Tetrahedron 65 (2009) 10142–10148

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of 8-oxypseudopalmatine and 8-oxypseudoberberine via ring-closing metathesis

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ARTICLE INFO

Article history:
Received 14 September 2009
Received in revised form
8 October 2009
Accepted 8 October 2009
Available online 13 October 2009

Keywords:
8-Oxypseudopalmatine
8-Oxypseudoberberine
3-Arylisoquinolinones
Ring-closing metathesis

ABSTRACT

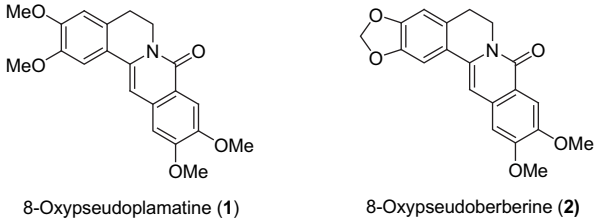
Concise synthesis of 8-oxypseudopalmatine and 8-oxypseudoberberine has been achieved using ruthenium-catalyzed ring-closing metathesis (RCM) as the key step, in which the RCM substrates, 3-arylisoquinolinones, were prepared by lithiated cycloaddition reaction with *o*-toluamides and benzonitriles.

1. Introduction

Protoberberines have been extensively investigated for their variety of interesting biological activities such as antifungal,[1] antitumor,[2] and antimicrobial[3] properties, and the syntheses of these alkaloids have been reported.[4] Recently, we reported the efficient synthesis of protoberberine and benzo[*c*]phenanthridine alkaloids via 3-arylisoquinolines as key intermediates.[5–7] To develop a novel synthetic method for these alkaloids, we next applied Ring-Closing Metathesis (RCM) to the construction of the C ring of protoberberines.

Among protoberberine alkaloids, we chose 8-oxypseudopalmatine and 8-oxypseudoberberine as target compounds. 8-Oxypseudopalmatine is an alkaloid found in *Stephama suberosa*, Forman (Menispermaceae).[8] In vitro tests for cytostatic activity in MDA-MB-231 mammary tumor cells showed that 8-oxypseudopalmatine inhibits cell proliferation more effectively than berberine or coralyne chloride (Fig. 1).[9]

RCM catalyzed by transition metal carbenes is a powerful tool for the conversion of acyclic dienes to cyclic rings.[10] While a large number of mono- and polycyclic compounds have been prepared by this method, RCM has not been applied to the construction of C ring of protoberberine alkaloids. Recent report showed the example of application of RCM for A ring formation on protoberberine synthesis.[11]



8-Oxypseudoplamatine (**1**) 8-Oxypseudoberberine (**2**)

Figure 1. Structure of 8-oxyprotoberberines.

2. Results and discussion

This strategy was based on preparation of 3-arylisoquinolines that retain olefins at the appropriate positions for the RCM reaction. For this, a coupling reaction between *N*,*N*-diethyl-*o*-toluamide **3** and benzonitrile **4** was carried out to yield the 3-arylisoquinoline **5**, which could be converted to the diene **6** via styrene preparation and N-vinylation of 3-arylisoquinoline **5** as depicted in Scheme 1. The RCM product **10** was then reduced by catalytic hydrogenation to afford the desired 8-oxyprotoberines. Recently, we reported isoquinoline alkaloid synthesis based on the coupling reaction of *o*-toluamides with benzonitriles.[5] Moreover, biological evaluations with molecular modeling studies of various isoquinolines such as isoindolo[2,1-*b*]isoquinolinones,[12] benz[*b*]oxepines, 12-oxobenzo[*c*]phenanthridinones,[13] and indeno[1,2-*c*]isoquinolines[14] were also reported. The advantages of our 3-arylisoquinoline synthesis methodology are easy accessibility to the staring materials and a one-pot procedure for construction of all carbon atoms for the alkaloids.

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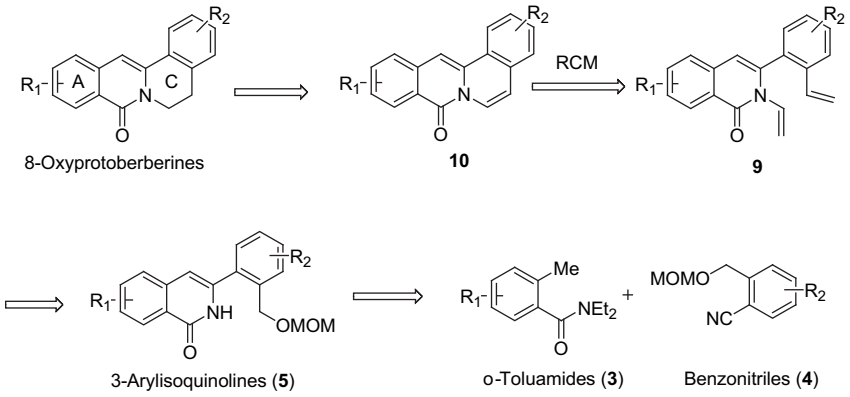
doi:10.1016/j.tet.2009.10.027



Scheme 1. Retrosynthetic pathway of 8-oxyprotoberberines.

As a model study, we first used simple starting materials. The coupling reactions were performed with *o*-toluamides **3a**–**c** and PMB-protected benzonitrile **4a** to afford 3-arylisoquinolines **5a**–**c** in moderate yield. To introduce the vinyl group on the amide nitrogen, we applied the aryl vinyl ether preparation conditions. Unsubstituted amide **5a** was treated with tetravinyl tin in the presence of $Cu(OAc)_2$ in acetonitrile under an atmosphere of pure O_2 to generate compound **6a** in 43% yield without an *O*-vinyl product.[15] This is the first example of the preparation of *N*-vinyl compounds with the above-mentioned reaction. The substituted amides **5b**–**e** also gave the corresponding *N*-vinyl compounds in 36–48% yield in the same reaction. Deprotection of the PMB group on **6a**–**c** was accomplished by DDQ oxidation to provide the hydroxymethyl compounds **7a**–**c**. MOM of **6d** was removed with 10% HCl to give **7d** and the TBDMS group of **6e** was deprotected by tetrabutylammonium fluoride in THF to afford the desired hydroxymethyl compound **7e** in 74% yield. Hydroxymethyl group of compound **6e** was protected by TBDMS instead of MOM because the corresponding MOM-protected hydroxymethyl compound could not afford the desired products in various acidic conditions. Instead, decomposed unknown products were obtained. PDC oxidation of **7a**–**e** gave the corresponding aldehydes **8a**–**e** in 57–84% yields. Wittig reactions of the aldehydes **8a**–**e** with Ph_3PCH_3Br and *n*-BuLi in THF provided the desired olefins **9a**–**e** in 53–85% yield, depending on the substituted pattern on the aromatic rings. RCM reactions of **9a**–**e** were performed with second-generation Grubbs catalyst in CH_2Cl_2 gave the desired cyclized compounds **10a**–**e** in 24–91% yield. Interestingly, dienes with more substituted benzene ring **9d**–**e** afforded much higher yield (91, 76%) in the above reaction. Finally, the double bonds on **10a**–**e** were selectively reduced by catalytic hydrogenation with 5% Pd/C or 10% PtO_2 under 70 psi hydrogen pressure to give the desired 8-oxyprotoberberines **1**,**2**, **11a**–**c** in moderate yield. The above regioselective catalytic hydrogen reaction could be explained by the fact that the di-substituted double bond hydrogenation of **10a**–**e** is preferred than tri-substituted double bond because the rate of hydrogenation decreases with an increase in the number of alkyl substituents of double bond.[16]

3. Conclusion

Herein, we successfully synthesized natural 8-oxy-pseudopalmatine and 8-oxypseudoberberine with other substitutions using RCM as a key reaction. Our synthesis illustrates a versatile method for synthesizing diversely substituted protoberberines and could be useful for structure–activity relationship studies of isoquinoline alkaloids that possess various biological properties (Scheme 2).

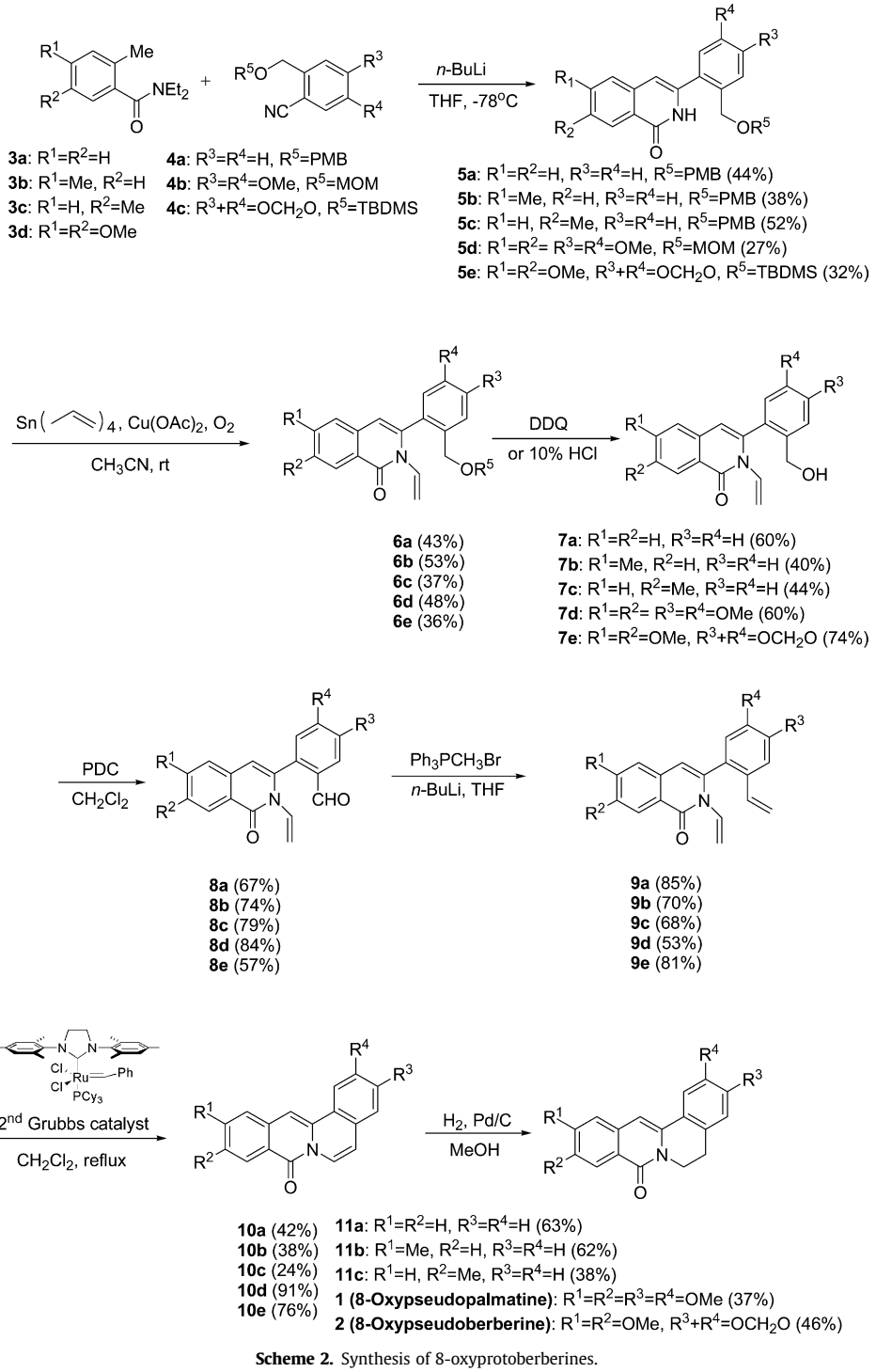
4. Experimental

4.1. General methods

Melting points were determined by the capillary method on an Electrothermal IA9200 digital melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) data for ^1H NMR were taken on a Varian Unity 300 Plus spectrometer and were reported in parts per million, downfield from the peak of the internal standard, tetramethylsilane. The data are reported as follows: chemical shift, number of protons, multiplicity (*s*: singlet, *d*: doublet, *t*: triplet, *q*: quartet, *m*: multiplet, *b*: broadened). IR spectra were recorded on JASCO-FT IR spectrometer using $CHCl_3$ and KBr pellets. Mass spectra were obtained on JEOL JNS-DX 303 applying the electron-impact (EI) method. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). TLC was performed using plates coated with silica gel 60 F254 (Merck). Chemical reagents were purchased from Aldrich Chemical Co. and used without further purification. Solvents were distilled prior to use: THF and ether were distilled from sodium/benzophenone.

*4.1.1. N,N-Diethyl-2-methylbenzamide (**3a**)*[17]. To a solution of thionyl chloride (68 ml) in an ice-bath, *o*-toluic acid (13.6 g, 100 mmol) was added portionwise. After removal from the ice-bath, the reaction mixture was warmed to about 50 °C for 45 min in order to completely dissolve the *o*-toluic acid. The reaction mixture was allowed to gradually cool to room temperature with stirring overnight. The excess thionyl chloride was removed by vacuum distillation. The residue was dissolved in CH_2Cl_2 (100 ml), and diethylamine (78 ml, 760 mmol) was added at 0 °C. After stirring overnight, the reaction mixture was diluted with water, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with water and brine, dried, and then concentrated. The residue was purified by column chromatography with *n*-hexane–ethyl acetate (1:1) to obtain compound **3a** as a yellow oil (18.7 g, 98%). IR (cm^{-1}): 1631 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.23–7.13 (m, 4H), 3.80 (s, 1H), 3.40 (s, 1H), 3.09 (q, J=6.9 Hz, 2H), 2.27 (s, 3H), 1.24 (t, J=6.9 Hz, 3H), 0.99 (t, J=7.2 Hz, 3H). EIMS: m/z 191 (M^+, 100).

*4.1.2. N,N-Diethyl-2,4-dimethylbenzamide (**3b**)*[13]. The procedure described for compound **3a** was used with 2,4-dimethylbenzoic acid (10 g, 66.7 mmol) and thionyl chloride (45 ml) to give amide



3a: R^1=R^2=H
3b: R^1=Me, R^2=H
3c: R^1=H, R^2=Me
3d: R^1=R^2=OMe

4a: R^3=R^4=H, R^5=PMB
4b: R^3=R^4=OMe, R^5=MOM
4c: R^3+R^4=OCH_2O, R^5=TBDMS

5a: R^1=R^2=H, R^3=R^4=H, R^5=PMB (44%)
5b: R^1=Me, R^2=H, R^3=R^4=H, R^5=PMB (38%)
5c: R^1=H, R^2=Me, R^3=R^4=H, R^5=PMB (52%)
5d: R^1=R^2= R^3=R^4=OMe, R^5=MOM (27%)
5e: R^1=R^2=OMe, R^3+R^4=OCH_2O, R^5=TBDMS (32%)

6a (43%)
6b (53%)
6c (37%)
6d (48%)
6e (36%)

7a: R^1=R^2=H, R^3=R^4=H (60%)
7b: R^1=Me, R^2=H, R^3=R^4=H (40%)
7c: R^1=H, R^2=Me, R^3=R^4=H (44%)
7d: R^1=R^2= R^3=R^4=OMe (60%)
7e: R^1=R^2=OMe, R^3+R^4=OCH_2O (74%)

8a (67%)
8b (74%)
8c (79%)
8d (84%)
8e (57%)

9a (85%)
9b (70%)
9c (68%)
9d (53%)
9e (81%)

10a (42%)
10b (38%)
10c (24%)
10d (91%)
10e (76%)

11a: R^1=R^2=H, R^3=R^4=H (63%)
11b: R^1=Me, R^2=H, R^3=R^4=H (62%)
11c: R^1=H, R^2=Me, R^3=R^4=H (38%)
1 (8-Oxypseudopalmatine): R^1=R^2=R^3=R^4=OMe (37%)
2 (8-Oxypseudoberberine): R^1=R^2=OMe, R^3+R^4=OCH_2O (46%)

Scheme 2. Synthesis of 8-oxyprotoberberines.

3b as a yellow oil (12.5 g, 92%). IR (cm^{-1}): 1632 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.06–7.01 (m, 3H), 3.60 (s, 2H), 3.12 (q, J=7.1 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H), 1.25 (t, J=7.1 Hz, 3H), 1.02 (t, J=7.1 Hz, 3H). EIMS: m/z 205 (M^+, 100).

*4.1.3. N,N-Diethyl-2,5-dimethylbenzamide (**3c**)*[13]. The procedure described for compound **3a** was used with 2,5-dimethylbenzoic acid (7.5 g, 50 mmol) and thionyl chloride (50 ml) to afford compound **3c** as a yellow oil (9.6 g, 94%). IR (cm^{-1}): 1632 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.05 (s, 2H), 6.96 (s, 1H), 3.75 (s, 1H), 3.40 (s, 1H), 3.15–3.09 (m, 2H), 2.29–2.20 (d, 6H), 1.25 (t, J=7.1 Hz, 3H), 1.02 (t, J=7.1 Hz, 3H). EIMS: m/z 205 (M^+, 100).

*4.1.4. 4,5-Dimethoxy-2-methoxymethoxymethylbenzonitrile (**4b**)*[12]. To the mixture of alcohol (5.5 g, 28.5 mmol) in CH_2Cl_2 (20 ml) was added diisopropylethylamine (DIPEA) (7.35 g, 57 mmol) and chloromethylmethyl ether (4.59 g, 57 mmol) at 0 °C. After the reaction was over, CH_2Cl_2 was removed in vacuo and the residue was purified by column chromatography with *n*-hexane–ethyl acetate (3:1) to give benzonitrile **4b** as a white solid (6.7 g,

99%). Mp: 54.5–56.4 °C. IR (cm^{-1}): 2222 (CN). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.07–7.03 (d, 2H), 4.76 (s, 2H), 4.71 (s, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.44 (s, 3H). EIMS: m/z 237 (M^+, 100).

4.1.5. 6-(^{t}*Butyldimethylsilanyloxymethyl)benzo[1,3]dioxole-5-carbonitrile (**4c**).* To a stirred mixture of 6-hydroxymethylbenzo[1,3]dioxole-5-carbonitrile (3.9 g, 22 mmol) and ^{t}butyl dimethyl silyl chloride (6.63 g, 44 mmol) in DMF (3 ml) was added triethylamine (4.44 g, 44 mmol) at room temperature. After stirring overnight at 35 °C, the mixture was diluted with water, extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The organic extracts were combined, concentrated in vacuo, and purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (4:1) to give the protected alcohol **4c** as a white solid (5.36 g, 84%). Mp: 48–49 °C. IR (cm^{-1}): 2219 (CN). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.07 (s, 1H), 6.95 (s, 1H), 6.04 (s, 2H), 4.79 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). EIMS: m/z 291 (M^+, 100).

*4.1.6. 3-[2-(4-Methoxybenzyloxymethyl)phenyl]-2H-isoquinolin-1-one (**5a**).* To a solution of *N*-methyl-*o*-toluamide **3a** (5.03 g, 33.7 mmol) in dry THF under nitrogen was added 2.5 M *n*-BuLi (22.8 ml, 57 mmol in *n*-hexane) at −20 °C, and the reaction temperature was maintained so as not to exceed 0 °C. After the addition was complete, the red orange solution was stirred for 1 h at the same temperature. To this solution was slowly added a solution of 2-(*p*-methoxybenzyloxymethyl)benzonitrile **4a**[18] (26.9 mmol, 6.82 g) in dry THF; the reaction mixture was then cooled to −50 °C and stirred for 20 min at the same temperature. The reaction was carefully quenched with water, stirred vigorously for 10 min, and extracted with ethyl acetate. The organic layers were washed with water and brine and dried over sodium sulfate. After removing the solvent, the residue was separated by column chromatography with hexane–ethyl acetate (3:1) on silica gel to afford compound **5a** as a yellow oil (2.74 g, 44%). IR (cm^{-1}): 3400 (NH), 1657 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.25 (s, 1H), 8.44 (m, 1H), 7.65 (m, 1H), 7.57–7.25 (m, 8H), 6.90 (m, 2H), 6.58 (s, 1H), 4.64 (s, 2H), 4.46 (s, 2H), 3.77 (s, 3H). EIMS: m/z 371 (M^+, 65). HRMS-EI (calcd for $C_{24}H_{21}NO_3$): 371.1521, found 371.1529.

*4.1.7. 3-[2-(4-Methoxybenzyloxymethyl)phenyl]-6-methyl-2H-isoquinolin-1-one (**5b**).* The procedure described for compound **5a** was used with toluamide **3b** (1 g, 6.1 mmol) and 2-(*p*-methoxy benzyloxymethyl)benzonitrile **4a** (7.7 mmol, 1.95 g) in the presence of 1.6 M *n*-BuLi in hexane (8.8 ml, 14.0 mmol) to give compound **5b** as a yellow oil (892 mg, 38%). IR (cm^{-1}): 3400 (NH), 1657 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.12 (s, 1H), 8.33 (d, 1H), 7.55–6.86 (m, 10H), 6.53 (s, 1H), 4.64 (s, 2H), 4.46 (s, 2H), 3.79 (s, 3H), 2.50 (s, 3H). EIMS: m/z 385 (M^+, 100). HRMS-EI (calcd for $C_{25}H_{23}NO_3$): 375.1678, found 385.1672.

*4.1.8. 3-[2-(4-Methoxybenzyloxymethyl)phenyl]-7-methyl-2H-isoquinolin-1-one (**5c**).* The procedure described for compound **5a** was used with toluamide **3c** (1.5 g, 9.2 mmol) and 2-(*p*-methoxy benzyloxymethyl)benzonitrile **4a** in the presence of *n*-BuLi (1.6 M in hexane) to give compound **5c** as a yellow oil (1.85 g, 52%). IR (cm^{-1}): 3400 (NH), 1657 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.2 (s, 1H), 8.25 (s, 1H), 7.54–7.41 (m, 8H), 6.90 (m, 2H), 6.56 (s, 1H), 4.64 (s, 2H), 4.45 (s, 2H), 3.78 (s, 3H), 2.50 (s, 3H). EIMS: m/z 385 (M^+, 100). HRMS-EI (calcd for $C_{25}H_{23}NO_3$): 375.1678, found 385.1670.

*4.1.9. 3-(4,5-Dimethoxy-2-methoxymethoxymethylphenyl)-6,7-dimethoxy-2H-isoquinolin-1-one (**5d**).* The procedure described for compound **5a** was used with *N*,*N*-diethyl-4,5-dimethoxy-2-methyl benzamide (5.62 g, 22.4 mmol), benzonitrile **4b** (6.7 g, 28 mmol), and *n*-butyl lithium (21.5 ml of 2.5 M in hexane, 53.8 mmol) in THF (50 ml) to afford compound **5d** as a white solid (2.5 g, 27%). Mp: 155–157 °C. IR (cm^{-1}): 3431 (NH), 1634 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.18 (s, 1H), 7.76 (s, 1H), 7.04 (s, 1H), 6.99 (s, 1H), 6.94 (s, 1H), 6.52 (s, 1H), 4.79 (s, 2H), 4.55 (s, 2H), 4.01 (m, 6H), 3.96 (m, 6H), 3.43 (s, 3H). Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.63; H, 6.05; N, 3.33. EIMS: m/z 415 (M^+, 64).

4.1.10. 3-[6-(^{t}*Butyldimethylsilanyloxymethyl)benzo[1,3]dioxol-5-yl]-6,7-dimethoxy-2H-isoquinolin-1-one (**5e**).* The procedure described for compound **5a** was used with *N*,*N*-diethyl-4,5-dimethoxy-2-methylbenzamide **3d** (5.0 g, 18.3 mmol), benzonitrile **4c** (5.33 g, 18.3 mmol), and *n*-BuLi (17.6 ml of 2.5 M in hexane, 43.9 mmol) in dry THF (10 ml) to afford compound **5e** as a yellow oil (2.8 g, 32%). IR (cm^{-1}): 3477 (NH), 1632 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.2 (s, 1H), 7.80 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 6.69 (s, 1H), 5.04 (s, 2H), 4.57 (s, 2H), 4.00 (s, 6H), 0.98 (s, 9H), 0.19 (s, 6H). EIMS: m/z 69 (M^+, 78). HRMS-EI (calcd for $C_{25}H_{31}NO_6Si$): 469.1921, found 469.1927.

*4.1.11. 3-[2-(4-Methoxybenzyloxymethyl)phenyl]-2-vinyl-2H-isoquinolin-1-one (**6a**).* Anhydrous $Cu(OAc)_2$ (1.527 g, 8.4 mmol) was added to a stirred solution of compound **8a** (2.6 g, 7 mmol) in CH_3CN (30 ml) under dry O_2 at room temperature. Tetravinyl tin (1.907 g, 8.4 mmol) was added to the turquoise mixture. After stirring the mixture for 6 h, the dark green reaction mixture was poured into aqueous 25% NH_4OAc (25 ml). After 10 min of stirring, the blue aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the residue, which was then purified by column chromatography with *n*-hexane–EtOAc (1:2) to afford compound **6a** as a yellow oil (1.2 g, 43%). IR (cm^{-1}): 1658 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.46 (m, 1H), 7.60–7.25 (m, 7H), 7.07 (m, 2H), 6.69–6.66 (m, 2H), 6.60–6.51 (m, 1H), 6.37 (s, 1H), 5.27(d, J=15.9 Hz, 1H), 5.00 (d, J=9.0 Hz, 1H), 4.46–4.28 (m, 4H), 3.67 (s, 3H). EIMS: m/z 397 (M^+, 100). HRMS-EI (calcd for $C_{26}H_{23}NO_3$): 397.1678, found 397.1669.

*4.1.12. 3-[2-(4-Methoxybenzyloxymethyl)phenyl]-6-methyl-2-vinyl-2H-isoquinolin-1-one (**6b**).* The procedure described for compound **6a** was used with compound **5b** (3 g, 7.78 mmol), tetravinyl tin (2.13 g, 9.4 mmol), and anhydrous $Cu(OAc)_2$ (1.7 g, 9.4 mmol) to afford compound **6b** as a yellow oil (1.7 g, 53%). IR (cm^{-1}): 1654 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, J=8.2 Hz, 1H), 7.54 (m, 1H), 7.43–7.22 (m, 5H), 7.12–7.10 (m, 2H), 6.74–6.72 (m, 2H), 6.59–6.51 (dd, J_1=9.0 Hz, J_2=15.9 Hz, 1H), 6.35 (s, 1H), 5.23 (d, J=15.8 Hz, 1H), 5.02 (d, J=9.0 Hz, 1H), 4.46–4.31 (m, 4H), 3.74 (s, 3H), 2.49 (s, 3H). EIMS: m/z 411 (M^+, 88). HRMS-EI (calcd for $C_{27}H_{25}NO_3$): 411.1834, found 411.1840.

*4.1.13. 3-[2-(4-Methoxybenzyloxymethyl)phenyl]-7-methyl-2-vinyl-2H-isoquinolin-1-one (**6c**).* The procedure described for compound **6a** was used with compound **8c** (3.5 g, 9.08 mmol), tetravinyl tin (2.47 g, 10.9 mmol), and anhydrous $Cu(OAc)_2$ (1.98 g, 10.9 mmol) to afford compound **6c** as a yellow oil (1.4 g, 37%). IR (cm^{-1}): 1661 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.46–7.23 (m, 5H), 7.11–7.06 (m, 2H), 6.71–6.66 (m, 2H), 6.61–6.53 (dd, J_1=9.0 Hz, J_2=16 Hz, 1H), 6.36 (s, 1H), 5.24 (d, J=16 Hz, 1H), 5.00 (d, J=9 Hz, 1H), 4.46–4.30 (m, 4H), 3.68 (s, 3H), 2.48 (s, 3H). EIMS: m/z 411 (M^+, 82). HRMS-EI (calcd for $C_{27}H_{25}NO_3$): 411.1834, found 411.1836.

*4.1.14. 3-(4,5-Dimethoxy-2-methoxymethoxymethylphenyl)-6,7-dimethoxy-2-vinyl-2H-isoquinolin-1-one (**6d**).* The procedure described for compound **6a** was used with compound **5d** (2.5 g, 6.02 mmol), tetravinyl tin (2.05 g, 9.03 mmol), and anhydrous $Cu(OAc)_2$ (1.63 g, 9.03 mmol) to afford compound **6d** as a yellow solid (1.3 g, 48%). Mp: 136–138 °C. IR (cm^{-1}): 1650 (C=O). ^1H NMR

(300 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 7.03 (s, 1H), 6.83 (s, 1H), 6.76 (s, 1H), 6.64–6.55 (m, 1H), 6.39 (s, 1H), 5.33 (d, 1H), 5.08 (d, 1H), 4.60 (s, 2H), 4.45–4.40 (m, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.87 (s, 3H), 3.27 (s, 3H). Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.27; H, 6.15; N, 3.14. EIMS: *m*/*z* 441 (M^+, 56).

*4.1.15. 3-[6-(^{t}Butyldimethylsilanyloxymethyl)benzo[1,3]dioxol-5-yl]-6,7-dimethoxy-2-vinyl-2H-isoquinolin-1-one (**6e**).* The procedure described for compound **6a** was used with the amide **5e** (2.7 g, 5.73 mmol), anhydrous copper acetate (1570 mg, 8.6 mmol), and tetravinyl tin (1960 mg, 8.6 mmol) in the presence of dry O_2 for 36 h to afford compound **6e** as a yellow solid (1.02 g, 36%). Mp: 59–61 °C. IR (cm^{-1}): 1654 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (s, 1H), 7.29 (s, 1H), 7.07 (s, 1H), 6.84 (s, 1H), 6.72 (s, 1H), 6.61 (dd, J_1=9.0 Hz, J_2=15.9 Hz, 1H), 6.37 (s, 1H), 6.05 (m, 2H), 5.36 (d, J=16.0 Hz, 1H), 5.12 (d, J=9.0 Hz, 1H), 4.47 (m, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H). Anal. Calcd for $C_{27}H_{33}NO_6Si$: C, 65.43; H, 6.71; N, 2.83. Found: C, 65.46; H, 6.70; N, 2.86. EIMS: *m*/*z* 495 (M^+, 78).

*4.1.16. 3-(2-Hydroxymethylphenyl)-2-vinyl-2H-isoquinolin-1-one (**7a**).* DDQ (1.048 g, 4.5 mmol) was added portionwise to a mixed solution of compound **6a** (1.2 g, 3.01 mmol) in CH_2Cl_2 (36 ml) and water (2 ml) at room temperature. After the reaction mixture was stirred overnight, satd aq $NaHCO_3$ (20 ml) was added to the mixture, which was then extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography on silica gel with *n*-hexane–EtOAc (2:1) to give compound **7a** as a yellow oil (500 mg, 60%). IR (cm^{-1}): 3398 (OH), 1648 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.34 (d, J=7.8 Hz, 1H), 7.62–7.57 (m, 2H), 7.44–7.3 (m, 3H), 7.34–7.22 (m, 2H), 6.54–6.46 (m, 1H), 6.41 (s, 1H), 5.18 (d, J=16.0 Hz, 1H), 4.96 (d, J=8.9 Hz, 1H), 4.52 (m, 2H), 3.30 (s, 1H). EIMS: *m*/*z* 277 (M^+, 100). HRMS-EI (calcd for $C_{18}H_{15}NO_2$): 277.1103, found 277.1108.

*4.1.17. 3-(2-Hydroxymethylphenyl)-6-methyl-2-vinyl-2H-isoquinolin-1-one (**7b**).* The procedure described for compound **7a** was used with compound **6b** (1.6 g, 3.9 mmol) and DDQ (1.36 g, 5.85 mmol) to afford compound **7b** as a yellow solid (460 mg, 40%). Mp: 82–84 °C. IR (cm^{-1}): 3436 (OH), 1655 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (d, J=8.3 Hz, 1H), 7.60–7.58 (m, 1H), 7.46 (m, 1H), 7.36–7.24 (m, 4H), 6.60–6.52 (m, 1H), 6.38 (s, 1H), 5.24 (d, J=16.0 Hz, 1H), 5.02 (d, J=9.0 Hz, 1H), 4.60 (s, 2H), 2.47 (s, 3H), 1.73 (s, 1H). EIMS: *m*/*z* 291 (M^+, 51). HRMS-EI (calcd for $C_{19}H_{17}NO_2$): 291.1259, found 291.1261.

*4.1.18. 3-(2-Hydroxymethylphenyl)-7-methyl-2-vinyl-2H-isoquinolin-1-one (**7c**).* The procedure described for compound **7a** was used with compound **6c** (1.2 g, 2.9 mmol) and DDQ (987 mg, 4.35 mmol) to afford compound **7c** as a yellow oil (367 mg, 44%). IR (cm^{-1}): 3402 (OH), 1652 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.52–7.40 (m, 2H), 7.35–7.24 (m, 3H), 6.58–6.50 (m, 1H), 6.40 (s, 1H), 5.19 (d, J=5.1 Hz, 1H), 4.98 (d, J=9.0 Hz, 1H), 4.55 (m, 2H), 2.46 (s, 3H). EIMS: *m*/*z* 291 (M^+, 66). HRMS-EI (calcd for $C_{19}H_{17}NO_2$): 291.1259, found 291.1251.

*4.1.19. 3-(6-Hydroxymethylbenzo[1,3]dioxol-5-yl)-6,7-dimethoxy-2-vinyl-2H-isoquinolin-1-one (**7e**).* To a solution of compound **6e** (1.05 g, 2.12 mmol) in dry THF (20 ml) was added tetrabutyl ammonium fluoride (6.4 ml solution of 1.0 mol in THF, 6.4 mmol) under N_2 at 0 °C. The resulting mixture was held at 0 °C for 5 min and then warmed to 25 °C and stirred overnight. Water was added to the reaction mixture, which was then extracted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. After removing solvent, the residue was purified by column chromatography with *n*-hexane–ethyl acetate (1:2) to afford compound **7e** as a white solid (605 mg, 74%). Mp: 197–198 °C. IR (cm^{-1}): 3524 (OH), 1651 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.06 (s, 1H), 6.81 (s, 1H), 6.73 (s, 1H), 6.62–6.53 (m, 1H), 6.37 (s, 1H), 6.03 (s, 2H), 5.30 (m, 1H), 5.09 (m, 1H), 4.45 (s, 2H), 4.01 (s, 3H), 3.98 (s, 3H). Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.15; H, 5.00; N, 3.69. EIMS: *m*/*z* 381 (M^+, 87).

*4.1.20. 2-(1-Oxo-2-vinyl-1,2-dihydroisoquinolin-3-yl)benzaldehyde (**8a**).* To a solution of alcohol **7a** (450 mg, 1.6 mmol) in methylene chloride (30 ml) was added PDC (1.28 g, 3.4 mmol) and the mixture was stirred for 2 h. The reaction mixture was then filtered and washed with CH_2Cl_2. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate to afford the aldehyde **8a** as a yellow oil (300 mg, 67%). IR (cm^{-1}): 1698, 1653 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 8.46 (m, 1H), 7.96 (m, 1H), 7.68–7.48 (m, 6H), 6.63–6.55 (m, 1H), 6.48 (s, 1H), 5.11–5.02 (m, 2H). EIMS: *m*/*z* 275 (M^+, 100). HRMS-EI (calcd for $C_{18}H_{13}NO_2$): 275.0946, found 275.0939.

*4.1.21. 2-(6-Methyl-1-oxo-2-vinyl-1,2-dihydroisoquinolin-3-yl)benzaldehyde (**8b**).* The procedure described for compound **8a** was used with compound **7b** (400 mg, 1.37 mmol) and PDC (1.08 g, 2.88 mmol) in CH_2Cl_2 (20 ml) to afford compound **8b** as a white solid (294 mg, 74%). Mp: 143–144 °C. IR (cm^{-1}): 1704, 1652 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 8.36 (d, J=8.4 Hz, 1H), 7.99 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H), 7.68–7.65 (m, 1H), 7.58 (m, 1H), 7.46 (m, 1H), 7.37–7.34 (m, 1H), 7.28 (s, 1H), 6.60 (dd, J_1=9 Hz, J_2=15.9 Hz, 1H), 6.41 (s, 1H), 5.10–5.00 (m, 2H), 2.49 (s, 3H). EIMS: *m*/*z* 289 (M^+, 63). HRMS-EI (calcd for $C_{19}H_{15}NO_2$): 289.1103, found 289.1110.

*4.1.22. 2-(7-Methyl-1-oxo-2-vinyl-1,2-dihydroisoquinolin-3-yl)benzaldehyde (**8c**).* The procedure described for compound **8a** was used with the alcohol **7c** (330 mg, 1.15 mmol) and PDC (902 mg, 2.4 mmol) in CH_2Cl_2 (20 ml) to afford the aldehyde **8c** as a yellow oil (260 mg, 79%). IR (cm^{-1}): 1698, 1654 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.03 (s, 1H), 8.28 (s, 1H), 7.98 (m, 1H), 7.68–7.39 (m, 5H), 6.62 (dd, J_1=9.0 Hz, J_2=15.9 Hz, 1H), 6.45 (s, 1H), 5.11–5.00 (m, 2H), 2.52 (s, 3H). EIMS: *m*/*z* 289 (M^+, 87). HRMS-EI (calcd for $C_{19}H_{15}NO_2$): 289.1103, found 289.1101.

*4.1.23. 2-(6,7-Dimethoxy-1-oxo-2-vinyl-1,2-dihydroisoquinolin-3-yl)-4,5-dimethoxy benzaldehyde (**8d**).* The procedure described for compound **8a** was used with compound **7d** (300 mg, 0.75 mmol) and PDC (496 mg, 1.3 mmol) in CH_2Cl_2 (20 ml) to afford compound **8d** as a yellow solid (250 mg, 84%). Mp: 196–198 °C. IR (cm^{-1}): 1665, 1597 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.92 (s, 1H), 7.84 (s, 1H), 7.49 (s, 1H), 6.8 (d, 2H), 6.62 (m, 1H), 6.43 (s, 1H), 5.10 (m, 2H), 4.04–3.97 (m, 12H). Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.87; H, 5.36; N, 3.51. EIMS: *m*/*z* 395 (M^+, 100).

*4.1.24. 6-(6,7-Dimethoxy-1-oxo-2-vinyl-1,2-dihydroisoquinolin-3-yl)benzo[1,3]dioxole-5-carbaldehyde (**8e**).* The procedure described for compound **8a** was used with compound **7e** (600 mg, 1.58 mmol) and PDC (1.25 g, 3.32 mmol) for 5 h to produce compound **8e** as a white solid (343 mg, 57%). Mp: 199–201 °C. IR (cm^{-1}): 1678, 1644 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.86 (s, 1H), 7.86 (s, 1H), 7.43 (s, 1H), 6.85–6.82 (m, 2H), 6.64 (m, 1H), 6.40 (s, 1H), 6.15 (m, 2H), 5.20–5.12 (m, 2H), 4.04 (s, 3H), 3.99 (s, 3H). Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.49; H, 4.52; N, 3.69. Found: C, 66.47; H, 4.55; N, 3.66. EIMS: *m*/*z* 379 (M^+, 54).

*4.1.25. 2-Vinyl-3-(2-vinylphenyl)-2H-isoquinolin-1-one (**9a**).* To a solution of methyltriphenylphosphonium bromide (1.96 g, 5.5 mmol) in dry THF (30 ml) was added *n*-butyl lithium (2.2 ml of 2.5 M in *n*-hexane, 5.5 mmol) at 0 °C and the solution was stirred at 0 °C for 1 h. To this mixture was added the aldehyde **8a** (300 mg,

1.1 mmol) in THF (10 ml) and the resulting mixture was stirred at room temperature for 1 h. The reaction was then quenched with water and extracted with ethyl acetate. The organic layers were washed with water and brine and dried over sodium sulfate. After removal of the solvent in vacuo, the residue was purified by column chromatography with *n*-hexane–ethyl acetate to afford the styrene **9a** as a yellow oil (255 mg, 85%). IR (cm^{-1}): 1655 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.47 (m, 1H), 7.65–7.60 (m, 2H), 7.52–7.49 (m, 2H), 7.46–7.29 (m, 3H), 6.62–6.53 (m, 2H), 6.45 (s, 1H), 5.70 (dd, J_1=1.0 Hz, J_2=17.4 Hz, 1H), 5.25–5.21 (d, J=10.0 Hz, 1H), 5.15–5.10 (d, J=15.0 Hz, 1H), 5.04–5.01 (d, J=8.4 Hz, 1H). EIMS: *m*/*z* 273 (M^+, 100). HRMS-EI (calcd for $C_{19}H_{15}NO$): 273.1154, found 273.1161.

*4.1.26. 6-Methyl-2-vinyl-3-(2-vinylphenyl)-2H-isoquinolin-1-one (**9b**).* The procedure described for compound **9a** was used with compound **8b** (280 mg, 0.97 mmol), methyltriphenylphosphonium bromide (1.73 g, 4.85 mmol), and *n*-BuLi (1.9 ml of 2.5 M in hexane, 4.85 mmol) in THF (20 ml) to afford compound **9b** as a yellow oil (196 mg, 70%). IR (cm^{-1}): 1660 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, J=8.2 Hz, 1H), 7.60 (m, 1H), 7.34–7.26 (m, 5H), 6.62–6.52 (m, 2H), 6.38 (s, 1H), 5.69 (dd, J_1=1 Hz, J_2=17.4 Hz, 1H), 5.22 (dd, J_1=1 Hz, J_2=12 Hz, 1H), 5.12–5.07 (d, 1H), 5.03–5.00 (d, 1H), 2.48 (s, 3H). EIMS: *m*/*z* 287 (M^+, 100). HRMS-EI (calcd for $C_{20}H_{17}NO$): 287.1310, found 287.1312.

*4.1.27. 7-Methyl-2-vinyl-3-(2-vinylphenyl)-2H-isoquinolin-1-one (**9c**).* The procedure described for compound **9a** was used with compound **8c** (240 mg, 0.83 mmol), methyltriphenylphosphonium bromide (1.48 g, 4.15 mmol), and *n*-BuLi (1.7 ml of 2.5 M in hexane, 4.15 mmol) in THF (20 ml) to afford compound **9c** as a yellow oil (162 mg, 68%). IR (cm^{-1}): 1653 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.59 (m, 1H), 7.47–7.28 (m, 5H), 6.64–6.51 (m, 2H), 6.40 (s, 1H), 5.71–5.65 (dd, J_1=1 Hz, J_2=17.5 Hz, 1H), 5.23–5.19 (m, 1H), 5.12–5.07 (m, 1H), 5.02–4.99 (m, 1H), 2.48 (s, 3H). EIMS: *m*/*z* 287 (M^+, 100). HRMS-EI (calcd for $C_{20}H_{17}NO$): 287.1310, found 287.1314.

*4.1.28. 3-(4,5-Dimethoxy-2-vinylphenyl)-6,7-dimethoxy-2-vinyl-2H-isoquinolin-1-one (**9d**).* The procedure described for compound **9a** was used with compound **8d** (250 mg, 0.63 mmol), methyltriphenylphosphonium bromide (1.12 g, 3.15 mmol) and *n*-butyl lithium (1.3 ml of 2.5 M in hexane, 3.15 mmol) to afford compound **9d** as a yellow oil (132 mg, 53%). IR (cm^{-1}): 1698 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 7.10 (s, 1H), 6.86 (s, 1H), 6.76 (s, 1H), 6.64–6.49 (m, 2H), 6.38 (s, 1H), 5.63–5.57 (d, 1H), 5.20 (d, 1H), 5.16 (d, 1H), 5.06 (d, 1H), 4.03 (s, 3H), 3.96 (d, 6H), 3.89 (s, 3H). EIMS: *m*/*z* 393 (M^+, 88). HRMS-EI (calcd for $C_{23}H_{23}NO_5$): 393.1576, found 393.1574.

*4.1.29. 6,7-Dimethoxy-2-vinyl-3-(6-vinylbenzo[1,3]dioxol-5-yl)-2H-isoquinolin-1-one (**9e**).* The procedure described for compound **9a** was used with compound **8e** (343 mg, 0.9 mmol), methyltriphenylphosphonium bromide (1.62 g, 4.5 mmol), and 2.5 M *n*-BuLi in hexane (4.5 mmol, 1.81 ml) to give compound **9e** as a white solid (276 mg, 81%). Mp: 95–98 °C. IR (cm^{-1}): 1652 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 7.08 (s, 1H), 6.84 (s, 1H), 6.75 (s, 1H), 6.63–6.43 (m, 2H), 6.35 (s, 1H), 6.04 (s, 2H), 5.56 (m, 1H), 5.20–5.07 (m, 3H), 4.03 (s, 3H), 3.99 (s, 3H). Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.04; H, 5.05; N, 3.74. EIMS: *m*/*z* 377 (M^+, 100).

*4.1.30. Isoquino[3,2-a]isoquinolin-8-one (**10a**).* A reaction mixture of compound **9a** (60 mg, 0.22 mmol) and second-generation Grubbs catalyst (38 mg, 20 mol %) in CH_2Cl_2 (30 ml) was refluxed overnight. The reaction mixture was then filtered and washed with CH_2Cl_2. The solvent was evaporated off and the residue was purified by column chromatography on silica gel to afford compound **10a** as a yellow solid (22 mg, 42%). Mp: 164–166 °C. IR (cm^{-1}): 1684 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.64 (d, J=8 Hz, 1H), 8.57 (m, 1H), 8.25 (m, 1H), 7.72–7.68 (m, 2H), 7.55–7.47 (m, 5H), 6.76 (d, J=8 Hz, 1H). EIMS: *m*/*z* 245 (M^+, 48). HRMS-EI (calcd for $C_{17}H_{11}NO$): 245.0841, found 245.0844.

*4.1.31. 11-Methylisoquino[3,2-a]isoquinolin-8-one (**10b**).* The procedure described for compound **10a** was used with compound **9b** (180 mg, 0.63 mmol) and second-generation Grubbs catalyst (107 mg, 0.13 mmol) to afford compound **10b** as a yellow solid (60 mg, 38%). Mp: 183–184 °C. IR (cm^{-1}): 1654 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.63 (d, J=7.9 Hz, 1H), 8.45 (d, J=8.3 Hz, 1H), 8.23 (m, 1H), 7.52–7.46 (m, 5H), 7.34–7.31 (m, 1H), 6.75–6.72 (d, 1H), 2.53 (s, 3H). EIMS: *m*/*z* 259 (M^+, 100). HRMS-EI (calcd for $C_{18}H_{13}NO$): 259.0997, found 259.0990.

*4.1.32. 10-Methylisoquino[3,2-a]isoquinolin-8-one (**10c**).* The procedure described for compound **10a** was used with compound **9c** (142 g, 0.5 mmol) and second-generation Grubbs catalyst (43 mg, 0.05 mmol) to afford compound **10c** as a yellow solid (31 mg, 24%). Mp: 200–202 °C. IR (cm^{-1}): 1691 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.65 (d, J=8 Hz, 1H), 8.36 (s, 1H), 8.24 (m, 1H), 7.64–7.42 (m, 6H), 6.75 (d, J=8 Hz, 1H), 2.53 (s, 3H). EIMS: *m*/*z* 259 (M^+, 100). HRMS-EI (calcd for $C_{18}H_{13}NO$): 259.0997, found 259.0993.

*4.1.33. 2,3,10,11-Tetramethoxyisoquino[3,2-a]isoquinolin-8-one (**10d**).* The procedure described for compound **10a** was used with compound **9d** (120 mg, 0.3 mmol) and second-generation Grubbs catalyst (76 mg, 30 mol %) to afford compound **10d** as a yellow solid (100 mg, 91%). Mp: 246–248 °C. IR (cm^{-1}): 1646 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.69 (d, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 7.28 (d, 2H), 7.04 (s, 1H), 6.91 (s, 1H), 6.76 (d, 1H), 4.09–4.01 (m, 12H). Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.02; H, 5.23; N, 3.80. EIMS: *m*/*z* 365 (M^+, 58).

*4.1.34. 10,11-Dimethoxy-[1,3]dioxolo[4,5-g]isoquino[3,2-a]isoquinolin-8-one (**10e**).* The procedure described for compound **10a** was used with compound **9e** (207 mg, 0.55 mmol) and second-generation Grubbs catalyst (140 mg, 0.17 mol) to afford compound **10e** as a yellow solid (146 mg, 76%). Mp: 297–299 °C. IR (cm^{-1}): 1648 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.62 (d, J=8 Hz, 1H), 7.83 (s, 1H), 7.54 (s, 1H), 7.18 (s, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 6.67 (d, J=8 Hz, 1H), 6.08 (s, 2H), 4.04 (d, 6H). Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 68.74; H, 4.31; N, 4.00. EIMS: *m*/*z* 349 (M^+, 100).

*4.1.35. 5,6-Dihydroisoquino[3,2-a]isoquinolin-8-one (**11a**).* The mixture of compound **10a** (22 mg, 0.09 mmol) and 5% Pd/C (20 mg) in MeOH (10 ml) was treated with hydrogen gas at 70 psi for 24 h using the Parr apparatus. The reaction mixture was filtered and the filtrate was evaporated to give a residue that was purified by column chromatography to give protoberberine **11a** as a yellow oil (14 mg, 63%). IR (cm^{-1}): 1646 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.44 (m, 1H), 7.83 (m, 1H), 7.66–7.56 (m, 2H), 7.49–7.43 (m, 1H), 7.37–7.33 (m, 2H), 7.28–7.25 (m, 1H), 7.03 (s, 1H), 4.40–4.36 (m, 2H), 3.03–2.99 (m, 2H). EIMS: *m*/*z* 247 (M^+, 100). HRMS-EI (calcd for $C_{17}H_{13}NO$): 247.0997, found 247.0994.

*4.1.36. 11-Methyl-5,6-dihydroisoquino[3,2-a]isoquinolin-8-one (**11b**).* The procedure described for compound **11a** was used with compound **10b** (70 mg, 0.27 mmol) and 5% Pd/C (40 mg) in MeOH (10 ml) to afford compound **11b** as a yellow solid (44 mg, 62%). Mp: 115–116 °C. IR (cm^{-1}): 1636 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.32 (d, J=8.2 Hz, 1H), 7.81–7.78 (m, 1H), 7.36–7.19 (m, 5H), 6.94 (s,

1H), 4.35 (m, 1H), 2.98 (m, 2H), 2.47 (s, 3H). EIMS: *m*/*z* 261 (M^+, 100). HRMS-EI (calcd for $C_{18}H_{15}NO$): 261.1154, found 261.1158.

*4.1.37. 10-Methyl-5,6-dihydroisoquino[3,2-a]isoquinolin-8-one (**11c**).* The procedure described for compound **11a** was used with compound **10c** (38 mg, 0.15 mmol) and 5% Pd/C (20 mg) in MeOH (10 ml) to afford compound **11c** as a yellow solid (15 mg, 38%). Mp: 140–142 °C. IR (cm^{-1}): 1641 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.25 (m, 1H), 7.83–7.80 (m, 1H), 7.48–7.47 (m, 2H), 7.36–7.34 (m, 2H), 7.28–7.25 (m, 1H), 7.01 (s, 1H), 4.40–4.36 (m, 2H), 3.04–2.99 (m, 2H), 2.50 (s, 1H). EIMS: *m*/*z* 261 (M^+, 100). HRMS-EI (calcd for $C_{18}H_{15}NO$): 261.1154, found 261.1148.

*4.1.38. 2,3,10,11-Tetramethoxy-5,6-dihydroisoquino[3,2-a]isoquinolin-8-one: 8-oxypseudopalmatine (**1**).* The procedure described for compound **11a** was used with compound **10d** (19 mg, 0.05 mmol) and 5% Pd/C (10 mg) in acetic acid (5 ml) to afford 8-oxypseudopalmatine as a yellow solid (7 mg, 37%). Mp: 187–189 °C (lit.[4a] 197–199 °C. lit.[19] 198–199 °C). IR (cm^{-1}): 1640 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.33 (s, 1H), 6.96 (s, 1H), 6.85 (s, 1H), 6.76 (s, 1H), 4.36 (t, *J*=6.0 Hz, 2H), 4.01(s, 3H), 4.01 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 2.90 (t, *J*=6.0 Hz, 2H). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81; O, 21.77. Found: C, 68.63; H, 5.75; N, 3.84. EIMS: *m*/*z* (%): 367 (M^+, 100), 352 (60).

*4.1.39. 10,11-Dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquino[3,2-a]isoquinolin-8-one: 8-oxypseudoberberine (**2**)*[7]. The procedure described for compound **1** was used with compound **10e** (17 mg, 0.05 mmol) and 10% PtO_2 (6 mg) in AcOH (5 ml) to afford compound **11c** as yellow solid (8 mg, 46%). Mp: 266–268 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.22 (s, 1H), 6.90 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.10 (s, 2H), 4.34 (t, *J*=6 Hz, 2H), 4.05 (d, 6H), 2.90 (t, *J*=6 Hz, 2H). Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.34; H, 4.89; N, 3.97. EIMS: *m*/*z* 351 (M^+, 100).

Acknowledgements

This work was supported by Korea Research Foundation grant (KRF-2007-521-E00190).

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