Stereospecific Synthesis of 2,3-Dihydro-4*H*-pyran-4-ones by Hg(II)-Catalyzed Rearrangement of 1-Alkynyl-2,3-epoxy Alcohols

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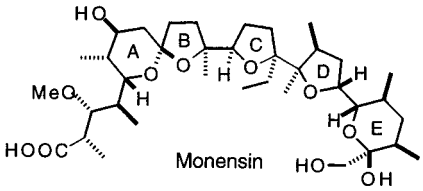
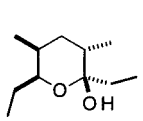
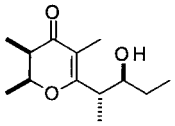
The stereocontrolled assembly of substituents on a pyranoid ring is of continuing importance.[3−7] The tetrahydropyran ring[3−6] is found in a wide variety of natural products, many possessing useful pharmacological and therapeutic properties. Examples of compounds containing a 3-methyltetrahydropyran unit include numerous spiroketals,[3a] the avermectins and the milbemycins,[8] broad-spectrum antiparasitic and insecticidal agents, the potent antitumor agents spongistatin 1,[5a] and serricornin, the sex pheromone of the cigarette beetle.[3b] Syntheses of avermectins and milbemycins require assembly of a spiroketal subunit,[3a] as do the oligomycin, rutamycin and cytovaricin family of antibiotics[3c] and the phyllanthostatins, a group of antineoplastic glycosides.[3d] The 3-methyltetrahydropyran unit in monensin[3e,f] is common in polyether antibiotics and is also present in the mycalamides, potent antiviral and antitumor agents that also possess 4-oxygenated substituents.[9]

2,3-Dihydro-4*H*-pyran-4-ones are key intermediates[7] in the synthesis of a wide range of tetrahydropyrans and carbohydrates. Additionally, the ring is present in several natural products, including stegobiol,[7a] vallartanones A and B,[7b] and the pheromone of the male swift moth.[7c] The best known route to 2,3-dihydro-4*H*-pyran-4-ones, the Lewis acid-catalyzed hetero Diels−Alder reaction of siloxy 1,3-dienes with aldehydes,[3g,7d−f] permits the introduction of 2,3-cis disubstitution. However, it does not afford pure trans 2,3-disubstitution, and indeed, appreciable quantities of both cis and trans products are often obtained.[7g,h] Nor may alkyl or other groups be readily introduced at the 6-position (Scheme 1). In the context of increasing the range of stereoselective syntheses of pyranoids, we report here the first examples of 1-alkynyl-2,3-epoxy alcohol rearrangements to give 3-substituted-2,3-dihydropyran-4-ones (Scheme 1, Table 1), a ring system readily adaptable to the synthesis of the above classes of natural products. The reactions proceed with additional 2- and/or 6-substituents and tolerate a variety of sensitive functionality.







1-Alkynyl-2-alken-1-ols[10] were epoxidized using either *tert*-butyl hydroperoxide−$VO(acac)_2$ or *m*-CPBA (for **1e**) to give the corresponding 1-alkynyl-2,3-epoxyalcohols[10] (Scheme 1). The alkene required for the preparation of **1g** was prepared as follows: reduction of (*Z*)-ethyl 2,4-dimethyl-2-pentenoate[11] with DIBAH gave 2,4-dimethyl-2-penten-1-ol, which was treated with TBHP and $VO(acac)_2$ to give a diastereoisomeric mixture of epoxy alcohols that underwent Swern oxidation to give 2,4-dimethyl-2,3-oxiranylpentanal, which was reacted with 1-heptynyllithium. The 1-alkynyl-2,3-epoxy alcohols were treated with 1.7 mol % Hg(II) in 4.0 mM aqueous sulfuric acid.[12] After neutralization, extraction, and chromatography, the corresponding 2,3-dihydropyran-4-ones were isolated (Table 1). Coupling constants and NOESY experiments (involving the methine hydrogen atoms at the 2- and 3-positions) confirmed the relative configurations of **2d**−**g**. The reaction proceeds for alkyl and aryl substituents at C-3, but when this position is not substituted, one example gave only a 2,5-disubstituted furan.[14] Position 2 need not be substituted, but if it is, the stereochemistry at C-2 is retained. The relative configuration of the 2,3-

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(12) General procedure for the preparation of dihydropyranones **2**: To a stirred solution of the epoxy alcohol **1** (1.5 mmol) in propanone (30 mL; HPLC grade) at 20 °C was added 0.25 mL of a freshly prepared Hg(II) solution, made by dissolving yellow mercury(II) oxide in dilute sulfuric acid, such that a stock solution 0.1 M in mercury(II) and 2.5 vol % of sulfuric acid was obtained. The optimum time of the reaction (TLC monitoring) was typically between 5 and 20 min.

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Scheme 1

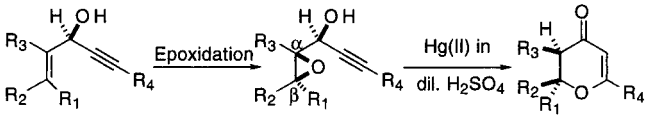


Table 1. Rearrangement of 2,3-Epoxy Alcohols To Give 2,3-Dihydro-4*H*-pyran-4-ones[a]

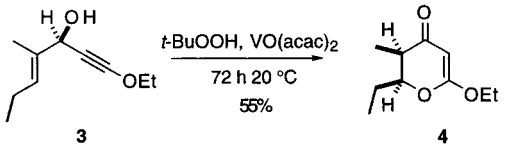
	entry	epoxy alcohol[b]	product[c]	yield[d] (%)
1		**1a**	**2a**	74
2		**1b**	**2b**	80
3		**1c**	**2c**	67
4		**1d**	**2d**	56
5		**1e**	**2e**	57
6		**1f**	**2f**	53
7		**1g**	**2g**	50

[a] All products depicted are racemic. [b] The major diastereoisomer is shown, although syn/anti mixtures[13] of **1** were used in the rearrangements [for which the ratios are as follows (entry): 7:3 (**1a**), 3:1 (**1b**), 6:1 (**1c**), 2:1 (**1d**), 2:1 (**1e**, *m*-CPBA), 21:1 (**1f**), 1:1 (**1g**)]. [c] Conditions as in footnote 12. [d] Isolated yields.

disubstituted dihydropyranones is determined solely by the configuration of the alkene (in the initial enynol); thus, the *(Z)*-alkene leads to epoxide **1g** and, hence, only to the trans product **2g**. The alternative stereochemistry in entries 3−6 (Table 1) leads to the dihydropyranone with only cis 2,3-disubstitution. This capability of stereocontrolled placement of several substituents would be of use in the synthesis of natural products such as the environmentally benign pesticide serricornin,[3b] which possesses *cis*-2-ethyl-3-methyl substitution, as obtained in entry 4 (Table 1).

Alkyl, aryl, and hydroxylated functionalities are tolerated at C-6, provided the group is not substantially electron-withdrawing. An electron-donating substituent at C-6 was found to enhance markedly the formation of the dihydropyranone ring, so much so that in the reaction of enynol **4** with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ no epoxide was isolated; instead, the reaction proceeded directly to the 2,3-dihydro-6-ethoxypyranone **5**, no Hg(II) catalysis being necessary (Scheme 2).

Scheme 2



3 **4**

The tolerance of the process to a ring fused across the epoxide function was tested by treatment of 1-(1,2-epoxycyclopentyl)-3-phenylprop-2-yn-1-ol with the acidic solution of catalytic Hg(II); no dihydropyranone was isolated, but instead 4-(5-phenyl-2-furyl)butanal was obtained (70%); such furans that have been previously obtained, but principally from *tertiary* alcohols.[14]

The stereospecificity of the reaction is shown by comparison of entry 7 with all other reactions in Table 1. In each reaction, only a single dihydropyran-4-one diastereoisomer was detected, the stereochemistry arising by exclusive inversion at Cα of the epoxide. The configuration at the carbinol carbon atom is immaterial,[15] free rotation enabling both epimeric alcohols to deliver hydride anti to the C−O bond of the epoxide undergoing cleavage. Since enol intermediates would result in loss of stereochemical integrity at Cα, it is presumed that a 1,2-hydride shift occurs with concomitant ring opening of the epoxide in a semipinacol rearrangement.[16] The rearrangement of alkynyl epoxy alcohols into dihydropyranones contrasts markedly with reactions of the analogous *tertiary* alcohols, from which *β*-hydroxy ketones,[16] cyclized products,[17] and substituted furans[14] have been obtained.

The feasibility of an enantioselective variant of the dihydropyran-4-one reaction was probed. Entry 4 was repeated, but by *asymmetric* epoxidation of the corresponding (±)-alkynyl allylic alcohol under conditions of kinetic resolution[18] (TBHP, 10 mol % $Ti(O\text{-}i\text{-}Pr)_4$, 15 mol % of (+)-diisopropyl tartrate, −20 °C, 9 h). Chromatography of the reaction mixture afforded two fractions: a 4:1 diastereoisomeric mixture of epoxy alcohols (42%) and unreacted enynol (48%). The diastereoisomeric mixture of epoxy alcohols was reacted with the acidic solution of catalytic Hg(II) to give diastereoisomerically pure **2d** (55%) in 60% ee (Chirex column, phase 3014, 1:9 ethyl acetate/petroleum ether eluent).

In summary, stereocontrolled routes to 2,3-dihydro-4*H*-pyran-4-ones by the Hg(II)-catalyzed rearrangement of 1-alkynyl-2,3-epoxy alcohols in acidic media have been demonstrated. The mild conditions are tolerant of a variety of sensitive functionalities. The scope, mechanistic aspects, and synthetic applications of these reactions are under investigation.

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Supporting Information Available: Experimental procedures and spectroscopic data are available for **1a**−**g**, **2a**−**g**, and **3**, and **4** (6 pages).

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(15) The epimers of **1e** were separated and separately treated with aqueous acidic Hg(II), each isomer affording the same dihydropyranone **2e**.

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