Macrolide Synthesis

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Total Synthesis of (−)-Ulapualide A: The Danger of Overdependence on NMR Spectroscopy in Assignment of Stereochemistry**

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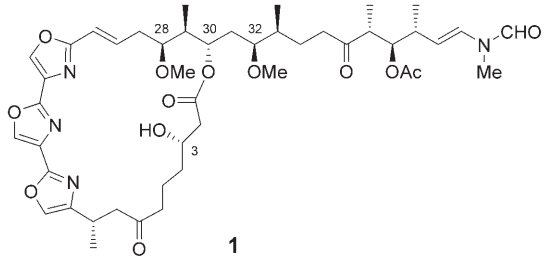
Ulapualide A (**1**) and its relatives, for example, mycalolide A (**2**), are an intriguing family of trisoxazole-based macrolides which have been isolated from marine nudibranchs (sea slugs) and sponges.[1] The metabolites show antifungal activity and ichthyotoxic properties, and they also show activity against L1210 leukemia cells. Although the ulapualides have been known since 1986, their complete stereochemistries were not defined until quite recently following degradation and synthetic studies,[2] and, in particular, X-ray studies of some of their complexes with the protein actin.[3]

Earlier, we described a total synthesis of the structure **3** for ulapualide A, whose stereochemistry we assigned on the basis of a molecular mechanics study of a hypothetical metal-chelated complex.[1b] The synthetic ulapualide A showed identical chromatographic behavior, as well as chiroptical and ^{1}H NMR spectroscopic data with those of naturally derived material, but very small differences were observed in the ^{13}C NMR spectra associated with the C32–C34 portions of the structures. The stereochemistry of natural ulapualide A (**1**), determined from an X-ray analysis of its complex with actin, differs from that of the diastereoisomer **3** at the stereocenters C3, C28, C29, C30, and C32. This situation makes it all the more bewildering, therefore, as to why the synthetic diastereoisomer **3** gave ^{1}H NMR spectroscopic and other data which were superimposable on those of the natural product. We have, therefore, undertaken a conceptually new, second generation, total synthesis of ulapualide A[4] to resolve any remaining ambiguities with regards to the stereochemistry of the free metabolite, which was isolated from the egg masses of the nudibranch *Hexabranchus sanguineus*.[5]



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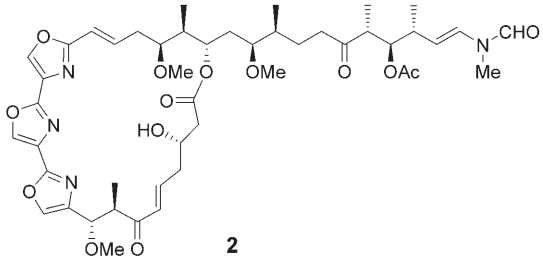

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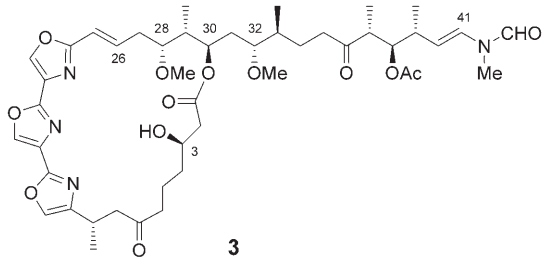

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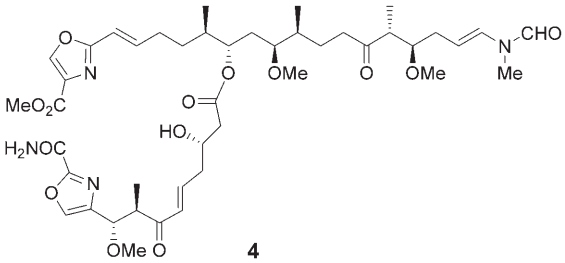

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Based on speculation of the biosynthetic origin of the contiguous trisoxazole unit in the ulapualides **1** and **2**,[6] alongside those co-metabolites that contain only two oxazole rings, for example, **4**,[7] we designed a synthesis of **1** that involved the macrolactamization of the intermediate **6**, leading to **5**, followed by elaboration of the central oxazole ring in **1** as a late step in the overall synthesis.[8] This approach required a synthesis of the ester **6** from the acid **8** and the alcohol **7**, which together contain all of the ten stereocenters in ulapualide A (**1**; Scheme 1).

In our synthesis of the diastereoisomer **3** of ulapualide A we applied a range of contemporary methods in asymmetric

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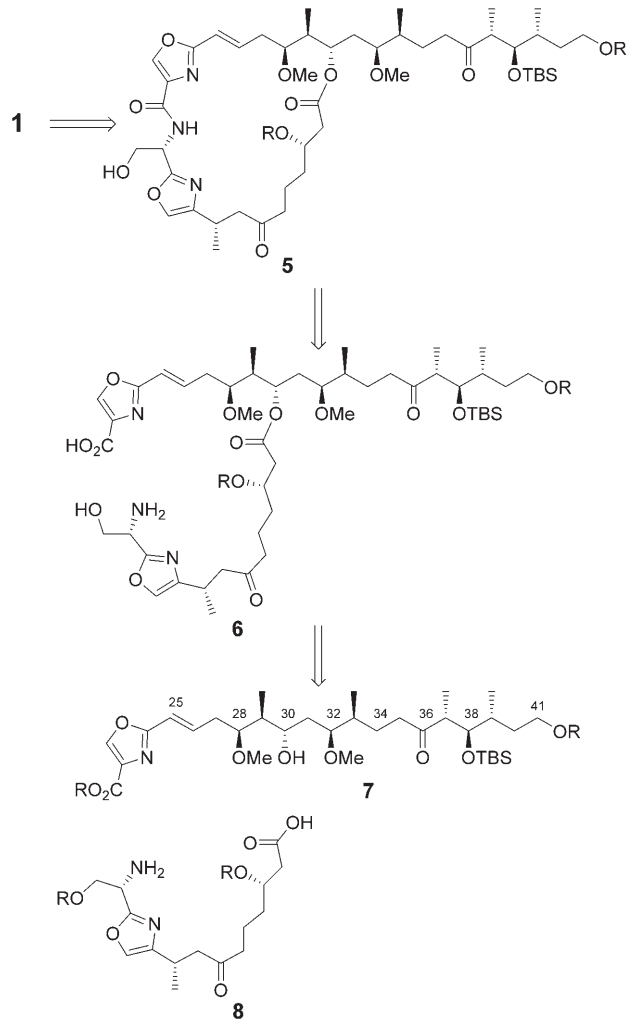
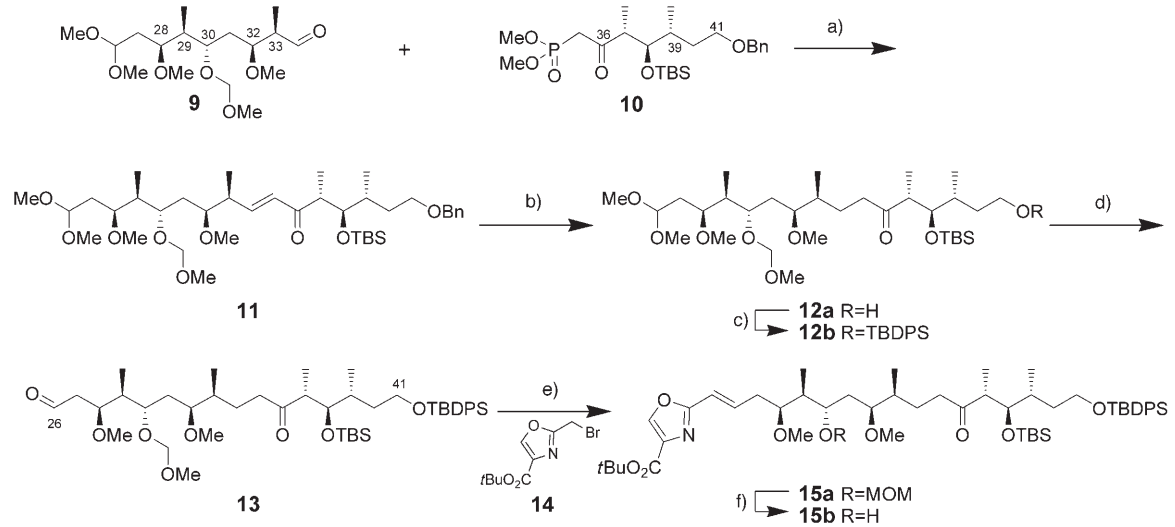


Scheme 1. Retrosynthesis of ulapualide A (**1**). TBS = *tert*-butyldimethylsilyl.

synthesis and examined a variety of hydroxy-protecting groups to prepare the C26–C41 (top-chain) portion in the target.[1] We therefore followed this overall strategy in preparing the functionalized C26–C41 unit **13**, with the modified stereochemistry between C28 and C32, from the aldehyde **9** and the phosphonate **10** en route to the alcohol **7**. Thus, the aldehyde **9** was made by using Evans aldol chemistry to introduce the *syn* stereochemistry at C32–C33 and the *anti* stereochemistry at C29–C30, and we applied the Brown allylboration chemistry to install the β-orientated hydroxy group at C28.[9] The absolute stereochemistry of the aldehyde **9** was established by X-ray analysis of the TBDPS ether of the corresponding primary alcohol.[10]

A Wadsworth–Emmons reaction between the aldehyde **9** and the known phosphonate ester **10**[1] using $Ba(OH)_2$ as base[11] gave the *E* alkene **11**, which, in one step, was then converted into the alcohol **12a** following hydrogenation/hydrogenolysis in the presence of the Pearlman catalyst[12] (Scheme 2). The primary alcohol group in **12a** was protected as its TBDPS ether **12b** and the dimethyl acetal group was then unmasked selectively using Me_2BBr in CH_2Cl_2 at −78 °C[13] to give the aldehyde **13** in excellent yield. A straightforward Wittig reaction between the aldehyde **13** and the phosphorus ylide, derived in situ from the oxazolemethyl bromide **14**[14] and Bu_3P in the presence of DBU, next gave the *E* alkene **15a**. Selective deprotection of the MOM ether group in **15a** using Me_2BBr in Et_2O at −78 °C then produced the alcohol **15b** (cf. **7**) in preparation for coupling to the carboxylic acid **8**.

The protected form of the substituted carboxylic acid **8**, that is, **24b**, which contains the two remaining stereocenters in **1**, was conveniently synthesized using a cobalt-mediated coupling reaction between the aldehyde **21** and the iodide **22** in the presence of vitamin B_{12}.[15] Thus, a chelation-controlled *syn* addition of lithium dimethylcuprate to the *R* α,β-unsaturated ester **16**[16] derived from the Garner aldehyde, first gave the adduct **17** with 9:1 *syn* selectivity (Scheme 3). Successive



Scheme 2. Synthesis of the side chain **15b**. Reagents and conditions: a) $Ba(OH)_2$, THF, H_2O, 68%; b) $Pd(OH)_2/C$, H_2, EtOAc, 96%; c) TBDPSCl, imidazole, DMF, 93%; d) Me_2BBr, CH_2Cl_2, −78 °C, 98%; e) PBu_3, **14**, DBU, DMF, 75%; f) Me_2BBr, Et_2O, −78 °C, 79%. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl.

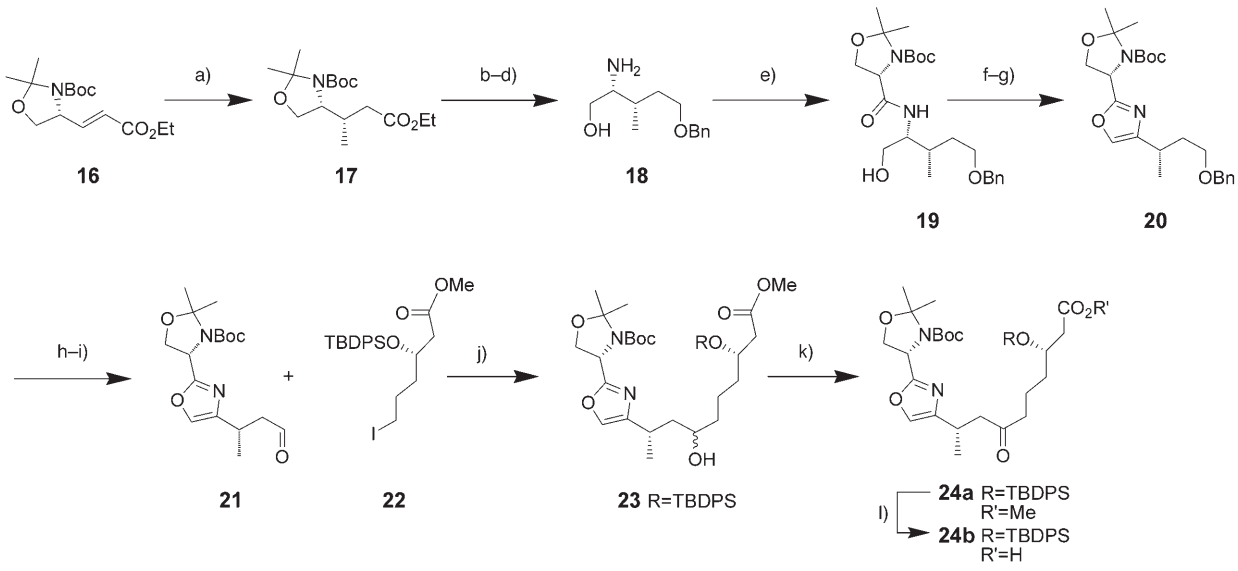
functional group interconversions next led to the amino alcohol **18** which was then reacted with the Garner acid,[17] to give the corresponding amide **19**. Oxidation of the primary alcohol group in **19** followed by cyclization of the resulting aldehyde[18] gave the substituted oxazole **20**, which was then elaborated to the new aldehyde **21** in two straightforward steps.

The aldehyde **21** was then coupled to the iodide **22**[19] in degassed DMF in the presence of vitamin B_{12} and $CrCl_2$,[15] to give a 1:1 mixture of epimers of the alcohol **23** in 88% yield. Finally, oxidation of **23** to the corresponding ketone **24a** under Swern conditions followed by saponification of the ester group in **24a** using LiOH/MeOH gave the carboxylic acid **24b**.

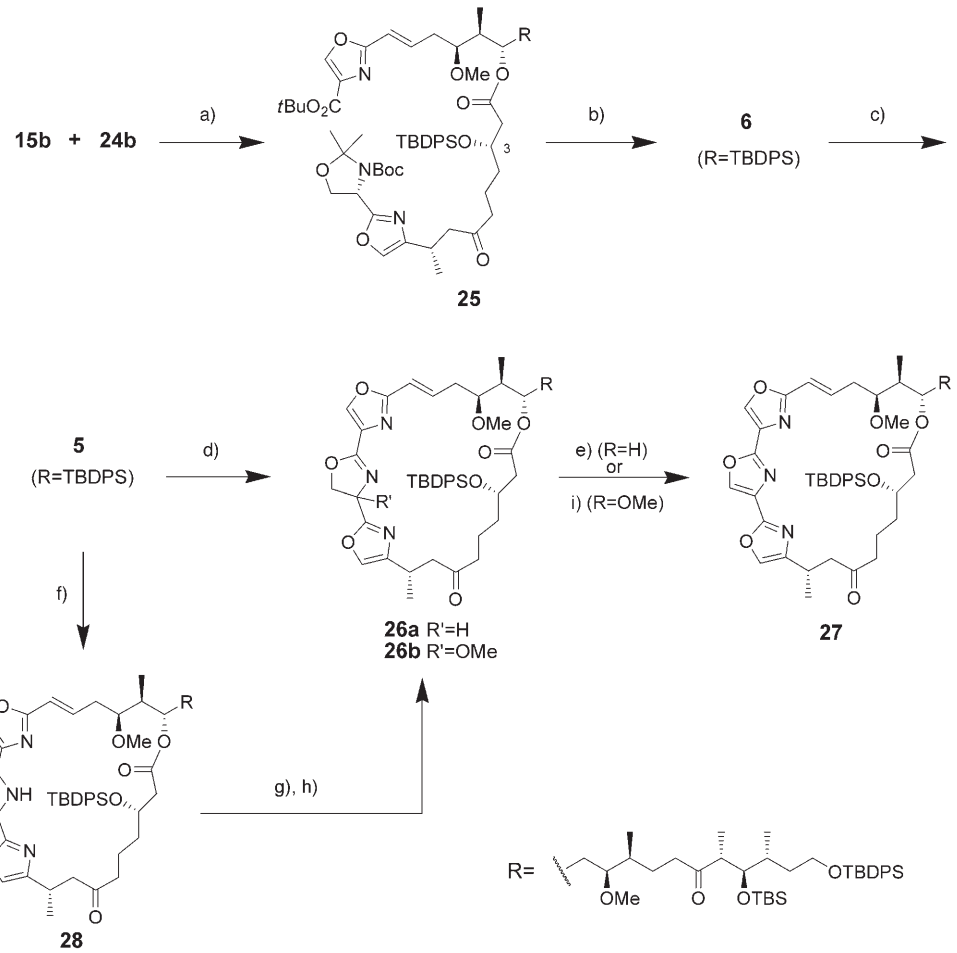
The esterification of the carboxylic acid **24a** with the alcohol **15b** proceeded smoothly under Yamaguchi conditions[20] to give the coupled product **25** in an excellent 93% yield (Scheme 4). The *tert*-butyl ester and the *N*-Boc protecting groups in **25** were removed simultaneously using TMSOTf in the presence of Et_3N[21] to give the ω-amino acid **6** (R = TBDPS; Scheme 4). The amino acid **6** was not isolated but instead was treated with HATU[22] at 0 °C which resulted in smooth macrolactamization to **5** (R = TBDPS) in an agreeable yield of 67% for the two steps. The conversion of the macrolactam **5** into the corresponding trisoxazole **27** did not turn out to be straightforward.[8] Although the intermediate **5** (R = TBDPS) was smoothly dehydrated to the oxazoline **26a** using DAST at −78 °C, the subsequent oxidation of **26a** to the corresponding trisoxazole **27** using NiO_2 in benzene heated at reflux[23] was unreliable and seldom gave yields greater than 25%. A more reliable, albeit more lengthy route to **27** from **5**, was via the enamide **28** that was produced after mesylation and elimination of $MeSO_2H$ from **5**. The enamide **28** could then be converted into the methoxyoxazoline **26b** by reaction with NBS in MeOH followed by dehydrobromination in the presence of Cs_2CO_3.[24] Finally, treatment of **26b** with CSA in benzene heated at reflux gave the same trisoxazole **27** as that obtained earlier.

The synthesis of ulapualide A (**1**) from the substituted macrolide intermediate **27** was completed in six relatively straightforward steps, which were made possible by the selective ease of removal of the silyl protecting groups in **27**, that is, TBS > primary TBDPS > secondary TBDPS.[25] Thus, deprotection of the TBS group in **27**, using TMSOTf at −78 °C followed by acetylation of the resulting secondary alcohol **29a** first gave the corresponding acetate **29b** (Scheme 5). Treatment of **29b** with HF/pyridine in CH_2Cl_2 for 1.5 h resulted in the selective deprotection of the $CH_2OTBDPS$ group to give the primary alcohol **30a**, which was then oxidized to the corresponding aldehyde **30b** using Dess–Martin periodinane. When a solution of the aldehyde **30b** in benzene was heated under reflux with *N*-methylformamide in the presence of pyridinium *p*-toluenesulfonate (PPTS) for 10 h, workup and chromatography gave (*E*)-alkenylformamide **31** which was isolated as a 3:2 mixture of rotamers in 25–40% yield. Removal of the TBDPS protection in **31** using HF/pyridine in THF at room temperature for 12 h, finally gave (−)-ulapualide A (**1**), $[\alpha]_D^{26} = -52.8$ ($c = 0.11$ in MeOH) as a colorless, viscous oil, in 60% yield.

The synthetic ulapualide A displayed ^1H and ^{13}C NMR spectroscopic data which were indistinguishable from those obtained for naturally derived material.[26] Significantly, whereas the synthetic diastereoisomer **3** displayed small differences in the chemical shifts of the ^{13}C NMR spectra with the natural product for the C32 atom ($\delta = 81.0$ ppm; cf. $\delta = 81.8$ ppm for natural), the C34 atom ($\delta = 26.6$ ppm; cf. $\delta =$



Scheme 3. Synthesis of the carboxylic acid **24b**. Reagents and conditions: a) Me_2CuLi, TMSCl, THF, 81%; b) DIBAL-H, THF, 100%; c) NaH, BnBr, TBAI, THF, 78%; d) HCl, dioxane; e) Garner acid, EDC, 4-methylmorpholine, THF, HOBt, 79%; f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 97%; g) PPh_3, 1,2-dibromotetrachloroethane, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, DBU, MeCN, 72%; h) Pd/C, EtOAc, H_2, 81%; i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 87%; j) Vitamin B_{12}, $CrCl_2$, DMF, 88%; k) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 85%; l) LiOH, MeOH, H_2O, 88%. Boc = *tert*-butoxycarbonyl, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxy-1*H*-benzotriazole, TBAI = tetra-*n*-butylammonium iodide, TMS = trimethylsilyl.



Scheme 4. Synthesis of the trisoxazole **27**. Reagents and conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, DMAP, 0 °C, 93 %; b) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; c) HATU, Et_3N, CH_2Cl_2, 0 °C, 67 %; d) DAST, CH_2Cl_2, −78 °C, 89 %; e) NiO_2, benzene, reflux, 25 %; f) MsCl, DIPEA, CH_2Cl_2, DBU, 0 °C, 75 %; g) NBS, MeOH, CH_2Cl_2, 92 %; h) Cs_2CO_3, dioxane, 60 °C, 92 %; i) CSA, benzene, 5-Å molecular sieves, reflux, 58 %. CSA = camphorsulfonic acid, DAST = (diethylamino)sulfur trifluoride, DIPEA = diisopropylethylamine, DMAP = 4-dimethylaminopyridine, HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-l-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate, Ms = methanesulfonyl, NBS = *N*-bromosuccinimide, Tf = trifluoromethanesulfonyl.

27.6 ppm for natural), and for the C33-methyl group (δ = 14.2 ppm; cf. δ = 15.5 ppm for natural), the synthetic ulapualide A (**1**) showed matching chemical shift data for these absorptions, that is, δ = 81.8 (C32), 27.7 (C34), and 15.6 ppm (C33-Me). This total synthesis of (−)-ulapualide A complements the X-ray studies made by Rayment and co-workers[3b] on an actin–ulapualide A complex. It also emphasizes how cautious synthetic chemists should be in relying on NMR spectroscopy when comparing data for some complex natural products and their synthetic counterparts. As this study has shown, profound changes in the stereochemistry of a natural product (compare **1** and **3**) are not always reflected in a significant way in their NMR spectroscopic data.

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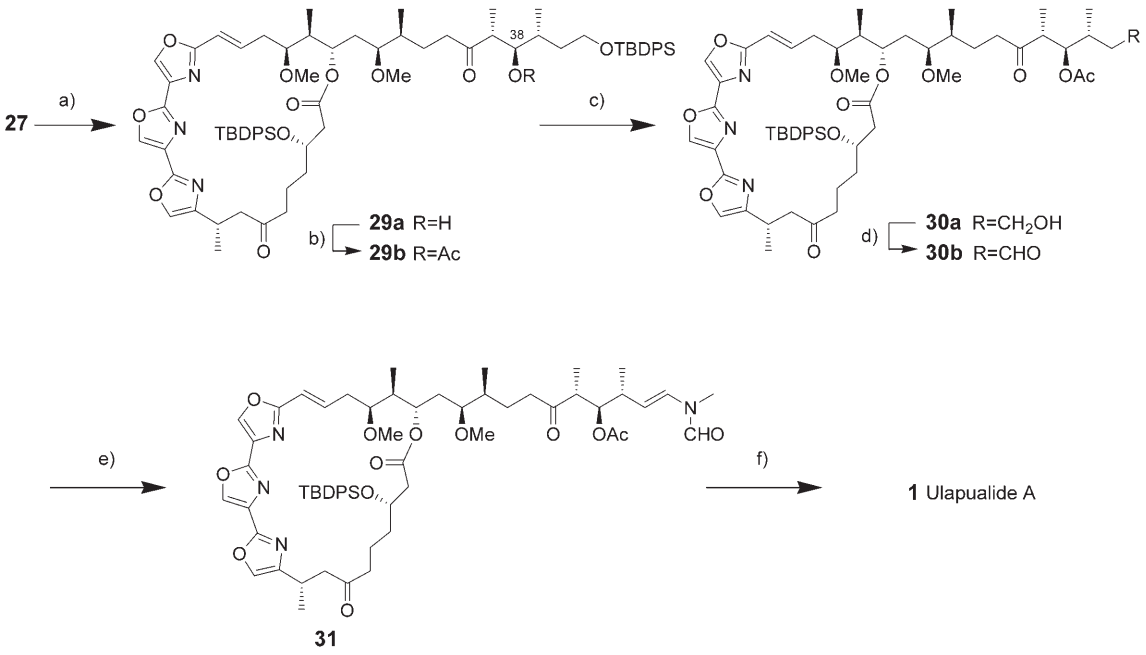

Scheme 5. Completion of the synthesis of **1**. Reagents and conditions: a) TMSOTf, CH_2Cl_2, −78 °C, 85 %; b) acetic anhydride, DMAP, CH_2Cl_2, pyridine, 84 %; c) HF/pyridine, CH_2Cl_2, pyridine, 61 %; d) Dess–Martin periodinane, CH_2Cl_2, 80 %; e) *N*-methylformamide, PPTS, benzene, reflux, 40 %; f) HF/pyridine, THF, 60 %.

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