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TWO NEW STEREOCHEMICALLY COMPLEMENTARY OXINDOLE SYNTHESES[1]

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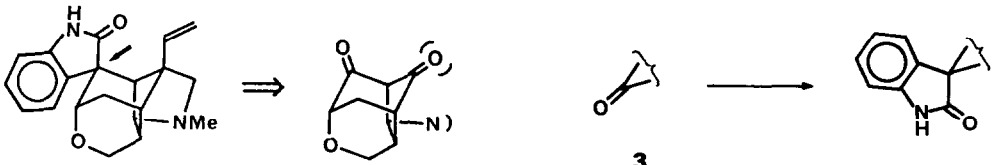
Summary-Two routes have been developed for the conversion of ketones to oxindoles in the general sense (**3**→**4**), with norbornanone, the two routes gave different oxindoles (**22** and **24**).

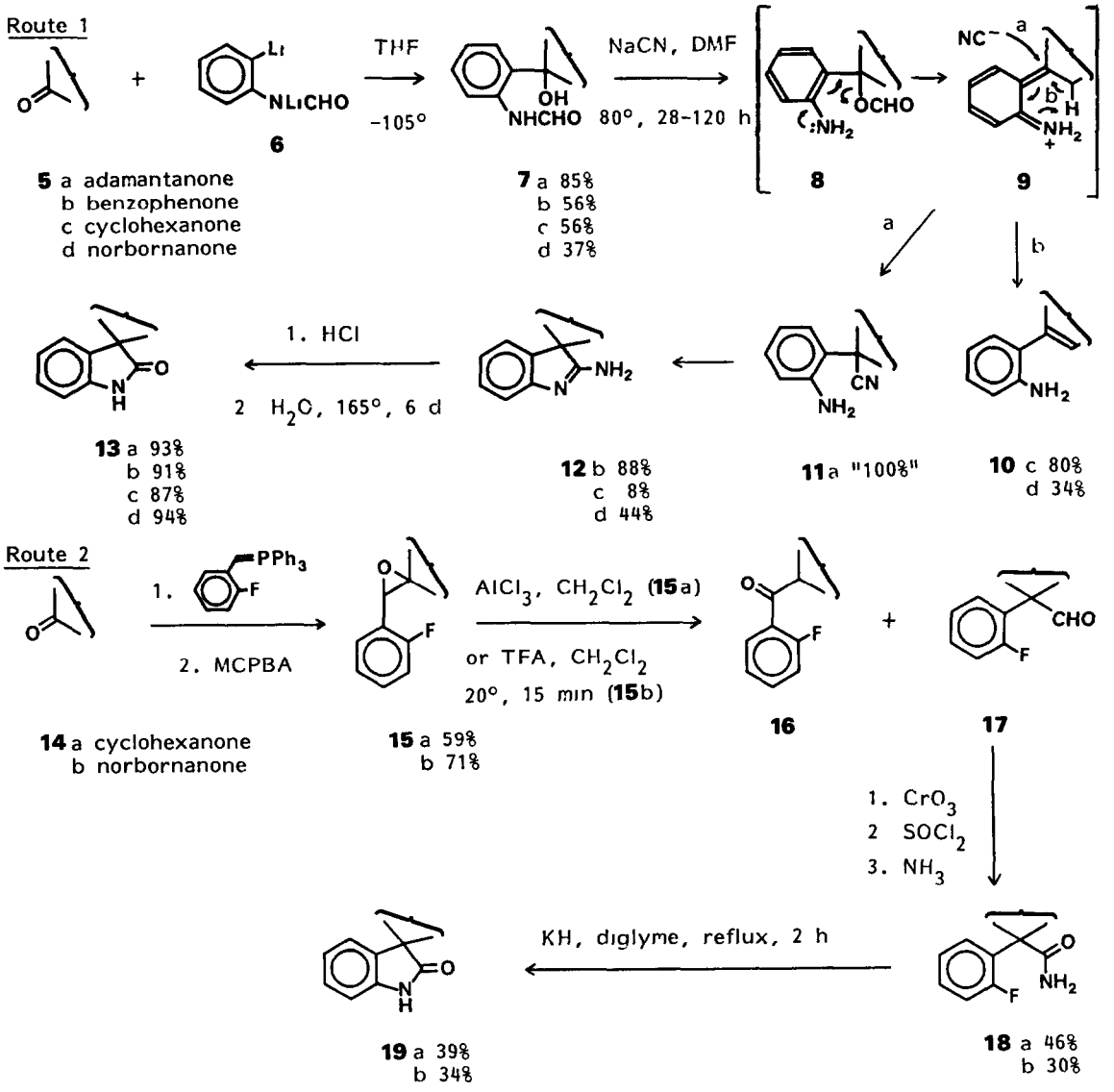
We have revealed elsewhere[2] our interest in the total synthesis of gelsemine (**1**), and that our plan is to prepare it from a ketone such as **2**. This idea has several attractive features, as others have also perceived,[3] one of which is that we are obliged to invent a synthesis of oxindoles in the general sense (**3**→**4**).[4] We report here two solutions to this problem, which have the advantage that they are stereochemically complementary



1 **2** **3** **4**

Route 1 In our first route, the aryl group was attached to the ketones (**5**) using the o-lithioformanilide salt (**6**), prepared by halogen-metal exchange between n-butyl-lithium and o-bromoformanilide. This reagent is not ideal halogen-metal exchange appears to be faster than the deprotonation of the amide, so that the first-formed intermediate quenches itself.[5,6] Nevertheless, this is minimised at -105°, and we got workable yields (37-56%) of the alcohols (**7**) from enolisable and non-enolisable ketones, when we used o-bromoformanilide and the ketone in a ratio of 1 1 In the case of adamantanone, we made some attempt to optimise the yield, and found that a 4 1 ratio gave conspicuously better results,[7] based on adamantanone, presumably because there was more of the reagent (**6**) actually present The alcohols (**7**) reacted with cyanide ion in DMF, without the need for acid catalysis, to give the aminonitriles (**11**). With adamantanone as starting material, we isolated **11**a directly by crystallisation, but with the other ketones, we found it easier to isolate the product after chromatography as the aminoindolenines (**12** b-d). Either the aminonitrile (**11**a) or the aminoindolenines (**12**b-d) gave the corresponding oxindoles (**13**)[8] in high yield when their hydrochlorides were heated in water.[9] The overall yield from adamantanone was 79% However, when the ketones were enolisable, the anilino-alkenes (**10**) were major by-products in the key step (**9**→**11**) We

speculate that the formyl group[10] is transferred from nitrogen to oxygen (**7** → **8**), and that the tertiary o-aminobenzyl formate (**8**) ionises to a highly stabilised cationic intermediate (**9**), which captures cyanide ion (**9** → **11**) or loses a proton (**9** → **10**), perhaps by a [1,5]-sigmatropic shift to nitrogen. Fortunately, this will not be a problem in the gelsemine synthesis

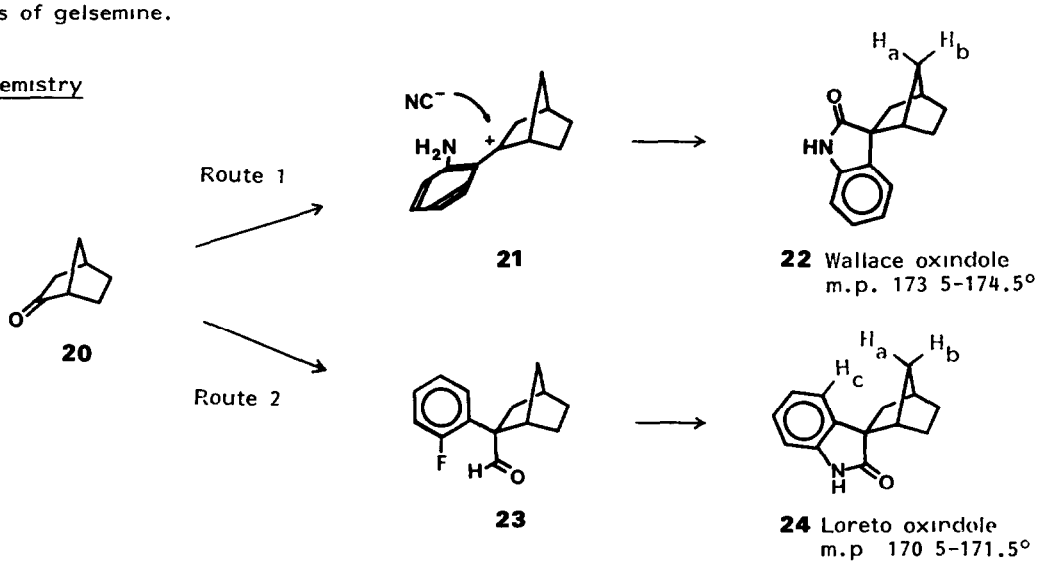


Route 2 In the second route, we prepared the epoxides (**15**) in two steps from o-fluorobenzyl bromide and the ketones (**14**), and then rearranged the epoxides in acid (**15** → **16** + **17**). In the cyclohexanone series, aryl migration was the major pathway (3 1), but, in the

norbornyl series, hydride shift was the major pathway (1.5 1) In both cases, much experimentation was needed before we found the best conditions. We then converted the aldehydes (**17**) into their amides (**18**), and these cyclised (**18** → **19**) in a reaction which is remarkable for the easy displacement of fluoride from an unactivated benzene ring.[11] We believe this step to have much potential, but we have not examined it in any detail yet, except to get the oxindoles (**19**) in characterisable amounts.

Stereochemistry In Route 1, the cyanide ion is the source of the carbonyl group in the oxindole ring, and we expected that it would approach the norbornyl-derived cation (**21**) from the exo direction to give the oxindole (**22**) Using this route, we got a single oxindole, m.p. 173 5-174.5°, which we call the Wallace oxindole. In Route 2, the aryl group is the second carbon to attack the carbon atom of the original carbonyl group, and again we expected that it would do so mainly from the exo side of the norbornyl ring, leading to the oxindole (**24**). In the event, the aldehyde produced (**23**) was a 5 1 mixture of stereoisomers, and the major isomer[12] was brought through to a single oxindole, m.p. 170.5-171.5°, which we call the Loreto oxindole. The two oxindoles were clearly different (spectroscopically[13] and mixed m p. 133-157°) The stereochemical assignments were confirmed when we took nuclear Overhauser difference spectra In each case we irradiated at the frequency of H_a, the Wallace oxindole showed strong enhancement only of the doublet from H_b, whereas the Loreto oxindole showed enhancement of the doublets both from H_b and from H_c. Thus Route 1 is appropriate for the synthesis of an oxindole in which the carbonyl carbon is to be attached to the less hindered face of a diastereotopic ketone group, and Route 2 is appropriate when the aryl ring is to be attached to the less hindered face. It remains to be seen which route is appropriate for the synthesis of gelsemine.

Stereochemistry



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NOTES and REFERENCES

1 No reprints available

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4 The existing methods for this transformation involve the homologation of a ketone either to an acid (and cyclisation of the hydrazide[14]) or to an α-hydroxy acid (and acid-catalysed cyclisation of the anilide[15])

5 This is not too surprising o-bromophenol[16] and o-bromobenzyl alcohol[17] probably do the same thing

6 Our attempts to deprotonate (LiH) before doing the halogen-metal exchange (BuLi) were frustrated by the precipitation of the lithium salt

7 n-Butyl-lithium (19 ml of a 1 6M solution in hexane, 3v 4 mmol) was added dropwise over 1 h to a stirred solution of o-bromoformanilide (3 12 g, 15 5 mmol) in dry THF (50 ml) under nitrogen keeping the internal temperature below -100°C After a further 3 h, a solution of adamantanone (0 62 g, 4 13 mmol) in dry THF (5 ml) was added, and the mixture allowed to warm to 0° over 3 5 h An aqueous ammonium chloride work-up using ethyl acetate as solvent gave a crude product (3 8 g), which was shaken with ethyl acetate (30 ml) The insoluble solid was virtually pure amino nitrile (**11a**)(920 mg 82%) and chromatography (SiO_2, EtOAc-light petroleum) gave a further crop (32 mg, 3%) A pure sample had m p 213-213 5° (from EtOAc)

8 The oxindole from adamantanone is new m p 245-247° (Found C 80 8 H 7 35 N 5 5 $C_{17}H_{19}NO$ requires C 80 6, H 7 55, N, 5 5%)

9 B Bobranski and Z Zborucki, Rocz Chim 42, 487 (1968)

10 We did not investigate to any significant extent the known o-aminophenyl-lithium reagents based on protection by a silyl group,[18] a pivaloyl group,[19] or a t-butoxycarbonyl group [20] We chose the formyl group in the hope that it would provide minimum steric hindrance to the step (**5** + **6** → **7**) and would be transferred from oxygen to nitrogen (**7** → **8**) particularly easily The ease of transfer is attested by the formation of benzoxazines when the alcohols (**7**) were kept in acetic acid for an hour or two

11 Displacement of fluoride from an unactivated benzene ring is not unknown B A Bolto, M Liveris and J Miller, J Chem Soc , 750 (1956)(MeONa MeOH, 200°), T Kauffmann and H Henkler, Chem Ber 96, 3159 (1963)(RNHNH$_2$, Et_2O, 34°, 4 h), C L Liotta and D F Pinholster, J Chem Soc , Chem Commun , 1245 (1969)(R_2NH, triethylene glycol, 195°), P Caubere and M -F Hochu, Bull Soc Chim Fr , 2854 (1969)(RSNa, HMPA-THF, 55°, 22 h, R_2NNa, HMPA-THF, 45°, 16 h), H Heany and A P Price, J Chem Soc Perkin Trans 1, 2911 (1972)(cyclisation of o-fluorocinnamic acid at 400°), R F Boswell, G C Helsley, R L Duncan, W H Funderburk, and D N Johnson, J Med Chem , 17, 1000 (1974)(RONa DMF, 70° 3 h) S M J Briscese and J M Riveros, J Am Chem Soc , 97, 230 (1975)(MeO^-, gas phase), A Walser, G Silverman, T Flynn, and R I Fryer J Heterocycl Chem , 12, 351 (1975)(cyclisation to a quinolone, NaH, DMF, reflux, 10 min), G M Brooke and R S Mathews, J Chem Soc , Perkin Trans 1, 372 (1979)(RONa, DMSO-Pr^{i}OH, 100° 10-1000 min), P Cogolli, F Maiolo, L Testaferri, M Tingoli, and M Tiecco J Org Chem 44, 2642 (1979)(RSNa, HMPA, 80°, 2 h)

12 The crude mixture of ketone (**16**) and aldehyde (**17**) was oxidised, and the acidic product (40%) separated from the non-acidic ketone (56%) The ratio of the stereoisomeric acids was measured using the MeO signals in the ^{1}H-NMR spectrum of the corresponding esters Recrystallisation of the acid removed the minor isomer, and gave the major in 30% yield based on the epoxide

13 Wallace oxindole ν_{max}($CHCl_3$) 3425, 3180br, 1700, and 1620, (Nujol) 3400 3150, 1700, and 1610 cm^{-1}, δ($CDCl_3$ 400 MHz) 7.50 (1H, br s, NH), 7 19 (1H t J 8 Hz, H_{O6}), 7 16 (1H d, J 8 Hz H_{O4}), 7 03 (1H t, J 7 5 Hz, H_{O5}), 6 86 (1H, d, J 8 Hz, H_{O7}), 2 60 (1H, d, J 10 Hz, $H_{B7\text{-}syn}$ = H_a), 2 47 (1H s with fine structure, H_{B1}), 2 30 (1H, s H_{B4}), 2 19 (1H, dt, J 12 and 1 Hz, $H_{B3\text{-}exo}$), 1 89 (1H, m, $H_{B6\text{-}endo}$), 1 80 (1H, m, $H_{B5\text{-}exo}$), 1 48 (3H, m, $H_{B3\text{-}endo}$ $H_{B5\text{-}endo}$, and $H_{B6\text{-}exo}$), and 1 41 (1H, d J 10 Hz, $H_{B7\text{-}anti}$ = H_b), ($CDCl_3$) 141 3s, 133 2s, 127 3d, 124 9d 121 5d, 109 5d 54 3s, 47 7d, 41 2t 38 0t 37 1d, 28 5t, and 26 5t, m/z 213 1158 (35%) and 146 (100%), Found C, 78 9 H, 7 2, N 6 4 $C_{14}H_{15}NO$ requires C, 78 8 H, 7 1 N 6 6% Loreto oxindole ν_{max}($CHCl_3$) 3425, 3180br, 1710, and 1610, (Nujol) 3265, 1700, 1665, and 1610 cm^{-1}, δ($CDCl_3$ 400 MHz) 8 24 (1H, br s, NH), 7 29 (1H, d, J 7 5 Hz, H_{O4} = H_c), 7 18 (1H ddd, J 8, 7 5 and 1 Hz, H_{O6}) 7 00 (1H, dd, J 8 and 7 Hz, H_{O5}), 6 86 (1H, d, J 8 Hz, H_{O4}) 2 50 (1H, s H_{B1}), 2 26 (1H, ddd, J 12, 5 δ, and 3 Hz, $H_{B6\text{-}endo}$), 2 21 (1H, d, J 2 5 Hz, H_{B4}), 2 10 (1H, d, J 10 Hz, $H_{B7\text{-}syn}$ = H_a), 1 90 (1H ddd? J 12 5, 3 5, and 3 Hz, $H_{B3\text{-}exo}$), 1 83 (1H, dd J 12 5 and 2 Hz, $H_{B3\text{-}endo}$), 1 63 (2H, m, $H_{B6\text{-}endo}$ and $H_{B6\text{-}exo}$), 1 47 (1H, d J 10 Hz, $H_{B7\text{-}anti}$ = H_b) and 1 26 (1H, m, $H_{B5\text{-}exo}$) ($CDCl_3$) 139 9 130 2, 127 4, 123 5, 122 1, 108 9 49 4, 42 0, 39 8 37 4, 28 0, and 23 6, m/z 213 1153 (25%) and 146 (100%), Found C 78 8 H 7 25 N, 6 8% The assignments were made with the help of double resonance experiments in the assignments, O = oxindole numbering B = bicycloheptane numbering, and syn and anti refer to the relationship of the bridge hydrogens to the oxindole ring

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