Synthesis of the FG Fragment of the Pectenotoxins

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Abstract: The synthesis of the FG subunit of the pectenotoxins is reported herein. The synthesis hinges on the preparation of an appropriately functionalized acyclic precursor using a *Z*-selective Wittig reaction. Further elaboration using two sequential cyclization reactions furnished the tetrahydrofuran F ring and the tetrahydropyran G ring, respectively.

Key words: cyclization, Wittig reaction, epoxidation, shellfish toxins, pectenotoxins

The pectenotoxins (PTXs) typified by pectenotoxin-2 (PTX-2, **1**, Figure 1) are a family of structurally complex polyether macrolides initially isolated in 1985 by Yasumoto et al.[1,2] from contaminated scallops (*Patinopecten yessoensis*) off the coast of Japan.

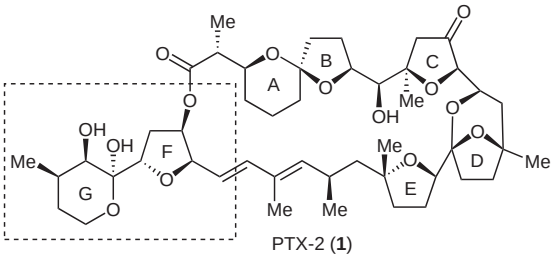

Figure 1 Pectenotoxin-2 (**1**)

These marine biotoxins, mainly produced by the dinoflagellate *Dinophysis fortii*,[1] accumulate in the shellfish that feed upon them and the toxins are then transferred to humans upon consumption of the contaminated shellfish. The resultant shellfish poisoning events not only have implications for public health[3] but also have economic consequences on the global shellfish industry. The isolation of the pectenotoxins has not been limited to Japan and these shellfish toxins have now been isolated from many major coastal regions.[4–8] PTX-2 (**1**) exhibits potent cytotoxic effects against human colon, lung and breast carcinomas[9] and has since been found to induce its cytotoxic activity by binding to intracellular F actin.[10,11] Further experiments have shown that this actin damage triggers apoptosis through mitochondrial dysfunction in p53-deficient tumour cells.[12] The important antimitotic activity reported for PTX-2 (**1**) has prompted considerable synthetic activity in this area by several research groups.

To date, only one elegant total synthesis of the PTXs (PTX-4 and PTX-8) has been completed by Evans et al.[13,14] The total synthesis involved a late stage assembly of the FG unit of PTX-4 by attaching an F-ring fragment that also contained the G-ring backbone to an ABCDE portion of PTX using a Julia olefination. Subsequent deprotection-induced cyclization to provide the G-ring hemiacetal thus completed the synthesis of PTX-4. A synthesis of an FG-ring fragment has previously been reported from the laboratories of Murai et al.[15,16] in which the main backbone of the FG rings was prepared by reaction of an anion generated from a chiral α-lithio tetrahydrofuranyl ring, representing the F ring, with a five-carbon aldehyde fragment. Studies toward the F ring have also emanated from the work of Paquette et al.[17,18] who employed an elegant hydroxyl-directed hydrogenation of a dihydrofuran to generate the desired chirality present in the tetrahydrofuran F ring.

We envisaged a modular approach to the preparation of the PTXs in which several key fragments could be prepared individually that would later be joined in a convergent manner. The work reported herein on the synthesis of the FG fragment of the pectenotoxins continues on from the successful synthesis of the ABC ring of PTX-7 completed by this research group.[19]

Our retrosynthetic analysis of the key FG bicyclic fragment **2** is depicted in Scheme 1. It was envisioned that installation of the tetrahydropyran G ring could be effected by simultaneous deprotection of benzyl ether **3** followed by 6-*exo*-trig cyclization of the resultant alcohol onto ketone **3**. The tetrahydrofuran F ring is then constructed via 5-*exo*-tet cyclization of masked γ-hydroxy epoxide **4**, itself obtained via stereocontrolled epoxidation of *Z*-olefin **5**. Olefin **5** in turn is assembled via *Z*-selective Wittig reaction of aldehyde **6** with phosphonium salt **7**. The key stereocenters in intermediates **6** and **7** are then established by Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation, respectively.

The synthesis of aldehyde **6** (Scheme 2) began with Horner–Wadsworth–Emmons reaction of known[20] benzyl-protected aldehyde **8** with commercially available triethyl phosphonoacetate. Use of potassium carbonate as base[21] in a biphasic solvent of diethyl ether and water afforded *E*-conjugated ester **9** stereoselectively in 86% yield. DIBAL-H reduction of the resultant ester to the corresponding allylic alcohol (DIBAL-H, CH_2Cl_2, –78 °C, 87%) followed by Sharpless asymmetric epoxidation[22] using (L)-(+)-diethyl tartrate as the chiral catalyst proceeded

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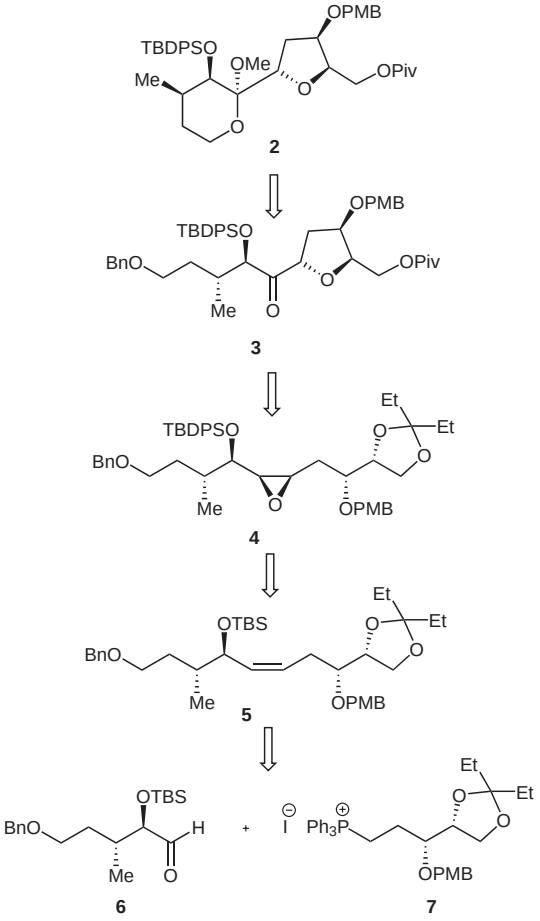
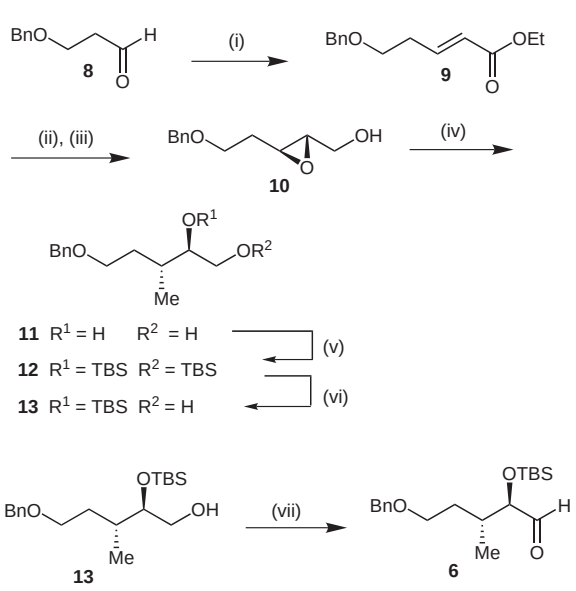


Scheme 1 Retrosynthetic analysis of FG fragment **2**

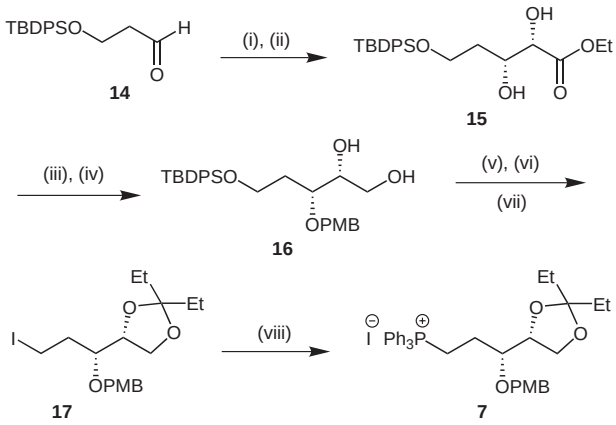


Scheme 2 *Reagents and conditions*: (i) $(EtO)_2P(O)CH_2CO_2Et$, K_2CO_3, Et_2O, H_2O, O °C to r.t., 86%; (ii) DIBAL-H, CH_2Cl_2, –78 °C, 87%; (iii) Ti(*i*-OPr)$_4$, (+)-DET, MS 4 Å, CH_2Cl_2, –20 °C, 30 min then *t*-BuOOH, 91%; (iv) $AlMe_3$, CH_2Cl_2, 0 °C to r.t., 66%; (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 89%; (vi) HF–pyridine, THF, 0 °C to r.t., quant.; (vii) Dess–Martin periodinane, pyridine, THF, r.t., 96%.

smoothly {91%, $[\alpha]_D^{23}$ –27.5 (*c* 2.00, $CHCl_3$)} to provide known epoxide **10** (> 86% ee).[23] Opening of epoxide **10** with trimethylaluminium[24] afforded enantiopure *R*,*R*-vicinal diol **11**. Protection of diol **11** with TBSOTf and 2,6-lutidine gave the bissilyl ether **12** in good yield (89%).

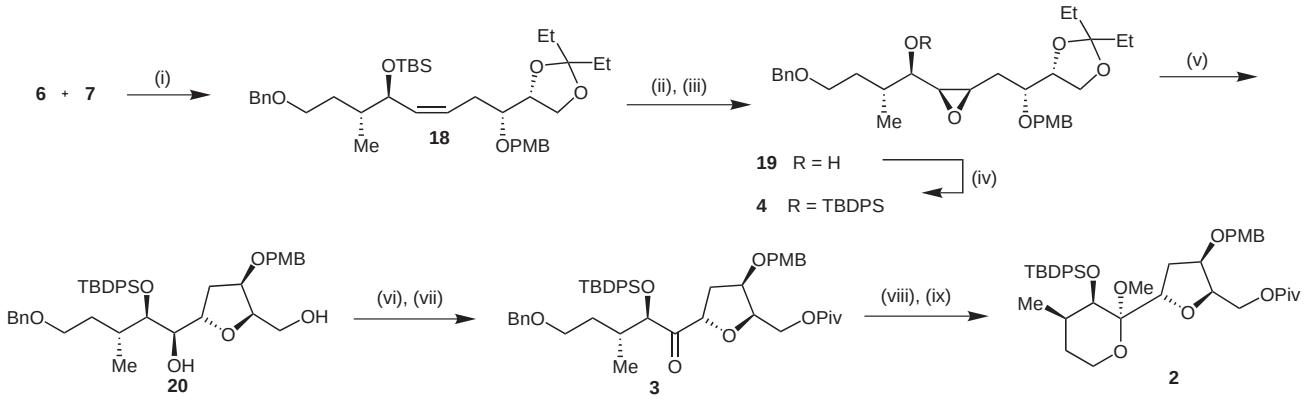
Selective deprotection of the primary TBS group in the presence of the secondary[25] was then undertaken using HF–pyridine in THF with close monitoring of the reaction. Only moderate yields were achieved for this step due to the formation of the undesired diol species **11**. Fortunately, diol **11** and the unreacted starting material **12** were able to be recycled resulting in an overall quantitative yield of the desired monosilyl ether **13**. Finally, Dess–Martin periodinane oxidation[26] of primary alcohol **13** furnished aldehyde **6** in excellent yield (96%).

The synthesis of phosphonium salt **7** (Scheme 3) commenced with reaction of known[27] aldehyde **14** with triethyl phosphonoacetate, using the aforementioned biphasic conditions.[21] Sharpless asymmetric dihydroxylation using 5 mol% $(DHQD)_2PHAL$ proceeded in 95% ee as determined by Mosher ester analysis[28] of the resultant *R*,*S*-diol. Diol **15** was transformed via a sequence of protection as a *p*-methoxybenzylidene acetal followed by DIBAL-H reduction which effected reduction of the ester to a primary alcohol and concomitant, regioselective acetal cleavage affording PMB-protected alcohol **16**. The terminal diol was then protected as a diethyl acetal and the primary TBDPS group removed. After conversion of the resultant primary alcohol to iodide **17**, conversion to phosphonium salt **7** was effected by heating iodide **17** with triphenylphosphine and Hünig's base under reflux in acetonitrile.



Scheme 3 *Reagents and conditions*: (i) $(EtO)_2P(O)CH_2CO_2Et$, K_2CO_3, Et_2O, H_2O, 0 °C to r.t., 86%; (ii) $K_3Fe(CN)_6$, $(DHQD)_2Phal$, $MeSO_2NH_2$, *t*-BuOH–H_2O, K_2CO_3, OsO_4, r.t., 2 h, then olefin, 0 °C to r.t., 93%, 95% ee; (iii) $MeOC_6H_4CH(OMe)_2$, CSA, PhH, r.t., 170 mbar, 76%; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 77%; (v) 3,3-dimethoxypentane, PTSA, PhH, r.t., 70%; (vi) TBAF, THF, r.t., 84%; (vii) imidazole, PPh_3, CH_2Cl_2, I_2, r.t., 85%; (viii) PPh_3, *i*-Pr_2EtN, MeCN, reflux, 60%.

With both coupling partners **6** and **7** in hand, attention next turned to the union of these fragments via a *Z*-selective Wittig reaction (Scheme 4). The key Wittig reaction proceeded smoothly in good yield (93%) using *n*-BuLi to



Scheme 4 *Reagents and conditions*: (i) *n*-BuLi, HMPA, THF, –78 °C, 93%; (ii) TBAF, THF, r.t., 81%; (iii) MCPBA, CH_2Cl_2, 0 °C, 99%, >95% de; (iv) TBDPSCl, imidazole, CH_2Cl_2, r.t., 85%; (v) 50% aq TFA, CH_2Cl_2, r.t., 53%; (vi) PivCl, pyridine, CH_2Cl_2, –5 °C, 97%; (vii) Dess–Martin periodinane, pyridine, CH_2Cl_2, r.t., 99%; (viii) Raney nickel, EtOH, H_2, r.t.; (ix) CSA, $CH(OMe)_3$, MeOH, r.t., 70%, 2 steps.

generate the ylide and 7% HMPA as a lithium ion sequestering agent.[29,30] The use of KHMDS as base, with and without HMPA additive, also gave the desired product but in lower yield (45% and 72%, respectively). The *Z*-stereochemistry of olefin **18** was confirmed by the magnitude of the vinylic coupling constant, $J_{5,6}$ = 9.8 Hz. The undesired *E*-olefin was not observed in the crude ^{1}H NMR spectrum. Deprotection of the secondary TBS ether **18**[31] gave the corresponding allylic alcohol in good yield although long reaction times were required (TBAF, THF, 5 h, r.t., 81%). Substrate-directed epoxidation[32,33] of the resultant allylic alcohol using MCPBA afforded epoxy alcohol **19** as the sole diastereomer which was then reprotected as a TBDPS ether.

Cyclization to form the tetrahydrofuran F ring was accomplished by deprotection of the diethyl acetal protecting group using 50% aqueous TFA in dichloromethane to unmask the γ-hydroxyepoxide thus facilitating the 5-*exo*-tet cyclization to afford tetrahydrofuran **20**.[34] Attempts to induce this desired deprotection–cyclization sequence using CSA and PPTS led to the formation of complex mixtures with none of the desired tetrahydrofuran moiety being formed. Selective pivaloyl protection of the primary alcohol over the resultant secondary alcohol was achieved in 97% yield using pivaloyl chloride and pyridine as base in dichloromethane at –5 °C. Dess–Martin periodinane oxidation[26] of the remaining secondary alcohol proceeded in high yield (99%) thus providing the appropriately functionalized acyclic framework for the final cyclization step. Debenzylation was achieved in the presence of the PMB group[35] using freshly prepared Raney nickel[36,37] in ethanol under an atmosphere of hydrogen. The resultant hemiacetal was obtained cleanly as a single isomer[38,39] that was immediately converted to the corresponding methyl acetal **2** to facilitate purification (CSA, MeOH, trimethyl orthoformate, 2 h, r.t., 70%, 2 steps).

In summary, a convergent synthesis of the FG fragment of the pectenotoxins has been successfully achieved in preparation for union with the previously prepared ABC fragment. Synthetic studies towards the D and E rings are under way.

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(31) **Selected Spectral Data**
Compound **18**: $[\alpha]_D$ +7.2 (*c* 7.20, $CHCl_3$). HRMS: *m/z* calcd for $C_{37}H_{57}O_6Si$: 625.3924; found: 625.3919 $[M - H]^+$. IR: ν_{max} = 3433, 2929, 2856, 1613, 1514, 1463, 1249, 1083, 835, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 (3 H, s, Me_2*t*-BuSi), 0.03 (3 H, s, Me_2*t*-BuSi), 0.85–0.94 (18 H, m, Me_2*t*-BuSi, CH_3, H-2″), 1.25–1.30 (1 H, m, H-2), 1.61–1.71 (5 H, m, H-1″, H-3), 1.82–1.94 (1 H, m, H-2), 2.10–2.30 (2 H, m, H-7), 3.45–3.50 (3 H, m, H-1, H-8), 3.60–3.67 (1 H, m, H-5′), 3.80 (3 H, s, OMe), 3.94–4.00 (1 H, m, H-5′), 4.17–4.20 (2 H, m, H-4, H-4′), 4.49–4.71 (4 H, m, CH_2Ar), 5.40–5.54 (2 H, m, H-5, H-6), 6.86–6.89 (2 H, m, ArH), 7.26–7.35 (7 H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8 (CH_3, Me_2*t*-BuSi), –4.2 (CH_3, Me_2*t*-BuSi), 8.1 (CH_3, C-2″), 8.3 (CH_3, C-2″), 15.4 (CH_3, Me), 18.1 (C, Me_2*t*-BuSi), 25.8 (CH_3, Me_2*t*-BuSi), 29.2 (CH_2, C-7), 29.6 (2 × CH_2, C-1″), 31.6 (CH_2, C-2), 37.3 (CH, C-3), 55.2 (CH_3, OMe), 66.4 (CH_2, C-5′), 68.9 (CH_2, C-1), 72.6 (CH_2Ar), 72.8 (CH_2Ar), 72.6 (CH, C-4), 78.5 (CH, C-4′), 79.1 (CH, C-8), 113.2 (C, C-2′), 113.7 (CH, ArH), 125.4 (CH, C5 or C6), 127.4 (CH, ArH), 127.6 (CH, ArH), 128.3 (CH, ArH), 129.4 (CH, ArH), 130.7 (C, Ar), 134.0 (CH, C5 or C6), 138.7 (C, Ar), 159.2 (C, Ar). MS–FAB: *m/z* (%) = 627 (0.1) $[MH^+]$, 625 (0.2), 598 (0.2), 495 (0.2), 211 (3), 137 (3), 121 (100), 91 (25) $[CH_2Ph]$, 73 (16).
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(34) **Selected Spectral Data**
Compound **20**: $[\alpha]_D$ –6.9 (*c* 1.75, $CHCl_3$). HRMS: *m/z* calcd for $C_{42}H_{55}O_7Si$: 699.3717; found: 699.3721 $[MH^+]$. IR: ν_{max} = 3469, 3069, 2930, 2856, 1612, 1513, 1247, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (3 H, d, *J* = 6.85 Hz, CH_3), 1.08 (9 H, s, Ph_2*t*-BuSi), 1.41–1.61 (2 H, m, H-4), 1.65–1.69 (2 H, dd, *J* = 11.5, 4.0 Hz, H-3′), 1.50–1.72 (1 H, m, H-3), 2.20–2.27 (1 H, br, C-1″-OH), 2.66 (1 H, d, *J* = 8.0 Hz, C-1-OH), 3.15–3.34 (2 H, m, H-5), 3.34–3.42 (1 H, m, H-1), 3.56–3.72 (3 H, m, H-1″, H-2), 3.80 (3 H, s, OMe), 3.88 (1 H, m, H-5′), 4.06–4.10 (2 H, m, H-4′, H-2′) 4.22 (1 H, d, *J* = 11.5 Hz, CH_2Ar), 4.35–4.41 (2 H, m, CH_2Ar), 4.44 (1 H, d, *J* = 11.5 Hz, CH_2Ar), 6.85–6.88 (2 H, m, ArH), 7.16–7.37 (13 H, m, ArH), 7.66–7.69 (4 H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (CH_3, $CHCH_3$), 19.6 (C, Ph_2*t*-BuSi), 27.2 (3 × CH_3, Ph_2*t*-BuSi), 32.5 (CH_2, C-4), 33.9 (CH_2, C-3′), 34.7 (CH, C-3), 55.3 (CH_3, OMe), 62.0 (CH_2, C-1″), 68.6 (CH_2, C-5), 71.1 (CH_2, CH_2Ar), 72.0 (CH, C-1), 72.9 (CH_2, CH_2Ar), 76.5 (CH, C-2), 79.2 (CH, C-4′), 79.8 (CH, C-2′), 81.5 (CH, C-5′), 113.9 (CH, Ar), 127.5 (C, Ar), 127.5 (C, Ar), 127.6 (C, Ar), 128.3 (CH, Ar), 129.0 (CH, Ar), 129.8 (CH, Ar), 129.8 (CH, Ar), 133.6 (C, Ar), 133.7 (C, Ar), 136.0 (CH, Ar), 136.1 (CH, Ar), 138.4 (C, Ar), 159.3 (C, Ar). MS–FAB: *m/z* (%) = 699 (0.2) $[MH^+]$, 199 (10), 197 (8), 137 (14), 136 (13), 135 (9), 122 (10), 121 (100), 91 (27).
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(38) **Selected Spectral Data**
Compound **2**: $[\alpha]_D$ –6.0 (*c* 0.2, $CHCl_3$). HRMS: *m/z* calcd for $C_{41}H_{55}O_8Si$: 703.3666; found: 703.3670 $[M - H]^+$. IR: ν_{max} = 2932, 1729, 1613, 1514, 1428, 1248, 1170, 1093, 821, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03–1.16 (20 H, m, Ph_2*t*-BuSi, H-3′), 1.21 (3 H, d, *J* = 7.2 Hz, C-4-CH_3), 1.34–1.40 (1 H, m, H-5), 1.64–1.76 (1 H, m, H-5), 1.99–2.09 (1 H, m, H-4), 3.39 (3 H, s, C-2-OMe), 3.42–3.47 (2 H, m, H-6), 3.61 (1 H, d, *J* = 5.0 Hz, H-3), 3.73–3.77 (1 H, m, H-4′), 3.80 (3 H, OMe, OPMB), 3.93–3.98 (1 H, m, H-5′), 4.03–4.07 (1 H, m, CH_2, OPMB), 4.10–4.21 (2 H, m, H-1″), 4.23–4.27 (1 H, m, CH_2, OPMB), 4.41 (1 H, t, *J* = 7.5 Hz, H-2′), 6.82–6.86 (2 H, m, ArH), 7.09–7.12 (2 H, m, ArH), 7.30–7.42 (6 H, m, ArH), 7.65–7.76 (4 H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 ($CHCH_3$), 19.7 (C, Ph_2*t*-BuSi), 27.1 (CH_3, *t*-Bu), 27.1 (CH_3, *t*-Bu), 27.2 (CH_3, *t*-Bu), 30.4 (CH_2, C-5), 31.6 (CH, C-4), 32.6 (CH_2, C-3′), 50.4 (CH_3, C-2-OMe), 55.3 (OCH_3, OPMB), 56.4 (CH_2, C-6), 63.0 (CH_2, C-1″), 70.4 (CH_2, OPMB), 73.0 (CH, C-3), 78.2 (CH, C-4'), 79.8 (CH, C-5′), 80.0 (CH, C-2′), 100.6 (C, C-2), 113.8 (CH, OPMB), 127.4 (CH, Ar), 127.5 (CH, Ar), 128.8 (CH, Ar), 129.5 (CH, Ar), 129.6 (CH, Ar), 130.3 (C, Ar), 133.8 (C, Ar), 134.1 (C, Ar), 136.2 (CH, Ar), 136.2 (CH, Ar), 159.1 (C, OPMB), 178.2 (C=O). MS–FAB: *m/z* (%) = 703 (0.1) $[M - H]^+$, 673 (2), 647 (0.2), 617 (2), 597 (2), 383 (18), 239 (7), 197 (7), 121 (100), 89 (18).
(39) The stereochemistry at C2 in **2** was assumed to be that in which the OMe group adopts an axial position due to stabilization by the anomeric effect.