Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An unexpected effect of acetal stereochemistry on the course of its reductive cleavage

Marta E. Wenzler, Gary A. Sulikowski *

Department of Chemistry, Institute of Chemical Biology, Vanderbilt University, Nashville, TN 77842–3012, USA

ARTICLE INFO

Article history:
Received 11 May 2016
Revised 10 June 2016
Accepted 14 June 2016
Available online xxxx

Keywords:
Reduction
Chemoselectivity
Reductive cleavage
Acetal
Bestmann–Ohira

ABSTRACT

During the course of studies toward the synthesis of the 'upenamide BC spirocycle a surprising effect of acetal stereochemistry on the course of its reductive cleavage was observed. Reduction of alpha acetal **6a** with diisobutylaluminum hydride led to PMB ether **10**, while the corresponding beta acetal **6b** was resistant to reduction with diisobutylaluminum hydride, but on treatment with sodium cyanoborohydride–trimethylsilyl chloride afforded PMB ether **8**.

In the preceding paper we described our latest advance toward the ABC tricycle of the marine alkaloid 'upenamide.[1–4] Key to this synthesis was preparation of anhydride **I** (P = TBS, Fig. 1) by way of a Diels–Alder reaction. A series of reduction conditions were then examined in anticipation of differentiating the anhydride carbonyls leading to a 1,4-differentiated carbon network (cf. **I** → **II**, Fig. 1). While the preceding paper described the utility of diol **II** (P = TBS, X = Y = H, OH) this Letter describes studies on the selective functionalization of triol **III**. Here we required 1,4 diol functionalization and protection of the C11 alcohol.

The selective reduction of anhydrides to lactones and/or lactols using Group III reducing reagents has been described.[5] In general, reduction of the more hindered carbonyl prevails and rationalized based on favored hydride addition by way of a Burgi–Dunitz trajectory. Indeed, reduction of anhydride **1** with lithium tri-*tert*-butoxyaluminum hydride provided lactone **2** in 42%. Reduction of **1** with lithium aluminum hydride gave triol **4** in 70% yield as well as trace amounts of TBS ether **3** (converted to **4** in near quantitative yield when treated with HF·pyridine). Reduction with aluminum hydride gave variable mixtures of **3** and **4**. As triol **4** incorporated both a 1,3- and a 1,4-diol we anticipated selective protection of the 1,3-diol could be accomplished by benzylidene or anisylidene acetal protection (Scheme 1).

Treatment of triol **4** with anisaldehyde and *p*-toluenesulfonic acid in dichloromethane afforded a near equal mixture of anisylidene isomers (**6a** and **6b**, Scheme 2). In contrast, exposure of readily derived *tris*-trimethylsilyl ether **5** under kinetic conditions (TMSOTf, *p*-$MeOC_6H_4CH(OMe)_2$, CH_2Cl_2, −78 °C)[6] afforded exclusively the beta-acetal **6b**. The latter stereoselective reaction turned out to be advantageous as reductive cleavage of acetal **6b** led to protection of the allylic secondary alcohol and released the primary alcohol poised for further functionalization (cf. Scheme 3).

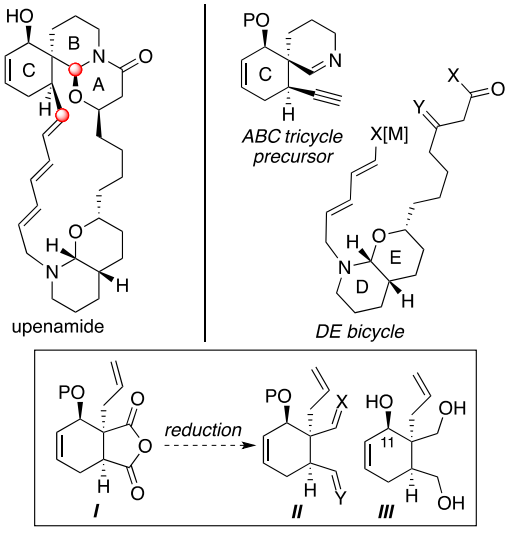
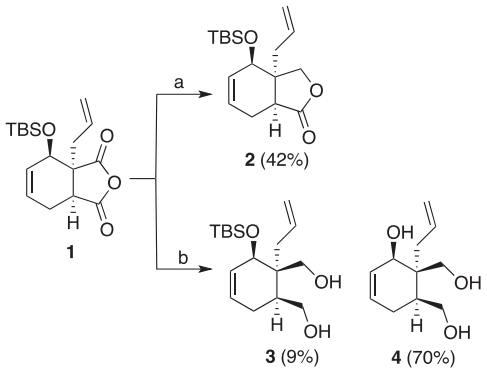


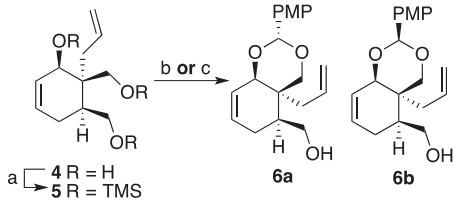
Figure 1. Structure of 'upenamide and advanced synthetic intermediates.

* Corresponding author.

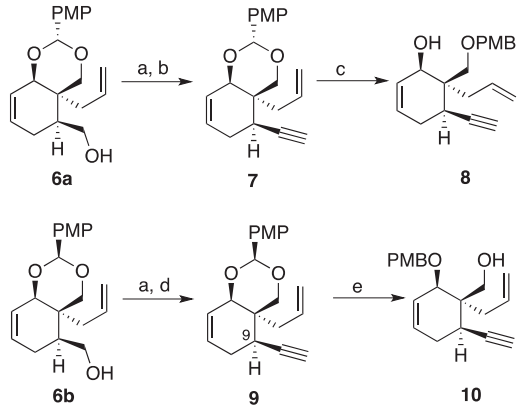
http://dx.doi.org/10.1016/j.tetlet.2016.06.067
0040-4039/



Scheme 1. Reagents and conditions: (a) Li(O*t*Bu)$_3$AlH, THF, 0 °C; (b) LiAlH$_4$, THF, 0 °C.



Scheme 2. Reagents and conditions: (a) TMSCl, pyridine, CH_2Cl_2, 97%; (b) *p*-TSA, *p*-$MeOC_6H_4CHO$, CH_2Cl_2, 32% **6a** and 21% **6b**; (c) TMSOTf, *p*-$MeOC_6H_4CH(OMe)_2$, CH_2Cl_2, −78 °C, 96% **6b**.



Scheme 3. Reagents and conditions: (a) IBX, DMSO, CH_2Cl_2; (b) $Me(CO)CN_2P(O)(OMe)_2$, K_2CO_3, MeOH, 61%; (c) $NaBH_3CN$, TMSCl, MeCN, 0 °C, 55%; (d) $Me(CO)CN_2P(O)(OMe)_2$, NaOMe, THF, −78 °C, 98%; (e) DIBAL-H, CH_2Cl_2, 78 to 0 °C, 72%.

Acetal isomers **6a** and **6b** were independently evaluated for advancing ABC tricycle assembly (Fig. 1). First, the primary alcohol of **6a** was oxidized to the corresponding aldehyde and subjected to Ohira–Bestmann alkynylation[7] conditions to afford **7** in 59% yield (two steps). Surprisingly, reductive cleavage of acetal **7** with diisobutylaluminum hydride resulted in no reaction. However, use of sodium cyanoborohydride and TMSCl gave PMB ether **8** in 55% yield.[8] Isomeric acetal **6b** showed quite different reactivity relative to **6a**. First, when the aldehyde derived from oxidation of **6b** was subjected to standard Ohira–Bestmann conditions a mixture of alkynes epimeric at C9 was produced. This loss of retention of C9 stereochemistry was remedied by substituting a sodium methoxide solution for potassium carbonate and cooling the reaction to −78 °C, resulting in production of **9** in 98% yield without any observed epimerization. Also, in contrast to acetal **7**, reduction of **9** with diisobutylaluminum hydride resulted in the desired

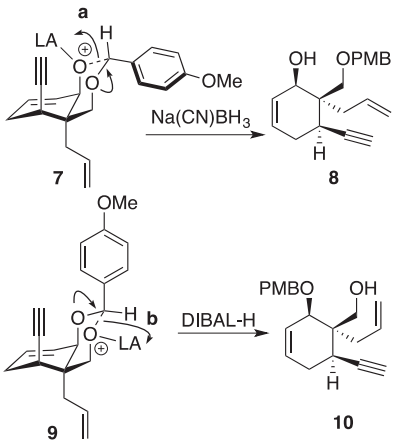


Figure 2. Rationalization of differing pathways in reductive cleavage of isomeric acetals **7** and **9**.

selective protection of the secondary alcohol and release of the primary alcohol (**10**).

Examination of molecular models allowed us to rationalize the observed difference in selectivity upon reduction of acetals **7** and **9** as illustrated in Figure 2. In general, the reductive cleavage of cyclic acetals with diisobutylaluminum hydride results in protection of the more hindered alcohol (often secondary over primary or tertiary over secondary) as an ether and release of the remaining less hindered (primary) alcohol. The selectivity has been rationalized based on the selective complexation of aluminum at the least hindered acetal oxygen.[8,9] In the case of alpha-acetal **9**, the *p*-methoxyphenyl group is oriented in the axial position effectively blocking access to the pseudo equatorial oxygen lone pairs. Of the remaining complexation sites, the oxygen lone pair positioned above the ring double bond appears to be the most accessible thus resulting in the production of PMB ether **8** on reduction with the sterically less demanding combination of sodium cyanoborohydride and TMSCl. In contrast, beta-acetal **9** accommodates complexation of Lewis acidic aluminum(III) to the equatorially oriented oxygen lone pairs on the *exo* face of **9** leading to the desired secondary PMB ether **10**. The utility of **10** as a synthetic intermediate en route to a total synthesis of 'upenamide is currently under investigation.

Acknowledgment

This research was supported by the National Science Foundation (CHE-1464864).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.067.

References and notes

1. Preceding paper reference
2. Jimenez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465–8469.
3. Andersen, R. J.; Van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, W. W., Ed.; Pergamon: New York, 1996; Vol. 10,. Chapter 3.
4. Unsworth, W. P.; Taylor, R. J. K. *Org. Biomol. Chem.* **2013**, *11*, 7250–7261.
5. Kayser, M. M.; Salvador, J.; Morand, P. *Can. J. Chem.* **1983**, *61*, 439–441.
6. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.
7. Habrant, D.; Rauhala, V.; Koskinen, A. P. *Chem. Soc. Rev.* **2010**, *39*, 2007–2017.
8. Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439–1442.
9. Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456–7467.