Dioxopyrrolines. LXII.¹⁾ Diels–Alder Reaction of 1-Aryl-4- and 5-methoxycarbonyl-1*H*-pyrrole-2,3-diones with Various 1,3-Dienes

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Received November 26, 2002; accepted February 19, 2003

Two new dioxopyrrolines (1-aryl-4-methoxycarbonyl-1*H*-pyrrole-2,3-dione **6** and the 5-methoxycarbonyl isomer **8**) behaved as good dienophiles to some kind of 1,3-dienes examined. In most cases, the products were explained by the reaction where the largest lobe of HOMO of dienes reacted to the larger LUMO of dienophiles in an expected *cis-endo* manner. However, in the reactions of **8** with alkylbutadienes, piperylene and isoprene, abnormality in the reaction was observed, which was well explained by taking account of steric factors.

Key words dioxopyrrolone; Diels–Alder reaction; steric factor; regioselectivity; 1-aryl-4-methoxycarbonyl-1*H*-pyrrole-2,3-dione; 1-aryl-5-methoxycarbonyl-1*H*-pyrrole-2,3-dione

1*H*-Pyrrole-2,3-diones (dioxopyrrolines) are useful synthon in the organic synthesis.^{2,3)} Particularly, the 4,5-dialkoxycarbonyl derivative (**1**) behaves as a strong dienophile to give hydroindoles.⁴⁾ The cycloaddition of **1** to 1-substituted butadiene such as 1-methoxy- or 1-sulphenyl-butadiene smoothly occurred in regio- and stereo-selective manners to give 4-substituted hydroindoles in good yields. Although two alkoxycarbonyl groups in **1** are obviously enhancing the dienophile activity of the dioxopyrrolone, it is hard to predict the respective contribution of each group to regioselectivity of this cycloaddition reaction. Therefore, we have newly prepared two differently substituted dioxopyrrolines, 4- and 5-methoxycarbonyl derivatives **6** and **8**, and examined their cycloaddition reaction to various butadienes hoping to evaluate the contribution of each methoxycarbonyl group in the dienophile on the regioselectivity of treated cycloaddition re-

action.

Results and Discussion

Preparation of the Dioxopyrrolines 4-Methoxycarbonyl and 5-methoxycarbonyl-dioxopyrrolines, **6** and **8**, were synthesized from *p*-anisidine **4** based on the known method, respectively. Oxalation of the enamine **5**⁵⁾ prepared from methyl propiolate and **4** with oxalyl chloride gave **6** as red-dish purple prisms in a quantitative yield. While oxalation of the condensation product (an equilibrium mixture of imine-enamine tautomers)⁶⁾ of methyl pyruvate and **4** gave 5-methoxycarbonyl derivative **8** as red prisms. The spectroscopic data [IR, ¹H-, ¹³C-NMR, and high resolution MS (HR-MS)] were compatible to the expected structures, respectively.

Diels–Alder Reaction of Dioxopyrrolines, **6** and **8**

Chart 1

	R ¹	R ²	R ³		R ¹	R ²	R ³
9:	H	H	H	14:	H	Me	H
10:	H	Me	Me	15:	H	H	OTMS
11:	Me	H	H	16:	OAc	H	Me
12:	OMe	H	H	17:	OTMS	H	Me
13:	H	H	Me				

Chart 2

Table 1. Diels–Alder Reaction of the Dioxopyrroline (**6**) with Various Butadienes^{a)}

Entry	Butadienes	Yield of products (%) ^{b)}
1	Butadiene (A)	9 (83)
2	2,3-Dimethylbutadiene (B)	10 (92)
3	Piperylene (C)	11 (73)
4	1-Methoxybutadiene (D)	12 (79)
5	Isoprene (E)	13 (47)+ 14 (16)
6	2-Trimethylsilyloxybutadiene (F)	18 (72)
7	1-Acetoxy-3-methylbutadiene (G)	16 (67)
8	3-Methyl-1-trimethylsilyloxybutadiene (H)	17 (69)
9	1-Methoxy-3-trimethylsilyloxybutadiene (I)	19 (29)

a) Reaction condition: In toluene, 80 °C, 15 h. b) Yield was calculated from enamine **5**.

Diels–Alder reaction of **6** with nine kind of butadienes (**A** to **I**) were carried out on heating two substrates in toluene at 80 °C for 15 h. In all cases, single product was produced usually in good yield except in the case of isoprene (**E**) where two regio isomers were produced as discussed below (see Table 1). When the dienes beared an OTMS group (**F**, **I**), the products were the expected adducts and/or its desilylated ketones. For them the structure determinations and yield calculations were made after converting the product into single ketones by treatment with acetic acid.

Butadiene (**A**) and 2,3-dimethylbutadiene (**B**) gave **9** and **10** in 83% and 92% yield, respectively. 1-Substituted (by alkyl or electron donating group) butadienes (**C**, **D**, **G**, **H**, **I**) gave expected *endo*-adducts (4 α -substituted hydroindoles), **11**, **12**, **16**, **17**, and **19**, respectively.

2-Trimethylsilyloxybutadiene (**F**) also gave a single adduct **15** (thereof **18**) in 72% yield. However, isoprene (**E**) gave two regio-isomers **13** and **14** in a ratio of 3 : 1.

5-Methoxycarbonyldioxopyrroline **8** also gave adducts, which were isolated as tautomeric enols. There was a notable difference between **6** and **8** in the reaction of piperylene (**C**) and isoprene (**E**). The addition product of **8** to **C** was a 1 : 1 mixture of two regio-isomers, **20** and **21**, which were separated by chromatography, while isoprene (**E**) gave a single adduct **23**. 1-Methoxybutadiene (**D**) gave compound **25** in

Table 2. Diels–Alder Reaction of the Dioxopyrroline (**8**) with Butadienes

Entry	Butadiene	Conditions			Yield of products (%)
		Solvent	Temp. (°C)	Time (h)	
1	Piperylene (C)	Benzene	90	15	20 (40) ^{a)} + 21 (40) ^{a)}
2	1-Methoxybutadiene (D)	Toluene	100	11	24 (23) ^{a)}
3	Isoprene (E)	Benzene	90	16	23 (75) ^{b)}

a) Yield was calculated from *p*-anisidine. b) Yield was calculated from dioxopyrroline **8**.

33% yield after isolation with silica gel chromatography, which is produced from the expected adduct **22** by loss of MeOH followed by aromatization with concomitant cleavage of C–N bond. By the chromatographic isolation of the product using CC-7 (Mallinckrodt, Inc.) column, the adduct **24** was obtained in 23% yield. Treatment of **24** with SiO₂ gave **25** in 70% yield.

Structure Determination of the Product The spectroscopic data (MS, IR, ¹H- and ¹³C-NMR) of the above isolated compounds from the reaction of **6** and dienes were compatible to the assigned structures, respectively. The regio-chemistry in this cycloaddition and stereochemistry of C-4 substituent were determined with the help of H–H two dimensional (2D) correlated spectroscopy (COSY) and nuclear Overhauser enhancement spectroscopy (NOESY).

Adducts (**9**–**19**) gave correlation peaks between ester methyl group and angular H-7a establishing their ring junctures to be *cis*. For other structure determinations, we will show the procedure by taking **11** as an example. Compound **11** showed clear COSY correlation between H-7a (δ 4.85–4.83, m) and methylene group at δ 2.47 (ddd) and 2.19–2.14 (m) indicating that C-7 position is CH₂. The NOESY spectrum showed a correlation between H-4 (geminal to the methyl) and H-7a. Therefore the 4-methyl group must be *trans* to the ring juncture. Compounds **12**, **16**, **17**, were analyzed in a similar way by the H–H COSY and NOE correlation.

The desilylated ketones **18** and **19** were determined as follows. In addition to the other spectral data (which are com-

Chart 3

patible to the expected structures), H-7a of **18** (δ 5.15, t) showed COSY correlation peak with methylene group at δ 2.80 (dd). This indicated that C-7 is CH₂. The structure of **19** was determined in a similar way where H-7a also exhibited a NOESY correlation with H-4 showing that the stereochemistry of 4-OMe group is α .

The product from the reaction of **6** and isoprene (**E**) was an oily mixture of two compounds in a ratio of 3 : 1 as shown by the ratio of two methyl signals at δ 1.60 and 1.70 in the ¹H-NMR spectrum. Since it was difficult to separate them by column chromatography, the structure of each component was determined without separation. Similar procedures as described above lead to the conclusion that the major product was 6-methyl **13** and the minor product was 5-methyl adduct **14**. The H-7a signal (δ 5.05 t, $J=3.8$ Hz) of **13** had a COSY correlation with a broad doublet ($J=3.8$ Hz) of H₂ at δ 2.25 which did not show the correlation with the olefinic H at δ 5.61 (m). On the other hand, two H at C-4 in **14** appeared at δ 2.78 and 2.55 as an ABq ($J=15.5$ Hz) which did not show the correlation with the olefinic H at δ 5.38 (m).

The enol structure of the products from the cycloaddition of **8** to dienes were indicated by their positive FeCl₃ test, appearance of OH absorption in the IR, and appearance of two new –C= signals (instead of CO, C-3 and C-3a) in the ¹³C-NMR spectrum.

The regiochemistries of two isomers **20** and **21** from the addition reaction of **8** to piperylene were determined as follows. The compound **20** was reduced with tetra-*n*-butylammonium borohydride⁷⁾ to the alcohol **26**, which showed, in the COSY spectrum, the sequence of H-3 (δ 4.32, dd) to H-3a (δ 2.16, dd) to H-4 (δ 2.60–2.46, m) and to Me (δ 1.19, d), thus confirming the position of the Me group at C-4. The stereochemistry of 4-Me group was revealed to be β (*cis* to the ring juncture) by the presence of NOE enhancements of H-3a (18.3%) on irradiation of the Me group. Irradiation of H-3 also produced enhancement of H-3a signal (12.9%). The fact implies that the reaction of **8** with piperylene proceeded unexpectedly through *exo*-stereochemistry. At the same time, the stereochemistry of the newly created hydroxy-group at C-

3 was determined as α .

Similarly, reduction of **21** gave the alcohol **27**. The NMR analysis gave the sequence of H-3 to H-3a to H₂-4 to H-5 to H-6 to H-7 and to Me, thus the position of methyl group and the stereochemistry of 3 α -OH group being established. The difference NOE spectrum of **27**, however, did not give clear-cut evidence for the stereochemistry of methyl group at C-7.

On the other hand, reduction of the addition product **23** of isoprene to **8** with potassium borohydride in EtOH under CO₂ gave α -alcohol **28** (66%) and β -alcohol **29** (21%). Treatment of **28** with conc. H₂SO₄ gave the ether **30** in 69% yield. This compound had the same molecular formula (m/z 331) with that before treatment but showed neither OH nor olefinic proton signal in the IR and ¹H-NMR spectra, indicating the ether formation. The structure was supported by the ¹³C-NMR and COSY spectra. Thus, the stereochemistry of 3 α -OH group and the position of Me group (at C-5) in **28** were determined.

Discussion The LUMO coefficient (LCO) of dioxopyrrolines **6** and **8** calculated by Gaussian 98 Rev. A7,⁸⁾ and the HOMO coefficient (HCO) of piperylene and isoprene in the literature^{9,10)} are shown in Fig. 1. The LCO's indicate that C-5 is more reactive than C-4. But the differences between those positions are smaller in **8** (0.141) than in **6** (0.304).

The addition reactions of **6** to dienes are expected by attack of the largest HCO's of dienes to the largest LCO (C-5) of the dioxopyrroline **6** to give the products in such manner yielding 4 α -substituted *cis-endo* adducts, except in the case of isoprene (**E**). Although the addition of piperylene (**C**) gave a single product, it also requires some comments.

Isoprene gave the normal product **13**, but accompanying with the formation of the regio-isomer **14**. Disturbance of the rule can be explained by taking account of the steric factor. The differences of HCO's of C-1 and C-4 in these alkyl-butadienes are very small (0.001 for **C** and 0.044 for **E**). This implies that the difference of the reactivity at C-1 and C-4 in these dienes is smaller than that in the other dienes bearing *O*-functional groups. The disturbance of the rule may be arisen from the steric reasons: obviously addition of isoprene

Chart 4

LUMO coefficients of dioxopyrrolines (6 and 8)^{a)}

	C ₂	C ₃	C ₄	C ₅	C=OOMe
6	-0.329	-0.362	-0.287	0.591	-0.134
8	-0.25	-0.379	-0.353	0.494	0.152

a) See ref. 8).

HOMO coefficients of piperylene and isoprene^{b)}

	C ₁	C ₂	C ₃	C ₄
Piperylene	0.314	0.288	-0.244	-0.315
Isoprene	0.340	0.275	-0.243	-0.296

b) See ref. 9,10).

Fig. 1

to **6** is sterically less favorable for C-1 than that for C-4. Thus, the reverse product **14**, which was initiated by attack of less hindered C-4 (of isoprene) to C-5 (of **6**), is accompanied in the reaction of isoprene. In the reaction of piperylene (**C**) to **6**, both the electronic and steric factors play in the same direction to give the single product **11**.

Similarly, the steric factor plays an important role in additions of **8** to piperylene and isoprene, where piperylene gave a 1 : 1 mixture of regio-isomers (**20**, **21**) and isoprene gave a single product (**23**) with reverse orientation. In compound **8** the difference of LCO between C-4 and C-5 is small (0.141) and the attack to C-5 is obviously more hindered than that to C-4. Thus in the reaction of isoprene, attack of C-1 in the diene to the less hindered C-4 of **8** occurred exclusively to

give the reverse oriented product **23**. In piperylene, its reactive position (C-4) is less hindered than that of isoprene (C-1). Thus, the addition reaction to **8** takes two paths: one is the attack of C-4 (of **C**) to C-5 of **8** (electronically more favored) and the other is the attack of C-4 (of **C**) to C-4 of **8** (sterically more favored). Equal formation of **20** and **21** implies that these two factors play equal role in the reaction of **C** to **8**. Although the reason of the formation of *exo*-adduct in this case is not clear, it is not exceptional that thermodynamically more stable *exo*-adduct (β -Me isomer is 0.4 kcal/mol more stable than the α -Me isomer in the dioxo form) is sometimes favored in the Diels–Alder reaction of dioxopyrrolines.^{11,12)}

Conclusion

In conclusion, new dioxopyrrolines **6** and **8** were shown to be good dienophiles in 4+2 cycloaddition reaction. Their LUMO coefficients showed that C-5 had larger values than those of C-4, but the difference is so small in **8** that the steric factor sometimes overcomes the electronic factor. Thus the reaction of 1-*O*-substituted dienes with **6** gave 4-substituted hydroindoles with expected *endo*-stereochemistry and 2-*O*-substituted dienes gave 6-substituted hydroindoles. They are the products where the largest lobe of HOMO of dienes reacted with the largest LUMO (C-5) of dioxopyrrolines.

Violations of the rule were observed particularly for the reactions of 1- and 2-methylbutadiene (piperylene and isoprene) in **8**, where the steric factors have to be taken into account.

Experimental

Unless otherwise stated, the following procedure was adopted. Melting points were determined on a Yanaco melting point apparatus and uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer, and data are given in cm^{-1} . ^1H - and ^{13}C -NMR spectra were taken with a JEOL JNM-EX90 (90 MHz for ^1H and 22.5 MHz for ^{13}C) or JEOL JNM-AL300 (300 MHz for ^1H and 75 MHz for ^{13}C) or JNM- α 500 (500 MHz for ^1H) spectrometer, in CDCl_3 solutions with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. MS and HR-MS were taken with a JEOL JMS D-300 and JEOL JMS-HX110A spectrometer and M^+ is given in m/z . Elemental analyses were performed with a Yanaco MT-3. TLC was performed on pre-coated Kieselgel 60 F₂₅₄ plates and spots were monitored by UV (254 nm), then developed by spraying 0.5% $\text{Ce}(\text{SO}_4)_2$ –0.5% $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$ in 5% H_2SO_4 and heating the plates until coloration

took place. Column chromatography was performed on Wakogel C-200 (silica gel). For medium-pressure liquid chromatography, a Kusano CPS-HS-221-1 column (silica gel, 22 mm i.d. × 100 mm) was used. All organic extracts were washed with brine, dried over anhydrous MgSO_4 , and concentrated to yield the products.

4-Methoxycarbonyl-1-(4-methoxyphenyl)-1H-pyrrole-2,3-dione (6) Methyl propiolate (16.8 g, 0.2 mol) was added to a solution of *p*-anisidine **4** (24.6 g, 0.2 mol) in MeOH (200 ml), and the mixture was stirred overnight at room temperature. The resultant precipitate was collected by filtration. The filtrate was purified by chromatography using AcOEt–hexane (1:1) as an eluent to afford further crops of crystals. The crystals were combined and recrystallized from AcOEt–MeOH to yield **5** (29.0 g, 72%).

To a solution of **5** (29.0 g, 0.14 mol) in THF (10 ml)–ether (400 ml) was added oxalyl chloride (12.2 ml, 0.14 mol) and the mixture was stirred at room temperature for 1 h. Dioxane (150 ml) and octane (150 ml) were added to the mixture, then evaporated *in vacuo*. The residue was purified by crystallization to give **6** (36.0 g, 98%), as reddish purple needles, mp 154–155 °C (from Et_2O). IR (KBr): 1730, 1695. ^1H -NMR: 8.94 (1H, s, =CH), 7.42, 6.99 (each 2H, d, $J=8.9$ Hz, Ar-H) 3.86, 3.85 (each 3H, s, OMe). HR-MS: Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_5$: 261.0635. Found: 261.0620.

5-Methoxycarbonyl-1-(4-methoxyphenyl)-1H-pyrrole-2,3-dione (8) A mixture of methyl pyruvate (5.1 g, 50 mmol) and *p*-anisidine **4** (616 mg, 5 mmol) was stirred for 1 h at room temperature, then distilled at 5 mmHg to remove excess methyl pyruvate. The residue was dissolved in ether (5 ml) and oxalyl chloride (0.87 ml, 10 mmol) in anhydrous ether (50 ml) was added dropwise to this solution. The resulting mixture was stirred at room temperature for 10 min. After addition of heptane (5 ml) and benzene (5 ml) the mixture was concentrated *in vacuo* and the residue was crystallized from Et_2O –hexane to give **8** (930 mg, 71%) as red prisms. mp 128–129 °C. IR: 1760, 1720. ^1H -NMR: 7.18–6.89 (4H, m, Ar-H), 5.97 (1H, s, =CH), 3.83, 3.81 (each 3H, s, OMe). ^{13}C -NMR: 184.6, 160.0, 159.7, 158.1, 156.6, 126.5, 127.7 × 2, 114.6 × 2, 104.0, 55.5, 53.5. HR-MS: Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_5$: 261.0634. Found: 261.0604.

Diels–Alder Reaction of Dioxopyrroline (6, 8) with Butadienes (General Procedure) A mixture of dioxopyrroline and a diene (4 eq mol, see Tables 1 and 2) in dry toluene or benzene was heated at appropriate temperature in a sealed tube with stirring. The reaction mixture was concentrated to dryness *in vacuo*. The residue was passed through a short column of SiO_2 with AcOEt–hexane. Concentration of the eluate gave a crude product.

(3aR*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**9**): Brown prisms. mp 134 °C (from AcOEt–hexane). IR (KBr): 1770, 1740, 1700, 1610, 1520. ^1H -NMR: 7.26, 7.01 (each 2H, d, $J=9.1$ Hz, Ar-H), 6.03–5.97 (1H, m, H-5), 5.79–5.75 (1H, m, H-6), 5.03–5.01 (1H, m, H-7a), 3.85, 3.80 (each 3H, s, OMe), 2.93 (1H, dd, $J=15.4$, 6.6 Hz) and 2.58 (1H, d, $J=15.4$ Hz, $-\text{CH}_2-$), 2.43–2.35 (1H, m) and 2.25 (1H, s, $-\text{CH}_2-$). ^{13}C -NMR: 195.8, 168.5, 159.0, 157.2, 128.6, 127.9, 126.1, 124.9 × 2, 114.8 × 2, 58.8, 55.3, 53.5, 55.0, 28.3, 26.3. HR-MS: Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_5$: 315.1107. Found: 315.1108. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.58; H, 5.54; N, 4.57.

(3aR*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-5,6-dimethyl-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**10**): Yellow prisms. mp 149–152 °C (from AcOEt–hexane). IR (KBr): 1770, 1740, 1710, 1620, 1520. ^1H -NMR: 7.43, 7.01 (each 2H, d, $J=8.9$ Hz, Ar-H), 5.00 (1H, t, $J=3.6$ Hz, H-7a), 3.85, 3.78 (each 3H, s, OMe), 2.64, 2.52 (each 1H, d, $J=14.6$ Hz, $-\text{CH}_2-$), 2.24 (2H, s, $-\text{CH}_2-$), 1.69, 1.54 (each 3H, s, Me). ^{13}C -NMR: 195.8, 168.5, 158.9, 157.2, 128.8, 127.4, 125.6, 124.7 × 2, 114.8 × 2, 59.5, 55.5, 53.4, 55.1, 34.8, 33.1, 19.0 × 2. HR-MS: Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: 343.1417. Found: 343.1396. Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.50; H, 6.24; N, 4.04.

(3aR*,4S*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-4-methyl-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**11**): Light yellow prisms. mp 136–140 °C (from AcOEt–hexane). IR: 1765, 1720, 1690, 1610, 1520. ^1H -NMR: 7.37, 6.99 (each 2H, d, $J=9.2$ Hz, Ar-H), 5.78 (1H, dt, $J=8.9$, 3.4 Hz, H-5), 5.73–5.69 (1H, m, H-6), 4.85–4.83 (1H, m, H-7a), 3.84, 3.81 (each 3H, s, OMe), 2.99–2.93 (1H, m, H-4), 2.47 (1H, ddd, $J=15.6$, 6.7, 1.8 Hz, H-7), 2.19–2.14 (1H, m, H-7), 1.41 (3H, d, $J=7.3$ Hz, Me). ^{13}C -NMR: 195.1, 169.7, 158.9, 157.7, 128.5, 135.0, 125.1, 124.9 × 2, 114.7 × 2, 60.4, 57.7, 55.5, 53.3, 34.8, 26.1, 14.8. HR-MS: Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_5$: 329.1267. Found: 329.1287. Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.72; H, 5.90; N, 4.26.

(3aR*,4S*,7aR*)-4-Methoxy-3a-methoxycarbonyl-1-(4-methoxyphenyl)-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**12**): Light yellow prisms. mp 132–134 °C (from AcOEt–hexane). IR (KBr): 1780, 1740, 1710, 1610, 1510. ^1H -NMR: 7.43, 6.99 (each 2H, d, $J=9.0$ Hz, Ar-H), 6.29–6.26 (1H,

m, H-5), 6.05–6.01 (1H, m, H-6), 4.87 (1H, t, $J=7.0$ Hz, H-7a), 4.72 (1H, d, $J=4.9$ Hz, H-4), 3.84, 3.80, 3.25 (each 3H, s, OMe), 2.53–2.47 (1H, m, H-7), 2.40–2.34 (1H, m, H-7). ^{13}C -NMR: 194.1, 167.8, 158.8, 157.1, 129.8 × 2, 125.0 × 2, 114.5 × 2, 128.5, 76.2, 59.5, 57.2, 55.2, 53.5, 56.2, 26.9. HR-MS: Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_6$: 345.1210. Found: 345.1208. Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.58; H, 5.61; N, 3.98.

(3aR*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-6-methyl-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**13**): ^1H -NMR: 7.61, 7.42 (each 2H, d, $J=9.2$ Hz, Ar-H), 5.62–5.60 (1H, m, H-5), 5.05 (1H, t, $J=3.8$ Hz, H-7a), 3.85, 3.79 (each 3H, s, OMe), 2.88 (1H, dd, $J=15.0$, 6.7 Hz) and 2.50 (1H, br d, $J=15.0$ Hz, H-4), 2.25 (2H, d, $J=3.8$ Hz, H-7), 1.60 (3H, s, Me). ^{13}C -NMR: 196.1, 168.6, 158.9, 157.2, 135.1, 128.5, 124.8 × 2, 114.8 × 2, 59.0, 55.5, 53.5, 54.8, 31.3, 28.8, 22.9.

(3aR*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-5-methyl-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**14**): ^1H -NMR: 7.44, 7.00 (each 2H, d, $J=9.2$ Hz, Ar-H), 5.38 (1H, m, H-6), 4.98 (1H, ddd, $J=5.5$, 2.8, 0.9 Hz, H-7a), 3.85, 3.79 (each 3H, s, OMe), 2.78 (1H, d, $J=15.5$ Hz) and 2.55 (1H, br d, $J=15.5$ Hz, H-4), 2.34–2.29 (1H, m) and 2.22–2.15 (1H, m) (H-7), 1.76 (3H, s, Me). ^{13}C -NMR: 196.0, 168.6, 156.0, 157.2, 137.4, 128.8, 124.8 × 2, 114.8 × 2, 118.6, 59.1, 55.6, 53.6, 55.3, 33.1, 26.8, 23.1.

(3aR*,4S*,7aR*)-4-Acetoxy-3a-methoxycarbonyl-1-(4-methoxyphenyl)-6-methyl-2,3-dioxo-2,3a,4,7,7a-hexahydroindole (**16**): Red oil. IR (CHCl_3): 1760, 1710, 1600, 1500. ^1H -NMR: 7.43 (2H, d, $J=9.0$ Hz, Ar-H), 7.02 (2H, d, $J=9.0$ Hz, Ar-H), 5.95 (1H, d, $J=5.2$ Hz, H-4), 5.91–5.89 (1H, m, H-5), 4.99 (1H, t, $J=6.9$ Hz, H-7a), 3.86, 3.82 (each 3H, s, OMe), 2.42 (1H, dd, $J=15.6$, 6.7 Hz, H-7), 2.33 (1H, dd, $J=15.6$, 6.7 Hz, H-7), 2.01 (3H, s, COMe), 1.71 (3H, s, Me). ^{13}C -NMR: 191.8, 169.2, 166.9, 158.9, 156.7, 138.9, 128.1, 124.9 × 2, 114.6 × 2, 121.7 (C-5), 69.5, 57.5, 56.4, 55.3, 53.6, 31.6 (C-7), 20.8, 14.0. HR-MS: Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_7$: 387.1318. Found: 387.1323.

(3aR*,4S*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-6-methyl-2,3-dioxo-4-trimethylsilyloxy-2,3a,4,7,7a-hexahydroindole (**17**): Red oil. IR (CHCl_3): 1820, 1770, 1660, 1560. ^1H -NMR: 7.41, 7.00 (each 2H, d, $J=9.2$ Hz, Ar-H), 5.88–5.85 (1H, m, H-5), 5.08 (1H, d, $J=5.5$ Hz, H-4), 4.99 (1H, t, $J=7.3$ Hz, H-7a), 3.85, 3.79 (each 3H, s, OMe), 2.45–2.40 (1H, m) and 2.34 (1H, dd, $J=15.3$, 7.3 Hz, H-7), 1.71 (3H, s, Me), 0.06 (9H, s, OTMS). ^{13}C -NMR: 193.3, 167.8, 158.7, 157.2, 138.2, 128.8, 125.1 × 2, 114.6 × 2, 124.8, 69.4, 60.1, 55.9, 55.5, 53.3, 31.9, 23.1. HR-MS: Calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_6\text{Si}$: 417.1606. Found: 417.1601.

(3aR*,7aR*)-3a-Methoxycarbonyl-1-(4-methoxyphenyl)-2,3,6-trioxo-2,3a,4,5,6,7,7a-octahydroindole (**18**): Light yellow prisms. mp 174–176 °C (from AcOEt–hexane). IR (KBr): 1770, 1740, 1720, 1700, 1610, 1590, 1520. ^1H -NMR: 7.31, 7.00 (each 2H, d, $J=9.0$ Hz, Ar-H), 5.15 (1H, t, $J=4.9$ Hz, H-7a), 3.85, 3.84 (each 3H, s, OMe), 2.80 (1H, dd, $J=16.2$, 4.9 Hz, H-7), 2.70–2.46 (4H, m, $-\text{CH}_2-\times 2$), 2.25–2.18 (1H, m). ^{13}C -NMR: 205.7, 194.9, 167.8, 159.7, 156.8, 127.5, 125.4 × 2, 115.1 × 2, 57.3, 55.6, 54.1, 53.3, 41.0, 34.9, 26.3. HR-MS: Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_6$: 331.1057. Found: 331.1095. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.34; H, 5.24; N, 4.30.

(3aR*,4S*,7aR*)-4-Methoxy-3a-methoxycarbonyl-1-(4-methoxyphenyl)-2,3,6-trioxo-2,3a,4,5,6,7,7a-octahydroindole (**19**): Yellow prisms. mp 160–163 °C (from AcOEt–hexane). IR (KBr): 1770, 1740, 1710, 1610, 1520. ^1H -NMR: 7.42, 7.00 (each 2H, d, $J=8.9$ Hz, Ar-H), 5.12 (1H, dd, $J=9.8$, 7.3 Hz, H-7a), 4.67 (1H, t, $J=2.8$ Hz, H-4), 3.84, 3.83, 3.33 (each 3H, s, OMe), 2.87 and 2.48 (each 1H, dd, $J=19.2$, 2.7 Hz, H-5), 2.82–2.80 (2H, m, H-7). ^{13}C -NMR: 204.4, 192.0, 166.4, 159.2, 152.0, 128.2, 124.8 × 2, 114.9 × 2, 78.2, 58.2, 55.6, 54.1, 56.9, 55.4, 42.9, 39.6. HR-MS: Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_6$: 361.1159. Found: 361.1144.

3-Hydroxy-7a-methoxycarbonyl-1-(4-methoxyphenyl)-4-methyl-2-oxo-2,4,7,7a-tetrahydroindole (**20**): Pale yellow needles. mp 204–206 °C (from AcOEt–hexane). IR (KBr): 3250, 1745, 1690. ^1H -NMR: 7.12, 6.88 (each 2H, d, $J=9.2$ Hz, Ar-H), 5.74–5.68 (1H, m, =CH), 5.60–5.54 (1H, m, =CH), 3.79, 3.65 (each 3H, s, OMe), 3.17–3.10 (1H, m, H-7), 3.08 (1H, d, $J=5.8$ Hz) and 2.22–2.15 (1H, m, H-4), 1.52 (3H, d, $J=7.3$ Hz, Me). ^{13}C -NMR: 170.2, 168.2, 158.8, 140.9, 128.0, 123.2, 131.8 (C-6), 127.4 × 2, 114.6 × 2, 121.9, 68.3, 55.4, 52.9, 33.1, 30.9, 17.7. HR-MS: Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_5$: 329.1261. Found: 329.1256.

3-Hydroxy-7a-methoxycarbonyl-1-(4-methoxyphenyl)-7-methyl-2-oxo-2,4,7,7a-tetrahydroindole (**21**): Pale yellow prisms. mp 205–207 °C (from CHCl_3 –hexane). IR (KBr): 3250, 1750, 1680. ^1H -NMR: 7.27, 6.90 (each 2H, d, $J=9.0$ Hz, Ar-H), 5.88–5.83 (1H, m, =CH), 5.65–5.60 (1H, m, =CH), 3.80, 3.63 (each 3H, s, OMe), 3.42–3.33 (1H, m, H-7), 3.33–3.27 (1H, m, H-4), 2.83 (1H, dt, $J=21.4$, 2.9 Hz, H-7), 0.79 (3H, d, $J=7.0$ Hz, Me). ^{13}C -NMR: 170.6, 168.4, 157.7, 141.5, 129.4, 118.4, 130.9, 124.3 × 2,

114.5×2, 121.9, 70.9, 55.4, 52.9, 34.5, 22.9, 14.9. HR-MS: Calcd for C₁₈H₁₉NO₅: 329.1260. Found: 329.1233.

3-Hydroxy-7a-methoxycarbonyl-1-(4-methoxyphenyl)-5-methyl-2-oxo-2,4,7,7a-tetrahydroindole (**23**): Light yellow prisms. mp 206–208 °C (from Et₂O–hexane). IR (KBr): 1740, 1680, 1600, 1500. ¹H-NMR: 7.19–6.84 (4H, m, Ar-H), 5.43 (1H, s, =CH), 3.81, 3.65 (each 3H, s, OMe), 3.48–2.09 (4H, m, –CH₂–×2), 1.77 (3H, s, Me). ¹³C-NMR: 170.4, 167.8, 158.6, 140.9, 131.8, 128.7, 121.0, 127.4×2, 114.5×2, 117.7, 66.9, 55.4, 52.8, 33.6, 27.4, 22.7. HR-MS: Calcd for C₁₈H₁₉NO₅: 329.1289. Found: 329.1276.

Diels–Alder Reaction of Dioxypyrraline (8) with 1-Methoxybutadiene A solution of **8** (261 mg, 1 mmol) and 1-methoxybutadiene (252 mg, 3 mmol) in dry toluene (10 ml) was heated at 100 °C for 11 h in a sealed tube. The reaction mixture was concentrated to dryness *in vacuo* and the residue was passed through a column of CC-7 with AcOEt–hexane. Concentration of the eluate gave a crystalline product which was recrystallized from AcOEt–hexane to give 7a-methoxycarbonyl-1-(4-methoxyphenyl)-2,3-dioxo-2,3,7,7a-tetrahydroindole (**24**, 72 mg, 23%) as yellow prisms, mp 155–157 °C. IR (KBr): 1740 (sh), 1720. ¹H-NMR: 7.15 (1H, d, *J*=5.0 Hz), 7.10 (2H, d, *J*=9.0 Hz), 6.96 (2H, d, *J*=9.0 Hz), 6.48–6.30 (2H, m), 3.83 (3H, s), 3.74 (3H, s), 3.34 (1H, dd, *J*=17.4, 6.0 Hz), 2.70–2.51 (1H, m). ¹³C-NMR: 183.1, 169.7, 161.9, 159.7, 136.8, 130.8, 127.3, 127.2, 126.9×2, 124.1, 115.0×2, 63.2, 55.5, 53.6, 30.7. MS: *m/z* 313 (M⁺), 163 (base peak). HR-MS: Calcd for C₁₇H₁₅NO₅: 313.0950. Found: 313.0985.

Work-up the reaction product by silica gel chromatography as in general procedure gave 2-(2-(4-methoxy)phenylamino-1,2-dioxoethyl)benzoic acid methyl ester (**25**, 103 mg, 33%) as light yellow prisms, mp 132–135 °C (from AcOEt–hexane). IR (KBr): 3350, 1715, 1680. ¹H-NMR: 8.84 (1H, s), 8.01 (1H, dd, *J*=7.6, 1.4 Hz), 7.67 (1H, dt, *J*=7.6, 1.3 Hz), 7.61 (1H, dt, *J*=7.6, 1.4 Hz), 7.59 (2H, d, *J*=9.1 Hz), 7.52 (1H, dd, *J*=7.6, 1.3 Hz), 6.89 (2H, d, *J*=9.1), 3.83, 3.80 (each 3H, s). ¹³C-NMR: 192.5, 166.7, 157.9, 156.8, 137.4, 132.6, 131.1, 130.8, 129.9, 129.1, 128.3, 121.1×2, 114.2×2, 55.4, 52.6. HR-MS: Calcd for C₁₇H₁₅NO₅: 313.0950. Found: 313.0966. Anal. Calcd for C₁₇H₁₅NO₅: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.14; H, 4.94; N, 4.36.

Treatment of 24 with Silica Gel A mixture of **24** (30 mg) and silica gel (300 mg) in AcOEt (20 ml) was stirred at room temperature for 1 h. The silica gel was filtered off and the filtrate was concentrated under pressure. Crystallization of the product from AcOEt–hexane gave **25** (21 mg, 70%).

Reduction of 20 A solution of **20** (121 mg, 0.37 mmol) in MeOH (7 ml) was stirred with tetra-*n*-butylammonium borohydride (378 mg, 1.47 mmol) for 68 h at room temperature. The reaction mixture was acidified with 5% HCl and extracted with CHCl₃. The product was purified by column chromatography [AcOEt–hexane (1 : 1)] to give the starting material **20** (37 mg, 31%) and the reduction product **26** (47 mg, 39%) as colorless flakes, mp 103–106 °C (from AcOEt–hexane). IR (KBr): 3450, 1720. ¹H-NMR: 6.99, 6.91 (each 2H, d, *J*=9.1 Hz, Ar-H), 5.64 (2H, d, *J*=2.8 Hz, H-5, H-6), 4.75 (1H, d, *J*=12.1 Hz, OH), 4.32 (1H, dd, *J*=12.1, 7.0 Hz, H-3), 3.80 (3H, s, OMe), 3.67 (3H, s, COOMe), 2.75–2.65 (1H, m, H-7), 2.60–2.46 (1H, m, H-4), 2.34–2.24 (1H, m, H-7), 2.16 (1H, dd, *J*=11.6, 7.2 Hz, H-3a), 1.19 (3H, d, *J*=7.0 Hz, Me). ¹³C-NMR: 175.7, 175.4, 159.2, 134.7, 128.2×2, 128.1, 123.4, 114.7×2, 70.5, 68.8, 55.4, 53.3, 52.1, 33.8, 28.7, 18.5. HR-MS: Calcd for C₁₈H₂₁NO₅: 331.1417. Found: 331.1409.

Reduction of 21 A solution of **21** (100 mg, 0.30 mmol) in MeOH (10 ml) was stirred with tetra-*n*-butylammonium borohydride (312 mg, 1.21 mmol) for 117 h at room temperature. The reaction mixture was worked up as described above. Chromatography of the product gave the starting material **21** (32 mg, 32%) and the reduction product **27** (29 mg, 29%), as colorless prisms, mp 164–166 °C (from AcOEt–hexane). IR (KBr): 3350, 1740, 1680. ¹H-NMR: 7.25, 6.86 (each 2H, d, *J*=9.0 Hz, Ar-H), 5.98–5.88 (1H, m, H-5), 5.47 (1H, dt, *J*=9.6, 2.6 Hz, H-6), 4.49 (1H, d, *J*=7.2 Hz, H-3), 4.17 (1H, br s, OH), 3.85 (3H, s, OMe), 3.80 (3H, s, COOMe), 3.08 (1H, ddd, *J*=9.4, 7.2, 4.6 Hz, H-3a), 3.03–2.92 (1H, m, H-7), 2.57 (1H, dt, *J*=18.4, 4.6 Hz, H-4), 2.21–2.05 (1H, m, H-4), 0.53 (3H, d, *J*=7.5 Hz, Me). ¹³C-NMR: 176.8, 174.3, 159.3, 130.3×2, 129.9, 129.7, 127.2, 114.2×2, 73.2, 70.2, 55.3, 52.9, 43.6, 34.4, 20.3, 15.9. HR-MS: Calcd for C₁₈H₂₁NO₅: 331.1418. Found: 331.1398.

Reduction of 23 Potassium borohydride (11 mg, 0.18 mmol) was added to a solution of **23** (116 mg, 0.35 mmol) in EtOH (5 ml) under CO₂ atmosphere and the mixture was stirred at room temperature for 12 h. The reaction mixture was acidified with 5% HCl and extracted with CH₂Cl₂ to give an

oily product, which was purified by ODS column chromatography using MeOH–H₂O (3 : 1) as an eluent to separate into **28** (65 mg, 66%) and **29** (48 mg, 21%). **28**: Colorless prisms. mp 148–150 °C (from AcOEt–hexane). IR (KBr): 3340, 1740, 1680. ¹H-NMR: 7.10, 6.89 (each 2H, d, *J*=9.0 Hz, Ar-H), 5.33–5.26 (1H, m, H-6), 4.64 (1H, d, *J*=7.2 Hz, H-3), 4.30 (1H, br s, OH), 3.80 (6H, s, COOMe, OMe), 2.99 (1H, dd, *J*=14.5, 7.2 Hz, H-3a), 2.62–2.50 (1H, m, H-7), 2.30–2.01 (3H, m, H-4, H-7), 1.77 (3H, s, Me). ¹³C-NMR: 176.2, 174.4, 159.0, 134.9, 129.1×2, 127.7, 116.2, 114.3×2, 70.7, 68.0, 55.3, 52.9, 41.7, 28.4, 25.4, 23.0. Anal. Calcd for C₁₈H₂₁NO₅: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.99; H, 6.41; N, 4.24. **29**: Light yellow prisms. mp 169–171 °C (from AcOEt–hexane). IR (KBr): 3350, 1740, 1680. ¹H-NMR: 7.23–6.82 (4H, m, Ar-H), 5.46 (1H, br s, =CH), 4.19 (1H, d, *J*=9.0 Hz, H-3), 3.79, 3.64 (each 3H, s, OMe), 3.31–2.32 (5H, m, –CH₂–×2, H-3a), 1.74 (3H, s, Me). ¹³C-NMR: 175.1, 172.0, 158.9, 132.7, 128.8, 127.8×2, 114.5×2, 117.7, 73.3, 67.0, 55.4, 52.8, 44.7, 30.9, 29.2, 23.3. Anal. Calcd for C₁₈H₂₁NO₅: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.01; H, 6.41; N, 4.27.

Reaction of 28 with c-H₂SO₄ Compound **28** (45 mg, 0.14 mmol) was treated with c-H₂SO₄ (120 μl) at room temperature for 10 min. The reaction mixture was adjusted to pH 5 by adding 10% aqueous NaOH solution and extracted with CH₂Cl₂. The product was purified by column chromatography followed by crystallization from AcOEt–hexane to give the ether **30** (31 mg, 69%) as colorless prisms, mp 124–126 °C. IR (KBr): 1740, 1690. ¹H-NMR: 7.08, 6.90 (each 2H, d, *J*=9.0 Hz, Ar-H), 4.43 (1H, d, *J*=5.9 Hz, H-3), 3.79 (3H, s, OMe), 3.73 (3H, s, COOMe), 3.31 (1H, t, *J*=4.9 Hz, H-3a), 2.04 (1H, d, *J*=12.3 Hz, H-4), 1.98–1.76 (4H, m, H-6, H-7), 1.66 (1H, dd, *J*=12.3, 4.2 Hz, H-4), 1.44 (3H, s, Me). ¹³C-NMR: 173.7, 172.5, 159.3, 129.3×2, 128.1, 114.6×2, 81.9, 78.4, 71.4, 55.4, 52.7, 44.1, 35.3, 33.6, 25.4, 23.3. HR-MS: Calcd for C₁₈H₂₁NO₅: 331.1417. Found: 331.1392.

References and Notes

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