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Diels–Alder Reaction

Industrial Applications of the Diels–Alder Reaction

Jacques-Alexis Funel* and Stefan Abele

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Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

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The Diels–Alder reaction is one of the most popular transformations for organic chemists to generate molecular complexity efficiently. Surprisingly, little is known about its industrial application for the synthesis of pharmacologically active ingredients, agrochemicals, and flavors and fragrances. This Review highlights selected examples, with a focus on large-scale applications (> 1 kg) from a process research and development perspective.

From the Contents

> *“The philosopher may very justly be delighted with the extent of his views, and the artificer with the readiness of his hands; but let the one remember that, without mechanical performances, refined speculation is an empty dream; and the other that, without theoretical reasoning, dexterity is little more than a brute instinct.”*
>
> Samuel Johnson (1709–1784)

1. Introduction

Since its discovery in 1928 by Diels and Alder,[1] the pericyclic reaction involving a conjugated diene and a dienophile—today known as the Diels–Alder reaction (DA reaction)—has been used for the diastereo- and regioselective generation of six-membered rings with up to four stereogenic centers in a single step. Nicolaou et al. aptly summarized the potential and impact of this reaction in an excellent review published in 2002.[2] In awarding the Nobel Prize to Otto Diels and Kurt Alder in 1950, Fredga cited the numerous applications of the substances obtained by using this reaction, especially as “raw materials for plastics”.[3] After 85 years of research, the understanding of the steric and electronic effects has increased and many different versions, including intramolecular [4+2] cycloadditions,[4] hetero-DA reactions, and catalytic asymmetric variants, have been developed.[5] Consequently, the range and power of this transformation, whose large potential had been anticipated by its inventors, have been tremendously broadened. This “grand old synthesis”, as designated by Corey,[6] has indeed opened the way to the synthesis of a plethora of organic substances, notably ones of natural origin.[2] There have been many comprehensive reviews on the applications of the DA reaction to the synthesis of elaborated targets,[7] thus underlining the power of this reaction for the rapid generation of molecular complexity. Except for a short review published in 1981 by Koenig[8] on industrial cycloadditions, we are not aware of any account discussing the large-scale applications of the DA reaction. Implementation of this transformation for production on a plant scale is indeed a testimony of its true usefulness, robustness, and efficiency in the face of the demanding requirements of process research, development, and optimization.[9]

According to a survey by Dugger et al.[10] in 2005 of the type of reaction scaled in a research facility at Pfizer, and an analysis of the reactions used for the preparation of drug candidate molecules by Carey et al. in 2006,[11] the DA reaction falls into the “miscellaneous” category that accounts for only 5 to 11 % of C–C bond-forming reactions performed under Good Manufacturing Practice. This observation mirrors the finding that C–C bond-forming reactions account for 11.5 % of the entire reaction repertoire used by medicinal chemists in the pursuit of drug candidates.[12] In this group, palladium-catalyzed reactions represent about 60 % of the occurrences, while the “other” category, into which the DA reaction falls, represents only 1.8 % of the total number of reactions. Careful examination of the top 200 pharmaceutical products by US retail sales in 2010[13] revealed that only one marketed drug, namely Buprenorphine, is produced industrially by using the DA reaction. Two other drugs were identified in the top 200 generic drugs of US retail sales in 2008: Calcitriol and its precursor Calciferol.[14] Since 2002, Liu and co-workers have been compiling the new drugs introduced each year to the market. From 2002 to 2010,[15] 174 new chemical entities were reported. Among them, two examples (Varenicline from Pfizer in 2006 and Peramivir by Shionogi in 2010) have been explicitly manufactured through a DA reaction. Similarly, and not surprisingly, our consultation with a large corpus of peers, colleagues, and experts in industry and academia worldwide revealed that the knowledge of such examples of the DA reaction run on a large scale is scarce, except perhaps in the field of fragrance chemistry.

The power of the DA reaction is universally acknowledged for the rapid, atom-economical build-up of complex structures of defined geometry with minimal waste. These criteria would fulfill the requirements of a scalable chemical process[16] as defined by Lipton and Barrett:[17] “*to be functional on large scales, it not only needs to be robust and predictable, it should also be operationally simple, safe and straightforward*”. To account for the apparently low number of industrial-scale DA reactions in the literature, one may suppose that safety issues might have deterred chemists from

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[*] Dr. J.-A. Funel, Dr. S. Abele
Process Research Chemistry
Actelion Pharmaceuticals Ltd.
Gewerbestrasse 16, 4123 Allschwil (Switzerland)
E-mail: jacques.funel@actelion.com

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pursuing them. Those safety concerns are often linked to the instability of the diene and/or dienophile and the intrinsic full-batch mode of this bimolecular reaction. In addition, the precursors that enable these efficient transformations might be difficult to access on a production scale, from a technical or economic perspective. The scarcity of examples of DA reactions on a large scale seemingly reflects the composition of current drug discovery pipelines, which are fueled by compounds emerging from a set of favorite reactions (namely Suzuki coupling and amide formation).[11,18]

A search of the Scopus database shows an impressive increase in the number of publications dealing with the DA reaction over the past 50 years. For a better comparison, Figure 1 shows this evolution normalized to the overall increase in publications over the same period (see also Table S1 in the Supporting Information).[19] Our study reveals that more drugs produced through a DA reaction were brought to the market in the 1960s–1980s than in the 1990s–2010s (Figure 2). The reason for this fact may be correlated with the high popularity[6] of the DA reaction in the 1970s and the subsequent rapid development of alternative methods, such as palladium-catalyzed cross-coupling reactions for a straightforward access to active compounds. It may also reflect the relative decline in the approval of new chemical entities in recent years.[20] Interestingly, this situation is only reflected in industry, with numerous reports of new applications of the DA reaction in academia having been published over the last few decades.

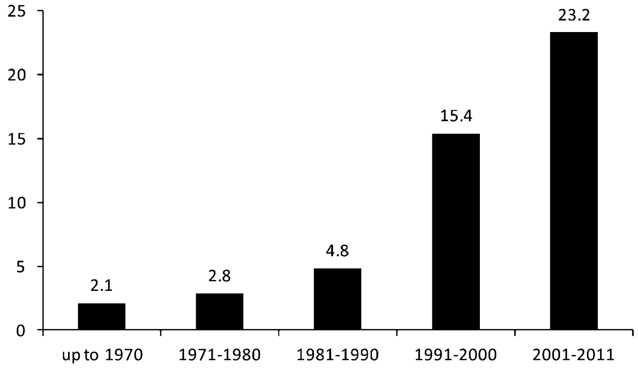


Figure 1. Ratio of chemistry publications mentioning the Diels–Alder reaction. (The data are plotted as the number of chemistry publications mentioning the Diels–Alder reaction over the total number of chemistry publications X 1000.)

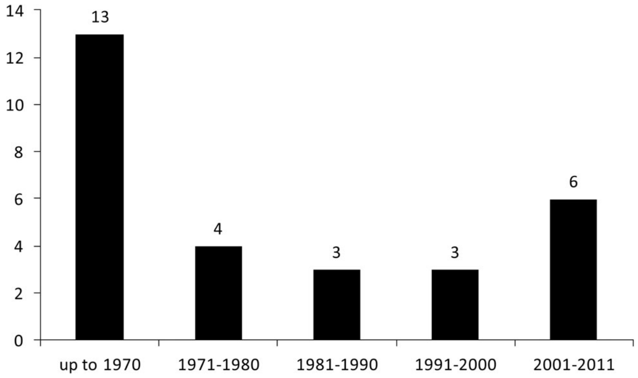


Figure 2. Approved chemical entities accessed by DA reactions, as identified in this Review.[21]

The purpose of this Review is to give an overview of the use of [4+2] cycloadditions[22] for the manufacture of active pharmaceutical or agrochemical ingredients as well as flavors and fragrances, on a scale above 1 kg, and covers examples from the 1950s until February 2012. It offers the opportunity to shed light on an underrated aspect of one of the most popular name reactions available to the organic chemist. In addition, we seek to provide snapshots of syntheses carried out on a large scale, highlighting some of the typical challenges, contributions, and achievements of process research and development teams.[23] In cases where sufficient information was disclosed, hints on scalability are offered. For a more comprehensive appreciation of the scale-up potential of each example in terms of, for example, costs of goods, green metrics analysis, or space-time yield, more data would be required for a sound analysis.[24] Examples are presented for which details of the synthesis on a kg scale have been disclosed, together with others for which there is reasonable evidence that the large-scale route incorporates such a cycloaddition step. For competitive reasons, the registered manufacturing route to a commercial product is rarely disclosed. This Review provides only a fraction of the examples and is not intended to be exhaustive, since, in addition to overlooked cases, it is assumed that some examples remain undisclosed as

Jacques-Alexis Funel graduated in 2001 from Ecole Nationale Supérieure de Techniques Avancées in Paris (France) and completed his PhD in organic chemistry at Ecole Polytechnique, Palaiseau (France) in 2004 with Prof. Dr. Joëlle Prunet. He then carried out postdoctoral studies (2005–2006) with Prof. Dr. Alois Fürstner at the Max Planck Institute for Coal Research, Mulheim an der Ruhr (Germany) working on the total synthesis of cytotoxic macrolides. Since 2006, he has worked for the Process Research group at Actelion Pharmaceuticals, Allschwil (Switzerland), where he is currently Senior Laboratory Head.

Stefan Abele studied chemistry at the University of Konstanz (Germany) and the Université Joseph Fourier, Grenoble (France). He received his diploma from the University of Konstanz with Prof. Dr. R. R. Schmidt. In 1999, he completed his PhD with Prof. Dr. D. Seebach at the ETH Zurich. He then spent seven years at Carbogen-Amcis (Switzerland), doing process research, development, and GMP manufacturing of pharmaceuticals. In 2006, he joined Actelion Pharmaceuticals Ltd, where he set up Process Research Chemistry for the design of novel routes to drug candidates and to produce kg amounts of pharmaceuticals.

trade secrets.[25] We therefore apologize for any example which may have escaped our attention.

This Review is organized into three main parts. A major section dealing with the manufacturing of active pharmaceutical ingredients (APIs) is followed by two sections that focus on the agrochemical industry and on flavors and fragrances.[26]

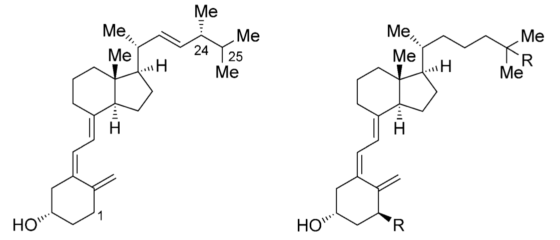
2. Active Pharmaceutical Ingredients

Among the more than 2400 active pharmaceutical substances that are or have been marketed, as referenced by Kleeman, Engel et al.,[27] several drugs that include a DA cycloaddition in their synthetic sequence have been identified. Drugs that have been granted market approval (but may have been withdrawn since then) or that are (or used to be) in clinical or preclinical development are covered. Even if no market authorization has yet been granted, carrying out any investigational program, be it either clinical or—to a lesser extent—preclinical, requires several kilograms of active ingredient. These examples clearly illustrate the applicability and reproducibility of the chemical transformation on a technical scale for the production of sufficient drug substance to cover the needs of a large patient population over several decades (from a few kilograms to several thousand tons per year).

Whenever available from the literature (either as exemplified in the experimental section or inferred from the text disclosing industrial applications of this transformation), the actual scale of the DA reaction is highlighted in the accompanying synthetic schemes. In all cases, even if only gram-scale protocols have been reported, the selected examples have been carried out on larger scales, from several 100 g to several tons. This section starts with the synthesis of vitamins and prostaglandins in the late 1960s. Although any classification will inevitably lead to overlaps, the examples have been ordered according to the type of most frequently used dienes and dienophiles. Hetero-, auxiliary-based, and intramolecular DA reactions are discussed in dedicated chapters.

2.1. Industrial-Scale Synthesis of Vitamins and Prostaglandins: A Seminal Illustration

Vitamins D and analogues thereof constitute seminal examples of approved active pharmaceuticals prepared by the DA reaction. Vitamin D_2 (ergocalciferol (**1**), derived from ergosterol produced in plants) and vitamin D_3 (cholecalciferol (**2**) derived from cholesterol produced in animals), which are the most common forms of vitamin D (Figure 3), have long been known for their importance in bone and mineral metabolism.



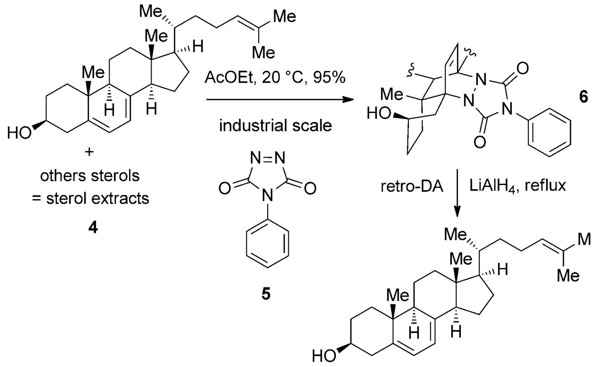
1: ergocalciferol (Vitamin D_2)

R = H, **2**: cholecalciferol (Vitamin D_3)
R = OH, **3**: calcitriol

Figure 3. Structures of vitamin D_2 and vitamin D_3.

Vitamin D_3 is produced in the skin (or alternatively acquired in the diet) by photolysis of 7-dehydrocholesterol to previtamin D_3 with UV light followed by a [1,7] sigmatropic rearrangement (see Scheme S1 in the Supporting Information). Hydroxylation at the C25-position in the liver and later at the C1-position in the kidney yields 1α,25-dihydroxyvitamin D_3, known as calcitriol (**3**; Scheme 2), which is the hormonally active form of vitamin D_3. Synthetic approaches toward vitamin D have been reviewed by Zhu and Okamura.[28] Industrially, calcitriol was first produced according to a biomimetic process established at Upjohn in 1969.[29] This strategy was inspired by Windaus, with 3β-hydroxychol-5-enic acid used as the starting material, which is available in bulk quantities as a by-product from the oxidative cleavage of the side chain of cholesterol (see Scheme S2 in the Supporting Information). The description of this process and subsequent improvements on a technical scale have been published.[30] However, the difficult formation of the 5,7-diene in ring B and the low-yielding photochemical electrocyclic opening of the ring have called for process improvements.

Protection of the $\Delta^{5,7}$-diene function within the ergosterol diene system and a successful DA/retro-DA sequence with a labile dienophile was described by Barton et al. in 1971,[31] and was judged to be suitable for large-scale production.[32] It allowed for an improved synthesis of vitamin D precursors and for the convenient isolation of the desired compound from sterol extracts (**4**). Scheme 1 shows the industrial isolation of 7-dehydrocholesterol (**7**) starting from yeast fermentation products.[33] The desired intermediate was separated from other by-products generated during the fermentation process by adjustment to pH 8, followed by extraction with heptane. The non-acidic sterol extracts were then treated with a dienophile to form a DA adduct of the 5,7-diene of the 7-dehydrocholesterol, while leaving unconju-

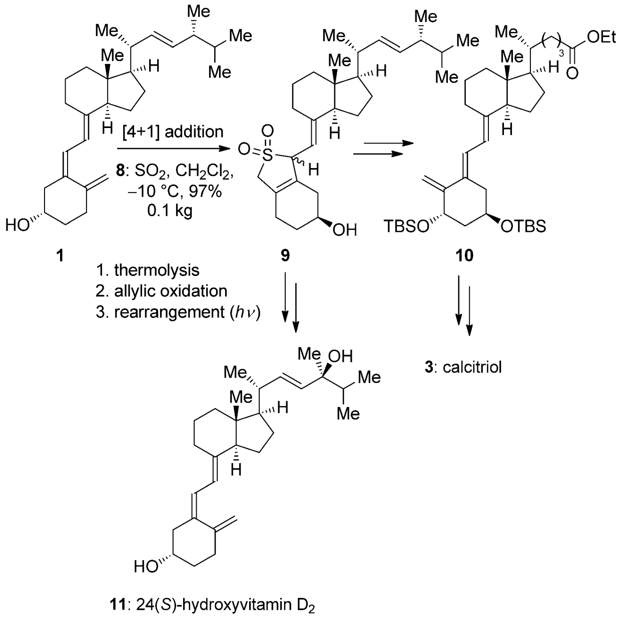


Scheme 1. Purification of sterol extracts by sequential DA/retro-DA reactions.[33]

gated dienes and others sterols untouched. For this purpose, 4-phenyl-1,2,4-triazoline-3-5-dione (**5**) was commonly used as the dienophile. The corresponding cycloadduct was then readily purified by chromatography. The diene function was liberated by a retro-DA reaction in the presence of LAH,[34] further purified, and used for the large-scale production of vitamin D_3 or analogues thereof (Scheme 1).

This concept has been widely applied in industry for the isolation and purification of vitamin D precursors. The principle of this approach is illustrated with the synthesis of 1α-hydroxy-7-dehydrocholesterol by Kaneko et al.[35] (see Scheme S3 in the Supporting Information). Alfacalcidol (see Scheme S4 in the Supporting Information) was initially devloped at the Research Institute for Medicine and Chemistry by Barton et al.[35c] Subsequently licensed to Leo Pharma, it was launched in 1978 for the treatment of osteomalacia.[36] It was prepared following such an approach, with **5** used as the dienophile. Analogously, doxercalciferol (see Scheme S4 in the Supporting Information, Genzyme) was approved in 1999 for the treatment of hyperparathyroidism.[37] In 2011, eldecalcitol (see Scheme S4 in the Supporting Information) was launched in Japan by Chugai for the oral treatment of osteoporosis.[38]

The strategy, based on the principle of protecting the 5,7-diene system, was extended to the use of sulfur dioxide by Barton, Hesse, and co-workers,[39] inspired by the pioneering work of Staudinger and Ritzenthaler in 1935.[40] The [4+1] cheletropic addition of SO_2 onto a 1,3-conjugated diene is beyond the scope of this Review devoted to [4+2] DA reactions. However, we deemed it appropriate to include examples of this reaction on a large scale in view of the industrial significance of this strategy. The conjugated diene function within vitamin D_2 was temporarily blocked after cheletropic addition of SO_2 (Scheme 2). Ozonolysis of the side chain followed by thermolysis of the sulfur dioxide adduct **9**, allylic oxidation by SeO_2, and photochemical rearrangement are the key steps of this synthetic sequence. A thorough purification of the targeted compound by column chromatography was required to achieve high purity. This protocol was applied successfully at Roche for the synthesis of 100 g of calcitriol (**3**).[41] A stereospecific synthesis of 24(*S*)-hydroxyvitamin D_2 (**11**) was developed by following a similar path that was judged amenable to larger scale preparation.[42] The use of the same SO_2 adduct **9** on a 200 g scale led to multigram amounts of active material (Scheme 2).



Scheme 2. Synthesis of 24(*S*)-hydroxyvitamin D_2 by Coutts et al.[42] and of calcitriol at Roche.[41a]

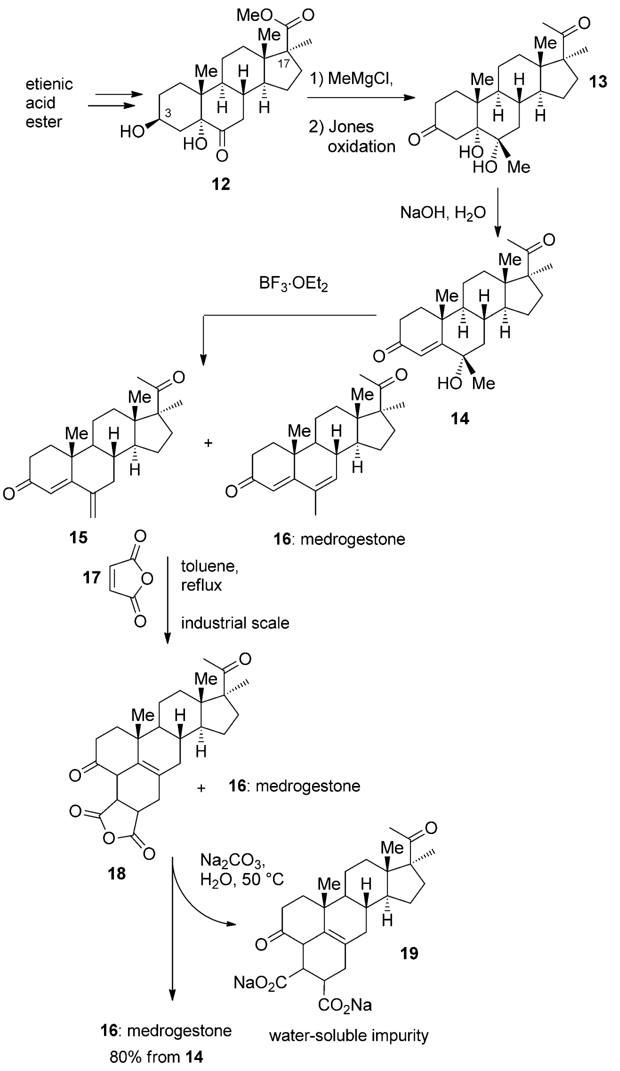
As indicated by Okabe,[41a] vitamin D analogues are in general very potent compounds, typically active at microgram doses. A rather small amount of material is required annually (100 g to 5 kg per year), thus explaining why the use of synthetic strategies and purification methods otherwise unsuitable for the large-scale manufacture of drug substances can be employed.

This addition/extrusion of SO_2 has been applied to the synthesis of a variety of vitamin D analogues (see Figure S1 in the Supporting Information). Calcipotriol[43] (Leo Pharma) was approved in 1991 for the treatment of psoriasis. Tisocalcitate[44] (Bayer) was clinically evaluated for the same indication, whereas seocalcitol[45] (Cougar Biotechnology) is being explored for the treatment of prostate and liver cancer.

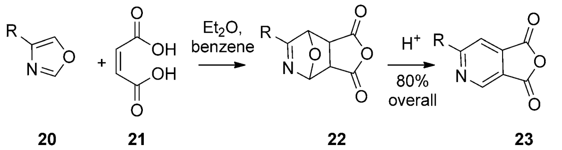
The large-scale synthesis of medrogestone[46] (**16**) is another illustration of the industrial purification of a desired compound after a sequential DA/retro-DA reaction. In this example, maleic anhydride was used as the dienophile to trap impurities containing a *s-cis*-conjugated diene moiety (Scheme 3). The $BF_3{\cdot}OEt_2$-catalyzed dehydration of **14** resulted in medrogestone (**16**) as the major product. However, the formation of some of the regioisomeric diene **15** could not be completely suppressed. Treatment of the mixture of **16** and **15** with maleic anhydride (**17**) allowed for an efficient removal of water-soluble impurities (**19**) after hydrolysis of the DA adduct **18** and subsequent phase separation, thereby leaving the *s-trans*-conjugated diene in medrogestone (**16**) unaffected.

Vitamin B_6/pyridoxine (**29**) plays a central role as a cofactor of a large number of essential enzymes in the human body. It is widely used in nutritional supplements to animal feed or human food for the prevention of various diseases,[47] and has an annual worldwide consumption of several thousand tons.[48] An approach based on an inverse-electron-demand DA reaction[49] was reported as early as 1957 by Kondratjewa[50] (Scheme 4).

In 1965, researchers at Roche[51] developed a new route based on the cycloaddition of 4-methyl-5-ethoxyoxazole (**24**) and 4,7-dihydro-(1,3)-dioxepin[52] (**25**), followed by treatment of the intermediate cycloadduct **26** with a mild acid, acetylation, and subsequent acidic hydrolysis. This process has since been used then for the industrial production of vitamin B_6 at DSM Nutritional Products (formerly Roche Vitamins)[53] and BASF.[54] In 2007, an optimized process amenable to continuous manufacturing was disclosed by DSM. The cycloaddition/cycloreversion sequence was performed under neat conditions to increase the rate of the reaction while minimizing side-product formation and to



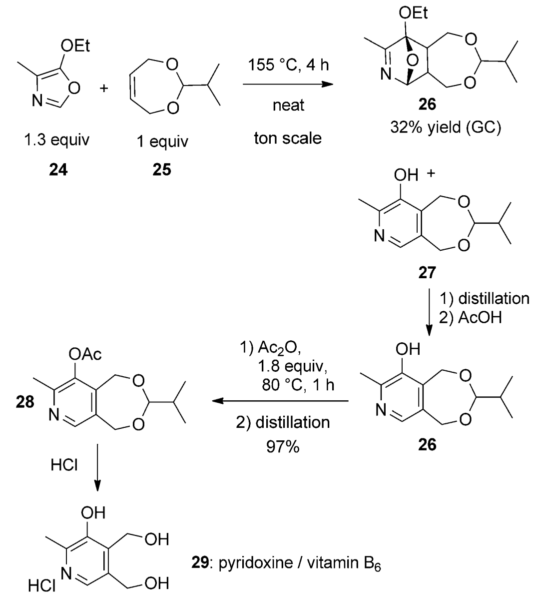
Scheme 3. Synthesis of medrogestone by Morand, Winkley et al.[46]



Scheme 4. Approach to the vitamin B_6 scaffold by Kondratjewa.[50a]

allow recycling of the starting material. Indeed, protected pyridoxine **27**, which arose from the in situ degradation of cycloadduct **26**, tended to react with the starting oxazole, thereby affecting the overall yield. The use of acetic acid rather than HCl allowed for a mild rearrangement of the cycloadduct and an improved yield. Furthermore, acetylation of the protected pyridoxine intermediate facilitated isolation of the targeted product by distillation and acidic hydrolysis. This industrial process is outlined in Scheme 5.

The DA-based synthesis of provitamins K_3 (**30**) and K_4 (**31**) as hemostatic drugs was disclosed by BASF[55] and Eisai[56] (Figure 4). Provitamin K_3 (**36**; menadione) was derived from the reaction of 1-acetoxy-buta-1,3-diene (**32**) and methylbenzoquinone (**33**) in xylene at reflux followed by treatment of the crude regioisomeric mixture (**34**, **35**; Scheme 6) with nitric acid (**36**).[55] The synthesis of lonapalene (**40**), which was investigated in a phase III clinical trial for the treatment of psoriasis, by using benzoquinone (**38**) as the dienophile and chlorobutadiene (**37**) was described by Roche (formerly Syntex, Scheme 7).[57]



Scheme 5. Preparation of vitamin B_6 at DSM.[53]

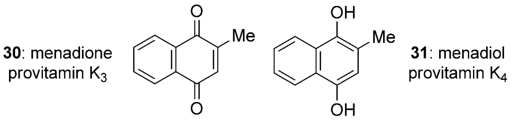
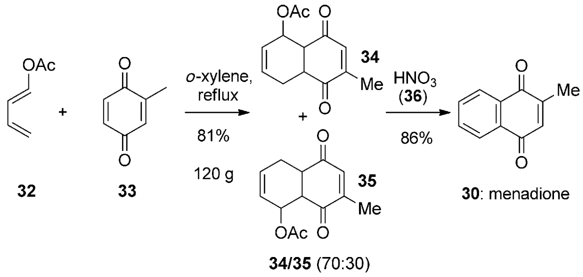
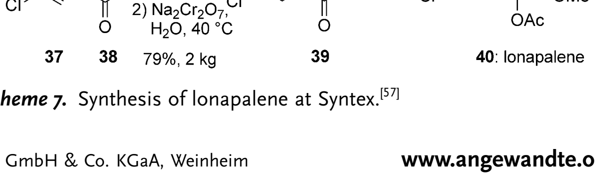


Figure 4. Chemical structures of provitamin K.

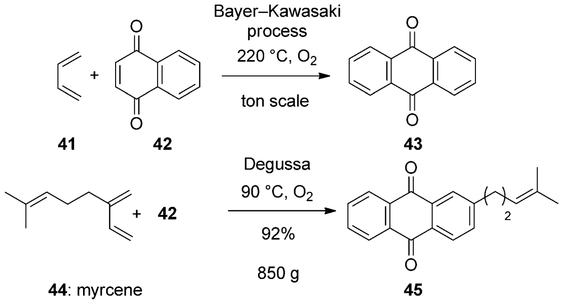


Scheme 6. Preparation of provitamin K_3.[55]



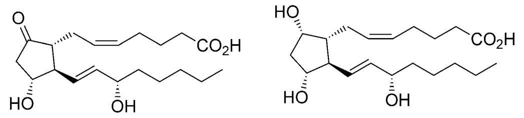
Scheme 7. Synthesis of lonapalene at Syntex.[57]

Similarly, the reaction of 1,4-benzoquinone (**42**) with 1,3-butadiene (**41**) has been used industrially since 1980 to produce anthraquinone (**43**).[58] The Bayer–Kawasaki process is said to produce 3000 tons of **43** per year.[59] Analogously, 2-(4-methyl-3-pentenyl)anthraquinone (**45**), used for the production of hydrogen peroxide, is manufactured from **42** and myrcene (**44**) at Degussa (Scheme 8).[60]



Scheme 8. Manufacture of anthraquinone derivatives.[59a,60]

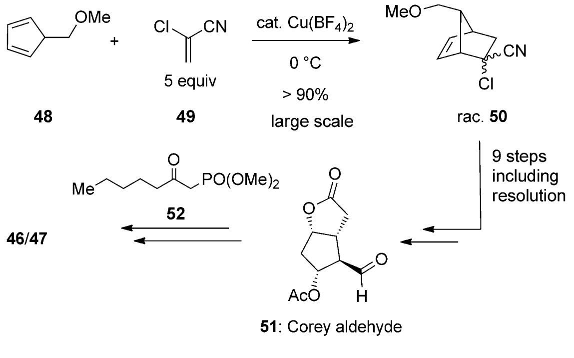
Prostaglandins are an important class of biologically active substances.[61] Prostaglandins of type E have found applications in the treatment of peptic ulcers and cardiovascular diseases, and prostaglandins of type F for the treatment of gynecological disorders and for fertility control, both for human and veterinary use. The DA reaction has been the cornerstone of the commercial preparation of a variety of analogues. The first stereospecific synthesis of prostaglandins (such as PGE_2 (**46**) and PGF_2 (**47**); Figure 5) was developed by Corey et al. in 1969.[62]



46: PGE_2/dinoprostone
47: PGF_2/dinoprost

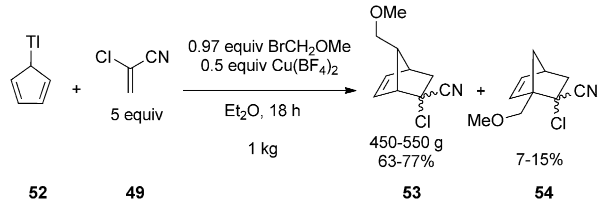
Figure 5. Chemical structures of PGE_2 and PGF_2.

5-Methoxy-1,3-cyclopentadiene (**48**) was treated with the ketene equivalent 2-chloroacrylonitrile (**49**) in the presence of a catalytic amount of cupric tetrafluoroborate to give the bicyclic adduct **50** in racemic form (Scheme 9; together with some regioisomeric by-products arising from the reaction of rearranged starting cyclopentadiene). Further details of this synthetic sequence to aldehyde **51**, known as the Corey aldehyde, have been nicely summarized.[62e] The subsequent stages of this strategy for manufacturing prostaglandins **46** and **47** are presented in Scheme S5 in the Supporting Information. As in the case of vitamin D production, the highly potent character of prostaglandin derivatives tolerates the use of toxic or expensive reagents on a larger scale, at least in the case of the first manufacturing campaigns.



Scheme 9. Synthesis of optically pure prostaglandins by Corey et al.

An improved procedure, published in 1971,[62b] involved the use of a benzyl ether instead of a methyl ether, the former being more conveniently removed by catalytic hydrogenation on a large scale, rather than the need for BBr_3 to remove the methyl ether. In addition, the use of thallium salts of cyclopentadiene (**52**) instead of sodium or lithium to access the required 5-substituted cyclopentadiene reagents proved to significantly prevent the undesired sigmatropic rearrangement leading to regioisomeric cycloadducts. The corresponding thallium salts could be stored and were reported to be relatively stable under air. Despite the known acute toxicity of thallium salts, which would nowadays most probably prevent the scale-up of this approach, a 5 kg scale process was reported[63] (Scheme 10), and even larger batches have been successfully carried out by Research Organics.[64]



Scheme 10. Use of thallium salts for prostaglandin synthesis.[63]

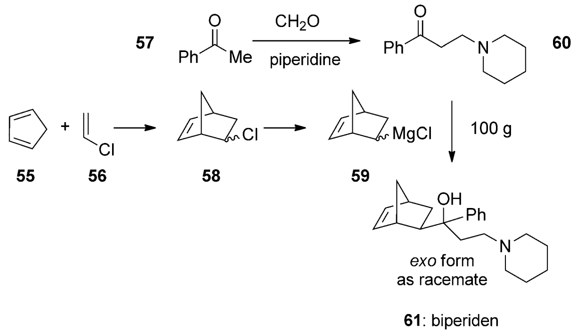
Even though Corey's original DA route delivered several kilograms of prostaglandin analogues, the use of toxic thallium salts and of tributyltin hydride for the deiodination of the Corey lactone (Scheme S5 in the Supporting Information) has prompted the search for improved strategies. Catalytic asymmetric DA reactions to synthesize key intermediates leading to prostaglandins have since been developed.[65] However, analysis of the available literature in the public domain has not yet revealed any industrial application of such a strategy based on a catalytic asymmetric DA reaction to produce prostaglandins. Since the seminal work by Corey et al., a variety of therapeutically useful prostaglandin analogues have been investigated. They are highly potent compounds with annual amounts produced ranging from a few grams to a few kilograms (see Figure S2 in the Supporting Information).[66] Epoprostenol (GSK 1982, Actelion 2009), Iloprost (Schering 1992, Actelion 2006), Tafluprost (Merck 2008), Latanoprost (Pfizer 1996), Travoprost (Alcon 2001), and Bimatoprost (Allergan 2001) are a few examples from a list of about 30 marketed analogues.[27,67] The last three drugs, indicated for the treatment of glaucoma, are among the most frequently prescribed prostaglandin analogues, with combined US sales in 2010 of about 1 billion US dollars.[13]

In 1973, Upjohn disclosed an alternative pathway amenable to commercial-scale manufacturing,[68] which followed the initial contribution of Meinwald et al.[69] Norbornadiene derived from cyclopentadiene and acetylene was used as the key starting material (see Scheme S6 in the Supporting Information). More than 50 kg of PGF_2 (**47**) have been produced per year following this pathway, which relies on a [2+2] cycloaddition. Later industrial approaches[70] to the Corey aldehyde (**51**) still rely on the use of norbornadiene,[71] as originally developed by Pfizer chemists[72] and independently by Peel and Sutherland[73] (see Scheme S7 in the Supporting Information). More than 40 years after the initial stereospecific synthesis of prostaglandin F by Corey et al. in 1969, multiple approaches toward analogues have emerged and have been scaled up industrially.[67,74] Among them, strategies that use norbornadiene as the DA cycloadduct are still proof of the applicability of this reaction on a commercial scale.[75]

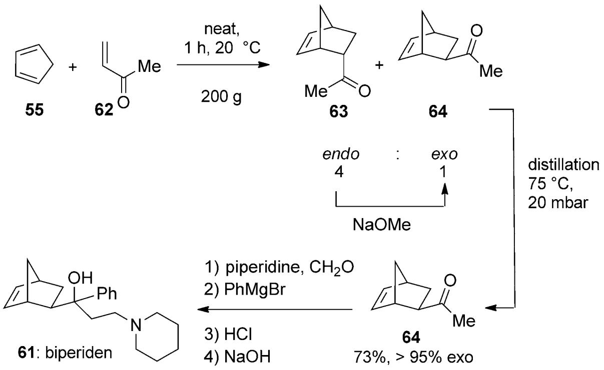
2.2. Cyclopentadiene as Diene

Cyclopentadiene is a widely available and highly active diene (obtained from the cracking of the cyclopentadiene dimer, see below) which has been used extensively in DA reactions. The rigidity of this scaffold allows the stereochemistry of the transformation to be predicted and controlled, thereby giving rise to bicyclic systems that have been further derivatized to access biologically active substances.

Biperiden (**61**), an anticholinergic agent which was introduced in 1954 by Knoll (formerly BASF, now Abbott), is one of the early examples of a pharmaceutical drug derived from cyclopentadiene. It is indicated for the treatment of Parkinson's disease. In the original patent,[76] biperiden was prepared as a racemate by the reaction of bicyclo[2.2.1]hept-5-en-2-yl magnesium chloride[75] (**59**, derived from 5-chloro-2-norbornene (**58**), as a mixture of *endo* and *exo* isomers) with 3-piperidinopropiophenone (**60**), followed by crystallization of the pure *exo* diastereoisomer (Scheme 11). A second approach relied on the cycloaddition of methyl vinyl ketone (**62**) with cyclopentadiene **55** (Scheme 12). This afforded, after equilibration and distillation, 2-acetyl-5-norbornene **63** as the *exo* isomer, which in turn was treated with the Mannich base derived from piperidine and formaldehyde before the addition of phenyl magnesium bromide. The DA reaction typically resulted in a 4:1 *endo*/*exo* mixture of diastereoisomers.[77] The *endo* isomer was then isomerized to the *exo* form in the presence of a catalytic amount of sodium methoxide. This approach seems amenable to the commercial manufacture of biperiden (**61**; Scheme 12).

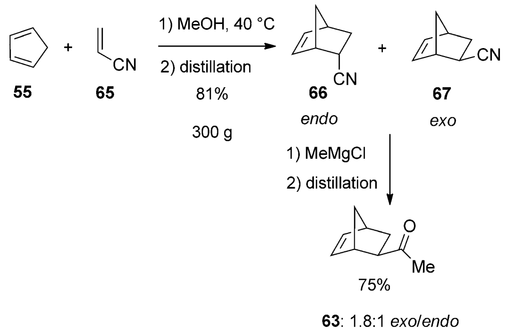


Scheme 11. Original synthesis of biperiden.[75,76]



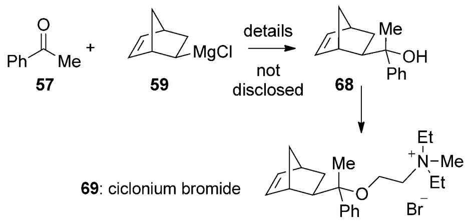
Scheme 12. DA-based synthesis of Biperiden.[77]

However, in view of the moderate reactivity of methyl vinyl ketone towards polymerization, its high toxicity, and the fact that its cycloaddition with cyclopentadiene is highly exothermic and, therefore, poses a challenge on a larger scale, an alternative approach was desirable. A synthesis suitable for an optimized industrial production of biperiden was disclosed in 2008 by Sairam Organics,[78] who used acrylonitrile (**65**) as the dienophile (Scheme 13).[79]



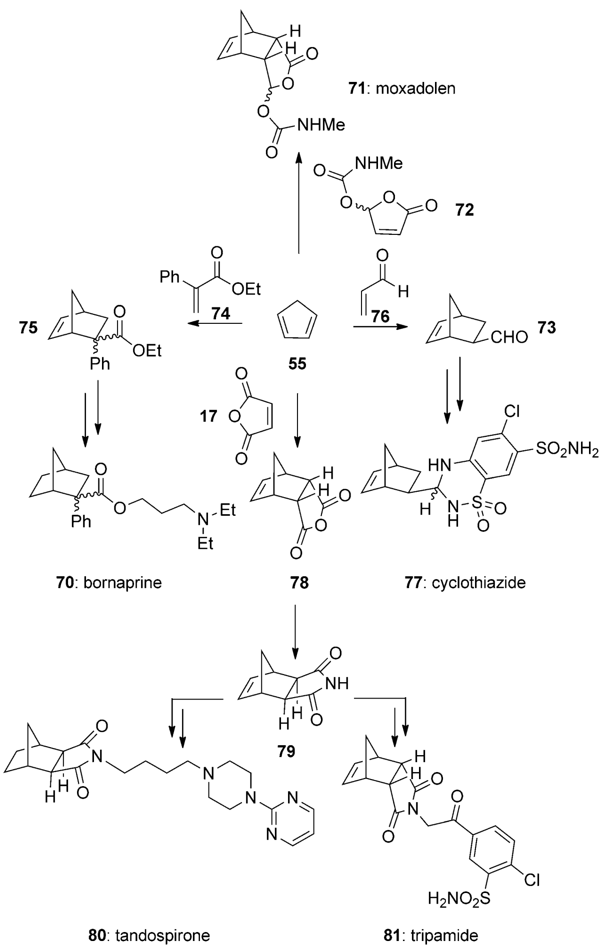
Scheme 13. Synthesis of the biperiden building block at Sairam Organics.[78]

Ciclonium bromide (**69**), an antispasmodic agent, was produced as a racemate by Asta-Werke in 1960, again by using bicyclo[2.2.1]hept-5-en-2-yl magnesium chloride **59** as the key reagent (Scheme 14).[80] Several drugs possessing such bicyclo[2.2.1] frameworks were produced in the 1970s by



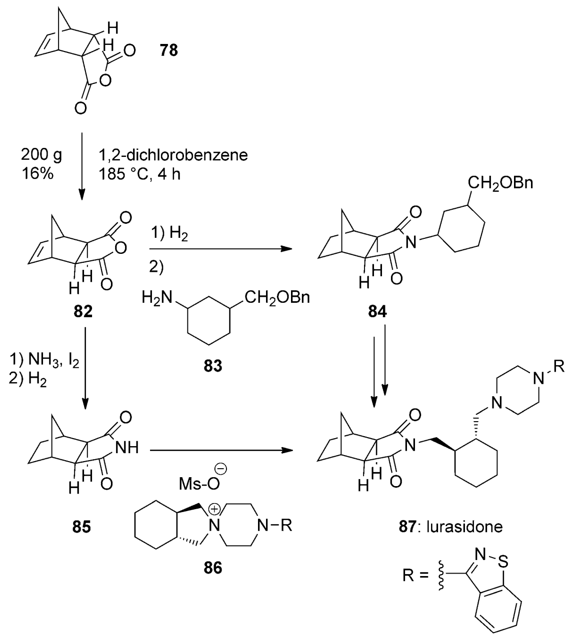
Scheme 14. Synthesis of ciclonium bromide at Asta-Werke.[80]

a DA reaction with cyclopentadiene as the starting diene. This illustrates how popular this reaction became in the decade following the award of the Nobel Prize to Diels and Alder in 1950. Bornaprine (**70**) was disclosed in 1956 by Lilly, and marketed since then by Abbott (formerly Knoll), as an agent for treating Parkinson's disease.[81] Cyclothiazide[81a] (**77**) was introduced in the US in 1963 by Eli Lilly for the treatment of hypertension. Moxadolen (**71**) was under preclinical investigation at BASF in 1975 as a non-opioid analgesic.[82] Tripamide[83] (**81**) is a diuretic agent commercialized by Eisai in Japan in 1982, whereas tandospirone[84] (**80**) was launched in Japan by Dainippon Sumitomo Pharma in 1996 for the oral treatment of depression. Scheme 15 summarizes this set of active ingredients derived from cyclopentadiene.



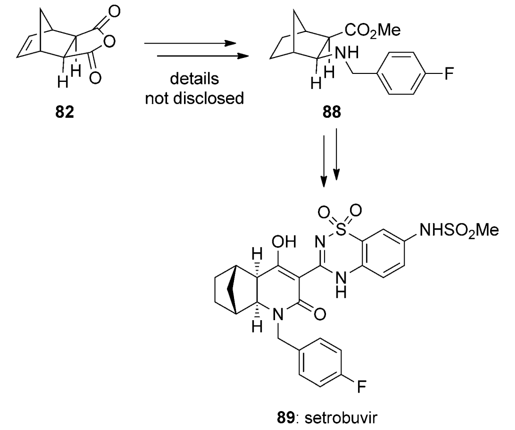
Scheme 15. Commercial compounds derived from cyclopentadiene.

Lurasidone (**87**; Sumitomo) was approved in 2010 by the FDA for the treatment of schizophrenia. Its synthesis proceeds via intermediate **85**, already used by Sumitomo for the preparation of tandospirone (Scheme 15). The sequence begins from the DA adduct between cyclopentadiene and maleimide or maleic anhydride (**78**; Scheme 16). Although the corresponding patents[85] disclose a protocol only on a 100 g scale, it is reasonable to assume that one of these two routes was selected for commercial manufacture.



Scheme 16. Industrial synthesis of lurasidone at Sumitomo.[85a,86]

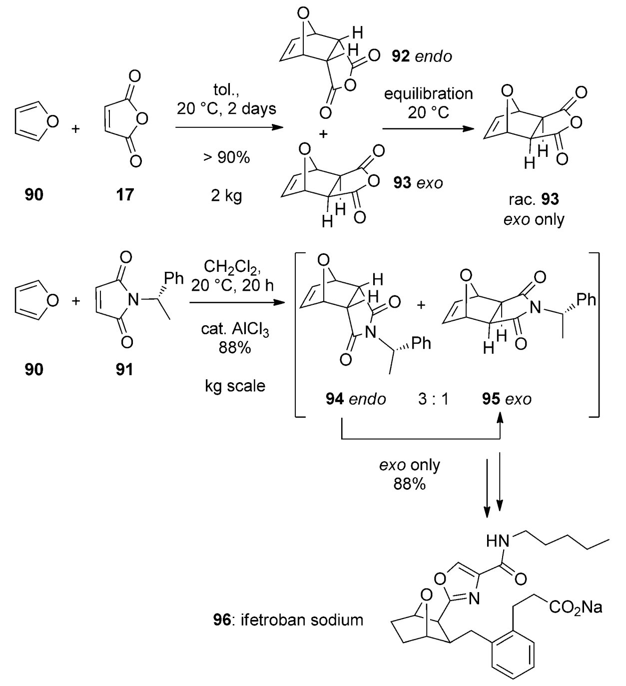
In 2011, setrobuvir (**89**; Anadys/Roche)[87] another drug for which the *exo*-cyclopentadiene–maleic anhydride adduct **82** is used as the starting material, was being investigated in phase IIb clinical trials for the oral treatment of hepatitis C (Scheme 17).



Scheme 17. Synthetic pathway toward setrobuvir.[87a]

2.3. Furan as Diene

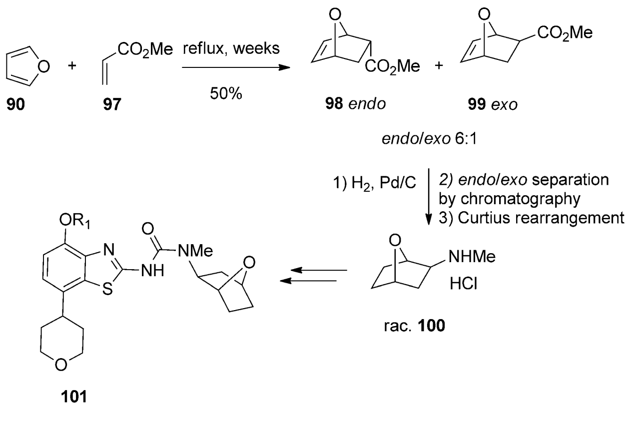
Furan has been used as the diene for the large-scale manufacture of pharmaceutical substances by a DA strategy. Ifetroban sodium (**96**) was a selective thromboxane receptor antagonist investigated as an antiplatelet agent therapy in phase II clinical trials at BMS. In 1997, the preparation of several kilograms of this active ingredient was disclosed to meet the phase II requirements.[88] An initial approach, which ultimately delivered 20 kg of material, relied on the DA reaction between furan (**90**) and maleic anhydride (**17**) at



Scheme 18. Synthesis of ifetroban by a DA reaction.[88]

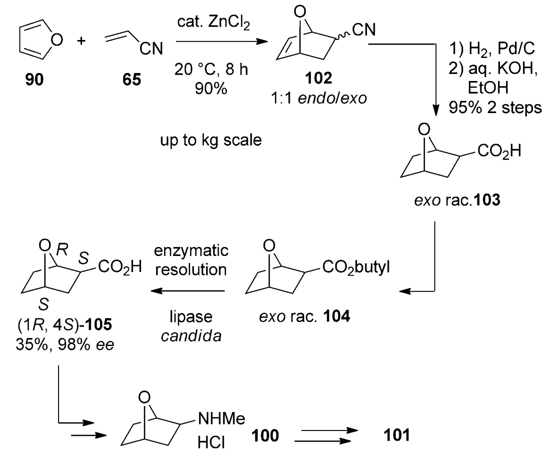
room temperature (Scheme 18). The *exo* and *endo* isomers thus obtained spontaneously isomerized to yield 7-*exo*-oxabicyclo[2.2.1]heptene (**93**), a key intermediate on the way toward ifetroban. Subsequent optimization aimed to avoid the isolation of this irritant. The use of maleimide **91** as the dienophile solved this issue. $AlCl_3$ was employed in a substoichiometric amount (0.3 equivalent) to effect the in situ equilibration to the desired *exo* compound (**95**).

Benzothiazole **101** was evaluated by Roche as an A2a receptor antagonist for the treatment of major depression (Scheme 19).[89] Its synthesis on a large scale relied on the use of an oxabicyclo[2.2.1] building block.[90] The first batches for the early supply of material were prepared by a thermal DA reaction between furan (**90**) and methyl acrylate (**97**), following a published procedure.[91] It afforded a 6:1 *endo*/*exo* mixture (**98**/**99**) of isomers that were separated by column chromatography after hydrogenation. The key precursor bicyclic *exo*-methylamine **100** was then prepared by Curtius rearrangement. In view of the poor selectivity and the need to perform an extra purification, this approach was not appropriate for large-scale manufacture.



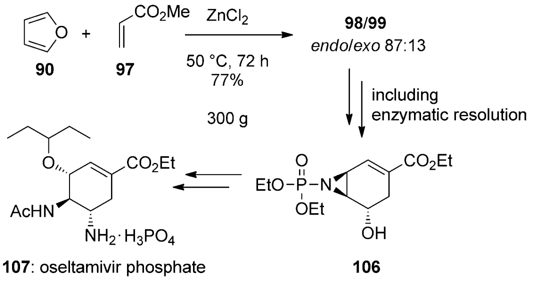
Scheme 19. Synthetic route for the early supply of material for the A2a receptor antagonist at Roche.[90a]

The use of acrylonitrile **65** as an alternative dienophile in conjunction with 0.3 equivalent of $ZnCl_2$ yielded a 1:1 mixture of *endo*/*exo* isomers (**102**; Scheme 20). After hydrogenation of nitrile adduct **102**, hydrolysis of the mixture of nitriles under basic conditions led exclusively to the desired *exo* bicyclic acid **103**, which was converted into the corresponding butyl ester **104**. The pure *exo*-oxabicyclic intermediate was then subjected to lipase-mediated kinetic resolution to give optically enriched carboxylic acid **105** as the key intermediate in 35% yield and 98% *ee*. This DA reaction was successfully scaled up to several kilograms. The *N*-methylamine function was later introduced in a stereospecific Curtius rearrangement. Attachment of the benzothiazole moiety completed the synthetic sequence.



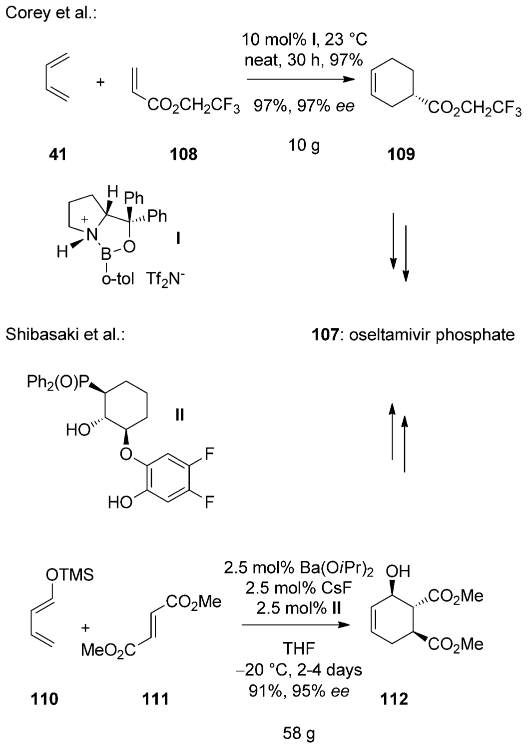
Scheme 20. Alternative use of acrylonitrile toward **101**.[90a]

Chemists at Roche explored the potential of the DA reaction for a new route toward the anti-influenza drug oseltamivir (**107**).[92] In a proof of concept study, the same synthetic sequence as in Scheme 19 was used, but with furan and methyl acrylate as the cycloaddition partners (Scheme 21). This DA reaction was the initial step of the first access to the enantiopure drug substance not involving shikimic acid or quinic acid. It offers the advantage of using

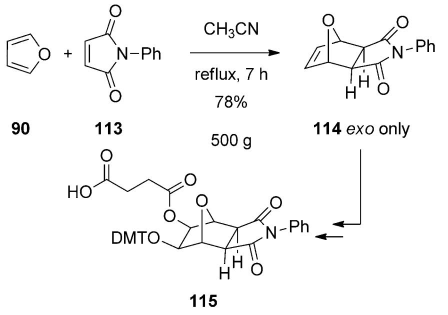


Scheme 21. DA approach toward oseltamivir at Roche.[92]

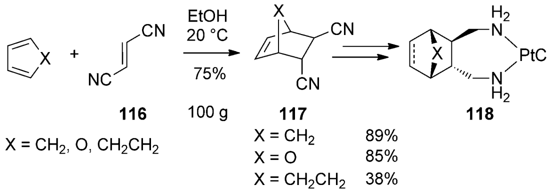
readily available starting materials and reagents, minimal protecting-group manipulations, and an early resolution (Scheme 21). Nevertheless, this sequence was demonstrated only on a gram scale and no information about its scalability has so far been published.[93] Catalytic asymmetric DA strategies invented by Corey and Shibasaki were summarized (Scheme 22) by Magano in reviews of synthetic approaches toward oseltamivir.[94] These elegant routes with high enantioselectivity bode well for scale-up; however, no information on their large-scale application has so far been disclosed.



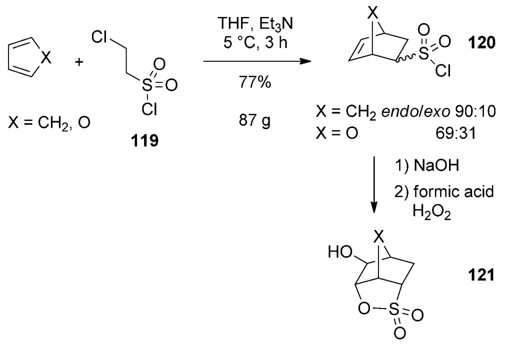
Scheme 22. DA routes toward the synthesis of oseltamivir.[94a]



Scheme 23. Synthesis of linker molecules on a 500 g scale at Isis Pharmaceuticals.[95]



Scheme 24. Use of fumaronitrile as a dienophile by Montaña and coworkers.[96]

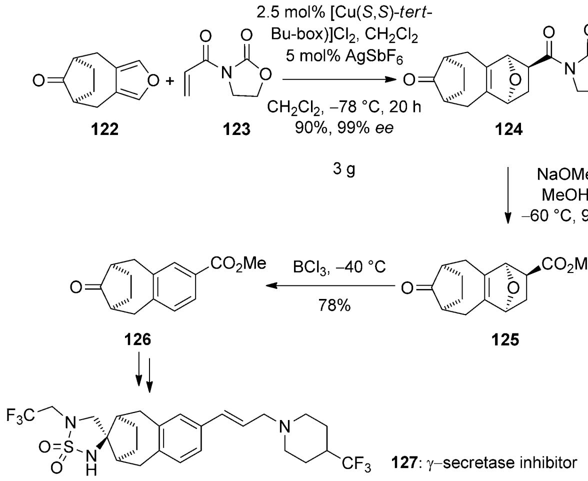


Scheme 25. Large-scale synthesis of bicyclic sultones at Kuraray.[99]

The use of furan as a diene on a kilogram scale was reported by Isis Pharmaceuticals in 2002 for the synthesis of a linker molecule used in nucleotide synthesis (**115**).[95] The bicyclic *exo* adduct (**114**) obtained from the reaction with *N*-phenylmaleimide (**113**) was isolated in pure form when the cycloaddition was conducted in acetonitrile as the solvent (Scheme 23). Platinum(II) complexes with 1,2-bis(aminomethyl)carbobicyclic ligands (**118**) that exhibit cytotoxic properties were derived from the cycloaddition of fumaronitrile (**116**) with cyclic dienes.[96] This sequence was performed on a several hundred gram scale by Montaña[97] following an original method disclosed by Walters and co-workers (Scheme 24).[98] Recently, chemists at Kuraray[99] have developed an industrial synthesis of bicyclic sultones **121**, derived from cyclopentadiene or furan, which are potentially useful for the synthesis of paints or pharmaceutically active compounds (Scheme 25).

γ-Secretase inhibitors, among them **127**, with a benzobicyclo[4.2.1]nonane core as the key structural motif were prepared at Merck.[100] An enantioselective route to tricyclic framework **126** has been reported that is based on a catalytic asymmetric DA reaction of furan tricycle **122** and acrylimide **123** catalyzed by the Evans bis(oxazoline)copper(II) complexes.[101] Very high yields (90%) and enantioselectivities (99% *ee*) were obtained (Scheme 26). To our knowledge, no example of a catalytic asymmetric DA reaction carried out on a large scale has so far appeared in the literature. The high cost and limited availability of the catalyst on a large scale, in addition to moderate selectivities (regio and enantioselectivities) may account for this observation.

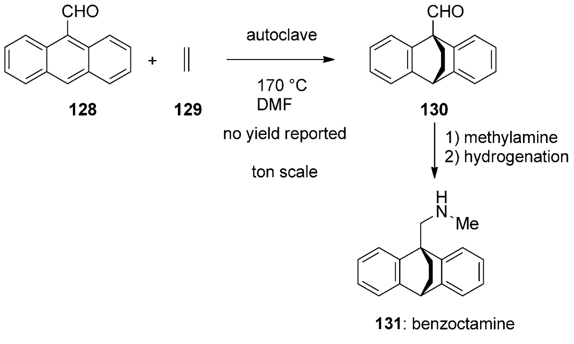
Interestingly, retrosynthesis rarely includes the formation of a benzene ring by a DA reaction involving furan as the dienophile followed by elimination. Other examples illustrating the use of furan as a precursor of benzene are disclosed in Section 2.8 (Schemes 64 and 65).



Scheme 26. Synthesis of γ-secretase inhibitor **127** through a catalytic asymmetric DA reaction.[100a]

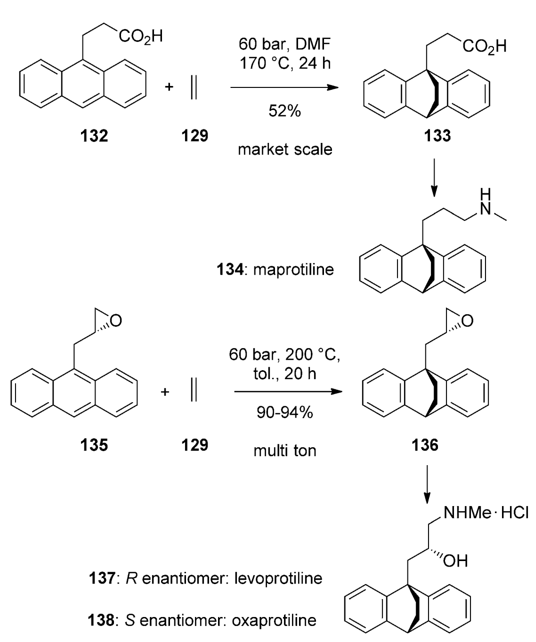
2.4. Anthracene-Derived Dienes

Our literature search identified a few examples of drugs prepared on a large scale by using dienes derived from anthracene. Since its introduction in the late 1960s, benzoctamine (**131**; Novartis formerly Ciba) has been used to treat anxiety. Its manufacture relied on a DA reaction[102] between anthracene-9-carboxaldehyde (**128**) and ethylene (**129**), followed by reductive amination with methylamine (Scheme 27).[103]



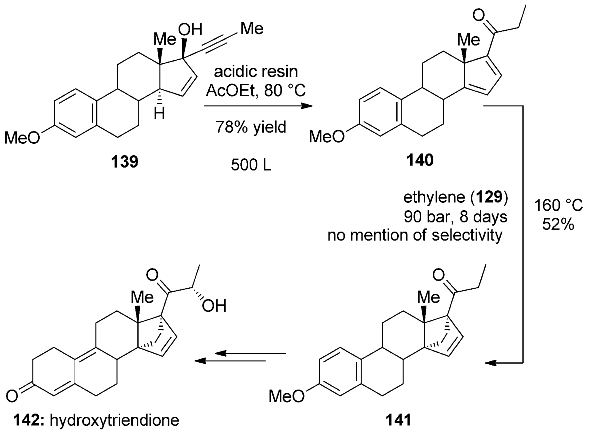
Scheme 27. Preparation of benzoctamine.[103]

Maprotiline[104] (**134**) and levoprotiline[105] (**137**) or its enantiomer oxaprotiline (**138**), which were investigated as psychotropic drugs (between 1975 and 1994), were similarly prepared on a multi-ton scale by using pressurized ethylene (Scheme 28). The successful transfer of this protocol to a manufacturing scale is a true achievement that must have been preceded by a thorough safety assessment of all the process parameters, especially in view of the high operating pressure and temperature, and the use of the polymerization-prone and flammable ethylene.



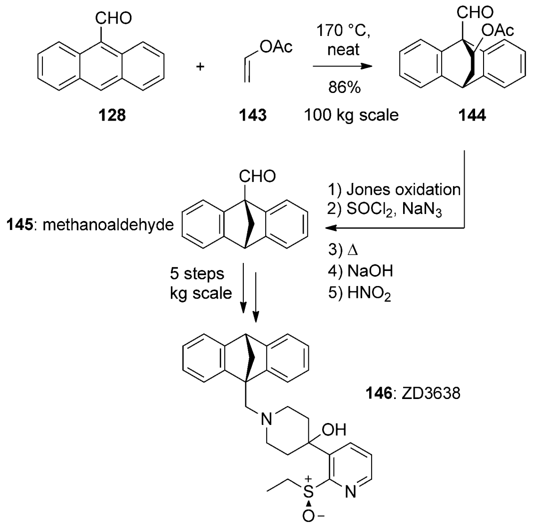
Scheme 28. Commercial manufacturing of maprotiline and oxaprotiline.[104,105]

The synthesis of hydroxytriendione (**142**), a new steroidal substance with no androgenic potential, was reported by Schering.[106] In this example, ethylene was also used as the dienophile. After a vinylogous Rupe rearrangement of an estrone-derived intermediate[107] (**139**), the obtained diene (**140**) was treated with ethylene (**129**) to afford intermediate **141**, which was later converted into **142** (Scheme 29).



Scheme 29. Synthesis of hydroxytriendione **142** at Schering AG.[107]

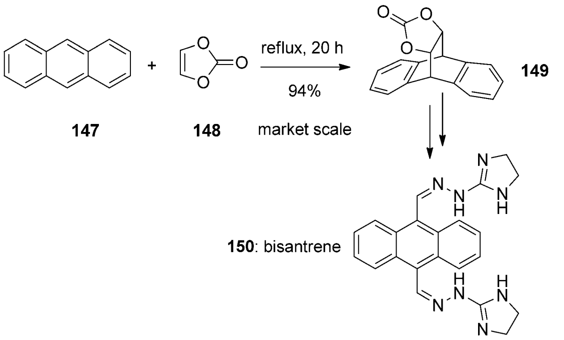
Anthracene-9-carboxaldehyde (**128**) was used at Sumitomo[108] for the six-step preparation of methanoaldehyde (**145**; Scheme 30), which underwent a [4+2] DA reaction with vinyl acetate (**143**). The adduct **144** was further transformed into methanoaldehyde (**145**) by Jones oxidation, conversion into the corresponding acyl azide, rearrangement to the isocyanate, basic hydrolysis, and a final Tiffeneau–Demjanov rearrangement[109] to give the expected aldehyde after treatment with nitrous acid (Scheme 30). Methanoaldehyde (**145**) was also an intermediate in the synthesis of ZD3638 (**146**), an antipsychotic agent that was in phase I clinical trials for the



Scheme 30. Preparation of methanoaldehyde **145** by Sumitomo for the synthesis of ZD3638 at Astra Zeneca.[108]

treatment of schizophrenia (Scheme 30). Large amounts of this material were produced by Astra Zeneca to satisfy a 170 kg demand for the active pharmaceutical ingredient.[110]

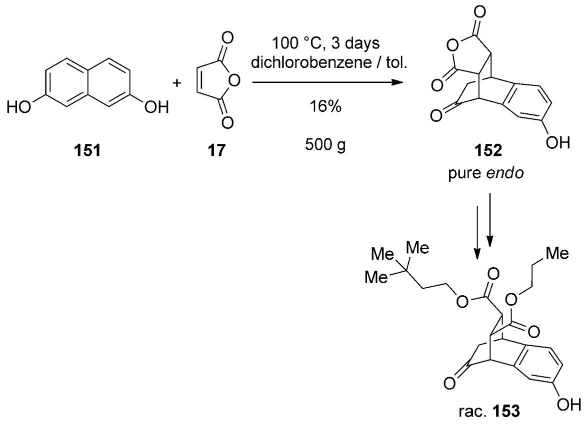
The reaction between anthracene (**147**) and vinylene carbonate (**148**) led to bisantrene (**150**; Scheme 31).[111] Bisantrene was introduced into the market in 1989 by Pfizer (formerly Wyeth) for the treatment of leukemia, but was withdrawn in 1993. Structurally related to previous examples, naphthalene-2,7-diol (**151**) was used by UCB CellTech (formerly CellTech) as the starting material for the synthesis of benzobicyclooctanes such as **153**, with potential use in the treatment of inflammation (Scheme 32).[112]



Scheme 31. Synthesis of bisantrene from anthracene at Wyeth.[111]

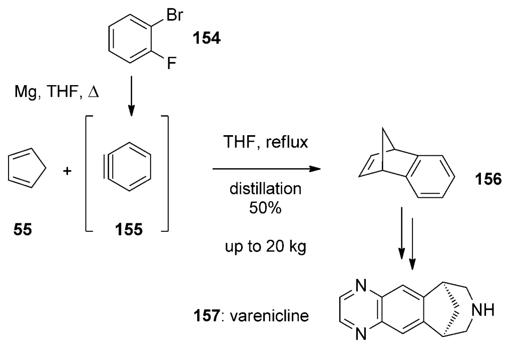
2.5. Benzynes as Dienophiles

In view of the reactivity of benzyne and the associated safety hazards in terms of the potential uncontrolled exothermic decomposition of the reaction mixture, one may have questioned the feasibility of its use in a large-scale reaction. The following examples illustrate that these obstacles can be overcome for a successful transfer from the laboratory to the plant.



Scheme 32. Large-scale synthesis of anti-inflammatory agent **153** at Cell Tech.[112]

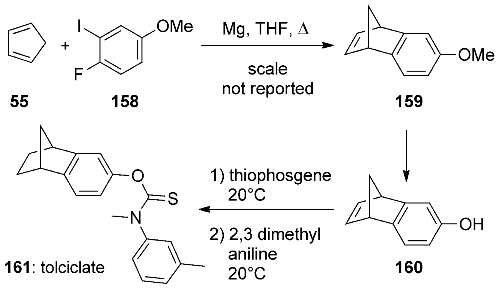
Varenicline (**157**; Pfizer) was approved in 2006 by the FDA for the cessation of smoking, and generated sales close to 400 million US dollars in 2010.[13] Coe et al.[113] have described the quest for a viable commercial route to varenicline in detail from a process research perspective. Following the original discovery route, the bridged system within this active ingredient was constructed by a DA reaction between two highly reactive species, namely benzyne (**155**, generated from 2-bromofluorobenzene **154** and magnesium turnings) and cyclopentadiene **55** (Scheme 33). After aqueous work-up, the corresponding benzonorbornadiene (**156**) was isolated by distillation (in ca. 50 % yield) under reduced pressure to separate it from other benzyne-derived by-products.[114]



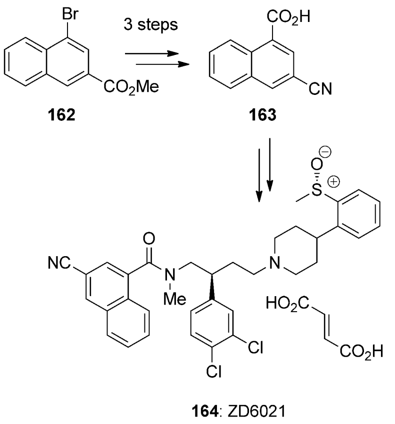
Scheme 33. Kilogram synthesis of varenicline at Pfizer.[113]

After extensive safety studies, the scale-up of this approach to batch sizes of several kilograms ultimately delivered 5 kg of varenicline, which was sufficient material for phase II trials. The authors especially underscore the fact that access to the cyclopentadiene monomer on a kilogram scale through cracking of its dimer posed a major safety concern in the absence of dedicated cracking equipment and low-temperature storage facilities to prevent any explosive dimerization.[115] This unit operation may be difficult to carry out on a medium scale, typically a few kilograms, for which a dedicated cracker operating in a continuous fashion would be too large. A patent by Albemarle[116] describes the typical issues associated with cracking cyclopentadiene in the plant, such as clogging of the heat-transfer surfaces, which causes frequent shutdowns for cleaning. This contrasts with a common conception that such cracking is a textbook exercise[117] which can be uneventfully scaled up. It is indeed recommended by the authors "to immediately dilute the cyclopentadiene directly from the cracker with ten volumes of hexanes held cold (at around −40 °C)" and "to store the pure cyclopentadiene packed in dry ice at −40 to −50 °C".[113] These safety limitations, which are impediments to batch manufacturing, compromised such a DA approach for commercial production. This prompted the search for an alternative strategy, not based on a DA reaction, which ultimately proved to be compatible with commercial-scale requirements.[113,118] This example illustrates the typical difficulties of scaling up a DA reaction (especially when using cyclopentadiene monomer as a reagent) because of the heat of formation of the product and polymerization of the starting material. In this example, even though clinical batches were prepared by using this [4+2] cycloaddition pathway, a more competitive route was eventually found for industrial manufacturing. Whereas cyclopentadiene cracking was deemed not to be feasible in a multipurpose pilot plant for manufacturing pharmaceuticals, this operation is routinely performed in dedicated facilities, as illustrated by the numerous examples we have identified in the fragrance industry (see Section 4).

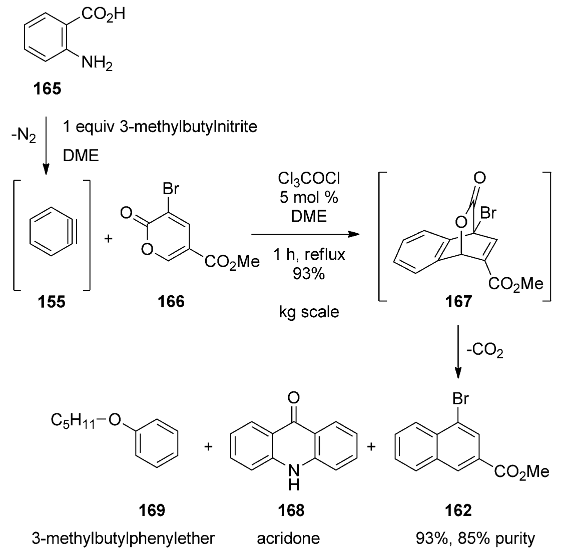
In the early 1970s, Pfizer (formerly Pharmacia) had already followed a similar benzyne-based approach to prepare tolciclate[119] (**161**), an antifungal substance still on the market today (Scheme 34). ZD6021 (**164**), a tachykinin receptor antagonist under preclinical investigation at Astra Zeneca[120] for the treatment of depression and asthma, was prepared from 3-cyano-1-naphthalenecarboxylic acid[121] (**163**; Scheme 35).



Scheme 34. Preparation of tolciclate from benzonorbornadiene.[119]



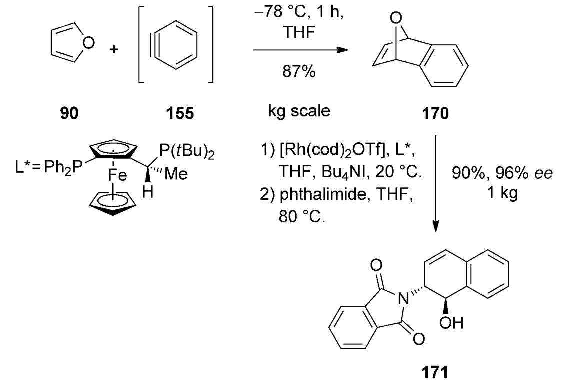
Scheme 35. Synthetic strategy toward ZD6021.[121a]



Scheme 36. Synthesis of the naphthalene building block of ZD6021 by a DA reaction.[121a]

The build-up of the naphthalene ring by a DA reaction turned out to be a viable alternative to previous routes that suffered from low selectivity. Bromocoumalate **166** was treated with in situ generated benzyne to give methyl-1-bromo-3-naphthalene carboxylate (**162**) in 93 % yield after decarboxylation (Scheme 36). The diazonium salt formed from anthranilic acid (**165**) with 3-methylbutylnitrite in DME as the solvent was used as the benzyne precursor. The successful scale-up of this approach required extensive safety studies in view of the thermal instability of the diazonium betaine and the bridgehead benzylic tertiary bromide intermediate (prior CO_2 extrusion) in addition to the high reactivity of benzyne. The portion-wise, slow addition of 3-methylbutylnitrite and anthranilic acid to a solution of **166** in DME under reflux not only minimized the accumulation and formation of side products (such as 3-methylbutyl phenyl ether or acridone), but allowed control of the gas evolution, thus rendering this process amenable to plant-scale manufacturing.

In 2010, Spielvogel[122] reported on the rhodium-catalyzed ring opening of oxabenzonorbornadiene (**170**) to **171** introduced by Lautens et al.[123] The synthesis of this building block, based on the DA reaction of benzyne with furan (**90**), was performed on a scale of up to 10 kg (Scheme 37). It was judged to be feasible up to 1 ton.[124] The fact that this cycloaddition proceeds at low temperature (−78 °C) is especially noteworthy.



Scheme 37. Rhodium-catalyzed opening of 1,4-epoxydihydronaphthalene on a kg scale.[122]

The following sections have been ordered according to the reaction type rather than by the nature of the DA reagents to underscore the important strategic scopes of hetero-, auxiliary-based, and intramolecular DA reactions.

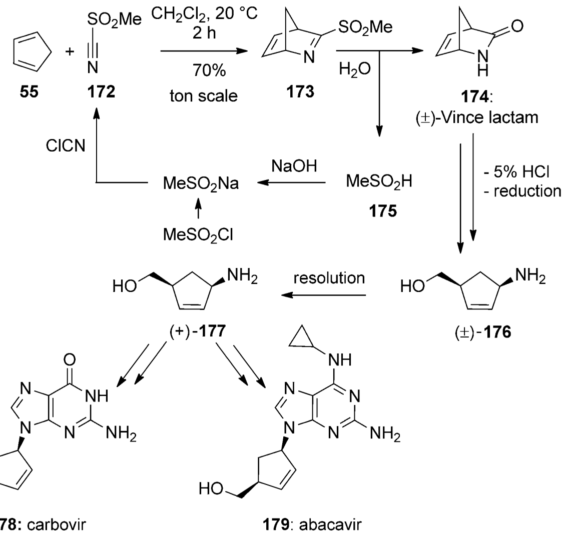
2.6. Hetero-DA Reactions

The introduction of heteroatoms into a pharmaceutical scaffold has proven to be beneficial for modulating the biological properties. The hetero-DA reaction is well-suited for this purpose. It has been implemented on a manufacturing scale on several occasions.

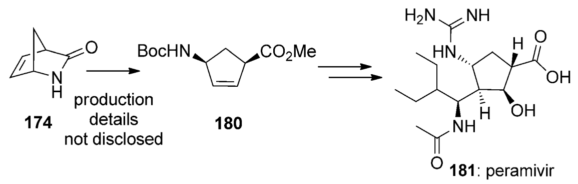
Abacavir (**179**) is a reverse transcriptase inhibitor that was launched in 1999 by GSK for the oral treatment of HIV infection. The key to the synthesis was the use of azabicyclo[2.2.1]hept-5-en-3-one (**174**) as an intermediate, which was also utilized for the preparation of carbovir (**178**), a related preclinical candidate.[125] The bicyclic lactam **174** (also known as Vince lactam after its inventor[126]) is prepared by Lonza on a 50 ton scale per year through a DA cycloaddition between cyclopentadiene (**55**) and methanesulfonyl cyanide (MSC, **172**).[127] The use of stoichiometric amounts of the explosive and moderately stable MSC led to reduced productivity. After extensive process optimization, it was found that MSC could be elegantly generated in situ and treated with cyclopentadiene in a continuous fashion:[128] hydrolysis of intermediate **173** in a two-phase CH_2Cl_2/water solvent system generated lactam **174** and enabled methanesulfinic acid (**175**) to enter a new cycle of MSC formation. In addition, cyclopentadiene is no longer used under neat conditions, which had required its removal prior to acidic hydrolysis. Racemic **174** was eventually converted enzymatically into (4-aminocyclopent-2-en-1-yl)methanol (**177**) on the way toward **178** and **179** (Scheme 38).[127a]

Peramivir[129] (**181**) was launched in 2010 by Shionogi for the treatment of influenza infection. Its synthesis is based on the use of the Vince lactam (**174**), as described for abacavir (Scheme 39).[130]

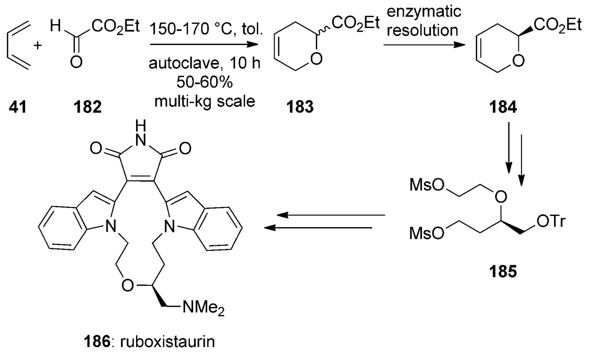
One of the rare examples of a large-scale hetero-DA reaction was disclosed in 2002[131] for the synthesis of ruboxistaurin mesylate (**186**), a protein kinase C beta inhibitor that was preregistered in 2006 by Eli Lilly in the US for the oral treatment of diabetic retinopathy. A key 3,6-dihydropyrane intermediate **184** had been previously manufactured using expensive (*R*)-1-chloro-2,3-propanediol as the starting material. In view of the relatively high cost of the starting material on a large scale, the dihydropyrane system was built up by a hetero-DA reaction (Scheme 40). A catalytic asymmetric approach was not pursued further, either because of the low enantiomeric excess in test experiments or the expected high contribution cost of the catalyst.[132] Instead, the reaction between the readily accessible butadiene (**41**) and ethyl glyoxylate (**182**) was considered to compete favorably



Scheme 38. Industrial preparation of abacavir and carbovir from the Vince lactam.

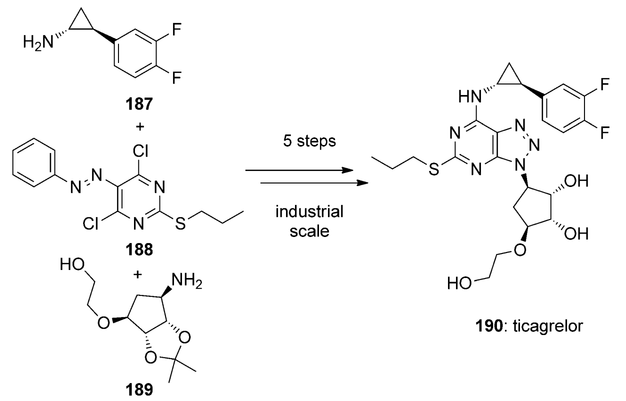


Scheme 39. Industrial preparation of peramivir from the Vince lactam.[129]

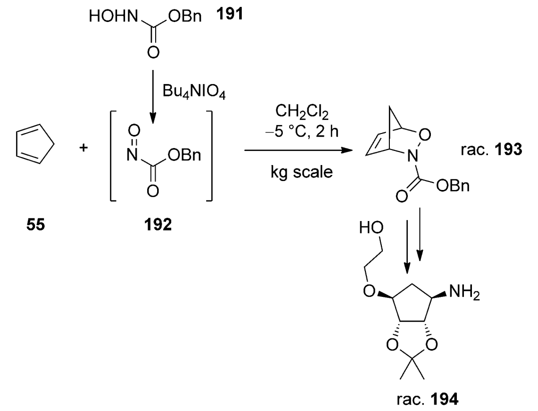


Scheme 40. Industrial preparation of ruboxistaurin.[131]

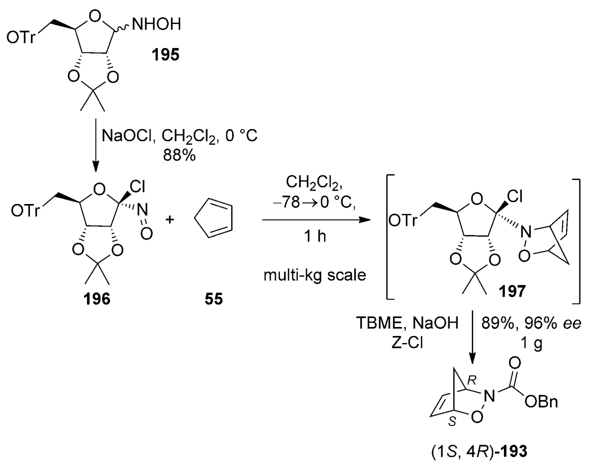
with the first established manufacturing route. The cycloaddition was carried out at 170 °C at an operating pressure of 10 bar. Butadiene (1.2–1.4 equiv) was gradually added to the autoclave containing a solution of ethyl glyoxylate in toluene and hydroquinone (1 % w/w) to minimize exothermic polymerization at higher temperature. The corresponding adduct (**183**) was isolated as a racemic mixture in 50–60 % yield (based on the recovery of any starting glyoxylate) after fractional distillation. This material was subsequently subjected to enzymatic hydrolysis to yield the desired *S* enantiomer (**184**) in pure form. This process has been carried out successfully in a pilot plant and has now become a commercial route to ruboxistaurin (**186**).[131] Additional details on the industrial production of the same racemic 3,6-dihydro-2*H*-pyran-2-carboxylic esters by a similar protocol have been disclosed by Bayer.[133]



Scheme 41. Industrial preparation of ticagrelor.[16d,134]



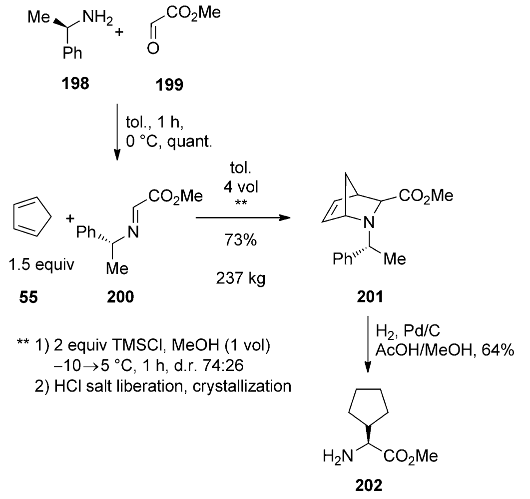
Scheme 42. Synthesis of the ticagrelor building block through a hetero-DA reaction of cyclopentadiene.



Scheme 43. Production of the oxaazabicycloheptene building block through a hetero-DA reaction at Lonza.[137]

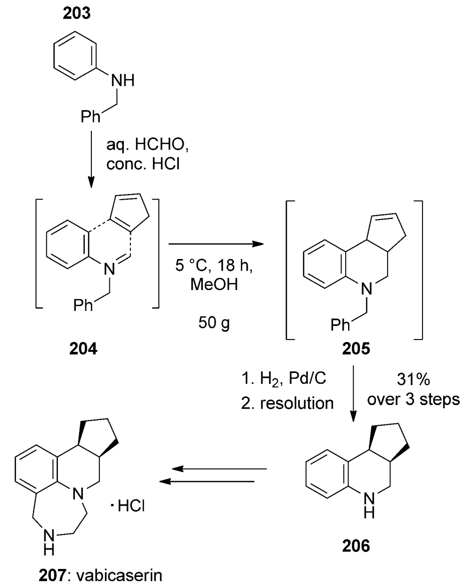
Ticagrelor (**190**), a P_2Y_{12} antagonist from Astra Zeneca, was granted approval in 2010 (Europe) and 2011 (US) for the prevention of atherothrombotic events in adult patients with acute coronary syndromes. The synthesis of ticagrelor comprises 28 steps (Scheme 41).[16c,d,134] The tetrasubstituted cyclopentane moiety (**189**) was built up in racemic form through a hetero-DA reaction of cyclopentadiene to yield 2-oxa-3-azabicyclo[2.2.1]hept-5-ene (**193**). The benzyl nitrosoformate dienophile (**192**) was prepared according to a protocol described on a 1 mol scale (93 % yield after chromatography) at Lilly (Scheme 42).[135] The nitrosocarbonyl hetero-DA reaction has been reviewed recently.[136] As mentioned by Federsel at Astra Zeneca,[16d] "this process has been [first] successfully scaled-up to multi-kg pilot production" and is most probably being used on a commercial scale for the production of ticagrelor. A diastereoselective variant of this hetero-DA approach was disclosed in 2011 by Lonza through the use of chiral auxiliary **196** derived from D-ribofuranose (Scheme 43).[137] This process is amenable to industrial manufacturing.[138]

A few examples illustrate the use of the aza-DA reaction on a large scale following the seminal work by Abraham and Stella.[139] In 2005, Hashimoto et al. at Fujisawa disclosed details of the scale-up of an aza-DA reaction between cyclopentadiene and imine **200** prepared in situ from methyl glyoxylate (**199**) and (*R*)-α-methylbenzylamine (**198**).[140] It was exemplified on a 237 kg scale in a 4000 L reactor. It was found for this DA reaction that a biphasic solvent system (toluene/MeOH 4:1) in the presence of TMSCl (2 equiv) and excess cyclopentadiene (1.5 equiv) led to the highest ratio of the desired diastereoisomer **201** relative to the other isomers (ratio of 74:26). After liberation of the obtained HCl salt under basic conditions, the expected product was crystallized from heptane as a white solid (103 kg) in 32 % yield with 94.6 % *de* (Scheme 44). After a second crystallization, the diastereoisomeric excess was upgraded to 98.3 %. Calorimetric studies revealed that this aza-DA reaction displayed only a modest exotherm, which allowed the addition of freshly distilled cyclopentadiene to the reaction mixture in one portion. Hence, standard cooling equipment in a pilot plant (−15 °C, brine) was sufficient to control the reaction temperature. Hydrogenation of this material under acidic conditions led to the concomitant cleavage of two C−N bonds, thus producing optically pure cyclopentyl glycine derivatives (**202**). These compounds are used to prepare biologically active peptides and chiral catalysts.



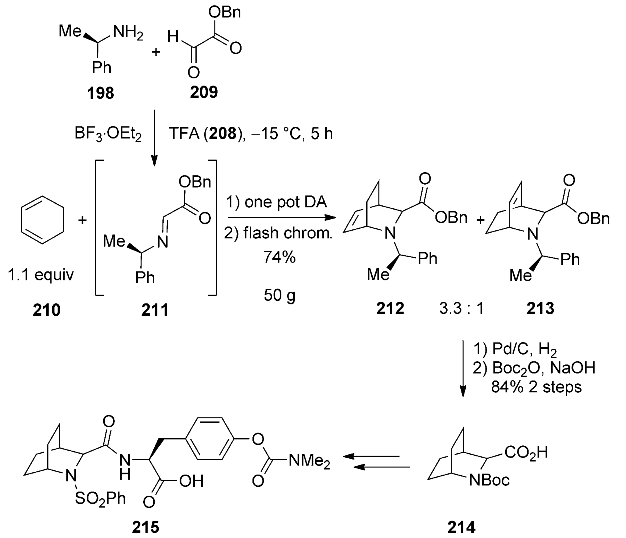
Scheme 44. Synthesis of optically active cyclopentyl glycine derivatives at Fujisawa.[140]

The synthesis of vabicaserin (**207**), which was investigated in phase II clinical trials at Pfizer (formerly Wyeth) for the treatment of schizophrenia, is another illustration of the use of cyclopentadiene as a dienophile in an aza-DA reaction with diene **204** derived from *N*-benzylaniline (**203**). In 2007, this transformation was claimed in a process patent and exemplified only on a gram scale.[141] It seemed robust enough though for the supply of material for phase II trials (Scheme 45).



Scheme 45. Aza-DA reaction in the synthesis of vabicaserin at Pfizer.[141a]

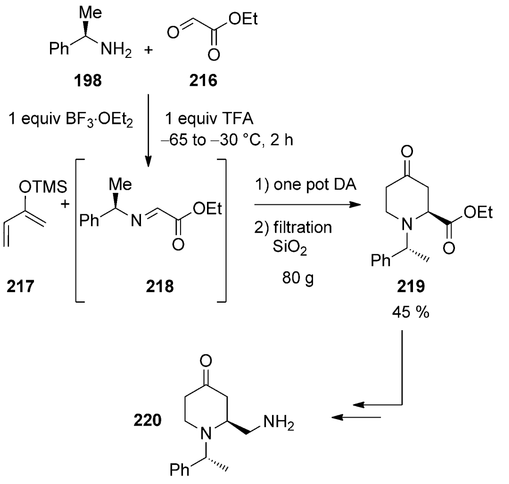
Another example of an aza-DA reaction performed with cyclohexadiene, en route to an integrin antagonist (**215**) for development as an inhaled antiasthmatic agent, was disclosed at Johnson and Johnson.[142] TFA and $BF_3{\cdot}OEt_2$ were used to promote the formation of imine **211** from benzyl glyoxylate (**209**) and (*R*)-α-methylbenzylamine (**198**) and a subsequent cycloaddition with cyclohexadiene at −25 °C (Scheme 46).



Scheme 46. Multigram synthesis of integrin antagonist **215** through an aza-DA reaction at Johnson and Johnson.[142]

After chromatography, a mixture of isomers (**212**, **213**) was obtained in 74 % yield.[143] Performing the reaction at higher temperature (−25 °C instead of −78 °C) improved the yield significantly (from 38 %). Both purified isomers were hydrogenated exhaustively to give the corresponding Boc-protected [2.2.2]bicyclo amino acid as a single enantiomer (**214**). Before considering a larger scale-up of this reaction, further optimization would certainly be required, especially with the aim of omitting the purification by flash chromatography.

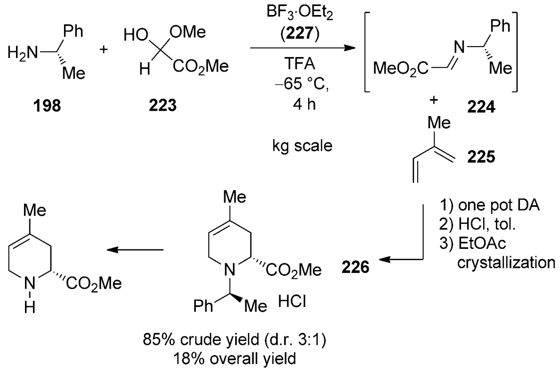
In a related example performed at Novo Nordisk,[144] the synthesis of protected 2-substituted 4-oxopiperidine derivatives **220** was reported on a scale of several tens of grams through a reaction between 2-trimethylsilyloxy-1,3-butadiene (**217**) and the imine **218** derived from ethyl glyoxalate (**216**) and (*R*)-α-methylbenzylamine (**198**; Scheme 47). TFA and $BF_3{\cdot}OEt_2$ were also used as activators. The two diastereoiso-



Scheme 47. Preparation of 2-substituted 4-oxopiperidine derivatives through an aza-DA reaction at Novo Nordisk.[144]

mers were formed in a 1.4:1 ratio. After filtration of the mixture through a short plug of silica gel, the addition of hot *n*-heptane induced crystallization of the major diastereoisomer **219**, which was isolated in 45 % yield and with excellent purity.

The asymmetric aza-DA reaction shown in Scheme 48 was scaled up at Pfizer in the early 1990s to prepare the chiral pipecolic acid derivative **222**.[145] This intermediate was required for the development of the orally active thrombin inhibitor candidate UK-156406 (**221**; Figure 6). This aza-DA reaction constitutes another large-scale application of the method of Abraham and Stella. Although the diastereoselectivity for the desired *S*,*R* diastereoisomer derived from imine **224** and isoprene (**225**) was modest (d.r. 3:1 by ^{1}H NMR spectroscopy) and an upgrade of the optical purity (by recrystallization of the HCl salt) led to a lower yield, this reaction was performed up to 1.6 kg scale (Scheme 48). After further optimization, this process was eventually used to manufacture 80 kg of intermediate **222**. A key factor in scaling-up this process was the commercial availability of methyl glyoxylate methyl hemiacetal (**223**), a stable, easily handled source of methyl glyoxylate.



Scheme 48. Aza-DA approach on a kg scale in the synthesis of UK-156406 at Pfizer.

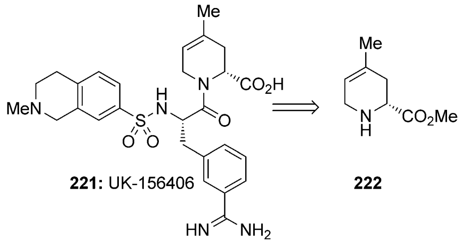
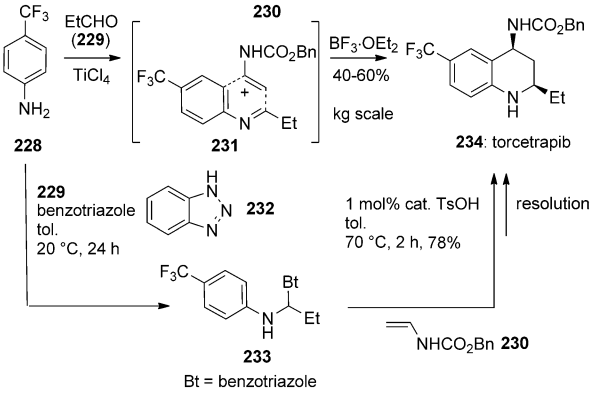


Figure 6. Retrosynthetic analysis of UK-156406 at Pfizer.[145]

Torcetrapib (**234**) was investigated in phase III clinical trials at Pfizer for the prevention and treatment of atherosclerosis. Its development was discontinued in 2006 because of an unfavorable safety profile. The commercial manufacturing route to this clinical candidate has been published.[146] Its synthesis relied on the build-up of the tetrahydroquinoline moiety with all the substituents in a *cis* configuration by an aza-DA reaction (Scheme 49). Originally, the imine **231** was generated in situ in CH_2Cl_2 from *p*-trifluoromethylaniline (**228**) and *n*-propanal (**229**) by using $TiCl_4$ as a dehydrating agent and was treated with *N*-vinylbenzyl carbamate (**230**) in the presence of $BF_3{\cdot}OEt_2$. The yield turned out to be only moderate (40–60 %) and purification proved cumbersome. The chemists at Pfizer suspected that the instability of the reacting imine was the reason. Accordingly, it was trapped with benzotriazole (**232**), which led to the crystalline imine surrogate **233**. The latter was isolated and treated with vinyl carbamate **230** in the presence of a catalytic amount of pTsOH (1 %) to yield the expected racemic adduct in 78 % yield and with no trace of the *trans* by-product. Torcetrapib (**234**) was eventually produced by resolution of an advanced intermediate by diastereoselective salt formation. Even though this improved protocol delivered several kilograms of material, an asymmetric route to form the tetrahydroquinoline core was desirable for commercial production. The rather poor stability of *N*-vinylbenzyl carbamate and the safety issue raised by the long-term storage of trifluoromethylaniline were additional caveats.[146a] An asymmetric route was eventually registered in which the first aza-DA approach was replaced by the cyclization of a functionalized imide.[146b]

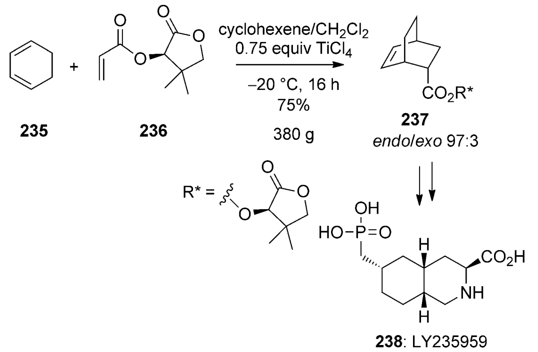


Scheme 49. Synthesis of torcetrapib on a kg scale through an aza-DA reaction.[146a]

2.7. Auxiliary-Based DA Reactions

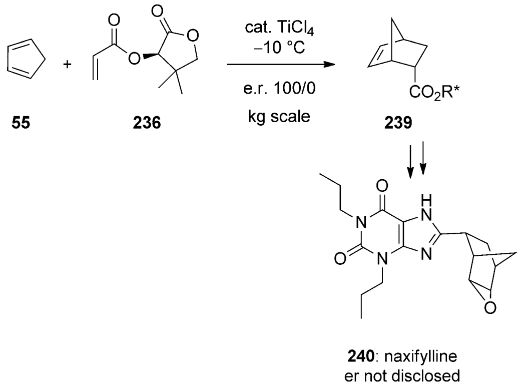
The control of the regio- and enantioselectivity of the DA reaction is often a challenge, especially when large-scale production is considered. Isolation of the desired isomer by flash chromatography is often too costly an option on a large scale, and thus optimization of the reaction conditions is a necessity. The use of a chiral auxiliary is an acceptable means to maximize the selectivity if it allows for a straightforward isolation of the major isomer by crystallization. In this section, we would like to highlight some successful implementations of this strategy on a kilogram scale.

LY235959 (**238**) was under development at Lilly[147] for the treatment of neurodegenerative disorders. The key to the successful synthesis of this candidate on a kilogram scale was access to a [2.2.2]bicyclic framework through a $TiCl_4$-medi-

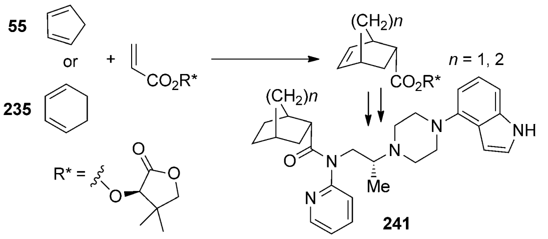


Scheme 50. Use of the (*R*)-pantolactone-derived dienophile on a kg scale for the synthesis of LY235959 at Eli Lilly.[147]

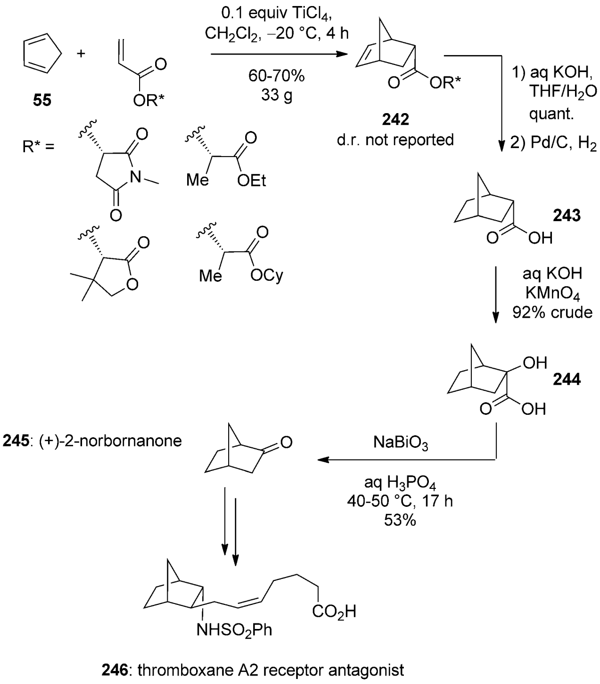
ated diastereoselective DA reaction based on the pioneering work of Helmchen and co-workers (Scheme 50).[148] Cyclohexadiene **235** was treated with dienophile **236**, which was derived from acryloyl chloride and (*R*)-pantolactone. The expected *endo* adduct **237** was isolated in 75% yield with a high diastereomeric excess of up to 97:3. This method has been used for the synthesis of naxifylline (**240**; Scheme 51), an adenosine receptor agonist investigated in phase II clinical trials at Biogen Idec (formerly Biogen) for the potential treatment of cardiac arrhythmia.[148a,149] The scale-up of this reaction, with a focus on recycling the chiral auxiliary, has been described (Scheme 51).[150] A patent application[151] from Pfizer (formerly Wyeth) describes the use of a similar approach for the synthesis of bicyclic indolyl derivatives **241** as serotonergic agents, potentially indicated for the treatment of depression and anxiety (Scheme 52).



Scheme 51. Synthesis of naxifylline on a kg scale at Biogen Idec.[150]



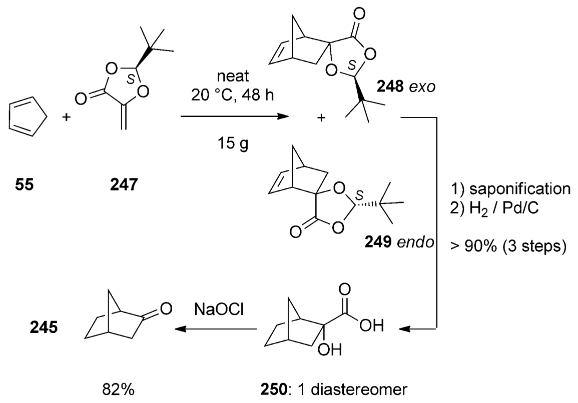
Scheme 52. Synthesis of **241** by a diastereoselective DA reaction.[151]



Scheme 53. Syntheses of (+)-2-norbornanone for the synthesis of thromboxane receptor antagonist **246** at Chisso.[152]

Another example of a diastereoselective DA reaction using a chiral auxiliary was disclosed at Chisso.[152] Optically active 2-norbornanone (**245**) was synthesized as an intermediate for the synthesis of thromboxane receptor antagonist **246**.[153] The synthesis and use of a variety of chiral acrylates (including (*S*)-pantolactone, (*S*)-(−)-*N*-methyl-2-hydroxysuccinimide, or (*S*)-alkyl lactate) was described, with $TiCl_4$ used as the catalyst for the cycloaddition (Scheme 53). The *endo* cycloadduct (**242**) was saponified, and then submitted to catalytic hydrogenation. Oxidative decarboxylation of **243** was achieved with potassium permanganate and sodium bismuthate, and a subsequent distillation afforded **245** in 29–34% yield over five steps.

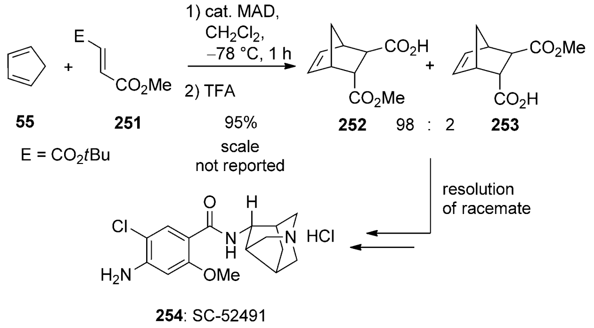
In view of the drawbacks of the previous approach (i.e. the use of heavy metals) an alternative pathway, more suitable for an industrial scale, was developed by chemists from Kuraray.[154] It relied on the use of chiral 5-methylenedioxolan-4-one **247** as the dienophile, which was prepared from (*S*)-lactic acid and pivaldehyde following a method developed by Mattay et al. (see Scheme S8 in the Supporting Information).[155] The activated dienophile **247** was treated with cyclopentadiene (neat conditions, 20°C) over 48 h to give the expected crude spiro compound (**248**; Scheme 54).[154] The enantio- and diastereoselectivity were not mentioned. Roush and Brown[156] reported that performing the reaction in benzene at 55°C using an excess of cyclopentadiene led to a diastereoselectivity of 94:6 (GC, 200 mg scale) in favor of the desired *exo* regioisomer **248**, which was isolated with 99% enantiomeric purity. Several kilograms of 2-norbornanone (**245**) were prepared by this pathway (Scheme 54).[157] No



Scheme 54. Use of 5-methylenedioxolan-4-one **247** as a dienophile for the synthesis of (+)-2-norbornanone **245**.[154,156]

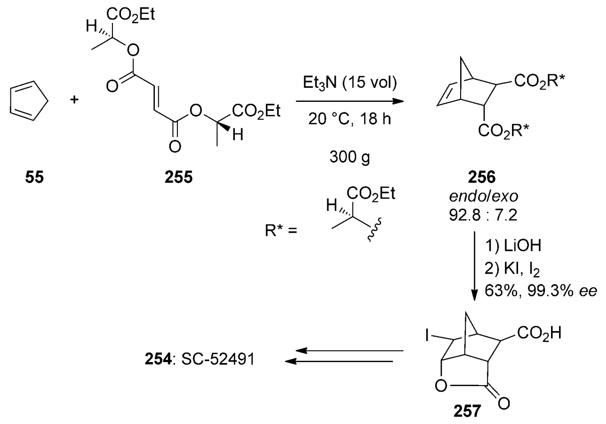
information was given in these publications regarding the cracking or handling of the cyclopentadiene monomer.

The synthesis of SC-52491 (**254**) as a potent serotonin 5-HT_4/5-HT_3 antagonist for gastrointestinal diseases is another illustration of a diastereoselective DA reaction applied on a large scale. It was originally synthesized at Pfizer (formerly Searle)[158] by using cyclopentadiene and *tert*-butyl methyl fumarate (**251**) in CH_2Cl_2 and in the presence of Yamamoto's MAD catalyst[159] to produce the racemic mono acid **252**. Even though the yield (95 %) and the *endo*/*exo* selectivity (98:2) were high, this process required the racemate to be separated later in the synthesis (Scheme 55). An asymmetric DA reaction would be more favorable for a large-scale production.

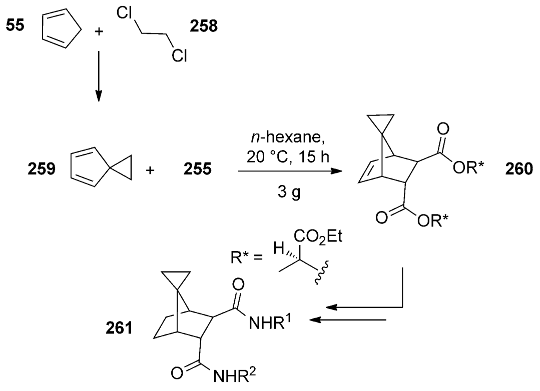


Scheme 55. Catalytic DA reaction in the synthesis of SC-52491 at Pfizer.[158]

In this context, the approach developed by Helmchen et al.[148b] using fumaric acid diethyl (*S*)-lactate (**255**) as the chiral dienophile was considered (Scheme 56). On a 300 g reaction, with Et_3N used as a substitute for the toxic carbon tetrachloride, the DA adduct (**256**) was produced with high diastereoselectivity and an *endo*/*exo* ratio of 92.8:7.2 after 18 h stirring at 20 °C.[158] After saponification and iodolactonization, the corresponding crystalline acid **257** was obtained in 63 % yield (over three steps) and excellent optical purity (> 99 % *ee*, HPLC) after recrystallization. In 2010, chemists at Actelion[160] applied this method to the diastereoselective synthesis of bridged spiro[2.4]heptane derivatives **261**, obtained from spiro[2.4]hepta-4,6-diene (**259**), as FPR2 receptor agonists (Scheme 57). Similar compounds were disclosed by Allergan in 2011.[161]



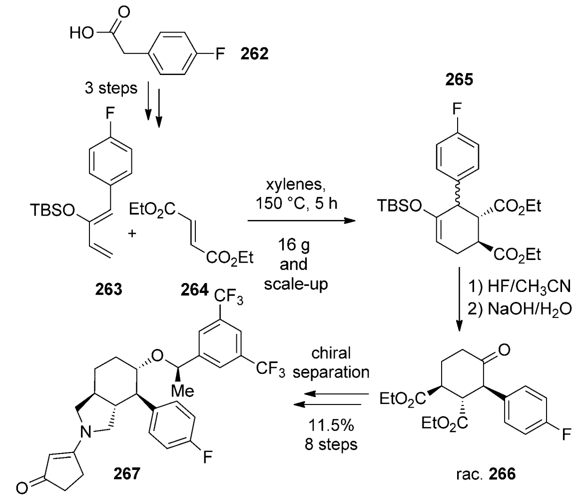
Scheme 56. Large-scale synthesis of SC-52491 at Pfizer following the approach of Helmchen et al.[158]



Scheme 57. Synthesis of bridged spiro[2.4]heptane derivatives at Actelion.[160]

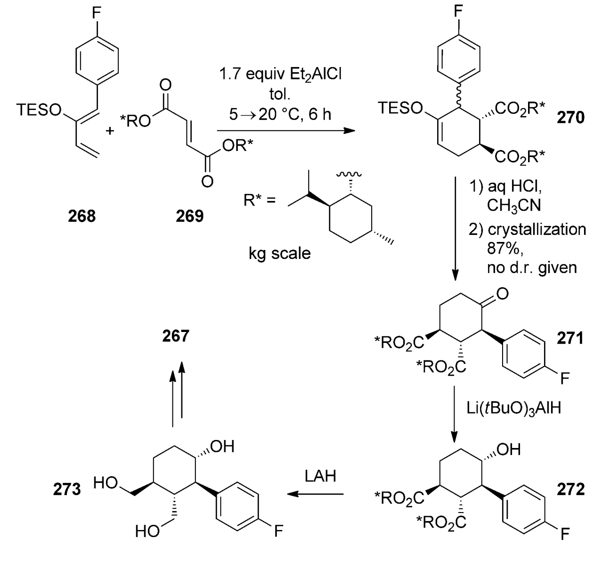
Recently, the use of diethyl fumarate as a dienophile was considered by Merck chemists for the preparation of tachykinin receptor antagonist **267**.[162] This compound exhibits improved properties compared to aprepitant, approved in 2003 by the FDA for the prevention of chemotherapy-induced nausea and vomiting. The required diene **263** was prepared in three steps from 4-fluorophenylacetic acid (**262**). A DA reaction was carried out in the presence of diethyl fumarate (**264**) in xylenes at 150–160 °C for 5 h (ratio of diastereomers not specified). The mixture of isomers obtained was then subjected to HF/CH_3CN treatment followed by epimerization under basic conditions (NaOH/water) to give the corresponding racemic *trans,trans* racemic ketone (**266**; Scheme 58). The desired enantiomer was isolated by chomatography on a chiral stationary phase and subsequently converted into the API (17 % yield from diene **263**). This sequence, which was exemplified on a 16 g scale, was further scaled up, as mentioned in the original publication.

In a related process patent,[163] a route was disclosed that relied on di-(−)-menthyl fumarate (**269**) as a chiral auxiliary



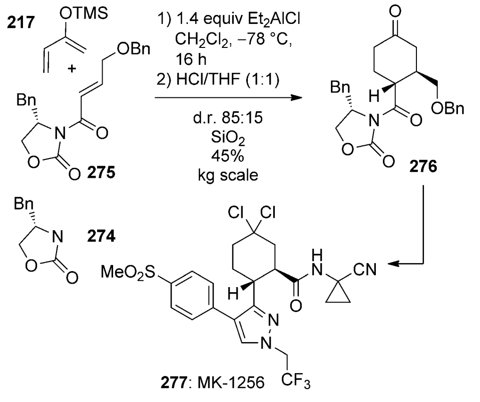
Scheme 58. Formation of a racemic DA adduct in the synthesis of **267** at Merck.[162]

and TES-protected diene **268**. It thus offered direct access to the targeted diastereomerically pure ketone (**271**) and avoided the original separation of enantiomers by HPLC on a chiral stationary phase. The DA reaction was detailed only on a gram scale (Scheme 59). However, the fact that the ensuing stages were described on a kilogram scale implies that this DA reaction has been further scaled up.[162]



Scheme 59. Auxiliary-based synthesis of **267** at Merck.[163]

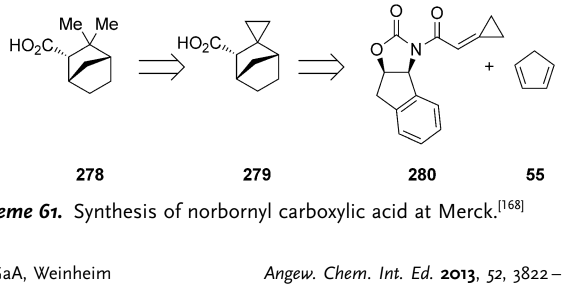
2-Trimethylsilyloxybutadiene (**217**) was used for the synthesis of MK-1256 (**277**),[164] a cathepsin K inhibitor undergoing clinical testing for the treatment of osteoporosis. The 19-step synthesis of 2 kg of the API featuring an Evans auxiliary-controlled DA reaction[165] on a 70 kg scale was disclosed in 2009 by Merck/DSM.[166] This example is a rare illustration of the scale-up of a Lewis acid catalyzed diastereoselective process involving a highly functionalized dienophile. Oxazolidinone auxiliaries[167] (such as **274**) lend themselves to large-scale use thanks to their moderate cost, their commercial availability in both optical forms, and their convenient recycling after cleavage from the substrate. Chiral dienophile **275** was obtained in three steps from commercially available (*S*)-4-benzyl-2-oxazolidinone. Instead of dosing an excess (3.5 equiv) of diene **217** to a solution of the Lewis acid and the dienophile in CH$_2$Cl$_2$/toluene at −78 °C, as performed in the original route, the solution of Et$_2$AlCl was added to a solution of the diene and the dienophile at −50 °C in the pilot plant. Such a mode of addition allowed the reaction to be carried out at the higher temperature of −50 °C (which is desirable from a cost perspective in an industrial setting) and to reduce the loading of the diene to two equivalents. After acidic hydrolysis of the intermediate silylated cycloadduct and subsequent work-up, filtration through a silica plug to isolate ketone **276** was still needed on the larger scale because of the presence of polymeric material that was not removed by simple crystallization. The yield upon scale-up (45 %) was gratifyingly identical to that of the initial experiment performed on a 350 g scale (Scheme 60).



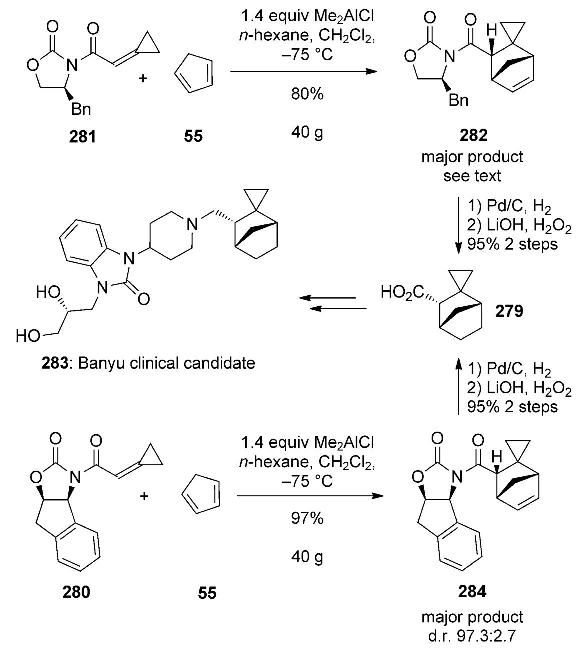
Scheme 60. DA reaction on a 70 kg scale en route to MK-1256.[166]

Another use of an Evans-type chiral auxiliary for conducting a diastereoselective DA reaction on a large scale was reported by the Merck Process Research Group[168] for the production of *gem*-dimethylnorbornyl carboxylic acid **278** (Scheme 61).

Enantiopure imide dienophile **281** was first treated with cyclopentadiene (**55**; Scheme 62) in the presence of Me$_2$AlCl as a catalyst following a protocol similar to the one developed for the 70 kg scale reaction that led to MK-1256 (Scheme 60). 1.4 Equivalents of Me$_2$AlCl (as a 1 M solution in *n*-hexane) was added to a mixture of the dienophile and 1.6 equivalents of cyclopentadiene at −75 °C. A set of four diastereomers was



Scheme 61. Synthesis of norbornyl carboxylic acid at Merck.[168]



Scheme 62. Large-scale use of **279** at Merck.[168]

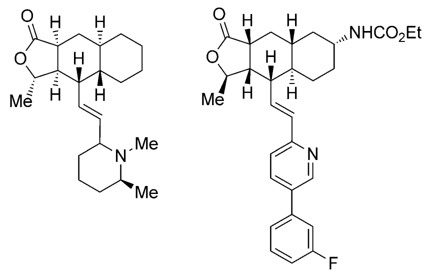
formed in a ratio of 91:1.9:6.6:0.5 in a combined yield of 97%. The major compound (**282**, *endo* adduct) was isolated with d.r. > 99:1 and in 80% yield after recrystallization of the isolated product from *n*-heptane. Based on precedents at Merck,[169] it was assumed that the use of chiral auxiliaries derived from aminoindanol might provide higher levels of stereocontrol than those reported for the Evans-type oxazolidinone. Indeed, when cyclopentadiene was treated with such a conformationally constrained imide dienophile (**280**)[170] in the presence of Me_2AlCl, only two diastereomers were obtained, the expected one (**284**) being formed in a more favorable ratio of 97.3:2.7. The resulting cycloadduct was hydrogenated and the chiral auxiliary was liberated using 30% H_2O_2 and LiOH to afford the expected cyclopropylnorbornyl carboxylic acid **279** in > 90% yield over three steps (Scheme 62).

The method described here is efficient and practical. It affords the target compound with high selectivity and purity. Even if the experimental section describes the reaction only on a 50 g scale, it is speculated that this approach would be applicable for a larger application. In 2009, chemists at Banyu disclosed the structure of the clinical candidate **283** as an opioid receptor antagonist (Scheme 62).[171] It was stated that the norbornyl unit of the molecule was prepared following the Merck DA-based approach. Hence, we can assume that the DA sequence was conducted on a large scale for the supply of clinical material. The implementation of this highly diastereoselective process is an elegant improvement on the racemic first generation approach,[172] in which 2-norbornanone was used as the starting material and required HPLC separation on a chiral stationary phase. The low temperature used in the cycloaddition reaction (−75 °C to 20 °C) is a salient feature of these examples of stereoselective DA reactions involving a dienophile[173] functionalized with a chiral auxiliary and cyclopentadiene or a silylated diene.

2.8. Intramolecular DA Reactions

The intramolecular DA reaction is a precious—sometimes the only—method for the construction of complex structures in a selective manner. From a scale-up point of view, if the cycloaddition proceeds efficiently, most of the efforts of the development teams are focused on finding a scalable supply of the elaborated cyclization precursor. The cases presented below illustrate the successful transfer of this elegant concept to industrial practice.

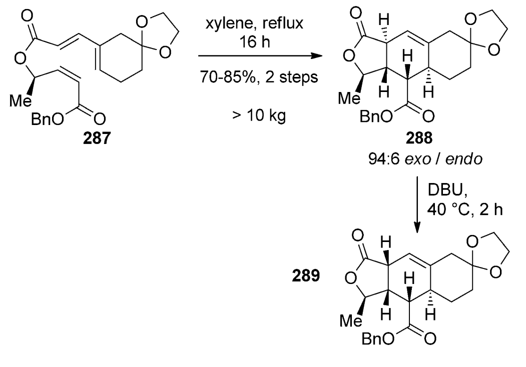
The manufacture of SCH-530348 (**286**) constitutes one of the few examples of an intramolecular DA cycloaddition[7d,e] performed on a several hundred kilogram scale.[174] SCH-530348 is a protease-activated thrombin receptor (PAR-1) antagonist currently undergoing phase III clinical trials at Merck/Schering-Plough for the oral prevention of arterial thrombosis.[175] This clinical candidate is a synthetic analogue of himbacine (**285**), a natural product known for its activity as a muscarinic receptor antagonist (Figure 7).[176]



285: himbacine **286**: SCH-530348

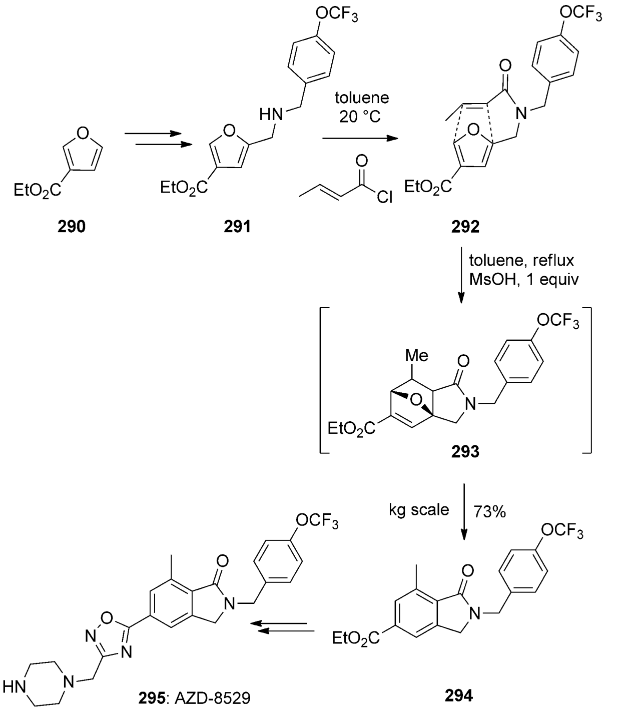
Figure 7. Structures of himbacine and its analogue SCH-530348.

By using a similar approach as the one designed to access himbacine and analogues thereof, the synthesis of SCH-530348 relied on a highly diastereoselective intramolecular DA reaction of **287**, which was prepared in a straightforward fashion from 3-bromocyclohex-2-enone[173] (see Scheme S9 in the Supporting Information). The tetracyclic intermediate **288** was obtained with a high preference for the *exo* form. The carbon atom α to the lactone carbonyl group was then epimerized in situ by treatment with DBU to form **289** (Scheme 63).[177]



Scheme 63. Intramolecular DA reaction in the synthesis of SCH-530348 at Schering-Plough.[177]

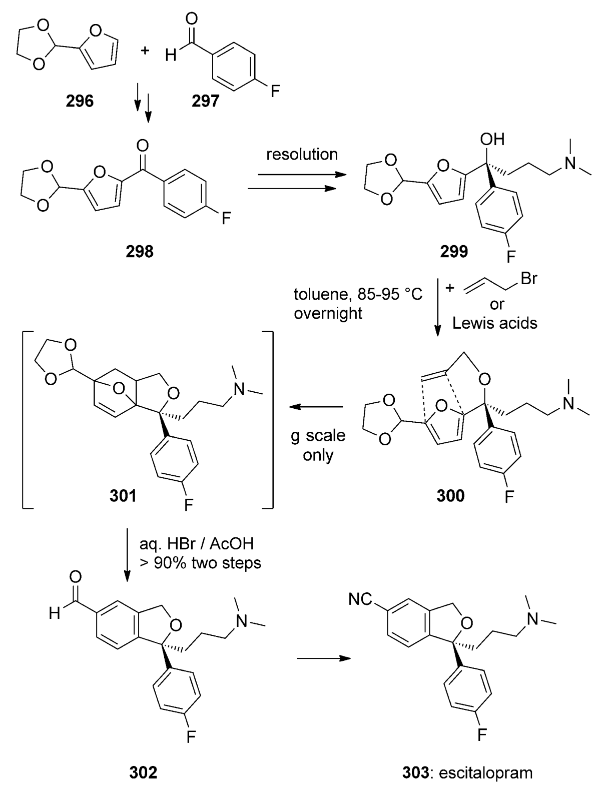
AZD-8529 (**295**) was in phase II trials for the treatment of schizophrenia, but in 2011 its development was discontinued by Astra Zeneca. Among the various approaches tested for scale-up,[178] an intramolecular DA approach was finally selected to access key intermediate **294** on a kilogram scale from inexpensive starting materials. Following a strategy reminiscent of the industrial synthesis of vitamin B_6 (Scheme 5), the secondary amine **291** was acylated with crotonoyl chloride. The furan-containing moiety was then heated to reflux to induce cyclization followed by aromatization to yield **294** (Scheme 64). In contrast to previous routes, a single isomer was obtained with no need for cryogenic conditions.[178b]



Scheme 64. Synthesis of AZD-8529 on a kg scale through an intramolecular DA reaction.[178a, b]

The objectives of process research and development chemists include the identification of alternative methods to prepare the targeted candidate. Some approaches may be pursued further and eventually become a manufacturing route of choice, as already previously discussed, while others may prove less competitive from a scale-up point of view for technical or economic reasons, as illustrated in the following example.

Escitalopram (**303**; Lundbeck, Forest) was approved in 2002 by the FDA for the treatment of adults with major depressive disorders. It is the *S* enantiomer of citalopram (marketed since 1989 by Lundbeck). An innovative approach to escitalopram makes use of the intramolecular DA reaction of **300** to give **301** (Scheme 65).[179] This alternative route, which has so far only been reported on a gram scale, employs hazardous chemicals (potassium hydride) or expensive ones (stoichiometric amount of [18]crown-6), thereby reducing its suitability for industrial production.[180]



Scheme 65. Access to escitalopram through an intramolecular DA reaction.[179]

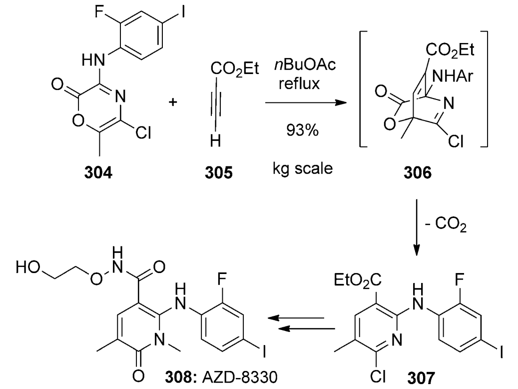
Other examples of large-scale DA reactions have been identified in the field of API synthesis. In view of their industrial significance, they are highlighted in the following section.

2.9. Other DA-Based Kg Syntheses of APIs

Two examples carried out industrially used propiolic acid derivatives as dienophiles, which allowed access to novel scaffolds after extrusion of carbon dioxide. The release of gaseous by-products poses safety concerns for a manufacturing-scale synthesis that must be addressed early on by adequate technical design of the reaction vessel and of the venting lines.

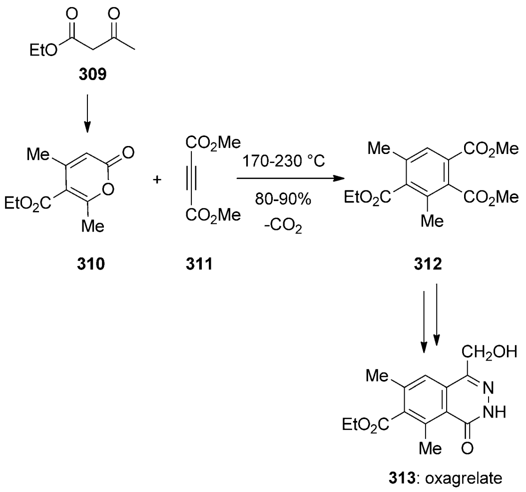
AZD-8330 (**308**; Astra Zeneca) is currently being investigated in phase I clinical trials as an anticancer drug. The central substituted pyridine ring was efficiently built up by a sequence involving a DA cycloaddition of unsymmetrical azadiene **304** with ethyl propiolate (**305**) followed by CO_2 extrusion to yield **307**, thereby achieving a high level of stereocontrol with readily available starting materials (Scheme 66).[178b] This approach was deemed “suitable for the manufacture of [this] compound on a commercial scale”.[181]

The synthesis of oxagrelate (**313**), a phosphodiesterase inhibitor investigated for the treatment of thrombosis, was



Scheme 66. Synthesis of AZD-8330 on a kg scale at Astra Zeneca.[178b]

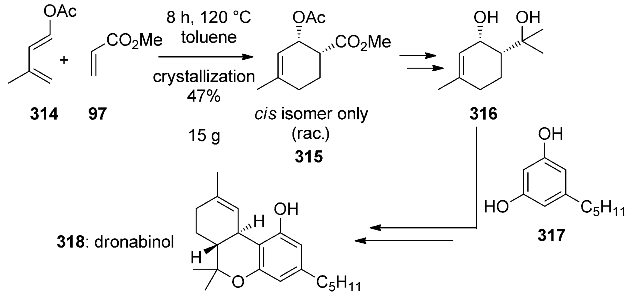
disclosed in 1975.[182] Alder and Rickert used a sequence starting from the cycloaddition of ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (**310**) with dimethylacetylene dicarboxylate (**311**; Scheme 67).[183] The drug was investigated by Banyu in phase III clinical trials of cerebral vascular disease and diabetic retinopathy before its development was discontinued in 1985.



Scheme 67. Synthesis of oxagrelate at Banyu according to Ziegler et al.[183b]

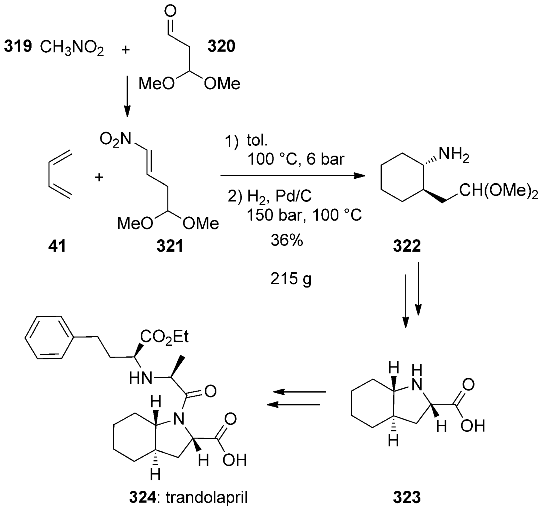
A last set of DA reactions is characterized by the use of 1,3-butadiene derivatives, ranging from simple butadiene to 2-alkyl or 2-silyl ethers. For the latter, see Schemes S8–S60. Two examples involving cyclohexadiene derivatives are also discussed in this section.

Dronabinol (**318**) is the principal psychoactive constituent of the cannabis plant. It was first launched in 1986 for the treatment of chemotherapy-induced nausea. Monoterpene **316**, so far prepared industrially by a process not involving a DA reaction, is a key starting material for the manufacturing of dronabinol (**318**).[184] In 2006, chemists at Alphora research[185] designed a process that relied on the use of diene **314** and methyl acrylate (**97**) to generate **316**. (Scheme 68)



Scheme 68. Synthesis of dronabinol through a DA reaction.[184,185]

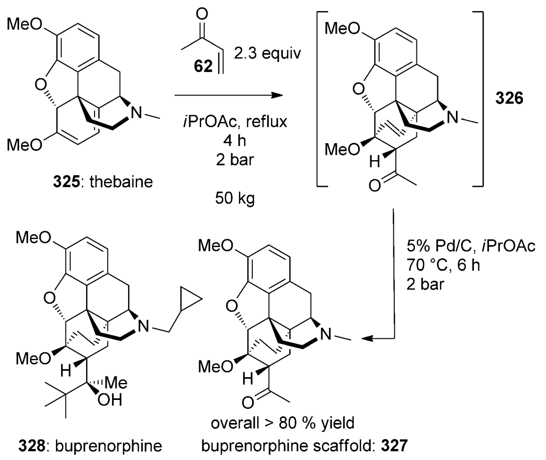
Trandolapril (**324**) was launched in 1993 by Abbott for the treatment of hypertension. The DA reaction between butadiene (**41**) and (*E*)-4,4-dimethoxy-1-nitrobut-1-ene (**321**) was described on a 215 g scale (Scheme 69).[186] However, as this route utilizes toxic and shock-sensitive nitromethane, it mandates manufacturing specialists with dedicated equipment and expertize, thus making it less attractive for scale-up in a conventional pilot plant.[187]



Scheme 69. Synthesis of trandolapril from butadiene and (*E*)-4,4-dimethoxy-1-nitrobut-1-ene.[186]

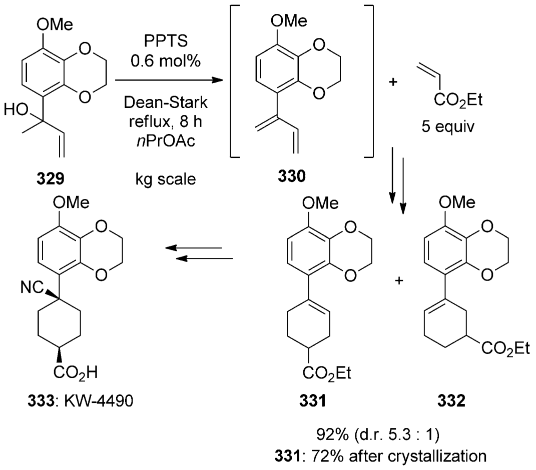
A 2010 patent[188] by researchers at Mallinckrodt disclosed a one-pot sequence (DA cycloaddition then hydrogenation) starting from thebaine (**325**) and methyl vinyl ketone (**62**) en route to buprenorphine (**328**), which has been used for the treatment of opioid addiction since 1978. By using such a strategy as an adaptation to existing processes, exposure to toxic methyl vinyl ketone was minimized. Even though the ratio of isomers or by-products formed during this sequence was not specified, it is mentioned that the product obtained after crystallization was of sufficient quality (epimer levels not detectable) to proceed to the next steps (Scheme 70). Etorphine, a structurally related potent analgesic was produced by a similar strategy.[189]

KW-4490 (**333**), a PDE4 inhibitor, was a clinical candidate investigated in 2002 by Kyowa Hakko Kirin for the treatment



Scheme 70. Industrial preparation of the buprenorphine scaffold from thebaine by a DA reaction.[188]

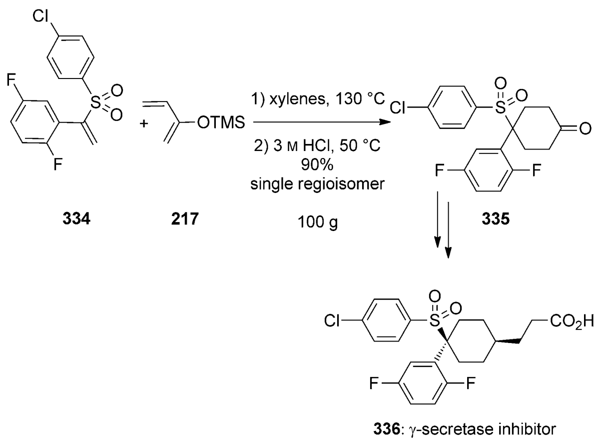
of asthma.[190] The low yield and poor reproducibility of the first generation approach and the need to isolate the desired compound by column chromatography called for an alternative route (see Scheme S10 in the Supporting Information). A new process based on a DA cycloaddition was thus developed, which proved robust enough for the delivery of kilogram amounts of the drug (Scheme 71).[190] The unstable 2-aryl-1,3-butadiene **330** required for the build-up of the cyclohexene ring within KW-4490 was prepared in situ by dehydration of benzyl vinyl alcohol **329** through a DA reaction with ethyl acrylate as the dienophile in the presence of a catalytic amount of PPTS. Five equivalents of the dienophile were applied at 100 °C to afford the desired adduct with 5.3:1 regioselectivity (**331**/**332**). The authors made no comment regarding the potential formation of polymeric material in the presence of excess acrylate. This one-pot dehydration/DA sequence (72 % yield after isolation of the major isomer by crystallization) was judged to be superior to other strategies based on lithiation or Suzuki–Miyaura cross-coupling because no low-temperature reactions or column chromatography were required.



Scheme 71. Second generation synthesis of KW-4490.[190]

The introduction of a DA reaction sequence specifically to optimize an existing route for production on a large scale is quite uncommon to our knowledge and makes this example unique in this Review. The DA-based approach was finally abandoned for the commercial synthesis of varenicline (**157**; Scheme 33), torcetrapib (**234**, Scheme 49) or escitalopram (**303**; Scheme 65).

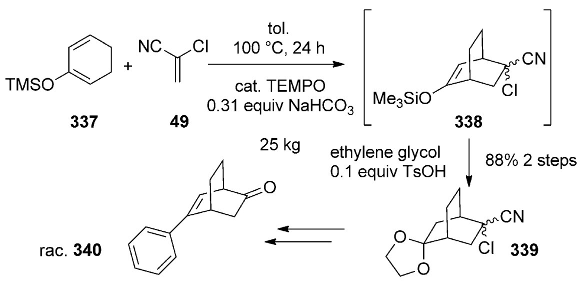
Another team of researchers at Merck reported the synthesis of a γ-secretase inhibitor (**336**) for the potential treatment of Alzheimer's disease which utilizes a DA reaction amenable to operation on a multi-kilogram scale.[191] 2-Trimethylsilyloxybutadiene (**217**)[192] derived from methyl vinyl ketone was treated with vinyl sulfone **334**, derived from commercially available 2,5-difluorobenzyl bromide and 4-chlorothiophenol (see Scheme S11 in the Supporting Information for synthetic details).[193] The DA reaction was carried out in xylenes at 130 °C for 16 h to produce the desired cycloadduct in 90 % yield as a single regioisomer (**335**; Scheme 72) after crystallization.



Scheme 72. Synthesis of a γ-secretase inhibitor at Merck by using 2-trimethylsilyloxybutadiene.[191]

Any remaining diene was removed by distillation prior to acidic hydrolysis of the cycloadduct, thereby reducing the formation of polymeric material originating from the degradation of the starting diene. The need to conduct this reaction under strictly anhydrous conditions and to use an excess of diene (2 equiv) to drive the reaction to completion within 16 h was noted. The thermal safety hazards of this reaction were not discussed. The fact that kilogram amounts of material have been produced can be deduced from the experimental description of the subsequent stages, which provides amounts in kilograms.

A DA approach, developed recently at Actelion, made use of a silylated diene (**337**) derived from 2-cyclohexenone.[194] Large quantities of the intermediate **340** were required.[195] The first pragmatic approach or so-called "fit-for-purpose" route relied on α-acetoxyacrylonitrile as a dienophile and **337** as a diene. It rapidly delivered kilogram amounts of the targeted material. Safety concerns[196] trig-



Scheme 73. Use of **49** for the kg synthesis of **340** at Actelion.[194]

gered the development of an alternative pathway involving the use of α-chloroacrylonitrile as the dienophile (Scheme 73). 450 kg of **338** and 180 kg of **340** of acceptable quality for downstream reactions were produced without the need for any purification of these oily products by chromatography or distillation.

3. Agrochemicals

The agrochemical and pharmaceutical industries share common goals in terms of optimizing chemical processes for the set-up of commercially viable manufacturing routes to active substances. However, the emphasis on lowering the cost of goods is probably more prominent in the former because of the amounts typically produced annually, the different markets, and specific cost structure. When implemented early on in the synthetic sequence, the DA reaction has also proven to be industrially viable in this area, as exemplified in this section.

Aldrin (**341**), bromodan (**342**), chlordane (**343**), chlordecone (**344**), dieldrin (**345**), endrin (**346**), heptachlor (**347**), isobenzan (**348**), kelevan (**349**), and mirex (**350**) are insecticides manufactured from hexachlorocyclopentadiene (**351**) through a DA cycloaddition (Scheme 74).[197] These compounds were widely used during the 1950s to 1970s. Several hundred thousand tons had been produced before they were found to be persistent organic pollutants and consequently banned. Endosulfan[198] (**352**) introduced by BayerCropScience (formerly Hoechst) has been used worldwide with an annual consumption of approximately 10000 tons, as estimated by the World Health Organization.[199] In contrast to the other organochlorine insecticides described above, endosulfan is biodegradable because of the presence of sulfite ester bonds. This is probably the reason why the ecological impact of this organochlorine insecticide was noticed only later, in 2001.

MGK-24 (**353**) and captan (**354**) are two other examples of agrochemicals prepared through a DA reaction. MGK-24 is an ingredient of pyrethroid pesticides which enhances their activity (Figure 8). This *N*-octylbicycloheptene dicarboximide was prepared by treating the maleic anhydride/cyclopentadiene adduct with 2-ethylhexylamine in toluene with removal

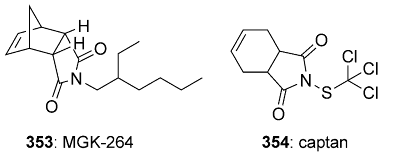
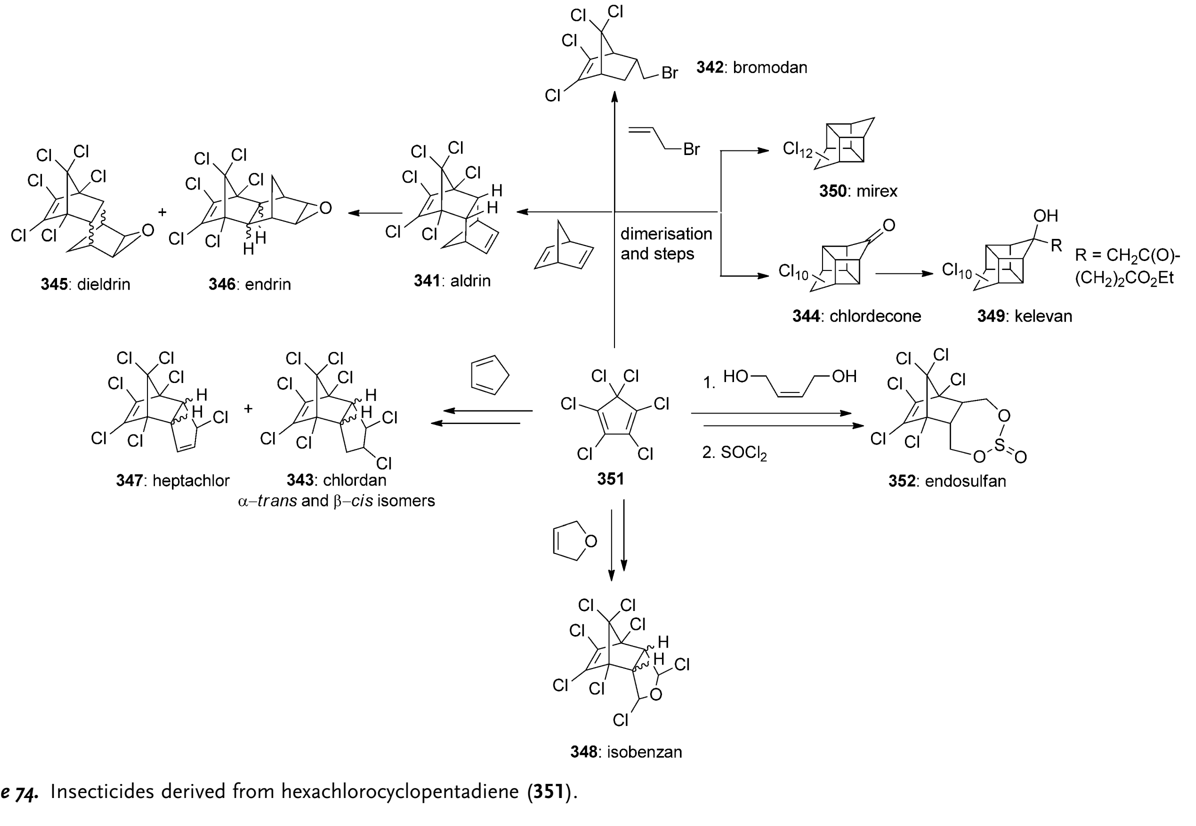


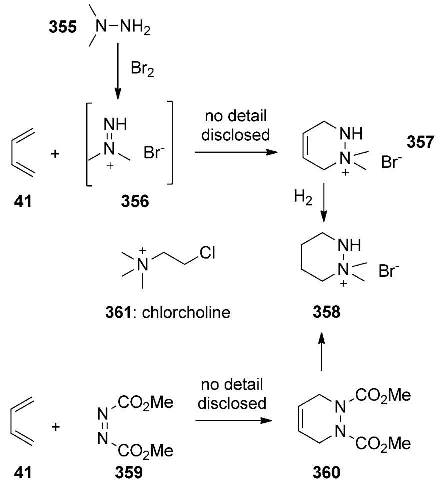
Figure 8. Chemical structures of MGK-264 and captan prepared by a DA reaction.



Scheme 74. Insecticides derived from hexachlorocyclopentadiene (**351**).

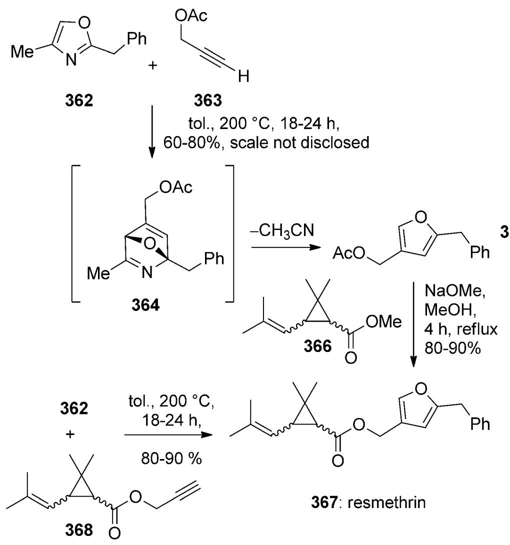
of water by azeotropic distillation.[200] Captan, which is a plant-growth regulator, was prepared from butadiene in the presence of maleic anhydride followed by treatment with ammonia and perchlorylmercaptan.[201]

Chlorcholine (**361**) also known as cycocel is a widely used synthetic plant-growth regulator produced at BASF. Two industrial syntheses of an active analogue **358** based on a DA reaction have been reported (Scheme 75).[202]



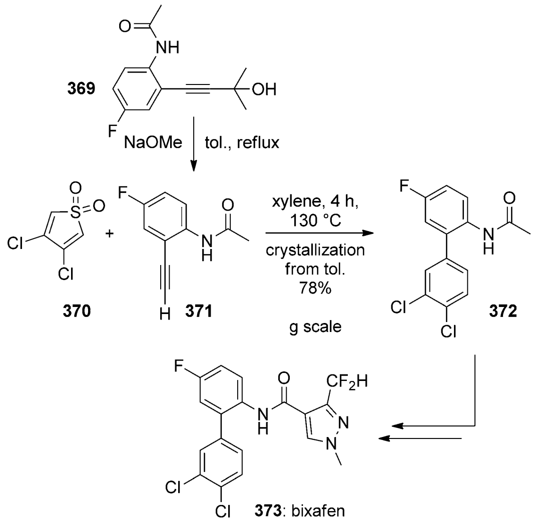
Scheme 75. Manufacturing of **358** by a DA reaction at BASF.[202]

Resmethrin (**367**) is an approved insecticide with a chrysanthemate structure. The furan core structure was prepared industrially at BASF[8,203] via a cycloaddition/cycloreversion sequence (in analogy to the vitamin B_6 synthesis described in Scheme 5) between 2-benzyl-4-methyloxazole (**362**) and propargyl acetate (**363**) at elevated temperature (200 °C) followed by transesterification (Scheme 76).[204] Alternatively, direct reaction with a functionalized alkyne substrate (**368**) allowed the direct isolation of the targeted compound after distillation.



Scheme 76. Large-scale preparation of resmethrin by a cycloaddition/cycloreversion sequence.[203,204]

The cereal fungicide bixafen (**373**; BayerCropScience) was launched in 2010 in the UK as a succinate dehydrogenase inhibitor. The biphenyl system within bixafen was accessed through a cycloaddition/cycloreversion sequence involving 3,4-dichlorothiophene-1,1-dioxide (**370**) and phenylacetylene **371** (Scheme 77).[205] Slow addition of diene **370** to a solution of **371** at 130 °C minimized dimer formation. **370** was obtained by the reaction of sulfur dioxide and butadiene according to a protocol originally developed by Shell,[206] followed by chlorination and elimination of HCl (see Scheme S12 in the Supporting Information).[207] An alternative approach based on the Suzuki coupling of deactivated aromatic rings was successfully developed.[208] While both pathways appear amenable to scale-up, the final manufacturing route to bixafen remains, to date, confidential. The need for high temperatures in these two examples (Schemes 76 and 77) reflects the low reactivity of electron-poor dienes and phenylacetylene.



Scheme 77. Preparation of bixafen through a tandem cycloaddition/cycloreversion at Bayer Crop Science.[205a]

Isopyrazam (**374**) was registered in the UK in 2010 by Syngenta as a new cereal fungicide (Figure 9) and is sold as a mixture of *syn* and *anti* diastereoisomers. This active substance was selected from a series of active substances belonging to the class of (difluoromethyl)pyrazole compounds.[209] Their synthesis relied on the DA reaction of 3-nitrobenzyne (**376**), generated from 6-nitroanthranilic acid

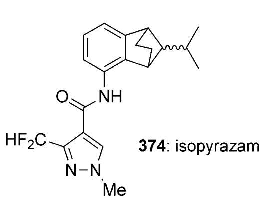
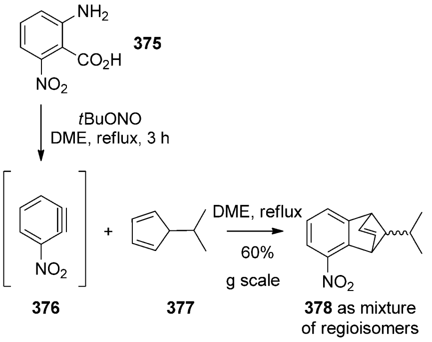
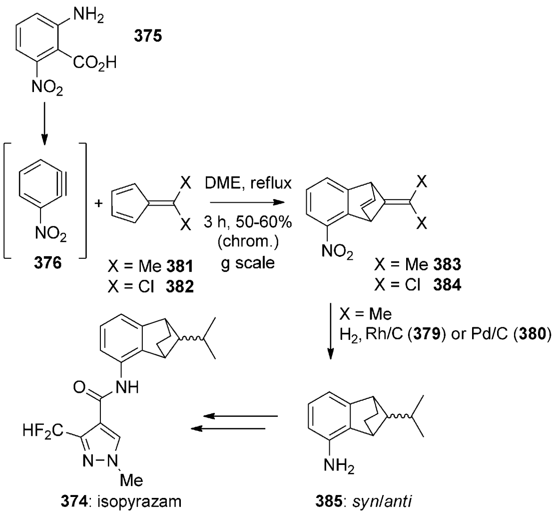


Figure 9. Chemical structure of isopyrazam.

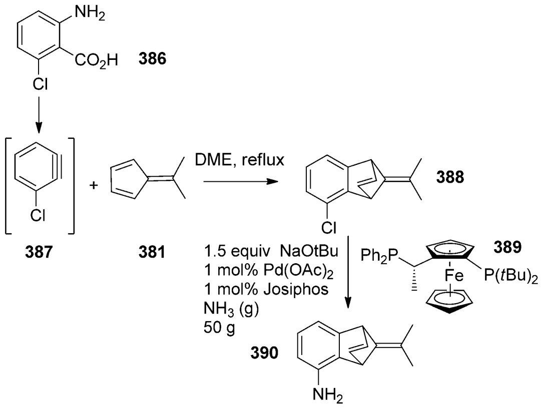


Scheme 78. Synthesis of the isopyrazam scaffold on a kg scale from nitrobenzyne and 5-isopropylcyclopentadiene at Syngenta.[211]

(**375**) upon aprotic diazotation using *tert*-butyl nitrite[210]. When subjected to these reaction conditions, 5-isopropylcyclopentadiene (**377**) yielded a mixture of stereoisomers **378** as the main products along with unwanted regioisomeric impurities (Scheme 78).[211] The subsequent reduction of the nitro group, saturation of the double bond to afford **385**, and attachment of the (difluoromethyl)pyrazole moiety then afforded the isopyrazam fungicide **374** as a mixture of *syn* and *anti* isomers. In view of the poor selectivity observed during the preparation of 5-nitrobenzonorbornadiene from 5-isopropylcyclopentadiene, 6,6-dimethylfulvene (**381**) was used instead to yield exclusively, after hydrogenation, all four *syn*/*anti* isomers **385** devoid of any regioisomer (Scheme 79).[209b] A Pd-catalyzed amination reaction[211] was later developed that allowed the use of 6-chloroanthranilic acid (**386**) as a less-expensive starting material. The Cl–N exchange to yield **390** was carried out under Buchwald–Hartwig conditions (Scheme 80).[212]



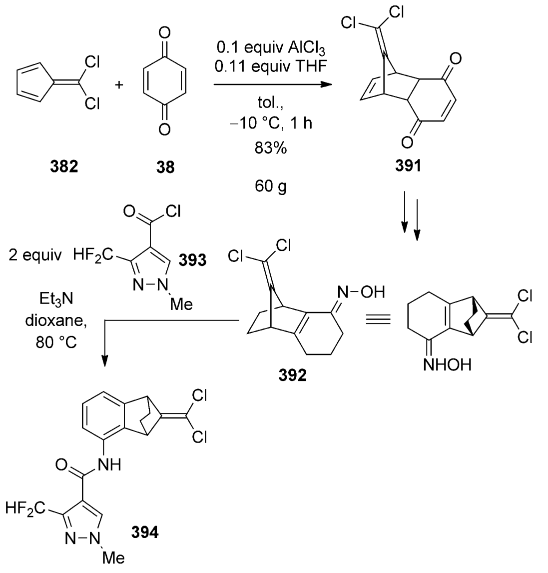
Scheme 79. Synthesis of isopyrazam on a kg scale by using 6,6-dimethylfulvene as the diene.[209b]



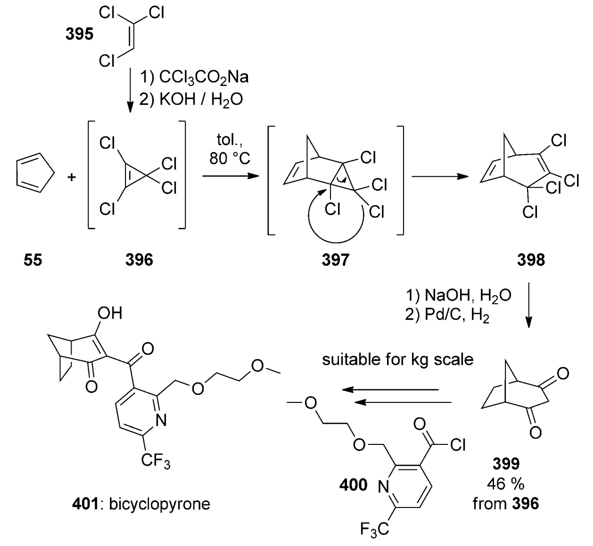
Scheme 80. Pd-catalyzed amination reaction en route to isopyrazam.[211]

In 2011, a process patent[213] described the optimized synthesis of fungicide **394** (Scheme 81) analogous to that of isopyrazam but using 6,6-dichlorofulvene (**382**) as the starting material. Originally, **394** was prepared from the cycloadduct **383** derived from dimethylfulvene (**381**) and **376**. Ozonolysis and Wittig olefination in the presence of carbon tetrachloride afforded the expected dichloromethylene intermediate **384**. Neither reaction was deemed amenable to a cost-competitive scale-up. Alternatively, **382** was treated with 1,4-benzoquinone (**38**) in toluene using $AlCl_3{\cdot}THF$ as the catalyst under mild conditions. The adduct **391** was converted into the corresponding monooxime **392**, which afforded the desired aromatized system after a Semmler–Wolff rearrangement.[214] For that purpose, two equivalents of (difluoromethyl)pyrazole acyl chloride (**393**) were elegantly used to induce first the rearrangement and second the acylation of the aniline thus formed. One equivalent of this reagent was recycled as the corresponding carboxylic acid (Scheme 81).

Bicyclopyrone (**401**) is a crop herbicide recently marketed by Syngenta.[215] A first approach to bicyclopyrone[216] suitable for synthesis on a multi-kilogram scale relied on the preparation of bicyclo[3.2.1]octane-2,4-dione (**399**) as the key intermediate (Scheme 82). It was manufactured in a one-



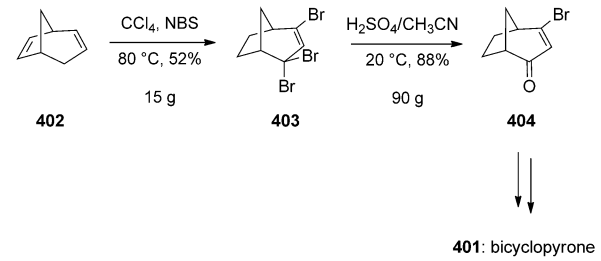
Scheme 81. Synthesis of isopyrazam analogue **394**.[213]



Scheme 82. Industrial preparation of bicyclopyrone at Syngenta.[216]

pot process (4 steps, 46% overall) by a DA reaction of cyclopentadiene with in situ prepared tetrachlorocyclopropene (**396**), followed by concerted disrotatory ring opening with chloride migration to yield **398**. Basic hydrolysis, followed by hydrogenation and acylation gave the targeted product **401**.

An alternative pathway to bicyclopyrone (**401**) based on the radical bromination of bicyclo[3.2.1]oct-2-ene (**402**) to give **403** in toxic CCl_4 as the solvent has been disclosed only on a gram scale (Scheme 83).[217] Although it can be reasonably assumed that both routes have delivered several kilograms of final substance, the current manufacturing process remains a trade secret. Other recent herbicidal compounds from Syngenta were prepared by a [4+2] cycloaddition process.[218] However, only small-scale examples have been disclosed, and their stage of development is presently not disclosed.



Scheme 83. Alternative preparation of bicyclopyrone building block **404** by radical bromination.[219]

In view of the large material requirement for the agrochemical industry, those examples are a nice illustration of the applicability of DA reactions on a multi-ton scale, especially bearing in mind that the use of such highly reactive dienophiles and dienes clearly requires thorough safety testing and an adequate risk assessment.

At the end of these two sections devoted to the manufacturing of pharmaceutical and agrochemicals substances by DA reactions, some trends can be highlighted. Cyclopentadiene is by far the most frequently used diene (ca. 40%), followed by 1,3-butadiene derivatives (16%) and furan (11%). The exceptional reactivity of cyclopentadiene combined with its high selectivity may account for this observation. Michael acceptors (which generally contain activated double bonds) appear to be the most popular reacting partners, and used in approximately 70% of the cases. Among this set of intermolecular reactions, 10% are represented by hetero-DA reactions, whereas only 3% of the total number of DA reactions carried out on a large scale relied on an intramolecular variant. Whether such bicyclic systems would lead to more druglike substances through the introduction of structural features that have a favorable impact on the absorption, distribution, metabolisms, and excretion (ADME) properties is still an open debate.[220]

4. Flavors and Fragrances

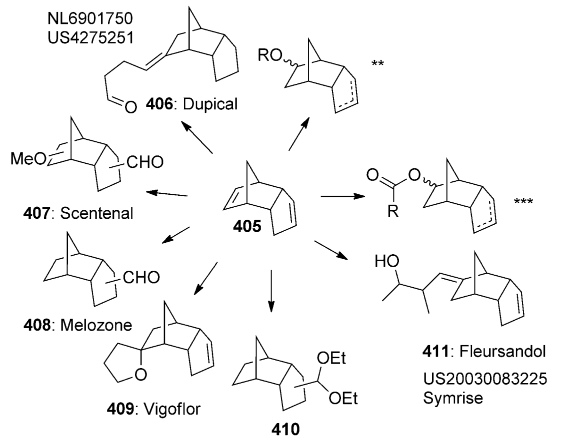
The use of cyclopentadiene and 1,3-butadienes is more evenly distributed for the synthesis of flavors and fragrances. These two types of dienophiles are well-suited to access a large range of volatile substances. This aspect is now presented in more details in this section.

The DA reaction has found many applications in the flavor and fragrance industry for the elaboration of fragrance bases and concentrates, perfumes and eaux de toilette used in soaps, hygiene products, cosmetic preparations, air fresheners, textile detergents, and cleaning products.[221] They are often mixed or dissolved in a suitable solvent and are used to impart a desired odor to the skin or product. Since the perception of odor and aroma is a subjective phenomenon, the availability of a wide range of affordable scents with a long shelf life is desirable. The DA reaction appears to be well-suited to pursue these goals since it allows the efficient construction of six-membered ring structures with diverse olfactory profiles. This has been performed both thermally and in the presence of a Lewis acid. The resulting adducts are used as such or are further derivatized.[222] Many olfactory substances have been prepared by the reaction of a diene—frequently derived from cyclopentadiene, butadiene, or cyclohexadiene—with an acrylate system. These raw materials are available in bulk quantities at a low price, and thus are compatible with the typical guidelines of this industry. According to Birkbeck,[223] costs of 10–500 US dollars per kg are typical for fragrance materials. The compounds are obtained as a mixture of diastereo- and/or regioisomers (and so are depicted as such in the accompanying schemes, unless otherwise stated) and are usually purified by distillation. Distillation is indeed the method of choice for the isolation of volatile compounds, in contrast to the pharmaceutical or agrochemical industries, where crystallization (often of heteroaromatic compounds) is the preferred option. In the context of the intensive use of distillation under reduced pressure, the corresponding production units are capable of operating under a vacuum higher than the standard 30–100 mbar that is commonly obtained in a chemical plant. Some products are commercialized as a defined mixture of structurally related compounds with unique olfactory properties. The information regarding the composition of each olfactory ingredient is often limited to GC purity information, usually referred to as "a sum of isomers". This is in contrast to pharmaceutical substances that are regulated by the FDA[224] and EMEA.[225] These authorities indeed recommend targeting diastereomeric and enantiomeric purities as high as possible, with upper acceptable limits set by preliminary toxicological evaluation.

In a competitive environment, the exact annual volumes of these processes are usually kept confidential. Hence, a choice was made to concentrate on those examples where there was full disclosure of reaction conditions. Other examples carried out on a large scale but barely explained are presented in the Supporting Information. Some of them (see Sections 4.1 and 4.2) are prepared on a multi-ton scale each year,[226] thus making the flavors and fragrances industry a large user of the DA reaction on a manufacturing scale. For a more general discussion of the chemistry of fragrances, the reader is referred to two comprehensive reviews by Fráter, Kraft, and co-workers.[227] In view of the large number of examples of olfactory compounds produced by DA reactions, we thought that they would be best described by grouping them by the type of diene used, starting with cyclopentadiene.

4.1. Cyclopentadiene

A variety of fragrances are derived from the unselective addition of carboxylic acids or alcohols to the bridged double bond within the cyclopentadiene dimer (**405**), as summarized by Sell.[228] Consequently, a mixture of regioisomers is obtained and used as such, thereby offering subtle nuances of floral and fruity character. Jasmacyclene (**413**; Givaudan), one of the most important products derived from dicyclopentadiene, is produced on a scale of thousands of tons per annum. It has a fruity, jasmine-like odor and is used in home- and fabric-care products. Florocyclene (**414**; Givaudan), which has an odor significantly softer than Jasmacyclene (as its ethyl ester analogue) is used in personal care products and fine fragrances. Gardocyclene (**415**; Givaudan) has a less anise-like smell than the other cyclenes. Florocyclene and Gardocyclene are also produced annually on a multi-ton scale. The amounts of Dupical (**406**; Givaudan), a modifier and enhancer of the muguet character in a fragrance, and Scentenal (**407**, Firmenich) with ozone marine notes are produced in lower amounts (1–10 tons[229]). Scheme 84[228] presents a selection of fragrances derived from dicyclopentadiene.

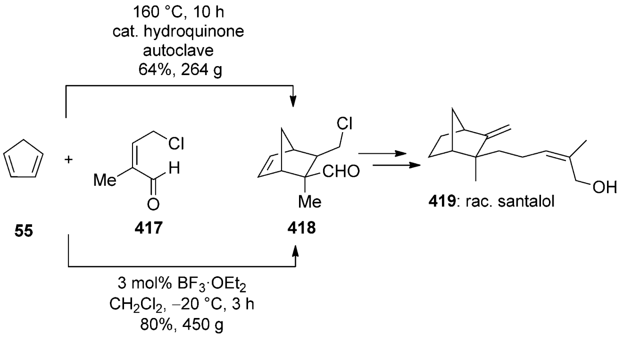


** R = Me, Verdalia A
R = $CH_2CH{=}CH_2$, Fleuroxene **412**
see DE 2642519 and DE2654268

*** R = Me, Jasmacyclene: **413**
R = Et, Florocyclene: **414**
R = *i*Pr, Gardocyclene: **415**
R = *t*Bu, Pivacyclene: **416**

Scheme 84. Fragrances (as a mixture of isomers) derived from dicyclopentadiene.[230] Adapted from Ref. [228].

Many fragrances are derived from a DA reaction with cyclopentadiene. This reaction is either carried out thermally at elevated temperature (140–180 °C) in an autoclave in the presence of a polymerization inhibitor such as hydroquinone, or at a lower temperature (typically −20 to 25 °C) in the presence of a catalytic amount of a Lewis acid such as $BF_3{\cdot}OEt_2$. Compounds are isolated by fractional distillation as a mixture of *endo*/*exo* isomers and used as racemic mixtures. When the cycloaddition reaction is performed thermally, dicyclopentadiene can be employed since under the reaction conditions it is fragmented in situ into the monomer. Yields are usually higher for a catalytic process compared to a thermal reaction because of the milder reaction conditions.[231] Scheme 85 illustrates this feature for the synthesis of **418**, which is used as an intermediate en route to racemic santalol (**419**).



Scheme 85. Synthesis of a santalol precursor from cyclopentadiene.[231]

For the fragrance industry, (−)-β-santalol (**420**; Figure 10) is the most valuable constituent (20 % content) of East Indian sandalwood oil, a high-priced essential oil (USD 1000 kg[223]) that is extracted from the santalum tree and also contains (+)-α-santalol (**421**; 50 % content) and (+)-epi-β-santalol (**422**; 5 % content).

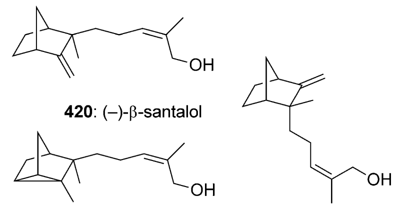
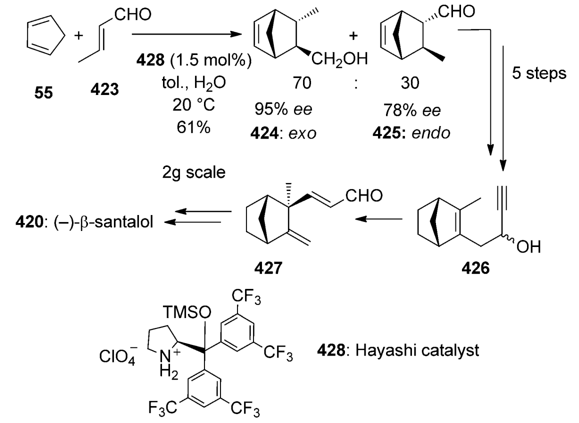


Figure 10. Structures of the main constituents of sandalwood oil.

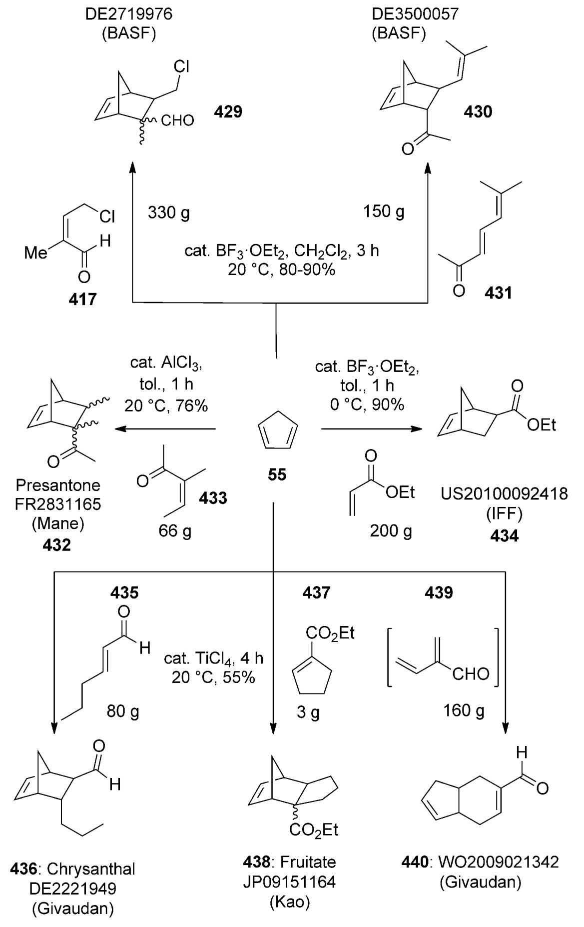
Two potential scalable racemic syntheses were published, both in 1979, by Christenson and Willis[232] as well as Baumann and Hoffmann at BASF.[233] The latter process is based on a DA cycloaddition of cyclopentadiene as the first step (Scheme 85). Krotz and Helmchen have reported the first synthesis of optically pure β-santalol by using diastereoselective DA reactions with (*R*)-pantolactone (**236**) as the dienophile.[234] This example again underscores, in addition to previously discussed examples (Schemes 50 and 51), the significance of (*R*)-pantolactone-derived acrylate (**236**) as a powerful chiral auxiliary for diastereoselective DA reactions. Despite extensive efforts,[223] β-santalol is still, to date, not manufactured by chemical synthesis. The first catalytic enantioselective synthesis of (−)-β-santalol was disclosed in 2009 by Fehr et al.[235] at Firmenich by using the Hayashi[236] catalyst **428** (Scheme 86). An acceptable degree of *exo* selectivity in favor of **424** was achieved in a two-phase toluene/water mixture by using 1.5 mol% catalyst at 20°C. However, the DA adduct was obtained as a mixture of regioisomers **424** and **425**. This mixture was then converted into enynol **426**, which was subjected to a copper-catalyzed cyclization/fragmentation to afford **427** almost exclusively after crystallization. Should the challenge to scale-up this approach for industrial manufacture be solved, this will constitute, to our knowledge, the first example of a catalytic asymmetric DA reaction developed in industry for large-scale supplies.



Scheme 86. Synthesis of (−)-β-santalol at Firmenich.[235]

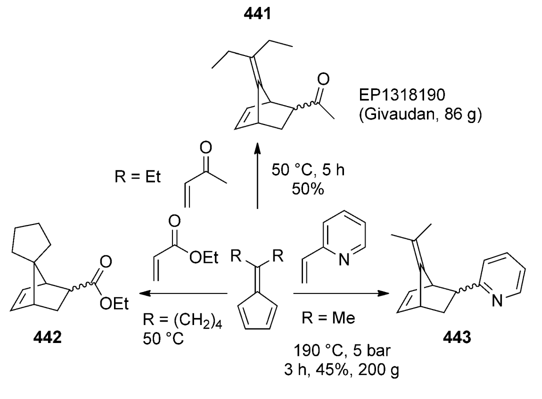
Scheme 87 provides a selection of examples (**429**–**440**) with accompanying references to patents disclosing protocols on a several hundred gram scale.[237] The organoleptic compounds thus obtained generally exhibit fruity or floral tonalities. The quantity in parentheses shows, whenever disclosed, the scale of the described reaction.

The production of other olfactory substances such as Methylsandeflor[239] (see Scheme S13 in the Supporting Information) from Takasago, has been described on a large scale through the use of methylcyclopentadiene.[240] Symrise[241] and IFF[230b] have disclosed olfactory compounds derived from the methylcyclopentadiene dimer. Examples are not as numerous as in the case of cyclopentadiene, most probably because of the complexity of the mixture of bicyclic compounds derived from the use of an unsymmetrical diene.



Scheme 87. Industrial preparation of a selection of olfactory compounds derived from the cyclopentadiene monomer.[231,237,238]

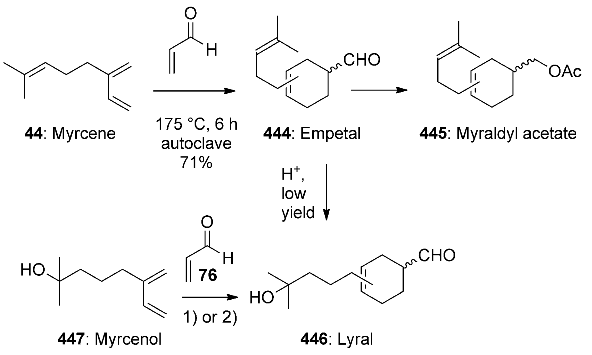
Dialkyl fulvenes[242] (Scheme 88) have been used at Givaudan for the synthesis of several bicyclic fragrances displaying woody, floral, and green notes. The cycloaddition was performed under neat thermal conditions in each case. Other examples of the use of 2-vinylpyridine in this DA reaction have been disclosed[243] for the preparation of pyridine-containing compounds, such as **443**, that exhibit a powerful cassis smell.



Scheme 88. Production of olfactory compounds from fulvenes.[243]

4.2. Myrcene

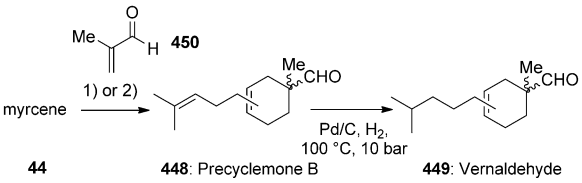
Myrcene (**44**), a 1,3-diene, is a monoterpene often used in the fragrance industry as a substrate for the DA reaction with a variety of dienophiles.[244] The use of myrcene as a diene was pioneered by Diels and Alder in 1929 as one of the very first illustrations of the scope of this transformation.[245] The four isomers obtained from the reaction of acrolein with myrcene are the olfactory vectors of Empetal (**444**; Givaudan), also known as myrac aldehyde, which has the smell of citrus and marine. The large-scale reaction of myrcene with acrolein was reported as early as 1946.[246] Hydration of the nonconjugated trisubstituted double bond led, albeit in low yield, to Lyral (**446**), which has a sweet and floral odor reminiscent of lily of the valley. Lyral (**446**) can also be accessed directly from myrcenol (**447**) at high temperature[247] or by using a Lewis acid catalyst, as described by IFF.[248] The estimated world consumption of Lyral (**446**) in 1996 was close to 520 tons.[226] Reduction of the aldehyde function of Empetal (**444**) followed by acetylation gives access to Myraldyl acetate (**445**), which is produced in the range of 1 to 10 tons per annum[249] (Scheme 89)



1) 150 °C, 4 h, 1.2 kg, 60% after distillation (IFF, US2947780)
2) cat. $TiCl_4$, tol., 0 °C, 1 h, 3.8 kg, 58% after distillation (IFF, US4007137)

Scheme 89. Synthesis of fragrances derived from myrcene and acrolein (compounds depicted as mixtures of regioisomers).[247,248]

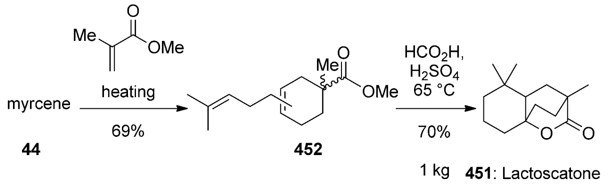
Precyclemone B[250] (**448**; IFF) and Vernaldehyde[227b,251] (**449**; Givaudan) are produced upon reaction with in situ prepared methacrolein (**450**; Scheme 90). Lactoscatone[252] (**451**; Symrise), with an animal note, is in turn derived from myrcene (**44**) and methyl methacrylate followed by lactonization of the DA product **452** (Scheme 91).



1) cat. hydroquinone, 140 °C, 30 h, 680 g, 68% (Hercules, US2406101)

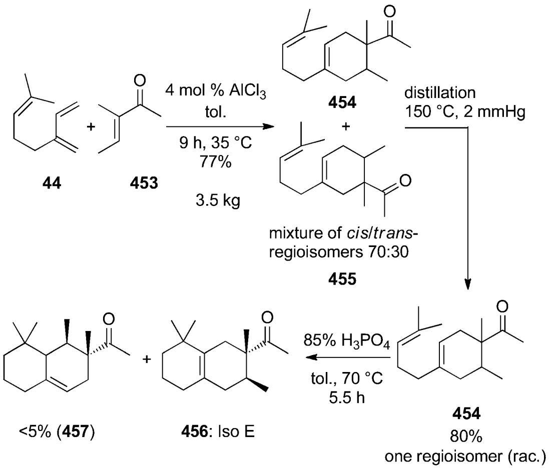
2) cat. Et_2AlCl, 60 °C, 1 h, 320 g, 54% (IFF, US4250338)

Scheme 90. Production of fragrances derived from myrcene.[246,250]



Scheme 91. Kg production of Lactoscatone.[252]

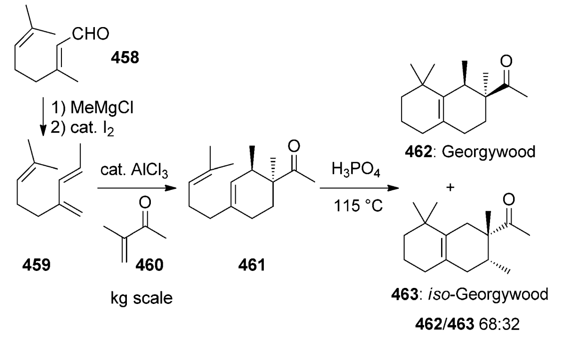
Analogously, the industrial preparation of Iso E (**456**) was patented first by Dragoco (now Symrise)[253] and later on by IFF.[254] It has become one of the most important fragrance components in the woody-ambery family, with an annual production of 500 tons per annum.[255] Its synthesis started from myrcene (**44**), which was treated with 3-methylpent-3-en-2-one (**453**) in toluene and $AlCl_3$ as the catalyst, thereby yielding a 70:30 mixture of regioisomers **454** and **455** as a *cis*/*trans* mixture. Pure **454** was obtained after distillation. A subsequent H_3PO_4-mediated cyclization afforded Iso E (**456**), which has a woody and floral smell (Scheme 92).



Scheme 92. Industrial preparation of Iso E by a DA reaction.[253,254]

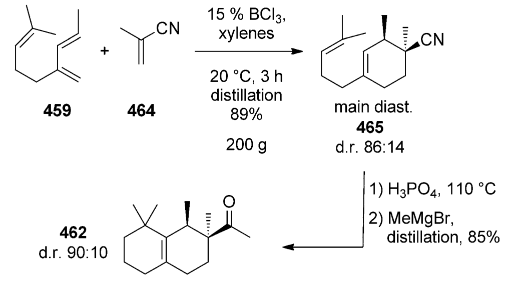
It was later discovered that the impurity **457** within Iso E (**456**) was actually responsible for the intense olfactory properties of this fragrance. This compound was derived from isomerization of the endocyclic double bond within **454** to form a further intermediate prior to cyclization to **457** (see Scheme S14 in the Supporting Information). The isolation of this compound as a by-product of a reaction was not a suitable operation for an industrial manufacturing process.[227b] Consequently, a structurally related analogue was prepared and became known as Georgywood (**462**). Its large-scale synthesis was originally described at Givaudan[256] (Scheme 93), starting from geranial (**458**) to prepare homomyrcene (**459**) as the diene and using isopropenyl methyl ketone (**460**) as the dienophile.

The selectivity of this process in favor of **462** instead of **463** was modest (68:32). Schröder[257] at Givaudan has shown that the use of an aluminum-based catalyst allows the product ratio of the cyclization to be improved compared to the use of a mineral acid such as aqueous phosphoric acid. The cycliza-



Scheme 93. Industrial preparation of Georgywood at Givaudan.[256]

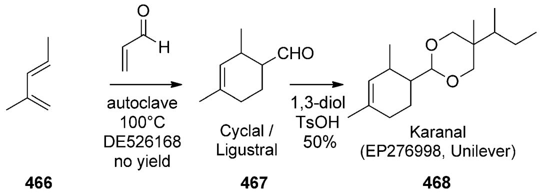
tion of DA adduct **461** proceeded with high regioselectivity (>90%) in the presence of 2.5 equivalents of pyrophoric $MeAlCl_2$. The use of a catalytic amount of in situ generated $MeAlCl_2$ or $AlMe_3$ resulted in a significant reduction of aluminum waste. The evolution of gaseous methane was minimized compared to the original stoichiometric protocol, thereby improving the overall safety of the process.[255a,257,258] A recently disclosed variant, also amenable to scale-up, featured the use of methacrylonitrile (**464**) as the dienophile (Scheme 94).[259] Phosphoric acid mediated cyclization of adduct **465**, followed by treatment with methyl magnesium bromide gave Georgywood (**462**) with high yield and selectivity.



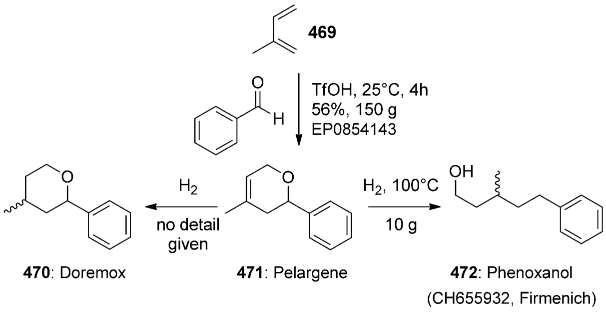
Scheme 94. Scalable, alternative preparation of Georgywood.[259]

4.3. 1,3-Butadiene Derivatives

A variety of odorant compounds have been produced industrially by DA reactions of diversely substituted 1,3-butadienes. The compounds are obtained as mixtures and displayed as such in the synthetic schemes. Examples were identified using 2-methylpenta-1,3-diene (**466**; Scheme 95) or isoprene as dienes (**469**; Scheme 96). The use of penta-1,3-diene has also been reported.[260] Details about the experimental conditions can be found in the references depicted in Schemes 95 and 96. More comprehensive schemes can be found in the Supporting Information (Schemes S15 and S16). Among the numerous substances prepared by perfumers through DA reactions with 2-methylpenta-1,3-diene, Karanal and Cyclal are widely used for their woody and amber character (Scheme 95).



Scheme 95. Industrial preparation of Cyclal and Karanal.[261]

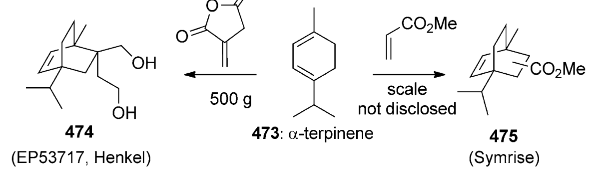


Scheme 96. Industrial preparation of scents derived from isoprene.[262a,264]

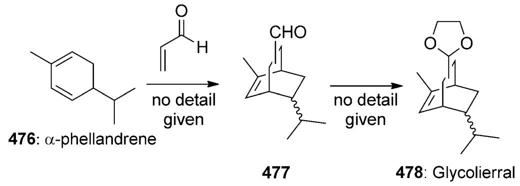
The synthesis of compounds derived from isoprene has also been carried out industrially. Of note is the synthesis of commercial fragrances derived from benzaldehyde such as Pelargene (**470**), Doremox (**471**), and Phenoxanol (**472**), which have rose, geranium, or metallic notes, respectively (Scheme 96).[262] These are rare illustrations of the application of a hetero-DA reaction on a multi-ton scale in the fragrance industry. For example, Phenoxanol[263] is sold globally in the range of 100–1000 tons per year.

As another example, technical mixtures of fatty acids (ricinene fatty acid), with either methyl acrylate or maleic anhydride as the dienophile, were used by Henkel and Grillo-Werke, respectively, for the synthesis of coating agents[265] and deodorants[266] on a commercial scale. Their patented synthesis has been exemplified on a 90 kg scale (see Scheme S17 in the Supporting Information).

Cyclohexadiene derivatives have also been used intensively for the preparation of fragrance from 1,3-dienes of natural origin, for example, α-terpinene (**473**; Scheme 97)[227a,267] or α-phellandrene (**476**; Scheme 98).[268] This is in contrast to the synthesis of pharmaceuticals where cyclohexadiene-derived dienes have only rarely been employed. With these scaffolds, woody, fresh, and herblike perfume notes or patchouli-like nuances can be imparted to a composition. Glycolierral (**478**) derived from low-cost α-phellandrene (**476**), with floral and woody notes, is marketed by Givaudan (Scheme 98).[227b]

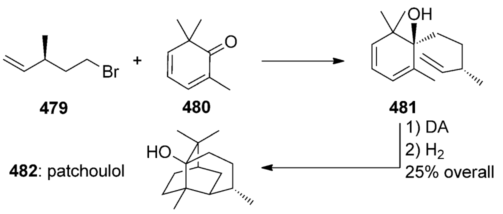


Scheme 97. Industrial preparation of scents from **473**.[267a]



Scheme 98. Industrial preparation of Glycolierral.[264b]

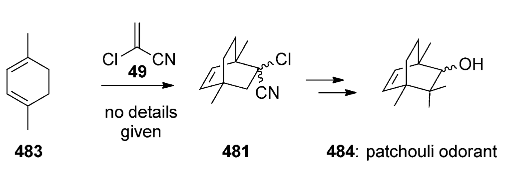
Essential oils and natural extracts of botanical or animal origin are an important source of aromatic materials for the flavors and fragrances industry. Isolation of these olfactory substances by simple distillation, solvent extraction, or maceration is often more competitive than their chemical syntheses. One example of such an essential oil is patchouli oil, which has a high worldwide demand of approximately 1200 tons per year, as stated by Birkbek.[223] However, its fluctuating price and high demand have prompted investigations aimed at the total synthesis of its major component—patchoulol (**482**)—which has a woody, earthy, camphoraceous smell. The racemic synthesis of patchoulol by an intramolecular DA reaction was reported by Naef and Ohloff in 1974 (Scheme 99).[223,269]



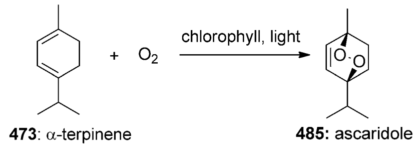
Scheme 99. Synthesis of racemic patchoulol by an intramolecular DA reaction.[269a]

The low yield of this general approach cannot compete economically with isolation by steam distillation. It has stimulated intense research into non-natural, industrially feasible, patchouli-like odorants. In 1973, the synthesis of patchouli-like derivatives by an intramolecular DA reaction was patented by Roche (see Scheme S18 in the Supporting Information).[270] In 1993, Weyerstahl et al.[271] reported a DA approach for the synthesis of a more accessible patchouli odorant **484** (with cedarwood and camphor notes) by using **483** and α-chloroacrylonitrile (**49**) that was "judged to be competitive in terms of synthetic accessibility and production costs" as pointed out by Kraft and co-workers (Scheme 100).[227a]

Ascaridole (**485**) is a naturally occurring organic peroxide extracted from chenopodium plants. Used as a food flavoring agent in Latin American cuisine, it exhibits anthelmintic properties and has been used to treat parasitic infections. Its synthesis from α-terpinene and singlet oxygen through a [4+2] cycloaddition process was reported in 1944 by Günther et al.,[272] and is at the present time run on a large scale (Scheme 101).[273] In 2002, a continuous-flow variant by de Mello and co-workers[274] was reported that avoids the caveats of the previous batch approach, namely an efficient irradiation and cooling of the reactor. Another example of the transfer of a DA reaction to continuous mode was disclosed by Ley and co-workers in 2007.[275] Henkel[276] and IFF[277] have patented olfactory compounds with woody and sea-shore-like characters, respectively, which are obtained from more elaborated 1,3-butadiene derivatives (see Scheme S19 in the Supporting Information).



Scheme 100. Industrially feasible synthesis of patchouli odorant **484**.[271]



Scheme 101. Production of ascaridole.[272]

With this selection of examples of odorant compounds produced by [4+2] cycloaddition we have shown that applications of such a transformation are in fact numerous in the fragrance industry. This may in part be explained by the fact that the inherently modest selectivity of this process can actually be turned into a true asset since a mixture of isomers, when mixed with other compounds, allows for an almost infinite array of olfactory tonalities. With a method in hand to control the ratio of *endo*/*exo* isomers (by racemization or equilibration), a way to enhance a perfume composition is indeed to use variable proportions of the isomers to fine-tune the olfactory properties of the scent.[237a] Pursuing a similar approach, the enantioselective synthesis of a chiral fragrance allows for controlled amounts of each enantiomer to be mixed as well as only the racemic mixture to be used.[278] After the "chiral switch"[279] encountered in the pharmaceutical industry—namely, the use of single enantiomers versus racemic drugs—the increased use of modern enantioselective synthetic methods in the fragrance industry may open innovative pathways for the preparation of new fragrances. This could also solve the issue of the supply of rare ingredients that have previously been extracted from the natural pool. Further developments in this area are indeed becoming desirable to meet future expectations of the consumers.

5. Summary and Outlook

> "*The significant problems we face today cannot be solved at the same level of thinking we were at when we created them.*"
> Albert Einstein (1879–1955)

The DA reaction is undoubtedly one of the most favored transformations available to the synthetic organic chemist for the rapid construction of complex molecular frameworks. This Review has focused specifically on industrial applications of this method. Although doubts were initially expressed regarding the availability of examples in an industrial setting, a thorough search, carried out for the first time to our knowledge, provided the opportunity to instead unravel a broad (however, noncomprehensive) variety of cases produced on a kilogram scale. A total of 161 examples, including pharmaceutical drugs (82), agrochemical compounds (20), and flavors and fragrances (59), have been identified. It still holds true, however, that the beautiful developments in the field of catalytic asymmetric DA reactions that appeared in recent years have not yet been applied on a large scale or so far remain undisclosed.[280]

The registration of a chemical route featuring the DA reaction as a key step is a tribute to the perseverance of drug, agrochemical, and fragrance hunters, be they discovery or process-development chemists. This illustrates the potential benefit of overcoming common prejudices or seemingly fixed borders that tend to lock up the DA reaction a priori into the field of "nonscalable transformations". In the quest for a first scalable route for the delivery of material for clinical use, the process chemist will surely excel best when considering the complete repertoire of organic reactions, including the DA reaction.

This Review testifies that examples indeed exist, without minimizing the underlying challenges of such a scale-up. Assessing the safety of this reaction with polymerization-prone substrates, mastering the complex synthesis of advanced DA reagents, and controlling the selectivity of the reaction are indeed genuine challenges. However, these objectives are not specific to the DA reaction, but rather typical for the scale up of any chemical reaction. In the context of increasing hurdles to the development of new, innovative, and safe active substances, the unbiased use of the complete portfolio of chemical reactions may inaugurate efficient pathways to new promising chemical compounds. The attrition of a compound in development is seldom due to technical difficulties, as adequate investment in research and development may often lead to a viable route from a technical and an economic perspective, should the clinically unmet need justify it. Minimizing both the ecological and financial footprint of an industrial synthesis has been the motto of good process research and development. Nowadays, this approach has become a true commandment. Simple synthetic routes with reduced costs of goods have an important leverage on the affordability[281] of medications for life-threatening illnesses. They help to lower production costs and to secure important investments into the research of innovative new drugs.

6. Addendum (January 31, 2013)

After the submission of this Review the following publications appeared. The industrial syntheses of vitamins, including vitamin B_6 (see Section 2.1), have been reviewed.[282] A review on the use of 2-azabicyclo[2.2.1]hept-5-en-3-one (Vince lactam; Section 2.6) has been published.[283] In this publication, new drugs accessed by means of a DA reaction are highlighted (see Figure S3 in the Supporting Information): Melogliptin (Glenmark; in phase II tests for the treatment of type 2 diabetes) and MK-0812 (Merck; in phase II tests for the treatment of multiple sclerosis). We also became aware of the large-scale synthesis of Tecovirimat (Siga), which was preregistered in the US in 2012 for the treatment of smallpox infection. Its industrial synthesis is based on the thermal [4+2] cycloaddition of maleic anhydride with cycloheptatriene.[284]

Abbreviations

AIBN	2,2′-azobisisobutyronitrile
API	active pharmaceutical ingredient
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bt	benzotriazole
chrom	chromatography
m-CPBA	*meta*-chloroperbenzoic acid
Cy	cyclohexyl
diast.	diastereoisomer
DA	Diels–Alder reaction
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DME	dimethoxyethane
DMF	dimethylformamide
DMT	dimethoxytrityl
GMP	Good Manufacturing Practice
LAH	lithium aluminum hydride
MAD	bis(2,6-di-*tert*-butyl-4-methylphenoxide)
Ms	methanesulfonyl
MSC	methanesulfonylcyanide
NBS	*N*-bromosuccinimide
PPTS	pyridinium *p*-toluenesulfonate
pTsOH	*p*-toluenesulfonic acid
SiO_2	silica
TBME	*tert*-butyl methyl ether
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
tol.	toluene
TMS	trimethylsilyl
Tr	triphenylmethyl
Z	benzyloxycarbonyl

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[23] For more detailed descriptions of the chemical transformation, the reader is invited to consult the cited publications. In view of the thousands of hits (> 35000) retrieved in the Chemical Abstracts using Diels–Alder as keyword or using the structure search engine, we opted for a more focused search with the use of specific key words or through personal communications with a corpus of several hundreds of experts worldwide, limiting the scope to industrial applications of this transformation.

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