Natural Product Synthesis

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Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis**

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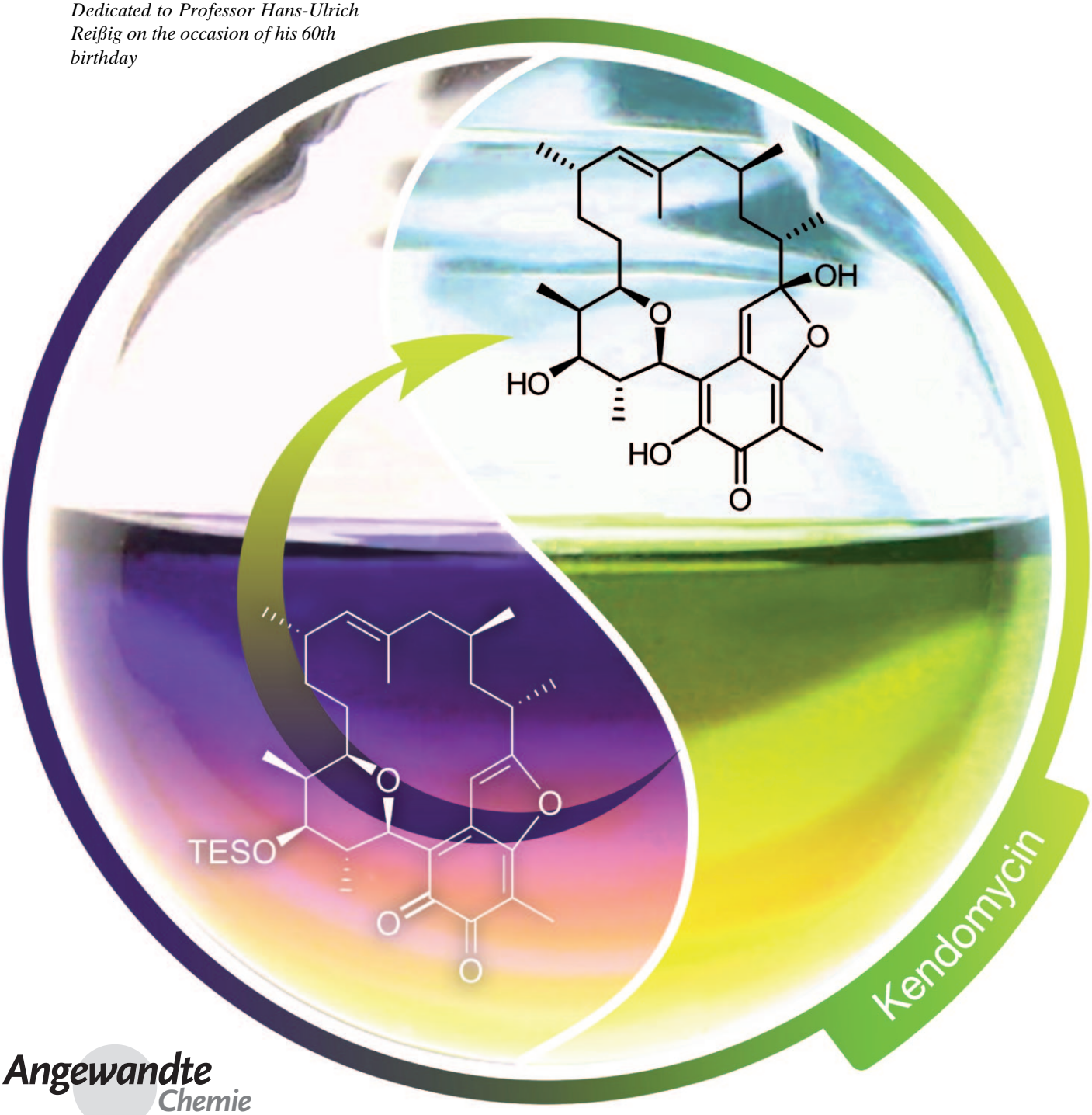
Dedicated to Professor Hans-Ulrich Reißig on the occasion of his 60th birthday

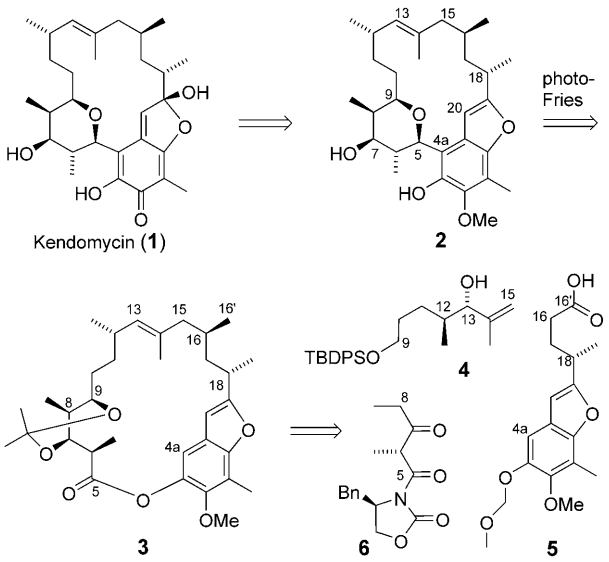


Kendomycin [**1**, (−)-TAN2162], an ansamycin isolated from different *Streptomyces* species, has been shown in studies over the last decade to be a potent endothelin receptor antagonist and antiosteoperotic compound with remarkable antibacterial and cytostatic activity.[1] The challenging structure and diverse pharmacological profile of kendomycin[1,2] has motivated us[3] and, sometime later a number of other groups,[4–6] to carry out studies towards its synthesis. To date, three total syntheses[4] and one formal synthesis[5] have been reported, along with a number of fragment preparations.[6] The main problem for all the approaches has been the formation of the strained macrocyclic *ansa*-ring. For example, macrocyclizations were performed using C-glycosidation,[4a] Barbier-type organometallic addition,[4d] Prins reaction,[5] and Horner–Wadsworth–Emmons olefination.[6e] Most strikingly, all attempts to achieve 13,14-macrocyclization by ring-closing metathesis (RCM)[4b,6a,e] were plagued by low yields and formation of the undesired 13,14-*Z*-olefin. We tested alternative locations for RCM connections; however to our disappointment, both the 9,10- and the 19,20-positions proved to be unsuited.[7] Nonetheless, we were still convinced that RCM should be a highly serviceable tool for ring closure.

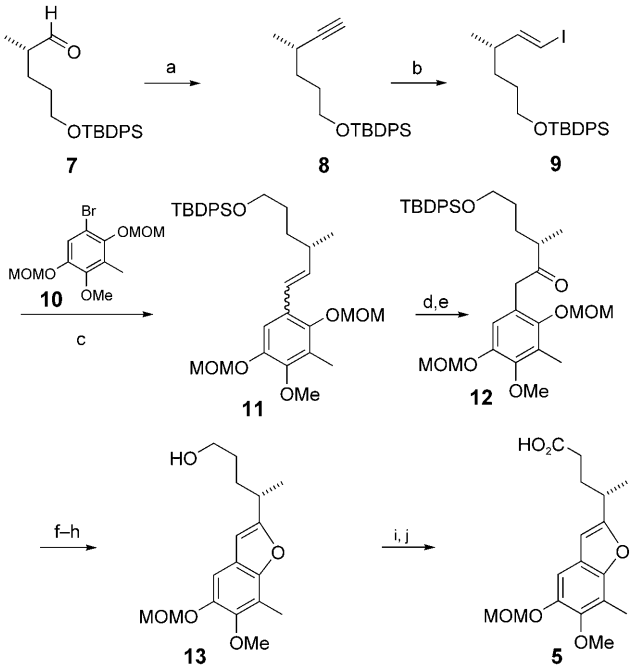
As we have demonstrated in previous studies,[3,6e] hindered rotation around the C4a/C5 bond connecting the tetrahydropyran ring and the aromatic system makes ring closure difficult. Therefore, we decided to postpone tetrahydropyran formation until after macrocyclization, and consequently, we report herein two novel ring closures: the first by a photo-Fries ring contraction[8] connecting C4a/C5, and the second by a RCM to form a 10,11-olefin. Both routes would lead to the known benzofuran intermediate **2**.[4a]

The photo-Fries route (Scheme 1) centers around macrolactone **3** as a key intermediate, which was assembled from building blocks **4**, **5**, and **6** by a Claisen–Ireland rearrangement (C15/C16 connection) and Evans aldolization (C8/C9-connection).

The synthesis of the benzofuran fragment **5** (Scheme 2) started with known aldehyde **7**,[4a] which is easily available from citronellene (see the Supporting Information). A Colvin C_1 chain elongation[9] furnished alkyne **8**, which was converted into vinyl iodide **9**. Negishi coupling[10] with aryl bromide **10**[6e] led to styrene **11**, which after epoxidation was subjected to palladium(0)-mediated rearrangement[11] to ketone **12**. Acid-catalyzed formation of the furan ring concomitantly removed the 3-OMOM group, which was reinstalled. Desilylation delivered alcohol **13**, which was oxidized to carboxylic acid **5**.



Scheme 1. Retrosynthesis of **1**: Photo-Fries approach. TBDPS = *tert*-butyldiphenylsilyl, Bn = benzyl.



Scheme 2. Synthesis of carboxylic acid **5**. a) $TMSCHN_2$, *n*BuLi, THF, −78 °C to RT, 83%; b) $[Cp_2ZrHCl]$, benzene, 50 °C; I_2, 0 °C, 76%; c) $[Pd(PPh_3)_4]$, *t*BuLi, $ZnCl_2$, Et_2O/THF, 0 °C, 67%; d) DMDO, acetone, RT, 99% (d.r. 1.1:1); e) $Pd(OAc)_2$, PBu_3, *t*BuOH, reflux, 81% (2 steps); f) TfOH, toluene/EtOH (4:1), molecular sieves 4 Å, 80 °C, 5 min; g) MOMCl, NaH, DMF, 0 °C, 90% (2 steps); h) TBAF, THF, RT, 89%; i) IBX, DMSO, RT, 97%; j) $NaClO_2$/NaH_2PO_4, 2,3-dimethylbut-2-ene, *t*BuOH/H_2O, 99%. MOM = methoxymethyl, TMS = trimethylsilyl, Cp = cyclopentadienyl, DMDO = dimethyldioxirane, Tf = trifluoromethanesulfonyl, DMF = dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran, IBX = *o*-iodoxybenzoic acid, DMSO = dimethylsulfoxide.

Allylic alcohol **4**,[12] which was available from aldehyde **7** by Nozaki–Hiyama–Kishi addition[13] of isopropenyl bromide

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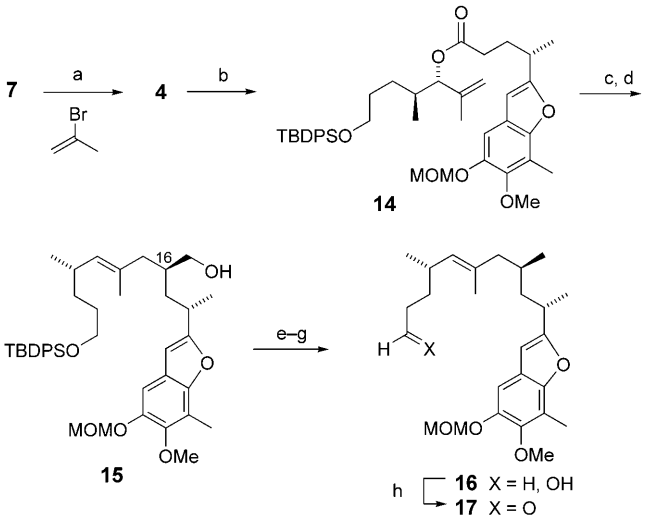
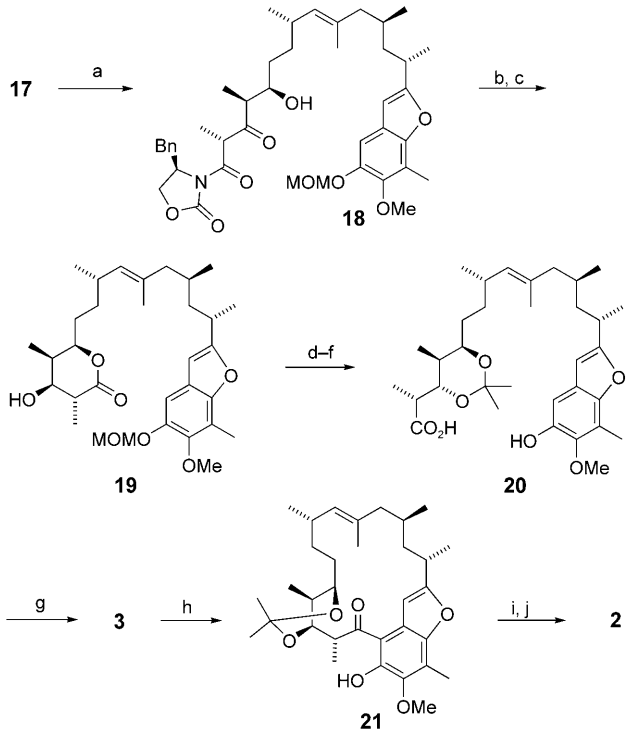
(Scheme 3), was connected with carboxylic acid **5** to furnish ester **14** as the substrate of an Claisen–Ireland rearrangement, which, after reduction, led to primary alcohol **15** as an easily separable 4:1 diastereomeric mixture at C16.[14] Reduction and desilylation gave alcohol **16**, which was oxidized to aldehyde **17**.



Scheme 3. Synthesis of aldehyde **17**. a) $CrCl_2$ (4 equiv), $NiCl_2$ (0.04 equiv), DMF, 0 °C to RT, 86% (d.r. 1.4:1); b) EDCI, DMAP, **5**, CH_2Cl_2, 85%; c) LHMDS, HMPA, TBSCl, −78 °C to reflux; d) $LiAlH_4$, Et_2O, 0 °C, 84% (d.r. 4:1, 2 steps); e) MsCl, Et_3N, CH_2Cl_2, 0 °C; f) $LiAlH_4$, Et_2O, 0 °C, 94% (2 steps); g) TBAF, THF, RT, 93%; h) IBX, DMSO, RT, 93%. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-(dimethylamino)pyridine, HMDS = hexamethyldisilazane, HMPA = hexamethylphosphoramide, TBS = *tert*-butyldimethylsilyl, Ms = methanesulfonyl.

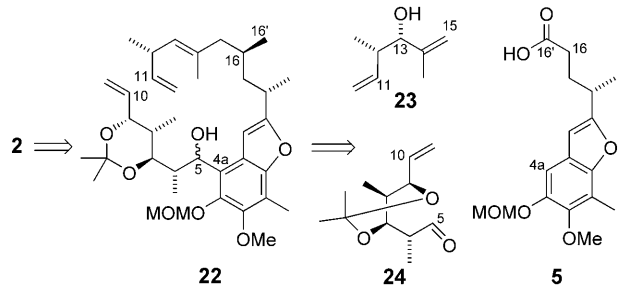


Scheme 4. Synthesis of benzofuran **2**. a) **6**, $Sn(OTf)_2$, CH_2Cl_2, Et_3N, −20 °C, then −78 °C, then **17**, 87% (d.r. 6:1); b) $Me_4NBH(OAc)_3$, CH_3CN/AcOH (2:1), −32 °C to 0 °C, 72% (d.r. 20:1); c) LiOH, H_2O_2, THF/H_2O (3:1), 96%; d) 3 M HCl, dioxane, 50 °C; e) $(CH_3)_2C(OMe)_2$, CSA, RT, 85% (2 steps); f) LiOH, THF/MeOH/H_2O (2:1:1), 12 h, RT, 84%; g) EDCI, DMAP, DMAP·HCl, $CHCl_3$, reflux, 20 h, 55%; h) *hν* (254 nm), cyclohexane, 50 min, 75%; i) $NaBH_4$, MeOH, RT, then 0.5 M HCl; j) TsOH, toluene, 60 °C, 71% (2 steps). CSA = camphorsulfonic acid, Ts = 4-toluenesulfonyl.

Aldol addition with the Evans ketoimide **6**[15] furnished intermediate **18**, which has the full carbon skeleton of kendomycin. Reduction[16] of the ketone and hydrolytic removal of the auxiliary led to lactone **19**, which was converted into *seco*-acid **20** by formation of the acetonide-protected methylester. Macrolactonization under modified Boden–Keck conditions[17] gave monomer **3** in 55% yield, which underwent clean photo-Fries rearrangement to give ketone **21**. Reduction to the secondary alcohol, followed by removal of the acetonide and S_N1 cyclization, furnished key intermediate **2** (Scheme 4).

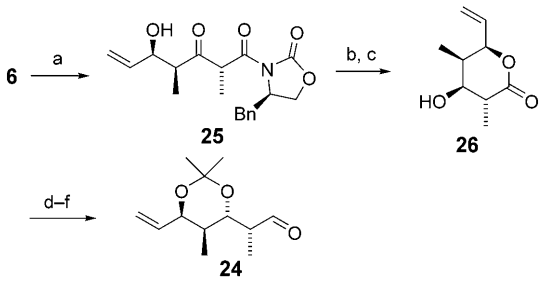
Our second route is outlined in Scheme 5. In contrast to earlier RCM attempts, RCM of triene **22** should not meet with major ring strain and thus proceed smoothly, as two monosubstituted olefins are connected. The tetrahydropyran ring is formed later, such that the above-mentioned atropisomerism cannot impede the macrocyclization. Triene **22** was to be constructed from building blocks **23**, **24**, and **5**.

Aldehyde **24** was obtained by Evans aldolization from ketoimide **6** and acrolein (Scheme 6) to give adduct **25** with good diastereoselectivity, which was converted into lactone **26** by reduction and removal of the auxiliary. For the conversion of **26** into aldehyde **24**, an analogous sequence was used as for the preparation of **20** from **19**.

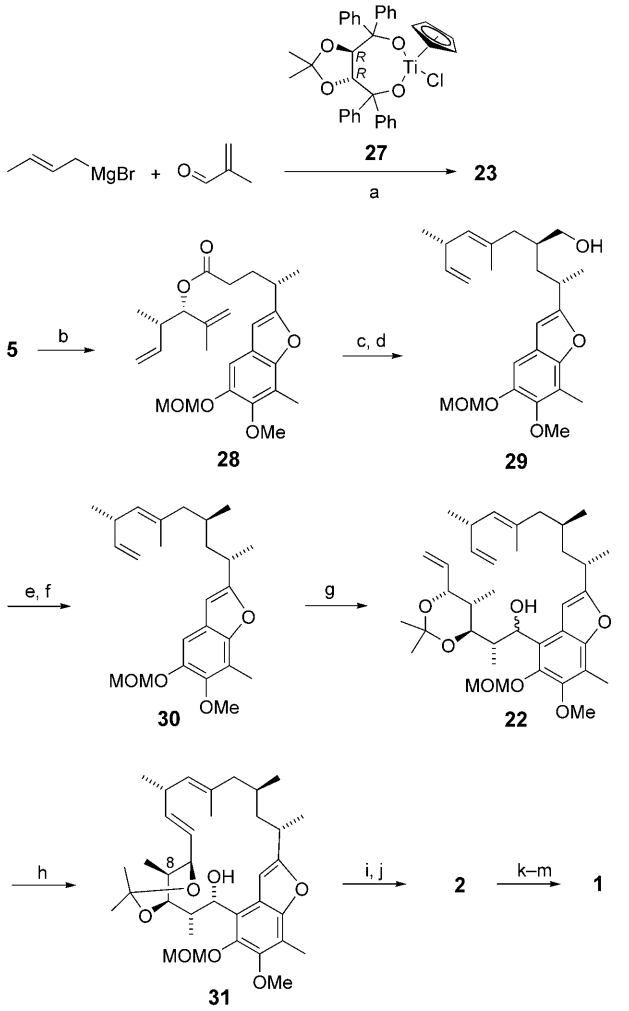


Scheme 5. Retrosynthesis of **2**: RCM route.

For the preparation of allylic alcohol **23**, a Duthaler–Hafner crotylation[18] of methacrolein with titanate **27** was the method of choice (Scheme 7). Esterification of acid **5** with alcohol **23** paved the way for the Claisen–Ireland rearrangement, by which ester **28** was smoothly converted into the acid, and after reduction, into alcohol **29**. Deoxygenation furnished diene **30**. Subsequent *ortho*-directed metalation and addition of aldehyde **24** gave alcohol **22** as a mixture of diastereomers. RCM with second-generation Grubbs catalyst[19] induced smooth ring closure to form the 10,11-*E*-olefin **31** exclusively. The extremely broad ^1H NMR signal of the 8-CH_3 group, which sharpens to a doublet on raising the temperature to



Scheme 6. Synthesis of aldehyde **24**. a) $Sn(OTf)_2$, CH_2Cl_2, Et_3N, −20 °C, −78 °C, then acrolein, 91% (d.r. 5:1); b) $Me_4NBH(OAc)_3$, CH_3CN/AcOH (2:1), −32 °C to 0 °C, 70% (d.r. 6:1); c) LiOH, H_2O_2, THF/H_2O (2:1), RT, 72%; d) $(CH_3)_2C(OMe)_2$, CSA, RT, 91%; e) $LiAlH_4$, Et_2O, 0 °C, 96%; f) pyridine·SO_3, Et_3N, CH_2Cl_2/DMSO, −5 °C, 99%.



Scheme 7. RCM and synthesis of **1**. a) Reaction of but-2-enyl-MgBr with **27**, then methacrolein, Et_2O, −78 °C, 52% (d.r. 50:1, 86% *ee*); b) DMAP, EDCI, CH_2Cl_2, RT, then **23**, 81%; c) LHMDS (4 equiv), HMPA, THF, then **28** dissolved in TBSCl, −78 °C to RT, then DMF, microwave irradiation (10 min, 180 °C); d) $LiAlH_4$, Et_2O, 0 °C, 89% (d.r. 4:1, 2 steps); e) MsCl, CH_2Cl_2, 0 °C; f) $LiAlH_4$, Et_2O, 0 °C, 89% (2 steps); g) *n*BuLi, TMEDA, THF, then **24**, −78 °C to −30 °C, 90% (d.r. 3.2:1); h) Grubbs II catalyst, 20 mol%, CH_2Cl_2, reflux, 16 h, 62% (*E* only); i) $N_2(COOK)_2$, AcOH, CH_2Cl_2, 40 h, reflux, 60%; j) 3 M HCl, MeOH, RT, 96%; k) TESOTf, Et_3N, CH_2Cl_2, 0 °C, 82%; l) IBX, DMF, RT, 24 h; m) 0.1 M HF, MeCN, RT, 30% (2 steps). TMEDA = tetramethylethylendiamine, TES = triethylsilyl.

350 K (see Supporting Information), indicates that the conformational mobility in **31** is significantly restricted. Selective reduction of the double bond with diimide,[20] followed by acid-catalyzed formation of the tetrahydropyran ring and removal of the OMOM group, led to intermediate **2**, which was oxidized to **1**.[4a] The analytical data of the synthetic material were in full agreement with those of an authentic sample kindly provided by Professor Zeeck.

In conclusion, we have presented two novel approaches to the antibiotic kendomycin (RCM route: 23 linear steps, photo-Fries route: 29 linear steps). Apart from Claisen–Ireland rearrangements of unusual complexity, this work not only demonstrates the hitherto unrecognized capability of the photo-Fries ring contraction for the formation of macrocycles, but also reemphasizes the unparalleled potential of RCM for connecting monosubstituted olefin residues.

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