Pergamon

Tetrahedron Letters, Vol. 38, No. 48, pp. 8307-8310, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10208-8

One-Pot Transformation of *p*-Toluenesulfonates of 2,3-Epoxy Alcohols into Allylic Alcohols

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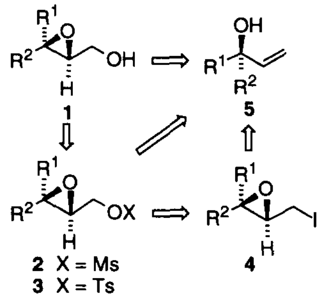
Abstract: A convenient and efficient method for the synthesis of synthetically useful non-racemic allylic alcohols from 4-methylbenzenesulfonates of non-racemic 2,3-epoxy alcohols is described. Satisfactory yields are obtained by treatment of 4-methylbenzenesulfonates of non-racemic 2,3-epoxy alcohols with potassium iodide followed by zinc powder and ammonium chloride in a one-pot manner. The method has been successfully applied to the synthesis of a key building block of C_{30}-C_{37} botryococcenes. © 1997 Elsevier Science Ltd.

The allylic alcohol functionality-bearing compounds can be found in many natural compounds of biological importance.[1] Currently, there is considerable interest in the synthesis and reaction of non-racemic allylic alcohols as key intermediates for the synthesis of various types of biologically important compounds.[2]

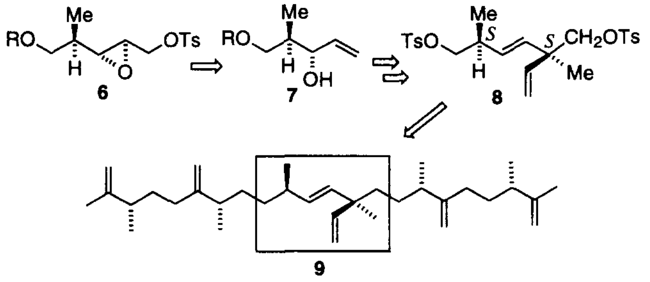
As part of an ongoing program aimed at the synthesis of biologically active natural compounds, we needed a reliable procedure which would allow the convenient preparation of allylic alcohols **5** with high optical purity as key synthetic intermediates from readily available non-racemic 2,3-epoxy alcohols **1** or related compounds **2**, **3**, and **4** (Scheme 1).

Scheme 1



$R^1 = R^2$ = alkyl, aryl, or H

Scheme 2



Existing synthetic methods of allylic alcohols from 2,3-epoxy alcohols or related substrates include: (i) telluride (II)-mediated[3] or metallic sodium-mediated[4] reduction of mesylates **2**; (ii) titanocene (III)-induced deoxygenation of 2,3-epoxy alcohols **1**;[5] (iii) reduction of tosylates **3** with a zinc-copper couple in the presence of NaI;[6] (iv) reduction of iodides **4** with a zinc-copper couple under sonication;[7] (v) reduction of iodides **4** with activated zinc in refluxing ethanol;[8] (vi) reduction of iodides with alkyllithiums;[9] (vii) iodination of a 2,3-epoxy alcohol with I_2-PPh_3-imidazole followed by reduction with zinc in ethanol for 4 h at 23 °C,[10] and (viii) others.[11]

We reported previously that non-racemic allyl alcohols **5** could be obtained by treatment of tosylates **3** with potassium iodide followed by triphenylphosphine and iodine in a one-pot manner.[12] However, in cases where the protective groups in substrate tosylates are rather acid-labile, expensive 4-(dimethylamino)-phenyldiphenyl-phosphine must be used instead of triphenylphosphine. Routine use of this phosphine as a reducing agent has however been limited by its high cost.

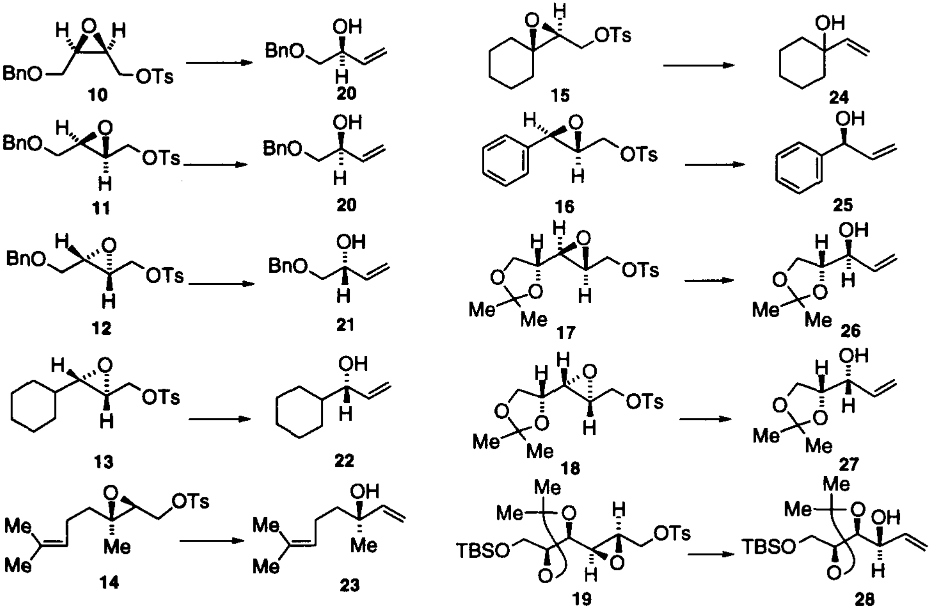
As described above, although a number of groups have made important contributions to this transformation, these methods involved some reactions which still fell short of our goal. In addition, a simple and convenient synthesis of **5**, which should be of high interest for the potential large-scale preparation of the compounds, is still rare.[6a] This is a prime requisite if transformation reactions are to be used to produce the key compounds.

The focus of this research was to prepare various allylic alcohols of type **5** from tosylates of 2,3-epoxy alcohols in a simple and efficient manner. In addition, as shown in Schemes 2 and 4, to evaluate the generality of this new protocol, we have briefly examined the applicability of the reaction to the synthesis of the non-racemic 1,4-diene **8**, a core building block for the synthesis of many naturally occurring botryococcene terpenoids such as C_{34}-botryococcene **9**.[13]

In this paper, we report an efficient one-pot reaction of readily available tosylates of 2,3-epoxy alcohols leading to the corresponding allylic alcohols.

The requisite non-racemic tosylates **10-19** (ee or de > 87%) shown in Scheme 3 for the present study were readily prepared in high yields from the corresponding non-racemic 2,3-epoxy alcohols which, in turn, were obtained by Sharpless asymmetric epoxidation[14] of the respective allylic alcohols.

Scheme 3



The reduction of tosylates could easily be accomplished in the following fashion. Typically, the tosylate **11** was converted into the corresponding allylic alcohol **20** by treatment with potassium iodide (3 equiv.) in DMF at 50 °C for 1.5 h followed by reduction at 0 °C for 20 min with zinc dust (20 equiv.) and ammonium chloride (10 equiv.) in a one-pot manner. Filtration to remove inorganic salts followed by usual workup and flash chromatography gave the pure allylic alcohol **20** in 80% yield. As shown in Scheme 3 and Table 1, in all the cases examined, satisfactory results were obtained by the use of the above simple protocol.

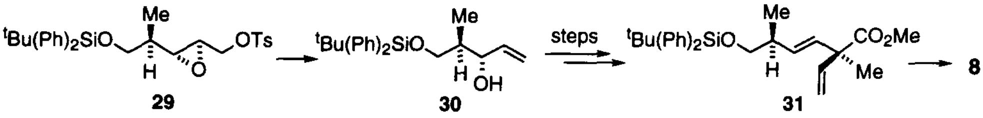
For the successful transformations, the following conclusions may be drawn with regard to reaction conditions: (i) DMF is the solvent of choice. Although conversion of the tosylates into the corresponding iodides by treatment with potassium iodide in refluxing acetone or ethanol is rather slow (Table 1, entries 1 and 2), use of DMF accelerates the reaction rates; (ii) without isolation of the rather labile intermediate iodides, their effective transformation into the corresponding allylic alcohols can be accomplished by addition of zinc dust and ammonium chloride to a stirred solution of the iodides at 0 °C; (iii) although activated zinc in refluxing ethanol has been used for the preparation of an allylic alcohol,[8] activation of zinc is not necessary and, hence, unactivated aged zinc dust can be used in DMF; (iv) this procedure allows the preparation of the tertiary allylic alcohol **23** from the tosylate **14** in good yield; (v) although the allylic alcohol **25** could not be obtained from the tosylate **16** using our previous protocol,[12] it was obtained in pure state by the use of the present procedure albeit in rather low yield. This is a consequence of a lower yield in the iodination step rather than in the zinc dust reduction step. The low yield of **25** from **16** would not be a limitation to the present new protocol; and (vi) although the reported reduction of iodides with alkyllithiums needs anhydrous solvent(s),[9] commercially available DMF involving water (ca. 0.15%) can be used without purification.

Table 1. Synthesis of Allylic Alcohols from the Corresponding Tosylates

Entry	Substrate	Solvent	Iodination condition	Reduction with Zn[a]	Product	Yield	*Ee* (or *De*)[b]
1	**10**	Me_2CO	56 °C, 15.0 h	0 °C, 1 h	**20**	36%	ND[c]
2	**10**	EtOH	78 °C, 20.0 h	0 °C, 1 h	**20**	20%	ND[c]
3	**10**	DMF	50 °C, 1.5 h	0 °C, 20 min	**20**	80%	87%
4	**11**	DMF	50 °C, 1.5 h	0 °C, 20 min	**20**	90%	91%
5	**12**	DMF	50 °C, 1.5 h	0 °C, 20 min	**21**	84%	91%
6	**13**	DMF	50 °C, 1.5 h	0 °C, 20 min	**22**	84%	99%
7	**14**	DMF	50 °C, 1.0 h	0 °C, 20 min	**23**	90%	ND[c]
8	**15**	DMF	50 °C, 1.5 h	0 °C, 20 min	**24**	78%	---
9	**16**	Me_2CO-DMF[d]	45 °C, 1.0 h	25 °C, 10 min	**25**	60%	99%
10	**17**	DMF	55 °C, 1.5 h	0 °C, 20 min	**26**	86%	96%
11	**18**	DMF	55 °C, 1.0 h	0 °C, 20 min	**27**	89%	96%
12	**19**	DMF	50 °C, 1.0 h	0 °C, 20 min	**28**	86%	ND[c]

[a] All reductions were carried out with 10 equiv. of zinc powder except entry 3 (20 equiv. of zinc powder). [b] *Ees* or *Des* were determined by HPLC after derivatized to the MTPA ester. [c] Not determined. [d] Me_2CO-DMF = 4:1.

Scheme 4



In order to evaluate the potential of the above described new method for the synthesis of allylic alcohols, we examined its utility for preparing the enantiopure central substructure **8** of the botryococcene hydrocarbons.[13] The tosylate **29**, derived from the corresponding known epoxy alcohol,[9a] was treated with potassium iodide in DMF at 55 °C followed by zinc dust and ammonium chloride in a one-pot manner at 0 °C, giving the allylic alcohol **30** in 92% yield. The zinc dust should be added only after the starting tosylate has been consumed (as noted by TLC). Needless to say, the compatibility of diverse protecting groups under the reaction conditions used for the present transformation is also an advantage of this technology. The alcohol **30** was converted into the ditosylate **8** via the 1,4-diene **31** by a sequence of reactions.[15] The ^1H- and ^{13}C-NMR spectra were found to be superimposable to the authentic spectra of the bis-tosylate **8**,[13c] which has been transformed into C_{34}-botryococcene **9** by White and associates.[13c]

In summary, a new one-pot method for synthesizing allylic alcohols from the corresponding tosylates of 2,3-epoxy alcohols has been developed.

The following procedure for the synthesis of allylic alcohol **27** from **18** is representative.

A mixture of the tosylate **18** (200 mg, 0.601 mmol), KI (304 mg, 1.83 mmol), and DMF (3 mL) was heated at 55 °C for 1 h. It was then cooled to 0 °C, and zinc powder (380 mg, 6.1mmol) and NH_4Cl (163 mg, 3.05 mmol) were added sequentially with stirring, and the whole was stirred at 0 °C for 20 min. The mixture was filtered and the filtrate was extracted with Et_2O. The filtrate was washed with water and dried over $MgSO_4$. The usual workup followed by chromatography over silica gel with *n*-hexane-Et_2O (3:2) gave 86 mg (89% yield) of the allyl alcohol **27** as a colorless oil. Kugelrohr distillation, 140 °C (2 mm Hg); $[\alpha]^{19}_D$ + 9.46 (*c* 0.423, $CHCl_3$).

ACKNOWLEDGMENT

We thank Professor J. D. White, Oregon State University, for providing us with the authentic ^1H- and ^{13}C NMR spectra of **8**. Financial support from a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan, is gratefully acknowledged.

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15. Details will be reported elsewhere.

(*Received in Japan* 21 *August* 1997; *accepted* 18 *September* 1997)