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Total synthesis and stereochemical reassignment of (+)-dolastatin 19, a cytotoxic marine macrolide isolated from *Dolabella auricularia*

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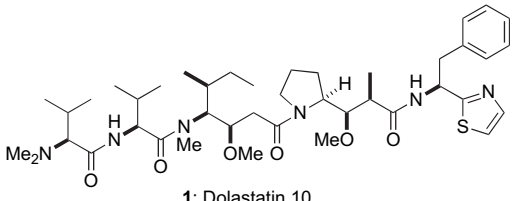
Abstract—Using conformational analysis and biogenetic considerations, a revised configurational assignment for the cytotoxic marine macrolide dolastatin 19 is proposed, together with its validation by completion of the first total synthesis. Key features of the highly stereocontrolled route include an asymmetric vinylogous Mukaiyama aldol reaction to simultaneously install both the remote C13 stereocenter and the C10–C11 (*E*)-trisubstituted olefin, two sequential 1,4-*syn* boron-mediated aldol reactions, and a late-stage, α-selective Mukaiyama glycosylation to append the L-rhamnose-derived pyranoside.

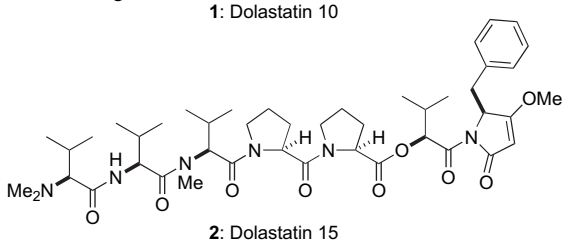
1. Introduction

Marine organisms provide an enormous reservoir of structurally diverse secondary metabolites with unique molecular architectures.[1] *Dolabella auricularia*, a sea hare from the *aplysiidae* family of marine opisthobranchs, has proven to be a prolific source of bioactive marine natural products.[2] A collection of this shell-less mollusc from the Indian Ocean by the Pettit group led to the isolation of a novel series of potent cytotoxic depsipeptides, designated as the dolastatins.[3] These include dolastatins 10 (**1**, Fig. 1) and 15 (**2**), both of which possess potent anticancer activity[4] and have progressed into clinical trials.[5] It is generally believed that the majority of these bioactive secondary metabolites are not produced by the sea hare itself, but are instead of cyanobacterial origin, consumed by the sea hare whilst grazing on algae and seaweeds, and then concentrated in the digestive glands. Conceivably, these sequestered compounds may function as a chemical defence for the sea hare against predators.[6]

Examination of the cytotoxic extracts of Japanese specimens of *D. auricularia* by Yamada and co-workers led to the isolation and characterization of the 14-membered macrolides, aurisides A (**3**, Fig. 2) and B (**4**).[7] The marked structural variations in the peptidic and polyketide constituents of *D. auricularia* prompted the Pettit group to extract a sample collection from the Gulf of California. In 2004, this work led to the isolation of a novel marine polyketide, designated as dolastatin 19.[8] Initial biological screening indicated significant cancer cell growth inhibitory activity (GI_{50} values of 0.72 μg/mL and 0.76 μg/mL for breast MCF-7 and colon KM20L2 cell lines, respectively). However, further biological evaluation of dolastatin 19, including elucidation of the mechanism of action, was precluded by its scarce availability from the natural source (0.5 mg was obtained from 600 kg of *D. auricularia*), inspiring our efforts towards the realization of a total synthesis.[9] Herein, we now report the full details of the evolution of our proposed stereochemical reassignment of dolastatin 19 and its subsequent validation, achieved through completion of the first total synthesis.



1: Dolastatin 10



2: Dolastatin 15

Figure 1. Structures of dolastatin 10 (**1**) and dolastatin 15 (**2**).

Keywords: Macrolide; Cytotoxic; Conformational analysis; Stereochemical reassignment; Aldol reaction; Glycosylation.
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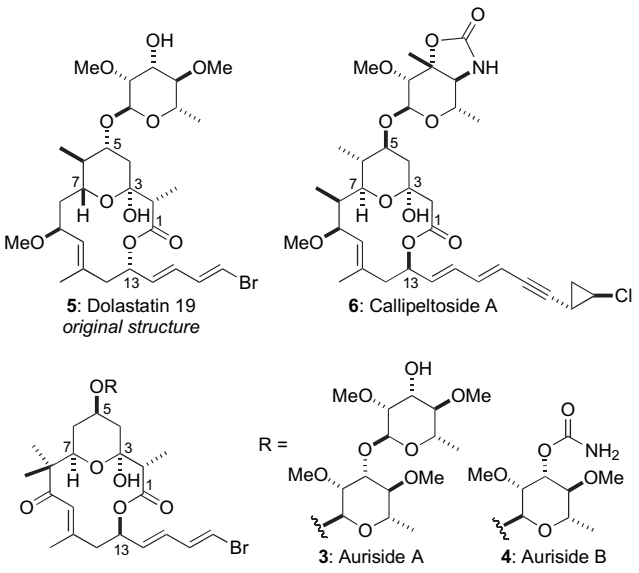


Figure 2. Dolastatin 19 (**5**) and structurally related 14-membered marine macrolides.

2. Proposed stereochemical reassignment of dolastatin 19

Following extensive spectroscopic analysis by Pettit and co-workers, the original structure of dolastatin 19 was proposed as **5** (Fig. 2).[8] As a 14-membered macrolide containing a six-membered cyclic hemiacetal and appended with an (*E*,*E*)-diene and a 2,4-di-*O*-methyl-L-rhamnopyranoside, dolastatin 19 is related to aurisides A (**3**) and B (**4**), and also to callipeltoside A (**6**), isolated from the lithistid sponge *Callipelta* sp.[10] Examination of the linear *seco*-acids **7** and **8** of these macrocycles (Fig. 3) serves to highlight the structural similarities. Notably, the stereochemistry of the aurisides and callipeltoside has been rigorously established by total synthesis, as reported by ourselves[11] and other groups.[12] On careful inspection, the pseudo-enantiomeric assignment of the configuration of dolastatin 19 across C5–C7 and at C13 in the corresponding *seco*-acid **9** appears inconsistent with the anticipated common bacterial biogenesis of these polyketides.[13]

Prior to the onset of a synthetic venture towards dolastatin 19, these noted structural ambiguities prompted us to consider the possibility that the initial stereochemical

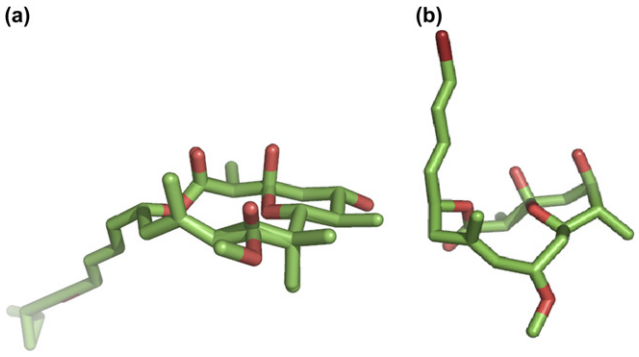


Figure 4. (a) Overlay of global minimum energy conformations of the auriside and callipeltoside aglycons and (b) calculated minimum energy conformation of dolastatin 19 aglycon (Pettit assignment).

assignment proposed by Pettit and co-workers may have been incorrect. To gain further insight into the preferred conformations adopted by these related marine macrolides, detailed molecular modelling studies were performed on the parent aglycons. Using Macromodel (Version 8.0), a 10,000 step Monte Carlo conformational search was performed with the MM2* force field and chloroform solvent model. Reassuringly, both the auriside and callipeltoside aglycons share a similar diamond lattice arrangement of the macrolide rings. The six-membered hemiacetal ring adopts a chair conformation, in which all the substituents are equatorially disposed and anomeric stabilization is achieved at C3 (Fig. 4). This preferred conformation also facilitates a stabilizing hydrogen bond between the anomeric C3–OH and the oxygen of the lactone carbonyl, and minimizes steric interactions throughout the carbon framework. By contrast, examination of the structure proposed by Pettit for dolastatin 19 predicts a boat conformation for the pyran ring.[14] Consequently the structure gains no anomeric stabilization, as the C3–OH is now essentially equatorially disposed, and the remaining region of the macrolide is highly distorted relative to the common, and presumably favourable, diamond lattice conformation adopted by the auriside and callipeltoside aglycons.

This evidence, together with the assumption of a common biogenesis, prompted us to propose configurational inversions of both the C5–C7 stereotriad and the isolated C13 carbinol stereocentre, leading to the putative structure **10** (Scheme 1).

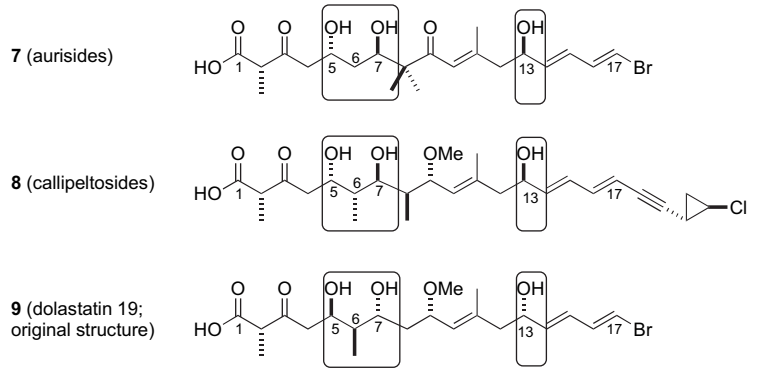
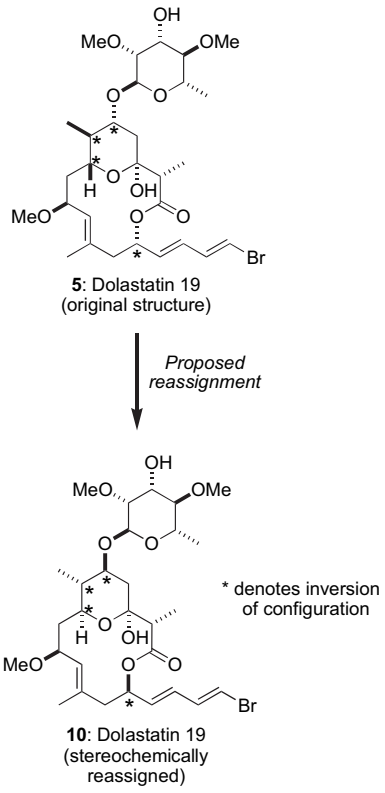


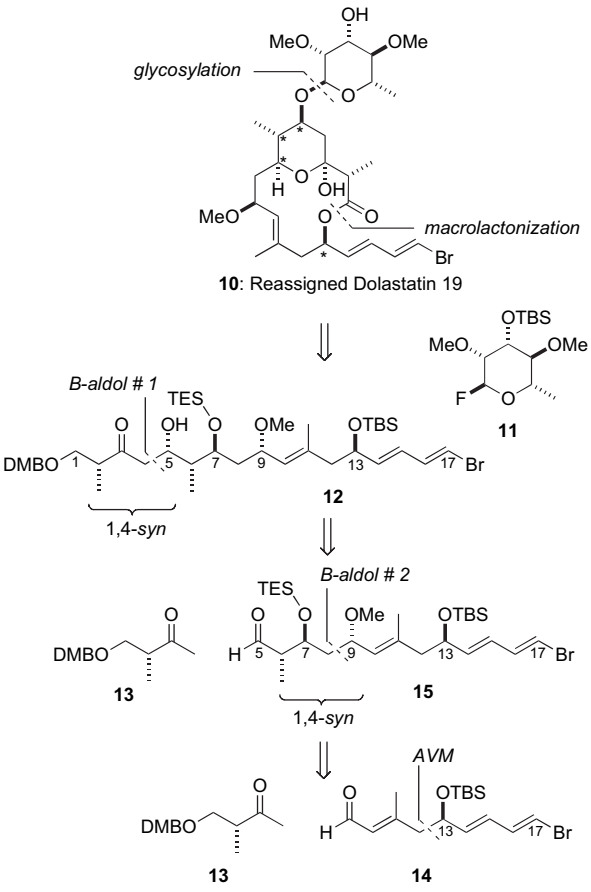
Figure 3. Open chain *seco*-acids of dolastatin 19 and related macrolides.



Scheme 1. Proposed stereochemical reassignment of dolastatin 19.

3. Retrosynthetic analysis and general synthetic strategy

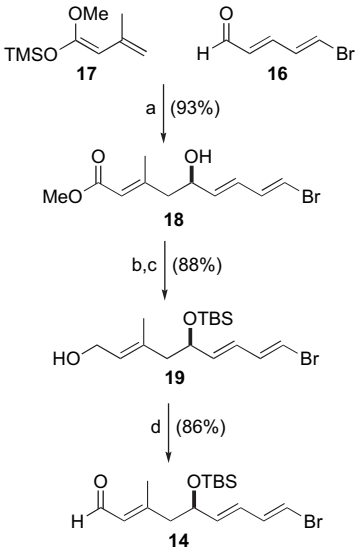
Our retrosynthetic analysis of dolastatin 19, outlined in Scheme 2, envisaged a late-stage glycosylation of the putative dolastatin 19 aglycon with L-rhamnose-derived fluorosugar **11**, following macrolactonization and hemiacetal formation at C3 of the acyclic C1–C17 precursor **12**. Careful inspection of the complete aglycon framework reveals two 1,4-*syn* relationships that can be selectively installed using iterative boron-mediated aldol reactions, both involving α-chiral ketone **13**.[15] The first 1,4-*syn* aldol coupling, between aldehyde **14** and ketone **13**, would introduce the requisite C9 stereocenter, while the second coupling would involve the more complex aldehyde **15**. Aldehyde **14** can in turn be accessed utilizing an asymmetric vinylogous Mukaiyama (AVM) aldol reaction, as developed in our previous syntheses of callipeltoside A and the aurisides,[11] to install both the C13 stereocenter and (10*E*)-trisubstituted double bond.



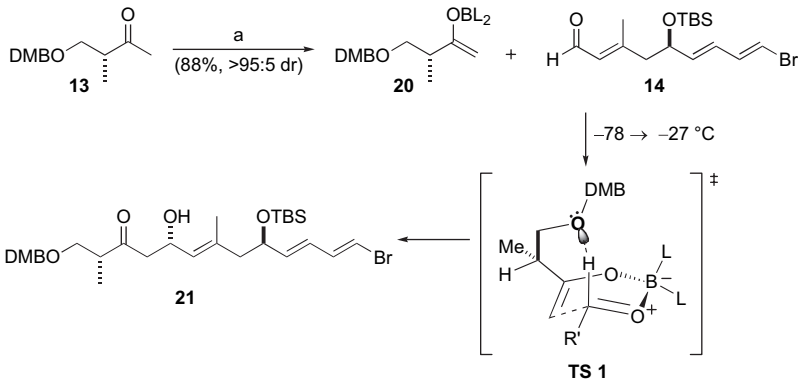
Scheme 2. Retrosynthetic analysis for dolastatin 19 leading to key building blocks **13** and **14**.

4. Results and discussion

In initiating our synthetic efforts, we focused on construction of the C9–C17 subunit **14** via an asymmetric vinylogous Mukaiyama aldol coupling[16] between (*E*,*E*)-bromodienal **16**[17] and silyl dienolate **17** (Scheme 3).[18] The conditions had been optimized during our earlier synthesis of callipeltoside A (**6**),[11] where (*R*)-BINOL-Ti(O*i*-Pr)$_2$, formed in situ from (*R*)-BINOL and Ti(O*i*-Pr)$_4$, had been identified as an optimal chiral Lewis acid promoter. Under these conditions, the desired aldol adduct **18** was obtained in high yield (93%) and enantioselectivity (94% ee). In this single step, the regioselectivity (γ-addition vs α-addition), *E*/*Z* geometry of the C10–C11 trisubstituted double bond, and the absolute configuration of the C13 stereocenter (as determined by Mosher ester analysis[11]) were all effectively controlled. With adduct **18** in hand, a series of functional and protecting group



Scheme 3. (a) (*R*)-BINOL, Ti(O*i*-Pr)$_4$, THF, −78 °C; (b) TBSCl, imidazole, CH_2Cl_2, rt; (c) DIBAL-H, CH_2Cl_2, −78 °C; (d) MnO_2, Et_2O, rt.

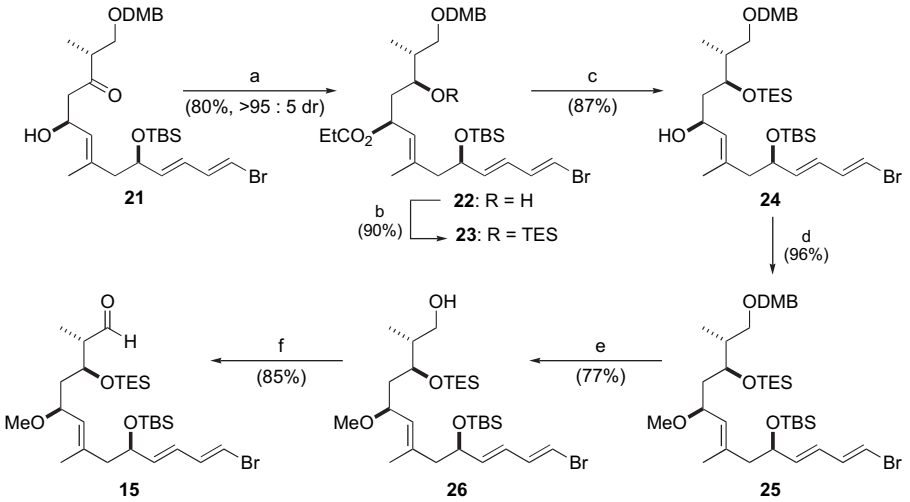


Scheme 4. (a) (+)-Ipc_2BCl, Et_3N, Et_2O, 0 °C; **14**, −78→−27 °C.

manipulations were required to access the aldehyde **14**. Protection of the newly introduced C13 hydroxyl in **18** (TBSCl/imidazole) was followed by DIBAL-H reduction of the ester to provide allylic alcohol **19**. Subsequent MnO_2-mediated oxidation of alcohol **19** gave aldehyde **14** (75% over three steps) in preparation for the first boron-mediated aldol reaction.

The stage was now set for the first 1,4-*syn* aldol reaction with methyl ketone **13**.[19] Experience gained in our synthesis of callipeltoside A[11] proved useful in selecting a suitable protecting group. The 3,4-dimethoxybenzyl (DMB)[20] ether in **13** was chosen in place of the more standard 4-methoxybenzyl (PMB) variant, to alleviate potential chemoselectivity complications relating to competitive DDQ-mediated oxidation of the allylic TBS ether at C13 in the later stages of the synthesis. Treatment of methyl ketone **13** with (+)-Ipc_2BCl and Et_3N provided the intermediate boron enolate **20** which, upon addition of aldehyde **14**, generated the expected[15] 1,4-*syn* aldol adduct **21** in 88% yield and >95:5 dr (Scheme 4). Recent *in silico* studies by Goodman and Paton regarding the origin of remote stereoinduction in the boron-mediated aldol reactions of β-alkoxy methyl ketones have shown such processes to proceed via a boat-like transition state.[21] The high levels of enolate π-facial selectivity observed are governed by the formation of a stabilizing formyl hydrogen bond in the aldol transition state with the oxygen of the DMB ether, acting in unison with the minimization of steric interactions between the α-stereocenter of the enolate and the aldehyde, leading to **TS 1** for the preferred reaction pathway. To enhance the inherent levels of diastereoselectivity observed in the aldol coupling of ketone **13** and aldehyde **14**, the matched chiral boron reagent (+)-Ipc_2BCl was used, leading to essentially complete stereocontrol in favour of 1,4-*syn* adduct **21**.

Elaboration of aldol adduct **21** to the C5–C17 aldehyde **15** began with an Evans–Tischenko 1,3-*anti* reduction (Scheme 5).[22] Treatment of **21** with a premixed solution of SmI_2 and propionaldehyde provided the alcohol **22** (80%, >95:5 dr).[23] Protection of the free hydroxyl at C7 in **22** with TESOTf/2,6-lutidine (90%) was followed by reductive removal of the C9 propionate ester with DIBAL-H to provide alcohol **24** (87%). The requisite C9 methyl ether of dolastatin 19 was then introduced via treatment of **24** with Meerwein's salt ($Me_3O\cdot BF_4$) and Proton Sponge™ to provide **25** in 96% yield.[24] At this point, cleavage of the primary DMB ether at C5 in the presence of the potentially labile allylic TBS ether at C13 was required. Pleasingly, use of conditions employed in our synthesis of callipeltoside A[11] (treatment with DDQ in CH_2Cl_2/pH 7 buffer (10:1), 60 °C, 10 min) provided alcohol **26** in 77% yield (99% based on recovered starting



Scheme 5. (a) SmI_2, EtCHO, THF, −10 °C; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (c) DIBAL-H, CH_2Cl_2, −78 °C; (d) $Me_3O\cdot BF_4$, Proton Sponge™, CH_2Cl_2, rt; (e) DDQ, CH_2Cl_2, pH 7 buffer, 60 °C; (f) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt.

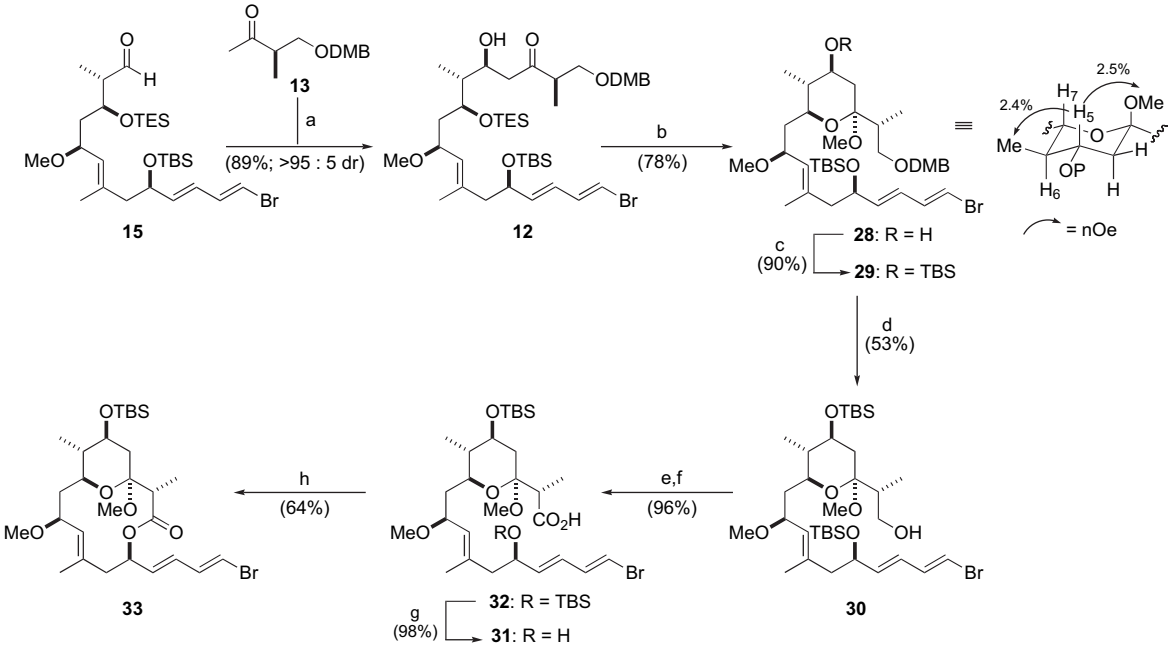
material **25**). Finally, Dess–Martin periodinane oxidation[25] of **26** completed the preparation of C5–C17 aldehyde **15** (85%), in readiness for the second 1,4-*syn* aldol coupling with ketone **13**.

This complex aldol coupling was achieved by enolization of methyl ketone **13** with *c*-Hex_2BCl/Et_3N, followed by addition of aldehyde **15**, to provide the expected Felkin–Anh adduct **12** in excellent yield and diastereoselectivity (89%, >95:5 dr) (Scheme 6). The high levels of substrate control for the 1,4-*syn* product can be attributed to the matched diastereofacial selectivity of the coupling partners. With the complete C1–C17 carbon backbone in place, attention was now focused on the assembly of the putative aglycon **27** of stereochemically reassigned dolastatin 19. Treatment of **12** with PPTS and trimethyl orthoformate in MeOH triggered cleavage of the C7-TES ether, with concomitant cyclization and methyl acetal formation, to provide **28** (78%). Confirmation of the stereochemical relationship across the hemiacetal moiety was provided by NOE analysis, with irradiation of H5 providing diagnostic enhancements of C3–OMe and C6–Me, which is consistent with their 1,3-diaxial and 1,2-*syn* orientations, respectively. Following TBS protection of the C5 hydroxyl (90%), the stage was set to prepare the C1 terminus for macrolactonization. In initial experiments, treatment of **29** with DDQ under the conditions used previously for the DMB deprotection of **25** led to hydrolysis of the methyl acetal at C3, along with undesired oxidation[25] of the C13-TBS ether. Following extensive optimization, oxidative cleavage of the primary DMB ether was achieved by treatment of **29** with DDQ in CH_2Cl_2 and pH 9 buffer (4:1) at 0 °C for 10 min, to provide primary alcohol **30** in 53% yield.

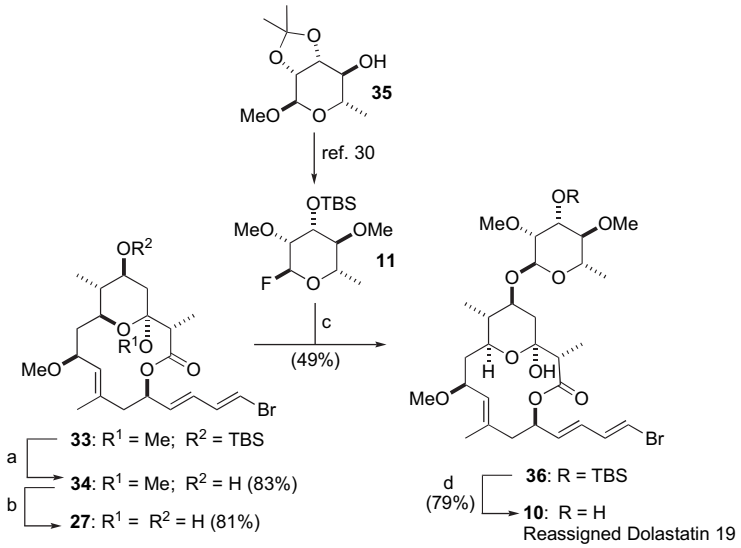
Gratifyingly, the subsequent three-step elaboration of alcohol **30** to the *seco*-acid **31** proved straightforward. Oxidation of **30** with Dess–Martin periodinane[26] was followed by Pinnick oxidation[27] of the intermediate aldehyde to provide the corresponding carboxylic acid **32** in 96% yield. Selective cleavage of the allylic TBS ether at C13 was achieved by treatment of **32** with TBAF to give the requisite *seco*-acid **31** (98%). The 14-membered macrolide was readily formed under standard Yamaguchi macrolactonization conditions.[28] Thus, treatment of **31** with 2,4,6-trichlorobenzoylchloride and Et_3N, followed by slow addition of the intermediate anhydride to DMAP in toluene at 60 °C, provided the protected aglycon **33** in 64% yield.

As shown in Scheme 7, completion of the dolastatin 19 aglycon **27** was achieved by cleavage of the remaining silyl group at C5 with TBAF (83%), followed by mild acidic hydrolysis (PPTS) of the methyl acetal **34** (81%). At this stage, an early indication of the likely validity of our stereochemical reassignment was provided by the remarkably close correlation of both the ^1H and ^{13}C NMR spectra of the synthetic aglycon **27** with the reported data for the macrolide region of dolastatin 19.[8]

Completion of the synthesis of dolastatin 19 required the stereocontrolled glycosylation of aglycon **27**. L-Rhamnose derived fluorosugar **11**, previously utilized in our synthesis of aurisides A and B,[11] was prepared in seven steps from alcohol **35**.[29] The coupling of **27** and **11** was performed using Mukaiyama's conditions ($SnCl_2/AgClO_4$)[30] to yield **36** with complete α-selectivity (49%). Finally, removal of the remaining TBS ether with HF·pyridine provided stereochemically reassigned dolastatin 19 (**10**) in 79% yield. Gratifyingly, the spectroscopic data obtained for synthetic **10** (^1H and ^{13}C NMR, IR and MS), together with the measured specific rotation ($[\alpha]_D^{20}$ +2.2 (*c* 0.18, MeOH) cf. +7.5 (*c* 0.04, MeOH)), correlated fully with that of natural dolastatin 19.[8] Molecular modelling (Fig. 5) of the structure indicated in **10** (i.e., 2*S*, 3*S*, 5*S*, 6*R*, 7*S*, 9*S*, 13*R*) reveals that



Scheme 6. (a) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C; **13**, −78 → −27 °C; (b) PPTS, $(MeO)_3CH$, MeOH; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (d) DDQ, pH 9 buffer, CH_2Cl_2, 0 °C; (e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt; (g) TBAF, THF, 0 °C → rt; (h) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, **31**, toluene, rt; then DMAP, 60 °C.



Scheme 7. (a) TBAF, THF, 0 °C→rt; (b) PPTS, wet MeCN, rt; (c) $SnCl_2$, $AgClO_4$, Et_2O, 4 Å molecular sieves, 0 °C→rt; (d) HF·pyridine, THF, 0 °C→rt.

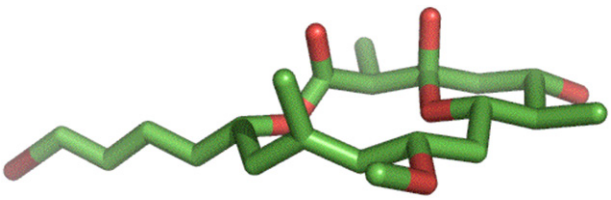


Figure 5. Global minimum energy conformation of dolastatin 19 aglycon (stereochemically reassigned).

this structure is indeed also predicted to adopt a similar conformation as both the auriside and callipeltoside aglycons.

Further convincing evidence in support of our stereochemical reassignment of the natural product is provided by the comparable levels of biological activity displayed by synthetic dolastatin 19 to that isolated in nature. In screening assays against three representative cancer cell lines HT-29 (colon), NSCLC (lung) and MDA-MB-231 (breast), synthetic dolastatin 19 displayed GI_{50} values of 0.89, 1.04 and 1.20 μg/mL, respectively, consistent with the biological activity reported for natural dolastatin 19.[31]

5. Conclusions

In summary, a stereochemical reassignment of the cytotoxic marine macrolide (+)-dolastatin 19, isolated from the sea hare *D. auricularia*, has been made, based upon information gained from conformational analysis and comparison with related natural products.[32] This reassignment has been validated by completion of the first total synthesis of dolastatin 19 (23 steps, 1.7% overall yield). The highly stereocontrolled route utilizes contemporary aldol methodology and has generated sufficient quantities of material to facilitate biological studies which, in turn, provided further compelling evidence for the validity of our stereochemical reassignment and should give valuable information about the potential of dolastatin 19 as an anticancer agent.

6. Experimental

6.1. General

Molecular modelling was performed using Macromodel (Version 8.0).[33] To thoroughly probe the conformational potential surface, a 10,000 step Monte Carlo Multiple Minimum[34] search was performed using the MM2 force field,[35] in conjunction with the generalized Born/surface area (GB/SA) chloroform solvent model.[36]

6.1.1. Aldol adduct 18. To a stirred solution of (*R*)-BINOL (5.33 g, 18.6 mmol) and powdered CaH_2 (250 mg) in THF (60 mL) at rt was added Ti(O*i*-Pr)$_4$ (5.50 mL, 18.6 mmol) dropwise. The resultant orange solution was stirred at rt for 1 h before being cooled to −78 °C. Silyl dienolate **17**[18] (6.00 g, 37.3 mmol) in THF (50 mL) was added via cannula and the solution was stirred for 10 min before a solution of (*E*,*E*)-bromodienal **16**[17] (14.8 g, 74.5 mmol) in THF (50 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 72 h and quenched by addition of saturated aqueous $NaHCO_3$ (200 mL). The resultant suspension was filtered through Celite with CH_2Cl_2 (400 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (10% EtOAc/hexane) to yield aldol adduct **18** as a colourless oil (9.58 g, 93%; 94% ee); R_f 0.28 (30% EtOAc/hexane); $[\alpha]_D^{20}$ +19.7 (*c* 2.2, $CHCl_3$); IR (neat) 3452, 1646, 1228, 1153, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, dd, 13.6, 10.9 Hz, H_{16}), 6.35 (1H, d, J=13.6 Hz, H_{17}), 6.20 (1H, dd, J=15.0, 10.9 Hz, H_{15}), 5.77–5.69 (2H, m, H_{10} and H_{14}), 4.36 (1H, m, H_{13}), 3.69 (3H, s, OCH_3), 2.35 (2H, d, J=6.8 Hz, H_{12a} and H_{12b}), 2.19 (3H, s, Me_{11}), 1.80 (1H, br s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.3, 136.4, 135.7, 127.9, 118.3, 109.6, 69.7, 50.9, 48.5, 19.0; HRMS (ES+) Calculated for $C_{11}H_{15}BrO_3Na$ [M+Na$^+$] 297.0102, found 297.0104.

6.1.2. TBS ether 18a. To a stirred solution of aldol adduct **18** (1.61 g, 5.85 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added TBSCl (2.21 g, 14.6 mmol) followed by imidazole (1.08 g, 15.8 mmol). The reaction mixture was stirred at rt for 2 h before partitioning between $NaHCO_3$ and CH_2Cl_2 (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (5–10% EtOAc/hexane) to yield TBS ether **18a** as a colourless oil (2.28 g, 99%); R_f 0.43 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +5.1 (*c* 3.1, $CHCl_3$); IR (neat) 3064, 1719, 1648, 1584, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, dd, 13.5, 10.8 Hz, H_{16}), 6.30 (1H, d, J=13.5 Hz, H_{17}), 6.10 (1H, dd, J=15.3, 10.9 Hz, H_{15}), 5.69 (1H, obsd, H_{14}), 5.68 (1H, s, H_{10}), 4.30 (1H, m, H_{13}), 3.69 (3H, s, OCH_3), 2.34 (2H, dd, J=13.0, 7.3 Hz, H_{12a}), 2.26 (1H, dd, J=13.0, 5.4 Hz, H_{12b}), 2.17 (3H, s, Me_{11}), 0.87 (9H, s, SiC(CH_3)$_3$, 0.02 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 155.7, 137.0, 136.6, 126.9, 118.3, 108.8, 71.2, 50.8, 49.6, 25.7, 25.3, 19.6, −4.5, −5.0; HRMS (ES+) Calculated for $C_{17}H_{29}BrSiO_3Na$ [M+Na^+] 411.0967, found 411.0958.

6.1.3. Allylic alcohol 19. To a stirred solution of ester **18a** (2.69 g, 9.82 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added DIBAL-H (1 M in CH_2Cl_2, 18.7 mL, 18.7 mmol). The resulting solution was stirred at −78 °C for 30 min and then added via cannula to a mixture of CH_2Cl_2 (50 mL) and saturated aqueous sodium potassium tartrate (50 mL). The mixture was stirred at rt for 1 h and the phases were then separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/hexane) yielded alcohol **19** (1.97 g, 88%); R_f 0.21 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +0.3 (*c* 3.0, $CHCl_3$); IR (neat) 3331, 3063, 1667, 1584, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, dd, 13.4, 10.9 Hz, H_{16}), 6.27 (1H, d, J=13.5 Hz, H_{17}), 6.07 (1H, dd, J=15.2, 10.9 Hz, H_{15}), 5.70 (1H, dd, J=15.2, 6.0 Hz, H_{14}), 5.42 (1H, dd, J=6.8, 6.0 Hz, H_{10}), 4.24 (1H, m, H_{13}), 4.12 (2H, m, CH_2OH), 2.24 (1H, dd, J=13.3, 7.1 Hz, H_{12a}), 2.15 (1H, dd, J=13.3, 5.8 Hz, H_{12b}), 1.68 (3H, s, Me_{11}), 1.24 (1H, m, OH), 0.88 (9H, s, SiC(CH_3)$_3$, 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.9, 135.6, 127.0, 126.4, 108.2, 71.5, 59.3, 48.4, 29.7, 25.8, 25.3, 17.1, −4.5, −4.9; HRMS (ES+) Calculated for $C_{16}H_{29}BrSiO_2Na$ [M+Na^+] 383.1018, found 383.1013.

6.1.4. Aldehyde 14. To a stirred solution of alcohol **18** (1.64 g, 4.54 mmol) in Et_2O (5 mL) at rt was added MnO_2 (3.95 g, 45.4 mmol). After 30 min, TLC analysis showed some reaction proceeding and further MnO_2 (3.95 g, 45.4 mmol) was added. The suspension was stirred for 1 h before addition of more MnO_2 (3.95 g, 45.4 mmol). After a further 1 h, the mixture was then filtered through a short plug of Celite and washed thoroughly with Et_2O. Flash column chromatography (20% EtOAc/hexane) afforded the desired aldehyde **14** (1.40 g, 86%); R_f 0.51 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +3.81 (*c* 1.1, $CHCl_3$); IR (neat) 1674, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.97 (1H, d, J=7.9 Hz, H_9), 6.68 (1H, dd, J=13.4, 10.9 Hz, H_{16}), 6.31 (1H, d, J=13.4 Hz, H_{17}), 6.10 (1H, dd, J=15.2, 10.9 Hz, H_{15}), 5.87 (1H, d, J=7.9 Hz, H_{10}), 5.68 (1H, dd, J=15.2, 6.3 Hz, H_{14}), 4.31 (1H, m, H_{13}), 2.40 (1H, dd, J=13.1, 7.2 Hz, H_{12a}), 2.34 (1H, dd, J=13.1, 5.2 Hz, H_{12b}), 2.18 (3H, s, Me_{11}), 0.87 (9H, s, SiC(CH_3)$_3$), 0.02 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 159.6, 136.6, 136.5, 130.0, 127.3, 109.2, 71.5, 49.1, 25.7, 18.6, 18.1, −4.4, −4.9; HRMS (ES+) Calculated for $C_{16}H_{27}BrSiO_2Na$ [M+Na^+] 381.0861, found 381.0864.

6.1.5. Methyl ketone 13. To a stirred solution of methyl-(*R*)-3-hydroxy-2-methylpropionate (6.04 mL, 54.5 mmol) was added 3,4-dimethoxybenzyl-2,2,2-trichloroacetimidate (20.4 g, 65.4 mmol) in CH_2Cl_2 (150 mL) at rt followed by PPTS (1.64 g, 6.54 mmol). After stirring for 1 h the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow solid was triturated with ice-cold hexane (3×100 mL). The hexane fractions were concentrated in vacuo and purified by flash silica column (20–30% EtOAc/hexane) to yield the corresponding dimethoxybenzyl ether (9.94 g, 68%) as a colourless oil; R_f 0.49 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −8.5 (*c* 1.14, $CHCl_3$); IR (neat) 2950, 2861, 1737, 1593, 1516, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85–6.79 (3H, m, ArH), 4.43 (2H, s, OCH_2Ar), 3.86 (3H, s, ArOCH_3), 3.84 (3H, s, ArOCH_3), 3.66 (3H, s, OCH_3), 3.62 (1H, dd, J=9.3, 7.3 Hz, H_{1a}), 3.44 (1H, dd, J=9.2, 5.9 Hz, H_{1b}), 2.80–2.71 (1H, m, H_2), 1.15 (3H, d, J=7.0 Hz, Me_2), 1.07 (3H, s, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 148.9, 148.5, 130.6, 120.0, 110.9, 110.8, 72.9, 71.6, 55.8, 55.7, 51.6, 40.1, 13.9; HRMS (ES+) Calculated for $C_{14}H_{24}NO_5$ [M+NH_4^+] 286.1654, found 286.1649.

N,*O*-Dimethylhydroxylamine hydrochloride (5.42 g, 55.6 mmol) was placed in a flask and dried by stirring under vacuum (1 mmHg) for 1 h. The flask was flushed with argon and a solution of dimethoxybenzyl ether (9.94 g, 37.0 mmol) in THF (150 mL) was added via cannula. The resulting slurry was cooled to −20 °C and isopropylmagnesium chloride (2.0 M in THF, 55.6 mL, 111 mmol) was added dropwise, maintaining the temperature at −20 °C. After stirring for 1.5 h the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. Purification by flash column chromatography (50% EtOAc/hexane) yielded the corresponding Weinreb amide (9.17 g, 83%) as a colourless oil; R_f 0.21 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −7.9 (*c* 1.04, $CHCl_3$); IR (neat) 3820, 1650, 1593, 1514, 1462, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87–6.80 (3H, m, ArH), 4.45 (2H, AB spin system, J=12.0 Hz, OCH_2Ar), 3.87 (3H, s, ArOCH_3), 3.86 (3H, s, ArOCH_3), 3.71–3.67 (1H, m, H_{1a}), 3.69 (3H, s, NOCH_3), 3.40 (1H, dd, J=8.8, 5.8 Hz, H_{1b}), 3.30–3.23 (1H, m, H_2), 3.20 (3H, s, NCH_3), 1.11 (3H, d, J=7.0 Hz, Me_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 148.9, 148.4, 130.9, 120.0, 110.9, 110.8, 73.0, 72.3, 65.1, 61.4, 55.8, 55.7, 35.8, 14.1; HRMS (ES+) Calculated for $C_{15}H_{24}O_5Na$ [M+H^+] 298.1654, found 298.1651.

To a stirred solution of Weinreb amide[19] (5.94 g, 20.0 mmol) in THF (80 mL) at 0 °C was added methylmagnesium iodide (3.0 M in Et_2O, 16.6 mL, 49.9 mmol). The resulting solution

was stirred for 1.5 h and quenched by the addition of saturated aqueous NH_4Cl (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×80 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (25–30% EtOAc/hexane) to yield ketone **13** as a colourless oil (3.85 g, 77%); R_f 0.30 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −7.7 (*c* 1.04, $CHCl_3$); IR (neat) 1712, 1515, 1464, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84–6.80 (3H, m, ArH), 4.46 (2H, s, OCH_2Ar), 3.89 (3H, s, ArOCH_3), 3.87 (3H, s, ArOCH_3), 3.66 (1H, dd, *J*=9.0, 8.0 Hz, H_{1a}), 3.49 (1H, dd, *J*=9.0, 5.3 Hz, H_{1b}), 2.92–2.83 (1H, m, H_2), 1.09 (3H, s, Me_2), 1.07 (3H, s, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 149.0, 148.6, 130.6, 120.1, 111.0, 110.9, 73.1, 71.8, 55.9, 55.8, 47.2, 29.0, 13.4; HRMS (ES+) Calculated for $C_{14}H_{20}O_4Na$ [M+Na^+] 275.1259, found 275.1259.

6.1.6. Aldol adduct 21. To a stirred solution of (+)-Ipc_2BCl (12.9 g, 40.2 mmol) [dried by stirring under vacuum (1 mmHg) at rt for 1.5 h] in Et_2O (25 mL) at 0 °C was added triethylamine (7.32 mL, 52.5 mmol), followed by ketone **13** (7.76 g, 30.9 mmol) in Et_2O (30 mL) via cannula. The reaction mixture was stirred for 1 h, cooled to −78 °C and a solution of aldehyde **14** (3.70 g, 10.3 mmol) in Et_2O (30 mL) then added via cannula. The reaction mixture was stirred at −78 °C for 1 h and at −27 °C for 16 h. The reaction then was quenched by the addition of pH 7 buffer (100 mL) and stirred at 0 °C for 1 h. The phases were separated and the aqueous phase was extracted with Et_2O (3×60 mL). The combined organic layers were washed with brine (100 mL) and stirred over silica gel for 30 min. The resulting slurry was filtered, concentrated in vacuo, and purified by flash column chromatography (20–50% EtOAc/hexane) to yield aldol adduct **21** as a pale yellow oil (5.54 g, 88%); R_f 0.26 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −5.84 (*c* 1.25, $CHCl_3$); IR (neat) 3464, 2929, 2856, 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85–6.81 (3H, m, ArH), 6.68 (1H, dd, *J*=13.6, 11.0 Hz, H_{16}), 6.27 (1H, d, *J*=13.6 Hz, H_{17}), 6.06 (1H, dd, *J*=15.2, 11.0 Hz, H_{15}), 5.69 (1H, dd, *J*=15.2, 5.8 Hz, H_{14}), 5.20 (1H, d, *J*=8.4 Hz, H_{10}), 4.85–4.77 (1H, m, H_9), 4.42 (2H, s, OCH_2Ar), 4.25 (1H, dd, *J*=12.4, 5.9 Hz, H_{13}), 3.88 (3H, s, ArOCH_3), 3.87 (3H, s, ArOCH_3), 3.60 (1H, dd, *J*=8.7, 8.4 Hz, H_{5a}), 3.46 (1H, dd, *J*=8.9, 5.1 Hz, H_{5b}), 2.97 (1H, d, *J*=3.3 Hz, O*H*), 2.91–2.84 (1H, m, H_6), 2.72–2.66 (1H, m, H_{8a}), 2.66–2.62 (1H, m, H_{8b}), 2.22 (1H, dd, *J*=13.6, 7.1 Hz, H_{12a}), 2.12 (1H, dd, *J*=13.4, 5.8 Hz, H_{12b}), 1.68 (3H, s, Me_{11}), 1.07 (3H, d, *J*=7.0 Hz, Me_6), 0.88 (9H, s, SiC(CH_3)$_3$), 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 149.1, 148.7, 137.8, 136.9, 134.9, 130.4, 129.1, 127.9, 126.4, 111.0, 110.9, 108.2, 73.2, 71.7, 71.4, 64.6, 55.9, 55.8, 48.7, 48.2, 46.9, 25.8, 18.2, 17.4, 13.2, −4.4, −4.9; HRMS (ES+) Calculated for $C_{30}H_{47}O_6Si^{79}BrNa$ [M+Na^+] 633.2223, found 633.2217.

6.1.7. Hydroxy ester 22. To a stirred solution of propionaldehyde (3.90 mL, 54.1 mmol) in THF (45 mL) at −10 °C was added freshly prepared samarium diiodide (45.1 mL, 0.1 M in THF, 4.51 mmol). A solution of aldol adduct **21** (5.54 g, 9.01 mmol) in THF (45 mL) was added via cannula and the resulting yellow solution was stirred at −10 °C for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and stirred for 10 min. The phases were separated and the aqueous phase was extracted with Et_2O (3×60 mL). The combined organic layers were dried ($MgSO_4$), washed with brine (100 mL), concentrated in vacuo and purified by flash column chromatography (20–25% EtOAc/hexane) to yield hydroxy ester **22** as a colourless oil (4.81 g, 80%); R_f 0.29 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −16.9 (*c* 1.0, $CHCl_3$); IR (neat) 3498, 2934, 2856, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88–6.81 (3H, m, ArH), 6.66 (1H, dd, *J*=13.6, 10.8 Hz, H_{16}), 6.26 (1H, d, *J*=13.6 Hz, H_{17}), 6.03 (1H, dd, *J*=15.5, 11.0 Hz, H_{15}), 5.78–5.71 (1H, m, H_9), 5.66 (1H, dd, *J*=15.3, 5.9 Hz, H_{14}), 5.15 (1H, d, *J*=9.2 Hz, H_{10}), 4.44 (2H, s, OCH_2Ar), 4.25 (1H, dd, *J*=12.7, 6.3 Hz H_{13}), 3.88 (3H, s, ArOCH_3), 3.88 (3H, s, ArOCH_3), 3.54–3.44 (3H, m, H_{5a}, H_{5b} and H_7), 3.35 (1H, d, *J*=4.2 Hz, O*H*), 2.29 (2H, dq, *J*=8.0, 3.1 Hz, OC(O)CH_2CH$_3$), 2.23 (1H, dd, *J*=13.2, 6.8 Hz, H_{12a}), 2.12 (1H, dd, *J*=12.9, 6.3 Hz, H_{12b}), 1.87–1.78 (2H, m, H_6 and H_{8a}), 1.75 (3H, s, Me_{11}), 1.53–1.46 (1H, m, H_{8b}), 1.20 (3H, t, *J*=7.5 Hz, OC(O)CH$_2$CH_3), 0.92 (3H, d, *J*=7.0 Hz, Me_6), 0.88 (9H, s, SiC(CH_3)$_3$), 0.02 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 149.0, 148.6, 137.8, 136.9, 136.0, 130.7, 127.1, 126.4, 120.2, 111.0, 111.0, 108.1, 73.8, 73.2, 71.3, 70.7, 68.4, 55.9, 55.8, 48.4, 40.4, 38.8, 27.8, 25.8, 18.2, 17.5, 13.9, 9.2, −4.4, −4.9; HRMS (ES+) Calculated for $C_{33}H_{57}O_7Si^{79}BrN$ [M+NH_4^+] 686.3082, found 686.3105.

The 1,3-*anti* stereochemistry was proved using Rychnovsky's method for the assignment of diol stereochemistry.[23]

6.1.8. TES ether 23. To a stirred solution of alcohol **22** (950 mg, 1.42 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added 2,6-lutidine (0.66 mL, 5.67 mmol). The reaction mixture was stirred at −78 °C for 10 min before triethylsilyl trifluoromethanesulfonate (0.96 mL, 4.26 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min and then quenched by the addition of saturated aqueous NH_4Cl (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (15–20% EtOAc/hexane) to yield TES ether **23** (1.00 g, 90%); R_f 0.55 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −3.7 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2877, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89–6.81 (3H, m, ArH), 6.64 (1H, dd, *J*=13.6, 11.2 Hz, H_{16}), 6.24 (1H, d, *J*=13.8 Hz, H_{17}), 6.02 (1H, dd, *J*=15.3, 10.8 Hz, H_{15}), 5.64 (1H, dd, *J*=15.5, 5.9 Hz, H_{14}), 5.52–5.45 (1H, m, H_9), 5.02 (1H, d, *J*=9.1 Hz, H_{10}), 4.43 (2H, AB spin system, *J*=12.4 Hz, OCH_2Ar), 4.23 (1H, dd, *J*=12.5, 6.1 Hz, H_{13}), 3.93–3.85 (1H, obsd, H_7), 3.88 (3H, s, ArOCH_3), 3.88 (3H, s, ArOCH_3), 3.35 (1H, dd, *J*=9.2, 7.3 Hz, H_{5a}), 3.26 (1H, dd, *J*=9.2, 6.6 Hz, H_{5b}), 2.26–2.18 (1H, obsd, H_{12a}), 2.22 (2H, q, *J*=7.1 Hz, OC(O)CH_2CH$_3$), 2.08 (1H, dd, *J*=12.9, 6.6 Hz, H_{12b}), 2.03–1.98 (1H, m, H_6), 1.76 (3H, s, Me_{11}), 1.69–1.61 (1H, m, H_{8a}), 1.47–1.38 (1H, m, H_{8b}), 1.08 (3H, t, *J*=7.7 Hz, OC(O)CH$_2$CH_3), 0.95 (9H, t, *J*=8.2 Hz, Si(CH$_2$CH_3)$_3$), 0.89 (3H, d, *J*=7.1 Hz, Me_6), 0.87 (9H, s, SiC(CH$_3$)$_3$), 0.58 (6H, q, *J*=7.8 Hz, Si(CH_2CH$_3$)$_3$), 0.02 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 149.0, 148.5, 137.9, 137.0, 135.2, 131.3, 127.6, 126.3, 120.0, 110.9, 110.8, 108.0, 72.9, 72.5, 71.1, 69.4, 68.9, 55.9,

55.8, 48.7, 39.7, 37.7, 27.8, 25.8, 18.2, 17.2, 11.6, 9.1, 6.9, 5.1, −4.5, −4.9; HRMS (ES+) Calculated for $C_{39}H_{67}O_7Si_2{}^{79}BrNa$ [M+Na$^+$] 805.3506, found 805.3510.

6.1.9. Alcohol 24. To a stirred solution of ester **23** (1.00 g, 1.28 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added DIBAL-H (1 M in CH_2Cl_2, 6.38 mL, 6.38 mmol). The resulting solution was stirred at −78 °C for 30 min and then added via cannula to a mixture of CH_2Cl_2 (20 mL) and saturated aqueous sodium potassium tartrate (20 mL). The mixture was stirred at rt for 1 h and the phases were then separated. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the organic phases were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/hexane) yielded alcohol **24** as a colourless oil (0.80 g, 87%); R_f 0.41 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −0.96 (*c* 1.05, $CHCl_3$); IR (neat) 3443, 2953, 1594 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91–6.80 (3H, m, ArH), 6.68 (1H, dd, *J*=13.6, 11.2 Hz, H_{16}), 6.26 (1H, d, *J*=13.4 Hz, H_{17}), 6.06 (1H, dd, *J*=15.0, 11.0 Hz, H_{15}), 5.70 (1H, dd, *J*=15.3, 5.9 Hz, H_{14}), 5.21 (1H, d, *J*=8.2 Hz, H_{10}), 4.64–4.57 (1H, m, H_9), 4.43 (2H, AB spin system, *J*=11.8 Hz, OCH_2Ar), 4.25 (1H, dd, *J*=12.2, 6.1 Hz, H_{13}), 4.01 (1H, dd, *J*=10.1, 5.9 Hz, H_7), 3.88 (3H, s, ArOCH_3), 3.87 (3H, s, ArOCH_3), 3.44 (1H, dd, *J*=8.9, 5.6 Hz, H_{5a}), 3.30 (1H, dd, *J*=8.7, 6.6 Hz, H_{5b}), 2.56 (1H, d, *J*=3.0 Hz, O*H*), 2.21 (1H, dd, *J*=13.1, 7.1 Hz, H_{12a}), 2.14–2.07 (1H, obsd, H_6), 2.11 (1H, dd, *J*=12.4, 5.6 Hz, H_{12b}), 1.68 (3H, s, Me_{11}), 1.57–1.51 (2H, m, H_{8a} and H_{8b}), 0.97 (9H, t, *J*=8.0 Hz, Si(CH$_2$CH_3)$_3$), 0.93 (3H, d, *J*=7.0 Hz, Me_6), 0.87 (9H, s, SiC(CH_3)$_3$), 0.63 (6H, q, *J*=7.8 Hz, Si(CH_2CH$_3$)$_3$), 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.5, 138.0, 136.9, 133.4, 131.7, 131.2, 126.3, 120.1, 111.0, 110.9, 108.1, 72.9, 72.4, 71.5, 71.4, 65.4, 55.9, 55.8, 48.4, 39.5, 38.9, 25.8, 18.2, 17.2, 12.8, 6.9, 5.0, −4.4, −4.9; HRMS (ES+) Calculated for $C_{36}H_{63}O_6Si^{79}BrNa$ [M+Na$^+$] 749.3244, found 749.3244.

6.1.10. Methyl ether 25. To a stirred solution of alcohol **24** (2.93 g, 4.02 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Proton Sponge™ (9.49 g, 44.3 mmol), followed by trimethyloxonium tetrafluoroborate (5.39 g, 36.4 mmol). The resulting solution was stirred at rt for 1 h and quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with citric acid (40 mL, 10% weight solution), dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (10–15% EtOAc/hexane) to yield **25** as a colourless oil (2.86 g, 96%); R_f 0.55 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −10.9 (*c* 1.0, $CHCl_3$); IR (neat) 2953, 1593, 1516 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91–6.80 (3H, m, ArH), 6.66 (1H, dd, *J*=13.4, 10.8 Hz, H_{16}), 6.25 (1H, d, *J*=13.4 Hz, H_{17}), 6.05 (1H, dd, *J*=15.2, 10.8 Hz, H_{15}), 5.69 (1H, dd, *J*=15.3, 6.3 Hz, H_{14}), 5.03 (1H, d, *J*=9.2 Hz, H_{10}), 4.42 (2H, s, OCH_2Ar), 4.26 (1H, dd, *J*=12.7, 6.3 Hz, H_{13}), 4.08–4.00 (2H, m, H_9 and H_7), 3.88 (3H, s, ArOCH_3), 3.87 (3H, s, ArOCH_3), 3.39 (1H, dd, *J*=9.4, 6.1 Hz, H_{5a}), 3.23–3.17 (1H, m, H_{5b}), 3.17 (3H, s, OCH_3), 2.28 (1H, dd, *J*=13.2, 6.4 Hz, H_{12a}), 2.15 (1H, dd, *J*=13.2, 6.6 Hz, H_{12b}), 2.03–1.95 (1H, m, H_6), 1.67 (3H, s, Me_{11}), 1.48–1.39 (1H, m, H_{8a}), 1.39–1.30 (1H, m, H_{8b}), 0.97 (9H, t, *J*=7.8 Hz, Si(CH$_2$CH_3)$_3$), 0.91 (3H, d, *J*=7.1 Hz, Me_6), 0.88 (9H, s, Si(CH_3)$_3$), 0.62 (6H, q, *J*=7.7 Hz, Si(CH_2CH$_3$)$_3$), 0.03 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 148.4, 137.9, 136.9, 134.7, 131.4, 129.9, 126.5, 119.9, 110.8, 110.8, 108.2, 73.4, 72.8, 72.7, 71.5, 69.6, 55.9, 55.8, 55.4, 48.7, 40.0, 39.0, 25.8, 18.2, 17.2, 12.0, 7.0, 5.2, −4.4, −4.9; HRMS (ES+) Calculated for $C_{37}H_{65}O_6Si_2{}^{79}BrNa$ [M+Na$^+$] 763.3401, found 763.3401.

6.1.11. Alcohol 26. To a refluxing (60 °C), stirred solution of DMB ether **25** (200 mg, 0.27 mmol) in CH_2Cl_2/pH 7 buffer (25 mL/2.5 mL) was added DDQ (73 mg, 0.32 mmol). After 10 min, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the organic phases were combined, dried ($MgSO_4$) and purified by flash column chromatography (15–20% EtOAc/hexane) to yield alcohol **26** as a colourless oil (123 mg, 77%) and unreacted starting material **25** (45 mg, 22%); R_f 0.46 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −14.5 (*c* 2.14, $CHCl_3$); IR (neat) 3425, 2954 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (1H, dd, *J*=13.5, 10.9 Hz, H_{16}), 6.26 (1H, d, *J*=13.6 Hz, H_{17}), 6.05 (1H, dd, *J*=15.3, 11.0 Hz, H_{15}), 5.69 (1H, dd, *J*=15.3, 6.2 Hz, H_{14}), 5.03 (1H, d, *J*=9.0 Hz, H_{10}), 4.26 (1H, dd, *J*=12.6, 6.4 Hz, H_{13}), 4.03–3.98 (2H, m, H_9 and H_7), 3.73–3.67 (1H, m, H_{5a}), 3.53–3.47 (1H, m, H_{5b}), 3.19 (3H, s, OCH_3), 2.48–2.44 (1H, m, H_6), 2.30 (1H, dd, *J*=13.6, 6.3 Hz, H_{12a}), 2.18 (1H, dd, *J*=13.3, 6.6 Hz, H_{12b}), 1.78–1.73 (1H, m, O*H*), 1.69 (3H, s, Me_{11}), 1.65–1.61 (1H, m, H_{8a}), 1.53–1.47 (1H, m, H_{8b}), 0.99 (9H, t, *J*=8.0 Hz, Si(CH$_2$CH_3)$_3$), 0.96 (3H, d, *J*=6.7 Hz, Me_6), 0.89 (9H, s, SiC(CH_3)$_3$), 0.65 (6H, q, *J*=7.9 Hz, Si(CH_2CH$_3$)$_3$), 0.04 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 136.9, 135.4, 129.4, 126.6, 108.3, 73.9, 72.4, 71.7, 65.2, 55.4, 48.7, 40.6, 40.5, 25.8, 18.2, 17.4, 13.1, 6.9, 5.2, −4.4, −4.9; HRMS (ES+) Calculated for $C_{28}H_{55}{}^{79}BrO_4Si_2Na$ [M+Na$^+$] 613.2720, found 613.2720.

6.1.12. Aldol adduct 12. To a solution of alcohol **26** (416 mg, 0.70 mmol) and pyridine (0.57 mL, 7.03 mmol) in CH_2Cl_2 (6 mL) at rt was added Dess–Martin periodinane (1.19 mg, 2.81 mmol). After stirring at rt for 1 h, hexane (6 mL) was added and the resultant suspension filtered through a silica plug (10% EtOAc/hexane) to provide aldehyde **15** as a colourless oil (350 mg, 85%), which was used directly without further purification.

To a solution of ketone **13** (196 mg, 0.78 mmol) in Et_2O (2 mL) at 0 °C was added triethylamine (39.1 μL, 0.28 mmol) and dicyclohexylboron chloride (51.2 μL, 0.23 mmol). The reaction mixture was stirred at 0 °C for 1 h, cooled to −78 °C and aldehyde **15** (92 mg, 0.16 mmol) in Et_2O (1 mL) was added via cannula. After 1 h at −78 °C and 16 h at −27 °C, the reaction mixture was quenched by the addition of pH 7 buffer (3 mL) and stirred at 0 °C for 1 h. The phases were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (1% Et_3N in 20% EtOAc/hexane) to yield aldol adduct **12** as a pale yellow oil (120 mg, 89%); R_f 0.25 (30%

EtOAc/hexane); $[\alpha]_D^{20}$ +17.7 (*c* 2.15, $CHCl_3$); IR (neat) 3497, 2953, 2930, 2857, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87–6.80 (3H, m, ArH), 6.67 (1H, dd, *J*=13.4, 11.2 Hz, H_{16}), 6.26 (1H, d, *J*=13.4 Hz, H_{17}), 6.05 (1H, dd, *J*=15.2, 11.0 Hz, H_{15}), 5.69 (1H, dd, *J*=15.3, 6.3 Hz, H_{14}), 5.01 (1H, d, *J*=9.1 Hz, H_{10}), 4.44–4.40 (1H, obsd, H_5) 4.42 (2H, AB spin system, *J*=12.0 Hz, OCH_2Ar), 4.26 (1H, dd, *J*=12.7, 6.3 Hz, H_{13}), 4.04–3.92 (2H, m, H_7 and H_9), 3.88 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 3.64–3.56 (1H, m, H_{1a}), 3.48–3.42 (1H, m, H_{1b}), 3.18 (3H, s, OCH_3), 2.94–2.83 (1H, m, H_2), 2.73 (1H, dd, *J*=17.1, 8.0 Hz, H_{4a}), 2.55 (1H, dd, *J*=16.7, 4.7 Hz, H_{4b}), 2.30 (1H, dd, *J*=12.9, 5.6 Hz, H_{12a}), 2.17 (1H, dd, *J*=13.1, 7.1 Hz, H_{12b}), 1.75–1.60 (3H, obsd, H_{8a}, H_{8b} and H_6), 1.67 (3H, s, Me_{11}), 1.07 (3H, d, *J*=7.3 Hz, Me_2), 0.98 (9H, t, *J*=8.0 Hz, $Si(CH_2CH_3)_3$), 0.96 (3H, d, *J*=7.5 Hz, Me_6), 0.89 (9H, s, $SiC(CH_3)_3$), 0.64 (6H, q, *J*=7.8 Hz, $Si(CH_2CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 149.0, 148.6, 137.6, 136.9, 135.6, 130.6, 129.2, 126.7, 120.1, 111.0, 110.9, 108.3, 73.8, 73.5, 73.1, 71.9, 71.8, 67.3, 55.9, 55.8, 55.3, 48.7, 47.0, 46.9, 41.7, 41.0, 25.8, 18.2, 17.5, 13.3, 10.6, 6.9, 5.2, −4.4, −4.9; HRMS (ES+) Calculated for $C_{42}H_{73}{}^{79}BrO_8Si_2Na$ [M+Na^+] 863.3925, found 863.3925.

6.1.13. Methyl acetal 28. To a stirred solution of ketone **12** (120 mg, 0.14 mmol) and trimethyl orthoformate (0.46 mL) in MeOH (4.6 mL) at rt was added PPTS (3.6 mg, 0.014 mmol). The resulting solution was stirred at rt for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine (8 mL), dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (1% Et_3N in 40% EtOAc/hexane) to yield methyl acetal **28** as a pale yellow oil (81 mg, 78%); R_f 0.23 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −19.2 (*c* 1.2, $CHCl_3$); IR (neat) 3450, 2932, 2857, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93–6.81 (3H, m, ArH), 6.67 (1H, dd, *J*=13.4, 11.2 Hz, H_{16}), 6.26 (1H, d, *J*=13.2 Hz, H_{17}), 6.06 (1H, dd, *J*=15.3, 11.0 Hz, H_{15}), 5.69 (1H, dd, *J*=15.3, 6.1 Hz, H_{14}), 5.09 (1H, d, *J*=8.7 Hz, H_{10}), 4.45 (2H, AB spin system, *J*=12.0 Hz, OCH_2Ar), 4.26 (1H, dd, *J*=12.5, 6.3 Hz, H_{13}), 4.23–4.17 (1H, m, H_9), 3.89 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 3.67–3.61 (1H, m, H_5), 3.57 (1H, dd, *J*=8.9, 3.3 Hz, H_{1a}), 3.48–3.41 (1H, m, H_7), 3.19 (1H, obsd, H_{1b}), 3.15 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 2.33–2.25 (2H, m, H_{12a} and H_2), 2.16 (1H, dd, *J*=13.2, 6.1 Hz, H_{12b}), 1.87–1.81 (1H, m, H_{8a}), 1.77 (1H, dd, *J*=12.5, 5.1 Hz, H_{4a}), 1.66 (3H, s, Me_{11}), 1.48–1.40 (1H, m, H_{4b}), 1.34–1.24 (1H, m, H_{8b}) 1.15–1.08 (1H, m, H_6), 1.06 (3H, d, *J*=7.1 Hz, Me_2), 0.95 (3H, d, *J*=6.4 Hz, Me_6), 0.88 (9H, s, $SiC(CH_3)_3$), 0.03 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.5, 137.9, 136.9, 134.7, 131.2, 130.0, 126.5, 120.0, 110.9, 110.9, 110.1, 101.4, 73.2, 73.1, 71.5, 71.1, 70.1, 69.7, 55.9, 55.8, 55.7, 48.6, 46.6, 43.7, 39.7, 37.7, 37.5, 25.8, 18.2, 17.0, 13.3, 12.6, −4.4, −4.9; HRMS (ES+) Calculated for $C_{37}H_{61}{}^{79}BrO_8SiNa$ [M+Na^+] 763.3217, found 763.3243.

6.1.14. TBS ether 29. To a stirred solution of methyl acetal **28** (108 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added 2,6-lutidine (66 μL, 0.57 mmol). The reaction mixture was stirred at −78 °C for 10 min before *t*-butyldimethylsilyl trifluoromethanesulfonate (99 μL, 0.52 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h and then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography (1% Et_3N in 20% EtOAc/hexane) to yield TBS ether **29** (108 mg, 90%); R_f 0.70 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −13.1 (*c* 1.3, $CHCl_3$); IR (neat) 2929, 2857, 1594 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.92–6.88 (2H, m, ArH), 6.65 (1H, d, *J*=8.2 Hz, ArH), 6.54 (1H, dd, *J*=13.3, 10.8 Hz, H_{16}), 5.93 (1H, d, *J*=13.3 Hz, H_{17}), 5.87 (1H, dd, *J*=15.3, 11.0 Hz, H_{15}), 5.48 (1H, dd, *J*=15.5, 6.4 Hz, H_{14}), 5.28 (1H, d, *J*=8.6 Hz, H_{10}), 4.46–4.38 (1H, m, H_9), 4.41 (2H, d, *J*=2.2 Hz, OCH_2Ar), 4.18 (1H, dd, *J*=13.1, 6.1 Hz, H_{13}), 3.95 (1H, dt, *J*=10.3, 4.8 Hz, H_7), 3.83 (1H, dt, *J*=10.5, 1.6 Hz, H_5), 3.74 (1H, dd, *J*=8.7, 3.4 Hz, H_{1a}), 3.49 (3H, s, $ArOCH_3$), 3.43 (3H, s, $ArOCH_3$), 3.43–3.40 (1H, m, H_{1b}), 3.25 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 2.56–2.48 (1H, m, H_2), 2.28 (1H, dd, *J*=13.6, 6.9 Hz, H_{12a}), 2.14 (1H, dd, *J*=13.3, 6.1 Hz, H_{12b}), 2.12–2.04 (2H, m, H_{8a} and H_{4a}), 1.78 (1H, dd, *J*=12.7, 10.8 Hz, H_{8b}), 1.70 (3H, s, Me_{11}), 1.51 (1H, ddd, *J*=13.7, 10.8, 2.0 Hz, H_{4b}), 1.44–1.38 (1H, m, H_6), 1.32 (3H, d, *J*=7.0 Hz, Me_2), 1.02 (3H, d, *J*=6.7 Hz, Me_6), 0.99 (9H, s, $SiC(CH_3)_3$), 0.98 (9H, s, $Si(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 150.3, 149.7, 138.2, 137.2, 134.6, 131.9, 131.1, 128.6, 126.9, 120.1, 112.1, 112.0, 108.9, 102.1, 73.6, 73.4, 72.0, 71.5, 70.4, 55.7, 55.6, 55.6, 49.0, 46.7, 44.6, 40.5, 39.0, 38.3, 26.2, 26.1, 18.4, 18.3, 17.2, 13.6, 13.4, −3.8, −4.1, −4.5, −4.7; HRMS (ES+) Calculated for $C_{43}H_{75}{}^{79}BrO_8Si_2Na$ [M+Na^+] 877.4082, found 877.4082.

6.1.15. Alcohol 30. To a solution of DMB ether **30** (300 mg, 0.35 mmol) in CH_2Cl_2/pH 9 buffer (40 mL/10 mL) at 0 °C was added DDQ (399 mg, 1.76 mmol). After stirring at this temperature for 10 min, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (40 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×40 mL) and the organic phases were combined, dried (Na_2SO_4) and purified by flash column chromatography (1% Et_3N in 15% EtOAc/hexane) to yield alcohol **30** as a colourless oil (130 mg, 53%); R_f 0.56 (30% EtOAc/hexane); $[\alpha]_D^{20}$ −14.4 (*c* 0.50, MeOH); IR (neat) 3489, 2930, 1516, 1464, 1257 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.53 (1H, dd, *J*=13.3, 11.8 Hz, H_{16}), 5.92 (1H, d, *J*=13.7 Hz, H_{17}), 5.87 (1H, dd, *J*=15.4, 11.1 Hz, H_{15}), 5.47 (1H, dd, *J*=13.5, 6.3 Hz, H_{14}), 5.27 (1H, d, *J*=9.3 Hz, H_{10}), 4.40 (1H, m, H_9), 4.18 (1H, m, H_{13}), 3.92–3.89 (1H, obsd, H_7), 3.81 (1H, t, *J*=10.5 Hz, H_5), 3.74–3.68 (1H, m, H_{1a}), 3.41–3.37 (1H, m, H_{1b}), 3.22 (3H, s, OCH_3), 3.19 (3H, s, OCH_3), 2.31–2.22 (2H, m, H_2 and H_{12a}), 2.15 (1H, dd, *J*=13.4, 6.3 Hz, H_{4a}), 2.10–2.00 (2H, m, H_{12b} and H_{8a}), 1.71 (3H, s, Me_{11}), 1.68–1.62 (1H, obsd, H_{8b}), 1.52–1.45 (1H, m, H_{4b}), 1.42–1.35 (1H, m, H_6), 1.02 (3H, obsd, Me_2), 1.01 (9H, s, $SiC(CH_3)_3$), 1.00 (9H, s, $Si(CH_3)_3$), 0.94 (3H, obsd, Me_6), 0.13 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz,

C_6H_6) δ 138.1, 137.1, 134.7, 131.0, 127.0, 108.9, 102.8, 73.6, 72.0, 71.3, 70.5, 64.6, 55.7, 49.0, 47.1, 44.4, 40.4, 39.1, 38.6, 26.1, 26.1, 18.4, 18.3, 17.2, 13.3, 12.5, −3.8, −4.1, −4.6, −4.7; HRMS (ES+) Calculated for $C_{34}H_{65}{}^{79}BrO_6Si_2Na$ [M+Na$^+$] 727.3401, found 727.3395.

6.1.16. *seco*-Acid 31. To a stirred solution of alcohol **30** (30 mg, 43 μmol) in CH_2Cl_2 (1.5 mL) at rt was added $NaHCO_3$ (29 mg, 0.34 mmol) followed by Dess–Martin periodinane (72 mg, 0.17 mmol). The resulting solution was stirred at rt for 1 h and then quenched by the addition of hexane (2 mL). The resulting suspension was filtered through a silica plug (1% Et_3N in 10% EtOAc/hexane) to provide the product aldehyde, which was used directly. To a stirred solution of aldehyde (29 mg, 41 μmol) in *t*-BuOH (4.0 mL) at rt was added 2-methyl-2-butene (0.5 mL). The resulting solution was cooled to 0 °C and a solution of sodium chlorite (60 mg, 0.51 mmol) and sodium dihydrogen phosphate (84 mg, 0.45 mmol) in H_2O (1.3 mL) was added. The resulting solution was stirred at this temperature for 10 min and then allowed to warm to rt. The solution was stirred at rt for 1.5 h, recooled to 0 °C and quenched by the addition of pH 7 buffer (3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine (4 mL), dried (Na_2SO_4) and concentrated in vacuo to yield crude acid **32**, which was used without further purification. To a stirred solution of acid **32** (30 mg, 41 μmol) in THF (3 mL) at rt was added TBAF (1 M in THF, 46 μL, 46 μmol). The resulting solution was stirred at rt for 1 h, recooled to 0 °C and further TBAF was added (1 M in THF, 46 μL, 46 μmol). After stirring at rt for 4 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine (4 mL), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (2.5% MeOH/CH_2Cl_2) to yield *seco*-acid **31** as a pale yellow oil (25 mg, 94% based on **30**); R_f 0.27 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −15.6 (*c* 0.10, MeOH); IR (neat) 2929, 2857, 1714, 1252 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.55 (1H, dd, *J*=13.5, 11.0 Hz, H_{16}), 5.95 (1H, d, *J*=13.5 Hz, H_{17}), 5.90 (1H, dd, *J*=15.2, 11.0 Hz, H_{15}), 5.39 (1H, dd, *J*=15.3, 5.8 Hz, H_{14}), 5.20 (1H, d, *J*=8.9 Hz, H_{10}), 4.32–4.27 (1H, m, H_9), 3.99 (1H, dd, *J*=12.5, 6.2 Hz, H_{13}), 3.88 (1H, dt, *J*=10.3, 4.9 Hz, H_5), 3.79 (1H, dt, *J*=10.4, 1.3 Hz, H_7), 3.37 (3H, s, OCH_3), 3.13 (3H, s OCH_3), 3.09–3.03 (1H, m, H_2), 2.50 (1H, dd, *J*=13.0, 5.0 Hz, H_{4a}), 2.44 (1H, br s, O*H*), 2.13–2.03 (2H, m, H_{12a} and H_{12b}), 2.03–1.95 (1H, m, H_{8a}), 1.77 (1H, dd, *J*=12.9, 11.1 Hz, H_{4b}), 1.60 (3H, s, Me_{11}), 1.44–1.35 (1H, m, H_{4b}), 1.35–1.28 (1H, m, H_6), 1.25 (3H, d, *J*=7.2 Hz, Me_2), 1.00 (9H, s, Si(CH_3)$_3$), 0.95 (3H, d, *J*=6.5 Hz, Me_6), 0.14 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, C_6H_6) δ 175.9, 137.4, 137.2, 135.3, 130.6, 127.2, 109.0, 101.5, 73.4, 71.4, 71.0, 69.8, 55.6, 47.8, 47.8, 45.4, 43.9, 40.0, 39.9, 26.1, 18.3, 16.8, 13.3, 12.9, −3.8, −4.6; HRMS (ES+) Calculated for $C_{28}H_{49}{}^{79}BrO_7SiNa$ [M+Na$^+$] 627.2329, found 626.2347.

6.1.17. Macrolactone 33. Triethylamine (35 μL, 0.25 mmol) and 2,4,6-trichlorobenzoylchloride (32 μL, 0.21 mmol) were added to a stirred solution of *seco*-acid **31** (25 mg, 0.041 mmol) in toluene (4 mL) at rt. After stirring for 40 min, the solution was diluted with toluene (15 mL) and added to a stirred solution of DMAP (25 mg, 0.21 mmol) in toluene (25 mL) at 80 °C over 4 h via syringe pump. The reaction mixture was allowed to cool to rt and quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography (1% Et_3N in 5% EtOAc/hexane) to yield macrolactone **33** as a colourless oil (16 mg, 64%); R_f 0.60 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +12.4 (*c* 1.1, MeOH); IR (neat) 2928, 1732, 1582, 1187 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (1H, dd, *J*=13.5, 10.9 Hz, H_{16}), 6.35 (1H, dd, *J*=13.7 Hz, H_{17}), 6.16 (1H, dd, *J*=15.2, 10.8 Hz, H_{15}), 5.71 (1H, dd, *J*=15.2, 10.8 Hz, H_{14}), 5.66 (1H, m, H_{13}), 5.20 (1H, d, *J*=9.4 Hz, H_{10}), 3.90 (1H, m, H_9), 3.52 (1H, dt, *J*=10.4, 4.8 Hz, H_7), 3.30 (1H, m, H_5), 3.24 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 2.57 (1H, q, *J*=7.5 Hz, H_2), 2.41 (1H, t, *J*=13.1 Hz, H_{12a}), 2.28 (1H, dd, *J*=13.3, 2.9 Hz, H_{12b}), 2.11 (2H, m, H_{8a} and H_{4a}), 1.76 (1H, m, H_{8b}), 1.73 (3H, s, Me_{11}), 1.28 (2H, m, H_6 and H_{4b}), 1.16 (3H, d, *J*=7.2 Hz, Me_2), 0.92 (3H, d, *J*=6.5 Hz, Me_6), 0.87 (9H, s, Si(CH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, C_6H_6) δ 173.5, 136.1, 132.4, 132.2, 132.1, 129.1, 109.6, 100.8, 75.2, 74.2, 70.1, 69.7, 54.5, 49.3, 48.5, 45.1, 43.9, 43.4, 39.7, 25.5, 17.6, 15.7, 13.2, 12.7, −4.4, −5.1; HRMS (ES+) Calculated for $C_{28}H_{47}{}^{79}BrO_6SiK$ [M+K$^+$] 625.1962, found 625.1957.

6.1.18. Alcohol 34. To a stirred solution of TBS ether **33** (10.5 mg, 17.9 μmol) in THF (1.8 mL) at 0 °C was added TBAF (1 M in THF, 179 μL, 179 μmol). The resulting solution was allowed to warm to rt, stirred for 2 h and then quenched by the addition of saturated aqueous NH_4Cl (3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine (4 mL), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (1% Et_3N in 0–100% EtOAc/hexane) to yield alcohol **34** as a pale yellow oil (7 mg, 83%); R_f 0.35 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +13.1 (*c* 0.43, MeOH); IR (neat) 3430, 2920, 1730, 1180 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.41 (1H, dd, *J*=13.2, 10.8 Hz, H_{16}), 5.85 (1H, dd, *J*=13.6 Hz, H_{17}), 5.85 (1H, dd, *J*=15.2, 10.5 Hz, H_{15}), 5.72 (1H, m, H_{13}), 5.39 (1H, d, *J*=9.4 Hz, H_{10}), 5.35 (1H, dd, *J*=15.4, 6.5 Hz, H_{14}), 3.91 (1H, dt, *J*=9.7, 2.0 Hz, H_9), 3.44 (1H, br s, H_5), 3.29 (3H, s, OCH_3), 3.26 (1H, m, H_7), 3.20 (3H, s, OCH_3), 2.61 (1H, q, *J*=7.3 Hz, H_2), 2.28 (2H, m, H_{12a} and H_{8a}), 2.10 (1H, dd, *J*=12.5, 5.0 Hz, H_{4a}), 2.00 (1H, dd, *J*=13.1, 2.6 Hz, H_{12b}), 1.88 (1H, dt, *J*=13.9, 10.0 Hz, H_{8b}), 1.66 (3H, s, Me_{11}), 1.21 (1H, m, H_6), 1.17 (3H, d, *J*=7.3 Hz, Me_2), 0.95 (1H, m, H_{4b}), 0.88 (3H, d, *J*=6.6 Hz, Me_6); ^{13}C NMR (125 MHz, C_6H_6) δ 173.3, 136.3, 133.3, 132.8, 131.4, 128.7, 109.7, 100.9, 75.3, 74.5, 70.0, 68.9, 54.2, 49.6, 49.1, 45.3, 44.1, 43.6, 40.3, 15.7, 12.9, 12.7; HRMS (ES+) Calculated for $C_{22}H_{33}{}^{79}BrO_6Na$ [M+Na$^+$] 495.1358, found 495.1358.

6.1.19. Dolastatin 19 aglycon, 27. To a stirred solution of methyl acetal **34** (9 mg, 19.0 μmol) in MeCN/H_2O (1 mL/200 μL) at rt was added PPTS (approx. 1 mg, catalytic).

Table 1. Comparison of ^{1}H NMR data for synthetic and natural dolastatin 19

Position	Synthetic dolastatin 19 (CD_3CN, 500 MHz)	Natural dolastatin 19 (CD_3CN, 500 MHz)	$\Delta\delta_{syn-nat}$ (+/− ppm)
1	—	—	—
2	2.49 q (7.1)	2.49 q (7.5)	—
3	—	—	—
3-OH	4.47 d (2.6)	4.47 d (2.0)	—
4a	2.17 dd (12.2, 5.0)	2.18 m	−0.01
4b	1.24 m	1.23 m	+0.01
5	3.51 m	3.51 m	—
6	1.18 m	1.18 m	—
7	3.59 app. dt (11.3, 1.7)	3.57 m	+0.02
8a	2.03 app. dt (13.5, 2.1)	2.01 m	+0.02
8b	1.46 app. dt (13.5, 10.9)	1.46 m	—
9	3.78 app. dt (10.7, 1.9)	3.78 ddd (10.8, 9.0, 2.0)	—
9-OMe	3.11 s	3.12 s	−0.01
10	4.94 d (9.4)	4.94 d (10.8)	—
12a	2.31 d (13.3)	2.30 d (14)	+0.01
12b	2.22 dd (12.8, 12.0)	2.23 d (14)	−0.01
13	5.75 m	5.75 m (10.5, 6)	—
14	5.83 dd (15.4, 6.0)	5.82 dd (15, 6)	+0.01
15	6.27 dd (15.2, 10.9)	6.27 dd (15, 11)	—
16	6.77 dd (13.5, 10.7)	6.77 dd (14, 11)	—
17	6.50 d (13.7)	6.50 d (14)	—
2-Me	1.08 d (7.2)	1.08 d (7.5)	—
6-Me	0.93 d (6.4)	0.93 d (6.5)[a]	—
11-Me	1.71 s	1.71 s	—
1′	4.86 d (1.1)	4.86 d (1)	—
2′	3.35 dd (3.4, 1.5)	3.35 dd (3.5, 1)	—
2′-OMe	3.38 s	3.39 s	−0.01
3′	3.56 dt (9.0, 3.6)	3.55 m (3.5, 9.5)	+0.01
3′-OH	2.97 d (8.4)	2.97 s	—
4′	2.86 t (9.6)	2.86 t (9.5)	—
4′-OMe	3.46 s	3.46 s	—
5′	3.52 m	3.53 m (9.5, 6.0)	−0.01
6′	1.15 d (6.2)	1.15 d (6.0)	—

^{1}H NMR data recorded in the order: chemical shift (δ_H in parts per million) (multiplicity, coupling constant in hertz). ^{1}H NMR spectrum of synthetic **10** calibrated to H10 (4.94 ppm in Ref. 8).
[a] Proton chemical shift altered relative to value quoted in isolation paper (based upon inspection of copies of original NMR spectra)—Me_6 is 0.93 ppm (0.98 ppm in Ref. 8).

Table 2. Comparison of ^{13}C NMR data for synthetic and natural dolastatin 19

Position	Synthetic dolastatin 19 (CD_3CN, 100 MHz)	Natural dolastatin 19 (CD_3CN, 100 MHz)	$\Delta\delta_{syn-nat}$ (+/− ppm)
1	177.04	177.03[a]	+0.01
2	48.62	48.62	—
3	98.24	98.24	—
4	40.33	40.33	—
5	80.17	80.17	—
6	43.57	43.58	−0.01
7	73.62	73.62	—
8	40.21	40.22	−0.01
9	76.75	76.75[b]	—
9-OMe	54.75	54.74	+0.01
10	133.55	133.53	+0.02
11	133.38	133.38[c]	+14.25
12	46.89	46.89	—
13	71.72	71.71	+0.01
14	133.31	133.32	−0.01
15	129.33	129.33	—
16	137.62	137.61[d]	+0.01
17	110.90	110.89[e]	+0.01
2-Me	12.86	12.86	—
6-Me	13.44	13.44	—
11-Me	16.36	16.36	—
1′	100.03	100.02	+0.01
2′	82.00	82.00	—
2′-OMe	59.11	59.11	—
3′	72.18	72.19	−0.01
4′	84.31	84.32	−0.01
4′-OMe	60.93	60.92	+0.01
5′	68.38	63.38	—
6′	18.07	18.07	—

^{13}C NMR data recorded: δ_C in parts per million. ^{13}C NMR spectrum of synthetic material **10** calibrated to C18 (12.86 ppm in Ref. 8). Footnotes a–e denote carbon chemical shift altered relative to value quoted in Ref. 8 (based upon inspection of copies of original NMR spectra).
[a] C1 is 177.03 ppm (177.43 ppm in Ref. 8).
[b] C9 is 76.75 ppm (76.62 ppm in Ref. 8).
[c] C11 is 133.38 ppm (119.13 ppm in Ref. 8).
[d] C16 is 137.61 ppm (137.76 ppm in Ref. 8).
[e] C17 is 110.89 ppm (110.77 ppm in Ref. 8).

The resulting solution was stirred at rt for 16 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×1.5 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and purified by flash chromatography (1% Et_3N in 45% EtOAc/hexane) to yield aglycon **27** as a colourless oil (7.1 mg, 81%); R_f 0.35 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +30.6 (*c* 0.33, MeOH); IR (neat) 3441, 2927, 1705, 1185 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 6.79 (1H, dd, J=13.5, 10.9 Hz, H_{16}), 6.51 (1H, d, J=13.5 Hz, H_{17}), 6.28 (1H, dd, J=15.9, 11.0 Hz, H_{15}), 5.84 (1H, dd, J=15.2, 6.1 Hz, H_{14}), 5.78–5.73 (1H, m, H_{13}), 4.95 (1H, d, J=9.5 Hz, H_{10}), 4.43 (1H, d, J=2.7 Hz, 3-O*H*), 3.83–3.75 (1H, m, H_9), 3.58–3.52 (1H, m, H_7), 3.51–3.43 (1H, m, H_5), 3.12 (3H, s, OCH_3), 2.78 (1H, d, J=6.1 Hz, 5-O*H*), 2.51 (1H, q, J=7.2 Hz, H_2), 2.32 (1H, d, J=13.7 Hz, H_{12a}), 2.24 (1H, d, J=11.6 Hz, H_{12b}), 2.06–2.01 (2H, m, H_{4a} and H_{8a}), 1.72 (3H, s, Me_{11}), 1.46 (1H, m, H_{8b}), 1.11 (3H, d, J=7.2 Hz, Me_2), 1.09–1.05 (2H, m, H_{4b} and H_6), 0.94 (3H, d, J=6.6 Hz, Me_6); ^{13}C NMR (125 MHz, CD_3CN) δ 177.4, 137.6, 133.6, 133.4, 133.3, 129.3, 110.9, 98.4, 76.9, 73.7, 71.7, 69.5, 54.8, 48.8, 46.9, 45.3, 41.7, 40.4, 16.4, 13.4, 12.9; HRMS (ES+) Calculated for $C_{21}H_{32}{}^{79}BrO_6Na$ [M+Na$^+$] 481.1202, found 481.1196.

6.1.20. TBS ether 36. A solution of fluorosugar **11**[11,29] (2.8 mg, 8.97 μmol) and aglycon **27** (1.5 mg, 3.27 μmol) in Et_2O (1.0 mL) was stirred over activated 4 Å molecular sieves (200 mg) for 10 min. The suspension was cooled to 0 °C, whereupon tin(II) chloride (1.7 mg, 8.97 μmol) and silver perchlorate (1.9 mg, 8.97 μmol) were added. After 8 h with warming to rt, the resulting suspension was filtered through a Celite plug with Et_2O (10 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL), then brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (1% Et_3N in 10–30% EtOAc/hexane) gave **36** as a pale yellow oil (1.2 mg, 49%); R_f 0.56 (30% EtOAc/hexane); $[\alpha]_D^{20}$ +28.0 (*c* 0.20, MeOH); IR (neat) 2930, 1710, 1460, 1380, 1190 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 6.78 (1H, dd, J=13.6, 10.9 Hz, H_{16}), 6.51 (1H, d, J=13.4 Hz, H_{17}), 6.28 (1H, dd, J=15.2, 10.6 Hz, H_{15}), 5.84 (1H, dd, J=15.3, 6.0 Hz, H_{14}), 5.78–5.74 (1H, m, H_{13}), 4.95 (1H, d, J=9.6 Hz, H_{10}), 4.82 (1H, d, J=1.8 Hz, $H_{1'}$), 4.47 (1H, d, J=2.7 Hz, 3-O*H*), 3.83–3.78 (2H, m, H_9 and $H_{3'}$), 3.63–3.57 (1H, m, H_7), 3.56–3.45 (2H, m, H_5 and $H_{5'}$), 3.43 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 3.32 (1H, dd, J=3.1, 2.0 Hz, $H_{2'}$), 3.12 (3H, s, OCH_3), 2.94 (1H, t, J=9.6 Hz, $H_{4'}$), 2.50 (1H, q, J=7.1 Hz, H_2), 2.32 (1H, d, J=12.7 Hz, H_{12a}), 2.24 (1H, J=11.7 Hz, H_{12b}), 2.21–2.18

(1H, m, H_{4a}), 2.06–2.01 (1H, m, H_{8a}), 1.72 (3H, s, Me_{11}), 1.52–1.43 (1H, m, H_{8b}), 1.28–1.19 (2H, m H_6 and H_{4b}), 1.16 (3H, d, J=6.4 Hz, $Me_{6'}$), 1.09 (3H, d, J=7.1 Hz, Me_2), 0.94 (3H, obsd, Me_6), 0.92 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, CD_3CN) δ 177.0, 137.6, 133.5, 133.3, 133.3, 129.3, 110.9, 100.5, 98.2, 84.0, 82.5, 80.1, 76.7, 73.8, 73.6, 71.7, 69.1, 61.4, 59.5, 54.7, 48.6, 46.8, 43.5, 40.3, 40.1, 26.2, 18.7, 18.1, 16.3, 13.4, 12.8, −4.5, −4.6; HRMS (ES+) Calculated for $C_{35}H_{59}{}^{79}BrO_{10}SiNa$ [M+Na$^+$] 769.2959, found 769.2959.

6.1.21. Dolastatin 19. To a stirred solution of TBS ether **36** (3 mg, 4.02 μmol) in THF (1.5 mL) in a polypropylene vessel at 0 °C was added HF·pyridine (60 μL). After 16 h at rt the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (12 mL) and CH_2Cl_2 (12 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (1% Et_3N in 0–60% EtOAc/hexane) gave the title compound **10** as an amorphous solid (2.0 mg, 79%); R_f 0.50 (100% EtOAc); $[\alpha]_D^{20}$ +2.2 (*c* 0.18, MeOH); IR (neat) 3440, 2930, 1710, 1380, 1190 cm^{-1}; ^1H NMR (500 MHz, CD_3CN)—see Table 1; ^{13}C NMR (100 MHz, CD_3CN)—see Table 2; HRMS (ES+) Calculated for $C_{29}H_{45}{}^{79}BrO_{10}Na$ [M+Na$^+$] 655.2094, found 655.2094.

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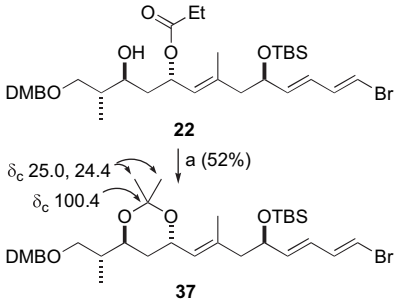

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