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Diastereoselective vinylalumination for the synthesis of pericosine A, B and C†

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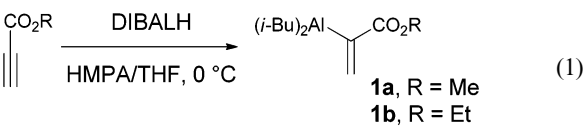
The vinylalumination of α-substituted aldehydes gave *anti*- and *syn*-adducts with moderate diastereoselectivity. The diastereomeric ratio was inverted by the addition of lithium or sodium perchlorates. Thus, both *anti*- and *syn*-adducts were isolated and transformed into the biologically active conduritols, pericosine B and C, respectively. Formal synthesis of pericosine A was achieved with the *anti*-adduct. The rationales for the different diastereoselectivity are discussed.

Introduction

[α-(Alkoxycarbonyl)vinyl]diisobutylaluminum (**1**), generated *in situ* from alkyl propiolate and diisobutylaluminum hydride in tetrahydrofuran/hexamethylphosphoramide (THF/HMPA), was introduced by Tsuda, Saegusa and colleagues in 1987 (eqn (1)).[1] The reaction of the nucleophilic aluminium reagents **1** and aldehydes/ketones provided alkyl α-(1-hydroxyalkyl)acrylates, the same products furnished by the Morita–Baylis–Hillman reaction.[2] This vinylalumination process circumvented the common drawbacks of the Morita–Baylis–Hillman reaction, such as slow reaction rates and the low reactivity of ketones and β-substituted acrylates. Vinylalumination is also applicable to other electrophiles, including allyl bromides,[1a] oxiranes and sulfinimines.[3] Recently, Ramachandran's group improved the preparation of **1** by replacing the hazardous HMPA with environmentally benign 4-methylmorpholine *N*-oxide (NMO) increasing the applicability of this vinylalumination.[4] Here, we report the application of this method to synthesize pericosine A, B and C (**2a–c**), which are cytotoxic metabolites of the sea hare-derived fungus *Periconia byssoides* OUPS-N133 reported in 1997 and 2007 by Numata and colleagues.[5] It is interesting to note that both enantiomers of pericosine C were found in nature with a slight preference for the (−)-isomer.[5b]



(1)

Pericosines belong to the family of conduritols and display a variety of biological activities including antitumour activity against some human cancer cell lines, inhibitory activity against epidermal growth factor receptor (EGFR), topoisomerase II and P388 leukaemia cells in mice;[6] therefore, these compounds attract considerable attention from synthetic chemists (Fig. 1).[7] Conventional approaches to access the six-membered cyclitol structure of pericosines include the use of shikimic acid, quinic acid and 3,5-cyclohexadiene-*cis*-1,2-diols prepared by the chemoenzymatic modification of substituted benzenes.[8–10] Recently, both Chen's and Vankar's groups utilized ring-closing metathesis (RCM) to generate the cyclitol skeletons of pericosines, where the required dienes for RCM were prepared by the Nozaki–Hiyama–Kishi and Morita–Baylis–Hillman reactions, respectively (Scheme 1).[11,12] We envisioned that the vinylalumination of the corresponding aldehydes could be a new method to synthesize the substrates for RCM, and the manipulation of the diastereoselectivity in this process could lead to the synthesis of both pericosine B and C. To our knowledge, the stereochemistry of the vinylalumination with α-substituted aldehydes has not been previously addressed.[13]

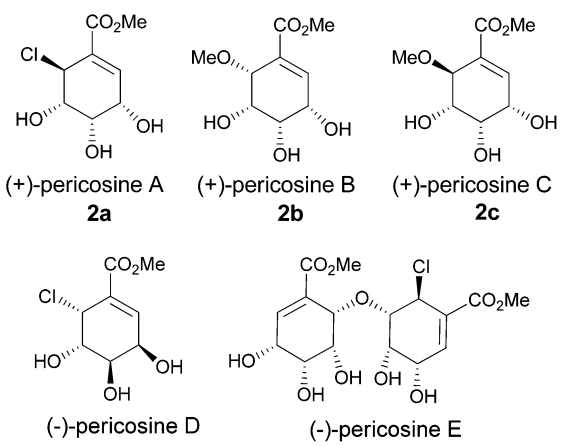


Fig. 1 Pericosine A–E.

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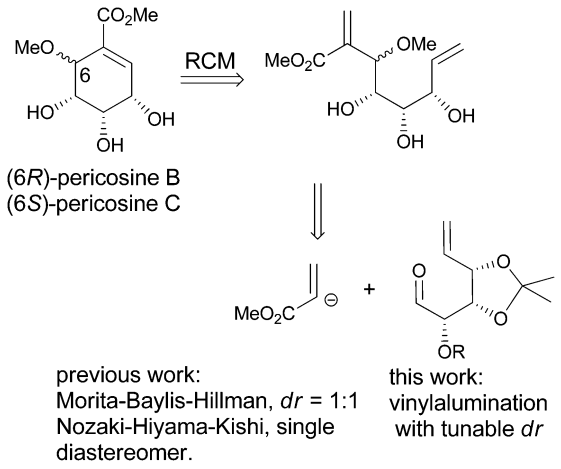
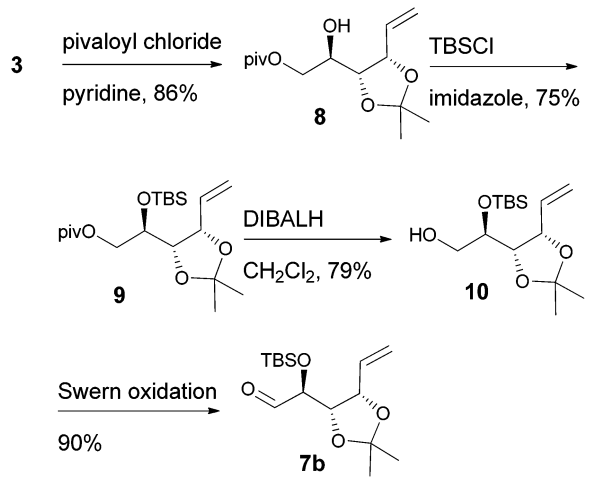
† Electronic supplementary information (ESI) available: Copies of the ^{1}H NMR and ^{13}C NMR spectra for the new compounds. See DOI: 10.1039/c3ra45871g



Scheme 1 Strategy for the synthesis of pericosines *via* RCM.

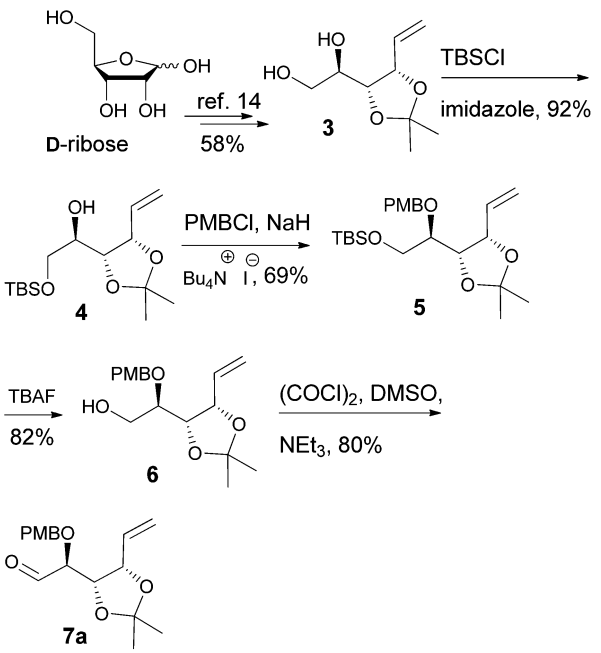


Scheme 3

Results and discussion

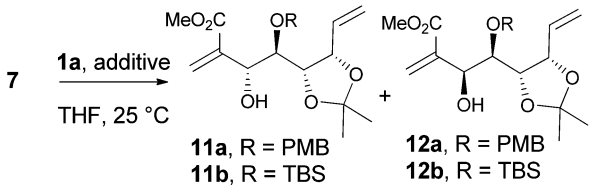
D-Ribose was converted to the diol **3** according to the reported procedures.[14] The terminal hydroxyl group was differentiated by the formation of *tert*-butyldimethylsilyl ether **4**[15] or pivalate **8.** The remaining, secondary hydroxyl group was further protected as *p*-methoxybenzyl ether **5** or *tert*-butyldimethylsilyl ether **9,** and the desired aldehydes **7a** and **7b** were prepared after the sequence of deprotection and Swern oxidation (Schemes 2 and 3).[16]

The vinylalumination of aldehyde **7** is summarized in Table 1. Consistent with previous reports, no product could be found when the additive was absent (entry 1).[1a] In the presence of HMPA, the reactions of **7a** generated the two diastereomers **11a** and **12a** with a moderate diastereoselectivity (4 : 1) and reasonable yields (entry 2). The two diastereomers were separable and isolated by column chromatography. Although our attempt to determine their stereochemistry by NMR analysis was inconclusive at this stage, this stereochemical outcome was later validated by further syntheses to pericosine B and C, respectively (*vide infra*). When the TBS-protected aldehyde **7b** was used, the diastereoselectivity diminished to 1.2 : 1 (entry 3), this ratio is close to that observed in the Morita–Baylis–Hillman reaction (1 : 1) promoted by DABCO.[11] Several Lewis acids were screened to improve the diastereoselectivity of this vinylalumination, and we found that alkali perchlorates had a strong influence on the reactions of **7a.** As the equivalence of $LiClO_4$ increased, the major product of the vinylalumination gradually



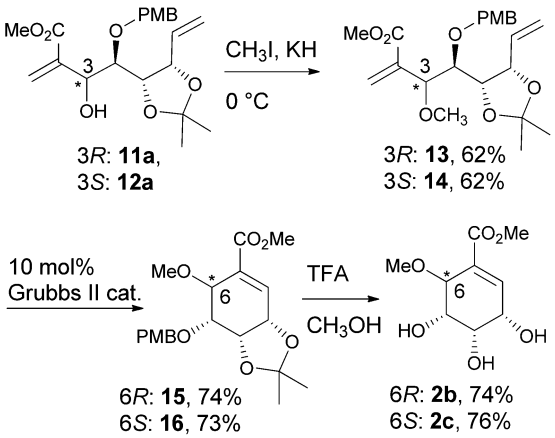
Scheme 2

Table 1 Vinylalumination of aldehyde **7**[a]



Entry	Substrate	Additive	**11** : **12**[b]	Yield[c] (%)
1	**7a**	—	—	0
2	**7a**	HMPA	4 : 1	60
3	**7b**	HMPA	1.2 : 1[d]	28
4	**7a**	HMPA, $LiClO_4$ (1 equiv.)	5 : 4	64
5	**7a**	HMPA, $LiClO_4$ (4 equiv.)	1 : 2	60
6	**7a**	HMPA, $LiClO_4$ (10 equiv.)	1 : 3	61
7	**7a**	HMPA, $NaClO_4$ (4 equiv.)	1 : 2	58
8	**7a**	HMPA, $NaClO_4$ (10 equiv.)	1 : 4	37
9	**7a**	HMPA, $KClO_4$ (4 equiv.)[e]	2 : 1	55
10	**7b**	HMPA $LiClO_4$ (4 equiv.)	1.4 : 1[d]	27

[a] The reactions were stirred in THF for 14 h at rt with 3 equiv. of **1a**, prepared from the addition of methyl propiolate to the solution of DIBALH, HMPA and THF at 0 °C. [b] Ratios were determined by ^1H NMR of crude reaction mixtures. [c] Isolated yields. [d] The exact stereochemistry of **11b** and **12b** was not determined as they were inseparable. [e] Most $KClO_4$ was insoluble.



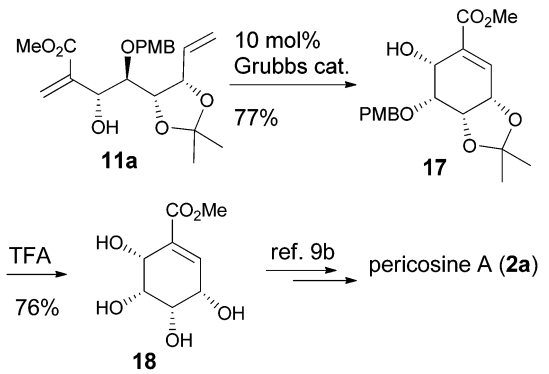
Scheme 4 Synthesis of pericosine B and C.

shifted from **11a** toward **12a** (entries 4–6). The same trend was also observed when sodium perchlorate was applied (entries 7 and 8). The effect of $KClO_4$ was negligible due to the much lower solubility of this salt in organic solvents (entry 9).[17] The addition of $LiClO_4$ has little effect on the vinylalumination of the TBS-protected aldehyde **7b** (entry 10). Other Lewis acids, such as $Mg(ClO_4)_2$, $Ca(ClO_4)_2$, $ZnBr_2$, $MgBr_2(OEt_2)$ and $AlMeCl_2$, did not generate the desired product, and the starting material **7a** was recovered. The vinylalumination became very sluggish when a lower reaction temperature (0 °C) was applied.

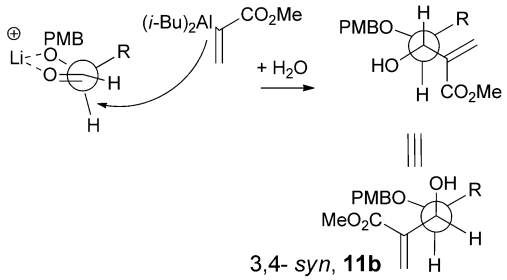
The vinylalumination adducts, **11a** and **12a**, were methylated to give **13** and **14**, respectively. The following cyclisation by RCM and the removal of the acid labile protecting groups by TFA gave pericosine B (**2b**) and C (**2c**).[18] The NMR spectra and optical rotation values of the synthetic **2b** and **2c** were consistent with the reported data,[9b,5b] which allowed us to confirm the stereochemical assignment of the vinylalumination adducts, **11a** and **12a** (Scheme 4).

Direct RCM of **11a** gave the cyclohexenyl alcohol **17**, and the following deprotection provided the tetraol **18**, which was the key intermediate for the synthesis of pericosine A by Stevenson's group (Scheme 5).[9b]

The stereochemistry of this vinylalumination merits further discussion. In the absence of $LiClO_4$, the addition of **1** to **7a** gave the 3,4-*anti* **11a** as the major product. This result is consistent with previous reports, where the addition of lithium enolate or



Scheme 5 Formal synthesis of pericosine A.



Scheme 6 Chelation control for the formation of **11b**.

allyl zinc to 2-*O*-benzyl-3,4-*O*-isopropylidene-erythrose, a truncated stereochemical analogue of **7a**, also gave the *anti*-adducts as the major product,[19] in accord with the Felkin–Ahn model.[20] On the other hand, the formation of the 3,4-*syn*-adduct **12a** from **7a** is unusual.[21] We propose that the excess amount of lithium or sodium cation enforced chelation control to generate the *syn*-adduct (Scheme 6) as the major product.[22] However, the moderate diastereoselectivity (dr = 4) also suggested that the facial discrimination induced by this chelation control is mild. The insignificant effect of $LiClO_4$ on the reaction of the highly sterically demanding, TBS-protected **7b** supports the explanation of chelation control (Table 1, entries 3 and 10).[23]

Conclusions

Diastereoselective vinylalumination using α-substituted aldehydes was achieved to provide α-methylene-β-hydroxy-γ-alkoxy-esters, such as **11** and **12**. Therefore, the vinylalumination could be an alternative and stereoselective method to generate the same adducts as the Morita–Baylis–Hillman reaction. The addition of alkali perchlorates allowed us to manipulate the ratio of the two diastereomers (the 3,4-*anti versus* 3,4-*syn*) from the original 4 : 1 to 1 : 4. Three further steps transformed the *anti*- and *syn*-adducts to the conduritols, pericosine B and C, respectively. Formal synthesis of pericosine A was also achieved *via* RCM and deprotection of the *anti*-adduct. Further study utilizing this stereoselective vinylalumination for natural product synthesis is ongoing.

Experimental section

tert-Butyl((*R*)-2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-((4-methoxybenzyl)oxy)ethoxy)dimethylsilane (5)

A solution of **4** (2.0 g, 6.62 mmol), 4-methoxybenzyl chloride (2.07 g, 13.24 mmol) and THF (5 mL) was added to the suspension of sodium hydride (0.63 g, 26.47 mmol) and THF (20 mL) 0 °C. The reaction mixture was stirred at rt for 20 h, quenched with sat. $NH_4Cl_{(aq)}$ (2 mL), concentrated, diluted with water (30 mL) and extracted with ethyl acetate (25 mL × 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 12; R_f 0.50) to give **5** (1.92 g, 4.56 mmol, 69%) as a colourless oil. $[\alpha]_D^{20}$ −21.9 (*c* 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.33 (s, 3H), 1.46 (s, 3H), 3.46–3.52 (m, 1H), 3.71–3.77 (m, 1H), 3.78 (s, 3H), 3.99 (d, J = 11.1 Hz, 1H), 4.16–4.22 (m,

1H), 4.37 (d, J = 10.6 Hz, 1H), 4.65 (dt, J = 6.4 Hz, J = 0.9 Hz, 1H), 4.75 (d, J = 10.6 Hz, 1H), 5.22 (dd, J = 10.6 Hz, J = 1.5 Hz, 1H), 5.36 (dd, J = 17.1 Hz, J = 1.5 Hz, 1H), 5.93 (ddd, J = 6.7 Hz, J = 10.4 Hz, J = 18.2 Hz, 1H), 6.84 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 134.5, 130.7, 129.3, 117.0, 113.7, 108.4, 78.7, 78.2, 76.6, 71.7, 63.8, 55.2, 27.8, 25.9, 25.3, 18.3, −5.4; IR (neat): 2987, 2931, 2857, 1614, 1513, 1463, 1377, 1249, 1087, 1037, 836, 777 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{23}H_{38}O_5SiNa$) 445.2386, found 445.2384.

(*R*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-((4-methoxybenzyl)oxy)ethanol (6)

Tetrabutylammonium fluoride trihydrate (821 mg, 2.61 mmol) was added to the solution of **5** (1.0 g, 2.37 mmol) and THF (20 mL). The reaction mixture was stirred at rt for 2 h and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 2; R_f 0.30) to give **6** (599 mg, 1.95 mmol, 82%) as a colourless oil. $[\alpha]_D^{20}$ −17.5 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.46 (s, 3H), 2.08 (br, 1H), 3.46 (m, 1H), 3.78 (s, 3H), 3.80–3.88 (m, 2H), 4.24 (dd, J = 9.0 Hz, J = 8.7 Hz, 1H), 4.36 (d, J = 10.5 Hz, 1H), 4.47 (d, J = 10.5 Hz, 1H), 4.70 (dd, J = 6.4 Hz, J = 6.4 Hz, 1H), 5.25 (dd, J = 10.6 Hz, J = 1.4 Hz, 1H), 5.39 (dd, J = 17.1 Hz, J = 1.4 Hz, 1H), 5.91 (ddd, J = 6.5 Hz, J = 10.5 Hz, J = 17.0 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.4, 133.9, 129.9, 129.4, 117.2, 113.9, 108.6, 78.5, 77.4, 77.1, 71.0, 61.3, 55.3, 27.7, 25.3; IR (neat): 3471, 2987, 2935, 1612, 1513, 1461, 1378, 1249, 1072, 1035, 873, 823, 514 cm^{-1}. HRMS (MALDI) calcd for $[M + Na]^+$ ($C_{17}H_{24}O_5Na$) 331.1522, found 331.1536.

(5*R*,6*R*)-8,8,9,9-Tetramethyl-5-((*R*)-oxiran-2-yl)-6-vinyl-2,4,7-trioxa-8-siladecane (7a)

Dimethyl sulfoxide (126 μL, 1.62 mmol) was added to the solution of oxalyl chloride (67 μL, 0.81 mmol) and dichloromethane (3 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, then added to a solution of **6** (100 mg, 0.324 mmol) and dichloromethane (0.5 mL), stirred for another 40 min at −78 °C and added with triethylamine (489 μL). The mixture was warmed up to rt, diluted with CH_2Cl_2 (25 mL) and washed with water (5 mL × 3). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 2; R_f 0.60) to give **7a** (80 mg, 0.26 mmol, 80%) as a light yellow oil. $[\alpha]_D^{20}$ 13.3 (c 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H), 1.47 (s, 3H), 3.74 (dd, J = 7.8 Hz, J = 2.8 Hz, 1H), 3.78 (s, 3H), 4.32–4.37 (m, 2H), 4.45 (d, J = 10.5 Hz, 1H), 4.72 (t, J = 6.2 Hz, J = 6.2 Hz, 1H), 5.25 (dd, J = 10.5 Hz, J = 1.4 Hz, 1H), 5.42 (dd, J = 17.1 Hz, J = 1.4 Hz, 1H), 5.89 (ddd, J = 6.2 Hz, J = 10.6 Hz, J = 16.9 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 9.61 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.9, 159.6, 132.7, 130.1, 128.9, 118.0, 113.9, 109.6, 81.5, 78.3, 77.0, 72.4, 55.3, 27.4, 25.2; IR (neat): 2987, 2935, 2838, 1733, 1610, 1513, 1461, 1378, 1251, 1074, 1035, 871, 825, 514 cm^{-1}. HRMS (MALDI) calcd for $[M + Na]^+$ ($C_{17}H_{22}O_5Na$) 329.1365, found 329.1552.

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethyl pivalate (9)

Tert-butyldimethylsilyl chloride (872 mg, 5.78 mmol) was added to the solution of **8**[24] (1.05 g, 3.85 mmol), imidazole (393 mg, 5.78 mmol), 4-(dimethylamino)pyridine (47 mg, 0.38 mmol) and dichloromethane (25 mL). The reaction mixture was stirred at 40 °C for 14 h and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 9; R_f 0.70) to give **9** (1.12 g, 2.89 mmol, 75%) as a colourless liquid. $[\alpha]_D^{20}$ −10.75 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.84 (s, 9H), 1.19 (s, 9H), 1.31 (s, 3H), 1.42 (s, 3H), 3.91 (m, 1H), 4.07–4.21 (m, 3H), 4.57 (t, J = 6.9 Hz, J = 6.9 Hz, 1H), 5.22 (d, J = 10.4 Hz, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.92 (ddd, J = 7.5 Hz, J = 10.2 Hz, J = 17.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.3, 134.3, 118.3, 108.4, 78.7, 77.8, 69.4, 66.1, 38.9, 27.8, 27.2, 25.8, 25.3, 18.0, −3.9, −4.6. HRMS (ESI) calcd for $[M + Na]^+$ ($C_{20}H_{38}O_5SiNa$) 409.2386, found 409.2393.

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethanol (10)

Diisobutylaluminium hydride (1.1 M in cyclohexane, 2.93 mL, 3.23 mmol) was added dropwise to the solution of **9** (500 mg, 1.29 mmol) and dichloromethane (20 mL) at −78 °C. The reaction mixture was stirred at −78 °C for another 2 h, warmed up to rt, quenched with methanol (3 mL) and citric $acid_{(aq)}$ (w/w, 10%, 5 mL), concentrated. The residue was added with water (10 mL) and extracted with dichloromethane (12 mL × 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 7; R_f 0.33) to give **10** (308 mg, 1.02 mmol, 79%) as a colourless liquid. $[\alpha]_D^{20}$ −24.2 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 1.34 (s, 3H), 1.44 (s, 3H), 2.16 (br, 1H), 3.68–3.81 (m, 3H), 4.16 (t, J = 13.8 Hz, J = 13.8 Hz, 1H), 4.59 (t, J = 6.6 Hz, J = 6.6 Hz, 1H), 5.22 (d, J = 10.7 Hz, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.90 (ddd, J = 7.2 Hz, J = 10.2 Hz, J = 17.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.1, 118.4, 108.5, 79.5, 78.8, 70.8, 65.0, 27.8, 25.9, 25.4, 18.1, −3.7, −4.4. HRMS (ESI) calcd for $[M + Na]^+$ ($C_{15}H_{30}O_4SiNa$) 325.1811, found 325.1807.

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)acetaldehyde (7b)

Dimethyl sulfoxide (89 μL, 1.15 mmol) was added to the solution of oxalyl chloride (47 μL, 0.58 mmol) and dichloromethane (3 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, then added with a solution of **10** (87 mg, 0.29 mmol) and dichloromethane (0.5 mL), stirred for another 40 min at −78 °C and added with triethylamine (400 μL). The mixture was warmed up to rt, diluted with CH_2Cl_2 (20 mL) and washed with water (5 mL × 3). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 7; R_f 0.65) to give **7b** (77 mg, 0.26 mmol, 90%) as a colourless oil. $[\alpha]_D^{20}$ 0.5 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.31 (s, 3H), 1.45 (s,

3H), 4.08 (m, 1H), 4.35 (t, $J = 6.8$ Hz, $J = 6.8$ Hz, 1H), 4.64 (t, $J = 6.8$ Hz, $J = 6.8$ Hz, 1H), 5.23 (dd, $J = 10.4$ Hz, $J = 1.2$ Hz, 1H), 5.32 (dd, $J = 17.2$ Hz, $J = 1.2$ Hz, 1H), 5.98 (ddd, $J = 7.3$ Hz, $J = 10.2$ Hz, $J = 17.4$ Hz, 1H), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.8, 134.0, 119.2, 109.2, 79.3, 78.6, 76.7, 27.1, 25.8, 24.9, 18.1, −4.3, −4.7. HRMS (ESI) calcd for $[M + H]^+$ ($C_{15}H_{29}O_4Si$) 301.1835, found 301.1831.

General procedure for the vinylalumination of aldehydes

Methyl propiolate (204 μL, 3.23 mmol) was added to the solution of diisobutylaluminum hydride (1.1 M in cyclohexane, 2.67 mL, 2.94 mmol), HMPA (766 μL, 4.41 mmol) and THF 10 mL at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture became a yellow solution and was warmed up to rt in 20 min. A solution of **7a** (300 mg, 0.98 mmol) and THF (4 mL) was added to the above solution of [α-(methoxycarbonyl)vinyl]diisobutylaluminum (**1a**). The resulting mixture was stirred for another 14 h at rt, quenched with methanol (3 mL), added with citric acid$_{(aq)}$ (10%, w/w), stirred for 3 min, concentrated to remove THF and extracted with diethyl ether (10 mL × 3). The organic layers were separated, dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 3; **11a**, R_f 0.30; **12a**, R_f 0.25) to give **11a** (184 mg, 0.47 mmol, 49%) and **12a** (46.3 mg, 0.12 mmol, 12%) as colourless oils.

11a. $[\alpha]_D^{20}$ −26.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 1.43 (s, 3H), 3.67 (s, 3H), 3.77 (s, 3H), 3.78–3.82 (m, 1H), 4.14 (dd, $J = 8.0$ Hz, $J = 6.7$ Hz, 1H), 4.42 (d, $J = 10.5$ Hz, 1H), 4.60–4.64 (m, 2H), 4.78 (dd, $J = 5.1$ Hz, $J = 3.9$ Hz, 1H), 5.24 (dd, $J = 10.9$ Hz, $J = 1.2$ Hz, 1H), 5.34 (dd, $J = 17.2$ Hz, $J = 1.2$ Hz, 1H), 5.90–6.02 (m, 2H), 6.24 (d, $J = 0.9$ Hz, 1H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 159.2, 138.3, 134.7, 130.1, 129.4, 126.3, 117.7, 113.7, 108.6, 79.6, 79.1, 77.4, 72.9, 72.8, 55.3, 51.8, 27.9, 25.3; IR (neat): 3482, 2987, 2937, 1718, 1614, 1513, 1440, 1378, 1249, 1079, 1035, 871, 819, 516 cm^{-1}; HRMS (MALDI) calcd for $[M + Na]^+$ ($C_{21}H_{28}O_7Na$) 415.1733, found 415.1744.

12a. $[\alpha]_D^{20}$ −26.51 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.54 (s, 3H), 3.06 (br, 1H, O*H*), 3.72 (s, 3H), 3.77 (s, 3H), 3.78 (m, 1H), 4.23 (dd, $J = 8.7$ Hz, $J = 6.0$ Hz, 1H), 4.32 (d, $J = 9.9$ Hz, 1H), 4.42 (d, $J = 9.9$ Hz, 1H), 4.69 (t, $J = 6.1$ Hz, $J = 6.1$ Hz, 1H), 4.94 (d, $J = 1.3$ Hz, 1H), 5.25 (dd, $J = 10.6$ Hz, $J = 1.5$ Hz, 1H), 5.40 (dd, $J = 17.2$ Hz, $J = 1.5$ Hz, 1H), 5.89–5.98 (m, 1H), 6.00 (t, $J = 1.3$ Hz, $J = 1.3$ Hz, 1H), 6.34 (t, $J = 1.3$ Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 2H), 7.12 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 159.3, 141.4, 133.8, 129.8, 129.4, 125.6, 117.3, 113.8, 108.9, 78.6, 77.2, 72.8, 72.5, 69.3, 55.3, 51.9, 27.8, 25.5; IR (neat): 3498, 2989, 2950, 1720, 1612, 1513, 1440, 1378, 1249, 1179, 1079, 1035, 871, 821, 514 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{21}H_{28}O_7Na$) 415.1733, found 415.1731.

General procedure for the vinylalumination of aldehydes with alkali perchlorates

The premixed solution of **7a** (300 mg, 0.98 mmol), lithium perchlorate (417 mg, 3.92 mmol, 4 equiv.) and THF (6 mL) was added to the solution of **1a**, prepared from methyl propiolate (272 μL, 4.31 mmol), DIBALH (1.1 M in cyclohexane, 3.56 mL, 3.92 mmol), HMPA (1.02 mL, 5.88 mmol) and THF (12 mL), as describe above. The reaction mixture was stirred at rt for 14 h, and the same work-up procedure was followed to give **11a** (77 mg, 0.19 mmol, 20%) and **12a** (154 mg, 0.39 mmol, 40%).

11b and 12b. The procedure used to prepare **11a** and **12a** was followed. Starting with **7b** (294 mg, 0.98 mmol), methyl propiolate (204 μL, 3.23 mmol), HMPA (766 μL, 4.41 mmol) and diisobutylaluminium hydride (1.1 M in cyclohexane, 2.67 mL, 2.94 mmol), the inseparable mixture of **11b** and **12b** (106 mg, 0.27 mmol, 28%) was produced after column chromatography (SiO_2, EtOAc–hexanes, 1 : 8; R_f 0.45) as a colourless oil. HRMS (ESI) calcd for $[M + H]^+$ ($C_{19}H_{35}O_6Si$) 387.2197, found 387.2200.

(3*R*,4*R*)-Methyl 4-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methoxy-4-((4-methoxybenzyl)oxy)-2-methylenebutanoate (13)

A solution of **11a** (50 mg, 0.13 mmol), iodomethane (25 μL, 0.38 mmol) and THF (1 mL) was added to the suspension of potassium hydride (15 mg, 0.38 mmol) and THF (2.5 mL) at 0 °C. The reaction mixture was stirred for another 20 min, quenched with sat. $NH_4Cl_{(aq)}$ (7 mL), concentrated to remove THF and extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 3; R_f 0.50) to give **13** (32 mg, 0.079 mmol, 62%) as a colourless oil. $[\alpha]_D^{20}$ −16.6 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H), 1.43 (s, 3H), 3.32 (s, 3H), 3.67–3.71 (m, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 4.17 (dd, $J = 8.6$ Hz, $J = 6.2$ Hz, 1H), 4.36 (d, $J = 10.5$ Hz, 1H), 4.50 (d, $J = 2.4$ Hz, 1H), 4.59 (t, $J = 6.5$ Hz, $J = 6.5$ Hz, 1H), 4.65 (d, $J = 10.5$ Hz, 1H), 5.19 (ddd, $J = 10.4$ Hz, $J = 1.8$ Hz, $J = 1.5$ Hz, 1H), 5.33 (ddd, $J = 17.2$ Hz, $J = 1.8$ Hz, $J = 1.5$ Hz, 1H), 5.89–6.01 (m, 2H), 6.36 (d, $J = 1.4$ Hz, 1H), 6.81 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 159.1, 137.4, 134.6, 130.5, 129.4, 126.9, 116.9, 113.6, 108.4, 80.8, 79.4, 78.9, 77.19, 72.7, 57.7, 55.3, 51.7, 27.9, 25.4; IR (neat): 2987, 2935, 1718, 1612, 1513, 1440, 1371, 1247, 1081, 1035, 873, 821, 514 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{22}H_{30}O_7Na$) 429.1889, found 429.1888.

(3*S*,4*R*)-Methyl 4-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methoxy-4-((4-methoxybenzyl)oxy)-2-methylenebutanoate (14)

The procedure used to prepare **13** was followed. Starting with **12a** (50 mg, 0.13 mmol), iodomethane (25 μL, 0.38 mmol) and potassium hydride (15 mg, 0.38 mmol), compound **14** (32 mg, 0.079 mmol, 62%) was produced after column chromatography (SiO_2, EtOAc–hexanes, 1 : 3; R_f 0.40) as a colourless oil. $[\alpha]_D^{20}$ −30.3 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.51 (s, 3H), 3.32 (s, 3H), 3.67–3.71 (m, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 4.27–4.40 (m, 4H), 4.66 (t, $J = 6.6$ Hz, $J = 6.6$ Hz, 1H), 5.21 (dd, $J = 10.6$ Hz, $J = 1.5$ Hz, 1H), 5.37 (dd, $J = 17.1$ Hz, $J = 1.5$ Hz, 1H), 5.96 (ddd, $J = 6.6$ Hz, $J = 10.5$ Hz, $J = 17.1$ Hz, 1H), 6.06 (d, $J = 1.1$ Hz, 1H), 6.42 (d, $J = 1.1$ Hz, 1H), 6.78 (d, $J = 8.6$ Hz, 2H), 7.09 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 159.1, 137.3, 134.3, 130.3, 129.1, 127.2, 117.1, 113.6, 108.4, 79.6, 78.7,

77.6, 77.4, 72.3, 57.9, 55.3, 51.9, 28.1, 25.8; IR (neat): 2987, 2935, 1722, 1612, 1513, 1440, 1378, 1249, 1087, 1035, 873, 821, 514 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{22}H_{31}O_7$) 407.2070, found 407.2068.

(3a*S*,6*R*,7*R*,7a*S*)-Methyl 6-methoxy-7-((4-methoxybenzyl)-oxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]-dioxole-5-carboxylate (15)

The second generation Grubbs catalyst (10.4 mg, 0.012 mmol) was added to the solution of **13** (50 mg, 0.12 mmol) and toluene (12.8 mL), and the resulting solution was refluxed for 14 h under an atmosphere of nitrogen and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 2; R_f 0.35) to give **15** (32.3 mg, 0.088 mmol, 74%) as a light brown oil. $[\alpha]_D^{20}$ −45.5 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.39 (s, 3H), 3.47 (dd, $J = 4.4$ Hz, $J = 2.6$ Hz, 1H), 3.67 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 4.34 (d, $J =$ 4.4 Hz, 1H), 4.47–4.56 (m, 2H), 4.69 (d, $J = 12.3$ Hz, 1H), 4.71 (d, $J = 12.3$ Hz, 1H), 6.71 (d, $J = 3.2$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 7.31 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 159.4, 137.1, 130.2, 129.8, 129.5, 113.9, 111.5, 73.9, 72.9, 72.8, 71.2, 70.6, 61.3, 55.3, 52.2, 27.9, 26.2; IR (neat): 2933, 1720, 1614, 1513, 1440, 1376, 1249, 1052, 825, 511, 412 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{20}H_{26}O_7Na$) 401.1576, found 401.1581.

(3a*S*,6*S*,7*R*,7a*S*)-Methyl 6-methoxy-7-((4-methoxybenzyl)oxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-5-carboxylate (16)

The procedure used to prepare **15** was followed. Starting with **14** (50 mg, 0.12 mmol) and the second generation Grubbs catalyst (10.4 mg, 0.012 mmol), compound **16** (31.5 mg, 0.088 mmol, 73%) was produced after column chromatography (SiO_2, EtOAc–hexanes, 1 : 2; R_f 0.45) as a light brown oil. $[\alpha]_D^{20}$ 44.45 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.40 (s, 3H), 3.44 (s, 3H), 3.74 (m, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.26 (d, $J = 6.2$ Hz, 1H), 4.42 (dd, $J = 5.8$ Hz, $J = 3.1$ Hz, 1H), 4.59–4.64 (m, 2H), 4.70 (d, $J = 12.0$ Hz, 1H), 6.70 (d, $J = 3.0$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 159.3, 135.9, 132.4, 130.1, 129.7, 113.8, 110.3, 75.4, 75.2, 73.9, 72.7, 71.8, 59.8, 55.3, 52.0, 27.1, 25.9; IR (neat): 2985, 2933, 1722, 1612, 1513, 1438, 1375, 1249, 1097, 1033, 858, 821, 516 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{20}H_{26}O_7Na$) 401.1576, found 401.1568.

Pericosine B (2b)

Trifluoroacetic acid (1.7 mL) was added to the solution of **15** (20 mg, 0.055 mmol) and methanol (0.66 mL) at 0 °C. The reaction mixture was stirred at rt for 5 h and concentrated. The crude product was further purified by column chromatography (SiO_2, methanol–ethyl acetate, 1 : 4; R_f 0.45) to give **2b** (8.9 mg, 0.041 mmol, 74%) as a colourless, viscous oil. $[\alpha]_D^{20}$ 24.4 (*c* 0.65, EtOH); ^1H NMR (acetone-d_6/D_2O, 300 MHz) δ 3.56 (s, 3H), 3.76 (s, 3H), 3.83 (dd, $J = 2.0$ Hz, $J = 4.4$ Hz, 1H), 3.99 (m, 1H) 4.22 (m, 1H), 6.71 (dd, $J = 2.2$ Hz, $J = 1.3$ Hz, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 166.6, 141.7, 130.6, 76.8, 72.4, 69.8, 69.1, 61.4, 52.2; IR (neat): 3421, 2940, 1712, 1438, 1259, 1201, 1070 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_9H_{14}O_6Na$) 241.0688, found 241.0683.

Pericosine C (2c)

The procedure used to prepare **2b** was followed. Starting with **16** (20 mg, 0.055 mmol) and trifluoroacetic acid (1.7 mL), compound **2c** (9.1 mg, 0.042 mmol, 76%) was produced after column chromatography (SiO_2, methanol–ethyl acetate, 1 : 4; R_f 0.45) as a colourless, viscous oil. $[\alpha]_D^{20}$ 82.1 (*c* 0.5, EtOH); ^1H NMR (acetone-d_6/D_2O, 300 MHz) δ 3.45 (s, 3H), 3.72 (s, 3H), 3.88 (m, 1H), 3.93 (dd, $J = 4.8$ Hz, $J = 2.1$ Hz, 1H), 4.17 (d, $J = 4.8$ Hz, 1H), 4.23 (t, $J =$ 3.3 Hz, $J = 3.3$ Hz, 1H), 6.70 (d, $J = 3.8$ Hz, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 167.8, 140.7, 131.4, 79.0, 73.0, 70.4, 67.4, 59.5, 52.2; IR (neat): 3428, 2921, 1712,1648, 1440, 1272, 1070 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_9H_{14}O_6Na$) 241.0688, found 241.0686.

(3a*S*,6*R*,7*R*,7a*S*)-Methyl 6-hydroxy-7-((4-methoxybenzyl)oxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-5-carboxylate (17)

The procedure used to prepare **15** was followed. Starting with **11a** (50 mg, 0.13 mmol) and the second generation Grubbs catalyst (11.0 mg, 0.013 mmol), compound **17** (35.6 mg, 0.098 mmol, 77%) was produced after column chromatography (SiO_2, EtOAc–hexanes, 1 : 2; R_f 0.25) as a light brown oil. $[\alpha]_D^{20}$ −38.78 (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.40 (s, 3H), 3.42 (d, $J = 10.2$ Hz, 1H), 3.53 (dd, $J = 4.3$ Hz, $J = 2.0$ Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.53–4.65 (m, 3H), 4.81 (m, 1H), 4.87 (d, $J = 11.9$ Hz, 1H), 6.73 (dd, $J = 3.1$ Hz, $J = 1.1$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 7.32 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 159.5, 135.8, 131.8, 129.8, 129.3, 113.9, 111.5, 75.7, 73.3, 71.8, 69.7, 62.1, 55.3, 52.4, 28.1, 26.4; IR (neat): 3318, 2935, 1722, 1612, 1513, 1438, 1375, 1249, 1106, 1051, 827, 518 cm^{-1}; HRMS (MALDI) calcd for $[M + Na]^+$ ($C_{19}H_{24}O_7Na$) 387.1420, found 387.1431.

(3*S*,4*S*,5*R*,6*R*)-Methyl 3,4,5,6-tetrahydroxycyclohex-1-enecarboxylate (18)

Trifluoroacetic acid (1.7 mL) was added to the solution of **17** (20 mg, 0.055 mmol) and methanol (0.66 mL) at 0 °C. The reaction mixture was stirred at rt for 5 h and concentrated. The crude product was further purified by column chromatography (SiO_2, methanol–ethyl acetate, 1 : 4; R_f 0.35) to give **18** (7.7 mg, 0.038 mmol, 76%) as a colourless oil. ^1H NMR (D_2O, 300 MHz) δ 3.84 (dd, $J = 4.6$ Hz, $J = 1.8$ Hz, 1H), 3.87 (s, 3H), 4.20 (d, $J = 3.8$ Hz, 1H), 4.49 (m, 1H), 4.62 (m, 1H), 6.92 (t, $J = 1.7$ Hz, $J = 1.7$ Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 168.0, 141.1, 131.0, 71.5, 67.9, 65.2, 52.7.[9b]

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