

Selected Paper

Synthesis of α-Carbolines by Copper-Catalyzed Radical Cyclization of β-(3-Indolyl) Ketone *O*-Pentafluorobenzoyloximes

Kenichi Tanaka, Mitsuru Kitamura, and Koichi Narasaka*

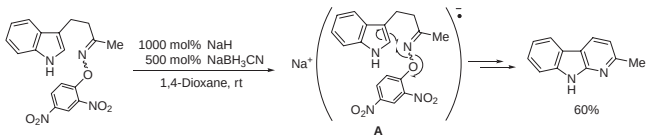
Department of Chemistry, Graduate School of Science, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

Received March 4, 2005; E-mail: narasaka@chem.s.u-tokyo.ac.jp

Radical cyclization of β-(3-indolyl) ketone *O*-pentafluorobenzoyloximes proceeds by the treatment with a catalytic amount of copper powder in 1,2-dichloroethane to generate 3,4-dihydro-α-carbolines, which are oxidized to α-carbolines with chloranil.

Pyrido[2,3-*b*]indoles (α-carbolines) have attracted considerable interest due to recent discoveries of their marked pharmacological activities as antitumor[1] and anxiloytic[2] agents, and much effort has been devoted to develop synthetic methods.[3] The typical approaches for α-carbolines involve the formation of an indole ring from substituted anilines and pyridines,[4] or construction of the pyridine moiety from 2-aminoindoles or their equivalents.[5] However, these methods have difficulties to control the regioselectivity, preparation and/or handling[6] of the starting materials. To overcome the above problems, the intramolecular amination of indole derivatives was recently reported for the synthesis of α-carboline.[7] For instance, a functionalized α-carboline has been prepared by the palladium-catalyzed cyclization of 3-(3-amino-1-propenyl)-2-bromoindole derivative.[7a] Ila et al. demonstrated that the displacement of the alkylthio group of β,β-bis(alkylthio)enones with oxindole enolates and successive condensation with ammonium acetate afforded 4-alkylthio-α-carbolines.[7b] While the above synthetic methods employed 2-functionalized indoles as the starting materials, there was little precedent for α-carboline synthesis by direct intramolecular amination of the 2-nonfunctionalized indole ring.[8]

Our group has communicated that α-carbolines are synthesized from β-(3-indolyl) ketone *O*-2,4-dinitrophenyloximes by treatment with sodium hydride and sodium cyanoborohydride (Eq. 1).[9e] Although the detailed reaction mechanism is not obvious, the reaction proceeds by radical cyclization[10] initiated by the one-electron reduction of *O*-dinitrophenyloximes.[9a–d] Our attention was then directed to improve this radical cyclization to a catalytic process. This paper describes the synthesis of α-carbolines by the copper-catalyzed radical cyclization of β-(3-indolyl) ketone *O*-pentafluorobenzoyloximes.



(1)

Results and Discussion

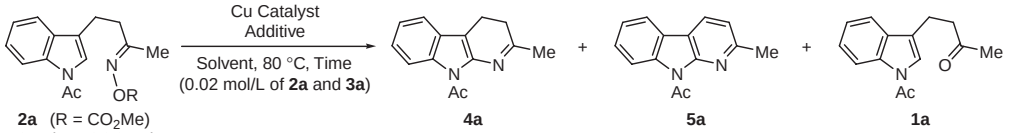
Copper-Catalyzed Radical Cyclization of β-(3-Indolyl) Ketone *O*-Pentafluorobenzoyloxime. As reported from our laboratory,[9f] the radical cyclization of γ,δ-unsaturated *O*-methoxycarbonyl- or *O*-pentafluorobenzoyloximes is effected by a catalytic amount of $CuBr \cdot Me_2S$, giving 3,4-dihydro-2*H*-pyrroles. It was, therefore, expected that β-(3-indolyl) ketone *O*-acyloximes would also undergo radical cyclization by treatment with copper compounds. We chose 4-(1-acetyl-3-indolyl)butan-2-one *O*-methoxycarbonyloxime **2a** and *O*-pentafluorobenzoyloxime **3a** as cyclization precursors for preliminary investigations (Table 1). Oxime derivatives **2a** and **3a** were readily prepared by the Michael addition of indole to methyl vinyl ketone.[11a]

Oxime **2a** and **3a** were firstly treated with a 0.05 molar amount of $CuBr \cdot Me_2S$ and 3.0 molar amounts of lithium bromide in 1,4-dioxane at 80 °C. Although the reaction completed within 30 min, 3,4-dihydro-α-carboline **4a** and α-carboline **5a** were obtained only in ca. 40% combined yield (Entries 1 and 2). Then, diamines were added instead of LiBr, because Itoh developed the copper-catalyzed radical cyclization of polyhalo ketones in the presence of TMEDA and 2,2′-bipyridine.[12] However, the cyclization did not take place by the use of $CuBr \cdot Me_2S$ with TMEDA or 2,2′-bipyridine. The combination of copper powder (0.2 molar amount) and an equimolar amount of *N*,*N*′,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) in 1,2-dichloroethane was found to effect the smooth cyclization of *O*-pentafluorobenzoyloxime **3a**, yielding 3,4-dihydro-α-carboline **4a** in 75% yield and a trace amount of α-carboline **5a** (Entry 3). The addition of LiBr into the above catalyst system resulted to slow the reaction with a lower yield of the cyclized products **4a** and **5a** (Entry 4). Interestingly, when oxime **3a** was treated with copper powder and PMDETA in 1,4-dioxane, the reaction did not take place at all (Entry 5, vide infra).

The results given in Table 1 suggest that the copper-catalyzed cyclization of β-(3-indolyl) ketone *O*-acyloximes **2a** and **3a** gave 3,4-dihydro-α-carboline **4a** as a preliminary product, which was partially oxidized to α-carboline **5a** during iso-

Published on the web August 30, 2005; DOI 10.1246/bcsj.78.1659

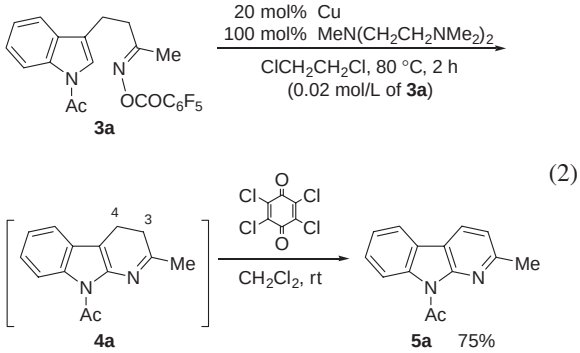
Table 1. Reaction of β-(3-Indolyl) Ketone Oxime Derivatives **2a** and **3a** with Catalytic Copper Compound[a)]



Entry	Oxime	Cu catalyst (mol%)		Additive (mol%)		Solvent	Time	**4a**	**5a**	**1a**
1	**2a**	$CuBr\cdot SMe_2$	(5)	LiBr	(300)	1,4-Dioxane	<0.5 h	22%	15%	14%
2	**3a**	$CuBr\cdot SMe_2$	(5)	LiBr	(300)	1,4-Dioxane	<0.5 h	18%	26%	18%
3	**3a**	Cu	(20)	$MeN(CH_2CH_2NMe_2)_2$	(100)	$ClCH_2CH_2Cl$	2 h	75%	trace	9%
4[b)]	**3a**	Cu	(20)	$MeN(CH_2CH_2NMe_2)_2$ LiBr	(100) (100)	$ClCH_2CH_2Cl$	5 h	34%	8%	37%
5[c)]	**3a**	Cu	(20)	$MeN(CH_2CH_2NMe_2)_2$	(100)	1,4-Dioxane	6 h	trace	trace	trace

a) Yields were estimated by NMR (anthracene as an internal standard). b) **3a** was recovered in 13% yield. c) Almost no reaction.

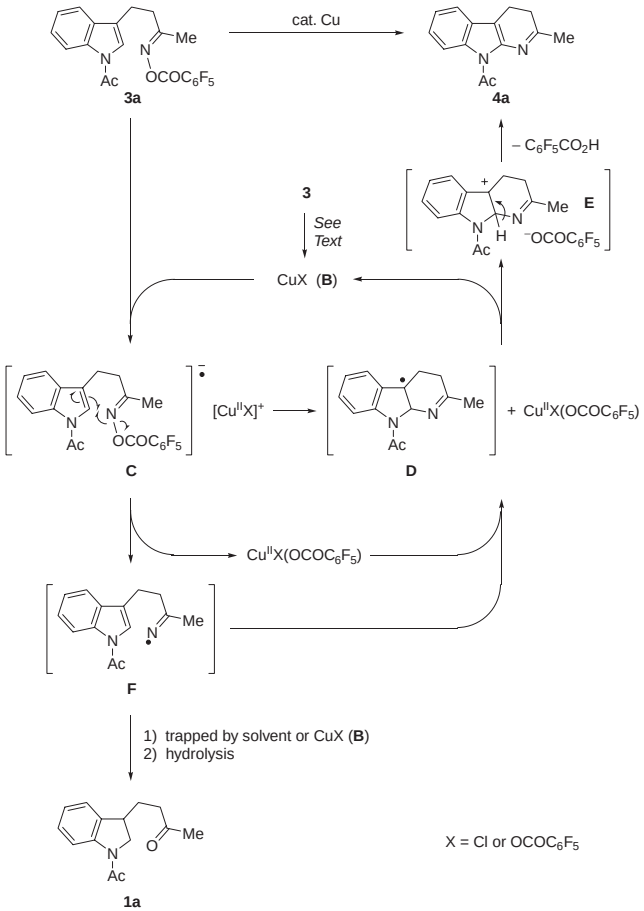
lation or in the reaction mixture (Entries 1, 2, and 4). Dihydrocarboline **4a** was readily oxidized with chloranil to afford α-carboline **5a** quantitatively. On the whole, the cyclization of *O*-pentafluorobenzoyloxime **3a** in with a catalytic amount of copper powder and PMEDTA in 1,2-dichloroethane gave α-carboline **5a** in 75% yield, after the oxidation of the crude products with chloranil (Eq. 2).



(2)

In Scheme 1 is depicted the plausible mechanism of the present copper-catalyzed reaction. It is assumed that copper(I) species **B** are in situ generated by one-electron transfer from copper powder to oxime derivatives **3a** and/or by the reaction with 1,2-dichloroethane. The latter path would explain that the cyclization of oxime **3a** proceeded much faster in 1,2-dichloroethane than in 1,4-dioxane (Table 1, Entries 3 vs 5). Elemental copper reacts with 1,2-dichloroethane to afford copper(II) chloride, which is converted to copper(I) salt by coproportionation with copper powder. In fact, when the copper powder and PMDETA were warmed up to 80 °C in 1,2-dichloroethane, the reaction mixture gradually became blue due to the formation of copper salts. The generation of active copper(I) spieces by oxidation with 1,2-dichloroethane is also supported by the fact that the cyclization of oxime **3a** in 1,4-dioxane with excess 1,2-dibromoethane or a trace amount of iodine as an additive gave a similar yield of the cyclized products (**4a** and **5a**) within 2 h. Although copper(I) species such as $CuBr\cdot Me_2S$ would work as an active catalyst, the use of copper(I) salt as a catalytic reagent did not give satisfactory results (Table 1, Entries 1 and 2).

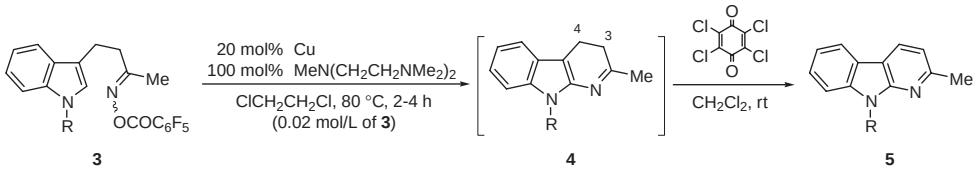
The cyclization proceeds as follows: one-electron transfer occurs from the copper(I) species to *O*-pentafluorobenzoyl-



Scheme 1. Plausible mechanism.

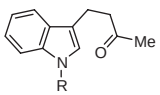
oxime **3a**, giving anion radical **C** and the copper(II) species. Anion radical **C** cyclizes to the 2-position of the indolyl moiety with cleavage of the N–O bond. Subsequently, copper(II) salt in the reaction mixture rapidly oxidizes the resulting radical **D** with the regeneration of the copper(I) species. Finally, the elimination of a proton from cation **E** yields 3,4-dihydro-α-carboline **4a** and pentafluorobenzoic acid. As a side reaction, radical anion **C** suffers from cleavage of the N–O bond to afford the free alkylideneaminyl radical **F** and copper(II)

Table 2. Synthesis of α-Carbolines Having a Substituent on the Indole Nitrogen



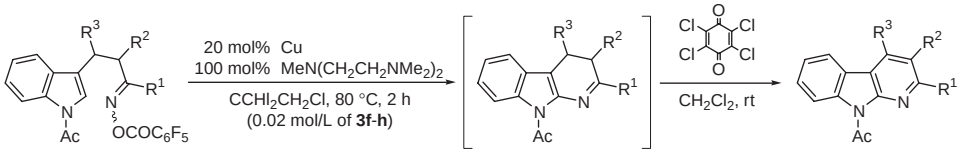
Entry	3	R	5	1
1	**3a**	Ac	75% (**5a**)	9% (**1a**)
2	**3b**	Me	64% (**5b**)	12% (**1b**)
3	**3c**[c)]	$SiMe_2t$-Bu	74% (**5c**)	15% (**1c**)
4[a),b)]	**3d**	CO_2t-Bu	46% (**5d**)	22% (**1d**)
5[a),b)]	**3e**[d)]	H	33% (**5e**)	35% (**1e**)

a) Oxidation with chloranil was not required. b) 20 mol % amount of PMDETA was used. c) *E*:*Z* = 3:1 mixture. d) *E*:*Z* = 3:5 mixture.



1

Table 3. Synthesis of α-Carbolines Having Substituents on the Pyridine Ring



Entry	Oxime	R^1	R^2	R^3	Yield
1	**3f**	Me	Me	H	83% (**5f**)
2	**3g**[b)]	Me	H	CO_2t-Bu	67% (**5g**)
3[a)]	**3h**	$-(CH_2)_4-$		H	39% (**5h**)

a) Oxidation with chloranil was not needed. b) *E*:*Z* = 3:2 mixture.

salt. Free radical **F**, which might cyclize to yield dihydrocarboline **4a** via intermediate **D**, is trapped by solvent or copper(I) compounds to afford imine or alkylideneaminyl copper(II) species, respectively, which were converted to ketone **1a** after hydrolysis.

Synthesis of Various α-Carbolines. Concerning the substituent on the indole nitrogen, it was revealed that several protecting groups other than the acetyl group could be introduced in the synthesis of α-carbolines from β-(3-indolyl) ketone *O*-pentafluorobenzoyloximes (Table 2). *N*-Methylindolyl oxime **3b** gave the corresponding α-carboline **5b** in 64% yield (Entry 2). Also, α-carboline **5c** having a bulky *tert*-butyldimethylsilyl group on the indole nitrogen was prepared in good yield from oxime **3c** (Entry 3). The cyclization of β-(3-indolyl) oximes **3d** and **3e** having a *tert*-butoxycarbonyl group or no substituent at the indole nitrogen gave the corresponding α-carbolines without the oxidation with 4-chloranil. However, the yields were lower than 50% with an increased formation of by-products such as β-(3-indolyl) ketones **1d** and **1e** (Entries 4 and 5).

The copper-catalyzed radical cyclization was further attempted by employing β-(3-indolyl) ketone *O*-pentafluorobenzoyloximes having substituents at the α- and β-positions (Table 3). 3- and 4-substituted α-carbolines **5f** and **5g** were obtained in good yields from α- and β-substituted oximes **3f** and **3g**, respectively (Entries 1 and 2). The cyclohexanone oxime derivative **3h** gave tetracyclic α-carboline **5h** without oxidation (Entry 3), which can be transformed to 6*H*-indolo[2,3-*b*]-quinoline by oxidation with DDQ.[7d] Various 6*H*-indolo[2,3-*b*]-quinoline derivatives such as cryptotackiene[13,14] are known to show biological activities.

In conclusion, α-carbolines were synthesized by the copper-catalyzed radical cyclization of β-(3-indolyl) ketone *O*-pentafluorobenzoyloximes followed by oxidation with chloranil. Since β-(3-indolyl) ketones are readily prepared from enones and indoles,[11] this method would provide a convenient method for the synthesis of a variety of α-carbolines.

Experimental

General. ^{1}H NMR (500 MHz) spectra were recorded on Bruker DRX 500 and Bruker AVANCE 500 spectrometers in $CDCl_3$ using chloroform (for ^{1}H, $\delta = 7.24$) as internal standard. ^{13}C NMR (125 MHz) spectra were recorded on Bruker DRX 500 and Bruker AVANCE 500 spectrometers in $CDCl_3$ using chloroform (for ^{13}C, $\delta = 77.0$) as an internal standard. IR spectra were recorded on a Horiba FT 300-S spectrophotometer by the ATR method. High-resolution mass spectra were obtained with a JOEL JMS700P mass spectrometer. The melting points were uncorrected. Elemental analyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, The Univerisity of Tokyo. Flash column chromatography

was performed on Merck silica gel 60N and Kanto Chemical silica gel 60N (spherical, neutral). Preparative thin-layer chromatography was carried out using Wako gel B-5F. Dichloromethane and 1,2-dichloroethane were distilled from phosphorus pentoxide, and then from calcium hydride, and were stored over molecular sieves 4A. Triethylamine and pyridine were distilled from calcium hydride, and stored over potassium carbonate. Pentafluorobenzoyl chloride and *N*,*N*′,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) were purchased from Tokyo Chemical Industry and used after distillation. Indium(III) chloride tetrahydrate was purchased from Kanto Chemical and used as-received. Chloranil was purchased form Tokyo Chemical Industry and used after recrystallization from toluene.

Synthesis of β-(3-Indolyl) Ketone *O*-Pentafluorobenzoyl- and *O*-Methoxycarbonyloximes. The Michael addition of indoles to enones mediated by acetic acid[11a] or catalyzed by indium(III) chloride[11c] gave β-(3-indolyl) ketones, which were converted to *O*-pentafluorobenzoyloximes **3a–h** by treating the corresponding oximes with pentafluorobenzoyl chloride and triethylamine. *O*-Methoxycarbonyloxime **2a** was prepared from the corresponding β-(3-indolyl) ketone oxime by a reaction with methyl chloroformate and excess pyridine.

Spectral Data for β-(3-Indolyl) Ketone *O*-Pentafluorobenzoyloximes.[15] **4-(1-Acetyl-3-indolyl)butan-2-one (*E*)-*O*-Pentafluorobenzoyloxime (3a):** Colorless solid; mp 122–127 °C (dec.) (dichloromethane–hexane); IR (ZnSe) 3116, 2935, 1749, 1704, 1493, 1448, 1383, 1321, 1194, 989, 854, 750 cm^{-1}; ^1H NMR δ 2.06 (3H, s), 2.62 (3H, s), 2.83 (2H, t, $J = 7.3$ Hz), 3.06 (2H, t, $J = 7.3$ Hz), 7.28 (1H, ddd, $J = 8.4$, 7.7, 1.0 Hz), 7.35 (1H, ddd, $J = 8.4$, 7.0, 1.2 Hz), 7.41 (1H, s), 7.51 (1H, dd, $J = 7.7$, 1.2 Hz), 8.42 (1H, dd, $J = 7.0$, 1.0 Hz); ^{13}C NMR δ 16.2, 20.9, 23.9, 35.1, 106.9 (complex), 116.7, 118.4, 120.5, 122.9, 123.4, 125.3, 130.2, 135.8, 137.8 (d complex, $J = 243.2$ Hz), 143.4 (d complex, $J = 260.6$ Hz), 145.4 (d complex, $J = 249.3$ Hz), 156.5, 168.0, 168.6; Anal. Found: C, 57.30; H, 3.67; N, 6.12%. Calcd for $C_{21}H_{15}F_5N_2O_3$: C, 57.54; H, 3.45; N, 6.39%.

4-(1-Methyl-3-indolyl)butan-2-one (*E*)-*O*-Pentafluorobenzoyloxime (3b): White powder; mp 154–156 °C (dec.) (ethyl acetate–hexane); IR (ZnSe) 1751, 1506, 1321, 1198, 991, 854, 771 cm^{-1}; ^1H NMR δ 2.06 (3H, s), 2.78–2.81 (2H, m), 3.06–3.09 (2H, m), 3.74 (3H, s), 6.92 (1H, s), 7.10 (1H, dd, $J = 7.9$, 7.0 Hz), 7.22 (1H, dd, $J = 8.1$, 7.0 Hz), 7.28 (1H, d, $J = 8.2$ Hz), 7.57 (1H, d, $J = 7.9$ Hz); ^{13}C NMR δ 16.1, 21.8, 32.6, 36.5, 107.2 (t, $J = 16.2$ Hz), 109.2, 112.8, 118.6, 118.8, 121.7, 126.5, 127.5, 136.9, 137.7 (d complex, $J = 255.3$ Hz), 143.3 (d complex, $J = 260.2$ Hz), 145.4 (d complex, $J = 256.4$ Hz), 156.6, 168.9; Anal. Found: C, 58.62; H, 3.96; N, 6.65%. Calcd for $C_{20}H_{15}F_5N_2O_3$: C, 58.54; H, 3.68; N, 6.83%.

4-(1-*tert*-Butyldimethylsilyl-3-indolyl)butan-2-one *O*-Pentafluorobenzoyloxime (3c): *E*:*Z* = 3:1 mixture; colorless plates; mp 132–134 °C (dec.) (dichloromethane–hexane); IR (ZnSe) 2929, 1757, 1495, 1452, 1323, 1192, 1138, 995, 837, 810, 788, 739 cm^{-1}; ^1H NMR *E* isomer: δ 0.56 (6H, s), 0.88 (9H, s), 2.05 (3H, s), 2.80–2.83 (2H, m), 3.05–3.08 (2H, m), 7.02 (1H, s), 7.09–7.12 (1H, m), 7.13–7.16 (1H, m), 7.46 (1H, d, $J = 8.0$ Hz), 7.55 (1H, d, $J = 8.0$ Hz); *Z* isomer: δ 0.55 (6H, s), 0.88 (9H, s), 2.04 (3H, s), 2.86 (2H, t, $J = 7.6$ Hz), 2.99 (2H, t, $J = 7.6$ Hz), 6.91 (1H, s), 6.99–7.02 (1H, m), 7.06–7.07 (1H, m), 7.42 (1H, d, $J = 8.3$ Hz), 7.48 (1H, d, $J = 7.1$ Hz); ^{13}C NMR *E* isomer: δ −4.0, 16.0, 19.4, 21.9, 26.2, 35.9, 107.2 (m), 114.0, 116.1, 118.4, 119.4, 121.5, 128.4, 130.5, 137.7 (d complex, $J = 255.3$ Hz), 141.4, 143.2 (d complex, $J = 260.3$ Hz), 145.4 (d complex, $J = 259.3$ Hz), 156.5, 168.8; *Z* isomer: δ −4.1, 19.4, 20.1, 21.6, 26.2, 31.7, 107.2 (m), 114.0, 115.8, 118.2, 119.2, 121.4, 128.1, 130.3, 137.7 (d complex, $J = 255.3$ Hz), 141.5, 143.2 (d complex, $J = 260.3$ Hz), 145.4 (d complex, $J = 259.3$ Hz), 156.3, 169.3; Anal. Found: C, 58.62; H, 5.53; N, 5.28%. Calcd for $C_{25}H_{27}F_5N_2O_2Si$: C, 58.81; H, 5.33; N, 5.49%.

4-(1-*tert*-Butoxycarbonyl-3-indolyl)butan-2-one (*E*)-*O*-Pentafluorobenzoyloxime (3d): Colorless needles; mp 121–137 °C (ethyl acetate–hexane); IR 2983, 1757, 1732, 1651, 1496, 1454, 1373, 1325, 1196, 1159, 1088, 1003, 866 cm^{-1}; ^1H NMR δ 1.65 (9H, s), 2.08 (3H, s), 2.79–2.82 (2H, m), 3.00–3.04 (2H, m), 7.23 (1H, dd, $J = 7.7$, 7.2 Hz), 7.31 (1H, dd, $J = 8.3$, 7.2 Hz), 7.43 (1H, s), 7.51 (1H, d, $J = 7.7$ Hz), 8.12 (1H, d, $J = 8.3$ Hz); ^{13}C NMR δ 16.1, 21.4, 28.0, 35.4, 83.5, 107.0 (m), 115.2, 118.6, 118.9, 122.4, 122.6, 124.4, 130.0, 135.4, 137.6 (d complex, $J = 254.0$ Hz), 143.3 (d complex, $J = 255.8$ Hz), 145.3 (d complex, $J = 258.2$ Hz), 149.6, 156.4, 168.2; Anal. Found: C, 57.96; H, 4.48; N, 5.41%. Calcd for $C_{24}H_{21}F_5N_2O_4$: C, 58.07; H, 4.26; N, 5.64%.

4-(3-Indolyl)butan-2-one *O*-Pentafluorobenzoyloxime (3e): *E*:*Z* = 3:5 mixture; white powder; mp 146–148 °C (dichloromethane–hexane); IR (ZnSe) 3340, 1743, 1496, 1324, 1203, 1003, 744 cm^{-1}; ^1H NMR *E* isomer: δ 2.06 (3H, s), 2.80–2.83 (0.75H, m), 2.87 (1.25H, t, $J = 7.4$ Hz), 3.01 (1.25H, t, $J = 7.4$ Hz), 3.07–3.11 (0.75H, m), 6.96 (0.63H, s), 6.99 (0.63H, dd, $J = 8.2$, 7.1 Hz), 7.07–7.13 (1.37H, m), 7.19 (0.37H, dd, $J = 8.1$, 7.0 Hz), 7.28 (0.63H, d, $J = 8.2$ Hz), 7.36 (0.37H, d, $J = 8.1$ Hz), 7.95 (0.63H, s), 8.00 (0.37H, s); ^{13}C NMR *E* isomer: δ 16.1, 21.9, 36.2, 107.1 (m), 111.2, 114.5, 118.5, 119.4, 121.6, 122.2, 127.1, 136.2, 137.7 (d complex, $J = 247.9$ Hz), 143.2 (d complex, $J = 259.8$ Hz), 145.3 (d complex, $J = 259.3$ Hz), 156.7, 168.9; *Z* isomer: δ 20.1, 21.6, 31.8, 107.1 (m), 111.2, 114.0, 118.3, 119.2, 121.5, 122.1, 126.9, 136.2, 137.7 (d complex, $J = 247.9$ Hz), 143.2 (d complex, $J = 259.8$ Hz), 145.3 (d complex, $J = 259.3$ Hz), 156.4, 169.1; HRMS (FAB^+) Found: *m*/*z* 397.0973, Calcd for $C_{19}H_{14}F_5N_2O_2$: $(M + H)^+$, 397.0975.

4-(1-Acetyl-3-indolyl)-3-methylbutan-2-one (*E*)-*O*-Pentafluorobenzoyloxime (3f): Colorless solid; mp 131–134 °C (dec.) (dichloromethane–hexane); IR (ZnSe) 2974, 2935, 1753, 1701, 1496, 1450, 1387, 1325, 1192, 1001, 862, 748 cm^{-1}; ^1H NMR δ 1.29 (3H, d, $J = 6.7$ Hz), 1.98 (3H, s), 2.61 (3H, s), 2.83 (1H, dd, $J = 14.7$, 6.0 Hz), 3.03–3.11 (2H, m), 7.27 (1H, dd, $J = 7.9$, 7.3 Hz), 7.34 (1H, dd, $J = 8.1$, 7.3 Hz), 7.43 (1H, s), 7.49 (1H, d, $J = 7.9$ Hz), 8.42 (1H, d, $J = 8.1$ Hz); ^{13}C NMR δ 13.5, 18.3, 23.9, 28.7, 39.6, 107.0 (m), 116.8, 118.5, 119.3, 123.4, 123.7, 125.3, 130.5, 135.7, 137.7 (d complex, $J = 258.3$ Hz), 143.3 (d complex, $J = 260.7$ Hz), 145.4 (d complex, $J = 254.4$ Hz), 156.6, 168.7, 171.7; Anal. Found: C, 58.33; H, 3.98; N, 6.03%. Calcd for $C_{22}H_{17}F_5N_2O_3$: C, 58.41; H, 3.79; N, 6.19%.

***tert*-Butyl 2-(1-Acetyl-3-indolyl)-4-(*O*-pentafluorobenzoyloxyimino)pentanoate (3g):** *E*:*Z* = 3:2 mixture; colorless oil; IR (ZnSe) 2979, 1759, 1712, 1496, 1450, 1325, 1196, 1146, 1003 cm^{-1}; ^1H NMR *E* isomer: δ 1.39 (3H, s), 2.02 (3H, s), 2.63 (3H, s), 2.90 (1H, dd, $J = 16.2$, 6.7 Hz), 3.20 (1H, dd, $J = 16.2$, 8.4 Hz), 4.29 (1H, dd, $J = 8.4$, 6.7 Hz), 7.27 (1H, dd, $J = 7.7$, 7.2 Hz), 7.34 (1H, dd, $J = 8.3$, 7.2 Hz), 7.47 (1H, s), 7.62 (1H, d, $J = 7.7$ Hz), 8.43 (1H, d, $J = 8.3$ Hz); *Z* isomer: δ 1.37 (3H, s), 2.02 (3H, s), 2.60 (3H, s), 3.12 (1H, dd, $J = 13.7$, 8.3 Hz), 3.16 (1H, dd, $J = 13.7$, 7.2 Hz), 4.03 (1H, dd, $J = 8.3$, 7.2 Hz), 7.18 (1H, dd, $J = 8.1$, 7.1 Hz), 7.28 (1H, dd, $J = 7.8$, 7.1 Hz), 7.32 (1H, s), 7.53 (1H, d, $J = 7.8$ Hz), 8.36 (1H, d, $J = 8.1$ Hz); ^{13}C NMR *E* isomer: δ 16.8, 23.9, 27.8, 38.0, 39.9, 82.0,

107.0 (m), 116.8, 119.1, 119.2, 123.6, 123.7, 125.5, 129.0, 135.9, 137.7 (d complex, $J = 259.3$ Hz), 143.4 (d complex, $J = 252.1$ Hz), 145.4 (d complex, $J = 258.2$ Hz), 156.2, 166.3, 168.7, 171.4; *Z* isomer: δ 20.6, 23.9, 33.4, 40.6, 82.4, 107.0 (m), 116.7, 118.8, 119.0, 123.0, 123.4, 125.6, 128.6, 135.9, 137.7 (d complex, $J = 259.3$ Hz), 143.4 (d complex, $J = 252.1$ Hz), 145.4 (d complex, $J = 258.2$ Hz), 156.2, 167.0, 168.3, 171.1; HRMS (FAB$^+$) Found: m/z 539.1592, Calcd for $C_{26}H_{24}F_5N_2O_5$: $(M + H)^+$, 539.1605.

2-[(1-Acetyl-3-indolyl)methyl]cyclohexanone (*E*)-*O*-Pentafluorobenzoyloxime (3h): Colorless powder; mp 138–142 °C (dec.) (dichloromethane–petroleum ether); IR 2939, 2862, 1753, 1705, 1523, 1497, 1450, 1387, 1327, 1198, 1003, 750 cm^{-1}; ^{1}H NMR δ 1.49–1.61 (3H, m), 1.81–1.86 (2H, m), 2.03–2.06 (1H, m), 2.10–2.15 (1H, m), 2.64 (3H, s), 2.75–2.81 (1H, m), 2.83–2.87 (1H, m), 2.97–3.01 (1H, m), 3.24–3.29 (1H, m), 7.27 (1H, dd, $J = 7.7$, 7.1 Hz), 7.33 (1H, dd, $J = 8.3$, 7.1 Hz), 7.49 (1H, d, $J = 7.7$ Hz), 7.60 (1H, s), 8.43 (1H, d, $J = 8.3$ Hz); ^{13}C NMR δ 23.7, 24.1, 25.8, 26.5, 27.0, 33.6, 43.1, 107.2 (m), 116.8, 118.4, 119.5, 123.3, 124.9, 125.0, 130.9, 135.7, 137.8 (d complex, $J = 243.1$ Hz), 143.3 (d complex, $J = 253.5$ Hz), 145.4 (d complex, $J = 257.2$ Hz), 156.9, 169.0, 172.2.

4-(1-Acetyl-3-indolyl)butan-2-one (*E*)-*O*-Methoxycarbonyloxime (2a): Colorless powder; mp 92–94 °C (dec.) (dichloromethane–hexane); IR 3012, 2956, 1770, 1699, 1450, 1387, 1333, 1234, 883, 750 cm^{-1}; ^{1}H NMR δ 2.01 (3H, s), 2.60 (3H, s), 2.75 (2H, dd, $J = 7.9$, 7.2 Hz), 2.99 (2H, dd, $J = 7.9$, 7.2 Hz), 3.87 (3H, s), 7.27 (1H, dd, $J = 7.6$, 7.5 Hz), 7.34 (1H, dd, $J = 7.7$, 7.6 Hz), 7.36 (1H, s), 7.49 (1H, d, $J = 7.5$ Hz), 8.41 (1H, d, $J = 7.7$ Hz); ^{13}C NMR δ 15.3, 21.0, 23.8, 34.8, 55.0, 116.6, 118.4, 120.6, 122.6, 123.3, 125.2, 130.1, 135.7, 154.4, 165.3, 168.5; Anal. Found: C, 63.57; H, 6.06; N, 9.11%. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27%.

Synthesis of α-Carbolines by the Copper-Catalyzed Radical Cyclization of β-(3-Indolyl) Ketone *O*-Pentafluorobenzoyloximes. The experimental procedure is shown below as a typical example for the synthesis of *tert*-butyl 9-acetyl-2-methyl-9*H*-pyrido[2,3-*b*]indole-4-carboxylate (**5g**) (Table 3, Entry 3).

Copper powder (2.7 mg, 0.0425 mmol) and *N*,*N*′,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) (0.058 mL, 0.278 mmol) were warmed up to 80 °C in 1,2-dichloroethane (7 mL). After 5 min, a solution of *tert*-butyl 2-(1-acetyl-3-indolyl)-4-(*O*-pentafluorobenzoyloxyimino)pentanoate (**3g**) (148.6 mg, 0.276 mmol) in 1,2-dichloroethane (7 mL) was added in one-portion and the reaction mixture was vigorously stirred at the same temperature. The mixture was extracted 3 times with dichloromethane 5 min after quenching the reaction with brine and *N*,*N*,*N*′,*N*′-tetramethylpentanediamine (1 mL). The combined extracts were washed with water and brine and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded crude 3,4-dihydro-α-carboline, which was dissolved with dichloromethane (5 mL) and treated with chloranil (68.1 mg, 0.277 mmol) for 1 h. Solvent was removed again and the crude product was purified by thin-layer chromatography (Wako gel B-5F, ethyl acetate:hexanes = 1:3) to give *tert*-butyl 9-acetyl-2-methyl-9*H*-pyrido[2,3-*b*]indole-4-carboxylate (**5g**) (60.4 mg, 67%).

Spectral Data for α-Carbolines. 9-Acetyl-2-methyl-9*H*-pyrido[2,3-*b*]indole[16a] **(5a):** Colorless solid; IR (ZnSe) 3039, 2925, 1689, 1587, 1450, 1371, 1309, 1180, 1014, 779, 748, 734 cm^{-1}; ^{1}H NMR δ 2.64 (3H, s), 3.12 (3H, s), 7.13 (1H, d, $J = 7.8$ Hz), 7.34–7.37 (1H, m), 7.46–7.49 (1H, m), 7.86 (1H, d, $J = 7.7$ Hz), 8.07 (1H, d, $J = 7.8$ Hz), 8.67 (1H, d, $J = 8.4$ Hz); ^{13}C NMR δ 24.7, 28.0, 116.3, 117.7, 118.4, 119.5, 123.0, 123.8, 127.8, 128.2, 138.0, 150.9, 155.5, 171.6.

2,9-Dimethyl-9*H*-pyrido[2,3-*b*]indole[16b] **(5b):** Pale-yellow oil; IR (ZnSe) 3051, 2922, 1591, 1576, 1474, 1435, 1402, 1227, 1124, 779, 733 cm^{-1}; ^{1}H NMR δ 2.70 (3H, s), 3.93 (3H, s), 7.01 (1H, d, $J = 7.8$ Hz), 7.25 (1H, dd, $J = 7.8$, 7.1 Hz), 7.42 (1H, d, $J = 8.1$ Hz), 7.48 (1H, dd, $J = 8.1$, 7.1 Hz), 8.01 (1H, d, $J = 7.8$ Hz), 8.18 (1H, d, $J = 7.8$ Hz); ^{13}C NMR δ 24.9, 27.5, 108.9, 113.1, 114.7, 119.5, 120.5, 120.5, 125.9, 128.2, 140.0, 151.8, 154.4.

9-*tert*-Butyldimethylsilyl-2-methyl-9*H*-pyrido[2,3-*b*]indole (5c): Pale-yellow oil; IR (ZnSe) 2952, 2925, 2856, 1589, 1452, 1392, 1296, 1252, 1215, 1194, 825 cm^{-1}; ^{1}H NMR δ 0.77 (6H, s), 0.98 (9H, s), 2.59 (3H, s), 6.97 (1H, d, $J = 7.8$ Hz), 7.20 (1H, t, $J = 7.4$ Hz), 7.34 (1H, dd, $J = 8.3$, 7.4 Hz), 7.60 (1H, d, $J = 8.3$ Hz), 8.10 (1H, d, $J = 7.8$ Hz); ^{13}C NMR δ −1.5, 20.1, 24.7, 26.9, 113.9, 114.9, 114.9, 119.7, 120.1, 124.3, 125.4, 127.3, 143.7, 154.5, 157.7; HRMS (FAB$^+$) Found: m/z 297.1810, Calcd for $C_{18}H_{25}N_2Si$: $(M + H)^+$, 297.1787.

***tert*-Butyl 9-Acetyl-2-methyl-9*H*-pyrido[2,3-*b*]indole-9-carboxylate (5d):** Colorless oil; IR (ZnSe) 3053, 2979, 2929, 1720, 1456, 1392, 1333, 1252, 1153, 1119, 781 cm^{-1}; ^{1}H NMR δ 1.75 (9H, s), 2.72 (3H, s), 7.16 (1H, d, $J = 7.8$ Hz), 7.34 (1H, dd, $J = 7.7$, 7.2 Hz), 7.46 (1H, dd, $J = 8.5$, 7.2 Hz), 7.91 (1H, d, $J = 7.7$ Hz), 8.11 (1H, d, $J = 7.8$ Hz), 8.23 (1H, d, $J = 8.5$ Hz); ^{13}C NMR δ 25.2, 28.4, 84.0, 116.0, 116.2, 118.4, 119.8, 122.8, 123.1, 127.2, 128.0, 137.5, 149.8, 151.4, 156.7; HRMS (FAB$^+$) Found: m/z 283.1443, Calcd for $C_{17}H_{29}N_2O_2$: $(M + H)^+$, 283.1446.

2-Methyl-9*H*-pyrido[2,3-*b*]indole[16c] **(5e):** Pale-yellow solid; IR (ZnSe) 3136, 3080, 2966, 1603, 1583, 1458, 1417, 1338, 1274, 1223, 733 cm^{-1}; ^{1}H NMR δ 2.73 (3H, s), 7.06 (1H, d, $J = 7.8$ Hz), 7.24 (1H, dd, $J = 8.1$, 7.5 Hz), 7.43 (1H, dd, $J = 7.8$, 7.5 Hz), 7.49 (1H, d, $J = 8.1$ Hz), 8.00 (1H, d, $J = 7.8$ Hz), 8.21 (1H, d, $J = 7.8$ Hz), 9.53 (1H, s); ^{13}C NMR δ 24.5, 111.1, 113.9, 115.1, 119.9, 120.6, 121.2, 126.3, 128.6, 138.4, 151.9, 155.0.

9-Acetyl-2,3-dimethyl-9*H*-pyrido[2,3-*b*]indole (5f): Colorless needles; mp 130–131 °C (dichloromethane–hexane); IR (ZnSe) 2993, 2922, 1693, 1402, 1367, 1313, 1188, 750 cm^{-1}; ^{1}H NMR δ 2.05 (3H, s), 2.59 (3H, s), 3.13 (3H, s), 7.35 (1H, ddd, $J = 7.7$, 7.3, 1.0 Hz), 7.47 (1H, ddd, $J = 8.4$, 7.3, 1.3 Hz), 7.86 (1H, ddd, $J = 7.7$, 1.3, 0.6 Hz), 7.99 (1H, s), 8.68 (1H, ddd, $J = 8.4$, 1.0, 0.6 Hz); ^{13}C NMR δ 19.2, 23.1, 27.8, 116.8, 117.6, 119.4, 123.0, 123.7, 126.5, 127.6, 128.8, 138.0, 149.2, 154.1, 171.5; Anal. Found: C, 75.37; H, 6.03; N, 11.57%. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%.

***tert*-Butyl 9-Acetyl-2-methyl-9*H*-pyrido[2,3-*b*]indole-4-carboxylate (5g):** Colorless needles; mp 148 °C (dichloromethane–hexane); IR (ZnSe) 2981, 2933, 1722, 1697, 1589, 1450, 1365, 1313, 1244, 1149, 1090, 1018, 764 cm^{-1}; ^{1}H NMR δ 1.69 (9H, s), 2.69 (3H, s), 3.13 (3H, s), 7.36–7.39 (1H, m), 7.47 (1H, s), 7.51–7.54 (1H, m), 8.58 (1H, d, $J = 8.0$ Hz), 8.73 (1H, d, $J = 8.3$ Hz); ^{13}C NMR δ 24.4, 28.2, 28.5, 82.9, 114.0, 116.8, 118.4, 121.7, 123.8, 124.4, 128.5, 134.9, 138.6, 151.8, 154.9, 165.5, 171.5; Anal. Found: C, 70.22; H, 6.18; N, 8.48%. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64%.

6-Acetyl-1,2,3,4-tetrahydro-6*H*-indolo[2,3-*b*]quinoline (5h): Colorless needles; mp 147–148 °C (dichloromethane–hexane); IR 3006, 2935, 1682, 1577, 1375, 1319, 1232, 746 cm^{-1}; ^{1}H NMR δ 1.85–1.89 (2H, m), 1.92–1.96 (2H, m), 2.91 (2H, t, $J = 6.3$ Hz), 3.01 (2H, t, $J = 6.3$ Hz), 3.11 (3H, s), 7.34 (1H, dd, $J = 7.7$, 7.3

Hz), 7.46 (1H, dd, $J = 8.3$, 7.3 Hz), 7.85 (1H, d, $J = 7.7$ Hz), 8.67 (1H, d, $J = 8.3$ Hz); ^{13}C NMR δ 23.0, 23.1, 27.8, 28.9, 33.1, 116.9, 117.6, 119.5, 123.1, 123.7, 127.4, 127.7, 128.4, 138.3, 149.4, 154.5, 171.5; Anal. Found: C, 77.14; H, 6.10; N, 10.39%. Calcd for $C_{19}H_{20}N_2O_3$: C, 77.25; H, 6.10; N, 10.60%.

This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" and a Grant-in-Aid for The 21st Century COE Program for Frontiers in Fundamental Chemistry from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

1 a) C. Moquin-Pattey and M. Guyot, *Tetrahedron Lett.*, **45**, 3445 (1989). b) A. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut, and C. Francisco, *J. Nat. Prod.*, **57**, 528 (1994). c) T. P. Blackburn, D. Bolton, I. T. Forbes, C. N. Johnson, R. T. Martin, D. R. Thomas, M. Thompson, and N. Upton, *Bioorg. Med. Chem. Lett.*, **4**, 279 (1994). d) S. A. Abas, M. Bilaijet Hossain, D. van der Helm, and F. J. Schmitz, *J. Org. Chem.*, **61**, 2709 (1996).

2 a) D. Bolton, I. T. Forbes, C. J. Hayward, D. C. Piper, D. R. Thomas, M. Thompson, and N. Upton, *Bioorg. Med. Chem. Lett.*, **3**, 1941 (1993). b) J.-S. Kin, K. Shin-ya, K. Furihata, Y. Hayakawa, and H. Seto, *Tetrahedron Lett.*, **38**, 3431 (1997).

3 A review article for the preparation of α-carbolines: A. A. Sememov and V. V. Tolstikhina, *Chem. Heterocycl. Compd.*, **1984**, 345.

4 a) P. Rocca, F. Marsais, A. Godard, and G. Queguiner, *Tetrahedron*, **49**, 49 (1993). b) S. Achab, M. Guyot, and P. Potier, *Tetrahedron Lett.*, **34**, 2127 (1993). c) S. Achab, M. Guyot, and P. Potier, *Tetrahedron Lett.*, **36**, 2615 (1995).

5 a) R. S. Sagitullin, N. N. Modyanov, A. N. Kost, and N. A. Modyanov, *Chem. Heterocycl. Compd.*, **1971**, 58. b) I. T. Forbes, C. N. Johnson, and M. Thompson, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 275. c) V. Levacher, N. Boussad, G. Dupas, J. Bourguignon, and G. Queguiner, *Tetrahedron*, **48**, 831 (1992). d) T. Chosi, S. Yamada, E. Sugino, T. Kuwada, and S. Hibino, *J. Org. Chem.*, **60**, 5899 (1995). e) M. Mayer and M. Guyot, *Tetrahedron Lett.*, **37**, 4931 (1996). f) P. Molina, P. M. Fresneda, and M. A. Sanz, *Tetrahedron Lett.*, **38**, 6909 (1997). g) P. Molina, P. M. Fresneda, M. A. Sanz, C. Foces-Foces, and M. Carmen Ramirez de Arellano, *Tetrahedron*, **54**, 9623 (1998).

6 With a few exceptions, 2-aminoindoles are reported to be unstable. See: A. Tahri, K. J. Buysens, E. V. van der Eychen, D. M. Vandenberghe, and G. J. Hoornaert, *Tetrahedron*, **54**, 13211 (1998).

7 a) A. Abouabdellah and R. H. Dodd, *Tetrahedron Lett.*, **39**, 2119 (1998). b) O. Barum, P. K. Patra, H. Ila, and H. Junjappa, *Tetrahedron Lett.*, **40**, 3797 (1999). c) E. M. Beccalli, F. Clerici, and A. Marchesini, *Tetrahedron*, **57**, 4787 (2001). d) G. S. M. Sundaram, C. Venkatesh, U. K. Syam Kumar, H. Ila, and H. Junjappa, *J. Org. Chem.*, **69**, 5760 (2004).

8 For the direct amination of indole ring at the 2-position. See: a) G. T. Bourne, D. Crich, J. W. Davies, and D. C. Horwell, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1693. b) M. Somei, A. Tanimoto, H. Orita, F. Yamada, O. Fumio, and T. Ohta, *Heterocycles*, **54**, 425 (2001).

9 a) K. Uchiyama, Y. Hayashi, and K. Narasaka, *Synlett*, **1997**, 445. b) A. Ono, K. Uchiyama, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, **1998**, 437. c) K. Uchiyama, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, **1998**, 1261. d) K. Uchiyama, A. Ono, Y. Hayashi, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **71**, 2945 (1998). e) A. Ono and K. Narasaka, *Chem. Lett.*, **2001**, 146. f) Y. Koganemaru, K. Kitamura, and K. Narasaka, *Chem. Lett.*, **2002**, 784.

10 Example of the radical cyclization to the indolyl moiety at the 2-position: F. E. Ziegler and L. O. Jeroncic, *J. Org. Chem.*, **56**, 3479 (1991).

11 a) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957). b) K. B. Jensen, J. Thorhauge, R. G. Hazell, and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, **40**, 160 (2001). c) J. S. Yadav, S. Abraham, B. V. S. Reddy, and G. Sabitha, *Synthesis*, **2001**, 2165. d) M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, and A. Umani-Ronchi, *J. Org. Chem.*, **67**, 3700 (2002). e) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, and J. Wu, *J. Am. Chem. Soc.*, **125**, 10780 (2003).

12 a) H. Nagashima, K. Ara, H. Wakamatsu, and K. Itoh, *Chem. Commun.*, **1985**, 518. b) H. Nagashima, N. Ozaki, K. Seki, M. Ishii, and K. Itoh, *J. Org. Chem.*, **54**, 4497 (1989). c) H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama, and K. Itoh, *J. Org. Chem.*, **58**, 464 (1993). d) M. Benedetti, L. Forti, F. Ghelfi, U. M. Pagnoni, and R. Ronzoni, *Tetrahedron*, **53**, 14031 (1997). e) S. Iwamatsu, H. Kondo, K. Matsubara, and H. Nagashima, *Tetrahedron*, **55**, 1687 (1999). f) S. Iwamatsu, K. Matsubara, and H. Nagashima, *J. Org. Chem.*, **64**, 9625 (1999). g) A. J. Clark, F. De Campo, R. J. Deeth, R. P. Filik, S. Gatard, and N. A. Hunt, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 671.

13 For the isolation and biological activities of cryptotackiene, see: a) J.-L. Pousset, M.-T. Martin, A. Jossang, and B. Bodo, *Phytochemistry*, **39**, 735 (1995). b) M. H. M. Sharaf, P. L. Schiff, Jr., A. N. Tackie, C. H. Phoebe, Jr., and G. E. Martin, *J. Heterocycl. Chem.*, **33**, 239 (1996). c) K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys, and A. Vlietnck, *Tetrahedron Lett.*, **37**, 1703 (1996). d) K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys, and A. Vlietnck, *J. Nat. Prod.*, **60**, 688 (1997).

14 For the total synthesis of cryptotackiene, see: a) W. Peczynska-Czoch, F. Pognan, L. Kaczmarek, and J. Boratynski, *J. Med. Chem.*, **37**, 3503 (1994). b) M. Alajarin, P. Molina, and A. Vidal, *J. Nat. Prod.*, **60**, 747 (1997). c) G. Timari, T. Soos, and G. Hajos, *Synlett*, **1997**, 1067. d) P. Molina, P. M. Fresneda, and S. Delgado, *Synthesis*, **1999**, 326. e) C. Shi, Q. Zhang, and K. K. Wang, *J. Org. Chem.*, **64**, 925 (1999).

15 Four ^{13}C NMR peaks of the C_6F_5 moiety were split by C–F couplings, which include geminal and vicinal couplings.

16 a) L. Stephenson and W. K. Warburton, *J. Chem. Soc. C*, **1970**, 1355. b) P. I. Abramenko, *Zh. Vses. Khim. Ova. im. D. I. Mendeleeva*, **18**, 715 (1973). c) P. A. Sharbatyan, A. N. Kost, V. V. Men'shikov, L. G. Yudin, and N. B. Chernyshova, *Heterocycl. Compd.*, **1980**, 926.