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

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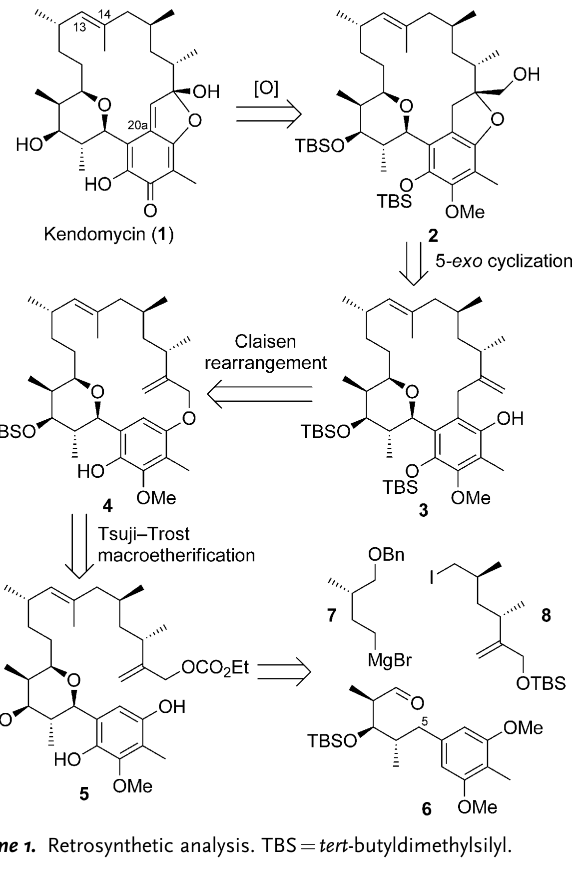
Abstract: *A highly stereocontrolled, convergent total synthesis of kendomycin [(−)-TAN2162], an ansa-macrocyclic antibiotic, is reported. The key of the strategy is an unprecedented Tsuji–Trost macrocyclic etherification, followed by a transannular Claisen rearrangement to construct the 18-membered 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 antiosteoporotic 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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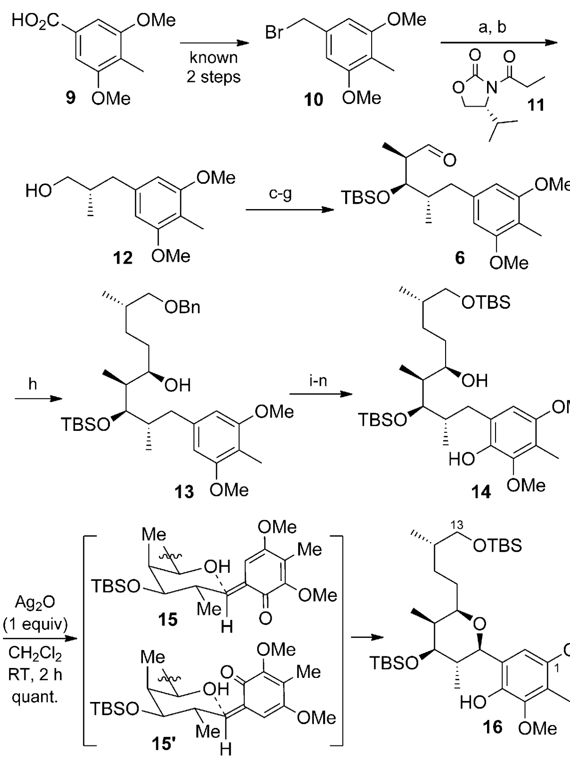
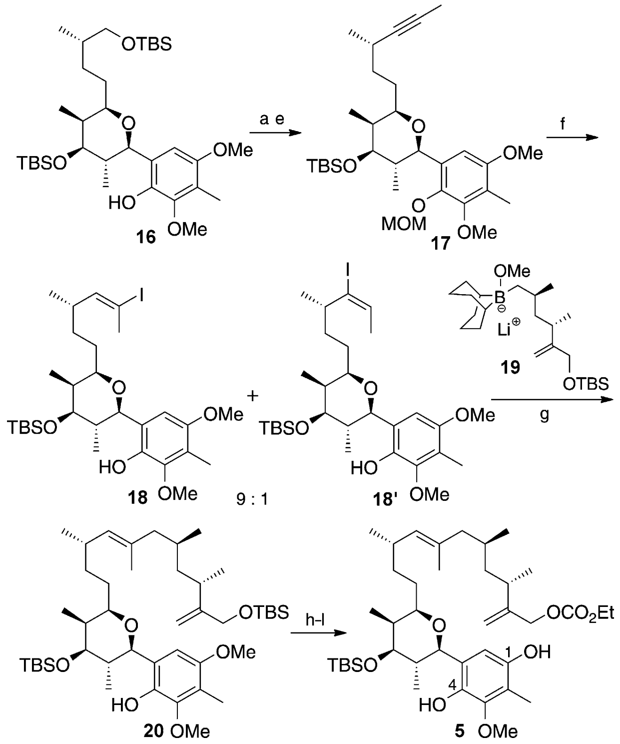
tion. The macrocyclization precursor **5** would be prepared convergently from the aldehyde **6**, alkylmagnesium **7**, and iodide **8**. The tetrahydropyran ring could be cyclized diastereoselectively at the unfunctionalized C5-position by a Ag_2O-triggered cascade reaction, as we have previously reported.[8a]

We have previously reported on the preparation of the C1–C13 segment of **1**,[8a] and herein, we present a modified scalable synthetic route (Scheme 2). The modified route commenced with the commercially available benzoic acid **9**, which was easily converted into the aryl bromide **10** with a two-step procedure.[9] Evans asymmetric alkylation[10] and reduction furnished the *S*-alcohol **12** with more than 99% *ee*, which was determined using the modified Mosher's method.[11] Swern oxidation and Roush crotylation[12] afforded a single diastereomer containing the three desired contiguous stereogenic centers, which was further transformed to aldehyde **6**. Nucleophilic addition of the Grignard compound **7**[13] to **6** gave a 15:1 diastereomer mixture of the secondary alcohol **13**, favoring the expected Felkin–Anh-type product. This selectivity is higher than our previous result (5.5:1) which was obtained using a similar alkyllithium nucleophile.[8a] After introduction of a phenolic hydroxy group to the aromatic ring, **14** was stereoselectively cyclized at the unfunctionalized benzylic position under phenol oxidation conditions (Ag_2O[14]) and quantitatively afforded the tetrahydropyran **16** as a single diastereomer. The excellent selectivity was thought to be due to the chair-form oxa-Michael-addition transition-state **15** or **15′** with the bulky quinone methide in an equatorial position. This result also proposed another possibility for the unclear biosynthetic mechanism of kendomycin's pyran ring formation.[5] With this modified route, **16** was obtained on a 3 gram scale.



Scheme 2. Synthesis of C1–C13 segment **16**: a) **11**, NaHMDS, THF, −60 °C; b) $LiAlH_4$, THF, −78 °C to 0 °C, 82% (2 steps); c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; d) (*R*,*R*)-[(*E*)-2-butenyl]diisopropyl tartrate boronate, 4 Å M.S., PhMe, −78 °C, 77% (2 steps); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; f) OsO_4 (cat.), NMO, acetone/H_2O (4:1), RT; g) $NaIO_4$, EtOH/H_2O (1:1), RT, 93% (2 steps); h) **7**, −78 °C, THF, quant. (d.r. 15:1); i) H_2, $Pd(OH)_2/C$, EtOAc, RT; j) TBSCl, DMAP, Et_3N, CH_2Cl_2, RT, 85% (2 steps); k) $HBr_3{\cdot}Py$, K_2CO_3, Py, 0 °C to RT; l) ethyl vinyl ether, PPTS, RT, quant. (2 steps); m) *n*BuLi, $B(OMe)_3$, THF, −78 °C to RT, then 30% H_2O_2 aq., Na_2CO_3, RT, 90%; n) PPTS, *n*PrOH, RT, 99%. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMSO = dimethylsulfoxide, HMDS = hexamethyldisilazide, M.S. = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, PPTS = pyridinium *p*-toluenesulfonate, Py = pyridine, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

The conversion of phenol **16** into **5** is shown in Scheme 3. After a manipulation of the protecting groups, Swern oxidation and Corey–Fuchs protocol furnished the alkyne **17**. Hydrozirconation with the Schwartz reagent[15] and subsequent iodination proceeded with high regioselectivity (9:1) along with removal of a MOM ether. The regioisomers **18** and **18′** were not easily separable from each other, and



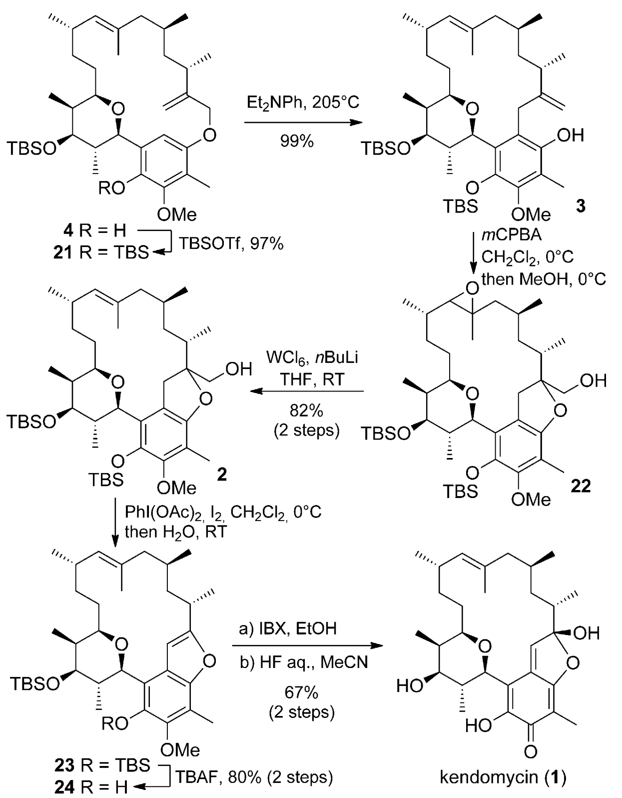
Scheme 3. Synthesis of the macrocyclization precursor **5**: a) MOMCl, NaH, THF, RT; b) PPTS, THF/MeOH (1:1), RT, 92% (2 steps); c) $(COCl)_2{\cdot}DMSO$, Et_3N, CH_2Cl_2, −78 °C; d) CBr_4, PPh_3, Et_3N, CH_2Cl_2, −78 °C, 72% (2 steps); e) *n*BuLi, MeI, THF, −78 °C to RT, 98%; f) $[HZrCp_2Cl]$, PhH, RT, then I_2; g) **8** (2 equiv), *t*BuLi, Et_2O, −78 °C, then MeO-9-BBN, THF, −78 °C to RT, then **18** + **18′**, $[Pd(dppf)_2Cl_2]{\cdot}CH_2Cl_2$ (20 mol%), 3 M K_3PO_4 aq., DMF, RT, 87% (2 steps); h) MOMCl, NaH, THF, RT, 95%; i) PPTS, THF/MeOH (1:1), RT, 73%; j) $ClCO_2Et$, Py, RT, 94%; k) $(NH_4)_2Ce(NO_3)_6$, $MeCN/H_2O$ (2:1), RT; l) $Na_2S_2O_4$, $MeCN/H_2O$ (1:1), 0 °C, quant. (2 steps). BBN = borabicyclo[3.3.1]nonane, Cp = cyclopentadienyl, DMF = *N*,*N*-dimethylformamide, dppf = 1,1′-bis(diphenylphosphino)ferrocene, MOM = methoxymethyl.

were thus used as a mixture for the Suzuki–Miyaura cross-coupling reaction[16] with boranate **19**. The boranate was prepared by lithiation and transmetalation of **8**.[17] 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 a well-established synthetic protocol,[18] 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 $[Pd_2(dba)_3]$ 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 CH_2Cl_2 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 $[Pd(PPh_3)_4]$ or $Pd(OAc)_2$ gave either no reaction or decomposed byproducts.[20] Although the solvent has been shown to play a key role in the ion-pairing in the Tsuji–Trost reaction,[21] the specific reason for the selectivity in this study is still not clear.

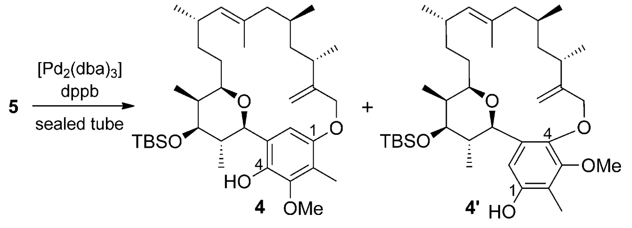
After obtaining the 18-membered macrocyclic ether, we next attempted a ring contraction through a Claisen rearrangement[22] (Scheme 4). We have reported this transformation with an acyclic substrate in refluxing Me_2NPh.[8a] This time, after TBS protection of the phenol **4** and heating at 205 °C in Et_2NPh (a more stable solvent), **21** was smoothly converted into the desired carbocyclic **3** in 99% yield.[23] 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 *m*CPBA in CH_2Cl_2, the 5-*exo*-tet cyclization proceeded smoothly by just adding a protic solvent, MeOH, and furnished predominately one diastereomer of **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 obtained by the groups of Lee[7a] and Mulzer.[7e,f] Finally, the selective removal of the phenolic TBS group, oxidation, and acidic rearrangement of the resulting *o*-quinone, with the simultaneous TBS removal, accomplished the total synthesis 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



Scheme 4. Complete total synthesis of **1**. *m*CPBA = *m*-chloroperoxybenzoic acid, TBAF = tetra-*n*-butylammonium fluoride.

Table 1: Regioselective macrocyclization using Tsuji–Trost etherification.[a]



Entry	$[Pd_2(dba)_3]$ (equiv)	dppb (equiv)	Solvent	*T* [°C]	**4**/**4'**[b]	Yield **4** [%][c]
1	0.15	0.4	THF	RT	1:3[d]	–
2	0.5	2	toluene	RT	1:1	–
3	1.1	20	DMF	60	3:5	–
4	0.2	1.6	$(ClCH_2)_2$	70	–[e]	–
5	0.4	10	CH_2Cl_2	50	10:1	80
6	0.14	0.86	CH_2Cl_2	70	10:1	71

[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.

palladium-catalyzed regioselective Tsuji–Trost macroetherification/transannular Claisen rearrangement sequence to construct the macrocyclic framework. Other synthetic features include the tetrahydropyran installation by stereoselective nucleophilic addition to an aldehyde and a Ag_2O-triggered stereoselective cyclization and the establishment of a five-membered ring by one-pot epoxidation/5-*exo*-tet cyclization process.

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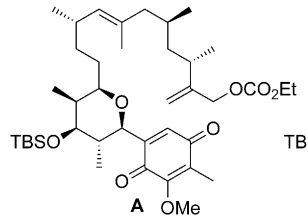

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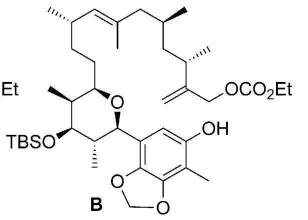

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