# Asymmetric synthesis of a tricyclic benzofuran motif: a privileged core structure in biologically active molecules†

**Henrik Sundén[a] and Roger Olsson*[a,b]**

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**An efficient synthetic strategy for the asymmetric synthesis of a hexahydrodibenzofuran core structure, with a quaternary stereogenic center, emerges by employing a chiral reduction using Corey's (*S*)-Me-CBS-oxazaborolidine reagent followed by a Mitsunobu reaction to set the stereochemistry. A Pd-mediated intramolecular Heck reaction concludes the tricyclic core structure. Finally, a Pd/C catalyzed reduction yields the target molecule in 21% overall yield over 6 steps.**

Tricyclic benzofurans incorporating an all-carbon asymmetric quaternary center are featured in many biologically interesting molecules and have therefore received considerable attention from the synthetic community, *e.g.*, morphine,[1–6] galantamine[7–10] and lunarine[11,12] (Fig. 1). These natural products have proven to be highly potent drugs and are used in several different therapies.[11–13] Recently, we disclosed a series of selective Estrogen Receptor β (ERβ) agonists based on the tricyclic benzofuran core structure (Fig. 1). The reported synthesis gave a low yield and the diastereomers and enantiomers were separated by crystallization and chiral chromatography, respectively.[14] Clearly, to be able to efficiently establish a structure–activity relationship (SAR) and to further evaluate these molecules' biological activity it was necessary to develop a more efficient enantioselective synthesis. Compounds bearing these quaternary centers are in general difficult to synthesize on a reasonable scale and have traditionally been obtained *via* classical resolution, similar to our original strategy.[2,8] Recently, however, asymmetric strategies toward these molecules based on metal catalysis have been reported.[15,16]

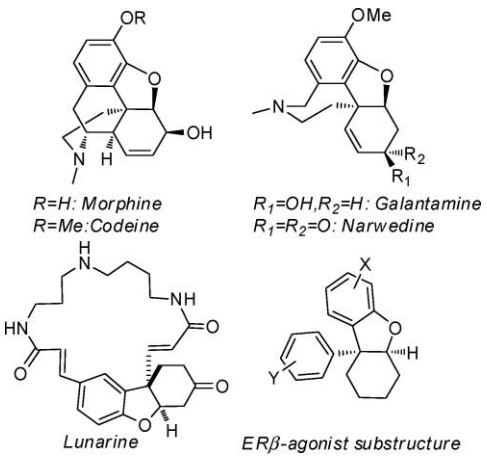
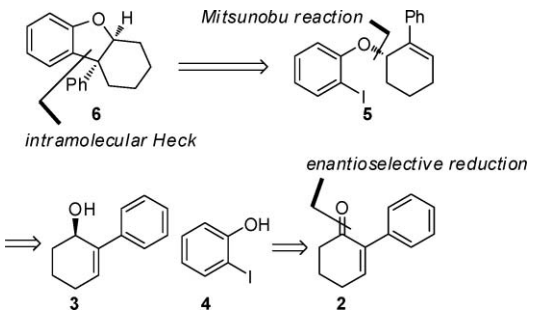


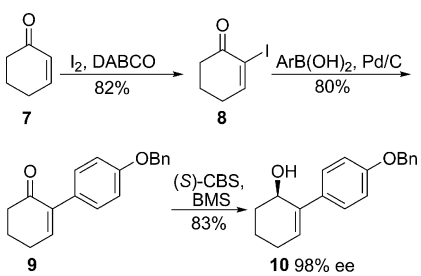

**Fig. 1** Bioactive molecules containing the tricyclic benzofuran moiety.

A retrosynthetic analysis of the tricyclic benzofuran ring system as found in **6** identified the enantiomerically pure allylic alcohol **3** as a key intermediate, potentially obtained by an enantioselective reduction of α,β-unsaturated ketone **2** (Scheme 1). A subsequent Mitsunobu reaction between phenol **4** and the allylic alcohol **3** would yield ether **5** by an inversion of the stereochemistry at the allylic carbon. However, the seemingly trivial Mitsunobu reaction could be a challenge, due to the potential reaction path *via* a stabilized cation which would erode the enantiopurity of the compound. Nevertheless, these steps would set-up the synthesis for a final ring-closing reaction generating the furan ring. An intramolecular Mizoroki–Heck reaction would then be efficient for the formation of the asymmetric congested quaternary center.




**Scheme 1** Retrosynthetic analysis.

The synthesis of the tricyclic benzofurans starts from the α,β-unsaturated ketone **7** that undergoes a DABCO-catalyzed iodo-Baylis–Hillman reaction[17,18] yielding **8** in 82% yield (Scheme 2). A convenient microwave assisted Pd/C-catalyzed Suzuki reaction transforms iodo-carbonyl **8** into the aryl ketone **9** in 80% yield.[19] This reaction protocol is practical and fast with reaction times between 15–20 min. In addition, the extractive work-up can readily be performed in the microwave vial and gives the pure product




**Scheme 2** Synthesis of allylic alcohol **10**.[23]

[a]*Department of Chemistry/Medicinal Chemistry, University of Gothenburg, SE-41296, Gothenburg, Sweden*
[b]*ACADIA Pharmaceuticals AB, Medeon Science Park, S-20512, Malmö, Sweden. E-mail: rolsson@acadia-pharm.com; Fax: +46 40 601 34 01; Tel: +46 768 87 42 17*

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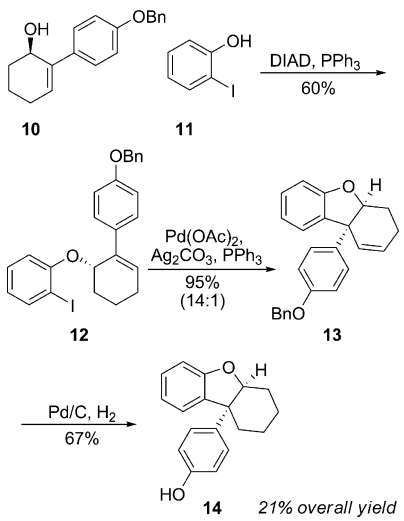
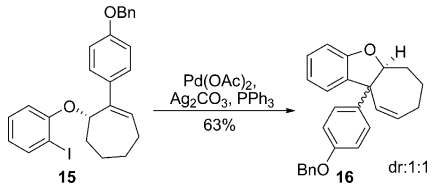
well within one hour. The enone **9** was thereafter subjected to an enantioselective (*S*)-CBS catalyzed reduction. In order to obtain optimal enantioselectivity the α,β-unsaturated ketone **9** was added with syringe pump to the reaction mixture at 0 °C yielding optically active alcohol **10** in an excellent ee of 98% and 83% yield.[20,21] Alternatively, reduction of **9** using the (*R*)- enantiomer of the oxazaborolidine catalyst provided *ent*-**10** in a similar yield.[22] In addition, the reaction was chemoselective, hence no formation of the corresponding saturated products was detected.

The enantioenriched allylic alcohol **10**, was then reacted with 2-iodophenol **11** under Mitsunobu conditions at room temperature using diethyl azodicarboxylate (DEAD) and triphenyl phosphine ($PPh_3$) (Scheme 3).[24] Disappointingly, the reaction facilitated an erosion of the enantiomeric excess; ether **12** was isolated in 83% yield and 68% ee. As speculated, the enantio-detrimental outcome was probably due to a competing cationic reaction path, which has been observed in Mitsunobu reactions with benzylic and allylic alcohols.[25–28] A series of optimization reactions found diisopropyl azodicarboxylate (DIAD) and $PPh_3$ in toluene at 0° C to be the best reaction conditions. Compound **12** was obtained in 60% yield and 90% ee.[29] A palladium-mediated intramolecular Mizoroki–Heck coupling using $Pd(OAc)_2$, $Ag_2CO_3$ and $PPh_3$ converted ether **12** to the tricyclic benzofuran **13** in excellent yield of 95% and 14 : 1 dr in preference for the *cis*-fused ring system.[9] The relative stereochemistry was assigned with a NOESY-NMR experiment (see the ESI†).[30] Notably, the all-carbon quaternary stereocenter is formed with a high diastereoselectivity and only traces of double bond isomers could be found.[31] The double bond isomers will however have no impact on the purification as the final step is a reduction. Thus, the double bond and the protecting group were removed with Pd/C and $H_2$ to yield **14** in 67% yield.




**Scheme 3** The synthesis of dihydrobenzofuran **14**.

Interestingly, when applying the Mizoroki–Heck reaction conditions to seven-membered rings *e.g.*, compound **15** undergoes cyclization but gives **16** in a 1 : 1 diastereomeric mixture (Scheme 4). This difference in diastereoselectivity as compared to the six-membered ring may be rationalized with the higher flexibility of the seven-membered ring.




**Scheme 4** Mizoroki–Heck reaction on the 7-membered ether **15**.

## Conclusions

In summary, we have developed a practical and fast total synthesis of compounds containing a tricyclic benzofuran core which are abundant in many biologically active molecules. The six-step sequence proceeds in 21% overall yield and high enantioselectivity. The first asymmetric center is assembled in a highly enantio- and chemo-selective oxaborolidine reduction of a cyclic α,β-unsaturated ketone. Moreover, the final tricyclic benzofuran core is constructed in a highly stereoselective intramolecular Mizoroki–Heck reaction efficiently giving the all-carbon quaternary center.

## Acknowledgements

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29 The phenol ethers can readily be crystallized to obtain enantiopure material for example, (*S*)-1-(4-(benzyloxy)phenyl)-7-(3-fluoro-2-iodophenoxy)cyclohept-1-ene was obtained in >98% ee after recrystallization in MeOH–toluene.
30 Compound **14** provided a spectrum suitable for $^{1}$H–$^{1}$H NOESY NMR investigations. Details are described in the ESI†.
31 The *trans*-fused benzofuran was never isolated.