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Transformation of barakol into cassiarins A, B, and their derivatives

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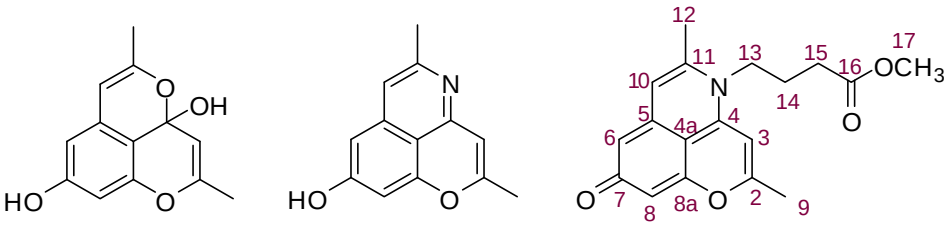
ABSTRACT

Three semi-syntheses of cassiarins A and B from barakol are described. The route involving use of anhydrobarakol chloride as a key precursor showed most versatility because it does not require an expensive catalyst, protection of functional groups, or chromatographic purification, allowing the facile preparation of eight cassiarin derivatives. The photophysical properties of these compounds were characterized by UV–vis absorption, fluorescence emission, and quantum yield.

1. Introduction

Cassia siamea is a common plant in Southeast Asia and has been used extensively as a source of traditional medicines. One of the most abundant chemical constituents of *C. siamea*[1–5] is barakol, being first extracted from fresh young leaves and flowers.[6] In 2007, Morita and co-workers discovered two new alkaloids, cassiarins A and B in the plant. These are much less abundant than barakol, but are interesting for their potent antiplasmodial activity against *Plasmodium faciparum*.[7]



Two total syntheses of cassiarin A have been reported first by Rudyanto and co-workers[8] and subsequently by Yao and co-workers.[9] Yao's work also described the total synthesis of cassiarin B and three new analogues of cassiarin A bearing different substituents at C-11.[9] While the work described here was in progress, Morita also reported the synthesis and bioactivity of cassiarin A and some derivatives.[10] Our work described here exploits the convenient access to gram quantities of barakol, and features conversion of its pyran-2-ol moiety to pyridinium salts with the framework of cassiarins A and B.

2. Results and discussion

2.1. Syntheses of cassiarin A

Scheme 1 shows our three synthetic approaches to cassiarin A. The first (Scheme 1a) begins with the reaction of barakol and triethylamine in aqueous methanol[11] to obtain 5-acetonyl-7-hydroxy-2-methyl chromone (**1**) in moderate yield. This compound was also an intermediate in Morita's recent synthesis.[10] Attempt to simplify the published conditions for cassiarin A formation by using shorter reaction time and no chromatographic purification resulted in a lower yield of chromone **1** (58 vs 91%). Therefore, this approach is suggested when chromatography should be avoided.

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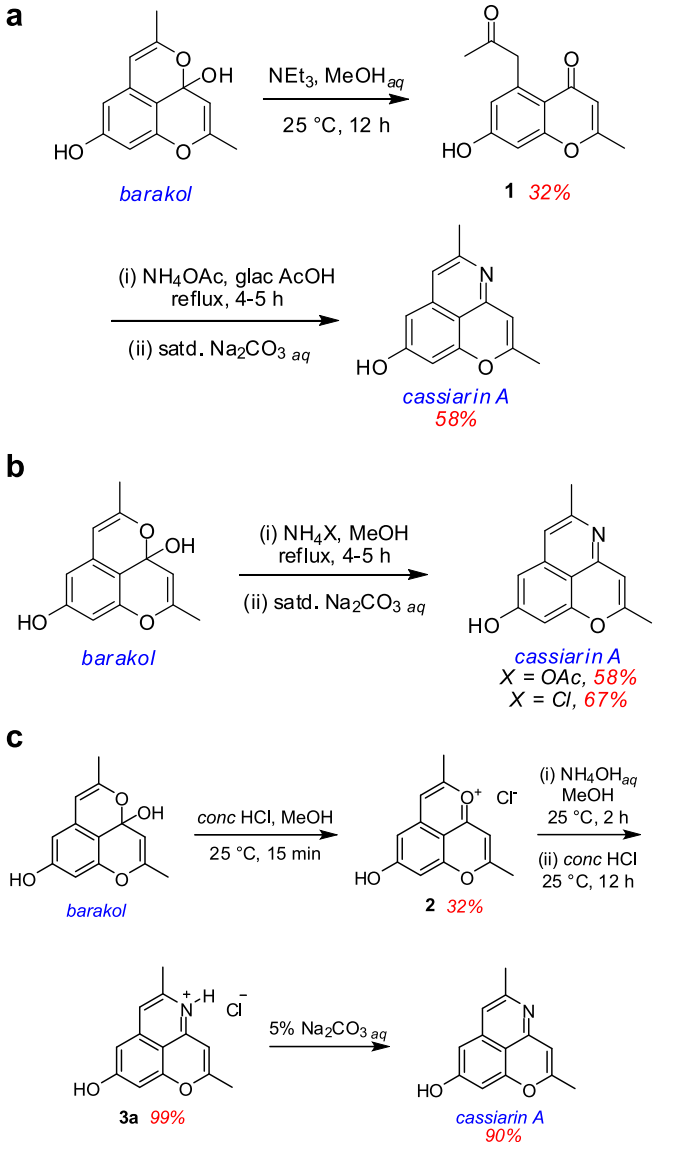
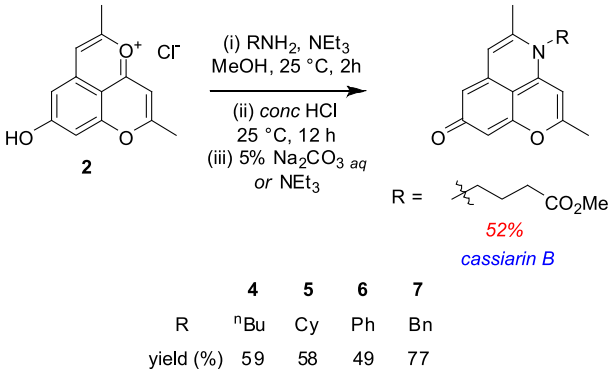


Scheme 1. Three routes to cassiarin A from barakol.



Scheme 2. Synthesis of cassiarin B and derivatives from **2**.

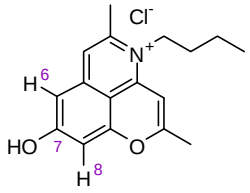
Our second approach (Scheme 1b) features a one-pot condensation of barakol with ammonium ions in refluxing methanol. Cassiarin A precipitated in good yields and chromatographic purification was not required.

Scheme 1c shows our third method exploits the known[11] conversion of barakol to stable anhydrobarakol chloride **2**. This compound was reacted with an excess of ammonium hydroxide solution followed by treatment with concentrated hydrochloric acid to give cassiarin A hydrochloride **3a**. The product was isolated in almost quantitative yield by removal of the solvent and then washing with THF. The free base was formed by treatment with 5% w/v aqueous sodium carbonate solution and was isolated in 90% yield without the need of chromatographic purification.

2.2. Synthesis of cassiarin B and derivatives

In a similar manner as described for the synthesis outlined in Scheme 1c, cassiarin B and some *N*-substituted derivatives were obtained (Scheme 2). For instance, reaction of the compound **2** with methyl-4-aminobutyrate in methanol with triethylamine, followed by formation of salt **3b**, then liberation of the free base afforded Cassiarin B in 52%; again no chromatographic purification was required.

The spectroscopic characterization of the products is illustrated with the hydrochloride intermediate **3b**. The presence of the phenolic carbon (C-7) in the salt **3b** was proven by HMBC correlation spectroscopy: Protons H-6 (δ_H 6.38 ppm) and H-8 (δ_H 6.48 ppm) correlated with C-7 at δ_C 163.5 ppm (see Supplementary data). In the free base cassiarin B, protons H-6 (δ_H 6.22 ppm) and H-8 (δ_H 6.35 ppm) correlated with C-7 at δ_C 177.7 ppm, the latter was therefore assigned as the conjugated carbonyl carbon.



3b

Ring-opening of pyrylium ions and ring closure to form pyridiniums,[12] as depicted in Scheme 1c, enabled us to prepare several *N*-substituted derivatives of the cassiarins featuring straight-chain alkyl, bulky alkyl, aryl, or benzyl substituents. From the formation of the corresponding salts **3c**–**f**, compounds **4**–**7** were obtained in 49–77% overall yield from **2**. Within this series the yield of the phenyl derivative **6** was diminished due to the reduced nucleophilicity of aniline[13] relative to alkyl amines. The spectroscopic data of **4** and **6** are consistent with those previously reported.[10]

2.3. Comparative characterization of synthetic and natural cassiarins

The formation of synthetic cassiarins A and B was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Compared with the previously reported data of the natural products,[7] both synthetic cassiarins obtained from this study gave consistent ^{1}H and ^{13}C NMR results as summarized in Table 1.

However, to some extent, the melting points (decomposition point) of the synthetic cassiarins were found to be higher than the reported values and their color appeared to be different from the natural products. Although the reason of the melting point difference is unclear, it is likely that the natural source contains a trace amount of colored components, which might be difficult to be completely removed by common purification techniques.

2.4. Photophysical properties of cassiarin derivatives

Amongst all the cassiarin compounds, cassiarin A showed a distinct absorption maximum at 323 nm and its chloride salt at

Table 1
^{1}H and ^{13}C NMR data of synthetic cassiarins A and B compared with those of natural cassiarins[7] (shown in the square brackets)

Carbon position	Cassiarin A[a]		Cassiarin B[a]	
	δ_H[b]	δ_C[b]	δ_H[b]	δ_C[b]
2		163.0 [161.5]		166.7 [168.0]
3	6.06 (s, 1H) [6.03 (s, 1H)]	103.2 [103.7]	6.70 (s, 1H) [6.74 (s, 1H)]	96.5 [97.3]
4		150.7 [150.6]		147.2 [148.6]
4a		111.5 [111.5]		108.1 [109.3]
5		139.2 [138.8]		135.1 [136.5]
6	6.47 (s, 1H) [6.46 (s, 1H)]	103.2 [102.9]	6.55 (s, 1H) [6.48 (s, 1H)]	107.3 [107.9]
7		166.2 [164.6]		173.3 [174.6]
8	6.49 (s, 1H) [6.48 (s, 1H)]	101.7 [100.7]	6.69 (s, 1H) [6.60 (s, 1H)]	104.5 [105.1]
8a		156.9 [156.4]		155.5 [156.7]
9	2.22 (s, 3H) [2.20 (s, 3H)]	20.6 [20.1]	2.52 (s, 3H) [2.43 (s,3H)]	20.0 [21.0]
10	6.70 (s, 1H) [6.70 (s, 1H)]	114.3 [113.7]	6.75 (s, 1H) [6.78 (s, 1H)]	116.1 [117.1]
11		148.4 [149.5]		139.8 [141.4]
12	2.34 (s, 3H) [2.34 (s,3H)]	22.5 [22.7]	2.57 (s, 3H) [2.50 (s,3H)]	20.9 [20.2]
13			4.16 (t, J=8.4 Hz, 2H) [4.10 (t, J=8.5 Hz, 2H)]	47.2 [48.0]
14			2.00–2.12 (m, 2H) [1.98 (m, 2H)]	23.1 [23.8]
15			2.68 (t, J=6.3 Hz, 2H) [2.57 (t, J=6.3 Hz, 2H)]	29.7 [30.3]
16				173.2 [174.4]
17			3.85 (s, 3H) [3.72 (s, 3H)]	52.0 [50.9]

[a] All spectra were recorded in $CD_3OD/CDCl_3$ (1:1).
[b] δ_H and δ_C are chemical shifts of ^{1}H and ^{13}C NMR, respectively, and reported in parts per million (ppm).

293, 338, and 363 nm. Cassiarin B derivatives exhibited absorption at 316–317 and 369–372 nm, while their chloride salts exhibited a slight absorption shift to 302–304 and 372–374 nm. For all cassiarin compounds, absorption coefficients of the neutral forms are higher than those of the corresponding chloride salts. Upon excitation at the maximum absorption wavelength of each compounds, cassiarin A and its salt showed an emission at 456 nm, while cassiarin B derivatives and their salts exhibited emissions at 482–489 nm. Fluorescence quantum yields of all compounds range from 0.05 to 0.10 in methanol. Quantum yields for the compounds bearing bulky *N*-substituents, i.e., cyclohexyl and phenyl, are slightly lower in the series. Cassiarin A and its corresponding salt **3a** give highest quantum yields of these compounds, indicating the *N*-alkyl/aryl substituents provide pathways to accelerate non-radiationless decay. In most cases, the neutral form of cassiarin compounds had higher quantum yields than their corresponding chloride salts.

3. Conclusions

This study describes the use of naturally abundant barakol to prepare bioactive cassiarins A and B and their *N*-substituted derivatives. The anhydrobarakol chloride **2** proved to be a useful intermediate for efficient synthesis of cassiarin derivatives bearing different *N*-substituent providing simple routes, obviating expensive catalysts, protection, and time consuming purification steps. The distinct photophysical properties of cassiarin A and its salt from other cassiarin derivatives indicated the significant effect of *N*-substituent on those properties. Cassiarins A, B, and their derivatives tend to be fluorescent, and the correlation between N-substitution and quantum yields was also observed.

4. Experimental

4.1. Materials and methods

All reagents were analytical grade, purchased from Fluka, or Aldrich Chemicals Co., Ltd. and were used as received without further purification. Melting points were uncorrected and recorded under ambient condition, except Cassiarins A and B whose melting points were measured under N_2 atmosphere. Solvents for reactions were AR grade. ^{1}H NMR, ^{13}C NMR, and HMBC spectra were obtained in CD_3OD, unless noted otherwise, using Varian Mercury NMR spectrometer at 400 MHz for ^{1}H, and 100 MHz for ^{13}C nuclei unless stated otherwise. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak. Coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded by electrospray ionization mass spectrometry (ESI-MS) on a Bruker Daltonics micro TOF Mass Spectrometer. Absorption spectra were recorded in methanol at room temperature with a Varian Cary-3 G UV/Vis spectrophotometer. Emission spectra were measured in methanol at room temperature on a Horiba Fluorolog-3 spectrophotometer. Absorption coefficients (ϵ) are expressed in $M^{-1}\,cm^{-1}$.

4.2. Experimental procedure

4.2.1. Extraction of barakol. Following a standard procedure[14] with slight modification, fresh young leaves and flowers of *C. siamea* (2 kg) were boiled with 0.5% (v/v) aqueous sulfuric acid (2.5 L) for 30 min and filtered. The filtrate was basified with a saturated sodium carbonate solution to pH 9–10. The resulting basic solution was divided into four portions and each was extracted with dichloromethane (200 mL×4). The combined dichloromethane extracts were concentrated under reduced pressure until the volume of organic extract was one-fourth of the starting volume, and then equal volume of distilled water was added. The mixture was shaken vigorously, to give a yellow needle crystalline solid of barakol (9.7 g on average) that was collected by filtration. The spectroscopic data are consistent with those described in the literature.

*4.2.2. 5-Acetonyl-7-hydroxy-2-methyl chromone (**1**).* Following a published procedure[11] with slight modification, a mixture of barakol (0.232 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) in 5% v/v aqueous methanol (5.0 mL) was reacted at room temperature for 12 h. The mixture was concentrated under reduced pressure. The resulting residual crude was purified by a silica column using ethylacetate as eluent to obtain chromone **1** (0.075 g, 32%). The spectroscopic data are consistent with those described in the literature.

*4.2.3. Anhydrobarakol chloride (**2**).* Following a published procedure[11] with slight modification, to a solution of barakol (0.232 g, 1.00 mmol) in methanol (2.0 mL), concentrated hydrochloric acid

(0.5 mL) was slowly added at room temperature. The mixture was stirred during the addition of the acid until greenish-yellow needles were obtained. The mixture was cooled to 0–5 °C in an ice bath and the stirring was continued at this temperature for additional 15 min. The residual mixture was precipitated by adding THF (10.0 mL). The resulting solid was filtered and washed with THF to give **2** (0.147 g, 58%). The spectroscopic data are consistent with those described in the literature.

*4.2.4. Cassiarin A. Method A: from chromone **1**.* A mixture of chromone **1** (0.232 g, 1.00 mmol) and ammonium acetate (0.154 g, 2.00 mmol) were reacted in glacial acetic acid (5.0 mL) under reflux for 4–5 h (TLC monitoring; $MeOH/CH_2Cl_2$ (1:4)). The reaction mixture was diluted with distilled water (5.0 mL) and cooled to 0–5 °C in an ice bath. The resulting mixture was basified with a saturated sodium carbonate solution to pH 9–10 and the stirring was continued until the precipitates were appeared. The resulting solid was filtered off and washed with water to afford cassiarin A (0.124 g, 58%). The spectroscopic data are consistent with those described in Method C.

4.2.5. Method B: from direct condensation of barakol with ammonium salts. Barakol (0.232 g, 1.00 mmol) and ammonium acetate (0.154 g, 2.00 mmol) or ammonium chloride (0.107 g, 2.00 mmol) were mixed in methanol (10.0 mL). The mixture was stirred and refluxed for 4–5 h (TLC monitoring; $MeOH/CH_2Cl_2$ (1:4)). The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in distilled water (5.0 mL). The resulting solution was cooled in an ice bath and basified with a saturated sodium carbonate solution to pH 9–10, and the stirring was continued until the solid were appeared. The resulting solid was filtered off and washed with water to afford cassiarin A (0.122, 57% and 0.143 g, 67% when ammonium acetate and ammonium chloride was employed, respectively). The spectroscopic data are consistent with those described in Method C.

*4.2.6. Method C: from anhydrobarakol chloride (**2**).* A solution of salt **2** (0.125 g, 0.501 mmol) in methanol (2.0 mL) was reacted with a 25% w/v aqueous ammonium hydroxide solution (0.5 mL) at room temperature for 2 h. The resulting mixture was further reacted with concentrated hydrochloric acid (0.5 mL) and the stirring was continued at this temperature for 12 h. Methanol was removed under reduced pressure, and THF (10.0 mL) was added to the residual solid. The solid was filtered and washed with THF to afford a pure cassiarin A chloride (**3a**) as a light green solid (0.124 g, 99%). Mp 327 °C (dec); ^{1}H NMR δ 2.45 (s, 3H), 2.46 (s, 3H), 6.50 (s, 1H), 6.85 (d, J=1.6 Hz, 1H), 6.89 (d, J=1.6 Hz 1H), 7.06 (s, 1H); ^{13}C NMR δ 17.5, 19.1, 98.0, 101.1, 104.4, 109.4, 114.2, 138.1, 140.6, 148.3, 156.4, 166.1, 168.1; ESI-MS m/z 214.1 ($[M-Cl]^+$); ESIHRMS obsd 214.0882 ($[M-Cl]^+$), calcd 214.0863 ($[M-Cl]^+$), 249.0557 (M^+; M=$C_{13}H_{12}ClNO_2$). λ_{abs} nm (ϵ) 298 (6840), 338 (4945), 363 (6505); λ_{em} nm (λ_{ex}=363 nm) 456. Φ=0.10.

To a solution of **3a** (0.125 g, 0.501 mmol) in water (5.0 mL), was added a 5% w/v aqueous sodium carbonate solution (1.0 mL). The resulting mixture was stirred for 20 min. The resulting precipitate was filtered and washed with water to give cassiarin A as a light greenish-yellow solid (0.096 g, 90%). Mp 316–318 °C (dec); ^{1}H NMR ($CDCl_3/CD_3OD$ 1:1, 300 MHz) δ 2.22 (s, 3H), 2.34 (s, 3H), 6.06 (s, 1H), 6.47 (s, 1H), 6.49 (s, 1H), 6.70 (s, 1H); ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1) δ 20.6, 22.4, 101.7, 103.2, 111.5, 114.3, 139.2, 148.4, 150.7, 156.9, 163.1, 166.2; ESI-MS m/z 214.1 ($[M+H]^+$); ESIHRMS obsd 214.0870 ($[M+H]^+$), calcd 214.0868 ($[M+H]^+$), 213.0790 (M^+; M=$C_{13}H_{11}NO_2$); λ_{abs} nm (ϵ) 323 (7043); λ_{em} nm (λ_{ex}=323 nm) 456. Φ=0.10.

Cassiarin B. Following a procedure described for cassiarin A (Method C), a mixture of **2** (0.125 g, 0.501 mmol), methyl-4-aminobutyrate hydrochloride (0.154 g, 1.00 mmol), and triethylamine (0.101 g, 1.00 mmol) in methanol (2.0 mL) was reacted at room temperature for 2 h. The resulting mixture was further reacted with concentrated hydrochloric acid (0.5 mL) at this temperature for additional 12 h. Methanol was removed under reduced pressure, and the residual solid was precipitated by adding THF (10.0 mL). The product was filtered and washed with THF to obtain *N*-4-methoxy-4-oxobutyl cassiarin A chloride (**3b**) as a light yellow solid (0.152 g, 87%). Mp 243 °C (dec); ^{1}H NMR (D_2O/DMSO-d_6 (9.5:0.5)) δ 1.83–1.91 (m, 2H), 2.28 (s, 3H), 2.36 (s, 3H), 2.47 (t, J=6.6 Hz, 2H), 3.55 (s, 3H), 3.98 (t, J=8.0 Hz, 2H), 6.38 (d, J=1.6 Hz, 1H), 6.48 (d, J=2.0 Hz, 1H), 6.54 (s, 1H), 6.76 (s, 1H); ^{13}C NMR (D_2O/DMSO-d_6 (9.5:0.5)) δ 175.4, 169.1, 163.5, 155.0, 148.7, 142.6, 135.6, 116.7, 110.1, 103.8, 101.1, 97.1, 52.2, 47.7, 29.7, 22.1, 20.1, 19.2; ESI-MS m/z 314.1 ($[M-Cl]^+$); ESIHRMS obsd 314.1382 ($[M-Cl]^+$), calcd 314.1387 ($[M-Cl]^+$), 349.1081 (M^+; M=$C_{18}H_{20}ClNO_4$); λ_{abs} nm (ϵ) 302 (10,612), 373 (6852); λ_{em} nm (λ_{ex}=373 nm) 488. Φ=0.07.

To a solution of **3b** (0.152 g, 0.435 mmol) in water (4.0 mL), was added a 5% (w/v) aqueous sodium carbonate solution (1.0 mL). The mixture was stirred at room temperature for 5 min. The aqueous solution was extracted with chloroform (4×15.0 mL). The combined chloroform extracts were concentrated under reduced pressure until the volume of organic extract was reduced to approximately 1.0 mL. The resulting mixture was kept at the room temperature until the precipitate was formed. After filtration and washing with a small amount of chloroform, cassiarin B was obtained as a yellow solid (0.081 g, 60%). Mp 116–118 °C (dec); ^{1}H NMR ($CDCl_3/CD_3OD$ 1:1, 300 MHz) δ 2.00–2.12 (m, 2H), 2.52 (s, 3H), 2.57 (s, 3H), 2.68 (t, J=6.3 Hz, 2H), 3.85 (s, 3H), 4.16 (t, J=8.4 Hz, 2H), 6.55 (s, 1H), 6.69 (s, 1H), 6.70 (s, 1H), 6.75 (s, 1H); ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1) δ 20.0, 20.9, 23.1, 29.7, 47.2, 52.0, 96.5, 104.5, 107.3, 108.1, 116.1, 135.1, 139.8, 147.2, 155.5, 166.7, 173.2, 173.3; ESI-MS m/z 314.1 ($[M+H]^+$); ESIHRMS obsd 314.1387 ($[M+H]^+$), calcd 314.1387 ($[M+H]^+$), 313.1314 (M^+; M=$C_{18}H_{19}NO_4$); λ_{abs} nm (ϵ) 316 (15,629), 370 (11,107); λ_{em} nm (λ_{ex}=370 nm) 485. Φ=0.08.

4.3. A General procedure for synthesis of *N*-substituted cassiarin A chlorides 3c–f

A mixture of **2** (0.125 g, 0.501 mmol) and amine (1.00 mmol) in methanol (2.0 mL) was stirred at room temperature for 2 h. The resulting mixture was further reacted with concentrated hydrochloric acid (0.5 mL) at room temperature for additional 12 h. The solvent was removed under reduced pressure and the residual solid was then treated with THF (10.0 mL). The resulting solid was collected by filtration and washed with THF to afford a light yellow solid of *N*-substituted cassiarins A chlorides **3c–f**.

*4.3.1. 4-Butyl-8-hydroxy-2,5-dimethylpyrano[2,3,4-ij]isoquinolin-4-ium chloride (**3c**).* Yield (0.135 g, 88%). Mp 245 °C (dec); ^{1}H NMR δ 1.04 (t, J=7.4 Hz, 3H), 1.44–1.53 (m, 2H), 1.67–1.75 (m, 2H), 2.53 (s, 3H), 2.62 (s, 3H), 4.27 (t, J=8.2 Hz, 2H), 6.84 (s, 1H), 6.89 (s, 1H), 6.90 (s, 1H), 7.21 (s, 1H); ^{13}C NMR δ 12.6, 18.9, 19.2, 19.5, 29.8, 48.5, 97.4, 101.4, 104.2, 110.7, 117.2, 136.4, 142.7, 149.2, 155.8, 165.4, 168.8; ESI-MS m/z 270.1 ($[M-Cl]^+$); ESIHRMS obsd 270.1531 ($[M-Cl]^+$), calcd 270.1489 ($[M-Cl]^+$), 305.1183 (M^+; M=$C_{17}H_{20}ClNO_2$); λ_{abs} nm (ϵ) 302 (9057), 372 (7697); λ_{em} nm (λ_{ex}=372 nm) 484. Φ=0.07.

*4.3.2. 4-Cyclohexyl-8-hydroxy-2,5-dimethylpyrano[2,3,4-ij]isoquinolin-4-ium chloride (**3d**).* Yield (0.145 g, 87%). Mp 338 °C (dec); ^{1}H NMR ($CD_3OD/CDCl_3$ (1:4)) δ 1.35–1.41 (m, 1H), 1.46–1.56 (m, 2H), 1.82 (d, J=13.2 Hz, 1H), 1.96 (d, J=11.6 Hz, 2H), 2.05 (d, J=13.2 Hz, 2H), 2.33–2.41 (m, 2H), 2.54 (s, 3H), 2.63 (s, 3H), 4.61 (t, J=12.0 Hz, 1H), 6.83 (s, 1H), 6.87 (s, 1H), 6.93 (s, 1H), 7.14 (s, 1H); ^{13}C NMR ($CD_3OD/CDCl_3$ (1:4)) δ 20.9, 21.5, 24.4, 25.98, 25.98, 28.71, 28.71, 63.3, 99.3, 102.6, 105.0, 111.9, 118.9, 136.0, 142.2, 149.4, 155.7, 165.9, 166.9; ESI-MS m/z 296.2 ($[M-Cl]^+$); ESIHRMS obsd 296.1674 ($[M-Cl]^+$), calcd 296.1645

([M−Cl]$^+$), 331.1339 (M$^+$; M=$C_{19}H_{22}ClNO_2$); λ_{abs} nm (ϵ) 302 (10,517), 376 (5568); λ_{em} nm (λ_{ex}=376 nm) 489. Φ=0.08.

*4.3.3. 8-Hydroxy-2,5-dimethyl-4-phenylpyrano[2,3,4-ij]isoquinolin-4-ium chloride (**3e**).* Yield (0.123 g, 76%). Mp 258 °C (dec); ^{1}H NMR δ 2.15 (s, 3H), 2.35 (s, 3H), 5.81 (s, 1H), 6.99 (d, J=1.6 Hz, 1H,), 7.01 (d, J=1.6 Hz, 1H), 7.33 (s, 1H), 7.50–7.51 (m, 2H), 7.75–7.77 (m, 3H); ^{13}C NMR δ 19.3, 19.7, 98.3, 101.5, 104.8, 110.0, 116.0, 127.10, 127.10, 130.97, 130.97, 130.97, 136.8, 136.9, 142.8, 150.5, 156.4, 166.3, 169.1; ESI-MS m/z 290.1 ([M−Cl]$^+$); ESIHRMS obsd 290.1110 ([M−Cl]$^+$), calcd 290.1176 ([M−Cl]$^+$), 325.0870 (M$^+$; M=$C_{19}H_{16}ClNO_2$); λ_{abs} nm (ϵ) 304 (7803), 372 (5943); λ_{em} nm (λ_{ex}=372 nm) 482. Φ=0.07.

*4.3.4. 4-Benzyl-8-hydroxy-2,5-dimethylpyrano[2,3,4-ij]isoquinolin-4-ium chloride (**3f**).* Yield (0.152 g, 89%). Mp 291 °C (dec); ^{1}H NMR δ 2.43 (s, 3H), 2.54 (s, 3H), 5.64 (s, 2H), 6.80 (s, 1H), 6.96 (d, J=1.6 Hz, 1H), 7.00 (d, J=2.0 Hz, 1H), 7.15 (d, J=7.2 Hz, 2H), 7.32 (s, 1H), 7.36 (d, J=7.2 Hz, 1H), 7.39–7.43 (m, 2H); ^{13}C NMR δ 18.9, 19.4, 51.4, 97.6, 101.6, 104.6, 110.7, 117.2, 125.26, 125.26, 128.0, 129.13, 129.13, 133.3, 136.7, 143.1, 150.5, 156.2, 166.0, 169.4; ESI-MS m/z 304.1 ([M−Cl]$^+$); ESIHRMS obsd 304.1365 ([M−Cl]$^+$), calcd 304.1332 ([M−Cl]$^+$), 339.1026 (M$^+$; M=$C_{20}H_{18}ClNO_2$); λ_{abs} nm (ϵ) 304 (8713), 374 (6533); λ_{em} nm (λ_{ex}=374 nm) 486. Φ=0.08.

4.4. A general procedure for synthesis of *N*-substituted cassiarin derivatives 4–7

To a solution of *N*-substituted cassiarin A chloride **3c–f** (0.30 mmol) in water (5.0 mL), was added triethylamine (0.061 g, 0.60 mmol). The mixture was stirred at room temperature for 5 min. The resulting solution was then extracted with chloroform (15 mL×4) or, in the case of **7**, the resulting solid was filter off. For **4–6**, the combined chloroform extracts were concentrated under reduced pressure until the volume of organic extract was reduced to 1.0 mL. The crude extract was kept at room temperature until the yellow precipitate was obtained. The solid product was filtered off and then dried under vacuum to give the *N*-substituted cassiarin B derivative **4–7**.

*4.4.1. 4-Butyl-2,5-dimethylpyrano[2,3,4-ij]isoquinolin-8-(4H)-one (**4**).* Yield (0.054 g, 67%). Mp 167 °C (dec); ^{1}H NMR δ 1.02 (t, J=7.4 Hz, 3H), 1.43–1.53 (m, 2H), 1.61–1.68 (m, 2H), 2.35 (s, 3H), 2.41 (s, 3H), 3.96 (t, J=8.2 Hz, 2H), 6.21 (s, 1H), 6.33 (s, 1H), 6.34 (s, 1H), 6.63 (s, 1H); ^{13}C NMR δ 12.6, 18.7, 19.2, 19.2, 30.2, 47.2, 95.6, 104.9, 106.9, 107.7, 115.2, 135.4, 140.1, 146.6, 155.7, 165.9, 177.7; ESI-MS m/z 270.2 ([M+H]$^+$); ESIHRMS obsd 270.1538 ([M+H]$^+$), calcd 270.1489 ([M+H]$^+$), 269.1416 (M$^+$; M=$C_{17}H_{19}NO_2$); λ_{abs} nm (ϵ) 316 (13,193), 369 (9016); λ_{em} nm (λ_{ex}=369 nm) 484. Φ=0.09.

*4.4.2. 4-Cyclohexyl-2,5-dimethylpyrano[2,3,4-ij]isoquinolin-8(4H)-one (**5**).* Yield (0.059 g, 67%). Mp 136 °C (dec); ^{1}H NMR (CD_3OD/$CDCl_3$ (1:4)) δ 1.21–1.31 (m, 1H), 1.39–1.48 (m, 2H), 1.80 (d, J=12.8 Hz, 1H), 1.90 (d, J=12.4 Hz, 2H), 2.00 (d, J=13.2 Hz, 2H), 2.22–2.26 (m, 2H), 2.43 (d, J=5.6 Hz, 3H), 2.43 (s, 3H), 4.32–4.39 (m, 1H), 6.32 (s, 1H), 6.39 (s, 1H), 6.49 (s, 1H), 6.63 (s, 1H); ^{13}C NMR (CD_3OD/$CDCl_3$ (1:4)) δ 20.8, 21.4, 24.7, 26.14, 26.14, 29.34, 29.34, 61.5, 97.7, 106.2, 108.5, 108.7, 116.9, 135.0, 139.4, 146.9, 155.9, 163.6, 178.4; ESI-MS m/z 296.2 ([M+H]$^+$); ESIHRMS obsd 296.1676 ([M+H]$^+$), calcd 296.1645 ([M+H]$^+$), 295.1572 (M$^+$; M=$C_{19}H_{21}NO_2$); λ_{abs} nm (ϵ) 316 (12,139), 372(8925); λ_{em} nm (λ_{ex}=372 nm) 483. Φ=0.09.

*4.4.3. 2,5-Dimethyl-4-phenylpyrano[2,3,4-ij]isoquinolin-8(4H)-one (**6**).* Yield (0.056 g, 65%). Mp 132 °C (dec); ^{1}H NMR δ 2.01 (s, 3H), 2.21 (s, 3H), 5.45 (s, 1H), 6.43 (d, J=1.2 Hz, 1H), 6.49 (d, J=1.2 Hz 1H), 6.86 (s, 1H), 7.45–7.47 (m, 2H), 7.68–7.72 (m, 3H); ^{13}C NMR δ 19.1, 19.5, 96.6, 104.9, 106.3, 108.6, 114.1, 127.74, 127.74, 130.4, 130.62, 130.62, 135.8, 137.3, 140.3, 147.8, 156.5, 166.2, 178.4; ESI-MS m/z 290.1 ([M+H]$^+$); ESIHRMS obsd 290.1137 ([M+H]$^+$), calcd 290.1176 ([M+H]$^+$), 289.1103 (M$^+$; M=$C_{19}H_{15}NO_2$); λ_{abs} nm (ϵ) 317 (13,350), 372 (10,350); λ_{em} nm (λ_{ex}=372 nm) 484. Φ=0.07.

*4.4.4. 4-Benzyl-2,5-dimethylpyrano[2,3,4-ij]isoquinolin-8(4H)-one (**7**).* Yield (0.079 g, 87%). Mp 192 °C (dec); ^{1}H NMR δ 2.27 (s, 3H), 2.37 (s, 3H), 5.38 (s, 2H), 6.31 (s, 1H), 6.38 (d, J=2.0 Hz, 1H), 6.47 (d, J=1.6 Hz, 1H), 6.82 (s, 1H), 7.10 (d, J=7.6 Hz, 2H), 7.30–7.33 (m, 1H), 7.36–7.40 (m, 2H); ^{13}C NMR δ 18.7, 19.2, 50.3, 95.9, 105.1, 106.9, 108.3, 115.2, 125.14, 125.14, 127.7, 128.99, 128.99, 134.3, 135.6, 140.7, 147.8, 156.1, 166.4, 178.3; ESI-MS m/z 304.1 ([M+H]$^+$); ESIHRMS obsd 304.1365 ([M+H]$^+$), calcd 304.1332 ([M+H]$^+$), 303.1259 (M$^+$; M=$C_{20}H_{17}NO_2$); λ_{abs} nm (ϵ) 317 (14,361), 372 (10,412); λ_{em} nm (λ_{ex}=372 nm) 488. Φ=0.09.

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Supplementary data

Spectral data, including ^{1}H NMR, ^{13}C NMR, and high resolution mass spectra for new compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.07.053. These data include MOL files and InChIKeys of the most important compounds described in this article.

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