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Total synthesis of aryl *C*-glycoside antibiotics

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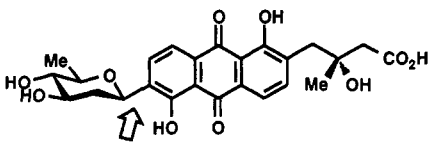
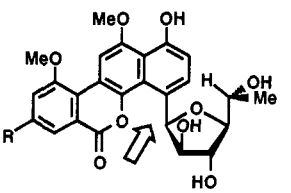
Abstract: An approach to the regio- and stereocontrolled synthesis of aryl *C*-glycoside antibiotics is described. The key reaction is the Lewis acid-mediated formation of aryl *O*-glycosides and its in situ conversion to *C*-glycosides (*O*→*C*-glycoside rearrangement). The utility of this reaction is demonstrated in the total syntheses of vineomycinone B_2 (**1**) and gilvocarcin M (**2**) and V (**3**). The latter synthesis established the absolute stereochemistry of the gilvocarcins.

Introduction

Aryl *C*-glycoside antibiotics constitute an emerging class of bioactive natural products, posing us challenging synthetic problems of both strategical and tactical levels (ref. 1). The most fundamental is the formation of the aryl *C*-glycoside bond in regio- and stereo-controlled manner. Toward this end, we have developed a promising approach by utilizing a key reaction, "*O*→*C*-glycoside rearrangement", which involves the Lewis acid-mediated formation of aryl *O*-glycoside and its in situ conversion to *C*-glycoside (eq. 1; ref. 2). Successful total syntheses of vineomycinone B_2 (**1**) and gilvocarcin M (**2**) and V (**3**) illustrate the versatility of this approach. Cp_2HfCl_2–$AgClO_4$, a glycosidation promoter we developed earlier (ref. 3), plays prominent roles in this context.



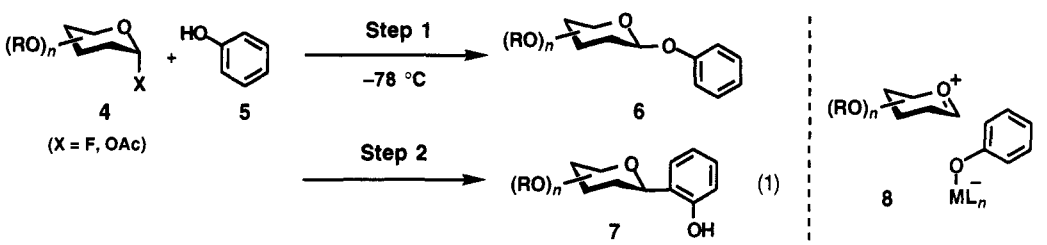
Vineomycinone B_2 (**1**)



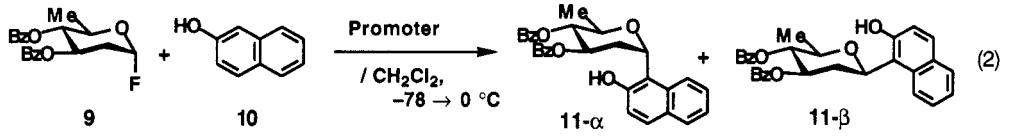
Gilvocarcin M (**2**): R = methyl
Gilvocarcin V (**3**): R = vinyl

Results and Discussion

1. *O*→*C*-Glycoside Rearrangement. The reaction profile is outlined in eq 1. In the presence of a Lewis acid, glycosyl fluoride **4** quickly reacts with phenol at low temperature (typically at –78 °C) to give *O*-glycoside **6** (Step 1). Phenol is quite reactive in such occasions, glycosyl fluoride can be replaced by less reactive glycosyl donors, such as glycosyl acetates (ref. 2b). By raising the temperature, *O*-glycoside **6** is gradually converted to the corresponding *C*-glycoside **7** (Step 2), which proceeds through an oxonium–phenolate ion pair as **8**, and recombination at an aromatic carbon leads to the formation of **7**. The most distinctive feature is the regioselectivity in that the aryl *C*-glycoside bond forms at the position *ortho* to the phenolic hydroxyl.



While step 1 proceeds easily, the latter step 2 is highly dependent on the Lewis acid utilized. A model reaction in the total synthesis of vineomycinone B_2 (**1**) clearly illustrates the aspects (eq 2). The BF_3•OEt_2-mediated reaction gives **11** in 70% yield along with unconverted *O*-glycoside, while the hafnocene couple drives the reaction to completion below 0 °C. The more significant difference is seen in the stereoselectivity. The α isomer is favored with BF_3•OEt_2, whereas the Hf-promoter leads to almost perfect β-selectivity (ref. 4).

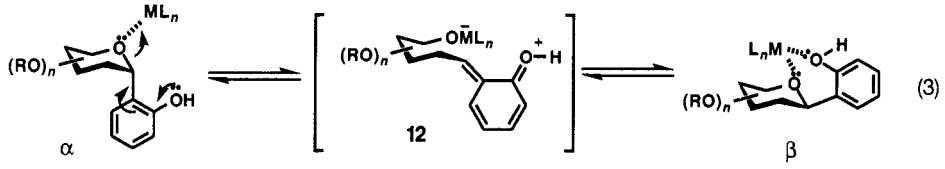


9 **10** **11-α** **11-β**

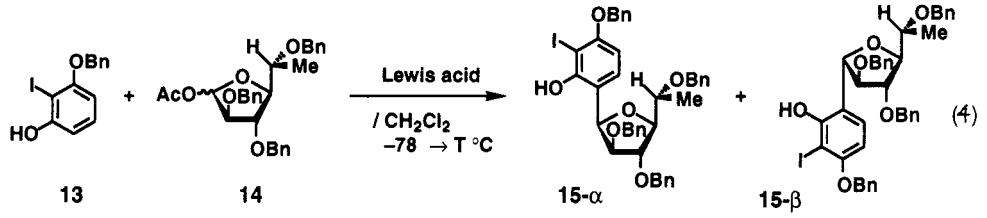
BF_3•OEt_2	70% yield[a)]	α/β = 3.4/1
Cp_2HfCl_2–$AgClO_4$	98% yield	α/β = <1/>99

a) *O*-Glycoside was obtained in 28% yield.

The contrast in the stereoselectivity is accounted by considering the existence of an additional step, i.e. the α→β-anomerization, which is better promoted by the hafnocene complex. Indeed, **11**-α undergoes anomerization upon treatment with the Hf-reagent to give more stable **11**-β. The anomerization proceeds through the Lewis acid mediated generation of quinone methide species as **12**, and the ring opening-reclosure drives the system to the thermodynamic control (eq 3). It should be noted that the coordination effect is responsible, at least partly, for determining the equilibrium point as suggested by the following example.

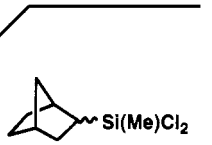


The reaction of phenol **13** and glycosyl acetate **14** was studied in detail as the key step in the total synthesis of the gilvocarcins (*vide infra*). The most challenging issue is the stereoselective formation of the apparently unfavorably disposed *C*-glycoside linkage, 1,2-cis and 1,4-cis. In addition to the challenge in the kinetic selectivity, the anomerization again complicates the problem.



13 **14** **15-α** **15-β**

Run	Lewis acid	T/°C	Yield/%	α / β
1	$SnCl_4$	−20	67	2.6 / 1
2	$SnCl_4$	0	75	1 / 2.5
3	$SnCl_4$–$AgClO_4$	−40	60	5.1 / 1
4	$SnCl_4$–$AgClO_4$	−20	69	1 / 58
5	Cp_2HfCl_2–$AgClO_4$	−20	86	8.2 / 1
6	Cp_2HfCl_2–$AgClO_4$	+25	88	7 / 1



16

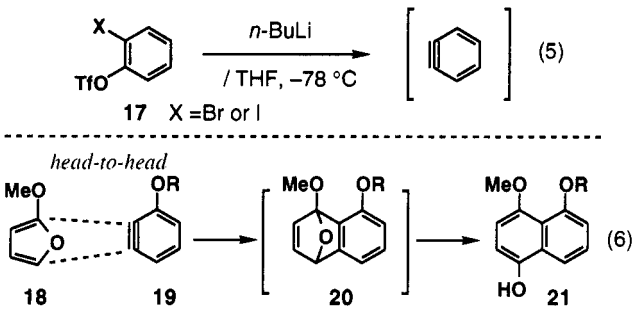
$SnCl_4$ gives **15** slightly rich in the α-isomer at the final temperature of −20 °C (run 1), whereas β-**15** becomes dominant at 0 °C (run 2). The anomerization is even more impressive by the co-addition of $AgClO_4$, which occurs at lower temperature, and impressively high β-selectivity results at −20 °C (runs 3, 4). In sharp contrast, the hafnocene combination turned out to give the desired α-anomer with 8/1 selectivity at −20 °C (run 5), the anomerization was sluggish in this particular case, holding a 7/1 level of α-selectivity even after the warm-up to room temperature (run 6).

These results suggest that the anomeric composition reflects the stability difference of the α- and β-anomers *coordinated to the Lewis acid rather than their free forms.* $SnCl_4$–$AgClO_4$ not only promotes

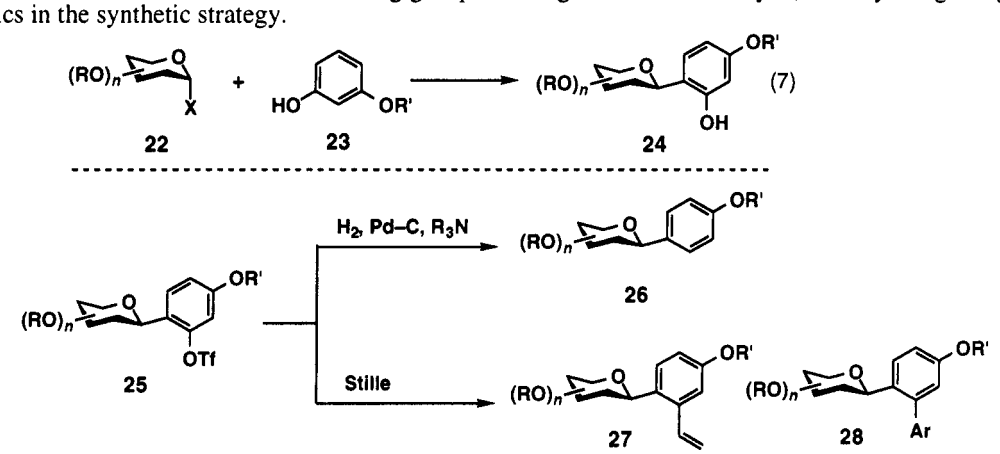
anomerization via quinone methide but also contributes to accumulate the β-anomer by complexation, although the precise nature of the coordination state is not clear. Variation of the center metal, ligands, and the coordination states endows Lewis acids with greatly different characters in terms of the ability to ease the anomerization and also the fixing effect. The latter effect may also be operative to fix the kinetically formed α anomer in the Hf-promoted cases. More recently, we found that silicon behaves as an "α-selective center metal", and in particular, an exotic organosilane **16**, in combination with $AgClO_4$, leads to an excellent α-selectivity (α/β = 26/1).

2. Total Synthesis of the Gilvocarcins. The gilvocarcins and related compounds share a tetracyclic nucleus to which rare sugars are attached as a *C*-glycoside. Three congeners are present which differ in the C(8) substituent, methyl, vinyl and ethyl) Among these, **3** has attracted attention by its remarkable antitumor activity and exceptionally low toxicity. The vinyl group is essential to the biological activities, and its DNA photobiology has been studied. These compounds have stimulated synthetic interest by their significant pharmacological potential and also by the challenge presented by unusual *C*-glycoside structures linked to the highly functionalized aromatics. The strategies and tactics which enabled the first total synthesis of the gilvocarcins are described in the following.

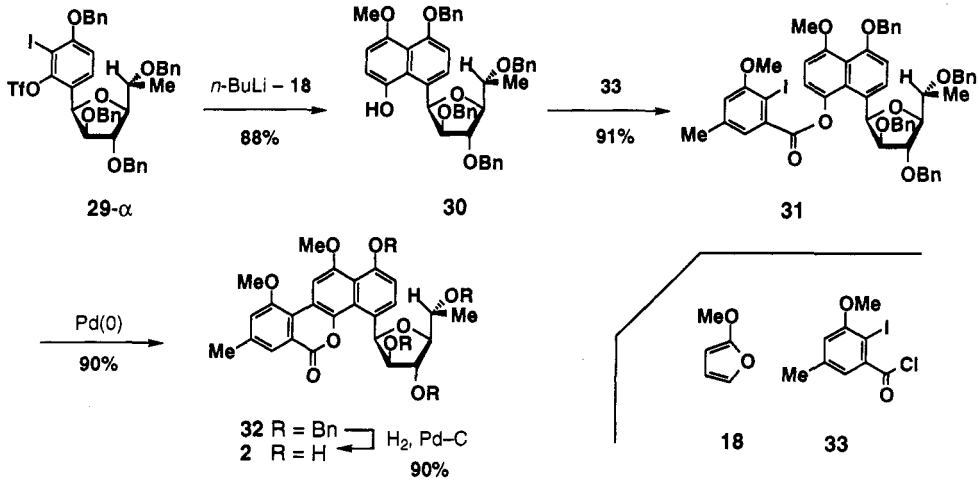
Tactics 1. Regioselective Benzyne–Furan Cycloaddition. A benzyne–furan cycloaddition process (eq 6) works well for regioselective construction of the aromatic skeleton (ref. 5). Two points are notable. (1) *o*-Haloaryl triflate **17** serves as an excellent benzyne precursor via treatment with *n*-BuLi at low temperature (eq 5). Quickness of halogen–lithium exchange matches the super laving ability of the neighboring triflate to allow the rapid and quantitative generation of benzynes. (2) In the cycloaddition with 2-methoxyfuran (**18**), the alkoxy substituent in **19** cleanly directs the regiochemistry (*head-to-head*) to open a direct access to naphthol **21** in which all three hydroxyls are suitably differentiated (eq 6).



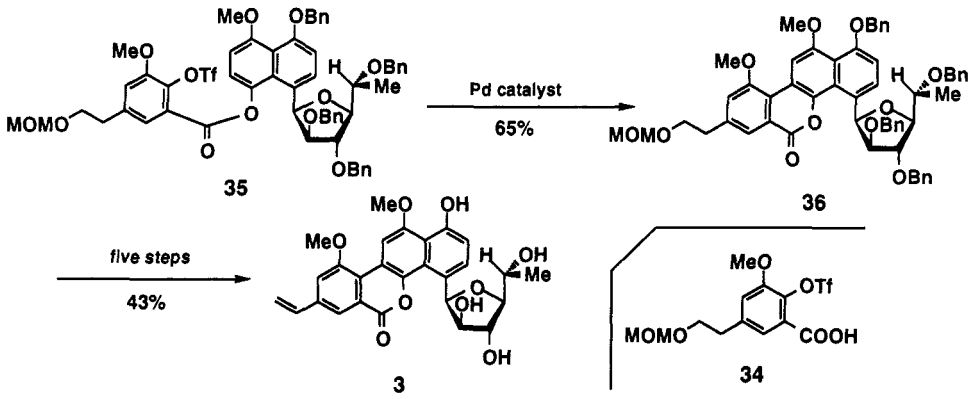
Tactics 2. Regiocontrolled Aryl *C*-Glycoside Formation. The "ortho selectivity" of *O*→*C* rearrangement holds for mono-protected resorcinol **23** to deliver *C*-glycoside **24** with *the additional oxygen functionality at the para position* (eq 7). The derived triflate **25** then serves as a versatile precursor for various aryl *C*-glycosides. For example, hydrogenolysis gives the deoxygenated product **26** having a *para*-oxygen function. Stille coupling, using organotin reagents, enables the preparation of elaborated aryl *C*-glycosides, such as **27** and **28** (ref. 6). In the execution of the total synthesis, this triflate serves also as an excellent leaving group for the generation of benzyne, thereby integrating both tactics in the synthetic strategy.



The gilvocarcins have been successfully synthesized via the strategy and tactics stated above. The synthesis served to establish the absolute stereochemistry of the natural product (ref. 7a). The total synthesis of the natural enantiomer of gilvocarcin M (**2**) is illustrated below.



Gilvocarcin V (**3**) was also synthesized via virtually the same synthetic scheme, starting with the acylation of the above naphthol **30** with a benzoic acid derivative **34** armed with a latent vinyl group.



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