SYNTHESIS OF (5R*,6R*)-6-(3-(TERT-BUTYLDIMETHYLSILYLOXY)PROP-1-YNYL)-5-HYDROXYPIPERIDIN-2-ONE

Dau Xuan Duc*, Vo Cong Dung

Faculty of Chemistry, Vinh University, 182 Le Duan Street, Vinh city, Nghe An

*Email: xuanduc80@gmail.com

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ABSTRACT

The synthesis of racemic (5R*,6R*)-6-(3-(tert-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one was accomplished in 10.3% overall yield over 7 steps. The key steps involved a Sonogashira coupling reaction to make an ene-yne ester and an azidolysis reaction of an epoxide ester to form a γ-lactone.

Keywords: piperidine, azide, Stemona alkaloids, epoxidation.

1. INTRODUCTION

The Stemona alkaloids represent a unique class of natural products exclusively isolated from the monocotyledonous family Stemonaceae, mainly distributed in South East Asia [1]. Structurally the alkaloids are characterised by the presence of either a pyrrolo[1,2-a]azepine or a pyrido[1,2-a]azepine core structure [2]. The dried roots from these species, known as ’Bai Bu’ in Chinese traditional medicine, ’Bach Bo’ in Vietnam and ’Non Tai Yak’ or ’Pong Mot Ngam’ in Thailand, are used to suppress coughing, and are claimed to have antituberculosis, antibacterial, antifungal and antihelmintic properties [3]. Although the total syntheses of many pyrrolo[1,2-a]azepine Stemona alkaloids have been reported [3], none of them involves the synthesis of a member of the stemocurtisine group possessing a pyrido[1,2-a]azepine core. The cis-5,6-disubstituted- piperidinones are necessary synthon for the synthesis of Stemocurtisine alkaloids. In this paper, we report our synthesis of (5R*,6R*)-6-(3-(tert-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one in our study on the synthesis of stemocurtisine.

Figure 1. Core structure of the Stemona alkaloids.
2. EXPERIMENTAL SECTION AND SUPPORTING DATA

All reactions were monitored by thin-layer chromatography (TLC) using silica gel (Merck, 60–120 mesh). Column chromatography was performed using Merck silica gel (40–63 µm) packed by the slurry method, under a positive pressure of air. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Varian Inova NMR Spectrometer (\(^1\)H NMR running at 500 MHz and \(^{13}\)C NMR running at 125 MHz) instrument. CDCl\(_3\) was used as the NMR solvent unless otherwise stated. Low-resolution mass spectra were obtained on a Shimadzu GC spectrometer (EI) or Waters LCZ single quadrupole (ESI). High resolution spectra were obtained on a VG Autospec mass spectrometer (EI) or Waters QTOF (ESI). Infrared spectra were obtained as neat samples on a Smart Omni-Sampler Avator ESP Nicolet-Brand. The melting points were recorded on a Gallenhamp MF-370 capillary tube, melting point apparatus and are uncorrected. The values are expressed in degree Celsius (ºC). Uncertainties in the quoted values are ± 2 ºC.

(Z)-Methyl 7-(trimethylsilyl)hept-4-en-6-ynoate (4): Compound 4 was prepared following the procedure described in reference [4]. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.94 (dt, \(J = 10.5, 7.5\) Hz, 1H), 5.52 (d, \(J = 10.5\) Hz, 1H), 3.67 (s, 3H), 2.62 (q, \(J = 7.5\) Hz, 2H), 2.43 (t, \(J = 7.5\) Hz, 2H), 0.18 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.5, 142.8, 111.0, 101.6, 100.0, 51.9, 33.4, 25.9, 0.3. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)) : 2958, 1734, 1507, 1249, 1168, 841. Satisfactory EI or ESI MS data could not be obtained on this compound.

Dihydroxylation of alkene 4: The dihydroxylation of 4 was followed procedure described in reference [5] and products were purified by column chromatography to give three compounds 3, 8 and 9.

\((R^*)-5-((S^*)-1-Hydroxy-3-(trimethylsilyl)prop-2-ynyl)dihydrofuran-2(3H)-one\) (3): White solid. Mp = 92 - 94 ºC. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.32 (m, 2H), 2.52 (m, 2H), 1.94 (m, 1H), 1.84 (m, 1H), 0.18 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.9, 103.1, 92.5, 73.7, 66.9, 30.7, 27.6, 0.12. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)) : 3402, 2957, 2170, 1757, 1181, 1060, 992, 838. ESIMS \(m/z\) 235 [(M+Na)\(^{+}\) 100 %]. HRESIMS calcd. for C\(_{10}\)H\(_{16}\)O\(_3\)NaSi, (M+Na)\(^+\) 235.0766, found: 235.0757.

\((R^*)-5-((S^*)-1-Hydroxyprop-2-ynyl)dihydrofuran-2(3H)-one\) (8): White solid. Mp = 73 – 74 ºC. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.61 (m, 2H), 2.70 – 2.59 (m, 1H), 2.51 – 2.42 (m, 1H), 2.49 (s, 1H), 2.39 – 2.24 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 178.3, 81.7, 80.3, 75.5, 63.8, 28.5, 22.0. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)) : 3280, 2921, 2312, 2180, 1763, 1184, 1054, 1015, 990, 938. NMR spectroscopic data matched with the published data [6].

\((4S^*\,5R^*)\)-Methyl 4,5-dihydroxy-7-(trimethylsilyl)hept-6-ynoate (9): Colourless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.32 (d, \(J = 3.5\) Hz, 1H), 3.67 (s, 4H), 2.52 (dd, \(J = 6.5, 4.5\) Hz, 2H), 1.97-1.90 (m, 1H), 1.88-1.80 (m, 1H) 0.16 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.9, 103.1, 92.5, 73.7, 66.9, 52.1, 30.7, 27.6, 0.12. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)) : 3431, 2960, 2179, 1763, 1184, 1054, 1015, 990, 938. NMR spectroscopic data matched with the published data [6].

Conversion of 9 to 3: The conversion of 9 to 3 was followed procedure described in reference [7].

\(((4-Fluorophenyl)ethynyl)trimethylsilane\) (10): Similar fashion for preparation of compound 4 was applied to prepare compound 10 from 4-floro-iodobenzene. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.48 (dd, \(J = 8.5, 5.5\) Hz, 1H), 7.02 (t, \(J = 8.5\) Hz, 2H), 0.28 (s, 9H).

Methyl 3-(4-fluorophenyl)propiolate (11): Compound 11 was prepared following the procedure described in reference [8]. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.56 (dd, \(J = 8.5, 5.5\) Hz, 2H), 2.30 (s, 3H), 2.52 (dd, \(J = 6.5, 4.5\) Hz, 2H).
Compound 12 was prepared in 63 % yield from compound 4 following similar fashion for compound 10. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.24 (dt, \(J = 11.0, 7.5\) Hz, 1H), 5.58 (d, \(J = 11.0\) Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 2.65 (q, \(J = 7.5\) Hz, 2H), 2.43 (t, \(J = 7.5\) Hz, 2H), \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.0, 154.6, 148.7, 108.2, 85.3, 83.0, 53.0, 52.00, 33.1, 26.4. Satisfactory EI or ESI MS data could not be obtained on this compound.

**Attempted to prepare 14 from compound 3:** Similar fashion for preparation of compound 11 was applied to prepare compound 14 from compound 3. However the desired product 14 was not formed in this reaction, only the undesired product 8 was formed in 93% yield.

(Z)-Methyl 8-(tert-butyldimethylsilyloxy)oct-4-en-2-ynoate (19) Compound 19 was prepared in 78 % yield from vinyl 7 following similar fashion for compound 4: colourless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.90 (dt, \(J = 10.5, 7.5\) Hz, 1H), 5.53 (d, \(J = 10.5\) Hz, 1H), 4.46 (s, 2H), 3.68 (s, 3H), 2.61 (dd, \(J = 15.0, 7.5\) Hz, 2H), 2.42 (t, \(J = 7.5\) Hz, 2H), 0.91 (s, 9H), 0.13 (s, 6H). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.6, 141.6, 110.6, 93.2, 81.4, 52.6, 52.0, 33.6, 26.2, 25.9, 18.7, -4.8. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)): 2956, 1710, 1168, 1022, 919. ESIMS \(m/z\) 305 [(M+Na)\(^+\) 100%]. HRESIMS calcd. for \(\text{C}_{21}\text{H}_{30}\text{O}_{3}\text{SiNa}, (M+Na)^+\) 305.1563, found: 305.1544.

Methyl 3-(2R\(^*\)*,3S\(^*\*))-3-(3-(tert-butyldimethylsilyloxy)prop-1-yn-2-yl)propanoate (17) Compound 17 was prepared from compound 19 following the procedure described in reference 10. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.34 (s, 2H), 3.70 (s, 3H), 3.48 (d, \(J = 4.0\) Hz, 1H), 3.14 (s, 3H), 2.67 (m, 1H), 2.53 (m, 1H), 2.35 (m, 1H), 2.26 – 2.16 (m, 1H), 0.91 (s, 9H), 0.12 (s, 6H). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 176.2, 88.9, 79.6, 76.0, 56.0, 51.8, 30.1, 26.0, 23.7, 18.6, -4.8. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)): 2930, 2857, 2220, 2140, 1774, 1153, 1062, 814, 777. ESIMS \(m/z\) 321 [(M+Na)\(^+\) 100%]. HRESIMS calcd. for \(\text{C}_{13}\text{H}_{20}\text{O}_{3}\text{SiNa}, (M+Na)^+\) 321.1498, found: 321.1488.

**Azidolysis of epoxide 17:** The azidolysis of 17 was followed the procedure described in reference [9] to provide the azide 16 as a colourless oil and the diol 20 as a colourless oil.

(R\(^*\*))-5-((R\(^*\*))-1-Azido-4-(tert-butyldimethylsilyloxy)but-2-ynyl)dihydrofuran-2(3H)-one (16). Colourless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.06 – 4.95 (m, 1H), 4.34 (s, 2H), 4.20 (d, \(J = 6.5\) Hz, 1H), 3.64 (dd, \(J = 9.5, 6.5, 3.0\) Hz, 1H), 2.53 – 2.40 (m, 2H), 2.00 (dd, \(J = 10.5, 7.5, 3.0\) Hz, 1H), 1.79 (qd, \(J = 14.5, 7.5\) Hz, 1H), 1.23 (d, \(J = 6.0\) Hz, 6H), 0.89 (s, 9H), 0.11 (s, 6H). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.9, 85.5, 83.1, 74.5 (C4), 68.3, 66.5, 52.0, 31.4, 27.9, 26.1, 22.1, 18.6, -4.8. IR (neat, \(\nu_{\text{max}}/\text{cm}^{-1}\)): 3293, 2924, 2313, 1764, 1647, 1398, 1136. ESIMS \(m/z\) 367 [(M+Na)\(^+\) 100%]. HRESIMS calcd. for \(\text{C}_{19}\text{H}_{28}\text{O}_{3}\text{SiNa}, (M+Na)^+\) 367.1917, found: 367.1917.

(R\(^*\*))-5-((R\(^*\*))-1-Amino-4-(tert-butyldimethylsilyloxy)but-2-ynyl)dihydrofuran-2(3H)-one (21) Compound 21 was prepared from compound 16 following the procedure described in reference [10]. A mixture of amine 21 and Ph\(_3\)PO was used in the next step without further
purification. 1H NMR (500 MHz, CDCl₃) δ 4.46 (dd, J = 7.0, 7.0 Hz, 1H), 4.32 (s, 2H), 3.78 (d, J = 7.0 Hz, 1H), 2.70 – 2.47 (m, 2H), 2.42 – 2.29 (m, 1H), 2.24 – 2.10 (m, 1H), 0.91 (s, 9H), 0.11 (s, 6H).

\[(5R^*,6R^*)-6-(3-(\text{tert-Butyldimethylsilyloxy})\text{prop-1-ynyl})-5\text{-hydroxypiperidin-2-yl}] (15)\]

To the above mixture of amine 21 and Ph₃P(O) were added MeOH (1 mL) and Et₃N (200 µL) and the reaction mixture was heated and stirred at reflux temperature for 14 h. The solvent was removed in vacuo and the residue was purified by column chromatography (9:1, EtOAc/MeOH) to provide the lactam 15 (21 mg, 88 % yield from 16) as a colourless oil. 1H NMR (500 MHz, CDCl₃) δ 5.75 (bs, 1H), 4.40 (s, 1H), 4.36 (s, 2H), 4.12 – 3.07 (m, 1H), 2.66 – 2.57 (m, 1H), 2.38 – 2.29 (m, 1H), 2.19 – 2.10 (m, 1H), 1.93 – 1.85 (m, 1H), 0.91 (s, 9H), 0.12 (s, 6H). 13C NMR (125 MHz, CDCl₃) δ 171.0, 86.3, 80.3, 65.4, 51.9, 51.1, 27.1, 26.6, 26.2, 18.6, -4.82 (CH₃Si). IR (neat, νₓₓₓ/cm⁻¹): 3242, 2927, 1638, 1329, 1250, 1195, 1060, 834, 776. ESIMS m/z 284 [(M+H)]⁺ 100 %. HRESIMS calcd. for C₁₄H₂₆O₃NₓSi, (M+H)⁺ 284.1682, found: 284.1678.

3. RESULT AND DISCUSSION

We first investigated a synthetic route to prepare the piperidinone 1 following the retrosynthetic analysis shown in Scheme 1 starting from 4-pentyn-1-ol.

![Scheme 1. Retrosynthesis of piperidinone 1.]

For the synthesis of 4, iodination of 4-pentyn-1-ol with I₂/KOH in MeOH led to the iodide 5, which underwent syn-reduction of the alkyne by diimide (NH=NH), prepared in situ from KOOCN=NCOOK and AcOH, to give the (Z)-vinyl iodide 6 in 61 % yield. Jones’ oxidation of the primary alcohol 6 gave the corresponding acid, which was converted to the methyl ester 7 by treatment with Me₂SiCl in MeOH. Sonogashira coupling [11] of 7 with trimethylsilylacetylene and PdCl₂(PPh₃)₃/CuI provided the novel ene-ene 4 in 81 % yield (Scheme 2).

![Scheme 2. Synthesis of ene-ene 4.]

Syn-Dihydroxylation of the alkene 4 with catalytic OsO₄, prepared in situ from K₂OsO₄ and NMO, gave a chromatographically separable mixture of the racemic desired lactone 3, the desilylated lactone 8 and the diol ester 9 [5]. The diol 9 could be converted to the hydroxy-
lactone 3 in 88 % yield by treatment with TsOH (1.5 equiv) in MeOH at rt for 2 h (Scheme 3) [7].

Scheme 3. Dihydroxylation of 4.

The next step in the synthesis was to replace the terminal TMS substituent of 3 with an ester group. Under Kondo’s conditions [8], the methyl ester 11 was obtained in 62 % yield from 10 (Scheme 4 (a)). Then we obtained the diester 12 in 63 % yield from 14 (Scheme 4 (b)). Unfortunately, the desired ester 14 was not formed when we applied the same conditions to 3. Only the undesired alkyne 8 was formed via a proto-desilylation reaction (Scheme 4 (c)). This unsuccessful step prevented us from continuing this pathway to prepare the piperidinone 1.

Scheme 4. Model work and attempts to convert compound 3 to compound 14.

We then tried another pathway to prepare the piperidinone 15 following the retrosynthetic analysis outlined in Scheme 5.

Scheme 5. Retrosynthesis of the piperidinone 15.

Following this synthetic route, Sonogashira coupling of the Z-vinylliodide 7 with the alkyne 18 proceeded smoothly to provide the ene-yne 19 in good yield. Epoxidation of 19 with m-CPBA gave a chromatographically separable mixture of the racemic epoxide 17 and the starting
material (14%). The ring opening of epoxide 17 with azide under Kesselmayer’s conditions [8] gave the desired azide 16 in good yield and the diol 1-propyl ester 20 in 19% yield (Scheme 6).


The azide 16 was then converted to amine 21 by treatment with PPh3 in THF for 1 d, followed by reduction with NaBH4 and MeOH. Amine 21 was obtained as a mixture with Ph3PO and used in the next step without purification. This mixture then was heated with Et3N in methanol at reflux temperature for 14 h to form the lactam 15 in 88% yield from 16 (Scheme 7).

Scheme 7. Synthesis of piperidinone 15.

4. CONCLUSION

We have examined two pathways to synthesize a cis disubstituted piperidinone. The first one was not efficient due to the failure in conversion of 3 to 14. Following the second route we have synthesized the racemic (5R*,6R*)-6-(3-(tert-butylidimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one in 10.3% overall yield over 7 steps.

REFERENCES


