Pergamon

Tetrahedron 54 (1998) 7765–7776

TETRAHEDRON

# Intramolecular Heck Reaction: Synthesis of Benzo[4,5]cyclohepta[*b*]indole Derivatives[1]

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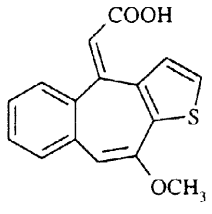
Received 26 January 1998; accepted 28 April 1998

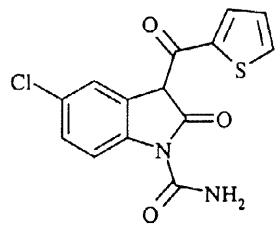
***Abstract:*** *An intramolecular Heck reaction was performed with palladium(II) acetate on iodoethylenic esters 6-7 to afford an ethylenic seven-membered system 8-9. α-alkylation of 8 was investigated to afford the corresponding α-methyl compound 10. This new family of compounds 11-12 gave access to potential antiinflammatory agents.* © 1998 Elsevier Science Ltd. All rights reserved.

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for treatment of acute and chronic inflammatory disorders such as osteoarthritis and rheumatoid arthritis.[2] These agents reduce the pain by blocking the production of prostaglandins from arachidonic acid *via* the cyclooxygenase pathway.[3] Unfortunately, the use of these drugs has been linked to the induction of gastrointestinal mucosal lesions, perforations and bleeding in part of the population.[4]

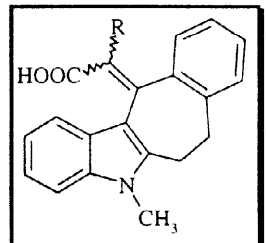
On the other hand, a number of synthetic compounds have been reported to inhibit the biosynthesis or release of interleukin-1β (IL-1β) from monocytes and macrophages.[5] This inflammatory mediator is known to affect many different tissues, eliciting and amplifying the inflammatory response.[6] Drugs that interfere with IL-1β represent a new therapeutic approach for the treatment of inflammation. Among them, two substances IX207-887 (**1**)[7] and Tenidap (**2**),[8] has retained our attention.




**1**




**2**




**11** R= H
**12** R= $CH_3$

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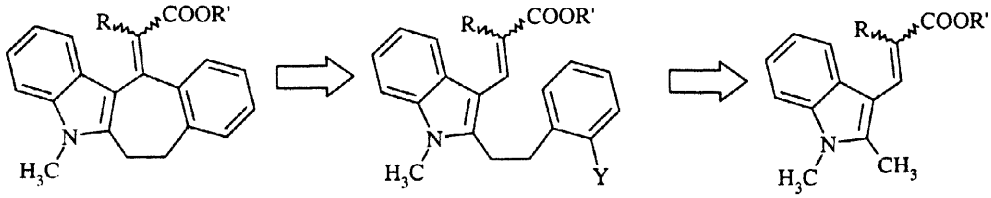
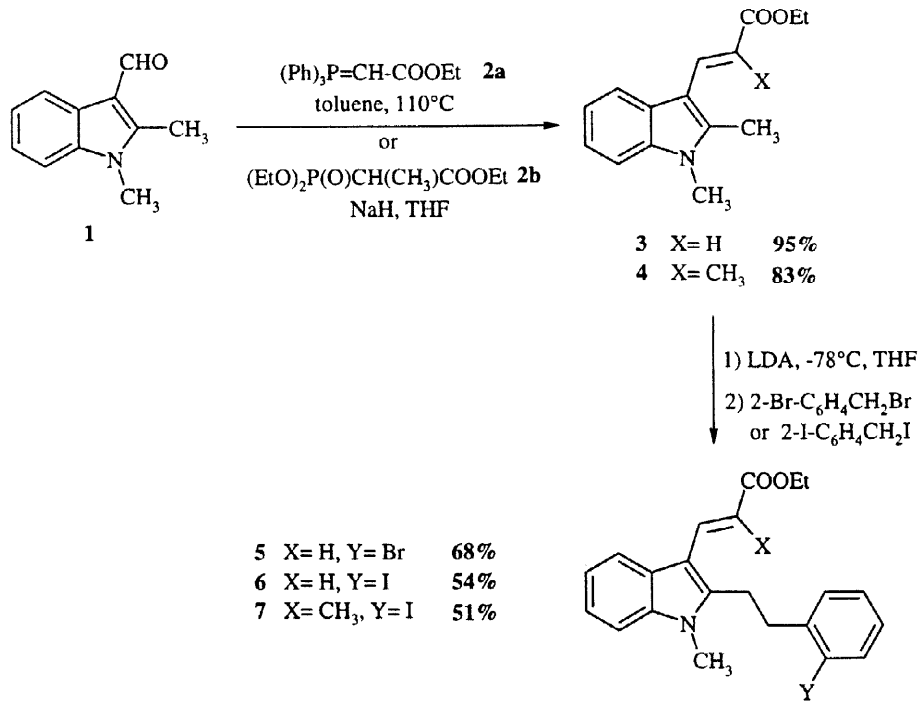
*PII:* S0040-4020(98)00412-8

Taking the above structure into consideration, we report herein our results concerning the synthesis of a new family of compounds having an indole and a phenyl rings around a central seven-membered ring bearing an acetic acid side chain in order to obtain the previously unknown tetracyclic compounds **11, 12** as candidates for potential new antiinflammatory drugs.

The first attempts to construct the target compound were based on the Wittig or Wadsworth-Emmons reactions of 5-methyl-6,7-dihydrobenzo[4,5]cyclohept[*b*]indol-12(5*H*)-one.[9] Unfortunately, this synthetic pathway failed, so an intramolecular Heck annulation[10] of ethylenic esters was investigated to provide the fused seven-membered ring.



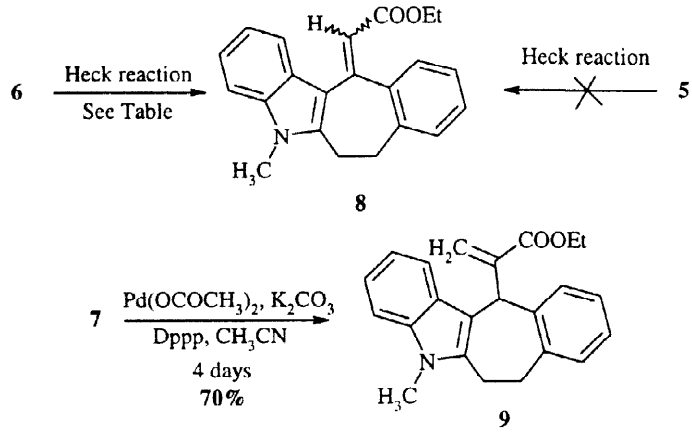

The synthesis of the esters is outlined in Scheme 1. 3-Formyl-1,2-dimethylindole (**1**)[11] was treated either with (carbethoxymethylene)triphenylphosphorane (**2a**) in refluxing toluene to give α,β ethylenic ethyl ester **3**[12] in 95% yield or with ethyldiethylphosphonopropanoate (**2b**) in the presence of sodium hydride in THF to afford **4** in 83% yield. These compounds are obtained as *E* isomers (assignment by NMR analysis and NOE experiments for **4**). Lithiation of the methyl in 2-position of **3** with LDA in THF at -78 °C gave a bright red solution in 5 minutes, then 2-bromobenzyl bromide was added to afford **5** in 68% yield.




**Scheme 1**

Similarly, anion intermediates of **3** and **4** were also condensed with freshly prepared 2-iodobenzyl iodide to afford **6** and **7** in 54% and 51% yield respectively. For information, we observed for **4** a regioselective alkylation on the C-2 methyl group of the indole moiety.

Heck reaction of ester **5-7** was then undergone (Scheme 2). Intramolecular cyclisation, first, was performed with the bromo derivative **5** under different conditions. This compound failed to give **8**, the starting material **5** being recovered unchanged. As reported in the literature, iodoarenes are often better starting material than bromoarenes.[13] The compound **8** was obtained as a mixture of *Z,E* isomers from the iodo derivative **6** in moderate to good yield according to the conditions applied (See Table). Gilschrist indicated also a mixture of stereoisomers in the Heck cyclisation of ethyl (*E*) 1-(2-iodobenzyl)indole-2-propenoate.[13] Optimized yield was obtained when the starting material was stirred 4 days in refluxing acetonitrile in the presence of palladium(II) acetate, 1,3-bis-(diphenylphosphino)propane (Dppp), potassium carbonate and benzyltriethylammonium chloride.




**Scheme 2**

In the same conditions, the cyclisation of **7** was carried out to afford the unexpected compound **9** (70%). The formation of **9** may be either the result of the isomerisation of α-methyl compound **10** in the presence of $Pd(OAc)_2$, or a favorable β–elimination of the C-H of the methyl substituent in the palladium intermediate.

Table: Synthesis of **8** by Heck reaction from **6**

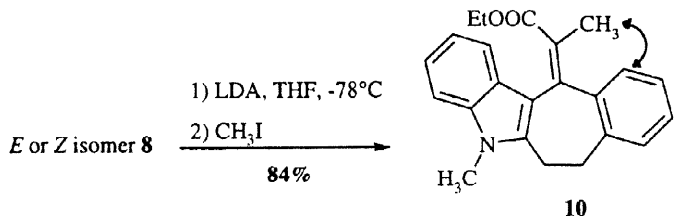
| Palladium catalyst | Ligands added | Base | Solvent | Yield (%) |
|---|---|---|---|---|
| $Pd(OCOCH_3)_2$ (0.1 eq.) | $Ph_3P$ (0.2 eq.) | $(CH_3COO)_2Tl$ ( 2 eq.) | $CH_3CN$ | 20 |
| $Pd(OCOCH_3)_2$ (0.05 eq.) | $Ph_3P$ (0.2 eq.) | $K_2CO_3$ (2 eq.) | $CH_3CN$ | 36 |
| $(PPh_3)_4Pd$ (0.05 eq.) | / | $K_2CO_3$ (5 eq.) | $CH_3CN$ | 42 |
| $(PPh_3)_2PdCl_2$ (0.05 eq.) | / | $(CH_3CH_2)_3N$ | $(CH_3CH_2)_3N$ | 70 |
| $Pd(OCOCH_3)_2$ (0.2 eq.) | Dppp (0.4 eq.)[a] | $K_2CO_3$ (5 eq.) | $CH_3CN$ | 83 |

a) Benzyltriethylammonium chloride (0.15 eq.) were also added.

From the cyclisation reaction, a mixture of *E/Z* stereomers of **8**,[14] separated by column chromatography, was obtained where the *E* isomer was initially predominant (8:2 *E/Z* ratio) according to the usual tenets of *cis*-addition and *syn*-elimination of the Heck reaction.[15] The $^1$H NMR spectrum for the *E* isomer showed a singulet at 6.18 ppm attributable to the ethylenic proton, in the case of the *Z* isomer the same proton was observed at 6.49 ppm as a singulet. At room temperature in a chloroform solution, the pure *E* isomer of **8** was slowly equilibrated into a mixture of stereomers (3:7 *E/Z* ratio).

We decided to investigate briefly the metallation of the ethylenic carbon[16] in the aim to obtain the α-methyl compound **10** from **8**.

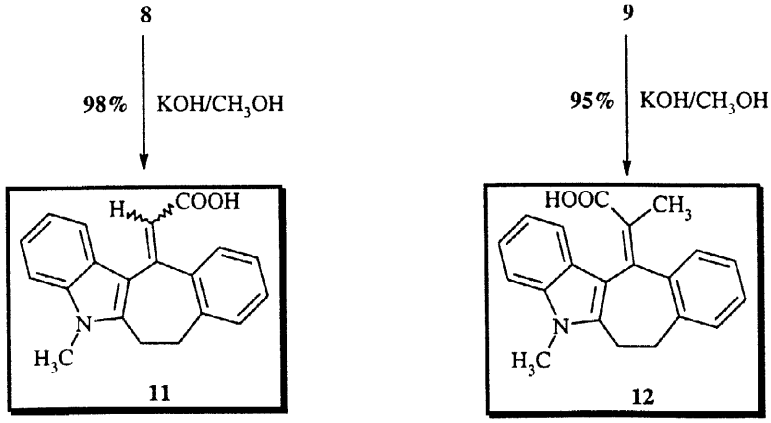
Lithiation of only *E* isomer of **8** was performed with 1 equivalent of LDA at -78 °C in THF, followed by the addition of iodomethane to afford **10** as only one isomer in fair yield (Scheme 3). Following the same procedure, *Z* isomer of **8** gave also **10**. Assignment of the configuration of the compound **10** was based on H-H interactions in NOE spectrum in DMSO-$d_6$. The connectivities observed between the α-methyl group and H-11 proton showed that the compound **10** possessed the *Z* configuration.




**Scheme 3**

In all attempts in our laboratory, no methyl alkylation was observed on the seven-membered ring. α-Alkylation of compound **8** is effective and introduction of miscellaneous groupments can be considered.

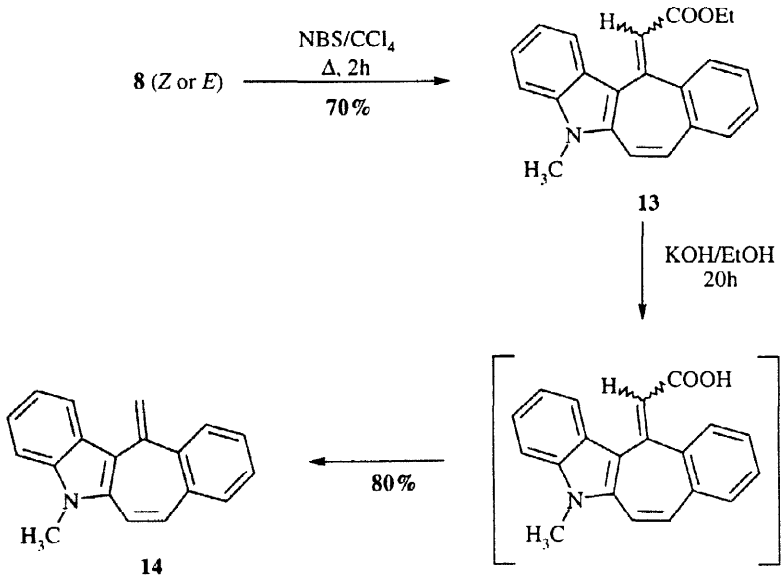
Finally, the esters **8** (*Z* or *E* isomer) and **10** were converted into the corresponding acids **11** (1:1 *E/Z* ratio, not separable) and **12** in good yields (Scheme 4).




**Scheme 4**

The $^1$H NMR spectrum in DMSO-$d_6$ for **11** showed two signals for ethylenic proton at 6.28 (*Z* isomer) and 6.01 (*E* isomer) as singulets. For **12**, one signal for the α-methyl group was observed at 3.60 as a singulet.

Finally, we planned the preparation of the insaturated acid in two steps. Bromination of *E* or *Z* isomer **8** with one equivalent of *N*-bromosuccinimide and subsequent spontaneous dehydrobromination (without addition of base) in boiling $CCl_4$ gave **13** (3:2 *E/Z* ratio, not separable).[17] The use of AIBN in this reaction gave a mixture of brominated products. Alkaline hydrolysis of the ester **13** afforded the unstable acid which spontaneously lost $CO_2$ to give **14** (Scheme 5).




**Scheme 5**

In summary, the present article developed an effective synthetic route to a new series of compounds via an intramolecular Heck reaction. The lead compound **8** was obtained in good yield as a mixture of stereomers separated by column chromatography. Metallation of the ethylenic carbon of the ester **8** gave access to α-alkyl **10**. Final saponification of ethylenic esters **8** and **10** afforded the tetracyclic acids **11** and **12** as potent antiinflammatory drugs.

## Experimental

*General*: Melting points were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. The infrared spectra of compounds were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. NMR spectra were recorded at 300 °K in $CDCl_3$ or DMSO-$d_6$ on a Bruker Avance DPX 250. Chemical shifts are expressed in parts per million and referenced to TMS. Mass spectra were recorded on Perkin-Elmer SCIEX API 300 using ionspray methodology. Thin layer chromatography was performed on

precoated plate of silica gel $60F_{254}$ (Merck) and the spots visualised using an ultraviolet lamp. Column chromatography was performed with Merck silica gel 60 (0.040 mm-0.063 mm) as the stationary phase. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone before use. All air and moisture sensitive reactions were conducted under a prepurified argon atmosphere in flame-dried glassware. Anhydrous solvents or reactifs were transferred via syringe.

**Ethyl (*E*)-3-(1,2-dimethyl-*1H*-3-indolyl)-2-propenoate[12] (3)**

To a suspension of (carbethoxymethylene)triphenylphosphorane (**2a**) (1.0 g, 2.87 mmol) in toluene (20 ml) was added 1,2-dimethyl-3-formylindole (**1**)[11] (200 mg, 1.15 mmol). The reaction mixture was stirred at reflux for 5 days under argon atmosphere. After cooling to room temperature, the reaction was diluted with water (20 ml) and extracted with toluene (2 x 10 ml). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by column chromatography (eluent petroleum ether-ethyl acetate 8:2) to give **3** (265 mg, 95%) as crystals; m.p. 70-72 °C (methanol); IR (KBr) ν 1693 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.1 Hz, $CH_3$), 2.52 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 4.31 (q, 2H, J = 7.1 Hz, $CH_2$), 6.43 (d, 1H, J = 15.8 Hz, CH=CH), 7.21-7.28 (m, 3H, $H_{Ar}$), 7.88-7.92 (m, 1H, $H_{Ar}$), 7.98 (d, 1H, J = 15.8 Hz, CH=CH); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 10.7 ($CH_3$), 14.5 ($CH_3$), 29.8 ($CH_3$), 59.9 ($CH_2$), 109.0 (C), 109.3 (CH), 111.4 (CH), 120.1 (CH), 121.3 (CH), 122.1 (CH), 125.7 (C), 137.6 (C), 137.7 (CH), 141.7 (C), 168.8 (CO); Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.37; H, 7.19; N, 5.61; MS m/z 244 $(M+1)^+$.

**Ethyl (*E*)-3-(1,2-dimethyl-*1H*-3-indolyl)-2-methyl-2-propenoate (4)**

To a suspension of sodium hydride (60 mg, 2.50 mmol, 60% mineral oil dispersion) in THF (10 ml) was added slowly a solution of ethyldiethylphosphonopropanoate (**2b**) (550 mg, 2.30 mmol) in THF (10 ml) at 0 °C. After 10 min, a solution of 1,2-dimethyl-3-formylindole **1**[11] (200 mg, 1.15 mmol) in THF (10 ml) was added. The solution was heated at 50 °C for 2 h. After cooling and the solvent removed under reduced pressure, the residue obtained was hydrolysed with 20 ml of water, then neutralised with 10% hydrochloric acid and finally extracted with dichloromethane (2 x 10 ml). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by column chromatography (eluent petroleum ether-ethyl acetate 8:2) to give **4** (260 mg, 88%) as crystals; m.p. 78-79 °C (methanol); IR (KBr) ν 1697 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.37 (t, 3H, J = 7.1 Hz, $CH_3$), 1.97 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 3.70 (s, 3H, $CH_3$), 4.29 (q, 2H, J = 7.1 Hz, $CH_2$), 7.11-7.31 (m, 3H, $H_{Ar}$), 7.47 (d, 1H, J = 7.6 Hz, $H_{Ar}$), 7.86 (s, 1H, CH=); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 11.7 ($CH_3$), 14.4 ($CH_3$), 15.7 ($CH_3$), 29.7 ($CH_3$), 60.5 ($CH_2$), 108.9 (C), 109.0 (CH), 119.7 (CH), 119.8 (CH), 121.2 (CH), 126.3 (C), 126.5 (C), 132.8 (CH), 136.4 (C), 136.9 (C), 168.9 (CO); Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.26; N, 5.53; MS m/z 258 $(M+1)^+$.

**Ethyl (*E*)-3-[2-(2-bromophenethyl]-1-methyl-*1H*-3-indolyl]-2-propenoate (5)**

To a stirred solution of **3** (300 mg, 1.23 mmol) in anhydrous THF (20 ml) was added slowly a solution of 2 M lithium diisopropylamide in heptane (0.93 ml, 1.85 mmol) under argon atmosphere at -78 °C. After 5 min, a solution of 2-bromobenzyl bromide (922 mg, 3.69 mmol) in THF (20 ml) was added dropwise with vigorous stirring at -78 °C. The mixture was stirred 1/2 h at -78 °C, then 1 h at room temperature. The reaction was quenched with water and THF was evaporated to dryness *in vacuo*. The residue was partitioned between dichloromethane (10 ml) and 10% hydrochloric acid (10 ml), the aqueous phase separated and extracted with dichloromethane (2 x 10 ml). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude oil was purified by column chromatography using petroleum ether-ethyl acetate 9:1 as the eluting solvent to afford **5** (346 mg, 68%) as crystals; m.p. 96-98 °C (petroleum ether-dichloromethane); IR (KBr) ν 1699 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.1 Hz, $CH_3$), 3.02-3.08 (m, 2H, $CH_2$), 3.22-3.28 (m, 2H, $CH_2$), 3.61 (s, 3H, $CH_3$), 4.28 (q, 2H, J = 7.1 Hz, $CH_2$), 6.42 (d, 1H, J = 15.8 Hz, CH=), 7.04-7.29 (m, 6H, $H_{Ar}$), 7.56 (br d, 1H, J = 7.2 Hz, $H_{Ar}$), 7.89-7.92 (m, 1H, $H_{Ar}$), 7.95 (d, 1H, J = 15.8 Hz, CH=); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 14.5 ($CH_3$), 24.9 ($CH_2$), 29.8 ($NCH_3$), 37.0 ($CH_2$), 59.9 ($OCH_2$), 109.3 (C), 109.6 (CH), 112.0 (CH), 120.4 (CH), 121.4 (CH), 122.3 (CH), 125.6 (C), 125.9 (CH), 127.8 (CH), 128.4 (CH), 130.8 (CH), 132.9 (C), 137.2 (CH), 137.6 (C), 139.3 (C), 144.0 (C), 168.6 (CO); Anal. Calcd. for $C_{22}H_{22}BrNO_2$: C, 64.09; H, 5.38; N, 3.40. Found: C, 64.18; H, 5.54; N, 3.31; MS m/z 411 $(M+1)^+$, 413 $(M+3)^+$.

**Ethyl (*E*)-3-[2-(2-iodophenethyl]-1-methyl-*1H*-3-indolyl]-2-propenoate (6)**

Following the procedure used for **5** but substituting 2-bromobenzyl bromide by 2-iodobenzyl iodide, purification of the residue by column chromatography (eluent petroleum ether-ethyl acetate 9:1) afforded **6** (54%) as crystals; m.p. 92-94 °C (petroleum ether-dichloromethane); IR (KBr) ν 1696 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.1 Hz, $CH_3$), 3.00-3.06 (m, 2H, $CH_2$), 3.18-3.23 (m, 2H, $CH_2$), 3.57 (s, 3H, $CH_3$), 4.27 (q, 2H, J = 7.1 Hz, $CH_2$), 6.42 (d, 1H, J = 15.8 Hz, CH=), 6.45-7.27 (m, 6H, $H_{Ar}$), 7.82 (d, 1H, J = 8.0 Hz, $H_{Ar}$), 7.89-7.91 (m, 1H, $H_{Ar}$), 7.95 (d, 1H, J = 15.8 Hz, CH=); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 14.6 ($CH_3$), 25.1 ($CH_2$), 29.9 ($NCH_3$), 41.3 ($CH_2$), 59.9 ($OCH_2$), 100.0 (C), 109.3 (C), 109.6 (CH), 112.0 (CH), 120.3 (CH), 121.4 (CH), 122.3 (CH), 125.6 (C), 128.4 (CH), 128.7 (CH), 129.9 (CH), 137.2 (CH), 137.6 (C), 139.5 (CH), 142.6 (C), 143.8 (C), 168.5 (CO); Anal. Calcd. for $C_{22}H_{22}INO_2$: C, 57.53; H, 4.83; N, 3.05. Found: C, 57.35; H, 4.91; N, 3.22; MS m/z 460 $(M+1)^+$.

**Ethyl (*E*)-3-[2-(2-iodophenethyl]-1-methyl-*1H*-3-indolyl]-2-methyl-2-propenoate (7)**

Following the procedure used for **6** but substituting **3** by **4**, purification of the residue by column chromatography (eluent petroleum ether-ethyl acetate 9:1) afforded **7** (68%) as an yellow oil; IR (film) ν 1697 (CO) $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.37 (t, 3H, J = 7.1 Hz, $CH_3$), 1.94 (d, 3H, J = 1.6 Hz, $CH_3$), 2.93-2.99 (m, 2H, $CH_2$), 3.04-3.11 (m, 2H, $CH_2$), 3.63 (s, 3H, $CH_3$), 4.28 (q, 2H, J = 7.1 Hz, $CH_2$), 6.80-7.42 (m,

7H, $H_{Ar}$), 7.68 (d, 1H, J = 1.6 Hz, CH=), 7.75 (dd, 1H, J = 1.2, 7.9 Hz, $H_{Ar}$); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 14.5 ($CH_3$), 15.8 ($CH_3$), 25.7 ($CH_2$), 29.7 ($NCH_3$), 40.6 ($CH_2$), 60.3 ($OCH_2$), 100.1 (C), 109.1 (CH), 109.3 (C), 119.8 (CH), 120.5 (CH), 121.2 (CH), 125.8 (C), 126.2 (C), 128.2 (CH), 128.4 (CH), 129.8 (CH), 132.5 (CH), 136.9 (C), 139.3 (C), 139.4 (CH), 142.7 (C), 168.6 (CO); Anal. Calcd. for $C_{23}H_{24}INO_2$: C, 58.36; H, 5.11; N, 2.96. Found: C, 58.02; H, 5.19; N, 2.93; MS m/z 473 $(M+1)^+$.

**Ethyl 2-(5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-yliden)acetate (8)**

To a solution of indole **6** (300 mg, 0.65 mmol) in $CH_3CN$ (15 ml), was added palladium acetate(II) (29 mg, 0.13 mmol), Dppp (109 mg, 0.26 mmol), potassium carbonate (451 mg, 3.26 mmol) and triethyl benzyl ammonium chloride (23 mg, 0.1 mmol). The mixture was then stirred at reflux for 4 days. After cooling, the solvent was evaporated. The crude product was purified by chromatography on silica gel (petroleum ether-ethyl acetate 3:7 as eluent) to afford **8** (*Z* isomer: 36 mg; *E* isomer: 144 mg; 83% overall yield).

*Z* isomer: m.p. 170-172 °C (petroleum ether-dichloromethane); IR (KBr) ν 1696 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.20 (t, 3H, J = 7.3 Hz, $CH_3$), 2.80-3.60 (m, 4H, $CH_2$), 3.60 (s, 3H, $CH_3$), 4.11 (q, 2H, J = 7.3 Hz, $CH_2$), 6.49 (s, 1H, CH=), 7.08-7.35 (m, 7H, $H_{Ar}$), 7.92-7.95 (m, 1H, $H_{Ar}$); $^{13}C$ NMR ($CDCl_3$) δ 14.2 ($CH_3$), 27.7 ($CH_2$), 29.3 ($NCH_3$), 31.2 ($CH_2$), 59.7 ($OCH_2$), 108.8 (CH), 112.6 (C), 116.6 (CH), 119.2 (CH), 120.4 (CH), 121.8 (CH), 125.1 (C), 125.7 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 136.2 (C), 136.9 (C), 138.3 (C), 141.3 (C), 151.9 (C), 166.5 (CO); Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.53; H, 6.50; N, 4.35; MS m/z 332 $(M+1)^+$.

*E* isomer: m.p. 218-220 °C (*n*-Butanol); IR (KBr) ν 1696 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.10 (t, 3H, J = 7.3 Hz, $CH_3$), 2.80-3.60 (m, 4H, $CH_2$), 3.59 (s, 3H, $CH_3$), 4.11 (q, 2H, J = 7.3 Hz, $CH_2$), 6.18 (s, 1H, CH=), 7.08-7.35 (m, 8H, $H_{Ar}$); $^{13}C$ NMR ($CDCl_3$) δ 14.1 ($CH_3$), 27.8 ($CH_2$), 29.3 ($NCH_3$), 30.6 ($CH_2$), 60.1 ($OCH_2$), 108.7 (CH), 110.4 (C), 117.5 (CH), 119.7 (CH), 120.0 (CH), 121.3 (CH), 125.5 (C), 125.5 (CH), 126.9 (CH), 127.8 (CH), 128.3 (CH), 136.6 (C), 136.8 (C), 137.8 (C), 145.8 (C), 150.8 (C), 166.8 (CO); Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 80.03; H, 6.49; N, 4.11; MS: m/z 332 $(M+1)^+$.

**Ethyl 2-(5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-yl)acrylate (9)**

Following the procedure used for **8** but substituting **6** by **7**, purification of the residue by column chromatography (eluent petroleum-ethyl acetate 9:1) afforded **9** (55%) as crystals; m.p. 169-170 °C (petroleum ether-dichloromethane); IR (KBr) ν 1715 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz, $CH_3$), 2.77-2.90 (m, 2H, $CH_2$), 3.13-3.23 (m, 1H, $CH_2$), 3.57-3.67 (m, 1H, $CH_2$), 3.61 (s, 3H, $CH_3$), 4.04-4.24 (m, 2H, $CH_2$), 5.40 (broad s, 1H, $CH_2$=), 5.48 (broad s, 1H, $CH_2$=), 6.15 (broad s, 1H, CH), 7.06-7.26 (m, 6H, $H_{Ar}$), 7.48-7.55 (m, 2H, $H_{Ar}$); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 26.7 ($CH_2$), 29.2 ($NCH_3$), 29.8 ($CH_2$), 44.2 (CH), 60.6 ($OCH_2$), 108.4 (CH), 108.7 (C), 117.5 (CH), 119.0 (CH), 121.0 (CH), 125.0 ($CH_2$=), 125.8 (C), 126.3 (CH), 127.0 (CH), 127.4 (C), 129.6 (CH), 131.4 (CH), 136.4 (C), 136.6 (C), 140.4 (C), 143.4

(C), 167.4 (CO); Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.86; H, 6.79; N, 4.23; MS m/z 346 $(M+1)^+$.

**Ethyl 2-(5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-yliden)propanoate (10)**

To a stirred solution of **8** *Z* isomer (100 mg, 0.30 mmol) in anhydrous THF (5 ml) at -78 °C was added dropwise a solution of 2M lithium diisopropylamide in heptane (0.20 ml, 0.39 mmol) under argon atmosphere. The red mixture was stirred for 20 min at - 78 °C then a solution of iodomethane (0.06 ml, 0.90 mmol) in THF (1 ml) was added dropwise. When addition was complete, the solution was stirred 10 min at -78 °C, then finally brought to room temperature. THF was distilled off at reduced pressure. The residue was partitioned between dichloromethane (5 ml) and 10% hydrochloric acid (5-6 drops), the aqueous phase separated and extracted with dichloromethane (2 x 5 ml). The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude oil was purified by column chromatography using petroleum ether-ethyl acetate 9:1 as the eluting solvent to afford **10** (88 mg, 84%) as crystals; m.p. 220-222 °C (petroleum ether-dichloromethane); IR (KBr) ν 1712 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.2 Hz, $CH_3$), 2.13 (s, 3H, $CH_3$), 2.77-3.01 (m, 2H, $CH_2$), 3.23 (dt, 1H, J = 3.8, 16.9 Hz, $CH_2$), 3.51 (td, 1H, J = 3.8, 16.9 Hz, $CH_2$), 3.57 (s, 3H, $CH_3$), 3.97 (q, 2H, J = 7.2 Hz, $CH_2$), 7.04-7.27 (m, 7H, $H_{Ar}$), 7.44-7.52 (m, 1H, $H_{Ar}$); $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 13.7 ($CH_3$), 18.4 ($CH_3$), 27.5 ($CH_2$), 29.2 ($NCH_3$), 30.1 ($CH_2$), 60.6 ($OCH_2$), 108.6 (CH), 110.9 (C), 119.4 (CH), 120.0 (CH), 120.9 (CH), 125.2 (C), 125.7 (CH), 126.0 (CH), 126.7 (CH), 127.8 (CH), 136.1 (C), 131.2 (C), 136.4 (2C), 139.4 (C), 145.4 (C), 170.4 (CO); Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.30; H, 6.87; N, 3.98; MS m/z 346 $(M+1)^+$.

**2-(5-Methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-yliden)acetic acid (11)**

A solution of ester **8** (366 mg, 1.10 mmol, *E* or *Z* isomer) in ethanol 95% (15 ml) and sodium hydroxide (250 mg, 6.25 mmol) was stirred at reflux for 16 h. The solvent was removed *in vacuo*, water (20 ml) was added to the residue and the pH was adjusted to 1 by careful addition of 10% hydrochloric acid. After extraction with dichloromethane (2 x 20 ml), the combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to give **11** (330 mg, 98%) as a white solid (*E/Z* isomer ratio: 1:1); m.p. 220-222 °C (ethyl acetate washing); IR (film) ν 3300-2600 (OH), 1681 (CO) $cm^{-1}$; *Z* isomer $^1H$ NMR (250 MHz, DMSO-$d_6$) δ 2.87-3.30 (m, 4H, $CH_2$), 3.61 (s, 3H, $CH_3$), 6.28 (s, 1H, CH=), 7.01-7.43 (m, 7H, $H_{Ar}$), 7.73-7.77 (m, 1H, $H_{Ar}$), 11.91 (broad s, 1H, COOH); $^{13}C$ NMR (62.90, DMSO-$d_6$) δ 27.6 ($CH_2$), 29.7 ($NCH_3$), 31.0 ($CH_2$), 110.1 (CH), 111.8 (C), 117.8 (CH), 118.8 (CH), 120.6 (CH), 121.9 (CH), 125.1 (C), 126.0 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 137.0 (C), 137.1 (C), 139.3 (C), 141.7 (C), 150.3 (C), 167.8 (CO). *E* isomer $^1H$ NMR (250 MHz, DMSO-$d_6$) δ 2.82-3.33 (m, 4H, $CH_2$), 3.61 (s, 3H, $CH_3$), 6.01 (s, 1H, CH), 7.00-7.39 (m, 8H, $H_{Ar}$), 11.91 (br s, 1H, COOH); $^{13}C$ NMR (62.90 MHz, DMSO-$d_6$) δ 27.6 ($CH_2$), 29.7 ($NCH_3$), 30.4 ($CH_2$), 109.8 (CH), 110.1 (C), 118.7 (CH), 119.7 (CH), 120.0 (CH), 121.2 (CH), 125.6 (CH et C), 127.3 (CH), 128.3 (CH), 129.0 (CH),

137.0 (C), 137.2 (C), 138.8 (C), 146.0 (C), 149.6 (C), 168.0 (CO); Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.41; H, 5.40; N, 4.83; MS m/z 304 $(M+1)^+$.

**2-(5-Methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-yliden)propanoic acid (12)**

Following the procedure used for **11** but substituting **8** by **10**, **12** was obtained in 95% yield as a white solid; m.p. 292-295 °C (ethyl acetate washing); IR (KBr) ν 3300-2600 (OH), 1693 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$) δ 1.95 (s, 3H, $CH_3$), 2.70-2.97 (m, 2H, $CH_2$), 3.20-3.31 (m, 2H, $CH_2$), 3.60 (s, 3H, $CH_3$), 6.98-7.13 (m, 5H, $H_{Ar}$), 7.22-7.30 (m, 2H, $H_{Ar}$), 7.33-7.40 (m, 1H, $H_{Ar}$), 12.1 (broad s, 1H, COOH); $^{13}C$ NMR (62.90 MHz, DMSO-$d_6$) δ 19.0 ($CH_3$), 27.3 ($CH_2$), 29.6 ($NCH_3$), 30.0 ($CH_2$), 109.8 (CH), 110.5 (C), 119.7 (2 CH), 121.0 (CH), 125.2 (CH), 126.1 (CH and C) 127.0 (CH), 128.5 (CH), 136.4 (C), 136.8 (C), 137.2 (C), 145.6 (C), 168.0 (CO); Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.81; H, 5.98; N, 4.29; MS m/z 318 $(M+1)^+$.

**Ethyl 2-(5-methyl-5,12-dihydrobenzo[4,5]cyclohepta[*b*]indol-12-yliden)acetate (13)**

To a solution of **8** (200 mg, 0.60 mmol, *E* or *Z* isomer) in dry carbon tetrachloride (30 ml) at 60 °C was added *N*-bromosuccinimide (130 mg, 0.72 mmol). The mixture was stirred 1 h at the same temperature. After cooling and evaporation of the solvent, the residue was taken up in dichloromethane-water (20 ml, v/v) and extracted. The organic phase was dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by column chromatography using dichloromethane as eluting solvent to give **13** (144 mg, 73%) as an oil (*E/Z* ratio 3:2); IR (KBr) ν 1698 (CO) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) *E* isomer δ 0.92 (t, 3H, J = 7.5 Hz, $CH_3$), 3.78 (s, 3H, $CH_3$), 3.91-4.01 (m, 2H, $CH_2$), 6.03 (s, 1H, CH=), 7.00 et 7.07 (d, 1H, J = 11.8 Hz, CH=CH), 7.10-7.67 (m, 8H, $H_{Ar}$). $^1H$ NMR (250 MHz, $CDCl_3$) *Z* isomer δ 1.14 (t, 3H, J = 7.5 Hz, $CH_3$), 3.77 (s, 3H, $CH_3$), 4.03-4.14 (m, 2H, $CH_2$), 6.31 (s, 1H, CH), 6.60 et 7.12 (d, 1H, J = 11.8 Hz, CH=CH), 7.10-7.57 (m, 7H, $H_{Ar}$), 8.4 (d, 1H, J = 8.0 Hz, $H_{Ar}$). $^{13}C$ NMR (62.90 MHz, $CDCl_3$) δ 13.9 ($CH_3$), 14.2 ($CH_3$), 29.8 ($CH_2$), 59.8 ($CH_2$), 60.0 ($CH_2$), 109.3 (CH), 109.4 (CH), 114.3 (C), 117.2 (CH), 117.5 (CH), 118.5 (CH), 119.6 (CH), 120.0 (CH), 120.2 (CH), 120.3 (CH), 120.7 (CH), 123.1 (CH), 123.5 (CH), 124.3 (C), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.7 (CH), 129.3 (CH), 129.5 (CH), 129.7 (CH), 130.7, (CH), 131.8 (CH), 132.3 (CH), 133.1 (C), 133.3 (C), 134.3 (C), 134.6 (C), 134.6 (C), 138.7 (C), 139.4 (C), 148.0 (C), 149.3 (C), 166.3 (CO), 166.5 (CO). Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.43; H, 5.67; N, 4.40. MS m/z 330 $(M+1)^+$.

**5-methyl-12-methylene-5,12-dihydrobenzo[4,5]cyclohepta[*b*]indole (14)**

A solution of ester **13** (200 mg, 0.61 mmol) in ethanol 95% (15 ml) and sodium hydroxide (122 mg, 3.05 mmol) was stirred at reflux for 16 h. The solvent was removed *in vacuo*, water (10 ml) was added to the residue and the pH was adjusted to 1 by careful addition of 10% hydrochloric acid. After extraction with dichloromethane (2 x 10 ml), the organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was separated by column chromatography (petroleum ether-dichloromethane 6:4) to give **14** (146 mg, 93%) as

crystals; m.p. 127-129 °C (dichloromethane-methanol); $^1$H NMR (250 MHz, $CDCl_3$) δ 3.77 (s, 3H, $CH_3$), 5.37 (d, 1H, J = 1.8 Hz, $CH_2$=), 5.60 (d, 1H, J = 1.8 Hz, $CH_2$=), 6.83 et 6.91 (d, 1H, J = 12.0 Hz, CH=CH), 7.13-7.44 (m, 6H, $H_{Ar}$), 7.62 (broad d, 1H, J = 7.5 Hz, $H_{Ar}$), 7.95 (broad d, 1H, J = 8.0 Hz, $H_{Ar}$); $^{13}$C NMR (62.90 MHz, $CDCl_3$) δ 29.6 ($NCH_3$), 109.2 (CH), 116.7 ($CH_2$), 117.3 (C), 118.1 (CH), 119.5 (CH), 120.0 (CH), 122.9 (CH), 125.3 (C), 127.1 (CH), 128.9 (CH), 129.8 (CH), 130.0 (CH), 131.7 (CH), 133.4 (C), 134.0 (C), 138.8 (C), 140.4 (C), 142.3 (C); Anal. Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.79; H, 5.63; N, 5.31; MS m/z 258 $(M+1)^+$.

**Acknowledgments:** The authors gratefully acknowledge the technical assistance of Mr Etienne Perrine and Ms Isabelle Collet.

**References and note**

1. Preliminary communication: Joseph, B.; Cornec, O.; Mérour, J.-Y. *Tetrahedron Lett.*, **1995**, *36*, 8587-8590.
2. Insel, P.A. In Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed.; Hardman, J.G.; Limbird, L.E.; Molinoff, P.B.; Ruddon, R.W.; Gilman, A.G.; eds, Mac Graw-Hill; New York, 1996; pp 617-658.
3. (a) Vane, J. *Nature (New Biol.)*, **1971**, *231*, 232-235; (b) Smith, J.; Willis, A.L. *Nature (New Biol.)*, **1971**, *231*, 235-237.
4. Allison, M.C.; Howatson, A.G.; Torrence, C.J.; Lee, F.D.; Russel, R.I. *N. Eng. J. Med.*, **1992**, *327*, 749-754.
5. (a) Bender, P.E.; Lee, J.C. *Annu. Rep. Med. Chem.*, **1989**, *25*, 185-193; (b) Cooper, K.; Masamune, H. *Annu. Rep. Med. Chem.*, **1992**, *27*, 209-218
6. Dinarello, C.A. *Blood*, **1991**, *77*, 1627-1652.
7. (a) Bollinger, P.; Cooper, P.; Gubler, H.U.; Leutwiler, A.; Payne, T. *Helv. Chim. Acta*, **1990**, *73*, 1197-1204; (b) Schnyder, J.; Bollinger, P.; Payne, T. *Agents Actions*, **1990**, *30*, 350-362.
8. (a) Otterness, I.G.; Bliven, M.L.; Downs, J.T.; Natoli, E.J.; Hanson, D.C. *Cytokine*, **1991**, *3*, 277-283; (b) Batt, D.G.; Goodman, R.; Jones, D.G.; Kerr, J.S.; Mantegna, L.R.; McAllister, C.; Newton, R.C.; Nurnberg, S.; Welch, P.K.; Covington, M.B. *J. Med. Chem.*, **1993**, *36*, 1434-1442.
9. Joseph, B.; Cornec, O.; Mérour, J.-Y.; Solans, X.; Font-Bardia, M. *J. Heterocyclic Chem.*, **1997**, *34*, 525-531.
10. (a) Heck, R.F. *Org. React.*, **1982**, *27*, 345-390; (b) Heck, R.F. *Acc. Chem. Res.*, **1979**, *12*, 146-151; (c) De Meijere, A.; Meyer, F.E. *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 2379-2411; (d) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.*, **1991**, *37*, 4937-4940; (e) Harris Jr, G.D.; Herr,

R.J.; Weinreb, S.M. *J. Org. Chem.*, **1992**, *57*, 2528-2530; (f) Rawal, V.H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583-5584; (g) Gibson, S.E.; Middleton, R.J. *Contemp. Org. Synth.*, **1995**, *3*, 447-472.

11. Leete, E. *J. Am. Chem. Soc.*, **1959**, *81*, 6023-6026.
12. Pfeuffer, L.; Pindur, U. *Helv. Chim. Acta*, **1987**, *70*, 1419-1428.
13. Gilchrist, T.L.; Kemmitt, P.D.; Germain, A.L. *Tetrahedron*, **1997**, *53*, 4447-4456.
14. Determined by analysis of NMR spectra.
15. Chen, C.; Crich, D. *Tetrahedron*, **1993**, *36*, 7943-7954.
16. (a) Almansa, C.; Gomez, L.A.; Cavalcanti, F.L.; de Arriba, A.F.; Rodriguez, R.; Carceller, E.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.*, **1996**, *39*, 2197-2206; (b) Harrowven, D.C.; Poon, H.S. *Tetrahedron Lett.* **1994**, *35*, 9101-9102.
17. Noda, M.; Yamaguchi, M.; Ando, E.; Takeda, K.; Nokihara, K. *J. Org. Chem.*, **1994**, *59*, 7968-7975.