ORGANIC LETTERS

2001
Vol. 3, No. 26
4161−4164

Diastereoselective Synthesis of 2*H*,5*H*-Dihydrofurans by Cobalt-Mediated Cycloisomerization of Allyl Propargyl Ethers. Application to Poly-THF Molecules

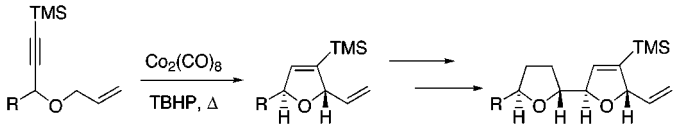
Alain Ajamian and James L. Gleason*

Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, QC, Canada H3A 2K6

jim@gleason.chem.mcgill.ca

Received September 17, 2001

ABSTRACT

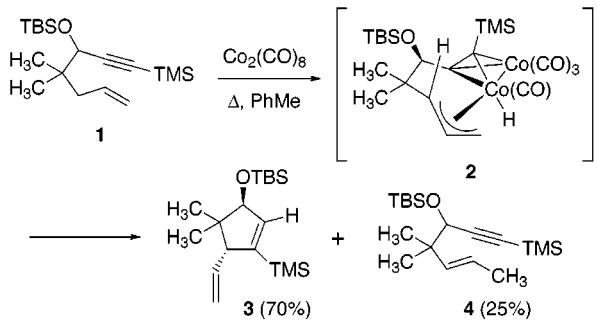


Allyl propargyl ethers undergo cobalt-mediated cycloisomerization reactions to form dihydrofurans in good yield and with excellent diastereoselectivity. The reaction works with a range of substrates, and its utility in synthesis is exemplified by the preparation of a bistetrahydrofuran unit.

Tetrahydrofurans are a common subunit found in many bioactive natural products. They are prevalent in the polyether ionophore antibiotics[1] and in the annonaceous acetogenins.[2] Numerous pathways for their synthesis have been developed,[3] and in recent years much work has focused on metal-mediated approaches. Many of the metal-mediated processes, including those which utilize ruthenium,[4] rhenium,[5] and chromium[6] oxo species, are based on oxidative cyclizations of bishomoallylic alcohols and 1,5 dienes.

Recently, we reported a cobalt-mediated cycloisomerization of 1,6-enynes that produces vinylcyclopentenes in high yield with excellent diastereoselectivity (Scheme 1).[7] The reaction proceeds by an oxidative insertion into an allylic C−H bond to form an allylcobalt hydride (e.g., **2**), followed by sequential C−C and C−H reductive eliminations to form the cyclopentene **3**. In this letter, we report that this novel cycloisomerization may be extended to the highly diastereoselective preparation of 2*H*,5*H*-dihydrofurans. The reaction provides ready access to the corresponding tetrahydrofurans and is amenable to poly-THF synthesis.

Scheme 1



(1) Westley, J. W. *Polyether Antibiotics: Naturally Ocurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. I and II.

(2) (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

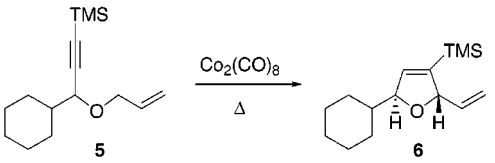
(3) For reviews on tetrahydrofuran synthesis, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (c) Koert, U. *Synthesis* **1995**, 115.

(4) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

10.1021/ol016768l CCC: $20.00 © 2001 American Chemical Society
Published on Web 11/28/2001

We began the study of dihydrofuran synthesis using the allyl propargyl ether **5**, which is readily prepared from cyclohexane carboxaldehyde in two steps. Treatment of **5** under the standard conditions developed for **1**, namely, addition of $Co_2(CO)_8$ (1.1 equiv) to a solution of **5** in toluene followed by thermolysis under an argon atmosphere, failed to provide any characterizable products. In contrast, when the reaction was conducted at 65 °C for 24 h, dihydrofuran **6** was produced as a single diastereomer in a modest 40% yield (Table 1). Allowing the reaction to go for longer periods

Table 1. Optimization of 2H,5H-dihydrofuran Formation[a]



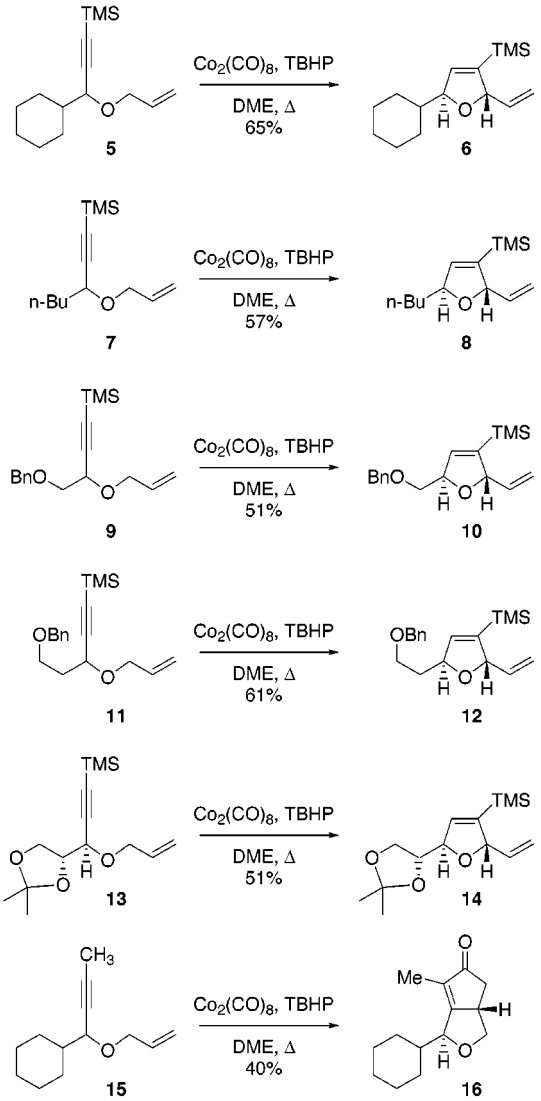
entry	solvent	temp (°C)	atmosphere	additive[b]	yield (%)
1	PhMe	110	argon		0
2	PhMe	65	argon		40
3	PhH	80	argon		5
4	DME	85	argon		40
5	DME	85	argon	NMO	63
6	DME	85	air		45
7	DME	85	air	NMO	58
8	DME	85	air	TBHP	65

[a] All reactions were conducted with 1.1 equiv of $Co_2(CO)_8$ for 24 h. [b] In all cases, 3.3 equiv of additive were used.

of time resulted in a decreased yield, presumably as a result of decomposition of the product. Equivalent yields were obtained if the reaction was conducted at reflux in 1,2-DME, while very little reaction was observed in benzene at reflux. The yield of the reaction could be improved by adding an oxidant such as *N*-methylmorpholine-*N*-oxide or *tert*-butylhydroperoxide (3.3 equiv) to a solution of the cobalt complex in DME prior to thermolysis.[8] The use of excess NMO (>4 equiv) in DME produces significant amounts of the Pauson−Khand product, even at room temperature. In contrast, even a large excess of TBHP (>10 equiv) produces only traces of Pauson−Khand products, making it the oxidant of choice for this reaction. Conveniently, it was found that the reaction proceeds in air with no significant change in either yield or stereoselectivity. The yields using this procedure are comparable to those obtained in the carbocyclization of **1**. Unlike the cyclization of **1**, no alkene isomerization was observed. However, this may be due to decomposition of the enol ether, which would be formed by such an isomerization, under the reaction conditions.

The method was found to work well with a series of allyl propargyl ethers (Scheme 2). Notably, in all cases only the

Scheme 2



trans-diastereomer was observed. The stereochemical assignment was made by observation of weak NOEs between the 5-position and the vinyl group (Figure 1) and was further substantiated by the lack of any NOE between the protons at the 2- and 5-positions of the dihydrofuran. As with the previous carbocyclization reaction, the dihydrofuran cyclization only proceeds with silyl-protected acetylenes. Use of an internal alkyne pushes the reaction down the more conventional Pauson−Khand pathway (e.g., **15** → **16**).

To explore the utility of this cyclization, we sought to utilize the dihydrofuran products in a synthesis of a simple bis-THF unit (Scheme 3). This would require the removal of the trimethylsilyl group, hydrogenation of the endocyclic

(5) (a) Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303. (d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133. (e) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750. (f) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447. (g) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022. (h) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076.

(6) (a) Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 379. (b) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727.

(7) Dolaine, R.; Gleason, J. L. *Org. Lett.* **2000**, *2*, 1753.

(8) Shambayani, S.; Crowe, W. E.; Schreiber, S. L. *Tetetrahedron Lett.* **1990**, *31*, 5289.

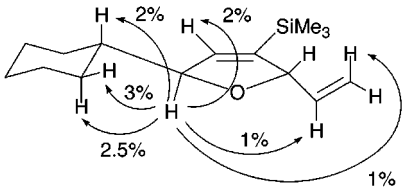
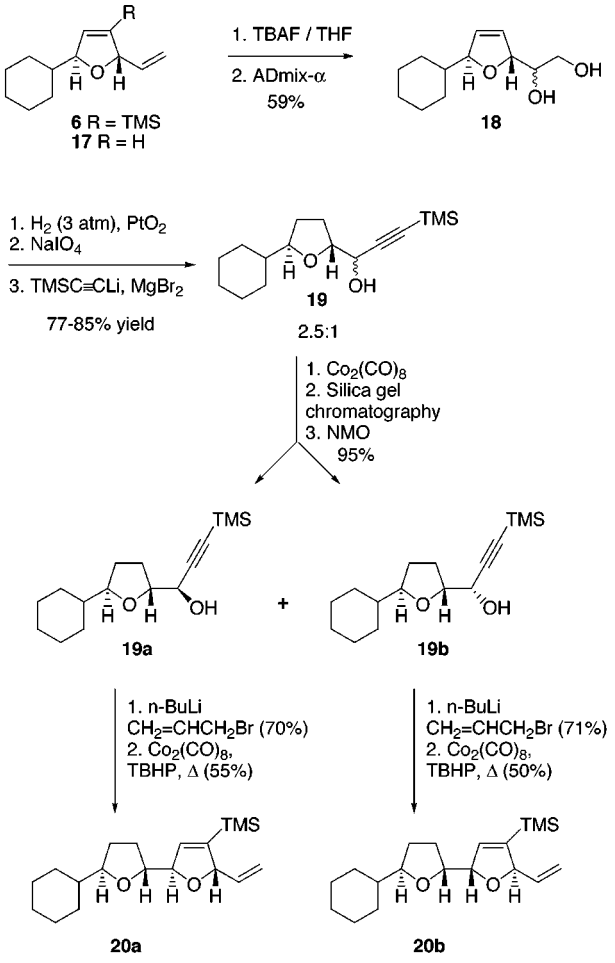


Figure 1. Observed NOE signals in **6**.

alkene, and transformation of the acyclic alkene into a new allyl propargyl ether. Direct oxidation of the terminal alkene proved to be difficult. Ozonolysis of **6** did not lead to the desired aldehyde, and dihydroxylation was sluggish owing to the proximity of the trimethylsilyl group. In the end, after conducting the dihydroxylation at reflux in acetone with NMO and catalytic OsO_4, only a 36% yield of the dihydroxylated product could be obtained. To remove the steric hindrance to oxidation, the silyl group was removed by treatment with TBAF (6 equiv) in THF at reflux for 6 h, affording diene **17** in 99% yield. Dihydroxylation of **17** was much more facile, proceeding to completion within 4 h at room temperature. The yield of isolated diol was still modest (51%), possibly owing to reduced selectivity in the oxidation of the diene. Some improvement was realized when the oxidation was conducted using Sharpless' asymmetric dihydroxylation conditions. Thus, treatment of **17** with AD-mix-α at room temperature for 23 h afforded a 59% yield of the diol.[9]

Scheme 3



Hydrogenation of the remaining olefin in **18** proved to be less than straightforward. Isomerization of the double bond was observed under standard conditions ($Pd(OH)_2$/C, EtOAc, H_2 (1 atm)), leading to a 1:1 mixture of the *cis*- and *trans*-tetrahydrofurans. After examining several sets of conditions and catalysts, it was found that using PtO_2 as catalyst under 45 psi H_2 provided the tetrahydrofuran in 99% overall yield with less than 4% of the *cis*-tetrahydrofuran being formed.

To set the stage for the second cycloisomerization reaction, the diol was cleaved to the corresponding aldehyde with $NaIO_4$. Addition of the Grignard reagent formed from lithium trimethylsilylacetylide and magnesium bromide etherate proceeded cleanly and in high yield. However, under the best conditions found (5 equiv $MgBr_2$, −40 °C, Et_2O), the stereoselectivity of the addition was only modest, ranging from 1.5 to 2.5:1. As expected, the major product resulted from a Cram-chelate attack on the aldehyde.[10] Use of the corresponding triisopropoxy-titanium reagent gave a modest reversal of selectivity (1:2),[11] whereas other metals such as zinc and lithium gave no selectivity whatsoever. The mixture of alcohols could be oxidized to a single ketone with Dess−Martin periodinane in 92% yield. However reduction with a series of reducing agents such as $NaBH_4$, $Zn(BH_4)_2$, $LiBHEt_3$, and L-Selectride gave no significant improvement in diastereoselectivity relative to the Grignard reaction.

Direct separation of the alcohol diastereomers **19a** and **b** proved impossible by chromatography. However, conversion to the corresponding dicobalt hexacarbonyl complexes allowed a very easy separation by chromatography (R_f difference of 0.2 in 10% EtOAc/hexanes). After separation of the isomers, the cobalt could be removed by oxidation with NMO to afford the alcohols **19a** and **19b**, with a mass balance of 95%. In several cases, we have found that the formation of cobalt complexes allows facile separation of diastereomeric propargylic alcohols (e.g., precursor to **13**). This may prove to be a general method for separating this class of stereoisomers.

Allylation of the major addition product, **19a**, with *n*-butyllithium and allyl bromide proceeded in 70% yield. Finally, subjection of the allyl ether to the cycloisomerization conditions defined above readily furnished the diether **20a** in 55% yield. A similar sequence with **19b** afforded **20b**, also in good yield. Both reactions proceeded with complete stereocontrol, and NOE studies again confirmed that both

(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(10) The stereochemistry of **19a** and **b** was determined by coupling constant analysis, which has been shown to be reliable for this class of compounds. See: (a) Horton, D.; Tronchet, J. M. J. *Carbohydr. Res.* **1966**, *2*, 315. (b) Horton, D.; Hughes, J. B.; Thomson, J. K. *J. Org. Chem.* **1968**, *33*, 728. (c) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468.

(11) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986. See also ref 11c and Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.

reactions afforded the *trans*-stereoisomers. Thus, the method can be used for the preparation of both *trans-syn-trans* and *trans-anti-trans* polyethers.

In conclusion, we have developed a method for the formation of polytetrahydrofurans in good yield and with excellent diastereoselectivity using a cobalt-mediated cycloisomerization of allyl propargyl ethers. The method compliments other metal-mediated methods for the formation of tetrahydrofurans and should find utility in the total synthesis of poly-THF containing molecules.

Acknowledgment. Financial support for this work from NSERC is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016768L