Applications of Norrish type I and II reactions in the total synthesis of natural products: a review

Sasadhar Majhi¹

Received: 18 May 2021 / Accepted: 6 September 2021 / Published online: 18 September 2021

© The Author(s), under exclusive licence to European Photochemistry Association, European Society for Photobiology 2021

Abstract

Natural products and their analogue have played a key role in the drug discovery and development process. In the laboratory, the total synthesis of secondary metabolites is very useful in ascertaining the hypothetical complex structure of molecules of natural origin. Total synthesis of natural products using Norrish type I and II reactions as a crucial step has been explored in this overview. Norrish reactions are important photo-induced transformations of carbonyl compounds in organic synthetic chemistry and are connected in numerous industrially and biologically relevant procedures and the processing of carbonyl compounds in the atmosphere. The present review tries to focus on the brilliant applications of Norrish type I and II photochemical reactions as a key step in the total synthesis of natural products and highlights on natural sources, structures, and biological activities of the promising natural products for the first time elegantly.

Graphic abstract

Keywords Drug discovery · Norrish type I and II reactions (Norrish–Yang cyclization) · Pharmacological aspects · Photochemistry · Sustainable chemistry

1 Introduction

Natural products have been the greatest fruitful source of potential drug leads [1, 2]. Historically, secondary metabolites and their structural derivatives have played a crucial role in drug discovery, especially for cancer and infectious diseases [3]. They have also made a remarkable contribution

in other therapeutic areas, comprising cardiovascular diseases (for example, statins) and multiple sclerosis (for instance, fingolimod) [4, 5]. For the drug discovery process, natural products offer eminent features in comparison with conventional synthetic compounds, which provide both advantages and challenges. Plenty of scaffold diversity and structural complexity is the main characteristics of secondary metabolites. Besides natural products include a higher number of sp^3 carbon atoms and heteroatoms such as oxygen, nitrogen, sulfur, phosphorus, and halogen atoms, minor calculated octanol–water partition coefficients (indicating greater hydrophilicity), greater numbers of H-bond acceptors

✉ Sasadhar Majhi
sasadharmajhi@gmail.com; mahi_sdvb@yahoo.com

¹ Department of Chemistry (UG and PG Department),
Triveni Devi Bhalotia College, Kazi Nazrul University,
Raniganj 713347, West Bengal, India

and donors, and higher molecular rigidity compared with synthetic molecule libraries [1, 2, 6]. These differences can be superior; for instance, the greater rigidity of secondary metabolites can be worthy in drug discovery tackling protein–protein interactions [7]. Despite these advantages and many successful drug discovery instances, various weaknesses of secondary metabolites have led pharmaceutical companies to decrease natural product-based drug discovery programs. Such bioactive secondary metabolites are present in insufficient amounts and isolation and characterization of a complex bioactive natural product may also be challenging in several cases [3]. So we need the total synthesis of natural products in confirming the hypothetical complex structures of secondary metabolites despite sophisticated analytical and spectroscopic instrumentation and techniques that are available presently. Moreover, total synthesis is also efficient to prepare rare bioactive secondary metabolites in the laboratory as various natural products are originated in small quantities from natural sources, especially those from higher plants and marine organisms [8–14].

Currently, the uses of photochemistry in organic synthesis are expanding to avoid toxic reagents and photochemical transformation is induced by light absorption, which promotes one of the reagents to its excited state. A key feature of all light-promoted reactions is the participation of electronically excited states which leads to the formation of transient reactive intermediates [15–20]. Hence the reactivity of a chemical compound is altered remarkably, a process that can be controlled to give the desired product in high yield and with excellent selectivity [21, 22]. However, a majority of the thermal transformations need additional reagents for activation, such as Brønsted acids, bases, or metal catalysts although a key feature of all light-promoted transformations includes absorption of photons. Norrish reactions are important photo-induced transformations of carbonyl compounds in organic synthetic chemistry and are connected in numerous industrially and biologically relevant procedures and the processing of carbonyl compounds in the atmosphere and the transformation are named after Ronald George Wreyford Norrish [15–20, 23, 24].

The application of Norrish type reactions is a powerful strategy in the total synthesis that permits for the generation of a high degree of molecular complexity in natural products from simple and readily available materials. Hence, the primary goal of this overview is to summarize the brilliant applications of Norrish type I and II photochemical reactions as a key step in the total synthesis of natural products and highlights the natural sources, structures, and biological properties of the promising natural products elegantly.

2 Norrish type I photochemical reaction (Norrish type I process or α -cleavage)

Photo fragmentation transformation of carbonyl compounds was commenced by $n\text{-}\pi^*$ transition through excited singlet (S_1) or triplet (T_1) state is generally known as Norrish type reaction. When a primary photochemical reaction is started by an $n\text{-}\pi^*$ excitation, from the ground state (S_0) to its first excited singlet state (S_1), followed by an α -cleavage to give an acyl and an alkyl radical pairs it is called as Norrish type I reaction or Norrish type I α -cleavage [23, 24]. Fragmentation can take place of the carbon–carbon single bond (C–C) adjacent to carbonyl to furnish acyl and alkyl radical in the Norrish type I process [25]. In the *reluctant* Norrish type I reaction, the α -cleavage occurs from the triplet excited state [26]. It is evident in the various product distributions between the reactions in the gas phase and the solution phase that this transformation is affected by both the structure of the substrate and the reaction conditions [27]. Even in the solution phase, the product distribution is not the same as that when cyclodextrin is arrived, which frequently results in a cage effect [23, 34]. Similarly, in the solid-state, [25, 28] or in zeolite [29] the product distribution is also different. It has been shown that the Norrish type I reaction includes small cyclic ketones up to cycloheptanone [30] and aliphatic cyclic imides only [31], from both singlet and triplet excited states. However, the Norrish type I reaction does not include acetophenone and benzophenone; they are frequently employed as the Norrish type I photosensitizers [32].

2.1 General reaction scheme and proposed mechanisms

General reaction scheme of Norrish type I reaction may be represented as:

General mechanistic pathways for the Norrish type I process include decarbonylation with subsequent cyclization to give cyclic products, the formation of ketenes along with other fragmented products, and C–H abstraction as shown below (Scheme 1) [33]:

Scheme 1 Depiction of the Norrish type I reaction and the possible photoproducts

3 Norrish type II photochemical reaction (Norrish type II process, Norrish–Yang cyclization)

When alkanones contain a hydrogen atom in the γ -position, α -cleavage is normally suppressed and γ -hydrogen abstraction by the excited carbonyl function takes place through the Norrish type II process. The Norrish type II reaction includes intramolecular hydrogen transfer from the γ -carbon to the carbonyl oxygen (1,5-hydrogen shift) to generate a 1,4-diradical likely through a six-membered cyclic transition state. Next, the resulting diradical undergoes a secondary reaction cleaving α,β -carbon–carbon bond to produce an alkene and an enol that tautomerizes to the aldehyde or ketone product [23, 34, 35]. The intermediate 1,4-diradical can also undergo cyclization by radical combination to give cyclic alcohol, a process known as Norrish–Yang cyclization as Yang at the University of Chicago extensively extended this reaction [36]. A skew 1,4-diradical is formed initially from the excited

triplet state for an aryl ketone, which isomerizes to either a *cis*-diradical or a *trans*-diradical. After the intersystem crossing, the singlet *trans*-diradical can generate the fragmentation product, whereas the *cis*-diradical cyclizes to give the cyclobutanol [37]. This transformation is affected by both environmental and structural factors [37]. For example, the lifetime of the 1,4-diradical in a solution-phase reaction is influenced by the solvent polarity [38], although the solvent dynamics barely influence the intersystem crossing rate [39]. Besides, the interior size and shape governance the behavior of a triplet ketone and 1,4-diradical when a ketone is encapsulated inside the zeolites [40].

3.1 General reaction scheme and proposed mechanisms

The general reaction scheme of Norrish type II reaction may be represented as:

Scheme 2 Depiction of the Norrish type II reaction involving γ -hydrogen abstraction

A general mechanism for the formation of a 1,4-diradical and possible products due to cyclization and α, β -carbon-carbon bond cleavage is exhibited here (Scheme 2).

4 Applications of Norrish type I and II reactions (Norrish–Yang cyclization) in the total synthesis of natural products

This section begins with a brief discussion about the class of natural products such as antibiotic alkaloid, polyketide, pseudodisaccharide, terpenoid, etc. and next, it tries to cover brilliant applications of Norrish type I and II photochemical reactions in the total synthesis of secondary metabolites, sources of natural products, structures, and biological activities of promising secondary metabolites elegantly.

4.1 Antibiotic

Antibiotics are antimicrobial molecules as well as ‘wonder drugs’ to fight microbes. Antibiotics frequently act by restricting the synthesis of a bacterial cell, synthesis of proteins, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), with a membrane disorganizing agent, or other particular actions [41]. Antibiotic use plays a vital role in therapeutic purposes and the majority of antibiotic use occurs in other industries such as agriculture and animal husbandry. Increased demand for antibiotics across many sectors it has allowed the production of millions of metric tons of newer types of antibiotics. The enormous and irresponsible application of antibiotics has contributed remarkably to the appearance of resistant strains [42]. Antibiotic resistance is one of the most challenging to global health, and the emergence of resistance has outpaced the improvement of new antibiotics. So we need the total synthesis of antibiotics.

4.1.1 Total synthesis of spiroxin A

Suzuki et al. accomplished the first total synthesis of (–)-spiroxin A (**8**) by the photo-irradiation as a green tool through a Norrish type II reaction (1,5-hydrogen shift) as a crucial step in 2019 [43]. Spiroxins A–E were originated from a marine-derived fungal strain LL-37H248 and it displays antibacterial property against Gram-positive bacteria and the antitumor property against ovarian carcinoma in nude mice [44]. A marine antibiotic spiroxin A includes a unique naphthoquinone dimer structure with interesting epoxide moieties, multiple stereogenic centers, and sensitive functional groups with the distorted caged structure. Synthetic chemists and the biological community are interested in its total synthesis because of highly complex architectures bearing chlorine atom and attractive biological activity [45–48]. Hence the first total synthesis of a natural enantiomer (–)-spiroxin A (**8**) initiated with chiral, non-racemic

tetralone (*R*)-(1). It was able to react with bromonaphthalene (**2**) to afford key conformer (**3**) over several steps. The main conformer (**3**) was best suited for the photo-induced transformation due to the presence of the vicinal relationship of the methine hydrogen and the quinone carbonyl. Now upon photo-irradiation, a Norrish type II 1,5-hydrogen abstraction took place in major conformer (**3**) to furnish diradical (**4**) and then zwitterion (**5**) through single-electron transfer (SET) (Scheme 3). Cyclization product (**6**) was obtained from zwitterion (**5**) as well as a spontaneous internal redox method occurred to generate (*S*)-(7). The enantioselective total synthesis of (–)-spiroxin A (**8**) was completed from key intermediate (*S*)-(7) successfully over several steps [43].

4.1.2 Total synthesis of spiroxin C

In another work, Suzuki and co-workers disclosed the first enantioselective total synthesis of (–)-spiroxin C (**14**) in

Scheme 3 Total synthesis of spiroxin A using Norrish type II reaction

Scheme 4 Total synthesis of spiroxin C using Norrish type II reaction

2017 [49]. The utilization of Norrish type II reaction can be found in the total synthesis of secondary metabolite spiroxin C (14), one of the members of a class of marine antibiotics. Herein naphthoquinones undergo an intramolecular photoredox reaction to afford oxycyclization product to follow Norrish-type II intramolecular 1,5-hydrogen shift as a key step [50]. Unusual structural features of it such as complex hexacyclic structure with six stereogenic centers having dense oxygen functionalities as well as remarkable biological activity attracted the attention of the synthetic community [46–48, 51–53]. The total synthesis of (–)-spiroxin C (14) begun with readily available tetralone (9), which was transformed to the essential photosubstrate (10). Naphthoquinone (10) was prone to undergo Norrish-type II intramolecular 1,5-hydrogen shift as a central step. Irradiation of photosubstrate (10) provided diradical (11) and subsequent electron transfer to zwitterion (12) that undergoes oxycyclization to generate key intermediate spiroether (13) in 65% yield over two steps with a xenon lamp (> 380 nm, 300 W) at room temperature for 1 h (Scheme 4). Spiroether (13) was effective

to complete the total synthesis of bioactive (–)-spiroxin C (14) over several steps successfully [49].

4.1.3 Total synthesis of punctatin A

Paquette et al. disclosed the first enantiospecific total synthesis of antibiotic (–)-punctatin A (19) applying Norrish type I photochemistry as a central step from (+)-diketone (15), commercially available in an enantiomeric purity of 99.6% [54]. The crystalline levorotatory substance punctatin A (19), originally called antibiotic M95464, was isolated from the dung fungus *Poronia punctata* [55–57]. Structurally, antibiotic trishydroxylated sesquiterpene includes a tricyclic framework having a *trans*-fused tertiary cyclobutanol unit; the authors are interested in its total synthesis because of its biological activity and attractive structure particularly the presence of a *trans*-fused tertiary cyclobutanol. First, essential photosubstrate (16) bearing γ -hydrogen was obtained from starting material diketone (15) over several steps. Next bicyclic ketone (16) in benzene was irradiated with 253.7-nm light (Rayonet reactor) to afford key intermediate tricyclic alcohol (18) through the formation of

Scheme 5 Total synthesis of punctatin A using Norrish type II reaction

diradical (**17**) under Norrish type II reaction in 49% yield (Scheme 5). This crucial step includes the construction of the entirely functionalized four-membered ring in correct stereochemical disposition by the use of Norrish type II reaction as a green methodology. The desired secondary metabolite (-)-punctatin A (**19**) was then obtained from this advanced intermediate (**18**) elegantly and made evident in the absolute configuration of the antibiotic [54].

4.1.4 Total syntheses of (-)-punctatin A and (+)-punctatin D

In another work, the same group (Paquette et al.) also achieved enantiospecific total syntheses of the dextrorotatory enantiomer of punctatin D (**21**) (antibiotic M167906) and the levorotatory enantiomer of punctatin A (**19**) (antibiotic M95464) for the first time using classic Norrish–Yang cyclization as a key step [58]. This cyclization furnishes cyclobutane by a γ -hydrogen abstraction of a photoexcited carbonyl group through a formation of 1,4-diradical as an important intermediate [59]. The syntheses of the sesquiterpene antibiotics (-)-punctatin A (**19**) and its C9 epimer (+)-punctatin D (**21**) is a beautiful application of Norrish–Yang cyclization in the total synthesis of natural products. Irradiation of benzene solution of bicyclic diketone (**15**) produced the cyclization product (**18**) through the short-lived 1,4-diradical intermediate (**17**) (Scheme 6). It should be noted that the relative configuration of the desired product is ascertained by

the chair-like structure of the 1,4-diradical intermediate (**17**). Next cyclization product (**18**) was transformed into desired unsaturated ketones (**19a**) and (**20**) which were efficient to generate antibiotics (-)-punctaporonin A (**19**) and (+)-punctaporonin D (**21**) successfully [58].

4.2 Alkaloids

The name of alkaloids obtains from the “alkaline” and it was frequently employed to represent any nitrogen-containing base. Alkaloids may be classified into three categories such as (1) true alkaloids (molecules obtained from amino acid and a heterocyclic ring having nitrogen), (2) protoalkaloids (molecules, in which the nitrogen atom obtained from an amino acid is not a part of the heterocycle), and (3) pseudoalkaloids (molecules, the basic carbon skeletons of which are not obtained from amino acids) [60]. So alkaloids are nitrogen-containing secondary metabolites and they display various biological properties such as antidepressant, antitumor, antimicrobial, antihypertensive, anticholinergic, anti-inflammatory, antiulcer, and many more [61]. Many alkaloids are employed presently or within the last 50 years for clinical application and they became critical components of the global pharmaceutical armamentarium [62].

Scheme 6 Total syntheses of (–)-punctatin A and (+)-punctatin D using Norrish–Yang cyclization

4.2.1 Total synthesis of psychotriadine

In 2020, Garg and co-workers accomplished the total synthesis of psychotriadine (**28**) applying Norrish type I photodecarbonylation as a crucial step [63]. The main feature of the synthetic route includes a stereospecific solid-state photodecarbonylation reaction of a ketone as a green methodology to access the requisite vicinal quaternary stereocenters [63]. *Calycanthus* alkaloid psychotriadine (**28**), a previously unknown bis(cyclotryptamine) alkaloid was identified in extracts of the flower *Psychotria colorata* [63] and interest in these *calycanthus* alkaloids has been fueled by an amalgamation of their biological properties and intricate structures [64–67]. Structurally, secondary metabolite psychotriadine (**28**) contains vicinal quaternary stereocenters, six interwoven rings, and four nitrogen atoms [68]. The discovery and total synthesis of psychotriadine (**28**) having

the elusive piperidinoindoline scaffold was initiated from arylmalonic ester (**22**) to furnish Norrish type I precursor ketone (**23**) over several steps as a single diastereomer which is validated by X-ray crystallography. Next, the authors conducted the key solid-state photodecarbonylation of ketone (**23**) to deliver the desired product (**27**) with a low yield (8%) through intermediates (**24**), (**25**), and (**26**) by Norrish type I reaction (Hg lamp, > 290 nm) as a central step (Scheme 7) along with undesired yields. However, the authors explored structural derivatives of ketone substrate (**23**) to enhance the efficiency of the solid-state photodecarbonylation transformation. The investigators were excited to find that hemiacyl ketone underwent Norrish type I reaction under similar conditions to deliver the desired products after *N*-deprotection in 42% yield over two steps. Finally, the key intermediate (**27**) was effective to deliver alkaloid psychotriadine (**28**) elegantly [63].

Scheme 7 Total synthesis of psychotriadine using Norrish type I photodecarbonylation

4.2.2 Total synthesis of daphenylline

Li and co-workers achieved the first total synthesis of daphenylline (**35**), a *Daphniphyllum* hexacyclic alkaloid through a photo-induced olefin isomerization/ 6π -electrocyclization cascade reaction as a key step in 2013 [69]. The *Daphniphyllum* alkaloids exhibit several types of biological properties possessing antioxidant, anticancer, and vasorelaxation activities as well as elevation of nerve growth factor [70]. Daphenylline (**35**) was originated from the fruits of *Daphniphyllum longeracemosum* [71] and from a structural perspective it includes a tetrasubstituted arene moiety mounted on a sterically compact hexacyclic core [70]. Herein, Norrish type I fragmentation was employed for the verification of the stereochemical outcome of the conrotatory

6π -electrocyclization indirectly by the structural determination of pentacyclic primary alcohol (**34**). The total synthesis of daphenylline (**35**), with an unprecedented rearranged 22-nor-calyciphylline skeleton, commenced with known enantioenriched hydroxy enone (**29**) which was prepared from *m*-methylanisole over six steps. The starting material (**29**) was efficient to deliver key intermediate *trans*-triene (**30**); the formation of *trans*-triene was crucial as it can furnish the precursor of the Norrish type I fragmentation (**31**) (Scheme 8). Irradiation of the photosubstrate (**31**) afforded the diradical species (**32**); cleavage of the O–O bond took place homolytically and recombine with the diradical (**32**) to give the desired pentacyclic alcohol (**34**), the structure of which was determined by X-ray crystallographic analysis. The secondary metabolite daphenylline (**35**) was obtained

Scheme 8 Total synthesis of daphenylline using Norrish type I fragmentation

from the key intermediate (**30**) over several steps delicately [69].

4.2.3 Total synthesis of ambiguine H

Baran and co-workers disclosed the total synthesis of (+)-ambiguine H (**41**), a marine alkaloid using a Norrish-type cleavage as a crucial step [72, 73]. Ambiguine isonitriles A-F were isolated from the terrestrial cyanophytes *Fischerella ambigua* UTEX 1903, *Hapalosiphon hibernicus* BZ-3-1, and *Westiellopsis prolifica* EN-3-1 [74]; ambiguine H isonitrile exhibits antibacterial and antimycotic activity [75]. Secondary metabolite ambiguine H (**41**) possesses tetra-carbon skeletons obtained from tryptophan and geranyl diphosphate [76] and the ambiguine isonitriles include an additional 1,1-dimethylallyl moiety at the 2 position of the indole ring. The total synthesis of (+)-ambiguine H (**41**) begun with the readily available terpene subunit (**36**) to furnish Norrish-type precursor (**38**) through the synthesis of another alkaloid (–)-hapalindole U (**37**). Photoexcitation of the chloroimidate (**38**) followed by a Norrish type cleavage and fragmentation cascade [76] for 5 h led to desired alkaloid ambiguine H (**41**) (63% yield based on recovered

(**38**) starting material) through formations of important intermediates (**39**) and (**40**) (Scheme 9). It is interesting to be noted that the total synthesis of (+)-ambiguine H (**41**) was completed from starting material (**36**) without using any protecting groups [72].

4.3 Polyketides

In the 1890s polyketides were named to refer to a structurally diverse group of secondary metabolites that included many carbonyls and alcohols, normally separated by methylene carbons. They exhibit diverse functions with clinical applications and biological properties such as antimicrobial, anticancer, and immunosuppressive activities [77] are precious treasures for mankind. Polyketide synthases are multifunctional enzymes accountable for the biosynthesis of plentiful natural products, numerous of which are presently employed as antibiotics (e.g., erythromycin), valuable cholesterol-lowering agents (e.g., lovastatin), antiparasitic medication (e.g., ivermectin), cancer chemotherapy (e.g., epothilone), immunosuppressants (e.g., FK506), and many more [78].

Scheme 9 Total synthesis of ambiguine H using Norrish-type cleavage

4.3.1 Total synthesis of zaragozic acid C

Inoue and co-workers disclosed the total synthesis of a polyketide zaragozic acid C (**48**) using Norrish–Yang cyclization under violet LED irradiation as a crucial step in 2017 [79]. Bioactive natural product zaragozic acid C (**48**) was isolated from *Leptodontium elatius* var. *elatius*, ATCC 70411 as a potent squalene synthase inhibitor [80] and it is considered as a representative instance of a family of secondary metabolites, zaragozic acids [81], and squalostatins [82]. These molecules comprise a type of potent inhibitors of mammalian squalene synthase ($K_i = 29\text{--}78\text{ pM}$) [83]. Zaragozic acids/squalostatins are considered to be encouraging lead structures for the improvement of cholesterol-lowering drugs as squalene synthase plays a vital role in catalyzing the transformation of presqualene pyrophosphate into squalene at the last branching point of cholesterol biosynthesis. Zaragozic acid C (**48**) is characterized

by a hydrophilic 2,8-dioxabicyclo[3.2.1]octane-4,6,7-trihydroxy-3,4,5-tricarboxylic acid core having six stereogenic centers, one alkyl side-chain (C1), and a hydrophobic one acyloxy (C6) group. It is also decorated with two hydroxyls (C4,7) and three hydroxy carbonyls (C3,4,5) groups [79] which represent a further challenge for its total synthesis. Inspired by the complex architecture and potential biological activities the authors began its total synthesis from commercially available persilylated D-gluconolactone (**42**). Next, the highly oxygenated substrate (**43**) was prepared over several steps from D-gluconolactone (**42**) which shares the C6,7-stereochemistry with Norrish–Yang precursor (**43**). Now the regio- and stereoselective conversion from 1,2-diketone (**43**) to the desired C4,5-*cis*-fused cyclobutanone (**46**) took place under mild and neutral conditions illustrated the power and reliability of the Norrish–Yang cyclization in 26% yield only applying the blue LED light (460 nm) through the formation of important intermediates (**44**) and (**45**). However,

Scheme 10 Total synthesis of zaragozic acid C using Norrish–Yang cyclization

the *cis*-fused bicycle (**46**) was formed as the sole isomer in 85% yield established on the ^1H NMR analysis when a benzene solution of diketone (**43**) was irradiated at 405 nm (violet LED) that matches λ_{max} of 1,2-diketone (**43**) to attain this crucial conversion after optimization of the flow rate (50 $\mu\text{L}/\text{min}$) (Scheme 10) [79]. Finally, bioactive zaragozic acid C (**48**) was obtained from *cis*-fused cyclobutanone (**46**) over several steps involving the photochemical $\text{C}(\text{sp}^3)\text{-H}$ functionalization for the formation of the unique molecular structure that is difficult to be obtained by conventional polar transformations [79].

4.4 Pseudodisaccharide

It is widely accepted that carbohydrates play key roles in a large variety of biological systems and considerable attention has been given to the design and synthesis of carbohydrate derivatives for manifesting therapeutic potentials in the treatment of the diseases linked to carbohydrate

metabolism [84]. It includes diabetes, metastatic cancer, human immunodeficiency virus (HIV) infection, and lysosomal storage diseases. For example, the heterocycle-related disaccharide derivatives which constructed a novel nucleoside-like pseudodisaccharide carrying two sugar moieties on the heterocycle have been prepared and were shown to be of good antitumor and/or anti-HIV-RT activities [85]. Besides, the synthesis of novel isoxazoline-connected pseudodisaccharide derivatives displays inhibitory properties against glycosidase and HIV-RT, and antitumor activity [86].

4.4.1 Total synthesis of trehazolin

Carreira et al. [87] developed an enantioselective total synthesis of trehazolin (**54**), an aminocyclopentitol-derived natural pseudodisaccharide using Norrish type II cleavage as a key step. Aminocyclopentitol-derived secondary metabolites such as trehazolin, allosamidin, and mannostatin A

Scheme 11 Total synthesis of trehazolin using Norrish type II cleavage

are significant inhibitors of glycosidases. These glycoside processing enzymes play crucial roles in intra- and inter-cellular methods containing cell adhesion and recognition, membrane transport, and signal transduction. So the application of such molecules and their derivatives as glycosidase inhibitors has significant implications in immunology, virology, and oncology [88]. Trehalase inhibitor trehazolin (**54**) was originated from the culture broth of *Micromonospora* strain SANK 62390 [89]. The total synthesis of trehazolin (**54**) started with optically active 1-(hydroxymethyl) spiro[2.4]cyclohepta-4,6-diene (**50**) which is obtained from (*R*)-(-)-epichlorohydrin (**49**) in multigram quantities. (*R*)-epichlorohydrin (**49**) was able to produce Norrish type II precursor (**51**) over several steps through the formation of the diene (**50**). Next, irradiation of aryl ketone (**51**) delivered the alkene (**53**) in quantitative yield via Norrish type II reaction as a central step. In this crucial step, intramolecular γ -H atom abstraction of (**51**) occurred to generate 1,4-diradical (**52**) and then α,β C–C bond cleavage took place to furnish vital alkene (**53**) (Scheme 11). Bioactive natural pseudodisaccharide trehazolin (**54**) was obtained from key alkene (**53**) over several steps successfully [87].

4.5 Terpenoids

Terpenoids represent the most widespread group of secondary metabolites and can be found in all types of living

things including diverse genera of plants, fungi, algae, and sponges. Terpenoid structures contain an immense range of complexity and execute equally diverse biological functions. They are classified into monoterpenes, sesquiterpenes, diterpenes, sesterpenes, and triterpenes depending on their carbon atoms by head to tail joining of isoprene units. Terpenoids display several types of biological properties like antitumor, anti-inflammatory, antimalarial, antibacterial, and many more [90–92] and are employed worldwide for the treatment of many diseases.

4.5.1 Monoterpene

4.5.1.1 Total synthesis of lavandulol Piva accomplished the total synthesis of (*R*)-(-)-lavandulol (**60**), a monoterpene alcohol by asymmetric protonation of photodienols derived from the irradiation of prochiral α,β -unsaturated esters through a Norrish type II process [93, 94]. Lavandulol (**60**) includes an unusual monoterpene skeleton which found in a diversity of essential oil such as lavender oil [95]. There are two enantiomer of it such as the (*R*)-enantiomer which is natural and the (*S*)-enantiomer which includes only a weak odor. Lavandulol (**60**) and its esters are employed in the perfume industry and have been also obtained as a defensive pheromone of the red-lined carrion beetle [96]. So many efforts have been devoted to its total synthesis because of

Scheme 12 Total synthesis of lavandulol using Norrish type II cleavage

its type of importance. Hence the total synthesis began with ethyl ester (**56**) which was prepared from readily available ethylacetoacetate (**55**) to follow the procedure described by Wolf and Pfander [97]. Next, the ethyl ester (**56**) was subjected to the enantioselective irradiation conditions to afford unsaturated ester (**59**) via 1,5-hydrogen shift (Norrish type II) as a key step. Irradiation of ester (**56**) provided the β,γ -unsaturated ester (**59**) through the formation of the 1,4-diradical intermediate at 254 nm in methylene chloride at low temperature ($-40\text{ }^{\circ}\text{C}$) in the presence of catalytic amounts of *endo,endo*-3-(isopropylamino)-2-hydroxybornane (**58**), readily prepared from (+)-camphor [98]. However, the yield of the β,γ -unsaturated ester (**59**) was good but enantioselectivities during this transformation were moderate (40% *ee*). In contrast, the irradiation of another

DAG-ester (**61**) afforded the desired unsaturated ester (**62**) in 99% yield with high *de* ($>95\%$) in the presence of achiral β -amino alcohol namely (*N,N*-dimethylamino)ethanol (Scheme 12). The next simple reduction of the ester group occurred in the presence of the LiAlH₄ to yield desired secondary metabolite (*R*)-(-)-lavandulol (**60**) without loss of optical purity [93].

4.5.2 Sesquiterpenes

4.5.2.1 Total synthesis of herbertenolide Garcia-Garibay et al. achieved the total synthesis of ($\pm$)-herbertenolide (**67**) by the stereospecific formation of vicinal quaternary centers in seven steps from readily available 2-bromo-4-methylanisole (**63**) applying Norrish type I reaction as a

Scheme 13 Total synthesis of herbertenolide using Norrish type I reaction

key step under the solvent-free condition as a green methodology [99]. The aromatic sesquiterpene herbertenolide (**67**) with the *ent*-herbertane skeleton was originated from the leafy liverwort *Herberta adunca*, the extract of which has been found to display a prominent growth suppression of certain plant pathogenic fungi [100, 101]. The starting material 2-bromo-4-methylanisole (**63**) was converted to

the essential photosubstrate (**64**) over several steps. Now Norrish type I reaction was applied to furnish the desired cyclopentane (**66**) through the formation of diradical intermediate (**65**). In the crucial step, the photochemical irradiation of finely powdered samples of crystalline (**64**) took place to produce Norrish type I product (**66**) in 76% yield using a medium-pressure Hanovia mercury lamp for 6–12 h

Scheme 14 Total synthesis of specionin using Norrish type I reaction

at 0 °C (Scheme 13). The main feature of the key step includes the exceptional simplicity, high chemoselectivity, and stereospecificity. Next one additional step was needed to complete the total synthesis of the secondary metabolite ($\pm$)-herbertenolide (**67**) [99].

4.5.2.2 Total synthesis of specionin Vandewalle and co-workers reported the revised structure of sesquiterpene specionin (**74**) and the revised structure of it was confirmed by total synthesis using a Norrish I type fragmentation of a norbornanone precursor as the central step [102]. The iridoid insect antifeedant specionin (**74**) was originated from the leaves of *Catalpa speciosa* Warder and it was investigated that it is a potent inhibitor of the feeding of the spruce budworm [103, 104]. Structurally it contains (hydroxymethyl) octahydrooxireno [4, 5] cyclopenta [1,2-c] pyran core with two ethoxy groups and 4-hydroxybenzoate ester at the side chain. The total synthesis of ($\pm$)-specionin (**74**) was initiated from the known compound (**68**) in confirming the structure for specionin (**74**). The starting material (**68**) was effective to deliver Norrish I type precursor aldehyde (**69**) having norbornanone framework over several steps. Irradiation of bicyclic aldehyde (**69**) at 254 nm in ethanol provided the crude intermediates of (**71**) and (**72**) under Norrish I type reaction as a key step through the formation of diradical (**70**) (Scheme 14). Direct acid treatment of the crude intermediates (**71**) and (**72**) delivered primary alcohol (**73**) in 64%

overall yield. Finally, the desired product ($\pm$)-specionin (**74**) was obtained from primary alcohol (**73**) successfully [102].

4.5.3 Diterpene

4.5.3.1 Total synthesis of deacetoxyalcyonin acetate Molander et al. [105] developed a general route to the eunicellin diterpenes as well as a short asymmetric total synthesis of deacetoxyalcyonin acetate (**79**) using Norrish type I cleavage with subsequent oxacarbene trapping as a key step. The eunicellin diterpenes are considered as a family of marine secondary metabolites originated from gorgonian and soft corals [106]. Eunicellin, the first member of this family, was isolated from the coral *Eunicella strictu*, and the related structures including (-)-7-deacetoxyalcyonin acetate was isolated from a *Cladiella* species of soft coral [107, 108]. These diterpenes have received considerable attention from the organic synthetic community due to their structural complexity such as they are distinguished by a unique tricyclic ring system possessing hydroisobenzofuran and oxonane subunit as well as exciting biological activity including anti-inflammatory activity [109, 110]. The total synthesis of deacetoxyalcyonin acetate (**79**) commenced with commercially available α -phellandrene (**75**) when it was treated with methoxyacetyl chloride in NEt_3 to afford Norrish type I precursor cyclobutanone (**76**). Next, the photochemical rearrangement of cyclobutanone (**76**) occurred

Scheme 15 Total synthesis of deacetoxyalcyonin acetate using Norrish type I reaction

to generate oxacarbene (**77**), which could be trapped with acetic acid to provide the desired mixed acetal (**78**) in 86% yield with complete retention of the stereocenter adjacent to the carbonyl using Norrish type I cleavage as a crucial step (Scheme 15). The mixed acetal (**78**) could be advanced to deliver deacetoxyalcyonin acetate (**79**) over several steps elegantly [105].

4.6 Miscellaneous

4.6.1 Total synthesis of lactacystin

Inoue and co-workers accomplished a total synthesis of a potent inhibitor of the 20S proteasome (+)-lactacystin (**86**) from (*S*)-pyroglutaminol (**80**) using Norrish–Yang cyclization of a 1,2-diketone as a key step in 2015 [111]. Bioactive secondary metabolite (+)-lactacystin (**86**) was originated from *Streptomyces* sp. OM-6519; it displays neurite outgrowth property in the murine neuroblastoma cell line Neuro-2a [112]. A detailed study of the mode of biological action disclosed that lactacystin (**86**) inhibits the proteolytic property of the 20S proteasome in an irreversible way [113]. As the proteasome machinery plays a significant role in the cell cycle control, apoptosis, differentiation, immune response, and antigen processing, proteasome inhibitors have emerged as potential candidates for the improvement of pharmaceuticals and the investigation of proteasome functions [114]. Due to its interesting biological activity and attractive structure lactacystin (**86**) has attracted significant

attention as a synthetic target, and hence the authors commenced the total synthesis of (**86**) from commercially available (*S*)-pyroglutaminol (**80**) as a starting material. Now, Norrish–Yang precursor (**81**) was prepared from (*S*)-pyroglutaminol (**80**) over several steps involving stereoselective C(sp³)–H functionalization as a central step. Next, 1,2-diketone (**81**) undergoes Norrish–Yang cyclization to afford monoketone (**84**) via the formation of the intermediate (**82**) and 1,4-diradical (**83**) with the irradiation of the mercury lamp. However, the transformation gave a complex mixture presumably because of undesired reaction pathways linked with concomitant photoexcitation of monoketone (**84**) in the presence of UV light (<360 nm). Hence the authors applied a blue LED instead of the mercury lamp for selective photoactivation of the diketone moiety as it emits light of a higher wavelength (approximately 460 nm) than that of the mercury lamp. Hence the chemo- and stereoselective conversion from 1,2-diketone (**81**) to the desired *cis*-fused cyclobutanone (**84**) occurred smoothly through Norrish–Yang cyclization as a crucial step (Scheme 16). Although (**82**) contains two types of γ -hydrogens such as ethereal C(sp³)–H at C9 and aliphatic C–H at C6 but the site-selective H-abstraction at C9 took place over C6 which reflected the more electron-rich nature of the ethereal C(sp³)–H bond in comparison to the aliphatic C–H bond. Subsequent oxidative ring-opening of cyclobutanone (**84**) employing lead tetraacetate [Pb(OAc)₄] and sodium carbonate (Na₂CO₃) generated ketoester (**85**) as a single isomer in 66% yield over two steps. Finally, the desired bioactive natural monocyclic lactam (+)-lactacystin (**86**)

Scheme 16 Total synthesis of lactacystin using Norrish–Yang cyclization

(86) was obtained from *cis*-fused cyclobutanone (84) over several steps through homologation at C10, construction of C6,7-stereocenters, and connection of the cysteine moiety successfully [111].

5 A summary of the challenge and the possibility of Norrish reactions

In nature, photochemistry plays a crucial role in the field of vision, photosynthesis as well as the formation of vitamin D with the help of sunlight [115]. Photochemical transformations proceed differently compare to thermal protocols because paths of photochemical transformations access high energy intermediates that cannot be achieved by the conventional thermal transformations usually. Hence, photochemical reactions can overcome higher activation barriers in a short time, and permitting transformations that are not accessible by thermal protocols [15–20]. Since one of the most significant photo-induced transformations of carbonyl molecules, Norrish reaction is a vital issue of photochemistry, which could provide chemists with both challenges and opportunities to access versatile and influential toolboxes for organic synthesis. Norrish type reactions like other photochemical transformations provide transient reactive intermediates and significantly change the reactivity of a chemical substance. The input of energy furnished by light thus offers a means to generate strained and unique desired molecules that cannot be assembled by the conventional thermal transformations [15–20]. Synthetic studies of natural products with complex structures using Norrish photoreactions are very beneficial environmentally as classical thermal protocols require toxic, explosive materials, tedious, and long procedures frequently. The total synthesis of most of the molecules of natural origin and their analogues is one of the great challenges for organic synthesis due to their chemical diversity, and difficult stereochemistry [8–14]. As energy is essential for chemical conversions, this energy to an organic synthesis along with a total synthesis of natural products can be provided by light as a non-polluting powerful tool that enables the selective production of chemical bonds under mild reaction conditions with the help of photoredox catalyst. Recently, the artistic aspect of the total synthesis of complex secondary metabolites continues to be praised since it may provide environmental protection through the concept of sustainable chemistry. The use of light as a non-contaminating source of energy is of great interest in the field of green and pharmaceutical chemistry. So the present review will definitely make some impact in this direction as it inspires the next generation of practitioners of the art and science of Norrish type reactions in the total synthesis of molecules of natural origin and related compounds to exploit their ability as opportunities to improve our knowledge in

medicinal and chemical sciences and apply it to invent new medicines for the community. Moreover, Norrish reactions are potential photo-induced reactions of carbonyl compounds in organic synthetic chemistry and are associated in numerous industrially and biologically relevant procedures and in the processing of carbonyl compounds in the atmosphere, as illustrated by the photodegradation of plastics also.

6 Conclusions

Mother Nature is a precious source of secondary metabolites and they have played a crucial role in the drug development and discovery process. The total synthesis of secondary metabolites is one of the great challenges for organic chemists due to their chemical diversity, characteristic biochemical specificity, and difficult stereochemistry. The greenest reagent in organic synthetic chemistry is light. A central feature of all light-promoted transformations includes the absorption of photons, which promotes one of the reagents to its excited state. Most of the thermal reactions need additional reagents for activation, such as Brønsted acids, bases, or metal catalysts although a key feature of all light-promoted conversion includes absorption of green reagent photons. However, the role of the visible light photoredox catalysis is crucial as a potential technology that provides the selective construction of chemical bonds under mild reaction conditions. Norrish reactions are important photo-induced transformations of carbonyl compounds in organic synthetic chemistry and are connected in numerous industrially and biologically relevant procedures and in the processing of carbonyl compounds in the atmosphere. The present review tries to focus on the brilliant applications of Norrish type I and II photochemical reactions as a key step in the total synthesis of natural products, natural sources, structures, and biological activities of the promising natural products for the first time elegantly. Photochemistry serves as an effective tool for mastering novel and environmentally benign reactions. In the future, it can also be employed to enlarge the classical chemical toolbox by offering improved reaction conditions and can facilitate the invention of new transformations for diligent bond construction.

Acknowledgements The author gratefully acknowledges the moral support from his mother Sadeswari Majhi and he is also thankful to his heavenly father Tarani Majhi. The author is also grateful to the principal of the Triveni Devi Bhalotia College for his support and inspiration throughout.

Funding Self-funding, no funding is available in this manuscript.

Declarations

Conflict of interest The author declares no conflict of interest.

Ethics approval Not applicable.

References

- Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., & Supuran, C. T. (2021). Natural products in drug discovery: Advances and opportunities. *Nature*, 20, 200–216.
- Mishra, B. B., & Tiwari, V. K. (2011). Natural products: An evolving role in future drug discovery. *European Journal of Medicinal Chemistry*, 46, 4769–4807.
- Harvey, A. L., Edrada-Ebel, R., & Quinn, R. J. (2015). The re-emergence of natural products for drug discovery in the genomics era. *Nature Reviews. Drug Discovery*, 14, 111–129.
- Tintore, M., Vidal- Jordana, A., & Sastre- Garriga, J. (2019). Treatment of multiple sclerosis—success from bench to bedside. *Nature Reviews Neurology*, 15, 53–58.
- Newman, D. J., & Cragg, G. M. (2016). Natural Products as Sources of New Drugs from 1981 to 2014. *Journal of Natural Products*, 79, 629–661.
- Barnes, E. C., Kumar, R., & Davis, R. A. (2016). The use of isolated natural products as scaffolds for the generation of chemically diverse screening libraries for drug discovery. *Natural Products Reports*, 33, 372–381.
- Lawson, A. D. G., MacCoss, M., & Heer, J. P. (2018). Importance of rigidity in designing small molecule drugs to tackle protein-protein interactions (PPIs) through stabilization of desired conformers. *Journal of Medicinal Chemistry*, 61, 4283–4289.
- Nicolaou, K. C., & Rigol, S. (2020). Perspectives from nearly five decades of total synthesis of natural products and their analogues for biology and medicine. *Natural Products Reports*, 37, 1404–1435.
- Li, L., Chen, Z., Zhang, X., & Jia, Y. (2018). Divergent strategy in natural product total synthesis. *Chemical Reviews*, 118, 3752–3832.
- Majhi, S. (2020). Diterpenoids: Natural Distribution, Semisynthesis at Room Temperature and Pharmacological Aspects-A Decade Update. *ChemistrySelect*, 5, 12450–12464.
- Majhi, S., & Das, D. (2021). Chemical derivatization of natural products: Semisynthesis and pharmacological aspects—a decade update. *Tetrahedron*, 78, 131801.
- Majhi, S. (2021). The art of total synthesis of bioactive natural products via microwaves. *Current Organic Chemistry*, 25, 1047–1069.
- Majhi, S. (2021). Applications of Yamaguchi method to esterification and macrolactonization in total synthesis of bioactive natural products. *ChemistrySelect*, 6, 4178–4206.
- Majhi, S. (2021). Applications of ultrasound in total synthesis of bioactive natural products: A promising green tool. *Ultrasonics Sonochemistry*, 77, 105665.
- Albini, A. (2021). Norrish' type I and II reactions and their role in the building of photochemical science. *Photochemical & Photobiological Sciences*, 20, 161–181.
- Marchetti, B., Karsili, T. N. V., & Ashfold, M. N. R. (2019). Exploring Norrish type I and type II reactions: An *ab initio* mechanistic study highlighting singlet-state mediated chemistry. *Physical Chemistry Chemical Physics: PCCP*, 21, 14418–14428.
- Sivaguru, P., Wang, Z., Zanon, G., & Bi, X. (2019). Cleavage of carbon-carbon bonds by radical reactions. *Chemical Society Reviews*, 48, 2615–2656.
- Karkas, M. D., Porco, J. A., Jr., & Stephenson, C. R. J. (2016). Photochemical approaches to complex chemotypes: Applications in natural product synthesis. *Chemical Reviews*, 116, 9683–9747.
- Bach, T., & Hehn, J. P. (2011). Photochemical reactions as key steps in natural product synthesis. *Angewandte Chemie International Edition*, 50, 1000–1045.
- Hoffmann, N. (2008). Photochemical reactions as key steps in organic synthesis. *Chemical Reviews*, 108, 1052–1103.
- Schapiro, I., Melaccio, F., Laricheva, E. N., & Olivucci, M. (2011). Using the computer to understand the chemistry of conical intersections. *Photochemical & Photobiological Sciences*, 10, 867–886.
- Olivucci, M., & Santoro, F. (2008). Chemical selectivity through control of excited-state dynamics. *Angewandte Chemie International Edition*, 47, 6322–6325.
- Norrish, R. G. W., & Bamford, C. H. (1936). Photodecomposition of aldehydes and ketones. *Nature*, 138, 1016.
- Norrish, R. G. W., & Kirkbride, F. W. (1932). Primary photochemical processes. Part I. The decomposition of formaldehyde. *Journal of Chemistry Society*, 1982, 1518–1530.
- Reddy, G. D., Usha, G., Ramanathan, K. V., & Ramamurthy, V. (1986). Modification of photochemistry by cyclodextrin complexation. Competitive Norrish type I and type II reactions of benzoin alkyl ethers. *Journal of Organic Chemistry*, 51, 3085–3093.
- Johnston, L. J., & Scaiano, J. C. (1987). One- and two-photon processes in the photochemistry of 1,3-bis(1-naphthyl)-2-propanone: An example of a “reluctant” Norrish type I reaction. *Journal of the American Chemical Society*, 109, 5487–5491.
- Yamashita, H., Takada, S., Hada, M., Nakatsuji, H., & Anpo, M. (2003). Experimental study and *ab initio* molecular orbital calculation on the photolysis of *n*-butyrophenone included within the alkali metal cation-exchanged ZSM-5 zeolite. *Journal of Photochemistry and Photobiology, A: Chemistry*, 160, 37–42.
- Kang, T., & Scheffer, J. R. (2001). An unexpected Paternò-Büchi reaction in the crystalline state. *Organic Letters*, 3, 3361–3364.
- Corbin, D. R., Eaton, D. F., & Ramamurthy, V. (1988). Modification of photochemical reactivity by zeolites: Norrish type I and type II reactions of benzoin derivatives. *Journal of the American Chemical Society*, 110, 4848–4849.
- Ramamurthy, V., Lei, X.-G., Turro, N. J., Lewis, T. J., & Scheffer, J. R. (1991). Photochemistry of macrocyclic ketones within zeolites: Competition between norrish type I and type II reactivity. *Tetrahedron Letters*, 32, 7675–7678.
- Kanaoka, Y., Okajima, H., & Hatanaka, Y. (1979). Photoinduced reactions. 39. Photochemistry of the imide system. 9. Norrish type I reaction of aliphatic cyclic imides. General reaction pattern, competition with type II processes, and some synthetic application. *Journal of Organic Chemistry*, 44, 1749–1751.
- Adam, W., Arnold, M. A., Nau, W. M., Pischel, U., & Saha-Moller, C. R. (2002). A comparative photomechanistic study (spin trapping, EPR spectroscopy, transient kinetics, photo-products) of nucleoside oxidation (dG and 8-oxodG) by triplet-excited acetophenones and by the radicals generated from α -oxy-substituted derivatives through Norrish-Type I cleavage. *Journal of the American Chemical Society*, 124, 3893–3904.
- Weiss, D. S. (1981). The Norrish type I reaction in cycloalkanone photochemistry. *Organic Photochemistry*, 5, 347–420.
- Norrish, R. G. W., & Appleyard, M. E. S. (1934). Primary photochemical reactions. Part IV. Decomposition of methyl ethyl ketone and methyl butyl ketone. *Journal of Chemical Society*, 1934, 874–880.
- Stark, M., & Thiem, J. (2006). Highly functionalized glycoconjugated hexahydroazepindiones from saccharide imides via the Norrish type II reaction. *Carbohydrate Research*, 341, 1543–1556.
- Yang, N. C., & Yang, D. H. (1958). Photochemical reactions of ketones in solution. *Journal of the American Chemical Society*, 80, 2913–2914.

37. Kell, A. J., & Workentin, M. S. (2001). Aryl ketone photochemistry on monolayer protected clusters: Study of the Norrish Type II reaction as a probe of conformational mobility and for selective surface modification. *Langmuir*, 17, 7355–7363.
38. Zimmt, M. B., Doubleday, C., & Turro, N. J. (1987). Substituent and solvent effects on the lifetimes of hydrocarbon-based biradicals. *Chemical Physics Letters*, 134, 549–552.
39. Morita, A., & Kato, S. (1993). Theoretical study on the intersystem crossing mechanism of a diradical in Norrish type II reactions in solution. *Journal of Physical Chemistry*, 97, 3298–3313.
40. Ramamurthy, V., Corbin, D. R., & Johnston, L. J. (1992). A study of Norrish type II reactions of aryl alkyl ketones included within zeolites. *Journal of the American Chemical Society*, 114, 3870–3882.
41. Levy, S. B., & Marshall, B. (2004). Antibacterial resistance worldwide: Causes, challenges and responses. *Nature Medicine*, 10, S122–S129.
42. Chopra, R., Alderborn, G., Podczek, F., & Newton, J. M. (2002). The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets. *International Journal of Pharmaceutics*, 239, 171–178.
43. Yoshio, A., Daisuke, T., Ryota, S., Ken, O., & Keisuke, S. (2019). Stereochemical dichotomy in two competing cascade processes: Total syntheses of both enantiomers of spiroxin A. *Angewandte Chemie International Edition*, 58, 12507–12513.
44. McDonald, L. A., Abbanat, D. R., Barbieri, L. R., Bernan, V. S., Discafani, C. M., Greenstein, M., Janota, K., Korshalla, J. D., Lassota, P., Tischler, M., & Carter, G. T. (1999). Spiroxins, DNA cleaving antitumor antibiotics from a marine-derived fungus. *Tetrahedron Letters*, 40, 2489–2492.
45. Wang, T., Shiota, O., Nakanishi, K., Berova, N., McDonald, L. A., Barbieri, L. R., & Carter, G. T. (2001). Absolute stereochemistry of the spiroxins. *Canadian Journal of Chemistry*, 79, 1786–1791.
46. Kwan, A., Stein, J., & Carrico-Moniz, D. (2011). A catalytic asymmetric entry to enantioenriched tertiary naphthoquinols via a facile tandem oxidation/ring-opening sequence. *Tetrahedron Letters*, 52, 3426–3428.
47. Miyashita, K., Sakai, T., & Imanishi, T. (2003). Total Synthesis of (±)-Spiroxin C. *Organic Letters*, 5, 2683–2686.
48. Nabatame, K., Hiram, M., & Inoue, M. (2008). A simple desymmetrization approach to the spiroxin framework. *Heterocycles*, 76, 1011–1016.
49. Ando, Y., Hanaki, A., Sasaki, R., Ohmori, K., & Suzuki, K. (2017). Stereospecificity in intramolecular photoredox reactions of naphthoquinones: Enantioselective total synthesis of (–)-spiroxin C. *Angewandte Chemie International Edition*, 56, 11460–11465.
50. Ando, Y., Matsumoto, T., & Suzuki, K. (2017). Intramolecular photoredox reaction of naphthoquinone derivatives. *Synlett*, 28, 1040–1045.
51. Krohn, K., Florke, U., John, M., Root, N., Steingrover, K., Aust, H.-J., Draeger, S., Schulz, B., Antus, S., Simonyi, M., & Zsila, F. (2001). Biologically active metabolites from fungi. Part 16: New preussomerins J, K and L from an endophytic fungus: Structure elucidation, crystal structure analysis and determination of absolute configuration by CD calculations. *Tetrahedron*, 57, 4343–4348.
52. Vilella, D., Sanchez, M., Platas, G., Salazar, O., Genillound, O., Royo, I., Cascales, C., Martin, I., Diez, T., Silverman, K. C., Lingham, R. B., Singh, S. B., Jayasuriya, H., & Pelaez, F. (2000). Inhibitors of farnesylation of Ras from a microbial natural products screening program. *Journal of Industrial Microbiology and Biotechnology*, 25, 315–327.
53. Zhou, L., Zhao, J., Shan, T., Cai, X., & Peng, Y. (2010). Spiro-bisnaphthalenes from fungi and their biological activities. *Mini Reviews in Medicinal Chemistry*, 10, 977–989.
54. Paquette, L. A., & Sugimura, T. (1986). Enantiospecific total synthesis and absolute configurational assignment of (–)-punctatin A (antibiotic M95464). *Journal of the American Chemical Society*, 108, 3841–3842.
55. Anderson, J. R., Briant, C. E., Edwards, R. L., Mabelis, R. P., Poyser, J. P., Spencer, H., & Whalley, A. J. S. (1984). Punctatin A (antibiotic M95464): X-ray crystal structure of a sesquiterpene alcohol with a new carbon skeleton from the fungus, *Paronia punctata*. *Journal of the Chemical Society, Chemical Communications*, 7, 405–406.
56. Herz, W., & Wahlberg, I. (1974). Punctatin: A new germacra-dienolide from *Liatris punctata*. *Phytochemistry*, 13, 318.
57. Anderson, J. R., Edwards, R. L., Freer, A. A., Mabelis, R. P., Poyser, J. P., Spencer, H., & Whalley, A. J. S. (1984). Punctatins B and C (antibiotics M95154 and M95155): further sesquiterpene alcohols from the fungus *Paronia punctata*. *Journal of the Chemical Society, Chemical Communications*, 1984, 917–919.
58. Sugimura, T., & Paquette, L. A. (1987). Enantiospecific total synthesis of the sesquiterpene antibiotics (–)-punctatin A and (+)-punctatin D. *Journal of the American Chemical Society*, 109, 3017–3024.
59. Wagner, P. J., & Park, B.-S. (1991). Photoinduced hydrogen atom abstraction by carbonyl compounds. *Organic Photochemistry*, 11, 227–366.
60. Eagleson, M. (1994). *Concise Encyclopedia Chemistry* (1st ed.). Berlin: Walter de Gruyter.
61. Henriques, A. T., Lopes, S. O., Paranhos, J. T., & Gregianini, T. S. (2004). N, beta-D-glucopyranosyl vincosamide, a light regulated indole alkaloid from the shoots of *Psychotria leiocarpa*. *Phytochemistry*, 65, 449–454.
62. Amirkia, V., & Heinrich, M. (2014). Alkaloids as drug leads—a predictive structural and biodiversity-based analysis. *Phytochemistry Letters*, 10, 5.
63. Dotson, J. J., Bachman, J. L., Garcia-Garibay, M. A., & Garg, N. K. (2020). Discovery and total synthesis of a Bis(cyclotryptamine) alkaloid bearing the elusive piperidinoin-doline Scaffold. *Journal of the American Chemical Society*, 142, 11685–11690.
64. May, J. A., & Stoltz, B. (2006). The structural and synthetic implications of the biosynthesis of the calycanthaceous alkaloids, the communesins, and nomofungin. *Tetrahedron*, 62, 5262–5271.
65. Schmidt, M. A., & Movassaghi, M. (2008). New strategies for the synthesis of hexahydropyrroloindole alkaloids inspired by biosynthetic hypotheses. *Synlett*, 2008, 313–324.
66. Xu, J.-B., & Cheng, K.-J. (2015). Studies on the alkaloids of the calycanthaceae and their syntheses. *Molecules*, 20, 6715–6738.
67. Kirby, G. W., Shah, S. W., & Herbert, E. J. (1969). Biosynthesis of chimonanthe from [2–3H]tryptophan and [2–3H]tryptamine. *Journal of the Chemical Society C: Organic*, 14, 1916–1919.
68. Steven, A., & Overman, L. E. (2007). Total synthesis of complex cyclotryptamine alkaloids: Stereocontrolled construction of quaternary carbon stereocenters. *Angewandte Chemie International Edition*, 46, 5488–5508.
69. Lu, Z., Li, Y., Deng, J., & Li, A. (2013). Total synthesis of the *Daphniphyllum* alkaloid daphenylline. *Nature Chemistry*, 5, 679–684.
70. Kobayashi, J., & Kubota, T. (2009). The *Daphniphyllum* alkaloids. *Natural Products Reports*, 26, 936–962.
71. Zhang, Q., Di, Y.-T., Li, C.-S., Fang, X., Tan, C.-J., Zhang, Z., Zhang, Y., He, H.-P., Li, S.-L., & Hao, X.-J. (2009). Daphenylline, a new alkaloid with an unusual skeleton, from *Daphniphyllum longracemosum*. *Organic Letters*, 11, 2357–2359.

72. Baran, P. S., Maimone, T. J., & Richter, J. M. (2007). Total synthesis of marine natural products without using protecting groups. *Nature*, *446*, 404–408.
73. Maimone, T. J., Ishihara, Y., & Baran, P. S. (2015). Scalable total syntheses of (–)-hapalindole U and (+)-ambiguine H. *Tetrahedron*, *71*, 3652–3665.
74. Smitka, T. A., Bonjouklian, F., Doolin, L., Jones, N. D., & Deeter, J. B. (1992). Ambiguine isonitriles, fungicidal hapalindole-type alkaloids from three genera of blue-green algae belonging to the Stigonemataceae. *Journal of Organic Chemistry*, *57*, 857–861.
75. Raveh, A., & Carmeli, S. (2007). Antimicrobial ambiguines from the cyanobacterium *Fischerella* sp. collected in Israel. *Journal of Natural Products*, *70*, 196–201.
76. Moore, R. E., Cheuk, C., & Patterson, G. M. L. (1984). Hapalindoles: New alkaloids from the blue-green alga *Hapalosiphon fontinalis*. *Journal of the American Chemical Society*, *106*, 6456–6457.
77. Raja, A., & Prabakarana, P. (2011). Actinomycetes and drug-an overview. *American Journal of Drug Discovery and Development*, *1*, 75–84.
78. Nivina, A., Yuet, K. P., Hsu, J., & Khosla, C. (2019). Evolution and diversity of assembly-line polyketide synthases. *Chemical Reviews*, *119*, 12524–12547.
79. Kawamata, T., Nagatomo, M., & Inoue, M. (2017). Total synthesis of zaragozic acid C: Implementation of photochemical C(sp³)–H acylation. *Journal of the American Chemical Society*, *139*, 1814–1817.
80. Bergstrom, J. D., Kurtz, M. M., Rew, D. J., Amend, A. M., Karkas, J. D., Bostedor, R. G., Bansal, V. S., Dufresne, C., VanMiddlesworth, F. L., & Hensens, O. D. (1993). Zaragozic acids: A family of fungal metabolites that are picomolar competitive inhibitors of squalene synthase. *Proceedings of the National Academy of Sciences of the United States of America*, *90*, 80–84.
81. Dufresne, C., Wilson, K. E., Zink, D., Smith, J., Bergstrom, J. D., Kurtz, M., Rew, D., Nallin, M., Jenkins, R., Bartizal, K., Trainor, C., Bills, G., Meinz, M., Huang, L., Onishi, J., Milligan, J., Mojena, M., & Pelaez, F. (1992). The isolation and structure elucidation of zaragozic acid C, a novel potent squalene synthase inhibitor. *Tetrahedron*, *48*, 10221–10226.
82. Sidebottom, P. J., Highcock, R. M., Lane, S. J., Procopiou, P. A., & Watson, N. S. (1992). The squalenestatsins, novel inhibitors of squalene synthase produced by a species of *PHOMA*. *Journal of Antibiotics*, *45*, 648–658.
83. Dawson, M. J., Farthing, J. E., Marshall, P. S., Middleton, R. F., O'Neill, M. J., Shuttleworth, A., Stylli, C., Tait, R. M., Taylor, P. M., Wildman, H. G., Buss, A. D., Langley, D., & Hayes, M. V. (1992). The squalenestatsins, novel inhibitors of squalene synthase produced by a species of *Phoma*. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activity. *Journal of Antibiotics*, *45*, 639–647.
84. Sears, P., & Wong, C. H. (1999). Carbohydrate mimetics: A new strategy for tackling the problem of carbohydrate-mediated biological recognition. *Angewandte Chemie International Edition*, *38*, 2300–2324.
85. Chen, H., Zhang, H. Z., Feng, J. N., Li, X. L., Jiao, L. L., Qin, Z. B., Yin, Q. M., & Zhang, J. C. (2009). A convenient synthesis and biological evaluation of novel pseudonucleosides bearing a thiazolidin-4-one moiety by tandem Staudinger/azawittig/cyclization. *European Journal of Organic Chemistry*, *2009*, 6100–6103.
86. Zhang, P., Wei, C., Wang, E., Wang, W., Liu, M., Yin, Q., Chen, H., Wang, K., Li, X., & Zhang, J. (2012). Synthesis and biological activities of novel isoxazoline-linked pseudodisaccharide derivatives. *Carbohydrate Research*, *351*, 7–16.
87. Brian, E. L., & Erick, M. C. (1995). Total synthesis of (+)-trehazolin: optically active spirocycloheptadienes as useful precursors for the synthesis of amino cyclopentitols. *Journal of the American Chemical Society*, *117*, 11811–11812.
88. Elbein, A. D. (1987). Inhibitors of the biosynthesis and processing of N-linked oligosaccharide chains. *Annual Review of Biochemistry*, *56*, 497–534.
89. Uchida, C., Yamagishi, T., Kitahashi, H., Iwaisaki, Y., & Ogawa, S. (1995). Further chemical modification of trehalase inhibitor trehazolin: Structure and inhibitory-activity relationship of the inhibitor. *Bioorganic & Medicinal Chemistry*, *3*, 1605–1624.
90. Breitmeier, E. (2006). *Terpenes-Flavors, Fragrances, Pharmaca, Pheromones*, Wiley-VCH, Weinheim, ISBN: 978-3-527-31786-8.
91. Sun, L. C., Li, S. Y., Wang, F. Z., & Xin, F. G. (2017). Research progresses in the synthetic biology of terpenoids. *Biotechnology Bulletin*, *33*, 64–75.
92. Galle, M., Crespo, R., Kladniew, B. R., Villegas, S. M., Polo, M., & de Bravo, M. G. (2014). Suppression by geraniol of the growth of A549 Human lung adenocarcinoma cells and inhibition of the mevalonate pathway in culture and in vivo: Potential use in cancer chemotherapy. *Nutrition and Cancer*, *66*, 888–895.
93. Piva, O. (1995). Enantio- and diastereoselective protonation of photodienols: Total synthesis of (R)-(-)-Lavandulol. *Journal of Organic Chemistry*, *60*, 7879–7883.
94. Henin, F., M'Boungou-M'Passi, A., Muzart, J., & Pete, J. P. (1994). Photoreactivity of α -tetrasubstituted arylketones: Production and asymmetric tautomerization of arylenols. *Tetrahedron*, *50*, 2849–2864.
95. Schinz, H., & Seidel, C. F. (1942). Über lavandulol, einen neuen monoterpenalkohol aus lavendelöl. *Helvetica Chimica Acta*, *25*, 1572–1591.
96. Eisner, T., Deyrup, M., Jacobs, R., & Meinwald, J. (1986). Necrodols: Anti-insectan terpenes from defensive secretion of carrion beetle (*Necrodes surinamensis*). *Journal of Chemical Ecology*, *12*, 1407–1415.
97. Wolf, J. P., & Pfander, H. (1986). C₄₅- und C₅₀-carotinoide. 3. Mitteilung. Synthese von (S)-trisanhydrobacterioruberin. *Helvetica Chimica Acta*, *69*, 62–68.
98. Tanaka, K., Ushio, H., Kawabata, Y., & Suzuki, H. (1991). Asymmetric synthesis of (R)-(-)- and (S)-(+)-muscone by enantioselective conjugate addition of chiral dimethylcuprate to (E)-cyclopentadec-2-en-1-one. *Journal of the Chemical Society Perkin Transactions*, *1*, 1445–1452.
99. Ng, D., Yang, Z., & Garcia-Garibay, M. A. (2004). Total synthesis of (+/-)-herbertenolide by stereospecific formation of vicinal quaternary centers in a crystalline ketone. *Organic Letters*, *6*, 645–647.
100. Matsuo, A., Yuki, S., & Nakayama, M. (1983). (–)-Herbertenediol and (–)-herbertenolide, two new sesquiterpenoids of the *Ent*-herbertane class from the liverwort *Herberta adunca*. *Chemistry Letters*, *7*, 1041–1042.
101. Matsuo, A., Yuki, S., & Nakayama, M. (1986). Structures of *ent*-herbertane sesquiterpenoids displaying antifungal properties from the liverwort *Herberta adunca*. *Journal of the Chemical Society Perkin Transactions*, *1*, 701–710.
102. der Eycken, E. V., der Eycken, J. V., & Vandewalle, M. (1985). Iridoids: the revised structure of specionin. *Journal of the Chemical Society, Chemical Communications*, *1985*, 1719–1720.
103. Chang, C. C., & Nakanishi, K. (1983). Specionin, an iridoid insect antifeedant from *Catalpa speciosa*. *Journal of the Chemical Society, Chemical Communications*, *1983*, 605–606.

104. Curran, D., Jacobs, P. B., Elliott, R. L., & Kim, B. H. (1987). Total synthesis of (-)-specionin. *Journal of the American Chemical Society*, 109, 5280–5282.
105. Molander, G. A., Jean, S. T., David, J., & Haas, J. (2004). Toward a general route to the *Eunicellin diterpenes*: The asymmetric total synthesis of deacetoxyalcyonin acetate. *Journal of the American Chemical Society*, 126, 1642–1643.
106. Coll, J. C. (1992). The chemistry and chemical ecology of octocorals (Coelenterata, Anthozoa, Octocorallia). *Chemical Reviews*, 92, 613–631.
107. Kennard, O., Watson, D. G., Riva di Sanserverino, L., Tursch, B., Bosmans, R., & Djerassi, C. (1968). Chemical studies of marine invertebrates. IV. Terpenoids LXII. Eunicellin, a diterpenoid of the gorgonian *Eunicella stricta*. X-ray diffraction analysis of *Eunicellin dibromide*. *Tetrahedron Letters*, 9, 2879–2884.
108. Uchio, Y., Kodama, M., Usui, S., & Fukazawa, Y. (1992). Three new eunicellin-based diterpenoids from an Okinawan *Cladiella* species of soft coral. *Tetrahedron Letters*, 33, 1317–1320.
109. Yamada, K., Ogata, N., Ryu, K., Miyamoto, T., Komori, T., & Higuchi, R. (1997). Bioactive terpenoids from octocorallia. 3. A new eunicellin-based diterpenoid from the soft coral *Cladiella sphaeroides*. *Journal of Natural Products*, 60, 393–396.
110. Gutiérrez, M., Santamaría, R., Gómez-Reyes, J. F., Guzmán, H. M., Ávila-Román, J., Motilva, V., & Talero, E. (2020). New eunicellin-type diterpenes from the panamanian octocoral *Brasero asbestinum*. *Marine Drugs*, 18, 84.
111. Yoshioka, S., Nagatomo, M., & Inoue, M. (2015). Application of two direct C(sp³)-H functionalizations for total synthesis of (+)-lactacystin. *Organic Letters*, 17, 90–93.
112. Omura, S., Fujimoto, T., Otoguro, K., Matsuzaki, K., Moriguchi, R., Tanaka, H., & Sasaki, Y. (1991). Lactacystin, a novel microbial metabolite, induces neuritogenesis of neuroblastoma cells. *Journal of Antibiotics*, 44, 113–116.
113. Fenteany, G., Standaert, R. F., Lane, W. S., Choi, S., Corey, E. J., & Schreiber, S. L. (1995). Inhibition of proteasome activities and subunit-specific amino-terminal threonine modification by lactacystin. *Science*, 268, 726–731.
114. Goldberg, A. L. (2012). Development of proteasome inhibitors as research tools and cancer drugs. *Journal of Cell Biology*, 199, 583–588.
115. Glusac, K. (2016). What has light ever done for chemistry? *Nature Chemistry*, 8, 734–735.