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Enantioselective Synthesis of a Key Tricyclic Intermediate *en Route* to (+)-Gelsemine

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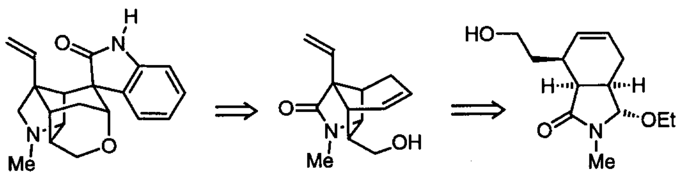
Abstract

The efficient synthesis of an enantiopure tricyclic lactam starting from (*S*)-5-isopropoxypyrrolin-2-one is described. The racemate of this tricyclic lactam is an intermediate in our previously published total synthesis of racemic gelsemine, so that the present work paves the way for the synthesis of the enantiopure alkaloid. The synthetic route includes a Sonogashira coupling, a highly selective Diels-Alder reaction and a trimethylsilyl triflate-mediated *N*-acyliminium ion cyclization as key steps.

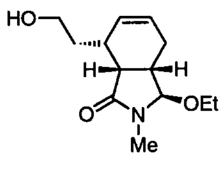
Keywords: alkaloids, pyrrolinones, palladium and compounds, Diels-Alder reactions, iminium salts

The oxindole alkaloid gelsemine (**1**) has challenged synthetic chemists ever since its structure was determined in 1959 [1-3] The first two total syntheses were published in 1994, simultaneously, by Johnson's [4] and our group [5]. Subsequently, Hart [6,7] and Fukuyama [8] have published their total syntheses. Several other groups have reported on alternative approaches towards gelsemine [8-12].

All total syntheses published sofar have produced racemic gelsemine. Key intermediates in our synthesis were racemic tricyclic alcohol **2** and ethoxylactam **3** [5]. In 1992 we published the preparation of enantiopure ethoxylactam **4** from inexpensive (*S*)-malic acid via (*R*)-pyrrolinone **5** [13], so that that work can be viewed as a formal synthesis of (*ent*)-gelsemine. Recently, an expedient enantioselective synthesis of the enantiomer of **5**, i.e. (*S*)-pyrrolinone **6** has become available [14,15]. In this letter we report the transformation of **6** into enantiopure **3**, via a route which contains a number of improvements compared to our racemic total synthesis. This work illustrates the versatile synthetic utility of the chiral building blocks **5** and **6** and paves the way for an eventual total synthesis of the natural enantiomer of gelsemine.



gelsemine (1) **2** **3**



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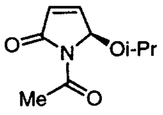

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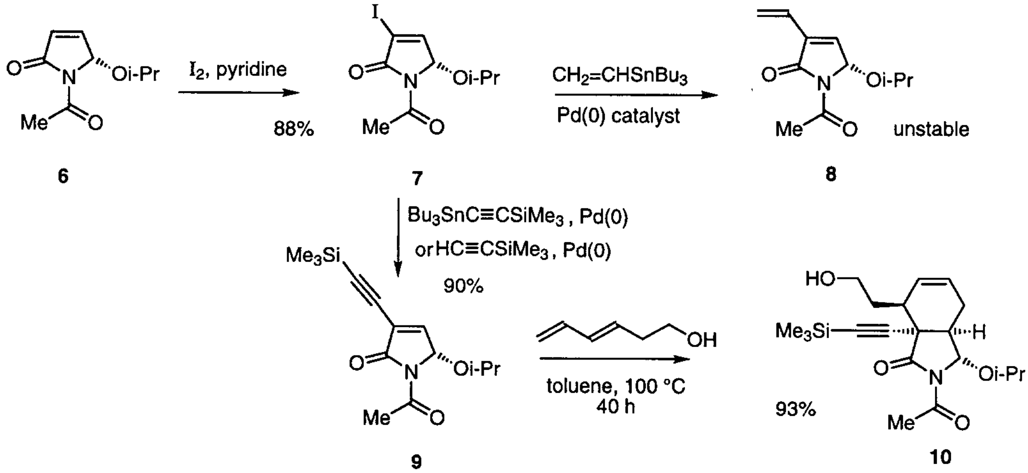
In our previous synthesis of **2** the vinyl group was introduced by reaction of the lactam enolate of **3** with phenylselenoacetaldehyde and subsequent elimination [5,16]. This method was unsatisfactory, so that our new approach was directed at the introduction of the vinyl group early in the synthesis prior to the Diels-Alder reaction. Our synthetic endeavour began with the synthesis of (*S*)-pyrrolinone **6** (see Scheme 1) from the corresponding 5-acetoxypyrrolinone [14] on 40 g scale by using the palladium-catalyzed substitution published by Feringa and Kellogg [15]. Pyrrolinone **6** was readily converted into the crystalline iodide **7** [mp 92-94 °C, α_D^{19} = +57.0 ($CHCl_3$, *c* 0.9)] in excellent yield according to Johnson's protocol [17,18]. Stille coupling [18,19] of **7** with tributylvinylstannane proceeded very well according to the ^1H NMR spectrum of the crude product, but unfortunately diene **8** was too unstable for further use. We then turned our attention to a synthetic equivalent of vinylpyrrolinone **8**, *viz* acetylene **9*** which appeared a to be a stable compound. It was readily accessible via either a Stille coupling or a Sonogashira reaction [20] in similar yields. Compounds **7**–**9** are enantiopure synthons with interesting functionality which may have broader utility in synthesis.



Scheme 1. Details: Synthesis of **7**: iodine (3 equiv), pyridine, CCl_4, 0 °C → rt, 68 h, 88%. **8**: $H_2C=CHSnBu_3$ (1.2 equiv), Pd_2dba_3 (2%), Ph_3As (4%), *N*-methylpyrrolidinone, 40 °C, 16 h. **9**: $Me_3SiCCSnBu_3$ (1.2 equiv), $PdCl_2(MeCN)_2$ (5%), DMF, rt, 15 min, 89% or Me_3SiCCH (2 equiv), CuI (10%), $PdCl_2(MeCN)_2$ (5%), diisopropylamine (3 equiv), THF, rt, 1 h, 91%. **10**: ammonia rinsed flask, (*E*)-3,5-hexadien-1-ol (1.2 equiv), hydroquinone (trace), toluene, 100 °C, 40 h, 93%.

The key Diels-Alder reaction with (*E*)-3,5-hexadien-1-ol [21] required 100 °C for 40 h, but proceeded with excellent selectivity to give enantiopure adduct **10**# as a single regio- and

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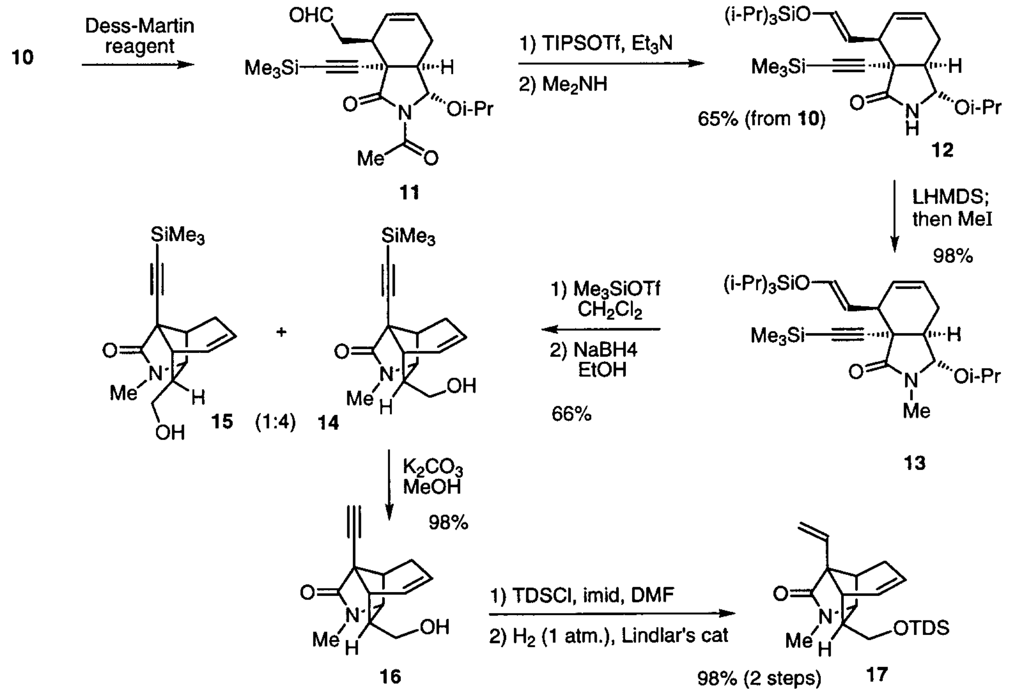
* Data for **9**: mp 103-104 °C, α_D^{19} ($CHCl_3$, *c* 1.13) = +67.8. IR: ν 1747, 1705 cm^{-1}. ^1H NMR: δ 0.23 (s, 9H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H), 2.53 (s, 3H), 4.22 (hept, *J* = 6.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), ^{13}C NMR: δ -0.7, 22.7, 22.8, 24.7, 72.9, 84.4, 93.0, 104.4, 122.4, 147.1, 165.6, 169.5 ppm. Anal. calcd for $C_{14}H_{21}NO_3Si$: C 60.18; H 7.58; N 5.01; found: C 59.89; H 7.55; N 4.91.

Data for **10**: oil, α_D^{17} ($CHCl_3$, *c* 1.37)= +68.0. IR: ν1744, 1709 cm^{-1}. ^1H NMR: δ 0.13 (s, 9H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.69 (s, 1H), 2.04-2.10 (m, 1H), 2.14 (ddd, *J* = 16.0, 6.6, 1.8 Hz, 1H), 2.30-2.42 (m, 3H), 2.72 (s, 3H), 2.72 (br.d, *J* = 8.2 Hz, 1H), 3.67 (ddd, *J* = 5.3, 8.2, 10.6 Hz, 1H), 3.81 (ddd, *J* =5.3, 5.9, 10.6 Hz, 1H), 3.89 (hept, *J* =6.1 Hz, 1H), 5.10 (d, *J* =0.9 Hz, 1H), 5.71 (dt, *J* =9.3, 3.2 Hz, 1H), 5.82 (tdd, *J* =3.2, 9.3, 6.3 Hz, 1H). ^{13}C NMR: δ 172.6, 170.7, 132.2, 127.1, 104.9, 90.0, 88.9, 70.7, 61.3, 49.8, 46.6, 39.5, 32.7, 26.3, 25.0, 22.7, 22.0, -0.4 ppm. HRMS observed (EI): 377.2010, calcd for $C_{20}H_{31}NO_4Si$: 377.2022.

stereoisomer. Thus, in three steps from **6**, both the introduction of a synthetic equivalent of the vinyl group and the Diels-Alder reaction were accomplished in a very efficient way.

To prepare for the *N*-acyliminium ion cyclization to a tricycle of type **2** the hydroxyethyl group in **10** was transformed into a π-nucleophile in two steps. Oxidation of **10** with the Dess-Martin reagent [22,23] gave the corresponding aldehyde **11** which was not purified but directly subjected to silyl enol ether formation using triisopropylsilyl triflate and triethylamine in dichloromethane [24,25]. Under these condition the desired (*E*)-isomer was obtained as the preponderant product. The crude mixture was then treated with dimethylamine to effect removal of the acetyl group from nitrogen [13]. The product was purified by flash chromatography to give the pure (*E*)-silyl enol ether **12** in 65% overall yield from **10**. The introduction of the required methyl group on nitrogen in **12** proceeded in excellent yield by using lithium hexamethyldisilazide as the base to give the cyclization precursor **13**.



Scheme 2. Details: Synthesis of **11**: Dess-Martin reagent (2 equiv), CH_2Cl_2, 0 °C → rt, 2h. **12**: Triisopropylsilyl triflate (1.3 equiv), triethylamine (1.5 equiv), CH_2Cl_2, 2h, 0 °C → rt; then work-up with cold aq $NaHCO_3$; then dimethylamine (excess), CH_2Cl_2, 0 °C → rt, 2 h, 65% from **10**. **13**: Methyl iodide (1.1 equiv), THF; then lithium hexamethyldisilazide (1M in THF, 1 equiv), -70 °C → rt, 4 h, 98%. Mixture of **14** and **15** (4:1): Trimethylsilyl triflate (1.2 equiv), CH_2Cl_2, -13 °C, 25 min; then work-up with cold aq $NaHCO_3$; then $NaBH_4$ (2 equiv), ethanol, 0 °C, 66%. **16**: K_2CO_3 (1 equiv), methanol, 19 h, rt, 98%. **17**: Dimethylthexylsilyl chloride (TDSCl, 1.3 equiv), imidazole (1.3 equiv), DMF, 18 h, rt; then quinoline (1.2 equiv), EtOAc, Lindlar's cat, hydrogen (1 atm.), 20 min, 99%.

The second key step, the *N*-acyliminium cyclization of **13** was best achieved by using 1.5 equiv of trimethylsilyl triflate as the Lewis acid for 6 h at -15 °C. In this manner a 4:1 mixture of the two expected aldehydes, with the desired isomer in excess, was obtained according to the ^1H

NMR spectrum of the crude product.This mixture was immediately reduced to a 4:1 mixture of the alcohols **14*** and **15**, which could be separated by recrystallization and flash chromatography. The relative stereochemistry of the products was directly clear from a comparison of their ^{1}H NMR spectra with the analogous compounds with a vinyl substituent on the bridgehead adjacent to the carbonyl [16]. The desired isomer **14** was then desilylated to alcohol **16** followed by protection of the hydroxyl function with a dimethylthexylsilyl (TDS) function. Finally, partial hydrogenation of the alkyne proceeded cleanly to furnish enantiopure vinyl-substituted **17**# in excellent yield. This compound had been made before in racemic form as intermediate in our total synthesis of gelsemine [5]. All spectroscopic data of **17** were identical to those of the racemate except for the optical rotation.

In conclusion, we have prepared the enantiopure tricyclic lactam **17** in 12 steps from the readily available (*S*)-pyrrolinone **6**. As racemic **17** has been transformed into racemic gelsemine [5] the completion of the total synthesis of the pure natural enantiomer of the alkaloid is only a matter of time. The present synthesis of **17** features a number of improvements compared to our previous work, in particular the palladium-catalyzed introduction of the acetylene group and the highly selective Diels-Alder process.

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* Data for **14**: mp 141-142 °C, α_D^{18} ($CHCl_3$, *c* 1.23)= +8.7. IR: ν 3437, 2173, 1699 cm^{-1}. ^{1}H NMR: δ 5.90 (dddd, *J* = 9.0, 7.2, 2.8, 1.1 Hz, 1H), 5.76 (ddd, *J* = 9.0, 4.3, 2.5 Hz, 1H), 3.55 (ddd, *J* = 11.0, 7.1, 3.9 Hz, 1H), 3.44 (ddd, *J* = 11.0, 8.6, 6.1 Hz, 1H), 3.35 (d, *J* = 1.6 Hz, 1H), 2.79 (dt, *J* =7.4, 1.6 Hz, 1H), 2.76 (s, 3H), 2.51 (dddd, *J* = 19.6, 7.5, 4.3, 1.0 Hz, 1H), 2.41 (dd, *J* =7.4, 1.7 Hz, 1H), 2.08 (dt, *J* = 19.6, 2.7 Hz, 1H), 2.06 (m, 1H), 1.40 (m, 1H), 0.14 (s, 9H). ^{13}C NMR: δ 174.8, 127.2, 126.7, 101.2, 89.8, 65.1, 61.7, 52.3, 51.3, 51.0, 41.0, 27.6, 27.2, -0.1 ppm. Anal. calcd for $C_{16}H_{23}NO_2Si$: C 66.39; H 8.01; N 4.84; found: C 66.05; H 7.94; N 4.72.

\# Data for **17**: oil, α_D^{18} ($CHCl_3$, *c* 0.915) = +94. IR: ν 2958, 1686 cm^{-1}. ^{1}H NMR: δ 5.99 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.81 (ddd, *J* = 9.1, 7.2, 1.9 Hz, 1H), 5.64 (dd, *J* = 9.1, 4.1 Hz, 1H,), 5.30 (dd, *J* =11.0, 1.5 Hz, 1H), 5.18 (dd, *J* = 17.7, 1.5 Hz, 1H), 3.47 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.36 (d, *J* = 1.1 Hz, 1H), 3.32 (t, *J* =10.2 Hz, 1H), 2.74 (s, 3H), 2.59 (t, *J* = 7.2 Hz, 1H), 2.30-2.38 (m, 2H), 1.98-2.08 (m, 2H), 1.61 (sept, *J* = 6.9 Hz, 1H), 0.88 (d, *J* = 6.9 Hz, 6H), 0.83 (s, 6H,), 0.07 and 0.06 (2 × s, 6H). ^{13}C NMR: δ 178.4, 133.2, 127.4, 126.9, 118.3, 65.4, 62.0, 59.1, 52.1, 48.3, 39.4, 34.3, 27.3, 27.1, 24.9, 20.3, 18.6, -3.5, -3.6 ppm. HRMS observed (EI): 361.2437, calcd for $C_{21}H_{35}NO_2Si$: 361.2437. HPLC (Chiralcel OD, heptane/isopropanol 9:1, 0.5 mL/min, 215 nm) one peak, R_f 18.00; racemate: 15.14, 17.96.

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