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Ir-Catalyzed Reverse Prenylation of 3-Substituted Indoles: Total Synthesis of (+)-Aszonalenin and (−)-Brevicompanine B

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Supporting Information

ABSTRACT: The selective reverse prenylation of 3-substituted-1*H*-indoles at C3 is described. The iridium-catalyzed reaction proceeds with high branched to linear selectivity (>20:1) for a variety of indoles. In addition, a diastereoselective reverse prenylation of tryptophan methyl ester is disclosed, and its synthetic utility is demonstrated in the synthesis of (+)-aszonalenin and (−)-brevicompanine B.

Prenylated indole alkaloids from fungi, bryozoans, and cyanobacteria are an important class of natural products encompassing a wide array of unusual structures that display a diverse range of biological activities.[1] A subset of this class of natural products includes hexahydropyrrolo[2,3-*b*]indoles with an embedded 1-(1,1-dimethylallyl) substituent at an indoline C3 quaternary center. The introduction of this characteristic substitution pattern has been referred to as "reverse prenylation" as a means of differentiating it from the less common isomeric prenylation involving the installation of 1-(3,3-dimethylallyl) substituents. The embedded substructures bearing reversed prenyl groups present several key challenges to the design of synthetic strategies en route to the attendant complex natural products. Accordingly, reverse prenylation at a substituted indole carbon must contend with problems involving (1) reactivity, leading to the formation of two vicinal quaternary centers, (2) regioselectivity in the reaction of the dimethyl allyl fragment, divergently leading to prenyl versus reverse prenylation, (3) chemoselectivity, or site selectivity, at the indole, which may furnish N- versus C-isomers, and (4) stereoselectivity of the transformation. The identification of general catalytic methods for reverse prenylation would provide fresh new strategies for the synthesis of a number of biologically active, natural product targets. Herein, we report a catalytic method for the C3 reverse prenylation of 3-substituted indoles that employs tertiary carbonate **2** and a catalyst generated from a simple phosphoramidite ligand and [{Ir(cod)Cl}$_2$] (Figure 1). The reaction furnishes adducts **3** displaying high regiocontrol (reverse (branched) versus normal (linear) prenylation selectivity b/l > 20:1), chemoselectivity for the indole C3, and diastereocontrol in the course of installing two vicinal quaternary centers. Additionally, we also document the implementation of the method in the total synthesis of (+)-aszonalenin and (−)-brevicompanine B.

Metal-catalyzed reverse prenylation of oxindoles,[2a] isatins,[2b] and C3 unsubstituted indoles[2c−f] has been reported under a variety of conditions. These can involve the use of electrophilic and nucleophilic dimethyl allyl fragments. Additionally, a large number of substitution reactions of 3-substituted indoles have been described involving simple allyl or monosubstituted allyl fragments and benzylations.[3] However, to the best of our knowledge, general methods for the one-step reverse prenylation of 3-substituted indoles at C3 have not been described previously.[4] Of additional importance, iridium-catalyzed allylations to access products with vicinal quaternary centers is unprecedented.[5]

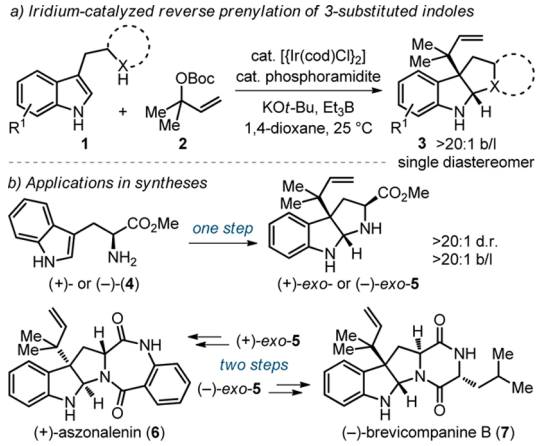

Figure 1. (a) Ir-catalyzed, reverse prenylation of 3-substituted indoles and (b) applications in syntheses.

We began our methodological investigations with N-protected tryptamine **1a** as substrate, (Boc)-carbonate **2** as the prenyl source, and a catalyst generated *in situ* from simple phosphoramidite ligands and [{Ir(cod)Cl}$_2$].[6] The fluoride in **1a** simplifies analysis during the screening and optimization phase of the investigations because of the use of ^{19}F NMR spectroscopy. The formation of reverse prenylated adduct **3a** was only observed when the reaction was conducted with KO*t*-Bu and Et$_3$B as additives, which serve to activate the indole through the generation of the N-borylated intermediate.[7]

Examination of various carbonates and phosphoramidite ligands (see Supporting Information for details) revealed **8**[8] as the optimal ligand, with the reaction reaching full conversion in 1 h at ambient temperature with 0.5 equiv of Et$_3$B and KO*t*-Bu. Chiral ligands were also examined, however while good conversion and regioselectivity was observed with various phosphoramidite ligands, the chiral induction was found to be

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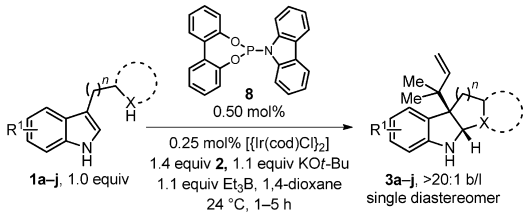
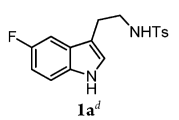
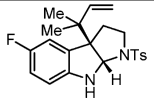
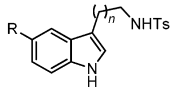
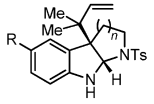
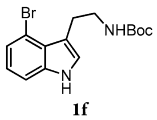
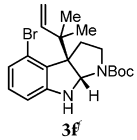
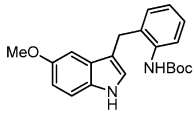
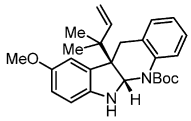
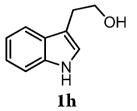
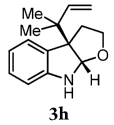
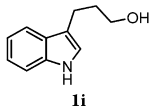
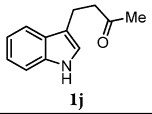
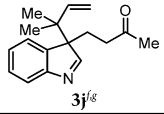
low (<20% ee) with both a 1:1 and 2:1 ligand to metal ratio. Furthermore, the use of more sterically hindered alkylboranes did not increase the observed enantioselectivity.

The scope of reverse prenylation of 3-substituted-1*H*-indoles was then examined (Table 1). The use of 0.5 equiv each of Et_3B and KO*t*-Bu was sufficient for tryptamine derived sulfonamides **1a,b,d,e**; however, a full equivalent of each was needed for **1c,f–j** in order to achieve good levels of conversion. Both electron-rich and electron-deficient 5-substituted indoles were well tolerated (**1b–e**). A 4-substituted indole (**1f**) could be used as substrate without impairing the *b*/*l* selectivity. The formation of other *cis*-5,5- or *cis*-5,6-heterocycles was readily achieved from the corresponding 3-substituted indoles **1g–i**. For the synthesis of **3c**, the cyclization of the indole imine intermediate is facilitated by the addition of ethanolamine, which we hypothesize is functioning as an amphoteric mediator, namely both as a mild Brønsted acid and base. In the absence of a pendant nucleophile in the substrate, the indole imine is isolated as product, as demonstrated by the formation of **3j**.[9]

Table 1. Reverse Prenylation of 3-Substituted-1*H*-Indoles[a,b,c]

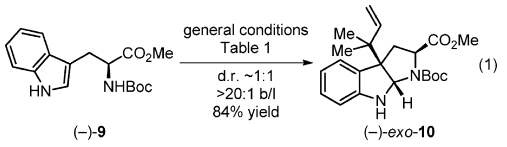


substrate	product	yield
 **1a**[d]	 **3a**	92%
 **1b**[d] R = H, n = 1 **1c** R = H, n = 2 **1d**[d] R = Br, n = 1 **1e**[d] R = OMe, n = 1	 **3b** R = H, n = 1 **3c**[e] R = H, n = 2 **3d** R = Br, n = 1 **3e** R = OMe, n = 1	95% 79% 93% 93%
 **1f**	 **3f**[f]	90%
 **1g**	 **3g**	88%
 **1h**	 **3h**	72%
 **1i**	 **3i**	62%
 **1j**	 **3j**[f,g]	88%

[a]Standard procedure: **1a–j** (1.0 mmol, 1.0 equiv), **8** (0.50 mol%), [{Ir(cod)Cl}$_2$] (0.25 mol%), KO*t*-Bu (1.1 equiv), Et_3B (1.1 equiv), **2** (1.4 equiv), 1,4-dioxane, 24 °C, 1–5 h. [b]Yields of purified products. [c]Branched to linear selectivity determined by ^{1}H NMR analysis of the unpurified reaction mixture. [d]0.50 equiv KO*t*-Bu and 0.50 equiv Et_3B. [e]After 2 h ethanolamine (2.0 equiv) was added, and the reaction was stirred 1 h at 24 °C. [f]1.0 mol% [{Ir(cod)Cl}$_2$] and 2.0 mol% **8**. [g]Reaction conducted at 50 °C.

Notable features of the reaction include low catalyst loading (0.5 mol%) and >20:1 *b*/*l* selectivity for all products as determined by ^{1}H NMR analysis of the unpurified reaction mixture. The reaction proceeds with high site selectivity at C3 of the indole, and accordingly, in all cases, no N-prenylated products were observed. In line with previous reports, 7-substituted-1*H*-indoles are not suitable substrates when trialkylboranes are used to activate the indole.[3a,d,7a]

In the various total syntheses that have been reported of natural products incorporating reverse prenyl groups at a substituted indoline C3, introduction of the reverse prenyl group has been implemented through multistep processes.[10] For example, a common strategy involves oxidative cyclization of a tryptophan derivative with halogen or selenium reagents and subsequent reverse prenylation with an organotin reagent.[11] Because of our interest in applying the Ir-catalyzed reverse prenylation method described above to the synthesis of complex targets, we then examined whether the reaction could be carried out with relative stereocontrol, commencing with tryptophan derivatives.[12] In the reaction of N-Boc protected tryptophan methyl ester under the reaction conditions described in Table 1, the corresponding pyrroloindole **10** could be isolated, albeit with no diastereocontrol (~1:1) as shown in eq 1:



The use of tryptophan (free) amino ester **4** as substrate[13] in a reaction gave product **5** in 50% yield and low diastereoselectivity (*exo*/*endo* 1.3:1). However, the replacement of Et_3B with 9-BBN-*n*C_6H_{13}[3a] led to considerable improvement with the reaction proceeding with increased diastereoselectivity (*exo*/*endo* > 20:1). The yield could be improved by replacing KO*t*-Bu with KHMDS and conducting the reaction at 0 °C, whereupon hexahydropyrrolo[2,3-*b*]indole (−)-*exo*-**5** was isolated from tryptophan methyl ester (−)-**4** in 58% yield and >20:1 d.r. (Scheme 1). Importantly, no racemization was detected over the course of the reaction, as determined by SFC analysis and comparison to an authentic racemic mixture.

Hexahydropyrrolo[2,3-*b*]indole (−)-*exo*-**5** has been previously employed for the syntheses of various ardeemins and amauromine alkoids.[11a–c] As such, its synthesis can be considered formal synthesis of these two alkaloids. However, in order to convincingly illustrate the utility of intermediate *exo*-**5**, short syntheses of two other indole alkaloids with diverse biological activity were crafted (Scheme 2). Aszonalenin **6**[14] and its derivatives display remarkable activity as substance P inhibitors for the human neurokinin-1 receptor. Brevicompa-

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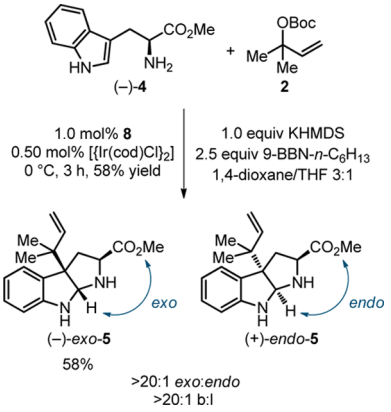
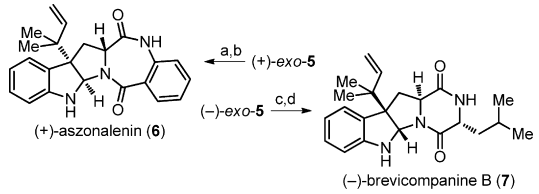
Scheme 1. Ir-Catalyzed, Reverse Prenylation of Tryptophan Methyl Ester



Scheme 2. Synthesis of (+)-Aszonalenin and (−)-Brevicompanine B[a]



[a]Reagents and conditions: (a) 2-aminobenzoic acid (1.4 equiv), Et_3N (2.0 equiv), HATU (1.4 equiv), CH_2Cl_2 25 °C, 30 h; (b) $AlMe_3$ (4.0 equiv), toluene, 0 °C, 1 h, 85% (two steps); (c) (*R*)-Fmoc-Leu (1.5 equiv), Et_3N (2.0 equiv), HATU (1.1 equiv), CH_2Cl_2, 0 to 19 °C, 19 h, 82%; (d) Et_2NH (35 equiv), THF, 0 to 22 °C, 14 h, 83%. HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate.

nine B[15] is a plant growth regulator isolated from *Penicillium brevicompactum*. (+)-Aszonalenin was accessed in two steps from (+)-*exo*-**5** by coupling with 2-aminobenzoic acid and subsequent treatment with $AlMe_3$. The natural product was obtained as single diastereomer, and the structure was confirmed by X-ray crystallographic analysis. In a parallel approach, (−)-brevicompanine B[15a] was readily obtained by coupling (−)-*exo*-**5** to (*R*)-Fmoc-Leu, followed by deprotection and cyclization. The synthesis of **7** we have described is effected in three steps from commercially available (*S*)-tryptophan methyl ester (39% overall yield), which compares favorably to the only synthesis reported so far (9 steps, 11% overall yield).[15b]

In summary, we have developed the first method for direct, C3 selective, reverse prenylation of 3-substituted indoles. The reaction employs a readily accessible Ir-catalyst and a simple carbonate as precursor for the prenyl group with a variety of 3-substituted-1*H*-indoles as substrates. All products are obtained in good regioselectivity (>20:1), involving the formation of vicinal quaternary centers. The diastereoselective reaction with tryptophan methyl ester enables access to a versatile hexahydropyrrolo[2,3-*b*]indole intermediate, which we employ as precursor for the stereoselective synthesis of two bioactive natural products, aszonalenin, and brevicompanine B. Interestingly, the Ir-catalyzed cyclization reactions of these systems were observed to work best with the free (unprotected) amine. The same intermediate and its derivatives are expected to be useful for the streamlined synthesis of other C3 reverse prenylated indole alkaloids. In a broader context, an additional salient and important feature of the method described is that it represents the first use of Ir-catalysis to effect reverse prenylation of C3 substituted indoles. This significantly expands the reaction scope of Ir-catalyzed allylations and suggests additional avenues for investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on the structures and biosynthesis of prenylated indoles, see: (a) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57. (b) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97. For a review of methods of prenylation and reverse prenylation, see (c) Lindel, T.; Marsch, N.; Adla, S. K. *Top. Curr. Chem.* **2012**, *309*, 67.

(2) For enantioselective, reverse prenylation of oxindoles, see: (a) Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328. For enantioselective, reverse prenylation of isatins, see: (b) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. For selected examples of one-step C3 reverse prenylation of C3 unsubstituted indoles, see: (c) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (d) Usui, L.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207. (e) Gruber, S.; Zaitsev, A. B.; Woerle, M.; Pregosin, P. S.; Veiros, L. F. *Organometallics* **2008**, *27*, 3796. (f) Sundararaju, B.; Achard, M.; Demerseman, B.; Toupet, L.; Sharma, G. V. M; Bruneau, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2782.

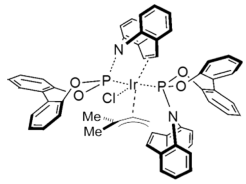
(3) For selected enantioselective allylations, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) Liu, Y.; Du, H. *Org. Lett.* **2013**, *15*, 740. (c) Zhang, X.; Han, L.; You, S.-L. *Chem. Sci.* **2014**, *5*, 1059. (d) Kaiser, T. M.; Yang, J. *Eur. J. Org. Chem.* **2013**, 3983. For selected racemic benzylation and allylations, see: (e) Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140. (f) Zhang, X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Org. Lett.* **2013**, *15*, 3746.

(4) For chemoenzymatic studies of reverse prenylation, see: (a) Yin, W.-B.; Cheng, J.; Li, S.-M. *Org. Biomol. Chem.* **2009**, *7*, 2202. (b) Yin, W.-B.; Xie, X.-L.; Matuschek, M.; Li, S.-M. *Org. Biomol. Chem.* **2010**, *8*, 1133. (c) Yin, W.-B.; Yu, X.; Xie, X.-L.; Li, S.-M. *Org. Biomol. Chem.* **2010**, *8*, 2430. (d) Fan, A.; Li, S.-M. *Adv. Synth. Catal.* **2013**, *355*, 2659. (e) Luk, L. Y. P.; Qian, Q.; Tanner, M. E. *J. Am. Chem. Soc.* **2011**, *133*, 12342. (f) Rudolft, J. D.; Wang, H.; Poulter, C. D. *J. Am. Chem. Soc.* **2013**, *135*, 1895.

(5) For a selected example of a Pd-catalyzed asymmetric construction of vicinal quaternary stereocenters, see: (a) Trost, B. M.; Osipov, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9176. For selected examples of an enantio- and diastereoselective Ir-catalyzed allylic alkylation to form vicinal tertiary and all-carbon quaternary stereocenters, see: (b) Liu,

W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626. (c) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 17298.

(6) For selected enantio- and diastereoselective Ir-catalyzed allylic substitution reactions from our group, see: (a) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276. (b) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (c) O, F.; Kravina, A. G.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12166. (d) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3020. (e) On the basis of our previous studies, we believe the high regioselectivity in the allylic displacement reactions can be explained by the putative intermediate structure shown below. The highly congested binding site leads to a binding mode in which positioning of the dimethyl end group and attack by the nucleophile occur far from the partially dissociated ligand. In the work presented herein, a similar putative intermediate may be envisioned, with one ligand being phosphoramidite **8** and the other a 1,5-cyclooctadiene (cod) or solvent molecule.



(7) The use of KO*t*-Bu and Et_3B for the activation of 1*H*-indoles has been described, see: (a) Lin, A.; Yang, J.; Hashim, M. *Org. Lett.* **2013**, *15*, 1950. (b) For related reports documenting the use of Et_3B, see ref 2c and references therein.

(8) Diebolt, O.; Tricas, H.; Freixa, Z.; van Leeuwen, P. W. N. M. *ACS Catal.* **2013**, *3*, 128.

(9) (a) Both, 2,3-substituted and 3-unsubstituted indoles are also suitable substrates: 2,3-dimethylindole gave the corresponding indole imine in 55% yield and 5-methoxyindole afforded the C3 reverse prenylated indole in 80% yield. (b) In preliminary studies, indoles with malonates or phenols as pendant nucleophiles gave a complex mixture.

(10) For selected examples, see: (a) Bhat, B.; Harrison, D. M. *Tetrahedron Lett.* **1986**, *27*, 5873. (b) Takase, S.; Itoh, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1986**, *42*, 5887. (c) Kawasaki, T.; Shinada, M.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem.* **2008**, *73*, 5959. (d) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63. (e) Takiguchi, S.; Iizuka, T.; Kumakura, Y.-s.; Murasaki, K.; Ban, N.; Higuchi, K.; Kawasaki, T. *J. Org. Chem.* **2010**, *75*, 1126. (f) Adla, S. K.; Golz, G.; Jones, P. G.; Lindel, T. *Synthesis* **2010**, 2161.

(11) For selected examples, see: (a) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (b) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963. (c) Wang, Y.; Kong, C.; Du, Y.; Song, H.; Zhang, D.; Qin, Y. *Org. Biomol. Chem.* **2012**, *10*, 2793. (d) Ideguchi, T.; Yamada, T.; Shirahata, T.; Hirose, T.; Sugawara, A.; Kobayashi, Y.; Omura, S.; Sunazuka, T. *J. Am. Chem. Soc.* **2013**, *135*, 12568.

(12) For selected reviews on the chemistry of hexahydropyrrolo[2,3-*b*]indoles, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Hino, T.; Nakagawa, M. *Alkaloids* **1989**, *34*, 1.

(13) Pd-catalyzed *endo*-selective C3 allylation of tryptophan methyl ester has been reported, see ref 2c.

(14) Biological activity: (a) Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471. Isolation: (b) Kimura, Y.; Hamasaki, T.; Nakajima, H.; Isogai, A. *Tetrahedron Lett.* **1982**, *23*, 225. Chemoenzymatic synthesis: (c) Bhat, B.; Harrison, D. M.; Lamont, H. M. *Tetrahedron* **1993**, *49*, 10663. (d) See also ref 4a.

(15) Isolation: (a) Kusano, M.; Sotoma, G.; Koshino, H.; Uzawa, J.; Chijimatsu, M.; Fujioka, S.; Kawano, T.; Kimura, Y. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 2823. Synthesis: (b) Matsumura, K.; Kitahara, T. *Heterocycles* **2001**, *54*, 727.