New Stereocontrolled Synthesis of Substituted Tetrahydrofurans from 1,3-Dioxolan-4-ones

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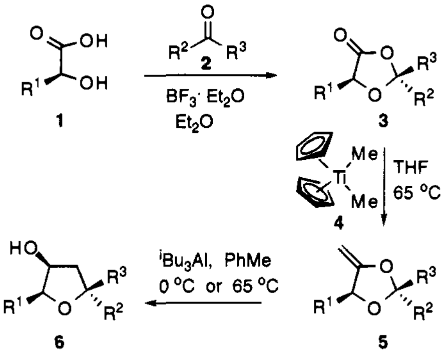
The synthesis of heterocyclic molecules is of increasing interest due to the many important biological properties of such compounds. Herein we introduce a new, concise, convergent, and highly stereocontrolled approach to certain types of heterocycles which involves only three steps from readily available precursors: (a) condensation of an aldehyde or ketone with a heteroatom-substituted carboxylic acid; (b) titanium-mediated carbonyl olefination; and (c) aluminum-mediated rearrangement involving an overall transposition of a ring heteroatom with a carbon atom. While this sequence is applicable to the synthesis of several heterocyclic rings, in this paper we demonstrate its application to tetrahydrofurans.

Among the synthetic approaches to tetrahydrofurans[1] most common are those involving C–O bond cyclizations,[1] although several methods based on the intramolecular formation of C–C bonds via oxocarbenium ions[2] or other intermediates[3] have also been reported. The three-step strategy described herein relies on a novel aluminum-mediated rearrangement which also involves an intramolecular C–C bond forming process.

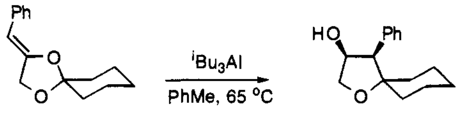
The first step in this sequence involves the acid-catalyzed condensation of an α-hydroxy acid (**1**) with an aldehyde or ketone (**2**) to form 1,3-dioxolan-4-ones (**3**).[4] When $R^1 \neq H$ and $R^2 \neq R^3$, this process generates a chiral acetal carbon in a highly stereocontrolled manner,[4] resulting from the minimization of the strong 1,3-steric interactions. Titanium-mediated methylenation of the carbonyl group of **3** to give **5** can be done efficiently with our recently developed method[5] using dimethyltitanocene (**4**) at 65 °C. The nonacidic nature of this mild olefination process[5c] allows the isolation of the highly acid-labile intermediate **5**, without significant decomposition. Reaction of **5** with 2 equiv of a trialkylaluminum reagent results in the formation of tetrahydrofurans **6**. Interestingly, when R^1 = Me, the Al-mediated rearrangement proceeds rapidly at 0 °C, while the unsubstituted derivatives (R^1 = H) require heating at 65 °C. Several illustrative examples are given in Table 1.



The trialkylaluminums are the most effective reagents that we have found for the conversion of **5** to **6**. As shown in Table 1, $^iBu_3Al$ gave secondary alcohols (**6**), while Me_3Al (entries 2, 11) formed the methyl addition products (**7**) and Et_3Al (entry 3) led to the corresponding ethyl addition product (**8**). More acidic Lewis acids, such as $BF_3{\cdot}Et_2O$, $SnCl_4$, $LiClO_4$, $EtAlCl_2$, Et_2AlCl, TMSOTf, $TiCl_4$, etc., did not mediate this rearrangement. Instead, they resulted in the rapid decomposition of the substrate.

An important feature of this reaction is that it proceeds with a high degree of stereocontrol. In general, the configuration of the acetal carbon established during the acetalization step is retained or enhanced during the rearrangement. Interestingly, when stereochemically pure **5g** and **5h** were subjected to the same rearrangement conditions, they both gave the same tetrahydrofuran, **6h**,[6] even at low temperatures.

The use of other titanocenes in the olefination step can lead to a different substitution pattern. Thus, compound **9**, obtained by carbonyl benzylidenation of **3a** with dibenzyltitanocene,[7] reacted with $^iBu_3Al$ to afford the crystalline alcohol **10**, as the major product.[6]



9 10, 75% (97 % syn)

Mechanistically, the formation of the tetrahydrofuran ring implies an Al-mediated [1,3]-sigmatropic rearrangement, which is less common[8] than the well-known Al-catalyzed Claisen rearrangement.[9] Similarly to other variants of this symmetry-forbidden process,[10] this rearrangement is apparently a stepwise transformation. Presumably, initial coordination of the aluminum with the enolic O atom leads to ring opening assisted by the antiperiplanar lone pair of the other O atom. Unlike other

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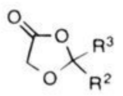
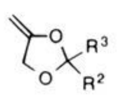
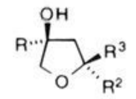
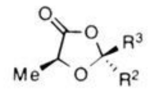
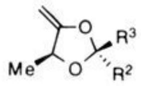
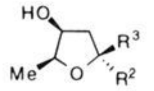
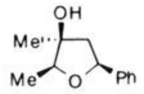
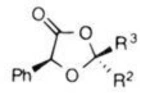
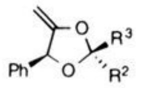
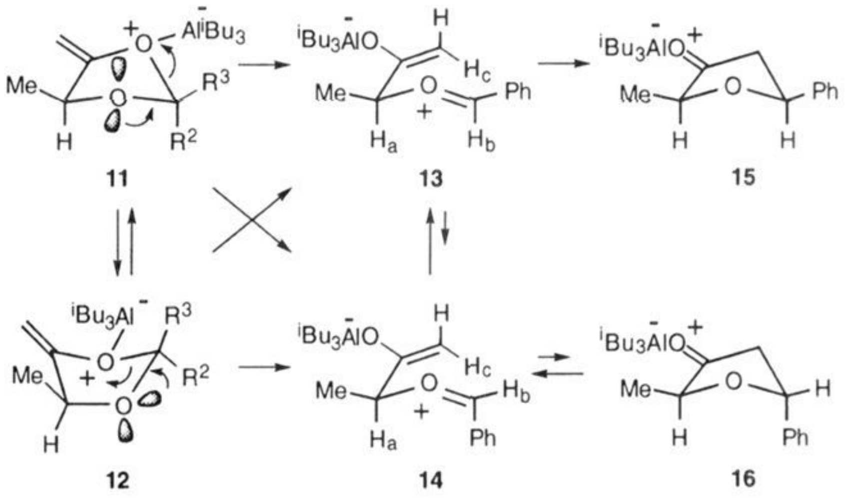
Table 1. Synthesis of Tetrahydrofuranyl Alcohols by Methylenation of 1,3-Dioxolan-4-ones, Followed by Reductive Aluminum-Mediated [1,3]-Rearrangement

Entry	1,3-Dioxolan-4-one[a,b]	Vinyl acetal / ketal[b,c]	Conditions[d]	Tetrahydrofuran[b]
				
1	**3a**, $R^2, R^3 = (CH_2)_5$	**5a**, 88%	$^iBu_3Al$, 65 °C	**6a**, 65% (R = H)
2			Me_3Al, 65 °C	**7a**, 50% (R = Me)
3			Et_3Al, 65 °C	**8a**, 55% (R = Et)
4	**3b**, $R^2 = H, R^3 = {}^tBu$	**5b**, 83%	$^iBu_3Al$, 65 °C	**6b**, 78% (80% syn)
5	**3c**, $R^2 = H, R^3 = CH_2Ph$	**5c**, 89%	$^iBu_3Al$, 65 °C	**6c**, 75% (61% syn)
6	**3d**, $R^2 = H, R^3 = (CH_2)_9Me$	**5d**, 88%	$^iBu_3Al$, 65 °C	**6d**, 83% (62% syn)
				
7	**3e**, $R^2, R^3 = (CH_2)_5$	**5e**, 90%	$^iBu_3Al$, 0 °C	**6e**, 91% (91% syn)
8	**3f**, $R^2 = Me, R^3 = {}^tBu$	**5f**, 86%	$^iBu_3Al$, 0 °C	**6f**, 90% (71% syn)
9	**3g**, $R^2 = Ph, R^3 = H$	**5g**, 55%	$^iBu_3Al$, 0 °C	**6h**, 90% (> 99% syn)
10	**3h**, $R^2 = H, R^3 = Ph$	**5h**, 55%	$^iBu_3Al$, 0 °C	**6h**, 90% (> 99% syn)
				
11			Me_3Al, 0 °C	**7h**, 77% (> 99% syn)
				
12	**3i**, $R^2 = H, R^3 = {}^tBu$	**5i**, 91%	$^iBu_3Al$, -78 °C	dec.
13	**3j**, $R^2 = H, R^3 = Ph$	**5j**, 74%	$^iBu_3Al$, -78 °C	dec.
14	**3k**, $R^2 = R^3 = Me$	**5k**, 76%	$^iBu_3Al$, -78 °C	dec.

[a] Prepared according to literature procedures as follows: **3a**,[4c] **3e**,[4a] **3f−h**,[4d] **3i**,[4b] **3j,k**.[4a] Compound **3b** was prepared via the TMSOTf-catalyzed reaction between ^tBuCHO and the bis-TMS derivative of glycolic acid,[4c] while compounds **3c,d** were prepared from the aldehyde and glycolic acid in the presence of $BF_3{\cdot}OEt_2$.[4a] [b] Yields were determined following isolation by distillation or chromatography and were not optimized. [c] Prepared by the reaction of **3** with dimethyltitanocene at 65 °C in THF.[5a] [d] All reactions were carried out with 2 equiv of the aluminum reagent in toluene at the indicated temperature.

reactions of cyclic acetals initiated by Lewis acids, which result in an overall *intermolecular* nucleophilic attack at the acetal carbon,[11] cleavage of the activated C−O bond in the vinyl acetal results in the simultaneous formation of a reactive aluminum enolate. This species then undergoes an *intramolecular* reaction with the oxocarbenium moiety,[2,12] in a rare example of a 5-(enolendo)-endo-trig cyclization.[13] Finally, further reaction with the aluminum reagent[9] leads to the obtained alcohol products.

The observed formation of a single isomer (**6h**) from either **5g** or **5h** can be attributed to a number of factors. It is possible that this selectivity results from a different conformational preference[14] of the initial aluminum adduct (e.g., **5h** → **11h** vs **5g** → **12g**), while the subsequent ring opening of both **11h** and **12g** forms only the (*E*)-oxocarbenium species (**13**). Alternatively, if any *Z*-isomer (**14**) is formed, it can undergo a fast isomerization[2e,f,15] to the *E*-isomer (**13**), which is expected to be more stable due to a double allylic 1,3-strain[16] resulting from the preferred axial disposition of H_a with both H_b and H_c. This would imply either that the cyclization of **14** to **16** is a much slower process or that an overall equilibration[12d] of **16** with **15** can take place prior to the final stereoselective reduction step.



In summary, we have found that carbonyl olefination of 1,3-dioxolan-4-ones followed by aluminum-mediated rearrangement results in the stereoselective formation of tetrahydrofurans. Similar transformations with other hydroxy acids and amino acids are under investigation.

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Supplementary Material Available: Spectroscopic data of new compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfiche version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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