# Stereoselective Route to the Highly Oxidated Sidechain Moiety of Terpentecin and Related Antibiotics

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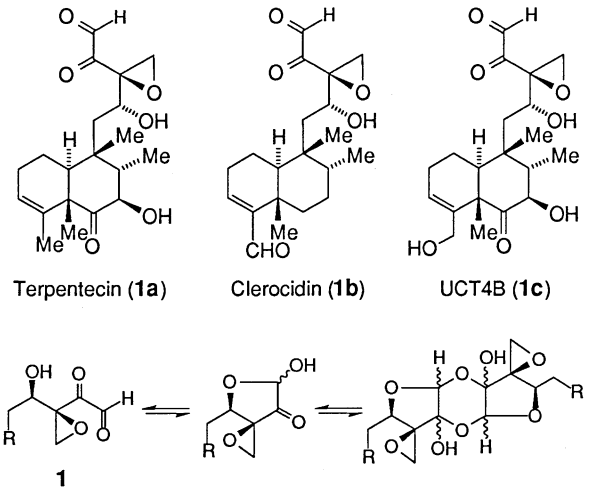
Highly oxidated sidechain moiety of antitumor terpentecin and related antibiotics is prepared in a stereoselective manner from diacetone glucose through furanoside intermediates.

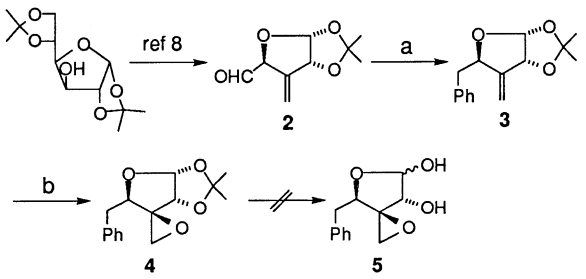
Terpentecin (**1a**)[1], clerocidin (**1b**)[2] and UCT4B (**1c**)[3] are a clerodane family antibiotics which exhibit significant antitumor activity through topoisomerase II mediated DNA cleavage.[4] Quite different from other topo poisons,[5] these antibiotics do not contain aromatic heterocycles. Instead, they have a highly oxidated common sidechain which is thought to be responsible for their antitumor activity.[6] Interested in the structure-activity relationships of this class of antibiotics, we have been carrying out the synthetic study on terpentecin and related antibiotics. We wish to describe here a stereoselective preparation of the side chain moiety.




**Scheme 1.**

There has been only one report concerning the synthetic study on the sidechain moiety.[7] Thus, Ollis *et al.* attempted the oxidation of an acyclic epoxy ketone derivative, however, yield and characterization of the oxidation product were not described.[7] Therefore, although such a direct oxidation of an acyclic precursor seems most straightforward, another methodology is indeed required even for such a small part of the molecule. It has also been reported that these antibiotics exist as an equilibrium mixture[2] as shown in Scheme 1. We assumed that the highly oxidated sidechain is stabilized by forming hemiacetal structures. This led us to examine the strategy which involves furanoside derivatives rather than acyclic ones as intermediates.

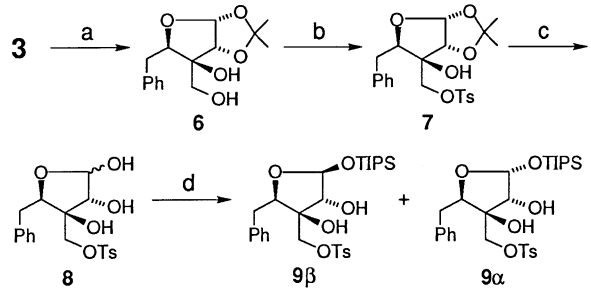
Aldehyde **2**, readily prepared from diacetone glucose,[8] was converted to benzyl derivative **3**[9] by Grignard reaction followed by reduction through xanthate in 62% overall yield. Epoxidation of **3** with MCPBA proceeded stereoselectively to obtain the β-epoxide **4** in 66% yield. However, all attempts to realize the selective removal of the isopropylidene group in **4** were unsuccessful due to the presence of acid labile epoxy function. (Scheme 2)




**a**; (1) PhMgBr, $Et_2O$, 82%, (2) NaH, imidazole, $CS_2$, MeI, THF, 87%, (3) n-$Bu_3SnH$, AIBN, toluene, 87%. **b**; MCPBA, phosphate buffer, $ClCH_2CH_2Cl$, 66%.

**Scheme 2.**

We then examined an alternative approach in which the epoxide ring formation is planned at a later stage of the synthesis. Thus, *exo*-methylene derivative **3** was oxidized with $OsO_4$ to give diol **6** exclusively in 94% yield. The structure of **6** was confirmed by $^1$H-NMR spectrum analysis including NOESY experiment.[10] The diol **6** was selectively monotosylated to **7**, which was subjected to an acid hydrolysis giving triol **8** in 85% yield from **6**. Selective protection of OH-1 in **8** was achieved by the reaction with TIPSOTf and 2,6-lutidine in $CH_2Cl_2$ at -78 °C to obtain 1-*O*-TIPS ethers **9β** and **9α** in 44% and 55% yields, respectively. (Scheme 3) Employment of silyl triflate was critical for the selective silylation. Otherwise, substantial amount of 2-*O*-silyl ethers were also formed.

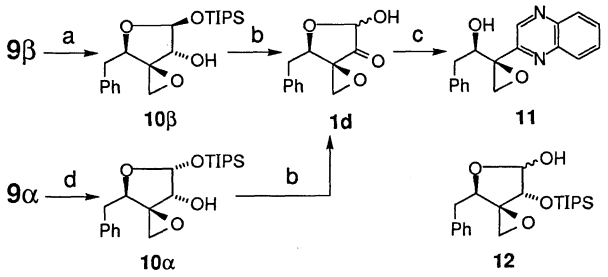



**a**; $OsO_4$, NMO, aq. acetone, 94%. **b**; TsCl, DMAP, pyridine, quant. **c**; 4M HCl, THF, 85%. **d**; TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, **9β** 44%, **9α** 55%.

**Scheme 3.**

Treatment of **9β** with NaOMe gave the epoxide **10β** in almost quantitative yield. Dess-Martin oxidation[11] of **10β**, followed by

desilylation with HF•pyridine afforded the desired **1d** in 50% yield from **10β**. As anticipated, synthetic **1d** gave a quite complicated $^1$H-NMR spectrum which is associated with equilibration mentioned above. Further, IR spectrum of **1d** showed no C=O absorption, which indicates that **1d** exists mainly as a dimeric dioxane form (*vide supra*). The keto aldehyde structure of **1d** was unambiguously confirmed by conversion to the quinoxaline derivative **11** (53%) by the reaction with *o*-phenylenediamine.[3]




**a**; NaOMe, MeOH, 98%. **b**; (1) Dess-Martin, $CH_2Cl_2$, 89% for **10β**, 95% for **10α**, (2) HF•pyridine, THF, 56% for **10β**, 60% for **10α**. **c**; *o*-phenylenediamine, $CH_3CN$, 53%. **d**; LiHMDS, toluene, 80%.

**Scheme 4.**

On the other hand, migration of silyl group to OH-2 was problematic in the case of *syn* **9α**. For example, similar treatment of **9α** with NaOMe in MeOH at 0 °C resulted in the formation of **10α** and **12** in *ca.* 1:1 ratio.[12] After systematic survey of base and solvent, we found that the employment of LiHMDS in toluene did not accompanied the undesirable silyl migration. Thus, treatment of **9α** with LiHMDS in toluene at 0 °C gave **10α** as a sole product in 80% yield. As analogously described for **10β**, the isomeric **10α** was also successfully converted into **1d** in 57% overall yield.

In conclusion, we could develop the stereoselective method for the preparation of highly oxidated sidechain moiety of terpentecin and related antibiotics. Although the present approach requires 10 steps for the preparation of small moiety from the common intermediate **2**, the overall yield from **2** is estimated to be over 20%. Preparation of other derivative, and synthetic studies on the carbobicyclic decalin moiety of terpentecin toward total synthesis are also in progress, and will be reported in due course.

## References and Notes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9 All new compounds were fully characterized by $^1$H-NMR (400 MHz) and IR spectra, and satisfactory combustion analysis or high-resolution MS were obtained for them. Selected data are as follows: **3**: $^1$H-NMR δ 1.35 (3H, s), 1.49 (3H, s), 2.85 (1H, dd, *J*=7.2, 14.4 Hz), 3.04 (1H, dd, *J*=4.4, 14.4 Hz), 4.78 (1H, dd, *J*=1.0, 4.1 Hz), 4.97-5.01 (1H, m), 5.16 (1H, dd, *J*=1.2, 2.2 Hz), 5.40 (1H, dd, *J*=1.0, 2.2 Hz), 5.75 (1H, d, *J*=4.1 Hz), 7.19-7.31 (5H, m). **6**: $[\alpha]_D^{20}$ +32.6° (*c* 2.40, MeOH), $^1$H-NMR δ 1.32 (3H, s), 1.50 (3H, s), 1.86 (1H, t, *J*=5.9 Hz, OH), 2.55 (1H, s, OH), 2.91 (1H, dd, *J*=6.0, 14.4 Hz), 3.06 (1H, dd, *J*=7.5, 14.4 Hz), 3.28 (1H, dd, *J*=5.9, 11.3 Hz), 3.74 (1H, dd, *J*=5.9, 11.3 Hz), 4.18 (1H, dd, *J*=6.0, 7.5 Hz), 4.43 (1H, d, *J*=3.9 Hz), 5.95 (1H, d, *J*=3.9 Hz), 7.22-7.32 (5H, m). **10β**: $[\alpha]_D^{20}$ +16.7° (*c* 0.985, $CHCl_3$), $^1$H-NMR δ 1.05-1.22 (21H, m), 1.95 (1H, br, OH), 2.45 (1H, d, *J*=4.6 Hz), 2.73 (1H, dd, *J*=5.6, 14.3 Hz), 2.98 (1H, dd, *J*=7.8, 14.3 Hz), 3.00 (1H, d, *J*=4.6 Hz), 3.81 (1H, dd, *J*=1.4, 5.6 Hz), 4.54 (1H, dd, *J*=5.6, 7.8 Hz), 5.32 (1H, d, *J*=1.4 Hz), 7.16-7.27 (5H, m). **10α**: $[\alpha]_D^{20}$ +114° (*c* 1.28, $CHCl_3$), $^1$H-NMR δ 0.97-1.19 (21H, m), 2.58 (1H, d, *J*=4.8 Hz), 2.63 (1H, d, *J*=9.3Hz, OH), 2.65 (1H, dd, *J*=4.6, 14.4 Hz), 2.78 (1H, dd, *J*=7.9, 14.4 Hz), 3.14 (1H, d, *J*=4.8 Hz), 4.00 (1H, dd, *J*=4.7, 9.3 Hz), 4.49 (1H, dd, *J*=4.6, 7.9 Hz), 5.51 (1H, d, *J*=4.7 Hz), 7.17-7.28 (5H, m). **1d**: *Rf* 0.17 (EtOAc/hexane, 1:1), $[\alpha]_D^{20}$ +70.3° (*c* 0.765, $CHCl_3$), HRMS calcd for $C_{12}H_{12}O_4$ ($M^+$) *m/z* 220.0734, found 220.0728. **11**: mp 96-98 °C; $[\alpha]_D^{20}$ -38.4° (*c* 0.535, $CHCl_3$); $^1$H-NMR δ 2.99 (1H, dd, *J*=8.2, 14.0 Hz), 3.08 (1H, d, *J*=4.8 Hz), 3.35 (1H, d, *J*=4.8 Hz), 3.20 (1H, dd, *J*=3.7, 14.0 Hz), 4.18 (1H, dt, *J*=3.7, 8.2 Hz), 4.23-4.26 (1H, m, OH), 7.13-7.27 (5H, m), 7.78-7.85 (2H, m), 8.04-8.16 (2H, m), 8.81 (1H, s). Anal. Found: C, 73.79; H, 5.45; N, 9.57%. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58%.

10 NOE was observed between C3-OH (δ 2.55, s) and C2-H (δ 4.43, d, $J_{1,2}$=3.9 Hz) in NOESY spectrum.

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12 When the reaction was carried out with other conditions such as (NaHMDS or LiHMDS, THF, -78 °C), and (DBU, toluene, rt), a mixture of **12** and **10α** was obtained (**12**:**10α** = *ca.* 1:1 ~ 1:2).