# A Formal Total Synthesis of Ipalbidine

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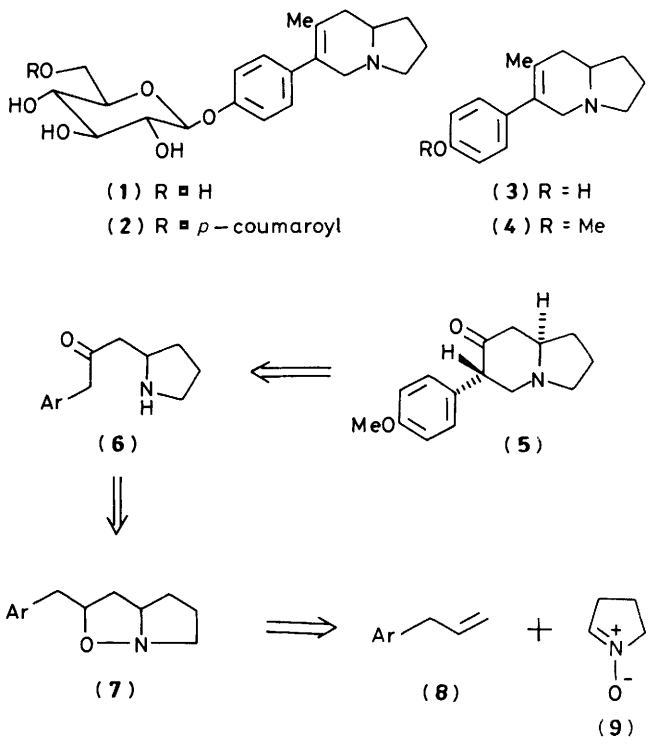
The synthesis of 1,2,3,5,8,9-hexahydro-6-(4-methoxyphenyl)indolizin-7(6*H*)-one (**5**), a key intermediate in the synthesis of (±)-ipalbidine (**3**), is described. The 1,3-dipolar cycloaddition of the nitrone (**9**) to *p*-methoxy(allyl)benzene (**8**) proceeded highly regio- and stereo-selectively to give the *trans*-hexahydropyrroloisoxazole (**10**). Reduction of compound (**10**) with zinc–aqueous acetic acid yielded the aminoalcohol (**14**) which was then converted into the amino ketone (**16**) *via* amino protection (carbamate), Collins oxidation, and deprotection. The direct cyclization of compound (**16**) to the indolizinone (**5**) by a Mannich reaction failed; however, treatment of the ketoformate (**20**), prepared from compound (**14**) *via N*-formylation followed by Collins oxidation, with aluminium t-butoxide resulted in cyclization to furnish the bicyclic ketone (**5**). This constitutes a formal total synthesis of (±)-ipalbidine.

The Ipomoea alkaloids, isolated from seeds of *Ipomoea alba* and *Ipomoea muricata*, comprise the two glycoside alkaloids ipalbine (**1**)[1] and ipomine (**2**),[2,3]† and their aglycone ipalbidine (**3**).[1] A unique structural feature of this class of alkaloids is that the *C*-methyl group is found on the hexahydroindolizine nucleus. They are the only example of naturally occurring indolizidine alkaloids.[4] We envisaged a synthetic approach to ipalbidine (**3**) *via* the bicyclic ketone (**5**) which can directly be transformed into *O*-methylipalbidine (**4**), a synthetic precursor of ipalbidine. Of the reported syntheses of ipalbidine,[5] three involved the intermediate (**5**); this has been prepared by Dieckmann condensation,[5a] intramolecular cyclization of an enamine,[5c] and vinylogous urethane.[5e] Our strategy for the synthesis of the bicyclic ketone (**5**) is outlined retrosynthetically in Scheme 1. The key features are the nitrone dipolar cycloaddition[6] yielding the isoxazolidine (**7**) and the methylene bridging of the pyrrolidine (**6**) between the nitrogen and the benzylic carbon.

The reaction of the nitrone (**9**) with *p*-methoxy(allyl)benzene (**8**) in refluxing toluene produced the cycloadduct (**10**) in 70% yield as a single diastereoisomer (Scheme 2). The high regioselectivity and stereoselectivity observed in this reaction are rationalized on the basis of the preference for dipole LUMO control[7] and an *exo*-oriented transition state,[8] respectively, when non-conjugated, electron-rich olefins such as (**8**) are used as dipolarophiles. Our first approach to the bicyclic ketone intermediate (**5**) was to employ the Mannich reaction with the β-amino ketone (**16**). The isoxazolidine (**10**) was thus converted into the β-aminoalcohol (**12**) in 68% yield *via* reductive N–O bond cleavage of the quarternary salt (**11**) with zinc and aqueous acetic acid. Oxidation of compound (**12**) using Collins reagent or pyridinium chlorochromate (PCC)–sodium acetate, however, resulted in unsatisfactory yields (6 and 31%, respectively) of the *N*-benzyl derivative of (**16**), *i.e.* (**13**).

We then considered utilizing the carbamate group for *N*-protection from oxidants; N–O bond cleavage of compound (**10**) by hydrogenolysis over palladium–carbon [affording (**14**)] followed by selective acylation provided the carbamate (**15**), which in turn was subjected to Collins oxidation to yield the ketocarbamate (**17**) in 73% yield. After deprotection of compound (**17**) by catalytic hydrogenation, the resulting labile amino ketone (**16**) was immediately heated with paraformaldehyde in 3-methylbutanol according to the reported




**Scheme 1.** Ar = *p*-$MeOC_6H_4$

Mannich procedure;[9] however, it gave an intractable mixture of polymerized products.

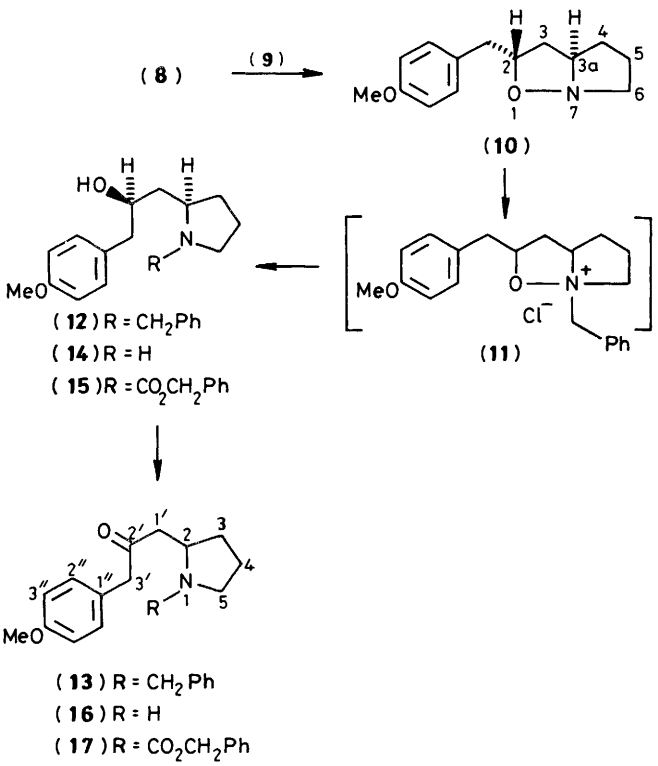
We then therefore tried another approach *via* internal aldol condensation using a more stable intermediate (Scheme 3). Thus, the aminoalcohol (**14**) was heated with formic acid in toluene to furnish the *N*-formylmethanol (**18**) together with the *N,O*-diformate (**19**). To selectively hydrolyse the *O*-formate group, this crude mixture was treated with ammonia in methanol to give the desired *N*-formylmethanol (**18**) in 69% yield [from (**14**)]. Subsequent Collins oxidation yielded the *N*-formyl ketone (**20**) in 72% yield. In the $^1H$ n.m.r. spectra of compounds (**18**) and (**20**), some of the signals appear in pairs, each with the same multiplicity, with intensities in the ratio 2.2:1 and 1:1, respectively. This is probably due to restricted rotation about the C–N bond of the *N*-formyl moiety caused by the partial double bond character. This conclusion was supported by the $^{13}C$ n.m.r. spectra which also showed pairs of

† The position of the *p*-coumaroyl group in ipomine previously published (4-position)[2] has been revised and is that represented in the present formula (**2**) (6-position).[3] In both the papers[2,3] cited, the ipalbidinyl portion in the formula for ipomine was depicted incorrectly.

**Table 1.** $^{13}C$ N.m.r. data (δ/p.p.m.) for the 1-pyrrolidinyl-3-(*p*-methoxyphenyl)propanes (**12**)—(**15**), (**17**), (**18**), and (**20**)[a]

| | Compound | | | | | | |
|---|---|---|---|---|---|---|---|
| Carbon | (**12**) | (**13**) | (**14**) | (**15**) | (**17**) | (**18**)[b] | (**20**)[c] |
| C-2 | 63.0 (d) | 60.1 (d) | 56.3 (d) | 54.6 (d) | 54.0 (d) | 51.7 (d) [51.7 (d)] | 51.7 (d), 53.0 (d) |
| C-3 | 28.1 (t) | 31.1 (t) | 30.2 (t) | 31.1 (t) | 30.9 (t) | 30.8 (t) [30.8 (t)] | 31.0 (t), 31.2 (t) |
| C-4 | 23.3 (t) | 22.2 (t) | 25.2 (t) | 23.5 (t) | 23.6 (t) | 23.1 (t) [22.1 (t)] | 22.3 (t), 23.8 (t) |
| C-5 | 53.8 (t) | 50.1 (t) | 45.7 (t) | 46.3 (t) | 45.7 (t) | 46.1 (t) [46.1 (t)] | 43.1 (t), 45.0 (t) |
| C-1′ | 34.6 (t) | 47.0 (t) | 38.2 (t) | 42.4 (t) | 46.4 (t) | 42.1 (t) [41.7 (t)] | 46.5 (t), 47.3 (t) |
| C-2′ | 70.0 (d) | 208.1 (s) | 70.1 (d) | 68.8 (d) | 207.0 (s) | 68.5 (d) [68.5 (d)] | 206.0 (s), 206.6 (s) |
| C-3′ | 43.6 (t) | 53.9 (t) | 43.1 (t) | 43.0 (t) | 49.5 (t) | 42.5 (t) [43.6 (t)] | 49.4 (t), 49.9 (t) |
| C-1″ | 131.0 (s) | 126.9 (s) | 131.2 (2) | 131.3 (s) | 126.1 (s) | 131.0 (s) [131.0 (s)] | 125.3 (s), 125.9 (s) |
| C-2″ | 130.2 (d) | 130.4 (d) | 130.3 (d) | 130.3 (d) | 130.3 (d) | 130.1 (d) [130.2 (d)] | 130.3 (d), 130.5 (d) |
| C-3″ | 113.6 (d) | 114.2 (d) | 113.7 (d) | 113.6 (d) | 114.1 (d) | 113.4 (d) [113.7 (d)] | 114.1 (d), 114.3 (d) |
| C-4″ | 157.9 (s) | 158.6 (s) | 158.0 (s) | 157.9 (s) | 158.6 (s) | 157.7 (s) [158.0 (s)] | 158.6 (s), 158.8 (s) |
| 4″-OMe | 55.1 (q) | 55.3 (q) | 55.2 (q) | 55.1 (q) | 55.2 (q) | 54.9 (q) [54.3 (q)] | 55.2 (q) |
| 1-$CO_2CH_2Ph$ | | | | 156.7 (s) | 154.6 (s) | | |
| 1-CHO | | | | | | 162.6 (d) [161.7 (d)] | 160.9 (d), 161.3 (d) |
| $C_6H_5CH_2$ | 58.8 (t) | 58.8 (t) | | 67.1 (t) | 66.6 (t) | | |
| $-C(CH)_4CH$ | 138.3 (s) | 139.2 (s) | | 136.6 (s) | 136.9 (s) | | |
| *o*-$C_6H_5$ | 128.9 (d) | 128.8 (d) | | 127.7 (d) | 127.9 (d) | | |
| *m*-$C_6H_5$ | 128.3 (d) | 128.2 (d) | | 128.4 (d) | 128.4 (d) | | |
| *p*-$C_6H_5$ | 127.1 (d) | 126.1 (d) | | 128.0 (d) | 127.9 (d) | | |

[a] Signal multiplicity is given in parentheses. [b] Signals belonging to the minor rotamer are reported in square brackets. [c] The duplicate sets of signals belonging to the two rotamers are reported.




**Scheme 2.**

signals, each with the same multiplicity, for each of the carbons in the molecule (Table 1).

The type of aldol reaction required in the present case is unusual as the amide C=O group is normally unreactive as the electrophilic partner.[10] However, the intramolecular aldol condensation of compound (**20**) was finally accomplished by treatment with aluminium t-butoxide in xylene and heating, according to Ban's method,[11] providing the bicyclic enaminone (**21**).

In the final stage to compound (**5**), lithium aluminium hydride reduction* of compound (**21**) resulted in (**22**), an over-reduction product, and a crystalline material that sublimed which was tentatively assigned the structure (**23**)† on the basis of the elemental analysis and spectral data (see Table 2 and Experimental section). Selective reduction of the olefinic moiety of compound (**21**) was achieved with lithium in liquid ammonia, giving the desired bicyclic ketone (**5**) in 54% yield. The synthetic compound (**5**) gave a satisfactory elemental analysis and $^{13}C$ n.m.r. data (Table 2). The stereochemical features of the product

* Reduction of enaminones with lithium aluminium hydride normally gives β-amino ketones (M. E. Kuehne, in 'Enamines: Synthesis, Structure, and Reactions,' ed. A. G. Cook, Mercel Dekker, New York, 1969, part XVI, ch. 8). However the alternative reduction of the carbonyl function in the enaminone group has also been claimed.[12]

† The conversion of compound (**21**) into (**23**) is tentatively explained by the sequence below, involving reduction to (i) followed by the formation of the aziridinium intermediate (**ii**),[13] which undergoes opening to give (**23**).[14]

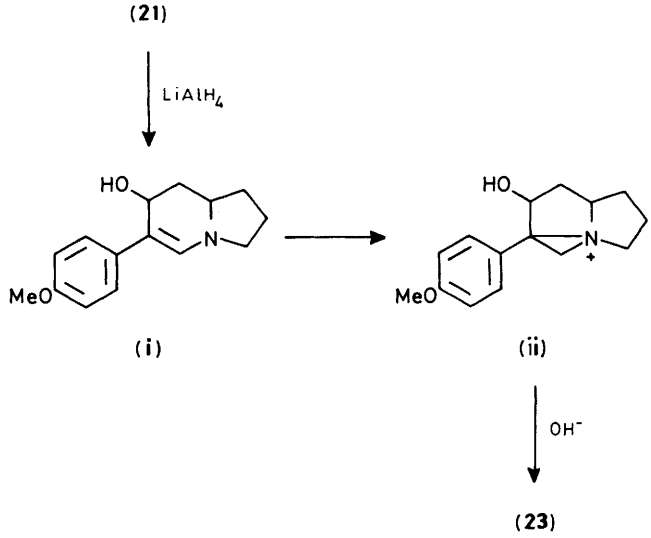
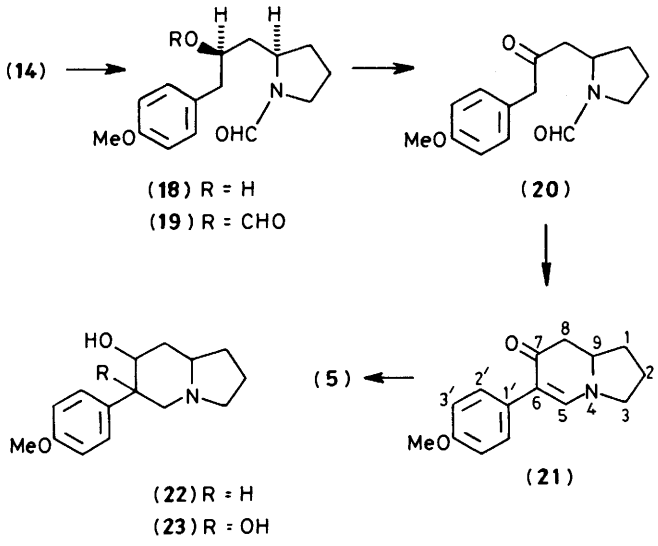


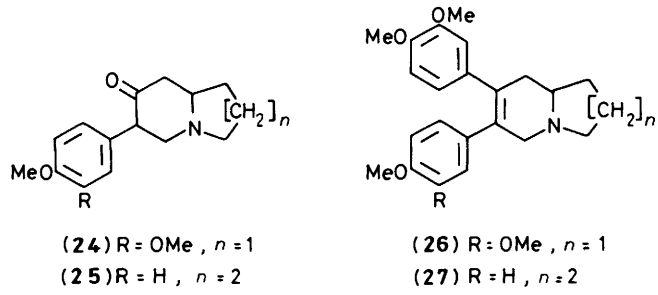
**Table 2.** $^{13}C$ N.m.r. data (δ/p.p.m.) for the indolizines (**21**)—(**23**) and (**5**)[a]

| Carbon | Compound (21) | (22) | (23) | (5) |
|---|---|---|---|---|
| C-1 | 32.9 (t) | 30.1 (t) | 29.9 (t) | 31.4 (t) |
| C-2 | 24.3 (t) | 21.8 (t) | 22.3 (t) | 22.5 (t) |
| C-3 | 49.7 (t) | 53.1 (t) | 53.0 (t) | 52.9 (t) |
| C-5 | 148.7 (d) | 57.1 (t) | 61.8 (t) | 58.2 (t) |
| C-6 | 109.4 (s) | 50.6 (d) | 74.5 (s) | 55.4 (d) |
| C-7 | 189.0 (s) | 73.5 (d) | 77.3 (d) | 208.1 (s) |
| C-8 | 42.2 (t) | 38.1 (t) | 35.5 (t) | 47.1 (t) |
| C-9 | 57.8 (d) | 63.1 (d) | 62.6 (d) | 64.9 (d) |
| C-1′ | 129.4 (s) | 132.0 (s) | 134.2 (s) | 128.5 (s) |
| C-2′ | 128.7 (d) | 129.2 (d) | 129.4 (d) | 130.2 (d) |
| C-3′ | 113.5 (d) | 114.3 (d) | 113.0 (d) | 113.9 (d) |
| C-4′ | 157.4 (s) | 158.9 (s) | 158.8 (s) | 158.7 (s) |
| 4′-OMe | 55.3 (q) | 55.3 (q) | 55.2 (q) | 55.2 (q) |

[a] Signal multiplicity is given in parentheses.



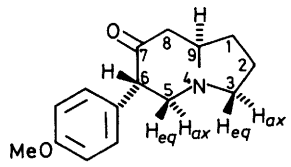

Scheme 3.




were established unequivocally by a detailed analysis of the 270 MHz $^1H$ n.m.r spectrum, facilitated by a series of decoupling experiments (Table 3). The other spectral data (i.r. and mass spectra) were identical with those reported in the literature.[5e] Compound (**5**) has already been converted into (±)-ipalbidine (**3**) *via* *O*-methylipalbidine (**4**);[5a,c] thus our preparation of the ketone intermediate (**5**) represents a formal total synthesis of racemic compound (**3**).

We believe that the synthetic methodology developed here involving a [3 + 2] dipolar cycloaddition followed by an intramolecular ring closure with the *N*-formyl aldol acceptor should be generally applicable to the preparation of bicyclic ketone intermediates, *e.g.* (**24**) and (**25**), of other related alkaloids such as septicine (**26**) and julandine (**27**).

**Table 3.** $^1H$ N.m.r. data for 1,2,3,5,8,9-hexahydro-6-(*p*-methoxyphenyl)-indolizin-7(6*H*)-one (**5**)




| Hydrogen | δ(p.p.m.)[a] | J(Hz) | Double resonance experiments[b] |
|---|---|---|---|
| 1-, 2-H | 1.5—2.1 (m) | | |
| 3-$H_{ax}$ | 2.28 (q)[c] | 9.0 | 3-$H_{eq}$→t |
| 3-$H_{eq}$ | 3.18 (dt)[c] | 9.0, 1.5 | 3-$H_{ax}$→br d |
| 5-$H_{ax}$ | 2.56 (dd) | 11.4, 11.2 | 5-$H_{eq}$→d |
| 5-$H_{eq}$ | 3.47 (dd) | 11.4, 6.3 | 5-$H_{ax}$→d, 6-H[d]→d |
| 6-H | 3.77—3.84 (m) | | 5-$H_{eq}$→br d |
| 8-, 9-H | 2.42—2.64 (m) | | |
| 3′-, 5′-H | 6.87 (ABq) | 8.9 | |
| 2′-, 6′-H | 7.06 (ABq) | 8.9 | |
| OMe | 3.79 (s) | | |

[a] Chemical shifts with multiplicities in parentheses. [b] The signal irradiated and the resulting multiplicity. [c] Assigned according to ref. 15. [d] Irradiated at δ 3.80.

## Experimental

M.p.s were determined on a Yanagimoto micro apparatus. I.r. spectra were recorded on a Hitachi 215 spectrophotometer. $^1H$ and $^{13}C$ N.m.r. spectra were measured with a JEOL JNM-FX 270 instrument at 270 and 67.8 MHz, respectively, using tetramethylsilane as the internal standard and deuteriochloroform as the solvent. Mass spectra were obtained with a JEOL JMS-D 300 mass spectrometer and a Hitachi M-80 double focusing mass spectrometer equipped with Hitachi M-003 data processing system. Gas chromatographic analysis was conducted on a Shimadzu GC-7AG instrument with a 1-m column of Silicone 2% OV-1 on Chromosorb W AW DMCS (60—80 mesh). T.l.c. was run on Merck precoated silica gel 60-F 254 plates. Merck silica gel 60 (230—400 mesh) was used for column chromatography.

trans-2,3,3a,4,5,6-*Hexahydro*-2-(4-*methoxybenzyl*)*pyrrolo*-[1,2-b]*isoxazole* (**10**).—A mixture of *p*-allylanisole (**8**) (1.60 g, 10.8 mmol) and the dihydropyrrolium oxide (**9**) (0.92 g, 10.8 mmol) in toluene (15 ml) was heated under reflux for 4 h. After removal of the solvent under reduced pressure, the residual oil was purified by column chromatography [silica gel, diisopropyl ether–benzene (1:9 v/v)] to give the *isoxazolidine* (**10**) (1.76 g, 70%) as a colourless oil (Found: $M^+$, 233.1389. $C_{14}H_{19}NO_2$ requires *M* 233.1414); $\nu_{max.}$($CHCl_3$) 1 615, 1 230br, and 1 030 $cm^{-1}$; $\delta_H$ 1.46—2.22 (6 H, series of m, 3-$H_2$, 4-$H_2$, and 5-$H_2$), 2.69, 2.94 (each 1 H, dd, *J* 13.5, 6.5 Hz, Ar$CH_2$), 3.13 (2 H, t, *J* 6.8 Hz, 6-$H_2$), 3.66—3.85 [1 H, m, 3a-H with 3 H, s at δ 3.78 (OMe)], 4.22 (1 H, m, 2-H), and 6.83, 7.13 (4 H, ABq, *J* 8.4 Hz, ArH); *m/z* 233 ($M^+$, 10%), 199 (17), 148 (13), 121 (100), and 86 (36). G.l.c. analysis (180 °C column temperature) showed this product to be a single isomer.

1-*Benzyl*-2β-[(2R*)-*hydroxy*-3-(4-*methoxyphenyl*)*propyl*]-*pyrrolidine* (**12**).—A mixture of compound (**10**) (2.21 g, 9.5 mmol) and benzyl chloride (1.32 g, 10.4 mmol) in methanol (30 ml) was stirred at ambient temperature overnight and con-

centrated under reduced pressure. The residual oil was dissolved in 50% aqueous acetic acid (80 ml) and to this solution was added zinc dust (7 g). The mixture was stirred at 50 °C for 10 h, cooled, basified with 30% KOH, extracted with chloroform, and filtered through a Celite pad. The organic phase was washed with saturated aqueous NaCl and dried ($Na_2SO_4$). The solvent was evaporated to give a pale yellow oil, which was solidified by cooling. The solid material was recrystallized from hexane to give the *benzylaminoalcohol* (**12**) (2.1 g, 68%) as pale yellow prisms, m.p. 68—70 °C (Found: C, 77.6; H, 8.45; N, 4.3. $C_{21}H_{27}NO_2$ requires C, 77.5; H, 8.35; N, 4.3%); $\nu_{max.}$($CHCl_3$) 3 400—3 100 $cm^{-1}$; $\delta_H$ 1.45—1.90 (6 H, series of m, 3-$H_2$, 4-$H_2$, and $ArCH_2CHCH_2$), 2.06 (1 H, dd, *J* 16.0, 9.9 Hz, 5-H), 2.59 [1 H, dd, *J* 13.3, 6.7 Hz, $ArCHCH(OH)$], 2.83—2.91 [3 H, m, 2-, 5-H, and $ArCHCH(OH)$], 3.07 (1 H, d, *J* 12.5 Hz, $NCHPh$), 3.79 (3 H, s, OMe), 4.15—4.30 [1 H, m, $CHOH$ with 1 H, d, *J* 12.5 Hz at δ 4.20 ($NCHPh$)], 6.83 (2 H, d, *J* 8.6 Hz, 3″- and 5″-ArH), 7.17 (2 H, d, *J* 8.6 Hz, 2″- and 6″-ArH), and 7.2—7.3 (5 H, unresolved, phenyl); *m/z* 325 ($M^+$, 0.5%), 204 (8), 160 (90), 121 (43), and 91 (100).

1-(1-*Benzylpyrrolidin*-2-*yl*)-3-(4-*methoxyphenyl*)*propan*-2-*one* (**13**).—(*a*) *Collins oxidation of compound* (**12**). To a stirred and cooled (5—10 °C) solution of the Collins reagent,[16] prepared from $CrO_3$ (8.09 g) in dichloromethane (80 ml), was added a solution of compound (**12**) (2.0 g, 6.15 mmol) in the same solvent.The mixture was stirred at ambient temperature for 40 min, then poured into ice–water (150 ml) containing conc. ammonia (15 ml) and the organic phase was separated, dried ($Na_2SO_4$), and evaporated. The dark red oily product was purified by column chromatography on silica gel (chloroform) to give the *benzylamino ketone* (**13**) (120 mg, 6%) as a pale yellow oil (Found: $M^+$, 323.1902. $C_{21}H_{25}NO_2$ requires *M*, 323.1884); $\nu_{max.}$($CHCl_3$) 1 705 $cm^{-1}$; $\delta_H$ 1.36 (1 H, m, 3-H), 1.64 (2 H, m, 3- and 4-H), 2.06 (1 H, m, 4-H), 2.14 (1 H, dd, *J* 17.8, 8.9 Hz, 5-H), 2.49 (1 H, dd, *J* 16.5, 8.6 Hz, $ArCH_2COCH$), 2.73—2.88 (3 H, m, 2-, 5-H, and $ArCH_2COCH$), 3.24 (1 H, d, *J* 13.0 Hz, $ArCHCO$), 3.60 (2 H, s, $NCH_2Ph$), 3.77 (3 H, s, OMe), 3.83 (1 H, d, *J* 13.0 Hz, $ArCHCO$), 6.84 (2 H, d, *J* 8.6 Hz, 3″- and 5″-ArH), 7.08 (2 H, d, *J* 8.6 Hz, 2″- and 6″-ArH), and 7.15—7.3 (5 H, m, phenyl); *m/z* 323 ($M^+$, 10%), 164 (10), 160 (48), 121 (87), and 91 (100).

(*b*) *Oxidation of compound* (**12**) *with PCC*. To a stirred, ice-cooled mixture of PCC (4.00 g, 18.6 mmol) and sodium acetate (0.30 g, 3.7 mmol) in dichloromethane (50 ml) was added a solution of compound (**12**) (2.00 g, 6.15 mmol) in the same solvent (20 ml). The mixture was stirred at ambient temperature for 1 h, the supernatant was separated by decantation and the precipitated dark red gum was washed with dichloromethane. The combined organic phase was washed with 10% $Na_2CO_3$, dried ($Na_2SO_4$), and evaporated. The resulting dark red gum was diluted with chloroform (5 ml) and developed on a silica gel column. Elution with benzene then benzene–methanol (99:1 v/v) gave a pale yellow oil (**13**) (620 mg, 31%). The following fraction contained recovered starting material (210 mg, 11%).

2β-[(2R*)-*Hydroxy*-3-(4-*methoxyphenyl*)*propyl*]*pyrrolidine* (**14**).—To a stirred solution of compound (**10**) (6.20 g, 26.6 mmol) in methanol (150 ml) was added 5% Pd–C (2.3 g) and a stream of hydrogen was passed over the mixture for 24 h. Removal of the catalyst by filtration and evaporation of the solvent gave a colourless viscous oil which solidified with time on cooling. It was recrystallized from benzene–hexane to give the *aminoalcohol* (**14**) (5.13 g, 82%) as colourless needles, m.p. 95—97 °C; $\nu_{max.}$($CHCl_3$) 3 350—3 100 $cm^{-1}$; $\delta_H$ 1.35—1.95 (6 H, series of m, 3-, 4-$H_2$, and $ArCH_2CHCH_2$), 2.60 (1 H, dd, *J* 13.5, 6.5 Hz, $ArCH$), 2.75—2.95 [2 H, m, 5-$H_2$ with 1 H, dd, *J* 13.5, 6.5 Hz at δ 2.76 ($ArCH$)], 3.42 (1 H, br s, 2-H), 3.75 (3 H, s, OMe), 4.00 (1 H, br s, $CHOH$), *ca.* 5.5 (1 H, br s, NH), and 6.81, 7.10 (4 H, ABq, *J* 8.5 Hz, ArH); *m/z* 234 ($M^+$ − 1, 8%), 216 (9), 215 (13), 200 (5), 121 (11), 114 (21), and 70 (100). The analytical sample was prepared as the *picrate* which was recrystallized from ethanol to give yellow needles, m.p. 164—165 °C (Found: C, 51.45; H, 5.2; N, 11.9. $C_{14}H_{21}NO_2 \cdot C_6H_3N_3O_6$ requires C, 51.7; H, 5.2; N, 12.05%).

1-*Benzyloxycarbonyl*-2β-[(2R*)-*hydroxy*-3-(4-*methoxyphenyl*)*propyl*]*pyrrolidine* (**15**).—To a stirred, cooled (0—5 °C) solution of compound (**14**) (3.00 g, 12.8 mmol) in chloroform (30 ml) containing pyridine (1.5 ml) was added dropwise a 30% w/w solution (7.27 g) of benzyloxycarbonyl chloride (2.18 g, 12.8 mmol) in toluene during 30 min. The mixture was then allowed to warm to room temperature and stirring was continued overnight. After the mixture had been concentrated under reduced pressure the residual oil was diluted in chloroform, washed successively with water, 5% HCl, and 5% NaOH, and dried ($Na_2SO_4$). Evaporation of the solvent and purification by chromatography on a silica gel column, eluting with benzene followed by benzene–methanol (99:1 v/v), gave the *hydroxycarbamate* (**15**) (2.64 g, 56%) as a colourless oil [Found: ($M^+$ − 1) 368.1845. $C_{22}H_{26}NO_4$ requires (*M* − 1) 368.1860; Found: ($M^+$ − 2) 367.1796. $C_{22}H_{25}NO_4$ requires (*M* − 2) 367.1782]; $\nu_{max.}$($CHCl_3$) 3 430 and 1 675 $cm^{-1}$; $\delta_H$ 1.36—2.04 (6 H, series of m, 3-, 4-$H_2$, and $ArCH_2CHCH_2$), 2.62 (1 H, dd, *J* 13.8, 5.6 Hz, $ArCHCHOH$), 2.78 (1 H, dd, *J* 13.8, 7.2 Hz, $ArCHCHOH$), 3.37 (2 H, m, 5-$H_2$), 3.66—3.85 [1 H, m, $ArCH_2CHOH$ with 3 H, s at δ 3.77 (OMe)], 4.25 (1 H, br s, 2-H), 5.12 (2 H, s, $PhCH_2O$), 6.82 (2 H, d, *J* 8.2 Hz, 3″- and 5″-H), 7.12 (2 H, d, *J* 8.2 Hz, 2″- and 6″-H), and 7.33 (5 H, s, phenyl); *m/z* 367 ($M^+$ − 2, 75%), 351 ($M^+$ − $H_2O$, 3), 248 (32), 232 (24), 204 (84), 160 (100), 121 (93), and 91 (91).

1-(1-*Benzyloxycarbonylpyrrolidin*-2-*yl*)-3-(4-*methoxyphenyl*)*propan*-2-*one* (**17**).—To a stirred solution of the Collins reagent, prepared from $CrO_3$ (10.0 g) in dichloromethane (130 ml), was added a solution of compound (**15**) (1.80 g, 4.88 mmol) in the same solvent (60 ml) and the mixture was stirred at ambient temperature for 3 h. Ice–water (120 ml) was added to the mixture and the separated organic layer was washed with water, 5% HCl, then 5% $Na_2CO_3$, and dried ($Na_2SO_4$). After removal of the solvent by evaporation, the resulting product was purified by chromatography on a silica gel column, eluting with benzene then benzene–methanol (99:1 v/v), to give the *ketocarbamate* (**17**) (1.30 g, 73%) as a colourless oil (Found: $M^+$, 367.1777. $C_{22}H_{25}NO_4$ requires *M*, 367.1781); $\nu_{max.}$($CHCl_3$) 1 700sh and 1 680 $cm^{-1}$; $\delta_H$ 1.57 (1 H, m, 3-H), 1.76 (2 H, m, 4-$H_2$), 2.04 (1 H, m, $ArCH_2COCH$), 2.46 (1 H, m, 3-H), 3.13 (1 H, m, $ArCH_2COCH$), 3.38 (2 H, m, 5-$H_2$), 3.49 (1 H, br s, $ArCHCO$), 3.64 (1 H, br s, $ArCHCO$), 3.78 (3 H, s, OMe), 4.22 (1 H, br s, 2-H), 5.09, 5.12 (2 H, ABq, *J* 12.0 Hz, $PhCH_2O$), 6.80—7.12 (4 H, m, ArH), and 7.34 (5 H, s, phenyl); *m/z* 367 ($M^+$, 68%), 246 (7), 232 (16), 204 (30), 160 (34), 121 (53), and 91 (100).

3-(4-*Methoxyphenyl*)-1-*pyrrolidin*-2-*ylpropan*-2-*one* (**16**).—Compound (**17**) (180 mg, 0.49 mmol) was hydrogenated at 1 MPa over 5% Pd–C (80 mg) in methanol at room temperature for 4 h. Removal of the catalyst by filtration followed by evaporation of the solvent gave the ketocarbamate (**16**) as a viscous oil; $\nu_{max.}$($CHCl_3$) 3 350, 3 200, and 1 710 $cm^{-1}$. There was no carbonyl absorption due to the benzyloxycarbonyl group in the expected 1 675—1 680 $cm^{-1}$ range. After several hours in the air this product became coloured, and dark after a few days.

1-*Formyl*-2β-[(2R*)-*hydroxy*-3-(4-*methoxyphenyl*)*propyl*]-*pyrrolidine* (**18**).—A mixture of compound (**14**) (3.60 g, 15.3

mmol) and formic acid [0.71 g, 15.4 mmol (0.72 g of 99% $HCO_2H$)] in toluene (150 ml) was heated under reflux using a Dean–Stark trap for the azeotropic removal of water for 5 h. Evaporation of the solvent under reduced pressure left an oil. The i.r. spectrum of the product exhibited a weak to medium carbonyl band due to the formate group at 1 725 $cm^{-1}$ as well as very strong band due to the formamide group at 1 650 $cm^{-1}$, suggesting the concomitant formation of a small amount of the diformyl compound (**19**). The resulting product was then diluted in methanol (50 ml), a saturated methanolic solution of ammonia (1 ml) was added, and the mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was diluted with chloroform, washed with saturated aqueous NaCl, and dried ($Na_2SO_4$). The oily product was chromatographed on a silica gel column, eluting initially with benzene followed by benzene–methanol (99:1 v/v), to give the N-*formylmethanol* (**18**) (2.78 g, 69%) as a colourless oil [Found: ($M^+ - H_2O$) 245.1411. $C_{15}H_{19}NO_2$ requires ($M - H_2O$), 245.1414]; $\nu_{max.}$($CHCl_3$) 3 400 and 1 650 $cm^{-1}$; $\delta_H$ 1.41 – 2.12 (6 H, series of m, 3-, 4-$H_2$, and $ArCH_2CHCH_2$), 2.60, 2.77 (1:2.2 ratio, total 2 H, dd, *J* 13.5, 6.5 Hz, $ArCH_2$), 3.31 (1 H, m, 5-H), 3.48 (1 H, br m, 5-H), 3.64—3.82 [1 H, br m, CHOH including signals at δ 3.74, 3.75 (2.2:1 ratio, total 3 H, s each, OMe)], 4.11, 4.33 (1:2.2 ratio, total 1 H, br s each, 2-H), 6.79, 6.80 (2.2:1 ratio, total 2 H, A part of ABq each, *J* 9.0 Hz, 3′- and 5′-ArH), 7.10, 7.12 (1:2.2 ratio, total 2 H, B part of ABq each, *J* 9.0 Hz, 2′- and 6′-ArH, and 8.10, 8.22 (2.2:1 ratio, total 1 H, s each, N···CH···O); *m/z* 263 ($M^+$, 0.2%), 245 ($M^+ - H_2O$, 22), 142 (81), 122 (37), 121 (52), 99 (25), 98 (100), and 70 (64).

1-(1-*Formylpyrrolidin*-2-*yl*)-3-(4-*methoxyphenyl*)*propan*-2-*one* (**20**).—A solution of compound (**18**) (2.95 g, 11.2 mmol) in dichloromethane (50 ml) was treated with the Collins reagent, prepared from $CrO_3$ (21 g), in a manner similar to that described for compound (**17**). Purification of the crude oil by column chromatography (silica gel, benzene) gave the N-*formyl ketone* (**20**) (2.11 g, 72%) as a colourless oil (Found: $M^+$, 261.1351. $C_{15}H_{19}NO_3$ requires *M*, 261.1363); $\nu_{max.}$($CHCl_3$) 1 710 and 1 655 $cm^{-1}$; $\delta_H$ 1.57 (1 H, m, 4-H), 1.71—2.24 (3 H, series of m, 3-$H_2$ and 4-H), 2.48—2.80 (1 H, m, $ArCH_2COCH$), 3.16—3.22 (1 H, m, $ArCH_2COCH$), 3.38—3.56 (2 H, m, 5-$H_2$), 3.61, 3.64 (1:1 ratio, total 2 H, s each, $ArCH_2$), 3.79, 3.80 (1:1 ratio, total 3 H, s each, OMe), 4.26 (1 H, m, 2-H), 6.85, 6.87 (1:1 ratio, total 2 H, A part of ABq each, *J* 9.0 Hz, 3′- and 5′-ArH), 7.09, 7.11 (1:1 ratio, total 2 H, B part of ABq each, *J* 9.0 Hz, 2′- and 6′-ArH), and 8.21, 8.22 (1:1 ratio, total 1 H, s each, N···CH···O); *m/z* 261 ($M^+$, 52%), 140 (63), 122 (22), 121 (100), 112 (8), 99 (21), 98 (78), and 70 (83).

2,3,8,9-*Tetrahydro*-6-(4-*methoxyphenyl*)*indolizin*-7(1H)-*one* (**21**).—A mixture of compound (**20**) (2.00 g, 7.66 mmol) and aluminium t-butoxide (3.0 g, 12.2 mmol) in xylene (130 ml) was heated under reflux for 10 h, then cooled, poured into a flask containing ice–water (30 ml), and basified with conc. aqueous ammonia. After filtration through Celite, the organic phase was separated and the aqueous phase was extracted with chloroform. Both organic phases were combined and dried ($Na_2SO_4$). Evaporation of the solvent and column chromatography [silica gel, benzene–chloroform (1:1 v/v)] of the residue gave the *enaminone* (**21**) (670 mg, 36%) as colourless needles (acetone–hexane), m.p. 121—122 °C (Found: C, 73.85; H, 6.95; N, 5.6. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.05; N, 5.75%); $\nu_{max.}$ ($CHCl_3$) 1 625sh and 1 587 $cm^{-1}$; $\delta_H$ 1.70—2.28 (4 H, series of m, 1- and 2-$H_2$), 2.50 (2 H, m, 8-$H_2$), 3.54 (2 H, m, 3-$H_2$), 3.71—3.88 [1 H, br m, 9-H with 3 H, s at δ 3.77 (OMe)], 6.85, 7.29 (4 H, ABq, *J* 9.0 Hz, ArH), and 7.36 (1 H, s, 5-H); *m/z* 243 ($M^+$, 100%), 228 (56), 200 (5), 186 (5), 132 (18), 122 (7), 117 (9), 96 (18), and 89 (9).

*Lithium Aluminium Hydride Reduction of Compound* (**21**).—To a stirred, ice-cooled mixture of $LiAlH_4$ (40 mg) in dry THF (20 ml) was added dropwise a solution of compound (**21**) (40 mg, 0.165 mmol) in dry THF (10 ml) during 15 min and the mixture was stirred at room temperature. After 15 h t.l.c. showed that no starting material remained. The crude product after work-up was chromatographed on a neutral alumina column eluting with benzene then benzene–methanol (99:1 v/v). The first fraction was found to consist of 7-*hydroxy*-6-(4-*methoxyphenyl*)*indolizidine* (**22**) (4 mg, 10%) as a colourless oil (Found: $M^+$, 247.1564. $C_{15}H_{21}NO_2$ requires *M*, 247.1570); $\nu_{max.}$($CHCl_3$) 3 350br $cm^{-1}$; $\delta_H$ 1.4—2.3 (9 H, series of m, 1-, 2-$H_2$, 3-$H_{ax}$, 6-H, 8-$H_2$, and 9-H), 2.80 (1 H, m, 5-$H_{ax}$), 3.10 (1 H, m, 3-$H_{eq}$), 3.15 (1 H, m, 5-$H_{eq}$), 3.72—3.82 (1 H, m, 7-H with 3 H, s at δ 3.81 (OMe)] and 6.89, 7.20 (4 H, ABq, *J* 8.0 Hz, ArH); *m/z* 247 ($M^+$, 22%), 246 (21), 149 (2), 135 (14), 134 (100), 122 (12), 121 (14), 100 (28), and 84 (45).

The second fraction contained 6,7-*dihydroxy*-6-(4-*methoxyphenyl*)*indolizidine* (**23**) (15 mg, 35%) as colourless needles (ethyl acetate–hexane), m.p. 193—194 °C (with sublimation) (Found: C, 68.5; H, 8.2; N, 5.3. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%); $\nu_{max.}$($CHCl_3$) 3 560 and 3 420 $cm^{-1}$; $\delta_H$ 1.3—2.2 (8 H, series of m, 1-, 2-$H_2$, 3-$H_{ax}$, 8-$H_2$, and 9-H), 2.33 (1 H, A part of ABq, *J* 10.9 Hz, 5-$H_{ax}$), 3.03 (1 H, br t, *J* 8.0 Hz, 3-$H_{eq}$), 3.35 (1 H, B part of ABq, *J* 10.9 Hz, 5-$H_{eq}$), 3.71 (1 H, dd, *J* 11.5, 4.5 Hz, 7-H), 3.81 (3 H, s, OMe) 6.88 (2 H, d, *J* 9.0 Hz, 3′-and 5′-ArH), and 7.93 (2 H, dd, *J* 9.0 Hz, 2′- and 6′-ArH); *m/z* ($M^+$, 34%), 245 ($M^+ - H_2O$, 17), 160 (11), 150 (13), 134 (25), 128 (42), 114 (23), 98 (40), 97 (45), and 84 (100).

1,2,3,5,8,9-*Hexahydro*-6-(4-*methoxyphenyl*)*indolizin*-7(6H)-*one* (**5**).—To a solution of lithium (16 mg, 2.3 mmol) in liquid ammonia (40 ml) was added dropwise with stirring at −78 °C a solution of compound (**21**) (240 mg, 0.99 mmol) in dry THF (7 ml). The initial purple colour disappeared during the reaction. After 30 min, the mixture was quenched by the addition of ammonium chloride and allowed to warm to room temperature to evaporate the ammonia. The residual mixture was poured into a flask containing ice–water (30 ml) and extracted with chloroform. The organic layer was washed with saturated aqueous NaCl, dried ($Na_2SO_4$), and evaporated. The resulting residue was chromatographed on a silica gel column with benzene–chloroform (5:1 v/v) to give the product (**5**) (130 mg, 54%) as colourless prisms (hexane), m.p. 109—110 °C (lit., m.p. 105—106 °C;[5a] 105.5—106 °C;[5c] 109—110 °C[5e]) (Found: C, 73.1; H, 7.75; N, 5.75. $C_{15}H_{19}NO_2$ requires C, 73.45; H, 7.8; N, 5.7%); $\nu_{max.}$($CHCl_3$) 2 940, 2 800, 1 715, 1 620, and 1 516 $cm^{-1}$; *m/z* 245 ($M^+$, 30%), 134 (100), 133 (18), 131 (2), 119 (8), 97 (16), 96 (17), 91 (10), and 69 (8).

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