Tetrahedron: *Asymmetry* 22 (2011) 149–152

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Aldol reaction of butane-2,3-diacetal protected methyl glycerate

Simon E. Fern [a], Peter Heath [b], Alexander J. A. Cobb [a,*]

[a] School of Pharmacy, University of Reading, Whiteknights, Reading, Berks RG6 6AD, UK
[b] Chemical Analysis Facility (CAF), University of Reading, Whiteknights, Reading, Berks RG6 6AD, UK

ARTICLE INFO

Article history:
Received 16 November 2010
Accepted 12 January 2011

Dedicated to Professor Steven V. Ley CBE FRS on the occasion of his 65th birthday

ABSTRACT

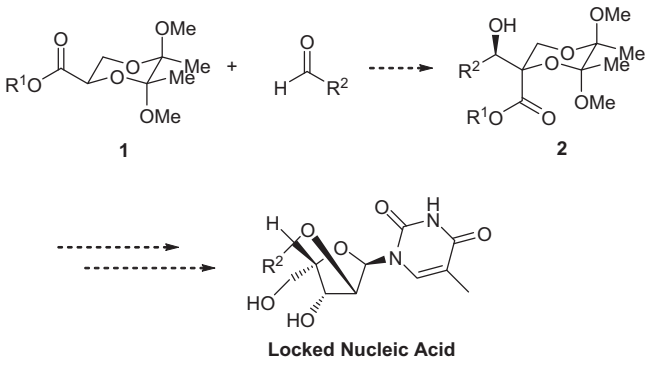
The addition of aldehydes to butane-2,3-diacetal protected glycerates has been investigated. The reaction was shown to be diastereoselective by ^{1}H NMR spectroscopy thus confirming the ability of the diacetal to influence the stereochemical outcome of the new stereogenic center, the configuration of which was determined by Mosher's ester analysis.

1. Introduction

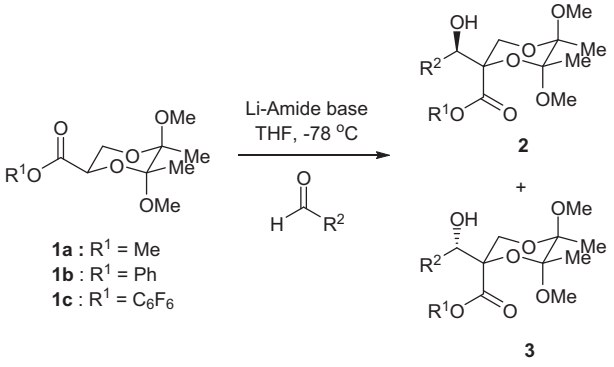
1,2-Diacetal units are an extremely useful and a dynamic class of structure in organic synthesis.[1] Their ease of preparation and rigid structure have seen them being utilized in a wide range of synthetic applications, particularly in the construction of natural products. Of particular interest to us is their ability to access quaternary stereogenic centers with an excellent stereocontrol. In particular we wished to utilize butane-2,3-diacetal (BDA) protected methyl glycerate **1**[2] for the construction of a novel class of locked nucleic acid (LNA) (Scheme 1).[3] The synthesis of LNAs is often hampered by the requirement for multi-step transformations[3c] and we envisaged that the use of an asymmetric synthesis using BDA would provide a more direct route to this class of molecule. Our aim, therefore, was to generate the quaternary stereocenter in the locked nucleic acid, through the aldol addition of BDA methyl ester **1** to an aldehyde to generate aldol product **2** (Scheme 1).[4]

We found, however, that this initial aldol step has not been extensively investigated. Although Ley et al. detail the addition of a range of electrophiles to ester **1**, including acetone, no aldehydes were reported in detail.[4a] Pohmmakotr et al. have utilized the enantiomer of ester **1** in an aldol process, but interestingly reported that no diastereoselectivity was observed.[4b]

Therefore, we decided to study this reaction in much more detail in order to understand what effect, if any, the butane-diacetal framework might have upon the formation of the new stereocenter (Scheme 2).



Scheme 1. Proposed synthesis of a locked nucleic acid (LNA) utilizing butane-2,3-diacetal chemistry.



Scheme 2. Aldol reaction of butane-2,3-diacetal glycerates with aldehydes.

2. Results and discussion

Our investigation began by studying the effect of the BDA ester upon the reaction. We, therefore, tested methyl glycerate **1a** alongside phenyl **1b** and perfluorophenyl **1c** glycerates using benzaldehyde as an electrophile and standard enolate forming conditions

* Corresponding author.
E-mail address: a.j.a.cobb@reading.ac.uk (A.J.A. Cobb).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.01.004

(Scheme 2 and Table 1, entries 1–3). Under these conditions, we found that methyl ester (Table 1, entry 1) gave us a 2.1:1 diastereomeric ratio of aldol products **2**:**3**,[5] suggesting that butane-2,3-diacetal backbone does exert some stereochemical preference on the aldol reaction. The phenyl ester gave a slightly improved ratio of 2.7:1, but to the detriment of the yield (Table 1, entry 2), while the perfluorophenyl ester gave no reaction at all (Table 1, entry 3). In all cases, and as has been previously observed, none of the diastereoisomer, whereby the ester group lies in the equatorial position was observed.

Table 1
Optimization study

Entry	Ester	Base	Aldehyde	Product	Yield (%)	dr[a]
1	**1a**	LDA	PhCHO	**2a**/**3a**	66	2.1:1
2	**1b**	LDA	PhCHO	**2b**/**3b**	56	2.7:1
3	**1c**	LDA	PhCHO	**2c**/**3c**	0	—
4	**1a**	(−)-**5**	PhCHO	**2a**/**3a**	64	3:2
5	**1a**	(+)-**5**	PhCHO	**2a**/**3a**	60	7:4
6	**1a**	(−)-**5**	PhCH=CHCHO	**2d**/**3d**	40	2:1
7	**1a**	(+)-**5**	PhCH=CHCHO	**2d**/**3d**	51	3:2

[a] Based on isolated yield.

In an attempt to improve the diastereoselectivity, we then decided to see the influence that the chiral bases might have on the reaction. Commonly used chiral lithium amides **4** and **5** (Fig. 1) were applied under the same conditions, but in all cases the diastereoselectivity was adversely affected, although the major diastereoisomer remained the same (Table 1, entries 4–7).

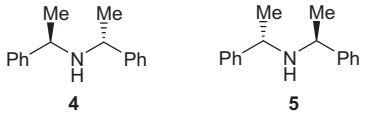
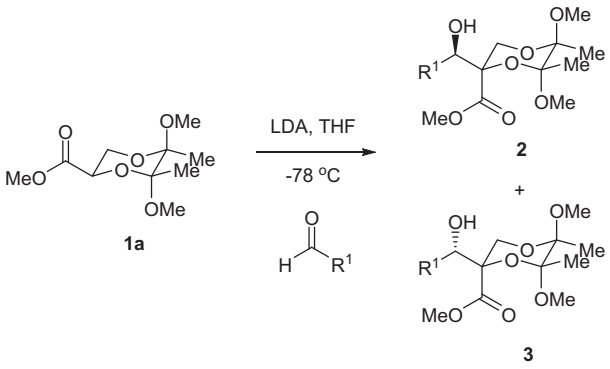


Figure 1. Chiral lithium amide bases.

We, therefore, proceeded to test a variety of aldehydes using the original conditions and saw that in each case, a degree of diastereoselectivity was obtained. In every case, the diastereoisomers were separable (Table 2).

Table 2
Substrate scope



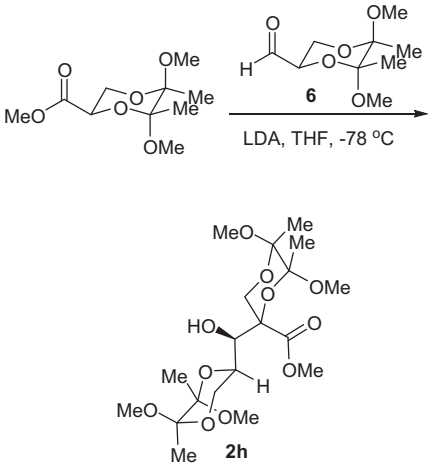
Entry	Aldehyde	Yield (%)	Product	dr[a]
1	PhCHO	66	**2a**:**3a**	2.1:1
2	PhCH=CHCHO	56	**2d**:**3d**	1.4:1
3	*n*-C_6H_{11}CHO	60	**2e**:**3e**	2.3:1
4	*p*-$MeOC_6H_4$	40	**2f**:**3f**	1.7:1
5	*p*-F-C_6H_4	46	**2g**:**3g**	2.3:1
6[b]	*n*-C_6H_{11}CHO	92	**2e**:**3e**	3:1
7[b]	*p*-$MeOC_6H_4$	95	**2f**:**4f**	2:1

[a] Based on isolated yield.
[b] With 10% v/v HMPA.

In each case, the formation of (*R*)-secondary alcohol was favored, as determined by Mosher's ester analysis, and in roughly similar diastereoselectivities. Changes in the electronic nature of the aromatic aldehyde had little effect on diastereoselectivity compared to benzaldehyde, but usefully, the non-aromatic aldehyde hexanal also reacted to form the predicted major diastereoisomer.

The yields of the reactions using hexanal and *p*-anisaldehyde (entries 6 and 7) were significantly improved via the addition of HMPA, as were (though not significantly) the diastereoselectivities, although this additive did not seem to enhance the reaction of other electrophiles.

We also used the BDA aldehyde **6**[2] as an electrophile and only obtained the single diastereoisomer **2h**, though in a modest 34% yield (Scheme 3), again favoring the (*R*)-isomer.[4c]



Scheme 3. A bulky aldehyde appears to only give one diastereoisomer.

In order to explain the diastereoselectivity of the process, we first needed to know the nature of the enolate, and this was achieved by trapping it with trimethyl silyl chloride and examination of the resulting 2D NOE NMR signals. This suggested that it was the *Z*-enolate, which was formed (Fig. 2).

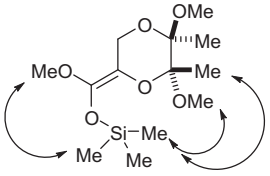


Figure 2. Relevant 2D NOE correlations showing the enolate geometry.

This geometry is in agreement with the predicted outcome using the Ireland model[6] (see Fig. 3) and generates an enolate with concave and convex character. The facial selectivity of the aldol addition may well be a consequence of this structural feature, as the electrophile is much more likely to prefer an approach from the more open convex face (Fig. 3).

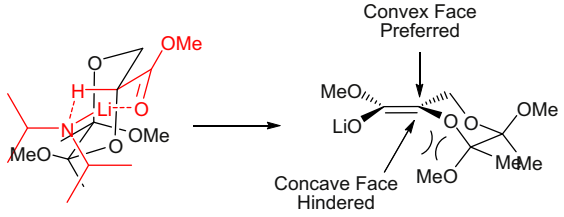


Figure 3. Deprotonation of the ester gives the *Z*-enolate, which is concave/convex in character and where the electrophile is likely to prefer approach from the least hindered face.

The preference for compound **2** over compound **3** can be explained by invoking the Zimmerman–Traxler model for lithium-amide mediated aldol reactions, whereby there are two possible transition states.[7] The first, requires the R-group of the aldehyde (in Fig. 4, this is a phenyl-group) to lie over the sterically crowded BDA group. In terms of the transition state, this is the equatorial position (Fig. 4A), and this appears quite unfavorable. The second possibility is where the R-group points away from the BDA framework but is forced to adopt an axial position within the transition state. Although this gives rise to a 1,3-diaxial interaction between it and the OMe group of the ester (Fig. 4B), it appears more favorable than the former option.

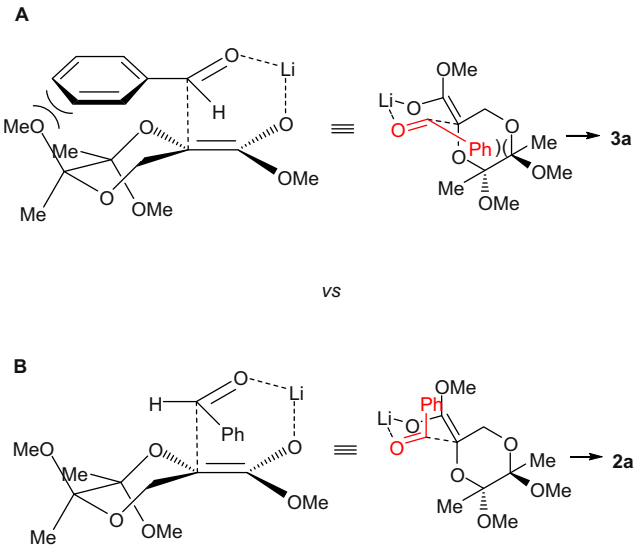
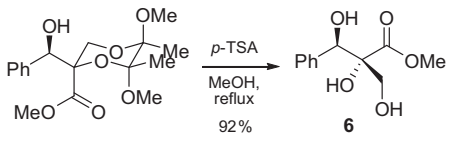


Figure 4. Although there is a 1,3-diaxial interaction between the phenyl group of the aldehyde and the OMe group of the ester (B), it is still slightly more favorable than if the phenyl group were to lie directly over the BDA group (A).

This explanation might also go some way to explaining the excellent diastereoselectivity when using aldehyde **2h**. The increased steric bulk of this aldehyde, makes the corresponding transition state shown in Figure 4A extremely unfavorable. Additionally, it has previously been shown that organometallic addition to this aldehyde leads to predominantly the same *syn*-(*R*)-product, as a result of Felkin control.[8] It is possible that this, along with our proposed mode of selectivity, leads to a matched chirality effect and this could explain the formation of a single diastereoisomer.

Finally, another advantage of the BDA group is the ease with which it can be removed; this was demonstrated by exposing substrate **2a** to *p*-toluenesulfonic acid, whereupon triol **6** was obtained in 92% yield (Scheme 4).



Scheme 4. BDA deprotection.

3. Conclusion

In conclusion, we have demonstrated that the BDA framework has the ability to control an intermolecular aldol process with aldehydes to generate both a new secondary alcohol and a quaternary center. The new stereocenter is to a certain extent, controlled by the BDA group, but conveniently where two diastereoisomers are produced, they are easily separable. We are continuing in our efforts to utilize these adducts in the synthesis of novel locked nucleic acids.

4. Experimental

4.1. Typical experimental procedure

To a solution of diisopropyl amine (1.1 equiv) in anhydrous tetrahydrofuran (0.9 mL $mmol^{-1}$) was added drop-wise *n*-BuLi (1.1 equiv, 1.6 M in hexanes) under an inert atmosphere at −78 °C. The resulting mixture was stirred for 10 min at −78 °C, before being transferred under an inert atmosphere via cannula to a −78 °C solution of the butane-2,3-diacetal methyl glycerate (1 equiv) in anhydrous tetrahydrofuran (8 mL $mmol^{-1}$). After 10 min at this temperature, the aldehyde (4.8 equiv) was added dropwise. The resulting mixture was stirred at −78 °C for 3.5 h, whereupon it was quenched with satd ammonium chloride. The quenched reaction was allowed to warm to room temperature and ether was added. The resulting mixture was washed with water and brine and the organic layer dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography (ethyl acetate/hexanes, 1:3.4).

4.1.1. (2*R*)- and (2*S*)-2-(Hydroxy-phenyl-methyl)-5,6-dimethyl-5,6-dimethoxy-[1,4]-dioxane-2-carboxylic acid methyl ester 2a and 3a

Following the above general procedure, butane-2,3-diacetal methyl glycerate was reacted with benzaldehyde in the presence of LDA. (*R*)-Isomer **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.19 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.59 (3H, s, CO_2CH_3), 3.76 (1H, d, *J* 12, C*H*H), 4.00 (1H, d, *J* 12, CH*H*), 4.77 (1H, s, CH), 7.24–7.36 (5H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 17.69, 17.74, 48.13, 50.56, 51.97, 59.94, 75.64, 97.98, 99.74, 126.86, 127.96, 128.30, 137.89, 171.24. $[\alpha]_D = -107.1$ (*c* 0.7, $CHCl_3$). HRMS (*m*/*z*) Calcd for $C_{17}H_{24}O_7$: 340.1522. Found: 363.1413 (MNa^+). (*S*)-Isomer **3a**: 1.24 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.23 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.65 (3H, s, CO_2CH_3), 3.74 (1H, d, *J* 12, C*H*H), 4.16 (1H, d, *J* 12, CH*H*), 4.92 (1H, s, CH), 7.20–7.35 (5H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 17.68, 17.72, 48.24, 50.44, 52.08, 56.53, 76.68, 97.74, 100.17, 126.52, 128.24, 128.40, 135.66, 171.56. $[\alpha]_D = -76.2$ (*c* 0.6, $CHCl_3$). HRMS (*m*/*z*) Calcd for $C_{17}H_{24}O_7$: 340.1522. Found: 363.1412 (MNa^+).

Acknowledgments

We wish to thank a Cancer Research UK and the University of Reading (Reading Endowment Trust Fund) for funding this work (S.E.F.). We also wish to thank Dr. Geoff Brown for useful NMR discussions.

References

1. For reviews see: (a) Ley, S. V.; Polara, A. *J. Org. Chem.* **2007**, *72*, 5943; (b) Ley, S. V.; Sheppard, T. D.; Myers, R. M.; Chorghade, M. S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1451; Also see: (c) Michel, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 3898; For related chemistry, see: (d) Knudsen, K. R.; Stepan, A. F.; Michel, P.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1471; (e) Bridgwood, K. L.; Tzschucke, C. C.; O'Brien, M.; Wittrock, S.; Goodman, J. M.; Davies, J. E.; Logan, A. W. J.; Hüttl, M. R. M.; Ley, S. V. *Org. Lett.* **2008**, *10*, 4537; (f) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Palomero, M. A.; Polara, A.; Rodrígez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3618; (g) Dixon, D. J.; Guarna, A.; Ley, S. V.; Polara, A.; Rodrígez, F. *Synthesis* **2002**, 1973.
2. Michel, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 3898.

3. For reviews see: (a) Kaur, H.; Babu, B. R.; Maiti, S. *Chem. Rev.* **2007**, *107*, 4672; (b) Cobb, A. J. A. *Org. Biomol. Chem.* **2007**, *5*, 3260; (c) Mathé, C.; Périgaud, C. *Eur. J. Org. Chem.* **2008**, 1489.
4. (a) Ley, S. V.; Michel, P.; Trapella, C. *Org. Lett.* **2003**, *5*, 4553. It is mentioned in a footnote to this reference, that when unspecified aldehydes are used, a 2:1 diastereomeric ratio of products is obtained; (b) Pohmakotr, M.; Kambutong, S.; Tuchinda, P.; Kuhakarn, C. *Tetrahedron* **2008**, *64*, 6315; Related processes include: (c) Areces, P.; Carrasco, E.; Light, M. E.; Plumet, J. *Synlett* **2009**, 2500; (d) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Rodríguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2005**, *3*, 4095; (e) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. *Org. Lett.* **2001**, *3*, 3749. And Ref.[1g].
5. Absolute stereochemistry determined by Mosher's Ester analysis: see: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512; (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protocols* **2007**, *2*, 2451.
6. Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *16*, 3975.
7. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
8. Boyer, J.; Allenbach, Y.; Ariza, X.; Garcia, J.; Georges, Y.; Vicente, M. *Synlett* **2006**, 1895.