ORGANIC LETTERS

2005
Vol. 7, No. 2
235−238

Application of the Dötz Reaction to Construction of a Major Portion of the Ansa Macrocycle (–)-Kendomycin

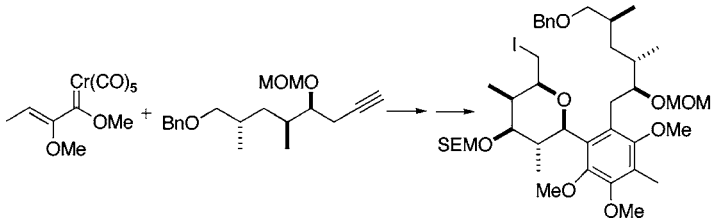
James D. White* and Helmars Smits

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@oregonstate.edu

Received October 28, 2004

ABSTRACT



A Dötz reaction employing a terminal alkyne and a Fischer-type alkenylchromium carbenoid led to a pentasubstituted benzene from which a major portion of the *Streptomyces* metabolite (–)-kendomycin was synthesized.

The announcement in a 1996 patent by scientists at Takeda Pharmaceutical Company of a substance, (−)-TAN 2162, isolated from *Streptomyces violaceoruber* (strain 3844-33C) brought to light a novel ansamycin with pronounced endothelin receptor antagonist and antiosteoporotic activity.[1−3] The same substance was isolated later from a different *Streptomyces* strain by Zeeck and co-workers and was named kendomycin. Zeeck's group established the structure, including absolute configuration, of kendomycin as **1** and reported that it possessed antibacterial and cytostatic activity.[4,5]

The unique structure of kendomycin, in which an ansa macrocycle incorporating a fully substituted tetrahydropyran bridges a quinone methide core, presents a challenging target for synthesis.[6] Toward that goal, we have laid down a route to a major portion of **1** that comprises all but C11−C14 of the macrocycle as well as a hexasubstituted benzene that will serve as the progenitor of the quinone methide nucleus of this structure. A key component of our strategy is a Dötz annulation[7] that creates the benzenoid system **2** by addition of α,β-unsaturated chromium carbenoid **3** to a terminal alkyne **4** (Scheme 1). In his studies of Fischer-type carbenoids, Dötz has shown that alkenylchromium carbenes undergo addition to terminal alkynes accompanied by carbonyl insertion to yield substituted phenols in which the position of substituents on the aromatic ring is highly predictable.[8] Wulff has made elegant use of this feature of the Dötz benzannulation process in the synthesis of natural products.[9]

The first task in our plan for the acquisition of **2** was synthesis of the previously unknown chromium carbene **3**,[10] and this was accomplished as shown in Scheme 2. 1-Meth-

(1) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Jpn. Patent 08231551 [A2960910], 1996; *Chem. Abstr*. **1996**, *126*, 6553.
(2) Funahashi, N.; Kawamura, N. Jpn. Patent 08231552, 1996; *Chem. Abstr*. **1996**, *126*, 326518.
(3) Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. U.S. Patent 5728727, 1998; *Chem. Abstr*. **1998**, *128*, 239489.
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(5) Bode, H. B.; Zeeck, A. J. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2665.
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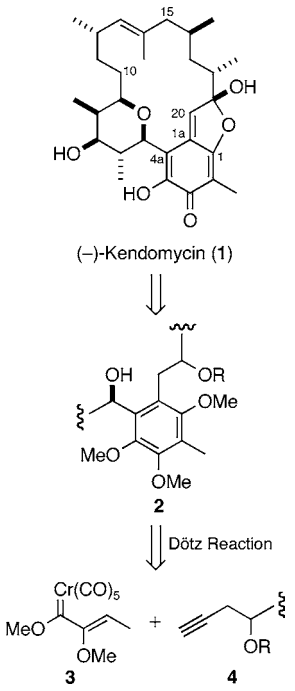
(8) (a) Dotz, K. H.; Dietz, R. *Chem. Ber*. **1978**, *111*, 2517. (b) Dotz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (c) de Meijere, A.; Schrimer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964.
(9) (a) Wulff, W. D.; Tang, P.-C. *J. Am. Chem. Soc.* **1984**, *106*, 434. (b) Wulff, W. D.; Xu, Y. C. *J. Am. Chem. Soc.* **1988**, *110*, 2312. (c) Manish, R.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329.

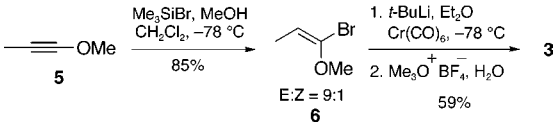
10.1021/ol047779s CCC: $30.25
Published on Web 12/30/2004

Scheme 1. Retrosynthetic Analysis of the Quinone Methide Core of Kendomycin



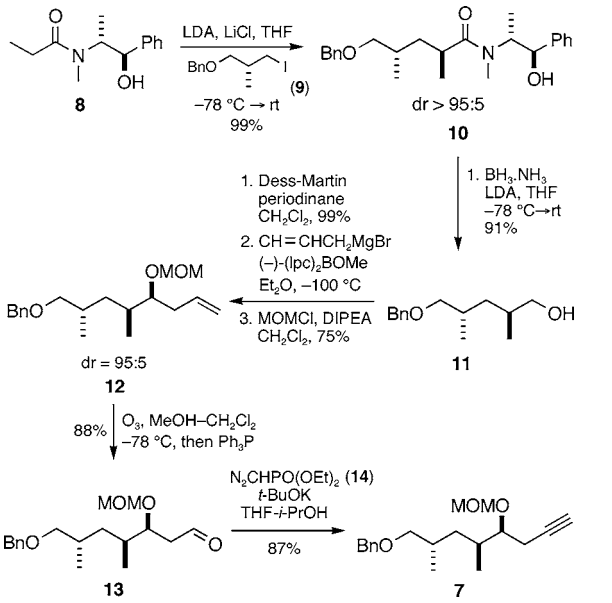
oxypropyne (**5**), prepared from chloroacetaldehyde dimethyl acetal,[11] was reacted with trimethylsilyl bromide and methanol to give (*E*)-1-bromo-1-methoxypropene (**6**).[12] Halogen–metal exchange of **6** with *tert*-butyllithium followed by exposure of the lithioalkene to chromium hexacarbonyl yielded a carbene complex that was methylated in situ with trimethyloxonium tetrafluoroborate. The resultant (*Z*)-unsaturated chromium carbene **3** was obtained as a dark red oil that is easily oxidized but can be preserved indefinitely as a solution in benzene.

Scheme 2. Synthesis of Chromium Carbenoid **3**



The efficient preparation of **3** persuaded us to explore its application toward the synthesis of a hexasubstituted benzene derivative bearing ortho-oriented side chains that could serve as the core subunit of **1**. For this purpose, a reaction partner for **3** was identified that possesses the structural features of the C15–C18 portion of kendomycin. In practical terms, the component required for our projected Dötz reaction was the 1-octyne derivative **7**. The synthesis of **7** began with alkylation of Myers' (1*R*,2*R*)-(+)-*N*-propionylpseudoephedrine (**8**)[13] with (*R*)-iodo compound **9**,[14] which led to **10**[15] as the sole detectable diastereomer but as a mixture of rotamers according to its proton NMR spectrum (Scheme 3). Reductive cleavage of the auxiliary[13] from **10** gave alcohol **11**,[16] which was oxidized to the corresponding aldehyde and then subjected to Brown asymmetric allylation.[17] The resulting homoallylic alcohol was protected as its methoxymethyl (MOM) ether **12**, from which it was deduced by proton NMR that the dr of allylation was 95:5. Ozonolytic cleavage of terminal alkene **12** furnished aldehyde **13**, which, upon exposure to the Seyferth–Gilbert diazophosphonate **14**[18] in the presence of base, afforded alkyne **7**.

Scheme 3. Synthesis of Alkyne **7** for Dötz Reaction with **3**



The Dötz reaction of **3** with **7** was initiated in deoxygenated THF at 50 °C, after which workup involving the passage of air through the mixture gave the 2,3,4,6-tetrasubstituted phenol **15** as the sole isomer (Scheme 4). Methylation of **15** produced the trimethyl ether **16**, and bromination of the open benzenoid site in the latter led to the hexasubstituted benzene **17**. This aryl bromide was advanced to aldehyde **18** in the hope that the second alkyl chain of kendomycin could be attached at this site. In practice, the aldehyde carbonyl of

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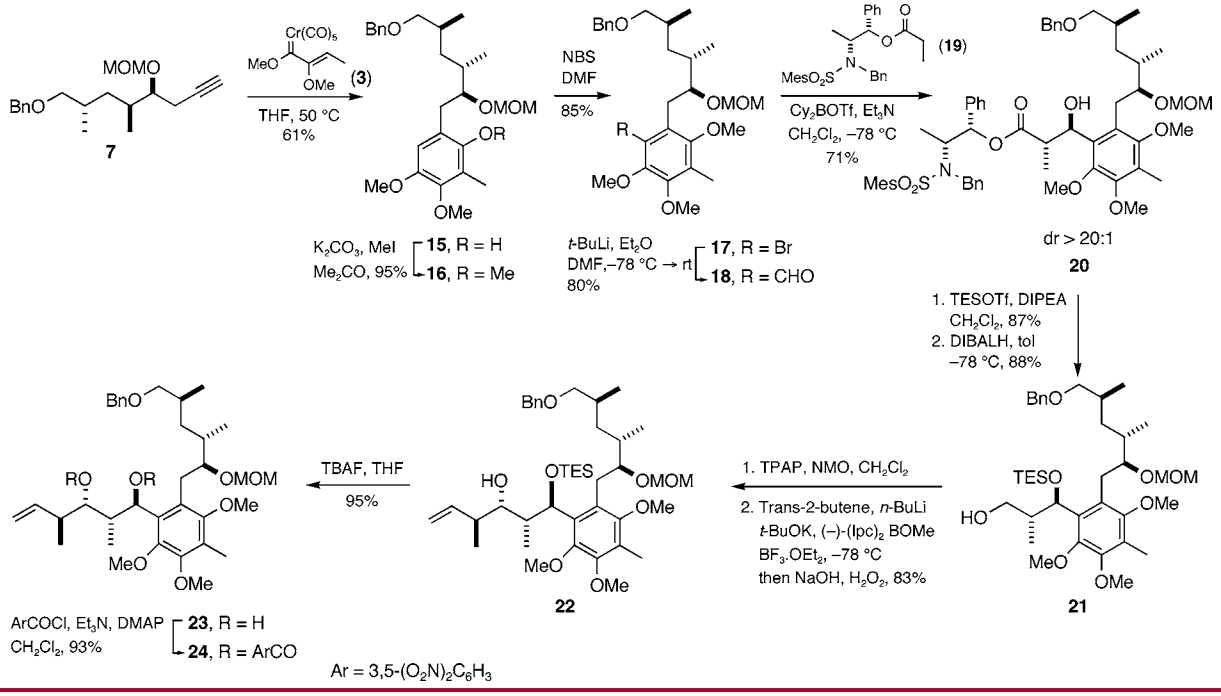
Scheme 4. Dötz Reaction and Further Elaboration of the Product Toward Kendomycin



18 was too sterically hindered for reactions intended to install a precursor to the tetrahydropyran segment of **1**. These included asymmetric crotylation[19] as well as Evans' anti-selective aldol process.[20] Oppolzer's sultam methodology[21] was only slightly more successful, but the reaction of aldehyde **18** with the dicyclohexylborinate of propionate **19** bearing Masamune's chiral auxiliary[22] led smoothly to hydroxy ester **20** in high diastereomeric excess. After protection of secondary alcohol **20** as its triethylsilyl (TES) ether, the auxiliary was cleaved by reduction to yield primary alcohol **21**. This was oxidized to an aldehyde that was subjected to Brown asymmetric crotylation[19] to give homoallylic alcohol **22**.

At this stage, we were presented with an opportunity to establish that the structural features of **22**, including the

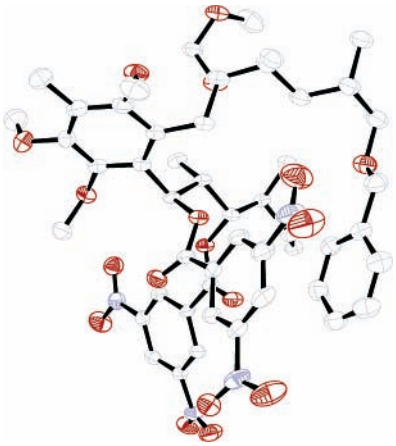
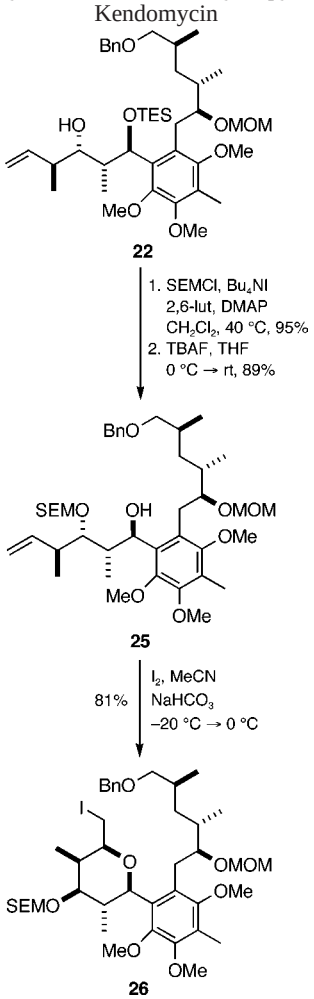


Figure 1. ORTEP representation of the X-ray crystal structure of **24**. Ellipsoids are drawn at the 50% level.

Scheme 5. Synthesis of the Tetrahydropyran Segment of Kendomycin



configuration of its seven stereogenic centers, were correctly assigned, since cleavage of the triethylsilyl (TES) ether and esterification of the resulting diol **23** with 3,5-dinitrobenzoyl chloride yielded crystalline bis-dinitrobenzoate **24**. X-ray crystallographic analysis of **24** (Figure 1) not only confirmed the structure of its parent substance **22** but also established that **24** exists as the (*R*)-atropisomer around the alkyl−aryl bond.

Continuation of the synthesis from **22** necessitated an interchange of protecting groups, for which alcohol **22** was converted to its trimethylsilylethoxymethyl (SEM) ether and the TES ether was cleaved to afford alcohol **25**. Several attempts were made to cyclize the hexenyl substituent of **25** to a tetrahydropyran using palladium(II)-mediated alkoxycarbonylation methodology that has been successful in other contexts,[23] but this plan failed. Mercuration of **25** did lead to cyclization; however, a stereoisomeric mixture of tetrahydropyrans was produced, and oxidative cleavage of the alkylmercury species resulted in decomposition. However, iodocyclization of **25** led rapidly and cleanly to tetrahydropyran **26**,[24] which was found by NMR to exist as a 3.7:1 mixture of atropisomers. The observation of atropisomerism in a similar structure has been noted by Mulzer.[6a]

In summary, we have completed the synthesis of a major portion of (−)-kendomycin, including seven of its nine stereogenic centers. Our route illustrates the utility of the Dötz reaction for the construction of a heavily substituted benzene ring, from which elaboration of the quinone methide nucleus of **1** is envisioned through a deprotection−oxidation sequence.

Acknowledgment. We are grateful to Professor Alexandre F.T. Yokochi of our department for the X-ray crystal structure of **24**. Financial support was provided by the National Institute of General Medical Sciences through Grant GM50574.

Supporting Information Available: Experimental procedures and spectroscopic data for new compounds and X-ray crystallographic data for **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047779S

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