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Synthesis of 3-acyltetrahydrofurans from formaldehyde acetals of allylic diols†

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Abstract

3-Acyltetrahydrofurans having hydrogen substituents at C5 can be prepared with high stereocontrol and enantiopurity from alkoxymethyl or thioalkoxymethyl derivatives of allylic diols. © 2000 Published by Elsevier Science Ltd.

Substituted tetrahydrofuran rings are found in numerous natural products and various medicinally useful agents. Not surprisingly, a wide variety of methods have been developed for stereocontrolled construction of tetrahydrofurans.[1] A common theme is to establish functionality and stereochemistry in an acyclic fragment that is evolved to a substituted tetrahydrofuran by an intramolecular etherification reaction. Less common are methods that construct tetrahydrofurans by C–C bond formation. A versatile method of this latter type is the assembly of substituted 3-acyltetrahydrofurans from allylic diol and carbonyl components.[2–5] As illustrated in Scheme 1, this distinctive process stitches the carbonyl carbon of an aldehyde or ketone between the alkene and alcohol termini of an allylic diol. High stereoselectivity is a signature characteristic of this tetrahydrofuran synthesis and has allowed this reaction to serve as the cornerstone of stereocontrolled total syntheses of various oxacyclic natural products.[6–10] A limitation of the method as constituted in Scheme 1 is the inability to prepare tetrahydrofurans having two hydrogen substituents at C5. In this case, the 1,3-dioxolane **2** is extremely stable[§] and

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† We are delighted to dedicate this paper to Harry Wasserman on the occasion of his 80th birthday. His creative scholarship and leadership have immeasurably enriched organic chemistry.

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§ 4-Alkenyl-1,3-dioxolanes are likely intermediates in the direct condensation of **1** with aldehydes and ketones to form **4**.

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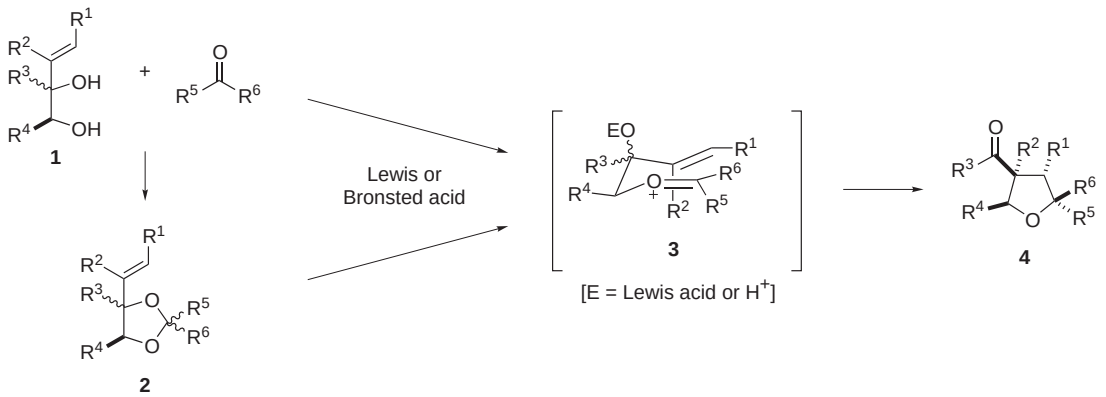


Scheme 1. Formation of 3-acyltetrahydrofurans from allylic diols and aldehydes or ketones

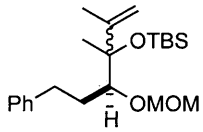
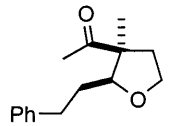
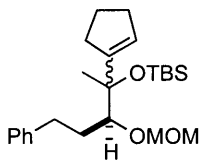
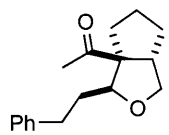
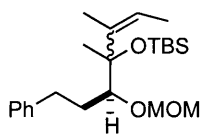
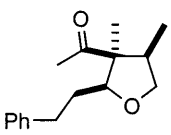
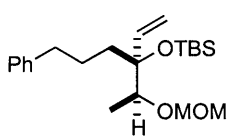
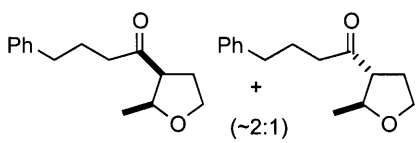
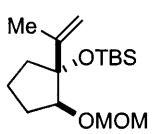
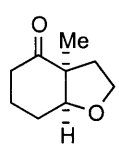
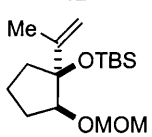
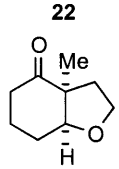
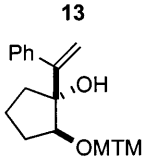
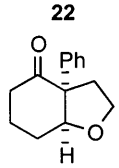
does not undergo ring-opening to generate the obligatory intermediate **3** under conditions mild enough to avoid heterolytic cleavage of the allylic C–O bond.[4,5] In this communication, we report a modification of the sequence depicted in Scheme 1 that allows 5-unsubstituted tetrahydrofurans **4** ($R^5 = R^6 = H$) to be prepared. Moreover, we report the best evidence to date that this tetrahydrofuran synthesis takes place by a Prins cyclization–pinacol rearrangement pathway.

Our approach for generating formaldehyde oxonium ions **3** ($R^5 = R^6 = H$) was to access these intermediates from allylic diol precursors having the homoallylic alcohol protected as an alkoxymethyl or thioalkoxymethyl ether. Initial scouting experiments showed that methoxymethyl (MOM) and methylthiomethyl (MTM) derivatives functioned well, and that to prevent 1,3-dioxolane formation the allylic alcohol was best protected with a *tert*-butyldimethylsilyl (TBS) group. The cyclization substrates depicted in Table 1 were prepared in 41–81% overall yield from commercially available starting materials by reaction of α-alkoxyketone intermediates[¶] with alkenyl Grignard or lithium reagents followed by silylation (TBS-OTf, 2,6-lutidine) of the intermediate alcohols.[**] We initially surveyed a variety of Lewis acids for the conversion of propenyl substrate **6** to acyltetrahydrofuran **17**. Strong Lewis acids or reagents that convert the methoxymethyl group to more labile halomethyl intermediates[11] were required (Table 1). For example, the conversion of **6**→**17** was realized within hours at −78°C in CH_2Cl_2 in the presence of 1 equiv. of $TiCl_4$ or BCl_3 (entries 1 and 3). While bromodimethylborane could also be employed,[12] this Lewis acid was not strong enough to promote ionization of the initially produced bromomethyl derivative except at elevated temperatures; as a result yields of **17** were improved by promoting this ionization at −78°C by adding $AgBF_4$ (entry 2). A single

[¶] (a) (±)-3-(Methoxymethoxy)-5-phenyl-2-pentanone was prepared in 58% overall yield from 2-methyl-5-phenyl-1-penten-3-ol by the following sequence: (i) MOM-Cl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, rt; (ii) cat. OsO_4, $NaIO_4$, dioxane–H_2O, rt. (b) (*S*)-2-(Methoxymethyl)-6-phenyl-3-hexanone was prepared in 52% overall yield from ethyl (*S*)-lactate by the following sequence: (i) $(MeO)_2CH_2$, $BF_3{\cdot}OEt_2$, 4 Å molecular sieves, CH_2Cl_2, rt; (ii) $Ph(CH_2)_3Li$, Et_2O, −100°C. (c) (±)-2-(Methoxymethoxy)cyclopentanone was prepared in 52% yield from 2-hydroxycyclopentanone by reaction with MOM-Cl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, rt. (d) (±)-2-[(Methylthio)methoxy]cyclopentanone was prepared in 54% yield from 2-hydroxycyclopentanone by reaction with MTM-Cl, $AgNO_3$, 2,6-lutidine, toluene, 60°C.

[**] The stereochemistry of the cyclization precursors was confirmed by ^1H NMR NOE experiments. The enantiopurity of (*S*)-lactate-derived **10** was established by HPLC analysis using a Daicel OJ column.

Table 1
Synthesis of 5-unsubstituted 3-acyltetrahydrofurans[a]

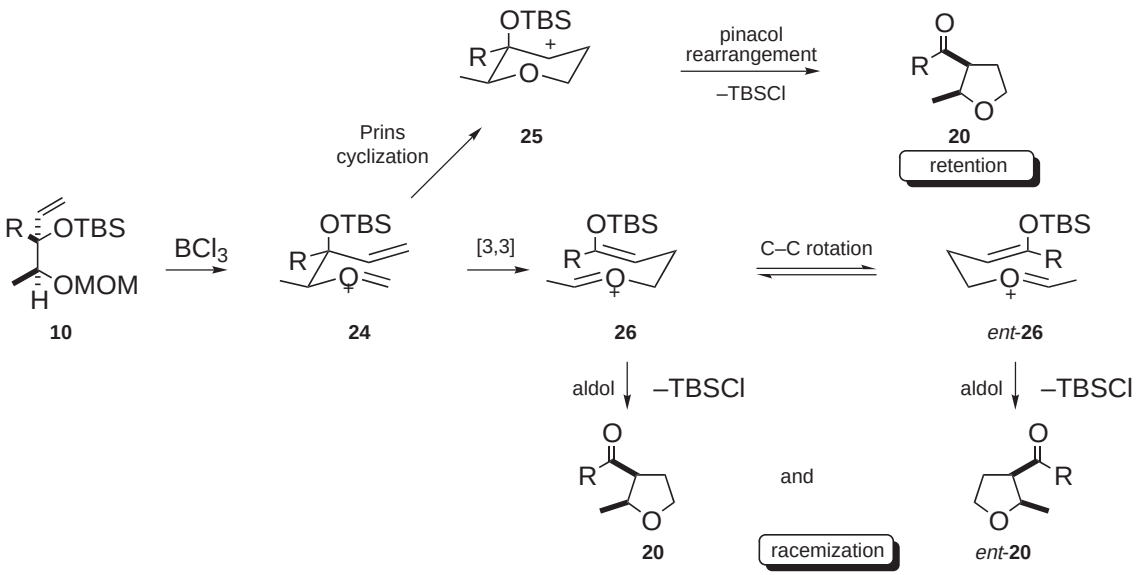
entry	substrate	promoter	product(s)	yield
1	 **6**[b]	$TiCl_4$	 **17**	71%
2		$BrBMe_2$; $AgBF_4$		73%
3		BCl_3		85%
4	 **7**[b]	BCl_3	 **18**	61%
5	 **8**[b]	BCl_3	 **19**	67%
6	 **10** (er >98:2)	BCl_3	 **20** (er >98:2) **21**	53%
7	 **12**	BCl_3	 **22**	80%
8	 **13**	BCl_3	 **22**	10%
9	 **15**	$Me_2SSMe^+ BF_4^-$	 **23**	62%

[a]One equivalent of a 1 M CH_2Cl_2 solution of BCl_3 was added to a CH_2Cl_2 solution of the substrate (0.1 M) at –78 °C (bath temperature). The reaction, which was complete within 1–2 h (TLC analysis), was quenched at –78 °C by adding excess pH 7 NH_4Cl–NH_3 buffer. Products were purified by flash chromatography on silica gel. Reaction conditions for other promoters are described in the text. [b] A 2–3:1 mixture of epimers.

tetrahydrofuran **17**, whose stereochemistry was secured by ^{1}H NMR NOE experiments, was produced (dr >98:2) under all three reaction conditions. Attempted conversion of the congener of **6** lacking the TBS group to **17** under similar conditions provided only the corresponding 1,3-dioxolane. Since the yield of **17** from **6** was highest with BCl_3, this Lewis acid was chosen for subsequent experiments.

The scope of this synthesis of 3-acyl-5-unsubstituted tetrahydrofurans is summarized in Table 1. The nucleophilicity and stereochemistry of the alkene component can be varied widely (entries 3–6), which allows substituents to be introduced with high stereocontrol at carbons 2, 3 and 4 of the tetrahydrofuran ring. With the exception of entry 6, a single tetrahydrofuran stereoisomer was produced.[††] The minor *trans* isomer formed in the rearrangement of **10** likely arises by epimerization of **20** subsequent to its formation, since the amount of **21** produced varied from run to run. Significantly, there was no detectable loss of enantiopurity in the conversion of **10**→**20**.[††] Entries 7 and 9 show that *cis*-hexahydrobenzofuranones can be prepared in useful yields from cyclization precursors derived from *trans*-1-alkenylcyclopentane-1,2-diols. Moreover, entry 9 illustrates that this tetrahydrofuran synthesis can be carried out under milder, more selective conditions by using dimethyl(methylthio)sulfonium tetrafluoroborate to activate the MTM precursor.[13] This entry also shows that when the 1,3-dioxolane derived from the rearrangement substrate has some degree of strain, protecting the allylic hydroxyl group is not essential. The major product produced from exposure of *cis*-1-alkenylcyclopentane-1,2-diol-derived precursor **13** to BCl_3 was the corresponding 1,3-dioxabicyclo[3.3.0]octane (1,3-dioxolane formation).

As we have discussed in some detail previously,[4] two possible mechanisms for the formation of 3-acyltetrahydrofurans from allylic diol and carbonyl precursors are Prins cyclization[14] followed by pinacol rearrangement,[15] and 2-oxonia[3,3]-sigmatropic rearrangement followed by aldol-type cyclization. These possibilities are illustrated in Scheme 2 for the conversion of **10**→**20**.



Scheme 2. Mechanistic possibilities (R = $CH_2CH_2CH_2Ph$)

[††] Stereochemical assignments were made by ^{1}H NMR NOE experiments. Enantiopurity of **20** was established by HPLC analysis using a Daicel OD column.

A cyclization–pinacol sequence must proceed with retention of configuration at the homoallylic stereogenic center.[15] In contrast, a [3,3]-sigmatropic rearrangement–aldol process would yield racemic products if the rearranged oxonium ion (**26** in the example illustrated in Scheme 2) contained no stereogenic centers and the barrier for aldol cyclization was higher than that of C–C single bond rotation.[§§] The complete preservation of enantiomeric purity in the conversion of **10**→**20** is consistent with a cyclization–pinacol pathway. This result constitutes a more convincing mechanistic proof than the one reported earlier,[4] since the weakly nucleophilic terminal vinyl group of **10** provides no bias towards Prins cyclization.

In summary, 3-acyl-5-unsubstituted tetrahydrofurans can be prepared with high stereocontrol and enantiopurity from methoxymethyl or (methylthio)methyl derivatives of allylic diols. These transformations, and related reactions reported earlier,[3–10] most likely proceed by Prins cyclization–pinacol rearrangement pathways.

Acknowledgements

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[§§] A reasonable assumption considering the low barriers of C–C single bond rotations.[16]