One-Pot Preparation of Pyranoquinolinones by Ytterbium(III) Trifluoromethanesulfonate-Catalyzed Reactions: Efficient Synthesis of Flindersine, *N*-Methylflindersine, and Zanthosimuline Natural Products

Yong Rok Lee,*[a] Hyuk Il Kweon,[a] Wha Soo Koh,[a] Kyung Rak Min,[b] Youngsoo Kim,[b] Seung Ho Lee[c]

[a] School of Chemical Engineering and Technology, Yeungnam University, Kyongsan 712-749, Korea

[b] College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

[c] College of Pharmacy, Yeungnam University, Kyongsan 712-749, Korea
Fax +82(53)8148790; E-mail: yrlee@yeungnam.ac.kr

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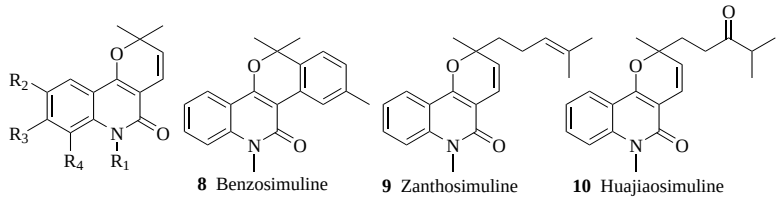
Abstract: An efficient synthesis of pyranoquinolinones is achieved by ytterbium(III) triflate-catalyzed reaction of 4-hydroxy-2-quinolones with a variety of α,β-unsaturated aldehydes in moderate yields. This new method has been applied to the synthesis of pyranoquinolinone alkaloids.

Key words: pyranoquinolinone alkaloids, $Yb(OTf)_3$, flindersine, *N*-methylflindersine, zanthosimuline

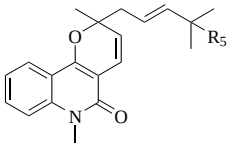
Pyranoquinolinone alkaloids are widely distributed in nature (Figure 1).[1] They have a variety of interesting biological activities and potential medical applications.[2] They are also used as synthetic precursors for the preparation of other dimeric quinoline alkaloids and polyheterocycles.[3] Flindersine (**1**) is the parent compound among the known pyranoquinoline natural products.[4] Although several synthetic approaches of pyranoquinolinone derivatives have been reported, general and efficient approaches still remain scarce.[5] The many steps and low yields reported in the literature[5a–d] for the preparation of pyranoquinolinones have prompted our research for a better synthesis of pyranoquinolinone derivatives.[5a–d]

Ytterbium(III) triflate-catalyzed reactions have become an important method in organic synthesis.[6] Recently, the ytterbium(III) triflate-catalyzed Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds in water and in solvent-free conditions has been reported by Feringa[7] and Kotsuki.[8] However, in contrast to these previous reported results, we found that ytterbium(III) triflate was a useful reagent for a 1,2-addition reaction to α,β-unsaturated aldehydes. We report here a convenient and efficient one-pot synthesis of pyranoquinolinone derivatives and pyranoquinolinone natural products using a tandem Knoevenagel-electrocyclic reaction starting from 4-hydroxy-2-quinolones and a variety of α,β-unsaturated aldehydes in the presence of ytterbium triflate.

Starting materials, 4-hydroxy-2-quinolones **13a** and **13c**, were readily prepared from isatoic anhydride by the Coppola method in 50 and 77% yields, respectively.[9] The other material **13b** is commercially available (Figure 2).



1 R_1=R_2=R_3=R_4=H Flindersine
2 R_1=Me, R_2=R_3=R_4=H *N*-Methylflindersine
3 R_1=R_3=R_4=H, R_2=OMe Haplamine
4 R_1=Me, R_2=R_3=OMe, R_4=H Oricine
5 R_1=Me, R_2=H, R_3=R_4=OMe Veprisine
6 R_1=Me, R_2=R_3=H, R_4=OMe Zanthobungeanine
7 R_1=CH_2OAc, R_2=R_3=H, R_4=OMe Zanthophylline



11 R_5=OH Simulenoline
12 R_5=OOH Peroxysimulenoline

Figure 1 Structures of some naturally occurring pyranoquinolinones alkaloids

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1437-210X,E;2001,0,12,1851,1855,ftx,en;F04001ss.pdf.

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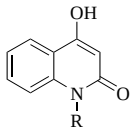
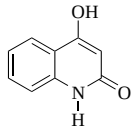
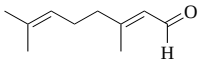
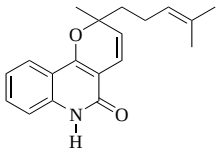
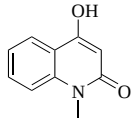
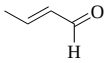
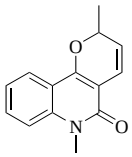
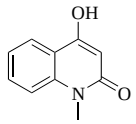
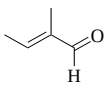
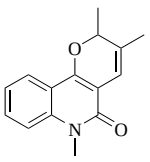
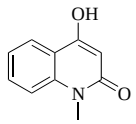
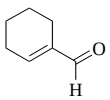
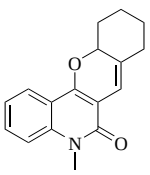
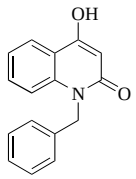
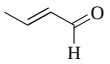
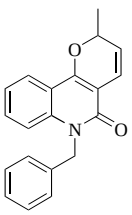


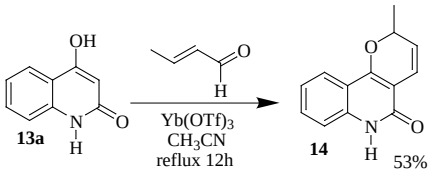
13a R=H
13b R=Me
13c R=Bn

Figure 2 Structures of 4-hydroxy-2-quinolones **13a–c**

Reaction of **13a** with crotonaldehyde in refluxing acetonitrile for 12 hours in the presence of 10 mol% of ytterbium triflate as a catalyst afforded pyranoquinolinone **14** in 53% yield (Scheme 1). The formation of **14** is supported by the observation of a peak in the IR spectrum at 1651 cm^{-1} (enone C=O of amide) and the expected chemical shifts associated with two vinylic protons as a doublet at 6.76 ppm (J = 9. 9 Hz) and as a doublet of doublet at 5.52 ppm (J = 9.9 and 3.3 Hz) in the ^{1}H NMR spectrum. In this case, only a single product was seen and no Michael addition product was found. Similarly, reaction of **13a** with citral gave the desired pyranoquinolinone **15** in 40% yield. The other similar results are summarized in the Table. Interestingly, in the case of cyclohex-1-ene-1-carbaldehyde (Table, entry 4) with a ring system, the expected pyranoquinolinone **18** was also produced in 40% yield. These results provide a concise synthetic entry into pyranoquinolinone derivatives and polyheterocycles as a one-pot reaction.

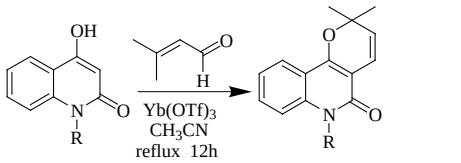
Table Synthesis of Pyranoquinolinone Derivatives

Entry	4-Hydroxy-2-quinolone	α,β-Unsaturated Aldehyde	Product	Yield (%)
1	 **13a**		 **15**	40
2	 **13b**		 **16**	52
3	 **13b**		 **17**	48
4	 **13b**		 **18**	40
5	 **13c**		 **19**	42



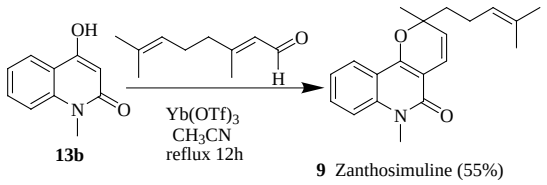
Scheme 1

The synthesis of natural products demonstrates an interesting application of this methodology. Flindersine (**1**) and *N*-methylflindersine (**2**) have been primarily isolated from Rutaceous plants, *Fagara heitzii*,[4a] *Geijera balansae*,[4b] *Haplophyllum saveolens*,[4c] *Atalantia roxburghiana*,[4d] *Micromelum minutum*[4e] and *Zanthoxylum coco*.[4f] In addition, *N*-methylflindersine (**2**) was isolated from antifeedant active species,[10] *Fagara chalybea*, *F. hostil*, *Xylocarpus granatum* and *Orixa japonic*a.[11] The steams and leaves of *O. japonica* were formerly used in Japan as an insecticide for livestock.[11] Reaction of **13a** and **13b** with 3-methylbut-2-enal afforded flindersine (**1**) and *N*-methylflindersine (**2**) in 50 and 57% yields, respectively (Scheme 2). The spectroscopic properties of our synthetic materials **1** and **2** agreed well with those reported in the literature.[5d,11]



Scheme 2

As another application of this methodology, synthesis of zanthosimuline (**9**) was next examined. Zanthosimuline (**9**), a monoterpenoid pyranoquinolinone alkaloid, has been isolated from the root bark of Taiwanese *Zanthoxylum simulans*.[1c] This natural product has a general cytotoxic activity when evaluated with a variety of cultured human cancer cell lines and the expression of cellular markers associated with cell differentiation in cultured HL-60 cells.[2b,12] Reaction of **13b** with citral in the presence of ytterbium triflate for 12 hours at reflux gave **9** in 55% yield (Scheme 3). Spectral data of our synthetic material **9** are also in agreement with those reported in the literature.[1c]



Scheme 3

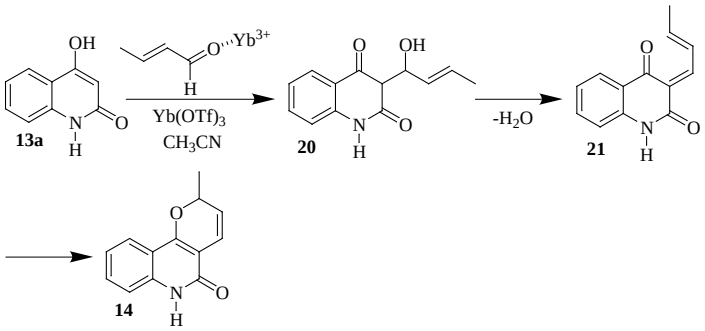
Although the exact mechanism of the reaction is still not clear, it is best described as shown in Scheme 4. The 4-hydroxy-2-quinolone (**13a**) first attacks aldehyde to yield the alcohol **20**, which is dehydrated on heating under acidic condition to give **21**. The intermediate **21** then undergoes electrocyclic reaction to furnish cycloadduct **14**.

In conclusion, the ytterbium(III) triflate-catlyzed reaction of 4-hydroxy-2-quinolones with α,β-unsaturated aldehydes has been carried out in refluxing acetonitrile solution to yield the pyranoquinolinone derivatives. This new method has been also applied to the synthesis of naturally occurring pyranoquinolinone alkaloids such as flindersine (**1**), *N*-methylflindersine (**2**) and zanthosimuline (**9**) in moderate yields.

All experiments were conducted under N_2. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined with microcover glasses on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS spectra were obtained VG-Micromass Autospec spectrometer.

Pyranoquinolinones 1, 2, 9, 15–19; General Procedure

The appropriate 4-hydroxy-2-quinolone **13** (1.0 mmol) and α,β-unsaturated aldehyde (2.0 mmol) were dissolved in MeCN (10 mL), and $Yb(OTf)_3$ (62 mg, 0.1 mmol) was added at r.t. The mixture was refluxed for 12 h and then cooled to r.t. Removal of the solvent left an oily residue, which was then purified by column chromatography



Scheme 4

(EtOAc-Hexanes) on silica gel to give the pyranoquinolinone product.

2-Methyl-2,6-dihydropyrano[3,2-*c*]quinolin-5-one (14)
Reaction of **13a** (161 mg, 1.0 mmol) with crotonaldehyde (140 mg, 2.0 mmol) in MeCN (10 mL) afforded **14** (113 mg, 53%) as a solid; mp 121–122 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.40 (1 H, s), 7.80 (1 H, d, *J* = 8.0 Hz), 7.45 (1 H, dd, *J* = 8.0, 7.2 Hz), 7.31 (1 H, d, *J* = 8.0 Hz), 7.16 (1 H, dd, *J* = 8.0, 7.2 Hz), 6.76 (1 H, d, *J* = 9.9 Hz), 5.52 (1 H, dd, *J* = 9.9, 3.3 Hz), 5.15 (1 H, m), 1.50 (3 H, d, *J* = 6.6 Hz).

IR (KBr): 3198, 2978, 1651, 1615, 1499, 1435, 1410, 1372, 1269, 1249, 1190, 1138, 1118, 1032, 910 cm^{-1}.

HRMS: *m*/*z* (M^+) Calcd for $C_{13}H_{11}NO_2$: 213.0790. Found: 213.0787.

2-Methyl-2-(4-methylpent-3-enyl)-2,6-dihydropyrano[3,2-*c*]quinolin-5-one (15)[5f]
Reaction of **13a** (161 mg, 1.0 mmol) with citral (304 mg, 2.0 mmol) in MeCN (10 mL) afforded **15** (118 mg, 40%) as a solid; mp 143–144 °C (Lit.[5f] mp not reported).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.72 (1 H, s), 7.86 (1 H, d, *J* = 8.0 Hz), 7.47 (1 H, dd, *J* = 8.2, 7.1 Hz), 7.35 (1 H, d, *J* = 8.2 Hz), 7.17 (1 H, dd, *J* = 8.0, 7.1 Hz), 6.79 (1 H, d, *J* = 10.0 Hz), 5.48 (1 H, d, *J* = 10.0 Hz), 5.08 (1 H, m), 2.20–1.66 (4 H, m), 1.60 (3 H, s), 1.53 (3 H, s), 1.48 (3 H, s).

IR (KBr): 3161, 2969, 1651, 1601, 1564, 1499, 1433, 1414, 1362, 1277, 1184, 1128, 1117, 1076, 918 cm^{-1}.

2,6-Dimethyl-2,6-dihydropyrano[3,2-*c*]quinolin-5-one (16)
Reaction of **13b** (175 mg, 1.0 mmol) with crotonaldehyde (140 mg, 2.0 mmol) in MeCN (10 mL) afforded **16** (118 mg, 52%) as a solid; mp 115–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (1 H, d, *J* = 8.0 Hz), 7.53 (1 H, dd, *J* = 8.5, 7.2 Hz), 7.30 (1 H, d, *J* = 8.5 Hz), 7.20 (1 H, dd, *J* = 8.0, 7.2 Hz), 6.78 (1 H, d, *J* = 9.9 Hz), 5.57 (1 H, dd, *J* = 9.9, 3.3 Hz), 5.19 (1 H, m), 3.67 (3 H, s), 1.49 (3 H, d, *J* = 6.5 Hz).

IR (KBr): 3080, 2975, 1652, 1557, 1505, 1464, 1423, 1372, 1161, 1124, 1096, 1044, 1002, 918 cm^{-1}.

HRMS: *m*/*z* (M^+) Calcd for $C_{14}H_{13}NO_2$: 227.0946. Found: 227.0948.

2,3,6-Trimethyl-2,6-dihydropyrano[3,2-*c*]quinolin-5-one (17)
Reaction of **13b** (175 mg, 1.0 mmol) with *trans*-2-methylbut-2-enal (168 mg, 2.0 mmol) in MeCN (10 mL) afforded **17** (116 mg, 48%) as a solid; mp 123–124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (1 H, d, *J* = 8.0 Hz), 7.51 (1 H, dd, *J* = 8.3, 7.1 Hz), 7.29 (1 H, d, *J* = 8.3 Hz), 7.20 (1 H, dd, *J* = 8.0, 7.1 Hz), 6.52 (1 H, s), 5.02 (1 H, m), 3.68 (3 H, s), 1.82 (3 H, s), 1.40 (3 H, d, *J* = 6.5 Hz).

IR (KBr): 2961, 2927, 1636, 1618, 1458, 1417, 1404, 1182, 1096, 754 cm^{-1}.

HRMS: *m*/*z* (M^+) Calcd for $C_{15}H_{15}NO_2$: 241.1103. Found: 241.1103.

5-Methyl-5,8,9,10,11,11a-hexahydro-12-oxa-5-azabenzo[*a*]anthracen-6-one (18)
Reaction of **13b** (175 mg, 1.0 mmol) with cyclohex-1-ene-1-carbaldehyde (224 mg, 2.0 mmol) in MeCN (10 mL) afforded **18** (107 mg, 40%) as a solid; mp 128–129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (1 H, d, *J* = 8.0 Hz), 7.48 (1 H, dd, *J* = 8.6, 7.1 Hz), 7.26 (1 H, d, *J* = 8.6 Hz), 7.17 (1 H, dd, *J* = 8.0, 7.1 Hz), 6.40 (1 H, s), 5.12 (1 H, m), 3.65 (3 H, s), 2.53–1.34 (8 H, m).

IR (KBr): 2938, 1638, 1618, 1578, 1503, 1459, 1420, 1321, 1249, 1194, 1163, 1122, 1097, 1041, 952, 755 cm^{-1}.

HRMS: *m*/*z* (M^+) Calcd for $C_{17}H_{17}NO_2$: 267.1259. Found: 267.1263.

6-Benzyl-2-methyl-2,6-dihydropyrano[3,2-*c*]quinolin-5-one (19)
Reaction of **13c** (251 mg, 1.0 mmol) with crotonaldehyde (140 mg, 2.0 mmol) in MeCN (10 mL) afforded **19** (127 mg, 42%) as a solid; mp 157–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (1 H, d, *J* = 8.0 Hz), 7.43–7.35 (2 H, m), 7.29–7.13 (6 H, m), 6.84 (1 H, d, *J* = 10.0 Hz), 5.61 (1 H, dd, *J* = 10.0, 3.3 Hz), 5.51 (2 H, s), 5.24 (1 H, m), 1.53 (3 H, d, *J* = 6.5 Hz).

IR (KBr): 3063, 3032, 2976, 1634,1556, 1497, 1454, 1375, 1325, 1192, 1151, 910 cm^{-1}.

HRMS: *m*/*z* (M^+) calcd for $C_{20}H_{17}NO_2$: 303.1259. Found: 303.1260.

Flindersine (1)
Reaction of **13a** (161 mg, 1.0 mmol) with 3-methylbut-2-enal (168 mg, 2.0 mmol) in MeCN (10 mL) afforded **1** (113 mg, 50%) as a solid; mp 195 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.5 (1 H, s), 7.87 (1 H, d, *J* = 8.1 Hz), 7.46 (1 H, dd, *J* = 8.2, 7.4 Hz), 7.31 (1 H, d, *J* = 8.2 Hz), 7.17 (1 H, dd, *J* = 8.1, 7.4 Hz), 6.75 (1 H, d, *J* = 9.9 Hz), 5.54 (1 H, d, *J* = 9.9 Hz), 1.53 (6 H, s).

IR (KBr): 3152, 2975, 1651, 1630, 1599, 1499, 1433, 1411, 1361, 1278, 1132, 872 cm^{-1}.

***N*-Methylflindersine (2)**
Reaction of **13b** (175 mg, 1.0 mmol) with 3-methylbut-2-enal (168 mg, 2.0 mmol) in MeCN (10 mL) afforded **2** (137 mg, 57%) as a solid; mp 80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (1 H, d, *J* = 8.0 Hz), 7.51 (1 H, dd, *J* = 8.3, 7.3 Hz), 7.28 (1 H, d, *J* = 8.3 Hz), 7.19 (1 H, dd, *J* = 8.0, 7.3 Hz), 6.73 (1 H, d, *J* = 10.0 Hz), 5.51 (1 H, d, *J* = 10.0 Hz), 3.67 (3 H, s), 1.49 (6 H, s).

IR (KBr): 2976, 1645, 1505, 1464, 1418, 1360, 1325, 1211, 1154, 1123, 1092, 1044, 1005, 987, 895 cm^{-1}.

Zanthosimuline (9)
Reaction of **13b** (175 mg, 1.0 mmol) with citral (304 mg, 2.0 mmol) in MeCN (10 mL) afforded **9** (170 mg, 55%) as a solid; mp 127–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (1 H, d, *J* = 7.8 Hz), 7.52 (1 H, dd, *J* = 8.0, 7.5 Hz), 7.29 (1 H, d, *J* = 8.0 Hz), 7.20 (1 H, dd, *J* = 7.8, 7.5 Hz), 6.77 (1 H, d, *J* = 10.0 Hz), 5.46 (1 H, d, *J* = 10.0 Hz), 5.07 (1 H, m), 3.67 (3 H, s), 2.09 (2 H, m), 1.90–1.66 (2 H, m), 1.60 (3 H, s), 1.52 (3 H, s), 1.46 (3 H, s).

IR (KBr): 2970, 2926, 1651, 1570, 1502, 1464, 1420, 1362, 1325, 1209, 1163, 1123, 1096, 1076, 1044, 1003, 906 cm^{-1}.

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