Chapter 10
Applications in Total Synthesis

Several types of carbonylative transformation of C–X bonds have been discussed in previous chapters. In this chapter, the applications of carbonylation reactions in total synthesis will be summarized and discussed.

Total synthesis is, in principle, the complete chemical synthesis of complex organic molecules from simpler pieces [1, 2]. Total synthesis provides unique opportunities to discover and invent new strategies and tools for constructing organic molecules, which have experienced an explosion in their development over the last few decades [3–21]. In all synthetic methods used on organic synthesis, transition metal catalysts as a powerful tool have also been applied in the total synthesis of natural products. More specifically, transition metal-catalyzed carbonylation reactions, which are even more interesting and important, have also been applied. As carbon monoxide is inexpensive, and using cheap molecular for building high valuable compounds is interesting from both academic and industrial.

There is an impressive number of publications on the application of transition metal-catalyzed carbonylation reactions in total synthesis. In 1980 Tsuji and colleagues applied palladium-catalyzed alkoxycarbonylation in the synthesis of Zearalenone [22] and Curvularin [23]. Starting from the corresponding aryl iodides or benzyl chlorides and alcohols, the parent molecules for Zearalenone and Curvularin were prepared in good yields and finally transferred to the target products by a few more steps (Scheme 10.1).

Anthramycin [24], prothracarcin and tomaymycin [25] were synthesized by Ban and colleagues by using aminocarbonylation as the key step. In the presence of a palladium catalyst under low pressure of carbon monoxide, the reaction finished with good yields of desired products (Scheme 10.2).

Stille and colleagues developed a general palladium-catalyzed carbonylative coupling of vinyl triflates with organostannanes and applied in the total synthesis of Capnellene, a naturally occurring hydrocarbon derived from Capnella imbricata as well [26]. Starting from easily available ketone, via vinyl triflate, by two times carbonylative coupling with organostannanes, the core structure for Capnellene synthesis was produced in good yield (Scheme 10.3).

M. Beller and X.-F. Wu, *Transition Metal Catalyzed Carbonylation Reactions*,
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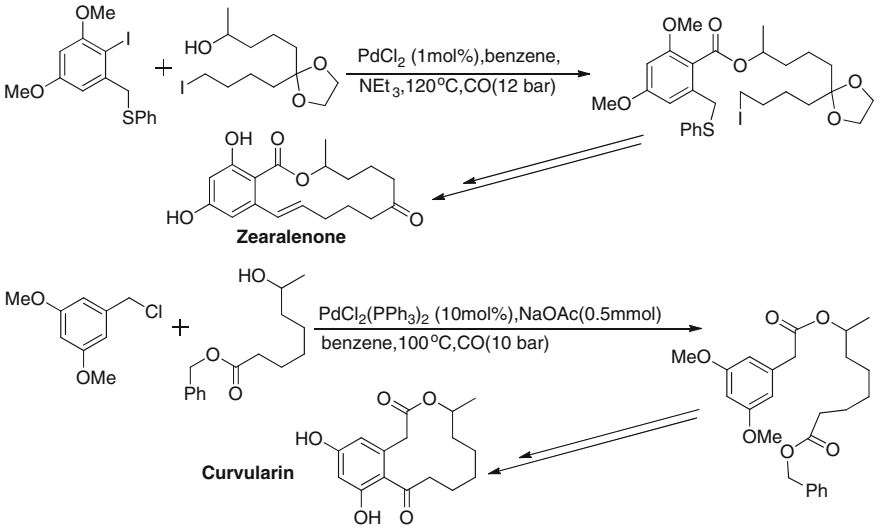
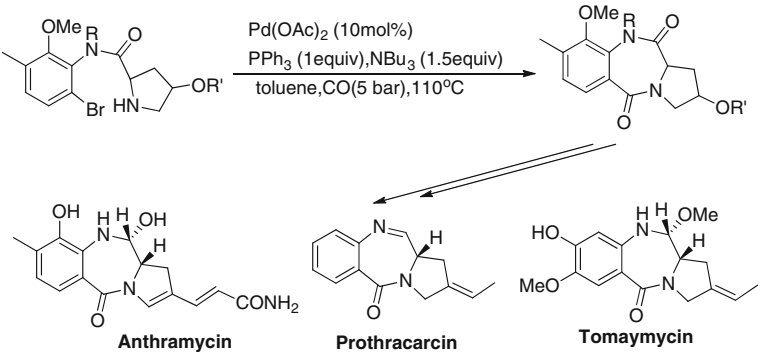


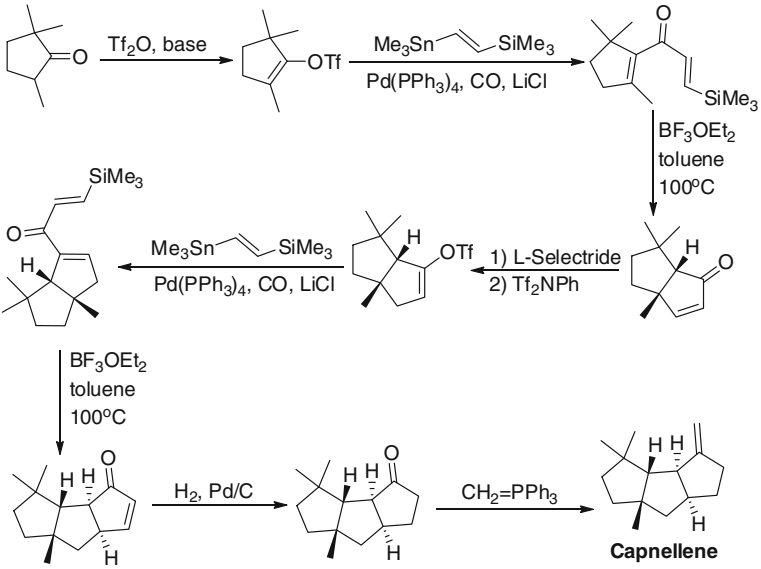
Scheme 10.1 Application in the synthesis of Zearalenone and Curvularin



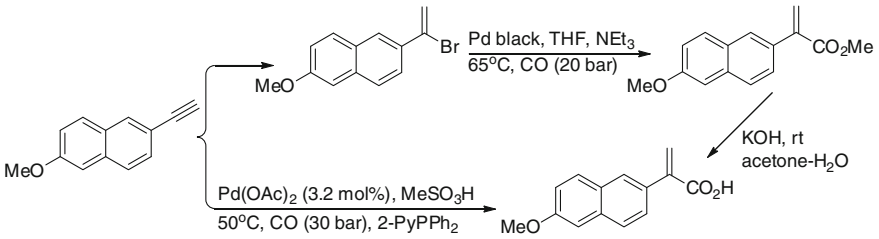
Scheme 10.2 Application in the synthesis of Anthramycin, Prothracarcin and Tomaymycin

As vinyl triflates can be easily prepared from the corresponding ketones or aldehydes, which are abundant and wildly available, the use of vinyl triflates as starting materials in total synthesis has attracted a lot of attention [27–39]. Murai's group synthesized glycinoeclepin A by palladium-catalyzed carbonylation, using vinyl triflate as the key intermediate [40, 41]. Holt and colleagues prepared bioactive steroids [42, 43], while McDonald's team prepared cephalosporins [44].

(*S*)-2-(6-Methoxy-2-naphthyl)propanoic acid is also called naproxen, an anti-inflammatory agent. Several procedures have been developed for its preparation; among them, the reduction of 2-(6-methoxy-2-naphthyl)propenoic acid is certainly one of the most direct routes. For this reason, methodologies have been developed



Scheme 10.3 Application in the synthesis of Capnellene

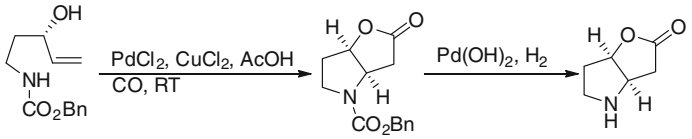


Scheme 10.4 Synthesis of 2-(6-methoxy-2-naphthyl) propenoic acid

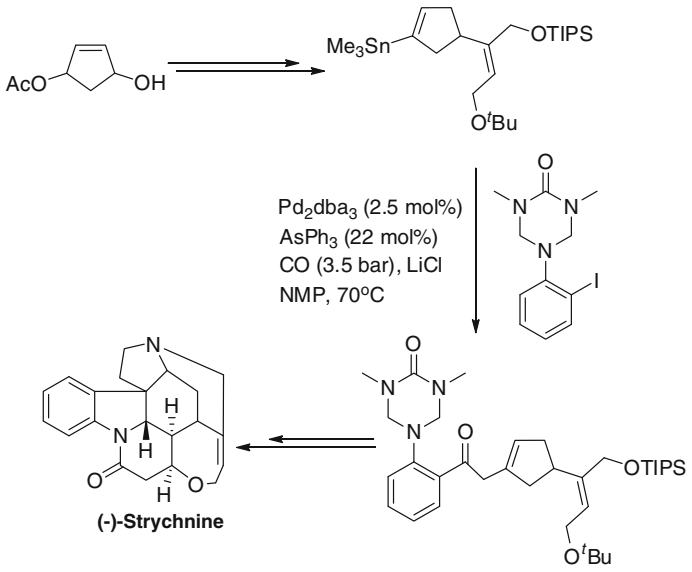
that include carbonylation reactions (Scheme 10.4). They all started from the corresponding alkyne, then transformed into vinyl halides and were followed by hydroxycarbonylation [45] or direct hydrocarbonylation of the alkynes [46].

Geissman-Weiss lactone is an important intermediate in the synthesis of a number of necine bases (pyrrolizidine alkaloids). The palladium-catalyzed carbonylative cyclization of 3-hydroxy-4-pentenylamine to the Geissman–Weiss lactone was reported in 1991 and later in 1996 (Scheme 10.5) [47–49]. This methodology was also applied in the total synthesis of C_{19} lipid diols [50].

(−)-Strychnine was first isolated in 1818 from *Strychnos ignatii* by Pelletier and Caventou. Overman and colleagues did the first asymmetric total synthesis of strychnine [51]. A palladium-catalyzed carbonylative coupling of aryl iodide with an organostannanes reagent was used for the preparation of one of the intermediates (Scheme 10.6). The entire synthesis was accomplished in 20 steps and



Scheme 10.5 Synthesis of Geissman–Weiss lactone



Scheme 10.6 Synthesis of (−)-Strychnine

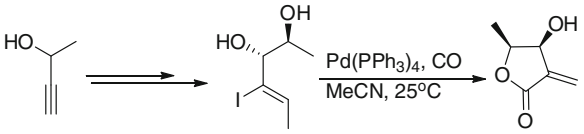
a ∼3 % overall yield from enantiopure hydroxyl cyclopentenyl acetate was successful.

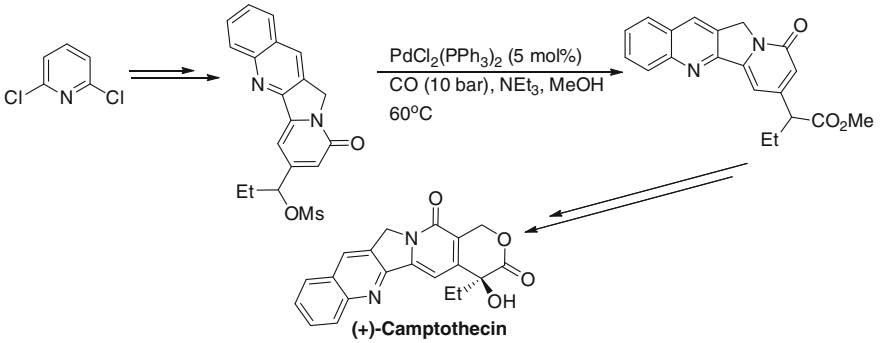
3-Alkylidene-4,5-dihydro-4-hydroxy-5-methyl-2-(3*H*)-furanones are a class of natural products isolated from plants of the *Lauraceae* family, which have interesting biological activities. In 1994 Adam and Klug reported a methodology for their preparation, and palladium-catalyzed carbonylation was applied [52]. Starting from readily available alkynes or propargylic alcohols, furanones were prepared in good yields (Scheme 10.7).

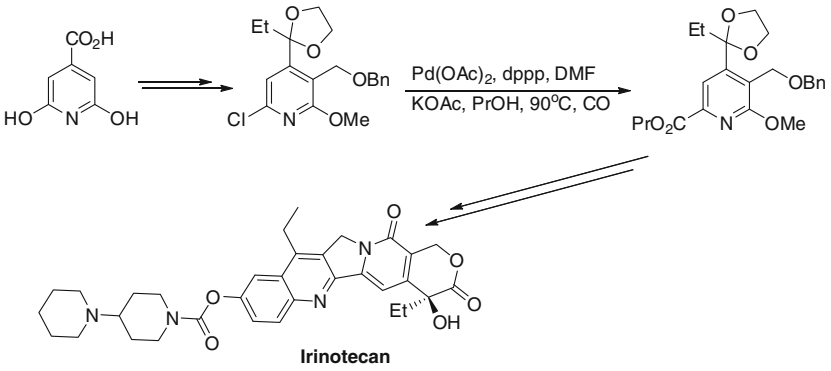
Additionally, carbonylation reactions were applied by various groups for the preparation of phosphatase inhibitors [53–56].

(+)-Camptothecin was isolated from *Chinese tree* by Wall and colleagues in 1966; its potent antitumor property has attracted interest from synthetic chemists. In 1997 Murata, Sakamoto and their team reported a methodology for the functionalization of heteroaromatics, and also applied it in the total synthesis of camptothecin [57]. Palladium-catalyzed carbonylation of benzylic substrates was

Scheme 10.7 Synthesis of furanones





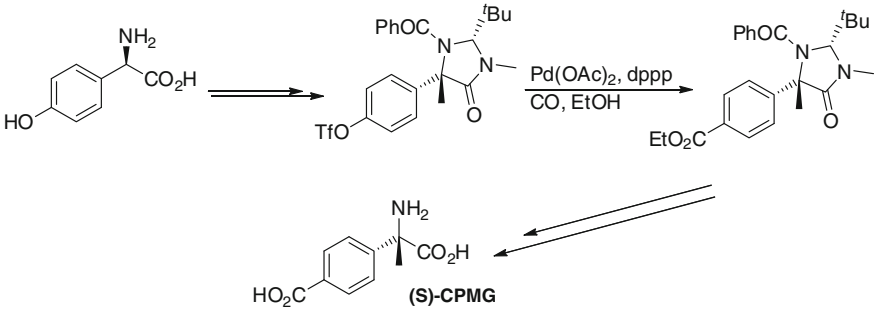


Scheme 10.8 Synthesis of camptothecin and irinotecan

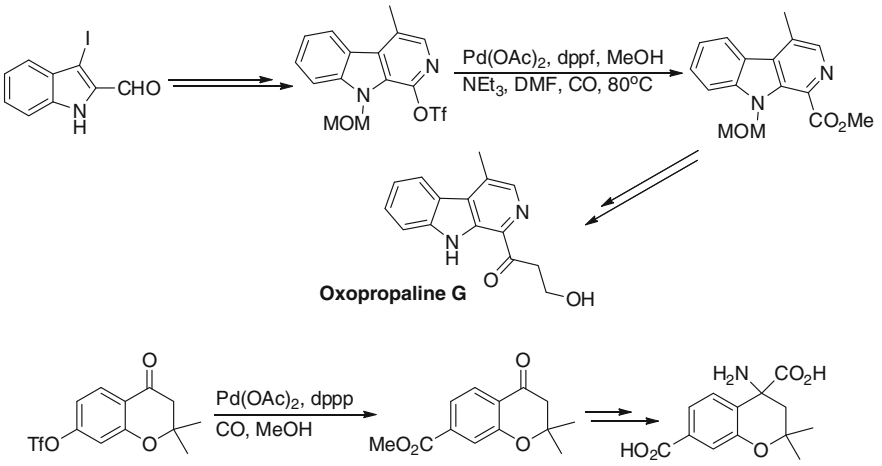
used to extend the carbon chain and introduce an ester group. That same year, Henegar's group reported the use of citrazinic acid as a starting material for the synthesis of camptothecin and irinotecan [58]. This procedure offers another pathway for the preparation of these derivatives (Scheme 10.8).

Ma and Tian reported the synthesis of (S)-(+)-αM4CPG from 4-hydroxyphenylglycine [59–61]. A palladium-catalyzed alkoxycarbonylation of aryl triflates was applied (Scheme 10.9).

Several methodologies based on the carbonylation of aryl triflates were developed and applied in the synthesis of bio-active molecules [62–70]. They all use a palladium-catalyzed carbonylative transformation of aryl triflates as the key step to preparing intermediates; oxopropaline, phenylglycines and phenylalanine were prepared (Scheme 10.10).



Scheme 10.9 Synthesis of (S)-(+)-αM4CPG



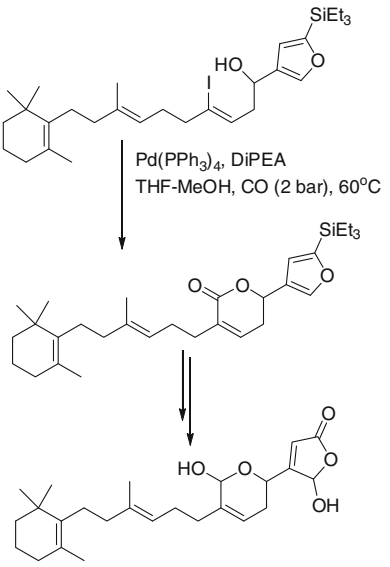
Scheme 10.10 Using aryl triflates as substrates

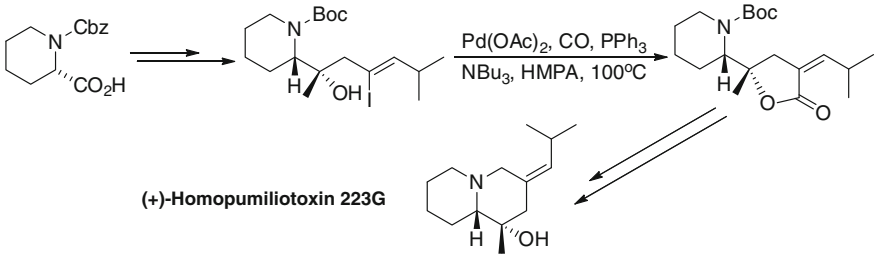
Vinyl halides, as an interesting family of substrates in addition to vinyl triflates, were applied and used in total syntheses as well. In 1997 manoalide as a marine anti-inflammatory sesterterpenoid was synthesized [71, 72]. Palladium-catalyzed alkoxycarbonylation of vinyl iodide was the key step in the synthetic procedure (Scheme 10.11).

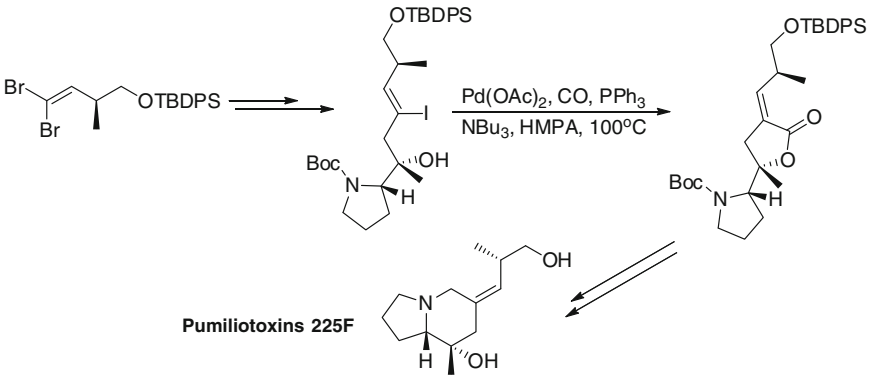
(+)-Homopumiliotoxin and Pumiliotoxin were totally synthesized in the late twentieth century by Kibayashi's goup [73–75]. Intramolecular alkoxycarbonylation for the formation of lactone frames were taken as a fundamental step (Scheme 10.12). Negishi and Liao reported a palladium-catalyzed carbonylative lactonization of (Z)-σ-iodoalkenols and applied that in the total synthesis of (+)-hamabiwalactone B [76].

Additionally, the carbonylation of alkene or alkyne with various nucleophiles offers alternative procedures for organic synthesis [77, 78]. Different kinds of

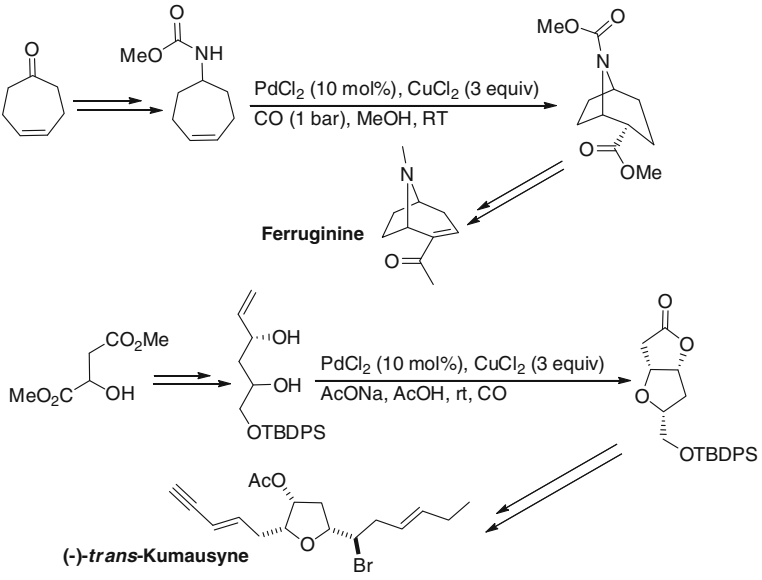
Scheme 10.11 Synthesis of Manoalide







Scheme 10.12 Synthesis of (+)-homopumiliotoxin and pumiliotoxins



Scheme 10.13 Synthesis of ferruginine, kumausyne and anatoxin

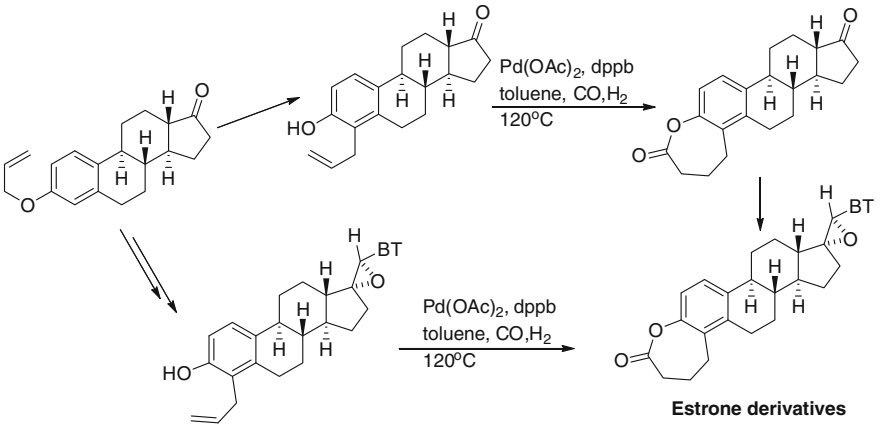
heterocycles can be prepared by these methodologies, and applied in the total synthesis of natural products by different groups [79–83]. Ferruginine, kumausyne and anatoxin were prepared by using carbonylation as the key step (Scheme 10.13).

The $Pd(OAc)_2$/dppb system was applied in the cyclocarbonylation of 4-allylsteroids for the formation of 7-membered lactone rings [84]. Based on this methodology, novel estrone derivatives were prepared in a different manner (Scheme 10.14).

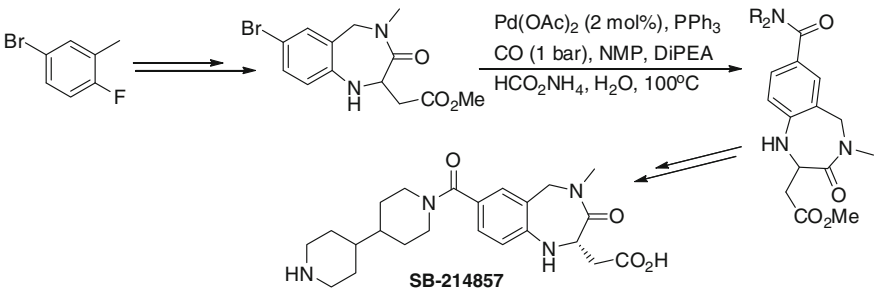
In 1999, Hayes and colleagues reported the synthesis of SB-214857, a potent GP IIb/IIIa antagonist, which had been proposed for clinical trials for the prevention of secondary thrombotic events such as heart attack and stroke [85]. 4-Bromo-1-fluoro-2-methylbenzene was used as a starting material, and palladium-catalyzed aminocarbonylation was applied for the preparation of one of the intermediates (Scheme 10.15). Carey's group did the synthesis from 2-nitrobenzyl alcohol, and palladium-catalyzed aminocarbonylation was applied [86, 87].

(+)-Bicuculline as an effective antagonist of an inhibitory neurotransmitter, γ-aminobutyric acid (GABA), many procedures have been developed for its preparation. Orito and colleagues applied palladium-catalyzed alkoxycarbonylation as the key step in its total synthesis (Scheme 10.16) [88].

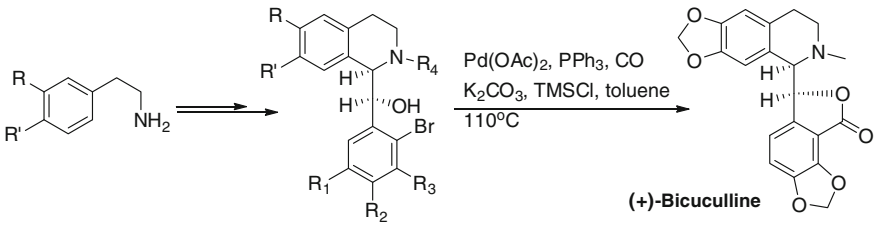
Boger and Boyce synthesized 1,2,9,9a-tetrahydrocyclopropa[c]pyrido[3,2-*e*]indol-4-one-7-carboxylate (CPyI), a parent molecular for antitumor molecular synthesis [89]. Starting from an aminophenol derivative and applied carbonylation as one of the steps, CPyI was prepared and further modified (Scheme 10.17).



Scheme 10.14 Synthesis of estrone derivatives

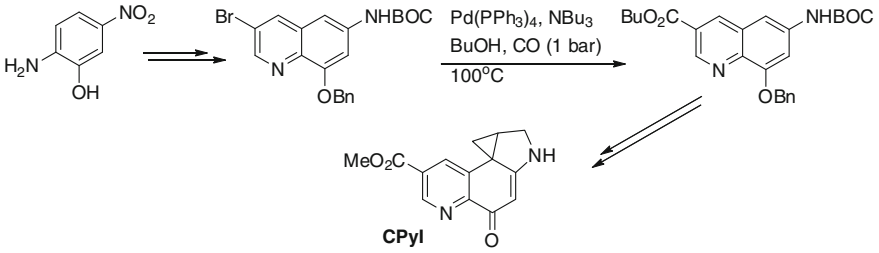


Scheme 10.15 Synthesis of SB-214857



Scheme 10.16 Synthesis of (+)-Bicuculline

Leighton and Bio reported the total synthesis of CP-263,114 in 1999 [90–92]. CP-263,114 is active against protein farnesyl transferase, and is now a medicinal target of great interest. This group totally synthesized Leucascandrolide A as well; a compound was isolated from the sponge *Leucascandra caveolata* shown activity



Scheme 10.17 Synthesis of CPyI

in antifungal, inhibiting the growth of *Candida albicans* [93]. Palladium-catalyzed carbonylation was applied in this total synthesis procedure and gave the key intermediate in moderate yield (Scheme 10.18).

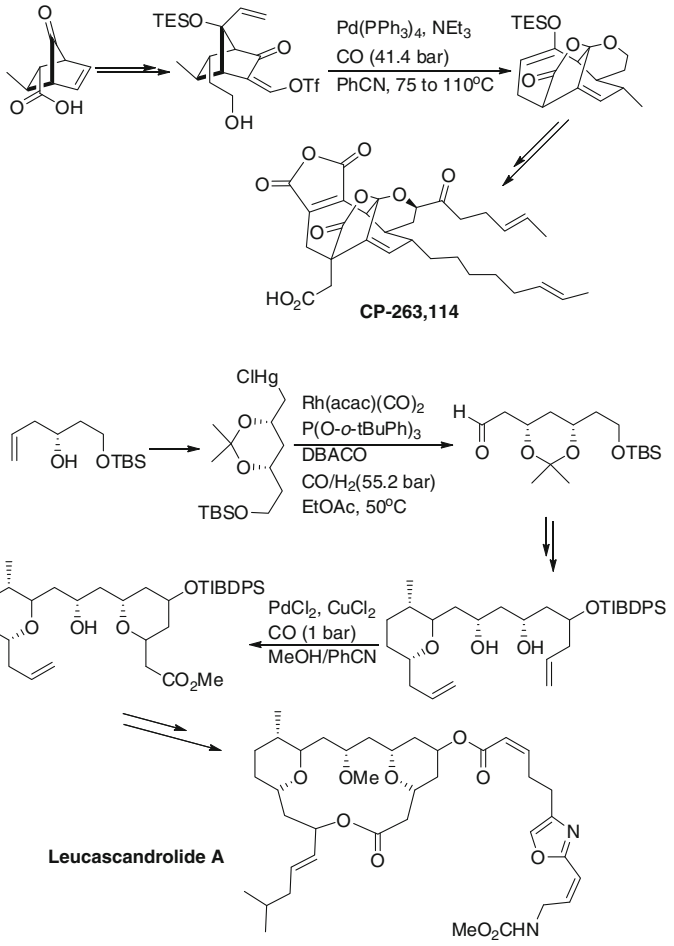
Yuehchukene is a novel class of bisindole alkaloids, first isolated as a racemate from *Murraya paniculata*, with a basic structure of hexahydroindeno[2,1-*b*]indole. It has been suggested that this compound exhibits mixed estrogen and anti-estrogen activities as well as potent anti-implantation. In 2000 Ishikura and his team reported a concise procedure for their preparation; a carbonylation reaction was applied for intermediate synthesis (Scheme 10.19) [94].

Cyclic pentapeptide is a potent inhibitor of $\alpha 4\beta 1$-mediated cell adhesion to CS-1 site and VCAM with IC_{50} ranging from 2 to 9 μM in cell adhesion assays. Under this background, Ho and Broka reported the synthesis of peptidomimetic tricyclic tetrahydrobenzo [*ij*] quinolone in 2000 [95]. Palladium-catalyzed alkoxycarbonylation of aryl triflate was applied and produced the needed intermediate in moderate yield (Scheme 10.20).

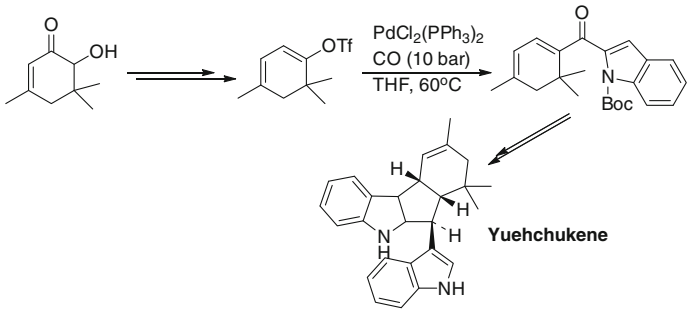
As 1-bromocodeine is readily prepared in multigram quantities, Davies and colleagues reported a procedure for its modification [96]. By palladium-catalyzed carbonylation reactions, codeines and morphines were elaborated. Wentland's team studied the carbonylative functionalization of 3-triflate substituted codeine derivatives and the biological activities of the products [97, 98].

(+)-Nodulisporic acid A, a novel indole terpene, which displays potent oral systemic activity against fleas in dogs, was isolated in 1997. In 2001 Smith III and colleagues reported the total synthesis of this compound [99, 100]. Palladium-catalyzed reductive carbonylation of vinyl triflate was applied, the formed intermediate was isolated in good yield and further transformed into the target product. That same year they also reported the total synthesis of (−)-cylindrocyclophanes A and F [101]. The compounds were isolated in 1990 and were found to be the major cytotoxic components in three different strains of the terrestrial blue-green algae *Cylindrospermun lichenforme*. Palladium-catalyzed reductive carbonylation of aryl iodides was applied in this total synthesis (Scheme 10.21).

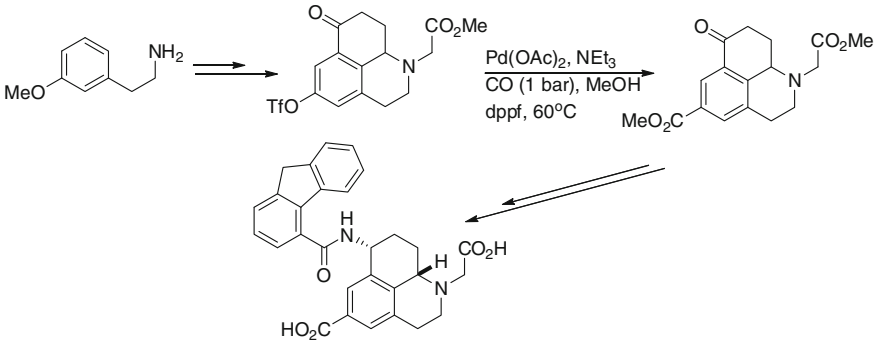
The 5-substituted-2-picolinic acids, such as fusaric acid and (*S*)-(+)-fusarinolic acid, are a class of alkaloid natural products with important biological activities. In particular, fusaric acid was shown to be a potent inhibitor of dopamine *β*-



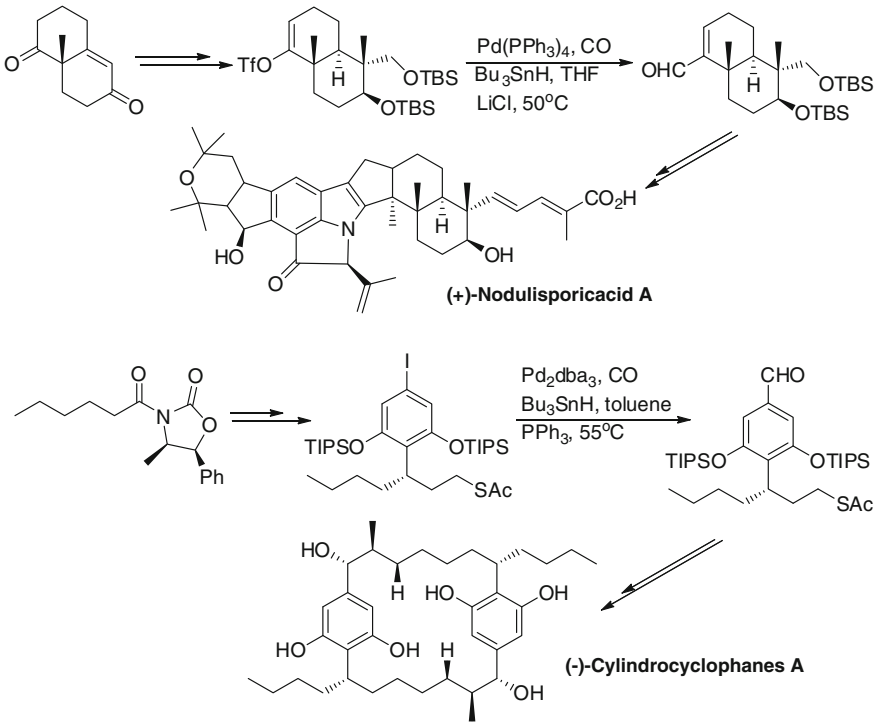
Scheme 10.18 Synthesis of CP-263, 114



Scheme 10.19 Synthesis of yuehchukene

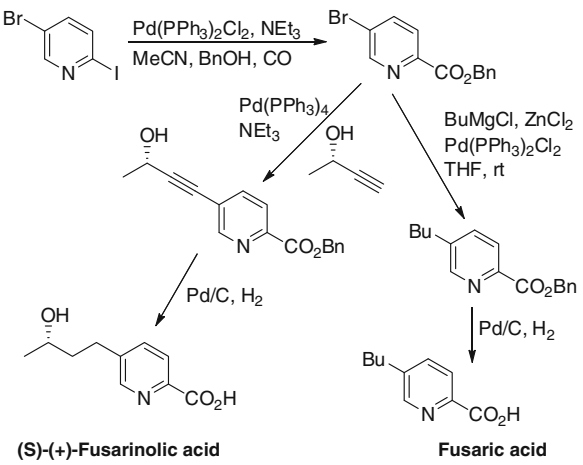


Scheme 10.20 Synthesis of peptidomimetic tricyclic tetrahydrobenzo [*ij*] quinolone



Scheme 10.21 Synthesis of (+)-nodulisporic acid A and (−)-cylindrocyclophanes A

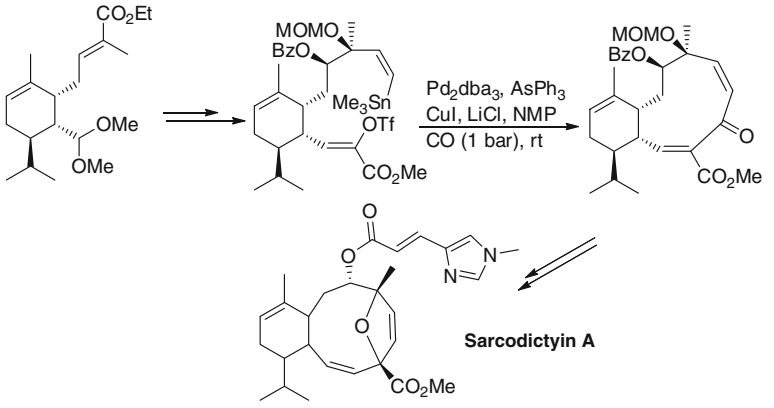
hydroxylase in vitro and in vivo and displayed notable antihypertensive activity. Fusaric acid also exhibited marked antitumor activity on human colon adenocarcinoma cell lines LoVo, SW48, SW480, and SW742, as well as the human mammary adenocarcinoma cell line MDA-MB-468. Other biological activities of



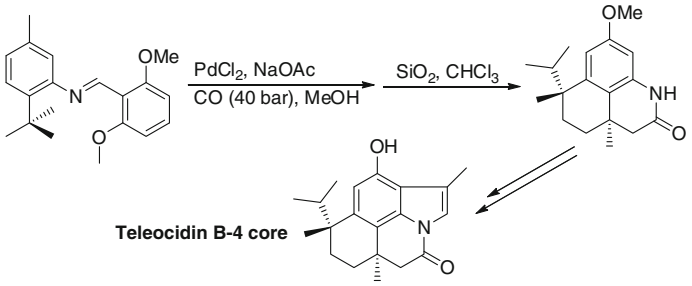
Scheme 10.22 Synthesis of fusaric acid and (*S*)-(+)-Fusarinolic acid

fusaric acid and its derivatives include neurogenic, wilting, and herbicidal activities, which were summarized in a recent review article [102]. In 2001 Song and Yee reported a concise procedure for the synthesis of fusaric acid and (*S*)-(+)-fusarinolic acid (Scheme 10.22) [103]. In this report, they systematically studied the monocarbonylation of 2,5-dibromopyridine under different conditions. And 5-bromo-2-iodopyridine was found to be the best starting material. This methodology was later applied in total to the synthesis of phosphodiesterase IV inhibitor [104].

A total synthesis of sarcodictyins was reported by Cennari and colleagues [105]. A palladium-catalyzed carbonylative Stille coupling of vinyl triflate was designed and used (Scheme 10.23).



Scheme 10.23 Synthesis of Sarcodictyins

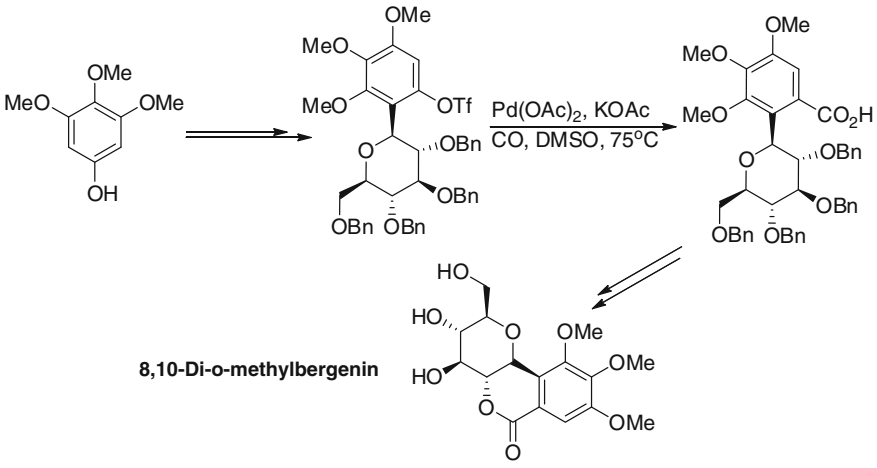


Scheme 10.24 Synthesis of teleocidin B4 core

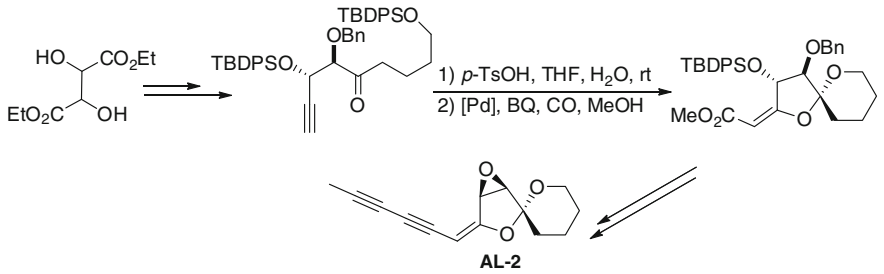
A process for the multigram preparation of 5-(2-methoxy-4-nitrophenyl)oxazole, a key intermediate for the preparation of the hepatitis C drug candidate VX-497 (merimepodib), was developed by Herr and colleagues [106]. Palladium-catalyzed reductive carbonylation of diazonium salt was applied and the formed aldehyde was subsequently used in the preparation of oxazole.

N-[4-[1-Ethyl-2-(2,4-diaminofuro[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid as an antifolate was synthesized by Gangjee and colleagues [107], and palladium-catalyzed alkoxycarbonylation of aryl triflate was applied. A palladium-mediated carbonylative C–H activation was developed by Sames and team and applied in the total synthesis of teleocidin B4 core (Scheme 10.24) [108].

C-Glycoside natural products exhibit medicinally interesting properties and have potential as antifungal and antitumorigenic treatments. Seeberger's group developed a short synthesis of *C*-glucoside 8,10-di-*O*-methylbergenin with a 33 % overall yield in only four steps from common glycosyl donors [109]. A palladium-catalyzed hydroxycarbonylation of aryl triflate was applied (Scheme 10.25).



Scheme 10.25 Synthesis of *C*-glycoside



Scheme 10.26 Synthesis of (−)-AL-2

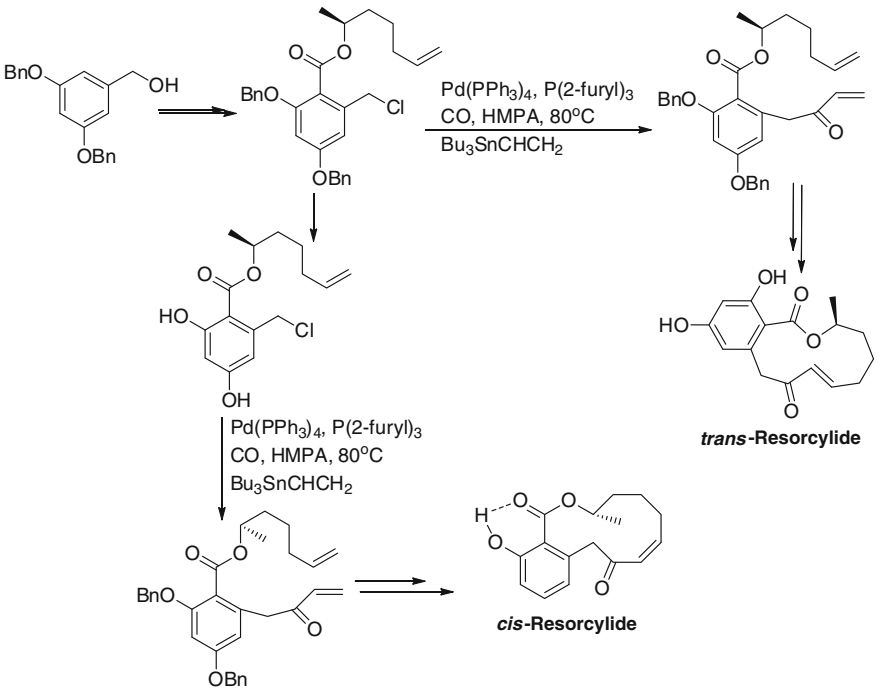
Mukai and Miyakoshi reported the total synthesis of (−)-AL-2, an example of a class of molecules with antitumor activities [110]. With 5 mol% of $Pd_2(dba)_3$ $CHCl_3$ and 20 equiv. of benzoquinone in methanol under a carbon monoxide atmosphere at room temperature, the intermediate was produced in a 41 % yield (Scheme 10.26).

Weinreb and colleagues reported the total synthesis of marine ascidian metabolite perphoramidine via a halogen-selective tandem Heck/carbonylation strategy [111].

In 2004, *trans*- and *cis*-resorcylide were totally synthesized, and palladium-catalyzed carbonylative Stille coupling was applied for the preparation of the intermediate (Scheme 10.27) [112]. *Trans*- and *cis*-resorcylides are both natural macrocyclic plant growth inhibitors, isolated independently from different *Penicillium* species. Together with zearalenone, lasiodiplodin, and the important antitumor agent radicicol, they constitute an important class of bioactive resorcylic macrolides.

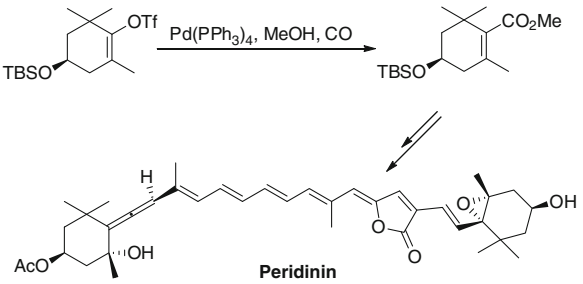
Peridinin, which was isolated from the planktonic algae dinoflagellates causing red tides, is a highly oxidized carotenoid containing an allene and a characteristic (*Z*)-γ-ylidenebutenolide function in the main conjugated polyene chain in addition to functionalized cyclohexane rings at both ends of the molecule. Peridinin was first isolated from the planktonic algae dinoflagellates causing red tides in 1890. In 2004 Katsumura and his colleagues reported the first example of controlling the stereochemistry of polyfunctional allenic carotenoids, and peridinin was totally synthesized [113]. The palladium-catalyzed alkoxycarbonylation of vinyl triflate was applied as the first step to increase the carbon chain (Scheme 10.28).

Coumestrol was first isolated from alfalfa, strawberry, Lucerne, and Ladino clover by Bickoff et al. in the 1950s, and has been reported to inhibit bone resorption and stimulate bone mineralization. In 2005 Larock and colleagues reported the synthesis of coumestrol and coumestans by the iodocyclization of acetoxy-containing 2-(1-alkynyl)anisoles and subsequent direct palladium-catalyzed carbonylation/lactonization [114]. The naturally occurring products were produced in good to excellent yields (Scheme 10.29).



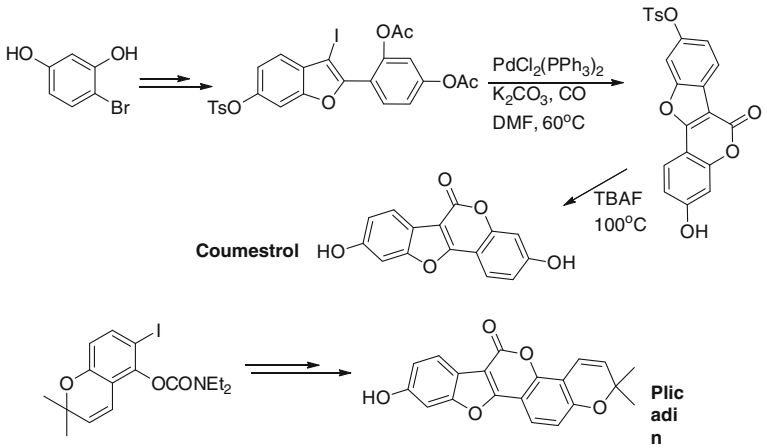
Scheme 10.27 Synthesis of *trans*- and *cis*-resorcylide

Scheme 10.28 Synthesis of peridinin

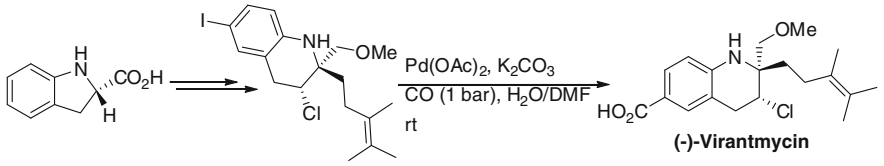


Hallberg's group applied aminocarbonylation in the functionalization of C_2-symmetric HIV-1 protease inhibitors [115]. $Mo(CO)_6$ was used as a CO source and microwave was used as a heating system.

The benzastatin family and virantmycin are a novel class of indoline and tetrahydroquinoline alkaloids isolated from *Streptomyces nitrosporeous*. Benzastatins show inhibitory activity against glutamate toxicity and lipid peroxidation in rat liver microsomes that can be used to prevent brain ischemia injury, and consists of indoline alkaloids such as benzastatin E, and tetrahydroquinoline alkaloids such as benzastatin C that are structurally related to virantmycin. (−)-Virantmycin, a



Scheme 10.29 Synthesis of coumestrol and plicadin



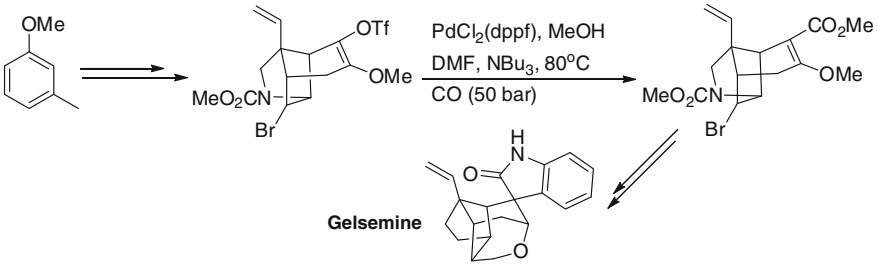
Scheme 10.30 Synthesis of (−)-virantmycin

potent inhibitor of RNA and DNA viruses, is a unique 2,2-disubstituted tetrahydroquinoline alkaloid with contiguous quaternary and tertiary stereocenters. In 2005 Kogen and colleagues reported the stereospecific synthesis of 2,2,3-trisubstituted tetrahydroquinolines and applied in the total syntheses of benzastatin E and natural virantmycin [116]. Palladium-catalyzed hydroxycarbonylation was used at the last stage for carboxylic acid formation (Scheme 10.30).

Overman and colleagues reported the total synthesis of (±)-Gelsemine in 2005 [117]. 1.1 % of the overall yield from 3-methylanisole was succeeded via 26 isolated intermediates. Palladium-catalyzed alkoxycarbonylation of vinyl triflate was applied (Scheme 10.31).

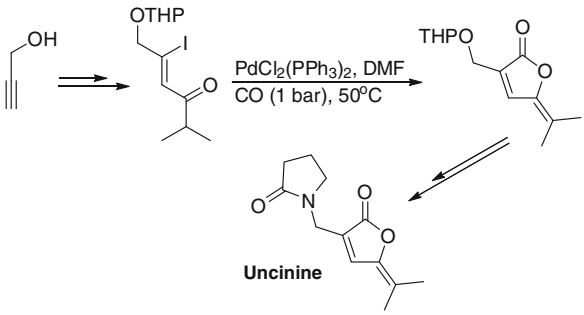
Uncinine is a novel butenolide alkaloid, isolated from *Artabotrys uncinatus*, a plant used as a traditional folk medicine in China for the treatment of nasopharyngeal carcinoma. Pour and colleagues did the total synthesis, and palladium-catalyzed carbonylation of vinyl iodide was applied (Scheme 10.32) [118].

The pyrrolo[2,3-*d*]pyrimidine skeleton is often encountered in important pharmacologically active substances, and more recently it has been observed in a class of marine natural products known as rigidins. These alkaloids have been obtained from tunicates obtained near Okinawa and New Guinea and they have been shown to exhibit very significant calmodulin antagonist activities. Gupton's



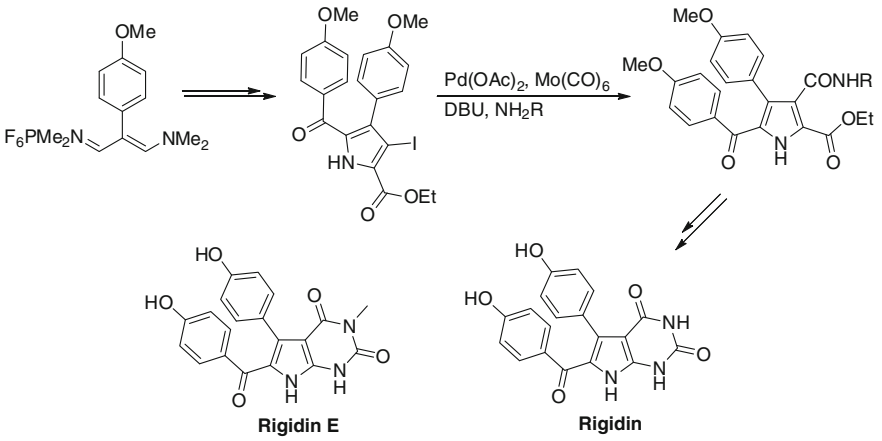
Scheme 10.31 Synthesis of (±)-gelsemine

Scheme 10.32 Synthesis of uncinine

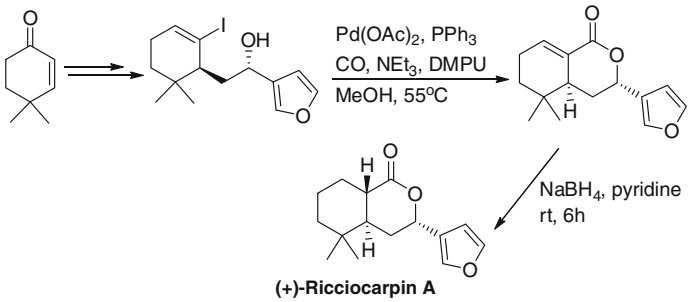


group reported the total synthesis of rigidin and rigidin E [119]. Palladium-catalyzed aminocarbonylation was applied as the key step (Scheme 10.33).

(+)-Ricciocarpin A, a furanosesquiterpene lactone, was first isolated from an axenic culture of the European liverwort *Ricciocarpos natans* in 1990. It bears a δ-



Scheme 10.33 Synthesis of rigidin and rigidin E



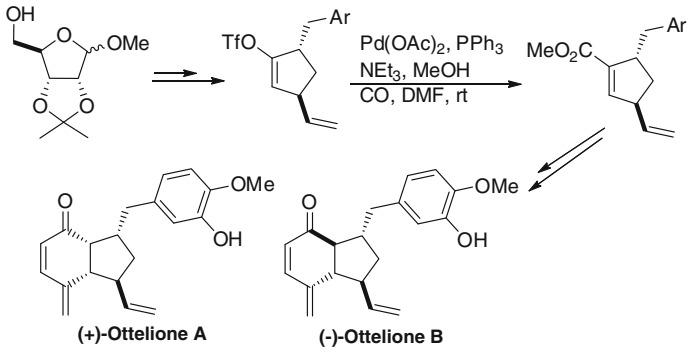
Scheme 10.34 Synthesis of (+)-ricciocarpin A

lactone functionality appended with a 3-furyl group and displays high molluscicidal activity against the water snail *Biomphalaria glabrata*, one of the vectors of schistosomiasis. Liu and Jan used palladium-catalyzed carbonylation of vinyl iodide in the total synthesis of (+)-ricciocarpin A in 2006, with 4,4-domethyl-2-cyclohexenone used as the starting material (Scheme 10.34) [120].

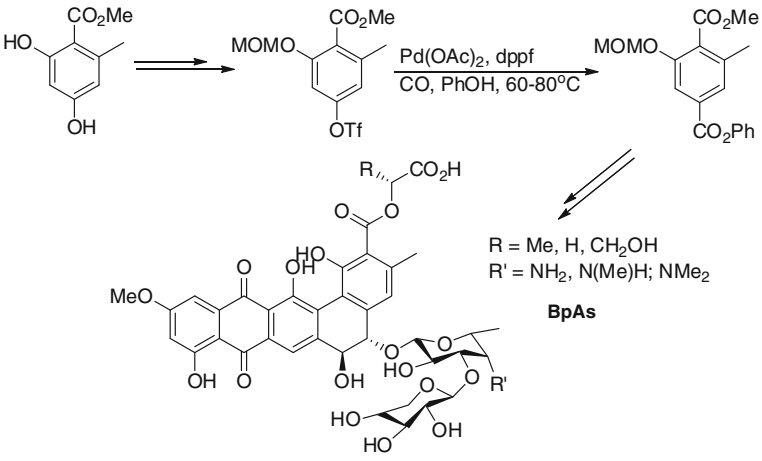
The otteliones are exceedingly powerful anticancer agents, as judged by in vitro tests against a large panel of tumor cell lines. Both compounds were isolated from a freshwater plant, *Ottelia alismoides*, collected in Egypt. Clive and Liu reported the total synthesis of these compounds in 2008 [121]. They started from optical pure cyclopropane formed from a chiral pool, and a carbonylation reaction was applied (Scheme 10.35).

The benanomicin-pradimicin antibiotics (BpAs) were isolated from the culture of the Actinomyces species in 1988, with potent antifungal and anti-HIV activities. Many procedures have been reported for their synthesis. Suzuki and colleagues reported a general route to BpAs [122]. A palladium-catalyzed alkoxycarbonylation of aryl triflates with phenol was used in this procedure (Scheme 10.36).

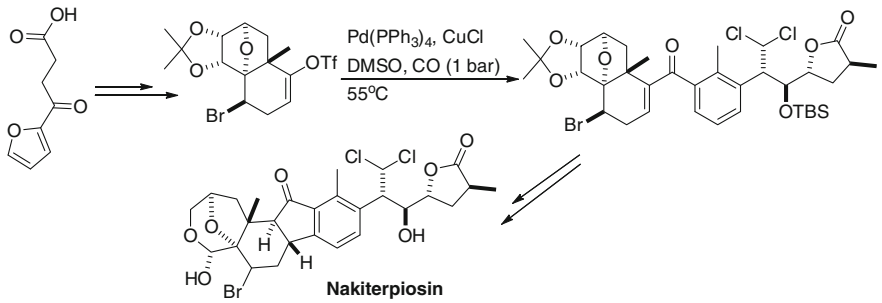
Nakiterpiosin is a marine sponge metabolite that exhibits potent cytotoxicity against the P388 murine leukemia cell line (GI_{50} 10 ng/mL). It was the first C-nor-



Scheme 10.35 Synthesis of otteliones



Scheme 10.36 Synthesis of BpAs

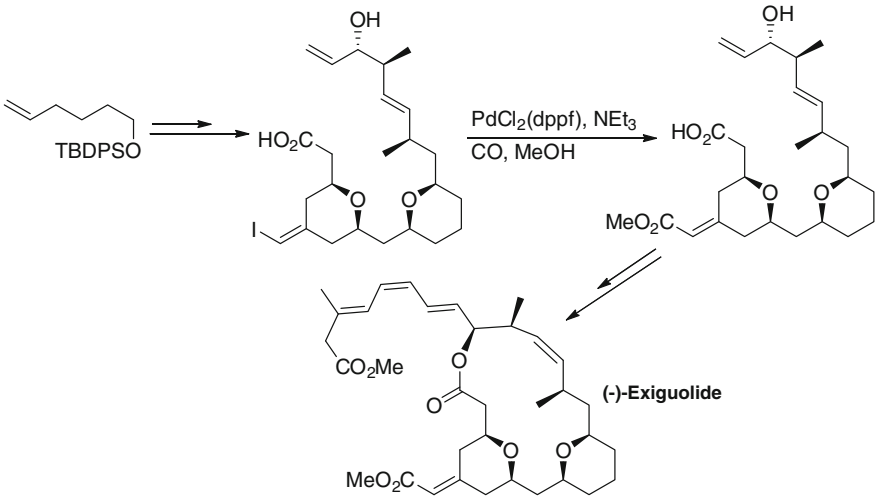


Scheme 10.37 Synthesis of nakiterpiosin

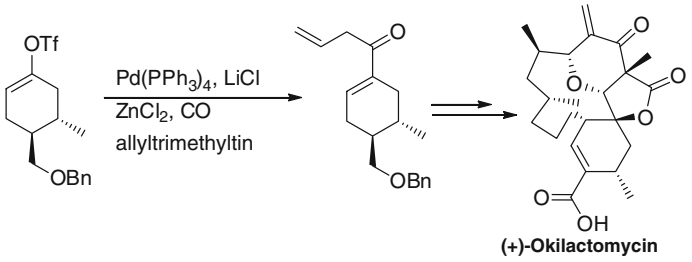
D-homosteroid isolated from a marine source. In 2008 Chen's group reported the total synthesis of this compound by using a palladium-catalyzed carbonylative Stille-coupling of vinyl triflate as the key step (Scheme 10.37) [123, 124].

(−)-Exiguolide was isolated by Ikegami's group in 2006 from the marine sponge *Geodia exigua.* (−)-Exiguolide inhibits the fertilization of sea urchin gametes, which indicates that this compound could inhibit the fusion of viruses with cell membranes. In 2010 Roulland and colleagues reported the total synthesis of (−)-exiguolide with carbonylation as one of the steps (Scheme 10.38) [125, 126].

(+)-Okilactomycin was isolated by Imai and associates in 1987; it is an architecturally complex polyketide antitumor antibiotic derived from a bioactive filtrate produced by the actinomycetes, *Streptomyces griseoflavus*, obtained from a soil sample on the island of Zamami, Okinawa, Japan. (+)-Okilactomycin exhibits significant in vitro cytotoxicity when assayed against a number of human cancer cell lines, including lymphoid leukemia L1210 and leukemia P388



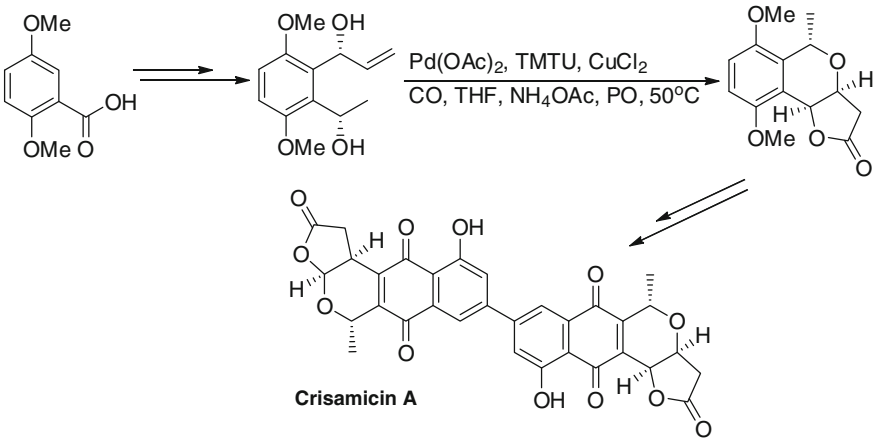
Scheme 10.38 Synthesis of (−)-exiguolide



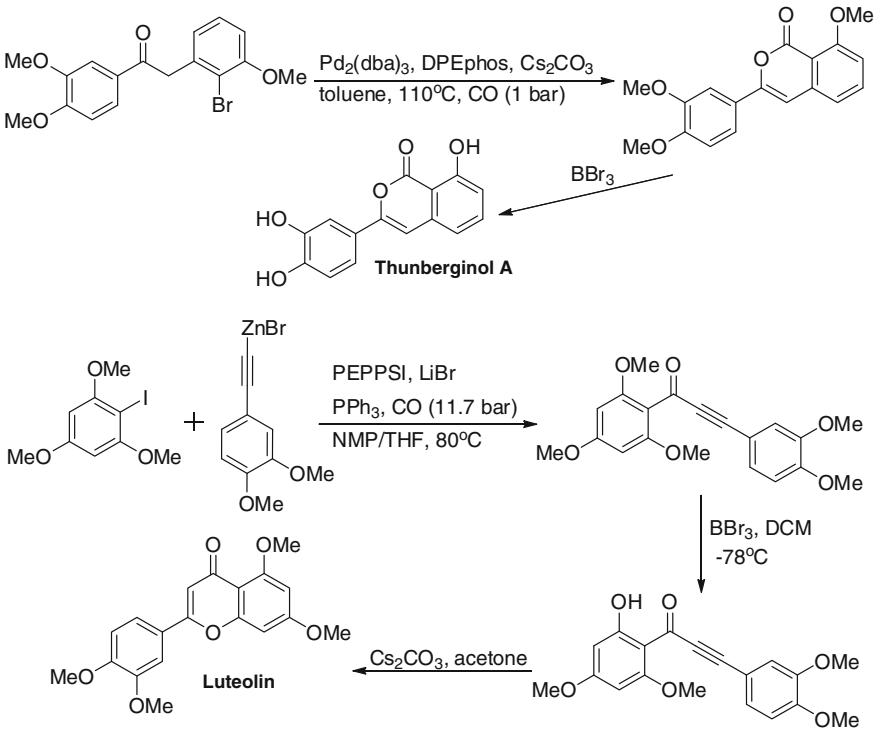
Scheme 10.39 Synthesis of (+)-okilactomycin

($IC_{50} = 0.09$ and 0.037 μg/mL, respectively), as well as in vivo activity against Ehrlich ascites carcinoma. Smith and colleagues reported the total synthesis in 2009 which involve palladium-catalyzed carbonylative Stille coupling as one of the steps (Scheme 10.39) [127].

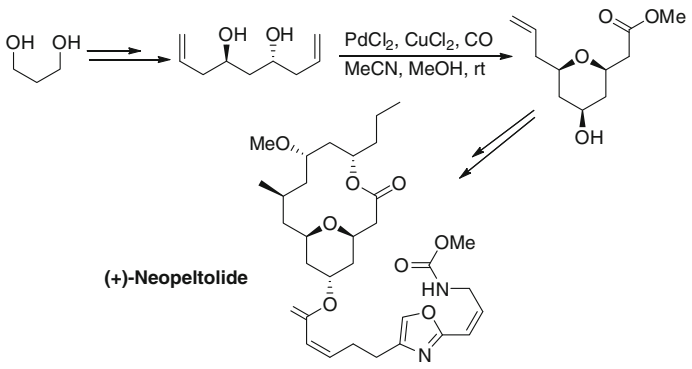
Crisamicin A, a natural product that contains two pyran-fused lactones that are C_2-symmetric to each other, represents a prominent member of the dimeric pyranonaphthoquinone family of antibiotics and was first isolated in 1986 from the micro-organism *Micromonospora purpureochromogenes* that was obtained from a mud sample in the Philippines. Crisamicin A exhibited activity against B16 murine melanoma cells, the herpes simplex, and vesicular stomatitis viruses. Yang, Wang and their colleagues for the first time did the total synthesis and Pd/TMTU-catalyzed alkoxycarbonylative annulation to generate a unique *cis*-pyran-fused lactone (Scheme 10.40) [128].



Scheme 10.40 Synthesis of crisamicin A



Scheme 10.41 Synthesis of luteolin and thunberginol A



Scheme 10.42 Synthesis of neopeltolide

Flavanoids and isocoumarin are common substructures found in many natural products. Palladium-catalyzed carbonylation reactions were applied in the synthesis of luteolin [129] and thunberginol A [130] as well (Scheme 10.41).

Neopeltolide was isolated from a deep-water sponge of the neopeltidae family by Wright and colleagues in 2007. Neopeltolide exhibits significantly potent in vitro cytotoxicity toward several different cancer cell lines, including A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and P388 murine leukemia cell lines, with IC50s of 1.2, 5.1, and 0.56 nM, respectively. Neopeltolide also inhibited the growth of the fungal pathogen *Candida albicans* with a minimum inhibitory concentration of 0.62 μg/ml. A concise total synthesis was reported in 2011 [131]. Palladium-catalyzed alkoxycarbonylation as one of the key steps was included in the route (Scheme 10.42).

In this chapter we have summarized and discussed the applications of transition metal catalyzed carbonylation reactions in total synthesis. A number of biologically active molecules have been synthesized by using carbonylation as one of the key steps. These examples of total synthesis greatly increased the values of carbonylation reactions and encouraged the basic methodology development in this area.

In next chapter we will try to give a short discussion from the aspects of reaction mechanism.

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