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Synthesis of C_6 Acetylenic Alcohols

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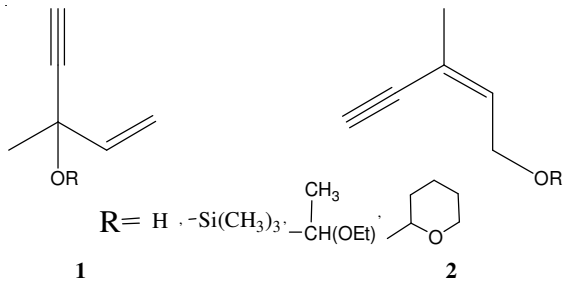
C_6 acetylenic alcohols are important intermediates in the synthesis of Vitamin A and carotenoids. New synthesis methods of the C_6 acetylenic alcohols and their four derivatives are reported. These designed synthesis methods are useful improvement to the present methodologies. Structures of these compounds are confirmed by ^{1}H NMR, IR and mass spectra analysis.

Keywords: C_6 acetylenic alcohols, Vitamin A, Carotenoids.

INTRODUCTION

C_6 acetylenic alcohols and their derivatives **1** and **2** (Fig. 1) are important intermediates in the synthesis of Vitamin A and carotenoids which play key roles in many physiological processes such as vision, reproduction, immune competence, cell differentiation and brain function[1-3]. Compound **1** and **2** (Fig. 1) can be coupling with carbonyl compounds followed by a serial of transformations to give Vitamin A[4] and other carotenoids such as zeaxanthix[4], canthaxanthin[5] and astaxanthin[6,7]. Therefore, it is important to find a better way to prepare C_6 acetylenic alcohols and their derivatives in organic synthesis.

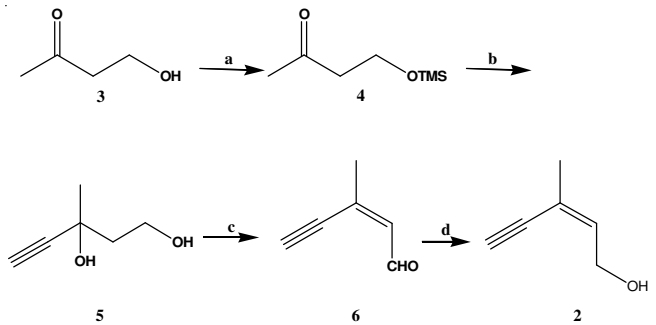


1 **2**

Fig. 1. Structures of C_6 acetylenic alcohols compounds **1** and **2**

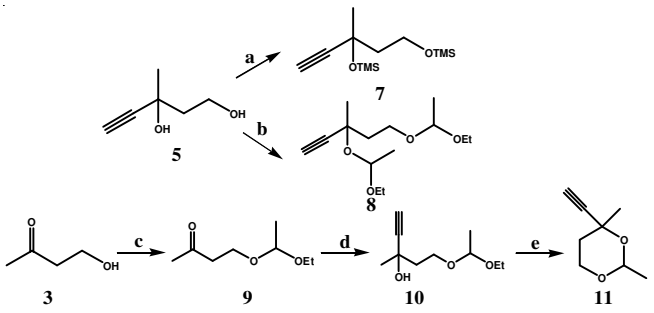
The current methods to access C_6 acetylenic alcohols are based upon the ethynylation reactions of methyl vinyl ketone with sodium acetylide at -55 °C in liquid ammonia[8-11]. Then the ethynylation product 3-methylpent-1-en-4-yn-3-ol 1 (Fig. 1, R = H) can smoothly isomerized with dilute sulphuric acid to yield the primary alcohol, 3-methylpent-2-en-4-yn-1-ol 2 (Fig. 1, R = H). However, this method may cause three potential safety hazards: 1) methyl vinyl ketone with lachrymatory effect is extremely hazardous; 2) liquid ammonia as the solvent requires extreme low temperatures in industry, which is costly and energy-consuming; 3) metallic sodium or potassium used for the preparation of metal acetylide is highly flammable and difficult to handle industrially.

To avoid the prior disadvantages, we proposed herein a new method for the synthesis of C_6 acetylenic alcohols (**Scheme-I**). In contrast to the current methods, this safe alternative synthetic route has no requirement of hazardous reagents and no extremely low temperatures.



Scheme-I: Synthetic route of C_6 acetylenic alcohols compounds **2** and **5**; Reagents and conditions: (a) TMSCl, Et_3N, CH_2Cl_2, 0-5, 2 h; (b), [i] ethynylmagnesium bromide, THF, 0-5 °C; [ii] dilute HCl; (c) [i] CrO_3, pyridine, dichloromethane, 0-5 °C, 0.5 h; [ii] 20 % H_2SO_4, EtOH, N_2, 60 °C, 5-8 h; (d) $NaBH_4$, EtOH, r.t., 1h

In order to develop new method for the synthesis of Vitamin A and carotenoids, we designed and synthesized four acetylenic alcohol derivatives **7**, **8**, **10** and **11** (**Scheme-II**), which shared the same characteristics of six-carbon backbones bearing an alkynyl group. These four acetylenic alcohol



Scheme-II: Synthetic route of C_6 acetylenic alcohol derivatives compounds **7**, **8**, **10** and **11**; Reagents and conditions: (a) TMSCl, Et_3N, CH_2Cl_2, 0-5 °C, 10 h; (b) ethyl vinyl ether, pyridine, *p*-TsOH, CH_2Cl_2, r.t., 12 h; (c) ethyl vinyl ether, pyridine, *p*-TsOH, CH_2Cl_2, r.t., 3 h; (d) [i] ethynylmagnesium bromide, THF, 0-5 °C; [ii] saturated NH_4Cl; (e) HCl (g), EtOH, r.t., 1.5 h

derivatives could be potentially utilized in the synthesis of Vitamin A and carotenoids.

EXPERIMENTAL

Most of the chemical reagents used in this study were acquired from commercial sources without further purification. Solvents were purchased and dried using standard methods. The IR spectra were recorded on a Perkin-Elemer 16PC-FT spectrometer. HR-MS spectral were acquired with the Agilent 6210 (DOF-MAS) spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionisation (ESI) method and GC-MS spectral were recorded on an Agilent 6890N GC connected to an Agilent 5975 mass selective detector. ^{1}H NMR spectra were recorded on a varian Unity Inova-400 spectrometer (Varian Inc., Palo Alto, CA, USA) with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Spectral data of known compounds **4**[12], **5**[13], **6**[14], **2**[15] are in accordance with previous reports.

Synthesis of 4-(trimethylsilyloxy)butan-2-one (4): Chlorotrimethylsilane (0.9 mol) was added dropwise to the mixture of compound **3** (0.75 mol) and triethylamine (0.98 mol) in dry dichloromethane (300 mL) at 0-5 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 2 h as required to complete the reaction (monitored by TLC). The precipitated solid was filtered off and washed with dichloromethane. The filtrate was condensed in vacuo and then distilled to afford a colorless liquid. Yield 95 %, b.p. 52-54 °C/10 mmHg (lit.[16] 52 °C/10 mmHg); FT-IR (film) (cm^{-1}): 2955, 2896, 1713, 1358, 1248, 1175, 1101, 876, 840; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.84 [t, *J* = 6.4 Hz, 2H, $CH_2OSi(CH_3)_3$], 2.63 (t, *J* = 6.4 Hz, 2H, $COCH_2$), 2.16 (s, 3H, CH_3CO), 0.10 [s, 9H, $Si(CH_3)_3$]; GC-MS: 160.

Synthesis of 3-methylpent-4-yne-1,3-diol (5): A solution of compound **4** (0.375 mol) in THF (30 mL) was added dropwise to ethynylmagnesium bromide[14] (0.75 mol) at 0-5 °C over a period of 1 h. After addition of compound **4** the reaction mixture was hydrolyzed with 5 % HCl. The aqueous layer was extracted with ethyl acetate (4 × 50 mL), the combined extracts were dried Na_2SO_4 and evaporated and the residue was distilled to afford a colorless oil. Yield 55 %, b.p. 76-78 °C/3 mmHg; FT-IR (film) (cm^{-1}): 3369, 3294, 2933, 2110, 1374; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.13 (td, *J* = 10.4, 3.2 Hz, 1H), 3.88 (dt, *J* = 11.2, 4.4 Hz, 1H), 3.77 (br s, 2H, OH), 2.49 (s, 1H, ethynyl), 1.96 (ddd, *J* = 14.4, 10.0 4.4 Hz, 1H), 1.79 (ddd, *J* = 14.5, 4.5, 3.6 Hz, 1H), 1.51 (s, 3H, CH_3).

Synthesis of 3-methylpent-2-en-4-ynal (6): CrO_3 (0.6 mol) was slowly added over pyridine (1.2 mol) in dry dichloromethane (150 mL). After 15-20 min, dry celite (20 g) was added and then a solution of diol compound **5** (0.1 mol) in dry dichloromethane (10 mL) was slowly added. When most of the starting diol was consumed, the reaction mixture was filtered through a pad of silica. The filtrate was treated with hydroquinone (0.01 mol) and a solution of 20 % H_2SO_4 (30 mL) and EtOH (10 mL). The mixture was heated to distill dichloromethane and then was heated for 7-8 h at 60 °C in nitrogen atmosphere. When the reaction was completed, the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4 and evaporated. The residue was distilled to afford a pale yellow liquid. Yield 25 %, b.p. 44-47°C/5 mmHg (lit.[17] 58-60°C/10 mmHg); FT-IR (film) (cm^{-1}): 3266, 2843, 2089, 1669, 1598, 1379, 1175; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.04 (d, *J* = 8 Hz, 1H, CHO), 6.24 (dd, *J* = 8.2, 1.6 Hz, 1H, C = CH), 3.58 (s, 1H, ethynyl), 2.15 (d, *J* = 1.6 Hz, 3H, CH_3); GC-MS: 94.

Synthesis of 3-methylpent-2-en-4-yn-1-ol (2, R = H): $NaBH_4$ (31.3 mmol) was added in batches to a solution of compound **6** (10.4 mmol) in ethanol (10 mL) at 25 °C. The reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with H_2O and extracted with ethyl acetate (3 × 5 mL). The solvent was evaporated and the residue was distilled to afford colorless oil. The combined organic layer was washed with brine, dried with Na_2SO_4 and concentrate *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford a yellow oil. Yield 95 %, FT-IR (film) (cm^{-1}): 3293, 2926, 2875, 2094, 1630, 1435, 1379, 1243, 1086, 1006; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.95 (ddd, *J* = 6.7, 3.7, 0.7 Hz, 1H, C = CH), 4.33 (dd, *J* = 6.8, 0.8 Hz, 1H, CH_2OH), 3.19 (s, 1H, ethynyl), 2.28 (s, 1H, OH), 1.90 (d, *J* = 1.2 Hz, 3H, CH_3); GC-MS: 96.

Synthesis of 3,5-*bis*(trimethylsilyloxy)-3-methylpent-1-yne (7): Chlorotrimethylsilane (0.12 mol) was added dropwise to the mixture of compound **5** (0.05 mol) and triethylamine (0.13 mol) in dry dichloromethane (40 mL) at 0-5 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 9 h as required to complete the reaction (monitored by TLC). The precipitated solid was filtered off and washed with dichloromethane. The filtrate was condensed *in vacuo* and then distilled to afford a colorless liquid. Yield 91 %, b.p. 64-68 °C/13 mmHg; FT-IR (film) (cm^{-1}): 3307, 2955, 2899, 2106, 1677, 1369, 1251, 1085, 837; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.81 [t, *J* = 6.8 Hz, 2H, -$CH_2OSi(CH_3)_3$], 2.47 (s, 1H, ethynyl), 1.97-1.90 (m, 2H, CH_2), 0.19 [s, 9H, $Si(CH_3)_3$], 0.14 [s, 9H, $Si(CH_3)_3$]; HR-MS (ESI): Calcd. for $C_{12}H_{26}NaO_2Si_2$ [M + Na]$^+$: 281.1369, Found 281.1363.

Synthesis of 3,5-*bis*(1-ethoxyethoxy)-3-methylpent-1-yne (8): *p*-Toluenesulfonic acid monohydrate (40 mmol) was added to pyridine (43 mmol) with stirring in dichloromethane (350 mL) at room temperature (slightly exothermic). After

stirring for 0.5 h, a mixture of compound **5** (0.2 mol) and ethyl vinyl ether (1.2 mol) was added. After reaction was stirred at room temperature for 13 h, the reaction mixture was washed with H_2O (2 × 50 mL), brine (50 mL) and finally dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford a pale yellow liquid. Yield 95 %; FT-IR (film) (cm^{-1}): 3301, 2982, 2935, 2103, 1683, 1447, 1373, 1337, 1136, 1080, 959, 864; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.15-5.09 (m, 1H, $CHCH_3$), 4.69 (q, *J* = 5.2 Hz, 1H, $CHCH_3$), 3.90-3.96 (m, 4H), 3.56-3.45 (m, 2H), 2.50 (s, 1H, ethynyl), 2.13-1.94 (m, 2H), 1.47 (s, 3H, CH_3), 1.35-1.30 (m, 6H, CH_3), 1.23-1.17 (m, 6H, CH_3); HR-MS (ESI): Calcd. for $C_{14}H_{26}NaO_4$ $[M + Na]^+$: 281.1729, found 281.1721.

Synthesis of 4-(1-ethoxyethoxy)butan-2-one (9): *p*-Toluenesulfonic acid monohydrate (75 mmol) was added to pyridine (82.5 mmol) with stirring in dichloromethane (400 mL) at room temperature (slightly exothermic). After stirring for 0.5 h, a mixture of compound **3** (750 mmol) and ethyl vinyl ether (1.5 mol) was added, followed by stirring for 6 h. The reaction mixture was washed with H_2O (2 × 40 mL), brine (40 mL) and finally dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 12:1) to afford a colorless liquid. Yield 92 %; FT-IR (film) (cm^{-1}): 3349, 2973, 2884, 1716, 1379, 1127, 1092, 1050, 947, 879; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.68 (q, *J* = 4.4 Hz, 1H, $CHCH_3$), 3.86-3.81 (m, 1H), 3.72-3.60 (m, 2H), 3.49-3.44 (m, 1H), 2.68 (t, *J* = 5.4 Hz, 2H, CH_3COCH_2), 2.19 (s, 3H, CH_3CO), 1.29 (d, *J* = 4.8 Hz, 3H, $CHCH_3$), 1.20 (t, *J* = 6.4 Hz, 3H, CH_2CH_3); HR-MS (ESI): Calcd. for $C_8H_{16}NaO_3$ $[M + Na]^+$: 183.0997, found 183.0994.

Synthesis of 5-(1-ethoxyethoxy)-3-methylpent-1-yn-3-ol (10): A solution of compound **9** (0.1 mol) in THF (10 mL) was added dropwise to ethynylmagnesium bromide12 (0.2 mol) at 0-5 °C over a period of 0.5 h. After addition of compound **9** the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford a pale yellow liquid. Yield 65 %; FT-IR (film) (cm^{-1}): 3443, 3295, 2979, 2929, 2884, 2106, 1716, 1379,1130, 1086, 947, 917; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.16-5.10 (m, 1H, $CHCH_3$), 4.05-3.80 (m, 2H), 3.71-3.42 (m, 2H), 2.52 (s, 1H, ethynyl), 1.90-1.77 (m, 1H), 1.57-1.53 (m, 1H), 1.50-1.48 (m, 3H, CH_3), 1.30-1.27 (m, 3H, $CHCH_3$), 1.22-1.15 (m, 3H, OCH_2CH_3); HR-MS (ESI): Calcd. for $C_{10}H_{18}NaO_3$ $[M + Na]^+$: 209.1154, found 209.1150.

Synthesis of 4-ethynyl-2,4-dimethyl-1,3-dioxane (11): Dry hydrogen chloride was bubbled for about 1 h through a mixture of compound 10 (2.7 mmol) and ethanol (15 mL) at 10-15 °C. After the reaction was completed, the resulting mixture was washed with saturated sodium bicarbonate, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford a green yellow liquid. Yield 57 %; FT-IR (film) (cm^{-1}): 3293, 2988, 2929, 2867, 2106, 1728, 1402, 1260, 1192, 1136, 1095, 944, 858; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.16 (q, *J* = 5.2 Hz, 1H, $CHCH_3$), 4.08-3.94 (m, 2H, CH_2O), 2.54 (s, 1H, ethynyl), 1.89 (td, *J* = 12.8, 4.8 Hz, 1H), 1.59 (td, *J* = 13.2, 1.6 Hz, 1H), 1.53 (s, 3H, CH_3), 1.31 (d, *J* = 5.2 Hz, 3H, $CHCH_3$); GC-MS: 140.

RESULTS AND DISCUSSION

New synthetic method of C_6 acetylenic alcohols: Previous studies[13] disclosed a costly procedure to access diol compound **5**. Reaction of 3-acetyl-4-benzyloxazolidin-2-one with 3-butyn-2-one furnished aldol condensation product in the presence of LDA at -78 °C and the condensation product was reduced with $LiBH_4$ to provide diol compound **5**. Compared with above reported method, present new synthetic route to compound **5** is concise and the starting materials are commercially available and inexpensive (**Scheme-I**). 4-Hydroxy-2-butanone (**3**) was protected by chlorotrimethylsilane to give silyl ether (**4**) in high yield at room temperature. After that, compound **4** was ethynylated with ethynylmagnesium bromide followed by easy deprotection of trimethylsiyl group with dilute HCl to afford diol compound **5** in moderate yield at room temperature.

Our method employed inexpensive chlorotrimethylsilane as silylating agents, which is better than the expensive hexamethyldisilazane as silylating regent in the previous method[12]. This new route to compound **5** avoided the use of expensive starting materials and the reaction conditions were very mild.

In the preparation for enynyl aldehyde (**6**), a selective oxidation of compound **5** with the aid of collins reagent was developed. As the product obtained in the collins oxidation was unstable, the oxidation product was directly dehydrated with dilute H_2SO_4 to furnish compound **6**. The ^{1}H NMR spectrum of compound **6** displayed signals for both geometric isomers (E/Z = 1 : 8.6).

Finally, reduction of compound **6** in the presence of $NaBH_4$ gave a E/Z-mixture of compound **2** (R = H) (E/Z = 1 : 6.3) in 95 % yield.

New derivatives of C_6 acetylenic alcohols: The new C_6 acetylenic alcohol derivatives compounds (**7**, **8**, **10** and **11**) synthesized in this study contain six-carbon backbone bearing alkynyl group and hydroxy-protected silyl ethers or acetals. It is anticipated that the alkynyl group of these derivatives can react with the carbonyl compounds such as C_{14}-aldehyde[8], 4-hydroxy-2,2,6- trimethylcyclohexanone[18] to get the carbon skeleton of Vitamin A and carotenoids. The silyl ethers or acetals can be easily deprotected under acidic conditions followed by the elimination of hydroxy to afford the polyenic compounds, which can be further converted into Vitamin A and carotenoids.

Di-silylated compound **7** was obtained in 89 % yield by treatment of diol compound **5** with chlorotrimethylsilane and Et_3N in dichloromethane. The reaction was easy to handle and the yield was excellent. Compound **7** possesses two silylated protecting groups which can be easily deprotected under weakly acidic conditions. So compound **7** may be appropriate for synthesizing precursors of carotenoids which were obtained in weakly acidic conditions.

Mixed acetals compound **8** was prepared in 95 % yield by addition of diol compound **5** with ethyl vinyl ether under

the catalysis of pyridine and *p*-TsOH. Compared with compound **7**, the compound **8** was more stable and could be suitable for the synthesis of carotenoids' precursors which are acquired under harsh conditions.

Acetal compound **10** was synthesized in 65 % yield by the ethynylation reaction of 4-hydroxy-2-butanone (**3**) with ethynylmagnesium bromide.

Cyclic acetal compound **11** was achieved in 57 % yield *via* a convenient cyclization of compound **10** in the presence of HCl (g). Acetal compound **11** possessing a quite stable six-membered ring can be used to prepare carotenoids' precursors. In addition, analogues of acetal compound **11** had been widely used in the synthesis of important natural products[19-21], especially oxygen-containing heterocyclic compounds. So this method will find its potential applications and advantages in building similar structures of acetal compound **11**.

The structural elucidation of these new derivatives was assigned on the basis of their IR, ^{1}H NMR and mass spectra analysis. The IR spectra of compounds **7**, **8**, **10**, **11** showed the absorption bands at 2140-2100 cm^{-1} related to ethynyl groups. In the ^{1}H NMR spectra, a singlet at δ = 2.47-2.55 ppm was assigned to the absorption peak of ethynyl groups. The absorption peaks of all other protons were also appeared in the expected region.

In conclusion, it is reasonable to assume that these C_6 acetylenic alcohol derivatives will be potentially utilized in the synthesis of Vitamin A and carotenoids. Further efforts to synthesize Vitamin A and carotenoids using these new C_6 acetylenic alcohol derivatives are now in progress and will be reported in the near future.

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