Total Synthesis

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Total Synthesis and Structural Revision of (+)-Uprolide G Acetate**

*Liangyu Zhu, Yuan Liu, Renze Ma, and Rongbiao Tong**

Abstract: *The first, asymmetric total synthesis of the proposed structure of (+)-uprolide G acetate (UGA) is reported, and the spectral properties of the synthetic compound clearly differed from those reported for natural UGA. On the basis of comprehensive analysis of the NMR data, two possible structures for the natural UGA were proposed and their total synthesis achieved, thus leading to the identification and confirmation of the correct structure and absolute configuration of the natural UGA. This synthesis was enabled by development of a novel synthetic strategy, which revolved around three key cyclization reactions: an Achmatowicz rearrangement, Sharpless asymmetric dihydroxylation/lactonization, and ring-closing metathesis. These synthetic studies pave the way for further studies on this class of structurally unusual cytotoxic cembranolides.*

Cembranolides are a large growing family of marine natural products mainly isolated from marine soft corals and gorgonians and display a wide array of biological activities, particularly of cytotoxic properties.[1,2] In particular, the α-methylene-γ-lactone-bearing cembranolides (αmγl cembranolides; Figure 1) such as sinularolides,[3] crassocolides,[4] michaolides,[5] eupalmerins,[6] and uprolides[7] represent an interesting and unique group within the family because most of these secondary metabolites, having a range of structural diversity, have demonstrated a potent cytotoxicity against various cancer cell lines. It is believed that the α-methylene-γ-lactone[8] moiety provides the basis of the biological activities (e.g., cytotoxicity) because they are excellent Michael acceptors for biological nucleophiles (e.g., cysteine residues of proteins and enzymes).[9] Notably, in 1995 Rodriguez[7b] and co-workers reported five structurally novel cytotoxic αmγl cembranolides, uprolides D–G (**1**–**5**; Figure 1), from gorgonians of *Eunicea mammosa* indigenous to Puerto Rico. The most striking structural characteristic of these cembranolides is the presence of a rare 4,7-oxa-bridged cyclic ether ring (tetrahydrofuran; THF), and it was reported that many cembranolides containing cyclic ether functionalities possess potent antileukemic activities.[10] Subsequent studies by Rodriguez et al. prompted them to make structural revisions

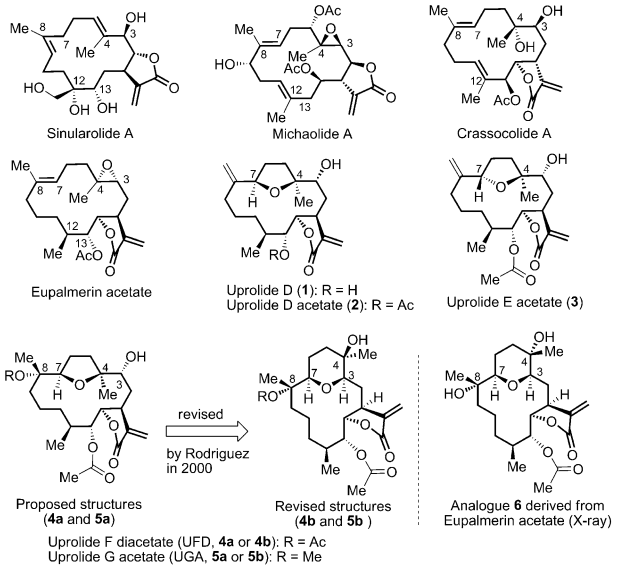

Figure 1. Selected α-methylene-γ-lactone-bearing cembranolides.

of uprolide F diacetate (UFD; **4a** and **4b**) and uprolide G acetate (UGA; **5a** and **5b**) on the basis that NMR data for UFD and UGA were, surprisingly, in almost perfect congruity with those of the cembranolide analogue **6**, which was unambiguously substantiated by single-crystal X-ray diffraction analysis.[11]

The intriguing structural novelty, diversity, and complexity coupled with potent biological activities, however, have stimulated only very limited synthetic studies on the αmγl cembranolides.[12] One of the few and recent synthetic endeavors was made by Marshall and co-workers, who reported in 2010 an elegant synthesis of a lactone diastereomer of uprolide D by an intramolecular Barbier-type reaction to construct the 14-membered cembrane framework with concomitant introduction of a fused α-methylene-γ-lactone.[13] However, total synthesis of these complex natural αmγl cembranolides such as sinularolides, michaolides, crassocolides, and uprolides has not yet been realized to date. Given the fact that an increasing number of αmγl cembranolides (> 100 known natural products)[2] has been reported and most of them possess significant biological activities, we initiated a program directed to the total synthesis of these αmγl cembranolides. Structurally, the uprolides D–G represent one of the most complex αmγl-cembranolides and present considerable synthetic challenges. In contrast, cembranolides containing an oxa-bridged cyclic ether subunit displayed potent cytotoxicity against many cancer cell lines,[10] and suggested that they were promising lead compounds for the development of new anticancer drugs. Intrigued by the

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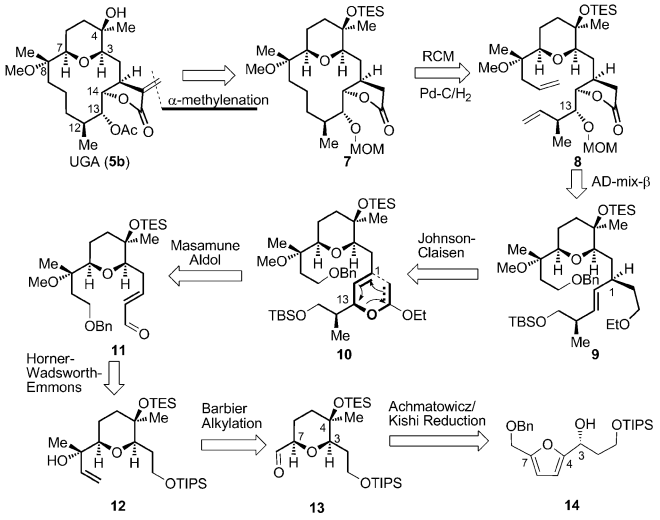
complex structure and potential pharmacological properties, coupled with the scarcity of the natural uprolides, we first undertook the total synthesis of UGA (**5b**) with the intention of confirming the structural revision by Rodriguez and co-workers and providing a synthetic strategy amenable to other αmγl cembranolides with and without an embedded cyclic ether motif and their analogues for further biological activity evaluation.

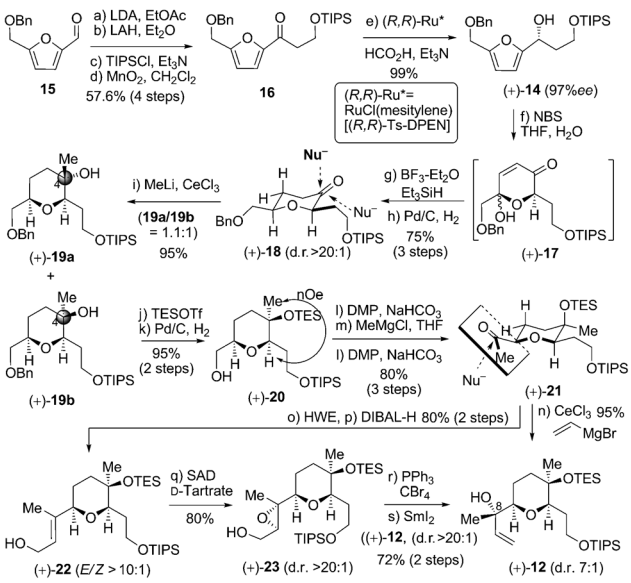
As depicted in Scheme 1, we formulated plans for a total synthesis of UGA and it featured three key cyclization



Scheme 1. Retrosynthetic analysis of UGA (**5b**). TES = triethylsilyl, TIPS = triisopropylsilyl.

reactions: 1) Achmatowicz rearrangement and subsequent Kishi reduction for a stereoselective construction of the highly functionalized tetrahydropyran core (**14**→**13**);[14] 2) Sharpless asymmetric dihydroxylation and concomitant lactonization for an enantioselective installation of the γ-butyrolactone (**9**→**8**);[15] and 3) olefin ring-closing metathesis (RCM)[16] and subsequent palladium-catalyzed hydrogenation for the formation of the 14-membered cembranolide skeleton (**8**→**7**).[17] Although such an RCM macrocyclization strategy has not been employed in the total synthesis of cembranolides, it was noted that the RCM macrocyclization of 2,6-*cis*-tetrahydropyran (THP) and 2,5-*cis*-tetrahydrofuran (THF) dienes usually proceeded more efficiently than that of the 2,6-*trans*-THP and 2,5-*trans*-THF,[16b] and supported our intended macrocyclization plan. Successful execution of these key cyclizations entailed several other key transformations including Johnson–Claisen rearrangement[18] (**10**→**9**) with 1,3-chirality transfer from C13 to C1, Abiko–Masamune[19] asymmetric *anti*-aldol reaction of the α,β-unsaturated aldehyde **11**, diastereoselective vinyl Grignard addition, and Horner–Wadsworth–Emmons (HWE) olefination.[20]

Our synthesis (Scheme 2) began with preparation of enantiomerically pure furfuryl alcohol (+)-**14** from the aldehyde **15** by a high-yielding five-step sequence: acetate aldol, $LiAlH_4$ (LAH) reduction, chemoselective protection of the resulting alcohol as a TIPS ether, MnO_2-mediated

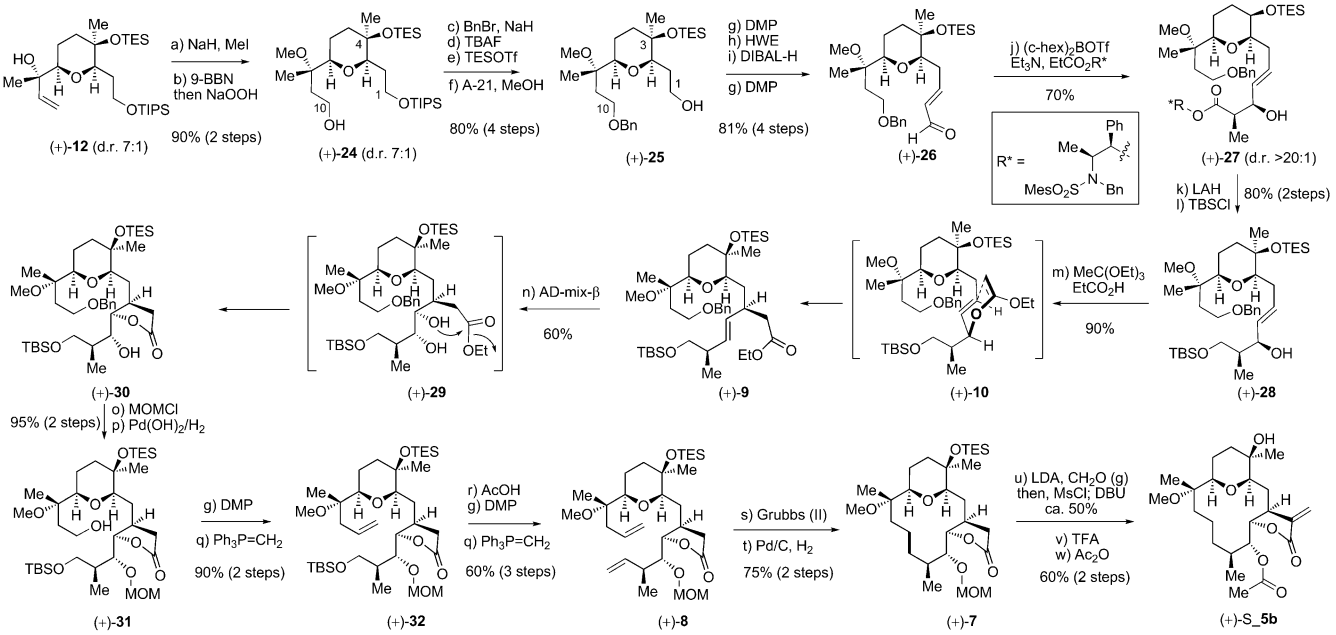


Scheme 2. Synthesis of tetrahydropyran core (+)-**12**. LDA = lithium diisopropylamide, SAD = Sharpless asymmetric dihydroxylation, Tf = trifluoromethanesulfonyl.

oxidation to **16**, and Noyori asymmetric transfer hydrogenation using formic acid.[21] The enantiomeric purity of (+)-**14** was determined by normal-phase HPLC to be 97–98% *ee*. Treatment of (+)-**14** with NBS in THF/H_2O effected Achmatowicz rearrangement and produced the dihydropyranone acetal (+)-**17**, which subsequently was reduced by BF_3-Et_2O/Et_3SiH (Kishi reduction)[22] and palladium-catalyzed chemoselective hydrogenation to provide the 2,6-*cis*-dihydropyranone (+)-**18** in 75% yield over three steps as the single diastereomer. $CeCl_3$-mediated MeLi addition[23] to the ketone (+)-**18** provided a 1.1:1 mixture of diastereomers (+)-**19a** and (+)-**19b**, which could be separated by careful flash column chromatography on silica gel. The relative stereochemistry at C4 of (+)-**19b** was established by nOe experiments on (+)-**20**, and was found to be the desired stereochemistry. Other methyl nucleophile reagents such as MeMgBr and MeLi (without additive) gave a 3:1 to 7:1 diastereomeric mixture favoring (+)-**19a**, with an equatorial alcohol, probably because of the preference of axial approach of the methyl nucleophile to minimize the torsional strain.[24] It was noted that CuI-mediated MeLi addition resulted in a dominant formation of the product (+)-**19a** (d.r. >= 15: 1) with excellent yield. Protection of the alcohol (+)-**19b** as the triethylsilyl (TES) ether and subsequent palladium-catalyzed hydrogenation to remove the benzyl protecting group gave (+)-**20** in 95% yield over two steps. Upon oxidation of (+)-**20** with Dess–Martin periodinane (DMP) and MeMgCl addition, the resulting secondary alcohol was oxidized again by DMP to give methyl ketone (+)-**21** in 80% yield over three steps. $CeCl_3$-mediated nucleophilic addition of vinyl Grignard to ketone (+)-**21** delivered the key intermediate (+)-**12** in 95% yield as a 7:1 diastereomeric mixture. The stereochemical outcome of this carbonyl addition was predicted based on the Felkin–Anh polar model[25] and the major diastereomer might be the desired one. To confirm that the major diastereomer had the correct stereochemistry at C8 as proposed in UGA

(**5b**), an alternative diastereoselective approach to (+)-**12** was devised. Specifically, the ketone (+)-**21** was subjected to HWE olefination and DIBAL-H reduction to yield the allylic alcohol (+)-**22** as 10:1 mixture of *E*/*Z* isomers. Sharpless asymmetric epoxidation[26] of (+)-**22** using D-(−)-diisopropyl tartrate produced the epoxy alcohol (+)-**23** with greater than 20:1 diastereomeric ratio after column chromatography. Bromination of the alcohol with Ph_3P/CBr_4 and SmI_2-promoted reductive epoxide opening[27] provided the desired tertiary alcohol (+)-**12** as a single diastereomer, which was identical to the major diastereomer obtained previously by direct vinyl Grignard addition to (+)-**21**.

With a reliable and efficient supply of the fully functionalized tetrahydropyran core (+)-**12** (> 5 g), we continued our synthetic venture (Scheme 3). O-Methylation of the tertiary alcohol of (+)-**12** followed by hydroboration/oxidation provided (+)-**24** in excellent yield. After protection of the alcohol (+)-**24** as its benzyl ether, regio- and chemoselective desilylation of triisopropylsilyl (TIPS) ether was attempted under various reaction conditions including HOAc/THF/H_2O, HF-Py, and K_2CO_3/MeOH. Unfortunately, removal of TES was observed in all cases. A three-step sequence was then employed: desilylation with TBAF, double silylation with TESOTf, and regioselective desilylation with amberlyst-21 in methanol, which reproducibly provided (+)-**25** in excellent overall yield. DMP oxidation of (+)-**25** was followed by HWE olefination, DIBAL-H reduction, and DMP oxidation to provide the two-carbon-elongated aldehyde (+)-**26**. Abiko–Masamune asymmetric *anti*-aldol reaction of (+)-**26** provided the compound (+)-**27** with enantioselective installation of both a methyl group at C12 and a secondary alcohol at C13. After reductive cleavage of the chiral auxiliary of (+)-**27** with $LiAlH_4$, the resulting primary alcohol was protected as its TBS ether [(+)-**28**)], a precursor for Johnson–Claisen rearrangement. Gratifyingly, treatment of (+)-**28** in ethyl orthoacetate (as the solvent) with a catalytic amount of propionic acid effectively promoted a Johnson–Claisen rearrangement to provide the key compound (+)-**9** with exclusive diastereoselectivity, which might arise from a putative chairlike six-membered ring transition state **10**). Sharpless asymmetric dihydroxylation[28] of (+)-**9** with AD-mix-β at 0 °C for two days accompanied by concomitant lactonization,[15] however, produced a 2:1 mixture of diastereomeric lactones favoring the desired lactone (+)-**30**, whose relative configuration was confirmed later by X-ray diffraction analysis of (+)-**33** (note that the relative configuration of the minor diastereomer could not be determined). The diastereoselectivity of Sharpless asymmetric dihydroxylation could not be improved, and was not unprecedented for internal *trans*-disubstituted alkenes.[29] Protection of the secondary alcohol as the MOM ether followed by palladium-catalyzed hydrogenation afforded the alcohol (+)-**31**, which was subjected to DMP oxidation and Wittig olefination to provide the alkene (+)-**32**. Similarly, the TBS ether of (+)-**32** was converted into the terminal alkene (+)-**8** by chemoselective desilylation, DMP oxidation, and Wittig olefination. Therefore, we arrived at another key transformation, that is the RCM macrocyclization.[16,17] To our delight, ring-closing metathesis of (+)-**8** with the Grubbs(II) catalyst in dilute CH_2Cl_2 solution proceeded smoothly at reflux for 12 hours to produce the desired 14-membered cembrane skeleton (+)-**7** after palladium-catalyzed saturation of the resulting double bond. Upon removal of the protecting groups (TES and MOM) on (+)-**7**, we were lucky to obtain a single crystal of (+)-**33** suitable for X-ray diffraction analysis (Figure 2), and confirmed the carbon skeleton and relative configurations of (+)-**7**. Next, we focused on introduction of an α-*exo*-methylene on the γ-lactone.[30] Initial attempts on using Eschenmoser's methyle-



Scheme 3. Total synthesis of the proposed structure of uprolide G acetate (**5b**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MOM = methoxymethyl, Ms = methanesulfonyl, TFA = trifluoroacetic acid.

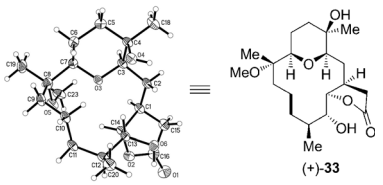


Figure 2. ORTEP diagram of (+)-**33**. Thermal ellipsoids shown at 40% probability.[36]

nation[31] under various reaction conditions resulted in very low yields (<20%). Finally, we found that a three-step sequence could reproducibly provide the α-methylene-γ-lactone, which subsequently was subjected to removal of both the TES and MOM groups with TFA in CH_2Cl_2 and regioselective acetylation with acetic anhydride to furnish UGA (**5b**) in a good overall yield. However, the NMR data of our synthetic compound clearly differed from those reported for the natural UGA,[32] and suggested that the proposed structure (**5b**) for UGA was incorrect.

To get some insight into the true structure for the natural UGA, we re-examined the reported NMR data for UGA (**5b**) and the analogue **6** (see Table S1 in the Supporting Information). After some minor reassignments of the original NMR signals to UGA (**5b**) and a comprehensive analysis of these NMR data, we found that 1) the proton and carbon chemical shifts at C7, C8, C9, and C19 reported for UGA were nearly identical to those reported for compound **6**, and might suggest that a free tertiary alcohol should be at C8 of UGA, instead of methyl ether, and 2) the proton and carbon chemical shifts at C3, C4, C5, C6, and C18 reported for UGA had a significant difference from those reported for compound **6**, and might arise from opposite stereochemistry at C4, methyl ether at C4 or both cases. In contrast, the NMR data of our synthetic compound (proposed UGA, re-numbered as S_**5b**) were substantially different from those of the natural UGA with a maximum deviation of 8.9 ppm (C18) for the carbon chemical shift and of 0.52 ppm (C5) for the proton chemical shift. Combination of these findings and the comparative analysis of NMR data of **6** led us to propose two possible structures (**34a** and **34b**; Figure 3) for UGA.

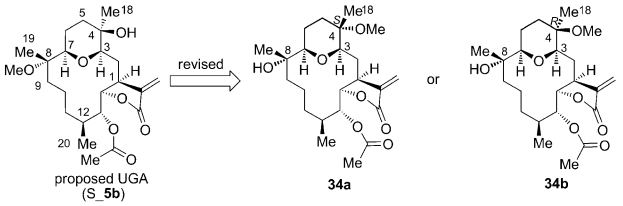
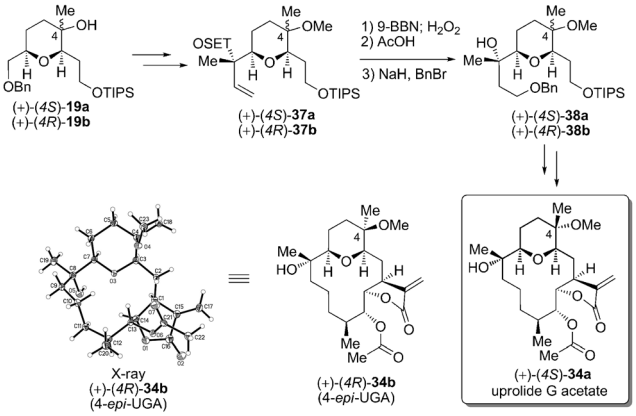


Figure 3. Possible structures for uprolide G acetate.

The stereochemistry at C4 could not be fully determined at this stage, although we had a strong preference for **34a** over **34b** given the to the biogenetic consideration: the THP was formed by opening of the C3–C4 epoxide. In addition, the substituent effects[33] on carbon NMR chemical shifts also supported our preference for **34a**. For example, a methyl group on the oxygen at C4 (e.g., **34a**) would have a positive β-effect (C4: +3.7 ppm) and a negative γ-effect (C3: −0.8 ppm, C5: −5.4 ppm, and C18: −4.5 ppm) when compared with those of **6** at C4 (a free alcohol), and was consistent with our observation that in the case of S_**5b** and **6** the methyl group on the oxygen atom at C8 has a positive β-effect (C8: +4.2 ppm) and a negative γ-effect (C7: −5.1 ppm and C19: −6.1 ppm).[34] Nevertheless, we were still not able to rule out the possibility of **34b** for UGA, particularly because a nOe effect was reported to be observed for H(C3)–H(Me18).[7a,11]

To resolve the uncertainty and reach a conclusive and true structure for the natural UGA, we undertook a total synthesis of both **34a** and **34b** using a similar synthetic strategy (Scheme 4; for details see the Supporting Information). By



Scheme 4. Total syntheses of uprolide G acetate (**34a**) and 4-*epi*-uprolide G acetate (**34b**). Thermal ellipsoids shown at 40% probability.[36]

making full use of the 1.1:1 mixture of diastereomers (+)-**19a** and (+)-**19b** obtained previously in Scheme 2, we separated these diastereomers [(+)-**19a** and (+)-**19b**] by careful flash column chromatography on silica gel and subjected them to transformations in a parallel manner to give **34a** and **34b**, respectively. It was noted that benzyl protection of the alcohol adduct derived from hydroboration/oxidation of (+)-**37a** and (+)-**37b** was not efficient as a result of the base-promoted 1,5-silyl migration.[35] Hydroboration/oxidation of (+)-**37a** and (+)-**37b** followed by chemoselective desilylation of the TES ether with acetic acid in THF/H_2O, produced diols which could be regioselectively protected as the corresponding benzyl ethers (+)-**38a** and (+)-**38b**. The relative configuration and carbon skeleton of (+)-(4*R*)-**34b** were confirmed by single-crystal X-ray diffraction analysis. However, the NMR data of (+)-**34b** were significantly different from those reported for the natural UGA.[32] To our delight, the NMR data of (+)-(4*S*)-**34a** were identical to those reported for the natural UGA.[32] Furthermore, the value of optical rotation of (+)-**34a** ($[\alpha]_D$ +110, c = 0.20, $CHCl_3$) was close to that of the natural UGA ($[\alpha]_D$ +145, c = 0.66, $CHCl_3$),[7b] and confirmed the absolute configuration of the natural UGA. Therefore, we have achieved the first, asymmetric total synthesis and structural revision of uprolide G acetate.

In summary, we have achieved the first, asymmetric total synthesis of the purported structure of uprolide G acetate (UGA) and discovered the spectroscopic discrepancies between our synthetic compound and the natural UGA. We then proposed two possible structures for UGA on the basis of comprehensive analysis of NMR data and achieved their total syntheses, which led us to identify and confirm the correct structure and absolute configuration of the natural UGA. Some features of our synthetic strategy included 1) Achmatowicz rearrangement/Kishi reduction to construct the highly functionalized tetrahydropyran ring, 2) cascade Sharpless asymmetric dihydroxylation/lactonization to stereoselectively install the γ-lactone, and 3) RCM to build the 14-membered cembranolide framework. Our synthetic studies lay the groundwork for further investigations on this class of structurally unusual cytotoxic cembranolides.

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[36] CCDC 1020911 [(+)-**33**] and CCDC 1020910 [(+)-(4*R*)-**34b**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

