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A novel approach to conformationally restricted analogues of nicotine and anabasine by an intramolecular Hamaguchi–Ibata reaction

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Abstract

A short synthesis of methyl (*SR*)-8,10-dichloro-1,2,3,4,5,6-hexahydro-6-hydroxy-1-methyl-1,9-phenanthroline-6-carboxylate (**14**) has been achieved en route to conformationally restricted analogues of nicotine and anabasine. The key feature of this process involves an efficient intramolecular Hamaguchi–Ibata reaction of **11**.

Keywords: azaisobenzofuran; intramolecular cycloaddition; domino reaction; 1,9-phenanthroline.

The examination of the role of particular conformations on the pharmacological properties of important biologically active molecules has remained an active area of investigation. One approach to such a study is to modify the parent molecule in such a fashion that its original conformational mobility is severely limited to one particular conformation.[1] In light of this, recently a series of conformationally restricted analogues, e.g. **1** and **2** of nicotine (**3**) and anabasine (**4**) have been synthesized and evaluated as agonists of neuronal acetylcholine receptors (nAChRs).[2] In particular, compound **1** which selectively activates human recombinant $\alpha 2\beta 4$ and $\alpha 4\beta 4$ nAChRs has been shown to be active in animal models of Parkinson's disease and pain. The long and circuitous synthetic route[2] described for the ring systems **1** and **2** does not appear to be viable for the synthesis of a large variety of bridged nicotines and anabasines required for biological testing. Hence, the development of an alternative and more flexible route which overcomes these limitations was felt desirable.

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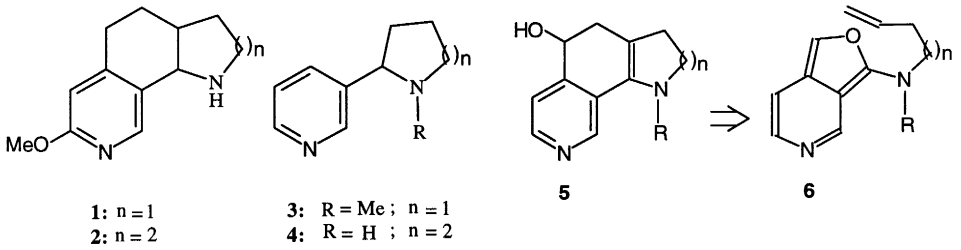
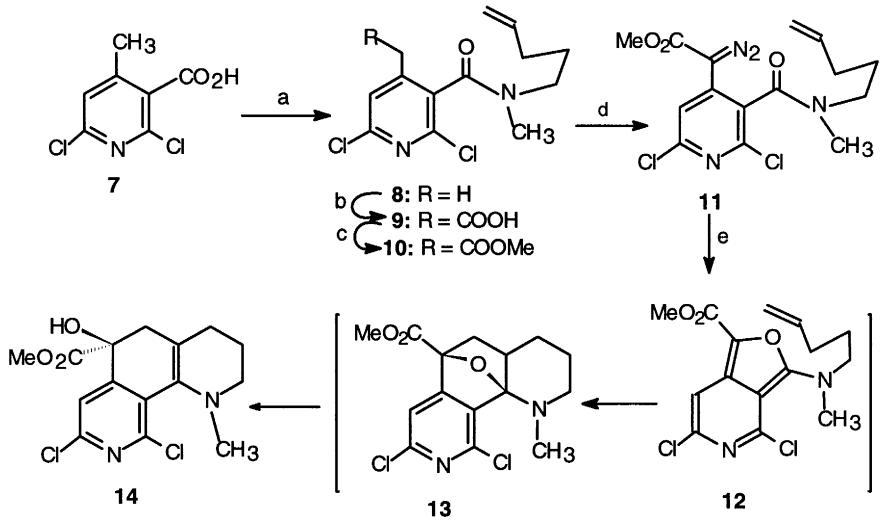


We have recently reported on a Hamaguchi–Ibata reaction involving a stable azaisobenzofuran to give functionalized isoquinolines.[3] In this letter, we describe for the first time an intramolecular[4] version **6→5** of this methodology which has allowed synthesis of **14**, a molecule which incorporates the basic ring system present in bridged anabasines.

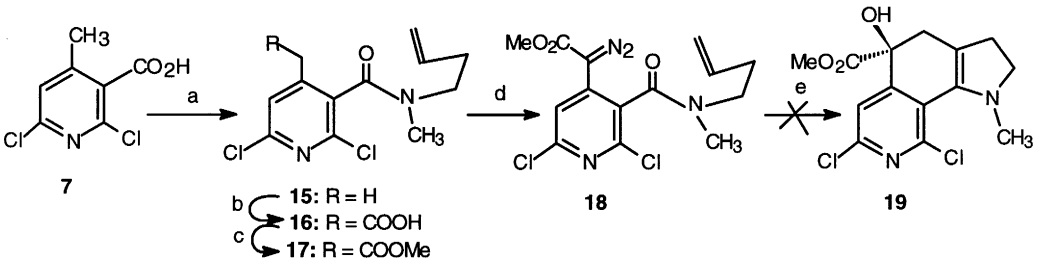
The substituted diazoacetic ester **11** (IR: 2110,1715,1637 cm^{-1}), the substrate for the intramolecular Hamaguchi–Ibata reaction, was made from the readily available carboxylic acid **7**[3] by a standard synthetic protocol as shown in Scheme 1.[5] When **11** was exposed to 1 mol% $Rh_2(OAc)_4$ in refluxing benzene for 1 h, the bridged anabasine **14** (mp 165–167°C) was obtained in 52% yield as a yellow crystalline solid via intramolecular cycloaddition **12→13** followed by ring opening of **13** and subsequent proton transfer. The structure of **14** is supported by its elemental analysis, ^1H and ^{13}C NMR spectra[6] (Scheme 1).



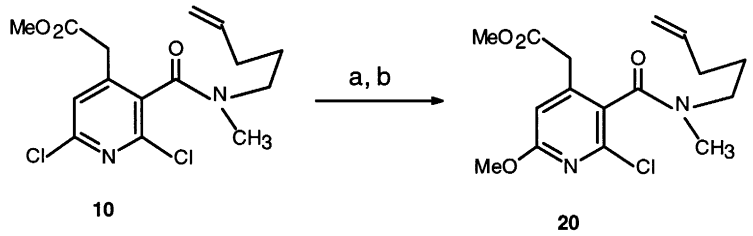
Scheme 1. (a) $(COCl)_2$, PhH, reflux and then *N*-methylpent-4-enylamine, py, rt, 72%; (b) LDA, THF, −78°C and then CO_2, 83%; (c) CH_2N_2, 94%; (d) 4-acetamidobenzenesulfonyl azide, Et_3N, 0°C to rt, 12 h (Ref. 7), 93%; (e) $Rh_2(OAc)_4$, PhH, reflux, 1 h, 52%

Unfortunately, when the dienophile tether was shortened by one methylene unit, no intramolecular cycloaddition leading to a bridged nicotine analogue **19** was obtained (Scheme 2).[5] This difficulty may be overcome as recently shown by Padwa et al[8] by replacing the amine tether (cf. **6**) by an amide tether.[9]

A noteworthy feature of our approach is that one of the chloro substituents flanking the nitrogen atom in **10** can be selectively replaced by a nucleophile, if desired. It is evident that there is considerable steric hindrance to nucleophilic attack at C-2 in **10**. Indeed, exposure of **10**[5,10] to aqueous alkali in methanol and a follow-up treatment with diazomethane gave practically a single product to which structure **20**[5,11] is assigned based on ^1H NMR analysis[12] (Scheme 3).



Scheme 2. (a) $(COCl)_2$, PhH, reflux and then *N*-methylbut-3-enylamine, py, rt, 66%; (b) LDA, THF, −78°C and then CO_2, 80%; (c) CH_2N_2, 92%; (d) 4-acetamidobenzenesulfonyl azide, Et_3N, 0°C to rt, 12 h (Ref. 7), 89%; (e) $Rh_2(OAc)_4$, PhH, reflux, 1 h



Scheme 3. (a) 10% aq. KOH, MeOH, 12 h, rt; H_3O^+; (b) CH_2N_2 (73% from **10**)

In conclusion, the domino cascade sequence[13] presented herein has allowed ready access to a bridged anabasine analogue. Further work on bridged nicotines and their biological activities are in progress and will be reported in due course.

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5. Compounds **8**–**11**, **15**–**18** and **20** exist as mixtures of rotamers in solution.
6. IR (KBr) ν_{max}: 3378, 1745, 1616 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.41 (s, 1H), 3.69 (s, 3H), 3.20 (bs, 1H), 3.19–3.09 (m, 1H), 2.90–2.75 (m, 1H), 2.65 (1H, dt, *J*=15 and 1.8 Hz), 2.44 (1H, d, *J*=15.1 Hz), 2.40 (s, 3H), 2.20–2.10 (m, 2H), 1.80–1.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$); δ 173.4, 152.6, 147.7, 145.1, 138.2, 125.9, 118.5, 113.7, 74.9, 52.9, 51.3, 41.2, 40.8, 28.8, 18.5. Anal. calcd for $C_{15}H_{16}N_2O_3Cl_2$: C, 52.49; H, 4.69; N, 8.16; found: C, 52.73; H, 4.62; N, 8.10.
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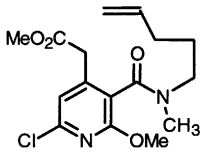
9. This possibility is under investigation.
10. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 and 7.28 (s, 1H), 5.91–5.78 and 5.71–5.60 (m, 1H), 5.12–4.90 (m, 2H), 3.80 (d, 1H, *J*=16.2 Hz), 3.72 and 3.71 (s, 3H), 3.56 (d, 1H, *J*=16.2 Hz), 3.70–3.43 and 3.17–2.96 (m, 2H), 3.11 and 2.87 (s, 3H), 2.20–1.66 (m, 4H).

11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 and 6.64 (s, 1H), 5.93–5.77 and 5.76–5.60 (m, 1H), 5.11–4.90 (m, 2H), 3.95 and 3.94 (s, 3H), 3.77 (d, 1H, *J*=16.2 Hz), 3.70 and 3.68 (s, 3H), 3.51 (d, 1H, *J*=16.2 Hz), 3.72–3.42 and 3.17–3.01 (m, 2H), 3.09 and 2.88 (s, 3H), 2.35–1.65 (m, 4H).
12. Compound **20** is contaminated with a trace of its regioisomer **21**. In **20**, the C-5 proton resonates at δ 6.69 and 6.64 (two rotamers), whereas the C-5 proton in **21** resonates at δ 6.96 and 6.92 (two rotamers); all these signals have moved upfield in comparison to the C-5 signals (δ 7.34 and 7.28) in **10**. The chemical shifts of C-5 proton in the two rotamers of **20** match with the chemical shift of the C-5 proton in **22** (δ 6.6)[14] and not **23** (δ 6.9).[14]



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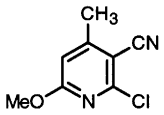

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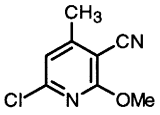

23

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