ORGANIC LETTERS

2001
Vol. 3, No. 13
2033−2036

Stereoselective Synthesis of the Axially Chiral A–B Ring System of Vancomycin Utilizing a Planar Chiral Arene Chromium Complex

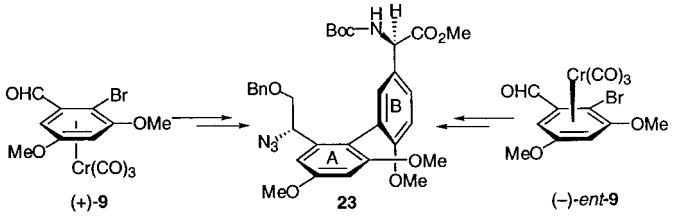
Ken Kamikawa,[†,‡] Atsushi Tachibana,[†] Suguru Sugimoto,[†] and Motokazu Uemura*[,†,‡]

Department of Chemistry, Faculty of Integrated Arts and Sciences, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan, and Research Institute for Advanced Sciences and Technology, Osaka Prefecture University, Sakai, Osaka 599-8570, Japan

uemura@ms.cias.osakafu-u.ac.jp

Received April 18, 2001

ABSTRACT



The axial biaryl ring system of vancomycin was stereoselectively synthesized by utilizing a planar chiral tricarbonyl(arylhalide)chromium complex. Both enantiomers of the planar chiral (arylbromide)chromium complexes, (+)-9 and *ent*-(–)-9, can be stereoselectively transferred to an absolutely identical key intermediate 23 for the vancomycin A–B ring system by the diastereoselective Suzuki–Miyaura cross-coupling reaction as key step.

Vancomycin (**1**) and the related family of antibiotics have attracted multidisciplinary interest for decades due to their clinical use and have been enlisted as the drug of last resort for the treatment of infections due to methicillin-resistant *Staphylococcus aureus* and other Gram-positive organisms resistant to β-lactam antibiotics (Figure 1).[1] Its unique structure and the recent emergence of the vancomycin-resistance phenomenon have provided stimulus to the development of efficient methodologies for the synthesis of this natural product.[2] In recent years, the Evans, Nicolaou, and Boger groups have independently accomplished landmark total syntheses of vancomycin agylcon.[3] One essential problem in the total synthesis of vanconycin is the stereoselective construction of the axially chiral A−B biaryl ring system.[3,4] The Evans group demonstrates the synthesis of biaryl system of vancomycin by the intramolecular oxidative

* Fax: 81-722-54-9931. Tel: 81-722-54-9698.
† Department of Chemistry.
‡ Research Institute for Advanced Sciences and Technology.

(1) (a) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1173−1193. (b) Zhu, J. *Exp. Opin. Ther. Pat.* **1999**, *38*, 1005−1019.

(2) (a) Nicolau, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096−2152. (b) Zhu, J. *Synlett* **1997**, 133−144. (c) Rama Rao, A. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2167.

(3) (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704; 2704−2708. (b) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584−2601. (c) Nicolau, K. C.; Boddy, C. N. C.; Li, H.; Koumbis, A. E.; Hughes, R.; Natarajan, S.; Jain, N. F.; Ramanjulu, J. M.; Bräse, S.; Solomon, M. E. *Chem. Eur. J.* **1999**, *5*, 2602−2621. (d) Nicolau, K. C.; Koumbis, A. E.; Takayanagi, M.; Naatarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chem. Eur. J.* **1999**, *5*, 2622−2647. (e) Nicolau, K. C.; Natarajan, S.; Li. H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2708−2714; 2714−2716; 2717−2729. (f) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226−3227. (g) Nicolau, K. C.; Mitchell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 240−244.

10.1021/ol010076f CCC: $20.00
Published on Web 06/01/2001

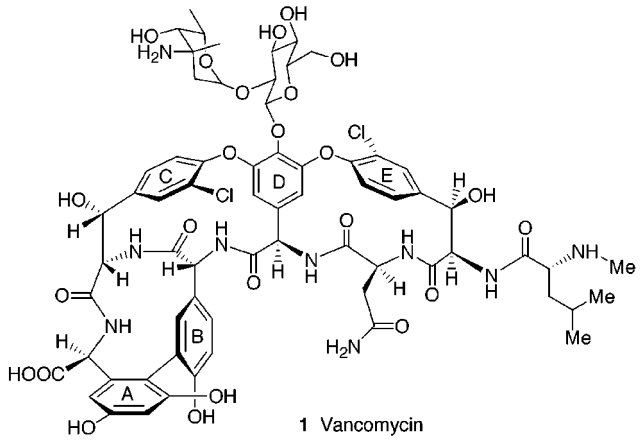
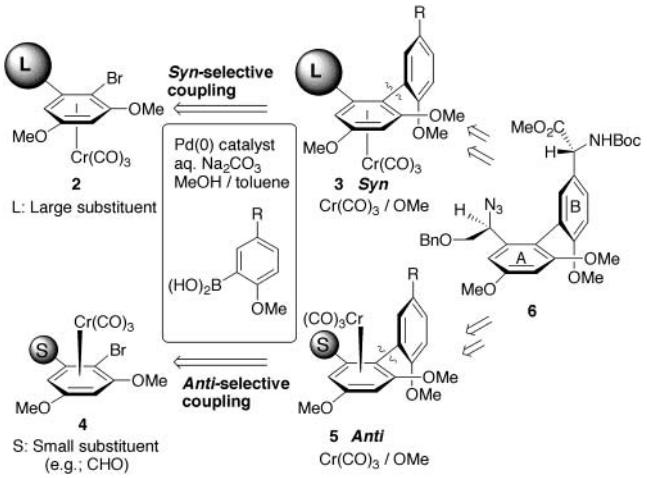


Figure 1.

coupling of electron-rich arenes.[3a] In this method, an introduction of an additional methoxy group on the B-ring at the oxidative coupling step and subsequent axial isomerization of the initially formed unnatural A−B ring system are required for the synthesis of natural vancomycin. On the other hand, the Nicolau[3e] and Boger[3f] groups employed the intermolecular Suzuki−Miyaura cross-coupling for the construction of the biaryl system. In the palladium(0)-catalyzed cross-coupling of both arenes, the asymmetric synthesis of the axially chiral vancomycin A−B biaryl was achieved by Nicolaou via the intermolecular coupling reaction of iodoarene containing the chiral benzylic center, the precursor of the C−O−D ring system, with arylboronic acid in the presence of a chiral palladium catalyst.[3c] Generally, the asymmetric version of the intermolecular cross-coupling process is not easy to accomplish for highly enantioselective synthesis of the axial biaryls, particularly in the case of cross-coupling between two aromatic substrates without the chiral center in the neighborhood at the bond-forming position. In this paper, we wish to report the asymmetric synthesis of the axially chiral A−B ring system of vancomycin utilizing planar chiral arylbromide chromium complexes.

In continuation of our studies on development of a planar chiral (arene)chromium complex in the asymmetric reaction, we have already reported that both enantiomers of the axial biaryls could be stereoselectively synthesized starting from an identical planar chiral (arylhalide)chromium complex.[5] Thus, the planar chiral tricarbonyl(2,6-disubstituted bromobenzene)chromium was coupled with *o*-substituted phenylboronic acids in refluxing aqueous methanol to give kinetically controlled coupling products with *syn*-relationship between the tricarbonylchromium fragment and *o*-substituents derived from phenylboronic acids. Subsequent heating of the *syn*-coupling products in a higher boiling solvent, e.g., toluene or xylene, caused them to be axially isomerized to the thermodynamically stable *anti*-isomers. Herein, we have designed a method so that both enantiomers of the planar chiral phenylbromide chromium complex could be utilized for the preparation of the vancomycin A−B ring biaryl system by sterically modifying of the *ortho*-substituent as shown in Scheme 1. It is, therefore, presumed that the planar chiral arylbromide chromium complex **2** possessing a bulky *ortho*-substituent such as an sp^3 carbon is coupled with *o*-methoxyphenylboronic acid derivative to afford the *syn*-coupling product **3**, while the corresponding antipode of the planar chiral arene chromium complex **4** with a small substituent such as a formyl group gives the *anti*-product **5** by cross-coupling with the identical phenylboronic acid under the same reaction conditions. Both coupling products, *syn*-**3** and *anti*-product **5**, could be converted to an identical vancomycin A−B ring precursor **6**, since the axial chirality in both *syn*- and *anti*-coupling products is the same configuration.

Scheme 1



Both enantiomers of the planar chiral (2-bromo-3,5-dimethoxybenzaldehyde)$Cr(CO)_3$ complexes, (+)-**9** and *ent*-(−)-**9**, as a coupling partner were stereoselectively prepared (Scheme 2).[6] Diastereoselective *ortho* lithiation of benzaldehyde acetal chromium complexes **7** and **8** derived from (*S*)-1,2,4-butanetriol and α-D-glucopyranoside, subsequent bromination, and finally acidic hydrolysis gave (+)-**9** and *ent*-(−)-**9**, respectively, in good yields with high optical purity.[6]

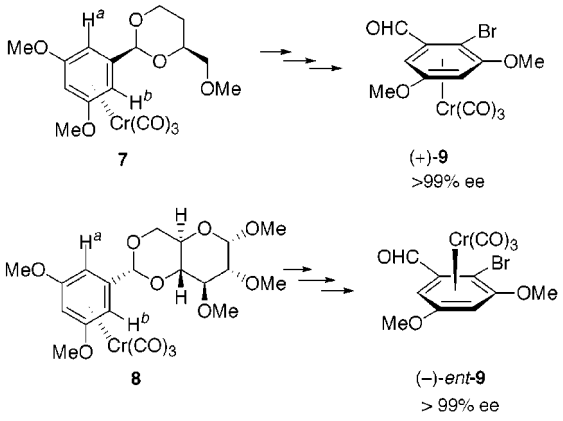
We initially employed (+)-(2-bromo-3,5-dimethoxybenzaldehyde)$Cr(CO)_3$ (**9**) for the construction of the axially chiral vancomycin A−B ring system (Scheme 3). The formyl group of the (+)-**9** chromium complex should be modified to a bulky substituent with an sp^3 carbon center for the preparation of a *syn*-biphenyl chromium complex in the palladium-

(4) (a) Lipshutz, B. H.; Peter-Müller, P.; Leinweber, D. *Tetrahedron Lett.* **1999**, *40*, 3677−3680. (b) Boisnard, S.; Neuville, L.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2000**, *2*, 2459−2462. (c) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426−6427.

(5) (a) Uemura, M.; Kamikawa, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2697−2698. (b) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375−1384. (c) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938−949.

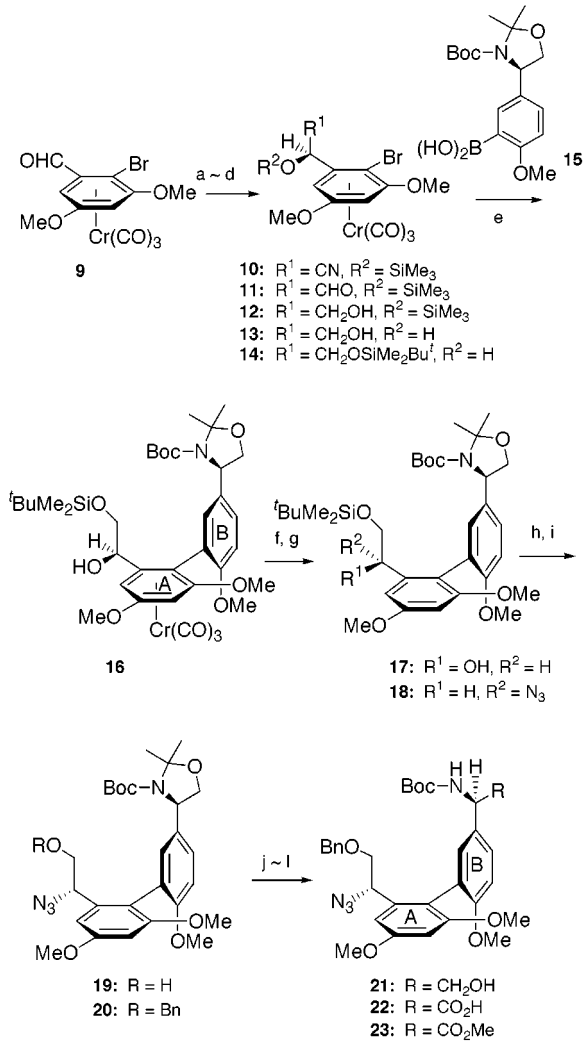
(6) Watanabe, T.; Shakadou, M.; Uemura, M. *Inorg. Chim. Acta*. **1999**, *296*, 80−85.

Scheme 2



(0)-catalyzed cross-coupling reaction. The chromium complex (+)-**9** ($[\alpha]^{21}_D$ +960, >99% ee) was treated with trimethylsilylcyanide in the presence of a catalytic amount of zinc iodide to give a single diastereomeric cyano hydrine chromium complex **10** ($[\alpha]^{29}_D$ −105.9, *c* 0.92 $CHCl_3$) in 95% yield.[7] Extremely high stereoselectivity in the nucleophilic addition step would be attributed to the conformation of the tricarbonylchromium-complexed benzaldehyde, in which the carbonyl oxygen is in *anti*-orientation to the *ortho* substituent as the result of a stereo-electronic effect.[8] Reduction of the nitrile of **10** with diisobutylaluminum hydride, subsequent further reduction of the resulting formyl group with zinc borohydride, and deprotection of the trimethylsilyl group produced a diol chromium complex **13** ($[\alpha]^{27}_D$ −254.8, *c* 0.23 $CHCl_3$). The homobenzylic alcohol of chromium complex **13** was regioselectively protected with *tert*-butyldimethylsilyl triflate to give a monosilyl-protected arene chromium complex **14** ($[\alpha]^{26}_D$ −77.3, *c* 0.44 $CHCl_3$) in 87% yield. With the sterically bulky *o*-substituted bromobenzene chromium complex in hand, we next examined the palladium-catalyzed cross-coupling with phenylboronic acid. The complex **14** was reacted with *o*-methoxyphenylboronic acid **15**[9] under the conditions[10] of 5 mol % of $Pd_2(dba)_3$, 0.2 equiv of $(o\text{-tolyl})_3P$ in a mixture of toluene/MeOH/1 M aqueous Na_2CO_3 (3/3/1), 80 °C, 10 min to give the expected *syn*-coupling product **16** ($[\alpha]^{22}_D$ −124, *c* 0.51 $CHCl_3$) in 85% yield without formation of the corresponding *anti*-isomer. The stereochemistry of the coupling product **16** was predicted by ^1H NMR, in which the OMe proton on the B-ring appeared at low field, 3.92 ppm, as the result of an anisotropic effect of the tricarbonylchromium fragment.[11] Conversion of the benzylic (*S*)-hydroxy group of **16** to a nitrogen atom with stereochemical inversion was easily achieved under Mitsunobu conditions.[12] Thus, the *syn*-coupling product **16** was oxidatively demetalated by exposure to sunlight, followed by treatment with $(PhO)_2PON_3$ in the presence of DEAD and PPh_3 to give (*R*)-azido compound **18** ($[\alpha]^{21}_D$ +9.1, *c* 0.13, $CHCl_3$). Both axial and benzylic stereochemistries of **18** were completely consistent with those of natural vancomycin. The azide compound **18** could be converted to

Scheme 3[a]



[a] Reagents and conditions: (a) Me_3SiCN, ZnI_2, CH_2Cl_2, 0 °C (95%); (b) DIBAL, CH_2Cl_2, −78 °C (56%); (c) (i) $Zn(BH_4)_2$, ether (72%); (ii) *n*-Bu_4NF, THF (62%); (d) ^{t}BuMe$_2$SiOTf, Et_3N, CH_2Cl_2 (87%); (e) (*S*)-**15**, $Pd_2(dba)_3$, $(o\text{-tolyl})_3P$, toluene/MeOH/1 M aq Na_2CO_3, 80 °C, 10 min (85%); (f) *hν* O_2, ether (73%); (g) $(PhO)_2PON_3$, DEAD, PPh_3, THF, rt (92%); (h) *n*-Bu_4NF, THF (83%); (i) BnBr, NaH, DMF (93%); (j) *p*-TsOH, MeOH (85%); (k) 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), NaOCl; (l) CH_2N_2 (53% from **21**).

(7) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55−56.

(8) Solladié-Cavallo, A. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, pp 99−133. (b) Davies, S. G.; McCarthy, T. D. In *Comprehensive Oragnometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 1039−1070.

(9) Phenylboronic acid **15** was prepared from (−)-*p*-methoxyphenylglycine by a modified procedure in ref 4a.

(10) (a) Brown, A. G.; Crimmine, M. J.; Edwards, P. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 123−130. (b) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226−3227.

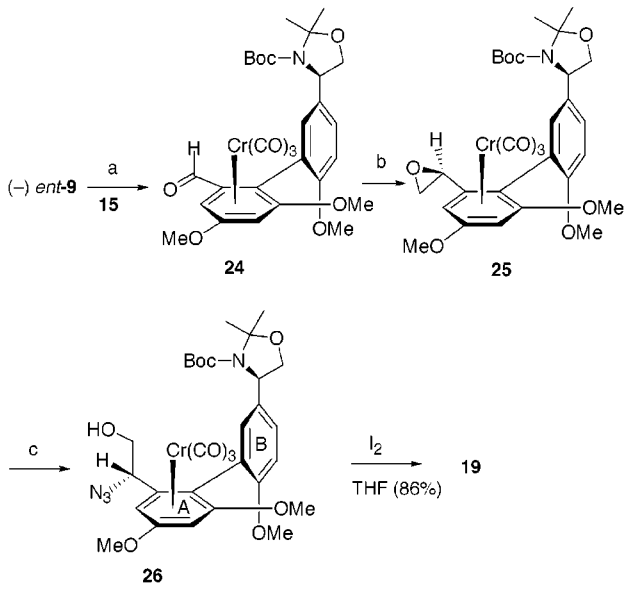
(11) (a) Uemura, M.; Nishimura, H.; Kamikawa, K.; Shiro, M. *Inorg. Chim. Acta* **1994**, *222*, 63−70. (b) Bringmann, G.; Göbel, L.; Peters, K.; Peters, E.-M.; Schnering, H. G. *Inorg. Chim. Acta* **1994**, *222*, 255−260.

(12) Mitsunobu, O. *Synthesis* **1981**, 1−28.

Nicolaou's key intermediate for the A−B ring system of vancomycin synthesis as follows. Thus, the *tert*-butyldimethylsilyl ether was changed to benzyl ether **20** ($[\alpha]^{23}_D$ −6.8, *c* 0.3 $CHCl_3$) under the usual conditions. Hydrolysis of the acetal function of **20** with *p*-toluenesulfonic acid and subsequent oxidation with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[13] and finally esterification with diazomethane gave the compound **23**, whose spectral data were consistent with reported values.[3e]

Similarly, *ent*-(−)-**9** was stereoselectively converted to the same key intermediate for the vancomycin A−B ring system via *anti*-selective cross-coupling (Scheme 4). *Ent*-(−)-**9** (99% ee) was coupled with *o*-methoxyphenylboronic acid derivative **15** to give a thermodynamically controlled *anti*-product **24** ($[\alpha]^{22}_D$ −223.1, *c* 0.26 $CHCl_3$) in 72% yield without formation of the *syn*-diastereomer under the same reaction conditions. The methoxyl proton on the B-ring of *anti*-isomer **24** appeared at 3.72 ppm. The *anti*-coupling product **24** would be formed by axial isomerization of the *syn*-coupling product as a result of sterically small substituents at both *ortho* positions under the reaction conditions. We next designed stereoselective construction of the benzylic chiral center with introduction of a nitrogen atom from aldehyde of the *anti*-coupling product **24**. Epoxidation of the chromium complex **24** was carried out using chloromethyliodide and MeLi in THF solution at −78 °C to give an epoxide **25** ($[\alpha]^{31}_D$ +24.9, *c* 0.53 $CHCl_3$) as a single diastereomer in 73% yield.[14] The stereoselctive epoxide formation is based on the nucleophilic addition of the reagent from the opposite face to the *anti*-oriented carbonyl group of the chromium-complexed benzaldehyde. Subsequent ring-opening of the epoxide **25** with a nitrogen nucleophile is required with stereochemical retention at the benzylic position for synthesis of the vancomycin system. Therefore, we next investigated S_N1 type reaction via a chromium-stabilized benzylic carbocation intermediate for the nitrogen nucleophile introduction with stereochemical retention.[15] After several experiments, we fortunately found that treatment of the epoxide **25** with timethylsilyl azide in the presence of $BF_3{\cdot}OEt_2$ in THF at −10 °C gave an azide compound **26** ($[\alpha]^{17}_D$ +39.5, *c* 0.40 $CHCl_3$) as a single diastereomer in 80% yield. The azide chromium complex **26** was treated with iodine in THF to give tricarbonylchromium free compound in 86% yield, in which all spectral data and optical rotation were completly consistent with those of the key intermediate **19** ($[\alpha]^{23}_D$ −32.7 (*c* 0.42 $CHCl_3$) prepared from the *syn*-coupling product **16**. In this way, the *anti* biphenyl chromium complex was also stereoselectively converted to the key intermediate for the vancomycin A−B ring system.

Scheme 4[a]



[a] Reagents and conditions; (a) $Pd_2(dba)_3$, (*o*-tolyl)$_3$P, toluene/MeOH/1 M aq Na_2CO_3 (3/3/1), (72%); (b) $ClCH_2I$, MeLi, THF (73%); (c) $TMSN_3$, $BF_3{\cdot}OEt_2$, THF, −10 °C (80%).

In conclusion, both enantiomers of the planar chiral arylbromide chromium complex could be stereoselectively converted to the identical key intermediate for the synthesis of the axially chiral A−B ring system of vancomycin. Thus, the planar chiral arene chromium complexes play a significant role for the stereoselective construction of the axially chiral biaryl and creation of the benzylic stereogenic center. We are currently investigating the synthesis of the C−O−D−O−E ring system of vancomycin.

Supporting Information Available: This work was supported by a Grant-in-Aid from The Ministry of Education, Science, Sports and Culture of Japan and Grant-in-Aid for Faculty of Integrated Arts and Sciences from Osaka Prefecture University (to K.K.).

Supporting Information Available: Experimental procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010076F

(13) (a) Annelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Nooy, A. E. J.; Besemer, A. C.; Bekkum Van, H. *Synthesis* **1996**, 1153−1174.

(14) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795−798.

(15) (a) Uemura, M.; Kobayashi, T.; Isobe, K.; Minami, T.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 2859−2863. (b) Davies, S. G.; Donohoe, T. J. *Synlett* **1993**, 323−332.