Tetrahedron xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pd-porphyrin complex-catalyzed allylation of indole with allylic alcohols through C3–C2 coupling

Alaa A. Atia, Masanari Kimura*

Division of Chemistry and Materials Science, Faculty of Engineering, Graduate School of Science and Technology, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki, 852-8521, Japan

ARTICLE INFO

Article history:
Received 15 February 2021
Received in revised form
28 April 2021
Accepted 1 May 2021
Available online xxx

Keywords:
Indole
Porphyrin
Allylic alcohol
Homocoupling

ABSTRACT

Appropriate and efficient way for the preparation of 3-allyl-2,3-dihydro-2,3′-bisindoles has been developed via homocoupling of *N*–H indole. Pd-porphyrin-catalyzed allylation of indoles with allylic alcohols in the presence of PBr_3 and a base is developed. The reaction involves dimerization at the C3 and C2 positions of the indoles, giving 2-allylated 3-(indolin-2-yl)-1*H*-indoles in moderate to good yields. 3-(Indolin-2-yl)-1*H*-indole derivatives serve as intermediates for the synthesis of pharmaceutically active molecules.

1. Introduction

Transformation of an inactive *C*–H bond into a *C*–C bond is considered as one of the most prevailing strategies to introduce molecular complexities in organic synthesis [1]. There are selective *C*–H functionalization strategies for the indole skeleton, which is a key component of many pharmacophores [2], natural products [3], and synthetic building blocks [4]. Direct preparation of indole alkaloids has attracted significant attention because indole derivatives are a class of pharmaceutically important molecules [5]. Particularly, the bisindole moieties are prevalent in various bioactive natural products [6], pharmaceutical compounds [7], and agrochemicals and are used in many synthetic methods. 2,3-Dihydro-2,3′-bisindole as a confidential framework shows a broad range of biological activity [8]. For example, 2,3-dihydro-2,3′-bisindoles are potent androgen receptor (AR) and binding function 3 (BF_3) inhibitors that exhibit excellent antiandrogen potency [9] and anti-PSA activity [10] and abrogate the proliferation of androgen-sensitive [11] and enzalutamide-resistant cells [12]. Recent studies focus on the development of a simple, effective, and economical strategy to prepare biologically active bisindoles such as the tumor growth inhibitor rebeccamycin and protein kinase C inhibitor staurosporine [13–15]. Bisindole is also effective in increasing the estrogen metabolism in humans and hence, can be used for breast cancer treatment having antibacterial activities [16,17]. Literature survey revealed three important bisindole derivatives that exerted a significant effect in medicine. While one of them exhibited cytotoxic activity against MCF-7 breast cancer cell line [18], another exhibited acetylcholinesterase (AChE) inhibition activity [19]. The third derivative, yuehchukene, exhibited anti-implantation and estrogenic activities [20].

Several methods have been used for the synthesis of bisindole using Lewis acid catalysts [21]. However, these methods require harsh reaction conditions and expensive reagents and give low yields with intractable impurities [22]. Although some methods have been developed for the preparation of 2,3′-bisindole via the direct dimerization of indoles [23], such studies are limited. Liu et al. synthesized 2,3-dihydro-2,3′-bisindoles in good yields in the presence of $InCl_3$ or $SnCl_2$; however, the method had some obvious drawbacks [24]. 2,3′-Bisindole and 3-(indolin-2-yl)-1*H*-indole were prepared by the dimerization of 1*H*-indole with one equivalent of $SnCl_4$ and used as the starting materials to give the corresponding indolo [2,3-α] carbazole [25]. A one-pot cascade reaction was employed for synthesizing an extremely important indoline-3-one like 2-(3-indolyl)indolin-3-one scaffold that is found in the natural antiviral product isatisine A and has anti-infective activity against the respiratory syncytial virus and Zika virus [26].

The oxidative homocoupling of indoles is one of the most

* Corresponding author.
E-mail address: masanari@nagasaki-u.ac.jp (M. Kimura).

https://doi.org/10.1016/j.tet.2021.132213
0040-4020/

efficient and convenient methods to synthesize bisindoles [27]. The primary methods for the oxidation of indoles to bisindoles involve the use of mCPBA [28], molybdenum pentoxide [29], DDQ [30], and dimethyldioxirane [31]. However, these methods have many limitations. For instance, they lead to toxic metal pollution, are incompatible with many functional groups, give low yields, and have poor selectivities [32]. In this regard, the transition metal-catalyzed *C*—H bond activation strategy has received significant attention [33]. Based on this, we focus on using an efficient, inexpensive, and environmentally friendly catalyst such as Pd-porphyrin to realize the homocoupling of indoles. Hung et al. demonstrated that Pd(II) complexes such as palladium carboxylate and Pd(TTP) are good catalysts for intramolecular *C*—H insertion reactions [34]. Carretero et al. demonstrated that $Pd(OAc)_2$ is an efficient catalyst for the dehydrogenating homocoupling of indole to achieve the conversion of indole to 2,2′-bisindole [35]. The palladium-catalyzed cross-coupling of two different 2-functionalized indole derivatives has been proven to be an ideal synthetic route to unsymmetrical 2,2′-bisindoles [7]. Incorporation of a heavy metal like Pd into the porphyrin pocket promotes efficient intersystem crossing upon chemical reactions [36]. The functional diversity of the metalloporphyrin complexes lies in their ability to bind with numerous metals through the porphyrin ring system, because of which they have important roles in many biological and catalytic systems [37].

In this study, we investigated the Pd-porphyrin complex-catalyzed direct allylation of indole with allylic alcohols, which involved the homocoupling of indole at C2 and C3 positions to generate 3-allyl-2,3-dihydro-2,3′-bisindoles. Furthermore, 3-allyl-2,3-dihydro-2,3′-bisindole is considered a valid starting material for the preparation of several pharmaceutical compounds.

2. Results and discussion

2.1. Pd-catalyzed allylative dimerization of indole

We investigated the coupling reactions of indole with allyl alcohol using 5 mol% of different Pd(II) catalysts at 50 °C under nitrogen atmosphere. The results are shown in Table 1.

For the various Pd catalysts investigated, porphyrins were found to be the most appropriate ligands for the allylative coupling reactions. There was no reaction in the presence of the $Pd(PPh_3)_4$ catalyst, and the indole was recovered quantitatively (entry 2, Table 1). We examined the reactions using Pd-porphyrin complexes for the allylative dimerization of indole. Although no coupling product was obtained in the presence of the Pd-TPP (R = H) catalyst, Pd-porphyrin complexes bearing electron-withdrawing groups, such as Pd-TCPP (R = COOH), Pd-TCMPP (R = COOMe), and Pd-TSTPSPP (R = SO_3Na), were effective for this reaction (entries 3–6, Table 1). The Pd-TSTPSPP catalyst was found to be particularly useful as it was highly water-soluble and could be easily isolated from the reaction mixture upon extraction with water and ethyl acetate

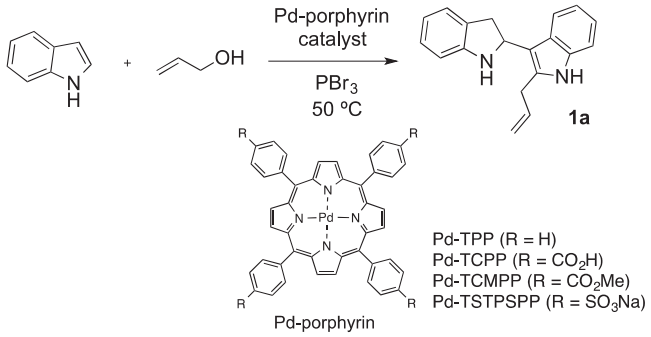


Table 1
Pd-porphyrin-catalyzed coupling reaction of indole with allyl alcohol.[a].

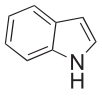
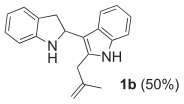
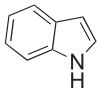
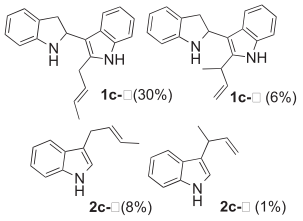
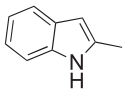
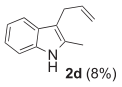
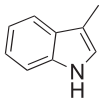
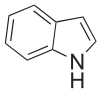
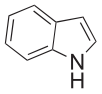
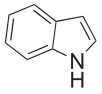
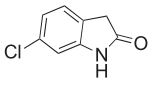
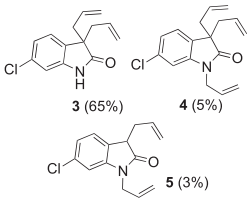
entry	catalyst	additive	base	solvent	time (h)	yield (%)
1	Non	PBr_3	NaOH	THF	12	0
2	$Pd(PPh_3)_4$	PBr_3	NaOH	THF	12	0
3	Pd-TPP	PBr_3	NaOH	THF	12	trace
4	Pd-TCMPP	PBr_3	NaOH	THF	12	30
5	Pd-TCPP	PBr_3	NaOH	THF	12	35
6	Pd-TSTPSPP	PBr_3	NaOH	THF	8	70
7	Pd-TSTPSPP	PBr_3	NaOH	THF-H_2O	8	67
8	Pd-TSTPSPP	PBr_3	NaOH	H_2O	8	65
9	Pd-TSTPSPP	PBr_3	NaOH	DMF	8	60
10	Pd-TSTPSPP	PBr_3	NaOH	Dioxane	8	0
11	Pd-TSTPSPP	BEt_3	NaOH	THF	8	0
12	Pd-TSTPSPP	PCl_3	NaOH	THF	8	0
13	Pd-TSTPSPP	PBr_3	KOH	THF	8	62
14	Pd-TSTPSPP	PBr_3	Na_2CO_3	THF	8	60
15	Pd-TSTPSPP	PBr_3	none	THF	8	0
16	Pd-TSTPSPP	none	NaOH	THF	8	0
17	Pd-TSTPSPP	PBr_3	TFA	THF	8	0

[a] Reaction conditions: indole (1 mmol), catalyst (5 mol%), allyl alcohol (3 mmol), base (1.5 mmol), additives (1 mmol), and solvent (2.5 mL) at 50 C under nitrogen atmosphere.

Solvent screening revealed that THF was the optimal solvent for this reaction, affording the desired product **1a** in reasonable yields. Solubility of the Pd-porphyrin catalyst is very important. The moderate to good product yields under the reaction conditions listed in entries 7–9 (Table 1) can be attributed to the solubility of Pd-TSTPSPP in water and dipolar solvents. The effects of additives and base were investigated in a similar manner, and higher yields were obtained when inorganic bases such as sodium hydroxide, potassium hydroxide, and sodium bicarbonate (entries 6, 13, and 14, Table 1) were used. Although the combination of a Pd catalyst and triethylborane is effective in promoting the directed electrophilic allylation of indole with allylic alcohols to afford 3-allyl indoles [38], the present allylative coupling reaction did not occur at all when phosphorus tribromide was replaced with triethylborane (entry 11, Table 1). Phosphorous trichloride was also ineffective in promoting the coupling reaction (entry 12, Table 1). Thus, the combination of a base and phosphorus tribromide is essential for the desired reaction, as the reaction did not proceed at all in the absence of either of them (entries 15–17, Table 1).

Scope and limitations of the Pd-catalyzed allylation of indole derivatives with substituted allylic alcohols are presented in Table 2 β-Methallyl alcohol could participate in a similar coupling reaction with indole to produce the desired product **1b** in 50% yield (entry 1, Table 2). Although crotyl alcohol reacted with indole in a similar manner, a mixture of linear and branched regioisomers **1c** was produced, along with C3 allylated products **2c-γ** and **2c-α** as the byproducts (entry 2, Table 2). 2-Methylindole underwent direct electrophilic allylation at C3 to give 3-allyl-2-methylindole **2d** in moderate yields, and the desired product was not detected (entry 3, Table 2). 3-Methylindole did not react with allyl alcohol at all, and the substrate was recovered quantitatively (entry 4, Table 2). Thus, 2- and 3-substituted indoles inhibited the C2 and C3 homocoupling reaction. No reaction occurred when allylbromide and allyl acetate were used as the substrate (entries 5 and 6, Table 2). Propyl alcohol did not react with indole, indicating that allylic alcohols are essential for the desired sequential coupling reactions (entry 7,

Table 2
Substrate scope of the Pd-catalyzed coupling reaction.[a].

entry	indole derivatives	allylic alcohol	isolated yields (%)
1			 **1b** (50%)
2			 **1c-**□(30%) **1c-**□ (6%) **2c-**□(8%) **2c-**□ (1%)
3			 **2d** (8%)
4			no reaction
5			no reaction
6			no reaction
7			no reaction
8			 **3** (65%) **4** (5%) **5** (3%)

[a] Reaction conditions: indole derivatives (1 mmol), Pd^{II}TSTpSPP (0.05 mmol), allylic alcohols (3 mmol), NaOH (1.5 mmol), PBr_3 (1 mmol), and THF (2.5 mL) at 50 C under nitrogen atmosphere.

Table 2). Electrophilic allyation at the α-position and the amide nitrogen atom of the substrate proceeded with 6-chlorooxindole, and diallylated and triallylated products were obtained in reasonable yields (entry 8, Table 2). The structures of these products were determined by ^{1}H and ^{13}C NMR spectroscopies, mass spectrometry, IR spectroscopy, and COSY and NOESY measurements. The spectral data are provided in Supporting Information. Representative NOE experimental data for the structure determination of **1b** are exemplified in Fig. 1.

Although it is too early to rationalize the behavior of this reaction, a plausible mechanism for the allylation of indoles is shown in Scheme 1. The allyl alcohol reacts with phosphorous tribromide to form an allyloxydibromophosphane species [39]. Indole successfully dimerizes to produce 2′-bromo-2,3′-bisindoline, which undergoes Pd-catalyzed allylation with allyloxydibromophosphane. The allylpalladium complex undergoes reductive elimination, followed by rotation insertion of the allylhydridepalladium species to

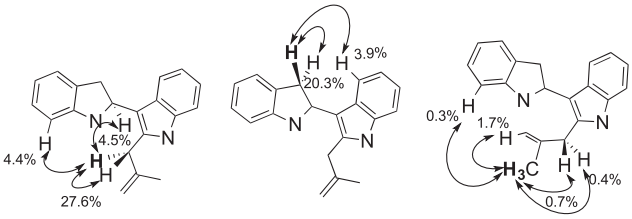
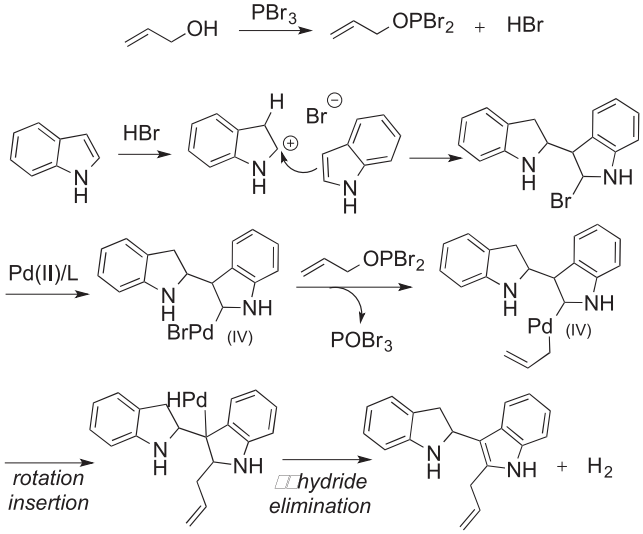
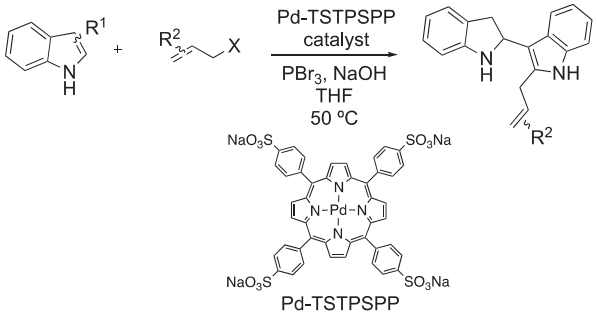


Fig. 1. NOE experimental data of compound **1b** upon irradiation at the bold-faced proton.



Scheme 1. Plausible mechanism for the allylation of indole with allylic alcohol through indole dimerization.

give a Pd-indolinyl complex, 2-allyl-3-(indolin-2-yl)-1*H*-indole [40].



3. Conclusion

We have developed an unprecedented method for the directed synthesis of 2,3-dihydro-2,3′-bisindole derivatives via the reaction of indole and allyl alcohols in the presence of phosphorous tribromide. Pd(II)-porphyrin complexes were prepared and served as an efficient catalyst for the allylative dimerization of indoles.

4. Experimental section

4.1. Materials and methods

All the chemicals were purchased and used without further

purification. The reactions were followed by thin-layer chromatography (TLC) using glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F254). Flash chromatography columns were packed with 230–400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted, and samples were eluted with a continuous gradient from hexane to the indicated solvent. All the products were identified from the proton and carbon NMR data obtained on a JEOL-GX (500) NMR spectrometer using tetramethylsilane as an internal standard. Infrared spectroscopy was performed on a JASCO A-100 FTIR spectrophotometer. High-resolution mass spectrometry (HRMS) was performed on a JEOL JMS-DX303 mass spectrometer.

meso-Tetraphenylporphyrin H_2(TPP), 5,10,15,20-tetrakis(4-(methoxycarbonyl)phenyl)porphyrin H_2(TMCPP), and 5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin H_2(TCPP) were prepared according to our previously reported procedure [41].

H_2(TPP). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (s, 8H), 8.22 (dd, J = 7.6, 1.4 Hz, 8H), 7.79–7.73 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 134.3, 132.0, 130.0, 127.6, 126.6, 120.1. Elemental analysis: calculated for $C_{44}H_{30}N_4$: C, 85.97H, 4.92; N, 9.11; found: C, 85.55; H, 4.90; N, 9.01. HRMS: calcd for $C_{44}H_{30}N_4$: 614.2470, found: 614.9781.

H_2(TMCPP). UV–Vis (DMF) λ_{max}: 419 nm (Soret band); 517, 550, 591, and 647 nm (Q bands).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (s, 8H), 8.43 (d, J = 10.3 Hz, 8H), 8.27 (d, J = 10.3 Hz, 8H), 4.00 (s, 12H), −2.83 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.5 (CO_2CH_3), 119.4 (Cmeso), 128.0 (ArCmeta), 129.8 (Cβ), 134.5 (ArCortho), 146.6 (Cα), 167.2 (C=O). Elemental analysis: calculated for $C_{52}H_{38}N_4O_8$: C 73.82, H 4.52, N 6.62; found: C 73.25, H 4.25, N 6.55. HRMS: calcd for $C_{52}H_{38}N_4O_8$: 846.2690, found: 846.2801.

H_2(TCPP). UV–Vis (DMF) λ_{max}: 422 nm (Soret band); 515, 552, 592, and 648 nm (Q bands).

^{1}H NMR (500 MHz, $CDCl_3$): δ 13.3 (br, 4H), 8.84 (s, 8H), 8.37 (d, J = 8.2 Hz, 8H), 8.33 (d, J = 8.2 Hz, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.8 (Cmeso), 128.4 (ArCmeta), 131.0 (Cβ), 134.9 (ArCortho), 145.8 (Cα), 167.9 (C=O). Elemental analysis: calculated for $C_{48}H_{30}N_4O_8$: C 72.90, H 3.82, N 7.09; found: C 72.11, H 3.67, N 6.75. HRMS: calcd for $C_{48}H_{30}N_4O_8$: 790.2064, found: 790.0068.

Tetrasodium tetra(*p*-sulfonatophenyl)porphyrin (TST*p*SPP) was prepared by stirring *meso*-tetraphenylporphyrin (0.5 g) in concentrated sulfuric acid (40 mL) at room temperature till the solution was uniform. The reaction mixture was heated at 60 °C and kept at this temperature for 12 h. Then, the solution was cooled in an ice bath, and 10–20 mL of ice water was added slowly and carefully, resulting in the formation of a green precipitate. It is worth noting that an increase in the volume of added water will dissolve the precipitate to form a green solution. The solution was diluted with acetone, filtered by suction, and washed with methylene chloride three times. The precipitate was basified until the pH 9 with a solution of Na_2CO_3, following which the solution was filtered and evaporated. Finally, the solid was purified by column chromatography using an acetone–methanol (7:3) solution as the eluent to obtain a dark blue 60% solution of tetrasodium tetra(*p*-sulfonatophenyl)porphyrin [42].

UV–Vis (DMSO) λ_{max}: 420 nm (Soret band); 519, 551, and 650 nm (Q bands).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (s, 8H), 8.16 (d, J = 8.3 Hz, 8H), 8.01 (d, J = 8.3 Hz, 8H). HRMS, calcd for $C_{48}H_{30}N_4O_8$: 1022.0021. Found m/z: 1022.8712.

Pd(TPP) and Pd(TMCPP) were prepared according to a literature method [17]. Free basic porphyrins and palladium(II) acetate were stirred with toluene (25 mL) in a round-bottom flask and refluxed for 12 h under nitrogen atmosphere. The mixture was cooled to room temperature and evaporated under vacuum. The precipitate was purified by column chromatography on silica gel using a $CHCl_3$–methanol (95:5) solution as the eluent.

Pd(TCPP) and Pd(TST*p*SPP) were prepared according to a literature method [34]. Free basic porphyrins and palladium chloride were stirred with DMF (40 mL) in a round-bottom flask, and the mixture was heated to 150 °C for 2 h under nitrogen atmosphere. The contents were cooled to room temperature and evaporated. The residue was washed with methylene chloride and dissolved in methanol. The solution was evaporated, and the pure metalloporphyrins were obtained by column chromatography using an acetone–methanol (8:2) solution as the eluent.

4.2. General procedure for allylation of indoles

Under nitrogen atmosphere, PBr_3 (1 mmol), THF (2.5 mL), and allyl alcohol (3 mmol) were injected with a syringe into a mixture of indole (1 mmol), catalyst (5 mol%), and NaOH (1.5 mmol), and the mixture was stirred at 50 °C. The reaction was followed by TLC, and was diluted with 20 mL of ethyl acetate. It was washed with 50 mL of water three times, following which the organic layer was dried with magnesium sulfate and filtered. The solution was evaporated, and the product, 3-(indolin-2-yl)-1*H*-indole, was obtained by column chromatography using an ethyl acetate–*n*-hexane (1:40) solution as the eluent.

4.2.1. ***2-Allyl-3-(indolin-2-yl)-1H-indole* (*1a*)**

R*f* = 0.56 (EtOAc:hexane = 1:4, v/v), IR (thin film) 3400, 3060, 2926, 1662, 1485, 1456, 1417, 1353, 1336, 1317, 1263.3, 1095, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.58 (d, J = 9.8 Hz, 1H), 7.25 (d, J = 10.4 Hz, 1H), 7.10 (t, J = 9.8 Hz, 1H), 7.06 (d, J = 9.2 Hz, 1H), 7.01 (t, J = 10.4 Hz, 1H), 6.97 (t, J = 9.8 Hz, 1H), 6.60 (t, J = 9.2 Hz, 1H), 6.47 (d, J = 9.8 Hz, 1H), 5.70 (dddd, J = 9.2, 10.7, 11.0, 18.0 Hz, 1H), 5.05 (dm, J = 18.0 Hz, 1H), 5.01 (dm, J = 11.0 Hz, 1H), 4.85 (dd, J = 9.2, 10.7 Hz, 1H), 3.73 (dm, J = 16.6 Hz, 1H), 3.39 (dd, J = 7.3, 16.6 Hz, 1H), 3.25 (dd, J = 9.2, 15.4 Hz, 1H), 3.14 (dd, J = 10.7, 15.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 136.8, 133.9, 129.0, 127.5, 126.2, 124.1, 122.7, 122.2, 120.1, 119.4, 117.5, 117.0, 116.8, 111.2, 107.3, 61.6, 48.9, 37.6. HRMS: calcd for $C_{19}H_{18}N_2$: 274.1470, found: 274.2179.

4.2.2. ***3-(Indolin-2-yl)-2-(2-methylallyl)-1H-indole* (*1b*)**

R*f* = 0.63 (EtOAc:hexane = 1:4, v/v), IR (thin film) 3413, 3031, 2914, 2850, 2245, 1654, 1604, 1556, 1483, 1421, 1334, 1228, 1186, 1139, 1083, 908, 842, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 6.8 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.68 (t, J = 6.8 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 4.94 (dd, J = 8.8, 10.2 Hz, 1H), 4.91 (br s, 1H), 4.80 (br s, 1H), 3.38 (dd, J = 8.8, 16.1 Hz, 1H), 3.37 (d, J = 16.1 Hz, 1H), 3.25 (dd, J = 8.8, 16.1 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 142.3, 136.8, 128.7, 127.5, 126.2, 124.0, 122.7, 120.2, 120.1, 119.5, 117.3, 117.2, 111.2, 111.1, 107.1, 62.4, 53.2, 37.5, 20.6. HRMS: calcd for $C_{20}H_{20}N_2$: 288.1626, found: 288.2833.

4.2.3. ***(E)-2-(But-2-en-1-yl)-3-(indolin-2-yl)-1H-indole* (*1c-γ*)**

R*f* = 0.60 (EtOAc:hexane = 1:4, v/v), IR (thin film) 3406, 3236, 2922, 2248, 1606, 1556, 1456, 1417, 1226, 966, 910, 885, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (br s, 1H), 7.69 (d, J = 7.95 Hz, 1H), 7.39 (d, J = 8.15 Hz, 1H), 7.21 (tm, J = 7.95 Hz, 1H), 7.04–7.13 (m, 3H), 6.67 (td, J = 8.1, 0.8 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 5.55 (dm, J = 16.2 Hz, 1H), 5.45 (dm, J = 16.2 Hz, 1H), 4.94 (td, J = 9.1, 2.05 Hz, 1H), 3.79 (dm, J = 16.0 Hz, 1H), 3.41 (dm, J = 16.0 Hz, 1H), 3.29 (dm, J = 16.0 Hz, 1H), 3.24 (dm, J = 16.0 Hz, 1H), 1.61 (dd, J = 6.2, 0.85 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 143.5, 136.8, 129.1128.3, 127.4, 126.5, 126.2, 124.1, 122.6, 120.2, 119.4, 117.2, 111.2, 109.4, 107.3, 61.1, 47.8, 37.6, 17.7. HRMS: calcd for $C_{24}H_{26}N_2$: 288.1626, found:

288.2901.**2-(But-2-en-1-yl)-3-(indolin-2-yl)-1*H*-indole** (**1c-α**): δ 8.15 (br s, 1H), 7.75 (d, *J* = 7.95 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.21 (m, 1H), 7.04–7.13 (m, 3H), 6.77 (t, *J* = 7.0 Hz, 1H), 6.50 (d, *J* = 7.4 Hz, 1H), 6.00 (m, 1H), 5.20 (dd, *J* = 13.75, 1.45 Hz, 2H), 4.54 (t, *J* = 5.4 Hz, 1H), 3.60 (m, 1H), 1.50 (d, *J* = 6.75 Hz, 3H).

4.2.4. *(E)-3-(But-2-en-1-yl)-1H-indole (2c-γ)*

Obtained as a mixture of **2c-γ** and **2c-α** in 8:1 ratio; R*f* = 0.43 (EtOAc:hexane = 1:4, v/v), IR (thin film) 3419, 3260, 2856, 1620, 1488, 1417, 1417, 1224, 1089, 1010, 966, 806, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (br s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 5.69 (dq, *J* = 15.0, 6.0 Hz, 1H), 5.61 (dt, *J* = 15.0, 6.0 Hz, 1H), 3.48 (d, *J* = 6.0 Hz, 1H), 1.69 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 129.9, 127.4, 125.8, 122.0, 121.5, 119.2, 112.8, 111.2, 111.1, 28.7, 18.0. HRMS: calcd for $C_{12}H_{13}N$: 171.2430, found: 171.3121.**3-(But-2-en-2-yl)-1*H*-indole** (**2c-α**): ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (br s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.07 (ddd, *J* = 6.9, 10.2, 17.0 Hz, 1H), 5.13 (dm, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 3.76 (quint, *J* = 6.9 Hz, 1H), 1.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 136.5, 127.5, 122.0, 120.4, 119.6, 115.6, 112.8, 111.2, 111.1, 34.9, 20.3.

4.2.5. *1,3-Diallyl-6-chloroindolin-2-one (5)*

R*f* = 0.74 (EtOAc:hexane = 1:4, v/v), IR (thin film) 3078, 2925, 2854, 1718, 1681, 1645, 1614, 1589, 1487, 1371, 1170, 1112, 991, 921, 815, 796, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.9 Hz, 1H), 7.00 (dd, *J* = 1.9, 7.9 Hz, 1H), 6.79 (d, *J* = 1.9 Hz 1H), 5.80 (ddt, *J* = 10.4, 17.0, 5.2 Hz, 1H), 5.69 (ddt, *J* = 10.1, 16.5, 6.2 Hz, 1H), 5.22 (dm, *J* = 10.4 Hz, 1H), 5.20 (dm, *J* = 17.0 Hz, 1H), 5.09 (dm, *J* = 16.5 Hz, 1H), 5.04 (dm, *J* = 10.4 Hz, 1H), 4.36 (ddm, *J* = 5.2, 16.5 Hz, 1H), 4.26 (ddm, *J* = 5.2, 16.5 Hz, 1H), 3.50 (dd, *J* = 5.0, 7.7 Hz, 1H), 2.82 (ddm, *J* = 5.0, 14.5 Hz, 1H), 2.56 (ddm, *J* = 7.7, 14.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 144.6, 133.6, 133.4, 130.9, 126.8, 125.0, 122.0, 118.5, 117.7, 109.5, 44.7, 42.3, 34.8. HRMS: calcd for $C_{14}H_{14}NOCl$: 247.0764, found: 247.0524.

4.2.6. *3,3-Diallyl-6-chloroindolin-2-one (3)*

R*f* = 0.53 (EtOAc:hexane = 1:4, v/v), IR (thin film) 3003, 2000, 1874, 1849, 1330, 1191, 1122, 1066, 993, 908, 852, 769, 734, 696, 619 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.02 (dd, *J* = 1.9, 8.0 Hz, 1H), 6.90 (d, *J* = 1.9 Hz 1H), 5.44 (ddd, *J* = 7.5, 10.0, 17.0 Hz, 2H), 5.01 (dm, *J* = 17.0 Hz, 2H), 4.94 (dm, *J* = 10.0 Hz, 2H), 2.58 (dd, *J* = 5.0, 15.0 Hz, 2H), 2.53 (dd, *J* = 5.0, 15.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1, 141.9, 133.5, 131.7, 130.1, 124.6, 122.2, 119.2, 110.3, 53.0, 41.1. HRMS: calcd for $C_{14}H_{14}NOCl$: 247.0764, found: 247.0914.

4.2.7. *1,3,3-Triallyl-6-chloroindolin-2-one (4)*

R*f* = 0.64 (EtOAc:hexane = 1:4, v/v), ^1H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 13.0 Hz, 1H), 7.02 (dd, *J* = 3.0, 13.0 Hz, 1H), 6.76 (d, *J* = 3.0 Hz 1H), 5.75 (ddt, *J* = 12.6, 17.0, 8.3 Hz, 1H), 5.37 (ddt, *J* = 4.4, 12.2, 16.5 Hz, 2H), 5.19 (dm, *J* = 17.0 Hz, 1H), 5.16 (dm, *J* = 12.6 Hz, 1H), 4.98 (dm, *J* = 16.5 Hz, 2H), 4.91 (dm, *J* = 12.2 Hz, 2H), 4.28 (dm, *J* = 8.3 Hz, 2H), 2.58 (dd, *J* = 4.4, 15.0 Hz, 2H), 2.53 (dd, *J* = 4.4, 15.0 Hz, 2H). HRMS: calcd for $C_{17}H_{18}NOCl$: 287.1077, found: 287.9853.

4.2.8. *3-Allyl-2-methyl-1H-indole (2d)*

R*f* = 0.43 (EtOAc:hexane = 1:4, v/v), ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.10 (td, *J* = 7.2, 1.1 Hz, 1H), 7.06 (td, *J* = 7.2, 1.1 Hz, 1H), 5.96 (ddt, *J* = 9.9, 17.0, 6.0 Hz, 1H), 5.05 (dm, *J* = 17.0 Hz, 1H), 4.98 (dm, *J* = 9.9 Hz, 1H), 3.45 (d, *J* = 6.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 135.2, 131.6, 128.8, 120.9, 119.0, 118.16, 114.3, 110.0, 109.5, 28.5, 11.6. HRMS, calcd for $C_{12}H_{13}N$: 171.1048, found: 171.1011.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the faculty of Engineering, Nagasaki University, for the financial support. We express our gratitude to Prof. G. Onodera and Prof. T. Fukuda for their helpful discussion and critical comments. We thank Mr. Ohhama and Mr. Issei Harada, NMR Facility, for their splendid technical assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132213.

References

[1] S. Mahato, S. Haldar, C.K. Jana, Chem. Commun. 50 (2014) 332–334.
[2] S.I. Kozhushkov, L. Ackermann, Chem. Sci. 4 (2013) 886–896.
[3] M. Bandini, A. Eichholzer, Angew. Chem. Int. Ed. 48 (2009) 9608–9644.
[4] A. García, Rubia, B. Urones, R.G. Arrayás, J.C. Carretero, Chem. Eur J. 16 (2010) 9676–9685.
[5] Y.-Y. He, X.-X. Sun, G.-H. Li, G.-J. Mei, F. Shi, J. Org. Chem. 82 (2017) 2462–2471.
[6] G.R. Humphrey, J.T. Kuethe, Chem. Rev. 106 (2006) 2875–2911.
[7] T. Li, Y. Yang, B. Li, P. Yang, Chem. Commun. 55 (2019) 353–356.
[8] S. Koulouri, E. Malamidou-Xenikaki, S. Spyroudis, Tetrahedron 61 (2005) 10894–10902.
[9] R.S.N. Munuganti, M.D.H. Hassona, E. Leblanc, K. Frewin, K. Singh, D. Ma, F. Ban, M. Hsing, H. Adomat, N. Lallous, Chem. Biol. 21 (2014) 1476–1485.
[10] J. Bergman, J.-O. Lindström, U.L.F. Tilstam, Tetrahedron 41 (1985) 2879–2881.
[11] X. Ren-Sheng, Z. Qiao-Zhen, X. Yu-Yuan, J. Ethnopharmacol. 14 (1985) 223–253.
[12] L.C. Menikarachchi, J.A. Gascón, Curr. Top. Med. Chem. 10 (2010) 46–54.
[13] G.A. Meshram, V.D. Patil, Synth. Commun. 40 (2009) 29–38.
[14] B.P.C. Rao, O.N. Oliveira Jr., R. Varala, Scope sel. Heterocycles from org, Pharm. Perspective (2016) 83–114.
[15] J. Bergman, E. Koch, B. Pelcman, Tetrahedron Lett. 36 (1995) 3945–3948.
[16] K. Umezawa, T. Taniguchi, M. Toi, T. Ohse, N. Tsutsumi, T. Yamamoto, T. Koyano, M. Ishizuka, Drugs Exp. Clin. Res. 22 (1996) 35–40.
[17] A. McDougal, M.S. Gupta, D. Morrow, K. Ramamoorthy, J. Lee, S.H. Safe, Breast Canc. Res. Treat. 66 (2001) 147–157.
[18] J.G. Osiak, R.M. Vaden, B.E. Welm, M.S. Sigman, Tetrahedron 68 (2012) 5203–5208.
[19] M.M.F. Queiroz, E.F. Queiroz, M.L. Zeraik, S.N. Ebrahimi, L. Marcourt, M. Cuendet, I. Castro-Gamboa, M. Hamburger, V. da Silva Bolzani, J.-L. Wolfender, J. Nat. Prod. 77 (2014) 650–656.
[20] W.L. Chan, D.D. Ho, C.P. Lau, K.H. Wat, Y.C. Kong, K.F. Cheng, T.T. Wong, T.Y. Chan, Eur. J. Med. Chem. 26 (1991) 387–394.
[21] J. Wen, X. Fan, R. Tan, H.-C. Chien, Q. Zhou, L.W. Chung, X. Zhang, Org. Lett. 20 (2018) 2143–2147.
[22] V.D. Patil, N.R. Sutar, K.P. Patil, J. Chem. Pharmaceut. Res. 8 (2016) 608–613.
[23] X. Zhong, Y. Li, F. Han, Chem. Eur J. 18 (2012) 9784–9788.
[24] T. Guo, S.-L. Han, Y.-C. Liu, Y. Liu, H.-M. Liu, Tetrahedron Lett. 57 (2016) 1097–1099.
[25] G. Dupeyre, P. Lemoine, N. Ainseba, S. Michel, X. Cachet, Org. Biomol. Chem. 9 (2011) 7780–7790.
[26] B.J.P. Atienza, L.D. Jensen, S.L. Noton, A.K.V. Ansalem, T. Hobman, R. Fearns, D.J. Marchant, F.G. West, J. Org. Chem. 83 (2018) 6829–6842.
[27] Z. Liang, J. Zhao, Y. Zhang, J. Org. Chem. 75 (2010) 170–177.
[28] E. Desarbre, L. Savelon, O. Cornec, J.Y. Mérour, Tetrahedron 52 (1996) 2983–2994.
[29] C.I. Altinis Kiraz, T.J. Emge, L.S. Jimenez, J. Org. Chem. 69 (2004) 2200–2202.
[30] G.B. Feigelson, S.J. Danishefsky, J. Org. Chem. 53 (1988) 3391–3393.
[31] X. Zhang, C.S. Foote, J. Am. Chem. Soc. 115 (1993) 8867–8868.
[32] X.-Y. Zhou, X. Chen, L.-G. Wang, D. Yang, J.-H. Li, Synlett 29 (2018) 835–839.
[33] J. Dupont, C.S. Consorti, J. Spencer, Chem. Rev. 105 (2005) 2527–2572.
[34] H.-Y. Thu, W.-Y. Yu, C.-M. Che, J. Am. Chem. Soc. 128 (2006) 9048–9049.
[35] A. García-Rubia, B. Urones, R.G. Arrayás, J.C. Carretero, Chem. Eur J. 16 (2010) 9676–9685.

[36] C.O. Obondi, G.N. Lim, F. D'Souza, J. Phys. Chem. C 119 (2015) 176–185.
[37] D. Marsh, L. Mink, J. Chem. Educ. 73 (1996) 1188.
[38] M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, J. Am. Chem. Soc. 127 (2005) 4592–4593.
[39] a) X.-X. Xu, G.-K. Liu, A. Azuma, E. Tokunaga, N. Shibata, Org. Lett. 13 (2011) 4854–4857;
b) T. Guo, S.-L. Han, Y.-C. Liu, Y. Liu, H.-M. Liu, Tetrahedron Lett. 57 (2016) 1097–1099;
c) W.E. Noland, H.V. Kumar, C. Lu, C.D. Brown, E. Wiley-Schaber, A. Johansson, E.V. LaBelle, N.C. O'Brian, R.C. Jesnsen, K.J. Tritch, Tetrahedron Lett. 57 (2016) 2158–2160.
[40] a) J.L.S. Yang, H. Jiang, W. Wu, J. Zhao, J. Org. Chem. 78 (2013) 12477–12486;
b) L. Lin, C. Romano, C. Mazet, J. Am. Chem. Soc. 138 (2016) 10344–10350;
c) Y. Baumgartner, O. Baudoin, ACS Catal. 10 (2020) 10508–10515;
d) S.P. Ross, A.A. Tahmann, M.S. Sigman, J. Am. Chem. Soc. 142 (2020) 10516–10525.
[41] A.A. Atia, M. Kimura, Catalysts 10 (2020) 1262–1271.
[42] Y.-H. Zhang, D.-M. Chen, T. He, F.-C. Liu, Spectrochim. Acta Mol. Biomol. Spectrosc. 59 (2003) 87–101.