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Semi-pinacol strategy for constructing B-ring of pradimicin–benanomicin antibiotics

Ken Ohmori, Mitsuru Kitamura,† Yuji Ishikawa, Hirohisa Kato, Mami Oorui and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, and CREST, Japan Science and Technology Corporation (JST), O-okayama, Meguro-ku, Tokyo 152-8551, Japan

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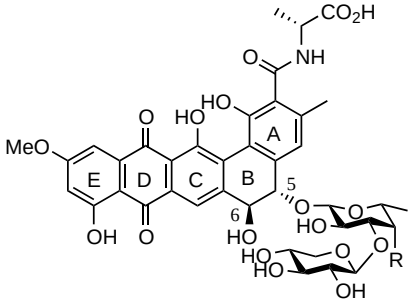
Abstract—Semi-pinacol cyclization of compound **8**, having an acetal and an aldehyde substituent, was achieved by employing SmI_2 and $BF_3{\cdot}OEt_2$, leading to the highly stereoselective formation of cyclized product **9**. The vicinal diol in **9** is discriminated, so as to allow selective glycosylation for the synthesis of pradimicin–benanomicin antibiotics.

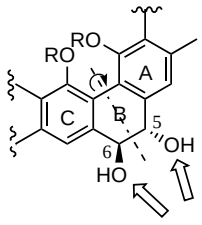
In our continuing synthetic study directed toward the pradimicin–benanomicin antibiotics (e.g. **1** and **2**),[1] we have completed the synthesis of the aglycon moiety,[2] and are currently focusing on the introduction of the sugar moiety. The obvious problem is the discrimination of the C(5)/C(6) hydroxyls, which is difficult due to the *pseudo* C_2-symmetrical nature of the diol. All attempts at direct glycosylation or masking one of these hydroxyls resulted in virtually no selectivity.[3]

At this juncture, an idea occurred to us that could be termed *semi-pinacol cyclization strategy*. Our previous approach to the B-ring construction was the pinacol cyclization of 2,2′-biaryldicarbaldehyde **I**, which afforded *trans*-diol **II** in high yield and stereoselectivity.[2a] If such a reductive cyclization was possible for *aldehyde–acetal* **III**, direct access to compound **IV** with the vicinal diol already discriminated would result (Scheme 1). Although several examples for such acetal–aldehyde coupling have been reported for *intermolecular* cases,[4] the *intramolecular* version is unprecedented to our knowledge.

We had a notion that realization of such 'semi-pinacol cyclization' would require careful choice of the reagent combinations and/or the reaction conditions, since the timing would be critical for generation of the oxocarbenium intermediate (**III**→**V**), and net two-electron reduction. Another requirement was the *trans*-stereoselectivity. In this communication, we wish to describe the successful development of a workable protocol.



1: Pradimicin A (R = N(Me)H)
2: Benanomicin A (R = OH)



pseudo C_2 symmetry

Keywords: pradimicin; benanomicin; pinacol; samarium diiodide.

* Corresponding author. Tel.: +81-3-5734-2228; fax: +81-3-5734-2228; e-mail: ksuzuki@chem.titech.ac.jp

† Present address: Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo, Japan.

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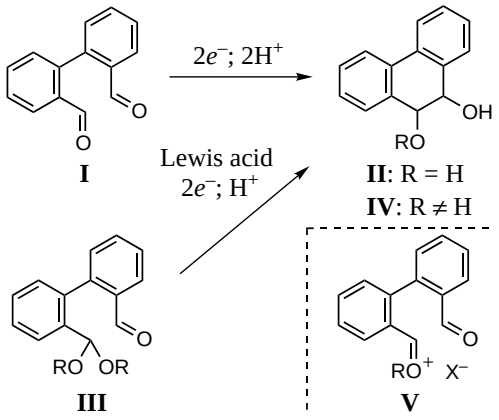
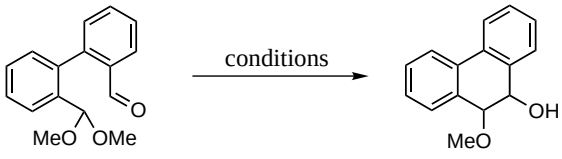


Scheme 1.

For the initial feasibility study, we employed compound **3** as a model substrate, which was treated with various reductants with/without an additional Lewis acid to activate the acetal (Table 1). Upon treatment of **3** with a low-valent titanium species generated from $TiCl_4$ and Zn,[5] the only detectable product was the dimeric 1,2-diol in 64% yield, suggesting that the acetal was not activated by $ZnCl_2$, generated in situ (run 1). Further attempts with various low-valent metal species, $TiCl_4/LiAlH_4$,[6] Cp_2TiCl_2/Zn,[7] and SmI_2,[8] gave no desired product, giving only a complex mixture of unidentified products (runs 2–4).

The initial clue for the successful reductive cyclization was provided by SmI_2 in the combination with $BF_3{\cdot}OEt_2$,[9] giving the cyclization product **4** in high stereoselectivity (*trans*/*cis* = 96/4), although the yield was low (run 5). High stereoselectivity was also observed with $NbCl_3(dme)$,[10] where again the chemical yield remained low (run 6). On the other hand, satisfactory yield was obtained by employing a low-valent vanadium, $VCl_3(thf)_3/Zn$ (run 7).[4b,11] However, the stereoselectivity was only modest (*trans*/*cis* = 75/25).

Table 1.



3 **4**

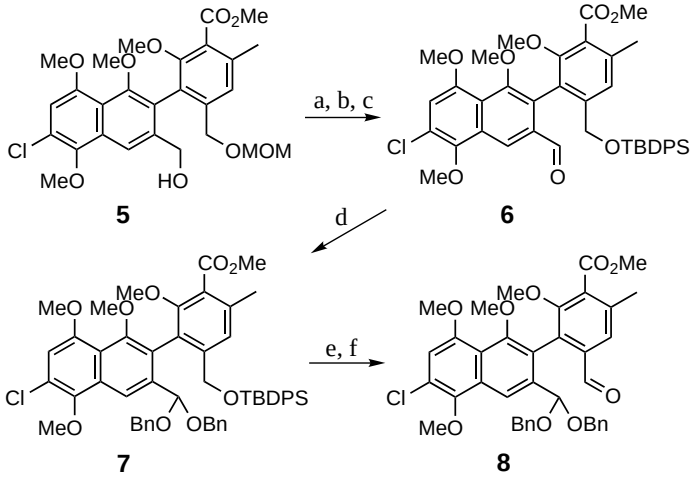
Run	Conditions[a]	Yield (%)	*trans*/*cis*
1	$TiCl_4/Zn$	–[c]	–
2	$TiCl_4/LiAlH_4$	–[d]	–
3	Cp_2TiCl_2/Zn	–[d]	–
4	SmI_2	–[d]	–
5	SmI_2, $BF_3{\cdot}OEt_2$	14	96/4
6	$NbCl_3(dme)$[b]	22	90/10
7	$VCl_3(thf)_3/Zn$[b]	78	75/25

[a] In THF at 0°C, 30 min.
[b] In CH_2Cl_2 at 0°C, 30 min.
[c] Dimeric 1,2-diol (64%).
[d] Complex mixture.

With these preliminary results in hand, we proceeded to the more elaborated cyclization precursor **8** relevant to the total synthesis.

Scheme 2 shows the preparation of aldehyde–acetal **8** from alcohol **5** that was used as an intermediate in our previous aglycon synthesis.[2b] After oxidation of **5** to the corresponding aldehyde, the MOM protecting group was replaced by a *t*-butyldiphenylsilyl (TBDPS) group to give **6** in 82% yield. Acetalization of **6** with benzyl trimethylsilyl ether in the presence of catalytic TMSOTf[12] gave acetal **7**, and subsequent detachment of the silyl group and oxidation afforded aldehyde–acetal **8**, which was subjected to the cyclization study.

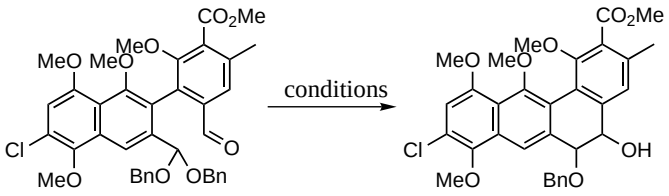
Cyclization of **8** was attempted with various reductants (Table 2). In contrast to the case of **3**, no reaction occurred with $TiCl_4/Zn$, suggesting deactivation of the Lewis acid by basic function in **8** (run 1, cf. run 1, Table 1). Increased sterics around the reaction site in **8** might



5 **6** **7** **8**

Scheme 2. *Reagents and conditions*: (a) MnO_2, CH_2Cl_2 (82%); (b) 6 M HCl aq., DME (1:2), 40°C (quant.); (c) TBDPSCl, imidazole, DMF (quant.); (d) TMSOBn, TMSOTf (96%); (e) *n*-Bu_4NF, THF (97%); (f) MnO_2, CH_2Cl_2 (95%).

Table 2.



8 **9**

Run	Conditions[a]	Yield (%)	*trans*/*cis*
1	$TiCl_4$/Zn	No reaction	–
2	CeI_2	–[c]	–
3	$VCl_3(thf)_3$/Zn[b]	71	50/50
4	SmI_2, $BF_3{\cdot}OEt_2$	81	>99/<1
5	SmI_2, CF_3CO_2H	26[d]	>99/<1
6	SmI_2, Ti(O*i*-Pr)$_4$	No reaction	–
7	SmI_2	37[e]	>99/<1

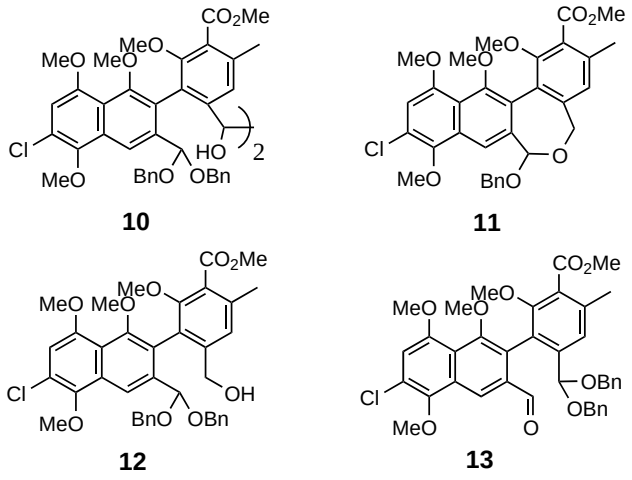
[a] In THF at 0°C, 30 min.
[b] In CH_2Cl_2 at 0°C, 30 min.
[c] Alcohol **12** (41%).
[d] Byproduct **11** (37%).
[e] Recovery of **8** (25%) and dimeric 1,2-diol **10** (18%).

also be relevant. CeI_2[13] only effected reduction of the aldehyde (run 2). $VCl_3(thf)_3$/Zn again effected the cyclization to give the product **9** in 71% yield, albeit as a 1:1 diastereomer mixture (run 3).

We were pleased, however, to find the best, and only reaction conditions to effect the stereoselective cyclization of **8**. Use of SmI_2 and $BF_3{\cdot}OEt_2$ in THF gave **9** in 81% yield with perfect *trans*-selectivity (run 4).[14] It was fortunate that the reaction proceeded much more smoothly for this substrate **8** than the model substrate **3**,[15] due presumably to moderation of the Lewis acidity appropriate for activation of the acetal.

The viability of this semi-pinacol approach had a narrow window in terms of the reaction conditions, since a slight change in the conditions led to side reactions, such as reduction or dimerization. Use of SmI_2 and trifluoroacetic acid[9] led to the formation of byproduct **11** via reduction of an aldehyde followed by transacetalization. Only a small amount of **9** was obtained, albeit with full *trans*-selectivity (run 5). In case when Ti(O*i*-Pr)$_4$ was used as an additive, the starting material was recovered (run 6),[16] whereas the use of SmI_2 in the absence of additives yielded *trans*-product **9** (37%) accompanied by the dimeric product **10** (18%) and 25% recovery of the starting material (run 7).

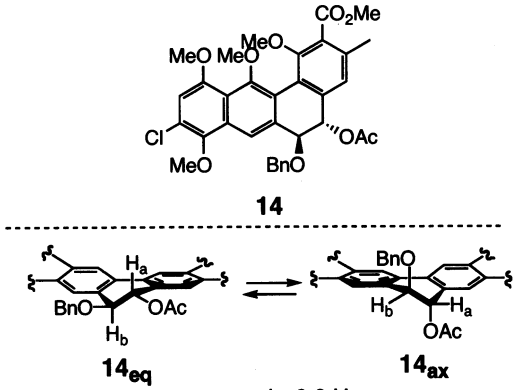
In any event, a nice access was established to the key compound **9** for the total synthesis of the pradimicin-class antibiotics, to which our current attention is focused. At this stage, behaviors of the cyclized product **9** and its derivatives are worth noting. As noted previously,[2a,17] the *pseudo*-rotation around the biaryl axis gives rise to a diequatorial conformer and its diaxial counterpart. The problem is the height of the rotational barrier and the point of equilibrium, since the reactivity to the glycosylation is conformer dependent.[18]



10 **11**

12 **13**

Fig. 1 shows the variable temperature ^{1}H NMR for acetate **14**. Their interconversion is slow judging from two doublets at low temperature (–40°C), assignable to **14**$_{eq}$



14

14$_{eq}$ **14**$_{ax}$

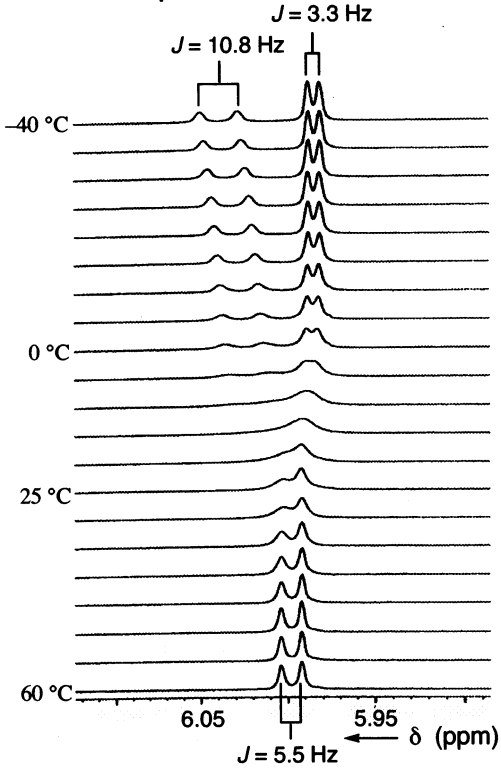


Figure 1. Variable-temperature NMR spectrum of H_a in **14** (500 MHz, $CDCl_3$, sealed tube).

($J=10.8$ Hz) and $\mathbf{14}_{ax}$ ($J=3.3$ Hz). The ratio of $\mathbf{14}_{eq}$ and $\mathbf{14}_{ax}$ was 31/69. Upon warming, these peaks became closer with broadening, went through coalescence, and further warming (60°C) led to a sharp doublet ($J=5.5$ Hz).

In contrast, the parent alcohol **9** showed greater preference of the diequatorial conformer, due to the internal hydrogen bonding between the hydroxy and benzyloxy groups.[17] The ratio of $\mathbf{9}_{eq}$ and $\mathbf{9}_{ax}$ was about 88/12 in $CDCl_3$ at −10°C.

In summary, semi-pinacol cyclization of aldehyde–acetal biaryl compounds has been described, enabling access to a useful intermediate for the synthesis of pradimicin-class antibiotics. Further studies directed toward the total synthesis are now in progress.

Acknowledgements

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14. **Experimental procedure for cyclization of 8 with SmI_2 and $BF_3{\cdot}OEt_2$**: To a mixture of SmI_2 (1.7 mL, 0.1 M THF solution, 0.17 mmol) and $BF_3{\cdot}OEt_2$ (36 mg, 0.25 mmol) in THF (1.6 mL) was added a solution of **8** (51 mg, 0.074 mmol) in THF (1.7 mL) at −78°C. After stirring for 10 min, the reaction mixture was warmed to 0°C, and stirred for 20 min. The reaction was stopped by adding 10% aqueous K_2CO_3, and the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc=4/1) to afford **9** (35 mg, 81%) as yellow solid. Compound **9**: IR (KBr): 3479, 2928, 1728, 1585, 1447, 1339, 1286, 1046, 813 cm^{-1}; ^1H NMR (400 MHz, C_6D_6 at 80°C): δ 2.32 (s, 3H), 3.35 (s, 3H), 3.45 (s, 3H), 3.47 (s, 3H), 3.66 (s, 3H), 3.81 (s, 3H), 4.43 (d, $J=9.1$ Hz, 1H), 4.64 (d, $J=9.1$ Hz), 4.68 (d, $J=12.0$ Hz), 4.80 (d, $J=12.0$ Hz), 6.71 (s, 1H), 7.10–7.23 (m, 3H), 7.38–7.40 (m, 3H), 8.24 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6 at 80°C): δ 19.2, 51.6, 57.0, 61.0, 61.4, 73.3, 73.4, 74.1, 82.7, 109.5, 119.89, 119.91, 121.0, 121.7, 124.0, 128.8, 129.5, 132.0, 136.7, 137.1, 138.9, 141.3, 146.7, 154.4, 156.0, 156.3, 168.7. Anal calcd for $C_{32}H_{31}ClO_8$: C, 66.38; H, 5.40. Found: C, 66.13; H, 5.34%.
15. For comparison, substrate **13**, in which positions of the acetal and aldehyde moieties were exchanged (cf. **8**), was subjected to the reaction of SmI_2 and $BF_3{\cdot}OEt_2$. Formation of many unidentified products was observed with substantial recovery of **13** (50%). Thus, the substituent on the aromatic ring exerts a significant influence on the activation of the acetal moiety. The electron-withdrawal by the methoxycarbonyl group in **13** retards activation of the acetal moiety by Lewis acid.
16. Change of the color of the reaction mixture (deep blue to bright orange) suggested that $Ti(O\textit{i}\text{-}Pr)_4$ was reduced by SmI_2. No reaction occurred with this reduced species.
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