A Novel and Concise Synthesis of Spirodienone Alkaloids Using Hypervalent Iodine(III) Reagents

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Received July 8, 2004; accepted July 29, 2004; published online July 30, 2004

Intramolecular oxidative coupling reaction of *N*-protected benzyltetrahydroisoquinoline derivatives using hypervalent iodine(III) reagents was investigated. The use of remarkable combination of phenyliodine bis (trifluoroacetate) (PIFA) and heteropoly acid (HPA) in wet acetonitrile smoothly afforded morphinandienone alkaloids, while neospirinedienone alkaloids were obtained in high yield under anhydrous conditions.

Key words hypervalent iodine reagent; heteropoly acid; spiro compound; C–C coupling; alkaloid

The oxidative coupling reaction of phenol derivatives comprises a key step in the biosynthesis of various types of spirodienone alkaloids.[1,2] A great deal of effort to develop biogenetic-type syntheses using heavy metal oxidizing reagents such as mercury(II), thallium(III), vanadium(V), or ruthenium(IV) salts, has been devoted.[3—8] However, the organic reaction with heavy metal reagents needs harsh acidic condition because of their low solubility in organic solvent and the yields and selectivity are not always satisfactory. Moreover, heavy metal reagents are highly toxic and must be handled with great care. Over several years, hypervalent iodine(III) reagents have received much attention due to low toxicity, ready availability, easy handling, and their reactivities similar to those of heavy metal reagents.[9—12] In continuation of our research on the use of hypervalent iodine(III) reagents in organic synthesis, the oxidative coupling reaction of phenol ether derivatives involving aromatic cation-radical intermediates was originally reported by us.[13] Recently, we have developed a new oxidative route to spirodienones by non-phenolic coupling reaction on treatment with a combination of hypervalent iodine(III) reagent, phenyliodine bis (trifluoroacetate) (PIFA) and heteropoly acids (HPAs) which are readily available, inexpensive, easy to handle, noncorrosive, nonvolatile, and oldorless solid acids.[14,15]

The oxidation of benzyltetrahydroisoquinoline derivatives is the key reaction in the synthesis of several types of alkaloids and has received considerable attention since the first indication of biosynthetic importance of this type of reaction by Barton and Cohen in 1957.[1,2,16] Much of this attention has been focused on the transformation into morphinandienone-type alkaloids.[17—25] Although electrochemical investigations demonstrated efficient conversion into morphinandienones *via* non-phenolic coupling reaction,[26—29] the approaches using chemical oxidation were unsuccessful in the main and did not afford practical routes to morphinandienones.[30—35]

Very recently, we examined potentiality of the use of novel combination of PIFA and HPA in the oxidation of benzyltetrahydroisoquinoline derivatives.[36] In that research, the inhibition of the oxidation owing to the influence of their tertiary amine was observed and the extra addition of strong acid (5 eq) such as, $BF_3 \cdot Et_2O$, TfOH, or FSO_3H with PIFA/HPA provided successful conversion into morphinandienones. During the research, we found that protection of the amine with trifluoroacetyl group can give another alternative to introduce the corresponding morphinandienone. It is noteworthy that the oxidation proceeds in the presence of PIFA/HPA and the extra addition of strong acid is not necessary, whereas most other approaches to morphinandienones require the harsh acidic condition.

As our continuing efforts to establish a concise and general synthesis of morphinandienones, we have described herein a full account of our studies on the intramolecular oxidative coupling reaction of a variety of *N*-protected benzyltetrahydroisoquinoline derivatives using hypervalent iodine(III) reagents.

Result and Discussion

To explore the feasibility of the oxidative cyclization of the *N*-protected benzyltetrahydroisoquinoline derivatives (**1**), the reactions using PIFA/HPA together with an emphasis on nitrogen protection[2] as illustrated in Table 1 were investigated. Although *N*-trifluoroacetyl or pentafluorobenzoyl protection caused a favorable cyclization leading to morphinandienones (**2**) upon treatment with a combination of PIFA and tungsto(VI) phosphoric acid ($H_3[PW_{12}O_{40}]$) (entries 1, 2), no coupling product was obtained from other substrates such as, *N*-carbamate, *N*-formate, or *N*-borane complex (entries 3—5). Unsuitable result exerted by **1c**—**e** may be due to the lower oxidation potential of the tertiary amine center of the substrates in comparison with the dimethoxydialkylbenzene moiety.[37]

In the reactions of **1a** and **1b**, neospirinedienones (**3a**, **b**),

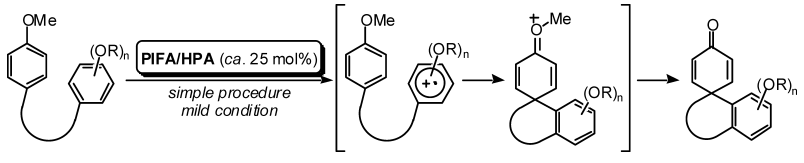

Chart 1. Formation of Spirodienones on Treatment with PIFA/HPA

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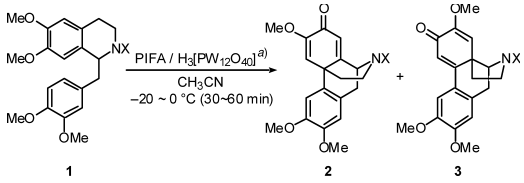
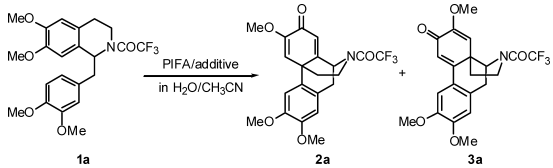
Table 1. Oxidative Coupling Reaction of *N*-Protected Benzyltetrahydroisoquinoline Derivatives (**1**) with PIFA-HPA



Entry	Substrate	NX	**2** (%)[b]	**3** (%)[b]
1	**1a**	$NCOCF_3$	63 (**2a**)	32 (**3a**)
2	**1b**	$NCOC_6F_5$	34 (**2b**)	28 (**3b**)
3	**1c**	NCHO	ND[c]	ND[c]
4	**1d**	NCO_2Et	ND[c]	ND[c]
5	**1e**	$NCH_3 \cdot BH_3$	ND[c]	ND[c]

a) HPA: *ca.* 30 mol%. *b*) Yield of isolated products. *c*) ND: not detected.

Table 2. Oxidative Coupling Reaction of Trifluoroacetylnorlaudanosine (**1a**)



Entry	Additive	H_2O	Temp. (°C)	Time (h)	**2a** (%)[a]	**3a** (%)[a]
1	$H_3[PW_{12}O_{40}]$[b]	None	−20—0	0.5	63	32
2	$H_3[PW_{12}O_{40}]$[b]	0.5%	−20—0	0.5	70	24
3	$H_3[PW_{12}O_{40}]$[b]	2.5%	−20—0	1	84	9
4	$H_3[PW_{12}O_{40}]$[b]	5%	−20—rt	2	57	3
5	$H_3[PMo_{12}O_{40}]$[b]	2.5%	−20—0	1	72	5
6	$H_4[SiW_{12}O_{40}]$[b]	2.5%	−20—0	1	87	8
7	$H_4[SiMo_{12}O_{40}]$[b]	2.5%	−20—0	1	54	5
8	$H_3[PW_{12}O_{40}]$[b]/ $(CF_3CO)_2O$[c]	None	−20—0	0.5	0	90
9	$BF_3 \cdot Et_2O$[d]	None	−40—0	0.5	0	90
10	$BF_3 \cdot Et_2O$[d]	0.5%	−20—0	1	39	51
11	$BF_3 \cdot Et_2O$[d]	2.5%	0—rt	3	43	13

a) Yield of isolated products. *b*) *ca.* 30 mol%. *c*) 4 eq. *d*) 2 eq.

which would be *Erythtrina* alkaloid precursors, were obtained as a side-product.[30] In order to achieve the selective synthesis of **2**, cyclization was carried out under various conditions (Table 2). Dominant formation of **2a** occurred in the presence of wet acetonitrile and the better results were observed in entries 3 and 6. It is noteworthy that the reaction proceeds under such mild conditions with simple experimental protocol. On the contrary, exclusive formation of **3a** in high yield was also observed under anhydrous conditions (entries 8, 9). These results therefore suggest that the presence of water in the reaction medium plays an important role in its selectivity.[14,15] We also carried out the reaction with PIFA/$BF_3 \cdot Et_2O$ in wet acetonitrile, but the yield and selectivity of **2a** were decreased relative to the reaction with PIFA/HPA (entries 10, 11).

Next, we investigated the oxidative cyclization of some other substrates (**1**) (Table 3). Similarly, treatment with PIFA/HPA in wet acetonitrile afforded morphinandienone-type products (**2**), while PIFA/$BF_3 \cdot Et_2O$ in dry acetonitrile produced neospirinedienone-type products (**3**).

As for formation of **3**, two plausible routes are envisaged

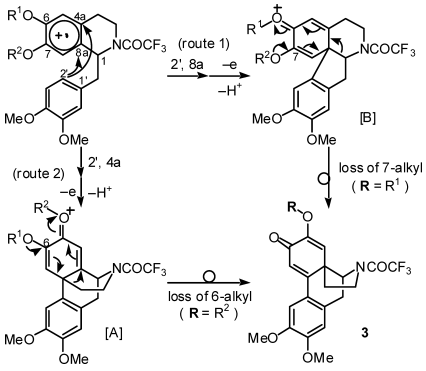
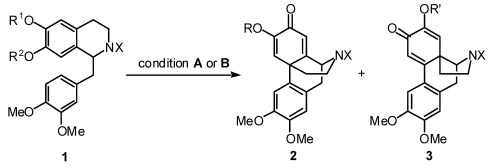


Chart 2. Possible Reaction Formation Mechanism for Neospirinedienones

Table 3. Synthesis of Morphinandienones (**2**) and Neospirinedienones (**3**)



[Condition **A**: PIFA/$H_3[PW_{12}O_{40}]$ (*ca.* 30 mol%) in H_2O (2.5%)/CH_3CN; −20—0 °C (60 min)
Condition **B**: PIFA/BF_3•Et_2O (2 eq)[a] in CH_3CN; −40—0 °C (30 min)]

Entry	Substrate	OR^1	OR^2	X	Condition	**2** (%)[b]	OR	**3** (%)[b]	OR′
1	**1a**	OMe	OMe	$COCF_3$	A	84	OMe (**2a**)	9	OMe (**3a**)
2	**1b**	OMe	OMe	COC_6F_5	A	67	OMe (**2b**)	Trace	OMe (**3b**)
3	**1f**	OBn	OMe	$COCF_3$	A	62	OBn (**2f**)	10	OMe (**3a**)
4	**1g**	OMe	OBn	$COCF_3$	A	72	OMe (**2a**)	Trace	OBn (**3g**)
5	**1a**	OMe	OMe	$COCF_3$	B	ND[c]	—	90	OMe (**3a**)
6	**1b**	OMe	OMe	COC_6F_5	B	ND[c]	—	53	OMe (**3b**)
7	**1f**	OBn	OMe	$COCF_3$	B	ND[c]	—	73	OMe (**3a**)
8	**1g**	OMe	OBn	$COCF_3$	B	ND[c]	—	98	OBn (**3g**)

a) 25 mg/ml. *b*) Yield of isolated products. *c*) ND: not detected.

as shown in Chart 2: route 1, *via* the proerthrinadienone intermediate [B] requires loss of the 7-alkyl group and route 2, *via* the morphinandienone intermediate [A] requires loss of the 6-alkyl group.[31] Giving results in Table 3, isolation of the spirodienone-type products (**2**), which should be introduced through nucleophilic addition of H_2O to intermediate [A] demonstrated the justification of route 2 (entries 1—4; wet condition). Additionally, formation of **3** with the present substituent (*R′*) will also follow this opinion (entries 5—8).

Conclusion

We have shown oxidative coupling reaction of the *N*-protected benzyltetrahydroisoquinoline derivatives using hypervalent iodine(III) reagents. A concise and efficient synthesis of morphinandienones has been achieved by the novel use of remarkable combination of PIFA and HPA. Alternatively, neospirinedienones have been smoothly synthesized by using PIFA/$BF_3 \cdot Et_2O$ or PIFA/HPA/TFAA. The simplicity of the

reaction protocol and the high yielding conversion in mild reaction systems may find much advantage for the application to the synthesis of other spirodienone alkaloids derivatives. Further studies along these lines are now in progress.

Experimental

All melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ with either TMS or residual $CHCl_3$ as the internal standard. Infrared (IR) absorption spectra (cm^{-1}) were recorded as KBr pellets. Aluminium oxide 60 (basic, Merck) and silica gel 60N (Kanto Chemical Company) were used for column chromatography. The organic layer was dried with anhydrous $MgSO_4$ or Na_2SO_4. PIFA is commercially available. $H_3[PW_{12}O_{40}]$ and $H_3[PMo_{12}O_{40}]$ were a Kanto Chemical Company product. $H_4[SiW_{12}O_{40}]$ were purchased from Aldrich. $H_4[SiMo_{12}O_{40}]$ was purchased from Wako Pure Chemical Industries. **1a**—**g** were prepared by known methods.[27]

***N*-Trifluoroacetyl-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (1a)**[28] Colorless solid; mp 136—137 °C; IR (KBr) cm^{-1}: 1688. ^{1}H-NMR ($CDCl_3$) δ: 2.61—2.67 (1 H, m), 2.82—3.24 (4H, m), 3.32—3.48 (1H, m), 3.69 (3H, s), 3.78 (3H, s), 3.85, 3.86 (total 6H, each s), 5.57 (1H, t, J=6.3 Hz), 5.94, 6.31 (total 1H, each s), 6.54—6.61 (3H, m), 6.74, 6.79 (total 1H, each d, J=8.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 28.5, 40.5, 41.3, 55.4, 55.7, 55.8, 55.8, 55.9, 110.2, 110.9 (2C), 112.6, 116.5 (J=287 Hz), 121.9, 125.0, 126.5, 129.3, 147.4, 147.9, 148.0, 148.7, 155.8 (J=35 Hz). *Anal*. Calcd for $C_{22}H_{24}F_3NO_5$: C, 60.13; H, 5.51; N, 3.19. Found: C, 60.21; H, 5.54; N, 3.23.

***N*-Pentafluorobenzoyl-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (1b)** Colorless solid; mp 182—183 °C. IR (KBr) cm^{-1}: 1651. ^{1}H-NMR ($CDCl_3$) δ: 2.44—2.52 (1H, m), 2.70—3.30 (4H, m), 3.34—3.42 (1H, m), 3.73 (3H, s), 3.75 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 5.82 (1H, t, J=6.3 Hz), 6.27, 6.48 (total 1H, each s), 6.59—6.64 (3H, m), 6.74 (1H, d, J=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 28.6, 41.5, 42.3, 54.5, 55.6, 55.8 (2C), 60.3, 110.2, 110.8, 110.9, 111.4, 112.7, 122.0, 125.2, 126.8, 129.4, 137.7 (J=252 Hz, 2C), 141.8 (J=239 Hz), 142.8 (J=243 Hz, 2C), 147.5, 147.9, 148.0, 148.6, 157.3. *Anal*. Calcd for $C_{27}H_{24}F_5NO_5$: C, 60.34; H, 4.50; N, 2.61. Found: C, 60.39; H, 4.53; N, 2.65.

***N*-Trifluoroacetyl-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6–benzyloxy-7-methoxyisoquinoline (1f)**[38] Colorless solid; mp 142—143°C. IR (KBr) cm^{-1}: 1682. ^{1}H-NMR ($CDCl_3$) δ: 2.54—2.61 (1H, m), 2.76—3.19 (4H, m), 3.35—3.45 (1H, m), 3.71 (3H, s), 3.78 (3H, s), 3.86 (3H, s), 5.11 (2H, s), 5.56 (1H, t, J=6.3 Hz), 5.98, 6.35 (total 1H, each s), 6.52—6.73 (3H, m), 6.74, 6.80 (total 1H, each d, J=8.1 Hz), 7.26—7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 28.4, 40.5, 41.3, 55.4, 55.7, 55.8, 55.9, 71.0, 110.8, 110.9, 112.6, 113.6, 121.9, 125.0, 127.1, 127.2 (2C), 127.9, 128.6 (2C), 129.3, 136.8, 147.2, 147.9, 148.1, 148.7, 155.8 (J=36 Hz). *Anal*. Calcd for $C_{28}H_{28}F_3NO_5$: C, 65.23; H, 5.47; N, 2.72. Found: C, 64.86; H, 5.58; N, 2.69.

***N*-Trifluoroacetyl-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-benzyloxy-6-methoxyisoquinoline (1g)**[8] Colorless solid; mp 164—165 °C (lit.[8] 159.5—160 °C). IR (KBr) cm^{-1}: 1688. ^{1}H-NMR ($CDCl_3$) δ: 2.46—2.67 (1H, m), 2.78—3.17 (4H, m), 3.26—3.34 (1H, m), 3.75 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 4.92 (1H, d, J=12.3 Hz), 5.00 (1H, d, J=12.3 Hz), 5.47 (1H, t, J=5.9 Hz), 6.04, 6.36 (total 1H, each s), 6.47—6.63 (3H, m), 6.72, 6.78 (total 1H, each d, J=8.1 Hz), 7.29—7.36 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 28.4, 40.5, 40.5, 55.2, 55.6, 55.7, 55.9, 70.9, 110.9, 111.4, 112.6, 113.1, 121.8, 125.6, 126.3, 127.0 (2C), 127.8, 128.4 (2C), 129.2, 136.7, 146.4, 147.9, 148.7 (2C), 155.7 (J=35 Hz). *Anal*. Calcd for $C_{28}H_{28}F_3NO_5$: C, 65.23; H, 5.47; N, 2.72. Found: C, 65.21; H, 5.43; N, 2.71.

General Coupling Procedure Leading to Morphinandienone Derivatives (2) by Treatment with PIFA/HPA (Condition A) To a stirred solution of **1** (0.10 mmol) in 2.5%-H_2O/CH_3CN (4.0 ml) was added HPA (100 mg) and PIFA (43.0 mg, 0.10 mmol) at −20 °C. Stirring was continued for 60 min at −20 to 0 °C. The solution was dilute with AcOEt and filtered through a pad of alumina. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N, 10 : 15 : 0.5) to morphinandienone derivatives (**2**).

6-Trifluoroacetylnorsebiferine (2a)[5,25,28] Colorless solid; mp 182—183 °C (lit.[25] 203—204 °C; lit.[5] 179.4—181.5 °C). IR (KBr) cm^{-1}: 1678, 1649. ^{1}H-NMR ($CDCl_3$) δ: 1.79—2.09 (2H, m), 2.89—3.29 (3H, m), 3.44, 4.45 (total 1H, each dd, J=18.3, 5.7, 14.1, 5.4 Hz), 3.81 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 4.99, 5.60 (total 1H, each d, J=5.4, 5.7 Hz), 6.36, 6.37 (total 1H, each s), 6.41 (1H, s), 6.62 (1H, s), 6.84 (1H, s). ^{13}C-NMR ($CDCl_3$) (major) δ: 37.9, 39.5, 41.6, 42.2, 52.0, 55.2, 55.9, 56.4, 108.7, 110.8, 117.4, 123.2, 126.7, 128.6, 148.7, 149.0, 151.9 156.6, 180.1. (minor) δ: 37.0, 38.7, 41.0, 42.1, 52.0, 55.3, 55.9, 56.3, 108.7, 110.5, 117.6, 122.7, 126.4, 128.6, 148.7, 149.0, 151.8 156.3, 180.1. EI-HR-MS *m/z*: 423.1292 (Calcd for $C_{21}H_{20}F_3NO_5$: 423.1293). EI-MS *m/z* (%): 423.2 (100) [M^+].

6-Pentafruorobenzoylnorsebiferine (2b) Colorless solid; mp 125—126 °C. IR (KBr) cm^{-1}: 1651, 1624. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.04 (2H, m), 2.83—3.35 (3H, m), 3.80, 3.82 (total 3H, each s), 3.86, 3.88 (total 3H, each s), 3.89, 3.91 (total 3H, each s), 3.47, 4.67 (total 1H, each dd, J=18.0, 5.1, 14.1, 5.7 Hz), 4.48, 5.81 (total 1H, each d, J=5.1, 5.7 Hz), 6.16, 6.34 (total 1H, each s), 6.39, 6.47 (total 1H, each s), 6.61, 6.66 (total 1H, each s), 6.83, 6.86 (total 1H, each s). ^{13}C-NMR ($CDCl_3$) (major) δ: 36.3, 38.5, 41.1, 42.3, 51.2, 55.2, 55.9, 56.3, 108.7, 110.8, 117.4, 123.0, 127.0, 128.5, 148.6, 148.9, 151.9 157.1, 180.2. (minor) δ: 36.6, 38.8, 41.4, 42.5, 51.2, 55.2, 55.9, 56.3, 108.6, 110.5, 117.7, 122.1, 126.2, 128.5, 148.6, 148.9, 151.7 156.8, 180.1. EI-HR-MS *m/z*: 521.1261 (Calcd for $C_{26}H_{20}F_5NO_5$: 521.1261). EI-MS *m/z* (%): 521.0 (100) [M^+].

3-Benzyloxy-6,7-dimethoxy-11-trifluoroacetyl-9,10-dihydro-4a,10-propanephenanthren-2-one (2f) Colorless solid; mp 214—215 °C. IR (KBr) cm^{-1}: 1682, 1651. ^{1}H-NMR ($CDCl_3$) δ: 1.71—2.03 (2H, m), 2.84—3.24 (3H, m), 3.27, 4.41 (total 1H, each dd, J=18.3, 5.4, 14.1, 4.8 Hz), 3.66, 3.67 (total 3H, each s), 3.83, 3.84 (total 3H, each s), 4.97, 4.98, 5.23 (total 2H, each d, s, d, J=13.2, 13.2 Hz), 4.96, 5.56 (total 1H, each d, J=4.8, 5.4 Hz), 6.37 (1H, s), 6.40 (1H, s), 6.45 (1H, s), 6.58 (1H, s), 7.28—7.40 (5H, m). ^{13}C-NMR ($CDCl_3$) (major) δ: 37.8, 39.4, 41.5, 42.3, 51.9, 55.9 (2C), 70.1, 108.3, 110.5, 120.4, 123.3, 126.5, 126.7 (2C), 126.7, 128.1, 128.8 (2C), 135.9, 148.5, 148.7, 150.5 156.3, 180.2. (minor) δ: 36.8, 38.6, 40.9, 42.2, 51.9, 56.2 (2C), 70.1, 108.2, 110.2, 120.6, 122.9, 126.2, 126.7 (2C), 128.1, 128.4, 128.8 (2C), 135.9, 148.6, 148.8, 150.5 155.9, 180.2; EI-HR-MS *m/z*: 499.1619 (Calcd for $C_{27}H_{24}F_3NO_5$: 499.1606). EI-MS *m/z* (%): 499.1 (100) [M^+].

General Coupling Procedure Leading to Neospirinedienone Derivatives (3) by Treatment with PIFA/$BF_3\cdot Et_2O$ (Condition B) To a stirred solution of **1** (0.10 mmol) in CH_3CN (4.0 ml) was added PIFA (43.0 mg, 0.10 mmol) and $BF_3\cdot Et_2O$ (25 μl, 0.2 mmol) at −20 °C. Stirring was continued for 30 min at −20 to 0 °C. The solution was diluted with AcOEt and then quenched with aq. $NaHCO_3$ (sat.). The mixture was extracted with AcOEt and washed with brine. The organic extract was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N, 10 : 15 : 0.5) to afford the neospirinedienone derivatives (**3**).

Coupling Procedure Leading to *N*-Trifluoroacetyl Neospirinedioenone (3a) by Treatment with PIFA/HPA/$(CF_3CO)_2O$ To a stirred solution of **1a** (43.9 mg, 0.10 mmol) in 1.0%-$(CF_3CO)_2O$/CH_3CN (4.0 ml) was added HPA (100 mg) and PIFA (43.0 mg, 0.10 mmol) at −20°C. Stirring was continued for 30 min at −20 to 0 °C. The solution was diluted with AcOEt and then quenched with aq. $NaHCO_3$ (sat.). The mixture was extracted with AcOEt and washed with brine. The organic extract was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N, 10 : 15 : 0.5) to afford the *N*-trifluoroacetyl neospirinedioenone (**3a**, 38.2 mg, 90%).

***N*-Trifluoroacetyl Neospirinedioenone (3a)**[28,39] Colorless solid; mp 250—251 °C (lit.[39] 247—248 °C). IR (KBr) cm^{-1}: 1693, 1639. ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.34 (4H, m), 2.87, 3.10 (total 1H, each dd, J=18.3, 6.3, 17.4, 3.0 Hz), 3.21, 3.47 (total 1H, each dd, J=17.4, 7.2, 18.3, 9.3 Hz), 3.68, 3.73 (total 3H, each s), 3.91 (6H, s), 4.49, 4.64 (total 1H, each dd, J=9.3, 6.3, 7.2, 3.0 Hz), 5.69, 5.83 (total 1H, each s), 6.60 (1H, s), 6.65, 6.76 (total 1H, each s), 6.98, 7.07 (total 1H, each s). ^{13}C-NMR ($CDCl_3$) (major) δ: 31.7, 41.2, 45.1, 47.4, 55.2, 56.1 (2C), 60.6, 108.0, 111.1, 116.4, 116.2 (J=287 Hz), 123.7, 125.2, 127.4, 148.7, 151.3, 151.8, 155.9 (J=37 Hz), 156.8, 180.8. (minor) δ: 33.3, 36.2, 45.0, 48.1, 55.2, 56.0 (2C), 60.7, 107.4, 110.5, 114.4, 116.1 (J=287 Hz), 122.6, 123.9, 127.0, 148.7, 151.8, 152.1, 154.4, 155.7 (J=37 Hz), 180.7. EI-HR-MS *m/z*: 423.1294 (Calcd for $C_{21}H_{20}F_3NO_5$: 423.1293). EI-MS *m/z* (%): 423.2 (100) [M^+]. *Anal*. Calcd for $C_{21}H_{20}F_3NO_5$: C, 59.57; H, 4.76; N, 3.31. Found: C, 59.34; H, 4.79; N, 3.32.

3,10,11-Trimethoxy-7-pentafluorobenzoyl-6,7,7a,8-tetrahydro-5*H*-bibenzo-[d,f]indol-2-one (3b) Colorless solid; mp 290—292 °C. IR (KBr) cm^{-1}: 1633, 1589. ^{1}H-NMR ($CDCl_3$) δ: 2.08—2.39 (4H, m), 2.88, 2.99 (total 1H, each dd, J=18.1, 6.5, 17.6, 3.2 Hz), 3.22, 3.48 (total 1H, each dd, J=17.6, 7.6, 18.1, 9.5 Hz), 3.69, 3.74 (total 3H, each s), 3.96 (6H, s), 4.49, 4.64 (total 1H, each dd, J=9.5, 6.5, 7.6, 3.2 Hz), 5.68, 5.82 (total 1H, each s), 6.60 (1H, s), 6.66, 6.77 (total 1H, each s), 6.98, 7.07 (total 1H, each s). ^{13}C-NMR ($CDCl_3$) (major) δ: 32.0, 40.6, 46.2, 48.6, 55.3, 56.1 (2C), 59.5, 107.7, 111.1, 116.8, 123.4, 125.3, 127.9, 148.6, 151.3, 151.7, 157.0 180.9. (minor) δ: 33.0, 37.5, 45.6, 47.5, 55.1, 56.0 (2C), 61.8, 107.4, 110.5, 114.7,

122.8, 123.9, 126.5, 148.7, 151.7, 152.1, 154.6 180.7. EI-HR-MS *m*/*z*: 521.1259 (Calcd for $C_{26}H_{20}F_5NO_5$: 521.1261).

3-Benzyloxy-10,11-dimethoxy-7-trifluoroacetyl-6,7,7a,8-tetrahydro-5*H*-bibenzo[d,f]indol-2-one (3g) Colorless solid; mp 190—191 °C. IR (KBr) cm^{-1}: 1692, 1659. ^{1}H-NMR ($CDCl_3$) δ: 1.78—2.30 (4H, m), 2.82, 2.90 (total 1H, each dd, J=18.3, 6.6, 17.7, 3.6 Hz), 3.26, 3.42 (total 1H, each dd, J=17.7, 7.8, 18.3, 8.7 Hz), 3.89 (3H, s), 3.90 (3H, s), 4.37, 4.53 (total 1H, each dd, J=8.7, 6.6, 7.8, 3.6 Hz), 4.96, 4.97, 5.10 (total 2H, each d, s, d, J=12.6, 12.6 Hz), 5.73, 5.83 (total 1H, each s), 6.58, 6.64 (total 1H, each s), 6.62, 6.77 (total 1H, each s), 6.99, 7.07 (total 1H, each s), 7.27—7.41 (5H, m). ^{13}C-NMR ($CDCl_3$) (major) δ: 31.5, 40.8, 44.7, 47.0, 55.9, 56.0, 60.2, 70.0, 107.7, 110.8, 119.3, 123.7, 124.5, 127.2, 127.3 (2C), 128.1, 128.6 (2C), 135.7, 148.5, 149.7, 151.7, 155.8, 180.7. (minor) δ: 33.1, 36.1, 44.6, 47.9, 55.8, 55.9, 60.3, 70.1, 107.2, 110.4, 117.5, 122.3, 123.8, 126.9, 127.2 (2C), 127.3, 128.7 (2C), 135.7, 148.6, 150.3, 152.0, 153.8, 180.7. EI-HR-MS *m*/*z*: 499.1610 (Calcd for $C_{27}H_{24}F_3NO_5$: 499.1606). EI-MS *m*/*z* (%): 499.3 (77.0) [M^+], 91.1 (100).

Acknowledgement This work was supported by a Grant-in-Aid for Scientific Research (S) (No.7690) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References

1) Sainsbury M., *Tetrahedron*, **36**, 3327—3359 (1980).
2) Dhingra O. P., "Oxidation in Organic Chemistry," part D, ed. by Trahanovsky W. S., Academic Press, New York, 1982.
3) Schwartz M. A., Holton R. A., Scott S. W., *J. Am. Chem. Soc.*, **91**, 2800 (1969).
4) Schwartz M. A., Rose B. F., Vishnuvajjala B., *J. Am. Chem. Soc.*, **95**, 612—613 (1973).
5) Kupchan S. M., Dhingra O. P., Kim C.-K., *J. Org. Chem.*, **41**, 4049—4050 (1976).
6) Schwartz M. A., Rose B. F., Holton R. A., Scott S. W., Vishnuvajjala B., *J. Am. Chem. Soc.*, **99**, 2571—2578 (1977).
7) Shimizu K., Tomioka K., Yamada S., Koga K., *Chem. Pharm. Bull.*, **26**, 3765—3771 (1978).
8) Kupchan S. M., Dhingra O. P., Kim C.-K., *J. Org. Chem.*, **43**, 4076—4081 (1978).
9) Stang P. J., Zhdankin V. V., *Chem. Rev.*, **96**, 1123—1178 (1996).
10) Wirth T., Hirt U. H., *Synthesis*, **1999**, 1271—1287 (1999).
11) Zhdankin V. V., Stang P. J., *Chem. Rev.*, **102**, 2523—2584 (2002).
12) Wirth T., "Hypervalent Iodine in Chemistry," Springer, Berlin, 2003.
13) Kita Y., Tohma H., Hatanaka K., Takada T., Fujita S., Mitoh S., Sakurai H., Oka S., *J. Am. Chem. Soc.*, **116**, 3684—3691 (1994).
14) Hamamoto H., Anilkmar G., Tohma H., Kita Y., *Chem. Eur. J.*, **8**, 5377—5383 (2002).
15) For recent review on heteropoly acids, see: Kozhevnikov I. V., *Chem. Rev.*, **98**, 171—198 (1998).
16) Kametani T., Fukumoto K., *Synthesis*, **1972**, 657—674 (1972).
17) Stuart K. L., *Chem. Rev.*, **71**, 47—72 (1971).
18) Kametani T., Fukumoto K., *J. Heterocycl. Chem.*, **8**, 341—357 (1971).
19) Kametani T., Fukumoto K., *Acc. Chem. Res.*, **5**, 212—219 (1972).
20) Kametani T., Fukumoto K., *Synthesis*, **1972**, 657—674 (1972).
21) Blaskó G., Cordell G. A., *Heterocycles*, **27**, 1269—1300 (1988).
22) Kametani T., Fukumoto K., Satoh F., *Bioorg. Chem.*, **3**, 430—497 (1974).
23) Franck B., Dunkelman G., Lubs H. J., *Angew. Chem., Int. Ed.*, **6**, 1075—1076 (1967).
24) Blaskó G., Dörnyel G., Bárczai-Bake M., Péchy P., Szántay C., *J. Org. Chem.*, **49**, 1439—1441 (1984).
25) Hara H., Komoriya S., Miyashita T., Hoshino O., *Tetrahedron Asymmetry*, **6**, 1683—1692 (1995).
26) Miller L. L., Stermitz F. R., Falck J. R., *J. Am. Chem. Soc.*, **93**, 5941—5942 (1971).
27) Miller L. L., Stermitz F. R., Falck J. R., *J. Am. Chem. Soc.*, **95**, 2651—2656 (1973).
28) Klünenberg H., Schäffer C., Schäfer H.-J., *Tetrahedron Lett.*, **23**, 4581—4584 (1982).
29) Bentley T. W., Morris S. J., *J. Org. Chem.*, **51**, 5005—5007 (1986).
30) Kupchan S. M., Liepa A. J., Kameswaran V., Bryan R. F., *J. Am. Chem. Soc.*, **95**, 6861—6863 (1973).
31) Kupchan S. M., Kameswaran V., Lynn J. T., Williams D. K., Liepa A. J., *J. Am. Chem. Soc.*, **97**, 5622—5623 (1975).
32) Kupchan S. M., Dhingra O. P., Kim C.-K., Kameswaran V., *J. Org. Chem.*, **43**, 2521—2529 (1978).
33) Taylor E. C., Andrade J. G., Rall G. J. H., McKillop A., *J. Am. Chem. Soc.*, **102**, 6513—6519 (1980).
34) Landais Y., Robin J. P., *Tetrahedron*, **48**, 7185—7196 (1992).
35) Planchenault D., Dhal R., Robin J. P., *Tetrahedron*, **49**, 5823—5830 (1993).
36) Hamamoto H., Shiozaki Y., Nambu H., Hata K., Tohma H., Kita Y., *Chem. Eur. J.*, in press.
37) Torii S., "Yukidenkaigosei," Kodansha, Tokyo, 1981, pp. 108—170, and references cited therein.
38) Hoshino O., Suzuki M., Ogasawara H., *Tetrahedron*, **57**, 265—272 (2001).
39) Kametani T., Takahashi K., Honda T., Ihara M., Fukumoto K., *Chem. Pharm. Bull.*, **20**, 1793—1798 (1972).