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Meldrum's acid and related compounds in the synthesis of natural products and analogs

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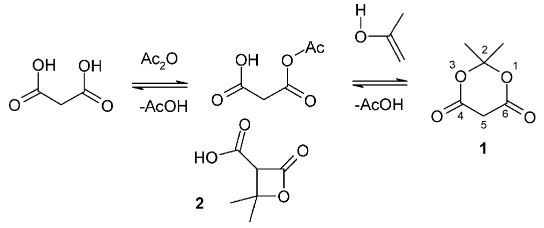
This *critical review* focuses on applications of Meldrum's acid and its derivatives to the synthesis of natural products and analogs. It covers all relevant literature from 1991 to August 2007 (181 references).

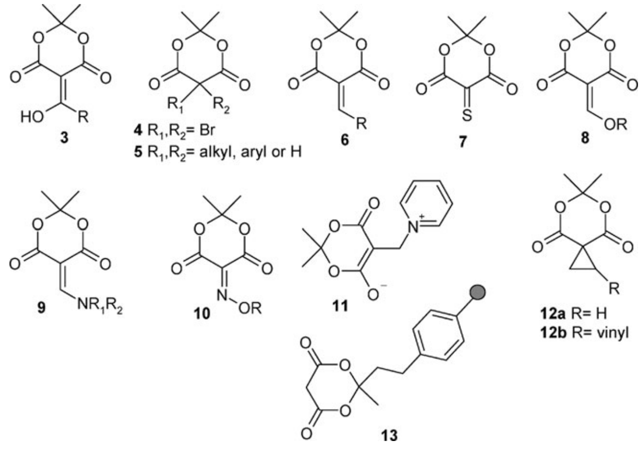
1. Introduction

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione; isopropylidene malonate) **1** is an organic compound, discovered in 1908 by A. N. Meldrum.[1] Meldrum misidentified the structure as β-lactone **2** with carboxylic acid group at position 3, and the correct cyclic acylal structure was only assigned 40 years later.[2] The chemistry of Meldrum's acid has been surveyed in comprehensive reviews[3,4] and a micro-review.[5] A single review is devoted to synthetic applications of the pyrolysis of Meldrum's acid derivatives.[6] Compound **1** can be classified as a cyclic acylal. Acylals are a group of organic compounds that share the functional group with the general structure $R_1R_2C(OOCR_3)_2$. Meldrum's acid is usually prepared by condensation of malonic acid with acetone in acetic anhydride in the presence of sulfuric acid (Scheme 1). Excellent yield of the product was achieved when acetic anhydride was added in a slow, controlled manner to a mixture of acetone, malonic acid and an acid catalyst.[7]

Acylal **1** is remarkably acidic (pK_a 7.3 in DMSO at 25 °C) as compared to the related dicarbonyl compounds: dimedone (pK_a 11.2 in DMSO at 25 °C) and an open-chain analog—dimethyl malonate (pK_a 15.9 in DMSO at 25 °C).[8] The high value for C–H acidity (comparable to acetic acid), rigid structure and low steric profile account for the unique chemical properties of **1**. Meldrum's acid derivatives have attracted considerable attention as valuable reagents and intermediates in organic synthesis (Scheme 2). Thus, acyl malonates of the general formula **3** are the most important class of Meldrum's acid derivatives, which are widely used for the preparation of various 1,3-dicarbonyl compounds.[9,10] The 5,5-dibromo malonate **4** is a mild agent for α-bromination of aldehydes and ketones.[11] Mono- and disubstituted alkyl and aryl derivatives of Meldrum's acid **5** are intermediates in the modified malonic ester synthesis, a classical reaction in organic chemistry. 5-Methylene Meldrum's acids **6** are substrates for selective conjugate addition of nucleophiles and for Diels–Alder reactions. The 5-thioxo malonate **7** is also a reactive dienophile.[12]



Scheme 1



Scheme 2

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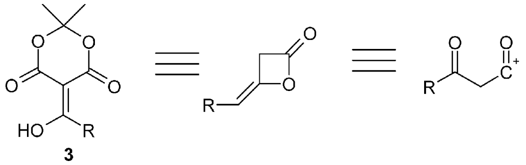
5-Alkoxymethylene **8** and 5-aminomethylene **9** malonates are versatile synthons for various heterocyclizations.[4] 5-Oximino derivatives **10** can be employed as synthetic equivalents of nitrosoketenes[13] and as reactive dienophiles.[14] Betaine **11** is a stable source of methylene Meldrum's acid.[15] Cyclopropanes **12a** and **12b**, which are enormously activated by the spiro-connection to the 1,3-dioxane-4,6-dione system, can react with a variety of nucleophilic agents under mild conditions.[16–18] Lastly, a resin bound cyclic malonic ester **13** has found application in the solid phase synthesis of various heterocyclic scaffolds.[19–21]

This brief survey of synthetic applications of the most important 2,2-dimethyl-1,3-dioxane-4,6-dione derivatives would not be complete without mentioning multicomponent and domino reactions that involve **1** and related compounds.[22–27] A domino reaction is usually defined as a process of two or more bond-forming reactions under identical conditions, in which the subsequent transformation takes place at the functionalities obtained in the former transformation. This principle allows efficient synthesis of complex molecules such as natural products from simple substrates. A multicomponent reaction (MCR) is a convergent process, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed structure. The concepts of domino and MCRs enable rapid synthesis of various heterocyclic compounds with diverse substitution patterns. The most commonly cited Meldrum's acid based MCR is the Yonemitsu reaction, involving Meldrum's acid, an aldehyde and an indole in a one-pot process, leading to indol-3-ylpropionic acid derivatives.[28–30] The latter have been efficiently used for the synthesis of ellipticine analogs.[31]

In the 1980s, the utility of Meldrum's acid in the synthesis of natural products was widely recognized. The unique reactivity of isopropylidene malonates **3**–**13** has been employed for the syntheses of many complex targets. This review offers a summary of the transformations of Meldrum's acid and its derivatives as applied to the synthesis of natural products and their analogs. The range of chemotypes available from this chemistry spans from simple lactones to complex terpenoids and alkaloids. The most impressive applications of cyclic acylals provide chemical transformations that emulate biosynthesis. These are the biologically patterned multicomponent domino reactions, leading to precursors of monoterpenoid indole and isoquinoline alkaloids, and cyclizations of Meldrum's acid derived polyketide analogs, building oxygen containing heterocyclic rings of natural products.

2. 1,3-Dicarbonyl compounds

1,3-Dicarbonyl compounds are among the most important intermediates in organic synthesis. Classical syntheses of β-keto esters *via* acetoacetic esters and *via* mixed malonic esters are practically useful, though not always satisfactory in yield and are incapable of modifying the ester group. Acyl derivatives of Meldrum's acid can be referred to as synthetic equivalents of mixed diketenes, which are usually not available (Scheme 3).[9]

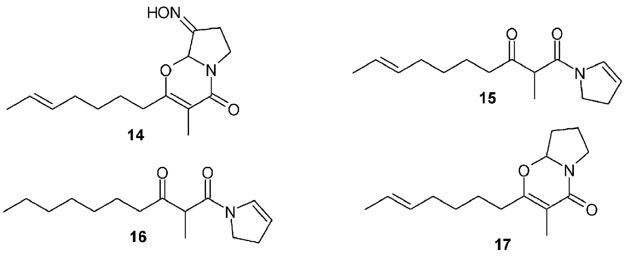


Scheme 3

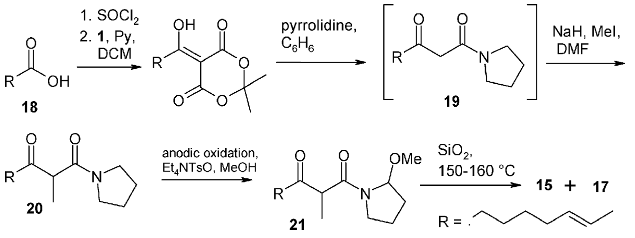
Acyl malonates **3** react with *O*-, *N*-, *S*- and *C*-nucleophiles to yield the corresponding 1,3-dicarbonyl compounds. One of the best practical methods for the preparation of β-keto esters consists of two simple steps: acylation of Meldrum's acid with an acyl halide, anhydride or carboxylic acid in the presence of a condensing agent and alcoholysis of the acyl Meldrum's acid by heating with (or refluxing in) the corresponding alcohol.[32] This protocol can be extended to preparations of β-keto amides, β-keto thioesters and similar compounds. The two steps can be efficiently combined in a one-pot process, which is advantageous for synthesis of β-keto carbonyl compounds on an industrial scale.[33] Kinetic study of the model transformation of an acyl Meldrum's acid to its β-keto amide performed using real-time IR monitoring of the reaction mixture and subsequent principal component analysis provided strong evidence that the reaction proceeds with the intermediacy of an acylketene species.[33] Because of the mild conditions necessary for the transformation, acyl malonates **3** are extensively used in multi-step syntheses of complex targets.

The β-keto amide system is incorporated in a number of biologically active fungal metabolites. *Penicillium* fungi are known to produce metabolites toxic to insects.[34] In particular, compounds **14**, **15**, **16** and **17**, isolated from *P. brevicompactum* (Scheme 4), demonstrated high levels of anti-juvenile-hormone and insecticidal activities.[35–38] The β-keto amide structural motifs in these natural products have been synthesized using acyl derivatives of Meldrum's acid.

Since compounds **15** and **17** originate from the same source and possess the same molecular skeleton, it was considered reasonable that compound **15** could be converted to **17** *via* intramolecular cyclization of the enolic form of the keto group. On this basis, the syntheses of both natural products have been merged into a single synthetic route (Scheme 5). Carboxylic acid **18** was converted to an acyl chloride, which was used to acylate Meldrum's acid. The acyl malonate obtained was subjected to aminolysis and the sodium salt of β-keto amide intermediate **19** was alkylated with iodomethane. Anodic oxidation of acyl pyrrolidine **20** in methanol afforded the 2-methoxy derivative **21**. Finally, elimination of methanol was achieved by the heating of compound **20** absorbed on silica gel to give a mixture of isomeric products **15** and **17**,



Scheme 4



Scheme 5

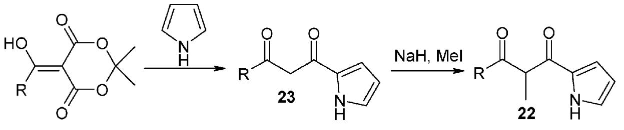
separable by column chromatography in 12% and 59% yields, respectively.[37] Compound **16** was synthesized in a similar manner.[38]

Reaction of pyrrole with acyl derivatives of Meldrum's acid produces pyrrole derivatives with a β-keto acyl group at position 2. This reaction was employed to prepare a series of structural analogs of *P. brevicompactum* metabolites **22**, with increased stability and an enhanced spectrum of fungicidal activities (Scheme 6). After acylation of the pyrrole ring at position 2 using acyl malonates, the activated methylene group of the side chain of **23** was mono-alkylated to yield **22**.[39]

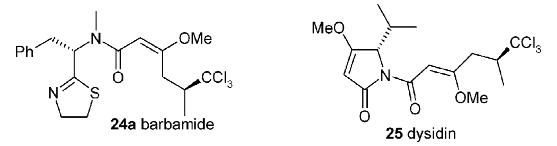
Acyl Meldrum's acids were utilized in the syntheses of marine secondary metabolites barbamide **24a** and dysidin **25** (Scheme 7). Barbamide was found in the extracts of the cyanobacterium *Lyngbya majuscula*.[40] The related compound dysidin, incorporating the same trichlorinated *O*-methylated β-keto amide motif, was isolated from the Indopacific sponge *Dysidea herbacea*.[41] It is noteworthy that the sponges of the genus *Dysidea* are known for their symbiotic association with cyanobacteria.[42] The synthetic plans for both natural products **24a** and **25** were based on acylation of the *N*-nucleophilic synthons with acyl Meldrum's acids as mixed diketene equivalents.

The enantiopure carboxylic acid **26** was converted to an acyl chloride and then coupled with Meldrum's acid to give the corresponding hydroxymethylene derivative **27**. The latter reacted with (*S*)-*N*-methyldolaphenine **28** to form amide **29**. Methylation under strongly basic conditions caused epimerization at C_7, yielding a mixture of barbamide **24a** and 7-epibarbamide **24b** which were separable by HPLC (Scheme 8).

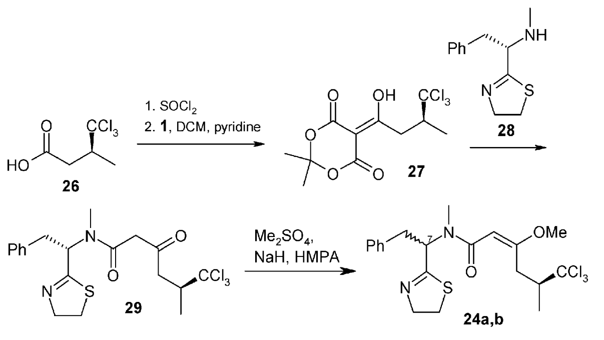
Similarly, the dysidin **25a** was synthesized in a convergent manner using the racemate of the same trichlorinated carboxylic acid **27**.[43] Reaction of acylmalonate **30** with the magnesium bromide salt of a *rac*-valine-derived tetramate **31** (Scheme 9) afforded a 1 : 1 mixture of pure dysidin **25a** and isodysidin **25b**, easily separable by fractional crystallization.



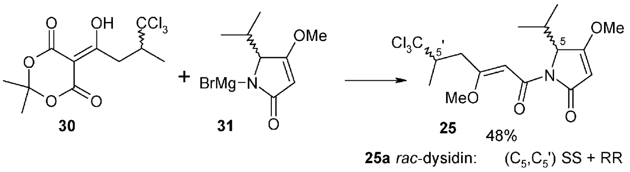
Scheme 6



Scheme 7

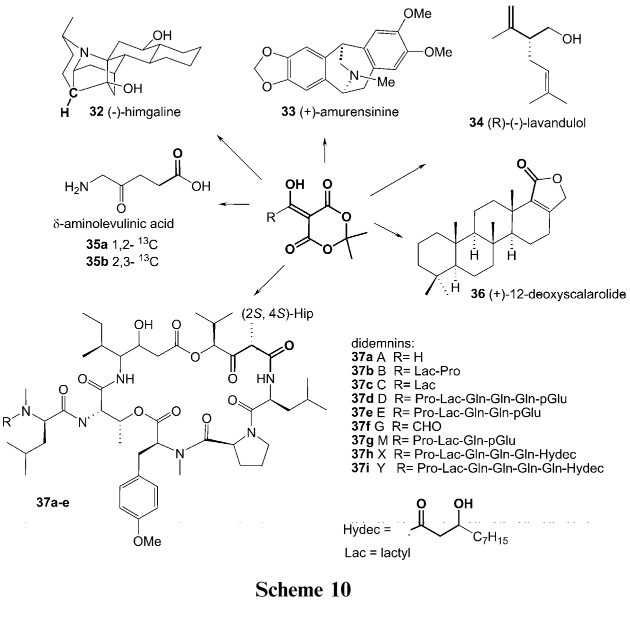


Scheme 8



Scheme 9

Transformations of acyl Meldrum's acids to β-keto esters have been efficiently used in the syntheses of a variety of complex natural compounds. Scheme 10 outlines the natural products which have been synthesized using β-keto ester intermediates obtained from the corresponding acyl Meldrum's acids. These are the rainforest tree *Galbulimima belgraveana* alkaloid (−)-himgaline **32**,[44] an isopavine alkaloid (+)-amurensinine **33**,[45] a terpene (*R*)-(−)-lavandulol **34**,[46] labeled [1,2-^{13}C]- (**35a**) and [2,3-^{13}C]-δ-aminolevulinic acid **35b**,[47] a terpenoid (+)-12-deoxyscalarolide **36**;[48] the (hydroxyisovaleryl)propionyl (Hip) units of cyclic marine depsipeptides didemnins A, B, C, D, E, G, M, X and Y **37a**–**37i** and related compounds didemnin N, nordidemnins A, B and R, methylenedidemnin A and acylcyclodidemnin A;[49,50] and the 3-hydroxydecanoyl (Hydec) unit of didemnins X and Y



Scheme 10

37h,i.[50] It is of note that the synthesis of labeled acid **35b** required the labeled [5-^{13}C]-Meldrum's acid, accessible from [2-^{13}C]-malonic acid.

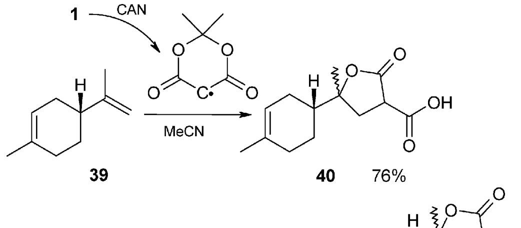
3. Furanones and pyranones

The first example of radical addition of Meldrum's acid to olefins was reported by Mane and co-workers in 2001 in their synthesis of norbisabolide **38** (Scheme 11).[51] This C_{12}-terpene lactone was isolated from the root bark of *Atalantia monophylla*.[52] On the first step of this synthesis, cerium(IV) ammonium nitrate (CAN) oxidized Meldrum's acid to generate a radical, which added to the *exo*-double bond of (*R*)-(+)-limonene **39**, affording the lactone carboxylic acid **40** in good yield. The regioselectivity of the radical addition can be explained on the basis of a steric effect where the bulky Meldrum's acid radical adds to the less hindered double bond in the side chain. Decarboxylation of **40** on heating with poly-4-vinylpyridine in DMF furnished norbisabolide **38** in nearly quantitative yield as a mixture of diastereomers (54 : 46).

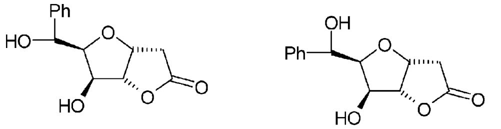
Meldrum's acid is known to react with aldo-pentoses and aldo-hexoses, providing facile access to *C*-glycosidic-1,4-lactones.[53,54] This reaction is remarkable due to its high bond-forming efficiency, resulting in formation of the fused lactones in a single step. (+)-Goniofufurone **41** and (+)-7-*epi*-goniofufurone **42** are natural anti-tumor styryl lactones, isolated from the *Goniothalamus* species (Annonaceae) (Scheme 12).

The reaction of D-glucose with Meldrum's acid led to triol **43** with the bicyclic goniofufurone framework. The *gem*-diol side fragment was oxidized to an aldehyde, the secondary hydroxyl was protected as a silyl ether, and the resulting compound **44** was reacted with phenylmagnesium bromide. Presumably, coordination of the aldehyde and furanoid ring oxygen by the magnesium ion led to preferred attack of the nucleophile from the *Si*-side, giving exclusively the L-glycero-D-*ido* diastereomer along with several by-products due to phenylation of the lactone ring. Deprotection of hydroxyl concluded this synthesis of (+)-7-*epi*-goniofufurone **42** (Scheme 13).[55]

Annonaceous acetogenins are a class of biologically active polyketide-derived fatty acids, containing from one to three tetrahydrofuran rings in the center of a long hydrocarbon chain.[56] The Meldrum's acid derived triol **43** has been used for the synthesis of 2,5-disubstituted bistetrahydrofurans **45a**–**45d** (Scheme 14), mimicking the central parts of annonaceous acetogenins.[57] Compounds **45a**–**45d** are useful building blocks for the synthesis of hydroxylated derivatives of annonaceous acetogenins for the determination of structure–activity relationships (SAR) of the natural compounds.

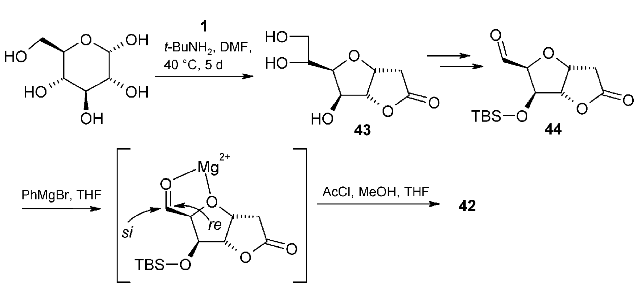


Scheme 11



41 (+)-goniofufurone **42** (+)-7-*epi*-goniofufurone

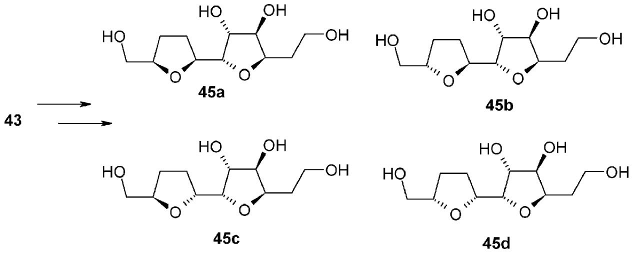
Scheme 12



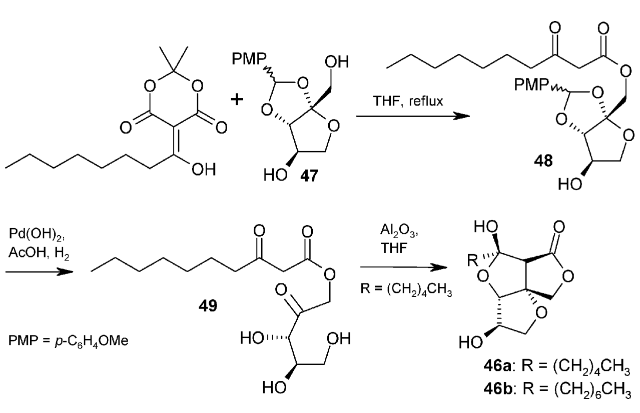
Scheme 13

Syringolides 1 **46a** and 2 **46b**[58,59] are *C*-glycosidic microbial elicitors, specific signal molecules produced by the bacterial plant pathogen *Pseudomonas syringae* pv. *tomato*, which trigger a hypersensitive defense response in resistant cultivars of soybean plants. Syringolides are supposed to originate biosynthetically from the appropriate β-ketoacyl-SCoA and D-xylulose.[59] Henschke and Rickards have worked out an efficient biomimetic approach to syringolide 2 (Scheme 15), using D-xylulose and octanoyl Meldrum's acid to produce a synthetic equivalent of the corresponding β-ketoacyl-SCoA.[60] Octanoyl Meldrum's acid selectively acylated the primary hydroxy group of the protected D-xylulose **47** in the presence of the unprotected secondary hydroxyl to give β-keto ester **48**. It is noteworthy that an alternative method for the preparation of intermediate **48** employing 3-oxodecanoic acid and dicyclohexylcarbodiimide (DCC) resulted in a lower yield and selectivity for the primary hydroxy group. After the removal of the anisylidene protecting group from **48**, the β-keto acyl xylulose ester **49** underwent an efficient, though low yielding, cascade cyclization to syringolide 2 **46b** on treatment with basic alumina. A similar approach has been employed for the preparation of syringolide 2 multiply deuterated in the side chain.[61]

Few methods for preparation of 3-alkyl-4-hydroxypyrones are known, and the majority of these are low yielding. Probably the most convenient and efficient one is based on



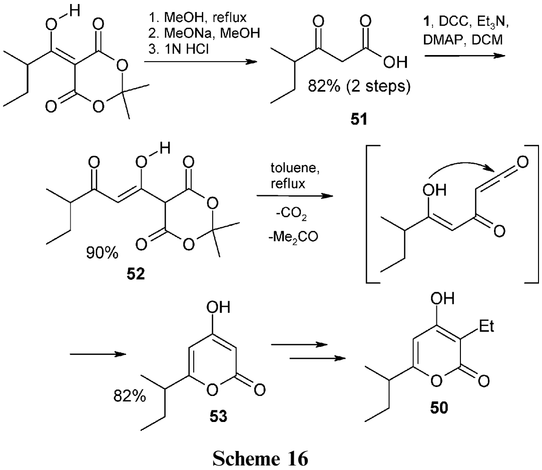
Scheme 14



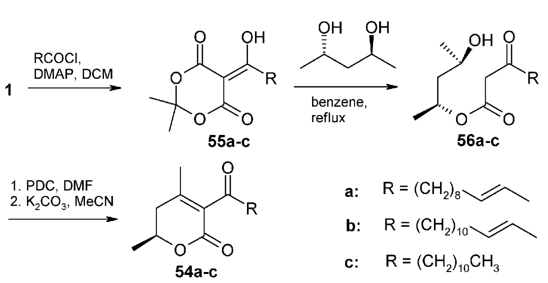
Scheme 15

the thermal recyclization of acetoacetyl derivatives of Meldrum's acid.[62] This approach has been applied to the first synthesis of racemic germicidine **50** (Scheme 16).[63,64] Germicidine is a 4-hydroxy-2-pyrone isolated from *Streptomyces viridochromogenes* NRRL B-1551. It was found to inhibit germination of arthrospores of its own producer at concentrations as low as 40 pg mL^{-1}. At higher concentrations it inhibited porcine Na$^+$/K$^+$ activated ATPase and retarded the germination of the cress *Lepidium sativum*.[65] 2-Methylbutyroyl malonate **51** was obtained by acylation of **1** with 2-methylbutyroyl chloride, and methanolysis followed by saponification of the methyl ester. Because of the instability of β-keto acyl chlorides, a combination of β-keto acid **51**, DCC, triethylamine, and a catalytic amount of DMAP was used to acylate Meldrum's acid. Thermal recyclization of the resulting β-keto acetyl derivative **52** efficiently formed the 4-hydroxy-2-pyrone system of **53**. Subsequent introduction of the ethyl group at position 3 completed the synthesis of *rac*-germicidine with 40% overall yield for 7 steps.

The 5,6-dihydropyran-2-one system is also accessible *via* the Meldrum's acid chemistry. During the study of the constituents of *Dictyostelium* slime molds, three novel metabolites were isolated. Dictyopyrones A **54a** and B **54b** have been extracted from *D. discoideum* and *D. rhizoposium* and dictyopyrone C **54c** from *D. longosporum*. The asymmetric synthesis (Scheme 17) enabled elucidation of the absolute configurations of all three dictyopyrones **54a**–**54c**.[66] Meldrum's acid was acylated with the corresponding acyl halides and the products **55a**–**55c** were subjected to reaction with (2*S*,4*S*)-pentanediol. After oxidation of the hydroxyl in **56a**–**56c** with pyridinium dichromate (PDC), the pyrone ring was formed by a base-catalyzed cyclization, affording compounds **54a**–**54c**. Application of the enantiomeric (2*R*,4*R*)-pentanediol led to the corresponding analogs of the natural dictyopyrones.



Scheme 16



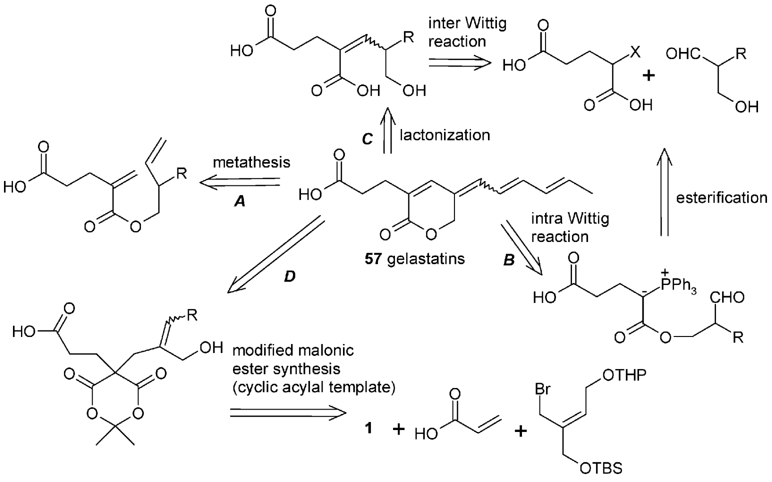
Scheme 17

Gelastatins **57** are another natural product containing a partially unsaturated pyrone ring that has been synthesized using Meldrum's acid. Gelastatins were isolated as a mixture of two stereoisomers (gelastatin A and gelastatin B) from the culture broth of *Westerdykella multispora* F50733.[67,68] Gelastatins A and B are separable by chromatography but readily isomerize back to the same mixture of isomers. Gelastatins exhibit high inhibitory activities against gelatinase A (MMP-2) and tumor necrosis factor-α converting enzyme (TACE) that play important roles in a number of inflammatory and degenerative diseases, including rheumatoid arthritis, stroke, multiple sclerosis, tumor invasion, and metastasis.[69] Retrosynthetic analysis of the gelastatin structure revealed a few possible synthetic routes starting from glutaric acid derivatives (Scheme 18). Ring closing olefin metathesis reaction ***A*** produced only a dimeric compound. Intramolecular Wittig reaction and aldol type condensations ***B*** of related compounds did not lead to cyclized products. Intermolecular Wittig reaction followed by lactonization ***C*** produced only scarce amounts of the esters of gelastatins. Lastly, the synthetic strategy based on transformations of a highly functionalized cyclic acylal template ***D*** resulted in the first successful total synthesis of gelastatins.[70]

The Michael addition reaction of Meldrum's acid with methyl acrylate yielded exclusively the mono-substituted derivative **58**.[71] The latter was alkylated with allylic bromide **59** to form the key intermediate **60**. Treatment with TBAF not only caused cleavage of the silyl ether but also facilitated lactonization and decarboxylation to give the lactone **61**. Unsaturation of the lactone ring was achieved using a Saegusa oxidation[72] of the corresponding silyl enol ether. Subsequent transformations on the side chains concluded the total synthesis of gelastatins (Scheme 19). The whole synthesis was reproducible on a gram scale and the synthetic gelastatins showed the same spectroscopic properties of the natural gelastatins with a 1 : 3 ratio of isomers A and B.

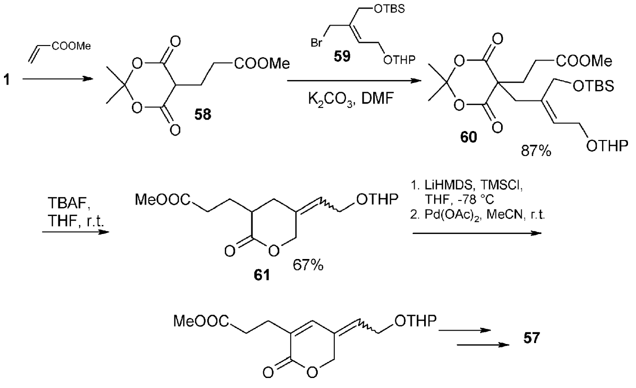
4. Tetramic acids and related compounds

The tetramic acid (pyrrolidine-2,4-dione) unit has been recognized as a common structural motif in a variety of natural



Scheme 18

products. Tetramic acids are found in different sources such as marine invertebrates, fungi, and bacteria. The broad spectrum of biological activity of this family of natural compounds spans from antibiotic to cytotoxic. Certain members of this class are responsible for the pigmentation of some sponges and molds.[73] Due to the mounting interest in tetramic acids, various synthetic routes towards their synthesis have been established (Scheme 20). The Lacey–Dieckmann cyclization is the most widely adopted strategy towards the pyrrolidine-2,4-dione core ***A***.[74] It is a base-induced cyclization of *N*-(β-keto acetyl)-α-amino esters **62**, which are often obtained from α-amino acids and acyl Meldrum's acids. This extremely flexible strategy allows the preparation of tetramic acids with various substituents at C_3 **63**. However, partial racemization of stereogenic centers at C_5 is an often observed unwanted side reaction of this method.[75] This reaction can also be carried out on a solid support.[76,77] Jouin *et al.* proposed an alternative approach ***B*** to construction of the tetramic acid core by condensation of *N*-protected amino acids with Meldrum's acid in the presence of isopropenyl chlorocarbonate (IPCC) and DMAP.[78] In this synthesis, Meldrum's acid is acylated with a mixed anhydride, generated *in situ* from a carboxylic acid and IPCC. Heating of the resulting acyl malonate **64** induces cycloelimination of carbon dioxide and acetone, to form an acylketene intermediate **65**, which undergoes an intramolecular cyclization to the corresponding tetramic acid derivative **66**. The transformation is run under neutral and non-racemizing conditions. Another efficient method ***C*** for the assembly of the tetramic acid core employs the carbodiimide-mediated acylation of cyclic acylal **13** with *N*-protected amino acids, followed by thermal cyclization.[19] Scheme 20 (***C***) depicts the solid phase version of this approach where Meldrum's acid is bound to a polymer support. Other strategies towards the tetramic acid system have been reviewed in ref. 73 and 79.



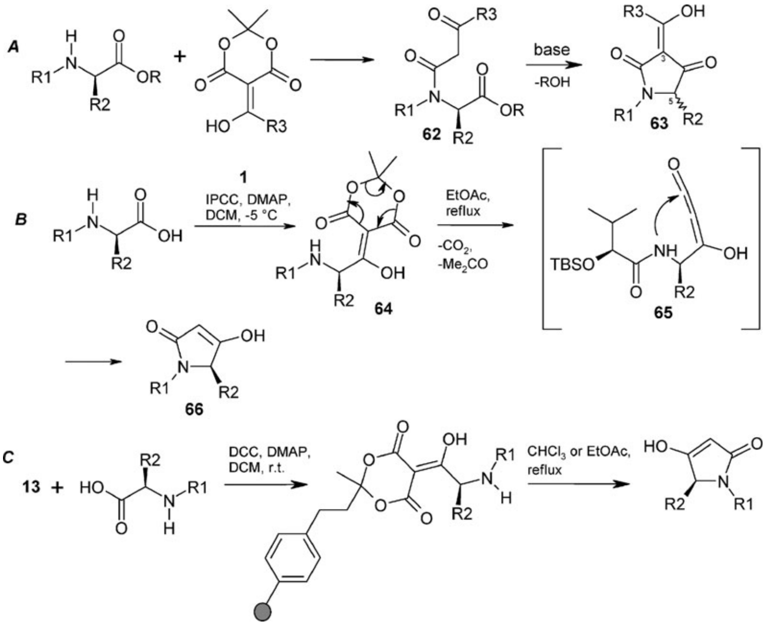
Scheme 19

The Lacey–Dieckmann protocol (Scheme 20, ***A***) has been employed in the synthesis of the tetramate unit of equisetin **67** (Scheme 21), the principal toxic fungal metabolite first isolated from the white mold *Fusarium equiseti*.[80,81] The compound has an impressive spectrum of biological activities including antibiotic, HIV-1 integrase inhibitory activity, phytotoxicity, cytotoxicity and mammalian DNA binding.[80,82] The molecule of equisetin consists of two units, an octalinoid system and a tetramic acid fragment. It contains five stereogenic centers, one of which is quaternary. In their total synthesis of equisetin, Dixon and co-workers envisaged that, due to the quaternary nature of the stereogenic center at C_1, it seemed unfeasible to append a pre-built tetramate unit to the octalinoid backbone.[83] Thus, the assemblage of the (*S*)-serine derived acyl-tetramate unit was reserved to late steps in the synthesis.

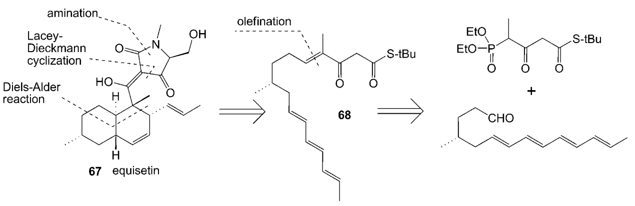
The key retrosynthetic intermediate **68** was designed to contain a conjugated triene fragment on one side and a β-keto thioester functionality on the other side, necessary for the construction of the octalinoid and tetramate units, respectively. Compound **68** was synthesized from Meldrum's acid *via* a sequence of acylation, thiolysis, halogen to phosphonate exchange, and a Horner–Wadsworth–Emmons reaction (Scheme 22).

A Lewis acid catalyzed intermolecular Diels–Alder cyclization reaction of compound **68** afforded the octalinoid intermediate **69**. Reaction of the β-keto thioester group with (*S*)-*N*-methyl-*O*-*tert*-butyldimethylsilyl serine methyl ester, deprotection of the *O*-TBS group with hydrogen fluoride and a base-catalyzed cyclization of **70** furnished the tetramate unit and completed the total synthesis of equisetin (Scheme 23).

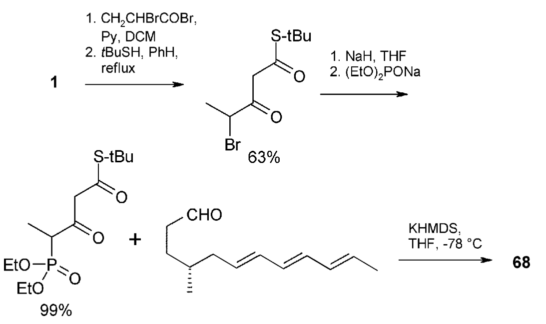
The method of Jouin *et al.* (Scheme 20, ***B***) was utilized in the synthesis of several lipophilic peptides containing amino acid derived tetramate moieties. One of such peptides is dolastatin



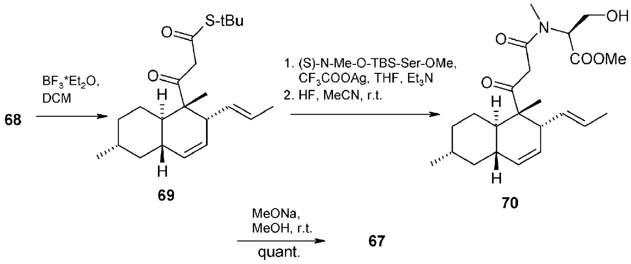
Scheme 20



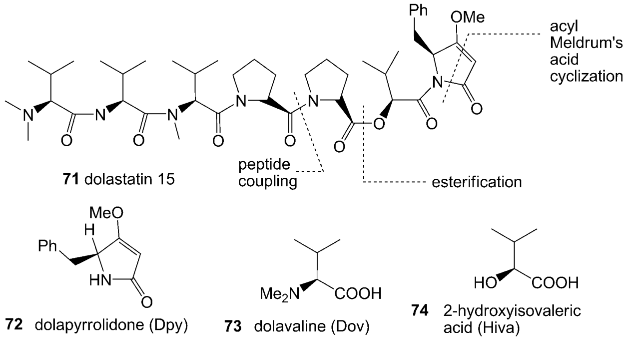
Scheme 21



Scheme 22



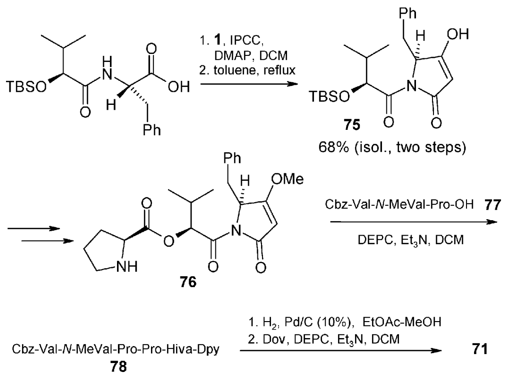
Scheme 23



Scheme 24

15 **71** (Scheme 24). It is a member of the dolastatin family of natural products that includes linear and cyclic antineoplastic and/or cytostatic peptides found in the marine opisthobranch mollusks. Dolastatin 15 **71** is a highly potent member of this family, isolated from *Dolabella auricularia* (Indian Ocean sea hare).[84] Chemical and biomedical aspects of dolastatins have been extensively reviewed.[85–87] Dolastatin 15 contains such unusual fragments as dolapyrrolidone (Dpy, **72**), dolavaline (Dov, **73**) and 2-hydroxyisovaleric acid (Hiva, **74**). In 1991, Pettit and co-workers reported the pilot total synthesis of the natural (−)-dolastatin 15,[88] which was improved in 1994 for the scale-up preparation.[89]

Since proline coupling is usually racemization free, a strategic disconnection was made between the two (*S*)-proline units. The eastern region of the target molecule was constructed on the basis of a protected molecule of Hiva-Phe. A combination of Meldrum's acid, IPCC and DMAP, followed by cyclization, provided tetramic acid **75**. Further modification of **75** afforded the depsipeptide Pro-Hiva-Dpy **76**, which was linked to the protected tripeptide Cbz-Val-*N*-MeVal-Pro-OH **77** using diethyl phosphorocyanidate (DEPC) as the coupling reagent. The benzyloxycarbonyl (Cbz) protecting group of **78** was cleaved from the terminal valine, and the target compound **71** was obtained after coupling with dolavaline **73** (Scheme 25).

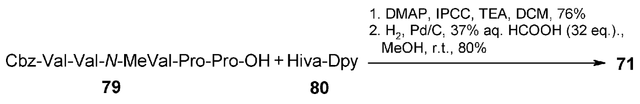


Scheme 25

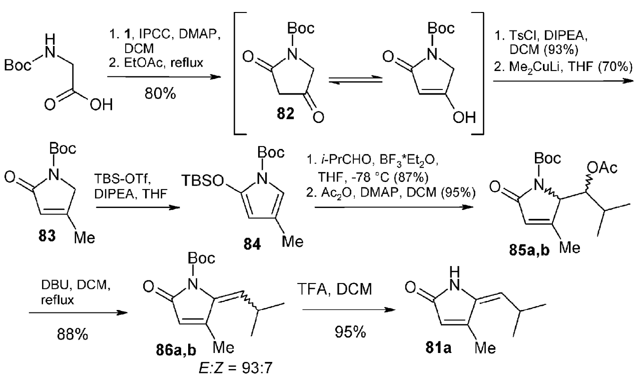
In a slightly different approach, dolastatin 15 **71** was synthesized by Patino *et al.* from another two building blocks: Cbz-protected pentapeptide Cbz-Val-Val-*N*-MeVal-Pro-Pro-OH **79** and Hiva-Dpy **80** (Scheme 26).[90] The tetrapeptide part was obtained through peptide coupling chemistry. Attempted preparation of **80** through the direct acylation of the dolapyrrolidone ring with Hiva derivatives under various conditions (symmetrical anhydride–DMAP, mixed anhydrides) failed and compound **80** was synthesized by a protocol analogous to that used by Pettit's group. However, it was found that partial epimerization took place during the synthesis of tetramate **75**, which was obtained as a mixture of (*S*,*S*) and (*S*,*R*) epimers in the ratio 9 : 1. These epimers were separated by column chromatography, and the necessary (*S*,*S*)-isomer was used on the next step. The two fragments **79** and **80** were linked together using the combination of IPCC and DMAP. After the coupling, the terminal Cbz-Val unit of the resulting product was debenzylated and dimethylated in a single step by catalytic hydrogenolysis in the presence of a large excess of aqueous formaldehyde to provide dolastatin 15 **71** after chromatographic purification.

Protein tyrosine phosphatases (PTPs) are enzymes that remove phosphate groups from phosphotyrosine residues in protein substrates. CD45 is a receptor-like transmembrane PTP, which plays a crucial role in activation of both B and T-cells[91] and represents a therapeutic target for various autoimmune and chronic anti-inflammatory diseases.[92] Pulchellalactam is a natural product, isolated from the marine fungus *Corollospora pulchella*, which was found to exhibit high inhibitory activity towards CD45.[93] The lactam was scarcely available from the natural source and its stereochemistry remained unassigned until the total synthesis. In order to obtain sufficient amounts of the compound for biological evaluation and determination of its geometry, synthesis of both *E*- **81a** and *Z*-pulchellalactam **81b** was performed.[94]

N-Boc protected tetramic acid **82** was synthesized by coupling *N*-Boc glycine with Meldrum's acid, followed by intramolecular cyclization and decarboxylation. Alkylation of **82** with organometallic reagents at the C_4 carbonyl failed because of a facile enolization, so the methyl group was introduced at position 4 *via* addition of an organocopper reagent to the corresponding tosyl enolate. After TBS-protection of the lactam carbonyl of **83**, the silyloxypyrrole **84** was reacted with isobutyraldehyde in the presence of boron trifluoride etherate as a Lewis acid catalyst. After acetylation with acetic anhydride, a DBU-catalyzed elimination of the *erythro* and *threo* acetates **85a,b** gave an inseparable mixture of *E*- and *Z*-alkenes **86a,b**. After deprotection of the mixture with trifluoroacetic acid, pure *E*-pulchellalactam **81a** was isolated by chromatography (Scheme 27).



Scheme 26

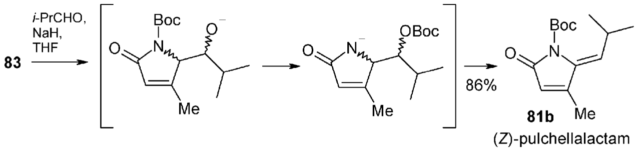


Scheme 27

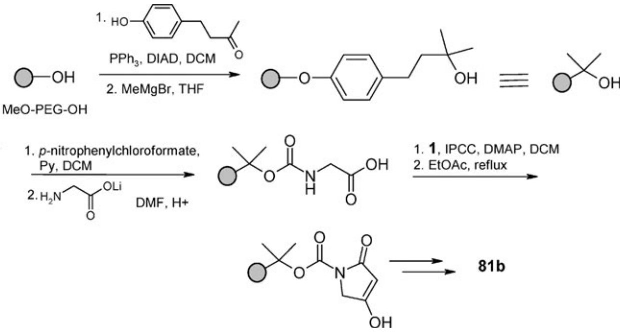
Pure *Z*-pulchellalactam **81b** was obtained by base-catalyzed condensation of **83** with isobutyraldehyde (Scheme 28). The reaction was assumed to proceed *via* the steps of deprotonation, condensation with aldehyde, migration of the *tert*-butyloxycarbonyl (Boc) group, and elimination through an E1cB mechanism. The spectroscopic data obtained for the *Z*-pulchellalactam were in agreement with those for the natural product. In order to permit combinatorial synthesis of the novel pyrrol-2-one containing compounds, the synthesis was ported to a liquid support. This new, traceless liquid-phase strategy afforded *Z*-pulchellalactam in 37% overall yield for nine steps as outlined in Scheme 29.

A method for synthesis of the tetramic acid system based on carbodiimide mediated coupling of Meldrum's acid with a chiral protected amino acid (Scheme 20, ***C***) is exemplified by the recent synthesis of malyngamide X **87a** and its (7′*S*)-epimer **87b**.[96] Malyngamide X is linear lipopeptide, which was isolated from the EtOAc extract of sea hare *Bursatella leachii*.[95] It was found to be active against malarial parasite *Plasmodium falciparum* (multidrug resistant strain) and tuberculosis bacterium *Mycobacterium tuberculosis*. As represented in Scheme 30, the molecule of malyngamide X is composed from four building blocks: a fatty acid ***A***, two amino acid derivatives ***B*** and ***C***, and a valine derived tetramate ***D***.

A mixture of *N*-Boc-valine **88**, Meldrum's acid, DCC and DMAP was stirred in dichloromethane. After the separation



Scheme 28



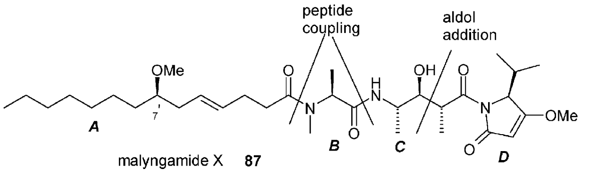
Scheme 29

of the insoluble *N*,*N*′-dicyclohexylurea, the crude intermediate **89** was subjected to thermal cyclization to **90** on heating in methanol. *N*-Boc-pyrrolidone **90** was *O*-methylated under Mitsunobu reaction conditions, deprotected, metallated with MeMgBr and *N*-acylated with propionyl chloride to give the propionyl tetramate **91** (portion ***D***) in 68% overall yield (Scheme 31). The compound obtained was stereoselectively connected with part ***C***, and then parts ***A*** and ***B*** were appended consequently.

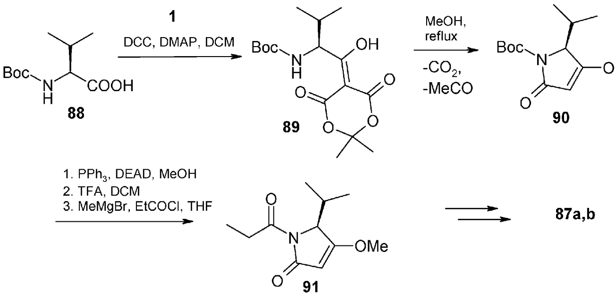
Microcolins A **92a** and B **92b** are potent immunosuppressive agents isolated from the Venezuelan blue-green algae *Lyngbya majuscula*, inhibiting the human two-way mixed lymphocyte response (MLR) with EC_{50} values of 0.02 and 4.1 nM for A and B, respectively.[97] The microcolins possess a linear lipopeptide structure related to the cytotoxins majusculamide D and deoxymajusculamide D, isolated from the same species.[98] Recently a total asymmetric synthesis of microcolin A has been accomplished in 21 steps with 1.7% overall yield.[99] The retrosynthetic approach invoked two disconnections, dividing the target molecule into the three building blocks ***A***, ***B*** and ***C*** (Scheme 32).

Fragment ***C*** of microcolin A represents an unusual *cis-allo*-hydroxyproline connected to 5-methylpyrrolidin-2-one. The initial approach to the synthesis of this unit was based on a modified procedure by Roux *et al.*.[100] Unfortunately, attempts to effect thermal decarboxylative cyclization of alkylidene Meldrum's acid **93** to pyrrolidone product **94** failed. However, thermal cyclization of acyl Meldrum's acid **95** (Scheme 33) afforded the hydroxypyrrolidone **96**. After deoxygenation, both the amino and the hydroxy group were deprotected to produce **97** (***C***).

Final assemblage of the microcolin A molecule was performed through standard peptide coupling chemistry using BOP as the coupling agent. The strategy applied is amenable to the synthesis of chemical analogs and different stereoisomers of the target compound for biological evaluation.



Scheme 30



Scheme 31

5. Terpenoids

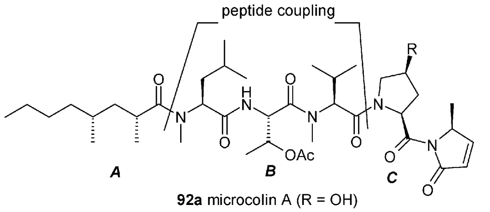
Classical malonic ester synthesis is substantially improved with the use of isopropylidene malonate **1** instead of dialkyl malonates. The high C–H acidity, flat structure and low steric profile of Meldrum's acid provide a unique template for various transformations at the active methylene site. After functionalization of position 5, the 1,3-dioxane-4,6-dione system can be converted to an acetic acid or acetic ester group by hydrolysis or alcoholysis respectively under mild conditions (Scheme 34). The alcoholysis reaction can be efficiently catalyzed by $Ni(acac)_2$.[12]

The cyclic acylal template has been used for the synthesis of sesquiterpenes ar-turmerone **98** and α-curcumene **99** (Scheme 35), the constituents of some essential oils.[101]

Syntheses of both natural products were designed to share the same intermediate, a benzyl derivative of Meldrum's acid **100**. Preparation of this pivotal compound has been accomplished by three different methods (Scheme 36). In the first method, acylal **100** was obtained by conjugate addition of methylmagnesium iodide to *p*-tolylidene Meldrum's acid **101**. In the second approach, a highly electrophilic olefin **102**, produced by condensation of *p*-methylacetophenone with Meldrum's acid, was selectively reduced with sodium borohydride to give **100**. In the third approach, compound **100** was prepared by direct alkylation of Meldrum's acid with 1-*p*-tolylethyl chloride.

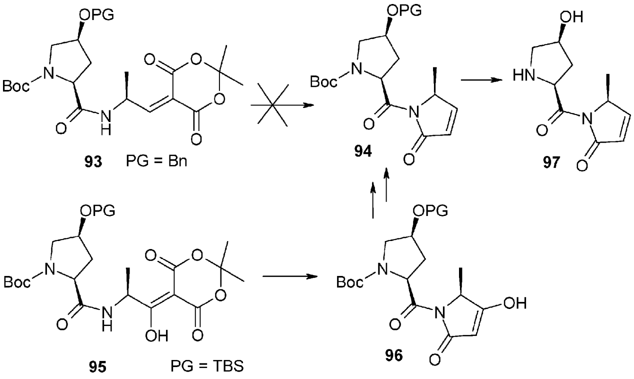
Compound **100**, on decarboxylative hydrolysis in aqueous pyridine, transformed to carboxylic acid **103**, which was further converted to ar-turmerone **98** by reaction with isobutenyllithium. Alternatively, the target compound **98** was prepared from **100** through a sequence of reactions, including acylation with 3,3-dimethylacryloyl chloride, alcoholysis, and hydrolysis of the β-keto ester **104** (Scheme 37).

The approach adopted for the synthesis of α-curcumene **99** was the stepwise alkylation of Meldrum's acid with different alkylating agents. The mono-substituted malonate **100** was

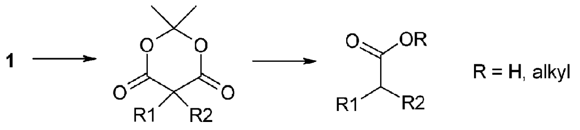


92a microcolin A (R = OH)
92b microcolin B (R = H)

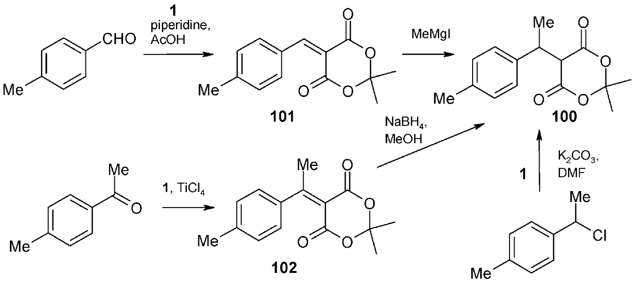
Scheme 32



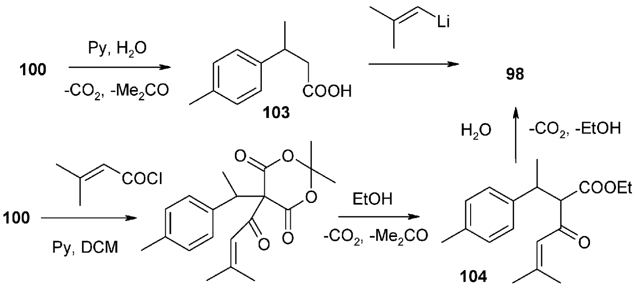
Scheme 33



Scheme 34



Scheme 36



Scheme 37

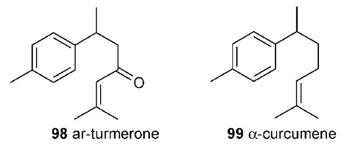
alkylated with 3,3-dimethylallyl bromide to give compound **105**. Alkaline hydrolysis of the 1,3-dioxane-4,6-dione system led to the corresponding dialkylmalonic acid **106**, which underwent oxidative decarboxylation with lead tetraacetate[102] to give the ketone **107**. Clemmensen reduction of **107** afforded α-curcumene **99** (Scheme 38).

Another terpenoid molecule, synthesized with the use of a cyclic acylal template, is taiwaniaquinol B **108**. This compound was isolated from a common Taiwanese pine tree *Taiwania cryptomerioides*. It is a 6-*nor*-5(6→7)*abeo*-abietane type diterpenoid possessing the uncommon fused tricyclic carbon skeleton with a complex pattern of substitution.[103] The discovery of aromatase inhibitory activity in this family of diterpenoids[104] stimulated efforts towards the total synthesis of taiwaniaquinol B.[105,106] In search of a flexible synthetic strategy to **108**, amenable to structure–activity relationship (SAR) studies, the assemblage of the tricyclic core was envisaged to emanate from an intramolecular α-*tert*-alkylation of the indanone synthon with a tethered alkene (Scheme 39). Since benzyl derivatives of Meldrum's acid are known to undergo metal triflate catalyzed intramolecular Friedel–Crafts acylation to the corresponding indanones,[107] the appropriately substituted benzyl Meldrum's acid **109** was identified as a key synthon for the assemblage of the tricyclic core.

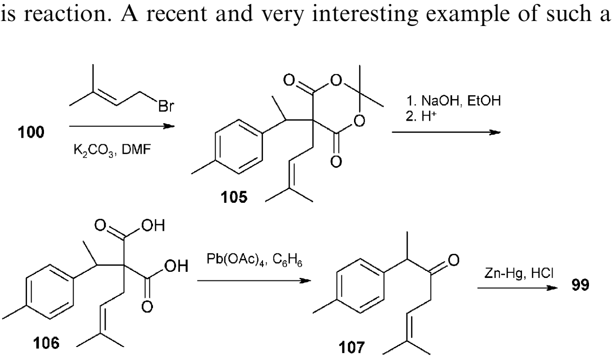
Knoevenagel condensation of aryl ketone **110** with Meldrum's acid yielded benzylidene derivative **111**, which further reacted with methylmagnesium bromide to give **109**. Upon treatment with an equimolar amount of TMSOTf, the malonate **109** was converted to indanone **112** in a good yield. Synthesis of the target compound was completed by selective deprotection of the methoxy group adjacent to the carbonyl and oxidation of the aromatic ring to quinone, which was catalytically reduced to hydroxy groups, affording taiwaniaquinol B **108** (Scheme 40).

A plausible mechanism for the key step, TMSOTf-mediated intramolecular Friedel–Crafts acylation–carbonyl α-*tert*-alkylation domino reaction, is depicted in Scheme 41. Treatment of the Meldrum's acid derivative **109** with TMSOTf generates the corresponding acylketene intermediate **113** *via* cycloelimination of acetone and release of triflic acid. The acylketene **113** undergoes intramolecular Friedel–Crafts acylation to form **114**. Subsequent intramolecular α-*tert*-alkylation of the triflic acid-activated alkene **114** produced the tricyclic intermediate **115**, which gave **112** after workup. It should be noted that creation of a quaternary-carbon asymmetric center is often a challenging problem. This elegant one-pot transformation provided construction of two asymmetric centers (one of which is quaternary) from the optically inactive Meldrum's acid derived precursor **109**. The first total synthesis of taiwaniaquinol B was accomplished in 15 steps and with 6% yield.

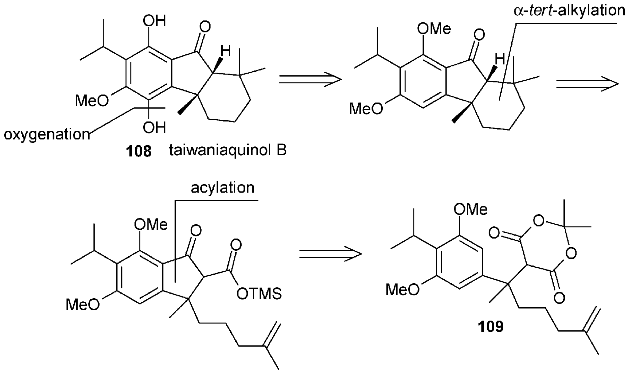
The intrinsic convergent nature of the Diels–Alder reaction often permits the rapid assembly of complex chemical structures of natural products. Certain derivatives of Meldrum's acid can be exploited as either "ene" or "diene" components in this reaction. A recent and very interesting example of such a



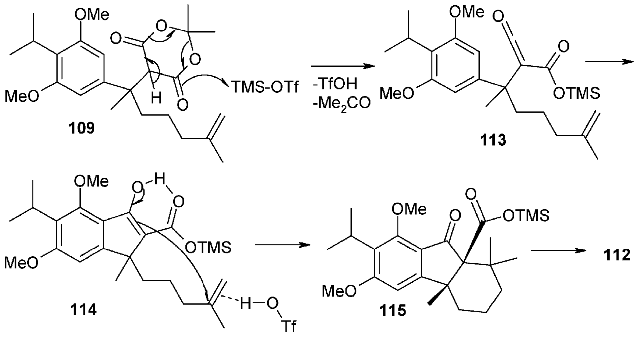
Scheme 35



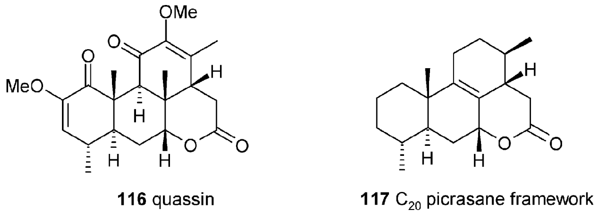
Scheme 38



Scheme 39



Scheme 41

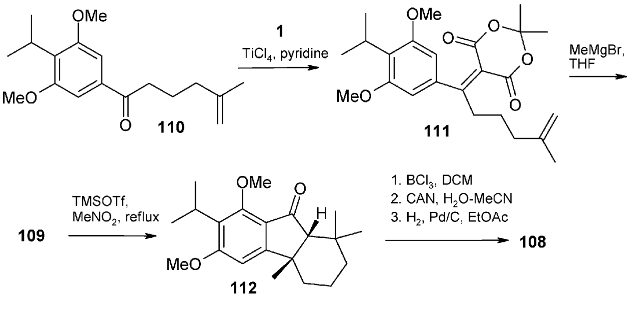


Scheme 42

Diels–Alder reaction is connected with the synthesis of a tetracyclic quassinoid framework. Quassinoids are a large family of naturally occurring compounds, isolated as bitter principles of subtropical shrubs and trees of the Simaroubaceae genera.[108] The majority of these degraded triterpenoids possess the carbon skeleton of a parent compound quassin **116**, known as the C_{20} picrasane framework **117** (Scheme 42). Quassinoids exhibit a wide range of beneficial biological properties including antimalarial, anticancer, insect antifeedant properties, and other activities.[109]

Due to their impressive biological profile, quassinoids represent attractive targets for synthesis. Nonetheless, due to their complex highly oxygenated structures, relatively few campaigns resulted in full total syntheses.[108] In the course of their investigations of quassinoid chemistry, Perreault and Spino synthesized a diene precursor **118** of the C_{20} picrasane framework.[12] It was envisioned that a [4 + 2]-cycloaddition involving **118** and a thioxomalonate synthon **119** would give the corresponding cycloadduct **120** (Scheme 43), suitable for the construction of quassinoid framework. The choice of dienophile was explained by the known fact that thiocarbonyls are more reactive with dienes than the corresponding carbonyls and the sulfide linker is easy to remove.

The thioxo malonates **121**, **122** and **7**, generated from the corresponding bromomalonates and sulfur powder in the presence of triethylamine, reacted with model diene **118** to give mixtures of cycloadducts **123a**–**123c** and **124a**–**124c** (Scheme 44). Diethyl thioxo malonate **121** gave a 1 : 2 mixture of products **123a** and **124a**. A sterically hindered di-*tert*-butyl thioxo malonate **122** afforded the products **123b** and **124b** in the reversed ratio 2 : 1. The best selectivity was observed in the case of thioxo Meldrum's acid **7**, which gave the cycloadducts **123c** and **124c** in the ratio 14 : 1 (Scheme 44).

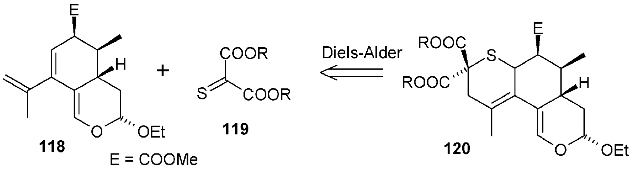


Scheme 40

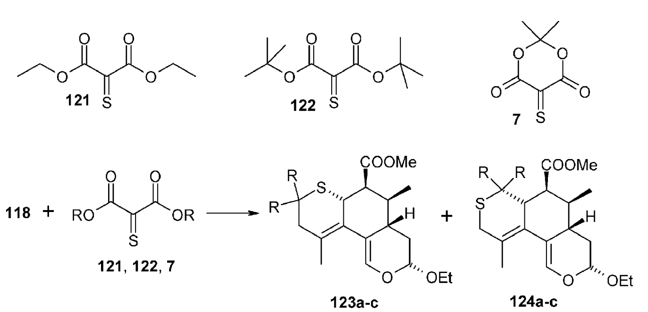
The superior regioselectivity of the cycloaddition of cyclic thioxo malonate **7** over the acyclic analogs can be rationalized on the basis of its rigid structure increasing the steric demand in the transition state **125** more effectively than in **126** (Scheme 45).

Finally, thioxo Meldrum's acid **7**, generated by thionation of **1** with phthalimidosulfenyl chloride,[110] reacted with diene **127** to form the desired cycloadduct **128** with even higher selectivity (30 : 1). Methanolysis and decarboxylation of the spiro-malonate **128** were achieved using catalytic $Ni(acac)_2$ in MeOH, and the sulfide linker was removed by treatment with Raney nickel. Further transformations of the methyl ester **129** furnished the synthesis of an advanced quassinoid precursor **130** (Scheme 46).[12]

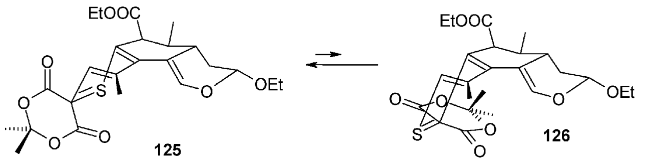
Methylene derivatives of Meldrum's acid can behave as reactive hetero-dienes in the inverse electron demand hetero-Diels–Alder reaction. Tietze and his group worked out an efficient multicomponent domino reaction between a 1,3-dicarbonyl compound, an aldehyde and an enol ether or an alkene in the presence of a mild base, such as ethylene diammonium diacetate (EDDA).[23] The reaction also proceeds on a polymer support and is thus suitable for combinatorial synthesis.[111] A plausible mechanism of this MCR, with the use of Meldrum's acid as the 1,3-dicarbonyl reagent, is depicted in Scheme 47. In this process, a highly reactive 1-oxa-1,3-butadiene, formed in the course of the Knoevenagel condensation



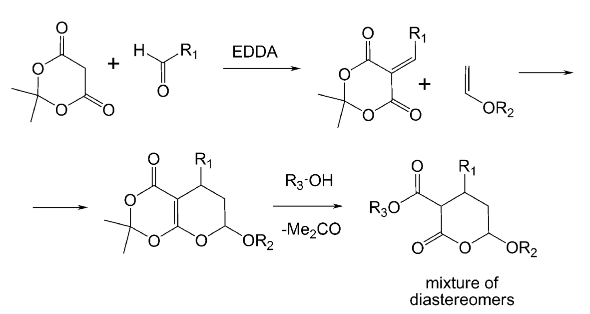
Scheme 43



Scheme 44



Scheme 45



Scheme 47

of a 1,3-dicarbonyl compound with an aldehyde, is involved in a hetero-Diels–Alder reaction with an alkene, followed by elimination of an acetone molecule and spontaneous decarboxylation to the dihydropyran product. The dihydropyranyl ether fragment can be regarded as a protected aldehyde group, which can participate in further reactions after deprotection.

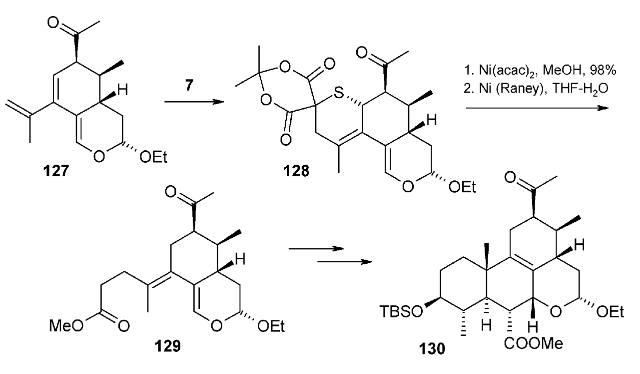
This highly efficient process has found wide application in the synthesis of complex molecules such as monoterpenoid alkaloids.

Monoterpenoid indole alkaloids are found in a number of plants belonging to the families Apocynaceae, Loganiaceae, Rubiaceae, and Nyssaceae. Several terpenoid indole alkaloids are used in modern medicine. Thus, vinblastine and vincristine find application as anticancer drugs, ajmalicine and reserpine as anti-hypertension drugs, and ajmaline as an anti-arrhythmic drug. Strictosidine **131a** is the general precursor in the biosynthesis of many monoterpenoid indole alkaloids. It is formed in plants by the condensation of tryptamine with the iridoid secologanin **132**, catalyzed by the enzyme strictosidine synthase.[112,113] Enzymatic glycolysis[114] of strictosidine **131a** provides the highly reactive aglucon **131b**, which reacts *in vivo via* its open dialdehyde form either by an N_4–C_{17} cyclization to give the indole alkaloids of the vallesiachotamine group **133**, including antirhine **134** and 18,19-dihydroantirhine **135**, or alternatively by an N_4–C_{21} cyclization leading to the indole alkaloids of the corynanthe group (*e.g.* geissoschizine **136**) (Scheme 48).

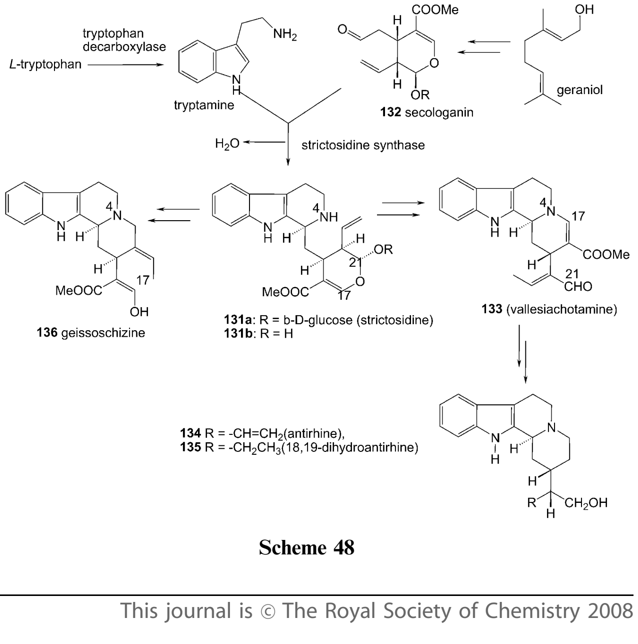
The domino Knoevenagel–hetero-Diels–Alder reaction has been successfully employed in the syntheses of a number of monoterpenoid alkaloids and their stereoisomers including dihydroantirhine **135**,[115] hirsutine **137**,[116] dihydrocorynantheine **138**,[116] emetine **139**,[117] and tubulosine **140** (Scheme 49).[118]

Since the domino Knoevenagel–hetero-Diels–Alder approach to the synthesis of heterocyclic natural products and analogs has recently been reviewed,[23,119,120] in this review only a single example of this highly important process will be described in full detail. This is an efficient though not stereoselective biologically patterned synthesis of dihydroantirhine **135**, an indole alkaloid of the vallesiachotamine group.[115]

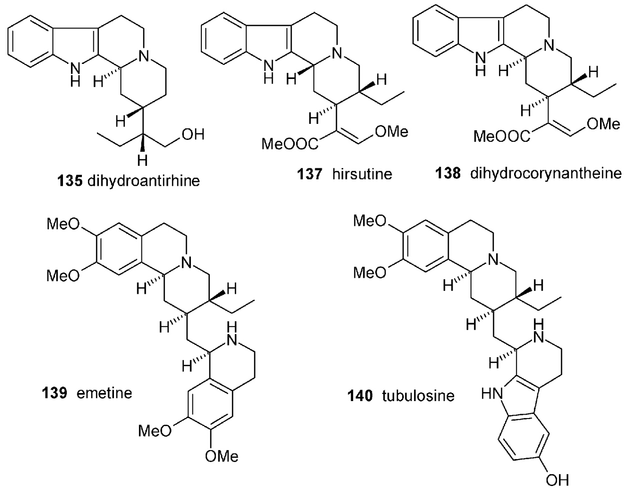
In the key step of the synthesis, the chiral aldehydes **141a,b** reacted under sonification with Meldrum's acid in the presence of catalytic EDDA, and the intermediate oxabutadienes **142a,b** interacted with (*E*)-enol ether (Scheme 50). The unstable bicyclic adducts **143a,b** transformed under the reaction conditions into the corresponding lactones **144a,b** with the loss of carbon dioxide and acetone molecules. The transformation proceeded with retention of the employed enol ether's configuration to give a mixture of diastereoisomeric products **144a,b**. Configurations of the newly formed stereogenic centers were dependent on the size of the substituent at the indole nitrogen. Hydrogenolysis of the mixture of diastereomeric cycloadducts



Scheme 46



Scheme 48

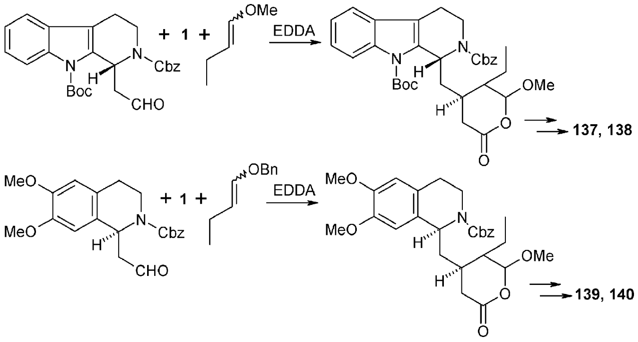


Scheme 49

144a,b caused cleavage of both the benzyloxy carbonyl and the benzyl groups. Subsequent transformations of the deprotected hemiacetal intermediates proceed by two pathways, leading to the formation of vallesiachotamine-type compounds **145** as the major products and corynantheine-type compounds **146** as the minor products. Reduction of vallesiachotamine-type compounds **145** with lithium aluminium hydride provided a mixture of diastereomeric 18,19-dihydroantirhines **147**. This synthesis represents a bioinspired construction of the 18,19-dihydroantirhine framework, emulating a process which in nature proceeds through cyclocondensation of N_4 by C_{17} in the pivotal metabolite strictosidine **131a** (Scheme 48).

Other monoterpenoid indole and tetrahydroisoquinoline alkaloids **137**–**140** have been synthesized by Tietze and co-workers using the same methodology (Scheme 51).[116–118]

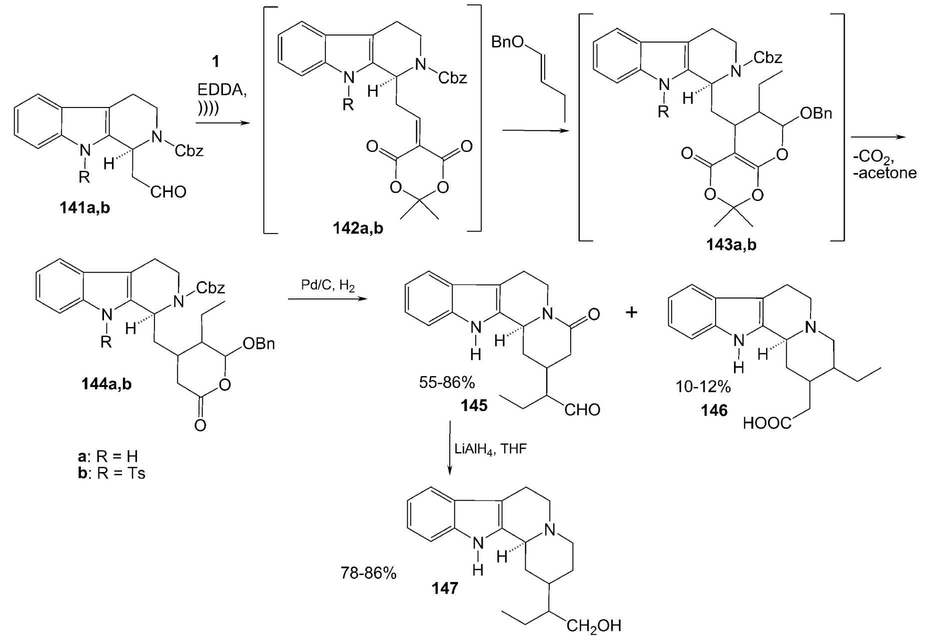
Betaine **11** is obtained by reaction of Meldrum's acid with 37% aqueous formaldehyde in pyridine (Scheme 52). Compound **11** is used as a stable source of methylene Meldrum's acid **148**. Diels–Alder and Michael reactions performed with this reagent produce the corresponding products in high yields.[15]



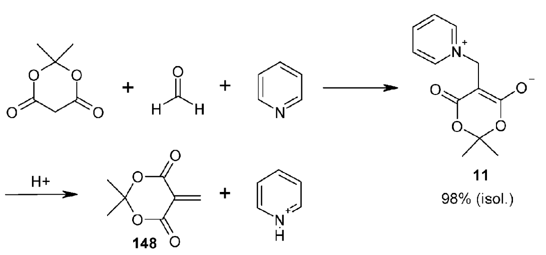
Scheme 51

Diels–Alder reaction of diene **149** with alkene **148**, generated *in situ* from betaine **11** in an acidic medium, gave a mixture of diastereomeric spiro-cycloadducts **150** and **151** in the ratio 1.2 : 1. The use of methylene Meldrum's acid dienophile in this reaction allowed the construction of a new quarternary all-carbon stereogenic center. After chromatographic separation of the spiro-cycloadduct **150**, the *p*-methoxybenzyl (PMB) protecting group was cleaved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a reaction that led directly to lactone carboxylic acid **152**. Further transformations furnished the highly functionalized cyclohexene subunit **153**[121] of the marine algal toxin (−)-gymnodimine **154** (Scheme 53).[122]

Ikarugamycin **155** (Scheme 54) is a naturally occurring antiprotozoan antibiotic produced by *Streptomyces phaeochromogenes* var. *ikaruganensis* Sakai. The macrocyclic structure of **155** incorporates an unusual perhydro-*as*-indacene ring system. Ikarugamycin was found to inhibit the uptake of



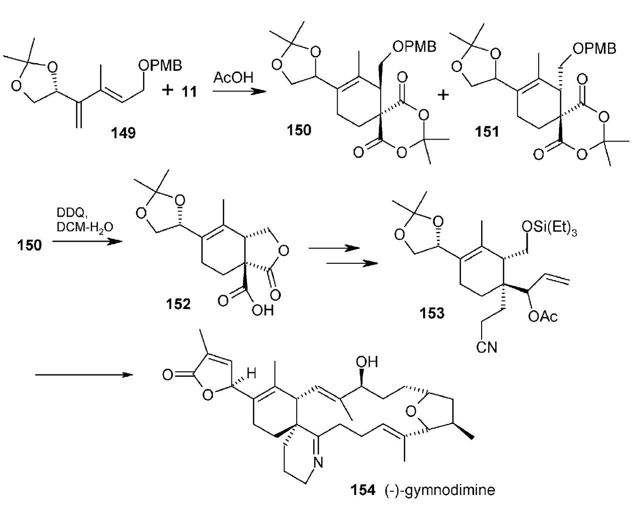
Scheme 50



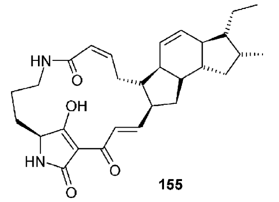
Scheme 52

oxidized low-density lipoprotein in mouse macrophages and to block phorbol myristate acetate (PMA) and Nef-mediated cell surface CD4 down-regulation.[123,124] Ikarugamycin is emerging as a general inhibitor of clathrin-coated pit-mediated endocytosis and appears to be a useful agent for studying the process of endocytosis.[124]

Roush and Wada have used a cyclic acylal template in the synthesis of the *as*-indacene fragment of ikarugamycin.[125] The synthesis started with asymmetric (*E*)-crotylboration of *meso*-(η^4-hexadien-1,6-dial)iron tricarbonyl **156**, resulting in the exclusive formation of the ψ-*exo* diastereomer **157** (≥ 98% ee). The aldehyde **157** was coupled with Meldrum's acid. After that, several steps were performed with retention of the cyclic acylal template. Conjugate addition of vinylmagnesium bromide gave the 1,4-adduct **158**. The Grignard reagent addition was highly stereoselective with addition from the side opposite to that blocked by iron tricarbonyl. After acetylation of hydroxyl, the acetate was substituted by ethyl on treatment with triethylaluminium. The nucleophilic substitution proceeded with retention of configuration, evidently due to anchimeric assistance from the $Fe(CO)_3$ functionality facilitating the departure of the acetate leaving group. When the required modification in the polyene chain was done, the iron tricarbonyl complexation in the functionalized malonate **159** was destroyed by treatment with $FeCl_3$. The cyclic acylal template was cleaved by hydrolysis and the newly formed carboxylic group converted to its methyl ester **160**. Further transformations finished the formation of the *as*-indacene core and the formal synthesis of ikarugamycin (Scheme 55) (the conversion of compound **161** to ikarugamycin **155** has been previously reported by Boeckman *et al.*).[126]



Scheme 53

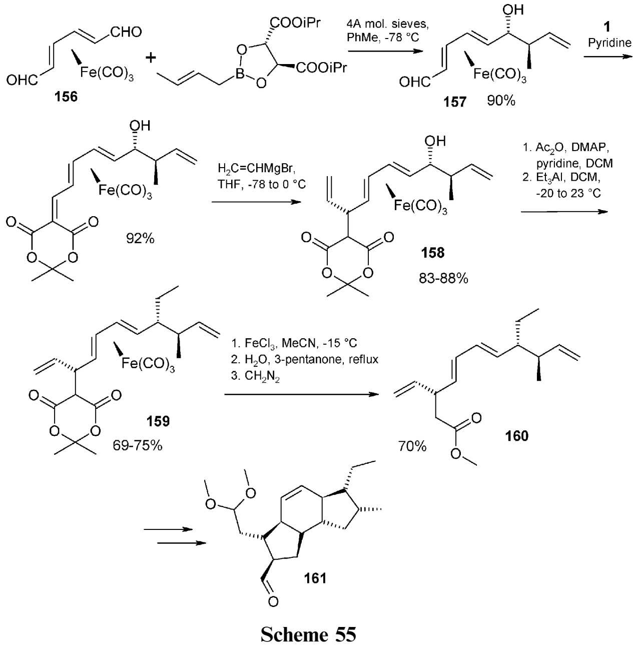


Scheme 54

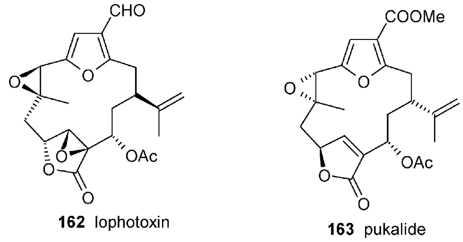
In a similar approach, Laabassi and Grée reported in 1988 a conjugate addition of Grignard reagent to a Meldrum's acid derivative used in the synthesis of (−)-verbenalol and (−)-epiverbenalol. The reaction proceeded stereospecifically due to facial desymmetrization of the molecule caused by complexation of $Fe(CO)_3$ to a diene fragment in the side chain.[127]

The macrocyclic terpenoids lophotoxin **162** and pukalide **163** (Scheme 56), with even more strongly marked structural complexity, are attractive targets for total synthesis because of their ability for selective irreversible binding to nicotinic acetylcholine receptors.[128]

Wipf and Soth accomplished the synthesis of the fully functionalized C_1–C_{18} segment **164** of lophotoxin and pukalide in 11 steps and 10% overall yield.[129] The synthetic plan was based on their previous work on the formation of 2-alkenylfurans by cyclization of α-propargyl-β-keto esters under palladium or base catalysis.[130] A carbodiimide-mediated acylation of Meldrum's acid with carboxylic acid **165**, followed by methanolysis,[131] provided the β-keto ester substrate **166**, necessary for the formation of the alkenyl furan system. Mono-alkylation of the sodium enolate of **166** with iodide **167** gave the intermediate **168** with all prerequisites for the palladium-catalyzed cyclization to the vinyl furan. After cyclization and conversion of the TMS group to methyl, (*E*)-**164** was obtained with high selectivity (*ca.* 15 : 1) (Scheme 57).



Scheme 55

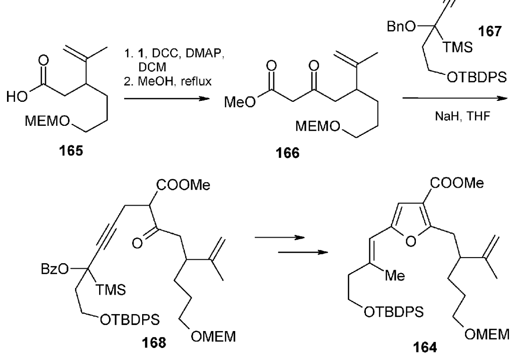


Scheme 56

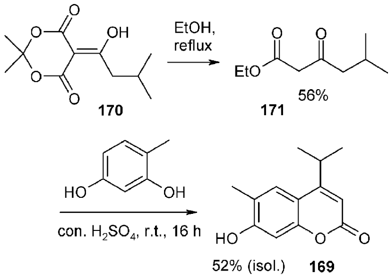
Coumarins are a class of naturally occurring benzopyrone derivatives, which are often found in green plants. The pharmacological and biochemical properties, and therapeutic applications of simple coumarins depend upon the pattern of substitution.[132] 7-Hydroxy-4-isopropyl-6-methylcoumarin **169** is a natural degraded bisnorsesquiterpene isolated from the fronds of *Macrothelypteris torresiana* Ching var. calvata Holtt (Thelypteridaceae).[133] In a short synthesis of this product, isobutyroyl Meldrum's acid **170** was first converted to ethyl isobutyroyl acetate **171** by refluxing in ethanol. Subsequent condensation with 2,4-dihydroxytoluene under acidic conditions afforded the target coumarin **169** (Scheme 58).[134]

6. Pyridine alkaloids

The structures of many natural products incorporate pyridine rings. An effective approach to the synthesis of substituted pyridines is based on an aza-Diels–Alder reaction. Renslo, Danheiser *et al.* reported a simple route to substituted pyridines based on [4 + 2]-cycloaddition of a reactive Meldrum's acid derived oximinosulfonate **172** to dienes (Scheme 59).[14,135] The reaction was found to be most effectively catalyzed by dimethylaluminium chloride in amounts of at least 2 equivalents, supporting the idea that the second equivalent of the Lewis acid promotes ionization of chloride from an initial 1 : 1 complex **173** of Me_2AlCl with oximinosulfonate **172**. This type of Lewis acid behavior is well documented.[136,137] Aromatization of the spiro-fused cycloadducts **174** was achieved by a combination of *N*-chlorosuccinimide (NCS) and sodium methoxide. Cleavage of the 1,3-dioxane-4,6-dione ring with concomitant elimination of acetone and carbon dioxide, followed by elimination of tosylate from the resulting ester enolate generated a dihydropyridine intermediate, which upon chlorination by NCS and elimination of HCl finally provided the desired picolinic esters **175**.



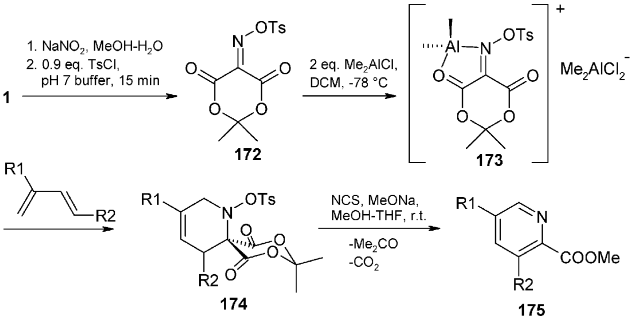
Scheme 57



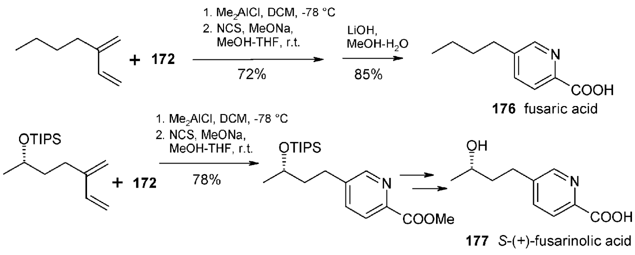
Scheme 58

Application of this approach to the construction of pyridine-containing natural products is demonstrated by the total syntheses of the two pyridine alkaloids, fusaric acid **176** and (*S*)-(+)-fusarinolic acid **177**.[135] Fusaric acid is a phytotoxin produced by several species of plant-pathogenic fungi of the genus *Fusarium*.[138] A related alkaloid, (*S*)-(+)-fusarinolic acid, has been isolated from *Gibberella fujikuroi*.[139] Scheme 60 outlines the key steps of these syntheses employing the aza-Diels–Alder methodology. Compounds **176** and **177** were obtained in four and six steps from the commercially available materials and in 35% and 33% overall yield, respectively.

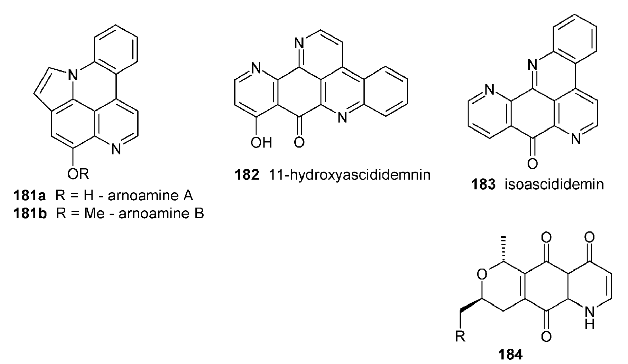
Arylaminomethylene Meldrum's acids are valuable intermediates in the synthesis of annulated pyridine-4-ones. An interesting two-step methodology for preparation of quinolin-4-ones from the corresponding anilines is based on a one-pot process involving Meldrum's acid, an aromatic amine and triethyl orthoformate. Thermal cyclization of the resulting *N*-arylaminomethylene derivatives of Meldrum's acid leads to formation of quinolin-4-one systems. This has been used in the syntheses of a number of pyridiacridine alkaloids. Illustrative is the total synthesis of meridine **178a** by Bontemps *et al.* with iterative application of the abovementioned methodology.[140] Meridine is a marine alkaloid, isolated from ascidian *Amphicarpa meridiana*.[141] The *peri*-fused ring of **178a** was constructed by reaction of an aromatic amine with ethoxymethylene Meldrum's acid **179**, generated from **1** and triethylorthoformate, producing arylaminomethylene malonate **180**, followed by thermal cyclization to quinolone **180b**. Repetitive application of this sequence on the last step of the synthesis furnished the pentacyclic core of meridine (Scheme 61). The 9% overall yield for this route to meridine constitutes a serious improvement over the previously reported route based on a hetero-Diels–Alder strategy.[142]



Scheme 59



Scheme 60



Scheme 62

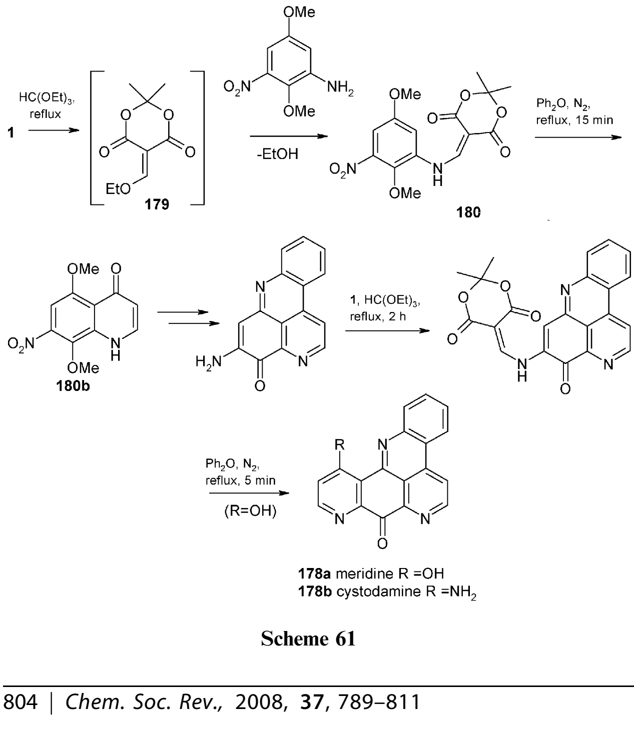
An analogous method for the conversion of anilines to the corresponding quinolones was reported in the synthesis of cystodamine **178b**,[143] pentacyclic alkaloids arnoamines A and B **181a** and **181b**,[144] 11-hydroxyascididemnin (an ascidian alkaloid isomeric to meridine) **182**,[145] and a non-natural alkaloid isoascididemin isomeric to ascididemin **183**.[146] Also, aza-analogs of benzisochromanequinone antibiotics **184** have been synthesized by this method (Scheme 62).[147] Interestingly, compounds **184** are inaccessible by the alternative azadiene approach, previously employed for the synthesis of other azabenzisochromanequinone compounds.[148]

Isoschizogamine **185**, a member of the schizozygane family of indole alkaloids, was recently isolated by Hájíček and coworkers from the shrub *Schizozygia caffaeoides*.[149,150] Isoschizogamine has a hexacyclic ring system with an aminal motif. A total synthesis of this molecule has been reported by Hubbs and Heathcock.[151] Scrutiny of the isoschizogamine structure led to the idea that the aminal group could result from an intramolecular addition of an arylamine to the double bond of an enamide group, activated by *C*-protonation. The tricyclic synthon **186** was supposed to emanate from the cyclocondensation of imine **187** and an α,β-unsaturated acid or its derivative **188** (Scheme 63).

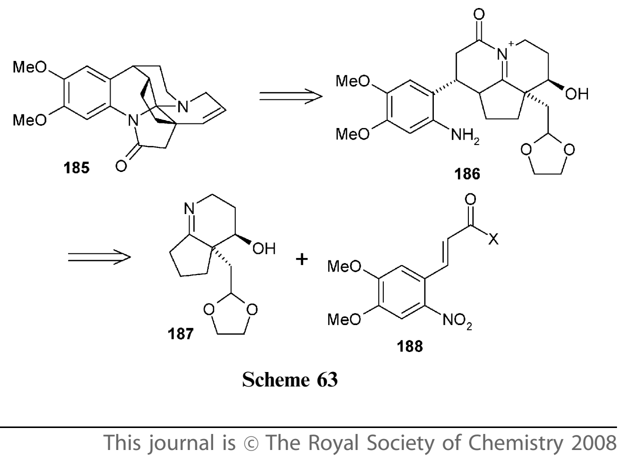
Experimentations with an α,β-unsaturated acid and its activated derivatives in reactions with imine **187** did not lead to the desired product **186**. This prompted attempts to try an arylmethylene derivative of Meldrum's acid **189** as a Michael acceptor in this reaction because such compounds are known as excellent Michael acceptors and the products formed from the Michael addition are good acylating agents. Arylmethylene malonate **189** (accessible through Knoevenagel condensation of 2-nitroveratraldehyde with Meldrum's acid) was reacted with imine **187** to give an intermediate **190** that, upon heating, underwent cyclization to give a mixture of diastereomeric lactams **191** and **192** in the ratio of 88 : 12 and in high yield. Diastereomer **191** on dehydration with Martin's sulfurane and reduction of the nitro group afforded amine **193**. The lactam carbonyl was reduced with $LiAlH_4$ and the product cyclized to **194** upon workup (Scheme 64). Further transformations of **194** led to (±)-isoschizogamine **185**.

Kobayashi *et al.* reported the isolation of the *Lycopodium* alkaloids cermizine C **195** from the club moss *Lycopodium cernuum* and a related alkaloid senepodine G **196** from the club moss *Lycopodium chinense*.[152] Very recently Snider and Grabowski have accomplished the syntheses of both alkaloids along with their epimers.[153] Retrosynthetic analysis identified lactam **197** as a possible precursor of both senepodine G and cermizine C, and two approaches (***A*** and ***B***) to this synthon have been considered (Scheme 65). Route ***A*** is based on a directed conjugate reduction of unsaturated Meldrum's acid derivative **198** to **199**, which could cyclize to lactam **197**. An alternative route ***B*** was based on the stereoselective conjugate addition of a lithium organocuprate to α,β-unsaturated lactam **200**.

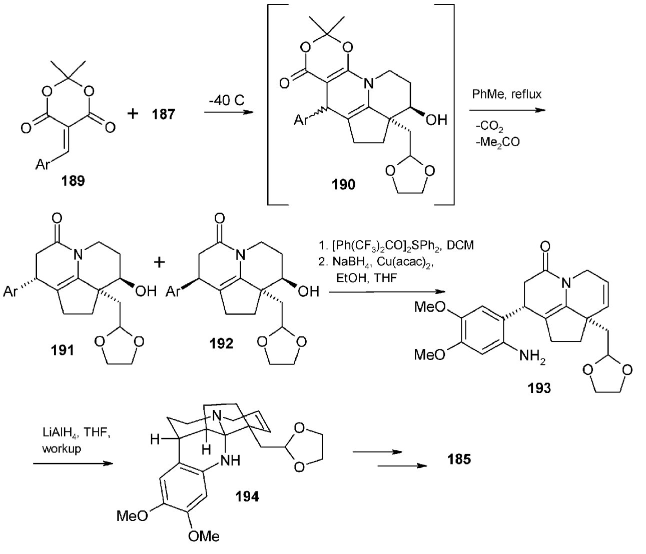
Reaction of (±)-pelletierine **201**, neutralized as its acetate salt, with Meldrum's acid did not stop on the formation of the Knoevenagel condensation product **202**, and led to the β,γ-



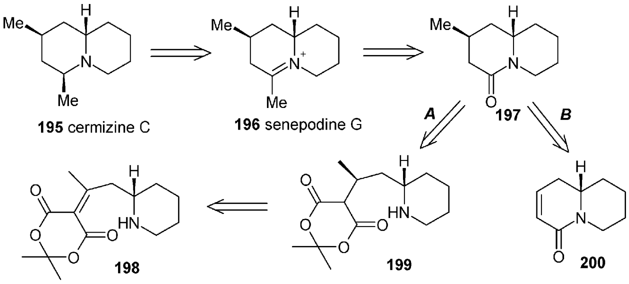
Scheme 61



Scheme 63



Scheme 64



Scheme 65

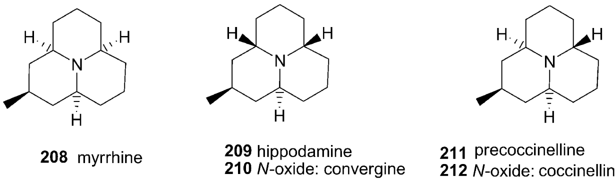
unsaturated lactam **203**. Equilibration of this compound in methanolic K_2CO_3 afforded a 3 : 1 mixture of α,β-unsaturated lactam **204** and β,γ-unsaturated lactam **203**. Hydrogenation of either **204** or the 3 : 1 mixture of **204** and **203** under different conditions afforded a 16 : 1 mixture of lactams **205** and **197**. Addition of methylmagnesium bromide, followed by treatment with methanolic HCl, led to (±)-7-*epi*-senepodine G **206** in quantitative yield. Reduction of **206** with sodium borohydride in methanol occurred stereospecifically by axial attack from the less hindered top face to give (±)-5-*epi*-cermizine C **207** (Scheme 66). Since the attempts to isolate the intermediate **202** failed, it was impossible to explore the directed conjugate reduction of this intermediate to **199**. Accordingly, cermizine C and senepodine G have been synthesized *via* the alternative approach ***B*** (Scheme 65).

β-Enamino esters are versatile synthons in the synthesis of many alkaloids such as camptothecin,[154] (±)-lupinine,[155] (±)-isoretronecanol and (±)-trachelanthamidine.[156] A convenient and well-established procedure for the preparation of cyclic β-enamino esters consists of two steps: nickel acetoacetate catalyzed condensation of lactim ethers with Meldrum's acid and alcoholysis of the resulting malonates.[157] Recently β-enamino ester intermediates have been effectively used for the synthesis of azaphenalene alkaloids.[158]

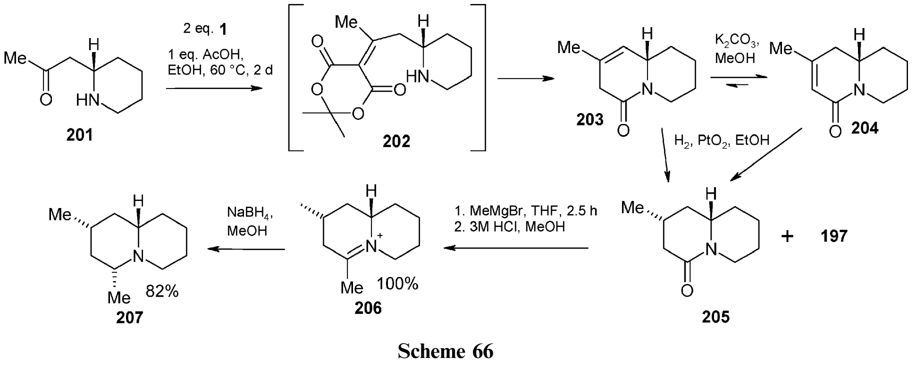
Ladybird beetles (Coccinellidae) use a reflex bleeding mechanism to protect themselves from their natural predators. In a defensive mode, they release an orange fluid from their joints that contains a mixture of alkaloids with azaphenalene structures: myrrhine **208**, hippodamine **209**, convergine **210**, precoccinelline **211** and coccinelline **212** (Scheme 67).[159]

Hsung and Gerasyuto have developed an efficient intramolecular aza-[3 + 3]-annulation reaction employing vinylogous amides tethered with α,β-unsaturated iminium salts and successfully applied this strategy to the total syntheses of gephyrotoxin, tangutorine, deplancheine, and cylindricine C. Recently, they extended this principle to the total synthesis of Coccinellidae alkaloids **208**–**212** (Scheme 68).[158]

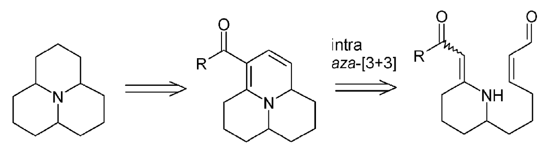
In order to estimate the stereochemical outcome of the strategic aza-[3 + 3]-annulation, a model study was carried out (Scheme 69). A nickel acetylacetonate catalyzed condensation of Meldrum's acid with lactim ether **213a** or lactim thioether **213b** led to the corresponding methylene derivatives **214a,b**, which were converted to the cyclic enamino ester **215** on treatment with sodium methylate. The Swern-type oxidation using pyridine sulfotrioxide–dimethyl sulfoxide[160] provided the desired unsaturated aldehyde **216** with *Z*-geometry. Piperidinium trifluoroacetate mediated the cyclization of enal **216** to the unstable azaphenalene product **217**, which was



Scheme 67



Scheme 66



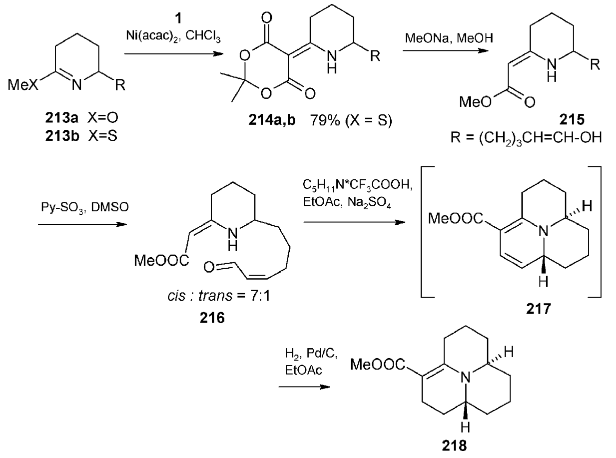
Scheme 68

hydrogenated to **218**. The stereochemistry of the product was that required for precoccinelline and hippodamine.

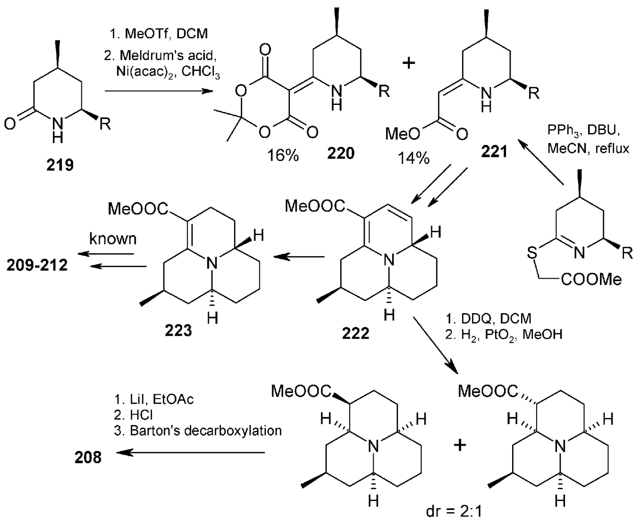
When transferring the results obtained from the model study to the actual synthesis of Coccinellidae alkaloids, the reaction of Meldrum's acid with the lactim ether prepared from **219** gave a low yield of the desired methylene derivative **220** along with a small amount of the corresponding cyclic enamino ester **221**, formed *via* a ring-opening of the 1,3-dioxanedione ring with methanol, generated during the condensation reaction, followed by decarboxylation (Scheme 70). This prompted synthesis of the key intermediate **222** by an Eschenmoser sulfide contraction reaction. Compound **222** was reduced to **223**. Stereodivergent conversions of **223** to Coccinellidae alkaloids **209**–**212** have been disclosed earlier.[161] In order to provide the stereochemistry required for the synthesis of myrrhine, the configuration of the stereogenic center of the intermediate **222** was inverted by aromatization–reduction of the dihydropyridine ring. Saponification of the ester group and a Barton decarboxylation concluded the total synthesis of myrrhine. Thus, all the five alkaloids of the 2-methylperhydro-9b-azaphenalene family shared the same intermediate **222** in their synthesis.

7. Other classes of natural products

It was Danishefsky who discovered the enormous reactivity of cyclic acylal **12a** towards a variety of nucleophiles. The cyclopropane ring-opening reaction of **12a** with piperidine proceeded at room temperature with nearly quantitative yield to afford betaine **224** (Scheme 71). Analogous reaction between piperidine and the non-spirocyclic diethyl ester analog **225** was achieved only at 105 °C. The facility of the ring-opening reactions of compound **12a** was attributed to enhanced stabilization provided by the conformationally constrained cyclic acylal system for the anionic leaving group. This phenomenon was called "spiroactivation".



Scheme 69



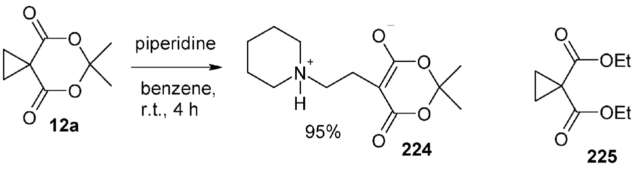
Scheme 70

Even more interesting is the behaviour of spiroactivated vinyl cyclopropane **12b** in reaction with nucleophilic agents. The reaction proceeds as a clear 1,5-homoconjugate addition at the substituted position in the cyclopropyl ring. At the same time, the diester analog **226** was susceptible to nucleophilic attack in both the 1,5- and 1,7-modes (Scheme 72).[16–18]

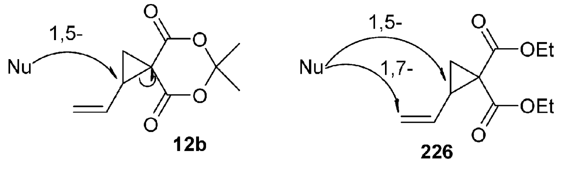
The phenomenon of the selective homoconjugate addition reaction of spiroactivated vinylcyclopropane **12b** with various nucleophiles has found application in the synthesis of natural products.

An unusual pyrroloquinoline system, previously unobserved in natural products, was found in alkaloids of *Martinell iquitosensis*. Martinellic acid **227a** and martinelline **227b** (Scheme 73) have been isolated from the roots of *M. iquitosensis* in 1995. These compounds, containing a pyrroloquinoline ring system with multiple guanidine side chains, were found to be non-peptide antagonists of the bradykinin B_1 and B_2 receptors.[162]

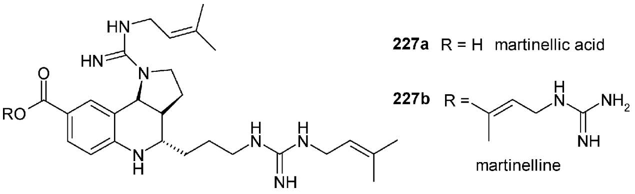
Snider and co-workers have reported the total synthesis of (±)-martinellic acid (Scheme 74).[163] Reaction of aniline **228** with Meldrum's acid-activated vinylcyclopropane **12b** afforded the vinylpyrrolidinone derivative **229** in a one-pot sequence involving addition of the aniline to the allylic cyclopropane carbon, cyclization with the loss of an acetone molecule, and decarboxylation. After the oxidation of benzylic alcohol **229** to the corresponding aldehyde, the pyrroloquinoline core of martinellic acid was efficiently constructed through an azomethine ylide [3 + 2] dipolar cycloaddition.[164] This one-pot reaction involved the steps of condensation of the aldehyde with *N*-benzylglycine, decarboxylation of the



Scheme 71



Scheme 72

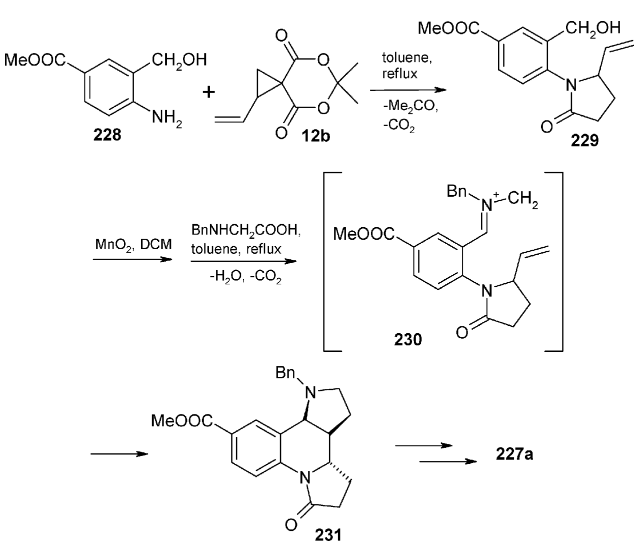


Scheme 73

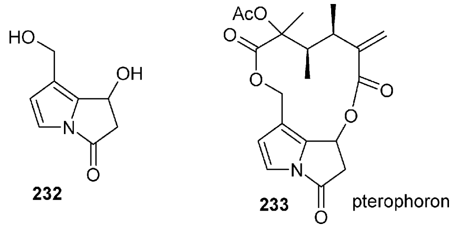
iminium intermediate, and cycloaddition of azomethine ylide **230** to the double bond. The dipyrroloquinoline **231** of the desired *cis*, *anti* configuration was obtained in good yield along with a small amount of the undesired *cis*, *syn* product. Further transformations of intermediate **231** resulted in the successful total synthesis of (±)-martinellic acid.

5,7-Didehydroheliotridin-3-one unit **232** is incorporated in several pyrrolizidine alkaloids such as pterophoron **233** (Scheme 75).[165]

Compound **232** has been synthesized by McNab and Thornley in six steps and 20% overall yield starting from 4-acetoxymethylpyridine-*N*-oxide (Scheme 76).[166] The formylpyrrole **234** was coupled with Meldrum's acid and the product **235** was subjected to flash vacuum pyrolysis (FVP) for cyclization.[167] Deprotection of the acetyl group in **236** was complicated by lactam ring opening, and the pyrrolizidine system was regenerated by a repeated FVP of *Z*-propenoate **237**. Due to resistance of the pyrrolizin-3-one system to conjugate addition of hard nucleophiles, such as OH^-, the hydroxyl had to be introduced into position 6 through electrophilic addition of hydrogen chloride followed by hydrolysis.



Scheme 74



Scheme 75

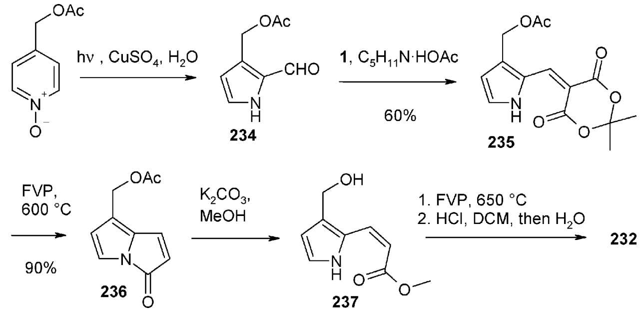
The 3-hydroxyisoxazole unit is a constituent of a number of naturally occurring and synthetic bioactive compounds. The alkaloids muscimol **238** and ibotenic acid **239** (Scheme 77) are constituents of the mushroom *Amanita muscaria*.[168] Muscimol is a potent selective agonist for one of the brain's primary neurotransmitters $GABA_A$.[169] Ibotenic acid, structurally similar to glutamate, interacts non-selectively with all types of (*S*)-glutamate receptors.[170]

Despite the importance of the 3-hydroxyisoxazole pharmacophore for biomedical research, the existing routes to 3-hydroxyisoxazoles normally required multi-step and low-yielding sequences. The most commonly used method for synthesis of 3-hydroxyisoxazoles is based on cyclization of β-keto esters with hydroxylamine. A considerable drawback of this method is the formation of substantial amounts of isoxazol-5-ones as byproducts due to the competitive reaction of hydroxylamine at the keto group (Scheme 78).[171] Although application of β-keto esters protected as acetals allowed the preparation of the 5-methyl derivative,[172] it was found to be highly dependent on the nature of the α- and β-substituents in the β-keto ester.[173]

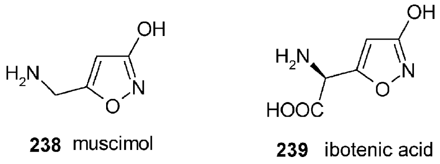
Krogsgaard-Larsen and co-workers proposed a novel and efficient approach to 5-substituted 3-hydroxyisoxazoles **240**.[174] Acyl malonates **241** reacted with *N*,*O*-di-Boc-hydroxylamine to give the corresponding *N*,*O*-di-Boc hydroxamic acids **242**. These compounds upon treatment with concentrated HCl smoothly cyclized to the 5-substituted 3-hydroxyisoxazoles **240** in high yields (Scheme 79).

Isocoumarins are a class of natural products that often occur as microbial metabolites and that have been found to exhibit a wide range of biological effects.[175] Thus, the naturally occurring cytogenin **243** and a synthetic isocoumarin NM-3 **244** (Scheme 80) were found to display anti-angiogenic effects in the mouse dorsal air sac assay system.[176]

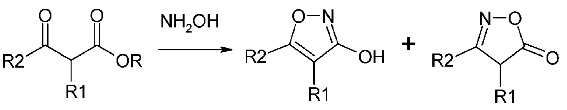
Taylor and co-workers reported the synthesis of NM-3 and other anti-angiogenic isocoumarins **245**, structurally related to



Scheme 76



Scheme 77

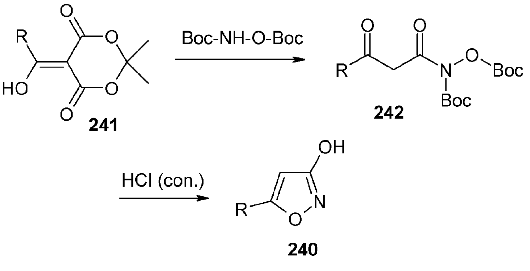


Scheme 78

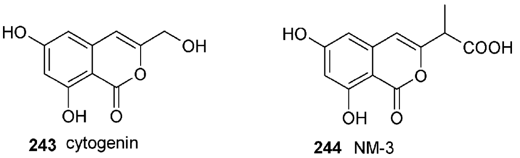
cytogenin using a Meldrum's acid derived precursor.[177] The homophthalic acid **246** was coupled with Meldrum's acid in the presence of DCC, and the crude product was heated with *tert*-butyl alcohol to yield the β-keto ester **247**. Base-catalyzed cyclization furnished the isocoumarin ring system **248** (Scheme 81).

The β-lactam ring is a common structural motif in several antibiotic families, principally the penicillins, cephalosporins, carbapenems and monobactams. Almqvist and co-workers attempted to assemble a bicyclic β-lactam framework directly by a Staudinger cycloaddition of acylketenes, generated from acyl Meldrum's acids, to an optically active Δ^2-thiazoline **249** under acidic conditions. After structure elucidation of the products it was found that the reaction gave rise to chiral 1,3-oxazinones **250**, not the 6-acylpenams **251** as was initially reported (Scheme 82).[178,179]

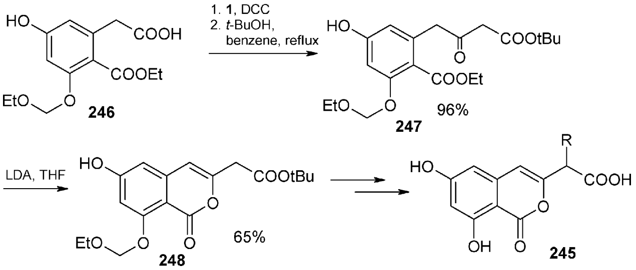
Successful construction of the carbapenem framework with the use of a Meldrum's acid precursor is exemplified by the classical total synthesis of racemic thienamycin **255**, a broad-spectrum antibiotic.[180] Reported in 1980 by the scientists from Merck, it is based on the readily available 1,3-acetonedicarboxylate and represents a very practical (more than 10% overall yield), adaptable to commercial scale production and preparation of chemical analogs route to the target compound (Scheme 83). The important feature of the synthetic strategy applied is that the unstable carbapenem framework is constructed in a late stage of the synthesis.[181] The acetic acid side chain in the β-lactam **252** was converted to the corresponding imidazolide to acylate the conjugate base of Meldrum's acid. Reaction of the acyl Meldrum's acid **253** with *p*-nitrobenzyl alcohol yielded *p*-nitrobenzyl β-keto ester **254**, which was used for the assembly of the carbapenem system of thienamycin **255**.



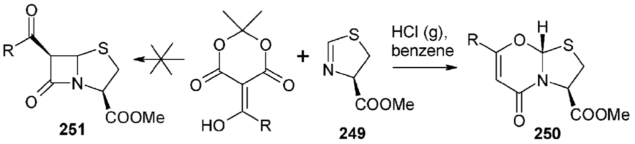
Scheme 79



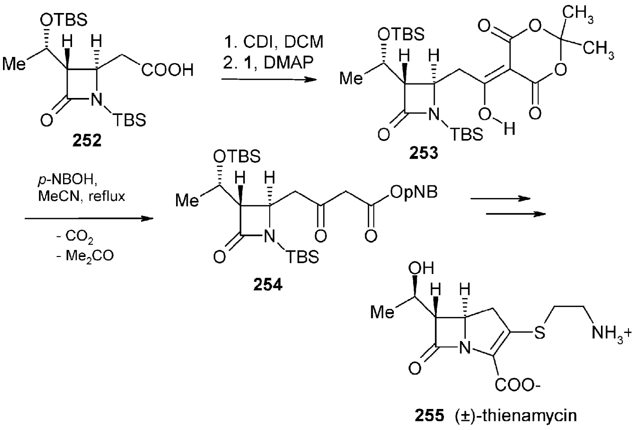
Scheme 80



Scheme 81



Scheme 82



Scheme 83

8. Conclusion

The natural environment continues to be an abundant source of biologically active and structurally diverse compounds. The mounting demand for new leads in medicinal chemistry stimulates research in the field of natural product chemistry. Total syntheses of such substances not only provide sufficient amounts of material for biological studies, but also result in novel synthetic methods and strategies. Due to their unique reactivity, Meldrum's acid and its derivatives have proven to be valuable reagents and intermediates in the synthesis of complex organic compounds such as natural products and their analogs. The ability of acyl derivatives of Meldrum's acid to generate acylketene species under pyrolysis conditions is the most fruitful field of their applications. For example, β-keto thioesters, easily accessible from reaction of thiols with acyl

Meldrum's acids, can be regarded as analogs of acyl-SCoA and exploited in biomimetic syntheses of polyketide derived natural products. As demonstrated in the present review, cyclic acylals have a potential for application in stereoselective synthesis of complex organic molecules. Another direction in their chemistry is the development of novel multicomponent and domino reactions, producing variously substituted privileged scaffolds. These reactions, along with Meldrum's acid based solid phase syntheses, are ideally suited for parallel and combinatorial processing. Parallelization techniques provide easy exploration of the chemical space around the biologically active scaffolds, enabling generation of "natural product-like" libraries for biological screening and SAR studies.

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