ORGANIC LETTERS

2005
Vol. 7, No. 7
1399−1401

Novel Enantioselective Synthesis of 1,3-Butadien-2-ylmethanols via Tandem Alkylbromide-epoxide Vinylations Using Dimethylsulfonium Methylide

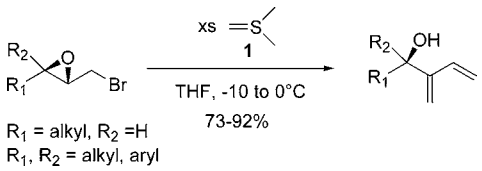
Lilian Alcaraz,* Katherine Cox, Andrew P. Cridland, Elizabeth Kinchin, James Morris, and Stewart P. Thompson

Department of Medicinal Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics, LE11 5RH, UK

lilian.alcaraz@astrazeneca.com

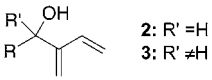
Received February 3, 2005

ABSTRACT



The treatment of chiral trans-disubstituted and trisubstituted 2,3-epoxy-1-bromides with an excess of dimethylsulfonium methylide 1 affords the corresponding 1,3-butadien-2-ylmethanols in good to excellent yields via a double one-carbon homologation.

The usefulness of substituted 1,3-butadien-2-ylmethanols of general structure **2** and **3** as valuable intermediates in the synthesis of natural[1] and unnatural[2,3] products is well documented.



This has resulted in the development of a number of methods for their preparation.[2a,c,3b,4−6] Many of these methodologies involve organometallic species such as 1,3-butadienyl-2-metal[4] or 2,3-butadienyl-1-metal,[5] which often suffer from poor regioselectivity or low chemical yield and, in some cases, require starting materials that are not readily accessible. Moreover, the most efficient of these methods have to be carried out using relatively complicated procedures at low

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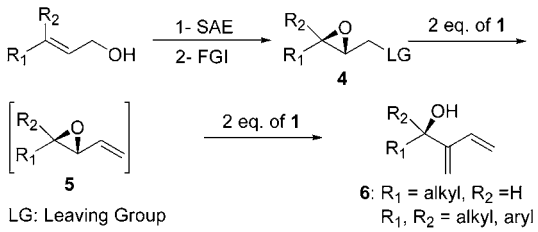
10.1021/ol0502329 CCC: $30.25
Published on Web 02/25/2005

temperature in the presence of a Lewis acid. More recently, attractive alternative methods such as indium-induced Barbier-type coupling of 1,4-dibromobutyne with carbonyls[2a,3b,6c] and ethylene-alkyne cross-metathesis of terminal propargyl alcohols[6b,d] have been reported for the preparation of these substrates. However, although efficient, the few methods applicable to the enantioselective synthesis of 1,3-butadien-2-ylmethanols have so far been limited to the synthesis of secondary hydroxydienes **2**, while a general method for the enantioselective preparation of tertiary hydroxydienes **3**, to the best of our knowledge, still remains elusive.

As a continuation of our work on developing new methodologies using dimethylsulfonium methylide **1**,[7] we have recently reported the interesting observation that **1** selectively reacts with unactivated 1,2-disubstituted *cis*-epoxides yielding one-carbon-homologated allylic alcohols, while the corresponding unactivated trans- and trisubstituted epoxides are inert under the reaction conditions.[8] It has also been shown previously by Mioskowski et al. that **1** can perform the conversion of halides to one-carbon-homologated terminal alkenes.[9] We envisaged that tactical combination of these methodologies could result in an unprecedented enantioselective synthesis of dienes **2** and **3**.

Our strategy was as outlined in Scheme 1: trans- (R_2 = H) or 3,3-disubstituted (R_1 and $R_2 \neq$ H) 2,3-epoxy-1-halides

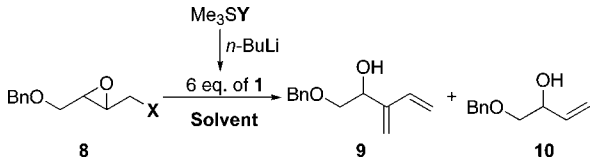
Scheme 1



4 are readily available by Sharpless asymmetric epoxidation (SAE) of suitable allylic alcohols[10] followed by conversion of the primary alcohol functionality into a suitable leaving group (LG). Exposure of compounds of generic structure **4** to an excess of ylide **1** should produce the corresponding one-carbon-homologated epoxyalkenes **5** in which the epoxide is now activated at the allylic position and should in turn undergo regioselective ring-opening homologation by the excess of **1** to yield the desired chiral 1,3-butadien-2-ylmethanols **6**.

We started our investigation by studying the proposed transformation on racemic epoxides **8** (Scheme 2).

Scheme 2



It rapidly became apparent that the outcome of the reaction was highly dependent on both the nature of the leaving group X and the solvent, whereas the trimethyl sulfonium salt counterion Y had no effect. Key results of this study are summarized in Table 1.

Table 1. Reaction Optimization

entry	X	Y	solvent	ratio **9**:**10**[a]
1	I	I	THF	>5:95
2	I	I	Et_2O	>5:95
3	I	BF_4	THF	>5:95
4	Cl	I	THF	complex mixture
5	Br	I	THF	>95:5
6	Br	BF_4	THF	>95:5
7	Br	I	Et_2O	>5:95

[a] Determined by crude ^{1}H NMR

Employing iodide as the leaving group X in epoxide **8** consistently afforded the unexpected elimination product **10** regardless of the nature of the sulfonium salt counterion Y and the solvent used (Table 1, entries 1−3). Formation of compound **10** is probably the result of a direct nucleophilic attack of the ylide on the iodide followed by β-elimination of the epoxide in a manner similar to that previously reported.[11] While the chloride gave a complex mixture of products (entry 4), employing bromide as the leaving group and using THF as the solvent gave complete conversion to the desired dienol **9** (entry 5). Changing the counterion Y to tetrafluoroborate caused no deleterious effects to the reac-

(6) (a) Phukan, P.; Bauer, M.; Maier, M. E. *Synthesis* **2003**, 1324−1328. (b) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788−1792. (c) Lu, W.; Ma, J.; Yang, Y.; Chan, T. H. *Org. Lett.* **2000**, *2*, 3469−3471. (d) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274. (e) Katritsky, A. R.; Serdyuk, L.; Toader, D.; Wang, X. *J. Org. Chem.* **1999**, *64*, 1888−1892. (f) Yu, C.-M.; Yoon, S.-K.; Lee, S.-J.; Lee, J.-Y.; Kim, S. *Chem. Commun.* **1998**, 2749−2750. (g) Halazy, S.; Krief, A. *Tetrahedron Lett.* **1980**, *21*, 1997−2000. (h) Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Lawrence, N. J.; Selim, M. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1893−1900.

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(9) (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5453−5456. For related methodology using arsonium ylides, see: (b) Seyer, A.; Alcaraz, L.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 7871−7874.

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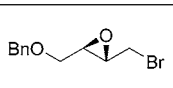
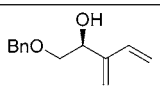
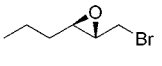
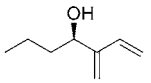
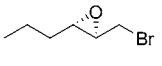
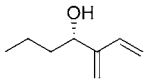
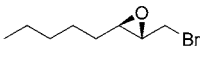
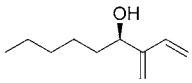
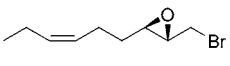
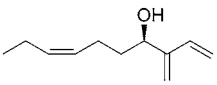
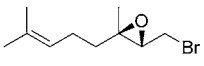
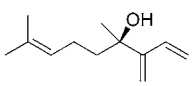
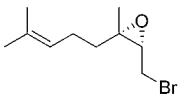
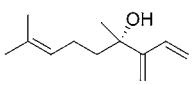
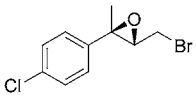
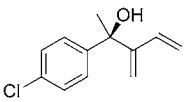
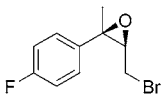
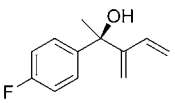
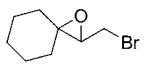
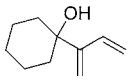
(11) (a) Concellón, J. M.; Llavona, L.; Bernad, P. L., Jr. *Tetrahedron* **1995**, *51*, 5573−5584. (b) Fujii, N.; Habashita, H.; Akaji, M.; Nakai, K.; Ibuka, T.; Fujiwara, M.; Tamamura, H.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 865−866.

Table 2. Tandem Alkylbromide-epoxide One-Carbon Vinylations

entry	substrate	product	yield (%)[a]
1			91%
2			80%
3			73%
4			88%
5			92%
6			82%
7			86%
8			78%
9			81%
10			76%

[a] Isolated yield.[14]

tion's outcome (entry 6); however, quite remarkably, switching solvent from THF to diethyl ether totally reversed the course of the reaction in favor of the undesired alcohol **10** (entry 7).

With our optimized conditions in hand, the scope of this methodology was explored (Table 2).[12]

Exposure of trans-1,2-disubstituted epoxides to 6 equiv of **1** at −10 °C in THF resulted in excellent yields of the corresponding dienols (entries 1−5). As expected, the enantiomeric purity of the original epoxy-alcohol was conserved in the final product (e.g., entry 5, 96% ee).[13] On moving to 1,2,2-trisubstituted epoxides (entries 6−10), it was necessary to increase the amount of ylide **1** from 6 to 9 equiv to achieve complete conversions to the tertiary dienols. Failing that, epoxyalkene intermediates **5** were isolated as major products of the reactions, which confirms that the reactions proceed through the proposed pathway (Scheme 1). Thus acyclic, aliphatic (entries 6 and 7), aromatic (entries 8 and 9), and cyclic (entry 10) epoxides afforded the desired products in good yields. It is worth noting that these reactions also had to be kept below 0 °C for longer periods than the disubstituted epoxides due to the increase in steric hindrance around the epoxide and the instability of **1** above 0 °C.

In summary, we have developed a novel and simple enantioselective synthesis of 1,3-butadien-2-ylmethanols from readily accessible chiral epoxides using dimethylsulfonium methylide, which leads to synthetically valuable intermediates. More importantly, this new methodology allows access to chiral tertiary dienols **3**.

Acknowledgment. We thank Dr. Mark Furber, Prof. Stephen Clark, and Prof. Nigel Simpkins for helpful discussions. We are also grateful to Hema Pancholi for her expert assistance in MS studies.

Supporting Information Available: ^{1}H and ^{13}C NMR data and literature references for the products illustrated in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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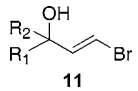
(12) **General Procedure.** To a −10 °C suspension of trimethylsulfonium iodide (6.5 equiv, 6.5 mmol, 1.33 g (or 10.0 equiv, 10.0 mmol, 2.0 g)) in THF (8 mL) was added *n*-BuLi (6.0 equiv, 6.0 mmol, 2.4 mL of 2.5 M hexane solution (or 9.0 equiv, 9.0 mmol, 3.6 mL of 2.5 M hexane solution)). After 20 min, epoxide (1.0 equiv, 1.0 mmol) in THF (1 mL) was introduced, and the reaction was slowly allowed to warm to 0 °C over 3 h. The mixture was then allowed to warm to ambient temperature and was stirred for 2 h. The reaction was quenched with water, and the mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel using pentane/ether to give the desired allylic alcohol.

(13) Determined by ^{1}H NMR of the corresponding (*S*)-Mosher's esters.

(14) In some cases, the formation of small quantities of vinyl bromides **11** (<5%) have also been observed as a result of ylide **1** acting as a base.



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For a related transformation using lithium diisopropyl amide, see: Barluenga, J.; Baragana, B.; Concellon, J. M. *J. Org. Chem.* **1999**, *64*, 2843−2846.