New Stereoselective Approach to 1,2,3-Triols: Application to a Straightforward Access to Polyoxamic Acid Array

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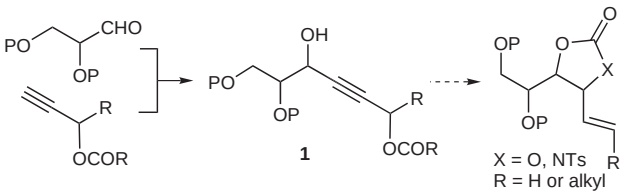
Received 14 April 2006

Abstract: An efficient approach to alk-4-yne-1,2,3,6-tetraols is described by stereoselective addition of terminal 2-alkyn-1-yl esters to Ley's butane-2,3-diacetal-protected glyceraldehyde. The application of this methodology to a convenient synthesis of a (–)-polyoxamic acid derivative is disclosed herein.

Key words: stereoselective synthesis, alkynes, natural products, addition reactions, palladium

Polyhydroxylated chains are a very common pattern in the structure of many natural products. Although carbohydrates and azasugars are probably the most representative examples, a plethora of naturally occurring compounds, including many polyketide metabolites, possess 1,2-diol or 1,2,3-triol arrays in their framework.[1] We have recently described the preparation of enantioenriched propargylic 1,4-diols[2] and their transformation into protected 1,2-amino alcohols and 1,2-diols through Pd-catalyzed alkylations.[3,4]

Looking to extend these processes to building more highly functionalized structures present in natural products, we envisaged a concise, stereoselective route to protected alk-4-yne-1,2,3,6-tetraols (**1**) based on a zinc-mediated addition of terminal 2-alkyn-1-yl esters to a protected glyceraldehyde (Scheme 1). According with our previous experience, the presence of the triple bond makes these compounds amenable to further transformations leading to polyhydroxylated or aminopolyhydroxylated chains. We wish to report here our findings in this connection.

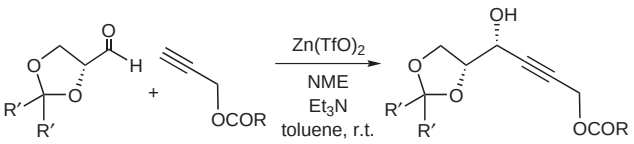


Scheme 1

We first considered (*R*)-isopropylidene glyceraldehyde (**2**), as an appropriate substrate for this purpose. This chiral synthon has been used extensively as a three-carbon building block for organic synthesis.[5] Particularly, Fettes and Carreira have recently described an example of diastereoselective addition of a zinc alkynylide to **2**.[6]

Based on these precedents, we carried out the addition of propargyl benzoate **4** or benzyl carbonate **5** to **2** under Carreira's conditions[2a,2c] in the presence of (–)-*N*-methyl ephedrine [(–)-NME] to afford the desired adduct in good yield and a ca. 11:1 *syn*/*anti* ratio (Table 1, entries 1 and 2). In contrast, higher selectivity (1:99 *syn*/*anti*) was observed when (+)-NME was used, indicating that **2** favors the *anti* relative configuration in such additions (matched case, entry 3).

Table 1 Addition of Zinc Alkynylides to Aldehydes **2** and **3**



2 R′ = Me
3 R′ = Et

4 R = Ph
5 R = BnO

Entry	Aldehyde	Alkyne	NME	Yield (%)	*syn*:*anti*
1	**2**	**4**	–	62	12:1
2	**2**	**5**	–	89	11:1
3	**2**	**5**	+	68	1:99
4	**3**	**4**	–	30	3:1
5	**3**	**4**	+	30	1:99

Unfortunately, yields and selectivities revealed to be strongly depending on the purity of **2** leading to serious problems in reproducing the results, especially when we scaled up the process. In fact, these drawbacks have been previously reported elsewhere[7] and they were generally associated with the high volatility as well as the propensity to polymerize, racemize, and form hydrates of this capricious aldehyde. The use of 3-pentylidene glyceraldehyde (**3**) did not improve the results.[7b]

Then, we turned our attention to butane-2,3-diacetals of glyceraldehyde, **6** and **7**, recently described by Steven Ley's group (Figure 1).[8] Both aldehydes are easily available from D-mannitol on large scale in which the only purification is a single distillation under vacuum at the final stage. On the other hand, the other enantiomeric series can be obtained from L-ascorbic acid.

SYNLETT 2006, No. 12, pp 1895–1898
Advanced online publication: 24.07.2006
DOI: 10.1055/s-2006-947361; Art ID: G13206ST

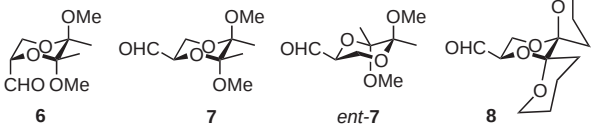
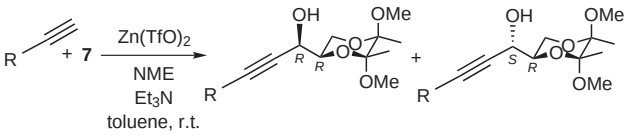


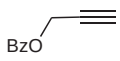
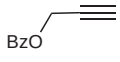
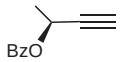
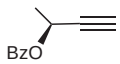
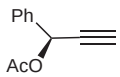
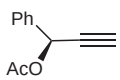
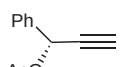
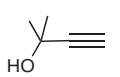
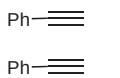
Figure 1

Whereas a strong *anti* stereochemical bias has been described in the addition of some nucleophiles to **6**, leading to protected 1,2,3-triols possessing a 2,3-*anti* relationship,[8a] marginal attention has been devoted to **7**.[9] Thus, to the best of our knowledge, the synthetic use of this robust aldehyde or its enantiomer (**7** or *ent*-**7**) is still undocumented.

To our satisfaction, we found that the zinc alkynylide of propargylic benzoate, prepared in situ with $Zn(OTf)_2$, (–)-*N*-methylephedrine, and Et_3N in toluene at room temperature, cleanly added to aldehyde **7** to obtain *syn*-**9a** (R = CH_2OBz, entry 1, Table 2) as the sole diastereomer in a remarkable 95% yield.[10,11] In addition, a noteworthy 1:16 *syn*/*anti* stereoselectivity was noted with (+)-NME as ligand (mismatched case) indicating that although the aldehyde **7** favors the *syn* relative configuration, the chiral ligand largely overcomes the stereochemical bias of **7**.

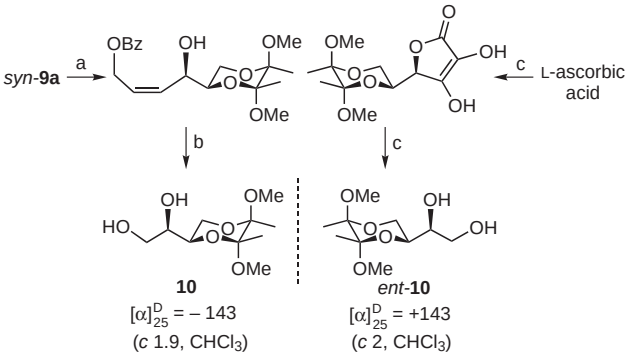
Table 2 Addition of Zinc Alkynylides to Aldehyde **7**



Entry	Alkyne	NME	Product	Yield (%)	*syn*:*anti*
1		–	*syn*-**9a**	95	>80:1
2		+	*anti*-**9a**	83	1:16
3		–	*syn*-**9b**	89	50:1
4		+	*anti*-**9b**	79	1:13
5		–	*syn*-**9c**	100	>80:1
6		+	*anti*-**9c**	98	1:50
7		–	*syn*-**9d**	94	>80:1
8		–	*syn*-**9e**	71	33:1
9		–	*syn*-**9f**	88	19:1
10		+	*anti*-**9f**	98	1:11
11		–	*syn*-**9g**	80	24:1

Similar trends were recorded for a set of terminal alkynes tested, leading to protected 2,3-*syn*- or 2,3-*anti*-1,2,3-triols **9** [when (–)- or (+)-*N*-methylephedrine was used, respectively] in high yield and excellent selectivities, specially when propargyl esters were used as nucleophiles (entries 1–7, Table 2). It is worth noting that the resident stereogenic center in the chiral alkyne reagents plays a negligible role in the stereoselectivity (compare entries 5 and 7).

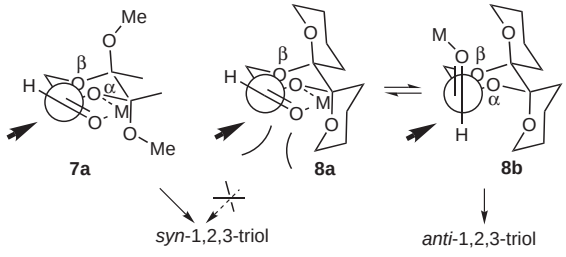
The *R*-configuration assumed for the new stereocenter formed was corroborated by chemical correlation between *syn*-**9a** and L-ascorbic acid as shown in Scheme 2. The spectral data of 1,2-protected-1,2,3,4-tetraol **10**, derived of *syn*-**9a** by partial hydrogenation followed by oxidative cleavage of the double bond, were identical to those obtained for *ent*-**10** arising from L-ascorbic acid by a known procedure,[8a] but opposite in its optical rotation.



Scheme 2 *Reagents and conditions*: (a) H_2, Lindlar's catalyst, quinoleine, EtOAc, r.t., 84%; (b) O_3, CH_2Cl_2, –78 °C; then $NaBH_4$, *i*-PrOH, 64%; (c) ref. 8a.

The observed facial stereoselectivity of the aldehyde can be rationalized by a chelation controlled model in which the α-coordination (**7a**) with the zinc predominates, leading to the *syn*-stereoisomer (Scheme 3).[12] A similar arrangement in **8** is less likely due to the rigidly defined geometry and the steric bulk the dispiroketal group. Accordingly, the *anti*-selectivity displayed by **8** has been explained through a Felkin's non-chelation-controlled model (**8b**).[13]

Encouraged by the good performance of aldehyde **7** in the alkynylation processes, we turned our attention to the



Scheme 3 Stereochemical arrangements in the addition of zinc alkynylides to protected glyceraldehyde

transformation of *syn*-**9a** into the lactone **12**, which contain the stereochemistry and functionality of (–)-polyoxamic acid. This amino acid is the key component of polyoxines (Figure 2), a family of antifungal antibiotics isolated from the culture broths of *Streptomyces cacaoi var. asoensis*.[14] These natural products are known to inhibit the chitin synthetase of a variety of phytopathogenic fungi[15] and of *Candida albicans*, a human fungal pathogen.[16]

The potent biological activity associated with polyoxines had led to the development of a number of syntheses of (+)-polyoxamic acid and its derivatives over the past several years, most of them from chiral pool sources.[17] The non-natural enantiomer has also been prepared in a stereoselective manner.[18]

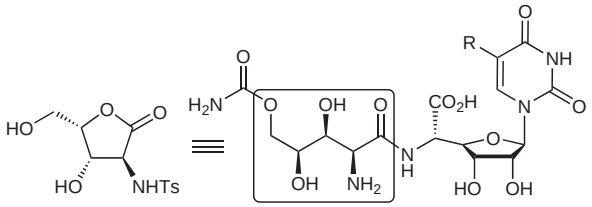
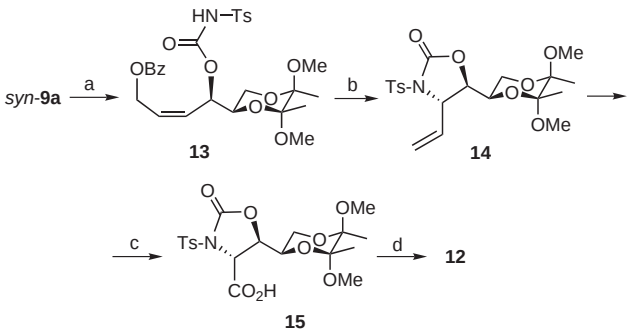


Figure 2

Thus, partial reduction of the triple bond of *syn*-**9a** followed by treatment with tosyl isocyanate yielded the allylic tosylcarbamate **13** in high yield. Pd(II)-catalyzed cyclization afforded *trans*-oxazolidinone (**14**) in 85% yield with complete stereoselectivity.[19] Transformation of **14** into acid **15** was successfully accomplished by ozonolysis followed by oxidation of the crude aldehyde with $NaClO_2$ without loss of stereochemical purity.[20] Finally, acid **15** was readily transformed into lactone **12**[21] in 63% overall yield by basic hydrolysis of carbamate group, followed by acidic treatment in an efficient one-pot process (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) H_2, Lindlar's catalyst, quinoleine, EtOAc, r.t., then TsNCO, THF, r.t. 71% overall yield; (b) $Pd(OAc)_2$, LiBr, THF, reflux, 85%; (c) *i*) O_3, CH_2Cl_2, –78 °C; *ii*) Me_2S; *iii*) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN–H_2O, 75% overall yield; (d) *i*) aq LiOH, reflux; *ii*) aq 2 M HCl, THF, 60 °C, 63% overall yield.

In conclusion, we have shown that butane-2,3-diacetal of (*R*)-glyceraldehyde **7** (or its enantiomer) is a convenient building block for the stereoselective construction of useful 2,3-alk-4-yn-1,2,3,6-tetraol synthons through a Zn-mediated alkynylation. We have applied this strategy to a stereoselective synthesis of a protected (–)-polyoxamic acid lactone in six steps with an overall yield of 29%.

Acknowledgment

This work has been supported by the Ministerio de Ciencia y Tecnologia (BQU2003-01269). We also thank Secretaría de Estado de Universidades e Investigación (MEC, Spain) for a postdoctoral fellowship to J.B., the Swiss National Science Foundation for a postdoctoral fellowship to Y.A., the Generalitat de Catalunya and Universitat de Barcelona for doctorate studentships to Y.G. and M.V., respectively.

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(9) As far as the reactivity of aldehyde **7** is concerned, the only reported data of addition of nucleophiles were found in ref. 8a where it was stated that: 'preliminary studies concerned with the addition of organomagnesium reagents to aldehyde **7** indicated that the *syn*/*anti* selectivity of addition is similar to that observed with dispiroketalaldehyde **8**.'

(10) **Synthesis of (*R*,*R*,*R*,*R*)-4-Hydroxy-4-(5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)but-2-ynyl Benzoate (9a).** $Zn(OTf)_2$ was previously activated by heating under vacuum for 15 min. A slurry mixture of dry $Zn(OTf)_2$ (1.590 g, 4.29 mmol) and (–)-*N*-methylephedrine (0.784 g, 4.28 mmol) in toluene (5 mL) was heated for 30 min at 50 °C. Then, Et_3N (0.65 mL, 4.66 mmol) was added and the mixture was stirred at 50 °C until the formation of a biphasic system (2.5 h). After cooling down to r.t., propargyl benzoate (0.632 g, 3.95 mmol) was added and the mixture was further stirred for 5 min. Then, aldehyde **7** (0.950 g, 4.66 mmol) was added dropwise (ca. 5–10 min) at r.t. The reaction was monitored by TLC and, after completion (3.5 h), the reaction was quenched with 5 mL of a sat. solution of NH_4Cl. The mixture

was extracted with Et_2O (30 mL) and EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 75:25) to afford pure **9a** (1.366 g, 3.75 mmol, 95% yield) as colorless oil; $[\alpha]_D^{20}$ –120 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.31 (s, 3 H), 2.40 (s, 1 H), 3.26 (s, 3 H), 3.28 (s, 3 H), 3.63 (m, 1 H), 3.98 (m, 1 H), 4.35 (m, 1 H), 4.95 (d, *J* = 2.0 Hz, 2 H), 7.45 (m, 2 H), 7.56 (m, 1 H), 8.04 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 17.9, 48.3, 48.4, 52.7, 60.1, 62.5, 70.5, 80.7, 83.8, 98.2, 99.7, 128.7. 129.6, 130.0, 133.6, 165.9. IR (NaCl): 3438, 2940, 2833, 1726, 1260 cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd for $C_{19}H_{24}NaO_7$ $[M + Na]^+$: 387.1408; found: 387.1414.

(11) (a) An experiment performed at 60 °C using 20 mol% $Zn(OTf)_2$ and (–)-*N*-methylephedrine according with Carreira's catalytic protocol (see ref. 11b) showed lower yield and stereoselectivity. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

(12) It is noteworthy that reactions of aldehyde **2** with nucleophilic reagents predominantly give the *anti*-isomer. A delicate balance of α-coordination (pro *syn*) and β- or α,β-coordination (both pro *anti*) is probably involved, leading to a broad range of selectivities depending of the reagent and experimental conditions: see ref. 5, pp. 456-458.

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(21) **Synthesis of (2*R*,3*R*,4*R*)-(+)-3-Hydroxy-4-hydroxymethyl-2-tosylaminobutyrolactone (12).**
To a solution of **15** (256 mg, 0.56 mmol) in THF (12 mL), 5 mL of 6 M LiOH were added. The mixture was then heated to reflux for 3 h. After cooling down to r.t., the mixture was acidified with 0.2 M HCl to pH 2. This solution was then extracted with CH_2Cl_2 (3 × 10 mL) and EtOAc (1 × 10 mL). The organic layers were then dried over anhyd $MgSO_4$, filtrated and concentrated under reduced pressure. The crude was dissolved in THF (40 mL) and 2 M HCl (10 mL) and the mixture was heated for 2.5 h at 60 °C. After cooling down, the mixture was extracted with CH_2Cl_2 (3 × 30 mL) and EtOAc (1 × 20 mL). The combined organic layer was dried over $MgSO_4$. After filtration and evaporation of solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to afford pure lactone **12** (106 mg, 0.35 mmol, 63% yield); mp 167–168 °C; $[\alpha]_D^{20}$ +26.1 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.75 (m, 2 H), 4.30 (m, 2 H), 4.36 (m, 1 H), 7.25 (dd, *J* = 7.4, 1.8 Hz, 2 H), 7.70 (dd, *J* = 7.4, 1.8 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.3, 62.9, 63.2, 79.9, 84.6, 131.0, 133.3, 142.8, 147.5, 177.4. IR (KBr): 3487, 3292, 2935, 1781, 1598, 1453, 1331, 1094, 922, 814, 664 cm^{-1}. HRMS (FAB$^+$): *m*/*z* calcd for $C_{12}H_{16}NO_6S$ $[M + 1]^+$: 302.0698; found: 302.0697.