Synthesis of *N*-Acetyl-1,3-dimethyltetrahydroisoquinolines by Intramolecular Amidomercuration: Stereochemical Aspects

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Abstract: Mercury(II)-mediated ring closure of *N*-[1-(2-allyl-3-benzyloxy-4,6-dimethoxyphenyl)ethyl]acetamide **4** afforded *N*-acetyl-5-benzyloxy-6,8-dimethoxy-1,3-*trans*-dimethyl-1,2,3,4-tetrahydroisoquinoline **3**. The product was shown to exist as a mixture of rotamers by NMR spectroscopy, since signals coalesced at higher temperatures. 2-[2-[1-(Acetylamino)ethyl]-6-(benzyloxy)-3,5-dimethoxyphenyl]-1-methylethyl methanesulfonate **8** was also cyclized with sodium hydride to afford rotameric products with the same isoquinoline skeleton, but as a mixture of 1,3-*cis*- and *trans*-dimethyl isomers.

Key words: amidomercuration, cyclization, isoquinoline, Mitsunobu, rotamers

The range of biological activities displayed by isoquinoline alkaloids makes them perennially interesting compounds to chemists and life scientists alike.[1] Much recent attention has been devoted, for example, to the korupensamines such as **1** (korupensamine B) and their binaphthyl dimers, for example michellamine B, which show antimalarial and anti-HIV properties respectively (Figure 1).[2]

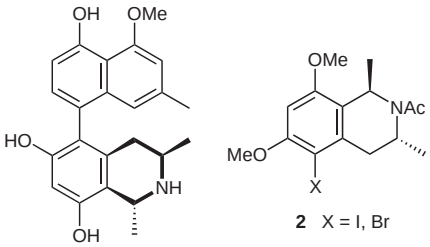

Figure 1

As a result, a number of groups have reported syntheses of these compounds[3] and their analogues.[4] In general the syntheses rely on the assembly of a suitably substituted tetrahydroisoquinoline, e.g. **2**, and the coupling of this unit with an appropriate naphthalene. Published syntheses of the tetrahydroisoquinoline nucleus of many naturally occurring products, including the michellamines, frequently make use of the Bischler–Napieralski,[5] Pomeranz–Fritsch[6] or Pummerer[7] reactions.

In this paper[8] we describe a novel approach to an *N*-acetyltetrahydroisoquinoline possessing a substitution pattern common to several of the korupensamine and michellamine naphthylisoquinoline alkaloids. This approach incorporates amidomercuration methodology for the construction of the tetrahydroisoquinoline **3** from **4** (Figure 2). This methodology relies on an unusual N/C-3 disconnection[9] as shown in the diagram below rather than the traditional N/C-1/Ar disconnection. Furthermore, the product is a mixture of *N*-acetyl rotamers.

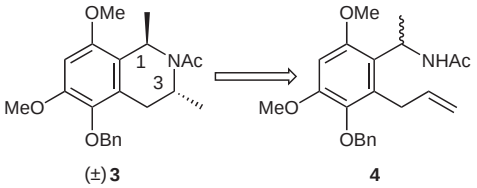

Figure 2

The aromatic alcohol **5**, an intermediate we have also used for making isochromane ring systems,[4h,i] was treated with phthalimide under Mitsunobu conditions[10] as shown in Scheme 1 to yield imide **6**. Exposure of **6** to methylamine[11] afforded an unstable primary amine that was immediately treated with acetic anhydride and pyridine to produce amide **4**.[12] We were now in a position to test whether we could access the tetrahydroisoquinoline system by forming the N/C-3 bond. Using as analogy the synthesis of isochromanes[13] by oxymercuration of hydroxyalkenes related to **4**, we envisaged making the target system by intramolecular amidomercuration. Although this type of reaction has been well investigated,[14,15] it appears to have no precedent in the isoquinoline series.

Reaction of **4** with mercury(II) acetate[13] in a 1:1 water–tetrahydrofuran mixture followed by reduction with sodium borohydride gave the desired *N*-acetyl-1,3-*trans*-dimethyltetrahydroisoquinoline **3** as a mixture of rotamers in a poor yield of 21%. The low yield was due to the competitive reaction of water with the mercurinium intermediate[14c] to give the secondary alcohol **7** as a mixture of diastereomers in 54% yield. The formation of unwanted alcohol **7** could be suppressed by reaction of amide **4** with mercury(II) acetate in dry tetrahydrofuran, affording the 1,3-*trans*-dimethyl product **3** as a mixture of rotamers in a yield of 56% as the major product.[16] A small amount (~10%) of the *cis*-isomer was also evident as shown by NMR spectroscopy.

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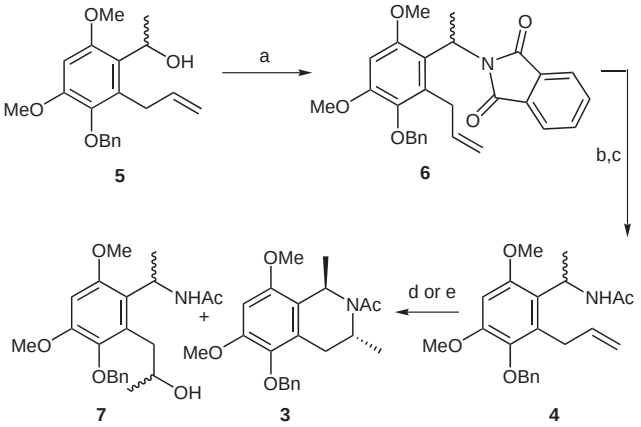


Scheme 1 *Reagents and conditions*: a, Phthalimide, DEAD, Ph_3P, THF (86%); b, $MeNH_2$, EtOH–C_6H_6; c, Ac_2O, pyridine (61% over 2 steps); d, $Hg(OAc)_2$, THF–H_2O, then $NaBH_4$–NaOH, then chromatography on SiO_2 (**3**, 21%; **7**, 54%); e, $Hg(OAc)_2$, THF, then $NaBH_4$–NaOH, then chromatography on SiO_2 (**3**, 56%; **7**, 0%).

The ^{1}H NMR spectrum of tetrahydroisoquinoline **3** was quite complex owing to substantial peak doubling.[17] It was postulated that rotamers of **3** exist in solution as a result of hindered rotation of the amide, giving rise to this doubling phenomenon.[18] This hypothesis was substantiated with variable temperature ^{1}H NMR spectroscopy experiments and molecular modelling.[19] NOE spectroscopy[20] indicated that the methyl groups on the heterocyclic core had a *trans*-relationship, implying that the heterocyclic ring adopts a boat-like conformation (Figure 3, a). Both methyl substituents appear to occupy *pseudo*-axial positions to minimise 1,3-allylic strain[21] (Figure 3, b).

As we had reasonable quantities of the unwanted alcohol **7** we also examined the conversion of this intermediate into tetrahydroisoquinolines. Reaction of **7** with methanesulfonyl chloride and triethylamine (Scheme 2) afforded mesylate **8** in quantitative yield. Exposure of **8** to sodium hydride resulted in cyclization to afford tetrahydroisoquinolines **3** and **9** (85% yield) as an equimolar, inseparable mixture of 1,3-*cis*- and *trans*-dimethyl isomers, each occurring as a pair of amide rotamers.[22] The formation of a mixture of *cis*- and *trans*-cyclized products by nucleophilic displacement of mesylate by the amide nitrogen is a consequence of **8** being a mixture of diastereomers.

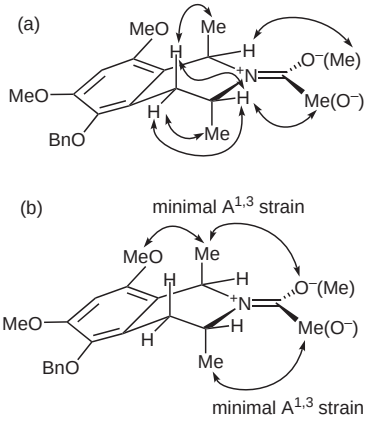
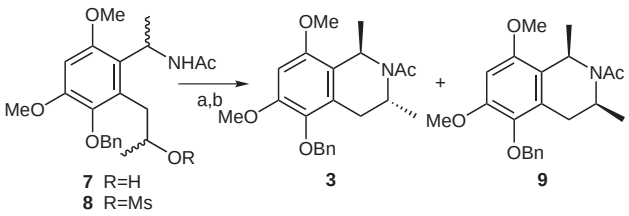


Figure 3 (a) Significant NOE interactions in **3**. (b) Minimisation of $A^{1,3}$ strain in **3**.



Scheme 2 *Reagents and conditions:* a, MsCl, CH_2Cl_2, Et_3N (100%); b, NaH, THF (85%).

We have thus been successful in synthesizing an isoquinoline with the aromatic substitution pattern common to several of the korupensamine and michellamine alkaloids, albeit in racemic form, using a novel amidocyclization reaction. Work is now in progress to investigate the generality of this approach for the preparation of substituted isoquinolines and we plan to extend this to other natural products.

Acknowledgment

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(12) **Spectroscopic Data for 4.** ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.47–7.26 (5 H, m, 5 × PhH), 6.79 (1 H, br d, *J* = 9.3 Hz, NH), 6.49 (1 H, s, 5-H), 6.01–5.93 (1 H, m, 2′-H), 5.46–5.42 (1 H, m, C*H*CH_3), 5.02–4.85 (2 H, m, 3′-H), 4.91 (1 H, d, *J* = 10.8 Hz, OCH_2), 4.86 (1 H, d, *J* = 10.8, OCH_2), 3.90 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.64–3.63 (2 H, m, 1′-H), 1.92 (3 H, s, $COCH_3$), 1.40 (3 H, d, *J* = 6.9 Hz, CHC*H*$_3$). ^{13}C NMR (100.63 MHz; $CDCl_3$): δ = 168.4 (C=O), 154.4, 152.1, 140.2 (3 × ArC–O), 137.9 (ArC–C), 136.9 (2′–C), 132.5 (ArC–C), 128.2, 127.8, 127.6 (3 × PhC), 122.2 (ArC–C), 115.4 (3′–C), 96.2 (5-C), 74.9 (OCH_2), 55.9, 55.6 (2 × OCH_3), 43.7 (*C*HCH$_3$), 30.7 (1′-C), 23.6 (CO*C*H$_3$), 20.9 (CH*C*H$_3$). IR (thin film): ν_{max} = 3331 br (N–H st), 2876 m (C–H st, O–CH_2), 2837 m (C–H st, O–CH_3), 1637 vs (C=O st), 1597 (ArC=C st) cm^{-1}; MS (EI): *m*/*z* = M$^+$ 369.1933 ($C_{22}H_{27}NO_4$ requires 369.1940), 369 (M$^+$, 14%) 326(1), 278(77), 219(86) 204(16), 193(84), 189(16), 91(40), 43(16).

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(16) $Hg(OAc)_2$ (0.27 g, 0.85 mmol, 1.5 mol equiv) was added to amide **4** (0.19 g, 0.51 mmol) dissolved in THF (10 cm^3). The yellow mixture was then stirred, in the dark, under argon for 21 h at 25 ºC. A further portion of $Hg(OAc)_2$ (0.18 g, 0.51 mmol, 1 mol equiv) was added and the mixture was stirred for a further 18 h. A mixture of $NaBH_4$ (0.049 g, 1.3 mmol, 2.5 mol equiv) in aq NaOH (5 cm^3, 2.5 M) was then added whilst stirring. After stirring for a further 1 h a sat. aq Na_2CO_3 solution (5 cm^3) was added and the mixture was stirred for 20 min. The reaction was allowed to stand for 30 min and the THF was removed under reduced pressure. Sat. brine solution (10 cm^3) and Et_2O (10 cm^3) were added and the mixture was extracted with diethyl ether (3 × 10 cm^3). The organic extracts were combined, filtered through alumina to remove traces of Hg, dried ($MgSO_4$) and evaporated in vacuo. Preparative layer chromatography on silica gel (EtOAc–hexane–aq NH_4OH, 66:33:1) afforded the 1,3-*trans*-dimethyl cyclized product **3** (0.11 g, 56%) as a light yellow oil.

(17) The product **3** showed two distinct sets of signals in its ^{1}H NMR spectrum, indicating rotamers about the amide C–N bond. **Spectroscopic Data for 3**. ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.43–7.32 (10 H, m, 10 × PhH), 6.44 (1 H, s, 7-H), 6.43 (1 H, s, 7-H), 5.50 (1 H, q, *J* = 6.4 Hz, 1-H), 5.16 (1 H, q, *J* = 6.6 Hz, 1-H), 4.95–4.86 (4 H, m, 2 × OCH_2), 4.68–4.62 (1 H, m, 3-H), 4.23–4.15 (1 H, m, 3-H), 3.91 (6 H, s, 2 × OCH_3), 3.86 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.99 (2 H, dd, *J* = 15.2 and 2.4 Hz, 4-H *pseudo*-equatorial), 2.64–2.54 (2 H, m, 2 × 4-H *pseudo*-axial), 2.24 (3 H, s, $COCH_3$), 2.17 (3 H, s, $COCH_3$), 1.28 (6 H, d, *J* = 6.6 Hz, 2 × 1-CH_3), 0.84 (3 H, d, *J* = 6.2 Hz, 3-CH_3), 0.83 (3 H, d, *J* = 6.1 Hz, 3-CH_3); ^{13}C NMR (50.32 MHz; $CDCl_3$): δ = 170.0, 169.7 (2 × N*C*OCH$_3$), 151.9, 151.5, 151.4, 150.7, 138.9, 139.0 (6 × ArC–O), 137.6, 137.5, 129.0 (3 × ArC–C), 128.5, 128.5, 128.3, 128.0 (4 × PhC), 119.5, 118.6 (2 × ArC–C), 95.2, 94.9 (2 × 7-C), 75.2 (OCH_2), 55.9, 55.6, 55.6 (3 × OCH_3), 49.1, 46.7 (2 × 1-C), 46.3, 44.4 (2 × 3-C), 28.6, 27.8 (2 × 4-C), 23.3, 22.3, 22.3, 21.3, 20.9, 19.2 (6 × CH_3). IR (thin film): ν_{max} = 2820 m (C–H st, OCH_3), 1635 vs (C=O st), 1583 m (ArC = C st) cm^{-1}; MS (EI): *m*/*z* = M$^+$ 369.1931 ($C_{22}H_{27}NO_4$ requires 369.1940), 369 (M$^+$, 20%) 354(83), 278(95), 263(9), 219(78), 193(100), 91(34), 43(16).
Heating compound **3** in an NMR tube in toluene-d_8 up to 90 °C resulted in coalescence of the two sets of signals. Characteristic chemical shifts in the ^{1}H NMR spectrum: δ = 2.99 ppm (doublet of doublets, *J* = 15.2 and 2.4 Hz) and δ = 2.64–2.54 ppm (multiplet) for the *pseudo*-equatorial and *pseudo*-axial protons at C-4 respectively. Four sets of signals corresponding to the two protons at C-1 and C-3 were also clearly visible as quartets at δ = 5.50 (*J* = 6.4 Hz) and 5.16 (*J* = 6.6 Hz) ppm and as multiplets at δ = 4.68–4.62 and 4.23–4.15 ppm respectively. The ^{13}C NMR spectrum also showed two characteristic sets of resonances: at δ = 49.1 and 46.7 (C-1) ppm, δ = 46.3 and 44.4 (C-3) ppm and δ = 28.6 and 27.8 (C-4) ppm.

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(20) For isomer **3**, the C-1 methyl substituent showed an NOE with the H-4 *pseudo*-axial proton, indicating that the C-1 methyl substituent must be *pseudo*-axial. For the *cis*-isomer **9** the same NOE was seen, as well as an NOE between the 1-methyl and 3-methyl substituents, thereby fixing the *cis*-arrangement. Therefore in isomer **3** the C-1 methyl and C-3 methyl groups must be *trans*.

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(22) NaH (60% in oil, 0.03 g, 0.86 mmol, 10 mol equiv) was added to mesylate **8** (0.040 g, 0.086 mmol), dissolved in anhyd THF (10 cm^3), under an argon atmosphere. The reaction mixture was stirred for 18 h, after which the mixture was cooled to 0 ºC. Water (10 cm^3) was added dropwise and the mixture was extracted with diethyl ether (2 × 10 cm^3). The organic solvent was washed with brine (10 cm^3), dried and concentrated in vacuo. Preparative layer chromatography on silica gel (EtOAc–hexane–aq NH_4OH, 66:33:1) afforded an equimolar mixture of the 1,3-*trans*-dimethyl product **3**, its 1,3-*cis*-dimethyl isomer **9** (0.027 g, 85%) as rotamers about the N–Ac bond.