

The Tetrahydrofuran Motif in Marine Lipids and Terpenes

Subjects: Chemistry, Medicinal

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Heterocycles are particularly common moieties within marine natural products. Specifically, tetrahydrofuranyl rings are present in a variety of compounds which present complex structures and interesting biological activities. Focusing on terpenoids, a high number of tetrahydrofuran-containing metabolites have been isolated. They show promising biological activities, making them potential leads for novel antibiotics, antiketoplastid drugs, amoebicidal substances, or anticancer drugs. Thus, they have attracted the attention of the synthetic community and numerous approaches to their total syntheses have appeared.

Keywords: oxygen heterocycles ; tetrahydrofuran ; total synthesis ; biological activity ; terpenes

1. Lipids

1.1. Lipid Alcohols

C19 Lipid Diols

Diastereomeric *trans*-oxylipids **1**, and *cis*-oxylipid **2** (Figure 1), were isolated in 1980 [1] and 1998 [2], respectively, from the brown alga *Notheia anomala*. Their structure and relative stereochemistry were assigned by 1D and 2D NMR spectral data and confirmed by single-crystal X-ray analysis. Their absolute configuration was determined by the Horeau method in the case of compound **1**, and by the advanced Mosher method for compound **2**. Both of them display in vitro antihelmintic activity, inhibiting larval development in parasitic nematodes. The *trans*-isomer **1** showed LD₅₀ values against *Haemonchus contortus* (1.8 ppm) and *Trichostrongylus colubriformis* (9.9 ppm), comparable to those of the commercial nematocides levamisole and closantel. Synthetic routes for these oxylipids were recently reviewed [3].

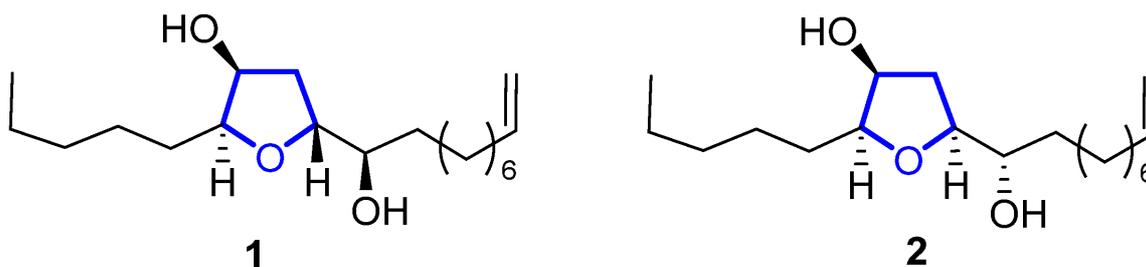
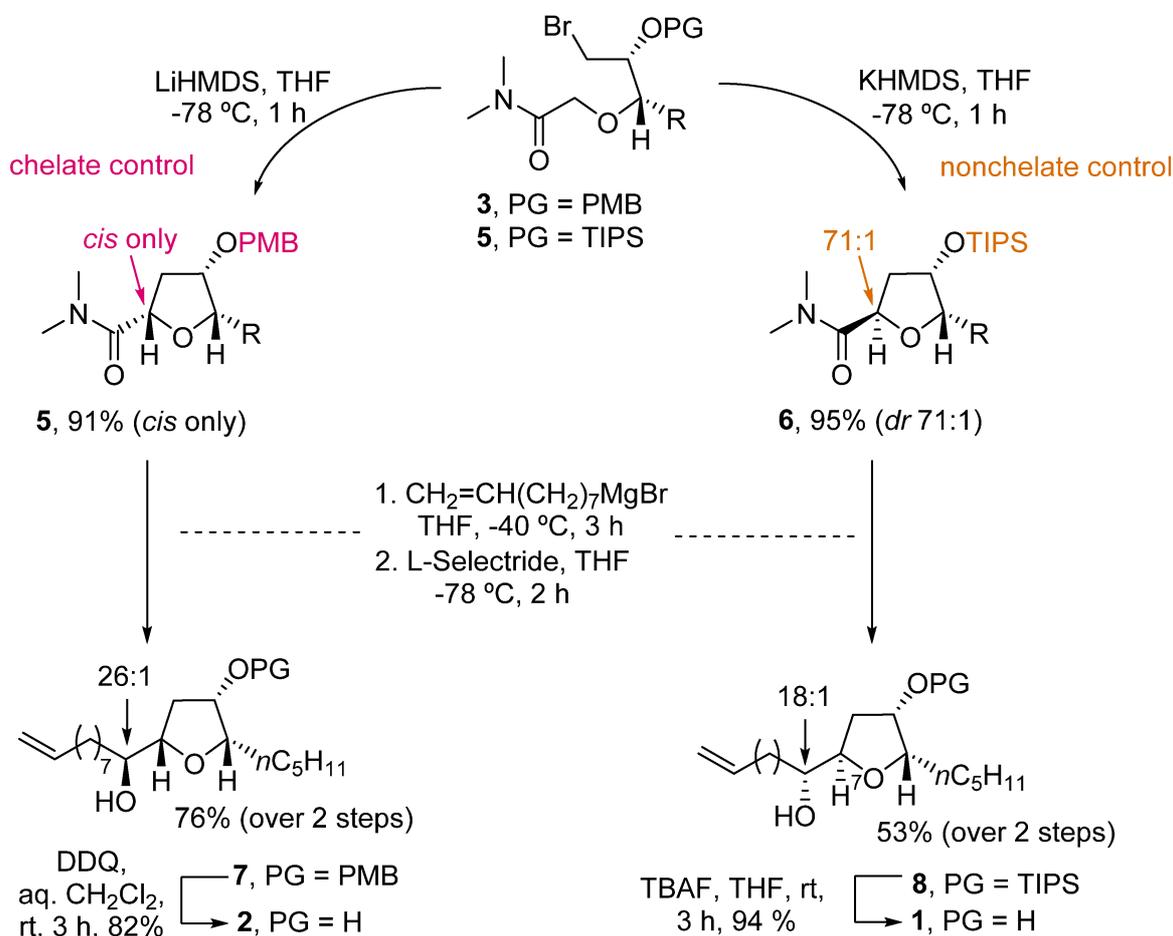


Figure 1. Structure of *trans*-oxylipid **1** and *cis*-oxylipid **2**.

An elegant example of the stereodivergent synthesis of both isomers was developed by Kim et al. [4]. They developed an intramolecular amide enolate alkylation, where the C3-hydroxy protecting group selection permits the formation of the desired isomer (Scheme 1). Thus, starting from PMB-protected bromoamide **3**, reaction with LiHMDS afforded only the *cis*-product **4**. The preferent formation of the *cis*-isomer was due to the chelating ability of the PMB group. Therefore, when using a nonchelating group such as TIPS (compound **5**), the reaction with KHMDS predominantly yielded the *trans*-THF **6**. Further reaction of **4** and **6** with CH₂=CH(CH₂)₇MgBr and reduction with L-selectride afforded **7** and **8** in good yields (76% and 53% over two steps, respectively). Deprotection of **7** with DDQ, and **8** with TBAF, respectively, gave *cis*-oxylipid **2** in 82% yield and the *trans*-isomer **1** in 94% yield.



Scheme 1. Stereodivergent synthesis of *trans*- and *cis*-oxylipids **1** and **2** by Kim.

1.2. Fatty Acids

1.2.1. Petromyroxols

In 2015, Li reported the isolation of (+)- and (-)-petromyroxols (**9**)^[5]. They are oxylipids isolated from water conditioned with larval sea lamprey *Petromyzon marinus* L. Interestingly, these molecules are the first tetrahydrofuran acetogenindols isolated from a vertebrate animal (**Figure 2**). The absolute configuration of each enantiomer was determined by a combination of Mosher ester analysis and comparison with related natural and synthetic products. The (+)-**9** shows a potent olfactory response of 0.01 to 1 μM in the sea lamprey, while the (-)-isomer has a softer effect. Synthetic routes towards them were recently reviewed^[3].

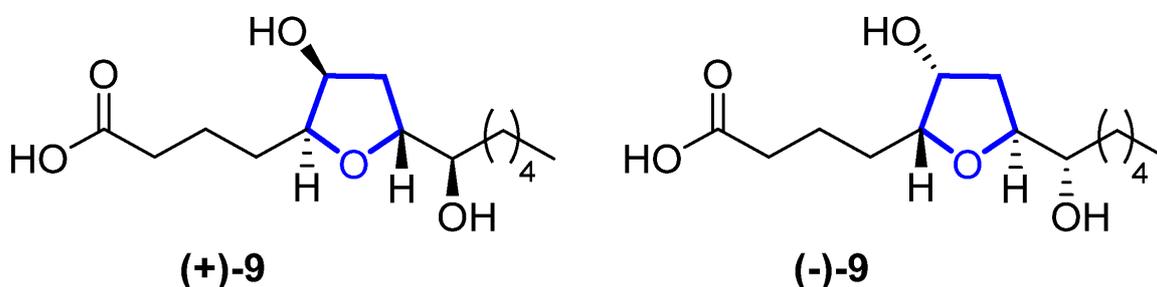
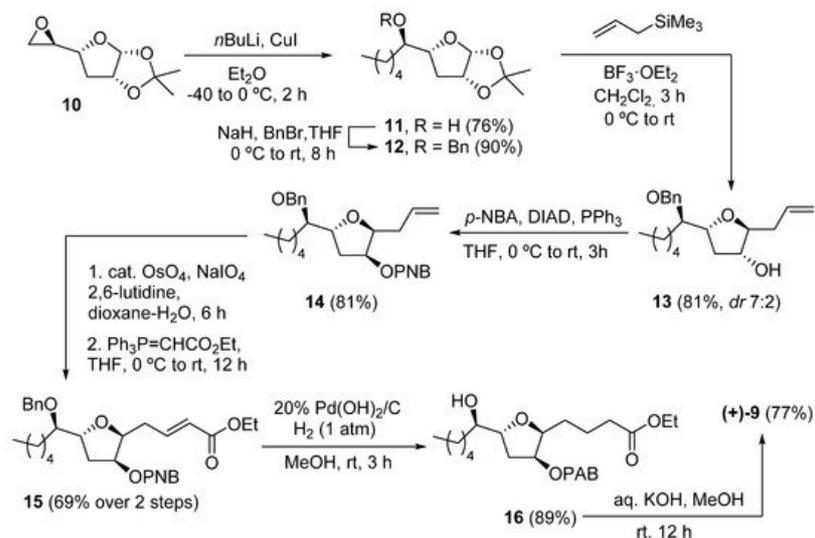


Figure 4. Structures of (+)- and (-)-petromyroxol **9**.

A recent example of the synthesis of (+)-**9**, along with all possible diastereoisomers, was presented in 2020 by Ramana and coworkers^[6]. The synthetic route started from the commercial THF compound **10** (**Scheme 2**). The alkyl chain was installed by reaction with the appropriate cuprate. Subsequent benzyl protection of **11** afforded **12**, which after reaction with allyltrimethylsilane, yielded the desired diastereomer (7:2 ratio) of the allylated THF **13**. After protection with a para-nitrobenzoate (PNB) group under Mitsunobu conditions, compound **14** was subjected to oxidative olefin cleavage with OsO₄/NaIO₄ and subsequent Wittig olefination to obtain α-β-unsaturated ester **15**. Hydrogenation with Pearlman catalyst (20% Pd(OH)₂/C) afforded **16** in 89% yield, where the benzyl group, the double bond, and the nitro group were all reduced. Finally, hydrolysis of both ester groups with KOH in methanol afforded the desired (+)-petromyroxol in 77% yield.



Scheme 2. Synthesis of (+)-petromyroxol by Ramana and coworkers.

1.2.2. PMA

Petromyric acids A and B (PMA and PMB) are dehydroxylated tetrahydrofuranyl fatty acids that were isolated from larval washing extracts from the sea lamprey *Petromyzon marinus* in 2018 [7]. From the washing extract, four fatty acids related to the acetogenin family were identified: (+)-PMA ((+)-17), (-)-PMA ((-)-17), (+)-PMB ((+)-18), and (-)-PMB ((-)-18) (Figure 5). Their chemical structure was elucidated by NMR spectroscopy and confirmed by chemical synthesis and X-ray crystallography.

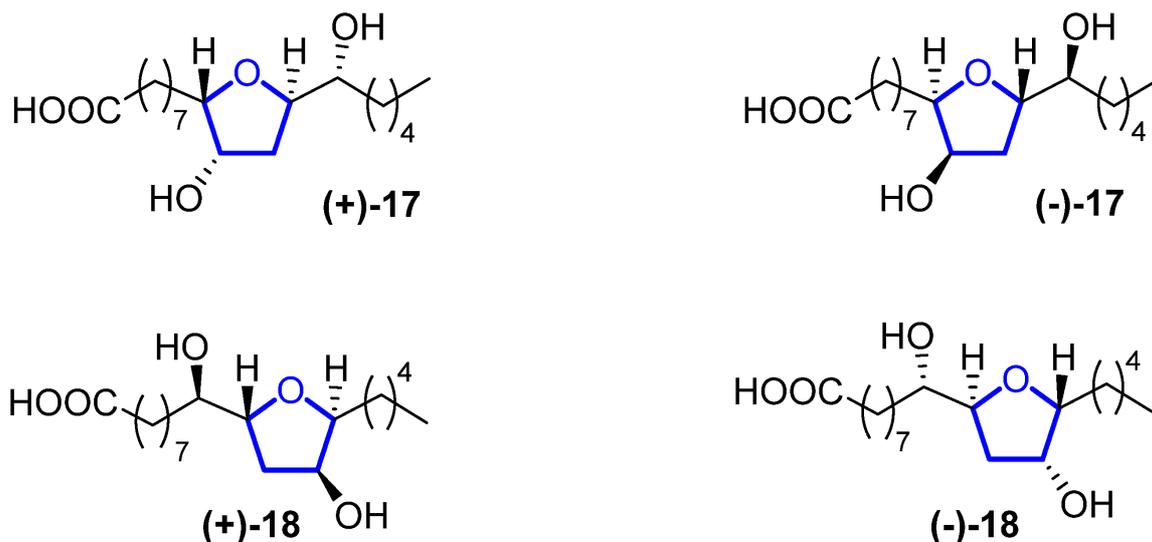


Figure 3. Structure of (+)-PMA ((+)-17), (-)-PMA ((-)-17), (+)-PMB ((+)-18), and (-)-PMB ((-)-18).

Sea lampreys are anadromous fishes that migrate, using their olfactory cues to orientate, from the ocean to freshwater to find a suitable spawning stream. When approaching river mouths, the decision of which stream is optimal to spawn in is taken using their olfactory system to detect a pheromone emitted from larval sea lampreys. When investigating larval washing extracts, four fatty acids were identified, but only (+)-17 has proven to be the pheromone that guides lamprey adults. However, its enantiomer, (-)-17, does not produce the same behavioral effect. Fatty acid analogues have been reported to be pheromones in insects, but this is the first identification in fish. The sea lamprey is a destructive invader in the Laurentian Great Lakes, while in Europe, its population has decreased precipitously, so (+)-17 can be used for the control and conservation of their populations.

Although they have a high potential for application, to the best of our knowledge, no total synthesis has been reported so far for these compounds.

1.2.3. Mutafurans

Mutafurans A–G (19–25) are brominated ene-yne-tetrahydrofurans (Figure 4) that were isolated by Molinski in 2007 from the marine sponge *Xestospongia muta* [8]. Later, Liu reported the isolation of mutafuran H (26), a brominated ene-

tetrahydrofuran isolated from sponge *Xestospongia testudinaria* within other sterols and brominated compounds [9]. Their structure and absolute configuration were determined by 1D and 2D magnetic resonance, mass spectrometry, and circular dichroism.

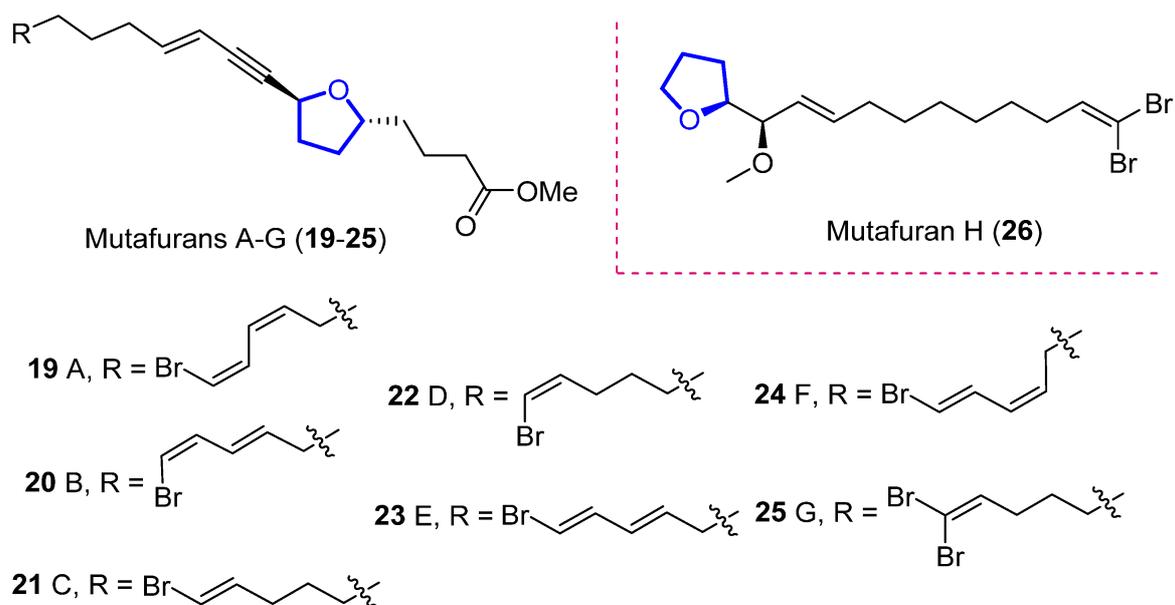


Figure 4. Structure of mutafurans A–G and the yne-lacking mutafuran H.

Mutafurans A–D showed moderate antifungal activity against the fungus *Cryptococcus neoformans var. grubii*, but were inactive against *Candida albicans* (ATCC14503 and 96–489) and *Candida glabrata* [8]. Furthermore, mutafuran H showed biological activity against *Artemia salina* larvae (LC₅₀ = 2.6 μM) and a significant acetylcholinesterase inhibitory activity (IC₅₀ = 0.64 μM) [9]. No synthetic approach has been reported to date.

1.2.4. Aspericacids

Aspericacids A (27) and B (28) were isolated in 2020 by Ding and He from the sponge-associated *Aspergillus* sp. LS78 [10]. Both compounds bear a 2,5-disubstituted tetrahydrofuran ring coupled with an unsaturated fatty acid (Figure 5). Their structure was determined by HRESIMS and 1D and 2D NMR spectroscopy, while their absolute configuration was established relying on electronic circular dichroism (ECD). Compound 27 presents a moderate inhibitory activity against *Candida albicans* and *Cryptococcus neoformans* with a MIC value of 50 μg/mL, although 28 has a weaker activity, MIC = 128 μg/mL. No synthetic approach has been reported to date.

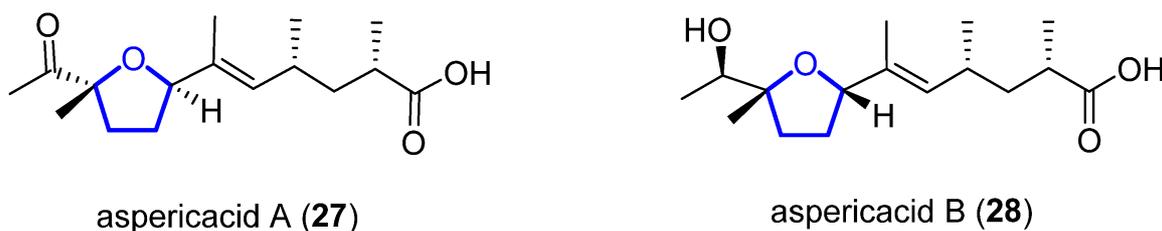


Figure 5. Structure of aspericacids A 27 and B 28.

2. Terpenes

2.1. Monoterpenes

2.1.1. Pantofuranoids

Pantofuranoids A–F (29–34) are monoterpenes that were isolated in 1996 from the Antarctic red alga *Pantoneura plocamioides* [11]. They are the first monoterpenes found to contain a tetrahydrofuran moiety, and their common framework (Figure 6) suggests that they all come from the same terpene precursor.

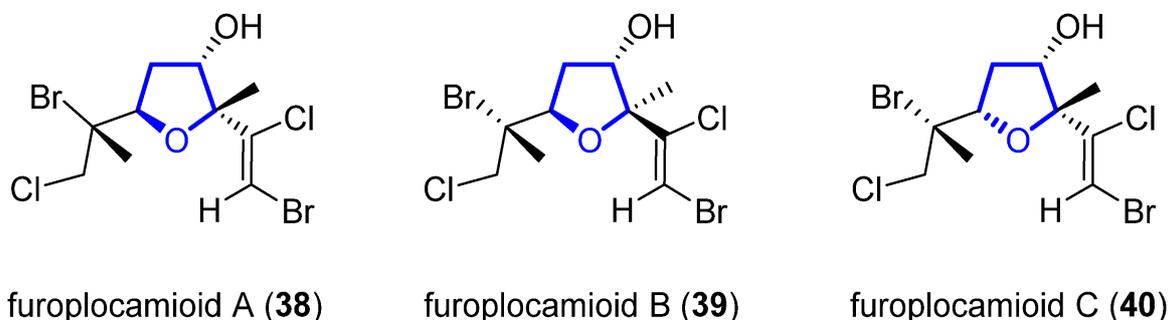
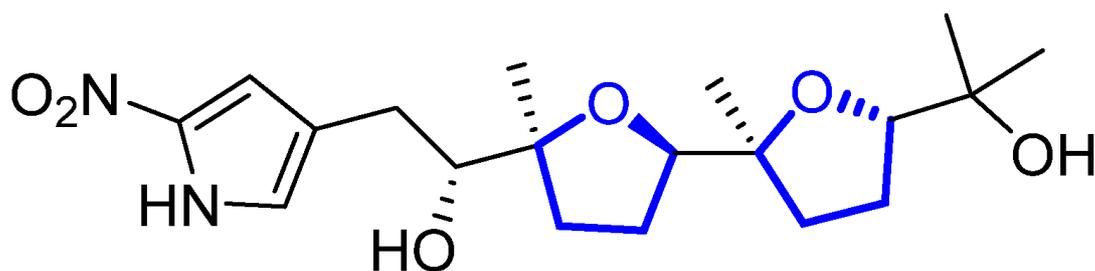


Figure 7. Structure of furoplocamioids A–C (**38–40**).

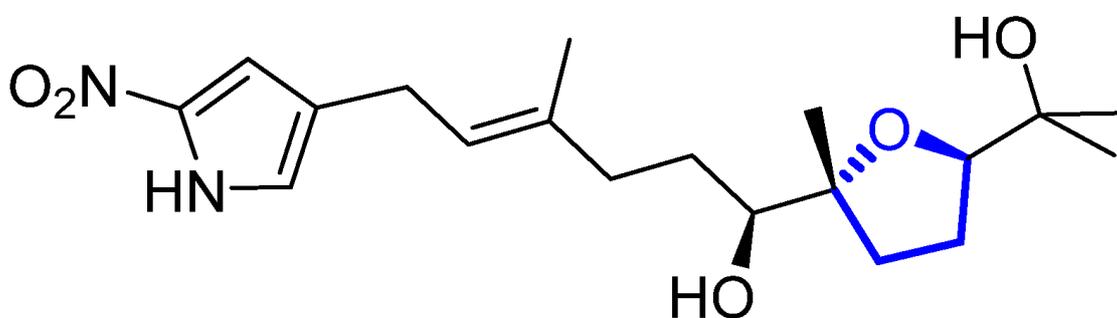
2.2. Sesquiterpenes

2.2.1. Heronapyrrols

Heronapyrrols A–C are pyrroloterpenes that were isolated in 2010 from a marine *Streptomyces* sp. CMB-M0423 ^[16]. They present bioactivity against Gram-positive bacteria *Staphylococcus aureus* ATCC 9144 and *Bacillus subtilis* ATCC 6633 but no mammalian cytotoxicity. Heronapyrrol C (**41**), apart from the characteristic and unusual 2-nitropyrrol moiety of this family, presents a *bis*-tetrahydrofuran core. Later, Capon and Stark first synthesized and then isolated heronapyrrol D (**42**) (Figure 8) from the same marine-derived microbe ^[17]. Heronapyrrol D displays bioactivity against Gram-positive bacteria *Staphylococcus aureus* ATCC 25923 ($IC_{50} = 1.8 \mu M$), *Staphylococcus epidermidis* ATCC 12228 ($IC_{50} = 0.9 \mu M$), and *Bacillus subtilis* ATCC 6633 ($IC_{50} = 1.8 \mu M$). However, it is inactive against the Gram-negative bacteria *Pseudomonas aeruginosa* ATCC 10145 and *Escherichia coli* ATCC 25922.



heronapyrrol C (**41**)



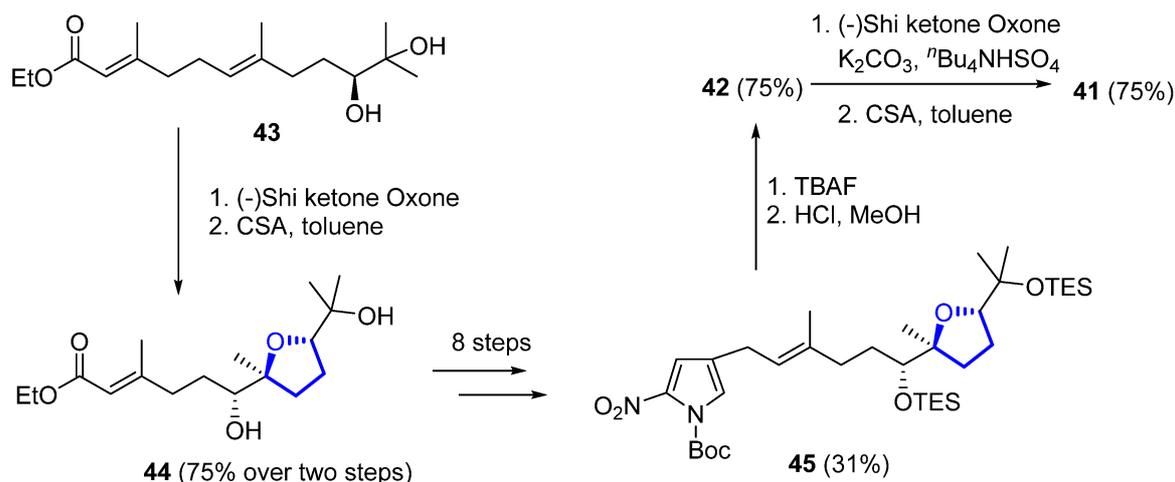
heronapyrrol D (**42**)

Figure 8. Structure of (+)-heronapyrrol C (**41**) and (+)-heronapyrrol D (**42**).

To determine the relative and absolute stereochemistry of (+)-**41**, Stark and coworkers proposed and synthesized the most likely stereostructure of its enantiomer (-)-**41**, based on a biomimetic polyepoxide cyclization [18]. The same authors also reported the preparation of a bioisosteric carboxylate analog of (-)-**41** [19].

The first total synthesis of (+)-**41** was reported in 2014 by Brimble and coworkers, who used as key steps to introduce the five stereogenic centers a Julia–Kocienski coupling, a Shi epoxidation, and a catalytic epoxide-opening reaction [20]. The same year, the first total synthesis of (+)-**42** was achieved by Capon and Stark using a similar approach [17]. In 2016, Brimble and Furkert reviewed the isolation and synthesis of this family of compounds [21].

Later on, the same authors reported another total synthesis for both (+)-**41** and (+)-**42** [22]. Shi epoxidation of diol **43**, followed by CSA-catalyzed epoxide opening and cyclization, produces diastereomerically pure **44** in 75% yield over two steps. A further eight steps, with 31% yield over them, produces intermediate **45**, which deprotection gives (+)-heronapyrrol D (**42**). Epoxidation of **42** with a Shi ketone catalyst, followed by CSA-catalyzed epoxide opening, produced enantiomerically pure (+)-heronapyrrol C (**41**) in 75% yield (Scheme 4).

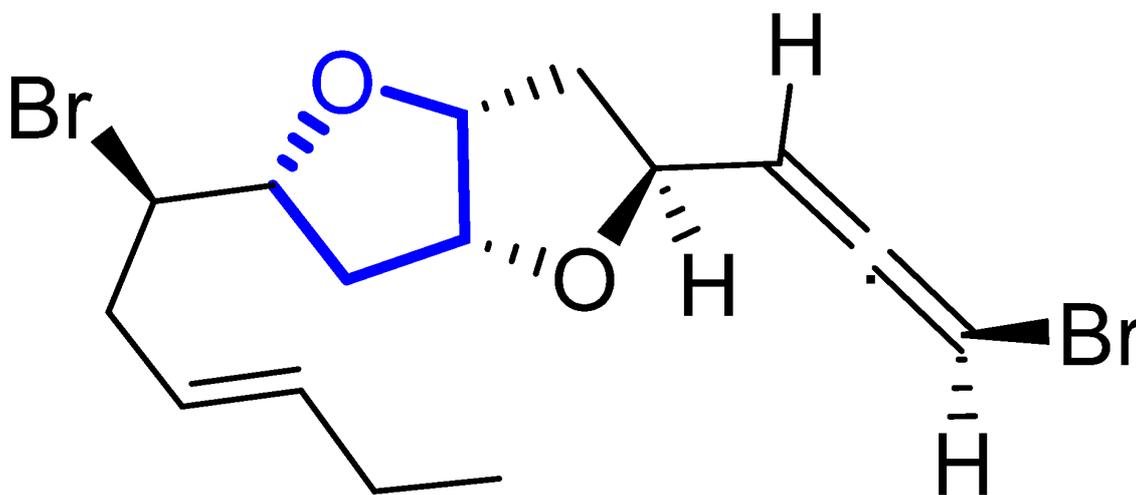


Scheme 4. Synthesis of (+)-heronapyrrol C (**41**) and (+)-heronapyrrol D (**42**).

Other synthetic approaches towards the 2-nitropyrrole system have been investigated by Brimble and Furkert, finding that Sonogashira coupling of 4-iodo-2-nitropyrrole with the appropriate alkyne was more effective than an approach relying on Stille coupling [23].

2.2.2. Kumausallene and Kumausyene

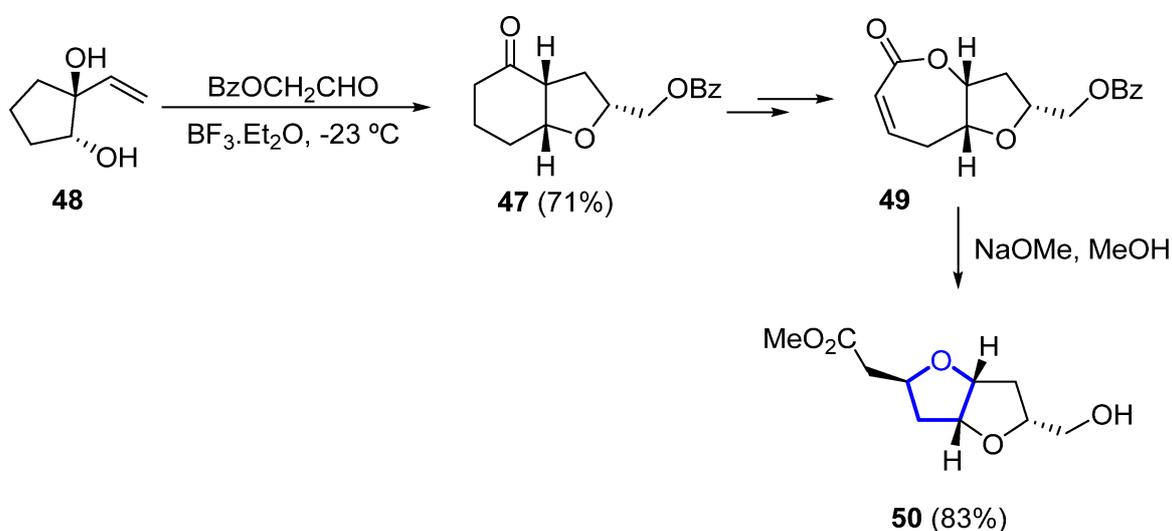
(-)-Kumausallene (**46**) was isolated in 1983 from the marine red alga *Laurencia nipponica* Yamada [24]. This compound belongs to a family of non-isoprenoid sesquiterpenes that contain a 2,6-dioxabicyclo [3.3.0]octane core with an *exo*-cyclic bromoallene (**Figure 9**).



(-)-kumausallene (**46**)

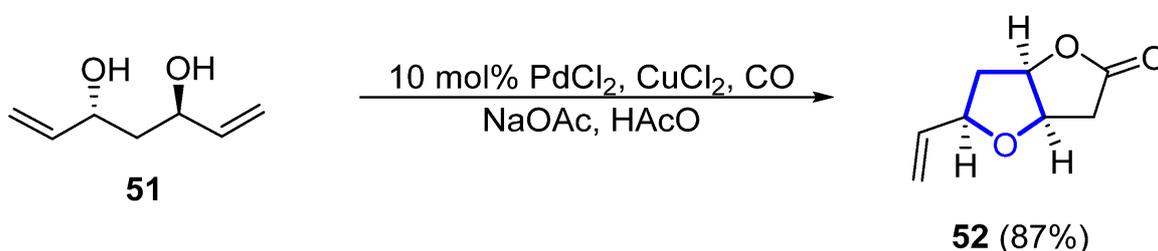
Figure 9. Structure of kumausallene.

In 1993, the first total synthesis of (\pm)-**46** was reported by Overman, who chose a hexahydrobenzofuranone **47** (obtained by a Prins cyclization–pinacol rearrangement from **48**) as the key intermediate for the construction of the *bis*-tetrahydrofuran unit (Scheme 5). Further transformation of **47** into bicyclic lactone **49** (within three further steps) and final methanolysis and tandem cyclization of the corresponding hydroxyester provided, in good yield, the desired dioxabicyclo [3.3.0]octane **50** [25].



Scheme 5. Synthesis of the dioxabicyclo [3.3.0]octane unit of (\pm)-kumausallene (**46**) by Overman.

In 2011, a synthetic approach for (-)-**46** by Tang employed a desymmetrization strategy for the formation of the 2,5-*cis*-substituted THF ring [26]. C_2 -symmetric diol **51** is desymmetrized by a palladium-catalyzed cascade reaction to form lactone **52** in 87% yield (Scheme 6). The total synthesis comprised just 12 steps from commercial acetylacetone. In 2015, Ramana et al. published a different formal total synthesis of (-)-**46** based on a chiral pool approach [27].



Scheme 6. Synthesis of the tetrahydrofuran ring of (-)-**46** through desymmetrization by Tang.

(+)-*Trans*-Kumausyne (**53**) (**Figure 12**) is a halogenated non-isoprenoid sesquiterpene isolated in 1983 from red alga *Laurencia nipponica* Yamada [28]. Its first total synthesis was achieved in 1991 by Overman and coworkers [29]. A review covering the synthetic approaches towards kumausallene and kumausyne, and other natural products containing a 2,3,5-trisubstituted tetrahydrofuran moiety, was published by Fernandes in 2020 [3].

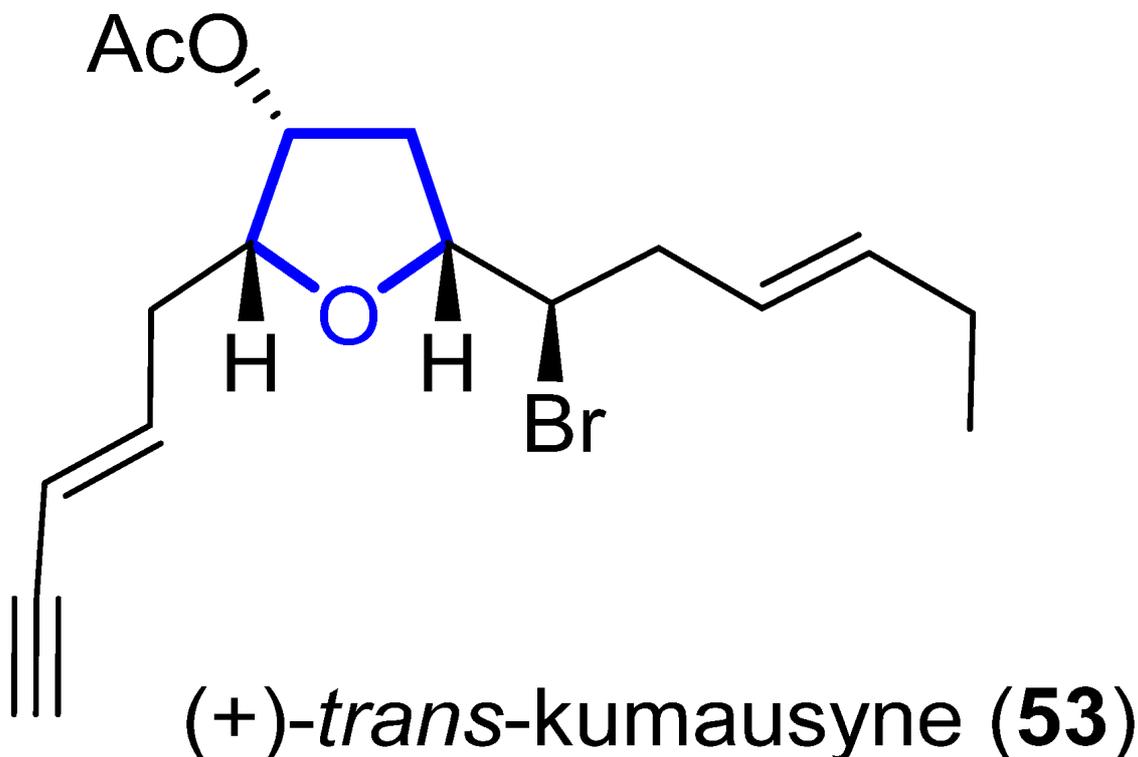


Figure 12. Structure of (+)-*trans*-Kumausyne (**53**).

2.3. Diterpenes

2.3.1. Darwinolide

(+)-Darwinolide (**54**) (**Figure 13**) is a diterpene isolated in 2016 by Baker from the Antarctic Dendroceratid sponge *Dendrilla membranosa* [30]. It presents fourfold selectivity against a biofilm phase of methicillin-resistant *Staphylococcus aureus* (IC₅₀ of 33.2 μM), compared to the planktonic phase (with the higher MIC of 132.9 μM). This interesting property and its low mammalian cytotoxicity (IC₅₀ of 73.4 mM) against a J774 macrophage cell line turn darwinolide into a possible scaffold for antibiofilm-specific antibiotics. Additionally, it was found to have modest activity (11.2 μM) against *L. donovani*-infected macrophages [31].

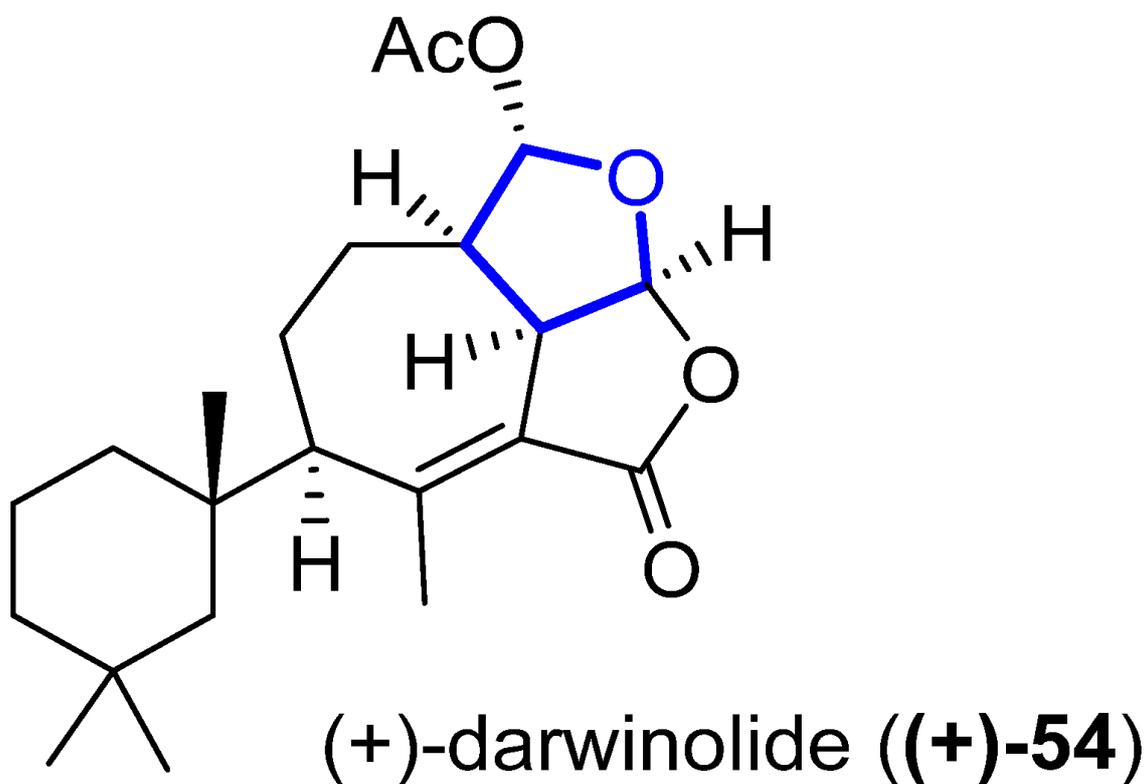
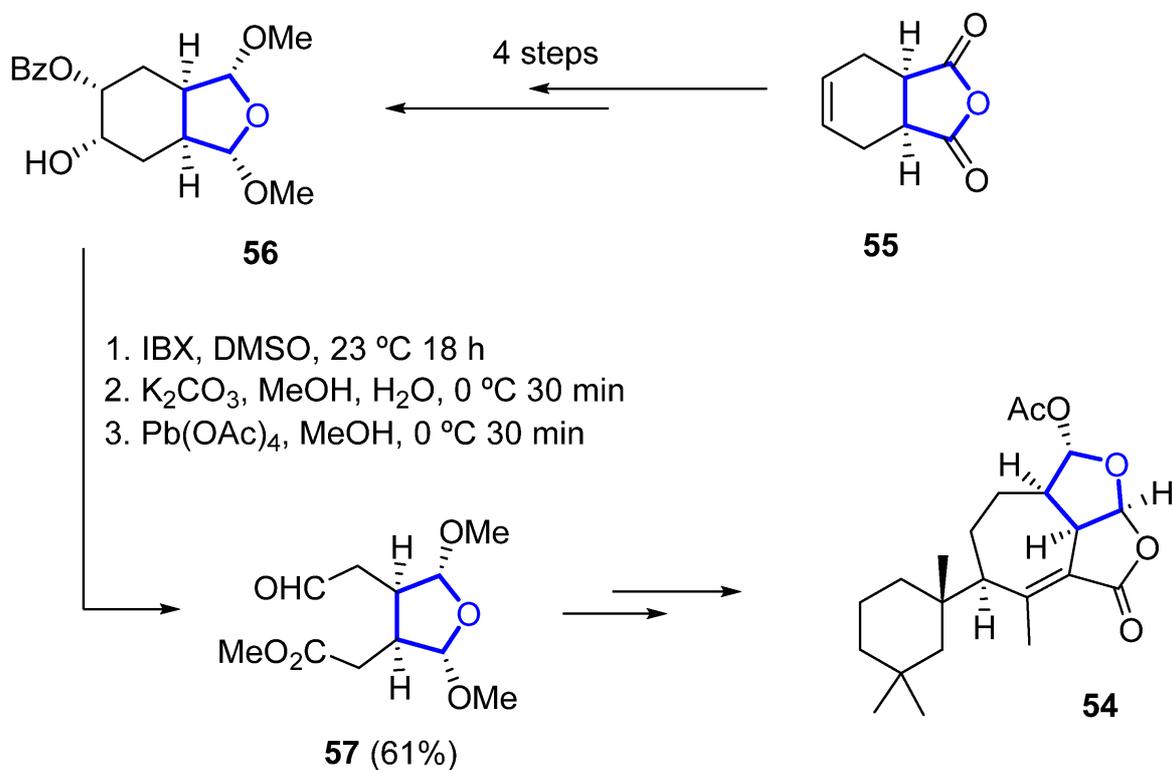


Figure 13. Structure of (+)-darwinolide ((+)-54).

Its total synthesis was reported in 2019 by Christmann ^[32]. The required tetrahydrofuranyl ring is installed starting from the commercially available anhydride **55**, which is converted to the 2,5-dimethoxylated tetrahydrofuran **56** in four steps. A sequence of oxidation (with *o*-iodoxybenzoic acid), saponification, and Criegee oxidation with $\text{Pb}(\text{OAc})_4$ is then used to convert **56** into **57** in 61% yield over three steps (Scheme 7). A further 14 linear steps are needed to complete the total synthesis of **54**, with an overall yield of 1.4%.



Scheme 7. Synthesis of the key THF-containing intermediate in Christmann's total synthesis of darwinolide.

Cembranolides are a family of compounds related to cembrene, which is a 14-membered macrocyclic diterpene with multiple (*E*)-double bonds. Among them, uprolides are a subfamily of compounds named after the University of Puerto Rico. Uprohides A–G were isolated in 1995 by Rodríguez and coworkers from the Caribbean gorgonian *Eunicea Mammosa* and their structure was assigned by spectroscopic methods and chemical interconversion [33][34]. They are the first natural cembranolides from a Caribbean gorgonian that bear a double bond at C6 or C8. While uprolides A–C show an epoxy moiety, uprolides D–G seemed to contain a tetrahydrofuran moiety instead. Uprohides D (**58**), D acetate (**59**), D diacetate (**60**), and E acetate (**61**) (Figure 14) present a moderate cytotoxicity against HeLa cells (IC_{50} = 2.5 to 5.1 $\mu\text{g}/\text{ml}$). Moreover, **59** shows cytotoxicity against the following human tumor cell lines: CCRF-CEM T-cell leukemia (IC_{50} = 7.0 $\mu\text{g}/\text{mL}$), HCT-116 colon cancer (IC_{50} = 7.0 $\mu\text{g}/\text{mL}$), and MCF-7 breast adenocarcinoma (IC_{50} = 0.6 $\mu\text{g}/\text{mL}$).

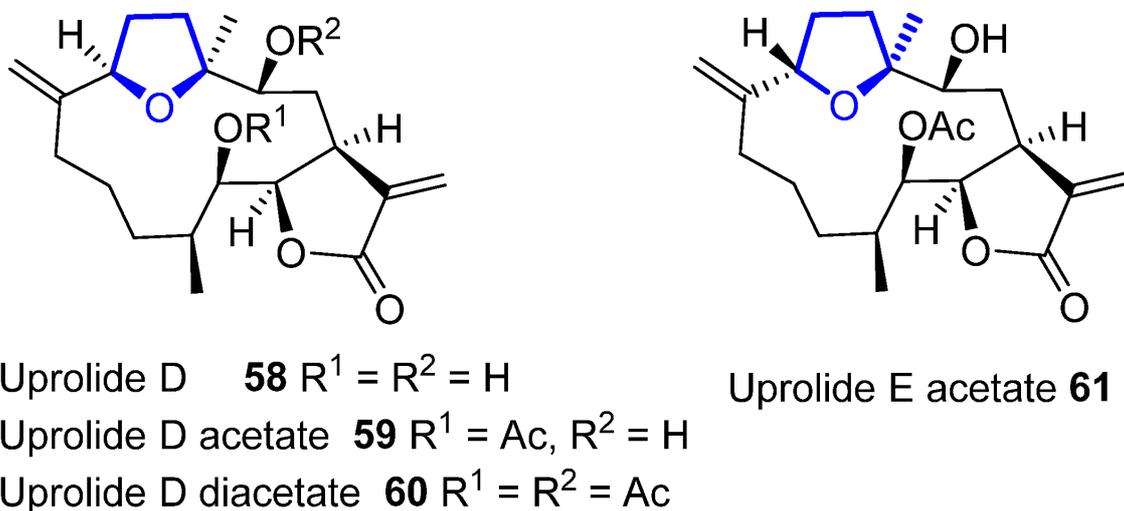
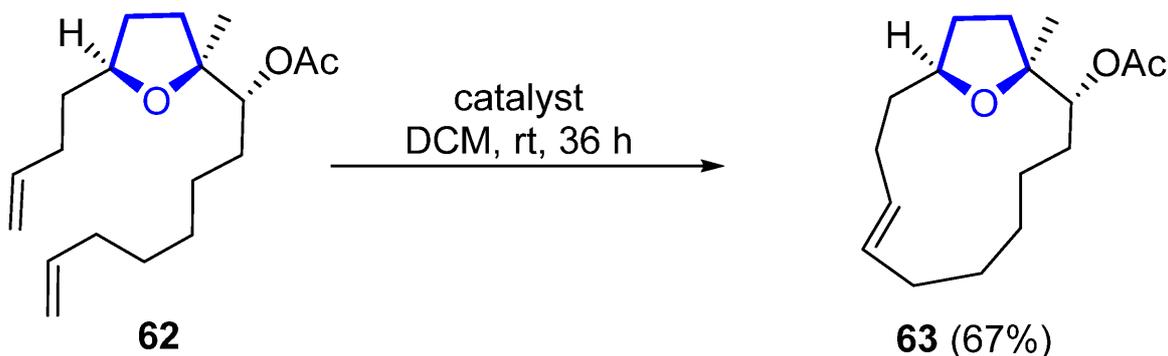


Figure 14. Structure of tetrahydrofuran-containing members of the uprolide family.

Later structural revisions determined the presence of a tetrahydropyran ring, instead of the previously proposed tetrahydrofuran, in uprolides F diacetate and G acetate, hypotheses that were confirmed by asymmetric total synthesis of these natural products [35][36][37][38].

In 2007, a synthetic approach to obtain the macrocyclic core of **58** was proposed by Ramana [39]. The formation of the macrocyclic core is produced by ring-closing metathesis (RCAM) using a Grubbs' first-generation catalyst. The RCAM of acetate **62** produces 13-membered macrocyclic **63** in 67% yield (Scheme 8). The macrocyclic core of uprolide E could not be synthesized using the same methodology.



Scheme 8. Synthesis of macrocyclic core of uprolide D by Ramana.

Marshall developed a synthetic route for C1/C14 *bis*-epimer of **58** in which the macrocyclization is produced by an intramolecular Barbier reaction [40]. Some years later, other members of the uprolide family, which lack the tetrahydrofuran ring, have been isolated from the gorgonian octocoral *Eunicea succinea* [41].

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