Pergamon

SCIENCE @ DIRECT®

Tetrahedron Letters 44 (2003) 9043–9045

TETRAHEDRON
LETTERS

Diastereoselective formation of seven-membered oxacycles by ring-expansion of cyclopropanated galactal☆

Rhys Batchelor and John O. Hoberg*

School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington, New Zealand

Received 4 August 2003; revised 14 September 2003; accepted 26 September 2003

Abstract—The cyclopropanation and ring-expansion of 4,6-*O*-di-(*tert*-butyl)silanediyl-D-galactal using catalytic amounts of TMSOTf and silated nucleophiles gave a range of substituted oxepanes. Good to excellent yields were obtained in addition to very high selectivities.

Seven-membered oxacycles are the central nuclei of numerous natural products.[1] From the complex polyether cytotoxins brevetoxins[2] and ciguatoxin,[3] to the simple zoapatanol[4] (Fig. 1), these molecules represent challenging synthetic targets. Given their frequent natural occurrence and unusual biological properties, numerous studies toward their synthesis have appeared.[5]

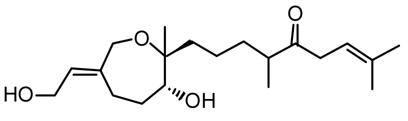
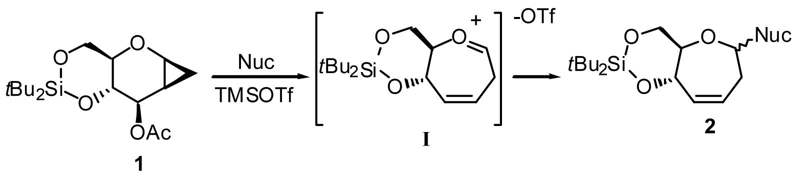


Figure 1. Zoapatanol.

As part of our interest in developing efficient synthetic methods for the preparation of oxepanes, we have introduced cyclopropanated carbohydrates as substrates for their formation (Eq. (1)).[6] We proposed that the reaction involves loss of acetate to give oxonium ion **I**, which is intercepted by a nucleophile to give the ring-expanded oxepane. This methodology thus incorporates the optical activity and multiple functionality inherent in carbohydrates. In a full report, we described a range of derivatives of **2** that were obtained in good to excellent yields, however, in all cases poor diastereoselectivity was obtained.[7] Subsequent to our introduction of this concept, Sugita and co-workers adapted it to the formation of oxepanones obtaining modest to good selectivities.[8] While our ring-expansion enables the efficient construction of the core oxepane structure, the poor stereochemical outcome diminishes this strategy's synthetic usefulness. Herein we report methodology that gives greatly improved selectivity for the reaction, and significantly enhances its synthetic utility.



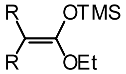
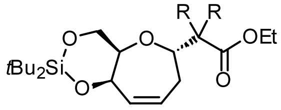
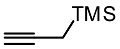
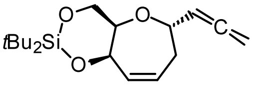
(1)

☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.09.222

* Corresponding author.

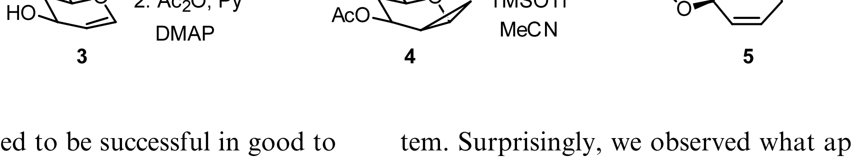
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.222

Table 1. Ring expansion of **4**

Entry	Nucleophile	Product (% yield)	Diastereoselectivity[a]
1	TMSallyl	**5a** (91)	80:1
2	TMSSPh	**5b** (85)	6:1
3	$TMSN_3$	**5c** (69)	2.5:1
4	TMSOallyl	**5d** (00)	-
			
5	R = Me	**5e** (77)	80:1
6	R = H	**5f** (68)	3:1
7		 **5g** (68)	7:1

[a] Determined on the crude reaction mixture by fused silica capillary gas chromatography.

In using the silyl protecting group in **1**,[9] a robust protecting group for the ring-expansion was obtained; however, this also resulted in a planar, intermediate oxonium ion, thus leading to poor facial selectivity. We reasoned that enhanced stereoselectivity would be obtained through use of the galactal system, which would result in hindrance of the upper face of the intermediate and direct attack of the nucleophile from below. The required cyclopropane was synthesized as shown in Eq. (2). Silanediyl protected galactal **3**,[10] obtained in one step from D-galactal, was cyclopropanated using Furukawa conditions[11] in over 250:1 diastereoselectivity. The stereochemistry of the cyclopropane was determined by comparison with our previously synthesized 1,2-cyclopropanated glycals[6,7] and is rationalized by an allylic oxygen-directed cyclopropanation.[12] Standard acetylation afforded acetate **4** in 65% overall yield from **3**.

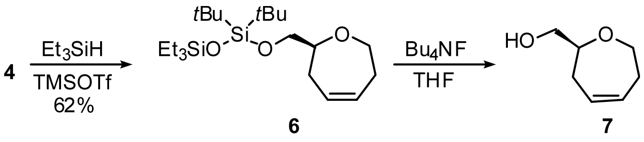


3 **4** **5** (2)

Ring-expansions of **4** proved to be successful in good to excellent yields with a variety of nucleophiles (Table 1). This shows the diverse range of nucleophiles that can be used but most importantly the high selectivity that results in this system. Using catalytic amounts of TMSOTf and 5 equiv. of a silylated nucleophile in acetonitrile, oxepane **5** was obtained with the α stereochemistry predominating. As seen, excellent selectivity and yields were obtained with the allyl, phenylsulfide, ketene acetal and propargyl nucleophiles, entries 1, 2, 5 and 7. As previously observed,[7] use of the allyloxy nucleophile, entry 4, does not produce any desired product and results in an intractable mixture. Finally, contrary to results obtained in the glucal system,[7] no elimination products across C-3–C-4 were observed in these reactions.

The stereochemistry of this reaction was established by assignment of the chemical shifts of the products using HSQC and COSY NMR. Subsequent NOESY 1D experiments with **5e** and **5g** showed positive NOEs from the methine H-1 proton to the *gem*-dimethyl of **5e** and in the case of **5g** to the allene methine proton. As the remainder of the products all had overlapping signals, we based the assignment of these by comparison to **5e** and **5g**.

During the course of these studies, we also reacted **4** with Et_3SiH to further establish the scope of this system. Surprisingly, we observed what appeared to be the formation of oxepane **6**, in which displacement of a silyloxy group had occurred (Eq. (3)). Examination of the ^1H and ^{13}C NMR of **6** showed two upfield methylene groups and an Et_3Si moiety. This structure was further substantiated by MS analysis and desilylation to give the volatile oxepane **7**. No isomers of **6** or **7** were observed, thus we assume that the formation of either an intermediate cation or radical species is not occurring. Given the small nature of the hydride nucleophile and the axial configuration of the silyloxy substituent that is being displaced, the appearance of **6** with only Et_3SiH, and only in this system (as compared to the glucose system in which **6** is not observed) can be rationalized. The formation of the Et_3SiO-linkage results from the Et_3SiOAc by-product of the ring-expansion reaction.



(3)

Finally, the geometries of both the original glucose and the current galactose based intermediates were modeled using a semi-empirical AM1 calculation and the results are shown in Figure 2.[13] As can be seen in the case of glucal derivative **B**, the planar intermediate leaves both faces of the oxepane intermediate unhindered to nucleophilic attack. However, the simple change in the stereochemistry of galactose results in a hindered top face and a greatly improved selectivity. Presumably, replacement of the tethered silanediyl in the glucose system with untethered protecting groups would resolve this issue. We have, however, reported earlier that a C-6 *tert*-butyldimethyl silyl group in the starting glucal is prone to cleavage in the ring-expansion reaction.[6b,c] In this work, we have attempted to use a trityl protecting group in the glucose system but cyclopropanation was prevented. Continued work on this is ongoing and will be reported in the future.

We have developed a facile method for the synthesis of highly functionalized seven-membered ring systems that uses readily available galactal as an enantiomerically pure, chiral template.[14] The ring-expansion greatly enhances the available methodology for oxepane synthesis in a highly stereochemical manner. Furthermore, the chemistry demonstrated above offers access to the framework of naturally occurring seven-membered ring systems such as isolaurepinnacin and rogioloxepane A.[1] Further research is underway to apply this methodology to natural product synthesis and to expand the selectivity in the glucal system.

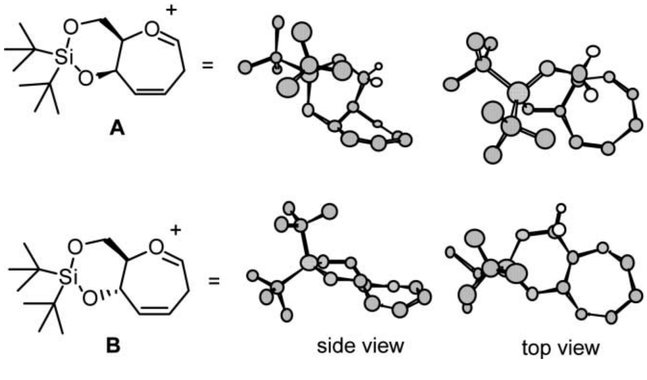


Figure 2. Oxonium intermediates from galactal system **A** and from glucal system **B** (all hydrogens, except for two methylenes are omitted for clarity).

References

1. (a) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37–48; (b) Marata, K.; Satake, M.; Naoki, H.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron* **1998**, *54*, 735–742; (c) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113–158; (d) Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259–302; (e) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75–125; (f) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223–269; (g) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909; (h) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. 5, p. 131.
2. Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589–607.
3. Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909.
4. Kocienski, P. J.; Love, C.; Whitby, R.; Roberts, D. A. *Tetrahedron Lett.* **1988**, *29*, 2867–2870.
5. For reviews, see: (a) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631–12670; (b) Sharp, J. T. *Rodd's Chemistry of Carbon Compounds*, 1999; Vol. IV, Part K, p. 101.
6. (a) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533–2536; (b) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831–6834; (c) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165–174.
7. Hoberg, J. O. *J. Org. Chem.* **1997**, *62*, 6615–6618.
8. (a) Sugita, Y.; Kimura, C.; Hosoya, H.; Yamadoi, S.; Yokoe, I. *Tetrahedron Lett.* **2001**, *42*, 1095–1098; (b) Sugita, Y.; Kimura, C.; Yokoe, I. *Heterocycles* **2001**, *55*, 855–859.
9. Hoberg, J. O. *Carbohydr. Res.* **1997**, *300*, 365–367.
10. Abdel-Rahman, A. A.-H.; Winterfeld, G. A.; Takhi, M.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 713–717.
11. (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58; (b) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *J. Org. Chem.* **1977**, *42*, 3031–3035.
12. (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370; (b) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860; (c) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525–3532; (d) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892–6894; (e) Chan, J. H. H.; Rickborn, B. *J. Am. Chem. Soc.* **1968**, *90*, 6406–6411.
13. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909. For examples of the use of semi-empirical AM1 calculations in oxonium ion geometries, see: (a) Jefferson, E. A.; Kresge, A. J.; Paine, S. W. *Can. J. Chem.* **1997**, *75*, 56–59; (b) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931–5943.
14. Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983.