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

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ABSTRACT

The synthesis of racemic (5*R**,6*R**)-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: piperidinone, 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 (5*R**,6*R**)-6-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one in our study on the synthesis of stemocurtisine.

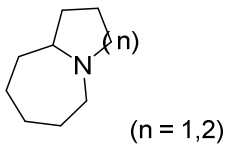


Figure 1. Core structure of the *Stemona* alkaloids.

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 Meck 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 Shimadu GC spectrometer (EI) or Water LCZ single quadropole (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 carpillary tube, melting point apparatus and are uncorrected. The values are expressed in degree Celcius (ºC). Uncertanties 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, $CDCl_3$) δ 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, $CDCl_3$) δ 173.5, 142.8, 111.0, 101.6, 100.0, 51.9, 33.4, 25.9, 0.3. IR (neat, ν_{max}/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(3*H*)-one** (**3**) White solid. Mp = 92 - 94 ºC ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 174.9, 103.1, 92.5, 73.7, 66.9, 30.7, 27.6, 0.12. IR (neat, ν_{max}/cm^{-1}): 3402, 2957, 2170, 1757, 1181, 1060, 992, 838. ESIMS *m/z* 235 [$(M+Na)^+$ 100 %]. HRESIMS calcd. For $C_{10}H_{16}O_3NaSi$, $(M+Na)^+$ 235.0766, found: 235.0757.

(*R)-5-((*S**)-1-Hydroxyprop-2-ynyl)dihydrofuran-2(3*H*)-one** (**8**). White solid. Mp = 73 - 74 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 178.3, 81.7, 80.3, 75.5, 63.8, 28.5, 22.0. IR (neat, ν_{max}/cm^{-1}): 3280, 2921, 2312, 2180, 1763, 1184, 1054, 1015, 990, 938. NMR spectroscopic data matched with the published data [6].

(4*S,5*R**)-Methyl 4,5-dihydroxy-7-(trimethylsilyl)hept-6-ynoate** (**9**). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 174.9, 103.1, 92.5, 73.7, 66.9, 52.1, 30.7, 27.6, 0.12. IR (neat, ν_{max}/cm^{-1}): 3431, 2960, 2179, 1763, 1249, 1180, 1016, 840, 759. ESIMS *m/z* 245 [$(M+H)^+$ 100 %]. HRESIMS calcd. for $C_{14}H_{26}O_3NaSi$, $(M+Na)^+$ 267.1029, found: 267.1026.

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, $CDCl_3$) δ 7.48 (dd, *J* = 8.5, 5.5 Hz, 2H), 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, $CDCl_3$) δ 7.56 (dd, *J* = 8.5, 5.5 Hz,

2H), 7.05 (t, *J* = 8.5 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 (d, *J* = 254 Hz), 154.6, 135.5 (d, *J* = 9 Hz), 116.4 (d, *J* = 10 Hz), 115.9 (d, *J* = 4.0 Hz), 85.7, 80.6, 53.1.

(*Z*)-Dimethyl oct-4-en-2-ynedioate (**12**) Compound **12** was prepared in 63 % yield from compound **4** following similar fashion for compound **10**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ 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-6-ynoate (**19**): Compound **19** was prepared in 78 % yield from vilnyl **7** following similar fashion for compound **4**: colourless oil ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ 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, ν_{max}/cm^{-1}): 2956, 1710, 1168, 1022, 919. ESIMS *m/z* 305 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{15}H_{26}O_3SiNa$, (M+H)$^+$ 305.1563, found: 305.1544.

Methyl 3-((2*R,3*S**)-3-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)oxiran-2-yl)propanoate** (**17**) Compound **17** was prepared from compound **19** following the procedure described in reference 10 ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (s, 2H), 3.70 (s, 3H), 3.48 (d, *J* = 4.0 Hz, 1H), 3.14 (ddd, *J* = 6.5, 5.5, 4.0 Hz, 1H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.11 – 1.92 (m, 2H), 0.90 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 85.0, 79.5, 57.2, 52.1, 52.0, 45.7, 30.7, 26.1, 25.3, 18.6, - 4.9. IR (neat, ν_{max}/cm^{-1}): 2955, 2239, 1767, 1251, 1185, 1041. ESIMS *m/z* 321 [(M+Na)$^+$ 100 %]. HRESIMS calcd. for $C_{15}H_{26}O_4SiNa$, (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(3*H*)-one** (**16**). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (dt, *J* = 7.0, 6.0 Hz, 1H), 4.41-4.37 (m, 1H), 4.39 (s, 1H), 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 88.9, 79.6, 76.0, 56.0, 51.8, 30.1, 26.0, 23.7, 18.6, -4.89 . IR (neat, ν_{max}/cm^{-1}): 2930, 2857, 2220, 2140, 1774, 1153, 1062, 814, 777. ESIMS *m/z* 310 [(M+H)$^+$ 100 %]. HRESIMS calcd. for $C_{14}H_{24}O_3N_3Si$, (M+H)$^+$ 310.1589, found: 310.1587.

(4*S,5*S**)-Isopropyl 8-(*tert*-butyldimethylsilyloxy)-4,5-dihydroxyoct-6-ynoate** (**20**). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 – 4.95 (m, 1H), 4.34 (s, 2H), 4.20 (d, *J* = 6.5 Hz, 1H), 3.64 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H), 2.53 – 2.40 (m, 2H), 2.00 (dtd, *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). ^{13}C NMR (125 MHz, $CDCl_3$) δ 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, ν_{max}/cm^{-1}): 3293, 2924, 2313, 1764, 1647, 1398, 1136, 1013. ESIMS *m/z* 367 [(M+Na)$^+$ 100 %]. HRESIMS calcd. for $C_{17}H_{32}O_5SiNa$, (M+Na)$^+$ 367.1918, 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_3PO was used in the next step without further

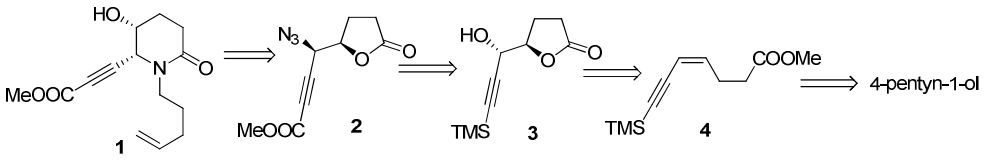
purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.32 (s, 2H), 3.78 (d, *J* = 7.0 Hz, 1H), 2.70 – 2.47 (m, 2H), 2.42 – 2.29 (m, 1H), 2.24 – 2.10 (m, 1H), 0.91 (s, 9H), 0.11 (s, 6H).

(5*R,6*R**)-6-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one (15)**

To the above mixture of amine **21** and Ph_3PO were added MeOH (1 mL) and Et_3N (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. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 86.3, 80.3, 65.4, 51.9, 51.1, 27.1, 26.6, 26.2, 18.6, -4.82 (CH_3Si). IR (neat, ν_{max}/cm^{-1}): 3242, 2927, 1638, 1329, 1250, 1195, 1060, 834, 776. ESIMS *m/z* 284 [$(M+H)^+$ 100 %]. HRESIMS calcd. for $C_{14}H_{26}O_3NSi$, $(M+H)^+$ 284.1682, found: 284.1678.

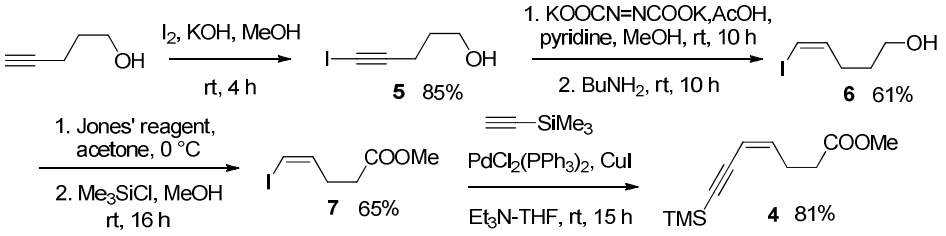
3. RESULT AND DISCUSSION

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**.

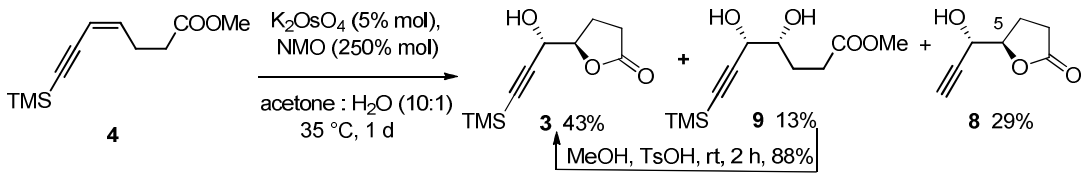
For the synthesis of **4**, iodination of 4-pentyn-1-ol with I_2/KOH in MeOH led to the iodide **5**, which underwent *syn*-reduction of the alkyne by diimide (NH=NH), prepared *in situ* from KOOCN=NCOOK and AcOH, to give the (*Z*)-vinyl iodide **6** in 61 % yield. Jones' oxidation of the primary alcohol **6** gave the corresponding acid, which was converted to the methyl ester **7** by treatment with Me_3SiCl in MeOH. Sonogashira coupling [11] of **7** with trimethylsilylacetylene and $PdCl_2(PPh_3)_2$/CuI provided the novel ene-yne **4** in 81 % yield (Scheme 2).



Scheme 2. Synthesis of ene-yne **4**.

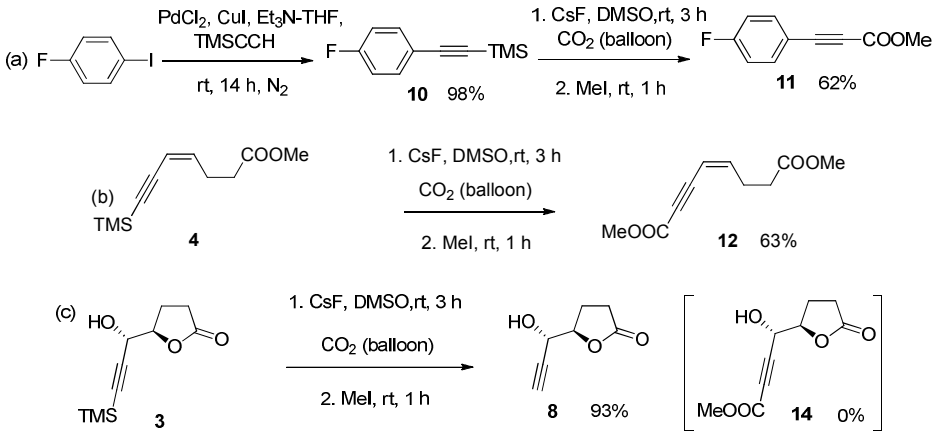
Syn-Dihydroxylation of the alkene **4** with catalytic OsO_4, prepared *in situ* from K_2OsO_4 and NMO, gave a chromatographically separable mixture of the racemic desired lactone **3**, the desilylated lactone **8** and the diol ester **9** [5]. The diol **9** could be converted to the hydroxy-

lactone **3** in 88 % yield by treatment with TsOH (1.5 equiv) in MeOH at rt for 2 h (Scheme 3) [7].



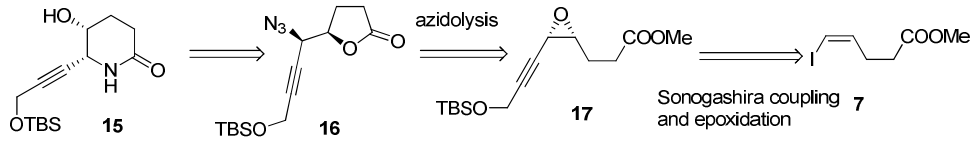
Scheme 3. Dihydroxylation of **4**.

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 continueing this pathway to prepare the piperidinone **1**.



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

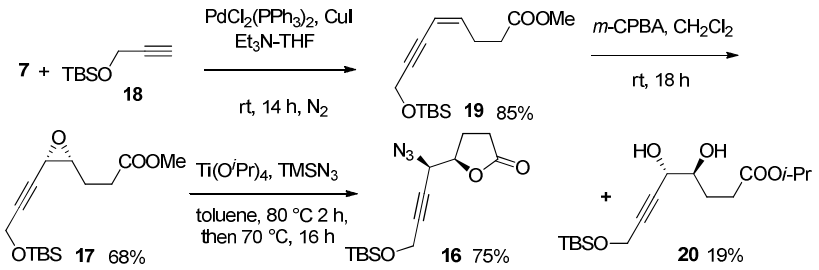
We then tried another pathway to prepare the piperidinone **15** following the retrosynthetic analysis outlined in Scheme 5.



Scheme 5. Retrosynthesis of the piperidinone **15**.

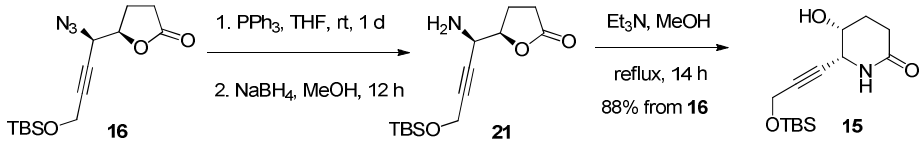
Following this synthetic route, Sonogashira coupling of the *Z*-vinyliodide **7** with the alkyne **18** proceeded smoothly to provide the ene-yne **19** in good yield. Epoxidation of **19** with *m*-CPBA gave a chromatographically separable mixture of the racemic epoxide **17** and the starting

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 *i*-propyl ester **20** in 19 % yield (Scheme 6).



Scheme 6. Synthesis of azide **16**.

The azide **16** was then converted to amine **21** by treatment with PPh_3 in THF for 1 d, followed by reduction with $NaBH_4$ and MeOH. Amine **21** was obtained as a mixture with Ph_3PO and used in the next step without purification. This mixture then was heated with Et_3N 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 (5*R**,6*R**)-6-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one in 10.3 % overall yield over 7 steps.

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12. Compounds **5**, **6**, **7**, **10**, **17** and **18** were prepared following procedures described in reference: Duc D. X., Willis A. C., Pyne S. - Diasteroselective Synthesis of the A-B-C Tricyclic Ring Structure of Stemocurtisine G. Eur. J. Org. Chem. **2015** (35) (2015) 7682. Their spectroscopic data match with the published data.