Synthetic approach to kendomycin: preparation of the C-glycosidic core†

Tetsuya Sengoku,[a] **Hirokazu Arimoto***[ab] **and Daisuke Uemura**[a]

[a] *Department of Chemistry, Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan. E-mail: arimoto@org.chem.nagoya-u.ac.jp; Fax: +81 52 789 5041; Tel: +81 52 789 2480*
[b] *Institute for Advanced Research, Nagoya University; and PRESTO, JST, Chikusa, Nagoya 464-8602, Japan*

Synthesis of the C13–C19 C-glycoside portion of kendomycin was achieved *via* oxidative pyran cyclization and Claisen rearrangement to construct the fully functionalized aromatic ring.

Since the recognition of vancomycin-resistant *enterococci* (VRE) in 1988, the emergence of vancomycin-resistant *Staphylococcus aureus* (VRSA) has been anticipated. The first clinical infection was reported in the USA in 2002. Thus, chemical study contributing to the design of a new anti VRSA drug has been of great importance.[1] In the course of our continuing interest in these problems, we have reported a "vancomycin polymer" with enhanced antibacterial activity against VRE.[2]

Recently, Zeeck has reported that kendomycin, which was originally isolated as an antagonist for endothelin receptor,[3] exhibits excellent antibacterial activities against the vancomycin-resistant *S. aureus* MU50 strain.[4] Our long-standing interest in vancomycin-resistance prompted us to initiate synthetic studies of **1**, with the intent of clarifying the structure–activity relationship. Here we describe our synthesis of the highly functionalized C13–C19 C-glycosidic core of kendomycin.[5]

Our synthetic plan is outlined in Fig. 1. We envisaged that the quinone-methide moiety of **1** could be constructed in the latter stage of the synthesis by oxidation of an aromatic precursor. Thus, we set our initial goal as the stereoselective synthesis of aldehyde **2**, with preparation of the fully substituted benzene ring along with stereocontrol at the C-glycosidic linkage being the primary synthetic challenge.

Our synthesis commenced with known benzoate **4** (Scheme 1).[6] Lithium aluminium hydride reduction of the ester to an alcohol, followed by methylation, gave the methyl ether. Treatment of the ether with sodium iodide and BF$_3$ etherate afforded the corresponding benzyl iodide **5**. Diastereoselective alkylation of D-valine-derived Evans oxazolidinone **6**[7] with **5** proceeded smoothly, and the crude product was reduced with lithium aluminium hydride to alcohol **7**. The optical purity of alcohol **7** was determined as > 99% ee from ¹H NMR spectra of the corresponding (+)- and (−)-MTPA esters.
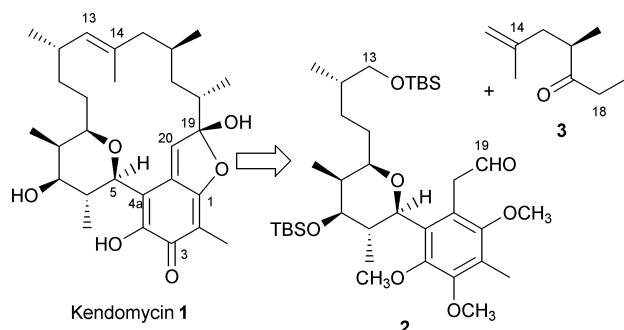
Alcohol **7** was oxidized by Dess–Martin periodinane[8] to aldehyde, and then reacted with Roush's crotyl boronate[9] to obtain alkene **8** as a diastereomerically homogeneous product. Cleavage of the terminal double bond with OsO$_4$–NaIO$_4$ afforded aldehyde **9**. Aldehyde **9** reacted with the organolithium species arising through the interaction of *t*-butyl lithium and iodide **10**, to furnish the adduct as a 5.5 : 1 diastereomeric mixture. The major isomer **11** (62% yield) was proved to be the expected Felkin–Anh isomer.

Installation of the hydroxyl group on the aromatic ring proved to be more difficult than anticipated, presumably due to over-oxidation. The secondary alcohol in **11** was protected as acetate (100% yield). Treatment of the acetate with 3 equivalents of mCPBA, followed by removal of the acetyl group afforded phenol **12** in moderate yield (66% yield).

Numerous attempts were made to improve this hydroxylation, and finally the four-step procedure described below was devised (Scheme 2).

Alcohol **11** was first monobrominated with pyridinium bromide-perbromide, and the secondary alcohol was protected as the ethoxyethyl ether (98% in 2 steps). Bromide **13** was lithiated with *n*-butyl lithium, and then trapped with B(OCH$_3$)$_3$. Oxidation by H$_2$O$_2$ afforded **14**. This protocol has more steps, but the overall yield (80% in 4 steps) was found to be superior to that of mCPBA hydroxylation. Moreover, the procedures were easy to conduct and reliable.

Fig. 1 Retrosynthetic analysis of kendomycin.
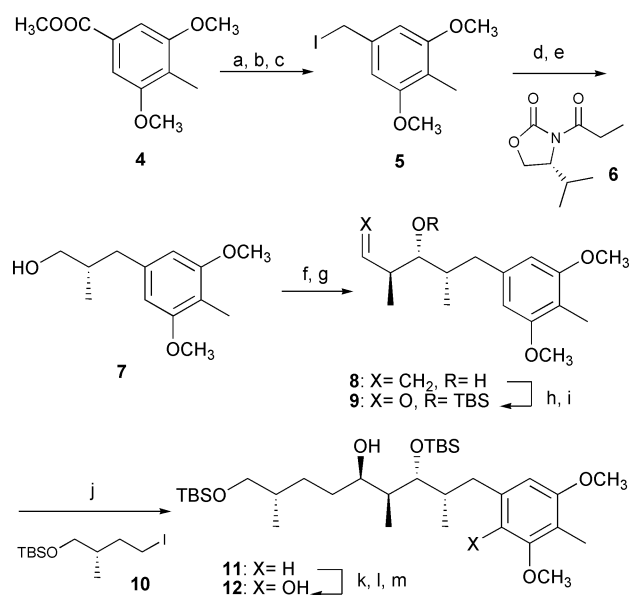
Scheme 1 a) LiAlH$_4$, THF, 40 °C; b) CH$_3$I, NaH, THF, 0 °C, 96% in 2 steps; c) NaI, BF$_3$ etherate, CH$_3$CN, room temp., 82%; d) **6**, NaHMDS, THF, −78 °C; e) LiAlH$_4$, THF, −78 °C to 0 °C, 91% in 2 steps; f) Dess–Martin periodinane, CH$_2$Cl$_2$, room temp.; g) (*R*,*R*)-diisopropyl tartrate, (*E*)-crotyl boronate, MS4A, toluene, −78 °C, 71% in 2 steps; h) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C, 100%; i) OsO$_4$, NaIO$_4$, aq. THF, room temp.; j) **10** (3 equiv.), *t*-BuLi (6 equiv.), THF, −78 °C, yield of major isomer **11** 62% in 2 steps; k) Ac$_2$O, DMAP, pyridine, room temp., 100%; l) mCPBA (3 equiv.), CH$_2$Cl$_2$, room temp.; m) DIBAL-H, CH$_2$Cl$_2$, −78 °C, 66% in 2 steps.
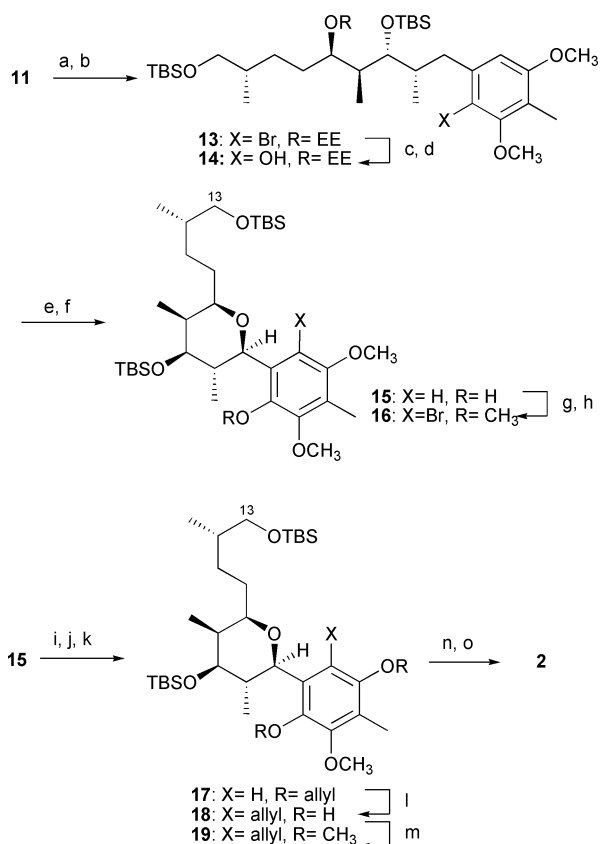
Scheme 2 a) Pyridinium bromide perbromide, K_2CO_3, CH_2Cl_2, 0 °C to room temp.; b) ethyl vinyl ether, PPTS, room temp., 98% in 2 steps; c) *n*-BuLi (2.5 equiv.), then $B(OCH_3)_3$, THF, −78 °C; d) H_2O_2, sat. Na_2CO_3 aq., 82% in 2 steps; e) PPTS, *n*-propanol, room temp., 94%; f) Ag_2O, CH_2Cl_2, room temp., 94%; g) CH_3I, K_2CO_3, acetone, reflux, 100%; h) pyridinium bromide perbromide, CH_2Cl_2, room temp., 40%; i) $(CF_3COO)_2IPh$, K_2CO_3, CH_3CN, H_2O, room temp.; j) $Na_2S_2O_4$, THF, H_2O, 0 °C, 83% in 2 steps; k) allyl bromide, K_2CO_3, acetone, reflux, 100%; l) *N*,*N*-dimethylaniline, reflux, 1.5 h, 66%; m) CH_3I, K_2CO_3, acetone, reflux, 100%; n) OsO_4, NMO, aq. acetone, room temp., 82%; o) $NaIO_4$, ethanol, room temp., 96%.

13: X= Br, R= EE
14: X= OH, R= EE

15: X= H, R= H
16: X= Br, R= CH$_3$

17: X= H, R= allyl
18: X= allyl, R= H
19: X= allyl, R= CH$_3$

The ethoxyethyl group in **14** was removed by mild acidic hydrolysis. The Ag_2O oxidation[10] of phenol proceeded at room temperature to form the pyran **15**. The mechanism for the formation of **15** is presumed to involve initial *o*-quinone methide formation. Intramolecular attack of the secondary alcohol on the quinone methide occurs so that the bulky aromatic substituent is oriented as equatorial. Actually, the coupling constant between C5-methine and adjacent C6-methine protons was 10.4 Hz in the ^1H NMR spectrum, clearly indicating the relationship of these protons as 1,2-diaxial.

Severe difficulties were also encountered in installing the sixth substituent on the aromatic nuclei. The pyran **15** could be converted to bromide **16** in 2 steps, however, attempts at Stille coupling with tributyl(vinyl)tin using $Pd(PPh_3)_4$ as a catalyst failed, presumably due to the steric hindrance.

Selective removal of a methyl ether in **15**,[11] followed by allylation, gave bis allyl ether **17**. The heating of **17** in dimethylaniline (degassed) at reflux, to our delight, formed **18** *via* a Claisen rearrangement in 66% yield. We anticipated that the allyl ether adjacent both to methoxy and pyranyl substituents would remain after the rearrangement; we could not, however, find any rearranged products with allyl ether. Efforts to provide more insight into this mechanism are underway.

The ^1H NMR spectrum of **18** in CDCl$_3$ revealed the existence of rotational isomerism at the C4a–C5 axis. The ratio of the major and minor rotamers was 5.1 : 1. When the two phenolic hydroxyl groups in **18** were methylated, the ratio of the rotamers was changed to 2.1 : 1.[12] Moreover, thin layer chromatographic analysis (silica gel, hexane–ether) of **19** gave two spots, indicating that the rotational isomerism was relatively slow at room temperature.

Oxidation of terminal alkene in **19** with OsO_4–NMO along with cleavage of the resultant diol with $NaIO_4$ afforded the desired aldehyde **2** (79% yield in 2 steps).

In summary, we have completed the asymmetric synthesis of the C-glycosidic core of kendomycin. Highlights of the synthesis are the Ag_2O-mediated oxidative cyclization of the pyran ring and also the Claisen rearrangement to construct fully substituted aromatic nuclei. Further efforts toward the total synthesis of kendomycin will be reported elsewhere.

Notes and references

† Electronic supplementary information (ESI) available: selected spectral data for compounds **7**, **8**, **10**, **11**, **12**, **15**, **16**, **17**, **18**, and **2**. See http://www.rsc.org/suppdata/cc/b4/b402391a/

1 D. H. Williams and B. Bardsley, *Angew. Chem., Int. Ed.*, 1999, **38**, 1172; K. C. Nicolaou, C. N. C. Boddy, S. Brase and N. Winssinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 2096; H. Arimoto, *J. Synth. Org. Chem. Jpn.*, 2003, **61**, 752.

2 H. Arimoto, K. Nishimura, T. Kinumi, I. Hayakawa and D. Uemura, *Chem. Commun.*, 1999, 1361; H. Arimoto, T. Oishi, M. Nishijima and T. Kinumi, *Tetrahedron Lett.*, 2001, **42**, 3347.

3 Y. Funahashi, N. Kawamura and T. Ishimaru, *Jap. Pat.*, 08 231 551 [A2 960 910] (1996) (*Chem. Abstr.*, 1997, **126**, 6553); Y. Funahashi, T. Ishimaru and N. Kawamura *Jap. Pat.*, 08 231 552 [A2 960 910] (1996) (*Chem. Abstr.*, 1996, **125**, 326518); M. H. Su, M. I. Hosken, B. J. Hotovec and T. L. Johnston, *US Pat.*, 5 728 727 [A9803 17] (1998) (*Chem. Abstr.*, 1998, **128**, 239489).

4 H. B. Bode and A. Zeeck, *J. Chem. Soc., Perkin Trans. 1*, 2000, 323; H. B. Bode and A. Zeeck, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2665.

5 Other synthetic studies: H. J. Martin, M. Drescher, H. Kahilg, S. Schneider and J. Mulzer, *Angew. Chem., Int. Ed.*, 2001, **40**, 3186; M. M. B. Marques, S. Pichlmair, H. J. Martin and J. Mulzer, *Synthesis*, 2002, 2766; S. Pichlmair, M. M. B. Marques, M. P. Green, H. J. Martin and J. Mulzer, *Org. Lett.*, 2003, **5**, 4657.

6 R. T. Borchardt and A. K. Sinhababu, *J. Org. Chem.*, 1981, **46**, 5021; F. A. Carey and R. M. Giuliano, *J. Org. Chem.*, 1981, **46**, 1366.

7 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127; D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.

8 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.

9 W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz and R. L. Halterman, *J. Am. Chem. Soc.*, 1990, **112**, 6339; W. R. Roush, A. D. Palkowitz and K. Ando, *J. Am. Chem. Soc.*, 1990, **112**, 6348.

10 S. R. Angle and K. D. Turnbull, *J. Am. Chem. Soc.*, 1989, **111**, 1136.

11 Y. Tamura, T. Yakuta, H. Tohma, K. Kikuchi and Y. Kita, *Synthesis*, 1989, 126.

12 ^1H NMR data of **19** (400 MHz, CDCl$_3$) for the major rotamer: δ 5.97 (1H, ddd, *J* = 17.1, 10.5, 5.4 Hz), 5.03 (1H, dd, *J* = 10.7, 1.5 Hz), 4.99 (1H, dd, *J* = 17.1, 1.5 Hz), 4.06 (1H, d, *J* = 10.3 Hz), 3.85 (3H, s), 3.81 (3H, s), 3.81–3.79 (1H, m), 3.64 (3H, s), 3.63–3.25 (4H, m), 2.64 (1H, m), 2.19 (3H, s), 2.02–1.96 (1H, m), 1.84–1.68 (2H, m), 1.59–1.39 (4H, m), 1.04 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.1 Hz), 0.91 (9H, s), 0.85 (9H, s), 0.62 (3H, d, *J* = 6.6 Hz), 0.07 (6H, s), 0.00 (6H, s); HRMS (ESI) calcd for $C_{37}H_{68}O_6Si_2Na$ (M + Na)$^+$ 687.4447 found 687.4463.