

HYDROISOQUINOLINE RING CONSTRUCTION VIA THE DIELS-ALDER REACTION OF ARECOLONE-DERIVED ENOL SILYL ETHERS

Jian Ma, Masako Nakagawa,* Yasuhiro Torisawa, and Tohru Hino

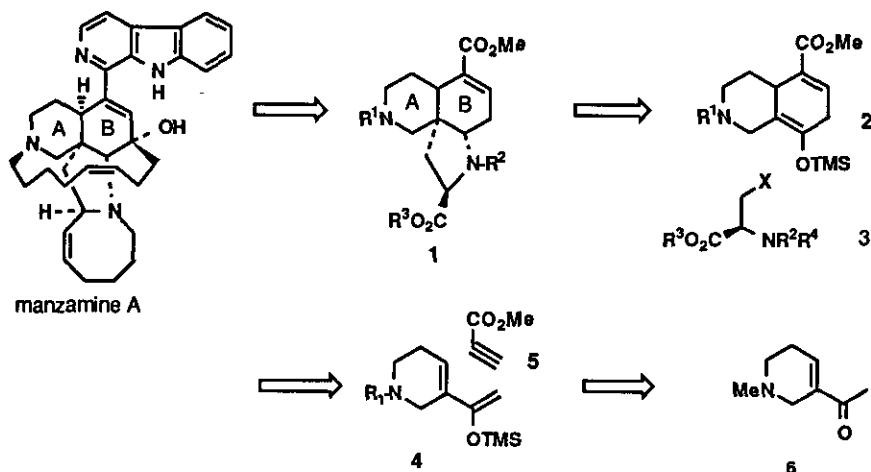
*Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku,
Chiba 263, Japan*

Abstract- Diels-Alder reaction of the arecolone-derived siloxydienes (**7**, **14**) was described. The hexahydroisoquinoline derivatives (**21**, **22**, **23**) were prepared from the reaction of **14** with methyl propiolate followed by Michael addition to the amido acrylates (**18**, **19**, **20**).

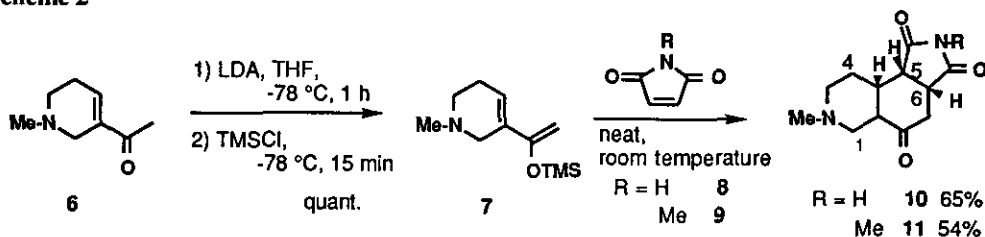
In connection with our work on the total synthesis of the marine alkaloid manzamine A,¹ efficient methods have been sought for the construction of the AB hydroisoquinoline ring system, which is the common core substructure of this marine alkaloid family. Several approaches² for this substructure have been reported, including our own approach *via* the Diels-Alder reaction of 3-alkyl-5,6-dihydro-2(*1H*)-pyridinones.³ As an extension of this tactic, a closely related Diels-Alder reaction using 3-phenylthio-5,6-dihydro-2(*1H*)-pyridinones has been developed quite recently.⁴ In the course of these investigations along the Diels-Alder tactics, we have also focused our attention on the preparation of a new pyrroloisoquinoline derivative (**1**), which is suitable for the construction of other part of this target manzamine A, especially for the β -carboline ring attachment.

We describe herein a part of this alternative synthetic approach employing the Diels-Alder reaction of the arecolone-derived siloxydiene (**4**) as a key strategy (Scheme 1).

Scheme 1



Scheme 2



Results and Discussion

We initiated our study on the Diels-Alder reaction of the siloxydiene (**7**), which was prepared from the readily available arecolone (**6**).⁵ To our disappointment, however, **7** was found to be unstable to both acid and moisture, so that the attempted Diels-Alder reaction of **7** with maleic anhydride or dimethyl maleate was proved to be unsuccessful probably due to acid contaminant in these reagents. In addition, no reaction was observed in the reaction of **7** with cyclohexenone in refluxing toluene.

Therefore, we turned our attention to other dienophiles such as maleimide (**8**) and *N*-methylmaleimide (**9**).

We were pleased to find that **7** reacted with these dienophiles at room temperature without solvent, furnishing

the corresponding adducts (**10** and **11**) in 65% and 54% yields, respectively (Scheme 2). The NOE experiments suggested the structures shown, in which all hydrogens indicated are in *cis* relation.

On the other hand, attempted reaction of **7** with some acetylene derivatives such as phenylacetylene, methyl propiolate and dimethyl acetylenedicarboxylate resulted in a complicated mixture due to polymerization of acetylenes caused by tertiary amine (**7**) itself. These results suggested that the replacement of the *N*-methyl group of **7** with an electron withdrawing protecting group was essential for successful cycloaddition.

Thus, the demethylative protection⁶ of **6** with trichloroethyl chloroformate (TrocCl) was carried out to form the desired *N*-Troc-3-acetyl-1,2,5,6-tetrahydropyridine (**12**) in 66% yield. It should be noted that the reaction of **6** with simple methyl chloroformate did not proceed at all.

Another demethylation was carried out using phenyl chloroformate to give **13** in 69% yield. Although attempted conversion of **12** into the corresponding siloxydiene proved unsuccessful because of the base-sensitive Troc group, the reaction of **13** with LDA and TMSCl at -78°C yielded the siloxydiene (**14**, 86%), which was stable enough to be purified by silica gel chromatography (Scheme 4).

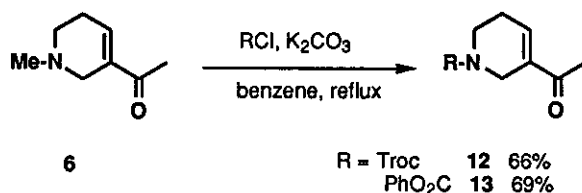
With the stable diene (**14**) in hand, we began the investigation of its Diels-Alder reaction with substituted acetylenes. Refluxing the siloxydiene (**14**) with excess methyl propiolate (9 equiv.) in *p*-cymene for 5 h afforded the expected Diels-Alder adduct (**15**) in 53% yield. The structure of **15** was confirmed unambiguously by spectroscopic means, including ¹H-nmr, C-H cosy, H-H cosy, ¹³C-nmr, and HRms. The yield was improved to 68% by carrying out the reaction in nitrobenzene instead of *p*-cymene for a shorter time (2 h).

We next turned our attention to the introduction of an amino acid chain into **15** for the elaboration of the required 5-membered ring. At first, the methylation of **15** with MeI was examined preliminarily. Thus, the treatment of the silyl enol ether (**15**) with MeI in the presence of BnMe₃NF⁷ gave **16** in 35% yield together with **17** in 9% yield (Scheme 5).

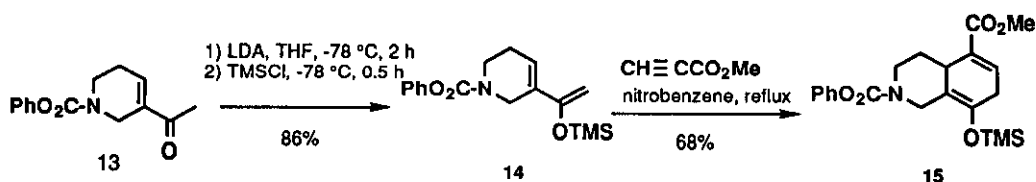
It was then anticipated that the introduction of an amino acid residue by a similar alkylation process would be more sluggish due to the bulkiness.

To overcome this point, we tried Michael addition of the acrylate derived from a protected amino acid. Thus, from the Michael addition of **15** to the acrylates such as **18**, **19**, and **20** under similar conditions in the presence of BnMe₃NF, the corresponding adducts (**21**) (49%), (**22**) (53%), and (**23**) (quantitative) were

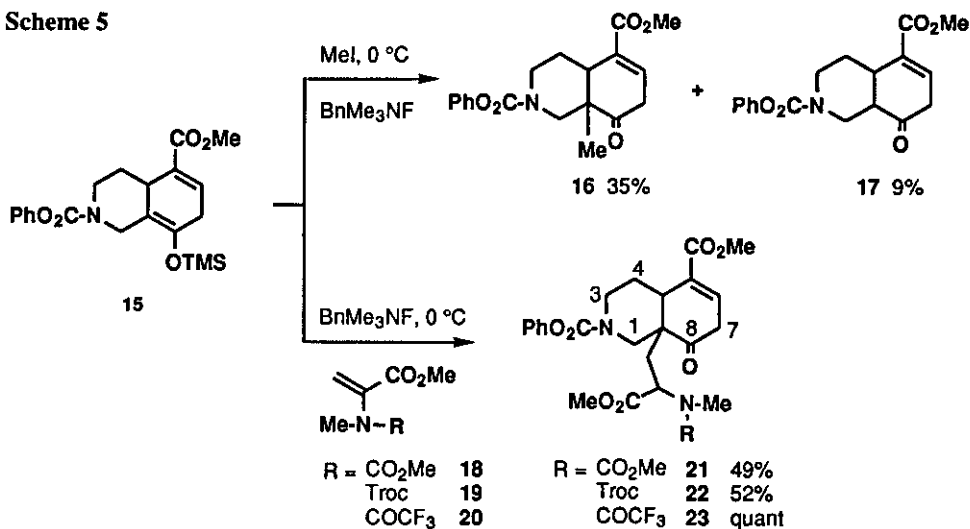
Scheme 3



Scheme 4



Scheme 5



obtained as a mixture of diastereoisomers, respectively. The electron-withdrawing *N*-protecting group in the amido acrylate increased the yield (Scheme 5).

Further work to obtain a pyrroloisoquinoline skeleton is now under investigation and will be reported in the due course.

EXPERIMENTAL

Melting points were determined with a Yamato MP-1 and a Yanagimoto micro melting point apparatus, and are uncorrected. Uv spectra were recorded on a Hitachi 323 spectrophotometer. Ir spectra were obtained with a Hitachi 260-10 spectrophotometer. Mass spectra (ms) were on a Hitachi M-60 or a JEOL-HX 100 mass spectrometer. ^1H -Nmr spectra were taken on a Hitachi R-24B and a JEOL JNM-GSX 500 instruments in CDCl_3 with Me_4Si as an internal standard. Chemical shifts are reported in δ values (ppm). Unless otherwise noted, uv spectra refer to a solution in 95% EtOH and ir spectra to KBr disks.

***N*-Methyl-3-(1-trimethylsiloxyvinyl)-1,2,5,6-tetrahydropyridine (7)** **6⁵** (0.50 g, 3.6 mmol) was added to a solution of LDA (4.0 mmol) in dry THF (20 ml) at -78°C under an argon atmosphere. After stirring for 50 min at -78°C , TMSCl (0.50 ml, 4.0 mmol) was added and the solution was kept stirring for 15 min. The reaction mixture was concentrated under reduced pressure and to the residue obtained, was added dry ether (10 ml) to precipitate LiCl, which was then removed by filtering. The filtrate was concentrated to yield **7** (0.71 g, 93%) as a light yellow oil: Ir (neat) 1700, 1660, 1640, 1590, 750 cm^{-1} ; uv 233 nm; ^1H -nmr δ (500 MHz) 0.21 (9H, s, SiCH_3), 2.40 (3H, s, NCH_3), 2.43-2.50 (4H, m, $\text{NCH}_2\text{CH}_2\text{C}=\text{C}$), 3.02 (1H, d, $J=4.1\text{ Hz}$, $\text{NCH}_2\text{C}=\text{C}$), 3.03 (1H, d, $J=4.1\text{ Hz}$, $\text{NCH}_2\text{C}=\text{C}$), 4.21 (1H, d, $J=0.6\text{ Hz}$, $\text{C}=\text{CH}_2$), 4.25 (1H, d, $J=0.6\text{ Hz}$, $\text{C}=\text{CH}_2$), 6.18 (1H, m, $\text{CH}=\text{C}$).

Diels-Alder reaction of 7 with maleimide A mixture of maleimide (0.34 g, 3.5 mmol) and **7** [prepared from **6** (0.50 g, 3.6 mmol) as above] was stirred for 2 h at room temperature and the reaction mixture was subjected to alumina column chromatography ($\text{AcOEt}:\text{n-hexane} = 5:1$) to yield the adduct (**10**, 0.52 g, 65%) as a white solid, which was recrystallized from AcOEt and n-hexane to furnish colorless prisms: mp $222.5\text{--}226.5^\circ\text{C}$; ir 3400, 2950, 1700, 1200, 780 cm^{-1} ; ^1H -nmr δ (500 MHz) 1.83 (1H, dd,

$J=11.2, 12.2$ Hz, 1-H), 1.89-1.98 (3H, m, 8a-, 4a-, 3-H), 2.06 (1H, dddd, $J=1.6, 3.2, 12.8, 14.4$ Hz, 4-H), 2.23 (1H, ddd, $J=4.8, 9.4, 14.4$ Hz, 4-H), 2.28 (3H, s, NCH₃), 2.56 (1H, dd, $J=7.7, 18.9$ Hz, 7-H), 2.97-3.00 (1H, m, 3-H), 3.01 (1H, dd, $J=1.9, 18.9$ Hz, 7-H), 3.15 (1H, dd, $J=6.4, 9.3$ Hz, 5-H), 3.30 (1H, ddd, $J=1.9, 7.7, 9.3$ Hz, 6-H), 3.42 (1H, dd, $J=4.5, 12.2$ Hz, 1-H); LREIms m/z 236 (M^+ , 96%), 235 (100), 221 (28), 219 (64). Anal. Calcd for C₁₂H₁₆N₂O₃: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.96; H, 6.86; N, 11.85.

Diels-Alder reaction of 7 with *N*-methymaleimide A mixture of *N*-methymaleimide (9, 0.79 g, 7.1 mmol) and 7 [prepared from 6 (1.00 g, 7.2 mmol) as above] was stirred for 1 h at room temperature and the reaction mixture was subjected to alumina column chromatography (AcOEt:n-hexane = 5:1) to yield **11** (0.96 g, 54%) as a white solid, which was recrystallized from AcOEt and n-hexane to furnish colorless prisms: mp 183.5-186.0 °C; ir 1760, 1700, 1680 cm⁻¹; ¹H-nmr δ (500 MHz) 1.72 (1H, dd, $J=10.5, 11.7$ Hz, 1-H), 1.82 (1H, td, $J=2.7, 13.0$ Hz, 3-H), 1.91-2.01 (3H, m), 2.11-2.18 (1H, m, 4-H), 2.27 (3H, s, NCH₃), 2.63 (1H, dd, $J=7.8, 16.9$ Hz, 7-H), 2.92 (1H, ddd, $J=1.6, 3.9, 13.0$ Hz, 3-H), 2.98 (3H, s, CONCH₃), 3.00 (1H, dd, $J=2.1, 7.8$ Hz, 7-H), 3.19 (1H, dd, $J=5.5, 9.1$ Hz, 5-H), 3.30 (1H, dd, $J=2.3, 11.7$ Hz, 1-H), 3.30 (1H, ddd, $J=2.1, 7.8, 16.9$ Hz, 6-H); ¹³C-nmr (100.40 Hz) 25.08 (CH₃), 28.04 (C₄), 36.01 (C_{4a}), 36.30 (C₇), 37.76 (C₆), 41.86 (C₅), 46.14 (CH₃), 47.44 (C_{8a}), 55.39 (C₃), 55.87 (C₁), 176.35, 178.00, 207.50 (C₈); LREIms m/z 250 (M^+ , 100%), 249 (91), 235 (45), 233 (66), 96 (41). Anal. Calcd for C₁₃H₁₈N₂O₃: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.36; H, 7.20; N 11.16.

***N*-Troc-3-acetyl-1,2,5,6-tetrahydropyridine (12)** K₂CO₃ (0.50 g, 3.6 mmol) was added to a stirred solution of 6 (1.00 g, 7.2 mmol) and trichloroethyl chloroformate (1.13 ml, 7.2 mmol) in benzene (30 ml). The reaction mixture was refluxed for 2 h, diluted with benzene, washed with water and brine, and dried over sodium sulfate. Filtration and evaporation gave a residue which was purified by silica gel column chromatography (AcOEt:n-hexane = 1:5) to yield **12** (1.33 g, 66%) as a colorless oil: Ir 2950, 1720, 1670, 720 cm⁻¹; ¹H-nmr δ (500 MHz, 27°C) 2.33 (3H, s, COCH₃), 2.44 (2H, d-like, $J=3.9$ Hz, 5-H), 3.60 (6/5H, s-like, 6-H), 3.65 (4/5H, s-like, 6-H), 4.25 (4/5H, s-like, 2-H), 4.27 (6/5H, s-like, 2-H), 4.78 (2H, s, CH₂CCl₃), 6.98 (4/5H, s-like, 4-H), 7.02 (1/5H, s-like, 4-H); (50°C) 3.61 (2H, s-like, 6-H), 4.25 (2H, s-like, 2-H), 6.97 (1H, s-like, 4-H); LRFABms m/z 300 (MH^+ , 20%), 154 (6).

***N*-Phenoxycarbonyl-3-acetyl-1,2,5,6-tetrahydropyridine (13)** K_2CO_3 (1.00 g, 7.2 mmol) was added to a stirred solution of **6** (3.00 g, 21.5 mmol) and phenyl chloroformate (3.50 ml, 27.89 mmol) in benzene (30 ml). The reaction mixture was refluxed for 2.5 h, diluted with benzene, washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt:n-hexane = 1:5) to yield **13** (3.63 g, 69%) as a colorless oil: Ir 2900, 1720, 1669, 1600, 1420, 1200, 760, 690 cm^{-1} ; uv 215 nm; ^1H -nmr δ (500 MHz) 2.35 (3H, s, CH_3), 2.49 (2H, brs, 5-H), 3.64 (6/5H, brs, 6-H), 3.73 (4/5, brs, 6-H), 4.27 (4/5H, brs, 2-H), 4.37 (6/5H, brs, 2-H), 7.06 (1H, brs, 4-H), 7.10-7.37 (5H, m, arom-H); LREIms m/z 245 (M^+ , 41%), 152 (38), 43 (100); HREIms Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$ (M^+): 245.1054. Found: 245.1074.

***N*-Phenoxycarbonyl-3-(1-trimethylsiloxyvinyl)-1,2,5,6-tetrahydropyridine (14)** To a solution of LDA (2.7 mmol) in dry THF (20 ml) at -78°C under an argon atmosphere was added **13** (0.60 g, 2.4 mmol) with stirring. After stirring for 2 h, TMSCl (0.34 ml, 2.7 mmol) was added and the solution was stirred for 30 min. The solvent was removed under reduced pressure. The residue was subjected to flash chromatography (AcOEt:n-hexane = 1:3) to yield **14** (0.67 g, 86%) as a colorless oil: Ir 2900, 1670, 1600 cm^{-1} ; uv 237 nm; ^1H -nmr δ (60 MHz) 0.15 (9H, s, SiCH_3), 2.20-2.50 (2H, m, 5-H), 3.50-3.80 (2H, t-like, 6-H), 4.05-4.40 (4H, m, $\text{C}_2\text{-H}$ and $\text{C}=\text{CH}_2$), 6.20-6.45 (1H, m, 4-H), 7.00-7.40 (5H, m, arom-H); LRFABms m/z 318 (MH^+ , 42%), 224 ($\text{MH}^+ - \text{PhO}$, 28), 73 (SiMe_3 , 100); HREIms Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Si}$ (M^+) 317.1447. Found: 317.1438.

Diels-Alder reaction of 14 with methyl propiolate A solution of **14** (253 mg, 0.8 mmol) and methyl propiolate (0.71 ml, 7.5 mmol) in nitrobenzene (4 ml) was refluxed for 2 h under an argon atmosphere. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (AcOEt:n-hexane = 1:3) to yield **15** (219 mg, 68%) as a colorless oil and **14** (37 mg, 15%) was recovered. **15**: Ir 1710, 1640, 1590, 1420, 760, 690 cm^{-1} ; uv 260 nm; ^1H -nmr δ (500 MHz) 0.21 (9H, s, SiCH_3), 1.32 (1H, m, 4-H), 2.27 (1H, m, 4-H), 2.85 (1/3H, dd, $J=2.2$, 7.2 Hz, 7-H), 2.90 (2/3H, dd, $J=2.2$, 7.2 Hz, 7-H), 2.94 (2/3H, dd, $J=3.6$, 7.2 Hz, 7-H), 2.99 (1/3H, dd, $J=3.6$, 7.2 Hz, 7-H), 3.05-3.09 (1H, m, 3-H), 3.21-3.26 (2H, m), 3.77 (3H, s, OCH_3), 4.30-4.35 (1H, m, 3-H), 5.24 (2/5H, d, $J=13.9$ Hz, 1-H), 5.33 (3/5H, d, $J=13.9$ Hz, 1-H), 6.86 (1H, dd, $J=2.2$, 3.6 Hz, 6-H), 7.10 (2H, d,

$J=7.4$ Hz, arom-H), 7.16 (1H, t, $J=7.4$ Hz, arom-H), 7.32 (2H, t, $J=7.4$ Hz, arom-H); (50°C) 2.89 (1H, dd, $J=2.2, 7.2$ Hz, 7-H), 2.93 (1H, dd, $J=3.6, 7.2$ Hz, 7-H), 3.17 (1H, brs, 3-H), 4.31 (1H, d-like, 3-H), 5.29 (1H, brs, 1-H); ^{13}C -nmr δ (125.65 MHz) 0.55 (SiC), 31.73 (C7), 33.20 (C4), 37.63 (C4a), 43.16 (C1), 44.83 (C3), 51.68 (OCH₃), 111.40 (arom-C), 121.77 (arom-C), 125.10 (arom-C), 129.21 (arom-C), 130.82 (C8a), 135.12 (C6), 135.85 (C5), 151.59 (C8), 153.64 (CO), 166.66 (NCO); LREIms m/z 401 (M^+ , 34%); HREIms Calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_5\text{Si}$ (M^+): 401.1658. Found: 401.1650.

Methylation of silyl enol ether (15) BnMe_3NF (152 mg, 0.90 mmol) was stirred with molecular sieves (0.90 g, dried at 80°C for 10 h) in THF (2 ml) for 8 h. To this was added the solution of **15** (300 mg, 0.75 mmol) and MeI (0.21 ml, 3.74 mmol) in THF (1.5 ml) at 0°C. After stirring for 1 h, the mixture was filtered through Celite. The filtrate was concentrated and separated by silica gel column chromatography (AcOEt:n-hexane=1:3) to yield **16** (89 mg, 35%, yellow oil) and **17** (22 mg, 9%, yellow oil). **16**: Ir 1720, 1680, 750 cm^{-1} ; uv 237^{sh} nm; ^1H -nmr δ (500 MHz) 1.61-1.63 (1H, m, 4-H), 1.69-1.73 (1H, m, 4-H), 1.843 (0.8H, s, CH₃), 1.84 (1.4H, s, CH₃), 1.85 (0.8H, s, CH₃), 2.83-2.85 (1H, m), 2.92 (1H, q-like, $J=3.7$ Hz), 2.98 (0.5 H, d, $J=12.1$ Hz, 1-H), 3.00 (0.5H, d, $J=12.1$ Hz, 1-H), 3.08 (1H, dd, $J=2.5, 13.2$ Hz, 7-H), 3.25 (1H, brs, 3-H), 3.78 (3H, s, OCH₃), 4.10 (1H, d, $J=12.1$ Hz, 1-H), 4.91 (1H, d, $J=13.0$ Hz, 3-H), 6.58 (1H, dt, $J=1.4, 5.6$ Hz, 6-H), 7.17-7.22 (3H, m, arom-H), 7.36 (2H, m, arom-H); (50°C) 1.62 (1H, dd, $J=3.5, 13.5$ Hz, 4-H), 1.70 (0.3H, dd, $J=4.1, 11.1$ Hz, 4-H), 1.73 (0.7H, dd, $J=4.1, 11.1$ Hz, 4-H), 3.03 (1H, brs, 1-H), 4.85 (1H, brs, 3-H); LRFABms m/z 344 (MH^+ , 22%); HRFABms Calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_5$ (MH^+): 344.1498. Found: 344.1504. **17**: Ir 1700, 1640 cm^{-1} ; uv 265, 335 nm; ^1H -nmr δ (500 MHz) 1.21-1.23 (1H, m, 4-H), 1.99 (1H, d-like, $J=13.7$ Hz, 4-H), 2.71 (1H, m, 4a-H), 2.85 (1H, t, $J=12.2$ Hz, 1-H), 2.99 (1H, m, 8a-H), 3.01 (2/5H, s-like, 7-H), 3.06 (3/5H, d, $J=3.0$ Hz, 7-H), 3.29-3.69 (1H, m, 3-H), 3.81 (3H, s, OCH₃), 4.32 (1H, d, $J=12.2$ Hz, 1-H), 4.95 (1/3H, m, 3-H), 5.05 (2/3H, d, $J=12.9$ Hz, 3-H), 7.02 (1H, t, $J=3.9$ Hz, 6-H), 7.14 (1H, brs, arom-H), 7.20 (2H, d, $J=7.0$ Hz, arom-H), 7.36 (2H, d, $J=7.0$ Hz, arom-H); LREIms m/z 329 (M^+ , 4%), 236 (M^+ -PhO, 100), 204 (33).

Michael reaction of 15 with the acrylate (18) Similar treatment of **15** (100 mg, 0.25 mmol) with **18** (47 mg, 0.28 mmol) in THF (2 ml) at 0°C in the presence of BnMe_3NF (50 mg, 0.30 mmol), followed by work-up as described above gave **21** (61 mg, 49%) as an orange color oil: Ir 1740, 1710, 1670, 740

cm^{-1} ; uv 235 nm; ^1H -nmr δ (500MHz, 50°C) 1.37-1.85 (3H, m, 4- H_2 and 9- H_a), 2.79-2.80 (3H, m, NCH_3), 2.58-3.14 (6H, m), 3.66-3.82 (9H, mixture of Me groups due to rotamers and diastereomers), 4.28 (1H, d-like, 1-H), 4.81-4.91 (1H, brs, 10-H), 5.13-5.15 (1H, m, 3-H), 6.83-6.89 (1/2H, m, 6-H), 6.58-6.62 (1/2H, m, 6-H), 7.15-7.23 (3H, m, arom-H), 7.28-7.38 (2H, m, arom-H).

Michael reaction of 15 with the acrylate (19) Similar treatment of 15 (100 mg, 0.25 mmol) with 19 (87 mg, 0.30 mmol) in THF (2 ml) at 0°C in the presence of BnMe_3NF (50 mg, 0.30 mmol), followed by work-up as described above gave 22 (79 mg, 52%) as a yellow oil: Uv 230^{sh} nm; ^1H -nmr δ (500 MHz, 50°C) 1.40-1.63 (3H, m), 2.87-2.92 (3H, m, NCH_3), 2.62-3.28 (6H, m), 3.72-3.79 (6H, mixture of Me groups due to rotamers and diastereomers), 4.11-4.28 (1H, m, 1-H), 4.65-4.79 (3H, m, 10-H and CH_2CCl_3), 5.15 (1H, d-like, 3-H), 6.64 (1/3H, brs, 6-H), 6.85-6.93 (2/3H, m, 6-H), 7.15-7.18 (3H, m, arom-H), 7.32-7.36 (2H, m, arom-H); LREIms m/z 620 ($\text{M}^+ + 2$, 3%), 618 (M^+ , 3), 525 ($\text{M}^+ - \text{PhO}$, 73); HRFABms: Calcd for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_9\text{Cl}_3$ (MH^+) 619.1017. Found: 619.1009.

Michael reaction of 15 with the acrylate (20) Similar treatment of 15 (300 mg, 0.75 mmol) with 20 (190 mg, 0.90 mmol) in THF (2 ml) at 0°C in the presence of BnMe_3NF (152 mg, 0.90 mmol) followed by work-up as described above gave 23 (406 mg, quant.) as a yellow oil: Ir 1740, 1720, 1690, 750, 690 cm^{-1} ; uv 235^{sh} nm; ^1H -nmr δ (500MHz, 50°C) 1.37-1.62 (3H, m), 3.03-3.07 (3H, m, NCH_3), 2.52-3.27 (6H, m), 3.75-3.81 (6H, mixture of Me groups due to rotamers and diastereomers), 4.10-4.31 (1H, m, 1-H), 4.85-4.91 (1H, m, 10-H), 5.06-5.30 (1H, m, 3-H), 6.62-6.87 (1H, m, 6-H), 7.16-7.19 (3H, m, arom-H), 7.33-7.35 (2H, m, arom-H); LREIms m/z 540 (M^+ , 4%), 447 ($\text{M}^+ - \text{PhO}$, 100); HRFABms Calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_8\text{F}_3$ (MH^+) 541.1798. Found: 541.1810.

ACKNOWLEDGEMENT

Financial support by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, and Uehara Memorial Foundation is gratefully acknowledged. We thank the Fugaku Trust for Medicinal Research and Hayashi Memorial Foundation for Female Natural Scientist. We also thank Ms. H. Seki, Ms. R. Hara, Mr. T. Kuramochi, Ms. S. Imamoto of the Chemical Analysis Center of Chiba University for spectral data (ms, nmr) and microanalysis.

REFERENCES

1. (a) R. Sakai, T. Higa, C. W. Jefford, and G. Bernardinelli, *J. Am. Chem. Soc.*, 1986, **108**, 6404; (b) H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, Y. Matsuzaki, and Y. Hirata, *Tetrahedron Lett.*, 1987, **28**, 621.
2. i) Diels-Alder approaches: (a) K. M. J. Brands and U. K. Pandit, *Tetrahedron Lett.*, 1989, **30**, 1423; (b) *idem*, *Heterocycles*, 1990, **30**, 257; (c) K. M. J. Brands, A. A. P. Meekel, and U. K. Pandit, *Tetrahedron*, 1991, **47**, 2005; (d) D. O. Imbroisi and N. S. Simpkins, *Tetrahedron Lett.*, 1989, **30**, 4309; (e) *idem*, *J. Chem. Soc., Perkin Trans. I*, 1991, 1815; (f) S. F. Martin, T. Rein, and Y. S. F. Liao, *Tetrahedron Lett.*, 1991, **32**, 6481; (g) J. Leonard, S. P. Fearnley, and D. M. B. Hickey, *Synlett*, 1992, 272; (h) I. E. Marko and A. Chesney, *ibid.*, 1992, 275; (i) S. F. Martin, Y. Liao, Y. Wong, and T. Rein, *ibid.*, 1994, **35**, 691; ii) Other approaches: (a) D. J. Hart and A. McKinney, *Tetrahedron Lett.*, 1989, **30**, 2611; (b) J. A. Campbell and D. J. Hart, *ibid.*, 1992, **33**, 6247; (c) J. D. Winkler, M. G. Siegel, and J. E. Stelmach, *ibid.*, 1993, **34**, 6509.
3. (a) M. Nakagawa, Z. Lai, Y. Torisawa, and T. Hino, *Heterocycles*, 1990, **31**, 999; (b) Y. Torisawa, M. Nakagawa, H. Arai, Z. Lai, T. Hino, T. Nakata, and T. Ohishi, *Tetrahedron Lett.*, 1990, **31**, 3195; (c) Y. Torisawa, M. Nakagawa, T. Hosaka, K. Tanabe, Z. Lai, K. Ogata, T. Nakata, T. Ohishi, and T. Hino, *J. Org. Chem.*, 1992, **57**, 5741; (d) M. Nakagawa, Y. Torisawa, T. Hosaka, K. Tanabe, T. Da-te, K. Okamura, and T. Hino, *Tetrahedron Lett.*, 1993, **34**, 4543.
4. Y. Torisawa, M. Nakagawa, H. Takami, T. Nagata, M. Ayman Ali, and T. Hino, *Heterocycles*, 1994, in press.
5. D. L. Coffen, U. H. David, A. Katonak, M. E. Mulligan, K. C. Burdick, G. L. Olson, and L. J. Todaro, *J. Org. Chem.*, 1984, **49**, 5109.
6. J. H. Cooley and E. J. Evain, *Synthesis*, 1989, 1.
7. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, 1982, **104**, 1025.

Received, 2nd March, 1994