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NOVEL SYNTHESIS OF 1,7-DIHYDROHEPT-4-YNE DERIVATIVES : APPLICATION TO THE TOTAL SYNTHESIS OF (±) PATULOLIDE A

J.S. Yadav*, P. Radha Krishna and M.K. Gurjar
Regional Research Laboratory, Hyderabad 500 007, India

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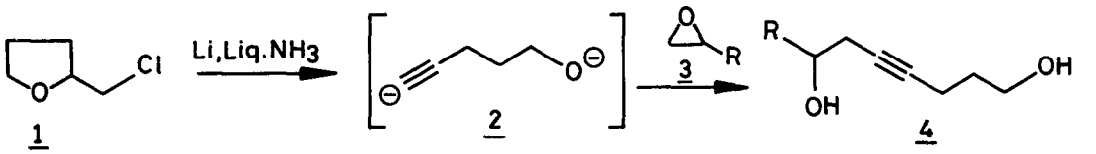
Summary Methodology for the synthesis of 1,7-dihydrohept-4-yne derivatives by the in situ alkylation of tetrahydrofurfuryl chloride (**1**) by the epoxides (**3a-e**) is developed and the importance of such an endeavour is exemplified in the synthesis of (±) Patulolide A.

Ring opening reaction of the epoxide with acetylenic precursor in the presence of a strong base has been well studied[1-4]. The influence of a Lewis acid to enhance the yield of the reaction is a particularly useful modification[5]. However, substrates with functionality vulnerable to the presence of Lewis acid, have been restricted from use in this type of operation. Previously, we have executed several in situ alkylation reactions of the dianion of 1-pentyne-5-ol (**2**), generated from tetrahydrofurfuryl chloride (**1**) and lithium in liquid ammonia, with alkyl halides in a remarkable high yield[6]. Inspired by this technique, we reasoned that in situ ring opening reaction of the dianion **2** with the corresponding epoxide would be an ideal protocol to follow provided it could offer product **4a-e** in high yield. More importantly, this process would evade the usage of Lewis acid.



1 2 3 4

The usefulness of the derivatives of 1,7-dihydrohept-4-yne (**4**) as versatile building blocks has been reconciled in literature particularly while attempting the synthesis of natural products belonging to 1,5-dioxaspiro [4,4] nonanes[7,8], substituted furans, 1,7-dihydroxy alkanes etc. This paper describes in situ ring opening reaction of epoxides with the dianion **2** and extends its application to the synthesis of Patulolide A (**13**)[9].

To a solution of $LiNH_2$, prepared in situ by dissolving Li in liquid ammonia, was added tetrahydrofurfuryl chloride (**1**) at -78°C. After 1.5 h epoxides (3a-e) in THF were introduced

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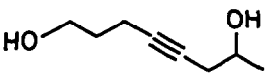
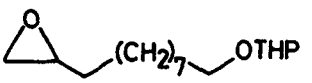
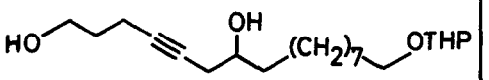
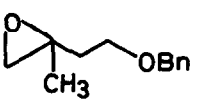
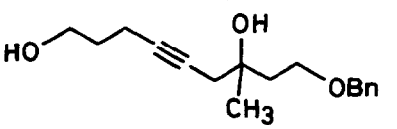
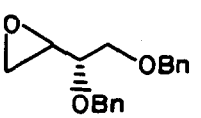
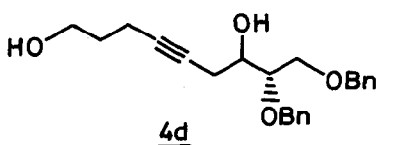
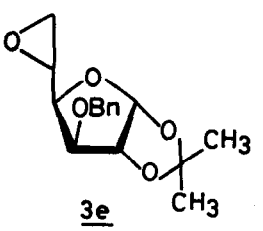
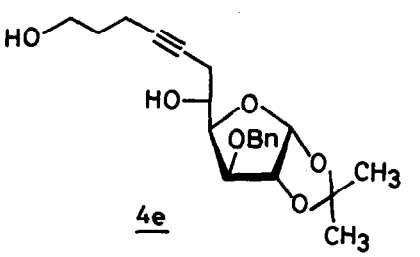
TABLE - 1

PREPARATION OF 1,7-DIHYDROHEPT-4-YNE DERIVATIVES

Entry	Epoxide Employed	Product[d]	Yield[a] %
1	 3a	 4a	Quantitative
2	 3b	 4b	85
3	 3c	 4c	75
4[b]	 3d	 4d	72
5[c]	 3e	 4e	70

a. Isolated yields are reported

b. Epoxide (3d) was prepared by treatment of mCPBA of the corresponding olefin which was obtained from tartaric acid.

c. Epoxide was prepared by employing the procedure reported in "Methods in Carbohydrate Chemistry" Vol.II 190, Academic Press, New York, 1963.

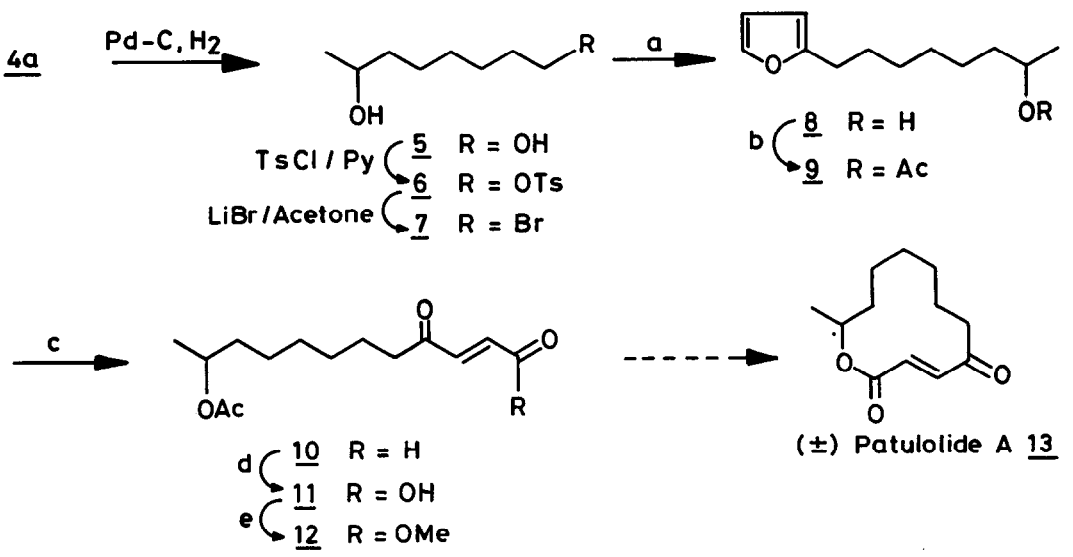
d. All new compounds gave expected spectral data and satisfactory elemental analysis.

and reaction continued for 2 h at -78°C. After usual workup and purification by chromatography, diols (**4a-e**) were obtained in 70-85% yield.

In order to illustrate the generality of this reaction, number of epoxides with varied functionalities have been studied (Table 1).

The ready availability of **4a** coupled with the unique structure of Patulolide A prompted us to execute the synthesis of Patulolide A (Scheme 2). Patulolide A (**13**) was isolated by Yamada and his coworkers[9] from the culture broth of Penicillium urticae mutant S11 R59. The structure of Patulolide was recently depicted as **13**[10a,11] and shown to possess both antifungal and antibacterial activities. The gross structure **13** of Patulolide A was confirmed by the synthesis of **13**[10a,b,c]. **13** belongs to a new class of 'ene dione' macrolides evident from structural features, hence an added interest in its synthetic endeavour.

SCHEME 1



a)  , n BuLi, 7, −40°C ; b) Ac_2O, Pyridine, RT ; c) H_2O − Acetone (4:1), Br_2 − Pyridine (1:2), −20°→ RT ; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH-H_2O$, RT ; e) 3% methanolic ferric chloride.

Thus, **4a** was hydrogenated with Pd-C, H_2, 1 atm to 5 in quantitative yield; which on selective tosylation with 1.2 eq tosyl chloride, pyridine at ambient temperature gave the monotosylate (**6**) in 80% yield. Subsequent nucleophilic displacement reaction of **6** with lithium bromide in acetone at reflux temperature afforded the monobromide **7**. The alkylation of furan with **7** was effected in the presence of n-butyl lithium, THF as solvent at -40°C to give the monoalkylated product **8** in 80% yield. The free hydroxyl group in **8** was conventionally acetylated using Ac_2O in pyridine to **9** and then subjected to oxidative ring opening[12] reaction in water-acetone with bromine-pyridine mixture to afford the corresponding 'ene dione' derivative **10** in 85% yield. The conversion of the aldehyde group in **10** to the acid **11** was carried out by employing sodium chlorite with sodium dihydrogen phosphate[13] as buffer and 2-methyl-2-butene as a chlorine scavenger in 75% yield. Subsequent esterification with methanolic ferric chloride of **11** gave the ester **12**. Since **12** has already been transferred[10a] into Patulolide A in one step, this synthesis constitutes the formal total synthesis of (±) **13**.

In conclusion, the methodology described herein has inherent advantages in that a) it always gives high yield of the alkylated product, b) regioselectivity is maintained in all the examples studied, i.e., the attack of the acetylenic anion proceeds at the primary carbon atom of the epoxide employed, finally and most importantly side products were never observed.

Experimental

IR spectra were recorded in nujol or neat on a Perkin Elmer model 683 spectrometer with NaCl optics. ^1H NMR spectra were obtained in a Varian FT-80 or Bruker WH-90 or Jeol 90 spectrometer in $CDCl_3$ solutions containing TMS as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS. Mass spectra were run on Finnegan MAT automated GC/MS 1020 electron impact 70 ev.

Typical procedure for the *in situ* alkylation of 1 with epoxides (3a-e)

To a solution of $LiNH_2$ prepared *in situ* by dissolving lithium (30 mmol) in liquid ammonia (50 ml), tetrahydrofurfuryl chloride (1, 10 mmol) was added at -78°C. After 1.5 h epoxides **3a-e** (10 mmol) in THF (anhydrous) were introduced and the reaction continued for 2 h at -78°C. Ammonia was allowed to evaporate and the reaction mixture was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate, dried over Na_2SO_4 concentrated and purified by chromatography to give diols **4a-e** in the yields mentioned against each entry in Table 1.

2,8-Oct-3-yne-diol (4a)

IR (Neat) : 3360 (O-H), 2100 cm^{-1} (C≡C), ^1H NMR ($CDCl_3$) : 3.7 (m, -$\underline{CH_2}$OH, 3H), 2.67 (bs, 2x-OH, 2H, D_2O exchangeable), 2.3 (m, $\underline{CH_2}$-C≡C-$\underline{CH_2}$, 4H), 1.75 (m, $\underline{CH_2}$-CH_2-OH, 2H),

1.20 (d, $\underline{CH_3}$-, 3H, J=6.5 Hz). Analysis calc for $C_8H_{14}O_2$: C, 67.6; H, 9.9; Found : C, 67.6; H, 9.9. MS m/z 142 (M^+).

1-O-Tetrahydropyranyl hexadec-12-yn-10,16-diol (4b)

Compound **4b** was prepared by using epoxide **3b** in 85% yield. IR (Neat) : 3300 cm^{-1} (O-H), 2100 cm^{-1} (C≡C), ^1H NMR ($CDCl_3$) : 4.6-4.5 (m, 1H), 4.0-3.4 (m, 7H), 2.2-2.0 (m, -$\underline{CH_2}$-≡-$\underline{CH_2}$, 4H), 1.8-1.6 (m, 4x-CH_2, 8H), 1.3 (bs, 9x-CH_2, 18H). Analysis calc for $C_{21}H_{38}O_4$: C, 71.14; H, 10.8; Found : C, 71.12; H, 10.5.

1-O-Benzyl-3-methyl non-5-yn-3,9-diol (4c)

Compound **4c** was prepared using the corresponding epoxide **3c** in 75% yield. IR (Neat): 3300 cm^{-1} (O-H), ^1H NMR ($CDCl_3$) : 7.36 (s, Ar-H, 5H), 4.4 (s, -O$\underline{CH_2}$, 2H), 3.6 (t, -$\underline{CH_2}$-OH, 4H, J=7 Hz), 2.2-2.0 (m, 4H), 1.8-1.6 (m, 4H), 1.1 (s, -$\underline{CH_3}$, 3H). Analysis calc for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; Found : C, 73.85; H, 8.65.

1,2(S)-Di-O-benzyl non-5-yn-3,9-diol (4d)

Compound **4d** was prepared in the usual manner employing epoxide **3d** in 72% yield. IR (Neat) : 3300 (O-H), 2200 cm^{-1} (C≡C), ^1H NMR ($CDCl_3$) : 7.36 (s, Ar-H, 10H), 4.8-4.5 (m, benzylic, 4H), 4.2 (m, 2H), 3.6 (t, -$\underline{CH_2}$-OH, 4H, J=7 Hz), 2.2-1.8 (m, 6H). Analysis calc for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66; Found : C, 74.96; H, 7.64.

3-O-Benzyl-1,2-O-isopropylidene-6-deoxy-6-(4-pentyn-1-ol)-α-D-glucofuranose (4e)

Compound **4e** was prepared using epoxide **3e** in 70% yield. IR (Neat) : 3300 cm^{-1} (O-H), ^1H NMR ($CDCl_3$) : 7.36 (s, Ar-H, 5H), 5.92 (d, H-1, 1H), 4.62-4.50 (m, benzylic, 2H), 4.4 (dd, H-2, 1H), 4.2-4.0 (m, H-3, H-4, H-5, 3H), 3.6 (t, -$\underline{CH_2}$-OH, 2H, J=7 Hz), 2.40-2.22 (m, -$\underline{CH_2}$-≡-$\underline{CH_2}$, 4H), 1.8-1.6 (m, 2H), 1.25 (2s, isopropylidene, 6H), $[\alpha]_D$ -15.05 (c 1.9, $CHCl_3$). Analysis calc for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50; Found : C, 67.00; H, 7.48.

Preparation of (±) octane-2,8-diol (5)

Compound **4a** (3.4 g, 23.9 mmol) in ethylacetate (15 ml) and Pd/C (0.5 g) was hydrogenated at normal pressure and temperature for 6 h. The catalyst was filtered through celite, washed with ethylacetate and the combined filtrates concentrated to give **5** (3.4 g, quantitative). ^1H NMR ($CDCl_3$) : 3.7 (m, 3H), 2.34 (bs, 2H, D_2O exchangeable), 1.3 (m, 10H), 1.20 (d, 3H, J=6.5 Hz). Analysis calc for $C_8H_{14}O_2$: C, 65.7; H, 12.4; Found : C, 65.54; H, 12.2. MS m/z 146 (M^+).

Preparation of (±) 1-bromo-octan-7-ol (7)

To a solution of **5** (3.4 g, 23.2 mmol) in anhydrous methylene chloride (100 ml) and pyridine (2.8 ml) at 0°C was added p-toluene-sulfonyl chloride (4.86 g, 25.5 mmol) over a period of 30

minutes. After stirring at room temperature for 5 h, the reaction mixture was washed with dilute hydrochloric acid, water, bicarbonate, water, dried and concenarated to afford **6** (5.5 g, 80%).

Compound **6** (5.5 g, 18.5 mmol) was dissolved in dry acetone (60 ml) containing lithium bromide (6 g) was heated under reflux for 4 h followed by usual workup and chromatographic purification on silica gel gave **7** (2.9 g, 60%). ^{1}H NMR ($CDCl_3$) : 3.7 (m, 1H), 3.4 (t, 3H, J=7 Hz), 1.3 (bs, 10H), 1.2 (d, 3H, J=6 Hz).

Preparation of (±) 8-(2-furyl)-octan-2-ol acetate (9)

A solution of furan (1.45 ml, 43.9 mmol) in anhydrous THF (10 ml) was cooled to -40°C under N_2, n-BuLi (10 ml, 2N in hexane) was slowly added. After 4 h at -40°C, 1-bromo-octan-7-ol (**7**, 2.1 g, 10 mmol) was added and stirring was continued for 1 h at -40°C and 12 h at ambient temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The non-aqueous layer was dried and concentrated to yield **8** (1.56 g, 80%). IR (Neat) : 3360 cm^{-1} (O-H), ^{1}H NMR ($CDCl_3$) : 7.30-7.15 (m, 1H), 6.30-6.15 (m, 1H), 6.00-5.85 (m, 1H), 4.0-3.6 (m, 1H), 2.70 (t, 2H, J=7 Hz), 1.3 (m, 10H), 1.20 (d, 3H, J=6.5 Hz). MS m/z 176 (M^+).

Compound **8** (1.37 g, 7 mmol) was treated with pyridine (1.13 ml) and acetic anhydride (0.7 ml) for 2 h at room temperature and workup conventionally. The resulting product **9** (1.49 g, 90%) was a thick syrup. IR (Neat) : 1740 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) : 7.3-7.2 (m, 1H), 6.25-6.15 (m, 1H), 5.95-5.85 (m, 1H), 5.00-4.75 (m, 1H), 2.60 (t, 2H, J=7 Hz), 2.00 (s, -OCOCH_3, 3H), 1.3 (m, 5x-CH_2, 10H), 1.20 (d, 3H, J=6.5 Hz). Analysis calc for $C_{14}H_{22}O_3$: C, 70.5; H, 9.3; Found : C, 70.4; H, 9.2.

Preparation of (±) (E)-11-Acetoxy-4-oxo-2-dodecenal (10)

To a vigorously stirred solution of **9** (1.42 g, 6 mmol), pyridine (1.9 ml) and 85:15 aqueous acetone (60 ml) at -20°C was added dropwise bromine (0.308 ml) in 4:1 acetone-water (10 ml). After the completion of bromine addition the reaction mixture was stirred at room temperature for 12 h and then poured over excess of ether. The organic layer was separated, washed with brine, saturated aqueous $CuSO_4$, dried and concentrated to yield a syrupy compound **10** (1.3 g, 85%). IR (Neat) : 1690 (C=O), 1730 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) : 9.75 (dd, 1H), 6.85-6.75 (m, 2H), 5.0-4.8 (m, 1H), 2.60 (t, 2H, J=7 Hz), 2.00 (s, -OCO$\underline{CH_3}$, 3H), 1.3 (m, 5x-CH_2, 10H), 1.2 (d, 3H, J=6.5 Hz). Analysis calc for $C_{14}H_{22}O_4$: C, 66.1; H, 8.7; Found : C, 66.0; H, 8.6.

Preparation of (±) Methyl-11-acetoxy-4-oxo-2-dodecenoate (12)

To the aldehyde **10** (1.27 g, 5 mmol) and 2-methyl-2-butene (25 ml) in tertiary butanol

(75 ml) was added a solution of sodium chlorite (4 g, 44 mmols) and sodium dihydrogenphosphate (4 g, 33.2 mmols) in water (40 ml) gradually. The characteristic pale yellow solution was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was extracted with dichloromethane. The aqueous layer was neutralized with dil. HCl and then extracted with chloroform. The organic layer was washed with water, dried and concentrated to give **11** (1.0 g, 75%). IR ($CHCl_3$) : 3300 (O-H), 1720 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) : 7.08 (d, 1H, J=16 Hz), 6.7 (d, 1H, J=16 Hz), 5.1-4.8 (m, 1H), 2.75 (t, 2H, J=7 Hz), 2.00 (s, $-OCOCH_3$, 3H), 1.3 (m, 5x-CH_2, 10H), 1.20 (d, 3H, J=6.3 Hz). MS m/z 270 (M^+).

The acid **11** (0.27 g, 1 mmol) and methanolic ferric chloride (3%, 4 ml) was stirred for 72 h at ambient temperature. Methanol was evaporated under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, saturated aqueous bicarbonate solution and dried to give **12** (0.213 g, 75%). IR (Neat) : 1740 cm^{-1} (C=O, br), ^1H NMR ($CDCl_3$): 7.00 (d, 1H, J=16 Hz), 6.75 (d, 1H, J=16 Hz), 5.15-4.80 (m, 1H), 4.0 (s, $-OCH_3$, 3H), 2.65 (t, 2H, J=7 Hz), 2.00 (s, $-OCOCH_3$, 3H), 1.3 (m, 5x-CH_2, 10H), 1.20 (d, 3H, J=6.3 Hz). Analysis calc for $C_{15}H_{24}O_5$: C, 63.34; H, 8.5; Found : C, 63.1; H, 8.4. MS m/z 284 (M^+).

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