A Concise Route to Dihydrobenzo[*b*]furans: Formal Total Synthesis Of (+)-Lithospermic Acid

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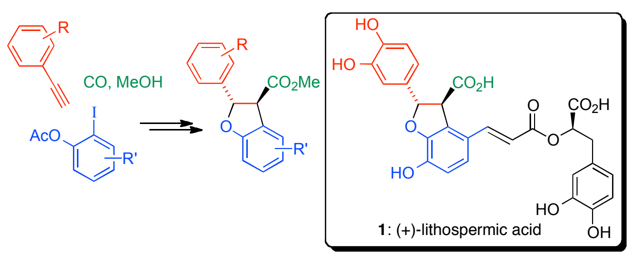
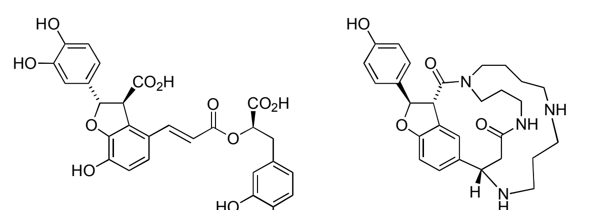
ABSTRACT



A sequence of Sonogashira coupling, Pd(II)-catalyzed carbonylative annulation and benzofuran reduction (Mg, MeOH, NH_4Cl) provides a convergent and modular synthetic route to *trans*-2-aryl-2,3-dihydrobenzo[*b*]furan-3-carboxylates, which are a common structural feature of a number of biologically active natural products. This versatile strategy has been applied to the formal total synthesis of the anti-HIV natural product (+)-lithospermic acid.

2-Aryl-2,3-dihydrobenzo[*b*]furans are a common structural feature of numerous natural products (e.g. **1**–**2**, Figure 1) exhibiting wide-ranging bioactivities, including antimitotic[1], antiangiogenic[2] antioxidant,[3] antimicrobial,[4] and neuritogenic[5] activities. The majority of natural products isolated with this skeleton are 2,3-*trans* configured,[6] with many that were initially assigned as *cis*-configured having their relative stereochemistry revised.[7]

Figure 1. Representative dihydrobenzo[*b*]furan natural products



1: (+)-lithospermic acid **2**: (-)-ephedradine A

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[1] Pieters, L.; Van Dyck, S.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemière, G. *J. Med. Chem.* **1999,** 42, 5475-81.
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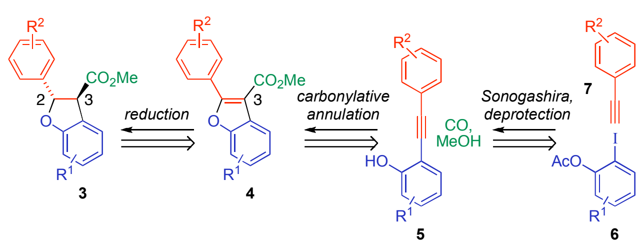
Considerable effort has been devoted to the synthesis of 2-aryl-2,3-dihydrobenzo[*b*]furans. Strategies employed for the diastereoselective synthesis of these systems[8] include the biomimetic oxidation of phenylpropenes, the Schmidt rearrangement, the rearrangement of chalcone epoxides and acid catalysed [3+2] cycloadditions of phenylpropenes with quinones.[Error! Bookmark not defined.] Enantioselective syntheses have also been achieved via Rh(II)-catalyzed intramolecular C–H insertions,[9,10] with this approach affording a predominance of the *cis*-2,3-dihydrobenzo[*b*]furan.

The closely related 2,3-disubstituted benzo[*b*]furans have attracted extensive synthetic interest and also exhibit a broad range of biological activities.[11] Among available strategies for the synthesis of benzo[*b*]furans, palladium-catalyzed cyclizations are particularly attractive, allowing for the simultaneous installation of a carbonyl substituent at C3, to give the 2,3-disubstituted systems.[12] Our synthetic approach would provide access to both 2-arylbenzo[*b*]furan and 2-aryl-2,3-dihydrobenzo[*b*]furan-containing natural products and analogues. Key to the success of the approach was developing a method to reduce the benzo[*b*]furan system to the corresponding *trans*-2,3-dihydrobenzo[*b*]furan. The retrosynthetic strategy depicted in Scheme 1 highlights the concise and highly modular approach we proposed to access this class of compounds.

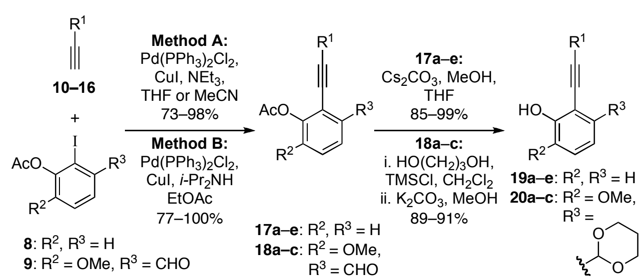
Scheme 1. Retrosynthetic Analysis of 2-aryl-2,3-dihydobenzo[*b*]furans-3-carboxylates (**3**)



We envisaged that dihydrobenzofuran **3** would be formed by stereoselective reduction of benzofuran **4**, which would be derived from *ortho*-hydroxydiarylalkyne **5**, using a carbonylative annulation reaction. *ortho*-Hydroxydiarylalkyne **5** would be derived from the Sonogashira coupling of protected aryl iodide **6** and arylalkyne **7**. Initial investigations focused on the development of this route, using aryl iodides (**8**, **9**) and a range of terminal alkynes (**10–16**). Subsequently, the utility of this method was demonstrated through the formal total synthesis of the anti-HIV natural product (+)-lithospermic acid (**1**).

The required diarylalkyne substrates were synthesised by Sonogashira coupling of aryl iodide **8**[13] with arylalkynes **10–14**,[14] and aryl iodide **9**[15] with arylalkynes **14–16** (Table 1). Traditional coupling conditions were well-suited for generating diarylalkynes **17a–e** (Method A), however yields of **18b** and **18c** were improved by using the conditions of Andrus *et al*.[16] (Method B). De-acetylation of **17a–e** was hampered by a competing side-reaction that produced unwanted protio-cyclized benzofurans, which lacked the carbomethoxy functionality at the 3-position. Through the use of Cs_2CO_3 in MeOH–THF at 0 °C, *ortho*-hydroxydiarylalkynes **19a–e** were afforded in good yield with no appreciable protio-cyclization.

Table 1. Synthesis of *ortho*-hydroxydiarylalkynes



entry	ArI	alkyne	R^1	product (yield, %)	product (yield, %)
1	**8**	**10**	Ph	**17a**[a] (98)	**19a** (99)
2	**8**	**11**	2-Np	**17b**[a] (68)	**19b** (98)
3	**8**	**12**	3,4,5-$(MeO)_3C_6H_2$	**17c**[a] (84)	**19c** (87)
4	**8**	**13**	3,5-$(MeO)_2C_6H_3$	**17d**[a] (77)	**19d** (95)
5	**8**	**14**	4-$(MeO)C_6H_4$	**17e**[a] (73)	**19e** (85)
6	**9**	**14**	4-$(MeO)C_6H_4$	**18a**[a] (100)	**20a** (89)
7	**9**	**15**	3,4-$(OCH_2O)C_6H_3$	**18b**[b] (97)	**20b**[c] (94)
8	**9**	**16**	TIPS	**18c**[b] (77)	**20c** (89)

[a] Method A. [b] Method B. [c] The intermediate acetal was purified and then deacetylated using Cs_2CO_3 in MeOH–THF.

At this stage it was necessary, in the case of benzaldehydes **18a–c** (Table 1), to protect the aldehyde

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[15] See supporting information for the acetate protection of 2-iodoisovanillin, which was prepared according to Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. J.; Shams, G.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992**, *35*, 466–479.

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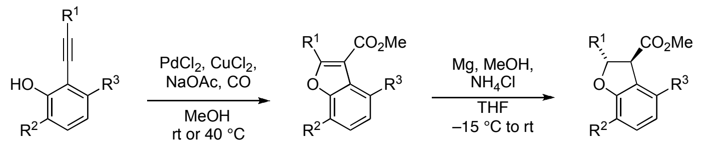
Table 2. Carbonylative Annulation and Mg-mediated benzofuran reduction



19a–e **20a–c** | **21a–e** **22a–c** | **23a–e** **24a–b**

entry	substrate	R[1]	R[2]	R[3]	product (yield, %)		product (yield, %)[a]		*trans*:*cis*[b]
1	**19a**	Ph	H	H	**21a**	(69)	**23a**	(84)[c]	94:6
2	**19b**	2-Np	H	H	**21b**	(86)	**23b**	(36)[d]	85:15
3	**19c**	3,4,5-$(MeO)_3C_6H_2$	H	H	**21c**	(80)	**23c**	(79)	95:5
4	**19d**	3,5-$(MeO)_2C_6H_3$	H	H	**21d**	(87)	**23d**	(66)[e]	91:9
5	**19e**	4-$(MeO)C_6H_4$	H	H	**21e**	(77)	**23e**	(85)	95:5
6	**20a**	4-$(MeO)C_6H_4$	MeO	1,3-dioxan-2-yl	**22a**	(55)[f]	**24a**[g]	(74)	81:19
7	**20b**	3,4-$(OCH_2O)C_6H_3$	MeO	1,3-dioxan-2-yl	**22b**	(75)[h]	**24b**[g]	(86)[i]	71:29
8	**20c**	TIPS	MeO	1,3-dioxan-2-yl	**22c**	(0)[j]	–	–	–

[a] Isolated yield of the *trans*-isomer. [b] Determined by ^{1}H NMR of crude isolate. [c] By-product isolated, R[1] = cyclohex-2-enyl (6%). [d] By-products isolated, R[1] = 1,2-dihydronaphthalen-2-yl (38%); R[1] = 1,2,3,4-tetrahydronaphthalen-2-yl (24%). [e] Reduction by-product isolated, R[1] = 3,5-dimethoxycyclohexa-2,5-dienyl (15%). [f] Accompanied by 8% of the trans-acetalised benzofuran product, analogous to **22a** where R[3]=$CH(OMe)_2$. [g] Aqueous acid workup led to acetal hydrolysis, providing the benzaldehyde (R[3]=CHO) directly. [h] Accompanied by *ca*. 10% of the dimethyl acetal, where R[3]=$CH(OMe)_2$. [i] Combined yield of *cis* and *trans*. [j] Trans-acetalised starting material isolated, analogous to **20c** where R[3]=$CH(OMe)_2$.

functionality in preparation for the carbonylative annulation and subsequent reduction step. Thus, benzaldehydes **18a–c** were subjected to a one-pot procedure that included protection of the aldehyde as the corresponding cyclic acetal, followed by *in situ* methanolysis of the acetate, to reveal the *ortho*-hydroxydiarylalkynes **20a–c**.

The carbonylative annulation conditions of Kondo[12a] and Scammells[12b] were found to be well-suited to our systems (Table 2). Applying these conditions to *ortho*-hydroxydiarylalkynes **19a–e** and **20a–c**, moderate to excellent benzofuran product yields were achieved for all but **20c** (entry 8, Table 2). Reaction rates were enhanced by heating to 40 °C, however, this had a detrimental effect on the yield of **22a–b**, so these reactions were conducted at rt. Interestingly, methyl acetal by-products, resulting from trans-acetalization, were observed in the cases of 1,3-dioxane substrates **20a–c**.[17]

Synthetic methods for reducing 2-arylbenzo[*b*]furan-3-carboxylates to the corresponding 2-aryl-2,3-dihydrobenzo[*b*]furan-3-carboxylate are scarce. Juhász *et al*.[18b] employed catalytic hydrogenation over Pd/C in methanol to reduce methyl 2-phenylbenzo[*b*]furan-3-carboxylate to the corresponding *cis*-2,3-dihydrobenzo[*b*]furan in a low 11% yield. Whilst catalytic reduction of simpler benzofuran systems has provided *cis*-dihyrobenzofurans,[7] to the best of our knowlegdge, no methods for the reduction of 2,3-disubstituted benzo[*b*]furans to the *trans*-dihydrobenzofuran have been reported. Common reduction conditions (e.g. H_2/Pd-C,[18] chiral “CuH”,[19] TFA/Et_3SiH[20]) applied to more complex benzofurans of type **21** and **22**, showed that none of these conditions were suitable for our systems: either recovered starting material or complex mixtures of products were obtained. Our investigations concentrated on using magnesium in MeOH to effect this reduction. Chemoselective reduction of α,β-unsaturated esters has been reported to proceed under these conditions even in systems in which the double bond is part of an aromatic system.[21] Our substrates provided a considerable challenge, requiring chemoselective reduction of a tetrasubstituted double bond within an aromatic system. Early attempts at the Mg–MeOH reduction proved low yielding and highly capricious, apparently due to low and variable activity of the magnesium and the low solubility of our substrates in MeOH. The addition of THF as a co-solvent alleviated solubility issues, but also resulted in markedly less active magnesium. Attempts to activate the magnesium surface by stirring vigorously (both neat and in solution), by addition of I_2 or 1,2-dibromoethane, or by prior treatment with dilute acid all proved inadequate or capricious. The introduction of NH_4Cl to the reaction mixture as an agent

[17] The methyl acetal counterparts could be separated by column chromatography, or carried on as a mixture with the 1,3-dioxane to the subsequent step.

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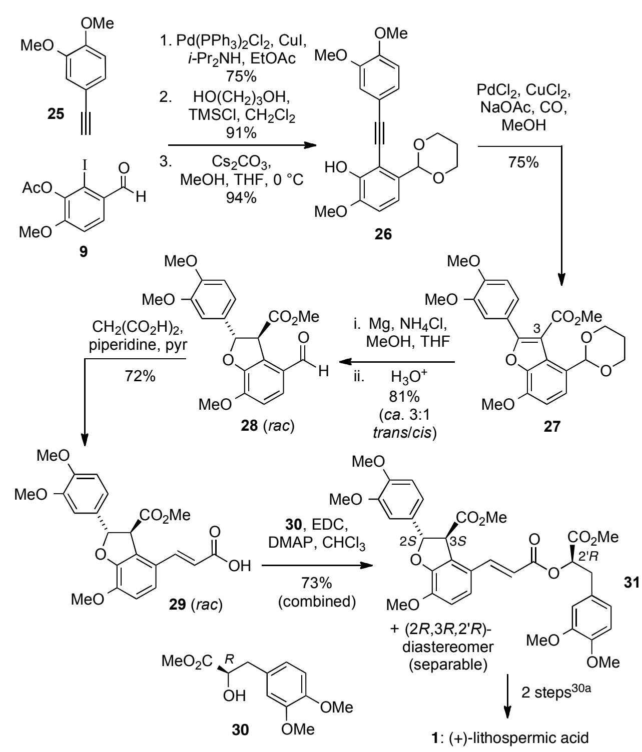
for Mg activation ,[22] was crucial to obtaining reproducible results and, gratifyingly, enabled the use of THF as co-solvent without deleterious effects on reaction rate and yield. Pleasingly, these conditions proved amenable to all the benzofuran substrates (Table 2) in our investigation. The reduction reactions were observed to initially proceed with some degree of diastereoselectivity for the *cis*-isomers, which then undergo magnesium methoxide promoted epimerisation to the more thermodynamically stable *trans*-isomers, **23a–e** and **24a–b**.[23] Partial reduction of the pendant R^1 aryl group was observed to compete with the desired 2,3-reduction in some substrates (Table 2, entries 1–2, 4). However, these unwanted reductions could be minimised by lowering the reaction temperature from rt to –15 °C. To obtain optimal yields of the *trans* diastereomer the reaction mixture was decanted from excess Mg when reduction was complete, allowing the magnesium methoxide reaction mixture to warm to rt, whereupon epimerization to the predominantly *trans*-isomer resulted. The protected aldehyde in **22a–b**, was unmasked by aqueous acid workup to afford the aldehyde products **24a–b** directly.

Having demonstrated the carbonylative annulation–reduction procedure to be a powerful, modular strategy for the synthesis of methyl 2-aryl-2,3-dihydrobenzo[*b*]furan-3-carboxylates, we sought to further highlight the versatility of this approach through the synthesis of lithospermic acid (**1**). (+)-Lithospermic acid (**1**) was first isolated from *Lithospermum ruderale* in 1963[24] and its structure elucidated in 1975.[25] (+)-Lithospermic acid (**1**) has also been isolated from *Salvia miltiorrhiza* (Danshen), a popular herb in traditional Chinese medicine,[26] and from many other sources.[27] It was not until 2002 that it was found to be a potent HIV integrase inhibitor.[28] Importantly, **1** was devoid of the collateral toxicity that plagued many other integrase inhibitors, rendering it an interesting lead compound. Previous approaches to the synthesis of **1** include the HBr-promoted cyclization used by Raths and co-workers, resulting in the synthesis of racemic heptamethyl lithospermate,[29] and the C–H bond activation strategies used by Bergman, Ellman and co-workers, and also by Yu and co-workers for the first total syntheses of (+)-lithospermic acid.[30]

Sonogashira coupling of aryl iodide **9** and arylalkyne **25**,[31] proceeded in 75% yield (Scheme 2). Sonogashira coupling, followed by protection of the aldehyde and removal of the acetate using Cs_2CO_3 in MeOH–THF, gave the *ortho*-hydroxydiarylalkyne **26**. Subjecting **26** to carbonylative annulation generated the desired tetrasubstituted benzofuran **27** in good yield. The previously developed conditions proved well-suited for reducing **27** to give the desired 2,3-dihydrobenzo[*b*]furan **28** (81%, *ca.* 3:1 *trans*:*cis*), following an acidic workup to remove the cyclic acetal protecting group. Knövenagel condensation of aldehyde **28** with malonic acid, and concomitant epimerisation, gave cinnamic acid **29** (*ca.* 6:1 2,3-*trans*:2,3-*cis*), which was subsequently coupled with known alcohol **30**[30a] to afford (2*S*,3*S*,2'*R*)-**31** and the corresponding (2*R*,3*R*,2'*R*)-diastereomer. The diastereomeric pair were separable by HPLC, providing diasteromerically pure **31**. All spectroscopic data obtained matched that reported by Bergman, Ellman and co-workers.[30a]

Scheme 2. Synthesis of (+)-Heptamethyl Lithospermate (**31**)



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[23] Notably, the J_{H2-H3} values were not a useful diagnostic tool for distinguishing the *cis* and *trans* isomers in these systems. Instead, the anisotropic effect of the C-2 aryl group causes chemical shifts of 3-C$\underline{H}$ and $CO_2C\underline{H}_3$ which are diagnostic for *cis* versus *trans* isomers (Refs. 7, 9 and 18b). Thus, the *trans* compound displayed an upfield 3-C$\underline{H}$ resonance, compared to the *cis* isomer.

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The two-step conversion of **31** to **1**, involving ester hydrolysis followed by global demethylation, has been reported,[30a] and hence the synthesis of (+)-heptamethyl lithospermate (**31**) by the sequence presented here constitutes a formal total synthesis of (+)-lithospermic acid (**1**).

We have demonstrated a versatile, modular synthetic approach to 2-aryl-2,3-dihydrobenzo[*b*]furans via Mg-mediated reduction of benzo[*b*]furans, and demonstrated its use in natural product synthesis with a synthesis of (+)-heptamethyl lithospermate (**31**) in 7 steps and in 8.4% overall yield from **9**, constituting a formal total synthesis of the anti-HIV natural product (+)-lithospermic acid (**1**).

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Supporting Information Available: Experimental procedures, product characterisation data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.