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

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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 ^{1}H NMR spectra of the corresponding (+)- and (−)-MTPA esters.

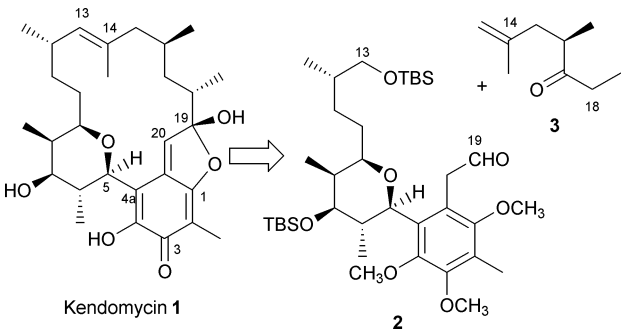


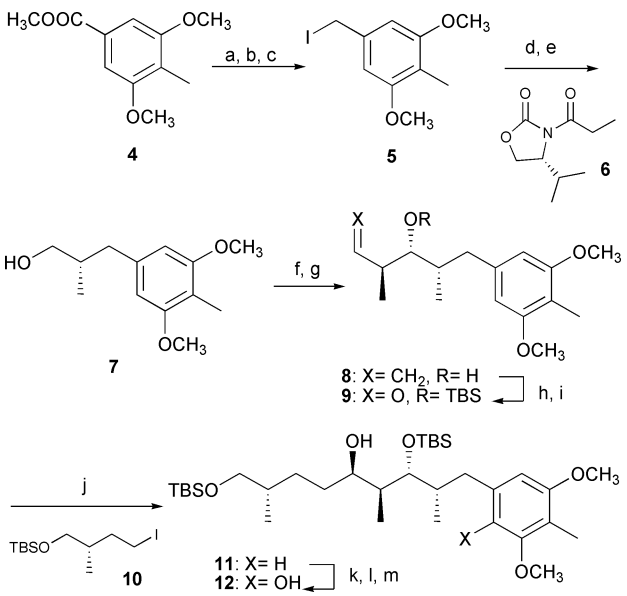
Fig. 1 Retrosynthetic analysis of kendomycin.

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_2O_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.



Scheme 1 a) $LiAlH_4$, THF, 40 °C; b) CH_3I, NaH, THF, 0 °C, 96% in 2 steps; c) NaI, BF_3 etherate, CH_3CN, 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_2Cl_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_2Cl_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_2O, DMAP, pyridine, room temp., 100%; l) mCPBA (3 equiv.), CH_2Cl_2, room temp.; m) DIBAL-H, CH_2Cl_2, −78 °C, 66% in 2 steps.

† 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/

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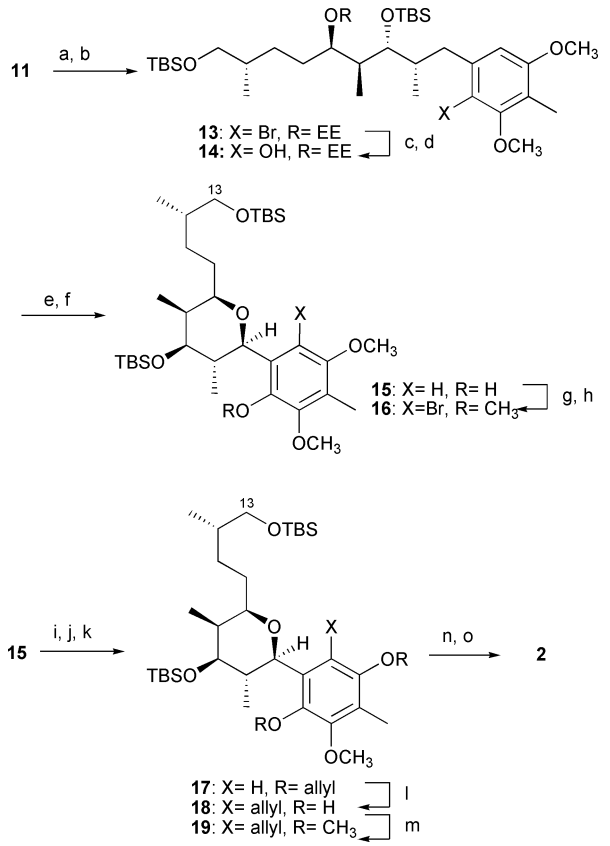

Scheme 2 a) Pyridinium bromide perbromide, K_2CO_3, CH_2Cl_2, 0 °C to room temp.; b) ethyl vinyl ether, PPTS, room temp., 98% in 2 steps; c) *n*-BuLi (2.5 equiv.), then $B(OCH_3)_3$, THF, −78 °C; d) H_2O_2, sat. Na_2CO_3 aq., 82% in 2 steps; e) PPTS, *n*-propanol, room temp., 94%; f) Ag_2O, CH_2Cl_2, 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%.

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 ^{1}H 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 ^{1}H 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.

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Notes and references

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12 ^{1}H 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.