Ring-closing Metathesis Approach to a 16-Membered Macrocycle of Kendomycin

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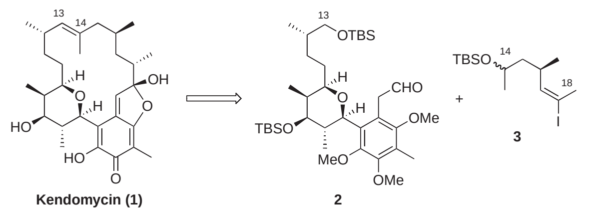
An approach to the macrocyclic core of kendomycin is described in which the Nozaki–Hiyama–Kishi coupling and a ring-closing olefin metathesis are the key reactions.

Kendomycin [(–)-TAN 2162, **1**] is a novel polyketide compound that was originally isolated as an antagonist for endothelin receptor.[1] It contains a characteristic quinonemethide chromophore within an ansa-macrocycle. Zeeck and Bode reported later the antibacterial activities of **1** against drug-resistant *Staphylococcus aureus* strains.[2] The architectural structure of **1** has naturally attracted the attention of synthetic chemists,[3] and two groups have thus far completed the total synthesis (Scheme 1).[4]

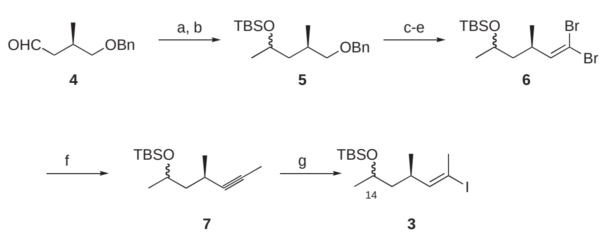


Scheme 1. Retrosynthesis of kendomycin.

One of the apparent obstacles in the endeavor to synthesize **1** is the construction of its macrocyclic core. A possible solution is a ring-closing metathesis (RCM) reaction, but there had been no precedent of such transformation for 16-membered trisubstituted cycloalkenes until Smith's recent synthesis of **1**.[4b,4c] We describe here our efforts to synthesize kendomycin via RCM.

Synthesis of the C14–C18 subunit was commenced with a known chiral aldehyde **4** (Scheme 2).[5]

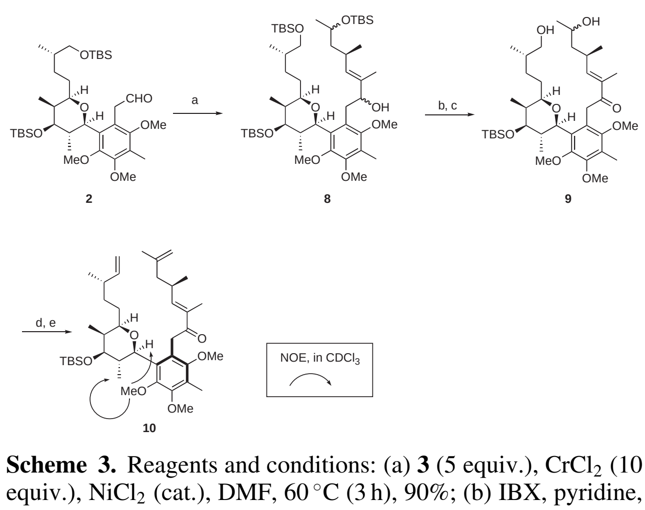
It was treated with MeLi–CuI, and the newly formed hydroxy group was protected with a *t*-butyldimethylsilyl group. Deprotection of the benzyl ether of **5** and subsequent alcohol oxidation furnished an aldehyde, which was transformed to an alkyne via the Corey–Fuchs procedure.[6] Hydrozirconation and iodination produced vinyl iodide **3** as a diastereomeric mixture at the C14 center.



Scheme 2. Reagents and conditions: (a) MeLi (6 equiv.), CuI (3 equiv.), Et_2O, $-78\,^\circ C$ (1 h) to rt (1 h); (b) TBSCl (1.1 equiv.), imidazole (2.2 equiv.), DMF, rt (1.5 h), 88% in 2 steps; (c) $Pd(OH)_2/C$, H_2, 1,4-dioxane, rt (3 h); (d) PDC (1 equiv.), MS4A, CH_2Cl_2, rt (3 h); (e) CBr_4 (2 equiv.), PPh_3 (4 equiv.), Et_3N (1 equiv.), CH_2Cl_2, $-78\,^\circ C$ (10 min), 51% in 3 steps; (f) *n*-BuLi (2.2 equiv.), then MeI (5 equiv.), THF, -20 to $0\,^\circ C$ (2.5 h), 97%; (g) Cp_2ZrHCl (2.2 equiv.), THF, rt (1 day), then I_2 (2.1 equiv.), rt (30 min), 71%.

The C14–C18 segment was installed to an aromatic segment **2**,[3d] the preparation of which was previously reported by us (Scheme 3). The Nozaki–Hiyama–Kishi coupling between the sterically hindered **2** and **3** was proven to proceed only at an elevated temperature ($60\,^\circ C$). The reaction at $80\,^\circ C$, however, gave significantly lower yield of the coupling product under otherwise the same conditions (ca. 25%). After oxidation of the resultant allylic alcohol to an enone, selective removal of two TBS groups was achieved by an acidic methanolysis to afford diol **9**. The IBX oxidation of **9** gave a tricarbonyl compound, and the subsequent Wittig methylenation occurred selectively at the terminals (C13 and C14). The RCM precursor **10**, thus obtained, was observed as a mixture of rotamers around the C4a–C5 axis in ^1H NMR spectrum. The ratio of these isomers was 3:1 favoring the isomer depicted in Scheme 3 ($CDCl_3$, $20\,^\circ C$).

The ring-closing metathesis of **10** was then investigated (Figure 1). The substrate concentration of the reaction was fixed to 2 mM. Attempts with the first-generation Grubbs catalyst **13** or the Schrock catalyst **14** failed to deliver macrocyclic products at room temperature, and starting material **10** was recovered. Eventually, the successful ring-closing was achieved by the second-generation Grubbs catalyst **11** (5 mol %) in benzene (45%, Table 1, Entry 6). Somehow, the yield of the RCM reac-



Scheme 3. Reagents and conditions: (a) **3** (5 equiv.), $CrCl_2$ (10 equiv.), $NiCl_2$ (cat.), DMF, $60\,^\circ C$ (3 h), 90%; (b) IBX, pyridine, DMSO–THF–pyridine (50:50:1), rt (2 h) to $45\,^\circ C$ (1 h), 71%; (c) PPTS, MeOH, rt, (28 h), 82%; (d) IBX (3.3 equiv.), DMSO, rt (4.5 h) to $45\,^\circ C$ (2 h); (e) CH_3PPh_3Br (5 equiv.), *n*-BuLi (5 equiv.), THF, rt (10 h), 50% in 2 steps.

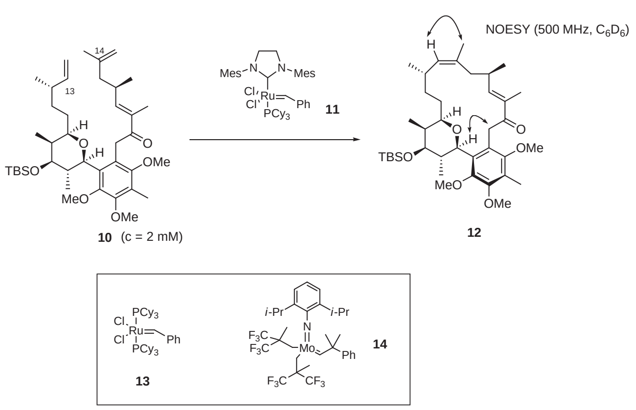


Figure 1.

Table 1. Macrocyclization of the precursor **10**

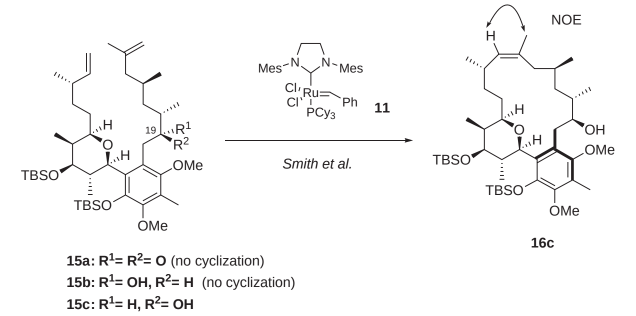
Entry	Catalyst (mol %)	Solvent	Conditions	Yield of **12**
1	**13** (5 mol %)	CH_2Cl_2	rt, 7 h	N.R.
2	**14** (10 mol %)	benzene	rt, 1 day	N.R.
3	**11** (5 mol %)	CH_2Cl_2	rt, 16 h	trace
4	**11** (5 mol %)	CH_2Cl_2	reflux, 12 h	trace
5	**11** (5 mol %)	benzene	rt, 1 day	trace
6	**11** (5 mol %)	benzene	60 °C, 1 day	trace ∼ 45%
7	**11** (60 mol %)	toluene	90 °C, 5 days	53%

tion varied largely from time to time, and the higher amount of catalyst (60 mol %) was needed to obtain reproducible results (53%, Entry 7).

Although several products were observed in the reaction mixture by TLC analysis, we could only isolate and characterize the major product **12**.[7] The NOESY experiment of NMR analysis revealed that the newly formed C13–C14 double bond existed in an unnatural *Z* geometry.

It has already been shown that success of the RCM tactic for kendomycin's macrocyclic ether is substrate-dependent. The first attempt by the Multzer group proved unsuccessful,[3c] and Smith also met with difficulty due to the delicate substrate dependence of the reaction (Scheme 4).[4c]

For example, they failed to cyclize 19-keto substrate **15a** or (19*R*)-alcohol **15b** (Scheme 4). In literature reports, only the alcohol **15c** can cyclize to **16c**.[4c,8] Thus, it was really fortunate for us to succeed in cyclizing a 19-keto compound **10**. Both compounds **12** and **16c** have *Z* configurations at C13–C14 alkene, which may be the result of thermodynamic stability of the macrocyclic ring. It is also noteworthy that the



Scheme 4. Reported selectivity in Smith's RCM approach.[4b,4c]

preferred rotational isomer at the *C*-glycocydic bond differs between **12** and **16c**.

In conclusion, we have described the preparation of kendomycins's macrocyclic core via the Nozaki–Hiyama–Kishi coupling and a ring-closing metathesis. These results would not only be useful for kendomycin synthesis but also would constitute a general basis of macrocycle-synthesis by RCM reactions. Efforts toward the total synthesis of **1** are underway in this laboratory.

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References and Notes

1 a) Y. Funahashi, T. Ishimaru, N. Kawamura, *Jpn. Kokai Tokkyo Koho* 08231552 [A2 960 910], **1996**. b) Y. Funahashi, N. Kawamura, T. Ishimaru, *Jpn. Kokai Tokkyo Koho* 08231551 [A2 960 910], **1996**.

2 a) H. B. Bode, A. Zeeck, *J. Chem. Soc., Perkin Trans. 1* **2000**, 323. b) H. B. Bode, A. Zeeck, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2665.

3 a) H. J. Martin, M. Drescher, H. Kahlig, S. Schneider, J. Mulzer, *Angew. Chem., Int. Ed.* **2001**, *40*, 3186. b) M. P. Green, S. Pichlmair, M. M. B. Marques, H. J. Martin, O. Diwald, T. Berger, J. Mulzer, *Org. Lett.* **2004**, *6*, 3131. c) J. Mulzer, S. Pichlmair, M. P. Green, M. M. B. Marques, H. J. Martin, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11980. d) T. Sengoku, H. Arimoto, D. Uemura, *Chem. Commun.* **2004**, 1220. e) J. D. White, H. Smits, *Org. Lett.* **2005**, *7*, 235. f) J. T. Lowe, J. S. Panek, *Org. Lett.* **2005**, *7*, 1529. g) D. R. Williams, K. Shamim, *Org. Lett.* **2005**, *7*, 4161. h) K. B. Bahnck, S. D. Rychnovsky, *Chem. Commun.* **2006**, 2388.

4 a) Y. Yuan, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 14720. b) A. B. Smith, III, E. F. Mesaros, E. A. Meyer, *J. Am. Chem. Soc.* **2005**, *127*, 6948. c) A. B. Smith, III, E. F. Mesaros, E. A. Meyer, *J. Am. Chem. Soc.* **2006**, *128*, 5292.

5 A. K. Ghosh, Y. Wang, *J. Org. Chem.* **2001**, *66*, 8973.

6 E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769.

7 **12**: $Rf = 0.41$ (SiO_2, hexane:EtOAc = 7:1); $[\alpha]^{15}_{D} + 106°$ (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 2960, 2930, 2860, 1460, 1410, 1380, 1050, 840 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.14 (d, $J =$ 11.2 Hz, 1H), 5.11 (d, $J = 8.8$ Hz, 1H), 4.20 (d, $J = 17.1$ Hz, 1H), 4.09 (d, $J = 17.1$ Hz, 1H), 3.80 (s, 3H), 3.79 (d, $J =$ 11.7 Hz, 1H), 3.61 (s, 3H), 3.50 (dd, $J = 6.8$, 6.8 Hz, 1H), 3.45 (s, 3H), 3.38 (dd, $J = 10.2$, 4.9 Hz, 1H), 3.21 (m, 1H), 2.69 (m, 1H), 2.39 (m, 1H), 2.28 (dd, $J = 13.7$, 11.7 Hz, 1H), 2.22 (s, 3H), 1.97 (s, 3H), 1.94 (m, 1H), 1.71 (br. d, $J = 14.7$ Hz, 1H), 1.60 (s, 3H), 1.58 (m, 2H), 1.52–1.47 (m, 2H), 1.32 (m, 2H), 1.27 (d, $J = 6.8$ Hz, 3H), 1.02 (s, 9H), 0.96 (d, $J = 6.3$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.69 (d, $J = 6.8$ Hz, 1H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (151 MHz, C_6D_6) δ 199.3, 154.1, 152.0, 150.1, 145.7, 138.2, 135.3, 134.2, 131.6, 129.5, 125.6, 82.1, 79.9, 79.8, 61.5, 60.3, 59.9, 39.7, 39.2, 38.1, 35.2, 34.3, 33.4, 31.7, 31.6, 26.1, 22.8, 21.6, 20.9, 18.4, 14.5, 12.0, 9.7, 6.6, −3.9, −4.5; MS (FAB) m/z 665 $[M + Na]^+$; HRMS (FAB) calcd for $C_{38}H_{62}O_6SiNa$ $[M + Na]^+$ 665.4213, found 665.4210.

8 Smith succeeded in isomerizing this *Z*-alkene to the *E* geometry via a multi-step procedure, leading to the completion of total synthesis.