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A UNIFIED APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF 2,6-*CIS* AND *TRANS* DISUBSTITUTED TETRAHYDROPYRANONES

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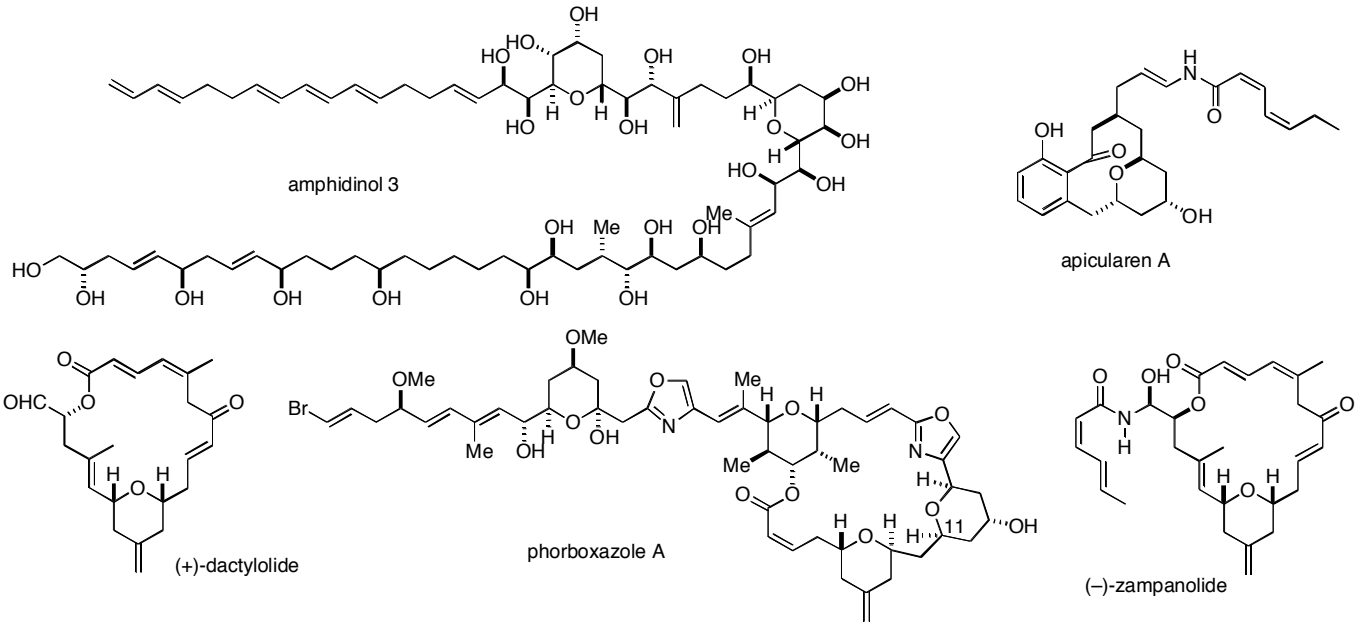
Abstract – A stereoselective construction of *cis*- and *trans*-2,6-disubstituted tetrahydropyranones, based on strategy which combines an asymmetric alkylation and ring closing metathesis for the formation of a cyclic enol ether, is reported.

Both *cis*- and *trans*-2,6-disubstituted tetrahydropyranones and closely related systems are common to a number of biologically important natural products. Included in this group are zampanolide,[1] apicularen A,[2] amphidinol 3,[3] dactylolide,[4] and the phorboxazoles.[5] The Petasis-Ferrier rearrangement is one general method for the construction of 2,6-disubstituted tetrahydropyranones, which stereoselectively provides the *cis*-isomer.[6] However, no unified approach is available to access either the *cis*- or the *trans*-diastereomer as needed. Based on our prior success with the use of the ring closing metathesis reaction in conjunction with the asymmetric glycolate alkylation for the enantioselective preparation of six-nine membered cyclic ethers,[7] it seemed reasonable that the strategy might be extended to tetrahydrohydropyranones.[8] For example, in the context of the synthesis of laulimalide,[7d] alkylation of oxazolidinone (**1**) with methallyl iodide led to selective formation of diene (**2**), which was readily converted to the dihydropyran (**3**) with the Grubbs catalyst. Thus, the possibility of executing the alkylation of a generic oxazolidinone (**4**) with an allylic halide containing an enol ether moiety might lead to diene (**5**), which could be converted through a metathesis reaction[9] to enol ether (**6**) and ultimately to the tetrahydropyranone (**7**).

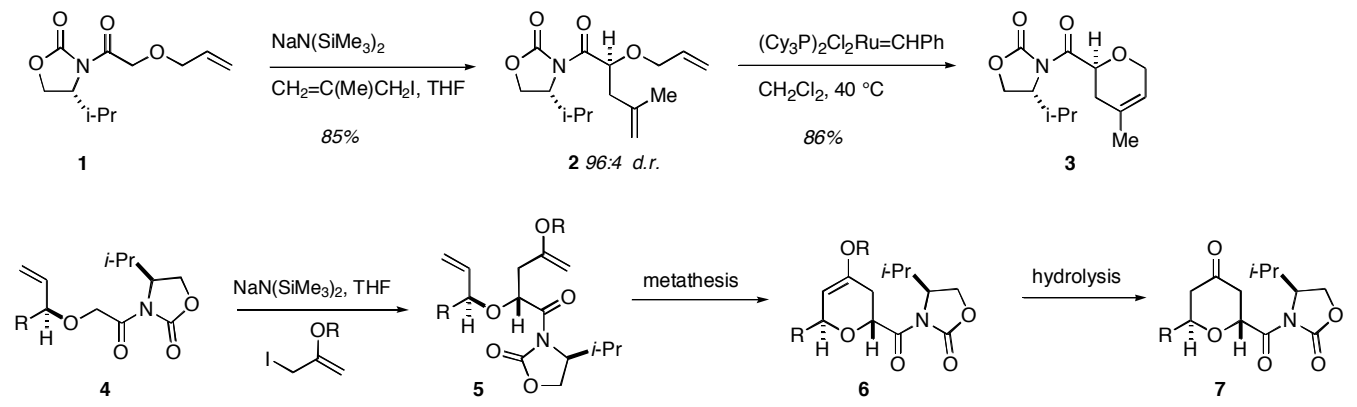
Given the need to further elaborate the substituted tetrahydropyranones, alcohols (**8**) and (**11**) were chosen as the starting point since these would incorporate a functionalized one carbon and two carbon substituent, respectively, for further manipulation (Scheme 3). Alcohol (**8**) was prepared by the known procedure for the conversion of glycidol derivatives to the homologated allylic alcohol with dimethylsulfonium methylide.[10] Alcohol (**11**) was readily obtained by a Sharpless kinetic resolution[11] of the corresponding racemic alcohol. Alcohol (**8**) was alkylated with sodium bromoacetate to deliver

the glycolic acid (**9**). Conversion of the acid to its mixed pivalic anhydride followed by treatment with the lithiated oxazolidinone [either *(R)* or *(S)*] provided the desired alkylation substrates (**10a**) and (**10b**). The homologated series (**13a**) and (**13b**) were prepared by a similar sequence from alcohol (**11**) (97% e.e.).

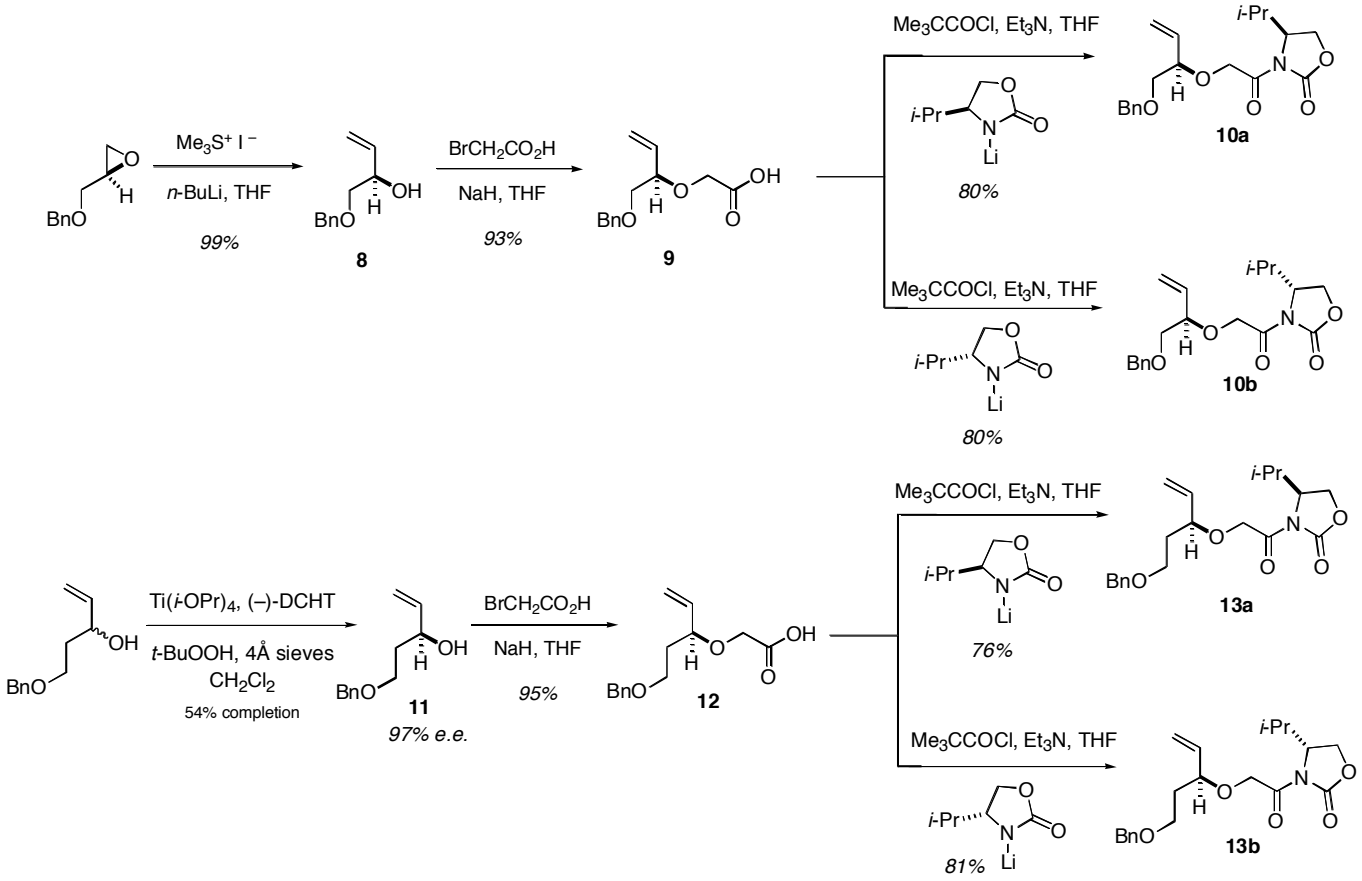


Scheme 1: Natural products containing 2,6-tetrahydropyranones and related structures.

Exposure of the sodium enolates of the four glycolyl oxazolidinones (**10a,b**) and (**13a,b**) to iodide (**14**)[12] led to the formation of the alkylated products (**15a,b**) and (**16a,b**) in yields of 60 – 79%.[13] A wide variety of conditions were explored leading ultimately to the use of 1.5 equiv NaHMDS to generate the enolate at –78 °C followed by the addition of 5 equiv. of alkylating agent and subsequent warming of the reaction mixture to –45 °C over 1.5- 2.5 h. In each case the alkylation product was a single detectable diastereomer by 400 MHz ^{1}H NMR spectrum.

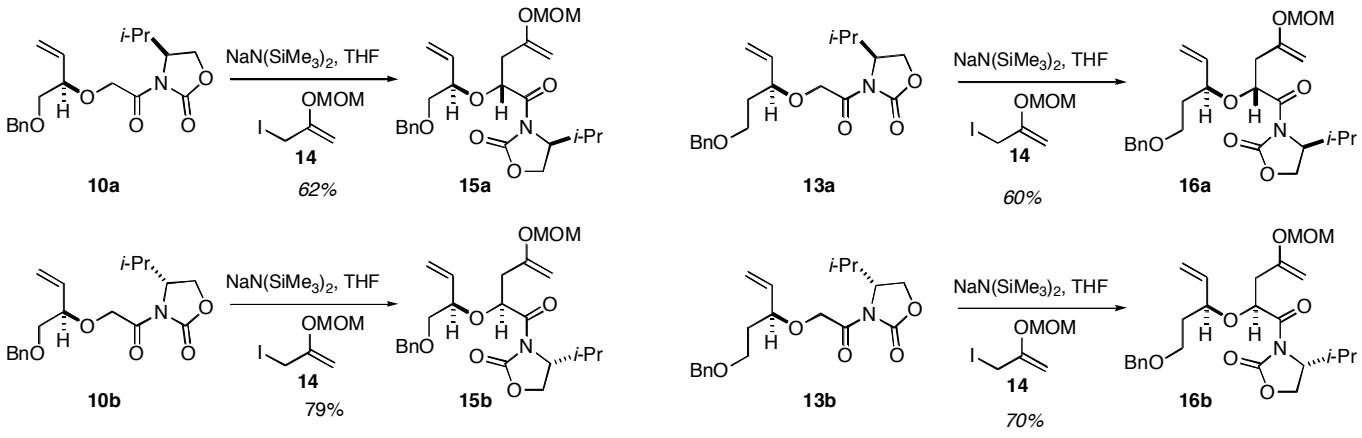


Scheme 2: A strategy for the preparation of substituted tetrahydropyranones



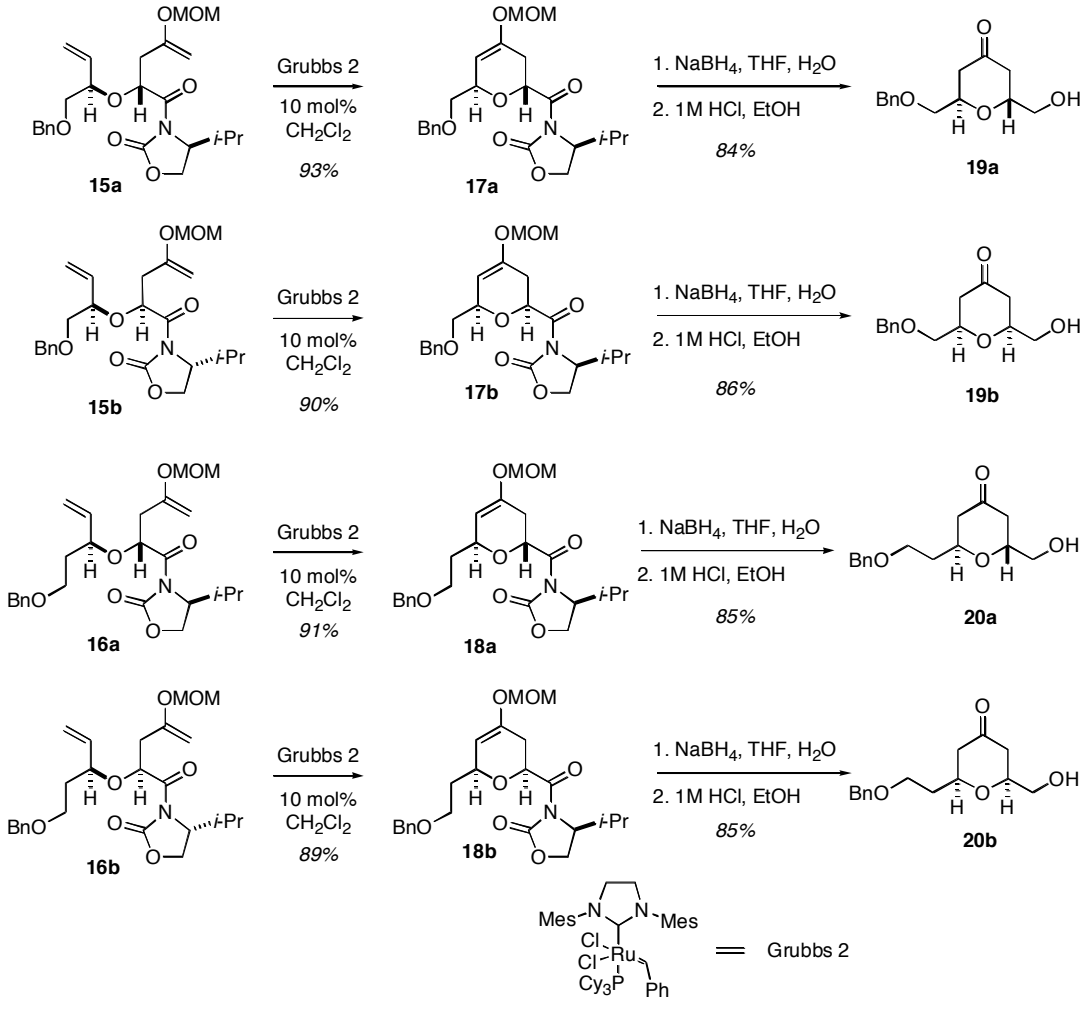
Scheme 3: Synthesis of alkylation substrates.

Scheme 5 illustrates the conversion of the dienes (**15a,b**) and (**16a,b**) to the desired disubstituted tetrahydropyranones. The dienes were exposed to the Grubbs second generation ruthenium carbene in dichloromethane at reflux.[14] While the reactions proceeded well with 5 mol% of the catalyst, generally 15-20% of the starting diene was recovered. However, when the catalyst loading was increased to 10



Scheme 4: Execution of the asymmetric glycolate alkylation with a halide containing an enol ether.

mol%, typically less than 5% of the diene was recovered and the yields of isolated products were approximately 90%. The disubstituted tetrahydropyranones were completed by reductive removal of the oxazolidinone auxiliary followed immediately by acid catalyzed hydrolysis of the enol ether to reveal the carbonyl group. Overall yields for the two steps were typically about 85%. The stereochemistry of the tetrhydropyranones was easily established by the presence of a strong cross peak between the two protons alpha to the ether oxygen in both (**19b**) and (**20b**) in the nOESY spectrum and the lack of the same interaction in the *trans*- diastereomers (**19a**) and (**20a**). Thus, the 2,6-disubstituted tetrahydropyranones could be prepared in high yield and high diastereoselectivity in 6 steps from the alcohols (**8**) and (**11**). The ability to access both the *cis* and *trans* diastereomers through this approach renders it advantageous over other methods. Finally, the regiospecific incorporation of the enol ether will undoubtedly be useful for further selective functionalization of these systems.



Scheme 5: Completion of disubstituted tetrahydropyranones.

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