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Formation and reaction of *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinolines (*o*-quinol acetates)

Osamu Hoshino,* Masaji Suzuki and Hiromichi Ogasawara

Faculty of Pharmaceutical Sciences, Science University of Tokyo, 12 Ichigaya Funagwara-machi, Shinjuku-ku, Tokyo 162-0826, Japan

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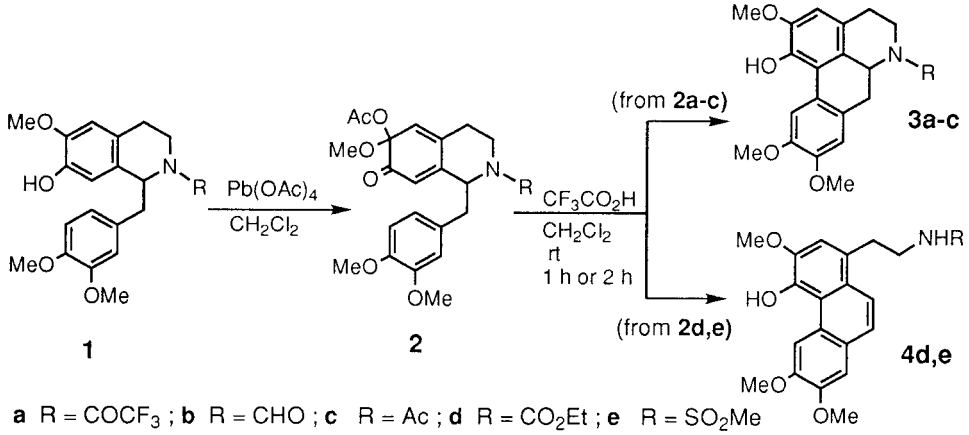
Abstract—Oxidation of *N*-acyl- and *N*-methanesulfonyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ols (**7**) with lead tetraacetate in dichloromethane produced quantitatively title compounds (*o*-QAs) (**8**). Treatment of *N*-trifluoroacetyl and *N*-formyl *o*-QAs (**8a**,**b**) with acetic acid at 30–40°C afforded *N*-trifluoroacetyl and *N*-formyl *p*-QAs (**9a**,**b**), while that of *N*-acetyl, *N*-ethoxycarbonyl and *N*-methanesulfonyl congeners (**8c**–**e**) gave *N*,*N*-dialkylacetamide (**10c**), ethyl *N*,*N*-dialkylcarbamate (**10d**), and *N*,*N*-dialkylmethanesulfonamide (**10e**), which are formed by elimination of a benzylic proton and subsequent cleavage of a C1–C8a bond in **9c**–**e**.

1. Introduction

It is known that lead tetraacetate (LTA) oxidation of tetrahydroisoquinolinols gives the corresponding acetoxyhexahydrooxoisoquinolines (*o*- or *p*-quinol acetates)[1] having a dienone moiety, which are valuable intermediates for synthesis of isoquinoline alkaloids.[2,3] Recently we have reported that oxidation of *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-methoxyisoquinolin-7-ols (**1**) with LTA in dichloromethane (CH_2Cl_2) gives quantitatively the corresponding *o*-quinol acetates (*o*-QAs) (**2**), treatment of which with trifluoroacetic acid (CF_3CO_2H) in CH_2Cl_2 affords *N*-acylnoraporphines (**3**) or *N*-acyl- and *N*-methanesulfonyl-phenanthrenes (**4**) (Scheme 1).[4] These findings focused our attention on a series of reaction of *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ols (**7**), which are a phenolic regioisomer of **1**, because formation of *N*-acyl and *N*-methanesulfonyl *o*-QAs from **7** could lead to the development of a novel methodology



Scheme 1.

Keywords: lead tetraacetate oxidation; *N*-acyltetrahydroisoquinolin-6-ol; *N*-acyl *o*- and *p*-quinol acetate.

* Corresponding author. Tel.: +81-33260-6725; fax: +81-33268-3045; e-mail: hoshino@ps.kagu.sut.ac.jp

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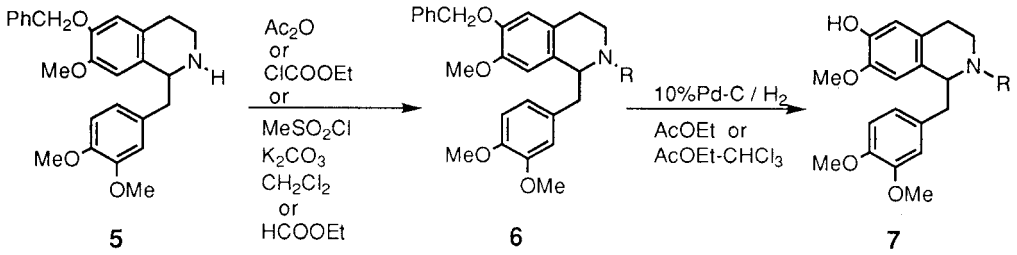


Scheme 2.

using LTA for synthesis in the tetrahydroisoquinolinol field. The present paper deals with formation and reaction of *N*-acyl and *N*-methanesulfonyl *o*-QAs (**8**).

2. Results and discussion

2.1. Formation of *N*-acyl and *N*-methanesulfonyl *o*-QAs (8)

The starting materials, *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ols (**7**) are prepared as follows. *N*-Acylation and *N*-methanesulfonylation of 6-benzyloxytetrahydroisoquinoline (**5**)[5] with trifluoroacetic anhydride, acetic anhydride, ethyl chloroformate, and methanesulfonyl chloride under basic conditions gave the corresponding *N*-acyl- and *N*-methanesulfonyl-tetrahydroisoquinolines (**6a**,**c**–**e**). The *N*-formyl congener (**6b**) was obtained by refluxing **5** in ethyl formate. Furthermore, their debenzylation with catalytic hydrogenation produced **7** in good yields (Scheme 2).

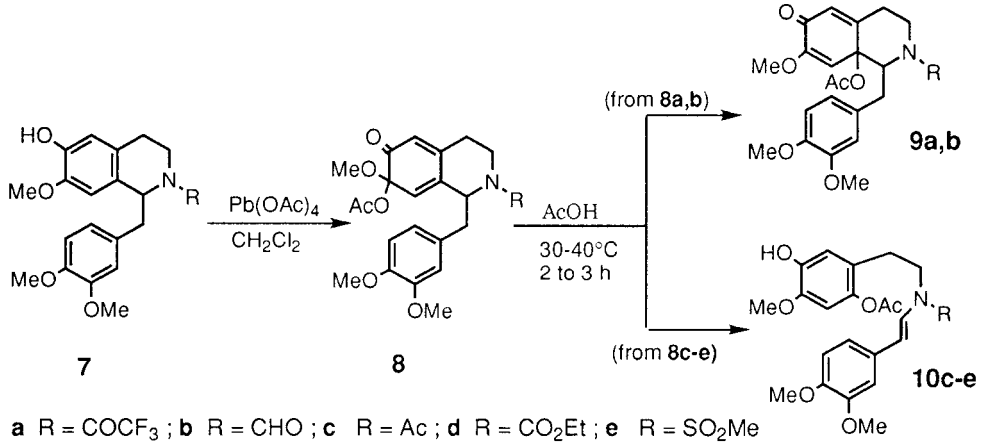
With **7** in hand, LTA oxidation in a manner similar to that reported previously[3a] was carried out. Oxidation of **7a** with LTA (1.1–1.2 equiv.) in CH_2Cl_2 at room temperature for 0.5 h gave quantitatively an oily product, IR ($CHCl_3$) and ^{1}H NMR spectra of which showed absorption bands at 1740 and 1680 cm^{-1} and two peaks due to an acetoxyl group at δ 2.05, 2.08 (3H, each s) and two peaks due to a methoxyl group at δ 3.28, 3.40 (3H, each s). The spectral data supported the assignment of the products as a diastereomeric mixture as well as the assignment of overall structure as *N*-trifluoroacetyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinoline (*o*-QA) (**8a**).

The analogous reaction of **7b**–**e** produced *N*-acyl and *N*-methanesulfonyl *o*-QAs (**8b**–**e**), the structures of which were confirmed by spectral evidence (IR, ^{1}H NMR) (see Experimental). As expected, it was found that oxidation of **7** afforded readily *N*-acyl and *N*-methanesulfonyl *o*-QAs (**8**) (Scheme 3) in a manner similar to that observed with **1**. The stability of *o*-QAs (**8**) was similar to that of *o*-QAs (**2**).

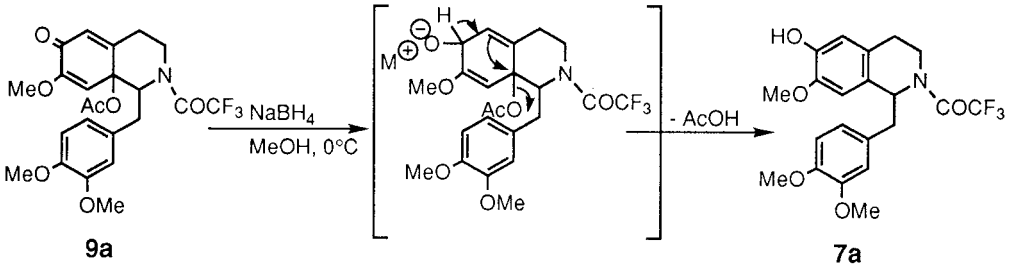
2.2. Reaction of *N*-acyl and *N*-methanesulfonyl *o*-QAs (8)

Treatment of **2** with CF_3CO_2H in CH_2Cl_2 at room temperature is found to produce *N*-acylnoraporphines (**3a**–**c**) or *N*-ethoxycarbonyl- and *N*-methanesulfonyl-phenanthrenes (**4d**,**e**) (Scheme 1).[4] Thus, the reaction of **8a** with CF_3CO_2H in CH_2Cl_2 or CH_3CN at room temperature was examined. Surprisingly, each reaction afforded a complex reaction mixture. With Ac_2O-concentrated H_2SO_4,[6] the reaction was also unsuccessful. The reaction of **8a** in refluxing CH_2Cl_2 and $CHCl_3$,or at 60°C (neat),[7] did not proceed.

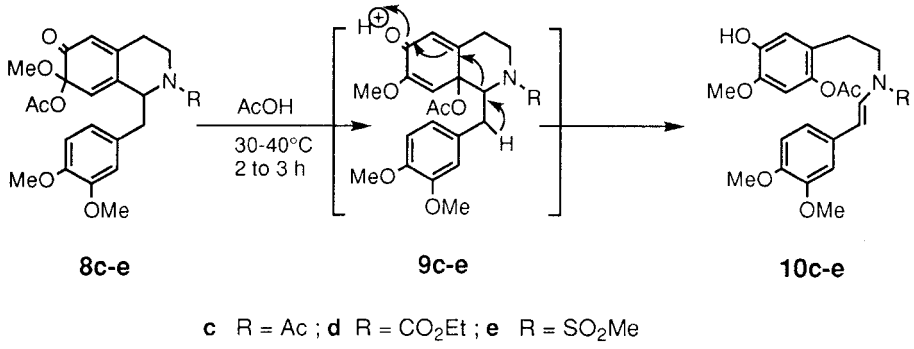
After several unfruitful attempts, treatment of **8a** with AcOH[8,9] at 30–40°C for 3 h gave a crystalline product (mp 165–167°C), the IR ($CHCl_3$) and the ^{1}H NMR spectra showed absorption bands at 1745, 1675, 1650, 1625 cm^{-1} and a peak due to an acetoxyl group at δ 2.01 (3H, s) and two peaks due to a methoxyl group at δ 3.26, 3.52 (3H, each s), respectively. The spectral and microanalytical data supported the assignment of the products as a diastereomeric



Scheme 3.



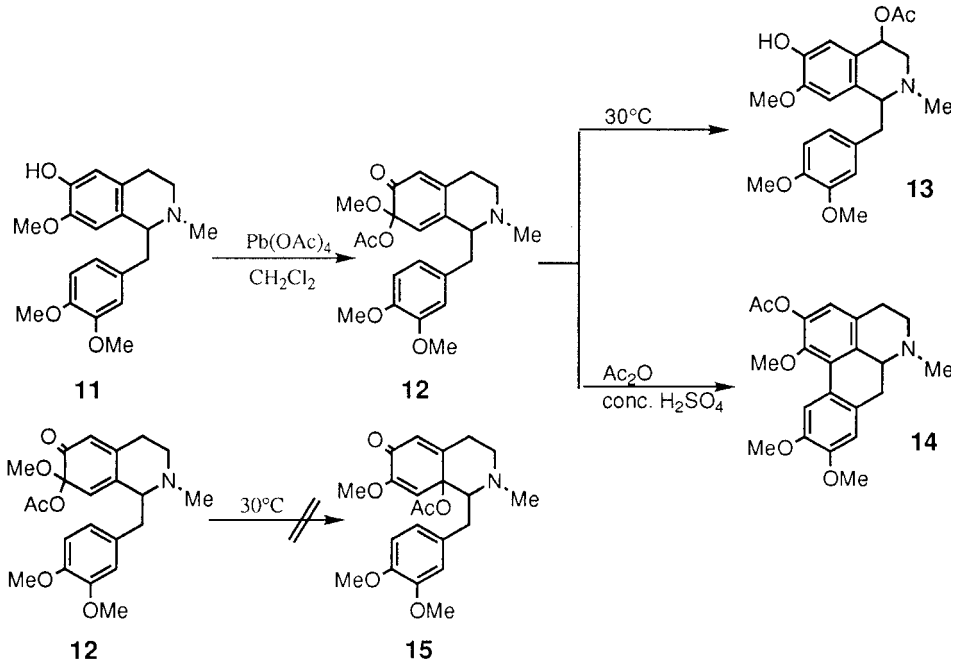
Scheme 4.



Scheme 5.

mixture, the structure of which was *N*-trifluoroacetyl-1-(3,4-dimethoxy)benzyl-8a-acetoxy-1,2,3,4,6,8a-hexahydro-7-methoxy-6-oxoisoquinoline (*p*-QA) (**9a**) (Scheme 3). Furthermore, the structure was confirmed chemically by conversion of **9a** into **7a** by reduction with $NaBH_4$ in MeOH[10] (Scheme 4).

It is notable that *N*-trifluoroacetyl *p*-QA (**9a**) was obtained, in contrast to the findings[7] that *N*-methyl *p*-QA (**15**) cannot be isolated in the case of *N*-methyl *o*-QA (**12**) (Scheme 6). The similar reaction of **8b** produced *p*-QA (**9b**). Unexpectedly, however, the reaction of **8c** in warm AcOH did not give *p*-QA (**9c**), but rather an *N*,*N*-dialkylacetamide containing product. The IR spectrum exhibited absorption bands at 3550, 1760, 1670 cm^{-1}. Furthermore, the ^1H NMR spectrum showed two pairs of two peaks due to two acetyl groups at δ 2.08, 2.24, 2.29, 2.32 (6H, each s) and four pairs of two peaks at δ 5.90, 5.93 (1H, J=14.3 Hz, each d) and 7.00, 7.86 (1H, J=14.3 Hz, each d) due to *trans*-olefinic protons. Thus, the spectral data supported the structure *N*-[2-(2-acetoxy-5-



Scheme 6.

hydroxy-4-methoxyphenyl)ethyl]-*N*-[2-(3,4-dimethoxyphenyl)ethenyl]acetamide (**10c**). The analogous reactions of **8d**,**e** gave also the corresponding amides (**10d**,**e**) (Scheme 3), the IR and ^{1}H NMR spectra of which indicated the presence of hydroxyl and acetoxyl groups and a *trans*-olefin moiety in the case of **10c** (Scheme 3).

A reaction pathway for formation of **10c**–**e** is depicted in Scheme 5. Namely, *N*-acyl and *N*-methanesulfonyl *p*-QAs (**9c**–**e**), which would be formed initially by the reaction of *N*-acyl and *N*-methanesulfonyl *o*-QAs (**8c**–**e**) in warm AcOH, undergo elimination of a benzylic proton and subsequent cleavage of the C1–C8a bond to give rise to amides (**10c**–**e**). This transformation appears to be remarkably dependent on the nature (probably the inductive effect) of the *N*-substituents.

It is noteworthy that the present reaction of *N*-acyl and *N*-methanesulfonyl *o*-QAs showed chemical behavior different from that of the *N*-methyl *o*-QAs (**12**) (derived from **11**), in which 4-acetoxy product (**13**)[7]or *O*-acetylaporphines (**14**)[6] are formed under warming or acidic conditions (Scheme 6). The results would be attributable to the inductive effect of *N*-substituents, because elimination of a benzylic proton takes place more readily.

In conclusion, it was found that LTA oxidation of *N*-acyl- and *N*-methanesulfonyl-tetrahydroisoquinolin-6-ols (**7**) gave corresponding *o*-QAs (**8**) similar to that of *N*-acyl- and *N*-methanesulfonyl-tetrahydroisoquinolin-7-ols (**1**) and their reaction in warm AcOH produced novel *N*-trifluoroacetyl and *N*-formyl *p*-QAs (**9a**,**b**) or *N*-acetyl-, *N*-ethoxycarbonyl-, and *N*-methanesulfonylamides (**10c**–**e**) depending on the nature of the *N*-substituents in the *o*-QAs. Furthermore, the chemical behavior of *N*-acyl *o*-QAs (**8a**–**d**) was distinctly different from that of *N*-methyl *o*-QA (**12**).[11]

Further examination on the effect of *N*-acyl groups in the reactions of *o*-QAs is in progress.

3. Experimental

All melting points were measured on Büchi melting point measuring apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JOEL JNM-FX 100 (100 MHz) instrument in $CDCl_3$ solution using tetramethylsilane as internal standard. IR spectra were measured on a Hitachi model 260-10 spectrophotometer in $CHCl_3$ solution. Mass spectra were taken with a Hitachi RMU-7M or M-80 instrument. Preparative TLC was performed on Merck Kieselgel 60F_{254} plates (20×20×0.5 cm).

3.1. A general procedure for preparation of *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinolines (6)

A mixture of **5**,[5] acetic anhydride or ethyl chloroformate or methanesulfonyl chloride, and K_2CO_3 in CH_2Cl_2 was stirred at room temperature for 0.5–2 h (except for **6b**). After addition of water to the reaction mixture, the product was taken up in CH_2Cl_2. Usual work-up of the organic layer gave solid product, which was purified by recrystallization.

3.1.1. *N*-Trifluoroacetyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (6a). 5 (1.08 g, 2.6 mmol), trifluoroacetic anhydride (1.0 mL, 3.2 mmol), K_2CO_3 (0.524 g, 3.8 mmol), and CH_2Cl_2 (20 mL) were used (reaction time: 0.5 h): **6a** (1.07 g, 82%), mp 139–141°C (EtOH). Anal. Calcd for $C_{28}H_{28}NO_5F_3$: C, 65.23; H, 5.47; N, 2.72; F, 11.06. Found: C, 65.37; H, 5.52; N, 2.79; F, 10.92. MS *m*/*z*: 515 (M^+); IR ν: 1675 cm^{-1}; ^{1}H NMR δ: 3.68, 3.76, 3.82 (each 3H, s), 5.55 (1H, t, *J*=7.4 Hz), 6.24–6.84, 7.10–7.60 (each 5H, m).

3.1.2. *N*-Formyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (6b). A solution of **5** (1.0 g, 2.4 mmol) in ethyl formate (20 mL) was refluxed for 3 h. Removal of excess ethyl formate in vacuo gave **6b** (0.89 g, 83%), mp 106–108°C (EtOH). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.53; H, 6.59; N, 3.24. MS *m*/*z*: 447 (M^+); IR ν: 1650 cm^{-1}; ^{1}H NMR δ: 3.68, 3.72, 3.82, 3.84 (9H, each s,), 4.28–4.64 (2H, m), 5.08, 5.10 (2H, each s), 6.22–6.86, 7.04–7.50 (each 5H, m), 7.64, 8.07 (1H, each s).

3.1.3. *N*-Acetyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (6c). 5 (0.69 g, 1.6 mmol), acetic anhydride (1.68 g, 16.5 mmol), K_2CO_3 (2.28 g, 16.5 mmol), and CH_2Cl_2 (10 mL) were used (reaction time: 1 h): **6c** (0.39 g, 51%), mp 174–175°C (benzene). Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; N, 3.03. Found: C, 72.84; H, 6.68; N, 2.87. MS *m*/*z*: 418 (M^+-43); IR ν: 1620 cm^{-1}; ^{1}H NMR δ: 1.62, 2.12 (3H, each s), 3.62, 3.74, 3.83 (each 3H, s,), 4.52–4.86 (1H, m), 5.08, 5.10 (2H, each s), 6.14–6.88, 7.08–7.50 (each 5H, m).

3.1.4. *N*-Ethoxycarbonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (6d). 5 (1.08 g, 2.8 mmol), ethyl chloroformate (0.56 g, 5.2 mmol), K_2CO_3 (0.71 g, 5.2 mmol), and CH_2Cl_2 (20 mL) were used (reaction time: 1 h): **6d** (1.03 g, 82%), mp 174–175°C (EtOH). Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.88; H, 6.73; N, 3.07. MS *m*/*z*: 446 (M^+-45); IR ν: 1670 cm^{-1}; ^{1}H NMR δ: 1.13, 1.24 (3H, each t, *J*=7.1 Hz), 3.62, 3.82, 3.87, 3.93 (9H, each s), 4.88–5.34 (3H, m), 6.08–7.48 (10H, m).

3.1.5. *N*-Methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (6e). 5 (0.94 g, 2.2 mmol), methanesulfonyl chloride (1.9 mL, 11.4 mmol), K_2CO_3 (3.37 g, 24.4 mmol), and CH_2Cl_2 (20 mL) were used (reaction time: 2 h): **6e** (1.04 g, 95%), mp 163–165°C (EtOH). Anal. Calcd for $C_{27}H_{31}NO_6S$: C, 65.17; H, 6.28; N, 2.81; S, 6.43. Found: C, 65.24; H, 6.45; N, 2.84; S, 6.48. MS *m*/*z*: 346 (M^+-151); IR ν: 1310, 1140 cm^{-1}; ^{1}H NMR δ: 2.47 (3H, s), 3.71, 3.80, 3.84 (each 3H, s), 4.96 (1H, t, *J*=7.1 Hz), 5.08 (2H, s), 6.32–6.86, 7.04–7.50 (each 5H, m).

3.2. A general procedure for preparation of *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ols (7)

A mixture of **6** and 10% Pd–C in AcOEt (for **6a**,**b**,**d**,**e**) or AcOEt–$CHCl_3$ (for **6c**) was shaken with hydrogen (1 atm) at room temperature for 2 h. After filtration of catalyst

followed by removal of the solvent gave a solid, which was purified by recrystallization.

3.2.1. *N*-Trifluoroacetyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ol (7a). 6a (1.02 g, 2.0 mmol), 10% Pd–C (0.42 g), and AcOEt (50 mL) were used: **7a** (0.784 g, 93%), mp 148–149°C (benzene). Anal. Calcd for $C_{21}H_{22}NO_5F_3$: C, 59.29; H, 5.21; N, 3.29; F, 13.40. Found: C, 59.29; H, 5.19; N, 3.40; F, 13.46. MS *m/z*: 425 (M^+); IR ν: 3530, 1675 cm^{-1}; ^1H NMR δ: 3.68, 3.76, 3.83 (each 3H, s), 5.36–5.60 (2H, m), 6.20–6.84 (5H, m).

3.2.2. *N*-Formyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ol (7b). 6b (1.3 g, 2.9 mmol), 10% Pd–C (0.62 g), and AcOEt (50 mL) were used: **7b** (0.9 g, 86%), mp 177–179°C (benzene). HRMS *m/z* Calcd for $C_{20}H_{23}NO_5$ (M^+): 357.1574. Found: C, 357.1552. MS *m/z*: 357 (M^+); IR ν: 3530, 1650 $cm^{-1;}$ ^1H NMR δ: 3.66, 3.76, 3.84 (each 3H, s), 6.22–6.83 (5H, m), 7.66, 8.08 (1H, each s).

3.2.3. *N*-Acetyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ol (7c). 6c (1.06 g, 2.3 mmol), 10% Pd–C (0.42 g), and AcOEt (20 mL)-$CHCl_3$ (30 mL) were used: **7c** (0.734 g, 86%), mp 141–142°C (benzene–ether). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.81; H, 6.74; N, 3.84. MS *m/z*: 371 (M^+); IR ν: 3530, 1620 cm^{-1}; ^1H NMR δ: 1.61, 2.12 (3H, each s), 3.60, 3.76, 3.83 (each 3H), 4.56–4.85 (1H, m), 5.40–5.65 (2H, m), 6.09–6.88 (5H, m).

3.2.4. *N*-Ethoxycarbonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ol (7d). 6d (0.93 g, 1.9 mmol), 10% Pd–C (0.37 g), and AcOEt (50 mL) were used: **7d** (0.737 g, 99%), mp 80–95°C (benzene). Anal. Calcd for $C_{22}H_{27}NO_6{\cdot}0.5H_2O$: C, 64.38; H, 6.88; N, 3.41. Found: C, 64.24; H, 6.62; N, 3.51. MS *m/z*: 400 (M^+-1); IR ν: 3430, 1670 cm^{-1}; ^1H NMR δ: 1.15, 1.24 (3H, each t, J=7.1 Hz), 3.60, 3.69, 3.76, 3.78, 3.84 (9H, each s), 4.87–5.28 (1H, m), 6.07–6.84 (5H, m).

3.2.5. *N*-Methanesulfonyl-1-(3,4-dimethoxy)benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinolin-6-ol (7e). 6e (0.91 g, 1.8 mmol), 10% Pd–C (0.39 g), and AcOEt (50 mL) were used: **7e** (0.59 g, 84%), mp 170–171°C (benzene). Anal. Calcd for $C_{20}H_{25}NO_6S$: C, 58.95; H, 6.18; N, 3.44; S, 7.87. Found: C, 59.10; H, 6.18; N, 3.60; S, 7.87. MS *m/z*: 407 (M^+); IR ν: 3530, 1310, 1140 cm^{-1}; ^1H NMR δ: 2.49 (3H, s), 3.70, 3.81, 3.84 (each 3H, s), 5.94 (1H, t, J=7.1 Hz), 6.21–6.82 (5H, m).

3.3. A general procedure for formation of *N*-acyl- and *N*-methanesulfonyl-1-(3,4-dimethoxy)benzyl-6-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinolines (8) (*o*-quinol acetates)

The reaction of **7** with $Pb(OAc)_4$ in CH_2Cl_2 was carried out in a manner reported previously[3a] (reaction time: 0.5 h) to produce quantitatively *o*-quinol acetates (**8**), which were used in the next reaction without further purification.

3.3.1. *N*-Trifluoroacetyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinoline (8a). 7a (100 mg, 0.24 mmol), $Pb(OAc)_4$ (127 mg, 0.29 mmol), and CH_2Cl_2 (1 mL) were used: **8a** (oil); IR ν: 1740, 1680 cm^{-1}; ^1H NMR δ: 2.05, 2.08 (3H, each s), 3.28, 3.40 (3H, each s), 3.84 (6H, s), 4.92–5.18 (1H, m), 5.60–5.74, 5.86–6.07 (each 1H, m), 6.52–6.84 (3H, m).

3.3.2. *N*-Formyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinoline (8b). 7b (100 mg, 0.28 mmol), $Pb(OAc)_4$ (149 mg, 0.34 mmol), and CH_2Cl_2 (5 mL) were used: **8b** (oil); IR ν: 1740, 1670 cm^{-1}; ^1H NMR δ: 2.05, 2.08, 2.10 (3H, each s), 3.32, 3.40, 3.42 (3H, each s), 3.84 (6H, s), 5.00–5.32 (1H, m), 5.60–6.04 (2H, m), 6.50–6.84 (3H, m), 7.69, 8.78, 8.12 (1H, each s).

3.3.3. *N*-Acetyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinoline (8c). 7c (100 mg, 0.27 mmol), $Pb(OAc)_4$ (143 mg, 0.32 mmol), and CH_2Cl_2 (5 mL) were used: **8c** (oil); IR ν: 1740, 1685, 1640 cm^{-1}; ^1H NMR δ: 2.02, 2.04, 2.08, 2.12, 2.14 (6H, each s), 3.20, 3.32 (3H, each s), 3.83, 3.85 (each 3H, s), 4.98–5.32 (1H, m), 5.48–6.02 (2H, m), 6.48–6.88 (3H, m).

3.3.4. *N*-Ethoxycarbonyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinoline (8d). 7d (100 mg, 0.25 mmol), $Pb(OAc)_4$ (133 mg, 0.30 mmol), and CH_2Cl_2 (5 mL) were used: **8d** (oil); IR ν: 1740, 1680 cm^{-1}; ^1H NMR δ: 1.28, 1.29 (3H, each t, J=7.1 Hz), 2.08, 2.28 (3H, each s), 3.20, 3.38 (3H, each s), 3.84 (6H, s), 5.44–5.68 (1H, m), 5.48–6.00 (2H, m), 6.48–6.92 (3H, m).

3.3.5. *N*-Methanesulfonyl-1-(3,4-dimethoxy)benzyl-7-acetoxy-1,2,3,4,6,7-hexahydro-7-methoxy-6-oxoisoquinoline (8e). 7e (100 mg, 0.25 mmol), $Pb(OAc)_4$ (139 mg, 0.31 mmol), and CH_2Cl_2 (1 mL) were used: **8e** (oil); IR ν: 1740, 1680 cm^{-1}; ^1H NMR δ: 2.04, 2.08 (3H, each s), 2.60, 2.88 (3H, each s), 3.24, 3.40 (3H, each s), 3.84, 3.85 (each 3H, s), 4.48–4.86 (1H, m), 5.64, 5.72 (1H, each s), 5.84–6.04 (1H, m), 6.56–6.84 (3H, m).

3.4. A general procedure for the reaction of *o*-QAs (8) with AcOH

A solution of *o*-QA (**8**) [prepared from **7**] in AcOH was stirred at 30–40°C for 2–3 h. The reaction mixture was diluted with water and basified with 10% aq. Na_2CO_3 solution. The product was taken up in CH_2Cl_2. A residue obtained on usual work-up of the organic layer was purified by preparative TLC (developing solvent: AcOEt:hexane=2:1) or recrystallization.

3.4.1. *N*-Trifluoroacetyl-1-(3,4-dimethoxy)benzyl-8a-acetoxy-1,2,3,4,6,8a-hexahydro-7-methoxy-6-oxoisoquinoline (9a). 8a [prepared from **7a** (100 mg)] and AcOH (10 mL) were used (reaction time: 3 h): **9a** (87 mg, 77%), mp 165–167°C (EtOH). Anal. Calcd for $C_{23}H_{24}F_3NO_7$: C, 57.14; H, 5.00; N, 2.90; F, 11.79. Found: C, 57.19; H, 5.08; N, 3.09; F, 11.89. MS *m/z*: 483 (M^+); IR ν: 1745, 1675, 1650, 1625 cm^{-1}; ^1H NMR δ: 2.01 (3H, s), 3.26, 3.52 (3H, each s), 3.84 (6H, s), 5.58 (1H, s), 6.08–6.36 (4H, m).

3.4.2. *N*-Formyl-1-(3,4-dimethoxy)benzyl-8a-acetoxy-1,2,3,4,6,8a-hexahydro-7-methoxy-6-oxoisoquinoline (9b). 8b [prepared from **7b** (100 mg)] and AcOH (5 mL) were used (reaction time: 2.5 h): **9b** (oil, 86 mg, 74%). MS *m/z*: 415 (M^+); IR ν: 1750, 1675, 1655, 1630 cm^{-1}; ^1H NMR δ: 2.02, 2.04, 2.32, 2.39 (3H, each s), 3.62, 3.82, 3.84 (9H, each s), 7.80, 7.98, 8.07 (1H, each s).

3.4.3. *N*-[2-(3,4-dimethoxyphenyl)ethenyl]-*N*-[2-(2-acetoxy-5-hydroxy-4-methoxyphenyl)ethyl]acetamide (10c). 8c [prepared from **7c** (100 mg)] and AcOH (5 mL) were used (the reaction time; 2 h): **10c** (oil, 66.3 mg, 57.4%). MS *m/z*: 429 (M^+); HRMS *m/z* Calcd for $C_{23}H_{27}NO_7$ (M^+): 429.1785. Found: 429.1789. IR ν: 3550, 1760, 1670, 1640 cm^{-1}; ^1H NMR δ: 2.08, 2.24, 2.29, 2.32 (6H, each s), 3.84, 3.88, 3.91 (each 3H, s), 5.36–5.68 (1H, m), 5.90, 5.93 (1H, each d, J=14.3 Hz), 6.55 (1H, s), 6.65–6.98 (4H, m), 7.00, 7.86 (1H, each d, J=14.3 Hz).

3.4.4. Ethyl *N*-[2-(3,4-dimethoxyphenyl)ethenyl]-*N*-[2-(2-acetoxy-5-hydroxy-4-methoxyphenyl)ethyl]carbamate (10d). 8d [prepared from **7d** (100 mg)] and AcOH (5 mL) were used (reaction time; 2 h): **10d** (oil, 40 mg, 35%). MS *m/z*: 459 (M^+); HRMS *m/z* Calcd for $C_{24}H_{29}NO_7$ (M^+): 459.1890. Found: 459.1873. IR ν: 3550, 1760, 1700, 1645 cm^{-1}; ^1H NMR δ: 1.30 (3H, t, J=7.1 Hz), 2.28 (3H, s), 3.84, 3.86, 3.90 (each 3H, s), 4.22 (2H, q, J=7.1 Hz), 5.36–5.62 (1H, m), 5.80 (1H, d, J=14.3 Hz), 6.55 (1H, s), 6.60–6.96 (4H, m), 7.24–7.68 (1H, m).

3.4.5. *N*-[2-(3,4-dimethoxyphenyl)ethenyl]-*N*-[2-(2-acetoxy-5-hydroxy-4-methoxyphenyl])ethyl]methanesulfonamide (10e). 8e [prepared from **7e** (100 mg)] and AcOH (20 mL) were used (reaction time; 2 h): **10e** (32 mg, 27%), mp 156–158°C (EtOH). MS *m/z*: 465 (M^+). Anal.Calcd for $C_{22}H_{27}NO_8S$: C, 56.77; H, 5.85; N, 3.01; S, 6.87. Found: C, 56.77; H, 5.75; N, 3.14; S, 6.62. IR ν: 3530, 1750, 1640 cm^{-1}; ^1H NMR δ: 2.18, 2.86 (each 3H, s), 3.84, 3.87, 3.91 (each 3H, s), 5.49 (1H, s), 5.85 (1H, d, J=14.9 Hz), 6.46–6.94 (5H, m), 7.06 (1H, d, J=14.9 Hz).

3.4.6. Reduction of 9a with $NaBH_4$. A solution of **9a** (100 mg, 0.21 mmol) and $NaBH_4$ (78 mg, 2.1 mmol) in MeOH (10 mL) was stirred at 0°C for 10 min. The reaction mixture was acidified with 10% HCl and the product was taken up in CH_2Cl_2. Usual work-up of the organic layer gave an oily residue (74.5 mg), which upon trituration in EtOH produced **7a** (71 mg, 81%), mp 148–149°C (benzene). This compound was identical to an authentic sample by each comparison (^1H NMR, IR, and mixed mp).

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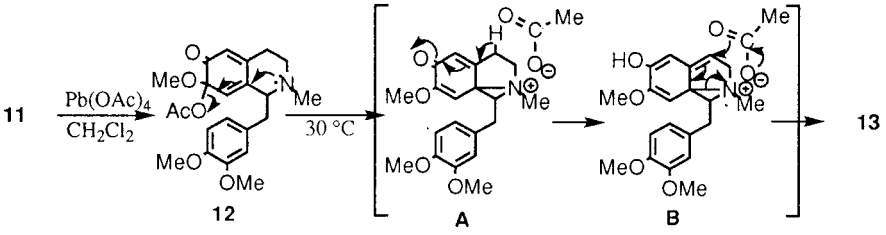
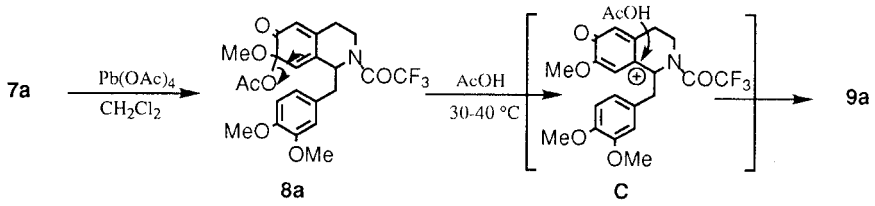
8. The reaction of **8a** in $CHCl_3$ containing AcOH at room temperature did not take place.
9. The reaction of **8a** in $CHCl_3$ containing silicic acid (40 times for weight of **8a**) at room temperature for 12 h produced **9a** in 33% yield.
10. Cf. In our laboratory, treatment of *N*-methyl-4a-acetoxy-1,2,3,4,4a,7-hexahydro-6-methoxy-7-oxoisoquinoline (*p*-QA) with $NaBH_4$ in MeOH at room temperature is found to give *N*-methyl-1,2,3,4-tetrahydro-6-methoxyisoquinolin-7-ol (corypalline).
11. A chemical behavior different between *N*-methyl *o*-QA (**12**) and *N*-acyl *o*-QA (**8**) would be ascribable to the stereoelectronic effect of each *N*-substituent. The former (**12**), in which the nitrogen atom is an sp^3 hybrid orbital, generates an aziridinium intermediate (**A**) by elimination of an acetoxyl group followed by intramolecularly nucleophilic attack of the nitrogen atom to the C8a position. Furthermore, **A** leads to 4-acetoxytetrahydroisoquinolinol (**13**) through **B** (Scheme 7).[12] On the other hand, the *N*-trifluoroacetyl *o*-QA (**8a**) generates a carbenium ion (**C**) by elimination of an acetoxyl



Scheme 7.



Scheme 8.

group followed by allylic rearrangement, because the nitrogen atom, which is an sp^2-like hybrid orbital, cannot attack to the C8a position. Accordingly, **9a** is formed by the intermolecular substitution[13] of **C** with AcOH (Scheme 8).

12. See Ref. 7.
13. LTA oxidation of (±)-*N*-trifluoroacetyl-1,2,3,4-tetrahydro-1-(3,4-dimethoxy)benzyl-6-methoxyisoquinolin-7-ol in (*S*)-(+)-2-phenylpropionic acid produces a mixture of diastereoisomers of optically active *N*-trifluoroacetyl *p*-quinol esters [Hara, H.; Komoriya, S.; Miyashita, T.; Hoshino, O. *Tetrahedron: Asymmetry*, **1995**, *6*, 1683]. These findings suggest the transformation of *N*-trifluoroacetyl *o*-QA (**8a**) in AcOH to **9a** to proceed in the intermolecular substitution.