $[\alpha]_D^{20}$ +25.0 (*c* 2.75, $CHCl_3$); IR (neat) 2959, 2930, 2858, 1618 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (1H, d, J=10 Hz, H13), 3.84 (1H, qd, J=6.2, 3.4 Hz, H15), 2.25 (1H, tdd, J=9.3, 5.0, 3.5 Hz, H14), 1.56–1.48 (1H, m, $H20_a$), 1.44–1.34 (1H, m, $H20_b$), 1.10 (3H, d, J=6.2 Hz, Me16), 0.90 (3H, t, J=7.5 Hz, Me21), 0.89 (9H, s, Si^{t}Bu), 0.05 (6H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 88.7, 69.6, 53.3, 25.8, 23.9, 21.9, 18.0, 11.8, −4.2, −4.9; HRMS (ES^-) calcd for $C_{13}H_{26}Br_3OSi$ ($[M+Br]^-$): 462.9309, found: 462.9293.

4.3.14. Vinyl bromide **9**

Vinyl dibromide **24** (300 mg, 0.78 mmol) was azeotroped from benzene before being dissolved in benzene (4 mL). Tributyltin hydride (0.31 mL, 0.14 mmol) was added dropwise and the solution degassed, before freshly prepared $Pd(PPh_3)_4$ (135 mg, 0.15 mol) was added, and stirred for 3.7 h. The reaction mixture was concentrated cautiously in vacuo and flash chromatography (pet. ether) afforded vinyl bromide **9** (196 mg, 82%) as a colourless oil. R_f 0.44 (pet. ether); $[\alpha]_D^{20}$ +22.8 (*c* 1.40, $CHCl_3$); IR (neat) 2959, 2930, 2858, 1646, 1622 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (1H, d, J=7.0 Hz, H12), 6.01 (1H, dd, J=9.7, 7.1 Hz, H13), 3.89 (1H, qd, J=6.3, 2.9 Hz, H15), 2.49 (1H, tdd, J=9.3, 5.0, 2.9 Hz, H14), 1.59–1.50 (1H, m, $H20_a$), 1.44–1.34 (1H, m, $H20_b$), 1.08 (3H, d, J=6.3 Hz, Me16), 0.89 (3H, t, J=7.5 Hz, Me21), 0.88 (9H, s, Si^{t}Bu), 0.05 (3H, s, SiMe), 0.05 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 108.8, 69.8, 49.3, 25.8, 24.0, 21.7, 18.0, 11.8, −4.2, −4.9.

4.3.15. Enone **7**

Prior to reaction, aldehyde **8** (177 mg, 0.52 mmol) was azeotroped from benzene, dissolved in dry Et_2O (2.4 mL) and further dried over CaH_2 for 1 h. Vinyl bromide **9** (233 mg, 0.76 mmol) was also azeotroped from benzene and then dissolved in dry Et_2O (5 mL) and cooled to −78 °C. ^{t}BuLi (0.81 mL, 1.7 M in pentane) was added dropwise and the resulting solution stirred for 10 min before addition of the ethereal solution of aldehyde **8** via cannula. The reaction mixture was stirred at −78 °C for 50 min, allowed to warm to 0 °C and quenched by the addition of satd aqueous NH_4Cl (10 mL). The phases were separated and the aqueous phase extracted with Et_2O (3×10 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated in vacuo to give an oil, which was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. $NaHCO_3$ (62 mg, 0.74 mmol) and Dess–Martin periodinane (306 mg, 0.72 mmol) were added and the resulting suspension stirred at rt for 2.5 h. Satd aqueous $NaHCO_3$ (8 mL) and sodium thiosulfate (8 mL) were added and the mixture was stirred for a further 30 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:30→1:19→1:1 Et_2O/pet. ether) yielded enone **7** (171 mg, 53%) as a yellow oil. R_f 0.54 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ +71.0 (*c* 1.72, $CHCl_3$); IR (neat) 2960, 2933, 2878, 2858, 1716, 1689, 1643, 1617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, dd, J=15.3, 10.6 Hz, H3), 6.38 (1H, d, J=11.8 Hz, H12), 6.20 (1H, dd, J=15.5, 10.6 Hz, H4), 6.12 (1H, dd, J=15.8, 6.7 Hz, H5), 6.11 (1H, dd, J=11.7, 10.3 Hz, H13), 5.79 (1H, d, J=15.4 Hz, H2), 4.20 (2H, q, J=7.1 Hz, CO_2CH_2Me), 3.90 (1H, qd, J=6.3, 2.7 Hz, H15), 3.59 (1H, dd, J=6.6, 4.9 Hz, H9), 3.45 (1H, dd, J=10.4, 4 Hz, H7), 3.35 (1H, dddd, J=10.6, 7.6, 5.4, 2.5 Hz, H14), 2.67 (1H, qd, J=6.9, 4.9 Hz, H10), 2.41–2.32 (1H, m, H6), 1.93–1.86 (1H, qnd, J=6.7, 4.1 Hz, H8), 1.56–1.51 (1H, m, $H20_a$), 1.36–1.30 (1H, m, $H20_b$), 1.29 (3H, t, J=7.1 Hz, CO_2CH_2Me), 1.28 (3H, s, Me), 1.24 (3H, s, Me), 1.13 (3H, d, J=6.9 Hz, Me19), 1.05 (3H, d, J=6.3 Hz, Me16), 0.95 (3H, d, J=6.8 Hz, Me17), 0.91 (3H, d, J=6.7 Hz, Me18), 0.88 (9H, s, Si^{t}Bu), 0.83 (3H, t, J=7.5 Hz, Me21), 0.05 (3H, s, SiMe), 0.04 (3H, s, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 167.4, 150.4, 147.6, 145.2, 127.6, 127.4, 119.4, 100.8, 75.5, 72.8, 69.9, 60.2, 50.8, 46.7, 36.7, 35.5, 25.8, 25.0, 24.8, 23.5, 22.3, 18.0, 15.6, 14.3, 12.1, 11.9, 11.3, −4.2, −4.9; HRMS (ES^+) calcd for $C_{32}H_{57}O_6Si$ ($[M+H]^+$): 565.3919, found: 565.3921.

4.3.16. Esters **25** and **26**

To a solution of TBS ether **7** (12 mg, 21.2 μmol) in THF/H_2O (10:1, 1.65 mL) in a polypropylene vessel at 0 °C was added HF·pyridine (300 μL). After 16 h at rt, the reaction mixture was partitioned between satd aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (7 mL). The phases were separated and the aqueous phase washed with CH_2Cl_2 (3×7 mL). The combined organic phases were then dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (1:4→1:3 EtOAc/pet. ether) afforded esters **25** (2.5 mg, 30%) and **26** (2.3 mg, 27%) as colourless oils. **25** had R_f 0.35 (30% EtOAc/40–60 pet. ether); $[\alpha]_D^{20}$ +21.3 (*c* 0.15, MeOH); IR (neat) 3438, 2972, 1715, 1638, 1140, 1032, 996 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.53 (1H, dd, J=15.4, 7.5 Hz, H3), 6.06 (1H, dd, J=15.3, 7.5 Hz, H5), 5.97 (1H, dd, J=15.3, 10.9 Hz, H4), 5.91 (1H, d, J=15.3 Hz, H2), 5.65 (1H, ddd, J=10.0, 5.5, 1.1 Hz, H13),

Table 1
Comparison of ^{1}H NMR data for synthetic and natural pteridic acids A and B

Position	Natural pteridic acid A[6] ($CDCl_3$, 400 MHz)	Synthetic pteridic acid A ($CDCl_3$, 500 MHz)	Natural pteridic acid B[6] ($CDCl_3$, 400 MHz)	Synthetic pteridic acid B ($CDCl_3$, 500 MHz)
2	5.77 (1H, d, 15.4)	5.77 (1H, d, 15.4)	5.76 (1H, d, 15.4)	5.76 (1H, d, 15.3)
3	7.25 (1H, dd, 10.0, 15.4)	7.25 (1H, dd, 10.2, 15.4)	7.26 (1H, dd, 10.5, 15.4)	7.26 (1H, obscured)
4	6.18 (1H, dd, 9.8, 15.4)	6.18 (1H, dd, 9.9, 15.4)	6.24 (1H, dd, 10.5, 15.4)	6.23 (1H, dd, 10.6, 15.2)
5	6.25 (1H, dd, 6.8, 15.4)	6.25 (1H, dd, 6.9, 15.4)	6.14 (1H, dd, 7.5, 15.4)	6.13 (1H, dd, 7.2, 15.3)
6	2.48 (1H, ddq, 9.8, 6.8, 6.8)	2.48 (1H, ddq, 9.8, 6.9, 6.9)	2.53 (1H, ddq, 10.0, 6.8, 6.8)	2.53 (1H, m)
7	3.75 (1H, dd, 2.2, 10.0)	3.75 (1H, dd, 2.2, 10.0)	3.26 (1H, dd, 2.0, 9.8)	3.26 (1H, dd, 1.8, 9.9)
8	2.06 (1H, ddq, 2.2, 4.6, 6.8)	2.06 (1H, m)	2.07 (1H, ddq, 1.7, 4.9, 6.8)	2.07 (1H, m)
9	3.85 (1H, dd, 2.2, 10.0)	3.85 (1H, dd, 4.7, 10.9)	3.70 (1H, dd, 4.6, 11.2)	3.69 (1H, dd, 4.9, 11.4)
10	1.62 (1H, quint, 6.9)	1.63 (1H, q, 7.0)	1.78 (1H, dq, 11.4, 6.8)	1.78 (1H, dq, 11.4, 6.7)
12	5.51 (1H, dd, 1.2, 10.2)	5.51 (1H, dd, 1.1, 10.2)	5.92 (1H, dd, 1.9, 10.7)	5.92 (1H, dd, 1.8, 10.5)
13	5.96 (1H, ddd, 1.0, 5.8, 10.2)	5.96 (1H, dd, 5.9, 10.3)	5.89 (1H, d, 10.7)	5.89 (1H, br d, 10.9)
14	1.61 (1H, dq, 11.0, 6.8)	1.60 (1H, dq, 11.0, 6.7)	1.86 (1H, m)	1.85 (1H, m)
15	3.91 (1H, q, 6.8)	3.91 (1H, q, 6.9)	3.89 (1H, dq, 9.8, 6.1)	3.89 (1H, dq, 9.9, 6.0)
16	1.24 (3H, d, 6.8)	1.24 (3H, d, 7.0)	1.22 (3H, d, 6.1)	1.22 (3H, d, 6.2)
17	1.00 (3H, d, 6.8)	1.00 (3H, d, 6.9)	0.97 (3H, d, 6.8)	0.97 (3H, d, 6.7)
18	0.91 (3H, d, 7.0)	0.92 (3H, d, 6.9)	0.97 (3H, d, 6.8)	0.97 (2H, d, 6.9)
19	0.90 (3H, d, 6.8)	0.90 (3H, d, 7.0)	0.91 (3H, d, 6.8)	0.91 (3H, d, 6.7)
20	1.45 (2H, quint, 7.3)	1.45 (2H, quint, 7.3)	1.20 (1H, m), 1.49 (1H, m)	1.20 (1H, m), 1.49 (1H, m)
21	0.93 (3H, t, 7.3)	0.92 (3H, t, 7.3)	0.87 (3H, t, 7.6)	0.87 (3H, t, 7.5)

5.42 (1H, dd J=9.9, 0.7 Hz, H12), 4.06 (2H, q, J=7.1 Hz, CO_2CH_2Me), 3.84 (1H, br q, J=7.0 Hz, H15), 3.78 (1H, dt, J=10.8, 4.9 Hz, H9), 3.66 (1H, dd, J=9.8, 2.3 Hz, H7), 2.37−2.29 (1H, m, H6), 1.79−1.73 (1H, m, H8), 1.60−1.57 (1H, dq, J=11.1, 6.6 Hz, H10), 1.40−1.26 (3H, m, H14, and H20), 1.21 (3H, d, J=7.0 Hz, Me16), 1.00 (3H, d, J=6.7 Hz, Me19), 0.99 (3H, t, J=7.0 Hz, CO_2CH_2Me), 0.92 (3H, d, J=7.0 Hz, Me18), 0.77 (3H, t, J=7.1 Hz, Me21), 0.71 (3H, J=6.7 Hz, Me17); ^{13}C NMR (125 MHz, C_6D_6) δ 166.9, 148.8, 145.3, 129.6, 128.7, 127.4, 120.0, 97.0, 74.6, 72.2, 71.6, 60.0, 41.0, 40.7, 38.8, 36.8, 26.7, 23.1, 15.0, 14.3, 12.9, 12.0, 4.8; HRMS (ES^+) calcd for $C_{23}H_{36}O_5$ ($[M+Na]^+$): 415.2455, found: 415.2450. **26** had R_f 0.23 (30% EtOAc/40−60 pet. ether); $[\alpha]_D^{20}$ −19.3 (c 0.11, MeOH); IR (neat) 2967, 1714, 1639, 1456, 1262, 1005 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 (1H, dd, J=15.0, 10.5 Hz, H3), 6.05 (1H, dd, J=15.5, 11.0 Hz, H4), 5.96 (1H, d, J=14.9 Hz, H2), 5.91 (1H, dd, J=14.6, 6.7 Hz, H5), 5.65 (2H, m, H12 and H13), 4.12 (1H, dd, J=9.9, 6.1 Hz, H15), 4.07 (2H, q, J=7.3 Hz, CO_2CH_2Me), 3.29 (1H, dt, J=11.3, 5.3 Hz, H9), 2.97 (1H, dd, J=9.8, 2.3 Hz, H7), 2.35−2.26 (1H, m, H6), 1.79−1.73 (1H, dq, J=11.3, 6.7, H10), 1.75 (1H, ddd, J=9.9, 8.2, 3.9 Hz, H14), 1.70−1.64 (1H, m, H8), 1.30−1.23 (1H, m, H20a), 1.16−1.10 (1H, obs., H20b), 1.14 (3H, d, J=6.4 Hz, Me16), 1.05 (3H, t, J=6.9 Hz, Me19), 1.00 (3H, t, J=7.1 Hz, CO_2CH_2Me), 0.92 (3H, d, J=7.0 Hz, Me18), 0.82 (3H, t, J=7.5 Hz, Me21), 0.76 (3H, J=6.9 Hz, Me17); ^{13}C NMR (125 MHz, C_6D_6) δ 166.8, 148.2, 145.5, 133.7, 128.5, 124.6, 119.9, 98.0, 75.7, 73.9, 68.0, 60.0, 42.6, 41.0, 38.7, 36.7, 23.6, 19.6, 15.3, 14.3, 11.8, 10.1, 4.9; HRMS (ES^+) calcd for $C_{23}H_{36}NaO_5$ ($[M+Na]^+$): 415.2455, found: 415.2447.

4.3.17. Pteridic acid A **5**

To a solution of ester **25** (2.5 mg, 6.3 μmol) in EtOH/H_2O (2:1, 300 μL) at rt was added aqueous KOH (10%, 25 μL) dropwise. After 16 h at rt, the reaction mixture was partitioned between pH 4 buffer (1 mL) and CH_2Cl_2 (2 mL). The phases were separated and the aqueous phase washed with CH_2Cl_2 (5×2 mL). The combined organic phases were then dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (1:2→1:3 pet. ether/EtOAc) afforded pteridic acid A (1.7 mg, 76%) as a white solid. R_f 0.52 (8% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +20.7 (c 0.07, $CHCl_3$); IR (neat) 3718, 2964, 2927, 1692, 1640, 1261 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$), see Table 2; HRMS (ES^+) calcd for $C_{21}H_{32}NaO_5$ ($[M+Na]^+$): 387.2147, found: 387.2163.

Table 2
Comparison of ^{13}C NMR data for synthetic and natural pteridic acids A and B

Position	Natural pteridic acid A[6] ($CDCl_3$, 100 MHz)	Synthetic pteridic acid A ($CDCl_3$, 125 MHz)	Natural pteridic acid B[6] ($CDCl_3$, 100 MHz)	Synthetic pteridic acid B ($CDCl_3$, 125 MHz)
1	171.97	171.55	171.85	171.21
2	118.37	118.20	118.28	118.17
3	147.47	147.47	147.57	147.52
4	126.84	126.83	127.44	127.45
5	150.11	150.13	149.33	149.28
6	38.49	38.50	38.37	38.38
7	74.48	74.48	75.57	75.57
8	36.24	36.23	36.24	36.23
9	72.48	72.46	74.25	74.25
10	40.86	40.86	40.74	40.79
11	96.86	96.84	96.87	97.86
12	127.52	127.50	134.00	134.00
13	130.25	130.25	123.43	123.44
14	40.35	40.36	42.26	42.27
15	71.60	71.58	68.13	68.13
16	22.87	22.88	19.51	19.54
17	15.17	15.17	15.29	15.31
28	4.51	4.51	4.85	4.87
19	12.48	12.49	11.48	11.51
20	26.20	26.20	23.34	23.36
21	11.88	11.90	9.92	9.95

4.3.18. Pteridic acid B ***6***

An identical procedure was used on ester **26** (2.3 mg, 5.8 μmol) to that reported above. Flash chromatography (1:2→1:3 pet. ether/EtOAc) gave pteridic acid B (1.5 mg, 73%) as a white solid. R_f 0.50 (8% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ −21.8 (*c* 0.22, $CHCl_3$); IR (neat) 3726, 2968, 2929, 1689, 1639, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$), see Table 2; HRMS (ES^+) calcd for $C_{21}H_{32}NaO_5$ ($[M+Na]^+$): 387.2147, found: 387.2136.

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References and notes

1. Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.
2. (a) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Acena, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055; (b) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Oballa, R. M.; Wallace, D. J.; Norcross, R. D. *Org. Biomol. Chem.* **2005**, *3*, 2399; (c) Paterson, I.; Coster, M.; Chen, D. Y.-K.; Gibson, K. R.; Wallace, D. J. *Org. Biomol. Chem.* **2005**, *3*, 2410; (d) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Acena, J. L.; Bach, J.; Keown, L.; Trieselmann, T. *Org. Biomol. Chem.* **2005**, *3*, 2420; (e) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Acena, J. L.; Bach, J.; Wallace, D. J. *Org. Biomol. Chem.* **2005**, *3*, 2431.
3. Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett.* **2002**, *4*, 391.
4. Paterson, I.; Findlay, A. D.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6699.
5. (a) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Loiseleur, O.; Maltas, P.; Moessner, C. *Pure Appl. Chem.* **2007**, *79*, 667; (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Genovino, J.; Lim, J. H.; Moessner, C. *Chem. Commun.* **2007**, 1852; (c) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Moessner, C. *Chem. Commun.* **2006**, 4186; (d) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4121; (e) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125.
6. Igarashi, Y.; Iida, T.; Yoshida, R.; Furumi, T. *J. Antibiot.* **2002**, *55*, 764.
7. (a) Nakahata, T.; Kuwahara, S. *Chem. Commun.* **2005**, 1028; (b) Nakahata, T.; Fujimura, S.; Kuwahara, S. *Chem.—Eur. J.* **2006**, *12*, 4584.
8. (a) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797; (b) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121.
9. (a) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185; (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.
10. Aldehyde **11** was prepared from methyl (*R*)-3-hydroxy-2-methylpropionate: (i) TBSCl, imidazole, DMF; (ii) DIBALH, CH_2Cl_2; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N.
11. For a review on asymmetric aldol reactions using boron enolates, see: Paterson, I.; Cowden, C. J. *Org. React.* **1997**, *51*, 1.
12. For DFT calculations on related aldol transition states, see: Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299.
13. (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151; (b) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439.
14. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
15. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
16. (a) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639; (b) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083; (c) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087.
17. The configuration was established by the advanced Mosher method, see: Ohtani, I.; Kusumi, Y.; Kashman, H.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. A reduced level of diastereoselectivity (90:10 dr) is observed for propyl ketone **21** relative to the analogous aldol reactions of the corresponding ethyl ketone (≥97:3 dr).
18. (a) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745; (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
19. (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, R. *J. Org. Chem.* **1996**, *61*, 5716; (b) Uenishi, J.; Kawahara, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965.