3-Diaroylaminopyrazin-2-carbonsäure-methylester 4a–f; allgemeine

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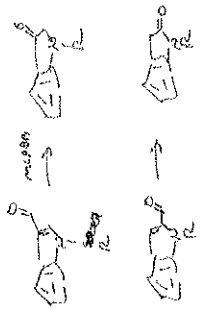

A Convenient Synthesis of 1,2-Dihydro-3*H*-indol-3-ones and 1,2-Dihydro-2*H*-indol-2-ones by Baeyer–Villiger Oxidation

A.S. Bourlot, E. Desarbre, J.Y. Mérour*

LCBA, URA-CNRS 499, Université d'Orléans, BP 6759, F-45067 Orléans Cedex 2, France

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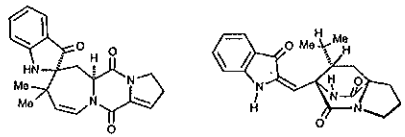
The Baeyer–Villiger rearrangement of substituted 1*H*-indole-3-carbaldehydes afforded the corresponding substituted 1,2-dihydro-3*H*-indol-3-ones. The influence of 3-carbonyl and 1-protecting groups has been examined. Reaction has been extended to 1*H*-indole-2-carbaldehydes and used for synthesis of 1-(phenylsulfonyl)-1*H*-indol-2-yl trifluoromethanesulfonate.

1,2-Dihydro-3*H*-indol-3-ones or indolinones **3** are useful synthetic intermediates for the synthesis of biologically active compounds such as indomethacin,[1] tryptamines[2,3] and ellipticine (via aldol reaction)[4,5] or alkaloids.[6] This framework is also found in natural compounds like austamide[7] or brevianamide D.[8]

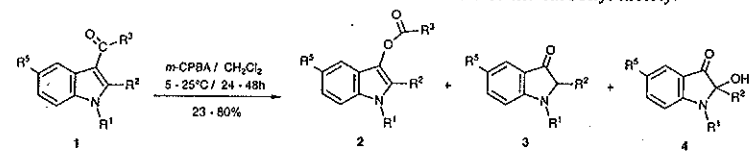


Austamide Brevianamide D

Although several methods of synthezing 1,2-dihydro-3*H*-indol-3-ones are known,[9,15] they are restricted by the limited number of substituents available in the 1- or 2-position; for example the 1-phenylsulfonyl group, which directed the 2-lithiation in indolic compounds, is not easily accessible. Therefore methods allowing the formation of different 1-substituted 1,2-dihydro-3*H*-indol-3-ones **3** will be of considerable use for further synthetic transformations.

We now wish to report an efficient synthesis of these compounds by Baeyer–Villiger-type oxidations on indolic substrates which are substituted in the 3-position by either a formyl or an acetyl group as shown in Scheme 1.

Oxidation of the indole nucleus is essentially under the influence of the substituents in the 1-, 2- or 3-positions; alkyl or aryl substituted indoles have been oxidized to give various compounds which depend on the different experimental conditions used.[15,16] The oxidation of tetrahydro-9-(10*H*)-acridone by sodium dichloroisocyanurate led to rearranged compounds which have the indolinone framework.[17] Hino has also reported the lead tetraacetate oxidation of compound **1a**.[18] Curiously, the Baeyer–Villiger oxidation has not been exploited much in heterocyclic chemistry and among the few examples, it was reported that only 5-chloroacetylindole, but not 5-acetylindole, gave 5-hydroxyindole[19] which shows the influence of the carbonyl moiety.



1 2 3 4

1	R^1	R^2	R^3	R^5	2 - 4	R^1	R^2	R^3	R^5
a	Ac	H	Me	H	a	Ac	H	Me	H
b	SO_2Ph	H	Me	H	b	SO_2Ph	H	Me	H
c	Ac	H	H	H	c	Ac	H	H	H
d	SO_2Ph	H	H	H	d	SO_2Ph	H	H	H
e	Ac	H	H	Br	e	Ac	H	H	Br
f	Ac	H	H	MeO	f	Ac	H	H	MeO
g	SO_2Ph	H	H	Br	g	SO_2Ph	H	H	Br
h	SO_2Ph	H	H	MeO	h	SO_2Ph	H	H	MeO
i	Ac	Me	H	H	i	Ac	Me	H	H
j	Ac	Ph	H	H	j	Ac	Ph	H	H
k	Me	CO_2Me	H	H	k	Me	CO_2Me	H	H
l	Ac	Cl	H	H	l	Ac	Cl	H	H

Scheme 1

Table 1. Experimental Conditions and Results

1	Equiv of *m*-CPBA	Reaction time (h)	Temperature conditions (°C)	Esters 2	Yield (%) Indolinones 3	2-Hydroxy Ketones 4
a	1–3	24–192	25–40		no reaction	
b	1.9	48	25	80[a]	–	–
c	1.1	24	5	not isolated	60[b]	–
d	1.1	24	5	not isolated	55[b]	–

[a] Determined by ^{1}H NMR.
[b] Isolated yield.

The required indolic products **1a–j** were easily obtained by Vilsmeier–Haack formylation from commercial products, followed by acetylation or phenylsulfonylation since protection of the nitrogen atom of indole is necessary to stabilize the final indolinones **3**.[42] Phenylsulfonylation was carried out by a phase-transfer reaction[20], **1g,h** and acetylation in the 1-position was performed according to various methods using acetic anhydride in the presence of triethylamine with dimethylaminopyridine in dichloromethane, **1f**, with sodium acetate, **1i,j,l**, or simply in refluxing acetic anhydride, **1e**.

Methylation (CH_3I/NaH) of methyl 3-formyl-1*H*-indole-2-carboxylate gives **1k** since acetylation or phenylsulfonylation only led to degradation.

When 1-substituted 3-acetyl-1*H*-indoles **1a,b** were treated with *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature for 48 hours with 1.9 equivalents of peracid, the acetate **2a** was not isolated nor identified in the crude reaction mixture, but acetate **2b** was obtained in 80% yield (Table 1). Changing experimental conditions to obtain **2a** or **3a** (temperature, oxidizing agents, quantities and reaction time) met with failure (Scheme 1, Table 1).

The nature of the N-protecting group in the 1-position greatly influenced the course of oxidation since only **1b** reacted and not **1a**. In the case of compounds **1a,b** the oxidizing agents used in the reaction have a determining influence on the outcome; magnesium monoperphthalate MMPP,[21] *m*-CPBA with KF[22] or dimethyloxirane[23] did not afford **2** or **3**.
In the literature, some methods (Na_2SO_3[11] or $NaHCO_3$/$NaHSO_3$[24]) are available for the acetate hydrolysis of **2a** to obtain **3a**. All these methods gave degradation with acetate **2b**.

The nature of the N-protecting group is less important for the oxidation step when the indole ring is substituted by a formyl group in the 3-position. The oxidation of **1c** and **1d** was performed at 5°C for 24 hours with only 1.1 equivalents of *m*-CPBA (Table 1). At room temperature, degradation can be immediately observed. During the purification step on silica gel, the formates **2c** and **2d** are converted to **3c** and **3d** with 60% and 55% yields respectively.

5-Substituted 1*H*-indole-3-carbaldehyde derivatives **1e–h** rapidly gave access to 5-bromoindolinones **3e,g** and 5-methoxyindolinones **3f,h** (Table 2).

1e,f were treated with 1.3 equivalents of *m*-CPBA in dichloromethane at room temperature and led to indolinones **3e,f** after silica gel chromatography; (slow reaction at 0°C). As with formates **2c,d**, formates **2e–h** were not isolated but the ^{1}HNMR spectra of crude products after oxidation of **1g** and **1h** have shown shielded H-2 proton signals which can be attributed to **2g** (δ = 6.34) and **2h** (δ = 6.37).

During the oxidation of **1g,h**, 2-hydroxy ketones **4g,h** in 18% and 15%, yields, respectively, were formed (Table 2). Vicinal coupling constants between OH and H-2 appeared if DMSO-d_6 was used instead of $CDCl_3$ as solvent in the ^{1}H NMR spectrum of **4g,h**. 2-Hydroxy ketones **4e,f** have not been observed during the oxidation of **1e,f**. Hydroxylation in the 2-position will be discussed later.[25]

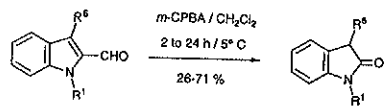
Compounds **1i–l** gave access to 1,2-dihydro-3*H*-indol-3-ones **3i–l** substituted in the 2-position, which were not easily accessible (Scheme 1, Table 2).[3,26] The products **1i–k** were treated with 1.3 equivalents of *m*-CPBA at 5°C in dichloromethane for 24 hours and either led to the formates **2i, k**, or to a mixture of the formates **2j** and the indolinones **3j**. **1l** was treated in the same way (but 3 hours instead of 24 hours) to give indolinone **3l** after silica gel chromatography.

Table 2. Oxidation of 1e–l.

1	Formates 2	Yield (%) Indolinones 3	2-Hydroxy Ketones 4
e	–	55	–
f	–	54	–
g	–	40	18
h	–	34	15
i	27	–	–
j	30	25	–
k	23	–	–
l	–	48	–

These results indicate that the yields are lower than those obtained with indole-3-carbaldehydes unsubstituted in the 2-position.

The Baeyer–Villiger rearrangement has been extended to the 1-substituted 1*H*-indole-2-carbaldehydes to obtain oxindoles[27] which are synthons in the preparation of *inter alia* anti-inflammatory drugs.[27]

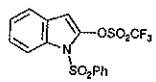


5-6	R^1	R^6
m	SO_2Ph	H
n	$COCH_3$	Cl

Scheme 2

Compound **5m** is obtained by formylation of 2-lithio-1-(phenylsulfonyl)-1*H*-indole[28] and compound **5n** by formylation of compound **3a**[29] (Scheme 2). The oxidation at 5°C leads directly to the oxindoles **6m** in 71% yield (reaction time: 2 hours) and **6n** in 26% yield (reaction time: 24 hours). In both cases, the rearranged formates have not been isolated. Attempts to obtain an authentic sample of **6m**, by phenylsulfonylation of the 2,3-dihydro-2*H*-indol-2-one, met with failure as Gribble has also reported recently.[30]

Compound **6m** reacts easily with trifluoromethanesulfonic anhydride to obtain compound **7** which is an intermediate for the synthesis of 2-substituted indoles via the Heck procedure.[31]



7

The Baeyer–Villiger rearrangement described is a simple and efficient way to obtain substituted indolinones and oxindoles from easily accessible starting materials.

Melting points were measured using a Kopfler apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer, ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer using TMS as internal reference and mass spectra on a Nermag R-10-10C spectrometer. Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). Satisfactory microanalyses were obtained for all compounds **2**, **3**, **6** and **7**.

Compounds **1a**,[32] **1b**,[33] **1c**,[34] **1d**,[28] **5m**[28] and **5n**[29] were prepared according to reported procedures. 2-Methyl-1*H*-indole-3-carbaldehyde was obtained from Aldrich. Commercial *m*-chloroperbenzoic acid was dried in a desiccator under reduced pressure with P_2O_5 for 1 week before use.

1-Acetyl-5-bromo-1*H*-indole-3-carbaldehyde (1e):
A suspension of 5-bromo-1*H*-indole-3-carbaldehyde[35] (0.450 g, 2.0 mmol) in Ac_2O (5 mL) was refluxed until the solution turned clear. After cooling, the precipitate was filtered and washed with cold H_2O (15 mL). The crude product was chromatographed over silica gel using CH_2Cl_2 as cluent to give **1e**; yield 0.452 g (85%); mp 198–200°C (EtOH).

IR (KBr): ν = 1675 ($COCH_3$), 1730 (CHO) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.74 (s, 3 H, CH_3), 7.56 (dd, J = 2.2, 8.8 Hz, 1 H, H-6), 8.06 (s, 1 H, H-2), 8.31 (d, J = 8.8 Hz, 1 H, H-7), 8.46 (d, J = 2.2 Hz, 1 H, H-4), 10.11 (s, 1 H, CHO).

MS (NH_3): m/z = 266 (M^+), 268 ($M^+ + 2$).

1-Acetyl-5-methoxy-1*H*-indole-3-carbaldehyde (1f):
In CH_2Cl_2 (4 mL) were added Ac_2O (0.30 g, 2.90 mmol), NEt_3 (0.30 g, 3.0 mmol), DMAP (0.03 g, 0.25 mmol) and 5-methoxy-1*H*-indole-3-carbaldehyde (0.175 g, 1.0 mmol).[36] The mixture was stirred for 1 h at r.t. H_2O (5 mL) and CH_2Cl_2 (3 mL) were added; the organic layer was separated and the aq layer was extracted twice with CH_2Cl_2 (2 × 10 mL). The organic extracts were washed with a solution of sat. $NaHCO_3$ (10 mL) then with H_2O (10 mL), and dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was chromatographed over silica gel using

Table 3. Compounds 3e–h and 4g, h Prepared

Product[a]	Yield (%)	mp (°C)	Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (CI, NH_3) m/z
3e	55	184–186 (EtOH)	(187–188[41])	1670 ($NCOCH_3$) 1710 (C=O)	2.30 (s, 3 H, CH_3), 4.30 (s, 2 H, CH_2), 7.73 (dd, J = 2.2, 8.8, 1 H, H-6), 7.85 (d, J = 2.2, 1 H, H-4), 8.47 (d, J = 8.8, 1 H, H-7)	–
3f	54	186–188 (EtOH)	(184–187[14])	1660 ($NCOCH_3$) 1710 (C=O)	2.30 (s, 3H, CH_3), 3.88 (s, 3 H, OCH_3), 4.30 (s, 2 H, CH_2), 7.16 (d, J = 2.2, 1 H, H-4), 7.27 (dd, J = 2.2, 9.6, 1 H, H-6), 8.5 (d, J = 9.6, 1 H, H-7)	–
3g	40	170–172 (EtOH)		1715 (C=O)	4.12 (s, 2H, CH_2), 7.40–7.62 (m, 3 H, H_{arom}), 7.72–7.86 (m, 4 H, H_{arom}), 7.95 (d, J = 9.5, 1 H, H-7)	352 (M^+), 354 ($M^+ + 2$)
4g	18	158–160 (EtOH)		3480 (OH) 1730 (C=O)	5.45 (s, 1 H, CHOH), 7.50–7.77 (m, 7 H, H_{arom}), 7.94 (dd, J = 7.3, 1 H, H_{arom})	368 (M^+), 370 ($M^+ + 2$) 350 ($M^+ - 18$), 352 ($M^+ - 16$)
3h	34	140–142 (EtOH)		1705 (C=O)	3.79 (s, 3 H, OCH_3), 4.12 (s, 2 H, CH_2), 7.04 (d, J = 2.8, 1 H, H-4), 7.28 (dd, J = 2.8, 9.0, 1 H, H-6), 7.40–7.80 (m, 5 H, H_{arom}), 7.97 (d, J = 9.0, 1 H, H-7)	304 ($M^+ + 1$)
4h	15	144–146 (EtOH)		3460 (OH) 1700 (C=O)	3.74 (s, 3 H, OCH_3), 5.35 (s, 1 H, CHOH), 7.05 (d, J = 2.9, 1 H, H-4), 7.22 (dd, J = 2.9, 8.8, 1 H, H-6), 7.40–7.60 (m, 3 H, H_{arom}), 7.67 (d, J = 8.8, 1 H, H-7), 7.86 (d, J = 7.3, 2 H, H_{arom})	320 ($M^+ + 1$), 302 ($M^+ - 17$) 337 ($M^+ + 18$)

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.16, N ± 0.15.

Table 4. Compounds 2i–k and 3j,l Prepared

Product[a]	Yield (%)	mp (°C)	Lit. mp (°C)	IR (KBr) ν (cm⁻¹)	¹H NMR (CDCl₃/TMS) δ, J (Hz)	MS (CI, NH₃) m/z
2i	27	Oil		1700 (OCHO, $NCOCH_3$)	2.54 (s, 3 H, CH_3), 2.75 (s, 3 H, $COCH_3$), 7.21–7.37 (m, 3 H, H_{arom}), 8.04 (d, J = 6.3, 1 H, H_{arom}), 8.04 (d, J = 6.3, 1 H, H_{arom}), 8.40, (s, 1 H, OCHO)	–
2j	30	90–92 (EtOH)		1740 (OCHO) 1700 ($NCOCH_3$)	2.03 (s, 3 H, CH_3), 7.25–7.54 (m, 8 H, H_{arom}), 8.22 (s, 1 H, OCHO), 8.45 (d, J = 6.8, 1 H, H_{arom}).	–
2k	23	72–74 (EtOH)		1760 (CO_2CH_3) 1700 (OCHO)	3.91 (s, 3 H, CH_3), 4.05 (s, 3 H, CO_2CH_3), 7.16–7.23 (m, 2 H, H_{arom}), 7.40 (d, J = 6.3, 1 H, H_{arom}), 7.57 (d, J = 7.5, 1 H, H_{arom}), 8.36 (s, 1 H, OCHO)	–
3j	25	138–140 (EtOH)	(139[1])	1720 (C=O), 1670 ($NCOCH_3$)	2.03 (s, 3 H, CH_3), 5.20 (s, 1 H, CH), 7.24–7.39 (m, 5 H, H_{arom}), 7.70–7.76 (m, 3 H, H_{arom}), 8.70 (d, J = 7.6, 1 H, H-7)	–
3l	48	Oil		1740 (C=O), 1690 ($NCOCH_3$)	2.53 (s, 3 H, CH_3), 5.80 (s, 1 H, CHCl), 7.30 (ft, J = 7.4, 1 H, H_{arom}), 7.72 (ft, J = 7.4, 1 H, H_{arom}), 7.82 (d, J = 7.4, 1 H, H_{arom}), 8.44 (d, J = 7.4, 1 H, H_{arom})	209 (M^+), 211 ($M^+ + 2$)

[a] Satisfactory microanalyses obtained: C ± 0.27, H ± 0.18, N ± 0.21.

CH_2Cl_2 as eluent to give 1f; yield 0.186 g (86%); mp 175–177°C (EtOH).

IR (KBr): ν = 1670 ($COCH_3$), 1730 (CHO) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.72 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 7.05 (dd, J = 2.9, 8.8 Hz, 1 H, H-6), 7.76 (d, J = 2.9 Hz, 1 H, H-4), 8.03 (s, 1 H, H-2), 8.29 (d, J = 8.8 Hz, 1 H, H-7), 10.11 (s, 1 H, CHO).

MS (NH_3): m/z = 218 ($M^+ + 1$).

5-Bromo-1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (1g):
NaOH (1.00 g, 25.00 mmol), previously ground, was dissolved in H_2O (3 mL). After cooling, 5-bromo-1*H*-indole-3-carbaldehyde[35] (0.450 g, 2.00 mmol) diluted in toluene (15 mL), was added to the basic solution. Benzyltriethylammonium chloride (0.045 g, 0.20 mmol) and phenylsulfonyl chloride (0.380 mL, 3 mmol) were added at r.t. The solution was stirred for 24 h. After cooling, H_2O (30 mL) and CH_2Cl_2 (30 mL) were poured into the mixture. The aq layer was neutralized with a solution of 10% HCl until pH = 7–8, decanted and extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with H_2O (40 mL) dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give 1g; yield 0.730 g (90%); mp 232–234°C (EtOH).

IR (KBr): ν = 1680 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 7.50–7.70 (m, 4 H, H_{arom}), 7.84 (d, J = 8.3 Hz, 1 H, H-7), 7.95 (dd, J = 7.5 Hz, 2 H, H_{arom}), 8.20 (s, 1 H, H-2), 8.40 (d, J = 2.7 Hz, 1 H, H-4), 10.06 (s, 1 H, CHO).

MS (NH_3): m/z = 364 ($M^+ + 1$).

5-Methoxy-1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (1h):
5-Methoxy-1*H*-indole-3-carbaldehyde[36] was treated by the same procedure used for 1g. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give 1h; yield 0.181 g (58%); mp 159–161°C (EtOH).

IR (KBr): ν = 1680 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 7.01 (dd, J = 2.8, 9.5 Hz, 1 H, H-6), 7.45–7.65 (m, 3 H, H_{arom}), 7.71 (d, J = 2.8 Hz, 1 H, H-4), 7.83 (d, J = 9.5 Hz, 1 H, H-7), 7.94 (d, J = 7.6 Hz, 2 H, H_{arom}), 8.17 (s, 1 H, H-2), 10.06 (s, 1 H, CHO).

MS (NH_3): m/z = 316 ($M^+ + 1$).

1-Acetyl-2-methyl-1*H*-indole-3-carbaldehyde (1i):
NaOAc (2.33 g, 28.4 mmol) was added to a solution of 2-methyl-1*H*-indole-3-carbaldehyde (2 g, 12.6 mmol) in Ac_2O (15 mL). The mixture was stirred for 45 min at r.t. then at 110°C for the same time. After cooling, the solution was diluted with a mixture of ice-water (20 mL). The resulting precipitate was filtered and washed with H_2O (30 mL). The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give 1i; yield 1.42 g (56%); mp 132–134°C (EtOH).

IR (KBr): ν = 1730 (C=O), 1680 ($NCOCH_3$) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.82 (s, 3 H, CH_3), 2.95 (s, 3 H, $COCH_3$), 7.25–7.38 (m, 2 H, H_{arom}), 7.76–7.81 (m, 1 H, H_{arom}), 8.32–8.37 (m, 1 H, H_{arom}), 10.36 (s, 1 H, CHO).

1-Acetyl-2-phenyl-1H-indole-3-carbaldehyde (1j):
Compound 1j was obtained by the same procedure used for compound 1i from 2-phenyl-1*H*-indole-3-carbaldehyde;[37] yield 0.836 g (75%); mp 128–130°C (EtOH).

IR (KBr): ν = 1720, 1660 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.04 (s, 3 H, $COCH_3$), 7.45 (m, 2 H, H_{arom}), 7.57 (m, 5 H, H_{arom}), 8.30 (m, 1 H, H_{arom}), 8.40 (m, 1 H, H_{arom}), 9.78 (s, 1 H, CHO).

1-Acetyl-2-chloro-1H-indole-3-carbaldehyde (1l):
Compound 1l was obtained by the same procedure used for compound 1i from 2-chloro-1*H*-indole-3-carbaldehyde,[39] yield 0.152 g (92%); mp 98–100°C (EtOH).

IR (KBr): ν = 1720, 1660 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.90 (s, 3 H, $COCH_3$), 7.39 (m, 2 H, H_{arom}), 8.21 (m, 1 H, H_{arom}), 8.29 (m, 1 H, H_{arom}), 9.28 (s, 1 H, CHO).

Methyl 3-Formyl-1-methyl-1*H*-indole-2-carboxylate (1k):
A solution of methyl 3-formyl-1*H*-indole-2-carboxylate[38] (0.500 g, 2.46 mmol) in dry THF (10 mL) was added to a suspension of NaH (0.074 g, 2.46 mmol) in dry THF (5 mL) at 0°C under an argon atmosphere. After stirring for 1 h at 0°C, MeI (0.7 mL, 11 mmol) was then added dropwise and the mixture was allowed to warm to r.t. overnight. The solvent was evaporated and the residue was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with H_2O (40 mL), then dried ($MgSO_4$) and concentrated in vacuo to give 1k; yield 0.400 g (75%); mp 150–152°C (EtOH).

IR (KBr): ν = 1750, 1680 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 4.06 (s, 3 H, NCH_3), 4.10 (s, 3 H, OCH_3), 7.28–7.47 (m, 3 H, H_{arom}), 8.50 (d, J = 7.9, 1 H, H_{arom}), 10.59 (s, 1 H, CHO).

1-(Phenylsulfonyl)-1*H*-indol-3-yl Acetate (2b):
At r.t., compound 1b (5.00 g, 16.70 mmol) was dissolved in CH_2Cl_2 (100 mL). *m*-Chloroperbenzoic acid (5.20 g, 30.00 mmol) was added and the solution was stirred for 2 days at r.t. H_2O (200 mL) was added and the mixture was neutralized with an aq solution of 10% Na_2SO_3. The aq layer was extracted with CH_2Cl_2 (2 × 75 mL). Organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave 2b (80%) as a solid contaminated with 1b (20%).

IR (KBr): ν = 1740 (CO ester) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.18 (s, 3 H, $OCOCH_3$), 6.22 (s, 1 H, H-2), 7.17–8.09 (m, 9 H, H_{arom}).

1-Acetyl-3-formyloxy-2-methyl-1*H*-indole (2i):
Compound 2i was obtained by the same procedure used for compound 3c; yield 0.145 g (27%) (see Table 4).

1-Acetyl-3-formyloxy-2-phenyl-1*H*-indole (2j) and 1-Acetyl-1,2-dihydro-2-phenyl-3*H*-indol-3-one (3j):
Compounds 2j and 3j were obtained by the same procedure used for compound 3c: yield 2j; 0.160 g (30%), yield 3j; 0.117 g (25%) (see Table 4).

Methyl 3-Formyloxy-1-methyl-1*H*-indole-2-carboxylate (2k):
Compound 2k was obtained by the same procedure used for compound 3c; yield 0.107 g (20%) (see Table 4).

1-Acetyl-1,2-dihydro-3*H*-indol-3-one (3c):
At 5°C, compound 1c[34] (0.560 g, 3.00 mmol) was dissolved in CH_2Cl_2 (20 mL). *m*-Chloroperbenzoic acid (0.520 g, 3.30 mmol) was added and the mixture was stirred at 5°C for 24 h. H_2O (20 mL) was added and the aq layer was neutralized with an aq solution of 10% Na_2SO_3. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 15 mL). Organic extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give 3c; yield 0.530 g (60%); mp 75–77°C (EtOH) (Lit.[11] 77°C).

IR (KBr): ν = 1670, 1710 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.34 (s, 3 Hm, CH_3), 4.29 (s, 2H, CH_2), 7.20 (t, J = 7.3 Hz, 1 H, H_{arom}), 7.66 (t, J = 7.3 Hz, 1 H, H_{arom}), 7.75 (d, J = 7.3 Hz, 1 H, H-4), 8.55 (d, J = 7.3 Hz, 1H, H-6).

1,2-Dihydro-1-(phenylsulfonyl)-3*H*-indol-3-one (3d):[9,40]
Compound 3d was obtained by the same procedure used for compound 3c; yield 0.450 g (55%); mp 129–131°C (EtOH) (Lit.[9] 128–130°C).

IR (KBr): ν = 1730 (C=O) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 4.14 (s, 2 H, CH_2), 7.14–7.21 (m, 1 H, H_{arom}), 7.44–7.53 (m, 2 H, H_{arom}), 7.56–7.71 (m, 3 H, H_{arom}), 7.80–7.89 (m, 2 H, H_{arom}), 8.04 (d, J = 8.4 Hz, 1 H, H_{arom}).

1-Acetyl-5-bromo-1,2-dihydro-3*H*-indol-3-one (3e):
Compound 1e (0.270 g, 1.00 mmol) was dissolved in CH_2Cl_2 (10 mL) and *m*-chloroperbenzoic acid (0.220 g, 1.3 mmol) was added to the solution. The suspension was stirred for 3 h at r.t. H_2O (20 mL) was added and the aq layer was neutralized with an aq solution of 10% Na_2SO_3. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give 3e; yield 0.156 g (54%) (see Table 3).

1-Acetyl-1,2-dihydro-5-methoxy-3*H*-indol-3-one (3f):
Compound 3f was obtained by the similar procedure used for compound 3e; the solution was stirred for 5 h at r.t. and the residue was chromatographed over silica gel using CH_2Cl_2 as eluent; yield 0.090 g (54%) (see Table 3).

5-Bromo-1,2-dihydro-1-(phenylsulfonyl)-3*H*-indol-3-one (3g) and 5-Bromo-1,2-dihydro-2-hydroxy-1-(phenylsulfonyl)-3*H*-indol-3-one (4g):
Compound 1g (0.330 g, 0.91 mmol) was dissolved in CH_2Cl_2 (10 mL) and *m*-chloroperbenzoic acid (0.20 g, 1.18 mmol) was added to the solution. The suspension was stirred for 24 h at r.t.. H_2O (20 mL) was added and the aq layer was neutralized with an aq solution of 10% Na_2SO_3. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel using first CH_2Cl_2 as eluent to give 3g; yield 0.128 g (40%) and then CH_2Cl_2/MeOH (99/1, v/v) as eluent to give 4g; yield 0.060 g (18%) (see Table 3).

1,2-Dihydro-5-methoxy-5-(phenylsulfonyl)-3*H*-indol-3-one (3h) and 1,2-Dihydro-2-hydroxy-5-methoxy-1-(phenylsulfonyl)-3*H*-indol-3-one (4h):
Compounds 3h and 4h were obtained by the same procedure used for compound 3g; yield of 3h; 0.041 g (34%), yield of 4h; 0.020 g (15%) (see Table 3).

1-Acetyl-2-chloro-1,2-dihydro-3*H*-indol-3-one (3l):
Compound 3l was obtained by a similar procedure used for compound 3e but the reaction time was reduced to 3 h; yield 0.020 g (48%) (see Table 4).

1,3-Dihydro-1-phenylsulfonyl-2*H*-indol-2-one (6m):
Compound 6m was obtained by a similar procedure used for compound 3e but the reaction time was reduced to 2 h; yield 0.336 g (71%); mp 70–72°C (EtOH).

IR (KBr): ν = 1760 (C=O), 1370 (SO_2) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 3.57 (s, 2 H, CH_2), 7.13 (t, J = 7.5 Hz, 1 H, H_{arom}), 7.22 (d, J = 7.5 Hz, 1 H, H_{arom}), t, J = 8.1 Hz, 1 H, H_{arom}), 7.53 (t, J = 8.0 Hz, 2 H, H_{arom}), 7.60 (t, J = 7.8 Hz, 1 H, H_{arom}), 7.93 (d, J = 7.8 Hz, 1 H, H_{arom}), 8.12 (d, J = 7.8 Hz, 2 H, H_{arom}).

MS (NH_3): m/z = 274 ($M^+ + 1$).

1-Acetyl-3-chloro-1,3-dihydro-2*H*-indol-2-one (6n):
Compound 6n was obtained by the same procedure used for compound 3c; yield 0.137 g (26%); mp 154–156°C (EtOH).

IR (KBr): ν = 1760 (C=O lactam), 1710 (C=O amide) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 2.70 (s, 3 H, CH_3), 5.31 (s, 1 H, CHCl), 7.27 (t, J = 7.7 Hz, 1 H, H_{arom}), 7.42 (t, J = 8.3 Hz, 1 H, H_{arom}), 7.47 (d, J = 7.7 Hz, 1 H, H_{arom}), 8.22 (d, J = 8.3 Hz, 1 H, H_{arom}).

MS (NH_3): m/z = 210 ($M^+ + 1$), 212 ($M^+ + 3$).

1-(Phenylsulfonyl)indol-2-yl Trifluoromethanesulfonate (7):
Compound 6m (0.070 g, 0.25 mmol) and diisopropylethylamine (0.05 mL, 0.3 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C under argon. Trifluoromethanesulfonic anhydride (0.05 mL, 0.3 mmol) was added dropwise. After 0.75 h at 0°C, H_2O (2 mL) was added to the brown solution and the aq layer was neutralized with an aq solution of sat. $NaHCO_3$. The aq layer was extracted with CH_2Cl_2 (2 × 3 mL) and the organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give 7; yield 0.071 g (70%); mp 70–72°C (EtOH).

IR (KBr): ν = 1440, 1380 (SO_2) cm^{-1}.

¹H NMR ($CDCl_3$): δ = 6.43 (s, 1 H, H-3), 7.26–7.62 (m, 6 H, H_{arom}), 7.89 (d, J = 7.4 Hz, 2 H, H_{arom}), 8.19 (d, J = 8.83 Hz, 1 H, H_{arom}).

MS (NH_3): m/z = 406 ($M^+ + 1$).

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Synthesis of Mono- and Sesquiterpenoids; XXIII.[1] Synthesis of (*E*)-*endo*-Bergamoten-12-oic Acids (α-form, β-form), Moth Oviposition Stimulants Isolated from Wild Tomato Leaves[2]

Kenji Mori,* Yoshitaka Matsushima
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan
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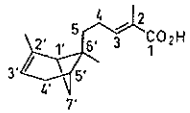
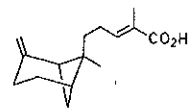
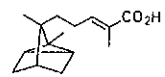
(*E*)-*endo*-Bergamoten-12-oic acids (α-form: 1, β-form: 2), moth oviposition stimulants isolated from wild tomato leaves, were synthesized starting from the lactone 7.

(*E*)-*endo*-Bergamoten-12-oic acids (α-form: **1**, β-form: **2**) are sesquiterpenes isolated from the leaves of wild tomato (*Lycopersicon hirsutum*) by Coates, Juvik, and their coworkers together with (+)-(*E*)-α-santalen-12-oic acid (**3**). They (**1** and **2**) stimulate the oviposition behaviour of female gravid moths (*Heliothis zea*), whose larvae are major agricultural pests of tomatoes, corn, and cotton.[3] The activity of these compounds prompted us to attempt a synthesis of enantiomerically pure **1** and **2**.

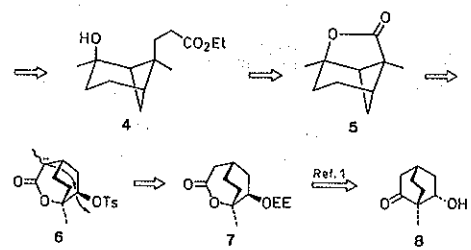

(*E*)-*endo*-Bergamoten-12-oic acid (α-form) **1**


(*E*)-*endo*-Bergamoten-12-oic acid (β-form) **2**


(*E*)-α-Santalen-12-oic acid **3**

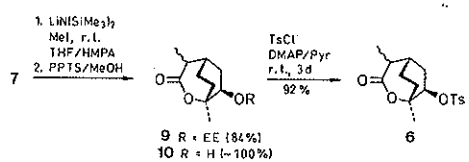
Our retrosynthetic analysis is shown in Scheme 1. We recently reported the synthesis of (+)-pinthunamide.[1] To construct the pinane-type carbon skeleton of the bergamotenoic acids we can use the intramolecular alkylation of the tosyloxylactone **6** as the key reaction as in the synthesis of (+)-pinthunamide.[1] The first stage of our work was the preparation of tosyloxylactone **6** as shown in Scheme 2. The starting material **7**, an intermediate in the synthesis of (+)-pinthunamide,[1] was obtained in enantiomerically pure form in three steps from β-hydroxy ketone **8**, the yeast reduction product.[1,4] The lactone **7** was alkylated with methyl iodide using lithium 1,1,1,3,3,3-hexamethyldisilazide [$LiN(SiMe_3)_2$] as a base to give **9**. After the removal of the 1-ethoxyethyl (EE) protecting group, the resulting alcohol **10** was treated with *p*-toluenesulfonyl chloride (TsCl) in the presence of 4-(dimethylamino)pyridine (DMAP) to give the key intermediate **6** as crystals.[1]

The next step was the crucial key intramolecular alkylation as shown in Scheme 3. We successfully executed this reaction by employing $LiN(SiMe_3)_2$ in tetrahydrofuran/hexamethylphosphoric triamide (HMPA) as the base. In addition to the desired tricyclic lactone **5** (ca. 52% yield) with $\nu = 1770\ cm^{-1}$, an undesired byproduct, a nitrile **11** ($\nu = 2245\ cm^{-1}$) was obtained in accord with our experience in the course of pinthunamide synthesis.[1]

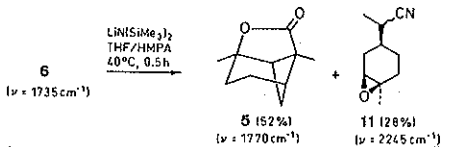


EE = CHMeOEt

Scheme 1



Scheme 2



Scheme 3

The remaining steps of the synthesis were the construction of the side chain and dehydration to afford bergamoten-12-oic acids as shown in Scheme 4. The lactone **5** was reduced with lithium aluminum hydride to give diol **12**, whose enantiomeric purity was determined to be almost 100% ee by the 300 MHz ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA monoesters. The primary hydroxy group of **12** was selectively protected as pivaloyl (Piv) ester. Compound **13** was then converted to the unsaturated ester **16** by the following sequence: (i) protection of the tertiary hydroxy group of **13** as trimethylsilyl ether to give **14**, (ii) removal of the Piv protective group of **14** with methyllithium to afford **15**, and (iii) Swern oxidation[5] of **15** to give crude unstable aldehyde, which was immediately submitted to Horner reaction. The double bond of the resulting ester **16** was hydogenated in the presence of Adams' platinum dioxide catalyst to furnish **17**, whose trimethylsilyl protecting group was removed to give hydroxy ester **4**. For the dehydration we used trifluoromethanesulfonyl chloride in the presence of excess DMAP to avoid acidic rearran-