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Amide rotamers of *N*-acetyl-1,3-dimethyltetrahydroisoquinolines: synthesis, variable temperature NMR spectroscopy and molecular modelling

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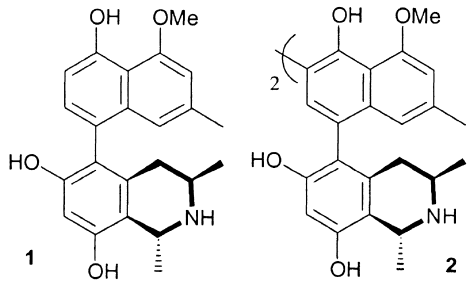
Abstract—Mercury(II)-mediated ring closure of *N*-[1-(2-allyl-3-benzyloxy-4,6-dimethoxyphenyl)ethyl]acetamide **9** afforded *N*-acetyl-5-benzyloxy-6,8-dimethoxy-1,3-*trans*-dimethyl-1,2,3,4-tetrahydroisoquinoline **8**. The product was shown to exist as a mixture of amide rotamers by NMR spectroscopy, since signals coalesced at higher temperatures. Variable temperature NMR spectroscopy and molecular modelling were used to investigate these rotamers and gave average values for the barrier of rotation in the range of 15–16 kcal mol^{-1}. 2-[2-[1-(Acetylamino)ethyl]-6-(benzyloxy)-3,5-dimethoxyphenyl]-1-methylethyl methanesulfonate **17** was also cyclized with sodium hydride to afford the same rotameric products with the same tetrahydroisoquinoline skeleton, but as a mixture of 1,3-*trans*- and *cis*-dimethyl isomers.

1. Introduction

Our interest in the isoquinoline alkaloids arises from their fascinating range of biological activities.[1] We[2] have been specifically interested in the naphthylisoquinoline alkaloids,[3] of which the korupensamines such as **1** (korupensamine B) and their binaphthyl dimers **2** (e.g. michellamine B) are prime examples. These intriguing compounds have been shown to possess anti-malarial and anti-HIV properties respectively.[4]



A number of groups have reported syntheses of these compounds[5] and their analogues.[2a,b,d,6] In general (Fig. 1), the syntheses rely on the assembly of a suitably substituted tetrahydroisoquinoline, e.g. **3**, and the coupling of this unit with an appropriate substituted naphthalene **4**.[7] Published syntheses of the tetrahydroisoquinoline nucleus[8] of many naturally occurring products, including the michellamines, frequently make use of well-known named reactions such as (a) the Bischler–Napieralski reaction which entails the formation of the C-1/Ar bond followed by reduction,[9] (b) the Pictet–Spengler[9a,10] reaction (N/C-1/Ar), (c) the Pummerer[11] reaction (C-4/Ar) or (d) the Pomeranz–Fritsch reaction.[12] The traditional disconnections for the first three methods are shown in Figure 1.

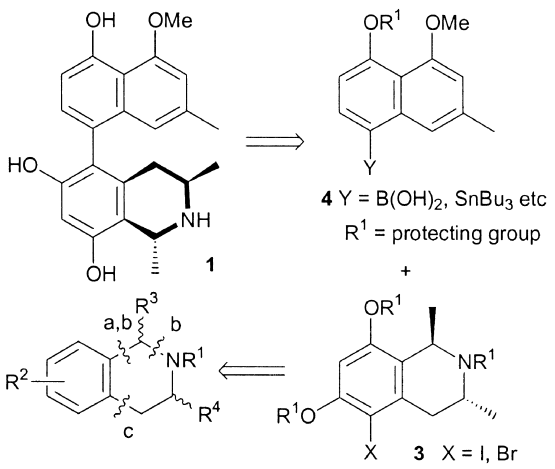


Figure 1. Traditional disconnections for naphthyltetrahydroisoquinoline alkaloids and substituted tetrahydroisoquinolines.

Keywords: isoquinolines; amides; mercury and compounds; rotamers; NMR; molecular modelling.

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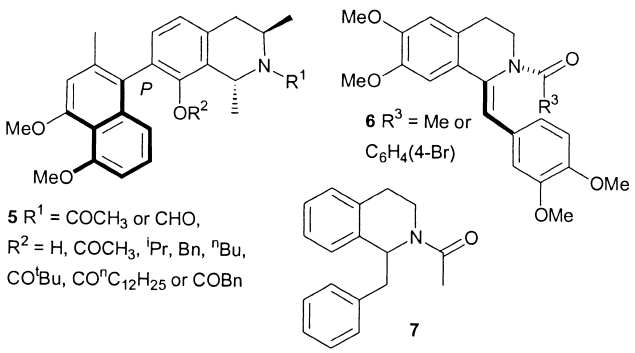
In a previous communication we have described the synthesis of *N*-acetyltetrahydroisoquinolines using novel methodology.[2d] Two of the compounds thus synthesized were obtained as amide rotamers in solution. This phenomenon in *N*-acyltetrahydroisoquinolines has been reported by other researchers, for example; Bringmann observed doubling of signals in the ^{1}H NMR spectra of tetrahydroisoquinolines **5** due to *N*-acetyl and *N*-formyl rotational isomers.[13] A literature search revealed a small number of publications describing the hindered rotation of *N*-acyltetrahydroisoquinoline derivatives. These included the work of Noyori[14] on compounds such as **6** and that done by Fraenkel[15] on compound **7**.



In this paper we describe the full experimental details of our communication on the synthesis of *N*-acetyltetrahydroisoquinoline possessing a substitution pattern common to several of the korupensamine and michellamine naphthylisoquinoline alkaloids.[2d] The products obtained by this method were a mixture of *N*-acetyl rotamers. Furthermore, we describe how this phenomenon was investigated using variable temperature NMR spectroscopy and molecular modelling.

In the synthesis described in this paper we have utilized amidomercuration methodology for the construction of the *N*-acetyltetrahydroisoquinoline **8** from **9**. This methodology relies on an unusual N/C-3 disconnection[16] as shown in Figure 2 below rather than the traditional disconnections outlined in Figure 1.

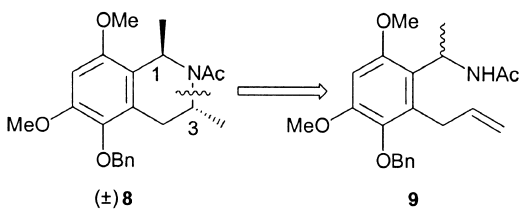
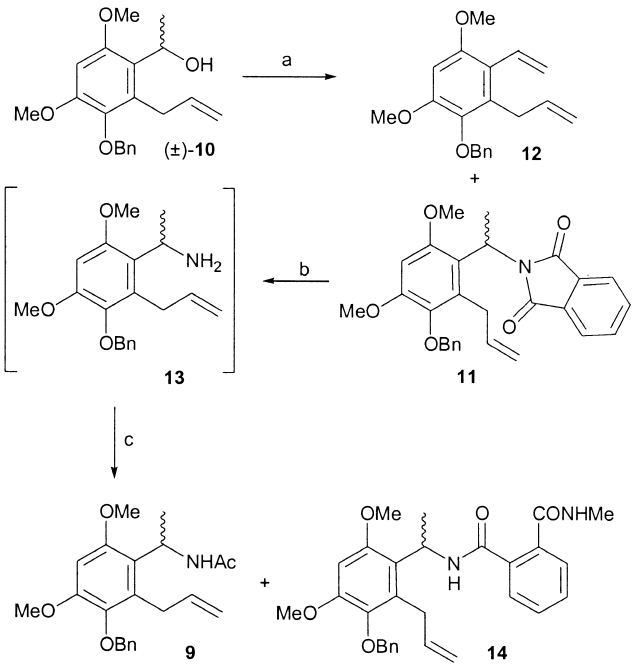


Figure 2. N/C-3 Disconnection of tetrahydroisoquinoline **8**.

2. Results and discussion: synthesis of 1,3-dimethyltetrahydroisoquinolines

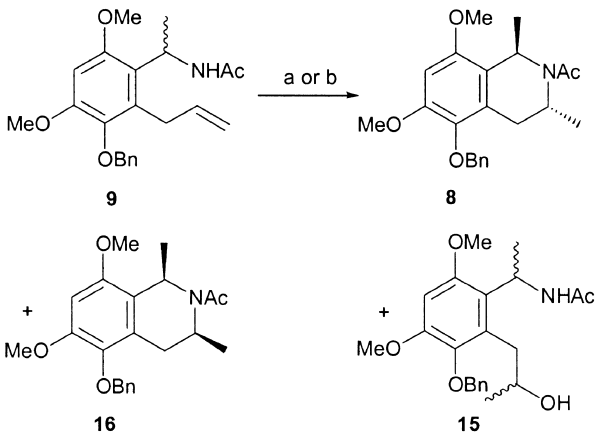
The aromatic alcohol (±)-**10**, an intermediate we have previously employed for making isochromane ring systems,[2a,b] was treated with phthalimide under Mitsunobu conditions[17] as shown in Scheme 1 to yield imide **11** and small amounts of the styrene **12**. Standard base-mediated hydrolyis[18] of compound **11** gave poor results and an



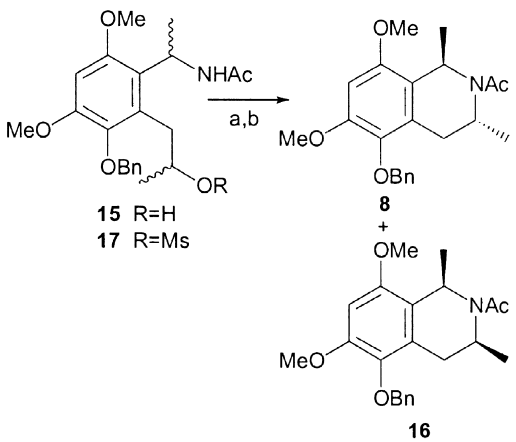
Scheme 1. *Reagents and conditions*: (a) Phthalimide, DEAD, Ph_3P, THF (**11**, 86%; **12** <5%); (b) $MeNH_2$, EtOH/C_6H_6; (c) Ac_2O, pyridine (**9**, 61% over 2 steps; **14**, <17% over 2 steps).

attempted Ing–Manske hydrazinolysis[19] of **11** led to the undesired reduction of the alkene. However, exposure of **11** to methylamine[20] afforded an unstable primary amine **13** that was immediately treated with acetic anhydride and pyridine to produce amide **9** in acceptable yields. The cleavage of the phthalimide group of **11** tended to be a fickle reaction and quite difficult to monitor by thin layer chromatography. One of the side products sometimes isolated was the partially cleaved phthalimide derivative **14** in yields of up to 17%.

We were now in a position to test whether we could access the tetrahydroisoquinoline system by forming the N/C-3 bond. Formation of heterocycles by the hydroamination of alkenes using transition metals[21] has been extensively studied but we decided to use the less popular amidomercuration methodology for the construction of the 1,3-dimethyltetrahydroisoquinolines. Using as an analogy the synthesis of isochromanes[22] by oxymercuration of hydroxyalkenes related to **9**, we envisaged making the target system by intramolecular amidomercuration. Although this type of reaction has been well investigated,[23] it appears to have no precedent in the isoquinoline series. Reaction of **9** with mercury(II) acetate[22] in a 1:1 water/tetrahydrofuran mixture followed by reduction with sodium borohydride gave the desired *N*-acetyl-1,3-*trans*-dimethyltetrahydroisoquinoline **8** as a mixture of rotamers in a poor yield of 21% (Scheme 2). The low yield was due to the competitive reaction of water with the mercurinium intermediate[23d,g] to give the secondary alcohol **15** as a mixture of diastereomers in 54% yield. The formation of unwanted alcohol **15** could be suppressed by reaction of amide **9** with mercury(II) acetate in dry tetrahydrofuran, affording the 1,3-*trans*-dimethyl product **8** as a mixture of rotamers in a yield of 56% as the major product. A small amount (~5–10%) of the *cis*-isomer **16** was also evident as shown by NMR spectroscopy.



Scheme 2. *Reagents and conditions*: (a) $Hg(OAc)_2$, THF/H_2O, then $NaBH_4/NaOH$, then chromatography on SiO_2 (**8**, 21%; **15**, 54%; **16**, <10%); (b) $Hg(OAc)_2$, THF, then $NaBH_4/NaOH$, then chromatography on SiO_2 (**8**, 56%; **15**, 0%; **16**, <10%).



Scheme 3. *Reagents and conditions*: (a) MsCl, CH_2Cl_2, Et_3N (100%); (b) NaH, THF (85%).

The ^1H NMR spectrum of tetrahydroisoquinoline **8** was quite complex owing to substantial peak doubling. It seemed likely that rotamers of **8** exist in solution as a result of hindered rotation of the amide C–N bond, giving rise to this doubling phenomenon.[13a] Heating compound **8** in an NMR tube in toluene-d_8 up to 90°C confirmed our hypothesis as this resulted in coalescence of the two sets of signals. We then decided to perform a more rigorous NMR spectroscopic investigation into the structure and conformation of these compounds. Initial nOe experiments indicated that among other effects for isomer **8**, the C-1 methyl substituent in both rotamers showed an nOe with the H-4 *pseudo*-axial proton (Fig. 3(a)), indicating that the C-1 methyl substituent must be *pseudo*-axial. In addition, the *cis*-isomer **16** exhibited the same nOe, as well as a nOe between the 1-methyl and 3-methyl substituents, thereby fixing the *cis*-arrangement. Therefore we infered that in isomer **8** the C-1 methyl and C-3 methyl groups must have a *trans*-relationship. This then implies that the heterocyclic ring adopts an unusual boat-like conformation (Fig. 3(a)) with both methyl substituents appearing to adopt *pseudo*-axial positions to minimize 1,3-allylic strain[24] (Fig. 3(b)). The high degree of stereoselectivity for the cyclization to afford the *trans* product was in line with the findings of Harding and Burks who have reported similar results.[25]

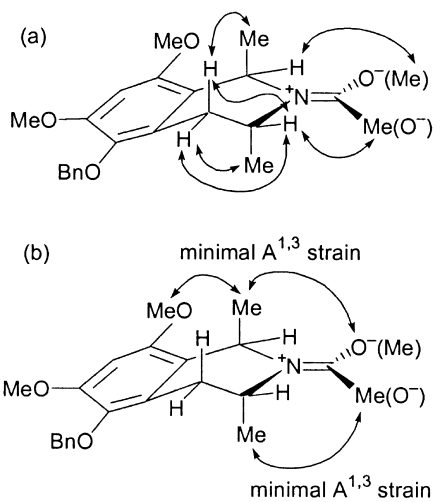


Figure 3. (a) NOe interactions for **8**, (b) postulated $A^{1,3}$ strain interactions for **8**.

With sufficient quantities of the alcohol **15** in hand we also examined the conversion of this intermediate into the desired *N*-acyltetrahydroisoquinolines. Reaction of **15** with methanesulfonyl chloride and triethylamine (Scheme 3) afforded mesylate **17** in quantitative yield. Exposure of **17** to sodium hydride resulted in cyclisation to afford tetrahydroisoquinolines **8** and **16** (85% yield) as an equimolar, inseparable mixture of 1,3-*trans*- and *cis*-dimethyl isomers,[26] each occurring as a pair of amide rotamers.[27] As the ^{13}C NMR spectrum clearly displayed four peaks for most carbons in the ^{13}C NMR spectrum, one each for the *cis*- and *trans*- isomers, and then one for each of their amide rotamers, comparison of the spectra and a $^1H-^{13}C$ NMR correlation spectrum then facilitated the identification of the *cis*-1,3-dimethyltetrahydroisoquinoline in the mixture.

3. Variable temperature NMR spectroscopy

In view of the paucity of literature examples describing *N*-acyltetrahydroisoquinoline amide rotamers we decided to investigate the influence of temperature on the rotamers of available *trans*-1,3-dimethyltetrahydroisoquinoline **8** using variable temperature ^1H NMR spectroscopy.[28,29] The ^1H NMR spectra of **8** in deuterated toluene were thus obtained over the temperature range 240–370 K. We identified four sets of signals that were doubled at room temperature and demonstrated coalescence over this temperature range. These were the signals at: (a) δ 3.2–2.8 (4-H), (b) 2.0–1.9 ($COCH_3$), (c) 1.6–1.3 (1-CH_3) and (d) 1.1–0.2 (3-CH_3) (Fig. 4).

The free energies of activation were then calculated as described by Bishop[30] et al. from the Eyring equation (Eq. (1))[†] in conjunction with the rate constant expression (Eq. 2)[30] to be in the range of 15.9±0.2 to 16.1±

[†] R=8.31 J mol^{-1} K^{-1}; T_c=convergence temperature (K); h=6.63×10^{-34} J s; k_B=1.38×10^{-23} J K^{-1}; $\Delta\delta_{AB}$=limiting δ peak separation (ppm); J_{AB}=coupling constant (Hz).

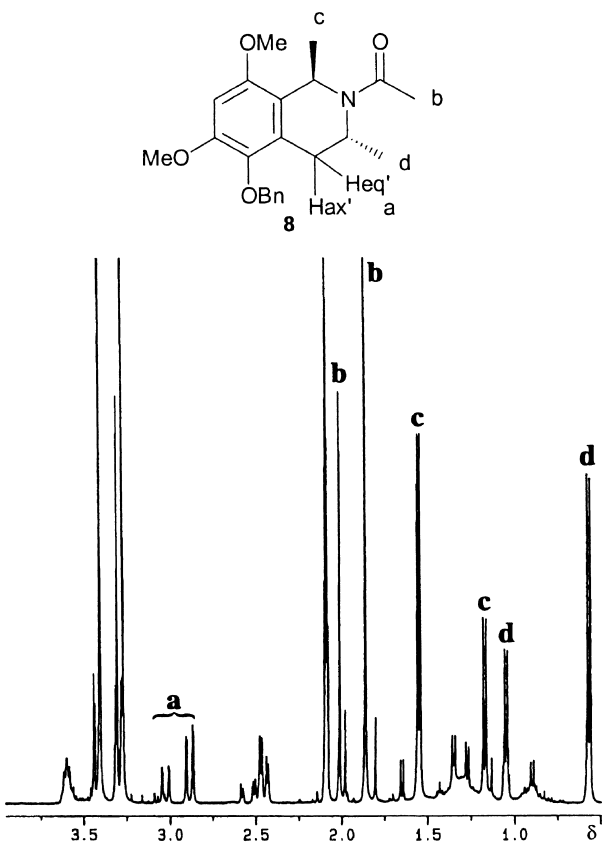


Figure 4. Portion of ^{1}H NMR spectrum of compound **8** in toluene-d_8 indicating signals used in variable temperature NMR spectroscopy work.

0.2 kcal mol^{-1}.[31] The quantities $\Delta\delta_{AB}$ at their limit were estimated by graphical extrapolation from the measured $\Delta\delta$ values at the various temperatures.[32]

$$\Delta G_c^{\ddagger} = -RT_c \ln(K_C h/k_B T_c) \quad (1)$$

$$K_C = \{\pi\{(\Delta\delta_{AB})^2 + 6J_{AB}^2\}^{1/2}/(2)^{1/2}\} \quad (2)$$

Evaluation of the NMR spectral signals in the range of 2.0–1.9 ($COCH_3$) using an approach tailored for obtaining the free energies of activation at the coalescence point of an unequal doublet using the Eqs. (3) and (4) was also performed.[33] The calculated values obtained using this method were $\Delta G_A^{\ddagger}$=16.6±0.2 kcal mol^{-1} (major isomer to minor) and $\Delta G_B^{\ddagger}$=16.1±0.2 kcal mol^{-1} (minor isomer to major) which are reasonable in comparison to the values obtained from the first method.[‡]

$$\Delta G_A^{\ddagger} = 4.57 \times T_c\{10.62 + \log\{X/2\pi(1 - \Delta P)\} + \log(T_c/\Delta\delta_{AB})\} \quad (3)$$

$$\Delta G_B^{\ddagger} = 4.57 \times T_c\{10.62 + \log\{X/2\pi(1 + \Delta P)\} + \log(T_c/\Delta\delta_{AB})\} \quad (4)$$

[‡] $\Delta P = P_A - P_B$ (P_A and P_B being the relative concentrations of species A and B obtained from the area under peaks A and B). The values of $\log\{X/2\pi(1\pm\Delta P)\}$ could be extrapolated directly from Figure 2 in the original reference.[33a] T_c=330±2 K and $\Delta\delta_{AB}$=63±2 ppm.

4. Molecular modelling

In addition to the results obtained by the variable temperature NMR spectroscopy we also investigated the rotameric phenomenon of the tetrahydroisoquinoline amide peak doubling with simple molecular modelling studies. In order to do so, we used the atomic coordinates determined in a published tetrahydroisoquinoline crystal structure[34] as a template for our computer simulations. The model system was modified[35] to represent compound **18** (Fig. 5) and a single point energy minimization[36] was performed on the molecule utilizing the MM+ force field.[37] An iterative full energy minimization calculation was then performed at 5° torsional angle intervals, with the torsional angle restrained at this particular value. The energies calculated were then scaled to the minimum at −175° and plotted against the torsional angle to afford energy-torsional angle plots for the *N*-acetyl-1,3-*trans*-dimethyltetrahydroisoquinoline (Fig. 6). A similar process afforded an energy-angle plot for the *cis*-compound **19**. From the values obtained, the calculated energy barrier for the amide N–CO bond rotation was 15.1 kcal mol^{-1} for the *trans* compound **18** and 14.9 kcal mol^{-1} for the related *cis*-compound, **19**.[38] For the *trans* compound **18** the calculated energy difference between the minima at +175 and 0° was 0.71 kcal mol^{-1} implying a Boltzmann distribution of ~3:1 which compared well with the ratio observed from the peak integration in the NMR spectrum of compound **18**.

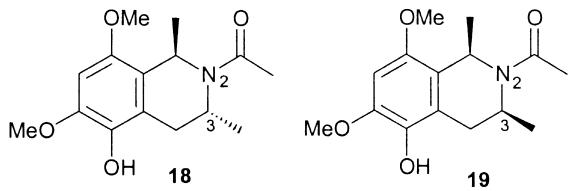


Figure 5. Simplified 1,3-*trans*-dimethyl- **18** and 1,3-*cis*-dimethyl- **19** *N*-acetyltetrahydroisoquinolines for molecular modelling. Preferred rotamer as drawn; the torsion angle changed in the modelling was C_3–N_2–C–O as labelled in the figure.

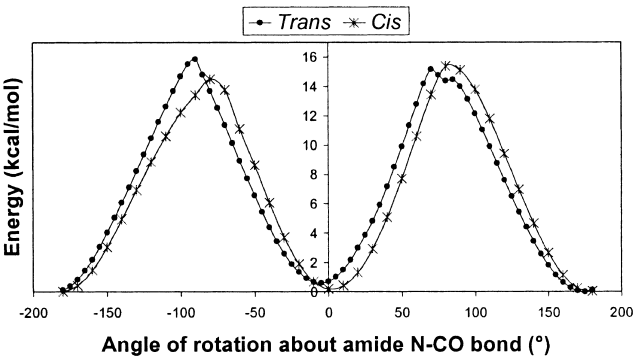


Figure 6. Plot of energy vs amide bond angle for simplified 1,3-*trans*-dimethyl- **18** and 1,3-*cis*-dimethyl- **19** *N*-acetyltetrahydroisoquinolines.

5. Discussion: molecular modelling and variable temperature NMR spectroscopy

The variable temperature NMR spectroscopy and molecular modelling (using the simplified analogues **18** and **19**) gave results that supported the existence of rotamers in solution arising from hindered rotation around the amide C–N bond,

as evidenced by the ^{1}H and ^{13}C NMR spectra of the 1,3-*trans*-dimethyl- and 1,3-*cis*-dimethyltetrahydroisoquinolines **8** and **16**. The former technique gave a rotational barrier of approximately 16 kcal mol^{-1} while the latter gave a barrier of about 15 kcal mol^{-1} for the model systems. Both these barriers are in the range of 15–16 kcal mol^{-1}, within the accepted range of many literature values.[39] Furthermore these barriers to rotation are high enough to explain the observation of the existence of amide rotamers in solution for compounds **8** and **16**.[40]

6. Conclusion

We have been successful in synthesizing an *N*-acetyltetrahydroisoquinoline with the aromatic substitution pattern common to several of the korupensamine and michellamine alkaloids, albeit in racemic form, using a novel amidocyclization reaction. Furthermore the observation of rotamers in solution due to hindered rotation about the amide bond in the tetrahydroisoquinoline compound formed was investigated by variable temperature NMR spectroscopy and molecular modelling methods. 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.

7. Experimental

7.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-200 or Bruker DRX 400 spectrometer at the frequency indicated. DEPT, CH-correlated and HMBC spectra were run on some samples to enable complete assignments of all the signals. NMR spectroscopic assignments with the same superscript may be interchanged. Infrared spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 CHN Elemental Analyser. Macherey–Nagel kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography and Macherey–Nagel kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography were distilled prior to use.

7.1.1. *N*-2-{1-[2-Allyl-3-(benzyloxy)-4,6-dimethoxyphenyl]-ethyl}-phthalimide 11 and 2-allyl-3-benzyloxy-4,6-dimethoxy-styrene, 12. Phthalimide (0.56 g, 3.8 mmol), freshly distilled diethyl azodicarboxylate (DEAD) (0.60 cm^3, 0.67 g, 3.8 mmol) and triphenylphosphine (1.01 g, 3.8 mmol) were added sequentially to alcohol **10** (1.05 g, 3.20 mmol) dissolved in dry tetrahydrofuran (THF) (50 cm^3). The reaction mixture was stirred at room temperature under argon, for 18 h, after which the solvent was removed in vacuo. Silica gel column chromatography (5–20% ethyl acetate/hexane) yielded the product **11** as a clear semi-solid (1.36 g, 93%). ν_{max} (film)/cm^{-1} 1707vs (C=O), 1597s (ArC=C) and 1487m (ArC=C, phthalimide); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.87–7.73 (3H, m, 3×ArH), 7.66–7.63 (2H, m, 2×ArH), 7.47–7.45 (2H, m, 2×ArH), 7.38–7.27 (2H, m, 2×ArH), 6.43 (1H, s, 5-H), 5.99–5.92 (1H, m, 2′-H), 5.51 (1H, q, *J*=7.4 Hz, C*H*CH$_3$), 4.94–4.87 (4H, m, OCH$_2$ and 3′-H), 3.85 (3H, s, OCH$_3$), 3.85–3.76 (2H, m, 1′-H), 3.76 (3H, s, OCH$_3$) and 1.93 (3H, d, *J*=7.4 Hz, CHC*H*$_3$); δ_C (100.625 MHz; $CDCl_3$; Me_4Si) 168.8 (2×NC=O), 154.9 and 152.4 (2×ArC–O), 139.9 (Ar*C*–C), 138.1 (Ar*C*–O), 137.3 (2′-C), 133.5 (2×Ar*C*–H), 133.2 (×2) and 132.2 (3×Ar*C*–C), 128.3 (×2), 127.8 (×2), 127.6 and 122.6 (×2) (7×Ar*C*–H), 120.7 (Ar*C*–C), 115.1 (3′-C), 96.1 (5-C), 74.6 (OCH$_2$), 55.8 and 55.7, (2×OCH$_3$), 48.5 (*C*HCH$_3$), 30.5 (1′-C) and 18.0 (CH*C*H$_3$); *m*/*z* (EI) 457.1878 (9%) (M$^+$, $C_{28}H_{27}O_5N$ requires 457.1889), 366 (44), 351 (1), 336 (1), 310 (3), 219 (36), 174 (100), 147 (11) and 91 (31).

Sometimes the styrene **12** was also isolated from the reaction mixture in yields of up to 5%. ν_{max} (film)/cm^{-1} 2837w (C–H, OCH$_3$) and 1595m (ArC=C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.50–7.23 (5H, m, 5×ArH), 6.69 (1H, dd, *J*=17.8, 11.8 Hz, ArC*H*=CH$_2$), 6.47 (1H, s, 5-H), 6.03–5.86 (1H, m, 2′-H), 5.67 (1H, dd, *J*=17.8, 2.5 Hz, *trans*-ArCH=HC*H*), 5.41 (1H, dd, *J*=11.8, 2.5 Hz, *cis*-ArCH=*H*CH), 5.04–4.84 (2H, m, 3′-H), 4.91 (2H, s, OCH$_2$), 3.89 and 3.83 (each 3H, s, OCH$_3$) and 3.54–3.50 (2H, m, 1′-H); δ_C (50.32 MHz; $CDCl_3$; Me_4Si) 154.4 and 152.1 (2×ArC–O), 140.1 (Ar*C*–C), 138.1 (Ar*C*–O), 137.0 (2′-C), 132.9 (Ar*C*–C), 130.7 (Ar*C*H=CH$_2$), 128.3 (×2), 127.8 (×2) and 127.6 (5×ArCH), 119.1 (1-C), 118.4 (ArCH=*C*H$_2$), 115.2 (3′-C), 95.7 (5-C), 74.8 (OCH$_2$), 55.9 (2×OCH$_3$) and 31.2 (1′-C); *m*/*z* (EI) 310.1573 (6%) (M$^+$, $C_{20}H_{22}O_3$ requires 310.1569), 219 (100), 204 (6), 189 (6), 174 (6) and 91 (33).

7.1.2. *N*-{1-[2-Allyl-3-(benzyloxy)-4,6-dimethoxyphenyl]-ethyl}-acetamide 9, *N*^{1}-{1-[2-allyl-3-(benzyloxy)-4,6-dimethoxy-phenyl]ethyl}-*N*^{2}-methyl-phthalamide 14 and 1-[2-Allyl-3-(benzyloxy)-4,6-dimethoxyphenyl]-ethylamine, 13. Phthalimido derivative **11** (0.60 g, 1.3 mmol) was dissolved in absolute ethanol (10 cm^3) and benzene (4 cm^3). Aqueous methylamine solution (25%, 1 cm^3) was added under nitrogen and the reaction was monitored by thin layer chromatography. A further portion of methylamine solution (1 cm^3) was added and the reaction was deemed complete after 2 h. Amine **13** could be isolated as an intermediate but proved to be unstable and susceptible to decomposition. ν_{max} (film)/cm^{-1} 3360br (NH$_2$), 1597s (ArC=C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.45–7.29 (5H, m, 5×ArH), 6.47 (1H, s, 5-H), 5.92–5.88 (1H, m, 2′-H), 5.02 (1H, br d, *J*=10.9 Hz, 3′-*cis*-H) 4.92–4.85 (1H, m, 3′-*trans*-H), 4.89 and 4.84 (each 1H, d, *J*=10.8 Hz, OCH$_2$), 4.49–4.48 (1H, m, C*H*CH$_3$), 3.90 and 3.88 (each 3H, s, OCH$_3$), 3.64–3.52 (2H, m, 1′-H), 3.60–3.20 (2H, br, NH$_2$) and 1.61 (3H, d, *J*=6.5 Hz, CHC*H*$_3$); δ_C (100.63 MHz; $CDCl_3$; Me_4Si) 154.5, 153.2 and 140.2 (3×Ar*C*–O), 137.8 (Ar*C*–C), 136.7 (2′-C), 132.5 (Ar*C*–C), 128.4 (×2), 127.9 (×2) and 127.8 (5×Ar*C*–H and Ar*C*–C), 116.0 (3′-C), 95.9 (5-C), 75.1 (OCH$_2$), 55.9 and 55.7 (2×OCH$_3$), 47.0 (*C*HCH$_3$), 30.4 (1′-C) and 18.4 (CH*C*H$_3$). The solvent was removed in vacuo and replaced with excess pyridine (10 cm^3) and acetic

anhydride (5 cm^3). Sodium sulfate (5 g) was added and the reaction mixture was stirred at ambient temperature for 18 h under an argon atmosphere, after which the solvent was removed in vacuo. The residue was purified by silica gel preparative layer chromatography (PLC) (50% ethyl acetate/49% hexane/1% aq. ammonia solution) to afford amide **9** (0.297 g, 61% over two steps). ν_{max} (film)/cm^{-1} 3331br (N–H), 1637vs (C=O) and 1597 (ArC=C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.47–7.30 (5H, m, 5×ArH), 6.79 (1H, br d, *J*=9.3 Hz, NH), 6.49 (1H, s, 5-H), 6.01–5.93 (1H, m, 2′-H), 5.44 (1H, dq, *J*=9.3, 6.9 Hz, C*H*CH_3), 5.02 (1H, dd, *J*=9.9, 1.7 Hz, 3′-*cis*-H), 4.94–4.82 (1H, m, 3′-*trans*-H), 4.91 and 4.86 (each 1H, d, *J*=10.8 Hz, OCH_2), 3.90 and 3.87 (each 3H, s, OCH_3), 3.65–3.62 (2H, br d, *J*=6.3 Hz, 1′-H), 1.92 (3H, s, $COCH_3$) and 1.40 (3H, d, *J*=6.9 Hz, CHC*H*$_3$); δ_C (100.63 MHz; $CDCl_3$; Me_4Si) 168.4 (*C*=O), 154.4, 152.1 and 140.2 (3×Ar*C*–O), 137.9 (Ar*C*–C), 136.9 (2′-C), 132.5 (Ar*C*–C), 128.2 (×2), 127.8 (×2) and 127.6 (5×Ar*C*–H), 122.2 (Ar*C*–C), 115.4 (3′-C), 96.2 (5-C), 74.9 (OCH_2), 55.9 and 55.6 (2×OCH_3), 43.7 (*C*HCH_3), 30.7 (1′-C), 23.6 (CO*C*H_3) and 20.9 (CH*C*H_3); *m/z* (EI) 369.1933 (14%) (M^+, $C_{22}H_{27}NO_4$ requires 369.1940), 326 (1), 278 (77), 219 (86), 204 (16), 193 (84), 189 (16), 91 (40) and 43 (16).

Compound **14** (0.108 g, 17%, over two steps) was also recovered from the column. ν_{max} (film)/cm^{-1} 3296br (N–H), 1643vs (C=O), 1597m (ArC=C) and 1514m (N–C=O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.70–7.67 (1H, m, ArH), 7.49–7.31 (9H, m, 8×ArH and NCH_3H), 6.79 (1H, br d, *J*=4.4 Hz, NH [D_2O exchangeable]), 6.49 (1H, s, 5-H), 6.02–5.98 (1H, m, 2′-H), 5.57 (1H, dq, *J*=9.2, 6.9 Hz, C*H*CH_3), 5.04 (1H, dd, *J*=10.2, 1.6 Hz, 3′-*cis*-H), 4.99 (1H, dd, *J*=17.1, 1.6 Hz, 3′-*trans*-H), 4.89 (2H, s, OCH_2), 3.89 and 3.87 (each 3H, s, OCH_3), 3.84–3.65 (2H, m, 1′-H), 2.66 (3H, d, *J*=4.4 Hz, NHCH_3) and 1.46 (3H, d, *J*=6.9 Hz, $COCH_3$); δ_C (100.63 MHz; $CDCl_3$; Me_4Si) 168.9 and 168.3 (2×NC=O), 154.6, 152.4 and 140.1 (3×ArC–O), 137.9 (Ar*C*–C), 136.9 (2′-C), 135.1, 134.4 and 132.3 (3×Ar*C*–C), 130.1, 129.9, 129.0, 128.4 (×2), 128.0 (×2), 127.8 and 127.5 (9×ArC–H), 121.1 (Ar*C*–C), 115.6 (3′-C), 96.0 (5-C), 75.1 (OCH_2), 56.0 and 55.6 (2×OCH_3), 44.7 (*C*HCH_3), 30.8 (1′-C), 26.4 (NCH_3) and 20.7 (CH*C*H_3); *m/z* (EI) 488.2303 (3%) (M^+, $C_{29}H_{32}N_2O_5$ requires 488.2311), 397 (9), 219 (100), 204 (9), 162 (39), 91 (21) and 43 (4).

7.1.3. *N*-Acetyl-5-benzyloxy-6,8-dimethoxy-1,3-*trans*-dimethyl-1,2,3,4-tetrahydroisoquinoline 8 and *N*-{1-[3-(benzyloxy)-2-(2-hydroxypropyl)-4,6-dimethoxyphenyl]ethyl}acetamide, 15. Mercury(II) acetate (0.27 g, 1.5 mmol) was added to amide **9** (0.19 g, 0.51 mmol) dissolved in tetrahydrofuran (THF) (10 cm^3). The yellow mixture was then stirred in the dark, under argon for 21 h at ambient temperature. A further portion of mercury(II) acetate (0.18 g, 0.56 mmol) was added and the mixture was stirred for a further 18 h. A mixture of sodium borohydride (0.050 g, 1.3 mmol) in aqueous sodium hydroxide (5 cm^3, 2.5 M) was then added whilst stirring. After stirring for a further 1 h a saturated aqueous Na_2CO_3 solution (5 cm^3) was added and the reaction was stirred for an extra 20 min. After the reaction had stood for a further 30 min, the THF was decanted and removed under reduced pressure. Saturated brine solution (10 cm^3) and ether (10 cm^3) were added to the residue and the mixture was subsequently extracted with diethyl ether (3×10 cm^3). The organic solvents were combined, filtered through alumina to remove traces of mercury residues, dried ($MgSO_4$) and evaporated in vacuo. Purification by silica gel preparative layer chromatography (20% hexane/79% ethyl acetate/1% aq. ammonia solution) afforded the *trans*-cyclized product **8** (mixture of two rotamers, 0.11 g, 56%) as a yellow oil. ν_{max} (film)/cm^{-1} 2820m (C–H, OCH_3), 1635vs (C=O) and 1583m (ArC=C); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.43–7.32 (10H, m, 10×ArH), 6.44 (1H, s, 7-H), 6.43 (1H, s, 7-H), 5.50 (1H, q, *J*=6.4 Hz, 1-H), 5.16 (1H, q, *J*=6.6 Hz, 1-H), 4.95–4.86 (4H, m, 2×OCH_2), 4.68–4.62 (1H, m, 3-H), 4.23–4.15 (1H, m, 3-H), 3.91 (6H, s, 2×OCH_3), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.99 (2H, dd, *J*=15.2, 2.4 Hz, 2×4-H *pseudo*-equatorial), 2.64–2.54 (2H, m, 2×4-H *pseudo*-axial), 2.24 (3H, s, $COCH_3$), 2.17 (3H, s, $COCH_3$), 1.28 (3H, d, *J*=6.6 Hz, 1-CH_3), 1.23 (3H, d, *J*=6.4 Hz, 1-CH_3), 0.84 (3H, d, *J*=6.4 Hz, 3-CH_3), 0.83 (3H, d, *J*=6.3 Hz, 3-CH_3); δ_C (50.32 MHz; $CDCl_3$; Me_4Si) 170.0, 169.7 (2×NCOCH_3), 151.9, 151.5, 151.4, 150.7, 139.1, 139.0 (6×ArC–O), 137.6, 137.5, 129.0 (3×Ar*C*–C), 128.5, 128.5, 128.3, 128.0 (4×ArC–H), 119.5, 118.6 (2×Ar*C*–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); *m/z* (EI) 369.1931 (20%) (M^+, $C_{22}H_{27}NO_4$ requires 369.1940), 354 (83), 278 (95), 263 (9), 219 (78), 193 (100), 91 (34) and 43 (16).

When this reaction was carried out using an equivalent amount of THF and water as solvent the yield of the *trans*-cyclized product **8** was only 21%. However, a large amount of alcohol **15** (54%) was then also recovered from the column as a clear oil. ν_{max} (film)/cm^{-1} 3460br (OH st), 3345br (N–H), 1649s (C=O), 1597s (ArC=C); δ_H (400 MHz; $CDCl_3$; Me_4Si; Assignments in brackets tentatively refer to the other diastereomer) 7.46–7.31 (10H, m, 10×ArH), 6.82 (2H, br d, NH), 6.49, (6.48) (each 1H, s, 5-H), 5.52–5.47 (2H, m, C*H*CH_3), 4.96, (4.92) (each 2H, d, *J*=11.2 Hz, OCH_2), 4.15–4.03, (3.90–3.88) (each 1H, m, C*H*OH), 3.90, 3.89, (3.89), (3.88) (each 3H, s, OCH_3), 3.05 (1H, dd, *J*=13.8, 3.9 Hz, 1′-H), (2.98) (1H, dd, *J*=13.8, 8.0 Hz, 1′-H), (2.84) (1H, dd, *J*=13.8, 4.2 Hz, 1′-H), 2.74 (1H, dd, *J*=13.8, 8.8 Hz, 1′-H), 2.50 (2H, br s, OH), 1.93, (1.92) (each 3H, $COCH_3$), 1.42, (1.42) (each 3H, d, *J*=7.0 Hz, CHCH_3) and 1.26, (1.23) (each 3H, d, *J*=6.2 Hz, 3′-H); δ_C (100.63 MHz; $CDCl_3$; Me_4Si) 169.1, (168.7) (2×NC=O), 154.4, 151.9, (140.5), 140.3 (6×ArC–O), 137.9, (137.7), 132.2, (131.9) (4×Ar*C*–C), (128.4), 128.3, 127.8, (127.7), 127.7 (6×ArC–H), 122.2 (2×Ar*C*–C), 96.3, (96.3) (2×5-C), 74.6 (2×OCH_2), 68.7, (68.6) (2×*C*HCH_3), 56.0, (55.9), 55.7, (55.6) (4×OCH_3), 44.2 (2×2′-C), 36.8, (36.3) (2×1′-C), 24.3, 23.5, (23.5) and 21.0, (20.8) (6×CH_3); *m/z* (EI) 387.2033 (2%) (M^+, $C_{22}H_{29}NO_5$ requires 387.2044), 343 (7), 252 (35), 193 (56), 91 (26) and 44 (20).

7.1.4. 2-[2-[1-(Acetylamino)ethyl]-6-(benzyloxy)-3,5-dimethoxy-phenyl]-1-methylethyl methanesulfonate, 17. Alcohol **15** (0.050 g, 0.13 mmol) was dissolved in dichloromethane (5 cm^3) and cooled to 0°C under an argon

atmosphere. Methanesulfonyl chloride (0.015 cm^3, 0.022 g, 0.19 mmol) and triethylamine (0.027 cm^3, 0.020 g, 0.19 mmol) were added sequentially to afford a pale yellow solution, which was warmed to ambient temperature. The reaction mixture was stirred for 60 h, after which the solvent was removed in vacuo. Purification by silica gel preparative layer chromatography (plc) (60% ethyl acetate/29% hexane/1% aq. ammonia solution) afforded the mesylate **17** (0.060 g, quantitative) as a dark oil. The product was isolated as a mixture of two diastereomers in an approximately even ratio. ν_{max} (film)/cm^{-1} 3442br (NH), 2868m (CH, OCH_2), 2842m (CH, OCH_3), 1655s (C═O), 1597m (ArC═C) and 1331s (R-SO-R); δ_H (400 MHz; $CDCl_3$; Me_4Si; Assignments in brackets are tentatively for the other diastereomer) 7.45–7.30 (10H, m, 10×ArH), 6.81, (6.74) (each 1H, d, J=9.3 Hz, NH), 6.52 (2H, s, 4-H), 5.47–5.42 (2H, m, 2′-H), 5.13 (1H, q, J=6.4 Hz, C*H*CH_3), (4.98–4.88) (1H, m, under OCH_2, C*H*CH_3), (5.06), 4.96 (each 1H, d, J=11.0 Hz, OCH_2), 4.89, (4.83) (each 1H, d, J=11.0 Hz, OCH_2), 3.91, (3.91) (each 3H, s, OCH_3), 3.89 (6H, s, OCH_3), (3.32) (1H, dd, J=14.0, 8.7 Hz, 1′-H), 3.14 (2H, dd, J=7.0, 4.8 Hz, 1′-H), (2.93) (1H, dd, J=14.0, 5.4 Hz, 1′-H), 2.86, (2.56) (each 3H, s, SO_2CH_3), 1.93 (6H, s, $COCH_3$), 1.47, (1.44) (each 3H, d, J=6.9 Hz, 3′-H) and 1.42, (1.35) (each 3H, d, J=6.4 Hz, CHC*H*$_3$); δ_C (100.63 MHz; $CDCl_3$; Me_4Si) (168.7), 168.6 (2×NC═O), (154.5), 154.4, 151.9, (151.8), 140.5 (6×ArC–O), (137.7), 137.6, (129.6), 129.1 (4×Ar*C*–C), 128.4, 128.4, 127.9 (6×ArC–H), (122.6), 122.4 (2×Ar*C*–C), 96.9, (96.8) (2×4-C), (80.9), 80.3 (2×2′-C), (74.8), 74.7 (2×OCH_2), 55.9, 55.7 (4×OCH_3), 44.0 (2×*C*HCH_3), 37.3, (37.2) (2×1′-C), (33.9), 33.4 (2×SO_2CH_3), 23.5, (23.4), 21.3 and (20.8), 20.7 (6×CH_3).

7.1.5. *N*-Acetyl-5-benzyloxy-6,8-dimethoxy-1,3-*trans*-dimethyl-1,2,3,4-tetrahydroisoquinoline 8 and *N*-acetyl-5-benzyloxy-6,8-dimethoxy-1,3-*cis*-dimethyl-1,2,3,4-tetrahydroisoquinoline, 16. Sodium hydride (60% in oil, 0.03 g, 0.86 mmol) was added to mesylate **17** (0.040 g, 0.086 mmol) dissolved in dry tetrahydrofuran (THF) (10 cm^3), under an argon atmosphere. The reaction mixture was stirred for 18 h, after which the mixture was cooled to 0°C. Water (10 cm^3) was added dropwise and the mixture was extracted with diethyl ether (2×10 cm^3). The combined organic solvents were washed with brine (10 cm^3), dried ($MgSO_4$) and concentrated in vacuo. Silica gel preparative layer chromatography (65% ethyl acetate/33% hexane/1% aq. ammonia solution) afforded the products **8** and **16** (0.027 g, 85%) as an equimolar mixture of *cis*- and *trans*-isomers and their rotamers which were not separated; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.43–7.31 (20H, m, 20×ArH), 6.44, 6.43, 6.43 (4H, 3×s, 7-H), 5.78 (1H, q, J=6.8 Hz, 1-H *cis*), 5.50 (1H, q, J=6.4 Hz, 1-H *trans*), 5.15 (1H, q, J=6.5 Hz, 1-H *cis*), 5.16 (1H, q, J=6.6 Hz, 1-H *trans*), 4.96–4.84 (8H, m, 4×OCH_2), 4.68–4.62 (1H, m, 3-H *trans*), 4.52 (1H, q, J=6.8 Hz, 3-H *cis*), 4.23–4.15 (1H, m, 3-H *trans*), 4.08–3.99 (1H, m, 3-H *cis*), 3.91–3.82 (24H, multiple singlets, 8×OCH_3), 3.04–2.97 (2H, m, 4-H *trans* and 4-H *cis*), 2.99 (1H, dd, J=15.2, 2.4 Hz, 4-H *pseudo*-equatorial *trans*), 2.84 (1H, dd, J=16.4, 6.8 Hz, 4-H *cis*), 2.68 (1H, dd, J=16.3, 4.4 Hz, 4-H *cis*), 2.64–2.54 (2H, m, 2×4-H *pseudo*-axial *trans*), 2.52 (1H, dd, J=16.4, 7.4 Hz, 4-H *cis*), 2.24 (3H, s, COC*H*$_3$ *trans*), 2.20 (3H, s, $COCH_3$ *cis*), 2.17 (3H, s, $COCH_3$ *trans*), 2.12 (3H, s, $COCH_3$ *cis*), 1.44 (3H, d, J=6.9 Hz, CH_3), 1.43 (3H, d, J=6.8 Hz, CH_3), 1.30–1.21 (12H, multiple doublets, 4×CH_3), 0.84 (3H, d, J=6.4 Hz, 3-CH_3 *trans*) and 0.83 (3H, d, J=6.3 Hz, 3-CH_3 *trans*); δ_C (50.32 MHz; $CDCl_3$; Me_4Si) 170.0, 169.7 (2×NC═O *trans*), 169.4, 169.0 (2×NC═O *cis*), 152.2, 151.8, 151.4, 151.1, 151.0, 139.5, 139.0, 138.7, 138.4 (12×ArC–O), 137.6, 137.5, 129.0, 128.6 (4×Ar*C*–C), 128.6, 128.5, 128.4, 128.4, 128.3, 128.0, 128.0 (12×ArC–H), 128.0, 127.9 (2×Ar*C*–C *cis*), 119.5 (2×Ar*C*–C *trans*), 119.2, 119.1 (2×Ar*C*–C *cis*), 118.6 (Ar*C*–C *trans*), 95.3 (7-C *cis*), 95.2 (7-C *trans*), 95.0 (7-C *cis*), 94.9 (7-C *trans*), 75.3, 75.0, 74.7 (4×OCH_2), 56.7, 56.1, 56.0, 56.0, 55.6, 55.6 (8×OCH_3), 49.1 (3-C *trans*), 47.5 (1-C *cis*), 47.5 (2×1-C *cis*), 46.7 (1-C *trans*), 46.3 (3-C *trans*), 44.4 (3-C *trans*), 44.4 (3-C *cis*), 43.6 (3-C *cis*), 29.1 (4-C *cis*), 28.6 (4-C *trans*), 28.4 (4-C *cis*), 27.8 (4-C *trans*), 23.2, 22.9, 22.6, 22.4, 22.3, 22.2, 21.8, 21.3, 21.0, 20.9 and 19.2 (12×CH_3).

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26. The formation of a mixture of *trans*- and *cis*- cyclized products by nucleophilic displacement of mesylate by the amide nitrogen is a consequence of **17** being a mixture of diastereomers.
27. Spectroscopic comparison with the pure *trans*-compound **8** isolated from the amidomercuration reaction proved that *trans*-1,3-dimethyltetrahydro-isoquinoline was present in the mixture and the peaks for the *cis*- product were much clearer because of its increased abundance.
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38. The minimum energy of the *trans*-compound **18** (5.4 kcal mol^{-1}) was 1.3 kcal mol^{-1} lower in energy than the minimum of the *cis*-compound **19** (6.7 kcal mol^{-1}). This energy difference could be attributed to the relative values of the angle strain [5.9 kcal mol^{-1} (*trans*) vs 6.8 kcal mol^{-1} (*cis*)—the origin of this angle strain was not evident when comparing the two structures], Van der Waals repulsion [10.6 kcal mol^{-1} (*trans*) vs 11.5 kcal mol^{-1} (*cis*)] and dihedral angle contributions [-4.4 kcal mol^{-1} (*trans*) vs -5.0 kcal mol^{-1} (*cis*)].
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