Total Synthesis of the Antibiotic Kendomycin: A Macrocyclization Using the Tsuji–Trost Etherification**

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Abstract: A highly stereocontrolled, convergent total synthesis of kendomycin [(-)-TAN2162], an ansa-macrocyclic antibiotic, is reported. The key of the strategy is an unprecedented Tsuji–Trost macrocyclic etherification, followed by a transannular Claisen rearrangement to construct the 18-membered carbocyclic framework. The oxa-six- and five-membered rings were also stereoselectively constructed respectively by a cascade oxidative cyclization at an unfunctionalized benzylic position and using a one-pot epoxidation/5-exo-tet epoxide opening.

Kendomycin [(-)-TAN2162; 1; for structure see Scheme 1] is an ansa-macrocyclic polyketide comprising a quinone methide chromophore, and was originally isolated as an antagonist for the endothelin receptor,[1] and as an antioestrogenic agent.[2] Zeeck and Bode reported that 1 exhibited not only cytotoxic effects against a number of human tumor cell lines but also a strong antibacterial activity against both Gram-positive and Gram-negative bacteria, notably methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin intermediate S. aureus (VISA) Mu50 strain.[3] The architectural structure and multiple biological activities of 1 have attracted significant interest in the past decade from biological,[4] biosynthetic,[5] and chemically synthetic[6] perspectives.

The macrocyclic carbon framework of 1 represents a major challenge for an efficient chemical synthesis. Among all the achieved total syntheses and formal total syntheses, several macrocyclization strategies, including C-glycosydation,[7a] ring-closing metathesis (RCM),[7b,c,e,f,8] the Barbier reaction,[7d] photo-Fries rearrangement,[7e,f] Dötz benzannulation,[7g] and Prins reaction[7h] have been reported, albeit in modest yields. We have attempted an RCM strategy for the macrocyclization at the C13–C14 double bond of 1.[8] Unfortunately, the unnatural Z diastereomer was the predominant product. However, in our studies the Claisen rearrangement was found to work as a powerful tool for the introduction of a carbon substituent at the highly hindered C20a position.[8a] We finally found that the macrocyclic etherification/Claisen rearrangement combination could be used for the construction of kendomycin’s carbon framework.

The retrosynthetic analysis of 1 is outlined in Scheme 1. It could be derived from 2 through aromatic oxidation and oxidative removal of the terminal hydroxymethyl group. The five-membered ring of 2 could possibly be constructed selectively by a 5-exo cyclization of the phenol and the neighboring olefin of 3. The macro-carbocycle of 3 was envisioned to be derived from the transannular Claisen rearrangement of the allyl aryl ether 4, which comes from hydroquinone 5 using a selective macrocyclization at the less hindered hydroxy group by means of Tsuji–Trost etherifica-

Scheme 1. Retrosynthetic analysis. TBS = tert-butyldimethylsilyl.
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were thus used as a mixture for the Suzuki–Miyaura cross-coupling reaction with boronate 19. The boronate was prepared by lithiation and transmetalation of 8. The desired coupling product 20 was isolated in 87 % yield (two steps). Protection of 20 with MOMCl, selective removal of the terminal TBS group, carbonate formation, and exposure of the two hydroxy groups of the p-hydroquinone yielded the Tsuji–Trost cyclization precursor 5.

The examination of the key palladium-catalyzed Tsuji–Trost cyclization is shown in Table 1. Although the Tsuji–Trost reaction is well-established synthetic protocol, to the best of our knowledge, the macroetherification with this reaction has not been reported in total synthesis studies of natural products. More challenging is that our substrate, 5, is actually a hydroquinone which contains two hydroxy nucleophiles, and is sensitive to oxidation, which may render the reaction more complicated. However, to avoid the tedious and poorly selective protecting strategy for the hindered C4-OH group, we decided to perform the cyclization with both free hydroxy groups. Eventually, it was found that the desired macrocyclic ether 4 was obtained with [Pd2(dba)3] and dppb at room temperature in THF[19] though the regioisomer 4’ was the major product (entry 1). Solvent effects were later found to have great influence on the regioselectivity, with CH2Cl2 giving the best result (4/4’ = 10:1, entries 5 and 6). Notably, when the concentration of 5 was higher than 10 mM, intermolecular coupling became significant. Other palladium catalysts such as [Pd(PPh3)4] or Pd(OAc)2 gave either no reaction or decomposed byproducts. Although the solvent has been shown to play a key role in the ion-pairing in the Tsuji–Trost reaction[20] the specific reason for the selectivity in this study is still not clear.

After obtaining the 18-membered macrocyclic ether, we next attempted a ring contraction through a Claisen rearrangement (Scheme 4). We have reported this transformation with an acyclic substrate in refluxing Me2NPh[21a] This time, after TBS protection of the phenol 4 and heating at 205 °C in Et3NPh (a more stable solvent), 21 was smoothly converted into the desired carbocyclic 3 in 99 % yield. Next, several strategies (iodoetherification, oxymercuration, etc.) were attempted to cyclize the five-membered ring of kendomycin. Eventually, epoxidation and subsequent intramolecular epoxide opening proved to be most efficient. Thus, after alkene epoxidation with mCPBA in CH2Cl2, the 5-exo-tet cyclization proceeded smoothly by just adding a protic solvent, MeOH, and furnished predominantly one diastereomer 22. Since the upper trisubstituted alkene was also epoxidized during the process, a subsequent deoxygenation[7b,c,24] afforded the compound 2 in 82 % yield (two steps) as a single diastereomer. Next a hypervalent-iodine-promoted β-fragmentation of the alkoxyl radical removed the terminal hydroxymethyl group, and presumably provided an unstable intermediate tert-iodide, which was gradually eliminated to give the benzofuran 23. This elimination process was accelerated by the addition of a small amount of water. The compound 23 has the same skeleton as intermediates of kendomycin. Eventually, epoxidation and subsequent intramolecular epoxide opening proved to be most efficient. Thus, after alkene epoxidation with mCPBA in CH2Cl2, the 5-exo-tet cyclization proceeded smoothly by just adding a protic solvent, MeOH, and furnished predominantly one diastereomer 22. Since the upper trisubstituted alkene was also epoxidized during the process, a subsequent deoxygenation[7b,c,24] afforded the compound 2 in 82 % yield (two steps) as a single diastereomer. Next a hypervalent-iodine-promoted β-fragmentation of the alkoxyl radical removed the terminal hydroxymethyl group, and presumably provided an unstable intermediate tert-iodide, which was gradually eliminated to give the benzofuran 23. This elimination process was accelerated by the addition of a small amount of water. The compound 23 has the same skeleton as intermediates of kendomycin.

In summary, we have achieved the total synthesis of the antibiotic kendomycin (1) by using a highly stereocontrolled convergent strategy. The key step of this synthetic route is the

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Table 1: Regioselective macrocyclization using Tsuji–Trost ethenification.[a]  
![Table Image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd2(dba)3] (equiv)</th>
<th>dppb (equiv)</th>
<th>Solvent</th>
<th>T °C</th>
<th>4/4’ [%]</th>
<th>Yield 4 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
<td>0.4</td>
<td>THF</td>
<td>RT</td>
<td>1:3[9]</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>2</td>
<td>toluene</td>
<td>RT</td>
<td>1:1</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>20</td>
<td>DMF</td>
<td>50</td>
<td>3:5</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>1.6</td>
<td>(CHCl3)</td>
<td>70</td>
<td>7:3[4]</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>10</td>
<td>CH2Cl2</td>
<td>50</td>
<td>10:1</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>0.14</td>
<td>0.86</td>
<td>CH2Cl2</td>
<td>70</td>
<td>10:1</td>
<td>71%</td>
</tr>
</tbody>
</table>

[a] The reaction was performed with 1–5 mm of 5 in the dark in a sealed tube.  
[b] Determined by 1H NMR analysis of the crude reaction mixture.  
[c] Yield of the isolated product.  
[d] Approximately 20 % of the starting material remained.  
[e] Only starting material recovered. dba = dibenzylideneacetone, dppb = 1,4-bis(diphenylphosphino)butane.

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Scheme 4. Complete total synthesis of 1. mCPBA = m-chloroperoxybenzoic acid, TBAF = tetra-n-butylammonium fluoride.
palladium-catalyzed regioselective Tsuji–Trost macroetherification/transannular Claisen rearrangement sequence to construct the macrocyclic framework. Other synthetic features include the tetrahydropyran installation by stereoselective nucelophilic addition to an aldehyde and a Ag₂O-triggered stereoselective cyclization and the establishment of a five-membered ring by one-pot epoxidation/5-exo-tet cyclization process.

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[17] For the synthesis of 8, see the Supporting Information.
[20] Among the byproducts, the quinone A and methylenedioxy arene B were structurally determined. A was speculated to derive from oxidation of the hydroquinone 5 by high-valence palladium intermediates. B might be generated from A by a light-triggered transformation. For similar examples, see: C. Thommen, C. K. Jana, M. Neuburger, K. Gademann, Org. Lett. 2003, 5, 1390 – 1393, and references therein.
[23] In a recent total synthesis of kendomycin (Ref. [7g]), Nakata’s group applied a set of reaction conditions, similar to our previously reported method, on a substrate which was more acidic than 21. In their case, Ac₂O had to be used for the in situ trap of the Claisen product to avoid further decomposition. In our substrate case, no decomposition was observed.
A new construct: The asymmetric total synthesis of the antibiotic kendomycin was accomplished by using a highly stereocontrolled convergent route. The key feature of the synthetic strategy is the construction of an 18-membered carbohydrate based on an intramolecular Tsuji–Trost etherification/transannular Claisen rearrangement sequence. TBS = tert-butyldimethylsilyl.