Synthesis of erythrina and related alkaloids. 17.[1] Total synthesis of *dl*-coccuvinine and *dl*-coccolinine

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Received June 2, 1986

This paper is dedicated to Dr. O. E. (Ted) Edwards

TAKEHIRO SANO, JUN TODA, NOBUTERU MAEHARA, and YOSHISUKE TSUDA. Can. J. Chem. **65**, 94 (1987).

Total synthesis of *dl*-coccuvinine **1***a* and *dl*-coccolinine **2***a*, "abnormal-type" erythrinan alkaloids lacking the C(16) O-function at the aromatic ring, was effectively achieved by using the Diels–Alder reaction of dioxopyrroline. Isoquinolinopyrrolinedione **6***a*, a key dienophile, was synthesized via the tetrahydroisoquinoline **5***a*, which was prepared by Bischler–Napieralski cyclization of the amide **4***a* at the unactivated position. The Diels–Alder adduct **7***a* of 1,3-bis(trimethylsilyloxy)-butadiene with **6***a* with converted stereoselectively into these alkaloids in short steps.

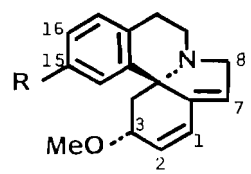
TAKEHIRO SANO, JUN TODA, NOBUTERU MAEHARA et YOSHISUKE TSUDA. Can. J. Chem. **65**, 94 (1987).

Faisant appel à une réaction de Diels–Alder de la dioxopyrroline, on a effectivement réalisé la synthèse totale de la (*dl*)-coccuvinine (**1***a*) et de la (*dl*)-coccolinine (**2***a*), des alcaloïdes de l'érythrinane d'un «type anormal» et qui ne portent pas de fonction oxygénée en position C(16) du cycle aromatique. On a synthétisé l'isoquinolinopyrrolinedione (**6***a*), un diénophile clé, par le biais de la tétrahydroisoquinoléine **6***a* qui a été préparée par une cyclisation de Bischler–Napieralski de l'amide **4***a* vers la position qui n'est pas activée. L'adduit de Diels–Alder **7***a* du bis(triméthylsilyloxy)-1,3 butadiène avec le composé **6***a* peut être transformé stéréosélectivement dans les deux alcaloïdes par des étapes courtes.

[Traduit par la revue]

Introduction

Coccuvinine **1***a*, the alkaloid isolated from *Cocculus laurifolius* DC. (Menispermaceae), is an "abnormal-type" erythrinan alkaloid in the sense that it contains no oxygen function at the C(16) position (1). Coccolinine **2***a* is the 8-oxo derivative of **1***a*. This non-basic lactam alkaloid was also isolated from the same plant (2). The synthesis of "abnormal-type" erythrinan alkaloids is of interest because of their biological activity, such as hypotensive and neuromuscular blocking action (3). We wish to report in detail the total synthesis of *dl*-coccuvinine **1***a* and *dl*-coccolinine **2***a*.



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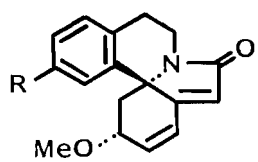

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a: R=OMe, b: R=H

We have recently developed a new effective synthetic route to the erythrinan alkaloids using Diels–Alder reaction of isoquinolinopyrrolinedione with 1,3-*O*-disubstituted butadiene as a key step (4–6). This method provides a short synthesis of these alkaloids, if the isoquinoline ring closure occurs at the *meta* position with respect to the methoxy group on the aromatic ring. Ju-ichi *et al.* (7), who accomplished the first total synthesis of the abnormal-type erythrinan alkaloids by the method developed by Mondon *et al.* (8, 9), solved this problem by the introduction of an ethoxycarbamide group at the C(16) position as a regioselective *para*-directing group. Eventually this function was replaced with hydrogen after ring closure. However, this conversion itself requires several additional steps, thus lowering the total yield. Therefore, to further prove the efficiency of our method of erythrinan alkaloid synthesis, we have chosen these alkaloids as target molecules.

Total synthesis of dl-*coccuvinine and* dl-*coccolinine*

Condensation of 2-(4-methoxyphenyl)-ethylamine **3***a* with methyl chloroformylacetate afforded the amide **4***a* in good yield. As anticipated, the isoquinoline ring closure of **4***a* was very difficult. Treatment of **4***a* with phosphorus oxychloride under reflux afforded the tetrahydroisoquinoline **5***a* in only 3% yield. No starting material was recovered. Heating of **4***a* with polyphosphate ester (PPE) (10) in chloroform under reflux for 18 h afforded **5***a* in 15% yield together with an appreciable amount of the starting material (22%). Increase of the reaction time (48 h) resulted in greater decomposition of **5***a*, thus lowering the yield of **5***a* (9%). A fairly good result, although not optimized, was obtained by heating **4***a* in PPE without solvent for 18 h. Under these conditions **5***a* was formed in 34% yield and the starting material recovered in 33% yield. Since the starting material can be recycled, the net yield of **5***a* was calculated to be 51%. Condensation of **5***a* with oxalyl chloride provided the isoquinolinopyrrolinedione **6***a* in 78% yield. The structure of the dioxopyrroline moiety was readily characterized by the visible absorption band at 430 nm (11). Thus the key intermediate **6***a* was obtained from the commercially available amine **3***a* in 38% overall yield.

The Diels–Alder reaction of **6***a* with 1,3-trimethylsilyloxy-butadiene proceeded in a regio- and stereoselective manner. Thus, heating of **6***a* with the diene in toluene at 130°C for 20 min afforded the adduct **7***a* in 71% yield. The stereochemical assignment of the C(1) OTMS group as having the *endo* configuration results from comparison of the nmr spectrum of **7***a* with those of the adducts reported in the previous papers

[1]For part 16 see ref. 6. This paper also constitutes Part XXXIX of Dioxopyrrolines.

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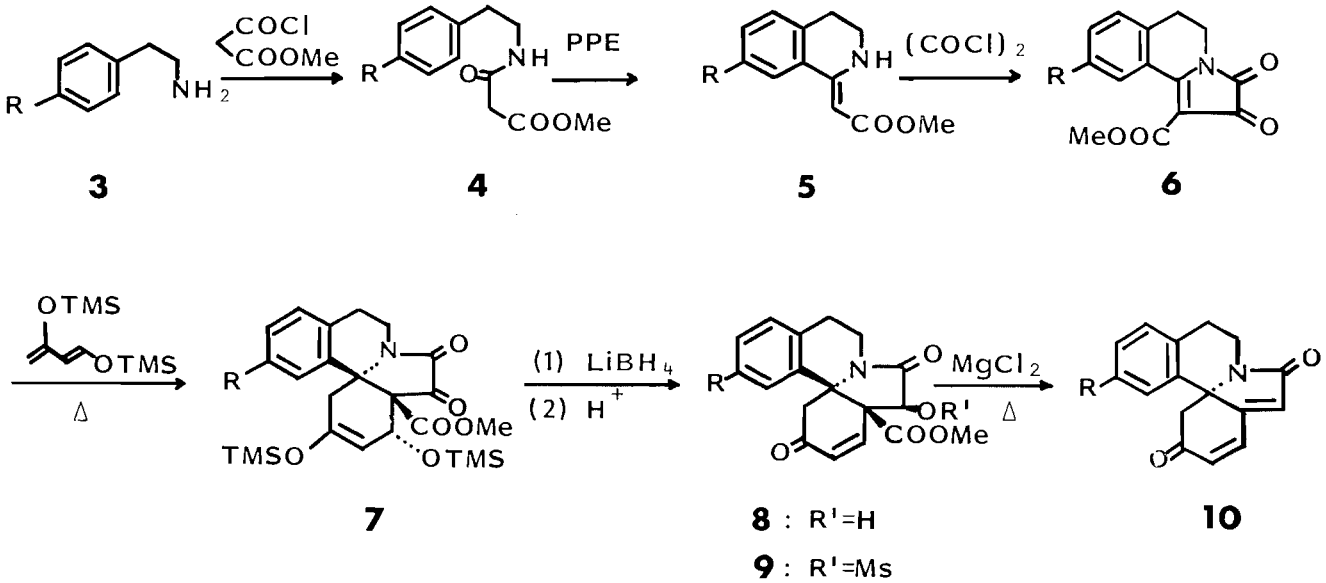
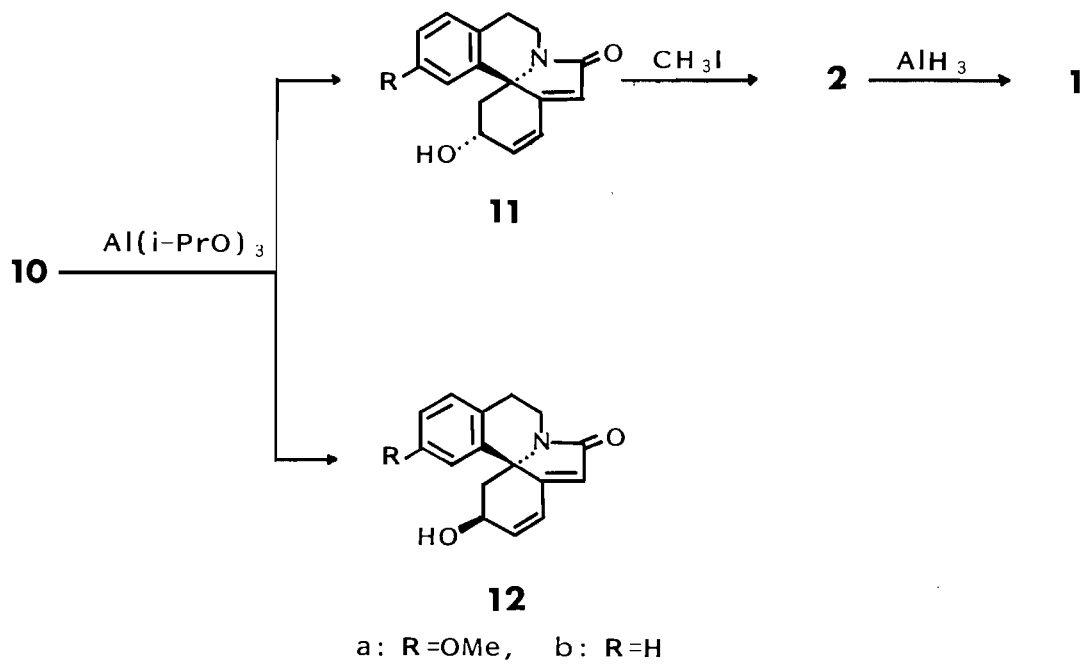


(6, 12). Reduction of **7***a* with lithium borohydride at −63°C occurred selectively at the C(7) keto group and treatment of the resulting alcohol with hydrochloric acid afforded the enone **8***a* in 56% yield. Removal of the methoxycarbonyl group at the C(6) position was effected by heating **8***a* with magnesium chloride in DMSO (13), giving rise to the dienone **10***a* with concomitant dehydration of the C(7) OH group in 32% yield. Substitution of the C(7) OH by a good leaving group markedly improved this step. Thus mesylation of **8***a* and demethoxycarbonylation of the resulting mesylate **9***a* under similar conditions produced **10***a* in 72% yield.

Meerwein–Ponndorf reduction of **10***a* occurred stereoselectively at the C(3) ketone to give the α-alcohol **11***a* and the β-alcohol **12***a* in 76 and 18% yields, respectively. Methylation of **11***a* with methyl iodide in the presence of a phase transfer catalyst afforded *dl*-coccolinine **2***a* in 93% yield. Reduction of **2***a* with aluminum hydride generated by lithium aluminum hydride, and aluminum chloride in THF occurred site-selectively at the C(8) lactam carbonyl group to furnish *dl*-coccuvinine **1***a* in 93% yield. The identity of **1***a* and **2***a* with authentic samples was confirmed by their spectral comparison. Thus, the total synthesis of *dl*-coccuvinine was effectively accomplished in 10 steps, proceeding in 6–7% overall yield from the commercially available amine **3***a*.

Synthesis of 15-demethoxycoccuvinine

Because of physiological interest, we have synthesized 15-demethoxycoccuvinine **1***b*, an unnatural erythrinan compound that lacks an O-function at the aromatic ring. The synthesis was achieved via the same route starting from phenylethylamine. Bischler–Napieralski cyclization of the amide **4***b*, using PPE as a condensing reagent as described above, afforded the tetra-



hydroisoquinoline **5***b* in 47% yield. The subsequent reactions proceeded in similar manner and afforded *dl*-15-demethoxycoccuvinine **1***b* in a comparable yield.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto hot-stage apparatus and are uncorrected. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography was performed on silica gel (Wakogel C-200). Thin-layer chromatographic (tlc) analyses were carried out by using silica gel plates (Merck precoated plates, silica gel 60F-254). Infrared spectra were taken in Nujol mulls with a Hitachi 260-10 spectrometer, and are given in cm^{-1}. Ultraviolet spectra were recorded in dioxane solution with a Hitachi 200-10 spectrophotometer. Proton nuclear magnetic resonance spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JEOL JNM-FX100 (FT-NMR; 100 MHz) spectrometer.

*General procedure for condensation reaction of arylethylamine **3** with methyl chloroformylacetate*

A solution of methyl chloroformylacetate (1.2 equiv. of **3**) in CH_2Cl_2 (50 mL) was added dropwise to a mixed solution of arylethylamine **3** in CH_2Cl_2 (100 mL) and 10% K_2CO_3 (1.2 equiv.) at 0°C, and stirring was continued for 1 h. The reaction mixture was neutralized with 5% HCl and the organic layer was washed with water, dried, and evaporated. Crystallization of the residue gave the amide **4**.

*Methoxycarbonylaceto-2-(4-methoxyphenyl)ethylamide (**4**a)*

Compound **4***a* (7.96 g, 96%) was prepared from **3***a* (5.00 g), mp 88–89°C, as colorless needles from AcOEt; ir ν_{max}: 3260, 1740, 1630 cm^{-1}; ^{1}Hmr δ: 2.77 (t, J = 7 Hz, 2H, $ArCH_2$—), 3.28 (s, 2H, —$COCH_2CO$—), 3.47 (t, J = 7 Hz, $>NCH_2$—), 3.72 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 6.85 (d, J = 9 Hz, 1H, ArH), 7.14 (d, J = 9 Hz, 1H, ArH). *Mol. Wt.* calcd. for $C_{13}H_{17}NO_4$: 251.1156; found (ms): 251.1143.

*Methoxycarbonylaceto-2-phenylethylamide (**4**b)*

Compound **4***b* (16.1 g, 88%) was prepared from **3***b* (10 g), mp 65–67°C, as colorless needles from AcOEt; ir ν_{max}: 3230, 1740, 1640 cm^{-1}; ^{1}Hmr δ: 2.83 (t, J = 7 Hz, 2H, $ArCH_2$—), 3.48 and 3.61 (d, J = 7 Hz, each 1H, $>NCH_2$—), 3.71 (s, 3H, $COOCH_3$), 7.24 (m, 5H, ArH). *Mol. Wt.* calcd. for $C_{12}H_{15}NO_3$: 221.1050; found (ms): 221.1033.

*General procedure for Bischler–Napieralski reaction of nonactivated amide **4***

A mixture of **4** and polyphosphate ester (PPE) (20 times the amount of **4**) was heated at 80°C for the appropriate time (18 h for **4***a* and 40 h for **4***b*). After the excess of PPE was decomposed with ice water, the solution was basified with 10% K_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel using $CHCl_3$ as eluent to give the isoquinoline **5**.

*(Z)-7-Methoxy-1-methoxycarbonylmethylidene-1,2,3,4-tetrahydroisoquinoline (**5**a)*

Compound **5***a* (1.60 g, 34%) was obtained from **4***a* (5.00 g) as a pale yellow oil; ir ν_{max}: 3300, 1650 cm^{-1}; ^{1}Hmr δ: 2.77 (t, J = 7 Hz, 2H, $ArCH_2$—), 3.39 (t, J = 7 Hz, 2H, $>NCH_2$—), 3.69 (s, 3H, $COOCH_3$), 3.78 (s, 3H, OCH_3), 5.12 (s, 1H, $>C$=$CHCO$—), 6.9–7.1 (m, 3H, ArH). *Mol. Wt.* calcd. for $C_{13}H_{15}NO_3$: 233.1052; found (ms): 233.1059.

The starting amide **4***a* (1.70 g, 33%) was recovered from the column chromatography.

*(Z)-1-Methoxycarbonylmethylidene-1,2,3,4-tetrahydroisoquinoline (**5**b)*

Compound **5***b* (2.20 g, 47%) was obtained from **4***b* (5.08 g) as a pale yellow oil; ir($CHCl_3$) ν_{max}: 3300, 1650 cm^{-1}; ^{1}Hmr δ: 2.81 (t, J = 6 Hz, 2H, $ArCH_2$—), 3.42 (m, 2H, $>NCH_2$—), 3.68 (s, 3H, $COOCH_3$), 5.15 (s, 1H, $>C$=$CHCO$—), 7.39 (m, 4H, ArH).

The starting amide **4***b* (709 mg, 14%) was recovered from the column chromatography.

*General procedure for condensation reaction of **5** with oxalylchloride*

Oxalylchloride (1.1 equiv. of **5**) was added dropwise to a solution of **5** in anhydrous ether (50 mL) at 0°C under stirring, and the stirring was continued for one additional hour. The precipitate was collected by filtration and chromatographed on silica gel, using $CHCl_3$ as eluent, to give the dioxopyrroline **6**.

*8-Methoxy-1-methoxycarbonyl-2,3-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline (**6**a)*

Compound **6***a* (892 mg, 78%) was obtained from **5***a* (930 mg), mp 181–185°C, as red prisms from AcOEt; ir ν_{max}: 1760, 1730, 1680 cm^{-1}; uv (dioxane, 25°C) λ_{max} (ε): 220 (15 800), 300 (12 600), 383 (4 900), 425 (4 100; sh); ^{1}Hmr δ: 3.03 (t, J = 6 Hz, 2H, $ArCH_2$—), 3.81 (t, J = 6 Hz, 2H, $>NCH_2$—), 3.87 (s, 6H, $COOCH_3$ and OCH_3), 7.17 (dd, J = 3 and 9 Hz, 1H, ArH), 7.29 (d, J = 9 Hz, 1H, ArH), 8.08 (d, J = 3 Hz, 1H, ArH). *Mol. Wt.* calcd. for $C_{15}H_{13}NO_4$: 287.0794; found (ms): 287.0797.

*1-Methoxycarbonyl-2,3-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline (**6**b)*

Compound **6***b* (1.15 g, 61%) was obtained from **5***b* (1.5 g), mp 203–206°C, as red prisms from AcOEt; ir ν_{max}: 1760, 1720, 1700 cm^{-1}; ^{1}Hmr δ: 3.10 (t, J = 4 Hz, 2H, $ArCH_2$—), 3.84 (t, J = 4 Hz, 2H, $>NCH_2$—), 3.88 (s, 3H, $COOCH_3$), 7.53 (m, 4H, ArH). *Mol. Wt.* calcd. for $C_{14}H_{11}NO_4$: 257.0687; found (ms): 257.0687.

*General procedure for Diels–Alder reaction of **6** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene*

A solution of **6** and the diene (5 equiv. of **6**) in toluene (10 mL) was heated at 130°C for 20 min in a sealed tube. The solution was concentrated to dryness to give a residue, which was triturated with *n*-hexane to give the adduct **7**.

(4R, 4aR*, 13bR*)-12-Methoxy-4a-methoxycarbonyl-5,6-dioxo-2,4-bis(trimethylsilyloxy)-4,4a,5,6,8,9-hexahydro-1H-indolo[7a,1-a]isoquinoline (**7**a)*

Compound **7***a* (256 mg, 71%) was prepared from **6***a* (200 mg), mp 144–146°C, as colorless prisms from EtOAc–*n*-hexane; ir ν_{max}: 1780, 1740, 1720, 1660 cm^{-1}; ^{1}Hmr δ: 0.05 and 0.12 (each s, 9H, $Si(CH_3)_3$), 2.90 (s, 3H, $COOCH_3$), 3.59 (s, 3H, OCH_3), 5.12 (d, J = 6 Hz, 1H, $>CHOTMS$), 5.25 (d, J = 6 Hz, 1H, C=CH—), 6.60–7.20 (m, 3H, ArH). *Mol. Wt.* calcd. for $C_{25}H_{35}NO_7Si_2$: 517.1952; found (ms): 517.1958.

(4R, 4aR*, 13bR*)-4a-Methoxycarbonyl-5,6-dioxo-2,4-bis(trimethylsilyloxy)-4,4a,5,6,8,9-hexahydro-1H-indolo[7a,1-a]isoquinoline (**7**b)*

Compound **7***b* (780 mg, 67%) was prepared from **6***b* (617 mg), mp 155–158°C, as colorless prisms from EtOAc; ir ν_{max}: 1760, 1710, 1650 cm^{-1}; ^{1}Hmr δ: 0.11 (s, 18H, 2 × $Si(CH_3)_3$), 2.83 (s, 3H, $COOCH_3$), 5.12 (d, J = 5 Hz, 1H, $>CHOTMS$), 5.22 (d, J = 5 Hz, 1H, C=CH—), 7.02 (m, 4H, ArH). *Mol. Wt.* calcd. for $C_{24}H_{35}NO_6Si_2$: 487.1844; found (ms): 487.1824.

*General procedure for reduction of **7** with $LiBH_4$*

A mixture of **7** and $LiBH_4$ in anhydrous THF was stirred for 20 min at −60°C under an argon atmosphere. The mixture was diluted with Et_2O, washed with saturated NaCl solution and water, dried, and evaporated. The residue in 5% HCl–THF (1:1) (10 mL) was heated on a water bath for 1 h. The mixture was extracted with $CHCl_3$, washed with water, dried, and evaporated. Recrystallization of the residue gave the enone **8**.

(4aS,5S*,13bR*)-5-hydroxy-12-methoxy-4a-methoxycarbonyl-2,6-dioxo-2,4a,5,6,8,9-hexahydro-1*H*-indolo[7a,1-a]isoquinoline (**8**a)*

Compound **8***a* (77 mg, 56%) was obtained by reduction of **7***a* (202 mg) with $LiBH_4$ (5 mg) in THF (6 mL), mp 189–192°C, as colorless prisms from Et_2O–acetone; ir ν_{max}: 3250, 1740, 1690 cm^{-1}; ^{1}Hmr δ: 3.27 (s, 3H, $COOCH_3$), 3.64 (s, 3H, OCH_3), 4.77 (s, 1H, >CHOH), 6.43 and 7.53 (each d, J = 11 Hz, 1H, —COCH=CH—), 6.5–7.0 (m, 3H, ArH). *Mol. Wt.* calcd. for $C_{19}H_{19}NO_6$: 357.1211; found (ms): 357.1206.

(4aS,5S*,13bR*)-5-Hydroxy-4a-methoxycarbonyl-2,6-dioxo-2,4a,5,6,8,9-hexahydro-1*H*-indolo[7a,1-a]isoquinoline (**8**b)*

Compound **8***b* (300 mg, 89%) was obtained by reduction of **7***b* (500 mg) with $LiBH_4$ (26 mg) in THF (9 mL), mp 191–194°C, as colorless prisms from Et_2O–MeOH; ir ν_{max}: 3250, 1740, 1690 cm^{-1}; ^{1}Hmr δ: 2.80 and 3.20 (d, J = 16 Hz, each 1H, —$COCH_2$—), 3.22 (s, 3H, $COOCH_3$), 4.79 (s, 1H, —COCH=CH—), 7.04 (m, 4H, ArH), 7.55 (d, J = 11 Hz, 1H, —COCH=CH—). *Mol. Wt.* calcd. for $C_{18}H_{17}NO_5$: 327.1105; found (ms): 327.1100.

*General procedure for mesylation reaction of **8** with methanesulfonylchloride*

A mixture of **8** and methanesulfonylchloride (4 equiv. of **8**) in pyridine (5 mL) was stirred at room temperature for 2 h. The reaction mixture was basified with 10% K_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. Recrystallization of the residue gave the mesylate **9**.

(4aS,5S*,13bR*)-5-Methanesulfonyloxy-12-methoxy-4a-methoxycarbonyl-2,6-dioxo-2,4a,5,6,8,9-hexahydro-1*H*-indolo[7a,1-a]isoquinoline (**9**a)*

Compound **9***a* (145 mg, 80%) was obtained by reaction of **8***a* (156 mg) and CH_3SO_2Cl (200 mg) in pyridine (2 mL), mp 211–212°C, as colorless prisms from Et_2O–MeOH; ir ν_{max}: 1750, 1725, 1695, 1620 cm^{-1}; ^{1}Hmr δ: 3.31 (s, 3H, $COOCH_3$), 3.37 (s, 3H, OSO_2CH_3), 3.65 (s, 3H, OCH_3), 5.50 (s, 1H, >CHOMs), 6.50 (d, J = 11 Hz, 1H, —COCH=CH—), 6.5–7.0 (m, 3H, ArH), 7.47 (d, J = 11 Hz, —COCH=CH—). *Mol. Wt.* calcd. for $C_{20}H_{21}NO_8S$: 435.0985; found (ms): 435.0985.

(4aS,5S*,13bR*)-5-Methanesulfonyloxy-4a-methoxycarbonyl-2,6-dioxo-2,4a,5,6,8,9-hexahydro-1*H*-indolo[7a,1-a]isoquinoline (**9**b)*

Compound **9***b* (329 mg, 81%) was prepared from **8***b* (328 mg), mp 181–183°C, as colorless prisms from Et_2O–MeOH; ir ν_{max}: 1740, 1720, 1690 cm^{-1}; ^{1}Hmr δ: 3.25 (s, 3H, $COOCH_3$), 3.37 (s, 3H, —OSO_2CH_3), 5.57 (s, 1H, >CH—OMs), 7.16 (m, 4H, ArH), 7.17 (d, J = 11 Hz, —COCH=CH—), 7.44 (d, J = 11 Hz, —COCH=CH—). *Mol. Wt.* calcd. for $C_{19}H_{19}NO_7S$: 405.0811; found (ms): 405.0896.

*General procedure for demethoxycarbonylation of the mesylate **9***

A mixture of **9** and $MgCl_2$ (5 equiv. of **9**) in DMSO (5 mL) was heated at 160°C for 2 h in a sealed tube. The mixture was extracted with $CHCl_3$. After an addition of water the extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel using $CHCl_3$ as eluent to give the dienone **10**.

*12-Methoxy-2,6-dioxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline (**10**a)*

Compound **10***a* (30 mg, 89%) was prepared from **9***a* (52 mg), mp 180–183°C, as pale yellow prisms from AcOEt; ir ν_{max}: 1690, 1665 cm^{-1}; ^{1}Hmr δ: 2.78 and 3.27 (d, J = 15 Hz, each 1H, —$COCH_2$—), 3.70 (s, 3H, OCH_3), 6.38 (d, J = 10 Hz, —COCH=CH—), 6.76–7.13 (m, 3H, ArH), 7.75 (d, J = 10 Hz, —COCH=CH—). *Mol. Wt.* calcd. for $C_{17}H_{15}NO_3$: 281.1052; found (ms): 281.1065.

*2,6-Dioxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline (**10**b)*

Compound **10***b* (22 mg, 68%) was prepared from **9***b* (52 mg), mp 147–149°C, as pale yellow prisms from AcOEt; ir ν_{max}: 1720, 1670 cm^{-1}; ^{1}Hmr δ: 2.79 and 3.27 (d, J = 15 Hz, each 1H, —$COCH_2$—), 6.37 (d, J = 10 Hz, 1H, —COCH=CH—), 6.38 (s, 1H, —C=CH—CO—), 7.18 (m, 4H, ArH), 7.76 (d, J = 10 Hz, 1H, —COCH=CH—). *Mol. Wt.* calcd. for $C_{16}H_{13}NO_2$: 251.0947; found (ms): 251.0965.

*General procedure for Meerwein–Ponndorf reduction of **10** with aluminium isopropoxide*

A mixture of **10** and Al(i-PrO)$_3$ (20 equiv. of **10**) in anhydrous i-PrOH was heated under reflux for 24 h under an argon atmosphere. The mixture was acidified with 5% HCl and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residue was purified by preparative tlc (developed by $CHCl_3$–MeOH (30:1)) to give two fractions. The more polar fraction gave the α-alcohol (**11**) and the less polar fraction gave the β-alcohol (**12**).

(2S,13bR*)-2-Hydroxy-12-methoxy-6-oxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline (**11**a)*

Compound **11***a* (38 mg, 76%) was prepared from **10***a* (50 mg), mp 102–103°C, as colorless prisms from MeOH; ir ν_{max}: 3350, 1640 cm^{-1}; ^{1}Hmr δ: 1.69 (dd, J = 5 Hz, 1H, H-1′), 2.79 (dd, J = 5 and 11 Hz, H-1′), 3.72 (s, 3H, C_{12}-OCH_3), 4.1–4.3 (m, 1H, —CH—OH), 5.97 (s, 1H, —COCH=C—), 6.25 (br d, J = 10 Hz, 1H, —COCH=CH—), 6.7–6.9 (m, 2H, ArH), 6.80 (dd, J = 2 and 10 Hz, 1H, —CH=CH—CH(OH)—), 7.13 (d, J = 9 Hz, ArH). *Mol. Wt.* calcd. for $C_{17}H_{17}NO_3$: 283.1208; found (ms): 283.1208. *Anal.* calcd. for $C_{17}H_{17}NO_3$: C 72.07, H 6.05, N 4.94; found: C 72.22, H 6.13, N 4.96.

(2R,13bR*)-2-Hydroxy-12-methoxy-6-oxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline (**12**a)*

Compound **12***a* (9 mg, 18%) was prepared from **10***a* (50 mg), mp 83–85°C, as colorless prisms from Et_2O; ir ν_{max}: 3300, 1640 cm^{-1}; ^{1}Hmr δ: 2.11 (dd, J = 5 and 14 Hz, 1H, H-1′), 2.73 (br d, J = 14 Hz, 1H, H-1′), 3.75 (s, 3H, C_{12}-OCH_3), 4.47 (br t, J = 5 Hz, 1H, —CH—OH), 6.01 (s, 1H, —COCH=C—), 6.29 (dd, J = 5 and 10 Hz, 1H, —CH=CH—CH(OH)—), 6.78 (dd, J = 3 and 8 Hz, ArH), 6.91 (d, J = 10 Hz, 1H, —CH=CH—CH(OH)—), 6.93 (d, J = 3 Hz, 1H, ArH), 7.20 (d, J = 8 Hz, 1H, ArH).

(2S,13bR*)-2-Hydroxy-6-oxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline (**11**b)*

Compound **11***b* (81 mg, 83%) was prepared from **10***b* (97 mg), mp 196–198°C, as colorless prisms from MeOH; ir ν_{max}: 3350, 1650 cm^{-1}; ^{1}Hmr δ: 4.12 (m, 1H, —CHOH), 5.96 (s, 1H, —COCH=C—), 6.25 (d, J = 10 Hz, 1H, H-4′), 6.80 (dd, J = 3 and 10 Hz, 1H, H-3′), 7.12 (m, 4H, ArH). *Mol. Wt.* calcd. for $C_{16}H_{15}NO_2$: 253.1101; found (ms): 253.1088.

(2R,13bR*)-2-Hydroxy-6-oxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1-a]isoquinoline (**12**b)*

Compound **12***b* (13 mg, 13%) was prepared from **10***b* (97 mg), mp 75–77°C, as colorless prisms from Et_2O; ir ν_{max}: 3200, 1670, 1650 cm^{-1}; ^{1}Hmr δ: 4.46 (t, J = 5 Hz, 1H, —CHOH), 6.02 (s, 1H, H-5′), 6.28 (dd, J = 5 and 10 Hz, 1H, H-3′), 6.93 (d, J = 10 Hz, 1H, H-4′), 7.27 (m, 4H, ArH). *Mol. Wt.* calcd. for $C_{16}H_{15}NO_6$: 253.1101; found (ms): 253.1076.

Synthesis of dl*-coccolinine (**2**a) and* dl*-15-demethoxycoccolinine (**2**b)*

A mixture of **11***a* (50 mg), CH_3I (280 mg), Et_4NBr (210 mg), and KOH (99 mg) in anhydrous THF (10 mL) was stirred for 18 h at room temperature. The mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. Recrystallization of the residue from MeOH gave *dl*-coccolinine **2***a* (49 mg, 93%) as colorless prisms, mp 152–154°C; ir ν_{max}: 1670, 1610 cm^{-1}; ^{1}Hmr δ: 2.82 (dd, J = 4 and 12 Hz, 1H, H-4′), 3.34 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.90 (m, 1H, —CHOMe), 6.03 (s, 1H, —COCH=C—), 6.30 (d, J = 9 Hz, 1H, H-1′), 6.70–7.30 (m, 3H, ArH), 6.79 (d, J = 9 Hz, 1H, H-2′). *Mol. Wt.* calcd. for $C_{18}H_{19}NO_3$: 297.1365; found (ms): 297.1365.

The ir and ^{1}Hmr spectra were identical with those of natural coccolinine. The difference in melting point of *dl*-coccolinine from

that reported (lit. (7) mp 179–180°C) might be attributable to the presence of dimorphic forms.

Similarly, a solution of **11***b* (67 mg) in anhydrous THF (10 mL) was treated with CH_3I (600 mg) in the presence of Et_4NBr (210 mg) and KOH (80 mg). Working up as described above, *dl*-demethoxycoccolinine **2***b* (65 mg, 95%) was obtained as colorless needles from AcOEt, mp 165–168°C; ir ν_{max}: 1675 cm^{-1}; ^{1}Hmr δ: 1.74 (d, J = 12 Hz, 1H, H-4′), 2.82 (dd, J = 5 and 12 Hz, 1H, H-4′), 3.33 (s, 3H, OCH_3), 3.99 (m, 1H, H-3′), 6.02 (s, 1H, H-8′), 6.30 (d, J = 10 Hz, 1H, H-1′), 6.88 (dd, J = 2 and 10 Hz, 1H, H-2′). *Mol. Wt.* calcd. for $C_{17}H_{17}NO_2$: 267.1257; found (ms): 267.1255.

Synthesis of dl-*coccuvinine (**1**a) and* dl-*15-demethoxycoccuvinine (**1**b)*

An ethereal solution of excess AlH_3 (prepared from $LiAlH_4$:$AlCl_3$ = 3:1) was added to a solution of **2***a* (60 mg) in anhydrous THF (15 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred for a further 2 h. The mixture was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to give *dl*-coccuvinine **1***a* (52 mg, 91%) as a colorless oil (picrate, yellow prisms from EtOH, mp 166–167°C); ^{1}Hmr δ: 1.90 (t, J = 11 Hz, 1H, H-4′), 2.52 (dd, J = 5.5 and 11 Hz, 1H, H-4′), 3.31 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.96 (m, 1H, H-3′), 5.72 (s, 1H, H-7′), 5.99 (d, J = 10 Hz, H-1′), 6.56 (dd, J = 2 and 10 Hz, 1H, H-2′), 6.70 (d, J = 2.7 Hz, 1H, ArH), 6.81 (dd, J = 2.7 and 8.0 Hz, 1H, ArH), 7.08 (d, J = 8.0 Hz, 1H, ArH).

The ir and ^{1}Hmr spectra were identical with those of natural coccuvinine.

Similarly, **2***b* (50 mg) in anhydrous THF (13 mL) was reduced with excess AlH_3 as described above to give 15-demethoxycoccuvinine **1***b* (44 mg, 93%) as a colorless oil (picrate, yellow prisms from EtOH, mp 191–193°C); ^{1}Hmr δ: 1.84 (t, J = 11 Hz, 1H, H-4′), 2.54 (dd, J = 6 and 11 Hz, 1H, H-4′), 3.29 (s, 3H, OCH_3), 3.85 (m, 1H, H-3′), 5.71 (s, 1H, H-7′), 5.97 (d, J = 10 Hz, 1H, H-1′), 6.55 (dd, J = 2 and 10 Hz, 1H, H-2′), 7.14 (m, 5H, ArH).

Acknowledgement

We are grateful to Professor M. Ju-ichi, Mukogawa Women's University, for providing the spectral data of coccolinine and coccuvinine.

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