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

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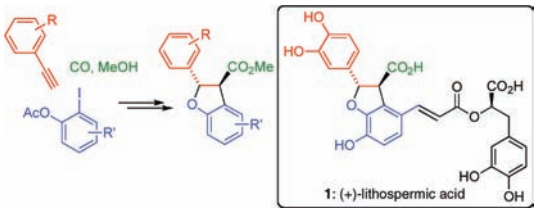
ABSTRACT



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 structural feature of numerous biologically active natural products. This versatile strategy was 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 bioactivities, such as antimitotic,[1] antiangiogenic,[2] antioxidant,[3] antimicrobial,[4] and neuritogenic.[5] Most natural products with this skeleton are 2,3-*trans* configured,[6] with many that were initially assigned as *cis*-configured having their relative stereochemistry revised.[7]

Considerable effort has been devoted to the synthesis of 2-aryl-2,3-dihydrobenzo[*b*]furans. Strategies employed for

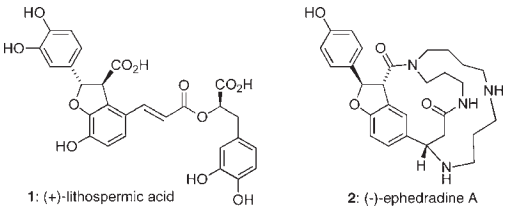


Figure 1. Representative dihydrobenzo[*b*]furan natural products.

the diastereoselective synthesis of these systems[8] include the biomimetic oxidation of phenylpropenes, the Schmidt rearrangement, the rearrangement of chalcone epoxides, and acid catalyzed [3 + 2] cycloadditions of phenylpropenes with quinones.[6] 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.

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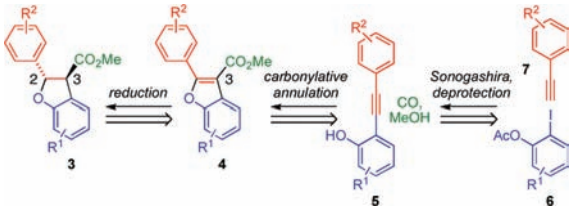
The closely related 2,3-disubstituted benzo[*b*]furans have attracted extensive synthetic interest and also exhibit a broad range of biological activities.[11] Among synthetic strategies for benzo[*b*]furans, Pd-catalyzed cyclizations are particularly attractive, allowing for the simultaneous installation of a carbonyl substituent at C3, to give the 2,3-disubstituted systems.[12] Our 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 its success was developing a method to reduce the benzo-[*b*]furan system to the corresponding *trans*-2,3-dihydrobenzo[*b*]furan. The retrosynthetic strategy (Scheme 1) highlights the concise and highly modular approach we proposed to access these compounds.

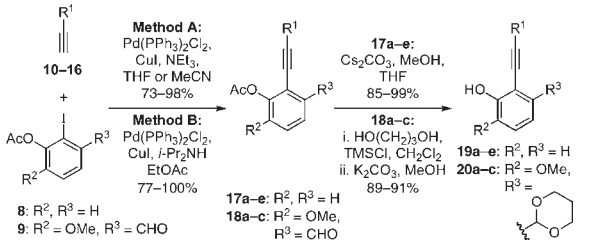
Scheme 1. Retrosynthetic Analysis of 2-Aryl-2,3-dihydobenzo-[*b*]furan-3-carboxylates (**3**)



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. Compound **5** would be derived from the Sonogashira coupling of protected aryl iodide **6** and arylalkyne **7**. Initial investigations focused on developing this route, using aryl iodides (**8**, **9**) and terminal alkynes (**10**–**16**). Subsequently, the utility of this method was demonstrated by the formal total synthesis of the anti-HIV natural product (+)-lithospermic acid (**1**).

The diarylalkyne substrates were synthesized 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). Deacetylation 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. Cs_2CO_3 in MeOH–THF at 0 °C, afforded *ortho*-hydroxydiarylalkynes **19a**–**e** 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**	$3,4,5\text{-}(MeO)_3C_6H_2$	**17c**[a] (84)	**19c** (87)
4	**8**	**13**	$3,5\text{-}(MeO)_2C_6H_3$	**17d**[a] (77)	**19d** (95)
5	**8**	**14**	$4\text{-}(MeO)C_6H_4$	**17e**[a] (73)	**19e** (85)
6	**9**	**14**	$4\text{-}(MeO)C_6H_4$	**18a**[a] (100)	**20a** (89)
7	**9**	**15**	$3,4\text{-}(OCH_2O)C_6H_3$	**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.

It was necessary, in the case of benzaldehydes **18a**–**c** (Table 1), to protect the aldehyde functionality in preparation for the carbonylative annulation and subsequent reduction step. Thus, **18a**–**c** were subjected to a one-pot procedure that included protection of the aldehyde as a 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 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; yet, this had a detrimental effect on **22a**–**b** yields, so these reactions were conducted at rt. Interestingly, a methyl acetal byproduct, resulting from trans-acetalization, was observed in the cases of 1,3-dioxane substrates **20a**–**c**.[17]

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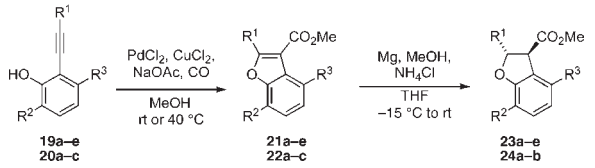
Table 2. Carbonylative Annulation and Mg-Mediated Benzofuran Reduction



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 ^1H NMR of crude isolate. [c] Byproduct isolated, R^1 = cyclohex-2-enyl (6%). [d] Byproducts isolated, R^1 = 1,2-dihydronaphthalen-2-yl (38%); R^2 = 1,2,3,4-tetrahydronaphthalen-2-yl (24%). [e] Reduction byproduct isolated, R^1 = 3,5-dimethoxycyclohexa-2,5-dienyl (15%). [f] Accompanied by 8% of the trans-acetalized benzofuran product, analogous to **22a** where R^3 = $CH(OMe)_2$. [g] Acetal hydrolysis by aqueous workup led to 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-acetalized material isolated, analogous to **20c** where R^3 = $CH(OMe)_2$.

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 11% yield. While catalytic reduction of simpler benzofuran systems has provided *cis*-dihyrobenzofurans,[7] to our knowlegdge, no methods for reducing 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** were not suitable for our systems: either recovered starting material or complex mixtures of products were obtained. Chemoselective reduction of α,β-unsaturated esters has been reported to proceed using Mg in MeOH, 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 capricious, apparently due to low and variable activity of the Mg and the low solubility of our substrates in MeOH. Adding THF as a cosolvent alleviated solubility issues, but also resulted in markedly less active Mg. Attempts to activate the Mg surface by stirring vigorously (both neat and in solution), by adding of I_2 or 1,2-dibromoethane, or by prior treatment with a dilute acid all proved inadequate. The introduction of NH_4Cl to the reaction mixture as an agent for Mg activation[22] was crucial to obtaining reproducible results and, gratifyingly, enabled the use of THF as cosolvent without deleterious effects on reaction rate and yield. These conditions proved amenable to all the benzofuran substrates (Table 2) in our investigation. The reduction reactions initially proceed with some degree of diastereoselectivity for the *cis*-isomers, which then undergo magnesium methoxide promoted epimerization to the more thermodynamically stable *trans*-isomers, **23a**−**e** and **24a**−**b**.[23] Partial reduction of the pendant R^1 aryl group competed with the desired 2,3-reduction in some substrates (Table 2, entries 1−2, 4). However, these unwanted reductions could be minimized by lowering the reaction temperature from rt to −15 °C. To optimize yields of the *trans* diastereomer the reaction mixture was decanted from excess Mg when reduction was complete,

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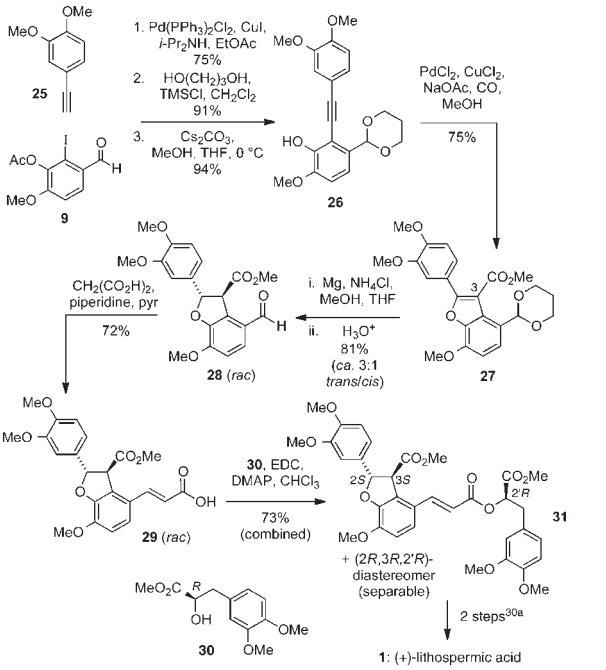
(23) Notably, the $J_{H2\text{-}H3}$ values were not a useful diagnostic tool for distinguishing the *cis* and *trans* isomers in these systems. Instead, the anisotropic effect of the C-2 aryl group causes chemical shifts of 3-CH and CO_2CH_3 which are diagnostic for *cis* versus *trans* isomers (refs 7, 9, and 18b). Thus, the *trans* compound displayed an upfield 3-CH resonance, compared to the *cis* isomer.

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 directly afford the aldehyde products **24a**–**b**.

(+)-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. 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 epimerization at C-3, gave cinnamic acid **29** with improved *dr* (*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 was separable by HPLC, providing diasteromerically pure **31**. All spectroscopic data obtained matched those reported by Bergman, Ellman and co-workers.[30a]

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



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**) 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**).

Acknowledgment. We thank the Australian Research Council for funding (DP556187), the CSIRO for a scholarship to J.F., and Dr. Natasha Hungerford (Griffith University) for assisting in preparing of this manuscript.

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

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