Synthesis of 2-allyl-2,3-dihydro-1*H*-indol-3-ones using *in situ* Claisen rearrangement of 2,3-dihydro-1*H*-indol-3-ones with allyl alcohols

Tomomi Kawasaki, Kouhei Masuda, Yasutaka Baba, Romi Terashima, Kana Takada and Masanori Sakamoto *

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

Treatment of 2,3-dihydro-1*H*-indol-3-ones with allyl alcohols in the presence of camphorsulfonic acid and magnesium sulfate at 130 °C gave, *via* condensation and a Claisen rearrangement, 2-allyl-2,3-dihydro-1*H*-indol-3-ones in good yields. The stereochemistry of the products was determined by NOE experiments.

2,3-Dihydro-1*H*-indol-3-ones are useful synthetic intermediates for the synthesis of alkaloids and biologically active compounds.[1] 2-(1,1-Dimethylallyl)indoles are particularly attractive intermediates for the synthesis of alkaloids such as austamide,[2] brevianamides,[3] neoechinuline[4] and others.[5] Recently, Williams and co-workers[6] proposed that the 2-(1,1-dimethylallyl)indol-3-one derivative is a possible biosynthetic intermediate of brevianamides. Although several methods for the synthesis of 2,3-dihydro-1*H*-indol-3-ones have been reported,[7] 2-allyl-2,3-dihydro-1*H*-indol-3-ones are still difficult to obtain. In a recent communication,[8] we showed that the tandem condensation–Claisen rearrangement of 2,3-dihydro-1*H*-indol-3-ones **1–8** with 3-methylbut-2-en-1-ol **9a** was a useful method for the synthesis of 2-(1,1-dimethylallyl)-2,3-dihydro-1*H*-indol-3-ones **10a–16a**. We now report the *in situ* Claisen rearrangement of 2,3-dihydro-1*H*-indol-3-ones **1–8** with various allyl alcohols **9b–j** to give 2-allylindol-3-ones **10b–j–16b–j**, the stereochemistries of the products and the reaction mechanism, including a full account of the work mentioned in our communication.[8]

Results and discussion

The 2,3-dihydro-1*H*-indol-3-ones **1–8** were readily available by our synthetic method.[9] Initially, we examined the reaction of 1-acetyl-2,3-dihydro-1*H*-indol-3-one **1** with 3-methylbut-2-en-1-ol **9a** (Scheme 1) and the results are summarized in Tables 1 and 2. Heating **1** with 3-methylbut-2-en-1-ol **9a** in the presence of catalytic toluene-*p*-sulfonic acid and magnesium sulfate† at 130 °C in a sealed tube for 6 h gave 1-acetyl-2-(1,1-dimethylallyl)-2,3-dihydro-1*H*-indol-3-one **10a** in 37% yield together with the isomeric 3-methylbut-2-enyl derivative **10b**[7b] (18%) (Table 2, entry 1). A higher reaction temperature and use of a solvent resulted in a reduction in the proportion of the Claisen product **10a** obtained (entries 2, 3 and 4). When the reaction was performed using camphorsulfonic acid (CSA) instead of toluene-*p*-sulfonic acid, the yield of (1,1-dimethylallyl)indol-3-one **10a** was improved (62%), although it was still accompanied by the formation of the isomer **10b** (11%) (entry 5). Similarly, the CSA-promoted reaction of the indol-3-ones **2–4** with **9a** afforded the corresponding **11a–13a** as the major product along with **11b–13b** respectively (entries 6–8). In the case of the 1-methoxycarbonyl derivative **5**, the reaction required prolonged heating, but the desired product **14a** was preferentially obtained in good yield (entry 9).

The difference between the ratio of products **10a** and **10b** in the reaction using CSA (5.5:1; entry 5) and that using toluene-*p*-sulfonic acid (2:1; entry 1) indicates that these acids influence not only the initial condensation step but also the Claisen rearrangement step. The formation of **10b** can be explained in terms of a [1,3] shift of the intermediate, 3-(3-methylbut-2-enyloxy)indole, rather than isomerization of **10a** or direct alkylation with allylic cation generated from **9a** at the 2-position of **1**, by the following facts. Prolonged heating of either **10a** or **10b** under the same reaction conditions, as shown in entry 5, showed no isomerization, and similar treatment of **1** with 2-methylbut-3-en-2-ol **9a** afforded a mixture of **10a** and **10b** in a different ratio (1.2:1, 50% yield; Table 2, entry 10) from that in entry 5 (5.5:1).

The reaction of **1** with nerol (*cis*-3,7-dimethylocta-2,6-dien-1-ol) **9c** for 13 h under the same conditions provided the Claisen product **10c** in 50% yield as a mixture of its diastereoisomers in a ratio of 3:1. Treatment of 2-substituted 2-allylindol-3-ones **6** or **7** with **9a**, however, failed to give the desired product.

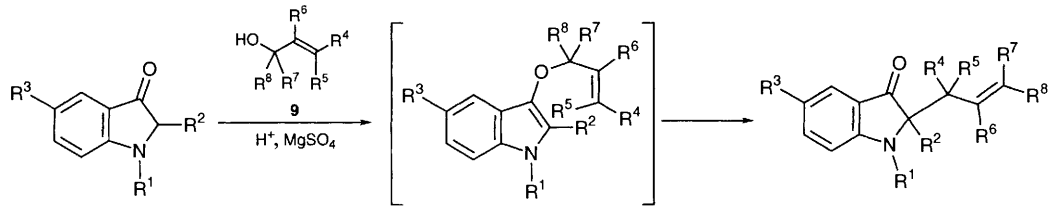
Next we investigated the reaction of **1** with various allyl alcohols **d–j**. When **1** was heated with allyl alcohol **9d** in the presence of catalytic CSA and magnesium sulfate at 130 °C in a sealed tube for 2 h, the desired *in situ* Claisen rearrangement proceeded smoothly to afford 2-allylindol-3-one **10d**[7b] in 73% yield. The reaction of 2-substituted indol-3-ones **6** and **7** with **9d**

Table 1 Treatment of indol-3-ones **1–7** with allyl alcohols **9a–j**

Indol-3-one	Allyl alcohol	Reaction time/h	Products (%, ratio of diastereoisomers)
1	**9a**	*a*	**10a,b**[a]
2	**9a**	*a*	**11a,b**[a]
3	**9a**	*a*	**12a,b**[a]
4	**9a**	*a*	**13a,b**[a]
5	**9a**	*a*	**14a**[a]
1	**9b**	*a*	**10a,b**[a]
1	**9c**	13	**10c** (50, 3:1)
1	**9d**	2	**10d** (73)
6	**9d**	20	**15d** (63)[b]
7	**9d**	42	**16d** (61)[c]
1	**9e**	3	**10e/10e'** (73, 1.7:1)
1	**9f**	5.5	**10f** (55, 1.2:1)
6	**9e**	18	**15e** (53, 2.2:1)
1	**9g**	10	**10g** (25)[d]
1	**9h**	9	**10h** (56), **10e** (9, 1.4:1)
1	**9i**	8	**10i** (67, 1:1)
1	**9j**	15.5	**10j** (97, 1.6:1)

[a] For details, see Table 2. [b] Starting **1f** was recovered in 9% yield. [c] Starting **1g** was recovered in 27% yield. [d] Starting **1a** was recovered in 28% yield.

† The reaction was slow unless magnesium sulfate was added.

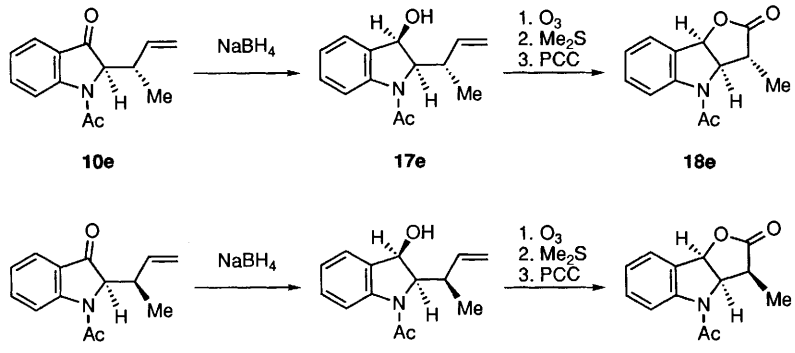


1-8 10-16

1, **10** R^1 = Ac, R^2 = R^3 = H
2, **11** R^1 = Ac, R^2 = H, R^3 = OMe
3, **12** R^1 = Ac, R^2 = H, R^3 = Br
4, **13** R^1 = COPh, R^2 = R^3 = H
5, **14** R^1 = CO_2Me, R^2 = R^3 = H
6, **15** R^1 = Ac, R^2 = Me, R^3 = H
7, **16** R^1 = Ac, R^2 = Ph, R^3 = H
8 R^1 = Ac, R^2 = CH_2Ph, R^3 = H

a R^4 = R^5 = Me, R^6 = R^7 = R^8 = H
b R^4 = R^5 = R^6 = H, R^7 = R^8 = Me
c R^4 = $CH_2CH_2CH{=}CMe_2$, R^5 = Me, R^6 = R^7 = R^8 = H
d R^4 = R^5 = R^6 = R^7 = R^8 = H
e R^4 = Me, R^5 = R^6 = R^7 = R^8 = H
f R^4 = Ph, R^5 = R^6 = R^7 = R^8 = H
g R^4 = R^5 = H, R^6 = Me, R^7 = R^8 = H
h R^4 = R^5 = R^6 = H, R^7, R^8 = Me, H
i R^4 = R^6 = R^8 = H, R^5–R^7 = $-CH_2CH_2CH_2-$
j R^4 = Me, R^6 = R^8 = H, R^5–R^7 = $-CH_2CH_2CH_2-$

Scheme 1



10e **17e** **18e**

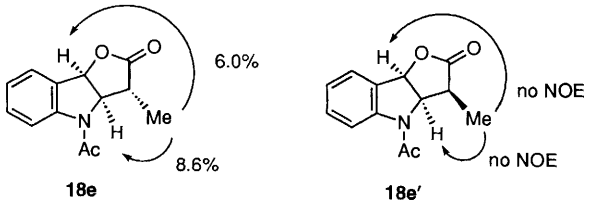
10e′ **17e′** **18e′**

Scheme 2

Table 2 Reaction of indol-3-ones **1**–**5** with allyl alcohols **9a** and **9b**

Entry	Indol-3-one	Allyl alcohol	Reaction conditions: Acid	T/°C	t/h	Products (yield, %)[a]	
1	**1**	**9a**	TsOH	130	6	**10a** (37)	**10b** (18)
2	**1**	**9a**	TsOH	150	4	**10a** (33)	**10b** (23)
3	**1**	**9a**	TsOH	180	3	**10a** (32)	**10b** (26)
4	**1**	**9a**	TsOH	110[b]	5.5	**10a** (24)	**10b** (18)
5	**1**	**9a**	CSA	130	3	**10a** (62)	**10b** (11)
6	**2**	**9a**	CSA	130	7	**11a** (66)	**11b** (11)
7	**3**	**9a**	CSA	130	6.5	**12a** (37)	**12b** (19)
8	**4**	**9a**	CSA	130	4	**13a** (59)	**13b** (13)
9	**5**	**9a**	CSA	130	10	**14a** (66)	—
10	**1**	**9b**	CSA	130	8	**10a** (27)	**10b** (23)

[a] Isolated yield. [b] In refluxing toluene.



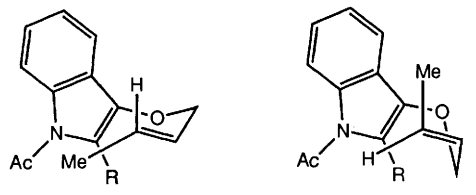
18e **18e′**

Fig. 1

required longer heating (20–42 h), but Claisen products **15d** and **16d** were obtained in 63 and 61% yields, respectively. In the case of 2-benzylindol-3-one **8**, however, the reaction gave a complex mixture, in which the desired product was not found.

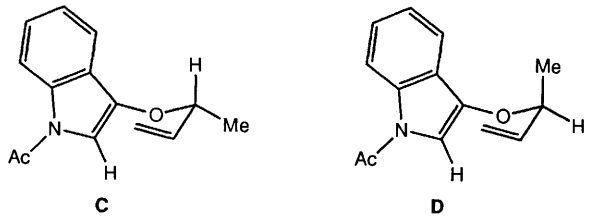
The similar reaction of **1** with but-2-en-1-ol **9e** (the mixture of *E*- and *Z*-isomers; 5.7:1) for 3 h gave a mixture of diastereoisomers of 2-(1-methylallyl)indol-3-ones **10e** and **10e′** (1.7:1) in 73% yield. The stereochemistries of the products **10e** and **10e′** were determined by NOE experiments (Fig. 1), after their separation followed by their transformation to the lactones **18e** and **18e′**, respectively (Scheme 2). Thus, the reduction of the indol-3-one **10e** and **10e′** with sodium borohydride proceeded stereoselectively to afford *cis*-alcohols **17e** and **17e′**, the stereochemistries of which were confirmed by NOE experiments. The ozonolysis of **17e** and **17e′** followed by PCC oxidation gave lactones **18e** and **18e′** respectively.‡ The

‡ The ^{1}H NMR spectra of **18e** and **18e′** show the existence of rotamers; for example, in the measurement of **18e** at room temperature, two broad signals due to the acetyl protons (in a 1:2 ratio) appear at δ 2.33 and 2.49, while at 80 °C the protons are observed as a single sharp signal at δ 2.49.



A R = H, Me B

Fig. 2



C D

Fig. 3

treatment of **1** with (*E*)-cinnamyl alcohol **9f** afforded a mixture of diastereoisomers (1.2:1) of the Claisen product **10f** in 55% yield.

The predominant product **10e** is produced *via* the chair-like transition state **A** (Fig. 2) derived from *E*-**9e** which is more favourable than the boat-like transition state **B** (R = H).[10] However, the stereoselectivity of this reaction was unexpectedly low. This is caused by epimerization of the product **10e** to **10e′**. Thus, heating of **10e** under the same conditions gave a mixture (8.8:1) of **10e** and **10e′**, while **10e′** was not epimerized. The reaction of 2-methylindol-3-one **6** with **9e** gave a mixture (2.2:1) of the diastereoisomers of the Claisen product **15e** in 53% yield. In this case, the cause of the low stereoselectivity is not the epimerization of **15e** but a smaller energy gap between the transition states **A** and **B** (R = Me).

The reaction of **1** with 2-methylallyl alcohol **9g** proceeded slowly to give the Claisen product **10g** (25%) with recovered **1** (28%).

As an example of a secondary rather than a primary allyl alcohol, the reaction of **1** with but-3-en-2-ol **9h** was carried out under the same conditions. The reaction proceeded stereoselectively to give (*E*)-2-(but-2-enyl)indol-3-one **10h** in 56% yield along with [1,3]-product **10e**/**10e′** (1.4:1) in 9% yield. The *E*-stereoselectivity is rationalized as the result of the lesser congestion of chair-like transition state **C** relative to the transition state **D** having a pseudo-1,3-diaxial interaction (Fig. 3).[10]

Finally, we treated **1** with cyclic allyllic alcohols. Similar treatment of **1** with cyclohex-2-enol **9i** afforded a mixture (1:1) of diastereoisomers of the corresponding indol-3-one **10i** in 67% yield. In the case of 3-methylcyclohex-2-enol **9j**, the reaction proceeded through the [1,3]-rearrangement instead of the Claisen rearrangement to give the indol-3-one **10j** in 97% yield as a mixture of its diastereoisomers with the ratio 1.6:1. The [1,3]-rearrangement occurs because the Claisen rearrangement is unfavourable due to steric interaction between the cyclohexenyl and indole rings in the transition state.

Experimental

All melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 270-30 or a Shimadzu FTIR-8100 spectrophotometer. NMR spectra were determined on a JEOL JNM-GX 270 spectrometer with tetramethylsilane (Me_4Si) as an internal standard. *J* Values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyser. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc., 100–200 mesh and Merck, 400 mesh). 2,3-Dihydro-1*H*-indol-3-ones **1**,[11] **2–6**[9] and **8**[6b] were prepared according to reported procedures.

Preparation of 1-acetyl-2-phenyl-2,3-dihydro-1*H*-indol-3-one 7

Following our reported procedure,[6b] **7** was obtained from 2-methoxy-2-phenyl-1-acetyl-2,3-dihydro-1*H*-indol-3-one[12] *via* reduction and demethoxylation. Sodium borohydride (0.76 g, 20 mmol) was added to a solution of the starting indol-3-one (0.57 g, 2 mmol) in methanol (20 cm^3) at 0 °C. After 20 min, the reaction mixture was concentrated under reduced pressure, and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to give an alcohol (0.52 g); mp 172–173 °C (from benzene). Stannyl chloride (0.62 g, 2.4 mmol) was added to a solution of the alcohol (0.52 g, 1.8 mmol) in methylene dichloride (40 cm^3) at 0 °C. After 30 min, the resultant mixture was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with methylene dichloride–hexane (1:1) to give the indol-3-one **7** (0.28 g, 60%), mp 128–129 °C (ethyl acetate–hexane) (Found: C, 76.2; H, 5.3; N, 5.6. $C_{16}H_{13}NO_2$ requires C, 76.45; H, 5.2; N, 5.55); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 and 1682; $\delta_H(CDCl_3)$ 2.07 (3 H, s), 5.02 (1 H, s), 7.2–7.3 (4 H, m), 7.34–7.41 (2 H, m), 7.71–7.76 (2 H, m) and 8.69 (1 H, d, *J* 7.6); *m/z* 251 (M^+, 80%), 209 (56), 208 (44), 180 (100), 152 (21), 104 (12) and 77 (17).

General procedure for the treatment of 1–8 with 9a–j

A mixture of the 1,2-dihydroindol-3-one **1–8** (1 mmol), allyl alcohol **9a–j** (5.9 cm^3), (±)-camphorsulfonic acid (CSA) or toluene-*p*-sulfonic acid (0.09 mmol), and magnesium sulfate (0.44 g) was heated in a sealed tube at 130 °C with or without toluene (17 cm^3) with stirring for the period indicated in Tables 1 and 2. After removal of the magnesium sulfate, the reaction mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel with diethyl ether–hexane (1:1 for **10c,f,h**, **15d,e** and **16d**; 2:1 for **10a,b,d,e,e′,i,j**, **11a,b**, **12a,b**, **13a,b** and **14a**; 3:1 for **10g**) as an eluent to give 2-allylindol-3-ones **10–16**. The yields are listed in Tables 1 and 2.

1-Acetyl-2-(1,1-dimethylallyl)-2,3-dihydro-1*H*-indol-3-one 10a. A viscous oil (Found: M^+, 243.1261. $C_{15}H_{17}NO_2$ requires *M*, 243.1259); $\nu_{max}(CHCl_3)/cm^{-1}$ 1721 and 1678; $\delta_H(CDCl_3)$ 0.96 (3 H, s), 1.12 (3 H, s), 2.33 (3 H, s), 4.32 (1 H, br s), 4.89 (1 H, d, *J* 8.9), 4.90 (1 H, d, *J* 18.8), 5.75 (1 H, ddd, *J* 17.5, 10.6 and 1.6), 7.15 (1 H, t, *J* 9.6), 7.53–7.60 (2 H, m) and 7.81 (1 H, br s); *m/z* 243 (M^+, 8%), 175 (70), 133 (100), 69 (38) and 41 (20).

1-Acetyl-2-(1,1-dimethylallyl)-5-methoxy-2,3-dihydro-1*H*-indol-3-one 11a. A viscous oil (Found: M^+, 273.1362. $C_{16}H_{19}NO_3$ requires *M*, 273.1365); $\nu_{max}(CHCl_3)/cm^{-1}$ 1716 and 1670; $\delta_H(CDCl_3)$ 0.97 (3 H, s), 1.17 (3 H, s), 2.30 (3 H, s), 3.76 (3 H, s), 4.30 (1 H, br s), 4.90 (1 H, d, *J* 10.6), 4.91 (1 H, d, *J* 17.5), 5.75 (1 H, dd, *J* 17.5 and 10.6), 7.02 (1 H, d, *J* 2.6), 7.14 (1 H, dd, *J* 8.9 and 3.0) and 7.70 (1 H, br s); *m/z* 273 (M^+, 22%), 205 (74), 163 (100), 148 (9), 69 (14) and 43 (13).

1-Acetyl-2-(1,1-dimethylallyl)-5-bromo-2,3-dihydro-1*H*-indol-3-one 12a. A viscous oil (Found: M^+, 321.0356. $C_{15}H_{16}BrNO_2$ requires *M*, 321.0366); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 and 1680; $\delta_H(CDCl_3)$ 1.03 (3 H, s), 1.20 (3 H, s), 2.37 (3 H, s), 4.34 (1 H, br s), 5.00 (1 H, d, *J* 10.6), 5.01 (1 H, d, *J* 17.5), 5.79 (1 H, dd, *J* 17.5 and 10.6), 7.68–7.77 (2 H, m) and 7.87 (1 H, br s); *m/z* 273 (M + 2, 12%), 271 (M^+, 12), 255 (87), 253 (88), 213 (96), 211 (100), 69 (54), 43 (27) and 41 (22).

1-Benzoyl-2-(1,1-dimethylallyl)-2,3-dihydro-1*H*-indol-3-one 13a. A viscous oil (Found: M^+, 305.1419. $C_{20}H_{19}NO_2$ requires *M*, 305.1416); $\nu_{max}(CHCl_3)/cm^{-1}$ 1717 and 1663; $\delta_H(CDCl_3)$ 1.13 (3 H, s), 1.23 (3 H, s), 4.86 (1 H, s), 4.94 (1 H, dd, *J* 10.6 and 1.0), 5.02 (1 H, dd, *J* 17.2 and 1.0), 5.82 (1 H, dd, *J* 17.2 and

10.6), 7.09 (1 H, t, *J* 7.9), 7.31 (1 H, t, *J* 7.9) and 7.48–7.69 (7 H, m); *m/z* 305 (M^+, 9%), 237 (68), 105 (100), 77 (24) and 69 (12).

2-(1,1-Dimethylallyl)-1-methoxycarbonyl-2,3-dihydro-1*H*-indol-3-one 14a. A viscous oil (Found: M^+, 259.1208. $C_{15}H_{17}NO_2$ requires *M*, 259.1208); $\nu_{max}(CHCl_3)/cm^{-1}$ 1717; $\delta_H(CDCl_3)$ 1.09 (3 H, s), 1.17 (3 H, s), 3.85 (3 H, s), 4.29 (1 H, s), 4.93 (1 H, d, *J* 10.6), 4.94 (1 H, d, *J* 17.2), 5.82 (1 H, dd, *J* 17.2 and 10.6), 7.15 (1 H, t, *J* 7.6), 7.58–7.65 (2 H, m) and 7.99 (1 H, t, *J* 7.9); *m/z* 305 (M^+, 9%), 237 (68), 105 (100), 77 (24) and 69 (12).

1-Acetyl-2-(3-methylbut-2-enyl)-2,3-dihydro-1*H*-indol-3-one 10b. Mp 154–158 °C (lit.,[6b] mp 155–160 °C); $\delta_H(CDCl_3)$ 1.45 (3 H, s), 1.51 (3 H, s), 2.33 (3 H, s), 2.76 (2 H, br s), 4.27 (1 H, br s), 4.78 (1 H, t, *J* 7.3), 7.14 (1 H, t, *J* 7.6), 7.55–7.67 (2 H, m) and 8.44 (1 H, br s).

1-Acetyl-5-methoxy-2-(3-methylbut-2-enyl)-2,3-dihydro-1*H*-indol-3-one 11b. A viscous oil (Found: M^+, 273.1367. $C_{16}H_{19}NO_3$ requires *M*, 273.1365); $\nu_{max}(CHCl_3)/cm^{-1}$ 1717 and 1669; $\delta_H(CDCl_3)$ 1.53 (3 H, s), 1.58 (3 H, s), 2.36 (3 H, br s), 2.82 (2 H, br s), 3.84 (3 H, s), 4.84 (1 H, t, *J* 7.5), 5.14 (1 H, t, *J* 7.5), 7.14 (1 H, t, *J* 7.6), 7.55–7.67 (2 H, m) and 8.44 (1 H, br s); *m/z* 273 (M^+, 54%), 258 (11), 205 (44), 163 (100) and 69 (12).

1-Acetyl-2-(3-methylbut-2-enyl)-5-bromo-2,3-dihydro-1*H*-indol-3-one 12b. A viscous oil (Found: M^+, 321.0357. $C_{15}H_{16}BrNO_2$ requires *M*, 321.0365); $\nu_{max}(CHCl_3)/cm^{-1}$ 1723 and 1680; $\delta_H(CDCl_3)$ 1.54 (3 H, s), 1.57 (3 H, s), 2.38 (3 H, s), 2.83 (2 H, br s), 4.35 (1 H, br s), 4.83 (1 H, t, *J* 7.6), 7.72 (1 H, dd, *J* 8.9 and 2.3), 7.38 (1 H, d, *J* 2.0) and 8.43 (1 H, br s); *m/z* 323 (M + 2, 32%), 321 (M^+, 33), 308 (17), 306 (17), 255 (72), 253 (73), 213 (99), 211 (100), 69 (60), 43 (60), 43 (32) and 41 (27).

1-Benzoyl-2-(3-methylbut-2-enyl)-2,3-dihydro-1*H*-indol-3-one 13b. A viscous oil (Found: M^+, 305.1419. $C_{20}H_{19}NO_2$ requires *M*, 305.1416); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 and 1662; $\delta_H(CDCl_3)$ 1.54 (3 H, s), 1.53 (3 H, s), 2.58–2.66 (2 H, m), 4.64 (1 H, dd, *J* 6.3 and 3.0), 4.80 (1 H, t, *J* 6.9), 7.18 (1 H, t, *J* 7.9), 7.45–7.60 (7 H, m) and 7.75 (1 H, d, *J* 6.6); *m/z* 305 (M^+, 22%), 237 (50), 105 (100) and 77 (26).

1-Acetyl-2-(3,7-dimethylocta-1,6-dien-3-yl)-2,3-dihydro-1*H*-indol-3-one 10c. A viscous oil (Found: M^+, 311.1890. $C_{20}H_{25}NO_2$ requires *M*, 311.1895); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 and 1675; $\delta_H(CDCl_3$; ratio of diastereoisomers, 1:3) 0.93 (3 H × 1/4, s), 1.18 (3 H × 3/4, s), 1.55 (3 H × 3/4, s), 1.60 (3 H × 1/4, s), 1.64 (3 H × 3/4, s), 1.67 (3 H × 1/4, s), 2.38 (3 H × 1/4, s), 2.41 (3 H × 3/4, s), 4.47 (1 H, br s), 4.90–5.09 (3 H, m), 5.60 (1 H × 3/4, dd, *J* 15.5 and 10.9), 5.80 (1 H × 1/4, dd, *J* 15.5 and 10.9), 7.20 (1 H, t, *J* 7.6), 7.58–7.66 (2 H, m) and 7.84 (1 H, br s); *m/z* 311 (M^+, 25%), 175 (90), 133 (100), 93 (14), 81 (29), 69 (52) and 41 (23).

1-Acetyl-2-allyl-2,3-dihydro-1*H*-indol-3-one 10d. Mp 91–94 °C (lit.,[7b] 92–94 °C); $\delta_H(CDCl_3)$ 2.42 (3 H, s), 2.90 (2 H, br s), 4.36 (1 H, br s), 4.99 (1 H, d, *J* 10.2), 5.11 (1 H, d, *J* 17.5), 5.49 (1 H, ddt, *J* 17.5, 10.6 and 7.3), 7.22 (1 H, t, *J* 7.9), 7.66 (1 H, t, *J* 7.3), 7.74 (1 H, d, *J* 7.9) and 8.52 (1 H, br s).

1-Acetyl-2-allyl-2-methyl-2,3-dihydro-1*H*-indol-3-one 15d. Mp 87–89 °C (from diethyl ether–hexane) (Found: C, 73.2; H, 6.6; N, 6.0. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1); $\nu_{max}(CHCl_3)/cm^{-1}$ 1716 and 1666; $\delta_H(CDCl_3)$ 1.65 (3 H, s), 2.52 (3 H, s), 2.77 (1 H, br s), 3.12 (1 H, br s), 4.88 (1 H, d, *J* 10.5), 5.03 (1 H, d, *J* 17.2), 5.75 (1 H, dddd, *J* 17.5, 10.6, 9.9 and 6.6), 7.21 (1 H, t, *J* 7.6), 7.66 (1 H, t, *J* 8.6 and 7.2), 7.80 (1 H, d, *J* 7.6) and 8.50 (1 H, br s); *m/z* 229 (M^+, 16%), 188 (32), 146 (100) and 43 (14).

1-Acetyl-2-allyl-2-phenyl-2,3-dihydro-1*H*-indol-3-one 16d. Mp 115–118 °C (from diethyl ether–hexane) (Found: C, 78.0; H, 5.95; N, 4.75. $C_{19}H_{17}NO_2$ requires C, 78.3; H, 5.9; N, 4.8); $\nu_{max}(CHCl_3)/cm^{-1}$ 1722 and 1668; $\delta_H(CDCl_3)$ 2.00 (3 H, br s), 3.16 (1 H, br s), 3.63 (1 H, br s), 5.01 (1 H, d, *J* 9.9), 5.18 (1 H, d, *J* 16.8), 5.41 (1 H, dddd, *J* 16.8, 9.9, 7.9 and 6.2), 7.2–7.42 (6 H, m), 7.69–7.77 (2 H, m) and 8.79 (1 H, br s); *m/z* 291 (M^+, 22%), 250 (28) and 208 (100).

1-Acetyl-2-(1-methylallyl)-2,3-dihydro-1*H*-indol-3-one 10e/10e′. A mixture of **10e** and **10e′** (1.7:1), mp 62–72 °C (from diethyl ether) (Found: M^+, 229.1103. $C_{14}H_{15}NO_2$ requires *M*, 229.1103); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 and 1673; *m/z* 229 (M^+, 33%), 186 (14), 175 (16), 132 (100) and 43 (20). After separation of the mixture; **10e** $\delta_H(CDCl_3)$ 1.35 (3 H, d, *J* 7.0), 2.43 (3 H, s), 3.07 (1 H, br s), 4.29 (1 H, br s), 4.86 (1 H, d, *J* 10.2), 5.02 (1 H, d, *J* 17.2), 5.43 (1 H, ddd, *J* 17.2, 10.2 and 6.9), 7.19 (1 H, d, *J* 7.6), 7.64 (1 H, dt, *J* 7.2 and 1.3), 7.69 (1 H, d, *J* 7.9) and 8.40 (1 H, br s); **10e′** $\delta_H(CDCl_3)$ 0.87 (3 H, d, *J* 6.9), 2.42 (3 H, s), 3.04 (1 H, br s), 4.36 (1 H, br s), 5.17 (1 H, d, *J* 9.6), 5.18 (1 H, d, *J* 17.2), 6.14 (1 H, ddd, *J* 17.2, 9.6 and 7.9), 7.22 (1 H, t, *J* 7.9), 7.66 (1 H, ddd, *J* 8.6, 7.5 and 1.3), 7.72 (1 H, d, *J* 7.5) and 8.40 (1 H, br s).

1-Acetyl-2-(1-phenylallyl)-2,3-dihydro-1*H*-indol-3-one 10f. A mixture of diastereoisomers (1.2:1), as a viscous oil (Found: M^+, 291.1259. $C_{19}H_{17}NO_2$ requires *M*, 291.1259); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 and 1670; $\delta_H(CDCl_3$; the ratio of diastereoisomers, 1.2:1) 2.26 (3 H × 0.45, s), 2.43 (3 H × 0.55, s), 4.17 (1 H, br s), 4.62 (1 H × 0.45, br s), 4.71 (1 H × 0.55, br s), 5.06 (1 H × 0.55, d, *J* 9.9), 5.12 (1 H × 0.55, d, *J* 16.8), 5.28 (1 H × 0.45, d, *J* 9.9), 5.29 (1 H × 0.45, d *J* 17.2), 5.98 (1 H × 0.55, ddd, *J* 16.8, 9.9 and 9.6), 6.53 (1 H × 0.45, ddd, *J* 17.2, 9.9 and 9.6), 6.94–7.67 (8 H, m) and 7.15 (1 H × 0.55, br s); *m/z* 291 (M^+, 25%), 132 (25) and 117 (100).

1-Acetyl-2-(1-methylallyl)-2-methyl-2,3-dihydro-1*H*-indol-3-one 15e. A mixture of diastereoisomers (2.2:1), as a viscous oil (Found: M^+, 243.1268. $C_{15}H_{17}NO_2$ requires *M*, 243.1259); $\nu_{max}(CHCl_3)/cm^{-1}$ 1711 and 1668; $\delta_H(CDCl_3$; the ratio of diastereoisomers, 2.2:1) 0.74 (3 H × 0.31, d, *J* 6.9), 1.22 (3 H × 0.69, d, *J* 6.9), 1.65 (3 H × 0.31, s), 1.70 (3 H × 0.69, s), 2.53 (3 H × 0.69, s), 2.56 (3 H × 0.31, s), 3.41 (1 H, br s), 4.78 (1 H × 0.69, dd, *J* 9.9 and 1.9), 4.96 (1 H × 0.31, dd, *J* 16.8 and 1.9), 5.12 (1 H × 0.31, dd, *J* 9.9 and 1.8), 5.16 (1 H × 0.31, dd, *J* 16.8 and 1.8), 5.32 (1 H × 0.69, ddd, *J* 16.8, 9.9 and 9.2), 6.12 (1 H × 0.31, ddd, *J* 16.8, 9.9 and 9.2), 7.15–7.28 (1 H, m) and 7.6–7.8 (4 H, m); *m/z* 243 (M^+, 15%), 188 (27) and 146 (100).

1-Acetyl-2-(2-methylallyl)-2,3-dihydro-1*H*-indol-3-one 10g. A viscous oil (Found: M^+, 229.1106. $C_{14}H_{15}NO_2$ requires *M*, 229.1102); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 and 1664; $\delta_H(CDCl_3)$ 1.62 (3 H, s), 2.42 (3 H, s), 2.82 (2 H, d, *J* 4.6), 4.44 (1 H, br s), 4.73 (1 H, s), 4.78 (1 H, s), 7.21 (1 H, t, *J* 7.6), 7.63 (1 H, t, *J* 7.3), 7.74 (1 H, d, *J* 7.6) and 8.45 (1 H, br s); *m/z* 229 (M^+, 33%), 186 (10), 144 (11), 132 (100), 77 (18) and 43 (40)

(*E*)-1-Acetyl-2-(but-2-enyl)-2,3-dihydro-1*H*-indol-3-one 10h. A viscous oil (Found: M^+, 229.1099. $C_{14}H_{15}NO_2$ requires *M*, 229.1103); $\nu_{max}(CHCl_3)/cm^{-1}$ 1717 and 1667; $\delta_H(CDCl_3)$ 1.49 (3 H, dd, *J* 6.6 and 1.7), 2.48 (3 H, s), 2.81 (2 H, br s), 4.31 (1 H, br s), 5.11 (1 H, dtq, *J* 15.2, 7.3 and 1.7), 5.53 (1 H, dt, *J* 15.2 and 6.6), 7.21 (1 H, t, *J* 7.6), 7.66 (1 H, dt, *J* 7.3 and 1.3), 7.73 (1 H, d, *J* 7.6) and 8.52 (1 H, br s); *m/z* 229 (M^+, 32%), 186 (17), 175 (12), 132 (100), 77 (13) and 43 (41).

1-Acetyl-2-(cyclohex-2-enyl)-2,3-dihydro-1*H*-indol-3-one 10i. A mixture of diastereoisomers (1:1), mp 135–136 °C (from ethyl acetate–hexane) (Found: C, 74.8; H, 6.75; N, 5.3. $C_{16}H_{17}NO_2$ requires C, 75.3; H, 6.7; N, 5.5%) (Found: M^+, 255.1263. $C_{16}H_{17}NO_2$ requires *M*, 255.1260); $\nu_{max}(CHCl_3)/cm^{-1}$ 1729, 1714, 1670 and 1654; $\delta_H(CDCl_3)$ 1.41–2.11 (6 H, m), 2.41 (3 H, s), 3.04 (1 H, br s), 4.30 (1 H, br s), 5.21 (1 H × 1/2, br d, *J* 10.2), 5.67 (1 H × 1/2, br dd, *J* 10.2 and 3.2), 5.78 (1 H × 1/2, br d, *J* 10.2), 5.90 (1 H × 1/2, br dd, *J* 10.2 and 3.2), 7.24 (1 H, t, *J* 7.6), 7.65 (1 H, t, *J* 7.3), 7.69 (1 H, d, *J* 7.6) and 8.31 (1 H, br s); *m/z* 255 (M^+, 21%), 175 (68), 133 (100), 81 (24) and 43 (11).

1-Acetyl-2-(1-methylcyclohex-2-enyl)-2,3-dihydro-1*H*-indol-3-one 10j. A mixture of diastereoisomers (1.6:1), as a viscous oil, mp 133–137 °C (from ethyl acetate–hexane) (Found: M^+ 269.1412. $C_{17}H_{19}NO_2$ requires *M*, 269.1416); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 and 1663; $\delta_H(CDCl_3)$ 1.40–2.01 (6 H, m), 2.39 (3 H, s), 2.99 (1 H, br s), 4.27 (1 H, br s), 4.94 (1 H × 0.62, br s),

5.47 (1 H × 0.38, br s), 7.20 (1 H, t, *J* 7.6), 7.60–7.69 (2 H, m) and 8.33 (1 H, br s); *m/z* 269 (M^+, 8%), 175 (68), 133 (99), 133 (96), 95 (100), 77 (25), 67 (21) and 43 (29).

Conversion of 10e into (3*R,3a*R**,8b*R**)-4-acetyl-3-methyl-2,3,3a,8b-tetrahydro-4*H*-furo[3,2-*b*]indol-2-one 18e**

***cis*-1-Acetyl-3-hydroxy-2-(1-methylallyl)indoline 17e.** To a solution of indol-3-one **10e** (298 mg, 1.3 mmol) in methanol (30 cm^3), was added sodium borohydride (493 mg, 13 mmol) at 0 °C. The mixture was stirred for 30 min, and then concentrated under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate and the solvent evaporated. The residue was chromatographed on silica gel with diethyl ether–hexane (3:1) as an eluent to give the alcohol **17e** (243 mg, 81%) as a viscous oil (Found: M^+, 231.1258. $C_{14}H_{17}NO_2$ requires *M*, 231.1259); $\nu_{max}(CHCl_3)/cm^{-1}$ 3430 and 1639; $\delta_H(CDCl_3)$ 1.11 (3 H, d, *J* 6.9), 2.39 (3 H, s), 2.28 (1 H, s), 2.38 (1 H, d, *J* 8.9), 2.78 (1 H, br s), 4.91 (1 H, d, *J* 10.2), 5.03 (1 H, d, *J* 17.5), 5.56 (1 H, t, *J* 7.9), 5.83 (1 H, ddd, *J* 17.5, 10.2 and 6.3), 7.04 (1 H, t, *J* 7.6), 7.18 (1 H, d, *J* 7.6), 7.23 (1 H, t, *J* 8.9) and 7.95 (1 H, br s); *m/z* 231 (M^+, 18%), 213 (38), 176 (51), 171 (48), 156 (52), 134 (100) and 43 (14).

Furo[3,2-*b*]indol-2-one 18e. A solution of the alcohol **17e** (50 mg, 0.22 mmol) in methylene dichloride (5.5 cm^3) and methanol (0.5 cm^3) was cooled to −78 °C, and ozone was bubbled into the mixture until the colour of the solution turned blue. The excess ozone was purged with argon, and dimethyl sulfide (0.047 cm^3, 0.65 mmol) was added. The mixture was allowed to warm to room temperature overnight, and then concentrated under reduced pressure. An ethyl acetate–hexane (3:2) solution of the residue was passed through a silica gel column to give a product (11.3 mg). A solution of the product in methylene dichloride (0.2 cm^3) was added to a solution of pyridinium chlorochromate (PCC, 98%, 53.6 mg, 0.24 mmol) in methylene dichloride (1.5 cm^3) at room temperature. After stirring for 3 h, diethyl ether (3 cm^3), magnesium sulfate (0.4 g) and molecular sieves (4 Å) were added to the mixture, and the mixture was stirred for 10 min. The solids were removed by filtration, and the filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography with ethyl acetate–hexane (3:2) to give lactone **18e** (6.3 mg, 12%), mp 145–148 °C (diethyl ether–hexane) (Found: M^+, 231.0891. $C_{13}H_{13}NO_3$ requires *M*, 231.0895); $\nu_{max}(CHCl_3)/cm^{-1}$ 1776 and 1664; $\delta_H(CDCl_3$, at 24 °C) 1.61 (3 H, d, *J* 7.6), 2.33 (3 H × 1/3, s), 2.49 (3 H × 2/3, s), 2.85 (1 H, br s), 4.68 (1 H × 1/3, br s), 4.81 (1 H × 2/3, br s), 5.97 (1 H × 2/3, br s), 6.12 (1 H × 1/3, br s), 7.05–7.27 (4/3 H, m), 7.30–7.71 (5/3 H, m) and 8.25 (1 H, br s); δ_H[$^2H_6$]DMSO, at 80 °C) 1.46 (3 H, d, *J* 7.6), 2.49 (3 H, s), 2.85 (1 H, br s), 3.00 (1 H, m), 4.88 (1 H, dd, *J* 7.9 and 3.0), 6.17 (1 H, *J* 7.9), 7.13 (1 H, t, *J* 7.3), 7.39 (1 H, t, *J* 7.3), 7.49 (1 H, d, *J* 6.9) and 7.88 (1 H, br s); *m/z* 231 (M^+, 100%), 189 (95), 144 (69), 133 (52), 130 (78) and 43 (37).

Conversion of 10e′ into (3*S,3a*R**,8b*R**)-4-acetyl-3-methyl-2,3,3a,8b-tetrahydro-4*H*-furo[3,2-*b*]indol-2-one 18e′**

***cis*-1-Acetyl-3-hydroxy-2-(1-methylallyl)indoline 17e′.** Using a procedure similar to that described above for the preparation of **17e**, **10e′** (63 mg, 0.28 mmol) was treated with sodium borohydride (104 mg, 2.8 mmol) in methanol (7 cm^3) to afford **17e′** (50 mg, 77%), as a viscous oil (Found: M^+, 231.1251. $C_{14}H_{17}NO_2$ requires *M*, 231.1258); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410 and 1643; $\delta_H(CDCl_3)$ 1.10 (3 H, d, *J* 6.9), 2.35 (3 H, s), 2.42 (1 H, d, *J* 8.3), 2.91 (1 H, br s), 4.90 (1 H, d, *J* 9.6), 5.00 (1 H, d, *J* 17.5), 5.29–5.74 (2 H, m), 7.11 (1 H, t, *J* 7.3), 7.25 (1 H, d, *J* 7.6), 7.29 (1 H, t, *J* 7.6) and 7.90 (1 H, br s); *m/z* 231 (M^+, 21%), 213 (26), 176 (58), 171 (30), 156 (34), 134 (100) and 43 (13).

Furo[3,2-*b*]indol-2-one 18e′. Using a procedure similar to that described above for the preparation of **18e**, **17e′** (35 mg, 0.15 mmol) was converted into **18e′** (7.3 mg, 21%), mp 122–126 °C (diethyl ether–hexane) (Found: M^+, 231.083. $C_{13}H_{13}NO_3$ requires *M*, 231.0895); $\nu_{max}(CHCl_3)/cm^{-1}$ 1774 and 1658; $\delta_H(CDCl_3$, at 24 °C) 1.15 (3 H, d, *J* 7.6), 2.23 (3 H × 1/2, br s), 2.40 (3 H × 1/2, br s), 3.05 (1 H, br s), 5.12 (1 H × 1/2, br s), 5.40 (1 H × 1/2, br s), 6.05 (1 H, br s), 7.09 (1 H, t, *J* 7.6), 7.33 (1 H, d, *J* 7.3), 7.41 (1 H, br s) and 8.20 (1 H, br s); δ_H([$^2H_6$]DMSO, at 80 °C) 0.89 (3 H, d, *J* 7.9), 2.19 (3 H, s), 3.16 (1 H, dq, *J* 9.2 and 7.9), 5.27 (1 H, dd, *J* 9.2 and 8.9), 6.16 (1 H, *J* 8.9), 7.06 (1 H, t, *J* 7.3), 7.30 (1 H, t, *J* 7.9), 7.38 (1 H, d, *J* 7.6) and 7.82 (1 H, d, *J* 7.9); *m/z* 231 (M^+, 36%), 189 (44), 144 (58), 133 (32), 130 (100) and 43 (50).

Acknowledgements

This work was supported by Special Coordination Funds of the Science and Technology Agency of the Japanese Government. We are grateful to Miss T. Koseki for her technical assistance, and to Mr N. Eguchi, Miss S. Yoshioka and Miss T. Koseki for measurements of microanalytical, NMR (NOE experiment) and mass spectral data.

References

1 J. Y. Merour, J. Y. Coadou and F. Tatibouet, *Synthesis*, 1982, 1053; A. Buzas, C. Herisson and G. Lavielle, *Synthesis*, 1977, 129; K. N. Kilminster and M. Sainsbury, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2264; F. Nivoliers, A. Decormeille, A. Godard and G. Quequiner, *Tetrahedron Lett.*, 1980, **21**, 4485; G. Argiropoulos, L. W. Deady and M. Dorkos, *Aust. J. Chem.*, 1991, **44**, 481; T. Kawasaki, Y. Nonaka, M. Uemura and M. Sakamoto, *Synthesis*, 1991, 701; T. Kawasaki, Y. Nonaka, M. Akahane, N. Maeda and M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1777.

2 P. S. Steyn, *Tetrahedron Lett.*, 1971, 3331.

3 A. J. Birch and J. J. Wright, *J. Chem. Soc., Chem. Commun.*, 1969, 644; A. J. Birch and R. A. Russell, *Tetrahedron*, 1972, **28**, 2999.

4 M. Barbetta, G. Casnati, A. Pochini and A. Silva, *Tetrahedron Lett.*, 1969, 4457.

5 T. A. Smitka, R. Bonjouklian, L. Doolin, N. D. Jones, J. B. Deeter, W. Y. Yoshida, M. R. Prinsep, R. E. Moore and G. M. L. Patterson, *J. Org. Chem.*, 1992, **57**, 857; C. Christopherson, *The Alkaloids*, 1985, **24**, 25; M. A. O'Leary and J. R. Hanson, *Tetrahedron Lett.*, 1982, **23**, 1855.

6 J. F. Sanz-Cervera, T. Glinka and R. M. Williams, *J. Am. Chem. Soc.*, 1993, **115**, 347.

7 (*a*) J.-Y. Mérour, L. Chichereau and J.-P. Finet, *Tetrahedron Lett.*, 1992, **33**, 3867; (*b*) T. Kawasaki, Y. Nonaka, M. Kobayashi and M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2445 and references cited therein; (*c*) S. C. Conway and G. W. Gribble, *Heterocycles*, 1990, **30**, 627; (*d*) A. Buzas and J.-Y. Mérour, *Synthesis*, 1989, 458; (*e*) H. Plieninger, H. Sirowej and D. Rau, *Chem. Ber.*, 1971, **104**, 1863; (*f*) E. Houghton and J. E. Saxton, *J. Chem. Soc.* (*C*), 1969, 595.

8 T. Kawasaki, K. Masuda, Y. Baba, K. Takada and M. Sakamoto, *Chem. Pharm. Bull.*, 1994, **42**, 1974.

9 C.-S. Chien, A. Hasegawa, T. Kawasaki and M. Sakamoto, *Chem. Pharm. Bull.*, 1986, **34**, 1493.

10 P. Wipf, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, p. 827; F. E. Zieglar, *Chem. Rev.*, 1988, **88**, 1423; S. J. Rhoads and N. R. Raulins, *Org. React.* (N. Y.), 1975, **22**, 1.

11 C.-S. Chien, T. Suzuki, T. Kawasaki and M. Sakamoto, *Chem. Pharm. Bull.*, 1984, **32**, 3945.

12 T. Kawasaki, H. Ohtsuka, C.-S. Chien, M. Omata and M. Sakamoto, *Chem. Pharm. Bull.*, 1987, **35**, 1339.

Paper 5/05265C
Received 7*th August* 1995
Accepted 16*th October* 1995