Natural Products Synthesis

Concise Total Synthesis and Structure Assignment of TAN-1085**

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TAN-1085 (**1**), an antibiotic produced by *Streptomyces* sp. S-11106,[1] has attracted considerable synthetic interest, not only for its important biological activities, angiogenesis and aromatase inhibition, but also for its unique structural features, that is, a curved tetracyclic chromophore with a vicinal diol, one of which is glycosylated with a rhodinose unit.[1,2] The relative and absolute stereochemistries of this compound, however, remained to be assigned.

Herein we report the first total synthesis of **1** and its 5,6-bis-epimer, thereby finally establishing the remaining stereochemical questions. The synthesis features three key transformations: 1) a tandem electrocyclic reaction for the facile construction of the aglycon precursor, 2) its stereoselective conversion into a *trans*-diol by SmI_2-mediated pinacol cyclization, and 3) discrimination of the resulting C5/C6 hydroxy groups by in situ benzoylation. Furthermore, the stereochemical assignment of **1** was effected by exploiting the CD exciton chirality method.[3]

Scheme 1 outlines our retrosynthetic analysis, predicated upon the construction of tetracyclic aglycon **I** from biaryl

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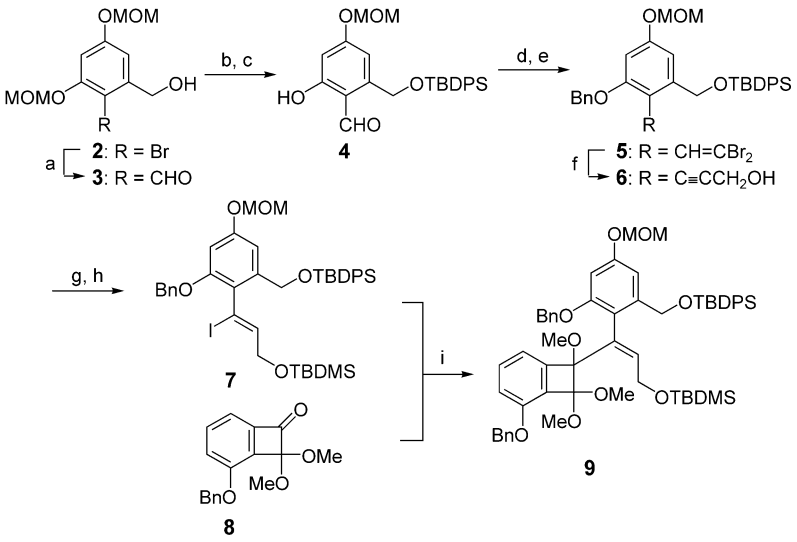
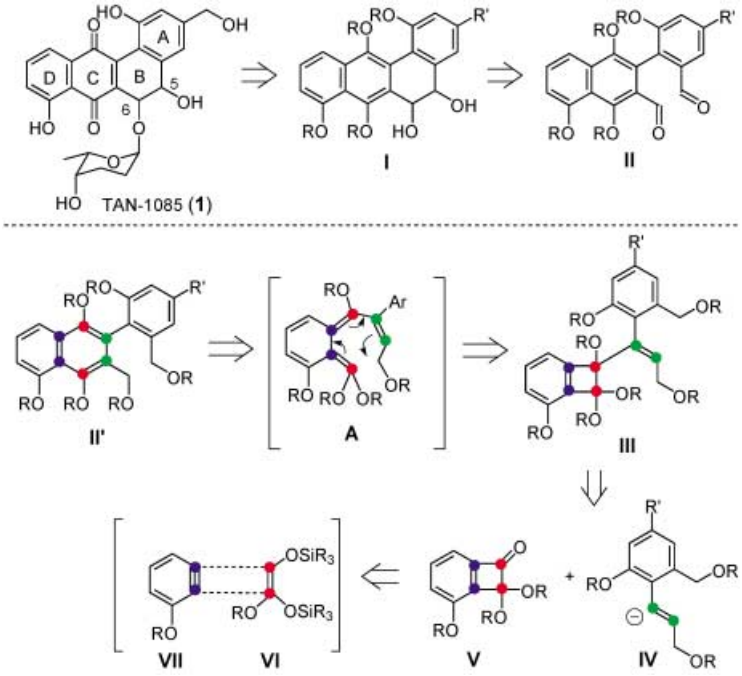
dialdehyde **II** by pinacol cyclization.[4] We hoped that the sterically encumbered biaryl structure in **II** (or the precursor **II′**) could be accessible by the ring enlargement of benzocyclobutene **III** by way of tandem thermal electrocyclic reactions via **A**.[5,6] The key intermediate **III** could be obtained by assembly of styryl anion **IV** and the selectively protected benzocyclobutenedione **V**, which in turn is readily available from silyl enol ether **VI** and benzyne **VII**.[7]

Scheme 2 illustrates the preparation of **9** for the key electrocyclizations. Known bromide **2**[8] was converted into aldehyde **3** by successive treatment with MeLi and *n*BuLi[9] followed by DMF. After silylation, the MOM group proximal to the carbonyl function was selectively removed, giving phenol **4** in good yield. Benzylation of **4** was followed by dibromoolefination[10] to give **5** in 85% yield, which was successively treated with *n*BuLi and paraformaldehyde to afford propargyl alcohol **6** in 91% yield. Hydroalumination of **6** with Red-Al followed by quenching with iodine gave, after silylation, vinyl iodide **7**. Union of benzocyclobutenone **8**[7] and the vinyllithium species generated from **7** followed by treatment with methyl triflate in situ gave **9**, ready for the key tandem electrocyclic reaction.

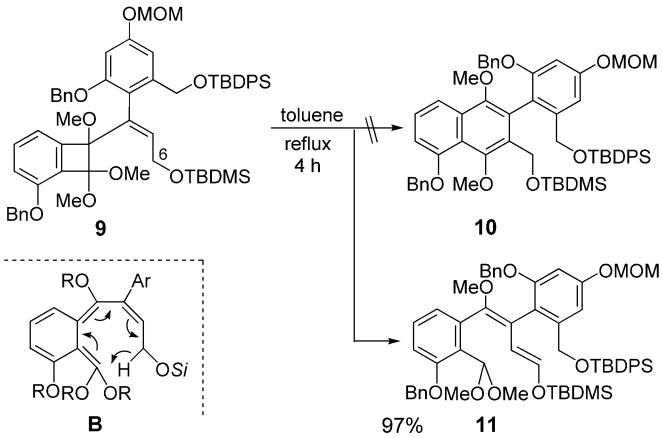


Scheme 2. Preparation of **9**. a) MeLi (1.1 equiv), THF, −78°C, 10 min; then *n*BuLi (1.2 equiv), DMF, −78°C, 5 min (97%); b) TBDPSCl, imidazole, DMF, 0°C→RT, 78%; c) Montmorillonite K-10, benzene, room temperature, 11 h, 40°C, 50 min; d) BnBr, NaH, DMF, 0°C→RT, 10 h, 75% (two steps); e) CBr_4, PPh_3, CH_2Cl_2, 0°C, 20 min, 85%; f) *n*BuLi (2.0 equiv), THF; then $(HCHO)_n$, −78°C→RT, 91%; g) Red-Al, Et_2O, −78→−10°C, 50 min; then EtOAc, −10°C, 15 min; then I_2, THF, −78→0°C, 1 h; h) TBDMSCl, imidazole, DMF, 0°C→RT, 1.5 h, 93%; i) **7** (1.0 equiv), *t*BuLi (2.1 equiv), Et_2O, −78°C, 20 min; then **8** (1.5 equiv), THF, −78°C, 25 min; then MeOTf (3.0 equiv), −78→0°C, 1.5 h, 85%. DMF = *N*,*N*-dimethylformamide, TBDPS = *tert*-butyldiphenylsilyl, TBDMS = *tert*-butyldimethylsilyl, Red-Al = $NaAlH_2(OCH_2CH_2OCH_3)_2$, Tf = trifluoromethanesulfonyl.

The planned reactions of **9**, however, were uniformly unsuccessful under various conditions owing to the prevalence of another pericyclic process, the 1,7-hydrogen shift shown in **B** (Scheme 3). For example, although the starting material **9** was completely consumed upon refluxing in toluene for 4 h, only silyl ether **11** was obtained.

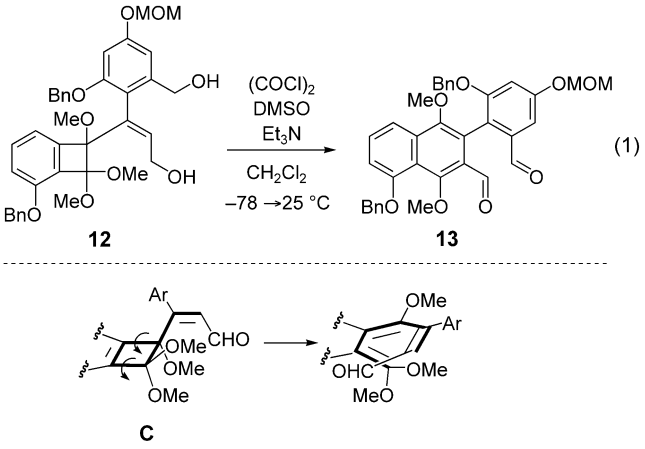


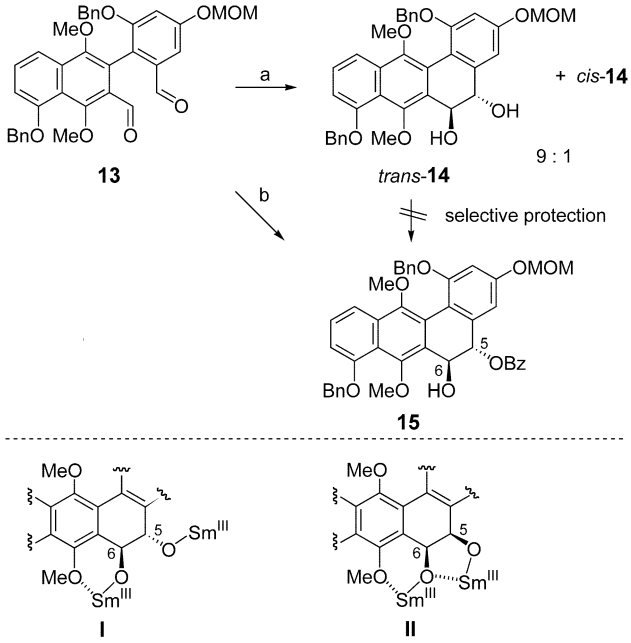
Scheme 1. Retrosynthetic analysis of **1**.



Scheme 3. Attempts at thermal electrocyclic reactions.

After considerable experimentation, we discovered a highly efficient solution to this problem [Eq. (1)]. Simply by raising the oxidation level of C6 in **9**, the 1,7-shift was completely suppressed, and the desired 6π process was remarkably facilitated. Thus, after removal of the two silyl groups in **9**, the resulting diol **12** was subjected to Swern oxidation. Importantly, when the Swern oxidation mixture was warmed to 25°C and kept standing for 8 h, the ring opening of **C** and subsequent 6π-closure occurred, thereby directly giving the biaryl dialdehyde **13**, the key intermediate in our synthetic plan. This remarkable rate enhancement of the pericyclic processes could be rationalized by the cooper-





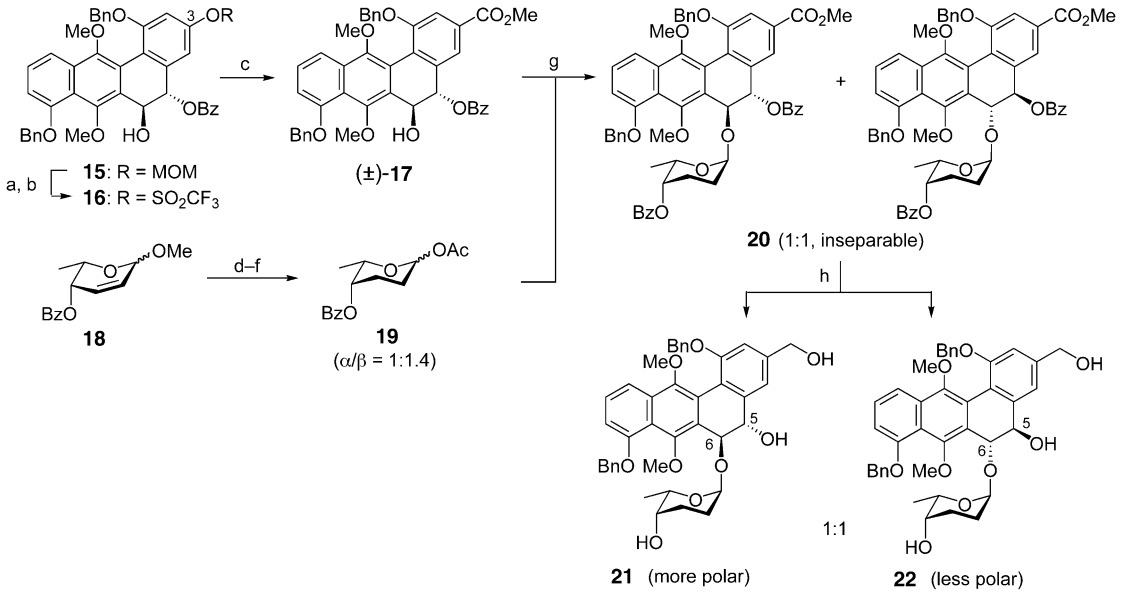
ative effect of the electron-donating (2 × OMe) and the electron-withdrawing (enal) substituents of the four-membered ring toward the required conrotation.[11]

The biaryl dialdehyde **13** was subjected to a pinacol cyclization to the tetracyclic structure (Scheme 4). Treatment of **13** with SmI_2[12] gave the corresponding diols, *trans*-**14** and *cis*-**14** (9:1), which were separable by column chromatography.[13,14] For the regioselective introduction of the sugar moiety, discrimination of the C5/C6 hydroxy groups in *trans*-**14** was required, a challenging task owing to the local C_2 symmetry. All attempts at the monofunctionalization of diol **14** were unfruitful; no regioselectivity and/or double reaction at the C5/C6 diols occurred.

Gratifyingly, a felicitous solution to this issue was offered by direct quenching of the pinacol cyclization (see above). Thus, after treatment of **13** with SmI_2 as above, benzoyl chloride (1.5 equiv) was directly added to give C5-benzoate *trans*-**15** in 86% yield. Neither the C6 benzoate nor the dibenzoate was detected, which could be rationalized by the difference in the nucleophilicity of two oxygen functions: The C6 samarium alkoxide is chelated as in **I**, and is therefore less reactive than the C5 alkoxide.[15]

Scheme 4. Pinacol cyclization and discrimination of the two hydroxy groups. a) SmI_2, THF, 0 °C, 2 min, 96%, *trans*/*cis* = 9:1; b) SmI_2, THF, 0 °C, 2 min; then BzCl (1.5 equiv), 86%.

Construction of the aglycon portion was completed in three steps to give methyl ester **17**, primed for introduction of the sugar moiety (Scheme 5). Tetracyclic **17** was glycosylated by reaction with L-rhodinosyl acetate **19**[16,17] in the presence



Scheme 5. Construction of the aglycon **17** and its glycosylation with L-rhodinoside **19**. a) H_2SO_4 (aq., 0.5 M), DME, 60 °C, 12 h, 91%; b) $PhNTf_2$, K_2CO_3, acetone, 0 °C, 3 h, 98%; c) CO (3 atm), $Pd(OAc)_2$ (30 mol%), dppp (30 mol%), Et_3N, MeOH, DMF, 65 °C, 30 h, 91%; d) H_2, Pd/C, MeOH, room temperature, 30 min; e) HCl (2 M), AcOH, THF (1:1:1), room temperature, 7 h, 80% (two steps); f) Ac_2O, pyridine, room temperature, 30 min, 94%, α/β = 1:1.4; g) $BF_3{\cdot}OEt_2$ (1.1 equiv), **19** (2.0 equiv, α/β = 1:1.4), molecular sieves (4 Å), CH_2Cl_2, 95%, 1:1 mixture of diastereomers; h) DIBAL, CH_2Cl_2, −78 → −20 °C, 1 h, 98%. dppp = 1,3-bis(diphenylphosphanyl)propane, DIBAL = diisobutylaluminum hydride.

of $BF_3{\cdot}OEt_2$ to give the α glycoside **20** as an inseparable mixture of diastereomers (1:1). These isomers were the diastereomers arising from the racemic nature of the aglycon relative to the L-rhodinoside. The anomeric stereochemistries of the diastereomers were both shown to be α by ^{1}H NMR spectroscopic analysis.[18] Without separation, methyl ester **20** was treated with DIBAL, which led to the simultaneous removal of the two benzoyl groups to give diastereomeric products, which were separable by column chromatography ($CHCl_3$/EtOAc = 1:30); **21** ($R_f = 0.10$), **22** ($R_f = 0.17$).

In spite of considerable efforts, we were frustrated by the inability to directly assign the stereochemistry of these diastereomers, and decided to rely on indirect methods. Thus, the sugar was detached from the more-polar isomer **21** to obtain the "resolved" aglycon **23** (with unknown absolute stereochemistry at this stage), which was converted into benzoate **24**[19] for measuring the CD exciton chirality effects (Figure 1 a).[3]

The CD spectrum of alcohol **23** showed strong and complicated Cotton effects because of the markedly twisted π-electron system in the dihydrobenz[*a*]anthracene skeleton (blue line, Figure 1 b). The CD spectrum of benzoate **24** also showed intense and complicated Cotton effects similar to those of **23** (red line). Therefore, to detect the genuine exciton CD Cotton effects due to the interaction between the long axes of naphthalene and benzoate chromophores, the difference CD curve was calculated: $\Delta\Delta\varepsilon = \Delta\varepsilon(\mathbf{24}) - \Delta\varepsilon(\mathbf{23})$. As shown in Figure 1 c, the difference CD curve shows a typical pattern of exciton split CD, $\Delta\Delta\varepsilon = -32$ at 236 nm (the first Cotton effect) and $\Delta\Delta\varepsilon = +35$ at 224 nm (the second Cotton effect), $A = \Delta\Delta\varepsilon$ (1st) $- \Delta\Delta\varepsilon$ (2nd) $= -67$; the negative sign of the A value proved the counterclockwise relationship between these chromophores (Figure 1 d). The 5*S*,6*S* configuration was thus unambiguously assigned.[20]

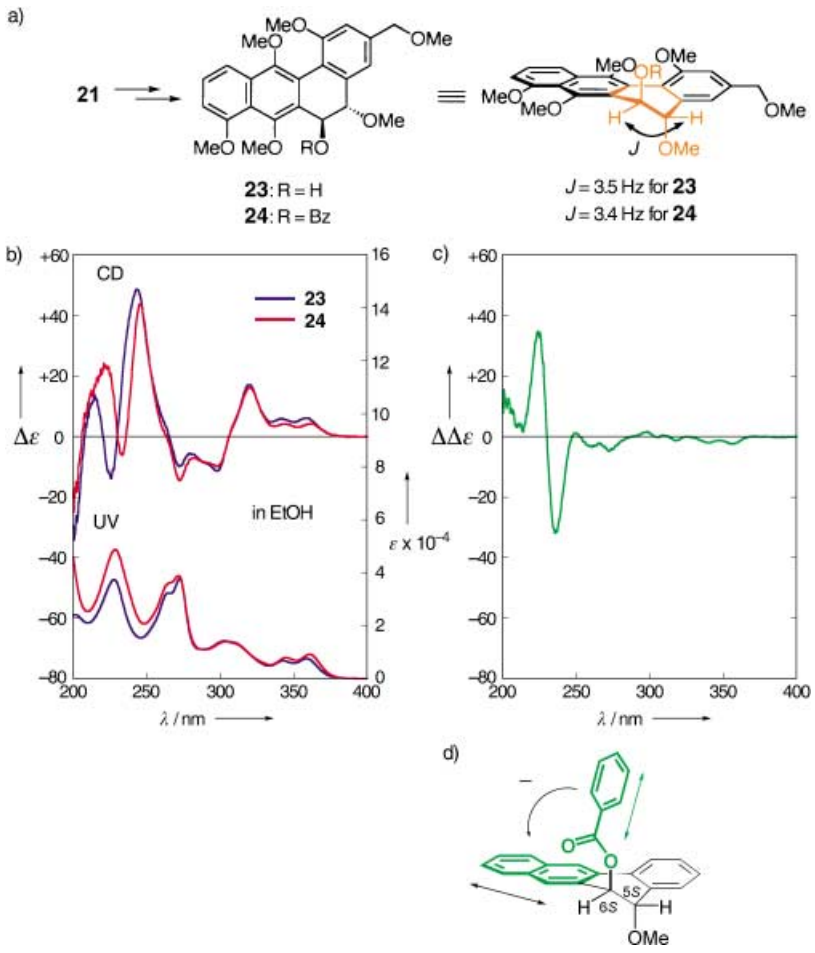
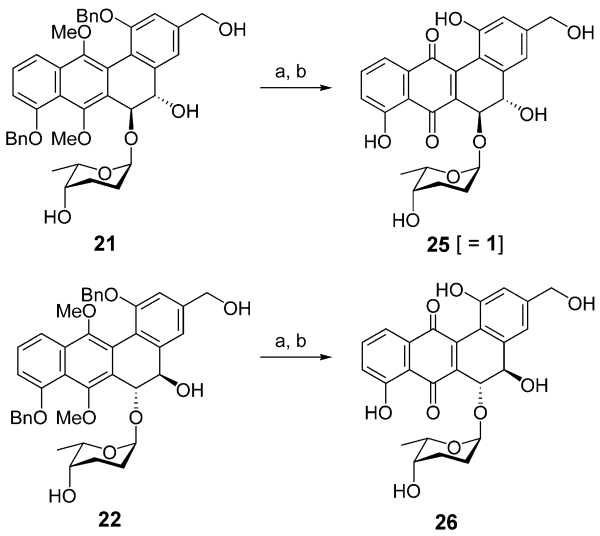


Figure 1. Application of the exciton chirality method. a) Conformations of tetracycle **23** and **24**, b) CD and UV spectra of **23** and **24**, c) difference CD curve between **24** and **23**: $\Delta\Delta\varepsilon = \Delta\varepsilon(\mathbf{24}) - \Delta\varepsilon(\mathbf{23})$, d) Anticlockwise relationship between the long axis of the naphthalene and the benzoate chromophores.



Scheme 6. Construction of **1**. a) CAN, H_2O, CH_3CN, 0 °C, 20 min, b) H_2, Pd/C, MeOH (53 % for **25** from **21**, 56 % for **26** from **22**). CAN = ceric ammonium nitrate.

With the structures secured, diastereomeric triols **21** and **22** were converted into the final products by oxidation with CAN followed by deprotection (Scheme 6). Of the diastereomers **25** (from **21**) and **26** (from **22**), the former coincided with the authentic specimen of **1**.[21]

In conclusion, the first synthesis of TAN-1085 was completed through the concise and efficient construction of the aglycon. The stereochemistry of natural product was concluded to be that of **25**.

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Keywords: antibiotics · electrocyclic reactions · glycosylation · structure elucidation · total synthesis

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[18] For both diastereomers, the coupling constants between the anomeric proton and the methylenic protons at C2′ were small (< 3.2 Hz), suggesting the α-stereochemistry of these anomeric centers. The conclusions were further supported by the observation of ^{13}C–^{1}H coupling constants at anomeric centers, that is, $^{1}J_{C(1'),H(1')} = 167.4$ and 165.8 Hz; see: K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293 – 297.
[19] The more-polar isomer **21** was easily converted into alcohol **23** (1. H_2, Pd/C, MeOH; 2. NaH, MeI; 3. $TsOH \cdot H_2O$, MeOH) in 87% overall yield. Alcohol **23** was further converted into benzoate **24** (BzCl, pyridine) in 95% yield. The coupling constants between 5- and 6-H (3.5 Hz for **23**, 3.4 Hz for **24** in CD_3OD) suggest that the C5 and C6 substituents of both compounds adopted pseudoaxial orientations (Figure 1a), a prerequisite for determining the stereochemistry by CD.
[20] This conclusion was further confirmed by the ^{1}H NMR anisotropy method (see Supporting Information).
[21] All physical data of synthetic **25** (^{1}H and ^{13}C NMR, IR, $[\alpha]_D$) were identical to those of an authentic specimen of **1**.

