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AN EXPEDITIOUS APPROACH FOR THE SYNTHESIS OF OPTICALLY ACTIVE ACETYLENIC ALCOHOLS

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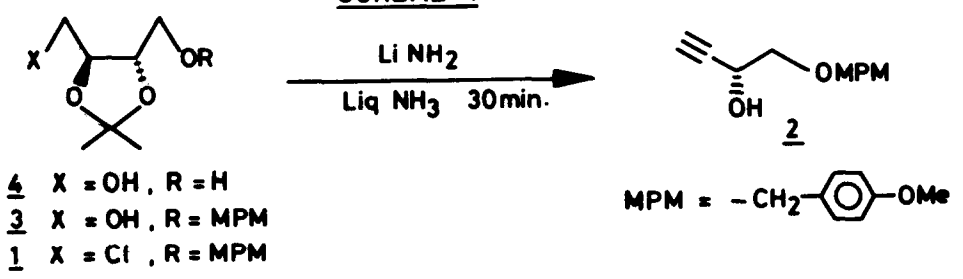
Summary: A *practical method for the synthesis of acetylenic alcohols by base induced elimination of β-alkoxy chlorides is described.*

Optically active acetylenic alcohols have found widespread use in natural product synthesis because the acetylenic unit provides a convenient handle for further elaborations[1]. Several novel methods for the preparation of enantiomerically pure acetylenic alcohols have recently been reported[1,2],most commonly employed among them is the reduction of acetylenic ketones with chiral reagents[2]. In our programme[3] on the synthesis of hydroxy fatty acids and other related natural products of useful biological activity, we required yet simpler and more convenient method for the preparation of acetylenic alcohols from simple chiral precursors such as tartaric acid, which is abundantly available in both the enantiomeric forms. We have developed an expeditious, novel and practical method for the preparation of optically pure acetylenic alcohols from tartaric acid.

Our strategy is based on the base induced elimination of β-alkoxy chloride **1**, to acetylenic alcohol **2** as exemplified in scheme 1.

SCHEME-1

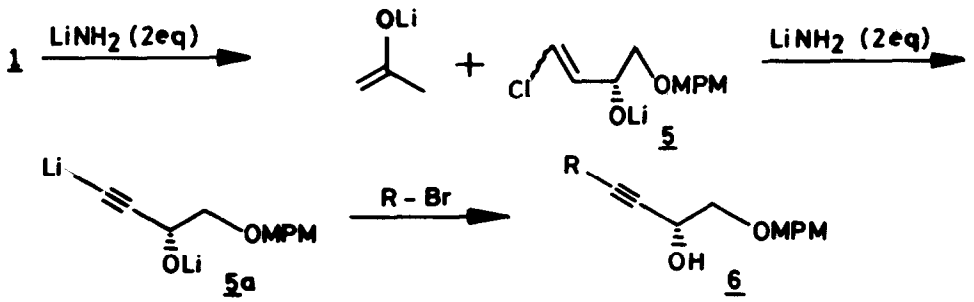


The requisite chloride **1** was prepared in two steps from known diol **4**, easily obtained from natural L-(+)-tartaric acid[4]. The diol **4** was converted into mono-4-methoxybenzyl ether **3** by using sodium hydride (1 eq.) and 4-methoxybenzyl bromide (1 eq.) (THF, 25°, 1 h) in 90% yield. **3** was smoothly converted to the chloride **1** on refluxing with triphenylphosphine (2 eq.) in carbon tetrachloride. The chloride **1** on treatment with lithium amide (6 eq.) in liquid ammonia afforded the acetylenic alcohol **2** [$\alpha]_D$ -4.8° (c 2,$CHCl_3$) in 90% isolated yield[5].

A plausible mechanism[6] for the formation of **2** may be depicted as in scheme 2, in which the base $LiNH_2$ picks up the hydrogen α to the chlorine atom followed by the elimination of the β-alkoxy group to produce the vinyl chloride **5**. Further reaction of **5** with $LiNH_2$ results in the formation

of the dianion **5a**. We envisioned that the dianion **5a** produced in this reaction may be chemoselectively reacted in situ with electrophiles to produce several useful chiral acetylenic diols. For instance, **1** on treatment with lithium amide (6 eq.) in liquid ammonia produced anticipated dianion **5a**, which

SCHEME - 2



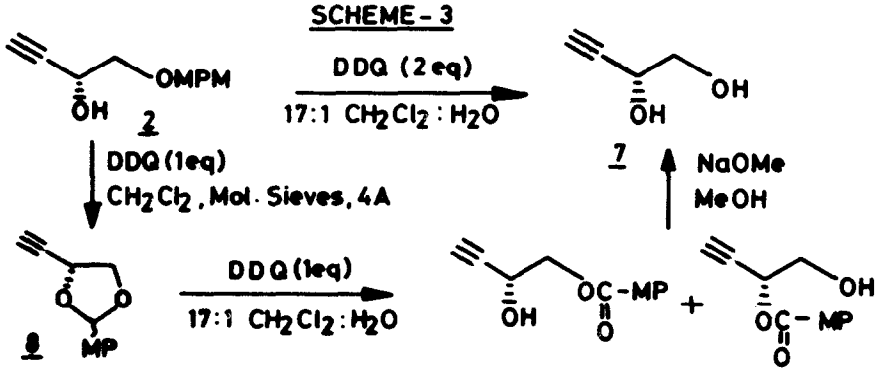
on treatment with n-hexyl bromide (0.9 eq) gave rise to **6** (R=n-hexyl), in 80% yield. To test its generality towards alkylation, several alkylbromides having different functionalities were reacted with **5a** to prepare substituted chiral alkynols in excellent yields(Table 1). However the attempted alkylation with allyl and propargyl bromides was met with failure under these experimental conditions.

TABLE 1 : Preparation of alkynols 6

ENTRY	R-	YIELD	$[\alpha]_D$ $CHCl_3$
a	n-butyl-	81%	-3.4° (c, 2)
b	n-hexyl-	80%	-3.7° (c, 2)
c	$HOOC(CH_2)_7$-	81%	-3.1° (c, 1)
d	$THPO(CH_2)_8$-	75%	-
e	CH_2=CH-$(CH_2)_3$-	82%	-4.6° (c, 2)
f	$CH_3(CH_2)_3C{\equiv}C(CH_2)_3$-	85%	-3.2° (c, 1)
g		65%	-3.3° (c, 1)

The attractiveness of the acetylenic intermediates **2** and **6** was augmented due to the presence of MPM as protecting group. For instance, the ease with which MPM group in **2** was cleaved[7] in presen-

SCHEME - 3



ce of DDQ (2 eq.) in 17:1 dichloromethane-water (25°, 1h) to produce the diol 7 $[\alpha]_D$ -38° (c 1, $CHCl_3$) without affecting the sensitive acetylenic functionality was particularly gratifying. In addition under controlled conditions compound **2** with DDQ (1 eq.) in dry dichloromethane in presence of molecular sieves was converted into the benzylidene derivative **8** (90%) which indeed would serve as yet another chiral building block. Finally **8** on treatment with DDQ (1 eq.) in 17:1 dichloromethane-water gave rise to a mixture of monobenzoates whose hydrolysis (NaOMe-MeOH) produced the same diol **7** as depicted in scheme 3. Similarly, the MPM group can be also removed easily from the alkylated alkynols **6**. For example, the removal of the MPM group in alkynol **6** (where R=n-hexyl) was performed successfully to obtain the corresponding diol $[\alpha]_D$ -19.8° (c 3, $CHCl_3$) under similar conditions (DDQ, 17:1 CH_2Cl_2:H_2O, R.T. 1 h) in 75% yield.

In summary L-(+)-tartaric acid has been transformed into the potentially useful bifunctional chiral acetylenic diol **7** or its derivative **2** & **8**, which are powerful chiral precursors for the synthesis of variety of biologically active compounds. For example, acetylenic functionality can be used for C-C bond formation as well as a source for cis and trans double bond. The substituted alkynols **6** (R=n-alkyl) can be easily converted to terminal acetylenic diols by Zipper reaction[8], hence it opens an easy access to the synthesis of several long chain acetylenic chiral diols. In addition, 1,2-diol moiety in **2** & **6** may be exploited as handle for useful transformations.

A typical experimental procedure is as follows:

1. Alkynol 2: To a freshly prepared $LiNH_2$ (prepared in situ dissolving 12 mg atom of lithium metal) in liq. NH_3 (30 ml) at -33°C was added the chloride **1** (2 mmol) in THF (2 ml) during 3 min. After 30 min. solid NH_4Cl (2 gm) was added and ammonia was allowed to evaporate. The residue was partitioned between water and ether and the ether layer was dried, concentrated to obtain the residue which was purified by silica-gel column chromatography to get the pure **2** in 90% yield.

2. Alkynol 6: To a freshly prepared $LiNH_2$ (obtained from 12 mg atom of lithium metal) in liquid NH_3 (30 ml) at -33°C was added the solution of chloride **1** (2 mmol) in THF (2 ml) during 3 min. and stirred. After the disappearance of the chloride **1** (TLC, approximately 30 min.) n-hexyl bromide (1.8 mmol) in THF (2 ml) was introduced and reaction mixture was stirred further for 30 min. Solid NH_4Cl was added and worked up as above to obtain alkynol **6** (R=n-hexyl) in 80% yield.

References and Notes

1. a) M.M. Midland in "Asymmetric Synthesis" Ed. J.D. Morrison, Vol.2, Part A, p. 45, Academic Press (1983).
   b) K.K. Chan, N. Cohen, J.P. DeNoble, A.C. Specian Jr., and G. Saucy, J. Org. Chem., **41**, 3497 (1976).
   c) W.H. Pirkle and C.W. Boeder, J. Org. Chem., **43**, 2091 (1978).
   d) K.K. Chan, A.C. Specian Jr., and G. Saucy, J. Org. Chem., **43**, 3435 (1978).
   e) K. Mori and H. Akao, Tetrahedron Lett., **19**, 4127 (1978).
   f) J.P. Vigneron, R. Meric, M. Larcheveque, A. Debal, G. Kunesch, P. Zagatti and M. Gallois, Tetrahedron Lett., **23**, 5051 (1982).
   g) G. Stork and J. Poirier, J. Am. Chem. Soc., **105**, 1073 (1983).
   h) A. Mori, K. Ishihara and H. Yamamoto, Tetrahedron Lett., **27**, 987 (1986).
   i) P. Pianetti, P. Rollin and J.R. Pougny, Tetrahedron Lett., **27**, 5853 (1986).
   j) Y. Kobayashi, S. Okamoto, T. Shimazaki, Y. Ochiai and F. Sato, Tetrahedron Lett., **28**, 3959 (1987).

2. a R.S. Brinkmeyer and V.M. Kapoor, J. Am. Chem. Soc., **99**, 8339(1977).
b) W.S. Johnson, R.S. Brinkmeyer, V.M. Kapoor and T.M. Yarnell, J. Am. Chem. Soc., **99**, 8341 (1977).
c) T. Mukaiyama, K. Suzuki, K. Soai and T. Sato, Chemistry Lett., 447 (1979).
d) T. Mukaiyama and K. Suzuki, Chemistry Lett., 255 (1980).
e) J.P. Vigneron and V. Bloy, Tetrahedron Lett., **20**, 2683 (1979).
f) M.M. Midland, D.C. McDowell, R.L. Hatch and A. Tramontano, J. Am. Chem. Soc., **102**, 867 (1980).
g) L.E. Overman and K.L. Bell, J. Org. Chem., **46**, 1512 (1981).
h) R. Noyori, Pure and Appl. Chem., **53**, 2315 (1981).

3. a) A.V. Rama Rao, E. Rajarathnam Reddy, G.V.M. Sharma, P. Yadagiri and J.S. Yadav, Tetrahedron Lett., **26**, 465 (1985).
b) J.S. Yadav, B.V. Joshi and M.K. Gurjar, Carbohydrate Res., **165**, 116 (1987).
c) A.V. Rama Rao, E.R. Reddy, B.V. Joshi and J.S. Yadav, Tetrahedron Lett., **28**, 6497 (1987).

4. P.W. Feit, J. Med. Chem., **7**, 14 (1964).

5. All new compounds exhibited satisfactory spectral data.

6. G. Eglinton, E.R.H. Jones and M.C. Whiting, J. Chem. Soc., 2873 (1952).

7. a) Y. Oikawa, T. Yoshioka and O. Yonemitsu, Tetrahedron Lett., **23**, 885, 889 (1982).
b) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and O. Yonemitsu, Tetrahedron,**42**, 3021 (1986).

8. C.A. Brown and A. Yamashita, J.C.S. Chem. Commun., 959 (1976).

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