Strategies for the synthesis of 2,3-dihydrobenzofurans

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Tom Sheppard grew up in Lancashire, UK. He obtained his MSc degree from the University of Cambridge in 1999. After a year working in the pharmaceutical industry at GlaxoWellcome, he went on to obtain his PhD from the University of Cambridge in 2004, working under the supervision of Professor Steven Ley on the development of butane-2,3-diacetal desymmetrised glycolic acid. He then carried out postdoctoral research with Professor William Motherwell at University College London, working on new methods for cyclopropane synthesis and novel multi-component reactions. In 2007, he was awarded an EPSRC Advanced Research Fellowship and appointed to a lectureship at University College London where his research is focussed on the development and application of novel organocatalytic and metal-catalysed reactions.

This article gives an overview of synthetic approaches to the 2,3-dihydrobenzofuran ring system with an emphasis on recently developed methods. The synthetic approaches are classified according to the key bond(s) formed during the construction of the dihydrobenzofuran skeleton, and approaches of relevance to the synthesis of natural products are highlighted.

Keywords: dihydrobenzofurans, natural products, heterocycles, cyclisation, catalysis

1 Introduction

The 2,3-dihydrobenzofuran (DHB) skeleton **1** comprises a saturated 5-membered oxygen heterocycle fused to a benzene ring with the oxygen atom adjacent to the aromatic system (Fig. 1). This ring system confers a rigid shape to a molecule, with a well defined spatial arrangement of substituents in a similar manner to strained small rings such as cyclopropanes and cyclobutanes. However, the ring-strain in the DHB system is moderate, and somewhat smaller than in the corresponding dihydrofuran system **2** without the fused benzene ring.[1]

Many bioactive molecules containing the DHB structural motif have been reported including a vast array of natural products (selected examples shown in Fig. 2, **3–8**)[2–7] and numerous synthetic compounds with useful biological activity (selected examples shown in Fig. 3, **9–14**). DHB containing natural products have been reported with activity against cancer (**4–5**),[2,4,8–10] tuberculosis,[11] malaria[12] and cataracts,[13] as well as activity at specific targets such as HIF-1 (**8**),[6] α-glucosidase,[14] aldose reductase,[6] 5-LOX (**7**),[7] COX-2 (**7**),[7] NF-κβ[4] and the muscarinic M_3 receptor.[15,16,17] Other DHB natural products show antioxidant and/or cytoprotective properties[18] and insecticidal activity.[19] Figure 1 shows only a fraction of the many known DHB natural products — more than 500 DHB-containing natural products were reported in 2009–2010 alone. [A Reaxys® search of DHB containing natural products reported during this time period produced 562 substance hits. Note that this includes previously known structures (re-isolations, *etc*) as well as structurally novel natural products.]
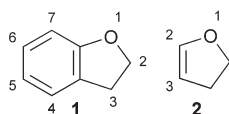

Fig. 1 The structures of 2,3-dihydrobenzofuran (DHB) and 2,3-dihydrofuran.

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It should also be noted that a DHB system forms part of the skeleton of the morphine alkaloids, although the synthesis of these more complex polycyclic systems will not be considered here.

Synthetic DHB derivatives include recently reported molecules such as the GPR4 Agonist **9**,[20] imidazolium compound **10** (cytotoxic),[21] triazole **11** (antitubercular),[22] diester **12** (active against leishmaniasis),[23] and the drugs Prucalopride **13**[24] (treatment of constipation) and Efaroxan **14** (α₂-adrenoceptor antagonist).[25]

As a consequence of the diverse biological activities displayed by these compounds, synthetic chemists have developed many effective methods for accessing the DHB skeleton. This review article will summarise the different synthetic approaches to DHBs, focusing largely on recent reports since a previous review of the field in 2009.[26] The synthetic approaches are classified according to the method by which the saturated oxygen ring is constructed.

Plausible synthetic approaches to the DHB skeleton are shown in Scheme 1. The most obvious strategy involves a classical phenol alkylation approach (**I**, O-alkyl bond formation). Alternatively, the O-aryl bond can be constructed via a transition-metal catalysed cross coupling (**II**). The direct construction of the aromatic ring itself (**III**) is an approach that has rarely been applied in DHB synthesis. In contrast, the construction of the C-aryl bond (**IV**) is a well explored approach (*e.g.* via lithation of an aryl halide). The formation of the alkyl C–C bond (**V**) is commonly achieved via transition-metal mediated carbene C–H insertion processes using diazo compounds. Finally, more complex strategies involving either the formation of two or more bonds in a single reaction (**VI**), or the rearrangement of an existing ring system (**VII**) can be employed.

2 Formation of the O-alkyl bond

The intramolecular alkylation of a phenol is perhaps the most common method for the construction of DHBs. Given that many natural products contain a hydroxyalkyl group
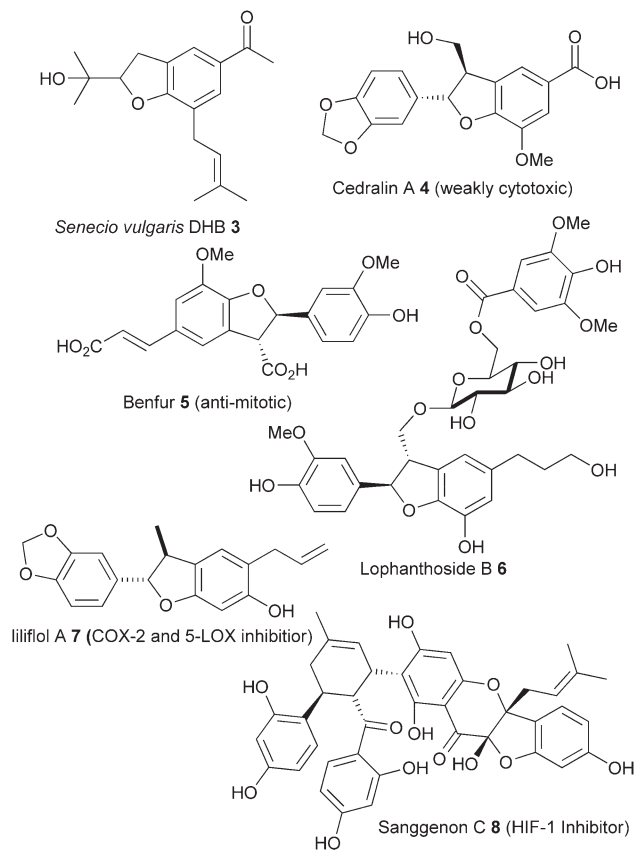
Fig. 2   Selected DHB natural products.

Senecio vulgaris DHB **3**

Cedralin A **4** (weakly cytotoxic)

Benfur **5** (anti-mitotic)

Lophanthoside B **6**

liliflol A **7 (**COX-2 and 5-LOX inhibitior)

Sanggenon C **8** (HIF-1 Inhibitor)
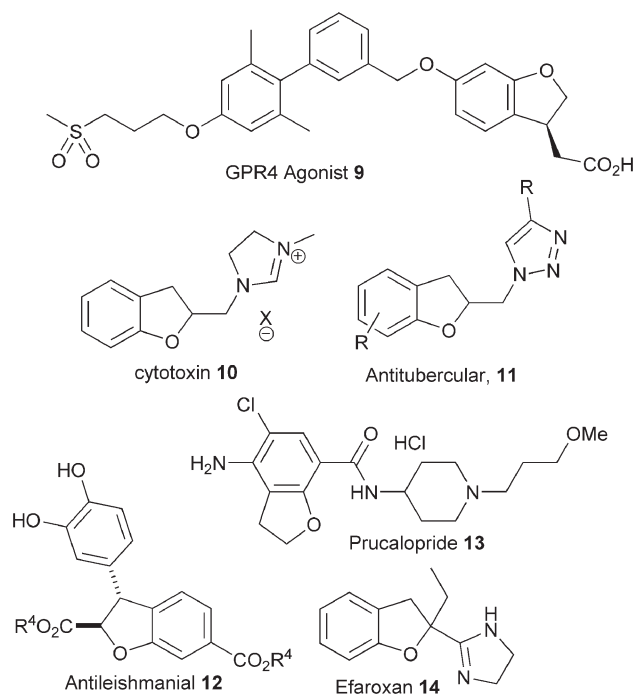
Fig. 3   Some synthetic DHBs with useful biological activity.

GPR4 Agonist **9**

cytotoxin **10**

Antitubercular, **11**

Prucalopride **13**

Antileishmanial **12**

Efaroxan **14**

joined to the ring system at C_2, the ring opening of an epoxide is a particularly useful approach and has been explored extensively in recent years. For example, the chiral ketone **15** was used to access enantioenriched epoxides **17** which gave the corresponding DHB derivatives **18** in good yield and high ee (Scheme 2), after deprotection of the phenol with
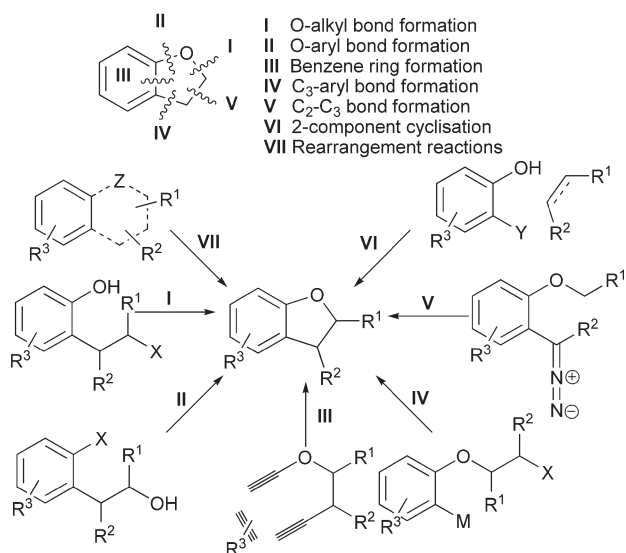

Scheme 1   Strategies for DHB synthesis.

I   O-alkyl bond formation
II   O-aryl bond formation
III   Benzene ring formation
IV C_3-aryl bond formation
V C_2-C_3 bond formation
VI   2-component cyclisation
VII   Rearrangement reactions
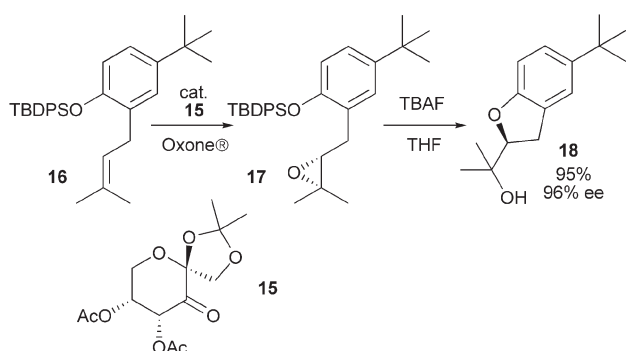
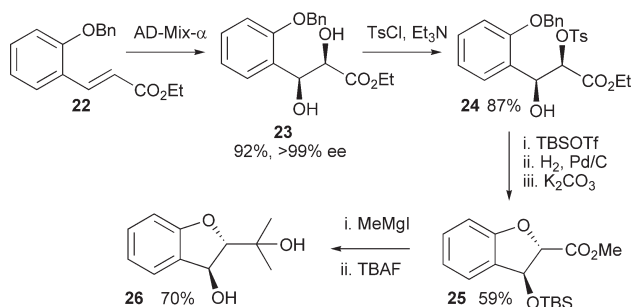**Scheme 2**   Enantioselective synthesis of DHBs using a Shi epoxidation.

fluoride.[27] This approach was used in the synthesis of the DHB containing natural product (+)-marmesin.[28]

In a similar fashion, Sharpless asymmetric epoxidation of allylic alcohols such as **19** gave enantioenriched epoxides **20** (Scheme 3). Deprotection of the phenol and cyclisation with base enabled chiral diol **21** to be synthesised in good yield.[29] This approach was used to access the core structure (**22**) of heliannuols G and H.[30]
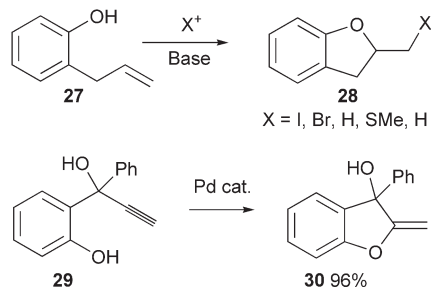
A very similar approach using a Sharpless asymmetric dihydroxylation enabled ring systems such as **25** to be synthesised, via regioselective monotosylation of the diol **23** (Scheme 4).[31] After protection of the remaining free hydroxyl group, DHB formation readily took place upon deprotection of the
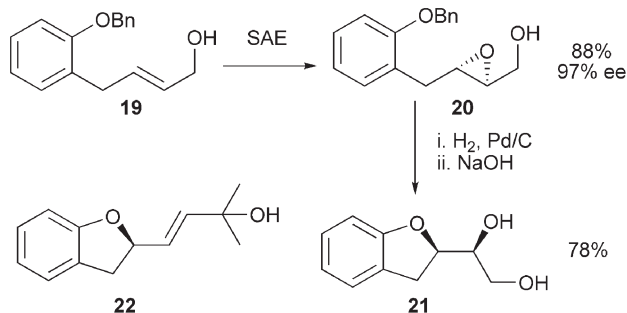
Scheme 3   Enantioselective synthesis of DHBs using a Sharpless asymmetric epoxidation (SAE).

Scheme 4 Enantioselective synthesis of DHBs using a Sharpless asymmetric dihydroxylation (AD).
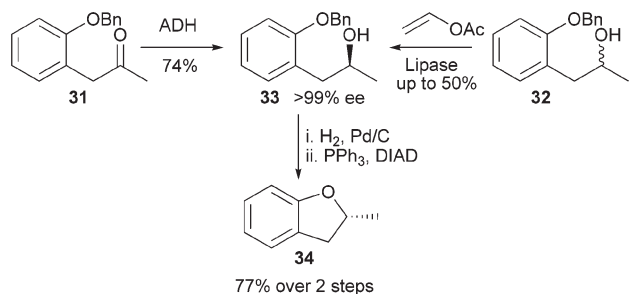

Scheme 5 Synthesis of DHBs via cyclisation of phenols onto activated C-C multiple bonds

Scheme 7 Enantioselective oxidative cyclisation of ketophenols using a chiral iodide salt.

Scheme 8 Synthesis of DHBs via an intramolecular Chan-Lam coupling strategy.

phenol and treatment with base. This approach was used to synthesise both enantiomers of the core structure **26**, present in a variety of natural products including Avicenol A[32] and Brosimacutin G.[33]
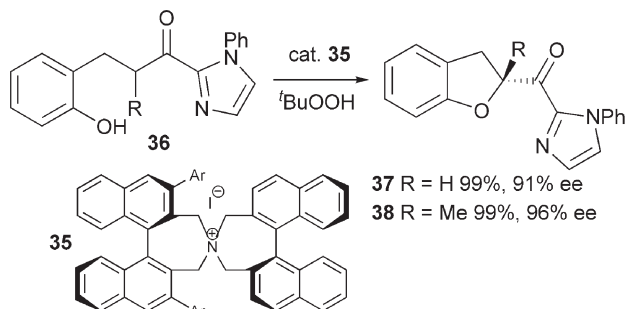
A very common strategy for constructing the DHB ring system involves the electrophile-mediated cyclisation of *o*-allylphenols (Scheme 5).[34–38] Thus, activation of *o*-allylphenol **27** with suitable electrophiles can provide access to DHBs **28** containing halogens,[38] thioethers[35] or simple alkyl groups[34,37] in the side chain. In a similar vein, Pd-mediated cyclisation of propargylic phenols **29** was shown to give access to the exocyclic alkenes **30** which are potentially useful building blocks for further elaboration.[39]

A practical biocatalytic strategy for accessing simple DHBs in high ee was recently reported (Scheme 6).[40] Two complementary methods were developed: enantioselective reduction of ketone **31** with alcohol dehydrogenase (ADH) and kinetic resolution of alcohol **32** with vinyl acetate/Lipase. In both cases the resulting enantiopure alcohols **33** were cyclised via a Mitsunobu reaction with clean inversion of stereochemistry to give the enantiopure DHB products **34**.
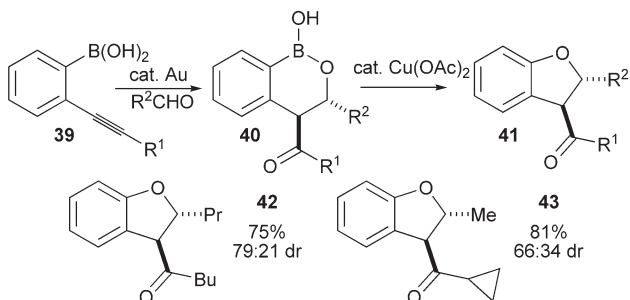
A catalytic enantioselective DHB formation was recently reported using chiral iodide **35** in the presence of ^{t}BuOOH for the oxidative cyclisation of ketophenols **36** (Scheme 7).[41]

Scheme 6 Biocatalytic synthesis of enantiopure DHBs.

A range of DHBs (*e.g.* **37**) could be prepared in excellent ee and high yield, with even 2,2-disubstituted products such as **38** being produced efficiently. The imidazole group could be cleaved to give a more synthetically useful ethyl ester without loss of ee, by treatment with MeOTf followed by ethanol and base. The authors proposed that the chiral cation of **35** directs the reaction of a phenolate anion with the ketone, which is activated by a hypervalent iodine species generated *in situ*.

3 Formation of the O-aryl bond

The intramolecular copper or palladium-catalysed coupling of an aliphatic alcohol with an aryl halide is an effective strategy to access DHB derivatives which was developed several years ago.[42–45] Surprisingly there have been few recent developments in this area, despite the high level of interest in the development of novel catalytic methods for aryl-heteroatom bond formation. An unusual approach to DHBs via a catalytic intramolecular Chan–Lam coupling reaction has recently been reported (Scheme 8).[46] *o*-Alkynlbenzeneboronic acids **39** undergo Au-catalysed enolate formation and aldol reaction to give cyclic borates **40**. These compounds can be cyclised to the corresponding 2,3-disubstituted DHBs **41** containing a pendant ketone group at C$_3$ with very good yields over this three step reaction process. It is notable that this cross-coupling reaction involves the arylation of an aliphatic alcohol and also only requires catalytic quantities of copper; both of these factors being somewhat unusual in Chan-Lam coupling reactions.[47] This approach is potentially quite versatile as variation of the groups at R[1] and R[2] can easily be achieved (*e.g.* **42**–**43**).

Yu and co-workers recently reported a Pd-mediated C–H activation protocol for the direct cyclisation of homo-benzylic alcohols **44**, which proceeds in high yield to give 2,2-disubstituted DHBs **45** (Scheme 9).[48] These reactions were much more efficient for the formation of 2,2-disubstituted DHBs (*e.g.* **46**–**47**), with the corresponding reactions of secondary alcohols proceeding in lower yield. Nevertheless, this methodology is potentially very powerful as it does not require
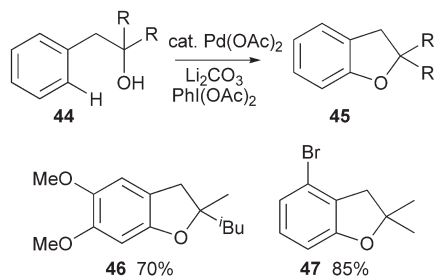
Scheme 9   Synthesis of DHBs via C-H activation of homo-benzylic alcohols.
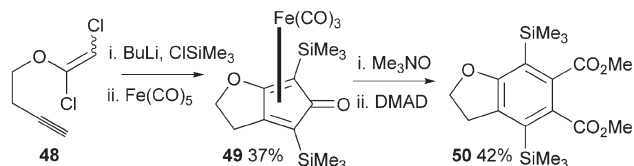
**Scheme 10**   Iron-mediated cycloaddition route to a highly substituted DHB.

pre-functionalisation of the aromatic ring. It is also compatible with the presence of aryl bromides, enabling the construction of halogenated DHBs (**47**) which can then be further elaborated via traditional transition-metal catalysed coupling reactions.

4 Formation of the aromatic ring

The direct formation of the benzene ring has rarely been used in the construction of DHBs, despite the fact that Rh-catalysed [2+2+2] cycloadditions for the formation of closely related fused benzofurans have been reported.[49] An iron-mediated approach proceeding via the Fe-complexed cyclopentadienone **49** was reported in 2001 (Scheme 10).[50] An alkynyl homo-propargyl ether, generated from the dichlorovinyl ether **48**, underwent cyclisation in the presence of iron pentacarbonyl to give **49** in moderate yield over the two steps. After oxidative decomplexation, the free cyclopentadienone system readily undergoes cycloaddition with dimethyl acetylenedicarboxyl-ate (DMAD) followed by extrusion of CO, to give the polysubstituted DHB **50** in moderate yield over two steps. This example serves to illustrate how this type of approach can be used to construct DHBs containing a highly substituted aromatic ring.

5 Formation of the aryl-C$_3$ bond

The formation of the aryl-carbon bond has been used to access a number of DHB systems. Chiral ligand **53** was pre-pared via a reaction sequence which involved the one-pot
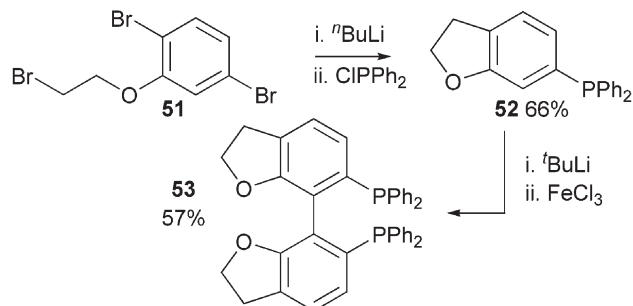
**Scheme 11**   Formation of a DHB chiral ligand via a lithiation strategy.
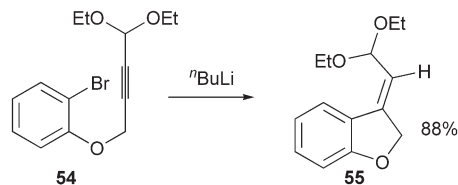
**Scheme 12**   A *trans*-selective intramolecular carbolithiation.

double lithiation/cyclisation/phosphination of tribromide **51** (Scheme 11).[51] The DHB phosphine **52** was obtained in 66% yield and was then dimerised to give the racemic bidendate ligand **53** which was subsequently resolved by HPLC. Although enantioselective reactions of ligand **53** were not reported, more recently a different DHB-containing phosphine has been employed in enantioselective Pd-catalysed [3+2] cycloaddition reactions.[52]

Bromoarylalkynes such as **54** were shown to selectively undergo *trans* carbolithiation upon treatment with [n]BuLi (Scheme 12).[53] The resulting alkenes **55** are potentially useful compounds for further elaboration.

One obvious approach to the construction of the aryl-C$_3$ bond is to employ a Heck reaction to cyclise an allylic ether of an *o*-halophenol (Scheme 13). This provides a product with an unsaturated side chain at C$_3$ which can be exploited in further reactions. For example, Heck reaction of aryliodides **56** containing a pendant chiral allylic ether (prepared by asymmetric reduction of a cyclohexenone) was shown to give DHBs fused to a cyclohexene ring **57**, with predominantly *cis* stereochem-istry.[54] Carbonylative Heck cyclisation of aryldiazonium salts **58** onto pendant alkenes was shown to give DHBs **59** contain-ing a carboxylic acid group on the C$_3$ side chain in moderate yield.[55] Using aryl bromide **60**, a series of Pd-catalysed tandem cyclisation/coupling reactions were investigated.[56] For example, tandem cyclisation/Stille coupling yielded 3,3-disubstituted DHB **61** in good yield in the presence of 1,3-dimethyl-1,2-imidazolidinone (DMI). Tandem Suzuki coupling reactions with a range of aryl boronic acids were also successful, and these reactions could even be combined with the preparation of **60** *in situ* by alkylation of the parent phenol. Very recently, a potentially useful procedure for Heck cyclisa-tion and concomitant cyanation was reported.[57] Treatment of
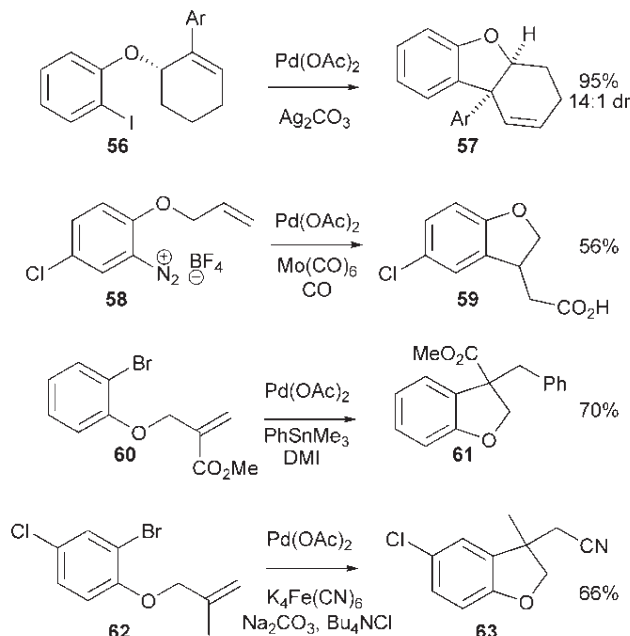
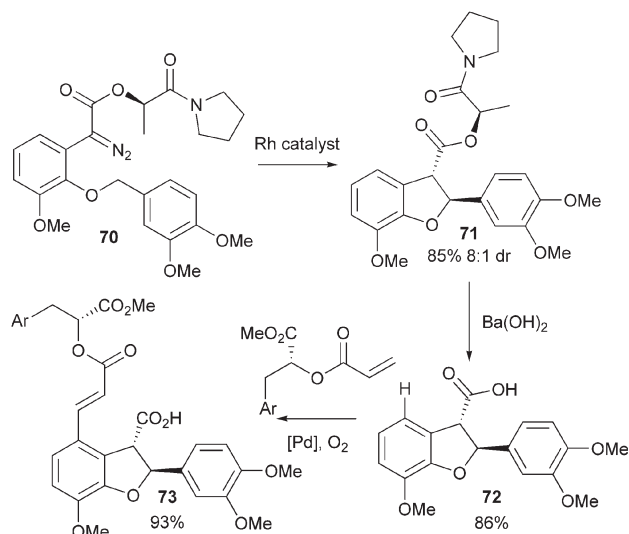**Scheme 13**   Synthesis of DHBs via Heck reaction.
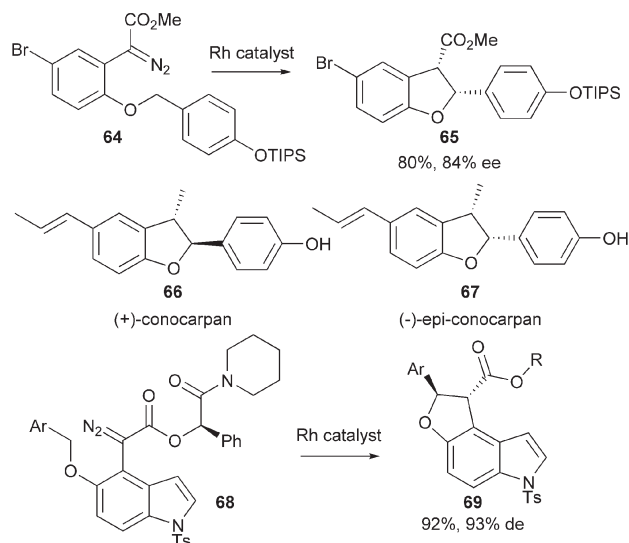
Scheme 14 Total synthesis of DHB natural products using Rh-catalysed carbene insertion.

Scheme 16 Organocatalytic asymmetric formation of *cis*-2,3-disubstituted DHBs.

6 Formation of the alkyl C_2–C_3 bond

Surprisingly, one of the most common approaches to the synthesis of DHBs has been the formation of the alkyl C_2–C_3 bond. The most widely used approach exploits the asymmetric carbene C–H insertion reactions originally developed by Davies.[58–60] These reactions proceed with high stereoselectivity and through the use of chiral ligands and/or a chiral auxiliary,[61] highly enantioselective reactions are possible. For example, diazo compound **64** cyclised efficiently to give **65** in high ee and with good yield in the presence of a Rh catalyst (Scheme 14).[62] This reaction was used in the synthesis of conocarpan **66**[63] and *epi*-cococarpon **67**.[64] Similarly, the Rh-catalysed asymmetric C-H insertion reaction of **68** was used to construct the DHB core (**69**) of Serotobenine.[65, 66]

In a recent example, Yu employed a chiral auxiliary directed carbene insertion reaction to construct **71** containing the DHB

methallyl ether **62** with palladium acetate in the presence of $K_4Fe(CN)_6$ as a cyanide source led to the formation of a 3,3-disubstituted DHB **63** containing a cyanomethyl substituent at C_3 in moderate yield.
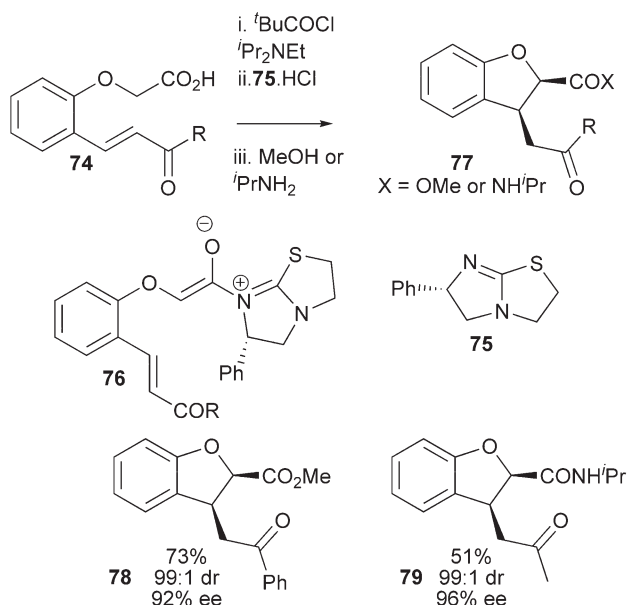
skeleton of Lithospermic acid **73** (Scheme 15).[67] This was then followed by a late-stage Pd-catalysed carboxylate-directed C-H alkenylation reaction to introduce the complete side chain of the natural product at the final stage.
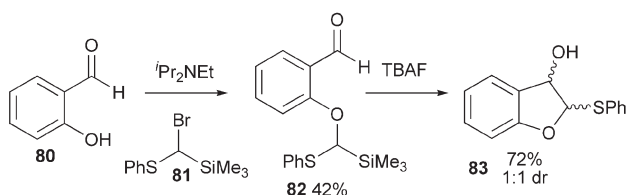
An alternative strategy for C_2–C_3 bond formation is the asymmetric organocatalytic cyclisation of carboxyenones **74** (Scheme 16).[68] Generation of the mixed anhydride from the acid **74**, followed by reaction with the catalyst **75** leads to ammonium enolate intermediate **76**, which cyclises via reaction with the pendant Michael acceptor. These reactions proceed with high diastereoselectivity and excellent enantioselectivity to give the corresponding *cis* 2,3-disubstituted DHBs **77** in good to excellent yield. This provides a useful asymmetric method for accessing *cis*-subsituted DHB systems (*e.g.* **78**–**79**) which can be difficult to obtain via many other approaches.

The formation of the C_2–C_3 bond by generation of an anion on the carbon adjacent to the oxygen atom is an unusual alternative strategy. This was accomplished by reaction of phenol **80** with **81** to give α-silylthioether **82**, which could be cyclised in the presence of fluoride to give a mixture of diastereoisomers of the 2,3-disubtituted DHB **83** in good yield (Scheme 17).[69]
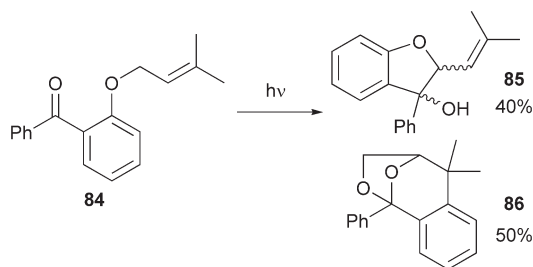
The C_2–C_3 bond has also been constructed photochemically. Benzophenone **84**, bearing a prenyl ether subsituent was shown to cyclise under irradiation to give DHB **85** in 40% yield as a mixture of diastereoisomers (Scheme 18).[70] However, the major product of this reaction was acetal **86**.
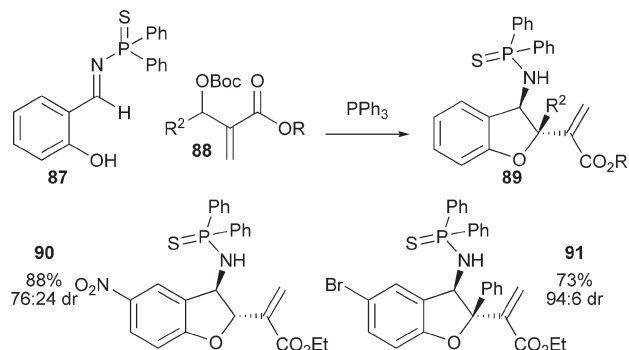
7 Two-component cyclisation approaches

Concerted cyclisation approaches in which two bonds are formed in the same reaction are highly attractive, as subsitutents can readily be varied at many different locations on

Scheme 15 Total synthesis of Lithospermic acid via carbene insertion and late-stage C-H activation.

Scheme 17 Fluoride-mediated carbanion cyclisation.

Scheme 18   Photochemical cyclisation approach to a DHB.

Scheme 21   One-pot diazotization/Pd-catalysed cyclisation of 2-aminophenols.

Scheme 19   Phosphine-catalysed reaction of iminophenols with O-Boc Bayliss-Hilman adducts.

Scheme 22   Biomimetic oxidative dimerisation of a caffeic acid ester with AgO.

cinerins A-C, lignans isolated from *Pleurothyrium cinereum* which show platelet activating factor (PAF) antagonist activity.[74]

The oxidative dimerisation of caffeic acid esters **102** with silver(I) oxide has been applied to the synthesis of *trans*-DHBs **103** in a biomimetic fashion in several reports (Scheme 22).[23,75–77] Oxidative coupling of the same substrates with Mn salts did not give DHBs, with benzoxanthenes and aryldihydronaphthalenes being produced.[78] This reaction has also been achieved biocatalytically. In a very recent example, the oxidative dimerisation of related esters using crude peroxidase derived from onions has been reported, although the resulting products had no optical rotation.[78]

Arylmethyl cyclopropyl ketones **104** were shown to undergo ring-opening and condensation with ethyl acetoacetate **105** in the presence of trimethysilyl triflate to give DHBs **106** in moderate yield (Scheme 23).[79] The reaction is thought to proceed via ring opening of the cyclopropyl ketone to give a γ-hydroxyketone **107**, which undergoes aldol condensation with **105** to give **108**, followed by a second condensation to give **109**, and finally cyclisation and condensation of the pendant hydroxyl group to give the DHB **106**. Notably this involves the synthesis of both the benzene ring and the oxygen heterocycle in the same reaction.

Quinones and their derivatives have frequently been employed in DHB synthesis (Scheme 24). In a recent example, the reaction of quinone mono imine **110** with α,β-unsaturated hydrazone **111** was reported to give 2,2-disubstituted DHB **112** in 90% yield.[80] This compound was subsequently employed in a total synthesis of the α₂-adrenergic receptor antagonist Efaroxan **14**, and a range of related amino derivatives. The
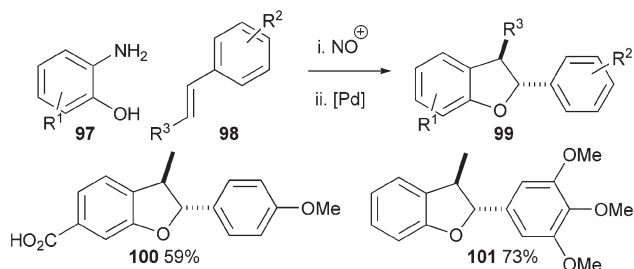
the DHB ring system by changing the two components employed in the reaction. One such approach is the reaction of iminophenols **87** with carbonates **88** in the presence of a phosphine catalyst, to give the 3-amino DHBs **89** with good yield and moderate to high stereoselectivity (Scheme 19).[71] DHBs with two (**90**) or three (**91**) substituents on the oxygen heterocycle could be obtained.

An improved procedure was recently reported for the Pd-catalysed reaction of 2-iodophenyl acetates **92** with dienes **93** to give DHBs **94** (Scheme 20).[72] A range of 2,2-disubstituted DHBs (*e.g.* **95**) could be accessed in good yield, although the effect of substituents at all positions on the diene was not investigated simultaneously. Only two examples were reported in which more than one diastereoisomer can be formed, though these products were formed with high *trans* diastereoselectivity (*e.g.* **96**).
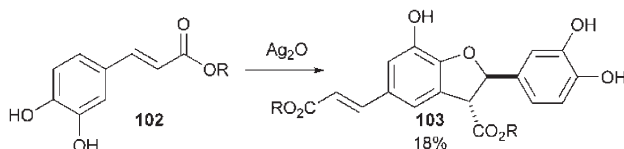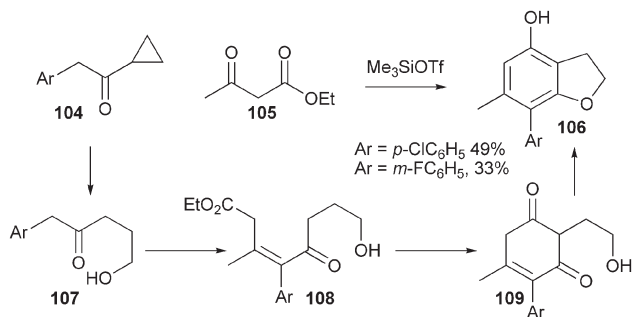
In a related approach, aminophenols **97** were converted directly into *trans*-2,3-disubstituted DHBs **99** in a one-pot process (Scheme 21).[73] Diazotisation of the aniline was followed by treatment with a palladium catalyst in the presence of a β-substituted styrene **98** to give DHBs **99**. A range of electron rich styrenes **98** were used to access a variety of 2,3-disubstituted DHBs (*e.g.* **100–101**). This approach was used to construct a DHB intermediate in the synthesis of

Scheme 20   Pd-catalysed reaction of *ortho*-iodophenyl acetates with dienes.

Scheme 23   A Me₃SiOTf-mediated formation of DHBs from ethyl acetoacetate and arylmethyl cyclopropyl ketones.
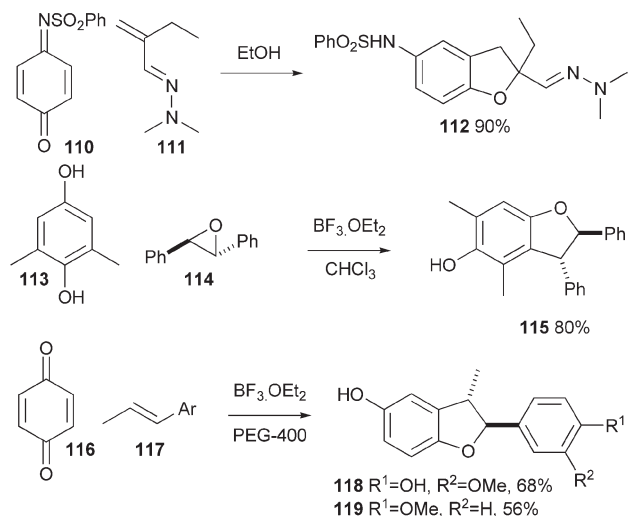
Scheme 24 Use of quinone derivatives in DHB synthesis.
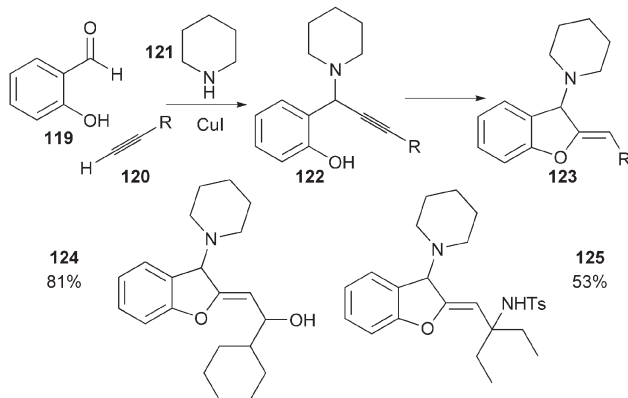
Scheme 25 3-component reaction of piperidine, salicylaldehyde and an alkyne in the presence of CuI.

Scheme 26 Photochemical synthesis of the antimalarial DHB Decursivine.

Scheme 27 Au-catalysed rearrangement of furans bearing an alkynyl ether.

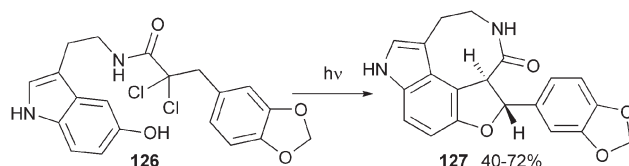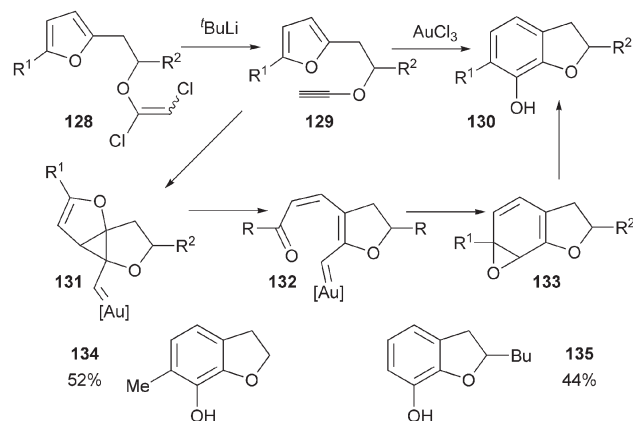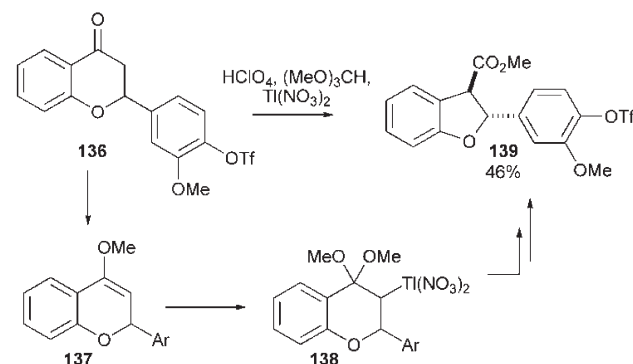previous syntheses of the related natural product Serotobinine (Scheme 14).

8 Rearrangement reactions

DHB systems have occasionally been synthesised by rearrangement of other ring systems. This can provide a method to construct DHBs with unusual substitution patterns which may not be readily accessible by other means. For example, furans bearing a pendant alkynyl ether substituent **129** were shown to undergo rearrangement in the presence of catalytic AuCl₃ to give 2,6,7-trisubsituted DHBs **130** (Scheme 27).[86] The reaction is thought to proceed via formation of the tricyclic cyclopropane **131**, which undergoes ring opening and then re-cyclisation to the benzene epoxide **133**. Rearrangement of this intermediate then gives the polysubstituted DHB **130** in moderate yield over two steps from the dichlorovinyl ether **128**.

A Tl(NO₃)₃ mediated ring contraction[87] of **136**, was recently employed in a synthesis of the proposed Lawsonicin skeleton, during a study which led to a revision of the original structural assignment of the natural product (Scheme 28).[88] The reaction

reaction of hydroquinone **113** with stilbene oxide **114** was reported to proceed well in the presence of BF₃.OEt₂, giving polysubstituted DHB **115** in good yield.[81] This reaction was initially observed during the development of a method for benzofuran synthesis using the corresponding quinones. In a similar reaction, quinone **116** was reported to react with β-methylstyrenes **117** using catalytic BF₃.OEt₂ in PEG-400 to give DHBs **118**–**119** in moderate yield.[82]

The copper or silver catalysed 3-component coupling of salicylaldehydes **119**, alkynes **120** and piperidine **121** was found to give 3-amino DHBs **123** in good yield.[83] The reaction proceeds via initial formation of propargylic amine **122**. Metal-catalysed cyclisation of the phenol onto the alkyne then takes place to give exclusively the Z-alkene, provided there is a heteroatom in the R-group on the alkyne (*e.g.* **124**–**125**). The heteroatom was thought to be required in order to assist the transition-metal activation of the alkyne for cyclisation. Substrates which do not contain a heteroatom on the R group are able to undergo the initial reaction to give **122**, but do not cyclise to the DHB.

Recently, two research groups have simultaneously reported an elegant approach to the antimalarial natural product Decursivine **127**, via photochemical rearrangement of dichloroamide **126** (Scheme 26).[84, 85] The reaction leads to diastereoselective formation of the fused lactam-DHB core of the natural product in a single photochemical reaction in moderate to good yield. This synthetic approach is considerably more concise than

Scheme 28 Tl(NO₃)₃-mediated ring-contraction to generate a DHB.

Scheme 29   Ring contraction of a 3-aminodihydrobenzopyran with BBr₃.

is thought to involve acid-catalysed formation of the enol ether **137**, which reacts with the thallium salt and then undergoes a ring-contraction of intermediate **138** to give **139** via aryl migration with concomitant reduction of the thallium from Tl(III) to Tl(I).

In the presence of Lewis acids, 3-aminodihydrobenzopyrans **140** were recently reported to rearrange to the corresponding 2-aminomethyl DHBs **141** (Scheme 29).[89] In a brief study, boron tribromide was found to be the most effective Lewis acid for inducing this transformation.

As can be seen from this article, there have been numerous recent developments in the chemical synthesis of DHBs, many of which provide excellent control over the relative or absolute stereochemistry of substituents on the saturated oxygen heterocycle. It should be noted that most of the synthetic strategies outlined above enable DHBs to be constructed via short reaction sequences from readily available starting materials. Such methods enable the synthesis of even very highly complex DHB systems to be readily achieved, with excellent scope for structural variation on the DHB scaffold. The diverse biological activities exhibited by both synthetic and naturally occurring DHBs suggest that they have great potential as lead compounds in the study of biological processes and the treatment of disease. It is hoped that this article, by providing a general overview of the synthetic strategies available, will serve to stimulate greater interest in the study of DHBs in medicinal chemistry, and further improvement of the synthetic strategies available for constructing them.

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