Total Synthesis

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Stereochemical Relay via Axially Chiral Styrenes: Asymmetric Synthesis of the Antibiotic TAN-1085**

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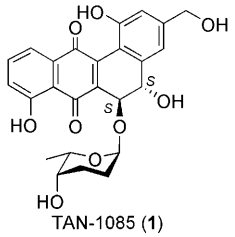
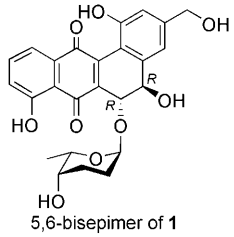
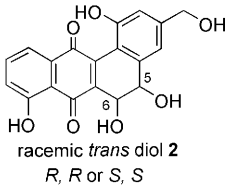
We previously reported the first synthesis and stereochemical assignment of the antibiotic TAN-1085 (**1**).[1,2] The aglycon **2** was prepared diastereoselectively (*trans*), but not enantioselectively. The racemate was glycosylated with an L-rhodinose moiety to enable diastereomer separation and the assignment



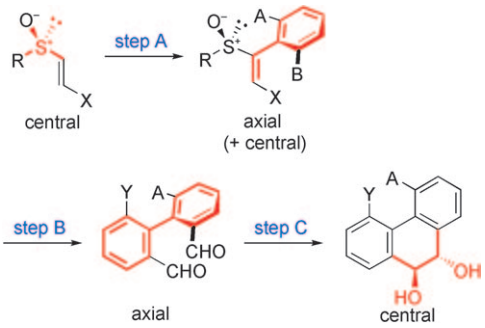




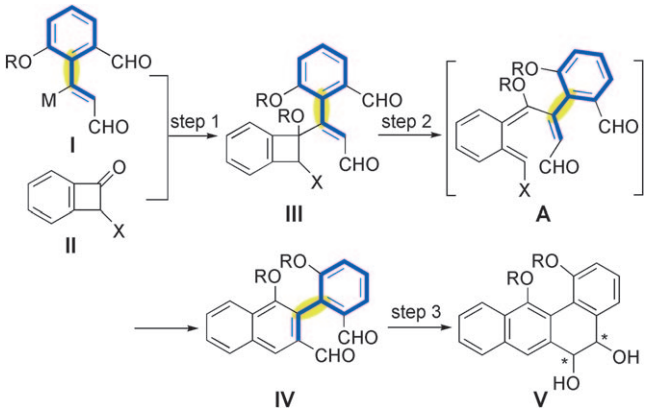
of the *S*,*S* configuration to the natural product. We next turned our attention to the asymmetric synthesis of the aglycon **2**, with the fully stereocontrolled synthesis of **1** as our goal.

We now report a stereochemical-relay approach involving the consecutive transcription of two chirality elements (central⇄axial; Scheme 1) in three chirality-transfer steps: central-to-axial (step A), axial-to-axial (step B), and axial-to-central (step C).

The idea for this approach came from the identification of a "styrene motif" (blue) in our previous racemic synthetic route to **2** (Scheme 2).[3–5] If the styrene moiety in **I** has stable axial stereochemistry (yellow), which is maintained in steps 1 and 2, the stereochemical information should be relayed to



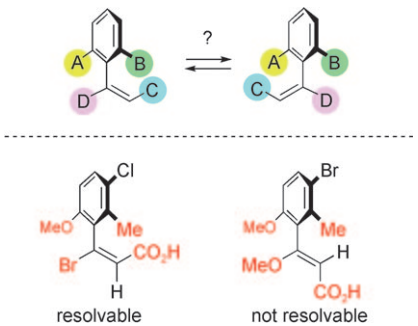
Scheme 1. Stereochemical-relay strategy.



Scheme 2. Synthetic access to the aglycon of **1**.

the axial stereochemistry in biaryl **IV**. Finally, the pinacol cyclization (step 3) would proceed stereospecifically[5,6] to give the tetracyclic diol **V** in enantiomerically enriched form.

In analogy to the axial stereochemistry of biaryl compounds, the key to this approach is hindered rotation about the sp^2–sp^2 single bond in styrenes (Scheme 3). Interestingly, this topic was studied intensively by Adams and co-workers in



Scheme 3. Axially chiral styrene motif.

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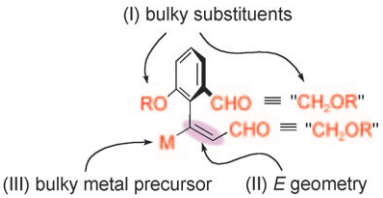
the 1940s.[7] Their general conclusion was the necessity for fairly large substituents to prevent rotation about the styryl sp^2–sp^2 single bond. We became intrigued in exploiting this stereochemical motif, which has been overlooked in the past, in our synthetic design.

We considered two key points for designing the axially chiral styrene building blocks: 1) access to the starting material, and 2) stereochemical fidelity during the stereochemical relay. Taking the studies by Adams and co-workers into account, we considered three factors to suppress stereochemical mutation: I) the use of bulky substituents, II) a switch in the olefin geometry from *Z* to *E* so that the CHO equivalent "CH_2OR" and the aryl group are on the same side of the C=C bond, and III) the use of a bulky metal precursor M (Scheme 4).



Scheme 4. Design of an axially chiral styrene building block.

We prepared vinylstannane **3**[8] as a candidate that meets these criteria and examined its stereochemical stability. It turned out that **3** was resolvable by preparative HPLC on a chiral phase (Daicel chiralcel OD, *n*-hexane/*i*PrOH 85:15; Figure 1). The rate of racemization of **3** was slow enough ($k = 1.5 \times 10^{-7}\ s^{-1}$) to enable its use as a chiral building block:[9]

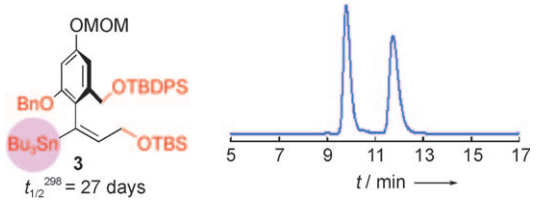
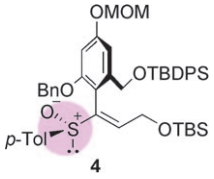


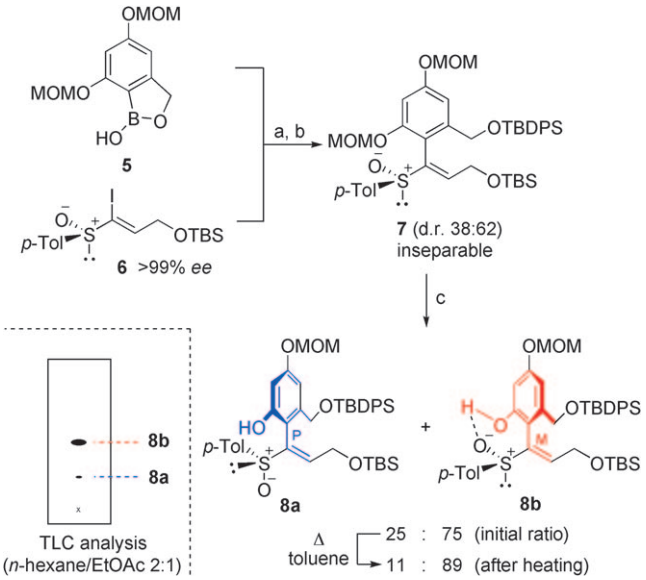
Figure 1. Structure of vinyl stannane **3** and separation of the enantiomers of **3** (resolution of the racemate) by HPLC on a chiral phase (Daicel chiralcel OD-H, ϕ 0.46 cm × 25 cm, *n*-hexane/*i*PrOH 99:1 (85:15 on a preparative scale), 1.0 mL min^{-1}, 20 °C, 254 nm). Bn = benzyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.



The half-life ($t_{1/2}$) of the axial stereochemistry of **3** is 27 days at 298 K.

The chiral sulfoxide **4** was also designed as a styryl anion precursor in the hope that the chiral sulfinyl moiety might aid in isomer enrichment and resolution.[10]

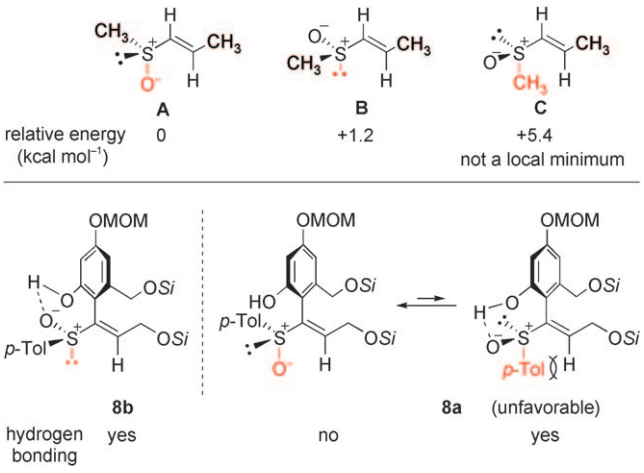
The synthesis of the axially chiral styrene **8** started with Suzuki coupling of boronic acid **5** with vinyl iodide **6** (Scheme 5). Protection of the resulting alcohol with a TBDPS group gave styryl sulfoxide **7** in 90% yield (2 steps).



Scheme 5. Synthesis of the axially chiral styrenes **8**: a) **5** (1.2 equiv), **6** (1.0 equiv), $[Pd(PPh_3)_4]$ (10 mol%), K_3PO_4, 1,2-dimethoxyethane, H_2O, 90 °C, 1 h; b) *t*$BuPh_2SiCl$, imidazole, DMF, room temperature, 4 h, 90% (2 steps from **6**); c) $SnBr_2$, toluene, 63 °C, 4 h, 70%. DMF = *N*,*N*-dimethylformamide.

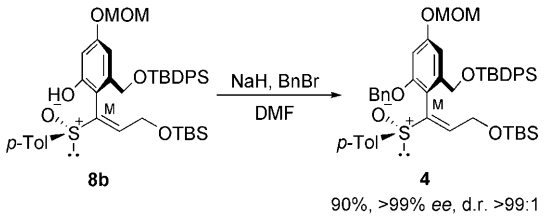
Unfortunately, two inseparable diastereomers were produced in a 38:62 ratio, as determined by ^{1}H NMR spectroscopy. Upon liberation of the phenol hydroxy group near the sulfoxide group in **7**,[11] the diastereomer ratio was improved slightly (**8a**/**8b** 25:75).[12] The markedly different chromatographic behavior of isomers **8a** and **8b** (**8a**: $R_f = 0.23$, **8b**: $R_f = 0.50$, silica gel, *n*-hexane/EtOAc 2:1) enabled their straightforward separation. We ascribe the large difference in the mobility of these compounds on silica to the presence/absence of a hydrogen bond between the sulfinyl oxygen atom and the phenol; the less polar isomer **8b** has a hydrogen bond, as indicated by the low-field resonance of the phenol proton ($\delta = 8.6$ ppm), whereas the more polar isomer **8a** does not ($\delta = 6.3$ ppm). The diastereomeric ratio was further improved (to **8a**/**8b** 11:89) by simple heating (toluene, reflux, 0.5 h). This ratio proved to be the equilibrium ratio, as it was reached from either **8a** or **8b** upon heating (toluene, reflux, 0.5 h).

High selectivity (in this case for **8b** over **8a**) and the ease of purification (large difference in the R_f values) make this method an attractive route to axially chiral styrenes. What is the origin of these phenomena? Scheme 6 shows results of a conformational study by Tietze et al. on vinyl sulfoxides:[13] Conformers **A** and **B**, in which the S–O bond or the lone pair is coplanar to the C=C bond, are two local minima, whereby conformer **A** is slightly preferred. In contrast, conformer **C**, in which the S–C(sp^3) bond is coplanar to the C=C bond, is much less favored and not a local minimum. These features coupled with hydrogen bonding account for the preference for **8b** over **8a**: The energy benefit from intramolecular hydrogen bonding outweighs the slight energy loss associated with the placement of the lone pair coplanar to the C=C bond. By contrast, hydrogen bonding in isomer **8a** would impose coplanarity of the tolyl group with the C=C bond and is therefore not favored.



Scheme 6. Conformations of vinyl sulfoxides. *Si* = silyl protecting group.

The phenol in **8b** was protected with a benzyl group (NaH, BnBr, DMF, 0 °C, 0.5 h, 90 %) to give the styryl sulfoxide **4** (> 99 % *ee*, d.r. > 99:1; Scheme 7).[14] Importantly, no stereochemical mutation was observed during protection of the phenol.

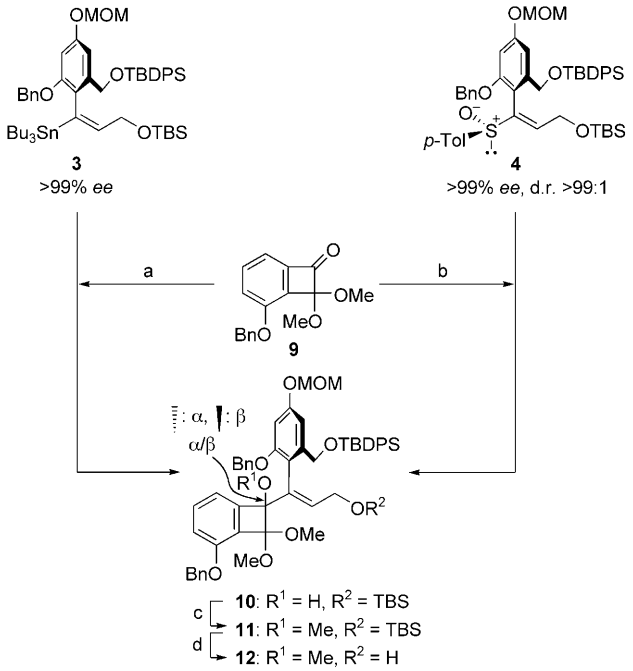


Scheme 7. Synthesis of the axially chiral styrene **4**.

Having prepared the two precursor styrene derivatives **3** and **4** in enantiomerically pure form, we attempted the synthesis of **1** on the basis of a stereochemical relay (Scheme 8). The initial coupling was the most critical step in terms of preserving the axial chirality, as it formally involves conversion of bulky tin and sulfoxide precursors into a much smaller lithium species.

Upon the treatment of stannane **3** with MeLi[15] (−78 °C, 2 h, THF), followed by the addition of ketone **9** and methylation of the resulting tertiary alcohol in situ, the desired adduct **11** was obtained in 82 % yield as a separable mixture of diastereomers with respect to the styryl axis and the newly formed sp^3 stereogenic center (**11α**/**11β** 1.8:1). The *ee* value was assessed after detachment of the TBS group of **11**: 98 % *ee* was found for **12α** and **12β**.[16] Thus, the axial chirality was retained completely, despite the prolonged lithiation.

By contrast, special precautions were needed to maintain the stereochemical integrity of the styryl derivatives when sulfoxide **4** was used as the starting material. After the treatment of **4** with *t*BuLi,[17] the immediate addition of ketone **9** (within 5 min) was essential; otherwise, the *ee* value decreased substantially. With suitable care, however, adduct

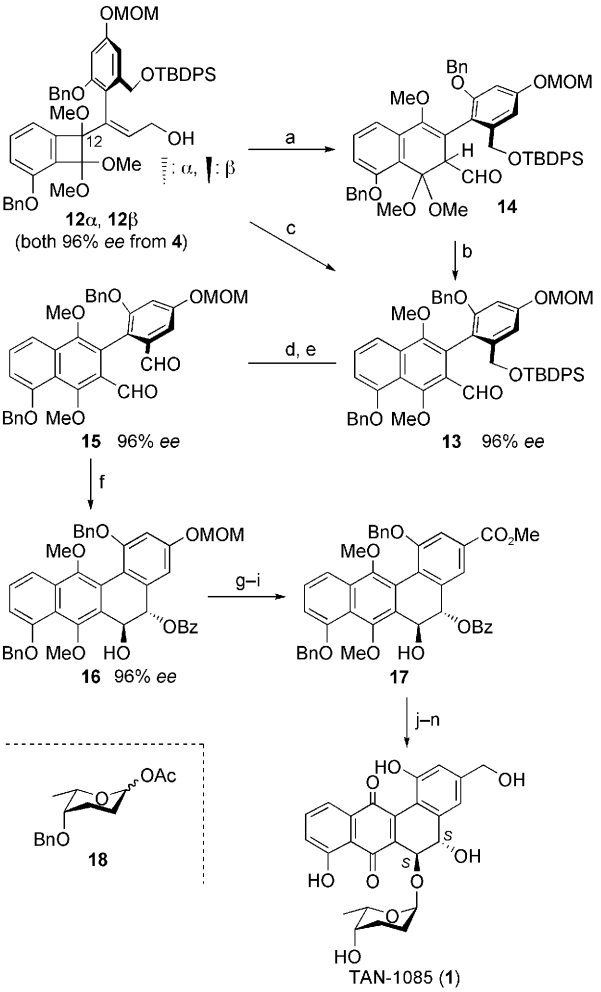


Scheme 8. Coupling of the enantiomerically pure styrene **3** or **4** with the benzocyclobutenone **9**: a) MeLi, THF, −78 °C, 2 h; MeOTf, Et_2O, −78 → −0 °C, 1 h, 82 %; b) *t*BuLi, toluene, −78 °C, then 0 °C, 30 min; c) *n*BuLi, Et_2O, −78 °C, 10 min; MeOTf, −78 → 0 °C, 3 h; d) PPTS, MeOH, THF, 5 h, 74 %, 98 % *ee*, α/β, 1.8:1 from **3**, 73 %, 96 % *ee*, α/β 1:1.2 from **4**. PPTS = pyridinium *p*-toluenesulfonate, Tf = trifluoromethanesulfonyl.

12 was obtained in 73 % yield (**12α**/**12β** 1:1.2), albeit with at best 96 % *ee*. The dependence of the *ee* value and the diastereoselectivity on the precursor (stannane **3** or sulfoxide **4**) suggests the involvement of different species in the C–C bond formation.[18]

Allylic alcohols **12α** and **12β** were subjected to the Swern oxidation to trigger ring enlargement (Scheme 9).[2] Monitoring of the reaction by TLC showed that **12** was consumed after the temperature was raised to 0 °C. Surprisingly, the product was not the expected biaryl compound **13**, but dihydronaphthalene **14**. Thus, although the desired ring opening of the four-membered ring and closure to the six-membered ring proceeded, aromatization by elimination of methanol was sluggish.[2]

We were pleased to find that dihydronaphthalene **14** could be converted readily into the desired biaryl compound **13** by treatment with DBU, a stronger base than Et_3N (Scheme 9). Furthermore, the *ee* value of **13** was 96 % when we started from **4** (96 % *ee*); thus, we observed complete transfer of the styryl axial stereochemistry in **12** to the biaryl axial stereochemistry through these consecutive processes.[19,20] Although the "styrene structure" is lost at the stage of **14**, the stereochemical information is maintained during these transformations. In a more convenient one-pot procedure for the formation of **13** from **12**, DBU was added to the reaction mixture after the Swern oxidation of **12** was complete. In this way, the biaryl compound **13** was formed, stereochemically intact (96 % *ee*), in excellent yield.[20]



Scheme 9. Final stages of the synthesis of **1**: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C→RT, 12 h, 83 %; b) DBU, CH_2Cl_2, 0 °C, 1 h, 98 %; c) $(COCl)_2$, DMSO, Et_3N; then DBU, CH_2Cl_2, −78→0 °C, 3 h, 98 %; d) TBAF, THF, room temperature, 2 h, quantitative; e) MnO_2, CH_2Cl_2, room temperature, 10 h, 98 %; f) SmI_2, 0 °C, 10 min; BzCl (1.5 equiv), THF, 0 °C, 4 h, 87 %; g) 0.5 M H_2SO_4, 1,2-dimethoxyethane, 60 °C, 12 h, 91 %; h) $PhNTf_2$, K_2CO_3, acetone, 0 °C, 8 h, 98 %; i) CO (3 atm), $Pd(OAc)_2$ (30 mol %), dppp (30 mol %), Et_3N, MeOH, DMF, 65 °C, 30 h, 91 %; j) $BF_3{\cdot}OEt_2$ (1.0 equiv), **18** (2.0 equiv, α/β 1:1.4), CH_2Cl_2, −78→−20 °C, 1 h, 95 % (d.r. 98:2); k) iBu_2AlH, CH_2Cl_2, −78→−20 °C, 1 h, 98 %; l) diastereomer separation; m) $Ce(NH_4)_2(NO_3)_6$, H_2O, CH_3CN, 0 °C, 20 min; n) H_2, Pd/C, MeOH, room temperature, 1 h, 53 %. Bz = benzoyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethyl sulfoxide, dppp = 1,3-bis(diphenylphosphanyl)propane, TBAF = tetrabutylammonium fluoride.

Having secured the second chirality transfer (styryl→biaryl), the stage was set for the final chirality transfer by the pinacol cyclization. Detachment of the TBDPS group in **13** and oxidation of the resulting alcohol gave the enantiomerically enriched dialdehyde **15** (96 % *ee*). Upon the treatment of **15** with SmI_2, followed by quenching with benzoyl chloride,[2] the monobenzoate **16** was obtained in 87 % yield. The axial-to-central chirality transfer was perfect, with the *trans*-benzoate **16** formed with 96 % *ee*.[5,6,20] The final steps of the synthesis were identical to those in our previous synthesis of **1**.[2] A small amount of the 5,6-bisepimer was removed after the glycosylation of **17**. The target antibiotic TAN-1085 (**1**) was obtained in enantio- and diastereomerically pure form.

In conclusion, an asymmetric synthetic route to TAN-1085 (**1**) has been developed by making use of an axially chiral styrene motif. We believe that this stereochemical-relay strategy may have broader implications for stereoselective syntheses.

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[9] For details on the time course of the change in the *ee* value of stannane **3**, see the Supporting Information.
[10] For a review, see: T. Toru, C. Bolm, *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2008**.
[11] The MOM group was removed selectively owing to the directing effect of the sufinyl group.
[12] Assignment of the configuration of **8a** and **8b** was based on single-crystal X-ray analysis of a triol derived from **8a** (see the Supporting Information for details).

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[14] Compound **8a** was not detected by TLC.
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[18] We assume that the *ee* value of **12** decreases when the free vinyllithium species, generated by the collapse of the ate species, becomes involved in the reaction. The stannate derived from **3** can be assumed to be chemically and configurationally stable, whereas the sulfurane derived from **4** collapses faster to the corresponding lithio species, which is supposedly configurationally labile.
[19] When the corresponding diol without the TBDPS group was used as the starting material, the *ee* value of **15** was substantially lower (30% *ee* from **12α**, 68% *ee*, from **12β**).
[20] The *ee* value was determined by HPLC analysis on a chiral phase (see the Supporting Information).

