ORGANIC LETTERS

2010
Vol. 12, No. 8
1700−1703

Total Synthesis of Kendomycin Featuring Intramolecular Dötz Benzannulation

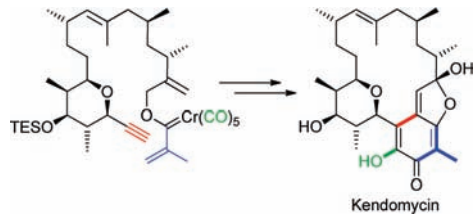
Kyosuke Tanaka, Masahito Watanabe, Kodai Ishibashi, Hiroshi Matsuyama, Yoko Saikawa,* and Masaya Nakata*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

saikawa@applc.keio.ac.jp; msynktxa@applc.keio.ac.jp

Received January 28, 2010

ABSTRACT



One-step formation of the ansa-skeleton realized the synthesis of kendomycin, an ansa-type quinone methide. The Fischer carbene complex derived from the ansa-chain portion was subjected to the intramolecular Dötz benzannulation to afford the desired oxametacyclophane with exclusive regioselectivity. Subsequent Claisen rearrangement, ortho oxidation of the resulting phenol derivative, and mild transformation from *p*-quinone to *p*-quinone methide on a silica gel plate furnished kendomycin.

Natural ansamycins are quite attractive for organic chemists and biologists from the point of both their fascinating structures and impressive pharmacological profiles.[1] The complex ansamycin, kendomycin (**1**), has a unique quinone methide architecture connected to a highly substituted tetrahydropyran and possesses potent antibacterial and cytotoxic activities as well as activities as an endothelin receptor antagonist and an antiosteoporotic agent.[2] Since kendomycin (**1**) was isolated from *Streptomyces* species,[2] it has been targeted by a number of synthetic organic chemists, and four total syntheses[3] and one formal total synthesis[4] manipulating each elaborated synthetic strategy have been reported. The most common route for total syntheses of kendomycin and other ansamycins generally involves elongation of an aliphatic ansa-chain from one or both sides of an aromatic core followed by macrocyclization. In contrast, we conceived a unique strategy to construct an ansa-framework featuring an intramolecular Dötz benzannulation[5,6] with simultaneous macrocyclization. This challenging one-step formation of an ansa-compound from a Fischer-type chromium−carbene

(1) For recent reviews on ansamycins, see: (a) Funayama, S.; Cordell, G. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 2000; Vol. 23, pp 51−106. (b) Floss, H. G.; Yu, T.-W. *Chem. Rev.* **2005**, *105*, 621–632. (c) Bryskier, A. In *Antimicrobial Agents*; BryskierA., Ed; ASM Press: Washington, DC, 2005; pp 906−924.

(2) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. *Jpn. Kokai Tokkyo Koho* 1996, 08231551; *Chem. Abstr.* **1996**, *125*, 326518. (b) Funahashi, Y.; Ishimaru, T.; Kawamura, N. *Jpn. Kokai Tokkyo Koho* 1996, 08231552; *Chem. Abstr.* **1997**, *126*, 6553. (c) Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. U. S. Patent 5728727, 1998;*Chem. Abstr.* **1998**, *128*, 239489. (d) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 323–328.

(3) (a) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721. (b) Smith, A. B., III.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949. (c) Smith, A. B., III.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299. (d) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813–3816. (e) Magauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6032–6036. (f) Magauer, T.; Martin, H. J.; Mulzer, J. *Chem.—Eur. J.* **2010**, *16*, 507–519.

(4) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181.

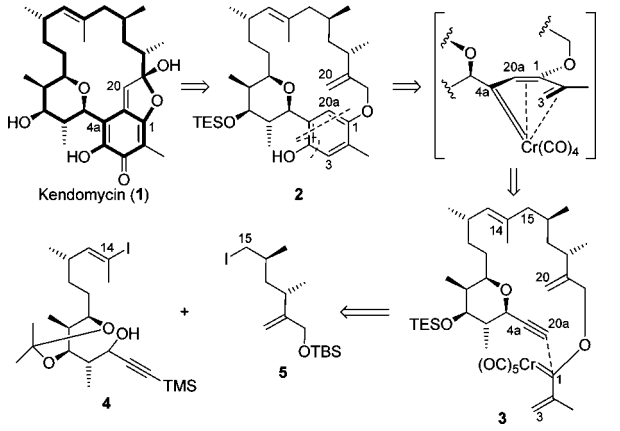
(5) (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644–645. (b) Waters, M. L.; Wulff, W. D. In *Organic Reactions*; Overman, L. E., Ed.; Jon Wiley & Sons, Inc.: Hoboken, 2008; pp 121−623.

(6) For a partial synthesis of kendomycin using the intermolecular Dötz reaction, see: White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235–238.

10.1021/ol100229f
Published on Web 03/12/2010

complex having a long ω-alkynyloxy chain has realized total synthesis of kendomycin (**1**), which is the subject of this communication.

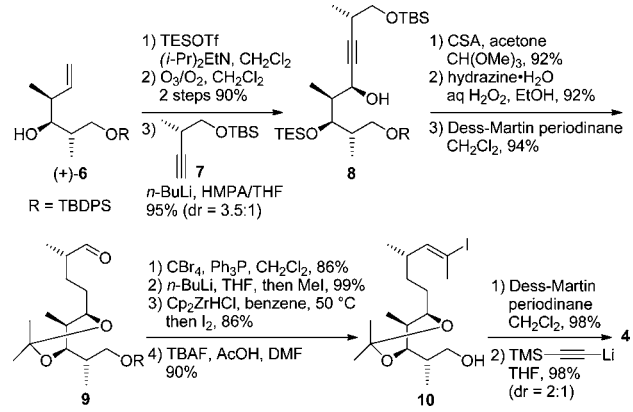
Scheme 1. Synthetic Strategy of Kendomycin (**1**)



Our synthetic strategy is outlined in Scheme 1. Regarding kendomycin (**1**) as an oxametacyclophane (bold lines), we designed the precursor **2** with an allyl ether positioned as a foothold for Claisen rearrangement to connect C20 to the aromatic ring (C20a). The oxametacyclophane **2** was expected to be the favored product of the intramolecular Dötz benzannulation of chromium-carbene complex **3**, whose alkyne terminus C20a would regioselectively insert to the carbene center C1[5b] and then the resulting complex would cyclize via CO insertion between C3 and C4a to give an aromatic core. Indeed, our previous fundamental studies using simple substrates demonstrated that vinylidene chromium−carbene complexes having a sufficient length of ω-alkynyloxy chain tended to macrocyclize to give oxametacyclophanes while short chains produced oxa-orthocyclophanes.[7] The excellent regioselectivity of the long tethered carbene complex prompted us to challenge a highly substituted complex **3**. The complex **3** would be synthesized via Suzuki−Miyaura coupling between the left- and right-half segments **4** and **5** followed by chromium complexation.

The left- and right-half segments **4** and **5** were synthesized from (+)- and (−)-enantiomers of the known homoallyl alcohol **6**,[8] respectively (Schemes 2 and 3). The terminal olefin of (+)-**6** was oxidatively cleaved after silylation of the hydroxy group, and the resulting aldehyde was treated with alkynyllithium prepared from **7**[9] and *n*-BuLi to give adduct **8** with a 3.5:1 diastereoselectivity (Scheme 2). Sequential acetalization, diimide hydrogenation, and Dess−Martin oxidation led to aldehyde **9**. Alkynylation of **9** followed by

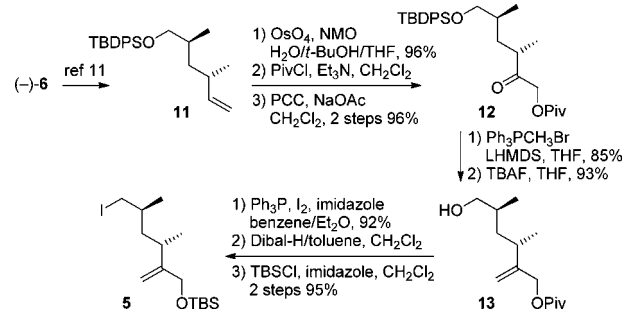
Scheme 2. Synthesis of Left-Half Segment **4**



hydrozirconation−iodination[4,10] and desilylation gave vinyl iodide **10**. Oxidation to the aldehyde followed by addition of alkynyllithium afforded the left-half segment **4**.

On the other hand, (−)-**6** was deoxygenated in two steps, and the resulting olefin **11**[11] was transformed into **13** through a conventional five-step sequence involving Wittig olefination of ketone **12** (Scheme 3). After iodination of **13**, the protecting group was exchanged to give the right-half segment **5**.

Scheme 3. Synthesis of Right-Half Segment **5**



The Suzuki−Miyaura coupling was realized by palladium-catalyzed cross-coupling of **4** with the alkyl borane derived from **5** to cleanly afford the adduct in 98% yield (Scheme 4).[3a,4] This was oxidized to ynone **14** from which the tetrahydropyran **15** was derived by acetal exchange followed by deoxygenation of the resulting methyl acetal with Et_3SiH. After silylation and selective deprotection, allyl alcohol **16** was introduced to the acetoxychromium carbene complex prepared from chromate **17**[12] in situ, giving the key carbene complex **3** in 95% yield. The crucial Dötz reaction was conducted under our optimized conditions[7] (in toluene,

(7) Watanabe, M.; Tanaka, K.; Saikawa, Y.; Nakata, M. *Tetrahedron Lett.* **2007**, *48*, 203–206.

(8) (a) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359, for (+)-**6.** (b) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331–11332, for (−)-**6.**

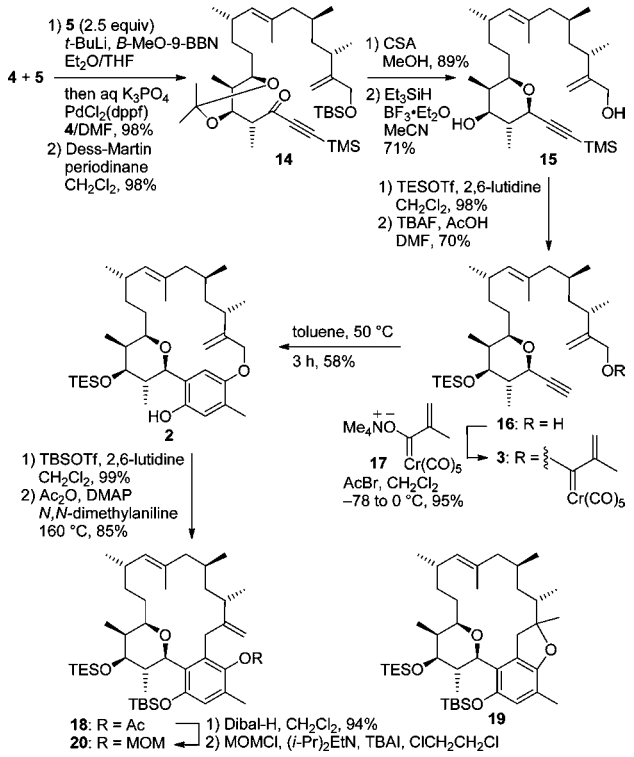
(9) Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703–706, and references therein.

(10) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.

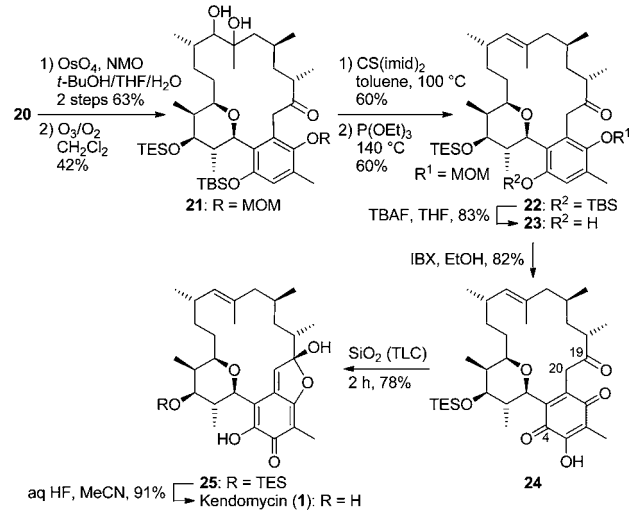
(11) Yokokawa, F.; Asano, T.; Okino, T.; Gerwick, W. H.; Shioiri, T. *Tetrahedron* **2004**, *60*, 6859–6880.

(12) Chamberlin, S.; Wulff, W. D.; Bax, B. *Tetrahedron* **1993**, *49*, 5531–5547.

Scheme 4. Intramolecular Dötz Benzannulation and Macrocyclic Claisen Rearrangement



Scheme 5. Quinone Methide Formation and Completion of Total Synthesis of Kendomycin (**1**)



50 °C) under degassed atmosphere to provide the desired oxametacyclophane **2** in 58% yield as the sole isolable product. After silylation of **2**, the macrocyclic Claisen rearrangement in the presence of Ac_2O and DMAP provided acetate **18** in 85% yield. Without addition of Ac_2O and DMAP, the unexpected dihydrobenzofuran **19** was obtained as a major product.[13] Aiming at the further conversion, the resulting **18** was transformed to MOM ether **20**.

Next, we addressed the troublesome oxidative cleavage of the exomethylene group in **20** to the carbonyl group (Scheme 5). Indeed, the electron-rich, inner double bond was selectively dihydroxylated to give the diol under all conditions attempted. The diol function was used to mask the inner double bond, and treatment with O_3 yielded the desired ketone **21**. The double bond was then regenerated, and the resulting **22** was converted to phenol **23** in order to prepare for the next oxidation.

The climax of the final stage was adjustment of the oxidation state of the aromatic ring and quinone methide formation. The final two-step conversion by other research groups[3,4] consisted of a mild oxidation of the catechol monomethyl ether[14] to the unstable *o*-quinone by IBX or Dess−Martin periodinane and subsequent acid-catalyzed quinone methide formation with HF. Our oxidation, in contrast, required direct ortho oxidation of phenol **23**. This task was realized by IBX oxidation[15] in EtOH, accompanied by deprotection of the MOM ether, to afford 2-hydroxy-1,4-quinone **24** in 82% yield. Furthermore, the subsequent quinone methide formation also succeeded under the mild conditions, just applying **24** on silica gel TLC to give **25** in 78% yield (22% recovered **24**). Desilylation of **25** furnished the total synthesis of kendomycin (**1**) in 91% yield, whose data were identical with those of the natural sample.

We have a great interest in the last smooth transformation from *p*-quinone **24** to *p*-quinone methide **25** on silica gel TLC and, therefore, investigated the role of silica gel. After **24** (λ_{max} 401 nm in $CHCl_3$) was applied on silica gel powder, its yellow color immediately turned red as the solvent evaporated. We could not isolate the red compound which easily returns to the yellow **24** by elution with $CHCl_3$ from silica gel. To clarify the structure of the red intermediate, the behavior of **24** on silica gel was monitored by UV−vis spectra on diffuse reflectance mode (Figure 1). The absorption maximum of the adsorbed red compound was observed at 528 nm and this absorption gradually decreased as the pale-yellow quinone methide **25** (λ_{max} 365 nm (sh) in $CHCl_3$) formed. The resulting mixture was a ca. 3.5:1 ratio of **25** and **24**. Since applying the isolated **25** on silica gel powder also gave the same mixture with the same ratio, **24** and **25** were found to be in equilibrium. We next synthesized simple two model compounds **26** and **27** to compare their UV spectra with that of the red intermediate. 2-Hydroxy-1,4-quinone **26**[16] (λ_{max} 405 nm in $CHCl_3$) also showed λ_{max} 534 nm on silica gel powder, suggesting that neither the acetal

(13) Shih, T. L.; Wyvratt, M. J.; Mrozik, H. *J. Org. Chem.* **1987**, *52*, 2029–2033.

(14) Catechol monomethyl ether as an early-stage intermediate of kendomycin synthesis was prepared via the Dötz reaction, see ref 6.

(15) For formation of *o*-quinone from monoprotected hydroquinone, see: Magdziak, D.; Rodriquez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285–288.

(16) For the synthesis of **26**, triethylamine salt of **26**, and **27**, see the Supporting Information.

(17) The spontaneous irreversible solvolysis of kendomycin (**1**) in DMSO-H_2O was reported. See Janssen, C. O.; Lim, S.; Lo, E. P.; Wan, K. F.; Yu, V. C.; Lee, M. A.; Ng, S. B.; Everett, M. J.; Buss, A. D.; Lane, D. P.; Boyce, R. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5771–5773.

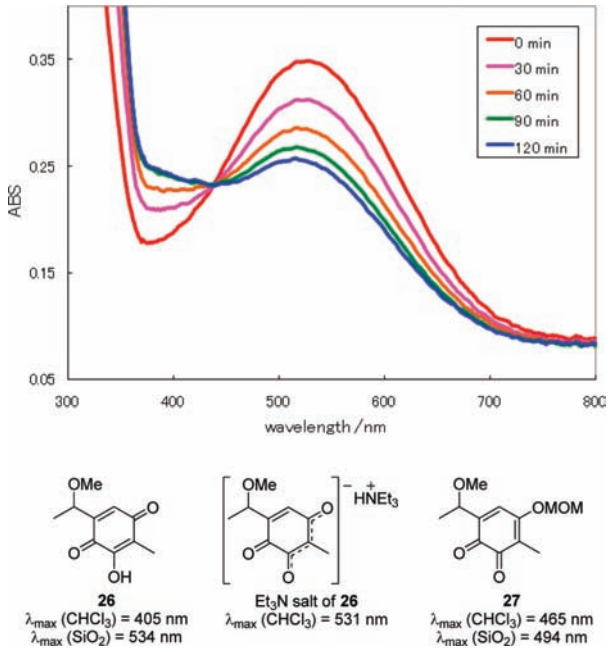


Figure 1. Time-course UV−vis spectra of the transformation from **24** to **25** (time after applying **24** on silica gel) and UV−vis absorption maxima of **26**, Et_3N salt of **26**, and **27**.

formation nor the enolization from C20 into any side (C4 or C19) is essential for the initial color change of **24** (from yellow to red). Furthermore, the red absorption maximum was close to that of the triethylamine salt of **26**[16] (λ_{max} 531 nm in $CHCl_3$) rather than that of the MOM-protected *o*-quinone **27**[16] (λ_{max} 465 nm in $CHCl_3$ and λ_{max} 494 nm on silica gel powder). Based on these data, we considered that the red intermediate formed as the result of coordination with silica gel has a charge-delocalized structure similar to diketonate. The equilibrium between **24** and **25** has not been observed during preservation of these compounds.[17] The silica gel-promoted charge delocalization would lead to the smooth equilibrium between **24** and **25** via the acetal formation/cleavage and tautomerization.

In summary, the total synthesis of kendomycin (**1**) was accomplished featuring the intramolecular Dötz benzannulation of an unprecedented chromium-carbene complex tethered to a highly substituted long ω-alkynyloxy chain, Claisen rearrangement of the macrocycle, ortho oxidation of phenol, and a mild conversion from *p*-quinone to *p*-quinone methide on silica gel. The success of this macrocyclization of a highly functionalized carbene complex demonstrates that this method would be applicable to the divergent synthesis of ansa-type compounds.

Acknowledgment. We thank Takeda Pharmaceutical Co. Ltd. for providing us natural kendomycin (TAN 2162) and Drs. Hiroaki Imai and Yuya Oaki (Keio University) for the use of the diffuse reflectance UV−vis spectrometer.

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

OL100229F