Raquel Alexandra Germano Nunes

Licenciatura em Química Aplicada

From sugar based bio renewable resources to new chemical building blocks and bioactive molecules

Dissertação para obtenção do Grau de Mestre em

Química Bioorgânica

Orientador: Prof. Doutor Carlos Alberto Mateus Afonso, FF-UL

Co-orientador: Rafael Filipe Teixeira Arbuéz Gomes, MSc, FF-UL

Presidente: Prof. Doutora Paula Cristina de Sério Branco, FCT-UNL

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FACULDADE DE CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

Março 2017

LOMBADA

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And for last, to my grandfather, I hope I have made you proud.

Abstract

The 4-hydroxycyclopentenones are a family of compounds found in nature, not only with medicinal properties, but can also be used as pesticides. Although with no knowledge of it, traditional medicine used of herbs and plants with healing properties for numerous diseases, which later came to be assign to this family of compounds.

Due to its many applications, the synthesis of 4-hydroxycyclopentenones is an area of great interest in chemical research. In this work was applied the method developed by Piancatelli, in furan rings derivatives, with the aim of creating a library of new biologically active 4-hydroxycyclopentenones derivatives.

This method has been used for the synthesis of simple cyclopentenones. Excellent yields were obtained by various research groups, having been one of the reasons for the choice of this method. The other was its simplicity, as it's an acid catalysis reaction with a Lewis acid or even, in a greener version, with microwave catalysis in water.

Resumo

As 4-hidroxiciclopentenonas são uma família de compostos encontrados na natureza, não só com propriedades medicinais, mas também são usadas como pesticidas. Embora sem conhecimento na medicina tradicional antiga era comum o uso de ervas e plantas com propriedades curativas de inúmeras doenças, que mais tarde se veio atribuir a esta família de compostos.

Devidas as suas inúmeras aplicações, a síntese de 4-hidroxiciclopentenonas é uma área de grande interesse na investigação. Neste trabalho foi aplicado o método desenvolvido por Piancatelli a derivados de anéis de furano, com o objectivo de criar uma biblioteca de novos derivados de 4-hidroxiciclopentenonas biologicamente activos.

Este método tem sido bastante utilizado para a síntese de ciclopentenonas simples. Foram obtidos excelentes rendimentos por parte de vários grupos de investigação, tendo sido esta uma das razões da escolha deste método. A outra, foi a sua simplicidade, visto tratar-se de uma reacção de catálise ácida por parte de um ácido de Lewis ou até, numa versão mais verde, de catálise de micro-ondas em água.

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List of abbreviations

4-Ac-CP	4-hydroxy-2-cyclopentenone with acetyl side chain
4-Boc-CP	4-hydroxy-2-cyclopentenone with *tert*-butyloxycarbonyl side chain
4-Bz-CP	4-hydroxy-2-cyclopentenone with benzoyl side chain
4HCP	4-hydroxy-2-cyclopentenone
4-phenylacethyl-CP	4-hydroxy-2-cyclopentenone with phenylacethyl ether side chain
4-PMP-CP	4-hydroxy-2-cyclopentenone with 4-methoxybenzyl ether side chain
4-TBDMS-CP	4-hydroxy-2-cyclopentenone with *tert*-butyldimethylsilyl ether side chain
4-TBS-CP	4-hydroxy-2-cyclopentenone with *tert*-butylsilyl ether side chain
4-THP-CP	4-hydroxy-2-cyclopentenone with 2-tetrahydropyranyl side chain
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc_2O	Di-*tert*-butyl dicarbonate
CAL-B	*Candida antarctica*
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIPE	Diisopropyl ether
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EKR	Enzymatic Kinetic Resolution
ER	endoplasmic reticulum

ERK	Extracellular signal-regulated protein kinase
HIV	human immunodeficiency virus
HMF	5-(hydroxymethyl)furfural
LA catalyst	Lewis acid catalyst
MITF	Microphthalmia-associated transcription factor
MTBE	Methyl *tert*-butyl ether
NCS	Neocarzinostatin
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium Chlorochromate
PG	Prostaglandin
rt	Room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl ether
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPS	*tert*-butyldiphenylsilyl ether
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TG	thapsigargin
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
TLC	Thin Layer Chromatography
TM	tunicamycin
TMS	Trimethylsilyl ether

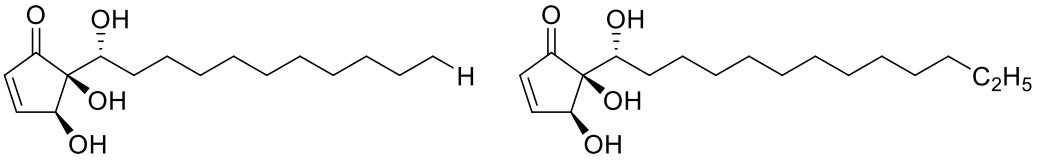
Chapter I – Introduction

I.I – The cyclopentenones

Natural occurring 4-hydroxy-cyclopentenones

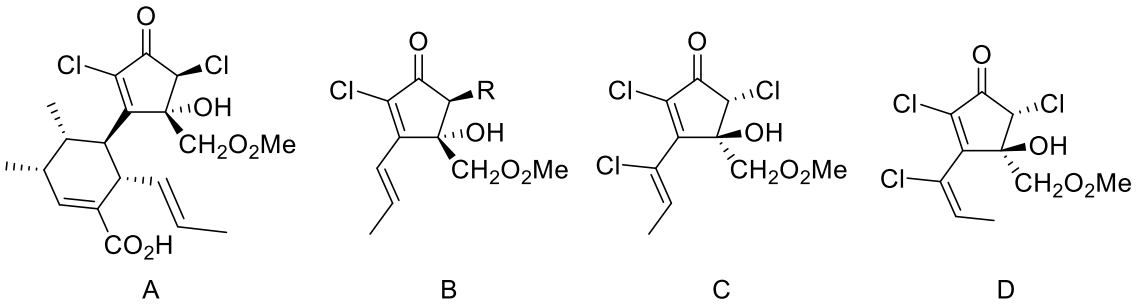
Natural compounds have been used for centuries in the cure of diseases. Although the reasons behind the cure had never been fully understood in the past, nowadays, scientists used them to extract their multiple active compounds in order to created them synthetically. 4HCP are no exception and examples of naturally occurring 4HCP will be presented below.

A. Otto *et al.* [1] isolated two 4HCP from fruiting bodies of the basidiomycete *Hygrophorus abieticola*. These compounds have been structural elucidated and their activity was studied, being the most active compound the compound B, in **Scheme 1**, being active against both ascomycetous fungi and oomycetes. This structure will be used in the future development of against both ascomycetous fungi and oomycetes. Eileen Bette *et al.* [2] also describe the isolation of this natural compound from the same species.



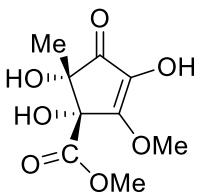
Scheme 1: Natural 4HCP isolated from the fruiting bodies of the basidiomycete *Hygrophorus abieticola* [1, 2].

Everton L. F. Ferreira *et al.* [3] report the structural elucidation of a second metabolite of the marine-derived strain of the fungus *Roussoella sp.* DLM33, molecule A in **Scheme 2**. Other metabolites, and 4HCP, of this fungus have been reported and are illustrated in **Scheme 2** as the molecules B – D.



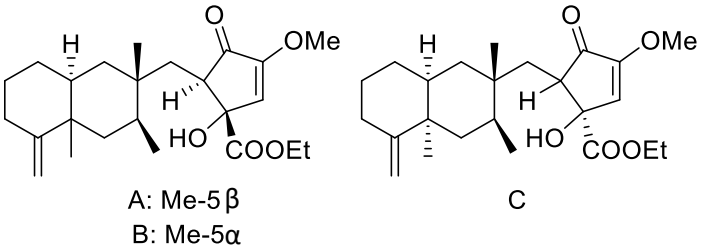
Scheme 2: Structures elucidated by Everton L. F. Ferreira *et al.* [3], from the fungus *Roussoella sp.* DLM33.

Jinhua Wang and co-workers [4] isolated a 4HCP as a metabolite of the endophytic fungus *Alternaria sp.* presented in **Scheme 3**. Full characterization and biological activity analysis was performed and showed that this compound as potential as antioxidant drug or can lead to compounds for constructing an antioxidant compound library and showed, as well, a potent inhibitory activity against *Fusarium graminearum*.



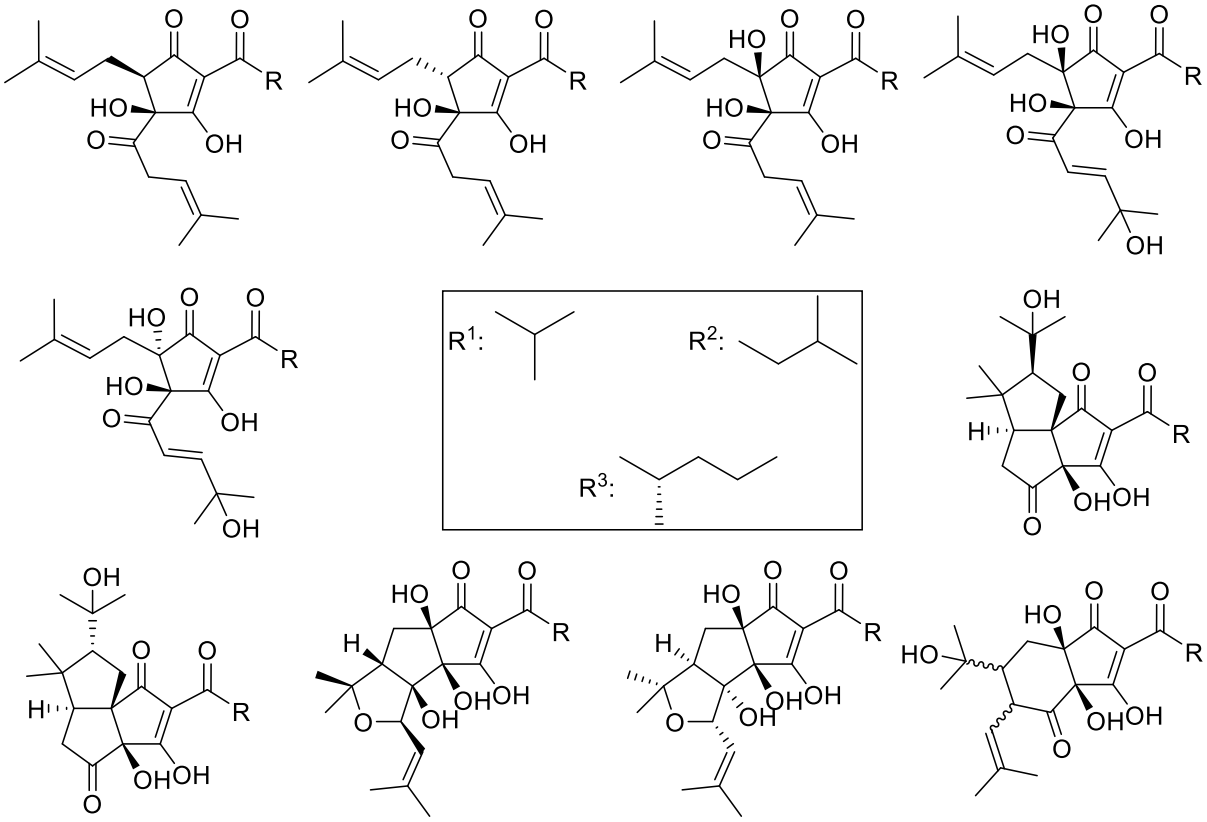
Scheme 3: Metabolite of the endophytic fungus Alternaria sp [4].

In Hyun Hwang *et al.* [5] discovered three 4HCP while searching for sponge-derived potent anticancer prototypes in *Verongula rigida*, generated by biotransformation. Those compounds are illustrated in **Scheme 4** and they can be potentially used in the development of colon cancer inhibitory agents, through suppression of CRT via promoting the degradation of β-catenin.



Scheme 4: 4HCP isolated in the work of Hyun Hwang *et al.* [5], from *Verongula rigida.*

Yoshimasa Taniguchi *et al.* [6-8] were able to isolate and characterize some derived products of the *Humulus lupulus* L. (Hops), present in beer and used, in ancient history as medicinal plant. The structures presented in **Scheme 5** were studied/mentioned by several other research groups such as Jan Urban *et al.* [9], Lupinacci *et al.* [10], T. Hofmann *et al.* [11], A.J. Hall *et al.* [12], Jaskula *et al.* [13], García-Villalba *et al.* [14], L. I.Nord *et al.* [15] and C. I. Chappel *et al.* [16]

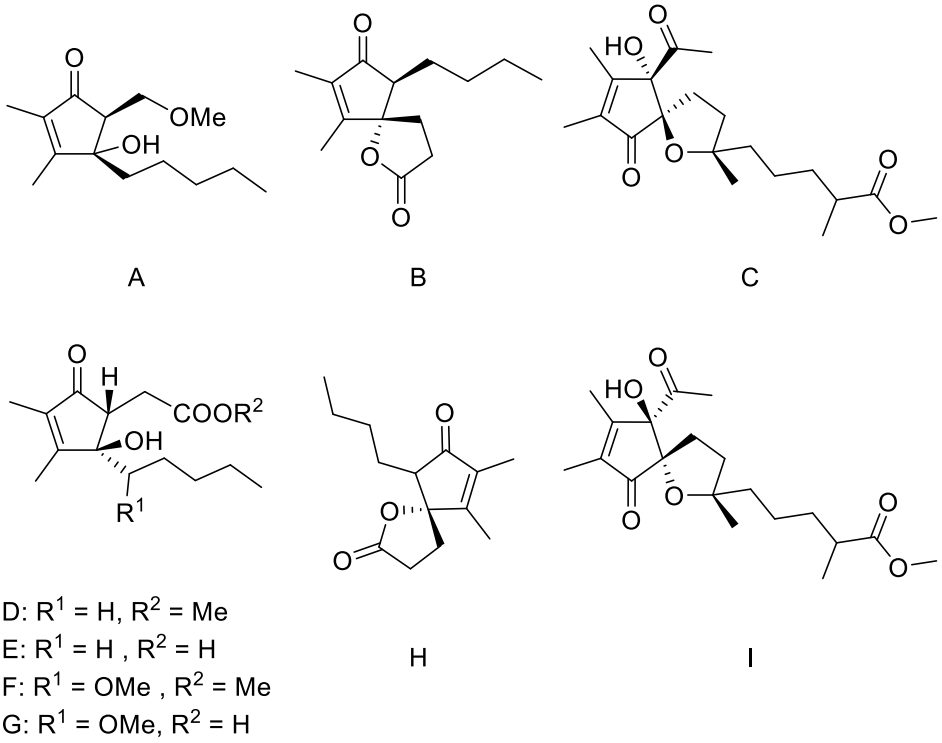


Scheme 5: 4HCP isolated from *Humulus lupulus* L. (Hops) [6-16]

Nai-Xia Zhang *et al.* [17] isolated two 4HCP in their studies on biologically active metabolites from marine organisms, such as the soft coral *Sinularia acuta* founded in the Weizhou Island of Guangxi Province in the South China Sea. Both compounds (**Scheme 6 A and B**) were isolated and characterized, but no interesting biological activity was yet found.

The same species of coral was also studied by Bin Yang *et al.* [18] that found the remaining 4HCP derivatives in **Scheme 6**. From this selection of molecules, F and H showed moderate effects for the inhibition of NF-κB activation.

This species produces such interesting compounds that other research groups explored and attempt to identify and characterize them, among them are Haiyan Shi and co-workers [19].



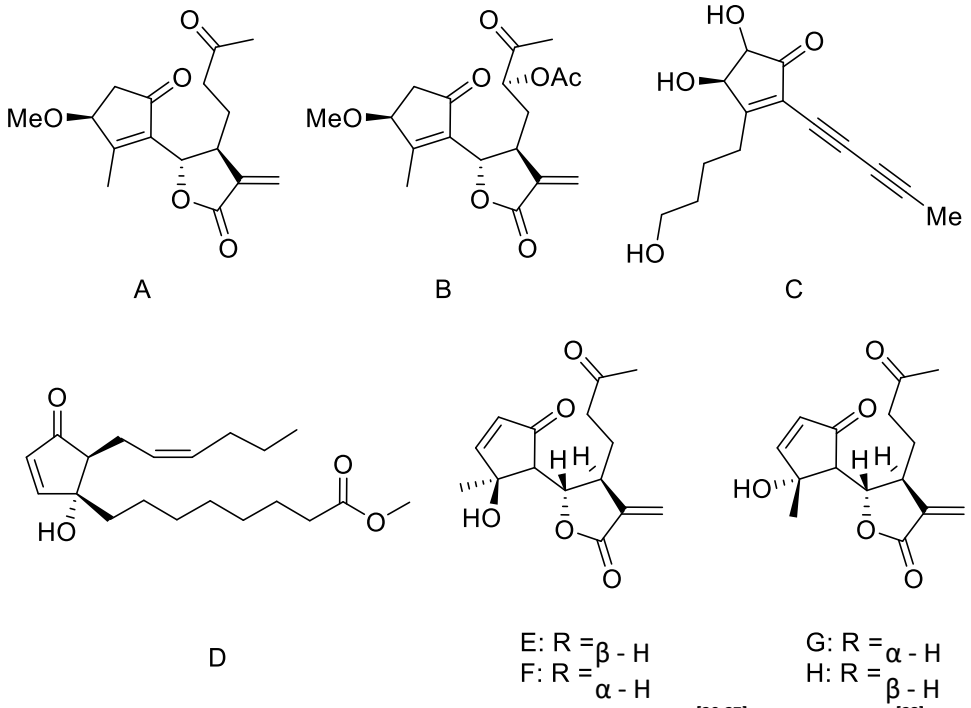
Scheme 6: Biologically active metabolites from marine organism *Sinularia acuta* [17-19].

Hajdú Z *et al.* [20] studied the compounds found on *Artemisia asiatica* Nakai, a plant native to Asia, which has been used in traditional oriental medicine for the treatment of several disorders. In this search were found multiple compounds, but only one 4HC derivative (**Scheme 7A**). This 4HCP was evaluated, *in vitro*, for tumor cell proliferation-inhibitory activity, and the results were promising [20]. The same 4HCP was isolated by Verma *et al.* [21] from *Artemisia sylvatica*.

A very similar compound was found by Snežana Trifunović *et al.* [18] while exploring the compounds present in the aereal parts of *Achillea clavennae*, a plant from Montenegro. In this study was found a 4HCP (**Scheme 7B**), isolated and structurally examined, and was found that it triggers apoptotic death of glioma cells as a result of the induction of oxidative stress and mitochondrial depolarization.

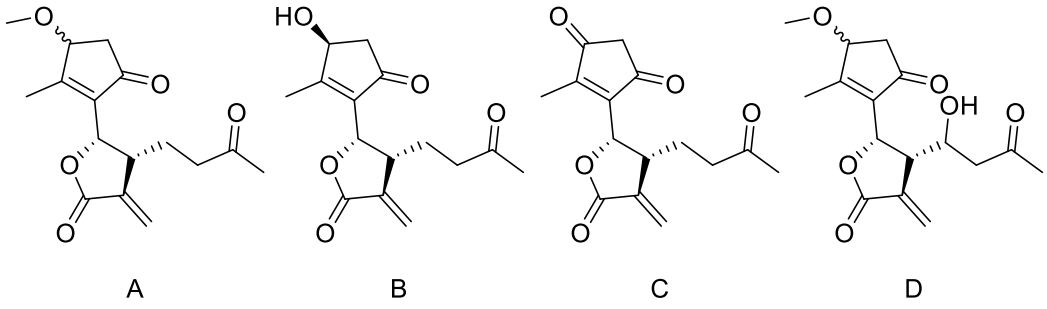
A novel 4HCP was found by M.-t. Xiao *et al.* [22] from the aerial parts of a similar species, *Artemisia lactiflora*. This molecule was named artemisidiyne A (**Scheme 7C**) and its cytotoxic activity revealed positive results in the inhibition the growth of three solid tumor cell lines, proving it's an interesting compound to be used as potent tumor inhibitor.

Due to a big interest in the *Artemisia* species, two more research groups K. Zan *et al.* [23] and Kazuyoshi Kawazoe *et al.* [24], isolated compounds and characterize them. K. Zan *et al.* [23] found the 4HCP D in **Scheme 7**, from *Artemisia anomala* S.Moore, a perennial herbaceous plant from China. Kazuyoshi Kawazoe *et al.* [24] found 4HCP E-H (**Scheme 7**) from the aerial parts of *Artemisia gilvescens*, a plant from the same species as before and also found in China. More research was carried on by different groups on this species [25-27], and the same compounds were found.



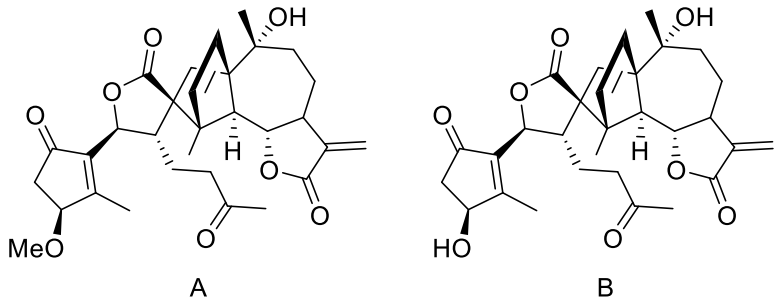
Scheme 7: Metabolites isolated from the species *Artemisia* [20-27] and *Achillea* [28].

A resemble set of compounds (**Scheme 8**) was isolated from the plant *Achillea falcate*, by Rita Tohme *et al.* [29] and by A. Ghantous *et al.* [30]. These compounds were isolated, purified and elucidated as shown. They were also tested for biologic activity but no interesting results were revealed.



Scheme 8: Compound isolated from *Achillea falcate*, by Rita Tohme *et al.* [29] and by A. Ghantous *et al.* [30].

Achillinin B and C (**Scheme 9A and B**, respectively) were isolated from the species *Achillea millefolium* by Y. Li et al. [31]. In this study, the compounds were elucidated and a possible biosynthetic pathway was design.



Scheme 9: Achillinin B and C, isolated from the species *Achillea millefolium* by Y. Li *et al* [31].

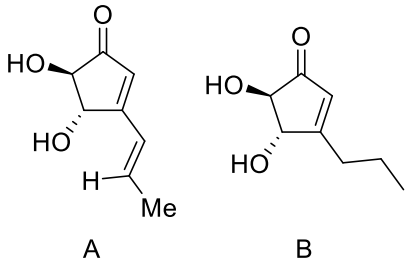
The metabolites from the marine endophytic fungus *Aspergillus terreus* have been a common interest in many research groups [32-50], which isolated the 4HCP in **Scheme 10**. From these many

groups, M.H. Haroon *et al.* [32] tested compound A for β-glucuronidase inhibitory activity, but no activity was found. M. Ubukata *et al.* [51] found this 4HCP to be a weak inhibitor of adipocyte differentiation.

Wen-Ying Liao *et al.* [33] found that 4HCP A also displays cytotoxicity against MCF-7 breast cancer cells, pancreatic cancer PANC-1 cells and liver cancer HepG2 cells, as so it may serve as a potential via for the treatment for these types of cancer.

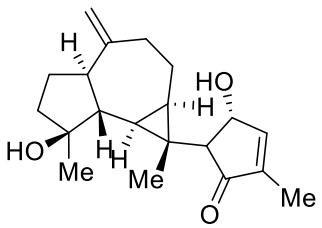
Yi Wang *et al.* [34] evaluated the same 4HCP for its cytotoxicity against HL-60 and BEL-7402 cell lines, antimicrobial activity against *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* and antiviral activity against influenza virus (H1N1). All results obtained in this study were positive.

This 4HCP (**Scheme 10A**), known as terrain, was also found in the metabolites of a microorganism identified as *Penicillium* species 20135, by S-H. Park et al. [52]. In this study, terrain was also found to be non-cytotoxic against Mel-Ab cells but has a strong hypopigmentary effect on those same cells, induces the persistent activation of ERK and reduces MITF protein levels, suppresses the transcriptional activity of MITF, reduced tyrosinase protein levels in Mel-Ab cells and terrein-induced MITF down-regulation is correlated with ERK activation. Other researchers found this compound, and derivatives (e.g. **Scheme 10B**), in different species such as the fungus *Pestilotiopsis microspore* [53] and *Emericella variecolor* [54].



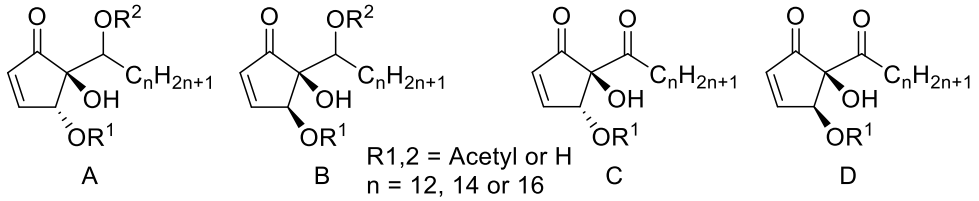
Scheme 10: Terrein (and derivative) found in the marine endophytic fungus *Aspergillus terreus* [32-50], *Penicillium* species 20135 [52] and the fungus *Pestilotiopsis microspore* [53] and *Emericella variecolor* [54].

Yan-gai Wang *et al.* [55] conducted a chemical analysis on the gum resin of *Boswellia carterii* Birdw. (*Burseraceae*) and found 4HCP in **Scheme 11**. This compound was tested for cytotoxicity against five human tumor cell lines, HCT-8 (human ileocecal adenocarcinoma), Bel-7402 (human hepatoma), BGC-823 (human gastric cancer), A549 (human lung epithelial), and A2780 (human ovarian cancer), for neuroprotective activity against MPP^+- induced neural injury and hepatoprotective activity against D-galactosamine-induced toxicity in HL-7702 cells. Unfortunately, the 4HCP, has showed no activity in these testes.



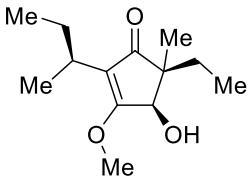
Scheme 11: 4HCP foun in *Boswellia carterii* Birdw. (*Burseraceae*) by Yan-gai Wang *et al.* [55].

Volker Schmidts *et al.* [56] isolated and studied the 4HCP from the *Hygrophorus* species: *H. persoonii* (A), *H. olivaceoalbus* (B), *H. pustulatus* (C) and *H. latitabundus* (D), in **Scheme 12**. From these isolated natural 4HCP derivatives, the work was focused on the full characterization of the structure A with $R^{1,2}$=Ac and n=12, in order to determine the three stereogenic centres.



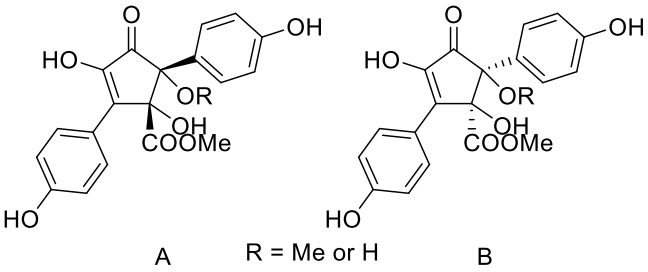
Scheme 12: Compound isolated from the *Hygrophorus* species *H. persoonii* (A), *H. olivaceoalbus* (B), *H. pustulatus* (C) and *H. latitabundus* (D), by Volker Schmidts *et al.* [56].

Ya-Chih Chang *et al.* [57] studied the ethyl acetate extracts of the fermented broths of the fungal strain *Pseudallescheria boydii* NTOU2362 and found the 4HCP in **Scheme 13**. Its structure was fully characterized and its absolute configuration determined. This compound's activity against the A549 non-small-cell lung cancer cell line was checked and it showed growth inhibitory activity.



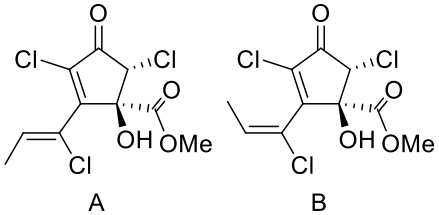
Scheme 13: 4HCP found in fungal strain *Pseudallescheria boydii* NTOU2362 by Ya-Chih Chang *et al.* [57].

The biological active compounds in **Scheme 14** were isolated and characterized by Takashi Fukuda *et al.* [58] from the fruiting bodies of *Tylopilus eximius*. These compounds, a known class of aromatic pigments, had been previously isolated from other fungus.



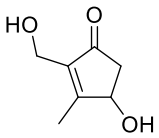
Scheme 14: Compounds found by Takashi Fukuda *et al.* [58] in the fruiting bodies of *Tylopilus eximius*.

Takunori Matsumoto *et al.* [59] isolated the 4HCP A and B, in **Scheme 15**, from the discomycete *Lachnum palmae*. These compounds were evaluated for antimicrobial activity against four Gram-positive bacteria and five Gram-negative bacteria, four fungi, and one yeast. 4HCP A shoed stronger antimicrobial activity against *Micrococcus luteus*, *Mycobacterium smegmatis*, *Escherichia coli*, *Xanthomonas campestris* and *Mucor racemosus* than B.



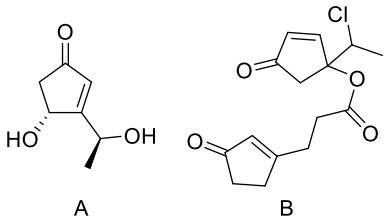
Scheme 15: 4HCP isolated from the discomycete *Lachnum palmae* [59].

In the pursuit for active ER stress protecting compounds, J.-H. Choi et al. [60] found a 4HCP (**Scheme 16**), isolated from the mushroom *Mycoleptodonoides aitchisonii*. This 4HCP was subjected to a series of testes to confirm its activity against toxicity of TM and TG, but it only showed protective activity for the TG.



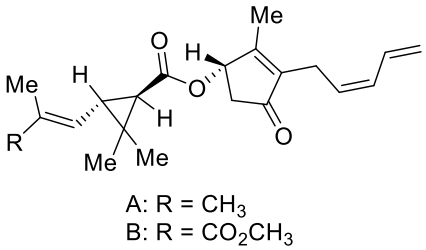
Scheme 16: 4HCP isolated from the mushroom *Mycoleptodonoides aitchisonii* [60].

G.-H. Li *et al.* [61] found the new 4HCP A and B (**Scheme 17**) from the isolation from strain *Trichoderma sp.* YLF-3. Both compounds were characterized and assayed for antibacterial activity against Staphyloccocus aureus and Bacillus cereus, but the results weren't positive.



Scheme 17: New 4HCP found in the strain *Trichoderma sp.* YLF-3 by G.-H. Li *et al.* [61].

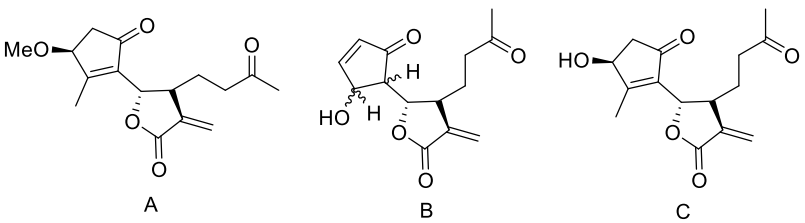
In their studies of natural pesticides for organic agriculture, Pierluigi Caboni and co-workers [62, 63], found Pyrethrum extract from the plant *Chrysanthemum cinerariaefolium*. This extract contains three esters of chrysanthemic acid and three corresponding esters of pyrethric acid, and isolated two 4HCP (**Scheme 18**), pyrethrin I and pyrethrin II, which were found to be fast acting and toxic to insects at low doses and unfortunately unstable toward heat, light, and air. Several other research groups [64-83] took interest in this compound/species.



Scheme 18: Pyrethrin I (A) and Pyrethrin II (B) found in the extracts of plant Chrysanthemum cinerariaefolium [62-83].

Mohamed-Elamir F. Hegazy *et al.* [84] isolated a 4HCP (**Scheme 19A**) from the plant identified as *Tanacetum sinaicum*. This isolated compound was tested for activity against nitric oxide production, and showed lower activity than the already commercial available. Others [85] found the same compound from this plant species and similar ones like *Tanacetum cilicium* [86] and *Tanucetum parthenium* [87].

Similar compounds were found by A.F. Barrero *et al.* [88] from aerial parts of *Artemisia granatensis* (**Scheme 19B and C**). These compounds showed important antifeedant activities against insects, but further analysis is necessary to determine its role as medicine. C. Zdero *et al.* [89] isolated the same 4HCP from the species *Pentzla zncana*.

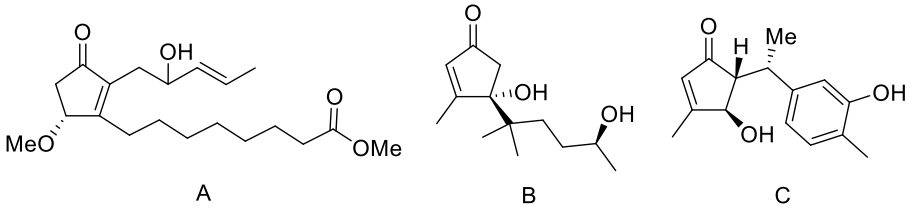


Scheme 19: A - 4HCP found in the Tanacetum species, T. sinaicum [84], T. cilicium [86] and T. parthenium [87]. B and C – 4HCP found in the aerial parts of Artemisia granatensis [88] and Pentzla zncana [89].

Vitex quinata is the species of a tree that can be found in temperate and tropical Asia. Y. Deng *et al.* [90] studied the compounds isolated from its leaves. In this study a 4HCP (**Scheme 20A**) was found, elucidated and tested for its cytotoxicity against LNCaP hormone-dependent prostate, Lu1 human lung, and MCF-7 human breast cancer cells, but no activity was shown.

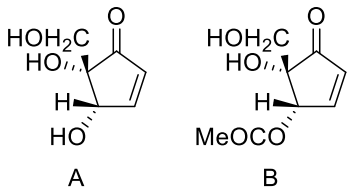
4HCP B, in **Scheme 20**, was isolated from the aerial parts of *Aphanamixis grandifolia* and elucidated, by Quan Liu *et al.* [91]. Cytotoxicity analysis revealed moderate activity against human leukemia and human cervical carcinoma cancer cell lines.

Xian-Wen Yang *et al.* [92] isolated and elucidated 4HCP C in **Scheme 20**, from the species *Abies delavayi*. This compound was given then the name cycloabiesesquine A.



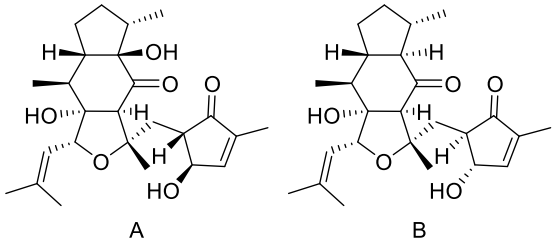
Scheme 20: A – 4HCP found in the leaves of the species *Vitex quinata* [90]. B – 4HCP found in the aerial parts of *Aphanamixis grandifolia* [91]. C – Cycloabiesesquine A found in the species *Abies delavayi* [92].

Pentenomycin I and II (**Scheme 21A and B**, respectively), two 4HCP, were isolated and elucitated from the culture of *Streptomyces eurythermus* MCRL 0738 by Kimio Umino *et al.* [93]. These compounds showed activity against Gram negative bacteria, making them antibiotics.



Scheme 21: Pentenomycin I and II isolated from *Streptomyces eurythermus* MCRL 0738 by Kimio Umino *et al.* [93].

Two new 4HCP were found, by Shi-Hong Luo *et al.*[94], in the leaves of *Leucosceptrum canum*. Both compounds were purified and elucidated and are known as leucosceptroids C and D (**Scheme 22A and B**, respectively).



Scheme 22: leucosceptroids C and D isolated from the leaves of Leucosceptrum canum by Shi-Hong Luo et al. [94].

4-hydroxy-2-cyclopentenones and hydroxyl side chain derivatives

4-Hydroxy-2-cyclopentenones (4HCP) have been widely studied as they appear in numerous natural products and biologically active compounds [95]. They are also important as its structure allows them to be the building block for several products, natural or synthetic, as it be highlighted above.

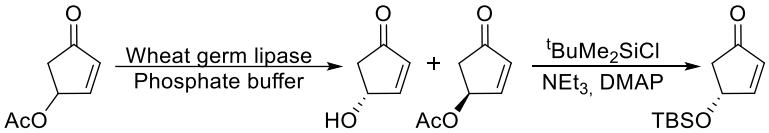
Many scientists have dedicated their efforts on developing and optimizing the synthesis of 4HCP and its analogues as well as the many possible compounds originated by them. The synthesis known for this compounds will be presented below, as well as its numerous applications.

4-hydroxy-2-cyclopentenone can be easily converted in many analogues by simple and known reactions (**Scheme 31**). It can also be prepared by numerous ways that have been developed according to the needs (**Scheme 43**) to create various compounds (**Scheme 50**).

Over the years, the pathways leading to 4HCP have been changed and perfected so it would lead to the best yield, as well as to higher enantiomeric excesses (ee) of the desired enantiomer.

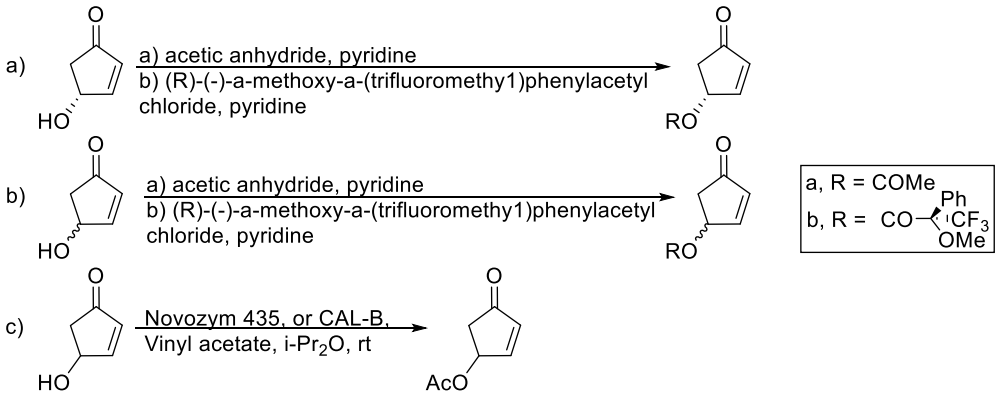
Protection, unprotection and resolution

Leo A. Paquette and co-workers [96] managed to obtain pure (R)-4HCP from its acetate derivate (R)-4-Ac-CP (**Scheme 23**), through an enzymatic reaction with wheat germ lipase with a phosphate buffer, in 60% yield. They also prepared the TBDMS derivate, (R)-4-TBDMS-CP, in 64% yield, from the (R)-4HCP using 4-dimethylaminopyridine, triethylamine and TBDMSCl in DCM (**Scheme 23**). In 1998, Timothy J. N. Watson and co-workers [97] also protected 4HCP with TBDMSCl in 76% yield, with triethylamine and DMAP (**Scheme 23**, only second step).



Scheme 23: Methods described by Leo A. Paquette and co-workers [96] and Timothy J. N. Watson and co-workers [97].

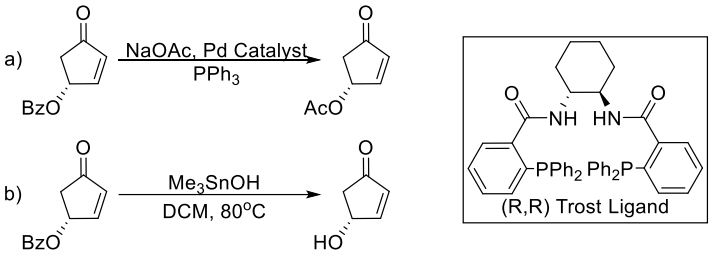
Subhash P. Khanapure *et al.* [98] prepared the (S) and racemic products of the 4-Ac-CP and respective Mosher esters. The first ones were obtained using acetic anhydride in pyridine, in 80% yield, from the (S) and racemic 4HCP (**Scheme 24a)**). The second ones from acylation with (R)-(-)-a-methoxy-a-(trifluoromethy)-phenylacetylchloride in pyridine (**Scheme 24b)**), from the same starting materials. O'Byrne *et al.* [99] also described the conversion of 4HCP in its acetyl side chain analogue by enzymatic kinetic resolution (EKR) with Novozym 435 (or CAL-B) in a total yield of 96% (**Scheme 24c)**).



Scheme 24: a) and b) Subhash P. Khanapure et al. [98] synthesis for (S) and racemic products of the 4-Ac-CP and respective Mosher esters; c) O'Byrne et al. [99] description of the synthesis of 4-Ac-CP.

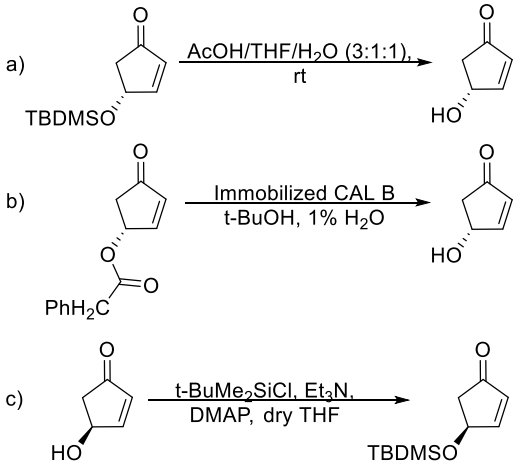
T.T. Curran *et al.* [100] prepared several 4-O-protected cyclopentenones in order to study the effect of the protecting group on the stereoselective ketone reduction. These compounds were prepared in 30% to 80% yield from the 4HCP. S. Specklin *et al.* [101] were also able to protect 4HCP with TIPS, TMS, TBDMS and TBDPS from the 4HCP, in 81-85% yield.

Barry M. Trost and co-workers [102] were able to convert the 4-Bz-CP in its other analogue, 4-Ac- CP, in 64% yield and 93% ee, using a Pd-catalyzed allylic alkylation reaction with NaOAc. They deprotected the benzoyl group with Me_3SnOH in DCM, to covert the 4-Bz-CP in the 4HCP with 69% yield and 95% ee.



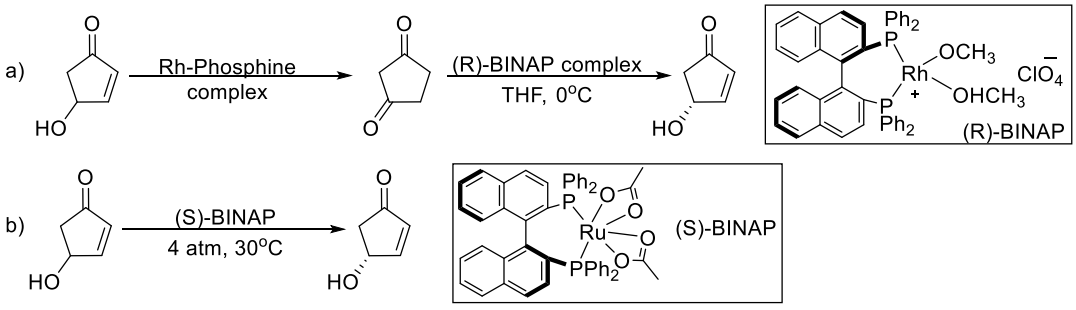
Scheme 25: Methods employed by Barry M. Trost and co-workers [102].

At last, B. S. Morgan *et al.* [103] successfully converted (R)-4-TBDMS-CP to (R)-4HCP using AcOH in THF in a yield of 75% (**Scheme 26a**). Later, T. Kumaraguru and co-workers [104] successfully converted (R)-4HCP analogue with a phenylacetate protecting group to the 4HCP in 95% yield with immobilized lipase B from CAL-B (**Scheme 26b**). They also describe the deprotection of TBDMS from the (S)-4HCP has successfully performed with TBAF (**Scheme 26c**).



Scheme 26: Methods described by B. S. Morgan *et al.* [103] and T. Kumaraguru and co-workers [104].

Kitamura and co-workers [105] (**Scheme 27a**) described, in 1987, a way to resolve 4HCP using *(R)*-BINAP giving the *(R)*-enantiomer in 91% ee and 72% conversion. One year later, Kitamura [106] (**Scheme 27b**) used *(S)*-BINAP to obtain the same enantiomer in 68% conversion and 98% ee.

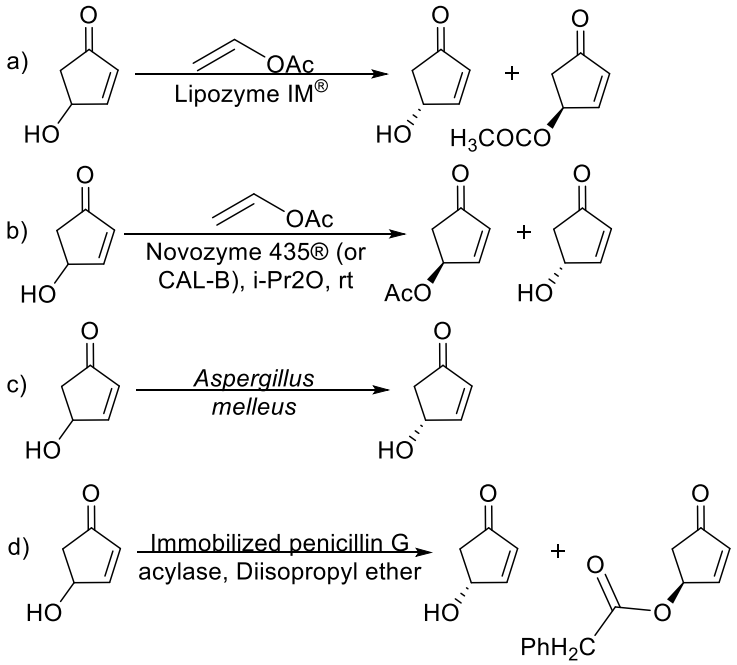


Scheme 27: Synthesis by Kitamura and co-workers [105, 106].

In 1999, S. R. Ghorpade *et al.* [107] endeavoured a transesterification reaction using vinyl acetate as acyl donor and Lipozyme IM® as bio catalyst in dry diisopropyl ether (DIPE) to resolve a racemic mixture of 4HCP (**Scheme 28a)**). As the highest values obtained for this method were only 28% conversion and 30.8% ee, this resolution pathway was abandoned. In 2016, Daniele Mantione and co-workers [95], also used Lipozyme IM® to enantiomerically enriched 4-Ac-CP, obtaining 70% yield and an ee of 55% (**Scheme 28a)**).

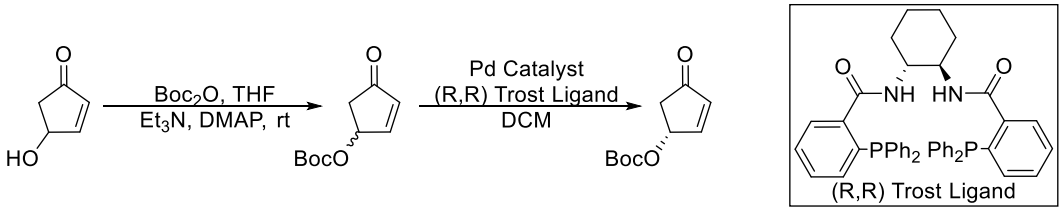
O'Byrne *et al.* [99] proceeded through a EKR with Novozym 435 (or CAL-B) facilitated *(S)*-derivatisation reaction which gave *(R)*- and *(S)*-4HCP with an ee of 77% and 84%, respectively (**Scheme 28b)**). According to B. S. Morgan *et al.* [103] racemic 4HCP can also be resolved with *Aspergillus melleus* lipase-catalysed esterification reaction, obtaining the *(R)*-4HCP in only 12% ee with 47% conversion (**Scheme 28c)**).

T. Kumaraguru *et al.* [108], in 2012, attempted to hydrolyze the O-phenylacetyl derivative with immobilized penicillin G acylase in a phosphate buffer (50 mM, pH 7.5) containing 20% (v/v) acetonitrile which gave the unstable ester in 91% ee. So, another attempt was made, this time in diisopropyl ether. The 4HCP was not isolated, but treated with TBDMSCl giving the corresponding (S)-TBDMS-protected alcohol with a 90–92% theoretical yield and ee >99% (**Scheme 28d**). One year later, T. Kumaraguru *et al.* [104] resolved the 4-phenylacetyl-CP (4HCP analogue with the phenylacetyl side chain) with immobilized penicillin G acylase in DIPE and obtained a mixture of (S)-4HCP and (R)- 4-TBDMS-CP with >99% ee. This mixture was separated by conversion of the (S)-4HCP to its TBDMS derivative followed by column chromatography, giving a yield of 45−46% (**Scheme 28d**).



Scheme 28: Enzymatic-catalysed methods employed by a) S. R. Ghorpade et al. [107] and Daniele Mantione and co-workers [95]; b) B. S. Morgan et al. [103]; c) O'Byrne et al. [99]; d) T. Kumaraguru et al. [104, 108].

Finally, Kathrin Ulbrich and co-workers [109] also applied palladium-catalyzed allylic substitutions with *(R,R)*-Trost ligand to several nucleophiles, in order to resolve the racemic mixture of 4-Boc-CP (4HCP analogue with the Boc side chain) giving an ee of 25-99% and 23-50% yield of its *(R)*_ enantiomer. Nanaji Arisetti *et al.* [110] resolved, as well, a racemic mixture of 4HCP using Boc_2O to obtain, another racemic mixture, of 4-Boc-CP 87% yield, making it to react with 4-methoxyphenol to give the *(R)*- 4-Boc-CP, in 42% yield and > 99% ee, and *(S)*-4-PMP-CP (4HCP analogue with the PMP side chain), in 48% yield and > 92% ee (**Scheme 29**).

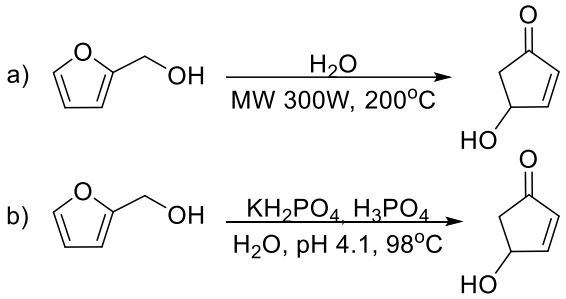


Scheme 29: Pd-catalyzed method for the resolution of 4HCP.

Construction of the 4-hydroxy-2-cyclopentenone building block

There are multiple methods to reach each enantiomer of 4HCP. In **Scheme 43** is provided the general reported pathways and bellow is described in detail those transformations.

The most common route to racemic 4HCP is the preparation from furfuryl alcohol. There are multiple descriptions [97, 99-101, 103, 104, 109-111] in literature, all in yields between 30 and 81%. The best results obtained are using the microwave reactor in water, firstly described by Kathrin Ulbrich and co-workers [111] in 2010 (**Scheme 30a)**), with the best yield of 87%. Before that, the most efficient procedure was the one described by Nanni *et al.* [97, 100] using a phosphate buffer at pH = 4.1(**Scheme 30b)**), but with much lower yields.

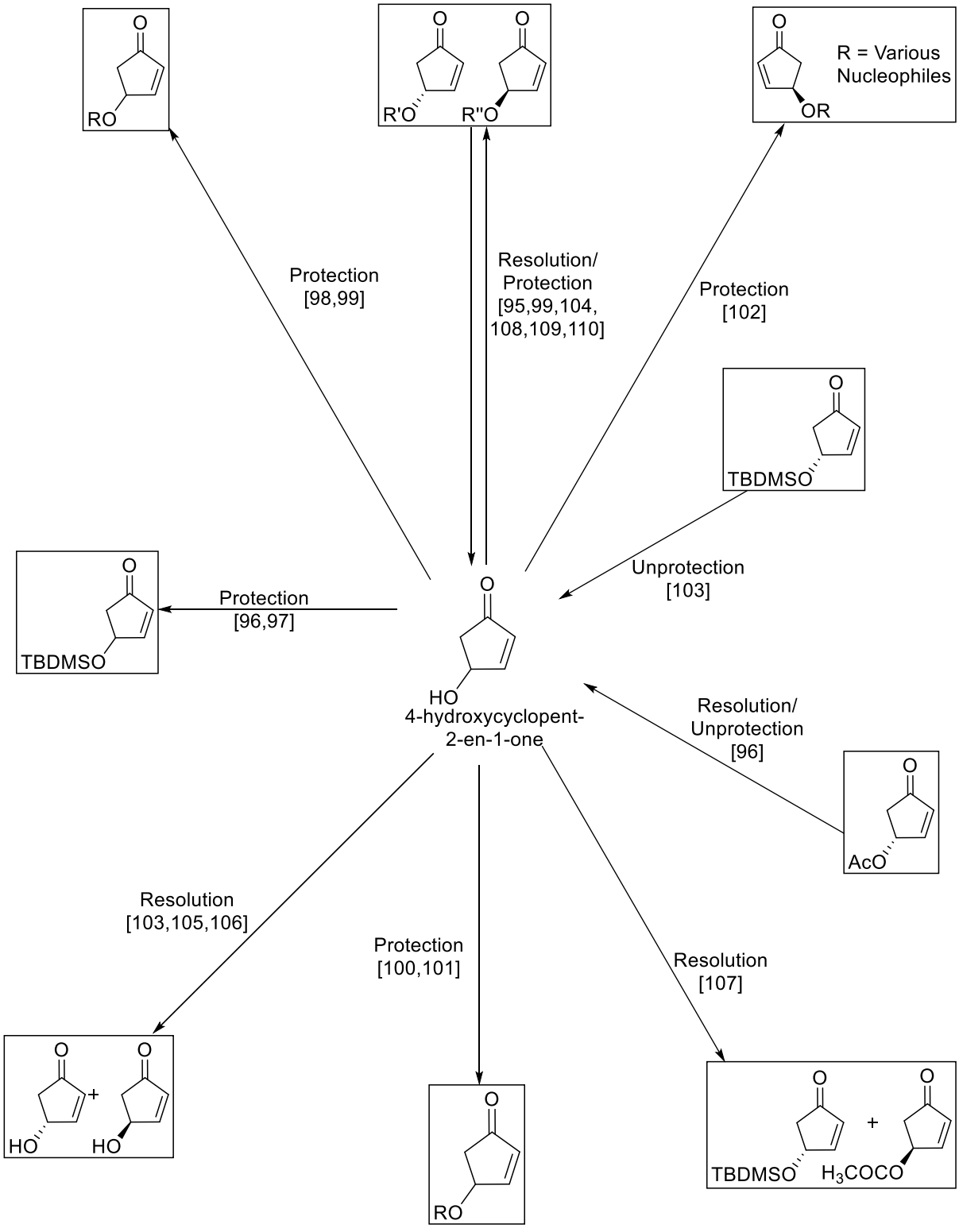


Scheme 30: Most common pathways to the synthesis of 4HCP [97, 99-101, 103, 104, 109-111].

M. Suzuki and co-workers described not only one, but two different pathways. The first one (**Scheme 32a)**) in 1979 [112], in which an epoxide suffers a palladium (0) catalysed reaction resulting in a 4HCP in 66% yield. The second (**Scheme 32b)**), in 1981 [113], in which an epiperoxide suffers the same type of reaction, giving the same 4HCP, but in a lower yield, 54%. Masaaki Suzuki and co-workers [114] obtained a 4HCP as a side product in 5% yield (**Scheme 32c)**), while performing a ruthenium(II)-catalyzed reaction in a similar starting material as M. Suzuki in 1981.

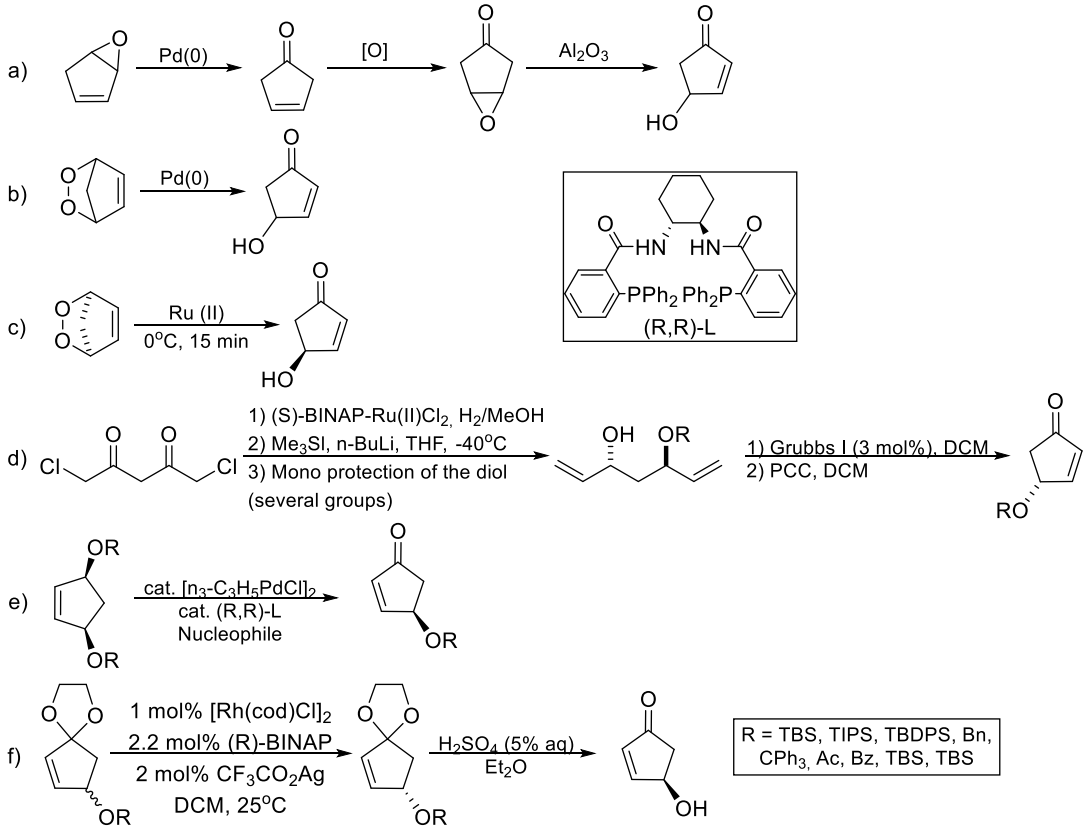
Gurpreet Singh [114] created a route that allows access to the *(R)*- and *(S)*- enantiomers through asymmetric conversion of the diketone 1,5-dichloro-2,4-pentanedione, followed by ring-closing metathesis, obtaining yields of 20,3%-31,2%, for the *(R)*- enantiomer, and 29,7% for the *(S)*-enantiomer, with an enantiomeric ratio of 93:3 to >99:1 and 99:1, respectively. The difference between the two methods are de catalyst used. In the synthesis of the *(R)*- enantiomer is used the *(S)*-BINAP-Ru(II)Cl_2 (**Scheme 32d**), and in the synthesis of the (S) enantiomer is used the (R)-BINAP-Ru(II)Cl_2.

Barry M. Trost and co-workers [102] also used a palladium-catalyzed reaction, an allylic alkylation reaction (**Scheme 32e)**), to oxidise allylic esters. In their work, *(1R,3S)*-cyclopent-4-ene-1,3-diyl dibenzoate gives *(R)*-4HCP analogue with a Bz side chain, in the presence of a (R,R) chiral ligand (named (R,R)-L in **Scheme 32**), with 78% conversion and 99% ee. Previously, Barry M. Trost *et al.* [115] had proceed to synthetize (S)-4-Bz-CP with the same Palladium-catalysed asymmetric oxidation (**Scheme 32e)**). This final product was obtained with 61% yield an 99% ee. Using a similar starting material as the reaction elucidated before, Kai Ren [116] describes a ways to obtain the *(R)*-4HCP



Scheme 31: Pathways known to Protect/Unprotect or Resolve 4HCP and its analogues.

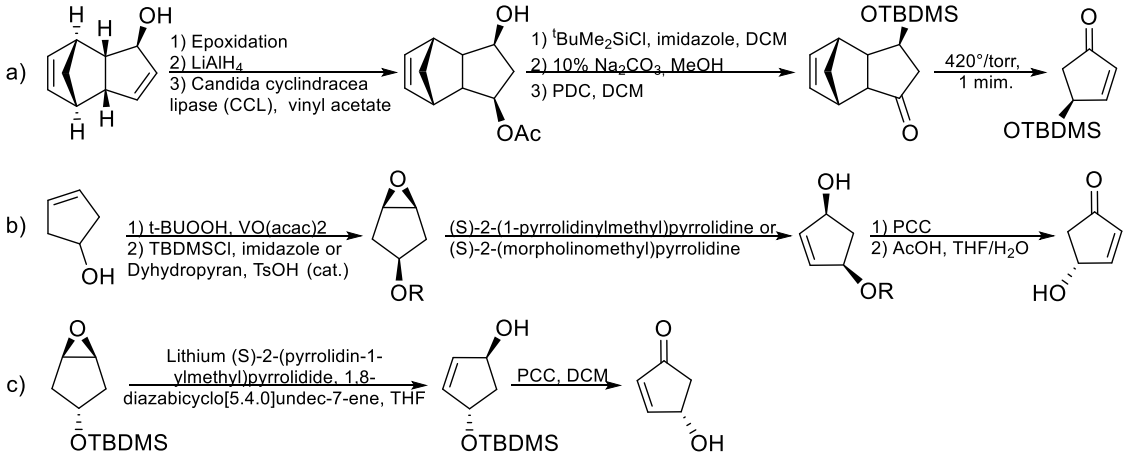
enantiomer, through the kinetic resolution of 1,4-dioxaspiro[4.4]non-8-en-7-ol with 1 mol% of $[Rh(cod)Cl]_2$ as the catalyst, in 86.8% ee and an overall yield of 50% (**Scheme 32f)**).



Scheme 32: Catalytic pathways described by several research groups [102, 112-114, 116].

According to Z.-Y. Liu *et al.* [117], *(S)*-4-TBDMS-CP is obtained from (*1S,3aR,4S,7R,7aS*)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-ol, in >98%ee and an overall yield of 51% (**Scheme 33a)**).

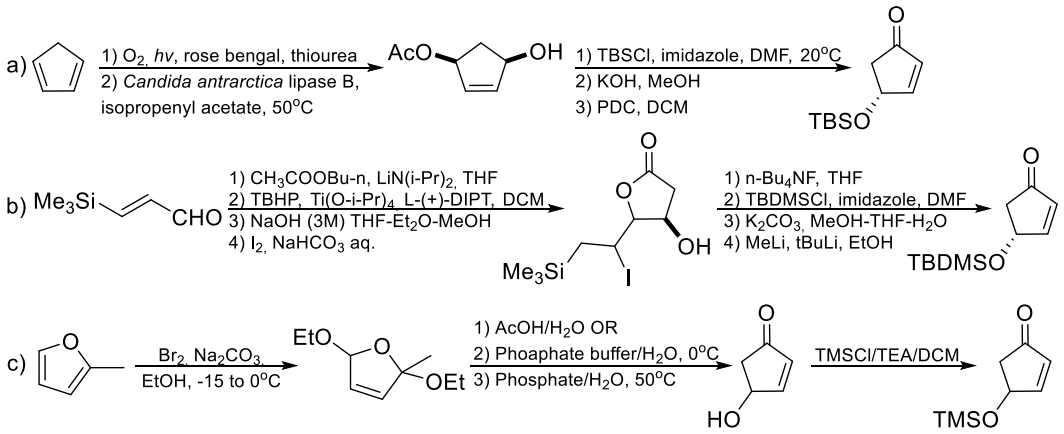
Masatoshi Asami [118] was able to obtain both *(R)* and *(S)* enantiomers through two different pathways in 5 and 7 steps, respectively, from cyclopent-3-en-1-ol, in ee of 94% and 86%, and yields of 43% and 34% (**Scheme 33b)**). Five years later, Masatoshi Asami and his team [119], used the (S)-4-TBDMS-CP to confirm the ee obtained of *trans*-4-t-butyldiiethylsiloxy-l,2-epoxycyclopentane (**Scheme 33c)**).



Scheme 33: Synthetic pathway described by Z.-Y. Liu *et al.* [117] and Masatoshi Asami [118, 119].

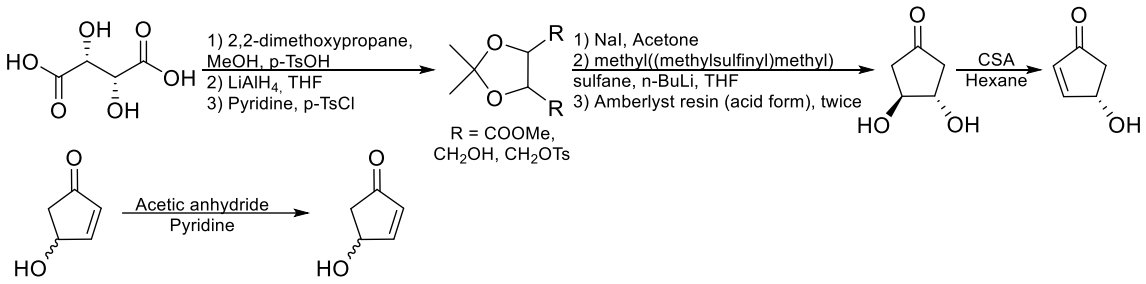
Carl R. Johnson *et al.* [120-122] reported an enzymatic asymmetrization of *meso* diol by the biocatalyst SP-435 (**Scheme 34a)**), giving the well-known *(R)*-4-TBS-CP in yields around 80%. In 1989,

two groups designed a synthetic pathway to the same analogue of the 4HCP. One, Yasunori Kitano [123], achieved the (R)-4-TBS-CP from (E)-3-trimethyl-silyl-2-propenal (**Scheme 34b)**) in seven steps with 15% overall yield. The other was Philip R. Hamann and co-workers [124] that designed a synthesis from 2-methylfuran in 4 steps in an overall yield between 49% and 65% (**Scheme 34c)**).



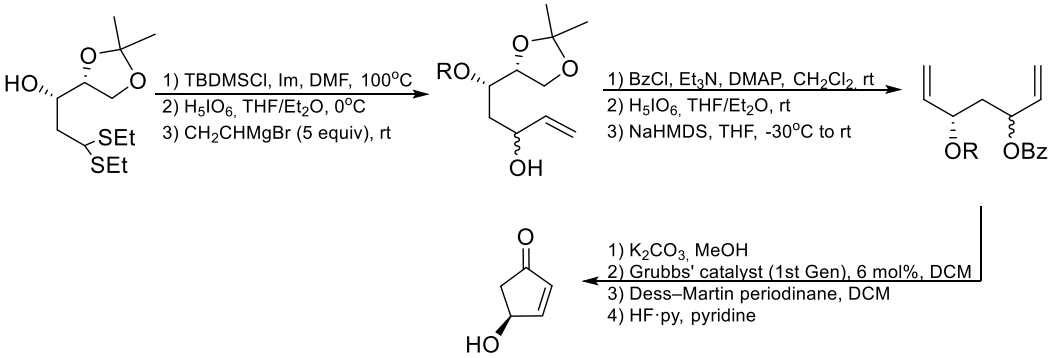
Scheme 34: Reports of Carl R. Johnson *et al.* [120-122], Yasunori Kitano [123] and Philip R. Hamann and co-workers [124].

In 1995, Subhash P. Khanapure *et al.* [121] used a synthetic method with the *L*-tartaric acid as chiral source (**Scheme 35a)**). This synthetic pathway was first mentioned by Hiroaki Miyaoka and co-workers [125], in 1989.This method is a bit time consuming and divided into 6 steps, afforing the (S)-4HCP in an overall yield of 26,5% and an ee of 88%. The same group [98] also described the synthesis of the racemic mixture of 4HCP (**Scheme 35b)**), in a yield of 40%, from the reaction of 4-cyclopentene-1,3-dione with $CeCl_3$.



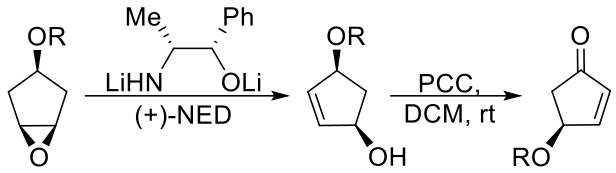
Scheme 35: Methods elucidated by Subhash P. Khanapure *et al.* [98].

A new synthetic pathway was develop by C.-T. Chang *et al.* [126], in which (S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-bis(ethylthio)propan-1-ol is transformed into (S)-4HCP in >96% ee and 43% yield over a 9 step reaction (**Scheme 36**).



Scheme 36: Synthesis of C.-T. Chang et al. [126].

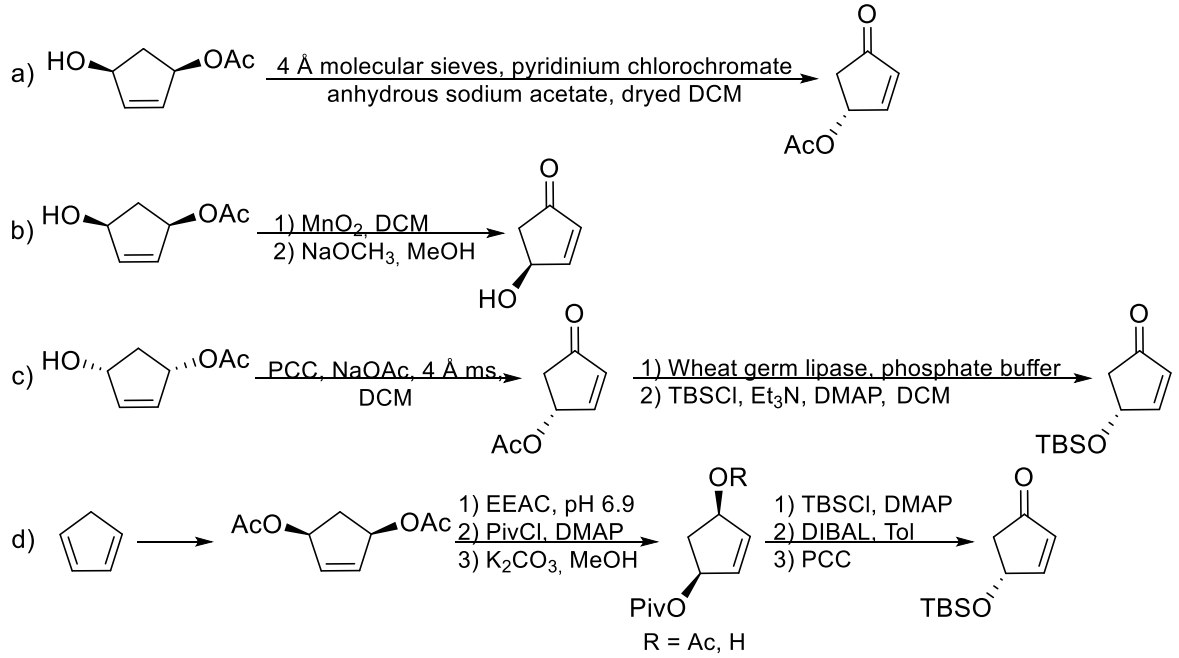
P. C. Brookes *et al.* [127] rearranged the *cis*-epoxide using dilithiated (1S,2R)-norephedrine, giving the respective alcohols (**Scheme 37**), that was then reacted with pyridinium chlorochromate generating 4-Bz-CP and 4-TBDMS-CP with 71% and 55% yield, respectively.



Scheme 37: Rearrangement described by P. C. Brookes *et al.* [127].

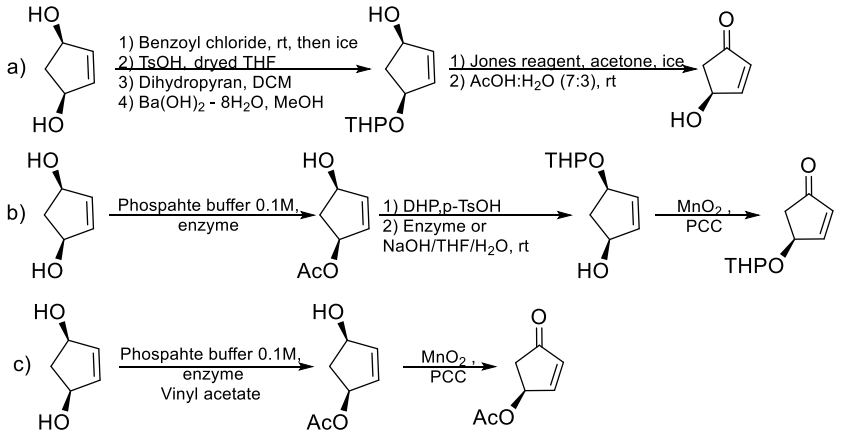
One of the pathways found by Leo A. Paquette and co-workers [96] was to convert *(1R,4S)*-(+)-4-hydroxy-2-cyclopentenyl acetate into *(R)*-4-Ac-CP with pyridinium chlorochromate (**Scheme 38a)**), in a yield of 83%.

The other pathway found by Leo A. Paquette *et al.* [128] was to obtain *(S)*-4-TBDMS-CP, in 87–90% yield, from the reaction of *(1R,4S)*-4-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl acetate with manganese dioxide (**Scheme 38b)**). A similar method was followed by Andrew G. Myers and co-workers [129] to prepare *(R)*-TBS-CP, in >99% ee and an overall yield of 68%, with only 2 more steps, but faster preparation (**Scheme 38c)**). This method was also followed by Michael E. Jung [130], in which *(R)*-4TBDMS-CP was prepared from *(1R,3S)*-cyclopent-4-ene-1,3-diyl diacetate with an overall yield around 50% (**Scheme 38d)**).



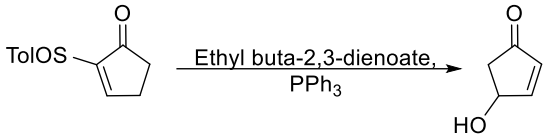
Scheme 38: Synthetic pathways exposed by Leo A. Paquette and co-workers [96, 128], Andrew G. Myers and co-workers [129] and Michael E. Jung [130].

In 1980, M. Nara [131] reported a synthesis from *(1R,3S)*-cyclopent-4-ene-1,3-diol to obtain 4HCP with an overall yield of around 30% (**Scheme 39a)**). A few years later, a similar starting material (*(1S,4R)*-4-hydroxycyclopent-2-en-1-yl acetate) was used by Kurt Laumen and co-workers [132] to synthetize the *(S)*-4-THP-CP (**Scheme 39b)**) and in an oxidation technique with MnO_2 and PCC to convert it into *(S)*-4-Ac-CP (**Scheme 39c)**). This method was used throughout the years [133-136] to synthetize the *(R)*- and *(S)*-4HCP (and hydroxy side chain derivatives), with the same or similar starting materials, obtaining yields between 90 – 94,5% and 79 – 96%, to the *(R)* and *(S)* enantiomers, respectively.



Scheme 39: Reports with similar starting materials of M. Nara [131], Kurt Laumen and co-workers [132] and others [133-136].

At last, in 2013 a completely new method is presented by J.L. García Ruano *et al.* [137] (**Scheme 40**). In this method sulfinylcyclopentenone reacts with ethyl 2,3-butadienoate in the presence of PPh_3 to afford 4HCP with 40% yield.



Scheme 40: New synthetic method elucidated by J.L. García Ruano *et al.* [137].

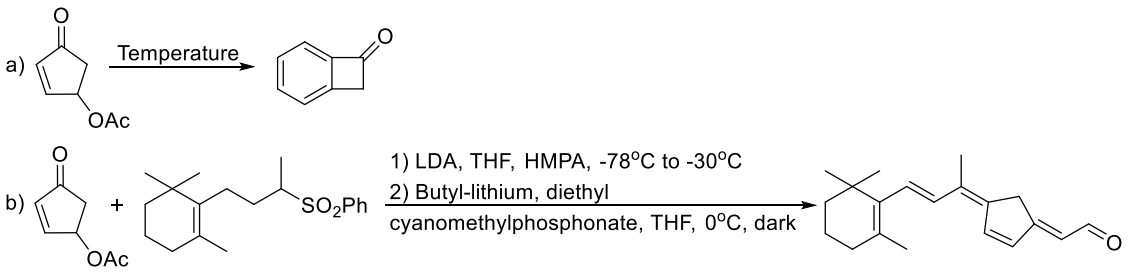
In **Scheme 43** is provided an overview of the reported methods for the synthesis of 4-hydroxy-2-cyclopentenones (4HCP).

4-hydroxy-2-cyclopentenones as starting material

4-hydroxy-2-cyclopentenones have also proven to be very useful in many synthetic pathways, to different compounds, as showed in Scheme 3, and this synthetic pathways will be briefly explained above.

In 1964, C. H. DePuy and co-workers [138] studied cyclopentadienones and observed its dimerization upon synthesis (**Scheme 41a)**). In their studies they concluded that 4-Ac-CP can be heated under reflux without decomposition, but when heated to 450°C and dropped in a vertically mounted pyrolysis tube, acetic acid and indanone are produced and the dimer is formed very quickly.

Masayoshi Ito *et at.* [139, 140] design a series of 11 -cis-locked-cyclopentatrienylideneretinals from the reaction of β-ionyl sulphone with the same analogue (**Scheme 41b)**). The synthesis is first mentioned in 1982, where only the synthesis of this compounds is mentioned, and then again in 1986, where not only the synthesis is described, but also the properties were studied.



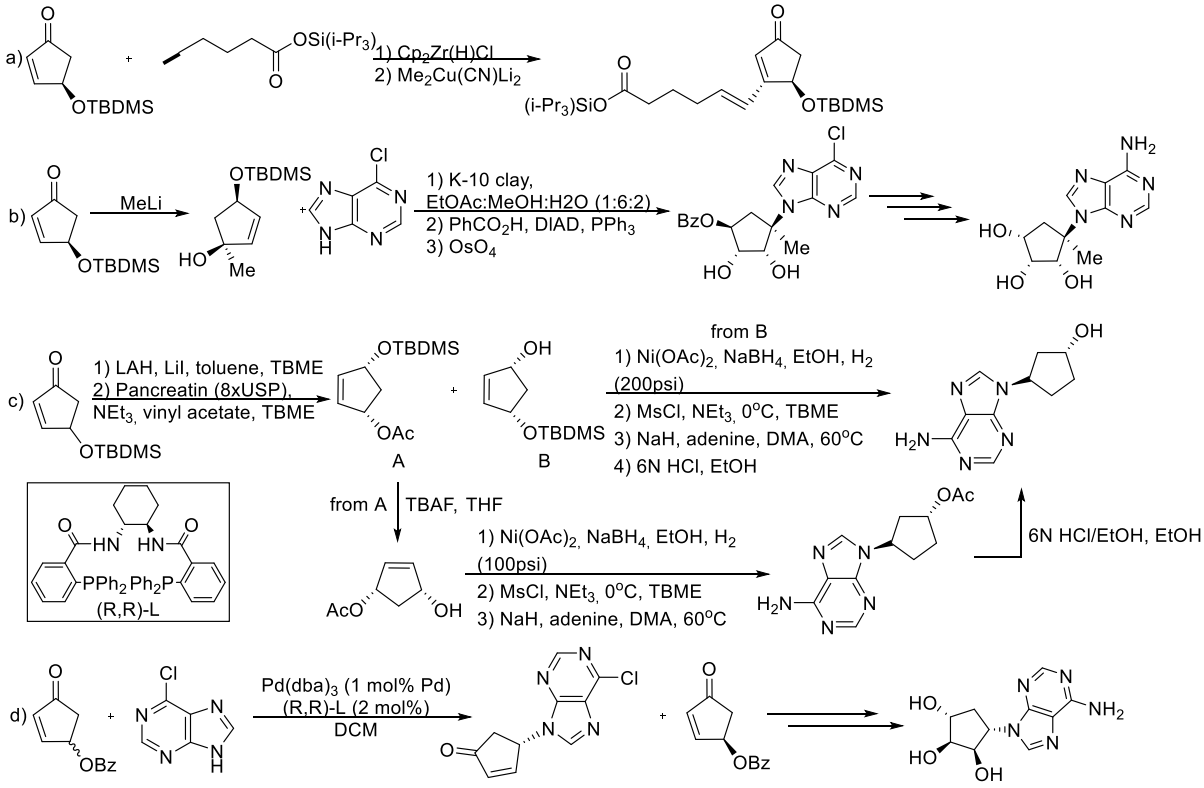
Scheme 41: Methods developed by . H. DePuy and co-workers [138] and Masayoshi Ito *et at.* [139, 140].

Bruce H. Lipshutz and Robert Keil [141] tested the reaction of several α,β-ketones with newly generated vinylic lithiocuprates (**Scheme 42a)**). This reaction was tested in (R)-TBDMS-CP, giving the expected 1,4-adduct in 76% yield (**Scheme 42a)**).

4'- and 1'-methyl-substituted 5'-norcarbanucleosides (**Scheme 42b)**) have been prepared by Atanu Roy and Stewart W. Schneller [136] from the same enantiomer with 6-chloropurine, through a series of known reactions such as Mitsunobu reactions and dihydroxylation followed by ammonolysis, to obtain the 1'-methyl-substituted 5'-norcarbanucleoside. The 4'-methyl-substituted 5'-norcarbanucleoside was obtained with isopropylidenation, a Mitsunobu reaction followed by ammonolysis. Both products were obtained with a very low overall yield.

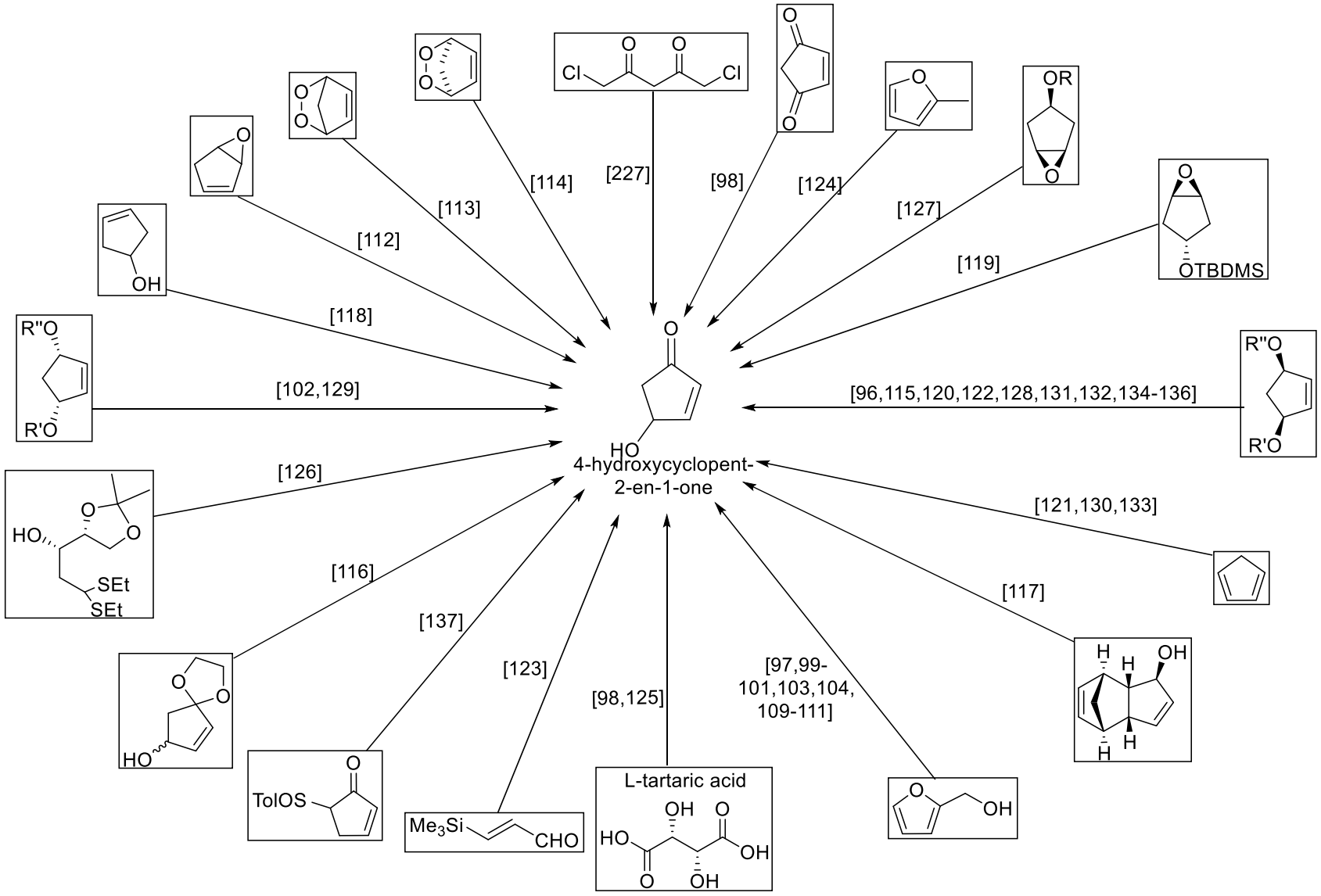
In 1998, Timothy J. N. Watson and co-workers [97] developed two routes to MDL 201449A from 4HCP (**Scheme 42c)**). In both routes, the product is obtained with high level of purity, >98%, and ee's over 99%. The main difference between them is that in route 1 it is used a salt purification of the penultimate intermediate, whilst route 2 employed the crystalline properties of acetyl-protected diol.

Kathrin Ulbrich and co-workers [109] describe the synthesis of the antiviral and antitumor drug, ent-Noraristeromycin (**Scheme 42d)**). The synthetic pathway starts with 4-Boc-CP via via Pd-catalyzed asymmetric allylic substitution with 6-chloropurine, giving the desired product in 46% yield and 94% ee, which can be raised to 98% ee (39% yield) by a single recrystallization.

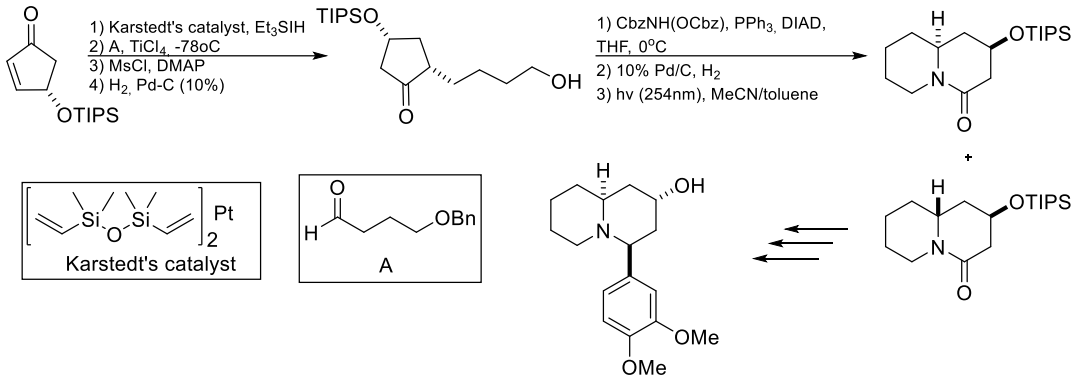


Scheme 42: Pathways chosen by a) Bruce H. Lipshutz and Robert Keil [141], b) Atanu Roy and Stewart W. Schneller [136], c) Timothy J. N. Watson and co-workers [97] and d) Kathrin Ulbrich and co-workers [109].

In the synthesis of quinolizidine alkaloids, Vijaya Gracias *et al.* [142] ascertains a protected analogue, the 4-TIPS-CP as a practicable precursor to the synthesis of (-)-2-*epi* lasubine II (**Scheme 44**). This method comprises a conjugate reduction/alkylation sequence, a nitrogen ring expansion and the addition of an arylmetallic species, obtaining the desired final product in 19% overall yield with a total of 11 steps.



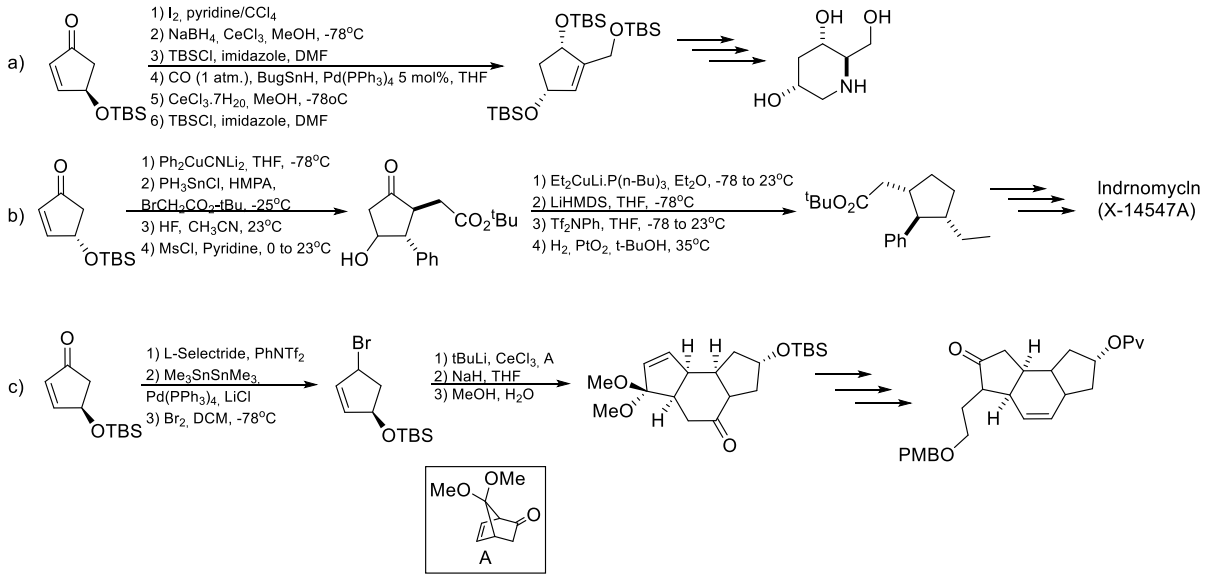
Scheme 43: Pathways known to prepare 4HCP and its analogues



Scheme 44: Methodology chosen by Vijaya Gracias *et al.* [142].

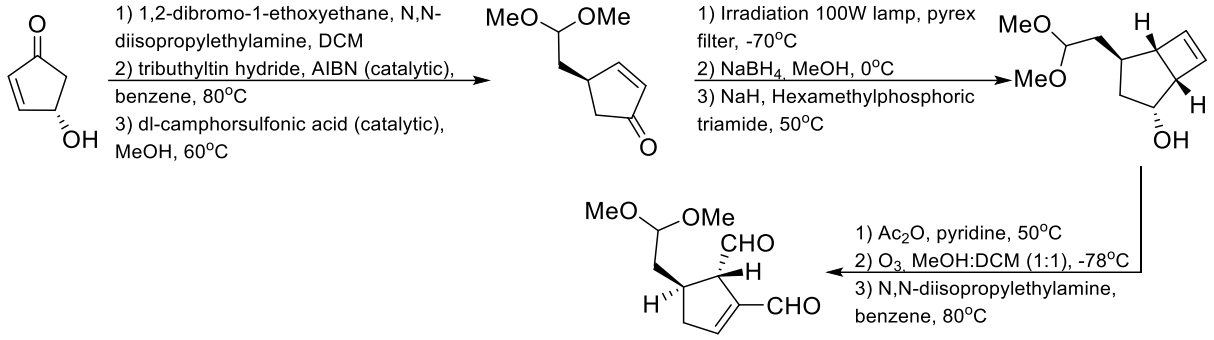
In 1994, Carl R. Johnson and co-workers [121] synthetize 1,3-dideoxynojirimycin from (R)-TBDMS-CP (**Scheme 45a)**) through a series of known reactions, such as Luche reduction, Pd(O)-mediated carbon monoxide coupling, ozonolysis and reductive amination, in 31% yield over 8 steps. In the same year Burke *et al.* [143] successfully used (S)-TBDMS-CP in the synthesis of the right wing of Indanomycin (X-14547A) (**Scheme 45b)**). The first step of this synthesis is the three-component coupling of the (S)-TBDMS-CP, to create a PG-like compound, followed by a reductive removal of the ketone carbonyl via the intermediary of the enol triflate, then an oxidative degradation of the phenyl substituent with RuO_4. This intermediary was achieved in 45% yield from the (S)-TBDMS-CP, over seven steps.

The same starting material as the first example was used by Leo A. Paquette and co-workers [144] in the attempt to the total synthesis of spinosyn A (**Scheme 45c)**). They stopped their synthetic pathway at a possible intermediary, confirm by degradation of the spinosyn A molecule. The synthesis reported is 24 steps long, starting from (R)-TBDMS-CP, with a unified, highly convergent synthesis.



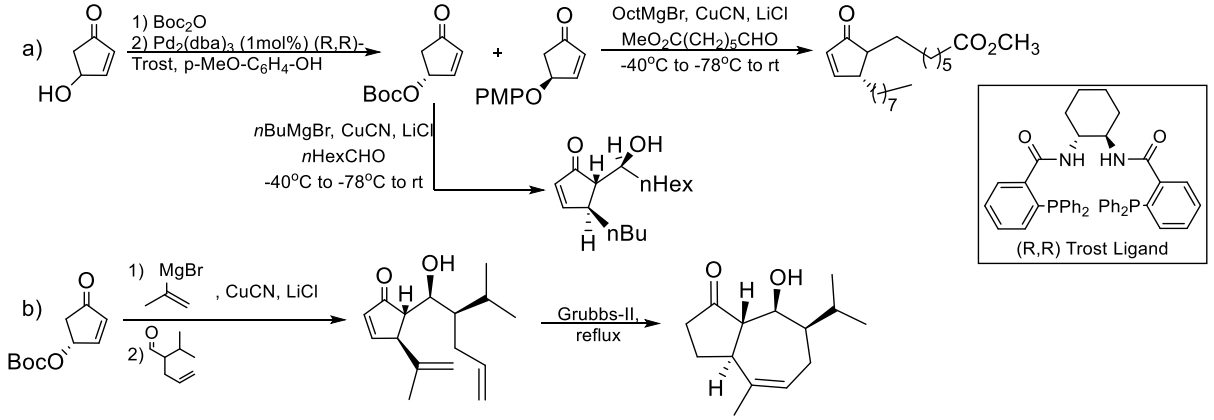
Scheme 45: Synthesis of a) Carl R. Johnson and co-workers [121], b) Burke *et al.* [143] and c) Leo A. Paquette and co-workers [144].

In the discovery for the synthesis of halimedatrial, Hiroaki Miyaoka *et al.* [125] claimed that the first step was to synthetize the diformylcyclopentenone moiety of halimedatrial from (S)-4HCP (**Scheme 46**). The synthesis of the intermediary compound is achieved with six steps and an overall yield of 30%.



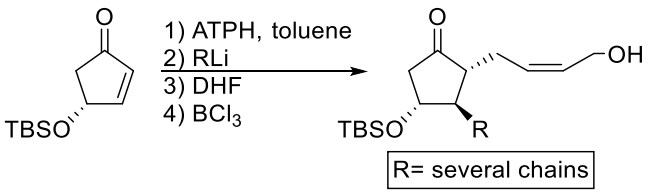
Scheme 46: Synthesis of the moiety of halimedatrial by Hiroaki Miyaoka *et al.* [125].

Through copper(I)-catalysed Grignard additions, Nanaji Arisetti *et al.* [110], synthetize a series of compounds, such as chiral 4-alkyl-5-(1-hydroxyalkyl) substituted-2-cyclopentenones, two anticancer drugs, (3aS,4S,4aS,7aS)-4-hydroxy-8-methyl-3,3a,4,4a,6,7,7a,9a-octahydroazuleno [6,5-b]furan-2,5--dione and (-)-Teuclatriol. All the reactions had the same conditions, CuCN·2LiCl in THF and the respective Grignard reagent (**Scheme 47**). The reactions yields and ee depended on the Grignard reagent applied, which were 30-78% and 95-99% for the 4-alkyl-5-(1-hydroxyalkyl) substituted-2-cyclopentenones, 38-48% and 98-99% for the anticancer drugs, 53% and 98% for the (3aS,4S,4aS,7aS)-4-hydroxy-8-methyl-3,3a,4,4a,6,7,7a,9a-octahydroazuleno[6,5-b]furan-2,5-dione and finally for the (-)-Teuclatriol was obtained 18% yield over 8 steps from (R)-Boc-CP.



Scheme 47: Copper(I)-catalysed Grignard additions by Nanaji Arisetti *et al.* [110].

Susumu Saito *et al*. [145] develop a method to synthetize jasmonates with one-pot three-component coupling reactions in which was used an organolithium reagent, aluminum tris(2,6-diphenylphenoxide) and cyclopentenones (**Scheme 48**). In the screening for the cyclopentenones was used (R)-TBS-CP to synthetize di-substituted cyclopentanones, although in relatively good yields, proved useless in the synthesis of the desired jasmonates.

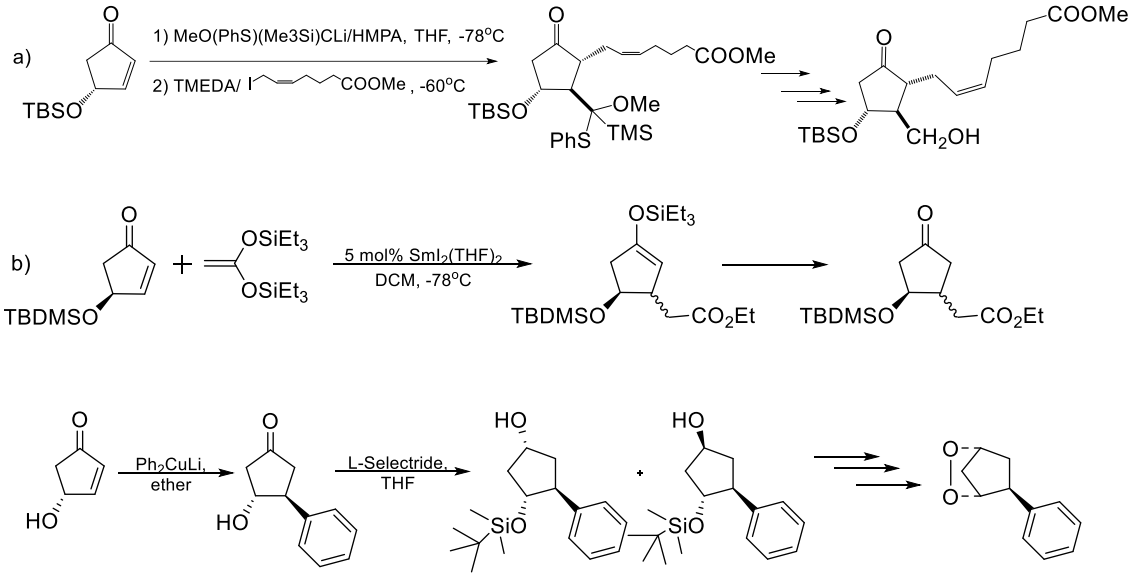


Scheme 48: Method developed by Susumu Saito *et al*. [145].

There are several known methods to synthetize PG as the conjugate addition of α-Lithio-γ-methoxyallyl phenyl sulfide, developed by Tsuneo Sato and co-workers [146]. This method (**Scheme 49a)**) differs from the three coupling method in the way that the ω-side chain cannot be incorporated directly but also there is no need for alkenyl organometallics.

Junzo Otera and co-workers [147] also attempt to make a viable synthesis to prostaglandins by dialkylation of 4HCP using an organolithium reagent (**Scheme 49b)**). Unfortunately, they stopped the synthetic pathway in the possible intermediate to the PG synthesis, methyl (Z)-7-((1R,2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-formyl-5-oxocyclopentyl)hept-5-enoate.

Nicolas Giuseppone and Jacqueline Collin [148] also developed a different method to prostaglandins (**Scheme 49c)**). They used (S)-TBDMS-CP in tandem Mukaiyama Michael-aldol reactions catalysed by samarium diiodide in 75% yield. While, Kimio Takahashi *et al.* [149] developed a PGH_2 model compound, 5-phenyl-2,3-dioxabicyclo[2.2.l]heptane from (R)-4HCP, but the synthesis cannot be seen as a valuable option to the synthesis of PG as it is a very long synthetic pathway and the desired product is not the major product obtained in the end.

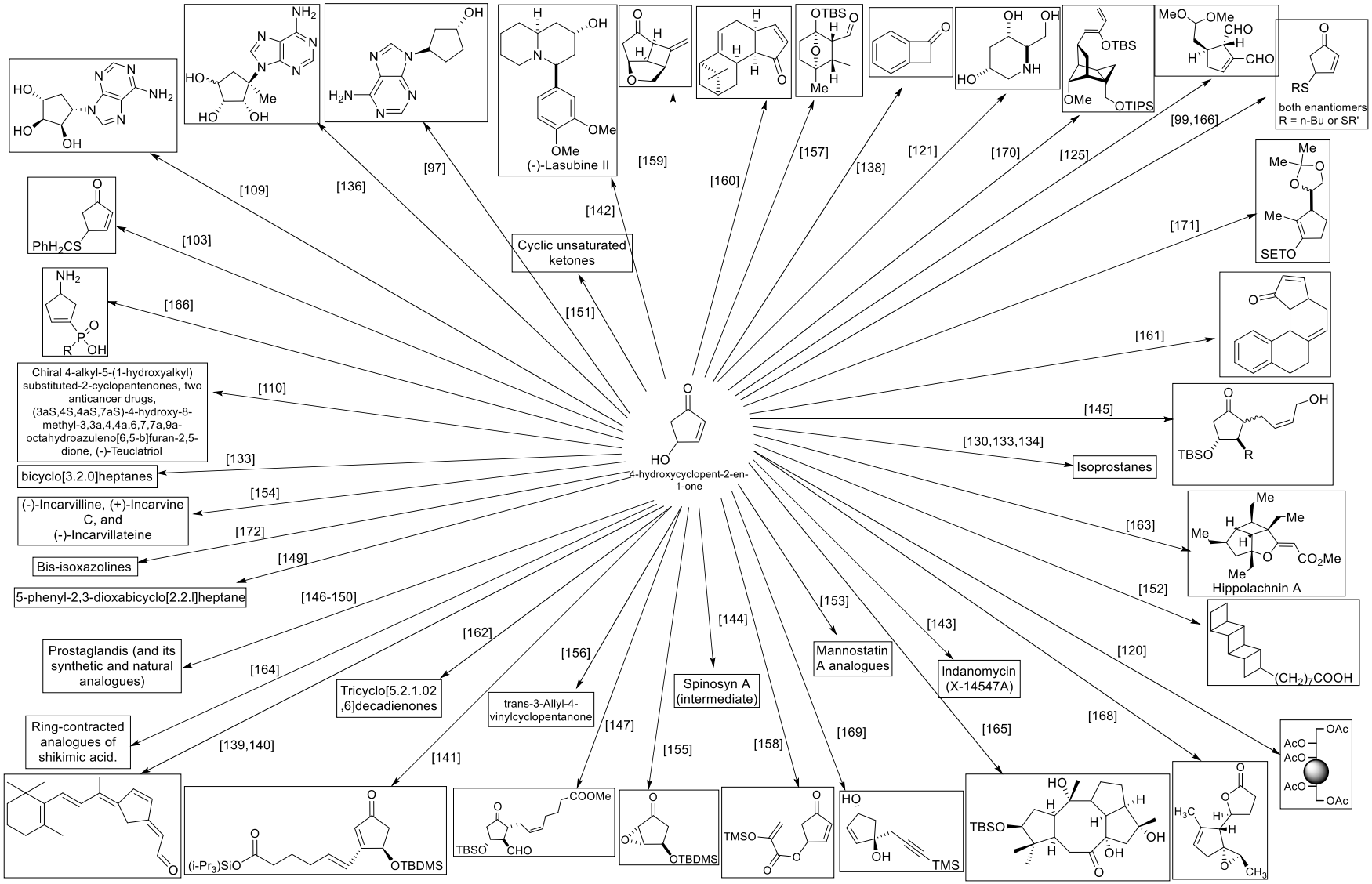


Scheme 49: Pathways chosen by a) Tsuneo Sato and co-workers [146], b) Junzo Otera and co-workers [147] and c) Nicolas Giuseppone and Jacqueline Collin [148].

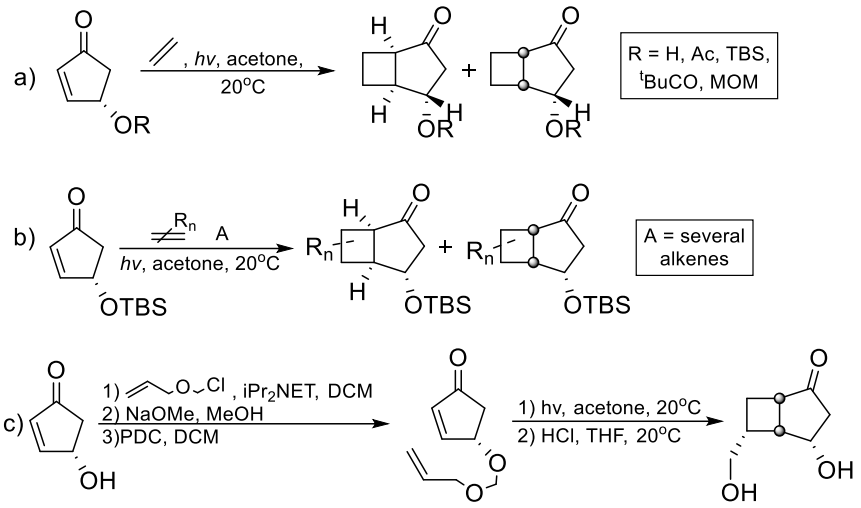
Isoprostanes are prostaglandin-like compounds of great importance as these metabolites aren't formed under enzymatic control, therefore efforts were made by Thomas O. Schrader and co-workers [150] to create a library of 15-F_2 isoprostanes (**Scheme 51a)**). Their strategy was to begin with the an 4HCP analogue, converting it into a functionalized bicyclo[3.2.0]heptenyl ring system with a [2+2] photocycloaddition reaction followed by ring-opening metathesis reactions, and, to finalize the synthesis, resolution of the enantiomers formed and removal of the protecting groups. Years later, M. Shizuka and co-workers [134] used the same technique to synthetize ent-15-epi-F2t-isoprostane.

Michael E. Jung *et al.* [130] also describe a method for the total synthesis of isoprostanes (**Scheme 51b)**), the epoxy isoprostane phospholipid, from the (R)-TBS-CP, in low yields, through a series of known reactions such as 1,4-addition of allylcopper, elimination of the silyloxy group and elimination of the hydroxy group. This synthetic pathway gave four analogues, all with possible biological activity.

Matthieu Le Liepvre *et al.* [133] also carried out [2+2] photocycloaddition reactions on several (S)-4HCP derivatives with different alkenes (**Scheme 51c)**), to establish a synthetic pathway to prepare a range of highly functionalized bicyclo[3.2.0]heptanes, in acceptable yields but the low selectivities.

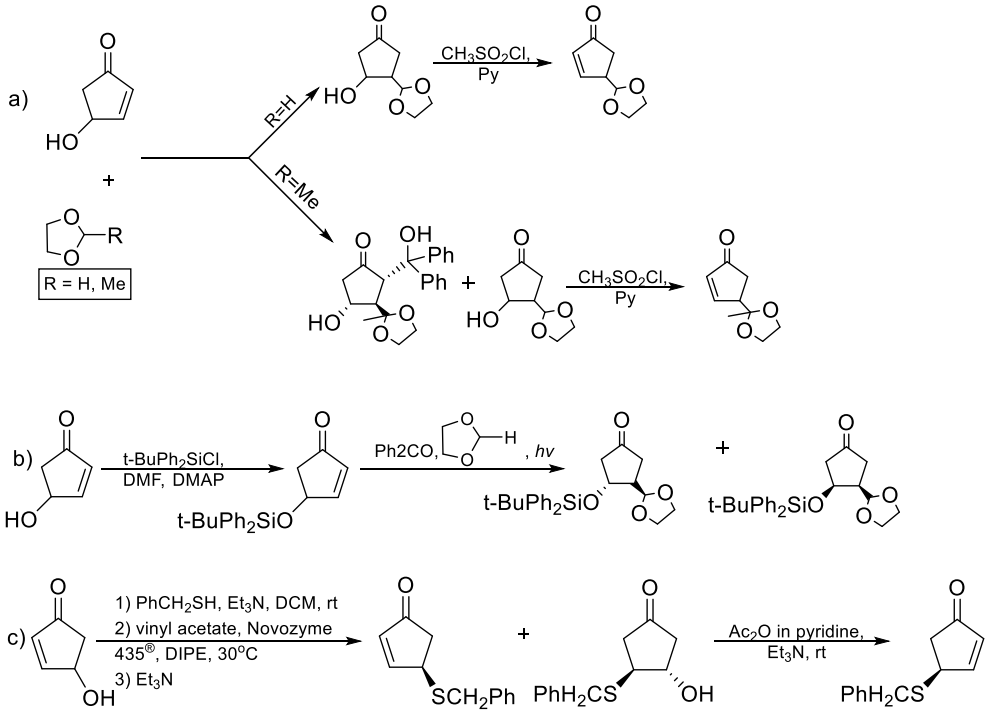


Scheme 50: 4HCP as starting material



Scheme 51: Methodology used by a) Thomas O. Schrader and co-workers [150], b) Michael E. Jung *et al.* [130] and c) Matthieu Le Liepvre *et al.* [133].

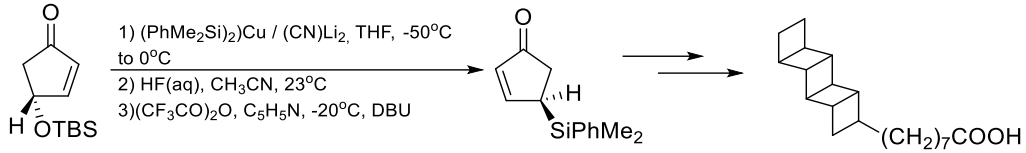
The photoinduced alkylation of the 4HCP was conducted by Mosca *et al.* [151] for possible application to PG synthesis, followed by an elimination reaction (**Scheme 52a) and b)**). The cyclic α,β-unsaturated ketones were obtained in good yields, 32-40%, over 2 steps in an one-pot synthesis method from 4HCP. B. S. Morgan *et al.* [103] design a synthetic pathway to optically active 4-thiacyclopent-2-enones (**Scheme 52c)**) through an enzymatic reaction with Novozyme 435®, giving the (R) and (S) enantiomers in 86% and 75% yield, in one and two steps respectively, from the previously mentioned starting material.



Scheme 52: Methods described by a) and b) Mosca *et al.* [151] and c) B. S. Morgan *et al.* [103].

Vincent Mascitti and E. J. Corey [152] synthetize 8-((1S,2S,3R,6S,7S,8R,9S,12R)-pentacyclo[6.4.0.0^{2,7}.0^{3,6}.0^{9,12}]dodecan-4-yl)octanoic acid (**Scheme 53**) through a series of ultraviolet irradiations, the most important one is the irradiation of the tricyclic olefin with (R)-4-

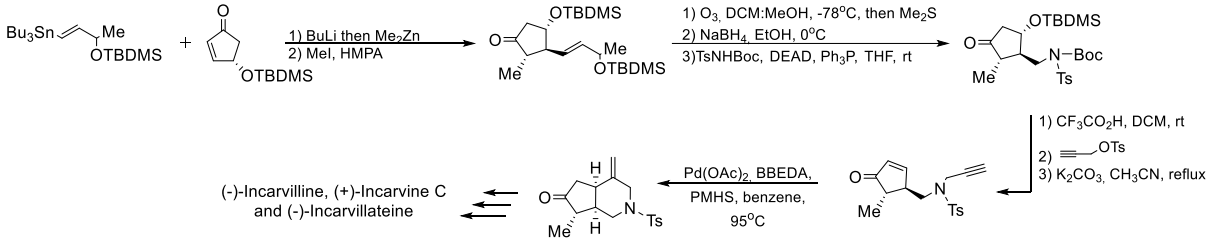
dimethylphenylsilyl-2-cyclopentenone, which solves the problem of creating an enantioselective version of [2+2]-photocycloaddition version. The overall synthetic pathway has 10 steps and a very low overall yield from the cyclopentenone.



Scheme 53: Synthesis of Vincent Mascitti and E. J. Corey [152].

In order to synthetize mannostatin A analogues, Nishimura *et al.* [153] recurred to the (S)-4-TBDMS-CP as a starting material. This new synthetize compounds can behave as carbohydrate mimics, possibly being potent glycosidase inhibitors.

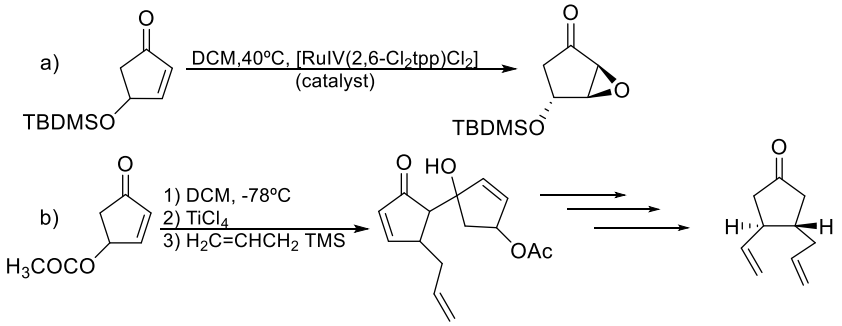
The same analogue used before, was described by Ichikawa *et al.* [154] in the first total synthesis of the monoterpene alkaloids (-)-Incarvilline, (+)-Incarvine C and (-)-Incarvillateine (**Scheme 54**), using (+)-6-*epi*-incarvilline as a common precursor. The synthetic pathway involves well-known reactions , such as stereoselective construction of an appropriately trisubstituted cyclopentanone via a three-component coupling reaction and ring closure to the *cis*-perhydro-2-pyrindine skeleton by means of a reductive Heck-type reaction.



Scheme 54: Synthesis of (-)-Incarvilline, (+)-Incarvine C and (-)-Incarvillateine by Ichikawa *et al.* [154].

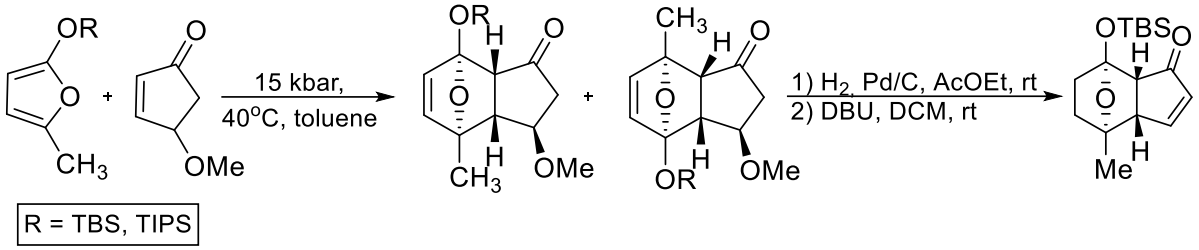
C.-M. Che *et al.* [155] studied epoxidation of conjugated enynes and electron-deficient alkenes (such as α,β-unsaturated ketones). In their studies (**Scheme 55a)**), they manage to synthetize (1S,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-6-oxabicyclo[3.1.0]hexan-2-one from 4-TBDMS-CP with $[Ru^{IV}(2,6\text{-}Cl_2tpp)Cl_2]$-catalysed 2,6- Cl_2pyNO in 99% yield and 95% conversion.

V. Helbling *et al.* [156] studied Sakurai reaction in 4-Ac-CP to obtain *trans*-3-allyl-4-vinylcyclopentanone (**Scheme 55b)**). The most important reactions mentioned in this method is the $TiCl_4$ induced reaction with allyl-trimethylsilane and the Cu(I) induced 1,4-addition of vinyl magnesiumbromide. The desired product was obtained with an overall yield of 28%.



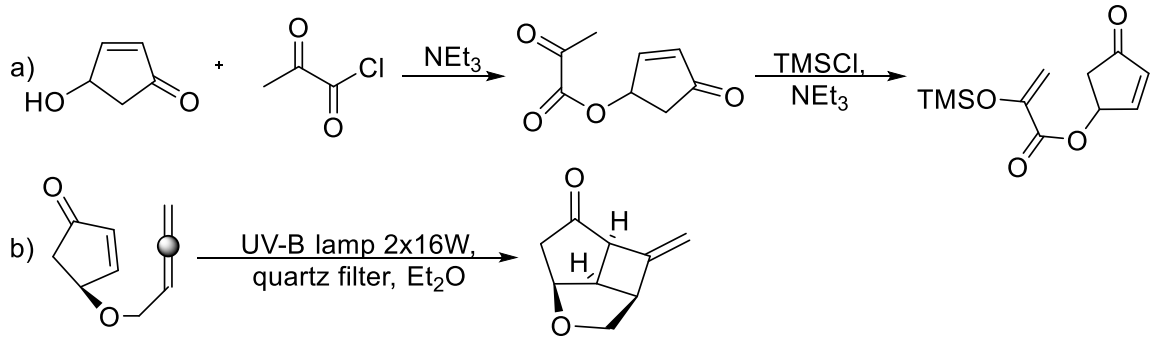
Scheme 55: Methods described by a) C.-M. Che et al. [155] and b) V. Helbling et al. [156].

Laurent Trembleau *et al.* [157] assembled an ottelione A precursor. The method design involves a Diels-Alder reaction of the cyclopentenone with an appropriately substituted furan to create the cis-hydrindenone system required for the percursor. It can be obtained with a good overall yield and in an enantiomerically pure form. The regioselectivity of the reaction can be controlled by the reaction conditions and the substituents of the furan ring.



Scheme 56: Synthesis of an ottelione A precursor [157].

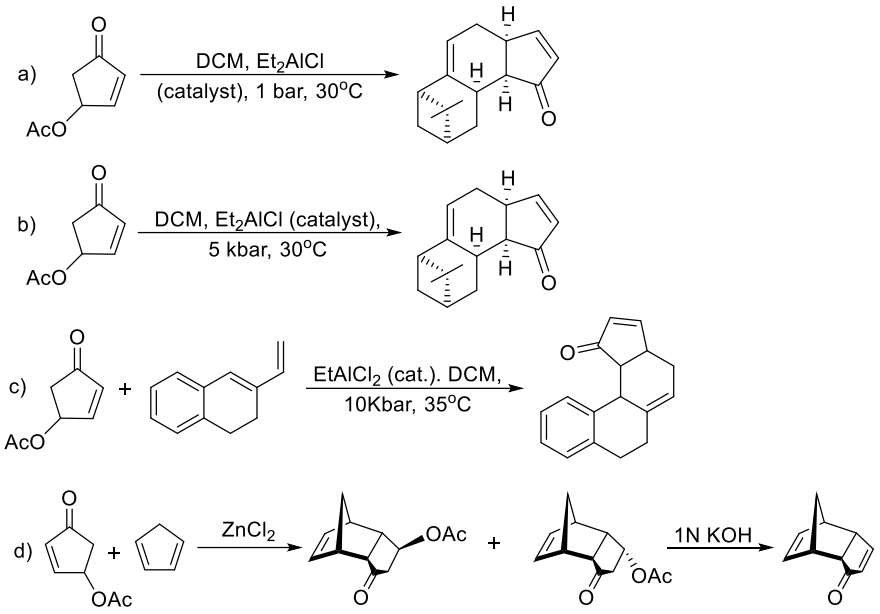
Ping Lu and co-workers [158] attempt to construct the (+)-lactiflorin skeleton starting with 4HCP. In this attempt, the 4-oxocyclopent-2-en-1-yl 2-((trimethylsilyl)oxy)acrylate compound was synthetize in 63% yield, but further synthesis was not possible due to degradation from the intramolecular [2+2] photocycloaddition, so the synthetic pathway was abandoned. J.-B. Farcet and co-workers [159] also tested intramolecular [2+2] photocyclization, under various conditions. The 4HCP analogue gave a tricyclic core in 60% yield, with the following conditions: UV-B lamp 2 X 16 W, quartz filter, Et_2O.



Scheme 57: Synthesis of Ping Lu and co-workers [158].

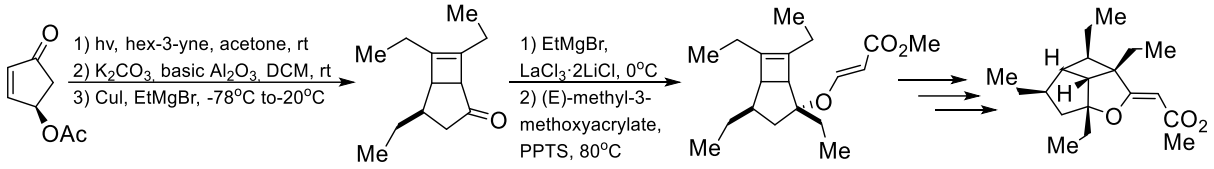
Minuti *et al.* [160] describe a series of Diels-Alder reactions using 4-Ac-CP as starting material with (+)-nopadiene originating α,β-unsaturated ketones in good yields (47-55%), regioselectively and anti-endo diastereoselectively, under an aluminium catalysis (**Scheme 58**). The same method was described previously by L. Mined *et al.* [161] forming α,β-unsaturated ketone regioselectively and endo-diastereoselectively in 70% yield. The treatment of this ketone with Pd/charcoal catalyst gave cyclopenta[c]phenanthren-I-one in 60% overall yield.

The Diels-Alder reactions were also described by P.P.M.A. Dols *et al*. [162] promoted by zinc chloride as Lewis acid catalyst (**Scheme 58d)**) and high pressures, giving the tricyclo[5.2.1.02,6]decadienones in good to excellent overall yields from the known 4-Ac-CP.



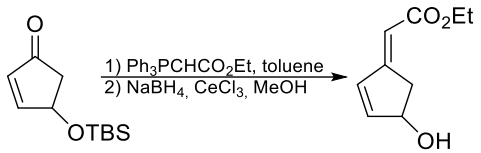
Scheme 58: Diels-Alder reactions by Minuti *et al.* [160] and P.P.M.A. Dols [162].

Stefan A. Ruider *et al.* [163] achieved the first total synthesis of hippolachnin A (**Scheme 59**) in a sequence of nine linear steps from the same 4-Ac-CP in 9% overall yield with a series of reactions such as photoadition, copper-mediated 1,4-addition of ethylmagnesium bromide and subsequent Grignard 1,2-addition, strategic ene cyclization and ester reduction.



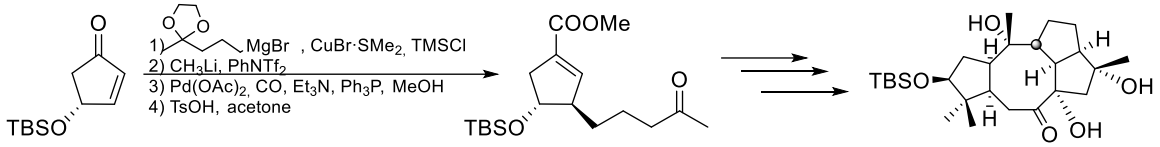
Scheme 59: Synthesis of hippolachnin A [163].

Ming An and co-workers [164] designed analogues of shikimate-3-phosphate in order to find more synthetically accessible inhibitors to the shikimate-chorismate pathway (**Scheme 60**). Their method was to design five-membered ring analogues of shikimate from 4HCP to best mimic the low energy conformation of the native substrate and, the other two, to retain the flexibility on the cyclopentenyl. Four compounds were synthetized in a reasonable overall yield, equal efficacy and with different characteristics. The intermediary compound, important for the synthesis of this analogues, is in **Scheme 60**.



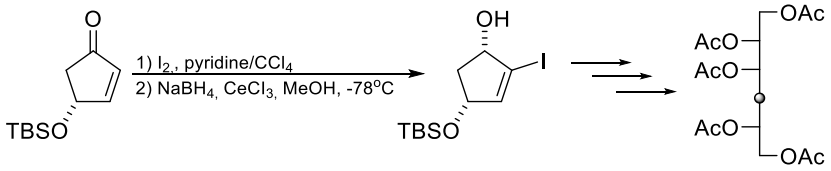
Scheme 60: Method of Ming An and co-workers [164].

Stephane Borrelly and Leo A. Paquette [165] synthetize 7-oxy-5,6-dideoxykalmanol from the same (R)-TBS-CP (**Scheme 61**) in 25 steps and 1,6% overall yield as a result of a Tebbe-Claisen reaction sequence, a Pd-(II)-catalyzed carbonylation and intramolecular aldol cyclization.



Scheme 61: Pathway chosen by Stephane Borrelly and Leo A. Paquette [165].

Carl R. Johnson *et al.* [120] also used (R)-TBS-CP as starting material for the synthesis of 3-deoxy-D-*ribo*-hexitol pentaacetate to establish its true absolute stereochemistry (**Scheme 62**). The synthesis developed is 8 steps long an provides the desired product in 12% overall yield, but allowed the purpose of the study to be full field successfully.

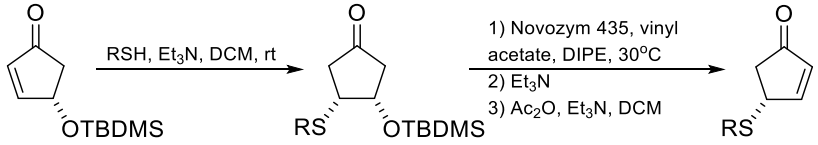


Scheme 62: Synthesis by Carl R. Johnson *et al.* [120].

The interest of 4HCP as starting material lead Kumar *et al.* [166] on the study of $GABA_C$ receptor. Their study lead them to synthesize antagonist compounds for an elucidating role on the receptor. The synthesis of this compounds started with both enantiomers of the 4HCP (**Scheme 63**), which were protected and then suffered a 1,4-reduction with trapping, followed by coupling of alkylphosphinate esters (RP(O)(OR')H), deprotection and Mitsunobu-Staudinger reaction. The reactions underwent with good overall yields and the results were promising.

Scheme 63: Synthetic pathway used by Kumar *et al.* [166]

J. F. Bickley *et al.* [167] found that 4HCP can react with thiols to give syn-adducts (**Scheme 64**), thus converting optically active 4HCP in 4-Thia-CP. Both enantiomers of the thiol can be obtained, in good yields, through addition of benzylthiol to the racemic 4HCP in DMC, lipase-mediated kinetic resolution, for the (S) enantiomer, followed by treatment with acetic anhydride and triethylamine, to afford the (R). The same synthetic method was used by Aisling O'Byrne and co-workers [99] in the synthesis of 4-Thia-CP, in 77% and 84% e.e., which was then used to prepare 4-butylcyclopent-2-en-1-one, through an oxidation–elimination sequence.

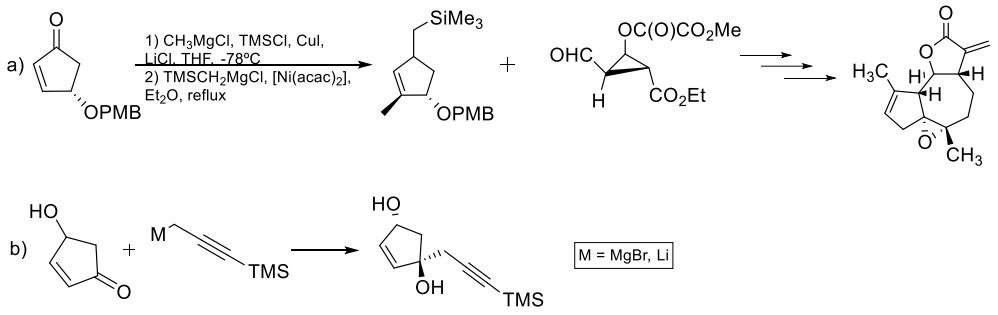


Scheme 64: Synthesis of 4-Thia-CP [167].

In 2007, Srinivas Kalidindi [168] synthetize (+)-Arglabin (**Scheme 65a)**) through a series of known reactions such as copper(I)-catalyzed asymmetric cyclopropanation, a stereoselective Sakurai allylation followed by a retroaldol/lactonization cascade, a second Sakurai allylation and ring-closing metathesis. The complete syntetic pathway has over 13 steps and allows the synthesis of the desired compound from (S)-PMB-CP in a very low overall yield.

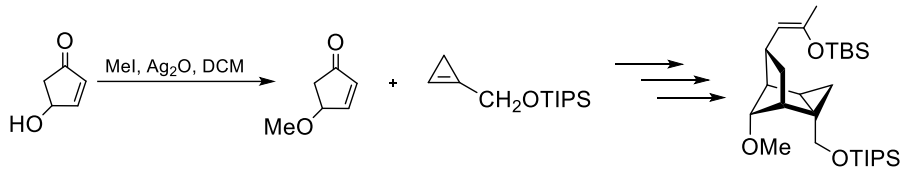
In the same year, Hukum P. Acharya and co-workers [169] tested the selectivity in the addition of propargyl and propargylic Grinard reagents (**Scheme 65b)**), prepared without Hg. The Grinard reagents used were prepared with $ZnBr_2$, and the addition reactions tested on 4HCP were performed

with good yield and high selectivity. The lithiation of the Grinard compound and respect addition to the 4HCP gave a precursor of clavulone II and its analogues.



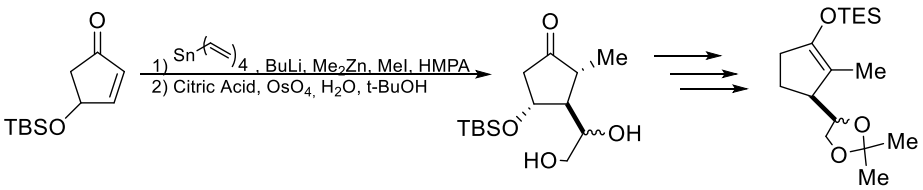
Scheme 65: Synthesis design by Srinivas Kalidindi [168] and Hukum P. Acharya and co-workers [169].

In 2013, Yuan Shi and co-workers [170] found interest in developing (+)-neofinaconitine (**Scheme 66**), as it has structural similarity to the natural product lappaconitine, which exhibits intriguing biological activities. They were able to synthetize the promised compound through convergent cyclopropene/cyclopentadiene and azepinone/siloxydiene Diels−Alder cycloadditions to assemble a key cyclization substrate, followed by successive Mannich-type N-acyliminium (Speckamp) and radical cyclizations. This proposed method is nevertheless very long, having 30 steps and inefficient for commercial use, as its yield is very low.



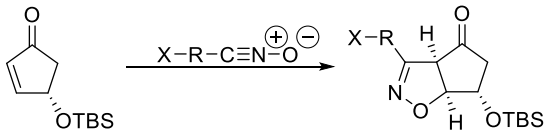
Scheme 66: Synthesis of (+)-neofinaconitine [170].

Michael E. Jung [171] attempt to synthetize Rhodexin A using 4-TBS-CP as starting material (**Scheme 67**). Although they couldn't reach the desired product, they could reach an intermediary compound starting with a zinc-mediated conjugate addition of a vinyl organometallic followed by trapping with methyl iodide, dihydroxylation of the alkene, acid-catalyzed elimination of the β-silyloxy group gave an enone, which was hydrogenated, and then protected and the migration of the alkene using Wilkinson's catalyst. When tried to use this intermediary in a Diels−Alder reaction, the reaction failed, with different times and conditions, so the method was exchanged for another more suitable.



Scheme 67: Method used by Michael E. Jung [171].

Lastly, Sanjivanjit K. Basra *et al.* [172] aimed to synthetize a library of compounds with two isoxazoline rings fused to a cyclopentenone (**Scheme 68**), each compound would carry a number of functional groups that would allow the production of more complex structures for possible biological evaluation. Their methodology allow the preparation of a large number of stereochemically pure bis-isoxazolines from the (S)-TBDMS-CP.



Scheme 68: Synthesis of Sanjivanjit K. Basra *et al.* [172].

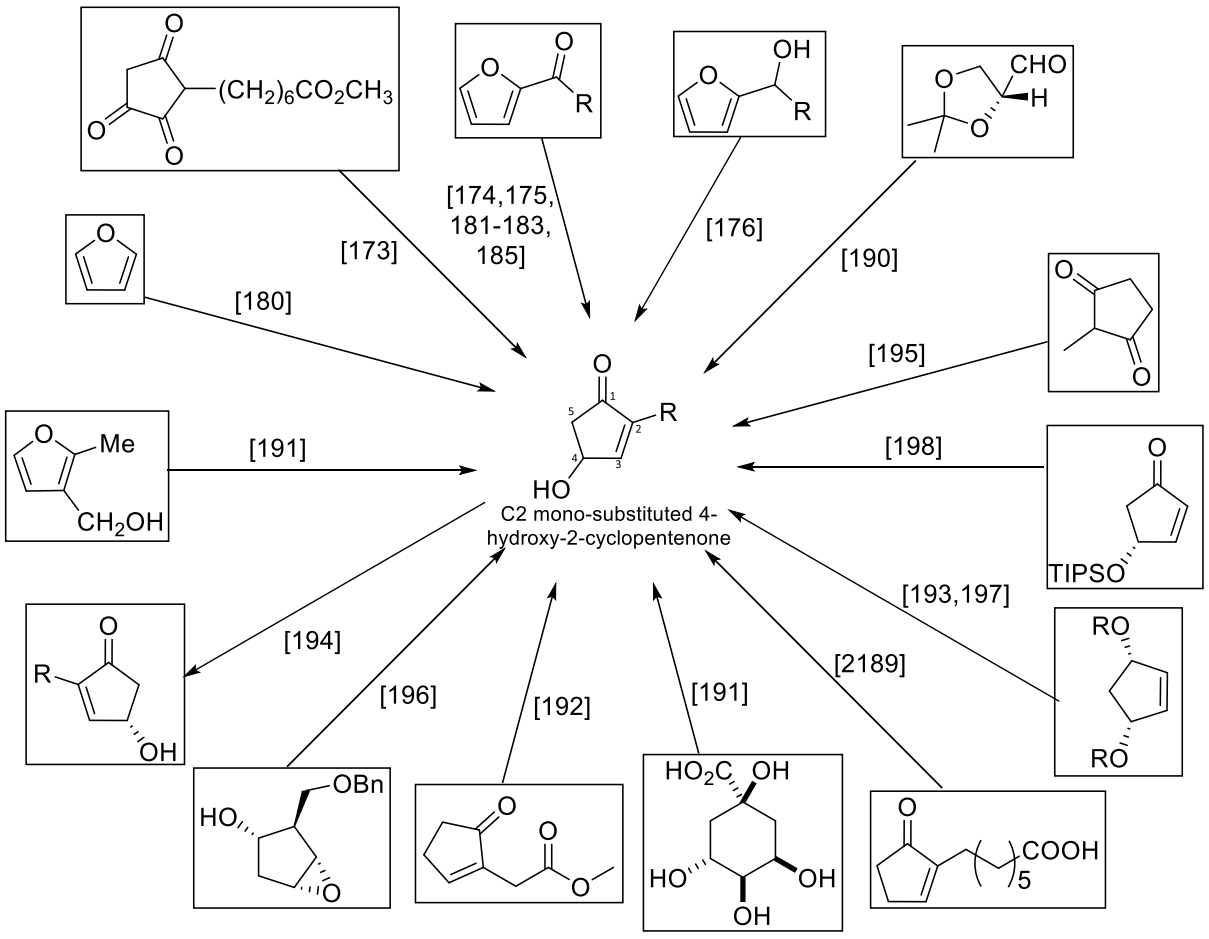
Mono-substituted 4-hydroxy-2-cyclopentenones and hydroxyl side chain derivatives

Mono-substituted 4-Hydroxy-2-cyclopentenones can be differentiated by the substituted carbon, the C2 (**Scheme 69**), C3 (**Scheme 82**) or C5 (**Scheme 83**).

There are numerous similarities between the 4HCP and the mono-substituted 4-Hydroxy-2-cyclopentenones in terms of the hydroxyl protection and deprotection, as well as some applications (to be explained below).

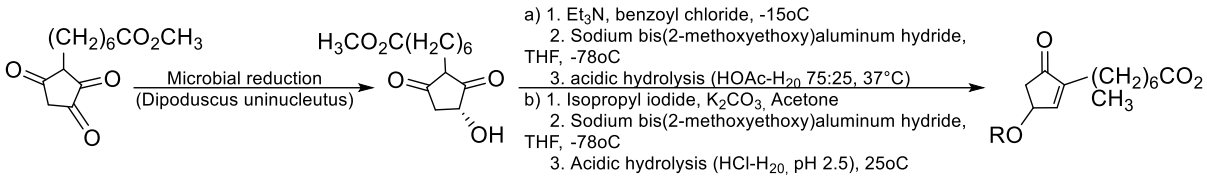
Construction of the mono-substituted 4-hydroxy-2-cyclopentenone building block

C2 substitution



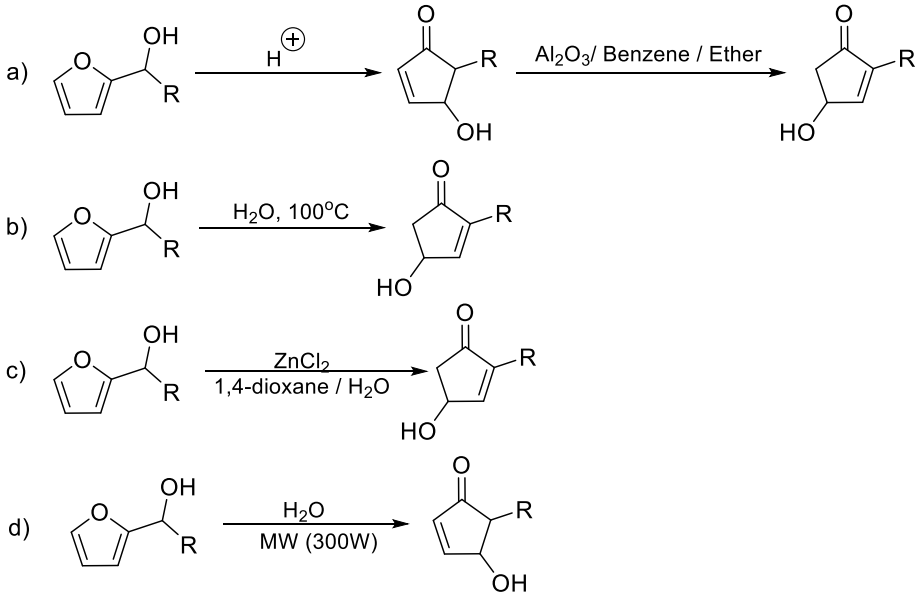
Scheme 69: Synthetic pathways to mono-substituted 4-Hydroxy-2-cyclopentenones in the C2 carbon.

In 1973, Charles J. Sih and co-workers [173] developed two methods (**Scheme 70a) and b)**) for the synthesis of the mono-substituted 4HCP via the same intermediate, which is obtained by microbial reduction. The method a), in **Scheme 70** represents the reaction with triethylamine and benzoyl chloride at - 15°C, followed by a reduction with excess sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at -78°C, and finally acidic hydrolysis. Method b), describes alkylation by refluxing with isopropyl iodide and K_2CO_3 in acetone, followed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at -78°C, finally acidic hydrolysis.



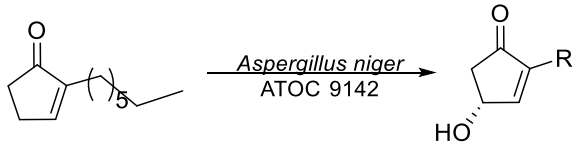
Scheme 70: Methods developed by Charles J. Sih and co-workers [173].

One of the most used methods to prepare the mono-substituted 4HCP is the Piancatelli rearrangement and isomerization from furfuryl alcohols or furaldehyde. This method has been used by many researchers, modified and optimized [111, 174-187]. In the original synthesis described by Piancatelli *et al.* [178], the reaction proceeds in an acidic medium at high temperature and the isomerization [188] in alumina (**Scheme 71a**). The modified and more eco-frieldly process uses just water and high temperature (**Scheme 71b**), while Aurelio G. Csákÿ and co-workers [184] modified it by means of a Zn acidic catalyst in water (**Scheme 71c**). The most recent and best optimized process uses a microwave catalysed reaction in water [111], described previously in the synthesis of 4HCP (**Scheme 71d**). In the usage of this methods, different furans were used and modified by organolithium or Grignard reagents. The rearrangement involved in this reactions will be explained in further detail later on.



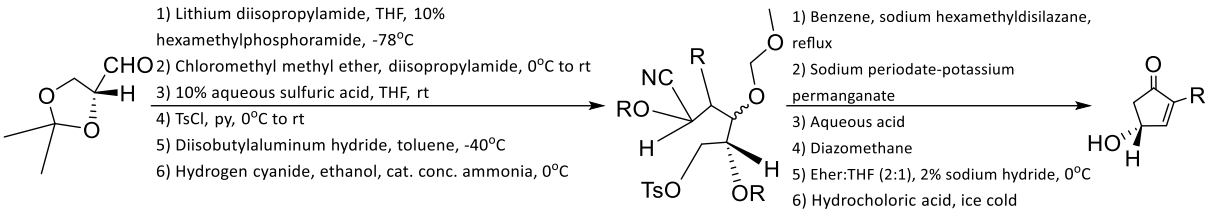
Scheme 71: Piancatelli rearrangement and isomerization (original, modified and optimized).

Seizi Kurozmi and co-workers [189] (**Scheme 72**), develop a simple way to synthetize the mono-substituted 4HCP, through a fermentation medium and *Aspergillus niger*, in 67% yield, so it could be used in the synthesis of prostaglandins.



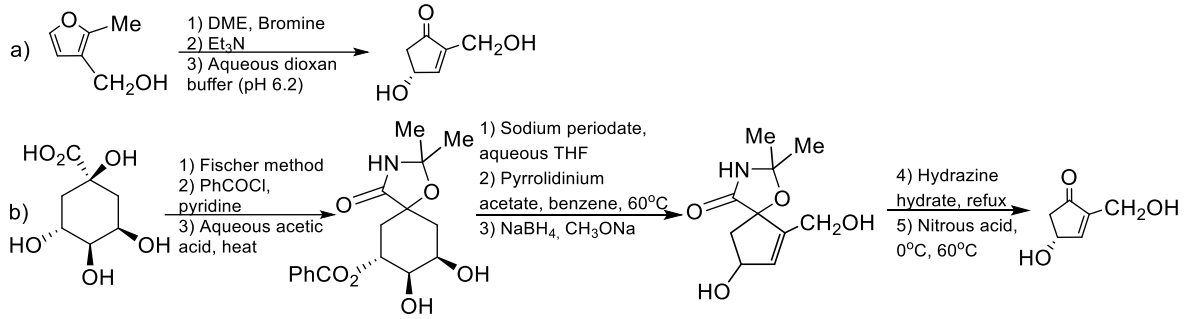
Scheme 72: Method of Seizi Kurozmi and co-workers [189].

Gilbert Stork and Takashi Takahashi [190] described the construction of a mono-substituted 4HCP from isopropylidene D-glyceraldehyde and methyl oleate (**Scheme 73**). The main steps involved in the synthesis are the protection of the secondary hydroxyl group, removal of the isopropylidene group and lactonization, transformation via the cyclic hemiacetal, cyclization and oxidation. This method provides the mono-substituted 4HCP in a very low overall yield.



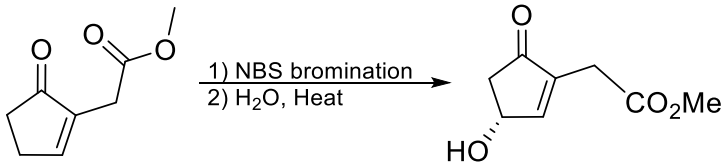
Scheme 73: Synthesis of Gilbert Stork and Takashi Takahashi [190].

John D. Elliot and co-workers [191] synthetized a mono-substituted 4HCP via two different methods (**Scheme 74**). In the first method described (**Scheme 74a**), the furan is treated in dimethoxyethane (DME) with bromine followed by triethylamine, the mixture is then refluxed in aqueous dioxan buffered at pH 6.2 followed by silica gel chromatography. This method gives the product in 50% yield. In the second method (**Scheme 74b**), (-)-quinic acid is transformed in the mono-substituted cyclopentenone through a series of reactions such as the Fischer method, benzoylation and oxidation. Method b) provides the desired product in 12% overall yield.



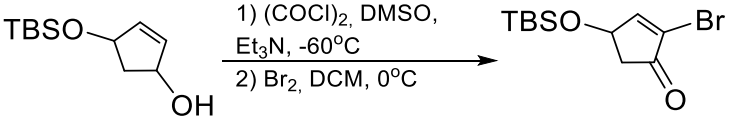
Scheme 74: Synthetic pathways developed by John D. Elliot and co-workers [191].

P. G. Baraldi *et al.* [192] prepared the cyclopentenone required for their prostaglandin synthesis in more than 60% overall yield from methyl 2-(5-oxocyclopent-1-en-1-yl)acetate, through NBS bromination followed by replacement of the bromide by an hydroxyl group with the addition of water and heating.



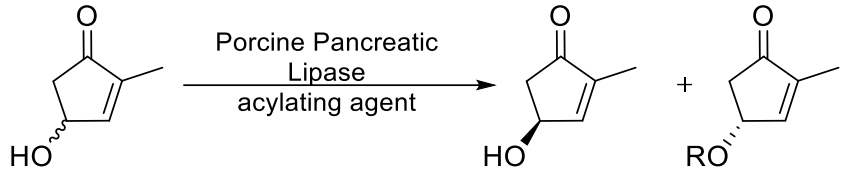
Scheme 75: Method elucidated by P. G. Baraldi *et al.* [192].

In order to achieve the synthesis of Neocarzinostatin (NCS), Masahiro Hirama and co-workers [193] synthetized the mono-substituted 4HCP present in the **Scheme 76**, a key intermediate in the synthesis of the desired product. In order to do so, they proceeded by a straightforward procedure, obtaining the cyclopentenone in 85% yield via hydroxyl oxidation followed by enone α-bromination.



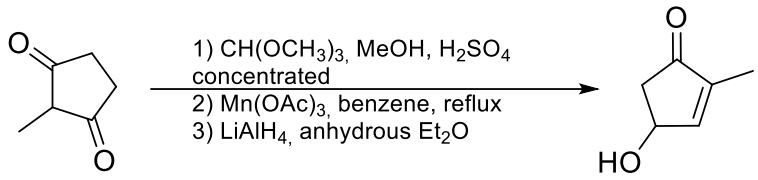
Scheme 76: Synthesis of Neocarzinostatin (NCS) by Masahiro Hirama and co-workers [193].

Tanis *et al.* [194] proceeded to an isolation of the (S) mono-substituted 4HCP in 98% ee and 34% overall yield (**Scheme 77**). In order to do so they exposed, repeatedly, the racemic mixture to PPL in neat vinyl acetate.



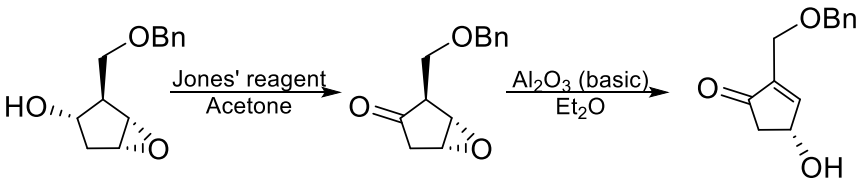
Scheme 77: Isolation procedure of Tanis *et al.* [194].

A. S. Demir *et al.* [195] developed a very simple synthesis from 2-methylcyclopentane-1,3-dione (**Scheme 78**) that delivered the desired product in very good yield.



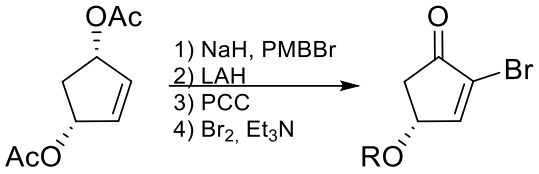
Scheme 78: Simple method of A. S. Demir et al. [195].

Towards obtaining the *(R)*-mono-substituted cyclopentenone presented in the **Scheme 79**, E. Ruediger *et al.* [196] used the regioselective ring opening of the epoxycyclopentanone and basic alumina in ether, followed by based-induced equilibration to give the desired *(R)*-mono substituded cyclopentenone, almost exclusively, in 87.4% yield.



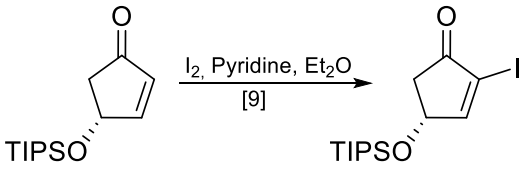
Scheme 79: Method to obtain (R) mono-substituted cyclopentenone of E. Ruediger *et al.* [196].

Michael E. Jung and co-workers [197] synthetize the mono-substituted cyclopentenone (**Scheme 80**) through conversion of the achiral diacetate. Firstly they protected the alcohol, followed by reductive removal of the pivalate, oxidation, and, at last, bromination.



Scheme 80: Synthesis developed by Michael E. Jung and co-workers [197].

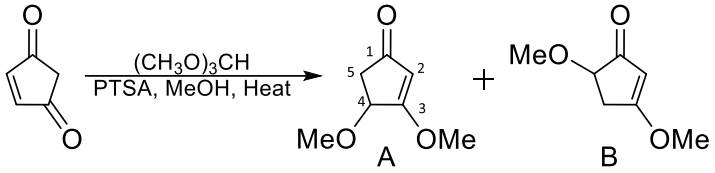
Gurpreet Singh *et al.* [198] synthetized both enantiomers of the α-iodo derivative from the 4HCP in 85% yield (**Scheme 81**), to apply it in in the synthesis of prostaglandins and other natural products.



Scheme 81: Synthesis of mono-substituted cyclopentenone from 4HCP by Gurpreet Singh *et al.* [198].

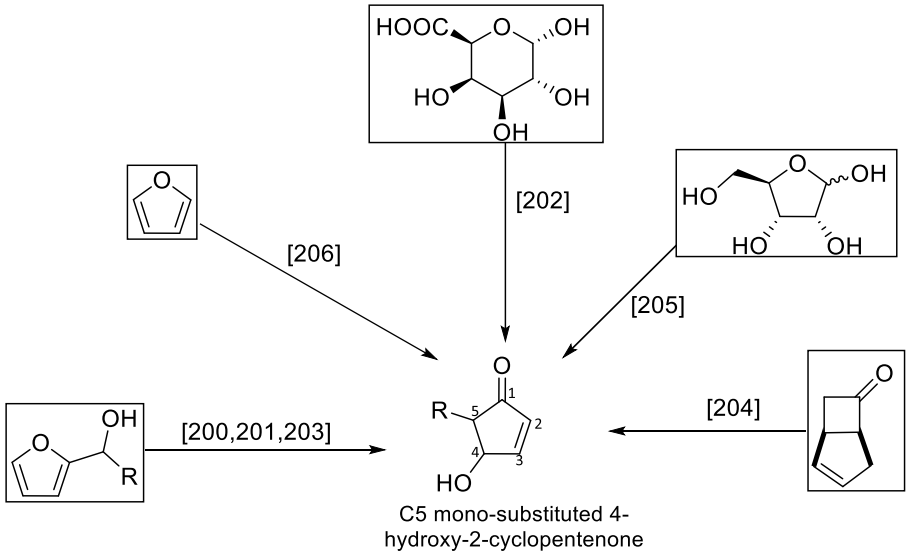
C3 substitution

Smith *et al.* [199] prepared the C3 substituted cyclopentenone, 3,4-dimethoxycyclopent-2-en-1-one (**Scheme 82**), with a very straightforward synthesis. They treated cyclopent-4-ene-1,3-dione with trimethyl orthoformate in acidic methanol, obtaining the cyclopentenone in a mixture with a regioisomer (Scheme 34) in 1:3, in 85-90% yield.



Scheme 82: Method developed by Smith *et al.* [199].

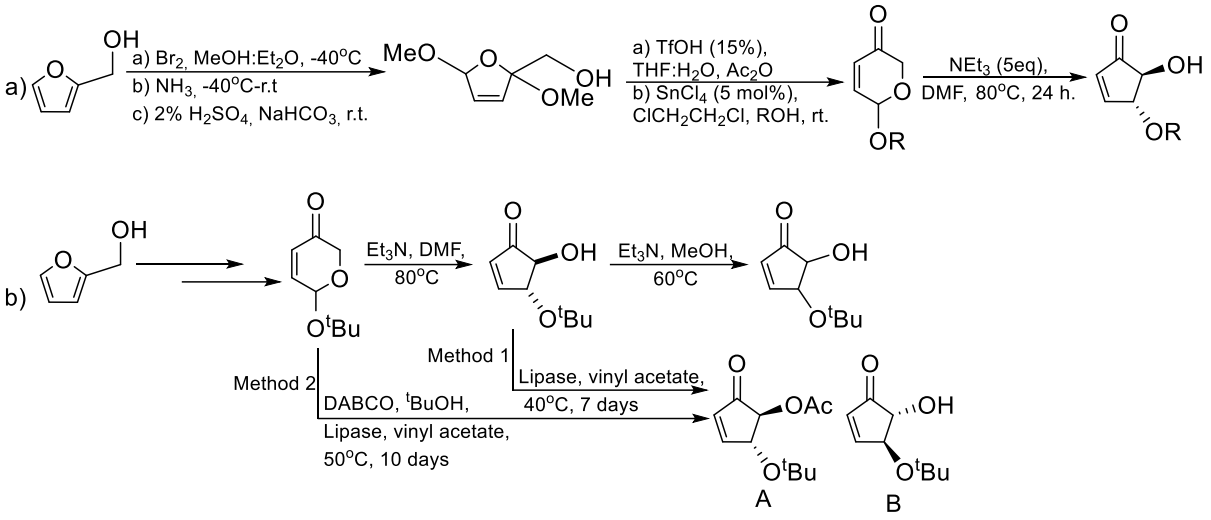
C5 substitution



Scheme 83: Pathways to the synthesis of mono-substituted 4-Hydroxy-2-cyclopentenones in the C5 carbon.

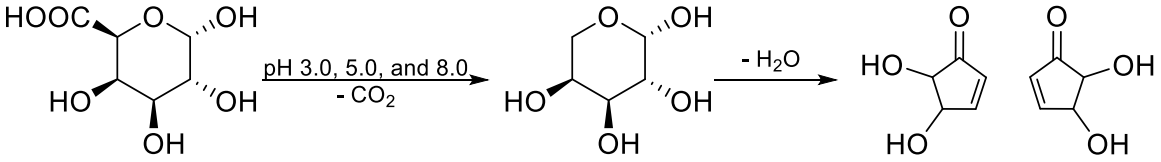
Caddick *et al.* [200] synthetize different substituted cyclopentenone (**Scheme 84a)**) from furfuryl alcohol. This reagent was treated with an excess of bromine in methanol, followed by mild hydrolysis and activation of the hemiacetal hydroxy functionality with the addition of a catalytic amount of trifluoromethane sulfonic acid. The last obtained product is then converted into various ethers using catalytic Lewis acid conditions and then converted to the desired cyclopentenone, with 5 equiv. of triethylamine in DMF at 80°C in a 24 h period, with an overall yield of 47%.

A similar procedure was carried out by J.P.M. Nunes *et al.* [201] which developed two different methods (**Scheme 84b)**) to obtain the same cyclopentenones. The fist method consists in a pyranone rearrangement followed by a classic lipase-catalysed kinetic resolution. The second method is done so that the rearrangement and the enzymatic resolution could be done within the same step. As so, the enzyme and vinyl acetate were directly added to the mixture of pyranone and DABCO in *tert*-butanol. With the first method, the desired cyclopentenone A was obtained in 39% overall yield and 95% ee, as for the second method, the same cyclopentenone was obtained in higher yield, 55%, but a lower ee, only 80%. This was the first case of dynamic kinetic resolution reported as asymmetric synthesis strategy for enantiomerically enriched *trans*-dioxygenated cyclopentenone.



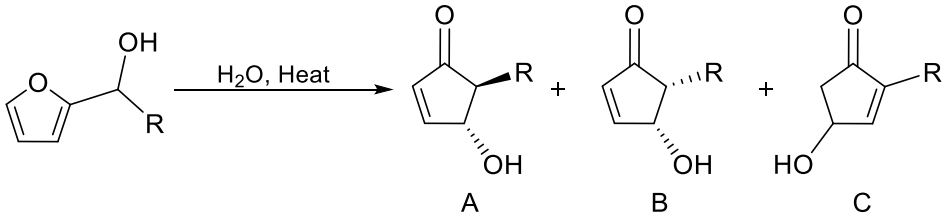
Scheme 84: Synthetic pathways of Caddick *et al.* [200] and J.P.M. Nunes *et al.* [201].

Maria-Anna Bornik and Lothar W. Kroh [202] found that di-hydroxy cyclopentenone can be obtained as a degradation product of D-galacturonic acid (**Scheme 85**) in aqueous unbuffered solutions at pH 3.0, 5.0, and 8.0, in different concentrations, being the highest at pH 3.0.



Scheme 85: Method developed by Maria-Anna Bornik and Lothar W. Kroh [202].

Jadwika Frelek *et al.* [203] obtained *(S)*- and *(R)*- C5 substituted 4HCP (**Scheme 86** A and B, respectively) as well as C2 substituted 4HCP (**Scheme 86** C) but only in 3% yield. The *(S)*-C5 substituted 4HCP was obtained in 91% yield and the *(R)*- in 4%, from a reaction in boiling water, extraction and then distillation under reduced pressure.

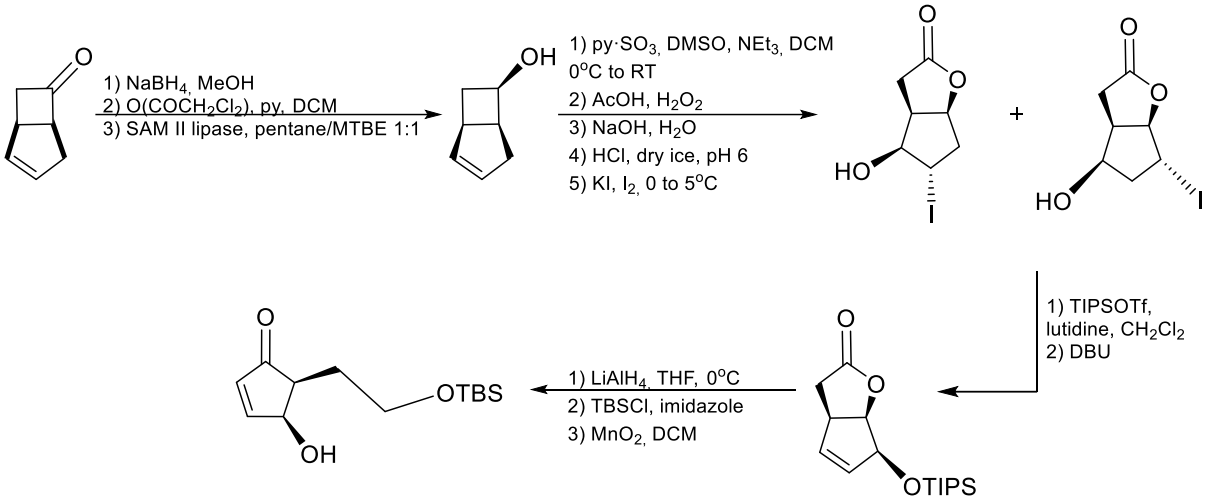


Scheme 86: Synthesis described by Jadwika Frelek *et al.* [203].

C. Lentsch *et al.* [204] designed a method were bicyclo[3.2.0]hept-2-en-6-ol was obtained from *(1R,5S)*-bicyclo[3.2.0]hept-2-en-6-one through diastereoselective reduction with sodium borohydride, followed by esterification and enzymatic resolution. The product obtained was then subjected to the Baeyer–Villiger oxidation, followed by iodolactonization at different pH values and formation of corresponding silyl ethers, so the two compounds formed could be easily separated.

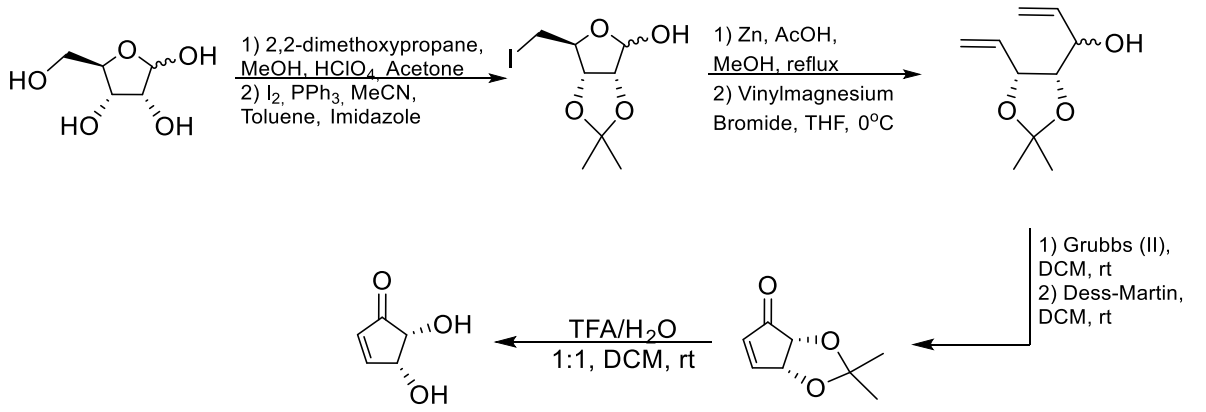
As the direct methylation of the iodide could not be achieved, C. Lentsch and co-workers [204] decided to install the methyl functionality by conjugate addition, through DBU mediated elimination

of the iodide. The lactone in the product of the last reaction was then reduced with lithium aluminum hydride and silylated to give the final cyclopentenone in 27% overall yield.



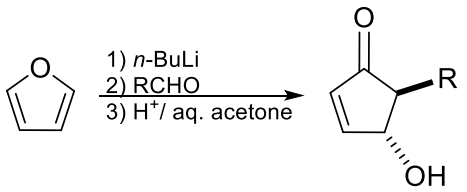
Scheme 87: Synthetic pathway developed by C. Lentsch *et al.* [204].

L. Leclere *et al.* [205] started the synthesis of the cyclopentenone (**Scheme 88**) with commercially available D-ribose. The desired product was achieved through a 7 step synthetic sequence, starting with the protection with isopropylidene, then iodination of the primary alcohol. That product suffered a reductive elimination, using zinc under acidic conditions, then was added vinyl Grignard. To end of the synthetic pathway, a ring closing metathesis, Dess–Martin oxidation and then cleaving under acidic conditions, to give the desired cyclopentenone in 20% yield.



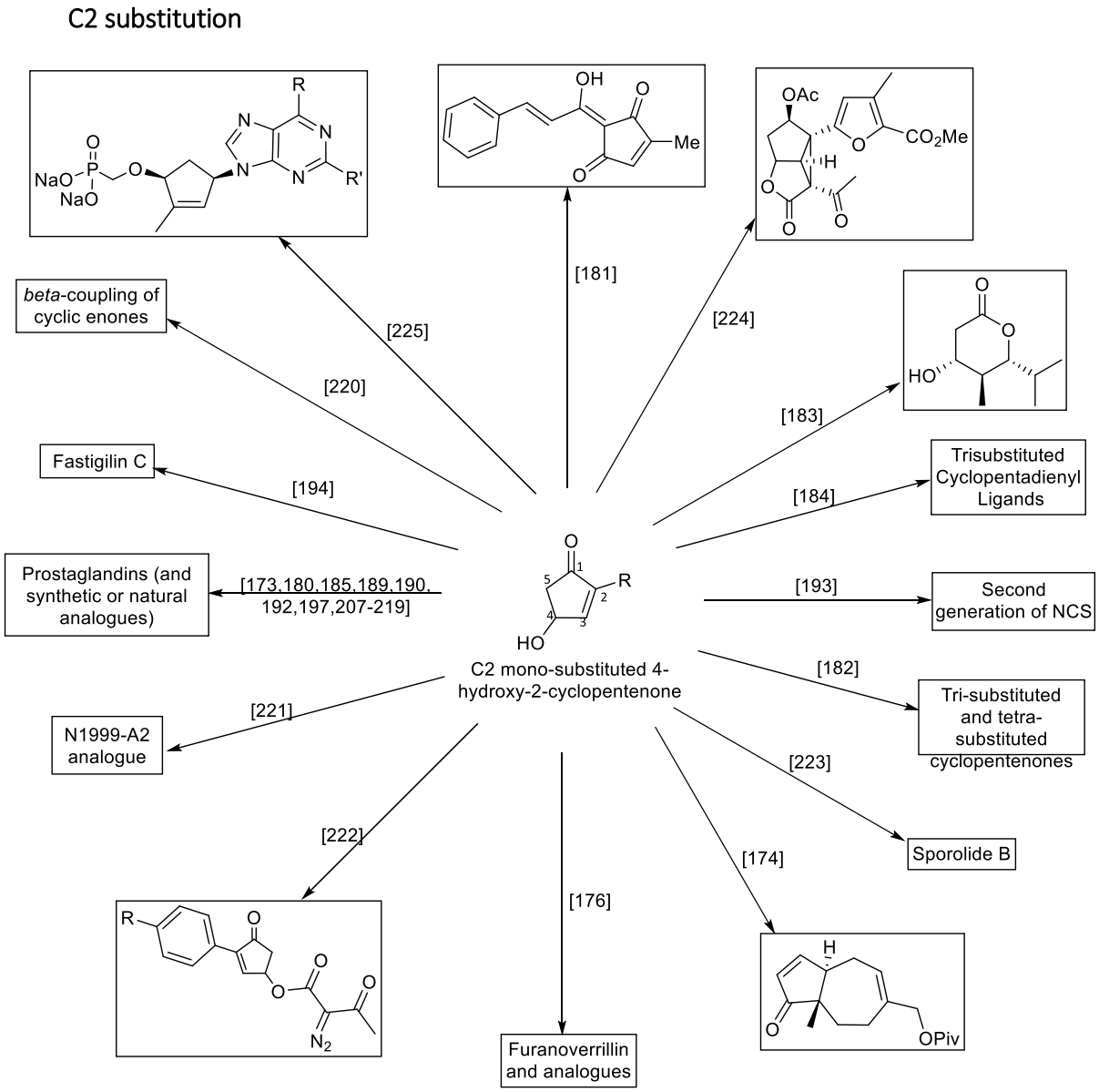
Scheme 88: Method developed by L. Leclere *et al.* [205].

West and Gunawardena [206] used the Piancatelli method to prepare a variety of C5 substituted cyclopentenones from furan in 15-46% yield (**Scheme 89**).



Scheme 89: Synthesis of West and Gunawardena [206].

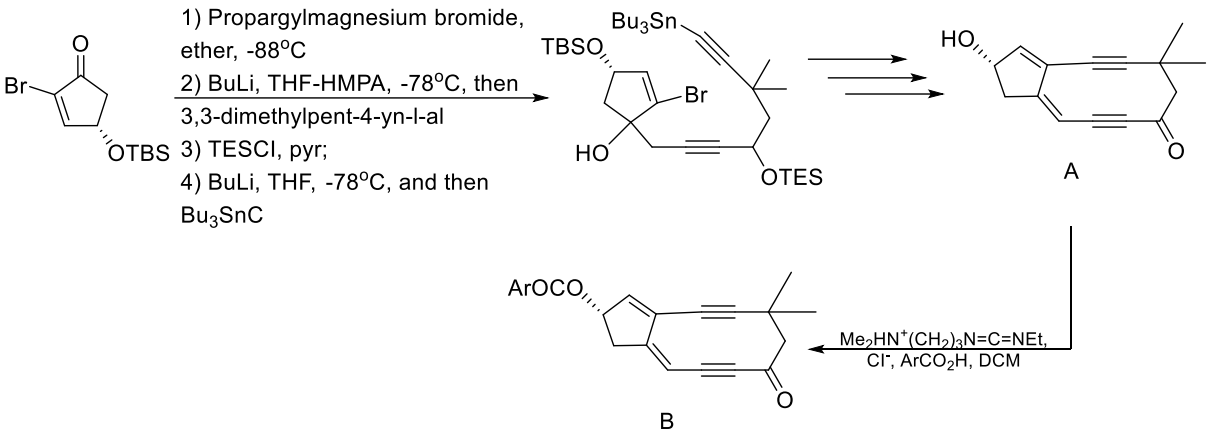
Mono-substituted 4-hydroxy-2-cyclopentenones as starting material



Scheme 90: Mono-substituted 4-Hydroxy-2-cyclopentenones in the C2 carbon as starting material.

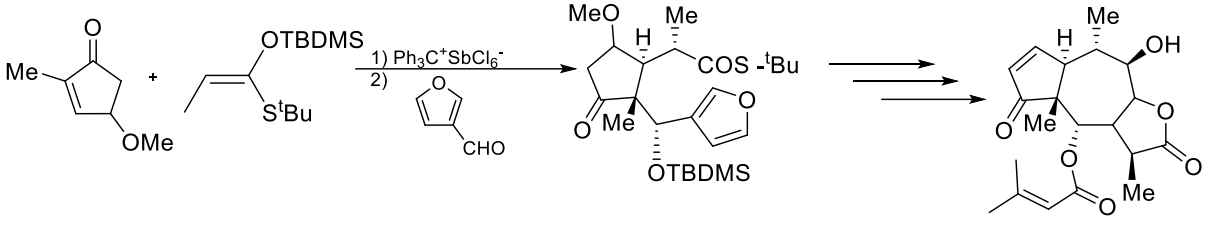
In the same line of work as the 4HCP, their mono-substituted analogues are used to synthetize prostaglandins, prostanoids, isoprostanes and similar molecules, with the three (or two) component coupling process and other methods described before. Using this methods, several research groups [173, 180, 185, 189, 190, 192, 197, 207-219] were able to achieve their desired prostaglandins (and analogues, like thia-prostaglandins) and isoprostanes.

Masahiro Hirama *et al.* [193] designed the second generation of Neocarzinostatin (NCS) analogues, one alcohol (**Scheme 90A**) and one naphthoate (**Scheme 90B**). In order to synthetize this molecules they started with the most suitable key intermediate, the *(S)*-2-bromo-4-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-one. Analogue A was synthesized in 7 steps, in 14.5% overall yield, as it was rather unstable, was esterified to originate B in 8% overall yield.



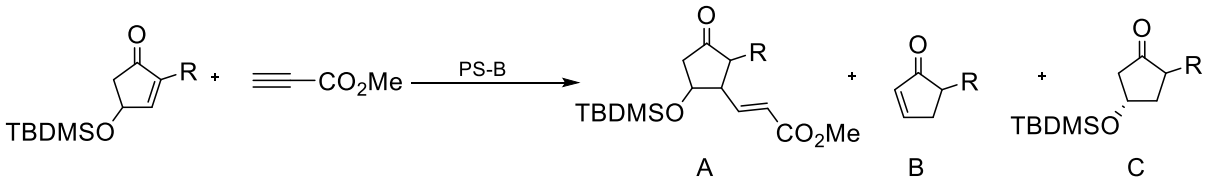
Scheme 91: Synthesis of Masahiro Hirama *et al.* [193].

In 1992 Tanis *et al.* [194] proceeded to the synthesis of fastigilin C, through a very important building block, synthesized from the well-known 4-methoxy-2-methylcyclopent-2-en-1-one. This valuable compound was obtained in an overall yield of 86%, allowing the synthesis of (±)-fastigilin C (**Scheme 91**). In their studies they also synthesized (-)-fastigilin C, using the same synthetic method, but using as starting material the (S)-4-methoxy-2-methylcyclopent-2-en-1-one.



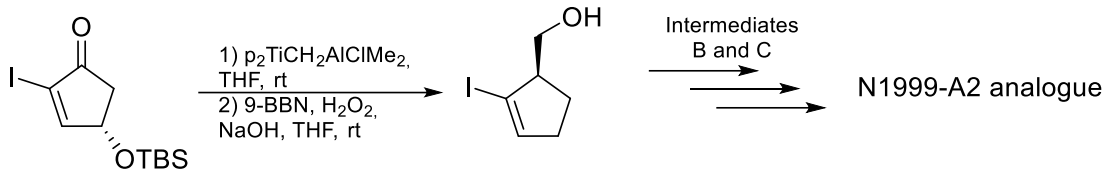
Scheme 92: Method developed by Tanis *et al.* [194].

Ganesh Pandey and colleagues [220] studied the β-coupling of cyclic enones (**Scheme 92**) in order to test the action of their previously developed photosystems for harvesting visible light photons into electrons. The reaction produced three products, product A in only 15% yield, B in 40% yield, suggesting that there is competition between enol isomerisation and an elimination reaction, and finally compound C in 20% yield.



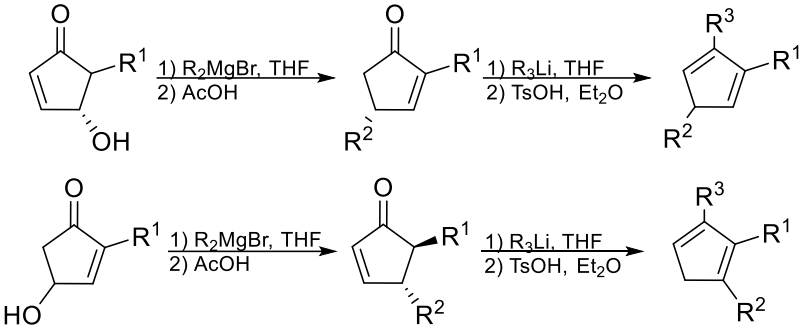
Scheme 93: Study of cyclic enones of Ganesh Pandey and colleagues [220].

In order to synthetize a N1999-A2 analogue, a compound isolated from the broth filtrate of *Streptomyces sp*., Shoji Kobayashi *et al.* [221] designed a method involving 3 important building blocks through retrossynthesis. One of those building block, A in **Scheme 93**, derivers from a C2 mono-substituted 4HCP. The synthesis of that building block is presented in **Scheme 93**.



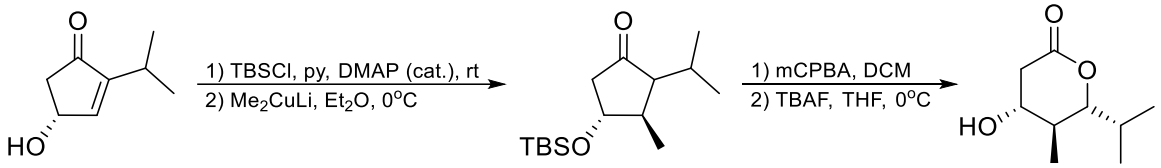
Scheme 94: N1999-A2 analogue of Shoji Kobayashi *et al.* [221].

Aurelio G. Csákÿ and co-workers [184] aimed to synthetize trisubstituted cyclopentadienyl to apply them as ligands in organometallic chemistry (**Scheme 94**). They synthetize a library of compounds with several substituents in different positions. The overall yields of the compounds obtained vary between 50 and 95%.



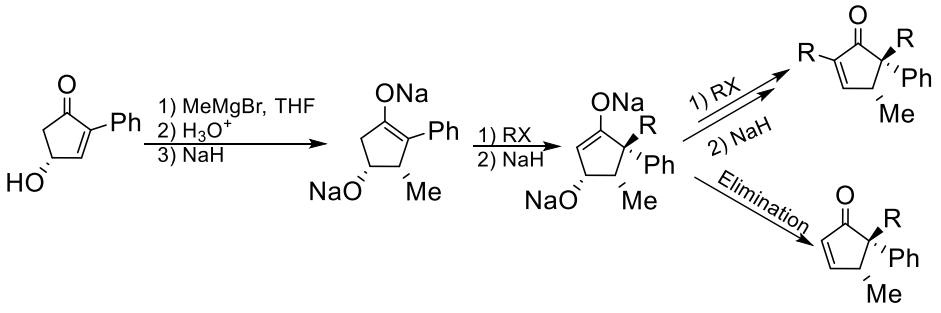
Scheme 95: Chemistry of Aurelio G. Csákÿ and co-workers [184].

(+)-Prelactone B is a β-hydroxy δ-lactones isolated from *Streptomyces griseus* and Aurelio G. Csákÿ and co-workers [183] found a synthetic pathway to achieve this same natural compound using, as starting material, a C2 mono-substituted cyclopentenone (**Scheme 95**). This method involves four steps and delivers the desired compound in 58% overall yield.



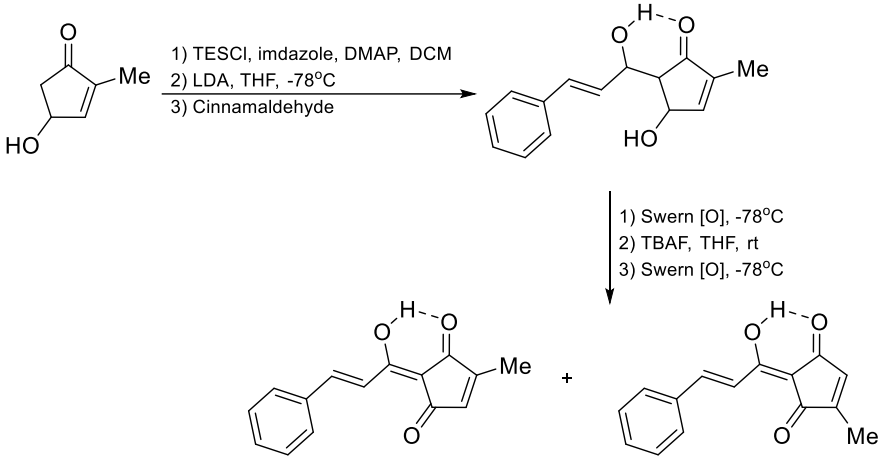
Scheme 96: Pathway chosen by Aurelio G. Csákÿ and co-workers [183].

A. G. Csákÿ *et al.* [182] also synthetized tri-substituted and tetra-substituted cyclopentenones (**Scheme 96**), through a common intermediate. This one-pot synthetic method delivers the tri-substituted cyclopentenones in yields between 65 and 90%, while the tetra-substituted cyclopentenones in only 10%.



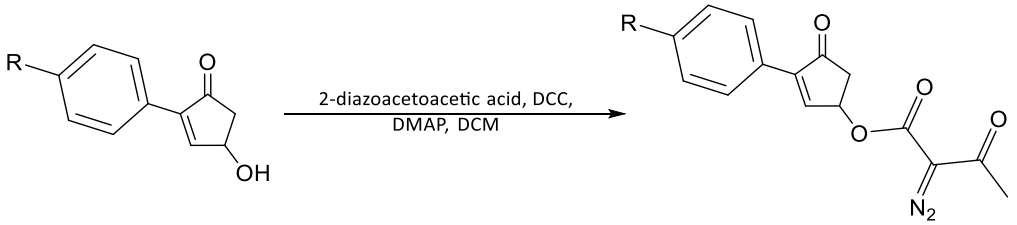
Scheme 97: Synthesis of A. G. Csákÿ *et al.* [182].

Luiz C. Dias *et al.* [181] developed a new improved method for the synthesis of cyclopentadiones, using as starting material a C2 mono-substituted cyclopentenone. The synthetic pathway allowed the synthesis of the mixture of cyclopentadienones in 40% yield (**Scheme 97**).



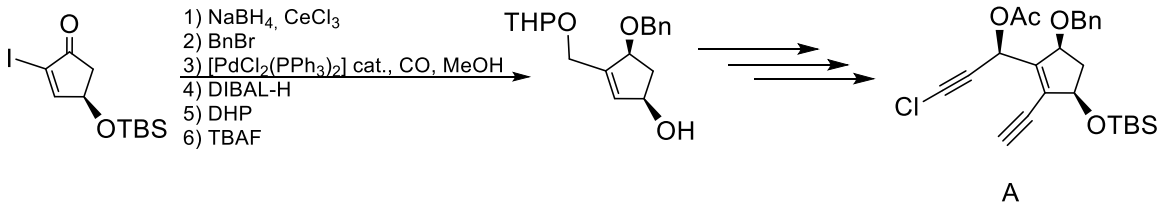
Scheme 98: Synthesis of Luiz C. Dias *et al.* [181].

Michael E. Meyer [222] synthetized a diazo acid with the main of coupling it with several different molecules. In between those were different cyclopentenones (**Scheme 98**). The reaction occurs under neutral conditions upon treatment with DCC and a catalytic amount of DMAP, giving the cyclopentenones in 77 and 95% yield.



Scheme 99: Method of Michael E. Meyer [222].

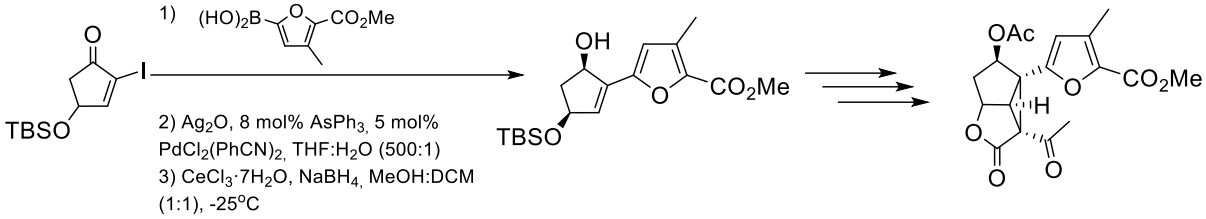
K. C. Nicolaou [223] used a C2 mono-substituted 4HCP in the synthesis of a building block (molecule A in **Scheme 99**) for the construction of the sporolide B molecule, isolated from the marine actinomycete *Salinospora tropica*. The pathway chosen involves the cycloaddition of two building blocks, being only one of them derivate of the 4HCP. This important building block was achieved in 30% over 18 steps.



A

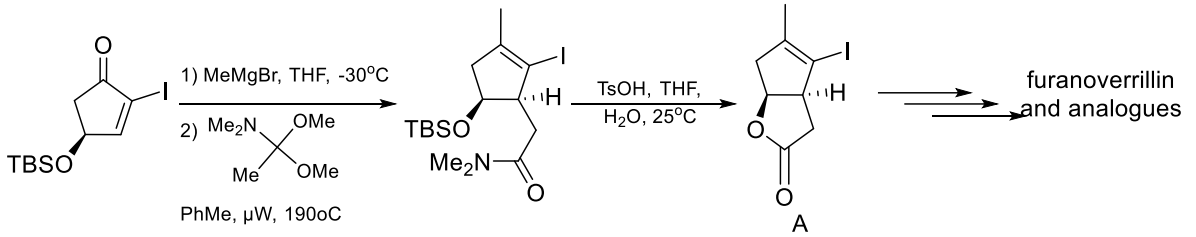
Scheme 100: synthesis of sporolide B by K. C. Nicolaou [223].

Michael E. Meyer and co-workers [224] attempt to synthetize bielschowskysin, a compound isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*, which had shown to be biological active. Even though they couldn't reach the desired compound, in their attempt was reached other important compounds (**Scheme 100**).



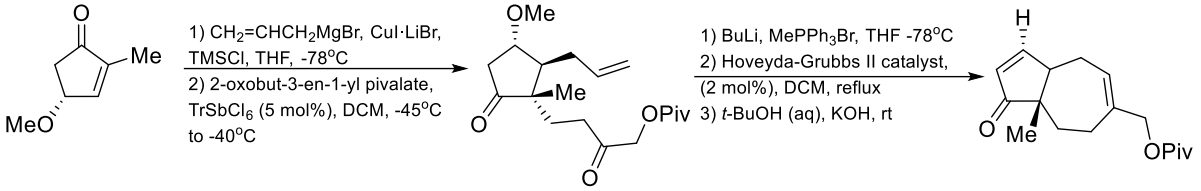
Scheme 101: Attempted synthesis of bielschowskysin by Michael E. Meyer and co-workers [224].

Alec Saitman and co-workers [176] found and synthetize furanoverrillin and several analogues, which are the core for Verrillin, from a C2 mono-substituted cyclopentenone. Their synthetic strategy is based on the synthesis of A in **Scheme 101**, which can be transformed according to the desired analogue. The synthesis of the interesting compound A englobes three steps and delivers it in 33% overall yield, from the cyclopentenone.



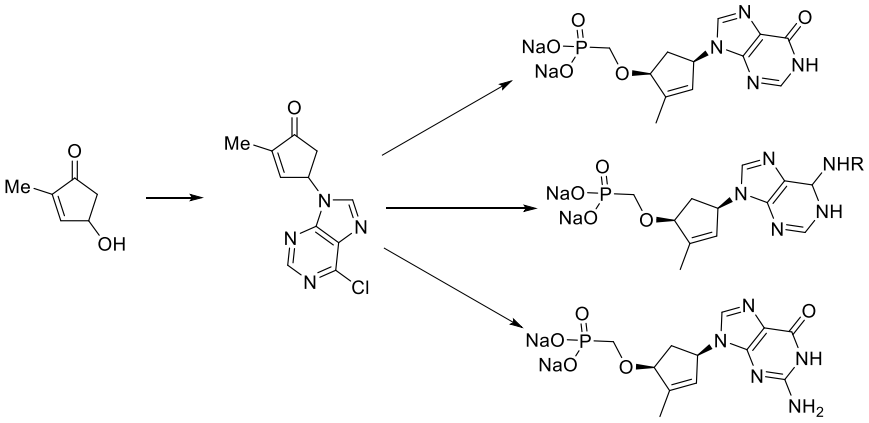
Scheme 102: Method developed by Alec Saitman and co-workers [176].

K. Michalak *et al.* [174] took interest in developing a key bicyclic building block for the synthesis of (+)-heptemerone G and (+)-guanacastepene A. This compound was achieved in 5 steps from the known C2 mono-substituted cyclopentenone in **Scheme 102** in 44% overall yield.



Scheme 103: Bicyclic building block developed by K. Michalak *et al.* [174].

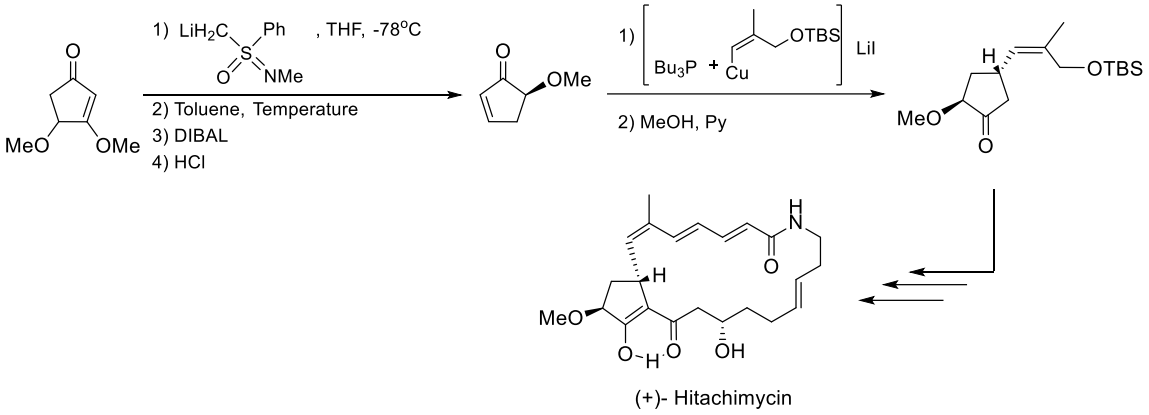
In an effort to develop to combat HIV, J.-P. Uttaro *et al.* [225] developed three new compounds to test as anti-HIV drugs. All this compounds have in common the starting material, the (±)-4-hydroxy-2-methyl-cyclopent-2-enone, and it only takes five steps to reach the desired compounds (**Scheme 103**) but the overall yields were low.



Scheme 104: Method developed by J.-P. Uttaro *et al.* [225].

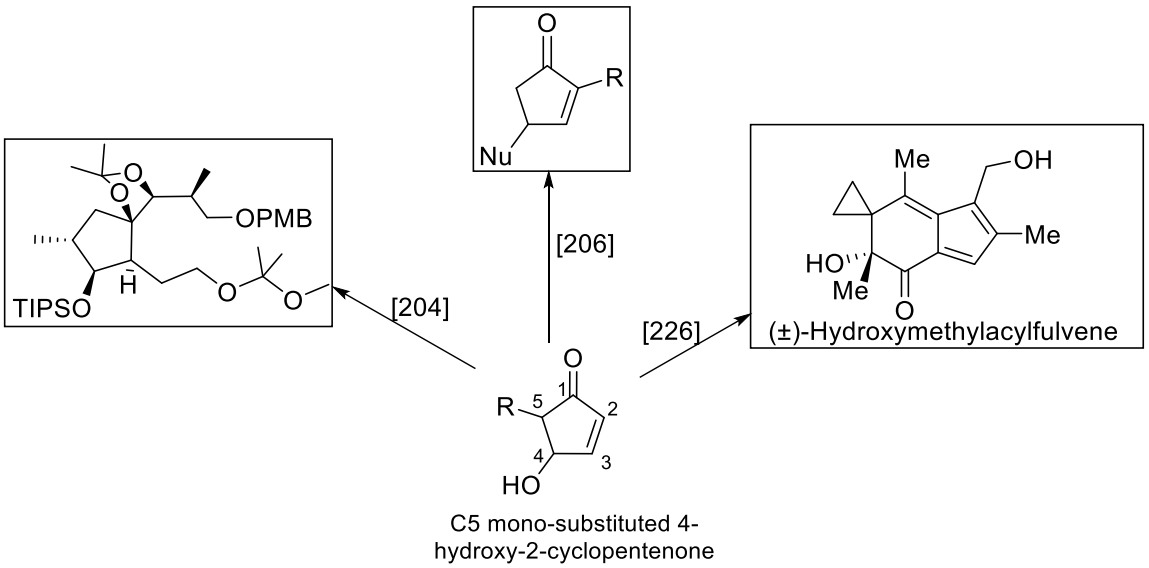
C3 substitution

Using a three component coupling similar to the synthesis of prostaglandins, Smith *et al.* [199] were able to successfully elucidate the synthesis of (+)-Hitachimycin, a macrocyclic antitumor antibiotic, also known as stubomycin (**Scheme 105**). The synthetic pathway design involves many steps, from the C3-substituted 4HCP. The procedures for the final steps include the Shioiri procedure, the Swern oxidation, Homer-Emmons macrocyclization induced from a deprotonation, DDQ oxidation and at last exposure of the penultimate compound to anhydrous trifluoroacetic acid, affording the synthetic (+)-hitachimycin identical to samples of the natural compound.



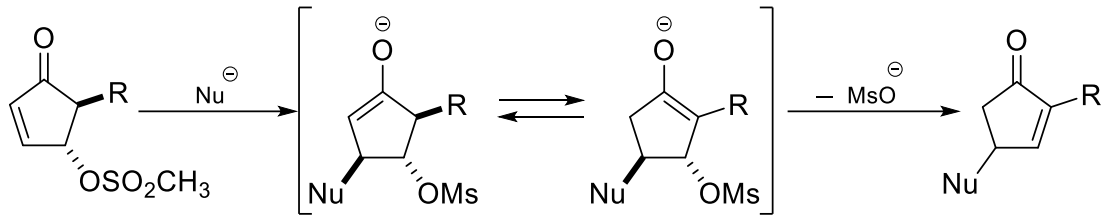
Scheme 105: Synthesis of (+)-Hitachimycin by Smith *et al.* [199].

C5 substitution



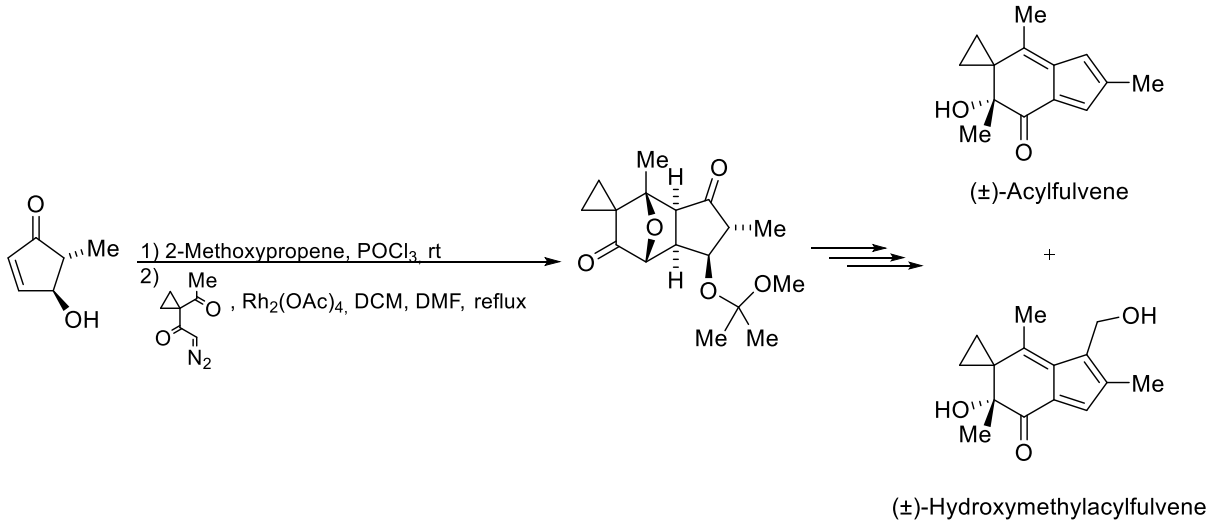
Scheme 106: C5 Mono-substituted 4-Hydroxy-2-cyclopentenones as starting material.

In 1993, F. G. West' and Gamini U. Gunawardena [206] studied the mechanism involving the addition of several nucleophiles to a C5-monosubstituted 4HCP, and concluded that the most likely mechanism is the one elucidated in **Scheme 106**. To support this conclusion, were design other possible mechanisms but he data obtained did meet those possibilities.



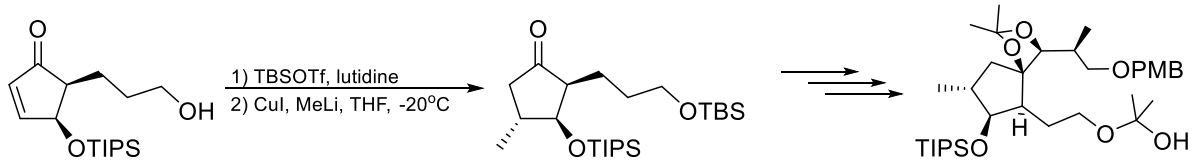
Scheme 107: Proposed mechanism involving the addition of several nucleophiles to a C5-monosubstituted 4HCP, design by F. G. West' and Gamini U. Gunawardena [206].

As its known, finding synthetic pathways to natural compounds is a major concern in the chemical word. As so, Trevor C. McMorris and his team [226] found a synthetic mean to obtain (±)-hydroxymethylacylfulvene, a derivative compound of the toxic sesquiterpene illudin S, produced in cultures of the basidiomycete *Omphalotus illudens.* This pathway (**Scheme 107**) involves a total of 14 steps from 4-hydroxy-5-methyl-2-cyclopenten-1-one, in which is possible to obtain the desired compound in 15% overall yield. The spectral analysis to compound achieved is identical to the ones from the hydroxymethylacylfulvene derived from illudin S.



Scheme 108: Synthetic pathway of Trevor C. McMorris *et al.* [226].

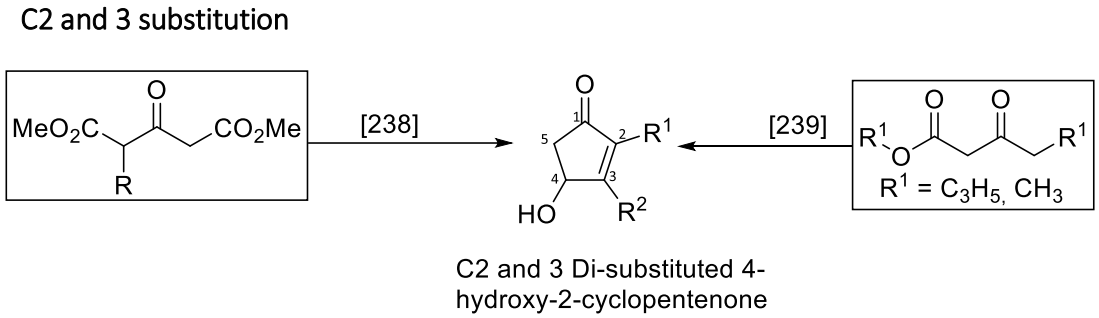
C. Lentsch and team [204] were able to synthetize the western fragment of Pl-3 in a stereoselective manner, through a quiral C5-monosubstititued 4HCP (**Scheme 108**). The technique chosen is similar to the two-coupling process and the desired product is achieved in 26% overall yield from the cyclopentenone.



Scheme 109: Method elucidated by C. Lentsch *et al.* [204].

Di-substituted 4-hydroxy-2-cyclopentenones and hydroxyl side chain derivatives

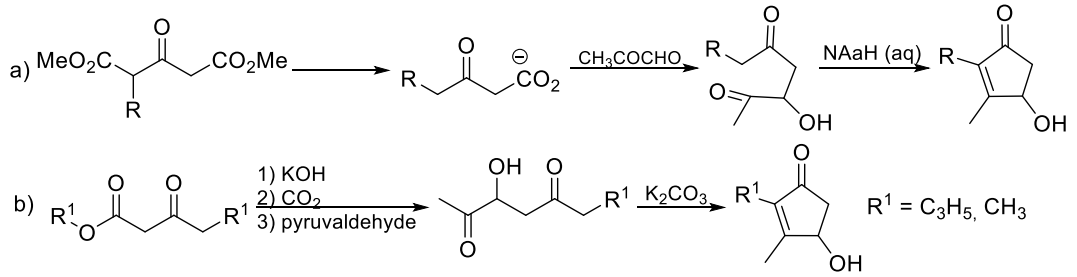
Construction of the di-substituted 4-hydroxy-2-cyclopentenone building block



Scheme 110: Sinthesis of C2 and C3 Di-substituted 4-Hydroxy-2-cyclopentenones.

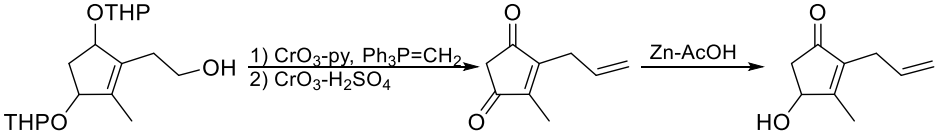
As described before, pyrethrin are a natural compounds with a potent insecticidal activity and many research groups attempt its synthesis [35, 227-231], or the synthesis of its derivatives, like rethrolone [232-236], but the most interesting synthesis is described by Noritada Matsuo *et al.* [237] in 1982 (**Scheme 110a)**). Tis method allows the possibility to synthesise derivatives from the pyrethrin.

In the study for the synthesis of pyrrole-substituted heteroaromatic derivatives, Christian Bongards *et al.* [238] synthesised a 4HCP as intermediary for further reactions (**Scheme 110b)**). The product obtained was similar to the one described before.



Scheme 111: Synthesis of a) Pyrethrin [237] and b) intermediary for pyrrole-substituted heteroaromatic derivatives [238].

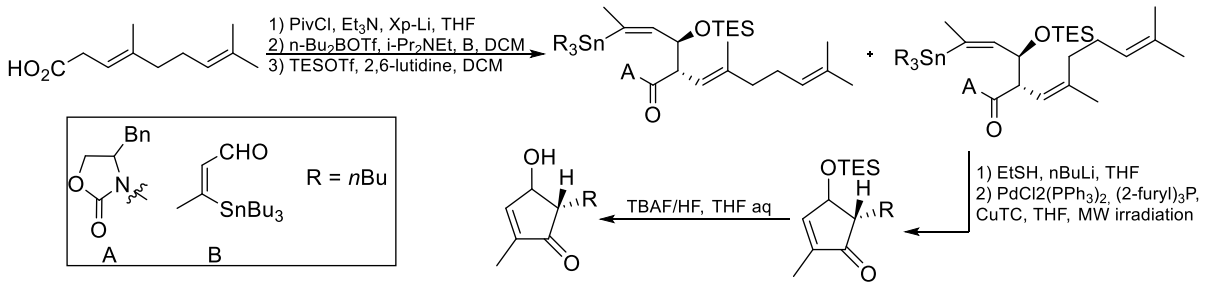
Tamotsu Fujisawa *et al.* [239] synthesise a 4HCP from tetrahydropyranylated triol (**Scheme 111**). This method uses known reactions as the Collins oxidation and Jones oxidation as key steps in the synthesis



Scheme 112: Synthetic method of Tamotsu Fujisawa *et al.* [239].

C2 and 5 substitution

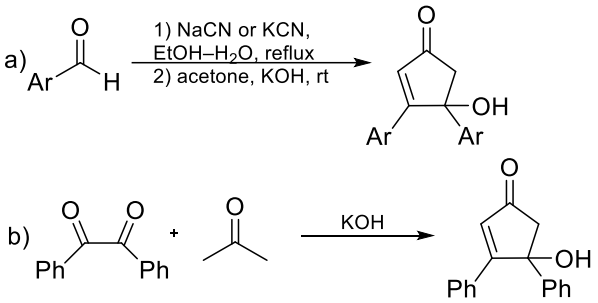
Akira Morita *et al.* [240, 241] describe the synthesis of litseaverticillol A and B (**Scheme 112**). This method requires six steps, starting with homogeranic acid. As key steps, can be highlighted, the employment of the Evans asymmetric aldol reaction and the microwave-promoted cyclization, as the C-C bond-forming steps.



Scheme 113: Sinthesis of C2 and C5 Di-substituted 4-Hydroxy-2-cyclopentenone, by Akira Morita *et al.* [240, 241].

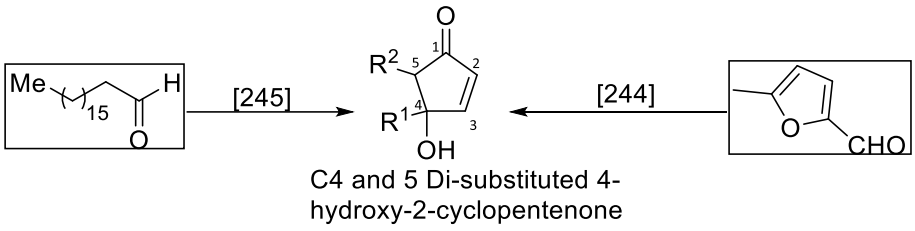
C3 and 4 substitution

David Bailey *et al.* [242] developed a method to synthetize 4HCP with different aromatic groups as substituents (**Scheme 113a)**). In this research a library of compounds is synthetized in order to be applied in Diels-Alder reactions. In similar manner, Arriola *et al.* [243], also synthetize a 4HCP (**Scheme 113b)**), to be posteriorly used in the synthesis of Ti complexes.



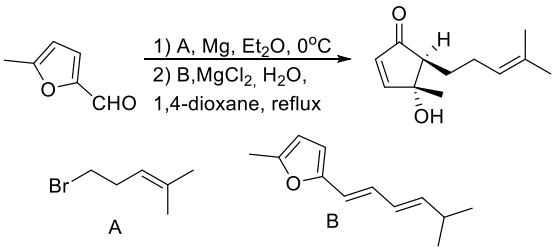
Scheme 114: Sinthesis of C2 and C5 Di-substituted 4-Hydroxy-2-cyclopentenones, by David Bailey *et al.* [242].

C4 and 5 substitution



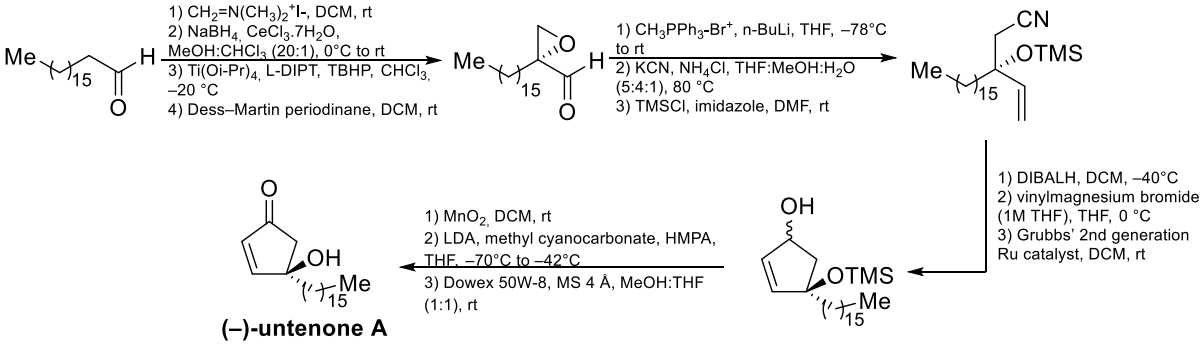
Scheme 115: : Sinthesis of C4 and C5 Di-substituted 4-Hydroxy-2-cyclopentenones.

R. Katsuta *et al.* [244] developed a simple synthetic pathway in order to achieve the 4HCP in **Scheme 115**. This compound was obtained in only two steps and in an overall yield of 54%.



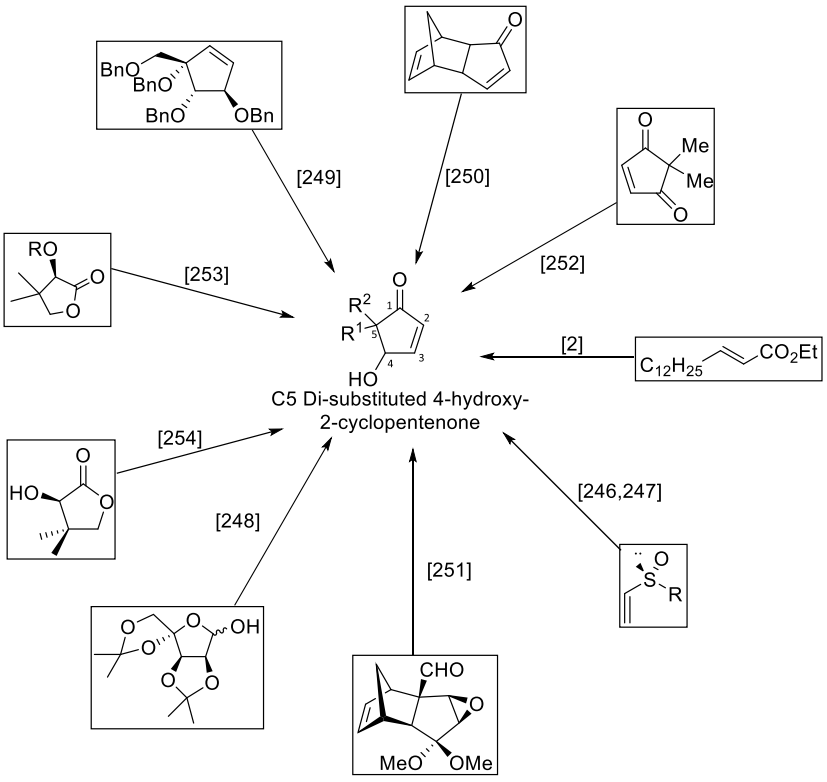
Scheme 116: Pathway developed by R. Katsuta *et al.* [244].

H. Mizutani *et al.* [245] were able to synthesize, enantioselectively, untenone A, a di substituted 4HCP , through ring-closing metathesis reaction as a key step in the construction of the cyclopentene ring.



Scheme 117: Synthesis of untenone A [245].

C5 substitution



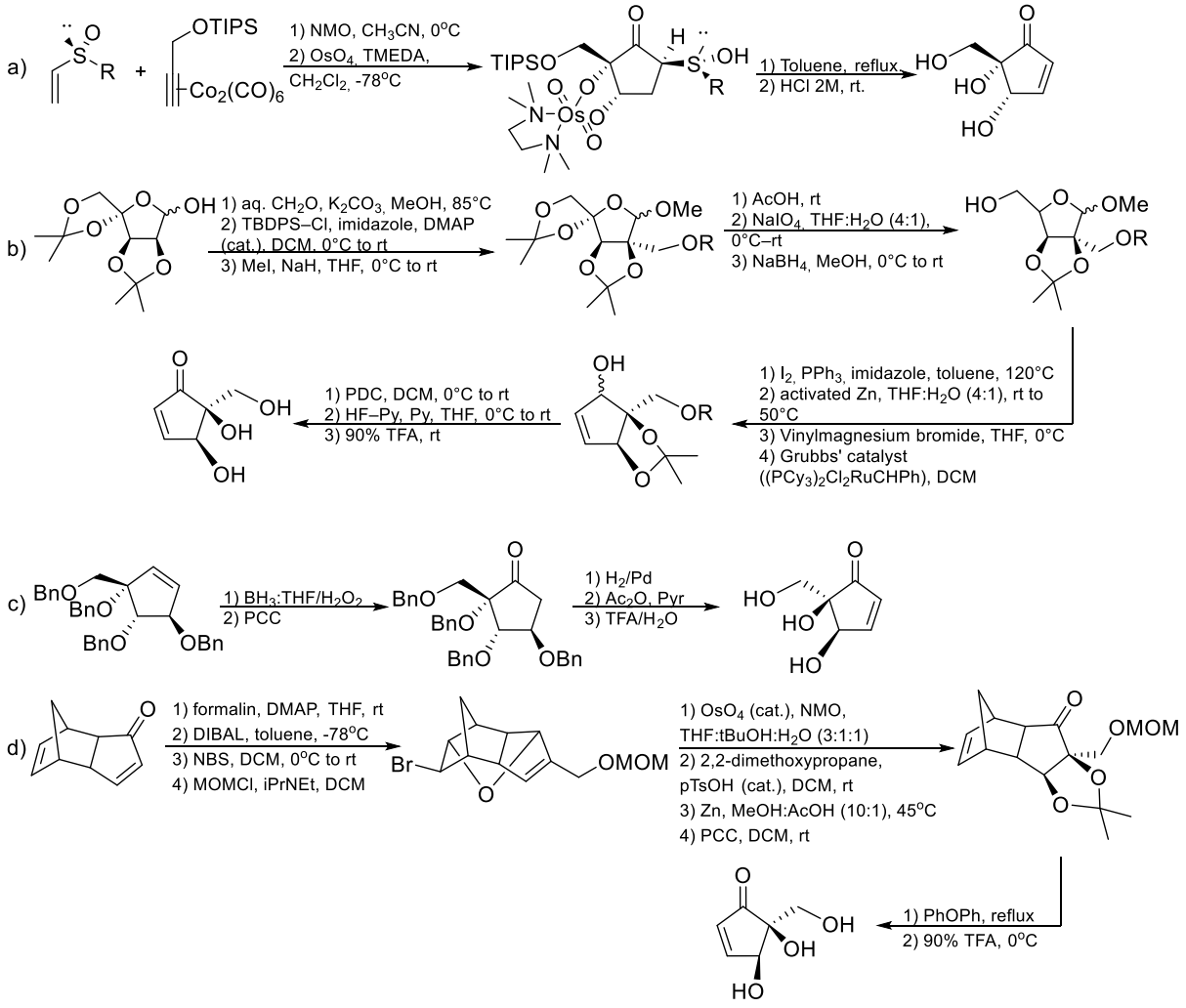
Scheme 118: Sinthesis of C5 Di-substituted 4-Hydroxy-2-cyclopentenones.

Pentenomycins are natural antibiotics and as so, its synthesis is of the utmost interest. Marta Rivero *et al.* [246, 247] synthesise (-)-pentenomycin I through a Pauson-Khand reaction with vinyl sulfoxides and cobalt-coordinating alkyne complexes (**Scheme 118a)**), in 27% yield.

G. Venkata Ramana *et al.* [248] approach this compound in a different manner, by using reductive iodo elimination and ring-closing metathesis from D-mannose. This method (**Scheme 118b)**) involves more steps and the yield, 9%, is lower than the one described before.

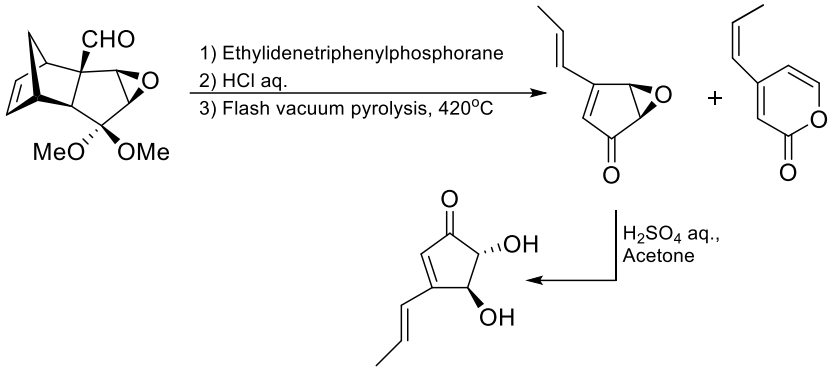
The most efficient and simple method is described by Mohindra Seepersaud *et al.* [249] were (-)-pentenomycin is synthetized in five steps an 46% yield (**Scheme 118c)**) from the key polyhydroxy cyclopentene

Tsutomu Sugahara *et al.* [250] developed a method for this synthesis with the Baylis-Hillman reaction as the key step, obtaining the (-)-pentenomycin in % yield (**Scheme 118d)**).



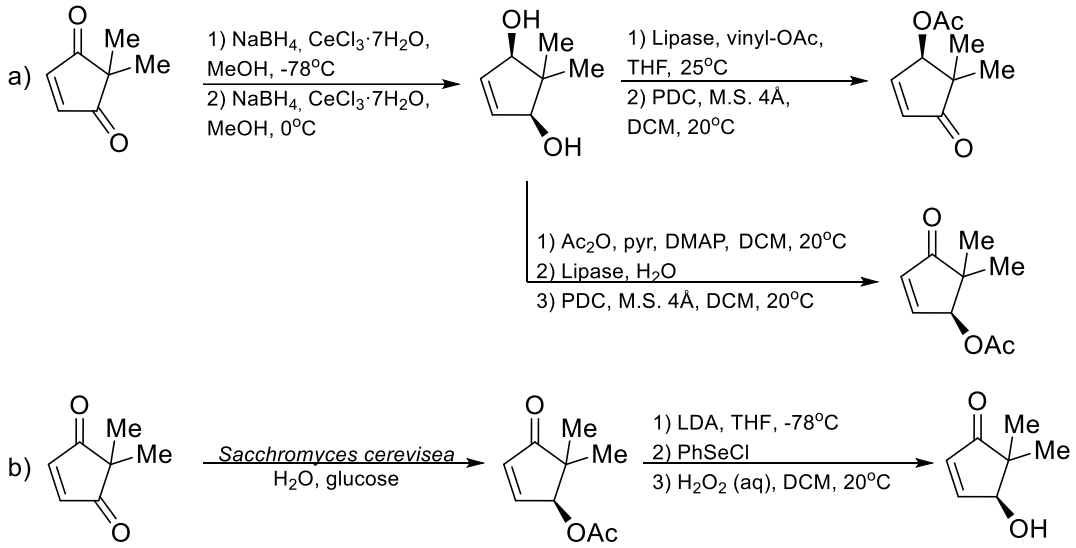
Scheme 119: Synthesis of (-)-pentenomycin I [246-250].

A.J.H. Klunder *et al.* [251] design a method that allowed the chemical synthesis of the natural compound, terrain. This synthesis involves several known reactions and procedures such as Wittig olefination and flash vacuum pyrolysis, affording terrain in four steps and 25% overall yield.



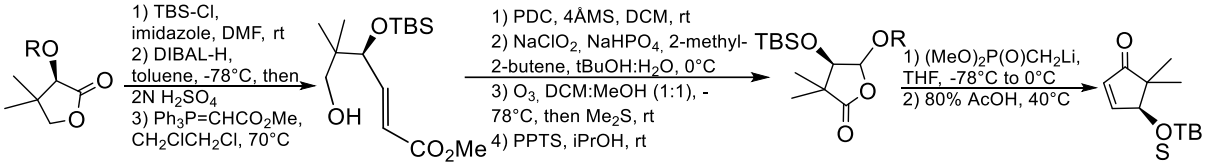
Scheme 120: Synthesis of terrain [251].

Wolfgang Kreiser *et al.* [252] synthesised di-substituted 4HCP as there are important building blocks for the synthesis of several natural compounds (**Scheme 120**). The method starts with an enedione and makes use of known reactions such as the Luche reduction or the reduction with sodium borohydride and cerium trichloride. Both enantiomers were obtained in 67 and 69%, for the (R) and (S) enantiomers, respectively.



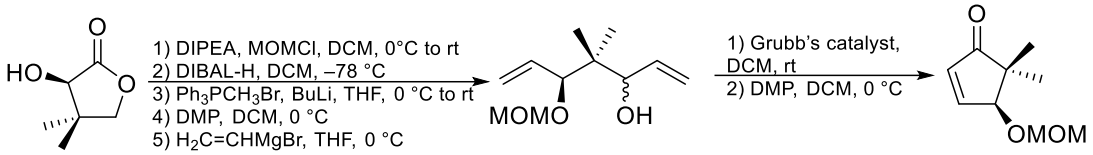
Scheme 121: Method developed by Wolfgang Kreiser *et al.* [252].

With the same goal, Hiroaki Miyaoka *et al.* [253] design a method for the synthesis of 4HCP (**Scheme 121**). This method provides the (R) enantiomer in 34%.



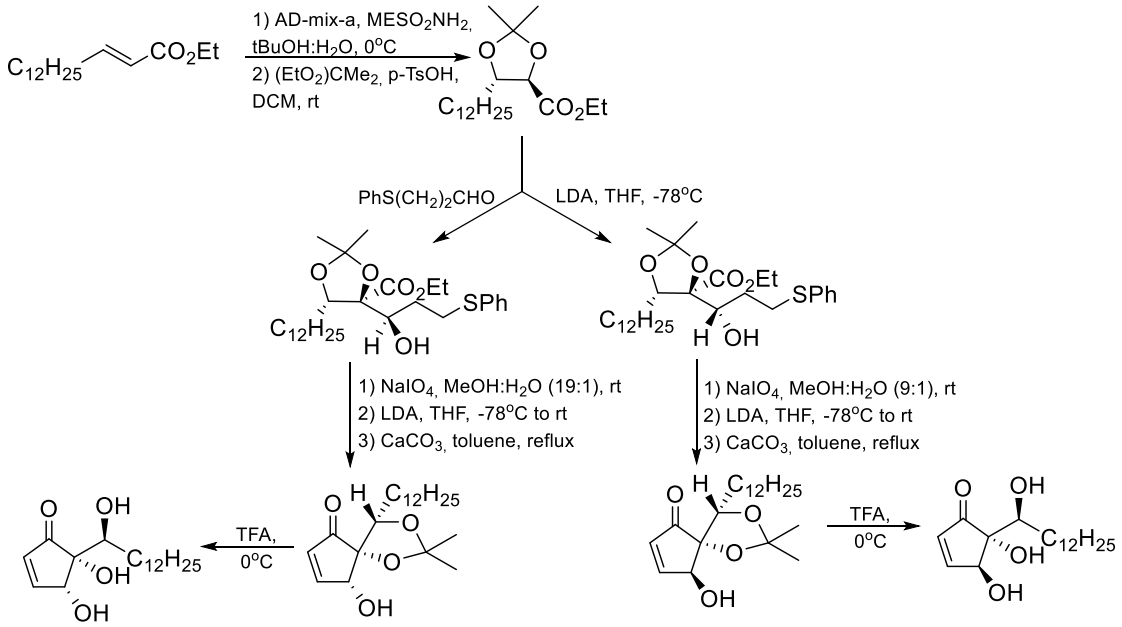
Scheme 122: Pathway of Hiroaki Miyaoka *et al.* [253].

Atul K. Hajare *et al.* [254] synthesise a di-substituted 4HCP in their studies of the *cis*- and *trans*-chrysanthemic acids compounds (**Scheme 122**). The synthesis involves seven steps and delivers the 4HCP in 35% yield.



Scheme 123: Synthetic pathway developed by Atul K. Hajare *et al.* [254].

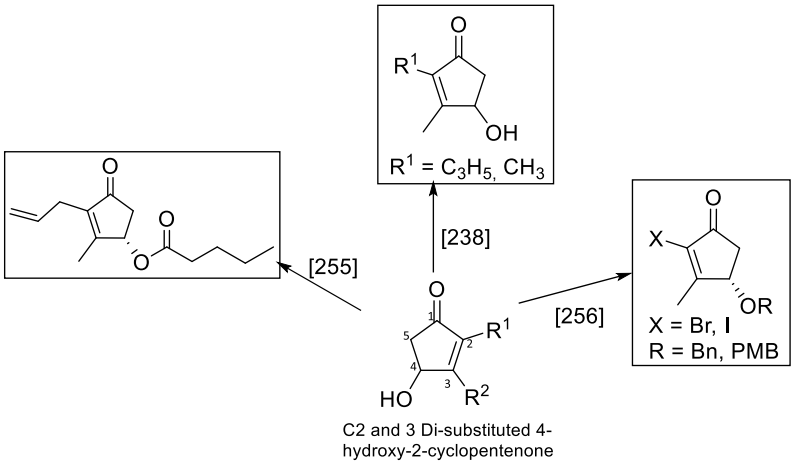
Eileen Bette *et al.* [2] also describe, not only the isolation Hygrophorone B, but also the total synthesis of Hygrophorone A and B (**Scheme 123**). The compounds were accomplished in nine steps with an overall yield of 12%, for the case of Hygrophorone B.



Scheme 124: Synthesis of Hygrophorone B [2].

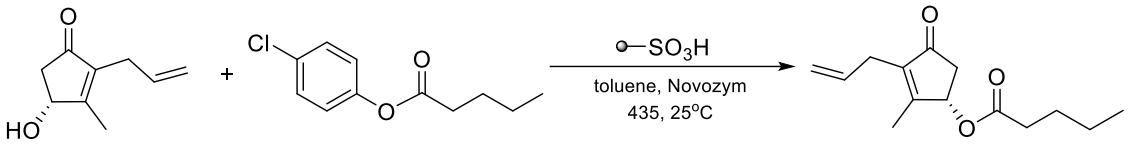
Di-substituted 4-hydroxy-2-cyclopentenones as starting material

C2 and 3 substitution



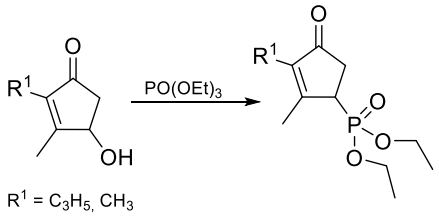
Scheme 125: : C2 and C3 Di-substituted 4-Hydroxy-2-cyclopentenones as starting material.

Jian-Ping Wu *et al.* [255] used a 4HCP in the study of a new highly efficient dynamic kinetic resolution system (**Scheme 125**) for secondary aromatic alcohol using low-cost sulfonated sepiolite as a racemization catalyst. This is greener than the ones developed before, as it operates at 25°C. The products were obtained with good ee_p (>99%) and substrate conversion ratio (>99%).



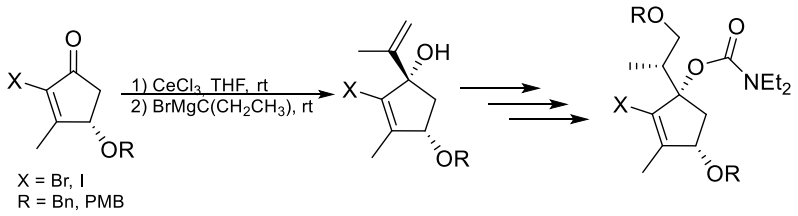
Scheme 126: Synthectic studies of Jian-Ping Wu *et al.* [255].

Christian Bongards *et al.* [238] used a previously synthesised 4HCP Michaelis–Arbuzov reaction with triethyl phosphite (**Scheme 126**), in order to obtain a novel cyclopentenones phosphonated in the 4th position.



Scheme 127: Michaelis–Arbuzov reaction developed by Christian Bongards *et al.* [238].

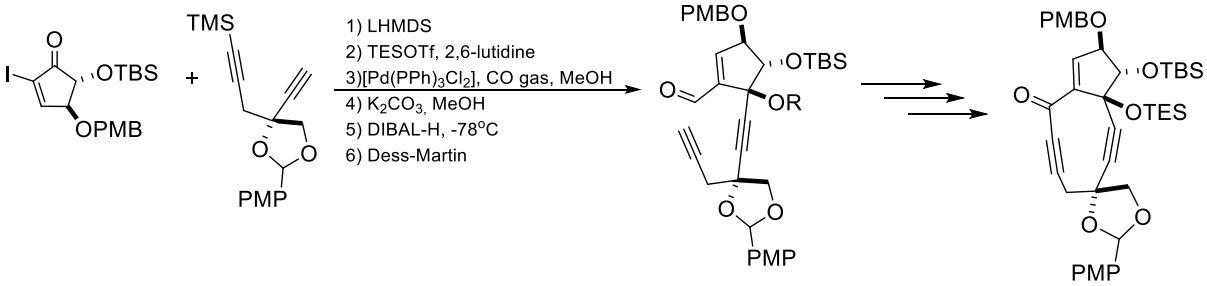
Anja Richter *et al.* [256] used a di-substituted 4HCP as starting material in the synthesis of a fragment of the natural compound Fusicoccin A (**Scheme 127**). This method used reactions such as asymmetric hydroboration with (+)-$(Ipc)_2BH$ and regular alcohol protections, to achieve the fragment with great success.



Scheme 128: Synthesis of Fusicoccin A [256].

C2 and 5 substitution

The synthesis of Cyanosporasides was achieved by Kei Yamada *et al.* [244] through a common precursor which synthesis starts with a 4HCP (**Scheme 128**). The synthesis to the final compounds is long and the overall yields are low, but the intermediary was obtained in 13% overall yield.



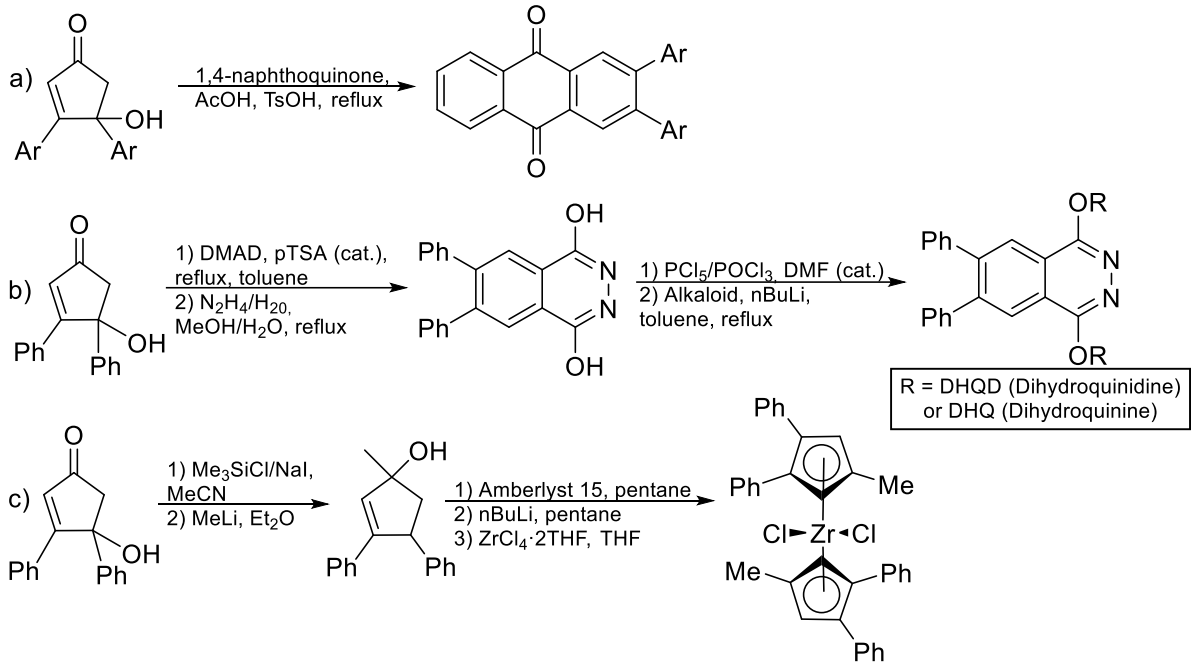
Scheme 129: C2 and C5 Di-substituted 4-Hydroxy-2-cyclopentenones as starting material.

C3 and 4 substitution

David Bailey *et al.* [242] applied several 4HCP in Diels–Alder reactions to afford highly substituted benzene derivatives. Several compounds were synthesised, in very low yields, but having the advantage of an inexpensive starting material and only one step (**Scheme 129a)**).

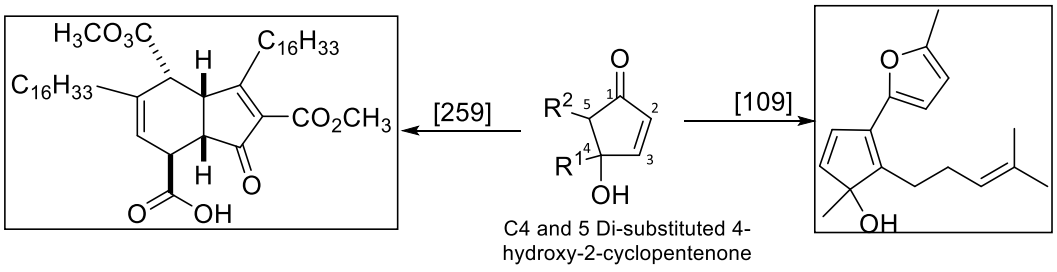
Heinrich Becker *et al.* [257] used a similar starting material to achieve new ligands for the improvement of the asymmetric dihydroxylation of olefins (**Scheme 129b)**).

The same 4HCP was used by Eleonora Polo *et al.* [258] to achieve the synthesis of zirconium complexes, as shown in **Scheme 129c)**. Other complexes, using the same 4HCP as starting material were synthesised by Arriola *et al.* [243].



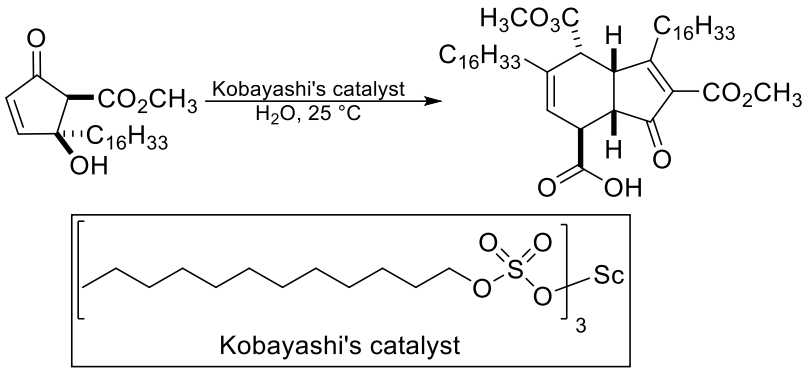
Scheme 130: C3 and C4 Di-substituted 4-Hydroxy-2-cyclopentenones as starting material.

C4 and 5 substitution



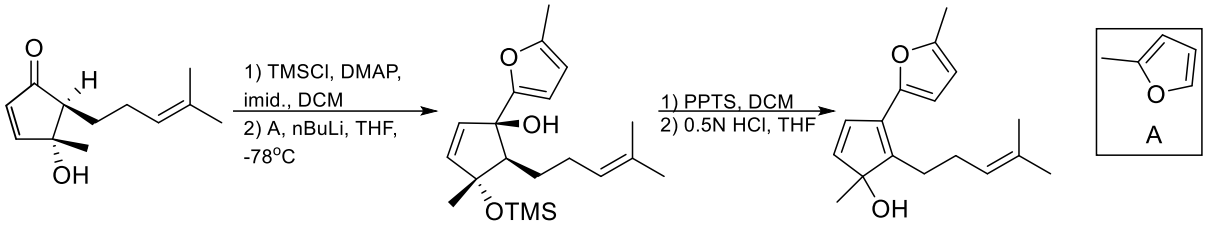
Scheme 131: C4 and C5 Di-substituted 4-Hydroxy-2-cyclopentenones as starting material.

Manzamenone A, as a natural compound catches the interest of many research groups for its synthesis [259-264]. The most interesting of those, described by J. R. Doncaster et al. [259], involving Kobayashi's surfactant catalyst and a 4HCP, giving the desired product in 78% yield in one step (**Scheme 132**).



Scheme 132: Synthesis of Manzamenone A [259].

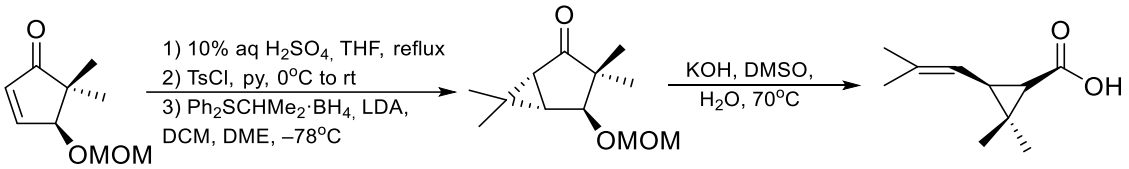
R. Katsuta *et al.* [109] achieved the synthesis of the core of framework of the proposed structure of sargafuran (**Scheme 132**), in in six steps and in 29% overall yield, from a previously synthetized di-substituted 4HCP.



Scheme 133: Method developed by R. Katsuta *et al.* [109].

C5 substitution

Atul K. Hajare *et al.* [254] synthesise *cis*-chrysanthemic acid (**Scheme 133**) from a previously synthesised 4HCP. This compound was obtained through known reactions in 32% overall yield.



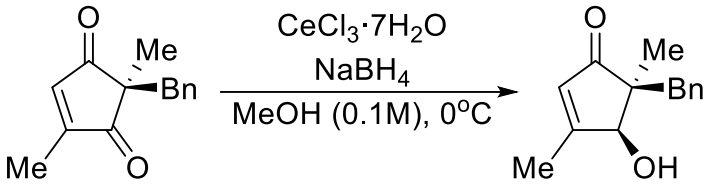
Scheme 134: Synthesise *cis*-chrysanthemic acid [254].

Tri-substituted 4-hydroxy-2-cyclopentenones and hydroxyl side chain derivatives

Construction of the tri-substituted 4-hydroxy-2-cyclopentenone building block

C3 and 5 substitution

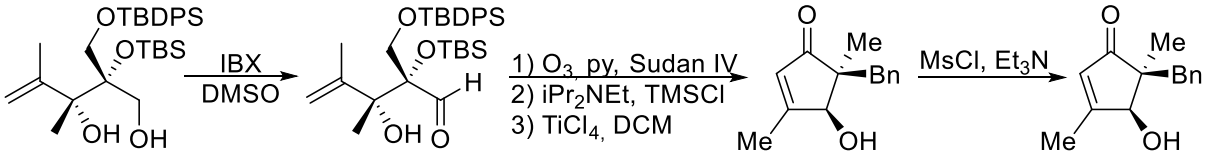
In order to show the utility of their synthetized desymmetrized cyclopentene-1,3-diones, Madhu Sudan Manna and Santanu Mukherjee [265] made a regioselective reduction reaction, under Luche conditions, to synthetize a tri-substituted 4HCP in 55% yield (**Scheme 134**).



Scheme 135: Synthetic pathway of Madhu Sudan Manna and Santanu Mukherjee [265].

C4 and 5 substitution

To show the potential of the vicinal tertiary diols, Brad M. Loertscher *et al.*[266] synthetize a tri-substituted 4HCP through oxidation of the primary alcohol, a one-pot ozonolysis/aldol cyclization process and at last selective dehydration, to afford the cyclopentenone in 38% yield (**Scheme 135**).



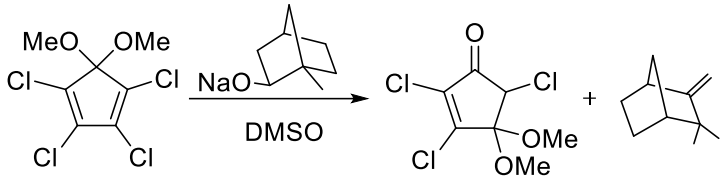
Scheme 136: Method elucidated by Brad M. Loertscher *et al.*[266].

Tetra-substituted 4-hydroxy-2-cyclopentenones and hydroxyl side chain derivatives

Construction of the tetra-substituted 4-hydroxy-2-cyclopentenone building block

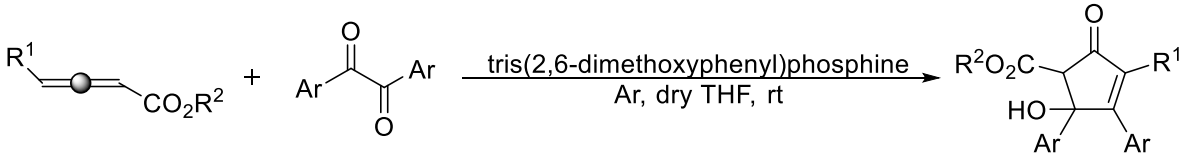
C2, 3, 4 and 5 substitutions

In 1996 O. M. Kuznetsov *et al.* [267] suggested a rather simple method with the addition of sodium alkoxide to a cyclopentadiene in DMSO. The tetra-substituted cyclopentenone is obtained after a month in 48% (**Scheme 136**).



Scheme 137: Method developed by O. M. Kuznetsov *et al.* [267].

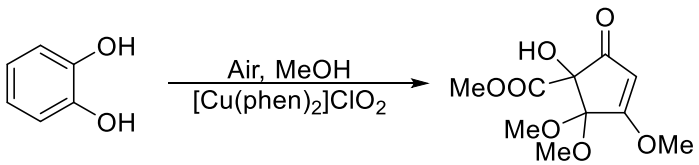
Anu Jose *et al.* [268] synthetized a series of tetra-substituted cyclopentenones in the scope of their work on the chemistry of zwitterions (**Scheme 137**), elucidating the optimised reaction conditions, with several subtracts, obtaining yields between 65 and 96%.



Scheme 138: Synthesis of Anu Jose *et al.* [268].

C3, 4 and 5 substitutions

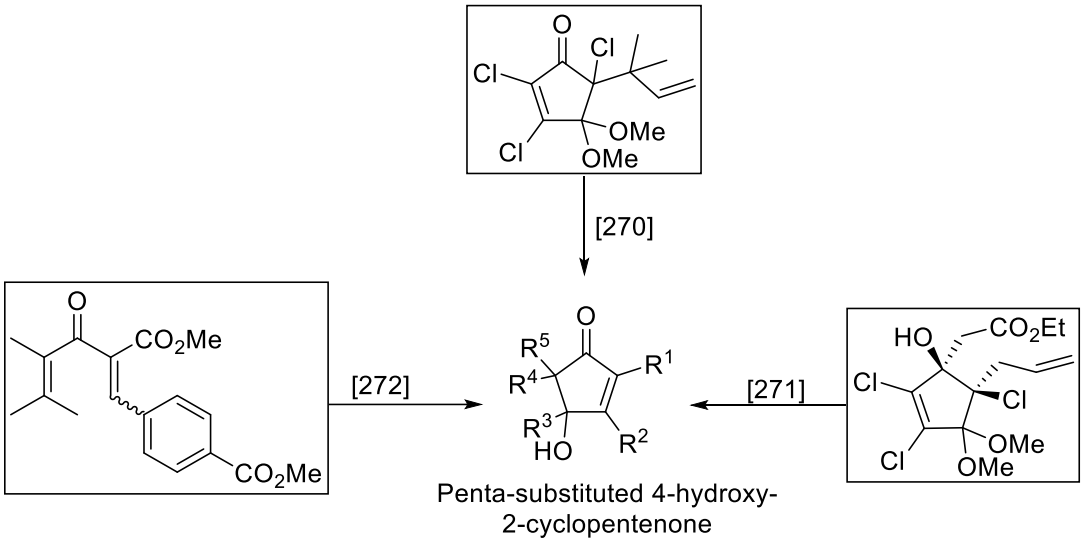
Md. Munkir Hossain *et al.* [269] discovered a way to synthetize the tetra-substituted cyclopentenone in **Scheme 138**, studying the unique aerobic oxidation of catechol with the complex $[Cu(phen)_2]ClO_2$ in MeOH. This cyclopentenone was obtained in 14% yield, after 40 hours of strirring the solution at room temperature and is the result of contraction of the aromatic ring of catechol through C–C bond-breaking and bond-making reaction, though the mechanism of this transformation is unknown.



Scheme 139: Synthetic pathway of Md. Munkir Hossain *et al.* [269].

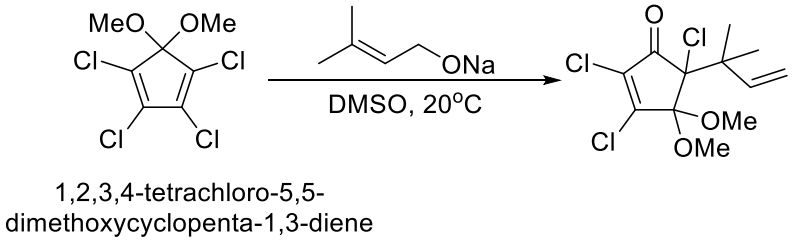
Penta-substituted 4-hydroxy-2-cyclopentenones and hydroxyl side chain derivatives

Construction of the penta-substituted 4-Hydroxy-2-cyclopentenone building block



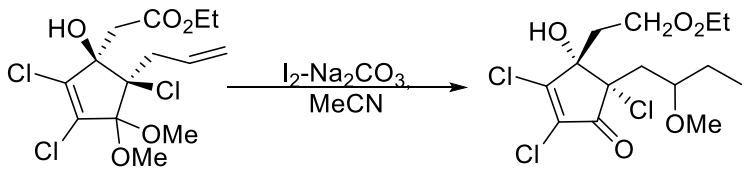
Scheme 140: Synthesis described to the construction of the Tetra-substituted 4-Hydroxy-2-cyclopentenone building block.

F. A. Gimalova *et al.* [270] synthetized a penta-substituted cyclopentenone using a previous developed procedure, starting with 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene and prenol, obtaining yields between 40 and 50% (**Scheme 140**).



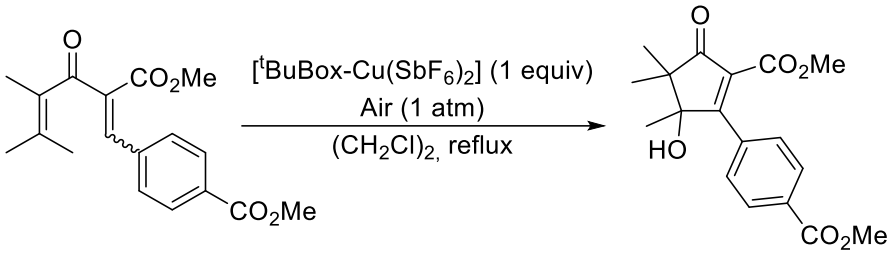
Scheme 141: Synthesis of F. A. Gimalova *et al.* [270].

Vostrikov *et al.* [271], synthetized a penta-substituted cyclopentenone in 51% yield recurring to a reaction with iodine in the presence of sodium carbonate (**Scheme 141**), similar to the method used before to synthetize an analogue of 1,2-adduct.



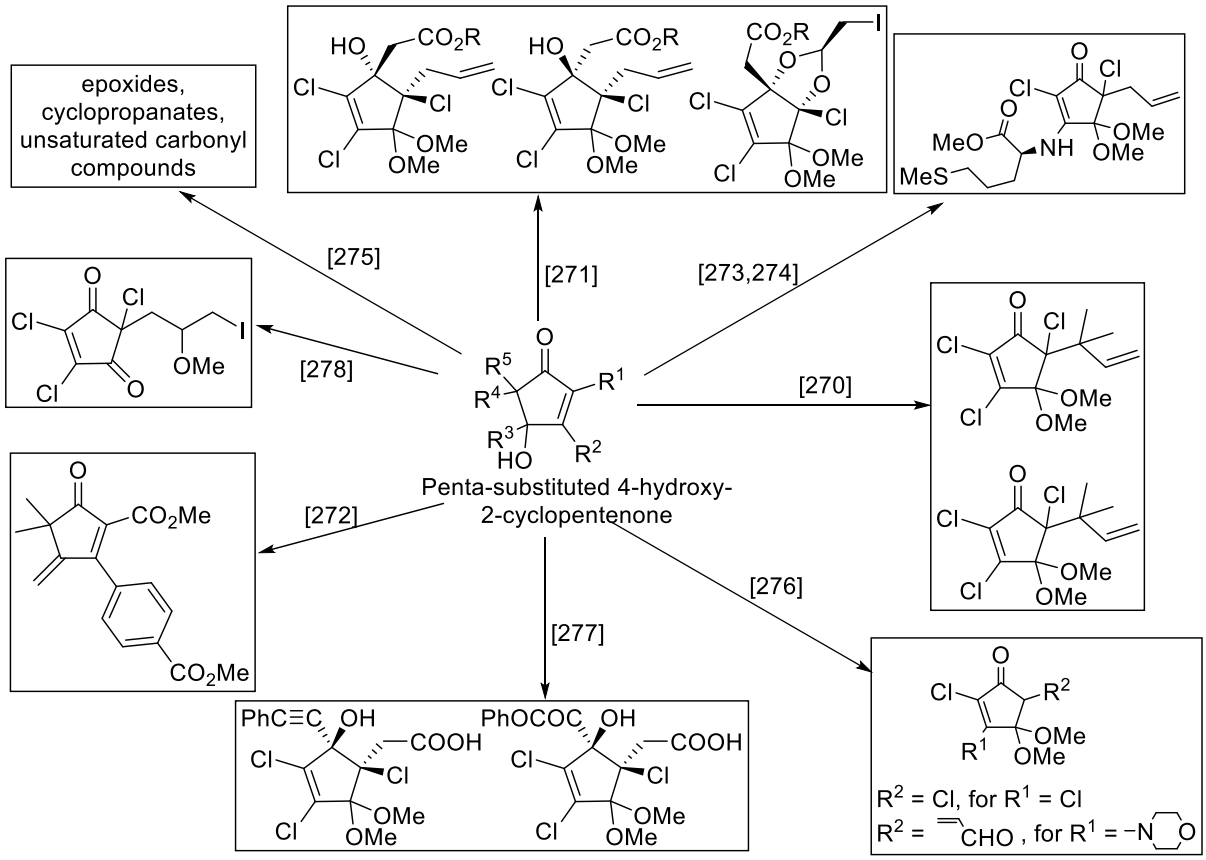
Scheme 142: Method used by Vostrikov *et al.* [271].

In light of mechanistical studies to the synthesis of 4-alkylidene cyclopentenones, A. J. Frontier *et al.* [272], were able to synthetize a penta-substituted 4HCP in 22% yield, in a rather simple method (**Scheme 142**).



Scheme 143: Synthesis of A. J. Frontier *et al.* [272].

Penta-substituted 4-hydroxy-2-cyclopentenone as starting material



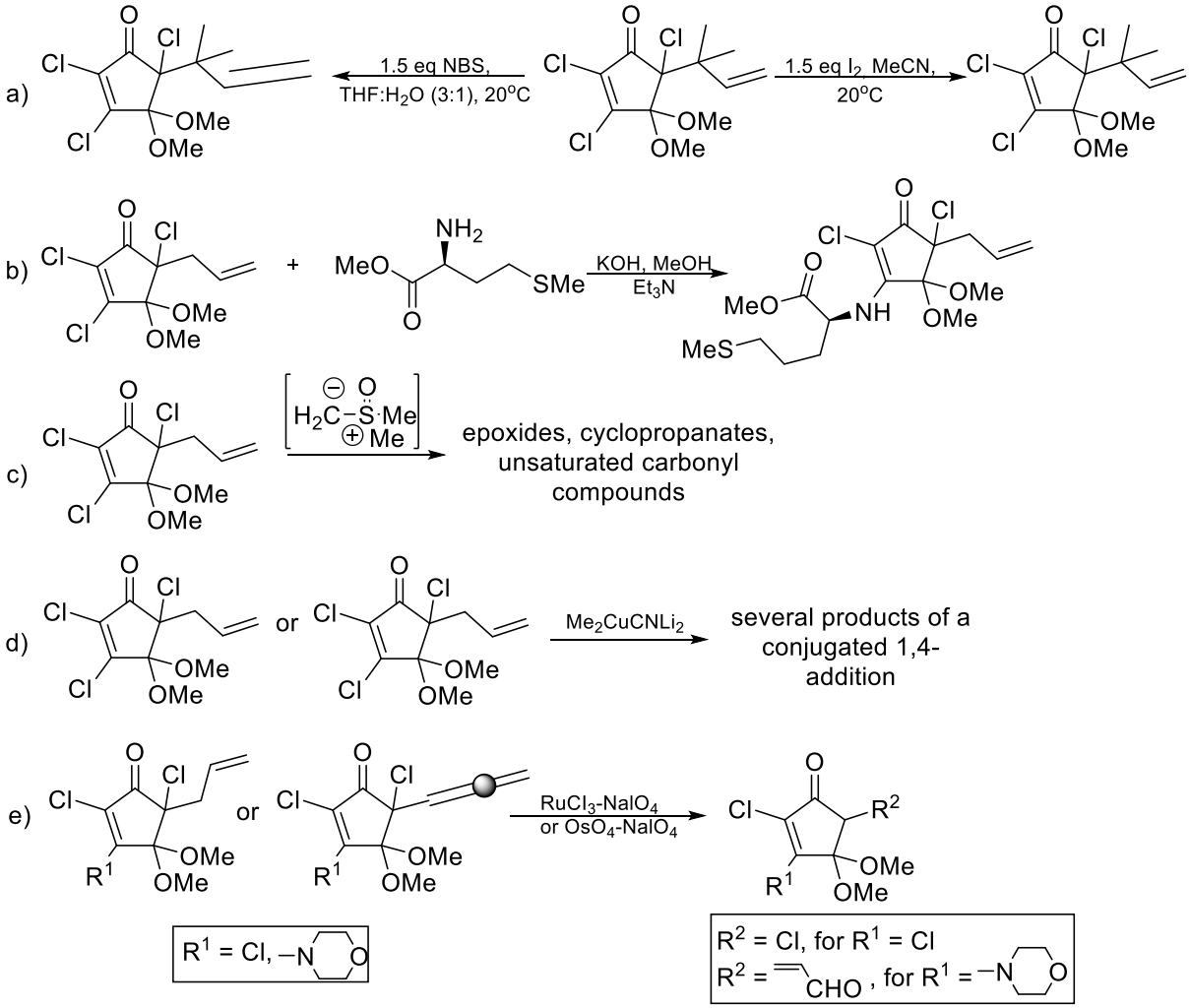
Scheme 144: Penta-substituted cyclopentenone as starting material.

In order to achieve a building block for the eight membered ring of taxol, F. A. Gimalova *et al.* [270] synthetized two similar compounds. The compound on the left in **Scheme 144a)** was obtained with almost quantitative yield by the addition of NBS, in aqueous THF, to the penta-substituted cyclopentenone previously synthetized. The compound on the right was obtained in only 40% yield with the addition of I_2 to the same 4HCP.

A similar starting material was used by V. A. Egorov *et al.* [273, 274] in the conjugation of penta-substituted 4HCP to different amino-acids (**Scheme 144b)**). In their synthesis was obtained a mixture of diastereoisomers that were isolated with 35% yield of the diastereomerically pure isomer R. In their last work was also used a tetra-substituted 4HCP in the exact same conditions to give a similar product. While N. A. Ivanova and co-workers [267] studied the properties and synthetic applications of the same starting material, making it react with dimethylsulfoxonium methylide to give several compounds such as epoxides, cyclopropanates and α,β-unsaturated carbonyl compounds (**Scheme 144c)**).

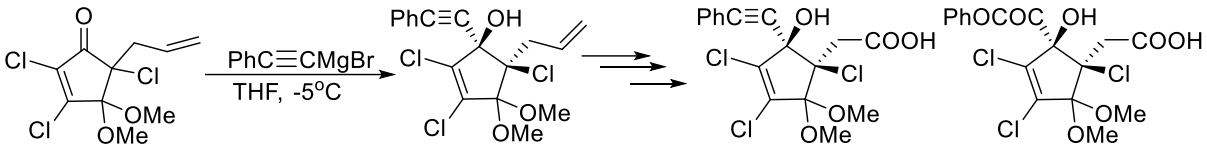
R. R. Akhmetvaleev *et al.* [275] used the same starting material, although, in a different study. This study involves the reaction of the cyclopentenone in a conjugated 1,4-addition with dimethyldilithium cyanocuprate (**Scheme 144d)**). The conclusions retained from this study were that the substituted 4HCP used are good acceptors of nucleophiles in the Michael reaction with $Me_2CuCNLi_2$, reacting according to the Ad_NE-mechanism.

N. S. Vostrikov *et al.* [276] studied the effects of selective ozonolysis in the cleavage of the exocyclic double bond on a similar penta-substituted 4HCP as before (**Scheme 144e)**) but, with different catalytic systems.



Scheme 145: Synthesis of several penta-substituted cyclopentenones [267, 273-276].

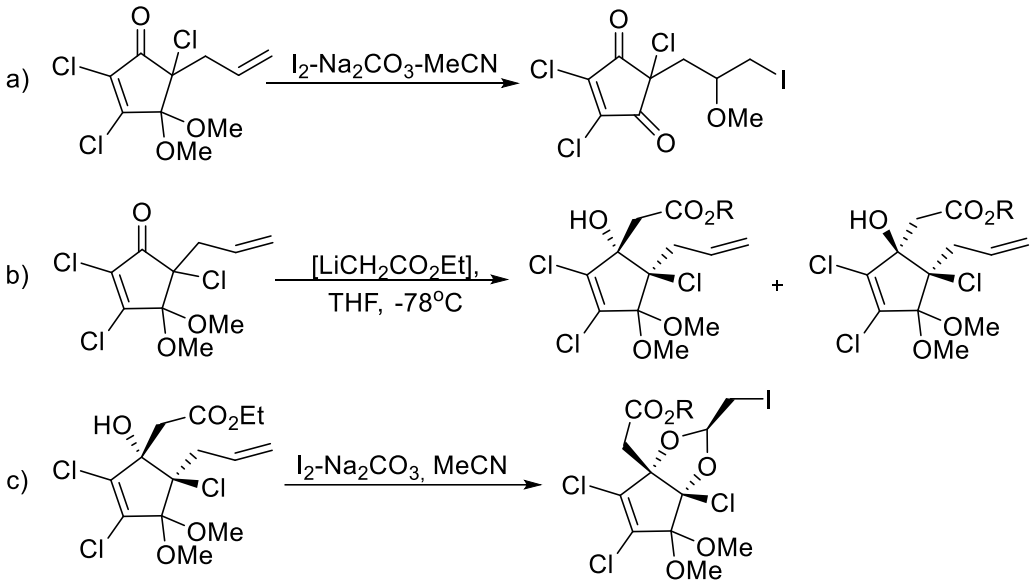
In 2001, Akbutina *et al.*[277] synthetize analogues of marine prostenoids, recurring to some well-known transformations beginning with a penta-substituted cyclopentenone (**Scheme 145**).



Scheme 146: Method elucidated by Akbutina *et al.*[277].

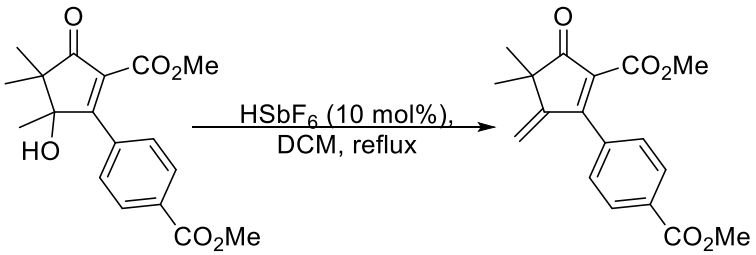
Vostrikov and team [278] synthetize in 2001, the 2,4,5-trichloro-2-(3-iodo-2-methoxypropyl)cyclopent-4-ene-1,3-dione regarding the study of the intramolecular migration of one methoxy group in the penta-substituted cyclopentenone (**Scheme 146a)**). The product was obtained in 65% yield with a rather straightforward method.

In continuation of their previous work, Vostrikov *et al.* [271] synthetize a series of 1,2-adducts at the carbonyl group of a penta-substituted 4HCP, catalysing the reaction with lithium, obtaining yields above 90% (**Scheme 146b) and c)**).



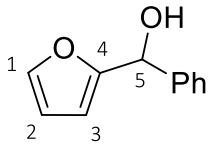
Scheme 147: Pathways used by Vostrikov *et al.* [271, 278].

Having synthetized the cyclopentenone in **Scheme 147**, A. J. Frontier *et al.* [272] proceeded to the synthesis of their desired compound, the 4-alkylidene cyclopentenone. Through a dehydration with a catalytic amount of $HSbF_6$ (10 mol%) (**Scheme 147**), the penta-substituted 4HCP was totally converted in the desired product.



Scheme 148: Pathway chosen by A. J. Frontier *et al.* [272].

Structures of compounds synthesized or attempted



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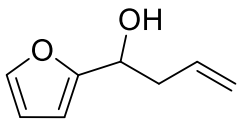

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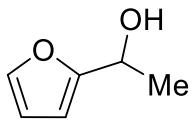

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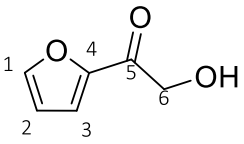

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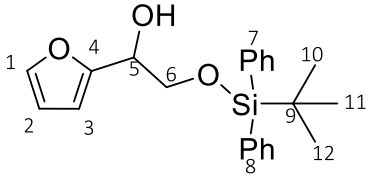

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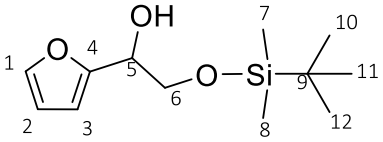

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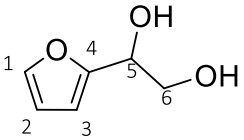

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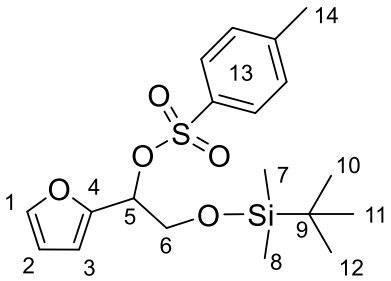

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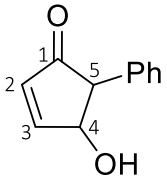

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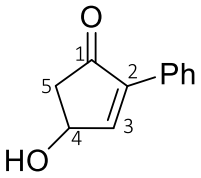

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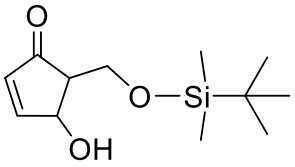

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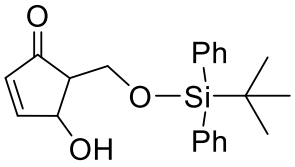

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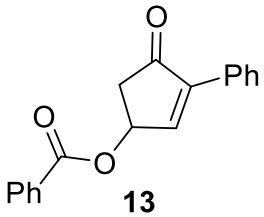
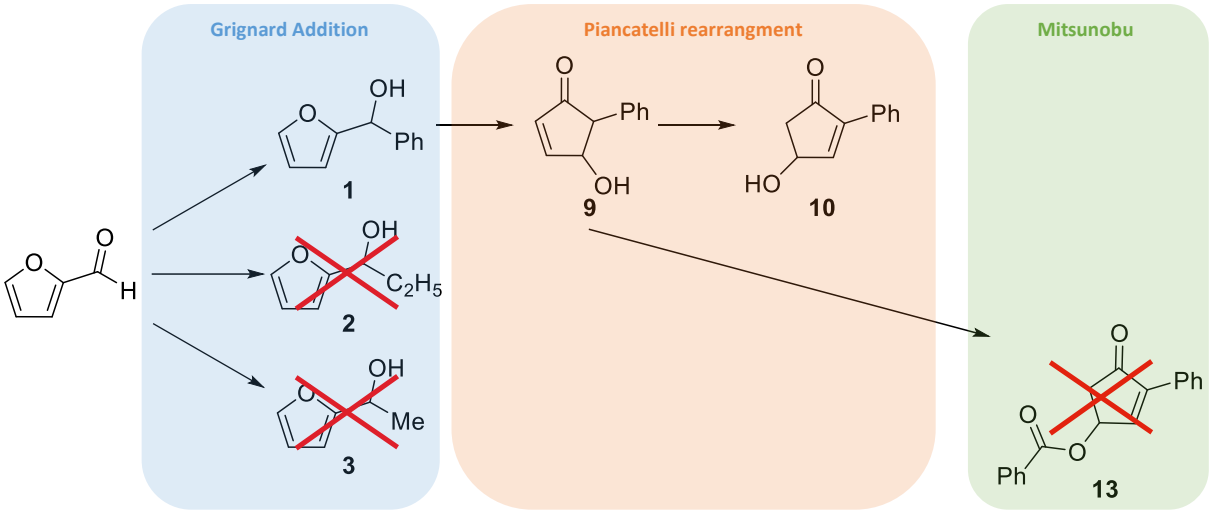


13

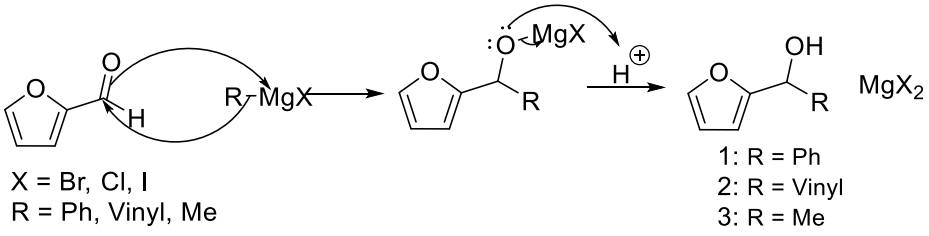
The need for discovery of new bioactive molecules is growing every day. To give a response to this crescent need, scientists attempt every day to found new methodologies, with known bio molecules, to form building block useful for a variety of new drugs.

With this interest at heart, several attempts were made in the effort to synthesised new building blocks from sugar based bio renewable resources, as HMF, furfural and other similar derivatives (**Scheme 148**). Innumerous set backs were encountered, as predicted, but the overall results can be considerate as progress in this area.



Scheme 149: First attempts in the synthesis of cyclopentenones.

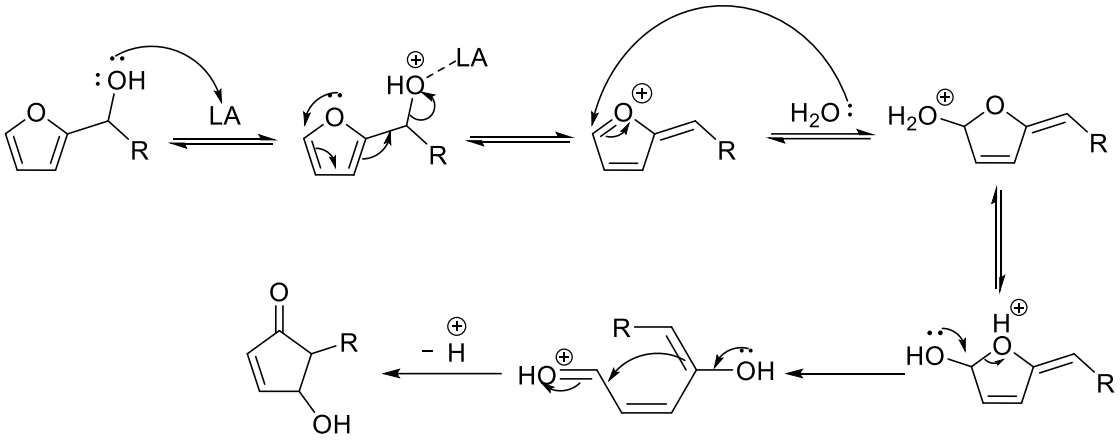
The synthesis of compound 1 was achieved through a Grignard addition to furfural [279] (**Scheme 149**). Attempts were made with a Grignard reagent synthetized *in situ* but better yields were obtained with the commercial solution. The conducted NMR analysis of the product was in agreement with the literature [179].



Scheme 150: Mechanism of the addition of Grignard reagent.

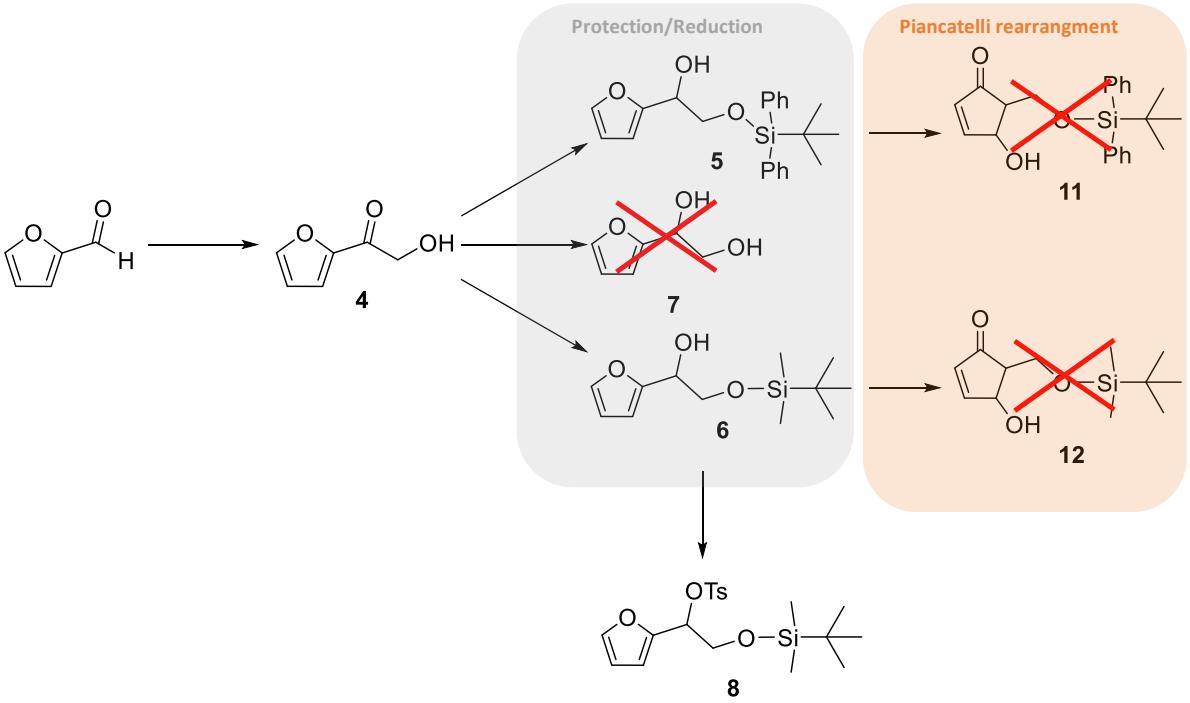
The synthesis of the compounds 2 and 3 was explored via Grignard addition procedure [279]. In the case of compound 2, the product degraded on silica upon the purification step, so this synthesis was abandoned. Compound 3, revealed to be more difficult to synthesise than the previous two and much more unstable to temperature and air conditions, so this synthesis was also abandoned.

For the synthesis of 4-hydroxy-5-phenylcyclopent-2-en-1-one, compound 9 [280], and 4-hydroxy-2-phenylcyclopent-2-en-1-one, compound 10 [188], was used the Piancatelli rearrangement (**Scheme 150**), using compound 1 as starting material. For both compounds was followed the method exactly as described [188, 280], so the yields obtained for both compounds were very good, above 90%, and NMR analysis was according the literature. Compound 9 was found to be unstable in silica, so it's not recommended its application in silica upon purification.



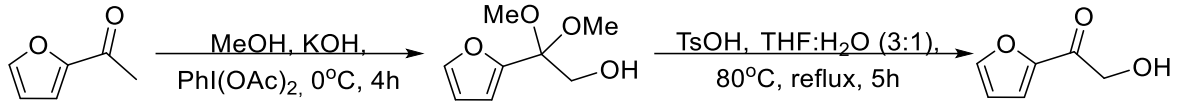
Scheme 151: Mechanism accepted as the Piancatelli rearangment mechanism.

The product obtained from the Mitsunobu reaction was speculated to be compound 13, but it was too unstable and degraded to be absolutely sure that the compound was indeed formed. Due to this instability this pathway was abandoned and others more viable were perused.

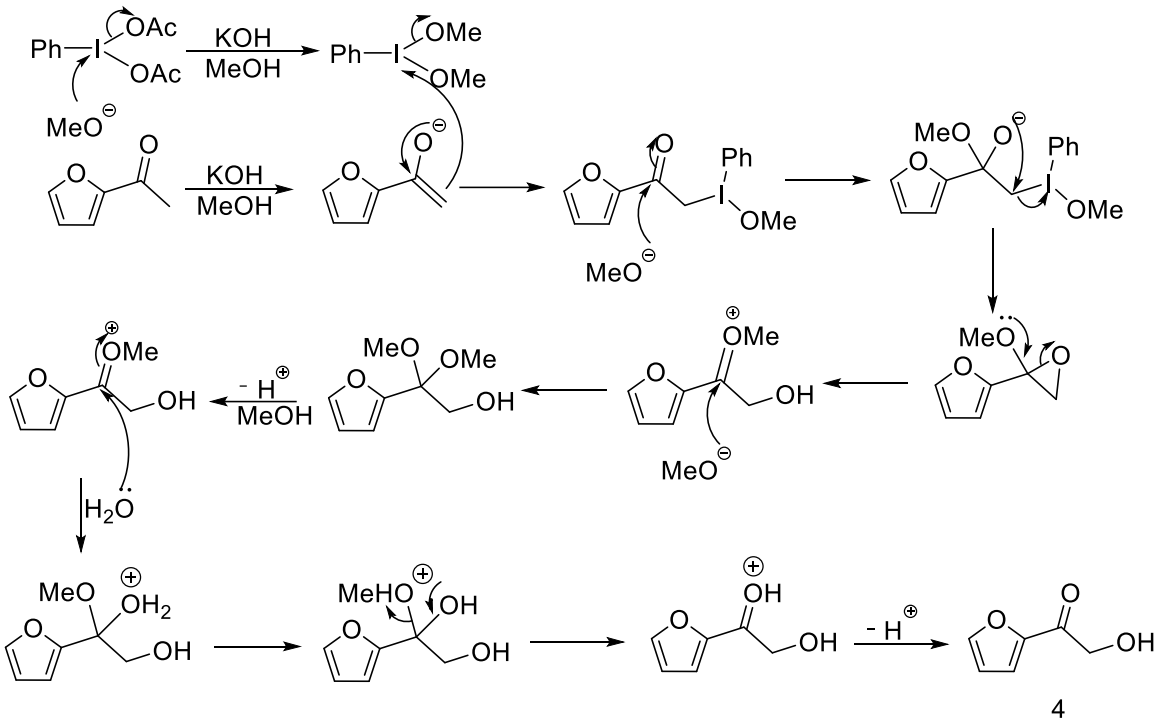


Scheme 152: Second attempts in the synthesis of cyclopentenones.

The method chosen for the synthesis of compound 4 was the hypervalent iodine reaction (**Scheme 153**), a method previously described in literature [281] (**Scheme 152**), but with lower yield and two steps with an unstable intermediary compound, which degraded with temperature (upon evaporation of the solvents) and air exposure, caused difficulties in the purification process. The higher yield obtained in this method is thanks to the acidic quenching process applied which avoids the unnecessary second step, preventing thus the exposure of its not very stable intermediary, through the hydrolysis of the ketal. NMR analysis of the compound was in agreement with the literature found for the 1-(furan-2-yl)-2-hydroxyethan-1-one.

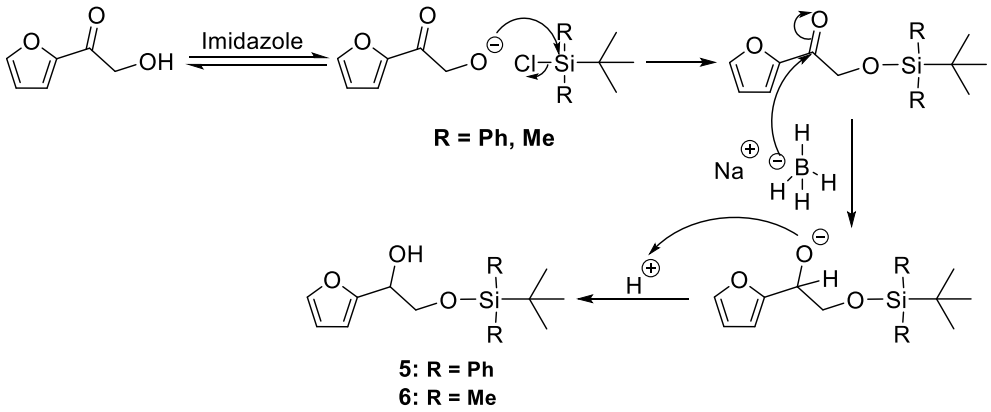


Scheme 153: Method described in literature for the hypervalent iodine reaction.



Scheme 154: Mechanism of the hypervalent iodine reaction.

The procedure adopted for the synthesis of compounds 5 and 6 was the protection of the alcohol group with a silyl protecting group, as this protecting groups can sustain the conditions needed in the next step, which is the reduction of the ketone to an alcohol (**Scheme 154**). The procedure for both steps is well documented in literature. Purification between the two steps is not necessary as the excess reagents added in the first step do not interfere with the reduction step. Both reactions proceeded as planed but the purification step, through flash chromatography, did not, as it was not possible to completely separate the excess protecting group and the desired compound. Even though the compounds weren't obtained 100% pure, it didn't affect the synthetic pathway planned.



Scheme 155: Mechanism of protection and reduction reactions.

The synthesis of the diol 7 didn't went according to plans as the diol has great affinity for water, being hard to extract and purify. Apart from its affinity for water and difficult purification, the diol is obtained in a very low yield, and as so it was not viable to procced with this pathway.

Every attempt to synthesise the cyclopentenones 11 or 12, with LA catalyst or MW, methods described for the Piancatelli rearrangement, gave only degraded samples, starting material or only traces of the desired compounds, which were not obtained in the scale up. All the samples were analysed by NMR to scan for interesting compounds, but there weren't any.

A resume of all the reactions, as well as each catalyst and solvent, for the Piancatelli rearrangement (**Table 1**) and for the MW reactions (**Table 2**), are presented below.

Table 1: Experimental conditions used in the attempts of preparation of cyclopentenones with the Piancatelli method.

Entry	Starting material	LA catalyst	Solvent	Concentration	Oil bath Temperature	Obs.
1	5	$Dy(OTf)_3$ [a]	t-BuOH:H_2O (5:1)	0.2M	80°C	Degradation
2	5	$Dy(OTf)_3$ [a]	t-BuOH:H_2O (5:1)	0.025M	80°C	No reaction
3	5	$Dy(OTf)_3$ [a]	t-BuOH:H_2O (5:1)	0.1M	80°C	Degradation
4	5	$Dy(OTf)_3$ [b]	t-BuOH:H_2O (5:1)	0.025M	80°C	Degradation
5	5	$ZnCl_2$ [a]	1,4-Dioxane:H_2O (3:2)	0.1M	60°C	No reaction
6	5	TsOH	Acetonitrile	0.1M	60°C	Degradation
7	5	$ZnCl_2$	Acetonitrile	0.1M	60°C	Degradation
8	5	$GdCl_3$	Acetonitrile	0.1M	60°C	No reaction
9	5	$Dy(OTf)_3$	Acetonitrile	0.1M	60°C	Degradation
10	5	$AlCl_3$	Acetonitrile	0.1M	60°C	Degradation
11	5	$BF_3{\cdot}OEt_2$	Acetonitrile	0.1M	60°C	Degradation
12	5	$LaCl_3$	Acetonitrile	0.1M	60°C	No reaction
13	5	TsOH	Nitromethane	0.1M	60°C	Degradation
14	5	$ZnCl_2$	Nitromethane	0.1M	60°C	Degradation
15	5	$GdCl_3$	Nitromethane	0.1M	60°C	No reaction
16	5	$Dy(OTf)_3$	Nitromethane	0.1M	60°C	Degradation
17	5	$AlCl_3$	Nitromethane	0.1M	60°C	Degradation
18	5	$BF_3{\cdot}OEt_2$	Nitromethane	0.1M	60°C	Degradation
19	5	$LaCl_3$	Nitromethane	0.1M	60°C	Degradation
20	6	TsOH	Acetonitrile	0.1M	60°C	Traces of desired compound

21	6	$ZnCl_2$	Acetonitrile	0.1M	60°C	Traces of desired compound
22	6	$GdCl_3$	Acetonitrile	0.1M	60°C	No reaction
23	6	$Dy(OTf)_3$	Acetonitrile	0.1M	60°C	Traces of desired compound
24	6	$AlCl_3$	Acetonitrile	0.1M	60°C	Degradation
25	6	$BF_3{\cdot}OEt_2$	Acetonitrile	0.1M	60°C	Degradation
26	6	$LaCl_3$	Acetonitrile	0.1M	60°C	Degradation
27	6	TsOH	Nitromethane	0.1M	60°C	Degradation
28	6	$ZnCl_2$	Nitromethane	0.1M	60°C	Degradation
29	6	$GdCl_3$	Nitromethane	0.1M	60°C	Traces of desired compound
30	6	$Dy(OTf)_3$	Nitromethane	0.1M	60°C	Degradation
31	6	$AlCl_3$	Nitromethane	0.1M	60°C	Degradation
32	6	$BF_3{\cdot}OEt_2$	Nitromethane	0.1M	60°C	Traces of desired compound
33	6	$LaCl_3$	Nitromethane	0.1M	60°C	Degradation

***a*: procedure described in literature by Piancatelli.**

***b:* To this reaction was added TFA (0.1 eq) in the attempt to better catalyse the reaction.**

Table 2: Experimental conditions for the microwave methodology used.

Entry	Starting material	P (W)	T (°C)	Time (minutes)	Obs.
1	6	300	120	30	Degradation
2	6	300	150	30	Degradation
3	6	300	200	4	Degradation
4	6	300	200	5	Degradation
5	6	300	200	10	Degradation
6	6	300	200	30	Degradation

Compound 8 was synthesised with the hope that it would help activate the alcohol, to a Piancatelli rearrangement, when in contact with a Lewis Acid catalyst. The procedure used in this reaction was quite simple but, to have a complete conversion, consumes a lot of time, and so another pathway was preferred. NMR analysis was produced and the compound obtained, although the time and quantity obtained weren't enough to test the Piancatelli rearrangement.

Chapter III – Conclusion

In conclusion, furan ring derivatives were achieved successfully through previously design methods, some of which even optimized, and in good yields. Though, the Piancatelli rearrangement has been wildly used in the synthesis of simple cyclopentenones, more complex furan rings turned out not to be convertible to cyclopentenones through this great method.

To sum up, the Piancatelli method is good when applied to the synthesis of simple cyclopentenones, but when it comes to more complex ones another method would be desirable, perhaps due to the instability of the cyclopentenones that may have been formed.

Nevertheless, the efforts to synthetize a new library of 4HCP will continue after the end of this thesis in order to create new possibilities for new and more effective medicine in the future.

Chapter IV – Experimental Section

General Remarks

All reactions were carried out in argon or nitrogen atmosphere with stirring at room temperature, unless stated otherwise. All catalysts were purchased from Sigma-Aldrich or Alfa-Aesar. Methanol and dichloromethane were dried from calcium chloride and distilled at atmospheric pressure. Acetonitrile and tetrahydrofuran (THF) were dried from Na and distilled at atmospheric pressure prior to use. The remaining reagents and solvents were purchased from commercial sources and used as supplied or purified/dried by regular methods.

The reaction mixtures were analyzed by TLC using Merck TLC silica gel 60 F_{254}, and visualization of TLC spots was effected using ultraviolet (UV) lamp at 254 and 365nm and phosphomolybdic acid solution stain. Column chromatography was performed using CombiFlash Rf automated apparatus.

NMR spectra were recorded in $CDCl_3$, on a Bruker Fourier 300 NMR spectrometer (^{1}H 300MHz; ^{13}C 75MHz). ^{1}H and ^{13}C chemical shifts (δ) are expressed in ppm (parts per million) and are relative to the corresponding resonance of non-deuterated solvent. Coupling constants (J) are reported in Hz.

Procedure for preparation of furan-2-yl(phenyl)methanol (1)

Experimental procedure adapted from literature [279].

On a flame dried flask was added furfural (0.86mL, 10.38mmol) and dried THF (2mL) in inert atmosphere. A solution of 1M phenylmagnesium bromide in THF (15.61mL, 15.61mmol) was added dropwise at 0°C. The reaction was then left stirring at rt for one hour and monitored by TLC, after which was done the quenching with H_2O and NH_4Cl sat. and extraction with MTBE. The combined organic layers were dried over with Na_2SO_4, filtrated and concentrated under reduced pressure.

The mixture was purified in combi flash with a gradient of Hex:DCM (1:1). Furan-2-yl(phenyl)methanol was isolated in 95% yield.

Spectral data (^{1}H NMR) comparable to reported by Maurizio D'Auria [179].

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.31 (m, 6H, Ph), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H, CH, H^3), 6.12 (dt, *J* = 3.2, 0.7 Hz, 1H, CH, H^2), 5.84 (s, 1H, CH, H^5).

Procedure for preparation of 1-(furan-2-yl)prop-2-en-1-ol (2)

Experimental procedure adapted from literature [279].

On a flask was added furfural (0.86mL, 10.38mmol) and THF (1mL) in inert atmosphere. The flask was then put on an ice bath (0°C) and a solution of vinylmagnesium chloride (15.7mL, 15.70mmol) was added dropwise. The reaction was then left stirring at rt for three hours and monitored by TLC, after which was done the quenching with HCl 3% and extraction with Et_2O. The combined organic layers were dried over with Na_2SO_4, filtrated and concentrated under reduced pressure.

There was an attempt to purify the mixture and to characterize the compound by ^{1}H NMR analysis.

Procedure for preparation of 1-(furan-2-yl)ethan-1-ol (3)

Experimental procedure adapted from literature [279].

On a two-necked flask, flame dried, was added magnesium (516.5mg, 21.25mmol), a catalytic amount of iodine and THF (15.1mL), finally was added the iodomethane (0.88mL, 14.14mmol) dropwise.

With the Grignard reagent solution in hands, was prepared the solution of furfural (0.86mL, 10.38mmol) in THF (2mL), in inert atmosphere and a flame dried flask. The flask with the Grignard solution was then put at -50°C and the furfural solution was added with more THF (1mL). The reaction was left for 1.5 hours at -60°C, while monitored by TLC, after which was warm up rt and left overnight.

After 12h, with no consumption of the starting material, the reaction was heated, in oil bath, to 40°C, and after 4 hours, up to 63°C and reflux. Two hours later the quenching was done with H_2O and NH_4Cl sat. and extraction with MTBE. The combined organic layers were dried over with Na_2SO_4, filtrated and concentrated under reduced pressure.

There was an attempt to purify the mixture and to characterize the compound by ^1H NMR analysis.

Procedure for preparation of 1-(furan-2-yl)-2-hydroxyethan-1-one (4)

Experimental procedure adapted from literature [281].

In a flame dried flask was added dried MeOH (55mL) and KOH (7.0822g, 126.23mmol), in inert atmosphere and ice bath. The solution was left stirring for five minutes and then was added 2-acetylfuran (3.0730g, 27.91mmol). To this mixture was added, portion wise, $PhI(OAc)_2$ (13.6432g, 42.36mmol) and left stirring for 4 hours, monitored by TLC. The reaction was given as complete after those 4 hours and quenched with HCl 10% (55mL), brine solution (30mL) and H_2O (20mL). MeOH was then evaporated under reduced pressure and the mixture extracted with EtOAc (4 x 25mL). The combined organic phases were dried with Na_2SO_4 and the solvents evaporated under reduced pressure.

The crude mixture was purified in combi flash with a gradient of Hex:EtOAc, starting with Hex:EtOAc 7:3 for 10 minutes and then up to 2:8 Hex:EtOAc. 1-(furan-2-yl)-2-hydroxyethan-1-one was isolated in 52% yield.

Spectral data (^1H NMR) comparable to reported by Lei Yang *et al.* [282].

^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 1.7, 0.7 Hz, 1H, H^1), 7.30 (dd, *J* = 3.6, 0.6 Hz, 1H, H^3), 6.59 (dd, *J* = 3.6, 1.7 Hz, 1H, H^2), 4.73 (s, 2H, H^6).

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.77 (C^5), 150.20 (C^4), 147.17 (C^1), 118.01 (C^3), 112.66 (C^2), 65.17 (C^6).

General procedure for preparation 2-(protecting group)-1-(furan-2-yl)ethan-1-ol

Experimental procedure adapted from literature [283].

To a flame dried flask, in inert atmosphere, was added 1-(furan-2-yl)-2-hydroxyethan-1-one (4) (10.70mmol, 1 eq.) and dried DCM (40mL), which was put stirring in ice bath. After a 10 minutes was added imidazole (23.83mmol, 2 eq.) and after complete dissolution, the silyl protecting group

(11.89mmol, 1 eq.). The reaction was left stirring for two hours, verified by TLC in Hex:EtOAc (2:1), upon which the quenching was done with saturated NH_4Cl and H_2O, then was procced to the extraction with 3x25 mL of EtOAc. The combined organic layers were dried over with Na_2SO_4 and the solvent evaporated under reduced pressure.

The crude mixture obtained previously was dissolved in MeOH (25mL) and put stirring in an ice bath. After, $NaBH_4$ (15.92mmol, 1.5 eq.) was added. Giving the reaction as complete was added saturated NH_4Cl and H_2O and extraction was done with 3x25 mL of EtOAc. The combined organic layers were dried over with Na_2SO_4 and the solvent evaporated under reduced pressure.

The crude mixture was purified in combi flash with a gradient of Hex:EtOAc, starting with 100% Hex for 10 minutes and then up to 30% EtOAc, for a 60 minutes range.

2-((tert-butyldiphenylsilyl)oxy)-1-(furan-2-yl)ethan-1-ol (5): The compound was obtained in 48% yield after purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 4H, Ph), 7.44 – 7.35 (m, 7H, 6H Ph, 1H H^1), 6.35 – 6.27 (m, 2H, H^2, H^3), 4.83 (dd, *J* = 6.0, 5.1 Hz, 1H, H^5), 3.91 (dd, *J* = 5.6, 1.9 Hz, 2H, H^6), 1.06 (s, 9H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.58 (C^4), 142.10 (C^1), 135.57 (Ph), 129.92 (Ph), 127.87 (Ph), 110.26 (C^3), 107.19 (C^2), 68.41 (C^6), 66.39 (C^5), 26.84 (C^9), 19.28 (CH_3).

2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethan-1-one (6): The compound was obtained in 66% yield after purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H, H^1), 6.36 – 6.28 (m, 2H, H^2, H^3), 4.81 – 4.72 (m, 1H, H^5), 3.84 (dd, *J* = 5.6, 2.6 Hz, 2H, H^6), 0.89 (s, 9H, CH_3), 0.06 (s, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.72 (C^1), 141.98 (C^4), 110.21 (C^3), 107.02 (C^2), 68.34 (C^5), 65.71 (C^6), 25.83 (CH_3), 18.28 (C^9), -5.45 (CH_3).

Procedure for preparation of 1-(furan-2-yl)ethane-1,2-diol (7)

Experimental procedure adapted from literature [283].

To a flask with 1-(furan-2-yl)-2-hydroxyethan-1-one (4) (101.3mg, 803.26µmol), was added MeOH (3mL) and put stirring in an ice bath. After giving the time for the mixture to cool to approximately 0°C, $NaBH_4$ (121.5mg, 3.21mmol) was added. Giving the reaction as complete was added saturated NH_4Cl and H_2O and extraction was done with 10x25 mL of EtOAc. The combined organic layers were dried over with Na_2SO_4 and the solvent evaporated under reduced pressure.

The crude mixture was purified in silica flash with a gradient of EtOAc:MeOH (9.5:0.5). 1-(furan-2-yl)ethane-1,2-diol was obtained in 5% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H, H^1), 6.35 (dt, *J* = 8.4, 2.5 Hz, 2H, H^2, H^3), 4.85 – 4.79 (m, 1H, H^5), 3.91 – 3.87 (m, 2H, H^6).

Procedure for preparation of 2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethyl 4-methylbenzenesulfonate (8)

In a flamed dried flask was added 2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethan-1-one (200.6mg, 827.59µmol) and dried DCM (8.5mL). The flask was left stirring in ice bath and inert atmosphere for 20 minutes, after which was added pyridine (11mL, 136.54mmol) and TsCl (465.6mg, 2,44mmol). The reaction was left in the same conditions for 26 hours, after which was quenched with H_2O. The mixture was extracted with DCM and the combined organic phases were dried with anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure.

The crude mixture was purified in combi flash with a gradient of Hex:EtOAc (9:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H, Ph), 7.38 (dd, *J* = 1.8, 0.9 Hz, 2H Ph), 7.31 (dd, *J* = 1.8, 0.9 Hz, 1H, H^1), 6.31 – 6.21 (m, 3H, H^2, H^3, H^5), 4.92 (dd, *J* = 7.5, 4.7 Hz, 1H, H^6), 4.80 (dd, *J* = 7.1, 4.6 Hz, 1H, H^6), 2.45 (s, 3H, CH_3), 0.84 (s, 9H, CH_3).

Procedure for preparation of 4-hydroxy-5-phenylcyclopent-2-en-1-one (via Piancatelli rearrangement) (9)

Experimental procedure followed according to literature [280].

In a flask was added the furan-2-yl(phenyl)methanol (1) (282.8mg, 1.62mmol), $Dy(OTf)_3$ (99.8mg, 163.69µmol, 0.1 eq.), t-BuOH:H_2O (17:3.8mL, 5:1). The reaction was left stirring overnight, in inert atmosphere, at 80°C. Giving the reaction as complete, was quenched with a saturated solution of $NaHCO_3$ and then H_2O. The mixture was extracted with DCM and the combined organic phases were dried with anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure.

The mixture was purified in combi flash with a gradient of Hex:DCM (1:1) for 20 minutes and then 100% DCM. 4-hydroxy-5-phenylcyclopent-2-en-1-one was isolated in 98% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 1H, Ph), 7.40 – 7.25 (m, 3H, 1H^3, 2H Ph), 7.14 (dd, *J* = 6.5, 1.5 Hz, 2H, Ph), 6.35 (dd, *J* = 5.8, 1.4 Hz, 1H, H^2), 5.00 (s, 1H, H^4), 3.45 (d, *J* = 2.7 Hz, 1H, H^5).

Procedure for preparation of 4-hydroxy-2-phenylcyclopent-2-en-1-one (via Piancatelli rearrangement) (10)

Experimental procedure followed according to literature [188].

4-hydroxy-5-phenylcyclopent-2-en-1-one (9) was put through Al_2O_3 (activity II – III) with DCM, until any compound could not be seen with TLC. The solvent was then evaporated under reduced pressure. 4-hydroxy-2-phenylcyclopent-2-en-1-one was afforded in quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 3H, Ph), 7.43 – 7.35 (m, 3H, 2H Ph, 1H H^3), 4.61 (dt, *J* = 5.9, 2.4 Hz, 1H, H^4), 2.91 (dd, *J* = 18.3, 6.0 Hz, 1H, H^5), 2.54 (dd, *J* = 18.3, 2.3 Hz, 1H, H^5).

General procedure for preparation of the cyclopentenones

To a flask was added furan ring derivative as starting material, a Lewis acid catalyst (10 mol%) and solvent. The reactions were left stirring in an oil bath, with reflow assembly, overnight. The crude mixture was filtrated through silica with EtOAc, when possible, or extracted when the reaction solvent included H_2O, and then ^{1}H-NMR analysis was obtained.

A microwave method was attempted as well, varying time, temperature and pressure.

General procedure for Mitsunobu reaction (13)

To a flame dried flask was added the 4-hydroxy-5-phenylcyclopent-2-en-1-one (9), the solvent (THF or DCM), DIAD (1.5eq) and PPh_3 (1.5eq), in an ice bath and inert atmosphere. The reaction mixture was left stirring, to cool down, for a few minutes and then was added the benzoic acid (1eq). After the addition of the acid, the ice bath was withdrawn and reaction was left stirring for 24 hours.

The crude mixture was purified in combi flash with a gradient of Hex:EtOAc (2:1). The product obtained was too unstable and degraded completely.

References

1. Otto, A., et al., *Structural and stereochemical elucidation of new hygrophorones from Hygrophorus abieticola (Basidiomycetes).* Tetrahedron, 2017. **73**(13): p. 1682-1690.
2. Bette, E., et al., *Isolation and Asymmetric Total Synthesis of Fungal Secondary Metabolite Hygrophorone B12.* European Journal of Organic Chemistry, 2015. **2015**(11): p. 2357-2365.
3. Ferreira, E.L., et al., *Structure and Biogenesis of Roussoellatide, a Dichlorinated Polyketide from the Marine-Derived Fungus Roussoella sp. DLM33.* Org Lett, 2015. **17**(21): p. 5152-5.
4. Wang, J., et al., *Identification and Bioactivity of Compounds from the Mangrove Endophytic Fungus Alternaria sp.* Mar Drugs, 2015. **13**(7): p. 4492-504.
5. Hwang, I.H., et al., *Cytotoxic activity of rearranged drimane meroterpenoids against colon cancer cells via down-regulation of beta-catenin expression.* J Nat Prod, 2015. **78**(3): p. 453-61.
6. Taniguchi, Y., et al., *Chemical Characterization of Beer Aging Products Derived from Hard Resin Components in Hops (Humulus lupulus L.).* J Agric Food Chem, 2015. **63**(46): p. 10181-91.
7. Taniguchi, Y., et al., *Analysis of the components of hard resin in hops (Humulus lupulus L.) and structural elucidation of their transformation products formed during the brewing process.* J Agric Food Chem, 2014. **62**(47): p. 11602-12.
8. Taniguchi, Y., et al., *Development of preparative and analytical methods of the hop bitter acid oxide fraction and chemical properties of its components.* Biosci Biotechnol Biochem, 2015. **79**(10): p. 1684-94.
9. Urban, J., et al., *Absolute configuration of beer's bitter compounds.* Angew Chem Int Ed Engl, 2013. **52**(5): p. 1553-5.
10. Lupinacci, E., et al., *Xanthohumol from hop (Humulus lupulus L.) is an efficient inhibitor of monocyte chemoattractant protein-1 and tumor necrosis factor-alpha release in LPS-stimulated RAW 264.7 mouse macrophages and U937 human monocytes.* J Agric Food Chem, 2009. **57**(16): p. 7274-81.
11. Intelmann, D., et al., *Structures of storage-induced transformation products of the beer's bitter principles, revealed by sophisticated NMR spectroscopic and LC-MS techniques.* Chemistry, 2009. **15**(47): p. 13047-58.
12. Hall, A.J., et al., *Safety, efficacy and anti-inflammatory activity of rho iso-alpha-acids from hops.* Phytochemistry, 2008. **69**(7): p. 1534-47.
13. Jaskula, B., et al., *A Kinetic Study on the Isomerization of Hop r-Acids.* J Agric Food Chem, 2008. **56**.
14. García-Villalba, R., et al., *Analysis of Hop Acids and Their Oxidized Derivatives and Iso-r-acids in Beer by Capillary Electrophoresis−Electrospray Ionization Mass Spectrometry.* J Agric Food Chem, 2006. **54**.
15. Nord, L.I., S.B. Sørensen, and J.Ø. Duus, *Characterization of reduced iso-α-acids derived from hops (Humulus lupulus) by NMR.* Magnetic Resonance in Chemistry, 2003. **41**(9): p. 660-670.
16. Chappel, C.I., S.Y. Smith, and M. Changnon, *Subchronic Toxicity Study of Tetrahydroisohumulone and Hexahydroisohumunone in Beagle Dog.* Food and Chemical Toxicology, 1998. **36**.
17. Zhanga, N.-X., et al., *Cyclopentenone Derivatives and Polyhydroxylated Steroids from the Soft Coral Sinularia acuta.* Chemistry & Biodiversity, 2015. **12**.

18. Yang, B., et al., *Sinulolides A-H, new cyclopentenone and butenolide derivatives from soft coral Sinularia sp.* Mar Drugs, 2014. **12**(10): p. 5316-27.

19. Shi, H., et al., *Sinularones A-I, new cyclopentenone and butenolide derivatives from a marine soft coral Sinularia sp. and their antifouling activity.* Mar Drugs, 2012. **10**(6): p. 1331-44.

20. Hajdu, Z., et al., *Antiproliferative activity of Artemisia asiatica extract and its constituents on human tumor cell lines.* Planta Med, 2014. **80**(18): p. 1692-7.

21. Verma, P.K., et al., *Therapeutic Potential of Natural Products from Terrestrial Plants as TNF-a Antagonist.* Current Topics in Medicinal Chemistry, 2012. **12**.

22. Xiao, M.-t., et al., *A novel polyacetylene from the aerial parts of Artemisia lactiflora.* Phytochemistry Letters, 2014. **8**: p. 52-54.

23. Zan, K., et al., *Prostaglandin-like fatty acid derivatives from Artemisia anomala.* J Asian Nat Prod Res, 2010. **12**(6): p. 492-7.

24. Kawazoe, K., et al., *Sesquiterpenoids from Artemisia gilvescens and an Anti-MRSA Compound.* J Nat Prod, 2003. **66**.

25. Marco, J.A., et al., *Sesquiterpene Lactones from Iranian Artemisia Species.* Phytochemistry, 1993. **43**.

26. Tan, R.X., et al., *Sesquiterpene Lactones and othe constituints from Artemisia xerophytica.* Phytochemistry, 1991. **30**.

27. Huneck, S., C. Zdero, and F. Bohlmann, *SECO-GUAIANOLIDES AND OTHER CONSTITUENTS FROM ARTEMISIA SPECIES.* Phytochemistry, 1986. **23**.

28. Trifunovic, S., et al., *Isolation, characterization, and in vitro cytotoxicity of new sesquiterpenoids from Achillea clavennae.* Planta Med, 2014. **80**(4): p. 297-305.

29. Tohme, R., et al., *Differential growth inhibitory effects of highly oxygenated guaianolides isolated from the Middle Eastern indigenous plant Achillea falcata in HCT-116 colorectal cancer cells.* Molecules, 2013. **18**(7): p. 8275-88.

30. Ghantous, A., et al., *Structure-activity relationship of seco-tanapartholides isolated from Achillea falcata for inhibition of HaCaT cell growth.* Eur J Med Chem, 2009. **44**(9): p. 3794-7.

31. Li, Y., et al., *Achillinin B and C, new sesquiterpene dimers isolated from Achillea millefolium.* Tetrahedron Letters, 2012. **53**(21): p. 2601-2603.

32. Haroon, M.H., et al., *A new beta-glucuronidase inhibiting butyrolactone from the marine endophytic fungus Aspergillus terreus.* Nat Prod Res, 2013. **27**(12): p. 1060-6.

33. Liao, W.Y., et al., *Asperjinone, a nor-neolignan, and terrein, a suppressor of ABCG2-expressing breast cancer cells, from thermophilic Aspergillus terreus.* J Nat Prod, 2012. **75**(4): p. 630-5.

34. Wang, Y., et al., *Three new compounds from Aspergillus terreus PT06-2 grown in a high salt medium.* Mar Drugs, 2011. **9**(8): p. 1368-78.

35. Kawakubo, J., et al., *Production of Phenolic Compounds by Aspergillus S-4 in Sake Cake Medium and Identification of Terrein.* Biosci Biotechnol Biochem, 1993. **57**(7): p. 1208-9.

36. Ghisalberti, E.L., M.J. Narbey, and C.Y. Rowland, *METABOLITES OF ASPERGILLUS TERREUS ANTAGONISTIC TOWARDS THE TAKE-ALL FUNGUS.* J Nat Prod, 1990. **53**.

37. Arai, K., et al., *Metabolic Products of Aspergillus terreus VIII. Astepyrone: a Novel Metabolite of the strain IFO 4100.* Chemical and Pharmaceutical Bulletin, 1983. **31**.

38. Kamata, S., H. Sakai, and A. Hirota, *Isolation of Acetylaranotin, Bisdethiodi(methylthio)acetylaranotin and Terrein as Plant Growth Inhibitors from a strain os Aspergillus terreus.* Agricultural and Biological Chemistry, 1983. **47**.

39. Kiriyama, N., Y. Higuchi, and Y. Yamamoto, *Studies on the metabolic products of Aspergillus terreus. II. Struture and Biosynthesis of the Metabolites of the Strain ATCC 12238.* Chemical and Pharmaceutical Bulletin. **25**.

40. Kong, F., et al., *New α-glucosidase inhibitors from a marine sponge-derived fungus, Aspergillus sp. OUCMDZ-1583.* RSC Adv., 2015. **5**(84): p. 68852-68863.

41. Chen, H., et al., *Inducing secondary metabolite production by the soil-dwelling fungus Aspergillus terreus through bacterial co-culture.* Phytochemistry Letters, 2015. **12**: p. 35-41.

42. Trabolsy, Z.B.K.A., et al., *Antioxidant activity, NMR, X-ray, ECD and UV/vis spectra of (+)-terrein: Experimental and theoretical approaches.* Journal of Molecular Structure, 2014. **1060**: p. 102-110.

43. Yurchenko, A.N., et al., *BIOLOGICALLY ACTIVE METABOLITES OF THE FACULTATIVE MARINE FUNGUS Aspergillus terreus.* Chemistry of Natural Compounds 2014. **49**.

44. Zaehle, C., et al., *Terrein biosynthesis in Aspergillus terreus and its impact on phytotoxicity.* Chem Biol, 2014. **21**(6): p. 719-31.

45. Demasi, M., et al., *Studies on Terrein as a New Class of Proteasome Inhibitors.* Journal of the Brazilian Chemical Society, 2010. **21**.

46. Arakawa, M., et al., *A New Terrein Glucoside, a Novel Inhibitor of Angiogenin Secretion in Tumor Angiogenesis.* Journal of antibiotics, 2008. **61**.

47. Hill, R.A., R.H. Carter, and J. Staunt, *Biosynthesis of Terrein, a Metabolite of Aspergillus ferreus Thorn.* Chemical Communications, 1975. **10**.

48. Barton, D.H.R. and E. Miller, *The Constitution and Stereochemistry of Terrein.* Journal of the Chemical Society, 1955.

49. Crombie, L., et al., *Oxidative Dirnerisations of Natural Rethrolones and Related Compounds with Manganese Dioxide.* JCS C - Organic, 1971.

50. Dunn, A.W., I.D. Entwistle, and R.A.W. Johnston, *Terrein and othe metabolites of Phoma species.* Phytochemistry, 1975. **14**.

51. Ubukata, M., et al., *Mycophenolic acid as a latent agonist of PPARgamma.* Bioorg Med Chem Lett, 2007. **17**(17): p. 4767-70.

52. Park, S.H., et al., *Terrein: a new melanogenesis inhibitor and its mechanism.* Cell Mol Life Sci, 2004. **61**(22): p. 2878-85.

53. Harper, J.K., et al., *Characterization of Stereochemistry and Molecular Conformation Using Solid-State NMR Tensors.* J Am Chem Soc, 2001. **123**.

54. Liangsakul, J., et al., *Emervaridione and varioxiranediol, two new metabolites from the endophytic fungus, Emericella variecolor.* Tetrahedron Letters, 2011. **52**(48): p. 6427-6430.

55. Wang, Y.G., et al., *Hepatoprotective prenylaromadendrane-type diterpenes from the gum resin of Boswellia carterii.* J Nat Prod, 2013. **76**(11): p. 2074-9.

56. Schmidts, V., et al., *RDC-based determination of the relative configuration of the fungicidal cyclopentenone 4,6-diacetylhygrophorone A12.* J Nat Prod, 2013. **76**(5): p. 839-44.

57. Chang, Y.C., et al., *Polyketides from the littoral plant associated fungus Pseudallescheria boydii.* J Nat Prod, 2013. **76**(9): p. 1796-800.

58. Fukuda, T., K. Nagai, and H. Tomoda, *(+/-)-Tylopilusins, diphenolic metabolites from the fruiting bodies of Tylopilus eximius.* J Nat Prod, 2012. **75**(12): p. 2228-31.

59. Matsumoto, T., et al., *Palmaenones A and B, Two New Antimicrobial Chlorinated Cyclopentenones from Discomycete Lachnum palmae.* Chemical and Pharmaceutical Bulletin, 2011. **59**.

60. Choi, J.-H., et al., *Thapsigargin-induced ER stress suppressive compounds from the mushroom Mycoleptodonoides aitchisonii.* Tetrahedron Letters, 2015. **56**(41): p. 5561-5563.

61. Li, G.H., et al., *New cyclopentenones from strain Trichoderma sp. YLF-3.* Nat Prod Res, 2009. **23**(15): p. 1431-5.

62. Caboni, P., et al., *Degradation of Pyrethrin Residues on Stored Durum Wheat after Postharvest Treatment.* J Agric Food Chem, 2007. **55**.

63. Caboni, P., et al., *Fast and Versatile Multiresidue Method for the Analysis of Botanical Insecticides on Fruits and Vegetables by HPLC/DAD/MS.* J Agric Food Chem, 2005. **53**.

64. Jeon, Y.J., et al., *Inhibition of cytochrome P450 2J2 by tanshinone IIA induces apoptotic cell death in hepatocellular carcinoma HepG2 cells.* Eur J Pharmacol, 2015. **764**: p. 480-8.

65. Leng, G., et al., *Metabolism of (S)-bioallethrin and related compounds in humans.* Toxicology Lett, 1999. **107**.

66. Miyake, S., et al., *Polyclonal and Monoclonal Antibodies Speciüc to the Chrysanthemic Acid Moiety of Pyrethroid Insecticides.* Pesticide Science, 1998. **54**.

67. Ando, T., et al., *Insecticidal Activity of New Fluorinated Pyrethroids and Their Stability Toward Chemical Oxidation and Photoreaction.* Pesticide Science, 1994. **40**.

68. Elliott, M., et al., *Metabolic Fate of Pyrethrin I, Pyrethrin II, and Allethrin Administered Orally to Rats.* Journal of Agricultural and Food Chemistry, 1972. **20**.

69. Yamamoto, I. and J.E. Casida, *Syntheses of 14C-Labeled Pyrethrin I, Allethrin, Phthalthrin, and Dimethrin on a Submillimole Scale.* Agricultural and Biological Chemistry, 1968. **32**.

70. Matsuda, K., et al., *Biosynthesis of pyrethrin I in seedlings of Chrysanthemum cinerariaefolium.* Phytochemistry, 2005. **66**(13): p. 1529-35.

71. Nakagawa, S., et al., *Insecticidal Tricycloalkanecarboxylic Esters.* Agricultural and Biological Chemistry, 1987. **51**.

72. Isobe, N., M. Matsuo, and J. Miyamoto, *NOVEL PHOTOPRODUCTS OF ALLETHRIN.* Tetrahedron Lett, 1984. **25**.

73. Begley, M.J., et al., *X-Ray Analysis of Synthetic (4S)-2-(Prop-2-enyl)rethron-4-yl (IR;3R)-Chrysanthemate 6- Bromo-2,4-dinitrophenyl hydrazone, and Chiroptical Correlation with the Six Natural Pyrethrin Esters.* Journal of the Chemical Society, Perkin Transactions 1, 1974.

74. Begley, M.J., et al., *Absolute configuration of ther Pyrethrins. Configuration and struture of (+)-Allethronyl (+)-trans-Chrysanthemate 6-Bromo-2,4-dinitrophenylhydrazone by X-Ray Methods.* Chemical Communications, 1972. **23**.

75. Bramwell, A.F., et al., *NUCLEAR MAGNETIC RESONANCE SPECTRA OF THE NATURAL PYRETHRINS AND RELATED COMPOUNDS.* Tetrahedron, 1969. **25**.

76. Berteau, P.E. and J.E. Casida, *Synthesis and Insecticidal Activity of Some Pyrethroid-like Compounds Including Ones Lacking Cyclopropane or Ester Groupings.* Journal of Agricultural and Food Chemistry, 1969. **17**.

77. Chen, Y.-L. and J.E. Casida, *Photodecomposition of Pyrethrin I, Allethrin, Phthalthrin, and Dimethrin.* J Agric Food Chem, 1969. **17**.

78. Godin, P.J., et al., *The Jasmolins, New lnsecticidally Active Constituents of Chrysanthemum cinerariaefofium VIS.* Journal of the Chemical Society C Organic, 1966.

79. Elliott, M., *The Pyrethrins and Related Compounds. Part V.l Puri$cation of (+)-Pyrethrolone as the Monohydrate, and the Nature of ''Pyrethrolone-C.".* Journal of the Chemical Society, 1964.

80. Katsuda, Y., T. Chikamoto, and Y. Inouye, *Relationship between Stereoisomerism and Biological Activity of Pyrethroids Part V. The Absolute Configuration of (+)-Pyrethrolone and (+)-Cinerolone.* Bulletin of the Agricultural Chemical Society of Japan, 1959. **23**.

81. Kikuta, Y., et al., *Requirement of catalytic-triad and related amino acids for the acyltransferase activity of Tanacetum cinerariifolium GDSL lipase/esterase TcGLIP for ester-bond formation in pyrethrin biosynthesis.* Biosci Biotechnol Biochem, 2013. **77**(9): p. 1822-5.

82. Bullivant, M.J. and G. Pattenden, *PHOTOLYSIS OF BIO-ALLETHRIN.* Tetrahedron Lett, 1973. **14**.

83. Miyano, M. and C.R. Dorn, *Prostaglandins. VI. Correlation of the Absolute Configuration of Pyrethrolone with That of the Prostaglandins.* J Am Chem Soc, 1973. **95**.

84. Hegazy, M.-E.F., et al., *Anti-inflammatory sesquiterpenes from the medicinal herb Tanacetum sinaicum.* RSC Adv., 2015. **5**(56): p. 44895-44901.

85. Hewlett, M.J., et al., *Sesquiterpene lactones from feverfew, Tanaceturn partlhenhm: isolation, structural revision, activity against human blood platelet function and implications for migraine therapy.* Journal of the Chemical Society - Perkin Transactions 1 1996. **16**.

86. Oksuz, S., *SESQUITERPENOIDS AND OTHER CONSTITUENTS FROM TANACETUM CILICIUM.* Phytochemistry, 1990. **29**.

87. Begley, M.J., M.J. Hewlett, and D.W. Knight, *REVISED STRUCTURES FOR GUAIANOLIDE a-METHYLENEBUTYRO-LACTONES FROM FEVERFEW.* Phytochemistry, 1989. **28**.

88. Barrero, A.F., et al., *Terpenes and polyacetylenes from cultivated Artemisia granatensis boiss (Royal chamomile) and their defensive properties.* Phytochemistry, 2013. **94**: p. 192-7.

89. Zdero, C. and F. Bohlmann, *GLAUCOLIDES, FULVENOGUAIANOLIDES AND OTHER SESQUITERPENE LACTONES FROM PENTZIA SPECIES.* Phytochemistry, 1990. **29**.

90. Deng, Y., et al., *Phytochemical and Bioactivity Studies on Constituents of the Leaves of Vitex Quinata.* Phytochem Lett, 2011. **4**(3): p. 213-217.

91. Liu, Q., et al., *Chemical Constituents from Aphanamixis grandifolia.* Chemical and Pharmaceutical Bulletin, 2010. **58**.

92. Yang, X.W., et al., *Cycloabiesesquine A, a unique sesquiterpenoid from Abies delavayi.* Chem Commun (Camb), 2009(25): p. 3771-3.

93. Umino, K., T. Yamaguchi, and Y. Ito, *Studies on Pentenomycins. IV. Preparation and Antimicrobial Activities of Pentenomycin Derivatives.* Chemical and Pharmaceutical Bulletin, 1974. **22**.

94. Luo, S.-H., et al., *Defensive Sesterterpenoids with Unusual Antipodal Cyclopentenones from the Leaves of Leucosceptrum canum.* Org Lett, 2011. **13**.

95. Mantione, D., et al., *4-Heterosubstituted Cyclopentenone Antiviral Compounds: Synthesis, Mechanism, and Antiviral Evaluation.* European J Org Chem, 2016.

96. Paquette, L.A., M.J. Earle, and G.F. Smith, *(4R)-(+)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one.* Organic Synthesis, 1996. **73**.

97. Watson, T.J.N., et al., *Development of the Carbocyclic Nucleoside MDL 201449A: A Tumor Necrosis Factor-a-Inhibitor.* Organic Process Research & Development, 1998. **2**.

98. Khanapure, S.P., et al., *An Efficient Synthesis of 4(S)-Hydroxycyclopent-2-enone.* J Org Chem, 1995. **60**(23).

99. O'Byrne, A., et al., *The thio-adduct facilitated, enzymatic kinetic resolution of 4-hydroxycyclopentenone and 4-hydroxycyclohexenone.* Org Biomol Chem, 2010. **8**(3): p. 539-45.

100. Curran, T.T., D.A. Hay, and C.P. Koegel, *The Preparation of Optically Active 2-Cyclopenten-l,4-Diol Derivatives from Furfuryl Alcohol.* Tetrahedron, 1997. **53**.

101. Specklin, S., et al., *Chemoenzymatic routes to cyclopentenols: the role of protecting groups on stereo- and enantioselectivity.* Tetrahedron Letters, 2014. **55**(51): p. 6987-6991.

102. Trost, B.M., et al., *Asymmetric synthesis of chiral cycloalkenone derivatives via palladium catalysis.* Chem Sci, 2014. **5**(4): p. 1354-1360.

103. Morgan, B.S., et al., *Facile biocatalytic syntheses of optically active 4-hydroxycyclohex-2-enone and 4-benzylthiacyclopent-2-enone.* Tetrahedron: Asymmetry, 2004. **15**(18): p. 2807-2809.

104. Kumaraguru, T., et al., *Synthesis of Enantiomerically Pure 4-Hydroxy-2-cyclopentenones.* Organic Process Research & Development, 2013. **17**(12): p. 1526-1530.

105. Kitamura, M., M. K, and R. Noyori, *KINETIC RESOLUTION OF 4-HYDROXY-2-CYCLOPENTENONE BY RHODIUM-CATALYZED ASYMMETRIC ISOMERIZATION.* Tetrahedron Lett, 1987. **28**.

106. Kitamura, M., et al., *Kinetic resolution of racemic allylic alcohols by BINAP-ruthenium(II) catalyzed hydrogenation.* The Journal of Organic Chemistry, 1988. **53**(3): p. 708-710.

107. Ghorpade, S.R., et al., *Enzymatic kinetic resolution studies of racemic 4-hydroxycyclopent-2-en-1-one using Lipozyme IM®.* Tetrahedron Asymmetry, 1999. **10**.

108. Kumaraguru, T. and N.W. Fadnavis, *Resolution of racemic 4-hydroxy-2-cyclopentenone with immobilized penicillin G acylase.* Tetrahedron: Asymmetry, 2012. **23**(10): p. 775-779.

109. Ulbrich, K., et al., *Enantioselective synthesis of 4-heterosubstituted cyclopentenones.* J Org Chem, 2013. **78**(8): p. 4202-6.

110. Arisetti, N. and O. Reiser, *Traceless stereoinduction for the enantiopure synthesis of substituted-2-cyclopentenones.* Org Lett, 2015. **17**(1): p. 94-7.

111. Reiser, O., K. Ulbrich, and P. Kreitmeier, *Microwave- or Microreactor-Assisted Conversion of Furfuryl Alcohols into 4-Hydroxy-2-cyclopentenones.* Synlett, 2010. **2010**(13): p. 2037-2040.

112. Suzuki, M., Y. Oda, and R. Noyori, *Palladium(0) Catalyzed Reaction of 1,3-Diene Epoxides. A Useful Method for the Site-Specific Oxygenation of 1,3-Dienes.* J Am Chem Soc, 1979. **101**.

113. Suzuki, M., Y. Oda, and R. Noyori, *PALLADIUM(O) CATALYZED REACTION OF 1,3-DIENE 1,4_EPIPEROXIDES.* Tetrahedron Lett, 1981. **22**.

114. Suzuki, M., et al., *Ruthenium(I1)-Catalyzed Reactions of 1,4-Epiperoxides.* J Org Chem, 1989. **54**.

115. Trost, B.M., J. Richardson, and K. Yong, *Palladium-Catalyzed Chemo- and Enantioselective Oxidation of Allylic Esters and Carbonates.* J Am Chem Soc Comm, 2006. **128**.

116. Ren, K., et al., *An Enantioselective Approach to 4-O-Protected-2-cyclopentene-l,4-diol Derivatives via a Rhodium-Catalyzed Redox-Isomerization Reaction.* J Org Chem, 2015. **80**(24): p. 12572-9.

117. Liu, Z.-Y., L. He, and H. Zheng, *Highly Enantioselective Synthesis of (+) and (-)Endo-Tricycle C5.2.1 .OzJjDeco-4.8-dien-3-one ond (-)-4-t-Butyldimethylsilyloxy-Cyclopentenone by Enzyme-Catalyzed Acetylotionl.* Tetrahedron Asymmetry, 1993. **4**.

118. Asami, M., *A Novel Asymetric Synthesis of Chiral Cyclopentanoid Building Blocks by the use of chiral Lithium Amide.* BCSJ, 1990. **63**.

119. Asami, M. and S. Inoue, *Reconfirmation of High Enantiomeric Excesses in the Enantioselective Transformation of meso-Epoxides.* Tetrahedron, 1995. **51**: p. 11725.

120. Johnson, C.R., L.S. Harikrishnan, and A. Golebiowski, *Enantioselective Synthesis of 7-Cycloocten-l,3,5,6-tetraol Derivatives by Enzymatic Asymmetrization.* Tetrahedron Lett, 1994. **35**.

121. Johnson, C.R., et al., *Chemoenzymatic Synthesis of 1,3-Dideoxynojirimycin.* Tetrahedron Lett, 1994. **35**.

122. Johnson, C.R. and M.P. Braun, *A Two-step, Three-Component Synthesis of PGEI: Utilization of a-Iodoenones in Pd(0)-Catalyzed Cross-Couplings of Organoboranes.* J Am Chem Soc, 1993. **115**.

123. Kitano, Y., S. Okamoto, and F. Sato, *A New Method for the Synthesis of Protected Chiral 4-Hydroxy-2-cyclopentenone.* Chemistry Lett, 1989. **18**.

124. Hamann, P.R. and A. Wissner, *The Efficient Synthesis of Two Prostaglandin Intermediates.* Synthetic Communications, 1989. **19**(9-10): p. 1509-1518.

125. Miyaoka, H., et al., *A Method for Synthesizing the Diformylcyclopentene Miety of Halimedatrial.* Chemical and Pharmaceutical Bulletin, 1989. **37**.

126. Chang, C.-T., et al., *A new synthetic approach for 4(S)-hydroxycyclopent-2-enone: a precursor to prostanoid synthesis.* Tetrahedron Letters, 2005. **46**(37): p. 6325-6328.

127. Brookes, P.C., et al., *Epoxide rearrangements using dilithiated aminoalcohols as chiral bases.* Tetrahedron, 2002. **58**.

128. Paquette, L.A. and T.M. Heidelbaugh, *(4S)-(−)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one.* Organic Synthesis, 1996. **73**.

129. Myers, A.G., M. Hammond, and Y. Wu, *An Improved Preparation of Highly Enantiomerically Enriched (R)-(+)-4-tert-Butyldimethylsiloxy-2-cyciopenten-1-one.* Tetrahedron Lett, 1996. **37**.

130. Jung, M.E., et al., *Studies towards the total synthesis of an epoxy isoprostane phospholipid, a potent activator of endothelial cells.* Chemical Communications, 2002(2): p. 196-197.

131. Nara, M., S.T. Shima, and S. Yamada, *SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS BY THE NOVEL USE OF MESO-COMPOUNDS-l. EFFICIENT SYNTHESIS OF TWO STRUCTURAL TYPES OF OPTICALLY PURE PROSTAGLANDIN INTERMEDIATES.* Tetrahedron, 1980. **36**.

132. Laumen, K. and M. Schneider, *ENZYMATIC HYDROLYSIS OF PROCHIRAL -C IS-1,4-DIACYL-2-CYCLOPENTENEDIOLS: PREPARATION OF (lS,4R)-AND (l_R,4g)-4-HYDROXY-2-CYCLOPENTENYLDERIVATIVES, VERSATILE BUILDING BLOCKS FOR CYCLOPENTANOID NATURAL PRODUCTS.* Tetrahedron Lett, 1984. **25**.

133. Le Liepvre, M., J. Ollivier, and D.J. Aitken, *Synthesis of Functionalized Bicyclo[3.2.0]heptanes - a Study of the [2+2] Photocycloaddition Reactions of 4-Hydroxycyclopent-2-enone Derivatives.* European Journal of Organic Chemistry, 2009. **2009**(34): p. 5953-5962.

134. Snapper, M. and M. Shizuka, *Selective Synthesis of ent-15-epi-F2t-Isoprostane and a Deuterated Derivative.* Synthesis, 2007. **2007**(15): p. 2397-2403.

135. Gais, H.-J., O. Bondarev, and R. Hetzer, *Palladium-catalyzed asymmetric synthesis of allylic alcohols from unsymmetrical and symmetrical racemic allylic carbonates featuring C–O-bond formation and dynamic kinetic resolution.* Tetrahedron Letters, 2005. **46**(37): p. 6279-6283.

136. Roy, A. and S.W. Schneller, *4'- and 1'-Methyl-Substituted 5'-Norcarbanucleosides.* J Org Chem, 2003. **68**.

137. García Ruano, J.L., et al., *Regio- and stereoselective synthesis of pyrrolo or azepine-fused cyclopenta[d]isoxazolines from 2-p-tolylsulfinylcyclopent-2-en-1-one.* Journal of Sulfur Chemistry, 2013. **34**(1-2): p. 17-32.

138. DePuy, C.H., et al., *The Formation of Cyclopentenones.* J Org Chem, 1964. **29**.

139. Ito, M., et al., *Retinoids and Related Compounds. Part 9.' Synthesis and Spectral Characteristics of Retinal Analogues involving the 11 -cis-Lockedcyclopentatrienylidene Structure.* Journal of the Chemical Society, Perkin Transactions 1, 1986. **1**.

140. Masayoshi, I., et al., *A Novel Rhodopsin Analogue Processing The Cyclopentatrienylidene Struture as the 11-cis-locked and Full Planar Chromophore.* Chemical and Pharmaceutical Bulletin, 1982. **30**.

141. Lipshutz, B.H. and R. Keil, *Preparation and Use of Vinylic Lithio cyanocuprates Containing an w-Electrophilic Center.* J Am Chem Soc, 1992. **114**.

142. Gracias, V., et al., *Ring Expansive Routes to Quinolizidine Alkaloids: Formal Synthesis of (−)-Lasubine II.* Org Lett, 2003. **5**(26).

143. Burke, S.D., et al., *Total Synthesis of Ionophore Antibiotic X-14547A (Indanomycin).* J Org Chem, 1994. **59**.

144. Paquette, L.A., et al., *Total Synthesis of Spinosyn A. 1. Enantioselective Construction of a Key Tricyclic Intermediate by a Multiple Configurational Inversion Scheme.* J Am Chem Soc, 1998. **120**.

145. Saito, S., S. Yamazaki, and H. Yamamoto, *Novel Three-Component Coupling Using Aluminum Tris(2,6-diphenylphenoxide) (ATPH): The Same Synthesic Strategy Leads to trans- and cis-Jasmonates.* Angew Chem Int Ed Engl, 2001. **40**.

146. Sato, T., H. Shima, and J. Otera, *A Highly Practical Route for Prostaglandins by Conjugate Addition of a-Li thio- y-me thoxyallyl Phenyl Sulfide.* J Org Chem, 1995. **60**.

147. Otera, J., Y. Niibo, and H. Nozaki, *A Divergent Entry into Prostaglandin Synthesis through 1,4-Addition of Methoxy(phenylthio)(trimethylsilyl)methyllithium to 4-Siloxy-2-cyclopentenone.* Tetrahedron Lett, 1992. **33**.

148. Giuseppone, N. and J. Collin, *Tandem Mukaiyama Michael-aldol reactions catalysed by samarium diiodide.* Tetrahedron, 2001. **57**.

149. Takahashi, K., M. Shiro, and M. Kishi, *Formation of l-Phenyl-2,3-dioxabicyclo[2.2.l]heptane in the Reaction of 1,3-Dibromo-4-phenylcyclopentanwe ith Hydrogen Peroxide in the Presence of Silver Trifluoroacetate.* J Org Chem, 1988. **53**.

150. Schrader, T.O. and M.L. Snapper, *Stereodivergent Synthesis of All 15-F2 Isoprostanes.* J Am Chem Soc Comm, 2002. **124**.

151. Mosca, R., et al., *Synthesis of monoprotected 1,4-diketones by photoinduced alkylation of enones with 2-substituted-1,3-dioxolanes.* Tetrahedron, 2001. **57**.

152. Mascitti, V. and E.J. Corey, *Enantioselective Synthesis of Pentacycloanammoxic Acid.* J Am Chem Soc Comm, 2006. **128**.

153. Nishimura, Y., et al., *Flexible Enantiodivergent Synthesis and Biological Activity of Mannostatin Analogues, New Cyclitol Glycosidase Inhibitors.* J Org Chem, 1996. **61**.

154. Ichikawa, M., et al., *Total Synthesis of (-)-Incarvilline, (+)-Incarvine C, and (-)-Incarvillateine.* J Am Chem Soc, 2004. **126**.

155. Zhang, J.L. and C.M. Che, *Dichlororuthenium(IV) complex of meso-tetrakis(2,6-dichlorophenyl)porphyrin: active and robust catalyst for highly selective oxidation of arenes, unsaturated steroids, and electron-deficient alkenes by using 2,6-dichloropyridine N-oxide.* Chemistry, 2005. **11**(13): p. 3899-914.

156. Helbling, V., M.K. Eberle, and R. Keese, *The Sakurai Reaction of 4-Acetoxycyclopentenone – Synthesis of trans-3-Allyl-4-vinylcyclopentanone.* Synlett, 1999. **Spec. Iss.**

157. Trembleau, L., L. Patiny, and L. Ghosez, *Diels-Alder reactions of activated furans to cyclopentenone derivatives: a regiodivergent Diels-Alder approach towards polyfunctionalised cis-hydrindanones.* Tetrahedron Lett, 2000. **41**.

158. Lu, P., E. Herdtweck, and T. Bach, *Intramolecular [2+2] photocycloaddition reactions as an entry to the 2-oxatricyclo[4.2.1.0(4,9)]nonan-3-one skeleton of lactiflorin.* Chem Asian J, 2012. **7**(8): p. 1947-58.

159. Farcet, J.-B., M. Himmelbauer, and J. Mulzer, *Photochemical and Thermal [2 + 2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin.* European Journal of Organic Chemistry, 2013. **2013**(20): p. 4379-4398.

160. Minuti, L., et al., *High pressure Diels–Alder reactions of (+)-nopadiene with cycloalkenones.* Tetrahedron: Asymmetry, 2004. **15**(7): p. 1187-1192.

161. Minuti, L., et al., *High Pressure Diels-Alder Reactions of 2-Vinyl-3,4-Dihydronaphthalene. Synthesis of Cyclopenta[c]- and Indeno[c]Phenanthrenones.* Tetrahedron, 1995. **51**.

162. Dols, P.P.M.A., et al., *4-ACETOXYCYCLOPENT-2-ENONE: A SYNTHETIC EQUIVALENT FOR CYCLOPENTADIENONE IN DIELS-ALDER REACTIONS.* Tetrahedron Lett, 1991. **32**.

163. Ruider, S.A., T. Sandmeier, and E.M. Carreira, *Total synthesis of (+/-)-hippolachnin A.* Angew Chem Int Ed Engl, 2015. **54**(8): p. 2378-82.

164. An, M., T. Toochinda, and P.A. Bartlett, *Five-Membered Ring Analogues of Shikimic Acid.* J Org Chem, 2001. **66**.

165. Borrelly, S. and L.A. Paquette, *Studies Directed to the Synthesis of the Unusual Cardiotoxic Agent Kalmanol. Enantioselective Construction of the Advanced Tetracyclic 7-Oxy-5,6-dideoxy Congener.* J Am Chem Soc, 1996. **118**.

166. Kumar, R.J., et al., *Novel γ-Aminobutyric Acid G1 Receptor Antagonists; Synthesis, Pharmacological Activity and Structure-Activity Relationships.* J Med Chem, 2008. **51**(13).

167. Bickley, J.F., et al., *Novel preparation of (−)-4-hydroxycyclohex-2-enone: reaction of 4-hydroxycyclohex-2-enone and 4-hydroxycyclopent-2-enone with some thiols.* Tetrahedron: Asymmetry, 2006. **17**(3): p. 355-362.

168. Kalidindi, S., et al., *Enantioselective synthesis of arglabin.* Angew Chem Int Ed Engl, 2007. **46**(33): p. 6361-3.

169. Acharya, H.P., K. Miyoshi, and Y. Kobayashi, *Mercury-Free Preparation and Selective Reactions of Propargyl (and Propargylic) Grignard Reagents.* Org Lett, 2007. **9**(18).

170. Shi, Y., et al., *Total synthesis, relay synthesis, and structural confirmation of the C18-norditerpenoid alkaloid neofinaconitine.* J Am Chem Soc, 2013. **135**(38): p. 14313-20.

171. Jung, M.E. and M. Guzaev, *Studies toward the enantiospecific total synthesis of rhodexin A.* J Org Chem, 2013. **78**(15): p. 7518-26.

172. Basra, S.K., et al., *A novel approach to bis-isoxazolines using a latent form of cyclopentadienone.* Journal of the Chemical Society, Perkin Transactions 1, 2000(21): p. 3592-3598.

173. Sih, C.J., et al., *Total Synthesis of Prostaglandins. IV. A Completely Stereospecific Synthesis of Prostaglandin E1.* J Am Chem Soc, 1973. **95**.

174. Wicha, J. and K. Michalak, *An Enantioselective Total Synthetic Approach to (+)-Heptemerone G and (+)-Guanacastepene A from 2-Furyl Methyl Carbinol.* Synlett, 2013. **24**(11): p. 1387-1390.

175. Nunes, J.P.M., C.A.M. Afonso, and S. Caddick, *Synthesis of 2,4-bifunctionalised cyclopentenones from 2-furaldehyde.* RSC Advances, 2013. **3**(35): p. 14975.

176. Saitman, A. and E.A. Theodorakis, *Synthesis of a Highly Functionalized Core of Verrillin*. Org Lett, 2013. **15**.

177. Henschke, J.P., et al., *The Manufacture of a Homochiral 4-Silyloxycyclopentenone Intermediate for the Synthesis of Prostaglandin Analogues.* Organic Process Research & Development, 2012. **16**(12): p. 1905-1916.

178. Piancatelli, G., A. Scettri, and S. Barbadoro, *A useful preparation of 4-substituted 5-hydroxy-3-oxo-cyclopentenoes.* Tetrahedron Lett, 1976. **39**.

179. D'Auria, M., *A NEW SIMPLE PROCEDURE FOR THE ISOMERIZATION OF 2-FURYLCARBINOLS TO CYCLOPENTENONES.* Heterocycles, 2000. **52**.

180. Harikrishna, M., et al., *Synthesis of 2-Normisoprostol, Methyl 6-(3-Hydroxy-2-((E)-4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopentyl)hexanoate.* Synthetic Communications, 2009. **39**(15): p. 2763-2775.

181. Dias, L.C., S.B. Shimokomaki, and R.T. Shiota, *Short Synthesis of a New Cyclopentene-1,3-dione Derivative Isolated from Piper carniconnectivum.* J Braz Chem Soc, 2005. **16**.

182. Csákÿ, A.G., M. Mba, and J.n. Plumet, *Asymmetric synthesis of cyclopentenones with benzylic α-quaternary carbon stereogenic centres from furans.* Tetrahedron: Asymmetry, 2004. **15**(4): p. 647-652.

183. Csákÿ, A.G., M. Mba, and J. Plumet, *Enantioselective Synthesis of γ,δ-Disubstituted β-Hydroxy δ-Lactones from Furans: Synthesis of (+)-Prelactone B and its C-4 Epimer.* Synlett, 2003(13): p. 2092-2094.

184. Csákÿ, A.G., et al., *Regioselective Synthesis of Trisubstituted Cyclopentadienyl Ligands from Furans.* Synlett, 2002. **9**.

185. Bannai, K., et al., *Synthesis of new sulfur-containing prostaglandine I.* Chemical and Pharmaceutical Bulletin, 1982. **30**.

186. Scettri, A., et al., *GENERAL ROUTE AND MECHANISM OF THE REARRANGEMENT OF THE SUBSTITUTED 5-HYDROXY-3-OXOCYCLOPENTENES INTO THE 2-SUBSTITUTED ANALOGS.* Tetrahedron, 1979. **35**.

187. Piutti, C. and F. Quartieri, *The Piancatelli rearrangement: new applications for an intriguing reaction.* Molecules, 2013. **18**(10): p. 12290-312.

188. Piancatelli, G. and A. Scettri, *A simple conversion of 4-substituted 5-hydroxy-3-oxo-cyclopentenones into the 2-substituted analogue.* Synthesis, 1977. **2**.

189. Kurozumi, S., T. Toru, and S. Ishimoto, *Preparation of 2-(-4-hydroxy-1-oxo-cyclopent-2-ene)heptanoic acid. An important prostaglandin synthon.* Tetrahedron Lett, 1973. **19**.

190. Stork, G. and T. Takahashi, *Chiral Synthesis of Prostaglandins (PGE1) from D-Glyceraldehyde.* J Am Chem Soc, 1977. **99**.

191. Elliott, J., M. Hetmanski, and R. Stoodly, *4-Hydroxy-2-hydroxyrnethylcyclopent-2-en-1-one : a Versatile Intermediatefor the Synthesis of Cyclopentanoid Natural Products.* Chemical Communications, 1980. **19**.

192. Baraldi, P.G., et al., *Stereospecific nitromethane conjugate addition 4-oxygenated-2-substituted-cyclo-pent-2-ones: A simple aproach to prostaglandins.* Tetrahedron, 1987. **43**.

193. Hirama, M., T. Gomibuchi, and K. Fujiwara, *Synthesis and DNA-Cleaving Abilities of Functional Neocarzinostatin Chromophore Analogues. Base Discrimination by a Simple Alcohol.* J Am Chem Soc, 1991. **113**.

194. Tanis, S.P., et al., *Furans in Synthesis. 11. Total Syntheses of (+-)- and (-)-Fastigilin C.* J Am Chem Soc, 1992. **114**.

195. Demir, A.S., H. Fındık, and E. Köse, *A new and efficient chemoenzymatic route to both enantiomers of α'-acetoxy-α-methyl and γ-hydroxy-α-methyl cyclic enones.* Tetrahedron: Asymmetry, 2004. **15**(5): p. 777-781.

196. Ruediger, E., et al., *Novel 3'-deoxy analogs of the anti-HBV agent entecavir: synthesis of enantiomers from a single chiral epoxide.* Tetrahedron Letters, 2004. **45**(4): p. 739-742.

197. Jung, M.E., et al., *Improved Synthesis of the Epoxy Isoprostane Phospholipid PEIPC and its Reactivity with Amines.* Org Lett, 2008. **10**.

198. Singh, G., A. Meyer, and J. Aube, *Stereodivergent synthesis of enantioenriched 4-hydroxy-2-cyclopentenones.* J Org Chem, 2014. **79**(1): p. 452-8.

199. Smith, A.B., et al., *Total Synthesis of the Cytotoxic Macrocycle (+)-Hitachimycin.* J Am Chem Soc, 1992. **114**.

200. Caddick, S., et al., *Studies toward the synthesis of natural an unnatural dienediynes. Part 2: A pratical approach to funcionalised cyclopentenones.* Tetrahedron, 2000. **56**.

201. Nunes, J.P.M., et al., *Asymmetric synthesis of trans-4,5-dioxygenated cyclopentenone derivatives by organocatalyzed rearrangement of pyranones and enzymatic dynamic kinetic resolution.* Tetrahedron, 2011. **67**(15): p. 2779-2787.

202. Bornik, M.A. and L.W. Kroh, *D-Galacturonic acid as a highly reactive compound in nonenzymatic browning. 1. Formation of browning active degradation products.* J Agric Food Chem, 2013. **61**(14): p. 3494-500.

203. Frelek, J., et al., *Chemoenzymatic approach to optically active 4-hydroxy-5-alkylcyclopent-2-en-1-one derivatives: an application of a combined circular dichroism spectroscopy and DFT calculations to assignment of absolute configuration.* Chirality, 2014. **26**(6): p. 300-6.

204. Lentsch, C., et al., *Jatrophane Diterpenes: Preparation of the Western Fragment of PI-3.* European Journal of Organic Chemistry, 2014. **2014**(5): p. 919-923.

205. Leclere, L., et al., *Identification of a cytotoxic molecule in heat-modified citrus pectin.* Carbohydr Polym, 2016. **137**: p. 39-51.

206. West, F.G. and G.U. Gunawardena, *Pseudocine Substitution of 4-(Mesyloxy)-2-cyclopentenones: An Efficient Route to 2,kDisubstituted 2-Cyclopentenones.* J Org Chem, 1993. **58**.

207. Csaky, A., et al., *An Efficient Synthesis of Enantiomerically Pure (1R,2S,5S)- and (1S,2R,5R)-Rosaprostol Methyl Esters.* Synlett, 2007. **2007**(10): p. 1553-1556.

208. Rodríguez, A.R. and B.W. Spur, *Total synthesis of isoprostanes via the two-component coupling process.* Tetrahedron Lett, 2002. **43**.

209. Gu, J., et al., *An Efficient Synthesis of 3-Hetero-13,14-dihydro Prostaglandin F1r Analogues.* Org Lett, 2001. **3**.

210. Wang, Y., et al., *Design and Synthesis of 13,14-Dihydro Prostaglandin F1r Analogues as Potent and Selective Ligands for the Human FP Receptor.* Journal of Medicinal Chemistry, 2000. **43**.

211. Lee, A.S.Y. and C.-W. Wu, *Stannyl-oriented Regioselective Allylation and Its Application to the Synthesis of Silyi Misoprostol.* Tetrahedron, 1999. **55**.

212. Barrosa, M.T., et al., *On the Diastereoselectivity of the 1,2-Reduction of 2-Aikyl-4-Hydroxycyclopentenones with Sodium Borohydride in the Presence of Cerium (III): Synthesis of Prostaglandin Precursors.* Tetrahedron Lett, 1995. **36**.

213. Okamoto, S., T. Yoshino, and F. Sate, *A Practical Synthesis of the O.I Side-chain Unit Present in Mexiprostil and Its Use for Synthesis of Mexiprostil via Two-component Coupling Process.* Tetrahedron Asymmetry, 1991. **2**.

214. Dygos, J.H., et al., *An efficient synthesis of the antisecretory prostaglandin enisoprost.* The Journal of Organic Chemistry, 1991. **56**(7): p. 2549-2552.

215. Tsujiyama, H., et al., *A HIGHLY PRACTICAL SYNTHESIS OF NATURAL PGEl, A2-TRANS-PGEl AND 2,2,3,3TETRADEHYDROPGEl VIA TWO-COMPONENT COUPLING PROCESS USING ZINC-COPPER REAGENTS.* Tetrahedron Lett, 1990. **31**.

216. Pappo, R., P. Collins, and C. Jung, *Resolution and Configurational Assignments of Methyl-3-hydroxy-5-oxo-cyclopent-l-eneheptanoate, an Important Prostaglandin Intermediate.* Tetrahedron Lett, 1973. **12**.

217. Kluge, A.F., K.G. Untch, and J.H. Fried, *Synthesis of 13-cis-Prostaglandins uia a Highly Stereoselective Conjugate Addition with a Functionalized Organocopper Reagent.* J Am Chem Soc, 1972. **94**.

218. Kluge, A.F., K.G. Untch, and J.H. Fried, *Synthesis of Prostaglandin Models and Prostaglandins by Conjugate Addition of a Functionalized Organocopper Reagent.* J Am Chem Soc, 1972. **94**.

219. Alvarez, F.S., D. Wren, and A. Prince, *Synthesis of (+-)-Prostaglandin E1, (+-)-11-Deoxyprostaglandins E1, F1a, and F1b, and (+-)-9-Oxo-13-cis-prostenoic acid by Conjugate Addition of Vinylcopper Reagents.* J Am Chem Soc, 1972. **94**.

220. Pandey, G., M.K. Ghorai, and S. Hajra, *The intermolecular [5-coupling of cyclic enones with activated alkenes and alkynes: Unexpected [5-alkoxy elimination from a 4-alkoxy-2-alkyl- 1-hydroxy-cyclopentenyl radical.* Tetrahedron Lett, 1998. **39**.

221. Kobayashi, S., et al., *Investigation of the Total Synthesis of N1999-A2: Implication of Stereochemistry.* J Am Chem Soc, 2001. **123**.

222. Meyer, M.E., E.M. Ferreira, and B.M. Stoltz, *2-Diazoacetoacetic acid, an efficient and convenient reagent for the synthesis of alpha-diazo-beta-ketoesters.* Chem Commun (Camb), 2006(12): p. 1316-8.

223. Nicolaou, K.C., Y. Tang, and J. Wang, *Total synthesis of sporolide B.* Angew Chem Int Ed Engl, 2009. **48**(19): p. 3449-53.

224. Meyer, M.E., et al., *Use of a palladium(II)-catalyzed oxidative kinetic resolution in synthetic efforts toward bielschowskysin.* Tetrahedron, 2013. **69**(36): p. 7627-7635.

225. Uttaro, J.-P., et al., *Synthesis of novel 3'-methyl-5'-norcarbocyclic nucleoside phosphonates as potential anti-HIV agents.* Tetrahedron, 2013. **69**(9): p. 2131-2136.

226. McMorris, T.C., et al., *Total synthesis of hydroxymethylacylfulvene, an antitumour derivative of illudin S.* Chemical Communications, 1997. **3**.

227. Chen, Y.-L. and W.F. Barthel, *Some New Pyrethrin-type Esters.* J Am Chem Soc, 1953. **75**.

228. Matsui, M., et al., *Studies on Pyrethrins. The Synthesis of Some R-Keto Esters.* BCSJ, 1953. **26**.

229. Crombie, L., et al., *Experiments on the 8ynthesis of the Pyrethrins. Part V. Synthesis of Side-chain Isomers and Analogues of Cinerone, Cinerobne, and Cinerin-I.* JCS, 1950.

230. LaForge, F.B. and S.B. Soloway, *Constituents of Pyrethrum Flowers. XXI. Revision of the Structure of Dihydrocinerolone.* J Am Chem Soc, 1947. **69**.

231. Wakasugi, K., et al., *Simple, Mild, and Practical Esterification, Thioesterification, and Amide Formation Utilizingp-Toluenesulfonyl Chloride andN-Methylimidazole.* Advanced Synthesis & Catalysis, 2003. **345**(11): p. 1209-1214.

232. Pattenden, G. and R. Storer, *Synthesis of Z-Rethrolones and Z-Rethrones.* Journal of the Chemical Society - Perkin Transactions 1, 1974.

233. Romanet, R.F. and R.H. Schlessinger, *A New and Highly Efficient Synthesis of Rethrolones.* J Am Chem Soc, 1974. **96**.

234. Biichi, G., D. Minster, and J.C.F. Young, *A New Synthesis of Rethrolones.* J Am Chem Soc, 1971. **93**.

235. Jondiko, I.J.O. and G. Pattenden, *A New Approach to Rethrolone Synthesis.* Journal of the Chemical Society - Perkin Transactions 1, 1983.

236. Matsui, M. and H. Meguro, *Studies on Chrysanthemic Acid. Part XIII. Preparation of Rethrins II and Rethrins II Isomers and Their Relative Toxicities to Rethrins.* Agricultural and Biological Chemistry, 1964.

237. Matsuo, N., et al., *A Convenient Synthesis of 4-Hydroxy-3-methyl-2-(2-propynyl)-cyclopent-2-enone, an Alcohol Moiety of a Synthetic Pyrethroid having strong killing and knockdown activity.* Agricultural and Biological Chemistry, 1982.

238. Bongards, C. and W. Gärtner, *Synthesis of Hetero Atom Modified Pyrromethenones.* European Journal of Organic Chemistry, 2007. **2007**(34): p. 5749-5758.

239. Fujisawa, T., et al., *THE REGIOSPECIFIC SYNTHESIS OF VICINALLY DIALKYLATED AND ITS APPLICATION CYCLOPENTADIENES*

TO A SYNTHESIS OF ALLETHROLON. Chemistry Lett, 1976.

240. Morita, A. and S. Kuwahara, *Enantioselective Total Synthesis of Litseaverticillols A and B.* Org Lett, 2006. **8**.

241. Morita, A., H. Kiyota, and S. Kuwahara, *Enantioselective Synthesis of the (1S,5R)-Enantiomer of Litseaverticillols A and B.* Bioscience, Biotechnology, and Biochemistry, 2014. **70**(10): p. 2564-2566.

242. Bailey, D., J.N. Murphy, and V.E. Williams, *From enolates to anthraquinones.* Canadian Journal of Chemistry, 2006. **84**(4): p. 659-666.

243. Arriola, D.J., et al., *Penultimate Effect in Ethylene-Styrene Copolymerization and the Discovery of Highly Active Ethylene-Styrene Catalysts with Increased Styrene Reactivity.* J Am Chem Soc, 2007. **129**.

244. Katsuta, R., et al., *Synthesis of the core framework of the proposed structure of sargafuran.* Tetrahedron Letters, 2013. **54**(4): p. 347-350.

245. Honda, T., H. Mizutani, and M. Watanabe, *Enantioselective Total Synthesis of Marine Natural Products Untenone A and Plakevulin A.* Synlett, 2005(5): p. 0793-0796.

246. Seepersaud, M. and Y. Al-Abed, Tetrahedron, 2000. **41**.

247. Sugahara, T. and K. Ogasawara, *Baylis-Hillman Protocol in an Enantiocontrolled Synthesis of Pentenomycin I.* Synlett, 1999. **4**.

248. Rodriguez Rivero, M., I. Alonso, and J.C. Carretero, *Vinyl sulfoxides as stereochemical controllers in intermolecular Pauson-Khand reactions: applications to the enantioselective synthesis of natural cyclopentanoids.* Chemistry, 2004. **10**(21): p. 5443-59.

249. Venkata Ramana, G. and B. Venkateswara Rao, *Stereoselective synthesis of (−)- and (+)-pentenomycins using RCM.* Tetrahedron Letters, 2003. **44**(27): p. 5103-5105.

250. Rivero, M.R., J.C.d.l. Rosa, and J.C. Carretero, *Asymmetric Intermolecular Pauson-Khand Reactions of Unstrained Olefins: The (-Dimethylamino)phenylsulfinyl Group as an Efficient Chiral Auxiliary.* J Am Chem Soc, 2003. **125**.

251. Klunder, A.J.H., W. Bos, and B. Zwanenburg, *AN EFFICIENT STEREOSPECIFIC TOTAL SYNTHESIS OF TERREIN.* Tetrahedron Lett, 1981. **22**.

252. Kreiser, W., et al., *SYNTHESIS OF 2,2-DIMETHYL-4-CYCLOPENTENE-1,3-DIONE AND 5,5-DIMETHYL-4-HYDROXY-2-*

CYCLOPENTEN-1-ONE. Tetrahedron Lett, 1996. **37**.

253. Miyaoka, H., et al., *Efficient Synthesis of Enantiomerically Pure 5,5-Dimethyi-4-hydroxy-2-cyclopentenone.* Tetrahedron Asymmetry, 1995. **6**.

254. Reddy, D., et al., *An Enantiospecific Route to (+)-(1R,3S)-cis-Chrysanthemic Acid from (-)-d-Pantolactone[1].* Synthesis, 2011. **2011**(07): p. 1067-1070.

255. Wu, J.-P., et al., *Highly efficient dynamic kinetic resolution of secondary aromatic alcohols at low temperature using a low-cost sulfonated sepiolite as racemization catalyst.* Tetrahedron Letters, 2014. **55**(37): p. 5129-5132.

256. Richter, A., C. Hedberg, and H. Waldmann, *Enantioselective synthesis of the C10-C20 fragment of fusicoccin A.* J Org Chem, 2011. **76**(16): p. 6694-702.

257. Becker, H., et al., *New Ligands and Improved Enantioselectivities for the Asymmetric Dihydroxylation of Olefins.* J Org Chem, 1995. **60**.

258. Polo, E., A. Barbieri, and O. Traverso, *The Effect of Phenyl Substituents on the Activity of Some Zirconocene Photoinitiators.* Eur J Inorg Chemistry, 2003. **2**.

259. Doncaster, J.R., H. Ryan, and R.C. Whitehead, *Organic Reactions in Water: Optimization of the Synthesis of (±)-Manzamenone A Using Surfactant Catalysts.* Synlett, 2003. **5**.

260. Al-Busafi, S., et al., *Exploitation of chemical predisposition in synthesis: an approach to the manzamenones.* Journal of the Chemical Society, Perkin Transactions 1, 2002(4): p. 476-484.

261. Al-Busafi, S. and R.C. Whitehead, *Predisposition in synthesis: efficient routes to (±)-untenone A and (±)-manzamenones A, C and F.* Tetrahedron Lett, 2000. **41**.

262. Etchells, L.L., et al., *Chemical predisposition in synthesis: application to the preparation of the pyrrolidine natural products, plakoridines A and B.* Tetrahedron, 2006. **62**(47): p. 10914-10927.

263. Doncaster, J.R., et al., *Synthetic analogues of the manzamenones and plakoridines which inhibit DNA polymerase.* Bioorg Med Chem Lett, 2006. **16**(11): p. 2877-81.

264. Etchells, L.L., A. Sardarian, and R.C. Whitehead, *A synthetic approach to the plakoridines modeled on a biogenetic theory.* Tetrahedron Letters, 2005. **46**(16): p. 2803-2807.

265. Manna, M.S. and S. Mukherjee, *Organocatalytic enantioselective formal C(sp(2))-H alkylation.* J Am Chem Soc, 2015. **137**(1): p. 130-3.

266. Loertscher, B.M., et al., *Diastereoselective Synthesis of Vicinal Tertiary Diols.* Org Lett, 3013. **15**.

267. Kuznetsov, O.M., et al., *Synthesis of (+)-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one.* Russian Chemical Bulletin, 1996. **45**.

268. Jose, A., et al., *Phosphine-Mediated Reaction of 3-Alkyl Allenoates and Diaryl 1,2-Diones: Efficient Diastereoselective Synthesis of Fully Substituted Cyclopentenones.* Org Lett, 2013. **15**.

269. Hossain, M.M., et al., *Synthesis, Structure, and Reactivity of [Cu(phen)2]ClO2: Aerobic Oxidation of Cl-to ClO2-at Room Temperature.* European Journal of Inorganic Chemistry, 2014. **2014**(1): p. 36-40.

270. Gimalova, F.A., et al., *Synthesis of 2-(3-Bromo-1,1-dimethyl-2-methoxypropyl)-2,4,5-triclorocyclopent-4-ene-1,3-dione.* Russian Journal of Organic Chemistry, 2006. **42**.

271. Vostrikov, N.S., et al., *1,2-Adducts of 5-Allyl-2,3,5-trichloro-4,4-dimethoxy-2-cyclo-pentenone with Ethyl Acetate Lithium Salt and Their Reactions with Iodine.* Russian Journal of Organic Chemistry, 2002. **38**.

272. Leboeuf, D., et al., *Efficient Nazarov cyclization/Wagner-Meerwein rearrangement terminated by a Cu(II)-promoted oxidation: synthesis of 4-alkylidene cyclopentenones.* Chemistry, 2013. **19**(15): p. 4842-8.

273. Egorov, V.A., et al., *Trichlorocyclopentenone conjugates with amino acids. Isolation and structure of diastereomerically pure N-[(4R)-4-allyl-2,4-dichloro-5,5-dimethoxy-3-oxocyclopent-1-en-1-yl]-L-methionine methyl ester.* Russian Journal of Organic Chemistry, 2016. **51**(12): p. 1721-1724.

274. Gimalova, F.A., et al., *Reaction of 5-Allyl-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one with amino acids.* Russian Journal of Organic Chemistry, 2007. **43**(7): p. 981-983.

275. Akhmetvaleev, R.R., et al., *(+)-2,3,5-Trichloro-4,4-ethylenedioxycyciopent-2-en-l-one and its 5-allyl-substituted derivative in conjugated 1,4-addition with dimethyldilithium cyanocuprate.* Russian Chemical Bulletin, 1997. **46**.

276. Vostrikov, N.S., et al., *Some aspects of selective ozonolysis of 5-allyl(allenyl)-4,4-dimethoxy-2,3,5-trichlorocyclopent-2-enones and their 3-morpholino derivatives.* Russian Chemical Bulletin, 1999. **48**.

277. Vostrikov, N.S., et al., *Unusual Intramolecular Assistance in the Functionalization of the Side-Chain Double Bond of 5-Allyl-2,3,5-trichloro-4,4-dimethoxy-2-cyclopentenone in the Reaction with Iodine.* Russian Journal of Organic Chemistry, 2001. **37**.

278. Akbutina, F.A., S.A. Torosyan, and M.S. Miftakhov, *Prostanoids: LXXVII. Synthetic Approaches to Sterically Overcrowded Cyclopentenones.* Russian Journal of Organic Chemistry, 2001. **37**.

279. Csáky, A.G., M. Mba, and J. Plumet, *Regio- and Stereoselective Addition of Grignard and Organolithium Reagents to 4-Hydroxy-2-cyclopentenones.* J Org Chem, 2001. **66**.

280. Fisher, D., et al., *Efficient synthesis of 4-hydroxycyclopentenones: dysprosium(III) triflate catalyzed Piancatelli rearrangement.* Tetrahedron, 2014. **70**(27-28): p. 4105-4110.

281. Zhang, Z. and X. Jiang, *Oxidative coupling of terminal alkyne with alpha-hydroxy ketone: an expedient approach toward ynediones.* Org Lett, 2014. **16**(17): p. 4400-3.

282. Yang, L., et al., *Direct conversion of cellulose to 1-(furan-2-yl)-2-hydroxyethanone in zinc chloride solution under microwave irradiation.* Carbohydrate Research, 2011. **346**(14): p. 2304-2307.

283. Wang, H.-Y., et al., *Iridium-Catalyzed Dynamic Kinetic Isomerization: Expedient Synthesis of Carbohydrates from Achmatowicz Rearrangement Products.* Angewandte Chemie International Edition, 2015. **54**(30): p. 8756-8759.