Synthesis of Furo[2,3-*f*]isoquinolines by Aromatic Claisen Rearrangement and Subsequent Cyclization

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Abstract: Furo[2,3-*f*]isoquinolines were prepared by reacting isoquinolin-5-ol with an allyl bromide. Reaction between the sodium salt of isoquinolinol and and allyl bromide led to the formation of an allyloxyisoquinoline, which was thermally rearranged. The resultant allylisoquinoline was then subjected to acid-catalyzed cyclization to afford the title compound.

Key words: furo[2,3-*f*]isoquinoline, allyl aryl ethers, Claisen rearrangement, ring closure, sonochemical conditions

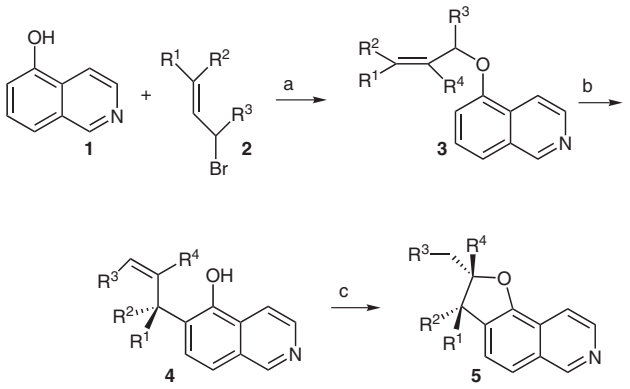
Derivatives of furo[3,2-*f*]isoquinolines were recently found to possess phosphodiesterase IV inhibitor activity.[1] Some of them are considered to be anti-inflammatory and/or anti-arteriosclerotic agents. The structural isomer furo[2,3-*f*]isoquinoline has not received as much attention – only one synthetic method has so far been reported for the preparation of highly substituted derivatives.[2]

Our interest in the preparation of new heterocyclic compounds which might be promising in the treatment of psychiatric disorders prompted us to elaborate novel methods for the synthesis of furo[2,3-*f*]isoquinoline derivatives. We now report a method for the preparation of furoisoquinolines **5a**,**b** and their cycloalkano analogues **5c**,**d**.

For the preparation of compounds **5a–d** we used the Claisen rearrangement of allyl aryl ethers. This thermal sigmatropic rearrangement is one of the most effective methods in the construction of carbon–carbon bonds.[3]

The syntheses of **5a–d** are depicted in Scheme 1. Treatment of isoquinolin-5-ol (**1**) with sodium hydride afforded the corresponding anion which was then reacted with allyl bromide **2a**. The ether **3a**[4] formed was subjected to microwave irradiation assisted [3,3] rearrangement to yield compound **4a**.[5] Acid-catalyzed intramolecular cyclization of the latter afforded furo[2,3-*f*]isoquinoline **5a** (Table 1, entries 1, 5 and 10).

Likewise, reaction between the sodium salt of **1** and methallyl chloride afforded ether **3b**. However, thermal rearrangement of the latter yielded an unexpected product **4b**. A plausible scheme for the formation of compound **4b** was based on the consecutive rearrangement reaction depicted in Scheme 2. In the initial step the [3,3]-sigmatropic rearrangement of ether **3b** afforded intermediate **4c**



Scheme 1 *Reagents and conditions*: (a) NaH, DME, r.t.; (b) chlorobenzene, reflux; or microwave oven, 120 °C; (e) H_2SO_4, 100 °C.

which then underwent a homo[1,5]-H shift to yield compound **6**. A [1,5]-H shift on compound **6** led to the formation of **4b**. Acid-catalyzed intramolecular cyclization of the latter furnished **5b** (Table 1, entries 2, 6 and 11).

The above type of abnormal Claisen rearrangement (**3b** → **4b**) was first reported by Lauer and Filbert.[6] The mechanism of these reactions has been identified as the result of consecutive processes: Claisen rearrangement followed by 1,5-hydrogen shifts.[7]

From the microwave-assisted reaction of **3b** we also isolated the product of the [3,3]-sigmatropic rearrangement (**4c**). The isolation of this intermediate supports the proposed mechanism.

Under similar conditions, the reaction between compound **1** and 3-bromocyclohex-2-enol (**2c**) gave the expected ether **3c**, which was then rearranged by heating in chlorobenzene. The reaction took place at 132 °C over 30 hours. The microwave-accelerated rearrangement reaction worked at a temperature below 120 °C and needed only five hours. Microwave heating was superior to conventional external heating in this rearrangement reaction (Table 1, entries 6 and 8).

Acid-catalyzed intramolecular cyclization of the isolated **4d** yielded an approximately 1:1 mixture of stereoisomers (**5c**). Small amounts of this mixture were separated by preparative HPLC and the stereochemistry of isomers was established by extensive ^{1}H and ^{13}C NMR studies. For example, in the *cis*-fused isomer we saw an NOE interaction between the 6b proton and the 10a proton (3.39 and 4.91,

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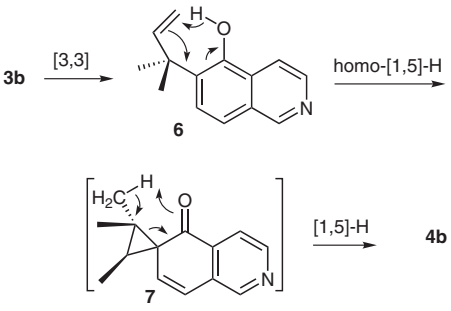
Table 1 Compounds Prepared by the Rearrangement of **3a–d** and Subsequent Cyclization

Entry	Substrate	Product	R^1	R^2	R^3	R^4	Temp (°C)	Time (h)	Yield[a] (%)
1	**2a**	**3a**	H	H	H	H	r.t.	48	48
2	**2b**	**3b**	Me	Me	H	H	r.t.	48	62
3	**2c**	**3c**	H	$(CH_2)_3$		H	r.t.	48	58
4	**2d**	**3d**	H	$(CH_2)_4$		H	r.t.	48	52
5	**3a**	**4a**	H	H	H	H	120[b]	6	44
6	**3b**	**4b**	Me	Me	H	H	132[c] 120[b]	30 6	74 72
7	**3b**	**4c**	H	Me	H	Me	120[b]	6	Trace amounts
8	**3c**	**4d**	H	$(CH_2)_3$		H	132[c] 120[b]	30 6	64 70
9	**3d**	**4e**	H	$(CH_2)_4$		H	120[b]	6	42
10	**4a**	**5a**	H	H	H	H	100	1	45
11	**4b**	**5b**	Me	H	H	Me	100	1	87
12	**4d**	**5c**	H	$(CH_2)_3$		H	100	1	82
13	**4e**	**5d**	H	$(CH_2)_4$		H	100	1	52

[a] Isolated and unoptimized yields.
[b] Method B (in microwave oven).
[c] Method A (in chlorobenzene).



Scheme 2

respectively). This coupling was absent in the case of the corresponding *trans*-isomer.

The reaction between **1** and 3-bromocyclohept-1-ene (**2d**) gave similar results (Table 1, entries 4, 9 and 13). The initially formed ether **3d** was irradiated with microwaves and the rearrangement product **4e** was submitted to acid-catalyzed cyclization. An approximately 3:1 mixture of stereoisomers **5d** was isolated and the isomers were separated by preparative HPLC.

In summary, furo[2,3-*f*]isoquinoline derivatives **5a–d** have been prepared from isoquinolin-5-ol (**1**) and allyl bromides **2a–d**. This convenient process involves the rearrangement reaction of ethers **3a–d**, followed by acid-catalyzed cyclization of the products **4a–d**.[8] The present synthetic scheme would enable access to a variety of furoisoquinolines, which would have interesting biological properties.

Solvents were used as received from commercial vendors and no further attempts were made to purify or dry them. Melting points were determined on a Büchi apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 500 MHz and 125 MHz, respectively. All NMR spectra are reported in ppm relative to TMS. Merck precoated silica gel 60 F_{254} plates were used for TLC and Kieselgel 60 for column chromatography. Solvents were mixed on a v/v basis. HPLC chromatographic analyses and separations were performed with a Waters 600 equipped with a photodiode array detector 990. The stationary phase for compound **5c** was Supelcosil™ SPLC-18-DB, 250 × 10 mm. For compound **5d** the stationary phase was Waters Symmetry C_{18}, 150 × 3.9 mm. For the separation of the isomers of **5c** we used a Supelcosil™ PLC-18 column, 250 × 21.2 mm, eluents MeOH–H_2O, 7:3. Microwave-accelerated reactions were conducted in an CEM Focused Microwave™ synthesis System (CEM Corporation, Metthews, NC, USA).

3-Bromocyclohex-1-ene (**2c**)[9] and 3-bromocyclohept-1-ene (**2d**)[10] were prepared using literature procedures.

Preparation of Ethers 3; General Procedure

To a cold stirred suspension of NaH (10 mmol, 63.7% in mineral oil) in DME (40 mL) a soln of isoquinolin-5-ol (**1**: 1.16 g, 8 mmol) in DME (150 mL) was added dropwise and the resulting mixture was stirred at 0 °C for 2 h. To this mixture was added dropwise the appropriate bromine (**2**: 10 mmol) and stirring was continued at r.t. for 48 h. The reaction mixture was quenched with sat. aq NaCl (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 1N NaOH soln and H_2O and then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure provided a residue which was purified by column chromatography on silica gel (acetone–CH_2Cl_2, 4:1).

5-Allyloxyisoquinoline (3a)
Yield: 48%; light brown oil; R_f = 0.62 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 4.71 (d, *J* = 4.0 Hz, 2 H, O-CH_2), 5.35 (dd, *J* = 10.5, 1.2 Hz, 1 H, H-3′), 5.52 (dd, *J* = 17.5, 1.3 Hz, 1 H, H-3′), 6.16 (m, 1 H, H-2′), 6.98 (d, *J* = 7.6 Hz, 1 H, H-6), 7.47 (t, *J* = 8 Hz, 1 H, H-7), 7.53 (d, *J* = 8.2 Hz, 1 H, H-8), 8.05 (d, *J* = 6.0 Hz, 1 H, H-4), 8.53 (d, *J* = 6.0 Hz, 1 H, H-3), 9.20 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 69.07 (C-1′), 108.83 (C-6), 115.10 (C-4), 117.86 (C-3′), 119.46 (C-8), 127.31 (C-7), 128.59 (C-4a), 129.49 (C-8a), 132.73 (C-2′), 142.67 (C-3), 151.82 (C-1), 153.33 (C-5).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.74; H, 6.23; N, 7.23.

5-(3-Methylbut-2-enyloxy)isoquinoline (3b)
Yield: 62%; yellow oil; R_f = 0.81 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 3 H, CH_3), 1.82 (s, 3 H, CH_3), 4.68 (d, *J* = 6.5 Hz, 2 H, O-CH_2), 5.58 (t, *J* = 6.5 Hz, 1 H, H-2′), 6.98 (d, *J* = 7.5 Hz, 1 H, H-6), 7.47 (t, *J* = 8.0 Hz, 1 H, H-7), 7.48 (d, *J* = 8.0 Hz, 1 H, H-8), 8.04 (d, *J* = 5.8 Hz, 1 H, H-4), 8.50 (d, *J* = 8.5 Hz, 1 H, H-3), 9.19 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 18.25 (CH_3), 25.73 (CH_3), 65.14 (C-1′), 108.43 (C-6), 114.99 (C-4), 118.77 (C-8), 118.99 (C-2′), 127.08 (C-7), 128.35 (C-4a), 129.09 (C-8a), 137.91 (C-3′), 141.88 (C-3), 151.18 (C-1), 153.25 (C-5).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.02; H, 6.83; N, 6.33.

5-(Cyclohex-2-enyloxy)isoquinoline (3c)
Yield: 58%; yellow oil; R_f = 0.75 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.66 (m, 1 H, H-5′), 1.89 (m, 1 H, H-5′), 1.98 (m, 2 H, H-6′), 2.02 (m, 1 H, H-4′), 2.14 (m, 1 H, H-4′), 4.94 (br s, 1 H, H-1′), 5.93 (d, *J* = 10.3 Hz, 1 H, H-2′), 5.98 (md, *J* = 10.3 Hz, 1 H, H-3′), 7.00 (d, *J* = 7.3 Hz, 1 H, H-6), 7.43 (m, 1 H, H-7), 7.45 (m, 1 H, H-8), 8.02 (d, *J* = 5.8 Hz, 1 H, H-4), 9.17 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 18.98 (C-5′), 25.04 (C-4′), 28.19 (C-6′), 71.19 (C-1′), 109.50 (C-6), 115.05 (C-4), 118.66 (C-8), 125.26 (C-2′), 126.97 (C-7), 128.85 (C-4a), 129.29 (C-8a), 132.19 (C-3′), 141.95 (C-3), 151.25 (C-1), 152.20 (C-5).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.74; H, 6.83; N, 6.03.

5-[(*Z*)-Cyclohept-2-enyloxy]isoquinoline (3d)
Yield: 52%; yellow crystalline solid; mp 54–58 °C; R_f = 0.58 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.46 (m, 1 H, H-5′), 1.73 (m, 1 H, H-6′), 1.75 (m, 1 H, H-5′), 1.93 (m, 1 H, H-7′), 2.11 (m, 1 H, H-6′), 2.15 (m, 2 H, H--4′, H-7′), 2.28 (m, 1 H, H-4′), 5.07 (d, *J* = 10.2 Hz, 1 H, H-1′), 5.89 (m, 1 H, H-2′), 5.92 (m, 1 H, H-3′), 6.94 (d, *J* = 7.4 Hz, 1 H, H-6), 7.46 (m, 1 H, H-7), 7.50 (m, 1 H, H-8), 8.03 (d, *J* = 5.8 Hz, 1 H, H-4), 8.51 (d, *J* = 5.8 Hz, 1 H, H-3), 9.19 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 26.51 (C-5′), 27.42 (C-6′), 28.55 (C-4′), 32.98 (C-7′), 77.79 (C-1′), 109.87 (C-6), 115.27 (C-4), 119.00 (C-8), 127.30 (C-7), 129.07 (C-4a), 129.68 (C-8a), 131.66 (C-3′), 134.94 (C-2′), 142.56 (C-3), 151.82 (C-1), 152.44 (C-5).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 79.94; H, 6.83; N, 6.07.

Rearrangement of Ethers 3a–d; General Procedure
Method A: A soln of ether **3** (5 mmol) in chlorobenzene (50 mL) was heated at reflux for 30 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–acetone, 9:1).

Method B: Ether **3** (10 mmol) was heated at 120 °C for 6 h in a microwave oven. After cooling, the reaction mixture was dissolved in a mixture of CH_2Cl_2–acetone (5:1) and purified by column chromatography (CH_2Cl_2–acetone, 5:1).

6-Allylisoquinolin-5-ol (4a)
Method B: Yield: 44%; yellow crystals; mp 108–112 °C; R_f = 0.4 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 3.69 (d, *J* = 6.3 Hz, 2 H, H-1′), 5.15 (d, *J* = 6.3 Hz, 2 H, H-3′), 5.17 (m, 1 H, H-3′), 6.05 (m, 1 H, H-2′), 7.41 (d, *J* = 8.4 Hz, 1 H, H-7), 7.52 (d, *J* = 8.4 Hz, 1 H, H-8), 8.14 (d, *J* = 6.0 Hz, 1 H, H-4), 8.42 (d, *J* = 6.0 Hz, 1 H, H-3), 9.15 (s, 1 H, H-1), 9.2 (br s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 35.26 (C-1′), 115.89 (C-4), 116.80 (C-3′), 119.51 (C-8), 125.33 (C-6), 128.74 (C-4a and C-8a), 130.38 (C-7), 135.80 (C-2′), 140.99 (C-3), 149.40 (C-5), 151.35 (C-1).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.54; H, 6.20; N, 7.28.

6-(2-Methylbut-3-en-2-yl)isoquinolin-5-ol (4b)
Yield: Method A: 74%; Method B: 72%; brown crystalline solid; mp 121–123 °C; R_f = 0.59 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 6 H, 2 CH_3), 5.44 (d, *J* = 10.5 Hz, 1 H, H-3′), 5.50 (d, *J* = 17.7 Hz, 1 H, H-3′), 6.30 (dd, *J* = 17.7, 10.5 Hz, 1 H, H-2′), 6.70 (br s, 1 H, OH), 7.54 (d, *J* = 8.7 Hz, 1 H, H-8), 7.56 (d, *J* = 8.7 Hz, 1 H, H-7), 7.98 (d, *J* = 5.9 Hz, 1 H, H-4), 8.48 (d, *J* = 5.9 Hz, 1 H, H-3), 9.17 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 26.93 (CH_3), 40.69 (C-1′), 114.44 (C-3′), 115.24 (C-4), 119.35 (C-8), 125.56 (C-7), 128.42 (C-4a), 128.69 (C-8a), 129.33 (C-6), 142.33 (C-3), 147.36 (C-2′), 149.05 (C-5), 151.64 (C-1).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.51; H, 6.82; N, 6.32.

6-(3-Methylbut-3-en-2-yl)isoquinolin-5-ol (4c)
Method B: Yield: trace amounts; brown crystalline solid; mp 95–103 °C. R_f = 0.39 ($CHCl_3$–acetone, 10:1).

^{1}H NMR ($CDCl_3$): δ = 1.47 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 3.96 (q, *J* = 6.9 Hz, 1 H, H-1′), 5.09 (s, 1 H, H-3′), 5.14 (s, 1 H, H-3′), 7.43 (d, *J* = 8.4 Hz, 1 H, H-7), 7.54 (d, *J* = 8.4 Hz, 1 H, H-8), 8.12 (d, *J* = 5.9 Hz, 1 H, H-4), 8.20 (br s, 1 H, OH), 8.43 (d, *J* = 5.8 Hz, 1 H, H-3), 9.15 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 18.76 (CH_3), 21.99 (CH_3), 41.65 (C-1′), 111.32 (C-3′), 115.78 (C-4), 119.48 (C-8), 128.11 (C-7), 128.49 (C-4a), 129.42 (C-6), 140.68 (C-3), 148.75 (C-5), 148.93 (C-8a), 150.88 (C-1).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.61; H, 6.86; N, 6.62.

6-(Cyclohex-2-enyl)isoquinolin-5-ol (4d)
Yield: Method A: 64%; Method B: 70%; brown crystalline solid; mp 149–152 °C; R_f = 0.63 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.69 (m, 2 H, H-4′, H-5′), 1.83 (m, 1 H, H-5′), 2.08 (m, 1 H, H-4′), 2.17 (br s, 2 H, H-6′), 3.92 (br s, 1 H, H-1′), 5.87 (d, *J* = 10.0 Hz, 1 H, H-2′), 6.12 (d, *J* = 7.8 Hz, 1 H, H-3′), 7.43 (d, *J* = 8.4 Hz, 1 H, H-7), 7.52 (d, *J* = 8.4 Hz, 1 H, H-8), 7.6 (br s, 1 H, OH), 8.12 (d, *J* = 5.9 Hz, 1 H, H-4), 8.43 (d, *J* = 8.4 Hz, 1 H, H-3), 9.15 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 21.45 (C-5′), 24.93 (C-6), 30.12 (C-4′), 38.04 (C-1′), 115.58 (C-4), 119.07 (C-8), 128.02 (C-8a), 128.30 (C-4a), 128.88 (C-2′), 129.18 (C-7), 130.31 (C-6), 131.14 (C-3′), 140.24 (C-3), 148.51 (C-5), 150.56 (C-1).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.53; H, 6.92; N, 6.01.

6-(Cyclohept-2-enyl)isoquinolin-5-ol (4e)
Method B: Yield: 42%; yellow solid; mp 74–78 °C; R_f = 0.45 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.50 (m, 1 H, H-5′), 1.65 (m, 1 H, H-6′), 1.81 (m, 1 H, H-5′), 1.88 (m, 2 H, H-7′), 1.94 (m, 1 H, H-6′), 2.21 (m, 1 H, H-4′), 2.31 (m, 1 H, H-4′), 4.15 (m, 1 H, H-1′), 5.78 (d, *J* = 8.4 Hz, 1 H, H-2′), 5.97 (m, 1 H, H-3′), 7.48 (d, *J* = 8.5 Hz, 1 H, H-7), 7.53 (d, *J* = 8.5 Hz, 1 H, H-8), 8.13 (d, *J* = 6.0 Hz, 1 H, H-4), 8.43 (d, *J* = 6.0 Hz, 1 H, H-3), 9.1 (br s, 1 H, OH), 9.14 (s, 1 H, H-1).

^{13}C NMR ($CDCl_3$): δ = 27.13 (C-5′), 28.88 (C-4′), 29.89 (C-6′), 34.67 (C-7′), 41.72 (C-1′), 115.97 (C-4), 119.73 (C-8), 128.37 (C-8a), 128.54 (C-7), 128.92 (C-4a), 132.92 (C-6), 133.81 (C-3′), 135.10 (C-2′), 141.10 (C-3), 147.82 (C-5), 151.30 (C-1).

Anal. Calcd for $C_{16}H_{17}NO$ (239.31): C, 80.30; H, 7.16; N, 5.85. Found: C, 79.98; H, 6.77; N, 6.07.

Furo[2,3-*f*]isoquinolines (5a–d); General Procedure
A mixture of compound **4** (1 mmol) and concd H_2SO_4 (0.1 g, 2.1 mmol) was heated in a water bath for 1 h. After cooling, the reaction mixture was poured onto ice (10 g), basified using 1 N NaOH (7 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was purified by column chromatography using CH_2Cl_2–acetone (5:1) as eluent.

2,3-Dihydro-2-methylfuro[2,3-*f*]isoquinoline (5a)
Yield: 45%; yellow oil; R_f = 0.68 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.55 (d, *J* = 16.3 Hz, 3 H, CH_3), 2.99 (dd, *J* = 15.6, 7.6 Hz, 1 H, H-3), 3.50 (dd, *J* = 15.6, 9.2 Hz, 1 H, H-3), 5.15 (m, 1 H, H-2), 7.40 (d, *J* = 8.2 Hz, 1 H, H-4), 7.45 (d, *J* = 8.2 Hz, 1 H, H-5), 7.70 (d, *J* = 5.8 Hz, 1 H, H-9), 8.44 (d, *J* = 5.8 Hz, 1 H, H-8), 9.17 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 21.99 (CH_3), 37.88 (C-3), 80.78 (C-2), 114.43 (C-9), 119.57 (C-5), 122.63 (C-9a), 124.36 (C-4), 124.79 (C-3a), 129.02 (C-5a), 142.22 (C-8), 152.31 (C-6), 153.85 (C-9b).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.52; H, 6.09; N, 7.79.

2,3-Dihydro-2,2,3-trimethylfuro[2,3-*f*]isoquinoline (5b)
Yield: 87%; yellow crystalline solid; mp 55–57 °C; R_f = 0.73 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.29 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 3.33 (q, *J* = 7.2 Hz, 1 H, H-3), 7.37 (d, *J* = 8.2 Hz, 1 H, H-4), 7.48 (d, *J* = 8.2 Hz, 1 H, H-5), 7.71 (d, *J* = 5.8 Hz, 1 H, H-9), 8.44 (d, *J* = 5.8 Hz, 1 H, H-8), 9.18 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 15.11 (CH_3), 22.18 (CH_3), 28.48 (CH_3), 46.45 (C-3), 91.08 (C-2), 114.62 (C-9), 119.47 (C-5), 122.88 (C-9a), 123.63 (C-4), 129.16 (C-5a), 130.34 (C-3a), 142.05 (C-3), 152.33 (C-6), 152.36 (C-9b).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.56; H, 6.80; N, 6.72.

6b,7,8,9,10,10a-Hexahydrobenzofuro[2,3-*f*]isoquinoline (5c)
Yield: 82%; light brown crystals; R_f = 0.8 (CH_2Cl_2–acetone, 2:1).

cis-Isomer: t_R = 14.19 min (MeOH–H_2O–H_3PO_4, 4:6:0.05).

^{1}H NMR ($CDCl_3$): δ = 1.40 (m, 1 H, H-8), 1.55 (m, 4 H, H-7, H-8, 2 H-9)C_7, C_8-H, and 2 C_9-H), 1.92 (m, 2 H, H-7, H-10), 2.10 (m, 1 H, H-10), 3.39 (q, *J* = 7.2 Hz, 1 H, H-6b), 4.91 (m, 1 H, H-10a), 7.43 (d, *J* = 8.1 Hz, 1 H, H-6), 7.51 (d, *J* = 8.1 Hz, 1 H, H-5), 7.74 (d, *J* = 6 Hz, 1 H, H-1), 8.46 (d, *J* = 6 Hz, 1 H, H-2), 9.20 (br s, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 20.29 (C-9), 21.76 (C-8), 27.40 (C-10), 28.16 (C-7), 41.31 (C-6b), 83.89 (C-10a), 114.52 (C-1), 120.00 (C-5), 123.07 (C-11b), 123.25 (C-6), 129.06 (C-4a), 131.57 (C-6a), 142.03 (C-2), 152.38 (C-4), 153.93 (C-11a).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.72; H, 6.89; N, 5.97.

trans-Isomer: t_R = 11.66 (MeOH–H_2O–H_3PO_4, 4:6:0.05).

^{1}H NMR ($CDCl_3$): δ = 1.28 (m, 1 H, H-9), 1.48 (m, 1 H, H-9), 1.67 (m, 1 H, H-10), 1.83 (m, 2 H, H-8), 2.00 (m, 2 H, H-7), 2.16 (m, 1 H, H-10), 3.13 (br s, 1 H, H-6b), 4.83 (br s, 1 H, H-10a), 7.22 (d, *J* = 8.2 Hz, 1 H, H-6), 7.41 (d, *J* = 8.2 Hz, 1 H, H-5), 7.96 (d, *J* = 6 Hz, 1 H, H-1), 8.46 (d, *J* = 6 Hz, 1 H, H-2), 9.14 (s, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 17.17 (C-9), 29.21 (C-7), 31.80 (C-6b), 32.42 (C-8), 33.33 (C-10), 71.66 (C-10a), 114.86 (C-1), 117.92 (C-5), 124.20 (C-6a), 126.93 (C-11b), 128.43 (C-6), 128.57 (C-4a), 142.17 (C-2), 150.42 (C-11a), 151.68 (C-4).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.02; H, 6.47; N, 5.98.

7,8,9,10,11,11a-Hexahydro-6bH-cyclohepta[4,5] furo[2,3-*f*]isoquinoline (5d)
Yield: 52%; yellow crystalline solid mp 32–39 °C; R_f = 0.73 (CH_2Cl_2–acetone, 2:1).

trans-Isomer: t_R = 4.4 min (MeOH–H_2O, 4:1).

^{1}H NMR ($CDCl_3$): δ = 1.25 (m, 1 H, H-9), 1.38 (m, 1 H, H-10), 1.53 (m, 1 H, H-10), 1.64 (m, 1 H, H-9), 1.80 (m, 2 H, H-7, H-11), 2.09 (m, 1 H, H-8), 2.14 (m, 2 H, H-7, H-11), 2.40 (m, 1 H, H-8), 3.18 (m, 1 H, H-6b), 4.95 (m, 1 H, H-11a), 7.30 (d, *J* = 8.3 Hz, 1 H, H-6) 7.43 (d, *J* = 8.3 Hz, 1 H, H-5), 7.94 (d, *J* = 5.8 Hz, 1 H, H-1), 8.48 (d, *J* = 5.8 Hz, 1 H, H-2), 9.12 (s, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 24.40 (C-10), 26.21 (C-9), 29.21 (C-8), 32.14 (C-6b), 35.51 (C-7), 36.70 (C-11), 73.31 (C-11a), 114.89 (C-1), 118.29 (C-5), 124.20 (C-6a), 128.26 (C-12b), 128.36 (C-4a), 128.60 (C-6), 142.49 (C-2), 148.04 (C-12a), 151.52 (C-4).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.04; H, 6.77; N, 5.91.

cis-Isomer: t_R = 5.24 min (MeOH–H_2O, 4:1).

^{1}H NMR ($CDCl_3$): δ = 3.76 (m, 1 H, H-6b), 5.18 (m, 1 H, H-11a), 7.35 (d, *J* = 8.2 Hz, H-6), 7.42 (d, *J* = 8.2 Hz, H-5), 7.70 (d, *J* = 5.8 Hz, 1 H, H-1), 8.44 (d, *J* = 5.8 Hz, 1 H, H-2), 9.18 (s, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 47.18 (C-6b), 88.25 (C-11a), 114.63 (C-1), 122.47 (C-6a), 123.74 (C-6), 129.14 (C-12b), 129.25 (C-4a), 142.20 (C-2), 152.29 (C-4), 153.25 (C-12a).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.44; H, 6.79; N, 5.52.

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References

(1) Yasuhiko, K.; Matsumoto, T.; Fujii, N. PCT Int. Appl. 20030103, *Chem. Abstr.* **2005**, *138*: 73247.
(2) Roger, R.; Guillaumel, J.; Demerseman, P.; Platzer, N.; Buisson, J.-P. *Bull. Soc. Chim. Fr.* **1972**, 4201.

(3) For excellent monographs on the Claisen rearrangement, see: (a) Tarbell, D. S. *Org. React.* **1944**, *2*, 2. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Murray, A. W. *Org. React. Mech.* **1980**, 517. (d) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (e) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (f) Nubbemeyer, U. *Synthesis* **2003**, 961. (g) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(4) Some ethers of isoquinolin-5-ol expressed strong bactericidal activity on *Helicobacter pylori*: Yoshida, Y.; Barrett, D.; Azami, H.; Morinaga, C.; Matsumoto, S.; Matsumoto, Y.; Takasugi, H. *Bioorg. Med. Chem.* **1999**, *7*, 2647.

(5) In recent years there has been an increasing interest in the use of microwave irradiation to heat chemical reactions, see: (a) Farand, J. A.; Denissova, I.; Barriault, L. *Heterocycles* **2004**, *62*, 735. (b) Kotha, S.; Mandal, K.; Deb, A. C.; Banerjee, S. *Tetrahedron Lett.* **2004**, *45*, 9603. (c) Rao, V. V.; Reddy, G. V.; Yadla, R.; Narsaiah, B.; Rao, P. S. *ARKIVOC* **2005**, *(iii)*, 211. (d) Jacob, A. M.; Moody, C. J. *Tetrahedron Lett.* **2005**, *46*, 8823. (e) Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651; and references cited therein.

(6) Lauer, W. M.; Filbert, W. F. *J. Am. Chem. Soc.* **1936**, *58*, 1388.

(7) (a) Hurd, C. D.; Pollack, M. A. *J. Org. Chem.* **1939**, *3*, 550. (b) Marwell, E. N. *J. Org. Chem.* **1960**, *25*, 676. (c) Lauer, W. M.; Douldoras, G. A.; Hileman, R. E.; Lupino, R. *J. Org. Chem.* **1961**, *26*, 4785. (d) Marwell, E. N.; Anderson, D. R.; Ong, J. *J. Org. Chem.* **1962**, *27*, 1109. (e) Roberts, R. M.; Landolt, R. G.; Greene, R. N.; Heyer, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 1404. (f) Scheinmann, F.; Barner, R.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1603. (g) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1974**, *22*, 1. (h) Schobert, R.; Siegfried, S.; Gordon, G.; Mulholland, D.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2001**, *42*, 4561.

(8) The Claisen rearrangement and subsequent cyclization under acidic conditions has been widely used for the preparation of cyclic compounds. For general reviews and selected examples, see: (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley & Sons: New York, **1989**. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, **1996**. (c) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (d) Rischke, H.; Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3106. (e) Murray, R. D. H.; Forbes, I. T. *Tetrahedron* **1978**, *34*, 1411. (f) Mohan, C.; Kumar, V.; Mahajan, M. P. *Tetrahedron* **2004**, *45*, 6075. (g) Miyata, O.; Takeda, N.; Kimura, Y.; Takemoto, Y.; Tohnai, N.; Miyata, M.; Naito, T. *Tetrahedron* **2006**, *62*, 3629.

(9) Cox, R. A.; Swallow, A. J. *J. Chem. Soc.* **1958**, 3727.

(10) Dondas, H. A.; Grigg, R.; Thibault, S. *Tetrahedron* **2001**, *57*, 7035.