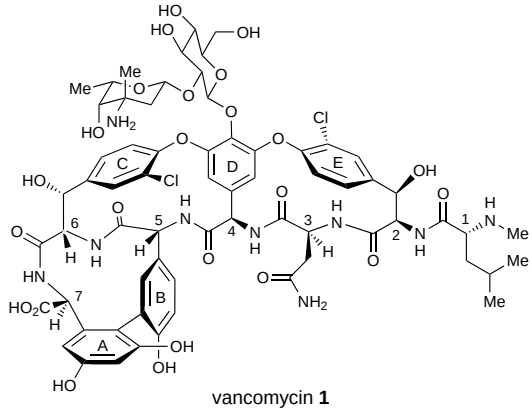
A Suzuki coupling–macrolactamization approach to the *AB-COD* bicyclic system of vancomycin

K. C. Nicolaou,* Joshi M. Ramanjulu, Swaminathan Natarajan, Stefan Bräse, Hui Li, Christopher N. C. Boddy and Frank Rübsam

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA and *Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA*

The effectiveness of the Suzuki coupling reaction in the formation of the *AB* biaryl moiety and the beneficial role of a preexisting *COD* ring system in a lactamization approach to the *AB-COD* ring system of vancomycin is demonstrated.

Vancomycin **1** is a polycyclic glycopeptide antibiotic effective against drug-resistant bacterial strains.[1] The daunting synthetic challenge posed by its structure[2,3] is largely due to the strained nature of the 12-membered biaryl framework (*AB* ring system) and the two 16-membered biaryl ethers (*COD* and *DOE* ring systems). While several approaches for the construction of the biaryl ether rings have been reported,[4–6] only two methods so far exist for the synthesis of the *AB* biaryl ring system.[7,8] Here we report a macrolactamization strategy to this system that has the potential of contributing to vancomycin's total synthesis.



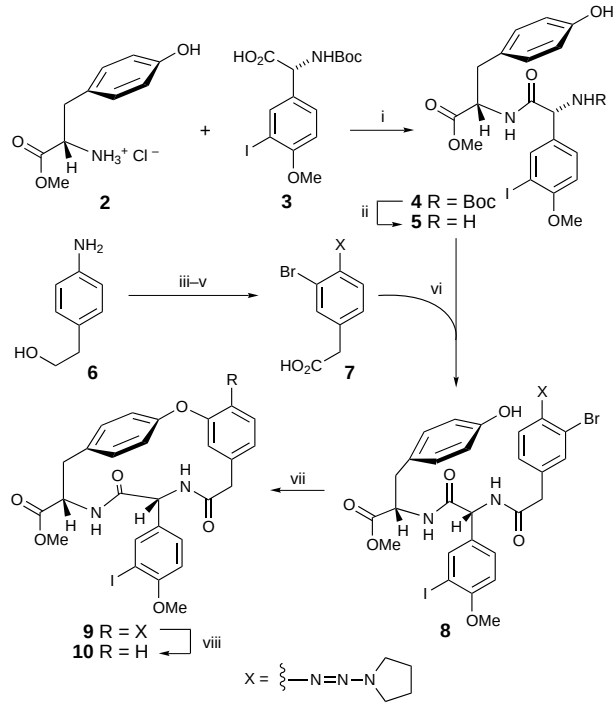
vancomycin **1**

Since attempts to form the *AB* framework of vancomycin as a single system by a lactamization approach were unsuccessful,[9] we reasoned that an attached *COD* structure might facilitate the process by preorganization, in much the same way as occurred in the elegant synthesis of a similar *AB-COD* framework by the Evans group, who employed a vanadium catalyst.[7] A Suzuki coupling reaction was chosen for the construction of the biaryl system which, of course, is potentially capable of atropisomerism.

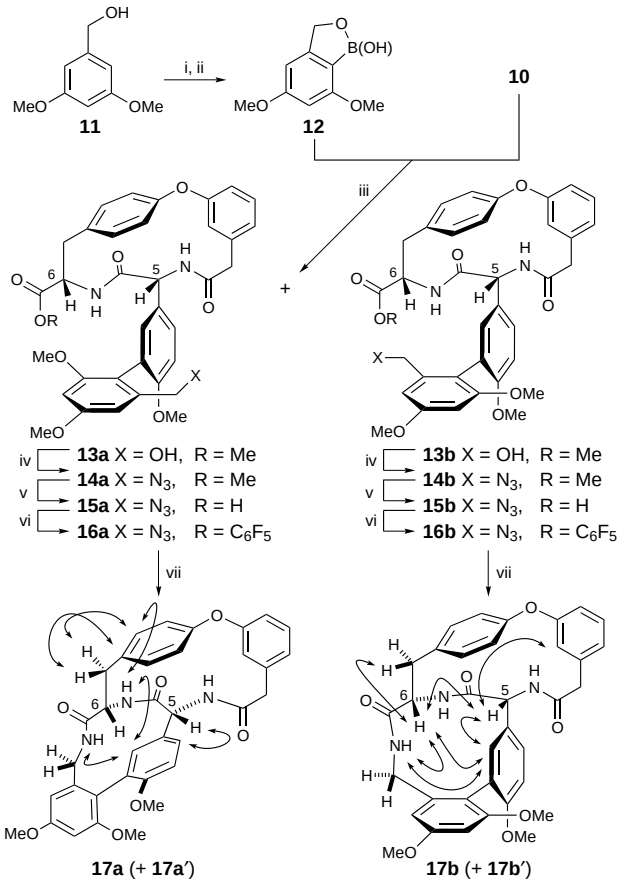
Scheme 1 summarizes the construction of the requisite *COD* model system **10**. Thus, (*S*)-tyrosine methyl ester **2** was coupled with (*R*)-4-methoxy-3-iodophenylglycine derivative **3**[8] in the presence of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and Et_3N to afford dipeptide **4**† in 80% yield.

Removal of the Boc group from **4** with TFA gave, in quantitative yield, amine **5**, which was coupled with triazene carboxylic acid **7** [prepared from **6** by monobromination (62%), triazene formation (83%) and 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO) oxidation (86%)] as described above for **2** and **3**, leading to tripeptide **8** (90% yield). Cyclization[5] of **8** in the presence of K_2CO_3–CuBr·SMe_2 in refluxing MeCN furnished triazene **9** in 67% yield, along with 10% recovered starting material and 6% of the arylglycine epimer of **9**. Chromatographic purification of **9** was followed by reductive removal of the triazene moiety with TFA–Cu_2O[10] at reflux to give the desired *COD* intermediate **10** (90% yield).

The elaboration of the *COD* building block **10** to the vancomycin bicyclic systems is shown in Scheme 2. Thus, 2,5-dimethoxybenzyl alcohol **11** was converted to boronic acid **12** by *N*-iodosuccinimide (NIS) iodination followed by reaction with BuLi and $B(OMe)_3$ in 27% overall yield (unoptimized). Suzuki coupling of iodide **10** with **12** was facilitated by $Pd(Ph_3P)_4$ catalyst and Na_2CO_3 to afford a 1 : 1 mixture of the two atropisomers **13a** and **13b** in 80% combined yield.[9,11] Suzuki coupling of the parent boronic acid corresponding to **12** (without the methoxy groups) with iodide **10** (Scheme 2) led to



Scheme 1 *Reagents and conditions*: i, HBTU (1.2 equiv.), Et_3N (3 equiv.), DMF 0 → 25 °C, 3 h, 90%; ii, TFA–CH_2Cl_2 (1 : 1), 0 °C, 1 h, 100%; iii, NBS (1.2 equiv.), DMF, 62%; iv, conc. HCl (1.2 equiv.), $NaNO_2$ (1 equiv.), 25 ml of 1 M NaOH, K_2CO_3 (2 equiv.), pyrrolidine (10 equiv.), 83%; v, TEMPO (1 equiv.), KBr (0.1 equiv.), NaOCl (1.3 equiv.), acetone–5% $NaHCO_3$ (1 : 1), 86%; vi, HBTU (1.2 equiv.), Et_3N (3 equiv.), DMF, 0 → 25 °C, 3 h, 90%; vii, CuBr·SMe_2 (2.9 equiv.), K_2CO_3 (2.4 equiv.), pyridine, (3 equiv.), MeCN, reflux, 36 h, 67%; viii, TFA (2.2 equiv.), Cu_2O (5 equiv.), MeCN–THF–H_2O (1 : 1 : 0.5), reflux, 1 h, 90%



Scheme 2 *Reagents and conditions*: i, NIS (1.2 equiv.), DMF, 25 °C, 12 h, 89%; ii, BuLi (2.1 equiv.), $B(OMe)_3$ (3 equiv.), THF, −40 → 25 °C, 3 h, dil. HCl, 30%; iii, $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (1 equiv.), MeOH–toluene–H_2O, 90 °C, 2 h, 80%; iv, HN_3 (5 equiv.), DEAD (5 equiv.), PPh_3 (5 equiv.), THF, 0 → 25 °C, 1 h, 69%; v, LiOH (1.5 equiv.), THF–H_2O (1 : 1), 0 °C, 0.5 h, 100%; vi, C_6F_5OH (2 equiv.), DCC (1.2 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 25 °C, 1 h; vii, 4-pyrrolidinopyrridine (3 equiv.), 10% Pd/C (30 mol%), dioxane–EtOH–cyclohexene (90 : 8 : 2), high dilution, 90 °C, 5 h, 30% from **15a**

a single compound by TLC and ^{1}H NMR spectroscopy, supporting the atropisomeric relationship of isomers **13a** and **13b** (no epimerization at C5 and C6). In contrast to the simpler coupling product, isomers **13a** and **13b** did not interconvert, even at 333 K. The two isomers were chromatographically separated and individually elaborated further. Thus, the more polar compound **13a** (R_f = 0.20, silica, 80% EtOAc in hexanes) was treated with HN_3–diethyl azodicarboxylate (DEAD)–PPh_3[9] (**CAUTION**: hydrazoic acid is toxic and explosive!) to afford azide **14a** (69% yield) which was saponified (LiOH, THF–H_2O, 0 °C) and converted to the corresponding pentafluorophenyl ester **16a** *via* carboxylic acid **15a**. Slow addition of a dioxane–cyclohexene solution of crude **16a** to a mixture of 10% Pd/C and pyrrolidinopyridine in dioxane and EtOH at 90 °C led to the formation of two cyclic products, **17a** and **17a′** epimeric at C-6 (*ca.* 1 : 2 ratio) in 30% combined yield overall from acid **15a**. The less polar atropisomer **13b** (R_f = 0.30, silica, 80% EtOAc in hexanes) was subjected to the same sequence of reactions, leading to **17b**‡ and **17b′** in similar yields. The observed epimerization at C-6, which is presumed to occur in the final step of the sequence, may not be an issue when the entire *AB-COD-DOE* framework of vancomycin is in place, particularly if thermodynamics favour the desired stereoisomer.

The stereochemical assignments of the four bicyclic systems **17a**, **17a′**, **17b** and **17b′** were based on ^{1}H–^{1}H NOESY experiments, which revealed the NOEs for **17a** and **17b** shown in Scheme 2.

In summary, we have demonstrated the power of the Suzuki coupling reaction in the formation of the fully substituted *AB* biaryl moiety[9,11] and the beneficial effect of a preexisting *COD* ring system in a lactamization approach to the *AB* ring system of vancomycin. The asymmetric version of the Suzuki reaction and its application in an intramolecular sense may offer further opportunities in this area of synthesis.

This work was financially supported by the National Institutes of Health (USA) and the Skaggs Institute for Chemical Biology.

J. M. R. acknowledges the NIH, S. B. the NATO/DAAD, and F. R. the Alexander von Humboldt-Stiftung for post-doctoral fellowships. Dedicated to Professor Madeleine Joullié on the occasion of her 70th birthday.

Footnotes and References

* E-mail: kcn@scripps.edu

† All new compounds exhibited satisfactory spectral and exact mass data.

‡ *Selected data* for **17b**: R_f = 0.31 [silica, 5% MeOH in $CHCl_3$]; $[\alpha]_D^{25}$ −31.5 (*c* 0.20 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2919, 2848, 1725, 1640, 1605, 1504, 1459, 1228, 1152, 1092; δ_H(600 MHz, $CDCl_3$, 323 K) 2.47 (dd, *J* 12.0, 13.2, 1 H, CH_2), 3.47 (s, 3 H, OCH_3), 3.45, 3.57 (AB system, J_{AB} 15.0, 2 H, CH_2), 3.65 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.72 (dd, *J* 2.7, 12.0, 1 H, CH_2), 3.74 (dd, *J* 5.9, 14.9, 1 H, CH_2), 4.16 (ddd, *J* 2.7, 11.4, 13.2, 1 H, CH), 4.2–4.3 (m, 1 H, CH_2), 5.04 (d, *J* 5.8, 1 H, CH), 5.12 (br d, 1 H, NH), 5.63 (br dd, 1 H, NH), 5.78 (br s, 1 H, Ar-H), 6.32 (br s, 1 H, Ar-H), 6.48 (d, *J* 2.0, 1 H, Ar-H), 6.57 (d, *J* 2.0, 1 H, Ar-H), 6.78 (d, *J* 7.2, 1 H, Ar-H), 6.94 (d, *J* 8.7 Hz, 1 H, Ar-H), 6.81 (dd, *J* 2.4, 8.1, 1 H, Ar-H), 7.03–7.05 (m, 3 H, Ar-H), 7.08 (d, *J* 8.1, 1 H, Ar-H), 7.20 (dd, *J* 2.3, 8.8, 1 H, Ar-H), 7.22 (d, *J* 6.3, 1 H, Ar-H), 7.29 (dd, *J* 2.0, 8.1, 1 H, Ar-H); δ_C(150.84 MHz, $CDCl_3$, 323 K) 35.0, 43.4, 43.6, 49.2, 55.1, 56.1, 56.6, 56.8, 99.23, 108.23, 111.9, 112.4, 114.1, 116.9, 119.7, 121.1, 122.1, 123.4, 125.6, 129.1, 130.0, 130.5, 132.9, 134.4, 135.5, 136.6, 137.7, 154.1, 156.9, 158.1, 160.0, 160.9, 169.1, 170.7, 171.3; HRMS (FAB): calc. for $C_{35}H_{33}N_3O_7$ (M + Cs^+), 740.1373. Found, 740.1398.

1 *Glycopeptide Antibiotics*, ed. R. Nagarajan, Dekker, New York, 1994.
2 G. M. Sheldrick, P. G. Jones, O. Kennard, D. H. Williams and G. A. Smith, *Nature*, 1978, **271**, 223; P. J. Loll, A. E. Bevivino, B. D. Korty and P. H. Axelson, *J. Am. Chem. Soc.*, 1997, **119**, 1516.
3 M. H. McCormick, W. M. Stark, R. C. Pittenger and G. M. McGuire, *Antibiot. Ann.*, 1955–1956, 606.
4 D. A. Evans, J. C. Barrow, P. S. Watson, A. M. Ratz, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, J. A. Ellman, S. D. Rychnovsky and J. Lacour, *J. Am. Chem. Soc.*, 1997, **119**, 3419; M. Boischoussy, L. Neuville, R. Beugelmans and J. P. Zhu, *J. Org. Chem.*, 1996, **61**, 9309; D. L. Boger, R. M. Borzilleri and S. Nukui, *J. Org. Chem.*, 1996, **61**, 3561; H. Konishi, T. Okuno, S. Nishiyama, S. Yamamura, K. Koyasu and Y. Terada, *Tetrahedron Lett.*, 1996, **37**, 8791; A. J. Pearson, G. Bignan, P. Zhang and M. Celliah, *J. Org. Chem.*, 1996, **61**, 3940; T. Inoue, T. Sasaki, H. Takayanagi, Y. Harigaya, O. Hoshino, H. Hara and T. Inaba, *J. Org. Chem.*, 1996, **61**, 3936.
5 K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T. Y. Yue, H. Li, S. Bräse and J. M. Ramanjulu, *J. Am. Chem. Soc.*, 1997, **119**, 3421.
6 For recent reviews for the synthesis of glycopeptides, see A. V. R. Rao, M. K. Gurjar, K. L. Reddy and A. S. Rao, *Chem. Rev.*, 1995, **95**, 2135; J. P. Zhu, *Synlett*, 1997, 133 and references cited therein.
7 D. A. Evans and C. J. Dinsmore, *Tetrahedron Lett.*, 1993, **34**, 6029; D. A. Evans, C. J. Dinsmore, A. M. Ratz, D. A. Evrard and J. C. Barrow, *J. Am. Chem. Soc.*, 1997, **119**, 3417.
8 K. C. Nicolaou, X.-J. Chu, J. M. Ramanjulu, S. Natarajan, S. Bräse, F. Rübsam and C. N. C. Boddy, *Angew. Chem.*, 1997, **109**, 1518; *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1539.
9 A. G. Brown, M. J. Crimmin and P. D. Edwards, *J. Chem. Soc., Perkin Trans. 1*, 1992, 123.
10 T. Cohen, A. G. Dietz, Jr. and J. R. Miser, *J. Org. Chem.*, 1977, **42**, 2053.
11 M. K. Gurjar and N. K. Tripathy, *Tetrahedron Lett.*, 1997, **38**, 2163.

Received in Corvallis, OR, USA, 14th July 1997; 7/05050J