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Natural and synthetic 2*H*-pyran-2-ones and their versatility in organic synthesis☆

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1. Introduction

The pyran ring system is widely present in the animal and plant kingdom and possesses diverse pharmacological activities. Pyran is a six-membered oxygen heterocycle with two double bonds. Out of the five carbon atoms of the pyran ring, four are sp^2 carbons and one is sp^3 hybridised. The pyran ring is not a true aromatic ring. In the nomenclature of this ring system, the position of the sp^3 carbon is designated by adding H or, in other words, the use of the suffix H locates the positions of the double bonds. In structure **I** (Fig. 1), the carbon at position 2 is sp^3 and it is named as 2*H*-pyran. Similarly, in the case of the structure **II**, C-4 is the sp^3 carbon and it is designated as 4*H*-pyran. Partially reduced pyrans such as **III** and **IV** are always named using the suffix 2H. The structure **III** is named as 3,4-dihydro-2*H*-pyran and, similarly, structure **IV** as 5,6-dihydro-2*H*-pyran. The same terminology is followed when the sp^3 carbon is replaced by a carbonyl function in the structures **V** and **VI**. Thus, compounds **V** and **VI** are named as 2*H*-pyran-2-one and 4*H*-pyran-4-one as per the IUPAC convention. They are also named as 2-pyranone and 4-pyranone, respectively.

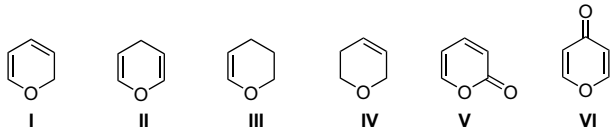
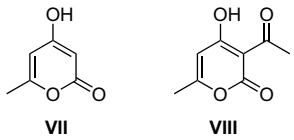


Figure 1.

In this review, we have restricted our efforts to compile the literature only to the aromatic 2*H*-pyran-2-one ring system present in an isolated form. We have not covered annulated 2*H*-pyran-2-ones like coumarins, chromones etc. Our intention is to provide an overview of the presence and significance of the 2*H*-pyran-2-one ring system found in various important natural products and their therapeutic importance. We have also covered various methodologies for the construction of 2*H*-pyran-2-ones together with their chemical reactivity due to the pyranone ring system and the substituents attached.

Compounds with the 2-pyranone ring system have been known for more than a century, but their versatility in organic synthesis to generate molecular diversity was recognised only after 1960. The presence of this ring system in plants, animals, marine organisms, bacteria, insects and its involvement in different biological processes such as defence against other organisms, biosynthetic intermediates and as metabolites have made this scaffold an important chemical entity. Many of the 2-pyranones have been used as precursors for the synthesis of pharmacologically active compounds such as HIV protease inhibitors,[1] antifungals,[2] cardiotonics,[3] anticonvulsants,[4] antimicrobials,[5] pheromones,[6] natural pigments,[7] antitumour agents,[8] and plant growth regulators.[9,10] Microbially derived 2-pyranones, obtained from fungi of various genera, are found to display a wide range of cytotoxic, neurotoxic and phytotoxic properties. Various pyranones such as triacetic acid lactone (**VII**) and tetraacetic acid lactone (**VIII**) (Fig. 2) have been used for the construction of various natural products of biological



VII VIII

Figure 2.

importance such as solanopyrones,[11] pheromones,[12] coumarins[13] and inhibitors of α-chymotrypsin,[14] and elastase enzymes.[15]

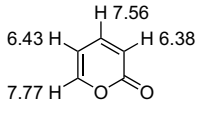
The 2-pyranone nucleus may be considered as a six-membered cyclic unsaturated ester that displays the physical and chemical characteristics of alkenes and arenes. Structurally, 2-pyranones closely resemble pyrylium salts, except that one of the methine carbons at C-2 or C-6 is replaced by a carbonyl function. The carbonyl oxygen in 2-pyranone (**V**) shows enhanced nucleophilicity and is methylated by trimethyloxonium tetrafluoroborate to give the pyrylium derivative.[16] The aromatic potential of 2-pyranones has been observed through their ease of electrophilic substitution such as nitration,[17] sulphonation[18] and halogenation.[19] The aliphatic character of 2-pyranones has been demonstrated through Diels–Alder reactions, functioning as dienes and dienophiles.

2. Characteristics of 2-pyranones

The structures of 2-pyranones have been assigned by UV, IR and NMR spectroscopy. The UV spectrum of unsubstituted 2-pyranone shows two characteristic absorption[20] peaks at 216 and 289 nm. The presence of chromophoric groups in the pyranone ring greatly influences the UV absorption. In contrast, the isomeric counter part 4-pyranone absorbs[21] at 246 and 260 nm. The wide difference in the UV absorption peaks of 2-pyranones and 4-pyranones helps in distinguishing both of the isomeric products.

The characteristic peak in the IR spectrum for the C=O stretching frequency[22] for 2-pyranones appears at 1730–1704 cm^{-1} and is sometime accompanied by less intense peaks at higher frequency[23] (1770–1740 cm^{-1}). The presence of functional groups in the pyran ring causes red or blue shifts in the IR absorption frequency, depending upon the nature and position of the substituent. The IR spectra of 5- and 6-formyl-2*H*-pyran-2-ones show a band at 1765–1745 cm^{-1} which has been assigned to the formyl group absorption. The unusually high stretching frequency has been attributed to a tightening of the bond due to the positive nature of the pyranone ring due to resonance. The IR spectra of 4-pyranones show absorption at ~ 1667 cm^{-1} in contrast to ~1730 cm^{-1} for 2-pyranones. This difference in IR frequency is possibly due to the stronger basicity of 4-pyranones. Substituents in 4-pyranones have little effect on the IR absorption maxima.

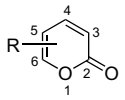
The proton NMR spectrum of unsubstituted 2-pyranone (**V**) (Fig. 3) shows two complex multiplets,[24] of equal intensity, at δ 6.38 and 6.43 ppm due to the C-3 and C-5 protons, and two others at δ 7.56 and 7.77 ppm for the C-4 and C-6 protons, respectively. The coupling constants for the C-3, C-4 protons (J=9.4 Hz), C-4, C-5 protons (J=6.3 Hz) and C-5, C-6 protons (J=5.0 Hz) have been reported.[24] The proton NMR spectra of different 3-halo-substituted-2*H*-pyran-2-ones[25] (**IX**–**XI**, Table 1) revealed no significant changes in the chemical shifts of the H-4, H-5 and H-6 protons, except an upfield shift of the H-4 proton (6.52 ppm) and a downfield shift of the H-6 proton (7.95 ppm) of 3-iodo-2*H*-pyran-2-one (**XI**), due to the influence of the iodo substituent at position 3 of the pyranone ring.



V

Figure 3.

Table 1
Chemical shifts (ppm) of ring protons and carbons in the ^1H and ^{13}C NMR of substituted 2*H*-pyran-2-ones[25,26] in $CDCl_3$



Entry	Compd (R)	^1H NMR				^{13}C NMR				
		H-3	H-4	H-5	H-6	C-2	C-3	C-4	C-5	C-6
IX	3-Cl	—	7.47	6.23	7.48	158.9	123.8	140.3	106.1	150.6
X	3-Br	—	7.51	6.15	7.69	158.0	112.6	144.0	106.5	150.1
XI	3-I	—	6.52	6.01	7.95	158.6	86.8	151.6	107.3	152.0
XII	4-Cl	6.41	—	6.29	7.45	160.1	114.8	150.8	108.9	151.3
XIII	4-Br	6.65	—	6.40	7.37	159.7	118.6	140.0	111.1	150.7
XIV	4-I	6.95	—	6.53	7.21	158.9	125.9	113.7	115.5	149.9
XV	5-Cl	6.30	7.34	—	7.59	159.9	118.0	146.4	101.2	150.1
XVI	5-Br	6.31	7.38	—	7.62	159.3	117.4	145.9	100.7	149.6
XVII	5-I	6.22	7.38	—	7.62	159.3	118.3	149.7	67.6	153.3

In the case of 4-halo-substituted-2*H*-pyran-2-ones (**XII**–**XIV**), the chemical shifts of the H-3 and H-5 protons increased, while that for the H-6 proton decreased with descending order of electronegativity. In the case of 5-halo-substituted-2*H*-pyran-2-ones, virtually no change in the chemical shifts of the H-3, H-4 and H-6 protons was observed.

A ^{13}C NMR study[25,26] of the 3-, 4- and 5-halo-2*H*-pyran-2-ones (**IX**–**XVII**, Table 1) indicated that the C-4 and C-6 carbons resonate downfield, compared to the C-3 and C-5 carbons, but there is virtually no effect of halogen substituents on the chemical shift of the C-2 carbon, as evident from the ^{13}C NMR data for some 2-pyranones. The presence of an iodo substituent greatly influenced the chemical shift of the carbon to which it is attached and caused it to resonate upfield, due to its shielding effect (**XI**, **XIV**, **XVII**), otherwise there is no major change in the resonances of the other carbons. For example, the C-3 carbon of 3-iodo-2*H*-pyran-2-one **XI** resonates upfield at δ 86.8 ppm, compared to its chloro- (**IX**, 123.8 ppm) and bromo- (**X**, 112.6 ppm) derivatives. Similarly, in the case of 4-halo-substituted-2*H*-pyran-2-ones, the C-4 carbon of iodo-substituted lactone (**XIV**) resonated upfield at δ 113.7, compared to its chloro- (**XII**, 150.8 ppm) and bromo- (**XIII**, 140.0 ppm) counterparts. A decrease in the chemical shifts of the carbons of 4-halo-2*H*-pyran-2-ones (**XII**–**XIV**) for the C-4 carbon and a marginal increase in those for the C-3 and C-5 carbons are directly related to the electronegativity of the halogen substituent.

The mass spectrum[26c] of methyl 4-methylsulfanyl-6-(2-thienyl)-2*H*-pyran-2-one-3-carboxylate (**XVIII**), depicted in Figure 4, shows three major peaks with the molecular ion peak at m/z 282 of high abundance. A loss of carbon monoxide from the molecular ion produces a fragment corresponding to $[C_{11}H_{10}O_3S_2]^{+\bullet}$ at m/z 254. A peak of medium intensity at m/z 223 has been observed, due to loss of a methoxy radical, and further loss of cyclopropenium ketene shows a peak at m/z 111 for thienyl carbonyl cation. This cation with loss of CO gives a peak of low intensity at m/z 83 for the thienyl cation. Other peaks at m/z 267 and m/z 251 are found, due to loss of methyl and methoxy radicals, respectively. The latter peak with loss of CO shows a peak at m/z 223.

3. Naturally occurring 2-pyranones of therapeutic importance

Nature is a phenomenal source of biologically relevant simple and complex molecules, which are transformed in a combinatorial fashion through various regio- and stereoselective enzymatic reactions. This section will cover the therapeutically important wide range of 2*H*-pyran-2-ones isolated from an eclectic array of natural sources.

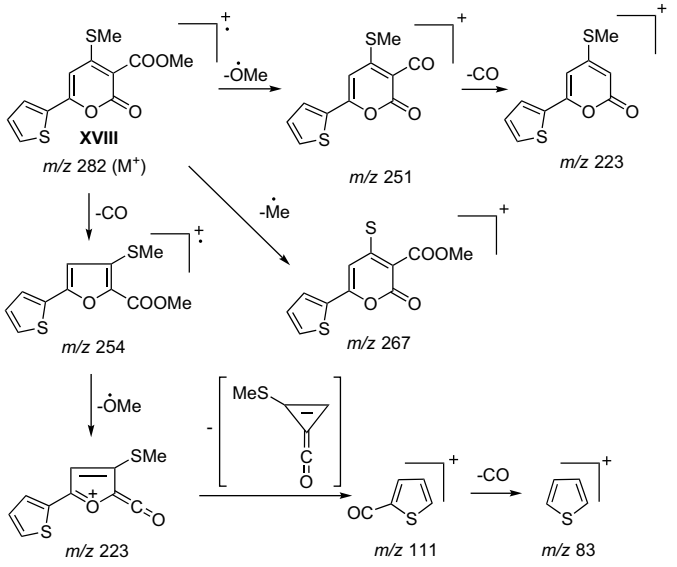


Figure 4. Mass fragmentation of substituted 2-pyranone.

3.1. Bufadienolides from plant origin

The bufadienolide class of compounds constitutes the core skeleton of structurally unique 2-pyranone natural products[27] in which a steroid moiety is attached at position five of the lactone ring, e.g., bufalin (**1**) (Fig. 5). This class of compounds is widely used in traditional remedies for the treatment of several ailments, such as infections, rheumatism, inflammation and disorders associated with the central nervous system.[28,29] On the contrary, bufadienolide glycosides represent a vital cause of mortality among cattle due to cardiac poisoning.[30,31] An extensive coverage of the bufadienolide class of pyran-2-ones has appeared, covering the progress made up to 1997 on their isolation, characterisation and biological activities.[32] In this review article, we provide an overview of bufadienolides that covers the majority of the natural products reported until 2005.

The plants belonging to the Crassulaceae and Hyacinthaceae families are rich sources of bufadienolides, which show conservity in the lactone scaffold and diversity in the steroid ring skeleton. Other plant families such as Iridaceae, Melianthaceae, Ranunculaceae and Santalaceae are also sources of the bufadienolide class of compounds. Several of the bufadienolides isolated from species of the *Kalanchoe* (syn. *Bryophyllum*), *Tylecodon* and *Cotyledon* of the plant

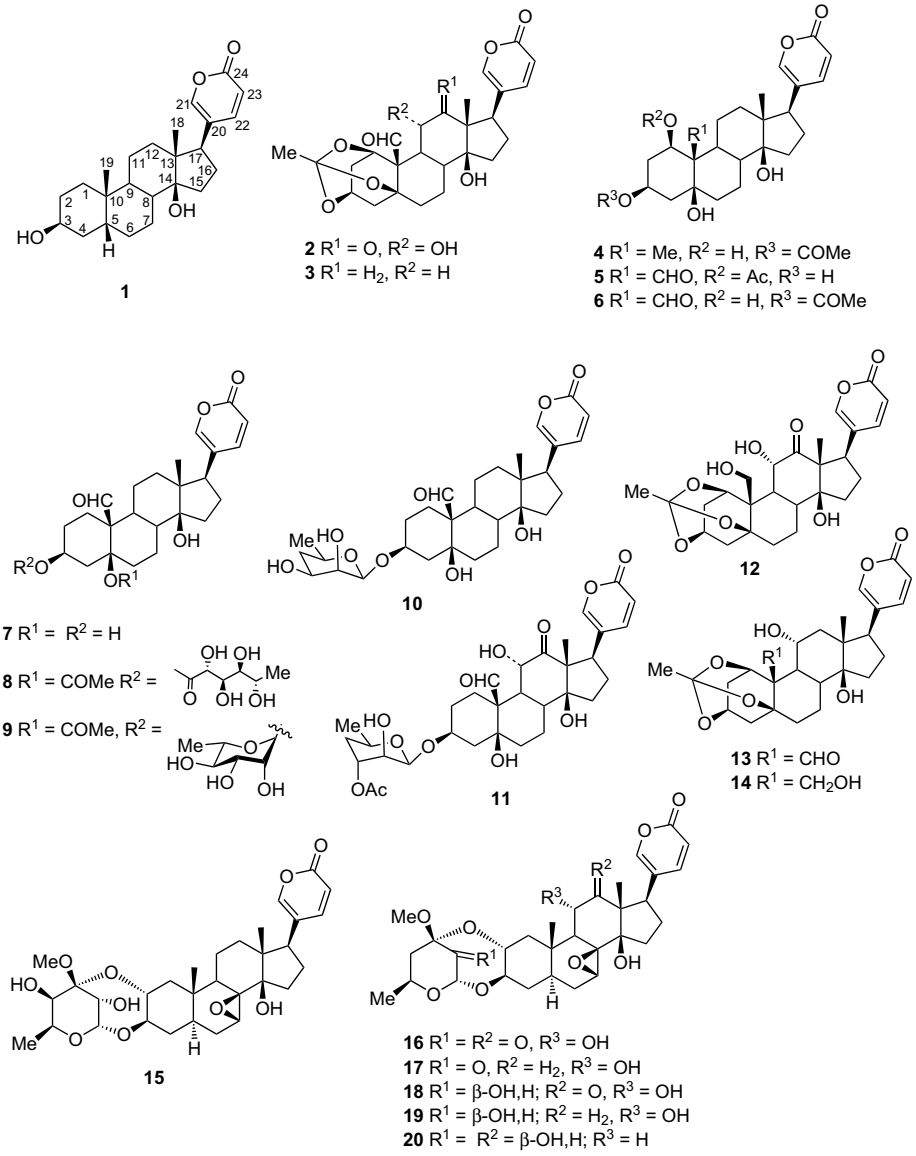
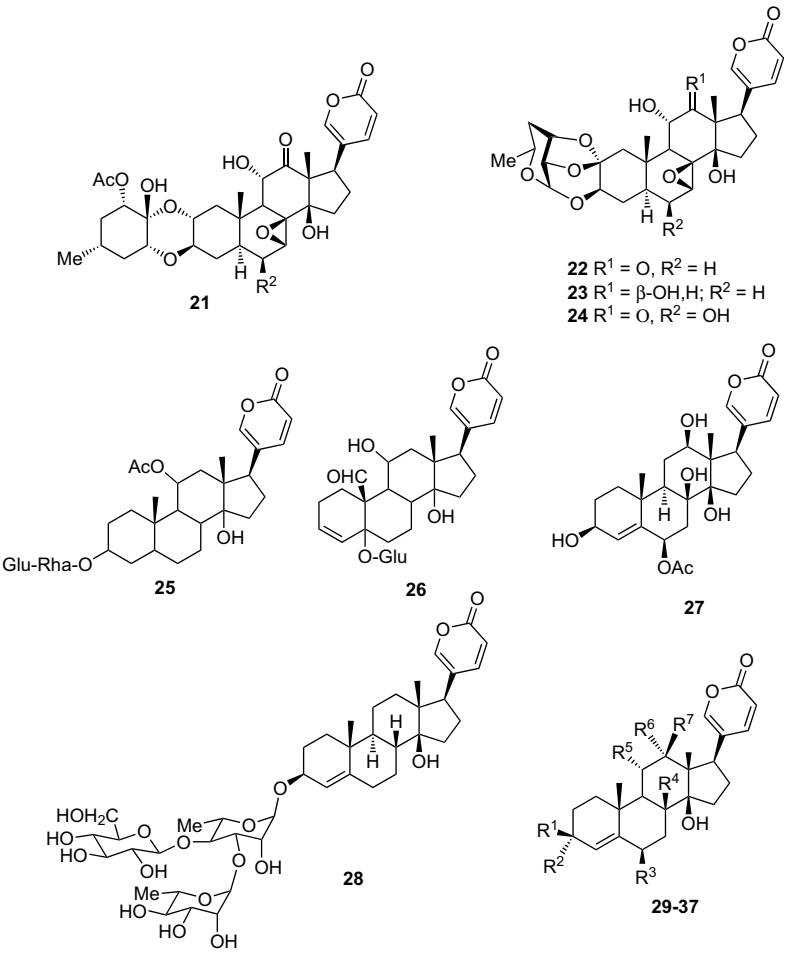


Figure 5.

family Crassulaceae cause acute and subacute intoxication affecting the central nervous system and muscular system and producing cardiac poisoning in small animals.[29,33] Numerous bufadienolides (Fig. 5) such as daigremontianin (**2**), bersaldegenin 1,3,5-orthoacetate[34] (**3**), 3-*O*-acetyldaigredorigenin (**4**), 1-*O*-acetylbersaldegenin (**5**) and 3-*O*-acetylbersaldegenin[34] (**6**) have been isolated from *Kalanchoe daigremontiana*,[35,36] and these are known to exhibit immunosuppressive effects in animal models. The toxic principles of *Kalanchoe lanceolata* have been ascribed to hellebrigenin (**7**), and a rare acyclic sugar derivative lanceotoxin A (**8**) and lanceotoxin B[37] (**9**). Several other bufadienolides, e.g kalanchoside[38] (**10**), bryotoxin A[39] (**11**), bryotoxin B[40] (**12**) and bryotoxin C (bryophyllin A)[40] (**13**), have been isolated from the extracts of *Kalanchoe tomentosa* and *Kalanchoe tubiflorum*. Recently, two insecticidal bufadienolides, bryophyllin A (**13**) and bryophyllin C (**14**), have been isolated from the leaf extracts of *Kalanchoe pinnata*, and these showed strong insecticidal activity against third instar larvae of the silkworm.[41] The major component of the active principles of *Tylecodon wallichii* was identified as cotyledoside[42] (**15**), which possesses a tetrahydropyran moiety linked with acetal bonds at the 1′ and 3′ positions of the sugar moiety. Several of the tyledoside metabolites, such as tyledoside A[43] (**16**), B (**17**), C (**21**), D (**18**), F (**19**) and G (**20**), have been isolated from *Tylecodon grandiflorus*,[44] and these are derived from 3-oxo-carbohydrates, except tyledoside C (Fig. 6). The active principles



	R1	R2	R3	R4	R5	R6	R7
29	H	OMe	H	H	H	H	OH
30	=O	-	H	H	OH	H	H
31	H	OH	H	H	OH	H	H
32	O-β-D-Glc	H	OAc	H	H	H	H
33	O-α-L-Rha$^{4\text{-}1}$β-D-Glc	H	OAc	H	H	H	H
34	O-α-L-Rha$^{4\text{-}1}$α-L-Rha	H	H	OH	H	H	H
35	O-α-L-Rha$^{4\text{-}1}$β-D-Glc	H	OAc	OH	H	H	H
36	O-3'-O-Ac-α-L-Rha$^{4\text{-}1}$β-D-Glc	H	H	H	H	H	H
37	O-2'-O-Ac-α-L-Rha$^{4\text{-}1}$β-D-Glc	H	H	H	H	H	H

Figure 6.

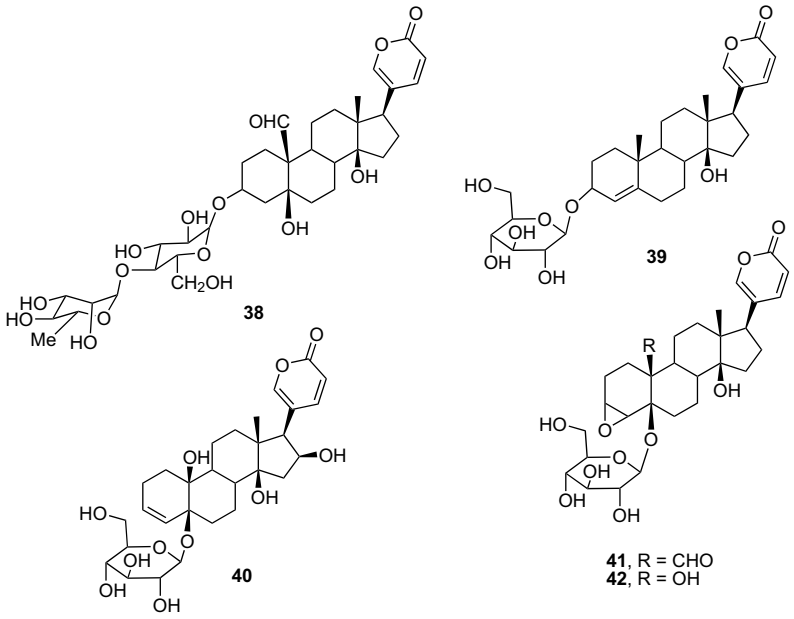


Figure 7.

of *Cotyledon orbiculata* have been isolated and characterised as orbicuside A (**22**), orbicuside B (**23**) and orbicuside C (**24**), which possess a 4,6-dideoxy sugar moiety in their skeleton.[45]

Urginea is a heterogeneous, poorly understood genus of the subfamily Urgineoideae of the Hyacinthaceae, which is phytochemically characterised by the ubiquitous presence of bufadienolides. Several of the bufadienolides have been isolated from various species of *Urginea* including *Urginea maritima*, which is commonly known as squill.[46] Recently, two new bufadienolides, 11α-acetylgamabufotalin 3-*O*-(4-*O*-β-D-glucosyl)-α-L-rhamnoside (**25**) and 11α-hydroxyscilliglaucoside (**26**), have been isolated from bulbs of the hexaploid *U. maritima* (Fig. 6).[47]

Pohl et al.[48] have isolated two new bufadienolides, 12β-hydroxyscillirosidin (**27**) and urginin (**28**), from *Drimia robusta* and *Urginea altissima*, respectively. Recently, nine new bufadienolides[49] (Fig. 6, **29**–**37**) have also been isolated from the bulbs of *U. maritima* (Liliaceae).

Mimosa pudica Linn (Leguminoseae) (the so-called sensitive plant) is found throughout India and the root of this plant is being used in traditional remedies for the treatment of biliousness, leprosy, dysentery, asthma, and leucoderma, while the seeds are used as an effective emetic. A novel bufadienolide, hellebrigenin-3-*O*-α-L-rhamnopyranosyl-(1→4)-*O*-β-D-galactopyranoside (**38**), from the seeds of *M. pudica* Linn, has been isolated (Fig. 7) and characterised by Yadava and Yadav.[50] The plant *Millettia ovalifolia* is commonly known as Gauj and belongs to the natural order Leguminosae. The stems of this plant are reported to be poisonous and possess a new cardenolide, 4,5-dehydro-14-β-hydroxyscilladienolide-3-O-β-D-glucopyranoside[51] (**39**).

Three bufadienolides, hellebortin A (**40**), hellebortin B (**41**) and hellebortin C (**42**), have been isolated (Fig. 7) from methanol extracts of the seeds of *Helleborus torquatus*.[52] The structure and relative stereochemistry of these bufadienolides were determined unambiguously by comprehensive analyses of their 1D and 2D NMR data. The biological activity of hellebortin A as an ecdysteroid agonist has been assessed.

3.2. Bufadienolides from animal sources

The animal sources of bufadienolides include *Bufo* (toad), *Photinus* (fireflies) and *Rhabdophis* (snake), in which an abundance of bufadienolides has been found in some species of toad. A comprehensive review on the isolation of several of bufadienolides from animal sources up to 1997 has been compiled by Steyn and van Heerden,[32] and we now cover the recent findings in this area.

Bufadienolides are the major bioactive constituents of the traditional Chinese drug Ch'an Su, and these are major products of the skin secretions of local toads such as *Bufo gargarizans* Cantor or *Bufo melanostrictus* Schneider.[53,54] Several bufadienolides have been isolated from the bodies of toads of the genus *Bufo*. Five new cancer cell growth- inhibitory bufadienolides (Fig. 8), 3β-formyloxyresibufogenin (**43**), 19-oxobufalin (**44**), 19-oxodesacetylcinobufagin (**45**), 6α-hydroxycinobufagin (**46**) and 1β-hydroxybufalin (**47**), have been isolated from the Ch'an Su drug, which is used traditionally to treat heart failure and cancer.[55]

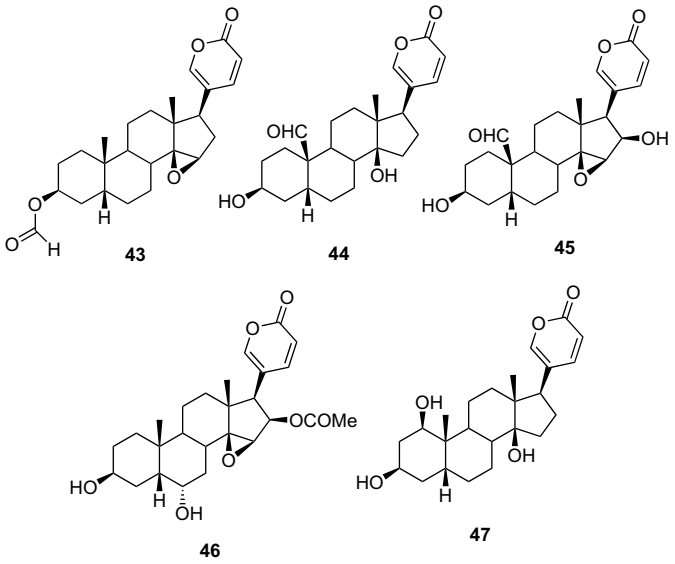


Figure 8.

Bufadienolides bearing epoxide substitution in the steroid nucleus, particularly at the C-14 and C-15 positions, are common, but bufadienolides bearing epoxide at the C-20 and C-21 positions are rare. Recently, five new 20,21-epoxybufenolides (Fig. 9),

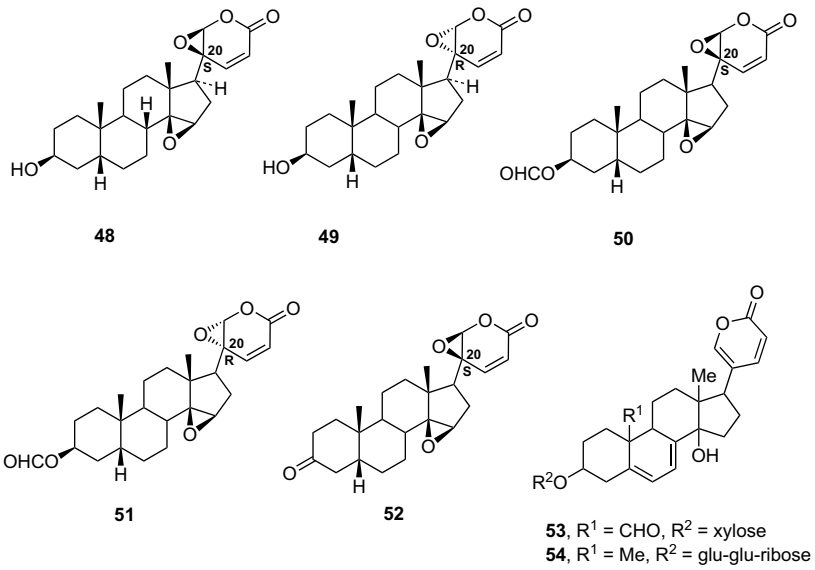


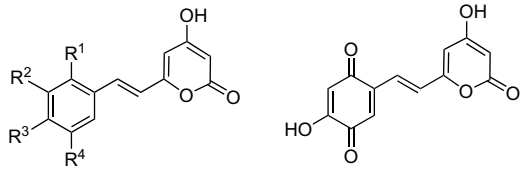
Figure 9.

20*S*,21-epoxyresibufogenin (**48**), 20*R*,21-epoxyresibufogenin (**49**), 3-*O*-formyl-20*S*,21-epoxyresibufogenin (**50**), 3-*O*-formyl-20*R*,21-epoxyresibufogenin (**51**) and 3-oxo-20*S*,21-epoxyresibufogenin (**52**), with the rarely encountered 17β-2-pyranone ring epoxide,[56] have been isolated from toad venom.

Some of the bufadienolide class of phytotoxins such as poaefusarin (**53**) and sporofusarin (**54**) (Fig. 9) have been isolated[57] from *Fusarium poae* and *Fusarium sporotrichiella*, respectively. The phytotoxic symptoms of these natural products include the death of branches of peas, beans, and tomatoes. In mammals, these phytotoxins caused temporary inflammation of skin, and haemorrhagic or leukocytosic reactions.[57]

3.3. Styryl-2-pyranones

Several naturally occurring 6-styryl-2-pyranones have been isolated from various plants of the genera *Piper*, *Aniba*, *Alpinia*, *Miliusa* and *Ranunculus*. A systematic study of the distribution of 6-styryl-2-pyranones and their derivatives has been made among the Strophariaceae and related genera.[58,59] Other sources of styryl-pyranones are from micro-organisms. Hispidin (**55**) (Fig. 10) has been isolated as a metabolite from various species such as *Polyporus hispidus*,[60,61] *Polyporus schweinitzii*, *Polyporus pomaceus*, *Polyporus igniarius* and *Gymnopilus* species. A hydroxystyryl-pyran-2-one, bisnoryangonin **56**, has been isolated from *Pholiota squarroso-adiposa*,[62] *Gymnopilus spectablis*[63] and *Gymnopilus decurrens*.[64] The hydroxylase enzyme from *P. hispidus* was isolated and shown to catalyse the hydroxylation of bisnoryangonin (**56**) to yield hispidin (**55**).[65,66] Other related metabolites such as leucohymenoquinone (**57**) and hymenoquinone (**58**) have been isolated from the fruit bodies of *Hymenochaete mougestii* (poriales).[67]



55, R^1= R^4 = H, R^2 = OH, R^3= OH,
56, R^1= R^4 = H, R^2 = H, R^3= OH
57, R^1= R^4 = H, R^2= H, R^3= OH

Figure 10.

A new polyhydroxystyryl-pyran-2-one derivative, phelligridin B (**59**), together with a new pyranopyrandione, have been isolated (Fig. 11) from the fruit bodies of the Chinese medicinal fungus *Phellinus igniarius*.[68a] Recently, a highly oxygenated and unsaturated 26-membered macrocyclic metabolite, phelligridimer A (**60**), has been isolated from the *n*-BuOH-soluble fraction of an ethanolic extract of the fruit bodies of *P. igniarius*.[68b] Phelligridimer A shows antioxidant activity with an IC_{50} value of 10.2 μM. The styryl derivative, 3,4-dimethoxy-6-styryl-pyran-2-one (**61**), has been isolated from the leaves and branches of the Chinese plant *Miliusa balansae* (Annonaceae), which is traditionally used for gastropathy and glomerulonephropathy.[69]

Two pyran-2-one kavalactones derivatives (**62** and **63**) have been reported (Fig. 11) from the root extracts of *Piper methysticum* (Kava Kava),[70] and two styrylpyran-2-ones (**64** and **65**) have been isolated from the trunk wood and bark of an *Aniba* species.[71]

Other synthetic and natural styrylpyrones include dihydro-5,6-dehydrokawain derivatives (**66** and **67**), which showed a reduction in the hypocotyl lengths of lettuce seedlings.[72] Two known styryl-pyran-2-ones, 5,6-dehydrokawain[73] (**62**), and 4′-hydroxy-5,6-dehydrokawain[74] (**68**), have been isolated from ethanolic extracts of the seeds of *Alpinia blepharocalyx*, and the latter (**68**) has shown significant antiproliferative activity against murine colon 26-L5 carcinoma (ED_{50}: 20.7 μM) and human HT-1080 fibrosarcoma (ED_{50}: 20.1 μM) cells.[75]

Two new dihydrostyrylpyrones (**70** and **71**) and a styrylpyrone (**72**), together with a known styrylpyrone (**69**), have been isolated from the ethyl acetate-soluble fraction of an aqueous ethanol (1:4) extract of the herb *Polygala sabulosa*,[76] which is used as a topical anaesthetic in folk medicine. 5,6-Dihydro-2-pyranones, dihydromethysticin **73** and methysticin **74**, have been reported from the root extracts of Kava.[77]

Diarylheptanoids, katsumadain A (**75**) and katsumadain B (**76**), have been isolated (Fig. 12) from the chloroform extracts of the seeds of *Alpinia katsumadai*[78] and display anti-emetic activity on copper sulfate-induced emesis in young chicks.

3.4. 4-Hydroxypyran-2-ones

Hydroxypyran-2-ones constitute an important class of naturally occurring pyran-2-ones and are of considerable interest from a chemical and biological perspective. Fusapyrone (**77**) and deoxyfusapyrone (**78**) and their esters (**79** and **80**) (Fig. 13) have been

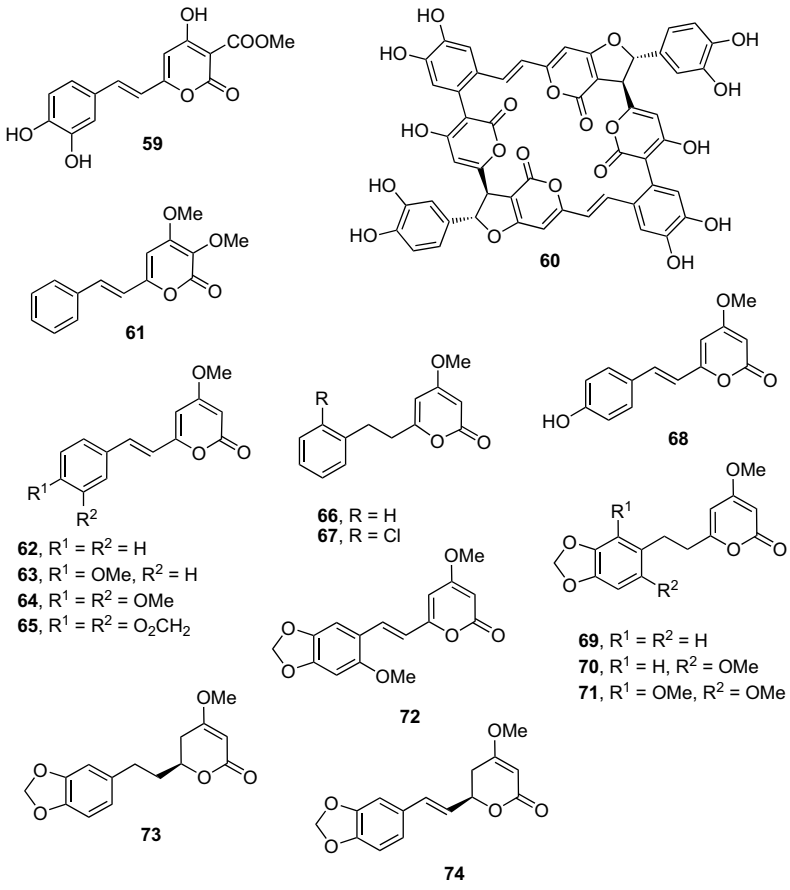


Figure 11.

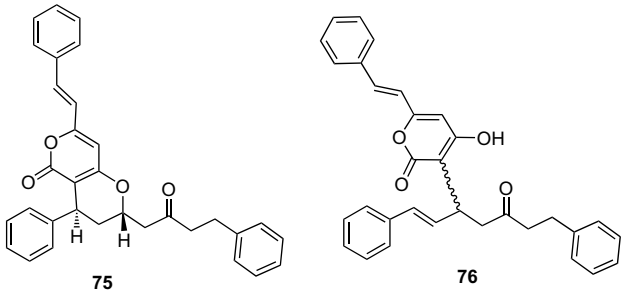


Figure 12.

isolated from the rice cultures of *Fusarium semitectum*.[79] The compounds **77** and **78** have shown significant activity against moulds with low toxicity and high selectivity,[80] while the compounds **79** and **80** have demonstrated increased toxicity. The compounds YM-202204 (**81**) and S39163/F-1 (**82**) have been isolated from a culture broth of the marine fungus *Phoma* sp. Q60596.[81] The π-conjugated 4-hydroxypyran-2-one (**83**), isolated from the culture broth of *Epicoccum purpurascens*, displays telomerase inhibitory activity.[82] The syntheses of the 4-hydroxypyran-2-one skeleton, such as 4-hydroxy-6-methyl-2-pyranone (**84**)[83] and 4-coumaroyltriacetic acid lactone[84] (**85**), have been reported from various *Gerbera hybrida*, 4-coumaroyl-CoA, chalcone synthases and related enzymes. 6-Acetonyl-4-hydroxypyran-2-one (**86**) has been isolated from stilbene synthase and ascosalipyrone (**87**) from the fermentation broth of *A. salicorniae*[85] and fistupyrone (**88**) from *Streptomyces* sp. TP-A0569 (Fig. 13).[86] A novel polycyclic polyketide, A-74528 (**89**), isolated from the culture broth of *Streptomyces* species SANK 61196, has been characterised by NMR techniques including natural abundance INADEQUATE, relative configuration and the conformation by analyses of the NOEs (Fig. 14). The polyketide A-74528 (**89**) inhibits purified human 2′,5′-oligoadenylate phosphodiesterase with an IC_{50} value of 34 μg/ml.[87]

Novel *N*-alkenylcarbamate pyrones, such as myxopyronins A (**90**) and B (**91**) (Fig. 15), have been isolated[88] from a gliding bacterium *Myxococcus fulvus* Mx f50. Other structurally related corallopyronins A (**92**), B (**93**), and C (**94**) have been isolated from *Corallococcus coralloides* Cc c127.[89] Myxopyronins A (**90**) and B (**91**) display activity against a wide range of Gram-positive bacteria, but were found to be less active against Gram-negative bacteria and resistant to yeasts and moulds.[90]

Myxopyronins had no acute toxicity for mice up to 100 mg/kg (s.c.). The corallopyronins (**92**–**94**) are found to inhibit bacterial RNA polymerases,[91] both in whole cells, and with the isolated enzyme.

Three new 6-substituted-pyran-2-one polyketide metabolites, phaeochromycins A-C (**95**-**97**), have been isolated (Fig. 16) from the fermentation broths of an actinomycete designated *Streptomyces phaeochromogenes* LL-P018.[92] Phaeochromycins A and C were found to be weak inhibitors of MAPKAP kinase-2 with IC_{50} values of 39 and 130 μM, respectively.

Four new pyrano-diterpene antibiotics, sesquicillins B to E (**99**–**102**, Fig. 17), isolated from the culture broth of *Albophoma* species FKI-1778, together with the known sesquicillin A (**98**), display moderate inhibitory activity against the growth of *Artemia salina* (brine shrimps) and Jurkat cells.[93]

Five chromones and a pyran-2-one, chaetoquadrin F (**103**) (Fig. 18), have been isolated from the ethyl acetate extract of an Ascomycete *Chaetomium quadrangulatum* guided by monoamine oxidase (MAO) inhibitory activity.[94] The marine natural product (+)-pectinatone (**104**) (Fig. 18), isolated from *Siphonaria* sp. molluscs displays antibacterial, antifungal, and cytotoxic activity.[95–97]

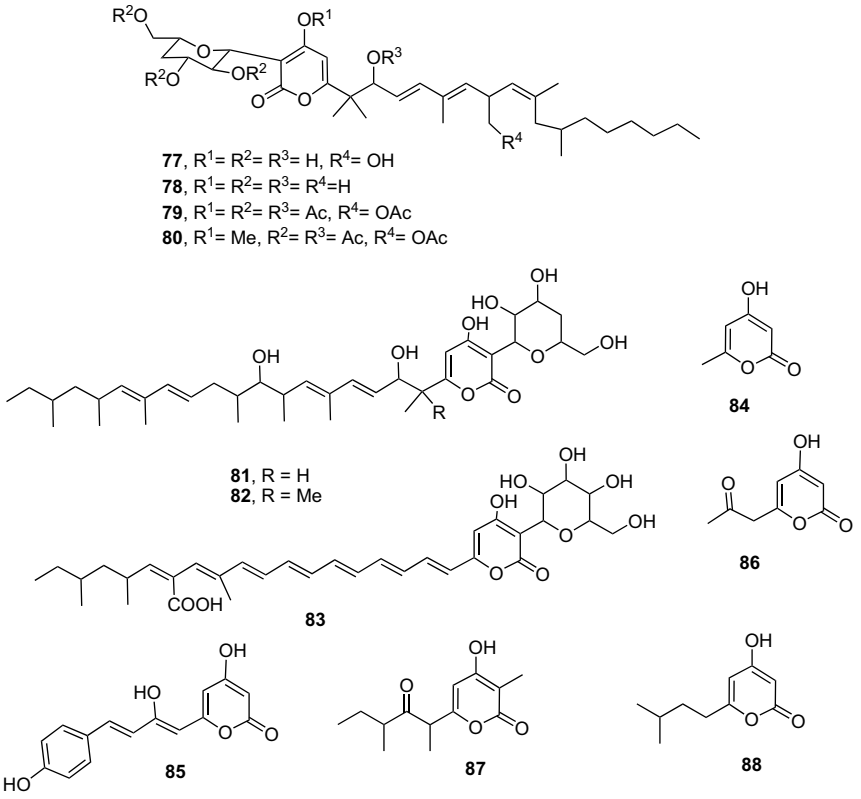


Figure 13.

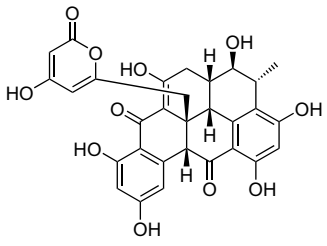


Figure 14.

Five new antibiotics, NF00659A1 (**105**), A2 (**106**), A3 (**107**), B1 (**108**) and B2 (**109**), having 4-hydroxy-2-pyrone and 4,5-seco-tricyclic diterpene moieties (Fig. 18), have been isolated from a culture mycelium of Aspergillus species NF 00659 and exhibit potent antitumour activities against human ovarian carcinoma A2780 and human colorectal adenocarcinoma SW480 cells, but were found to be inactive against Gram-positive and negative bacteria, yeasts and fungi at 1000 μg/ml.[98,99] A new 2-pyranone derivative, epimedokoreanone A (**110**) (Fig. 18), has been isolated from the aerial parts of *Epimedium koreanum* Nakai.[100]

Neocosmospora vasinfecta E. F. Smith is a pathogen which causes root- and fruit-rot and seedling damping off in the Malvaceae, Leguminosae, Piperaceae and Cucurbitaceae families. Two new metabolites, neovasipyrones A and B (**111** and **112**) (Fig. 18), have been isolated from the phytopathogenic fungus *Neocosmospora vasinfecta* NHL2298.[101]

A 4-hydroxy-2-pyranone, davallialactone (**113**) (Fig. 19), has been obtained from the rhizomes of a fern, *Davallia mariesii* Moore.[102] The absolute configuration of **113** was determined by circular dichroism and found to be 5′R,6′S.

3.5. 6-Alkyl/aryl-pyran-2-ones

The naturally occurring 6-alkylpyran-2-ones have been isolated from various strains of microorganisms of the genus *Trichoderma*.

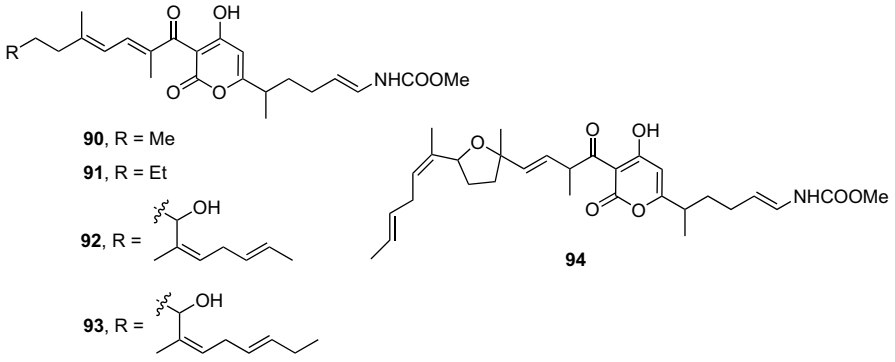


Figure 15.

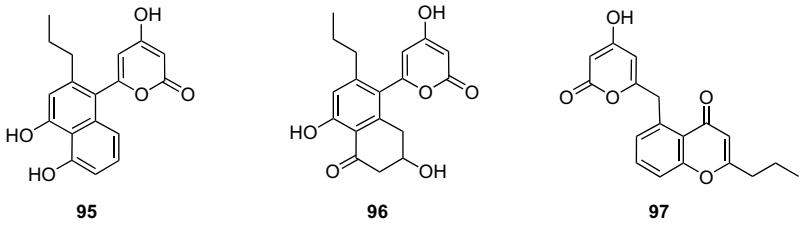


Figure 16.

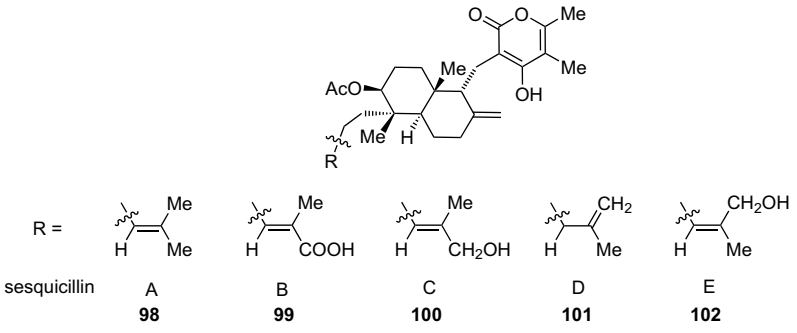


Figure 17.

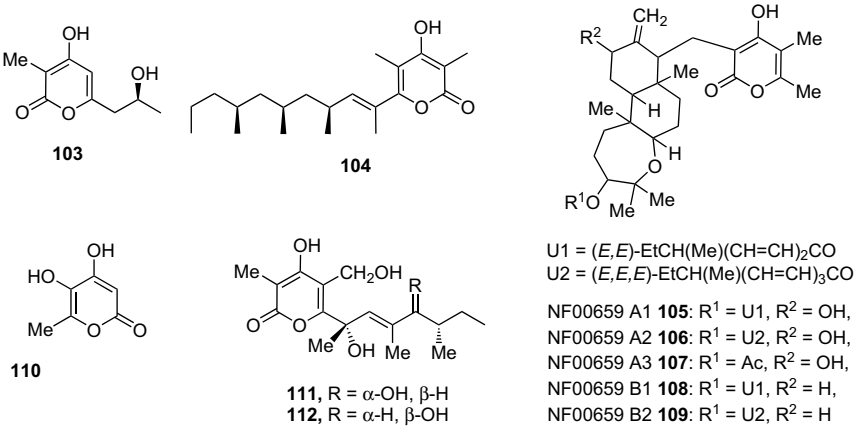


Figure 18.

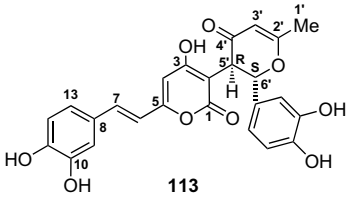


Figure 19.

6-Pentylpyran-2-one (**114**) (Fig. 20) was the first metabolite identified as a fungal product of *Trichoderma viride*.[103] The 2-pyranone (**114**) possesses a coconut aroma[104] and has been reported to be a component of peach[105] and nectarine[106–108] essence. The flavourant properties of the 6-alkylpyran-2-ones have attracted great interest in the food industry. Another 6-alkenylpyran-2-one (**115**) (Fig. 20), isolated as a metabolite from a strain of *T. viride*,[109] has been identified as a queen pheromone of the red fire ant, *Solenopsis invicta* (Buren), and of male mandibular gland secretions of ants of the genus *Camponotus*.[110] 6-Propenylpyran-2-one (**116**) (Fig. 20), named sibirinone, has been isolated from *Hypomyces semitranslucens* and synthesised by [4+2]-dimerisation of the crotonyl-derived ketene.[111]

6-*n*-Pentylpyran-2-one (**114**) was also isolated, together with cyclopentenones, from a marine algicolous fungus of the genus *Myrothecium*, and exhibited tyrosinase inhibitory activity with an IC_{50} value of 0.8 μM. Currently, it is being used as a functional personal-care product for skin-whitening effects and for preventive and therapeutic effects on local hyperpigmentation diseases.[112]

Recently, a new 6-(4-oxopentyl)pyran-2-one (**117**), along with 6-pentylpyran-2-one (Fig. 21) have been isolated from the cultural filtrate of *T. viride*.[113]

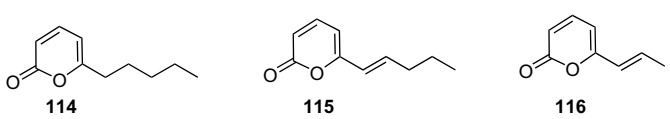


Figure 20.

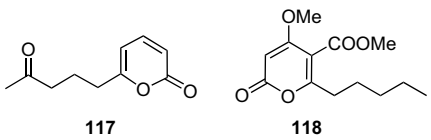


Figure 21.

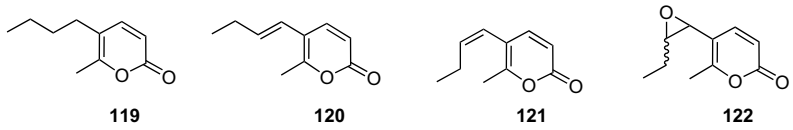


Figure 22.

A new methyl 4-methoxy-6-pentylpyran-2-one-3-carboxylate, daldiniapyrone (**118**), together with several polycyclic compounds, have been isolated from an EtOAc extract of the fruit bodies of *Daldinia concentrica*.[114]

Bioassay-guided isolation of four pyran-2-ones from cultures of an unidentified filamentous fungus LL-11G219 has produced four novel alkyl-2-pyranone fermentation products, 11G219α (**119**), 11G219β (**120**), 11G219γ (**121**) and 11G219δ (**122**) (Fig. 22).[115] Several closely related compounds produced by the fungal culture LL-11G219 have been isolated which possess androgen-like activity.[115]

A new species of *Pseudomonas* sp. F92S91, isolated from a marine sponge, was found to produce naturally occurring pyran-2-ones, pseudopyronines A (**123**) and B (**124**) (Fig. 23). These naturally occurring pyran-2-one antibiotics were found to be degraded to 3-furanone.[116]

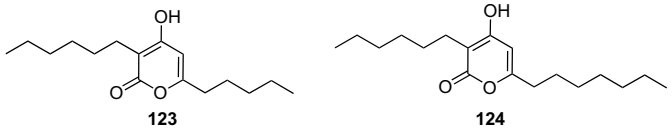


Figure 23.

The metabolite **124**, which has been previously isolated[117] from the fermentation culture broth of a bacterial strain *Pseudomonas fluorescens*, exhibited an MIC_{50} value of 2.5 μg/ml against a *Staphylococcus aureus* strain, and >64 μg/ml against *Escherichia coli*. The level of expression of the rpoE gene affected the biological activity of **124** against an *E. coli* laboratory strain. When the rpoE protein was constitutively overexpressed in *E. coli*, the MIC_{50} value of **124** was found to be 5 μg/ml.

Four new 2-pyrone-containing propionates (**125**–**128**) (Fig. 24), have been isolated from the mantle extract of *Placida dendritica*, a Mediterranean sacoglossan that lives upon the green alga *Bryopsis plumosa*.[118]

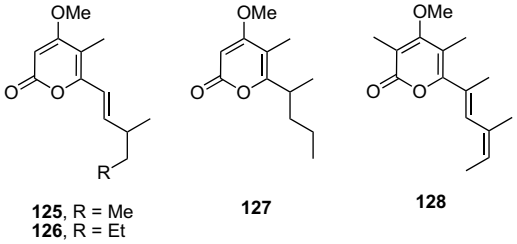


Figure 24.

3.5.1. Annularins

Freshwater aquatic fungi are potential sources of new bioactive secondary metabolites. Five new bioactive secondary pyran-2-one metabolites, annularins A–E (**129**–**133**) (Fig. 25), have been isolated from organic extracts of the freshwater fungus *Annulatascus triseptatus* (A-353-1B).[119] Some of the compounds, annularins A, B and C exhibited antibacterial activity.

A culture extract of the fungal strain VKM-3750 has produced a new 6-alkylated-pyran-2-one metabolite, nosporin B (**134**), using multistep chromatography. The structure of **134** was assigned on the basis of spectroscopic techniques.[120]

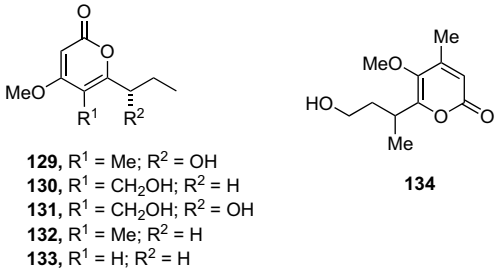


Figure 25.

3.5.2. Pyrenocines and macommelins

Naturally occurring pyran-2-ones, such as pyrenocine A (**135**), pyrenocine B (**136**) and pyrenocine C (**137**) (Fig. 26), have been isolated from *Pyrenochaeta terrestris*, a causal agent of onion pink root disease. Pyrenocines A (**135**) and B (**136**) were phytotoxic, preventing the germination of lettuce, rice and onion seeds, and inhibiting root elongation in seedlings.[121–123] The macomellins (**138**–**141**) have been isolated from *Macrophoma commelinae*, a casual agent of fruit rot disease of apple and other plants.[124]

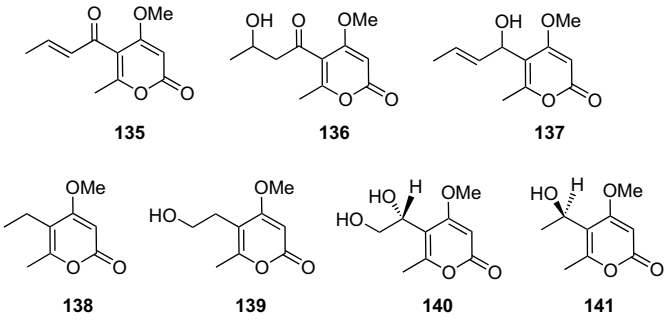


Figure 26.

3.5.3. Elijopyrone

Elijopyrones A–D (**142**–**145**) (Fig. 27), have been isolated from a cultured marine actinomycete (isolate CNB-880). The producing strain has been obtained from a sediment collected from the San Elijo Lagoon in Cardiff, California.[125]

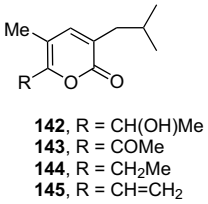
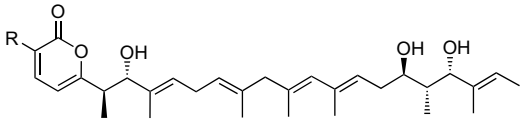


Figure 27.

Marine bacteria are considered to play a central role as symbionts of most marine invertebrates and they also represent one of the most novel biomedical resources remaining to be explored. Three novel cytotoxic acetogenins, lagunapyrones A–C (**146**–**148**)

(Fig. 28), have been produced[126] in a seawater-based medium by an unidentified marine Actinomycete (culture CNB-984) isolated from sediment collected in the Agua Hedionda Lagoon in Carlsbad, California. Lagunapyrone B (**147**) shows a modest in vitro cytotoxicity, ED_{50}=3.5 μg/ml, against the human colon cancer cell line HCT-116.

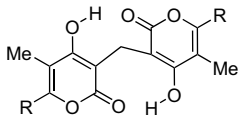


146, R = Me
147, R = Pr
148, R = Bu

Figure 28.

3.5.4. Colletopyrone and helipyrone

The dipyran-2-one class of compounds, colletopyrone (**149**) and helipyrone (**150**) (Fig. 29), have been isolated from a pathogenic fungus *Colletotrichum nicotianae*, a causative agent of tobacco anthracnose,[127] and a higher plant *Helichrysum italicum*, respectively.[128]

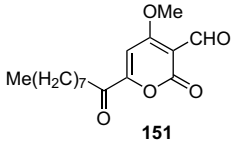


149, R = Me
150, R = Et

Figure 29.

3.5.5. Phacidin

Phacidin (**151**) (Fig. 30), isolated from the canker fungus *Potebniamyces balsamicola*,[129,130] displayed potent antifungal properties by inhibiting the growth of fungi in all the major groups. It also showed inhibitory activity against dermatophytes such as *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*, but was ineffective against opportunistic fungi such as Aspergillus species.

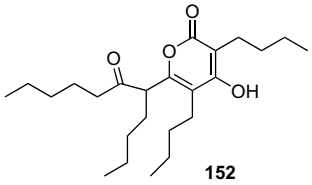


151

Figure 30.

3.5.6. Elasnin

Elasnin (**152**) (Fig. 31), has been isolated from *Streptomyces noboritoensis* and showed an inhibitory effect on human sputum (leukocyte) elastase.[131,132] Biosynthetic studies using [1,2-$^{13}C_2$]-acetate as a labelled precursor suggested that elasnin (**152**) has been derived from twelve molecules of acetate.[133,134] The LD_{50} values of **152** were found to be 290 mg/kg (ip) and >1000 mg/kg orally.[131]

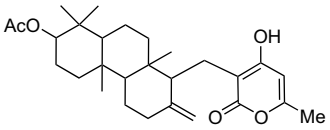


152

Figure 31.

3.5.7. Aszonapyrone A

Aszonapyrone A (**153**) (Fig. 32), isolated from Aspergillus zonatus, has shown antibacterial activity against *S. aureus* with an MIC value of 6.3 μg/ml [135] It has been biosynthesised by a combination of both the mevalonate-geranylgeranyl-pyrophosphate, and the acetate-polyketide routes.[135]

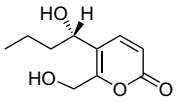


153

Figure 32.

3.5.8. Taiwapyrone

A 5,6-disubstituted 2-pyranone, taiwapyrone (**154**) (Fig. 33), has been isolated from the mycelium of *Cercospora taiwanensis*, grown on potato-agar. The structure was determined by spectroscopic means.[136]



154

Figure 33.

3.5.9. Lehualides A–D

Marine sponges of the family Plakinadae are known to be rich sources of structurally unique and biologically active metabolites. A new pyran-2-one, lehualide A (**155**) together with three pyran-4-ones, lehualides B–D (**156**–**158**) (Fig. 34), have been isolated from a Hawaiian sponge of the genus *Plakortis*.[137]

Three new 2-pyranones, opuntiol (**159**), opuntioside (**160**) and 4-ethoxy-6-hydroxymethylpyran-2-one (**161**) (Fig. 35), have been isolated from aqueous ethanolic extracts from the fresh stems of a cactus *Opuntia dillenii* Haw. The ethanolic extract showed potent radical-scavenging activity.[138]

3.5.10. Aloenin

Several naturally occurring 6-arylated-pyran-2-ones, aloenin aglycone (**162**), aloenin (**163**), aloenin 2′-*p*-coumaroyl ester (**164**), 10-*O*-β-D-glucopyranosyl aloenin (**165**) and aloenin B (**166**) (Fig. 36), have been isolated from a chloroform–acetone extract of Kenya aloe.[139] 6-[(5-Methyl-6-ethyl-4-hydroxypyrone-3-yl)methylene]glabranine (**167**) (Fig. 36), a new pyran-2-one, has been isolated and identified from the whole plant of *Anaphalis sinica* Hance.[140]

Aloe vera has been extensively used in health foods, cosmetics and traditional medicine. Various studies have shown the pharmaceutical activities of compounds isolated from Aloe, including antiinflammatory, antioxidative, antiaging, anticancer and immunomodulatory properties. Two new 2-pyranone-based dihydrocoumarin derivatives, **168** and **169** (Fig. 37), have been isolated from Aloe vera,[141] and these compounds demonstrated antioxidant activity against superoxide and hydroxyl radicals.

3.6. 6-Alkenyl-pyran-2-ones

3.6.1. Gibepyrones

Six new gibepyrones A–F (**170**–**175**) have been isolated (Fig. 38) as metabolites from *Gibberella fujikuroi*.[142] Among these, gibepyrones A (**170**) and B (**171**) exhibit growth inhibitory activity against several microorganisms.

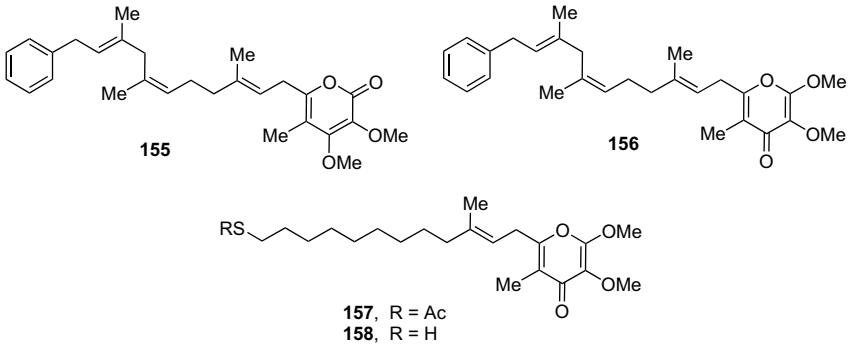


Figure 34.

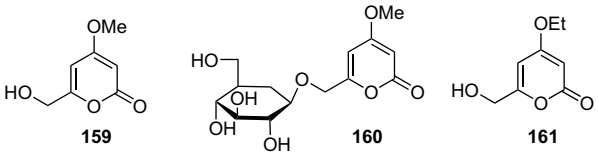


Figure 35.

3.6.2. Nectriapyrone and related compounds

Nectriapyrone (**176**), isolated from *Gyrostroma missouriense* and *Gliocladium vermoesenii*,[143] has been reported (Fig. 39) to display antibacterial activity against *S. aureus*.[144] A structurally related fusalanipyrone (**177**) has been isolated from *Fusarium solani*[145] and was found to be inactive against *Staphylococcus* and *E. coli*, but weakly active against *Candida albicans* and *Trichoderma koningii*.[145]

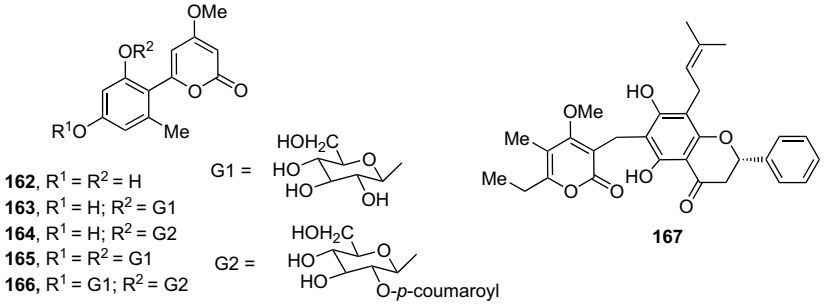


Figure 36.

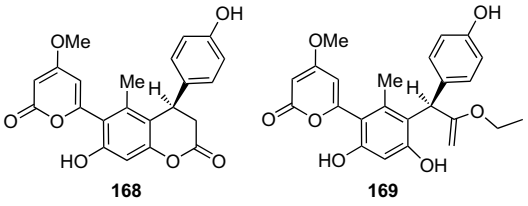


Figure 37.

Two new 6-alkenyl-5-methylpyran-2-ones, herbarin A (**178**) and herbarin B (**179**), have been isolated[146] from the sponges *Aplysina aerophoba* and *Callyspongia aerizusa*, and display inhibitory activity against *A. salina*.

3.6.3. Citreopyrones

Six new metabolites, citreopyrones A–F (**180**–**185**), have been isolated (Fig. 40) from the mycelium of a hybrid strain KO 0092 derived from *P. citreoviride* B IFO 4692 and 6200, and KO 0141 derived from *P. citreoviride* B IFO 4692 and *Penicillium pedemontanum*

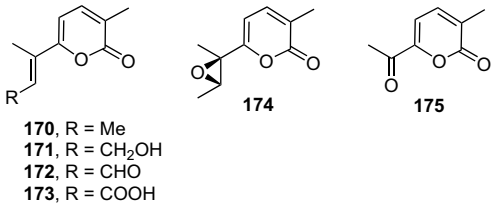


Figure 38.

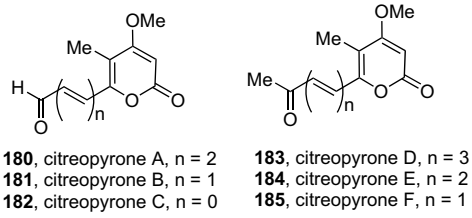


Figure 40.

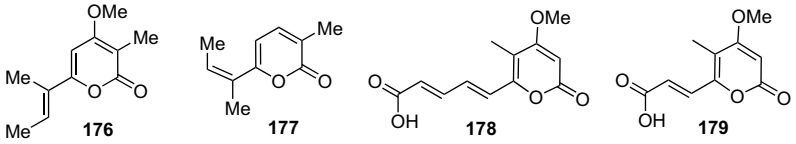


Figure 39.

IFO 9583. Citreopyrones A, B and C inhibited the growth of hypocotyls of lettuce seedlings.[147]

3.6.4. Luteoreticulin

Luteoreticulin **186** has been isolated as a toxic metabolite of *Streptomyces luteoreticuli*.[148] A recent analogue of luteoreticulin,[149,150] griseulin (**187**), has been reported (Fig. 41) to display inhibitory activity against nematodes (*P. redivivus*, *C. elegans* and *H. glycines*) and mosquitoes (*A. aegyptii*).[151]

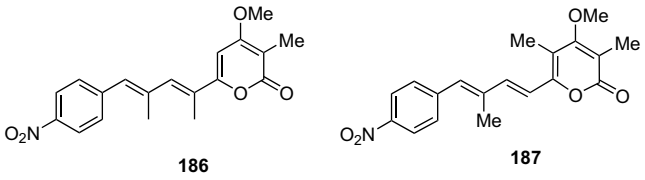
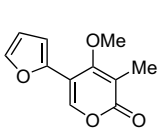
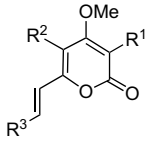


Figure 41.

Several novel 2-pyranones, namely **188**–**194**, have been isolated (Fig. 42) from fruit bodies of the fungus *Ganoderma lucidum*, which is a major constituent of a traditional Chinese drug '*Lin-Chi*' used in the treatment of mild ailments and to promote good health.[152]





189, R^1 = Me, R^2 = CHO, R^3 = Me
190, R^1 = Me, R^2 = CHO, R^3 = COOMe
191, R^1 = Me, R^2 = CH_2OH, R^3 = Me
192, R^1 = CH_2OH, R^2 = CHO, R^3 = COOMe
193, R^1 = H, R^2 = CH_2OH, R^3 = Me
194, R^1 = Me, R^2 = CH_2OH, R^3 = CH_2OH

Figure 42.

3.6.5. Citreoviridin and derivatives

The discovery of citreoviridin (**195**) was as a result of the search for the cause of acute cardiac beriberi, which occurred due to the eating of mouldy rice in East-Asian countries in the early part of the last century. Citreoviridin (**195**) has been isolated as a toxic metabolite from the active principle of the mould *Penicillium citreoviride* (*Penicillium toxicarium*)[153] and found to be responsible for the cause of cardiac beriberi. Several derivatives of citreoviridin, such as citreoviridins C (**196**) and D (**197**), citreoviridinol (**198**), isocitreoviridinol (**199**) and secocitreoviridin (**181**), have been isolated (Fig. 43) from various species of *Penicillium*.[154–160]

Three new metabolites, citreoazopyrone (**200**) and two 6-epoxy-2-pyranones (**201**) and (**202**), have been isolated (Fig. 43) from the mycelium of a hybrid strain KO 0011 derived from *P. citreoviride* B IFO 6200 and 4692.[161] Citreoazopyrone (**2000**) inhibited the growth of hypocotyls of lettuce seedlings by 83.5% relative to the control at 12.5 μg/cm^2.

3.6.6. Aurovertins

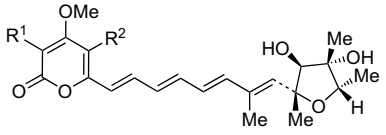
The aurovertins are a group of mycotoxins, which are closely related to citreoviridin. Aurovertins A (**203**), B (**204**), C (**205**), D (**206**) and E (**207**) have been isolated (Fig. 44) from the mycelial extracts of *Calcarisporium arbuscula*.[162–164] The aurovertins did not show any antibiotic activity against bacteria or pathogenic fungi, but showed toxicity against a number of animals. The oral LD_{50} value of **204** for mice is 1.65 mg/kg and *i.v.* injection of 1 mg/kg caused death in rabbits in less than 15 min, and in dogs in less than 50 min. Aurovertin A (**203**) was a powerful inhibitor of ADP-stimulated respiration, but was inactive as an inhibitor of ATPase activity. Aurovertins B (**204**) and D (**206**) have been shown to inhibit oxidative phosphorylation.

A polyene pyran-2-one, aurovertin E (**207**), has been isolated along with aurovertin B (**204**) from the culture mycelia of the basidiomycete *Albatrellus confluens*.[165] Recently a new secondary metabolite aurovertin F (**208**) has been isolated from the fermentation broth of the entomopathogenic fungus *Metarhizium anisopliae*.[166]

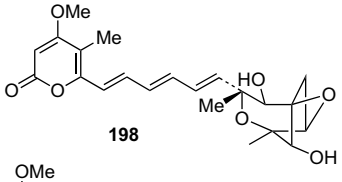
3.6.7. Asteltoxin and citreomontanin

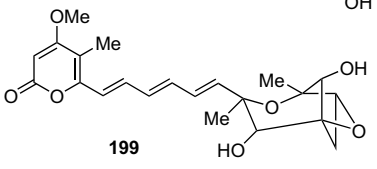
Asteltoxin (**209**), a mycotoxin, was first isolated from toxic maize meal cultures of Aspergillus stellatus, while the polyenepyrone, citreomontanin (**210**), has been isolated (Fig. 45) from *P. pedemontanum* and *Penicillium pulvillorum*.[167,168] The structures of **209** and **210** have been confirmed by X-ray crystallography, which showed that the double bonds exist in an all *E*-configuration.[169] Both **209** and **210** have been evaluated for their effects on ATPase activity in *E. coli* BF_1. The pyranone **210** was found to be completely inactive, while **209** demonstrated enzyme inhibition, but it did not enhance the binding affinity of BF_1 for inorganic phosphate.

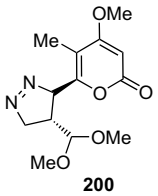
Rosellisin (**211**), a co-metabolite of the macommelins, has been isolated (Fig. 46) from *Hypomyces rosellus*.[170,171] Macrophin (**212**) and macrophic acid (**213**) that are structurally related to rosellisin have been obtained[170] from *M. commelinae*. A fungal metabolite macrophin (**212**) has been isolated[172] as an immunosuppressive

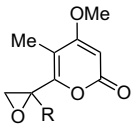


195, R^1 = H, R^2 = Me
196, R^1 = Me, R^2 = H
197, R^1 = Me, R^2 = Me



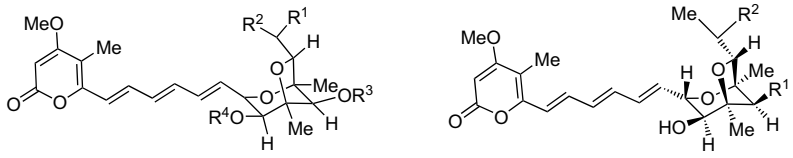






201, R = H
202, R = Me

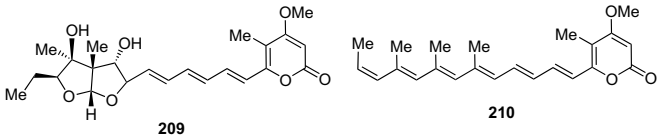
Figure 43.



203, R^1 = H, R^2 = Me, R^3 = R^4 = COMe,
205, R^1 = R^2 = R^4 = H, R^3 = COMe,
206, R^1 = OH, R^2 = Me, R^3 = COMe, R^4 = H,
207, R^1 = R^3 = R^4 = H, R^2 = Me

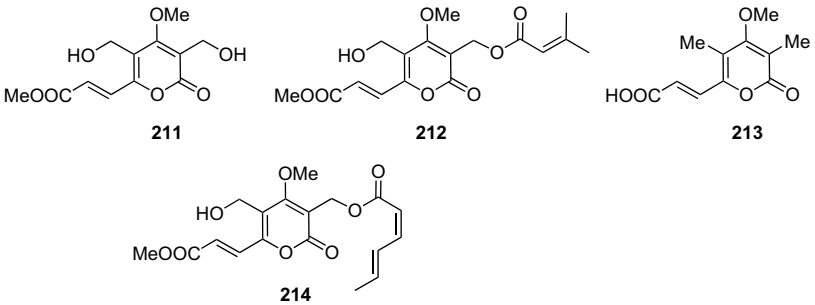
204, R^1 = OAc, R^2 = H
208, R^1 = OH, R^2 = OH

Figure 44.



209 **210**

Figure 45.



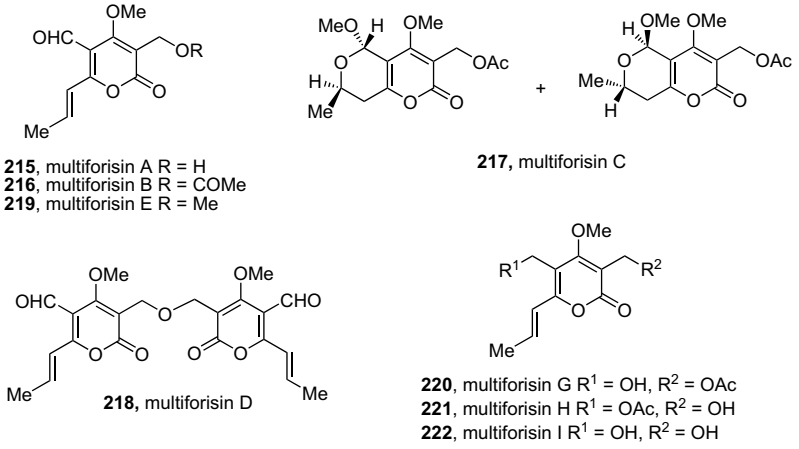
211 **212** **213** **214**

Figure 46.

principle from an Ascomycete, *Diplogelasinospora grovesii*. The IC_{50} values for macrophin (**212**) were found to be 0.4 and 0.3 μg/ml against concanavalin A- and lipopolysaccharide-induced proliferations of mouse spleen lymphocytes, respectively. Islandic acid (**214**), another natural pyran-2-one, has been isolated (Fig. 46) from *Penicillium islandicum*.[171] Rosellisin (**211**) has been found to be active against *Staphyloccoccus aureus* at low concentrations, while **214** exhibited cytotoxicity against Yoshida sarcoma cells in tissue culture, and inhibited the transfection of *Bacillus* phage M_2.[171]

3.6.8. *Multiforisin*

Fujimoto et al.[173–175] have isolated five new metabolites, multiforisins A–E (**215**–**219**) (Fig. 47) from the Ascomycete *Gelasinospora multiforis*. The immunosuppressant effects of these compounds were determined using mouse spleen cells induced to proliferate with either concavalin A or lipopolysaccharide (LPS). The IC_{50} values for the multiforisins A to E (**215**–**219**) and dihydromultiforisin A were 0.6, 24, 44, >50, 5 and 13 μg/ml (concavalin A), and 0.6, 22, 27, 37, 4 and 9 μg/ml (LPS).



215, multiforisin A R = H
216, multiforisin B R = COMe
219, multiforisin E R = Me

217, multiforisin C

218, multiforisin D

220, multiforisin G R^1 = OH, R^2 = OAc
221, multiforisin H R^1 = OAc, R^2 = OH
222, multiforisin I R^1 = OH, R^2 = OH

Figure 47.

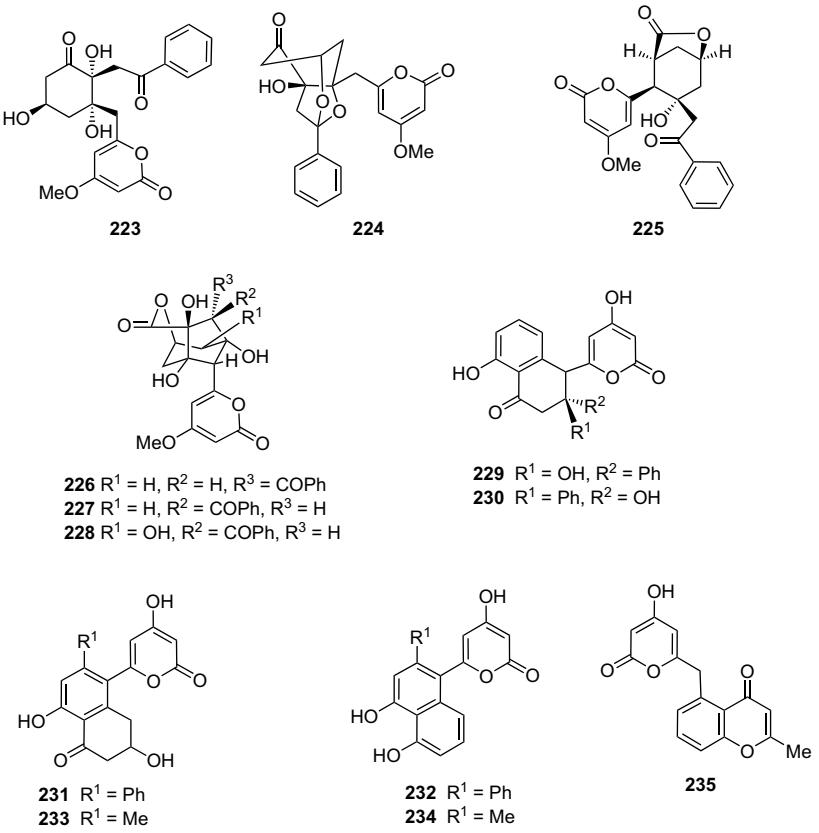


Figure 48.

Interestingly, there was some differential toxicity in the sense that the IC_{50} value for multiforisin A against KB cancer cells was 10 μg/ml.

Recently, three more 2-pyranones, called multiforisins G (**220**), H (**221**) and I (**222**), have been isolated[173] from an Ascomycete, *Gelasinospora heterospora*. Among them, **220** and **221** have proved to be the immunosuppressive components of the fungus. Compounds **220**–**222** have also been isolated from *G. multiforis*, together with multiforisin A (**215**), which was formerly isolated from this fungus and showed immunosuppressive features.

3.6.9. *Wailupemycins*

Several bacteriostatic polyketides, wailupemycins A-C (**223**–**225**) and three 3-*epi*-5-deoxyenterocins **226**–**228**, have been isolated[99,176] (Fig. 48) from a *Streptomycete*, cultured from shallow-water marine sediment. Compounds **223** and **226** showed antimicrobial activity against *E. coli* and *S. aureus*, respectively. Wailupemycin D (**229**) has recently been isolated as a minor component from the marine actinomycete, *Streptomyces maritimus*.[177] Recently, fermentation of *S. maritimus* provided three new polyketides wailupemycins E–G (**230**–**232**), which have been characterised by HRMS and 2D NMR spectroscopy.[178]

A novel polyketide, mutactin (**233**),[179] together with dehydromutactin (**234**)[180] and SEK34b[181] (**235**), have been isolated from recombinant strains of *Streptomyces coelicolor* A3(2), *Streptomyces roseofulvus* and *Streptomyces glaucescens* (Fig. 48).

Pedras and Chumala[182] have analysed a large number of blackleg-causing fungi and isolated the secondary metabolites, phomapyrones D (**239**), E (**240**) and G (**241**), together with phomapyrone A[183] (**236**), phomenin B[184] (**237**) and infectopyrone[185] (**238**), produced by a new group of isolates of the fungal pathogen, *Leptosphaeria maculans* (Desm.) Ces. et de Not., asexual stage *Phoma lingam* (Tode ex Fr.) Desm (Fig. 49).

The red pigments, auxarconjugatins A (**242**), B (**244**) and C (**245**), have been isolated from the mycelia of *Auxarthron conjugatum*, an

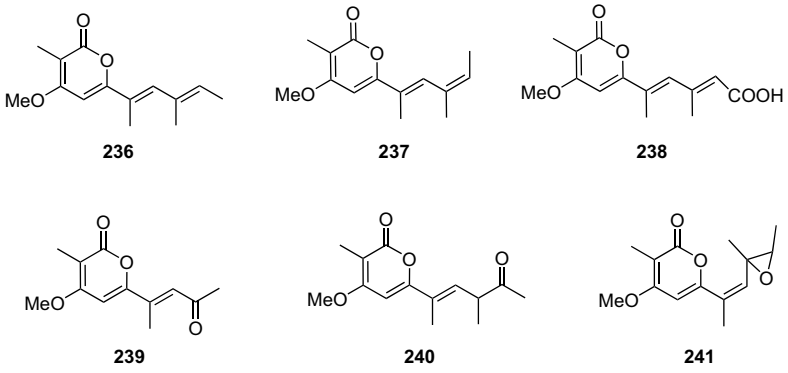


Figure 49.

ascomycetous fungus belonging to the Onygenaceae family. The structures of auxarconjugatins A (**242**), B (**244**) and C (**245**), including the stereochemistry of the conjugated tetraene, were established by spectroscopic analyses. Compound **243** was also isolated from the mycelial extract of *A. conjugatum*, along with **242** (Fig. 50). Compounds **242** and **243** are stereoisomers of auxarconjugatin A, the 3′-cis- and all-trans form, respectively.[186]

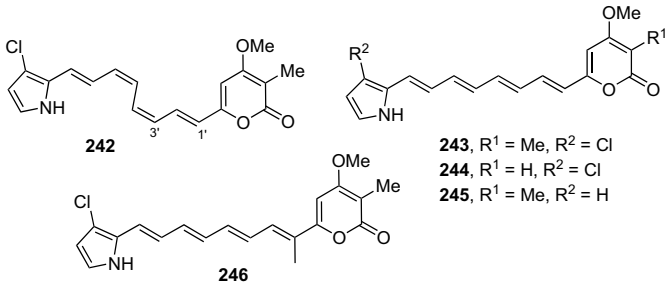


Figure 50.

A pyrrolyloctatetraenyl-α-pyrone, rumbrin (**246**), has been isolated (Fig. 50) from the mycelia of *Auxarthron umbrinum*[187] and acts as a cytoprotective substance and an antioxidant.[188] It has one cis-double bond at C-1′ in the conjugated tetraene residue, but might be in equilibrium with the all-trans form as in the case of **242** and **243**. The biological activities of **242**, **244** and **245** were speculated to be similar to that of **246**.

3.6.10. Solanopyrones

Solanopyrones A (**247**), B (**248**) and C (**249**) have been isolated (Fig. 51) from *Alternaria solani*, the causal organism of early blight disease of tomato and potato. Solanopyrone A (**247**) induced a potato-leaf necrotic lesion at concentrations of 100 μg/μl.[189]

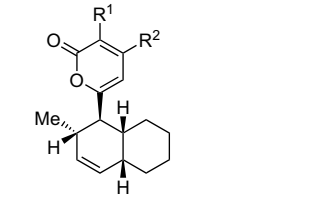


Figure 51.

Three new 2-pyranone secondary metabolites, solanopyrones E (**250**), F (**251**) and G (**252**), have been produced (Fig. 52) by an unidentified filamentous marine fungus, isolated[190] from the surface of the calcareous green alga, *Halimeda monile*. These solanopyrones exhibited substantial antialgal activity against the marine unicellular alga, *Dunaliella* sp., at concentrations as low as 100 μg/ml.

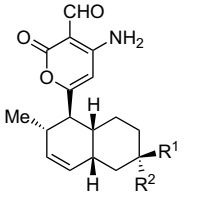


Figure 52.

Another related α-pyrone ACRL toxin II (**253**) has been reported from *Alternaria citri* (Fig. 53).[191] In a screening programme for fungal inhibitors of glucocorticoid- mediated signal transduction, sesquicillin (**254**), isolated[192] from an *Acremonium* species, inhibited glucocorticoid-induced reporter gene expression with an IC_{50} value of 0.1–0.5 μg/ml.

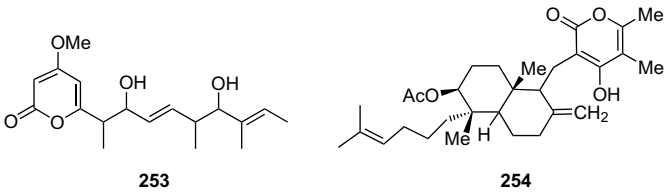


Figure 53.

Two unusual tetrahydrofurylhydroxypyran-2-ones, tetillapyrone (**255**) and nortetillapyrone (**256**), have been isolated from the marine sponge, *Tetilla japonica*, in the Bay of Thailand. The structure of tetillapyrone has been established by X-ray crystallography (Fig. 54).[193]

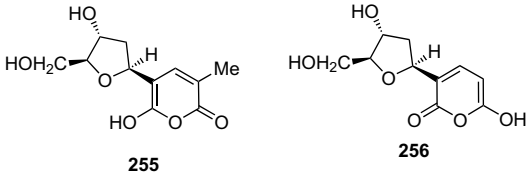


Figure 54.

3.7. 6-Carboxylic acid pyran-2-ones

A new lignan tricarboxylic acid, erimopyrone (**257**), has been isolated from the liverwort, *Moerckia erimona*, and its structure was established as [1*R*,2*S*]-1-(6-carboxy-2-oxo-2*H*-4-pyranyl)-6,7-dihydroxy-1,2-dihydro-2,3-naphthalenedicarboxylic acid by spectroscopic methods (Fig. 55).[194] A novel 3-naphthyl-2-pyranone, scapaniapyrone A (**258**), has been isolated as a polar constituent of *Scapania undulata*.[195]

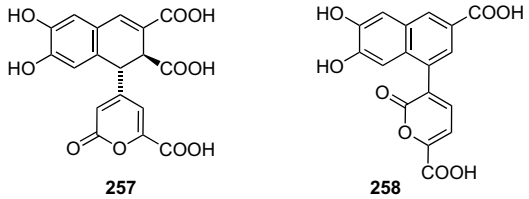


Figure 55.

3.7.1. Stizolobic acid and stizolobinic acid

An amino-acid-based natural pyran-2-one, stizolobic acid (**259**), has been isolated from *Stizolobium hassjoo* (velvet bean) and other species of *Stizolobium* and also from *Mucuna irukanda* (Leguminoseae). A related compound, stizolobinic acid (**260**), has been isolated as a co-metabolite from *S. hassjoo*.[196] These compounds have additionally been isolated from the fungus, *Amanita pantherina* (Fig. 56).[197]

The biosynthetic origin of both **259** and **260** revealed that these compounds are derived from tyrosine via DOPA, with extradiol cleavage of the aromatic ring of DOPA being invoked in order to explain the formation of the pyranone ring.[198–201]

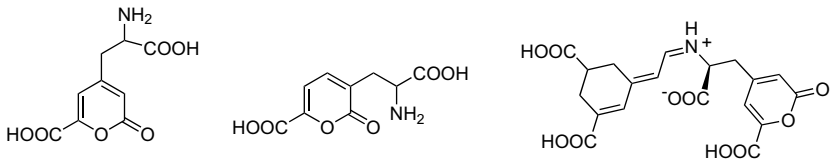


Figure 56.

3.7.2. Muscaurin II

An orange pigment, Muscaurin II (**261**), has been isolated (Fig. 56) from the caps of *Amanita muscaria* (Fly Agaric).[202] The thalloid liverwort, *Dumortiera hirsute*, is a subcosmopolitan species occurring in oceanic and warm-to-tropical areas and three carboxylate 2-pyrone derivatives, dumortins A–C (**262**–**264**), and a new flavone glycoside have been isolated (Fig. 57) from this species.[203]

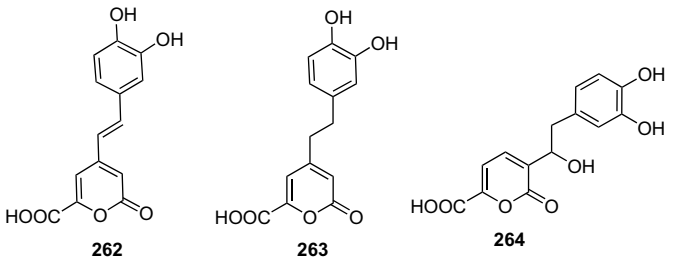


Figure 57.

3.8. Unusual pyran-2-ones

Two unique pyran-2-ones (**265**) and (**266**) embedded into a polyunsaturated macrocyclic structure were isolated (Fig. 58) as secondary metabolites from the red alga, *Phacelocarpus labillardieri*.[204]

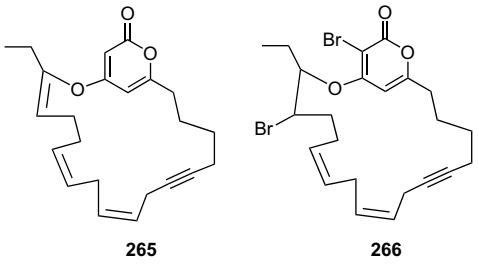


Figure 58.

Nitidon (**267**), a highly oxidised pyranone derivative produced by *Junghuhnia nitida* exhibits antibiotic and cytotoxic activities and induces morphological and physiological differentiation of tumour cells at nanomolar concentrations (Fig. 59).[205]

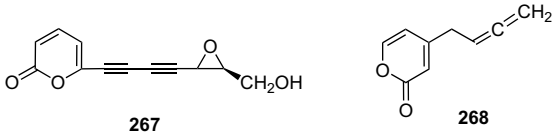
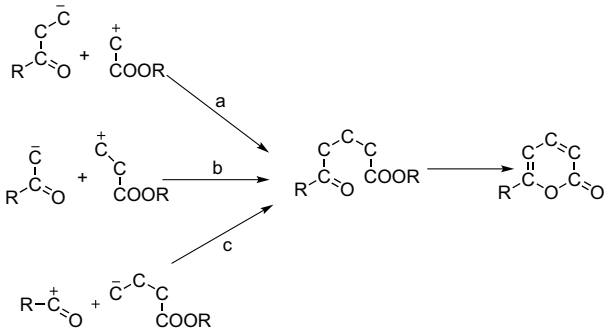


Figure 59.

Metabolites of the wood rot decay fungus, *Sistotrema raduloides* (P. Karst) Donk, have been reported to produce a unique allene-based α-pyrone, sistopyrone (**268**), which is very unstable and readily polymerises in the presence of air to give a black insoluble material.[206]

4. Synthesis of pyran-2-ones

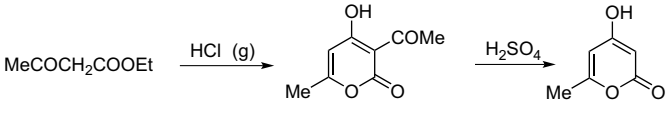
There are three possible strategies (a, b and c) for the construction of the pyran-2-one ring system based on retrosynthesis, as depicted in Scheme 1. Among these, route a is commonly practiced for the synthesis of 2-pyranones.



Scheme 1.

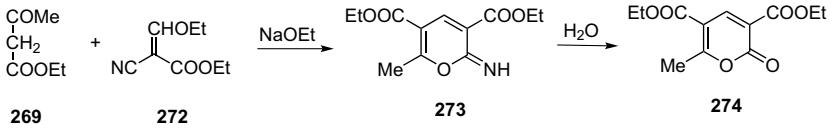
4.1. Condensation–cyclisation reactions

The most common strategy for the synthesis of the 2*H*-pyran-2-one ring system is through the acid-catalysed condensation–cyclisation of β-ketoesters. Thus, ethyl acetoacetate (**269**) in the presence of HCl gas undergoes self-condensation followed by cyclisation to yield 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one[207] (**270**) (Scheme 2). Deacetylation of **270** in sulfuric acid yields 4-hydroxy-6-methyl-2*H*-pyran-2-one (**271**).



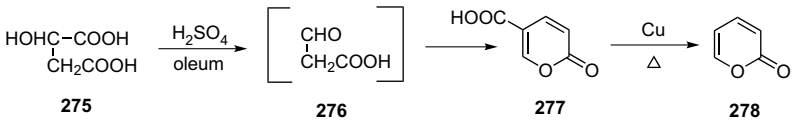
Scheme 2.

Base-catalysed condensation of ethyl acetoacetate (**269**) with ethyl ethoxymethylenecyanoacetate (**272**) yields ethyl 6-methyl-2*H*-pyran-2-one-3,5-dicarboxylate (**274**) via the intermediate **273** (Scheme 3).



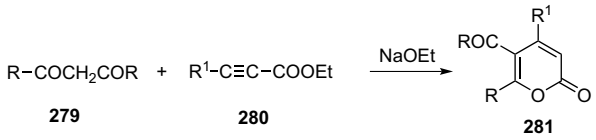
Scheme 3.

Coumalic acid (**277**), a 2*H*-pyran-2-one-5-carboxylic acid, has been synthesised[208] by the acid-catalysed selfcondensation of formylacetic acid (**276**), obtained from the decarbonylation of α-hydroxysuccinic acid (**275**), followed by dehydration (Scheme 4). Decarboxylation of coumalic acid (**277**) in the presence of Cu powder leads to the unsubstituted 2*H*-pyran-2-one (**278**) and is an example of the route b synthetic strategy.



Scheme 4.

A recent modification of the methodology for the preparation[209] of 2*H*-pyran-2-ones (**281**) involves the base-catalysed condensation of 1,3-dicarbonyl compounds (**279**) with acetylenic esters (**280**) (Scheme 5).



Scheme 5.

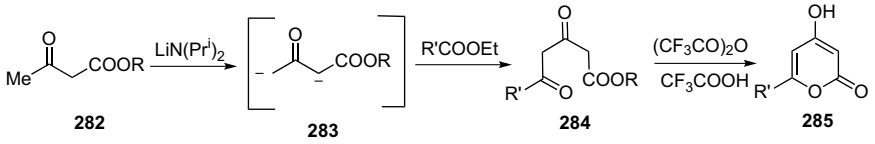
An alternative route for the synthesis[210] of 6-alkyl-4-hydroxy-2*H*-pyran-2-ones (**285**) has been developed by generating the dianion (**283**) of the β-ketoester **282** by $LiN(Pr^i)_2$, followed by condensation with an ester (Scheme 6). Narasimhan and Ammanamanchi[210b] prepared a 6-aryl-4-hydroxy-2*H*-pyran-2-one (**285**, R′=Ph) by heating a β,δ-diketoester (**284**, R=Et, R′=Ph) under vacuum in good yield. This efficient method for the synthesis of 2*H*-pyran-2-ones belongs to the example to the route c synthetic strategy.

4.3. From α,β-unsaturated enones

α,β-Unsaturated enones are important intermediates for the construction of 2-pyranones and are usually obtained by the acetylation of olefins.[213,214] Oxidation of pent-4-en-2-ol with Corey's oxidant[215] and oxidative cleavage of phenylselenolates[216] yield unsaturated enones. 1,2-Allenic ketones may be considered as α,β-unsaturated ketones and have broad applications in organic synthesis.[217]

Electron-deficient allenes (**292**) are prone to nucleophilic attack to afford β-substituted-β,γ-unsaturated functionalised alkenes (**294**) on reaction with diethyl malonate (**293**) using K_2CO_3 as a catalyst at room temperature and the alkenes (**294**) cyclise to yield highly substituted 2*H*-pyran-2-ones[218] (**295**) (Scheme 9).

1,3-Dioxin-4-ones (cyclic enones) have been used as synthons for the synthesis of various classes of compounds. 2,2-Dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones (**296**), under thermal or photochemical conditions, undergo ring opening to form a ketene intermediate, followed by cyclisation to yield the 6-substituted-4-hydroxy-2-pyrones[219] (**285**) (Scheme 10).

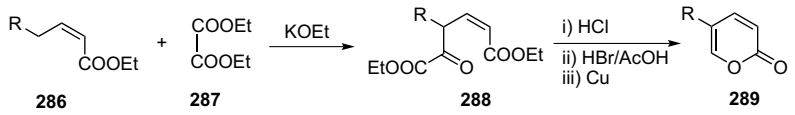


Scheme 6.

For introducing an alkyl group at position 5 of the 2-pyranone ring, a different strategy has been followed through base-catalysed acylation at the γ-position of the α,β-unsaturated esters (**286**) with diethyl oxalate (**287**). The acid-catalysed condensation of the resulting intermediate (**288**) leads to the 5-alkyl-2*H*-pyran-6-carboxylic acids, which on decarboxylation in the presence of Cu powder yield[211] the 5-substituted-2-pyranones (**289**) (Scheme 7).

(*Z*)-2-Alken-4-ynoates (**297**) are useful precursors for the synthesis of 5-halo-6-alkyl-2*H*-pyran-2-ones (**299**) in high yield (Scheme 11). The cyclisation of 2-alken-4-ynoates (**297**) is effected by ICl (**298**).[220]

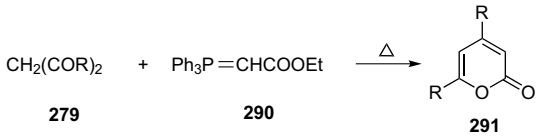
3-Substituted-2*H*-pyran-2-one-4-carboxaldehyde acetals (**302**) have been synthesised[221] from the reaction of an acetylenic dialdehyde monoacetal (**301**) and 5-substituted Meldrum's acid



Scheme 7.

4.2. By Wittig reactions

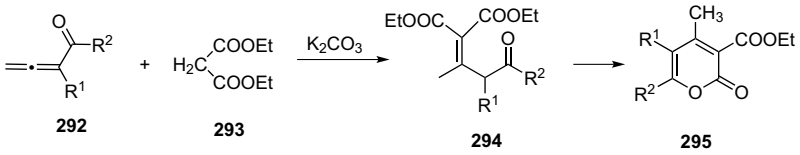
The Wittig reaction has been employed for the synthesis of 4,6-disubstituted-2*H*-pyranones[212] (**291**) by heating a phosphorane (**290**) with different 1,3-diketones (**279**) (Scheme 8).



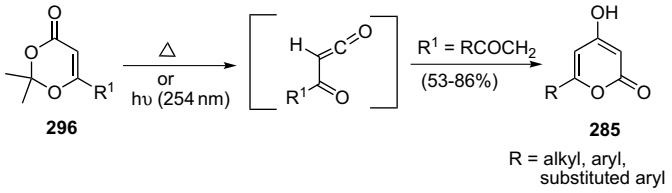
Scheme 8.

(**300**) at reflux for 24 h in trismethoxyethoxyethylamine (TMEEA) in good-to-high yields (Scheme 12).

3,4,6-Triaryl-2*H*-pyran-2-ones **306** have been synthesised from 1,3-diarylprop-2-yn-1-ols obtainable from the reaction of phenylacetylenes (**303**) and 4-substituted benzaldehydes (**304**) in the



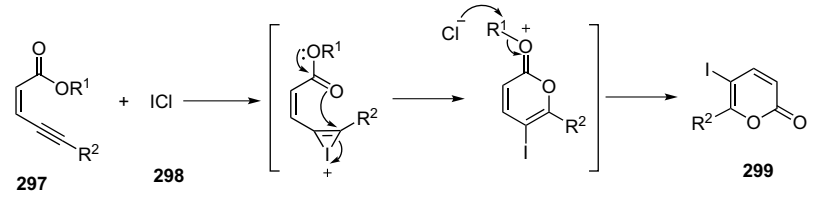
Scheme 9.



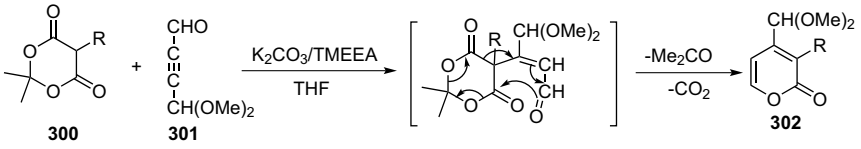
Scheme 10.

Treatment of cyclobutenones with 5 mol % of $[\{RuCl_2(CO)_3\}_2]$ in toluene at 100 °C for 12 h gave novel dimerisation products, 6-alkenyl-2-pyranones, in high yields with good (*Z*)-selectivity.[223] The use of $[\{RhCl_2(CO)_3\}_2]$ as catalyst instead of $[\{RuCl_2(CO)_3\}_2]$ led to a sharp reversal of stereoselectivity.

A convenient synthesis of 3-acylamino-2*H*-pyran-2-ones (**312**) has been developed[224] through a reaction of β-alkoxyvinylpolyfluoroalkyl-ketones (**310**) with *N*-acylglycines (**311**) (Scheme 15).



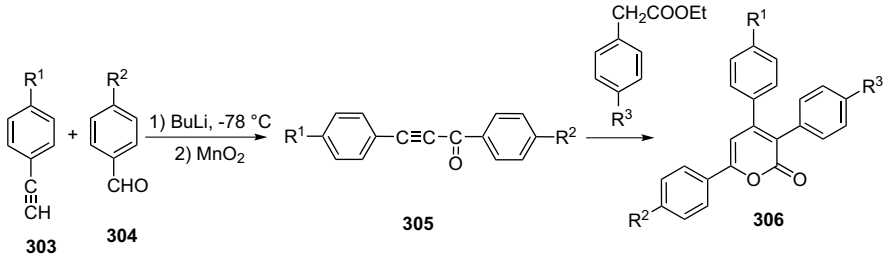
Scheme 11.



Scheme 12.

presence of *n*-butyllithium (Scheme 13). Subsequent oxidation of the intermediates by activated manganese dioxide (MnO_2) afforded the corresponding 1,3-diarylprop-2-yn-1-ones (**305**) in good yield,

Enaminones (**313**) also react analogously with *N*-acylglycines (**311**) to yield[225] 3-acylamino-6-substituted-2*H*-pyran-2-ones (**314**) (Scheme 16).



Scheme 13.

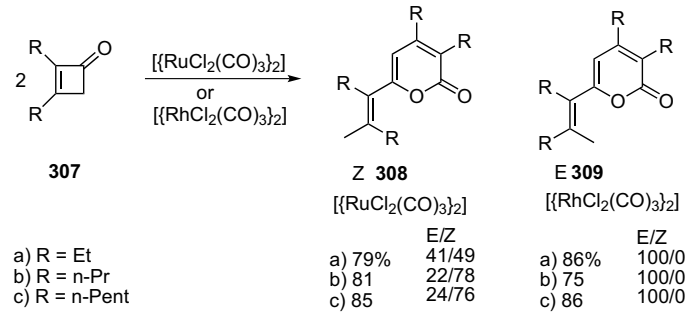
which on condensation with *para*-substituted-phenylacetic acid esters under basic conditions afforded the 3,4,6-triaryl-2*H*-pyran-2-ones (**306**) in moderate yields.[222]

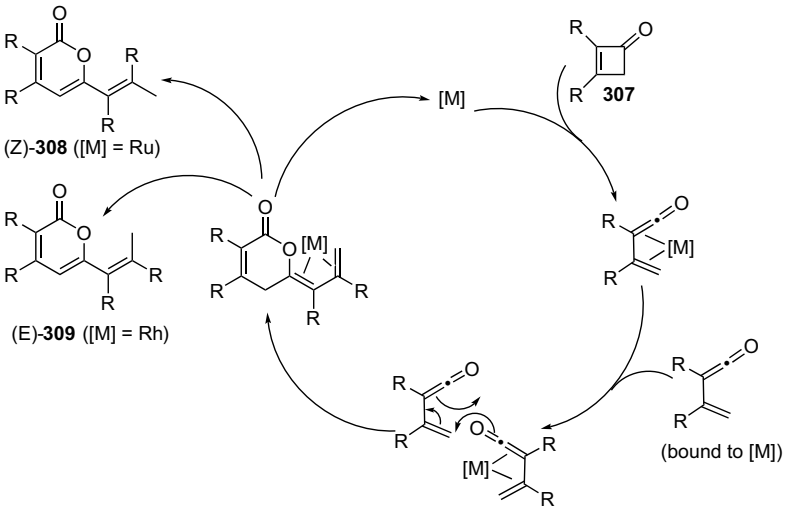
A novel stereoselective synthesis of 2-pyranones (**308** and **309**) by the ring-opening dimerisation of cyclobutenones (**307**), catalysed by ruthenium and rhodium complexe, has been developed (Scheme 14). In addition, a rhodium complex $[\{RhCl(CO)_2\}_2]$ showed high catalytic activity in the decarbonylative or direct coupling of cyclobutenones with alkenes by C–C bond cleavage. The present reactions are likely to involve both η^4-vinylketene and metallocyclopentenone intermediates.

4.4. From silyl reagents

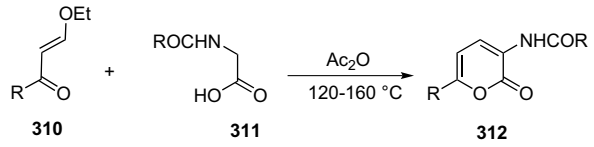
Silylketenes (**315**) easily undergo a [4+2] cycloaddition reaction with electron-rich 1,3-dienes (**316**) to yield 2-pyranones (**318**)[226] via the intermediate **317** (Scheme 17).

O-Silyl cyanohydrins on reaction with cyclobutenediones (**319**) give a spontaneous silyl migration with expulsion of cyanide ion to generate the key intermediate 4-acylcyclobutenone which undergoes facile rearrangement to the substituted 2-pyrones (**320**) (Scheme 18).[212,227]



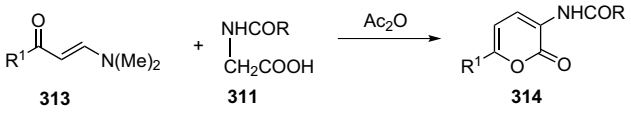


Scheme 14. Plausible mechanism for formation of 2-pyranones.

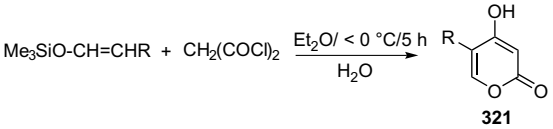


Scheme 15.

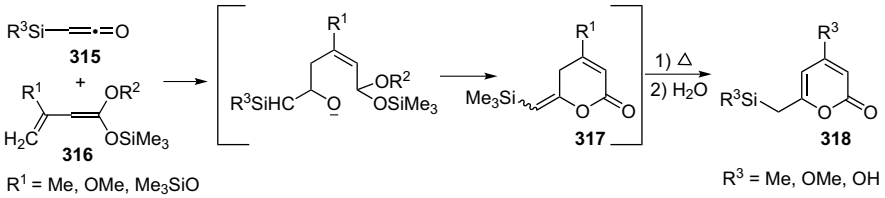
3,6-Unsubstituted-4-hydroxy-2*H*-pyran-2-ones **321** have been prepared by the reaction of 1-trimethylsiloxy-alkenes and malonyl dichloride at below 0 °C in good yields (Scheme 19).[228]



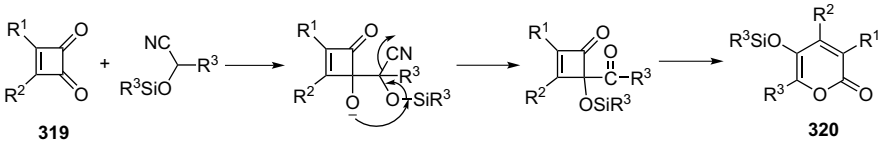
Scheme 16.



Scheme 19.



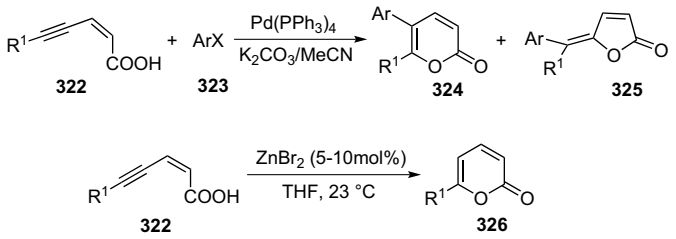
Scheme 17.



Scheme 18.

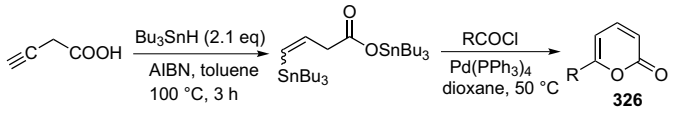
4.5. From (*Z*)-2-en-4-ynoic acids

6-Substituted-5-aryl-2*H*-pyran-2-ones (**324**) have been prepared from the reaction of (*Z*)-5-alkyl-2-en-4-ynoic acids (**322**) with aryl halides (**323**) in the presence of K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$, as a mixture of 2-pyranones (**324**) and stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]-2(5*H*)-furanones[229] (**325**) (Scheme 20). This reaction does not give satisfactory yields of the 2*H*-pyran-2-ones (**324**). Thus, (*Z*)-5-alkyl-2-en-4-ynoic acids (**322**), prepared by the Pd-catalysed alkynylzinc-β-haloacrylic acid coupling, on treatment with 5–10 mol % of $ZnBr_2$ produce 6-alkyl-2*H*-pyran-2-ones (**326**), along with minor amounts of (*Z*)-5-alkylidenefuran-2-(5*H*)-ones (Scheme 20).[230]



Scheme 20.

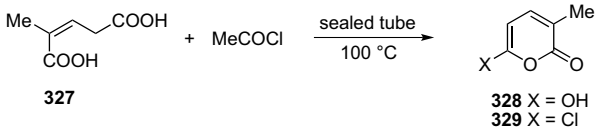
Recently, a stereoselective synthesis of 2-pyranones (**326**) in the presence of a palladium catalyst from a functional vinyltin derivative has been reported in very good yields (Scheme 21).[231,232] The required vinyltin precursor, has been easily obtained by radical hydrostannation[233] of but-3-ynoic acid with Bu_3SnH in 83% yield as a mixture of *E*/*Z* isomers (85:15), which on reaction with acid chlorides under standard Stille conditions, afforded the 6-substituted-2*H*-pyranones (**326**).



Scheme 21.

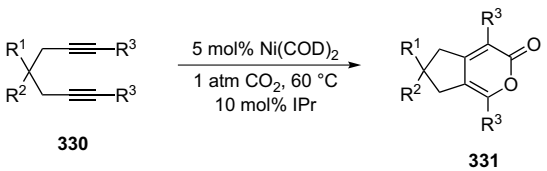
4.6. From cyclisation of glutaconic acid

A substituted glutaconic acid (**327**) on reaction with acetyl chloride in a sealed tube at 100 °C gives a mixture of 6-hydroxy-3-methyl-2*H*-pyran-2-one (**328**) and the corresponding 6-chloro-3-methyl-2*H*-pyran-2-one (**329**) (Scheme 22).[234]



Scheme 22.

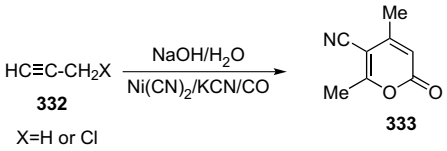
Recently, pyrones **331** have been prepared by a nickel-catalysed [2+2+2] cycloaddition of diynes **330** and carbon dioxide at atmospheric pressure in the presence of the ligand, 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) (Scheme 23).[235] The



Scheme 23.

mechanism involves an initial [2+2] cycloaddition of carbon dioxide and an alkynyl unit of the diyne, followed by insertion of a second alkynyl moiety and reductive elimination to furnish the pyrones in good yields.

Recently, a new methodology for the construction of the 2*H*-pyran-2-one ring system has been developed, using propargyl chloride or propargyl alcohol **332** as the substrate, which on reaction with carbon monoxide and KCN in the presence of $Ni(CN)_2$ in a basic aqueous medium, afforded 4,6-dimethyl-5-cyano-2-pyranone **333** (Scheme 24).[236]



Scheme 24.

Tominaga et al.[237] have reported an elegant synthesis of 6-alkyl/aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles (**335a**), and methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates (**335b**), from the reaction of various ketones with ketene dithioacetals (**334**) derived from methyl cyanoacetate and dimethyl malonate in the presence of powdered KOH in DMF/DMSO (Scheme 25). The compounds **335a** are aminated with secondary amines in refluxing ethanol to yield the 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles (**336**) in moderate yields.[238,239]

Tarhan et al.[240] have reported a one-pot synthesis of substituted 2*H*-pyran-2-ones (**339**) in good yields from the acid-catalysed reactions of 1,3-dicarbonyl compounds (**337**) with methyl 2-carbomethoxy-3-(*N*-methylanilino)acrylate (**338**) (Scheme 26).

5. Reactions of 2*H*-pyran-2-ones

It is evident from the topography of 2*H*-pyran-2-one (**340**) (Fig. 60) that the C-2, C-4 and C-6 positions of the pyranone ring are electrophilic in nature and prone to nucleophilic attack. The electron density at C-3 and C-5 remains unaffected and these positions are susceptible to electrophilic attack. The presence of alkyl, alkoxy or electron- releasing substituents at the C-4 and C-6 positions of the pyran ring facilitates electrophilic substitution in the ring. An electron-withdrawing substituent at C-3 makes the C-4 and C-6 positions more impoverished and thereby favours nucleophilic reactions. With regard to these two positions, the latter is comparatively more susceptible to nucleophiles. The presence of good leaving groups such as methoxy, methylsulphanyl and methylsulphoxide groups at C-4 makes the position more vulnerable to nucleophilic attack.

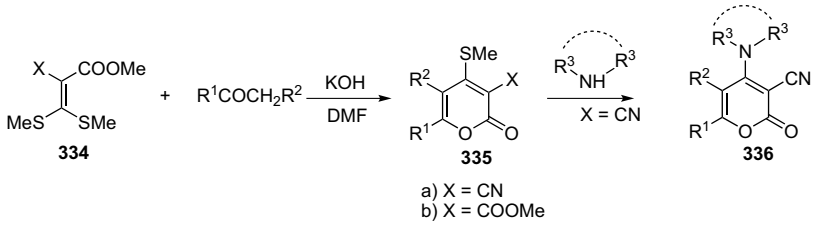
Besides electrophilic and nucleophilic reactions, the 2-pyranone ring system shows photochemical and cycloaddition reactions, as it behaves like a cyclic diene.

5.1. Electrophilic addition and substitution reaction

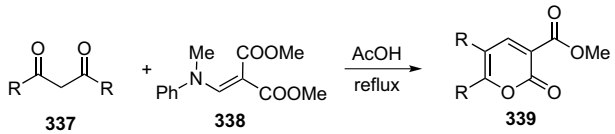
5.1.1. Halogenation

The presence of alkyl or electron-donating substituents on the pyran ring favours electrophilic reactions. In the absence of activating groups, electrophilic reactions require forcing conditions that lead to substitution and addition reactions.

Bromination of unsubstituted 2*H*-pyran-2-one (**278**) occurs at 60 °C in the presence of an excess of bromine and provides 3,4,5,6-tetrahydro-tetrabromopyran-2-ones (**341**), but in boiling carbon



Scheme 25.



Scheme 26.

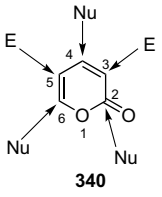
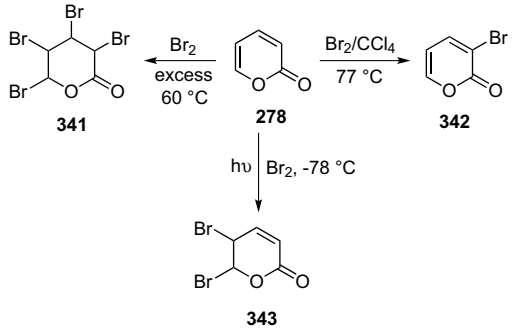


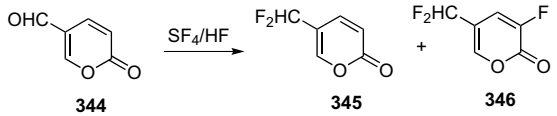
Figure 60.

tetrachloride at 77 °C yields 3-bromo-2*H*-pyran-2-one (**342**) as a substitution product.[24] Irradiation of **278** in 1,2-dichloroethane with Br_2 gives 5,6-dibromo-5,6-dihydro-2*H*-pyran-2-one (**343**) as an addition product (Scheme 27).[241]



Scheme 27.

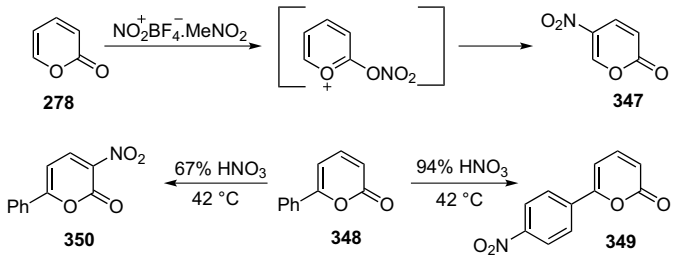
Sulphur tetrafluoride in hydrofluoric acid fluorinates 5-formyl-2*H*-pyran-2-one (**344**) at the ring atom as well as at the substituent at 100 °C to yield 5-difluoromethyl-2-pyranone (**345**) and 5-difluoromethyl-3-fluoro-2-pyranone (**346**) (Scheme 28).[242]



Scheme 28.

5.1.2. Nitration

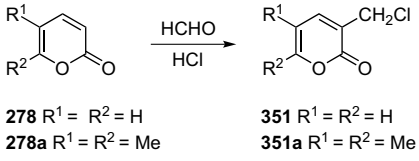
Nitration of unsubstituted 2*H*-pyran-2-one (**278**) with nitronium tetrafluoroborate yields 5-nitro-2-pyranone (**347**) in moderate yield (Scheme 29). In the presence of a phenyl ring at the C-6 position of the pyran ring (**348**), however, the aryl ring is nitrated preferentially with a mixture of nitric acid and sulphuric acid to yield **349**. Nitation of **348** with 67% nitric acid gives 3-nitro-2*H*-pyran-2-one (**350**).[17]



Scheme 29.

5.1.3. Chloromethylation

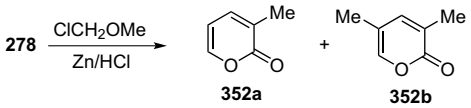
Chloromethylation of 2-pyranone (**278**) with formalin and hydrochloric acid yields 3-chloromethyl-2*H*-pyran-2-one (**351**) (Scheme 30).[243] The presence of alkyl substituents such as a methyl group at positions 5 and 6 of the pyran ring (**278a**) facilitates the chloromethylation reaction and forms 3-chloromethyl-5,6-dimethyl-2*H*-pyran-2-one (**351a**) (Scheme 30).[244]



Scheme 30.

5.1.4. Miscellaneous reactions

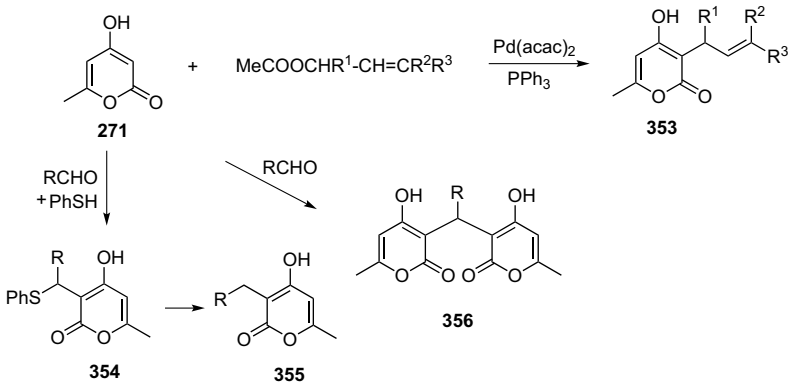
Alkylation of unsubstituted 2-pyranone (**278**) by a haloalkyl methyl ether in the presence of Zn/HCl yields the 3-alkyl- (**352a**) and 3,5-dialkyl-2-pyranone (**352b**) (Scheme 31).[242]



Scheme 31.

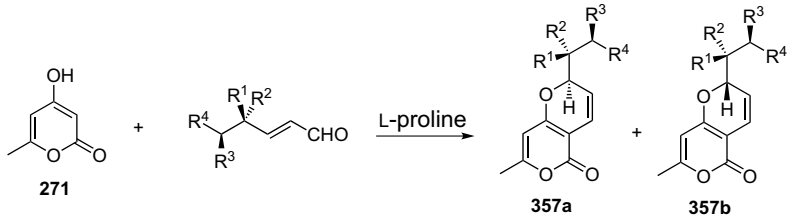
The alkylation chemistry of 4-hydroxy-2*H*-pyran-2-ones has been extensively explored by Moreno-Manas et al.[245,246] Some interesting enolate-type reactions are highlighted in this section. Alkylation of 4-hydroxy-2*H*-pyran-2-ones under the usual reaction conditions leads to the *O*-alkylated products. Thus, in order to obtain C3-alkylated products, more specific reaction conditions are generally required. Moreno-Manas et al.[245,246] demonstrated the stereoselective and regioselective synthesis of 3-alkyl-4-hydroxy-2*H*-pyran-2-ones

(**353**) through a palladium-catalysed allylation of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**271**) with allylic acetates in a thermodynamically controlled manner. Another useful approach[245] for C3-alkylation of **271** is through thioalkylation (**354**) followed by desulphuration to afford the alkylated lactone **355** as shown in Scheme 32. In the absence of benzenethiols, various aromatic and aliphatic aldehydes also react with 4-hydroxy-2*H*-pyran-2-ones to furnish the bis-lactones **356** in good yields[245,246] (Scheme 32).



Scheme 32.

Recently, Sagar et al.[247] have developed a diastereoselective synthesis of some pyrano-pyrones **357a**,**b** by an L-proline-catalysed condensation of **271** with substituted enals (Scheme 33).



Scheme 33.

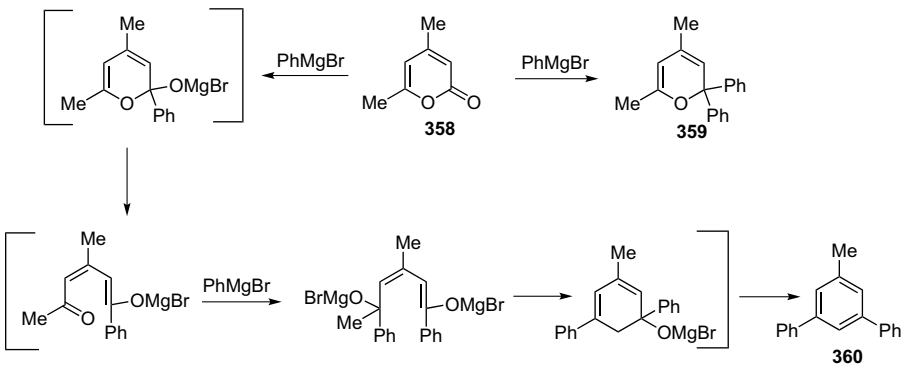
5.2. Nucleophilic reactions

Nucleophilic reactions on 2*H*-pyran-2-ones are greatly influenced by the substituents present. Good leaving groups and electron-withdrawing substituents favour nucleophilic substitution, ring-opening, ring-transformation and ring-contraction reactions, depending upon the type of nucleophile used.

5.2.1. Reactions due to C-nucleophiles

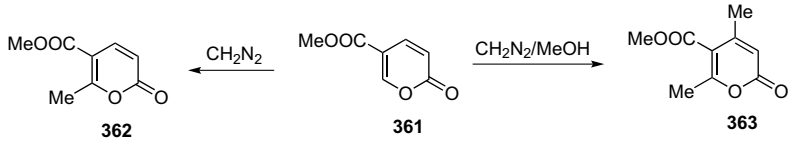
Carbanions are strong nucleophiles and are generated easily in situ from various organometallic reagents. The formation of the products depends upon the substituents present and the molar the ratio of the reactants. The reaction of 4,6-dimethyl-2*H*-pyran-2-one (**358**) with two moles of phenylmagnesium bromide yields[248] 2,2-diphenyl-4,6-dimethylpyran (**359**), whereas the use of an excess of the Grignard reagent changes the course of the reaction and, finally, 1,3-terphenyl (**360**) is formed (Scheme 34). The transformation of 2*H*-pyran-2-one to an arene is also effected by the use of a Reformatsky reagent, e.g., $BrZnCH_2COOEt$.

The carbanion of diazomethane easily methylates[249,250] the carbon atom adjacent to an electron-withdrawing substituent of



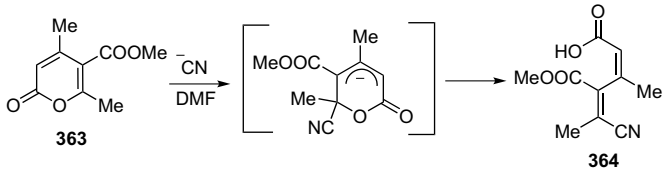
Scheme 34.

2-pyranone. Thus, the reaction of methyl 2*H*-pyran-2-one-5-carboxylate (**361**) with diazomethane forms methyl 6-methyl-2*H*-pyran-2-one-5-carboxylate (**362**) and methyl 4,6-dimethyl-2*H*-pyran-2-one-5-carboxylate (**363**) (Scheme 35).



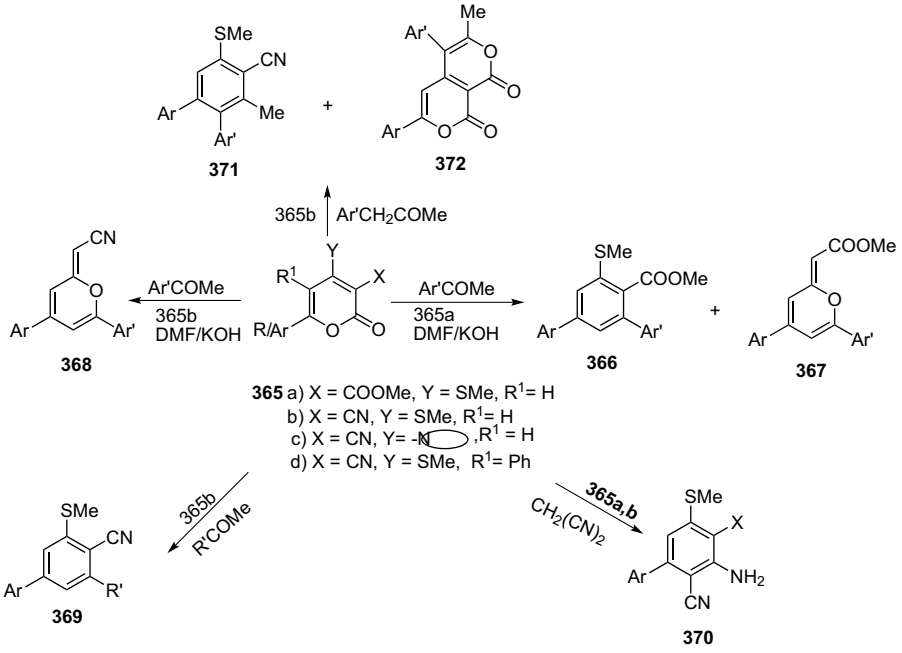
Scheme 35.

Cyanide ion, being a nucleophile, reacts with methyl 4,6-dimethyl-5-carboxylate (**363**) and gives 5-cyanohexa-2,4-dienoic acid (**364**) (Scheme 36).[251] The reaction possibly proceeds through a cyclic intermediate, followed by ring opening.



Scheme 36.

(iii) 6-alkyl/aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles, (iv) 5-alkyl-6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles/carboxylates, (v) 5-aryl-6-alkyl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles/carboxylates, (vi) 5,6-diaryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles, and (vii) methyl 5,6-diaryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylates as precursors. As evident from the topography of these 2-pyranones, positions C-6 and C-4 are prone to nucleophilic attack, possibly due to extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the pyranone ring. Carbonyl compounds having an α-methyl or methylene group adjacent to the carbonyl group in a cyclic or acyclic system or reactants with a reactive methylene group have been used as a source of the carbanion for the ring-transformation study. Thus, the base-catalysed ring transformation of suitably functionalised 2*H*-pyran-2-one by different carbanions produced various arenes and heteroarenes, which are difficult to obtain through classical routes (Scheme 37).



Scheme 37.

5.2.1.1. C-Nucleophile-induced ring transformations. The ring transformation of 2-pyranones is greatly influenced by the type and position of the substituents attached to the ring. Electron-withdrawing and good leaving groups favour ring-transformation reactions by the carbanion.

Ram and Goel et al. have recently made an extensive study of the ring transformations of 2-pyranones **365** by carbanions using (i) 6-alkyl/aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles, (ii) alkyl 6-alkyl/aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylates,

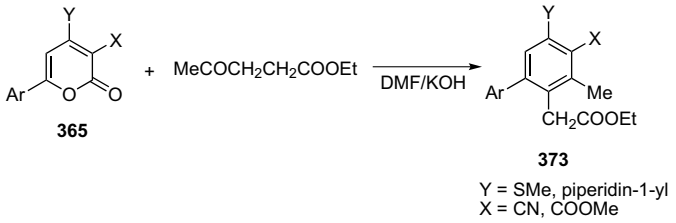
A base-catalysed ring transformation of **365a** by aryl methyl ketones in DMF, provided 1,3-teraryls[252,253] (**366**) as a major product and methyl (4,6-diarylpyran-2-ylidene)acetates (**367**) as a minor constituent. A change of the ester group to CN (**365b**) in the lactones changed the course of reaction and provided exclusively the (4,6-diarylpyran-2-ylidene)acetonitriles[254] (**368**). This discrepancy is possibly due to the high electron-attracting power of the CN substituent, compared to COOMe, that facilitates the enolisation and favours the ring-closure reaction to yield **368**.

Biaryls[255] **369** have also been obtained regioselectively from the reaction of 2-pyranones (**365b**) with aliphatic ketones under similar reaction conditions in good yields, which is in contrast to the reaction with aryl methyl ketones.

Highly congested biaryls (**370**) have also been prepared[256,257] from the reaction of 2-pyranones (**365b**) and malononitrile under analogous reaction conditions. This procedure is an alternative to the Suzuki reaction for preparing biaryls in which one of the aryl rings is highly functionalised.

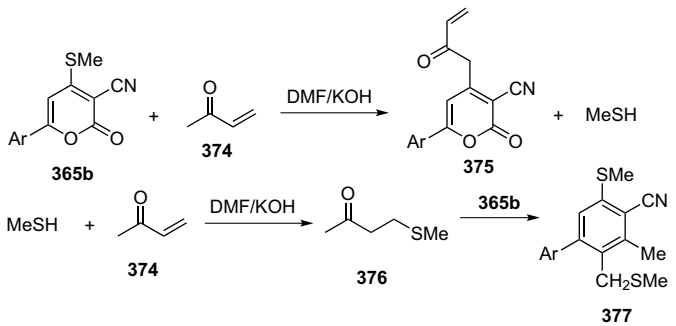
The reaction of 2-pyranones (**365b**) with aryl acetones under analogous reaction conditions provided 1,2-teraryls (**371**) in 11–21% yield,[258,259] together with pyrano[3,4-*c*]pyran-3,4-diones (**372**) as major constituents. The teraryls **371** were, however, regioselectively prepared from the ring transformation of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles (**365c**) with aryl acetones. In spite of these being two sites for the carbanion formation under the applied experimental reaction conditions, CH_2 is the preferred site, compared to methyl, due to the combined inductive and resonance effects of the substituents attached to it.

By means of a careful manoeuvering in the selection of the appropriate 2-pyranone and reactant, a variety of compounds can be derived in the shortest possible steps through ring-transformation reactions. Arylacetates (**373**), known for their diverse pharmacological activities, are easily prepared from the reaction of **365** and ethyl levulinate in excellent yields (Scheme 38).[260]



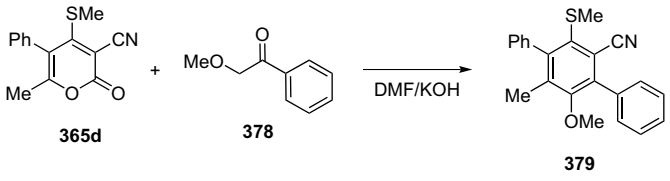
Scheme 38.

The ring transformation of **365b** by methyl vinyl ketone (**374**) was also studied during our exploratory work. This reaction was very interesting as the first step was a substitution on C-4 of the 2-pyranone to form **375** with loss of methylthiol, which in turn acted as a nucleophile and formed a 4-methylsulphanyl-2-butanone (**376**) intermediate in situ as a Michael adduct on reaction with methyl vinyl ketone. This intermediate further acted as a source of carbanion for the ring transformation. Thus, the reaction of **365b** and 4-methylsulphanyl-2-butanone (**376**) in DMF using KOH as a base produced 3-methylsulfanylmethyl-2-methyl-6-methylsulphanyl-4-arylbenzonitriles (**377**) in moderate yield (Scheme 39).[261] This reaction was further generalised through ring transformation of **365b** by 4-arylsulphanyl-2-butanones obtained from the reaction of **374** and thiophenols.



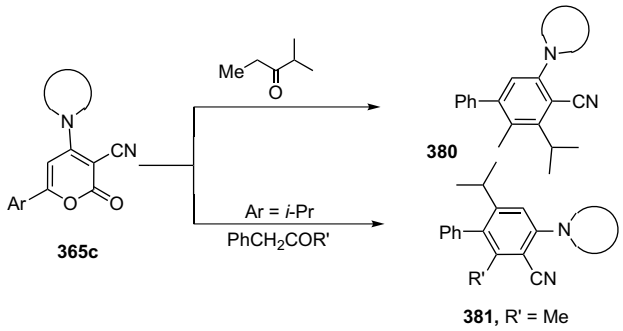
Scheme 39.

Recently, *para*-terphenyls such as **379** have been prepared by the reaction of 5-aryl-6-methyl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles, e.g., **365d**, with 2-methoxy-1-phenylethanone (**378**) in the presence of a base at room temperature (Scheme 40).[262]



Scheme 40.

Goel et al. have prepared *ortho*-cymene- (**380**) and *meta*-cymene- (**381**) cored biaryls through a ring transformation of **365c** with isopropyl methyl ketone as a source of carbanion (Scheme 41).[263]

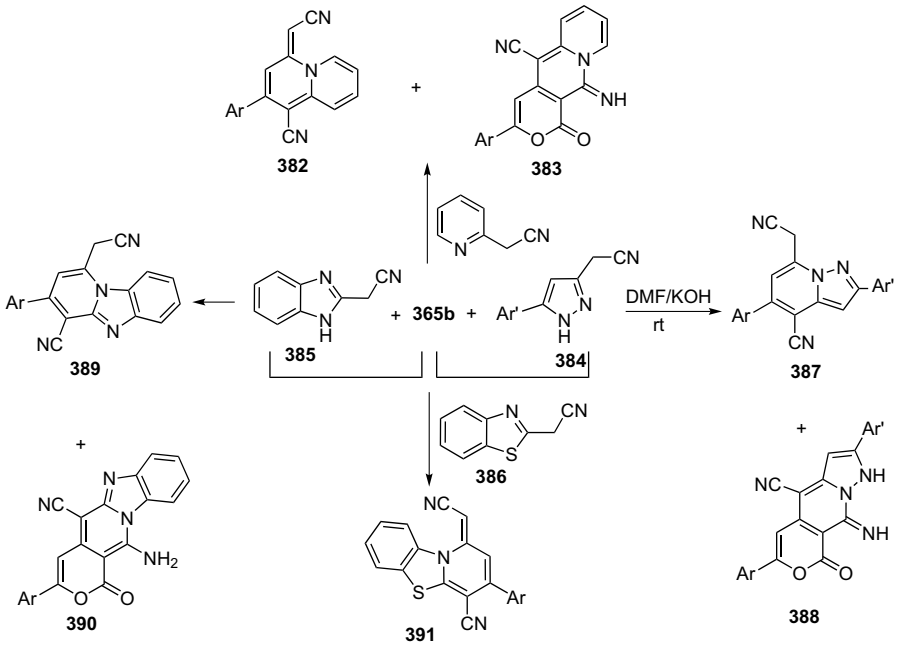


Scheme 41.

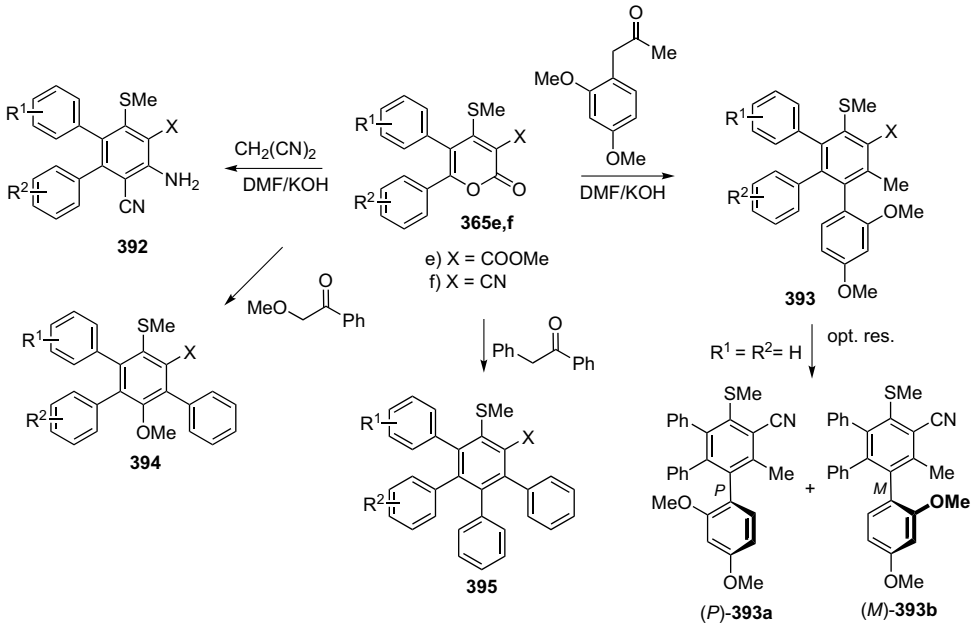
Compounds containing an activated methylene group, such as 2-pyridylacetonitrile, act as a source of carbanion and have been used for a ring-transformation study. The reaction of 2-pyranone with 2-pyridylacetonitrile in the presence of KOH in DMF led to two products **382** and **383**, depending upon the attack of the carbanion either at the C-4 or C-6 site. Attack at C-6 by the carbanion from 2-pyridylacetonitrile was followed by ring closure involving the ring nitrogen to yield quinolizines[264] (**382**), while attack at C-4 led to the production of pyranoquinolizines (**383**) involving the CN substituent at C-3 of the pyran ring in cyclisation (Scheme 42).

The versatility of the reaction was further explored using (5-aryl-1*H*-pyrazol-3-yl)acetonitriles **384**, (benzimidazol-2-yl)acetonitrile **385** and (benzothiazol-2-yl)acetonitrile **386** as the sources of carbanion. These reagents on reaction with **365b** separately produced a mixture of two products. Thus, reaction of **365b** with 3-cyanomethyl-5-aryl-1*H*-pyrazoles (**384**) provided pyrazolo[1,5-*a*]pyridines (**387**) and pyrano[4,3-*d*]pyrazolo[1,5-*a*]pyridines (**388**) as minor constituents.[265] Similarly, the reaction with (benzimidazol-2-yl)acetonitrile (**385**) under similar reaction conditions yielded pyrido[1,2-*a*]benzimidazoles (**389**) and pyrano[4,3-*d*]pyrido[1,2-*a*]benzimidazoles (**390**) as minor products,[265] while (benzthiazol-2-yl)acetonitrile (**386**) under analogous conditions provided only 3-aryl-1-[(*E*)-cyanomethylidene]-1*H*-pyrido[2,1-*b*]benzthiazole-4-carbonitriles (**391**), due to the non-availability of the other site for the ring closure.[266]

Recently, Goel et al. have systematically synthesised 1,2-diaryl- (**392**), 1,2,3-triaryl- (**393**), 1,2,4-triaryl- (**394**) and 1,2,3,4-tetraarylbenzenes (**395**)[267] through base-catalysed ring transformation of 5,6-diaryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles (**365**), obtained from the reaction of deoxybenzoins and methyl 2-cyano-3,3-dimethylthioacrylate (Scheme 43). A single crystal X-ray diffraction study of **395** (R^1=R^2=H, X=CN) revealed that all of the



Scheme 42.



Scheme 43.

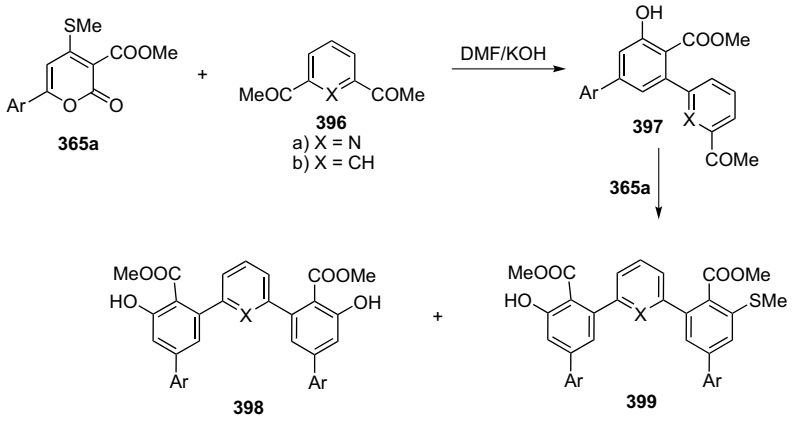
phenyl rings are arranged in a propeller like-conformation. A crystal packing analysis showed an N–π noncovalent interaction[267] in the molecule. These compounds (**393**–**395**) show inherent atropisomerism and one of the compounds of the prototype **393** has been resolved[267b] in to the atropo-enatiomerically pure quateraryls (**393a** and **393b**) and its absolute configuration was determined by LC–CD coupling in combination with quantum chemical CD calculations (Scheme 43).

The synthesis of hydroxylated dipyridinyls **397** and terpyridinyls with phenyl spacers (**398** and **399**) has been reported through carbanion-induced, ring-transformation reactions of 6-pyridyl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylates (**365a**) by either 2,6-diacetylpyridine (**396a**) or 1,3-diacetylbenzene (**396b**) in good yields (Scheme 44).[268]

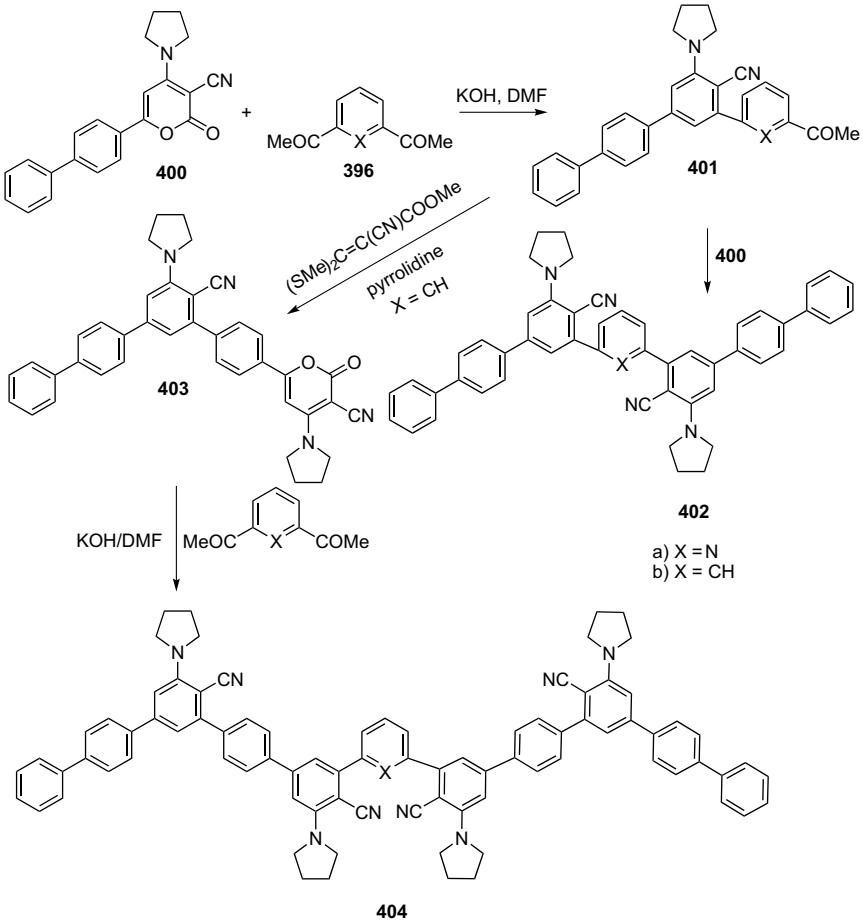
Attempts to make bent-core oligoarenes stepwise through ring transformation of a 6-aryl-4-(pyrrolidin-1-yl)pyran-2-one-3-carbonitrile (**400**) by 1,4-diacetylbenzene and 2,6-diacetylpyridine (**396a**) in DMF/KOH was successfully achieved (Scheme 45).[269] This methodology is applicable for the preparation of polyarenes ranging from tetraarenes **401,** heptaarenes **402** to undecaarenes **404** through intermediacy of **403** by manipulating the aryl substituent in the pyran ring and selecting the appropriate diacetylarenes.

5.2.1.2. Synthesis of fused cyclic arenes and heteroarenes.

5.2.1.2.1. Arenes. Polycyclic arenes and heteroarenes have been prepared through base-catalysed ring transformation of a suitably functionalised 2*H*-pyran-2-one by alicyclic ketones and heteroketones. Alicyclic ketones ranging from cyclobutanone to



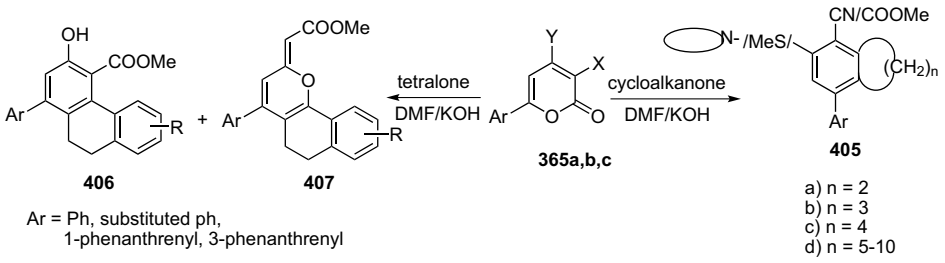
Scheme 44.



Scheme 45.

pentadecanone have been used as a source of carbanion for the ring transformation. Benzocyclobutanes are difficult to make using the four-membered cyclic ketone, due to ring strain, but Ram et al.[270] have successfully synthesised (**405a**) through base-catalysed ring transformation of 2*H*-pyran-2-ones (**365a,b**) by cyclobutanone separately in moderate yield in one step (Scheme 46). Analogously, 1*H*-2,3-dihydroindans[271](**405b**), tetrahydronaphthalenes[272] (**405c**) and dihydronaphthalenes[273] have been prepared through ring transformation by cyclopentanone, cyclohexanone and 2-cyclohexenone, respectively. Even macrocyclic compounds such as benzocycloalkenes[272,274] (**405d**) have been easily prepared from the reaction of **365a**,**b** with the appropriate macrocycloalkanones.

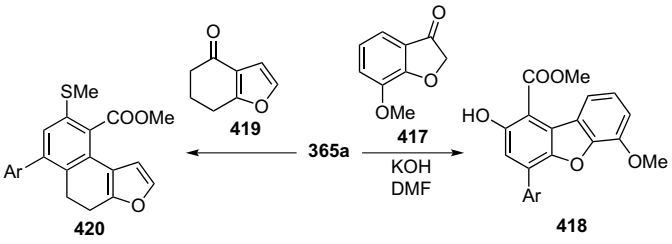
Highly congested angular hydrocarbons such as 1-aryl-3-hydroxy-4-methoxycarbonyl-9,10-dihydrophenanthrenes (**406**) as major products and 4-aryl-(5,6-dihydronaphtho[1,2-*b*]pyran-2-ylidene)acetates (**407**) as minor constituents have also been prepared and reported[275] through base-catalysed ring transformation of **365a** by 1-tetralone under similar reaction conditions.[276,277] This is a very efficient and novel approach to the synthesis of bisphenanthrenes **406** with positional isomers.



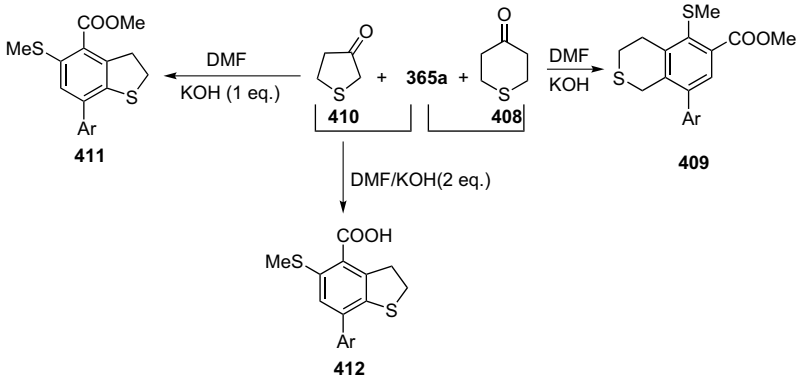
Scheme 46.

5.2.1.2.2. Heteroarenes. The feasibility of the methodology for the construction of various heterocycles as drug intermediates has been further explored using heterocyclic ketones as a source of carbanion.

The reaction of **365a** with tetrahydrothiopyran-4-one (**408**) at room temperature in the presence of powdered KOH in DMF smoothly provided the ring-transformed products, 6-carbethoxy-5-methylsulphanyl-3,4-dihydro-1*H*-isothiochromenes (**409**),[278] in moderate yield (Scheme 47). Analogous, the ring transformation of **365a** with tetrahydrothiophene-3-one (**410**) in the presence of 1 equiv of KOH provided the methyl 7-aryl-2,3-dihydro-5-methylsulphanylbenzothiophene-4-carboxylates (**411**). The use of 2 equiv of KOH, however, led to the corresponding acids (**412**), due to ester hydrolysis.[278]



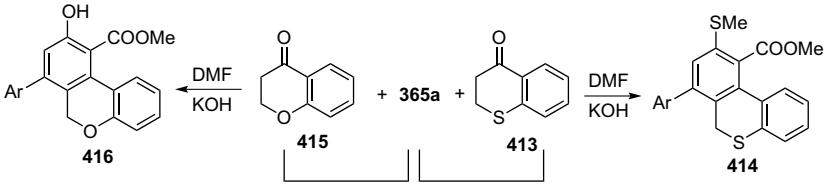
Scheme 49.



Scheme 47.

This reaction was further generalized as shown in Scheme 48, using thiochroman-4-one (**413**) and chroman-4-one (**415**) as the source of carbanion for the ring transformation of **365a**.

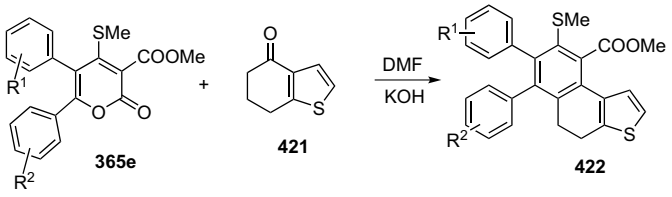
The interaction of methyl 5,6-diaryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylates (**365e**) with 6,7-dihydro-5*H*-benzo[*b*]thiophen-4-one (**421**) in the presence of a base in DMF furnished the functionalised naphthothiophenes[281](**422**) in good yields (Scheme 50).



Scheme 48.

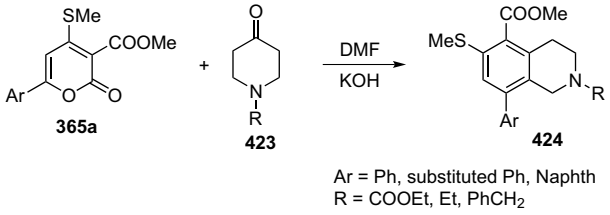
The usual work-up and purification by column chromatography provided[278] methyl 7-aryl-9-methylsulphanyl-6*H*-benzo[*c*]thiochromene-10-carboxylates (**414**) and methyl 7-aryl-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylates (**416**).

Highly functionalised dibenzofurans[279] (**418**) and 4,5-dihydronaphtho[2,1-*b*]furans[280] (**420**) have been synthesised and reported from the reaction of **365a** with 7-methoxybenzofuran-3-one (**417**) and 6,7-dihydro-5*H*-benzo[*b*]furan-4-one (**419**), respectively, in good yields (Scheme 49).



Scheme 50.

Nitrogen heterocycles such as *N*-substituted tetrahydroisoquinolines (**424**) have been synthesised[282] very elegantly through the carbanion-induced ring transformation of methyl 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylates (**365a**) by *N*-substituted-4-piperidones (**423**) in good yields (Scheme 51).



Scheme 51.

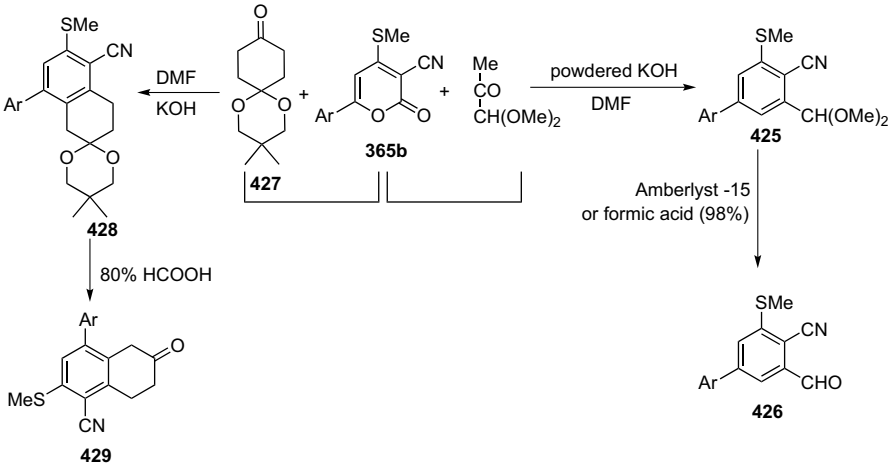
5.2.1.3. Synthesis of aryl aldehydes and aryl ketones. Suitably functionalised 2*H*-pyran-2-ones (**365b**) are very good substrates for the construction of highly congested arylaldehydes (**426**) and β-tetralones (**429**) through ring- transformation reactions in two steps (Scheme 52).

5.2.1.4. Synthesis of metallocenes. 6-Ferrocenyl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitrile (**430a**) and methyl 6-ferrocenyl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylate (**430b**) are obtained from the reaction of acetylferrocene with methyl 2-cyano/carbomethoxy-3,3-dimethylthioacrylate. The ring-transformation of 6-ferrocenyl-2*H*-pyran-2-ones (**430a**,**b**) by carbon and nitrogen nucleophiles separately led to the production of various ferrocenylarenes and heteroarenes.

Thus, the reaction of **430a** with hydrazine in methanol at reflux temperature provided 3-cyanomethyl-5-ferrocenyl-1*H*-pyrazole (**431**) in more than 40% yield (Scheme 53). The cyanomethyl-1*H*-pyrazole (**431**) was used further as a source of carbanion for the ring transformation of **430a** in a basic medium to produce the ferrocenylpyrazol[1,5-*a*]pyridine (**432**) and ferrocenyl-3-imino-2-oxopyrano[4,3-*d*]pyrazolo[1,5-*a*]pyridine (**433**) in poor yields. The reaction of **430a** with ammonium acetate in ethanol at reflux temperature and the usual work-up led to the formation of 2-amino-6-ferrocenyl-4-methylsulphanylpyridine (**434**). The diferrocenyl arene **435** has been obtained through ring transformation of **430b** by 1-acetylferrocene in 15–20% yield.[285,286] The ring transformation of **430a** by alkyl and aryl methyl ketones under analogous reaction conditions yielded the monoferrocenylarenes (**436a**–**d**) in moderate yields.

5.2.2. Nitrogen nucleophile-induced reactions

6-Aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles/carboxylates (**365a**,**b**) are indispensable synthons for the construction of nitrogen heterocycles through ring transformation by nitrogen nucleophiles. Thus, the reaction of **365b** with ambiphilic nitrogen nucleophiles such as hydrazine hydrate and arylhydrazines, separately provided (5-aryl-1*H*-pyrazol-3-yl)acetonitriles[287] (**438a**–**e**), an isomeric mixture of (5-aryl-1-phenylpyrazol-3-yl)acetonitriles (**437a**), and (3-aryl-1-phenylpyrazol-5-yl)acetonitriles (**437b**), together with a bicyclic product formed through a ring closure involving the cyano function and methylsulphanyl group as pyrano[4,3-*c*]pyrazoles **437c** (Scheme 54).[288]

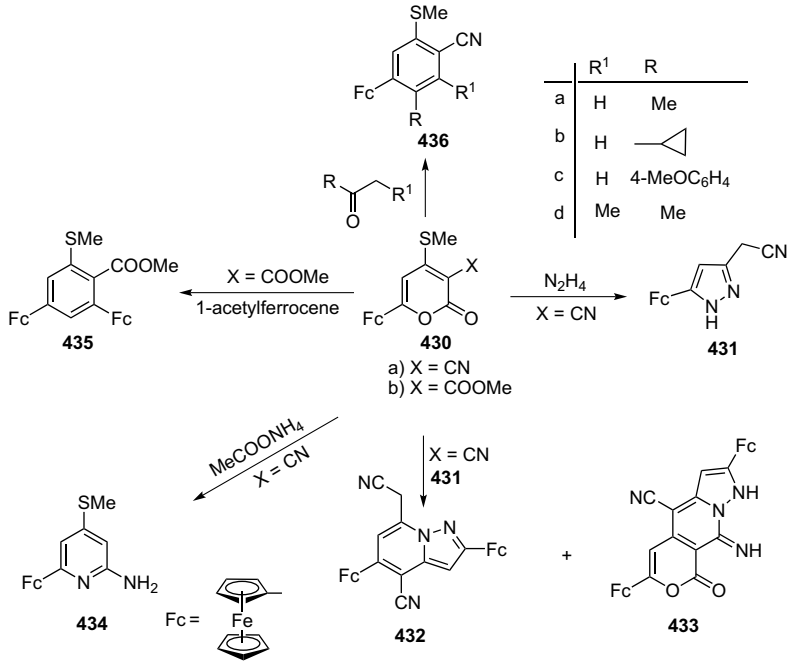


Scheme 52.

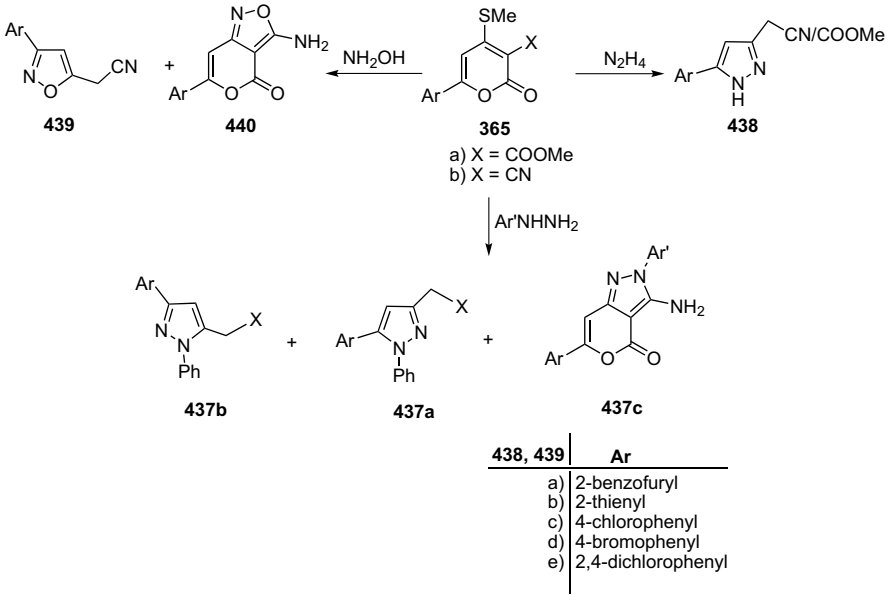
Thus, the reaction of 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles (**365b**) with pyruvaldehyde dimethyl acetals under similar experimental conditions provided highly substituted acetals **425**, which on stirring with Amberlyst-15 in chloroform at room temperature, deacetalated to the free aldehydes (**426**).[283] The analogous reaction of 2-pyranones (**365b**) with (2,2-dimethyltrimethylene) ketal (**427**) provided the tetrahydronaphthone ketals (**428**), which on stirring with 80% HCOOH, deketalated to the highly functionalised 2-tetralones (**429**).[284]

Using hydroxylamine as an ambiphilic nucleophile, its reaction with **365b** provided (3-arylisoxazol-5-yl)acetonitriles (**439a**–**e**) and pyrano[4,3-*c*]isoxazoles (**440**). The course of the reaction was ascertained by trapping and characterising the isolated intermediate.

Various amino acid esters were used as nitrogen nucleophiles successfully for the preparation of *N*-substituted pyridine derivatives. The reaction of **365b** with amino acid esters in refluxing pyridine produced 2-imino-*N*-substituted pyridines (**441**) in 40–52% yield. In cases where optically active amino acid esters were used as the nucleophile, the products isolated were optically inactive, due to racemisation in the presence of concentrated alkali. 2-Amino-4-methylsulphanylpyridines (**442**) have been synthesised[289] by heating a mixture of **365b** with ammonium acetate/carbonate in pyridine (Scheme 55). Hydrogenation of **442** in the presence of Raney Ni produced 2-aminopyridines (**443**) with elimination of the methylsulphanyl group. Bridgehead bicyclic (2-arylpyrido[1,2-*a*]pyrimidin-2-ylidene)acetonitriles (**444**) were obtained from the reaction of **365b** with 2-aminopyridine at 120 °C for 4 h. A base-catalyzed ring transformation of **365b** by cyanamide produced 2-amino-4-methylsulphanylnicotinonitriles[290] (**445**). 2-Aminothiazoles and 2-amino-1,3,4-thiadiazoles on fusion with **365b** separately underwent thermal ring transformation to yield (7-arylthiazolo[3,2-*a*]pyrimidin-5-ylidene)acetonitriles[291] (**446a**) and (7-arylthiadiazol[3,2-*a*]pyrimidin-2-ylidene)acetonitriles[291] (**446b**) in very good yields (Scheme 55).



Scheme 53.



Scheme 54.

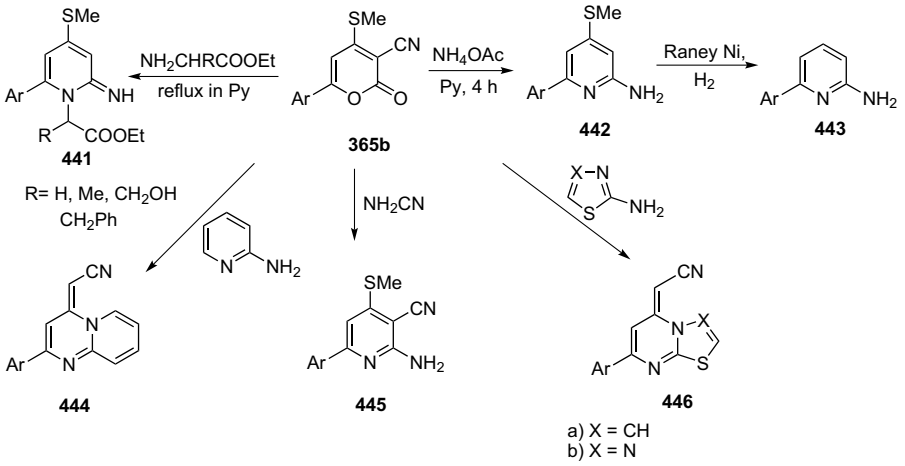
In order to prepare fused nitrogen heterocycles, the ring transformation of **365b** was carried out by 6-amino-1,3-dimethylpyrimidine-2,4-dione (**447**) in the presence of powdered KOH in DMF, yielding the 7-aryl-5-cyanomethyl-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidines (**448**) in 65–78% yield (Scheme 56).[292]

Reaction of 2-pyranone (**365b**) with a secondary amine provided C-4 substitution products, while interaction with a primary amine afforded nitrogen heterocycles and/or substitution products.

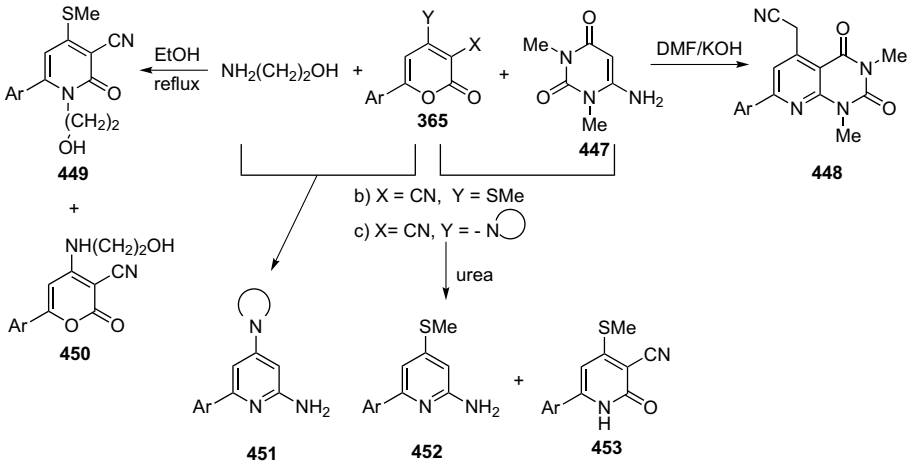
The reaction of **365b** with ethanolamine in ethanol at reflux temperature provided the nitrogen-inserted products, 6-aryl-1-(2-hydroxyethyl)-4-methylsulphanyl-2-pyridones (**449**), and the substitution products 6-aryl-4-(2-hydroxyethylamino)-2*H*-pyran-2-ones (**450**), but under similar experimental conditions **365c** reacted differently with ethanolamine and produced[293] the 2-amino-6-aryl-4-(piperidin-1-yl)pyridines (**451**) in 80–95% yield (Scheme 56). Fusion of **365b** with urea/thiourea at 150 °C yields[294] a mixture of two ring-transformed products, 2-amino-6-aryl-4-methylsulphanylpyridines (**452**) and 6-aryl-3-cyano-4-methylsulphanyl-1*H*-pyridin-2-ones (**453**), in an almost equal ratio, but the reaction in pyridine at reflux temperature produced 2-aminopyridines (**452**) in 82–92% yield.[295]

Methyl 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-2-carboxylates (**365a**) on fusion with urea for 10–15 min provided only 6-aryl-4-methylsulphanyl-1*H*-pyridin-2-ones (**454**)[295] without the formation of any anticipated products (**455**) (Scheme 57).

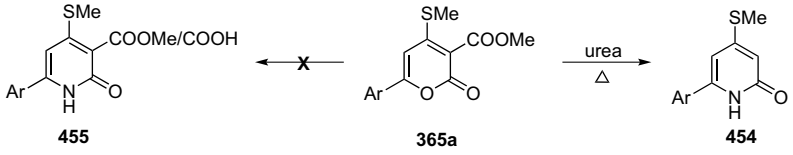
The formation of **454** possibly proceeds through an intermediate **455**. The reactions of 2-pyranone with guanidines and amidines have not been studied in detail. Only a single example is known, where 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**456**) on reaction with guanidine (**457**) provided (2-hydroxy-4-methylpyrimidin-6-yl)acetone[296,297] (**458**) (Scheme 58). This reaction possibly



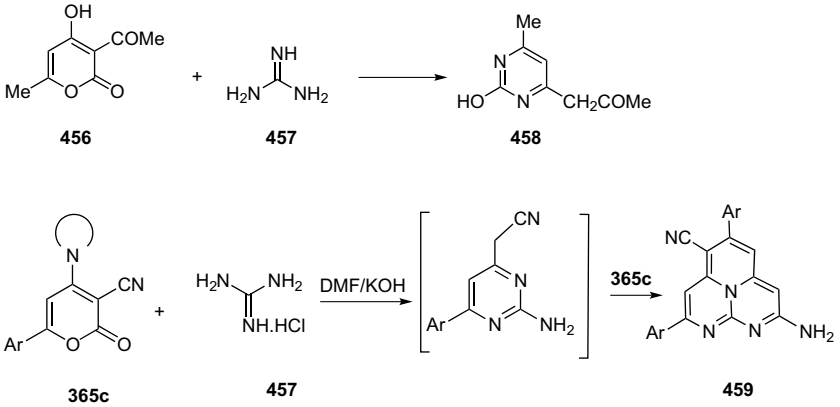
Scheme 55.



Scheme 56.



Scheme 57.

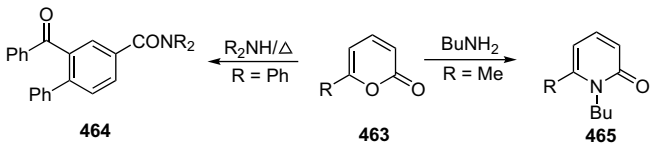


Scheme 58.

proceeded through a base-catalysed ring opening by nucleophilic attack at C-6 of the pyran ring, followed by ring closure and decarboxylation.

The reaction of (**365c**) with guanidine hydrochloride in the presence of powdered KOH in DMF, however, provided 1,9,9b-triazaphenalenes (**459**) in moderate yield through the intermediacy of pyrimidinylacetonitrile, which acted as a source of carbanion for successive ring transformations (Scheme 58).[298]

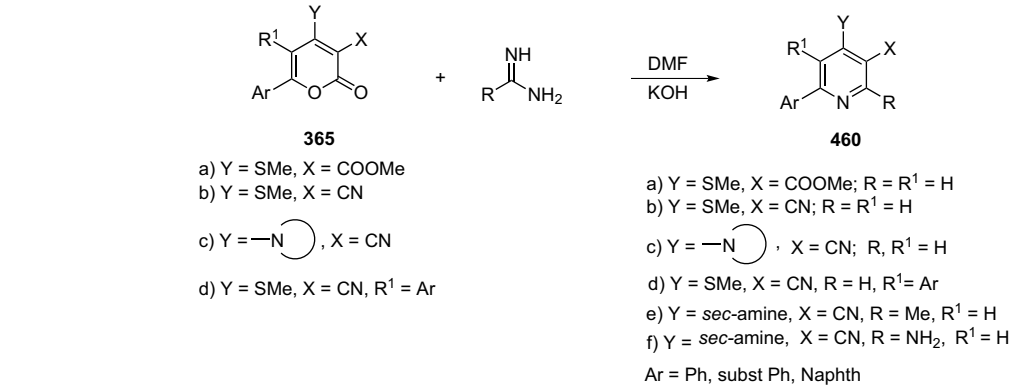
Ram et al. have prepared pyridines[299] using 2-pyranones (**365a–d**) as precursors and amidines as nucleophiles. The reaction of **365a–d** with formamidine acetate in the presence of powdered KOH in DMF provided excellent yields of the 6-aryl-3,4-disubstituted pyridines (**460a–d**) (Scheme 59).



464 463 465

Scheme 61.

5.2.2.1. Oxoketene cyclic aminals as nitrogen nucleophiles. Oxoketene cyclic aminals have been used as nucleophiles for various ring-transformation reactions to obtain polycyclic heterocycles, not easily obtainable by a classical route in short steps. Oxoketene cyclic aminals (**466**) have been obtained from the reaction of 3,3-bis(methylsulfanyl)-1-arylpropenones with 1,2- or 1,3-diaminoalkanes. The cyclic aminals (**466**) thus obtained react with 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles (**365b**) in THF using NaH as a base at room temperature in the presence of normal light to yield 4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a-diazacyclopenta[*a*]anthracene-6-carbonitriles[306] (**468**) (Scheme 62). In order to trap the intermediate (**467**), the reaction was carried out in the dark and, finally, the compounds isolated were characterised as 2-(5-aryl-8-aroyl/heteroaroyl-2,3-dihydroimidazo[1,2-*a*]pyridin-7(1*H*)-ylidene)-acetonitriles (**467**). The intermediate (**467**) on photolysis is transformed into the cyclic products[306] (**468**) and was found to be identical to the product obtained directly from the reaction of **365b** with **466** in the light. The aza analogs **468b** have also been synthesised from the reaction of **365b** and the cyclic aminals obtained from the reaction of 3,3-bis(methylsulphanyl)-1-(pyridin-3-yl)propenone and 1,2- or 1,3-diaminoalkane analogously.



365

a) Y = SMe, X = COOMe
b) Y = SMe, X = CN
c) Y = —N⌒, X = CN
d) Y = SMe, X = CN, R^1 = Ar

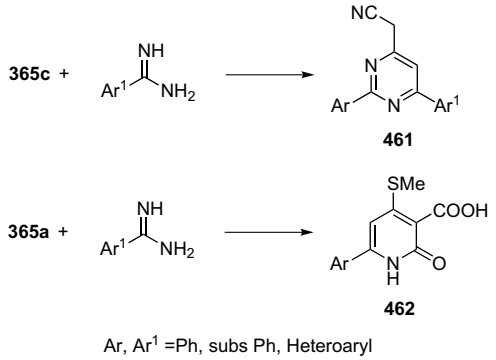
460

a) Y = SMe, X = COOMe; R = R^1 = H
b) Y = SMe, X = CN; R = R^1 = H
c) Y = —N⌒, X = CN; R, R^1 = H
d) Y = SMe, X = CN, R = H, R^1= Ar
e) Y = *sec*-amine, X = CN, R = Me, R^1 = H
f) Y = *sec*-amine, X = CN, R = NH_2, R^1 = H

Ar = Ph, subst Ph, Naphth

Scheme 59.

This reaction was further explored by using acetamidine as a nucleophile for the preparation of substituted α-picolines. The reaction proceeded analogously, but the yields of **460e** were poor. The ring transformation of **365b**,**c** by (pyrazol-1-yl)amidine or *S*-methylisothiourea under similar reaction conditions produced 2-amino-6-aryl-4-*sec*-aminopyridines (**460f**). It was surprising that the reaction of **365c** with arylamidines went differently and, instead of pyridines, (2,6-diarylpyrimidin-4-yl)acetonitriles (**461**) were isolated and characterised.[300] The reaction of arylamidines with methyl 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxylates (**365a**), however, produced 6-aryl-3-carboxylic-4-methylsulphanyl-1*H*-2-pyridones[301] (**462**) (Scheme 60). The unexpected acid isolated (**462**; Ar=Ph) was characterised by a single-crystal X-ray diffraction analysis. The substituents attached to the amidine carbon also influence the course of reaction.



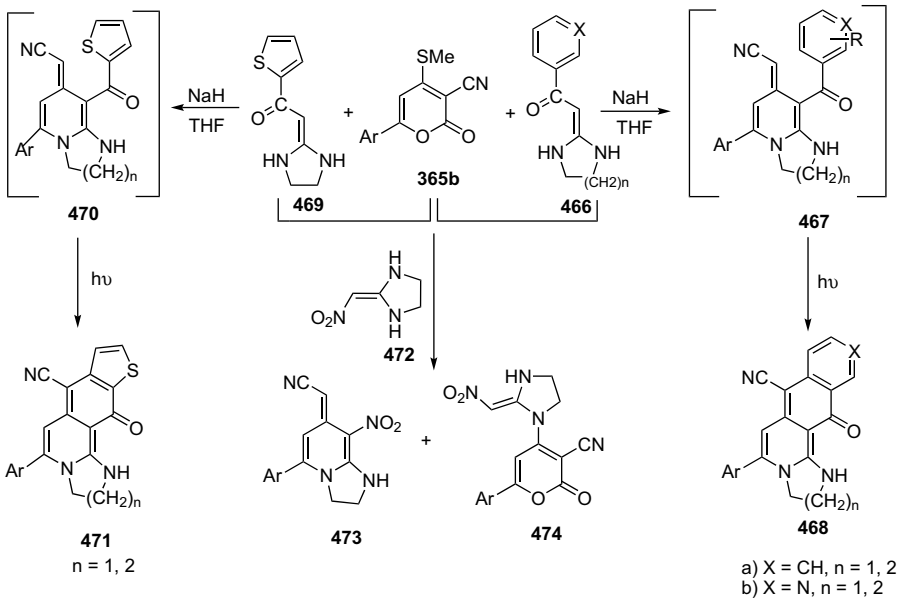
461

462

Ar, Ar^1 =Ph, subs Ph, Heteroaryl

Scheme 60.

6-Alkyl/aryl-2*H*-pyran-2-ones **463** react with amines or ammonia, through attack at C-2 with ring opening followed by acid-catalysed cyclisation, to yield arene (**464**) or pyridone (**465**) derivatives (Scheme 61).[302–305]



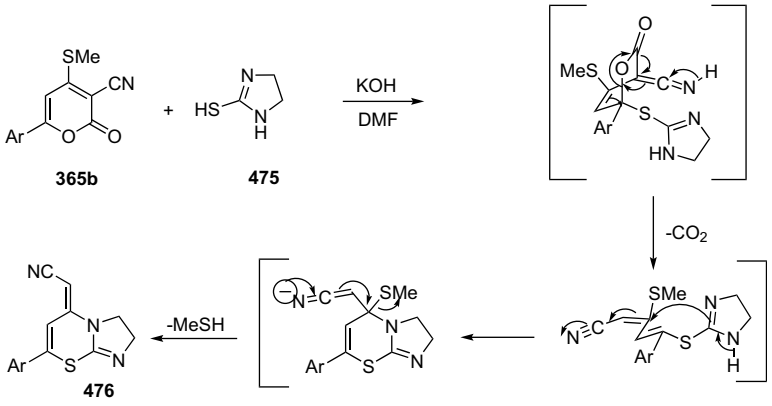
Scheme 62.

5.2.3. S-Nucleophile-induced ring-transformation reactions

2-Thioimidazolidine (**475**) has been used as a sulphur nucleophile for the ring-transformation reactions of 2*H*-pyranones **365b**. The reaction is basically initiated with ring opening by mercaptide ion, followed by ring closure with the elimination of carbon dioxide and methyl mercaptan to yield 2-[7-aryl-2,3-dihydro-5*H*-imidazo[2,1-*b*][1,3-thiazin-5-ylidene]acetonitriles **476**[291] (Scheme 63).

Finally, the structures of both the isolated products (**477**, **478**; Ar=Ph, Y=piperidin-1-yl) were confirmed by single-crystal X-ray diffraction (Scheme 64).

Under identical reaction conditions, 2,3,5-trisubstituted cyclopentadienones[310] (**479**) have been prepared through carbanion-induced ring contraction of **365c** by methyl cyanoacetate/cyanoacetamide. A plausible mechanism for the reaction is also shown in Scheme 65. This reaction provides an elegant route for the



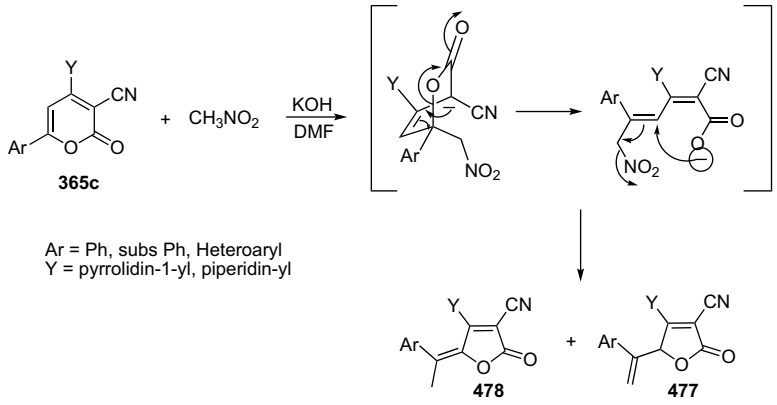
Scheme 63.

5.2.4. Ring-contraction reactions

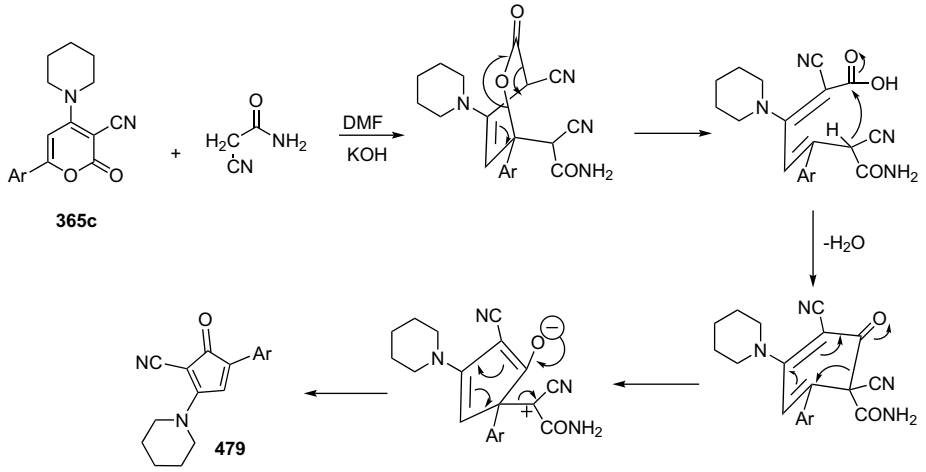
Suitably functionalised 2*H*-pyran-2-ones (**365c**) underwent ring-contraction reactions by carbanions under analogous experimental reaction conditions. Carbanion-induced ring contraction was observed from the reaction of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles (**365c**) with nitromethane using powdered KOH as a base in DMF by stirring the reaction mixture at room temperature. In this reaction two isomeric products[309] have been isolated and characterised as 2-oxo-5-(1-arylvinyl)-4-substituted-2,5-dihydrofuran-3-carbonitriles (**477**) as the major products and 2-oxo-5-(1-arylethylidene)-4-*sec*-amin-1-yl-2,5-dihydrofuran-3-carbonitriles (**478**) as the minor constituents. synthesis of highly congested cyclopentadienones, which are valuable drug intermediates.

The ring contraction of suitably functionalised 2*H*-pyranones has also been observed in the presence of alkali. When 3-chloro-4,5,6-triphenyl-2*H*-pyran-2-one (**480**) was heated with alcoholic KOH, the pyranone ring was contracted to 3,4,5-triphenylfuran-2-carboxylic acid (**481**) (Scheme 66).

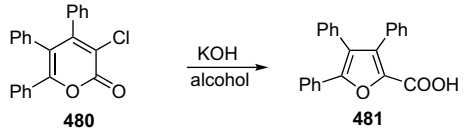
The yield of the product was further improved by using aqueous sodium carbonate as a base. 3-Bromo-5-carbomethoxy-2*H*-pyran-2-one (**482**) in the presence of aqueous KOH at 60 °C yielded 3-carbomethoxyfuran-2-carboxylic acid[311] (**483**) (Scheme 67).



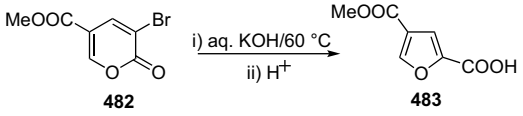
Scheme 64.



Scheme 65.

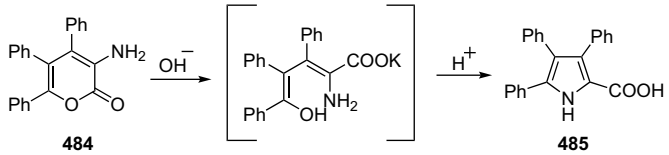


Scheme 66.



Scheme 67.

3-Amino-4,5,6-triphenyl-2*H*-pyran-2-one (**484**) under analogous reaction conditions provided the highly substituted pyrrole-2-carboxylic acid (**485**) after ring contraction (Scheme 68).[312,313]



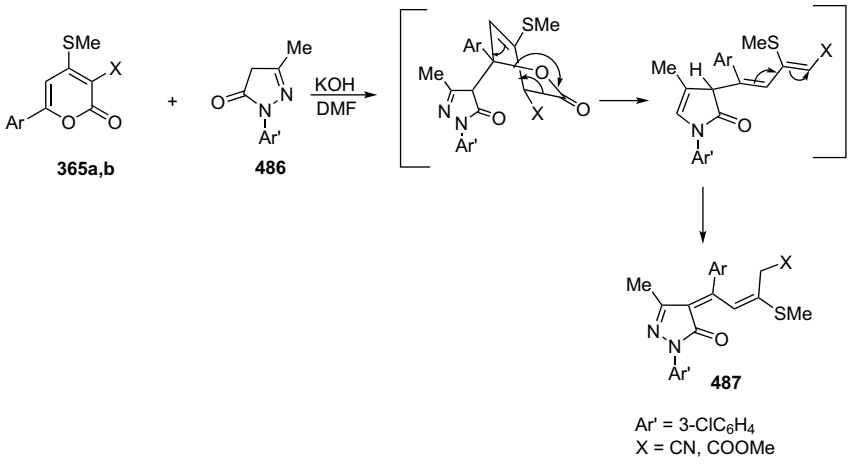
Scheme 68.

5.2.5. Ring-opening reactions

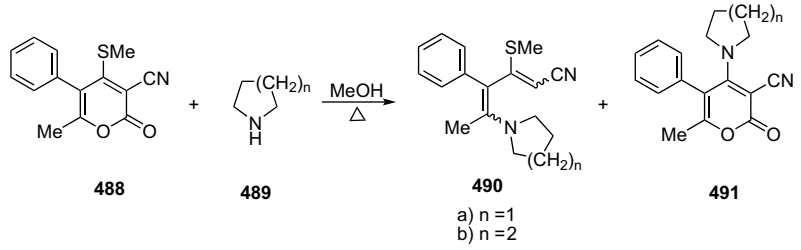
The base-catalysed ring-opening reactions of 2-pyranones (**365a**,**b**) by carbanions has been observed. Stereoselective alkenylation of 1,3-disubstituted-pyrazol-5-ones (e.g., **486**) with 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitriles/carboxylates (**365a**,**b**) in DMF using powdered KOH as a base yielded the (*E*,*E*)-5-aryl-5-[1-aryl-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]-3-methylsulphanylpent-3-en-carbonitriles/methyl carboxylates[314] (**487**) (Scheme 69). The stereochemistry of isolated compound (**487**, Ar=4-ClC$_6$H$_4$, X=COOMe) was ascertained by single-rystal X-ray diffraction.

The ring opening of 5-phenyl-6-methyl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitrile (**488**) by organic bases such as piperidine and pyrrolidine (**489**) provided a mixture of two products, one major product due to ring opening by pyrrolidine/piperidine to yield a mixture of the *Z*- and *E*-isomers of 3-methylsulphanyl-4-phenyl-5-pyrrolidin/piperidin-1-yl-hexa-2,4-dienenitrile[315] (**490**) and another minor product due to substitution at C-4 of the pyran ring (**491**) (Scheme 70).

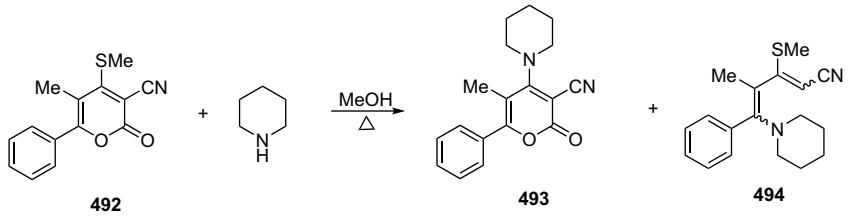
On the contrary, the reaction of 6-phenyl-5-methyl-4-methylsulphanyl-2*H*-pyran-2-one-3-carbonitrile (**492**), under analogous reaction conditions, in the presence of piperidine afforded 6-phenyl-5-methyl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitrile (**493**) as a major product. The other minor product obtained was characterised as a mixture of the *E*- and *Z*-isomers of 4-methyl-3-methylsulphanyl-5-phenyl-5-piperidin-1-yl-penta-2,4-dienenitrile [315] (**494**) (Scheme 71).



Scheme 69.

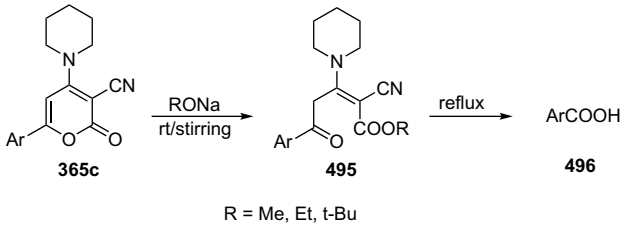


Scheme 70.



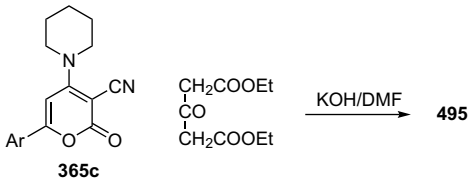
Scheme 71.

6-Aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles (**365c**) on stirring in alcohol in the presence of the respective alkoxide at room temperature provided alkyl 2-cyano-5-oxo-5-phenyl-3-(piperidin-1-yl)pent-2-enoates[316] (**495**), which on refluxing in the presence of alkoxide in alcohol produced the carboxylic acids (**496**) (Scheme 72). The same product was directly obtained by refluxing **365c** in the presence of alkoxide in alcohol.[317]



Scheme 72.

The reaction of **365c** with diethyl acetonedicarboxylate or ethyl acetate in DMF at room temperature using powdered KOH as a base afforded **495** in good yield. In this reaction, the ethoxide formed in situ acts as a nucleophile to open the 2*H*-pyran-2-one (**365c**) ring to yield **495** (Scheme 73).[316]

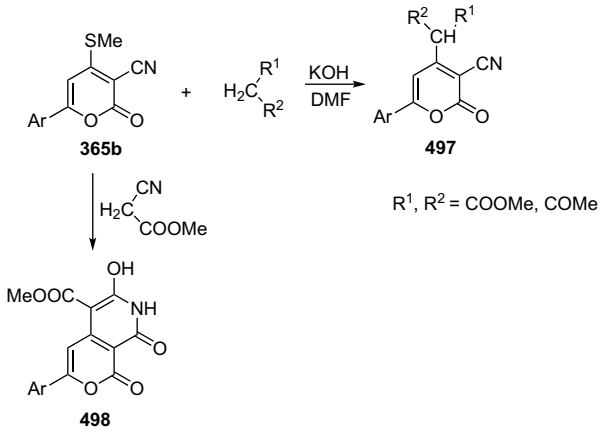


Scheme 73.

5.2.6. Reactions at substituents

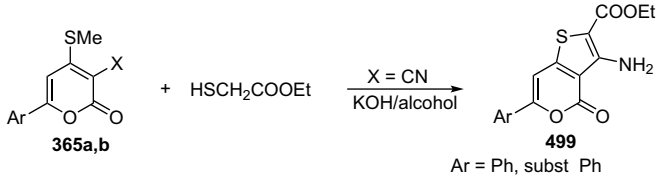
The methylsulphanyl substituent, being a good leaving group at C-4 of **365b**, is prone to simple substitution as well as substitution–cyclisation reactions involving the adjacent CN or COOMe substituents, depending upon the experimental reaction conditions. A base-catalysed reaction of pyran-2-ones (**365b**) with compounds containing reactive methylene group such as dimethyl malonate and acetylacetone gives substitution products[318]

(**497**), while methyl cyanoacetate provided pyrano[3,4-*c*]pyridines (**498**)[318] through substitution followed by cyclisation involving the cyano substituent at C-3 of the 2-pyranone ring (Scheme 74).



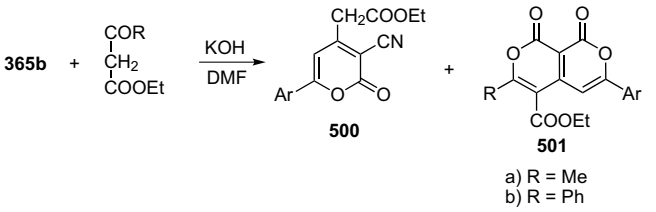
Scheme 74.

A base-catalysed reaction of **365a**,**b** with ethyl mercaptoacetate under mild reaction conditions in alcoholic KOH provided fused bicyclic compounds, thieno[3,2-*c*]pyran-4-ones[319] (**499**), in good yields (Scheme 75). This reaction is initiated by an attack of mercaptide ion at C-4, followed by cyclisation involving the substituent at C-3 of the pyran ring.



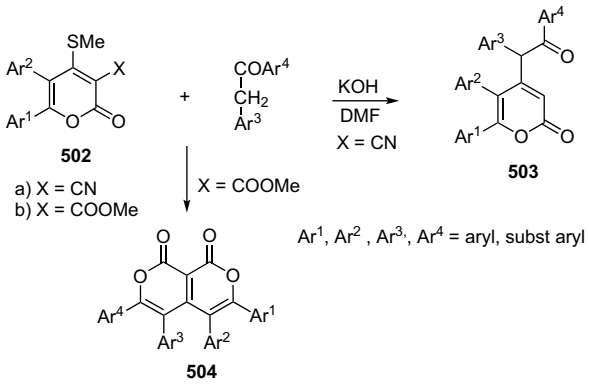
Scheme 75.

Base-catalysed reaction of 2*H*-pyran-2-ones (**365b**) with ethyl acetoacetate/ethyl benzoylacetate in DMF using powdered KOH as base at room temperature provided two different products,[320] one due to substitution at C-4 followed by ketonic hydrolysis to yield ethyl (6-aryl-3-cyano-2*H*-pyran-2-one-4-yl)acetates (**500**) and the other due to substitution-cyclisation involving the adjacent cyano group to give pyrano[3,4-*c*]pyran-3,4-diones (**501**) in nearly equal amounts (Scheme 76).



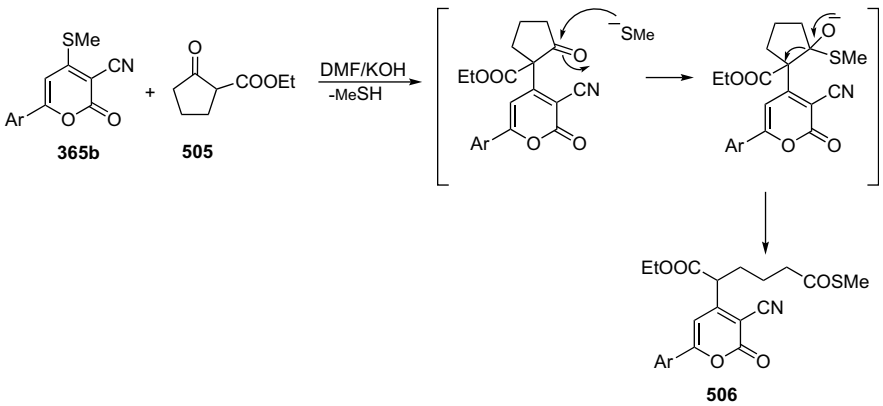
Scheme 76.

Recently, we have reported a general methodology for the synthesis of arylated 2*H*-pyran-2-ones and pyrano[3,4-*c*]pyran-1,8-diones, depending upon the electron-withdrawing substituent (nitrile or carbomethoxy) at position 3 of the 2*H*-pyran-2-ones **502a**,**b**. The reaction of 3-cyano-4-methylsulphanyl-5,6-diaryl-2*H*-pyran-2-ones **502a** with deoxybenzoin afforded the 4-(2-oxo-1,2-diarylethyl)-5,6-diaryl-pyran-2-ones **503** as the major products through an unusual decyanation, while the eaction of 3-carbomethoxy-5,6-diaryl-4-methylsulphanyl-2*H*-pyran-2-ones (**502b**) with deoxybenzoins furnished the pyrano[3,4-*c*]pyran-1,8-diones[321] (**504**) exclusively (Scheme 77).



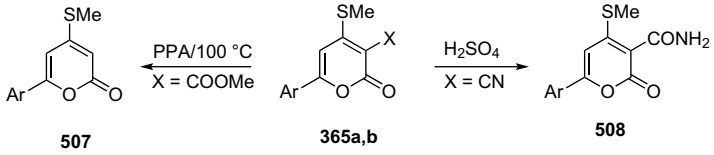
Scheme 77.

It is conspicuous that the reaction of **365b** with cyclopentanone in DMF using powdered KOH as a base at room temperature provided congested indans after the usual workup, while, with 2-carboethoxycyclopentanone (**505**), the course of the reaction was different, due to the presence of the carbomethoxy substituent adjacent to the carbonyl group which makes the position 2 of **505** more vulnerable to nucleophilic attack. Thus, the reaction of **365b** with **505** in the presence of KOH in DMF was initiated with substitution at C-4 followed by ring opening of carbethoxycyclopentanone by methyl mercaptide ion in situ to yield the thioesters (**506**)[322] in high yields (Scheme 78).



Scheme 78.

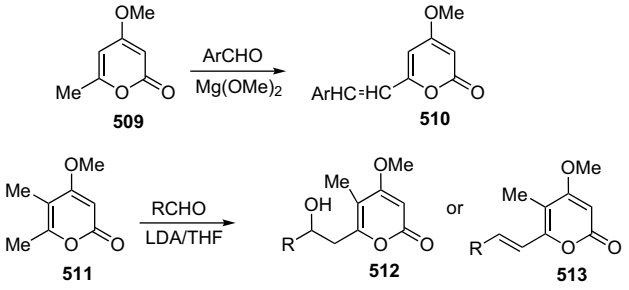
The decarboxylation of the ester group at position 3 of the 2-pyranones (**365a**) in poly phosphoric acid was effected by heating at ~120 °C for 4–5 h to give the 6-aryl-3-methylsulphanyl-2*H*-pyran-2-ones (**507**).[237,323] The CN substituent at C-3 of the 2-pyranones (**365b**) in concentrated sulphuric acid is hydrolysed to amide to yield the 6-aryl-4-methylsulphanyl-2*H*-pyran-2-one-3-carboxamides (**508**) in high yields (Scheme 79).



507 **365a,b** **508**

Scheme 79.

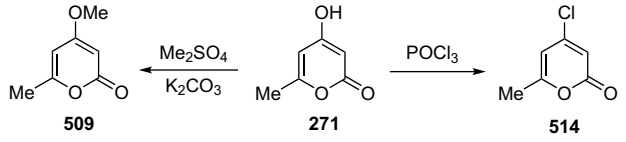
The 6-methyl substituent in the 2*H*-pyran-2-one (**509**) is highly activated, due to extended conjugation, and undergoes base-catalysed condensation with aldehydes to form the 6-styryl-2*H*-pyran-2-ones[324] (**510**) (Scheme 80). Similarly, the reaction of 5,6-dimethyl-4-methoxy-2*H*-pyran-2-one **511** with aldehydes in the presence of 1 equiv of LDA afforded either **512** or **513,** depending upon the substrate used.[246a] This approach has been applied to the synthesis of various natural products.[324]



509 **510** **511** **512** **513**

Scheme 80.

The hydroxy substituent at C-4 of the 2*H*-pyran-2-one (**271**) is halogenated by refluxing in $POCl_3$ to form the 4-chloro-2*H*-pyran-2-one (**514**) and alkylated by different alkylating agents to give the 6-methyl-4-alkoxy-2*H*-pyran-2-ones such as **509** (Scheme 81).[325]



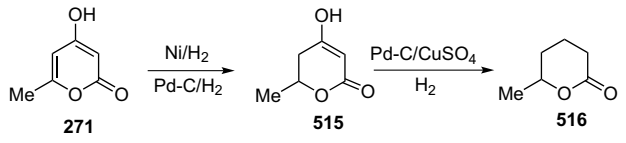
509 **271** **514**

Scheme 81.

5.3. Reduction

The reduction of 2*H*-pyran-2-ones strongly depends upon the nature of the catalyst used. Hydrogenation of 6-methyl-4-hydroxy-2-pyranone (**271**) in the presence of Ni or Pd–C at 5 kg/cm pressure reduces only the 5,6-double bond to form 5,6-dihydro-4-hydroxy-2*H*-pyran-2-one (**515**) (Scheme 82). On further hydrogenation of dihydro-2-pyranone (**515**) in the presence of Pd–C and $CuSO_4$ at 75 °C under 20 kg/cm pressure, the ring was completely reduced to 6-methyl-tetrahydro-2*H*-pyran-2-one (**516**).[326]

Other reducing agents such as $LiAlH_4$ and $NaBH_4$ did not reduce the pyran ring, but ring opened through attack at C-6. Reduction of 4,6-dimethyl-2*H*-pyran-2-one (**517a**) by LAH produced 3-methyl-hexa-2,4-dienoic acid (**518**), while reduction of **517b** with $NaBH_4$ produced the dicarboxylic acid **519**[327a] (Scheme 83).



271 **515** **516**

Scheme 82.

Reduction of 6-methyl-5-carbomethoxy-2*H*-pyran-2-one (**362**) by hydrogenation in the presence of PtO_2 as the catalyst gave two reduced products,[249] of which one is the tetrahydropyran-2-one due to complete reduction of the pyranone ring (**520**) and the other is the reduced ring-opened product (**521**) (Scheme 84).

5.4. Photochemical reactions

2-Pyranone rings underwent a wide range of photochemical reactions to produce a variety of interesting chemical entities, some of which are very difficult to obtain otherwise. The photolysis of 2-pyranones in aerobic and anaerobic conditions, as well as in solvents, decides the course of reaction. Irradiation of simple 2*H*-pyran-2-one **278** in an argon matrix between 8 and 20 K forms a ketene (**522**), which is a reversible reaction.[328a] Prolonged irradiation at a temperature of ~77 K leads to the formation of a lactone (**523**) in high yields, which is a prime intermediate in the butadiene (**524**) synthesis (Scheme 85). Warming of the solution of the butadiene (**524**), causes decomposition to the dimer (**525**) and acetylene.[328a]

Irradiation of a methanolic solution of 4,6-dimethyl-2-pyranone (**358**) provides an inseparable mixture of two reactive lactones **526** and **527**, which after mild acid treatment produced four different isomeric ketoesters[328b] (**528**–**531**), while, in benzene using benzophenone as a sensitiser, a symmetrical dimer (**532**) was formed (Scheme 86).

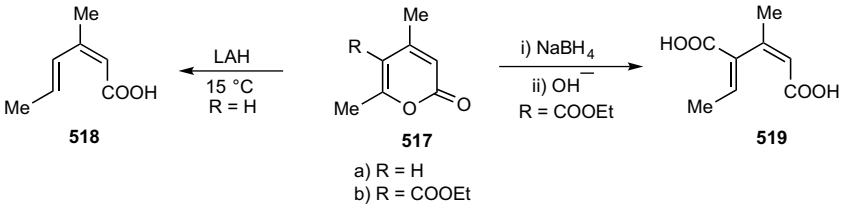
Pyran-2-one pendant alcohols (**533**; n=1) on irradiation in methanol in the presence of a catalytic amount of HCl were reduced to the dihydropyrans (**534**), while a homologous substrate (**533**; n=2, R=H) underwent an intramolecular 1,6-addition to furnish the spirolactone (**535**) (Scheme 87).[329]

Solvents and the use of sensitisers greatly influence the course of photochemical reactions. Photolysis of 2-pyranone (**278**) in methanol gave an olefinic ester (**536**), while, in the presence of a sensitiser, dimers (**537** and **538**) were isolated (Scheme 88).[330] Irradiation of a solution of 2-pyranone (**278**) aerobically in 1,2-dichloroethane in the presence of a sensitiser gave a high yield of the endoperoxide **539**,[330] which after decomposition provided the diformylalkene **540** (Scheme 88).

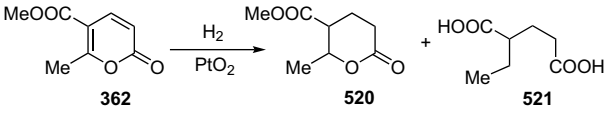
Cycloaddition of cyclohexene to dehydroacetic acid (**270**) in the presence of light produced a diastereomeric mixture of products[208] (**541**) (Scheme 89).

5.5. Cycloaddition reactions

Cycloaddition through a Diels–Alder reaction is one of the best methods, for stereocontrol led C–C bond formation in a single operation. The Diels–Alder cycloadditions of 2*H*-pyran-2-ones (**542**)

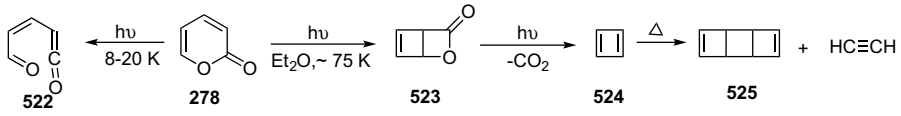


Scheme 83.

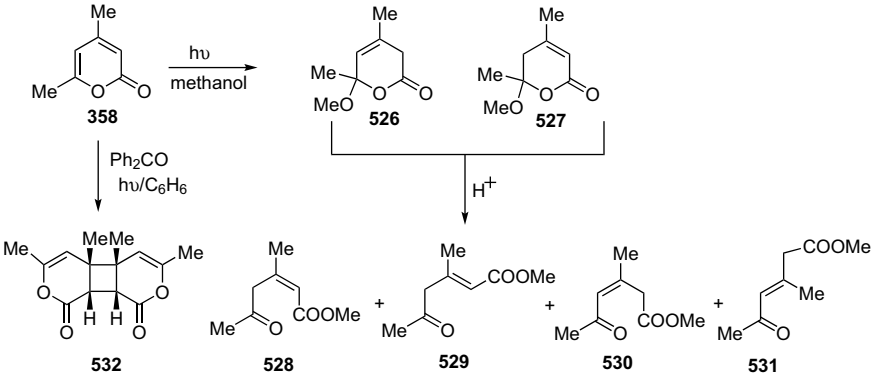


Scheme 84.

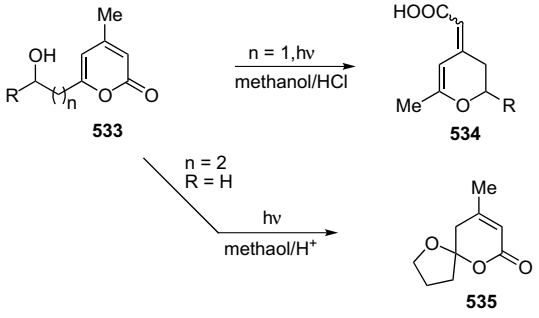
various natural products.[333,334] A classical example of the application of the Diels–Alder cycloaddition of 2*H*-pyran-2-one is the synthesis of the C- ring precursor of taxol reported by Nicolaou et al.[335] The synthesis of C-ring precursor (**546**) of taxol is initiated by the condensation reaction of phenylboronic acid with the diene, 3-hydroxy-2*H*-pyran-2-one, and the dienophile, allyl alcohol, to form



Scheme 85.



Scheme 86.



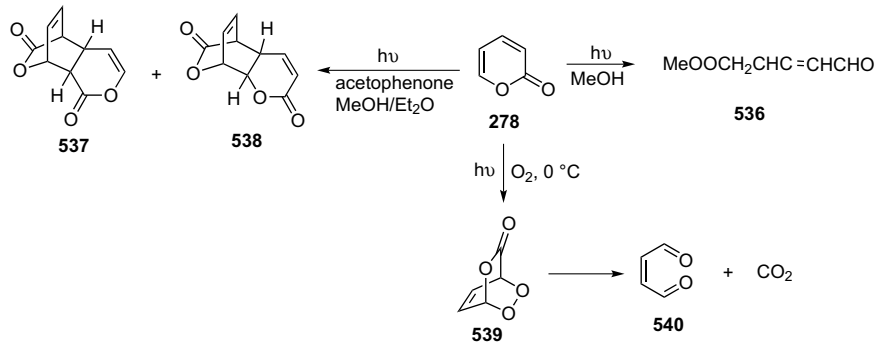
Scheme 87.

and their ring-substituted analogs with alkenes are synthetically important and useful reactions.[331,332] The first step in this reaction is the formation of bridged bicyclic Diels–Alder cycloadducts. Under forcing thermal conditions, these cycloadducts undergo loss of CO_2 to afford cyclohexadienes and aromatise by loss of hydrogen or by elimination to afford benzenes (**543**) (Scheme 90). The functionally rich bridged cycloadducts are very valuable products for the synthesis of highly functionalised six-membered rings, found in a boronic ester **544** (Scheme 90). The boronic acid then underwent an *endo*-Diels–Alder cycloaddition to furnish the bicyclic[2.2.2]lactone **545**, which on conversion into the diol, followed by rearrangement with the formation of a 5-membered lactone and ring opening of the 6-membered lactone, afforded the bicyclo[4.2.0]lactone **546** in good yield.

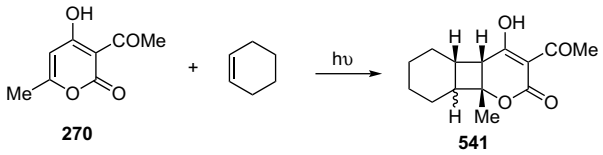
The success of the Diels–Alder cycloaddition reactions depends upon the electronic demand of the dienophile being compatible with that of the 2*H*-pyran-2-one by means of appropriate ring substitution, e.g., 3-phenylsulphanyl-2*H*-pyran-2-one (**547**) reacting with an electron-deficient[336, 337] dienophile to yield the cyclo adduct **548** (Scheme 91).

It was found that 3-bromo-2*H*-pyran-2-one (**342**) and 5-bromo-2*H*-pyran-2-one (**551**) have no electronic demand and react with electron-rich, -poor and - neutral dienophiles with good regio- and stereoselectivity[338] to afford the compounds **549**, **550** and **552**, **553**, respectively (Scheme 92).

In most of the Diels–Alder cycloaddition reactions, 2*H*-pyran-2-one acts as a diene and forms numerous [4+2] cycloadducts, which under thermal conditions are converted into arene cycloalkenes. Thus, the reaction of 2*H*-pyran-2-one (**278**) with alkynes and silyl alkynes such as **554** forms the disubstituted benzenes (**555**),[339,340]



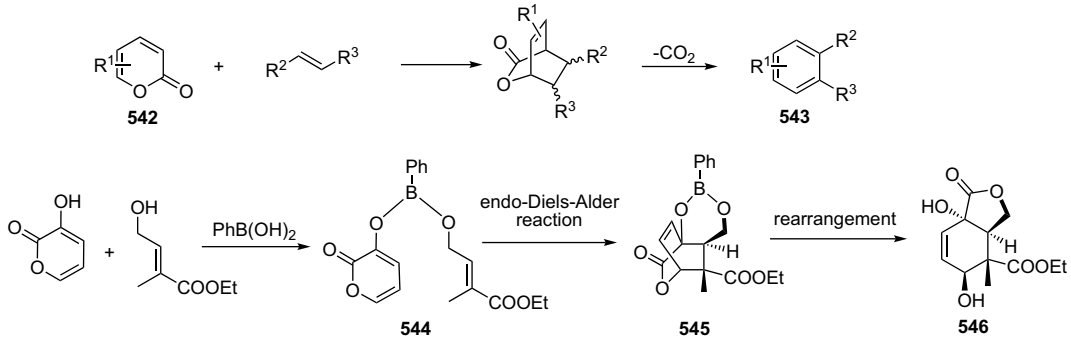
Scheme 88.



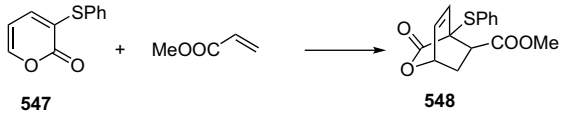
Scheme 89.

A similar strategy has been followed for the synthesis of 1,2-diphosphorylbenzenes. The cycloaddition of 2-pyranone (**278**) with diphosphorylacetylenes in 1,2-dichlorobenzene provides 60–80% of the diphosphorylbenzenes (**558**) (Scheme 94) .[341]

This strategy has successfully been used in the synthesis of cyclophanes.[342] Under cycloaddition conditions, the reaction of two moles of 2-pyranone (**278**) with one mole of a tetrasilylcyclobutyne in toluene (containing triethylamine) yields the [2,2]orthocyclo-



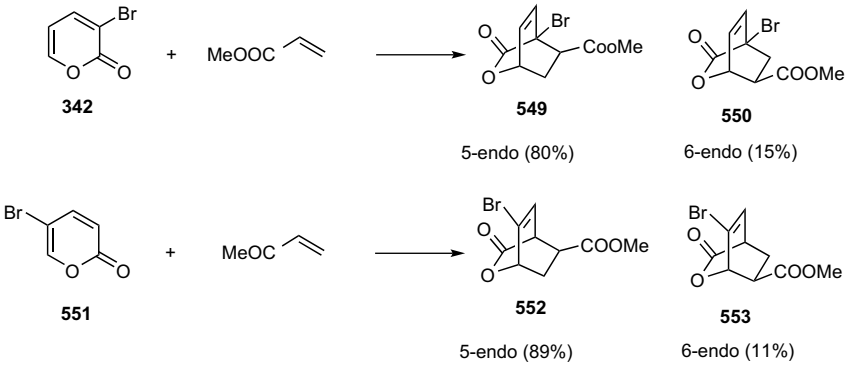
Scheme 90.



Scheme 91.

phane (**559**) (Scheme 95). On changing the solvent from toluene to bromobenzene, the [2,2]metacyclophane (**560**) was obtained in 22% yield. Prolonged heating of the [2,2]orthocyclophane (**559**) forms the [2,2]metacyclophane (**560**) in only 12% yield.

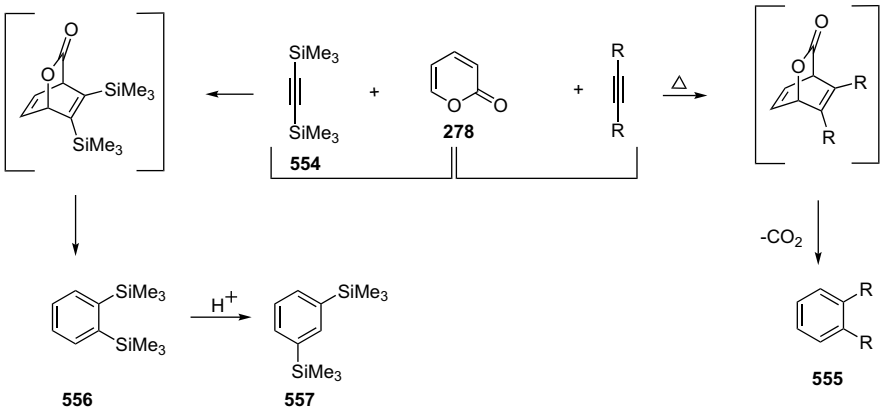
The 2*H*-pyran-2-one (**561**) with an electron-withdrawing substituent at C-3 underwent cycloaddition reactions to form initially



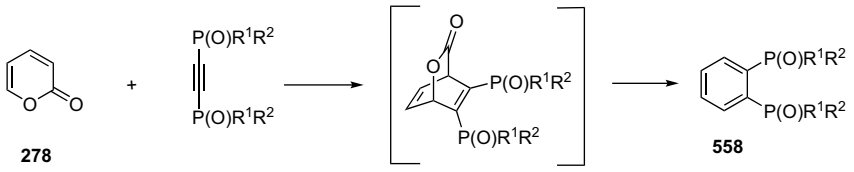
Scheme 92.

and the 1,2-disilyl-substituted benzene (**556**), which in the presence of acid rearranges to the 1,3-disilyl-substituted benzene (**557**) (Scheme 93).

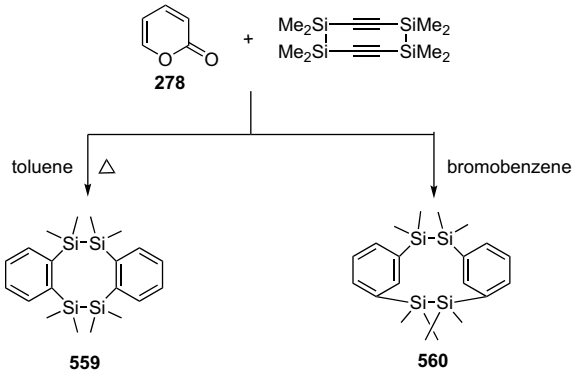
a cycloadduct which on loss of CO_2 at ~ 60 °C produced cyclohexadiene, and aromatised with elimination of HX to 1,3-disubstituted arenes **562** (Scheme 96).



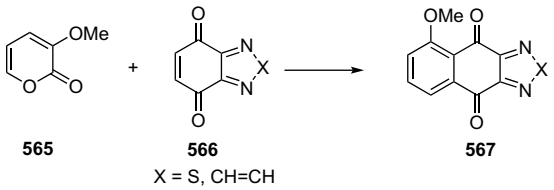
Scheme 93.



Scheme 94.

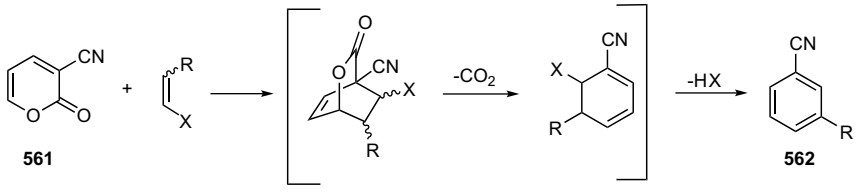


Scheme 95.



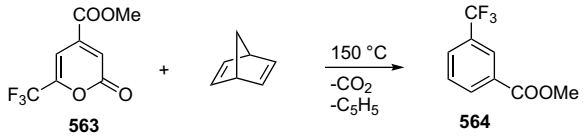
Scheme 98.

The same strategy has been followed for the synthesis of various natural products (**570**), starting from the reaction of 4-methyl-6-methoxy-2*H*-pyran-2-one (**568**) with substituted naphthoquinones (**569**) (Scheme 99).[345,346]



Scheme 96.

A 2-pyranone diene (**563**) reacts with norbornadiene to produce a substituted arene[343] (**564**) in 90% yield after elimination of CO_2 and cyclopentadiene (Scheme 97).



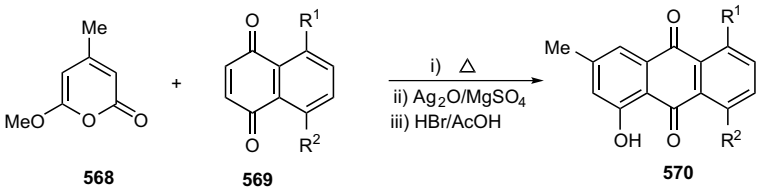
Scheme 97.

The normal electron-demand [4+2] cycloaddition between 3-methoxy-2*H*-pyran-2-one (**565**) and quinones (**566**) produced the anthraquinone analogs (**567**) in good yields (Scheme 98).[344]

The Diels–Alder cycloaddition of an electron-deficient 2-pyranone diene with an electron-rich dienophile such as enamine is one of the examples of an inverse electron-demand reaction. The reaction of a substituted coumalate (**571**) and enamines (**572**) in refluxing toluene yields the regioisomerically pure dihydrobenzenes[347] (**573**) (Scheme 100).

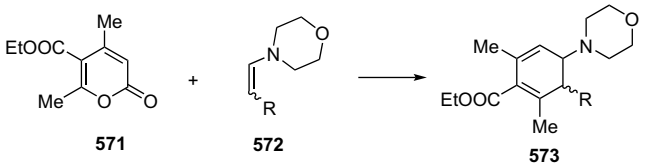
Cycloaddition of various electron-poor 2-pyranones (**574**) with 1*H*-cyclopropylbenzene (**575**) in THF at 50–55 °C provides highly strained cycloadducts with loss of carbon dioxide and ring opening of the cyclopropyl ring and formation of annulenes (**576**) (Scheme 101).[348]

Similarly, cycloaddition of 1,2,3-triphenylcyclopropene (**577**) with unsubstituted 2-pyranone (**278**) initially formed the cycloadduct with concomitant elimination of CO_2 and ring enlargement to provide 1,6,7-triphenyltropylidene[349] (**578**) (Scheme 102).



$R^1 = R^2$ = H, pachybasin (64%)
$R^1 = R^2$ = OH, helminthosporin (38%)
$R^1 = R^2$ = OH chrysophanol (62%)

Scheme 99.



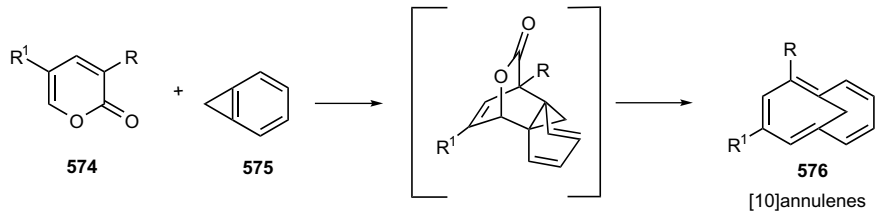
Scheme 100.

5.5.1. [2+2] Cycloaddition reactions

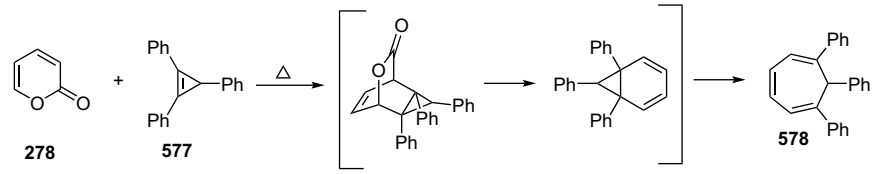
There are not many examples of [2+2] cycloaddition reactions using 2-pyranone as a precursor. Photosensitised cycloaddition of 4,6-dimethyl-2*H*-pyran-2-one (**358**) with an electrophilic olefin (**581**) yielded three types of cycloadducts (**582**), (**583**) and (**584**) (Scheme 104).[352]

5.5.2. [3+2] Cycloadditions

Not much literature is available on the [3+2] cycloaddition reactions. A [3+2] cycloaddition occurs when an electron-poor



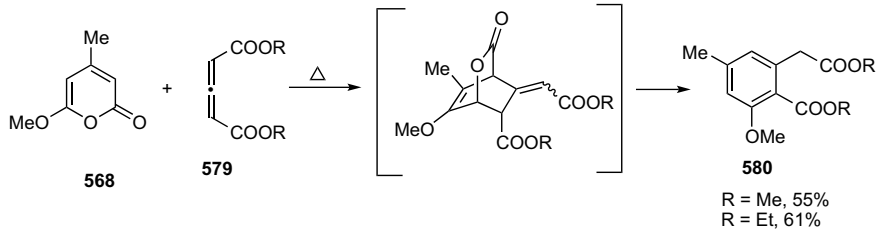
Scheme 101.



Scheme 102.

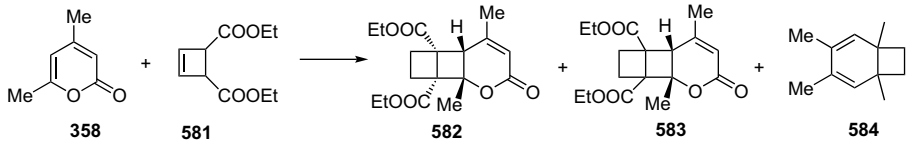
Allenes (**579**) like alkenes react with an electron-rich 2-pyranone (**568**) to form the cycloadducts and, finally, after elimination of CO_2 are converted into the substituted homophthalates (**580**) with high regiospecificity (Scheme 103).[350,351]

2-pyranone (**585**) reacts with trimethylenemethane **586** in the presence of a palladium catalyst ($[Pd(PrO_3)P]_2$) to form a cycloadduct[353] (**587**) in 71% yield (Scheme 105).

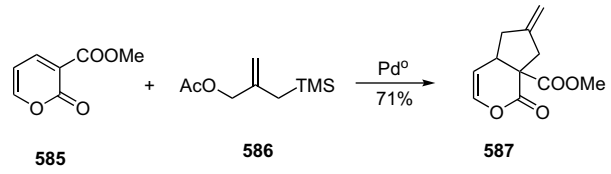


R = Me, 55%
R = Et, 61%

Scheme 103.



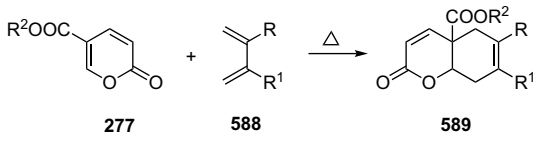
Scheme 104.



Scheme 105.

5.5.3. [4+2] Cycloadditions

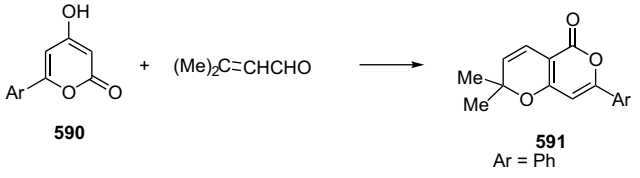
In certain cycloaddition reactions, 2-pyranone acts as a dienophile and reacts with the diene under high pressure in the presence of light to yield dimers. Methyl coumalate (**277**, R^2=Me) on reaction with acyclic dienes (**588**) forms cycloadduct products (**589**) (Scheme 106).[354]



Scheme 106.

5.5.4. [3+3] Cycloadditions

6-Aryl-4-hydroxy-2*H*-pyran-2-ones (**590**) undergo a formal [3+3] cycloaddition with enols. Thus, the reaction of **590** with Me_2C=CHCHO produces an adduct **591** (Ar=Ph) in 73% yield (Scheme 107) via the preliminary formation of piperidine iminium condensation products obtained from the reaction of the acetal with piperidine in ethyl acetate containing Ac_2O at 85 °C.[355]



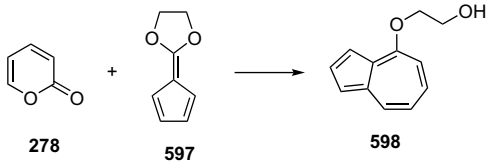
Scheme 107.

5.5.5. [4+3] Cycloadditions

An electron-rich 2*H*-pyranone diene (**592**) reacts with a trimethylenemethane palladium complex to form the [4+3] cycloadduct[352] (**593**) in 89% yield. A thermal cycloaddition of cyclopropenone ketals also gives the [4+3] cycloadduct (**594**),[356] but the reaction under high pressure at 25 °C forms the [4+2] cycloadduct (**595**), which finally yields cycloheptatrienone (**596**) (Scheme 108).

5.5.6. [6+4] Cycloadditions

Fulvene ketene acetal (**597**) on reaction with unsubstituted 2*H*-pyran-2-one (**278**) gives the [6+4] cycloaddition product, an azulene (**598**) (Scheme 109).[357]



Scheme 109.

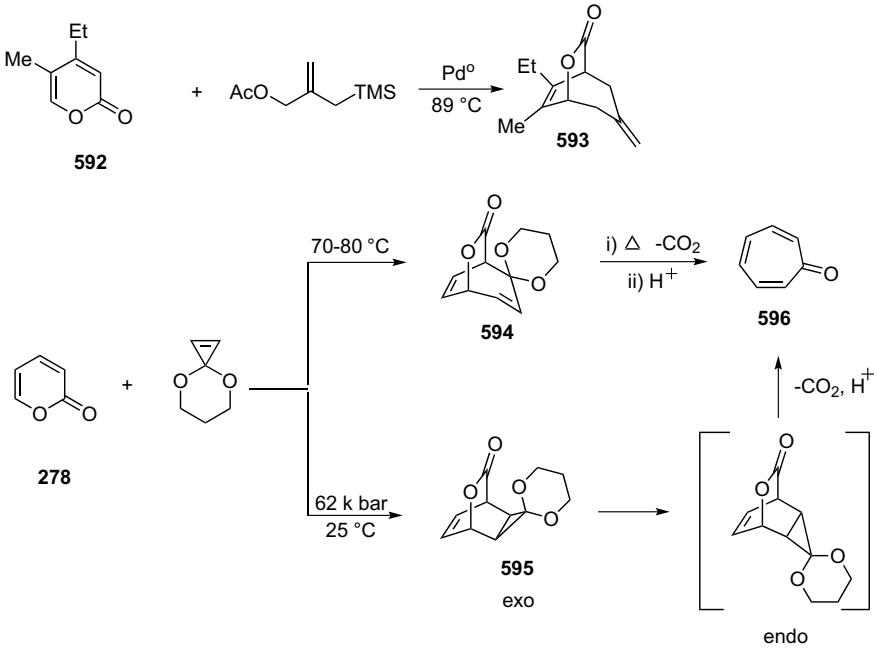
5.6. Miscellaneous reactions

Interactions of enaminones such as **599**, derived from 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, with hydroxylamine in the presence of aqueous alkali yield pyranopyridine derivatives **600** and **601** (Scheme 110).[358]

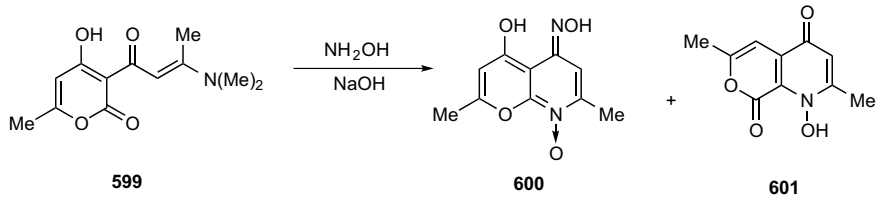
4-Hydroxy-6-methyl-2*H*-pyran-2-one (**271**) reacts with triethyl orthoformate (**602**) to form a pyrano[4,3-*b*]pyran-2,5-dione (**603**) through condensation-cyclisation (Scheme 111).[359] Further, reaction of 2-pyranone (**271**) with 3-bromochromone (**604**) yielded a furopyran derivative (**605**) through a ring transformation of the chromone.[360]

The condensation of 4-methoxy-6-methyl-2*H*-pyran-2-one (**509**) on condensation with methoxymethyl benzoate (**606**) led to the production of a semivioxanthins (**607**) (Scheme 112).[361]

Pyrano[4,3-*b*]quinolin-1-ones (**610**) have been synthesised (Scheme 113) from the reaction of 4-chloro-6-methyl-3-vinyl-2*H*-

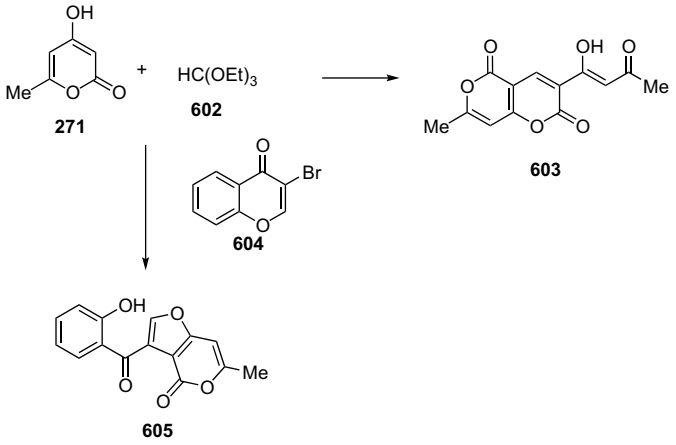


Scheme 108.

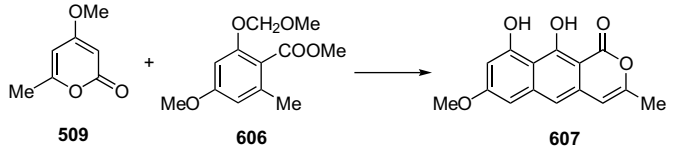


599 600 601

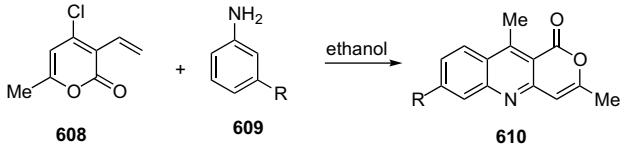
Scheme 110.



Scheme 111.



Scheme 112.



Scheme 113.

pyran-2-one (**608**) and aromatic amines (**609**) bearing an electron-donating substituent at position 3 of the ring.[362]

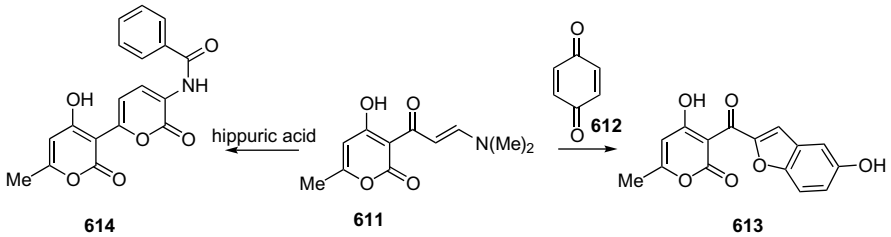
An enaminone (**611**), derived from the condensation of 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one and DMF dimethylacetal, on reaction with 1,4-benzoquinone (**612**) yields benzofuranopyran (**613**), while on reaction with hippuric acid, pyranopyran **614** has been isolated (Scheme 114).[363]

6. Conclusions

The necessity of finding molecules of unlimited potential for generating molecular diversity has always been realised by synthetic organic and medicinal chemists. Such molecules are the source of a vast molecular reservoir of immense synthetic applications in natural product synthesis, drug development, organic conductors, semiconductors, asymmetric catalysts and agrochemicals. The creation of molecular diversity by such molecules is based upon their for C–C and *C*-heteroatom bond-forming ability. We envisage a vast synthetic potential in suitably functionalised 2-pyranones. Numerous 2-pyranones either from natural or synthetic origin are known, but not all are suitable substrates for the ring-transformation reactions, although they may undergo substitution, addition and elimination reactions leaving the ring skeleton intact (with some exceptions). Recently, the oxidative rearrangement of 6-methoxypyran-2-ones by molecular oxygen to highly functionalised α,β-butenolides has been reported, otherwise 6-alkyl/aryl-4-methylsulphanyl/*sec*-amino-2*H*-pyran-2-one-3-carbonitriles/carboxylates are found as novel precursors for the ring-transformation reactions. The topography of these 2-pyrones is such that they possess three electrophilic centres C-2, C-4 and C-6 in which latter is highly electrophilic, due to extended conjugation and the presence of an electron-withdrawing substituent at C-3 of the pyran ring. The C-6 position of 2-pyranone is highly susceptible to nucleophilic attack by carbon, nitrogen and sulphur nucleophiles, followed by ring closure involving either the C-3 or C-4 positions to yield ring-transformed and -contracted products, depending upon the nature of the attacking reagents. The order of reactivity of the three electrophilic centres is C-6>C-4>C-2. Depending upon the the nucleophilicity of the nucleophiles, a substitution reacteion can also take place at C-4, followed by the ring closure involving the substituent at the C-3 position. Occasionally, the ring opening by strong nucleophiles has been observed through attack at C-2 of the pyran ring.

The other approach to generate molecular diversity that has been extensively studied is the Diels–Alder reactions using 2-pyranones as dienes as well as dienophiles. These reactions provide arenes, heteroarenes and ring-expanded and annelated products, depending upon the electron-poor and -rich 2-pyranones used as the diene or dienophile, but have synthetic limitations of harsh reaction conditions, high pressure and the requirement of electron-rich and -poor 2-pyranones.

Thus, 2-pyranones are very useful synthons for the construction of arenes such as biaryls, 1,2-, 1,3- and 1,4-teraryls, tetraaryls,



614 611 613

Scheme 114.

oligoarenes, and annulated arenes, as well as aryl-tethered heteroarenes such as pyrazoles, isoxazoles, pyridines, pyrimidines, quinolizines, pyrazolo[1,5-*a*]pyridines, deazalumazines, azaanthracenes, dibenzofurans, imidazo[2,1-*b*]thiazines, azolo[3,2-*a*]pyrimidines and many other biologically active ring systems. Thus, suitably functionalised 2-pyranone has unlimited synthetic potential for the construction of a variety of arenes and heteroarenes by manoeuvering the reactants for the ring-transformation reactions.

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References and notes

1. (a) Vara Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B., Jr.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. M. A.; Baldwin, E. T.; Erickon, J. W.; Swayer, T. K. *J. Am. Chem. Soc.* **1994**, *116*, 6989; (b) Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Mathias, D. S.; Degen, S. I.; Golding, G. M.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, I. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683; (c) Hagen, S. E.; Vara Prasad, J. V. N.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gjda, C.; Hamilton, H. W.; Markkoski, L. J.; Steinbangh, B. A.; Tit, B. D.; Lunney, E. A.; Tummino, P. J.; Fergnson, D.; Hupe, D.; Nouhan, C.; Gracheck, S. J.; Saunders, J. M.; Vander Roest, S. *J. Med. Chem.* **1997**, *40*, 3707.
2. (a) Claydon, N.; Allan, M. *Trans. Br. Mycol. Soc.* **1987**, *88*, 503; (b) Simon, A.; Dunlop, R. W.; Ghisalberti, E. L.; Silvasithamparam, K. *Soil Biol. Biochem.* **1988**, *20*, 263.
3. (a) Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693; (b) Chen, K. K.; Kovarikova, A. *J. Pharm. Sci.* **1967**, *56*, 1535.
4. Aytemir, M. D.; Calis, U.; Ozalp, M. *Arch. Pharm. Med. Chem.* **2004**, *337*, 281.
5. (a) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936; (b) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285.
6. Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71.
7. Allen, M. *Chem. Br.* **1996**, *May*, 35.
8. Kondoh, M.; Usui, T.; Kobayashi, S.; Tsuchiya, K.; Nishikawa, K.; Nishikiori, T.; Mayumi, T.; Osada, H. *Cancer Lett.* **1998**, *126*, 29.
9. Kobayashi, S.; Tsuchiya, K.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, Y. *J. Antibiot.* **1994**, *47*, 703.
10. Tsuchiya, K.; Kobayashi, S.; Nishikiori, T.; Nakagawa, T.; Tatsuta, K. *J. Antibiot.* **1997**, *50*, 259.
11. Ichihara, A.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1983**, *48*, 5373.
12. Chmielewski, M.; Jurczak, J. *J. Org. Chem.* **1981**, *46*, 2230.
13. Hernandez-Galan, R. J.; Salva, R.; Massannet, G. M.; Collado, I. G. *Tetrahedron* **1993**, *49*, 1701.
14. Boulanger, W. A.; Katzenellenbogen, J. A. *J. Med. Chem.* **1986**, *29*, 1159.
15. Cook, I.; Terna, B.; Ghosh, P. *J. Med. Chem.* **1987**, *30*, 1017.
16. Griffin, D. A.; Stannton, J. C. S. *J. Chem. Soc., Chem. Commun.* **1975**, 675.
17. Pirkle, W. H.; Dines, M. *J. Heterocycl. Chem.* **1969**, *6*, 313.
18. Shusherina, N. P.; Dmitrieva, N. D.; Levina, R. Y. *Zh. Obshch. Khim.* **1961**, *31*, 2794.
19. Pirkle, W. H.; Dines, M. *J. Org. Chem.* **1969**, *34*, 2239.
20. (a) Patzak, R.; Neugebauer. *Monatsh. Chem.* **1951**, *82*, 662; (b) Mangini, S.; Passerini, R. *Gazz. Chim. Ital.* **1957**, *57*, 47.
21. Engel, B. G.; Brzeski, W.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 1752.
22. Yamada, K. *Bull. Soc. Chem. Jpn.* **1962**, *35*, 1323.
23. Jones, R. N.; Angell, C. L.; Ito, T.; Smith, R. J. D. *Can. J. Chem.* **1959**, *37*, 2007.
24. Pirkle, W. H.; Dines, M. *J. Heterocycl. Chem.* **1969**, *6*, 1.
25. Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122.
26. (a) Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth.* **1995**, *73*, 231; (b) Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2003**, *68*, 7158; (c) Ram, V. J. Unpublished results.
27. (a) Repke, K. R. H.; Megges, R. *Expert Opin. Ther. Pat.* **1997**, *7*, 1; (b) Deepak, D.; Srivastava, S.; Khare, N. K.; Khare, A. *Fortschr. Chem. Org. Naturst.* **1996**, *69*, 71; (c) Ode, R. H.; Pettit, G. R.; Kamano, Y. *Int. Rev. Sci, Org. Chem. Ser. Two* **1976**, *8*, 145.
28. (a) Costa, S. S.; Jossang, A.; Bodo, B. *J. Nat. Prod.* **1996**, *59*, 327; (b) Rossi-Bergmann, B.; Costa, S. S.; Borges, M. B. S.; de Silva, S. A.; Noleto, G. R.; Souza, M. L. M.; Moraes, V. L. G. *Phytotherapy Res.* **1994**, *8*, 399.
29. Naude, T. W. *J.S. Afr. Biol. Soc.* **1977**, *18*, 7.
30. Kellerman, T. S.; Coetzer, J. A. W.; Naudé, T. W. *Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa*; Oxford University Press: Cape Town, 1988; p 99.
31. Kellerman, T. S.; Naudé, T. W.; Fourie, N. *Onderstepoort J. Vet. Res.* **1996**, *63*, 65 and references cited therein.
32. Steyn, P. S.; van Heerden, F. R. *Nat. Prod. Rep.* **1998**, 397.
33. Naude, T. W.; Schultz, R. A. *Onderstepoort J. Vet. Res.* **1982**, *49*, 247.
34. Kupchan, S. M.; Ognyanov, I. *Tetrahedron Lett.* **1969**, 1709.
35. Wagner, H.; Fischer, M.; Lotter, H. *Z. Naturforsch. Teil B* **1985**, *40*, 1226.
36. (a) Wagner, H.; Fischer, M.; Lotter, H. *Planta Med.* **1985**, 169; (b) Wagner, H.; Lotter, H.; Fischer, M. *Helv. Chim. Acta* **1986**, *69*, 359.
37. Anderson, L. A. P.; Steyn, P. S.; van Heerden, F. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1573.
38. Rasoanaivo, P.; Gale, C.; Multari, G.; Nicoletti, M.; Capolongo, L. *Gazz. Chim. Ital.* **1993**, *123*, 539.
39. Capon, R. J.; MacLeod, J. K.; Oelrichs, P. B. *J. Chem. Res., Synop.* **1985**, 333.
40. Capon, R. J.; MacLeod, J. K.; Oelrichs, P. B. *Aust. J. Chem.* **1986**, *39*, 1711.
41. Supratman, U.; Fujita, T.; Akiyama, K.; Hayashi, H. *Biosci. Biotecnol. Biochem.* **2000**, *64*, 1310.
42. Steyn, P. S.; van Heerden, F. R.; van Wyk, A. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 965.
43. Dillen, J. L. M.; van Heerden, F. R.; van Rooyen, P. H.; Vleggaar, R. *J. Chem. Res., Synop.* **1993**, 74.
44. Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Anderson, L. A. P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 429.
45. Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Anderson, L. A. P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1633.
46. (a) Septa, F. *Phyton* **1998**, *38*, 1; (b) Krenn, L.; Ferth, R.; Robien, W.; Kopp, B. *Planta Med.* **1991**, *57*, 560.
47. Krenn, L.; Jelovina, M.; Kopp, B. *Fitoterapia* **2000**, *71*, 126.
48. Pohl, T.; Koorbanally, C.; Crouch, N. R.; Mulholland, D. A. *Phytochemistry* **2001**, *58*, 557.
49. Iizuka, M.; Warashina, T.; Noro, T. *Chem. Pharm. Bull.* **2001**, *49*, 282.
50. Yadava, R. N.; Yadav, S. *Asian J. Chem.* **2001**, *13*, 1157.
51. Bose, C.; Chakrabarty, A. *Asian J. Chem.* **2002**, *14*, 671.
52. Meng, Y.; Whiting, P.; Sik, V.; Rees, H. H.; Dinan, L. *Phytochemistry* **2001**, *57*, 401.
53. Ye, M.; Guo, D. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 1881.
54. Kamano, Y.; Kotake, A.; Hashima, H.; Inoue, M.; Morita, H.; Takeya, K.; Itokawa, H.; Nandachi, N.; Segawa, T.; Yukita, A.; Saitou, K.; Katsuyama, M.; Pettit, G. R. *Bioorg. Med. Chem.* **1998**, *6*, 1103.
55. Nogawa, T.; Kamano, Y.; Yamashita, A.; Pettit, G. R. *J. Nat. Prod.* **2001**, *64*, 1148.
56. Kamano, Y.; Nogawa, T.; Yamashita, A.; Hayashi, M.; Inoue, M.; Drasar, P.; Pettit, G. R. *J. Nat. Prod.* **2002**, *65*, 1001.
57. Joffe, A. Z. *J. Stored Prod. Res.* **1969**, *5*, 211.
58. Gluchoff-Fiasson, K.; Kühner, R. *C.R. Acad. Sci., Scr. D.* **1977**, *284*, 1667.
59. Barry, M.; Gibbons, S.; Back, D.; Mulcahy, F. *Clin. Pharmacokinet.* **1997**, *32*, 194.
60. Bu'Lock, J. D.; Smith, H. G. *Experientia* **1961**, *17*, 553.
61. Edwards, R. L.; Lewis, D. G.; Wilson, D. V. *J. Chem. Soc.* **1961**, 4995.
62. Brady, L. R.; Benedict, R. G. *J. Pharm. Sci.* **1972**, *61*, 318.
63. Halfield, G. M.; Brady, L. R. *J. Pharm. Sci.* **1969**, *58*, 1298.
64. Hatfield, G. M.; Brady, L. R. *Lloydia* **1968**, *31*, 225.
65. Perrin, P. W.; Towers, G. H. N. *Phytochemistry* **1973**, *12*, 589.
66. Nambudiri, A. M. D.; Vance, C. P.; Towers, G. H. N. *Biochem. J.* **1973**, *134*, 891.
67. Klaar, M.; Steglich, W. *Chem. Ber.* **1977**, *110*, 1063.
68. (a) Mo, S. Y.; Yang, Y. C.; He, W. Y.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 704; (b) Wang, Y.; Wang, S. J.; Mo, S. Y.; Li, S.; Yang, Y. C.; Shi, J. G. *Org. Lett.* **2005**, *7*, 4733.
69. Kamperdick, C.; van Hong, N.; van Sung, T. *Phytochemistry* **2002**, *61*, 991.
70. Ganzera, M.; Khan, I. A. *Chromatographia* **1999**, *50*, 649.
71. Rossi, M. H.; Yoshida, M.; Maia, J. G. S. *Phytochemistry* **1997**, *45*, 1263.
72. Fujita, T.; Nishimura, H.; Kaburagi, K.; Mizutani, J. *Phytochemistry* **1994**, *36*, 23.
73. Itokawa, H.; Morita, M.; Mihashi, S. *Phytochemistry* **1981**, *11*, 2503.
74. Talapatra, B.; Pradhan, D. K.; Talapatra, S. K. *Indian J. Chem.* **1976**, *14B*, 300.
75. Ali, M. S.; Tezuka, Y.; Awale, S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 289.
76. Pizzolatti, M. G.; Luciano, C.; Monache, F. D. *Phytochemistry* **2000**, *55*, 819.
77. Dharmaratne, H. R. W.; Nanayakkara, N. P. D.; Khan, I. A. *Phytochemistry* **2001**, *59*, 429.
78. Yang, Y.; Kinoshita, K.; Koyama, K.; Takahashi, K.; Tai, T.; Nunoura, Y.; Watanabe, K. *J. Nat. Prod.* **1999**, *62*, 1672.
79. Evidente, A.; Conte, L.; Altomare, C.; Bottalico, A.; Sindona, G.; Segre, A. L.; Logrieco, A. *Nat. Toxins* **1994**, *2*, 4.
80. Altomare, C.; Perrone, G.; Zonno, M. C.; Evidente, A.; Pengue, R.; Fanti, F.; Polonelli, L. *J. Nat. Prod.* **2000**, *63*, 1131.
81. Nagai, K.; Kamigiri, K.; Matsumoto, H.; Kawano, Y.; Yamoka, M.; Shimoi, H.; Watanabe, M.; Suzuki, K. *J. Antibiot.* **2002**, *55*, 1036.
82. Kanai, A.; Kamino, T.; Kuramochi, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2837.
83. Eckermann, C.; Matthes, B.; Nimtz, M.; Reiser, V.; Lederer, B.; Boger, P.; Schroder, J. *Phytochemistry* **2003**, *64*, 1045.
84. Eckermann, C.; Schroder, G.; Eckermann, S.; Strack, D.; Schmidt, J.; Schneider, B.; Schroder, J. *Phytochemistry* **2003**, *62*, 271.
85. Osterhage, C.; Kaminsky, R.; Konig, G. M.; Wright, A. D. *J. Org. Chem.* **2000**, *65*, 6412.
86. Igarashi, Y.; Ogawa, M.; Sato, N.; Yoshida, R.; Kunoh, H.; Onaka, H.; Furumai. *J. Antibiot.* **2000**, *53*, 1117.
87. Fujita, Y.; Kasuya, A.; Matsushita, Y.; Suga, M.; Kizuka, M.; Iijima, Y.; Ogita, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4317.
88. Kohl, W.; Irschik, H.; Reichenbach, H.; Hofle, G. *Liebigs Ann. Chem.* **1983**, 1656.
89. Jansen, R.; Irschik, H.; Reichenbach, H.; Hofle, G. *Liebigs Ann. Chem.* **1985**, 822.
90. Irschik, H.; Gerth, K.; Hofle, G.; Kohl, W.; Reichenbach, H. *J. Antibiot.* **1983**, *36*, 1651.
91. Irschik, H.; Jansen, R.; Hofle, G.; Gerth, K.; Reichenbach, H. *J. Antibiot.* **1985**, *38*, 145.
92. Graziani, E. I.; Ritacco, F. V.; Bernan, V. S.; Telliez, J. B. *J. Nat. Prod.* **2005**, *68*, 1262.

93. Uchida, R.; Imasato, R.; Yamaguchi, Y.; Masuma, R.; Shiomi, K.; Tomoda, H.; Omura, S. *J. Antibiot.* **2005**, *58*, 397.
94. Fujimoto, H.; Nozawa, M.; Okuyama, E.; Ishibashi, M. *Chem. Pharm. Bull.* **2003**, *51*, 247.
95. Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1983**, *24*, 3055.
96. Norte, M.; Cataldo, F.; Gonzalez, A. G.; Rodriguez, M. L.; Ruiz-Perz, C. *Tetrahedron* **1990**, *46*, 1669.
97. Birkbeck, A. A.; Enders, D. *Tetrahedron Lett.* **1998**, *39*, 7823.
98. Suzuki, K.; Kuwahara, A.; Yoshida, H.; Fujita, S.; Nishikiori, T.; Nakagawa, T. *J. Antibiot.* **1997**, *50*, 314.
99. Suzuki, K.; Kuwahara, A.; Nishikiori, T.; Nakagawa, T. *J. Antibiot.* **1997**, *50*, 318.
100. Li, W. K.; Yang, J. S.; Xiao, P. G.; Pan, J. Q.; Lu, M. J.; Zhang, R. Y. *Chin. Chem. Lett.* **1996**, *7*, 23.
101. Furumoto, T.; Fukuyama, K.; Hamasaki, T.; Nakajima, H. *Phytochemistry* **1995**, *40*, 745.
102. Cui, C. B.; Tezuka, Y.; Yamashita, H.; Kikuchi, T.; Nakano, H.; Tamaoki, T.; Park, J. H. *Chem. Pharm. Bull.* **1992**, *40*, 1711.
103. Collins, R. P.; Halim, A. F. *J. Agric. Food Chem.* **1972**, *20*, 437.
104. Yong, F. M.; Lim, G. *MIRCEN J. Appl. Microbiol. Biotechnol.* **1986**, *29*, 483.
105. Harvat, A. J.; Chapman, G. W., Jr.; Robertson, J. A.; Meredith, F. I.; Scorza, R.; Callahan, A. M.; Morgens, P. *J. Agric. Food Chem.* **1990**, *38*, 234.
106. Takeoka, G. R.; Flath, R. A.; Guentert, M.; Jennings, W. *J. Agric. Food Chem.* **1988**, *36*, 553.
107. Engel, K. H.; Flath, R. A.; Buttery, R. G.; Mon, T. R.; Ramming, D. W.; Teranishi, R. *J. Agric. Food Chem.* **1988**, *36*, 549.
108. Engel, K. H.; Ramming, D. W.; Flath, R. A.; Teranishi, R. *J. Agric. Food Chem.* **1988**, *36*, 1003.
109. Moss, M. O.; Jackson, R. M.; Rogers, D. *Phytochemistry* **1975**, *14*, 2706.
110. Jones, T. H.; Fales, H. M. *Tetrahedron Lett.* **1983**, *24*, 5439.
111. Trahanovsky, W. S.; Surber, B. W.; Wilkes, M. C.; Preckel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779.
112. Li, X.; Kim, M. K.; Lee, U.; Kim, S. K.; Kang, J. S.; Choi, H. D.; Son, B. W. *Chem. Pharm. Bull.* **2005**, *53*, 453.
113. Evidente, A.; Cabras, A.; Maddau, L.; Serra, S.; Andol, A.; Motta, A. *J. Agric. Food Chem.* **2003**, *51*, 6957.
114. Quang, D. N.; Hashimoto, T.; Tanaka, M.; Baumgartner, M.; Stadler, M.; Asakawa, Y. *J. Nat. Prod.* **2002**, *65*, 1869.
115. Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **1998**, *54*, 13013.
116. Kong, F.; Singh, M. P.; Carter, G. T. *J. Nat. Prod.* **2005**, *68*, 920.
117. Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Zhao, W.; Black, T. A.; Chan, T. M. *J. Antibiot.* **2002**, *55*, 215.
118. Cutignano, A.; Fontana, A.; Renzulli, L.; Cimino, G. *J. Nat. Prod.* **2003**, *66*, 1399.
119. Li, C.; Nitka, M. V.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *J. Nat. Prod.* **2003**, *66*, 1302.
120. Kozlovsky, A. G.; Zhelifonova, V. P.; Adanin, V. M.; Ozerskaya, S. M.; Grafe, U. G. K. *Pharmazie* **2003**, *58*, 76.
121. Salo, M.; Konoma, K.; Sakamura, S. *Agric. Biol. Chem.* **1979**, *43*, 2409.
122. Sato, H.; Konoma, K.; Sakamura, S.; Furusaki, A.; Matsumoto, T.; Matsuzaki, T. *Agric. Biol. Chem.* **1981**, *45*, 795.
123. Sparace, S. A.; Mudd, J. B.; Burke, B. A.; Aasen, A. J. *Phytochemistry* **1984**, *23*, 2693.
124. Sakurai, I.; Shimizu, S.; Yamamoto, Y. *Chem. Pharm. Bull.* **1988**, *36*, 1328.
125. Toske, S. G.; Jensen, P. R.; Kauffman, C. A.; Fenical, W. *Nat. Prod. Lett.* **1995**, *6*, 303.
126. Lindel, T.; Jensen, P. R.; Fenical, W. *Tetrahedron Lett.* **1996**, *37*, 1327.
127. Gohbara, M.; Hyeon, S. B.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1976**, *40*, 1453.
128. Opitz, L.; Hansel, R. *Tetrahedron Lett.* **1970**, 3369.
129. Funk, A.; McMullan, E. E. *Can. J. Microbiol.* **1974**, *20*, 422.
130. Poulton, G. A.; Williams, M. E.; McMullan, E. E. *Tetrahedron Lett.* **1974**, 2611.
131. Omura, S.; Ohno, H.; Saheki, T.; Yoshida, M.; Nakagawa, A. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 704.
132. Ohno, H.; Saheki, T.; Awaya, J.; Nakagawa, A.; Omura, S. *J. Antibiot.* **1978**, *31*, 1116.
133. Omura, S.; Nakagawa, A.; Ohno, H. *J. Am. Chem. Soc.* **1979**, *101*, 4386.
134. Nakagawa, A.; Ohno, H.; Miyano, K.; Omura, S. *J. Org. Chem.* **1980**, *45*, 3268.
135. Kimura, Y.; Hamasaki, T.; Isogai, A.; Nakajima, H. *Agric. Biol. Chem.* **1982**, *46*, 1963.
136. Camarda, L.; Merlini, L.; Nasini, G. *Phytochemistry* **1976**, *15*, 537.
137. Sata, N.; Abinsay, H.; Yoshida, W. Y.; Horgen, F. D.; Sitachitta, N.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod.* **2005**, *68*, 1400.
138. Qiu, Y.; Chen, Y.; Pei, Y.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull.* **2002**, *50*, 1507.
139. Duri, L.; Morelli, C. F.; Crippa, S.; Speranza, G. *Fitoterapia* **2004**, *75*, 520.
140. Hua, Y.; Wang, H. Q. *J. Chin. Chem. Soc.* **2004**, *51*, 409.
141. Zhang, X. F.; Wang, H. M.; Song, Y. L.; Nie, L. H.; Wang, L. F.; Liu, B.; Shen, P. P.; Liu, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 949.
142. Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Cabrera, E.; Sanchez, J. F.; Quylez, J. F.; Rojas, F.; Reyes, J. F. *Tetrahedron* **1993**, *49*, 141.
143. Avent, A. G.; Hanson, J. R.; Truneh, A. *Phytochemistry* **1993**, *32*, 197.
144. Nair, M. S. R.; Carey, S. T. *Tetrahedron Lett.* **1975**, 1655.
145. Abraham, W. R.; Arfman, H. A. *Phytochemistry* **1988**, *27*, 3310.
146. Jadulco, R.; Brauers, G.; Edrada, R. A.; Ebel, R.; Wray, V.; Sudarsono, P. *J. Nat. Prod.* **2002**, *65*, 730.
147. Kosemura, S.; Kojima, S.; Yamamura, S. *Chem. Lett.* **1997**, 33.
148. Koyama, Y.; Fukakusa, Y.; Kyomura, N.; Yamagishi, S.; Arai, T. *Tetrahedron Lett.* **1969**, 355.
149. Koyama, Y.; Fukakusa, N.; Koymura, N.; Yamagishi, S. *Tetrahedron Lett.* **1969**, 359.
150. Yamagishi, S.; Koyama, Y.; Fukakusa, Y.; Kyomura, N.; Ohishi, J.; Hamamichi, N.; Arai, T. *Yakugaku Zasshi* **1971**, *91*, 51.
151. Nair, M. G.; Chandra, A.; Thorogood, D. L. *J. Antibiot.* **1993**, *46*, 1762.
152. Tezuka, Y.; Huang, Q.; Kikuchi, T.; Nishi, A.; Tubaki, K. *Chem. Pharm. Bull.* **1994**, *42*, 2612.
153. Ueno, Y. In *Mycotoxins*; Purchase, I. F. H., Ed.; Elsevier: New York, NY, 1974; p 283.
154. (a) Hirata, Y. *J. Chem. Soc. Jpn.* **1947**, *68*, 63; (b) Hirata, Y. *J. Chem. Soc. Jpn.* **1947**, *68*, 74.
155. Hirata, Y. *J. Chem. Soc. Jpn.* **1947**, *68*, 104.
156. Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron Lett.* **1964**, 1825.
157. Nagel, D. W.; Steyn, P. S.; Scott, D. B. *Photochemistry* **1972**, *11*, 627.
158. Nano, G. M.; Bellando, M. *Allionia* **1976**, *21*, 73; *Chem. Abstr.* **1978**, *89*, 176023m.
159. Sakabe, N.; Goto, T.; Hirala, Y. *Tetrahedron Lett.* **1977**, *33*, 307.
160. Cole, R. J.; Dorner, J. W.; Cox, R. H.; Hill, R. A.; Cutler, H. G.; Wells, J. M. *Appl. Environ. Microbiol.* **1981**, *42*, 677.
161. Kosemura, S.; Yamamura, S. *Tetrahedron Lett.* **1997**, *38*, 3025.
162. Baldwin, C. L.; Weaver, L. C.; Brooker, R. M.; Jacobsen, T. N.; Osborne, C. E., Jr.; Nash, H. A. *Lloydia* **1964**, *27*, 88.
163. Osselton, M. D.; Baum, H.; Beechey, R. B. *Biochem. Soc. Trans.* **1974**, *2*, 200.
164. Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, 874.
165. Wang, F.; Luo, D. Q.; Liu, J. K. *J. Antibiot.* **2005**, *58*, 412.
166. Azumi, M.; Ishidoh, K.; Kinoshita, H.; Nihira, T.; Ihara, F.; Fujita, T.; Igarashi, Y. *J. Nat. Prod.* **2008**, *71*, 278.
167. Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, 441.
168. Rebuffat, S.; Davoust, D.; Molho, L.; Molho, D. *Photochemistry* **1980**, *19*, 427.
169. Brassy, C.; Bachel, B.; Guidi-Morosini, C.; Rebuffat, S.; Molho, D. *Acta Crystallogr., Sect. B* **1982**, *38*, 1624.
170. Nair, M. S. R.; Carey, S. T. *Tetrahedron Lett.* **1975**, 3517.
171. Nair, M. S. R. *Photochemistry.* **1976**, *15*, 1090.
172. Fujimoto, Y.; Tsunoda, H.; Uzawa, J.; Tatsuno, T. *J. Chem. Soc., Chem. Commun.* **1982**, 83.
173. Fujimoto, H.; Sumino, M.; Nagano, J.; Natori, H.; Okuyama E.; Yamazaki, M.. *Chem. Pharm. Bull.* **1999**, *47*, 71.
174. Fujimoto, H.; Satoh, Y.; Nakayama, M.; Takayama, T.; Yamazaki, M. *Chem. Pharm. Bull.* **1995**, *43*, 547.
175. Fujimoto, H.; Nagano, J.; Yamaguchi, K.; Yamazaki, M. *Chem. Pharm. Bull.* **1998**, *46*, 423.
176. Sitachitta, N.; Gadepalli, M.; Davidson, B. S. *Tetrahedron* **1996**, *52*, 8073.
177. Piel, J.; Hoang, K.; Moore, B. S. *J. Am. Chem. Soc.* **2000**, *122*, 5415.
178. Xiang, L.; Kalaitzis, J. A.; Nilsen, G.; Chen, L.; Moore, B. S. *Org. Lett.* **2002**, *4*, 957.
179. Zhang, H. I.; He, X. G.; Adefarati, A.; Galucci, J.; Cole, S. P.; Beale, J. M.; Keller, P. J.; Chang, C. J.; Floss, H. G. *J. Org. Chem.* **1990**, *55*, 1682.
180. McDaniel, R.; Ebert-Khosla, S.; Fu, H.; Hopwood, D. A.; Khosla, C. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11542.
181. McDaniel, R.; Ebert-Khosla, S.; Hopwood, D. A.; Khosla, C. *J. Am. Chem. Soc.* **1994**, *116*, 10855.
182. Pedras, M. S. C.; Chumala, P. B. *Phytochemistry* **2005**, *66*, 81.
183. Pedras, M. S. C.; Erosa-Lopez, C. C.; Quail, J. W.; Taylor, J. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3291.
184. Tringali, C.; Parisi, A.; Piattelli, M.; Magnano Di San Lio, G. *Nat. Prod. Lett.* **1993**, *3*, 101.
185. Larson, T. O.; Perry, N. B.; Anderson, B. *Tetrahedron Lett.* **2003**, *44*, 4511.
186. Hosoe, T.; Fukushima, K.; Takizawa, K.; Miyaji, M.; Kawai, K. I. *Phytochemistry* **1999**, *52*, 459.
187. Yamagishi, Y.; Shindo, K.; Kawai, H. *J. Antibiot.* **1993**, *46*, 888.
188. Yamagishi, Y.; Matsuoka, M.; Odagawa, A.; Kato, S.; Shindo, K.; Mochizuki, J. *J. Antibiot.* **1993**, *46*, 884.
189. Ichihara, A.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1983**, *24*, 5373.
190. Jenkins, K. M.; Toske, S. G.; Jensen, P. R.; Fenical, W. *Phytochemistry* **1998**, *49*, 2299.
191. Kono, Y.; Gardner, J. M.; Suzuki, Y.; Takeuchi, S. *Phytochemistry* **1985**, *24*, 2869.
192. Engel, B.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 518.
193. Watanadilok, R.; Sonchaeng, P.; Kijjoa, A.; Damas, A. M.; Gales, L.; Silva, A. M. S.; Herz, W. *J. Nat. Prod.* **2001**, *64*, 1056.
194. Tazaki, H.; Hayashida, T.; Ito, M.; Minoshima, S. A.; Furuki, T.; Nabeta, K. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1238.
195. Mues, B.; Huneck, S.; Connolly, J. D.; Rycroft, D. S. *Tetrahedron Lett.* **1988**, *29*, 6793.
196. Senoh, S.; Imamoto, S.; Maeno, Y.; Tokuyama, T.; Sakan, T.; Komamine, A.; Hattori, S. *Tetrahedron Lett.* **1964**, 3431.
197. Chilton, W. S.; Hsu, C. P.; Zdybak, W. T. *Phytochemistry* **1974**, *13*, 1179.
198. Saito, K.; Komamine, A.; Senoh, S. *Z. Naturforsch. Teil C* **1975**, *30*, 659.
199. Saito, K.; Komamine, A.; Senoh, S. *Z. Naturforsch. Teil C* **1976**, *31*, 15.
200. Saito, K.; Komamine, A. *Eur. J. Biochem.* **1976**, *68*, 237.
201. Ellis, B. E. *Phytochemistry* **1976**, *15*, 489.
202. Musso, H. *Tetrahedron* **1979**, *35*, 2843.
203. Kraut, L.; Mues, R.; Speicher, A.; Wagmann, M.; Eicher, T. *Phytochemistry* **1996**, *42*, 1693.
204. (a) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Blackman, A. J. *Aust. J. Chem.* **1982**, *35*, 113; (b) Blackman, A. J.; Bremner, J. B.; Paano, A. M. C.; Skerratt, J. H.; Swann, M. L. *Aust. J. Chem.* **1990**, *43*, 1133; (c) Murray, L.; Currie, G.; Capon, R. J.

Aust. J. Chem. **1995**, *48*, 1485; (d) Shin, J.; Paul, V. J.; Fenical, W. *Tetrahedron Lett.* **1986**, *27*, 5189; (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (f) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
205. Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *Z. Naturforsch., C: Biosci.* **1998**, *53*, 89.
206. Amegadzie, A. K.; Ayer, W. A.; Sigler, L. *Can. J. Chem.* **1995**, *73*, 2119.
207. Arndt, F. In *Organic Synthesis*; Allen, C. F. H., Ed.; Wiley: New York, NY, 1940; p 26.
208. Takeshita, H.; Kikuchi, R.; Shoji, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 690.
209. Wiley, R. H.; Smith, N. R. *Org. Synth.* **1951**, *31*, 23.
210. (a) Harris, T. M.; Harris, C. M.; Hindley, K. B. *Fortschr. Chem. Org. Naturstoffe* **1974**, 217; (b) Narasimhan, N. S.; Ammanamanchi, R. K. *J. Org. Chem.* **1983**, *48*, 3945.
211. Buchner, E.; Schroder, H. *Ber.* **1902**, *35*, 782.
212. Mingo, P.; Zhang, S. L.; Liesbekind, S. *J. Org. Chem.* **1999**, *64*, 2145.
213. (a) Newman, M. S.; Both, W. T. *J. Am. Chem. Soc.* **1945**, *67*, 154; (b) Cala, R.; Dunogues, J.; Pillot, J. P.; Brain, C.; Pisciotti, F.; Arreguy, B. J. *J. Organomet. Chem.* **1975**, *85*, 149.
214. Kosugi, M.; Shimizu, Y.; Migita, T. *J. Organomet. Chem.* **1977**, *129*, 36.
215. Liedtke, R. J.; Gerrard, A. F.; Diekman, J.; Djrassi, C. *J. Org. Chem.* **1972**, *37*, 776.
216. Scarborough, R. M.; Smith, A. B. *Tetrahedron Lett.* **1977**, 4361.
217. (a) *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, NY, 1980; (b) *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic: New York, NY, 1982; Vols. 1–3.
218. Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996.
219. Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, S. *J. Org. Chem.* **2005**, *70*, 4854.
220. Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 740.
221. Akué-Gédu, R.; Hénichart, J.; Couturier, D.; Rigo, B. *Tetrahedron Lett.* **2004**, *45*, 9197.
222. Rao, P. N. P.; Uddin, Md. J.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 3972.
223. Kondo, T.; Taguchi, Y.; Kancko, Y.; Nimi, M.; Mitsuda, T. *Angew. Chem.* **2004**, *116*, 5483.
224. Gerus, I. I.; Tolmachova, N. A.; Vdovenko, S. I.; Frohlich, R.; Haufe. *Synthesis* **2005**, 1269.
225. Kepe, V.; Kocevar, M.; Polanc, S. *J. Heterocycl. Chem.* **1996**, *33*, 1707.
226. Ito, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6583.
227. Liebeskind, L. S.; Wang, J. Y. *Tetrahedron* **1993**, *49*, 5461.
228. Effenberger, F.; Ziegler, T.; Schönwälder, K.-H.; Kesmarszky, T.; Bauer, B. *Chem. Ber.* **1986**, *119*, 3394.
229. Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857.
230. Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673.
231. Thibonnet, J.; Abarbri, M.; Parrain, J.; Duchene, A. *J. Org. Chem.* **2002**, *67*, 3941.
232. Rousset, S.; Abarbri, M.; Thibonnet, J.; Parrain, J.; Duchene, A. *Tetrahedron Lett.* **2003**, *44*, 7633.
233. Thole, F. B.; Thorpe, J. F. *J. Chem. Soc.* **1911**, *99*, 2208.
234. Audin, P.; Piveteau, N.; Dussert, A.; Paris, J. *Tetrahedron* **1999**, *55*, 7847.
235. Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188.
236. Rosas, N.; Salmon, M.; Sharma, P.; Alvarez, C.; Ramirez, R.; Garcia, J.-L.; Azoumanian. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1493.
237. Tominaga, Y. *Trends Heterocycl. Chem.* **1991**, *2*, 43.
238. Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res., Synop.* **1991**, 98.
239. Ram, V. J.; Nath, M.; Srivastava, P.; Sarkhel, S.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3719.
240. Tanyeli, C.; Demir, A. S.; Ozarslan, O.; Mecidoglu, I.; Tarhan, O. *Heterocycles* **1994**, *37*, 1705.
241. Sib, S. *Tetrahedron* **1975**, *31*, 2229.
242. Kvita, V.; Fischer, W. *Chimia* **1992**, *46*, 457.
243. Susherina, N. P.; Dmitrieva, N. D.; Levina, R. *Dokl. Akad. Nauk S.S.S.R.* **1962**, 146.
244. Robertson, D. N.; Link, K. P. *J. Am. Chem. Soc.* **1953**, *75*, 1647.
245. (a) Moreno-Manas, M.; Ribas, J. *Tetrahedron Lett.* **1989**, *30*, 3109; (b) Moreno-Manas, M.; Pleixats, R. *Synthesis* **1984**, 430; (c) De March, P.; Moreno-Manas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. *J. Heterocycl. Chem.* **1984**, *21*, 85.
246. (a) Moreno-Manas, M.; Pleixats, R. *Adv. Heterocycl. Chem.* **1992**, *53*, 1; (b) Moreno-Manas, M.; Ribas, J.; Virgili, A. *J. Org. Chem.* **1988**, *53*, 5328; (c) De March, P.; Moreno-Manas, M.; Pi, R.; Trius, A. *J. Heterocycl. Chem.* **1982**, *19*, 335; (d) Cervera, M.; Moreno-Manas, M.; Pleixats, R. *Tetrahedron* **1990**, *46*, 7885.
247. Sagar, R.; Singh, P.; Kumar, R.; Maulik, P. R.; Shaw, A. K. *Carbohydr. Res.* **2005**, *340*, 1287.
248. Gompper, R.; Christmann, O. *Chem. Ber.* **1961**, *94*, 1796.
249. Fried, J.; Elderfield, R. C. *J. Org. Chem.* **1941**, *6*, 577.
250. Belil, C.; Pascual, J.; Serratosa, F. *Ann. Real Soc. Espan. Fis, Quim., Ser B* **1963**, *59*, 507; *Chem. Abstr.* **1964**, *60*, 5439.
251. Vogel, G. *J. Org. Chem.* **1965**, *30*, 203.
252. Ram, V. J.; Goel, A. *Tetrahedron Lett.* **1996**, *37*, 93.
253. Goel, A.; Srivastava, P.; Nath, M.; Ram, V. J. *Synthesis* **1998**, 167.
254. Ram, V. J.; Nath, M.; Srivastava, P.; Sarkhel, S.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3719.
255. Ram, V. J.; Srivastava, P.; Agarwal, N.; Sharon, A.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1593.
256. Agarwal, N.; Saxena, A. S.; Farhanullah; Goel, A.; Ram, V. J. *Tetrahedron* **2002**, *58*, 8793.
257. (a) Saxena, A. S.; Goel, A.; Ram, V. J. *Synlett* **2002**, 1491; (b) Ram, V. J.; Agarwal, N. *Tetrahedron Lett.* **2001**, *42*, 7127.
258. Pratap, R.; Sil, D.; Ram, V. J. *Tetrahedron Lett.* **2005**, *46*, 5025.
259. Pratap, R.; Ram, V. J. *Tetrahedron* **2006**, *62*, 8158.
260. Pratap, R.; Ram, V. J. *Tetrahedron Lett.* **2006**, *47*, 5389.
261. Sil, D.; Pratap, R.; Kumar, R.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2006**, *47*, 3759.
262. Goel, A.; Verma, D.; Singh, F. V. *Tetrahedron Lett.* **2005**, *46*, 8487.
263. Singh, F. V.; Kumar, A.; Goel, A. *Tetrahedron Lett.* **2006**, *47*, 7767.
264. Ram, V. J.; Srivastava, P.; Nath, M.; Saxena, A. S. *Synthesis* **1999**, 1884.
265. Nath, M.; Srivastava, P.; Goel, A.; Ram, V. J. *Eur. J. Org. Chem.* **1998**, 2083.
266. Ram, V. J.; Srivastava, P.; Agarwal, N. *J. Chem. Res., Synop.* **2001**, 421.
267. (a) Goel, A.; Singh, F. V.; Dixit, M.; Verma, D.; Raghunandan, R.; Maulik, P. R. *Chem. Asian J.* **2007**, *2*, 239; (b) Goel, A.; Singh, F. V.; Kumar, V.; Reichert, M.; Gulder, T. A. M.; Bringmann, G. *J. Org. Chem.* **2007**, *72*, 7765.
268. Ram, V. J.; Goel, A. *Chem. Lett.* **1997**, 1021.
269. Sil, D.; Goel, A.; Ram, V. J. *Tetrahedron Lett.* **2003**, *44*, 3363.
270. Sil, D.; Sharon, A.; Pratap, R.; Maulik, P. R.; Ram, V. J. *Synlett* **2004**, 2163.
271. Pratap, R.; Ram; Kumar; Brijesh, V. J. *Tetrahedron* **2007**, *63*, 10300.
272. Ram, V. J.; Goel, A. *Synthesis* **1999**, 467.
273. Sil, D.; Ram, V. J. *Tetrahedron Lett.* **2005**, *46*, 5013.
274. Ram, V. J.; Agarwal, N.; Saxena, A. S.; Farhanullah; Sharon, A.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1426.
275. Ram, V. J.; Goel, A. *J. Chem. Res., Synop.* **1997**, 460.
276. Sarkhel, S.; Goel, A.; Ram, V. J.; Chaudhuri, S.; Maulik, P. R. *Acta Crystallogr.* **1997**, *53*, 1713.
277. Sharon, A.; Maulik, P. R.; Vithana, C.; Ohashi, Y.; Ram, V. J. *Eur. J. Org. Chem.* **2004**, 886.
278. Ram, V. J.; Srivastava, P.; Saxena, A. S. *J. Org. Chem.* **2001**, *66*, 5333.
279. Goel, A.; Dixit, M. *Tetrahedron Lett.* **2004**, *45*, 8819.
280. (a) Goel, A.; Dixit, M.; Verma, D. *Tetrahedron Lett.* **2005**, *46*, 491; (b) Dixit, M.; Raghunandan, R.; Kumar, B.; Maulik, P. R.; Goel, A. *Tetrahedron* **2007**, *63*, 1610.
281. Dixit, M.; Goel, A. *Tetrahedron Lett.* **2006**, *47*, 3557.
282. Ram, V. J.; Goel, A. *J. Org. Chem.* **1999**, *64*, 2387.
283. Pratap, R.; Sil, D.; Ram, V. J. *Tetrahedron Lett.* **2004**, *45*, 5743.
284. Ram, V. J.; Agarwal, N.; Farhanullah. *Tetrahedron Lett.* **2002**, *43*, 3281.
285. Ram, V. J.; Srivastava, P.; Goel, A. *Synthesis* **2000**, 13.
286. Sil, D.; Farhanullah; Ram, V. J. *Tetrahedron Lett.* **2004**, *45*, 9029.
287. (a) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res., Synop.* **1991**, 98; (b) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *Liebigs Ann. Chem.* **1991**, 1229.
288. Ram, V. J.; Haque, N.; Singh, S. K.; Hussaini, F. A.; Shoeb, A. *Indian J. Chem.* **1993**, *32B*, 924.
289. Hussaini, F. A.; Pragya; Ram, V. J.; Singh, S. K.; Nath, M.; Shoeb, A.; Bhaduri, A. *J. Chem. Res., Synop.* **1994**, 86.
290. Farhanullah; Agarwal, N.; Goel, A.; Ram, V. J. *J. Org. Chem.* **2003**, *68*, 2983.
291. Ram, V. J.; Srivastava, P.; Goel, A. *Tetrahedron* **2003**, *59*, 7141.
292. Srivastava, P.; Saxena, A. S.; Ram, V. J. *Synthesis* **2000**, 541.
293. Goel, A.; Singh, F. V.; Verma, D. *Synlett* **2005**, 2027.
294. Goel, A.; Singh, F. V. Unpublished work.
295. Goel, A.; Singh, F. V.; Sharon, A.; Maulik, P. R. *Synlett* **2005**, 623.
296. Hubert-Habart, M.; Pene, C.; Royer, R. *Chim. Ther.* **1973**, *8*, 314.
297. Tagaki, K.; Hubert-Habart, M. *Bull. Soc. Chim. Fr.* **1977**, 369.
298. Pratap, R.; Roy, A. D.; Kushwaha, S. M.; Goel, A.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 5845.
299. Pratap, R.; Kumar, Brijesh; Ram, V. J. *Tetrahedron* **2007**, *63*, 10309.
300. Pratap, R.; Kushwaha, S. M.; Goel, A.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 549.
301. Pratap, R.; Raghunandan, R.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 4939.
302. Shusherina, N. P.; Laptova, V. L. *J. Org. Chem. USSR* **1974**, *10*, 852.
303. Peyman, A.; Renschig, D. B.; Linkies, A. H. *Chem. Abstr.* **1996**, *125*, 58332a.
304. Rosenstock, B.; Peyman, A.; Ruppert, D.; Riess, G. *Chem. Abstr.* **1997**, *126*, 7993c.
305. Lassalle, G.; Bellevergne, P.; Bourbier, J. C.; Galtier, D.; Martin, V. *Chem. Abstr.* **1998**, *129*, 175556v.
306. Sharon, A.; Pratap, R.; Maulik, P. R.; Ram, V. J. *Tetrahedron* **2005**, *61*, 3781.
307. Pratap, R.; Sharon, A.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2005**, *46*, 85.
308. Ram, V. J.; Agarwal, N.; Sharon, A.; Maulik, P. R. *Tetrahedron Lett.* **2002**, *43*, 307.
309. Sil, D.; Sharon, A.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2004**, *45*, 6273.
310. Sil, D.; Sharon, A.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2004**, *45*, 6619.
311. Kohly, I.; El-El., S.; Mishrikey, M. M.; Fuid-Alla, H. M. *J. Heterocycl. Chem.* **1975**, *12*, 129.
312. Ram, V. J.; Srivastava, P. *Curr. Org. Chem.* **2001**, *5*, 571.
313. Jones, R. C. F.; Bhaley, G.; Patience, J. M.; Patel, P. *J. Chem. Res.* **1999**, *4*, 250.
314. Sil, D.; Kumar, R.; Sharon, A.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2005**, *46*, 3807.
315. Singh, F. V.; Goel, A. Unpublished work.
316. Goel, A.; Verma, D. Unpublished work.
317. Pratap, R.; Ram, V.J. Unpublished work.
318. Tominaga, Y.; Ushirogochi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 3384.
319. Ram, V. J.; Goel, A.; Shukla, P. K.; Kapil, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3101.
320. Sil, D.; Ram, V. J. *Tetrahedron. Lett.* **2004**, *45*, 8195.
321. Singh, F. V.; Dixit, M.; Chaurasia, S.; Raghunandan, R.; Maulik, P. R.; Goel, A. *Tetrahedron Lett.* **2007**, *48*, 8998.
322. Pratap, R.; Ram, V. J. Unpublished work.
323. Ram, V. J.; Haque, N.; Nath, M.; Singh, S. K.; Hussaini, F. A.; Tripathi, S. C.; Shoeb, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3149.
324. (a) Bu'Lock, J. D.; Smith, H. G. *J. Chem. Soc.* **1960**, 502; (b) Edwards, R. L.; Mir, I. *J. Chem. Soc. C* **1967**, 411; (c) Douglas, J. L.; Money, T. *Tetrahedron* **1967**, *23*, 3545; (d) Israili, Z. H.; Smissman, E. E. *J. Org. Chem.* **1987**, *52*, 5067; (e) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470; (f) Tadano, K.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron* **1990**, *46*, 2353.

325. Van Dam, M. J. D.; Kögl, F. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 39.
326. Fried, J.; Elderfield, R. C. *J. Org. Chem.* **1941**, *6*, 566.
327. Leben, J. A. *Ber.* **1986**, *29*, 1673.
328. (a) Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950; (b) McIntosh, C. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1973**, *95*, 247.
329. Chase, C. E.; Jarstfer, M. B.; Arif, A. M.; West, F. G. *Tetrahedron Lett.* **1995**, *36*, 8531.
330. (a) De Mayo, P.; Yip, R. W. *Proc. Chem. Soc.* **1964**, 84; (b) Adam, W.; Erden, I. *J. Am. Chem. Soc.* **1979**, *101*, 5692.
331. Afarinkia, K.; Nelson, T. D.; Vinader, M. V.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.
332. Woodward, B. T.; Posner, G. H. *Adv. Cycloaddit.* **1999**, *5*, 47.
333. Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373.
334. (a) Posner, G. H.; Haces, A.; Harrison, W.; Kinter, C. M. *J. Org. Chem.* **1987**, *52*, 4836; (b) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967; (c) Afarinkia, K.; Mahmood, F. *Tetrahedron* **1999**, *55*, 3129.
335. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.
336. Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667.
337. Posner, G. H.; Nelson, T. D. *Tetrahedron* **1990**, *46*, 4573.
338. Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.* **1992**, *33*, 7839.
339. Goldstein, E.; Kallel, A.; Beauchamp, P. S. *J. Mol. Struct.* **1987**, *151*, 297.
340. Seyferth, D.; White, D. L. *J. Organomet. Chem.* **1972**, *34*, 119.
341. Kyba, E. P.; Rines, S. P.; Owens, P. W.; Chou, S. S. P. *Tetrahedron Lett.* **1981**, *22*, 1875.
342. Sakurai, H.; Nakadaria, Y.; Hosomi, A.; Eriyama, Y. *Chem. Lett.* **1982**, 1971.
343. Martin, P.; Streith, J.; Rihs, G.; Winkler, T.; Bellus, D. *Tetrahedron Lett.* **1985**, *26*, 3947.
344. Warren, J. D.; Lee, V. L.; Angier, R. B. *J. Heterocycl. Chem.* **1979**, *16*, 1617.
345. Jung, M. E.; Lowe, J. A., III; Lyster, M. A.; Node, M.; Pfluger, R. W.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751.
346. Jung, M. E.; Node, M.; Pfluger, R. W.; Lyster, M. A.; Lowe, J. A., III. *J. Org. Chem.* **1982**, *47*, 150.
347. Gingrich, H. L.; Roush, D. M.; Van saun, W. A. *J. Org. Chem.* **1983**, *48*, 4869.
348. Nedlein, R.; Kohl, M.; Kramer, W. *Helv. Chim. Acta* **1989**, *72*, 1311.
349. Barton, T. J.; Kippenhan, R. C., Jr.; Nelson, A. J. *J. Am. Chem. Soc.* **1974**, *96*, 2272.
350. Kozikowski, A. P.; Floyd, W. C.; Kunaik, M. P. *J. Chem. Soc., Chem. Commun.* **1977**, 582.
351. Ziegler, T.; Layh, M.; Effenberger, F. *Chem. Ber.* **1987**, *120*, 1347.
352. Shino, T.; Yamasaki, S.; Date, K.; Uemura, H.; Somekawa, K. *J. Heterocycl. Chem.* **1993**, *30*, 419.
353. Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213.
354. Kende, A. S.; Curran, D. P.; Tsay, Y. G.; Mills, J. E. *Tetrahedron Lett.* **1997**, 3537.
355. Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690.
356. Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805.
357. Hongm, B. C.; Sun, S. S. *Chem. Commun.* **1996**, 937.
358. Low, W.; Brawn, B.; Muller, B. *J. Heterocycl. Chem.* **1994**, *31*, 1577.
359. Rafiuddin, M. R.; Siddiqui, Z. S.; Zaman, A.; Chaudhary, A. R.; Mohammad, I. *Indian J. Chem., Sect. B* **1994**, *33*, 1023.
360. Udden, R.; Zaman, A. *Indian J. Chem. Sect. B* **1995**, *34*, 639.
361. Despande, V. H.; Khan, R. A.; Rai, B.; Ayyangar, N. R. *Synth. Commun.* **1993**, *23*, 2337.
362. Azuma, Y.; Sato, A.; Morone, M. *Heterocycles* **1995**, *38*, 1574.
363. Al-Saleh, B.; Al-Awadi, N.; Al-Kandari, H.; Abdel-Khalik, M. M.; Elnagdi, M. H. *J. Chem. Res., Synop.* **2000**, 201.

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