Total Synthesis of the Gilvocarcins

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Abstract: Convergent total syntheses of the aryl *C*-glycoside antibiotics gilvocarcin M (**1a**) and gilvocarcin V (**1b**) have been accomplished. Key steps include (1) contrasteric coupling of D-fucofuranosyl acetate **27** with iodophenol **26**, which was achieved by employing Cp_2HfCl_2–$AgClO_4$ or the related organosilane-derived reagents, and (2) regioselective [4 + 2] cycloaddition of a sugar-bearing benzyne species, generated by treatment of *o*-haloaryl triflate **33**-α with *n*-BuLi at −78 °C, with 2-methoxyfuran (**6**). The naphthol derivative **34**, selectively synthesized by these two tactics, served as the common intermediate to both **1a** and **1b**. Acylation of **34** with benzoic acid derivative **39** followed by Pd-catalyzed cyclization gave gilvocarcin M (**1a**), and a similar synthetic sequence starting with the coupling of **34** with **49** led to the first total synthesis of gilvocarcin V (**1b**).

The gilvocarcins[1] (**1**) and related compounds, **2** and **3**,[2] are metabolites of certain *Streptomyces* species and constitute a novel class of aryl *C*-glycoside antibiotics[3] (Figure 1). These compounds share a common tetracyclic aromatic nucleus, 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one, to which rare sugars are attached as a *C*-glycoside at the C(4) position.[4] Fucose, in furanosyl form, is the sugar of the gilvocarcins, and there are three congeners which differ in the C(8) substituent, i.e., *m*ethyl, *v*inyl, and *e*thyl. These are gilvocarcin M (**1a**), V (**1b**), and E (**1c**), respectively. Among these, the vinyl congener **1b** has attracted considerable attention with its remarkable antitumor activity and exceptionally low toxicity. The presence of the vinyl group is essential to the biological activities and is known to be responsible for enhancement of the biological activity under irradiation with low-energy UV or visible light. Recent studies have shown that **1b** is a DNA-targeting agent with potent intercalating ability, leading to covalent binding or strand breaking upon photoirradiation.[5,6]

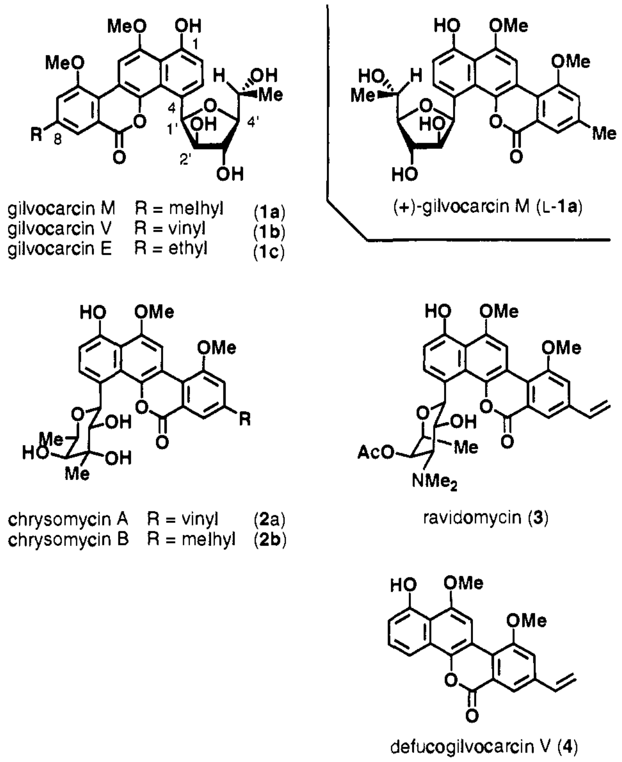

Figure 1. Gilvocarcin class antibiotics.

These compounds have stimulated considerable interest in their syntheses, due to their significant pharmacological potential and also because of the challenge presented by unusual *C*-glycoside structures linked to the highly functionalized aromatic skeleton. Approaches to the aglycon, defucogilvocarcin (**4**), have been extensively studied, and as many as ten successful routes have been documented so far.[7] However, the full structure of the natural product has remained a challenge because of the potential difficulty in *C*-glycoside formation.[8,9,10]

In our continuing study on the synthesis of aryl *C*-glycoside antibiotics,[11,12] the gilvocarcins have attracted our attention, and we have recently reported the first total synthesis of gilvocarcin M.[13] This synthesis established that the L-fucose-based structure (L-**1a**), long accepted without proof, is in fact antipodal to the natural product. The present paper details the total synthesis of

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(4) The gilvocarcin numbering is used throughout this paper.

(5) Gilvocarcin M (**1a**) exhibits practically no antitumor activity. It has been suggested that the C(8) vinyl group is relevant to the photochemical activation (see ref 6). McGee *et al.* recently showed that **1b**, at its vinyl group, undergoes [2 + 2] cycloaddition to thymine residue(s) on a double-stranded DNA under photoirradiation conditions (see ref 6v).

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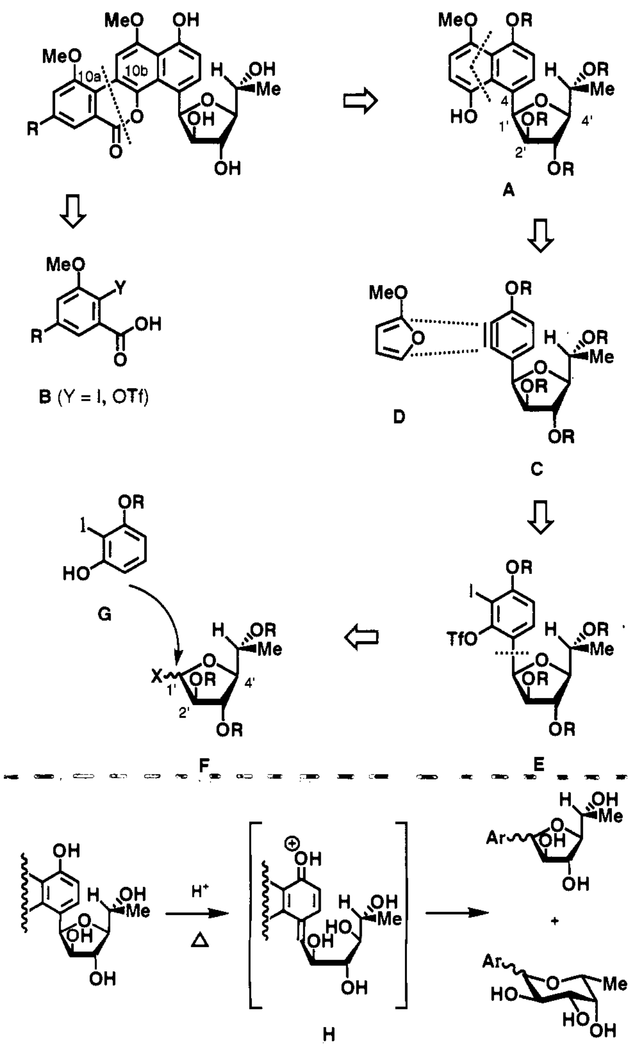
the natural enantiomer, (−)-gilvocarcin M (**1a**), and also that of gilvocarcin V (**1b**).

Synthetic Plan. Considering the potential difficulty in the regio- and stereocontrolled connection of a sugar to a fully elaborated aromatic skeleton, we chose to pursue a strategy based upon the initial glycosylation of a simple aromatic precursor, followed by incremental elaboration of the aromatic skeleton. Thus, the disconnections at the four C–C bonds in Scheme 1 were taken into consideration.

The disconnection at the C(10a)–C(10b) bond divided the molecule into naphthol **A** and benzoic acid **B**. Various methods have been devised for this particular biaryl bond formation. The Pd-catalyzed internal bond formation approach, developed by Martin,[7h] was ideally suited for our synthetic plan. Thus, the naphthol **A** bearing the sugar moiety was the key intermediate on which we focused our attention. Two conditions had to be met in the synthesis of **A**, (1) installation of the sugar at the correct position, C(4), with rigorous stereo- and regiochemical control, and (2) differential protection of the three hydroxyl groups on the aromatic ring to allow selective elaboration at a later stage(s). For further simplification of the aromatic moiety, we expected that a naphthalene structure, such as **A**, could be constructed by the cycloaddition of benzyne species **C** and 2-methoxyfuran (**D**). The viability of such an approach would depend on the regioselectivity of the cycloaddition and, more fundamentally, on the efficient generation of such a benzyne species bearing a carbohydrate (see model study 1). Finally, disconnection at the aryl *C*-glycoside linkage dissected the molecule into a resorcinol derivative **G** and a glycosyl donor **F**. We expected that the free hydroxyl group in **G** would not only serve as a pivot in the *C*-glycosidation stage (see model study 2) but also serve to generate the benzyne.

Scheme 1



A major challenge in the whole synthetic scheme comes from the apparently unfavorable disposition of the aryl *C*-glycoside linkage, 1′,2′-cis and 1′,4′-cis. Moreover, this linkage is liable to undergo anomerization and/or ring enlargement reactions, most probably via a quinone methide species **H**, to give an equilibrium mixture of the furanoside/pyranoside anomers.[1g,6v]

Model Study 1, Regioselective Benzyne–Furan Cycloaddition.[14] As a direct route to the 1,4,5-naphthalenetriol derivative (**A**,

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(8) Isolation of the aglycon **4** from the same origin (ref 2j) implicates that the biosynthesis may include introduction of the carbohydrate after the complete formation of the aromatic moiety. Such a putative biogenesis suggests an intriguing possibility in the chemical synthesis, and indeed, Danishefsky *et al.* have disclosed their pioneering approach along these lines (see ref 7d).

(9) For synthetic studies on glycosylated analogs of the gilvocarcins, see: Farr, R. N.; Kwok, D.-I.; Daves, G. D., Jr. *J. Org Chem.* **1992**, *57*, 2093–2100.

(10) For studies on the stereoselective construction of aryl *C*-glycoside structures related to the gilvocarcins, see: (a) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698–8700. (b) Martin, O. R.; Hendricks, C. A. V.; Deshpande, P. P.; Cutler, A. B.; Kane, S. A.; Rao, S. P. *Carbohydr. Res.* **1990**, *196*, 41–58. (c) Parker, K. A.; Coburn, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 8516–8518. (d) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 5547–5550. (e) Hart, D. J.; Leroy, V.; Merriman, G. H.; Young, D. G. J. *Ibid.* **1992**, *57*, 5670–5680.

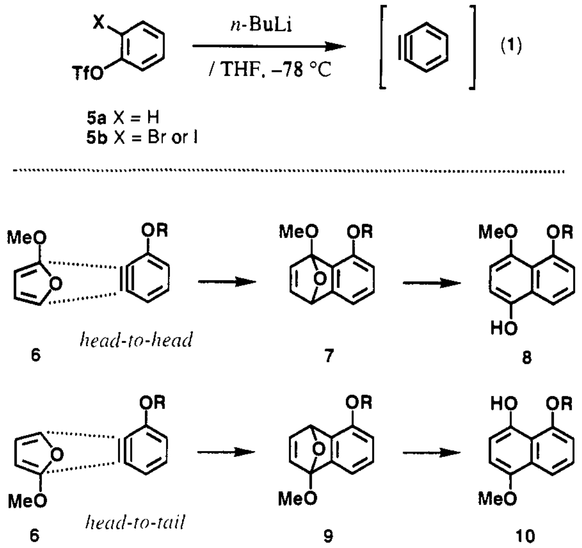
(11) Suzuki, K.; Matsumoto, T. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, pp 353–403.

(12) For the *O*- → *C*-glycoside rearrangement approach to aryl *C*-glycosides, see: (a) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935–6938. (b) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Ibid.* **1990**, *31*, 4629–4632. (c) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *Ibid.* **1989**, *30*, 6185–6188. (d) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, *113*, 6982–6992.

(13) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568–3570.

(14) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736.

Scheme 2



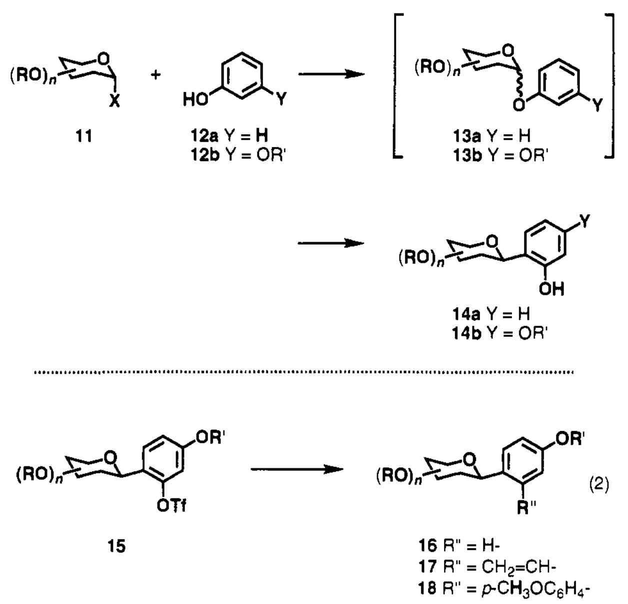
Scheme 1), we examined a benzyne–furan cycloaddition process (Scheme 2).[15]

Initial attempts to generate benzyne from the aryl triflate **5a** by using either alkyl lithium or lithium amide bases were unfruitful; the rate of deprotonation was so slow that benzyne, once generated, suffered attack by the unreacted base.[16] This analysis led us to use *o*-haloaryl triflate **5b** as a precursor in the hope that the extremely rapid rate of the halogen–lithium exchange reaction would be compatible with the excellent leaving group ability of the neighboring triflate.[17] Indeed, this proved to be the case, and treatment of **5b** with *n*-BuLi effected rapid benzyne generation at low temperature (eq 1).

As for the regiochemical control in the cycloaddition with 2-methoxyfuran (**6**), we reasoned that the alkoxy substituent in the benzyne would behave inductively as an electron-withdrawing group[18] to encourage *head-to-head* rather than *head-to-tail* cycloaddition. Indeed, the alkoxy benzyne species, generated by the above protocol, underwent the cycloaddition to give naphthol **8** in high yield.[19] This product was derived from the expected sequence of the aryne generation, *head-to-head* cycloaddition (**6** → **7**), followed by aromatization resulting from C–O bond cleavage. Note that this single operation affords direct access to naphthol **8**, in which all three hydroxyls are suitably differentiated.

Model Study 2, Regiocontrolled Aryl *C*-Glycoside Formation.[20] We reported previously a method for aryl *C*-glycoside synthesis, which may be termed as "*O*- → *C*-glycoside rearrangement".[12] Reaction of glycosyl donor **11** and phenol **12a** in the presence of a Lewis acid gives the *O*-glycoside **13a** at low temperature, which then rearranges in situ to *C*-glycoside **14a** when the reaction temperature is allowed to increase (Scheme 3). Of particular note is the regioselectivity of the process; the aryl *C*-glycoside bond forms selectively at a position *ortho* to the phenolic hydroxyl. The present targets **1** are, however, unique among the aryl *C*-glycoside antibiotics in that the *C*-glycoside bond is located at the position *para to a phenolic hydroxyl*, a serious obstacle to the adoption of the above methodology.

Scheme 3



Our idea was to translate this "*ortho* selectivity" into the "*para* selectivity" by applying the reaction to monoprotected resorcinol **12b**. Indeed, model studies showed that the *ortho* selectivity holds for **12b**, creating *C*-glycoside **14b** with *the additional oxygen functionality at the para position.* The triflate **15**, derived from **14b**, served as a versatile precursor for various aryl *C*-glycosides with *para*-oxygen functionalities (eq 2). For example, hydrogenolysis gave the deoxygenated product **16**. Stille coupling,[21] using organotin reagents, enabled the preparation of elaborated aryl *C*-glycosides, such as styryl **17** and biaryl **18**. In the execution of the total synthesis, this triflate serves also as an excellent leaving group for the generation of benzyne (*vide supra*), thereby integrating both tactics in the synthetic strategy.

Results and Discussion

For the aryl *C*-glycoside formation, an iodo resorcinol derivative **26** was synthesized (Scheme 4). The iodine was incorporated as the trigger for the benzyne generation at a later stage.[22] We chose to employ a benzyl protecting group, the same as those blocking the sugar, hoping for simultaneous deprotection at the end of the synthesis.

Contrasteric *C*-Glycoside Formation. We now were faced with most challenging step, the aryl *C*-glycoside bond formation. We examined the *O*- → *C*-glycoside rearrangement of phenol **26** and D-fucofuranosyl acetate **27**[23] in detail. The reaction was carried out in CH_2Cl_2 at an initial temperature of −78 °C. The formation

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(15) For reviews on aryne species, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Fields, E. K. In *Organic Reactive Intermediates*; McManus, S. P., Ed.; Academic Press: New York, 1973; pp 449–508. (c) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427–498. (d) Kessar, S. V. In *Comprehensive Organic Chemistry*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 483–515.

(16) For example, see: Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 2045–2050.

(17) For the extreme rapidity of the halogen–lithium exchange reaction, see: (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305. (b) Beak, P.; Musick, T. J.; Chen, C.-W. *J. Am. Chem. Soc.* **1988**, *110*, 3538–3542. (c) Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R.; Bonde, B. D. *Ibid.* **1990**, *112*, 4431–4435. For previous reports on reductive benzyne generation from haloaryl tosylates, see: (d) Tochtermann, W.; Stubenrauch, G.; Reiff, K.; Schumacher, U. *Chem. Ber.* **1974**, *107*, 3340–3352. (e) Gribble, G. W.; Perni, R. B.; Onan, K. D. *J. Org. Chem.* **1985**, *50*, 2934–2939. (f) Giles, R. G. F.; Sargent, M. V.; Sianipar, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1571–1579.

(18) Note that the relevant orbitals in the aryne are orthogonal to the aromatic π-orbitals so that the inductive effect, rather than the resonance effect, is responsible.

(19) Sargent *et al.* reported a systematic study on benzyne–furan cycloaddition: Giles, R. G. F.; Hughes, A. B.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1581–1587. We thank Prof. Sargent for sending reprints of their work.

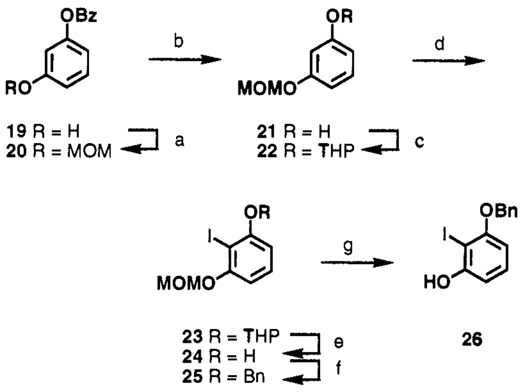
(20) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Synlett* **1991**, 709–711.

(21) (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

(22) Resorcinol mono-alkyl ether, without iodine, is a poor substrate in this reaction, since the aromatic portion is too electron rich, and thus, too reactive (see ref 20).

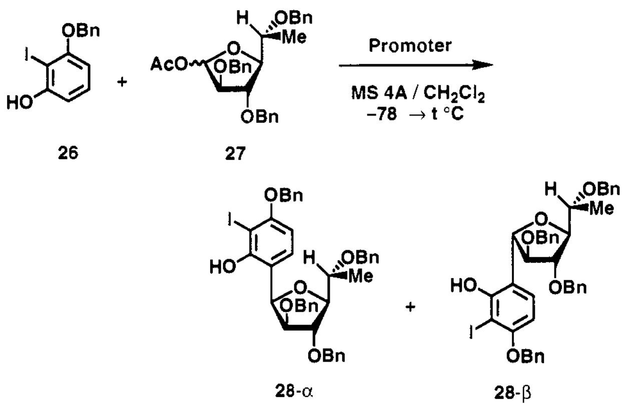
(23) Kinoshita, T.; Miwa, T. *Carbohydr. Res.* **1985**, *143*, 249–255. The acetate **27** was a ca. 1/1 mixture of anomers, which was used without separation. The corresponding glycosyl fluoride was too unstable for synthetic use. For the use of glycosyl acetate as an alternative glycosyl donor, see ref 12b.

Scheme 4[a]



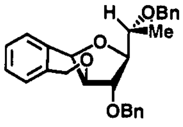
[a] (a) (MOM)Cl, i-Pr_2NEt/CH_2Cl_2, reflux, 18 h (quant); (b) 3 N NaOH (aq)/MeOH, 0 °C to room temperature, 2 h (quant); (c) DHP, cat. $PPTS/CH_2Cl_2$, room temperature, 60 h (95%); (d) n-BuLi/hexane, 0 °C, 3.5 h, then I_2/Et_2O, 0 °C, 30 min; (e) cat. PPTS/EtOH, 70 °C, 1.5 h (81%, two steps); (f) NaH, $PhCH_2Br$, cat. n-Bu_4NI/THF, room temperature, 1.5 h (98%); (g) 4 N HCl (aq)–MeOH–1,4-dioxane, 50 °C, 5 h (97%).

Table 1.[a] Glycosidation of Acetate **27** with Phenol **26**

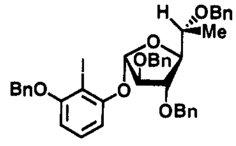


run	MX_n (–AgY)	t/°C	yield/%	α/β[b]
1	$SnCl_4$	–20	67	2.6/1
2	$SnCl_4$	0	75	1/2.5
3[c]	$SnCl_4$–$AgClO_4$	–40	60	5.1/1
4[c]	$SnCl_4$–$AgClO_4$	–20	69	1/58
5	$BF_3 \cdot OEt_2$	rt	42	1/1.8
6[d,e]	Cp_2HfCl_2–$AgClO_4$	–20	86	8.2/1[f]
7[d,e]	Cp_2HfCl_2–$AgClO_4$	rt	88	7/1
8[e]	Cp_2HfCl_2–AgOTf	rt	41	1/1.6
9[c]	$SiCl_4$–$AgClO_4$	–20	77	14/1
10[c]	Me_3SiCl–$AgClO_4$	–30	90	11/1
11[c]	Ph_3SiCl–$AgClO_4$	–40	91	17/1
12[e]	**31**–$AgClO_4$	–10	86	26/1

[a] Molar ratio of **26**:**27**:MX_n was 1.2:1.0:2.0. [b] Determined by ^1H NMR in C_6D_6 by integration of the anomeric proton. [c] MCl_n:AgY = 1:1. [d] Molar ratio of **26**:**27**:MX_n was 1.2:1.0:1.0. [e] MCl_n:AgY = 1:2. [f] Based on isolation.



29



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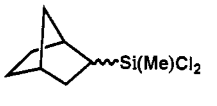

31

of O-glycoside **30** was complete generally in 10 min.[24] The temperature was then gradually raised while the conversion of the O-glycoside **30** to the C-glycoside **28** was monitored by TLC. The outcome of this C–C bond forming step was heavily dependent on the Lewis acid promoter. Selected data are shown in Table 1.[25,26]

The difficulties associated with this single step are cataloged in the results shown in runs 1–5. The reaction with $SnCl_4$ (–78 to –20 °C) afforded **28** with a slight excess of the desired α-anomer (run 1), while the β-anomer became dominant when the final reaction temperature was 0 °C (run 2). Even more impressive anomerization occurred in the presence of $AgClO_4$[27] at lower temperatures (runs 3 and 4). Thus, not only the kinetic stereoselectivity of the process but also the changeover to the thermodynamic control must be taken into account.[28] With $BF_3 \cdot OEt_2$, the reaction was sluggish, giving a poor yield of **28**. A side product **29**, obtained in 23% yield, arose from an internal Friedel–Crafts reaction (run 5).[29]

The crucial breakthrough came from employment of the glycosidation promoter, Cp_2HfCl_2–$AgClO_4$,[30] which cleanly effected the contrasteric C–C bond formation. The reaction of glycosyl acetate **27** and iodophenol **26** (1.2 equiv) in the presence of Cp_2HfCl_2 (1 equiv) and $AgClO_4$ (2 equiv) in CH_2Cl_2 (–78 to –20 °C) gave a high yield of C-glycoside **28** with high α-selectivity (α/β = 8.2/1, run 6). Interestingly, essentially no anomerization was observed even when the reaction was warmed to room temperature (run 7, cf. run 4). This was a remarkable outcome in view of our former experiences that this reagent combination often led to thermodynamic control.[12,28]

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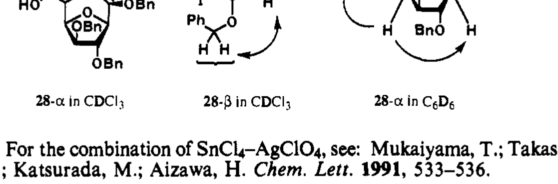
(24) Quenching the reaction mixture at –78 °C gave only β-O-glycoside **30**.

(25) By extending the carbohydrate convention of nomenclature to C-glycosides, let us designate the anomers as α and β as illustrated: Brakta, M.; Farr, R. N.; Chaguir, B.; Massiot, G.; Lavaud, C.; Anderson, W. R., Jr.; Sinou, D.; Daves, G. D., Jr. *J. Org. Chem.* **1993**, *58*, 2992–2998.

(26) Regio- and stereochemical assignments for C-glycosides **28**-α and **28**-β were based on NOE data. Location of the aryl C-glycoside in both anomers of **28** was established by NOE spectra in $CDCl_3$. The anomeric stereochemistry was deduced from the coupling constants (**28**-α, $J_{1'-2'}$ = 3.7 Hz; **28**-β, $J_{1'-2'}$ = 6.6 Hz) and was also supported by the NOE data in C_6D_6 for **28**-α.



28-α in $CDCl_3$ 28-β in $CDCl_3$ 28-α in C_6D_6

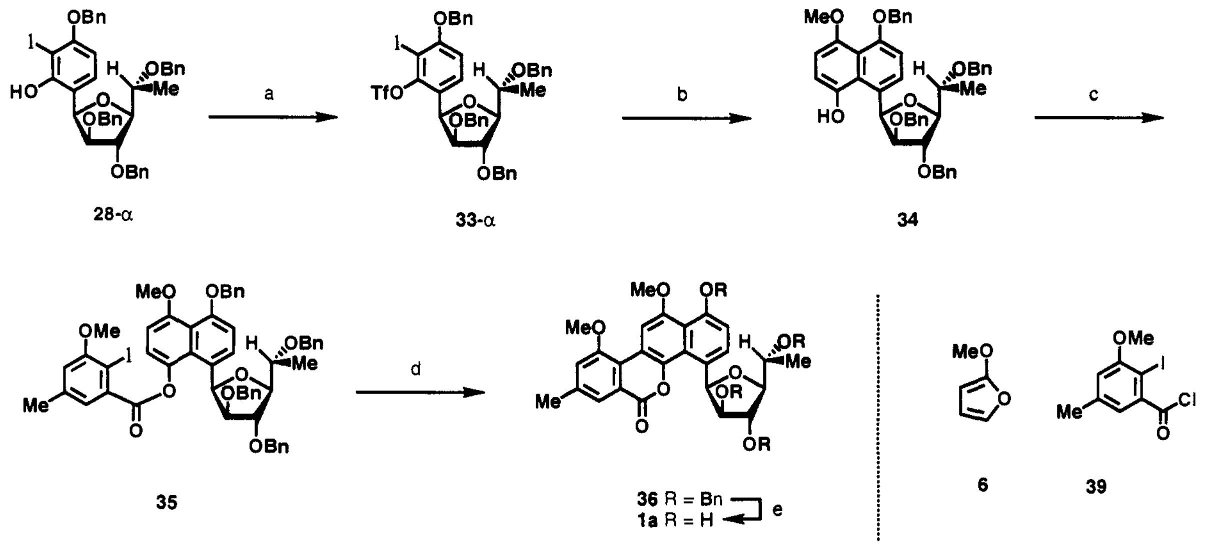
(27) For the combination of $SnCl_4$–$AgClO_4$, see: Mukaiyama, T.; Takashima, T.; Katsurada, M.; Aizawa, H. *Chem. Lett.* **1991**, 533–536.

(28) Thermodynamic preference in this context may reflect the stability difference between **28**-α and -β *coordinated to the Lewis acid rather than in their free forms.* Treatment of **28**-α and -β each with a protic acid under forcing conditions [10% $HClO_4$/1,4-dioxane (1:4), 100 °C, 8 h] resulted in a roughly 1/1 anomeric mixture, which seemingly refers to the equilibrium ratio of *uncomplexed* **28**. In contrast, exposure of **28**-α to $SnCl_4$–$AgClO_4$ (under conditions similar to those of run 4) led to clean anomerization to give a highly β-enriched mixture (α/β = 1/16), which suggested that this particular Lewis acid not only promotes the anomerization (via quinonemethide) but also contributes to accumulate the β-anomer by complexation, although the precise nature of coordination is not clear. Variation of the center metal, the ligands, and the coordination state endows Lewis acids with greatly different characters in terms of the ability to ease the anomerization and also the "fixing effect" stated above. The latter effect might also be operative to fix, vice versa, the kinetically formed α anomer in the hafnium or the silyl cases. We thank one of the reviewers for helpful suggestions on this stereochemical issue.

(29) (a) Martin, O. R. *Tetrahedron Lett.* **1985**, *26*, 2055–2058. (b) Araki, Y.; Mokubo, E.; Kobayashi, N.; Nagasawa, J.; Ishido, Y. *Ibid.* **1989**, *30*, 1115–1118. (c) Suzuki, K.; Maeta, H.; Suzuki, T.; Matsumoto, T. *Ibid.* **1989**, *30*, 6879–6882. (d) Matheu, M. I.; Echarri, R.; Castillón, S. *Ibid.* **1993**, *34*, 2361–2364.

(30) For use of Cp_2MCl_2–$AgClO_4$ (M = Hf, Zr) in O-glycoside synthesis, see: (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567–3570. (b) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Ibid.* **1988**, *29*, 3571–3574. (c) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Ibid.* **1988**, *29*, 3575–3578. (d) Suzuki, K.; Maeta, H.; Matsumoto, T. *Ibid.* **1989**, *30*, 4853–4856. (e) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Chem. Lett.* **1989**, 437–440.

Scheme 5[a]



[a] (a) Tf_2O, i-Pr_2NEt/CH_2Cl_2, −78 °C, 1 h (99%); (b) n-BuLi, **6**/THF, −78 °C, 10 min (88%); (c) **39**, i-Pr_2NEt, cat. DMAP/THF, room temperature, 2 h (91%); (d) 26 mol % $(Ph_3P)_2PdCl_2$, NaOAc/DMA, 125 °C, 5 h (90%); (e) H_2, 10% Pd–C/MeOH–THF, room temperature, 5 h (90%).

The silver perchlorate, used for ligand exchange to generate an electron-deficient hafnocene complex, was necessary to achieve high α-selectivity.[30d] The use of other silver salts with noncoordinating anions led to substantial decreases in yield and selectivity (run 8).

More recently, further improvements have been achieved by employing silyl derivatives to provide higher reactivity and stereoselectivity. For instance, the combination $SiCl_4$–$AgClO_4$ led to a high α-selectivity at a terminal temperature of −20 °C (run 9). The selectivity was influenced by subtle changes in the silyl ligands (runs 10 and 11).[31,32] Amazingly, the silane with a *norbornane* skeleton **31** led to the highest selectivity (α/β = 26/1, run 12).[33]

By chromatographic separation,[34] we now had stereodefined aryl *C*-glycoside **28-α** ready for the subsequent steps of the total synthesis. The previous observations alerted us to the potential for anomerization at any stage of the synthetic intermediates.[35]

Total Synthesis of Gilvocarcin M.[13] Scheme 5 illustrates the total synthesis of gilvocarcin M. Phenol **28-α** was converted to the corresponding triflate **33-α** quantitatively (Tf_2O, i-Pr_2NEt/CH_2Cl_2, −78 °C). Treatment of **33-α** with n-BuLi (2 equiv) in THF at −78 °C in the presence of 2-methoxyfuran (**6**, 3 equiv) resulted in sequential benzyne formation, [4 + 2] cycloaddition with the furan, and smooth aromatization to give naphthol **34**[35] in 88% yield. The regioisomeric adduct was also isolated in 7% yield. Thus, fortunately, the mode of cycloaddition held even for this sugar-containing benzyne species with better than 10:1 selectivity.

Acylation of **34** with acid chloride **39**[36] gave 91% yield of ester **35**. Treatment with $(Ph_3P)_2PdCl_2$ (26 mol %) and NaOAc (3 equiv) in *N,N*-dimethylacetamide at 125 °C to effect the intramolecular biaryl coupling[7b] produced the tetracycle **36** in 90% yield. For the final removal of the four benzyl protecting groups by hydrogenolysis, careful choice of the conditions was necessary.[37] Use of a mixed solvent system (MeOH–THF = 4:1) allowed clean hydrogenolysis (H_2, 10% Pd–C, 1 atm) to give (−)-gilvocarcin M (**1a**) in 90% yield [mp 246–249 °C (dec), lit.[1d] mp 245–248 °C (dec)]. The synthetic material proved to be identical with the natural product in all respects (^1H and ^{13}C NMR, IR, TLC, UV, and HRMS) including *the sign and magnitude of the optical rotation*, $[\alpha]^{23}_D$ −208° (c 0.21, DMSO) [lit.[1d] $[\alpha]^{20}_D$ −209° (c 0.2, DMSO)].

Total Synthesis of Gilvocarcin V. We then directed our attention to the total synthesis of gilvocarcin V (**1b**) bearing the vinyl group essential to antitumor activity. The synthesis was conducted in a manner parallel to that of **1a**. We prepared the benzoic acid unit **49**, armed with the latent vinyl group, by starting from 5-bromo-*o*-vanillin (**40**)[38] (Scheme 6).

Benzylation of **40** with benzyl bromide in the presence of K_2CO_3 gave ether **41**, which was then converted to acetal **42**. This bromide **42**, after halogen–lithium exchange (n-BuLi in THF at −78 °C), was treated with ethylene oxide to obtain alcohol **43** in

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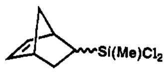
[31] For $(TMS)OClO_3$, see: (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255. For discussions on the nature of the silicenium ion, see: (b) Lambert, J. B.; Schilf, W. *J. Am. Chem. Soc.* **1988**, *110*, 6364–6367. (c) Olah, G. A.; Heiliger, L.; Li, X.-Y.; Prakash, G. K. S. *Ibid.* **1990**, *112*, 5991–5995.

[32] Use of other silver salts ((TMS)Cl–AgX; X = BF_4, PF_6, AsF_6, SbF_6, etc.) led to poor reactivity and/or stereoselectivity.

[33] The related reagent **32** with a norborn*ene* skeleton, in combination with $AgClO_4$, exhibited remarkably high reactivity, and the *O* → *C* rearrangement was completed at −78 °C (unpublished). The effect of the unsaturation on the enhanced reactivity is under investigation.

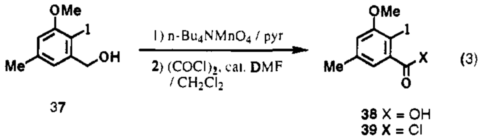


32

[34] Chromatographic separation of the α- and β-anomers is easier at the stage of triflate **33**. For the large-scale run, the α/β mixture of **28** was directly converted to triflate and separated to obtain pure **33-α** (see the Experimental Section).

[35] In contrast to the rather high configurational stability of monocyclic *C*-glycoside **28** toward protic acid (see ref 28), naphthol *C*-glycoside **34** is highly prone to anomerization even under weakly acidic conditions; e.g. when α-**34** was kept standing in $CDCl_3$ an almost 1/1 mixture of α- and β-anomers resulted after 1 h (by ^1H NMR), most probably by a trace of acid in the solvent. Acetone-d_6 proved to be the solvent of choice for the NMR measurement of **34**. Isolation of **34** was effected without any noticeable anomerization by silica gel flash column chromatography (hexane/Et_2O).

[36] Acid chloride **39** was prepared from known alcohol **37** (ref 7e). For n-Bu_4NMnO_4, see: Sala, T.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1978**, 253–254.



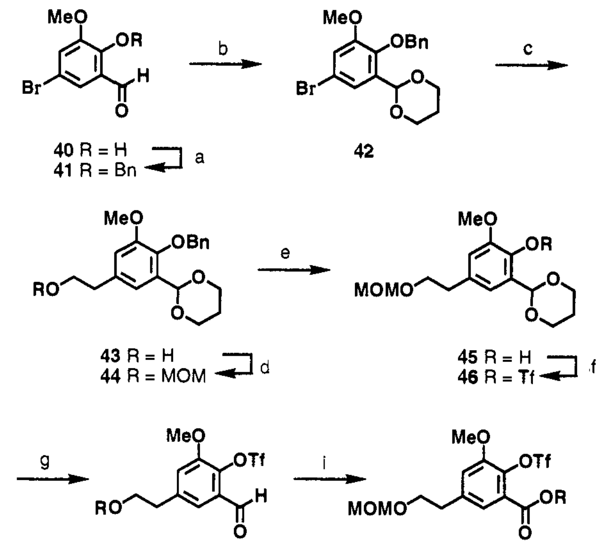
37

38 X = OH
39 X = Cl

[37] Use of 10% Pd–C in THF led to overreduction to result in the partial saturation of the tetracyclic moiety. We previously circumvented this problem by employing Raney Ni in EtOH as an overreduction-free protocol, which, however, required long reaction times (84 h; 72% yield, see ref 13).

[38] Comber, M. F.; Sargent, M. V. *Aust. J. Chem.* **1985**, *38*, 1481–1489.

Scheme 6[a]



[a] (a) $PhCH_2Br$, K_2CO_3/EtOH, reflux, 3 h (88%); (b) 1,3-propanediol, cat. TsOH/benzene, reflux, 1 h (quant); (c) *n*-BuLi/THF, −78 °C, 10 min, then ethylene oxide/Et_2O, −78 to 0 °C, 4 h (82%); (d) (MOM)Cl, *i*-Pr_2NEt/CH_2Cl_2, 0 °C to room temperature, 15 h (99%); (e) 10% Pd–C, HCO_2NH_4/MeOH, room temperature, 10 min; (f) Tf_2O, *i*-Pr_2NEt/CH_2Cl_2, −78 °C, 10 min (90%, two steps); (g) 8 N H_2SO_4 (aq)/THF, 50 °C, 2 h; (h) (MOM)Cl, *i*-Pr_2NEt/CH_2Cl_2, 0 °C to room temperature, 36 h (95%, two steps); (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/acetone–H_2O, room temperature, 30 min (90%); (j) CH_2N_2/Et_2O.

82% yield. The primary hydroxyl group in **43** was protected as an MOM ether to give **44** in 99% yield. Hydrogenolysis of the benzyl group in **44** under catalytic hydrogen-transfer conditions[39] proceeded without affecting the dioxane moiety to afford phenol **45**, which was then converted to triflate **46** in 90% yield. Several preliminary experiments had shown that it was difficult to hydrolyze the dioxane moiety while leaving the MOM group intact, and so we hydrolyzed both groups simultaneously and then reprotected the hydroxyl group to obtain MOM ether **48**. Oxidation[40] of the aldehyde gave 90% yield of carboxylic acid **49**.

Scheme 7 illustrates the final stages of the synthesis, which started with union of acid **49** with naphthol **34** by using the water-soluble carbodiimide EDCI[41] in the presence of DMAP to give **51** in 83% yield.[42] Initial attempts at internal C–C bond formation with triflate **51** met with poor yields when the reaction conditions described for iodide **35** were employed (cf. Scheme 5). After considerable experimentation, the yield was improved to an acceptable level by employing sodium pivalate in place of sodium acetate.[43] The reaction at a lower temperature gave 65% of the cyclized product **52** with 21% recovery of the starting triflate **51**. The four benzyl groups in **52** were removed by hydrogenolysis to give tetrol **53**, which was then fully acetylated to yield tetraacetate **54**. Generation of the vinyl function was nicely achieved by exploiting organoselenium chemistry. The MOM group in **54** was removed with bromotrimethylsilane[44] to give **55**, which was directly converted to selenide **56** with *o*-nitrophenyl selenocyanate and triphenylphosphine.[45] Exposure to 35% H_2O_2 in THF (0 °C, then room temperature, 1.5 h) gave rise to the vinyl derivative **57**.[46] Saponification of **57** with sodium methoxide in methanol gave gilvocarcin V (**1b**): mp 241–245 °C (dec); $[\alpha]^{23}_D$ −220° (*c* 0.22, DMSO) [lit.[1d] mp 264–267 °C (dec); $[\alpha]^{20}_D$ −216° (*c* 0.16, DMSO)].[47] The synthetic material proved identical with the natural product in all respects (^1H and ^{13}C NMR, IR, TLC, UV, and HRMS).

In summary, a total synthetic route to the gilvocarcin class antibiotics was established which will facilitate analog preparation in the search for new biologically active materials.

Experimental Section[48]

3-(Methoxymethoxy)phenyl Benzoate (20). To a solution of resorcinol monobenzoate (**19**) (commercially available from Kanto Chemical Co.) (25.0 g, 117 mmol) in CH_2Cl_2 (250 mL) were added *i*-Pr_2NEt (40.7 mL, 234 mmol) and (MOM)Cl (14.2 mL, 187 mmol) at 0 °C. Immediately, the ice bath was removed and the reaction mixture was refluxed for 18 h. After the mixture was cooled to room temperature, pH 7 phosphate buffer was added and the mixture was extracted with Et_2O. The combined organic extracts were washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to afford MOM ether **20** (30.1 g, 99.9%) as a colorless oil: bp 150 °C, 2.0 mmHg; R_f = 0.34 (hexane/EtOAc = 9/1); ^1H NMR ($CDCl_3$) δ 8.18–8.22 (m, 2 H), 7.60–7.66 (m, 1 H), 7.48–7.53 (m, 2 H), 7.33 (dd, 1 H, $J_1 = J_2 = 8.1$ Hz), 6.96 (ddd, 1 H, $J_1 = 8.1$, $J_2 = 2.4$, $J_3 = 1.0$ Hz), 6.94 (dd, 1 H, $J_1 = 2.4$, $J_2 = 2.0$ Hz), 6.88 (ddd, 1 H, $J_1 = 8.1$, $J_2 = 2.0$, $J_3 = 1.0$ Hz), 5.19 (s, 2 H), 3.48 (s, 3 H); IR (neat) 2970, 1740, 1600, 1490, 1450, 1320, 1265, 1245, 1215, 1155, 1135, 1080, 1060, 1010, 990, 930, 870, 780, 710, 690 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.77; H, 5.54.

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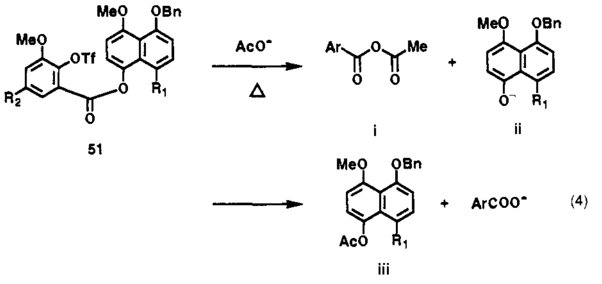
(39) Bieg, T.; Szeja, W. *Carbohydr. Res.* **1985**, *140*, C7–C8.

(40) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890.

(41) 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride: Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.

(42) The corresponding acid chloride could not be prepared, presumably due to the acid instability of the MOM group.

(43) Use of sodium acetate as the base led to the formation of a side product **iii**, derived from the acyl exchange via attack of an acetate anion at the ester carbonyl of **51** (highly electrophilic by the *o*-triflate!) to generate mixed anhydride **i** followed by counterattack of the expelled phenolate **ii** at the acetyl moiety of **i**. Indeed, this side reaction proceeded *in the absence of the Pd catalyst* at 100–120 °C. Use of a sterically hindered base, sodium pivalate, suppressed this side reaction. The coupling reaction of aryl triflate **51** proceeds at lower temperature than that of aryl iodide **35** in Scheme 5.



(44) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515–2518.

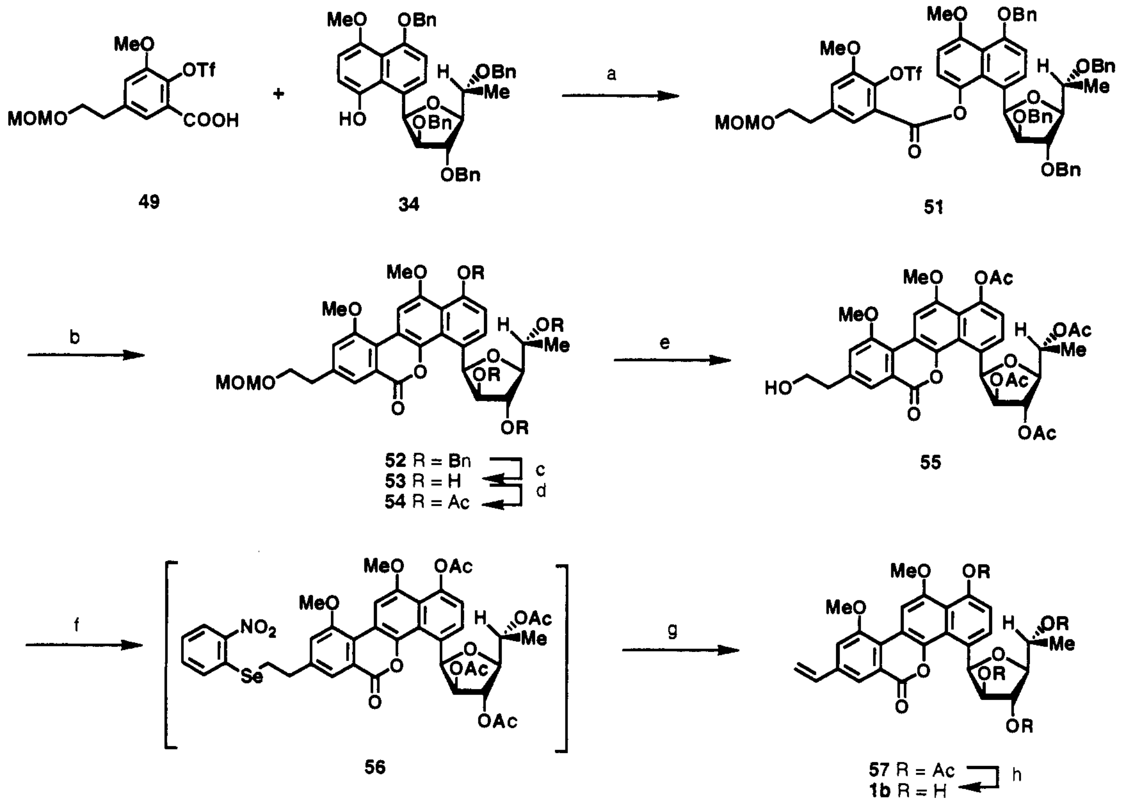
(45) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(46) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947–949.

(47) The reported melting points considerably differ by the origin of the sample: 255–260 °C (dec) (ref 1a), 264–267 °C (dec) (ref 1d), 220–230 °C (dec) (ref 1f), 251–253 °C (ref 6b), 234–235 °C (ref 1g). The discrepancy may be due to the potential contamination by gilvocarcin M, since gilvocarcins M and V are coproduced, and their separation is highly difficult. Jain attributed the difference to the hydration state (see ref 1g).

(48) **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 4-Å molecular sieves. 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) from 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's) 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. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ = 0). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Jasco IRA-202 spectrometer. 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 A 500 spectrometer. Optical rotations ($[\alpha]_D$) were measured on a Jasco DIP-360 polarimeter, and UV spectra were recorded on a Jasco UVIDEC-610A.

Scheme 7[a]



[a] (a) EDCI, DMAP/Et_2O, room temperature, 11 h (83%); (b) 27 mol % $(Ph_3P)_2PdCl_2$, NaOPiv/DMA, 80 °C, 1 h (65%); (c) H_2, Raney Ni/EtOH–Et_2O, room temperature, 60 h; (d) Ac_2O, cat. DMAP/pyr, room temperature, 5 h (68%, two steps); (e) TMSBr/CH_2Cl_2, −78 to −10 °C, 5 h (94%); (f) *o*-nitrophenyl selenocyanate, *n*-Bu_3P/THF, room temperature, 30 min; (g) 35% H_2O_2 (aq), 0 °C to room temperature, 1.5 h (95%, two steps); (h) NaOMe/MeOH, room temperature, 23 h (71%).

3-(Methoxymethoxy)phenol (21). To a solution of benzoate **20** (29.4 g, 114 mmol) in MeOH (80 mL) was added 3 N aqueous NaOH (77.8 mL, 233 mmol) at 0 °C over 15 min. This white suspension was allowed to warm to room temperature and stirred for 2 h. To this solution was added benzene (100 mL) and brine (50 mL). The mixture was cooled to 0 °C, and the pH was adjusted to ca. 6 by adding 4 N HCl (ca. 35 mL). After removal of the methanol in vacuo, the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 75/25) to afford phenol **21** (17.6 g, quantitative) as a colorless oil (solidified in a refrigerator as a white crystalline solid, mp < room temperature): bp 105 °C, 1.7 mmHg; R_f = 0.36 (hexane/EtOAc = 75/25); ^1H NMR ($CDCl_3$) δ 7.12 (dd, 1 H, J_1 = 8.3, J_2 = 8.1 Hz), 6.61 (ddd, 1 H, J_1 = 8.3, J_2 = 2.2, J_3 = 0.7 Hz), 6.55 (dd, 1 H, J_1 = 2.4, J_2 = 2.2 Hz), 6.49 (ddd, 1 H, J_1 = 8.1, J_2 = 2.4, J_3 = 0.7 Hz), 5.60–5.72 (broad, 1 H), 5.15 (s, 2 H), 3.48 (s, 3 H); IR (neat) 3400, 2960, 2850, 1600, 1490, 1460, 1410, 1335, 1315, 1290, 1215, 1140, 1075, 1020, 995, 940, 925, 850, 770, 690 cm^{-1}. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.19; H, 6.54.

1-(Methoxymethoxy)-3-((2-tetrahydropyranyl)oxy)benzene (22). A mixture of phenol **21** (17.5 g, 114 mmol), 3,4-dihydro-2*H*-pyran (26.1 mL, 288 mmol), and a catalytic amount of pyridinium *p*-toluenesulfonate in CH_2Cl_2 (100 mL) was stirred at room temperature for 60 h. The reaction was stopped by adding saturated aqueous $NaHCO_3$ at 0 °C, and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to afford THP ether **22** (25.8 g, 95.4%) as a colorless oil: bp 130 °C, 2.0 mmHg; R_f = 0.39 (hexane/EtOAc = 9/1); ^1H NMR ($CDCl_3$) δ 7.17 (dd, 1 H, J_1 = J_2 = 8.3 Hz), 6.76 (dd, 1 H, J_1 = J_2 = 2.4 Hz), 6.72 (ddd, 1 H, J_1 = 8.3, J_2 = 2.4, J_3 = 1.0 Hz), 6.67 (ddd, 1 H, J_1 = 8.3, J_2 = 2.4, J_3 = 1.0 Hz), 5.40 (dd, 1 H, J_1 = J_2 = 3.2 Hz), 5.15 (s, 2 H), 3.91 (ddd, 1 H, J_1 = 11.2, J_2 = 9.5, J_3 = 3.2 Hz), 3.60 (dddd, 1 H, J_1 = 11.2, J_2 = J_3 = 4.2, J_4 = 1.2 Hz), 3.47 (s, 3 H), 1.92–2.08 (m, 1 H), 1.78–1.91 (m, 2 H), 1.52–1.75 (m, 3 H); IR (neat) 2970, 1600, 1495, 1460, 1360, 1280, 1260, 1210, 1150, 1130, 1110, 1080, 1020, 1000, 970, 930, 900, 875, 775, 695 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.85; H, 7.41.

2-Iodo-3-(methoxymethoxy)phenol (24). To a solution of THP ether **22** (13.0 g, 54.6 mmol) in hexane (260 mL) was added *n*-BuLi (1.65 M hexane solution, 39.7 mL, 65.5 mmol) at 0 °C over 20 min. The mixture gradually turned into a white suspension. After the mixture was stirred for 3.5 h, a solution of I_2 (20.8 g, 82.0 mmol) in Et_2O (300 mL) was added dropwise over 30 min. After the mixture stirred for another 30 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with Et_2O. The combined organic extracts were washed successively with saturated aqueous $Na_2S_2O_3$ and brine and then dried (Na_2SO_4). Removal of the solvent in vacuo afforded crude **23**, which was dissolved in EtOH (300 mL). To this solution was added a catalytic amount of pyridinium *p*-toluenesulfonate, and the mixture was heated at 70 °C for 1.5 h. After the mixture was cooled to room temperature, brine was added and the mixture was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to afford phenol **24** (12.4 g, 81.2%) as a colorless oil (solidified in a refrigerator as a white crystalline solid, mp < room temperature): bp 120 °C, 1.9 mmHg; R_f = 0.24 (hexane/EtOAc = 9/1); ^1H NMR ($CDCl_3$) δ 7.16 (dd, 1 H, J_1 = 8.3, J_2 = 8.1 Hz), 6.69 (dd, 1 H, J_1 = 8.3, J_2 = 1.2 Hz), 6.62 (dd, 1 H, J_1 = 8.1, J_2 = 1.2 Hz), 5.52 (s, 1 H), 5.24 (s, 2 H), 3.51 (s, 3 H); IR (neat) 3480, 2970, 2850, 1585, 1460, 1405, 1320, 1295, 1255, 1210, 1190, 1150, 1085, 1030, 925, 770, 710, 650 cm^{-1}. Anal. Calcd for $C_8H_9O_3I$: C, 34.31; H, 3.24. Found: C, 33.94; H, 3.17.

1-(Benzyloxy)-2-iodo-3-(methoxymethoxy)benzene (25). To a suspension of NaH (60% dispersion in oil, 0.562 g, 14.1 mmol) in THF (20 mL) was added a solution of phenol **24** (3.03 g, 10.8 mmol) in THF (20 mL) at 0 °C. This suspension was allowed to warm to room temperature and stirred for 30 min. To this suspension was added *n*-Bu_4NI (0.428 g, 1.08 mmol) followed by a solution of $PhCH_2Br$ (2.78 g, 16.3 mmol) in THF (10 mL). After the mixture was stirred for 1.5 h, the reaction was stopped by adding saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The combined organic extracts were washed successively with brine, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 95/5) to afford benzyl ether **25** (3.91 g, 97.6%) as a colorless oil: bp 175 °C, 1.3 mmHg; R_f = 0.21

(hexane/EtOAc = 95/5); ^{1}H NMR (CDCl$_3$) δ 7.49–7.52 (m, 2 H), 7.36–7.41 (m, 2 H), 7.29–7.33 (m, 1 H), 7.19 (dd, 1 H, $J_1 = J_2 = 8.3$ Hz), 6.72 (dd, 1 H, $J_1 = 8.3$, $J_2 = 1.2$ Hz), 6.55 (dd, 1 H, $J_1 = 8.3$, $J_2 = 1.2$ Hz), 5.25 (s, 2 H), 5.15 (s, 2 H), 3.51 (s, 3 H); IR (neat) 2910, 1585, 1500, 1450, 1400, 1380, 1310, 1290, 1275, 1245, 1200, 1150, 1095, 1060, 1025, 1000, 920, 770, 740, 700, 650 cm^{-1}. Anal. Calcd for $C_{15}H_{15}O_3I$: C, 48.67; H, 4.08. Found: C, 48.54; H, 4.06.

3-(Benzyloxy)-2-iodophenol (26). A solution of MOM ether **25** (4.57 g, 12.3 mmol) in MeOH (45 mL)–1,4-dioxane (45 mL)–4 N HCl (9 mL) was heated at 50 °C for 5 h. After the solution was cooled to room temperature, saturated aqueous NaHCO$_3$ was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 75/25) to afford phenol **26** (3.91 g, 97.1%) as a colorless oil. This material solidified in a refrigerator, and recrystallization from hexane–CCl$_4$ gave white needles: mp 56.5–57 °C; $R_f = 0.40$ (hexane/EtOAc = 75/25), $R_f = 0.52$ (CCl$_4$/Et$_2$O = 8/2); ^{1}H NMR (CDCl$_3$) δ 7.47–7.50 (m, 2 H), 7.37–7.42 (m, 2 H), 7.30–7.35 (m, 1 H), 7.16 (dd, 1 H, $J_1 = 8.3$, $J_2 = 8.1$ Hz), 6.67 (dd, 1 H, $J_1 = 8.1$, $J_2 = 1.2$ Hz), 6.43 (dd, 1 H, $J_1 = 8.3$, $J_2 = 1.2$ Hz), 5.49 (s, 1 H), 5.14 (s, 2 H); IR (KBr) 3400, 2940, 2870, 1600, 1570, 1500, 1490, 1460, 1445, 1390, 1340, 1275, 1240, 1090, 1070, 1020, 960, 770, 740, 700, 655 cm^{-1}. Anal. Calcd for $C_{13}H_{11}O_2I$: C, 47.88; H, 3.40. Found: C, 47.88; H, 3.48.

***O*- → *C*-Glycoside Rearrangement of Fucofuranosyl Acetate 27 and Phenol 26. (Cp$_2$HfCl$_2$–AgClO$_4$ as the Promoter.)** The promoter was prepared in situ by stirring the mixture of Cp$_2$HfCl$_2$ (96 mg, 0.25 mmol) and AgClO$_4$ (105 mg, 0.506 mmol) in the presence of powdered 4-Å molecular sieves (ca. 700 mg) in CH$_2$Cl$_2$ (2 mL) for 15 min at room temperature. To this suspension at –78 °C was added a solution of phenol **26** (99 mg, 0.30 mmol) in CH$_2$Cl$_2$ (2 mL) and glycosyl acetate **27**[23] (121 mg, 0.254 mmol) in CH$_2$Cl$_2$ (6 mL). The reaction mixture was gradually warmed to –20 °C during 40 min, and the stirring was continued for 15 min. The reaction was quenched by the addition of saturated aqueous NaHCO$_3$. The mixture was acidified with 2 N HCl, filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were washed successively with saturated aqueous NaHCO$_3$ and brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by PTLC (CCl$_4$/Et$_2$O = 8/2, for separating *C*-glycosides **28** from phenol **26** and then hexane/EtOAc = 8/2, double developments for separating anomers **28-α** and **28-β**) to afford *C*-glycosides **28-α** (144 mg, 76.4%) and **28-β** (18 mg, 9.5%).

(Ph$_3$SiCl–AgClO$_4$ as the Promoter.) The promoter was prepared in situ by stirring the mixture of Ph$_3$SiCl (310 mg, 1.05 mmol) and AgClO$_4$ (221 mg, 1.07 mmol) in the presence of powdered 4-Å molecular sieves (ca. 1.0 g) in CH$_2$Cl$_2$ (20 mL) for 30 min at room temperature. To this suspension at –78 °C was added a solution of phenol **26** (257 mg, 0.788 mmol) in CH$_2$Cl$_2$ (6 mL) and glycosyl acetate **27** (250 mg, 0.525 mmol) in CH$_2$Cl$_2$ (6 mL). The reaction mixture was gradually warmed to –40 °C during 1 h, and the stirring was continued for 10 min. The reaction was quenched by the addition of saturated aqueous NaHCO$_3$. The mixture was acidified with 2 N HCl, filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were washed successively with saturated aqueous NaHCO$_3$ and brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by PTLC (CCl$_4$/Et$_2$O = 8/2 and hexane/EtOAc = 8/2) to afford an anomeric mixture of *C*-glycosides **28-α,β** (343 mg, 90.9%, $\alpha/\beta = 17/1$) as a colorless oil.

3-(Benzyloxy)-2-iodo-6-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)phenol (28-α): colorless oil; $R_f = 0.36$ (hexane/EtOAc = 8/2), $R_f = 0.68$ (CCl$_4$/Et$_2$O = 8/2); ^{1}H NMR (CDCl$_3$) δ 8.60 (s, 1 H), 7.48–7.51 (m, 2 H), 7.20–7.39 (m, 16 H), 7.00–7.03 (m, 2 H), 6.97 (d, 1 H, $J = 8.4$ Hz), 6.36 (d, 1 H, $J = 8.4$ Hz), 5.15 (s, 2 H), 5.05 (d, 1 H, $J = 3.7$ Hz), 4.68 (d, 1 H, $J = 12.1$ Hz), 4.51 (d, 1 H, $J = 12.1$ Hz), 4.43 (d, 1 H, $J = 12.1$ Hz), 4.38 (d, 1 H, $J = 12.1$ Hz), 4.21 (d, 1 H, $J = 12.1$ Hz), 4.13 (d, 1 H, $J = 12.1$ Hz), 3.94–4.00 (m, 3 H), 3.77 (dq, 1 H, $J_1 = 4.8$, $J_2 = 6.2$ Hz), 1.26 (d, 3 H, $J = 6.2$ Hz); ^{1}H NMR (C$_6$D$_6$) δ 9.00 (s, 1 H), 7.30–7.37 (m, 4 H), 7.02–7.22 (m, 16 H), 6.78 (d, 1 H, $J = 8.4$ Hz), 6.08 (d, 1 H, $J = 8.4$ Hz), 5.07 (d, 1 H, $J = 3.7$ Hz), 4.74 (d, 1 H, $J = 13.2$ Hz), 4.70 (d, 1 H, $J = 13.2$ Hz), 4.45 (d, 1 H, $J = 12.1$ Hz), 4.30 (d, 1 H, $J = 12.1$ Hz), 4.24 (d, 1 H, $J = 12.1$ Hz), 4.23 (d, 1 H, $J = 12.1$ Hz), 4.04–4.09 (m, 2 H), 3.97–4.02 (m, 2 H), 3.94 (d, 1 H, $J = 3.7$ Hz), 3.61 (dq, 1 H, $J_1 = 6.2$, $J_2 = 4.0$ Hz), 1.15 (d, 3 H, $J = 6.2$ Hz); ^{13}C NMR (CDCl$_3$) δ 158.3, 157.1, 138.3, 137.5, 136.8, 129.0, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.60, 127.59, 127.0, 114.0, 103.5, 87.2, 84.7, 84.5, 84.2, 78.7, 73.6, 72.0, 71.9, 71.2, 70.9, 16.2; IR (neat) 3380, 3050, 2890, 1615, 1565, 1490, 1455, 1380, 1355, 1300, 1205, 1065, 740, 700 cm^{-1}; $[\alpha]^{23}{}_D$ –4.8° (*c* 2.8, CHCl$_3$); HRMS *m/z* 742.1801 (742.1790 calcd for $C_{40}H_{39}O_6I$, M$^+$).

3-(Benzyloxy)-2-iodo-6-(2,3,5-tri-*O*-benzyl-β-D-fucofuranosyl)phenol (28-β): colorless oil; $R_f = 0.43$ (hexane/EtOAc = 8/2), $R_f = 0.71$ (CCl$_4$/Et$_2$O = 8/2); ^{1}H NMR (CDCl$_3$) δ 8.27 (s, 1 H), 7.49–7.52 (m, 2 H), 7.16–7.41 (m, 18 H), 7.09 (d, 1 H, $J = 8.4$ Hz), 6.40 (d, 1 H, $J = 8.4$ Hz), 5.16 (s, 2 H), 5.07 (d, 1 H, $J = 6.6$ Hz), 4.67 (d, 1 H, $J = 12.1$ Hz), 4.41–4.49 (m, 5 H), 4.20–4.24 (m, 2 H), 4.09–4.12 (m, 1 H), 3.67 (dq, 1 H, $J_1 = 6.2$, $J_2 = 4.8$ Hz), 1.24 (d, 3 H, $J = 6.2$ Hz); ^{13}C NMR (CDCl$_3$) δ 158.3, 155.3, 138.5, 137.7, 137.6, 136.7, 128.60, 128.59, 128.49, 128.47, 128.44, 128.0, 127.92, 127.90, 127.86, 128.83, 127.7, 127.0, 117.6, 104.2, 88.2, 85.9, 84.3, 82.8, 78.8, 74.1, 72.6, 72.1, 71.2, 71.0, 15.9; IR (neat) 3300, 2870, 1610, 1565, 1485, 1450, 1375, 1290, 1205, 1115, 1060, 1025, 735, 695 cm^{-1}; $[\alpha]^{22}{}_D$ –35° (*c* 3.1, CHCl$_3$); HRMS *m/z* 742.1786 (742.1790 calcd for $C_{40}H_{39}O_6I$, M$^+$).

(2*S*,3*S*,3a*S*,9b*R*)-3-(Benzyloxy)-2-[(1*R*)-1-(benzyloxy)ethyl]-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran (29): colorless oil; $R_f = 0.50$ (hexane/EtOAc = 8/2), $R_f = 0.65$ (CCl$_4$/Et$_2$O = 8/2); ^{1}H NMR (CDCl$_3$) δ 7.48–7.51 (m, 1 H), 7.19–7.34 (m, 12 H), 7.04–7.07 (m, 1 H), 4.75 (d, 1 H, $J = 14.7$ Hz), 4.70 (d, 1 H, $J = 3.2$ Hz), 4.66 (d, 1 H, $J = 11.5$ Hz), 4.63 (d, 1 H, $J = 14.7$ Hz), 4.59 (s, 2 H), 4.58 (d, 1 H, $J = 11.5$ Hz), 4.18 (d, 1 H, $J = 3.2$ Hz), 4.02 (dd, 1 H, $J_1 = 6.1$, $J_2 = 5.4$ Hz), 3.98 (d, 1 H, $J = 5.4$ Hz), 3.73 (dq, 1 H, $J_1 = J_2 = 6.1$ Hz), 1.17 (d, 3 H, $J = 6.1$ Hz); ^{13}C NMR (CDCl$_3$) δ 139.0, 137.7, 135.1, 130.7, 130.4, 128.4, 128.20, 128.17, 127.9, 127.81, 127.77, 127.28, 127.26, 124.1, 86.8, 86.3, 81.5, 74.7, 73.8, 72.2, 71.4, 67.2, 16.0; IR (neat) 3040, 2880, 1605, 1590, 1500, 1450, 1375, 1340, 1310, 1290, 1260, 1210, 1160, 1090, 1030, 950, 925, 880, 855, 810, 790, 750, 700, 670, 630, 610 cm^{-1}; $[\alpha]^{23}{}_D$ –19° (*c* 1.1, CHCl$_3$); HRMS *m/z* 416.1978 (416.1986 calcd for $C_{27}H_{28}O_4$, M$^+$).

3-(Benzyloxy)-2-iodophenyl 2,3,5-Tri-*O*-benzyl-β-D-fucofuranoside (30): white crystalline solid; mp 91–93 °C; $R_f = 0.44$ (hexane/EtOAc = 8/2), $R_f = 0.68$ (CCl$_4$/Et$_2$O = 8/2); ^{1}H NMR (CDCl$_3$) δ 7.50–7.53 (m, 2 H), 7.23–7.41 (m, 18 H), 7.18 (dd, 1 H, $J_1 = J_2 = 8.3$ Hz), 6.80 (dd, 1 H, $J_1 = 8.3$, $J_2 = 1.0$ Hz), 6.57 (dd, 1 H, $J_1 = 8.3$, $J_2 = 1.0$ Hz), 5.68 (d, 1 H, $J = 1.2$ Hz), 5.17 (s, 2 H), 4.42–4.71 (m, 7 H), 4.23 (dd, 1 H, $J_1 = 7.6$, $J_2 = 3.9$ Hz), 4.13 (dd, 1 H, $J_1 = 7.6$, $J_2 = 3.9$ Hz), 3.71 (dq, 1 H, $J_1 = 3.9$, $J_2 = 6.4$ Hz), 1.24 (d, 3 H, $J = 6.4$ Hz); ^{13}C NMR (CDCl$_3$) δ 158.6, 157.6, 138.5, 137.9, 137.5, 136.7, 129.6, 128.5, 128.4, 128.32, 128.28, 128.1, 128.0, 127.94, 127.90, 127.8, 127.7, 127.5, 127.0, 109.6, 107.0, 105.7, 88.8, 84.5, 82.9, 80.9, 73.1, 72.4, 72.2, 71.3, 71.1, 15.9; IR (KBr) 3050, 3000, 2950, 1590, 1500, 1455, 1380, 1360, 1310, 1250, 1170, 1140, 1120, 1070, 1040, 1030, 1020, 990, 960, 790, 740, 700 cm^{-1}; $[\alpha]^{23}{}_D$ –73° (*c* 0.79, CHCl$_3$). Anal. Calcd for $C_{40}H_{39}O_6I$: C, 64.69; H, 5.29. Found: C, 64.48; H, 5.29.

3-(Benzyloxy)-2-iodo-6-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)phenyl Trifluoromethanesulfonate (33-α). To a mixture of phenol **28-α** (389 mg, 0.524 mmol) and *i*-Pr$_2$NEt (135 mg, 1.05 mmol) in CH$_2$Cl$_2$ (10 mL) was added a solution of Tf$_2$O (443 mg, 1.57 mmol) in CH$_2$Cl$_2$ (2 mL) at –78 °C. After the mixture was stirred for 1 h, the reaction was quenched by adding saturated aqueous NaHCO$_3$ and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/Et$_2$O = 7/3) to afford triflate **33-α** (451 mg, 98.4%) as a colorless oil: $R_f = 0.44$ (hexane/Et$_2$O = 7/3), $R_f = 0.54$ (benzene); ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 1 H, $J = 8.8$ Hz), 7.23–7.51 (m, 18 H), 6.98–7.01 (m, 2 H), 6.86 (d, 1 H, $J = 8.8$ Hz), 5.30 (d, 1 H, $J = 3.7$ Hz), 5.19 (s, 2 H), 4.66 (d, 1 H, $J = 11.7$ Hz), 4.61 (d, 1 H, $J = 11.7$ Hz), 4.48 (d, 1 H, $J = 11.7$ Hz), 4.39 (d, 1 H, $J = 11.7$ Hz), 4.20 (d, 1 H, $J = 3.7$ Hz), 4.18 (d, 1 H, $J = 12.0$ Hz), 4.10 (d, 1 H, $J = 12.0$ Hz), 3.96–4.00 (m, 2 H), 3.80 (dq, 1 H, $J_1 = J_2 = 6.4$ Hz), 1.22 (d, 3 H, $J = 6.4$ Hz); ^{13}C NMR (CDCl$_3$) δ 158.9, 146.7, 138.9, 137.7, 137.6, 135.9, 132.6, 128.8, 128.5, 128.42, 128.37, 128.2, 127.91, 127.87, 127.74, 127.69, 127.5, 127.1, 124.7, 118.7 (q, $J_{C-F} = 321.4$ Hz), 111.9, 86.1, 84.8, 82.8, 82.6, 77.3, 74.4, 71.78, 71.76, 71.6, 71.3, 16.1; IR (neat) 3050, 2880, 1605, 1500, 1480, 1455, 1410, 1280, 1220, 1135, 1100, 1050, 1030, 965, 915, 850, 825, 740, 700, 665 cm^{-1}; $[\alpha]^{23}{}_D$ –60° (*c* 2.1, CHCl$_3$); HRMS *m/z* 874.1243 (874.1282 calcd for $C_{41}H_{38}O_8ISF_3$, M$^+$).

Experimental Procedure for Preparation of Triflate 33-α on a Larger Scale. The promoter was prepared in situ by stirring the mixture of Cp$_2$HfCl$_2$ (797 mg, 2.10 mmol) and AgClO$_4$ (435 mg, 2.10 mmol) in the presence of powdered 4-Å molecular sieves (ca. 4.0 g) in CH$_2$Cl$_2$ (12 mL) for 15 min at room temperature. To this suspension at –78 °C was added a solution of phenol **26** (506 mg, 1.55 mmol) in CH$_2$Cl$_2$ (12 mL) and glycosyl acetate **27** (667 mg, 1.40 mmol) in CH$_2$Cl$_2$ (32 mL). The reaction mixture was gradually warmed to –20 °C during 2 h, and the stirring was continued for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and acidified with 2 N HCl. The mixture was filtered through a Celite pad and 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. The residue was purified by flash column chromatography (CCl_4/Et_2O = 8/2) to afford crude mixture of *C*-glycosides **28**-α and **28**-β (1.01 g, 97%). To the mixture of crude *C*-glycosides **28**-α,β and *i*-Pr_2NEt (362 mg, 2.80 mmol) in CH_2Cl_2 (12 mL) was added a solution of Tf_2O (2.25 g, 7.98 mmol) in CH_2Cl_2 (4 mL) at –78 °C. After the mixture was stirred for 15 min, the reaction was terminated by adding saturated aqueous $NaHCO_3$, and the mixture was 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. The residue was purified by flash column chromatography (hexane/Et_2O = 8/2 to 5/5) to afford triflate **33**-β (93 mg, 7.6%, two steps) and triflate **33**-α. The triflate **33**-α was accompanied by a small amount of impurity. Repurification by flash column chromatography (benzene/hexane = 95/5 then benzene/Et_2O = 99/1) afforded pure triflate **33**-α (1.05 g, 85.8%, two steps).

3-(Benzyloxy)-2-iodo-6-(2,3,5-tri-*O*-benzyl-β-D-fucofuranosyl)phenyl Trifluoromethanesulfonate (33-β): colorless oil; R_f = 0.26 (hexane/Et_2O = 7/3), R_f = 0.37 (benzene); ^1H NMR ($CDCl_3$) δ 7.63 (d, 1 H, J = 8.8 Hz), 7.13–7.49 (m, 20 H), 6.83 (d, 1 H, J = 8.8 Hz), 5.45 (d, 1 H, J = 5.4 Hz), 5.15 (s, 2 H), 4.66 (d, 1 H, J = 12.0 Hz), 4.57 (d, 1 H, J = 12.0 Hz), 4.47 (d, 1 H, J = 12.2 Hz), 4.46 (d, 1 H, J = 12.0 Hz), 4.44 (d, 1 H, J = 12.2 Hz), 4.36 (d, 1 H, J = 12.0 Hz), 4.20 (dd, 1 H, J_1 = 6.1, J_2 = 3.4 Hz), 4.14 (dd, 1 H, J_1 = J_2 = 3.4 Hz), 4.05 (dd, 1 H, J_1 = 5.4, J_2 = 3.4 Hz), 3.71 (dq, 1 H, J_1 = J_2 = 6.1 Hz), 1.20 (d, 3 H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 158.9, 147.4, 138.8, 137.8, 137.6, 135.8, 130.2, 128.7, 128.5, 128.4, 128.3, 128.2, 127.91, 127.87, 127.80, 127.75, 127.72, 127.5, 127.1, 118.7 (q, J_{C-F} = 321.4 Hz), 112.4, 90.2, 87.0, 84.6, 83.9, 79.0, 74.7, 72.2, 72.0, 71.64, 71.55, 16.0; IR (neat) 3050, 2950, 1600, 1500, 1480, 1455, 1430, 1410, 1280, 1220, 1135, 1050, 1030, 950, 910, 850, 820, 740, 700 cm^{-1}; $[\alpha]^{22}_D$ –11° (*c* 1.8, $CHCl_3$); HRFABMS *m/z* 875.1355 (875.1363 calcd for $C_{41}H_{39}O_8ISF_3$, $M^+ + 1$).

5-(Benzyloxy)-4-methoxy-8-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)-1-naphthol (34). To a mixture of triflate **33**-α (920 mg, 1.05 mmol) and freshly distilled 2-methoxyfuran (**6**) (315 mg, 3.21 mmol) in THF (35 mL) was added *n*-BuLi (1.75 M hexane solution, 1.20 mL, 2.10 mmol) at –78 °C. After 10 min, the reaction was quenched by the addition of 2 N HCl (ca. 5 mL) to ensure the ring opening. Immediately, pH 7 phosphate buffer was added to avoid anomerization. The mixture was extracted with Et_2O, and the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/Et_2O = 7/3 to 5/5) to afford naphthol **34** (645 mg, 88.0%) as a light blue crystalline solid, which was recrystallized from hexane–toluene to give white needles (553 mg, 75.5%): mp 140–143 °C (dec); R_f = 0.29 (hexane/Et_2O = 5/5); ^1H NMR (acetone-d_6) δ 8.75 (s, 1 H), 7.93 (d, 1 H, J = 8.2 Hz), 7.66–7.69 (m, 2 H), 7.40–7.45 (m, 4 H), 7.24–7.35 (m, 9 H), 7.08–7.14 (m, 3 H), 7.08 (d, 1 H, J = 8.2 Hz), 6.91 (d, 1 H, J = 8.2 Hz), 6.84–6.87 (m, 2 H), 6.84 (d, 1 H, J = 8.2 Hz), 6.40 (d, 1 H, J = 3.7 Hz), 5.22 (s, 2 H), 4.76 (s, 2 H), 4.59 (d, 1 H, J = 3.7 Hz), 4.57 (d, 1 H, J = 11.9 Hz), 4.52 (d, 1 H, J = 11.9 Hz), 4.11 (d, 1 H, J = 12.2 Hz), 4.05 (d, 1 H, J = 4.3 Hz), 3.97 (dd, 1 H, J_1 = 6.1, J_2 = 4.3 Hz), 3.96 (d, 1 H, J = 12.2 Hz), 3.91 (dq, 1 H, J_1 = J_2 = 6.1 Hz), 3.83 (s, 3 H), 1.28 (d, 3 H, J = 6.1 Hz); ^{13}C NMR (acetone-d_6) δ 156.2, 152.0, 149.1, 140.5, 139.6, 139.5, 139.2, 129.1, 129.0, 128.7, 128.6, 128.4, 128.27, 128.25, 128.1, 128.0, 127.94, 127.90, 127.6, 126.9, 126.6, 120.9, 111.1, 109.5, 109.3, 86.9, 86.5, 85.1, 82.7, 76.0, 72.05, 72.01, 71.94, 71.87, 58.0, 16.6; IR (KBr) 3400, 3050, 2925, 1600, 1540, 1500, 1455, 1415, 1380, 1325, 1285, 1250, 1225, 1120, 1070, 1040, 1030, 810, 760, 740, 700 cm^{-1}; $[\alpha]^{22}_D$ –90° (*c* 1.0, 1,4-dioxane). Anal. Calcd for $C_{45}H_{44}O_7$: C, 77.56; H, 6.36. Found: C, 77.63; H, 6.29.

2-Iodo-3-methoxy-5-methylbenzoic acid (38). To a solution of benzyl alcohol **37**[7e] (3.52 g, 12.7 mmol) in pyridine (70 mL) was added a solution of *n*-Bu_4NMnO_4[36] (6.40 g, 17.7 mmol) in pyridine (70 mL) at room temperature over 50 min. This brown solution was stirred for 13.5 h and then poured into the mixture of crushed ice-concentrated HCl–$NaHSO_3$. The mixture was extracted with EtOAc, and the combined organic extracts were washed successively with 3 N HCl and brine and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a pale yellow crystalline solid, which was recrystallized from benzene–EtOAc to give benzoic acid **38** (3.35 g, 90.6%) as white needles: mp 209 °C (lit.[7h] mp 155–156 °C); ^1H NMR (acetone-d_6) δ 7.10 (d, 1 H, J = 1.1 Hz), 6.97 (d, 1 H, J = 1.1 Hz), 3.90 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 169.4, 160.0, 141.3, 141.0, 123.8, 115.3, 82.8, 57.5, 21.5; IR (KBr) 2940, 2620, 2340, 1695, 1590, 1445, 1400, 1310, 1280, 1250, 1220, 1175, 1060, 1015, 920, 900, 855, 780, 730 cm^{-1}. Anal. Calcd for $C_9H_9O_3I$: C, 37.01; H, 3.11. Found: C, 37.24; H, 3.07.

5-(Benzyloxy)-4-methoxy-8-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)-1-naphthyl 2-Iodo-3-methoxy-5-methylbenzoate (35). To a suspension of benzoic acid **38** (154 mg, 0.527 mmol) and one drop of *N,N*-dimethylformamide in CH_2Cl_2 (3 mL) was added a solution of oxalyl chloride (134 mg, 1.06 mmol) in CH_2Cl_2 (1 mL) at 0 °C. Immediately, the ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The resulting clear pale yellow solution was concentrated in vacuo to afford crude 2-iodo-3-methoxy-5-methylbenzoyl chloride (**39**) as a pale yellow crystalline solid. A solution of this crude acid chloride **39** in THF (2 mL) was added to a mixture of naphthol **34** (147 mg, 0.211 mmol) and *i*-Pr_2NEt (82 mg, 0.63 mmol) in THF (4.5 mL) at 0 °C. To this solution was added a catalytic amount of DMAP, and the reaction mixture was allowed to warm to room temperature. After the mixture was stirred for 2 h, *N,N*-dimethylethylenediamine (0.5 mL, 4.7 mmol) was added to this solution at 0 °C, and the stirring was continued for 10 min at room temperature. The mixture was diluted with Et_2O, washed successively with saturated aqueous $CuSO_4$, saturated aqueous Na_2SO_4, 1.5 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/CH_2Cl_2/Et_2O = 5/4/1) to afford naphthyl benzoate **35** (187 mg, 91.3%) as a pale yellow oil, which crystallized by concentrating from hexane–Et_2O as a pale yellow foam: mp 41–48 °C; R_f = 0.39 (hexane/CH_2Cl_2/Et_2O = 6/3/1), R_f = 0.56 (hexane/EtOAc = 7/3); ^1H NMR ($CDCl_3$) δ 7.98 (d, 1 H, J = 8.3 Hz), 7.59–7.62 (m, 2 H), 7.10–7.44 (m, 16 H), 7.04 (d, 1 H, J = 8.3 Hz), 6.96–6.99 (m, 2 H), 6.92 (d, 1 H, J = 8.3 Hz), 6.80–6.83 (m, 2 H), 6.41 (d, 1 H, J = 1.5 Hz), 5.78 (d, 1 H, J = 3.7 Hz), 5.24 (d, 1 H, J = 12.2 Hz), 5.20 (d, 1 H, J = 12.2 Hz), 4.69 (s, 2 H), 4.09 (d, 1 H, J = 3.7 Hz), 3.97 (s, 3 H), 3.93 (d, 1 H, J = 12.7 Hz), 3.89 (d, 1 H, J = 12.2 Hz), 3.87 (d, 1 H, J = 12.7 Hz), 3.84 (d, 1 H, J = 12.2 Hz), 3.79 (dq, 1 H, J_1 = J_2 = 6.3 Hz), 3.75 (dd, 1 H, J_1 = 6.3, J_2 = 4.8 Hz), 3.68 (d, 1 H, J = 4.8 Hz), 3.63 (s, 3 H), 2.22 (s, 3 H), 1.17 (d, 3 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 167.0, 158.5, 156.2, 156.0, 140.1, 140.0, 139.1, 138.3, 138.2, 137.6, 137.5, 129.0, 128.5, 128.3, 128.14, 128.09, 127.99, 127.95, 127.90, 127.7, 127.4, 127.22, 127.18, 127.0, 124.0, 123.5, 121.0, 119.6, 115.0, 109.4, 105.5, 86.7, 85.3, 83.5, 83.0, 81.3, 75.3, 71.9, 71.5, 70.8, 56.8, 56.5, 21.3, 16.2; IR (KBr) 3050, 2950, 2880, 1750, 1595, 1500, 1455, 1410, 1380, 1325, 1280, 1245, 1225, 1190, 1145, 1130, 1060, 1030, 1015, 740, 705 cm^{-1}; $[\alpha]^{23}_D$ –177° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{54}H_{51}O_9I$: C, 66.80; H, 5.29. Found: C, 66.98; H, 5.25.

1-(Benzyloxy)-10,12-dimethoxy-8-methyl-4-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (Gilvocarcin M Tetrabenzyl Ether) (36). A yellow suspension of naphthyl benzoate **35** (303 mg, 0.312 mmol), $(Ph_3P)_2PdCl_2$ (57 mg, 0.081 mmol, 26 mol %), and NaOAc (79 mg, 0.96 mmol) in *N,N*-dimethylacetamide (45 mL) was heated at 125 °C for 5 h. After the solution was cooled to room temperature, the resulting dark brown suspension was diluted with Et_2O, and the mixture was washed successively with 2 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 6/4) to afford gilvocarcin M tetrabenzyl ether (**36**) (235 mg, 89.3%) as a yellow oil, which crystallized by concentrating from hexane–Et_2O as a yellow foam: mp 37–45 °C; R_f = 0.35 (hexane/EtOAc = 7/3); ^1H NMR ($CDCl_3$) δ 8.45 (s, 1 H), 8.14 (d, 1 H, J = 8.3 Hz), 7.85 (s, 1 H), 7.60–7.63 (m, 2 H), 7.23–7.49 (m, 13 H), 7.16 (s, 1 H), 7.11 (d, 1 H, J = 8.3 Hz), 6.84–6.88 (m, 3 H), 6.71–6.74 (m, 2 H), 6.25 (d, 1 H, J = 3.4 Hz), 5.22 (s, 2 H), 5.11 (d, 1 H, J = 3.4 Hz), 4.92 (d, 1 H, J = 11.7 Hz), 4.77 (d, 1 H, J = 12.2 Hz), 4.74 (d, 1 H, J = 12.2 Hz), 4.53 (d, 1 H, J = 11.7 Hz), 4.20 (d, 1 H, J = 12.0 Hz), 4.12 (dd, 1 H, J_1 = 6.4, J_2 = 4.6 Hz), 4.07 (s, 3 H), ca. 4.07 (1 H, concealed in the singlet peak), 4.03 (d, 1 H, J = 12.0 Hz), 3.99 (s, 3 H), 3.94 (dq, 1 H, J_1 = J_2 = 6.4 Hz), 2.51 (s, 3 H), 1.30 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 160.4, 157.2, 154.8, 153.2, 141.5, 139.8, 139.2, 138.4, 138.1, 137.5, 129.2, 128.41, 128.38, 128.29, 128.25, 127.8, 127.7, 127.6, 127.5, 127.3, 127.09, 127.06, 126.1, 124.9, 122.4, 122.2, 122.1, 118.8, 118.1, 114.4, 110.4, 104.8, 86.4, 85.3, 82.4, 82.3, 75.3, 71.8, 71.7, 71.5, 71.3, 56.8, 56.3, 21.6, 16.3; IR (KBr) 2920, 2850, 1720, 1610, 1590, 1485, 1450, 1370, 1330, 1300, 1270, 1240, 1225, 1135, 1065, 1025, 960, 845, 785, 735, 700 cm^{-1}; $[\alpha]^{23}_D$ –220° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{54}H_{50}O_9$: C, 76.94; H, 5.98. Found: C, 76.83; H, 6.05.

4-(α-D-Fucofuranosyl)-1-hydroxy-10,12-dimethoxy-8-methyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (Gilvocarcin M) (1a). A suspension of tetrabenzyl ether **36** (36.3 mg, 43.1 μmol) and a catalytic amount of 10% Pd–C (19 mg) in MeOH (10 mL) and THF (2.5 mL) was stirred under H_2 (1 atm) at room temperature for 5 h. After changing the atmosphere to Ar, the mixture was filtered through a Celite pad (washed with CH_2Cl_2 and THF), and the solvent was removed in vacuo. The residue was washed with Et_2O several times on a funnel and well dried in vacuo to give gilvocarcin M (**1a**) (18.6 mg, 89.5%) as a yellow crystalline solid. Recrystallization from acetone–MeOH gave yellow needles: mp 246–249 °C (dec); ^1H NMR (4×10^{-3} M in DMSO-d_6) δ 9.71 (s, 1 H), 8.47 (s, 1 H), 8.05 (d, 1 H, J = 8.4 Hz), 7.78 (d, 1 H, J = 1.1 Hz), 7.51 (d, 1 H, J = 1.1 Hz), 6.93 (d, 1 H, J = 8.4 Hz), 6.19 (d, 1 H, J = 5.1 Hz), 5.10 (d, 1 H, J = 5.1 Hz), 4.83 (d, 1 H, J = 4.8 Hz), 4.65–4.70 (m, 1 H), 4.51 (d, 1 H, J = 7.0 Hz), 4.12 (s, 6 H), 3.82–3.89 (m, 2 H), 3.50 (dd, 1 H, J_1 = 5.5, J_2 = 4.4 Hz), 2.52 (s, 3 H), 1.24 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (2×10^{-2} M in DMSO-d_6) δ 159.7, 156.9, 152.6, 151.8, 141.9, 140.2, 129.0, 126.0, 123.7, 121.8, 121.1, 121.0, 118.9, 114.7, 113.0, 111.8, 101.5, 85.8, 80.8, 78.9, 78.7, 66.4, 56.6, 56.3, 21.1, 20.2; IR (KBr) 3420, 2940, 1680, 1615, 1590, 1450, 1430, 1375, 1350, 1305, 1250, 1200, 1135, 1070, 1050, 1005, 980, 790, 590 cm^{-1}; UV λ_{max} (MeOH) 244, 267, 275, 384 nm; $[\alpha]^{23}_D$ −208° (*c* 0.21, DMSO); HRMS *m/z* 482.1583 (482.1575 calcd for $C_{26}H_{26}O_9$, M$^+$). Anal. Calcd for $C_{26}H_{26}O_9 \cdot H_2O$: C, 62.39; H, 5.64. Found: C, 62.43; H, 5.35.

2-(Benzyloxy)-5-bromo-3-methoxybenzaldehyde (41). A suspension of 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**40**)[38] (20.0 g, 86.6 mmol), K_2CO_3 (35.9 g, 260 mmol), and $PhCH_2Br$ (15.4 mL, 130 mmol) in EtOH (1 L) was refluxed for 3 h. After being cooled to room temperature, the mixture was filtered through a Celite pad (washed with EtOAc). After removal of the solvent in vacuo, the residue was diluted with EtOAc, washed successively with brine, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 85/15 to 80/20) to afford benzyl ether **41** (24.4 g, 87.8%) as a white crystalline solid. Recrystallization from hexane gave white needles: mp 87–88 °C; R_f = 0.53 (hexane/EtOAc = 8/2), R_f = 0.53 (hexane/CH_2Cl_2 = 5/5); ^1H NMR ($CDCl_3$) δ 10.09 (s, 1 H), 7.48 (d, 1 H, J = 2.6 Hz), 7.30–7.39 (m, 5 H), 7.25 (d, 1 H, J = 2.6 Hz), 5.16 (s, 2 H), 3.94 (s, 3 H); IR (KBr) 3090, 2940, 2870, 1690, 1575, 1480, 1470, 1440, 1380, 1315, 1270, 1240, 1215, 1190, 1090, 960, 930, 910, 850, 760, 740, 700, 690, 580 cm^{-1}. Anal. Calcd for $C_{15}H_{13}O_3Br$: C, 56.10; H, 4.08. Found: C, 56.30; H, 4.14.

2-(Benzyloxy)-5-bromo-3-methoxybenzaldehyde Trimethylene Acetal (42). A solution of aldehyde **41** (22.0 g, 68.5 mmol), 1,3-propanediol (7.40 mL, 102 mmol), and a catalytic amount of $TsOH \cdot H_2O$ (261 mg, 1.37 mmol, 2 mol %) in benzene (440 mL) was refluxed for 1 h using a Dean–Stark apparatus for azeotropic removal of water. After being cooled to room temperature, the solution was diluted with EtOAc. The combined organic extracts were washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 85/15) to afford acetal **42** (25.9 g, 99.7%) as a white crystalline solid. Recrystallization from hexane–EtOAc gave white needles: mp 110–110.5 °C; R_f = 0.34 (hexane/CH_2Cl_2 = 5/5), R_f = 0.71 (hexane/EtOAc = 6/4); ^1H NMR ($CDCl_3$) δ 7.31–7.46 (m, 6 H), 7.03 (d, 1 H, J = 2.2 Hz), 5.68 (s, 1 H), 4.99 (s, 2 H), 4.14–4.18 (m, 2 H), 3.79–3.87 (m, 2 H), 3.85 (s, 3 H), 2.11–2.24 (m, 1 H), 1.34–1.39 (m, 1 H); IR (KBr) 2970, 2880, 1580, 1480, 1450, 1420, 1390, 1370, 1300, 1270, 1240, 1220, 1190, 1150, 1115, 1080, 1010, 1000, 970, 960, 915, 845, 750, 705 cm^{-1}. Anal. Calcd for $C_{18}H_{19}O_4Br$: C, 57.01; H, 5.05. Found: C, 56.71; H, 5.08.

2-(Benzyloxy)-5-(2-hydroxyethyl)-3-methoxybenzaldehyde Trimethylene Acetal (43). To a stirred solution of bromide **42** (10.0 g, 26.4 mmol) in THF (80 mL) was added *n*-BuLi (1.65 M hexane solution, 20.0 mL, 33.0 mmol) at −78 °C over 10 min. To the resulting white suspension was added a solution of ethylene oxide (20 mL, 395 mmol) in Et_2O (30 mL) at −78 °C. The mixture was warmed to 0 °C during 2 h to give a clear pale yellow solution, and the stirring was continued for 2 h. The reaction was stopped by adding pH 7 phosphate buffer, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/6 to 2/8) to afford alcohol **43** (7.40 g, 81.5%) as a white crystalline solid. Recrystallization from hexane–benzene gave colorless prisms: mp 101.5–102 °C; R_f = 0.24 (hexane/EtOAc = 4/6); ^1H NMR ($CDCl_3$) δ 7.46–7.49 (m, 2 H), 7.31–7.42 (m, 3 H), 7.08 (d, 1 H, J = 2.0 Hz), 6.81 (d, 1 H, J = 2.0 Hz), 5.75 (s, 1 H), 4.99 (s, 2 H), 4.15–4.20 (m, 2 H), 3.82–3.90 (m, 4 H), 3.87 (s, 3 H), 2.84 (t, 2 H, J = 6.6 Hz), 2.13–2.26 (m, 1 H), 1.58 (s, 1 H), 1.35–1.40 (m, 1 H); IR (KBr) 3450, 2930, 2880, 2850, 1600, 1490, 1470, 1450, 1430, 1400, 1370, 1320, 1270, 1240, 1220, 1150, 1110, 1075, 1050, 1035, 1020, 995, 945, 915, 890, 860, 850, 755, 705 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.77; H, 6.98.

2-(Benzyloxy)-3-methoxy-5-[2-(methoxymethoxy)ethyl]benzaldehyde Trimethylene Acetal (44). To a solution of alcohol **43** (4.99 g, 14.5 mmol) in CH_2Cl_2 (100 mL) was added a solution of *i*-Pr_2NEt (4.67 g, 36.1 mmol) in CH_2Cl_2 (5 mL) and (MOM)Cl (2.89 g, 35.9 mmol) in CH_2Cl_2 (5 mL) at 0 °C. Immediately, the ice bath was removed and the reaction mixture was stirred at room temperature for 15 h. The reaction was stopped by adding pH 7 phosphate buffer, and the mixture was extracted with EtOAc. 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 = 5/5) to afford MOM ether **44** (5.60 g, 99.5%) as a colorless oil: bp 220 °C, 0.15 mmHg; R_f = 0.41 (hexane/EtOAc = 6/4); ^1H NMR ($CDCl_3$) δ 7.46–7.49 (m, 2 H), 7.30–7.41 (m, 3 H), 7.08 (d, 1 H, J = 2.0 Hz), 6.82 (d, 1 H, J = 2.0 Hz), 5.74 (s, 1 H), 4.99 (s, 2 H), 4.63 (s, 2 H), 4.15–4.20 (m, 2 H), 3.81–3.89 (m, 2 H), 3.86 (s, 3 H), 3.76 (t, 2 H, J = 7.3 Hz), 3.33 (s, 3 H), 2.89 (t, 2 H, J = 7.3 Hz), 2.13–2.26 (m, 1 H), 1.34–1.39 (m, 1 H); IR (neat) 2950, 2850, 1595, 1490, 1460, 1395, 1375, 1330, 1310, 1275, 1235, 1220, 1150, 1110, 1080, 1030, 1015, 1000, 915, 860, 740, 700 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.93; H, 7.17.

2-Hydroxy-3-methoxy-5-[2-(methoxymethoxy)ethyl]benzaldehyde Trimethylene Acetal (45). Benzyl ether **44** (2.60 g, 6.69 mmol) in MeOH (110 mL) was stirred at room temperature in the presence of 10% Pd–C (3.0 g) and HCO_2NH_4 (2.08 g, 33.0 mmol) for 10 min. The reaction mixture was filtered through a Celite pad (washed with CH_2Cl_2) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 3/7 to 1/9) to give phenol **45** (2.08 g) as a colorless oil. Since this product was somewhat unstable, it was used in the next step immediately before complete removal of the solvent: R_f = 0.52 (hexane/EtOAc = 3/7); ^1H NMR ($CDCl_3$) δ 6.88 (d, 1 H, J = 2.0 Hz), 6.74 (d, 1 H, J = 2.0 Hz), 6.71 (s, 1 H), 5.76 (s, 1 H), 4.61 (s, 2 H), 4.25–4.30 (m, 2 H), 3.97–4.05 (m, 2 H), 3.86 (s, 3 H), 3.72 (t, 2 H, J = 7.3 Hz), 3.32 (s, 3 H), 2.83 (t, 2 H, J = 7.3 Hz), 2.19–2.32 (m, 1 H), 1.44–1.49 (m, 1 H); IR (neat) 3410, 2950, 2870, 1610, 1505, 1465, 1440, 1400, 1380, 1295, 1275, 1240, 1220, 1150, 1110, 1090, 1030, 990, 860, 810, 760 cm^{-1}; HRMS *m/z* 298.1432 (298.1415 calcd for $C_{15}H_{22}O_6$, M$^+$). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 59.96; H, 7.07.

2-(1,3-Dioxan-2-yl)-6-methoxy-4-[2-(methoxymethoxy)ethyl]phenyl Trifluoromethanesulfonate (46). To the phenol **45** (2.08 g), as obtained above, in CH_2Cl_2 (90 mL) was added a solution of *i*-Pr_2NEt (1.74 g, 13.5 mmol) in CH_2Cl_2 (10 mL) and Tf_2O (5.71 g, 20.2 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction was quenched by adding saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 6/4) to afford triflate **46** (2.59 g, 89.9%, two steps) as a colorless oil: R_f = 0.60 (hexane/EtOAc = 5/5); ^1H NMR ($CDCl_3$) δ 7.17 (d, 1 H, J = 1.8 Hz), 6.91 (d, 1 H, J = 1.8 Hz), 5.68 (s, 1 H), 4.61 (s, 2 H), 4.21–4.27 (m, 2 H), 3.94–4.02 (m, 2 H), 3.86 (s, 3 H), 3.76 (t, 2 H, J = 7.0 Hz), 3.29 (s, 3 H), 2.91 (t, 2 H, J = 7.0 Hz), 2.17–2.30 (m, 1 H), 1.41–1.46 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 150.7, 140.3, 134.6, 132.5, 119.3, 118.8 (q, J_{C-F} = 320.6 Hz), 114.1, 96.9, 96.5, 67.9, 67.5, 56.2, 55.3, 36.3, 25.6; IR (neat) 2950, 2860, 1600, 1485, 1465, 1415, 1380, 1350, 1335, 1320, 1280, 1210, 1175, 1130, 1080, 1020, 960, 915, 870, 740, 705, 620 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_8SF_3$: C, 44.65; H, 4.92. Found: C, 44.59; H, 4.72.

2-Formyl-6-methoxy-4-[2-(methoxymethoxy)ethyl]phenyl Trifluoromethanesulfonate (48). A solution of triflate **46** (4.27 g, 9.92 mmol) in THF (120 mL) and 8 N H_2SO_4 (90 mL) was heated at 50 °C for 2 h. After the solution was cooled to room temperature, brine was added and the mixture was extracted with EtOAc. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to afford crude **47** (4.02 g, R_f = 0.42 (hexane/EtOAc = 2/8)) as a colorless oil. Since this compound was unstable, it was used in the next step immediately without further purification.

The alcohol **47** (4.02 g), thus obtained, was dissolved in CH_2Cl_2 (80 mL), to which was added a solution of *i*-Pr_2NEt (2.85 g, 22.1 mmol) in CH_2Cl_2 (4 mL) and (MOM)Cl (1.64 g, 20.4 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 36 h. The reaction was stopped by adding pH 7 phosphate buffer, and the mixture was extracted with EtOAc. 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. The residue was purified by flash column chromatography (hexane/EtOAc = 5/5) to afford MOM ether **48** (3.50 g, 94.8%, two steps) as a colorless oil: R_f = 0.58 (hexane/EtOAc = 4/6), ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1 H), 7.41 (d, 1 H, J = 1.8 Hz), 7.21 (d, 1 H, J = 1.8 Hz), 4.61 (s, 2 H), 3.96 (s, 3 H), 3.80 (t, 2 H, J = 6.6 Hz), 3.28 (s, 3 H), 2.97 (t, 2 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 186.8, 151.5, 141.3, 137.9, 129.2, 121.3, 119.4, 118.7 (q, J_{C-F} = 320.6 Hz), 96.5, 67.4, 56.6, 55.3, 36.1; IR (neat) 2950, 2900, 1705, 1595, 1480, 1465, 1425, 1305, 1250, 1210, 1170, 1135, 960, 920, 870, 755, 735, 710, 610 cm^{-1}. Anal. Calcd for $C_{13}H_{15}O_7SF_3$: C, 41.94; H, 4.06. Found: C, 42.34; H, 3.71.

3-Methoxy-5-[2-(methoxymethoxy)ethyl]-2-[(Trifluoromethanesulfonyl)oxy]benzoic Acid (49). To a solution of aldehyde **48** (3.48 g, 9.35 mmol) and 2-methyl-2-butene (3 mL) in acetone (40 mL) was added an aqueous solution (40 mL) of $NaClO_2$ (6.82 g, 75.4 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (11.7 g, 75.0 mmol) at room temperature, and the stirring was continued for 30 min. The yellow reaction mixture was diluted with Et_2O, and 3 N HCl was added and extracted by Et_2O. The combined organic extracts were washed successively with brine, saturated aqueous $Na_2S_2O_3$, and brine and dried (Na_2SO_4). Removal of the solvent and drying in vacuo gave crude benzoic acid **49** (3.27 g, 90.1%) as a colorless oil, which crystallized on standing in a refrigerator as a white crystalline solid. This compound was used in the following esterification step without further purification.

For characterization purposes, a small portion of this product was quantitatively converted to the corresponding methyl ester **50** by treatment with CH_2N_2 in Et_2O, which exhibited following analytical data: colorless oil; bp 180 °C, 0.4 mmHg; R_f = 0.49 (hexane/EtOAc = 5/5); ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 1 H, J = 2.0 Hz), 7.10 (d, 1 H, J = 2.0 Hz), 4.62 (s, 2 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.79 (t, 2 H, J = 6.6 Hz), 3.28 (s, 3 H), 2.94 (t, 2 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 164.6, 151.5, 140.4, 136.1, 125.2, 123.4, 118.7 (q, J_{C-F} = 320.6 Hz), 117.6, 96.5, 67.5, 56.4, 55.3, 52.6, 36.1; IR (neat) 2960, 2900, 1735, 1600, 1470, 1430, 1350, 1330, 1270, 1250, 1220, 1140, 1070, 1040, 870, 790, 710, 605 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_8SF_3$: C, 41.79; H, 4.26. Found: C, 41.85; H, 4.18.

5-(Benzyloxy)-4-methoxy-8-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)-1-naphthyl 3-Methoxy-5-[2-(methoxymethoxy)ethyl]-2-[(trifluoromethanesulfonyl)oxy]benzoate (51). A mixed suspension of naphthol **34** (144 mg, 0.207 mmol), crude benzoic acid **49** (485 mg, ca. 1.25 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (239 mg, 1.25 mmol), and DMAP (111 mg, 0.909 mmol) in Et_2O (25 mL) was stirred at room temperature for 11 h. The reaction was stopped by adding water, and the mixture was 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. The residue was purified by flash column chromatography (hexane/EtOAc = 7/3) followed by PTLC (hexane/acetone = 7/3), affording ester **51** (182 mg, 82.5%) as a yellow oil: R_f = 0.59 (hexane/EtOAc = 5/5); ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1 H, J = 8.3 Hz), 7.59–7.61 (m, 2 H), 7.55 (d, 1 H, J = 2.0 Hz), 7.13–7.44 (m, 15 H), 7.02 (d, 1 H, J = 8.3 Hz), 6.98–7.00 (m, 2 H), 6.91 (d, 1 H, J = 8.3 Hz), 6.84–6.87 (m, 2 H), 6.81 (d, 1 H, J = 2.0 Hz), 5.81 (d, 1 H, J = 3.4 Hz), 5.23 (d, 1 H, J = 12.2 Hz), 5.19 (d, 1 H, J = 12.2 Hz), 4.67 (s, 2 H), 4.58 (s, 2 H), 4.10 (d, 1 H, J = 3.4 Hz), 4.05 (d, 1 H, J = 12.7 Hz), 3.99 (d, 1 H, J = 12.7 Hz), 3.97 (s, 3 H), 3.87 (d, 1 H, J = 12.2 Hz), 3.66–3.81 (m, 6 H), 3.65 (s, 3 H), 3.28 (s, 3 H), 2.84 (dt, 1 H, J_1 = 14.2, J_2 = 6.8 Hz), 2.78 (dt, 1 H, J_1 = 14.2, J_2 = 6.8 Hz), 1.13 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 163.6, 156.4, 156.0, 151.3, 140.6, 139.6, 139.0, 138.25, 138.18, 137.6, 136.2, 129.3, 128.4, 128.2, 128.02, 127.99, 127.84, 127.78, 127.7, 127.6, 127.3, 127.25, 127.16, 127.1, 127.0, 124.7, 124.0, 123.1, 121.4, 119.6, 118.8 (q, J_{C-F} = 321.3 Hz), 118.4, 109.3, 105.5, 96.5, 86.7, 85.5, 83.8, 81.0, 75.2, 72.1, 71.9, 71.4, 70.8, 67.4, 56.6, 56.0, 55.3, 35.9, 16.1; IR (neat) 3030, 2960, 2900, 1750, 1595, 1500, 1460, 1430, 1405, 1380, 1350, 1320, 1280, 1250, 1220, 1185, 1140, 1110, 1075, 1050, 1030, 920, 880, 815, 760, 705, 670, 605 cm^{-1}; $[\alpha]^{22}_D$ −141° (c 0.95, $CHCl_3$); HRFABMS m/z 1067.3580 (1067.3503 calcd for $C_{58}H_{58}O_{14}SF_3$, $M^+ + 1$).

1-(Benzyloxy)-10,12-dimethoxy-8-[2-(methoxymethoxy)ethyl]-4-(2,3,5-tri-*O*-benzyl-α-D-fucofuranosyl)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (52). A suspension of ester **51** (182 mg, 0.171 mmol), $(Ph_3P)_2PdCl_2$ (32 mg, 0.046 mmol, 27 mol %), and sodium pivalate (67.3 mg, 0.542 mmol) in *N*,*N*-dimethylacetamide (20 mL) was heated at 80 °C for 1 h. After the mixture was cooled to room temperature, the resulting dark brown suspension was diluted with Et_2O. The mixture was successively washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 55/45) to afford tetracyclic compound **52** (102 mg, 65.2%) as a yellow oil, and the starting material **51** (37.4 mg, 20.5%) was recovered. **52**: R_f = 0.37 (hexane/EtOAc = 5/5); ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1 H), 8.15 (d, 1 H, J = 8.5 Hz), 7.93 (d, 1 H, J = 1.0 Hz), 7.60–7.63 (m, 2 H), 7.25–7.49 (m, 14 H), 7.12 (d, 1 H, J = 8.5 Hz), 6.85–6.89 (m, 3 H), 6.71–6.74 (m, 2 H), 6.25 (d, 1 H, J = 3.4 Hz), 5.23 (s, 2 H), 5.12 (d, 1 H, J = 3.4 Hz), 4.92 (d, 1 H, J = 11.7 Hz), 4.77 (d, 1 H, J = 12.7 Hz), 4.74 (d, 1 H, J = 12.7 Hz), 4.65 (s, 2 H), 4.54 (d, 1 H, J = 11.7 Hz), 4.21 (d, 1 H, J = 12.2 Hz), 4.12 (dd, 1 H, J_1 =6.4, J_2 = 4.6 Hz), 4.10 (s, 3 H), 4.07 (d, 1 H, J = 4.6 Hz), 4.03 (d, 1 H, J = 12.2 Hz), 4.00 (s, 3 H), 3.93 (dq, 1 H, J_1 = J_2 = 6.4 Hz), 3.87 (t, 2 H, J = 6.6 Hz), 3.32 (s, 3 H), 3.06 (t, 2 H, J = 6.6 Hz), 1.30 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 160.3, 157.3, 154.9, 153.3, 141.7, 141.1, 139.2, 138.4, 138.1, 137.5, 129.3, 128.4, 128.3, 128.2, 127.8, 127.68, 127.66, 127.6, 127.5, 127.3, 127.1, 127.0, 126.2, 124.9, 122.9, 122.5, 122.1, 118.9, 118.0, 114.3, 110.6, 104.9, 96.5, 86.4, 85.3, 82.5, 82.3, 75.3, 71.8, 71.5, 71.3, 67.8, 56.9, 56.4, 55.3, 36.3, 16.3; IR (neat) 2950, 2870, 1725, 1610, 1590, 1500, 1490, 1450, 1370, 1340, 1320, 1300, 1270, 1250, 1230, 1140, 1110, 1070, 1030, 920, 850, 790, 740, 700 cm^1; $[\alpha]^{23}_D$ −206° (c 1.37, $CHCl_3$); HRFABMS m/z 917.3885 (917.3901 calcd for $C_{57}H_{57}O_{11}$, $M^+ + 1$).

1-Acetoxy-10,12-dimethoxy-8-[2-(methoxymethoxy)ethyl]-4-(2,3,5-tri-*O*-acetyl-α-D-fucofuranosyl)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (54). In the presence of Raney Ni catalyst, a solution of tetracycle **52** (41.8 mg, 45.6 μmol) in EtOH (10 mL) and Et_2O (2 mL) was stirred under H_2 (1 atm) at room temperature for 60 h. After the atmosphere was changed to Ar, the mixture was filtered through a Celite pad (washed with THF and CH_2Cl_2). The solvent was removed and dried in vacuo to give crude tetrol **53** as bright yellow crystalline solid. This compound was dissolved in pyridine (5 mL), to which was added Ac_2O (0.75 mL) and a catalytic amount of DMAP. After the mixture was stirred for 5 h at room temperature, the reaction was stopped by the addition of a small amount of water. The mixture was diluted with Et_2O and washed successively with 5% HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 2/8) to afford tetraacetate **54** (22.3 mg, 67.5%) as a pale yellow crystalline solid: mp 166.5–167.5 °C; R_f = 0.39 (hexane/EtOAc = 2/8), R_f = 0.37 (hexane/acetone = 6/4); ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1 H), 8.05 (d, 1 H, J = 8.3 Hz), 8.00 (d, 1 H, J = 1.5 Hz), 7.27 (d, 1 H, J = 1.5 Hz), 7.17 (d, 1 H, J = 8.3 Hz), 6.58 (d, 1 H, J = 3.2 Hz), 6.18 (dd, 1 H, J_1 = 3.2, J_2 = 1.0 Hz), 5.38 (dq, 1 H, J_1 = J_2 = 6.4 Hz), 5.18 (dd, 1 H, J_1 = 3.9, J_2 = 1.0 Hz), 4.65 (s, 2 H), 4.20 (dd, 1 H, J_1 = 6.4, J_2 = 3.9 Hz), 4.08 (s, 3 H), 3.99 (s, 3 H), 3.87 (t, 2 H, J = 6.6 Hz), 3.32 (s, 3 H), 3.06 (t, 2 H, J = 6.6 Hz), 2.38 (s, 3 H), 2.32 (s, 3 H), 2.14 (s, 3 H), 1.52 (s, 3 H), 1.43 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 170.50, 170.47, 169.8, 168.5, 160.2, 157.3, 151.0, 146.0, 141.7, 141.4, 129.9, 127.6, 124.3, 122.6, 122.5, 122.3, 120.4, 119.8, 118.2, 114.5, 104.9, 96.5, 83.4, 81.6, 78.9, 78.0, 69.8, 67.7, 56.4, 56.3, 55.3, 36.2, 21.3, 21.0, 20.9, 20.1, 16.4; IR (KBr) 2950, 1745, 1610, 1590, 1490, 1455, 1375, 1345, 1300, 1220, 1150, 1135, 1110, 1070, 1040, 920, 790, 600 cm^{-1}; $[\alpha]^{22}_D$ −165° (c 0.95, $CHCl_3$). Anal. Calcd for $C_{37}H_{40}O_{15}$: C, 61.32; H, 5.56. Found: C, 61.17; H, 5.32.

1-Acetoxy-8-(2-hydroxyethyl)-10,12-dimethoxy-4-(2,3,5-tri-*O*-acetyl-α-D-fucofuranosyl)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (55). To a solution of MOM ether **54** (48.5 mg, 66.9 μmol) in CH_2Cl_2 (4.5 mL) was added a solution of (TMS)Br (51.2 mg, 335 μmol) in CH_2Cl_2 (0.5 mL) at −78 °C. After 10 min, the reaction mixture was gradually warmed to −10 °C during 4 h, and the stirring was continued for 1 h at this temperature. The reaction was stopped by adding saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/acetone = 9/1) and PTLC (CH_2Cl_2/acetone = 8/2) to afford alcohol **55** (42.6 mg, 93.5%) as a pale yellow crystalline solid: mp 219–221 °C; R_f = 0.23 (EtOAc), R_f = 0.38 (EtOAc/acetone = 9/1), R_f = 0.36 (CH_2Cl_2/acetone = 8/2); ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 8.05 (d, 1 H, J = 8.1 Hz), 7.84 (d, 1 H, J = 1.2 Hz), 7.16 (d, 1 H, J = 8.1 Hz), 7.14 (d, 1 H, J = 1.2 Hz), 6.52 (d, 1 H, J = 3.2 Hz), 6.13 (d, 1 H, J = 3.2 Hz), 5.39 (dq, 1 H, J_1 = J_2 = 6.4 Hz), 5.15 (d, 1 H, J = 3.9 Hz), 4.22 (dd, 1 H, J_1 = 6.4, J_2 = 3.9 Hz), 3.92–3.96 (m, 5 H), 3.80 (s, 3 H), 2.93 (t, 2 H, J = 6.6 Hz), 2.39 (s, 3 H), 2.32 (s, 3 H), 2.20 (broad s, 1 H), 2.15 (s, 3 H), 1.51 (s, 3 H), 1.44 (d, 3 H, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 170.7, 170.5, 169.9, 168.6, 160.1, 157.3, 151.0, 146.1, 141.6, 141.3, 129.8, 127.6, 124.2, 122.3, 122.2, 122.1, 120.4, 119.8, 118.2, 114.5, 104.9, 83.4, 81.5, 79.0, 77.9, 69.8, 62.9, 56.2, 56.1, 39.0, 21.3, 21.1, 21.0, 20.1, 16.4; IR (KBr) 3520, 3180, 2950, 1740, 1610, 1590, 1560, 1490, 1470, 1450, 1370, 1340, 1300, 1220, 1150, 1130, 1110, 1070, 1040, 970, 910, 860, 790, 605, 590 cm^{-1}; $[\alpha]^{23}_{\mathrm{D}}$ −165° (c 0.62, $CHCl_3$); HRMS m/z 680.2101 (680.2102 calcd for $C_{35}H_{36}O_{14}$, M$^+$).

1-Acetoxy-10,12-dimethoxy-4-(2,3,5-tri-*O*-acetyl-α-D-fucofuranosyl)-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (Gilvocarcin V Tetraacetate) (57). To a solution of alcohol **55** (22.4 mg, 32.9 μmol) in THF (8 mL) was added *o*-nitrophenyl selenocyanate[46] (76.2 mg, 336 μmol) and *n*-Bu_3P (62.6 mg, 309 μmol) at room temperature. After the mixture was stirred for 30 min, TLC indicated the complete consumption of the starting material and a new spot appeared, corresponding most probably to selenide **56** ($R_f = 0.44$ (hexane/CH_2Cl_2/acetone = 5/3/2)). To this solution was added 35% aqueous H_2O_2 solution (0.4 mL) at 0 °C, and the ice bath was removed immediately. After being stirred for 1.5 h, the reaction mixture was diluted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/CH_2Cl_2/acetone = 5/3/2) to afford gilvocarcin V tetraacetate (**57**) (20.8 mg, 95.4%) as a yellow crystalline solid. Recrystallization from benzene–petroleum ether gave a yellow crystalline solid: mp 187–191 °C; $R_f = 0.47$ (hexane/EtOAc = 3/7), $R_f = 0.53$ (hexane/CH_2Cl_2/acetone = 5/3/2); ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1 H), 8.11 (d, 1 H, $J = 1.7$ Hz), 8.06 (d, 1 H, $J = 8.3$ Hz), 7.37 (d, 1 H, $J = 1.7$ Hz), 7.17 (d, 1 H, $J = 8.3$ Hz), 6.81 (dd, 1 H, $J_1 = 17.6$, $J_2 = 11.0$ Hz), 6.56 (d, 1 H, $J = 3.4$ Hz), 6.18 (dd, 1 H, $J_1 = 3.4$, $J_2 = 0.7$ Hz), 5.95 (d, 1 H, 17.6 Hz), 5.45 (d, 1 H, $J = 11.0$ Hz), 5.38 (dq, 1 H, $J_1 = J_2 = 6.6$ Hz), 5.18 (dd, 1 H, $J_1 = 3.9$, $J_2 = 0.7$ Hz), 4.20 (dd, 1 H, $J_1 = 6.6$, $J_2 = 3.9$ Hz), 4.08 (s, 3 H), 3.98 (s, 3 H), 2.38 (s, 3 H), 2.32 (s, 3 H), 2.14 (s, 3 H), 1.53 (s, 3 H), 1.43 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 170.50, 170.46, 169.8, 168.6, 160.1, 157.6, 151.1, 146.0, 142.0, 139.0, 135.3, 130.0, 127.7, 124.3, 123.8, 122.8, 120.6, 120.3, 120.0, 116.6, 114.5, 114.2, 104.8, 83.4, 81.6, 78.9, 78.0, 69.8, 56.34, 56.26, 21.3, 21.1, 20.9, 20.1, 16.4.; IR (KBr) 2950, 1745, 1610, 1450, 1375, 1340, 1305, 1230, 1135, 1080, 1045, 1020, 790 cm^{-1}; $[\alpha]^{22}_{\mathrm{D}}$ −183° (c 0.40, $CHCl_3$); HRMS m/z 662.2002 (662.1997 calcd for $C_{35}H_{34}O_{13}$, M$^+$).

4-(α-D-Fucofuranosyl)-1-hydroxy-10,12-dimethoxy-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (Gilvocarcin V) (1b). To a suspension of tetraacetate **57** (50.4 mg, 76.1 μmol) in MeOH (10 mL) was added a ca. 1.0 M solution of NaOMe in MeOH (0.15 mL) at room temperature. Stirring was continued for 23 h, during which time the reaction mixture turned to an orange suspension. The suspension was treated with AcOH (0.75 mL) and water (12 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 gilvocarcin V (**1b**) (26.7 mg, 71.0%) as yellow crystalline solid: mp 241–245 °C (dec); ^{1}H NMR (4×10^{-3} M in DMSO-d_6) δ 9.71 (s, 1 H), 8.48 (s, 1 H), 8.07 (d, 1 H, $J = 8.4$ Hz), 7.99 (s, 1 H), 7.76 (s, 1 H), 6.96 (dd, 1 H, $J_1 = 17.6$, $J_2 = 11.0$ Hz), 6.95 (d, 1 H, $J = 8.4$ Hz), 6.20 (d, 1 H, $J = 5.5$ Hz), 6.16 (d, 1 H, $J = 17.6$ Hz), 5.51 (d, 1 H, $J = 11.0$ Hz), 5.10 (d, 1 H, $J = 4.8$ Hz), 4.83 (d, 1 H, $J = 4.8$ Hz), 4.66–4.71 (m, 1 H), 4.51 (d, 1 H, $J = 6.6$ Hz), 4.18 (s, 3 H), 4.13 (s, 3 H), 3.82–3.90 (m, 2 H), 3.51 (dd, 1 H, $J_1 = 5.9$, $J_2 = 4.4$ Hz), 1.24 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR (1×10^{-2} M in DMSO-d_6) δ 159.5, 157.3, 152.6, 151.8, 142.3, 138.6, 135.2, 129.0, 126.1, 123.6, 122.9, 122.2, 119.0, 117.1, 114.8, 114.5, 112.8, 112.0, 101.4, 85.7, 80.7, 78.8, 78.6, 66.4, 56.7, 56.3, 20.1; IR (KBr) 3400, 2940, 1700, 1620, 1605, 1590, 1450, 1430, 1375, 1340, 1300, 1250, 1190, 1160, 1130, 1070, 1045, 1005, 975, 845, 790, 725, 595 cm^{-1}; UV $\lambda_{\max}$ (MeOH) 247, 287, 397 nm; $[\alpha]^{23}_{\mathrm{D}}$ −220° (c 0.22, DMSO); HRMS m/z 494.1562 (494.1578 calcd for $C_{27}H_{26}O_9$, M$^+$). Anal. Calcd for $C_{27}H_{26}O_9 \cdot H_2O$: C, 63.28; H, 5.51. Found: C, 63.32; H, 5.24.

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