TOTAL SYNTHESES OF BE-12406 A AND ITS C(8)-VINYL ANALOG#

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Abstract – Total syntheses of BE-12406 A (**3a**) and its C(8)-vinyl analog (**3c**) are described. The key step is the selective *O*-glycosylation of naphthol (**4**)with L-rhamnopyranosyl fluoride (**5**) by employing Cp_2HfCl_2–$AgClO_4$ in fluorobenzene at –20 °C in the presence of a hindered base, 2,6-di-*t*-butyl-4-methylpyridine (**12**), affording *O*-glycoside (**11**) in good yield.

BE-12406 A and B (**3a** and **3b**) are a pair of novel antibiotics isolated from the culture broth of *Streptomyces rutgersensis*.[1] They have a common benzonaphthopyranone chromophore, which is the same as those of the gilvocarcin–ravidomycin class antibiotics (Figure 1).[2] However, the carbohydrate in **3** is uniquely attached as an *O*-glycoside rather than a *C*-glycoside (cf. **1** and **2**). The potent antitumor activities of **3** stand in good contrast to those of the gilvocarcins that require the presence of the C(8) vinyl group as the essential structural element.[3] Intrigued by their novel structures as well as the discrepancy in the structure–activity relationship (*vide supra*), we decided to synthesize BE-12406 A and its C(8) vinyl analog, and the results are described herein.[4a]

Figure 1

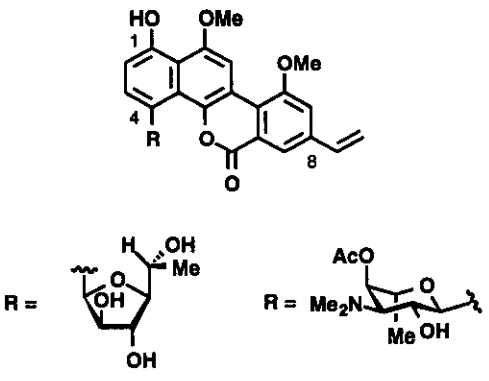
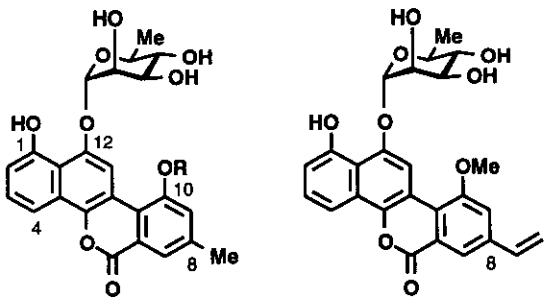


Figure 2

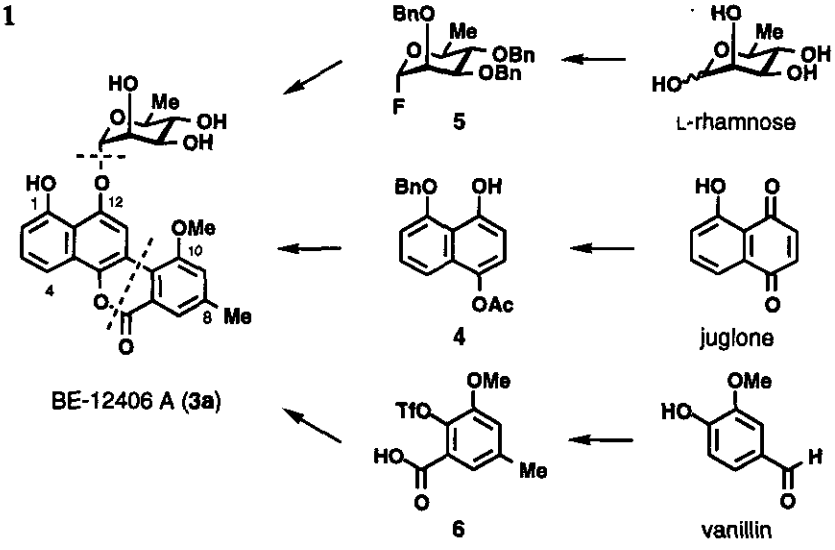


#Dedicated to the memory of the late Professor Yoshio Ban.

RESULTS AND DISCUSSION

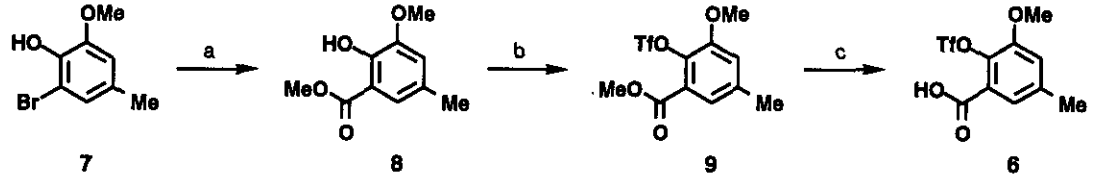
Synthetic plan: We expected that the synthetic strategy of the gilvocarcins[4b] would be basically applicable to the synthesis of these compounds. Considering the convergency, BE-12406 A (**3a**) was divided into three readily available components, naphthol (**4**), L-rhamnopyranosyl fluoride (**5**), and benzoic acid (**6**) (Scheme 1). According to the literature procedures, **4**[5] and **5**[6] were prepared from commercially available juglone (two steps) and L-rhamnose (four steps), respectively.

Scheme 1



Benzoic acid (**6**) was synthesized in three steps from the known bromophenol (**7**),[7] derived from vanillin (Scheme 2). Thus, Pd-catalyzed carbonylation of bromide (**7**) in the presence of methanol gave methyl ester (**8**), which was trifluoromethanesulfonylated to give triflate (**9**) in high yield. Acidic hydrolysis of **9** gave the desired carboxylic acid (**6**) in 73% yield after recrystallization (hexane–$CHCl_3$).

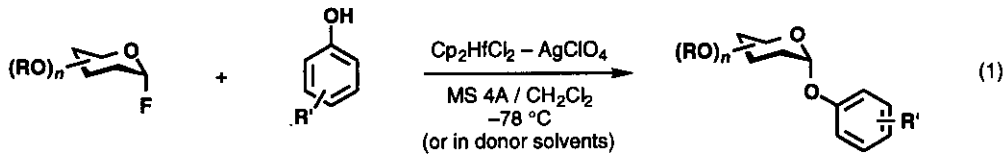
Scheme 2[a]



[a](a) CO, 3 mol% $Pd(OAc)_2$, 6 mol% 1,1'-bis(diphenylphosphino)ferrocene (dppf), MeOH, *n*-Bu_3N / DMF, 100 °C, 17 h (64%); (b) Tf_2O, DMAP / pyridine–CH_2Cl_2, 0 °C to room temperature, 1 h (99%); (c) conc. HCl / 1,4-dioxane, reflux, 60 h (73%).

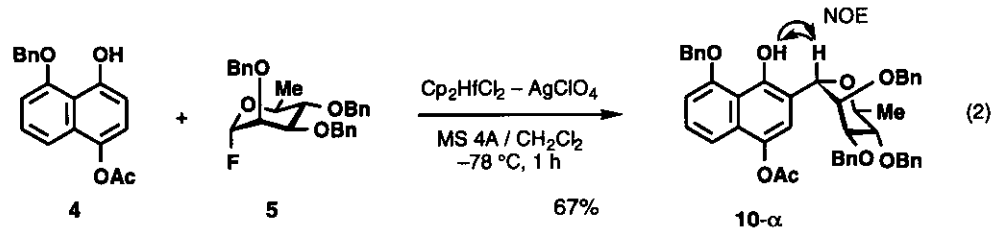
With these three components in hand, we took the strategy to connect the sugar with naphthol (**4**) first and then to construct the aromatic moiety. Another option, glycosylation at the final stage, was abandoned because of the extremely poor solubility of the fully elaborated tetracycle.[4c]

O-Rhamnosylation of naphthol (4): We previously reported an expeditious method for *O*-glycosylation of phenols by utilizing the combination of Cp_2HfCl_2–$AgClO_4$ as the activator of glycosyl fluoride.[8] This corresponds to the first step of the "*O*→*C*-glycoside rearrangement" reaction, which we established as an approach to aryl *C*-glycosides.[2b,9] Thus, the quenching at low temperature (e.g., –78 °C) or the use of donor solvents can provide the initially formed *O*-glycoside in high yield (eq 1). Along these lines, coupling of naphthol (**4**) with glycosyl fluoride (**5**) was attempted, which, however, turned out to be extremely difficult.



(1)

Upon reaction of naphthol (**4**) with glycosyl fluoride (**5**) under the above mentioned conditions (Cp_2HfCl_2–$AgClO_4$ / CH_2Cl_2, –78 °C),[8] a single product rapidly formed, which however, was not the desired *O*-glycoside but the *C*-glycoside (**10**-α) (eq 2).[10] The regiochemistry of the aromatic substitution in **10**-α was determined by the NOE experiments as shown below. It is worth noting that the *C*-glycoside was solely composed of the α-anomer, which underwent thorough anomerization to the corresponding β-anomer when the reaction was warmed up to 0 °C (67% yield).[10]



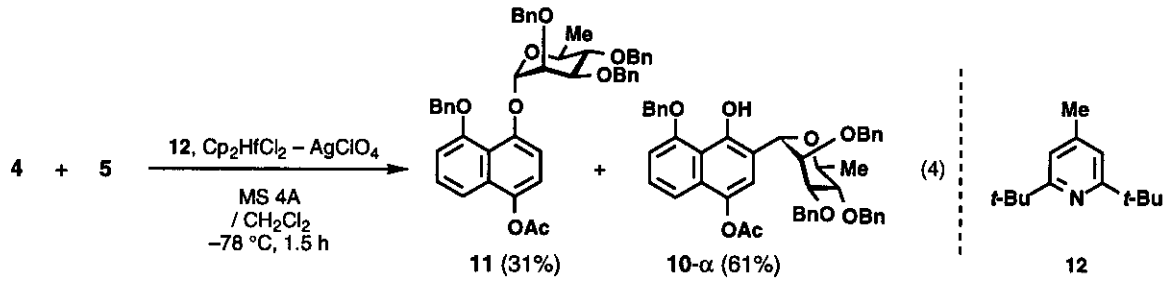
(2)

We initially surmised that *C*-glycoside (**10**) forms *via* the "*O*→*C*-glycoside rearrangement", that is, by the *in situ*-conversion of the kinetically formed *O*-glycoside.[9] However, the following observations suggested that the *C*-glycoside (**10**) is produced directly by the Friedel–Crafts reaction,[11] not by a two-stage process *via* *O*-glycoside. The tlc monitoring of the reaction showed no indication of the intermediacy of *O*-glycoside. Low temperature quenching (at –94 °C, 10 min) afforded *C*-glycoside (**10**-α) (21%) and the remaining naphthol (**4**) (74%), and none of the *O*-glycoside was detected.

Use of the donor solvents was also ineffective: MeCN totally retarded the reaction, while Et_2O led to the formation of a complex mixture of products. Various further attempts proved fruitless, e.g., other Lewis acid promoters, such as $SnCl_2$–$AgClO_4$,[12a] TMSOTf,[12b] or BF_3•OEt_2,[12c] uniformly gave **10**.

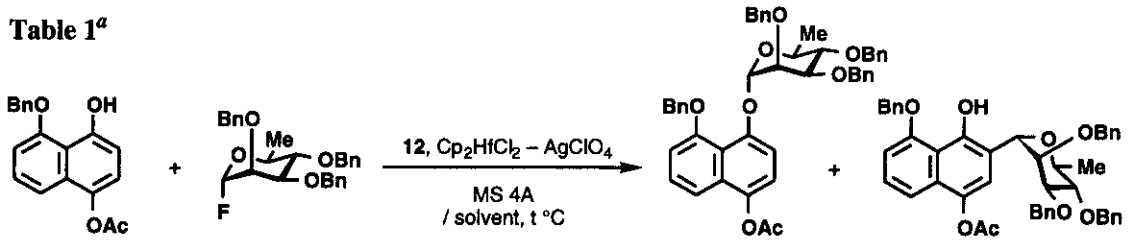
We reasoned that the failure of *O*-glycosylation is due to the hydrogen-bonding of the reacting hydroxyl group in **4** to the peri-oxygen functionality. Since the aromatic ring is highly electron rich, the naphthol is instead capable of undergoing a direct aromatic substitution at its most reactive carbon atom ortho to the phenolic hydroxyl group. At this stage, it occurred to us to attempt the reaction *in the presence of a base* that would hopefully weaken the hydrogen bond, thereby increasing the nucleophilicity of the

hydroxylic oxygen. Most of the bases tested, however, such as tetramethylguanidine[13] and 2,6-lutidine, totally retarded the reaction, most probably by deactivating the Lewis acid by coordination. Only 2,6-di-*t*-butyl-4-methylpyridine (**12**),[14] a sterically hindered pyridine, worked nicely for this purpose. Thus, the reaction in the presence of **12** (2.5 equiv) gave *O*-glycoside (**11**) for the first time, although the major product was still **10**-α (eq 4).



After considerable experimentation to improve the yield of (**11**), the solvent effect was found to be decisive in terms of the tendency that aromatic solvents suppress the formation of *C*-glycoside (**10**) (Table 1). For example, toluene gave **11** as the major product although the total yield was low, presumably due to the poor solubility of **4** (run 3). Use of a mixed solvent, toluene–CH_2Cl_2 (the latter being used for dissolving **4**), slightly improved the yield of **11** (run 4). Eventually, we found that halogenated aromatic solvents (chlorobenzene and fluorobenzene) lead to acceptable yield of **11** (runs 5, 6).

Table 1[a]

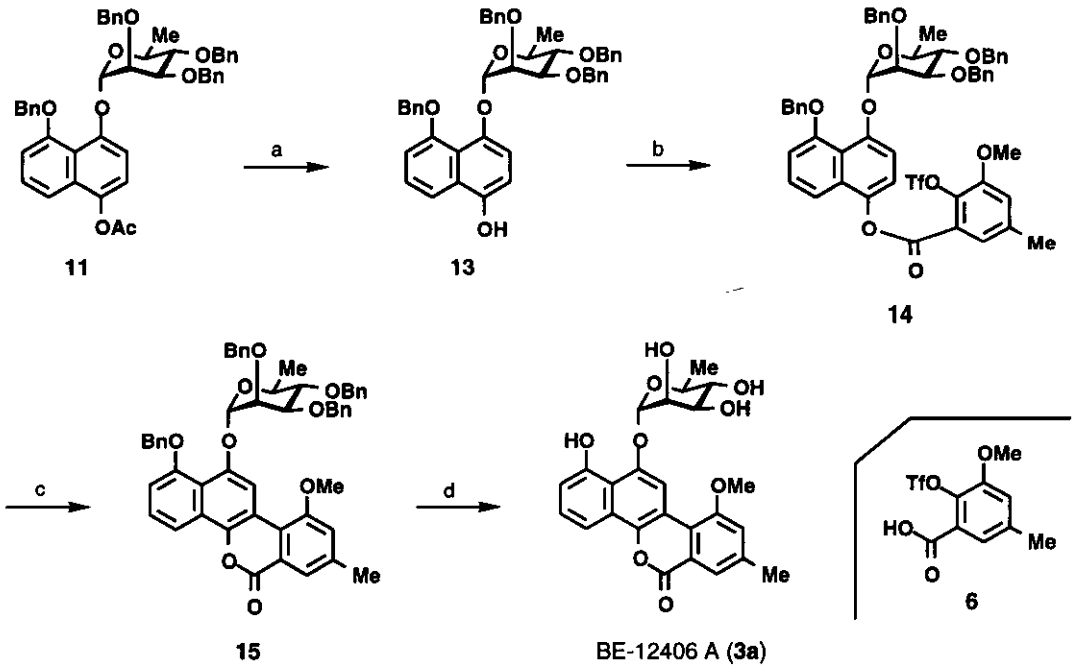


run	solvent	conditions	yield/%[b] 11[c]	yield/%[b] 10-α
1	CH_2Cl_2	–78 °C, 1.5 h	31	61
2	$CHCl_3$	–20 °C, 0.5 h	46	49
3	toluene	–20 °C → rt,[d] 2.5 h	38	18
4	toluene–CH_2Cl_2 (4:1)	–78 °C → rt,[d] 1.5 h	46	18
5	chlorobenzene	–20 °C, 1 h	56	24
6	fluorobenzene	–20 °C, 1 h	62	29

a) Molar ratio: **4** / **5** / Cp_2HfCl_2 / $AgClO_4$ / **12** = 1.1 / 1.0 / 1.5 / 3.0 / 2.5.
b) Isolated yields based on **5**.
c) In all runs, only α-anomer of *O*-glycoside was obtained.
d) Room temperature.

Total synthesis of BE-12406 A: With *O*-glycoside (**11**) in hand, completion of the synthesis was rather straightforward (Scheme 3). Saponification of acetate (**11**) followed by esterification with carboxylic acid (**6**)[7] by using water-soluble carbodiimide (EDCI)[15] afforded ester (**14**) in excellent yield. Construction of the tetracycle was nicely achieved *via* the Pd catalysis.[5] Thus, heating of **14** with a catalytic amount of $(Ph_3P)_2PdCl_2$ in the presence of sodium pivalate and Hünig base in *N,N*-dimethylacetamide provided the tetracycle (**15**) in 58% yield together with 32% recovery of **14**. This reaction is the *triflate version* of the Martin's ingenious approach[5] to the benzonaphthopyranone skeleton (cf. the original approach makes use of aryl iodide). Use of the triflate offered us two advantages; 1) the ready accessibility of **6** (*vide supra*)[7] and 2) the higher reactivity to allow the reaction at lower temperature (80 °C; cf. 120–130 °C for iodide).[4,9e] Finally, the four benzyl protecting groups of **15** were removed by hydrogenolysis to give BE-12406 A (**3a**) in 80% yield after recrystallization from MeOH: mp 238–244 °C (decomp.); $[\alpha]^{22}_D$ –89° (*c* 0.24, DMSO) [lit.,[1] mp 238–243 °C (decomp.); $[\alpha]^{25}_D$ –89.3° (*c* 1.01, DMSO)[16]]. All the data of synthetic **3a** (^{1}H- and ^{13}C-nmr, ir, ms, uv, and tlc mobilities in several solvent systems) were in full accordance with those of the natural product by direct comparison.

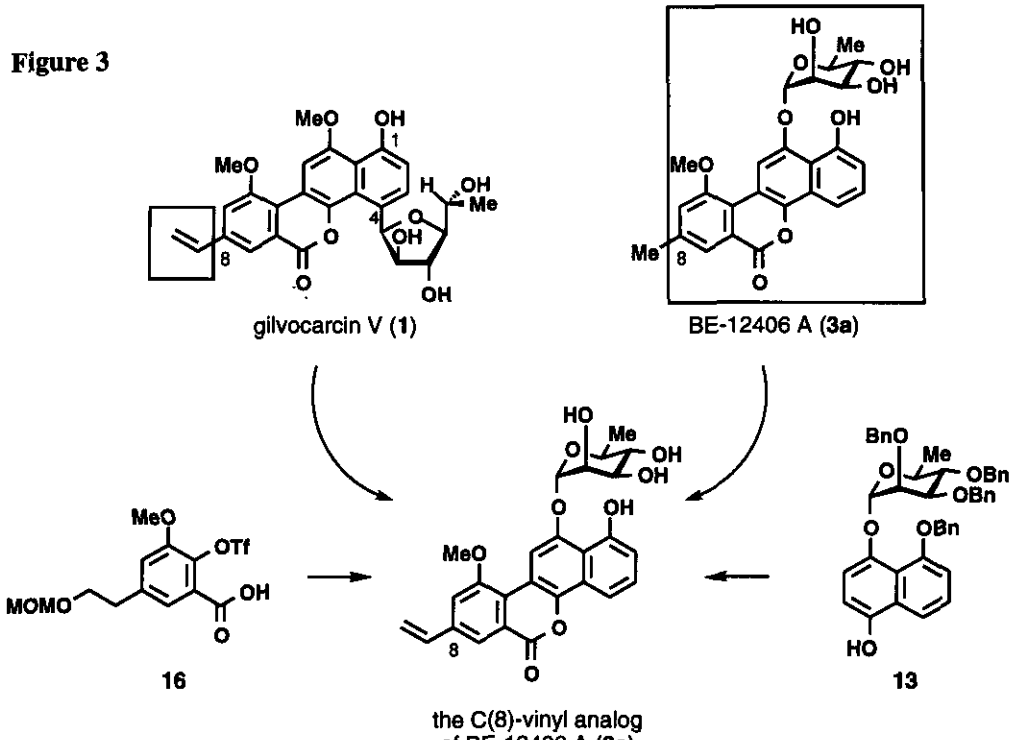
Scheme 3[a]



[a](a) 0.25 N aq. NaOH / MeOH–1,4-dioxane, 0 °C, 5 min (96%); (b) **6**, EDCI (= 1-Ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride), DMAP / Et_2O, room temperature, 10 h (quant.); (c) 28 mol% $(Ph_3P)_2PdCl_2$, *t*-BuCOONa, *i*-Pr_2NEt / DMA, 80 °C, 6 h (58%); (d) H_2, 10% Pd–C / MeOH–THF, room temperature, 19 h (80%).

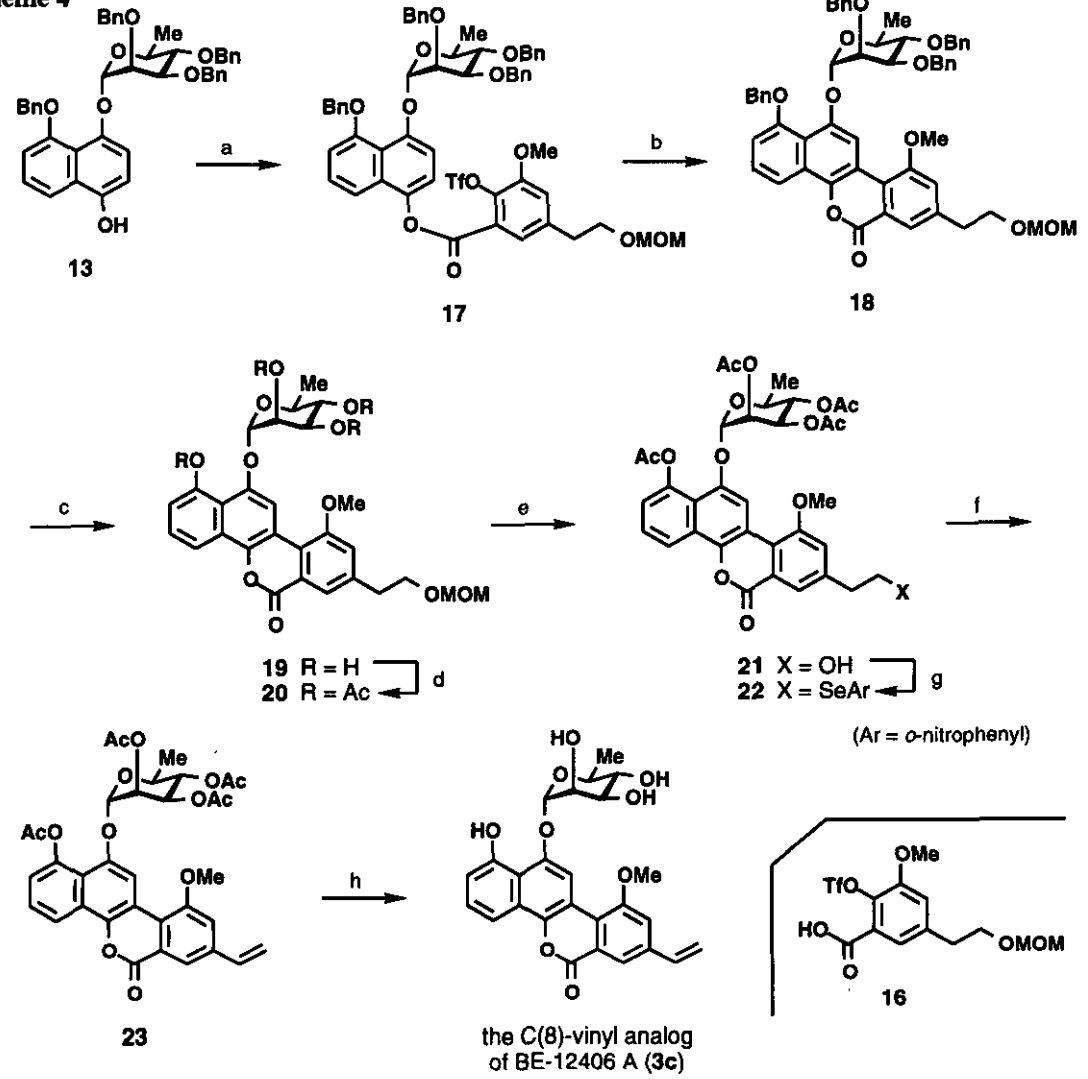
Total synthesis of the C(8)-vinyl analog of BE-12406 A: As mentioned before, BE-12406 A (**3a**) shows potent antitumor activities in spite of that the C(8)-substituent is a *methyl* rather than a *vinyl*, which stands in sharp contrast to the gilvocarcins which require the presence of the C(8)-vinyl group to the biological activities.[3] With a hope to improve the biological activities, we were interested in hybridizing these compounds, that is, the synthesis of the C(8)-vinyl analog of BE-12406 A (**3c**) (Figure 3). The synthetic plan was similar to that of gilvocarcin V (**1**), and the synthesis started with benzoic acid (**16**)[4] and naphthol (**13**).

Figure 3



Thus, the union of acid (**16**)[4] with naphthol (**13**) afforded ester (**17**) in 92% yield (Scheme 4). Subsequent Pd-catalyzed biaryl bond formation gave 52% of the cyclized product (**18**) with a recovery of the starting triflate (**17**) (14%). The four benzyl groups in **18** were removed by hydrogenolysis to give tetraol (**19**), which was then fully acetylated to yield tetraacetate (**20**). The MOM group in **20** was removed by treatment with bromotrimethylsilane[17] to give alcohol (**21**), which was directly converted to selenide (**22**) by using the combination of *o*-nitrophenyl selenocyanate and triphenylphosphine.[18] Exposure of selenide (**22**) to 35% H_2O_2 in THF (0 °C, then room temperature, 1 h), gave rise to the vinyl derivative (**23**) in 83% yield (two steps).[19] Finally, saponification of **23** with sodium methoxide in methanol gave the C(8)-vinyl analog (**3c**): mp 207–209 °C (decomp.); $[\alpha]^{22}_{D}$ –91° (*c* 0.11, DMSO). The biological properties of this compound are now under investigation.

Scheme 4[a]



[a](a) **16**, EDCI, DMAP / Et_2O, 24 h (92%); (b) 30 mol% $(Ph_3P)_2PdCl_2$, NaOPiv, *i*-Pr_2NEt / DMA, 80 °C, 4 h (52%); (c) H_2, 10% Pd–C / MeOH–THF, 42 h; (d) Ac_2O, cat. DMAP / py. 30 min (77%, two steps); (e) TMSBr / CH_2Cl_2, –20 °C, 1 h (90%); (f) *o*-nitrophenyl selenocyanate, *n*-Bu_3P / THF, 1 h; (g) 35% aq. H_2O_2 / 0 °C to room temperature, 1 h (83%, two steps); (h) NaOMe / MeOH, 20 min (98%).

In summary, the first total synthesis of BE-12406 A (**3a**) was achieved in a convergent and concise manner (five steps, 28% overall yield from **5**). The key step was the selective *O*-glycosylation of naphthol (**4**) with L-rhamnopyranosyl fluoride (**5**) by employing Cp_2HfCl_2–$AgClO_4$ in fluorobenzene at –20 °C in the presence of a hindered base (**12**), affording *O*-glycoside (**10**) in good yield. Also the synthesis of C(8)-vinyl analog of BE-12406 A (**3c**), a promising hybrid compound, was accomplished.

ACKNOWLEDGMENT

The authors are grateful to Dr. Hajime Morishima, Banyu Pharmaceutical Co., for kindly supplying an authentic sample of BE-12406 A.

EXPERIMENTAL SECTION

General procedure: All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Ethereal solvents were distilled from benzophenone ketyl immediately before use. Dichloromethane was distilled successively from P_2O_5 and CaH_2 and stored over molecular sieves 4A (MS 4A). For thin-layer chromatography (tlc) analysis, Merck precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. Silica-gel 60 K070-WH (70–230 mesh) of Katayama Chemical was used for flash column chromatography. Silica-gel preparative tlc (ptlc) was performed on Merck Kieselgel 60 PF_{254} (Art 7747). Melting point (mp) determinations were performed by using a Yanaco MP-S3 instrument and are uncorrected. Boiling points (bp) refer to the oven temperature of bulb-to-bulb distillations carried out with a Kugelrohr distillation apparatus. ^1H (400 MHz) and ^{13}C nmr spectra (100 MHz) were measured on a JEOL JNM GX-400 spectrometer or JEOL JNM EX-400 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ($\delta = 0$). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (ir) spectra were recorded on a Jasco IRA-202 spectrophotometer. High resolution mass spectra under electron impact conditions (HRms) were obtained with a Hitachi M-80 spectrometer, and those under positive fast atom bombardment conditions (HRFABms) were recorded with a JEOL JMS-HX110/HX110 spectrometer. Optical rotations ($[\alpha]_D$) were measured on a Jasco DIP-360 polarimeter, and uv spectra were recorded on a Jasco UVIDEC-610A.

4-Acetoxy-8-benzyloxy-1-naphthol (4)[5]

This compound was obtained as colorless needles according to the procedure of Giles *et al.*[20]; mp 159.5–160 °C (CCl_4); R_f = 0.46 (hexane/EtOAc = 7/3); ^1H nmr ($CDCl_3$) δ 9.34 (s, 1 H), 7.35–7.47 (m, 6 H), 7.32 (dd, 1 H, J_1 = 8.4, J_2 = 7.3 Hz), 7.11 (d, 1 H, J = 8.4 Hz), 6.86 (d, 1 H, J = 7.3 Hz), 6.81 (d, 1 H, J = 8.4 Hz), 5.23 (s, 2 H), 2.40 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 169.9, 155.5, 152.6, 138.6, 135.0, 129.3, 129.1, 128.9, 128.0, 126.5, 120.1, 115.6, 115.2, 109.5, 106.0, 71.8, 20.9; ir (KBr) 3450, 3070, 1755, 1630, 1605, 1590, 1450, 1435, 1405, 1375, 1280, 1250, 1215, 1195, 1150, 1040, 1020, 930, 915, 880, 825, 810, 770, 760, 710, 700 cm^{-1}; Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.23; H, 5.27.

2,3,4-Tri-*O*-benzyl-α-L-rhamnopyranosyl fluoride (5)[6]

To a solution of 2,3,4-tri-*O*-benzyl-L-rhamnopyranose[6a] (1.93 g, 4.44 mmol) in CH_2Cl_2 (13 ml) was added 68% $(HF)_x$•pyr (3.5 ml) at –20 °C, and the stirring was continued for 4 h. The reaction was stopped by pouring the mixture into crushed ice–saturated aqueous $NaHCO_3$–$CHCl_3$, and the products were extracted with Et_2O. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (hexane/ EtOAc = 9/1) afforded L-rhamnopyranosyl fluoride (**5**) (1.64 g, 84.6%) as colorless oil: R_f = 0.44 (hexane/ EtOAc = 9/1), R_f = 0.52 (hexane/CH_2Cl_2/Et_2O = 7/2/1); ^1H nmr ($CDCl_3$) δ 7.26–7.40 (m, 15 H), 5.48 (dd, 1 H, J_1 = 50.5, J_2 = 2.0 Hz), 4.94 (d, 1 H, J = 10.7 Hz), 4.81 (d, 1 H, J = 12.2 Hz), 4.62–4.70 (m, 4 H), 3.81–3.90 (m, 3 H), 3.66 (dd, 1 H, $J_1 = J_2$ = 9.3 Hz), 1.35 (d, 3 H, J = 6.1 Hz); ^{13}C nmr ($CDCl_3$) δ 138.3, 138.2, 137.8, 128.5, 128.45, 128.39, 127.99, 127.96, 127.94, 127.74, 127.69, 106.4 (d, J_{C-F} = 221.6 Hz), 79.6, 79.2, 75.4, 73.7 (d, $^2J_{C-F}$ = 35.2 Hz), 73.4, 72.6, 70.6, 17.9; ir (neat) 3025, 2910, 2870, 1495, 1450, 1390, 1365, 1310, 1285, 1245, 1210, 1185, 1120, 1095, 1070, 1045, 1030, 955, 845, 805, 740, 700 cm^{-1}; $[\alpha]^{23}_D$ –18° (*c* 1.0, $CHCl_3$) [*lit.*,[6c] $[\alpha]^{25}_D$ –15° (*c* 1, $CHCl_3$)], HRms *m/z* 436.2046 (436.2047 calcd for $C_{27}H_{29}O_4F$, M^+).

Methyl 2-hydroxy-3-methoxy-5-methylbenzoate (8)

A mixture of bromophenol (**7**)[7] (5.05 g, 23.3 mmol), $Pd(OAc)_2$ (157 mg, 0.699 mmol, 3 mol%), 1,1'-bis(diphenylphosphino)ferrocene (774 mg, 1.40 mmol, 6 mol%), *n*-Bu_3N (8.63 g, 46.6 mmol), and MeOH (18.8 ml, 467 mmol) in DMF (45 ml) was bubbled with CO gas for 40 min. After stirring at 100 °C for 17 h, the reaction mixture was cooled to room temperature. To this mixture was added brine (50 ml) and the mixture was carefully acidified with 3 N HCl (100 ml). The products were extracted with Et_2O containing little amount of CH_2Cl_2, and the combined organic extracts were washed successively with 1 N HCl and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (hexane/ EtOAc = 8/2) followed by recrystallization (hexane/benzene = 4/1) afforded methyl benzoate (**8**) (2.90 g, 63.5%) as colorless prisms: mp 90–91 °C; R_f = 0.41 (hexane/EtOAc = 8/2); ^{1}H nmr ($CDCl_3$) δ 10.79 (s, 1 H), 7.22 (d, 1 H, J = 1.1 Hz), 6.85 (d, 1 H, J = 1.1 Hz), 3.93 (s, 3 H), 3.88 (s, 3 H), 2.28 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 170.9, 149.9, 148.2, 127.9, 120.6, 118.0, 112.1, 56.1, 52.3, 21.0; ir (KBr) 3140, 2960, 1675, 1620, 1485, 1470, 1440, 1410, 1390, 1370, 1320, 1295, 1270, 1235, 1210, 1190, 1045, 1070, 990, 960, 895, 880, 860, 810, 800, 760, 735, 710 cm^{-1}; Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.29; H, 6.13.

Methyl 3-methoxy-5-methyl-2-(trifluoromethanesulfonyloxy)benzoate (9)

To a solution of phenol (**8**) (1.00 g, 5.10 mmol) and DMAP (30 mg, 0.25 mmol, 5 mol%) in pyridine (5 ml) and CH_2Cl_2 (5 ml) was added Tf_2O (1.75 ml, 10.4 mmol) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 1 h. The reaction was stopped by adding water at 0 °C, and the mixture was extracted with Et_2O. The combined organic extracts were washed successively with 1 N HCl and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/2) to afford triflate (**9**) (1.65 g, 98.6%) as a colorless oil: bp 110–115 °C / 0.4 mmHg; R_f = 0.40 (hexane/EtOAc = 8/2); ^{1}H nmr ($CDCl_3$) δ 7.36 (d, 1 H, J = 1.5 Hz), 7.01 (d, 1 H, J = 1.5 Hz), 3.93 (s, 3 H), 3.89 (s, 3 H), 2.39 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 164.7, 151.4, 139.1, 135.5, 125.1, 123.5, 118.8 (q, J_{C-F} = 320.6 Hz), 117.6, 56.3, 52.6, 21.4; ir (neat) 2970, 1730, 1595, 1470, 1420, 1385, 1340, 1295, 1265, 1250, 1215, 1140, 1125, 1070, 995, 900, 880, 790, 770, 715 cm^{-1}; HRms *m/z* 328.0226 (328.0227 calcd for $C_{11}H_{11}O_6F_3S$, M^+).

3-Methoxy-5-methyl-2-(trifluoromethanesulfonyloxy)benzoic acid (6)

A solution of ester (**9**) (3.27 g, 9.96 mmol) in 1,4-dioxane (15 ml) and conc. HCl (15 ml) was refluxed for 60 h. The reaction mixture was cooled to room temperature, diluted with water, and the products were extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by recrystallization (hexane/$CHCl_3$ = 1/1) afforded benzoic acid (**6**) (2.27 g, 72.5%) as colorless needles: mp 154–155 °C; ^{1}H nmr (acetone-d_6) δ 7.42 (d, 1 H, J = 1.8 Hz), 7.36 (d, 1 H, J = 1.8 Hz), 3.97 (s, 3 H), 2.43 (s, 3 H); ^{13}C nmr (acetone-d_6) δ 165.2, 152.3, 140.5, 136.4, 126.2, 124.1, 119.7 (q, J_{C-F} = 319.9 Hz), 118.9, 57.0, 21.3; ir (KBr) 2950, 2860, 2650, 2590, 1695, 1595, 1480, 1460, 1440, 1420, 1400, 1325, 1300, 1270, 1245, 1230, 1200, 1180, 1135, 1070, 910, 880, 860, 790, 740, 720, 710 cm^{-1}; HRms *m/z* 314.0086 (314.0072 calcd for $C_{10}H_9O_6F_3S$, M^+).

***O*-Glycosidation of naphthol (4) with L-rhamnopyranosyl fluoride (5).**

In the presence of well-dried, powdered molecular sieves 4A (*ca.* 230 mg), a suspension of Cp_2HfCl_2 (86.1 mg, 227 μmol), $AgClO_4$ (95.0 mg, 458 μmol), and naphthol (**4**) (54.1 mg, 175 μmol) in fluorobenzene (4.0 ml) was stirred for 30 min at room temperature. To this suspension at –20 °C was slowly added a solution of 2,6-di-*t*-butyl-4-methylpyridine (**12**) (84.2 mg, 410 μmol) in fluorobenzene (1.0 ml) followed by a solution of glycosyl fluoride (**5**) (65.0 mg, 149 μmol) in fluorobenzene (3.0 ml). The stirring was continued at –20 °C for 1 h, and the reaction was stopped by the addition of saturated

aqueous $NaHCO_3$. The mixture was acidified with 2 N HCl, and filtered through a Celite pad. The products were extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/CH_2Cl_2/Et_2O = 7/2/1) afforded *O*-glycoside (**11**) (66.5 mg, 61.6%) and *C*-glycoside (**10**-α) (31.6 mg, 29.4%).

1-Acetoxy-5-benzyloxy-4-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyloxy)naphthalene (11)
Colorless foam; R_f = 0.49 (hexane/EtOAc = 7/3), R_f = 0.25 (hexane/CH_2Cl_2/Et_2O = 7/2/1); ^1H nmr ($CDCl_3$) δ 7.12–7.38 (m, 24 H), 6.81 (dd, 1 H, J_1 = 7.8, J_2 = 0.7 Hz), 5.60 (d, 1 H, J = 2.0 Hz), 5.13 (d, 1 H, J = 13.4 Hz), 5.03 (d, 1 H, J = 13.4 Hz), 4.92 (d, 1 H, J = 11.0 Hz), 4.74 (d, 1 H, J = 12.5 Hz), 4.69 (d, 1 H, J = 12.5 Hz), 4.64 (d, 1 H, J = 11.0 Hz), 4.28 (d, 1 H, J = 11.7 Hz), 4.24 (d, 1 H, J = 11.7 Hz), 4.10 (dd, 1 H, J_1 = 9.5, J_2 = 3.2 Hz), 4.06 (dd, 1 H, J_1 = 3.2, J_2 = 2.0 Hz), 4.00 (dq, 1 H, J_1 = 9.5, J_2 = 6.1 Hz), 3.70 (dd, 1 H, J_1 = J_2 = 9.5 Hz), 2.41 (s, 3 H), 1.33 (d, 3 H, J = 6.1 Hz); ^{13}C nmr ($CDCl_3$) δ 169.7, 155.9, 151.2, 141.3, 138.72, 138.68, 138.4, 137.2, 130.1, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 126.9, 126.7, 119.2, 118.6, 114.0, 111.3, 109.1, 97.9, 80.6, 80.1, 75.2, 74.9, 72.8, 71.7, 71.0, 69.0, 21.0, 18.1; ir (neat) 3030, 2940, 1770, 1625, 1600, 1590, 1515, 1500, 1450, 1415, 1370, 1325, 1270, 1200, 1120, 1095, 1060, 1030, 970, 920, 875, 850, 810, 790, 755, 740, 700 cm^{-1}; $[\alpha]^{26}_D$ –53° (*c* 0.86, $CHCl_3$); HRFABms *m/z* 724.3030 (724.3036 calcd for $C_{46}H_{44}O_8$, M^+).

4-Acetoxy-8-benzyloxy-2-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-1-naphthol (10-α)
In the presence of well-dried, powdered molecular sieves 4A (*ca.* 100 mg), a suspension of Cp_2HfCl_2 (48.9 mg, 129 μmol) and $AgClO_4$ (50.2 mg, 242 μmol) in CH_2Cl_2 (1.0 ml) was stirred for 30 min at room temperature. To this suspension was added naphthol (**4**) (19.1 mg, 61.9 μmol) in CH_2Cl_2 (1.0 ml) followed by a solution of glycosyl fluoride (**5**) (26.4 mg, 60.5 μmol) in CH_2Cl_2 (1.5 ml) at –78 °C. The stirring was continued at –78 °C for 1 h, and the reaction was stopped by the addition of saturated aqueous $NaHCO_3$. The mixture was acidified with 2 N HCl, and filtered through a Celite pad. The products were extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/CH_2Cl_2/Et_2O = 5/3/2) afforded *C*-glycoside (**10**-α) (29.3 mg, 66.8%) as colorless foam: R_f = 0.39 (hexane/EtOAc = 7/3), R_f = 0.11 (hexane/CH_2Cl_2/Et_2O = 7/2/1); ^1H nmr ($CDCl_3$) δ 9.73 (s, 1 H), 7.16–7.50 (m, 23 H), 6.91 (dd, 1 H, J_1 = 7.3, J_2 = 1.5 Hz), 5.55 (d, 1 H, J = 5.9 Hz), 5.27 (s, 2 H), 4.64 (d, 1 H, J = 11.7 Hz), 4.60 (d, 1 H, J = 12.1 Hz), 4.54 (d, 1 H, J = 12.1 Hz), 4.52 (d, 1 H, J = 11.7 Hz), 4.50 (d, 1 H, J = 12.1 Hz), 4.45 (d, 1 H, J = 12.1 Hz), 4.33 (dd, 1 H, J_1 = 5.9, J_2 = 2.9 Hz), 4.00 (dq, 1 H, J_1 = 5.1, J_2 = 6.6 Hz), 3.77 (dd, 1 H, J_1 = 6.6, J_2 = 2.9 Hz), 3.61 (dd, 1 H, J_1 = 6.6, J_2 = 5.1 Hz), 2.41 (s, 3 H), 1.45 (d, 3 H, J = 6.6 Hz); ^{13}C nmr ($CDCl_3$) δ 169.6, 155.7, 149.8, 138.8, 138.72, 138.71, 138.5, 135.0, 129.04, 128.99, 128.91, 128.3, 128.2, 128.0, 127.80, 127.76, 127.5, 127.3, 127.2, 126.4, 119.7, 119.3, 115.6, 115.2, 106.3, 79.4, 77.9, 76.5, 73.2, 72.3, 72.2, 72.1, 71.9, 68.8, 20.9, 17.8; ir (neat) 3380, 3030, 2940, 1760, 1640, 1610, 1590, 1495, 1450, 1405, 1370, 1255, 1210, 1180, 1110, 1075, 1025, 915, 810, 755, 700 cm^{-1}; $[\alpha]^{25}_D$ +66° (*c* 1.6, $CHCl_3$); HRFABms *m/z* 724.2994 (724.3036 calcd for $C_{46}H_{44}O_8$, M^+); Anal. Calcd for $C_{46}H_{44}O_8$: C, 76.22; H, 6.12. Found: C, 76.06; H, 6.22.

4-Acetoxy-8-benzyloxy-2-(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)-1-naphthol (10-β)
In the presence of well-dried, powdered molecular sieves 4A (*ca.* 200 mg), a suspension of Cp_2HfCl_2 (88.6 mg, 233 μmol), $AgClO_4$ (100 mg, 482 μmol), and naphthol (**4**) (42.5 mg, 138 μmol) in CH_2Cl_2 (3.5 ml) was stirred for 30 min at room temperature. To this suspension was slowly added a solution glycosyl fluoride (**5**) (53.4 mg, 122 μmol) in CH_2Cl_2 (1.0 ml) at –78 °C and the reaction mixture was gradually warmed to 0 °C during 1 h. The reaction was stopped by the addition of saturated aqueous $NaHCO_3$ and the mixture was acidified with 2 N HCl, and filtered through a Celite pad. The products

were extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/CH_2Cl_2/Et_2O = 7/2/1) afforded *C*-glycoside (**10**-β) (59.1 mg, 66.7%) as a colorless foam: R_f = 0.47 (hexane/EtOAc = 7/3), R_f = 0.21 (hexane/CH_2Cl_2/Et_2O = 7/2/1); ^1H nmr ($CDCl_3$) δ 9.29 (s, 1 H), 7.24–7.50 (m, 18 H), 6.79–6.94 (m, 6 H), 5.26 (d, 1 H, J = 11.0 Hz), 5.22 (d, 1 H, J = 11.0 Hz), 4.98 (d, 1 H, J = 10.6 Hz), 4.78 (s, 1 H), 4.76 (d, 1 H, J = 12.8 Hz), 4.71 (d, 1 H, J = 12.8 Hz), 4.70 (d, 1 H, J = 10.6 Hz), 4.48 (d, 1 H, J = 12.1 Hz), 4.33 (d, 1 H, J = 12.1 Hz), 4.24 (d, 1 H, J = 1.1 Hz), 3.72–3.80 (m, 2 H), 3.52 (dq, 1 H, $J_1 = J_2$ = 6.2 Hz), 2.40 (s, 3 H), 1.43 (d, 3 H, J = 6.2 Hz); ^{13}C nmr ($CDCl_3$) δ 169.8, 155.7, 147.4, 138.8, 138.72, 138.67, 138.2, 135.1, 129.1, 129.0, 128.7, 128.5, 128.37, 128.35, 128.15, 128.10, 127.61, 127.57, 127.51, 127.47, 126.8, 125.8, 120.1, 119.8, 115.4, 115.0, 105.7, 84.9, 80.6, 76.1, 75.4, 74.4, 74.2, 73.6, 72.2, 71.8, 20.9, 18.3; ir (neat) 3390, 3030, 2880, 1765, 1640, 1610, 1590, 1495, 1450, 1405, 1365, 1295, 1255, 1210, 1155, 1125, 1105, 1090, 1025, 950, 915, 810, 755, 700 cm^{-1}; $[\alpha]^{24}_D$ –129° (*c* 0.89, $CHCl_3$); HRFABms *m/z* 724.3050 (724.3036 calcd for $C_{46}H_{44}O_8$, M^+).

5-Benzyloxy-4-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyloxy)-1-naphthol (13)

To a solution of *O*-glycoside (**11**) (416 mg, 574 μmol) in 1,4-dioxane (9 ml) and MeOH (9 ml) was added 0.25 N aqueous NaOH (4 ml) at 0 °C. After stirring for 5 min, the mixture was acidified by the addition of 2 N HCl, and the products were extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc = 8/2) afforded naphthol (**13**) (375 mg, 95.7%) as a colorless foam: R_f = 0.37 (hexane/EtOAc = 7/3); ^1H nmr ($CDCl_3$) δ 7.75 (dd, 1 H, J_1 = 8.3, J_2 = 1.0 Hz), 7.15–7.37 (m, 21 H), 6.90 (d, 1 H, J = 8.3 Hz), 6.83 (dd, 1 H, J_1 = 7.0, J_2 = 1.0 Hz), 6.63 (d, 1 H, J = 8.3 Hz), 5.49 (s, 1 H), 5.46 (d, 1 H, J = 1.7 Hz), 5.12 (d, 1 H, J = 13.2 Hz), 4.97 (d, 1 H, J = 13.2 Hz), 4.94 (d, 1 H, J = 11.0 Hz), 4.66 (d, 1 H, J = 12.5 Hz), 4.64 (d, 1 H, J = 11.0 Hz), 4.61 (d, 1 H, J = 12.5 Hz), 4.33 (d, 1 H, J = 11.7 Hz), 4.27 (d, 1 H, J = 11.7 Hz), 4.03–4.12 (m, 3 H), 3.71 (dd, 1 H, $J_1 = J_2$ = 9.5 Hz), 1.33 (d, 3 H, J = 6.4 Hz); ^{13}C nmr ($CDCl_3$) δ 155.3, 147.1, 146.3, 138.7, 138.6, 137.4, 128.6, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 126.9, 125.5, 119.7, 115.2, 114.8, 109.7, 108.8, 98.9, 80.6, 80.2, 75.3, 75.1, 72.7, 71.7, 71.3, 69.0, 18.0; ir (KBr) 3360, 3030, 2925, 1620, 1600, 1585, 1520, 1495, 1450, 1380, 1355, 1265, 1215, 1180, 1110, 1090, 1055, 1025, 980, 910, 810, 785, 750, 735, 700 cm^{-1}; $[\alpha]^{28}_D$ –82° (*c* 0.67, $CHCl_3$); Anal. Calcd for $C_{44}H_{42}O_7$: C, 77.40; H, 6.20. Found: C, 77.13; H, 6.20.

5-Benzyloxy-4-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyloxy)-1-naphthyl 3-methoxy-5-methyl-2-(trifluoromethanesulfonyloxy)benzoate (14)

To a mixed suspension of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (125 mg, 652 μmol), DMAP (56.0 mg, 458 μmol), and benzoic acid (**6**) (119 mg, 379 μmol) in Et_2O (10 ml) was added a solution of naphthol (**13**) (162 mg, 237 μmol) in Et_2O (10 ml) at room temperature. After stirring for 10 h, the reaction mixture was diluted with Et_2O. To this mixture was added brine and 1 N HCl, and the products were extracted with Et_2O. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (hexane/CH_2Cl_2/Et_2O = 7/2/1) afforded ester (**14**) (232 mg, 99.9%) as a colorless foam: R_f = 0.43 (hexane/EtOAc = 7/3), 0.64 (hexane/CH_2Cl_2/Et_2O = 5/4/1); ^1H nmr ($CDCl_3$) δ 7.66 (d, 1 H, J = 1.5 Hz), 7.14–7.42 (m, 24 H), 7.11 (d, 1 H, J = 1.5 Hz), 6.81 (d, 1 H, J = 7.3 Hz), 5.63 (d, 1 H, J = 1.7 Hz), 5.14 (d, 1 H, J = 13.4 Hz), 5.05 (d, 1 H, J = 13.4 Hz), 4.94 (d, 1 H, J = 11.0 Hz), 4.75 (d, 1 H, J = 12.7 Hz), 4.71 (d, 1 H, J = 12.7 Hz), 4.66 (d, 1 H, J = 11.0 Hz), 4.29 (d, 1 H, J = 11.7 Hz), 4.25 (d, 1 H, J = 11.7 Hz), 4.11 (dd, 1 H, J_1 = 9.3, J_2 = 3.2 Hz), 4.07 (dd, 1 H, J_1 = 3.2, J_2 = 1.7 Hz), 4.01 (dq, 1 H, J_1 = 9.3, J_2 = 6.1 Hz), 3.94 (s, 3 H), 3.71 (dd, 1 H, $J_1 = J_2$ = 9.3 Hz), 2.47 (s, 3 H), 1.35 (d, 3 H, J = 6.1 Hz); ^{13}C nmr ($CDCl_3$) δ 162.7, 155.9, 151.7, 151.6, 140.9, 139.3, 138.8, 138.7,

138.4, 137.2, 136.0, 130.1, 128.7, 128.4, 128.3, 128.2, 127.9, 127.79, 127.75, 127.6, 127.5, 127.3, 127.2, 127.1, 126.7, 124.4, 123.8, 119.3, 118.72 (q, J_{C-F} = 320.6 Hz), 118.70, 118.3, 114.0, 111.2, 109.2, 97.9, 80.6, 80.1, 75.3, 74.8, 72.8, 71.7, 71.0, 69.1, 56.4, 21.6, 18.1; ir (neat) 3030, 2940, 1750, 1625, 1595, 1580, 1515, 1495, 1460, 1450, 1420, 1380, 1335, 1270, 1250, 1205, 1135, 1120, 1095, 1060, 1030, 970, 920, 875, 850, 815, 755, 740, 700 cm^{-1}; $[\alpha]^{25}_D$ –41° (*c* 1.1, $CHCl_3$); HRFABms *m/z* 978.2925 (978.2897 calcd for $C_{54}H_{49}O_{12}F_3S$, M^+).

1-Benzyloxy-10-methoxy-8-methyl-12-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyloxy)-6*H*-benzo[*d*]na-phtho[1,2-*b*]pyran-6-one (15)

A suspension of ester (**14**) (265 mg, 271 μmol), $(Ph_3P)_2PdCl_2$ (52.9 mg, 75.4 μmol, 28 mol%), *i*-Pr_2NEt (134 mg, 1.04 mmol), and sodium pivalate (123 mg, 99.1 mmol) in *N,N*-dimethylacetamide (25 ml) was heated at 80 °C for 6 h. After cooling to room temperature, the resulting dark brown suspension was diluted with Et_2O. The mixture was successively washed with 3 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (hexane/CH_2Cl_2/ Et_2O = 7.0/2.5/0.5 to 5/4/1) afforded tetracyclic compound (**15**) (130 mg, 57.9%) as a colorless foam, and the starting material (**14**) (84.3 mg, 31.8%) was recovered: mp 171–173 °C; R_f = 0.49 (hexane/EtOAc = 7/3), 0.54 (hexane/CH_2Cl_2/Et_2O = 5/4/1); ^1H nmr ($CDCl_3$) δ 8.82 (s, 1 H), 8.22 (dd, 1 H, J_1 = 8.4, J_2 = 0.7 Hz), 7.96 (d, 1 H, J = 0.7 Hz), 7.17–7.43 (m, 22 H), 6.93 (dd, 1 H, J_1 = 7.3, J_2 = 0.7 Hz), 5.56 (d, 1 H, J = 1.8 Hz), 5.17 (d, 1 H, J = 13.2 Hz), 5.03 (d, 1 H, J = 13.2 Hz), 4.97 (d, 1 H, J = 11.0 Hz), 4.72 (d, 1 H, J = 12.8 Hz), 4.69 (d, 1 H, J = 11.0 Hz), 4.67 (d, 1 H, J = 12.8 Hz), 4.35 (d, 1 H, J = 11.7 Hz), 4.30 (d, 1 H, J = 11.7 Hz), 4.18 (dq, 1 H, J_1 = 9.5, J_2 = 6.2 Hz), 4.15 (dd, 1 H, J_1 = 9.5, J_2 = 3.3 Hz), 4.11 (dd, 1 H, J_1 = 3.3, J_2 = 1.8 Hz), 4.07 (s, 3 H), 3.75 (dd, 1 H, J_1 = J_2 = 9.5 Hz), 2.51 (s, 3 H), 1.39 (d, 3 H, J = 6.2 Hz); ^{13}C nmr ($CDCl_3$) δ 161.4, 157.5, 155.1, 148.7, 142.0, 140.0, 138.8, 138.7, 138.6, 137.1, 128.7, 128.3, 128.2, 127.93, 127.87, 127.6, 127.5, 127.34, 127.31, 126.9, 126.8, 123.1, 122.7, 121.8, 118.7, 118.2, 115.5, 113.7, 112.9, 110.5, 99.3, 80.5, 80.4, 75.3, 75.2, 72.8, 71.8, 71.3, 69.1, 56.2, 21.7, 18.0; ir (neat) 3430, 3030, 2920, 1730, 1615, 1580, 1495, 1450, 1390, 1370, 1335, 1305, 1270, 1240, 1215, 1150, 1120, 1095, 1060, 1030, 980, 855, 810, 790, 755, 740, 700 cm^{-1}; $[\alpha]^{25}_D$ –69° (*c* 0.88, $CHCl_3$); Anal. Calcd for $C_{53}H_{48}O_9$: C, 76.79; H, 5.84. Found: C, 76.62; H, 5.78.

1-Hydroxy-10-methoxy-8-methyl-12-α-L-rhamnopyranosyloxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (BE-12406 A) (3a)

A suspension of tetracycle (**15**) (70.6 mg, 85.2 μmol) and 10% Pd–C (43 mg) in MeOH (20 ml) and THF (5 ml) was stirred under H_2 (1 atm) at room temperature for 19 h. After changing the atmosphere to Ar, the mixture was diluted with CH_2Cl_2 and stirred for another 15 min. The mixture was filtered through a Celite pad (washed with CH_2Cl_2), and the solvents were removed in vacuo to give crude **3a**, which was recrystallized from MeOH to give pure **3a** (31.8 mg, 79.7%) as pale yellow needles: mp 238–244 °C (decomp.); R_f = 0.57 ($CHCl_3$/MeOH = 5/1); ^1H nmr (DMSO-d_6) δ 9.50 (s, 1 H), 8.74 (s, 1 H), 7.87 (dd, 1 H, J_1 = 8.5, J_2 = 1.0 Hz), 7.81 (d, 1 H, J = 1.2 Hz), 7.49 (dd, 1 H, J_1 = 8.5, J_2 = 7.6 Hz), 7.48 (d, 1 H, J = 1.2 Hz), 6.99 (dd, 1 H, J_1 = 7.6, J_2 = 1.0 Hz), 5.49 (d, 1 H, J = 2.2 Hz), 4.91–4.94 (m, 1 H), 4.71 (d, 1 H, J = 5.6 Hz), 4.54–4.57 (m, 1 H), 4.11 (dd, 1 H, J_1 = 3.4, J_2 = 2.2 Hz), 4.08 (s, 3 H), 3.75–3.83 (m, 2 H), 3.43 (dd, 1 H, J_1 = J_2 = 9.3, J_3 = 5.6 Hz), 2.50 (s, 3 H), 1.26 (d, 3 H, J = 6.1 Hz); ^{13}C nmr (DMSO-d_6) δ 159.7, 156.8, 153.4, 148.6, 140.7, 140.1, 127.7, 125.5, 122.1, 121.6, 120.6, 119.2, 115.6, 112.6, 112.1, 111.9, 108.6, 101.5, 71.8, 70.6, 69.9, 69.8, 56.2, 20.7, 17.5; ir (KBr) 3425, 2940, 1720, 1700, 1615, 1585, 1385, 1360, 1335, 1305, 1245, 1165, 1140, 1120, 1050, 975, 960, 915, 835, 810, 790 cm^{-1}; uv λ_{max} (MeOH) 210, 243, 265, 274, 303, 313, 326, 341, 376 nm; $[\alpha]^{22}_D$ –89° (*c* 0.24, DMSO); Anal. Calcd for $C_{25}H_{24}O_9 \cdot H_2O$: C, 61.72; H, 5.39. Found: C, 61.72; H, 5.25; HRFABms *m/z* 469.1509 (469.1499 calcd for $C_{25}H_{25}O_9$, M^++1).

5-Benzyloxy-4-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyloxy)-1-naphthyl 3-methoxy-5-[1-(2-(methoxymethoxy)ethyl)]-2-(trifluoromethanesulfonyloxy)benzoate (17)

To a mixed suspension of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (101 mg, 527 μmol) and DMAP (46.5 mg, 381 μmol) in Et_2O (2 ml) was added a solution of benzoic acid (**16**)[4b] (140 mg, 361 μmol) in Et_2O (5 ml) followed by a solution of naphthol (**13**) (118 mg, 173 μmol) in Et_2O (5 ml) at room temperature. After stirring for 24 h, the reaction was stopped by adding 3 N HCl, and the products were extracted with Et_2O. The combined organic extracts were washed successively with 1 N HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/EtOAc = 5/5) afforded ester (**17**) (167 mg, 91.8%) as a colorless foam: R_f = 0.40 (hexane/EtOAc = 5/5), 0.56 (hexane/CH_2Cl_2/Et_2O = 4/4/2); ^1H nmr ($CDCl_3$) δ 7.75 (d, 1 H, J = 2.0 Hz), 7.14–7.42 (m, 25 H), 6.81 (d, 1 H, J = 7.8 Hz), 5.64 (d, 1 H, J = 1.7 Hz), 5.14 (d, 1 H, J = 13.2 Hz), 5.04 (d, 1 H, J = 13.2 Hz), 4.94 (d, 1 H, J = 11.0 Hz), 4.76 (d, 1 H, J = 12.5 Hz), 4.71 (d, 1 H, J = 12.5 Hz), 4.66 (d, 1 H, J = 11.0 Hz), 4.64 (s, 2 H), 4.29 (d, 1 H, J = 11.7 Hz), 4.25 (d, 1 H, J = 11.7 Hz), 4.11 (dd, 1 H, J_1 = 9.3, J_2 = 3.2 Hz), 4.07 (dd, 1 H, J_1 = 3.2, J_2 = 1.7 Hz), 4.01 (dq, 1 H, J_1 = 9.3, J_2 = 6.1 Hz), 3.96 (s, 3 H), 3.84 (t, 2 H, J = 6.6 Hz), 3.71 (dd, 1 H, J_1 = J_2 = 9.3 Hz), 3.30 (s, 3 H), 3.01 (t, 2 H, J = 6.6 Hz), 1.35 (d, 3 H, J = 6.1 Hz); ^{13}C nmr ($CDCl_3$) δ 162.6, 155.9, 151.7, 151.6, 140.9, 140.7, 138.73, 138.68, 138.4, 137.2, 136.5, 130.0, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.74, 127.66, 127.5, 127.3, 127.2, 127.1, 126.7, 124.5, 123.7, 119.2, 118.70, 118.69 (q, J_{C-F} = 320.6 Hz), 118.2, 114.0, 111.1, 109.1, 97.8, 96.5, 80.6, 80.1, 75.3, 74.7, 72.8, 71.7, 71.0, 69.1, 67.4, 56.4, 55.4, 36.1, 18.1; ir (neat) 3050, 2950, 1750, 1600, 1580, 1500, 1470, 1455, 1425, 1390, 1355, 1325, 1275, 1250, 1210, 1185, 1140, 1125, 1110, 1060, 1030, 980, 920, 880, 815, 760, 705 cm^{-1}; $[\alpha]^{23}_D$ –36° (*c* 0.60, $CHCl_3$); HRFABms *m/z* 1052.3293 (1052.3264 calcd for $C_{57}H_{55}O_{14}F_3S$, M^+).

1-Benzyloxy-10-methoxy-8-[1-(2-(methoxymethoxy)ethyl)]-12-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyloxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (18)

A suspension of ester (**17**) (814 mg, 773 mmol), $(Ph_3P)_2PdCl_2$ (163 mg, 232 mmol, 30 mol%), *i*-Pr_2NEt (315 mg, 2.44 mmol), and sodium pivalate (302 mg, 2.43 mmol) in *N,N*-dimethylacetamide (68 ml) was heated at 80 °C for 4 h. After cooling to room temperature, the resulting dark brown suspension was diluted with Et_2O. The mixture was successively washed with 3 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc = 6/4) afforded tetracyclic compound (**18**) (363 mg, 52.0%) as a yellow oil, and the starting material (**17**) (117 mg, 14.4%) was recovered: R_f = 0.50 (hexane/EtOAc = 5/5), 0.46 (hexane/CH_2Cl_2/Et_2O = 4/4/2); ^1H nmr ($CDCl_3$) δ 8.83 (s, 1 H), 8.23 (dd, 1 H, J_1 = 8.6, J_2 = 0.7 Hz), 8.04 (d, 1 H, J = 1.5 Hz), 7.18–7.44 (m, 22 H), 6.94 (dd, 1 H, J_1 = 7.8, J_2 = 0.7 Hz), 5.55 (d, 1 H, J = 1.7 Hz), 5.17 (d, 1 H, J = 13.2 Hz), 5.03 (d, 1 H, J = 13.2 Hz), 4.98 (d, 1 H, J = 11.0 Hz), 4.73 (d, 1 H, J = 12.7 Hz), 4.69 (d, 1 H, J = 11.0 Hz), 4.67 (d, 1 H, J = 12.7 Hz), 4.65 (s, 2 H), 4.35 (d, 1 H, J = 11.7 Hz), 4.29 (d, 1 H, J = 11.7 Hz), 4.18 (dq, 1 H, J_1 = 9.5, J_2 = 6.3 Hz), 4.16 (dd, 1 H, J_1 = 9.5, J_2 = 2.9 Hz), 4.11 (dd, 1 H, J_1 = 2.9, J_2 = 1.7 Hz), 4.09 (s, 3 H), 3.87 (t, 2 H, J = 6.6 Hz), 3.75 (dd, 1 H, J_1 = J_2 = 9.5 Hz), 3.32 (s, 3 H), 3.06 (t, 2 H, J = 6.6 Hz), 1.39 (d, 3 H, J = 6.3 Hz); ^{13}C nmr ($CDCl_3$) δ 161.3, 157.4, 155.0, 148.7, 142.1, 141.2, 138.7, 138.65, 138.58, 137.1, 128.7, 128.3, 128.2, 127.94, 127.87, 127.6, 127.5, 127.35, 127.29, 126.93, 126.85, 126.7, 123.1, 122.5, 122.4, 118.7, 118.0, 115.4, 113.6, 112.9, 110.4, 99.3, 96.5, 80.45, 80.36, 75.3, 75.1, 72.7, 71.7, 71.2, 69.0, 67.7, 56.2, 55.3, 36.3, 18.0; ir (neat) 3040, 2940, 1730, 1610, 1585, 1560, 1500, 1485, 1450, 1390, 1365, 1340, 1320, 1300, 1275, 1240, 1215, 1150, 1110, 1065, 1030, 975, 920, 870, 840, 820, 805, 790, 750, 735, 700 cm^{-1}; $[\alpha]^{23}_D$ –65° (*c* 0.90, $CHCl_3$); HRFABms *m/z* 902.3698 (902.3666 calcd for $C_{56}H_{54}O_{11}$, M^+).

1-Acetoxy-10-methoxy-8-[1-(2-(methoxymethoxy)ethyl)]-12-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyloxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (20)

A suspension of tetracycle (**18**) (146 mg, 162 μmol) and 10% Pd–C (87 mg) in MeOH (32 ml) and THF (8 ml) was stirred under H_2 (1 atm) at room temperature for 42 h. After changing the atmosphere to Ar, the mixture was diluted with CH_2Cl_2 and stirred for another 15 min and the mixture was filtered through a Celite pad (washed with CH_2Cl_2). The solvents were removed and dried in vacuo to give crude tetraol (**19**) as colorless crystalline solid, which was dissolved in pyridine (6 ml). To this soluton was added Ac_2O (0.5 ml) and a catalytic amount of DMAP and stirred for 30 min at room temperature. The reaction was stopped by adding water and the products were extracted with EtOAc. The combined organic extracts were washed successively with 3 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/EtOAc = 3/7) afforded tetraacetate (**20**) (88.7 mg, 77.2%, two steps) as a colorless crystalline solid: mp 161–165 °C; R_f = 0.31 (hexane/EtOAc = 4/6); ^{1}H nmr ($CDCl_3$) δ 8.97 (s, 1 H), 8.54 (dd, 1 H, J_1 = 8.6, J_2 = 0.9 Hz), 7.99 (s, 1 H), 7.59 (dd, 1 H, J_1 = 8.6, J_2 = 7.7 Hz), 7.24 (s, 1 H), 7.23 (dd, 1 H, J_1 = 7.7, J_2 = 0.9 Hz), 5.64 (dd, 1 H, J_1 = 3.7, J_2 = 1.5 Hz), 5.58 (dd, 1 H, J_1 = 9.9, J_2 = 3.7 Hz), 5.48 (d, 1 H, J = 1.5 Hz), 5.21 (dd, 1 H, J_1 = J_2 = 9.9 Hz), 4.64 (s, 2 H), 4.18 (dq, 1 H, J_1 = 9.9, J_2 = 6.2 Hz), 4.07 (s, 3 H), 3.85 (t, 2 H, J = 6.6 Hz), 3.31 (s, 3 H), 3.02 (t, 2 H, J = 6.6 Hz), 2.53 (s, 3 H), 2.23 (s, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.27 (d, 3 H, J = 6.2 Hz); ^{13}C nmr ($CDCl_3$) δ 170.3, 170.04, 169.98, 169.9, 160.9, 157.2, 147.1, 145.8, 142.2, 141.6, 126.8, 126.3, 123.0, 122.5, 122.1, 122.0, 121.0, 120.0, 118.1, 113.4, 111.9, 98.3, 96.4, 71.0, 69.5, 69.1, 67.6, 67.1, 56.2, 55.3, 36.2, 21.3, 20.9, 20.8, 20.7, 17.3; ir (KBr) 2950, 1750, 1610, 1585, 1485, 1450, 1370, 1345, 1300, 1240, 1220, 1145, 1110, 1045, 980, 950, 920, 870, 830, 790, 760, 730 cm^{-1}; $[\alpha]^{24}_D$ –36° (*c* 0.84, $CHCl_3$); HRms *m/z* 710.2219 (710.2208 calcd for $C_{36}H_{38}O_{15}$, M^+).

1-Acetoxy-10-methoxy-8-(2-hydroxyethyl)-12-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyloxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (21)

To a solution of MOM ether (**20**) (36.0 mg, 50.7 μmol) in CH_2Cl_2 (5 ml) was added a solution of TMSBr (160 mg, 1.05 mmol) in CH_2Cl_2 (5 ml) at –20 °C. After stirring for 1 h at this temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$, and the products were extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (EtOAc) afforded alcohol (**21**) (30.4 mg, 90.0%) as a colorless crystalline solid: mp 148–150 °C (benzene); R_f = 0.41 (EtOAc); ^{1}H nmr ($CDCl_3$) δ 8.98 (s, 1 H), 8.57 (dd, 1 H, J_1 = 8.6, J_2 = 1.0 Hz), 8.01 (d, 1 H, J = 1.5 Hz), 7.61 (dd, 1 H, J_1 = 8.6, J_2 = 7.6 Hz), 7.26 (d, 1 H, J = 1.5 Hz), 7.24 (dd, 1 H, J_1 = 7.6, J_2 = 1.0 Hz), 5.63 (dd, 1 H, J_1 = 3.7, J_2 = 1.7 Hz), 5.58 (dd, 1 H, J_1 = 9.8, J_2 = 3.7 Hz), 5.47 (d, 1 H, J = 1.7 Hz), 5.20 (dd, 1 H, J_1 = J_2 = 9.8 Hz), 4.17 (dq, 1 H, J_1 = 9.8, J_2 = 6.4 Hz), 4.09 (s, 3 H), 3.99 (dt, 2 H, J_1 = J_2 = 6.1 Hz), 3.02 (t, 2 H, J = 6.1 Hz), 2.53 (s, 3 H), 2.22 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.54 (t, 1 H, J = 6.1 Hz), 1.26 (d, 3 H, J = 6.4 Hz); ^{13}C nmr ($CDCl_3$) δ 170.4, 170.1, 170.0, 169.9, 160.9, 157.3, 147.0, 145.8, 142.1, 141.3, 126.9, 126.3, 123.1, 122.5, 122.2, 122.0, 121.0, 120.0, 118.2, 113.4, 112.0, 98.3, 71.0, 69.5, 69.1, 67.1, 63.0, 56.2, 39.0, 21.3, 20.9, 20.8, 20.7, 17.3; ir (KBr) 3460, 2950, 1750, 1610, 1585, 1485, 1450, 1370, 1345, 1300, 1240, 1220, 1140, 1115, 1090, 1045, 980, 910, 875, 835, 790, 760, 730 cm^{-1}; $[\alpha]^{23}_D$ –41° (*c* 0.53, $CHCl_3$); HRms *m/z* 666.1947 (666.1946 calcd for $C_{34}H_{34}O_{14}$, M^+).

1-Acetoxy-10-methoxy-12-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyloxy)-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (23)[18,19]

To a solution of alcohol (**21**) (30.4 mg, 45.6 μmol) in THF (5 ml) was added *o*-nitrophenyl selenocyanate (145 mg, 639 μmol) and *n*-Bu_3P (206 mg, 1.02 mmol) in THF (1 ml) at room temperature. After stirring for 1 h, tlc indicated the complete consumption of **21** and a new spot corresponding to selenide (**22**)

appeared. To this solution was added 35% aqueous H_2O_2 solution (3 ml) at 0 °C, and the ice bath was removed immediately. After stirring for 1 h, the reaction mixture was diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/EtOAc = 4/6 and hexane/CH_2Cl_2/EtOAc = 3/4/3) afforded vinyl compound (**23**) (24.4 mg, 82.5%, two steps) as a yellow crystalline solid: mp 127–131 °C; R_f = 0.60 (hexane/EtOAc = 4/6); ^{1}H nmr ($CDCl_3$) δ 8.95 (s, 1 H), 8.53 (dd, 1 H, J_1 = 8.6, J_2 = 1.0 Hz), 8.11 (d, 1 H, J = 1.5 Hz), 7.59 (dd, 1 H, J_1 = 8.6, J_2 = 7.6 Hz), 7.33 (d, 1 H, J = 1.5 Hz), 7.23 (dd, 1 H, J_1 = 7.6, J_2 = 1.0 Hz), 6.78 (dd, 1 H, J_1 = 17.6, J_2 = 11.0 Hz), 5.93 (d, 1 H, 17.6 Hz), 5.64 (dd, 1 H, J_1 = 3.7, J_2 = 1.5 Hz), 5.58 (dd, 1 H, J_1 = 9.8, J_2 = 3.7 Hz), 5.49 (d, 1 H, J = 1.5 Hz), 5.44 (d, 1 H, J = 11.0 Hz), 5.21 (dd, 1 H, J_1 = J_2 = 9.8 Hz), 4.17 (dq, 1 H, J_1 = 9.8, J_2 = 6.1 Hz), 4.08 (s, 3 H), 2.53 (s, 3 H), 2.24 (s, 3 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 1.28 (d, 3 H, J = 6.1 Hz); ^{13}C nmr ($CDCl_3$) δ 170.3, 170.1, 170.0, 169.9, 160.8, 157.4, 147.2, 145.8, 142.3, 139.0, 135.2, 126.9, 126.2, 123.3, 123.2, 122.1, 121.0, 120.5, 120.1, 116.6, 114.1, 113.3, 111.7, 98.3, 71.0, 69.5, 69.1, 67.1, 56.1, 21.3, 20.9, 20.8, 20.7, 17.4; ir (KBr) 3000, 2950, 1750, 1630, 1605, 1585, 1555, 1485, 1450, 1430, 1375, 1350, 1330, 1300, 1245, 1220, 1145, 1120, 1090, 1050, 985, 950, 920, 875, 830, 790, 760 cm^{-1}; $[\alpha]^{23}_D$ –44° (*c* 0.70, $CHCl_3$); HRms *m/z* 649.1919 (649.1919 calcd for $C_{34}H_{33}O_{13}$, M^++1).

1-Hydroxy-10-methoxy-12-(α-L-rhamnopyranosyloxy)-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (3c, BE-12406 A C(8)-vinyl analog)

To a suspension of tetraacetate (**23**) (35.3 mg, 54.4 μmol) in MeOH (6 ml) was added *ca.* 1 M solution of NaOMe in MeOH (0.4 ml) at room temperature. Stirring was continued for 20 min, during which time the reaction mixture turned to a yellow solution. The solution was treated with AcOH (0.1 ml) and water (7.5 ml) at 0 °C and kept standing for 1 h. The resulting yellow precipitates were collected by filtration, and the yellow solid was washed with water and Et_2O several times on a funnel. Drying in vacuo afforded the vinyl analog (**3c**) (25.7 mg, 98.3%) as a yellow crystalline solid: mp 207–209 °C (decomp.) (MeOH); R_f = 0.31 ($CHCl_3$/MeOH = 9/1); ^{1}H nmr (DMSO-d_6) δ 9.53 (s, 1 H), 8.76 (s, 1 H), 8.03 (d, 1 H, J = 1.7 Hz), 7.89 (d, 1 H, J = 8.3 Hz), 7.72 (d, 1 H, J = 1.7 Hz), 7.51 (dd, 1 H, J_1 = 8.3, J_2 = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.93 (dd, 1 H, J_1 = 17.6, J_2 = 10.7 Hz), 6.11 (d, 1 H, J = 17.6 Hz), 5.495 (d, 1 H, J = 2.2 Hz), 5.490 (d, 1 H, J = 10.7 Hz), 4.91–4.94 (m, 1 H), 4.71 (d, 1 H, J = 5.6 Hz), 4.54–4.57 (m, 1 H), 4.14 (s, 3 H), 3.83–4.14 (m, 1 H), 3.76–3.82 (m, 2 H), 3.43 (ddd, 1 H, J_1 = J_2 = 9.0, J_3 = 5.6 Hz), 1.27 (d, 3 H, J = 6.4 Hz); ^{13}C nmr (DMSO-d_6) δ 159.6, 157.2, 153.4, 148.7, 141.1, 138.6, 135.0, 127.8, 125.5, 122.59, 122.57, 119.4, 116.8, 115.8, 115.1, 112.4, 112.2, 112.1, 108.6, 101.5, 71.7, 70.6, 69.9, 69.8, 56.4, 17.5; ir (KBr) 3440, 2940, 1725, 1630, 1610, 1590, 1555, 1510, 1490, 1450, 1390, 1360, 1335, 1305, 1245, 1175, 1145, 1125, 1090, 1050, 995, 975, 950, 915, 875, 835, 810, 790, 755, 730 cm^{-1}; uv λ_{max} (MeOH) 209, 220, 248, 284, 306, 316, 330, 349, 384 nm; $[\alpha]^{22}_D$ –91° (*c* 0.11, DMSO); HRFABms *m/z* 481.1491 (481.1498 calcd for $C_{26}H_{25}O_9$, M^++1).

1-Acetoxy-5-benzyloxy-4-methoxy-3-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)naphthalene (24-α)

To a suspension of NaH (60 % dispersion in oil, 43.3 mg, 1.08 mmol) in THF (1.5 ml) was added a solution of naphthol (**10**-α) (64.0 mg, 88.3 μmol) in THF (2.0 ml) followed by a solution of $(MeO)_2SO_2$ (146 mg, 1.16 mmol) in THF (2.0 ml) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction was stopped by adding Et_2NH (*ca.* 1 ml) followed by pH 7 phosphate buffer, and the products were extracted with EtOAc. The combined organic extracts were washed successively with 3 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/EtOAc = 7/3) afforded methyl ether (**24**-α) (50.4 mg, 77.3%) as a colorless foam: R_f = 0.43 (hexane/EtOAc = 7/3); ^{1}H nmr ($CDCl_3$) δ 7.10–7.57 (m, 23 H), 6.97 (dd, 1 H, J_1 = 7.6, J_2 = 1.2 Hz), 5.69 (d, 1 H, J = 8.3 Hz), 5.21 (s, 2 H), 4.77 (d, 1 H, J = 12.2 Hz), 4.59 (d, 1 H, J = 12.2 Hz), 4.51 (s, 2H), 4.32 (d, 1 H, J = 12.0 Hz), 4.28 (d, 1 H, J = 12.0 Hz), 4.08–

4.15 (m, 2 H), 3.89 (dd, 1 H, J_1 = 4.4, J_2 = 2.7 Hz), 3.68 (s, 3 H), 3.57 (dd, 1 H, J_1 = 4.4, J_2 = 2.7 Hz), 2.43 (s, 3 H), 1.49 (d, 3 H, J = 7.1 Hz); ^{13}C nmr ($CDCl_3$) δ 169.4, 155.6, 152.9, 142.7, 138.9, 138.6, 138.3, 137.0, 130.1, 129.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.73, 127.66, 127.61, 127.59, 127.4, 127.3, 126.8, 121.4, 118.4, 114.4, 109.1, 79.0, 77.2, 76.7, 73.0, 72.4, 72.2, 71.7, 65.8, 63.4, 21.0, 17.3; ir (neat) 3030, 2940, 1765, 1605, 1570, 1515, 1495, 1450, 1440, 1420, 1365, 1335, 1265, 1210, 1155, 1110, 1075, 1040, 1030, 935, 915, 850, 810, 740, 700 cm^{-1}; $[\alpha]^{22}_D$ +40° (*c* 1.1, $CHCl_3$); HRFABms *m/z* 738.3187 (738.3193 calcd for $C_{47}H_{46}O_8$, M^+).

1,5-Diacetoxy-4-methoxy-3-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)naphthalene (25-α)
A suspension of tetrabenzyl ether (**24**-α) (50.4 mg, 68.2 μmol) and 10% Pd–C (*ca.* 50 mg) in MeOH (4.0 ml) and THF (1.0 ml) was stirred under H_2 (1 atm) at room temperature for 1 h. After changing the atmosphere to Ar, the mixture was diluted with CH_2Cl_2 and filtered through a Celite pad (washed with CH_2Cl_2). The solvents were removed and dried in vacuo to give crude tetraol, which was dissolved in pyridine (1.0 ml). To this solution was added Ac_2O (0.2 ml) and a catalytic amount of DMAP and stirred for 15 min at room temperature. The reaction was stopped by adding water and the products were extracted with EtOAc. The combined organic extracts were washed successively with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/ EtOAc = 4/6) afforded tetraacetate (**25**-α) (33.0 mg, 88.5%, two steps) as a colorless foam: R_f = 0.42 (hexane/ EtOAc = 4/6); ^{1}H nmr ($CDCl_3$) δ 7.76 (dd, 1 H, J_1 = 8.6, J_2 = 1.2 Hz), 7.51 (dd, 1 H, J_1 = 8.6, J_2 = 7.6 Hz), 7.37 (s, 1 H), 7.18 (dd, 1 H, J_1 = 7.6, J_2 = 1.2 Hz), 5.66 (dd, 1 H, J_1 = 8.1, J_2 = 3.4 Hz), 5.52 (d, 1 H, J = 8.1 Hz), 5.40 (dd, 1 H, J_1 = 5.1, J_2 = 3.4 Hz), 4.98 (dd, 1 H, J_1 = 5.1, J_2 = 3.4 Hz), 4.02 (dq, 1 H, J_1 = 3.4, J_2 = 6.8 Hz), 3.88 (s, 3 H), 2.45 (s, 3 H), 2.41 (s, 3 H), 2.17 (s, 3 H), 2.15 (s, 3 H), 1.88 (s, 3 H), 1.51 (d, 3 H, J = 6.8 Hz); ^{13}C nmr ($CDCl_3$) δ 169.9, 169.8, 169.5, 169.1, 151.9, 146.1, 143.3, 130.2, 127.1, 127.0, 122.2, 121.0, 120.2, 118.0, 72.0, 71.7, 69.0, 68.5, 65.6, 63.6, 21.1, 21.0, 20.9, 20.8, 20.6, 16.3; ir (neat) 3030, 2950, 1755, 1630, 1610, 1580, 1510, 1425, 1365, 1210, 1155, 1125, 1110, 1065, 1025, 1000, 970, 950, 920, 880, 760, 730 cm^{-1}; $[\alpha]^{21}_D$ +41° (*c* 0.61, $CHCl_3$); HRms *m/z* 546.1745 (546.1736 calcd for $C_{27}H_{30}O_{12}$, M^+).

1-Acetoxy-5-benzyloxy-4-methoxy-3-(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)naphthalene (24-β)
To a suspension of NaH (60 % dispersion in oil, 47.0 mg, 1.18 mmol) in THF (2.0 ml) was added a solution of naphthol (**10**-β) (41.4 mg, 57.1 μmol) in THF (2.0 ml) followed by a solution of $(MeO)_2SO_2$ (110 mg, 872 μmol) in THF (1.0 ml) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 1 h. The reaction was stopped by adding Et_2NH (*ca.* 1 ml) followed by pH 7 phosphate buffer, and the products were extracted with EtOAc. The combined organic extracts were washed successively with 3 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/EtOAc = 7/3) afforded methyl ether (**24**-β) (30.4 mg, 72.0%) as a colorless foam: R_f = 0.50 (hexane/EtOAc = 7/3); ^{1}H nmr ($CDCl_3$) δ 7.52–7.57 (m, 3 H), 7.25–7.45 (m, 15 H), 6.87–7.00 (m, 6 H), 5.21 (d, 1 H, J = 13.2 Hz), 5.18 (d, 1 H, J = 13.2 Hz), 5.00 (d, 1 H, J = 11.0 Hz), 4.83 (s, 1 H), 4.75 (d, 1 H, J = 12.2 Hz), 4.72 (d, 1 H, J = 11.0 Hz), 4.70 (d, 1 H, J = 12.2 Hz), 4.47 (d, 1 H, J = 12.0 Hz), 4.31 (d, 1 H, J = 12.0 Hz), 4.15 (d, 1 H, J = 2.2 Hz), 3.79 (dd, 1 H, J_1 = 9.3, J_2 = 2.2 Hz), 3.74 (dd, 1 H, J_1 = J_2 = 9.3 Hz), 3.51–3.58 (m, 1 H), 3.56 (s, 3 H), 2.40 (s, 3 H), 1.43 (d, 3 H, J = 6.1 Hz); ^{13}C nmr ($CDCl_3$) δ 169.5, 155.3, 150.3, 142.6, 138.7, 138.5, 138.2, 137.0, 129.9, 129.1, 128.5, 128.39, 128.35, 128.1, 127.9, 127.7, 127.6, 127.55, 127.50, 127.1, 126.5, 120.7, 119.6, 114.6, 108.6, 84.8, 80.5, 76.3, 76.1, 75.4, 74.5, 74.3, 72.1, 71.6, 62.6, 20.9, 18.3; ir (neat) 3040, 2880, 1765, 1605, 1575, 1515, 1500, 1455, 1440, 1425, 1390, 1365, 1265, 1210, 1160, 1125, 1105, 1045, 1030, 950, 910, 820, 760, 740, 705 cm^{-1}; $[\alpha]^{24}_D$ –253° (*c* 1.1, $CHCl_3$); HRFABms *m/z* 738.3245 (738.3193 calcd for $C_{47}H_{46}O_8$, M^+).

1,5-Diacetoxy-4-methoxy-3-(2,3,4-tri-*O*-acetyl-β-L-rhamnopyranosyl)naphthalene (25-β)

A suspension of tetrabenzyl ether (**24**-β) (19.7 mg, 26.7 μmol) and 10% Pd–C (*ca.* 50 mg) in MeOH (2.0 ml) and THF (0.5 ml) was stirred under H_2 (1 atm) at room temperature for 1 h. After changing the atmosphere to Ar, the mixture was diluted with CH_2Cl_2 and filtered through a Celite pad (washed with CH_2Cl_2). The solvents were removed and dried in vacuo to give crude tetraol, which was dissolved in pyridine (1.0 ml). To this solution was added Ac_2O (0.2 ml) and a catalytic amount of DMAP and stirred for 15 min at room temperature. The reaction was stopped by adding water and the products were extracted with EtOAc. The combined organic extracts were washed successively with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by ptlc (hexane/ EtOAc = 4/6) afforded tetraacetate (**25**-β) (12.9 mg, 88.5%, two steps) as a colorless foam: R_f = 0.46 (hexane/ EtOAc = 4/6); ^{1}H nmr ($CDCl_3$) δ 7.75 (dd, 1 H, J_1 = 8.4, J_2 = 1.1 Hz), 7.48 (dd, 1 H, J_1 = 8.4, J_2 = 7.7 Hz), 7.43 (s, 1 H), 7.16 (dd, 1 H, J_1 = 7.7, J_2 = 1.1 Hz), 5.60 (dd, 1 H, J_1 = 3.3, J_2 = 1.1 Hz), 5.28 (dd, 1 H, J_1 = 9.9, J_2 = 3.3 Hz), 5.22 (d, 1 H, J = 1.1 Hz), 5.18 (dd, 1 H, J_1 = J_2 = 9.9 Hz), 3.86 (s, 3 H), 3.71 (dq, 1 H, J_1 = 9.9, J_2 = 6.2 Hz), 2.45 (s, 3 H), 2.38 (s, 3 H), 2.09 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.32 (d, 3 H, J = 6.2 Hz); ^{13}C nmr ($CDCl_3$) δ 170.4, 170.2, 170.1, 169.2, 169.1, 149.1, 145.8, 142.6, 129.7, 127.4, 126.7, 121.5, 120.7, 120.0, 118.9, 74.8, 72.8, 72.3, 70.8, 70.6, 63.4, 21.0, 20.9, 20.78, 20.75, 20.4, 17.8; ir (neat) 2950, 1750, 1610, 1575, 1510, 1430, 1365, 1310, 1250, 1220, 1200, 1150, 1120, 1100, 1085, 1055, 1020, 980, 965, 945, 910, 880, 855, 825, 810, 760, 725 cm^{-1}; $[\alpha]^{20}_D$ –62° (*c* 0.26, $CHCl_3$); HRms *m/z* 546.1736 (546.1735 calcd for $C_{27}H_{30}O_{12}$, M^+).

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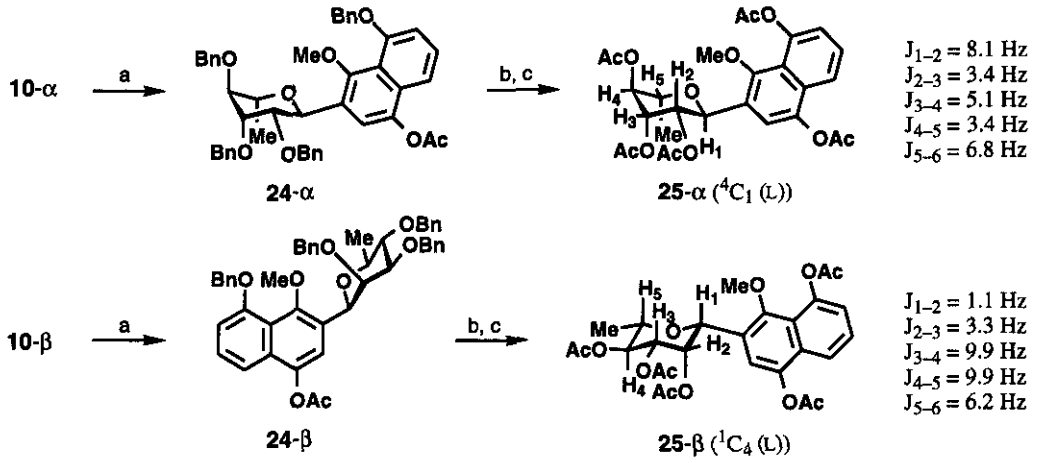

(a) NaH, $(MeO)_2SO_2$ / THF, 0 °C → room temperature, 2 h (77% from **10**-α and 72% from **10**-β); (b) H_2, 10% Pd–C / MeOH–THF, room temperature, 1 h; (c) Ac_2O, DMAP / pyridine, room temperature, 10 min (89% from both anomers of **24**, two steps).

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