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# Total synthesis of ravidomycin: revision of absolute and relative stereochemistry

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**Abstract**

First total synthesis of ravidomycin has been achieved, thereby establishing the relative and absolute stereostructure as **1**. 

We describe herein the first total synthesis of ravidomycin, an amino sugar congener of the gilvocarcin antibiotics with an enhanced antitumor activity.[1a–d] This synthesis has established the relative and absolute structure of this important compound as **1**, whereas the C(5′) epimer **1′** was originally proposed without specifying the absolute stereochemistry (Fig. 1).[1a]

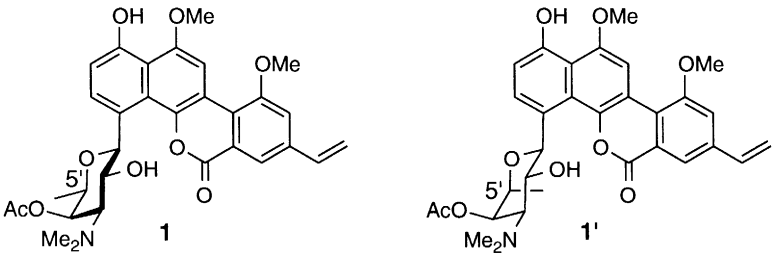


Fig. 1.

Scheme 1 shows a retrosynthesis, targeting **I** that is epimeric to the original proposal.[2] With a notion that some of the key steps used in our previous gilvocarcin synthesis,[3] e.g., the benzyne chemistry (vide infra), might be precluded by the presence of a dimethylamino function, we opted to introduce this group as late as possible. Thus, the neutral sugar **II** was envisaged as the precursor, and further disconnection by the [4+2] cycloaddition[4] led to an early synthetic intermediate **III**, where the problem is the selective access to the requisite β anomer. We could reasonably assume that the α and β anomers of **III** would

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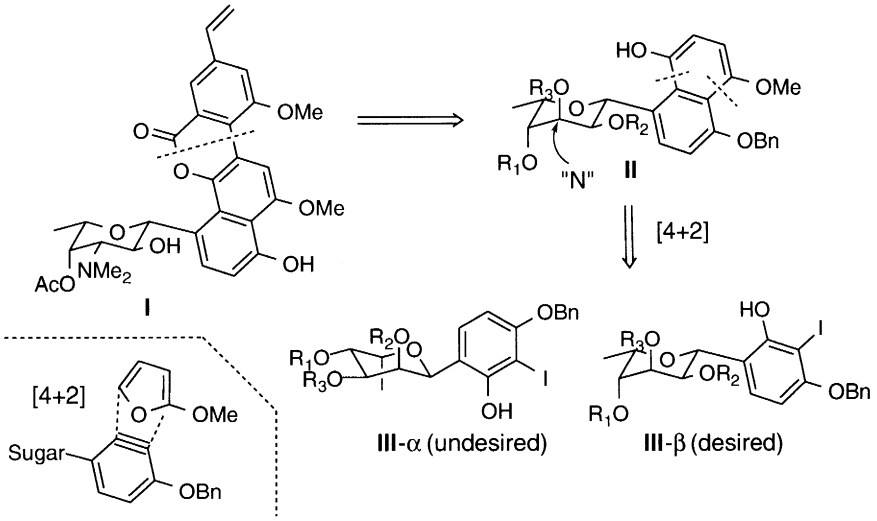
adopt the conformations shown below, respectively, given the strong tendency of aryl *C*-glycosides to dispose the aryl group equatorial. If so, there seemed to be no obvious preference between the anomers, because the other substituents are two equatorials and two axials, respectively. Thus, any additional factor(s) should be included that would encourage the formation of the β-anomer.




Scheme 1.

We envisaged the stereocontrol by exploiting the effect of large silyl protection that tends to favor the axial disposition (cf. the *gauche* interaction at the equatorial position; see Fig. 2).[5] Thus, the $^1C_4$ (L) conformation would be encouraged at the stage of the glycosyl donor **A**,[6] and if the derived oxonium species underwent the equatorial *C*-glycoside formation, the desired β anomer would be obtained. Even if a Lewis acid might induce an α/β equilibration through **B**, the α anomer would be unfavorable in such a case due to the *gauche* interaction (Fig. 3).[5a]

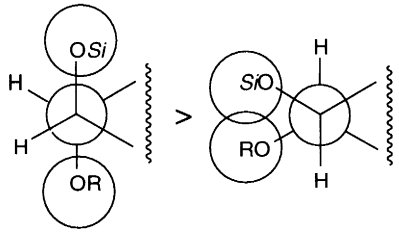



Fig. 2.

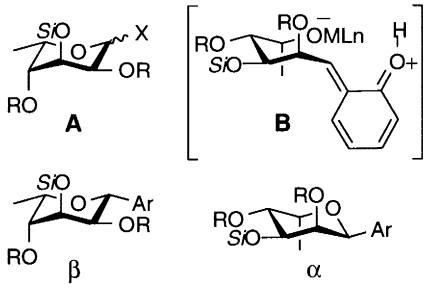
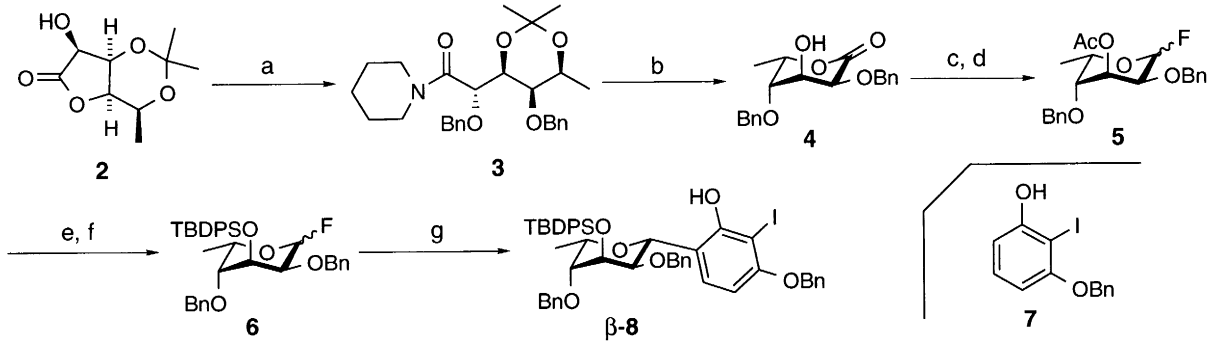



Fig. 3.

Along these lines, the silyl protected donor **6**[7] was prepared and its *C*-glycosidation was attempted (Scheme 2). With the absolute stereochemistry unknown, we deliberately chose an L-series sugar as **6**, which was prepared from the known lactone **2**.[8] A *t*-butyldiphenylsilyl group was introduced at C(3′) as the stereocontrolling factor. Indeed, the glycosyl donor **6** adopted the $^1C_4$ (L) conformation, and, pleasingly, the Hf-promoted reaction of **6** with the iodo phenol **7** gave β-**8** as the sole product in 83% yield.[6] Neither the α anomer nor the other conformers were detected.

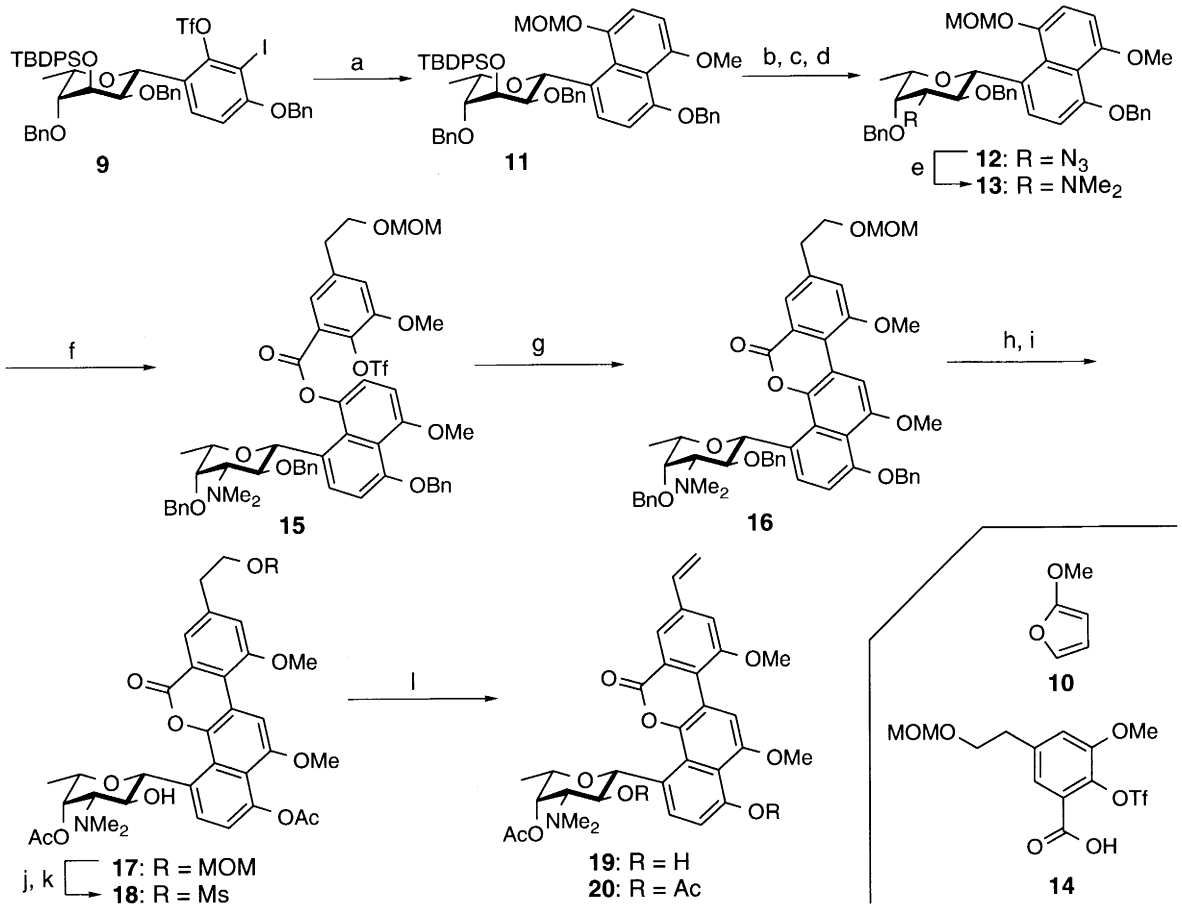



Scheme 2. Keys: (a) (i) piperidine, 60°C, 45 min; (ii) BnBr, NaH/THF, 20 h (two steps, 69%); (b) (i) 2 M $H_2SO_4$/MeOH, 5 h; (ii) $TsOH\cdot H_2O$/benzene, 10 h (two steps, 91%); (c) (i) DIBAL/toluene, −78°C, 15 min; (ii) $Ac_2O$, DMAP/pyr, 1 h (two steps, 91%); (d) $HF\cdot(pyr)_n/CH_2Cl_2$, 0°C, 15 min, 82%; (e) 0.2 M NaOH/MeOH, 0.5 h, 96%; (f) TBDPSCl, NaH/THF, 10 h, 97%; (g) **7**, $Cp_2HfCl_2$, $AgClO_4/CH_2Cl_2$, MS 4A, −78→−10°C, 1 h, 83%

With the aryl *C*-glycoside β-**8** in hand, the remaining tasks were the construction of the aromatic moiety and the introduction of the amino group at C(3′). The phenol **8** was converted to the triflate **9** ($Tf_2O$, *i*-$Pr_2NEt/CH_2Cl_2$, −78°C, 20 min, 88%), which was treated with *n*-BuLi in the presence of 2-methoxyfuran (**10**), where the benzyne-furan cycloaddition[4] proceeded in a regioselective manner to give, after protection of the phenol by an MOM group, the naphthyl glycoside **11** (Scheme 3). Installation of the azido group with inversion at C(3′) was achieved by a three-step protocol to give the azide **12**: desilylation, sulfonylation with *N*,*N*′-diimidazolylsulfonate,[9] and the reaction with $NaN_3$. Reduction of the azide with $LiAlH_4$ gave the corresponding *prim*-amine, which was converted to the dimethylamine **13** by reductive dimethylation.

After removal of the MOM protection in **13**, the phenol was acylated with the benzoic acid **14** to give the ester **15** ready for the biaryl bond formation. However, the attempted Pd-catalyzed reaction of **15** gave a disappointing result under the conditions used in our previous gilvocarcin synthesis.[3,10] The major issue was the catalyst deactivation, presumably due to the $Me_2N$-function, and related trials were all unfruitful. A breakthrough was provided by the Harayama conditions[11] using stoichiometric $Pd(OAc)_2$ coupled with $Bu_3P$ and DPPP [1,3-bis(diphenylphosphino)propane] in the presence of $Ag_2CO_3$, thereby quickly furnishing the tetracycle **16** in 70% yield. Catalytic hydrogenolysis under carefully controlled conditions enabled the selective and stepwise removal of two of the three benzyl groups, i.e., at the phenol (<5 min) and at the C(4′) OH (30 min), and subsequent acetylation and deprotection of the C(2′) OH gave the diacetate **17**. The MOM group in **17** was cleanly detached with TMSBr to give the corresponding diol, which was selectively mesylated to give the mesylate **18**. Finally, treatment of **18** with DBN effected: (1) the removal of the acetate protection for the phenol; and (2) the elimination of a $CH_3SO_3H$, to give the final product **19**.

All the spectroscopic data of **19** were identical with those of the natural product, thereby affirming the C(5′) stereochemistry of the sugar portion (cf. the original proposal[1a]). Furthermore, upon acetylation of **19**, the sign of $[\alpha]_D$ of the triacetate **20**, $[\alpha]_D^{31}$ −36 (*c* 0.045, $CHCl_3$), was opposite to that of




Scheme 3. Keys: (a) (i) *n*-BuLi, **10**/THF, −78°C, 0.5 h; (ii) MOMCl, NaH/DMF, 1 h (two steps, 77%); (b) CsF/DMF, 100°C, 3 h, 90%; (c) $(Imd)_2SO_2$, NaH/DMF, −40→0°C, 0.5 h, 93%; (d) $NaN_3$, $BnMe_3NCl$/DMF, 60°C, 3 h, 57%; (e) (i) $LiAlH_4$/THF, 0°C, 0.5 h; (ii) aq. HCHO, $NaBH_3(CN)/CH_3CN$, 0.5 h (two steps, 91%); (f) (i) 1 M HCl/acetone, reflux, 3 h; (ii) **14**, EDCI, DMAP/$CH_2Cl_2$, 2 h (two steps, 98%); (g) $Pd(OAc)_2$, DPPP, $Bu_3P$, $Ag_2CO_3$/DMF, 130°C, 15 min, 70%; (h) (i) $H_2$, Pd black, 2 M HCl/MeOH, 0.5 h; (ii) $Ac_2O$, DMAP/pyr, 45 min (two steps, 76%); (i) $H_2$, Pd black, 2 M HCl/MeOH, 3 h, 86%; (j) TMSBr/$CH_2Cl_2$, −78→−15°C, 45 min, 59%; (k) MsCl /pyr, −20°C, 0.5 h, quant.; (l) DBN/$CH_3CN$, 80°C, 0.5 h, 64%

the corresponding naturally derived triacetate, lit.[1b] $[\alpha]_D^{26}$ +33 (*c* 0.072, $CHCl_3$). Thus, the absolute stereochemistry of ravidomycin was proven to be the enantiomer of **19**, i.e., **1**.

## Acknowledgements

We thank Prof. J. A. Findlay, University of New Brunswick, for the copies of the $^1H$ NMR and IR spectra of ravidomycin, and also to Dr. Y. Lefebvre, Wyeth-Ayerst, for providing an authentic specimen of the natural product. We thank Prof. Harayama, Okayama University, for the kind information on the Pd-promoted coupling. This work was financially supported by the Ministry of Education, Science, Culture and Sports of Japanese Government [grant-in-aid for Scientific Research on Priority Area (08245103)].

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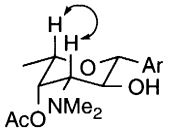
2. An NOE experiment gave a clue to the correct stereochemistry, where the NOE observed between C(3′) and C(5′) proton was conclusive. Also, personal communication from Dr. Y. Saito, Kyowa Hakko Co., is acknowledged.

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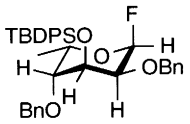
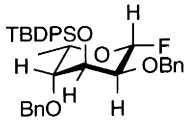
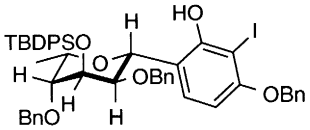
6. $^1$H NMR showed that each of the compounds, α-**6**, β-**6,** and **8**, adopts mostly the $^1C_4$ conformation.




α-**6** (α/β=3.9/1)




β-**6**




**8**

| | α-**6** | β-**6** | **8** |
|---|---|---|---|
| $J_{1'-2'}$ | 3.0 | 7.6 | 8.3 Hz |
| $J_{2'-3'}$ | 3.0 | 3.0 | ~0 Hz |
| $J_{3'-4'}$ | 3.0 | ~0 | 3.0 Hz |
| $J_{4'-5'}$ | 1.0 | 1.3 | ~0 Hz |
| $J_{5'-6'}$ | 6.6 | 6.6 | 6.3 Hz |

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