Corey-Seebach Reagent in the 21st Century

Subjects: Chemistry, Organic

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The Corey-Seebach reagent plays an important role in organic synthesis because of its broad synthetic applications. The Corey-Seebach reagent is formed by the reaction of an aldehyde or a ketone with 1,3-propane-dithiol under acidic conditions, followed by deprotonation with *n*-butyllithium. A large variety of natural products (alkaloids, terpenoids, and polyketides) can be accessed successfully by utilizing this reagent.

Corey-Seebach reagent | natural products | alkaloids

1. Introduction

Elias James Corey is an American chemist well-known for his contribution to the development of methodology and theory of organic synthesis, especially retrosynthetic analysis. He was awarded a Nobel Prize in 1990 for the development of retrosynthetic analysis. His research cooperation with other famous organic chemists has resulted in various name reactions, based on his name, in organic chemistry [1]. One of his famous reactions is the Corey-Seebach reaction which was a combined work of Corey and Dieter Seebach (a German chemist). The Corey-Seebach reagent is formed by the reaction of an aldehyde or a ketone with 1,3-propane-dithiol in the presence of acidic conditions (Lewis acid). Corey-Seebach is a nucleophilic moiety and has widespread applications in various organic transformations. This reaction was first published in 1965, which reported the synthesis of dicarbonyl derivative from 1,3-dithiane [2]. This acyl anion intermediate easily provides access to α-hydroxy ketones [3][4][5][6] by reacting with a range of electrophiles, including carbonyl compounds (**Figure 1**) [7].

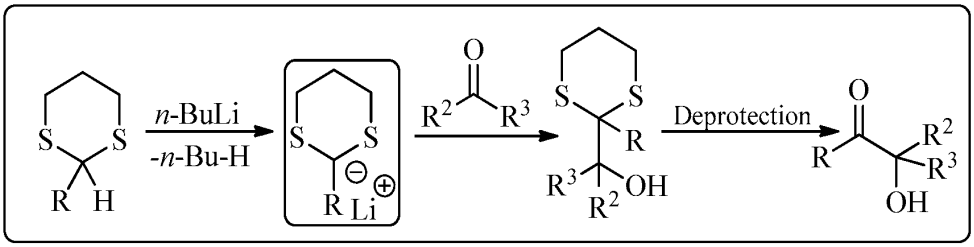


Figure 1. A typical Corey-Seebach reaction.

In order to regenerate the carbonyl group that was initially masked when dithiane was utilized as an acyl anion equivalent, it must be hydrolyzed at some point during synthesis. Deprotection has frequently been challenging to accomplish, especially for complicated and sensitive compounds, and as a result, numerous processes have been adopted. The use of traditional methods such as metal salts (mercury(II) chloride [8]) for the deprotection of 1,3-

dithiane requires toxic reagents that are generally harmful to the environment. However, there are some facile and efficient methods available in the literature, i.e., 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) deprotection [9] and the use of iodine catalyst/H_2O_2 [10] which are more environment friendly.

In a typical 1,3-dithiane addition process, 1,3-dithiane is combined with an equimolar quantity of a strong base, such as *n*-butyllithium, and the resultant 2-lithio-1,3-dithiane should serve as an appropriate nucleophile. According to a different procedure described by Andersen et al. [11] the 1,3-dithiane equivalent, 2-trimethylsilyl-1,3-dithiane (TMS-dithiane), could be activated by a stoichiometric quantity of tetrabutylammonium fluoride (TBAF), resulting in the matching carbanion. Corey et al. claim that various cesium salt mixtures that include cesium fluoride may be used as heterogeneous desilylating reagents. There are just a few cases when TMS-dithiane has been activated catalytically, and most of these reactions involve the use of fluoride reagents in equimolar amounts [12].

The Corey-Seebach umpolung technique has been extensively utilized to manufacture a wide variety of natural products such as Swinholide A [13] (**1**, a marine natural product, derived from sponge *Theonella swinhoei*, which shows antitumor and antifungal activity), pironetin [14][15][16] (**2**, derived from *Streptomyces* fermentation broths, which exhibits plant growth regulating action) (**Figure 2**), ciguatoxin 1B [17] (**3**, one of the main toxins responsible for ciguatera fish poisoning (**Figure 3**), discovered from moray eel *Gymnothorax javanicus*), and maytansine [18][19] (**4**, shows antitumor activity) (**Figure 4**). Many synthetic [20] compounds, such as photolabile safety benzoin linkers [21] and bis-3,4-dihydroisoquinolium salts [22], have also been attained using the Corey-Seebach reagent. Earlier, Foubelo et al. published a review article in 2003 concerning the use of 1,3-dithianes in the synthesis of natural products [23]. Until now, the Corey-Seebach reagent has found valuable applications in organic synthesis. The research focuses on the utilization of Corey-Seebach reagent in the synthesis of noteworthy natural and synthetic organic compounds reported post-2006.

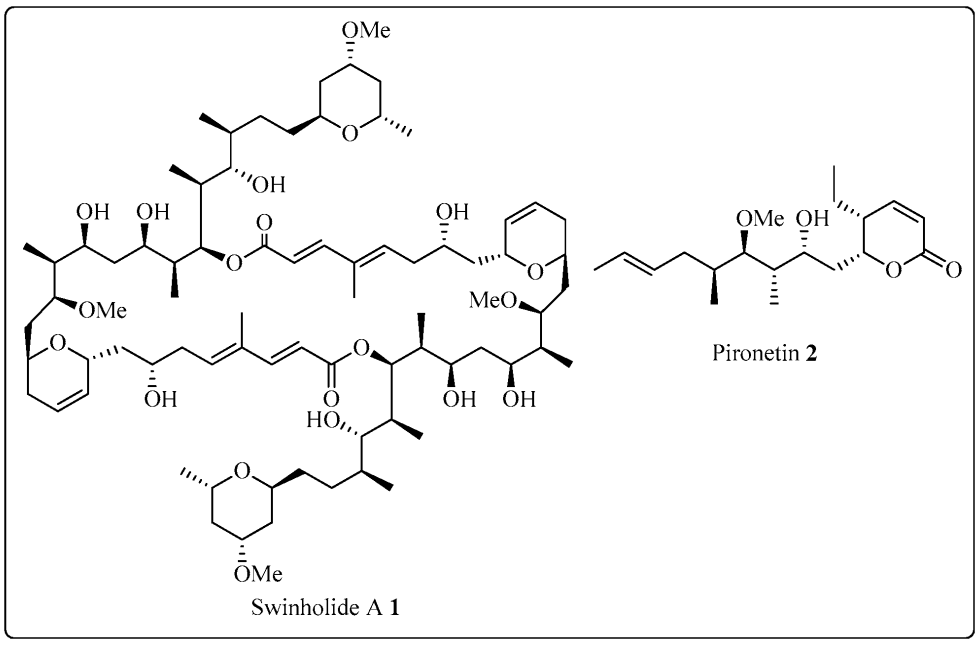


Figure 2. Structure of Swinholide A **1** and pironetin **2**.

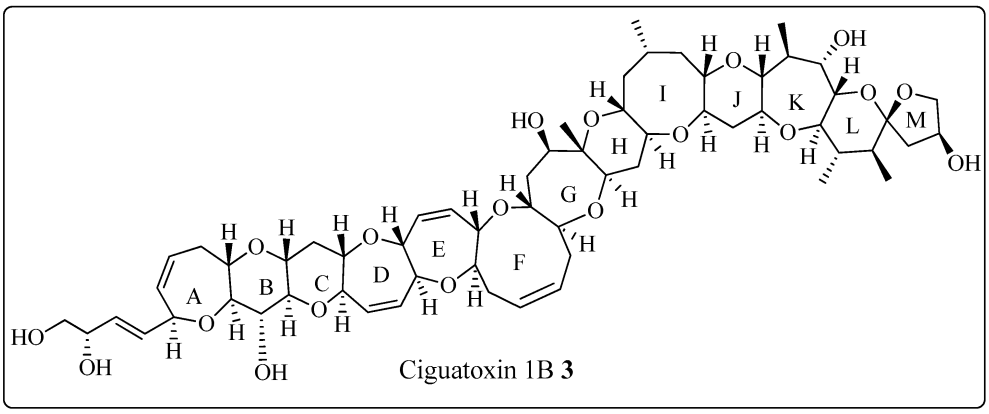


Figure 3. Structure of ciguatoxin 1B **3**.

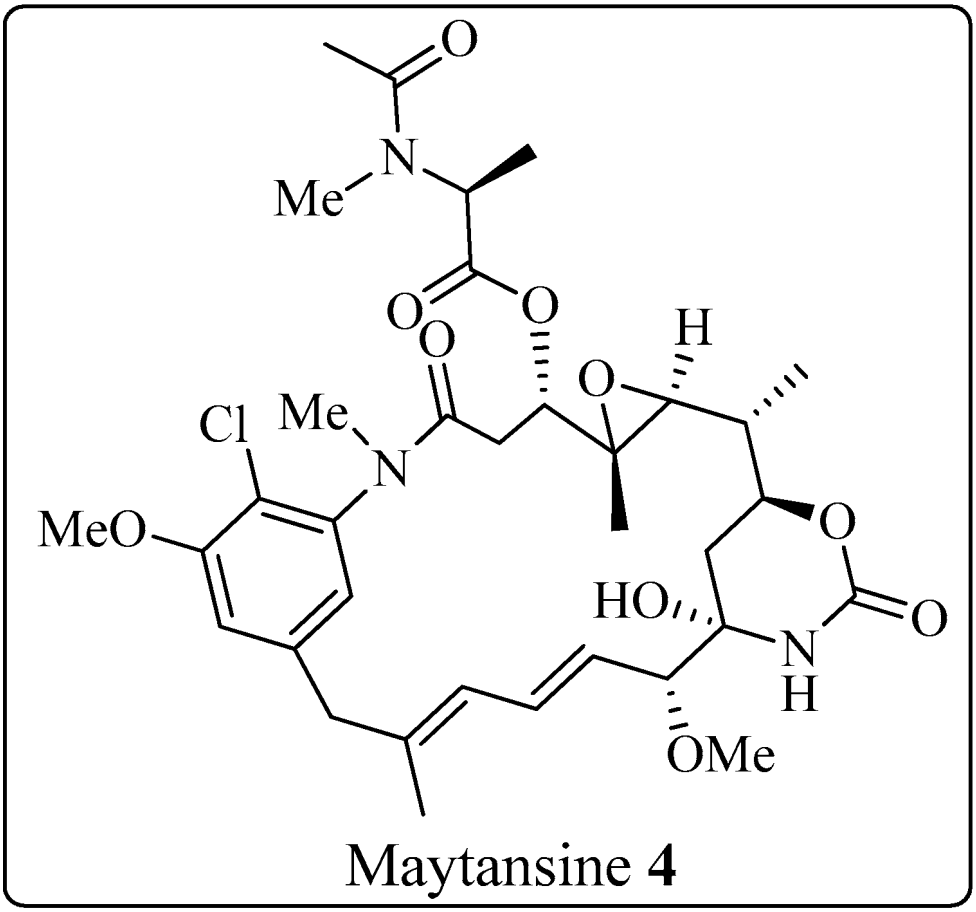


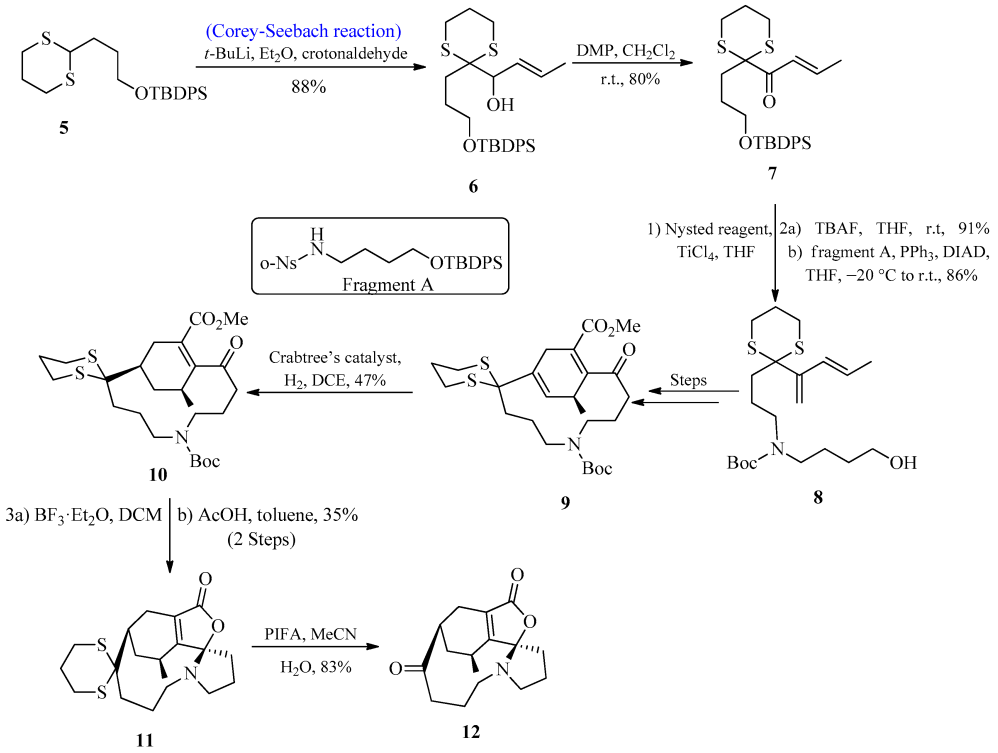
Figure 4. Structure of maytansine **4**.

2. Alkaloid-Based Natural Products Synthesis

2.1. Lycoplanine A Alkaloids

Lycopodium alkaloids are known to play an effective role in the medication of Alzheimer's disease [24][25][26]. Over 300 lycopodium alkaloids have so far been isolated, and a number of total syntheses of these alkaloids have been

published [27][28][29]. In 2017, Zhao and co-workers [30] first isolated lycoplanine A, a lycopodium alkaloid with the γ-lactone ring. According to biological investigations, lycoplanine alkaloid is a strong inhibitor of the calcium channel (C_{av}3.1 T-type) with an IC_{50} value of 6.06 μM. In 2021, Gao et al. [31] reported the synthesis of lycoplanine A isomer by utilizing the Corey-Seebach reagent. To achieve this task, the C=C bond was introduced by using 1,4-dithiane **5** and crotonaldehyde (*E*/*Z* > 98%) to afford alcohol **6** in an 88% yield, followed by oxidation to provide the product **7** with an 80% yield. Compound **7** was then treated with Nysted reagent for the introduction of the second C=C, followed by the introduction of fragment A to afford compound **8** by using the Mitsunobu reaction. After a few steps, compound **9** was formed, which upon reaction with Crabtree's catalyst provided a tetrasubstituted C=C bond product **10** with excellent stereo and regioselectivities. After deprotection of the Boc group, compound **10** was immediately exposed to AcOH, initiating a cascade reaction that produced the stereo-specific cyclized product **11** with a 35% yield. The deprotection of the thioketal group was achieved by using PIFA to afford lycoplanine A **12** isomer with an 83% yield (Scheme 1).

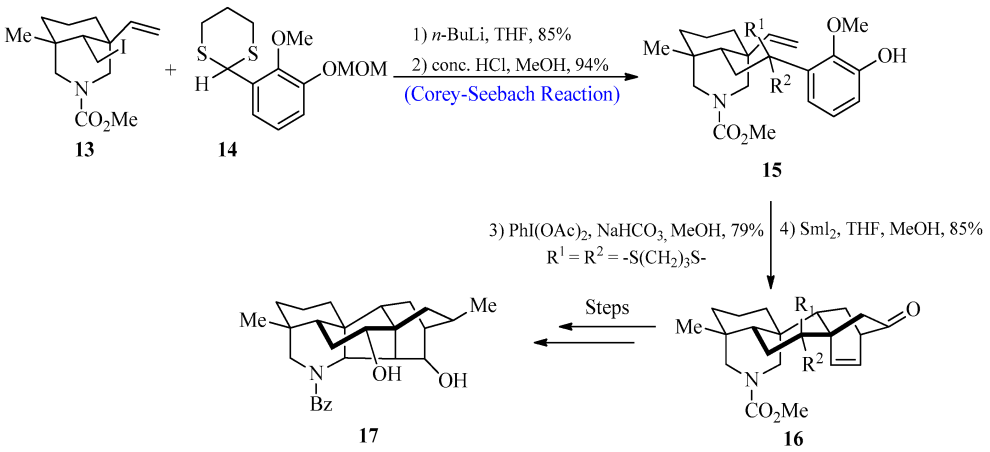


Scheme 1. Synthesis of lycoplanine A **12** isomer via Corey-Seebach reagent.

2.2. Diterpenoid Alkaloids

Diterpenoid alkaloids have been the focus of study by scientists all over the globe because of their fascinating bioactivities and complicated structures [32]. These biologically active compounds were extracted from *Delphinium* and *Aconitum* species that belong to the Ranunculaceae family [33]. In 2017, Min Zhu et al. [34] reported the synthesis of hetidine-type C_{20}-diterpenoid alkaloids by utilizing the Corey-Seebach reagent as a key step. For this purpose, 2-lithio-1,3-dithiane species **14** were reacted with iodide **13**, followed by the deprotection of methoxymethyl to afford olefinic phenol **15** with an 80% yield. In the next step, compound **15** was treated with

$PhI(OAc)_2$, followed by the addition of SmI_2 to obtain compound **16**, which could then be transformed into the desired hetidine-type diterpenoid alkaloid **17** after a series of reactions (Scheme 2).

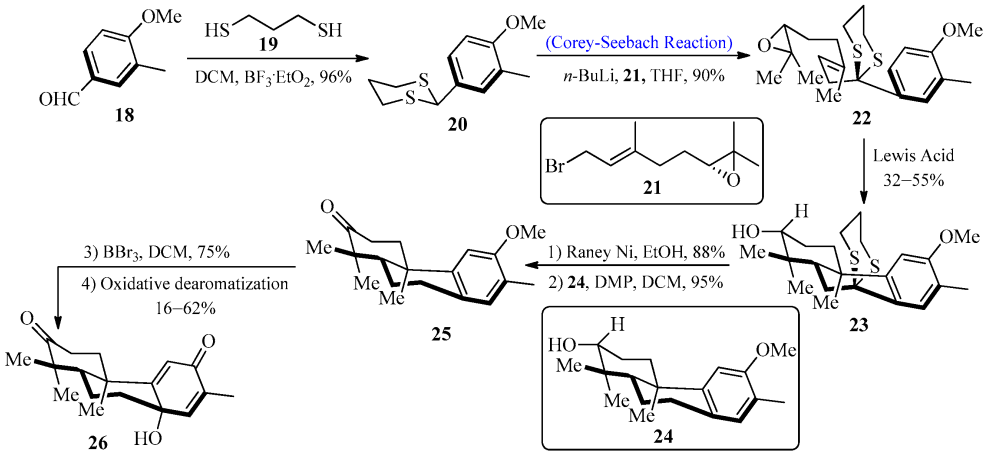


Scheme 2. Synthesis of hetidine-based diterpenoid **17** alkaloid.

3. Terpenoids-Based Natural Products Synthesis

3.1. Bisnorditerpene

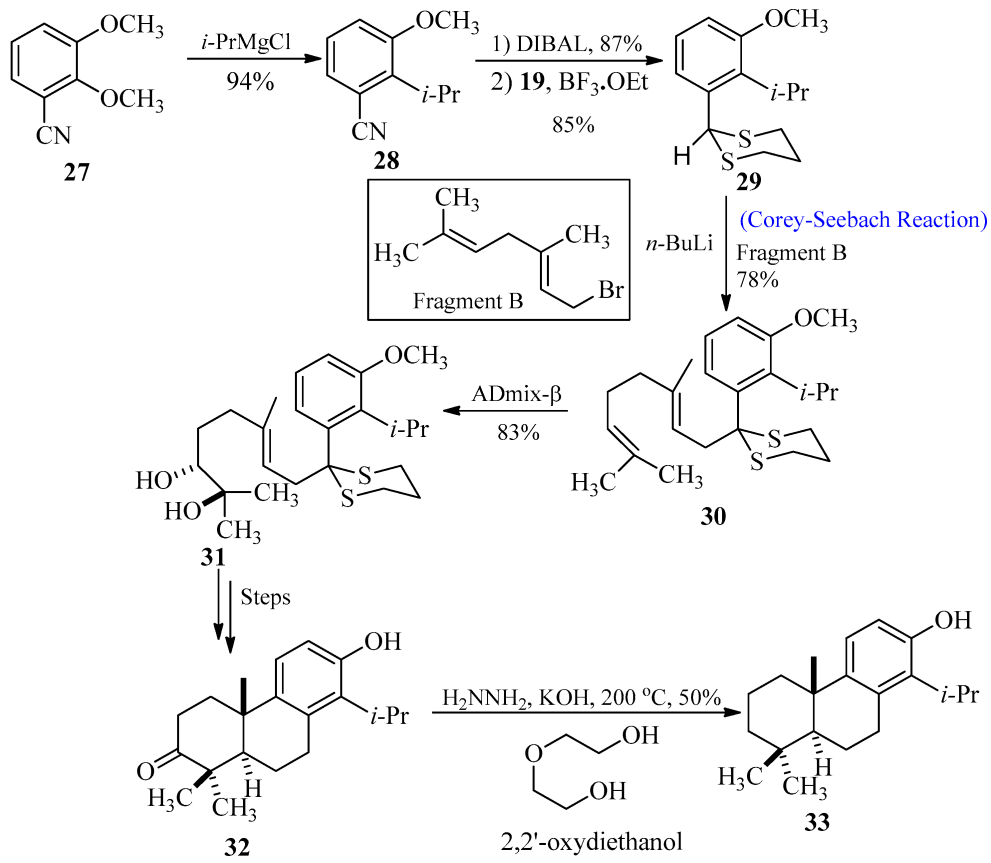
Diterpenoids are important natural products that display a wide range of chemical diversity and are useful both in medicine and industry. A large number of known diterpenoid compounds are isolated from plants and fungi, and investigations into these species have provided an understanding of their production [35]. In 2010, Pessoa et al. [36] first isolated a bisnorditerpene from *Croton regelianus* var. *matosii*. This herb is utilized in traditional medicine in the Northeastern state of “Caatinga”. In 2016, Xu et al. [37] designed a new strategy for the synthesis of bisnorditerpene by utilizing the Corey-Seebach reagent. To achieve this, an aldehyde **18** was allowed to react with 1,3-propane-dithiol **19** to furnish dithiane **20**, which upon lithiation with epoxide [38] **21** by using the Corey-Seebach reaction afforded precursor **22** followed by the addition of Lewis acid to obtain tricyclic alcohol **23** with a 55% yield. In the next step, secondary alcohol **24** was obtained by desulfurization of **23** with Raney-Ni, followed by the oxidation of **24** with Dess-Martin periodinane (DMP) to afford ketone **25** with a 95% yield. The final process involved the demethylation of ketone **25** with BBr_3 along with the addition of $PhI(OAc)_2$ in CH_3CN to generate bisnorditerpene **26** (Scheme 3).



Scheme 3. Synthesis of bisnorditerpene **26**.

3.2. Totarol Synthesis

Totarol belongs to diterpenes that are found in the sap of *podocarpus totara*, a New Zealand native conifer [39]. The antimicrobial properties [40][41][42][43] of the secondary metabolites in this sap are well known. The wood of this tree displays resistance against rot. Toothpaste and acne medications are just a couple of consumer goods that can contain totarol as an antibacterial ingredient. In 2010, Kim et al. [44] synthesized totarol by utilizing the Corey-Seebach approach as an important key step. The goal of their research was to synthesize totarol diterpenes as a part of a larger research project to determine the mechanism by which tiny molecules could inactivate FtsZ. In order to achieve this, benzonitrile **27** was treated with *i*-PrMgCl to produce compound **28**, followed by the reduction and thioacetal formation to obtain product **29**. In the next step, alkene **30** was synthesized through lithiation of **29** with fragment B followed by alkylation, respectively. Treatment of compound **30** with AD-mix-β afforded regio-isomeric diol **31** with 90–95% enantiomeric excess, and after a few steps, totarolone **32** was formed with a 33% yield. Totarolone **32** was transformed into the desired totarol **33** through the Wolff-Kishner reduction (Scheme 4).

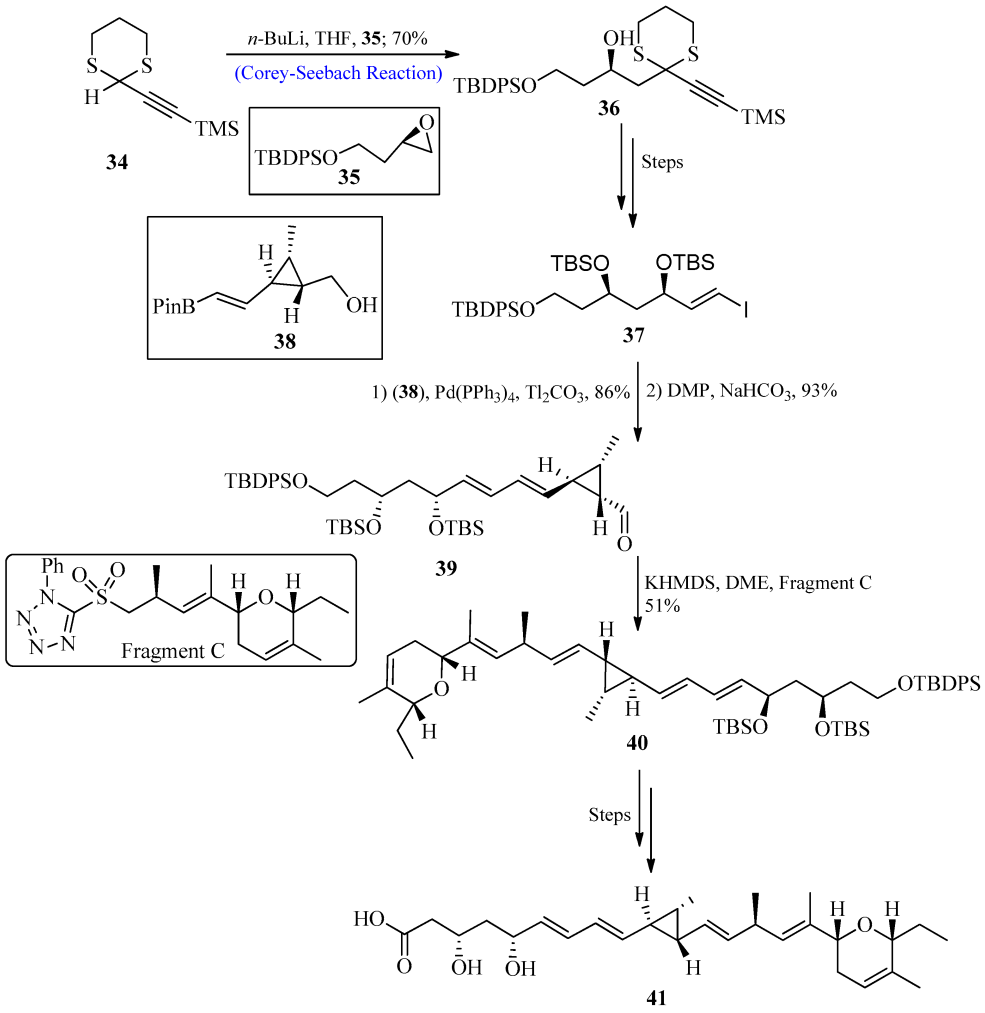


Scheme 4. Synthesis of totarol **33** via Corey-Seebach approach.

4. Polyketide Based Natural Products

4.1. Ambruticin J Synthesis

A significant class of polyketide-based natural compounds known as ambruticin was initially isolated from the bacterium *Sorangium cellulosum* in 1977. They display high biological advantages such as strong antifungal action [45][46][47][48][49][50]. The mechanistic studies of these compounds suggested that ambruticins target Hik1 kinase [51][52] by interacting with fungal osmoregulation. The influence of ambruticin VS3 on soil myxobacteria has recently been studied, and results showed that they are beneficial for the environment by preventing the emergence of antagonistic myxobacterial species. In 2021, Trentadue et al. [53] reported the total synthesis of ambruticin J by utilizing the Corey-Seebach reagent as a key step. For this purpose, dithiane **34** (synthesized from propargyl alcohol) was reacted with epoxide **35** by using the Corey-Seebach reaction to afford compound **36** with a 70% yield, and after a few steps, vinyl iodide **37** was formed. In the following stage, vinyl iodide **37** reacted with pinacol boronic ester **38** through Suzuki coupling, followed by oxidation using Dess–Martin periodinane (DMP) to afford aldehyde **39**. The aldehyde **39** was further treated with fragment C via Julia-Kocienski olefination to afford *E*-olefin **40**, and after a few steps, the desired ambruticin J **41** was formed (Scheme 5).

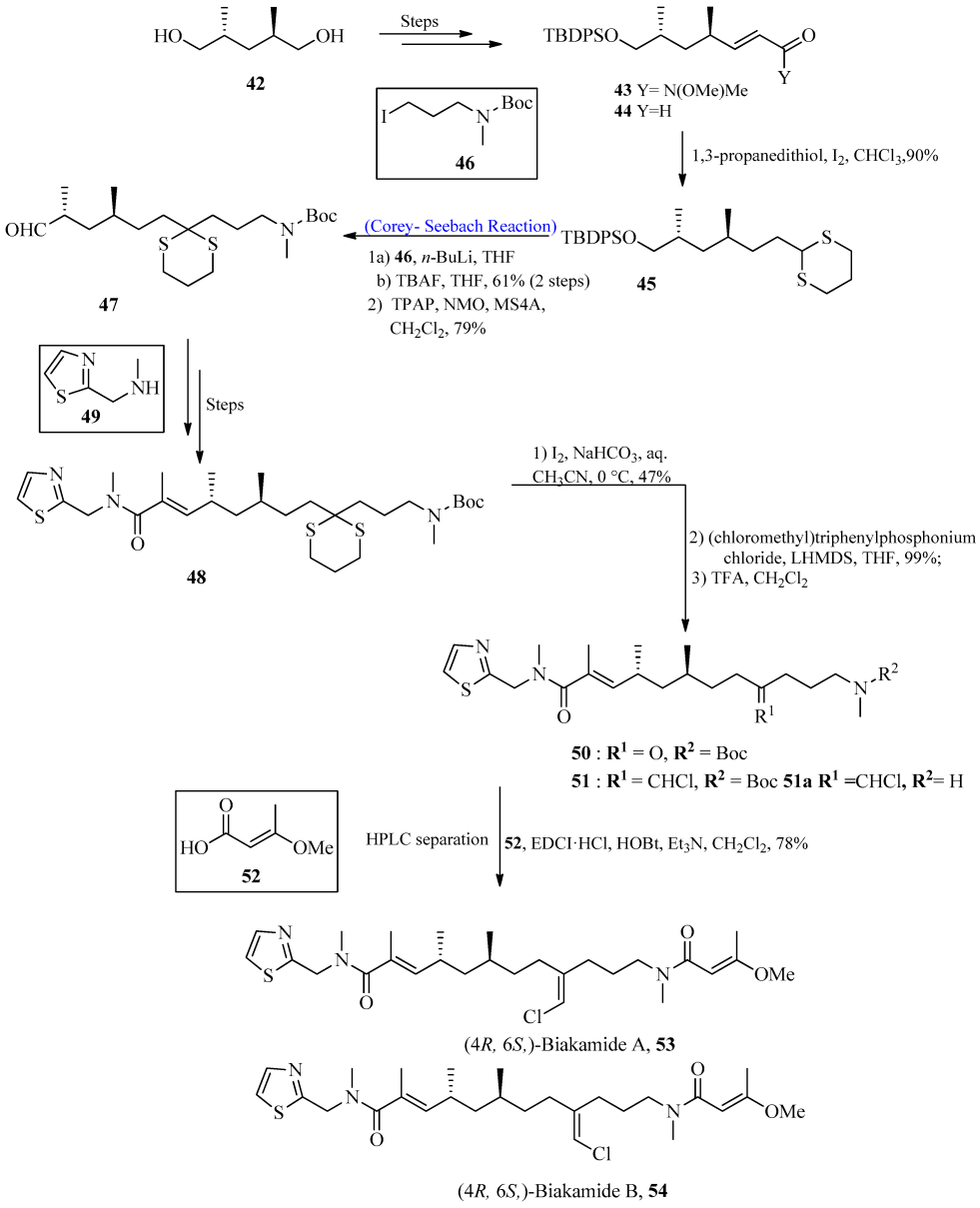


Scheme 5. Synthesis of ambruticin J **41**.

4.2. Biakamides

Biakamides are naturally occurring polyketides with significant biological activity [54][55]. In 2017, Kotoku et al. [56] first isolated biakamides from a marine sponge *Petrosaspongia* sp. The purpose of this research project was to isolate marine-based anti-cancer drugs. To achieve this, marine-based biakamides were isolated, and the total synthesis of these drugs has also been described by using the Corey-Seebach reaction in one of their key steps. The synthesis was initiated by using substituted penta-diol **42**, which was converted into corresponding Weinreb amide **43**, followed by reduction with DIBAL to obtain compound **44**. Aldehyde **44** was treated with 1,3-propane dithiol in the presence of iodine to afford 1,3-dithiane **45**. Compound **45** was then allowed to react with alkyl iodide **46** in the presence of *n*-BuLi by using the Corey-Seebach reaction followed by TBAF addition and subsequent tetrapropylammonium perruthenate (TPAP) oxidation to furnish aldehyde **47**. After a few steps, *N*-methyle-neamide **48** was synthesized from secondary amine **49**, followed by the deprotection of 1,3-dithiane to provide compound **50**. The chloromethylene moiety was introduced in the presence of (chloromethyl)triphenyl-phosphonium chloride with *E*/*Z* 3:2 by using the Wittig reaction, which resulted in compound **51**. In the last step, TFA was used for the deprotection of the amine, followed by a condensation reaction with *E*-3-methoxy-2-butenoic acid **52** to afford (4*R*,

6*S*)-biakamides **53** and **54** (Scheme 6). The antiproliferative activity of biakamides **53** and **54** was also examined against PANC-1 cell culture (glucose deficient conditions), which provided an IC_{50} value of 0.5 μM.



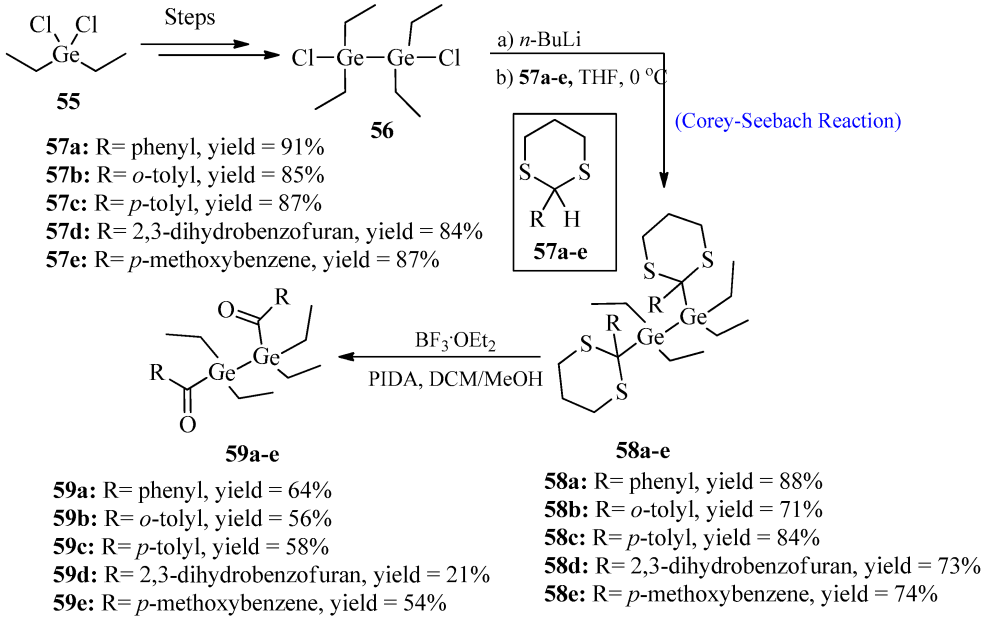
Scheme 6. Total synthesis of biakamides **53** and **54**.

5. Photoinitiators

5.1. Bisacyldigermanes

The synthesis of improved photoinitiator molecules for free radical polymerization has been a challenging task. So far, a large number of photoinitiators, such as acyl-phosphine oxides, have been successfully synthesized [57]. Among all types, germanium-based photoinitiators are of great importance due to their non-toxic behavior and excellent bleaching properties [58]. In 2022, Wiesner et al. [59] synthesized bisacyldigermanes **59** by utilizing the

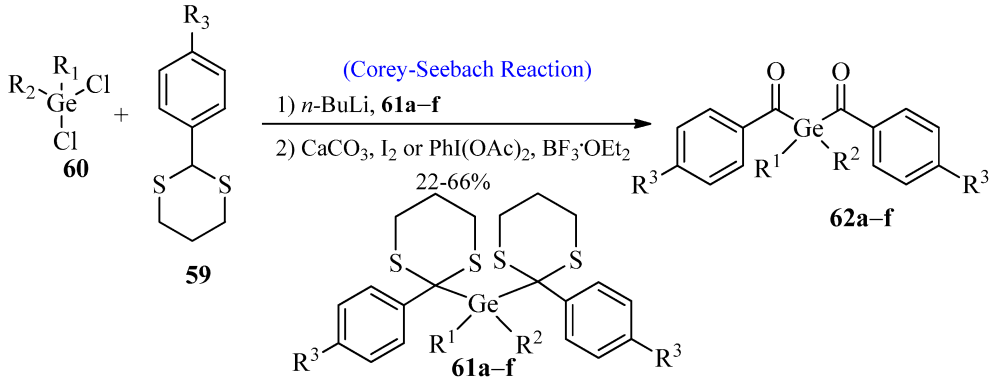
Corey-Seebach reaction. The purpose of this synthesis was to introduce double germanium content in order to achieve a higher polymerization rate. For this purpose, 1,2-dichloro-1,1,2,2-tetraethyldi-germane **56** was synthesized over four steps from diethyl dichloro germane **55,** followed by lithiation with thioketals **57a**–**e** to afford germane derivatives **58a**–**e**. In the last step, compounds **58a**–**e** were deprotected and oxidized using boron trifluoride etherate and (diacetoxyiodo)benzene (PIDA) to obtain bisacyldigermanes **59a**–**e** in good yields (Scheme 7).



Scheme 7. Synthesis of bisacyldigermanes **59**.

5.2. Benzoylgermanium Derivatives

Germanium-based photoinitiators have attained great importance due to their high radical polymerization capacity [60][61]. In 2009, Moszner et al. [62] synthesized benzoyl germanium derivatives using the Corey-Seebach reaction. These benzoyl germanium derivatives are used in dental cements and composites. In the first step, aromatic 1,3-dithianes **59** were reacted with *n*-BuLi by using the Corey-Seebach reaction, followed by the reaction with dichlorogermanium compound **60** to afford compound **61a**–**f**. In the last step, compound **61** was dithioketolized in the presence of $BF_3{\cdot}OEt_2$ and $PhI(OAc)_2$ or in the presence of excess iodine and $CaCO_3$ in THF to provide PIs **62a**–**f** (Scheme 8).



61, 62a = $R^1 = C_2H_5$ **61, 62a** = $R^2 = C_2H_5$ **61, 62a** = $R^3 = H$
61, 62b = $R^1 = CH_3$ **61, 62b** = $R^2 = CH_3$ **61, 62b** = $R^3 = H$
61, 62c = $R^1 = C_4H_9$ **61, 62c** = $R^2 = C_4H_9$ **61, 62c** = $R^3 = H$
61, 62d = $R^1 = C_2H_5$ **61, 62d** = $R^2 = C_2H_5$ **61, 62d** = $R^3 = OCH_3$
61, 62e = $R^1 = CH_5H_{10}$ **61, 62e** = $R^2 = CH_5H_{10}$ **61, 62e** = $R^3 = H$
61, 62f = $R^1 = CH_3$ **61, 62f** = $R^2 = Ph$ **61, 62f** = $R^3 = H$

Scheme 8. Synthesis of benzoyl germanium derivatives **61-a-f** via Corey-Seebach approach.

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