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From glyceraldehyde to functionalized enantiopure tetrahydronaphthalenes and indanes

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Abstract—Tricyclic tetrahydronaphthalenes comprising *cis*- and *trans*-fused lactones, and aryl substituted functionalized indanes were synthesized in enantiopure form.

Fused carbocyclic compounds containing an aromatic moiety such as hydronaphthalenes and indanes are important constituents of biologically active natural products and compounds exhibiting pharmacological properties.[1] More than often they contain one or more carbon or heteroatom substituents on the non-aromatic portion, thereby introducing elements of stereochemistry and functional diversity. Fig. 1 shows the structures of a select group of biologically and medically relevant molecules that harbor tetrahydronaphthalene and indane motifs.[1]

In spite of their merits, current methods for the synthesis of functionalized tetrahydronaphthalenes and indanes do not address the combined advantages of introducing diversity in the aromatic portion, while also considering functional and stereochemical issues relative to the carbocyclic core.[2] Lautens and co-workers[3]

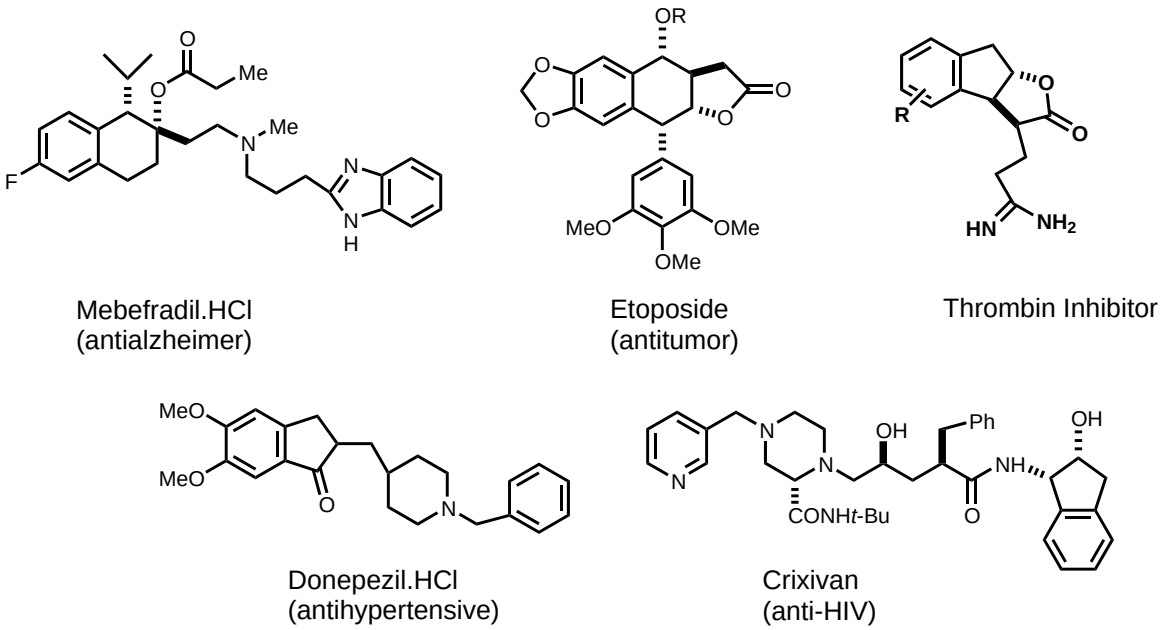

Figure 1.

Keywords: 1,2-induction; cuprate addition; Friedel–Crafts; lactone.

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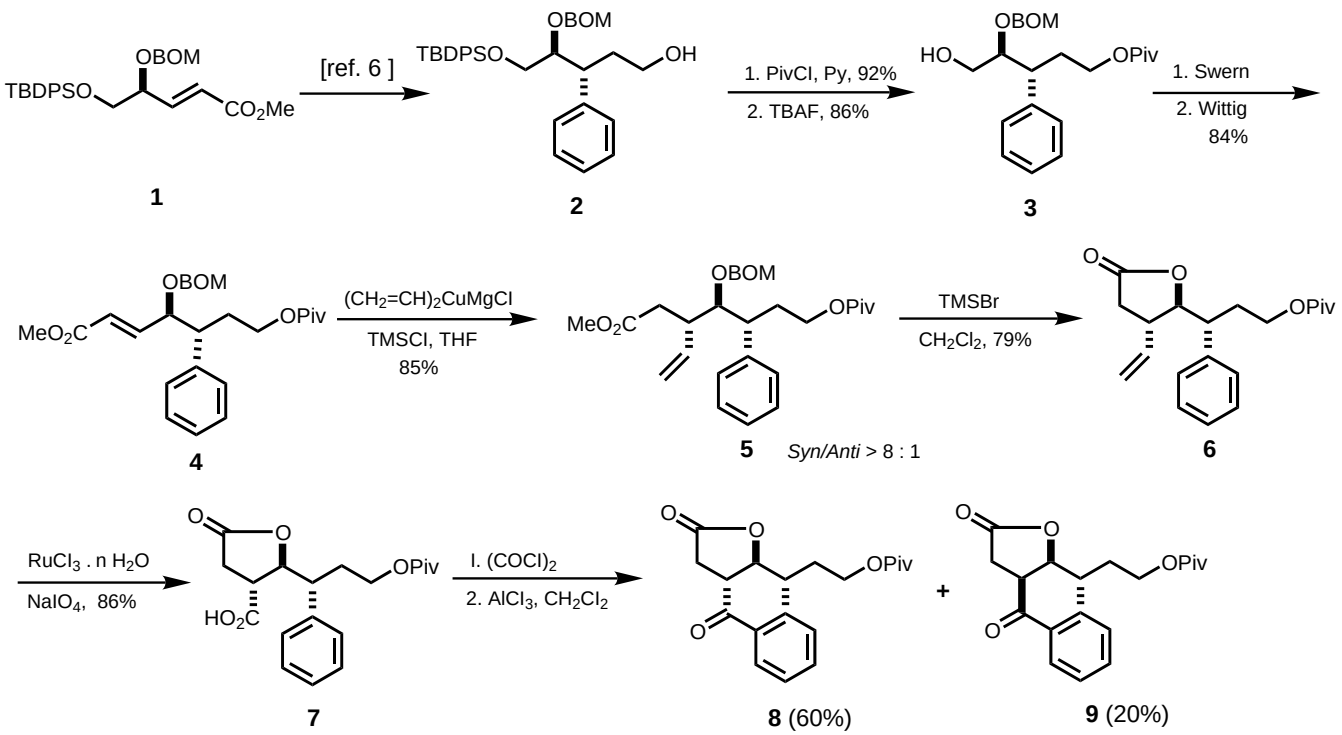
have reported on versatile rhodium- and palladium-catalyzed asymmetric methods for the introduction of hydroxy and amino groups in dihydronaphthalenes with considerable enantioenrichment.

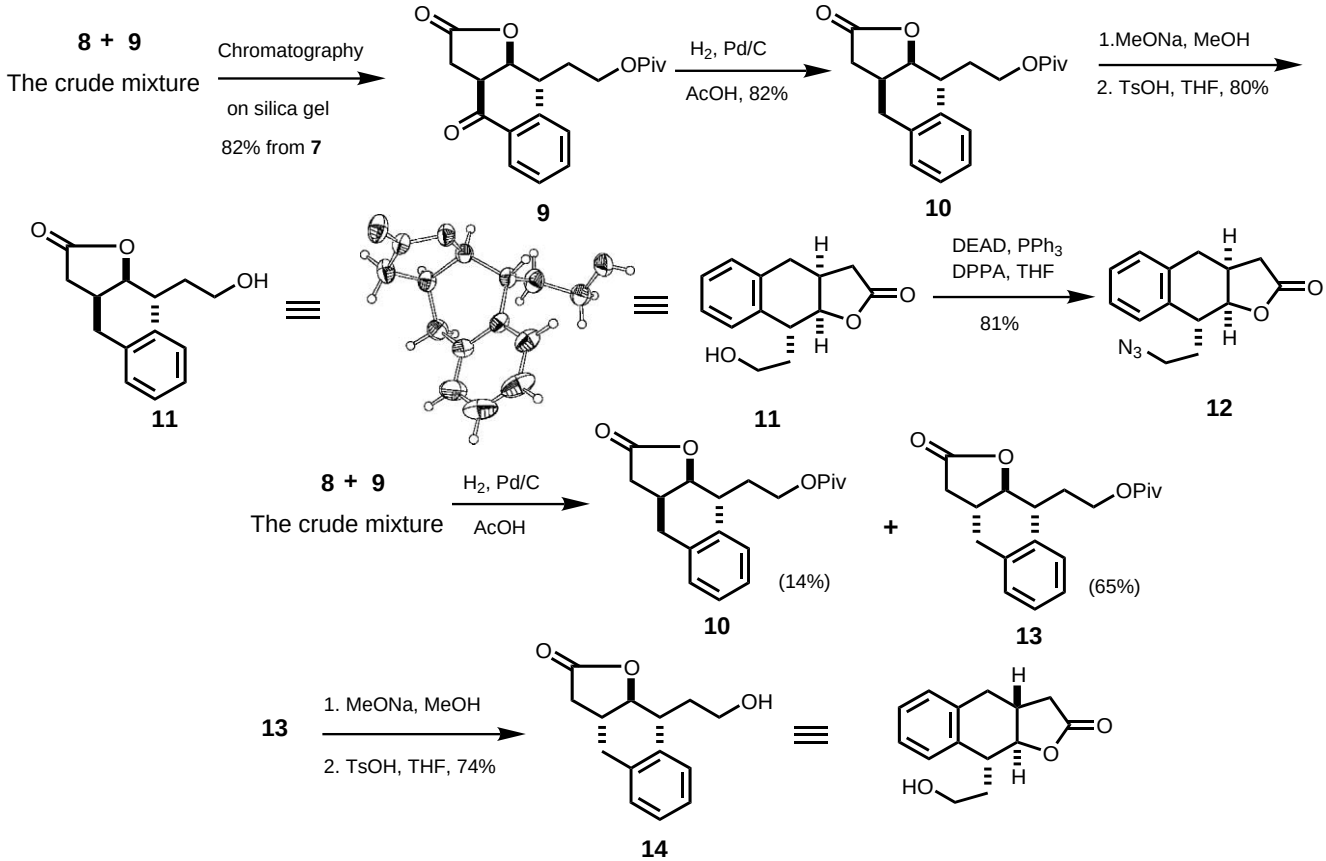
We report herein a versatile and highly stereocontrolled method for the synthesis of trisubstituted tetrahydronaphthalenes possessing usable functionality for diversification. The core structure can be considered as a semi-rigid scaffold for the deployment of biologically relevant appendages in the context of a library design.[4] Scheme 1 illustrates the methodology which capitalizes on a series of 1,2-asymmetric inductions using an acyclic motif **1**.[5] The addition of diphenylmagnesio cuprate (as well as other substituted analogs)[6] to **1** and subsequent modification of the ester group affords the conjugate addition product **2** in high yield. Protection and extension generates another γ-alkoxy-α,β-unsaturated ester which is subjected to a 2-directional[6] mixed cuprate addition affording the *anti*/*anti* vinylic product **5**. Transformation to the lactone, oxidative cleavage and ring closure of the corresponding acid chloride under the venerable Friedel–Crafts reaction conditions led to a 3:1 mixture of the *trans*-**8** and *cis*-**9** tricyclic lactones in good yield. Chromatography of the crude mixture over silica gel afforded the *cis*-lactone **9** in 82% yield, demonstrating the extreme tendency for the *trans*-lactone **8** to isomerize (Scheme 2). Catalytic reduction of **9** followed by removal of the pivalate ester led to the tricyclic lactone **11**, whose structure was definitively established by single-crystal X-ray analysis. Conversion of the primary alcohol to the corresponding azide as in **12** afforded an amine precursor for further diversification. Since the carbonyl group in **8** was undoubtedly responsible for the ready isomerization, we reduced the mixture of **8** and **9** to afford the tetrahydronaphthalene lactones **10** and **13** in 14 and 65% yields, respectively, demonstrating that the *trans*-lactone **8** was indeed the major product arising from the cyclization of the original *anti*/*anti* carboxylic acid motif via its acid chloride (Scheme 1). Further manipulation of **13** afforded the trisubstituted tricyclic compound **14** as the *trans*-lactone diastereomer of **11**. Lactones comprising tricyclic systems can be found in etoposides[7] and in a thrombin inhibitor consisting of a *trans*-fused lactone appended to an indane unit[8] (Fig. 1). Reduction of the ketone **9** with sodium borohydride in tetrahydrofuran afforded a 1:1 mixture of the corresponding benzylic alcohols, which are formally related to the etoposide skeleton.

Our approach to the indanol system also included functional diversity in the aromatic moiety (Scheme 3). Thus, conjugate addition of mixed diarylmagnesium cuprates to the enolate **1** in the presence of TMSCl afforded the corresponding adducts **16**–**19**. We then proceeded with the phenyl and *m*-methoxyphenyl analogs as representative examples for the construction of the indanols. A series of standard reactions generated intermediates such as **20**–**25** representing the two series. Conversion to the acid chloride and Friedel–Crafts cyclization led in each case to the indanone dipivaloates (**26**, **27**) in excellent yields. Finally, hydrogenation and deesterification afforded indane diols **28** and **29**, respectively. The structure and absolute configuration of the *m*-methoxyphenyl analog was ascertained by single-crystal X-ray analysis.

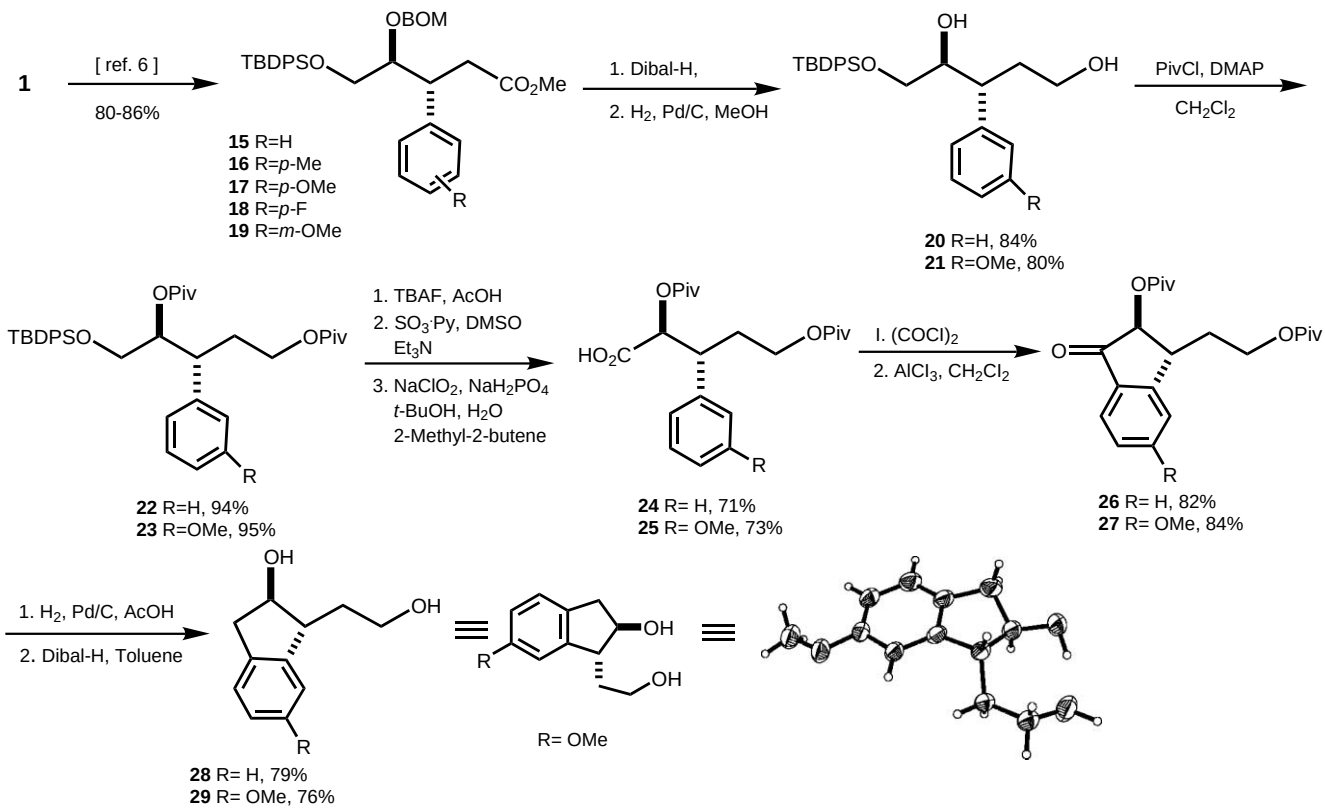
The prototypical enantiopure tetrahydronaphthalene and indane analogs prepared by the presently reported



Scheme 1.



Scheme 2.



Scheme 3.

methodology will be useful scaffolds in the context of drug design and natural product synthesis.[9]

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