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First Total Synthesis of BE-12406 A

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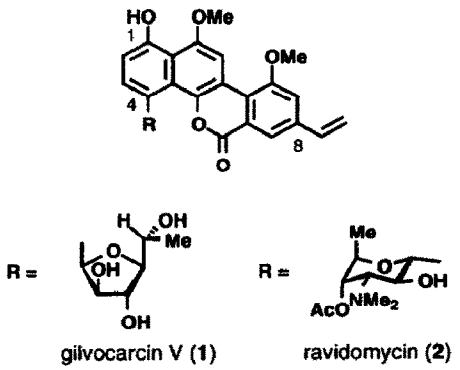
Abstract: A concise total synthesis of BE-12406 A (**3a**) was achieved. The key step was the selective *O*-glycosylation of naphthol **4** with L-rhamnopyranosyl fluoride **5**, employing Cp_2HfCl_2–$AgClO_4$ in fluorobenzene at –20 °C in the presence of a hindered base **9**, affording *O*-glycoside **8** in good yield.

Gilvocarcin V (**1**) and ravidomycin (**2**) represent a class of aryl *C*-glycoside antitumor antibiotics (Figure 1).[1] Their structures include two characteristic substituents on a benzonaphthopyranone skeleton, *i.e.*, the *C*-glycoside at C(4) and the vinyl group at C(8). The latter group is reportedly essential to the biological activities.[2] In connection with the total synthesis of **1**,[3] we were interested in the structures of BE-12406 A and B (**3a** and **3b**) which were recently isolated from the culture broth of *Streptomyces rutgersensis*.[4] These new antibiotics are structurally similar to **1** and **2**, but are distinct in that the sugar is attached as an *O*-glycoside rather than a *C*-glycoside. Also intriguing is that they show potent antitumor activities *in vivo* despite that the C(8) substituent is not a vinyl group.

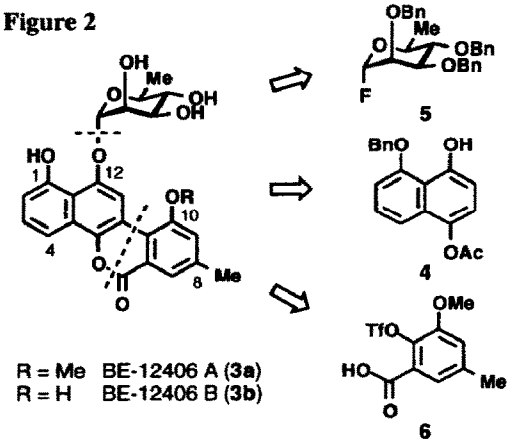
In this report, we wish to describe the first total synthesis of BE-12406 A (**3a**) based on the assembly of three readily available components, naphthol **4**,[5] L-rhamnopyranosyl fluoride **5**,[6] and benzoic acid **6**[7] (Figure 2). We chose a strategy to connect the sugar at the stage of naphthol **4** followed by construction of the aromatic moiety. We previously reported an effective method for rapid *O*-glycosylation of phenols by utilizing the combination of Cp_2HfCl_2–$AgClO_4$ as the activator of glycosyl fluoride.[8] Along these lines, coupling of naphthol **4** and glycosyl fluoride **5** was attempted, which turned out to be extremely difficult.

Figure 1



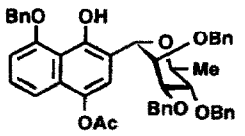
gilvocarcin V (**1**) ravidomycin (**2**)

Figure 2



R = Me BE-12406 A (**3a**)
R = H BE-12406 B (**3b**)

The initial attempt at the *O*-glycosylation of naphthol **4** with glycosyl fluoride **5** was done by using Cp_2HfCl_2–$AgClO_4$ (CH_2Cl_2, –78 °C, 10 min),[8] which rapidly provided a single product. However, the product was not the desired *O*-glycoside **8** but the *C*-glycoside **7α** (70% yield).[9,10] It is worth noting that the *C*-glycoside was solely the α-anomer, which completely anomerized to the β-anomer when the reaction was warmed up to 0 °C (67% yield).[9,10]

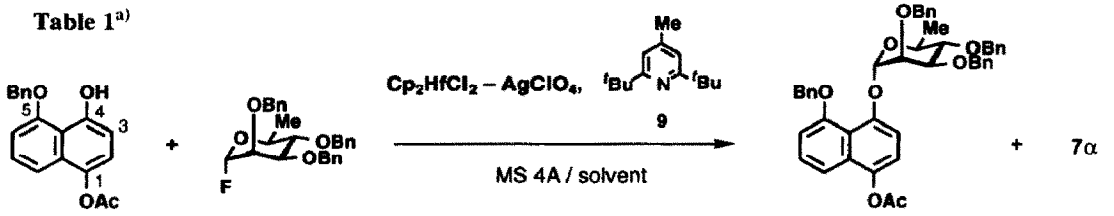


7α

We initially surmised that *C*-glycoside **7** is produced via the "*O*→*C*-glycoside rearrangement", that is, the in situ-conversion of the kinetically formed *O*-glycoside **8**.[11] However, following observations suggested that the *C*-glycoside **7** forms directly by the Friedel–Crafts reaction,[12] not by a two-stage process stated above. The tlc monitoring of the reaction showed no indication of the intermediacy of **8**. Low temperature quenching (–94 °C, 10 min) afforded *C*-glycoside **7α** (21%), the remaining naphthol **4** (74%), and none of the *O*-glycoside **8**. Use of the donor solvents was also ineffective: CH_3CN totally retarded the reaction, while Et_2O led to the formation of a complex mixture. Various further attempts proved fruitless, e.g., other Lewis acid promoters, such as $SnCl_2$–$AgClO_4$,[13a] TMSOTf,[13b] or BF_3•OEt_2,[13c] uniformly gave *C*-glycoside **7**.

We reasoned that the reacting OH group in **4** has a poor reactivity towards *O*-glycosylation due to the hydrogen-bonding to the peri-oxygen, and thus, the naphthol instead undergoes a direct aromatic substitution at the most reactive C(3)-position (see below). With a hope to weaken the hydrogen bond, thereby increasing the nucleophilicity of the hydroxyl oxygen, we attempted the reaction in the presence of a base.

Table 1[a)]



4 **5** **8**

Run	Solvent	Conditions	Yield/%[b)] 8[c)]	7α
1	CH_2Cl_2	–78 °C, 1.5 h	31	61
2	toluene	–20 °C → rt, 2.5 h	38	18
3	toluene–CH_2Cl_2 (4:1)	–78 °C → rt, 1.5 h	46	18
4	chlorobenzene	–20 °C, 1 h	56	24
5	fluorobenzene	–20 °C, 1 h	62	29

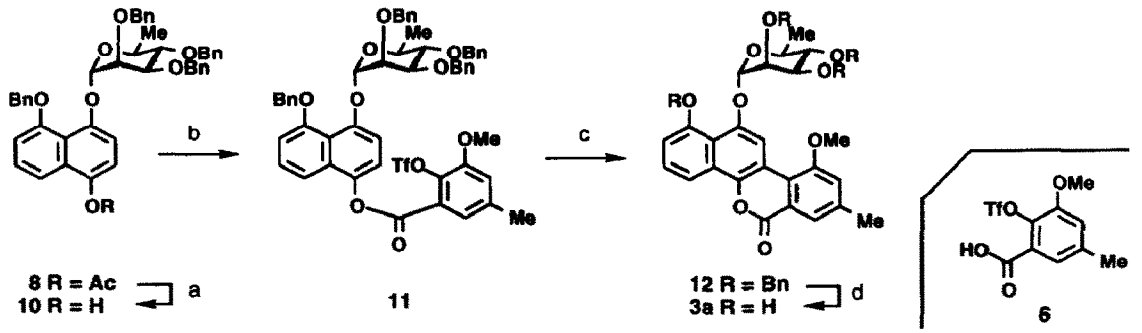
a) Molar ratio: **4** / **5** / Cp_2HfCl_2 / $AgClO_4$ / **9** = 1.1 / 1.0 / 1.5 / 3.0 / 2.5. b) Isolated yield based on **5**. c) In all runs only α-anomer of *O*-glycoside was obtained.

Most of the bases tested, such as tetramethylguanidine[14] and 2,6-lutidine, totally retarded the reaction, whereas 2,6-di-*tert*-butyl-4-methylpyridine (**9**)[15] nicely worked for this purpose. Thus, the reaction in the presence of **9** (2.5 equiv) gave the long sought *O*-glycoside **8**[9] for the first time, although the major product was still **7α** (Table 1, run 1). After considerable experimentation to improve the yield of **8**, we found that the

choice of the solvent is important. Use of an aromatic solvent tends to suppress the formation of *C*-glycoside **7**. For example, toluene provided **8** as the major product although the total yield was low presumably due to the poor solubility of **4** (run 2). Use of a mixed solvent of toluene–CH_2Cl_2, the latter used for dissolving **4**, slightly improved the the yield of **8** (run 3), and we eventually found that halogenated aromatic solvents (chlorobenzene and fluorobenzene) lead to acceptable yield of **8** (runs 4, 5).

Once *O*-glycoside **8** was in hand, completion of the synthesis was rather straightforward (Scheme 1). Saponification of acetate **8** followed by esterification with carboxylic acid **6**[7] using water-soluble carbodiimide (EDCI)[16] afforded ester **11**[9] in excellent yield. Construction of the tetracycle was nicely achieved via Pd catalysis.[5] Thus, heating of **11** with a catalytic amount of $(Ph_3P)_2PdCl_2$ in the presence of sodium pivalate and Hünig base in dimethylacetamide provided the tetracycle **12**[9] in 58% yield together with 32% recovery of **11**. This reaction is a triflate version of the Martin's ingenious approach[5] to benzonaphthopyranone skeleton (cf. the original approach makes use of aryl iodide), which offers two merits; 1) the ready accessibility of **6** (5 steps from vanillin)[7] and 2) the higher reactivity to allow the reaction at lower temperature (80 °C; cf. 120–130 °C for iodide).[3,11e] Finally, the four benzyl protecting groups of **12** were removed by hydrogenolysis to give BE-12406 A (**3a**) in 80% yield after recrystallization from MeOH {mp 238–244 °C (dec); $[\alpha]^{22}_D$ –89° (*c* 0.24, DMSO) [*lit.*[4] mp 238–243 °C (dec); $[\alpha]^{25}_D$ –89.3° (*c* 1.01, DMSO)[17]}.[9] All the data of synthetic **3a** (^{1}H- and ^{13}C-NMR, IR, MS, UV, and tlc mobility in several solvent systems) were in full accordance with those of the natural product by direct comparison.

Scheme 1[a]



[a]Key: (a) 0.25 N NaOH aq / 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) 32 mol% $(Ph_3P)_2PdCl_2$, ^{t}BuCOONa, ^{i}Pr$_2$NEt / DMA, 80 °C, 6 h (58%); (d) H_2, 10% Pd–C / MeOH–THF, room temperature, 19 h (80%).

In summary, the first total synthesis of BE-12406 A (**3a**) was achieved in a convergent and concise manner (5 steps, 28% overall yield from **5**). Further improvement of the glycosylation step and the synthesis of other derivatives are now in progress.

Acknowledgments: We are grateful to Dr. Hajime Morishima, Banyu Pharmaceutical Co., for an authentic sample of **3a**.

References and Notes

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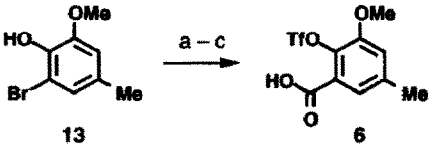
6 Fluoride **5** was prepared from 2,3,4-tri-*O*-benzyl-L-rhamnopyranose (Fréchet, J. M. J.; Baer, H. H. *Carbohydr. Res.* **1975**, *42*, 369–372.) by the Noyori procedure (68% pyr•$(HF)_x$/CH_2Cl_2, –20 °C, 2 h, 85%, α/β >95/5). Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747–1750. See also: Kamiya, S.; Esaki, S.; Ito, R. *Agric. Boil. Chem.* **1986**, *50*, 1321–1322.

7 Benzoic acid **6** was prepared from the known bromophenol **13** (Ueda, S. *Yakugaku Zasshi* **1962**, *82*, 714–718: *Chem. Abstr.* **1963**, *58*, 3419g.).



(a) CO, 3 mol% $(Ph_3P)_2PdCl_2$, 6 mol% 1,1'-bis(diphenylphosphino)ferrocene, MeOH, $^nBu_3N$ / DMF, 100 °C, 9 h (63%); (b) Tf_2O, DMAP / pyridine–CH_2Cl_2, 0 °C to room temperature, 1 h (98%); (c) conc. HCl / 1,4-dioxane, reflux, 60 h (72%).

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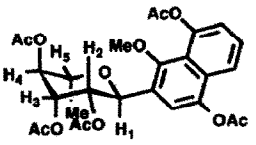
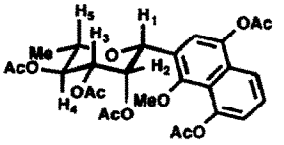
9 All compounds were fully characterized by ^{1}H-, ^{13}C-NMR, IR, HRMS and/or combustion analysis.

10 Stereochemical assignment of *C*-glycoside anomers, **7α** and **7β**, is based on 400 MHz ^{1}H-NMR spectroscopy of the pentaacetate derivatives **14α** and **14β**. Conversions (**7α→14α** and **7β→14b**) were done by the three steps, respectively: 1) NaH, Me_2SO_4 / THF, 0 °C to room temp., 2 h (77% and 72%, respectively); 2) H_2, 10% Pd–C / MeOH–THF, 1 h; 3) Ac_2O, DMAP / pyridine, 10 min (89% for both anomers, 2 steps). Note that **14α** adopts a flipped conformation as shown below.



14α ($^4C_1$ (L))
J_{1-2} = 8.1 Hz
J_{2-3} = 3.4 Hz
J_{3-4} = 5.1 Hz
J_{4-5} = 3.4 Hz
J_{5-6} = 6.8 Hz



14β ($^1C_4$ (L))
J_{1-2} = 1.1 Hz
J_{2-3} = 3.3 Hz
J_{3-4} = 9.5 Hz
J_{4-5} = 9.5 Hz
J_{5-6} = 6.2 Hz

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