Applications of Knoevenagel condensation reaction in the total synthesis of natural products

Majid M. Heravi1 · Fatemeh Janati2 · Vahideh Zadsirjan1

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Abstract
The Knoevenagel condensation reaction is a prominent organic reaction commonly being utilized in the total synthesis of natural and biologically potent products as a vital and frequently beginning step. Naturally occurring compounds having complex structures were demonstrated to exhibit significant biological properties. Due to numerous biological potencies, the total syntheses of them has fascinated and attracted much attention of synthetic organic chemists. In this review, we try to highlight the applications of the Knoevenagel reaction as the key step in the total synthesis of biologically active natural products.

Graphic abstract

Keywords  Knoevenagel reaction · Condensation · Total synthesis · Natural products · Biologically active compounds · Adduct

Introduction
It was Emil Albert Knoevenagel, the German chemist (between 1896 and 1898), who has explored and established a useful reaction which was named after him as Knoevenagel condensation reaction. As a matter of fact, Knoevenagel condensation is an organic transformation that is the reaction between an aldehyde or ketone with an activated methylene in the presence of a basic catalyst such as primary and secondary amines (but not tertiary amines), their respective salts and ammonia. Notably, when amine is used as a catalyst, it can react with the aldehyde or ketone to generate an iminium ion as an intermediate, which is concurrently attacked by the enolate.

In another word, a Knoevenagel condensation is indeed a nucleophilic addition of an active methylene compound to a carbonyl group of either aldehydes or ketones, followed by a dehydration reaction in which during the reaction a molecule of water is lost (therefore, condensation). The product frequently is an α, β-unsaturated ketone (hence, a conjugated enone). Knoevenagel condensation can be considered as a modification of the aldol condensation [1, 2].

Emil Knoevenagel demonstrated that primary and secondary amines, their respective salts, and ammonia (but not tertiary amines) are effective catalysts for the aldol
condensation reaction of \( \beta \)-keto esters or malonates with
either ketones or aldehydes [1–3]. The generation of iminium-type intermediates (Schiff’sche Körper or Schiff-type
intermediates) was proposed, which had a significant effect
for further investigations that finally resulted in the logical
development of amino-catalysis. The reaction is usually
performed under mild reaction conditions, it is scalable, tol-
erant towards several of substrates, and furnishes the respec-
tive \( \alpha, \beta \)-unsaturated esters, in satisfactory yields with an
atom-economic manner. As a matter of fact, the first paper
published by Knoevenagel himself was concerned with the
condensation reaction of formaldehyde (1) with diethyl
malonate (2) or with ethyl benzoylacetate (4) in the presence
of ethylamine as a catalyst to give the bisproducts 3 and 5,
respectively [4]. Different aldehydes were demonstrated to
condense likewise with diethyl malonate [5], ethyl benzoyl-
lacacetate [6], ethyl benzoyl-pyruvate, and acetylacetone [7]
in the presence of different primary and secondary amines.
Knoevenagel in 1896 exhibited that benzaldehyde (6) and
ethyl acetoacetate (7) can condense at ambient temperature
in the presence of piperidine to afford a bisproduct, how-
ever, when the reaction was performed in a freezing mixture
ethyl benzylidene acetoacetate (8) was obtained as a product
(Scheme 1) [8, 9]. Further study on Knovenagel reaction
established a wide generality and broad substrate scope. The
methylene groups sufficiently activated for being used as
substrates are those attached directly to moieties such as
the nitro, cyano, or acyl and in most cases two such groups.
Some disqualified methylene groups can undergo Knove-
nagel condensations in the presence of strong bases such as
NaOH or quaternary ammonium hydroxides. Knoevenagel
condensation reaction is a dependable, effective, scalable,
and accessible approach for the construction of carbon–car-
bon bonds, thus, extensively utilized in both academia and
industry [10, 11]. The resultant product is \( \alpha, \beta \)-unsaturated
compound, which is mostly applied as intermediate in the
construction of naturally occurring compounds [12], being
used as therapeutic agents [13], adequate chemicals [14],
polymers containing different functional groups [15], and
insecticides and pesticides. It is commonly performed in
organic solvents and mediated by organic bases for example
pyridine or piperidine [11]. The application of this reaction
is limited in chemical industry since they are associated with
hazardous and unsafe solvents and most of the used catalysts
are non-recoverable.

In the last five decades, the total synthesis of biologi-
cally active natural products and their synthetic analogues
has attracted much attention of synthetic organic chemists
and nowadays overgrowing in the ground of organic chemis-
try. New synthetic methods and accessible approaches have
been introduced that led to the effective construction of new
complex molecules or hithereto structurally determined natu-
ral products that some of them are established prescribed
drugs or medications [16]. Indisputably, alkaloids, are the
most significant and widespread group of naturally occur-
rings compounds in the plant kingdom. Most alkaloids show
important and versatile biological and physiological prop-
erties [17], thus have attracted remarkable attention of syn-
thetic organic chemists community. Notably, alkaloids are a
group of natural products mostly containing basic nitrogen
atoms. Alkaloids also may comprise some organized chemi-
cals showing neutral and some-times even weakly acidic
character [18]. There are also various synthetic molecules,
containing similar related structures, which are considered
as alkaloids. They definitely include carbon, nitrogen and
hydrogen, however; alkaloids may also involve sulfur, oxy-
gen and rarely other atoms such as Br, Cl, and P. Some of
them are known as clinically prescribed drugs, for example,
the local anesthetic and stimulating but notorious cocaine,
the hallucinogenic psilocin, the common stimulants caffeine
in coffee and nicotine in tobacco [19].

In the continuation of our efforts, presenting, the appli-
cations of name reactions in the total synthesis of natural
products [20–39], in this review, we try to underscore the
applications of Knoevenagel reaction as the key step in the
total synthesis of natural products.

**Applications of Knoevenagel reaction in the total synthesis of natural products**

The *Ipecacuanha* alkaloid emetine (14) and the *Alangium*
alkaloid tubulosine (15), the member of the family of tet-
rahydroisoquinoline alkaloids, were provided in nature
from dopamine and the monoterpene secologanin. Eme-
tine, extracted from the roots of *Psychotria Ipecacuanha*,
*Cephalisa cuminata*, and also Radix *Ipecacuanha* [40],
contains multifold fascinating biological properties such as
antiprotozoic properties [41] and activity in the reaction of
lymphatic leukaemia [42]. Remarkably, tubulosine (15) was

![Scheme 1](image-url)
extracted from the sap of *Pogonopus speciosus* [43–45] and the dried fruits of *Alangium lamarckii* [46–48]. It is significantly potent against various cancer cell lines [49] and also exhibited different other biological properties including inhibition of protein biosynthesis [50–52] and HIV reverse transcriptase inhibitory properties [53]. Lutz et al. reported [54] the first asymmetric synthesis of the ipecacuanha alkaloid emetine and the alangium alkaloid tubulosine using a domino Knoevenagel/hetero-Diels–Alder reaction and an asymmetric catalytic transfer hydrogenation reaction of imines as main steps. In this route, total synthesis of emetine and tubulosine were started from amine 9 and ethyl ester chloride 10 that upon ten steps transformed into isoquinolineacetalddehyde 11. Next, the Knoevenagel condensation of Meldrum’s acid (12) and isoquinolineacetalddehyde (15) 11 occurred to afford intermediate 13. In the following, compound 13 was converted into enantiopure natural product emetine (14, upon nine steps) and tubulosine (15, upon ten steps) in excellent purity (Scheme 2) [54].

(−)-Deguelin (21), extracted from the flowering plants *Lonchocarpus utilis* and *urucu* [55], is attributed to the pesticide rotenone. Deguelin exhibited chemopreventive property in mammary and skin carcinogenesis models [56]. (−)-Deguelin has exhibited important chemopreventive and chemotherapeutic potential in a wide range of in vivo and in vitro cancer models. Rebecca et al. developed [59] a stereoselective synthesis through a thiourea-mediated intramolecular cyclization reaction to efficiently access the natural and unnatural enantiomers of deguelin. Using coupling this enantioselective method with copper-improved arylation reaction, (−)-deguelin was attained in the shortest enantioselective synthesis to date (six linear steps with no masking groups) from 2,4-dihydroxymethyl benzoate with moderate levels of enantioselectivity. Total synthesis of (−)-deguelin was started from the reaction between 2,4-dihydroxyaceto-phenone (16) and 3,4-dimethoxyphenol (18). In this route, β-ketoester 17 was provided from 2,4-dihydroxyacetophenone upon three steps and also aldehyde 19 was formed from 3,4-dimethoxyphenol after two steps. Rebecca et al. attempted to directly couple the β-ketoester 17 and aldehyde 19 under Knoevenagel conditions (piperidine, PhMe, ACOH, and Dean-Stark [57]) to afford the corresponding alkylidene 20, however, the reaction afforded very low conversion and led to the formation of the racemic cyclized
material. Next, alkylidene 20, upon three steps, transformed into the target natural product deguelin (21) in 25% yield. Fascinatingly, there was no proof of the trans-fused product in this approach, but the fact that the report by Snider exhibited construction of both cis- and trans-fused [5, 6] systems [58]. Although, calculations of energy differences between the cis- and trans-fused systems in this method depicted that the natural configuration was energetically preferred that possibly clarifies the lack of transfused product. Hence, the efficacy of this significant bond disconnection made it a striking method to admittance the natural product in an effective and convergent approach (Scheme 3) [59].

The lycopodium alkaloid cermizine C (25) was extracted from the club moss Lycopodium cernuum and also the related alkaloid senepodine G, isolated from the club moss Lycopodium chinense [60–64]. Senepodine G is cytotoxic to murine lymphoma L1210 cells. Total synthesis of (±)-7-epi-senepodine G (24) was started from the Knoevenagel the reaction of (±)-pelletierine (22) and Meldrum's acid (12). This Knoevenagel reaction afforded unsaturated Meldrum's acid derivative 23 that upon six steps gave (±)-7-epi-senepodine G. In the following reduction of 24 with sodium borohydride in methanol happened stereospecifically by an axial attack from the less-hindered top face to make (±)-5-epi-cermizine C (25) in 82% yield (Scheme 4) [65].

The lupine alkaloids contain structurally various types of quinolizidine bases known in a number of leguminous plant and tree species, involving lupin, gorse, broom, and laburnum [66–68]. The sparteine subgroup of lupine alkaloids is found by a shared 3,11-diazatetracyclo[7.7.1.0^3,8] ^11,16-heptadecane ring scaffold identified by a bispidine core having peripheral quinolizidine scaffold flanking its unit [69].
Three diastereomeric forms for this inherently chiral tetra-
cyclic array are geometrically accessible, and each probable
isomeric difference is demonstrated by a natural alkaloid.
The three alkaloids were individually provided in stereo-
isomeric difference is demonstrated by a natural alkaloid.
Kobayashi et al. extracted the cortistatins unique abeo-
9(10,19)- and rostane-type steroidal alkaloids having an
Knoevenagel condensation adduct, \(a,\alpha'-\text{dicyanoglutaurimide}
27. Remarkably, \((\pm)-\alpha\)-isopartene \((29)\) was synthesized
from \(28\) in 28% overall yield using a two-directional syn-
thetic sequence including four reactions: double allyla-
ction reaction, ring-closing olefin metathesis (RCM),
hydrogenation reaction, and borane-catalyzed reduction.
\((\pm)-\beta\)-Isopartene \((30)\) was targeted along analogous lines
using a strategic reversal in allylation and reduction re-
actions on the core synthon. Therefore, \(28\) was advanced to \(30\)
in four steps and 12% overall yield. The target \((\pm)\)-sparteine
\((31)\) was secured from \(28\) in 11% overall yield and four steps
(Scheme 5) \([70]\).

Kobayashi et al. extracted the cortistatins unique abeo-
9(10,19)- and rostane-type steroidal alkaloids having an
oxacyclo[3.2.1]octane scaffold, from the marine sponge
\textit{Corticium simplex} \([71, 72]\). Cortistatin A, the most active
congener, exhibited potent inhibition against the prolifera-
tion of human umbilical vein endothelial cells having very
selectivity among cell lines. Total synthesis of cortistatin J
\((38)\) and A \((39)\) were started from the reaction of 2-methyl-
1,3-cyclopentadione \((32)\) and methyl vinyl ketone \((33)\), that
was transformed into aldehyde \(34\), upon 12 steps. Next, kno-
everegal condensation was accomplished between aldehyde
\(34\) and cyclohexane-1,3-dione \((35)\) using piperidine in ethyl
acetate to give tetracyclic compounds \(36\) (68%, \(dr = 5:1\))
together with the undesired side product \(37\) (29%). Notice-
ably, once piperidine hydrochloride was applied in place of
piperidine, no coupling products were provided. However,
the reaction using piperidinium acetate gave \(36\) in 71% yield,
an important quantity of \(37\) (25%) was also provided. Both

![Scheme 5](image)

**Scheme 5**

Three diastereomeric forms for this inherently chiral tetra-
cyclic triene \(36\) upon fourteen steps was transformed into the
anticipated natural products, cortistatin J and A (Scheme 6)
\([73]\).

Gelsemine \((45)\), as the major alkaloid component of
\textit{Gelsemium sempervirens} (Carolina jasmine) \([74, 75]\), has
obtained various synthetic efforts because of its uniquehexa-
cyclic cage structure \([76, 77]\). Fukuyama et al. reported a
total synthesis of gelsemine in 1996 \([79]\). This synthetic
method was commenced with the formation of the required
aldehyde \(41\), which is prepared from methyl acetoacetate
\((40)\) \([78]\). The Knoevenagel condensation of aldehyde \(41\)
and oxindole gave a 4:1 mixture of \(E\) - and \(Z\)-isomers of \(43\).
Enavored photochemical isomerization of the \(E\)-isomer
at the anticipated \(Z\)-isomer afforded a 1:1 mixture at best.
As anticipated, condensation reaction of 4-iodoxindole
\((42)\) with aldehyde \(41\) afforded \((Z)\)-alkylidene indolcaline
\(43\) in 89% yield as the only product. Next, \((Z)\)-alkylidene
indolcaline \(43\), upon fifteen steps was transformed into the
corresponding natural product \((\pm)\) oxogelsemine \((44)\).
\((\pm)\) Oxogelsemine was transformed into \((\pm)\)-gelsemine in
82% yield via selective reduction of the lactam with diisobu-
tylaluminum hydride (DIBAL) in toluene (Scheme 7) \([79]\).

A group of aryl C-glycoside comprising naturally occurr-
ing compounds, containing the gilvocarcins V \([80–83]\) was
extracted from various species of \textit{Streptomyces}. In addition,
the aglycon of one of them, defucogilvocarcin V \((50)\) was
extracted from the fermentation broth of \textit{Streptomyces are-
nae} 2064 \([84]\). Investigations demonstrated that the antitu-
mor property of defucogilvocarcin V \((50)\), on activation by
light, is analogous to that of the parent gilvocarcin V \([84, 85]\).
These compounds demonstrate significant biological activities
such as antibacterial \([81, 86]\) and strong antitumor
activities \([87–90]\). A short total synthesis of defucogilvo-
carcin V was achieved and reported by Nandaluru et al. in
2012. The main aspects of the method are the construction of
the C-ring via a vinyllogous Knoevenagel/transesterifi-
cation reaction and inverse electron demand Diels–Alder
driven domino reaction. This route was started from market
purchasable accessible juglone \((46)\) that was transformed
into the hydroxynaphthaldehyde \(47\), upon five steps. The
vinyllogous Knoevenagel reaction was performed from the
reaction of hydroxynaphthaldehyde \(47\) and dimethyl gluta-
conate \((48)\) to form the desired electron-deficient diene \(49\)
that after four steps gave defucogilvocarcin. Noticeably the
total synthesis of defucogilvocarcin V was performed in 12
steps from juglone in 5.3% overall yield (Scheme 8) \([91]\).

The antiinsectan leporin A \((56)\) was extracted from the
sclerotia of \textit{Aspergillusleporis} (NRRL 3126) by TePaske et al. \([92]\).
Leporin A shows satisfactory activity against the corn earworm
\textit{Helicoverpa zea}, making a reduction in growth rate once. In
addition, it demonstrates mild antibacte-
rial property against \textit{Bacillus subtilis} \([92]\). Total synthesis of
Scheme 6

\[
\text{32} + \text{33} \xrightarrow{12 \text{ steps}} \text{34} \xrightarrow{\text{piperidine, EtOAc}} \text{35}
\]

36 (68\%, dr = 5:1)

37 (29\%)

Scheme 7

\[
\text{40} \xrightarrow{4 \text{ steps}} \text{41} \xrightarrow{\text{piperidine, 23 °C, MeOH, 89\%}} \text{42} \xrightarrow{15 \text{ steps}} \text{43}
\]

\[
\text{DIBAL, Toluene} \rightarrow \text{(S)-Oxogelsemine (44)} \rightarrow \text{Gelsemine (45)}
\]
leporin A was achieved via Knoevenagel condensation reaction of 4-hydroxy-5-phenyl-2-pyridone (51) and 2-methyl-6E,8E-decadienal (52) to afford the unstable o-quinonemethide 53. The o-quinonemethide 53 an inverse electron demand intramolecular Diels–Alder reaction with the acyclic diene functioning as the dienophile and quinonemethide functioning as the diene to provide the tricyclic intermediate 54. It should be mentioned that tandem Knoevenagel condensation inverse electron demand intramolecular hetero Diels–Alder reactions of this kind were only established by Tietze [93–95]. In the following, N-hydroxylation [96, 97] of 54 afforded compound 55. Finally, after three steps, the natural product leporin A was synthesized (Scheme 9) [98].

Epolactaene (62), a microbial metabolite, was extracted from the fungal strain *Penicillium* sp. BM 1689-P by Kakeya et al. [99]. It is efficient in stimulating neurite outgrowth and arresting the cell cycle at the G1 phase in a human neuroblastoma cell line, it is considered as a potential treatment for different neurodegenerative diseases for example dementia [100]. In addition, epolactaene was known to prevent the activities of mammalian DNA human topoisomerase II and DNA polymer rases. A stereocontrolled total synthesis of both the (+)- and (−)-epolactaene enantiomers were started from tetrahydropyran-2-ol (57). In this approach, the subsequent reactions are significantly remarkable: the stereoselective formation of the conjugated (E,E,E)-triene via a combination of kinetic deprotonation and thermodynamic equilibration, the E selective Knoevenagel condensation reaction of γ,δ-unsaturated β-keto-thioester 58 and a chiral 2-alkoxyaldehyde 60, a diastereoselective epoxidation and also the mild hydrolysis of an R-epoxy nitrile. In this approach, total synthesis of epolactaene (62) was commenced from tetrahydropyran-2-ol that upon four steps gave the γ,δ-unsaturated β-ketothioester precursor 58. Upon
conversion of the thioester 58 to amide 59. The latter compound 59 treated with (R)-2-(tert-butylidimethylsiloxy)propanal (60) through Knoevenagel condensation reaction to make compound 61. Next, compound 61, upon epoxidation and deprotection of the masking group was transformed into the natural product (+)-epolactaene (62) (Scheme 10) [101].

Guanacastepene A (66) was extracted as part of a program to examine Endophytic fungi as sources of potential antibiotics [102–104]. Significantly, this compound exhibits activity against organisms (cf. Enterococcus faecalis and Staphylococcus aureus), which are resistant to agents including vancomycin and methicillin [102–104]. Noticeably, the structure of guanacastepene A, a diterpenoid that registered positive in this screening context, was elucidated by Clardy [102–104]. The total synthesis needed a mastery of an intramolecular Knoevenagel condensation reaction of a $\beta,\gamma$-unsaturated ketone. In fact, cyclization reaction was best performed once the terminal double bond of 64 was transformed into an epoxide. Total synthesis of guanacastepene A was started from 2-methylcyclopentenone (63) that after 14 steps afforded compound 64. Next, intermediate 64 was transformed into $\beta$-ketoester 65 using a catalytic quantity of a sodiummethoxide in EtOH at 50 °C. In the following, the resultant $\beta$-ketoester 65 was transformed into natural product guanacastepene A (66) after nine steps (Scheme 11) [105].

Hexacyclic Strychnos alkaloids (−)-leuconicine B (71) and A (72) were extracted from extracts of the Malaysian plant Leuconotis (Apocynaceae) maingayi by Kam et al. in 2009 [106]. Total synthesis of Strychnos alkaloids (−)-leuconicine B and A were completed in thirteen steps in 10% overall yields and fourteen steps in 9% overall yields, respectively. Key stages contain one-pot, sequential spirocyclization/intramolecular aza-Baylis–Hillman approach, domino acylation/Knoevenagel cyclization reaction, and an intramolecular Heck-cyclization reaction.
Total synthesis of (−)-leuconicine B (71) was started from N-tosylindole-3-carboxaldehyde (67) that was transformed into compound 68 in six steps. Best one-pot performance of this strategy involved heating a solution of 68, methyl malonyl chloride (69) and triethylamine in dichloromethane in which pentacycle 70 was extracted in 82% yield. Finally, compound 70, upon two steps transformed into natural product (−)-leuconicine B (71) in 82% yield. In addition, Weinreb aminolysis of 71 with Me₃Al [107] secured (−)-leuconicine A (72) in 91% yield (Scheme 12) [108].

Lithospermic acid (76) was first extracted from the root of Lithospermum ruder ale by Johnson et al. in 1963 [109]. Significantly, it was wholly identified as a trimer of caffeic acid A by Carmack et al. [110, 111] and Wagner et al. individually [112]. Lithospermic acid, an active ingredient of the Chinese herb Danshen, exhibits remarkable biological activities. It demonstrated inhibitory property on proliferation and migration of rat vascular smooth muscle cells [113]. An asymmetric synthesis of (+)-lithospermic acid, which is known as an active anti-HIV agent, was performed in a convergent method in nine steps. This synthesis exhibits an asymmetric intramolecular oxa-Michael addition, a hypervalent I₂-catalyzed rearrangement of chromanone to dihydrobenzofuran, an asymmetric R-oxyamination, and also an intermolecular carbon-hydrogen olefination. In this approach, for the total synthesis of lithospermic acid, alkylidene β-keto ester 75 was synthesized via Knoevenagel condensation reaction of β-keto ester 73 and 3,4-dibromobenzaldehyde (74) in the presence of piperidinium acetate (5 mol%) in benzene under reflux condition. Next, keto ester 75 was converted into the natural product (+)-lithospermic acid (76) after eight steps. It should be mentioned that the spectroscopic data of this synthetic (+)-lithospermic acid are in whole agreement with those of the target natural product 76 (Scheme 13) [114].

The antibiotic sesquiterpene, albaflavenone (82) was extracted from the Gram-positive soil bacteria S. albidoflavus by Gülter et al. in 1994 [115]. For the first time, total synthesis of albaflavenone was performed through the short generation of its zizaene moiety using consecutive intramolecular aldol condensation reaction followed by chemo- and diastereoselective reduction of the conjugated C–C double bond. The total synthesis of albaflavenone was performed in nine steps from 2-cyclopenten-1-one (77) as without the usage of masking groups and with excellent stereocontrol in 93% overlay yields. Moreover, the absolute configuration of naturally occurring albaflavenone was identified to be 1R,2S,8S. This method was commenced from the reaction...
of 2-cyclopenten-1-one with prenyl Grignard reagent (78) to give compound 79. The Knoevenagel condensation reaction between compound 79 and dimethyl malonate (80) afforded the unsaturated diester 81. Upon seven steps, the target natural product albaflavenone (82) was provided from compound 81 in 15% yields, as a single diastereomer (Scheme 14) [116].

Tricyclic ketal moieties and their architectural derivatives exhibit a varied group of structurally complex and biologically efficient scaffold [117–119], which are extremely known in various exciting biological active naturally occurring compounds [120, 121]. Averufin (85) was extracted from traditional medicinal plants or fungi having medical potential. A significant proline-mediated method, established a biosynthetic Knoevenagel condensation reaction/ [4 + 2] cycloaddition sequence, for the generation of oxygen bridged tricyclic ketal moieties. Based on this approach, a possible synthetic method efficiency was developed to complete the formal synthesis of averufin. Total synthesis of averufin was started by reacting the model substrates cyclohexane-1,3-dione (35) and 4-oxopentanal (83), easily provided via a Swern oxidation of 5-hydroxypentan-2-one [122, 123], with l-proline in CH$_2$Cl$_2$ under air at ambient temperature [124–126]. Remarkably, the Knoevenagel reaction was performed in 3 h to construct the corresponding compound 84 as the main product in 78% yield. Finally, the intermediate 84 was transformed into the target natural product averufin (85) upon six steps (Scheme 15) [127].

 Naturally occurring compounds having oxygen bridged tricyclic ketal scaffolding including dactyloidin (91) [121, 128] and demethyldactyloidin (90) [129] were extracted from traditional medicinal plants *Myristica ceylanica* and *Myristica dactyloides* individually. Both plants were extremely applied in the indigenous medicine of various countries with decoctions cattle wounds and to treat throat ailments [130]. The significant method toward the first racemic total synthesis of dactyloidin and demethyldactyloidin was demonstrated in 2013 by Tan et al. [131]. Their oxygen-bridged tricyclic ketal systems were quickly formed via an efficient biomimetic Knoevenagel condensation reaction/[4 + 2] cycloaddition cascade as the critical method and the 1,5-dicarbonyl fragment was connected by Grignard addition. This approach was started from 1,5-dicarbonyl substrate 88 that was provided from anisole (86) and glutaric anhydride (87) upon 10 steps. The key tricyclic ketal scaffold of precursor 89 was synthesized via the DL-proline-mediated Knoevenagel condensation reaction/[4 + 2] cycloaddition cascade from cyclohexane-1,3-dione (35) and 1,5-dicarbonyl substrate 88. Next, compound 89 was converted into the natural product (+)-demethyldactyloidin (90) and (+)-dactyloidin (91) upon three steps and five steps respectively (Scheme 16) [131].

Cadiolides containing a class of noncytotoxic, highly substituted butenolides were extracted in 1998 and 2012 from Indonesian and Korean ascidians, individually [132]. In 2014, cadiolide B exhibited to prevent Japanese encephalitis virus (JEV) [133]. A short, modular and effective synthesis of the naturally occurring compounds cadiolides A, B, and D was demonstrated by Boukouvalas et al. [136]. Noticeable stages contain one-pot assembly of a key
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\(\beta\)-aryl-\(\alpha\)-benzoylbutenolide scaffold by region controlled “click-unclick” oxazoleynone Diels–Alder cycloaddition/cycloreversion and ensuing 2-alkoxyfuran hydrolysis and also a masking group-free vinylogous Knoevenagel condensation reaction. Total synthesis of cadiolide was commenced from easily provided ynone 92 [134, 135], that upon four steps transformed into 93 in 84% yield. Next, the vinylogous Knoevenagel condensation reaction of 93 with market purchasable accessible aldehydes 94 or 96 or 98 has occurred. Butenolide 93 easily underwent Z-selective condensation reaction under classical Knoevenagel conditions using piperidine in methanol at room temperature with aldehyde 94 to give isomerically pure cadiolide A (95) (80%). Similarly, cadiolides B (97) and D (99), were provided from 93 (Scheme 17) [136].

In 1987, psammaplin A was initially extracted individually using three various groups from the psammaplysilla sponge or unidentified sponges [137–139]. Psammaplin A was extracted from an unidentified sponge from the south region of Korea by Hong and co-worker in 2012. Psammaplin A contain a unique symmetrical structure of bromotyrosine obtained disulfide dimer. Psammaplin A demonstrated different biological properties including antimicrobial [140], cytotoxicity against inhibition of DNA topoisomerase [141], and the leukemia cell-line P388 [137, 142], histone deacetylase [143], DNA gyrase [140], farnesyl protein transferase [144], and leucine aminopeptidase [145]. A short and effective method for the synthesis of psammaplin A (101) was established in 2012 by Hong et al. [146]. Noticeably, psammaplin A was provided in nine steps with 50% overall yield from \(p\)-hydroxybenzaldehyde and ethyl acetoacetate through Knoevenagel condensation reaction and direct nitrosation as main steps. Total synthesis of psammaplin A was achieved from the Knoevenagel reaction of 4-hydroxybenzaldehyde (94) and ethyl acetoacetate (7) using piperidine in HOAc that efficiently transformed into \(\alpha,\beta\)-unsaturated ester 100. Upon eight steps, compound 100 gave psammaplin A (101). It should be mentioned that this approach might be highly efficient to form a quite diverse library of psammaplin A type analogs (Scheme 18) [146].

The \(\gamma\)-benzylidenebutenolide scaffold containing two 4-hydroxyphenyl moieties, with or without halogen atoms, is a usual structural aspect of a group of biologically potent marine ascidian metabolites including rubrolides C (106)
and E (109). Rubrolides A to H were extracted from the colonial tunicate *Ritterella rubra* in 1991 [147]. The rubrolides are active non-nitrogenous antibiotics and also were known to contain satisfactory but selective inhibition of protein phosphatases 1 and 2A. Rubrolides I, K, L, and M were extracted from the red colonial tunicate *Synoicum blochmanni* [148] and exhibit important cytotoxicities against four various cancer cells lines [149–151]. A short and effective method for the synthesis of rubrolide C in 46% overall yield and E in 56% overall yield was achieved by an intramolecular Wittig reaction as a main stage for the simple formation of 4-aryl furan-2(5H)-one (106). Total synthesis of rubrolide C was started from inexpensive and market purchasable 4-methoxyacetophenone (102), which upon six steps transformed into aryl butenolide 103. Next, compound 103 through Knoevenagel condensation reaction with 3,5-dibromo-4-methoxybenzaldehyde (104) afforded butenolide 105. In the following, the demethylation reaction of aromatic methoxy groups with boron tribromide afforded corresponding rubrolide C (106) in 52% yield. On the other hand, compound 103 via Knoevenagel condensation reaction with *p*-anisaldehyde (107) gave only (Z)-butenolide 108 in 81% yield. Lastly, the demethylation reaction of aromatic methoxy groups by borontribromide gave rubrolide E (109) in 56% yield (Scheme 19) [152].

*Salvia miltiorrhiza*, found as danshen or red sage is a usual plant applied in traditional Chinese and Japan medicine for the treatment of cardiovascular diseases [153]. Noticeably, various compounds were extracted and identified from danshen. These compounds having hydrophilic
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activities such as specific mono- and polyphenolic acids, contain one of the subgroups present which are found in the plant. Danshensu (RDSS) (115), for example, R-3,4-dihydroxyphenyl lactic acid, looks to be its major potent illustrative [154]. The generation of sodium R-danshensu is commonly relied on the alkaline extraction of salvia miltiorrhiza herbs with ethanol precipitation to eliminate impurities. This R isomer of danshensu (DSS) (115) from the natural source demonstrates multiple pharmacological influences on the cardiovascular system [155, 156]. The synthesis and molecular structure details of R-3,4-dihydroxyphenyl lactic acid (danshensu) and similar compounds, i.e. S isomer and the key intermediates were demonstrated in 2018 by Sidoruky et al. [157]. The synthetic method was achieved via the Knoevenagel condensation reaction, enantioselective sharpless dihydroxylation reaction, reductive mono dihydroxylation, and final deprotection reaction. Initially, Meldrum’s acid (12) was treated with benzyl alcohol (110) to afford benzyl ester of malonic acid (111). Without isolation, this compound was treated with 112 via Knoevenagel reaction to make compound 113. In the following, compound 113, upon two steps transformed into R or S danshensu acid isomers, S-DSS (114) and R-DSS (115), by the whole elimination of benzyl masking groups through palladium/C-mediated hydrogenation at ambient temperature under continuous flow conditions, by hydrogen generator (Scheme 20) [157].

The alkaloid (benzonaphthyridine alkaloid) 119 was extracted from a mangrove derived Streptomyces albogriseolus in 2010 [158]. Compound 119 contains a fused tricyclic heteroaromatic system that is a member of diazaphenathrene group. The unit structure was clearly generated through various main conversions including Knoevenagel condensation reaction, curtius rearrangement, and also cyclic carbamate construction reduction sequence. Tian and et al. demonstrated that benzonaphthyridine alkaloid 119 could be provided via coupling reaction of the tricyclic heteroaromatic precursor 118 with the chiral unsaturated amine. This synthetic method was started from the 3-amino-2-methylquinoline-4-carboxaldehyde (117) that was constructed from isatin 116 after two steps [159– 161]. Then, Knoevenagel condensation reaction of 117 and diethyl malonate (2) using piperidine gave tricyclic heteroaromatic precursor 118 in 82% yields. In the following, compound 114, upon nine steps was transformed into benzonaphthyridine alkaloid 119 in 6.1% overall yields (Scheme 21) [162].

Cannabinoids were extracted from the plant Cannabis sativa [163]. G-protein coupled cellular receptors, CB1 and CB2, are the targets of the cannabinoids [164, 165]. Although, the CB1 receptor is found extremely in the central nervous system (CNS), particularly the brain, the CB2 receptor is less broadly spread [166, 167]. A multicomponent domino reaction, which gives 6H-dibenzo[b,d]pyran-6-one derivatives was achieved and reported in 2012 by Nandaluru et al. [168]. The overall conversion composed of six reactions comprising Knoevenagel reaction, transesterification, enamine construction, an inverse electron demand Diels–Alder reaction, 1,2-elimination, and also transfer hydrogenation take place during the MCR, in which both inverse electron demand Diels–Alder components are provided spontaneously. It should be mentioned that pyrrolidine
catalyzes two separate reactions (Knoevenagel reaction and enamine construction). This chemistry was used in the total synthesis of cannabinol (124). Generally, the yields (10–79%) are remarkably better than those provided using a stepwise method. Total synthesis of cannabinol (124) was commenced from salicycladehyde 121 [169, 170] that upon reaction with dimethyl glutaconate (122) through Knoevenagel reaction provided 123. Next, compound 123 was transformed into cannabinol (124) upon four steps (Scheme 22) [168].

Platensimycin (128) was extracted in 2006 from a strain of Streptomyces platensis. Because of significant aspects involving its new structure, a new mechanism of action, a significant and wide range of antibacterial properties, platensimycin has obtained much attention of chemists. Noticeably, various methods for total syntheses of this antibiotic were described previously [171–173]. This method was systematically demonstrated the acid improved intramolecular cycloaddition reaction of activated cyclopropanes that were theoretically categorized into intramolecular cross cycloadditions (IMCC) and intramolecular parallel cycloadditions. The intramolecular cross cycloadditions gave a common and effective method for the formation of structurally complex and different bridged bicyclic scaffolds. The potential of this method was revealed by the synthesis of naturally occurring compounds. As an example which exhibits the potential of
the established [3 + 2] intramolecular cross cycloadditions, a formal total synthesis of platensimycin was efficiently performed. Total synthesis of platensimycin (128) was started from 2-bromo-5-methoxybenzaldehyde (125), that upon three steps afforded aldehyde 126. Next, knoevenagel condensation reaction between 126 and dimethyl malonate (80) gave compound 127. In the following, compound 127 upon six steps were transformed into target natural product platensimycin (128) (Scheme 23) [174].

1,5-Diphenyl-2-penten-1-one and 1,5-diphenyl-1-pentanone were extracted from Stellera chamaejasme L. (Thymelaeaceae, used in Chinese traditional medicine) for the first time by Hou et al. in 2001 [175]. These two naturally occurring compounds are analogous in structure to daphneolone, a nematicidal substance extracted from Daphne odora [176]. These two compounds show potent contact properties and very moderate antifeedant property against Aphis gossypii and Schizaphis graminum. A wide range of 1,5-diphenyl-2-penten-1-one analogues having piperazine scaffold was provided on the basis of natural product 1,5-diphenyl-2-penten-1-one. At first, functionalized cinnamic acid 130 was provided via a Knoevenagel reaction between functionalized benzaldehydes 6 and malonic acid (129) using piperidine in pyridine. Then, functionalized cinnamic acid 130 was transformed into phenylpropanal (131) upon two steps. (E)-5-(Functionalized phenyl)pent-2-enoic acid 132 was provided via a similar method as compound 130. In the following, compound 132, upon three steps transformed into the target natural product 1,5-diphenyl-2-penten-1-one analogue 133 in 60% yield (Scheme 24) [177].

Structurally, lignans, a large class of dimeric propyl phenols, could be approximately categorized into eight groups in nature [178]. Among them, lignans including an aryl-naphthalene lactone unit, as represented by retrojusticidin B, retrochinensin, justicidin E, and helioxanthin, were extracted from a wide range of plant species from various parts [179], involving fruit, bark, leaf, root, and seed and belong to a group mentioned for diverse biological properties, including antiviral, antitumor, cytotoxic, antibacterial, HIV-1 reverse transcriptase, and phosphodiesterase inhibitory properties [180]. In 2014, helioxanthin was explored in vitro to prevent different stages included in brain tumor metastasis and retarded the migration of both melanoma and brain endothelial cell, demonstrating that naturally occurring products might exhibit a critical role in modern medicine as the horizon of biological knowledge expands [181]. Making use of a tandem free-radical cyclization method catalyzed by manganese(III) acetate as a key operation. Total synthesis of retrojusticidin B, justicidin E, and helioxanthin briefly was performed in four or five steps in an overall yield of 45%, 33%, and 44%. Total synthesis of retrojusticidin B (138) was started from an alkynol 134. The latter was exposed to esterification reaction to form cyano ester 135 in almost quantitative yield that in turn underwent Knoevenagel condensation reaction using aldehyde 136 to give the main intermediate 137. In the following, compound 137 was transformed into the target natural product retrojusticidin B (138) upon two stages in an overall yield of 45% (Scheme 25) [182].
An analogous method was applied to form justicidin E (143) and helioxanthin (144), which was started from α-cyano ester 135. Next, compound 135 was coupled with piperonal (139) to give the main intermediate 140 in satisfactory yield that in turn underwent manganese(III)-catalyzed oxidative cyclization reaction to provide a pair of inseparable regioisomers 141 and 142 in a ratio of 3:1 in 71% yield. Upon two steps, the mixture of compounds 141 and 142 was converted into justicidin E (143) and helioxanthin (144), in 59% and 20% yields respectively (Scheme 26) [182].

Dicaffeoylquinic acids (DCQAs) are components of coffee and artichoke extracts. DCQAs contain an extensive range of pharmacological activities such as antiviral, antioxidant, antihistaminic, and antibacterial [183–187]. For the first time, Raheem et al. reported [188] total synthesis of 3,5-O-dicaffeoylquinic acid (150) and its derivatives, 3,5-O-diferuloylquinic acid (151) and 3,5-(3,4-dimethoxycinnamyl)quinic acid (152), in a nine-step sequence. The synthesis of 150 and its derivatives were began from market purchasable (−)-quinic acid (145). Upon eight steps, the dimalonate ester of quinic acid (146) was provided in satisfactory yield. The last step of the syntheses included a double Knoevenagel condensation reaction without any masking groups. Therefore, the reaction between 146 and aldehydes 147–149, DMAP and piperidine in anhydrous dimethylformamide gave the desired products in satisfactory to good yields (3,5-DCQA (150, 68%), 3,5-diferuloylquinic acid (151, 72%), and 3,5-(3,4-dimethoxycinnamyl)quinic acid (152, 81%)). Noticeably, this method should be agreeable to a varied series of symmetrical difunctionalised derivatives (Scheme 27) [188].

Altissimacoumarin D was extracted from Ailanthus altissima (the tree of heaven), a plant applied in Chinese and Korean traditional medicine. Altissimacoumarin D was
recognized from the bark extract, that is Sirt1 activator [189].
The total synthesis of the plant natural product altissimacoumarin D (156) was started from 2,4-dihydroxybenzaldehyde (153), that after two steps gave 2,4-dihydroxy-3,5-dimethoxybenzaldehyde (154). Next, 154 was reacted with Mel-
with Bigi’s method in high yield [190]. After three steps, altissimacoumarin D (156) was obtained in a modest 54% yield. The ready admittance to altissimacoumarin D will assist its usage as a starting precursor for the formation of the more heavily oxygenated naturally occurring compounds in this group, while the modular route improves the synthesis of analogues for structure–activity relationship investigations (Scheme 28) [191].

The trichodermatides are a group of naturally occurring compounds having unusual aspects that extracted from the marine-derived fungus Trichoderma reesei by Pei et al. These compounds have exhibited a wide range of fascinating bioactivities [192]. Trichodermatide A contains a principally remarkable structure presenting a pentacyclic ring scaffold having eight stereocenters. A concise total synthesis of the reported structure of racemic trichodermatide A was demonstrated in 2014 by Myers et al. [193]. Total synthesis of trichodermatide A (161) was commenced from (E)-3-decen-1-ol (157), which after two steps transformed into aldehyde 158. Next, chiral dihydroxy aldehyde 158 through Knoevenagel condensation reaction with 6-hydroxycyclohexane-1,3-dione (159) gave alkylidenebiscyclohexane-1,3-dione 160 in high yield. Optimized conditions for this conversion involved the usage of piperidine as a catalyst and using an excess quantity of 1,3-cyclohexadione. In the following, upon four steps, compound 160 was transformed into the target natural product trichodermatide A (161) (Scheme 29) [193].

Daurichromenic acid (166) was extracted from the leaves and twigs of Rhododendron dauricum, a plant known in areas of eastern Siberia, northern China, Japan, and Hokkaido [194–196]. The dried leaves of this plant are found as “manshanfong” in China and applied the treatment of acute-chronic bronchitis [197, 198]. In addition, rhododaurichromanic acid A (165) exhibits potent anti-HIV property [194–196]. Moreover, rhododaurichromanic acid A (165) was demonstrated in developing an oxo-[3 + 3] annulation of vinyliminium salts with resorcinols as a 1,3-diketo equivalent. This annulation reaction contains an important cascade of Knoevenagel condensation-oxa-electrocyclization reaction to directly admitance chromene derivatives. This tandem sequence provides an efficient cascade and exhibits a bioinspired method [201] for the synthesis of naturally occurring compounds. An ultimate total synthesis of (±)-rhododaurichromanic acid A (165) was performed and demonstrated an intramolecular gasman-type cationic [2 + 2] cycloaddition. Total synthesis of (±)-rhododaurichromanic acid A was commenced from resorcinol 162 and enal 163, which upon Knoevenagel reaction in the presence of piperidine and acetic anhydride followed by heating the mixture at 130 °C resulted in the corresponding chromene 164 in 75% isolated yield. Next, compound 164 upon three steps resulted in the natural product of (±)-rhododaurichromanic acid A (165). A much more effective exercise is depicted in a synthesis of (±)-daurichromenic acid (166) from confluent in 164 through a concise two steps sequence (Scheme 30) [202].

Annulation reaction between 6-hydroxyindole (167) and citral (168) in the presence of piperidine and toluene as solvent at 100 °C resulted in compound 169 in 30% yield. This annulation constitutes a cascade of Knoevenagel condensation-oxa-electrocyclization leading to a direct access to chromenes. However, the yield is poor, it exhibits the possibility of using 1,3-aminohydroxybenzene (here protected as indole) as a resorcinol equivalent for such annulation, and that it provides a probable simple method toward (±)-murrayamine M (170) (Scheme 31) [202, 203].
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**Scheme 29**

1. **157** → **158**: 2 steps

2. **158** → **159**: piperidine 95%

3. **159** → **160**: 4 steps

**Trichodermatide A (161)**

**Scheme 30**

1. 1,3-benzenedimethanol + α-methylstyril acetaldehyde + Ac₂O + toluene → **163**

2. **163** → **164**: 3 steps

3. **164**: R¹ = prenyl

4. **164** → **165** (3 steps)

**Rhododaurichromanic acid A (165)**

5. **164** → (β)-Daurichromenic acid (166)

**β-Daurichromenic acid (166)**
A series of prenylated coumarins of derivatives iso-eriobrucinol A (175) and iso-eriobrucinol B (176) were extracted from the Australian shrub *Eriosternon brucei* [204]. 5,7-Dihydroxycoumarin (173) was synthesized using ZnCl₂-improved oxo-[3 + 3] annulation reaction between phologlucinol (171) and ethyl propiolate (172). This method resulted in a simple total synthesis of eriobrucinol [205, 206]. Noticeably, the Knoevenagel reaction and annulation reaction between 173 and citral (168) gave a complex mixture of double annulated products. In the following, the desired tricycle 174, upon two steps, was transformed into a mixture of iso-eriobrucinol A (175) and B (176) in 26% combined yield (Scheme 32) [202].

Verrubenzospirolactone (179) [207] is a meroterpenoid that was extracted from the soft coral *Sinularia verruca* together with its suggested biosynthetic precursor, the natural product capillobenzopyranol [208]. The total synthesis of (−)-verrubenzospirolactone was started from the reaction of methylhydroquinone 177 and citral (168) (85:15 mixture of geranial and neral) using phenylboronic acid to provide the 2H-chromene 178 in 14% yield via a Knoevenagel condensation reaction and oxo-6π-electrocyclization reaction. Upon six steps, compound 178 was transformed into the target natural product verrubenzospirolactone (179) in 41% overall yields (Scheme 33) [209].

Naturally occurring compounds inducing or stimulating neuron variation and neurite outgrowth were found as favorable small molecule alternatives to the nerve growth factor (NGF) that known a main protein mediating neuritogenesis in humans [210, 211]. A stimulating group of compounds demonstrating potent property as small molecule neurotrophins is demonstrated by the seco-prezi-zaane-sesquiterpenes, particularly those of the majucin-type. It should be mentioned that various such compounds
were exhibited to be neurotrophically potent [212, 213], for example, jiadifenin. Synthetic investigations toward extremely oxygenated seco-prezizaane sesquiterpenes were demonstrated that culminated in a formal total synthesis of the neurotrophic agent (−)-jiadifenolide. Total synthesis of (−)-jiadifenolide (184) was started from methylester 180, that after two steps gave aldehyde 181 [214, 215]. Next, for the joining of the A- and C-ring, Gomes et al. investigated a Knoevenagel condensation reaction of 181 and 182 to make the AC-ring fragment 183. Finally, compound 183 was transformed into the target natural product (−)-jiadifenolide (184) after six steps (Scheme 34) [216].

The carbazole alkaloids obtained much interest because of their potential biological properties [217, 218]. Various 2-oxygenated bioactive carbazoles, for example, murrayacine, girinimbine, and 2-hydroxy-3-methylcarbazole were extracted from plants of the genus Murraya and Clausena and from the family Rutaceae. Total synthesis of murrayacine (191) was started from market purchasable 2-methyl-5-nitroaniline (185) that was transformed into 9-benzyl-3-methyl-2-hydroxycarbazole (187) upon six steps [219]. Dai et al. demonstrated lewis acid-catalyzed reaction of 9-benzyl-3-methyl-2-hydroxycarbazole and α,β-unsaturated aldehyde 188 via a Knoevenagel condensation reaction, followed by 6π-electrocyclization. This method may be the most appropriate approach to make the six-membered oxacycle in murrayacine and girinimbine. The optimal reaction condition, for the construction of the six-membered oxacycle, gives compound 189 in 90% extracted yield involved the usage of phenylboronic acid (PhB(OH)₂) under refluxing in HOAc/toluene solution. The yield was poor without of HOAc (72% yield). Debenzylation with excess potassium t-butoxide/DMSO under an O₂ atmosphere gave girinimbine (190) in 94% yields. In addition, murrayacine (191) was provided from girinimbine by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant in high yield (Scheme 35) [220].

Plants of the myrtaceae group are rich in structurally varied and biologically important acylphloroglucinols and their meroterpenoids, and thus have motivated significant phytochemical efforts aimed at examining novel antibiotics related to their outstanding antibacterial properties described in recent years [221]. Rhodomyrtus tomentosa, an evergreen plant native to southern and southeastern Asia, is predominantly broadly spread in southern China [222]. The extract from this plant contains potent inhibitory properties against Gram-positive bacteria. The chemical components of R. tomentensa were demonstrated to contain triterpenes,
flavones, hydrolysable tannins, steroids, and acylphloroglu-
cinols [223]. In an investigation to explore for novel natu-
ral antibacterial products obtained from medicinal plants, a
widespread bioactivity guided fractionation led to the extrac-
tion of a strong antibacterial acylphloroglucinol meroter-
penoid containing a distinctive scaffold, which included a
free syncarpic acid having a terpenoid core, named tomen-
tosenol A (199), accompanied by a pair of meroterpenoids
4S-focifolidione (197) and 4R-focifolidione (198). Tomen-
tosenol A (199) was the first sample of a novel meroterpe-
noid group having a typical scaffold, which included a free
syncarpic acid coupled with a terpenoid core, and exhib-
ted high antimicrobial and cytotoxic properties. Total syn-
thesis of tomentosenol A was started from phloroglucinol
192, which upon two steps transformed into syncarpic acid
(193). The syncarpic acid via a facile modified Knoevenagel
condensation reaction with isovaleraldehyde (194) afforded
compound 195. Then, the intermediate 195 was subjected
into the neat (−)-β-pinene (196) intimately in a nitrogenous
environment to give the corresponding natural product
tomentosenol A (199) in satisfactory yield (21% yield) and
focifolidione epimers 197 and also 198 with an overall yield
of 57% (Scheme 36) [224].

Tomentodiones A (201) and B (202), a pair of C-11′
epimer of caryophyllene-conjugated phloroglucinols having
an unprecedented scaffold, were extracted from the leaves of
Rhodomyrtus tomentosa [222]. The biogenetic routes of
201 and 202 were demonstrated to include an intermolecu-
lar, inverse electron demand Diels–Alder cycloaddition as
the main step. Liu et al. [225] have revealed the extraction and
identification of two meroterpenoids tomentosone A and
tomentosenol C containing important growth inhibi-
tory property toward a panel of human cancer cell lines
and microbials [224, 226]. Relied on the assumption and
examination of other new meroterpenoids in this species,
an additional widespread phytochemical study on the non-
polar portion of this extract led to the extraction of two new
meroterpenoid epimers, tomentodiones A and B. For the bio-
mimetic synthesis of 201 and 202, diene 195 was provided
from a facile Knoevenagel condensation reaction of syn-
carpic acid (193) and isovaleraldehyde (194). As anticipated,
the biomimetic Diels–Alder cycloaddition happened effi-
ciently by the reaction between 195 and (−)-β-caryophyllene
(200) under neat condition or under reflux in toluene to fur-
nish the total synthesis of tomentodiones A (201) and B
(202) in high yield (62% or 57% yield) (Scheme 37) [225].

Han and Joab in 2013 demonstrated [227] total synthesis
of berkeleyamide D (213) that appeared from the structural
comparison of biosynthetically relevant naturally occur-
rning compounds and the biosynthetic hypothesis of struc-
turally relevant azaspirene (208) [228]. Berkeleyamide D
(213) was extracted from an aquatic microbe Penicillium
rubrum Stoll in berkeley pit by Stierle et al. in 2008 [229].
Berkeleyamide D shows MMP‐3 and caspase‐1 inhibi-
tion in poor micromolecular concentration. Notably, other
structurally related spirocyclic fungal secondary metabo-
lites exhibit remarkable biological properties [230, 231]. In
2002, Osada and co-workers discovered azaspirene (208), a
novel angiogenesis inhibitor isolated from the fungus Neo-
sartorya sp., which showed to inhibit endothelial migration
induced by vascular endothelial growth factor [232, 233].
In 2014, Tang et al. demonstrated a biosynthetic method
for the synthesis of azaspirene [228]. The total synthesis
was commenced from starting materials 203 and 204. They
examined the reduction of biosynthetically obtained thi-
ester 205 to afford linear aldehyde intermediate 206 that
via intramolecular Knoevenagel condensation reaction in
aqueous NaOH solution afforded unsaturated γ-lactam 207.

Scheme 35

| 186: R = H | 187: R = Bn |
|------------|------------|
| DDQ        | Girinimbine (190), R = CH₃ |
|            | Murrayacine (191), R = CHO |

DDQ

Girinimbine (190), R = CH₃
Murrayacine (191), R = CHO

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In the following, compound 207 upon epoxidation and cyclization reaction transformed into (±)-azaspirene (208) in 33% yields over four steps. In addition, for the synthesis of berkeleyamide D (213), linear aldehyde 211 was provided from a coupling reaction of ester derivative 210 and l-leucinol (209). Remarkably, the γ-lactam scaffold of 212 was constructed through a Knoevenagel type cyclization reaction of aldehyde 211. The spirocyclic unit of berkeleyamide D (213)
was performed through sequential epoxidation reaction and a late-stage base-catalyzed cyclization reaction of biosynthetically relevant precursor (Scheme 38) [227].

Illudalane sesquiterpenes are a group of secondary metabolites of both ferns of the Pteridaceae family and fungi of the Basidiomycotina subdivision [234]. They are identified by the existence of a benzo-fused substituted cyclopentane derivative. These sesquiterpenes exhibit cytotoxic [235, 236] and antispasmodic properties along with DNA binding properties [237]. Pettit et al. extracted coprinol (216) accompanied by two novel sesquiterpenes [238]. Coprinol includes an indane core with a highly functionalized aromatic ring.

For the first time, Suresh et al. [239] demonstrated the synthesis of coprinol, an illustrative of this group of illudalane sesquiterpenes. Total synthesis of coprinol was started with the transformation of 2-methoxy-3,5-dimethylbenzaldehyde (214) to cinnamic acid 138 via the Knoevenagel condensation reaction. Next, upon seven steps, compound 215 was transformed into natural product coprinol (216) with 41% overall yield (Scheme 39) [239].

The furanocembrane group of naturally occurring compounds contains structurally varied diterpenoids, which were extracted from various octocoral species [240, 241]. The first furanocembranoid completely identified was...
The furanocembranoids 7-epi-pukalide (225) and 7-acetylsinusimaximol B (226) were accomplished via a one-pot Knoevenagel condensation reaction and thioether-catalyzed furan-construction reaction. The generation of furan ring was performed through a sulfur ylide and leads to a fast introduction of structural complexity during the coupling reaction of two highly substituted parts. The target products were synthesized in 16 steps from (R)-perillyl alcohol (217). The original synthetic strategy had been planned with the expectation that the fragments would be coupled via a Knoevenagel condensation and the resultant ynenone would be exposed to macrocyclisation prior to the furan constriction. Although, the ynenone was unstable and so it was required to accomplish furan constriction prior to macrocyclisation. It transpired that Knoevenagel condensation and furan constriction could be produced in a facile one-pot method. In this approach, propargylic aldehydes 220 and 221 for the knoevenagel condensation reaction were synthesized from β-hydroxy amide 219 upon seven steps. Next, the Knoevenagel condensation reaction of the β-ketoester 218 with the aldehyde 220 using piperidine, H2OAc, and tetrahydrothiophene (THT), provided the epoxyfuran 222 (1:1 mixture of diastereoisomers) in 30% yield and the acetate 223 (≈ 3:2 mixture of diastereoisomers) in 32% yield. It should be mentioned that the selectivity of the reaction could be tuned by varying the quantity and type of carboxylic acid additive or by masking the tertiary alcohol. Once one equivalent of HOAc was applied in the one-pot Knoevenagel condensation reaction and cyclisation, the acetate 223 was provided in 50% yield and also the yield of the epoxide 222 was reduced to 16%. Noticeably, the epoxide 222 was provided totally in 62% yield from the reaction improved by pivalic acid, and the acetate 224 was provided in 85% yield (3:2 mixture of diastereomers) when the bis-protected aldehyde 221 was used as a substrate and the reaction was performed in the presence of 1.2 equivalents of acetic acid. In the following, product 222 was exposed to give the desired natural product 7-epi-pukalide (225) upon three steps in 46% yield. The acetate product 224 was subjected into the same three steps sequence deprotection, lactonisation, and RCM as the epoxide 222 to give the target natural product 7-acetylsinusimaximol B (226) (Scheme 40) [246].

The meroterpenoids that involve a tetramethylcyclohexenedioine or acylphloroglucinol scaffold obtained considerable interest from the synthetic community because of their stereochemical complexities and unusual structural diversities [247, 248]. Myrtucommulone K, a unique meroterpenoid that comprised a β-triketone scaffold and a unique sesquiterpene core was extracted from Myrtus communis L. by Cotiglia et al. in 2012 [249]. The first stereoselective total synthesis of myrtucommulone K (231) and its structural analogs were performed via a significant biomimetic spontaneous approach that mimics a biosynthetic heteroatom Diels–Alder cycloaddition sequence. In addition, this method provided a feasible synthetic route for the effective total synthesis of other naturally occurring compounds comprising the analogous meroterpenoid scaffold, as well as provided a common method to the formation of myrtucommulone K analogs. Zhou et al. started their valuable developed [250] proline-catalyzed Knoevenagel condensation method via the reaction of syncarpic acid (227) and isobutyraldehyde (228) at ambient temperature in dichloromethane in an air atmosphere. The main biomimetic Diels–Alder cycloaddition of β-caryophyllene (230) and hetero-diene 229 was accomplished under reflux in toluene or neat condition, providing the desired natural product myrtucommulone K (231) (Scheme 41) [250].

Psammaplysene A (236) are bromotyrosine alkaloids that were extracted from Indian Ocean marine sponge psammaplysilla sp. [251, 252] and provided by joining two bromotyrosine derived subunits via amide bonds. Psammaplysene A, an inhibitor of FOXO1a mediated nuclear export, synthesized by a short and amended pathway from tyrosine-derived acid and amine fragments [253]. Total synthesis of psammaplysene A (236) was started from 4-hydroxybenzaldehyde (94) that upon three steps transformed into compound 232. Next, compound 232 through Knoevenagel condensation reaction with malonic acid (138) using Et3N and a catalytic quantity of piperidine into tolune under reflux condition afforded the acid framework 233. The amide framework 235 could be easily available from tyramine (234).

Then, the amidation reaction of 233 and 235 were accomplished with N,N'-diisopropylcarbodiimide in the presence of a catalytic quantity of 4-(dimethylamino)pyridine and triethylamine in dichloromethane, resulting in the construction of the natural product psammaplysene A (236). This method gives an effective admittance of psammaplysene analogues, which can be examined for potential biological or pharmacological properties (Scheme 42) [254].

Indanone scaffolds are abundant substructures in naturally occurring compounds and biologically potent compounds...
Among these, 3-arylindanones containing the C3 substitution are privileged structure components of various pharmaceutical agents as well as used as various substituted intermediates in the formation of biologically active. A highly asymmetric synthesis of enantiomerically pure 3-aryl functionalized indanone derivatives was established via the C2-functionalized chiral methyl p-tolyl sulfoxide scaffold that established Knoevenagel condensation reaction. Particular enantiomerically pure indanone is merged into the divergent total syntheses of three resveratrol natural products, (+)-quadrangularin A, isopaucifloral F, and (+)-pallidol. The efficacy, stereoselectivity and regioselectivity of this method could be related to that enantiomerically pure methyl p-tolyl sulfoxide auxiliary containing an electron-withdrawing sulfoxide substituent, that improves the Knoevenagel reaction achieved via straightforward condensation reaction of aldehyde and enantiomerically pure β-arylketosulfoxide. The synthetic usage of this method was credibly demonstrated in the divergent total syntheses of three resveratrol-derived naturally occurring compounds, including (+)-quadrangularin A, isopaucifloral F, and (+)-pallidol via a usual intermediate.
Applications of Knoevenagel condensation reaction in the total synthesis of natural products

Scheme 41

\[ \text{product} + \text{aldehyde} \rightarrow \text{product} \]

(proline, CH\(_2\)Cl\(_2\))

95% yield

heat, 24 h or toulene, reflux, 6 h

60% or 54% yield

227 228 229

Myrtucommulone K (231)

Scheme 42

Scheme 42

CHO

3 steps

94 232

COOH

piperidine, TEA

toluene, reflux

233

DIC, DMAP

TEA, CH\(_2\)Cl\(_2\)

r.t., 85%

234 235

Psammaplysene A (236)
with excellent efficacy. At first, $\beta$-ketosulfoxide 238 containing an enantiomerically pure sulfoxide was selected as a model substrate meanwhile because it could be easily provided through a two-step method from enantiomerically pure sulfoxide methyl $p$-tolyl sulfoxide (237) [260]. Next, the knoevenagel condensation reaction of compound 238 and 3,5-dimethoxybenzaldehyde (239) was accomplished using catalytic piperidine and HOAc to make the corresponding enone 240 ($E/Z = 1:0.7$) in moderate overall yield. Then, 3-aryldanone 241 was provided upon two steps with satisfactory ee (86%). In the following, compound 241 was transformed into the natural product (+)-quadrangularin A (242) upon five steps in overall 22% yield. The natural product (+)-isopaucifloral F (243) was synthesized from intermediate 241 upon six steps. To furnish the construction of the hexacyclic natural product (+)-pallidol (244), the seven steps was used to attain (+)-pallidol (Scheme 43) [261, 262].

The Daphniphyllum alkaloids a structurally complex group of polycyclic naturally occurring compounds were extracted from deciduous shrubs and trees in southeast Asia and Japan. In comparison with the great number of isolates in this group, very few of these alkaloids were explored for biological properties. These compounds exhibit neurotrophic, antitumor and antibacterial properties [263, 264]. In 2018, Lopez et al. [265] demonstrated the establishment
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of Sn-free method for the efficient cyclization reaction of a number of internal alkyne-comprising N-chloroamine precursors to the ABC unit through cyclization reaction of a neutral aminyl radical. Deuterium labeling tests demonstrated that the solvent is the primary source of the final H atom in the cyclization cascade. These conditions provided an efficient pathway to a β-ketoester intermediate poised for intramolecular Knoevenagel condensation reaction to form the seven-membered D-ring of calyciphylline A alkaloids. It should be mentioned that the exposure to caesium fluoride in tert-butyl alcohol at high temperatures resulted in an unexpected decarboxylation to make a D-ring-contracted tetracyclic unit. Total synthesis of daphniyunnine C (248) was commenced from lactol 245, which upon eight steps transformed into β-ketoester 246. Then, compound 247 was provided using the assembly of the seven-membered ring from a ketone or β-ketoester 246 using aldol or Knoevenagel condensation reaction [266] of the desired enolates. Next, compound 247, upon several steps transformed into natural product daphniyunnine C (248) in 55% overall yield. An analogous method was further developed to make calyciphylline A (249) starting from lactol 245. Finally, intermediate 246 was transformed into calyciphylline A upon two steps and satisfactory yields (Scheme 44) [265].

Three-dimensionally complex extremely cage-like compounds exhibit several astonishing naturally occurring compounds which make both vast benefits and novel challenges to mankind. The polycyclic diterpenes and their alkaloidal congeners, both demonstrating difficult chemical structures and probable medicinal usages, fall into such a group [267–269]. From a biogenetic aspect, the construction of structurally different diterpenes relies on cyclization and oxidation step that was started from geranyl diphosphate [270] and also the introduction of nitrogen atoms into the well-developed diterpene scaffolds gives the diterpenoid alkaloids. Whereas the genera of Aconitum and Delphinium afforded rich sources for different kinds of these pseudo-alkaloids [271], merely a few of their parent diterpene compounds were extracted from nature. In 2016, Gong et al. demonstrated a short method to the formation of the unit structure of these compounds and the first total synthesis of (±)-atropurpuran [272]. Critical aspects of the synthesis contain an oxidative dearomatization/intramolecular Diels–Alder cycloaddition cascade reaction, sequential aldol reaction and ketyl-olefin cyclization reaction to make the highly caged scaffold, and a stereoselective and chemoselective reduction to provide the desired allylic hydroxyl substituent in the target natural product. Total synthesis of (±)-atropurpuran (254) was started from aldehyde 262, which upon six steps transformed into aldehyde 251. Then, a reductive Knoevenagel condensation reaction of 1,3-cyclohexanedione (252) and aldehyde 251 occurred efficiently using L-proline as the catalyst and Hantzsch ester as the hydrogen source. Assumed the restricted stability of the resultant product, this intermediate was protected instantly as an enol silane in one-pot reaction to give thioester intermediate. Then, the transformation of thioester into aldehyde 253 was easily performed relied on Fukuyama’s method. In the following, intermediate 253, upon ten steps were transformed into natural product (±)-atropurpuran (254) in 75% overall yield (Scheme 45) [272].

EBC-329 (259), the first diterpene to create the seco-casbane group of naturally occurring compounds, was extracted from a component of Croton insularis from the northern rainforest of Australia by Williams et al. in 2014 [273]. Croton is a prominent plant genus that contains
various groups of biologically active molecules including phorbols [274], ent-kaurenes, clerodanes [275], and halimanes [276]. EBC-329 has known to exhibit high biological properties. The first total synthesis of anti-leukemic diterpene natural product EBC-329 was performed using 6,6-dimethyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (255) that was converted into compound 256, upon eight steps. Next, piperidine-catalyzed Knoevenagel condensation reaction between aldehyde 256 and butyrolactone 257 to afford the corresponding butenolide 258 with E:Z mixture of 1:9. The major Z-isomer in compound 258 was isolated using column chromatography in 77% yield. Most of these natural butenolides exist in thermodynamically more stable Z isomer. In the following, compound 258 upon four steps was transformed into natural product EBC-329 (259) in 94% yield (Scheme 46) [277].

Morrison et al. were motivated by the illudalane group of 3,3-dimethylcyclopentane-fused aromatic sesquiterpene derivatives that show a striking range of structural complexities and also ambiguous biological properties. The illudalane sesquiterpenes contain a carbon scaffold having illudalic acid and its alkaloid congener, illudinine. Noticeably, illudinine is a metabolite of the jack o-lantern mushroom (Clitocybe illudens) that it was extracted and identified together with illudalic acid and illudacetalic acid in 1969 [278]. For the first time, total synthesis of these three naturally occurring compounds was reported and achieved in 17–19 steps by Woodward and Hoye in 1977 [279], who established a unified method relied on aromatic substitution chemistry. Remarkably, total synthesis of the illudalane sesquiterpene illudinine was accomplished in eight steps and 14% overall yield from dimedone. The current method demonstrates
tandem fragmentation/Knoevenagel-type condensation reaction and microwave-assisted oxidative cycloisomerization reaction to make the isoquinoline unit. Total synthesis of illudidine (264) was started from dimedone (260), that upon three steps was transformed into compound 261. Next, the Knoevenagel condensation reaction of 261 and 262 afforded 1,6-enyne 263 in 75% yield as a mixture of alkene isomers (ca. 2:1). In the following, compound 263 afforded the natural product illudidine (264) upon five steps in 14% overall yield. Considering the anion-stabilizing properties of the 4-pyridyl group, this method is possibly best categorized as a tandem fragmentation/Knoevenagel-type condensation reaction, and it proposes a broader potential of this prior approach (Scheme 47) [280].

Suffrutine A extracted from the roots of Flueggea suffruticosa, exhibited to promote neuro-2a cell differentiation [281]. A short pathway to 2-functionalized 3-cyanopyrroles was established that can possibly be extended to the formation of N-functionalized pyrrole derivatives. This approach uses 4,4-dimethoxybutyronitrile as a C4-framework and leaves subsequently the 4- and the 5-position of the pyrrole unfunctionalized and it is therefore, visualized to, act as an appropriate access to 2,3-difunctionalized pyrroles.

Total synthesis of Suffrutine A was begun from 4,4-dimethoxybutyronitrile (265), that after four steps, converted into aldehyde 266. Afterwards, aldehyde 266 was taken as an E/Z-mixture into the Knoevenagel condensation reaction with 2-coumaranone (267). Finally, product 268 was provided as a mixture of four diastereoisomers in a ratio of 41/32/15/12. The major components could be isolated in the dark and suffrutine A could be provided efficiently as the particular isomer (E,E)-268. It should be mentioned that all analytical data of this compound were equal to the previously stated data of the natural product [281]. The second extracted major component shows a different configuration at the double bond between the benzofuran-2(3H)-one carbon atom C3 and carbon atom C1 of the butenylidene bridge and also it could be found as (Z,E)-268, suffrutine B. The minor constituents could not be isolated, however, there is evidence for them to be isomers of suffrutines A and B and they are tentatively allocated the structure (E,Z)-268 and (Z,Z)-268 (Scheme 48) [282].

Polysubstituted cyclic ethers are the structural keystones of an extensive series of biologically potent naturally occurring compounds, such as polyether antibiotics [283], ladder marine toxins [284], annonaceous acetogenins, and...
lauroxanes [285]. Red and brown algae are very significant sources of marine naturally occurring compounds, which shows various biological activities such as antimicrobial, antitumor, antifeedant, pesticidal, and immunosuppres-
sant properties. Red algae of the genus *Laurencia* creates
various distinctive compounds involving a wide range of nonterpenoidal C15-metabolites, commonly named lau-
roxanes, obtained from metabolism of C16 fatty acids
(acetogenins). For instance, linear compounds, such as the enantiomers (3E,9Z,12E)-pentadeca-3,9,12-trien-1-yn-6,7-
diol (*trans*-laurediol, (*E*)-274) and (3Z,9Z,12E)-pentadeca-
3,9,12-trien-1-yn-6,7-diol (*cis*-laurediol, (Z)) [286], and
cyclic products including *trans*-(−)-kumausyne (273) and
*trans*-(+)-deacetylkumausyne (276) were extracted from
*Laurencia nipponica* [287]. All *Lauroxanes* include poly-
functionalized cyclic ether scaffolds having a defined group
stereochemistry and a ring size from five to nine atoms.
In addition, (2S,3S,5R)-5-[(1R)-1-hydroxydec-9-en-1-yl]-2-
pentyltetrahydrofuran-3-ol (280) and (2S,3S,5S)-5-[(1S)-
1-hydroxydec-9-en-1-yl]-2-pentyltetrahydrofuran-3-ol (281)
are C19-diols extracted from *Notheia anomala*, a member
of the *Notheiaceae* group. Total synthesis of *trans*-(*+*)-
laurorediol was commenced from butane-1,4-diol (269). The
required β,γ-unsaturated ester 271 was constructed from the desired aldehyde 270 using a modified Knoevenagel condensa-
tion reaction with malonic acid (138) under nonpolar condi-
tions in the presence of piperidine as an efficient catalyst.
Then, Sharpless enantioselective dihydroxylation reaction
with the suitable AD-mix afforded the chiral β-hydroxy-γ-
lactone 272. It was commenced with the masked lactone 272
that was exposed to transform the natural product *trans*-(+)-
laurorediol (274), upon two steps. The presence of instances
comparative to the total synthesis of *trans*-(−)-kumausyne from
β-hydroxy-γ-lactone 272 improved to provide a concise for-
mal synthesis of a lauroxane. In the following, β-hydroxy-
γ-lactone 272 was transformed into natural product *trans*-
(−)-kumausyne (273) upon six steps. Therefore, once *trans*-(+)-laurediol was subjected to a bromocyclization with 2,4,4,6-tetramethylhexa-2,5-dien-1-one, *trans*-(+)-deacetylkumausyne (276) was provided, but with low stereoselectivity (Scheme 49) [288].

An analogues method was developed for the formation of C19-dihydroxy tetrahydrofurans 280 and 281 using *n*-heptan.
Next, β,γ-unsaturated ester 278 was provided from the aldehyde 277 using a modified Knoevenagel condensation reaction with malonic acid using piperidine as a catalyst in MeOH. Then, sharpless enantioselective dihydroxylation reaction using the suitable AD-mix afforded the chiral β-hydroxy-γ-lactone 279. In the following, compound 279 was transformed into the target natural products (2S,3S,5R)-5-[(1R)-1-hydroxydec-9-en-1-yl]-2-pentyltetrahydrofuran-3-ol (280) and (2S,3S,5S)-5-[(1S)-1-hydroxydec-9-en-1-yl]-2-pentyltetrahydrofuran-3-ol (281), upon five steps in high *ees* (Scheme 50) [288].

A unique indano[2,1- *c*]chroman, (+)-pestalachloride C,
was extracted from an endophytic plant fungus *Pestalotiopsis*

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**Scheme 49**

![Scheme 49](image-url)
Applications of Knoevenagel condensation reaction in the total synthesis of natural products

In 2013, (±)-pestalachloride C (286), along with its epimer (±)-pestalachloride D (287) were extracted in a 3.6:1 ratio, from cultures of the marine fungus Pestalotiopsis sp., obtained from the soft coral Sarcophyton sp. [290]. It should be mentioned that the syn isomer, pestalachloride D, demonstrated no teratogenicity up to the assay limit of 50 μg/cm³, while the anti-isomer, pestalachloride C, demonstrated teratogenic influences in zebrafish embryos at multiple steps [291]. Oxygenated benzaldehyde 283 was synthesized from aldehyde 282. Then, aldehyde 283 and resorcinol 284 under base-mediated conditions (triethylamine) provided a complex mixture comprising less than 6% of indano[2,1-c]chromans 285. Using ethylenediamine-diacetic acid that improves iminium ion construction, the reaction is much more effective. The Knoevenagel/hetero Diels–Alder cascade reactions afforded the indano[2,1-c]chromans 285 in 85–90% yields and in 90% purity. The anti and syn isomers were generated in a 1.4-1.6:1 ratio, relied on the equivalents of 4,6-dichloroorcinol (284) and reaction time. In the following, compound 285 upon two steps was transformed into a mixture of (±)-pestalachloride C (286) and (±)-pestalachloride D (287) in a 1:6:1 ratio in 83–90% yield. Remarkably, the isomers were easily separated using reversed-phase HPLC (Scheme 51) [292].

The diterpenoid alkaloids, known in different plants of the genera Aconitum, Spiraea, and Delphinium exhibit a great family of naturally occurring compounds, which show potent biological properties [271]. It should be mentioned that structurally, these the C₁₈-, C₁₉-, and C₂₀-diterpenoid alkaloids [293] contain 18, 19, and 20 carbon atoms in their frameworks, respectively. Among these, the C₂₀-subfamily includes the most varied framework types that have obtained much interest from synthetic organic chemists. Noticeably, the arcutine-type C₂₀-diterpenoid alkaloids, architecturally identified by a congested hexacyclic scaffold, possess an azabicyclo[4.3.0]nonane core (AE rings), a tetracyclo[5.3.3.0⁴,9,0⁴,12]tridecane ring moiety and also three all carbon quaternary stereogenic centers in C4, C5, and C8 [293]. The characteristic arcutine-type molecules were extracted from Aconitum arcuatum by Saidkhodzhaeva et al.
whereas arcutinidine (291) was provided as a saponification product via chemical conversion from arcutinine (290) [294]. For the first time, total synthesis of an arcutine-type C20-diterpenoid alkaloid arcutinine was accomplished in 2019 by Nie et al. in both racemic forms [295]. Formation of the C4 quaternary center and the pyrrolidine E ring in an initial step demonstrated to be significant for accomplishing the effective construction of the desired alkaloid. Strategically, an enantioselective conjugate addition/aldol cascade reaction and a decarboxylative allylation reaction permitted the development of the vicinal all-carbon quaternary stereo-centers at C4 and C5. In addition, a sequence comprising of an intramolecular aza-Wacker cyclization reaction, an oxidative dearomatization/IMDA cascade, and also a ketyl-olefin cyclization reaction provided the assembly of the unit structure and resulted into the total synthesis of the target natal product arcutinine. Total synthesis of arcutinine was started from the reaction between 1,3-cyclohexanedione (35) and aldehyde 288. Remarkably, a reductive Knoevenagel condensation reaction of 1,3-cyclohexanedione and aldehyde 288 was accomplished using Hantzsch ester and l-proline in dichloromethane to provide intermediate 289. Next, the latter was transformed into the natural product (±)-arcutinine (290) upon 14 steps. In the following, arcutinidine (291) was synthesized after saponification of the synthetic arcutinine using NaOMe/MeOH in 70% yield (Scheme 52) [295].

The very huge family of monoterpene indole alkaloids are biosynthetically obtained from an enzyme-mediated Pictet–Spengler reaction of glycosylated monoterpene, a secologanin and tryptamine to provide strictosidine [296, 297]. Hence, different biosynthetic routes result in numerous sub-families having frameworks of great structural diversity. Among these, cymoside (298) has obtained much interest because of its distinctive structure; however, no biological property has been demonstrated [298]. Cymoside was extracted by Grougnet and co-workers from crushed leaves gathered from the tree Chimarrhis cymosa (Rubiaceae) in the French Caribbean island Martinique. This natural product shows an exceptional caged hexacyclic fused framework that still contains the glucose scaffold and also a rare furo[3,2-b]indoline scaffold. Total synthesis of cymoside was started from the reaction between aldehyde 292 and malondialdehyde 293. Methanolation, sulfoxide removal and release of the aldehyde from the dithiane provided seco- loganin aglycon 295. This group provided the furano[3,2-b]-indoline-containing hexacyclic fused-scaffold through an oxidative cyclization reaction of a strictosidine derivative 297 [299, 300]. It included a domino sequence of Knoevenagel condensation reaction of aldehyde 292 and masked malondialdehyde 293 generated enal 294. Unexcitingly, the Pictet–Spengler reaction between the Tietze secologanin aglycon 295 and tryptamine (296) and protection of the secondary amine with a para-nosy substitution afforded masked strictosidine aglycon ethyl ether 297a in a 1:4:1 mixture with its epimer 297b. In the following, strictosidine aglycon ethyl ether 297 was transformed into the natural product cymoside (298) in 47% after four steps (Scheme 53) [301].

Polycyclic polymethylated phloroglucinols (PPPs) comprising a tetramethylcyclohexeneidine scaffold have obtained significant attention because of architectural complexity, their structural diversity, and various biological properties [302, 303]. Among these, watsonianones A (299) and B (303) contain the first naturally occurring bistetramethylcyclohexatriene scaffold and a fascinating fused bisfuran β-triketone skeleton, respectively. Corymbone B (302) has been demonstrated to be a unique acyclic acylphloroglucinol [304]. These natural products demonstrated very important antiplasmodial properties against chloroquine-resistant (Dd2) and chloroquine-sensitive strains (3D7) of Plasmodium falciparum those are responsible for serious
malarial infections [305]. The total synthesis of watsonianone A (299) was started from market purchasable phloroacetophenone (192) that was transformed into the precursor syncarpic acid (193) after two steps. Then, Knoevenagel condensation reaction 193 and excess isovaleraldehyde (194) using proline was achieved to directly construct the isopentyl chain to give precursor 195 in 95% yield. Next, compound 195 was converted into the natural product watsonianone A (299) via a proline-catalyzed Michael addition reaction. In the following, the total syntheses of corymbone B (302) and watsonianone B (304) were accomplished and reported. For the synthesis of corymbone B, the necessary acylphloroglucinol 301 was provided from market purchasable aldehyde 300 in two steps. Once precursor 195 was exposed to a NaH/THF solution of dihydrochalcone 301, the Michael addition reaction gave corymbone B (302). In addition, the total synthesis of watsonianone B (304) was achieved using the construction of racemic peroxide intermediate 303, in which the photo ambient light conditions in an air atmosphere resulted in peroxide 303 in 13% yield. Finally, intermediate 303 was transformed into watsonianone B (304) upon four steps in 27% yield (Scheme 54) [306].

Monoterpenoid indole alkaloids were extracted from higher plants, comprising Rubiaceae, Loganiaceae, and Apocynaceae species [307]. The biosyntheses of monoterpenoid indole alkaloids were achieved via Pictet–Spengler cyclization reaction with either tryptamine or tryptophan, and (−)-secologanin as a usual intermediate [308]. Remarkably, naturally occurring main intermediate (−)-secologanin was extracted from Lonicera morrowii, Strychnos nuxvomica, and also Lathraea clandestina. However, two racemic total syntheses of secologanin aglycon have been reported, but there are no documents on the total synthesis of (−)-secologanin itself [309]. It should be mentioned that (−)-5-carboxystrictosidine (308) is the first metabolite provided from tryptophan and secologanin in nature, and the compound 308 was extracted from Rhazya orientalis, Uncaria tomentosa, Ophiopogon nutans, and Guettarda platypoda. (−)-Rubrene (309) was extracted in 1973 from Adina rubescens as a distinctive glycosylated monoterpenoid indole alkaloid [310]. Successfully, thioester derivative 307 was synthesized in 81% yield as an E1Z mixture by Knoevenagel condensation reaction of market purchasable 3-trimethylsilylpropanal (305) and methyl 3-ethylthio-3-oxopropanoate (306) using
trifluoroacetic acid (TFA). Then, the formation of (−)-5-carboxystrictosidine (308) and (−)-rubenine (309), that belong to the family of glycosylated monoterpenoid indole alkaloids, were accomplished from 307 through bioinspired conversations involving diastereoselective Pictet-Spengler reaction, site- and stereoselective epoxidation, and also site-selective epoxide opening reaction. The total yield of natural product (−)-5-carboxystrictosidine (308) from 305 was 11% over nine steps. In addition, the natural product (−)-rubenine (309) was synthesized from 305 in 4% over 14 steps (Scheme 55) [311].

Protein tyrosine phosphatase 1B (PTP1B) has been considered as an inspiring target for the treatment of various ailments, including cancer, diabetes, and also neurodegenerative diseases [312]. Granatumine A (318), a bislactone limonoid alkaloid extracted from the Chinese mangrove (Xylocarpus granatum), exhibited satisfactory inhibitory property against PTP1B, whereas the related limonoid alkaloid xylogranatopyridine F was inactive [313]. For the first time, Schuppe and co-workers demonstrated the total synthesis of (+)-granatumine A (318), a limonoid alkaloid having PTP1B inhibitory property, in ten steps [314]. Based on this approach, two main methodological improvements were provided including a cost-effective approach for ketone \( \alpha,\beta \)-dehydrogenation in the presence of allyl-Pd catalysis, and a palladium-mediated method to transform epoxyketones to 1,3-diketones. Significantly, the central tetra functionalized pyridine is provided via a convergent Knoevenagel condensation reaction and carbonyl-selective electrocyclization cascade that was followed by a direct conversation of a 2H-pyran to a pyridine. These investigations resulted in the structural revision of two members of this family. In this method, aldehyde 311 was synthesized from ketone 310 over five steps. For the synthetic pathway to the 1,3-diketone 313, this group recognized (+)-\( \alpha \)-ionone (312), an extremely accessible terpene framework, as a starting precursor goal. The 1,3-diketone 313 was provided from (±)-\( \alpha \)-ionone upon six steps. Through a scalable pathway to 313 and 311, the convergent fragment coupling reaction via a Knoevenagel condensation reaction was explored. In this route, the reaction of 313 and aldehyde 311 using ethylenediammonium diacetate (EDDA) afforded enedione intermediate 315 that based on thermal condition reaction in situ underwent an oxa-6π electrocyclization afforded 2H-pyran as the only product. In the following, intermediate 315 was transformed into the natural products, granatumine A (318, after four steps), (+)-xylogranatnin F (317, after three steps), and also (+)-xylogranatnin G (316, after five steps) via different routes (Scheme 56) [315].

Naturally occurring xanthones are abundant in bacteria and fungi as secondary metabolites [316]. Rugulotrosin A (323), a subgroup of dimeretetrahydroxanthones, was identified from cultures of a Penicillium sp. extracted from soil samples by Capon and co-workers in 2004 [317].
Rugulotrosin A showed important antibacterial properties against *Enterococcus faecalis, Bacillus cereus,* and also *Bacillus subtilis* [318]. A methyl ester substitution situated on the bridgehead (C-10a) results into an unstable scaffold, which tends to undergo isomerization through retro-oxa-Michael and recyclization methods. A new method was established to form the tetrahydroxanthone via a Knoevenagel condensation/6π-electronic cyclization/aromatization cascade beginning from easily accessible cyclohexane-1,3-diones and unsaturated aldehydes. This approach gave an innovative solution for the formation of monomeric tetrahydroxanthones having various functional substituents at C-12. As a synthetic usage, the enantioselective formal synthesis of rugulotrosin A was accomplished by Chen et al. in 2020 [319]. Noticeably, the cascade Knoevenagel condensation reaction followed by 6π-electronic cyclization is an effective strategy to assemble cyclic compounds having the pyran framework, which has been extremely used in total synthesis. To examine the feasibility of this approach for the formation of tricyclic xanthones, this group performed model investigations using substrates 320 and 321. Initially, chiral enone 319 was provided on a large scale from d-(−)-quinic acid (145). Using the known compound 319, this group established a two-step synthesis to provide 320 including masking of the carbonyl substituent as the cyclic acetal and formylation. Based on conditions established by Hirama and co-workers in the formation of cortistatin, reaction of 320 with 321 using piperidine in ethyl acetate provided the corresponding pyran 322 as a mixture of two diastereomers at C-3 (d.r.=1.1:1) in almost quantitative yield. This result demonstrated that the Knoevenagel condensation reaction of 320 and 321 generated the condensed intermediate 322. Finally, compound 322 was transformed into the natural product rugulotrosin A (323) after eight steps (Scheme 57) [319].
The 6-oxabicyclo[3.2.1]octane scaffold was first known in the natural products guignardones A, extracted by Yuan et al. in 2010 from the cultures of *Guignardia mangiferae* IFB-GLP-4, that are associated with the normal *Ilex cornuta* leaves [320]. In addition, other members of this family of naturally occurring compounds were extracted [321] and found to contain the 6-oxabicyclo[3.2.1]octane unit in common, that includes an oxygen on the bridged carbon center. Some of these tetracyclic meroterpenes demonstrated fascinating biological activities for example, TLR3-regulating activities and antibacterial cytotoxicity against MCF-7 cell lines [322]. Architecturally, guignardones A (328) and B (327) feature tricyclogenanes (TCAs) having an additional bridging tetrahydrofuran ring D, that contains a highly oxidized 6-oxabicyclo[3.2.1]octane having a 1,3-diketone and a bridgehead hydroxyl substituent. In this method, 6-oxabicyclo[3.2.1]octane 325 could be obtained from the market purchasable accessible chiral pool d-quinic acid (145) over 13 steps. On the other hand, the known unsaturated aldehyde 324 was provided from (−)-limonene in five steps. Then, intermolecular Knoevenagel condensation reaction was achieved to combine the aldehyde 324 and 1,3-cyclohexanedione 325, that set the step for the main 6π-electrocyclization reaction. The resultant crude
tetracyclic compound 326 using Dean–Stark reaction conditions, in the presence of piperidinium acetate was refluxed in benzene, to eliminate the produced water. Then, the stereoselective and chemoselective directed hydrogenation of compound 326, directed using the tertiary alcohol of the left wing, was occurred using Crabtree’s catalyst [323] in dichloromethane at ambient temperature and effectively gave (−)-guignardone B (327) in 30% yield in two steps from 1,3-cyclohexanedi-o-ne 325. Finally, Burgess reagent-catalyzed [324] dehydration of (−)-guignardone B supplied (−)-guignardone A (328) in 73% yield (Scheme 58) [325].

The humulanolides were considered as sesquiterpenes having humulene as the basic scaffold. These naturally occurring compounds contain structure in which butyrolactone is fused with the humulene scaffold to provide an eleven-membered cyclic compound [326]. Tri- or tetracyclic humulanolides, that are products of further intramolecular cyclization reaction of the 11-membered ring, are stimulating synthetic targets. Wilfolides, tricyclic humulanolides comprising of a bicyclo[6.3.0]undecane framework fused with butyrolactone, were the first humulanolides extracted from the roots of *Cynanchum wilfordii* by Zhao and co-workers in 2015 [327]. For the first time, total synthesis of tricyclic humulanolide wilfolide B (331) was achieved and reported in 2019 by Abe et al. [328]. The synthetic method included radical cyclization reaction using SmI2 to generate the bicyclic lactone from an acyclic compound, and ring-closing metathesis to create the eight-membered ring via
linking two side chains, hence providing the tricyclic scaffold. Total synthesis of wilfolide B was started from 1,3-diol 329. Then, mono-protection of the 1,3-diol of 329 with a TBS ether afforded the mono-TBS ether in quantitative yield. Upon oxidizing the other hydroxyl substituent to an aldehyde via Parikh-Doering oxidation, Knoevenagel condensation reaction of the resultant aldehyde with dimethyl malonate using titanium tetrachloride and triethylamine was achieved to afford the unsaturated diester 330. Upon 16 steps, compound 330 was converted into the natural product wilfolide B (331) (Scheme 59) [328].

**Conclusion**

Knoevenagel condensation reaction is an old but significant reaction in the art of organic synthesis, being applied in the synthesis of different heterocyclic systems via MCRs and more importantly extensively used in the total synthesis of a wide verity of biologically active natural products as a key step. In this review, we tried to disclose the importance of Knoevenagel reaction as a vital step in the total synthesis of natural products. They were found being a leading source of drug discovery and drug development, useful for the treatment of broad range of diseases.

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