GELSEMINE MODEL STUDIES: ALKOXYMETHYLATIONS OF DECALONES AND INDOLES

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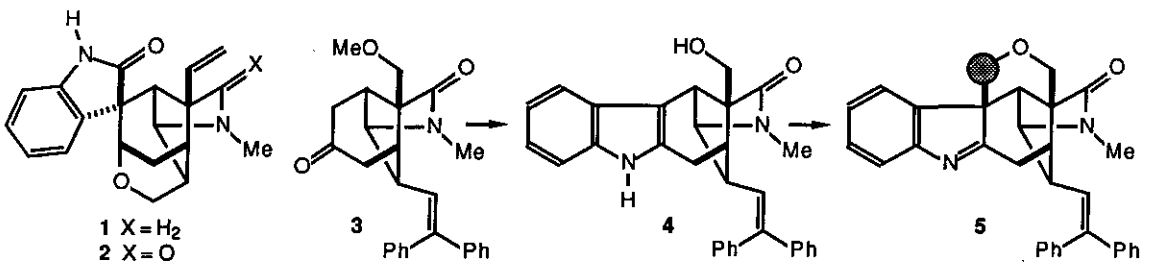
Abstract – Treatment of decalone (**11**) with acetone or dimethoxymethane and an appropriate acid gave tetrahydropyrans (**10**) (74%) and (**13**) (59%), respectively. Similar treatment of indole (**6**) with dimethoxymethane gave indoline (**14**) (59%). Attempts to effect similar reactions with indole (**4**) were unsuccessful.

During the course of studies directed toward syntheses of gelsemine (**1**) and 21-oxogelsemine (**2**), we examined an approach to the oxindole substructure outlined in Scheme 1.[1,2] We hoped to convert ketone (**3**) into indole (**4**) and then use the hydroxymethyl group to direct electrophilic reactions to afford indolines (**5**) that might serve as oxindole precursors. This communication describes model studies related to this goal.

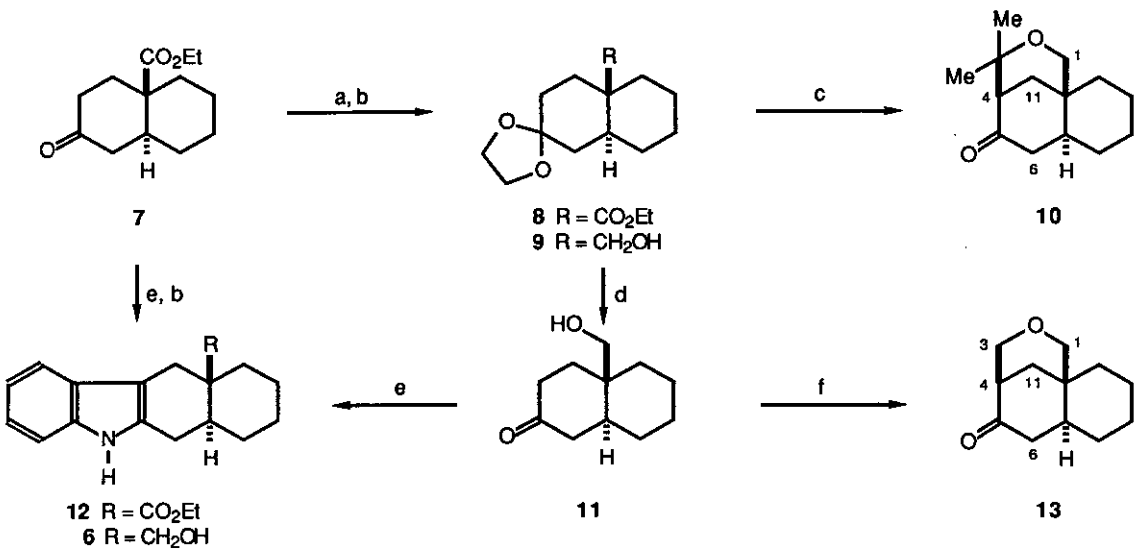
Scheme 1



Indole (**6**) was selected as a readily accessible model for **4**, and was prepared as outlined in Scheme 2. Ketalization of the known decalone (**7**) gave (**8**) (89%) which was subsequently reduced to afford **9** (88%).[3] Attempted ketal exchange gave tetrahydropyran (**10**) in 83% yield, but hydrolysis of **9** using hydrochloric acid in aqueous methanol did afford the desired ketol (**11**) in 81% yield.[4] Treatment of **11** with phenylhydrazine in acetic acid, followed by warming with boron trifluoride etherate, gave the target indole (**6**) in 76% yield.[4] A more efficient route from **7** to **6** was also developed. Thus, application of Fischer indole synthesis conditions to **7** gave **12** (80%) and lithium aluminum hydride reduction of the ester afforded indole (**6**) in 91% yield.[4]

The unexpected, although not surprising, conversion of **9** to **10** was encouraging, but before attempting reactions with **6**, alkoxymethylations of ketol (**11**) were examined. Thus, treatment of **11** with acetone and Dowex-50 (H^+) gave tetrahydropyran (**10**) in 74% yield. Conversion of **11** to **13** was also accomplished in 59% yield using excess dimethoxymethane and ethylaluminum dichloride in dichloromethane.[4,5]

Scheme 2

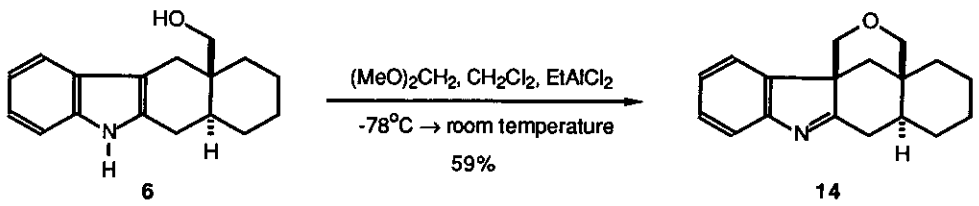


(a) $HOCH_2CH_2OH$, Dowex-50 (H^+) (b) $LiAlH_4$, THF (c) Dowex-50 (H^+), acetone (d) HCl, H_2O,MeOH (e) $PhNHNH_2$, AcOH, $BF_3 \bullet Et_2O$, 80°C (f) $(MeO)_2CH_2$, CH_2Cl_2, $EtAlCl_2$, -78°C → room temperature

We next examined methoxylation of **6** using conditions that had been successful with **11** and ultimately found that indoline (**14**) could be obtained in 59% yield (Scheme 3).[4] This result encouraged us to prepare indole (**4**), as shown in Scheme 4, to see if this result could be extended to a compound relevant to gelsemine.

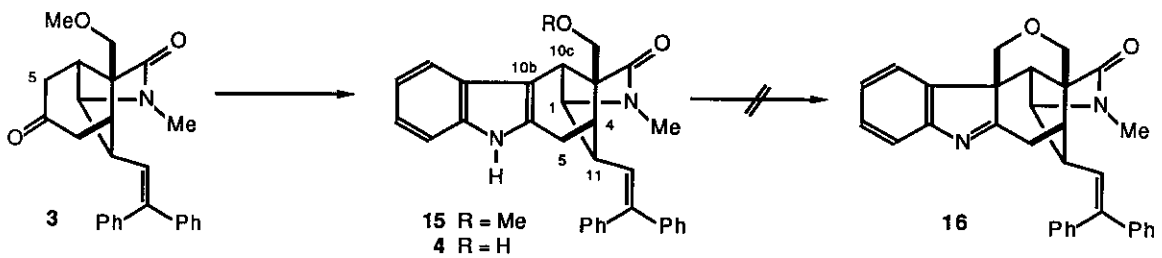
Treatment of the known ketone (**3**) with phenylhydrazine and boron trifluoride etherate in acetic acid gave indole (**15**) in 73% yield.[4,6] A series of decoupling experiments established the relationship between the C(4) methine proton and C(5) methylene protons, confirming that the expected regiochemical course had been followed in the Fischer indole synthesis.[6] Demethylation of **15** using boron tribromide in dichloromethane at -78°C proceeded smoothly to afford **4**.[4] Unfortunately, attempts to convert **4** to indoline (**16**) using a variety of conditions met with failure, as did attempts to direct other electrophiles to C(10b).[7] Thus, this approach to the oxindole portion of gelsemine was abandoned in favor of more promising results.[8]

Scheme 3



In conclusion, model studies directed toward alkaloids (**1**) and (**2**) have provided efficient access to complex tetrahydropyrans derived from decalone (**11**) and indole (**6**). Unfortunately, attempts to extend these results to indole (**4**) have not succeeded.

Scheme 4



REFERENCES AND NOTES

1. This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.
2. For other approaches to the oxindole portion of gelsemine see: I. Fleming and J. P. Michael, *J. Chem. Soc., Perkin Trans.* 1, 1981, 1549. I. Fleming, M. A. Loreto, J. P. Michael, and I. H. M. Wallace, *Tetrahedron Lett.*, 1982, **23**, 2053. I. Fleming, M. A. Loreto, I. H. M. Wallace, and J. P. Michael, *J. Chem. Soc., Perkin Trans. 1*, 1986, 349. K. Jones, M. Thompson, and C. Wright, *J. Chem. Soc., Chem. Commun.*, 1986, 115. G. Stork, M. E. Krafft, and S. A. Biller, *Tetrahedron Lett.*, 1987, **28**, 1035. M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130. W. G. Earley, E. J. Jacobsen, T. Oh, and L. E. Overman, *Tetrahedron Lett.*, 1988, **29**, 3785. A. Madin and L. E. Overman, *Tetrahedron Lett.*, 1992, **33**, 4859. R. J. Vijn, Ph. D. Thesis, University of Amsterdam, 1988. S. Wu, Ph. D. Thesis, The Ohio State University, 1991. J. K. Dutton, Ph. D. Thesis, University of Leeds, 1991.
3. A. Dreiding and A. J. Tomasewski, *J. Am. Chem. Soc.*, 1955, **77**, 411.
4. Selected data (mp, ^{1}H-nmr and ^{13}C-nmr) for new compounds are reported below. Compound **10**: ^{1}H-Nmr ($CDCl_3$) δ 1.02-1.62 (m with singlets at δ 1.08 and δ 1.29, 15H, CH_2 and CH_3), 1.78 (m, 1H, C(6a)H), 2.05 (dd, J = 14.4, 3.0 Hz, 1H, C(11)H), 2.23 (br s, 1H, C(4)H), 2.27 (dd, J = 14.7, 3.6 Hz, 1H, C(6)H), 2.80 (dd, J = 14.7, 12.1 Hz, 1H, C(6)H),

3.53 (d, J = 12.1 Hz, 1H, C(1)H), 4.26 (dd, J = 12.1, 2.7 Hz, 1H, C(1)H); ^{13}C-nmr ($CDCl_3$) δ 21.37 (t), 21.98 (q), 25.94 (t), 27.80 (q), 28.72 (t), 32.46 (s), 36.51 (t), 38.00 (t), 44.98 (d), 46.81 (t), 56.14 (d), 66.73 (t), 71.36 (s), 213.31 (s). Compound **6**: mp 241-242°C; ^{13}C-nmr ($CDCl_3$-DMSO) δ 21.37 (t), 26.03 (t), 26.99 (t), 28.65 (t), 30.58 (t), 34.06 (t), 37.30 (s), 40.44 (d), 57.36 (t), 107.58 (s), 109.92 (d), 117.05 (d), 117.68 (d), 119.68 (d), 127.40 (s), 132.71 (s), 135.58 (s). Compound **12**: mp 165-166.5°C; ^{13}C-nmr ($CDCl_3$) δ 14.08 (q), 23.58 (t), 26.43 (t), 28.29 (t), 29.65 (t), 34.22 (t), 38.23 (t), 41.11 (d), 47.06 (s), 59.73 (t), 107.92 (s), 110.30 (d), 117.62 (d), 118.96 (d), 120.87 (d), 127.49 (s), 133.97 (s), 135.91 (s), 175.10 (s). Compound **13**: ^{1}H-Nmr ($CDCl_3$) δ 1.04-1.81 (m, 11H, CH and CH_2 manifold), 2.39 (dd, J = 15.6, 1.3 Hz, 1H, C(6)H), 2.45 (br s, 1H, C(4)H), 2.71 (dd, J = 15.6, 13.0 Hz, 1H, C(6)H), 3.31 (dd, J = 11.7, 1.9 Hz, 1H, CH_2O), 3.58 (dd, J = 11.2, 2.1 Hz, 1H, CH_2O), 3.86 (d, J = 11.2 Hz, 1H, CH_2O), 4.49 (d, J = 11.7 Hz, 1H, CH_2O). Compound **14**: ^{13}C-Nmr ($CDCl_3$) δ 21.41 (t), 26.29 (t), 29.17 (t), 34.59 (s), 36.60 (t), 37.64 (t), 45.87 (d), 46.61 (t), 56.19 (s), 71.70 (t), 72.21 (t), 120.37 (d), 121.53 (d), 124.66 (d), 128.27 (d), 139.92 (s), 155.65 (s), 188.43 (s). Compound **15**: ^{1}H-Nmr ($CDCl_3$) δ 2.25 (br qu, 1H, C(4)H), 2.50 (dd, J = 16.8, 2.6 Hz, 1H, C(5)H), 2.80 (dt, J = 10.1, 2.5 Hz, 1H, C(11)H), 2.96 (dd, J = 16.8, 3.4 Hz, 1H, C(5)H), 3.11 (s, 3H, NMe), 3.24 (s, 3H, OMe), 3.34 (d, J = 9.6 Hz, 1H, CH_2O), 3.51 (t, J = 1.7 Hz, 1H, C(10c)H), 3.71 (d, J = 9.6 Hz, 1H, CH_2O), 3.73 (qu, J = 1.9 Hz, 1H, NCH), 5.90 (d, J = 10.1 Hz, 1H, =CH), 7.04-7.49 (m, 14 H, ArH), 7.82 (br s, 1H, NH); ^{13}C-nmr ($CDCl_3$) δ 27.68 (t), 30.84 (q), 42.36 (d), 47.00 (d), 49.74 (d), 59.72 (q), 59.75 (s), 67.49 (t), 70.95 (d), 108.81 (s), 110.81 (d), 117.50 (d), 119.53 (d), 121.28 (d), 126.95 (d), 127.12 (s), 127.29 (d), 127.33 (d), 128.11 (d), 128.20 (d), 128.40 (d), 129.42 (d), 132.40 (s), 136.31 (s), 139.62 (s), 141.69 (s), 143.26 (s), 176.15 (s). Compound **4**: ^{1}H-Nmr ($CDCl_3$) δ 2.25 (broad qu, 1H, C(4)H), 2.55 (dd, J = 17.0, 3.3 Hz, 1H, C(5)H), 2.86 (dt, J = 10.0, 2.5 Hz, 1H, C(11)H), 3.06 (dd, J = 17.0, 3.3 Hz, 1H, C(5)H), 3.13 (s, 3H, NMe), 3.38 (broad s, 1H, C(10c)H), 3.51 (d, J = 12.0 Hz, 1H, CH_2O), 3.75 (qu, J = 2.1 Hz, 1H, NCH), 3.84 (d, J = 12.0 Hz, 1H, CH_2O), 5.90 (d, J = 10.0 Hz, 1H, =CH), 7.04-7.45 (m, 14H, ArH), 7.91, (broad s, 1H, NH); ^{13}C-nmr ($CDCl_3$) δ 27.47 (t), 30. 91 (q), 41.87 (d), 48.38 (d), 49.18 (d), 56.75 (s), 59.60 (t), 71.70 (d), 111.22 (d), 115.20 (s), 117.53 (d), 119.90 (d), 121.67 (d), 127.13 (s), 127.26 (d), 127.68 (d), 127.72 (d), 128.04 (d), 128.53 (d), 128.74 (d), 129.69 (d), 132.90 (s), 136.54 (s), 139.84 (s), 141.96 (s), 143.96 (s), 178.55 (s).

5. To a solution of 100 mg (0.5 mmol) of **11** in 10 ml of dichloromethane-dimethoxymethane (1:1) at -78°C was added 1.5 ml (1.5 mmol) of 1.5 M ethylaluminum dichloride in dichloromethane. The mixture was stirred for 4 h at -78°C and 1 h at room temperature, cooled to -78°C, and 20 ml of 2 N aqueous sodium hydroxide was added. The aqueous layer was extracted with dichloromethane (3 x 20 ml). The extracts were dried (Na_2SO_4), concentrated, and the residue was chromatographed over 5 g of silica gel (EtOAc-hexane, 3:7) to give 63 mg (59%) of **13**.
6. For **3** and an indication that it enolizes toward C(5) see: J.-K. Choi, D.-C. Ha, D. J. Hart, C.-S. Lee, S. Ramesh, and S. Wu. *J. Org. Chem.*, 1989, **54**, 279.
7. For example, intramolecular trapping at C(10b) by Pummerer intermediates also failed: Y. Oikawa and O. Yonemitsu, *J. Org. Chem.* 1976, **41**, 1118. K. Cardwell, B. Hewitt, M. Ladlow, and P. Magnus, *J. Am. Chem. Soc.*, 1988, **110**, 2242 and references therein.
8. D. J. Hart and S. Wu, *Tetrahedron Lett.*, 1991, **32**, 4099.
9. We thank the National Institutes of Health for financial support.

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