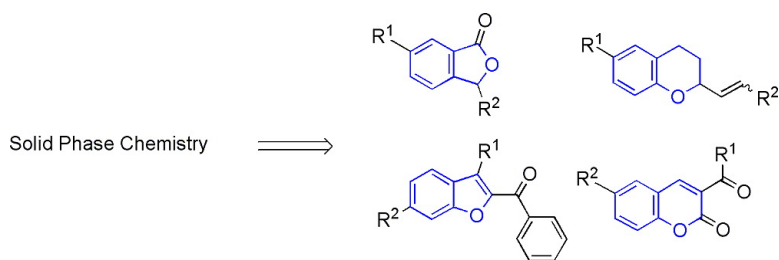Review

The Recent Impact of Solid-Phase Synthesis on Medicinally Relevant Benzoannelated Oxygen Heterocycles

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Reviews

The Recent Impact of Solid-Phase Synthesis on Medicinally Relevant Benzoannelated Oxygen Heterocycles

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1. Introduction

Biologically active compounds are often derived from heterocyclic structures, which frequently appear in natural and synthetic products.[1] These heterocyclic compounds show various pharmacological properties, and modifications of the core structures, that is, by substitution, provide a high degree of structural diversity, which has proven useful in the search for new therapeutic agents. Because of this, the synthesized heterocycles have received special attention within combinatorial chemistry, which has matured to become a key tool in many aspects of chemistry in general and in drug discovery process in particular.[2−5] Since the beginning, combinatorial libraries have been developed using primarily parallel synthesis and specific techniques, that is, resin-based chemistry. The rapid generation of small-molecule libraries can be executed effectively by employing combinatorial or simultaneous-parallel synthesis on solid supports.[6] The combination of solid-phase organic synthesis (SPOS), the development of high-throughput screening (HTS), and even ultrahigh-throughput screening (UHTS) has greatly increased the number of substances that are being tested and have emerged as a valuable tool in the search for novel lead structures.[7,8] Furthermore, SPOS offers the opportunity to synthesize druglike molecules via novel routes, which may

be difficult or impossible using traditional solution methods, and allows the possibility to rapidly synthesize druglike molecules without tedious and time-consuming purification.[9]

In this review, we focus on methods for the synthesis of benzoannelated oxygen heterocycles on solid supports, because benzoannelation is an efficient method for the diversification of heterocycles of biological value.[10] The benzo moiety is an integral part of numerous heterocyclic target molecules. In an earlier publication, we reviewed the synthesis of benzoannelated nitrogen heterocycles.[11] An overview on the synthesis of aromatic heterocycles, including oxygen heterocycles in liquid phase, was given by Gilchrist in 1999.[12]

The chapters in the present review have been subdivided according to the preparation of five- and six-membered benzoannelated oxygen heterocycles.

2. Five-Membered Benzoannelated Oxygen Heterocycles

2.1. Benzofurans. The benzofuran core is found in a large number of naturally occurring biologically active compounds. A small selection of biologically and pharmacologically active benzofuran compounds is shown in Figure 1. For example, a variety of benzofuran derivatives, such as ebenfuran I (**1**), have been investigated as estrogen receptor (ER) ligands.[13] Another example is prostaglandin D2 receptor agonist **2**, which belongs to a potent new class of antiallergic

ebenfuran I (**1**)

2
PGD$_2$ antagonist

RO-09-4609 (**3**, R = CO$_2$Et)
RO-09-4879 (**4**, R = CH$_2$-O-2,3,4-F$_3$-C$_6$H$_3$)

CI 1021 (**5**)

6
PDE 4 inhibitor

7
anti-tumor agent

pterocarpans **8**
(R = H, Ph, CH(CH$_3$)$_2$,
c-C$_6$H$_{11}$,α-Naph, β-Naph)

9
antiatherosclerotic agents
(X = CH, N and R = C$_2$H$_4$, C$_3$H$_6$, CH$_2$CH(OH)CH$_2$)

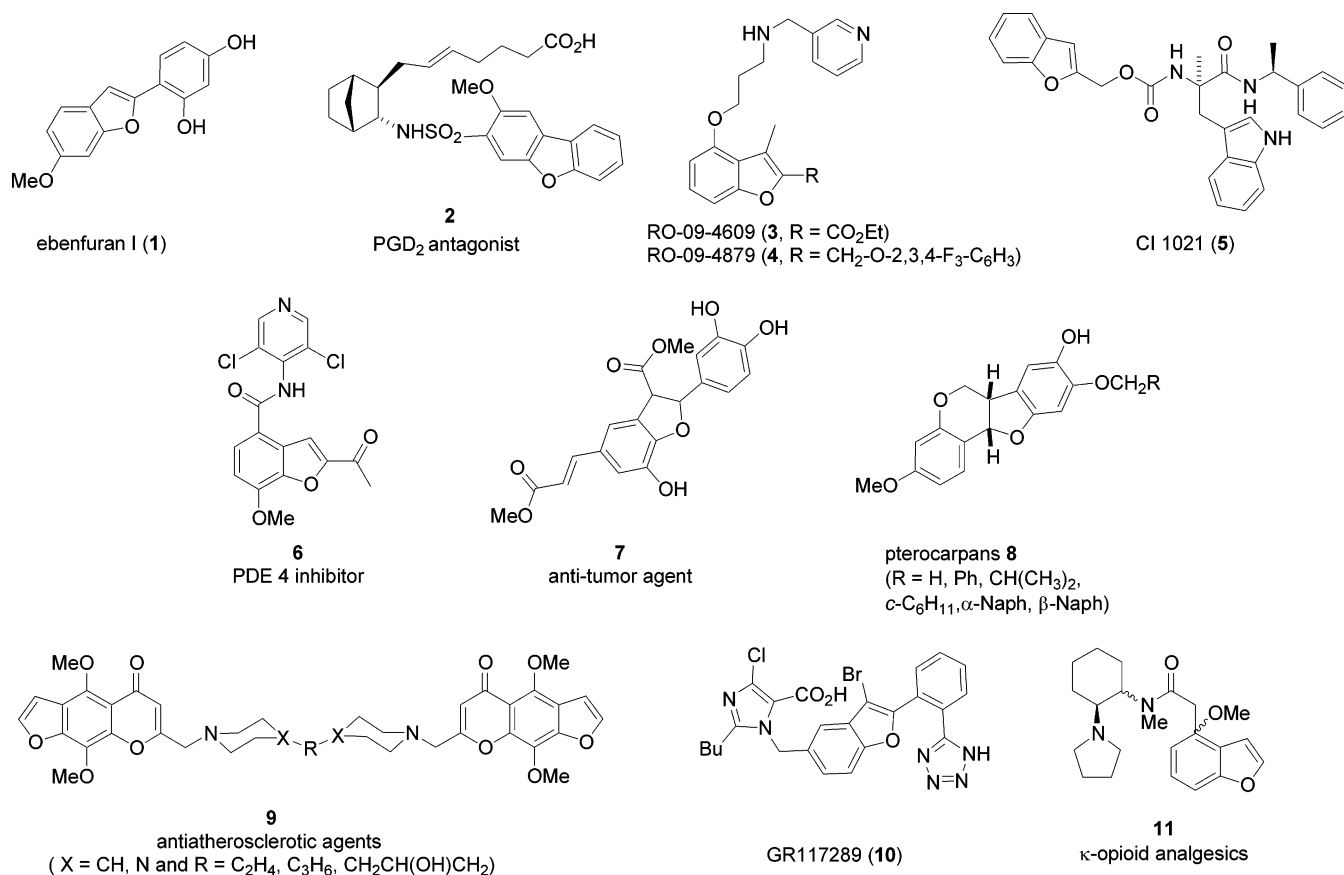GR117289 (**10**)

11
κ-opioid analgesics

Figure 1. A selection of natural compounds and biologically active compounds based on the benzofuran core.

agents. It has been shown that agonist **2** suppresses various allergic inflammatory responses, such as those observed in conjunctivitis and asthma models.[14] The potent and selective *Candida albicans N*-myristoyltransferase inhibitors RO-09-4609 (**3**) and RO-09-4879 (**4**) exhibit antifungal activity against *Candida albicans* in vitro.[15] The selective NK$_1$ receptor antagonist CI 1021 (**5**) was reported in 1994.[16] A potent selective PDE 4 inhibitor as antiasthmatic target is the methoxybenzofuran **6**.[17] The dihydrobenzofuran lignan **7** has proven to be a potential antitumor agent, which inhibits tubulin polymerization.[18] The pterocarpans **8** containing both a benzoannelated five-membered and a benzoannelated six-membered oxygen heterocycle show cytotoxic effects against HIV-1.[19] The pterocarpans **8** contain a five- and a six-membered benzoannelated heterocycle, which are annelated over the *b*[furan],*c*[pyran] bond to each other. In contrast to pterocarpans, the antiatherosclerotic agents **9** contain a furan and a pyran structure benzoannelated by the same benzene ring.[20] Further examples of benzofurans with an additional heterocycle in the side chains with pharmacological activities are the angiotensin II antagonist GR117289 (**10**)[21] and the κ-opioid analgesics **11**.[22]

Computer modeling studies of the benzofurans **13** indicated that these structures would fit the ligand-binding site of ER-α in a flipped orientation relative to raloxifene (**12**) (Figure 2). In this instance, the 6-hydroxy, 5-aroyl, and 3-substituent groups in **13** mimic the 6-hydroxy, 3-aroyl, and 2-aryl groups of raloxifene (**12**), respectively.[23]

The first solid-supported benzofuran synthesis was reported by Boehm and Showalter in 1996, who developed a
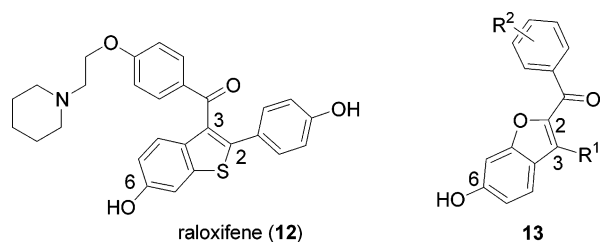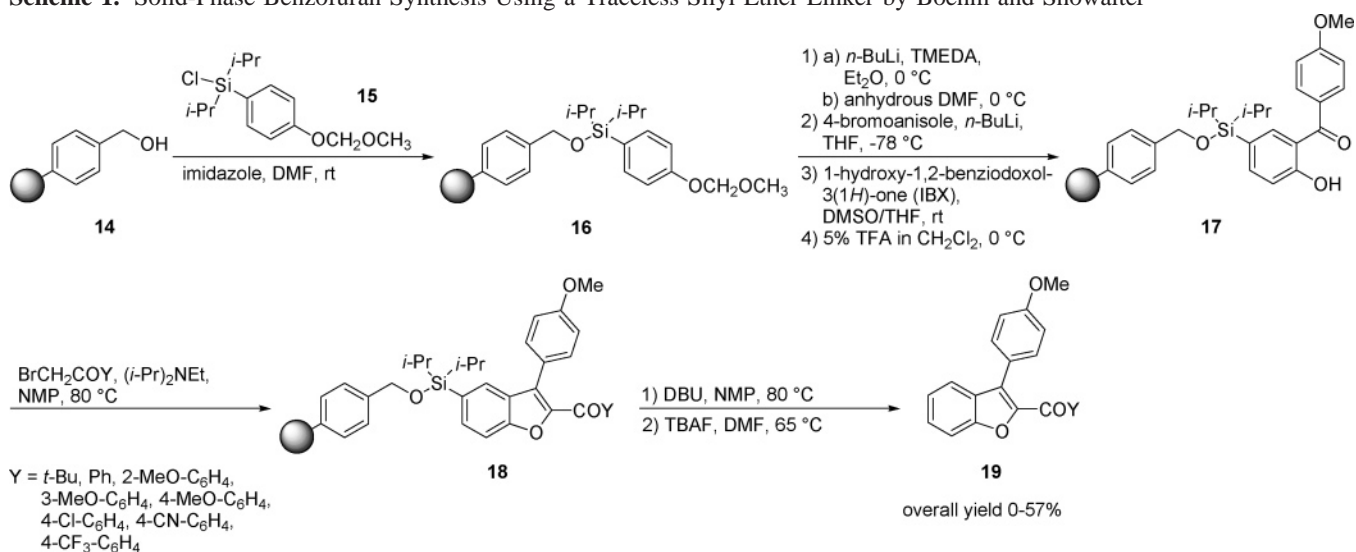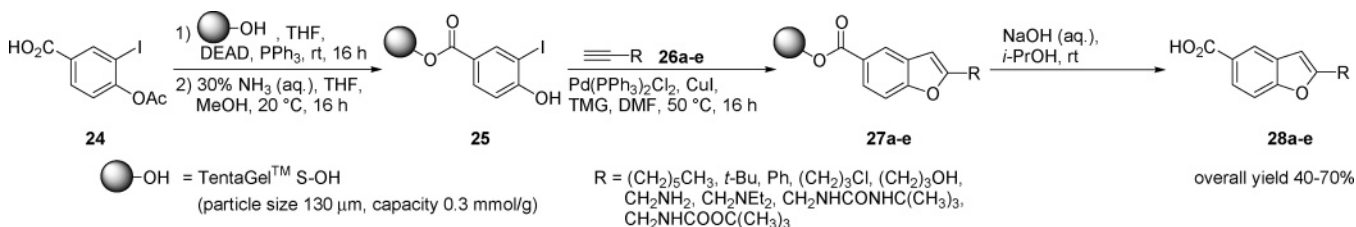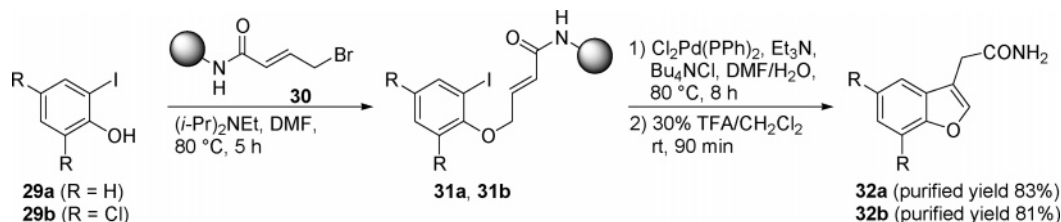

raloxifene (**12**)

13

Figure 2. Raloxifene (**12**) and the benzofuran based analogues **13**.[23]

novel silyl ether linker for solid-phase synthesis (Scheme 1).[24] After immobilizing silane **15** onto resin **14**, they synthesized the benzofurans **18** following an established solution-phase protocol via ortho-formylation, addition of para-lithiated anisole (from *para*-bromoanisole), Dess−Martin oxidation to the ketone, and deprotection of the hydroxyl function to yield the alcohol **17**. Treating phenol **17** with various α-bromoketones, a number of solid-bound diketones **18** were synthesized. After cyclization with DBU and cleavage with TBAF, the benzofurans **19** were obtained in 40−57% overall yields for Y = *t*-Bu, Ph, 3-MeO−C$_6$H$_4$, 4-MeO−C$_6$H$_4$, 4-Cl−C$_6$H$_4$, and 4-CF$_3$−C$_6$H$_4$, and no products were obtained for Y = 2-MeO−C$_6$H$_4$ and 4-CN−C$_6$H$_4$.

In 1997, Balasubramanian et al. introduced solid-supported intramolecular radical cyclizations to synthesize benzofurans (Scheme 2).[25] In this reaction, carboxylated polystyrene resin **21** was applied for the immobilization of **20,** and an excess of AIBN was used to force the cyclization reaction to completion. *t*-BuOH was added in order to suppress the formation of the β-hydride elimination product. In the case

Scheme 1. Solid-Phase Benzofuran Synthesis Using a Traceless Silyl Ether Linker by Boehm and Showalter[24]

Y = t-Bu, Ph, 2-MeO-C$_6$H$_4$,
3-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$,
4-Cl-C$_6$H$_4$, 4-CN-C$_6$H$_4$,
4-CF$_3$-C$_6$H$_4$

overall yield 0-57%

Scheme 2. Solid-Phase Benzofuran Synthesis Using Intramolecular Radical Cyclization Reactions by Balasubramanian et al.[25]

= carboxylated polystyrene resin (a) or
TantaGel^{TM}-COOH resin (b)

amount of AIBN: for a) >1 equiv.
for b) 6 mol%
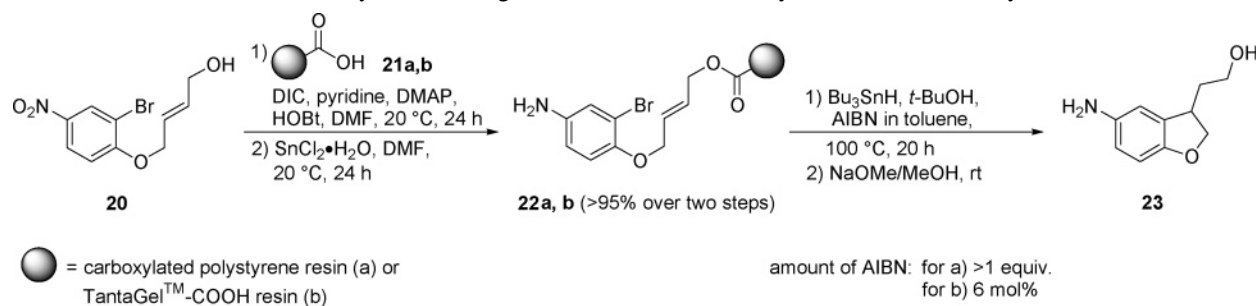
Scheme 3. Solid-Phase Synthesis of 2-Substituted Benzofurans **28a−e** via the Palladium-Catalyzed Heteroannelation of Acetylenes **26a−e** by Fancelli et al.[26]

-OH = TentaGel^{TM} S-OH
(particle size 130 μm, capacity 0.3 mmol/g)

R = (CH$_2$)$_5$CH$_3$, t-Bu, Ph, (CH$_2$)$_3$Cl, (CH$_2$)$_3$OH,
CH$_2$NH$_2$, CH$_2$NEt$_2$, CH$_2$NHCONHC(CH$_3$)$_3$,
CH$_2$NHCOOC(CH$_3$)$_3$

overall yield 40-70%

Scheme 4. Solid-Supported Benzofuran Synthesis by Zhang and Maryanoff[29]

29a (R = H)
29b (R = Cl)

31a, 31b

32a (purified yield 83%)
32b (purified yield 81%)

of TentaGel-COOH resin, 6 mol % of AIBN was sufficient for high conversion (>90%).

In 1997, Fancelli et al. reported the solid-phase synthesis of 2-substituted benzofurans via the palladium-catalyzed heteroannelation of acetylenes **26**,[26] which was previously established in solution-phase benzofuran synthesis (Scheme 3).[27] After immobilization of benzoic acid **24** on TentaGel, resin **25** reacted with the acetylenes **26** under palladium catalysis resulting in cyclization to the benzofurans **27**. After cleavage, the benzofurans **28** were obtained in moderate to good yields.

On the basis of solid-supported indole synthesis and the results of Larock and Stinn's benzofuran formation in solution phase from 1988,[28] Zhang and Maryanoff reported the construction of benzofurans on the solid phase via palladium-mediated cyclizations in 1997,[29] when two different *ortho*-iodo phenols **29a** and **29b** were immobilized on functionalized Rink amide resin **30** and followed by an intramolecular Heck-type reaction and cleavage with TFA to yield the benzofurans **32a** and **32b** in excellent purities and purified yields up to 81−83%.

In 1997, Du and Armstrong published the synthesis of

Scheme 5. Solid-Phase Synthesis of Benzofurans via a SmI$_2$-Mediated Cyclization by Du and Armstrong[30]
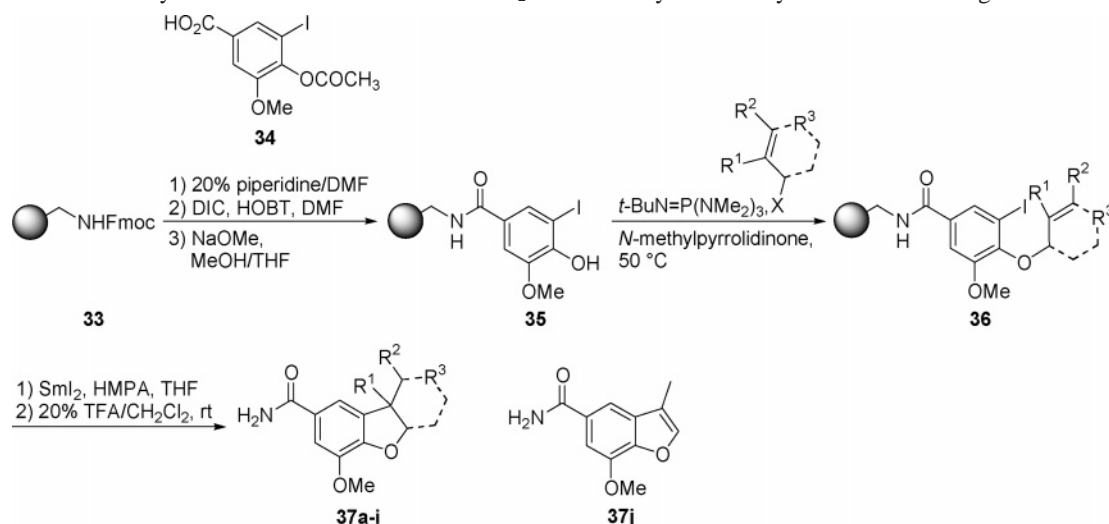
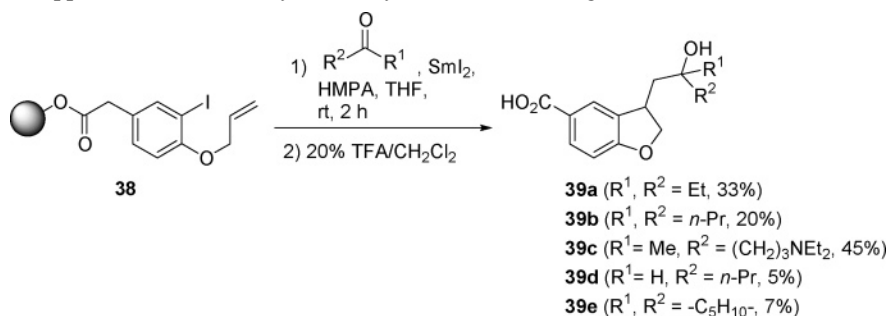

Table 1. Benzofurans Synthesized by Du and Armstrong[30]

product	R^1	R^2	R^3	yield (%)^a
37a	H	H	H	57
37b	H	Ph	H	63
37c	H	2-MeO−C$_6$H$_4$	H	58
37d	H	H	Me/=CH$_2$ (9:1)^b	61
37e	H	Me	Me/=CH$_2$ (7:3)^b	60
37f	H	H	CH$_2$OH/=CH$_2$	42/6
37g	H	H	−C$_3$H$_6$−	51
37h	Me	H	H	41
37i	Me	H	morpholinyl	11
37j				37

^{a} Overall yield. ^{b} Inseparable mixture.

benzofuran derivatives on solid phase via a SmI$_2$-mediated radical cyclization reaction (Scheme 5).[30] The benzoic acid **34** was coupled to the deprotected Rink resin. The acetate group of resin bound **34** was cleaved to yield phenol **35**. Radical cyclization with SmI$_2$ and TFA cleavage gave eight benzofurans **37a**−**j** in yields up to 63%. In two cases, two isomers in yields up to 61% of isomeric mixtures different were obtained (Table 1).

In 1998, Du and Armstrong used this method on TentaGel S bound benzoic acids **38** (Scheme 6).[31] In a similar manner, radical cyclization with SmI$_2$ and TFA cleavage provided benzofurans **39a**−**e** in poor to moderate yields.

A further application of radical chemistry to solid-supported synthesis[32] and a palladium-mediated cyclization[33] was reported by De Mesmaeker et al. in 1998. A number of hydroxyiodo phenols were immobilized on a polystyrene resin via an ester linker having a secondary amide spacer.

Starting from polymer-supported *ortho*-iodo phenols **40**, the cyclization substrates **42** and **43** were prepared by treatment with the allyl bromides **41a**−**c** and methyl propiolate, respectively. Radical cyclization followed by cleavage resulted in excellent yields of the benzofurans **45a**−**c** (95−97%, Scheme 7) and in moderate yield for the isobenzofuran **46a** (30−40%). Using the Rink linker on polystyrene resin, the isobenzofurans **46a** and **46b** were obtained in yields up to 95%. To increase library diversity, a tandem radical addition/cyclization reaction was introduced. After optimization, the benzofurans **44a**−**c** were obtained in moderate to good yields (Scheme 7). Palladium-mediated synthesis yielded the isobenzofuran **46b** in moderate yields.

In 1998, Wang and Huang reported the solid-phase synthesis of five- and six-membered nitrogen and oxygen heterocycles via a palladium-catalyzed annelation (Scheme 8).[34] For the synthesis of oxygen heterocycles, 4-carboxy-2-iodo phenols **47** were immobilized onto Rink resin (**48**). Palladium-catalyzed cyclization with diene **50** and cleavage with TFA yielded benzofuran **51** in excellent yield and high purity.

Rottländer and Knochel reported a cyclative cleavage approach toward benzofurans in 1999 (Scheme 9).[35] After immobilization of iodoarenes **53** on modified Wang resin **52**, an iodine−magnesium exchange was carried out. Different benzaldehydes **56a**−**f** were added to the arene magnesium species **55**, yielding the corresponding alcohols **57a**−**f**. Cyclative cleavage with TFA led to the benzofurans **58a**−**f** in high purities and excellent yields.

Scheme 6. TentaGel S Supported Benzofuran Synthesis by Du and Armstrong[31]

39a (R^1, R^2 = Et, 33%)
39b (R^1, R^2 = *n*-Pr, 20%)
39c (R^1 = Me, R^2 = (CH$_2$)$_3$NEt$_2$, 45%)
39d (R^1 = H, R^2 = *n*-Pr, 5%)
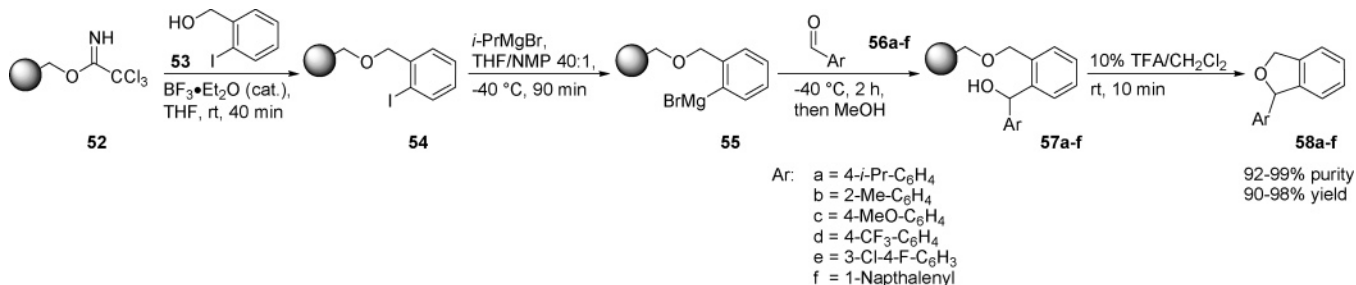**39e** (R^1, R^2 = -C$_5$H$_{10}$-, 7%)

Scheme 7. Solid-Supported Synthesis of Benzofurans **44a−c**, **45a−c** and Isobenzofurans **46a** and **46b** by Radical Cyclization Reaction, Tandem Radical Addition/Cyclization Reaction and Palladium-Mediated Cyclization Reaction by Berteina and De Mesmaeker[32,33]
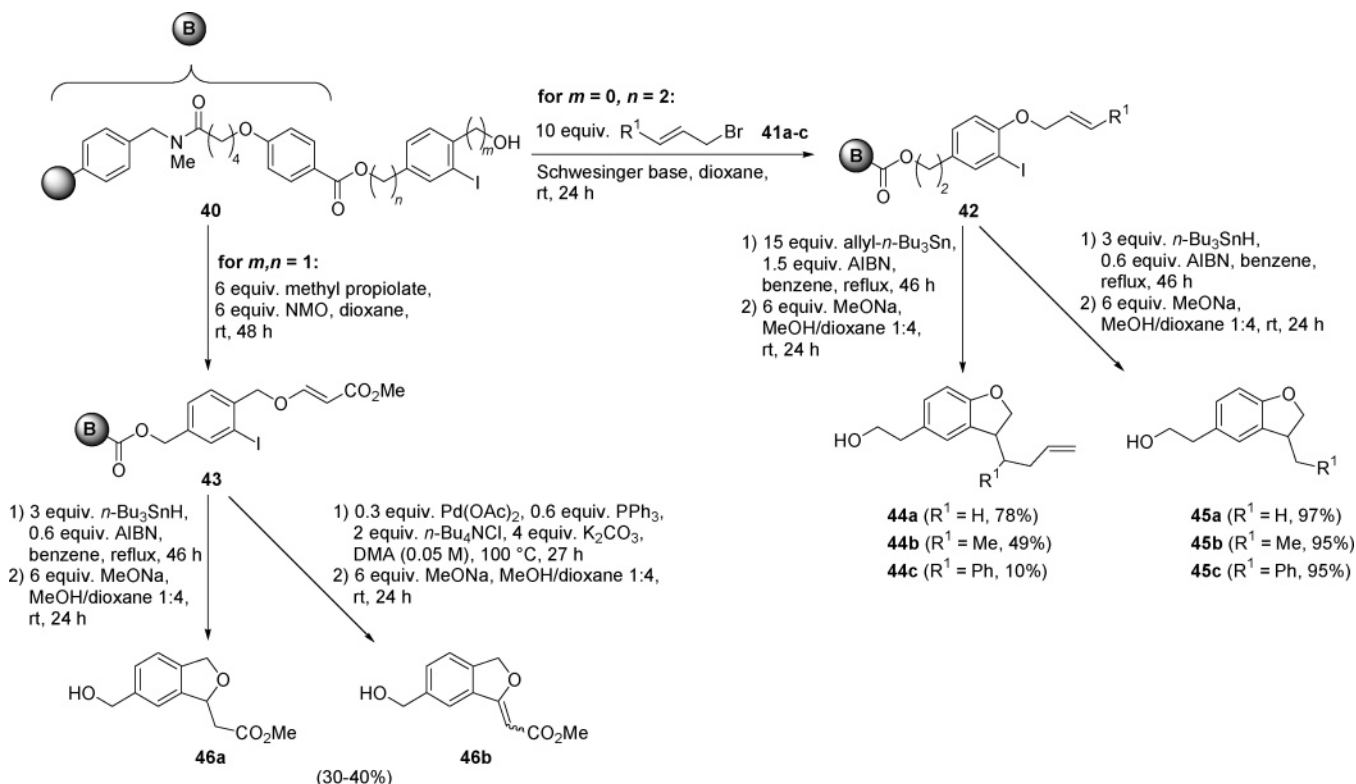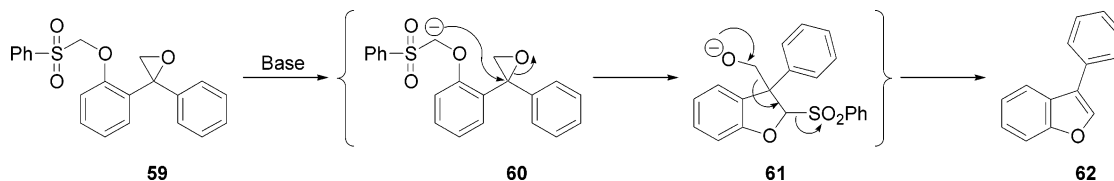

Scheme 8. Rink Resin-Supported Benzofuran **51** Synthesis by Wang and Huang[34]
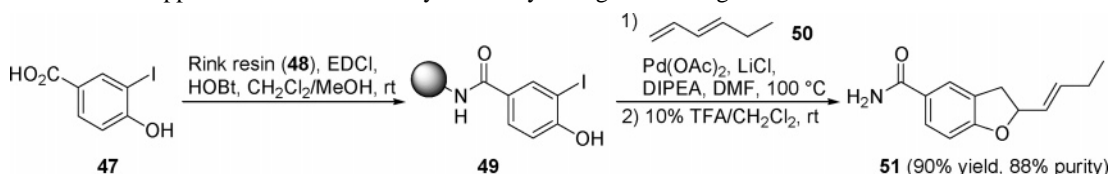
Scheme 9. Solid-Phase Benzofuran Synthesis Using a Cyclative Cleavage Approach by Rottländer and Knochel[35]

Ar: a = 4-*i*-Pr-C₆H₄
    b = 2-Me-C₆H₄
    c = 4-MeO-C₆H₄
    d = 4-CF₃-C₆H₄
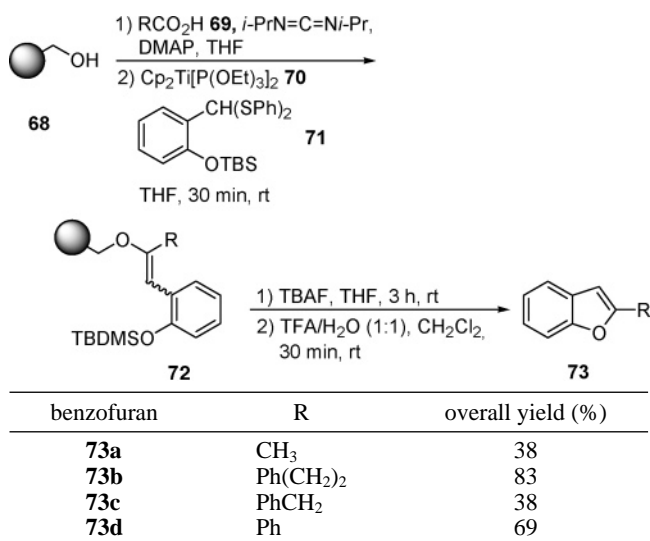   e = 3-Cl-4-F-C₆H₃
    f = 1-Napthalenyl

Scheme 10. Cyclofragmentation Release Pathway for the Benzofuran Synthesis by Nicolaou et al.[36]

In 2000, Nicolaou et al. introduced a solution and solid-phase synthesis of functionalized 3-arylbenzofurans **62** by a novel cyclofragmentation release strategy, as shown in Scheme 10.[36] This unexpected reaction was found instead of the formation of dihydrobenzofuran **61-H**. The deprotonation of the methylene group next to the sulfonic function

is followed by a selective epoxide opening and a 5-exo-trig cyclization. The elimination of formaldehyde and a phenylsulfimate anion yielded the benzofuran **62**, whereas the protonated species **61-H** was not observed (Scheme 10).

After optimization of the liquid-phase reaction, Nicolaou et al. transferred this approach to the solid-supported

Scheme 11. Solid-Supported Benzofuran Synthesis Using a Cyclofragmentation Release by Nicolaou et al.[36]

65a: R = H
65b: R = Me
65c: R = Cl

up to 29% yield
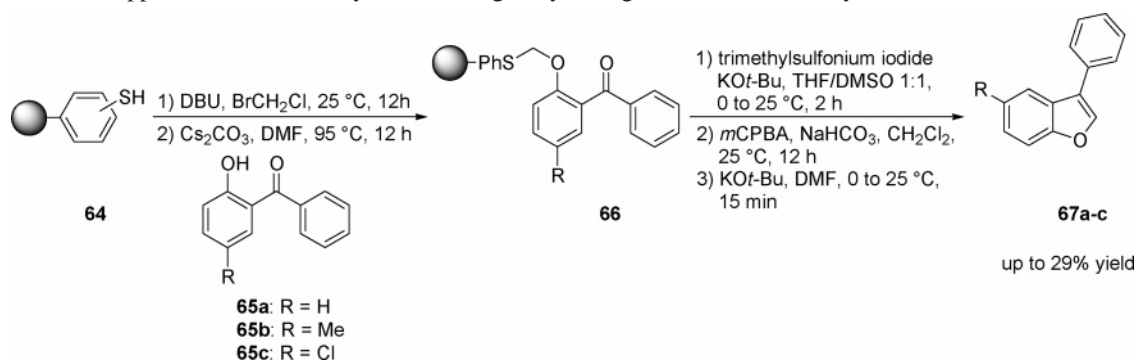
Table 2. Wang Resin-supported Benzofuran Synthesis by Hartley et al.[37]

benzofuran	R	overall yield (%)
73a	CH$_3$	38
73b	Ph(CH$_2$)$_2$	83
73c	PhCH$_2$	38
73d	Ph	69

synthesis of benzofurans. Examination of the proposed mechanism suggested that the requisite solid support could be tethered to the scaffold through a thiophenol group. Starting from polystyrene (1% DVB cross-linked), different hydroxy benzophenones **65a**−**c** were immobilized on resin

64. Cyclofragmentation release yielded benzofurans **67a**−**c** in moderate overall yields (Scheme 11). Nicolaou et al. also described a procedure in which benzophenones were prepared on solid phase starting from immobilized *ortho*-hydroxybenzaldehydes. The benzofurans could be prepared via a cyclofragmentation pathway in overall yields of 29%, with purities of the products >95%.

In 2000, Hartley et al. reported the traceless synthesis of 2-substituted benzofurans via alkylidenation of esters on solid support.[37] Starting with the immobilization of four carboxylic acids **69** on Wang resin **68**, the resulting esters were treated with thioacetal **71** and the titanocene **70** to yield enol ethers **72**. The phenols **72** were deprotected and cyclatively cleaved to give the benzofurans **73** in moderate to good yields (Table 2).

As previously mentioned, computer modeling studies carried out by Hubbard et al. predicted that the benzofurans **13** and raloxifen (**12**) should have similar biological properties (Figure 2).[23] Motivated by these studies, Smith et al. introduced the synthesis of **78** and **80** on solid supports (Scheme 12).[38] After immobilizing 2,4-dihydroxyphenyl ketones by attaching them to dihydropyran (DHP) resin,[39] the 2-hydroxy moiety was alkylated with bromoaceto-phenones **75** and cyclized to the benzofuran **76** using a
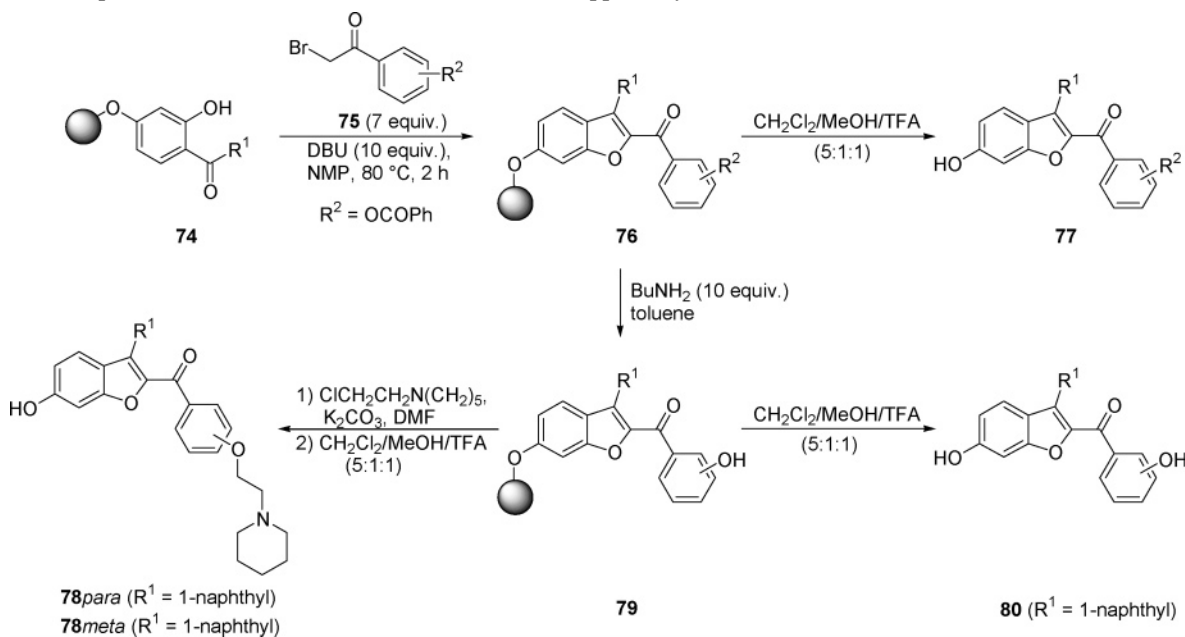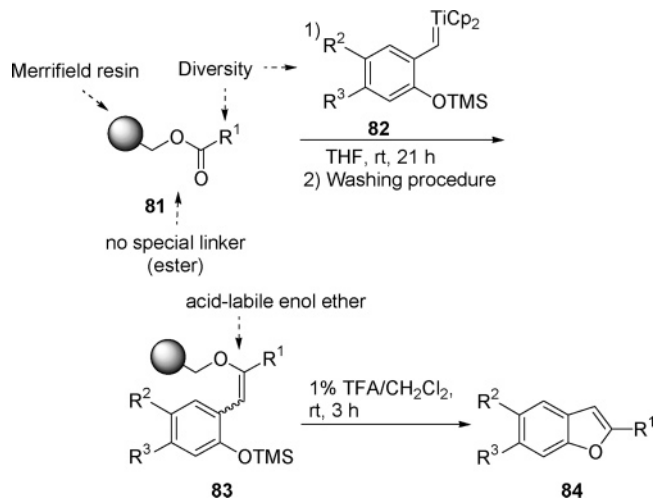
Scheme 12. Preparation of Benzofurans **78** and **80** on Solid Supports by Smith et al.[38]

78*para* (R^1 = 1-naphthyl)
78*meta* (R^1 = 1-naphthyl)

79

80 (R^1 = 1-naphthyl)

Table 3. General Procedure of the Solid-Supported Synthesis of the Benzofurans 84[a] by Hartley et al.[40]

benzofurane	R^1	R^2	R^3	yield (%)[b]
84a	(CH$_2$)$_2$Ph	H	H	80
84b	CH=CMe$_2$	H	H	67
84c	4-C$_6$H$_4$−OMe	H	H	60
84d	(CH$_2$)$_2$Ph	OH	H	74
84e	CH=CMe$_2$	OH	H	70
84f	4-C$_6$H$_4$−OMe	OH	H	43
84g	(CH$_2$)$_2$Ph	F	H	91
84h	CH=CMe$_2$	F	H	58
84i	4-C$_6$H$_4$−OMe	F	H	47
84j	(CH$_2$)$_2$Ph	H	NEt$_2$	54
84k	CH=CMe$_2$	H	NEt$_2$	69
84l	4-C$_6$H$_4$−OMe	H	NEt$_2$	33

[a] For synthesis of titanocene **82** and washing procedure, see ref 40. [b] Yields of benzofurans **84** based on loading of commercial Merrifield resin.

N-methyl-pyrrolidinone solution of DBU (a modification of the Boehm-Showalter protocol[24]). After cleavage with TFA in CH$_2$Cl$_2$/MeOH, the products were obtained in a 35% overall yield. Smith et al. introduced eight different R^1 groups and 40 variations of R^2 groups to generate a 320-compound library.

Recently, Hartley et al. reported the synthesis of 2-substituted benzofurans and indoles using functionalized titanium benzylidene reagents on solid supports following the general strategy shown in Table 3.[40] The titanium benzylidene reagents **82** can be generated by the reduction of the according thioacetals.[41] Using this strategy, Hartley et al. created a 12-membered library of benzofurans **84**. Release of the benzofurans **84** from the resin involved either cyclative cleavage or use of a postcleavage modification.
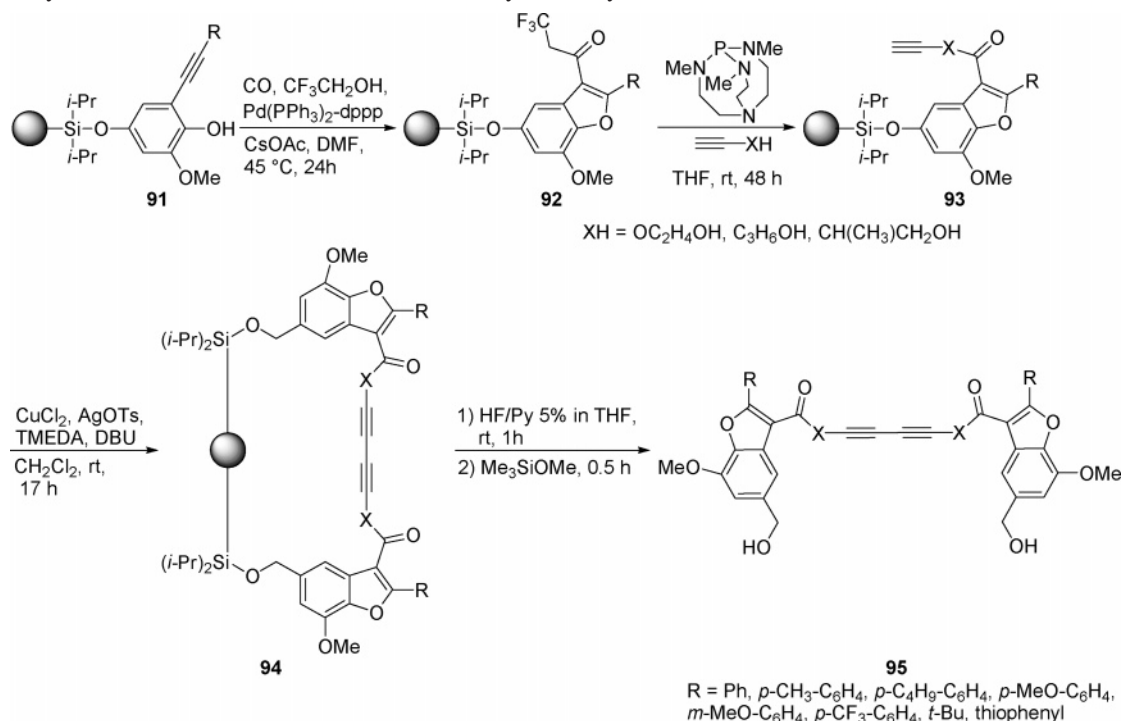
McKiernan and Hartley introduced this pathway also for the synthesis of boronated benzofurans **90**.[42] The boronate titanium alkylidene reagents **89** were formed via boronation of the according brominated thioacetal or via boronation of the brominated thioacetal precursor and following formation of thioacetal (Scheme 13). The titan boronates **89** were then used in the solid-phase benzofuran synthesis following the protocol described in Table 3 combined with a Suzuki cross-coupling reaction to increase the benzofuran diversity. Good to excellent yields and high purities for the benzofurans were obtained.

In 2003, Liao et al. described a novel catalytic system of AgOTs/CuCl$_2$/TMEDA for the homocoupling of aliphatic acetylenes on solid-supports, as shown in Scheme 14.[43] From monomeric **93** to the coupled and cleaved dimeric **95**, conversions up to 85% were observed in high purities (up to 90%).

Recently, Liao et al. reported the convergent solid-phase synthesis of symmetrical benzo[*b*]furan's dimerizer.[44] Inspired by the work of Schreiber,[45] Liao et al. described a general approach for the construction of benzo[*b*]furan-based dimeric molecules. The products were obtained using Sonogashira reactions,[46] palladium-mediated carbonylative annulations,[47] and olefin cross-metathesis[48] as key steps (Scheme 15). High-capacity silyl-linker-based polystyrene macrobeads were applied as solid supports.[49] The benzo[*b*]furan scaffold is often found in natural compounds and has a wide range of biological activities.[18,19] Using the pathway depicted in Scheme 15, Liao et al. synthesized a library with conversions of 80−95% for all intermediates and 70−80% for the final products **107**.

Very recently, Yang and co-workers disclosed the synthesis of conformationally restricted 2,3-diarylbenzo[*b*]furans by the palladium-catalyzed annelation of *ortho*-alkynyl-phenols **110** as a combinatorial approach on solid supports

Scheme 13. Boronated Benzofurans **90** and Synthesis of Boronate Titanium Alkylidene **89** by McKiernan and Hartley[42]
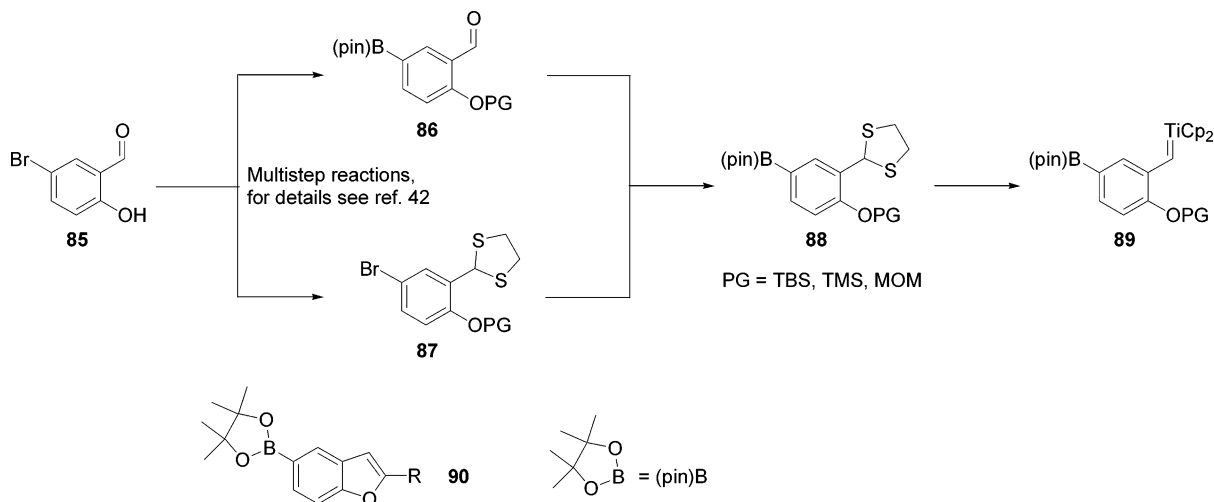
Scheme 14. Synthesis of Bis-benzo[*b*]furan-Linked 1,3-Diynes **95** by Liao et al.[43]

R = Ph, *p*-CH$_3$-C$_6$H$_4$, *p*-C$_4$H$_9$-C$_6$H$_4$, *p*-MeO-C$_6$H$_4$,
m-MeO-C$_6$H$_4$, *p*-CF$_3$-C$_6$H$_4$, *t*-Bu, thiophenyl

(Scheme 16).[50] After optimization of the palladium ligand system, a 210-membered library of 2-substituted 3-arylbenzo-[*b*]furans **112** was synthesized in a split pool sequence starting from five different iodophenols on bead **108**, seven acetylenes **109**, and six aryl iodides. The products were obtained in purities from around <50% up to >80%. The aryl iodides with electron-withdrawing groups gave better annelation results than the other types, what is in agreement with the results of the solution-phase reactions.

2.2. Benzobutyrolactones (Phthalides). Another class of oxygen heterocycles found in various natural products and bioactive compounds is the benzoannelated butyrolactones (phthalides). The 3-alkylated phthalides are found in natural products, such as fuscinarin (**112**),[51] 3-butylphthalide (**113**), (−)-hydrastine ((−)-narcotine) (**123**),[52] (−)-noscapine,[53] (−)-typhaphthalide (**119**),[54] spirolaxine (**114**),[55] (+)-monasco-dilone (**116**),[56] isoochracinic acid (**117**),[57] cryphonectric acid peracetate methyl ester (**121**),[58] vermistatin (**124**),[59] (−)-rubiginone H (**122**),[60] alcyopterosin E (**120**),[61] and cytospor-one E (**115**)[62] (Figure 3).

Phthalides possess a wide range of biological activity. They exhibit activity at the opiod receptor ((−)-hydrastine (**123**)) or the human CCR5 receptor, an important anti-HIV-1 target that interferes with HIV entry into cells (fuscinarin (**112**)).[51] Some members of this group are cytotoxic (vermi-statin (**124**), alcyopterosin E (**120**))[61] or antibacterial (e.g., cytosporone E (**115**)[62] and related compounds[63]). 3-Bu-tylphthalide (**113**), a constituent in the Chinese folk medicine, was isolated from celery seed oil[64] and has been used for seasoning and flavoring purposes, shows anticonvulsant action,[65] increases the duration of anesthesia,[66] and exhibits cerebral anti-ischemic action.[67] Various naturally occurring phthalides, such as 3-butylphthalide from *Angelica sinensis* roots or synthetic 3-alkenylphthalides, show relaxant effects on animal tracheal smooth muscle, indicating that the

phthalide moiety is the principal antiasthmatic component of phthalide derivatives of *Angelica* extractions.[68] In addition, since most of these chiral natural products are found only as one enantiomer and biological activity is strongly de-pendent on their configuration, the asymmetric syntheses of these active compounds is currently highly desirable.
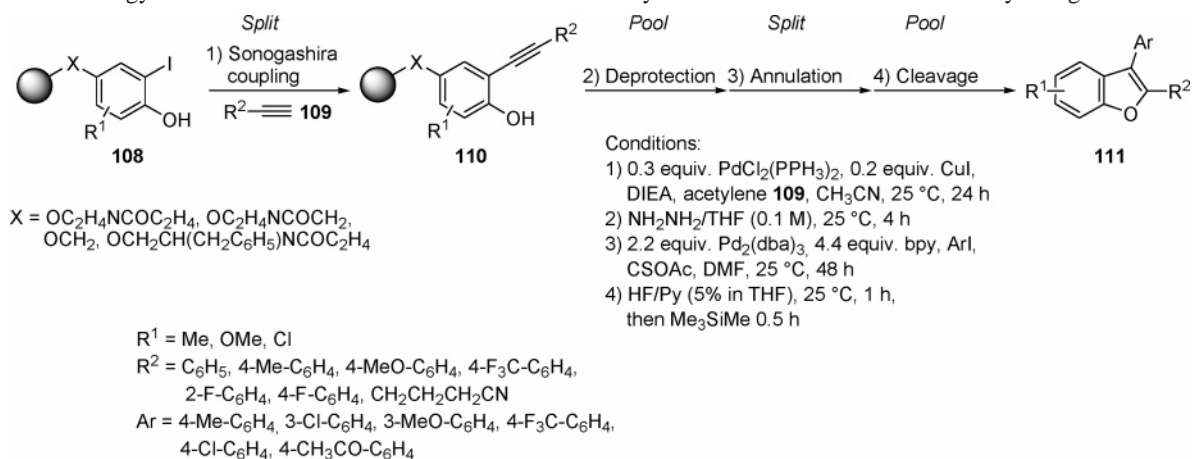
For the synthesis of 3-substituted benzobutyrolactones, two strategies are conceivable. Strategy I (Scheme 17) is the addition of *ortho*-metalated esters **125** (X = OR), amides **125** (X = NR$_2$), or their synthons to aldehydes **126** and cyclization to **130**. Strategy II is the treatment of formyl-substituted benzoic acids **129** with organometallic reagents, such as alkyllithium,[69] alkylzinc,[70] alkylsodium,[71] alkyltita-nium[72] or Grignard reagents.[73] The corresponding lactones **130** are formed during or after acidic workup. This strategy is particularly interesting for an asymmetric version to achieve enantiomerically enriched phthalides. Organometallic reagents such as **128** can be purified before use (i.e., removal of salts) and, hence, increase the asymmetric induction. In contrast, the more complex and immobilized organometallic reagents **127-M** have to be prepared in situ, and the formation of complexes with chiral ligand is inhibited. In addition, the species **128** can be symmetric in the case of divalent metals (i.e., R$_2$Zn).

The first strategy was introduced onto the solid phase by a number of groups.[74] In 1999, Janda et al. presented benzamide *ortho*-lithiation for the synthesis of a phthalide library (Scheme 18).[74c] Different amino methyl resins prepared from *N*-(4-vinylbenzyl)phthalimide, styrene, and three different polytetrahydrofuran-based resin cross-linkers (such as **134**) by suspension polymerization and following cleavage with hydrazine were benzoylated at the resulting amino functionality. After *ortho*-lithiation with *n*-BuLi, the aldehydes **132a**−**h** were added to give the phthalides **133a**−**h**. In 2001, Garibay et al. reported the directed *ortho*-

Scheme 15. Diagram of Split Pool Synthesis of Symmetric Dimeric Molecules by Liao et al.[a]
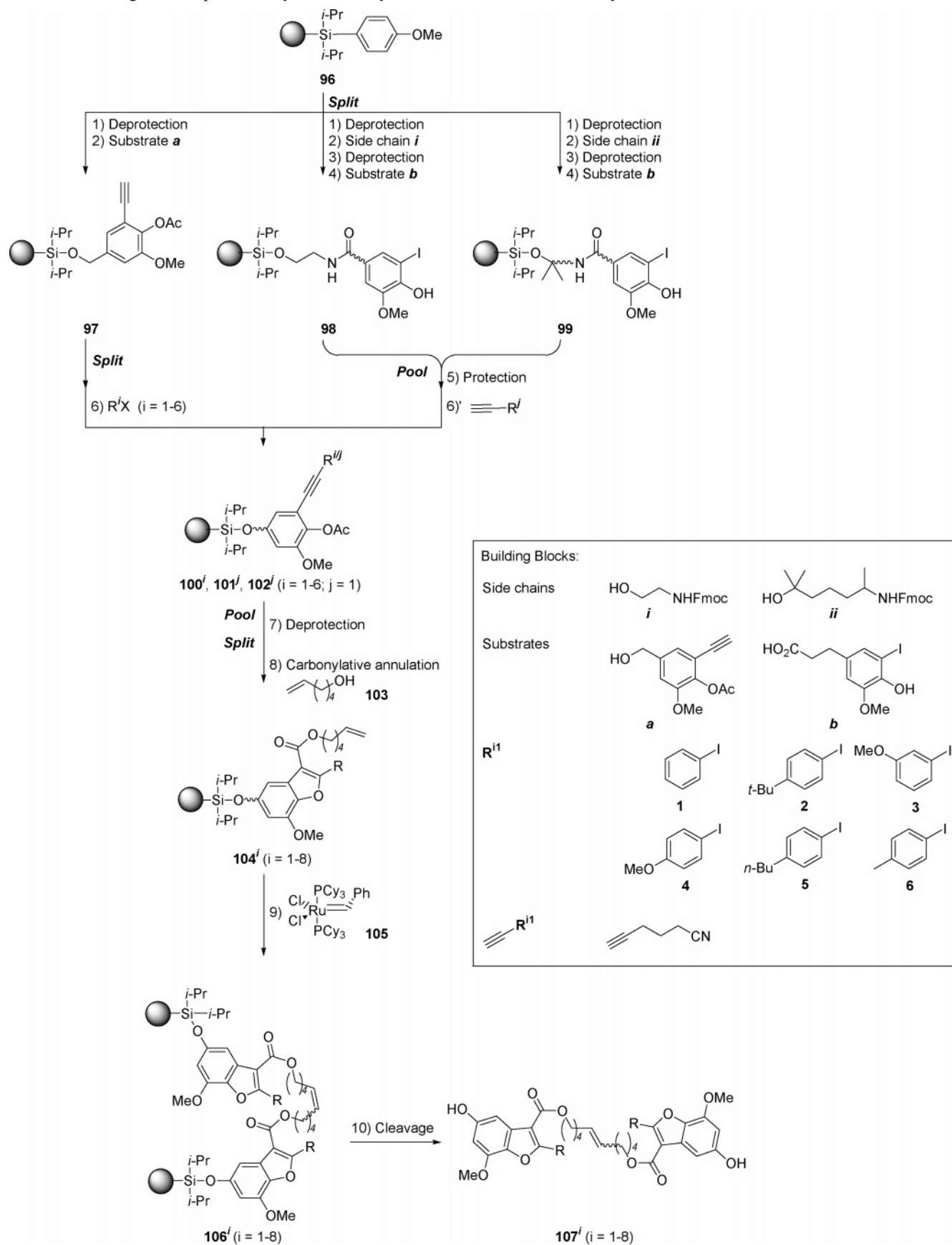
[a] For reaction conditions, see literature.[44]

lithiation on the solid phase and the preparation of a phthalide library.[75] Starting with either immobilization of aromatic

carboxylic acids **136a** or acid chlorides **136b** onto amino methylated polystyrene **135**, the resulting benzamides **137**
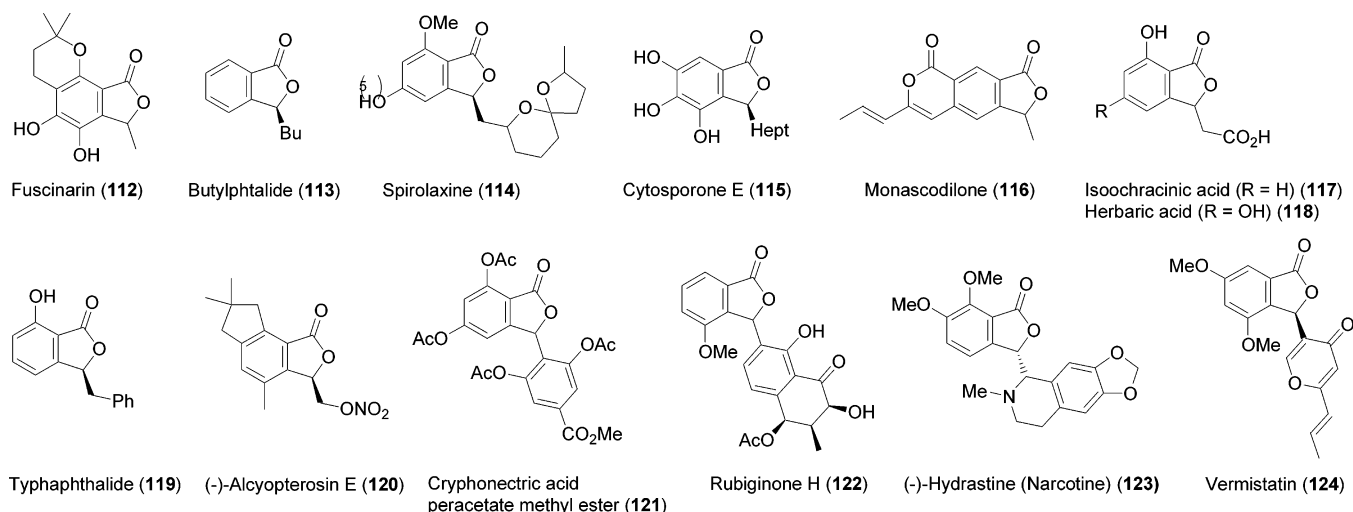
Scheme 16. Strategy and Reaction Conditions for the Solid-Phase Synthesis of 210 Benzofurans **111** by Yang et al.[50]

X = OC₂H₄NCOC₂H₄, OC₂H₄NCOCH₂,
    OCH₂, OCH₂CH(CH₂C₆H₅)NCOC₂H₄

Conditions:
1) 0.3 equiv. PdCl₂(PPH₃)₂, 0.2 equiv. CuI,
   DIEA, acetylene **109**, CH₃CN, 25 °C, 24 h
2) NH₂NH₂/THF (0.1 M), 25 °C, 4 h
3) 2.2 equiv. Pd₂(dba)₃, 4.4 equiv. bpy, ArI,
   CSOAc, DMF, 25 °C, 48 h
4) HF/Py (5% in THF), 25 °C, 1 h,
   then Me₃SiMe 0.5 h

R¹ = Me, OMe, Cl
R² = C₆H₅, 4-Me-C₆H₄, 4-MeO-C₆H₄, 4-F₃C-C₆H₄,
     2-F-C₆H₄, 4-F-C₆H₄, CH₂CH₂CH₂CN
Ar = 4-Me-C₆H₄, 3-Cl-C₆H₄, 3-MeO-C₆H₄, 4-F₃C-C₆H₄,
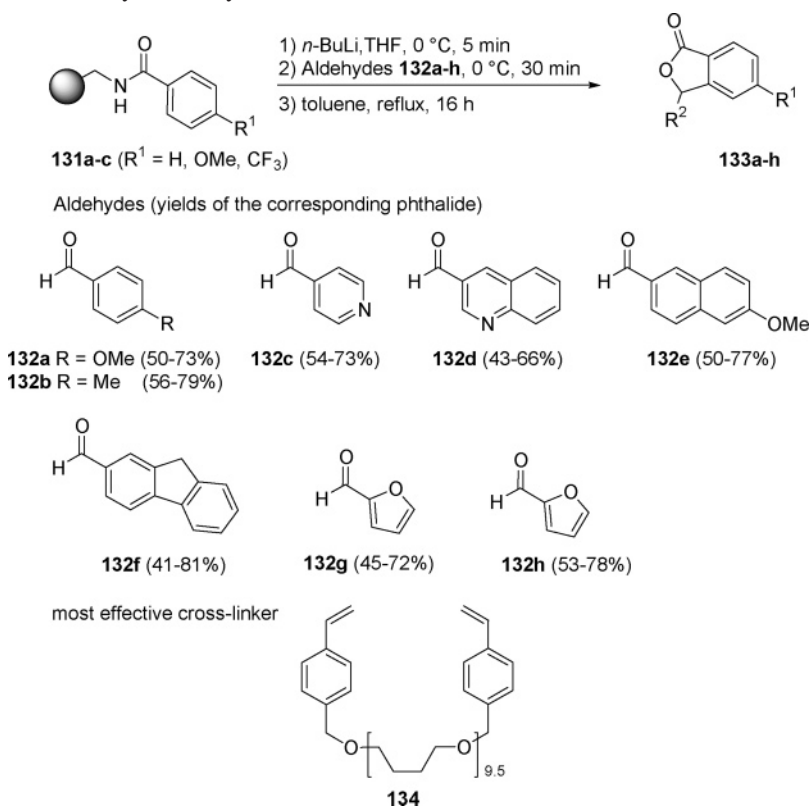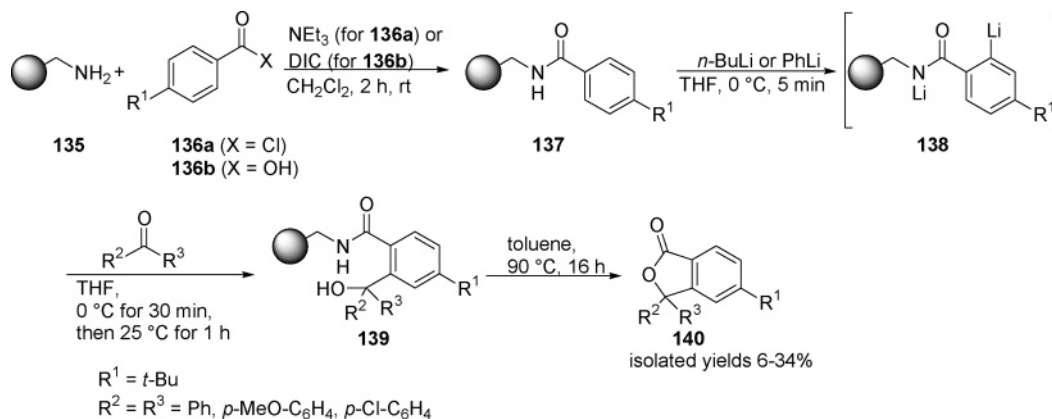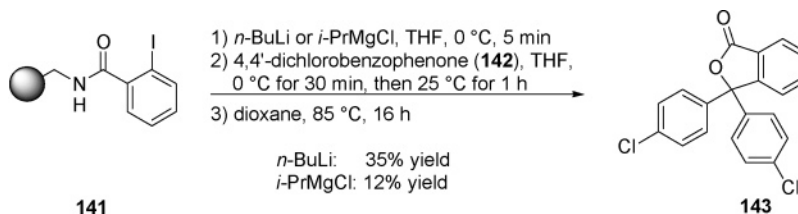   4-Cl-C₆H₄, 4-CH₃CO-C₆H₄

were *ortho*-lithiated with an excess of *n*-BuLi or PhLi to form the dianion **138**. The addition of aldehydes or ketones and heating of the alcohol **139** generate the phthalides **140** in poor to moderate yields. Under optimized reaction conditions, a 100-member phthalide library was formed with yields up to 76% and purities >90%.

Garibay et al. introduced metal−iodine exchange as an *ortho*-metalation technique to give phthalides with yields of 35% (for *n*-BuLi) and 12% (for *i*-PrMgCl) (Scheme 20).[75]

The introduction of a MBHA linker or a DHP linker failed to provide the desired products.

Recently, Tois and Koskinen reported the solid-phase lithiation of TIPS-protected 5-carboxyindole **145** with the following addition of aldehydes in order to form phthalides.[74a] After immobilization of **145** onto *J*anda*J*el-NH₂ resin under standard conditions, the resulting product was ortho-lithiated with *n*-BuLi, and the reaction was quenched with different substituted aldehydes (Scheme 21). After heating in toluene

Fuscinarin (**112**)   Butylphtalide (**113**)   Spirolaxine (**114**)   Cytosporone E (**115**)   Monascodilone (**116**)   Isoochracinic acid (R = H) (**117**)
                                                                                                                                       Herbaric acid (R = OH) (**118**)

Typhaphthalide (**119**)   (-)-Alcyopterosin E (**120**)   Cryphonectric acid peracetate methyl ester (**121**)   Rubiginone H (**122**)   (-)-Hydrastine (Narcotine) (**123**)   Vermistatin (**124**)

Figure 3. Some naturally occurring 3-alkyl and 3-aryl phthalides.[51−62]

Scheme 17. Strategies for the Synthesis of 3-Alkyl Phthalides
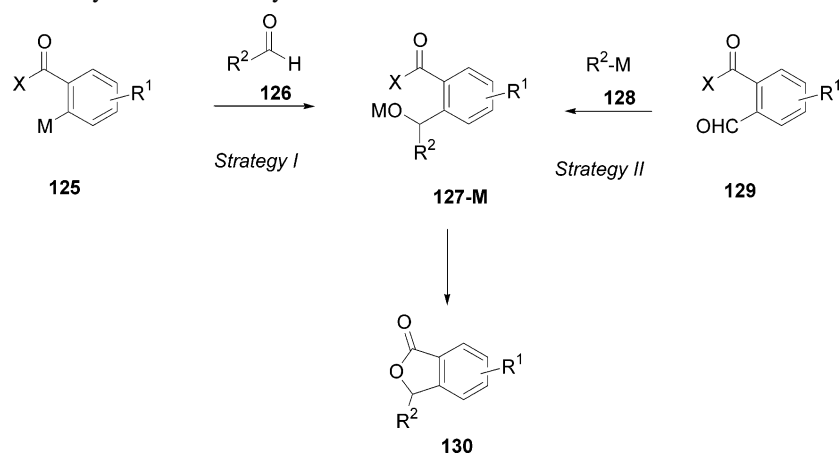
Scheme 18. Solid-Phase Phthalide Synthesis by Janda et al.[74c]

131a-c (R^1 = H, OMe, CF$_3$)

Aldehydes (yields of the corresponding phthalide)

132a R = OMe (50-73%)   **132c** (54-73%)   **132d** (43-66%)   **132e** (50-77%)
132b R = Me   (56-79%)

132f (41-81%)   **132g** (45-72%)   **132h** (53-78%)

most effective cross-linker

134

Scheme 19. Directed ortho-Lithiation and Preparation of Phthalides **140** by Garibay et al.[75]

135   **136a** (X = Cl)   **137**   **138**
       136b (X = OH)

R^1 = *t*-Bu
R^2 = R^3 = Ph, *p*-MeO-C$_6$H$_4$, *p*-Cl-C$_6$H$_4$

139   **140**
isolated yields 6-34%

Scheme 20. Solid-Phase Synthesis of Phthalide **143** Using Metal Iodine Exchange by Garibay et al.[75]

1) *n*-BuLi or *i*-PrMgCl, THF, 0 °C, 5 min
2) 4,4'-dichlorobenzophenone (**142**), THF,
   0 °C for 30 min, then 25 °C for 1 h
3) dioxane, 85 °C, 16 h

n-BuLi: 35% yield
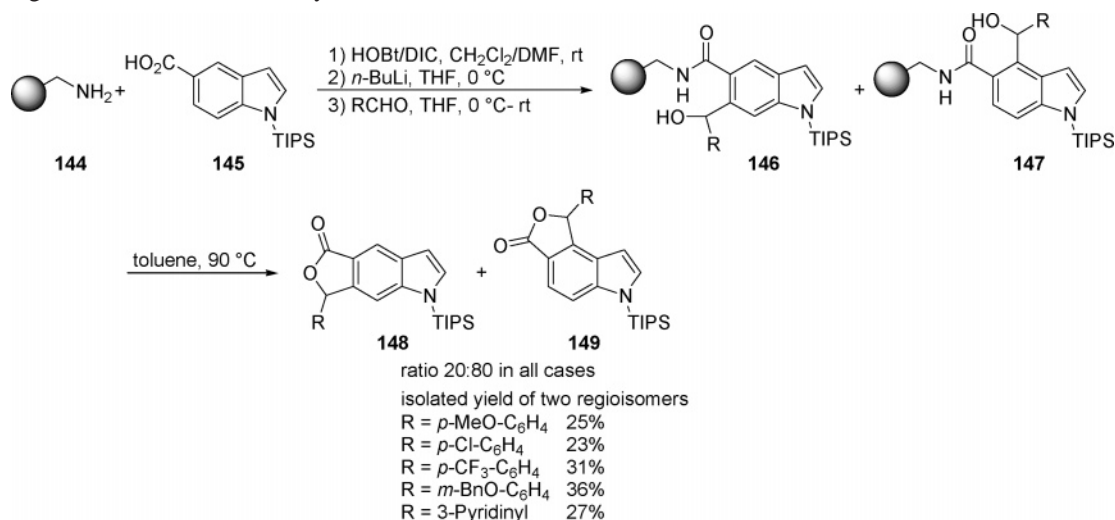*i*-PrMgCl: 12% yield

141   **143**

to 90 °C, the two regioisomeres of the corresponding phthalides **148** and **149** were obtained in a ratio of 20:80 with moderate yields in all cases.

In 2004, Albericio and co-workers published the solid-phase syntheses of furopyridine and furoquinoline systems.[76] The key step is deprotection/cyclization as shown in Scheme 22. Immobilized iodophenols were coupled to quinolines via a Sonogashira coupling reaction, providing **150**. After the

deprotection/cyclization and cleavage, the furoquinolines **152** were obtained in moderate to good yields.

Bräse et al. reported a cyclative-cleavage approach yielding benzobutyrolactones (phthalides).[77] The immobilized *ortho*-formyl benzoic acid **156** was treated with different organo-metallic reagents under various conditions. The resins **156** and **157** were introduced in a Sakurai-type reaction with various allylsilanes **160a−d** (Scheme 23). In addition, Bräse

Scheme 21. Solid-Phase Lithiation of TIPS-Protected 5-Carboxyindole **145** and Addition of Aldehyde to Form the Corresponding Phthalides **148** and **149** by Tois and Koskinen[74a]

ratio 20:80 in all cases
isolated yield of two regioisomers
R = *p*-MeO-C$_6$H$_4$ 25%
R = *p*-Cl-C$_6$H$_4$ 23%
R = *p*-CF$_3$-C$_6$H$_4$ 31%
R = *m*-BnO-C$_6$H$_4$ 36%
R = 3-Pyridinyl 27%

Scheme 22. Solid-Phase Syntheses of Furoquinoline Systems **152** by Albericio et al.[76]
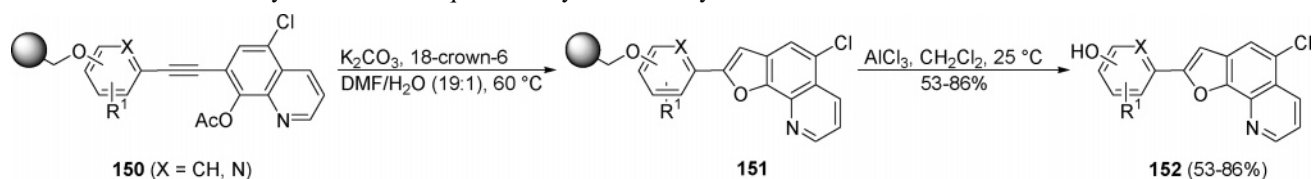
Scheme 23. Solid-Supported Phthalide Synthesis Using a Cyclative Cleavage Approach by Bräse et al.[77]
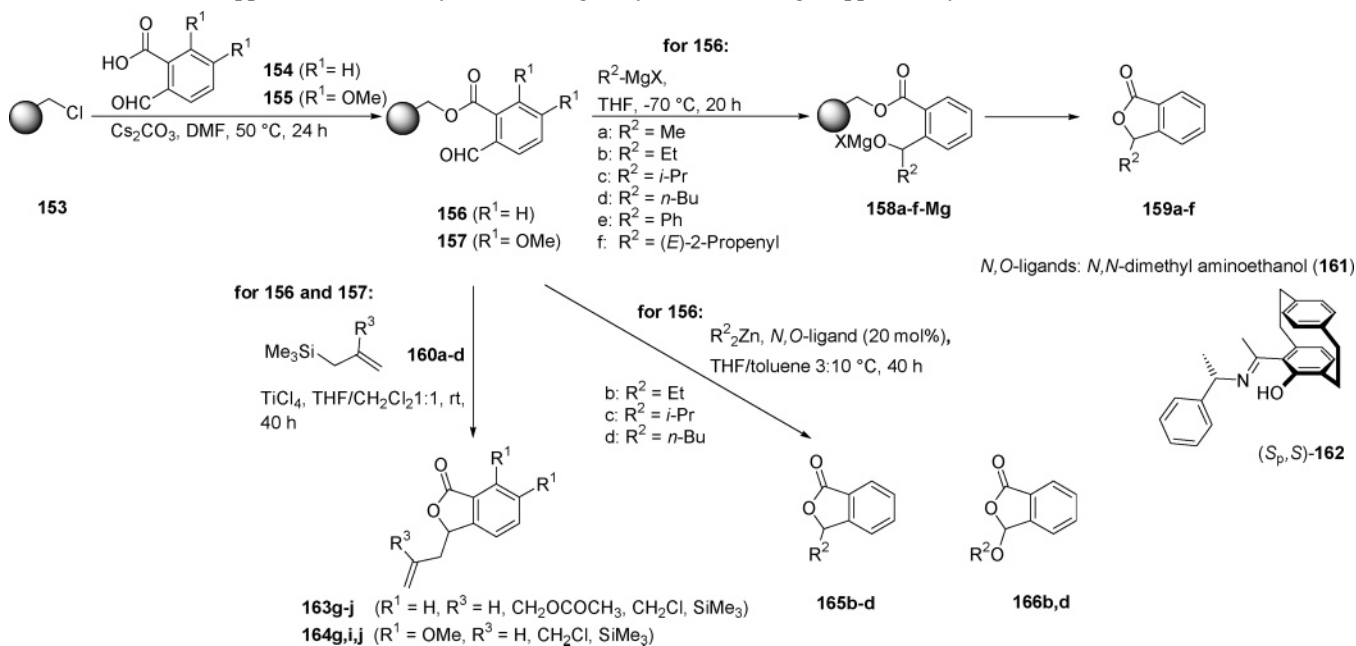
et al. showed that an asymmetric approach using a chiral *N,O*-ligand with a paracyclophane backbone **162** providing **165b–d** was possible. The results are given in Tables 4 and 5.

3. Benzoannelated Six-Membered Heterocycles

3.1. Benzopyrans (Chromanes, Chromenes). Benzopyrans are found not only in a wide range of biologically and pharmacologically active compounds, including natural

products (Scheme 24).[78] The 2,2-dimethylbenzopyrans especially are of great interest from a pharmacological point of view. The benzopyran HLC-2 (**168**)[79] shows antitumor activity, and mallotochromene (**169**) is an HIV-1 reverse transcriptase inhibitor.[80] Both compounds are highly potent. Compound **170** was extracted from *Bacillus subtilis* and shows antibacterial activity.[81] Other examples are the DNA cleaving agent **171**[78] and the potassium channel activator **167**.[82] The cannabinoid (−)-Δ^9-THC (**172**) is a biologically active compound isolated from the plant *Cannabis sativa*.

Table 4. Phthalide Synthesis by Addition of Metal Organic Reagents to Immobilized *ortho*-Carboxybenzaldehyde by Bräse et al.[77]

resin	reagent	ligand	product	purity (%)	yield, % (% ee)
156	MeMgCl		**165a**	89	15
156	*i*-PrMgCl		**165c**	87	16
156	*n*-BuMgCl		**165d**	85	23
156	PhMgCl		**165e**	85	13
156	(*E*)-CH$_3$CH=CHMgCl		**165f**	74	15
156	Et$_2$Zn	161	**165b**	80	14 (0)
156	Et$_2$Zn	(*S$_p$*,*S*)-**162**	**165b**	85	21 (37)
156	*i*-Pr$_2$Zn	(*S$_p$*,*S*)-**162**	**165c**	88	19 (60)
156	*n*-Bu$_2$Zn	161	**165d**	82	35 (0)
156	*n*-Bu$_2$Zn	(*S$_p$*,*S*)-**162**	**165d**	86	25 (35)

Table 5. Phthalide Synthesis Using a Sakurai-Type Reaction by Bräse et al.[77]

resin	R^3	product	purity (%)	yield (%)
156	H	**163g**	95	73
156	CH$_2$OCOCH$_3$	**163h**	85	67
157	CH$_2$Cl	**163i**	90	69
157	SiMe$_3$	**163j**	86	51
157	H	**164g**	88	51
157	CH$_2$Cl	**164i**	76	24
157	SiMe$_3$	**164j**	75	60

It interacts with the human cannabinoid receptors CB1 and CB2.[83]
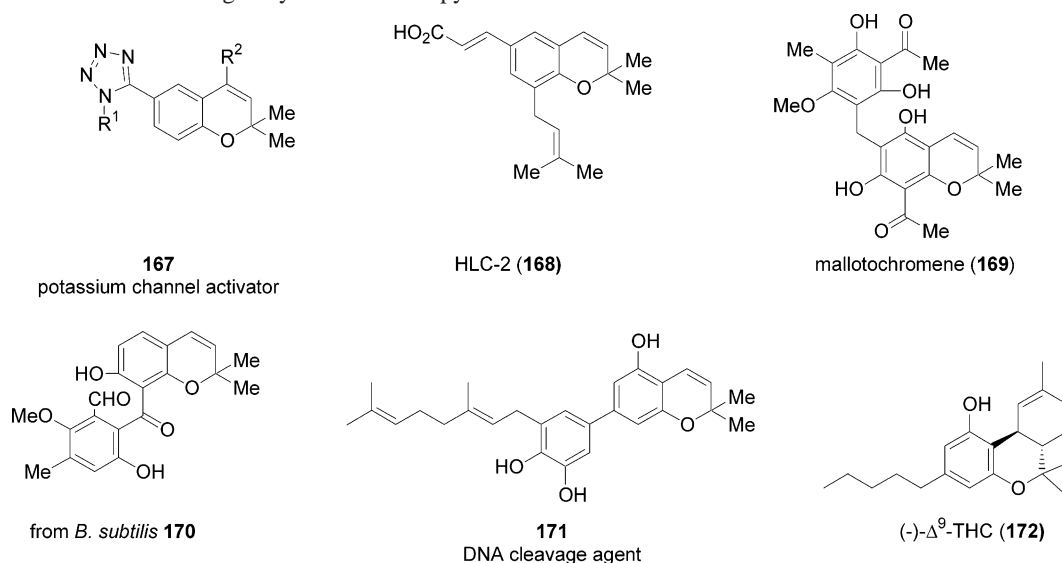
3.2. Chromanes. The chromane (hydrobenzopyran) core structure frequently appears in natural products and is of major pharmaceutical interest.[84] An approach to the solid-phase synthesis of indolines, tetrahydroquinolines, hydrobenzofurans, and chromanes via palladium-catalyzed annelation was reported by Wang and Huang.[85] Although most of their work was focused on the synthesis of benzoannelated heterocycles containing nitrogen, a single example on the chromane synthesis was given.
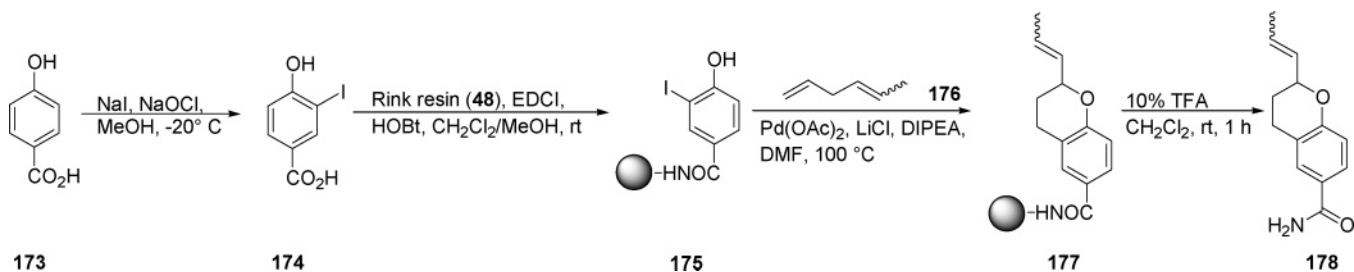
As depicted in Scheme 25, iodination of *p*-hydroxybenzoic acid **173** was achieved via a modified literature procedure[86] and led to 4-hydroxy-3-iodobenzoic acid **174**. Coupling to Rink resin (**48**) was performed using EDCI and HOBt and

yielded the resin-bound phenol **175**. The annulation reaction was carried out by heating resin **175** with 1,4-hexadiene **176** in the presence of 10 mol % of Pd(OAc)$_2$, LiCl, and diisopropylethylamine in DMF at 100 °C, yielding resin-bound chromane **177**. Cleavage was obtained upon treatment with 10% TFA in CH$_2$Cl$_2$ and afforded the chromane **178** (trans/cis = 5.3:1) in good yield (84%) and good purity (88%).

A different route toward the solid-phase synthesis of benzodihydropyrans was reported by Craig et al.[87] The key step in this approach was a hetero Diels−Alder reaction between benzaldehydes and resin-bound *o*-quinodimethane. Benzocyclobutenol **181** was used as the precursor for *o*-quinodimethane, as depicted in Scheme 26. Hydroxymethylpolystyrene **179** was treated with NaHMDS and trichloroacetonitrile, leading to resin **180**. Benzocyclobutenol **181** underwent reaction with resin **180** in the presence of catalytic TfOH, providing resin-bound *o*-quinodimethane **182**. Hetero Diels−Alder reactions between a variety of dienophiles **183** and resin **180** were performed at elevated temperature, providing resin-bound dihydrobenzopyrans **184**. Cleavage from the polymer support was performed under acidic conditions using either Brønsted or Lewis acid−nucleophile combinations, yielding the dihydrobenzopyrans **185a−f** in moderate to good yields and with excellent stereoselectivity for the anti-isomer.

3.3. Chromenes. A solid-phase route for the synthesis of the 2,2-dimethylbenzopyran moiety and the elaboration of the resin-bound scaffold has been published by Nicolaou.[88] In a series of preliminary studies,[88a] selenyl bromide resin **187** was treated with excess of ortho-prenylated phenols **186**, providing resin-bound dihydrobenzopyrans **189** via a [6-endo-trig] cycloaddition. The benzopyrans **191a−c** were released from the solid support upon oxidation with H$_2$O$_2$ and subsequent syn-elimination from intermediate resin **190**. High yields (>91%) and high purities (>95%) were obtained regardless of the electronic environment (**191a**, **191b**, or **191c**) of the phenolic substrate. After preliminary studies, the cycloloading strategy was investigated thoroughly by testing various ortho-prenylated phenols, resulting in the

Scheme 24. A Selection of Biologically Active Benzopyrans

167
potassium channel activator

HLC-2 (**168**)

mallotochromene (**169**)

from *B. subtilis* **170**

171
DNA cleavage agent

(-)-Δ^9-THC (**172**)

Scheme 25. Solid-Phase Synthesis of Chromane **178** as Reported by Wang and Huang[85]

Scheme 26. Solid-Phase Synthesis of Substituted Chromanes by Craig et al.[87]
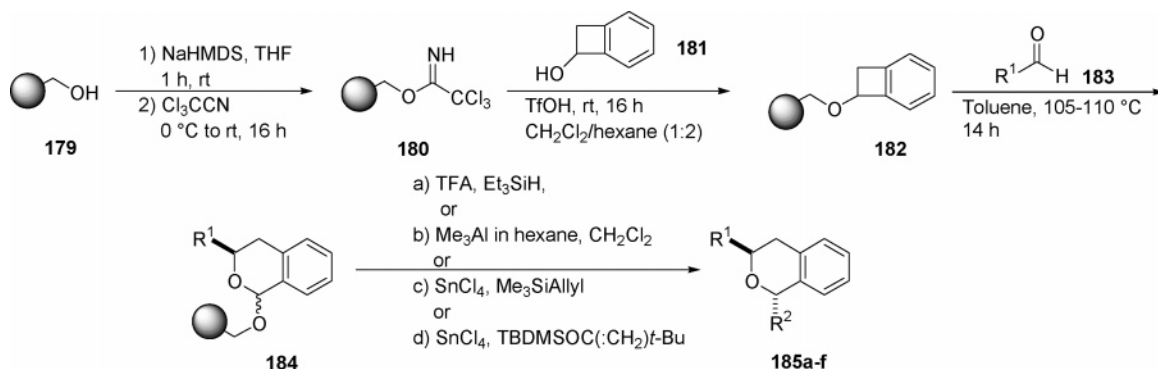
**Table 6.** Dihydrobenzopyrans Prepared by Craig et al.[87]

chromane	R^1	R^2	yield (%)
185a	4-$O_2NC_6H_4$	H	41
185b	4-$O_2NC_6H_4$	CH_3	26
185c	4-$O_2NC_6H_4$	$CH_2CH=CH_2$	24
185d	4-$O_2NC_6H_4$	CH_2COt-Bu	33
185e	MeO_2C	H	10
185f	4-BrC_6H_4	CH_3	18

creation of two libraries, one consisting of 35 benzopyrans[88a] and the other one of 47 benzopyrans.[88c] The acquired resin-bound benzopyran was subsequently used as a scaffold in the synthesis of several benzopyran-based combinatorial libraries (for example, a 52-membered library[88f] aimed at the development of new NADH/ubiquinone oxidoreductase inhibitors, and a 10 000-member library[88d] constructed by directed split-and-pool chemistry).

3.4. Benzopyranones and Cumarines. Like the benzopyrans, the benzopyranone structures have also been found in a large number of natural products (Figure 4), and they also show notable properties, for example, the antitumor agent tephrosin (**192**),[89] the HIV-1 reverse transcriptase inhibitor inophyllum B (**193**),[90] and the antibacterial 5-methyllupinifolinol (**196**).[91] 5-Methyllupinifolinol (**196**) was also extracted from *B. subtilis*. Other interesting pharmacologically active compounds are robustic acid (**194**),[92] which is a

selective protein kinase inhibitor and artonin E (**195**),[93] which is an inhibitor of arachidonate 5-lipoxygenase.

3.5. Benzopyranones. The benzopyranone ring system has been found in a number of naturally occurring compounds (i.e., flavonoids) which possess biological activity of pharmaceutical interest.[94] A combinatorial approach toward the synthesis of a library of compounds containing the benzopyranone moiety was published by Harikrishnan and Showalter in 1999.[94] Initially, solution-phase methodology was developed, in which benzyl alcohol was used as a surrogate for hydroxymethyl polystyrene. Using the diisopropylsilyloxy linker, this methodology was applied during the solid phase synthesis of a nine-member 2,3-disubstituted benzopyran-4-one library (Scheme 28). As previously described by Boehm and Showalter,[24] MOM-protected *p*-bromophenol **197** was subjected to lithium−halogen exchange and treated with dichlorodiisopropylsilane, providing arylchlorosilane **198**. Hydroxymethyl polystyrene **179** was treated with arylchlorosilane **198** and imidazole in DMF to provide the resin-bound silyl ether **199**. Formylation of **199** was achieved via ortho-lithiation followed by quenching with DMF to produce resin **200**. The resin-bound aldehyde **200** was treated with benzylic Grignard reagents, providing the corresponding alcohols, which were oxidized by subsequent treatment with IBX to the ketones **201**. Deprotection was

Scheme 27. Solid-Phase Synthesis of Benzopyrans via Cyclo-Loading Strategy as Described by Nicolaou et al.[88a]
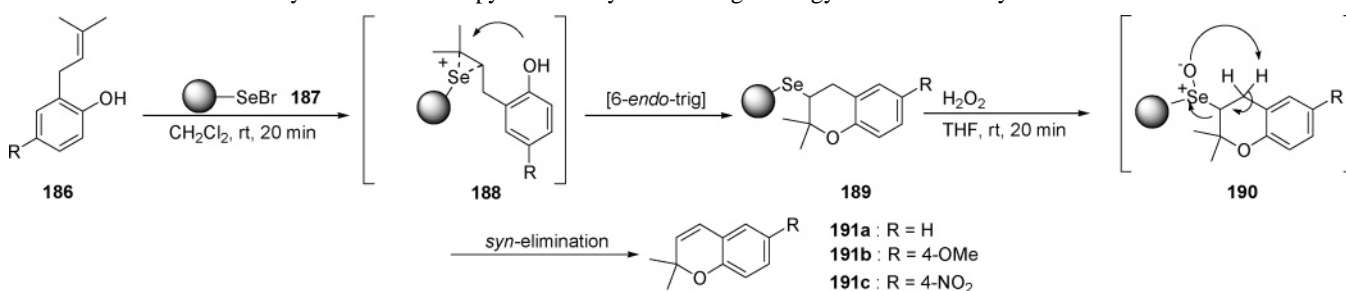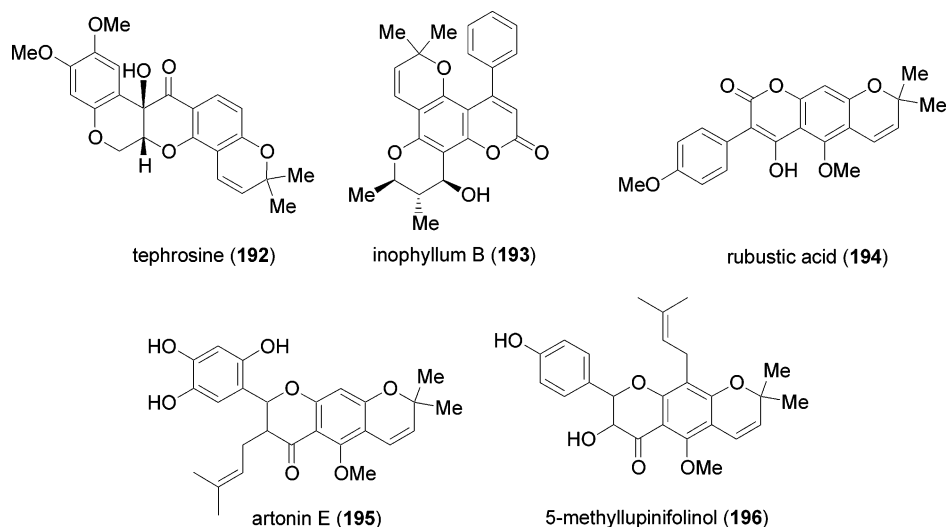
Figure 4. Examples of biologically active benzopyranones containing natural products.

Scheme 28. Solid-Phase Synthesis of 2,3-Disubstituted Benzopyran-4-ones by Harikrishnan, Boehm, and Showalter[24,94]
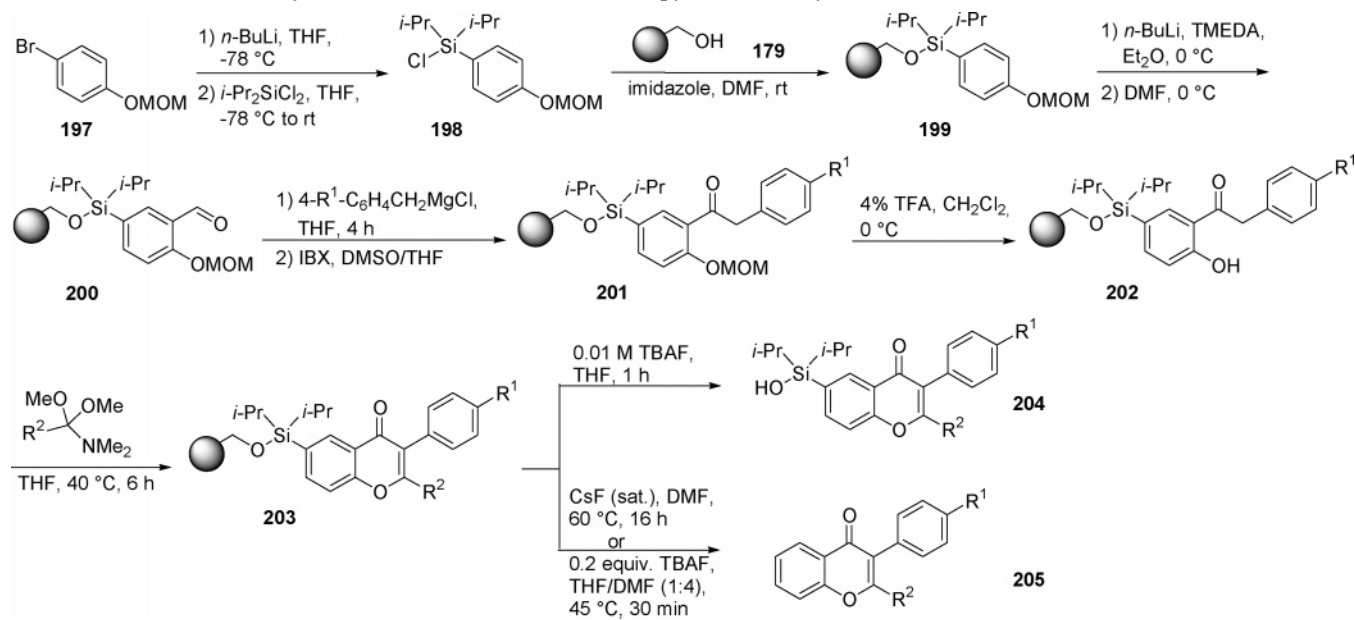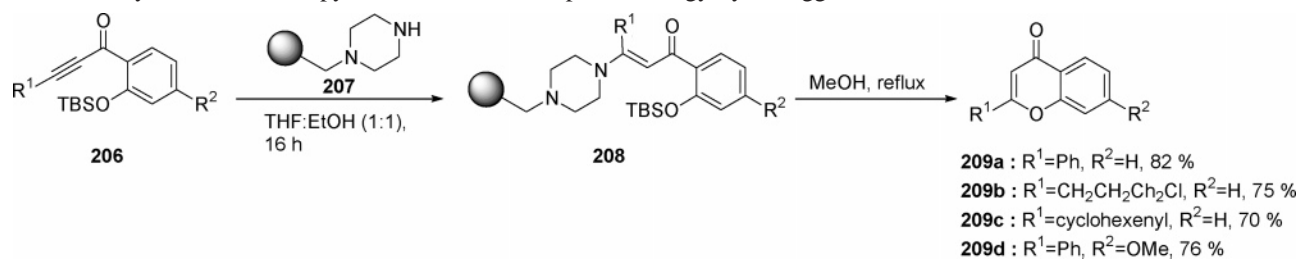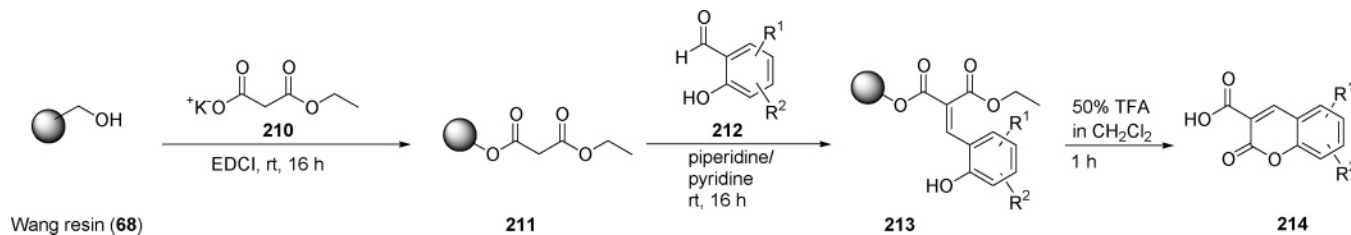

Table 7. Yields and Purities Obtained in Synthesis of 2,3-Disubstituted Benzopyran-4-ones Library by Boehm and Showalter[24]

benzopyranone	R^1	R^2	yield(%)	purity (%)
205a	H	H	65	99
205b	H	CH_3	57	97
205c	H	CH_2CH_3	46	100
205d	OCH_3	H	34	98
205e	OCH_3	CH_3	32	88
205f	OCH_3	CH_2CH_3	20	51
205g	Cl	H	73	91
205h	Cl	CH_3	74	93
205i	Cl	CH_2CH_3	30	98

achieved with TFA, providing the phenol **202**. Treatment with amide acetals in THF at elevated temperature gave the resin-bound benzopyranones **203**. Cleavage was carried out via three different procedures, providing two different classes of products. Silanols **204** were obtained by treatment with diluted TBAF solution, and traceless cleavage with either CsF or TBAF yielded benzopyranones **205**.

Brueggemeier et al. applied a resin capture strategy for the synthesis of benzopyranones.[95] The purpose was to develop a strategy for the synthesis of new anticancer agents containing the benzopyranone ring moiety. In this strategy, the resin-bound secondary amine **207** was used to affect the cyclization of alkynyl ketones **208**, as depicted in Scheme 29. A solution of alkynone **206** in EtOH was added to a THF/EtOH solution containing piperazinyl resin **207**. The formation of enaminone resin **208** was verified by IR analysis, revealing the presence of a carbonyl group. Cyclization was achieved by heating resin **208** in methanol for 16 h to give benzopyranones **209a−d**.

3.6. Coumarins. A solid-phase synthesis of coumarins was reported by Watson and Christiansen in 1998.[96] Using the Knoevenagel condensation reaction, a small library of coumarin-3-carboxylic acids was synthesized. The synthesis is outlined in Scheme 30. Ethyl potassium malonate **210** was attached to a Wang resin (**68**) to give resin **211**, which was then treated with the substituted salicylic aldehydes **212** in pyridine and a catalytic amount of piperidine. Cyclative

Scheme 29. Synthesis of Benzopyranones via Resin Capture Strategy by Brueggemeier et al.[95]

209a : R^1=Ph, R^2=H, 82 %
209b : R^1=CH$_2$CH$_2$Ch$_2$Cl, R^2=H, 75 %
209c : R^1=cyclohexenyl, R^2=H, 70 %
209d : R^1=Ph, R^2=OMe, 76 %

Scheme 30. Solid-Phase Synthesis of Coumarin-3-carboxylic Acids **214** by Watson and Christiansen[96]

Table 8. Yields and HPLC Purities Obtained in Library Synthesis of Substituted Coumarin-3-carboxylic Acids 214 by Watson and Christiansen[96]

| Coumarin	R^1	R^2	yield [%] (purity [%])	Coumarin	R^1	R^2	yield [%] (purity [%])
214a	H	H	36 (90)	**214h**	4-MeO	H	40 (68)
214b	3-Cl	H	39 (93)	**214i**	4-MeO	6-MeO	40 (70)
214c	3-MeO	H	16 (92)	**214j**	5-Br	H	35 (83)
214d	3-Br	5-Br	36 (74)	**214k**	5-MeO	H	35 (97)
214e	3-Br	5-Cl	39 (69)	**214l**	5-Cl	H	39 (97)
214f	3-I	5-I	34 (92)	**214m**	〈 〉		37 (98)
214g	4-OH	H	28 (96)				

cleavage of resin **203** was induced by treatment with TFA, providing 13 substituted coumarin-3-carboxylic acids **214** in good purities (68–98%) and low to moderate yields (16–40%), as depicted in Table 8.

The Knoevenagel condensation reaction was applied under similar conditions in the asymmetric solid-phase synthesis of (3′R,4′R)-di-O-cis-acyl 3-carboxyl khellactones by Xia et al.[97] Khellactones have been shown to possess biological activities, including antifungal, antitumor, and antiviral effects against HIV-1 replication.[98] Ethyl potassium malonate **210** was attached to a Wang resin (**68**), followed by a Knoevenagel condensation between resin-bound ethyl malonate **211**, and o-hydroxyarylaldehydes **215** in pyridine containing piperidine gave the resin-bound khellactone scarfold **216**. Resin **217** was obtained from **216** by a Sharpless asymmetric dihydroxylation reaction using (DHQ)$_2$ PHAL as the ligand and OsO$_4$ as a catalyst. Resin **218** was achieved via acylation of **217**. Cleavage was performed by treatment of resin **218** with TFA. A small set of compounds consisting of 3-carboxyl khellactones was prepared by this procedure in overall yields of 23–44%.

A third example of the Knoevenagel condensation reaction being used in the synthesis of a coumarin was reported by Svensson et al.[99] The syntheses of three fluorinated analogues of linkers commonly used in solid-phase peptide chemistry were described. The fluorinated linkers provided a basis for on-bead analysis of reactions via gel-phase ^{19}F NMR

spectroscopy. This principle was demonstrated by the solid-phase synthesis of an amide-bearing coumarin (Scheme 32). The fluoro-containing linker 3-fluoro-4-(hydroxymethyl)-phenoxyacetic acid (**220**) was prepared from 2-fluoro-4-propoxybenzoic acid **221** and was coupled to a TentaGel S NH$_2$ resin using a pentafluorophenyl ester. Acylation of resin **222** with bromoacetic acid provided resin **223**. The bromoacetate **223** was substituted with n-butylamine, and after amidation of **224** with ethyl malonyl chloride, resin **225** was obtained. Knoevenagel condensation of **225** with salicylaldehyde provided the resin-bound coumarin **226** which upon treatment with either TFA or LiOH was cleaved from the resin, providing **227** in 27 or 55% yield, respectively. Gel-phase ^{19}F NMR spectroscopy proved to be particularly efficient for monitoring the cleavage step.

3.7. Tricyclus Including a Six-Membered Oxygen Heterocycle. Phenolic naphthoisoxazole, like **228**, has been applied as scaffold in the synthesis of novel estrogen receptor modulators. To investigate the potential of benzopyrano-isoxazoles as steroid mimetic templates, the solid-phase synthesis of substituted benzopyranoisoxazoles, such as **229**, was developed by Chao et al (Scheme 33).[100] Commercially available 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene **230** was treated with butylamine and sodium triacetoxy-borohydride to generate resin amine **231**. 3-Formyl-4-hydroxybenzoyl chloride (**232**) was coupled to resin **231** using 2,6-lutidine. A small percentage (<5%) of ester

Scheme 31. Solid-Phase Synthesis of Khellactones **219** by Xia et al.[97]

219a (40%)   **219b** (44%)   **219c** (30%)

219d (24%)   **219e** (31%)   **219f** (29%)
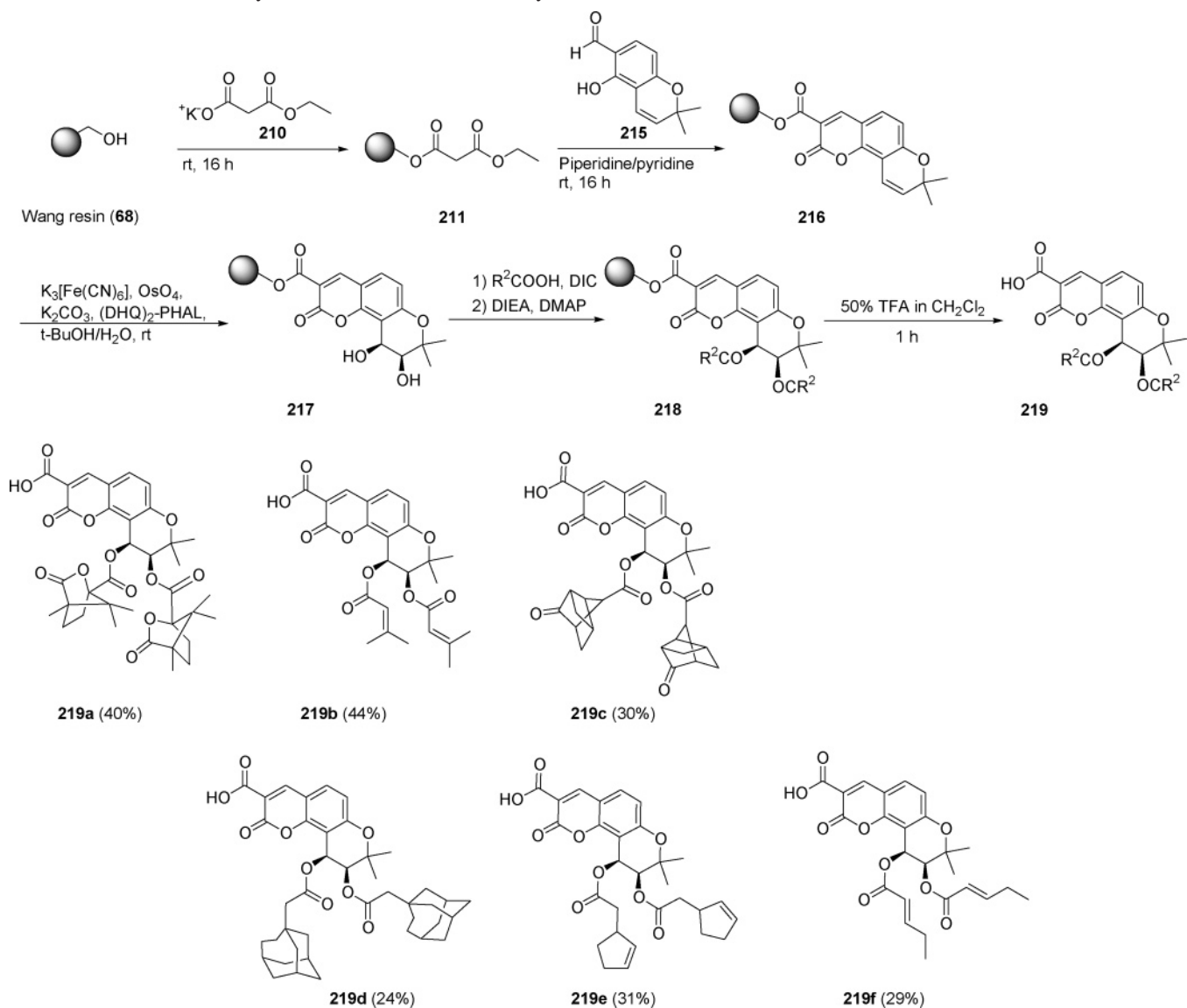
Scheme 32. Solid-Phase Synthesis of an Amide Bearing a Coumarin Moiety by Svensson et al.[99]
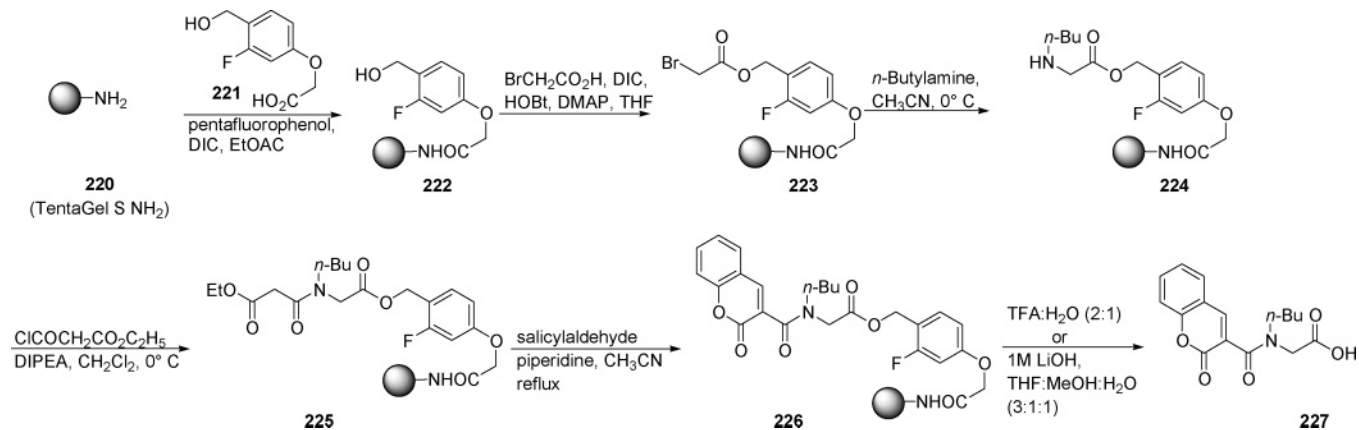
formation between resin-bound phenol and excess acid chloride was observed. After saponification of the ester to the desired resin-bound phenol **233**, a Mitsunobu reaction between resin-bound phenol **233** and propargyl alcohol **234** using sulfonamide betaine **235** gave resin **236**. Resin-bound aldoxime **237** was obtained upon treatment of resin **236** with

hydroxylamine hydrochloride and triethylamine. An intramolecular 1,3-dipolar cycloaddition was achieved with NBS and Et$_3$N in DMF generating resin-bound benzopyranoisoxazole **238**. Cleavage was obtained with 15% TFA in CH$_2$Cl$_2$, yielding benzopyranoisoxazoles **239a−i** in good overall yields and high purities (Table 9).
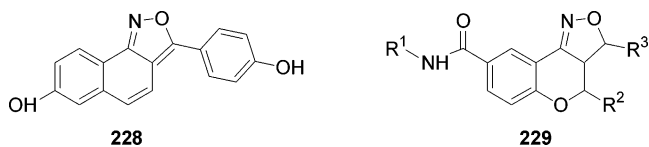
Figure 5. Benzopyranoisoxazole scaffolds described by Chao et al.[100]

4. Tetracyclic Framework and Carpanones

4.1. Tetracyclic Framework. The replacement of one or more carbon atoms of a steroid molecule with heteroatoms brings about notable modifications in its biological activity, and numerous studies exist that deal with the total and partial synthesis of so-called heterosteroids as well as their physiological activities.[101] The 11-oxoadenocortical hormones and heterosteroids, in which the methylene group at position 11 has been replaced by a heteroatom, are of special interest (Figure 6).[102] The hormone analogue 17-acetoxy-11-oxaprogesterone (**241**) shows little progestational activity but has significantly enhanced ovulation inhibitory activity. In addition, 11-oxaestradiol (**240**) shows extremely low estrogenic (uterotropic) activity and possesses antifertility activity.[103] 11-Oxasteroids, which have antiinflammatory, antiandrogenic, or corticoid activities, have been reported.[104] In 2000, Hong et al. reported a traceless solid-phase synthesis of a tetracyclic framework as a precursor for heterosteroids.[105] They developed a fulvene hetero [6 + 3] cycloaddition methodology for the synthesis of cyclopenta[c]chromenes[106] and applied this methodology in a traceless solid-phase synthesis of a 11-heterosteroid library, which in addition to being quite efficient is the first report on a [6 + 3] cycloaddition performed on solid phase (Scheme 34).[105]

Carboxylic acids **243** were immobilized on polystyrene amino resin **242** via coupling under standard conditions (DCC, HOBt, DMAP). The resin-bound amide **244** was treated with Et_3OBF_4 and then with sodium cyclopentadienide **245**, yielding resin **246**. A hetero [6 + 3] cycloaddition was achieved upon addition of fulvene resin **246** to a solution of benzoquinone **247** in benzene, resulting in the release of heterosteroids **248a−e** from the solid support.
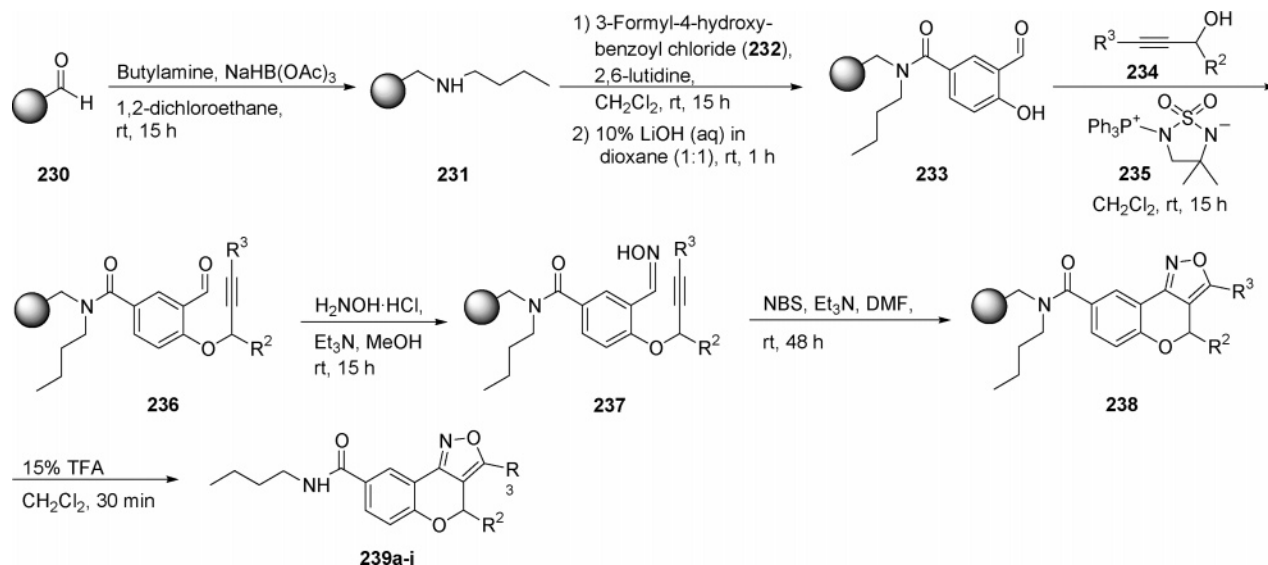
Table 9. Overall Yields and Purities of Substituted Benzopyranoisoxazoles Reported by Chao et al.[100]

benzopyranoisoxazole	R^1	R^2	yield (%)	purity (%)
239a	H	H	44	99
239b	Me	H	44	95
239c	Et	H	34	98
239d	*n*-Pr	H	55	99
239e	Ph	H	33	92
239f	H	Me	34	92
239g	H	$C_{10}H_{21}$	31	96
239h	H	Ph	37	99
239i	*i*-Pr	Ph	43	96

Column chromatography over silica gel yielded products **248a−e** in good purity (>95%) and acceptable overall yields (32−42%). In a combinatorial manner, five carboxylic acids, two cyclopentadienyl anions, and nine benzoquinones were reacted to generate a library of 90 different heterosteroids (of which five examples are given in Scheme 34). Subsequent in vitro screening of the library revealed that **248a** possesses moderate inhibiting activity against a variety of NCI cancer cell lines.
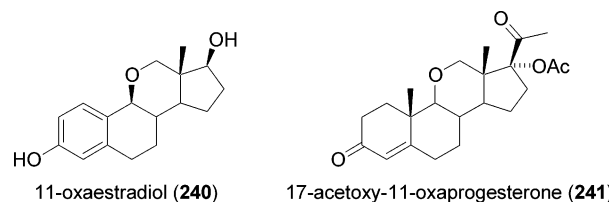

Figure 6. Hormone analogues 17-acetoxy-11-oxaprogesterone (**241**) and 11-oxaestradiol (**240**).[103]

4.2. Carpanones. Carpanone (**249**) is a hexacyclic molecule with five contiguous stereogenic centers which shows no formal element of symmetry and no optical activity (Figure 7).[107] It was first extracted from the bark of the Carpano tree from an island in the Pacific Ocean. In 1973, Chapman et al. reported an elegant biomimetic synthesis.[108] A concise synthesis of carpanone using solid-supported reagents and scavengers was introduced by Ley and co-workers in 2002.[107b] With the goal of constructing a split

Scheme 33. Solid-Phase Synthesis of Benzopyranoisoxazoles **239** Reported by Chao et al.[100]

Scheme 34. Traceless Solid-Phase Synthesis of 11-Heterosteroids **248a−e** by Hong et al.[105]

242
(Amino methyl
polystyrene)

248a **248b** **248c** **248d** **248e**
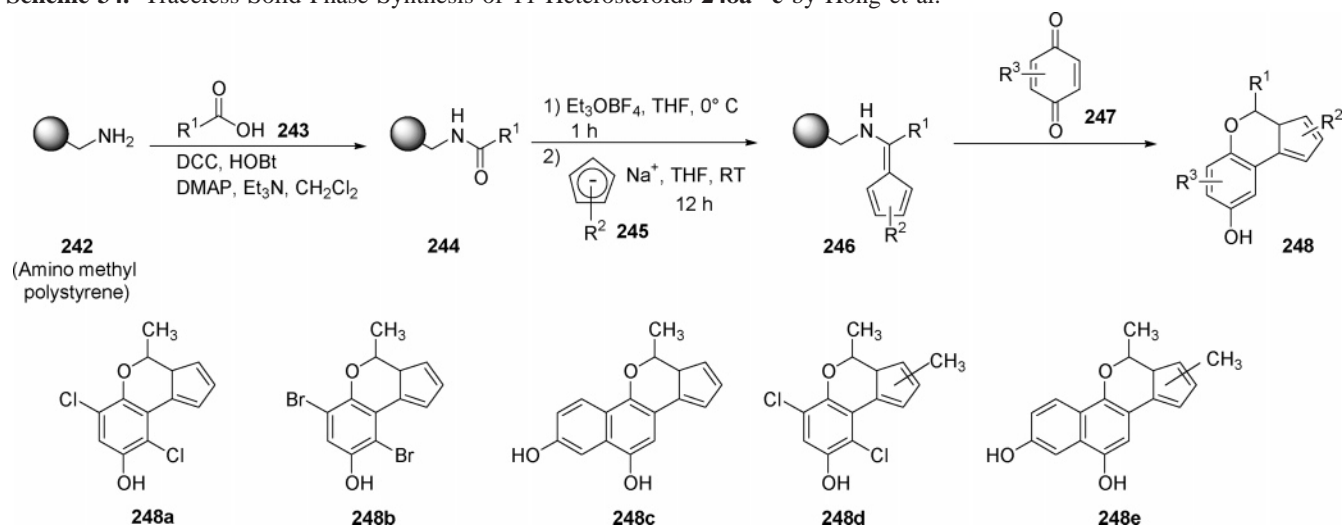
pool library of carpanone-like molecules, a biomimetic solid-phase synthesis was developed by Shair et al. in 2000
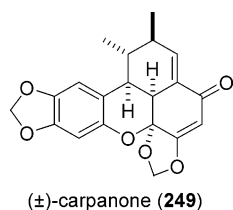
(±)-carpanone (**249**)

Figure 7. Natural product carpanone (**249**) isolated from the carpano tree.[107]

(Scheme 35).[109] Using similar chemistry as implicated in the biosynthesis of carpanone and other members of the benz-oxanthenone class of natural products, five different car-panones were synthesized. A mixture of electron-deficient phenols **251** and resin-bound electron-rich phenols **250** was

treated with PhI(OAc)₂ to promote oxidative heterocoupling. The electronically preferred transition state **252** provided the resin-bound tetracycles **253** via inverse electron demand Diels−Alder cycloaddition. Resin-bound tetracycles **253** were treated with HF-pyridine and then Me₃SiOMe to yield the carpanones **254a−e** in good yields. The synthesis is outlined in Scheme 35. Table 10 provides an overview of the different compounds prepared and the corresponding yields obtained.

5. Conclusion

The solid-phase synthesis of benzoannelated oxygene heterocycles that have been reported to date illustrates several different approaches to the challenging preparation of librar-ies containing bioactive products and incorporates the synthesis of many novel chemical structures. Due to the
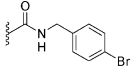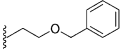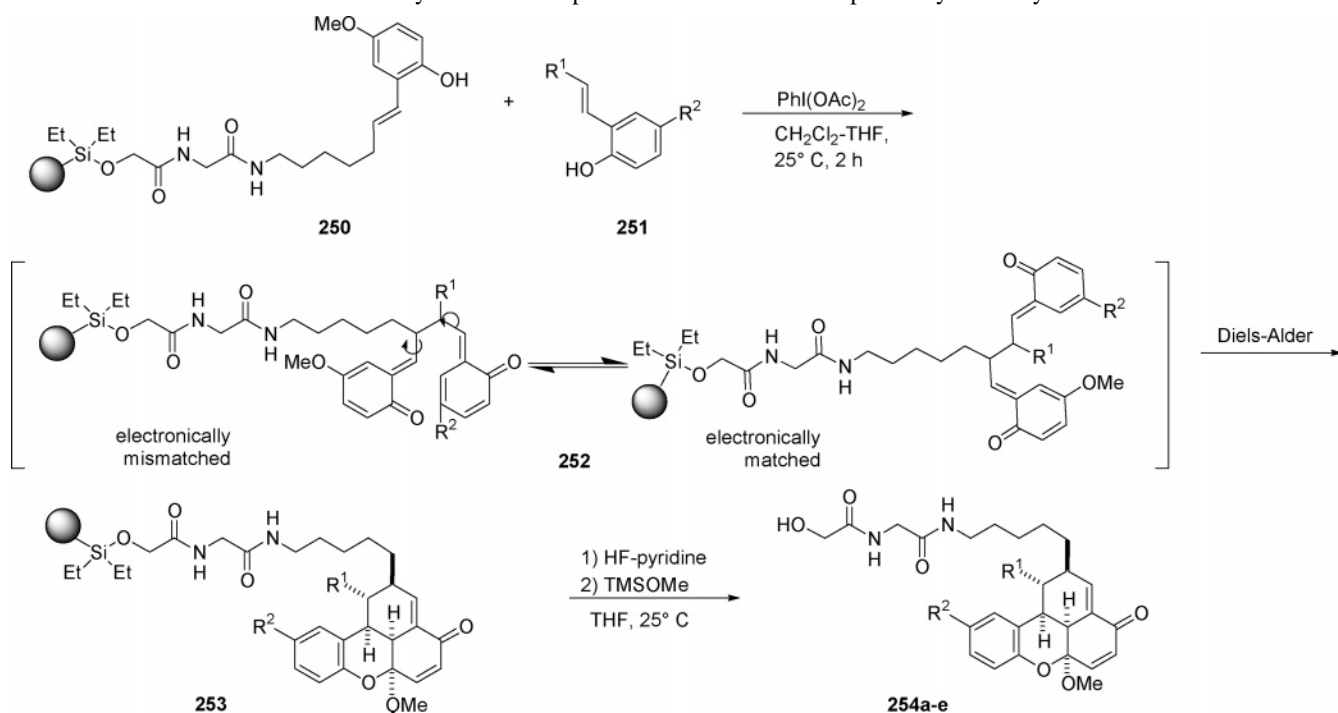
Scheme 35. Biomimetic Solid-Phase Synthesis of Carpanone-Like Molecules Reported by Lindsley et al.[109]

Table 10. Carpanone-Like Molecules Reported Prepared via Solid-Phase Synthesis by Lindsley et al.[109]

Carpanone	R^1	R^2	yield [%]
254a	*i*-Bu	(amide with benzyl 4-bromo group)	78
254b	Et	(amide with benzyl 2-bromo group)	77
254c	(propyl benzyl ether)	(ester OMe)	81
254d	Et	(succinimidyl ester)	77
254e	Me	(*t*-Bu ester)	79

impressive pharmacological activities of some heterocycles, such as benzofurans, phthalides, benzopyrans, or benzo-pyranones, oxygen heterocycles have been the target of intense synthetic efforts. A great number of approaches toward the synthesis of benzoannelated heterocycles in liquid and solid phase have been reported, including several strategies for the solid-phase synthesis of benzoannelated oxygen heterocycles. For benzofurans, cyclative cleavage pathways, palladium-catalyzed heteroannelation reactions, radical cyclization reactions, cyclofragmentation−release pathways, or cyclative cleavage approaches should be mentioned. Another strategy incorporates functionalized titanium benzylidene reagents on solid supports. A second class of five-membered benzoannelated oxygen heterocycles, the phthalides, can also be obtained via a cyclative cleavage approach. Like the five-membered benzoannelated oxygen heterocycles, the six-membered rings can be achieved by palladium-catalyzed cyclization reactions. In the case of the six-membered rings, the hetero Diels−Alder reaction is an effective pathway. The Knoevenagel condensation reaction was successfully applied for the synthesis of coumarins. Further benzoannelated oxygen heterocycles were also synthesized on solid supports, as shown in carpanones and tetracyclic systems. The area of the synthesis of benzoan-nelated oxygen rings continues to grow, and solid-phase chemistry will provide more and better methods for the synthesis of benzoannelated heterocycles, allowing the preparation of new libraries containing novel compounds.

Abbreviations

Ac	acetyl
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
bpy	bipyridine, 2,2′-bipyridyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
Cp	cyclopentadienyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*′-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DHP	dihydropyran
DHQ	dihydroquinine
DIC	*N,N*′-diisopropylcarbodiimide
DIEA/DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DVB	divinylbenzene
EDCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv	equivalents
ER	estrogen receptor
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
GC	gas chromatography
h	hour
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphorictriamide
HOBT	1-hydroxybenzotriazol
HPLC	high performance/pressure liquid chromatography
HTS	high-throughput-screening
IBX	1-hydroxy-1,2-benziodoxol-3(1H)-one
i-Pr	isopropyl
IR	infrared
m	meta
MBHA	methylbenzhydrylamine
*m*CPBA	*meta*-chloroperoxobenzoic acid
Me	methyl
MeOH	methanol
Mes	mesityl
min	minute
MOM	methoxymethyl
n-BuLi	*n*-butyllithium
NMO	*N*-methylmorpholine oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
n-Pr	*n*-propyl
Nu	nucleophile
o	ortho
p	para
Ph	phenyl
PHAL	1,4-phthalazinediyl diether
Pin	pinacolato
dppp	1,3-diphenylphosphinopropane
Py	pyridine, pyridyl
rt	room temperature
SPOS	solid-phase organic synthesis
T	temperature
t	time
t-Bu	*tert*-butyl
t-BuLi	*tert*-butyllithium
TBAF	tetrabutylammoniumfluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N,N,N,N*-tetramethylethylendiamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
UHTS	ultrahigh-throughput-screening

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