

Review

Chemistry and Biology of Bioactive Glycolipids of Marine Origin

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Abstract: Glycolipids represent a broad class of natural products structurally featured by a glycosidic fragment linked to a lipidic molecule. Despite the large structural variety of these glycoconjugates, they can be classified into three main groups, i.e., glycosphingolipids, glyco glycerolipids, and atypical glycolipids. In the particular case of glycolipids derived from marine sources, an impressive variety in their structural features and biological properties is observed, thus making them prime targets for chemical synthesis. In the present review, we explore the chemistry and biology of this class of compounds.

Keywords: glycolipids; glycosphingolipids; glyco glycerolipids; natural products; total synthesis

1. Introduction

Glycolipids represent a broad class of biologically active natural products with a wide variety of molecular structures and biological functions, many of which are essential for life [1,2]. Despite their extensive structural diversity, glycolipids can be classified by the nature of the lipidic fragment. According to this classification, these glycoconjugates are divided into three main groups, i.e., glyco glycerolipids, glycosphingolipids, and those comprising the rest of the glycolipids possessing atypical lipidic moieties. Whereas glyco glycerolipids are mainly distributed in the realm of micro-organisms and plants, glycosphingolipids are extensively found in all living beings. In fact, these molecules are found on the surface of cell membranes and, together with glycoproteins and glycosaminoglycans, which are known as glycocalyx, play critical roles for cell growth, cellular recognition, adhesion, neuronal repair, and signal transduction, which are essential for health and involved in a number of diseases such as cancer and inflammatory processes and infections [3–5]. Given their molecular complexity and diversity, glycosphingolipids are classified into the following subgroups: (a) neutral, which can be subdivided into the cerebrosides that contain only one uncharged sugar, the diacylceramides with two sugar units, and the neutral glycosphingolipids with more than two (up to 30) uncharged sugars; and (b) acidic, which can be subdivided into the gangliosides, characterized by the presence of one or more neuraminic acid residues, and, finally the sulfatides, which contain at least one sugar residue with a sulfate group. In any case, all of the glycosphingolipids share a common ceramide lipid unit, consisting of a long-chain amino-alcohol fragment, which can be a sphingosine or a phytosphingosine unit (sphingoid base) linked to a fatty acid via an amide bond. In the case of the glyco glycerolipids, their core structure is comprised of a 1,2-diacyl glycerol attached to a mono- or an oligosaccharide molecule, although some variations with respect to this general structure can be found, as will be described later. In contrast to the glycosphingolipids, the glyco glycerolipids are present in nature in much lower abundance, which, combined with the difficulty of their isolation from natural sources, have significantly hampered extensive and detailed biological studies. The third

group consists of the atypical glycolipids that include any glycoconjugate that contains a lipidic chain not present in the previous groups (Figure 1). The stunning and limitless wealth of secondary metabolites that marine organisms provide is extensive for this class of compounds, with a myriad of glycolipid-type natural products with impressive molecular diversity and a variety of biological activities, including antitumor, antiviral, and anti-inflammatory properties. Given the biological relevance and structural complexity of these classes of compounds, a large number of reviews [6–12], books, and book chapters [13–15] have been devoted to all aspects related to their chemistry and biology. More specifically, in the field of glycolipids of marine origin, several excellent reviews have been published, especially by Barnathan et al. [16], which represents an excellent description of all the glycolipids found in marine invertebrates, as well as by Li et al. [17], which focused on the chemistry and biology of glycosphingolipids from marine organisms. In addition, numerous reviews have been reported on very specific compounds, such as KRN7000 [18] and related glycosphingolipids [19] due to their outstanding biological activities and their potential pharmacological activity. In light of this publication landscape, this review intends to give a chemical and biological perspective of these fascinating natural products with a particular emphasis on recent contributions that were not covered in the aforementioned reviews and highlighting the importance of their synthesis given the particularly intricate requirements to obtain sufficient amounts from their natural sources. This review also provides an updated state of the art of this field that can attract the interest of chemists and biologists, revealing the potential and prospects that these compounds may provide in biology, chemistry, and biomedicine for the future.

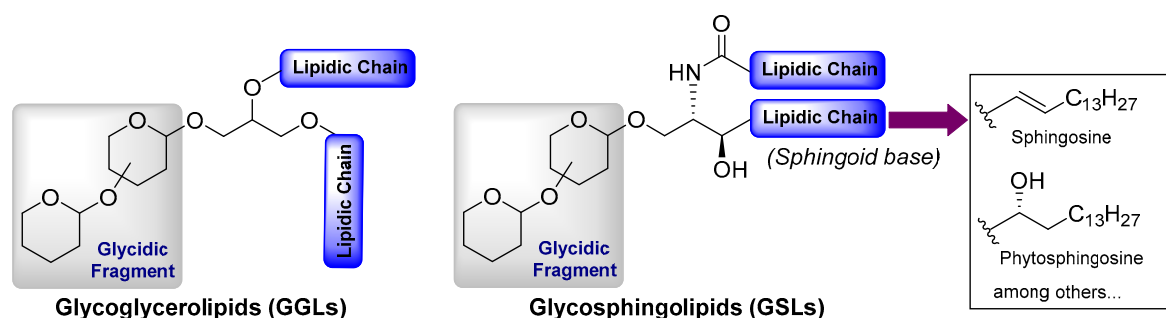


Figure 1. General structural feature of glycolipids.

2. Chemistry and Biology of Glycosphingolipids

2.1. Neutral Glycosphingolipids

2.1.1. Cerebrosides

Acanthacerebrosides, Astrocerebrosides, and Asteriacerebrosides

Among the wide and important family of marine glycosphingolipids containing a phytosphingosine unit, which confers the glycolipids outstanding immunostimulant properties, as will be described later, the acanthacerebrosides and astrocerebrosides represent interesting members isolated from different starfish species. It was in 1988 when Komori et al. [20] discovered the first members of the acanthacerebrosides (A–F, 1–6) from the starfish *Acanthaster planci*. These compounds were isolated as a mixture, which hindered a complete structural elucidation and biological evaluations. However, subsequent purification efforts by the same group led to the isolation of one of their members, acanthacerebroside B (2), which could be isolated as a pure compound from the starfish *Asterina pectinifera* and allowed full structural characterization by a complete NMR spectroscopic analysis. In the same year, these authors described the first total synthesis of acanthacerebroside A (1), establishing unambiguously the structure and absolute configuration of this new family of cerebrosides [21]. In addition, the investigations of Komori et al. [22] with the starfish *Astropecten latespinosus* led to

the discovery of three new related cerebrosides, which were named astrocerebrosides A (7), B (8), and C (9). Later, in 1991, the study of the starfish *Asterias amurensis versicolor* allowed Komori's group to isolate new cerebrosides: asteriacerebrosides A–F (10–15) [23]. Ten years later, Ishii et al. [24] discovered a new member of this class, asteriacerebroside G (16), from the starfish *Asterias amurensis* (Figure 2).

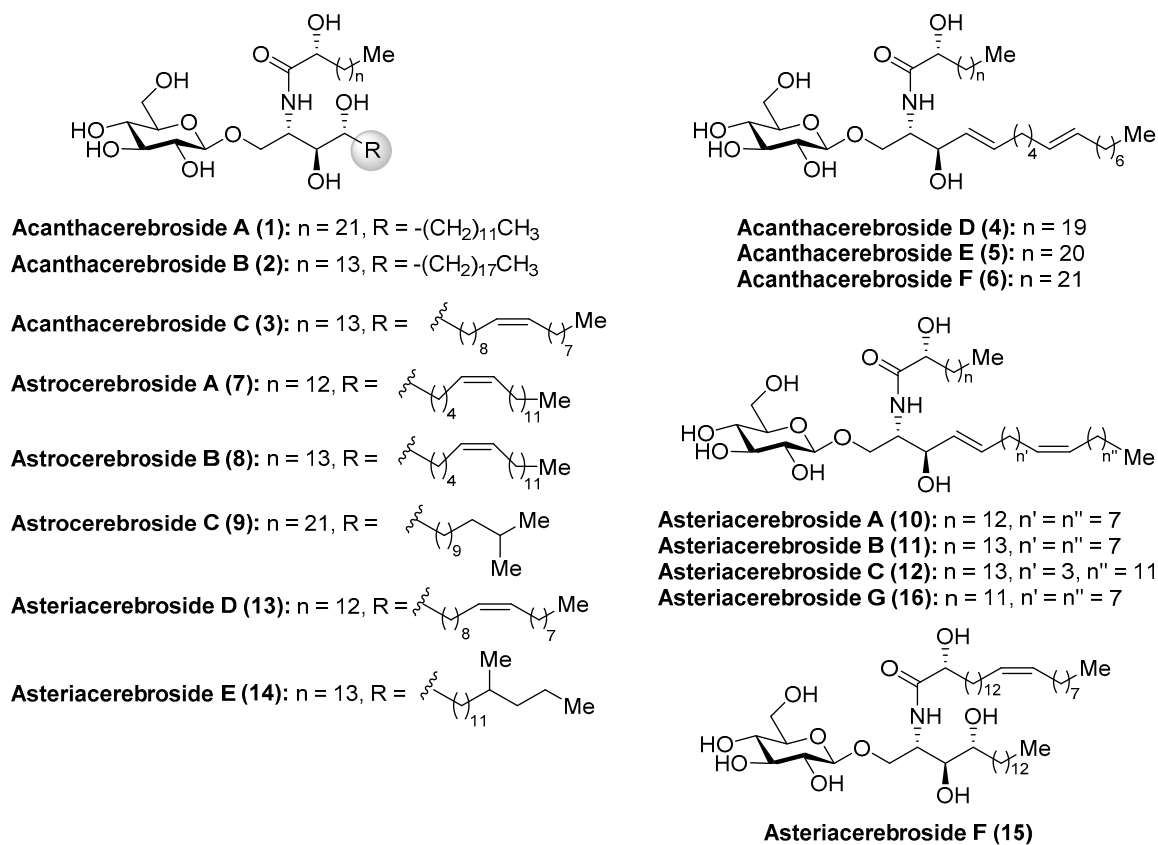
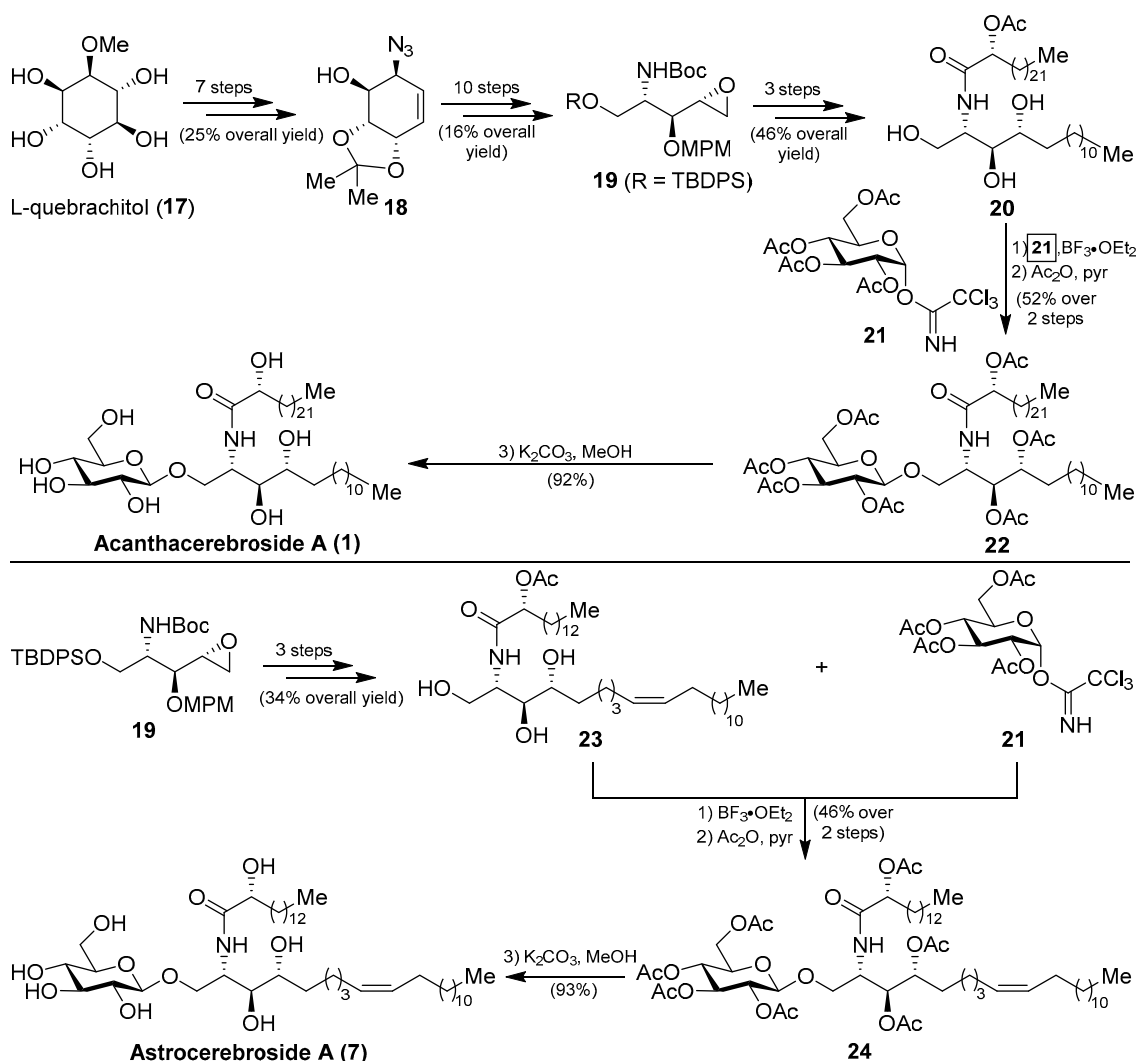


Figure 2. Structures of the acanthacerebrosides (1–6), astrocerebrosides (7–9), and asteriacerebrosides (10–16).

More recently, from the same starfish (*A. amurensis*), Kim et al. identified new members of related asteriacerebrosides, whose structures were established by mass spectrometric techniques [25]. After the synthesis of acanthacerebroside A (1) by Komori in 1998, the Chida group [26] reported a new synthesis for acanthacerebroside A (1) and astrocerebroside A (7), in which the preparation of the phytosphingosine moiety was achieved using the commercially available L-quebrachitol (17) (Scheme 1). Accordingly, L-quebrachitol (17) was transformed into the azide 18 in seven steps, which was directed towards the phytosphingosine fragment 20, contained in acanthacerebroside A (1). The coupling of 20 with the donor trichloroacetimidate 21 via a glycosylation reaction mediated by $BF_3 \cdot OEt_2$ provided the corresponding acanthacerebroside A derivative, which was derivatized to the peracetylated 22 to facilitate purification. After removing the acetate protecting groups, natural acanthacerebroside A (1) was obtained. In a similar manner, astrocerebroside A (7) was efficiently prepared from the phytosphingosine 23, synthesized from the common epoxide 19, and the same glycosyl donor (21). From a biological standpoint, surprisingly only the asteriacerebrosides were evaluated, showing that asteriacerebrosides A (10), B (11), and G (16) displayed growth-promoting activity against the plant *Brassica campestris*. This was the first report of a promotive plant-growth activity of this class of compounds.



Scheme 1. Total syntheses of acanthocerebroside A (1) and astrocerebroside A (7).

Agelasphins

Within the family of phytosphingosine-containing cerebroside of marine origin, the agelasphins (25–31) (Figure 3) occupy a privileged position by virtue of their striking and promising biological properties. The presence of a galactosyl fragment instead of a glucosyl moiety confers upon them unexpected and intriguing biological properties. After the isolation of the first members of this family by Natori et al. in 1993 [27] from the marine sponge *Agelas mauritianus*, the agelasphins were rapidly recognized as antitumor compounds with weak toxicity, which elicited a great interest in chemical and biological circles. Despite these antitumoral properties, the agelasphins did not exhibit cytotoxicity against B16 melanoma cells at 20 $\mu\text{g}/\text{mL}$, which led Natori, Koezuka, et al. [28] to undertake further biological studies for a rational explanation of these intriguing properties. These studies revealed that these compounds, for example agelasphin-11 (28), were capable of stimulating the immune system via activation of NK cells, which explained not only their potent antitumor activity but also their immunostimulatory property. These outstanding biological findings encouraged the Koezuka's group to achieve an extensive structure–activity relationship (SAR) study by preparation of a library of their analogues and subsequent antitumor activity evaluation from which the well-known analogue KRN7000 (32) was discovered [29]. At a molecular level, the activation of the immune system exerted by the agelasphins occurs because these compounds are potent ligands of the MHC class I-like CD1d protein, present on the surface of the antigen presenting cells (APCs), and, as a

consequence of this potent interaction, an overwhelming response by the immune system is triggered. Thus, the invariant natural killer T cells (iNKT cells) are initially activated by producing high levels of cytokines, which, in turn, activate other antitumor effector cells, resulting in a strong immunological response by the organism against tumor cells. These important findings rapidly propelled KRN7000 (32) as a novel and promising anticancer agent, which recently entered into phase I clinical trials against various types of cancers [30]. As a consequence of its intriguing biological properties, KRN7000 has elicited widespread interest and excitement in both the biological and chemical fields. Indeed, an indication of this great interest is a flurry of activity directed toward the synthesis of a plethora of analogues for SAR studies [31,32]. Related to the agelasphins, Mangoni's group [33] has recently identified a disaccharide derivative, named damicoside (33), from the marine sponge *Axinella damicornis*. This glycolipid represents the first disaccharide, structurally related to that of agelasphins, and with an immunostimulatory activity similar to the agelasphins, allowing the completion of the structure–activity relationship study of this fascinating class of compounds.

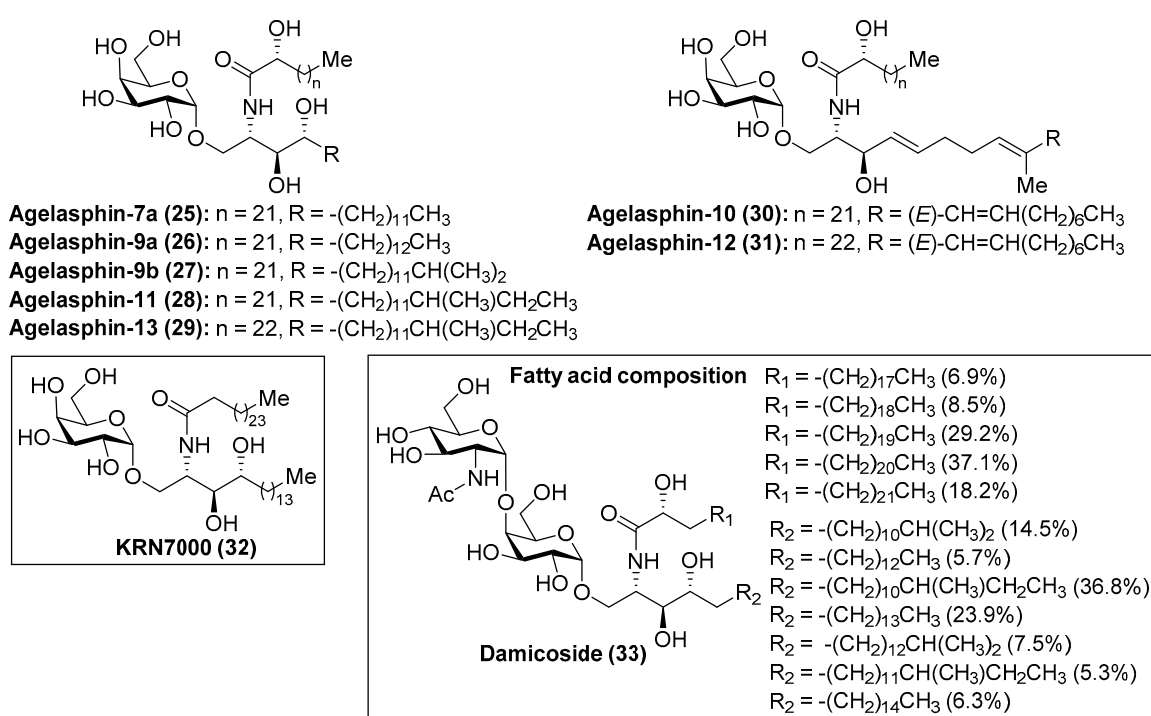
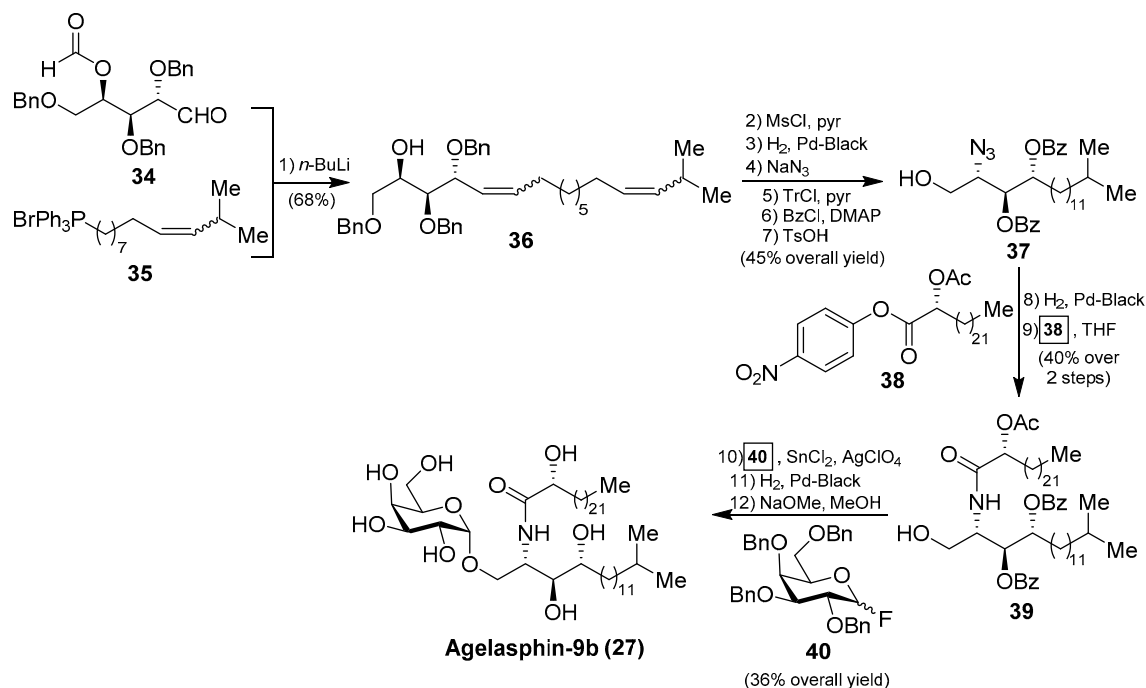


Figure 3. Structures of the agelasphins (25–31), KRN7000 (32), and damicoside (33).

In order to confirm the structures of the agelasphins, Natori, together with Akimoto et al. [34], achieved the first total synthesis of an agelasphin member, agelasphin-9b (27). Accordingly, the construction of the phytosphingosine fragment commenced with the Wittig reaction of aldehyde 34 with phosphonium salt 35 to give a mixture of isomeric alcohols 36 in 68% yield. The alcohol 36 was then converted into the azide 37 in six steps in 45% overall yield. Subsequent reduction of the azide and acetylation of the corresponding amine with *p*-nitrophenyl ester 38 afforded a protected ceramide 39 in 40% overall yield. Reaction of 39 with galactosyl fluoride 40, under Mukaiyama's glycosylation conditions, gave the corresponding α -galactoside in 36% yield, which was finally transformed into agelasphin-9b (27) after a deprotection of the protecting groups (Scheme 2). This synthesis was important not only because the authors were able to confirm the structures of these natural products, but also because the strategy for the future construction of these molecules was established and extended to the synthesis of other agelasphins and their analogues, such as KRN7000 (32) [18,19].



Scheme 2. Total synthesis of agelasphin-9b (27).

Axidjiferosides

Barnathan et al. [35] described the isolation of axidjiferosides A–C (41–43) (Figure 4) from the marine sponge *Axinyssa djiferi*, collected from mangrove tree roots in Senegal. Interestingly, the structure of these compounds contained the unusual Δ^6 -phytosphingosine and also the unusual β -configuration of the galactopyranosyl unit. These compounds showed significant antimalarial activity, with an IC₅₀ of $0.53 \pm 0.2 \mu\text{M}$ against a chloroquine-resistant strain of *Plasmodium falciparum*. In addition, the axidjiferosides also showed antiplasmodial activity, with low cytotoxicity against various human cancer cell lines, and no significant antitrypanosomal and antileishmanial activities. In contrast to the α -galactosylceramide derivatives, such as the agelasphins, which displayed immunostimulating properties, the antimalarial activity exhibited by the axidjiferosides was ascribed by the authors to the β anomeric configuration present in these natural products.

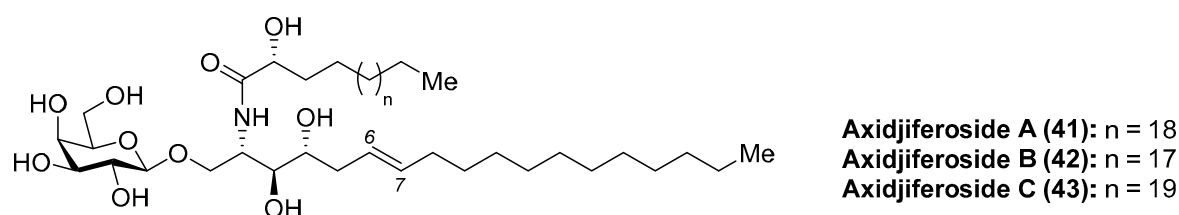


Figure 4. Structures of the axidjiferosides (41–43).

Cerebrosides CE

Cerebrosides CE (44–48) (Figure 5) were isolated, together with ganglioside CG-1 (See Section Ganglioside CG-1), from the sea cucumber *Cucumaria echinata* [36]. These cerebrosides showed toxicity in a brine shrimp lethality assay with the rates of 11–27%. However, no further chemical and biological studies about these cerebrosides have been carried out so far.

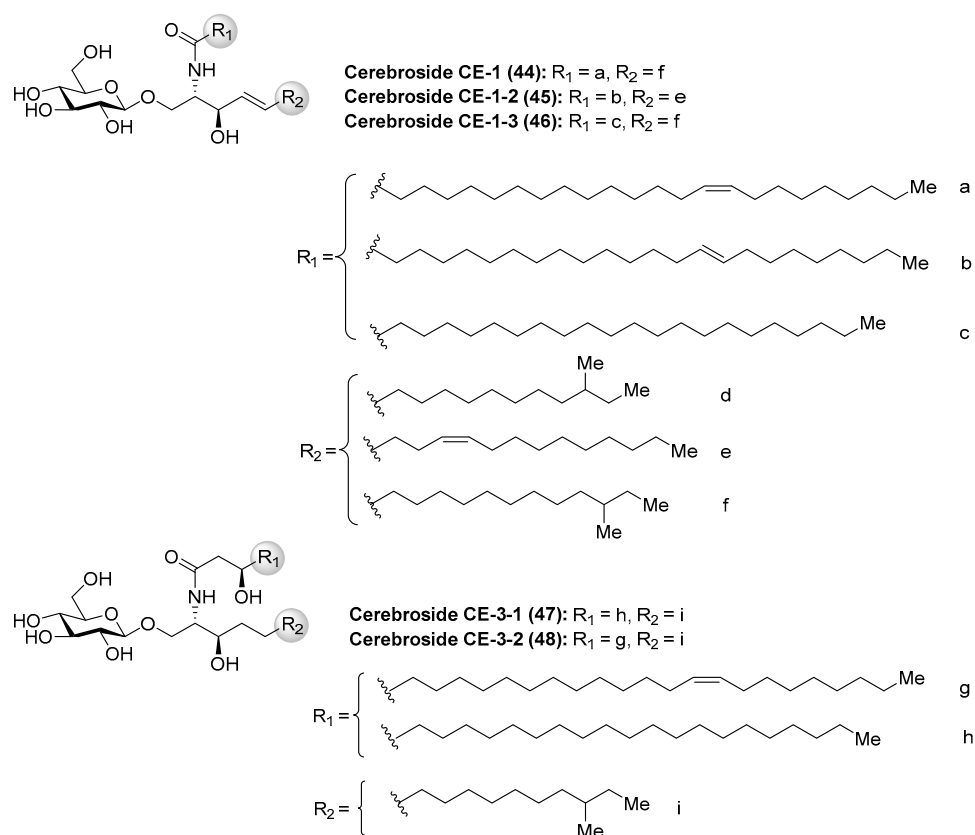


Figure 5. Structures of the cerebrosides CE (44–48).

Halicylindrosides

Within the family of cerebrosides of marine origin, the halicylindrosides (49–58) (Figure 6) were isolated and characterized by Fusetani's group in 1995 from the marine sponge *Halichondria cylindrata* [37]. These structural studies revealed that the halicylindrosides were a new family of phytosphingosine-containing cerebrosides, which promoted a great deal of expectation by virtue of their antifungal activity against *Mortierella remanniana* at 250 $\mu\text{g}/\text{disk}$ and cytotoxicity against P388 murine leukemia cells at 6.8 $\mu\text{g}/\text{mL}$, respectively.

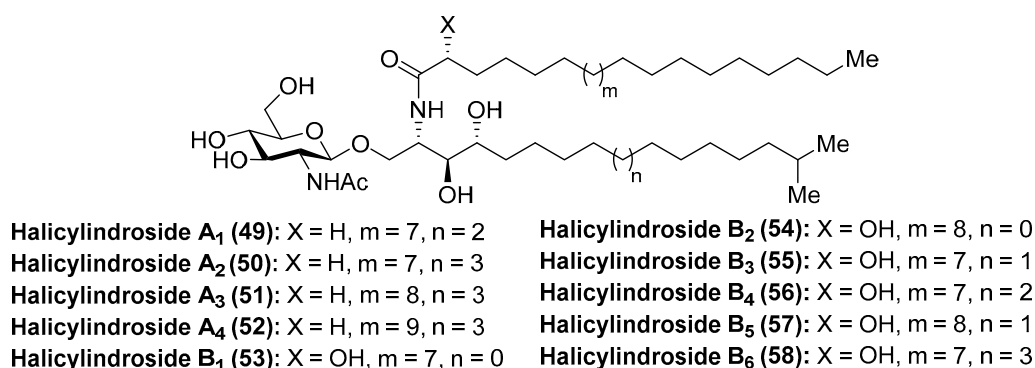
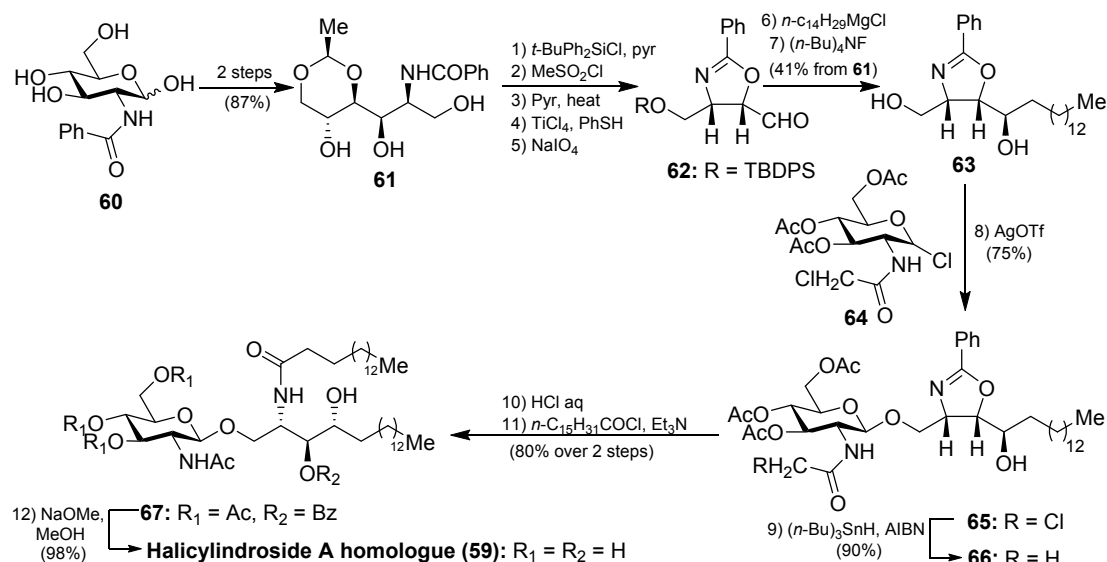


Figure 6. Structures of the halicylindrosides (49–58).

The synthesis of the halicylindroside A homologue 59 was carried out by Murakami et al. [38], paving the way for the synthesis of the natural congeners. Thus, 61, which was prepared from *N*-benzoyl-D-glucosamine 60 in 87% over two steps, was transformed into the oxazoline derivative 63 in seven steps in 41% overall yield, involving regioselective *O*-methanesulfonylation and diastereoselective

Grignard addition as key steps. The coupling between **63** and *N*-chloroacetyl glucosyl chloride **64**, which was chosen as a more efficient donor for the glycosylation reaction, was achieved by using silver trifluoromethanesulfonate as the promoter at 70 °C to obtain **65** in 75% yield. Reduction of the chloroacetyl **65** with *n*-Bu₃SnH afforded acetamide **66** in 90% yield. Subsequent acid-catalyzed ring opening of the oxazoline **66**, followed by reaction with palmitoyl chloride of the resulting amino alcohol provided **67**, which was finally transformed into halicylindroside A homologue (**59**) after a basic treatment (Scheme 3). In a similar manner, a homologue of halicylindroside B (**53**) was obtained by using (2*R*)-acetoxypalmitoyl imide.



Scheme 3. Total synthesis of halicylindroside A homologue **59**.

Phallusides

Phallusides (**68–71**) (Figure 7) were isolated from the Mediterranean ascidian *Phallusia fumigata* and from the starfishes *Allostichaster inaequalis* and *Cosmasterias lurida* [39] and their structures were elucidated by a combination of spectroscopic and chemical degradation studies. These studies revealed the presence of an unusual sphingoid base, which corresponded to the 2-amino-9-methyl-*D*-erythro-(4*E*,8*E*,10*E*)-octadeca-4,8,10-triene-1,3-diol. Prior to these findings, Karlsson et al. [40] had described isolation and structure elucidation of a closely related glycosphingolipid from the sea anemone *Metridium senite*, which was assigned as Sch II (**72**). Interestingly, this compound was also isolated from the basidiomycete *Schizophyllum commune* some years later [41].

The biological activity evaluation of phallusides 1–3 (**68–70**) revealed that these compounds possessed significant activity as antifungal agents against several phytopathogenic fungi (*Fusarium oxysporum* f. sp. *Niveum*, *F. solani* f. sp. *Cucurbitae*, *Pythium ultimum*, and *Alternaria solani*) [42].

The first synthetic explorations of these compounds were attempted by Kocienski et al. [43] leading to the total syntheses of phalluside-1 (**68**) and Sch II (**72**) via a Cu (I)-mediated 1,2-metallate rearrangement of a lithiated glycal as a key step for the stereoselective synthesis of the sphingoid base. In this direction, the authors envisioned the synthesis of the azidosphingatrienine **79** from iodoalkene **73** through two sequentially 1,2-metallate rearrangements involving cyanocuprate intermediates, derived from lithium derivatives **74** and **77**, to obtain the triene triol **78**. Conversion of **78** into the azide **79** proceeded in eight steps in 17% overall yield. The key Schmidt glycosylation reaction of the alcohol **79** with the donor **80**, using BF₃·OEt₂ as a promoter, afforded the glycoside **81** in a modest 34% yield. To complete the synthesis, a Staudinger reaction of the azide **81**, followed by an *N*-acetylation of the resulting amine with the acid **82** generated protected phalluside **83** in 63% yield over two steps. Final debenzoylation under basic conditions gave phalluside **68** in a 72% yield. For the synthesis of

Sch II (72), the authors employed the same synthetic strategy using the same lithium derivatives 74 and 77 but starting from a different iodoalkene (Scheme 4).

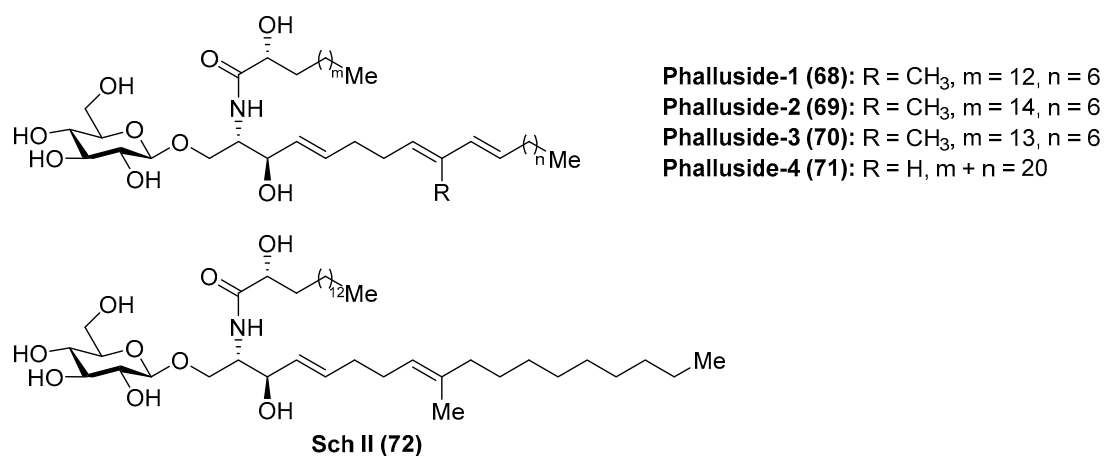
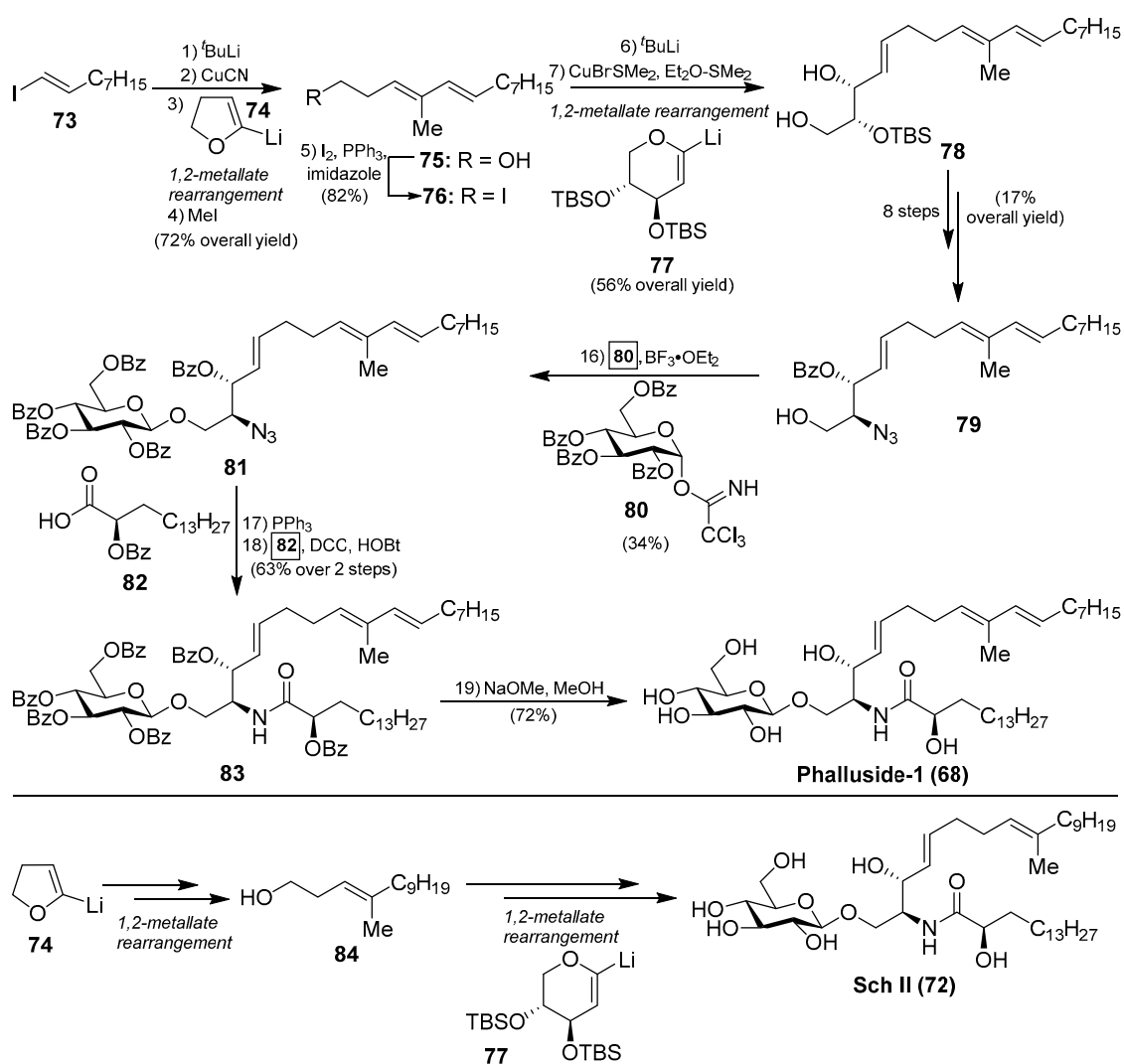


Figure 7. Structures of the phallusides (68–71) and Sch II (72).



Scheme 4. Total synthesis of phalluside-1 (68) and Sch II (72).

2.1.2. Diosylceramides

Amphiceramides

Amphiceramides A (85) and B (86) were isolated from the Caribbean sponge *Amphimedon compressa* by Mangoni et al. [44] (Figure 8). The structures of both glycolipids contain an unusual Δ^6 -phytosphingosine unit, which can be found in other secondary metabolites such as the aforementioned axidjiferosides A–C (41–43). In addition, amphiceramide A (85) contains an uncommon *N*-acetyl- β -glucosamine, which has never been found in any natural product. Amphiceramide B (86) was the first glycosphingolipid that possesses an allolactose [Gal(1 β →6)Glc] residue β -linked to the ceramide moiety.

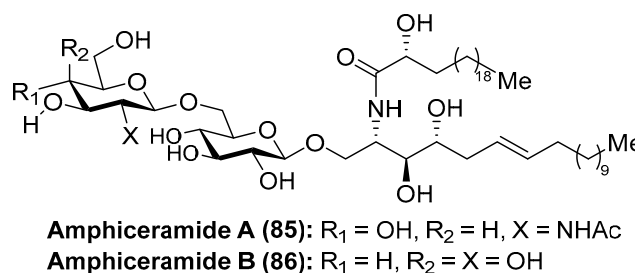


Figure 8. Structures of the amphiceramides A (85) and B (86).

Plakosides

Fattorusso et al. [45] described the isolation of plakosides (87–90) (Figure 9) from the marine sponge *Plakortis simplex*, which featured the presence of a cyclopropane ring in the lipidic chain and a 2-*O*-prenylation of the carbohydrate moiety. Interestingly, in contrast to the immunostimulating property of related glycosphingolipids, such as agelasphins, the plakosides exhibited potent immunosuppressive activity, with plakosides A (87) and B (88) as inhibitors of the proliferative response of lymph-node cells when T cells were stimulated with concavaline A in all doses tested (0.01–10 $\mu\text{g}/\text{mL}$). In addition, these natural products did not display cytotoxic property. This intriguing immunosuppressive activity was ascribed to the presence of the substituent on C-2 of the inner monosaccharide. Some years later, the same authors isolated two new related glycosphingolipids, plakosides C (89) and D (90), from another marine-sponge species, *Ectyoplasia ferox* [46]. Further investigations led to the conclusion that the plakosides are in fact biosynthesized by sponge-associated bacterial symbionts and not from the sponge itself [46].

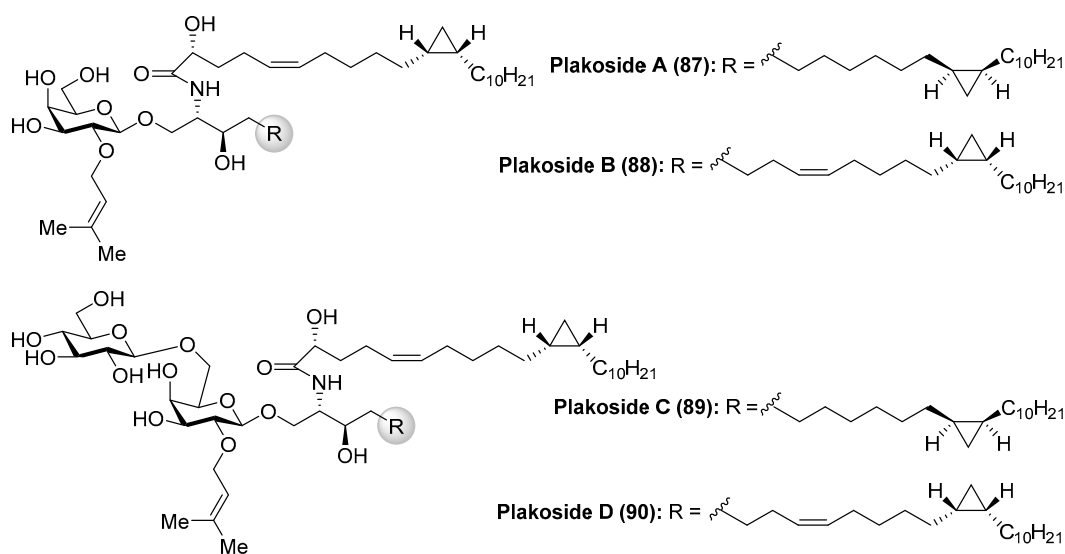
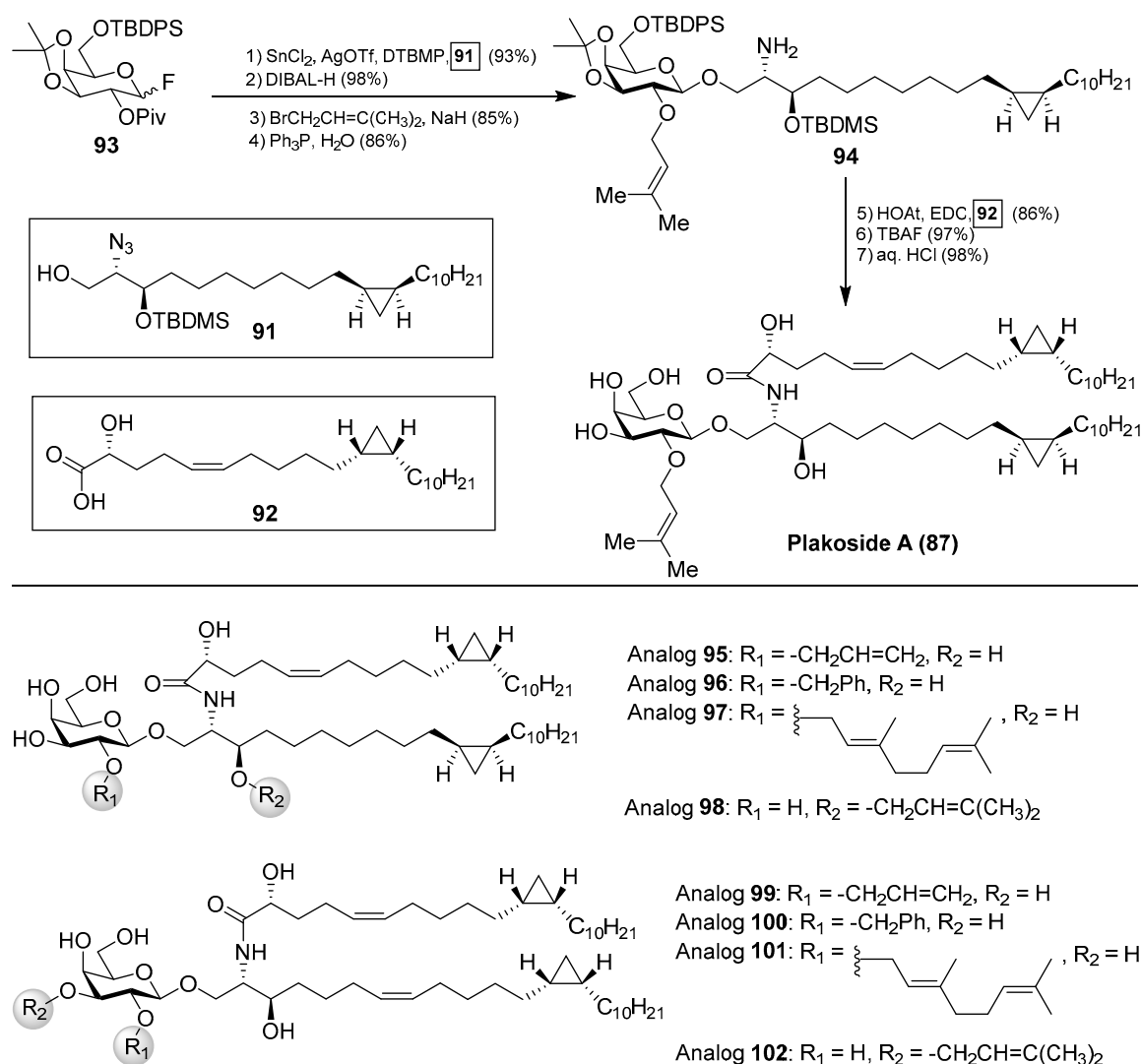


Figure 9. Structures of plakosides 87–90.

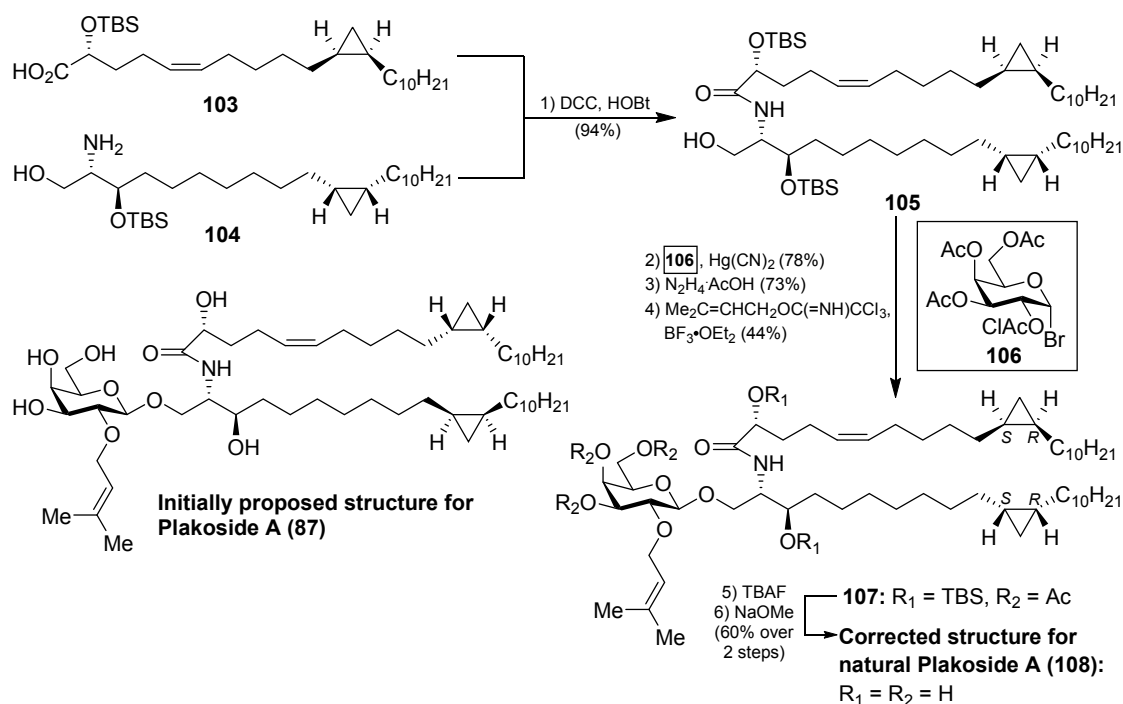
The interesting molecular structures of the plakosides, combined with their intriguing immunosuppressive activity, have prompted their total synthesis to further investigate their biological properties. Thus, Nicolaou et al. [47] reported an efficient and stereoselective total synthesis of these glycosphingolipids, which provided not only sufficient amounts of the compounds for further biological studies, but also some analogues that allowed the determination of key structural factors for the immunosuppressive activity through a structure–activity-relationship study. Having prepared the cyclopropane-containing derivatives **91** and **92** in stereoselective manner, a first assembly of **91** with the corresponding galactosyl fluoride **93** was achieved in an excellent 93% yield in a stereoselective glycosylation reaction mediated by $\text{SnCl}_2/\text{AgOTf}$. The introduction of the prenyl group was then carried out in two steps to obtain the key intermediate **94**, which was prepared for the final steps (Scheme 5). These steps consisted of an amide coupling between **94** and the fatty acid **92**, followed by a global protecting group deprotection in two additional steps.



Scheme 5. Total syntheses of plakoside A (**87**) and its analogues **95**–**102**.

In a similar manner, the synthesis of plakoside B (**88**) was efficiently accomplished by using the suitable sphingosine derivative. This synthetic strategy was extended to the preparation of a small collection of plakoside analogues **95**–**102**, in which the effect of the prenyl group upon the biological activities was analysed by modification of this group. In fact, with all these plakosides in hand, their biological activities were evaluated in three in vitro assays (the mixed-lymphocyte-reaction

proliferation (MLR) assay, the concanavalin A response assay, and the murine bone marrow cell proliferation assay). Surprisingly, the authors found that all these compounds (95–102), and the synthetic plakosides A (87) and B (88), displayed modest immunosuppressive activity compared to the reported activities for the natural compounds. Among them, analogue 95 was the most active in the series, albeit in a modest range, with an IC_{50} value of 7.1 μ M in the MLR proliferation assay. The discrepancy between the immunosuppressive activities of the synthetic plakosides and of the natural products reported in the literature could be explained by the work of Mori et al., who corrected the absolute configuration initially assigned for the plakosides [48,49]. These authors demonstrated, through their total synthesis described in Scheme 6, that the absolute configurations of the stereogenic carbons of the cyclopropane rings present in both lipidic chains, through compounds 103 and 104, were opposite to those initially proposed by the Fattorusso's group [50,51]. The incorrect configurations assigned for plakoside A (108) could explain the poor immunosuppressive activity exhibited by the synthetic plakosides A and B prepared by Nicolaou et al. which corresponded to the stereoisomers of the naturally occurring counterparts. It is interesting to point out that the structures of the synthetic plakosides obtained by Nicolaou's group possessed the same spectroscopic data and optical rotations as those from naturally occurring plakosides. This fact led them to conclude that the synthetic plakosides were the same as the naturally occurring counterparts.



Scheme 6. Total synthesis of the corrected structure of plakoside A (108).

Terpiosides

Terpioside A (109) and B (110) (Figure 10) were isolated from the marine sponge *Terpios* sp. by Costantino et al. [52] and represent the first glycosphingolipids reported from sponges of the genus *Terpios*. Later, Cutignano et al. [53] reported the isolation of the terpiosides from the Antarctic sponge *Lyssodendoryx flabellata*. The structure of terpioside A (109) was secured by a combination of extensive spectroscopic analysis, as well as chemical degradation studies, revealing the presence of a unique sugar moiety, comprised of an α -fucufuranoside, linked to the 3-position of a β -glucopyranoside, which is the sugar residue linked to the ceramide. Thus, terpioside A (109) represents the first natural glycosphingolipid that contains an L-fucose in a furanose form. On the other hand, terpioside B (110) contains a pentasaccharide chain, which possesses two terminal α -L-fucufuranose units. The biological

activity evaluation of terpioside B (**110**) led to the discovery that this compound was capable of inhibiting LPS-induced NO release, displaying higher activity than simpler glycosphingolipids, such as terpioside A (**109**) and monoglucosylceramide [54].

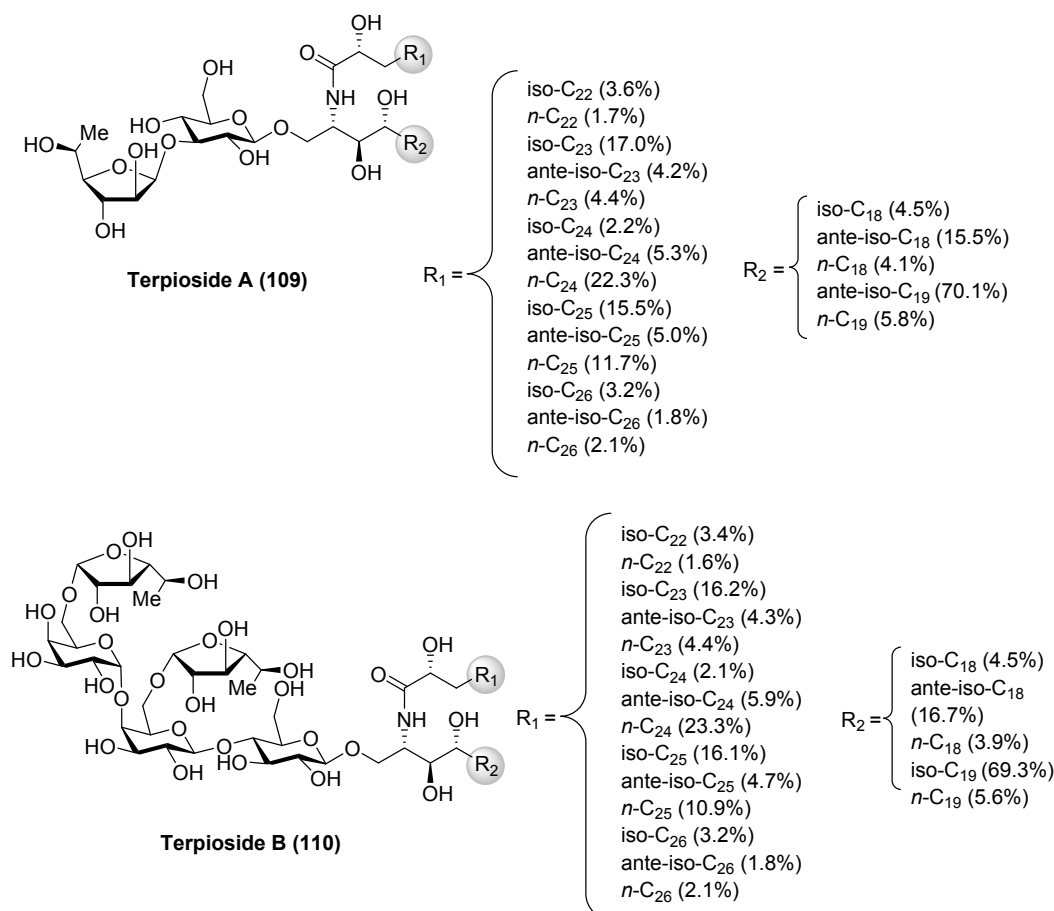


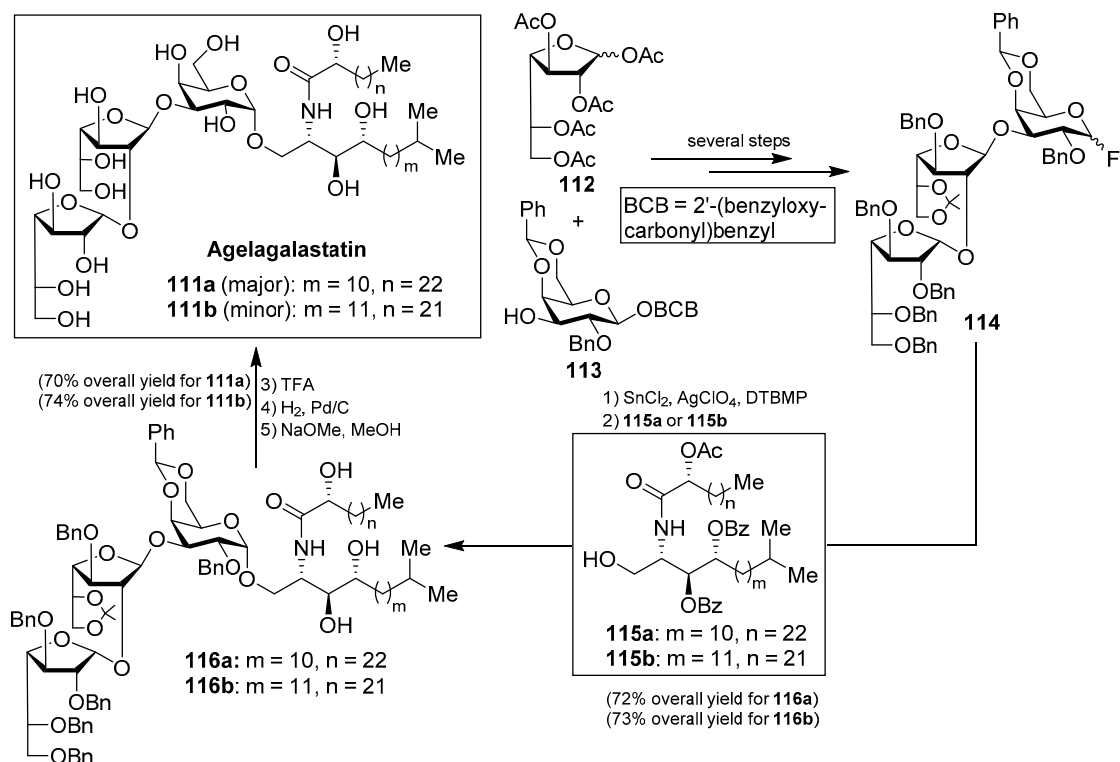
Figure 10. Structures of terpiosides A (**109**) and B (**110**).

2.1.3. Neutral Glycosphingolipids with Oligosaccharide Chains

Agelagalastatin

Agelagalastatin (**111**) was isolated from the Western-Pacific marine sponge *Agelas* sp. as a mixture of two isomers (**111a** and **111b**) through a human cancer cell line bioassay carried out by Pettit et al. [55]. Agelagalastatin showed significant in vitro antitumoral activity against various human cancer cell lines, including lung NCI-H460, brain SF-295, renal A498, colon KM20L2, melanoma SK-MEL-5, and the ovarian OVCAR-3, with a range of GI₅₀ values from 0.77 µg/mL to 2.8 µg/mL. Structurally, this natural product contains an unprecedented digalactofuranosyl unit, which has not been found before in a natural product.

This intriguing structure, in conjunction with its antitumor activity, drew the attention of many synthetic chemists and, as a consequence, a total synthesis of agelagalastatin (**111**) was reported by Kim et al. [56] based on an α -selective glycosylation of the ceramide **115a** or **115b** with the trisaccharide fluoride **114**, prepared from monosaccharide derivatives **112** and **113** after several steps. This key glycosylation reaction, performed in the presence of SnCl₂, AgClO₄, and DTBMP, furnished **116a** and **116b** in 72 and 73% yields, respectively. Completion of the synthesis involved the final deprotection of the benzyl, *O*-acetyl, and *O*-benzoyl groups in 70 and 74% overall yields to obtain agelagalastatins **111a** and **111b**, respectively (Scheme 7).



Scheme 7. Structures of agelagalastatins (**111a** and **111b**) and their total synthesis.

Clarhammosides

The clarhammosides **117a_xb_y** (Figure 11) were isolated as an inseparable mixture of different members from the marine sponge *Agelas clathrodes* by Costantino et al. [57]. The combination of 2D NMR and CD spectroscopic techniques allowed the structural determination of this complex glycosphingolipid mixture. Clarhammosides are the first α -galactoglycosphingolipids with a L-rhamnose unit in the sugar head. In addition, the sequential two 1,2-*cis*- α -D-galactopyranosidic linkages are also rare in nature.

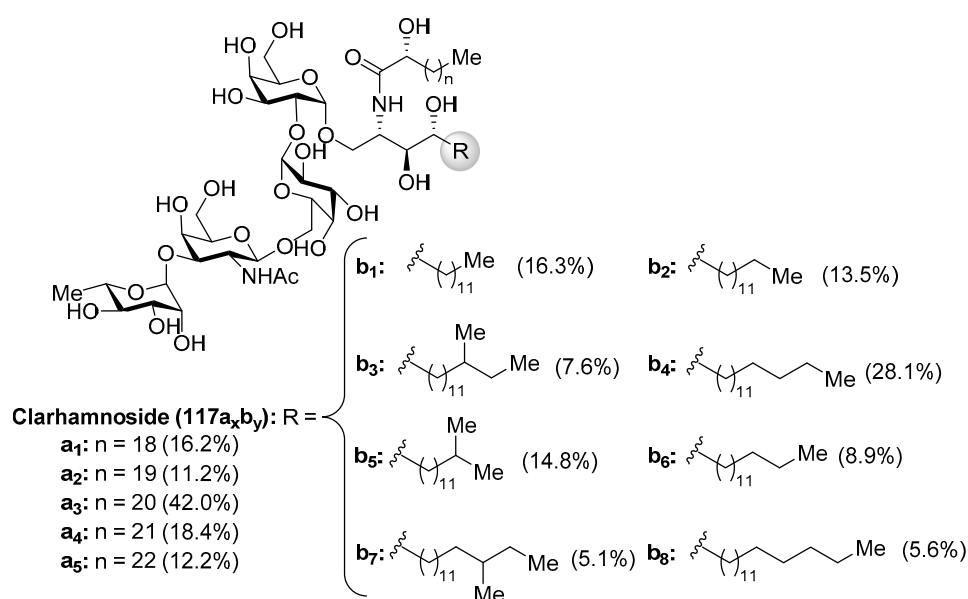
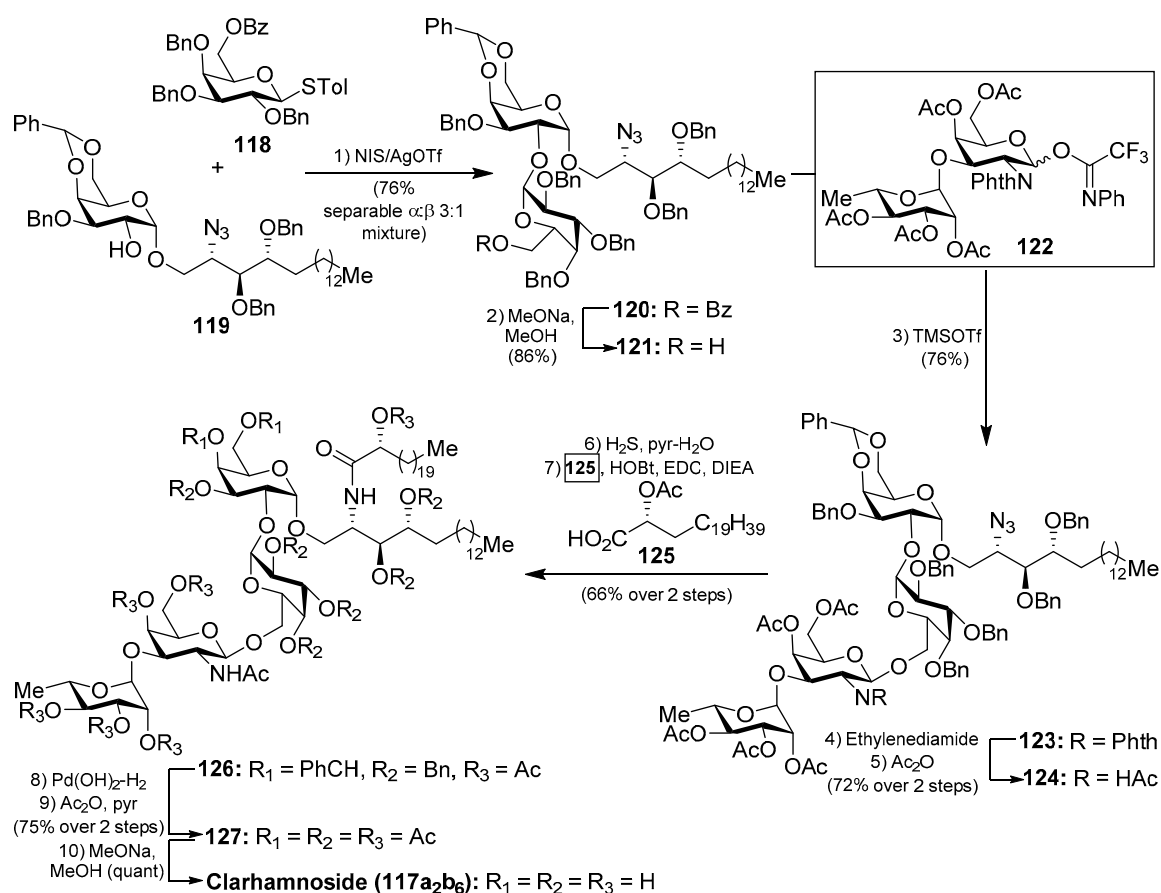


Figure 11. Structures of the clarhammosides (**117a_xb_y**).

The first total synthesis of a clarhamnoside member (**117a₂b₆**) was carried out by Li et al. [58]. According to this work, the glycosylation reaction between **118** and **119**, promoted by the NIS/AgOTf system, afforded a 3:1 α : β separable mixture of the disaccharide **120** in 76% yield. Removal of the benzoyl group in **120** gave the disaccharide **121** in 86% yield, which was used as an acceptor for the next glycosylation reaction. In this reaction, **121** was reacted with donor trifluoroacetimidate **122** employing TMSOTf and 4 Å MS at -20 °C to provide the β -glycoside **123** in 76% yield. Conversion of the *N*-phthalimido group into an acetamido group by sequential treatment with ethylenediamine and Ac₂O afforded **124** in 72% yield in two steps. The reduction of **124**, employing H₂S in pyridine/water, was prior to the corresponding coupling of the resulting amine with α -hydroxy acid **125** to provide **126** in 66% yield in two steps. Final hydrogenolysis afforded the corresponding tetrasaccharide intermediate, which was acetylated to obtain clarhamnoside peracetate **127**. Removal of the acetyl groups furnished clarhamnoside **117a₂b₆** in a moderately good yield (Scheme 8).



Scheme 8. Total synthesis of clarhamnoside **117a₂b₆**.

Vespariosides

After the isolation of vesparioside A (**128**) by Mangoni et al. [59] from *Sphaciospongia vesparia* in 2005, the same authors in 2008 reported the isolation and structural elucidation of a unique furanose-rich glycosphingolipid that was named vesparioside B (**129**) (Figure 12) [60]. Through an exhaustive spectroscopic analysis, supported by theoretical and degradation studies, the authors were able to establish the absolute configuration of this stunning molecule, which was unambiguously confirmed through the total synthesis carried out by Yang et al. in 2016 [61]. In this total synthesis, after an extensive exploration of various strategies, the authors decided to construct initially the glycosphingolipid derivative **133**, via a glycosylation reaction of the donor trichloroacetimidate **131**, prepared from the disaccharide **130**, and the phytosphingosine acceptor **132**.

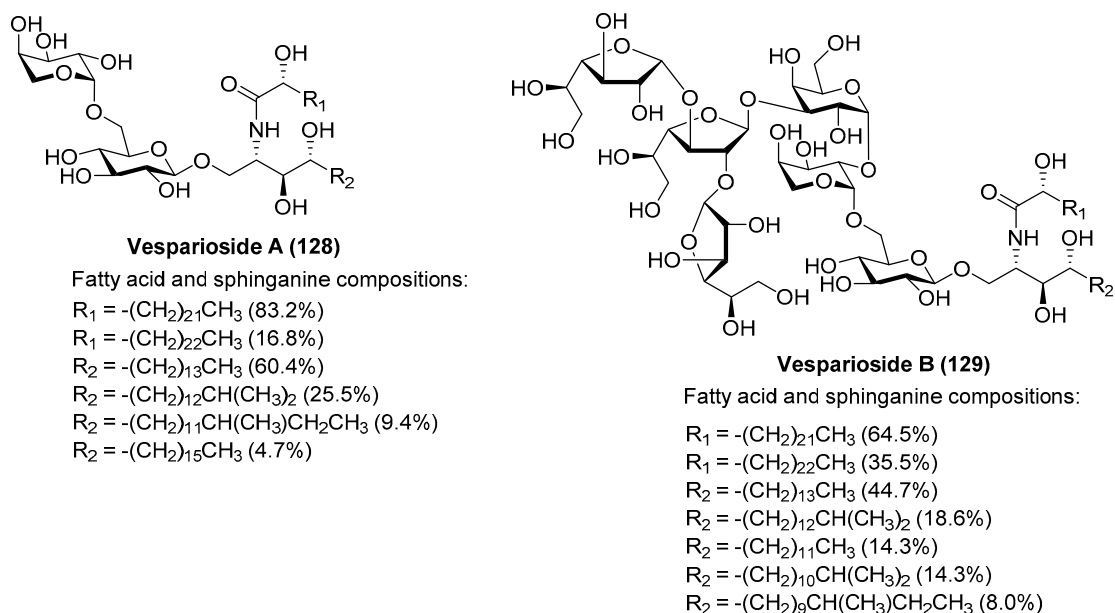
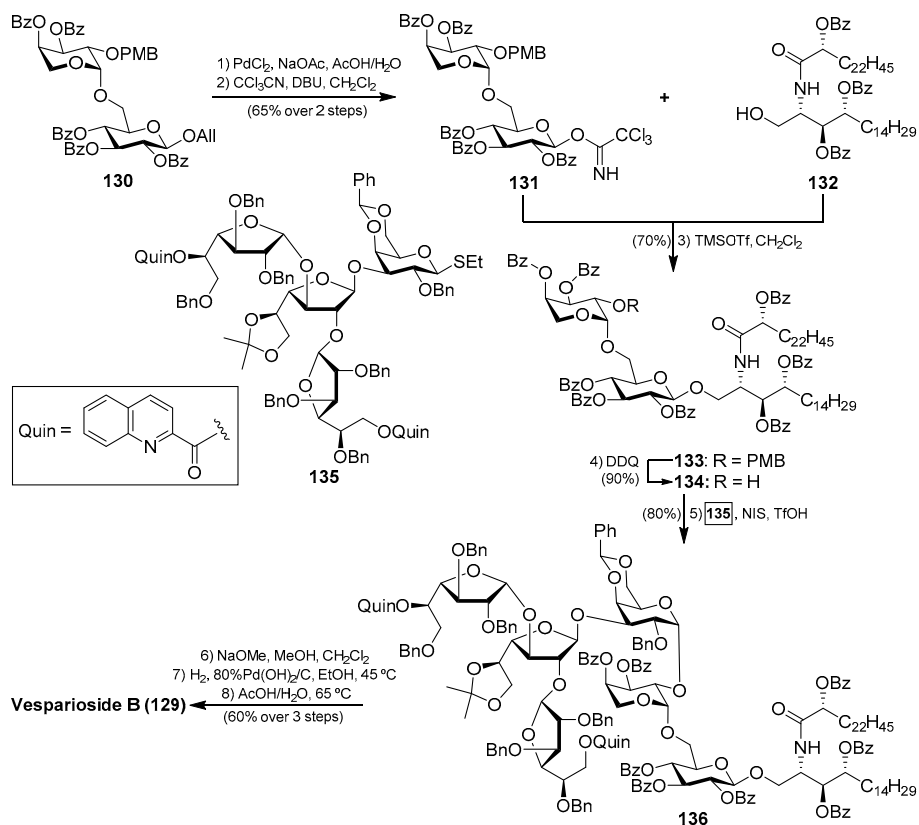


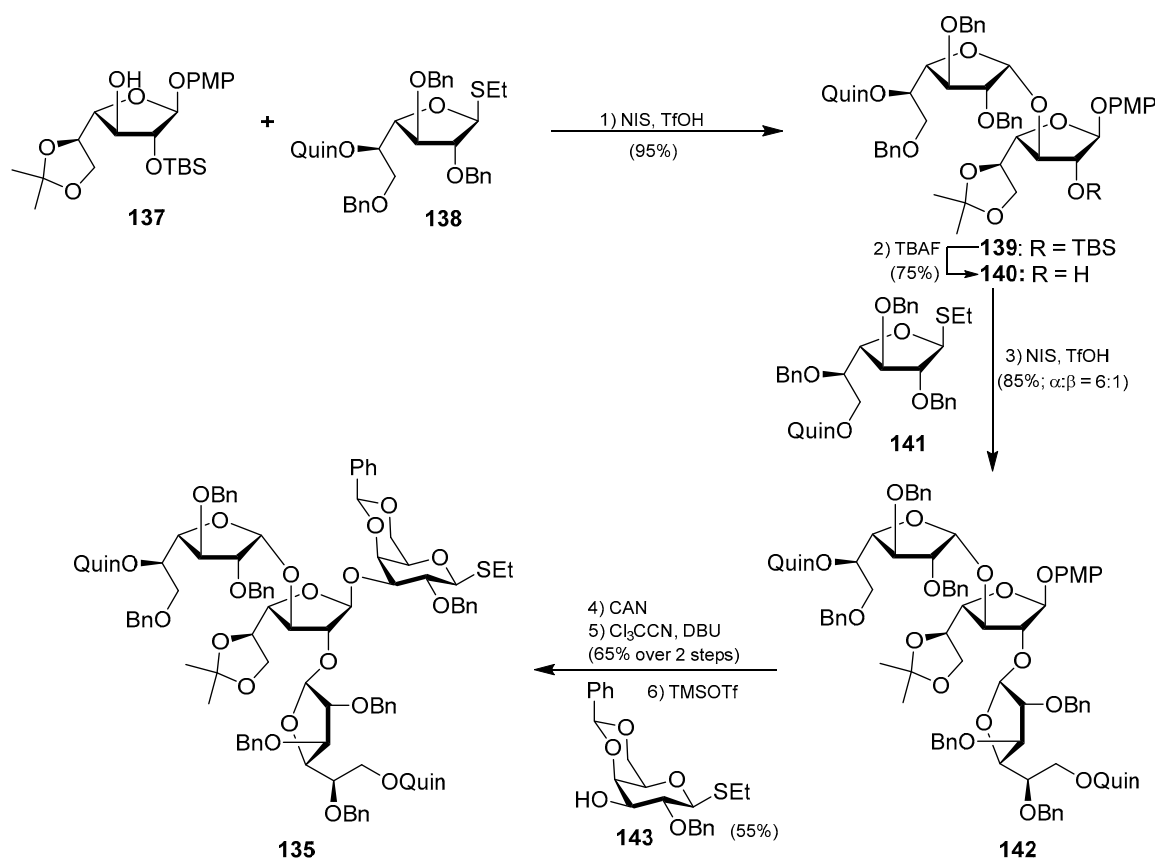
Figure 12. Structures of vespariosides A (128) and B (129).

The resulting glycosphingolipid **133** was then prepared for assembly with the tetrasaccharide fragment in the form of thioglycoside **135**. To this end, the removal of the PMB group of **133** by treatment with DDQ provided the alcohol **134**, which was reacted with the donor **135** under the action of the promoter NIS/TfOH. The resulting complex glycosphingolipid **136**, obtained in excellent yield and stereoselectively, was then transformed into natural vesparioside B (**129**) after removal of all the protecting groups in a 60% overall yield in three steps (Scheme 9).



Scheme 9. Total synthesis of vesparioside B (129).

Interestingly, the preparation of the tetrasaccharide **135** required the stereoselective synthesis of 1,2-*cis*- α -galactofuranoside units, for which some methods have been recently developed. In this case, Yang's group has developed an elegant methodology based on a hydrogen-bond-mediated aglycone delivery (HAD) strategy for which they employed a 2-quinolinecarbonyl (Quin) functionality. This group, acting as an H-bond acceptor and incorporated in the α -face of the galactofuranoside ring, displays a strong α -stereocontrol effect in glycosylation reactions when furanosyl thioglycoside donors are employed in reactions with various acceptors. The application of this strategy in the synthesis of tetrasaccharide **135** commenced with the glycosylation reaction of the readily available galactofuranosyl acceptor **137** and the donor **138**, which was armed with the Quin group at the 5-position. This reaction delivered exclusively the α -disaccharide **139** in an excellent 95% yield, proving the reliability and validity of this strategy. The assembly of the third galactofuranosyl derivative proved more challenging, as the use of the 5-*O*-Quin derivative **138** as a donor did not work, resulting in recovered starting materials. Fortunately, when the 6-*O*-Quin derivative **141** was used instead, the reaction afforded the expected trisaccharide **142** as a 6:1 α/β separable mixture in an 85% combined yield. Finally, the fourth glycoside was incorporated through a glycosylation reaction with the trichloroacetamidate derivative of **142** and the thioglycoside acceptor **143** to deliver tetrasaccharide **135** in a 55% yield as a single β -anomer (Scheme 10). This total synthesis not only confirmed the molecular structure of this fascinating glycosphingolipid, but also, more importantly, provided the opportunity for further biological exploration of this class of compounds, which was not achievable due to the scarcity of material from natural sources. These biological studies with synthetic vespariosides are currently in progress.



Scheme 10. Synthesis of the tetrasaccharide unit **135** of vespariosides.

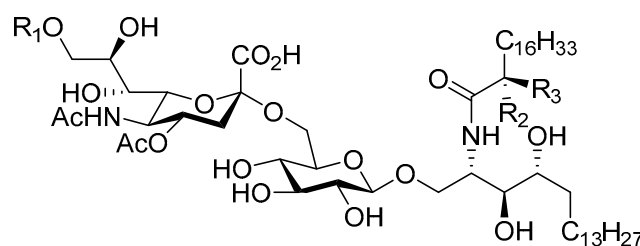
2.2. Acidic Glycosphingolipids

2.2.1. Gangliosides

Structurally characterized by the presence of one or more sialic acid units, the gangliosides of a marine origin are almost exclusively found in echinoderms, mainly from urchins. In other marine invertebrates, it has been demonstrated that the sialic acid unit is replaced by a glucuronic acid residue. Despite the limited distribution of this class of glycosphingolipids in the marine realm, a huge number of natural products belonging to this category has been discovered. As a consequence, we have selected for this section the most biologically relevant gangliosides.

Ganglioside Hp-s1

Ganglioside Hp-s1 (**144**) was isolated from the ovary of the sea urchin *Diadema setosum* or from the sperm of the sea urchin *Hemicentrotus pulcherrimus* [62]. This compound showed an interesting neurotogenic activity towards the rat pheochromocytoma PC-12 cell line in the presence of nerve growth factor (NGF) and, when compared to ganglioside GM-1 (25.4%), its effect was better (34.0%). Together with ganglioside Hp-s1, ganglioside DSG-A (**145**) (Figure 13), isolated also from *D. setosum*, displayed similar neurotogenic activity, which can be useful for the treatment of neurodegenerative diseases [63].



Ganglioside Hp-s1 (144): $R_1 = R_2 = R_3 = H$

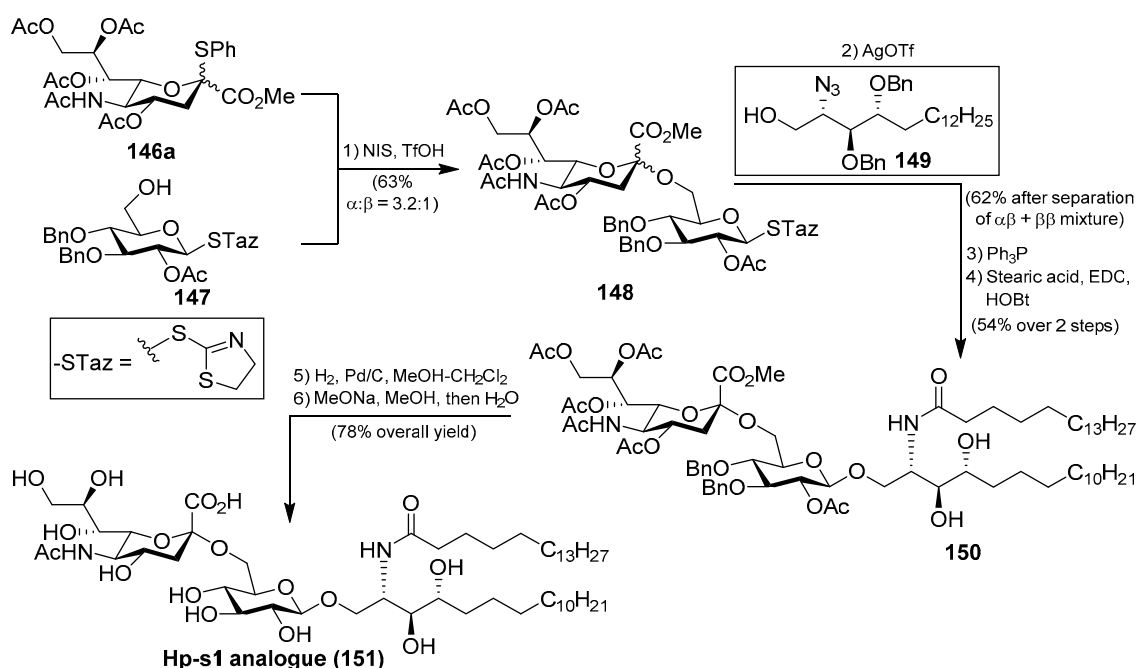
Ganglioside DSG-A (145): $R_1 = Me, R_2 = H, R_3 = OH$

Figure 13. Structures of ganglioside Hp-s1 (**144**) and DSG-A (**145**).

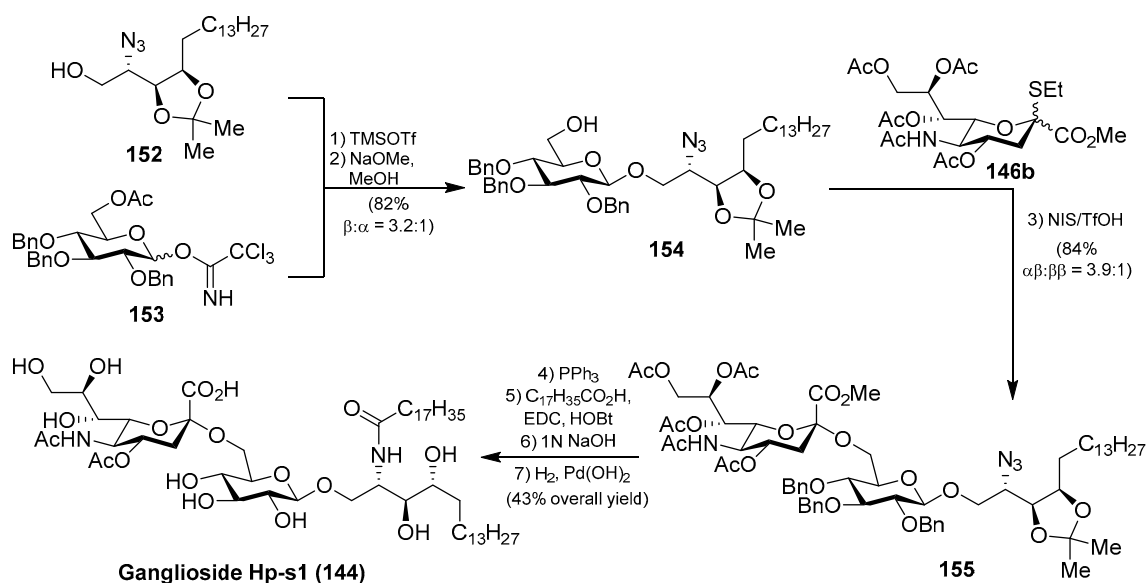
Several syntheses of these natural products have been reported [64]. Initial synthetic efforts were carried out by Tsai et al. [65], who prepared the ganglioside Hp-s1 analogue **151**. The synthesis was accomplished by a sequence of chemoselective glycosylation reactions as key steps. Thus, the disaccharide **148** was obtained by the sialylation of the acceptor **147** with the sialyl donor **146a**, mediated by NIS/TfOH as a promoter at $-30\text{ }^\circ\text{C}$ in the presence of 4 \AA molecular sieves, in 63% yield as an inseparable $\alpha:\beta$ 3.2:1 mixture. The next glycosylation reaction involved the resulting disaccharide **148** with the azidosphingosine derivative **149** in the presence of AgOTf and 3 \AA molecular sieves at room temperature to obtain the resulting disaccharide derivative as a separable mixture of $\alpha\beta$ and $\beta\beta$ anomers in 62% combined yield. From the corresponding $\alpha\beta$ anomer, a Staudinger reaction was followed by an amidation process to obtain **150** in 54% yield in two steps. Final debenzoylation and deacetylation reactions afforded the ganglioside Hp-s1 analogue **151** in 78% overall yield (Scheme 11). This analogue exhibited neurogenetic activity towards the human neuroblastoma cell line SH-SY5Y without the presence of NGF.

A different synthetic strategy was used in the first total synthesis of ganglioside Hp-s1 (**144**), achieved by Luo et al. [64], based on two key glycosylation reactions. According to this synthetic strategy, after an extensive optimization of the glycosylation reactions, the authors found that the first reaction of phytosphingosine **152** with benzyl protected imidate **153**, using TMSOTf as a promoter at $-30\text{ }^\circ\text{C}$ to room temperature, followed by a deacetylation step, afforded **154** in 82% ($\beta:\alpha$ 3.2:1) yield. The second glycosylation reaction involved the glycosyl acceptor **154** and the sialyl donor **146b**, mediated by NIS/TfOH as a promoter, to obtain **155** in 84% yield ($\alpha\beta:\beta\beta$ 3.9:1). From **155**, the conversion of the azide group into the corresponding amine, through a Staudinger reaction,

followed by amide formation, and final deprotection of acetyl, benzyl, and acetonide groups delivered ganglioside Hp-s1 (**144**) in 43% overall yield from **155** (Scheme 12).



Scheme 11. Total synthesis of Hp-s1 analogue **151**.



Scheme 12. Total synthesis of ganglioside Hp-s1 (**144**).

The same authors carried out an SAR study involving the synthesis of six Hp-s1 analogues (**156**–**161**) by replacing the glucosyl unit of Hp-s1 with α -glucose (**157**), α - and β -galactose (**158** and **159**), and α - and β -mannose (**160** and **161**), including the simple cerebroside **156** [66]. After the biological evaluation, the authors found that the C-2 hydroxyl group of the glucosyl unit played a crucial role in the stimulation of neurite outgrowth of SH-SY5Y cells. In addition, it was found that analogue **158** activated NKT cells, although it was inactive on neurite outgrowth of SH-SY5Y cells (Figure 14).

Based on these synthetic studies, the same authors developed an efficient method for α -selective sialylation based on a pre-activated 5-*N*,4-*O*-carbamate thiosialoside donor using *p*-TolSCI/AgOTf as promoters which was extended to the synthesis of gangliosides Hp-s1 and DSG-A [67]. Tsai et al. also achieved the total synthesis of ganglioside DSG-A (145) through a chemoselective glycosylation reaction in a [1 + 1 + 2] synthetic strategy for the assembly of the four fragments of this molecule [68].

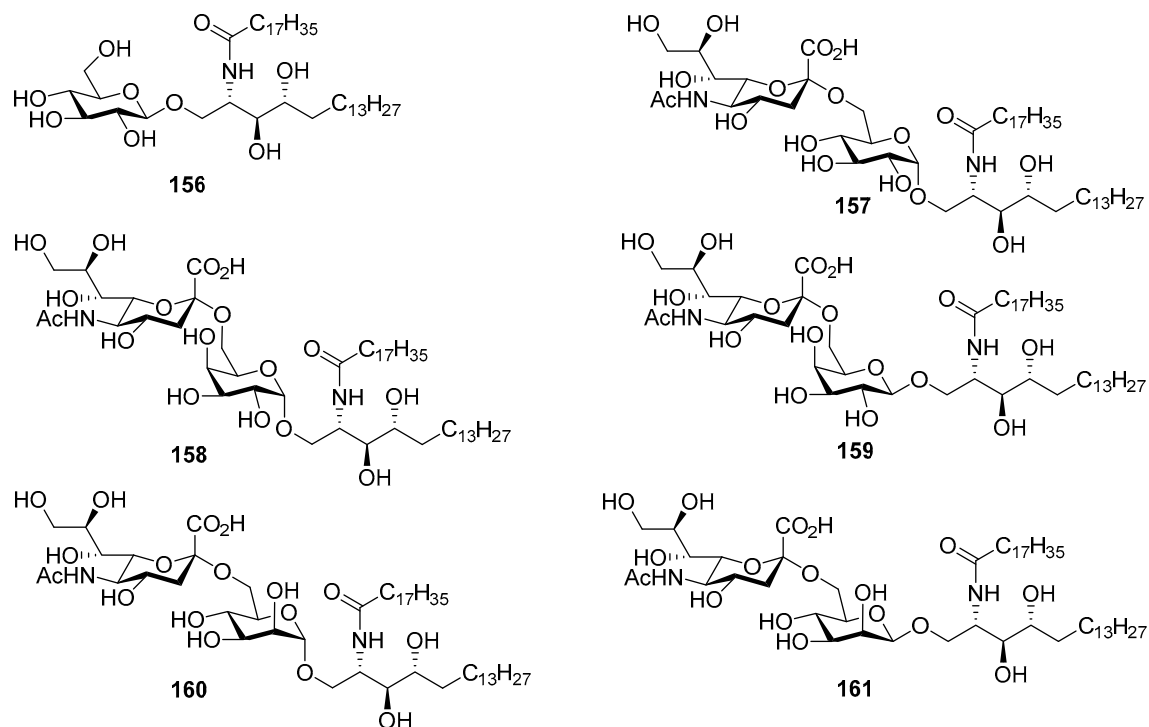


Figure 14. Gangliosides Hp-s1 analogues 156–161.

Gangliosides HLG

Gangliosides HLG-1 (162), HLG-2 (163) and HLG-3 (164) (Figure 15) were isolated from the sea cucumber *Holothuria leucospilota* by Higuchi et al. [69]. These compounds showed similar neuritogenic activity toward the rat pheochromocytoma cell line, PC-12 cell, in the presence of NGF as other marine-derived gangliosides. Structurally, these gangliosides contain a unique $\alpha(2,4)$ linkage between sialic acids, which captured the attention of many synthetic chemists.

The first total synthesis of ganglioside HLG-2 (163) was carried out by Kiso et al. [70]. To construct the glycan unit, sialylation at C-4 hydroxyl group of the sialic acid residue was achieved using the 1,5-lactam-sialyl unit **166** as a novel glycosyl acceptor and readily prepared from **165** by a basic treatment (refluxing NaOMe in MeOH) in 95% yield. The glycosylation reaction of **166** with Troc-sialyl donor **167** in the presence of NIS/TfOH took place exclusively at C-4 hydroxyl group in a stereoselective manner to give the trisaccharide **168** in 69% yield ($\alpha:\beta$ 60:9). To complete the synthesis, the next glycosylation reaction involved the donor **169**, obtained in eight steps from the trisaccharide **168**, and the ceramide acceptor **170** in the presence of TMSOTf as a promoter, to obtain the corresponding ganglioside in 49% yield, which was finally transformed into ganglioside HLG-2 (163) in a quantitative yield after a basic treatment (Scheme 13).

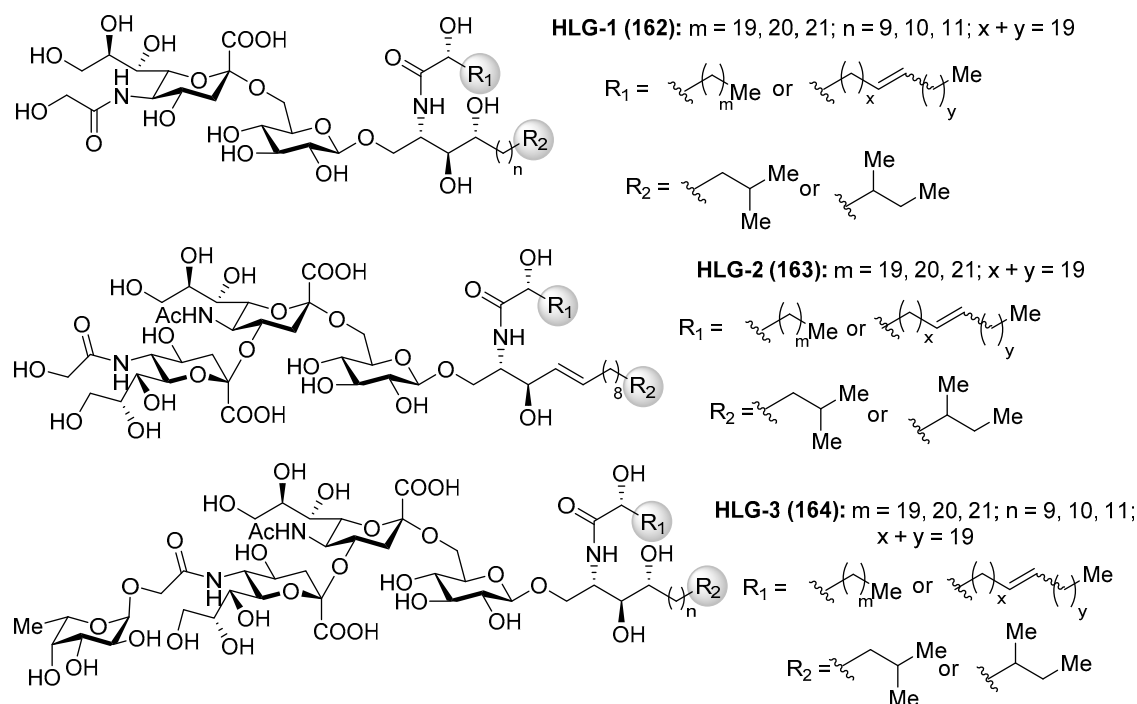
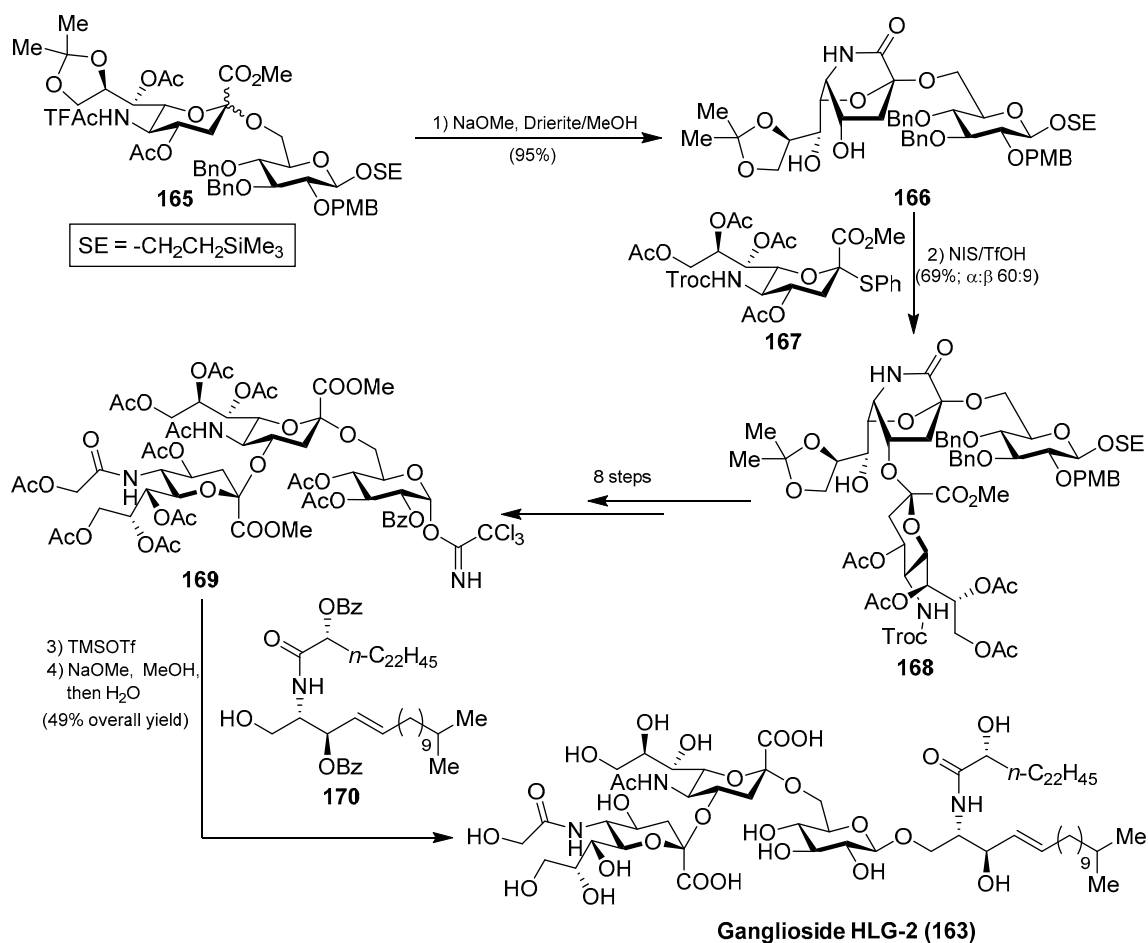
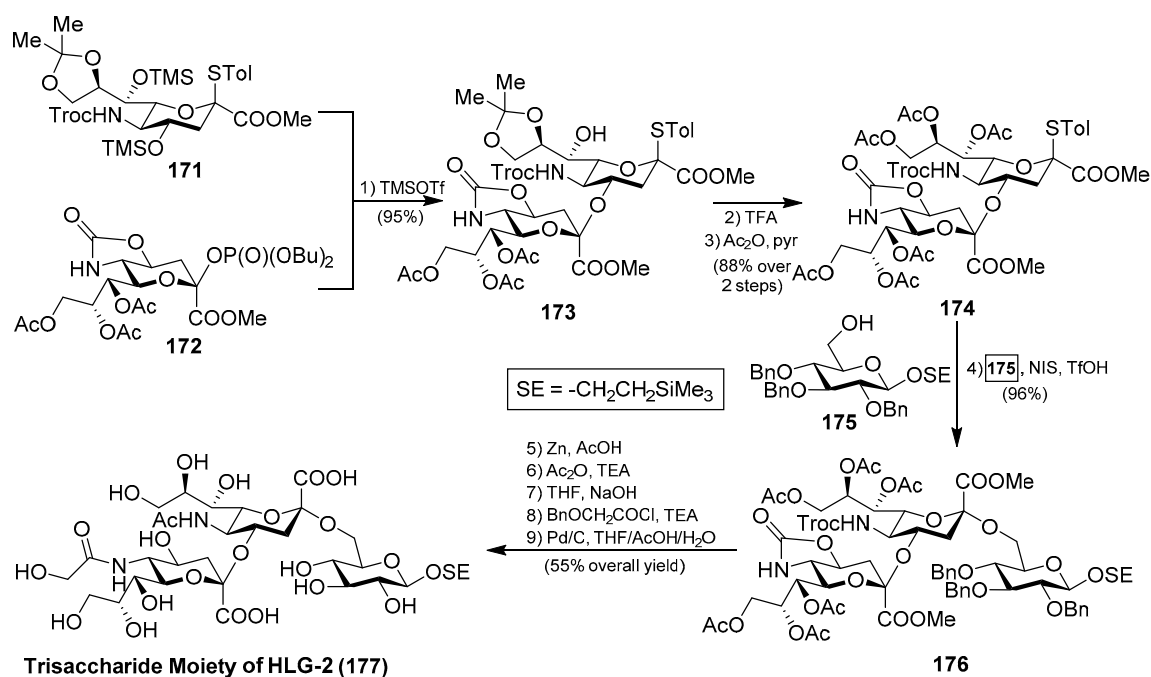


Figure 15. Structures of gangliosides HLG-1, -2, and -3 (162–164).



Scheme 13. Total synthesis of ganglioside HLG-2 (163).

Interesting was the synthetic approach by Ye et al., who achieved the synthesis of the glycan portion of ganglioside HLG-2 in a highly efficient and stereoselective manner, involving two key glycosylation reactions: first, for the construction of the disaccharide **173** using the phosphate donor **172**, in the presence of TMSOTf, in 95% yield; and, second, for the generation of the trisaccharide **176** by the use of NIS/TfOH in 96% yield, both with excellent α -stereoselectivity. From **176**, final conversion of functional groups and deprotection reactions afforded the trisaccharide core of ganglioside HLG-2 (**177**) [71] (Scheme 14).



Scheme 14. Total synthesis of the trisaccharide core **177** of ganglioside HLG-2 (**163**).

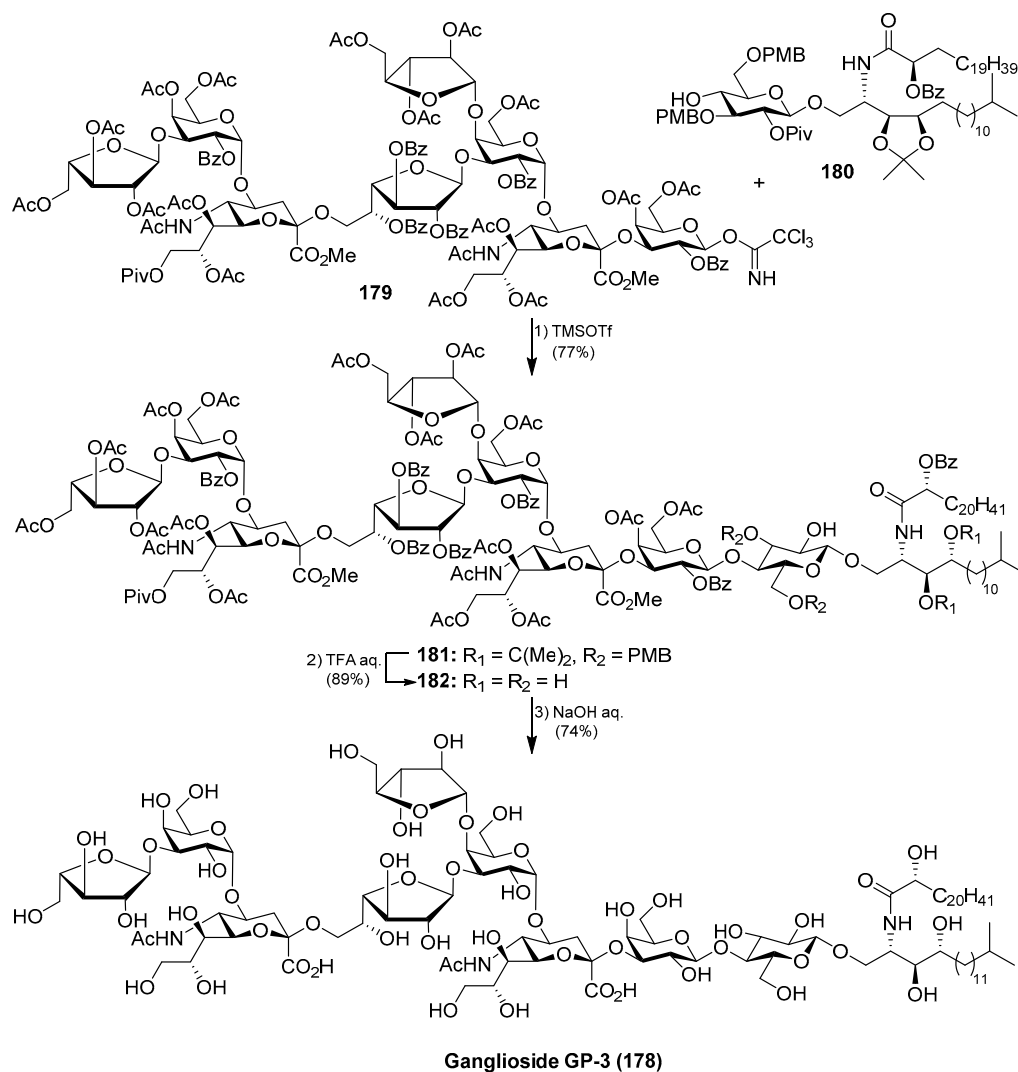
Ganglioside GP-3

Ganglioside GP-3 (**178**) was isolated from the starfish *Asterina pectinifera* by Higuchi et al. [72]. As previous gangliosides, GP-3 also exhibited neurotogenic activity toward the rat pheochromocytoma PC-12 cells, in the presence of the NGF, displaying, in this case, a lower effect when compared with ganglioside GM-1. Structurally, the glycan part contains nine monosaccharide units in a unique saccharide sequence with two internal sialic acid residues and three furanose residues.

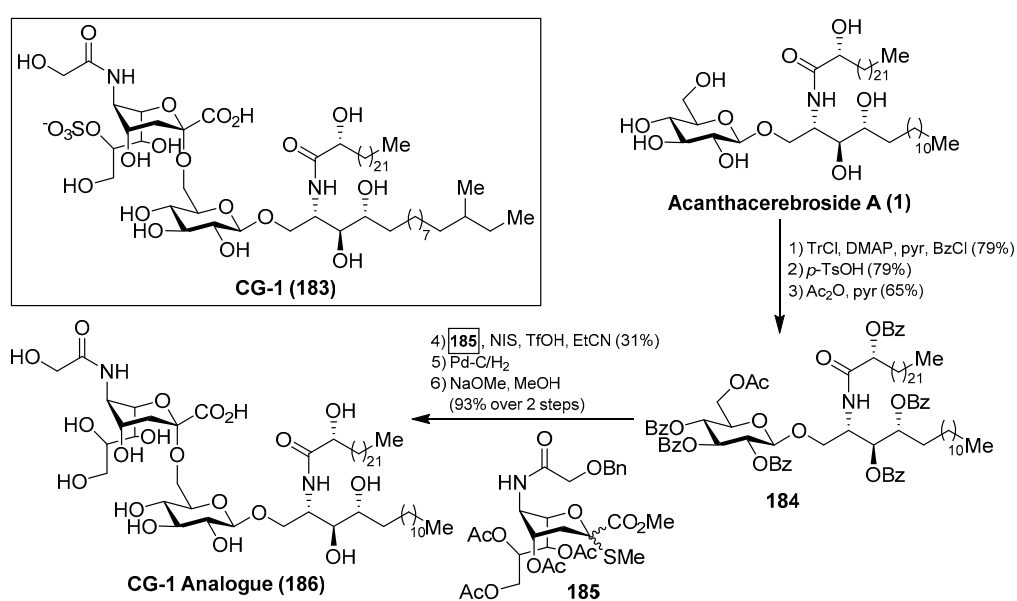
The total synthesis of ganglioside GP-3 (**178**) was achieved by Kiso et al. [73]. Briefly, the final glycosylation reaction of the octasaccharide donor **179** with the glucosphingolipic derivative **180** was promoted by TMSOTf to furnish the protected ganglioside GP-3 **181** in 77% yield. A final deprotection sequence, which included aqueous TFA and basic treatments, afforded ganglioside GP-3 (**178**) (Scheme 15).

Ganglioside CG-1

Ganglioside CG-1 (**183**), isolated from the sea cucumber *Cucumaria echinata* by Higuchi et al. [36], showed neurotogenic activity toward the rat pheochromocytoma PC-12 cells. The same authors carried out a partial synthesis of a related CG-1 ganglioside, which lacked the sulfate group in the natural product, by a coupling of 2-thioglycoside **185** with **184**, which was prepared from the natural acanthocerebroside (**1**), in the presence of NIS/TfOH, to obtain the corresponding α -sialoside in 31% yield. This advanced precursor of CG-1 was then subjected to stepwise deprotections to obtain the related CG-1 ganglioside **186** in 93% yield [74] (Scheme 16). This synthetic study can delineate the path towards the total synthesis of this natural product.



Scheme 15. Total synthesis of ganglioside GP-3 (178).



Scheme 16. Total synthesis of ganglioside CG-1 analogue 186.

Gangliosides SJG

Gangliosides SJG-1 (**187**) and SJG-2 (**188**) were isolated from the sea cucumber *Stichopus japonicus* by Higuchi et al. [75,76] (Figure 16). As the gangliosides described in previous sections, the SJG gangliosides also showed neuritogenic activity toward the rat pheochromocytoma PC12 cells in the presence of NGF. The effect of SJG-2 was higher than that of mammalian ganglioside (proportion of neurite bearing cells SJG-2 64.8%, SJG-1 35.4%, and GM-1 47.0%).

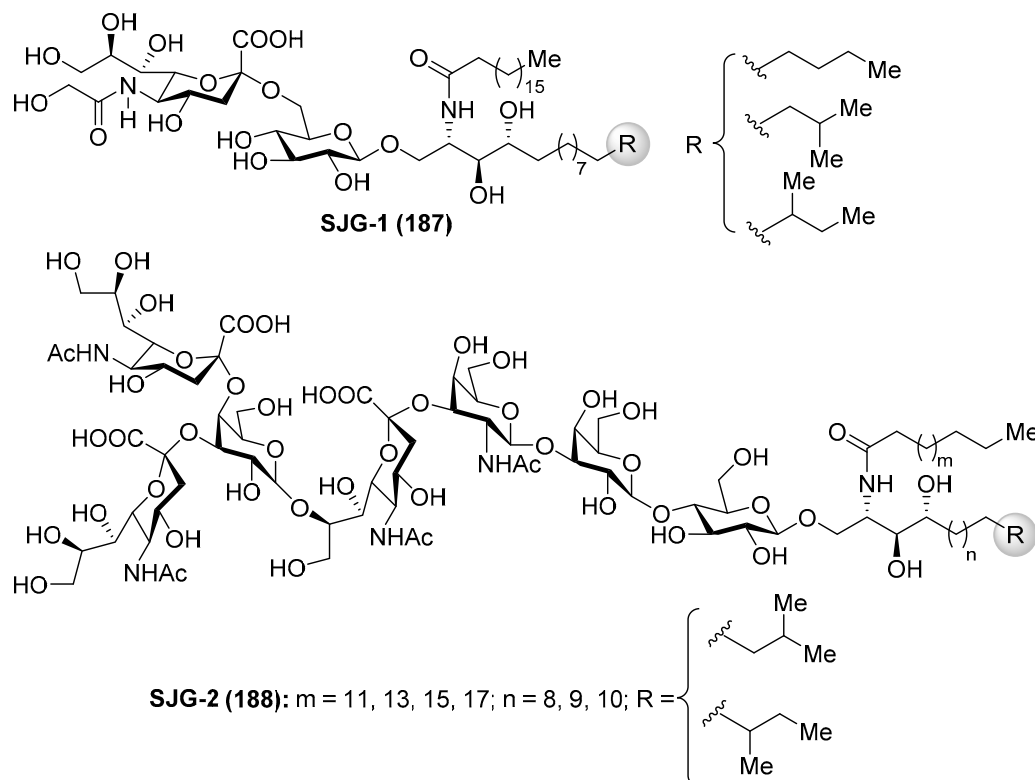


Figure 16. Structures of gangliosides SJG (**187** and **188**).

The same authors carried out an SAR study of a few gangliosides from Echinoderms involving trisialo-gangliosides (SJG-2 and LLG-5), disialo-gangliosides (LLG-3 [77], GAA-7 [78], HLG-2, LMG-4, HLG-3, and GP-3), and monosialo-gangliosides (AG-2, AG-3, HLG-1, SJG-1, LMG-2). Evaluation of the neuritogenic activity on a rat pheochromocytoma cell line (PC-12 cells) indicated that (a) the presence of sialic acid is essential; (b) the presence of two terminal sialic acids is key for strong activity; (c) gangliosides having an 8-O-Me sialic acid showed stronger activity; (d) gangliosides possessing sialic acid inside of the oligosaccharide unit showed better activity; (e) the different activity showed by HLG-1 and SJG-1 (44.7 and 35.4%, respectively), which have the same sugar unit, is due to the difference in the structure of their ceramide units; (f) SJG-2, LLG-5, LLG-3, and GAA-7 have better effect than mammalian ganglioside GM-1, which has positive effects in neuritogenic diseases; and (g) these gangliosides showed no activity without the presence of NGF [79].

Gangliosides CEG

Gangliosides CEG-3 (**189**), CEG-4 (**190**), CEG-5 (**191**), CEG-6 (**192**), CEG-8 (**193**), and CEG-9 (**194**) were isolated from the sea cucumber *Cucumaria echinata* by Higuchi et al. [80,81] (Figure 17). These compounds showed neuritogenic activity toward the rat pheochromocytoma cell line PC-12 in the presence of a nerve growth factor.

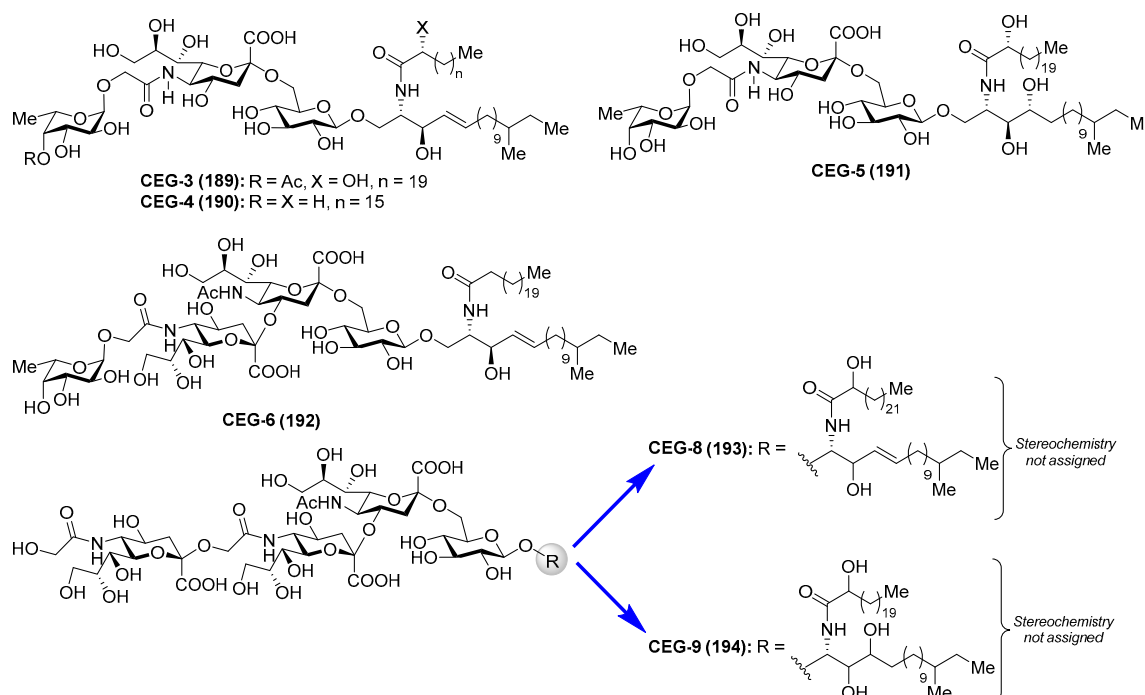


Figure 17. Structures of gangliosides CEG (189–194).

2.2.2. Sulfatides

Axinelloside A

Axinelloside A (195), a highly sulfated liposaccharide, was isolated from the lipophilic extract of the Japanese marine sponge *Axinella infundibula* by Fusetani et al. [82]. The structure of axinelloside A (195) was elucidated after an excellent spectroscopic work based on 2D NMR and MS techniques, determining the presence of twelve sugars including *scyllo*-inositol, *D*-arabinose, five *D*-galactoses, and five *L*-fucose units, to which one (*R*)-3-hydroxy-octadecanoic acid, three molecules of (*E*)-2-hexadecenoic acids and 19 sulfates groups were attached. This compound shows similar structure to sulfated polysaccharides from the marine sponge *Chondrilla nucula* and *Dysidea fragilis* (Figure 18).

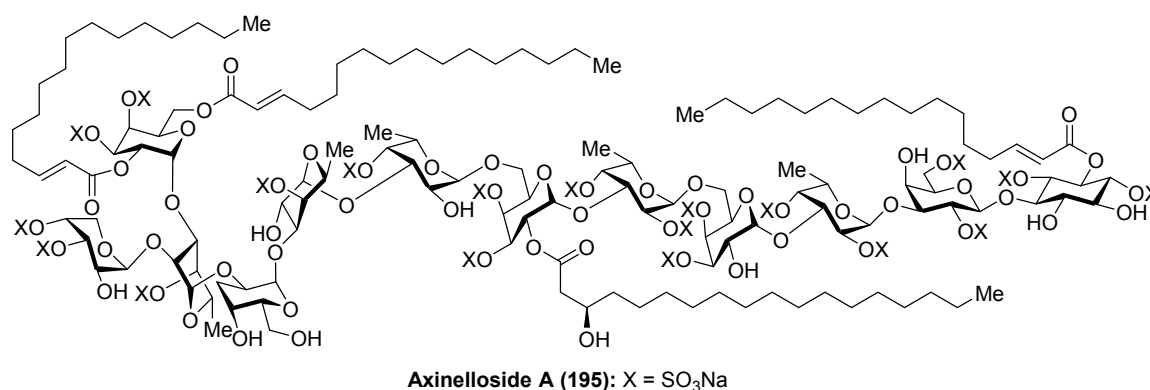


Figure 18. Structure of axinelloside A (195).

From a biological standpoint, axinelloside A (195) strongly inhibited the activity of human telomerase with an IC₅₀ value of 0.4 μM (2 μg/mL). In this biological activity, it is possible that the sulfate groups play a key role, since it was proven that the dictyodendrins [83], a family of sulfated pyrrolo-carbazoles isolated from the sponge *Dictyodendrilla verongiformis*, lost all telomerase inhibitory

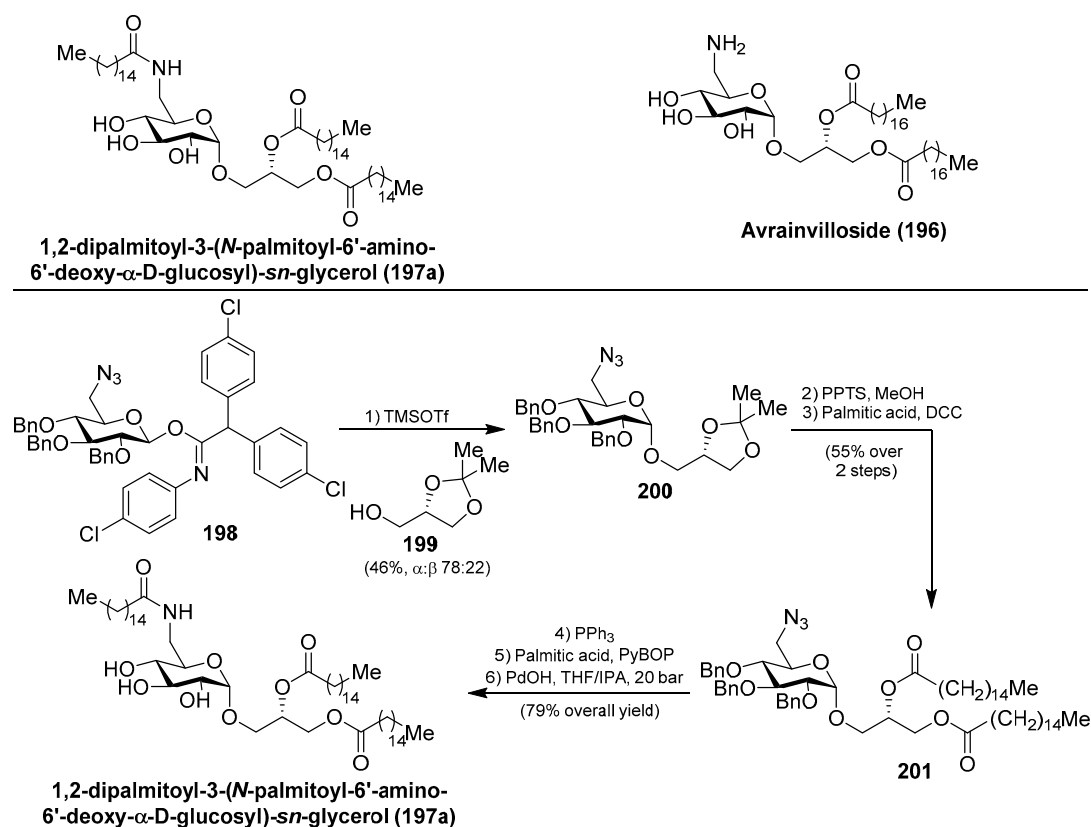
activity when their sulfate groups were removed. The mechanism of action of the telomerase inhibitory activity of axinelloside A (**195**) remains unknown.

Encouraged by the telomerase inhibitory activity of axinelloside A (**195**), Walczak et al. [84] achieved the synthesis of the *scyllo*-inositol fragment from D-glucose through a Ferrier rearrangement of a vinyl-acetate derivative and stereoselective reduction of the resulting ketone. The same authors established a synthetic sequence for the preparation of a series of simple sulfated D-galactosyl liposaccharides, inspired by axinelloside A (**195**), in order to evaluate their potential as new telomerase inhibitors [85]. However, the biological activities of these galactose derivatives have not been reported so far.

3. Chemistry and Biology of Glycoglycerolipids

3.1. Aminoglycoglycerolipids and Related Glycoglycerolipids

Within this class of glycoglycerolipids, it is noteworthy to mention avrainvilloside (**196**), isolated from the Dominican green alga *Avrainvillea nigricans* by Tagliatela-Scafati et al. [86]. Related to avrainvilloside (**196**), the aminoglycoglycerolipid 1,2-dipalmitoyl-3-(*N*-palmitoyl-6'-amino-6'-deoxy- α -D-glucosyl)-*sn*-glycerol (**197a**) was isolated from a marine alga, designated as UM2972M, by Kingston et al. This compound displayed potent inhibitory activity against the Myt1-kinase ($IC_{50} = 0.12$ mg/mL), an enzyme involved in the regulation of the cdc2/cyclin B kinase activity, which is essential for the growth of tumor cells [87]. Schmidt et al. [88] achieved the total synthesis of aminoglycoglycerolipid **197a** by glycosylation reaction of the imidate **198** and the alcohol **199**, promoted by TMSOTf, to obtain **200** in a 46% combined yield, as a separable α : β 78:22 mixture of anomers. Deprotection of the major α -anomer **200**, followed by an acylation step to introduce a palmitic-acid unit, afforded **201** in 55% yield in two steps. The final Staudinger reaction, followed by an amide coupling with the last palmitic acid unit and global deprotection, gave aminoglycoglycerolipid **197a** in 79% overall yield (Scheme 17).



Scheme 17. Synthesis of 1,2-dipalmitoyl-3-(*N*-palmitoyl-6'-amino-6'-deoxy- α -D-glucosyl)-*sn*-glycerol **197a**.

Later, Li et al. [89] completed the synthesis of the aminoglycoglycerolipid **197a** as well as its acyl analogues (**197b–h**) in an efficient method employing the trichloroacetimidate donor **202** to obtain **200**, by reaction with the glycerol derivative **199**, in 88% yield and high α -selectivity (α : β 33:1) as the key step. The same authors synthesized different mannosyl (**203a–h**) and galactosyl analogues related to **197** in a similar manner. Given the antiviral activity displayed by many glycoglycerolipids isolated from algae, the authors evaluated the inhibitory activity of these amino derivatives against the influenza A virus (IAV) by the cytopathic effects inhibition assay. These analogues displayed inhibition of the viral replication in MDCK cells and it was found that the type of the linkages and the length of the acids could influence the activity. Among them, **203g** showed the best activity with an IC_{50} of 69.9 μ M [90,91]. Later, new analogues **204–207** (Figure 19) were prepared and tested for anti-IAV activity, and the authors concluded that acylamino and glycerol groups of the glycolipids were essential for the inhibitory activity on IAV multiplication [92]. From this new series, **204d** was the most potent, with an IC_{50} of 60.8 μ M, and may provide a point of exploration of unique aminoglycoglycerolipids in drug discovery for pneumonia caused by viruses. In fact, this compound was selected for preliminary inhibitory studies on IAV infection *in vivo*. The results of this study showed that **204d** exhibited a significant reduction of viral titers in the lungs of IAV-infected mice at a dose of 5 mg/Kg/d, with a striking increase of the survival rate (90%) compared to the infected group treated with oseltamivir.

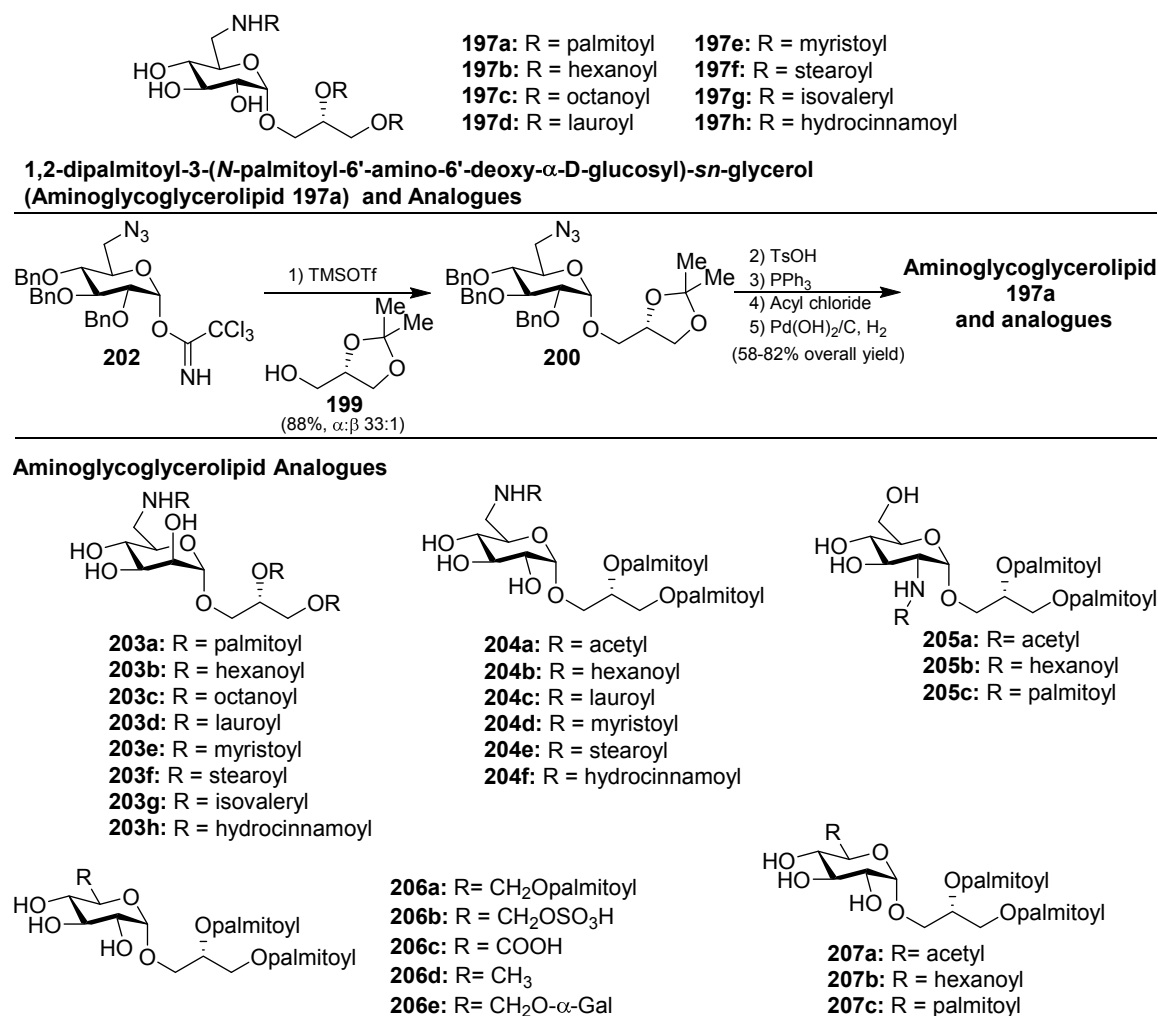


Figure 19. Structures of aminoglycoglycerolipids based on **197a**.

3.2. Crasserides and Isocrasserides

Crasserides (**208a–m**) (Figure 20), initially isolated by Fattorusso et al. [93] from the Caribbean sponge *Pseudoceratina crassa* (family Dysideidae), represent unique glycolipids that resemble common glycolipids by the replacement of an usual sugar by a five-membered cyclitol and the 1-*O*-acyl group present in the glycerol unit by an 1-*O*-alkyl group. Since their first isolation, the crasserides have been found in several families of sponges, including *Verongula gigantea* (family Dysideidae), *Aplysina fulva* (family Aplysinidae), *A. cauliformis* (family Aplysinidae), *Neofibularia nolitangere* (family Mycalidae), *Agelas clathrodes* (family Agelasidae), *A. dispar* (family Agelasidae), *A. conifera*, *A. longissima*, *Plakortis simplex* (family Plakinidae), *Ectyoplasia ferox* (family Raspailiidae), and *Siphonodictyon coralliphagum* (family Niphatidae) [94]. The structures of these interesting natural products were established and their stereochemistry was determined by exhaustive NMR spectroscopic analyses. Preliminary biological evaluations of these compounds revealed that the crasserides are potent feeding deterrents, with a concentration as low as 30 $\mu\text{g}/\text{cm}^2$ of food pellets according to the antifeedant assay on the fish *Carassius auratus*. Almost ten years later, the same authors discovered from the same sponges a new family of related compounds, which are termed isocrasserides (**209a–m**) [94], which accompanied the crasserides in minor amounts, demonstrating that these compounds are genuine natural metabolites and not artifacts, as initially suspected.

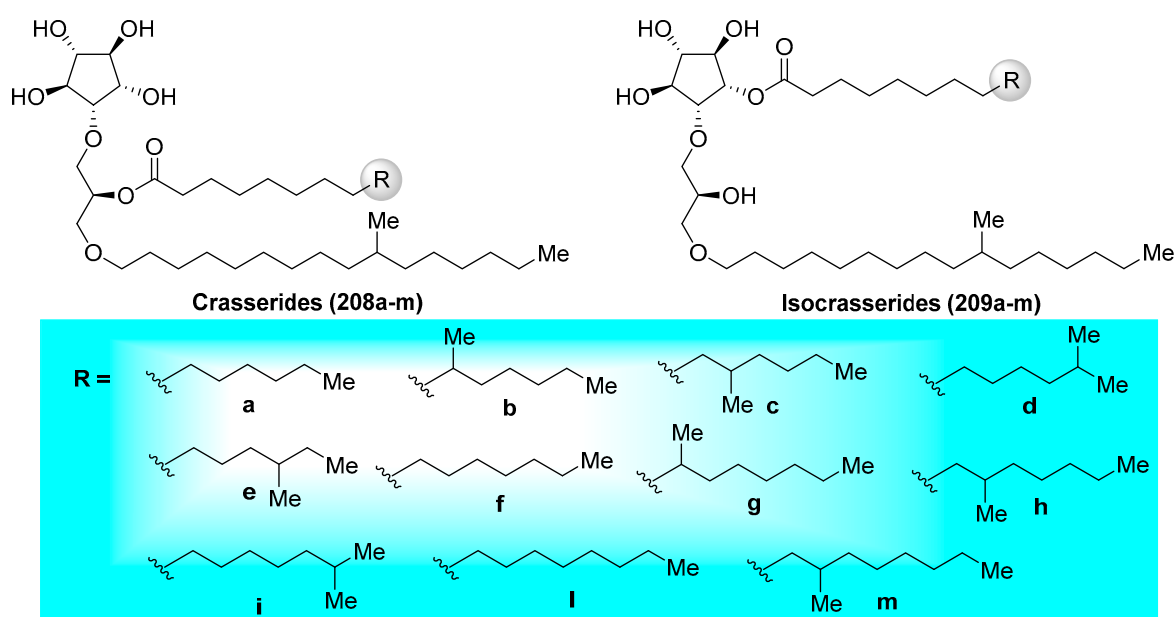
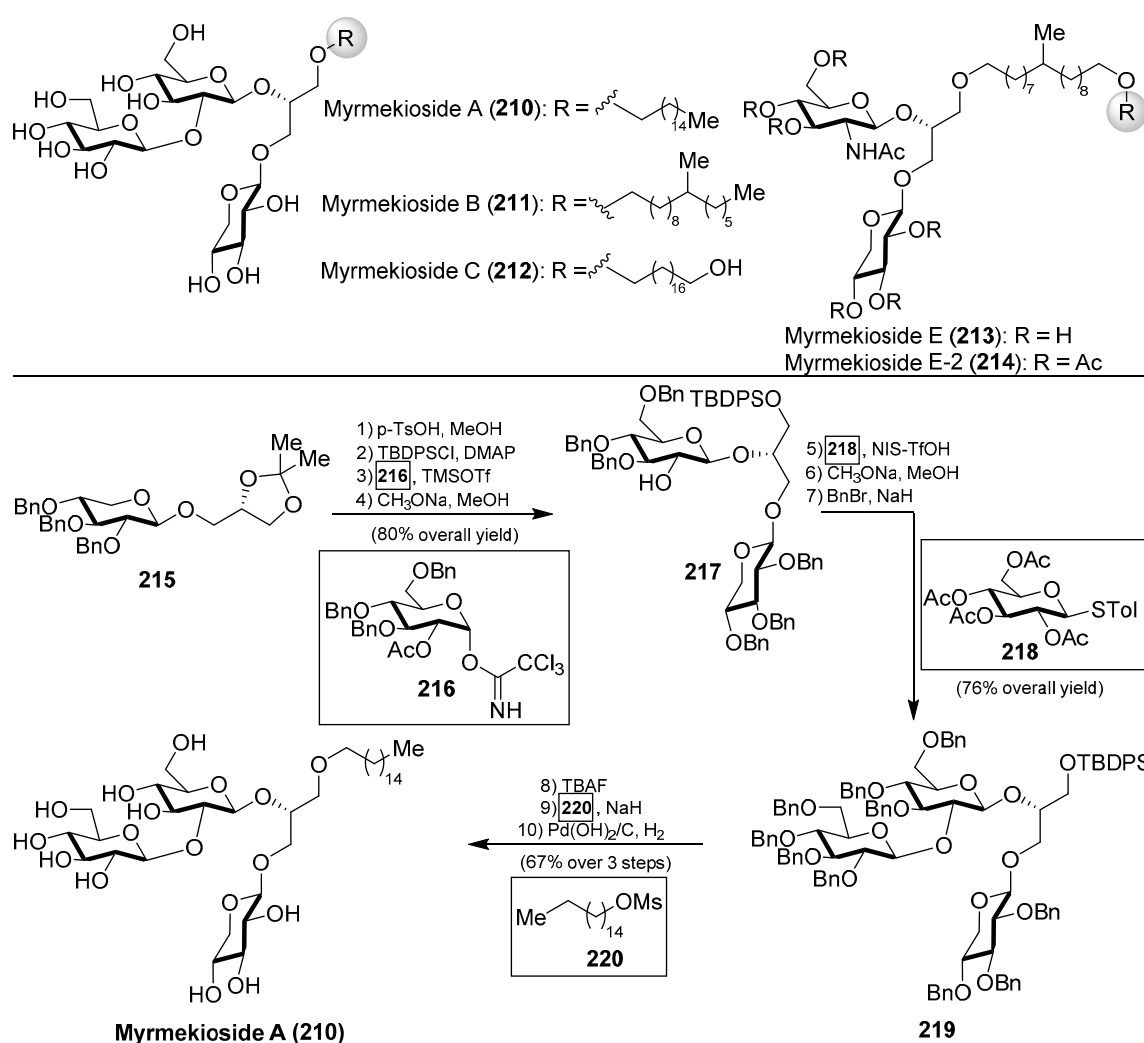


Figure 20. Structures of the crasserides (**208a–m**) and the isocrasserides (**209a–m**).

3.3. Myrmekiosides

The myrmekiosides (**210–212**) belong to the family of the glycolipids, isolated from the marine sponges *Myrmekioderma* sp. and *Trikenrion loeve* by Barnathan's group and displayed potent antitumor activity [95]. In fact, their preliminary biological evaluations revealed that myrmekiosides altered the tumor cell morphology of H-ras transformed NIH3T3 fibroblasts to normal at concentrations of 5 $\mu\text{g}/\text{mL}$. Later, Barnathan et al. isolated a new and related glycolipid from *M. dندی*, which was named myrmekioside E (**213**), and found that its peracetylated derivative (**214**) exerted significant cytotoxicity against NSCLC-N6 and lung tumor A549 cells with IC_{50} values of 7.3 and 9.7 μM , respectively [96]. Like metabolites isolated from a marine origin, the scarcity of a bioactive material demanded its chemical synthesis as the only way to provide access in sufficient quantities for further biological evaluations. Prompted by this requirement, together with the unique mono-*O*-alkyl-diglycosylglycerol structure, Li's group published in 2015 in what represents the first

and, so far, only total synthesis of myrmekioside A (**210**) [97]. Accordingly, careful inspection of this unprecedented molecular framework led the authors to prepare the xylosylglycerol **215** as the starting material to incorporate in subsequent steps other sugar units. Thus, the glycerol moiety was elaborated for the next glycosylation reaction with the trichloroacetimidate **216** to obtain, in very high yield, diglycosylglycerol **217**, after removal of the acetate group under basic conditions. Compound **217** was then reacted with thioglycoside **218**, using NIS/TfOH as a promoter, to give the corresponding glycolipid in an excellent 90% yield. At this point, the authors had to replace the acetyl protecting groups by benzyl ethers, and then the resulting derivative **219** was driven to the completion of the synthesis of myrmekioside A (**210**), for which the etherification reaction to introduce the pending lipidic chain was carried out by reaction of the alcohol resulting from the desilylation process of **219** with the mesylate **220** (Scheme 18). This synthesis demonstrated the proposed structure for this natural product and, in addition, that the modular character of the synthetic strategy could be useful for the preparation of other myrmekioside derivatives and analogues for further biological studies.



Scheme 18. Structures of the myrmekiosides (**210–214**) and total synthesis of myrmekioside A (**210**).

3.4. Nigricanosides

Isolated as methyl esters (**223** and **224**) from the green alga *Avrainvillea nigricans* in Dominica [98], the nigricanosides (**221** and **222**) represent a unique and unprecedented class of glycolipids with outstanding antitumoral activity in the low nM range with an IC_{50} value of 3 nM for **221** against human breast cancer MCF-7 and colon cancer HCT-116 cell lines (Figure 21). More intriguing was the

recognition of the ability of the nigricanosides to promote a polymerization of tubulins as the mechanism of action of their antiproliferative property. However, the tremendous scarcity of these natural products from the natural sources (Only 800 μg and 400 μg of the methyl esters of nigricanosides A and B, **223** and **224**, respectively, were obtained from 28 Kg of wet material!) represents a significant hurdle to gain further insight into the biological properties and to establish the absolute configuration of the compounds. Consequently, the total synthesis represents the only means to determine unambiguously the stereochemistry of the chiral centers and to have enough material for further biological screenings.

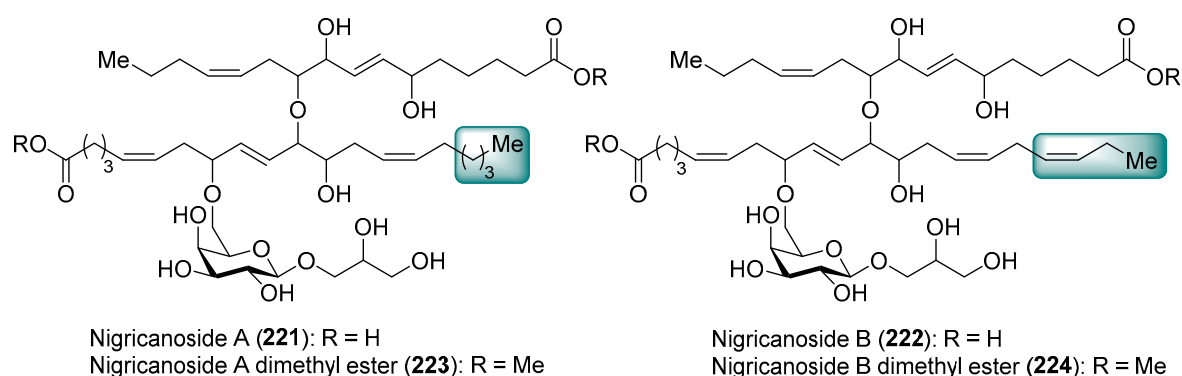
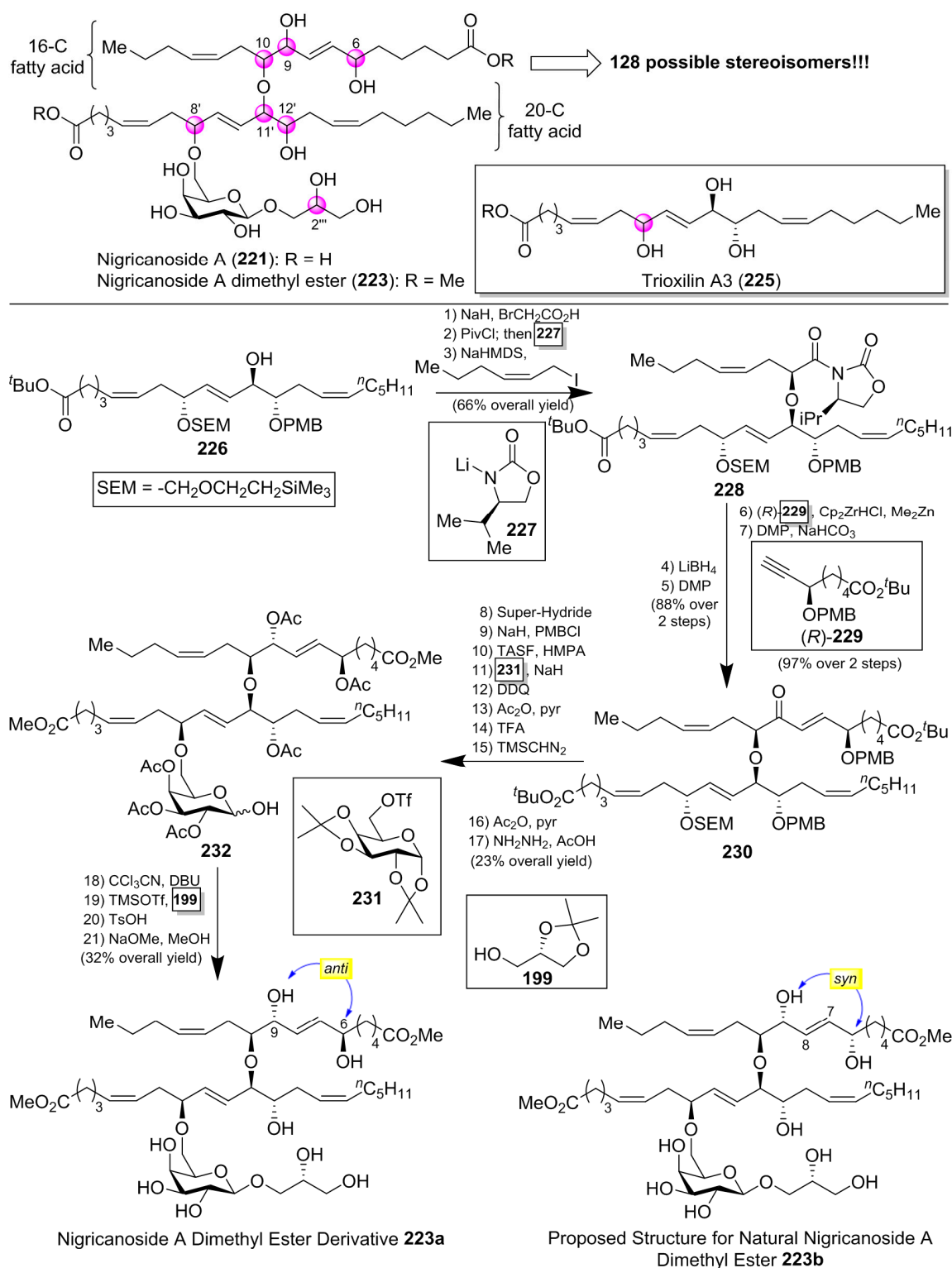


Figure 21. Structures of nigricanosides A (**221**), B (**222**), and their dimethyl esters, **223** and **224**.

Thus, several synthetic approaches have been initiated for the lipidic fragments [99–101], but many of them have not solved the stereochemical assignment problem. In fact, this stereochemical assignment represents a formidable synthetic challenge because of the presence of seven chiral centers in the lipidic unit, which could provide up to 128 possible stereoisomers, assuming that the configuration for the sugar unit and the geometry of the double bonds were correctly established (Scheme 19). This synthetic challenge was taken on by the McMillan [102] and Ready [103] groups, which used a flexible synthetic strategy capable of delivering all the possible stereoisomers. In addition, the knowledge of the stereochemistry of a related 20-C fatty acid, trioxilin A3 (**225**), isolated and identified as a hydrolysis product of the natural epoxide hepoxilin A3, led the authors to propose this stereochemistry for the 20-C unit of the nigricanosides. Thus, according to Scheme 19, they prepared the ester **226** in a convergent and efficient way from (*R*)-glycidol as the chiral source, which was prepared for the subsequent assembly of the 16-C fatty acid unit via an ether linkage. To this aim, the free alcohol of **226** was treated with 2-bromo acetic acid and, after the incorporation of the chiral auxiliary **227**, the alkylation with (*Z*)-1-iodo-2-hexene afforded, with a complete stereoselectivity, the corresponding alkylated product **228**. The use of the enantiomer *ent*-**227** provided the corresponding stereoisomer at this position. By continuation of the product **228**, the elongation of the second fatty acid was achieved in four additional steps, in which the chiral ester (*R*)-**229** was incorporated via a hydrozirconation reaction with the Schwartz reagent with a subsequent transmetalation with dimethylzinc. In a similar manner, the authors used the enantiomer (*S*)-**229** to generate all the possible stereochemical combinations of the lipidic fragment. The completion of the lipidic moiety was undertaken in five additional steps, in which the resulting product **230** was prepared for the introduction of the sugar moiety. In this event, the alcohol derived from the deprotection of the SEM group was treated with the galactosyl triflate **231** to obtain glycolipid **232**, which was finally directed towards the nigricanoside A methyl ester via a glycosylation reaction of the trichloroacetimidate derivative of **232** with the alcohol **199**. Unfortunately, the resulting synthetic nigricanoside **223a** did not match with the reported natural product and, furthermore, was inactive against HCT-116 and MCF7 tumoral cell lines. A detailed comparative analysis of the ^1H NMR spectra of synthetic diester **223a** and natural nigricanoside A dimethyl ester **223** revealed that the most important differences were located at the C7-C8 *trans* olefin region. These spectroscopic differences led the authors to propose a C6/C9 *syn* relationship for the natural product instead of the initially proposed *anti* relative configuration.



Scheme 19. Synthesis of proposed natural nigriganoside A dimethyl ester (**223a**).

Consequently, the nigriganoside derivative **223b** was prepared in the same way as for **223a**, and all its spectroscopic and physical properties matched with those reported for the natural product dimethyl ester. Despite this structural correspondence, it was surprising to find that neither **223b** nor its epimer at the glycerol subunit displayed cytotoxicity against HCT116 or MCF7 cells up to 10 μ M. Due to the lack of cytotoxicity for the synthetic material compared to the reported activity for the natural

product an explanation is warranted. One such explanation may be the presence of an unidentified product in the fractions corresponding to the natural nigrecanosides as the molecule responsible for the antitumoral activity exhibited by these natural products. The brilliant and outstanding synthetic work by McMillan and Ready's groups allowed the stereochemical assignment of these fascinating natural products. However, the biological properties of the synthetic nigricanosides have opened an important uncertainty about the identity of the compound responsible for the antitumoral activity detected for the isolated compounds, which must be resolved in future investigations.

4. Chemistry and Biology of Atypical Glycolipids

4.1. Agminosides

Agminosides A–E (233–237) were isolated from the New Zealand sponge *Raspailia agminata* by Northcote et al. [104] (Figure 22). Structurally, these compounds possess only one type of aglycone, and contain up to six partially acetylated glucose residues that differ only in the level of acetylation and the number of sugars. Their structural similarity made their separation challenging, which was achieved only after repetitive normal-phase chromatography, which was more difficult due to the lack of a chromophore. Mass spectrometry-guided isolation and extensive NMR analysis, together with chemical derivatization, were used for the identification of their structures.

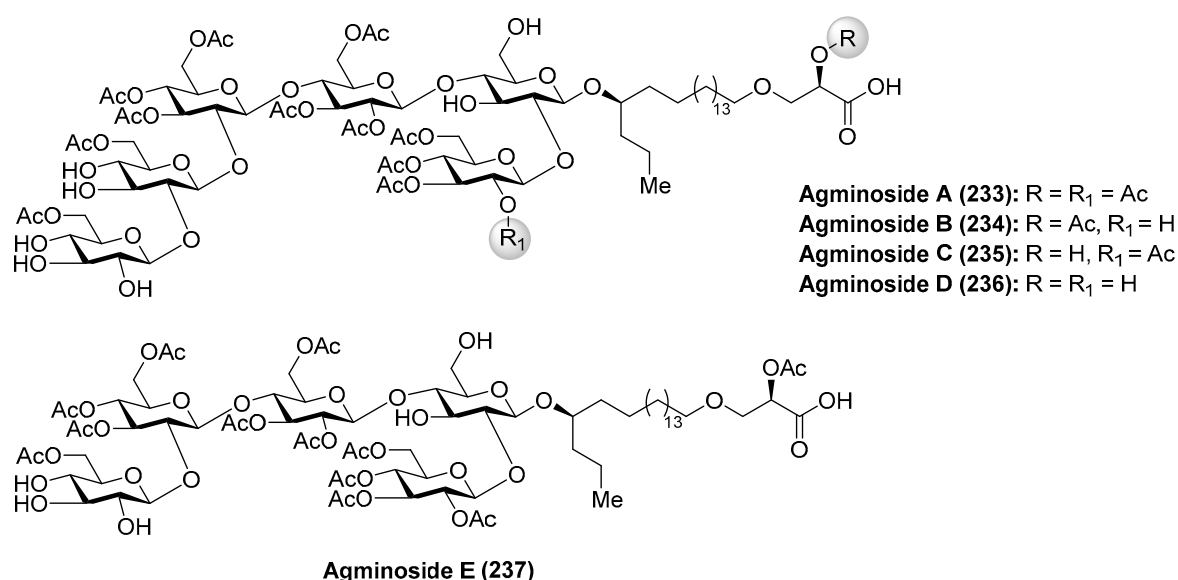


Figure 22. Structures of agminosides A–E (233–237).

4.2. Ancorinosides

Ancorinoside A (238) was isolated from the marine sponge *Ancorina* sp. by Ohta et al. [105] through bioassay-guided purification of the crude extract. This natural product is the first metabolite that possesses a tetramic acid ring derived from a D-amino acid, as well as a unique 21-methylene side chain. This compound was able to inhibit the blastulation of the starfish (*Asterina pectinifera*) embryo. Some years later, ancorinosides B–D (239–241) were isolated from the marine sponge *Penares sollasi* by Fusetani et al. [106] (Figure 23). Their structures were elucidated by spectroscopic and chemical methods, consisting of a tetramic acid glycoside related to ancorinoside A (238). In contrast to ancorinoside A (238), ancorinosides B–D (239–241) inhibited membrane type I matrix metalloproteinase (MT1-MMP) with IC₅₀ values in the range of 180–500 µg/mL. An SAR study carried out by the same authors, wherein the aglycone of ancorinoside B (242a), its methyl ester 242b, and tenuazonic acid (243) were tested, showed that 243 exhibited the best results, while 242a and 242b were slightly more potent

than ancorinoside B (**239**). These results indicated that the two carboxylic acid groups were irrelevant for the biological profile and pointed out the importance of the tetramic acid group for this biological activity. In the same year, Ikegami et al. [107] isolated the magnesium salt of ancorinoside A (**238**) from the marine sponge *Ancorina* sp., which exhibited an inhibitory activity of the blastulation of the starfish *Asterina pectinifera* embryo similar to ancorinoside A (**238**). This result indicated that the presence of Mg^{2+} ions, which act as transmembrane transport and influence the fluidity and permeability of the membrane, did not affect the inhibitory activity of ancorinoside A (**238**).

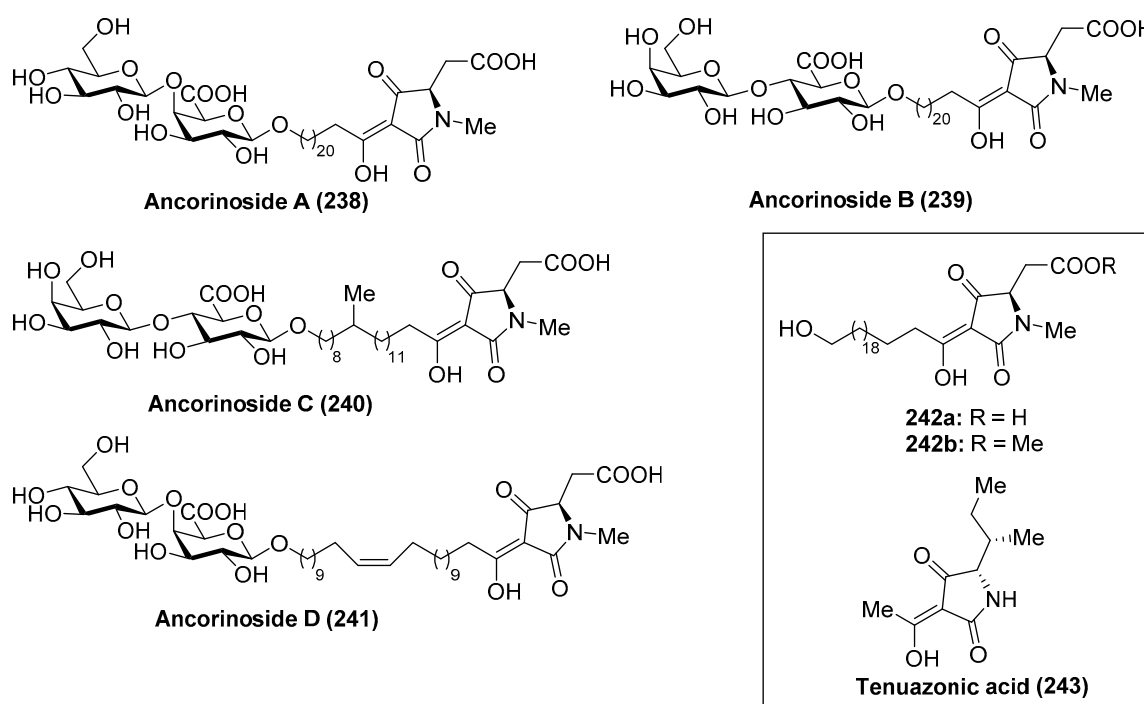
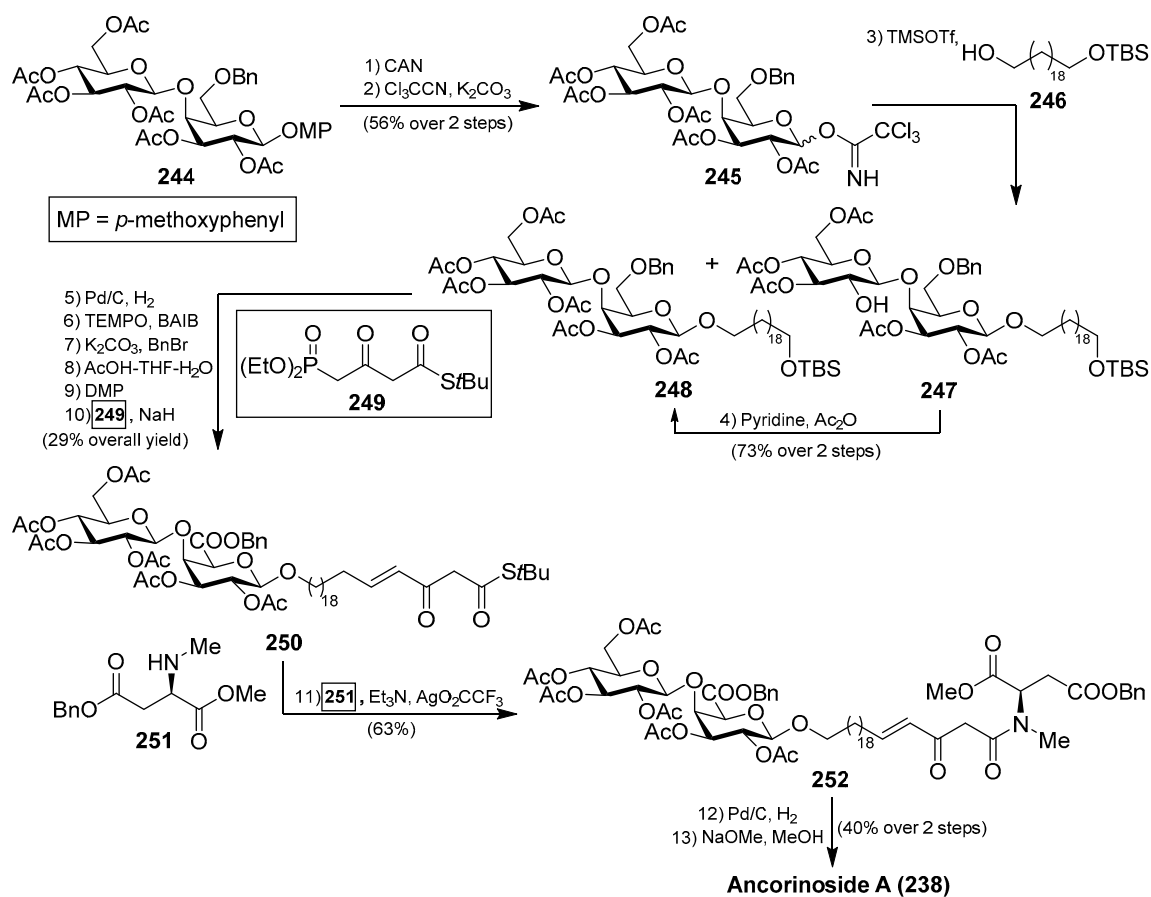


Figure 23. Structures of ancorinosides A–D (**238–241**).

A total synthesis of ancorinoside A (**238**) was achieved in 1.6% yield in 18 steps by Schobert et al. [108], as described in Scheme 20. The key steps were the Schmidt glycosylation for the introduction of the lipidic spacer, a TEMPO oxidation to the uronic acid, functionalisation of the spacer terminus, and final Dieckmann cyclisation for the construction of the tetramic residue. Thus, the authors started the synthesis from peracetylated β -D-galactose, which was rapidly transformed into the disaccharide **244** in six steps in 49% overall yield. Oxidative deprotection, employing CAN, followed by generation of the corresponding imidate, afforded a separable α/β mixture of **245** in 56% yield over two steps. From **245**, the glycosylation reaction with a spacer precursor **246** was achieved by the use of TMSOTf as an activator to obtain a mixture of the desired disaccharide **248** together with deacetyl **247**, which was reacylated to generate **248** in a 73% yield in two steps. Subsequent debenylation reaction, TEMPO oxidation of the alcohol to the corresponding uronic acid, esterification of the acid, removal of the silyl group, followed by Dess–Martin periodinane oxidation to the corresponding aldehyde, and a final *E*-olefination with Ley's β -ketophosphonate **249** afforded **250** in 29% overall yield. The coupling between **250** and **251** was achieved by the use of Ley's protocol mediated by a silver salt to obtain the β -ketoamide **252** in 63% yield. Debenzylation of **252**, followed by a final base-induced Dieckmann cyclisation with concomitant deacetylation, afforded ancorinoside A (**238**) (Scheme 20).



Scheme 20. Total synthesis of ancorinoside A (**238**).

4.3. Bartolosides

Bartoloside A (**253**) was isolated from the cyanobacterium *Nodosilinea* sp. LEGE 06102 [109] and bartolosides B–D (**254–256**) were isolated from the cyanobacterium *Synechocystis salina* LEGE 06155 through a bioassay-guided fractionation of the crude extract by Balskus et al. (Figure 24). A year later, Leao et al. [110] isolated bartolosides E–K (**257–263**) from the strain LEGE 06099 of *S. salina*.

Structurally, these glycolipids from marine cyanobacteria possess unique structures featured by the presence of a dialkyl-resorcinol core, decorated by one or two xylose units with chlorine groups in the aliphatic chains and a C-glycosyl moiety in the case of bartolosides B (**254**), C (**255**), and D (**256**). In the case of bartolosides E–K (**257–263**), these can be considered as analogues of bartoloside A (**253**) that differ in the alkyl chain lengths or halogenation patterns.

The chlorinated dialkylresorcinol core of the bartolosides conferred a challenge for their structural elucidation, which was finally established by combined biosynthetic and bioinformatic analysis. With regards to their biological features, the bartolosides are not known to possess strong biological activities, but their high abundance inside the cells suggests that they may have an important biological role that has to be investigated.

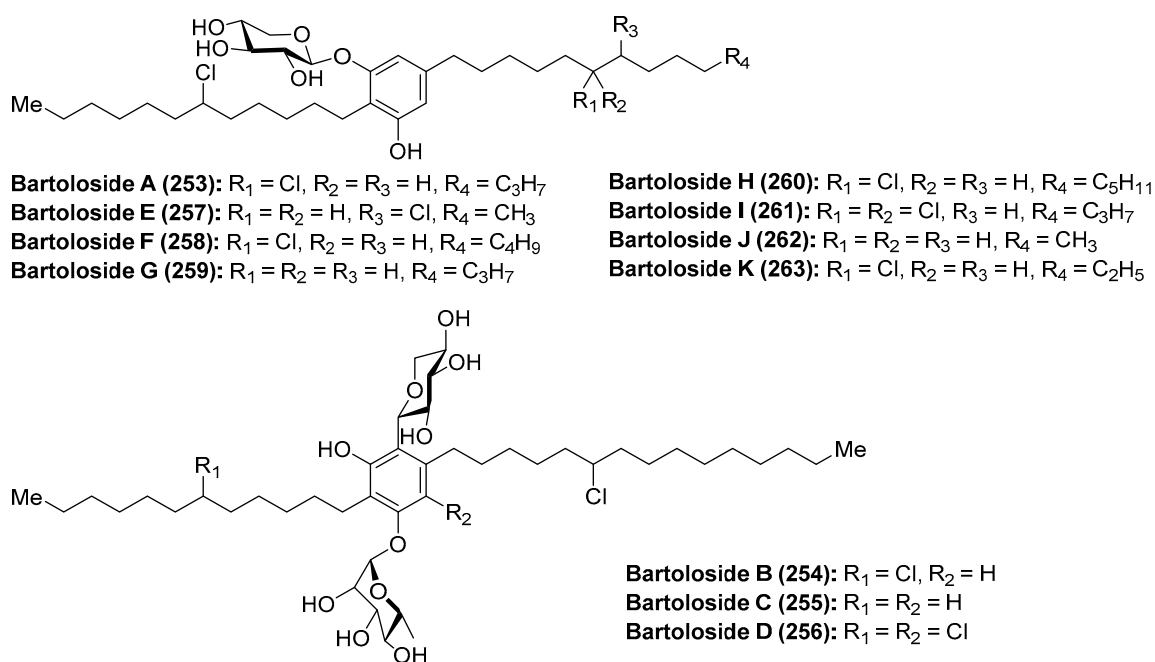


Figure 24. Structures of bartolosides A–K (253–263).

4.4. Caminosides

The caminosides (264–270) (Figure 25) are glycolipids with interesting antimicrobial activity isolated from the marine sponge *Caminus sphaeroconia* by Andersen et al. [111]. Firstly, caminoside A (264) was discovered after a biological screening of crude extracts of the marine sponge for its ability to inhibit the secretion of *Escherichia coli*-secreted proteins (EspS) by enteropathogenic *E. coli* (EPEC), a major cause of infantile diarrhea that actually represents the main cause of mortality of children in developing countries. Interestingly, pathogenic *E. coli*, and not nonpathogenic *E. coli*, employed the named type III secretory apparatus to deliver EspS. Thus, compounds capable of inhibiting the type III secretion system would affect the pathogenic *E. coli* and not the commensal *E. coli* flora. Actually, the inhibition of the type III secretion system produced the attenuation of the pathogenicity without killing the bacteria. Thus, caminoside A (264) displayed an IC_{50} of 20 μM , not inhibiting the growth of Gram-negative bacteria such as *E. coli* ($\text{MIC} > 100 \mu\text{g}/\text{mL}$). In addition, caminoside A (264) showed significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* ($\text{MIC} 12 \mu\text{g}/\text{mL}$) and vancomycin-resistant *Enterococcus* ($\text{MIC} 12 \mu\text{g}/\text{mL}$). Some years later, the same authors isolated and identified new members of the caminosides (B–D, 265–267) with similar biological activities [112]. In all the cases, the authors prepared the peracetylated derivatives 268–270 to facilitate their separation and structural determination. On the other hand, the unusual structure of these glycolipids is featured by the presence of a nonglycerol lipidic chain, whose stereochemistry at C-10 position was recently determined by circular dichroism [113].

The first synthesis of caminoside A (264) was reported by Yu et al. [114], wherein they succeeded in sorting out the different issues concerning the stereochemistry of the glycosidic bonds, particularly the 1,2-*cis*- β -mannopyranoside-type linkage of the 6-deoxy-talose unit. This issue was solved by the use of a 2-*O*-Lev (levulinyl) fucosyl derivative to obtain stereoselectively the β -glycosidic linkage with a glucopyranosyl derivative, and then an inversion of the C-2 configuration via oxidation/reduction of the alcohol. Having constructed the disaccharide 274, its assembly with the glucosyl derivative 273, prepared via glycosylation of the trichloroacetimidate 271 and alcohol 272, was undertaken after removal of the acetate and Wacker oxidation of 273. The resulting trisaccharide 275 was then prepared for the introduction of the 6-deoxy-L-glucosyl unit, for which 275 was benzylated at the 2-OH group of the deoxy-talose fragment, followed by the selective removal of the 2-(azidomethyl)benzoyl

group (Azmb) that was possible in the presence of the acetate and butyrate groups by treatment with tributylphosphine. With the resulting acceptor **277** in hand, the reaction with the donor **278**, under the action of catalytic TMSOTf, provided the corresponding caminoside derivative in 53% yield, exclusively as the α -anomer, which was finally subjected to a global deprotection step and acetylation to obtain caminoside A peracetate (**268**) (Scheme 21). More recently, Li et al. have reported the total synthesis of caminoside B (**265**) in a closely related strategy, as summarized in Scheme 22, through key intermediates **282–285** and by efficient and stereoselective glycosylation reactions [115].

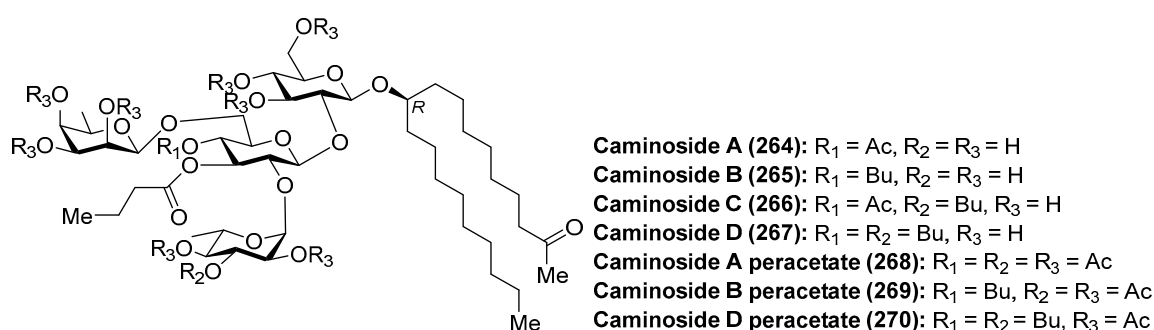
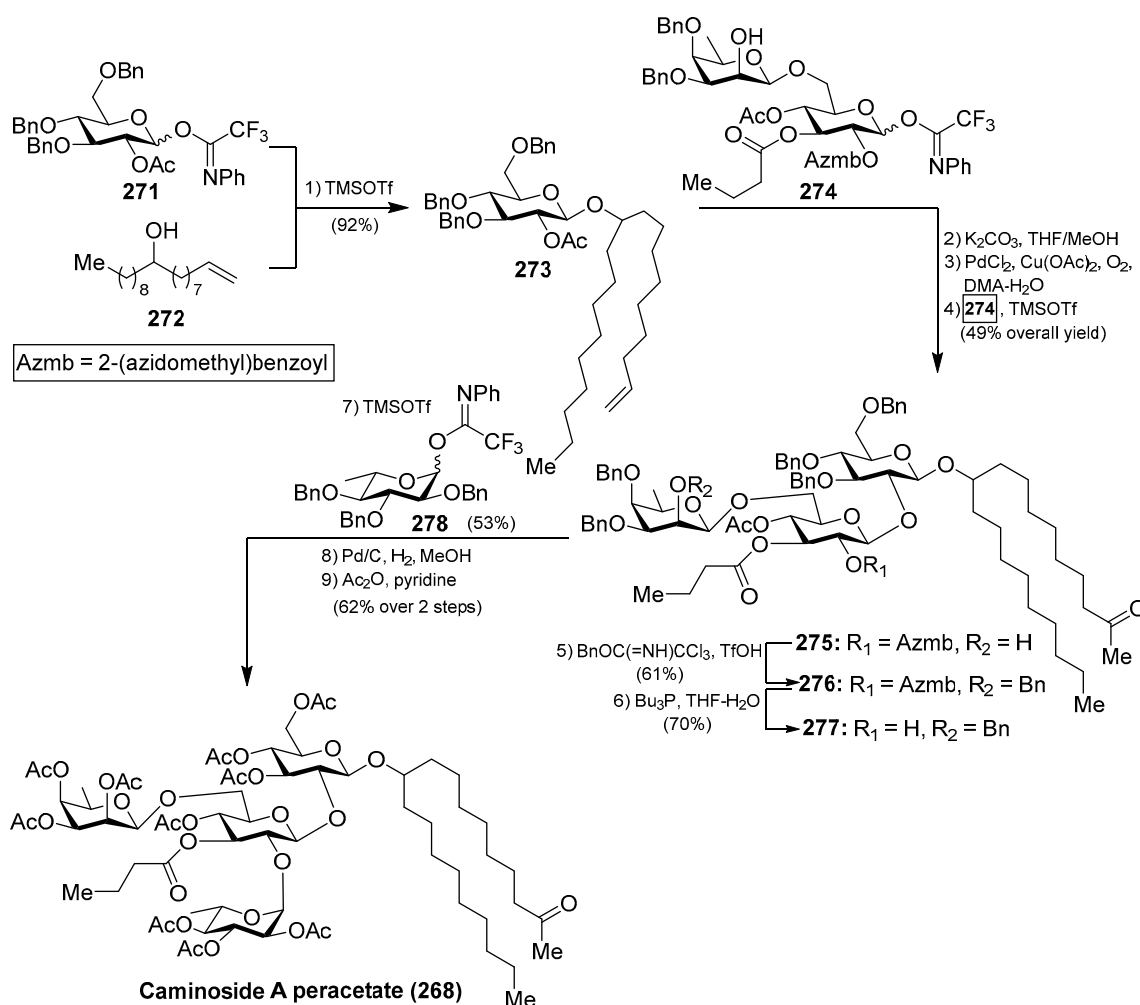
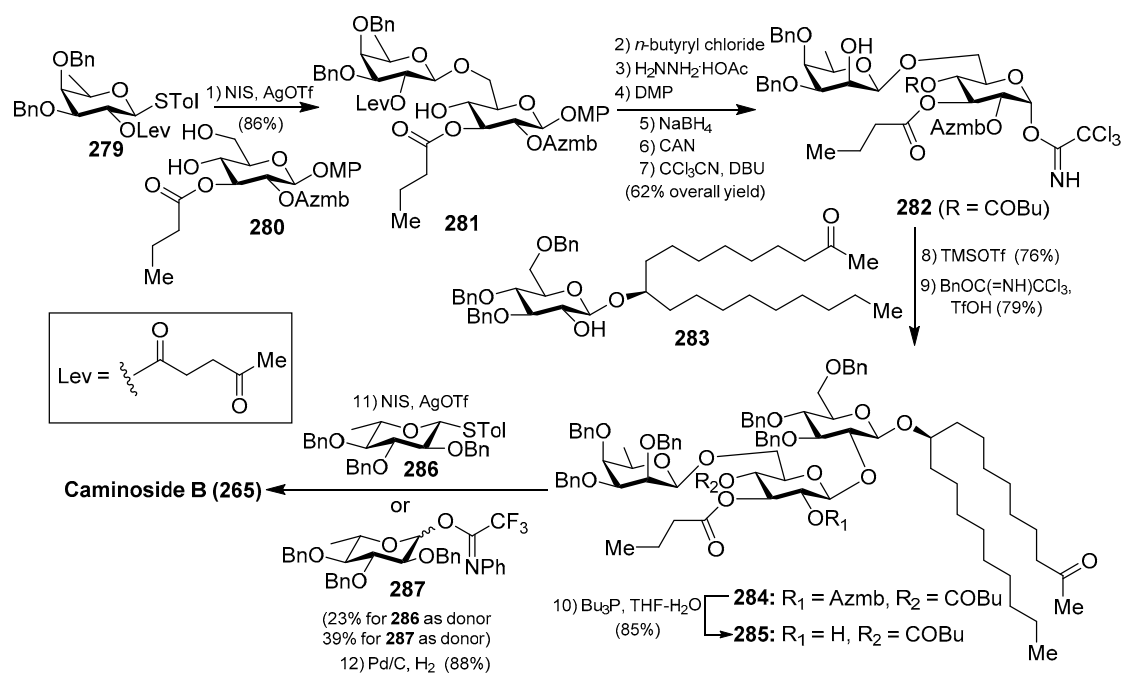


Figure 25. Structures of caminosides A–D (**264–267**) and their peracetylated derivatives (**268–270**).



Scheme 21. Total synthesis of caminoside A peracetate (**268**).



Scheme 22. Total synthesis of caminoside B (265).

4.5. Clathrosides and Isoclathrosides

Clathrosides A–C (**288–290**) and isoclathrosides A–C (**291–293**) (Figure 26), isolated from the Caribbean sponge *Agelas clathrodes* by Mangoni et al. [116], are glycosides containing a very long chain alcohol derived from fatty acids. The structural differences between the clathrosides and the isoclathrosides can be found in the configuration and in the branching of the alkyl chains. Stereostructures of the clathrosides were elucidated by NMR and CD spectroscopy, mass spectrometry, and chemical degradation studies. Clathroside A (**288**) and isoclathroside A (**291**) did not show significant activity on the immune system of mammals despite the structural similarity between clathrosides and the immunoactive simplexides, which will be described in the following section.

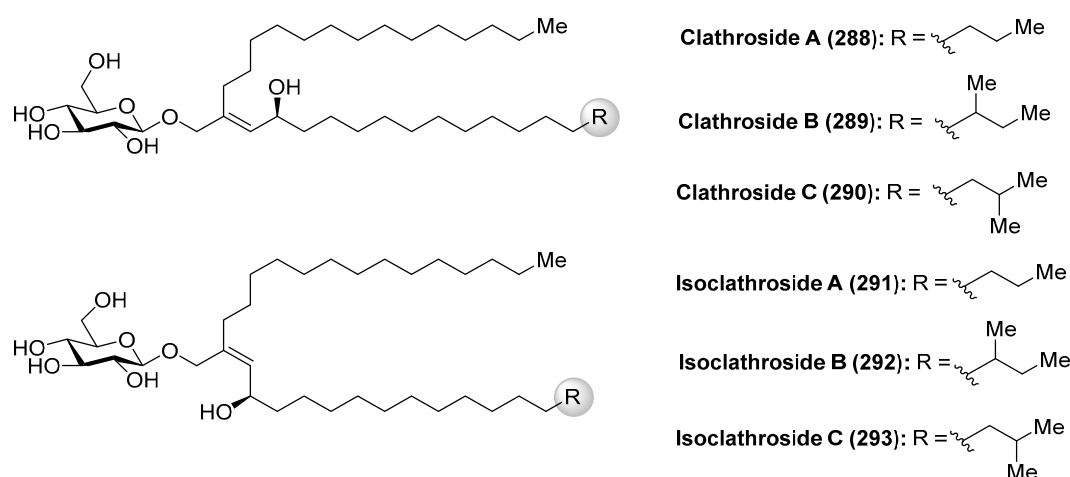


Figure 26. Structures of clathrosides A–C (288–290) and isoclathrosides A–C (291–293).

4.6. Discoside

Discoside (**294**) (Figure 27) was isolated as a mixture of homologues from the marine sponge *Discodermia dissoluta* by Fattorusso et al. [117]. The complete stereostructure of discoside was

determined by mass spectrometric and NMR spectroscopic techniques, together with CD analysis of degradation products. Interestingly, discoside (**294**) represents the first reported glycolipid with a 4,6-*O*-diacylated α -linked to the 2-hydroxyl group of a *myo*-inositol unit [2-*O*-(4,6-di-*O*-acyl- α -D-mannopyranosyl)-*myo*-inositol]. The *myo*-inositol mannoside is a well-known building block of phosphatidylinositol mannosides and of their multiglycosylated form, lipomannans, which exhibit immunoregulatory effects. However, such types of compounds have never been reported from marine sponges, 1-*O*-pentadecanoyl-2-*O*-(6-*O*-heptadecanoyl- α -D-mannopyranosyl)-*myo*-inositol being the only closely discoside-type compound, which was isolated from various strains of *Propionibacterium*. This finding suggests that discoside is synthesized by symbiotic cyanobacteria associated with the marine sponge.

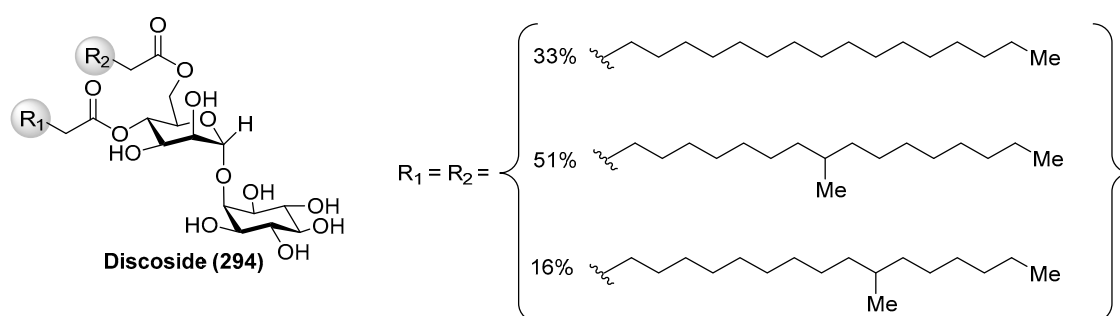
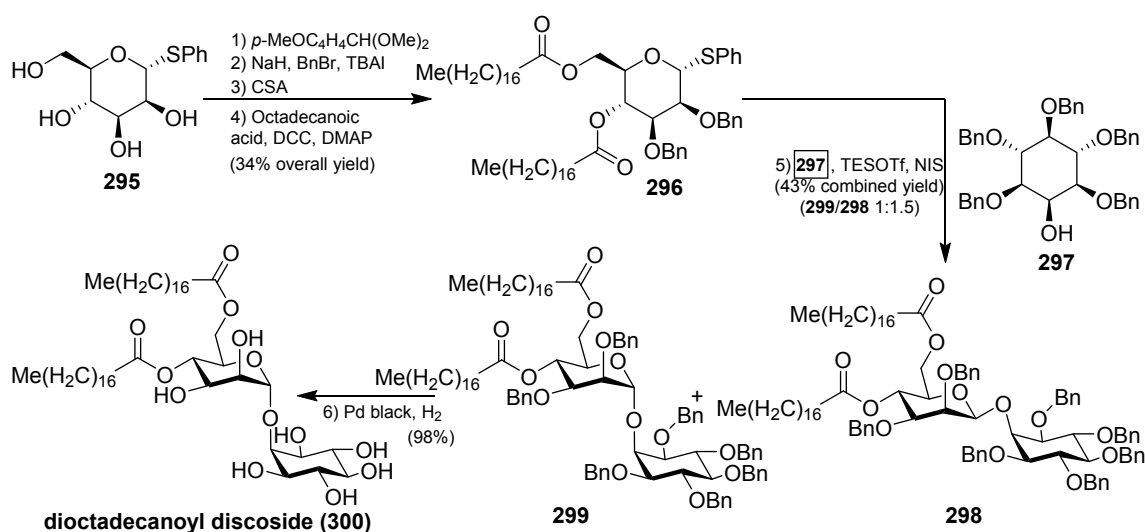


Figure 27. Structure of discoside (**294**).

The synthesis of 4,6-di-*O*-octadecanoyl discoside (**300**) was recently accomplished by Florence et al., starting with the preparation of the thiomannoside donor **296**. From α -D-phenylthiomannoside **295**, sequential protection of the 4- and 6-OH, benzylation of the remaining two hydroxyl groups, acidic methanolysis of the anisylidene acetal, followed by esterification under Steglich conditions, provided the donor **296** in 34% overall yield. The key glycosylation reaction between the donor **296** and the acceptor **297**, which was synthesized in six steps from a readily available orthoformate derivative of *myo*-inositol, was achieved with the activation of **296** using NIS and TESOTf, followed by the reaction with **297** to give a mixture of separable anomers **298** and **299** in 43% yield (α : β ratio 1:1.5). The total synthesis was completed by final debenzoylation of the minor α isomer **299** to provide 4,6-di-*O*-octadecanoyl discoside (**300**) in a 98% yield (Scheme 23) [118].



Scheme 23. Total synthesis of di-octadecanoyl discoside **300**.

4.7. Erylusamides

Erylusamides A–D (301–304) were isolated from the marine sponge *Erylus cf. deficiens* by Santos et al. through a bioassay-guided fractionation in order to find inhibitors of indoleamine 2,3-dioxygenase (IDO) [119]. The structures of erylusamides were established by NMR spectroscopy, HREIMS and chemical derivatization. These compounds possess a pentasaccharide moiety with unusual highly acetylated D-glucose, together with D-xylose and D-galactose units, and unprecedented aglycones, which are structurally featured by long chains of dihydroxyketo amides.

On the other hand, the related erylusamines A–E (305–309) were isolated from the marine sponge *Erylus placenta* by Fusetani et al. [120,121]. These compounds are interleukin-6 (IL-6) receptor antagonists. Erylusamine TA (310), erylusine (311), and erylusidine (312) (Figure 28) were isolated from *Erylus cf. lendenfeldi* by Kashman et al. [122]. These compounds were not tested for any biological activities due to the fact that they were not isolated as pure compounds but together with a small amount of other homologues.

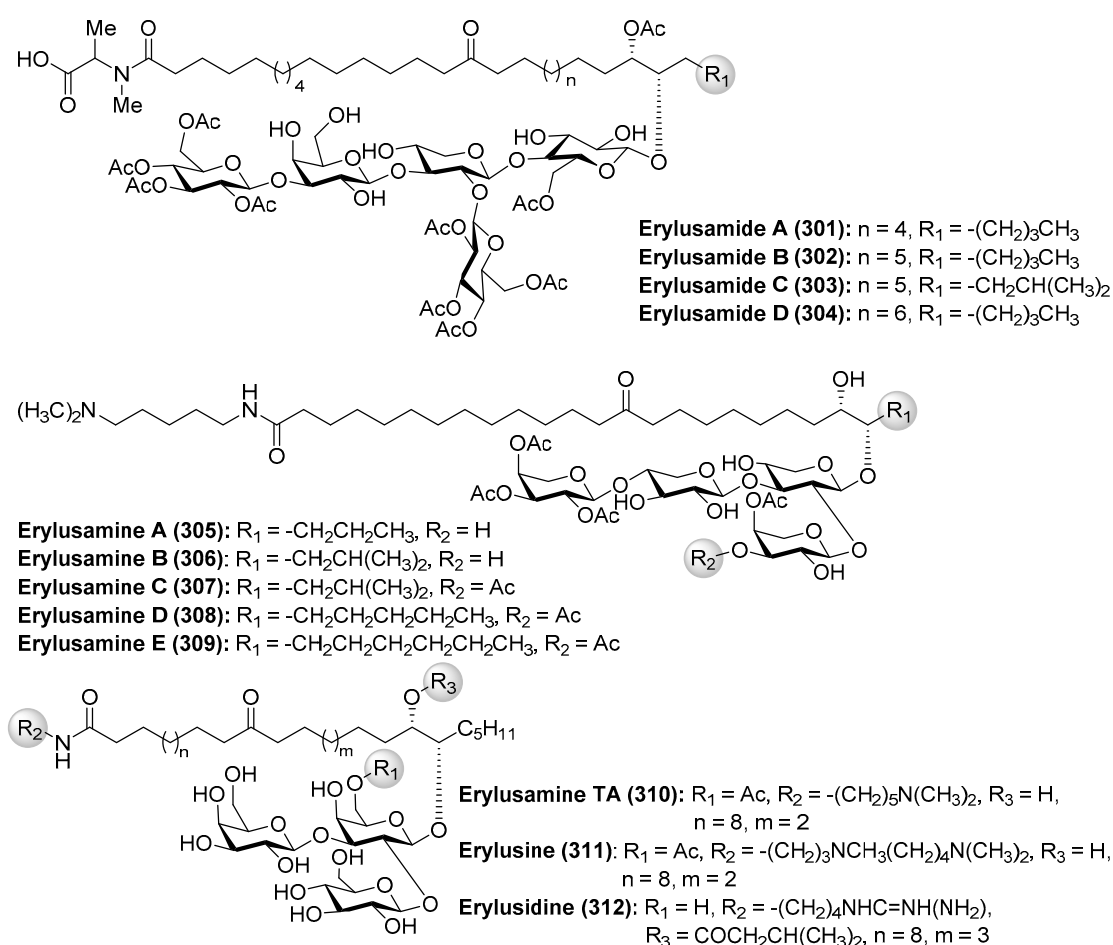


Figure 28. Structures of erylusamides A–D (301–304) and related glycolipids (305–312).

4.8. Ieodoglucomides and Ieodoglycolipid

Ieodoglucomides A (313) and B (314) (Figure 29) were isolated from a marine-derived bacterium, *Bacillus licheniformis*, in 2012 by Shin et al. [123] and their structures were elucidated by a combination of NMR spectroscopic analysis of the natural products with the spectroscopic and physical analyses of the products derived from their acid hydrolysis. Ieodoglucomides are unique glycolipopeptides that contain an amino acid (L-ala for ieodoglucomide A and glycine for ieodoglucomide B), an unprecedented fatty acid (14-hydroxy-15-methylhexadecanoic acid), succinic acid, and a sugar

(β -D-glucose). Iedoglucomide B (**314**) showed moderate antimicrobial activity against Gram-positive and Gram-negative bacteria, antifungal as well as growth inhibition against lung cancer (NCI-H23) and stomach cancer (NUGC-3) cell lines with GI_{50} values of 25.18 and 17.78 $\mu\text{g}/\text{mL}$, respectively.

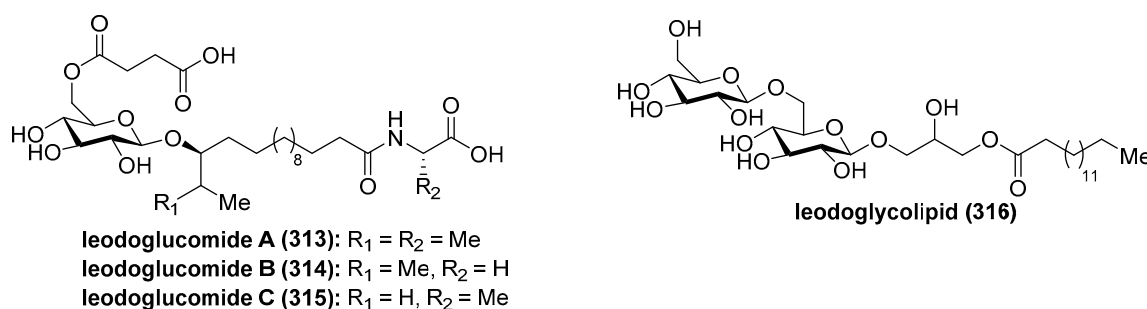
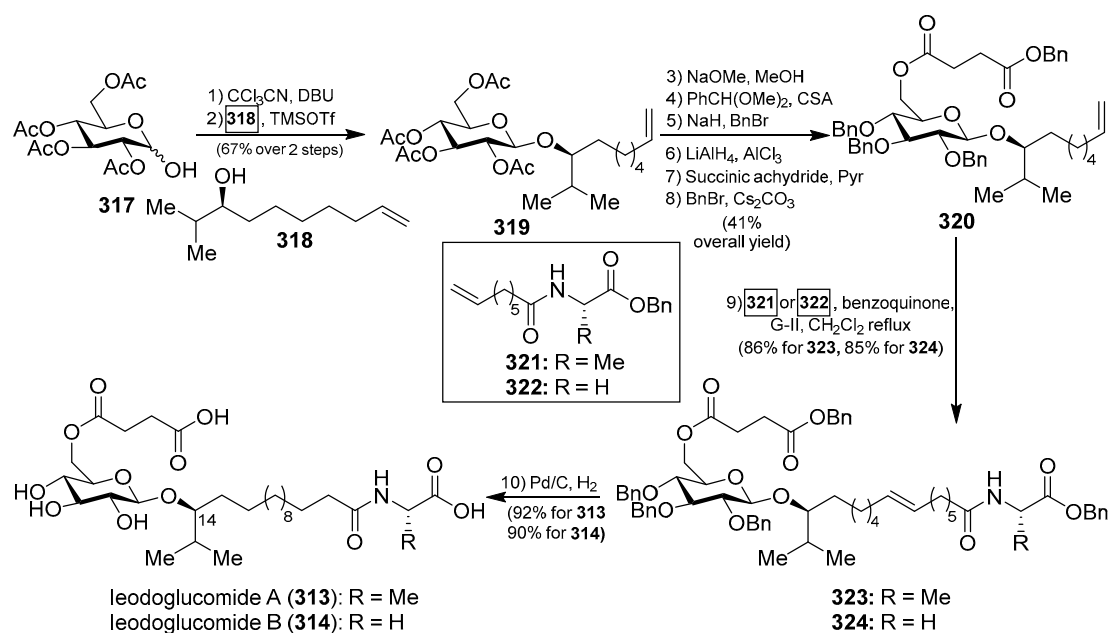


Figure 29. Structures of iedoglucomides A–C (**313–314**) and iedoglycolipid (**316**).

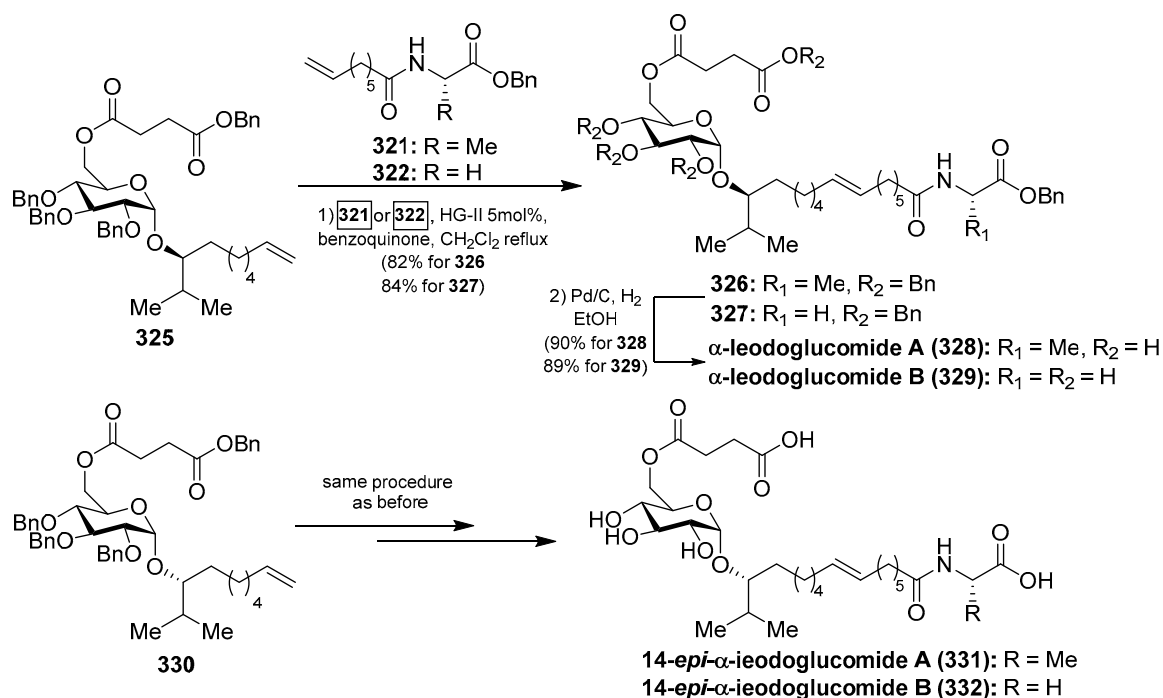
Iedoglucomide C (**315**) and iedoglycolipid (**316**) were isolated from the fermentation broth of the marine-derived bacterium *Bacillus licheniformis* [124]. In contrast to iedoglucomide B (**314**), these compounds showed good antibiotic properties against *Staphylococcus aureus*, *Bacillus subtilis*, *B. cereus*, *Salmonella typhi*, *Escherichia coli*, and *Pseudomonas aeruginosa* with MIC values in the 0.01–0.05 μM range. In addition, these compounds inhibit the mycelial growth of plant pathogenic fungi *Aspergillus niger*, *Rhizoctonia solani*, *Botrytis cinerea*, and *Colletotrichum acutatum* as well as the human pathogen *Candida albicans*, with MICs values of 0.03–0.05 μM . The antimicrobial profiles of iedoglucomide C (**315**) and iedoglycolipid (**316**) suggest that they could be potential bioprobes for the development of useful antibiotics and fungicides.

Total syntheses of iedoglucomide A (**313**) and B (**314**) were carried out by Reddy et al. [125] starting from D-glucose and using β -glycosylation and olefin cross-methathesis reactions as the key steps. Thus, the synthesis started with the conversion of **317**, prepared from D-glucose in two steps, into the corresponding α -trichloroacetimidate, which was employed in the key glycosylation reaction, promoted by TMSOTf, with the alcohol **318** to obtain the β -glycoside **319** in 67% yield in two steps. The introduction of the succinyl group onto the sugar to generate **320** was accomplished in six steps in 41% overall yield from **319**. Next, the key olefin cross-metathesis between **320** and **321** or **322**, under the action of the Grubbs 2nd generation catalyst, gave the protected glycolipids **323** and **324** in excellent 86% and 85% yields, respectively. Final hydrogenation provided iedoglucomides A (**313**) and B (**314**) in 92 and 90% yields, respectively (Scheme 24).

In order to identify analogs of iedoglucomides with improved biological properties, the same authors prepared the α -isomers of iedoglucomides A and B (**328** and **329**) and their C-14-epimers (**331** and **332**) (Scheme 25) [126]. As described in Scheme 25, the syntheses of these analogues were accomplished according to the same synthetic strategy employed for the synthesis of the natural products, starting from the α -anomer **325** for the synthesis of the analogues **328** and **329**, and from the epimer **330** for the syntheses of the analogues **331** and **332**. These stereochemical analogues, together with the natural iedoglucomides, were tested for cytotoxicity against various cancer cell lines and found that iedoglucomide A (**313**) and B (**314**), as well as their α -isomers (**328** and **329**), did not exhibit cytotoxicity in any cell lines tested. However, their α -C14 epimers (**331** and **332**) showed an inhibition of proliferation of DU145 and HeLa cells with IC_{50} values in the range of 15.2–35.5 μM . In addition, this biological study demonstrated that the activity of caspases-3 and -9 increased when these cell lines were treated with these compounds **331** and **332**, suggesting that the α -epi isomers of the iedoglucomides led to the activation of pathway-initiating apoptosis in DU145 and HeLa cells.



Scheme 24. Total synthesis of ieodoglucomides A (313) and B (314).



Scheme 25. Total synthesis of α -isomers of ieodoglucomide A (328) and B (329) and their α -14-epi analogues (331 and 332).

4.9. Pachymoside A

Pachymoside A (333) (Figure 30) was isolated from the North Sea marine sponge *Pachymatisma johnstonia* through a bioassay-guided fractionation in order to find inhibitors of the bacterial type III secretion system (TTSS), carried out by Andersen et al. [127]. Its structure was elucidated by NMR spectral analysis and chemical degradation. This structural study revealed that pachymoside A (333) possesses complete acetylation of the galactose residues (the eight galactose hydroxyls are acetylated)

and only partial acetylation of the glucose residues (the C-6 hydroxyls of β -glucose and D-glucose are acetylated). Despite its promising activity as a TTSS inhibitor, pachymoside A (333) is not a true TTSS inhibitor. It seems that the biological activity exhibited is due to its ability to activate extracellular bacterial proteases that rapidly degrade the excreted Esps, resulting in a false indication of inhibition.

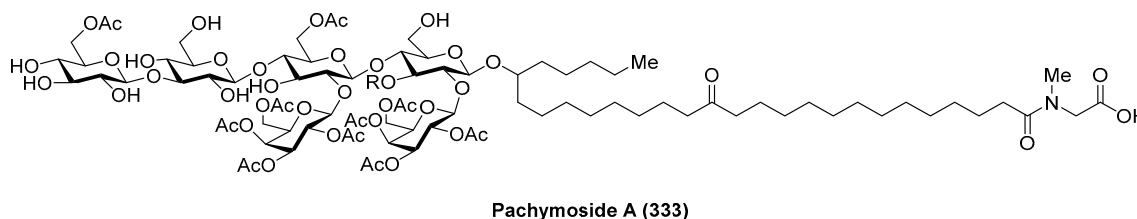


Figure 30. Structure of pachymoside A (333).

4.10. Plaxyloside

Plaxyloside (334) (Figure 31) was isolated as its peracetate from the Caribbean sponge *Plakortis simplex* by Fattorusso et al. [128]. Its structure was established by NMR spectral analysis and chemical methods. Plaxyloside (334) is a glycolipid with a long linear polyisoprenoid alcohol aglycone and a linear carbohydrate chain of β -xylopyranose units and represents the first natural oligosaccharide that contains more than three (1 \rightarrow 3) linked xylopyranosides. The biological activity of this compound was not evaluated.

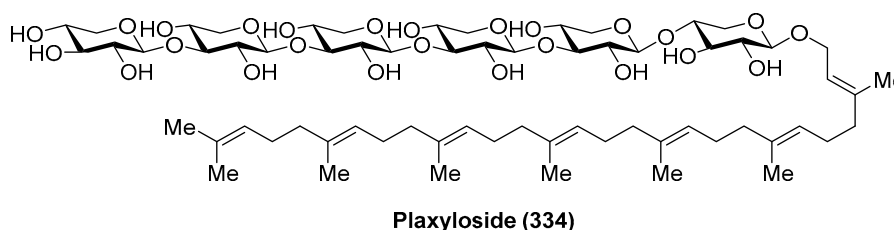


Figure 31. Structure of plaxyloside (334).

4.11. Roselipins

Roselipins (335–338) (Figure 32) were isolated from the culture broth of fungus *Gliocladium roseum* KF-1040 by Omura et al. [129–131]. Later, a mixture of five new roselipins derivatives, separated in two fractions, named roselipins mixture 1–2 (339a–b) and mixture 3–5 (340a–c), were isolated from an extract of the fungus *Clonostachys candelabrum* by Singh et al. [132]. These compounds differ by the position of esterification of the arabinitol residue. Overall, the roselipins have a unique structure featured by a highly methylated C-20 fatty acid skeleton modified with D-mannose and D-arabinitol residues. Extensive biological evaluations of the roselipins revealed that these compounds displayed a broad range of biological activities. In particular, these compounds inhibit diacylglycerol acyltransferase (DGAT) with IC_{50} values ranging from 15 to 22 μ M in an enzyme assay system using rat-liver microsomes, showing that are selective inhibitors of DGAT2 (IC_{50} = 30–50 μ M) [133]. An SAR study carried out by Omura et al. [134] revealed that demannosyl roselipins 3A (341) and 3B (342), prepared from the natural products via enzymatic degradation, conserved DGAT inhibitory activity, in contrast to the dearabinitoyl derivatives (343 and 344), which completely lost their activity, suggesting that the arabinitoyl fatty acid core is essential for eliciting DGAT inhibitory activity. In addition, the roselipin derivatives 3A (341) and 3B (342) were more potent in the cell assay than the roselipins 335–338, indicating that these derivatives are more membrane-permeable than natural roselipins. These compounds also exhibited antimicrobial activity against *Saccharomyces cerevisiae* and *Aspergillus niger* and showed a cytotoxic effect on Raji cells at 39 μ M. Furthermore, the mixture of roselipins

2A and 2B (336 and 338) inhibited HIV-1 integrase with $IC_{50} = 8.5 \mu\text{M}$ [135]. On the other hand, Ondeyka et al. [136] reported that roselipins 2A (336), 2B (338), and 1A (335) blocked the CXCR3 receptor interaction of IP-10 ligand with $IC_{50} = 14.6, 23.5,$ and $41 \mu\text{M}$. The roselipins were also identified as anthelmintic compounds [133].

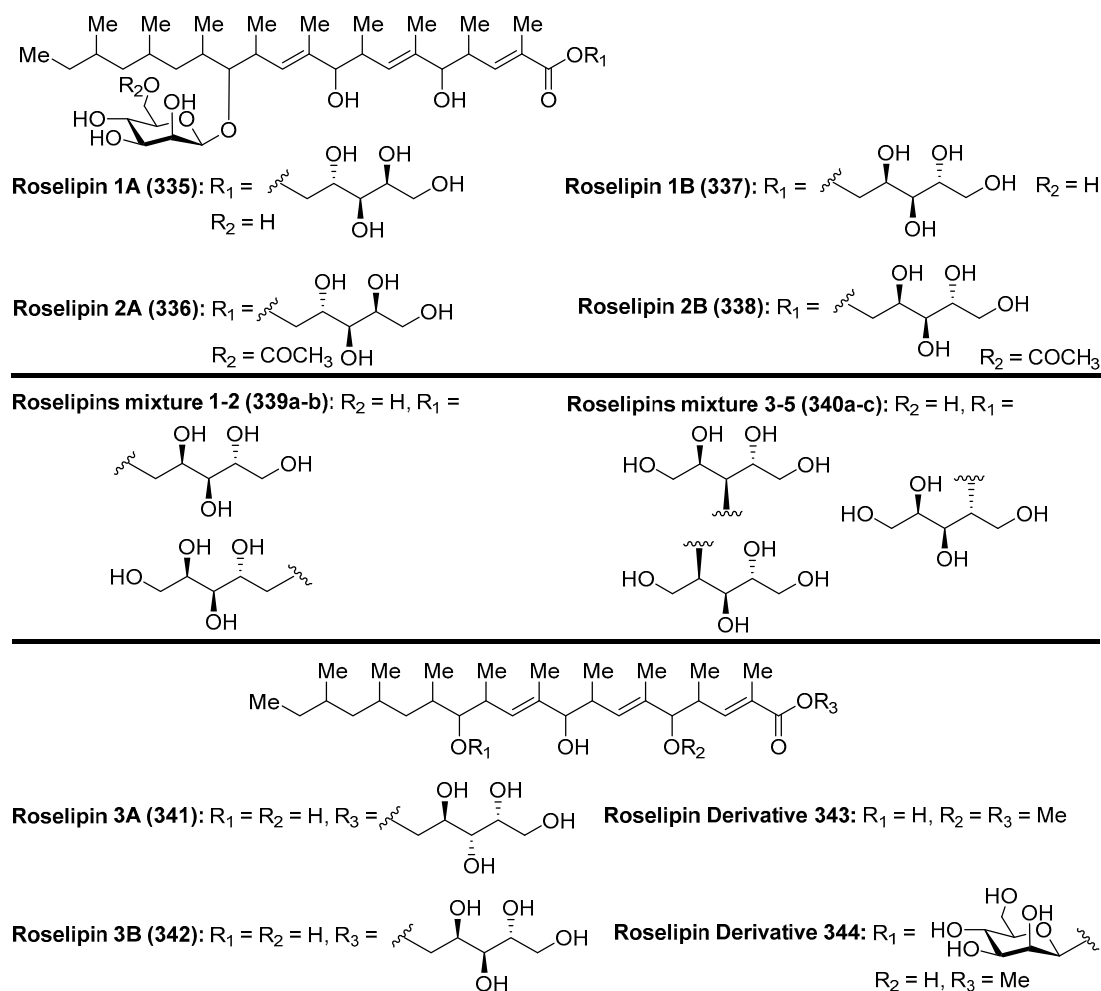
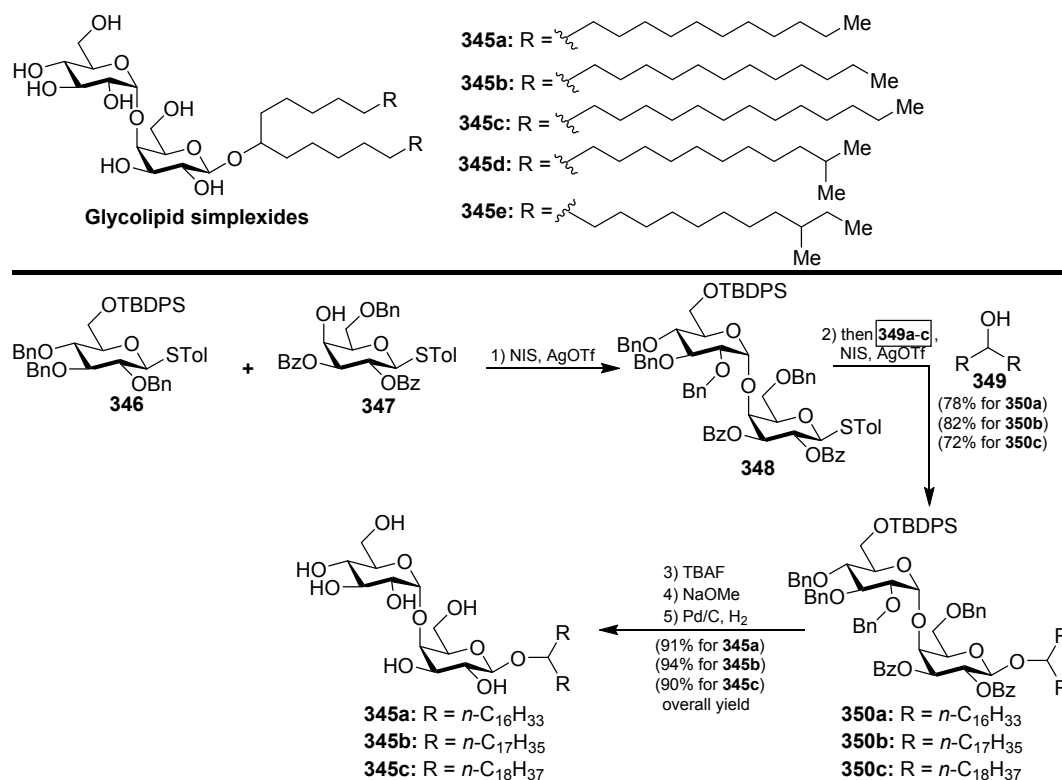


Figure 32. Structures of the roselipins (335–340) and derivatives 341–344.

4.12. Simplexides

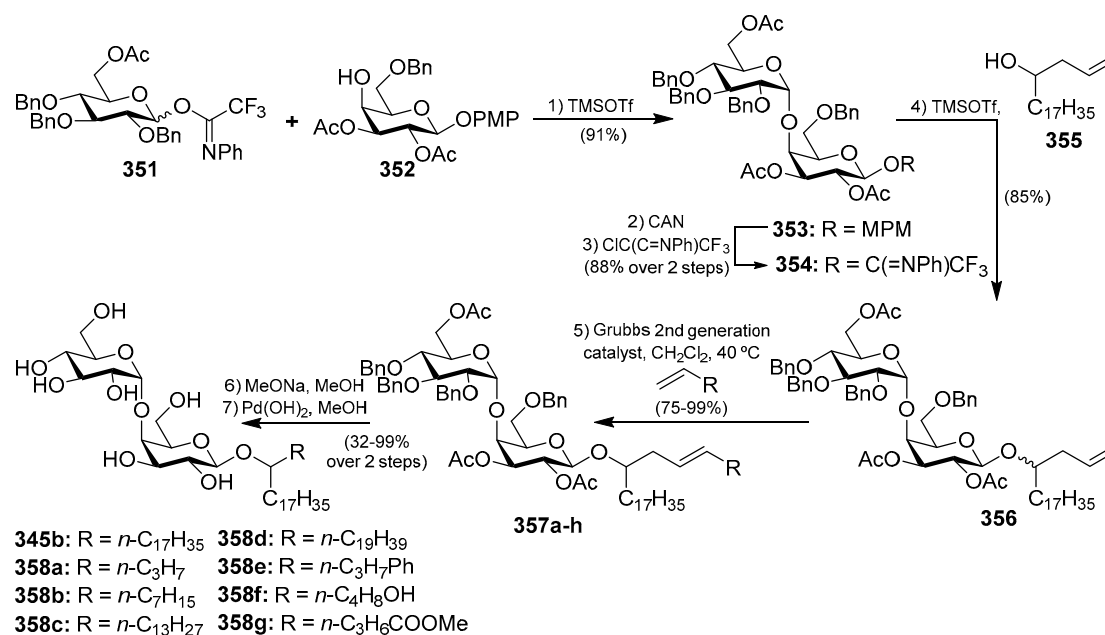
The same marine sponge that produces the plakosides and plaxyloside (Sections Plakosides and Plaxyloside), *Plakortis simplex*, has provided other types of glycolipids with immunosuppressive properties, the simplexides (345a–e), which were isolated as a mixture of related disaccharides [137]. Even though these compounds could not be separated by HPLC techniques, the authors were able to establish their structures via degradation and subsequent CG-MS analyses of the resulting methyl esters of the lipidic chains. Despite the remarkable structural differences with the plakosides, the simplexides share a very similar biological profile, showing potent inhibitory activity of the proliferation of T cells in the murine immune system when stimulated with concanavalin A through a noncytotoxic mechanism. Further biological studies demonstrated that the immunosuppressive effects of the simplexides are due to the induction that they exert on the expression and release of cytokines and chemokines from human monocytes by direct interaction with the CD1d receptors, expressed in these cells [138]. In addition, the simplexides induce the expansion of *i*NKT (natural killer T cells with an invariant T cell receptor alpha chain). An interesting synthesis for the simplexides was recently developed by Yingxia et al. [139], in which thioglycosides were employed to construct the complete simplexide scaffold in a one-pot

glycosylation method. Thus, the armed donor **346** reacted with the disarmed acceptor **347** by the action of the promoter system NIS/AgOTf to obtain, with a high α -selectivity, the disaccharide **348**. Without isolation of this product, the corresponding alcohol **349** was added to the crude mixture with additional promoters (NIS/AgOTf) to proceed with a second glycosylation reaction to provide **350a–c**, which were finally isolated in excellent yields and stereoselectivity. Final deprotection of **350a–c** gave simplexides **345a–c** (Scheme 26).



Scheme 26. Structures and synthesis of the simplexides (**345a–c**).

More recently, a synthesis of this class of glycolipids by Yu et al. [140] exploited the cross-metathesis reaction to build the lipidic chain from the allyl disaccharide **356**, efficiently prepared from glycosyl derivatives **351** and **352** via trichloroacetimidates. The crucial cross-metathesis reaction was achieved by the action of the Grubbs 2nd generation catalyst to obtain simplexides **357a–h** in very good yields, which were transformed into the final simplexides **345b** and **358a–g** in two additional steps (Scheme 27). This new efficient and concise synthesis of the simplexides and analogues will allow the determination of the structural factors that govern their interesting biological activities, a study that has yet to be completed by the authors.



Scheme 27. Synthesis of the natural simplexide **345b** and analogues **358a–g**.

5. Conclusions

Carbohydrates are often found as primary metabolites in the form of monomers, oligomers, or polymers, and play essential functions for life. However, in the realm of natural products, carbohydrates can be found mainly as components of glycoconjugates. In this case, they play important roles in conferring certain physical, chemical, and biological properties to the carrier molecules, being essential in cellular-recognition processes. A relevant example of the glycoconjugates are glycolipids and, notably, the glycolipids from a marine origin, which represent an important class of natural products with wide structural diversity and a broad range of biological activities, including antitumoral, antibiotic, antiviral, antimalarial, immunostimulatory, and neurotogenic activities. However, their difficult accessibility from natural sources, coupled with their extreme scarcity, has made their chemical synthesis essential to provide their access for additional studies. In addition, further understanding of their mechanisms of biological action allows for the rational design and synthesis of new analogues. Through the present review, we have presented the molecular and biological diversity of the glycolipids derived from marine sources, giving special emphasis on their syntheses as an important tool to confirm their molecular structures, gain insight into their biological activities, and the design of analogues for the development of new drugs. In conclusion, the readers have hopefully realized a greater interest in this class of natural products and the awesome power of chemical synthesis for the development of valuable bioactive compounds based on these natural products.

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References

1. Sasaki, D. *Glycolipids: New Research*; Nova Biomedical: New York, NY, USA, 2007; ISBN 978-1-60456-216-3.
2. Sweely, C.C. *Biochemistry of Lipids, Lipoproteins and Membranes*; Benjamin/Elsevier: Amsterdam, The Netherlands, 1991.

3. Hakomori, S.-I. Structure and Function of Sphingolipids in Transmembrane Signalling and Cell-Cell Interactions. *Biochem. Soc. Trans.* **1993**, *21*, 583–595. [[CrossRef](#)] [[PubMed](#)]
4. Varki, A. Biological Roles of Oligosaccharides: All of the Theories are Correct. *Glycobiology* **1993**, *3*, 97–130. [[CrossRef](#)] [[PubMed](#)]
5. Kolter, T. A View on Sphingolipids and Disease. *Chem. Phys. Lipids* **2011**, *164*, 590–606. [[CrossRef](#)] [[PubMed](#)]
6. Wennekes, T.; van den Berg, R.J.B.H.N.; Boot, R.G.; van der Marel, G.A.; Overkleeft, H.S.; Aerts, J.M.F.G. Glycosphingolipids—Nature, Function, and Pharmacological Modulation. *Angew. Chem. Int. Ed.* **2009**, *48*, 8848–8869. [[CrossRef](#)] [[PubMed](#)]
7. Mori, K.; Tashiro, T. Sphingolipids and Glycosphingolipids—Their Synthesis and Bioactivities. *Heterocycles* **2011**, *83*, 951–1003. [[CrossRef](#)]
8. Vankar, Y.D.; Schmidt, R.R. Chemistry of Glycosphingolipids—Carbohydrate Molecules of Biological Significance. *Chem. Soc. Rev.* **2000**, *29*, 201–216. [[CrossRef](#)]
9. Farwanah, H.; Kolter, T. Lipidomics of Glycosphingolipids. *Metabolites* **2012**, *2*, 134–164. [[CrossRef](#)] [[PubMed](#)]
10. Tan, R.X.; Chen, J.H. The Cerebrosides. *Nat. Prod. Rep.* **2003**, *20*, 509–534. [[CrossRef](#)] [[PubMed](#)]
11. Barreto-Bergter, E.; Sasaki, G.L.; de Souza, L.M. Structural Analysis of Fungal Cerebrosides. *Front. Microbiol.* **2011**, *2*, 239. [[CrossRef](#)] [[PubMed](#)]
12. Kolter, T. Ganglioside Biochemistry. *ISRN Biochem.* **2012**, *2012*, 506160. [[CrossRef](#)] [[PubMed](#)]
13. Kates, M. *Glycolipids, Phosphoglycolipids and Sulfoglycolipids. Handbook of Lipid Research*; Springer: Boston, MA, USA, 1990; Volume 6.
14. Schnaar, R.L.; Suzuki, A.; Stanley, P. Glycosphingolipids. In *Essentials of Glycobiology*, 2nd ed.; Varki, A., Cummings, R.D., Esko, J.D., Freeze, H.H., Stanley, P., Bertozzi, C.R., Hart, G.W., Etzler, M.E., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, USA, 2009; pp. 129–141.
15. Kulkarni, S.S. Synthesis of Glycosphingolipids. In *Glycochemical Synthesis: Strategies and Applications*; Hung, S.-C., Zulueta, M.M.L., Eds.; Wiley: Hoboken, NJ, USA, 2016; pp. 293–326.
16. Barnathan, G.; Couzinet-Mossion, A.; Wielgosz-Collin, G. Glycolipids from Marine Invertebrates. In *Outstanding Marine Molecules: Chemistry, Biology, Analysis*, 1st ed.; La Barre, S., Kornprobst, J.-M., Eds.; Wiley-VCH Verlag GmbH and Co., KGaA: Weinheim, Germany, 2014; pp. 99–162, ISBN 9783527681501.
17. Zhang, J.; Li, C.; Yu, G.; Guan, H. Total Synthesis and Structure–Activity Relationship of Glycoglycerolipids from Marine Organisms. *Mar. Drugs* **2014**, *12*, 3634–3659. [[CrossRef](#)] [[PubMed](#)]
18. Banchet-Cadeddu, A.; Hénon, E.; Dauchez, M.; Renault, J.-H.; Monneaux, F.; Haudrechy, A. The Stimulating Adventure of KR7000. *Org. Biomol. Chem.* **2011**, *9*, 3080–3104. [[CrossRef](#)] [[PubMed](#)]
19. Anderson, B.L.; Teyton, L.; Bendelac, A.; Savage, P.B. Stimulation of Natural Killer T Cells by Glycolipids. *Molecules* **2013**, *18*, 15662–15688. [[CrossRef](#)] [[PubMed](#)]
20. Kawano, Y.; Higuchi, R.; Isobe, R.; Komori, T. Isolation and Structure of Six New Cerebrosides. *Liebigs Ann. Chem.* **1988**, *1988*, 19–24. [[CrossRef](#)]
21. Sugiyama, S.; Honda, M.; Komori, T. Synthesis of Acanthacerebroside A. *Liebigs Ann. Chem.* **1990**, *1990*, 1063–1068. [[CrossRef](#)]
22. Higuchi, R.; Kagoshima, M.; Komori, T. Structures of Three New Cerebrosides, Astrocerebroside A, B, and C and of Related Nearly Homogeneous Cerebrosides. *Liebigs Ann. Chem.* **1990**, *1990*, 659–663. [[CrossRef](#)]
23. Higuchi, R.; Jhou, J.X.; Inukai, K.; Komori, T. Isolation and Structure of Six New Cerebrosides, Asteriacerebrosides A–F, and Two Known Cerebrosides, Astrocerebroside A and Acanthacerebroside C. *Liebigs Ann. Chem.* **1991**, *1991*, 745–752. [[CrossRef](#)]
24. Ishii, T.; Okino, T.; Mino, Y. A Ceramide and Cerebroside from the Starfish *Asterias amurensis* Lütken and Their Plant-Growth Promotion Activities. *J. Nat. Prod.* **2006**, *69*, 1080–1082. [[CrossRef](#)] [[PubMed](#)]
25. Park, T.; Park, Y.S.; Rho, J.-R.; Kim, Y.H. Structural Determination of Cerebrosides Isolated from *Asterias amurensis* Starfish Eggs using High-Energy Collision-Induced Dissociation of Sodium-Adducted Molecules. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 572–578. [[CrossRef](#)] [[PubMed](#)]
26. Chida, N.; Sakata, N.; Murai, K.; Tobe, T.; Nagase, T.; Ogawa, S. Total Synthesis of Acanthacerebroside A and Astrocerebroside A via a Chiral Epoxide Intermediate Derived from L-Quebrachitol. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 259–272. [[CrossRef](#)]
27. Natori, T.; Koezuka, Y.; Higa, T. Agelasphins, Novel α -Galactosylceramides from the Marine Sponge *Agelas mauritianus*. *Tetrahedron Lett.* **1993**, *34*, 5591–5592. [[CrossRef](#)]

28. Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. Agelasphins, Novel Antitumor and Immunostimulatory Cerebrosides from the Marine Sponge *Agelas mauritianus*. *Tetrahedron* **1994**, *50*, 2771–2784. [[CrossRef](#)]
29. Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. Structure-Activity Relationship of α -Galactosylceramides against B16-Bearing Mice. *J. Med. Chem.* **1995**, *38*, 2176–2187. [[CrossRef](#)] [[PubMed](#)]
30. Giaccone, G.; Punt, C.J.A.; Ando, Y.; Ruijter, R.; Nishi, N.; Peters, M.; von Blomberg, B.M.E.; Scheper, R.J.; van der Vliet, H.J.J.; van den Eertwegh, A.J.M.; et al. A Phase I Study of the Natural Killer T-Cell Ligand α -Galactosylceramide (KRN7000) in Patients with Solid Tumors. *Clin. Cancer Res.* **2002**, *8*, 3702–3709. [[PubMed](#)]
31. Motoki, K.; Kobayashi, E.; Uchida, T.; Fukushima, H.; Koezuka, Y. Antitumor Activities of α -, β -Monogalactosylceramides and Four Diastereomers of an α -Galactosylceramide. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 705–710. [[CrossRef](#)]
32. Reddy, B.G.; Silk, J.D.; Salio, M.; Balamurugan, R.; Shepherd, D.; Ritter, G.; Cerundolo, V.; Schmidt, R.R. Nonglycosidic Agonists of Invariant NKT Cells for Use as Vaccine Adjuvants. *ChemMedChem* **2009**, *4*, 171–175. [[CrossRef](#)] [[PubMed](#)]
33. Costantino, V.; D'Esposito, M.; Fattorusso, E.; Mangoni, A.; Basilico, N.; Parapini, S.; Taramelli, D. Damicoside from *Axinella damicornis*: The Influence of a Glycosylated Galactose 4-OH Group on the Immunostimulatory Activity of α -Galactoglycosphingolipids. *J. Med. Chem.* **2005**, *48*, 7411–7417. [[CrossRef](#)] [[PubMed](#)]
34. Akimoto, K.; Natori, T.; Morita, M. Synthesis and Stereochemistry of Agelasphin-9b. *Tetrahedron Lett.* **1993**, *34*, 5593–5596. [[CrossRef](#)]
35. Farokhi, F.; Grellier, P.; Clément, M.; Roussakis, C.; Loiseau, P.; Genin-Seward, E.; Kornprobst, J.-M.; Barnathan, G.; Wielgosz-Collin, G. Antimalarial Activity of Axidjiferosides, New β -Galactosylceramides from the African Sponge *Axinyssa djiferi*. *Mar. Drugs* **2013**, *11*, 1304–1315. [[CrossRef](#)] [[PubMed](#)]
36. Yamada, K.; Hara, E.; Miyamoto, T.; Higuchi, R.; Isobe, R.; Honda, S. Isolation and Structure of Biologically Active Glycosphingolipids from the Sea Cucumber *Cucumaria echinata*. *Eur. J. Org. Chem.* **1998**, *1998*, 371–378. [[CrossRef](#)]
37. Li, H.; Matsunaga, S.; Fusetani, N. Halicylindrosides, Antifungal and Cytotoxic Cerebrosides from the Marine Sponge *Halichondria cylindrata*. *Tetrahedron* **1995**, *51*, 2273–2280. [[CrossRef](#)]
38. Murakami, T.; Taguchi, K. Stereocontrolled Synthesis of Novel Phytosphingosine-type Glucosaminocerebrosides. *Tetrahedron* **1999**, *55*, 989–1004. [[CrossRef](#)]
39. Durin, R.; Zubia, E.; Ortega, M.J.; Naranjo, S.; Salv, J. Phallusides, New Glucosphingolipids from the Ascidian *Phallusia fumigata*. *Tetrahedron* **1998**, *54*, 14597–14602. [[CrossRef](#)]
40. Karlsson, K.-A.; Leffler, H.; Samuelsson, B.E. Characterization of Cerebroside (Monoglycosylceramide) from the Sea Anemone, *Metridium senile*. *Biochim. Biophys. Acta* **1979**, *574*, 79–93. [[CrossRef](#)]
41. Kawai, G.; Ikeda, Y. Fruiting-Inducing Activity of Cerebrosides Observed with *Schizophyllum commune*. *Biochim. Biophys. Acta* **1982**, *719*, 612–618. [[CrossRef](#)]
42. Hammami, S.; Bergaoui, A.; Boughalleb, N.; Romdhane, A.; Khoja, I.; Ben Halima Kamel, M.; Mighri, Z. Antifungal Effects of Secondary Metabolites Isolated from Marine Organisms Collected from the Tunisian Coast. *C. R. Chim.* **2010**, *13*, 1397–1400. [[CrossRef](#)]
43. Black, F.J.; Kocienski, P.J. Synthesis of Phalluside-1 and Sch II using 1,2-Metallate Rearrangements. *Org. Biomol. Chem.* **2010**, *8*, 1188–1193. [[CrossRef](#)] [[PubMed](#)]
44. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A.; Teta, R. Amphiceramide A and B, Novel Glycosphingolipids from the Marine Sponge *Amphimedon compressa*. *Eur. J. Org. Chem.* **2009**, *2009*, 2112–2119. [[CrossRef](#)]
45. Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A. Glycolipids from Sponges. 6. Plakoside A and B, Two Unique Prenylated Glycosphingolipids with Immunosuppressive Activity from the Marine Sponge *Plakortis simplex*. *J. Am. Chem. Soc.* **1997**, *119*, 12465–12470. [[CrossRef](#)]
46. Costantino, V.; Fattorusso, E.; Mangoni, A. Glycolipids from Sponges. Part 9: Plakoside C and D, Two Further Prenylated Glycosphingolipids from the Marine Sponge *Ectyoplasia ferox*. *Tetrahedron* **2000**, *56*, 5953–5957. [[CrossRef](#)]
47. Nicolaou, K.C.; Li, J.; Zenke, G. Total Synthesis and Biological Evaluation of Glycolipids Plakosides A, B and Their Analogs. *Helv. Chim. Acta* **2000**, *83*, 1977–2006. [[CrossRef](#)]

48. Seki, M.; Kayo, A.; Mori, K. Synthesis of (2S,3R,11S,12R,2''R,11'''S,12'''R)-Plakoside A, a Prenylated and Immunosuppressive Marine Galactosphingolipid with Cyclopropane-Containing Alkyl Chains. *Tetrahedron Lett.* **2001**, *42*, 2357–2360. [[CrossRef](#)]
49. Seki, M.; Mori, K. Synthesis of a Prenylated and Immunosuppressive Marine Galactosphingolipid with Cyclopropane-Containing Alkyl Chains: (2S,3R,11S,12R,2''R, 5'''Z,11'''S,12'''R)-Plakoside A and Its (2S,3R,11R,12S,2''R,5'''Z,11'''R,12'''S) Isomer. *Eur. J. Org. Chem.* **2001**, *2001*, 3797–3809. [[CrossRef](#)]
50. Mori, K.; Tashiro, T.; Akasaka, K.; Ohru, H.; Fattorusso, E. Determination of the Absolute Configuration at the Two Cyclopropane Moieties of Plakoside A, an Immunosuppressive Marine Galactosphingolipid. *Tetrahedron Lett.* **2002**, *43*, 3719–3722. [[CrossRef](#)]
51. Tashiro, T.; Akasaka, K.; Ohru, H.; Fattorusso, E.; Mori, K. Determination of the Absolute Configuration at the Two Cyclopropane Moieties of Plakoside A, an Immunosuppressive Marine Galactosphingolipid. *Eur. J. Org. Chem.* **2002**, *2002*, 3659–3665. [[CrossRef](#)]
52. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A.; Teta, R. Terpioside from the Marine Sponge *Terpios* sp., the First Glycosphingolipid Having an L-Fucofuranose Unit. *Eur. J. Org. Chem.* **2008**, *2008*, 2130–2134. [[CrossRef](#)]
53. Cutignano, A.; De Palma, R.; Fontana, A. A Chemical Investigation of the Antarctic Sponge *Lyssodendoryx flabellata*. *Nat. Prod. Res.* **2012**, *26*, 1240–1248. [[CrossRef](#)] [[PubMed](#)]
54. Costantino, V.; Fattorusso, E.; Mangoni, A.; Teta, R.; Panza, E.; Ianaro, A. Terpioside B, a Difucosyl GSL from the Marine Sponge *Terpios* sp. is a Potent Inhibitor of NO Release. *Bioorg. Med. Chem.* **2010**, *18*, 5310–5315. [[CrossRef](#)] [[PubMed](#)]
55. Pettit, G.R.; Xu, J.; Gingrich, D.E.; Williams, M.D.; Doubek, D.L.; Chapuis, J.-C.; Schmidt, J.M. Antineoplastic agents. Part 395. Isolation and Structure of Agelagalastatin from the Papua New Guinea Marine Sponge *Agelas* sp. *Chem. Commun.* **1999**, 915–916. [[CrossRef](#)]
56. Lee, Y.J.; Lee, B.-Y.; Jeon, H.B.; Kim, K.S. Total Synthesis of Agelagalastatin. *Org. Lett.* **2006**, *8*, 3971–3974. [[CrossRef](#)] [[PubMed](#)]
57. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. Glycolipids from Sponges. 13. Clarhamnoside, the First Rhamnosylated α -Galactosylceramide from *Agelas clathrodes*. Improving Spectral Strategies for Glycoconjugate Structure Determination. *J. Org. Chem.* **2004**, *69*, 1174–1179. [[CrossRef](#)] [[PubMed](#)]
58. Ding, N.; Li, C.; Liu, Y.; Zhang, Z.; Li, Y. Concise Synthesis of Clarhamnoside, a Novel Glycosphingolipid Isolated from the Marine Sponge *Agela clathrodes*. *Carbohydr. Res.* **2007**, *342*, 2003–2013. [[CrossRef](#)] [[PubMed](#)]
59. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. Vesparioside from the Marine Sponge *Sphaciospongia vesparia*, the First Diglycosylceramide with a Pentose Sugar Residue. *Eur. J. Org. Chem.* **2005**, *2005*, 368–373. [[CrossRef](#)]
60. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. Glycolipids from Sponges. 20. J-Coupling Analysis for Stereochemical Assignments in Furanosides: Structure Elucidation of Vesparioside B, a Glycosphingolipid from the Marine Sponge *Sphaciospongia vesparia*. *J. Org. Chem.* **2008**, *73*, 6158–6165. [[CrossRef](#)] [[PubMed](#)]
61. Gao, P.-C.; Zhu, S.-Y.; Cao, H.; Yang, J.-S. Total Synthesis of Marine Glycosphingolipid Vesparioside B. *J. Am. Chem. Soc.* **2016**, *138*, 1684–1688. [[CrossRef](#)] [[PubMed](#)]
62. Ijuin, T.; Kitajima, K.; Song, Y.; Kitazume, S.; Inoue, S.; Haslam, S.M.; Morris, H.R.; Dell, A.; Inoue, Y. Isolation and identification of novel sulfated and nonsulfated oligosialyl glycosphingolipids from sea urchin sperm. *Glycoconj. J.* **1996**, *13*, 401–413. [[CrossRef](#)] [[PubMed](#)]
63. Yamada, K.; Tanabe, K.; Miyamoto, T.; Kusumoto, T.; Inagaki, M.; Higuchi, R. Isolation and Structure of a Monomethylated Ganglioside Possessing Neuritogenic Activity from the Ovary of the Sea Urchin *Diadema setosum*. *Chem. Pharm. Bull.* **2008**, *56*, 734–737. [[CrossRef](#)] [[PubMed](#)]
64. Chen, W.-S.; Sawant, R.C.; Yang, S.-A.; Liao, Y.-J.; Liao, J.-W.; Badsara, S.S.; Luo, S.-Y. Synthesis of ganglioside Hp-s1. *RSC Adv.* **2014**, *4*, 47752–47761. [[CrossRef](#)]
65. Tsai, Y.-F.; Shih, C.-H.; Su, Y.-T.; Yao, C.-H.; Lian, J.-F.; Liao, C.-C.; Hsia, C.-W.; Shui, H.-A.; Rani, R. The Total Synthesis of a Ganglioside Hp-s1 Analogue Possessing Neuritogenic Activity by Chemoselective Activation Glycosylation. *Org. Biomol. Chem.* **2012**, *10*, 931–934. [[CrossRef](#)] [[PubMed](#)]
66. Hung, J.-T.; Yeh, C.-H.; Yang, S.-A.; Lin, C.-Y.; Tai, H.-J.; Shelke, G.B.; Reddy, D.M.; Yu, A.L.; Luo, S.-Y. Design, Synthesis, and Biological Evaluation of Ganglioside Hp-s1 Analogues Varying at Glucosyl Moiety. *ACS Chem. Neurosci.* **2016**, *7*, 1107–1111. [[CrossRef](#)] [[PubMed](#)]

67. Shelke, G.B.; Chen, B.-R.; Yang, S.-A.; Kuo, T.-M.; Syu, Y.-L.; Ko, Y.-C.; Luo, S.-Y. Mild and Highly α -Selective O-Sialylation Method Based on Pre-Activation: Access to Gangliosides Hp-s1, DSG-A, and Their Analogues. *Asian J. Org. Chem.* **2017**, *6*, 1556–1560. [[CrossRef](#)]
68. Wu, Y.-F.; Tsai, Y.-F.; Guo, J.-R.; Yu, C.-P.; Yu, H.-M.; Liao, C.-C. First Total Synthesis of Ganglioside DSG-A Possessing Neuritogenic Activity. *Org. Biomol. Chem.* **2014**, *12*, 9345–9349. [[CrossRef](#)] [[PubMed](#)]
69. Yamada, K.; Matsubara, R.; Kaneko, M.; Miyamoto, T.; Higuchi, R. Isolation and Structure of a Biologically Active Ganglioside Molecular Species from the Sea Cucumber *Holothuria leucospilota*. *Chem. Pharm. Bull.* **2001**, *49*, 447–452. [[CrossRef](#)] [[PubMed](#)]
70. Iwayama, Y.; Ando, H.; Ishida, H.; Kiso, M. A First Total Synthesis of Ganglioside HLG-2. *Chem. Eur. J.* **2009**, *15*, 4637–4648. [[CrossRef](#)] [[PubMed](#)]
71. Xu, F.-F.; Wang, Y.; Xiong, D.-C.; Ye, X.-S. Stereoselective Synthesis of the Trisaccharide Moiety of Ganglioside HLG-2. *J. Org. Chem.* **2014**, *79*, 797–802. [[CrossRef](#)] [[PubMed](#)]
72. Higuchi, R.; Inoue, S.; Inagaki, K.; Sakai, M.; Miyamoto, T.; Komori, T.; Inagaki, M.; Isobe, R. Isolation and Structure of a New Biologically Active Ganglioside Molecular Species from the Starfish *Asterina pectinifera*. *Chem. Pharm. Bull.* **2006**, *54*, 287–291. [[CrossRef](#)] [[PubMed](#)]
73. Goto, K.; Sawa, M.; Tamai, H.; Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. The Total Synthesis of Starfish Ganglioside GP3 Bearing a Unique Sialyl Glycan Architecture. *Chem. Eur. J.* **2016**, *22*, 8323–8331. [[CrossRef](#)] [[PubMed](#)]
74. Higuchi, R.; Mori, T.; Sugata, T.; Yamada, K.; Miyamoto, T. Partial Synthesis of a Sea Cucumber Ganglioside Analogue from a Starfish Cerebroside. *Eur. J. Org. Chem.* **1999**, *1999*, 145–147. [[CrossRef](#)]
75. Kaneko, M.; Kisa, F.; Yamada, K.; Miyamoto, T.; Higuchi, R. Structure of Neuritogenic Active Ganglioside from the Sea Cucumber *Stichopus japonicus*. *Eur. J. Org. Chem.* **1999**, *1999*, 3171–3174. [[CrossRef](#)]
76. Kaneko, M.; Kisa, F.; Yamada, K.; Miyamoto, T.; Higuchi, R. Structure of a New Neuritogenic-Active Ganglioside from the Sea Cucumber *Stichopus japonicus*. *Eur. J. Org. Chem.* **2003**, *2003*, 1004–1008. [[CrossRef](#)]
77. Tamai, H.; Ando, H.; Tanaka, H.-N.; Hosoda-Yabe, R.; Yabe, T.; Ishida, H.; Kiso, M. The Total Synthesis of the Neurogenic Ganglioside LLG-3 Isolated from the Starfish *Linckia laevigata*. *Angew. Chem. Int. Ed.* **2011**, *50*, 2330–2333. [[CrossRef](#)] [[PubMed](#)]
78. Tamai, H.; Imamura, A.; Ogawa, J.; Ando, H.; Ishida, H.; Kiso, M. First Total Synthesis of Ganglioside GAA-7 from Starfish *Asterias amurensis versicolor*. *Eur. J. Org. Chem.* **2015**, *2015*, 5199–5211. [[CrossRef](#)]
79. Kaneko, M.; Yamada, K.; Miyamoto, T.; Inagaki, M.; Higuchi, R. Neuritogenic Activity of Gangliosides from Echinoderms and Their Structure-Activity Relationship. *Chem. Pharm. Bull.* **2007**, *55*, 462–463. [[CrossRef](#)] [[PubMed](#)]
80. Kisa, F.; Yamada, K.; Miyamoto, T.; Inagaki, M.; Higuchi, R. Isolation and Structure of Biologically Active Monosialo-Gangliosides from the Sea Cucumber *Cucumaria echinata*. *Chem. Pharm. Bull.* **2006**, *54*, 982–987. [[CrossRef](#)] [[PubMed](#)]
81. Kisa, F.; Yamada, K.; Miyamoto, T.; Inagaki, M.; Higuchi, R. Isolation and Structure of Biologically Active Disialo- and Trisialo-Gangliosides from the Sea Cucumber *Cucumaria echinata*. *Chem. Pharm. Bull.* **2006**, *54*, 1293–1298. [[CrossRef](#)] [[PubMed](#)]
82. Warabi, K.; Hamada, T.; Nakao, Y.; Matsunaga, S.; Hirota, H.; van Soest, R.W.M.; Fusetani, N. Axinelloside A, an Unprecedented Highly Sulfated Lipopolysaccharide Inhibiting Telomerase, from the Marine Sponge, *Axinella infundibula*. *J. Am. Chem. Soc.* **2005**, *127*, 13262–13270. [[CrossRef](#)] [[PubMed](#)]
83. Warabi, K.; Matsunaga, S.; van Soest, R.W.M.; Fusetani, N. Dictyodendrins A-E, the First Telomerase-Inhibitory Marine Natural Products from the Sponge *Dictyodendrilla verongiformis*. *J. Org. Chem.* **2003**, *68*, 2765–2770. [[CrossRef](#)] [[PubMed](#)]
84. Rodriguez, J.; Walczak, M.A. Synthesis of Asymmetrically Substituted *scyllo*-Inositol. *Tetrahedron Lett.* **2016**, *57*, 3281–3283. [[CrossRef](#)]
85. Guang, J.; Rumlow, Z.A.; Wiles, L.M.; O'Neill, S.; Walczak, M.A. Sulfated Liposaccharides Inspired by Telomerase Inhibitor Axinelloside A. *Tetrahedron Lett.* **2017**, *58*, 4867–4871. [[CrossRef](#)]
86. Andersen, R.J.; Tagliatela-Scafati, O. Avrainvilloside, a 6-Deoxy-6-aminoglucoglycerolipid from the Green Alga *Avrainvillea nigricans*. *J. Nat. Prod.* **2005**, *68*, 1428–1430. [[CrossRef](#)] [[PubMed](#)]
87. Zhou, B.-N.; Tang, S.; Johnson, R.K.; Mattern, M.P.; Lazo, J.S.; Sharlow, E.R.; Harich, K.; Kingston, D.G.I. New Glycolipid Inhibitors of Myt1 Kinase. *Tetrahedron* **2005**, *61*, 883–887. [[CrossRef](#)]

88. Göllner, C.; Philipp, C.; Dobner, B.; Sippl, W.; Schmidt, M. First Total Synthesis of 1,2-dipalmitoyl-3-(*N*-palmitoyl-6'-amino-6'-deoxy- α -D-glucosyl)-sn-glycerol—A Glycoglycerolipid of a Marine Alga with a High Inhibitor Activity against Human Myt1-Kinase. *Carbohydr. Res.* **2009**, *344*, 1628–1631. [[CrossRef](#)] [[PubMed](#)]
89. Sun, Y.; Zhang, J.; Li, C.; Guan, H.; Yu, G. Synthesis of Glycoglycerolipid of 1,2-dipalmitoyl-3-(*N*-palmitoyl-6'-amino-6'-deoxy- α -D-glucosyl)-sn-glycerol and its Analogues, Inhibitors of Human Myt1-Kinase. *Carbohydr. Res.* **2012**, *355*, 6–12. [[CrossRef](#)] [[PubMed](#)]
90. Zhang, J.; Sun, Y.; Wang, W.; Zhang, X.; Li, C.; Guan, H. Synthesis and Antiviral Evaluation of 6'-acylamido-6'-deoxy- α -D-mannoglycerolipids. *Carbohydr. Res.* **2013**, *381*, 74–82. [[CrossRef](#)] [[PubMed](#)]
91. Li, C.; Sun, Y.; Zhang, J.; Zhao, Z.; Yu, G.; Guan, H. Synthesis of 6'-acylamido-6'-deoxy- α -D-galactoglycerolipids. *Carbohydr. Res.* **2013**, *376*, 15–23. [[CrossRef](#)] [[PubMed](#)]
92. Ren, L.; Zhang, J.; Ma, H.; Sun, L.; Zhang, X.; Yu, G.; Guan, H.; Wang, W.; Li, C. Synthesis and Anti-Influenza A Virus Activity of 6'-amino-6'-deoxy-glycoglycerolipids Analogs. *Mar. Drugs* **2016**, *14*, 116–130. [[CrossRef](#)] [[PubMed](#)]
93. Costantino, V.; Fattorusso, E.; Mangoni, A. Isolation of Five-Membered Cyclitol Glycolipids, Crasserides: Unique Glycerides from the Sponge *Pseudoceratina crassa*. *J. Org. Chem.* **1993**, *58*, 186–191. [[CrossRef](#)]
94. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. Glycolipids from Sponge. 11. Isocrasserides, Novel Glycolipids with a Five-Membered Cyclitol Widely Distributed in Marine Sponges. *J. Nat. Prod.* **2002**, *65*, 883–886. [[CrossRef](#)] [[PubMed](#)]
95. Aoki, S.; Higuchi, K.; Kato, A.; Murakami, N.; Kobayashi, M. Myrmekiosides A and B, Novel Mono-*O*-alkyl-diglycosylglycerols Reversing Tumor Cell Morphology of *ras*-Transformed Cells from a Marine Sponge of *Myrmekioderma* sp. *Tetrahedron* **1999**, *55*, 14865–14870. [[CrossRef](#)]
96. Farokhi, F.; Wielgosz-Collin, G.; Robic, A.; Debitus, C.; Malleter, M.; Roussakis, C.; Kornprobst, J.-M.; Barnathan, G. Antiproliferative Activity against Human non-Small Cell Lung Cancer of Two *O*-alkyl-diglycosylglycerols from the Marine Sponges *Myrmekioderma dendyi* and *Trikentrion laeve*. *Eur. J. Med. Chem.* **2012**, *49*, 406–410. [[CrossRef](#)] [[PubMed](#)]
97. Zhang, J.; Li, C.; Sun, L.; Yu, G.; Guan, H. Total Synthesis of Myrmekioside A, a Mono-*O*-alkyl-diglycosylglycerol from Marine Sponge *Myrmekioderma* sp.: Total Synthesis of Myrmekioside A. *J. Org. Chem.* **2015**, *2015*, 4246–4253. [[CrossRef](#)]
98. Williams, D.E.; Sturgeon, C.M.; Roberge, M.; Andersen, R.J. Nigricanosides A and B, Antimitotic Glycolipids Isolated from the Green Alga *Avrainvillea nigricans* Collected in Dominica. *J. Am. Chem. Soc.* **2007**, *129*, 5822–5823. [[CrossRef](#)] [[PubMed](#)]
99. Tsunoda, T.; Fujiwara, K.; Okamoto, S.; Kondo, Y.; Akiba, U.; Ishigaki, Y.; Katoono, R.; Suzuki, T. Double Bond Formation Based on Nitroaldol Reaction and Radical Elimination: A Prototype Segment Connection Method for the Total Synthesis of Nigricanoside A Dimethyl Ester. *Tetrahedron Lett.* **2018**, *59*, 1846–1850. [[CrossRef](#)]
100. Kinashi, N.; Fujiwara, K.; Tsunoda, T.; Katoono, R.; Kawai, H.; Suzuki, T. A stereoselective Method for the Construction of the C8'-*O*-C6'' Ether of Nigricanoside-A: Synthesis of Simple Models for the C20 Lipid Chain/Galactosyl Glycerol Segment. *Tetrahedron Lett.* **2013**, *54*, 4564–4567. [[CrossRef](#)]
101. Kurashina, Y.; Kuwahara, S. Stereoselective Synthesis of a Protected Form of (6*R*,7*E*,9*S*,10*R*,12*Z*)-6,9,10-trihydroxy-7,12-hexadecadienoic Acid. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 605–607. [[CrossRef](#)] [[PubMed](#)]
102. Espindola, A.P.D.M.; Crouch, R.; DeBergh, J.R.; Ready, J.M.; MacMillan, J.B. Deconvolution of Complex NMR Spectra in Small Molecules by Multi Frequency Homonuclear Decoupling (MDEC). *J. Am. Chem. Soc.* **2009**, *131*, 15994–15995. [[CrossRef](#)] [[PubMed](#)]
103. Chen, J.; Koswatta, P.; DeBergh, J.R.; Fu, P.; Pan, E.; MacMillan, J.B.; Ready, J.M. Structure Elucidation of Nigricanoside A through Enantioselective Total Synthesis. *Chem. Sci.* **2015**, *6*, 2932–2937. [[CrossRef](#)] [[PubMed](#)]
104. Wojnar, J.M.; Northcote, P.T. The Agminosides: Naturally Acetylated Glycolipids from the New Zealand Marine Sponge *Raspailia agminata*. *J. Nat. Prod.* **2011**, *74*, 69–73. [[CrossRef](#)] [[PubMed](#)]
105. Ohta, S.; Ohta, E.; Ikegami, S. Ancorinoside A: A Novel Tetramic Acid Glycoside from the Marine Sponge, *Ancorina* sp. which Specifically Inhibits Blastulation of Starfish Embryos. *J. Org. Chem.* **1997**, *62*, 6452–6453. [[CrossRef](#)]

106. Fujita, M.; Nakao, Y.; Matsunaga, S.; Seiki, M.; Itoh, Y.; van Soest, R.W.M.; Fusetani, N. Ancorinosides B–D, Inhibitors of Membrane Type 1 Matrix Metalloproteinase (MT1-MMP), from the Marine Sponge *Penares sollasi* Thiele. *Tetrahedron* **2001**, *57*, 1229–1234. [[CrossRef](#)]
107. Ohta, E.; Ohta, S.; Ikegami, S. Ancorinoside A Mg Salt from the Marine Sponge, *Ancorina* sp., which Specifically Inhibits Blastulation of Starfish Embryos. *Tetrahedron* **2001**, *57*, 4699–4703. [[CrossRef](#)]
108. Petermichl, M.; Schobert, R. Total Synthesis of the Diglycosidic Tetramic Acid Ancorinoside A. *Chem. Eur. J.* **2017**, *23*, 14743–14746. [[CrossRef](#)] [[PubMed](#)]
109. Leão, P.N.; Nakamura, H.; Costa, M.; Pereira, A.R.; Martins, R.; Vasconcelos, V.; Gerwick, W.H.; Balskus, E.P. Biosynthesis-Assisted Structural Elucidation of the Bartolosides, Chlorinated Aromatic Glycolipids from Cyanobacteria. *Angew. Chem. Int. Ed.* **2015**, *54*, 11063–11067. [[CrossRef](#)] [[PubMed](#)]
110. Afonso, T.B.; Costa, M.S.; Rezende de Castro, R.; Freitas, S.; Silva, A.; Schneider, M.P.C.; Martins, R.; Leão, P.N. Bartolosides E–K from a Marine Coccoid Cyanobacterium. *J. Nat. Prod.* **2016**, *79*, 2504–2513. [[CrossRef](#)] [[PubMed](#)]
111. Linington, R.G.; Robertson, M.; Gauthier, A.; Finlay, B.B.; van Soest, R.; Andersen, R.J. Caminoside A, an Antimicrobial Glycolipid Isolated from the Marine Sponge *Caminus sphaeroconia*. *Org. Lett.* **2002**, *4*, 4089–4092. [[CrossRef](#)] [[PubMed](#)]
112. Linington, R.G.; Robertson, M.; Gauthier, A.; Finlay, B.B.; MacMillan, J.B.; Molinski, T.F.; van Soest, R.; Andersen, R.J. Caminosides B–D, Antimicrobial Glycolipids Isolated from the Marine Sponge *Caminus sphaeroconia*. *J. Nat. Prod.* **2006**, *69*, 173–177. [[CrossRef](#)] [[PubMed](#)]
113. MacMillan, J.B.; Linington, R.G.; Andersen, R.J.; Molinski, T.F. Stereochemical Assignment in Acyclic Lipids Across Long Distance by Circular Dichroism: Absolute Stereochemistry of the Aglycone of Caminoside A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5946–5951. [[CrossRef](#)] [[PubMed](#)]
114. Sun, J.; Han, X.; Yu, B. First Total Synthesis of Caminoside A, an Antimicrobial Glycolipid from Sponge. *Synlett* **2005**, *3*, 437–440. [[CrossRef](#)]
115. Zhang, Z.; Zong, C.; Song, G.; Lv, G.; Chun, Y.; Wang, P.; Ding, N.; Li, Y. Total Synthesis of Caminoside B, a Novel Antimicrobial Glycolipid Isolated from the Marine Sponge *Caminus sphaeroconia*. *Carbohydr. Res.* **2010**, *345*, 750–760. [[CrossRef](#)] [[PubMed](#)]
116. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. Glycolipids from Sponges. Part 17. Clathrosides and Isoclathrosides, Unique Glycolipids from the Caribbean Sponge *Agelas clathrodes*. *J. Nat. Prod.* **2006**, *69*, 73–78. [[CrossRef](#)] [[PubMed](#)]
117. Barbieri, L.; Costantino, V.; Fattorusso, E.; Mangoni, A. Glycolipids from Sponges. Part 16. Discoside, a Rare *myo*-Inositol-Containing Glycolipid from the Caribbean Sponge *Discodermia dissoluta*. *J. Nat. Prod.* **2005**, *68*, 1527–1530. [[CrossRef](#)] [[PubMed](#)]
118. Florence, G.J.; Aslam, T.; Miller, G.J.; Milne, G.D.S.; Conway, S.J. Synthesis of the Marine Glycolipid Dioctadecanoyl Discoside. *Synlett* **2009**, *19*, 3099–3102. [[CrossRef](#)]
119. Gaspar, H.; Cutignano, A.; Grauso, L.; Neng, N.; Cachatra, V.; Fontana, A.; Xavier, J.; Cerejo, M.; Vieira, H.; Santos, S. Erylusamides: Novel Atypical Glycolipids from *Erylus cf. deficiens*. *Mar. Drugs* **2016**, *14*, 179–192. [[CrossRef](#)] [[PubMed](#)]
120. Sata, N.; Asai, N.; Matsunaga, S.; Fusetani, N. Erylusamines, IL-6 Receptor Antagonists, from the Marine Sponge, *Erylus placenta*. *Tetrahedron* **1994**, *50*, 1105–1110. [[CrossRef](#)]
121. Fusetani, N.; Sata, N.; Matsunaga, S. Isolation and Structure Elucidation of Erylusamine B, a New Class of Marine Natural Products, which Blocked an IL-6 Receptor, from the Marine Sponge *Erylus placenta* Thiele. *Tetrahedron Lett.* **1993**, *34*, 4067–4070. [[CrossRef](#)]
122. Goobes, R.; Rudi, A.; Kashman, Y.; Ilan, M.; Loya, Y. Three New Glycolipids from a Red Sea Sponge of the Genus *Erylus*. *Tetrahedron* **1996**, *52*, 7921–7928. [[CrossRef](#)]
123. Tareq, F.S.; Kim, J.H.; Lee, M.A.; Lee, H.-S.; Lee, Y.-J.; Lee, J.S.; Shin, H.J. Ieodoglucomides A and B from a Marine-Derived Bacterium *Bacillus licheniformis*. *Org. Lett.* **2012**, *14*, 1464–1467. [[CrossRef](#)] [[PubMed](#)]
124. Tareq, F.S.; Lee, H.-S.; Lee, Y.-J.; Lee, J.S.; Shin, H.J. Ieodoglucomide C and Ieodoglycolipid, New Glycolipids from a Marine-Derived Bacterium *Bacillus licheniformis* 09IDYM23. *Lipids* **2015**, *50*, 513–519. [[CrossRef](#)] [[PubMed](#)]
125. Reddy, C.R.; Jithender, E.; Prasad, K.R. Total Syntheses of the Proposed Structure for Ieodoglucomides A and B. *J. Org. Chem.* **2013**, *78*, 4251–4260. [[CrossRef](#)] [[PubMed](#)]

126. Reddy, C.R.; Jithender, E.; Singh, A.; Ummanni, R. Stereoisomers of Ieodoglucomides A and B: Synthesis and Evaluation of Anticancer Activity. *Synthesis* **2014**, *46*, 822–827. [[CrossRef](#)]
127. Warabi, K.; Zimmerman, W.T.; Shen, J.; Gauthier, A.; Robertson, M.; Finlay, B.B.; van Soest, R.; Andersen, R.J. Pachymoside A—A Novel Glycolipid Isolated from the Marine Sponge *Pachymatisma johnstonia*. *Can. J. Chem.* **2004**, *82*, 102–112. [[CrossRef](#)]
128. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. Plaxyloside from the Marine Sponge *Plakortis simplex*: An Improved Strategy for NMR Structural Studies of Carbohydrate Chains. *Eur. J. Org. Chem.* **2001**, *2001*, 4457–4462. [[CrossRef](#)]
129. Ōmura, S.; Tomoda, H.; Tabata, N.; Ohyama, Y.; Abe, T.; Namikoshi, M. Roselipins, Novel Fungal Metabolites Having a Highly Methylated Fatty Acid Modified with a Mannose and an Arabinitol. *J. Antibiot.* **1999**, *52*, 586–589. [[CrossRef](#)] [[PubMed](#)]
130. Tomoda, H.; Ohyama, Y.; Abe, T.; Tabata, N.; Namikoshi, M.; Yamaguchi, Y.; Masuma, R.; Ōmura, S. Roselipins, Inhibitors of Diacylglycerol Acyltransferase, Produced by *Gliocladium roseum* KF-1040. *J. Antibiot.* **1999**, *52*, 689–694. [[CrossRef](#)] [[PubMed](#)]
131. Tabata, N.; Ohyama, Y.; Tomoda, H.; Abe, T.; Namikoshi, M.; Ōmura, S. Structure Elucidation of Roselipins, Inhibitors of Diacylglycerol Acyltransferase Produced by *Gliocladium roseum* KF-1040. *J. Antibiot.* **1999**, *52*, 815–826. [[CrossRef](#)] [[PubMed](#)]
132. Ayers, S.; Zink, D.L.; Mohn, K.; Powell, J.S.; Brown, C.M.; Bills, G.; Grund, A.; Thompson, D.; Singh, S.B. Anthelmintic Constituents of *Clonostachys candelabrum*. *J. Antibiot.* **2010**, *63*, 119–122. [[CrossRef](#)] [[PubMed](#)]
133. Inokoshi, J.; Kawamoto, K.; Takagi, Y.; Matsuhama, M.; Ōmura, S.; Tomoda, H. Expression of Two Human Acyl-CoA: Diacylglycerol Acyltransferase Isozymes in Yeast and Selectivity of Microbial Inhibitors toward the Isozymes. *J. Antibiot.* **2009**, *62*, 51–54. [[CrossRef](#)] [[PubMed](#)]
134. Tomoda, H.; Tabata, N.; Ohyama, Y.; Ōmura, S. Core Structure in Roselipins Essential for Eliciting Inhibitory Activity against Diacylglycerol Acyltransferase. *J. Antibiot.* **2003**, *56*, 24–29. [[CrossRef](#)] [[PubMed](#)]
135. Guan, Z.; Collado, J.; Singh, S.B.; Jayasuriya, H.; Dewey, R.; Polishook, J.D.; Dombrowski, A.W.; Zink, D.L.; Platas, G.; Pelaez, F.; et al. Isolation, Structure, and HIV-1-Integrase Inhibitory Activity of Structurally Diverse Fungal Metabolites. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 721–731. [[CrossRef](#)] [[PubMed](#)]
136. Ondeyka, J.G.; Herath, K.B.; Jayasuriya, H.; Polishook, J.D.; Bills, G.F.; Dombrowski, A.W.; Mojena, M.; Koch, G.; DiSalvo, J.; DeMartino, J.; et al. Discovery of Structurally Diverse Natural Product Antagonists of Chemokine Receptor CXCR3. *Mol. Divers.* **2005**, *9*, 123–129. [[CrossRef](#)]
137. Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A. Glycolipids from Sponges. VII. Simplexides, Novel Immunosuppressive Glycolipids from the Caribbean Sponge *Plakortis simplex*. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 271–276. [[CrossRef](#)]
138. Loffredo, S.; Staiano, R.I.; Granata, F.; Costantino, V.; Borriello, F.; Frattini, A.; Lepore, M.T.; Mangoni, A.; Marone, G.; Triggiani, M. Simplexide Induces CD1d-Dependent Cytokine and Chemokine Production from Human Monocytes. *PLoS ONE* **2014**, *9*, 111326. [[CrossRef](#)] [[PubMed](#)]
139. Lü, G.; Wang, P.; Liu, Q.; Zhang, Z.; Zhang, W.; Li, Y. Reactivity-based One-pot Synthesis of Immunosuppressive Glycolipids from the Caribbean Sponge *Plakortis simplex*. *Chin. J. Chem.* **2009**, *27*, 2217–2222.
140. Li, J.; Li, W.; Yu, B. A Divergent Approach to the Synthesis of Simplexides and Congeners via a Late-Stage Olefin Cross-Metathesis Reaction. *Org. Biomol. Chem.* **2013**, *11*, 4971–4974. [[CrossRef](#)] [[PubMed](#)]

