FORMATION AND REACTION OF *p*-QUINOL ACETATES OF *N*-TRIFLUOROACETYLTETRAHYDROISOQUINOLIN-7-OLS#

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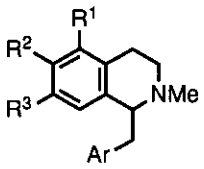
Abstract --- Lead tetraacetate oxidation of *N*-trifluoroacetyltetrahydroisoquinolin-7-ols (**13a**, **b**) in AcOH gave stable *p*-quinol acetates (**17a**, **b**). Reaction of **17** with trifluoroacetic acid in CH_2Cl_2 or MeCN gave morphinandienones (**15**) and aporphines (**16**), respectively. In contrast with *o*-quinol acetates (**14**), it was found that reaction of *p*-quinol acetates (**17**) in MeCN was considerably slower than that in CH_2Cl_2. A mechanistic pathway on the reaction is deduced.

Lead tetraacetate[$Pb(OAc)_4$] oxidation[1] of phenolic 1-benzyl-*N*-methyltetrahydroisoquinolines (**1**, **2**, and **3**) gives reactive quinol acetates (QAs) (**4**[2], **5**[3], and **6**[4]), which are treated with acids to afford aporphines (**7**, **8**, and **9**), respectively.[5] However, no morphinandienones (**10**)[6] except for 8-chloromorphinandienones (**11**)[7] and homomorphinandienones (**12**)[8] could be obtained by this methodology (Scheme 1).

In the course of our continuous studies on $Pb(OAc)_4$ oxidation of *N*-acyltetrahydroisoquinolinols,[9,10] we have recently[11,12] found that oxidation of *N*-trifluoroacetyltetrahydroiso-

Dedicated to Professor Edward C. Tayler on the occasion of his 70th birthday.



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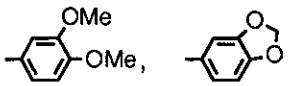
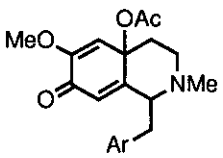
3 :	OH	OMe	H

Ar = 



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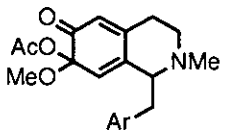

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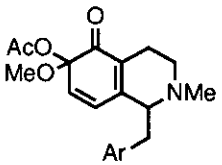

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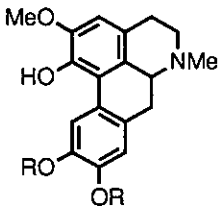

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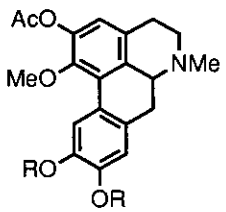

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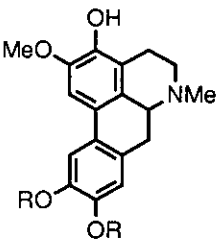

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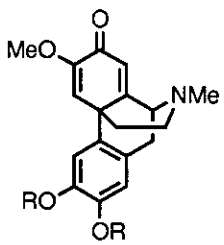

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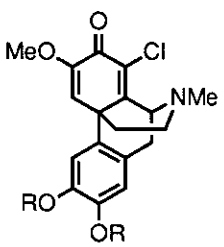

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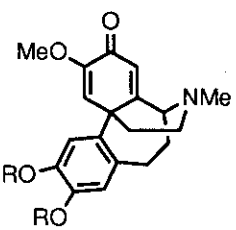

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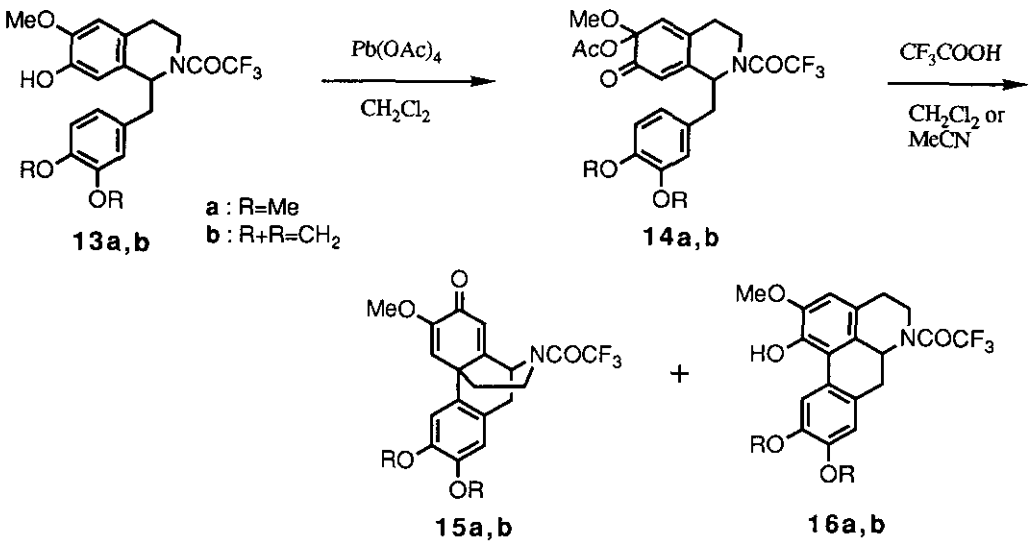
Scheme 1

quinolin-7-ols (**13**) with $Pb(OAc)_4$ in dichloromethane (CH_2Cl_2) gives stable *o*-QAs (**14**), treatment of which with trifluoroacetic acid (CF_3COOH) in acetonitrile (MeCN) at lower temperature affords morphinandienones (**15**) along with aporphines (**16**) (Scheme 2).

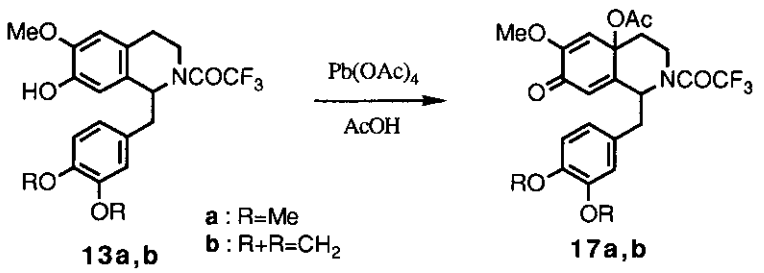


Scheme 2

These findings promoted us to reexamine formation and reaction of *p*-QAs of **13**. In this paper, we describe formation of stable *p*-QAs (**17**) by oxidation of **13** with $Pb(OAc)_4$ in acetic acid (AcOH) and reaction of *p*-QAs (**17**) with CF_3COOH giving morphinandienones (**15**) and aporphines (**16**), respectively.

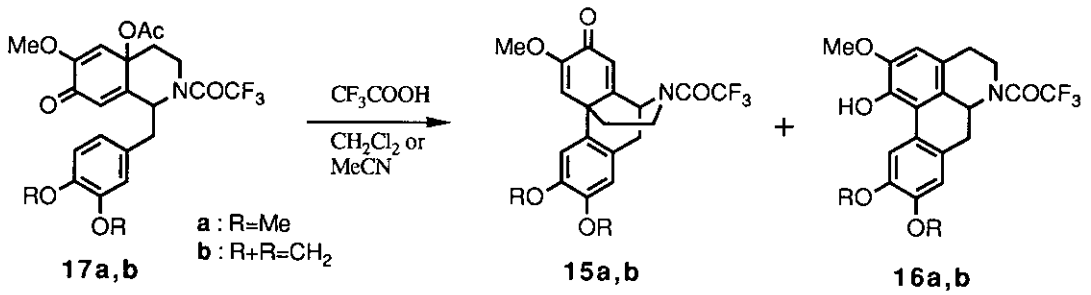
RESULT AND DISCUSSION

$Pb(OAc)_4$ Oxidation : The oxidation of **13a**[13] as reported previously[2] gave, after flash column chromatography,[14] *p*-QAs (**17a**) , mp 144 °C, in 53% yield as a mixture of diastereomers (3 : 2). Structure of **17a** was confirmed by the spectroscopy, although the stereochemistry was uncertain. Analogously, oxidation of **13b** with $Pb(OAc)_4$ produced a diastereomeric mixture (3 : 2) of *p*-QA (**17b**), mp 154-155 °C (decomp.) in 51% yield (Scheme 3). It was found that *p*-QAs (**17**) as well as *o*-QAs (**14**) were more stable than QAs (**4**) of *N*-methyl congeners and could be stored at room temperature for several weeks.



Scheme 3

Reaction of *p*-QAs (17) with CF_3COOH : For the purpose of comparing chemical behavior of *p*-QAs under acidic conditions with that of *o*-QAs,[12] the acid-catalized reaction of *p*-QA (**17**) was examined. Reaction of crude *p*-QA (**17a**) (see Experimental) derived from **13a** with CF_3COOH in CH_2Cl_2 at 0 °C for 5 min gave, after flash column chromatography, morphinandienone (**15a**) and aporphine (**16a**) in 16% and 71% yields,[15] respectively (Scheme 4). Each product was identical in all respects with authentic specimens.[12] Analogous reaction of *p*-QA



Scheme 4

(**17a**) in CH_2Cl_2 at lower temperature afforded the similar results as those observed in reaction of *o*-QAs (**14**). However, surprisingly, reaction of *p*-QA (**17a**) in MeCN showed chemical behavior remarkably different from that of *o*-QAs. Namely, reaction at -30 °C for 5 min gave morphinandienone (**15a**) and aporphine (**16a**) in each 4% yield along with unchanged *p*-QA (**17a**) (55%). Furthermore, to obtain in improved yield morphinandienone (**15a**) under the same conditions, the prolonged reaction times were required.[16] With *p*-QA (**17b**), the similar tendency as that of *p*-QA (**17a**) was observed. The results are listed in Table I.

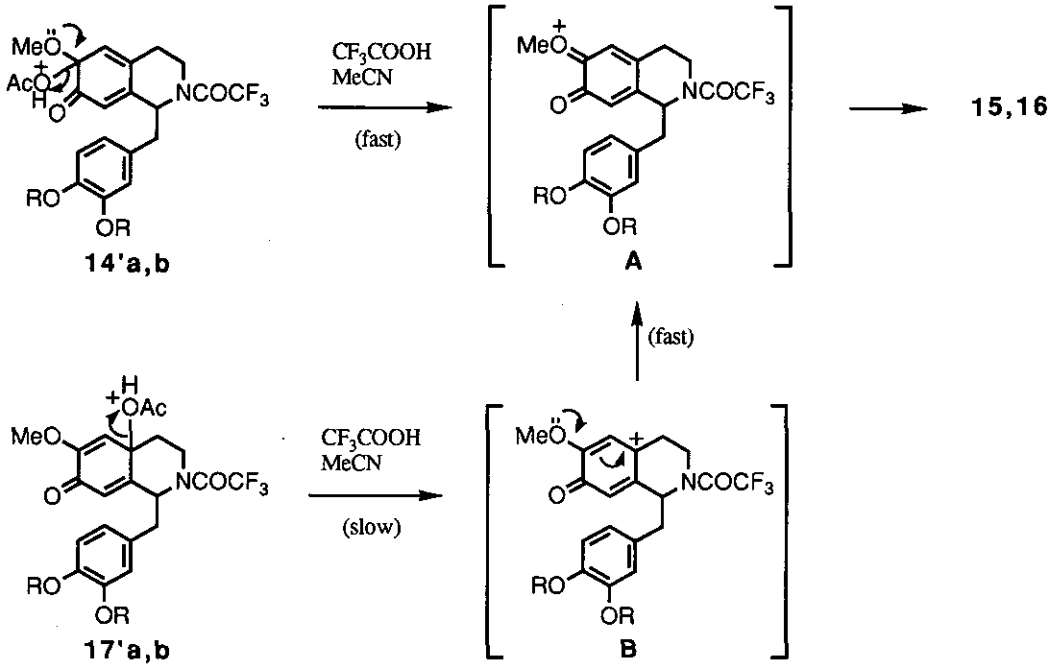
Table I. Acid-catalyzed Reaction of *p*-QAs (**17**)

run	*p*-QA	reaction conditions			products			
		solvent	reaction temperature (°C)	reaction time (*min*)	morphinan-dienone	yield[a] (%)	aporphine	yield[a] (%)
1	**17a**	CH_2Cl_2	0	5	**15a**	16	**16a**	71
2	**17a**	CH_2Cl_2	-40	60	**15a**	15	**16a**	70
3	**17b**	CH_2Cl_2	0	5	**15b**	17	**16b**	59
4	**17b**	CH_2Cl_2	-40	60	**15b**	12	**16b**	54
5[b]	**17a**	MeCN	-30	5	**15a**	4	**16a**	4
6	**17a**	MeCN	-30	300	**15a**	46	**16a**	40
7[c]	**17b**	MeCN	-30	*10*	**15b**	7	**16b**	7
8	**17b**	MeCN	-30	300	**15b**	41	**16b**	33

a) Based on starting phenol (**13**). b) *p*-QA (**17a**) was recovered in 55% yield.
c) *p*-QA (**17b**) was recovered in 38% yield.

From the present findings, it was discovered that *p*-QAs (**17**) in CF_3COOH-MeCN were more stable than *o*-QAs (**14**).

A remarkable difference in chemical behavior between *o*-QAs (**14**) and *p*-QAs (**17**) might be considered as follows. When QAs (**14**, **17**) are exposed to CF_3COOH in MeCN, protonated QAs (**14'**, **17'**) could be initially formed. Then, protonated *o*-QAs (**14'**) could readily generate a cation **A** by elimination of AcOH, since **14'** are less stable than **17'** owing to unfavorable stabilization by the solvation with MeCN. Furthermore, the cation **A** is attacked onto 4a- and 8-positions by activated aryl group to produce **15** and **16**, respectively. On the other hand, protonated *p*-QAs (**17'**) under the same conditions graduatedly generate a cation **B**, since **17'** are stabilized by the solvation with MeCN. The cation **B** would be rapidly lead to the cation **A** by participation of 6-methoxyl group, although formation of **15** and **16** from the cation **B** could not be ruled out (Scheme 5). From the present results, the stability of both QAs in CF_3COOH-MeCN seemed to play an important role in the reaction. However, the reason on remarkable effect of the solvent remained unclear. A mechanistic study on the reaction is now in progress.



Scheme 5

ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points were measured on a Büchi melting point apparatus or a Yanako micro melting point apparatus by the capillary method and are uncorrected. Infrared (ir) spectra were taken with a Hitachi model 260 spectrophotometer in $CHCl_3$ solution or on KBr disk. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were recorded on a JEOL model FX-100 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane in $CDCl_3$. Abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). CH_2Cl_2, MeCN, $CHCl_3$ and ethyl acetate are technical grade. CH_2Cl_2 for reaction solvent was distilled and passed through basic alminum. MeCN was distilled from CaH_2 before using. $CHCl_3$ for chromatography was freshly distilled and used. Ethyl acetate for chromatography and recrystallization was distilled after being

washed with successively 20% aqueous K_2CO_3 solution and brine and dried over anhydrous K_2CO_3. Flash chromatography was carried out by a method of Still[14] with Merck Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography (tlc) was performed on Merck silica gel plates containing a F-254 indicator. Visualization was accomplished by uv light and iodine. Preparative tlc was performed on 20 x 20 cm plates coated with 0.5 mm thickness of Merck Kieselgel 60 containing F-254 indicator.

1,2,3,4-Tetrahydro-6-methoxy-1-(3',4'-methylenedioxy)benzyl-*N*-trifluoroacetylisoquinolin-7-ol (**13b**) : To a stirred, ice-cooled suspension of 7-benzyloxy-3,4-dihydroisoquinoline hydrochloride[2b](8.05 g, 18.4 mmol) in methanol (80 ml), $NaBH_4$ (1.39 g, 36.8 mmol) was added portionwise and the mixture was stirred at room temperature for 1 h. Usual work-up of the mixture gave in quantitative yield the corresponding 7-benzyloxytetrahydroisoquinoline as an oil, which was used for next step without further purification. To an ice-cold, stirred mixture of the crude amine (6.17 g, 15.3 mmol) and K_2CO_3 (2.51 g, 18.2 mmol) in CH_2Cl_2 (100 ml) was added dropwise a solution of trifluoroacetic anhydride (3.2 ml, 22.7 mmol) in CH_2Cl_2 (10 ml), and the whole was stirred at room temperature for 30 min. Water was added to the mixture and the organic layer was separated. Aqueous layer was extracted with CH_2Cl_2. Combined organic extracts were washed with successively saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent gave 7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(3',4'-methylenedioxy)-benzyl-*N*-trifluoroacetylisoquinolin-7-ol as colorless crystals (6.78 g, 74.8%), mp 158-160 °C (CH_2Cl_2-hexane). Anal. Calcd for $C_{27}H_{24}NO_5F_3$: C, 64.92 ; H, 4.84 ; N, 2.80 ; F, 11.41. Found : C, 64.93 ; H, 4.73 ; N, 3.07 ; F, 11.55. Ir (KBr) : 1685 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 3.89 (3H, s, OMe), 5.00 (2H, s, OCH_2), 5.46 (2H, s, OCH_2O), 5.94 (1H, t, J=5.7 Hz, C_1-H), 6.32-6.80 (5H, m, 5 x arom-H), 7.16-7.52 (5H, m, $C_6\underline{H}_5CH_2O$). A mixture of benzyloxy-*N*-trifluoroacetamide (5.11 g, 10.2 mmol) obtained above and 10% Pd-C (3.3 g) in ethyl acetate (250 ml) was shaken with H_2 (1 atm) at room temperature until a spot of starting material on tlc disappeared. After filtration of the mixture, the solvent was removed *in vacuo* to leave **13b** as colorless crystals (3.75 g, 89.6%), mp 137-138 °C (CH_2Cl_2-hexane). Anal. Calcd for $C_{20}H_{18}NO_5F_3$: C, 67.91 ; H, 6.78 ; N, 3.77 ; F, 13.92. Found : C, 67.88 ; H, 6.74 ; N, 3.85 ; F, 13.94.

Ir (KBr) : 3350, 1670 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 3.81 (3H, s, OMe), 5.40-5.66 (1H, m, C_1-H), 5.94 (2H, s, OCH_2O), 6.08-6.34 (5H, m, 5 x arom-H).

4a-Acetoxy-1-(3',4'-dimethoxy)benzyl-6-methoxy-7-oxo-*N*-trifluoroacetyl-1,2,3,4,4a,7-hexahydroisoquinoline (**17a**) : Reaction of **13a**[13] (500 mg, 1.18 mmol) with $Pb(OAc)_4$ (782 mg, 1.76 mmol) in AcOH (15 ml) as reported previously[2] afforded crude product (498 mg), which was purified by flash column chromatography (eluent : CH_2Cl_2-ethyl acetate, 10 : 1, v / v) to give **17a** (301 mg, 53%) as colorless crystals, mp 141-142 °C. Analytical sample was obtained by recrystallization from benzene, mp 144 °C. Anal. Calcd for $C_{23}H_{24}NO_7F_3$: C, 57.14 ; H, 5.00 ; N, 2.90. Found : C, 57.23 ; H, 4.90 ; N, 2.72. Ir ($CHCl_3$) : 1760, 1695, 1665, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.17 (3H, s, OAc), 3.68 (3H, s, OMe), 3.83 (6H, s, 2 x OMe), 4.51-4.76 (0.4H, m, C_1-H), 5.30 (0.6H, br t, *J*=7.1 Hz, C_1-H), 5.95 (2H, s, olefinic H), 6.56-6.83 (3H, m, 3 x arom-H).

4a-Acetoxy-1-(3',4'-methylenedioxy)benzyl-6-methoxy-7-oxo-*N*-trifluoroacetyl-1,2,3,4,4a,7-hexahydroisoquinoline (**17b**) : Reaction of **13b** (500 mg, 1.22 mmol) with $Pb(OAc)_4$ (813 mg, 1.83 mmol) in AcOH (15 ml) as reported previously[2] afforded crude product (498 mg), which was purified by flash column chromatography (eluent : CH_2Cl_2-ethyl acetate, 20 : 1, v / v) to give **17b** (291 mg, 51%) as colorless crystals, mp 151-152 °C (decomp.). Analytical sample was obtained by recrystallization from ethyl acetate, mp 154-155 °C (decomp.). Anal. Calcd for $C_{22}H_{20}NO_7F_3$: C, 56.53 ; H, 4.31 ; N, 3.00. Found : C, 56.33 ; H, 4.35 ; N, 2.80. Ir ($CHCl_3$) : 1743, 1685, 1655, 1630 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 2.17 (3H, s, OAc), 3.68 (3H, s, OMe), 4.50-4.76 (0.4H, m, C_1-H), 5.27 (0.6H, br t, *J*=7.1 Hz, C_1-H), 5.83-6.11 (4H, m, olefinic H and OCH_2O), 6.44-6.83 (3H, m, 3 x arom-H).

Treatment of *p*-QAs (**17a, b**) with Trifluoroacetic Acid ; General Procedure

p-QA (**17**) obtained by oxidation of **13** (100 mg) as noted above was employed without further purification. Purification of the reaction mixture was carried out as follows. Flash column chromatography ($CHCl_3$ as an eluent) for runs 1-5, and 7 (Table I) and preparative tlc (ethyl acetate : hexane = 2 : 1, v / v, as a developing solvent) for runs 6 and 8 (Table I) were performed. These results are listed in Table I.

a) To a stirred solution of **17** in CH_2Cl_2 (10 ml) was added CF_3COOH (0.5 ml) at 0 °C. The whole was stirred for 5 min, and the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution. The mixture was diluted with CH_2Cl_2 and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3, and concentrated *in vacuo* to give a residue, which was purified as described above.

b) To a stirred, cooled solution of *p*-QAs (**17**) in CH_2Cl_2 or MeCN (10 ml) was slowly added at -30 °C a cooled solution (below -25 °C) of CF_3COOH (1 ml) in CH_2Cl_2 or MeCN (10 ml). After being stirred at -40 °C or -30 °C, the reaction mixture was worked up in a similar way as described above.

N-Trifluoroacetylnorsebiferine (**15a**) : mp 178-179 °C (ethanol-ether) (lit.,[12] mp 177-179 °C).

N-Trifluoroacetylwilsoniline (**16a**) : mp 190-191 °C ($CHCl_3$-methanol) (lit.,[11] mp 190-191 °C).

N-Trifluoroacetylnoramurine (**15b**) : mp 212-213 °C (benzene-isopropyl ether). (lit.,[12] mp 210-212 °C).

N-Trifluoroacetylnordomesticine (**16b**) : mp 287-289 °C (decomp.) (ethyl acetate). This was identical in all respects with authentic sample [mp 286-288 °C (decomp.) (ethyl acetate) ; Anal. Calcd for $C_{20}H_{16}NO_5F_3$: C, 58.97 ; H, 3.98 ; N, 3.44. Found : C, 58.94 ; H, 4.02 ; N, 3.62.] derived from *o*-QA (**14b**) .

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15. With crystalline *p*-QA (**17a**), **15a** and **16a** were also obtained in 13% and 78% yields, respectively.
16. The reaction of *p*-QA (**17a**) with CF_3COOH in MeCN was monitered by ^1H-nmr spectral measurements, showing that a peak (δ 2.1) due to acetoxyl group in **17a** disappeared completely after 5 h.

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