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Trans-2,5-Disubstituted Tetrahydrofurans via Addition of Carbon Nucleophiles to the Strained Bicyclic Acetal 2,7-Dioxabicyclo[2.2.1]heptane

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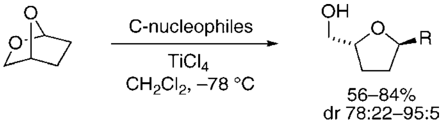
ABSTRACT



Addition of allyltributylstannane to 2,7-dioxabicyclo[2.2.1]heptane in the presence of TiCl$_4$ produces 5-allyl-2-(hydroxymethyl)tetrahydrofuran with a *trans*/*cis* ratio of 93:7. The *trans*-selectivity is also observed in additions of various other carbon nucleophiles.

Disubstituted tetrahydrofurans and bis(tetrahydrofurans) are prominent structural features in annonaceous acetogenins, a broad class of lipophilic natural products that includes a number of potent cytotoxins such as bullatacin, asimicin, and squamocin (Figure 1).[1] Such compounds exhibit potent inhibition of mitochondrial complex 1 (NADH/ubiquinone oxidoreductase), an effect which has been linked with induction of apoptosis. Recently, photoactive analogues of asimicin and squamocin have been prepared; a fluorescent analogue of squamocin lacking the butenolide portion was shown to specifically target mitochondria, implicating the tetrahydrofuran motif in a selective recognition event that may be of relevance to potential antitumor agents.[2] With such interest in their biological properties, tetrahydrofurans require synthetic methods for their rapid and diastereoselective assembly.[3]

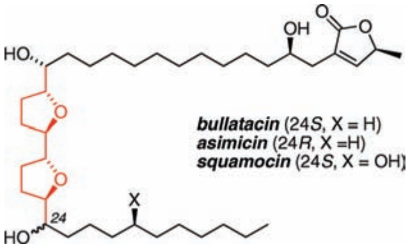


Figure 1. Tetrahydrofurans and bis(tetrahydrofurans) with a *trans*-2,5-dialkyl substitution pattern, highlighted in red in the structures above, are common among annonaceous acetogenins.

Key steps in the many valuable approaches to tetrahydrofurans include single or tandem cyclizations of hydroxy epoxides and haloalkanols,[4] oxidative cyclization of alkenes or polyenes,[5] intramolecular Prins reaction,[6] olefin metath-

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esis,[7] metal-catalyzed allylic substitution,[8] radical cyclization,[9] reductive cyclizations of carbonyl compounds,[10] and a variety of [3 + 2]-annulations.[11]

The C-glycosidic disconnection of oxacyclic compounds, i.e., addition to cyclic oxocarbenium ions (Figure 2a),[12] represents a simple yet powerful strategy in which C−C bond construction and stereoselection are achieved concurrently. Thus, there have been numerous studies of the fundamental stereochemical behavior of five-membered cyclic oxocarbenium ions, notably by Reissig[13] and Woerpel[14] (Figure 2). Woerpel concluded about *trans*-2,5-disubstituted tetrahydrofurans that "controlling this array has been challenging",[15] and Reissig noted that efforts to access this substitution pattern by allylsilane additions to oxocarbenium ions "seem to be the least predictable".[16] A number of recent efforts have addressed this limitation,[17] and new methods continue to warrant further development.

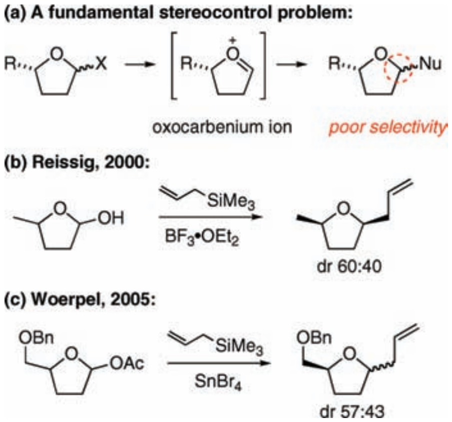

Figure 2. Stereocontrol by the 5-substituent in addition of C-nucleophiles to 5-membered cyclic oxocarbenium ions.

In developing potential solutions to the foregoing stereocontrol problem, our attention was drawn to two studies of bicyclic acetals. In 1999, Veyrieres reported a highly diastereoselective allylsilane addition reaction upon a 2,7-dioxabicyclo[2.2.1]heptane ring system (Figure 3a).[18] The tetrahydrofuran product was not accompanied by the tetrahydropyran regioisomer.[19] The preparation and reactivities of bicyclic acetal **1** (Figure 3b) were examined by Hall and co-workers, revealing rapid rates of acid-catalyzed hydrolysis (k_{rel} = 2.5 × 10^4 versus acyclic acetaldehyde dimethyl acetal).[20] Ring strain activation of the pathway to oxocarbenium ion intermediates is implied.[21] The acetals in bicyclic ring systems depicted in Figure 3 bear an internally tethered leaving group, a feature absent from the Reissig and Woerpel precedents (Figure 2). These considerations inspired the hypothesis that C−C bond forming reactions upon the 2,7-dioxabicyclo[2.2.1]heptane ring system might address the longstanding stereocontrol problem highlighted in Figure 2. We now report tests of this hypothesis, using reactions of bicyclic acetal **1** with various *C*-nucleophiles in the presence of Lewis acids.

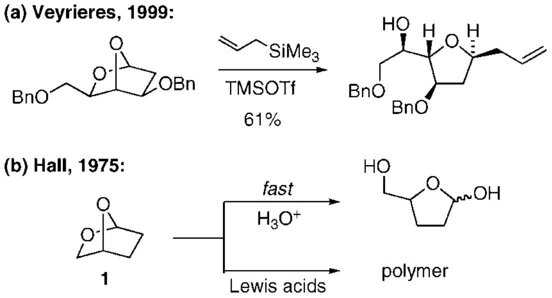

Figure 3. Reactivity of bicyclic acetals. (a) Reaction of an anhydropyranose with a C-nucleophile; the tetrahydropyran product is disfavored. (b) Relative rates of hydrolysis of **1** and acetaldehyde dimethyl acetal differ by a factor of 10^4.

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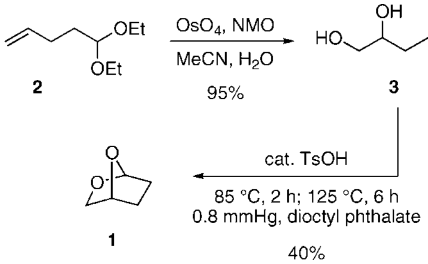
(21) Enhanced reactivity of **1** suggests that the range of conditions suitable for initiation of its reactions (i.e., combinations of Lewis acids and nucleophiles) might be broader than for other types of acetals.

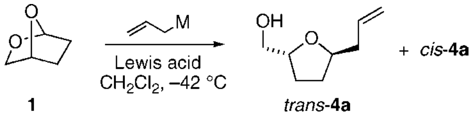
Racemic bicyclic acetal **1** was prepared from alkene **2**,[22] which was subjected to OsO_4-catalyzed dihydroxylation to afford diol **3** (Scheme 1).[23] According to Hall's method,[20] a solution of **3** in dioctyl phthalate was heated in the presence of catalytic TsOH at ca. 1 mmHg, producing first ethanol and then **1**, collected in a liquid nitrogen-cooled trap. Simple vacuum distillation through a standard short-path condenser afforded pure **1** in 40% yield.[24] This material was stored in the refrigerator and used over a few weeks time without significant degradation.

Scheme 1



Using allyltrimethylsilane as the *C*-nucleophile, an initial survey of the reactivity of **1** in the presence of Lewis acids showed facile production of allyl tetrahydrofuran **4a**[25] (Table 1). There were sharp distinctions in the *trans*/*cis* diastereomer ratio depending on the Lewis acid. In the presence of TMSOTf, $BF_3{\cdot}OEt_2$, and $Cu(OTf)_2$ there was no selectivity (entries 1−3), congruent with precedent. On the other hand, $TiCl_4$ gave a promising *trans*/*cis* ratio of 82:18 (entry 4), and a series of other Lewis acids were moderately effective (entries 5−8). With allyltributylstannane as the nucleophile, the selectivities generally increased (entries 9−12) with the exception of $SnCl_4$. In this initial screen, $AlCl_3$ and $InCl_3$ gave the highest ratios but were accompanied by incomplete conversion (entries 10 and 12). Thus, $TiCl_4$ was chosen for further development of this reaction.

Table 1. Survey of the Effects of Lewis Acids in Allylsilane and Allylstannane Additions to Bicyclic Acetal **1**[a]



entry	Lewis acid	M	*trans*/*cis*[c]
1	TMSOTf	$SiMe_3$	50:50[b]
2	$BF_3{\cdot}OEt_2$	$SiMe_3$	50:50[b]
3	$Cu(OTf)_2$	$SiMe_3$	50:50
4	**$TiCl_4$**	**$SiMe_3$**	**82:18**[b]
5	$AlCl_3$	$SiMe_3$	70:30
6	$SnCl_4$	$SiMe_3$	77:23
7	$Zn(OTf)_2$	$SiMe_3$	65:35
8	$InCl_3$	$SiMe_3$	59:41
9	**$TiCl_4$**	**$SnBu_3$**	**90:10**
10	$AlCl_3$	$SnBu_3$	94:6[d]
11	$SnCl_4$	$SnBu_3$	64:36
12	$InCl_3$	$SnBu_3$	94:6[d]

[a] Conditions: 0.1 M solution of **1** (1 mmol) in CH_2Cl_2, allylmetal reagent (1.5 mmol), Lewis acid (1 mmol); workup with saturated aqueous $NaHCO_3$. [b] Isolated yields: entry 1, 69%; entry 2, 91%; entry 4, 72%. Conversion was complete unless otherwise noted. [c] Ratio determined by GC. [d] Reaction was incomplete.

Next, the effects of temperature and solvent were assessed for the allylstannane addition to **1** in the presence of $TiCl_4$ (Table 2). Inverse dependence of selectivity on temperature was observed, with excellent selectivity available at −78 °C (entries 1−3). Diminished $TiCl_4$ (0.4 equiv) was not detrimental to selectivity but lowered the yield (entries 3 and 4). At ambient temperature in benzene and toluene, the reaction exhibited lower selectivity than in dichloromethane (entries 4−6), whereas in dichloroethane there was a slight improvement (entry 7). When operation at low temperatures is undesirable, the conditions of entry 7 offer an alternative.

Table 2. Effects of Temperature and Solvent on $TiCl_4$-Mediated Allyltributylstannane Additions to Bicyclic Acetal **1**[a]

entry	*T* (°C)	solvent	*trans*/*cis*[c]
1	**−78**	**CH_2Cl_2**	**93:7**[b]
2	−42	CH_2Cl_2	90:10
3	ambient	CH_2Cl_2	84:16[b]
4[d]	ambient	CH_2Cl_2	89:11[b]
5[d]	ambient	benzene	75:25
6[d]	ambient	toluene	77:23
7[d]	**ambient**	**$(CH_2Cl)_2$**	**89:11**
8[d]	−23	$(CH_2Cl)_2$	88:12

[a] Conditions: see entry 9, Table 1. [b] Isolated yields: entry 1, 84%; entry 3, 76%, entry 4, 57%. Conversion was complete in all cases. [c] Ratio determined by GC. [d] 0.4 equiv of $TiCl_4$.

With conditions enabling high selectivity established, scope became of interest, so the $TiCl_4$-mediated reaction

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(22) Bakina, E.; Wu, Z.; Rosenblum, M.; Farquhar, D. *J. Med. Chem.* **1997**, *40*, 4013–4018.

(23) Diol **3** has also been prepared in enantiomerically enriched form. Raifeld, Y. E.; Nikitenko, A. A.; Arshava, B. M.; Mikerin, I. E.; Zilberg, L. L.; Vid, G. Y.; Lang, S. A., Jr.; Lee, V. J. *Tetrahedron* **1994**, *50*, 8603–8616.

(24) Hall reported a yield of 85% of **1** using lower pressure and mechanical stirring. See ref 20b.

(25) Compounds **4a**, **4b**, and **4e** were identified by comparison to literature data. (a) **4a**: Pilli, R. A.; Riatto, V. B. *Tetrahedron: Asymmetry* **2000**, *11*, 3675–3686. (b) **4b**: Freifeld, I.; Holtz, E.; Dahmann, G.; Langer, P. *Eur. J. Org. Chem.* **2006**, 3251–3258. Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207–218. Iqbal, J.; Pandey, A.; Chauhan, B. P. S. *Tetrahedron* **1991**, *47*, 4143–4154. (c) **4e**: Chakraborty, T. K.; Reddy, V. R.; Sudhakar, G.; Kumar, S. U.; Reddy, T. J.; Kumar, S. K.; Kunwar, A. C.; Mathur, A.; Sharma, R.; Gupta, N.; Prasad, S. *Tetrahedron* **2004**, *60*, 8329–8339.

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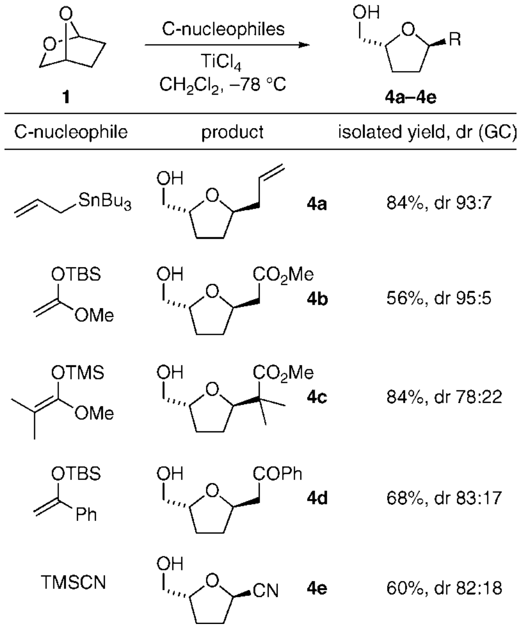
at low temperature was applied to a series of commercially available *C*-nucleophiles (Scheme 2). Excellent *trans*-selectivity (dr 95:5) was observed with the silyl enol ether derivative of methyl acetate, leading to **4b**[25] bearing ester functionality for flexible applications in total synthesis.

Scheme 2



From a mechanistic standpoint, if the reaction is S_N1-like (free oxocarbenium ion **A**, Figure 4), there should be little impact of the Lewis acid on selectivity, and the results would mirror the prior observations of poor selectivity, as highlighted in Figure 2. This appears to be the case for TMSOTf, $BF_3{\cdot}OEt_2$, and $Cu(OTf)_2$, which afford nonselective addition (entries 1−3 of Table 1). The other entries of Table 1 exhibit dramatic dependence of selectivity upon the identity of the Lewis acid, implying direct involvement of the Lewis acid in the configuration-determining step of the addition mechanism.

Figure 4. Intermediates of Suggested Relevance to Competitive Nonselective and Stereospecific Additions to Bicyclic Acetal **1**.

The departure from precedent in the *trans*-selective reactions of **1** may be explained by invoking a competition between **A** and intimate ion pair **B**[26,27] (Figure 4) for the nucleophile; the latter could react stereospecifically with inversion of configuration.[28] Relative populations of free ion and intimate ion pair may be expected to be impacted both by intramolecular tethering of the leaving group, and by the identity of the Lewis acid. Such a scenario implies that those Lewis acids affording higher selectivities ($TiCl_4$, $AlCl_3$, and $InCl_3$) avoid the S_N1-like stereorandom process[29] by increasing the reactivity and/or proportion of ion pair **B**.

In summary, addition of *C*-nucleophiles to 2,7-dioxabicyclo[2.2.1]heptane affords access to *trans*-2,5-disubstituted tetrahydrofurans, a structural subunit common in biologically active natural products. The preparative potential of the selectivity pattern established here merits further investigation, including adaptations to enantiomerically pure substances.

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Supporting Information Available: Preparative details and characterization data for **1** and **4a−e**.This material is available free of charge via the Internet at http://pubs.acs.org.

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