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Stereoselective approach to alk-2-yne-1,4-diols. Application to the synthesis of musclide B

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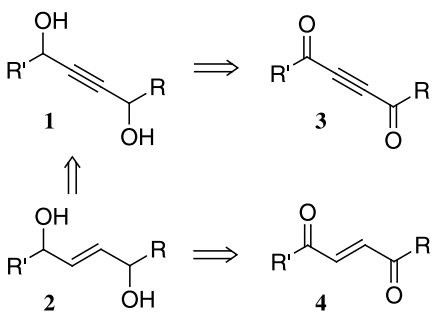
Abstract—An expedient method for the stereoselective preparation of alk-2-yne-1,4-diols has been achieved, based on the addition of chiral alk-1-yn-3-ols (or their protected derivatives) to aldehydes mediated by zinc triflate, Et_3N, and (+)- or (–)-*N*-methylephedrine. In general, the configuration observed at the emergent stereocenter depends on the *N*-methylephedrine employed resulting in good to excellent diastereoselectivities. This strategy has been applied to the enantioselective synthesis of musclide B, a bioactive metabolite from musk.

Achieving stereocontrol in the construction of acyclic systems is of considerable interest in organic synthesis. In particular, the efficient construction of chiral alk-2-yne-1,4-diols (**1**) and/or (*E*)-alk-2-ene-1,4-diols (**2**) is a challenging goal not only because these substructures are often present in natural products,[1] but also due to the fact that such compounds are amenable to conversion into saturated diols and other useful chiral synthons.[2]

In this connection, we have recently described a route (Scheme 1) to chiral C_2-symmetrical unsaturated 1,4-diols through the oxazaborolidine-mediated reduction of the parent acetylenic[3] (**3**) or ethylenic diketones (**4**).[4] Moreover, we have applied these diols to the syntheses of (–)-methylenolactocin and (–)-phaseolinic acid.[5] Nonetheless, this approach to compounds **1** and **2** suffers from some limitations: (i) unsymmetrical starting diketones **3** or **4** ($R \neq R'$) are not as easy to obtain as the symmetrical ones;[6] (ii) the reduction of diketones with a chiral reagent obviously tends to give rise to two stereocenters with the same configuration, leading to the *syn* products rather than the *anti* isomers (*meso* compounds when $R = R'$). In addition, if any derivative with one protected hydroxyl group is required, an additional, sometimes troublesome regioselective monoprotection step has to be achieved.



Scheme 1.

Very recently, Carreira et al. reported the enantioselective addition of Zn-alkynylides to aldehydes using commercially available zinc trifluoromethanesulphonate (zinc triflate), (+)- or (–)-*N*-methylephedrine and Et_3N to afford highly enantioenriched propargylic alcohols.[7] Based on these studies, we envisioned that addition of a chiral *O*-protected propargylic alcohol, **5**, to an aldehyde could provide a ready access to the *syn*- or *anti*-propargylic diols **1** in a predictable way by using Carreira's methodology. This would be the case if, as expected, the stereochemical course of the addition was ruled by the chiral auxiliary rather than by substrate control (see Scheme 2).[8] Since chiral compounds **5** are, in turn, available in both configurations by different ways, including the enantioselective reduction of the parent ketone[9] or the aforementioned addition of Zn-alkynylides to aldehydes, this strategy could constitute a flexible, modular approach to any stereoisomer of **1** (or their monoprotected derivatives **6**). We wish to report here our findings in this connection.

In order to assess the viability of this strategy, we launched the study of the addition of some representa-

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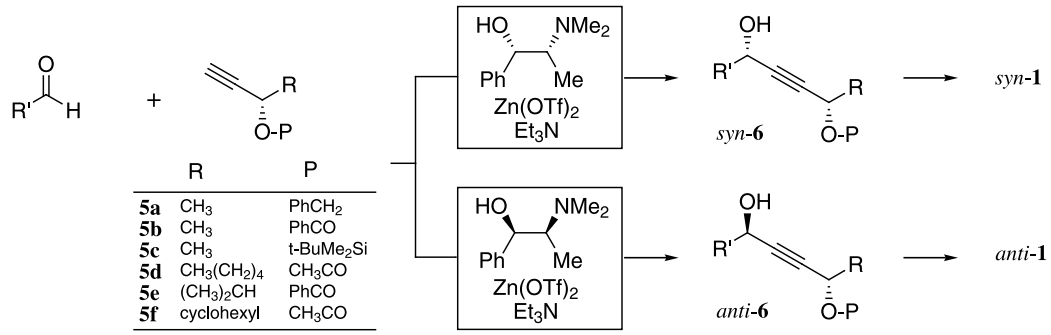


Scheme 2.

tive protected, highly enantioenriched alk-1-yn-3-ols (**5**)[10] with a few aldehydes in the presence of zinc triflate, (+)- or (–)-*N*-methylephedrine and Et_3N.[11] With regard to the results summarised in Table 1 some remarks should be noted:

(i) Reactions worked well in the absence of solvent or, even better, with a very small amount of dry toluene. Although not pointed out in Table 1 for the sake of simplicity, lower yields or longer reaction times were observed in a number of preliminary experiments using 0.3–0.5 M toluene solutions of terminal alkynes **5** (for instance, **6a** was obtained in 24% yield besides a 55% of recovered starting **5a**, after 1 day at 65°C, entry 1 in Table 1).

(ii) In general, good to excellent yields were noted in all the cases. With regard to the stereochemical control, the use of (+)- or (–)-*N*-methylephedrine mainly determined the configuration of the new stereocenter. Monoprotected diols were formed in excellent diastereoselectivities[12] in the matched cases (entries 2, 4, 6, 8–10, 12 and 14) but also good in the mismatched ones (entries 3, 5, 7, 11 and 13).

(iii) The process is tolerant with a range of protective groups (benzyl, benzoyl, acetyl, and *tert*-butyldimethylsilyl groups). However, faster reactions and, in general, better stereoselectivities were noted for alkynes with the hydroxyl protected as benzoate or acetate (2–4 hours at 20°C)[13] than for alkynes protected as silyl ethers (overnight at 20°C) or benzyl ethers (5–12 h at 65°C).[14] This fact can be attributed to the higher acidity of propargylic esters **5b** and **5d–f** in comparison with propargylic ethers **5a** and **5c**, which probably favours the formation of the Zn-alkynylide intermediate in the reaction media.

We then attempted to expand the scope of this reaction to simpler, unprotected alk-1-yn-3-ols. Although the successful addition to aldehydes of the Zn-alkynylide derived from 2-methylbut-3-yn-2-ol, which bears a free tertiary alcohol, has been recently reported by Carreira's group,[10] related additions with substrates containing a less hindered, unprotected alcohol were still undocumented. Since in a series of preliminary experiments using representative propargylic alcohols in the absence of solvents, we observed moderate yields of the expected unprotected diols **1**,[15] we turned our attention to toluene solutions. To our satisfaction, the expected diols were obtained in useful yields and good to excellent selectivities, as shown in Table 2.[16]

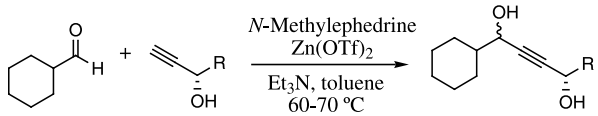
These goods results prompted us to apply this strategy to an enantioselective synthesis of musclide B, a cardiotonic potentiating principle present in musk. Musk, a dried secretion from the preputial follicles of a male musk deer (*Moschus moschiferus* L.), has been prescribed traditionally in Chinese medicines, based upon its three pharmacological actions, cardiotonic, sedative and anti-inflammatory properties. Kikuchi et al. have

Table 1. Addition of *O*-protected (*S*)-1-alkyn-3-ols (**5**) to aldehydes

Entry	Alkyne	R′ in R′-CHO	*N*-Methylephedrine	*T* (°C)	Product	Yield (%)	*syn*/*anti*
1[a]	**5a**	Cyclohexyl	(–)	65	**6a**	24	–
2	**5a**	Cyclohexyl	(–)	65	**6a**	70	94:6
3	**5a**	Cyclohexyl	(+)	65	**6a**	81	6:94
4	**5a**	Isopropyl	(–)	65	**6b**	75	93:7
5	**5a**	Isopropyl	(+)	65	**6b**	70	13:87
6	**5b**	Isopropyl	(–)	rt	**6c**	97	98:2
7	**5b**	Isopropyl	(+)	rt	**6c**	90	7:93
8	**5b**	*tert*-Butyl	(–)	rt	**6d**	64	99:1
9	**5c**	Isopropyl	(–)	rt	**6e**	85	96:4
10	**5d**	*tert*-Butyl	(–)	rt	**6f**	72	99:1
11	**5d**	*tert*-Butyl	(+)	rt	**6f**	78	7:93
12	**5e**	Isopropyl	(–)	rt	**6g**	84	95:5
13	**5e**	Isopropyl	(+)	rt	**6g**	72	10:90
14	**5f**	Cyclohexyl	(–)	rt	**6h**	76	98:2

[a] Reaction performed in a 0.3 M toluene solution.

Table 2. Addition of unprotected (*S*)-1-alkyn-3-ols to cyclohexanecarbaldehyde



Entry	Alkyne (*R*)	*N*-Methylephedrine	Time (h)	Yield (%)	*syn*/*anti*
1	Methyl	(–)	3	82	95:5
2	Methyl	(+)	4	99	17:83
3	Cyclohexyl	(–)	40	68	99:1
4	Cyclohexyl	(+)	40	60	3:97

reported that the cardiotonic activity is due to the presence of three aliphatic 1,4-diol monosulfates, musclides A1, A2 and B.[17] Very recently, Tezuka et al. have determined the structure of musclide B to be (2*R*,5*S*)-2-hydroxy-7-methyloct-5-yl hydrogen sulphate (**7**) (Fig. 1) by comparison of the natural product with the 2*S*,5*R* and the 2*R*,5*R* stereoisomers obtained from (*S*)-(–)-ethyl leucate.[18]

Our approach to musclide B is summarised in Scheme 3. The slow addition of 3-methylbutanal to the Zn-alkynylide derived from *ent*-**5a** in the presence of (+)-*N*-methylephedrine afforded the monoprotected diol **6i** in a 90:10 (*R*,*R*)/(*R*,*S*) ratio.[19] After reduction of **6i** with $LiAlH_4$ in THF, the minor *R*,*S* stereoisomer was separated by chromatography (MPLC, hexane/ethyl acetate 98:2) to obtain diol **8**. Finally, hydrogenation of **8** on Pt afforded the known saturated diol **9**.[20] Since an efficient transformation of **9** into **7** has been described,[18] this approach constitutes a formal, stereoselective synthesis of musclide B.

In summary, we have demonstrated that the stereoselective addition of chiral 1-alkyn-3-ols (or of their protected derivatives) to aldehydes mediated by zinc triflate, Et_3N, and (+)- or (–)-*N*-methylephedrine constitutes an efficient, modular way to prepare chiral *syn*- or *anti*-2-alkyne-1,4-diols (or their monoprotected derivatives). This strategy has been applied to the synthesis of musclide B, a bioactive metabolite from musk. It extends the scope of the enantioselective alkynylation of aldehydes recently described by Carreira's group.

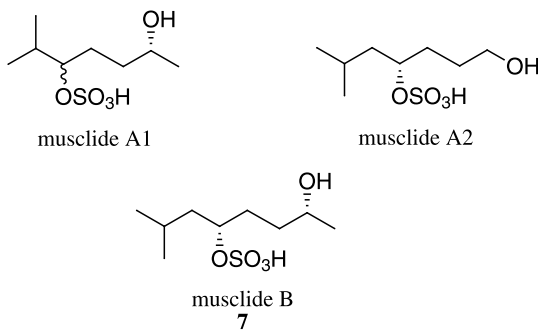


Figure 1.

Acknowledgements

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2. Ethylenic diols **2** or their *Z* isomers are easily obtainable from **1** by $LiAlH_4$ reduction and partial hydrogenation, respectively. These substrates are potentially amenable to transformation into other functionalities in a stereoselective way (see, for instance, Refs. 3–5). For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307–1370.
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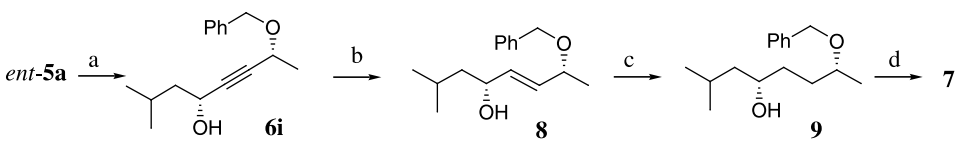

Scheme 3. *Reagents and conditions*: (a) $Zn(TfO)_2$ (1.1 equiv.), (+)-*N*-methylephedrine (1.2 equiv.), Et_3N (1.2 equiv.), 3-methylbutanal (1.1 equiv.), toluene (0.3 mL), 65°C, overnight, 73%; (b) $LiAlH_4$, THF, rt, 80%; (c) H_2 (1 atm.), Pt cat., rt, 85%; (d) Ref. 18.

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6. Symmetrical alk-2-yne-1,4-diols, obtained as mixtures of stereoisomers by one-pot double addition of dilithium (or magnesium) acetylide to aldehydes can be transformed into symmetrical diketones **3** by Jones oxidation in good yields. See: Sudweeks, W. B.; Broadbent, H. S. *J. Org. Chem.* **1975**, *40*, 1131–1136. See also: Choi, T.-L.; Lee, C. W.; Chaterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417–10418.
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8. Carreira and co-workers have very recently reported the addition of the Zn-alkynylide derived from propargyl acetate to (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal mediated by (+)- or (–)-*N*-methylephedrine (Ref. 7d). In that case, the stereochemical outcome observed was provided by the chiral amino alcohol employed. To the best of our knowledge, other exemples using chiral alkynes or other α-substituted chiral aldehydes are unpublished.
9. For leading references on enantioselective reduction of acetylenic ketones, see: (a) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725; (b) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379–2386; (c) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214–3217; (d) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021–9025; (e) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939; (f) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
10. Protected alcohols **5a–d** were obtained from the commercially available (*S*)-but-3-yn-2-ol or (*S*)-oct-1-yn-3-ol by standard procedures. Compounds **5e–f** were obtained according to: Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233–4236.
11. **General procedure for alkynes 5a–f**: To a mixture of $Zn(OTf)_2$ (dried overnight at 120°C under vacuum, 1.1 mmol), (+)- or (–)-*N*-methylephedrine (1.2 mmol) and alkyne **5** (1 mmol), Et_3N (1.2 mmol) was added under Ar at rt. In most cases, a small amount (~0.3 mL) of dry toluene was also added in order to obtain an almost homogeneous mixture. After vigorous stirring for 30 min at rt, the aldehyde (1.2 mmol) was added in one portion by syringe, and the mixture was stirred at 20°C or 65°C. The reaction was monitored by TLC and, after completion, the mixture was poured directly into a silica gel column and purified by flash chromatography to afford the desired diol **6**. NMR data for *syn*-**6b**: ^{1}H NMR ($CDCl_3$): δ 1.01 (d, $J=6.3$ Hz, 3H), 1.03 (d, $J=6.3$ Hz, 3H), 1.47 (d, $J=6.6$ Hz, 3H), 1.88 (m, 1H), 4.22–4.30 (m, 2H), 4.50 (A of an AB system, $J=11.7$ Hz, 1H), 4.77 (B of an AB system, $J=11.7$ Hz, 1H), 7.22–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 17.5, 18.1, 22.2, 34.6, 64.5, 67.9, 70.5, 84.9, 85.4, 127.7, 128.0, 128.4, 137.9. Compound *anti*-**6b**: ^{1}H NMR: δ 1.01 (d, $J=6.3$ Hz, 3H), 1.03 (d, $J=6.3$ Hz, 3H), 1.47 (d, $J=6.6$ Hz, 3H), 1.88 (m, 1H), 4.22–4.31 (m, 2H), 4.50 (A of an AB system, $J=11.7$ Hz, 1H), 4.77 (B of an AB system, $J=11.7$ Hz, 1H), 7.22–7.30 (m, 5H). ^{13}C NMR: δ 17.5, 18.2, 22.3, 34.5, 64.5, 67.9, 70.6, 84.9, 85.4, 127.6, 127.9, 128.3, 137.9.
12. Stereoselectivities were determined by ^{19}F analysis of the corresponding Mosher esters. The configuration of the new stereocenters were determined by the Kakisawa method (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096) and it always agreed with those expected on the basis of Carreira's work.
13. A few experiments performed at 65°C showed lower stereoselectivities (for example, reaction of **5b** with isobutyraldehyde gave **6c** in 92% yield but only in a 83:17 *syn*/*anti* ratio).
14. A few experiments performed at higher temperatures (i.e. 100°C) gave less satisfactory yields due to the formation of by-products (detected by TLC).
15. The reversible formation of ketals or/and hemiketals between the free hydroxyl groups and the aldehyde in the presence of Zn salts can be assumed, especially in a solvent-free mixture.
16. **General procedure for unprotected alkynes**: A mixture of $Zn(OTf)_2$ (dried overnight at 120°C under vacuum, 1.1 mmol), (+)- or (–)-*N*-methylephedrine (1.2 mmol) and Et_3N (1.2 mmol) in 2 mL of dry toluene was stirred under Ar at rt for 2 h. The alkyne (1 mmol) was then added and the mixture was vigorously stirred for additional 15 min before the aldehyde (1.2 mmol) was added in one portion by syringe. The reaction was stirred at 60–70°C until TLC revealed the disappearance of the starting alkyne, and then quenched by addition of saturated aqueous NH_4Cl (3 mL). The mixture was poured into a separatory funnel containing diethyl ether (20 mL) and the aqueous layer was washed with more diethyl ether (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography to afford the desired diol **1**. NMR data for *syn*-1-cyclohexylpent-2-yne-1,4-diol: ^{1}H NMR ($CDCl_3$): δ 1.00–1.35 (m, 6H), 1.45 (d, $J=6.3$ Hz, 3H), 1.65–1.90 (m, 5H), 4.17 (d, $J=5.7$ Hz, 1H), 4.57 (q, $J=6.3$ Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.2, 25.8, 26.3, 28.1, 28.6, 43.9, 58.0, 66.9, 84.0, 87.5. *anti* Isomer: ^{1}H NMR: δ 1.00–1.35 (m, 6H), 1.45 (d, $J=6.7$ Hz, 3H), 1.65–1.90 (m, 5H), 4.16 (dd, $J=6.5$, 1.2 Hz, 1H), 4.56 (qd, $J=6.7$, 1.2 Hz, 1H). ^{13}C NMR: δ 24.3, 25.9, 26.3, 28.1, 28.5, 43.9, 58.1, 67.0, 84.0, 87.6.
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19. The fact that α-unbranched aldehydes, like 3-methylbutanal, give products with lower yields and stereoselectivities has been previously reported (see Ref. 7a).
20. Spectral data of **9** fully agree with those reported in Ref. 18.