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Structural Revision of (+)-Uprolide F Diacetate Confirmed by Asymmetric Total Synthesis

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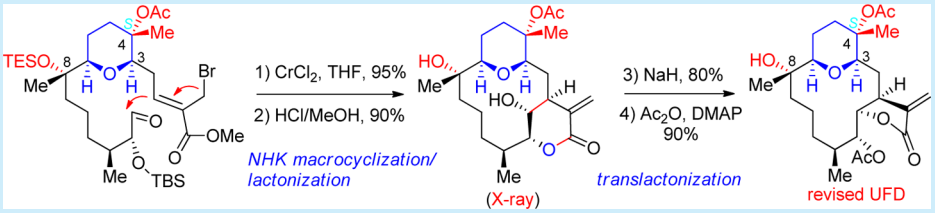
Supporting Information



ABSTRACT: A new structure for the cytotoxic cembranolide uprolide F diacetate (UFD) was proposed, and an enantioselective total synthesis was accomplished to confirm that our revised structure correctly represented the natural UFD and its absolute configuration. Our synthesis features a late-stage, highly efficient, and diastereoselective Nozaki–Hiyama–Kishi macrocyclization (95% yield) and an unexpected reagent-controlled reversible translactonization, which, being the first example within the cembranolide family, might have biogenetic implications and be of great importance to synthetic studies of the α-methylene-γ-lactone-bearing cembranolides.

In the family of 14-membered-ring diterpenoid cembranolides, over 100 members contain a characteristic α-methylene-γ-lactone (αmγl) on the cembrane skeleton[1] such as crassocolides,[2] eupalmerins,[3] and uprolides (Figure 1).[4] Most of these αmγl-cembranolides were reported to display potent biological activities (e.g., cytotoxicity),[1−4] while at the same time they pose significant synthetic challenges for the construction of the conformationally mobile 14-membered cyclic cembranes[5] with a dense array of oxygen functionalities and stereocenters and the stereoselective installation of the embedding α-methylene-γ-lactones.[6] In particular, the cyclized αmγl-cembranolides exemplified by recently isolated cytotoxic uprolides[4] upgraded considerably the synthetic difficulty. No total syntheses[7] have been documented in the literature in the past 20 years until in 2014 we reported the first total synthesis of uprolide G acetate (UGA) via macrocyclization with ring-closing metathesis and γ-lactonization by Sharpless asymmetric dihydroxylation.[8] Our synthetic studies led to the structural revision of UGA, which implied that the structure for uprolide F diacetate (UFD) revised by Rodríguez[4e] in 2000 might be incorrect and should be revised accordingly. On the basis of NMR spectra analysis and our previous synthetic studies of UGA, it was reasonable to propose a new structure (**1**) for UFD (Figure 1), which requires confirmation by total synthesis. Herein, we reported an asymmetric total synthesis of our revised structure (**1**) for UFD by developing a novel efficient strategy that revolved around Nozaki–Hiyama–Kishi (NHK) macrocyclization and lactonization.

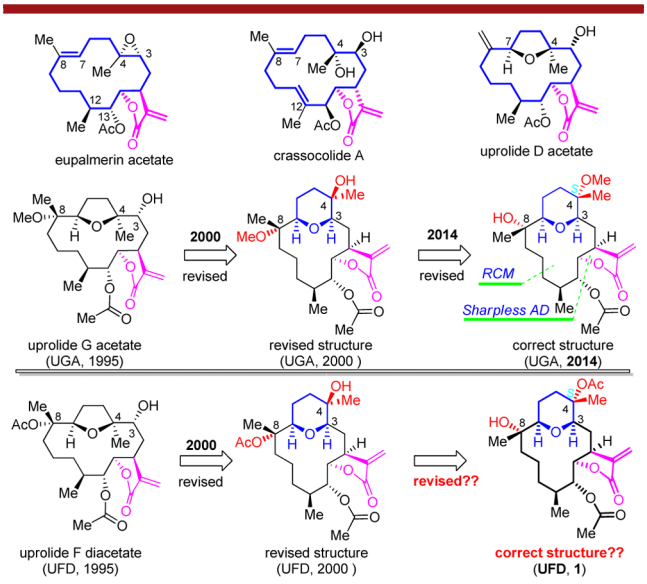


Figure 1. Representative members of α-methylene-γ-lactone-bearing cembranolides and a new revised structure for uprolide F diacetate.

Retrosynthetically, as depicted in Scheme 1, we proposed Nozaki–Hiyama–Kishi (NHK) macrocyclization[9] of **2** and subsequent (or simultaneous) γ-lactonization[10] as the key steps to construct the 14-membered-ring cembranolide skeleton fused with the α-methylene-γ-lactone in a stereoselective fashion. This late-stage macrocyclization strategy is highly risky because the two newly formed stereocenters at C1 and C14 could not be reliably predicted at our designing stage according to the previous NHK macrocyclization studies by Marshall[7b] and Paquatte.[9d,e] However, successful implementation of such a

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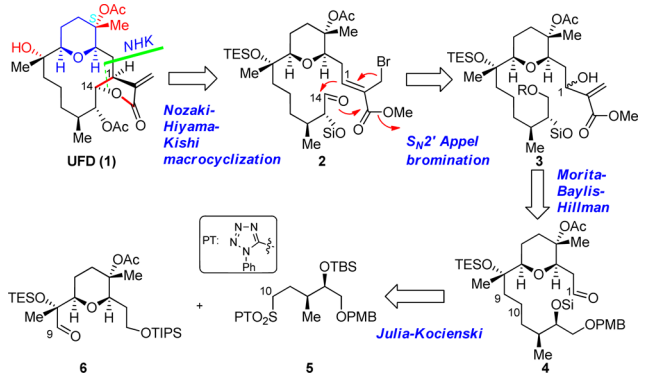
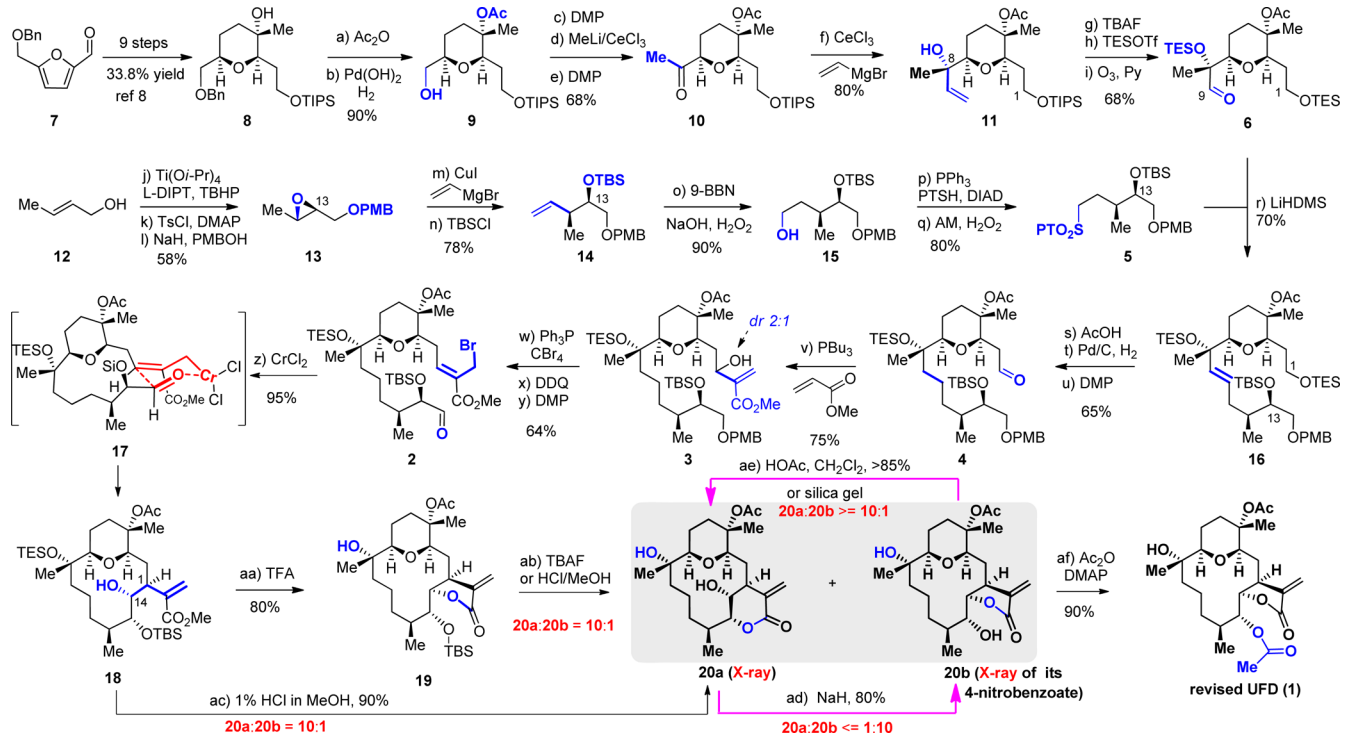
Scheme 1. Retrosynthetic Analysis of the Revised Strcuture for Uprolide F Diacetate



strategy would provide an expedient access to the uprolide family and structurally related natural products. The allylic bromide of **2** could be readily prepared by S_N2' Appel bromination of **3**, which was a Morita–Baylis–Hillman[11] (MBH) adduct of **4**. Julia–Kochienski[12] olefination would unite the fragments **5** and **6** via formation of the C9–C10 bond to provide **4** after functional group manipulations. The preparation of the fully functionalized tetrahydropyran **6** would be similar to our previous synthesis of UGA.[8]

Our synthesis began with the preparation of enantiomerically pure fragment **6** (Scheme 2). The tertiary alcohol of **8**, which was obtained previously with 33% yield in 9 steps from aldehyde **7**,[8] was acetylated with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) in 90% yield. Subsequent debenzylation with $Pd(OH)_2/H_2$ (1 atm) provided alcohol **9**, which was converted to tertiary alcohol **11** in 54% overall yield through a four-step sequence: Dess-Martin periodinane (DMP) oxidation,[13] $CeCl_3$-mediated methyl lithium addition, DMP oxidation, and $CeCl_3$-mediated vinyl Grignard addition. The stereochemical outcome at C8 was consistent with the prediction by the Felkin–Anh polar model[14] and our previous observation.[8] Replacement of the TIPS protecting group on the primary

Scheme 2. Asymmetric Total Synthesis of (+)-Uprolide F Diacetate (1)[a]



[a]Conditions: (a) Ac_2O (1.5 equiv), iPr_2NEt (2.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, rt, 4 h, 90%; (b) 10 wt % $Pd(OH)_2/C$ (10 mol %), H_2 (1.0 atm), EtOAc/MeOH = 1/4, rt, 2 h, 100%; (c) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, rt, 1 h, 95%; (d) $CeCl_3$ (3.0 equiv), MeLi (2.0 equiv), THF, −78 °C, 1 h, 80%; (e) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, rt, overnight, 90%; (f) $CeCl_3$ (3.0 equiv), vinylMgBr (2.0 equiv), THF, −78 °C, 1 h, 80%; (g) Bu_4NF (1.5 equiv), THF, rt, 3 h, 90%; (h) TESOTf (2.4 equiv), 2,6-lutidine (6.0 equiv), CH_2Cl_2, −78 °C, 1 h, 95%; (i) O_3, pyridine (4.0 equiv), −78 °C, 30 min, 80%; (j) $Ti(OiPr)_4$ (5 mol %), (+)-diisopropyl L-tartrate (6 mol %), *t*BuOOH (2.0 equiv), CH_2Cl_2, −20 °C, 2 h; (k) TsCl (1.2 equiv), Et_3N (2.0 equiv), DMAP (10 mol %), CH_2Cl_2, rt, overnight, 61% over 2 steps; (l) NaH (5.0 equiv), PMBOH (2.0 equiv), DMF, rt, overnight, 95%; (m) CuI (1.3 equiv), vinylMgBr (6.0 equiv), Et_2O, −78 °C → rt, 80%; (n) TBSCl (1.25 equiv), imidazole (2.5 equiv), DMF, rt, overnight, 98%; (o) 9-BBN (3.0 equiv), THF, rt, overnight, then 3 N NaOH, 30 wt % H_2O_2, rt, 6 h, 90%; (p) PPh_3 (1.5 equiv), PTSH (1.5 equiv), DIAD (1.5 equiv), THF, rt, overnight, 90%; (q) Ammonium molybdate tetrahydrate (10 mol %), 30 wt % H_2O_2 (10 equiv), EtOH, rt, overnight, 90%; (r) sulfone **5** (1.25 equiv), LHMDS (1.25 equiv), THF, −78 °C → rt, 2 h, 70%; (s) AcOH/THF/H_2O = 1/4/1, rt, 4 h, 80%; (t) 10 wt % Pd/C (10 mol %), H_2 (1.0 atm), EtOAc, rt, 2 h, 90%; (u) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, rt, 1 h, 90%; (v) methyl acrylate (2.0 equiv), PBu_3 (20 mol %), THF, rt, overnight, 75%; (w) CBr_4 (6.0 equiv), PPh_3 (6.0 equiv), iPr_2NEt (12.0 equiv), CH_2Cl_2, rt, overnight, 80%; (x) DDQ (1.5 equiv), pH = 7.0 buffer, CH_2Cl_2, rt, 2 h; (y) DMP (1.33 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, rt, 1 h, 80% over 2 steps; (z) $CrCl_2$ (20 equiv), 4 Å molecular sieves, THF, rt, 16 h, 95%; (aa) MeOH (10 equiv), CF_3COOH/CH_2Cl_2 = 1/4, rt, 1 h, 80%; (ab) Bu_4NF (2.0 equiv), THF, rt, 2 h, 80%; or 1% concn HCl in MeOH, rt, 2 h, 90%; (ac) 1% concn HCl in MeOH, rt, 4 h, 90%; (ad) NaH (3.0 equiv), THF, rt, 2 h, 80%; (ae) HOAc/CH_2Cl_2 = 1/4, rt, 24 h, 85%; (af) Ac_2O (15.0 equiv), iPr_2NEt (30 equiv), DMAP (3.0 equiv), CH_2Cl_2, rt, 1 h, 90%.

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alcohol of **11** with TES (desilylation with TBAF and silylation with TESOTf) substantially eased the regioselective desilylation at C1 at the later stage of synthesis. Oxidative cleavage (O_3/pyridine) of the alkene provided aldehyde **6** for Julia–Kocienski olefination. Fragment **5** was prepared from crotyl alcohol (**12**) with 32.6% overall yield in 8 steps, including some key transformations such as Sharpless asymmetric epoxidation to install the required stereochemistry at C13, regioselective epoxide opening with a vinyl Grignard reagent, hydroboration/oxidation, and Mitsunobu reaction.

Julia–Kocienski olefination of aldehyde **6** with sulfone **5** using LiHMDS as the base proceeded smoothly to provide compound **16** in 70% yield. Upon regioselective desilylation with acetic acid in THF/H_2O and Pd-catalyzed hydrogenation, DMP oxidation of the resulting primary alcohol provided aldehyde **4**, a substrate for MBH[11] reaction. After an extensive examination of various phosphine and amine promoters, we identified that tributylphosphine could catalyze the MBH reaction of **4** with methyl acrylate at rt for 24 h to give MBH adduct **3** as a 2:1 mixture of diastereomers in 75% yield. It was noteworthy that both diastereomers could deliver the allylic bromide as the single *Z*-isomer by either S_N2' Appel bromination or mesylation/S_N2' substitution with LiBr. Removal of the PMB protecting group with DDQ followed by DMP oxidation provided the key substrate **2** for NHK macrocyclization. To our delight, upon treatment of **2** with $CrCl_2$ in THF at rt, Nozaki–Hiyama–Kishi macrocyclization occurred smoothly to afford 14-membered macrocycle **18** as the single diastereomer in 95% yield. The excellent yield was remarkable for such a complex substrate. The high diastereoselectivity of NHK macrocyclization could be rationalized by a favorable Zimmerman–Traxler-type transition state[15] (**17**), which correlates the *Z* geometry of the double bond (allylic bromide) with the *syn* stereochemistry of the product (i.e., relative stereochemistry of C1 and C14) and most importantly conforms to the Felkin–Anh model that led to the desired absolute stereochemistry at C14. This diastereoselectivity outcome was in sharp contrast to Marshall's case,[16] while the related substrate with Z-allylic bromide investigated by Paquette did not undergo NHK macrocyclization under a variety of known conditions.[9d,e] It was noted that SmI_2,[17c] zinc,[17d–f] or indium[17g] did not initiate the Barbier-type macrocyclization[17] and only reductive debromination was observed. Treatment of **18** with trifluoroacetic acid in CH_2Cl_2 in the presence of the catalytic amount of MeOH effected both lactonization and cleavage of triethylsilyl ether to give the desired α-methylene-γ-lactone **19** in 80% yield. Surprisingly, removal of the dimethyl-*tert*-butylsilyl (TBS) group with TBAF, HF-pyridine, or HCl/MeOH generated a 10:1 mixture of δ-lactone **20a** and γ-lactone **20b** (**20a**:**20b** = 10:1), while other mild desilylation conditions (TBAF/HOAc, HF–Et_3N, TASF, TFA/MeOH) could not remove the TBS protecting group. This unexpected translactonization in the course of desilylation was not observed in our total synthesis of UGA.[8] It was found later that 1% HCl in MeOH at ambient temperature could efficiently promote both double desilylation of **18** and lactonization, leading to the identical 10:1 mixture of δ-lactone **20a** and γ-lactone **20b** in 90% yield. The structures of δ-lactone **20a** and the 4-nitrobenzoate derivative (**21**) of **20b** were confirmed by X-ray diffraction analysis (Figure 2), which substantiated the relative stereochemical outcome (C1 and C14) of the key NHK macrocyclization and the occurrence of the unexpected translactonization.

Fortunately, we were able to identify a condition to promote the corresponding reverse translactonization (**20a** → **20b**).

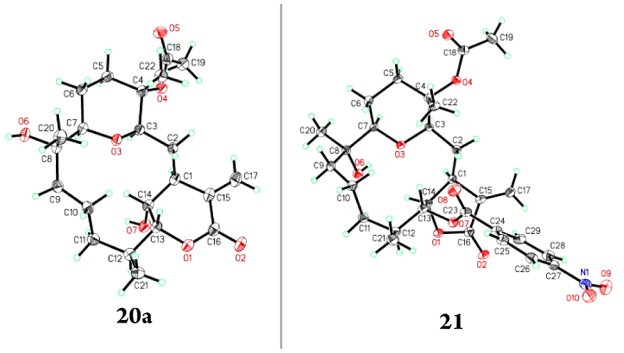

Figure 2. ORTEP diagrams of δ-lactone **20a** and 4-nitrobenzoate derivative (**21**) of γ-lactone **20b**.

Specifically, treatment of δ-lactone **20a** with NaH (3 equiv) in THF for 2 h at rt provided γ-lactone **20b** as a 10:1 isomeric mixture (**20b**:**20a** ≥ 10:1) in 80% yield. It was also noted that under mild acidic conditions such as acetic acid and silica gel the γ-lactone **20b** was able to undergo rearrangement back to the δ-lactone **20a** in 85% yield. To the best of our knowledge, this unexpected reagent-controlled reversible translactonization represents the first example within the cembranolide family[18] and might have biogenetic implications and synthetic applications for the natural γ- and δ-lactone-containing cembranolides.[19] Particularly, the ability to efficiently interconvert the δ- and γ-lactones is of great importance to the synthetic studies in this area. Regioselective acetylation of the secondary alcohol of **20b** with acetic anhydride and DMAP furnished the revised structure (**1**) of UFD. Pleasingly, all spectroscopic data for (+)-**1** were in good agreement with those reported for the natural UFD,[20] which confirmed our structural revision of UFD. The identical sign of optical rotation of synthetic and natural UFD confirmed its absolute configuration ($[\alpha]_D$ = +135.9, *c* 0. 1, $CHCl_3$; $^{lit}[\alpha]_D$ = +145.7, *c* 0.88, $CHCl_3$).[4b]

In summary, we proposed a new structure for the natural uprolide F diacetate (UFD) and achieved an asymmetric total synthesis that confirmed our revised structure correctly representing the natural UFD and its absolute configuration. This exemplifies an unusual case of structural revision of natural products because the originally proposed structure has not been synthesized. Our synthesis was enabled by a highly efficient and stereoselective Nozaki–Hiyama–Kishi (NHK) macrocyclization and a reagent-controlled, reversible translactonization, which allowed us to achieve an efficient total synthesis of UFD with 4.5% yield in 21 steps (longest linear sequence) from compound **8** (note: our previous synthetic strategy developed for UGA required 34 steps with 1.4% yield from **8**). The highly efficient and diastereoselective NHK macrocyclization to the cembranolide skeleton and the unexpected findings of the reversible translactonization would be of paramount importance to further synthetic studies of the uprolide family and other α-methylene-γ-lactone-bearing cembranolides.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterizations and copies of ^1H and ^{13}C NMR spectra of new compounds, and X-ray crystallographic data for **20a** (CCDC 1050099) and **21** (CCDC 1050100). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) See the Supporting Information.

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