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Synthesis of the C8–C20 and C21–C30 segments of pectenotoxin 2

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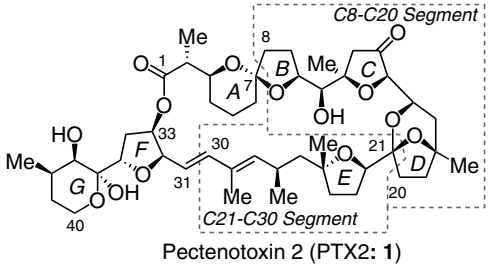
Abstract—In this study, we synthesized the C8–C20 and C21–C30 segments of the diarrhetic shellfish toxin pectenotoxin 2. The C8–C20 segment was assembled from a phosphonate corresponding to the C8–C15 segment (prepared from L-malic acid in 19 steps) and an aldehyde corresponding to the C16–C20 segment (synthesized from 3-methyl-3-butenol in nine steps) by a twelve-step process including the Horner–Wadsworth–Emmons reaction, regio- and stereoselective reduction of the resulting enone, diastereoselective epoxidation, and 5-*exo* epoxide cleavage forming the C-ring. The C21–C30 segment was constructed in 13 steps from (*S*)-glycidol via a route involving E-ring formation by 5-*exo* epoxide cleavage and stereoselective methylation at C27 by the Evans method.

The pectenotoxin (PTX) family of diarrhetic shellfish toxins, which were isolated from toxin infected scallop *Patinopecten yessoensis* and the dinoflagellate *Dinophysis fortii* by Yasumoto,[1] has an unusual thirty-four-membered macrolactone that includes a spirocyclic acetal AB-ring, a six-membered cyclic hemiacetal G-ring, a bicyclic acetal D-ring, and three oxolanes (C, E, and F-rings). While some PTXs show potent hepatotoxicity in mice,[2] recent studies have reported that PTX2 (**1**) (Fig. 1) also exhibits strong cytotoxicity against cancer cells[3] and actin-depolymerizing activity.[4] These remarkable structural and biological features of PTXs have attracted the attention of synthetic organic chemists.[5–7] As part of our goal toward total synthesis of PTXs, we describe herein the synthesis of the C8–C20 and C21–C30 segments (**2** and **3**, respectively; Scheme 1) of PTX2 (**1**).



Pectenotoxin 2 (PTX2: **1**)

Figure 1.

From the retrosynthetic perspective (Scheme 1), guided by our previous synthesis of the C8–C18 segment of PTX2,[7b] the C8–C20 synthetic segment (**2**) was envisioned to arise via a 5-*exo* epoxide cleavage reaction of **4**, which would be assembled from phosphonate **5** and aldehyde **6** through a route involving the Horner–Wadsworth–Emmons reaction, regio- and stereoselective reduction of the ketone at C14, and diastereoselective epoxidation. Although we previously synthesized the C8–C15 segment, which is structurally the same as **5** except for the protective group of the oxygen at C11, it required a lengthy 26 step process from 3-butynol.[7b] Therefore, we intended to prepare **5** by an alternative shorter route including formation of enone **9** from **10**, diastereoselective reduction of **9** affording **8**, diastereoselective epoxidation of **8** followed by protection giving **7**, and construction of the β-keto-phosphonate part of **5**. Aldehyde **6**, having a quaternary asymmetric center at C18, would be derived from epoxy alcohol **11** exploiting regioselective reductive cleavage followed by oxidation. We also undertook the synthesis of the C21–C30 segment (**3**) from **12** through the Evans alkylation[8] to make

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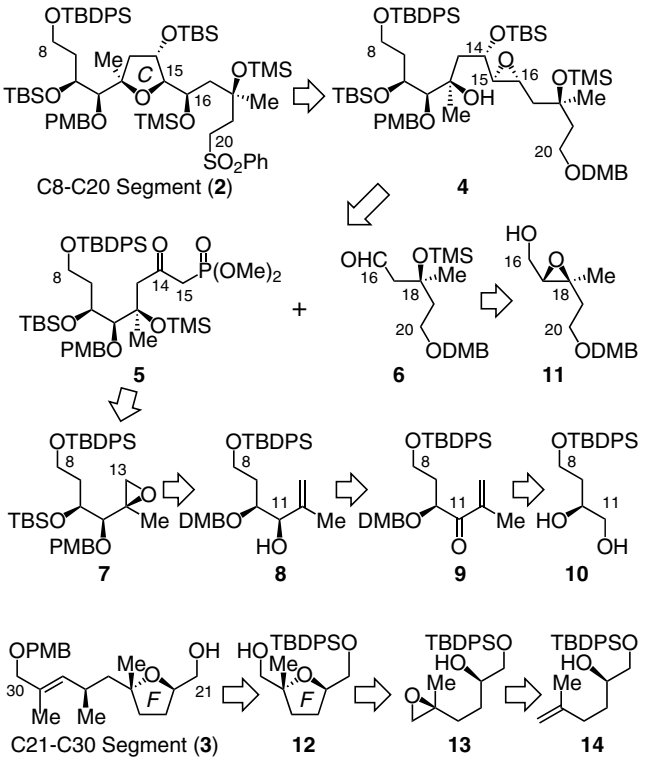
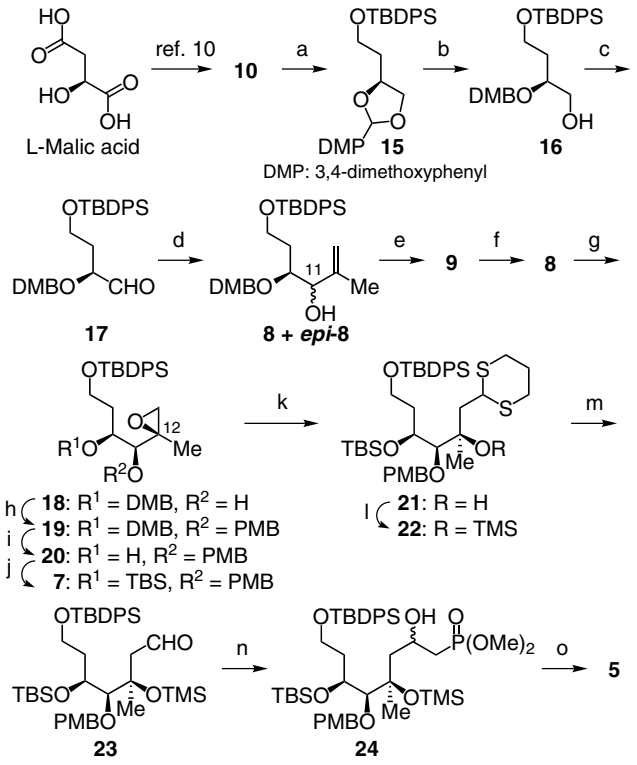


Scheme 1.



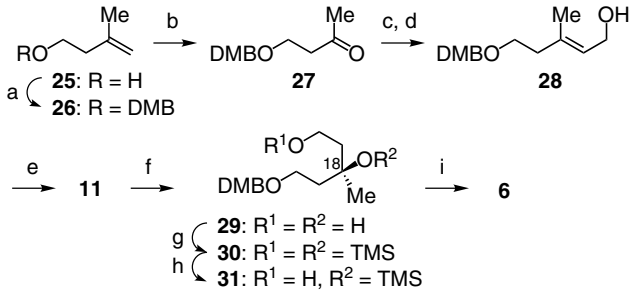
Scheme 2. Reagents and conditions: (a) 3,4-dimethoxybenzaldehyde, CSA (cat), toluene, reflux, 5 h, **15**: 47%, recovered **10**: 41%; (b) DIBALH, CH_2Cl_2, −78 to 0 °C, 30 min, 71%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min, then Et_3N, −78 to 0 °C, 15 min; (d) 2-propenylmagnesium bromide, THF, −78 °C, 10 min, 68% from **16**; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min, then Et_3N, −78 to 0 °C, 15 min, 90%; (f) $Zn(BH_4)_2$, Et_2O, −30 °C, 20 min, 71%; (g) $VO(acac)_2$, TBHP, CH_2Cl_2, 0 °C, 3.5 h, 67%; (h) NaH, PMBBr, Bu_4NI, THF, 23 °C, 2 h, 83%; (i) DDQ, CH_2Cl_2—pH 7 buffer (10:1), 26 °C, 3.5 h; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 71% from **19**; (k) 1,3-dithiane, *t*-BuLi, Bu_2Mg, THF, −20 °C, 30 min, then **7**, 23 °C, 1 h, 72%; (l) TMSOTf, 2,6-lutidine, DMF, 0 °C, 70 min, 87%; (m) $Hg(ClO_4)_2$, 2,6-di-*tert*-butylpyridine, THF–H_2O (5:1), 25 °C, 15 min, 72%; (n) $(MeO)_2P(O)CH_3$, BuLi, THF, −78 °C, 30 min, then **23**, −78 °C, 2 h, 97%; (o) DMPI, $NaHCO_3$, CH_2Cl_2, 23 °C, 5 min, 100%.

the stereocenter at C27 and the Wittig reaction to form the trisubstituted double bond at C28 (Scheme 1). In turn, the E-ring of **12** would arise via diastereoselective epoxidation of bishomoallyl alcohol **14** followed by the 5-*exo* epoxide cleavage reaction of the resulting epoxide **13**.[9]

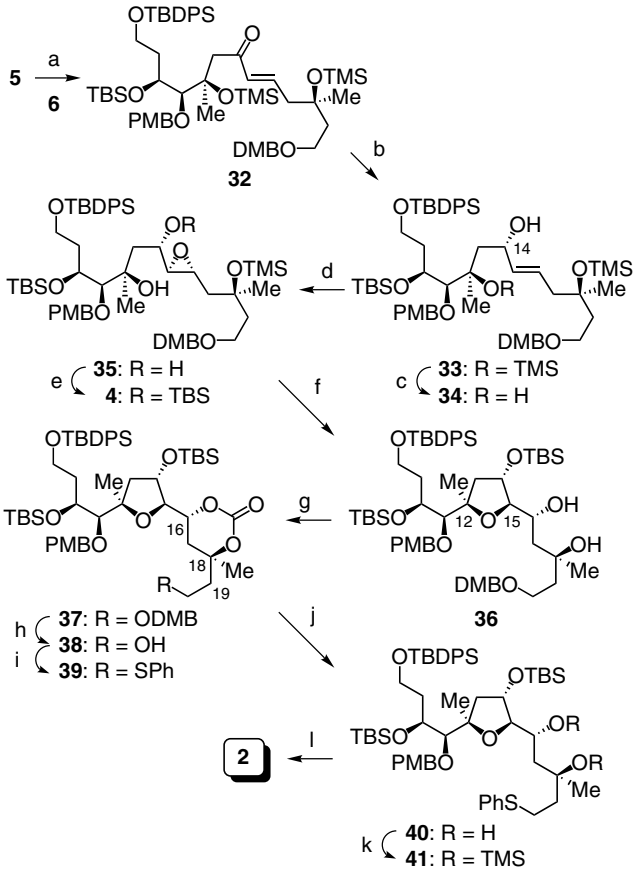
Scheme 2 illustrates synthesis of phosphonate **5**, starting from known diol **10** prepared in four steps from L-malic acid.[10] Diol **10** was converted to 3,4-dimethoxy benzyl (DMB) ether **16** through acetalization (47%: 79% based on recovery of **10**) followed by reductive cleavage with DIBALH (71%). Swern oxidation[11] of **16** and the subsequent reaction with 2-propenylmangesium bromide gave a 1:1 mixture of **8** and its diastereomer (***epi*-8**) (68% from **12**). To establish stereochemistry at C11, an oxidation/reduction process was applied. Swern oxidation[11] of the mixture of **8** and ***epi*-8** (90%) and reduction of the resulting **9** with $Zn(BH_4)_2$ afforded **8** as a sole product (71%).[12,13] Alcohol **8** was epoxidized with TBHP in the presence of VO(acac) to produce **18** as an almost single diastereomer (67%),[14,15] which was then converted to **7** through a three-step process [protection with PMBBr (83%), removal of DMB, and protection with TBSOTf (71% from **19**)]. Following Nakata's procedure, epoxide **7** was reacted with 1,3-dithiane to give **21** in good yield (72%).[16] After TMS-protection of **21**, the dithiane group was hydrolyzed with $Hg(ClO_4)_2$ in the presence of 2,6-di-*tert*-butylpyridine to produce **23** (72%),[17,18] which was reacted with lithiated dimethyl methylphosphonate to afford **24** (97%). Finally, alcohol **24** was oxidized with Dess–Martin periodinane (DMPI) to produce **5** (100%).[19] Phosphonate **5** was thus synthesized from L-malic acid in 19 steps.

Aldehyde **6** was synthesized from 3-methyl-3-butenol (**25**) (Scheme 3). Protection of **25** as a DMB ether (64%) followed by a one-pot dihydroxylation/diol-cleavage process afforded **27** (68%), which was converted to **28** stereoselectively via the Horner–Wadsworth–Emmons reaction (99%: $E/Z = \sim 2.7{:}1$) and DIBALH reduction (73% after separation). Katsuki–Sharpless asymmetric epoxidation[20] of **28** with (+)-diisopropyl tartrate gave **11** (97%) in good optical yield (95% ee).[21] Epoxide **11** was regioselectively cleaved with $LiAlH_4$ to produce **29** (100%),[22] which was transformed to **31** by a stepwise protection/deprotection process (95% and 89%, respectively). Alcohol **31** was oxidized with TPAP and NMO to aldehyde **6**.[23]

Scheme 4 shows the synthesis of C8–C20 segment **2**. The coupling reaction of **5** with **6** and the subsequent C-ring formation was performed following our previous procedure.[7b] Phosphonate **5** was coupled with **6** by the Horner–Wadsworth–Emmons reaction to afford **32** (85%), which was stereoselectively reduced to **33** under Luche



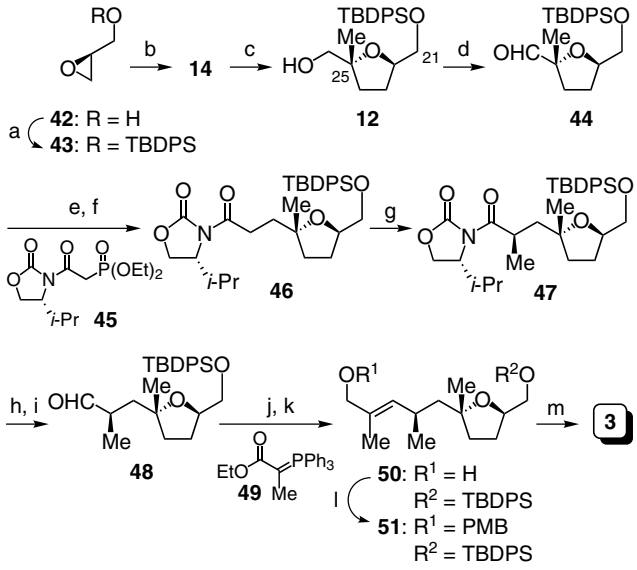
Scheme 3. Reagents and conditions: (a) NaH, 3,4-dimethoxybenzyl chloride, Bu_4NI, THF, 25 °C, 24 h, 64%; (b) OsO_4, NMO, 1,4-dioxane—pH 7 buffer (3:1), 23 °C, 1 h, then $NaIO_4$, 3 h, 68%; (c) $(EtO)_2(O)PCH_2CO_2Et$, NaH, THF, 23 °C, 12.5 h, 99% (E/Z = ~2.7:1); (d) DIBALH, CH_2Cl_2, −78 °C, 40 min, then separation, 73%; (e) (+)-diisopropyl tartrate, Ti(O*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, −30 °C, 12 h, 97% (95% ee); (f) $LiAlH_4$, THF, 24 °C, 1 h, 100%; (g) TMSOTf, 2,6-lutidine, CH_2Cl_2, −40 °C, 45 min, 95%; (h) K_2CO_3, MeOH, 23 °C, 90 s, 89%; (i) TPAP, NMO, MS4A, CH_2Cl_2, 0 °C, 30 min, 87%.



Scheme 4. Reagents and conditions. (a) NaH, benzene–THF (2:5), 0 °C, 5 min, then **6**, −78 °C, 8 h, 85%; (b) $NaBH_4$, $CeCl_3{\cdot}H_2O$, EtOH, −20 °C, 3 h, 98%; (c) K_2CO_3, MeOH, 24 °C, 2 h, 93%; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 95% (dr = 3:1); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 1 h, then separation, 66%; (f) CSA (cat.), CH_2Cl_2, 0 °C, 4 h, 77%; (g) $(CCl_3O)_2CO$, pyridine, CH_2Cl_2, 0 °C, 2 h, 95%; (h) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 95%; (i) *N*-(phenylthio)phthalimide, Bu_3P, CH_2Cl_2, 25 °C, 1 h, 94%; (j) $LiAlH_4$, Et_2O, −30 °C, 1.5 h, 100%; (k) TMSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C, 3 h, 93%; (l) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, 1 h, 100%.

conditions (98%).[24,25] Selective detachment of the TMS group at C12-oxygene (93%) followed by hydroxy-directed epoxidation with *m*-CPBA gave a 3:1 mixture of epoxide **35** and its diastereomer (95%).[26] After selective protection with TBSOTf, epoxide **4** was isolated with a 66% yield. Intramolecular 5-*exo* cyclization of **4** with a catalytic amount of CSA led to **36** (77%).[27] Thus, the C-ring was successfully constructed. Diol **36** was then transformed with triphosgene to carbonate **37** (95%), of which the DMB group was removed with TMSOTf/2,6-lutidine to give **38** (95%).[28] Installation of a phenylthio group to **38** with *N*-(phenylthio)phthalimide/Bu_3P to afford **39** (94%)[29] followed by a two-step process including removal of the carbonate of **39** with $LiAlH_4$ (100%) and protection of diol **40** with TMSOTf produced **41** in good yield (93%). Finally, sulfide **41** was oxidized with *m*-CPBA (100%), thereby completing the synthesis of the C8–C20 segment (**2**)[30] of PTX2 (**1**).

C21–C30 segment **3** was constructed from (*S*)-glycidol (**42**) (Scheme 5). Protection of **42** with TBDPSCl (100%) and the subsequent reaction with 2-methyl-3-propenylmagnesium chloride afforded **14** (100%). When bishomoallyl alcohol **14** was subjected to epoxidation with TBHP/$VO(acac)_2$ followed by treatment with CSA, the desired oxolane **12** was produced predominantly (57%) along with its diastereomer (*epi*-**12**: 18%) and recovered **14** (11%).[9,31] Swern oxidation of **12** afforded **44** (96%),[11] which was converted to **46** by the



Scheme 5. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 25 °C, 1 h, 100%; (b) 3-chloro-2-methylpropene, Mg, THF, 24 °C, 1 h, then **43**, −40 °C, 5 h, 100%; (c) $VO(acac)_2$ (cat.), TBHP, benzene, 55 °C, 21 h, then CSA (cat.), 21 °C, 2 h, **12**: 57%, *epi*-**12**: 18%, recovered **14**: 11%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 35 min, then Et_3N, −78 to 0 °C, 75 min, 96%; (e) **45**, NaH, THF, 23 °C, 30 min, then **44**, 23 °C, 1.5 h, 93%; (f) H_2, Pd/C, EtOH, 23 °C, 16 h, 100%; (g) NaHMDS, THF, −78 °C, 1 h, then MeI, −78 °C, 4 h, 93%; (h) $NaBH_4$, THF–H_2O (3:1), 23 °C, 22 h, 100%; (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 to −50 °C, 15 min, then Et_3N, −50 to 0 °C, 30 min, 97%; (j) **49** (excess), benzene, reflux, 56 h; (k) DIBALH, CH_2Cl_2, −78 °C, 25 min, 92% from **48**; (l) NaH, PMBBr, Bu_4NI, THF, 23 °C, 16 h, 96%; (m) Bu_4NF, THF, 23 °C, 1.5 h, 100%.

Horner–Wadsworth–Emmons reaction with **45** (93%)[32] and the subsequent hydrogenation (100%). Stereoselective methylation of **46** by the Evans method to give **47** (93%), reductive detachment of the chiral auxiliary (100%), and then Swern oxidation provided **48** (97%).[11] Aldehyde **48** was reacted with Wittig reagent **49**, and the resulting unsaturated ester was reduced with DIBALH to afford **50** stereoselectively (92% from **48**). The final protection/deprotection process transformed **50** to **3**[33,34] (96% for two steps). Thus, the synthesis of the C21–C30 segment (**3**) of PTX2 (**1**) was accomplished.

In conclusion, we successfully synthesized the C8–C20 and C21–C30 segments (**2** and **3**, respectively) of PTX2 (**1**). C8–C20 segment **2** was assembled from phosphonate **5** (prepared from L-malic acid in nineteen steps) and aldehyde **6** (synthesized from 3-methyl-3-butenol in nine steps) by a twelve-step process including the Horner–Wadsworth–Emmons reaction, regio- and stereoselective reduction of the resulting enone, diastereoselective epoxidation, and 5-*exo* epoxide cleavage forming the C-ring. C21–C30 segment **3** was constructed in thirteen steps from (*S*)-glycidol via a route involving E-ring formation by 5-*exo* epoxide cleavage, stereoselective methylation at C27, and formation of the trisubstituted olefin at C28. All newly generated stereocenters of **2** and **3** were properly confirmed by the NMR or $[\alpha]_D$ analysis of the intermediates or derivatives from the intermediates (Figs. 2–4).[13,15,22,25,27,31,33] Further efforts toward the total synthesis of PTX2 are currently underway in our laboratory.

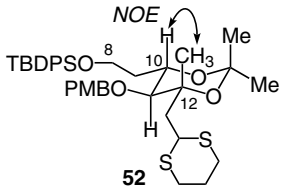


Figure 2.

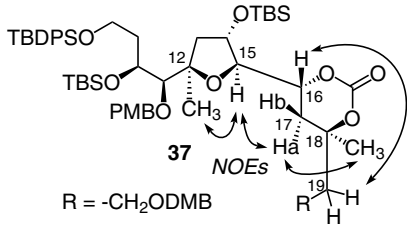


Figure 3.

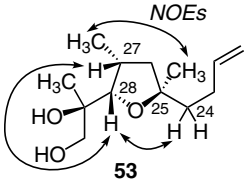


Figure 4.

Acknowledgments

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21. The optical yield of **11** was determined by HPLC using a chiral column [Daicel Chiralcel AD, eluent: hexane/2-propanol (9:1)].
22. The absolute stereochemistry at C18 of **29** was confirmed by the conversion of **29** to known (3*S*)-5-(*tert*-butyldiphenylsilyloxy)-3-methyl-3,5-pentanediol via a two-step process [(i) TBDPSCl, imidazole; (ii) H_2, Pd/C]. The $[\alpha]_D$ value of the synthetic compound was in good agreement with the reported value {$[\alpha]_D^{19}$ −7.7 ($CHCl_3$, *c* 0.975); lit. $[\alpha]_D^{20}$ −6.61 ($CHCl_3$, *c* 0.5): Krohn, K.; Meyer, A. *Liebigs Ann. Chem.* **1994**, 167}.
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25. The absolute stereochemistry at C14 of **33** was determined by new Mosher's method. See Ref. 13.
26. The presence of the TMS group at C12-oxygen reduced stereoselectivity of the epoxidation step.
27. The configurations at C15 and C16 of oxolane **36** were confirmed by the presence of NOEs between H15 and C12–CH_3, between H15 and H17a, between H17a and C18–CH_3, and between H16 and H19 in **37** (Fig. 3).
28. We found that a primary alkyl DMB ether was readily removed on treatment with TMSOTf/2,6-lutidine. This phenomenon was helpful for selective detachment of the DMB group of **37** in the presence of the PMB ether at C11. On the other hand, detachment of a DMB group from **29** during TMS ether formation was avoided by lowering the reaction temperature (Scheme 3). cf. Oriyama, T.; Yatabe, K.; Kawada, Y.; Koga, G. *Synlett* **1995**, 45.
29. Walker, K. A. M. *Tetrahedron Lett.* **1977**, *18*, 4475.
30. Selected spectral data of **2**: A colorless oil; $[\alpha]_D^{22}$ +13.2 (*c* 1.43, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6, C_6HD_5 as 7.15 ppm) δ 0.04 (3H, s), 0.08 (3H, s), 0.13 (3H, s), 0.14 (9H, s), 0.21 (3H, s), 0.28 (9H, s), 0.95 (9H, s), 0.97 (9H, s), 1.21 (9H, s), 1.29 (3H, s), 1.50–1.60 (1H, m), 1.56 (3H, s), 1.70 (1H, dd, $J = 3.0$, 12.7 Hz), 1.98–2.06 (2H, m), 2.12–2.30 (2H, m), 2.29 (1H, dd, $J = 7.6$, 12.7 Hz), 3.31–3.40 (1H, m), 3.36 (3H, s), 3.51 (1H, dt, $J = 5.8$, 12.7 Hz), 3.70 (1H, s), 3.86–3.99 (2H, m), 4.09–4.12 (2H, m), 4.21 (1H, dd, $J = 2.6$, 5.3 Hz), 4.50 (1H, br t, $J = 6.0$ Hz), 4.74 (1H, d, $J = 11.2$ Hz), 5.02 (1H, d, $J = 11.2$ Hz), 6.86–6.94 (5H, m), 7.04–7.29 (6H, m), 7.38 (2H, d, $J = 8.8$ Hz), 7.77–7.83 (4H, m), 7.87–7.91 (2H, m); ^{13}C NMR (75 Hz, C_6D_6, $^{13}C^{12}C_5D_6$ as 128.0 ppm) δ −4.7 (CH_3), −4.6 (CH_3), −4.3 (CH_3), −3.3 (CH_3), 1.0 ($CH_3 \times 3$), 2.6 ($CH_3 \times 3$), 18.0 (C), 18.3 (C), 19.4 (C), 23.2 (CH_3), 25.9 ($CH_3 \times 3$), 26.2 ($CH_3 \times 3$), 27.2 ($CH_3 \times 3$), 28.3 (CH_3), 36.0 (CH_2), 36.5 (CH_2), 42.9 (CH_2), 45.0 (CH_2), 52.8 (CH_2), 54.8 (CH_3), 61.3 (CH_2), 70.3 (CH), 70.9 (CH), 74.3 (CH), 74.5 (CH_2), 75.1 (C), 85.2 (C), 88.5 (CH), 89.4 (CH), 114.1 ($CH \times 2$), 128.05 ($CH \times 2$), 128.07 ($CH \times 2$), 128.5 ($CH \times 2$), 129.1 ($CH \times 2$), 129.3 ($CH \times 2$), 130.0 ($CH \times 2$), 131.8 (C), 132.9 (CH), 134.3 ($C \times 2$), 135.97 ($CH \times 2$), 136.03 ($CH \times 2$), 141.1 (C), 159.7 (C); IR (film) ν_{max} 3070, 2957, 2935, 2895, 2850, 1612, 1587, 1513, 1472, 1460, 1446, 1428, 1390, 1375, 1361, 1310, 1302, 1251, 1087, 940, 910, 904, 839, 775, 745, 702, 695 cm^{-1}; HR-FDMS calcd for $C_{63}H_{104}O_{10}Si_5S$ [M^+]: 1192.6196; found, 1192.6213.
31. The stereochemistry at C25 of **12** was determined by the presence of NOE between H21 and C25–CH_3.
32. Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725.
33. The stereochemistry at C27 of **3** was confirmed by the presence of NOEs between C25–CH_3 and C27–CH_3, between H27 and H28, and between H28 and H24 in oxolane **54** derived from **3** through a five-step process [(i) PPh_3, I_2, imidazole; (ii) Mg; (iii) DDQ, (iv) *m*-CPBA (yielding an almost single diastereomer); (v) CSA.] (Fig. 4).
34. Selected spectral data of **3**: A colorless oil; $[\alpha]_D^{26}$ −18.0 (*c* 1.70, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, d, $J = 6.8$ Hz), 1.21 (3H, s), 1.53–1.60 (2H, m), 1.63–1.65 (1H, m), 1.69 (3H, d, $J = 1.0$ Hz), 1.71–1.94 (3H, m), 2.53–2.63 (1H, m), 3.60 (1H, dt, $J = 5.8$, 11.7 Hz), 3.66 (1H, ddd, $J = 2.4$, 5.8, 11.2 Hz), 3.81 (3H, s), 3.85 (2H, m), 3.97–4.03 (1H, m), 4.37 (2H, s), 5.28 (1H, dd, $J = 1.3$, 9.6 Hz), 6.87 (2H, d, $J = 8.6$ Hz), 7.25 (2H, d, $J = 8.6$ Hz); ^{13}C NMR (75 Hz, $CDCl_3$, $^{13}CDCl_3$ as 77.0 ppm) δ 13.9 (CH_3), 22.6 (CH_3), 26.9 (CH_3), 27.5 (CH_2), 29.0 (CH), 37.9 (CH_2), 48.3 (CH_2), 55.2 (CH_3), 65.2 (CH_2), 71.0 (CH_2), 76.0 (CH_2), 78.7 (CH), 83.7 (C), 113.7 ($CH \times 2$), 129.2 ($CH \times 2$), 129.3 (C), 130.7 (C), 135.8 (CH), 159.1 (C); IR (film) ν_{max} 3443, 2959, 2930, 2867, 1614, 1454, 1373, 1302, 1248, 1173, 1070, 1038, 821 cm^{-1}; HR-EIMS calcd for $C_{21}H_{32}O_4$ [M^+]: 348.2301; found, 348.2300.