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Pyran Annulation: Asymmetric Synthesis of 2,6-Disubstituted-4-methylene Tetrahydropyrans

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Abstract

A reaction process for the asymmetric construction of a variety of *cis* or *trans* disubstituted pyrans is described. This sequences allows for the asymmetric convergent union of two aldehydes with silyl-stannane reagent 1 in a two-step process: catalytic asymmetric allylation of the first aldehyde using 1 with a BITIP catalyst, followed by reaction of the alcohol so obtained with a second aldehyde and TMSOTf.

An ever increasing number of biologically significant natural products, especially those of marine origin, possess functionalized tetrahydropyran rings as critical substructural motifs. Prominent examples of considerable current interest would include bryostatin 1 and phorboxazole (Figure 1).[1-2] Our interest in these structures, particularly bryostatin 1 and other potential therapeutic agents based upon this structural platform,[3] has led us to investigate new methods for the asymmetric synthesis of pyrans bearing the substitution patterns commonly encountered in these natural products. The occurrence of such pyran motifs in a number of biologically active natural products has inspired the development of many clever methods for obtaining these oxacycles. The intramolecular attack of an olefin on an oxocarbenium ion, or intramolecular Prins reaction, although one of the established methods, has been underutilized in this capacity. This is in part due to the paucity of methods for obtaining suitable substrates to provide appropriately functionalized *nonracemic* tetrahydropyrans.

There exists extensive precedent for the construction of oxygen-containing heterocycles, including tetrahydropyrans, by approaches based upon intramolecular versions of the basic Prins reaction.[4] Previous work has also documented the utility and enhanced reactivity of allylsilanes as intramolecular traps for oxocarbenium ions generated in various ways.[5] Kang

Supporting Information Available: Spectral and analytical data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

has described reactions of racemic hydroxy allylsilanes of general structure **2** with vinyl ethers and α-halo acetals to give acetals that were subsequently cyclized to afford pyrans.[6] Marko has developed an efficient pyran synthesis that combines the Noyori method[7] for generation of oxocarbenium ions with intramolecular allylsilane trapping and has coined the term ISMS (intramolecular silyl modified Sakurai) to describe this reaction (eq 1, Scheme 1).[8] Studies by Marko have also documented the use of racemic hydroxy allylsilanes in sequences leading to pyrans via an initial ene reaction; Marko has suggested the term "IMSC" (intramolecular Sakurai cyclization) to refer to the cyclization step of the process (eq 2, Scheme 1).[9] Very recently, during the preparation of our manuscript, Leroy and Marko reported on the use of a functionalized allylstannane in BF_3•OEt_2-promoted reactions with aldehydes, followed by Bi $(OTf)_3$-promoted cyclocondensation with a second aldehyde, to yield differentially substituted pyrans as shown in Scheme 1 below (eq 3).[10]

Rychnovsky has also developed a process termed "segment coupling Prins cyclization"[11] and applied it to an extremely concise construction of the C_{20}–C_{27} pyran subunit of phorboxazole.[12] Rychnovsky and Kopecky have also recently reported a tandem Mukaiyama aldol–Prins sequence utilizing allylsilanes, which bears similarity to the process described herein.[13] Both of these methods access nonracemic pyrans. Smith has utilized the Petasis–Ferrier rearrangement in efficient syntheses of nonracemic tetrahydropyrans, and Panek has employed nonracemic allylsilanes to access dihydropyrans.[14]

Herein we report an exceptionally facile enantioselective synthesis of 2,6-*cis*-disubstituted-4-methylenetetrahydropyran systems. These are obtained in a very brief *three steps* from commercially available starting materials. As indicated in Scheme 2, the overall two-step reaction process results in the convergent union of two aldehyde components with a four-carbon unit derived from the known 2-(trimethylsilylmethyl)allyltri-*n*-butylstannane reagent **1**.[15] For purposes of discussion, it is convenient to refer to these as the first aldehyde, R_1CHO, and the second aldehyde, R_2CHO.

The first step in the overall process is the preparation of the requisite hydroxy allylsilanes in nonracemic form. This was achieved for the present examples by catalytic asymmetric allylation of the first aldehyde R_1CHO with stannane **1**.[16] These reactions were found to proceed well using our previously described BINOL titanium tetraisopropoxide (BITIP) catalyst;[17] in general, the hydroxy allylsilanes were obtained in high yields and with high levels of enantioselectivity. (Table 1).

The second step of the process, the TMSOTf-promoted annulation of such silanes with the second aldehyde R_2CHO, was found to occur rapidly (generally within 15 min at −78°C) to provide the 2,6-*cis*-tetrahydropyran containing an *exo*-methylene in the 4-position. The *trans* diastereomer was not detected. The stereochemical outcome is in accord with previous observations and with the expectation that cyclization should occur via a chairlike transition state with R_1 and R_2 equatorially disposed. The results for several examples are provided in Table 2.

We have noticed an interesting combination of solvent effects and substrate dependence with respect to this annulation reaction. The reaction generally proceeded well in CH_2-Cl_2, but in all cases at least a trace amount of an *endo*cyclic olefin that was inseparable from the desired product was obtained. In the cases where the cyclization substrate is **2c**, this problem was greatly magnified. Previous attempts by Marko to cyclize similar preformed TMS ethers also resulted in mixtures of *endo* and *exo* olefins, which were very difficult to separate.[8a,18] However, noting that the substrates that performed best in this reaction contained α or β-alkoxy substituents, diethyl ether was also examined as solvent. A dramatic improvement was found

with this oxygenated solvent as no endocyclic olefins were obtained regardless of the substrate employed.

Another problem observed in these reactions is related to the use of substrates **2d** and **2e** (Table 1). In CH_2Cl_2, these substrates decomposed immediately upon exposure to TMSOTf. In ether at −78 °C no decomposition was observed; however, no cyclized product was obtained either. Under these conditions the alcohol is rapidly converted to the TMS ether, but the reaction stalls at this juncture.[19] We are currently still examining this issue.

It is also possible to use this pyran annulation to obtain access to 2,6-*trans*-disubstituted pyrans. As shown in eq 4,

the annulation reaction works very well when an ortho ester is used as the electrophile.[20] Thus, the reaction of **2a** with trimethylorthoformate smoothly provides methylacetal **4** in excellent yield (eq 4). Although **4** is obtained as an epimeric mixture, this is of little consequence. Reaction of a storable nucleophile (allylsilane, allylstannane, or enol silane) with the oxocarbenium ion generated upon treatment of such acetals with a Lewis acid is well-known to afford the 2,6-*trans* isomer with high selectivity as a consequence of stereoelectronically preferred axial addition to the intermediate oxocarbenium ion.[21]

This annulation process also lends itself to iterative applications that allow for the rapid assembly of structures containing multiple pyran rings, such as the bis pyran subunit of phorboxazole. Thus, if a pyran constructed using this process contains a latent or protected aldehyde, exposure of the aldehyde function and reaction with an appropriate hydroxy allylsilane in a second annulation affords a bis pyran. An example of this iterative annulation is shown in Scheme 3. In this case, bis pyran **6** is assembled from stannane **1**, α-benzyloxyacetaldehyde, and β-OTBDPS propionaldehyde in five linear steps. The compatibility of both α- and β-alkoxy aldehydes in these reactions thus easily provides pyrans containing three differentiated and highly malleable functional groups on the THP ring. Finally, this pyran synthesis is quite flexible since the annulation can be approached from two different directions for any given pyran. This should increase its utility and help to promote its application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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21. For two recent examples, see refs [2b] and [14b].

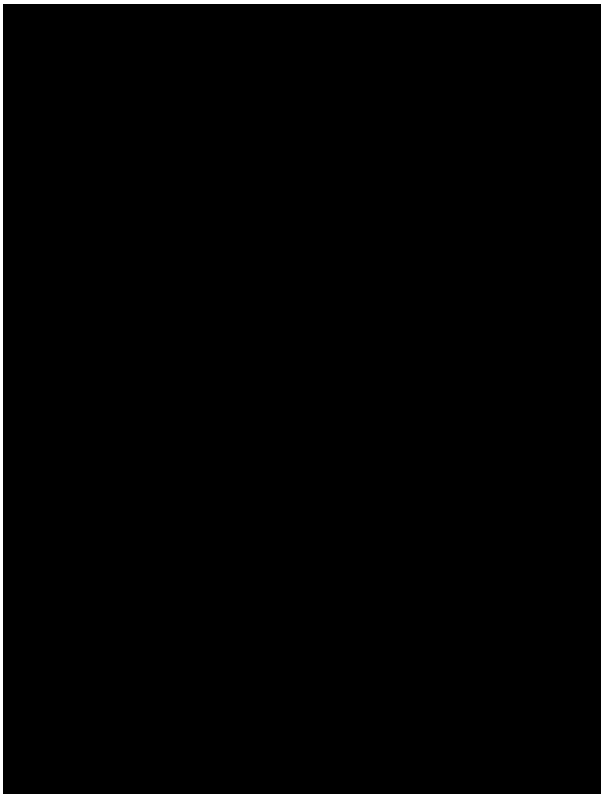
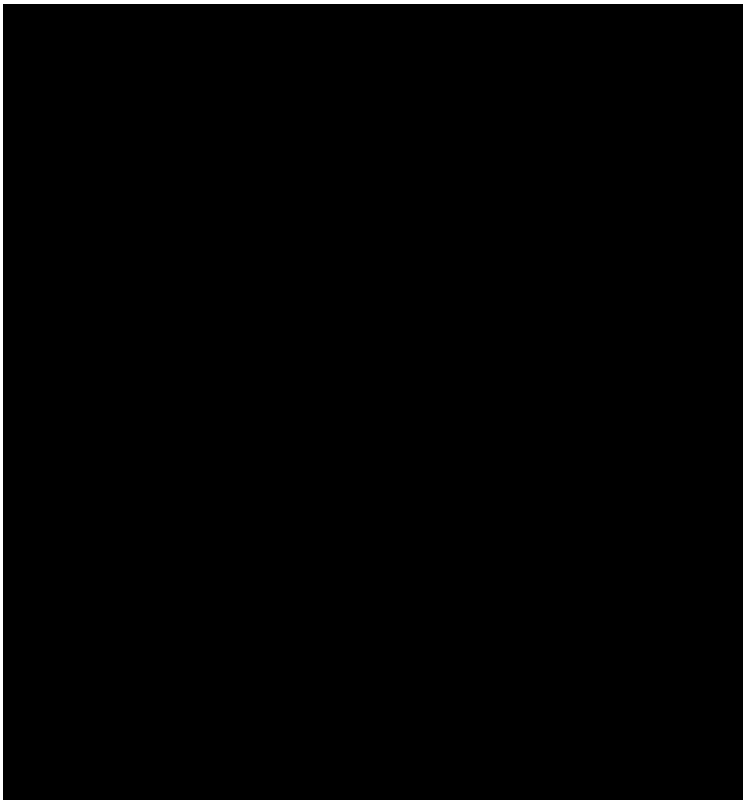


Figure 1.
Structures of bryostatin 1 and phorboxazole.



Scheme 1.
Related Racemic Pyran Syntheses

Scheme 2.
Overall Pyran Annulation Process

Table 1.
Isolated Yields and Enantiomeric Excesses for the Reaction of **1** with Aldehydes

Table 2.
Isolated Yields for TMSOTf-Promoted Annulations

Scheme 3.
Iterative Pyran Annulation