

## Synthesis and Stereochemical Assignment of Angucycline Antibiotic, PD-116740

Keiji Mori, Yuuya Tanaka, Ken Ohmori, and Keisuke Suzuki\*  
 Department of Chemistry, Tokyo Institute of Technology,  
 SORST-JST Agency, O-okayama, Meguro-ku, Tokyo 152-8551

(Received February 4, 2008; CL-080126; E-mail: ksuzuki@chem.titech.ac.jp)

The first total synthesis and absolute structure assignment of PD-116740 (**2**) was achieved by exploiting two key steps: 1) a thermal ring expansion of a benzocyclobutene derivative, and 2) pinacol cyclization of biaryl dialdehyde.

The angucycline antibiotics, sharing a curved tetracyclic skeleton, have attracted much synthetic attention due to their interesting biological activities.<sup>1</sup> Besides fully aromatized congeners as **1**, a structurally unique class of compounds have been identified, including PD-116740 (**2**)<sup>2</sup> and TAN-1085 (**3**), possessing a characteristic “off-aromatic” ring with dihydroxylation (Chart 1). The synthesis of the latter class is particularly challenging, due to the difficulty of the stereocontrolled construction of the diol moieties.<sup>3</sup> In spite of much endeavor, the only example of a total synthesis is limited to our recent synthesis of **3**.<sup>4</sup>

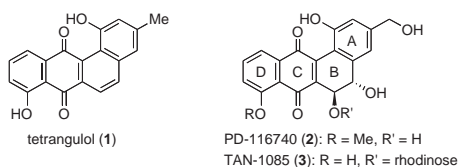
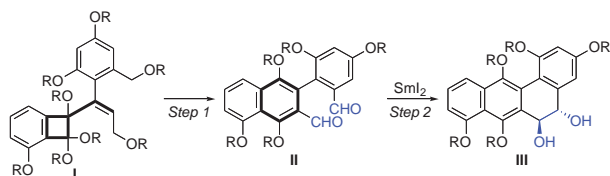


Chart 1.

Scheme 1 highlights two key steps in the synthesis of **3**: 1) a sequential electrocyclic reaction for facile construction of the biaryl **II**,<sup>5</sup> and 2) the SmI<sub>2</sub>-mediated pinacol cyclization to give *trans*-diol **III**.<sup>6</sup>

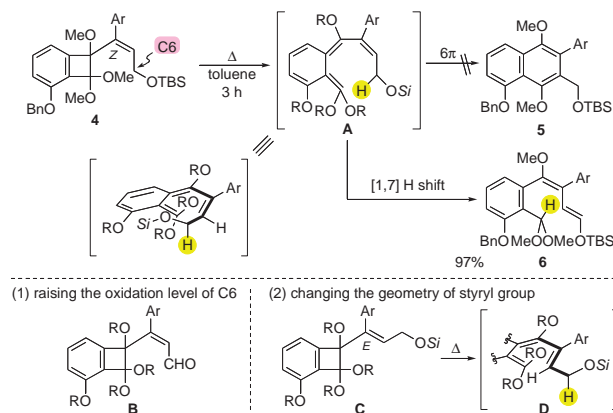
Among these, step 1 deserves a special note: all attempts to effect the ring expansion of benzocyclobutene **4** under thermal conditions failed, because of the competing [1,7] hydrogen shift (Scheme 2).<sup>7</sup>



Scheme 1. Outline of our synthetic route to **3**.

At this juncture, we envisioned two possible solutions. One was to “delete” the C6 hydrogen that participates in the sigmatropy. To our pleasant surprise, the ring expansion was remarkably facilitated at the aldehyde oxidation level as **B**, which was exploited in the synthesis of **3**.<sup>4</sup>

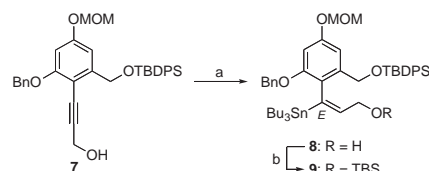
However, we had an alternative idea: If one employed the (*E*)-styryl group as **C**, the C6 hydrogens are disposed away from the cyclobutene ring as **D**, rendering the [1,7] hydrogen shift topologically impossible.



Scheme 2. Two solutions for suppressing [1,7] hydrogen shift.

In pursuit of a general synthetic route as well as clarifying the unknown absolute stereochemistry, we tested the latter idea within the context of the synthesis of **2**, which will be described in this communication.

The first task along these lines was the preparation of vinylstannane **9** (Scheme 3). 2-Propynyl alcohol **7**<sup>4</sup> was subjected to the Pd-catalyzed hydrostannylation, which proceeded smoothly in rigorous regioselectivity to give the vinylstannane **8** with desired *E* geometry. Silylation of the primary alcohol afforded **9**.

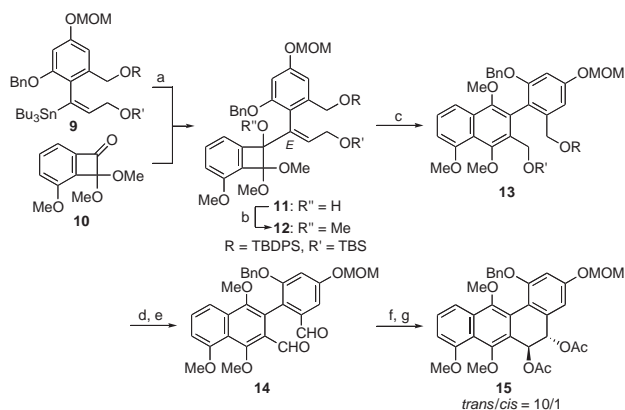


Scheme 3. (a) Bu<sub>3</sub>SnH, Pd(OAc)<sub>2</sub> (50 mol %), PPh<sub>3</sub> (100 mol %), THF, rt, 14 h, 90%; (b) TBSCl, imidazole, DMF, rt, 12 h, 92%; TBDPS = *t*-butyldiphenylsilyl, TBS = *t*-butyldimethylsilyl.

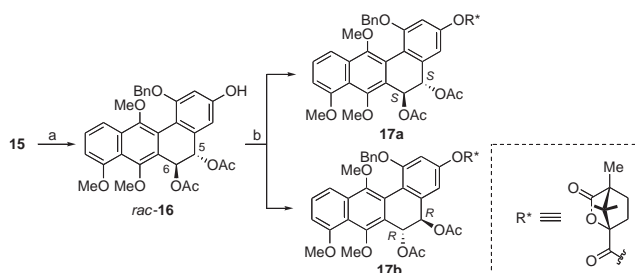
Scheme 4 illustrates the construction of the tetracycle. The vinyl lithium species generated from **9** (MeLi, THF, -78 °C, 2 h) was combined with benzocyclobutenone **10**<sup>8</sup> to afford adduct **11** in 83% yield. Alcohol **11** was converted to the corresponding methyl ether **12**, ready for the thermal ring expansion. Indeed, the planned reaction of **12** nicely proceeded upon refluxing in toluene for 3 h, giving the desired biaryl **13** in quantitative yield. Delightedly, no [1,7] hydrogen shift was observed.

Removal of two silyl groups in **13** followed by oxidation of the resulting diol gave dialdehyde **14**. Pinacol cyclization of **14** with SmI<sub>2</sub> proceeded smoothly to give, after acetylation of the resulting diol, diacetate **15** in 98% yield (*trans*/*cis* = 10/1, <sup>1</sup>H NMR). Recrystallization (hexane–EtOAc) afforded *trans*-**15** in pure form.

At this stage, optical resolution was carried out (Scheme 5).



**Scheme 4.** (a) MeLi, THF,  $-78^{\circ}\text{C}$ , 2 h; **10**, THF,  $-78 \rightarrow -10^{\circ}\text{C}$ , 2.5 h, 83%; (b) *n*-BuLi, Et<sub>2</sub>O,  $-78^{\circ}\text{C}$ , 15 min; MeOTf, Et<sub>2</sub>O,  $-78 \rightarrow 0^{\circ}\text{C}$ , 1 h, 88%; (c) toluene, reflux, 3 h, quant.; (d) TBAF, THF, rt, 4 h, 93%; (e) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \rightarrow 0^{\circ}\text{C}$ , 1.5 h, 83%; (f) SmI<sub>2</sub>, THF,  $0^{\circ}\text{C}$ , 5 min; (g) Ac<sub>2</sub>O, DMAP, pyridine, rt, 12.5 h, 98% (2 steps), trans/cis = 10/1.

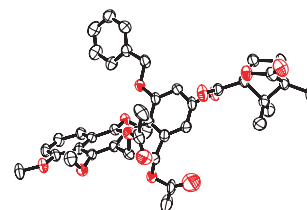


**Scheme 5.** (a) 0.5 M H<sub>2</sub>SO<sub>4</sub>, DME,  $60^{\circ}\text{C}$ , 5.5 h, 67%; (b) (–)-camphanic chloride, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h, 93%; DME = 1,2-dimethoxyethane.

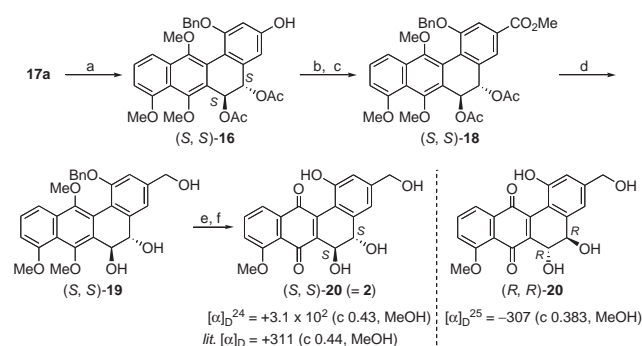
After detaching the MOM group in **15**, the resulting phenol **16** was combined with (–)-camphanic chloride and DMAP to give diastereomeric esters **17a/17b**. Separation by recycled HPLC with chiral stationary phase [DAICEL CHIRALPAK® IA (hexane/EtOAc = 2/1)] gave diastereomers **17a** (*t<sub>R</sub>* = 16.2 min) and **17b** (*t<sub>R</sub>* = 11.2 min).<sup>9</sup> The diastereomer **17a** gave nice single crystals (*i*-PrOH–EtOAc, colorless plates, mp 141.5–142.0 °C), and X-ray analysis established the (S, S) stereochemistry (Figure 1).<sup>10</sup>

Having assigned the stereostructures of the two diastereomers, removal of each camphanoyl group afforded an enantiomeric pair of diacetates (S, S)-**16** and (R, R)-**16**, which were further converted to the final product, respectively. Scheme 6 represents the transformation of (S, S)-**16**, which started with the Pd-catalyzed carbonylation of the corresponding triflate to methyl ester (S, S)-**18**. Treatment of (S, S)-**18** with DIBAL effected ester reduction and the removal of two acetyl groups to give triol (S, S)-**19**. Finally, hydrogenolysis of the benzyl group followed by oxidation with CAN afforded (S, S)-**20** in 67% yield. The same sequence of transformations converted (R, R)-**16** into (R, R)-**20**. It turned out that the sign and magnitude of optical rotation of (S, S)-**20** coincided to that of **2**, thereby establishing the absolute stereochemistry of the natural product as 5S, 6S.<sup>9</sup>

In summary, the first synthesis of **2** was achieved, establishing the absolute stereochemistry. Further work is now in



**Figure 1.** X-ray structure of **17a**. Hydrogen atoms are omitted for clarity.



**Scheme 6.** (a) *N,N*-dimethyl-1,3-propanediamine, THF, rt, 5.5 h, quant.; (b) Tf<sub>2</sub>O, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \rightarrow -35^{\circ}\text{C}$ , 1 h, 81%; (c) CO, Pd(OAc)<sub>2</sub> (30 mol %), dppf (30 mol %), Et<sub>3</sub>N, MeOH, DMF,  $60^{\circ}\text{C}$ , 2.5 h, 60%; (d) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \rightarrow -35^{\circ}\text{C}$ , 1 h, 98%; (e) H<sub>2</sub>, 10% Pd/C, MeOH, rt, 30 min; (f) CAN, CH<sub>3</sub>CN, H<sub>2</sub>O,  $0^{\circ}\text{C}$ , 20 min, 67% (2 steps); dppf = 1,1'-bis(diphenylphosphino)ferrocene, CAN = cerium ammonium nitrate.

progress to develop a general, enantioselective synthetic route to this class of compounds.

This work was partially supported by the Global COE Program (Chemistry) and a Grant-in-Aid for Scientific Research (JSPS). JSPS Research Fellowship for Young Scientists to K. M. is also acknowledged.

## References and Notes

- For a review, see: J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, 9, 103.
- J. H. Wilton, D. C. Cheney, G. C. Hokanson, J. C. French, H. Cunheng, J. Clardy, *J. Org. Chem.* **1985**, 50, 3936.
- On synthesis of angucyclines, see: a) D. S. Larsen, M. D. O'Shea, *J. Org. Chem.* **1996**, 61, 5681. b) F. M. Hauser, W. A. Dorsch, D. Mal, *Org. Lett.* **2002**, 4, 2237. c) M. C. Carreño, A. Urbano, *Synlett* **2005**, 1.
- K. Ohmori, K. Mori, Y. Ishikawa, H. Tsuruta, S. Kuwahara, N. Harada, K. Suzuki, *Angew. Chem., Int. Ed.* **2004**, 43, 3167.
- a) T. Matsumoto, T. Hamura, M. Miyamoto, K. Suzuki, *Tetrahedron Lett.* **1998**, 39, 4853. b) T. Hamura, M. Miyamoto, T. Matsumoto, K. Suzuki, *Org. Lett.* **2002**, 4, 229. c) T. Hamura, M. Miyamoto, K. Imura, T. Matsumoto, K. Suzuki, *Org. Lett.* **2002**, 4, 1675.
- a) K. Ohmori, K. Kitamura, K. Suzuki, *Angew. Chem., Int. Ed.* **1999**, 38, 1226. b) K. Kitamura, K. Ohmori, T. Kawase, K. Suzuki, *Angew. Chem., Int. Ed.* **1999**, 38, 1229.
- For computational study on these competing processes, see: Z. R. Akerling, J. E. Norton, K. N. Houk, *Org. Lett.* **2004**, 6, 4273.
- T. Hamura, T. Hosoya, H. Yamaguchi, Y. Kuriyama, M. Tanabe, M. Miyamoto, Y. Yasui, T. Matsumoto, K. Suzuki, *Helv. Chim. Acta* **2002**, 85, 3589, and references therein.
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett>.
- Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-676052.