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Acid-mediated three-component aza-Diels–Alder reactions of 2-aminophenols under controlled microwave heating for synthesis of highly functionalized tetrahydroquinolines. Part 9: Chemistry of aminophenols☆

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Abstract—The aza-Diels–Alder reactions of two 2-aminophenols in combination with six substituted benzaldehydes and two electron-rich cyclic alkenes were investigated under controlled microwave heating. The reactions were carried out in the presence of a catalytic amount of CF_3CO_2H in MeCN at 60 °C for 15 min, affording highly functionalized 8-hydroxy-1,2,3,4-tetrahydroquinolines in 39–59% isolated yields and in 36:64–16:84 diastereomer ratios in favor of the trans isomers. The microwave-heated three-component aza-Diels–Alder reactions completed in significantly reduced reaction time to give the same level of chemical yield and diastereomer ratio obtained from the room temperature reaction.

1. Introduction

1,2,3,4-Tetrahydroquinoline[1] is an important heterocyclic scaffold of medicinal and therapeutical interests. Among the currently available synthetic methodologies, the aza-Diels–Alder reaction is the most enabling and versatile approach to functionalized 1,2,3,4-tetrahydroquinolines.[2] The reaction can be carried out in one-pot fashion starting from an aniline, an aldehyde, and an electron-rich alkene, which is known as one of the three-component reactions.[2b] Activation of *N*-arylaldimines toward cycloadditions with alkenes is required. Lanthanide triflates, other Lewis acids,[3,4] and protic acids[5] are the catalysts of choice. In recent years miscellaneous promoters have been reported, including molecular iodine, perchlorates, montmorillonite clay, Selectfluor™ fluorinating reagent, and polymer-supported benzotriazole.[6] The aza-Diels–Alder reactions have been reported to proceed under photochemical conditions,[7] and in aqueous media,[8] fluorinated solvents,[9] and ionic liquids.[10] Moreover, it has been tailored for solid-phase synthesis[11] and used as the key step in alkaloid synthesis.[12] During the past few years, we have established methodologies for diversity-oriented synthesis of indoles,[13] benzofurans,[14] 1,4-benzoxazines,[15a–c] and dibenz[*b*,*f*][1,4]oxazepines[15d] by using readily available 2-aminophenols as the starting materials. In connection with our interest in microwave-assisted organic synthesis,[13c,15,16] we have successfully combined the Ugi four-component reaction (U-4CR) of 2-aminophenols with microwave chemistry for high-throughput synthesis of heterocycles.[15c,d] In this article, we report on aza-Diels–Alder reactions of 2-aminophenols under controlled microwave heating[17] for synthesis of highly functionalized 8-hydroxy-1,2,3,4-tetrahydroquinolines.[18]

2. Results and discussion

Although substituted anilines have been extensively used in the three-component aza-Diels–Alder reactions, there are very limited examples of 1,2,3,4-tetrahydroquinolines synthesized via the aza-Diels–Alder reactions of 2-aminophenols.[4c,h,o,p] Kobayashi and co-worker applied 2-aminophenol-derived *N*-arylaldimines in asymmetric aza-Diels–Alder reactions catalyzed by a chiral Yb complex.[4c] The phenolic hydroxy group proved to be essential for high asymmetric induction. Qian and co-workers reported the $GdCl_3$-catalyzed one-pot aza-Diels–Alder reaction of 2-aminophenol (**1a**) with benzaldehyde (**2a**) and 3,4-dihydro-2*H*-pyran (**3a**) in MeCN at room temperature for 90 min to afford the pyrano[3,2-*c*]quinolines **4a** and **5a** in 60% combined yield and in a 35:65 isomer ratio (Scheme 1).[4h] Similar reaction using 2,3-dihydrofuran (**3b**) as the alkene

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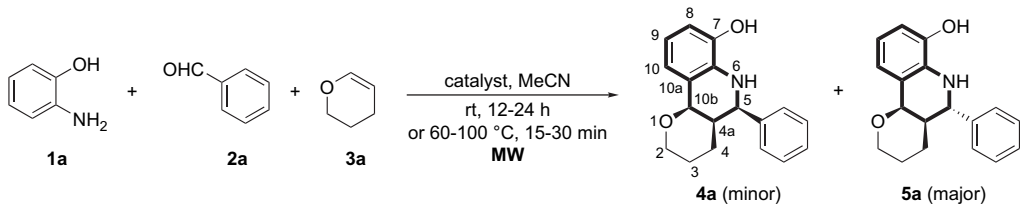

Scheme 1. Three-component aza-Diels–Alder reaction of 2-aminophenol **1a**.

component furnished the corresponding furo[3,2-*c*]quinolines in 67% combined yield and in a 48:52 isomer ratio. As compared to other anilines used by Qian et al.,[4h] lower chemical yields were observed for the aza-Diels–Alder reaction of 2-aminophenol (**1a**). In another report by Batey and co-worker, <20% yield was obtained for the aza-Diels–Alder reaction of 2-aminophenol (**1a**) with 2-ethoxytetrahydrofuran and cyclopentadiene catalyzed by $Dy(OTf)_3$ in MeCN at room temperature for 24 h.[4p] We began our investigation with the aza-Diels–Alder reaction of **1a** with **2a** and **3a** as shown in Scheme 1. Some results on optimization of reaction conditions under controlled microwave heating along with the room temperature entries are summarized in Table 1.

We first examined the room temperature reaction in MeCN in the presence of CF_3CO_2H (Table 1, entries 1 and 2). The adducts **4a** and **5a** were isolated in 43% and 57% yields by using 1.1 equiv (12 h) and 0.11 equiv (24 h) of the acid, respectively. The isomer ratio of **4a**:**5a** was 18:82 in both trials. An improved yield of 65% was obtained for the reaction conducted by using 11 mol % of $Yb(OTf)_3$ as the catalyst, but the isomer ratio of **4a**:**5a** decreased to 36:64 (Table 1, entry 3). The latter results are consistent with those of Qian et al. by employing 20 mol % of $GdCl_3$.[4h] We then performed the same aza-Diels–Alder reaction in MeCN in the presence of 0.01–0.11 equiv of CF_3CO_2H with microwave heating at 60–100 °C for 15–30 min (Table 1, entries 4–8). The reactions at 60 °C afforded better yields. After adjusting the reactant ratio of **1a**:**2a**:**3a** to 1.2:1.2:1.0, the adducts **4a** and **5a** were produced in 59% yield and in 18:82 ratio with microwave irradiation at 60 °C for 15 min in the presence of 0.13 equiv of CF_3CO_2H (Table 1, entry 9). Unfortunately, the microwave-assisted reactions with $Yb(OTf)_3$ catalyst gave inferior yields and isomer ratios (Table 1, entries 10–12).

In Kobayashi's[4c] and Qian's[4h] studies on aza-Diels–Alder reactions involving 2-aminophenol (**1a**), only two aromatic aldehydes, 1-naphthaldehyde and benzaldehyde (**2a**), were used. With the optimized reaction conditions given in the entry 9 of Table 1, we carried out the microwave-assisted aza-Diels–Alder reactions by combination of two aminophenols **1a**,**b**, six aromatic aldehydes **2a–f**, and two cyclic alkenes **3a**,**b** (Scheme 2). According to the results listed in Table 2, the reactions of 3,4-dihydro-2*H*-pyran (**3a**) generally gave higher yields (48–59%) and stereoselectivities (24:76–16:84) (Table 2, entries 1–4, 9, and 10) as compared to those of 2,3-dihydrofuran (**3b**). The latter afforded the

Table 1. Optimization of reaction conditions for three-component aza-Diels–Alder reaction of 2-aminophenol **1a**[a]

Entry	Conditions	Catalyst[b]	Combined yield (%)[c]	Ratio of **4a**:**5a**[d]
1	**1a**:**2a**:**3a**=1.0:1.1:1.2, rt, 12 h	CF_3CO_2H (1.1 equiv)	43	18:82
2	**1a**:**2a**:**3a**=1.0:1.1:1.2, rt, 24 h	CF_3CO_2H (0.11 equiv)	57	18:82
3	**1a**:**2a**:**3a**=1.0:1.1:1.2, rt, 24 h	$Yb(OTf)_3$ (0.11 equiv), $MgSO_4$	65 (60)[e]	36:64 (35:65)[e]
4	**1a**:**2a**:**3a**=1.0:1.1:1.2, 60 °C, 15 min	CF_3CO_2H (0.11 equiv)	46	17:83
5	**1a**:**2a**:**3a**=1.0:1.1:1.2, 60 °C, 30 min	CF_3CO_2H (0.11 equiv)	51	23:77
6	**1a**:**2a**:**3a**=1.0:1.1:1.2, 80 °C, 15 min	CF_3CO_2H (0.11 equiv)	43	25:75
7	**1a**:**2a**:**3a**=1.0:1.1:1.2, 100 °C, 30 min	CF_3CO_2H (0.11 equiv)	<33	21:79
8	**1a**:**2a**:**3a**=1.0:1.1:1.2, 100 °C, 15 min	CF_3CO_2H (0.01 equiv)	28	25:75
9	**1a**:**2a**:**3a**=1.2:1.2:1.0, 60 °C, 15 min	CF_3CO_2H (0.13 equiv)	59	18:82
10	**1a**:**2a**:**3a**=1.0:1.1:1.2, 60 °C, 30 min	$Yb(OTf)_3$ (0.11 equiv), 4 Å MS	52	41:59
11	**1a**:**2a**:**3a**=1.0:1.1:1.2, 60 °C, 30 min	$Yb(OTf)_3$ (0.11 equiv)	25	46:54
12	**1a**:**2a**:**3a**=1.2:1.2:1.0, 100 °C, 15 min	$Yb(OTf)_3$ (0.13 equiv)	39	40:60

[a] All microwave-assisted reactions were carried out on a technical microwave reactor with temperature and pressure controlling capacity.
[b] The catalyst loading was calculated according to the amount of **1a** used. The final concentrations of the catalyst were in the range of 30–33 mM except for entries 1 and 8.
[c] Isolated combined yields of **4a** and **5a**.
[d] Calculated according to the isolated weights of **4a** and **5a**.
[e] Data in the parentheses are quoted from Ref. 4h and were obtained with 20 mol % $GdCl_3$ and $MgSO_4$ in MeCN at room temperature for 90 min.

Scheme 2. Microwave-assisted synthesis of highly functionalized 1,2,3,4-tetrahydroquinolines **4** and **5**.

Table 2. Microwave-assisted one-pot synthesis of 8-hydroxy-1,2,3,4-tetrahydroquinolines[a]

Entry	2-Aminophenol (**1**)	Aldehyde (**2**)	Alkene (**3**)	Combined yield (%)[b]	Ratio of **4**:**5**[c]
1	**1a**: R^1=H	**2a**: R^2=R^3=H	**3a**: *n*=2	**4a+5a**: 59 (60)[e]	18:82 (35:65)[e]
2	**1b**: R^1=5-Me	**2a**: R^2=R^3=H	**3a**: *n*=2	**4b+5b**: 48	22:78
3	**1a**: R^1=H	**2b**: R^2=H, R^3=F	**3a**: *n*=2	**4c+5c**: 52	18:82
4	**1a**: R^1=H	**2c**: R^2=Cl, R^3=H	**3a**: *n*=2	**4d+5d**: 51	16:84
5	**1a**: R^1=H	**2a**: R^2=R^3=H	**3b**: *n*=1	**4e+5e**: 41 (67)[e]	29:71 (48:52)[e]
6	**1a**: R^1=H	**2d**: R^2=H, R^3=Cl	**3b**: *n*=1	**4f+5f**: 41	36:64[d]
7	**1b**: R^1=5-Me	**2a**: R^2=R^3=H	**3b**: *n*=1	**4g+5g**: 39	31:69
8	**1a**: R^1=H	**2e**: R^2=CO_2Me, R^3=H	**3b**: *n*=1	**4h+5h**: 40	25:75[d]
9	**1a**: R^1=H	**2e**: R^2=CO_2Me, R^3=H	**3a**: *n*=2	**4i+5i**: 56	16:84
10	**1a**: R^1=H	**2f**: R^2=NO_2, R^3=H	**3a**: *n*=2	**4j+5j**: 51	24:76

[a] A 1.2:1.2:1.0 mixture of **1**:**2**:**3** in MeCN along with 0.13 equiv of CF_3CO_2H to **1** was heated with microwave irradiation at 60 °C for 15 min. All microwave-assisted reactions were carried out on a technical microwave reactor with temperature and pressure controlling capacity.
[b] Isolated combined yields of **4** and **5**.
[c] Calculated according to the isolated weights of **4** and **5**.
[d] Inseparable mixture. The ratio was determined by ^{1}H NMR spectrum.
[e] Data in the parentheses are quoted from Ref. 4h and were obtained with 20 mol % $GdCl_3$ and $MgSO_4$ in MeCN at room temperature for 60–90 min.

products in 39–41% yields and in 36:64–25:75 isomer ratios (Table 2, entries 5–8). The diastereomers **4** and **5** could be separated in most cases and the stereochemistry of the known pairs of compounds **4a/5a** and **4e/5e** was assigned by comparision with the reported spectral data.[4h] For other new compounds, their stereochemistry was suggested analogously. In the cases of **4f/5f** and **4h/5h**, inseparable mixtures were obtained (Table 2, entries 6 and 8). Their ratios were estimated by ^{1}H NMR spectra (see Supplementary data). We tried the three-component reaction of **1b**, **3a**, and *p*-anisaldehyde under the optimized conditions, but the product yield was very low (data not shown). The result was consistent with the early finding of Baudelle and co-workers[5a] that electron-rich aromatic aldehydes were not advantageous for the CF_3CO_2H-mediated aza-Diels–Alder reactions with aniline and 3,4-dihydro-2*H*-pyran. Moreover, the reaction using 2-amino-4-chlorophenol as the amine component gave the pair of adducts in ca. 30% yield in total (data not shown). Due to low yields of the aza-Diels–Alder reactions of substituted 2-aminophenols, a further detail evaluation was not attempted.

3. Conclusion

In summary, we have established the microwave reaction conditions for the CF_3CO_2H-catalyzed three-component aza-Diels–Alder reactions involving 2-aminophenols as the amine building blocks. As compared to 24 h required for the room temperature reaction, the microwave-assisted version can be done at 60 °C for 15 min. In general, electron-deficient aromatic aldehydes provided the adducts in 39–59% isolated yields and in 36:64–16:84 isomer ratios in favor of the trans isomer. Despite the limitation in substrate scope, the above described aza-Diels–Alder reactions of 2-aminophenols under controlled microwave heating provide a high-throughput access to highly functionalized 8-hydroxy-1,2,3,4-tetrahydroquinolines.

4. Experimental

4.1. General methods and the microwave reactor

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C, respectively) with $CHCl_3$ or DMSO as the internal reference. IR spectra were taken on an FT-IR spectrophotometer. Mass spectra (MS) were measured by the +ESI or −ESI method. Melting points are uncorrected. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received. All microwave-assisted reactions were carried out on an Emrys creator from Personal Chemistry AB (now under *Biotage AB*, Uppsala, Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature.

4.2. General procedure for microwave-assisted synthesis of pyrano(or furo)[3,2-*c*]quinolines 4a–j and 5a–j

To a 10-mL pressurized process vial were added sequentially 2-aminophenol (**1**, 1.2 mmol), aldehyde (**2**, 1.2 mmol), MeCN (4 mL), CF_3CO_2H (10 μL, 0.13 mmol), and 3,4-dihydro-2*H*-pyran (**3a**, 1.0 mmol) or 2,3-dihydrofuran (**3b**, 1.0 mmol). The loaded vial was then sealed with a cap containing a silicon septum, and put into the microwave cavity and heated at 60 °C for 15 min (very high mode with maximum power input of 75 W). EtOAc (5 mL) was added to the reaction mixture and the organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL×2). Then the aqueous phase was extracted with EtOAc (5 mL). The combined organic layer was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with EtOAc and petroleum ether (60–90 °C) to afford **4a–j** and **5a–j**. The structures and yields of the products are given in Scheme 2 and Table 2.

4.2.1. (4a*R,5*R**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-5-phenyl-2*H*-pyrano[3,2-*c*]quinoline (4a).[4h]** A white crystalline solid; mp 210–212 °C (EtOAc–hexane) (lit.,[4h] 218–219 °C); R_f=0.58 (25% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (br s, 1H), 7.45–7.26 (m, 5H), 6.75 (d, *J*=7.6 Hz, 1H), 6.61 (d, *J*=7.6 Hz, 1H), 6.53 (t, *J*=8.0 Hz, 1H), 5.25 (d, *J*=4.8 Hz, 1H), 4.64 (br s,

1H), 4.51 (br s, 1H), 3.47 (d, J=11.2 Hz, 1H), 3.30–3.20 (m, 1H), 2.04 (br s, 1H), 1.36 (br s, 3H), 1.11 (br s, 1H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 7.00 (t, J=4.4 Hz, 1H), 6.59 (d, J=4.4 Hz, 1H), 5.32 (d, J=4.8 Hz, 1H), 5.30–5.03 (br s, 1H), 4.62 (s, 1H), 4.30–4.05 (br s, 1H), 3.55 (d, J=10.0 Hz, 1H), 3.39 (t, J=11.6 Hz, 1H), 2.12 (br s, 1H), 1.75–1.17 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.2, 134.3, 128.3 (×2), 127.4, 126.8 (×2), 121.2, 119.9, 117.2, 113.2, 72.9, 60.8, 59.1, 38.9, 25.4, 18.1; HRMS (+ESI) calcd for $C_{18}H_{20}NO_2$ ($M+H^+$), 282.1489; found, 282.1486.

4.2.2. (4a*R,5*S**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-5-phenyl-2*H*-pyrano[3,2-*c*]quinoline (5a).**[4h] A white crystalline solid; mp 188–190 °C (EtOAc–hexane) (lit.,[4h] 190–191 °C); R_f=0.45 (25% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 6.85 (br s, 1H), 6.56 (br s, 2H), 5.50–4.70 (br s, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.60–4.20 (br s, 1H), 4.42 (s, 1H), 4.13–4.10 (m, 1H), 3.73 (td, J=11.2, 2.0 Hz, 1H), 2.12–2.09 (m, 1H), 1.89–1.81 (m, 1H), 1.69–1.61 (m, 1H), 1.51–1.47 (m, 1H), 1.36–1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 142.0, 134.6, 128.5 (×2), 127.8 (×2), 127.7, 122.8, 120.7, 116.4, 114.8, 74.6, 68.6, 54.5, 36.8, 24.0, 22.0; HRMS (+ESI) calcd for $C_{17}H_{20}NO_2$ ($M+H^+$), 282.1489; found, 282.1487.

4.2.3. (4a*R,5*R**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-9-methyl-5-phenyl-2*H*-pyrano[3,2-*c*]quinoline (4b).** A pale-yellow oil; R_f=0.59 (25% EtOAc in hexane); IR (KBr) 3394 (br), 2923, 1597, 1491, 1452, 1042 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 7.434–7.272 (m, 5H), 6.57 (s, 1H), 6.45 (s, 1H), 5.20 (d, J=5.2 Hz, 1H), 4.57 (s, 1H), 4.33 (s, 1H), 3.47–3.44 (m, 1H), 3.28–3.25 (m, 1H), 2.14 (s, 3H), 2.02 (br s, 1H), 1.36 (br s, 3H), 1.10–1.08 (m, 1H); MS (+ESI) m/z 296 ($M+H^+$, 100).

4.2.4. (4a*R,5*S**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-9-methyl-5-phenyl-2*H*-pyrano[3,2-*c*]quinoline (5b).** A white crystalline solid; mp 180–182 °C (EtOAc–hexane); R_f=0.49 (25% EtOAc in hexane); IR (KBr) 3388, 3265 (br), 2944, 2859, 1525, 1456, 1254, 1026 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.41–7.28 (m, 5H), 6.45 (s, 1H), 6.44 (s, 1H), 4.75–4.30 (br s, 1H), 4.53 (d, J=15.2 Hz, 1H), 4.24 (d, J=2.4 Hz, 1H), 3.86 (d, J=11.2 Hz, 1H), 3.56 (t, J=10.4 Hz, 1H), 2.11 (s, 3H), 1.97–1.94 (m, 1H), 1.75–1.57 (m, 2H), 1.29–1.27 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.7, 143.4, 132.0, 128.9 (×2), 128.1 (×2), 128.0, 124.8, 121.7, 121.1, 114.8, 73.9, 67.5, 54.8, 38.9, 24.4, 22.4, 20.9; MS (+ESI) m/z 318 ($M+Na^+$, 45), 296 ($M+H^+$, 100); HRMS (+ESI) calcd for $C_{19}H_{22}NO_2$ ($M+H^+$), 296.1645; found, 296.1639.

4.2.5. (4a*R,5*R**,10b*R**)-5-(2′-Fluorophenyl)-3,4,4a,5,6,10b-hexahydro-7-hydroxy-2*H*-pyrano[3,2-*c*]quinoline (4c).** A white solid; R_f=0.45 (25% EtOAc in hexane); IR (KBr) 3398, 3254 (br), 2959, 1578, 1486, 1437, 1260 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.62 (t, J=6.8 Hz, 1H), 7.37–7.17 (m, 3H), 6.74 (d, J=7.2 Hz, 1H), 6.61 (d, J=7.6 Hz, 1H), 6.54 (t, J=7.2 Hz, 1H), 5.21 (d, J=5.6 Hz, 1H), 4.88 (s, 1H), 4.56 (s, 1H), 3.60–3.40 (m, 1H), 3.28–3.22 (m, 1H), 2.08 (br s, 1H), 1.38 (br s, 3H), 1.09 (br s, 1H); MS (+ESI) m/z 300 ($M+H^+$, 100).

4.2.6. (4a*R,5*S**,10b*R**)-5-(2′-Fluorophenyl)-3,4,4a,5,6,10b-hexahydro-7-hydroxy-2*H*-pyrano[3,2-*c*]quinoline (5c).** A white crystalline solid; mp 178–180 °C (EtOAc–hexane); R_f=0.36 (25% EtOAc in hexane); IR (KBr) 3400 (br), 2934, 1489, 1262, 1051 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.37–7.17 (m, 3H), 6.63 (t, J=4.8 Hz, 2H), 6.46–6.42 (m, 1H), 4.88–4.84 (m, 2H), 4.31 (d, J=3.2 Hz, 1H), 3.84 (d, J=6.8 Hz, 1H), 3.56 (t, J=6.4 Hz, 1H), 2.02 (d, J=8.0 Hz, 1H), 1.67 (d, J=8.4 Hz, 2H), 1.31 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 163.8, 147.8, 138.5, 134.2 (d, J_{C-F}=12.5 Hz), 133.7 (d, J_{C-F}=8.4 Hz), 129.2 (d, J_{C-F}=3.1 Hz), 125.4, 124.9, 120.4, 119.8 (d, J_{C-F}=22.5 Hz), 117.8, 77.6, 71.2, 51.8 (br), 42.1, 28.5, 26.7; MS (+ESI) m/z 300 ($M+H^+$, 100). Anal. calcd for $C_{18}H_{18}FNO_2$: C, 72.22; H, 6.06; N, 4.68. Found: C, 72.10; H, 6.15; N, 4.63.

4.2.7. (4a*R,5*R**,10b*R**)-5-(4′-Chlorophenyl)-3,4,4a,5,6,10b-hexahydro-7-hydroxy-2*H*-pyrano[3,2-*c*]quinoline (4d).** A white solid; R_f=0.45 (25% EtOAc in hexane); IR (KBr) 3396, 3211 (br), 2953, 1589, 1486, 1248, 1092 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.44 (dd, J=12.8, 8.4 Hz, 4H), 6.74 (d, J=7.6 Hz, 1H), 6.61 (d, J=7.6 Hz, 1H), 6.53 (t, J=7.6 Hz, 1H), 5.22 (d, J=5.6 Hz, 1H), 4.62 (s, 1H), 4.58 (s, 1H), 3.48–3.45 (m, 1H), 3.28–3.22 (m, 1H), 2.02 (br s, 1H), 1.40–1.25 (m, 3H), 1.06 (br s, 1H); MS (−ESI) m/z 316 ($M+2-H^+$, 33), 314 ($M-H^+$, 100).

4.2.8. (4a*R,5*S**,10b*R**)-5-(4′-Chlorophenyl)-3,4,4a,5,6,10b-hexahydro-7-hydroxy-2*H*-pyrano[3,2-*c*]quinoline (5d).** A white crystalline solid; mp 184–186 °C (EtOAc–hexane); R_f=0.35 (25% EtOAc in hexane); IR (KBr) 3390, 3312 (br), 2939, 2852, 1508, 1488, 1259, 1088 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.42 (s, 4H), 6.61 (d, J=7.6 Hz, 2H), 6.42 (t, J=7.6 Hz, 1H), 4.79 (br s, 1H), 4.53 (d, J=10.4 Hz, 1H), 4.28 (d, J=2.8 Hz, 1H), 3.84 (d, J=11.6 Hz, 1H), 3.57 (t, J=10.8 Hz, 1H), 1.96–1.93 (m, 1H), 1.72–1.60 (m, 2H), 1.28–1.26 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.7, 142.5, 134.3, 132.3, 130.0 (×2), 128.8 (×2), 121.4, 121.0, 116.2, 113.7, 73.6, 67.4, 54.0, 38.6, 24.3, 22.4; MS (+ESI) m/z 318 ($M+2+H^+$, 33), 316 ($M+H^+$, 100). Anal. calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.40; H, 5.85; N, 4.49.

4.2.9. (3a*R,4*R**,9b*R**)-6-Hydroxy-4-phenyl-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (4e).**[4h] A white crystalline solid; mp 200–201 °C (EtOAc–hexane) (lit.,[4h] 188–189 °C); R_f=0.37 (25% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.30 (m, 5H), 6.99 (d, J=6.8 Hz, 1H), 6.69–6.62 (m, 2H), 5.32 (d, J=8.0 Hz, 1H), 5.20–5.10 (br s, 1H), 4.68 (d, J=2.4 Hz, 1H), 4.31 (br s, 1H), 3.84 (td, J=8.4, 3.2 Hz, 1H), 3.73 (ddd, J=8.0, 8.0, 8.0 Hz, 1H), 2.84–2.77 (m, 1H), 2.29–2.18 (m, 1H), 1.58–1.52 (m, 1H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (br s, 1H), 7.49–7.27 (m, 5H), 6.69 (d, J=7.6 Hz, 1H), 6.61 (d, J=7.6 Hz, 1H), 6.53 (t, J=8.0 Hz, 1H), 5.15 (d, J=8.0 Hz, 1H), 4.59 (d, J=2.8 Hz, 1H), 4.48 (s, 1H), 3.57 (dd, J=8.4, 5.2 Hz, 2H), 2.78–2.68 (m, 1H), 2.02–1.92 (m, 1H), 1.37–1.30 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.1, 143.0, 134.6, 128.7 (×2), 127.5, 126.7 (×2), 123.1, 120.4, 117.8, 112.9, 75.6, 66.0, 56.6, 45.3, 24.7; MS (+ESI) m/z 290 ($M+Na^+$, 100), 268 ($M+H^+$, 68).

4.2.10. (3a*R,4*S**,9b*R**)-6-Hydroxy-4-phenyl-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (5e).**[4h] A white crystalline solid; mp 150–152 °C (EtOAc–hexane) (lit.,[4h] 155–156 °C); R_f=0.31 (25% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.34 (m, 5H), 7.04–7.02 (m, 1H), 6.65–6.62 (m, 2H), 5.21 (br s, 1H), 4.64 (d, *J*=4.8 Hz, 1H), 4.55 (br s, 1H), 4.04 (ddd, *J*=8.4, 8.4, 8.4 Hz, 1H), 3.85 (ddd, *J*=8.4, 8.4, 8.4 Hz, 1H), 3.76 (d, *J*=11.6 Hz, 1H), 2.52–2.46 (m, 1H), 2.05–1.98 (m, 1H), 1.77–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 141.5, 134.8, 128.5 (×2), 128.3 (×2), 128.0, 122.7, 120.2, 117.6, 114.1, 76.3, 65.0, 57.3, 43.1, 28.6; MS (+ESI) *m*/*z* 290 (M+Na$^+$, 65), 268 (M+H$^+$, 100).

4.2.11. (3a*R,4*R**,9b*R**)-4-(2′-Chlorophenyl)-6-hydroxy-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (4f) and (3a*R**,4*S**,9b*R**)-4-(2′-chlorophenyl)-6-hydroxy-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (5f).** A white crystalline solid of 36:64 mixture of two inseparable diastereomers **4f** and **5f**; mp 227–229 °C (EtOAc–hexane); R_f=0.35 (25% EtOAc in hexane); IR (KBr) 3400, 3210 (br), 2887, 1595, 1512, 1487, 1233, 1026 cm^{-1}; MS (+ESI) *m*/*z* 326 (M+2+Na$^+$, 13), 324 (M+Na$^+$, 42), 304 (M+2+H$^+$, 26), 302 (M+H$^+$, 100). Anal. calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.57; H, 5.29; N, 4.62. *NMR data assigned for **4f***: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (br s, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.50–7.32 (m, 3H), 6.73–6.52 (m, 3H), 5.16 (d, *J*=7.6 Hz, 1H), 4.90 (d, *J*=2.0 Hz, 1H), 4.58 (s, 1H), 3.60–3.56 (m, 2H), 2.90–2.80 (m, 1H), 2.08–1.92 (m, 1H), 1.37–1.20 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5, 144.0, 138.7, 136.0, 133.9, 133.2, 132.6, 131.8, 127.3, 124.6, 122.2, 117.1, 79.4, 70.2, 57.7, 45.9, 29.0. *NMR data assigned for **5f***: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.50–7.32 (m, 3H), 6.78 (d, *J*=7.2 Hz, 1H), 6.73–6.52 (m, 2H), 4.83 (s, 1H), 4.50 (d, *J*=4.8 Hz, 1H), 4.28 (d, *J*=10.4 Hz, 1H), 3.87 (ddd, *J*=8.4, 8.4, 8.4 Hz, 1H), 3.71 (dt, *J*=8.4, 5.6 Hz, 1H), 2.50–2.44 (m, 1H), 2.08–1.92 (m, 1H), 1.59–1.52 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 143.9, 139.0, 137.9, 134.0, 133.8, 133.7, 132.2, 125.9, 124.7, 121.3, 117.6, 79.8, 69.1, 56.4, 47.0, 32.7.

4.2.12. (3a*R,4*R**,9b*R**)-6-Hydroxy-8-methyl-4-phenyl-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (4g).** A white solid; R_f=0.42 (25% EtOAc in hexane); IR (KBr) 3415, 3239 (br), 2920, 1588, 1516, 1455, 1241, 1039 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.48–7.26 (m, 5H), 6.50 (s, 1H), 6.44 (s, 1H), 5.10 (d, *J*=8.0 Hz, 1H), 4.52 (s, 1H), 4.31 (s, 1H), 3.58–3.54 (m, 2H), 2.77–2.67 (m, 1H), 2.12 (s, 3H), 1.99–1.93 (m, 1H), 1.34–1.30 (m, 1H); MS (+ESI) *m*/*z* 282 (M+H$^+$, 100).

4.2.13. (3a*R,4*S**,9b*R**)-6-Hydroxy-8-methyl-4-phenyl-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (5g).** A white crystalline solid; mp 204–206 °C (EtOAc–hexane); R_f=0.40 (25% EtOAc in hexane); IR (KBr) 3393, 3215 (br), 2884, 1523, 1455, 1255, 1023 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.47–7.30 (m, 5H), 6.59 (s, 1H), 6.50 (s, 1H), 4.52 (s, 1H), 4.43 (d, *J*=5.2 Hz, 1H), 3.86 (ddd, *J*=8.0, 8.0, 8.0 Hz, 1H), 3.67–3.63 (m, 1H), 3.60 (d, *J*=11.2 Hz, 1H), 2.39–2.34 (m, 1H), 2.15 (s, 3H), 1.92–1.87 (m, 1H), 1.57–1.52 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.1, 142.8, 132.7, 128.9 (×2), 128.7 (×2), 128.2, 125.8, 122.0, 120.8, 114.5, 76.0, 64.8, 57.6, 43.4, 29.0, 21.0; MS (+ESI) *m*/*z* 282 (M+H$^+$, 100). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.87; H, 6.94; N, 5.08.

4.2.14. (3a*R,4*R**,9b*R**)-6-Hydroxy-4-[(4′-methoxycarbonyl)-phenyl]-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]-quinoline (4h) and (3a*R**,4*S**,9b*R**)-6-hydroxy-4-[(4′-methoxycarbonyl)-phenyl]-2,3,3a,9b-tetrahydro-2*H*-furo[3,2-*c*]quinoline (5h).** A pale-yellow gum of 25:75 mixture of two inseparable diastereomers **4h** and **5h**; R_f=0.23 (25% EtOAc in hexane). *Partial NMR data assigned for **4h***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J*=8.0 Hz, 2H), 6.82 (d, *J*=7.2 Hz, 1H), 6.62 (d, *J*=4.4 Hz, 1H), 5.23 (d, *J*=7.6 Hz, 1H). An enriched sample of **5h** was obtained by recrystallization of the mixture. *Compound **5h***: IR (KBr) 3375 (br), 2952, 1722, 1279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.0 Hz, 2H), 7.52 (d, *J*=7.6 Hz, 2H), 7.01 (br s, 1H), 6.62 (br s, 2H), 6.45–6.20 (br s, 1H), 4.64 (d, *J*=4.8 Hz, 1H), 4.59 (br s, 1H), 4.04 (ddd, *J*=8.0, 8.0, 8.0 Hz, 1H), 3.94 (s, 3H), 3.89–3.82 (m, 1H), 3.79 (d, *J*=11.2 Hz, 1H), 2.50–2.43 (m, 1H), 2.04–1.98 (m, 1H), 1.75–1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 147.0, 142.7, 134.5, 129.9 (×2), 129.8, 128.3 (×2), 122.9, 120.5, 117.8, 114.0, 76.1, 65.1, 57.2, 52.2, 43.3, 28.6; MS (−ESI) *m*/*z* 324 (M−H$^+$, 100); HRMS calcd for $C_{19}H_{19}NO_4Na$ (M+Na$^+$), 348.1206; found, 348.1201.

4.2.15. (4a*R,5*R**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-5-[(4′-methoxycarbonyl)phenyl]-2*H*-pyrano[3,2-*c*]quinoline (4i).** A pale-yellow solid; R_f=0.29 (25% EtOAc in hexane); IR (KBr) 3388 (br), 2949, 1719, 1280, 1026 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.97 (d, *J*=8.0 Hz, 2H), 7.58 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=7.6 Hz, 1H), 6.64–6.51 (m, 2H), 5.25 (d, *J*=5.6 Hz, 1H), 4.70 (d, *J*=2.0 Hz, 1H), 4.69 (d, *J*=7.6 Hz, 1H), 3.86 (s, 3H), 3.47 (d, *J*=11.6 Hz, 1H), 3.27–3.23 (m, 1H), 2.14–2.12 (m, 1H), 1.35 (br s, 3H), 1.03 (br s, 1H); MS (−ESI) *m*/*z* 338 (M−H$^+$, 100).

4.2.16. (4a*R,5*S**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-5-[(4′-methoxycarbonyl)phenyl]-2*H*-pyrano[3,2-*c*]quinoline (5i).** A pale-yellow solid; mp 164–166 °C; R_f=0.22 (25% EtOAc in hexane); IR (KBr) 3404 (br), 2926, 1721, 1508, 1437, 1282, 1259 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J*=8.5 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 2H), 6.82 (d, *J*=3.5 Hz, 2H), 6.55–6.51 (m, 2H), 4.70 (d, *J*=10.5 Hz, 1H), 4.41 (s, 1H), 4.13–4.08 (m, 1H), 3.92 (s, 3H), 3.72 (dd, *J*=11.5, 9.5 Hz, 1H), 2.09–2.07 (m, 1H), 1.84–1.81 (m, 1H), 1.67–1.64 (m, 1H), 1.42–1.34 (m, 2H) (OH not found); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 148.0, 142.5, 134.3, 130.1 (×2), 129.7, 128.1 (×2), 122.8, 121.1, 117.0, 114.8, 74.5, 68.7, 54.7, 52.4, 39.1, 24.2, 22.3; MS (+ESI) *m*/*z* 340 (M+H$^+$, 100); HRMS calcd for $C_{20}H_{21}NO_4$ (M+H$^+$), 340.1543; found, 340.1543.

4.2.17. (4a*R,5*R**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-5-(4′-nitrophenyl)-2*H*-pyrano[3,2-*c*]quinoline (4j).** A yellow solid; R_f=0.32 (25% EtOAc in hexane); IR (KBr) 3414, 3188 (br), 2949, 1517, 1349 cm^{-1}; ^{1}H NMR

(400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.23 (d, J=8.8 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H), 6.73 (d, J=7.6 Hz, 1H), 6.61 (d, J=7.6 Hz, 1H), 6.54 (t, J=7.6, 7.6 Hz, 1H), 5.24 (d, J=7.0 Hz, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 3.29–3.21 (m, 2H), 2.10 (br s, 1H), 1.34 (br s, 3H), 0.99 (br s, 1H); MS (−ESI) m/z 651 (2M−H$^+$, 100), 325 (M−H$^+$, 69).

4.2.18. (4a*R,5*S**,10b*R**)-3,4,4a,5,6,10b-Hexahydro-7-hydroxy-5-(4′-nitrophenyl)-2*H*-pyrano[3,2-*c*]quinoline (5j).** A yellow crystalline solid; mp 200–203 °C (EtOAc–hexane); R_f=0.24 (25% EtOAc in hexane); IR (KBr) 3463 (br), 2933, 1508, 1346, 1256 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.67 (d, J=8.4 Hz, 2H), 6.63 (d, J=7.2 Hz, 2H), 6.44 (t, J=7.6 Hz, 1H), 5.06 (s, 1H), 4.66 (d, J=9.2 Hz, 1H), 4.29 (d, J= 2.8 Hz, 1H), 3.83 (d, J=10.8 Hz, 1H), 3.58 (t, J=9.6 Hz, 1H), 2.03–1.99 (m, 1H), 1.74–1.62 (m, 2H), 1.33–1.22 (m, 2H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=8.8 Hz, 2H), 7.62 (d, J=9.2 Hz, 2H), 6.88 (d, J=6.8 Hz, 1H), 6.65–6.58 (m, 2H), 5.10 (br s, 1H), 4.81 (d, J=10.8 Hz, 1H), 4.43 (d, J=2.8 Hz, 1H), 4.42 (d, J=12.0 Hz, 1H), 4.13–4.09 (m, 1H), 3.74 (td, J=11.2, 2.0 Hz, 1H), 2.14–2.10 (m, 1H), 1.88–1.70 (m, 2H), 1.45–1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 147.3, 143.9, 134.1, 129.3 (×2), 124.0 (×2), 121.2, 120.9, 116.4, 113.8, 73.1, 67.0, 54.5, 38.7, 24.3, 22.6; MS (−ESI) m/z 651 (2M−H$^+$, 100), 325 (M−H$^+$, 11). Anal. calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.04; H, 5.70; N, 8.51.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.012.

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