J|A|C|S
COMMUNICATIONS

Published on Web 12/09/2006

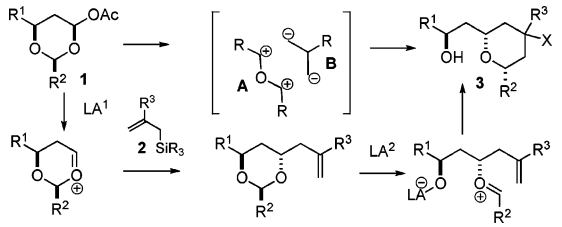
A Sakurai−Prins−Ritter Sequence for the Three-Component Diastereoselective Synthesis of 4-Amino Tetrahydropyrans

Oleg L. Epstein and Tomislav Rovis*
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received September 20, 2006; E-mail: rovis@lamar.colostate.edu

Multicomponent reactions play an important role in the preparation of complex organic molecules.[1] The tetrahydropyran ring has attracted significant attention in recent years, as it is a part of the backbone of many natural products.[2] We envisioned that the tetrahydropyran nucleus could be formed by [3+3] cyclocondensation which would complement [4+2] hetero-Diels−Alder methods[3] (see Scheme 1). This strategy calls for biselectrophile **A**, revealed sequentially, and 3-atom bisnucleophile **B**.[4] 4-Acetoxy-1,3-dioxane **1**[5] fulfills the requirement of a biselectrophile; the two acetals are sufficiently differentiated that their rates of ionization allow selective revelation of one over the other. Allyl silane **2** appeared to be an attractive option for the bisnucleophile component, since a Prins cyclization[6] could be used to close the ring after the initial Sakurai reaction. Herein, we report the successful execution of this strategy utilizing a Ritter reaction to quench the 4-tetrahydropyranyl cation, with the overall sequence proceeding in excellent diastereoselectivity.[7,8]

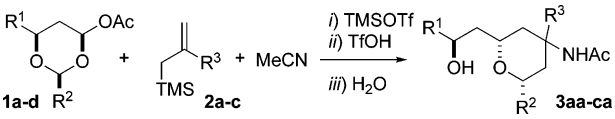
Scheme 1. [3+3] Cyclocondensation Strategy

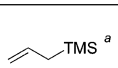
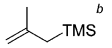
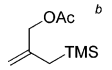


Rychnovsky has demonstrated that dioxanyl acetals undergo diastereoselective allylation to afford 1,3-anti relationships in excellent yield.[9] In ample studies investigating Prins cyclization reactions, Rychnovsky has shown that the reaction forms 2,6-*cis* tetrahydropyrans diastereoselectively.[10] In an attempt to develop a diastereoselective and efficient one-pot process, we have discovered that treatment of 4-acetoxy-1,3-dioxanes **1a**−**e**[5] with allyltrimethylsilane **2a** in the presence of TMSOTf, followed by the addition of TfOH[11] (2 equiv) in the presence of acetonitrile as a cosolvent, affords 4-acetamidotetrahydropyrans **3aa**−**3ae**[12] in good yields and high diastereoselectivities (entries 1−5, Table 1).[13] All three substituents on the tetrahydropyranyl ring occupy *equatorial* positions, as confirmed by NOE experiments. In each case, an excellent degree of selectivity was observed for the newly formed stereogenic centers at the 2-, 4-, and 6-positions of the tetrahydropyran ring.

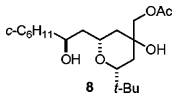
A rationale for the all-cis selectivity could be found in computational work from Alder.[14] This work suggests that Prins cyclization of an (*E*)-oxocarbenium ion proceeds through a chairlike transition state with the formation of tetrahydropyranyl cation **4** (R^3 = H) (Scheme 2), which has an increased stability relative to the open-chain oxocarbenium ion due to delocalization. The calculated optimal geometry for delocalization places the hydrogen atom at C4 in a pseudoaxial position, a deviation from the planarity expected at sp^2 hybridized carbon, thus favoring equatorial trapping of the nucleophile.

Table 1. Sequential Sakurai−Prins−Ritter Reactions

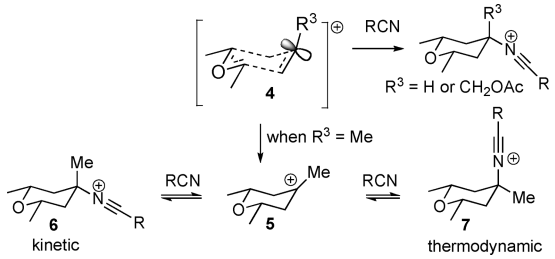


Entry	1,3-Dioxane	Allyl silane	Product, yield (%) (dr)
		 **2a**	
1	**1a**: R^1= *c*-C_6H_{11}; R^2=*t*-Bu		**3aa** 79 (97:3)
2	**1b**: R^1= *c*-C_6H_{11}; R^2=*n*-Pr		**3ba** 80 (97:3)
3	**1c**: R^1= $Ph(CH_2)_2$; R^2=*t*-Bu		**3ca** 77 (97:3)
4	**1d**: R^1= $Ph(CH_2)_2$; R^2=*n*-Pr		**3da** 75 (98:2)
5	**1e**: R^1= $PivO(CH_2)_2$; R^2=$(CH_2)_3Cl$		**3ea** 59 (90:10)
		 **2b**	
6	**1a**		**3ab** 88 (97:3)
7	**1b**		**3bb** 71 (97:3)
8	**1c**		**3cb** 80 (96:4)
9	**1d**		**3db** 72 (96:4)
		 **2c**	
10	**1a**		**3ac** 61 (99:1)[c]

[a] Procedure A: (i) TMSOTf (1 equiv), −45 °C; (ii) TfOH (2 equiv), −45 to −15 °C; (iii) Ac_2O, −15 to 0 °C, CH_2Cl_2/MeCN (1:1). [b] Procedure B: (i) TMSOTf (1 equiv), −45 °C; (ii) TfOH (2 equiv), −45 to 0 °C;(iii) $NaHCO_3$, MeCN; see Supporting Information for details. [c] Tertiary alcohol **8** was isolated in 8% yield as a 1:1 mixture of diastereomers at the 4-position.



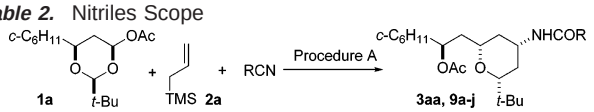
Scheme 2. Stereochemical Rationale Based on Alder's Model



High selectivity for the formation of 4-methyl-4-acetamidotetrahydropyrans **3ab**−**3db** was also observed when methallylsilane **2b** was used (entries 6−9, Table 1). In each case the major diastereomer possesses an *axial* acetamide substituent. Moreover, the temperature dependence of the diastereomeric composition of the products was clearly observed: the axial acetamide isomer predominated

10.1021/ja066794k CCC: $33.50

Table 2. Nitriles Scope



entry	product	R	dr	yield (%)
1	**3aa**	Me	97:3	79
2	**9a**	Et	96:4	84
3	**9b**	*i*-Pr	94:6	81
4	**9c**	*t*-Bu	95:5	71
5	**9d**	CH_2F	99:1	83
6	**9e**	CH_2Cl	97:3	79
7	**9f**	CH_2Br	95:5	89
8	**9g**	CH_2OMe	94:6	66[a]
9	**9h**	vinyl	98:2	75[a]
10	**9i**	allyl	95:5	42
11	**9j**	Ph	93:7	77

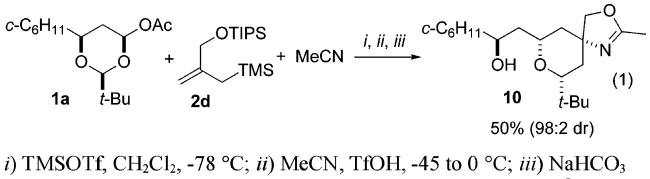
[a] Isolated yield after aqueous workup and acetylation of unpurified reaction mixture with Ac_2O/Py/DMAP.

when the reaction mixture was allowed to warm to 0 °C.[15] This, again, is consistent with Alder's model for the tetrahydropyranyl cation, where it was shown that 4-methyl substituted tertiary cation **5** is much more stable than the open form **4** (R^3 = Me). The trapping of the tertiary carbocation with the nitrile leads to the formation of equatorial nitrilium ion **6**, which then equilibrates to the apparently more thermodynamically stable axial isomer **7**.

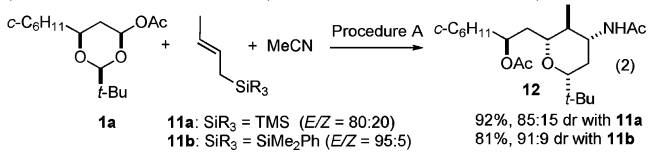
Destabilization of the intermediate tertiary cation with an electron-withdrawing acetoxymethyl substituent was observed when 2-acetoxymethyl allylsilane **2c** was used (entry 10, Table 1). In this case the formation of equatorial acetamide product was observed in addition to a small amount of tertiary alcohol **8**.[16]

This three-component coupling sequence allows the installation of added diversity at the 4-position. Indeed, a variety of nitriles successfully participate in the one-pot Sakurai−Prins−Ritter reaction (Table 2) to give substituted amides **9a**−**j** in good yield and excellent diastereoselectivity. The presence of functional groups in the amide moiety opens a way for further functionalization of the products, including attachment to the solid phase.

It was also shown that the intermediate nitrilium ion could be successfully trapped intramolecularly by a neighboring protected hydroxyl group to form spiro-oxazoline **10** with excellent selectivity (eq 1).



i) TMSOTf, CH_2Cl_2, -78 °C; *ii*) MeCN, TfOH, -45 to 0 °C; *iii*) $NaHCO_3$



A substantial advantage of this method is the potential to use substituted silanes to introduce additional groups around the tetrahydropyran ring. An excellent degree of stereochemical induction and transfer of geometry of the double bond was observed for crotyl silanes **11a**,**b** (eq 2).

In summary, we have developed an operationally simple procedure for the highly diastereoselective preparation of 4-acylamino-2,6-substituted tetrahydropyrans by a one-pot Sakurai−Prins−Ritter reaction from readily available reagents. We note that up to four new stereocenters may be controlled from a single stereocenter present in the hydroxyacid starting material.[5]

Acknowledgment. We thank Merck, Eli Lilly, Amgen, Johnson and Johnson, and Boehringer Ingelheim for support. T.R. is a fellow of the Alfred P. Sloan Foundation and thanks the Monfort Family Foundation for a Monfort Professorship.

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

References

(1) Reviews on multicomponent reactions: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933.

(2) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843. Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. Markó, I. E.; Bayston, D. J.; *Synthesis* **1996**, 297. Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. D. *J. Org. Chem.* **1997**, *62*, 3022. Smith A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834. Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485. Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, 1912. Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176. Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388.

(3) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398. Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059. Gouverneur, V.; Reiter, M. *Chem.—Eur. J.* **2005**, *11*, 5806.

(4) For similar approaches to 4-methylene tetrahydropyrans see: Yu, C.-M.; Lee, J.-Y.; So, B.; Hong, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 161. Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189.

(5) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191. Zhang, Y.; Rovis, T. *Tetrahedron* **2003**, *59*, 8979.

(6) Reviews on a Prins cyclization: Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. Vasconcellos, M. L. A. A.; Miranda, L. S. M. *Quim. Nova* **2006**, *29*, 834.

(7) For examples of natural products and related compounds, containing 4-aminotetrahydropyran moiety see: Snider, B. B.; Hawryluk, N. *Org. Lett.* **2000**, *2*, 635. Suhara, Y.; Yamaguchi, Y.; Collins, B.; Schnaar, R. L.; Yanagishita, M.; Hildreth, J. E. K.; Shimada, I.; Ichikawa, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1999. Höfle, G.; Steimnetz, H.; Gerth, K.; Reichenbach, H. *Liebigs Ann. Chem.* **1991**, 941. Michelet, V.; Genêt, J.-P. *Curr. Org. Chem.* **2005**, *9*, 405.

(8) Two examples of the use of a Ritter reaction to terminate a Prins cyclization have appeared: (a) Perron, F.; Albizati, K. F. *J. Org Chem.* **1987**, *52*, 4128. (b) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun.* **2001**, 835.

(9) Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555. Boons, G.-J.; Eveson, R.; Smith, S.; Stauch, T. *Synlett* **1996**, 536. Rychnovsky, S. D.; Sinz, C. J. *Tetrahedron Lett.* **1998**, *39*, 6811.

(10) Trapping of the intermediate cation proceeds in varying selectivity depending on Lewis acid, nucleophile, and substitution pattern across the tetrahydropyran ring. For selected examples, see: Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939. Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904. Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652. Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499. Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727. Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429.

(11) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. Puglisi, A.; Lee, A.-L.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2006**, *8*, 1871. (See also ref. 8b.)

(12) For convenience in isolation and analysis, the resulting secondary alcohols were acetylated in situ by addition of Ac_2O prior to workup.

(13) The transformation generates three new stereocenters for a total of eight possible diastereomers. However, we observe only two isomers (GC−MS).

(14) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.

(15) Conducting the reaction between **1a** and **2b** at −45 °C results in the formation of a 29:71 mixture of axial and equatorial acetamide **3ab**.

(16) The formation of **8** could arise by intramolecular trapping of the 4-tetrahydropyranyl cation with tethered acetate followed by hydrolysis.

JA066794K