THE TOTAL SYNTHESIS OF LYCOPODINE USING BRIDGEHEAD INTERMEDIATES

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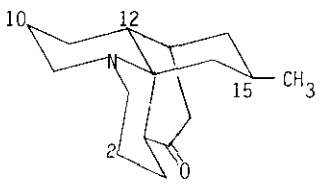
Abstract - The total synthesis of lycopodine has been achieved by two different routes. In one route a bridgehead carbocation is trapped by 3-benzyloxy-1-propanamine. In the second route a bridgehead enone is generated in situ and reacted with 3-hydroxy-1-propanamine.

Lycopodine (1) is an alkaloid produced by the genus Lycopodium.[1] Its structure was determined by Harrison and MacLean in 1960.[2] Since that time, many related alkaloids have been discovered. The lycopodine family now contains over 100 members.

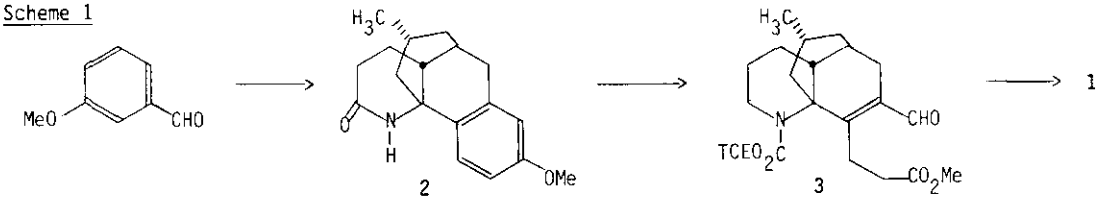


Lycopodine 1

Lycopodine, by virtue of its fascinating structure and biosynthetic significance, has been the synthetic objective of several research groups.[3] The pioneering synthetic work was done independently by Stork[4,5] and by Ayer.[6] Their research culminated in two total syntheses of lycopodine in 1968.

The Stork synthesis started from m-methoxybenzaldehyde. Key intermediates in this clever and well-conceived synthesis are illustrated in Scheme 1. The stereogenic center at C-15 (lycopodine

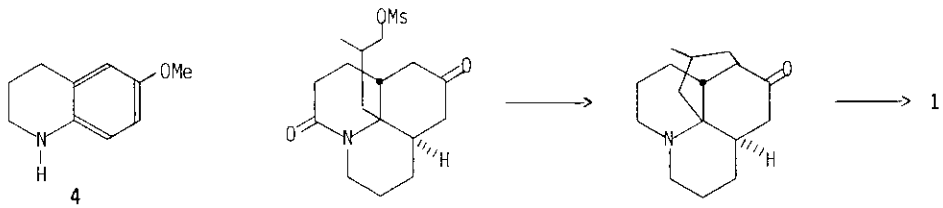
Scheme 1



numbering) was set by a copper-mediated conjugate addition of methyl magnesium iodide. The stereogenic center at C-13 was readily introduced by an intramolecular acid-mediated

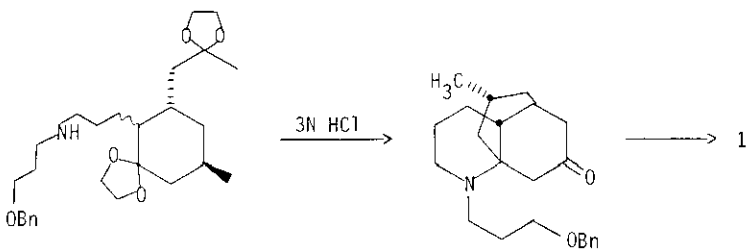
cyclization. The product, lactam 2, was then reduced, isomerized and oxidatively cleaved to produce aldehyde 3. This was then transformed into lycopodine in six steps. Starting from m-methoxybenzaldehyde, the Stork synthesis afforded lycopodine in 1.1% overall yield.

The Ayer synthesis started from thalline 4 and produced lycopodine in 17 steps in 0.06% yield. A key step in this interesting synthesis was an intramolecular alkylation of 5 to produce ketone 6. This ketone was then converted into racemic lycopodine in four steps.



4 5 6 eq. 1

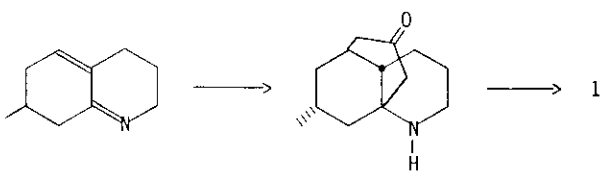
Heathcock and coworkers achieved the total synthesis of lycopodine in 1982.[7] This elegant and extremely direct synthesis featured an intramolecular Mannich condensation in which the A, B and C rings were formed in a single reaction. This cyclization is depicted in equation 2. In this reaction a bridgehead iminium ion is a likely intermediate. The synthesis proceeded in 13



eq. 2

steps from 5-methylcyclohexenone in 16.6% overall yield! Heathcock also developed another route which was even more direct, but produced 1 in a lower overall yield.

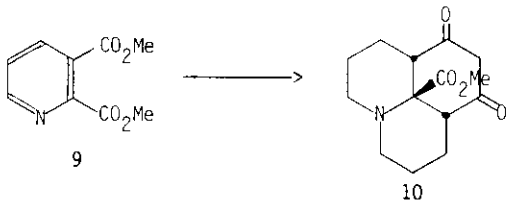
Schumann and coworkers reported a clever synthesis of lycopodine in 1982.[8] Their synthesis centered around the generation of unsaturated imine 7 and its reaction with acetonedicarboxylic



7 8 eq. 3

acid to provide aminoketone 8 with high stereoselectivity. Aminoketone 8 was then converted into 1 in three steps. The overall yield from 2-β-cyanoethyl-3-hydroxy-5-methylcyclohexenone was 10.5%.

Wenkert and Broka described an interesting total synthesis of 1 in 1984.[9] They started with dimethyl quinolinate 9 and prepared the symmetrical intermediate 10. Diketone 10 was converted into 1 in nine steps in 0.65% yield from 9. Four related alkaloids were also synthesized from intermediate 10.

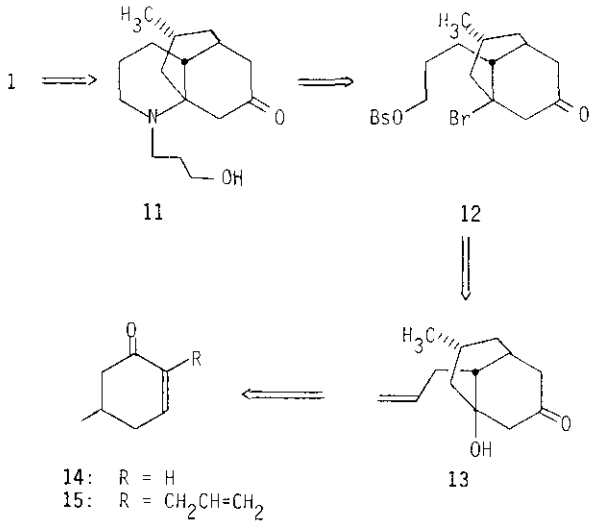


9 10

eq. 4

The retrosynthetic analysis of our route to 1 is shown in Scheme 2. Ketoalcohol 11, an advanced intermediate in the Heathcock synthesis, will be derived from bromoketone 12, which will be prepared from bicyclic ketone 13. The key stereogenic centers at C-12 and C-15 are both formed in the step that produces 13. Ketone 13 will be constructed from 5-methylcyclohexenone 14.[10]

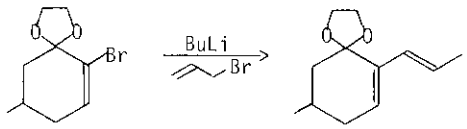
Scheme 2



11 12 13

14: R = H
15: R = $CH_2CH{=}CH_2$

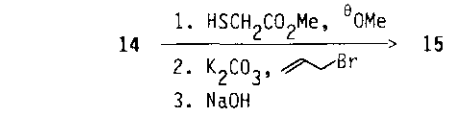
The most direct route to ketone 15 from 14 appeared to be via the α-bromovinyl ketal methodology developed by Smith.[11] While this reaction had been extremely useful to us in earlier work, in this case it furnished only the isomeric ketal 16. The allyl substitutent could be



16

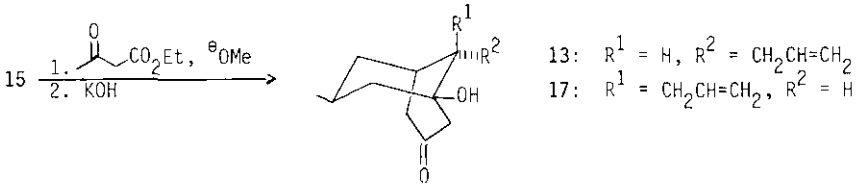
eq. 5

introduced by the method of Baraldi, which is illustrated in equation 6. This method seems to be a versatile one.[12] With ketone 15 now readily available, the formation of bicyclic ketone 13



eq. 6

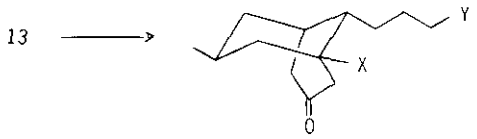
became the next goal. Fortunately, the preparation of 1-hydroxy-bicyclo[3.3.1]nonan-3-ones from cyclic ketones by Michael addition followed by aldol condensation was a well established pathway.[13] Moreover, the stereochemistry of the initial Michael addition reaction had been established as an axial addition. When ketone 15 was treated with ethyl acetoacetate and sodium methoxide in boiling methanol, two isomeric products were produced. After decarbomethoxylation, hydroxyketones 13 and 17 were isolated in a 20:1 ratio. Since the allyl group was expected to



13: R^1 = H, R^2 = $CH_2CH{=}CH_2$
17: R^1 = $CH_2CH{=}CH_2$, R^2 = H

eq. 7

epimerize to the equatorial position before the intramolecular aldol condensation, the major product was assigned structure 13. The C-13 NMR indicated that 13 was stereochemically homogeneous and supported the bicyclic ketoalcohol structure. The reaction of 13 with borane-THF was highly chemoselective, affording dihydroxyketone 18. Selective benzenesulfonylation of the primary alcohol over the tertiary alcohol was expected and worked well. Benzenesulfonylation not only activated the alcohol for displacement but also rendered the oxygen atom much less nucleophilic. This aspect was crucial to the success of our plan, since a carbocation was later to be generated only five carbon atoms away. The reaction of hydroxyketone 19 with phosphorus tribromide provided bromoketone 12.

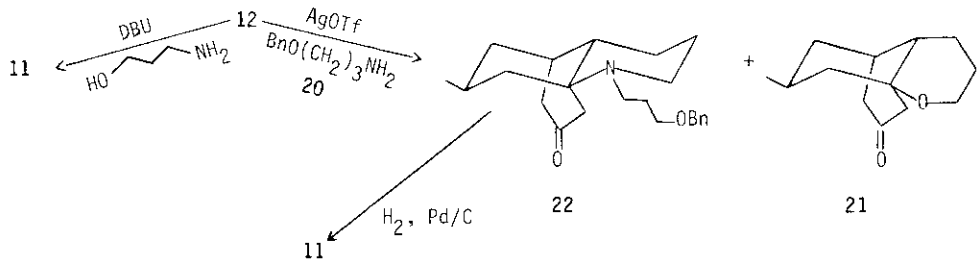


eq. 8

18: X = Y = OH
19: X = OH, Y = OBs
12: X = Br, Y = OBs

The conversion of 12 into 11 was accomplished by two different routes. One route proceeded by way of a bridgehead carbocation intermediate. The other, by way of a bridgehead enone. The transformations are shown below in Scheme 3.

Scheme 3



The bridgehead carbocation route was initiated by the reaction of 12 with silver triflate to generate the bridgehead triflate. Amine 20 must be added after triflate formation in order to prevent formation of a silver-amine complex. If 1.5 equivalents of the amine were added 1 minute after the formation of the triflate, then ether 21 was coproduced with aminoketone 22. Ether 21 was the major product of this reaction.[14] Ether 21 was formed by the intramolecular trapping of the bridgehead carbocation. It was independently synthesized from 13. However, if five equivalents of the amine were added immediately after the silver triflate was added, the yield of aminoketone 22 was 96% with only a trace of ether 21. The benzyl ether in aminoketone 22 was cleaved by catalytic hydrogenation to afford the crystalline ketone 11. The melting point, NMR, IR and ultraviolet spectra are all identical to those reported by Heathcock. The UV spectrum contains an absorption at 220 nm which has been observed in lycopodine and other Lycopodium alkaloids, but not in 12-epilycopodine.

The bridgehead enone route was inspired by House's indication that the reactions of nucleophiles with certain bridgehead bromoketones and DBU proceeded by way of in situ derived bridgehead enones.[15] Indeed, the reaction of 12 with 3-amino-1-propanol and DBU produced ketone 11 as the sole product in quantitative yield. Ketone 11 was converted into racemic lycopodine in two steps using Heathcock's procedures. Our racemic lycopodine has a C-13 spectrum which is identical to that reported in the literature.[9]

The total synthesis of lycopodine was effected in only nine steps and in 25% yield from ketone 15. The synthesis is a flexible one and should be readily modified to allow the synthesis of natural products containing a hydroxyl group at C-10. This represents only the second use of bridgehead enones in natural products synthesis.[16] Additionally, this constitutes the second use of a bridgehead carbocation strategy.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined

on a Varian EM 360 60 MHz instrument and on a Nicolet 300 MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform instrument. High resolution mass spectra were determined on a Kratos mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

5-Methyl-2-(2-propenyl)-2-cyclohexen-1-one (15).

To 33 ml of a 1.5 M sodium methoxide in methanol solution (50.2 mmol) was added 5.0 ml of ethyl 2-mercaptoacetate (45.7 mmol) dropwise at 0°C. To the resulting solution was then added a solution of 5.02 g of 5-methyl-2-cyclohexen-1-one (45.7 mmol) in 60 ml of methanol. The solution was refluxed overnight. After removal of the solvent, the brown residue was acidified by 3N hydrogen chloride and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 5:1 hexane:ethyl acetate to afford 5.71 g of product. (68% yield) NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 3 H), 3.25 and 3.62 (q, J = 16 Hz, 2 H), 4.1 (m, 1 H), 12 (b, 1 H); IR (film) 2970, 2940, 2880, 1750, 1720, 1660, 1600, 1460, 1395, 1345, 1275, 1230, 1140, 890, 800 cm^{-1}.

To a mixture of 96.23 g of the above product (523 mmol) in 500 ml of acetone was added 109 g of potassium carbonate (785 mmol) and 95 g of allyl bromide (785 mmol). The resulting solution was refluxed overnight. The inorganic salts were separated by filtration through sintered glass. The filtrate was concentrated and was taken on to the next step without further purification.

To the concentrated crude product was added 500 ml of ethyl ether and then 200 ml of a 5 M aqueous sodium hydroxide solution at room temperature. After stirring for 5 h, the solution was separated. The aqueous layer was extracted with ethyl ether. The combined organic layers were dried and concentrated. The product was purified by vacuum distillation to afford 44.07 g of product at 50-60°C (1-2 torr). (56% yield) NMR ($CDCl_3$) δ 1.0 (d, J = 5 Hz, 3 H), 1.5-3.1 (m, 7 H), 4.7-6.2 (m, 3 H), 6.6 (m, 1 H); IR (CH_2Cl_2) 3075, 2975, 2920, 2820, 1705, 1670, 1635, 1450, 1425, 1370, 1230, 990, 905 cm^{-1}. High resolution mass spectrum for $C_{10}H_{14}O$ requires 150.14447, measured 150.1044.

9-Allyl-3-carbomethoxy-1-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one

To the freshly prepared 2 M sodium methoxide in 400 ml of methanol (221 mmol) was added ethyl acetoacetate (28.7 g, 221 mmol) and compound **15** (30.1 g, 200 mmol). The resulting solution was heated under reflux for 84 h. The mixture was cooled to room temperature and then the methanol was removed. The concentrated mixture was neutralized by 3N HCl to pH = 6 and then extracted with methylene chloride. The organic layer was dried and concentrated. Flash column chromatography using 1:5 ethyl acetate:hexane afforded 10.33 g of recovered compound **15** and 28.6 g of a mixture of compounds. (84% net yield, 64% conversion) NMR ($CDCl_3$) δ 0.9 (d, J = 6 Hz, 3 H), 1.1-3.3 (m,

12 H), 3.75 (s, 3 H), 4.7-6.2 (m, 3 H); IR ($CDCl_3$) 3450, 3080, 2960, 2922, 2865, 1700, 1650, 1620, 1440, 1422, 1360, 1275, 1210, 1090, 1040, 900, 810, 730 cm^{-1}.

9-Allyl-1-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one **13**

To a solution of the above compounds (27.16 g, 102.1 mmol) in 100 ml of methanol was added 100 ml of 1.1 M aqueous potassium hydroxide (110 mmol). The solution was refluxed for 12 h. The methanol in the solution was removed in vacuo. The organic compound was extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 1:3 ethyl acetate:hexane to afford 19.70 g (94.7 mmol) of compound **13** and 1.02 g of compound **12** (4.90 mmol) in 98% yield. For compound **13**: NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.1-2.8 (m, 13 H), 4.8-6.2 (m, 3 H); C-13 NMR ($CDCl_3$) δ 22.04, 26.60, 30.95, 32.13, 40.84, 41.49, 46.37, 50.72, 51.18, 72.64, 116.34, 136.95, 211.15; IR ($CDCl_3$) 3440, 3090, 2960, 2930, 2880, 1700, 1645, 1460, 1410, 1310, 1230, 1110, 1035, 1000, 910, 730 cm^{-1}. High resolution mass spectrum for $C_{13}H_{20}O_2$ requires 208.14633, measured 208.1466. Elemental analysis calculated for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.63; H, 9.62.

1-Hydroxy-9-(3-hydroxypropyl)-7-methylbicyclo[3.3.1]nonan-3-one **18**

To a solution of compound **13** (2020 mg, 9.7 mmol) in 15 ml of THF was added 9.7 ml of 1 M Borane-THF complex (0.7 mmol) dropwise at 0°C. After 1.5 h, 14.6 ml of 1 M aqueous sodium hydroxide was carefully added and then 7.3 ml of 30% hydrogen peroxide at 0°C. The solution was then refluxed for 1.5 h until all of the white precipitate disappeared. The solution was cooled down and extracted with ethyl ether. The organic layer was dried and concentrated to afford 2459 mg of crude product. Without purification, compound **18** was taken on to the next step. NMR ($CDCl_3$) δ 0.9 (d, J = 6 Hz, 3 H), 1.1-3.3 (m, 17 H), 3.65 (m, 2 H); IR (film) 3360, 2930, 2880, 1710, 1460, 1410, 1380, 1320, 1250, 1110, 1055,, 945, 900, 735 cm^{-1}.

9-(3-Benzenesulfonyloxypropyl)-1-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one **19**

To a mixture of crude product **18** (2459 mg) in 20 ml of methylene chloride was added 1.1 ml of pyridine (14.1 mmol) and 1.3 ml of benzene-sulfonyl chloride (10.9 mmol) at 0°C. The solution was then stirred at room temperature overnight. The solution was poured into water and extracted with methylene chloride. The organic layer was dried and concentrated to afford 3590 mg of crude product. Without purification, it was taken on to the next step.

9-(3-Benzenesulfonyloxypropyl)-1-bromo-7-methylbicyclo[3.3.1]nonan-3-one **12**

To a mixture of crude product **19** (3590 mg) in 20 ml of ethyl ether was added phosphorus tribromide (1.01 ml, 10.8 mmol) dropwise at 0°C. The solution was warmed slowly to room temperature. After 2.5 h at room temperature, the solution was poured into ice water and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 5:1 hexane:ethyl acetate to afford 1.58 g of compound **12** as a brown oil (38% overall yield

from compound **13**). NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3 H), 1.1-2.6 (m, 13 H), 2.9 (s, 2 H), 4.15 (bt, J = 5 Hz, 2 H), 7.3-8.0 (m, 5 H); C-13 NMR ($CDCl_3$) δ 21.52, 25.95, 27.18, 27.90, 33.03, 40.58, 41.29, 48.19, 53.97, 55.34, 69.65, 70.36, 75.63, 77.06, 78.49, 127.72, 129.21, 133.70, 136.17, 207.19; IR (film) 3080, 2940, 2880, 1715, 1455, 1420, 1365, 1315, 1275, 1220, 1190, 1115, 1100, 1020, 1000, 940, 820, 760, 735 cm^{-1}. High resolution mass spectrum for $C_{19}H_{25}O_4{}^{81}BrS$-Br requires 349.1474, measured 349.1476.

(4aRS, 5SR, 8aSR, 10RS)-10-Methyl-1-[3-(phenylmethoxy)propyl]-hexahydro-1H-5,8a-propanoquinolin-7(8H)-one **22**

To a solution of compound **12** (194 mg, 0.45 mmol) in 1 ml of methylene chloride was added silver triflate (128 mg, 0.50 mmol), followed by 3-benzyloxy-1-propylamine (373 mg, 2.26 mmol) in 0.5 ml of methylene chloride at 0°C immediately. After 1 h at 0°C, the solution was diluted with brine and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 95:5 chloroform:methanol to afford 153 mg of compound **22** (96% yield). NMR ($CDCl_3$) δ 0.85 (d, J = 6 Hz, 3 H), 1.1-3.2 (m, 21 H), 3.5 (t, J = 6 Hz, 2 H), 4.45 (s, 2 H), 7.3 (s, 5 H); C-13 NMR ($CDCl_3$) δ 22.57, 25.43, 25.69, 29.13, 35.77, 39.28, 41.81, 42.27, 43.51, 44.74, 47.21, 59.05, 68.15, 72.70, 75.65, 77.00, 78.49, 127.33, 128.11, 138.45, 212.84; IR (film) 3070, 2940, 2870, 1700, 1455, 1270, 1105, 910, 730 cm^{-1}. MS (m/z) 91, 162, 192, 206, 220, 249, 264, 298, 312, 340, 355 (M^+). High resolution mass spectrum for $C_{23}H_{33}NO_2$ requires 355.2511, measured 355.2510.

(4aRS, 5SR, 8aSR, 10RS)-(3-Hydroxypropyl)-10-methylhexahydro-1H-5,9a-propanoquinolin-7(8H)-one **11**

To a solution of compound **22** (413 mg, 1.16 mmol) in 8 ml of absolute ethanol was added 1 ml of aqueous 3N hydrogen chloride solution. At this point 40 mg of 10% palladium on charcoal was added, and the mixture was stirred under hydrogen (1 atm) for 2.5 h. After filtration of the catalyst and removal of the solvent, the residue was diluted with aqueous sodium bicarbonate solution to pH = 8. The precipitate was extracted with methylene chloride. The organic layer was dried with potassium carbonate and concentrated. The crude product was chromatographed using 5:95 methanol:chloroform to afford 295 mg of compound **11** (96% yield) as a tan crystal, (mp = 86-87°C). NMR ($CDCl_3$) δ 0.93 (d, J = 5 Hz, 3 H), 1.1-3.5 (m, 21 H), 3.6-3.9 (m, 2 H), 5.4 (bs, 1 H); IR (film) 3320, 2900, 1700, 1460, 1410, 1335, 1310, 1220, 1170, 1110, 1060, 980, 725 cm^{-1}. MS (m/e) 55, 111, 149, 208, 220, 250, 265 (M^+).

(4aRS, 5SR, 8aSR, 10RS)-(3-Hydroxypropyl)-10-methylhexahydro-1H-5,8a-propanoquinolin-7(8H)-one **11** via bridgehead enone route

To a mixture of 254 mg of compound **12** (0.59 mmol) and 222 mg of 3-amino-1-propanol (2.95 mmol) in 3 ml of THF was added a mixture of 99 mg of DBU (0.65 mmol) in 1 ml of THF at -78°C. The solution was warmed slowly to room temperature. The solution was diluted with water and extracted with

methylene chloride. The organic layer was dried and concentrated to afford 172 mg of product **11**. It was chromatographed using 5:95 methanol:chloroform to afford 156 mg of purified compound **11** (quantitative yield).

(±)-3,4-Dehydrolycopodine

To a mixture of 2530 mg of benzophenone (13.9 mmol) and 467 mg of potassium tert-butoxide (4.2 mmol) in 14 ml of dry benzene under nitrogen was added a solution of 368 mg (1.39 mmol) of compound **11** in 5 ml of dry benzene. The resulting mixture was heated at reflux for 2 h. After cooling to room temperature, the solution was diluted with 3N HCl to pH = 3 and extracted with ether. The aqueous layer was made basic (pH = 11) with aqueous 6N sodium hydroxide solution and extracted with methylene chloride. The organic layer was dried with potassium carbonate and concentrated. The crude product was chromatographed using 5:95 methanol:chloroform to afford 245 mg of product as a yellow-brown solid, in 72% yield, (mp = 104-105°C). NMR ($CDCl_3$) δ 0.88 (d, J = 5 Hz, 3 H), 1.1-3.9 (m, 19 H), 7.0 (bt, 1 H); C-13 NMR ($CDCl_3$) δ 21.13, 22.50, 25.62, 25.88, 26.86, 34.08, 41.23, 42.40, 43.12, 43.83, 48.12, 49.75, 58.01, 135.59, 138.19, 199.51; IR (CH_2Cl_2) 3025, 2920, 1680, 1610, 1460, 1425, 1245, 1215, 1115, 1010, 905, 750 cm^{-1}. MS (m/z) 55, 77, 91, 160, 188, 245 (M^+).

(±)Lycopodine **1**

To a solution of 331 mg (1.35 mmol) of dehydrolycopodine in 13 ml of methanol was added 13 mg of platinum (IV) oxide, and the resulting mixture was stirred under 1 atm of hydrogen for 15 h. The catalyst was removed by filtration and the solvent was evaporated to obtain 326 mg of crude product as a yellow solid. Sublimation of this solid (100°C, 0.001 torr) afforded 291 mg (87% yield) of (±)lycopodine as white needles. (m.p = 127-129°C) NMR ($CDCl_3$) δ 0.85 (d, J = 6 Hz, 3 H), 1.2-2.7 (m, 17 H), 2.9 (dd, J = 7 Hz and 3 Hz, 1 H), 3.12 (td, J = 12 Hz and 3 Hz, 2 H), 3.35 (td, J = 15 Hz and 3 Hz, 2 H); C-13 NMR ($CDCl_3$) δ 18.73, 19.46, 22.77, 25.11, 25.20, 26.08, 36.67, 42.43, 42.71, 42.82, 43.18, 44.93, 46.55, 47.14, 59.65, 77.63, 77.06, 77.48, 213.27; IR (CCl_4) 2920, 2800, 1700, 1450, 1350, 1310, 1215, 1110, 1090, 970, 900 cm^{-1}.

ACKNOWLEDGMENT

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