Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5649-5652, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01196-3

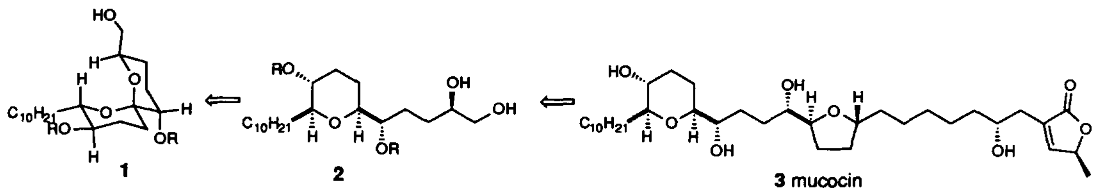
Regioselective and Stereoselective Reductive Cleavage of 1,7-Dioxaspiro[5.5]undecane Alcohols

Michael T. Crimmins* and Stephen W. Rafferty
Venable and Kenan Laboratories of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-3290

Key Words: Reductive cleavage, spiroketals, 1,7-dixaspiro[5.5]undecanes, tetrahydropyrans.

Abstract: *Lewis acid -promoted triethylsilane reduction of 6,6-spiroketal alcohols produces cis-2,6-disubstituted tetrahydropyrans with excellent regioselectivity and stereocontrol. An appended alcohol allows bidentate coordination of the Lewis acid to selectively activate one C—O bond of the anomeric center toward reductive cleavage.* Copyright © 1996 Elsevier Science Ltd

The significant presence of 1,7-dioxaspiro[5.5]undecanes (6,6-spiroketals) in natural products of biological interest[1] as well as the conformational rigidity and thermodynamic stability of spiroketals has led to a variety of imaginative synthetic applications in the use of the spiroketal scaffold as a template for stereocontrol.[2] The majority of these studies have centered on the synthesis of stereochemically complex spiroketals for their direct incorporation into complex molecules[3] or on the ring opening of the spiroketals to the corresponding hydroxyketones.[4] Applications involving reductive cleavage of the anomeric center have only recently been recognized for their potential utility.[5,6] We envisioned that regio and stereocontrolled reductive cleavage of unsymmetrical spiroketals such as **1** could be a valuable method for the synthesis of both 2,6-disubstituted tetrahydropyrans similar to **2** and acyclic stereochemical arrays as found, for example, in mucocin **3**, a known antitumor agent.[7]

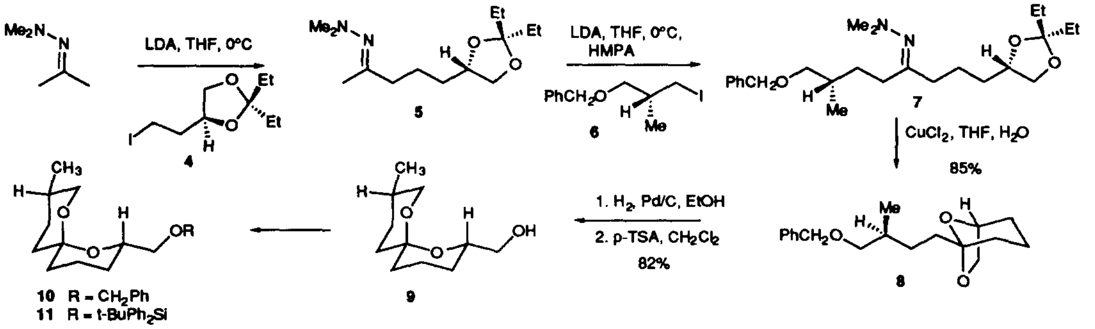


1 **2** **3** mucocin

One possible strategy for the selective cleavage of unsymmetrical spiroketals might take advantage of an adjacent oxygen functionality to form a bidentate chelate with one of the spiroketal anomeric oxygens.[8] In this manner, selective activation of one C—O bond could be effected to allow formation of one of the two possible oxocarbenium ions. A simple system to test this hypothesis was synthesized as shown in Scheme 1. Alkylation of the lithiated dimethylhydrazone of acetone with iodide **4** gave the ketal **5**[9] which was followed by a second alkylation with iodide **6** to produce the hydrazone **7** in 50% overall yield. Hydrolysis of the hydrazone with aqueous cupric chloride gave the bicyclic ketal **8** in 85% yield. Hydrogenolysis of the benzyl ether followed by brief treatment with acid gave the thermodynamically more stable spiroketal **9** in 82% yield. The primary alcohol of

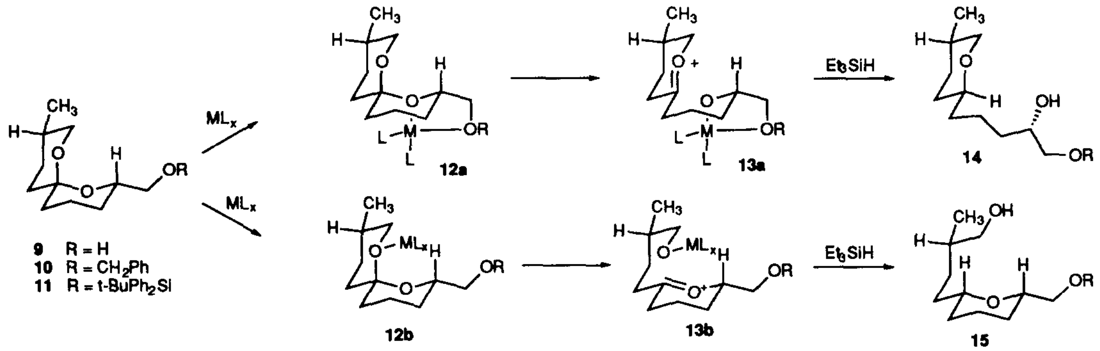
9 was readily converted to either the benzyl ether **10** (NaH, $PhCH_2Br$, THF, 85%) or the silyl ether **11** (t-$BuPh_2SiCl$, Et_3N, DMAP, CH_2Cl_2, 70%).

Scheme 1



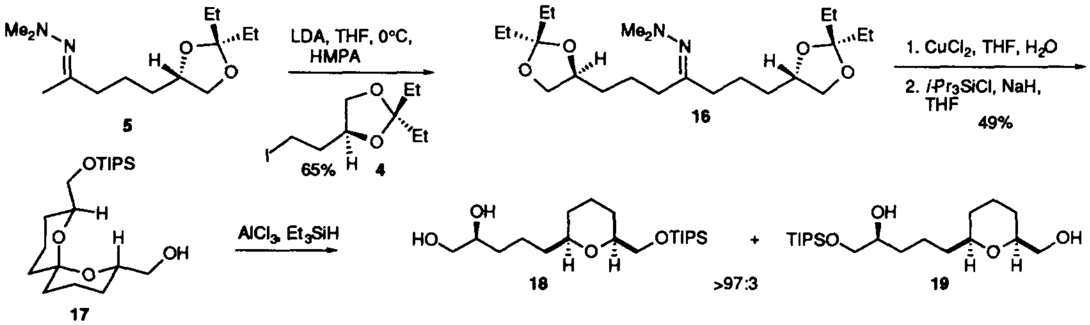
Spiroketal alcohol **9** was exposed to a variety of reduction conditions and the results are summarized in the Table. Diisobutyl aluminum hydride failed to effect reduction, instead generating the enol ether from ring opening. While treatment of spiroketal **9** with titanium tetrachloride-triethylsilane[6a] gave an 86:14 mixture of the two regioisomeric cleavage products **14** and **15**, both aluminum trichloride[10] and tin tetrachloride produced a single detectable product **14** by 300 MHz ^{1}H NMR. This highly selective reductive cleavage arises from bidentate coordination of the Lewis acid with the hydroxyl oxygen and the proximal anomeric oxygen as in **12a** resulting in selective formation of the oxocarbenium ion[11] **13a**. The apparent stereoelectronic preference for axial attack[12] on these intermediates results in a highly diastereoselective reduction to produce **14**. Interestingly, the benzyl ether **10** also underwent highly regioselective and stereoselective reduction under the same conditions, while the *t*-butyldiphenylsilyl ether **11** gave a 33:67 mixture of **14** and **15**, presumably due to steric or electronic[13] destabilization of the chelated intermediate **12a** in favor of the monodentate complex **12b**.

Scheme 2



A second model designed to determine if bidentate coordination to a hydroxyl goup could override coordination to a protected hydroxyl was then investigated (Scheme 3). Alkylation of the lithiated N,N-dimethylhydrazone **5** with a second equivalent of iodide **4** followed by hydrolysis and spiroketalization provided alcohol **17** after monosilylation with triisopropylsilyl chloride. Exposure of the alcohol **17** to aluminum trichloride-triethylsilane resulted in highly regioselective and stereoselective reductive cleavge of the anomeric center to give tetrahydropyran **18** as the only detectable product by 300 MHz ^{1}H NMR. Thus the greater effectiveness of a hydroxyl group on the regioselectivity of the reductive cleavage is demonstrated.

Scheme 3



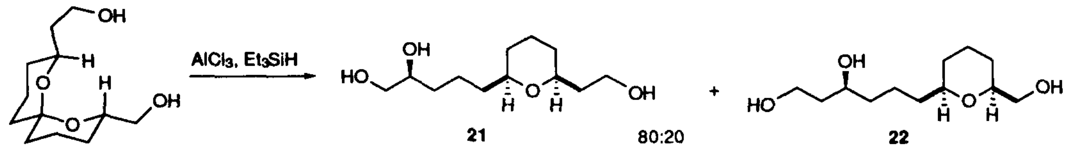
Entry	Substrate	Conditions[10]	Products (ratio)	Yield
1	**9**	$(i\text{-}C_4H_9)_2AlH$, 0 to 25°C	enol ether[14]	40%
2	**9**	$TiCl_4$, Et_3SiH, -78°C	**14**:**15** (86:14)	60%
3	**9**	Me_3Al, Et_3SiH, -78 to 25°C	no reaction	
4	**9**	Et_2AlCl, Et_3SiH, -78 to 25°C	no reaction	
5	**9**	$Ti(O\text{-}i\text{-}Pr)_4$, Et_3SiH, -78 to 25°C	no reaction	
6	**9**	$TiCp_2Cl_2$, Et_3SiH, -78 to 25°C	no reation	
7	**9**	$AlCl_3$, Et_3SiH, -78 to 25°C	**14**:**15** (>97:3)	80%
8	**9**	$SnCl_4$, Et_3SiH, -94 to -60°C	**14**:**15** (>97:3)	83%
9	**10**	$AlCl_3$, Et_3SiH, -78 to 25°C	**14**:**15** (>97:3)	91%
10	**10**	$SnCl_4$, Et_3SiH, -94 to -60°C	**14**:**15** (>97:3)	90%
11	**11**	$AlCl_3$, Et_3SiH, -78 to 25°C	**14**:**15** (33:67)	87%
12	**17**	$AlCl_3$, Et_3SiH, -78 to 25°C	**18**:**19** (>97:3)	84%
13	**20**	$AlCl_3$, Et_3SiH, -78 to 25°C	**21**:**22** (80:20)	60%

TABLE

The diol **20** (Scheme 4) was also synthesized to test the effect of ring size (five versus six membered ring chelate) in the regioselective activation of anomeric spiroketal C—O bonds. The reduction of diol **20** with aluminum trichloride-triethylsilane resulted in the formation of an 80:20 mixture of tetrahydropyrans **21**:**22** illustrating a modest preference for five membered ring bidentate coordination over six membered rings.

In conclusion, a method for the highly regioselective and stereoselective reduction of 1,7-dioxaspiro[5.5]undecanes has been developed. The effectiveness of pendant hydroxyl groups to control the regioselectivity of the cleavage of the anomeric center has been established. In addition, the preference for the formation of a five membered bidentate chelate has also been demonstrated. Further applications of this method for reductive cleavage of spiroketals are in progress.

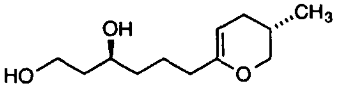
Scheme 4



Acknowledgement: We thank the National Institutes of Health (CA63572) for generous financial support. Thanks are also due to the Wellcome Foundation for a fellowship to S.W.R.

References and Notes

1. For two important recent examples see: a) Pettit, G.R.; Cichacz, Z.A.; Gao, F.; Herald, C.L.; Boyd, M.R.; Schmidt, J.M.; Hooper, J.N.A. *J. Org. Chem.* **1993**, *58*, 1302-1305. b). Fusetani, N.; Shinoda, K.; Matsunaga, S. *J.Am. Chem. Soc.* **1993**, *115*, 3977-3981.
2. For a review see: Perron, F.; Albizati, K.F. *Chem. Rev.* **1989**, *89*, 1617-1661.
3. For some recent examples see: Evans, D.A.; Ng. H.P.; Rieger, D.L. *J. Am. Chem. Soc.* **1993**, *115*, 11446-11459. Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031. White, J.D.; Bolton, G.L.; Dantanarayana, A.P.; Fox, C.M.J.; Hiner, R.N.; Jackson, R.W.; Sakuma, K.; Warrier, U.S. *J. Am. Chem. Soc.* **1995**, *117*, 1908-1939. Crimmins, M.T.; O'Mahony, R. *J. Org. Chem.* **1989**, *54*, 1157-1161.
4. a) Ireland, R.E.; Daub, J.P. *J. Org. Chem.* **1983**, *48*, 1303-1312.. b) Ireland, R.E.; Daub, J.P.; Mandel, G.S.; Mandel, N.S. *J. Org. Chem.* **1983**, *48*, 1312-1325. c) Schreiber, S.L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303-5305. d) Totah, N.L.; Schreiber, S.L. *J. Org. Chem.* **1991**, *56*, 6255-6256. e) Bernet, B.; Bishop, P.M.; Caron, M.; Kawamata, T.; Roy, B.L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818.
5. During the late stages of the completion of this manuscript, we became aware of a similar study, however, all our experiments were conducted independent of this work. Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048-5068.
6. a) Zhao, Y.; Pratt, N.E.; Heeg, M.J.; Albizati, K.F. *J. Org. Chem.* **1993**, *58*, 1300-1301. b) Pettit, G.R.; Albert, A.H.; Brown, P. *J. Am. Chem. Soc.* **1972**, *94*, 8095.
7. Shi, G.; Alfonso, D.; Fatope, M.O.; Zeng, L.; Gu, Z.; Zhao, G.; He, K.; MacDougal, J.M.; MaLaughlin, J.L. *J. Am. Chem. Soc.* **1995**, *117*, 10409-10410.
8. Takano, S.; Kurotaki, A.; Sekiguchi, Y.; Satoh, S.; Hirama, M.; Ogasawara, K. *Synthesis* **1986**, 811-817.
9. All new compounds gave consistent ^{1}H, ^{13}C, and IR spectra as well as satisfactory C, H combustion analyses or HRMS. All yields are for homogeneous, chromatographically pure products unless otherwise indicated.
10. Typical experimental procedure: To a 0.25 M solution of the spiroketal in dichloromethane at -78°C was added 1.0 equiv. of Et_3SiH. The mixture was stirred for 10 min whereupon a solution of the Lewis acid (1.0 equiv) was added dropwise. After stirring at -78°C for 4 h (for trialkylsilyl or benzyl derivatives), or warming to 25°C for 4 - 6 h (for the alcohols), the reaction was quenched with aqueous sodium bicarbonate and diluted with water. The aqueous layer was extracted with dichloromethane and the combined organic layers were combined, dried and concentrated. After determination of isomeric ratio of the crude product by NMR, the residue was purified by silica gel chromatography.
11. a) Sammakia, T.; Smith, R.S. *J. Am. Chem. Soc.* **1994**, *116*, 7915-7916. b) Denmark, S.E.; Almstead, N.G. *J. Am. Chem. Soc.* **1991**, *113*, 8089-8110.
12. Deslongchamps, P.; Stereoelectronic Effects in Organic Chemistry. Organic Chemistry Series, Vol. 1 Pergamon Press, Oxford, England, 1983. See also reference 6a.
13. Shambayati, S.; Blake, J.F.; Wierschke, S.G.; Jorgensen, W.L.; Schreiber, S.L. *J. Am. Chem. Soc.* **1990**, *112*, 697-703.
14. The major product from this reaction was the enol ether below.



(*Received in USA* 13 *May* 1996; *revised* 11 *June* 1996; *accepted* 12 *June* 1996)