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1-Phenylprop-2-ynyl Acetate: A Useful Building Block for the Stereoselective Construction of Polyhydroxylated Chains

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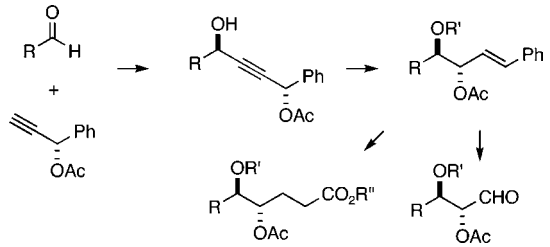
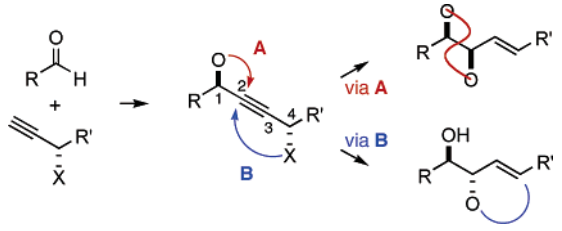
ABSTRACT



(*R*)- or (*S*)-1-phenylprop-2-ynyl acetate was added stereoselectively to aldehydes to afford 4-hydroxy-1-phenylalk-2-ynyl acetates. The transformation of such adducts into the corresponding allylic 1,4-diacetates allowed a highly efficient transfer of chirality from C1 to C3 by a regio- and stereoselective [3,3]-sigmatropic rearrangement. The obtained unsaturated 1,2-diacetates were useful synthetic intermediates whose double bond and/or phenyl group were transformed in different aldehydes, acids, or esters.

The stereoselective formation of 1,2-diols with the concomitant C(1)−C(2) bond formation has been mainly studied by addition of an enolate (either a glycolate or an α-hydroxyketone) to aldehydes.[1] However, very often only one of the two relative stereochemistries can be achieved. In the course of studies directed toward the construction of sugar-type polyhydroxylated frameworks with independent control of each chiral center, we envisaged a new approach to 1,2-diols based on a two-step process (Scheme 1): (i) stereoselective addition of an alk-1-yn-3-ol (or its acetate) to an aldehyde and (ii) transfer of chirality from the new alcohol formed to the vicinal C(2) position (via **A** in Scheme 1) or, alternatively, transfer of chirality from the C(4) stereocenter arising from the alkyne moiety to the C(2) position (via **B** in Scheme 1). Our initial efforts according to the first strategy only allowed us the preparation of 1,2-*syn* diols.[2] Gratifyingly, the second option has been demonstrated to be more versatile. Herein, we wish to report our findings in this connection.

Scheme 1. Chirality Transfer



First, we evaluated 1-phenylprop-2-yn-1-ol (**1**) as starting chiral alkynol since this compound can be prepared in enantiomerically enriched form through a lipase-catalyzed resolution. Thus, the kinetic resolution of racemic 1-phenylprop-2-yn-1-ol[3] using Novozym 435 (*Candida antarctica*

(1) (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995. (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (c) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304.

(2) Georges, Y.; Allenbach, Y.; Ariza, X.; Campagne, J.-M.; Garcia, J. *J. Org. Chem.* **2004**, *69*, 7387.

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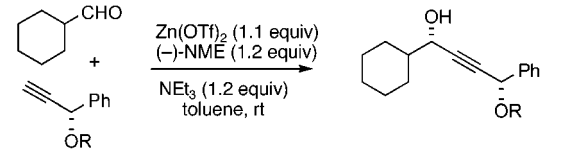
lipase B)[4] was very efficient at 60 °C,[4a] leading to (*S*)-(+)-**1** alcohol and (*R*)-(+)-1-phenylprop-2-yn-1-yl acetate ((*R*)-**2**) in up to 99% ee. Furthermore, acetylation of (*S*)-**1** afforded (*S*)-**2**, whereas hydrolysis of (*R*)-**2** gave (*R*)-**1** quantitatively. Therefore, any stereoisomer of alcohol **1** or acetate **2** can be obtained with high ee.

Next, we focused our attention on the addition of **1** to aldehydes. In 2000, Carreira et al. reported an efficient enantioselective Zn-mediated addition of alkynes to aldehydes.[5] Shortly thereafter, we extended this methodology to alkynols.[6] Based on these studies, we have explored the addition of **(***R***)-1** to cyclohexancarbaldehyde by using commercially available $Zn(OTf)_2$ (zinc triflate), (−)-*N*-methylephedrine (NME), and Et_3N in toluene (Scheme 2).

Scheme 2. Alkyne Addition



R = H (*R*)-**1**
R = Ac (*R*)-**2**

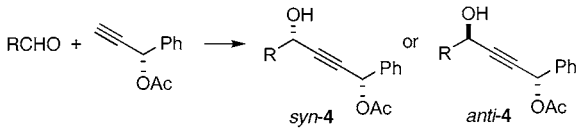
syn-**3a** (R = H , 47% 91:9 dr)
syn-**4a** (R = Ac, 94% >99:1 dr)

Since the reaction leading to diol *syn*-**3a** showed low conversion (37% of recovered alkyne **1**) and moderate selectivity, we turned our attention to the corresponding acetylated alkyne (*R*)-**2**. To our delight, alkynol *syn*-**4a** was obtained in 94% yield and >99:1 dr[7] in the addition of (*R*)-**2** to cyclohexancarbaldehyde in the presence of (−)-NME. Furthermore, the use of (+)-NME led to the *anti* isomer (*anti*-**4a**) in 71% yield (Table 1).

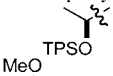
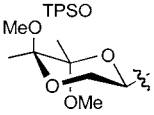
As shown in Table 1, similar results were noted in the addition of (*R*)-**2** to a set of aldehydes. It should be mentioned that the dominant stereochemical control was provided by the NME employed (compare entries 2 and 3, or 6 and 7, in Table 1) leading to >25:1 dr, with the resident stereogenic center of **2** or of aldehyde playing a subordinate role.

The last entries in Table 1 concerning protected lactaldehyde and glyceraldehyde[8] deserve special attention since the good results suggested that highly polyhydroxylated species could be obtained with a judicious choice of the stereochemistry of the aldehyde, the alkyne, and the NME (Figure 1). To assess this assumption, we explored further additions to such aldehydes using (*S*)-**2**.

Table 1. Additions of (*R*)-**2** to Aldehydes



syn-**4** *anti*-**4**

entry	R	NME	product	yield (%)
1	cyclohexyl	(+)	*anti*-**4a**	71
2	isopropyl	(−)	*syn*-**4b**	87
3	isopropyl	(+)	*anti*-**4b**	88
4	neopentyl	(−)	*syn*-**4c**	44[a]
5		(−)	*anti,syn*-**4d**	95
6		(−)	*syn,syn*-**4e**	100
7		(+)	*anti,anti*-**4e**	98

[a] 76% based on recovered starting material.

As result, a valuable *matched* case was observed for a Felkin−Ahn addition to the protected lactaldehyde leading to *anti*,*anti*-**4d** (Figure 1). More remarkably, Ley's butane-2,3-diacetal-protected glyceraldehyde proved to be an excellent group in terms of reactivity and selectivity for both type of additions (*syn* and *anti*).[9]

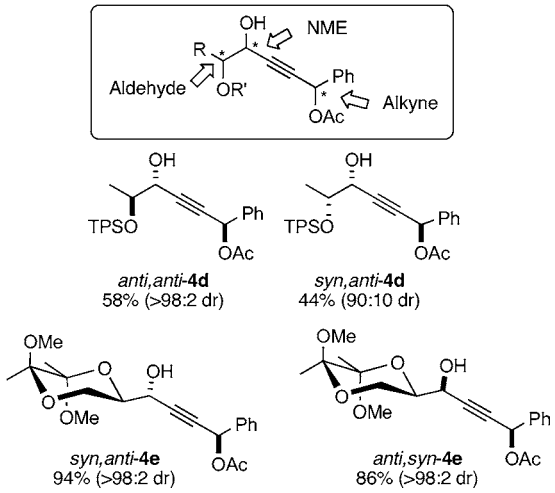
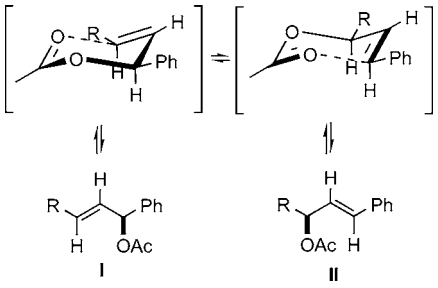


Figure 1. Carreira's additions to chiral aldehydes.

Keeping in mind the metal-catalyzed [3,3]-sigmatropic rearrangement of allylic acetates,[10] we then explored the chirality transfer from the benzylic position (via **B** in Scheme 1). These rearrangements usually occur under thermodynamical control and the more stable allylic acetate predominates (Scheme 3). Our hypothesis was that the conjugation of the double bond to the phenyl group might shift the equilibrium to the allylic acetate **II**.

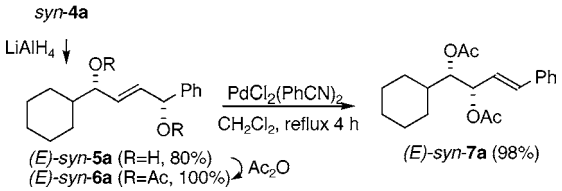
(3) Prepared by addition of lithium acetylide to benzaldehyde: Mortier, J.; Vaultier, M.; Carreaux, F.; Douin, J.-M. *J. Org. Chem.* **1998**, *63*, 3515.
(4) (a) Xu, D.; Li, Z.; Ma, S. *Tetrahedron Lett.* **2003**, *44*, 6343. (b) Raminelli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117.
(5) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
(6) (a) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, *43*, 2691. For propargyl acetate additions, see also: (b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017.
(7) Determined by HPLC analysis.
(8) (a) Michel, P.,; Ley, S. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 3898. (b) Michel, P.; Ley, S. V. *Synthesis* **2004**, 147.
(9) Boyer, J.; Allenbach, Y.; Ariza, X.; Garcia, J.; Georges, Y.; Vicente, M. *Synlett* **2006**, 1895.
(10) For recent stereoselective applications, see: (a) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687. (b) Saito, S.; Kuroda, A.; Matsunaga, H.; Ikeda S. *Tetrahedron* **1996**, *52*, 13919.

Scheme 3. [3,3]Sigmatropic Rearrangement



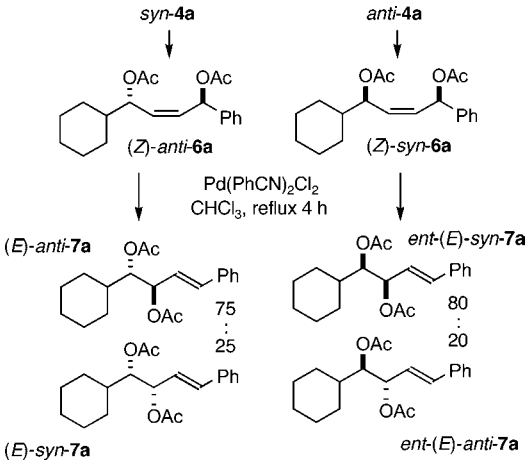
To confirm this assumption, the propargylic acetate *syn*-**4a** was first converted into the corresponding (*E*)-allylic diacetate [(*E*)-*syn*-**6a**] and then treated with $PdCl_2(PhCN)_2$.[11] We were gratified to observe the expected rearrangement with complete transfer of chirality to afford the diacetate (*E*)-*syn*-**7a** (Scheme 4). Very interestingly, only the benzylic

Scheme 4. Allylic Isomerization



acetate isomerizes. The same behavior was observed for the isomer (*E*)-*anti*-**6a** (96% yield).

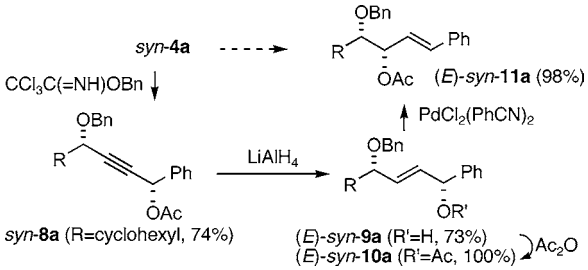
Scheme 5. Isomerization of (*Z*)-**6a**



The effect of the solvent was next tested. Samples of (*E*)-*anti*-**6** were stirred (6 h, rt) in the presence of 5% of $PdCl_2$-$(PhCN)_2$ in different solvents: CH_3CN (0%), THF (25%), toluene (65%), and CH_2Cl_2 (83%). Therefore, CH_2Cl_2 was chosen as standard solvent.

The partial hydrogenation of the triple bond of either *syn*- or *anti*-**4a** followed by acetylation afforded (*Z*)-**6a** (*syn* or *anti*). In sharp contrast with their *E* isomers, (*Z*)-**6a** did not rearrange in CH_2Cl_2 under Pd(II) catalysis. As shown in Scheme 5, the rearrangement only occurred with lower stereoselectivity at higher temperature ($CHCl_3$ at reflux).[12]

Scheme 6. Isomerization of Monoacetate (*E*)-*syn*-**10a**



Finally, looking for bearing different protecting groups in the final 1,2-diols (Scheme 6) we explored other protectors for the free hydroxyl group in adducts **4**.

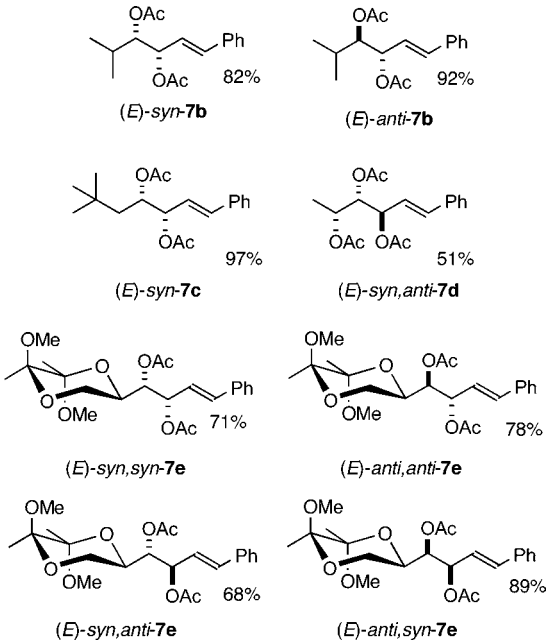


Figure 2. Pd(II)-catalyzed rearrangements.

Thus, *syn*-**4a** was protected as a benzyl ether and then transformed into the corresponding allylic acetate (*E*)-*syn*-**10a** (Scheme 6). When (*E*)-*syn*-**10a** was treated with Pd(II)

(11) The catalytic activity of other Lewis acids (BF_3·Et_2O, $Sc(OTf)_3$, TsOH, ...) was also explored but no reaction was observed after 2 h at rt in CH_2Cl_2 in any case.

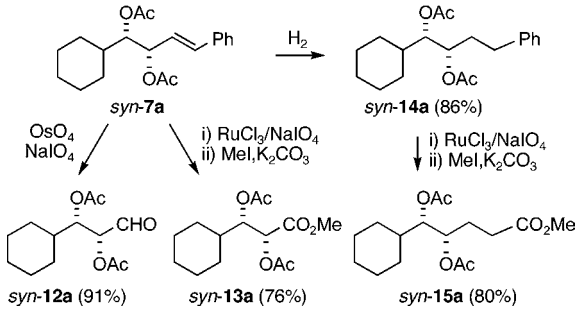
(12) The lower reactivity of (*Z*)-isomers was already reported for related substrates (ref 10b).

catalysis the expected product [(*E*)-*syn*-**11a**] was obtained in 85% yield (100% brsm) with perfect transfer of chirality. However, rearrangements failed in analogous substrates with the hydroxyl group unprotected or protected as TBS ether.

Under our optimized conditions [5% $PdCl_2(PhCN)_2$ in CH_2Cl_2 at reflux], several allylic 1,4-diacetates were rearranged to 1,2-isomers (Figure 2). In all cases, complete chirality transfer was observed being the starting material the only other compound detected. Despite the fact that allylic equilibrium is shifted toward the products, in some cases a significant amount of starting material was recovered.

At this point several transformations were attempted to convert these allylic acetates in convenient precursors for subsequent additions (Scheme 7). Thus, the unsaturated

Scheme 7. Useful Transformations of the Styryl Moiety

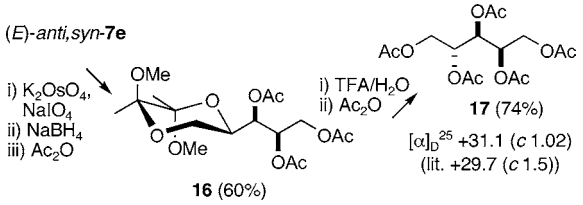


moiety in diacetate *syn*-**7a** was transformed in either a carbaldehyde (*syn*-**12a**) by an $OsO_4/NaIO_4$ oxidation or a methyl ester (*syn*-**13a**) by $RuCl_3/NaIO_4$ oxidation,[13] followed by methylation. On the other hand, *syn*-**7a** was hydrogenated to *syn*-**14a** and the phenyl group could be oxidized to methyl ester *syn*-**15a** in a two-step process.

(13) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

Having in hand this methodology, we undertook the preparation of D-arabitol pentaacetate (**17**, Scheme 8).

Scheme 8. Arabitol Pentaacetate



Oxidative cleavage of the olefin of (*E*)-*anti*,*syn*-**7e** to triacetate **16** followed by hydrolysis and in situ acetylation gave **17**.[14]

In summary, we have developed a new procedure for the stereoselective preparation of 1,2-diols, with independent control of both stereocenters. The above methodology can be potentially used for stepwise enantioselective synthesis of polyhydroxylated chains as exemplified in the preparation of D-arabitol pentaacetate.

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Supporting Information Available: Experimental procedures and analytical data for all of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) As expected, compound **17** showed identical spectral data as that reported in the literature: (a) Jarosz, S.; Skóra, S.; Szewczyk, K.; Ciunik, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 1895. (b) Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315. (c) Hirai, A.; Tonooka, T.; Tanino, K.; Miyashita, M. *Chirality* **2003**, *15*, 108.