CH), 7.50 (q, $CHCH_3$); MS (70eV), *m/e* (relative intensity) 774 (3), 773 (7), 772 (M^+, 10), 639 ((TPP)Al^+, 100), 562 (((TPP)Al - C_6H_5)$^+$, 2), 386 (M^{2+}, 4), 319.5 ((TPP)Al^{2+}, 28).

Formation of (EtioP)aluminum Enolate (eq 5). To a solution of (EtioP)AlCl (**4**) (0.5 mmol), synthesized in a similar manner to **1** in benzene (40 cm^3), was added a solution of $LiNEt_2$ (0.5 mmol in 1.35 cm^3) in hexane/diethyl ether. After 1 h, a ketone was added (0.6 mmol), the mixture was allowed to stand for one more hour, and the solution was evaporated to dryness under reduced pressure to give a red solid. This reaction product was analyzed by NMR spectroscopy. For example, (EtioP)-AlOCPh=CHMe (**6b**): ^1H NMR ($CDCl_3$) δ 6.71 (1 H, t, *p*-Ph), 6.37 (2 H, t, *m*-Ph), 3.98 (2 H, d, *o*-Phe, 2.30 (1 H, q, C*H*), -1.67 (3 H, d, CH_3); ^{13}C NMR ($CDCl_3$) δ 148.14 (s, *C*Ph=CHMe), 95.70 (d, CPh=*C*HMe), 6.75 (q, CPh=CHCH_3); MS (70 eV), *m/e* (relative intensity), 637 (1), 636 (M^+, 2), 524 (12), 480 (100).

Reaction of (TPP)AlSR with α,β-Unsaturated Ketone (eq 8, 9). (TPP)AlEt (**7**) (1.0 mmol) was prepared by the equimolar reaction between $TPPH_2$ and Et_3Al in benzene (20 cm^3) at room temperature.[29] To this reaction mixture was added a large excess (30 mmol) of a thiol, and the solution was magnetically stirred for 12 h under the irradiation of visible light. The green solution of **7** became dark blue when the thiol was added and then turned to brown red, characteristic of the solution of (TPP)AlSR (**10**).

The volatile materials were removed under reduced pressure; the resulting purple solid was dissolved in chloroform (10 cm^3). When nonvolatile thiol (benzenethiol) was used, hexane (20 cm^3) was added to the chloroform solution, and the precipitates formed were collected by filtration in a nitrogen atmosphere and washed with hexane to leave reddish purple solids, which were dissolved in chloroform. For example, (TPP)AlSPh (**10c**): ^1H NMR ($CDCl_3$) δ 6.58 (1 H, t, *p*-Ph), 6.23 (2 H, t, *m*-Ph), 3.93 (2 H, d, *o*-Ph).

To a solution of (TPP)AlSEt (**10a**) (0.16 mmol) in 5.0 cm^3 of $CDCl_3$ was added a solution of an equimolar amount of phenyl vinyl ketone (0.16 mmol, freshly distilled) in $CDCl_3$ (0.32 cm^3) at room temperature. The solution turned from brown red to orange red, and NMR analysis was performed. (TPP)-AlOCPh=$CHCH_2SEt$ (**11a**): ^1H NMR ($CDCl_3$) δ 6.73 (1 H, t, *p*-Ph), 6.45 (2 H, t, *m*-Ph), 4.29 (2 H, d, *o*-Ph), 2.77 (1 H, t, CH), 1.09 (2 H, q, CH_2CH_3), 0.10 (3 H, t, CH_2CH_3), -0.21 (2 H, d, $CHCH_2$); ^{13}C NMR ($CDCl_3$) δ 150.19 (*C*Ph=CH), 97.45 (CPh=*C*H), 23.58 (CH_2), 23.37 (CH_2), 13.84 (CH_3).

When dry HCl gas was introduced to a solution of **11a** in $CDCl_3$, the orange red solution immediately turned to dark red. ^1H NMR spectrum of this mixture showed the signals to be identical with those of β-ethylthiopropiophenone synthesized separately.[30]

(29) Inoue, S.; Takeda, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 984.

In order to isolate the product, β-ethylthiopropiophenone, the reaction mixture (phenyl vinyl ketone 0.19 mmol (25 mg), (TPP)AlSEt (**10a**) 0.20 mmol, benzene (4.4 mL), room temperature, 1 h) was poured into water and extracted successively by $CHCl_3$. The organic layer was dried by Na_2SO_4, and evaporated to leave a purple solid. This solid was chromatographed over silica (Wakogel C-300), eluted by ethyl ether/hexane (1:1). The first red band contained β-ethylthiopropiophenone, together with some porphyrins. The fraction corresponding to this band was evaporated to give a purple solid, which was again chromatographed over silica with CH_2Cl_2 as eluent. A fast moving, slightly yellow band was collected to obtain β-ethylthiopropiophenone, as identified by ^1H NMR spectrum; yield 34.0 mg (92%).

Reaction of (TPP)AlOCEt=CHMe 3d with Me_3SiI. To a vigorously stirred solution of **3d** (0.40 mmol) in $CDCl_3$ (4.0 cm^3) was added 0.06 cm^3 (0.42 mmol) of freshly distilled Me_3SiI at room temperature, and the solution was immediately sealed in a NMR tube (o.d. = 5 mm) under 1 atm of nitrogen. After 20 min, the ratio of the isomers of the silyl enol ether was determined by the intensities of the corresponding signals, assignments of which were made by using the authentic sample.[9]

Acknowledgment. We wish to thank Dr. Takuzo Aida for his helpful discussions and comments throughout this work, Fumitoshi Kojima for the preliminary experiments on the formation of (TPP)$AlNEt_2$, and Shizuo Mohara at Sagami Chemical Research Center for the measurement of the mass spectra.

Registry No. **1**, 71102-37-9; **2**, 118102-14-0; **3a**, 118102-15-1; **3b**, 118102-16-2; **3c**, 118102-17-3; **3d**, 118102-18-4; **3e**, 118102-19-5; **3f**, 118102-20-8; **4**, 55940-13-1; **6b**, 118102-21-9; **6c**, 118102-22-0; **6d**, 118102-23-1; **7**, 63256-30-4; **8**, 118102-24-2; **9**, 19078-97-8; **10a**, 118102-25-3; **10b**, 118102-26-4; **10c**, 118102-27-5; **11a**, 118102-27-5; **11b**, 118102-30-0; **11c**, 118102-29-7; $PhC(O)CH_3$, 98-86-2; $PhC(O)CH_2CH_3$, 93-55-0; $PhC(O)(CH_2)_2CH_3$, 495-40-9; $CH_3CH_2C(O)CH_2CH_3$, 96-22-0; $CH_3(CH_2)_2C(O)(CH_2)_2CH_3$, 123-19-3; $PhC(O)CH_2Ph$, 451-40-1; EtSH, 75-08-1; PrSH, 79869-58-2; PhSH, 108-98-5; $PhC(O)CH=CH_2$, 768-03-6; (*E*)-$CH_3CH_2C(OH)=CHCH_3$, 57643-01-3; (*Z*)-$CH_3CH_2C(OH)=CHCH_3$, 57643-02-4; *tert*-butyl vinyl ketone, 2177-30-2; β-(ethylthio)propiophenone, 55101-14-9.

(30) To a solution of phenyl vinyl ketone (3 mmol) in dichloromethane was added 3.1 mmol of ethanethiol at room temperature in a nitrogen atmosphere. After 4 days, volatile materials were evaporated to give β-ethylthiopropiophenone as a white solid: mp 44.5-45.0 °C (methanol); lit. mp (a) 47.0-47.5 °C (Weiss, M. J.; O'Donoghue, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 4771); (b) 45-46 °C (Böhme, H.; Heller, P. *Chem. Ber.* **1953**, *86*, 443).

Tandem 1,3-Dipolar Cycloadditions of Pyridinium or Isoquinolinium Methylides with Olefinic Dipolarophiles Leading to Cycl[3.2.2]azines. "Enamine Route" as a New Generation Method of Azomethine Ylides

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Pyridinium or isoquinolinium methylides undergo tandem 1,3-dipolar cycloadditions with two molecules of olefins to produce cycl[3.2.2]azine derivatives in a highly regioselective, stereoselective, and face-selective manner. A new generation of azomethine ylides is involved in the second cycloaddition, which consists of a thermal tautomerization of dienamines or enamines.

Cycloadditions of pyridinium methylides as representatives of heteroaromatic *N*-ylides[1] with electron-deficient olefins where the substituent R^1 is electron-withdrawing produce tetrahydro derivatives of indolizine in a highly

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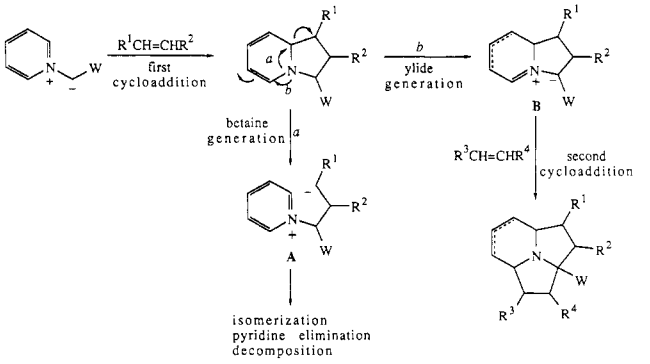
Table I. Tandem Cycloadditions of Pyridinium or Isoquinolinium Methylides

ylide	first cycloaddition: dipolarophile	first cycloaddition: conditions[b]	second cycloaddition: dipolarophile	second cycloaddition: conditions[c]	biscycloadduct	yield,[a] %
1a	*N*-methylmaleimide	10 min	*N*-methylmaleimide	48 h	**3**	54
1a	*N*-methylmaleimide	10 min	acrylonitrile	24 h	**4**	34
1a	*N*-methylmaleimide	10 min	phenyl vinyl sulfone	24 h	**5**	34
1a	*N*-(*p*-tolyl)maleimide	10 min	*N*-(*p*-tolyl)maleimide	48 h	**6**	29
1b	*N*-methylmaleimide	2 h	*N*-methylmaleimide	24 h	**7**	30
1a	acrylonitrile	1 h[d]	*N*-methylmaleimide	24 h[e]	**8**	8
1a	acrylonitrile	1 h[d]	phenyl vinyl sulfone	24 h	**9**	23
2	acrylonitrile	15 min	acrylonitrile	29 h	**11** + **12**	21 + 6

[a] Yields of isolated pure products based on the ylide precursor. [b] Equivalents of a ylide precursor, triethylamine, and a dipolarophile in chloroform were stirred at room temperature. [c] Equivalents of a crude monocycloadduct and a dipolarophile were heated under reflux in toluene. [d] Under reflux. [e] Heated at 160 °C in a sealed tube.

stereoselective and regioselective manner.[2] The cycloadducts are generally not stable and are reversibly transformed into the betaine intermediates A (route a in eq 1) which then undergo either recyclization with isomerization[2d] or elimination of the pyridine moiety followed by further decomposition.[3]

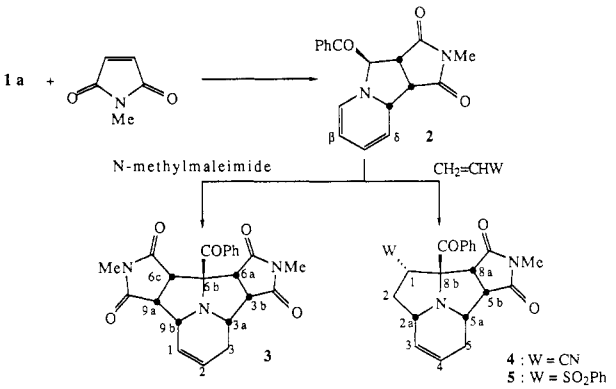


(1)

Since protonation of enamines leads to iminium salts, which are the precursors of azomethine ylide 1,3-dipoles,[4] stabilized azomethine ylides would be generated by thermal isomerization of the enamines bearing an α-hydrogen activated by an anion-stabilizing substituent.[5] However, no such generation example of azomethine ylides has been demonstrated so far to the best of our knowledge. It was only suggested that enamine intermediates were involved in the ylide generations by condensation of amines with aliphatic aldehydes.[4c]

The cycloadducts of pyridinium methylides possess a cyclic dienamine moiety in the fused dihydropyridine ring and an electron-withdrawing substituent W adjacent to the bridgehead nitrogen. Accordingly, all the functionalities are set for ready tautomerization into azomethine ylides (route b in eq 1).

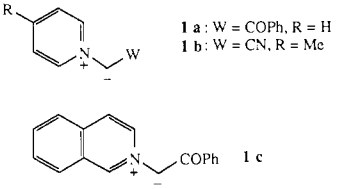
Scheme I



The present article describes the first example of double cycloadditions of pyridinium and isoquinolinium methylides with olefinic dipolarophiles in which two different olefins can be used. The second cycloaddition involves a new azomethine ylide generation based on a thermal tautomerization of dienamines or enamines.

Results and Discussion

Pyridinium phenacylide (**1a**) reacts with *N*-methylmaleimide at room temperature in a few minutes to give the endo cycloadduct **2** in a quantitative yield.[4a,c] This



cycloadduct **2** readily isomerizes into the corresponding betaine isomer in a polar solvent or under acidic conditions even at room temperature;[3] however heating **2** under reflux in dry toluene with a further equivalent of *N*-methylmaleimide for 48 h gave the 2:1 cycloadduct **3** as a sole isomer in 54% yield based on the ylide precursor, *N*-phenacylpyridinium bromide (Scheme I).

The stereochemistry of the product **3**, which was determined on the basis of spectral data as well as ^1H and ^{13}C NMR spectra as discussed later, corresponds to the endo- and face-selective cycloadduct of *N*-methylmaleimide to the azomethine ylide 1,3-dipole thermally generated along the perimeter of the fused pyrrolopyridine ring involved in the initial 1:1 cycloadduct **2**.

Use of an unsymmetrically substituted olefin such as acrylonitrile or phenyl vinyl sulfone instead of the male-

(1) Kröhnke, F. *Ber. Deutsch. Chem. Ges.* **1935**, *68*, 1177. See also the following reviews: Stuckwisch, C. G. *Synthesis* **1973**, *469*. Surpateanu, G; Lablache-Combier, A. *Heterocycles* **1984**, *22*, 2079. *N-Ylid Chemistry*; Zugrăvescu; I., Petrovanu, M., Eds.; McGraw-Hill International: New York, 1976.

(2) (a) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Heterocycles* **1983**, *20*, 1907. (b) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Chem. Lett.* **1985**, 355. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3137. (d) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Ibid.* **1985**, *58*, 3320.

(3) (a) Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Takenaka, S. *Chem. Lett.* **1984**, 281. (b) Miki, Y.; Hachiken, H.; Takemura, S. *Heterocycles* **1984**, *22*, 701. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Chem. Lett.* **1984**, 465. (d) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1489.

(4) Condensations of α-amino esters, nitriles, or acids with carbonyl compounds generating azomethine ylides are believed to occur via the corresponding iminium intermediates: (a) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1809. (b) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994. (c) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067. (d) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180. (e) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079.

(5) Spontaneous deprotonation occurs at the α-position of iminium salts when the α-hydrogen is activated by an electron-withdrawing substituent: Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109.

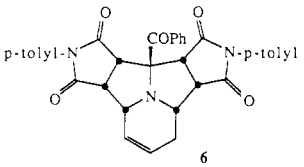
imide in the second cycloaddition stage led to a regioselective endo-selective, and face-selective biscycloadduct **4** or **5** (Scheme I and Table I). Based on these results, it should be emphasized that (1) the ylide generated from **2** was induced via the formal protonation at the δ-position, (2) the resulting azomethine ylide, which has a substitution pattern of 1-benzoyl and 3-vinyl ylide-stabilizing substituents, showed an unusual regioselectivity, opposite to that observed in the case of 1-aryl-3-(alkoxycarbonyl)-substituted ylides,[4c] and (3) the second cycloadditions are highly endo- and face-selective in spite of high steric congestion in the endo approach of olefins from the concave face.

Coupling constants between 3a-H and 3b-H (8.1 Hz) as well as 9a-H and 9b-H (9.7 Hz) of biscycloadduct **3** are consistent with the cis configuration between these hydrogens. On the basis of the NOE difference ^{1}H NMR spectra, the 6b-benzoyl moiety is cis to 6a-H, 6c-H, and 9b-H. Since one of the olefinic hydrogen (1-H) is adjacent to 9b-H (NOE), the stereostructure of **3** was finally characterized as shown in Figure 1.

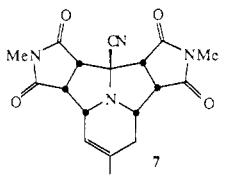
A similar cis sequence of 5a-H/5b-H/8a-H and adjacent location of 5a-H/CH_2 (5a-H: ddd) were observed in the case of **4**. Its whole stereostructure was determined on the basis of the following spectral characteristics: (1) the 8b-benzoyl moiety is cis to 1-H, 2a-H, and 8a-H (NOE); (2) the coupling patterns of 1-H (dd) and 2-H (each ddd) arise from the occupation of the 1-position with a cyano moiety (the cyano is 1-endo); (3) 2a-H and 3-H are adjacent to each other (NOE).

The production of the cycloadducts of vinyl-conjugated azomethine ylides is more probable since the generation of conjugated ylides is favored. Although a satisfactory explanation for the face-selective second cycloaddition from the sterically more hindered endo side is not obvious, one possibility is that the benzoyl moiety is located in the less congested exo face of the ylide plane so that the approach of the olefin dipolarophile can occur on the endo face.

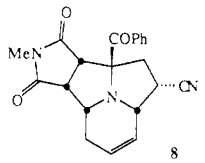
Biscycloadducts **6** and **7** were obtained from the tandem cycloadditions of ylide **1a** with *N*-(*p*-tolyl)maleimide (2 equiv) and of ylide **1b** with *N*-methylmaleimide (2 equiv), respectively (Table I). When the order of addition of two



6



7



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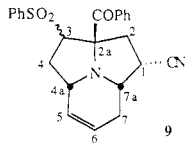
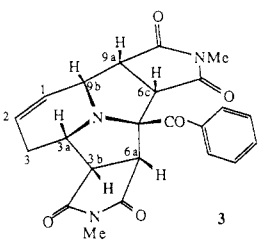


9

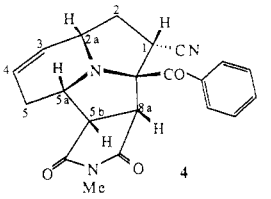
different olefins is reversed, two isomeric biscycloadducts are produced. For instance, the reaction of ylide **1a** with *N*-methylmaleimide and then with acrylonitrile gave the adduct **4**, while the reaction using acrylonitrile and then *N*-methylmaleimide yielded isomeric adduct **8**. However, in the latter case, the ylide structure for the second cycloaddition was not a conjugated type (5a-H appears as a doublet-doublet-doublet which couples with 5-H).

Two unsymmetrically substituted olefins can be employed in both cycloadditions to give a stereoselective, regioselective, and face-selective biscycloadduct. The exclusive formation of **9** is a case in point, although the stereochemistry at the 3-position was not determined.



3

NOE was observed between
o-H (benzoyl) and 6a-H
o-H (benzoyl) and 6c-H
o-H (benzoyl) and 9b-H
1-H and 9b-H

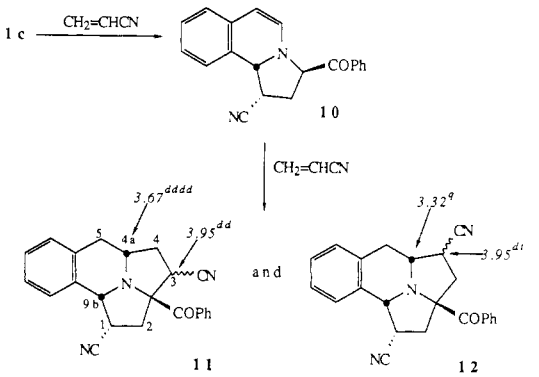


4

NOE was observed between
o-H (benzoyl) and 1-H
o-H (benzoyl) and 2a-H
o-H (benzoyl) and 8a-H
2a-H and 3-H

Figure 1. Stereostructures of biscycloadducts **3** and **4**.

Scheme II



The enamine–azomethine ylide tautomerism can be applied to the monocycloadducts of isoquinolinium methylides with olefinic dipolarophiles since there exists an enamine moiety along the perimeter of the fused pyrroloisoquinoline ring. This possibility was examined by using the endo cycloadduct **10**[2d] of isoquinolinium phenacylide (**1c**) to acrylonitrile. Two regioisomeric biscycloadducts **11** and **12** were obtained (Scheme II). Their regiochemistries were readily determined on the basis of the coupling patterns of 3-H (as dd) and 4a-H (as ddd) of **11** as well as 4-H (as dt) and 4a-H (as q) of **12**.

Therefore, tandem cycloadditions of pyridinium or isoquinolinium methylides with two identical or different olefins lead to sterically defined cycl[3.2.2]azine derivatives. The second cycloadditions involve a thermal enamine (or dienamine)–azomethine ylide tautomerism and constitute a new method for generation of azomethine ylides.

Experimental Section

General Methods. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken with a JASCO A-702 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-40 or a JEOL FX-100 instrument and ^{13}C NMR spectra on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Mass spectra were measured with a JEOL JMS-01SG-2 spectrometer at 70 eV of ionization energy. Elemental analyses were performed on a Hitachi 026 CHN microanalyzer. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was accomplished with ultraviolet light (254 and 365 nm) and iodine. Silica gel 60 (70–230 or 230–400 mesh, Merck) or Wakogel C-200 (100–200 mesh) was used for preparative column chromatography. Micro vacuum distillation was performed with a Shibata GTO-250R Kugelrohr distilling apparatus. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type V.

General Procedure for Tandem Cycloaddition of Pyridinium or Isoquinolinium Methylides with Olefinic Dipolarophiles. As a typical example the tandem cycloaddition

reaction of pyridinium phenacylide (**1a**) with *N*-methylmaleimide is described. A mixture of *N*-phenacylpyridinium bromide (0.278 g, 1 mmol) and *N*-methylmaleimide (0.11 g, 1 mmol) in dry chloroform (10 mL) was treated with triethylamine (0.12 g, 1.2 mmol). The mixture was stirred at room temperature for 10 min and poured into ice–water. The chloroform layer separated and was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the chloroform in vacuo gave quantitative yield of the monocycloadduct **2**, which was used for the subsequent reaction without purification. A mixture of the monocycloadduct **2** and another portion (0.11 g, 1 mmol) of the maleimide in dry toluene (5 mL) was heated under reflux for 48 h. The toluene was evaporated in vacuo and the residue was chromatographed over silica gel with hexane–ethyl acetate (2:1 v/v) to give the biscycloadduct **3** (0.226 g, 54%).

Purification of other biscycloadducts was carried out through silica gel column chromatography by using hexane–ethyl acetate (1:1 to 5:1 v/v). The reaction conditions and the yields of isolated biscycloadducts are summarized in Table I.

3: colorless prisms (diethyl ether); mp 236–237 °C dec; IR (KBr) 1770, 1700, 1690, 1600, 1580, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) 2.4–2.7 (3 H, m, 3-H (2 H) and 3a-H), 2.58 (3 H, s, 5-Me), 2.90 (3 H, s, 8-Me), 3.34 (1 H, dd, J_{3b-3a} = 8.1 and J_{3b-6a} = 7.7 Hz, 3b-H), 3.39 (1 H, dd, J_{9a-9b} = 9.7 and J_{9a-6c} = 8.1 Hz, 9a-H), 3.98 (1 H, br d, J_{9b-9a} = 9.7 Hz, 9b-H), 4.48 (1 H, br d, J_{6c-9a} = 8.1 Hz, 6c-H), 4.87 (1 H, d, J_{6a-3b} = 7.7 Hz, 6a-H), 6.00 (2 H, br s, 1- and 2-H), 7.42 (2 H, dd, Ph), 7.54 (1 H, dd, Ph), 8.22 (2 H, d, Ph); ^{13}C NMR ($CDCl_3$) 24.72, 25.36 (each q, 5- and 8-Me), 28.30 (t, 3-C), 47.46, 47.85, 50.08, 51.08 (each d, 3b-, 6a-, 6c-, and 9a-C), 58.30 (d, 3a-C), 61.59 (d, 9b-C), 84.72 (s, 6b-C), 123.35, 127.81, 128.22, 130.16, 133.09 (each d, Ph), 135.44 (s, Ph), 174.84, 175.90, 178.07 (each s, CON), 194.98 (s, COPh); MS, *m/z* (rel intensity) 314 (M^+ – 105, base peak), 118 (38), 117 (16), 112 (20), 105 (30), 77 (45). Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02. Found: C, 65.75; H, 5.24; N, 9.85.

4: colorless prisms (ethyl acetate–hexane); mp 200–201 °C; IR (KBr) 2240, 1770, 1700, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 2.29 (1 H, ddd, J_{gem} = 13.7, J_{2-2a} = 8.8, and J_{2-1} = 5.7 Hz, one of 2-H), 2.49 (1 H, ddd, J_{gem} = 13.7, J_{2-2a} = 8.4, J_{2-1} = 10.1 Hz, the other of 2-H), 2.5–2.6 (1 H, m, one of 5-H), 2.58 (3 H, s, 7-Me), 2.72 (1 H, m, the other of 5-H), 3.32 (1 H, ddd, J_{5a-5} = 10.7, 3.4 and J_{5a-5b} = 7.3 Hz, 5a-H), 3.57 (1 H, m, 2a-H), 3.62 (1 H, dd, J_{5b-5a} = 7.3 and J_{5b-8a} = 7.1 Hz, 5b-H), 4.08 (1 H, d, J_{8a-5b} = 7.1 Hz, 8a-H), 4.47 (1 H, br dd, J_{1-2} = 10.1 and 5.7 Hz, 1-H), 5.78 (1 H, ddd, J_{3-4} = 9.5 and J_{3-2a} (or J_{3-5}) = 3.6 (or 2.7) Hz, 3-H), 5.96 (1 H, dt, J_{4-3} = 9.5 and J_{4-5} = 1.4 Hz, 4-H), 7.39 (2 H, dd, Ph), 7.54 (1 H, dd, Ph), 8.21 (2 H, d, Ph); ^{13}C NMR ($CDCl_3$) 24.71 (q, 7-Me), 28.31 (t, 5-C), 35.57 (t, 2-C), 35.91 (d, 1-C), 47.46, 51.61 (each d, 5b- and 8a-C), 56.92 (d, 5a-C), 59.79 (d, 2a-C), 86.30 (s, 8b-C), 121.68 (s, CN), 125.92, 126.55, 128.20, 130.06, 133.27 (each d, 3-, 4-C, and Ph), 135.52 (s, Ph), 174.01, 174.89 (each s, CON), 195.06 (s, COPh); MS, *m/z* (rel intensity) 309 (M^+ – 53, 16), 258 (16), 257 (base peak), 171 (22), 118 (32), 117 (18), 105 (37), 79 (19), 76 (57), 51 (19). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.59; H, 5.36; N, 11.41.

5: colorless prisms (ethyl acetate–hexane); mp 249–252 °C; IR (KBr) 1780, 1700, 1680, 1600, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) 1.7–2.1 (2 H, m, 2-H), 2.3–2.6 (2 H, m, 5-H), 3.1–3.5 (2 H, m, 2a- and 5a-H), 3.52 (1 H, dd, J_{5b-5a} = 8.0 and J_{5b-8a} = 7.2 Hz, 5b-H), 4.74 (1 H, d, J_{8a-5b} = 7.2 Hz, 8a-H), 4.81 (1 H, dd, J_{1-2} = 9.8 and 8.8 Hz, 1-H), 5.63 (1 H, m, 3-H), 5.89 (1 H, m, 4-H), 7.2–7.7 (6 H, m, Ph), 7.7–7.9 (2 H, m, Ph), and 8.1–8.3 (2 H, m, Ph); ^{13}C NMR (DMSO-d_6) 24.18 (q, NMe), 28.12 (t, 5-C), 33.65 (t, 2-C), 47.66, 49.00 (each d, 5b- and 8a-C), 54.71 (d, 5a-C), 58.65 (d, 2a-C), 69.59 (d, 1-C), 85.47 (s, 8b-C), 126.60, 127.89, 129.89, 130.13, 132.95, 134.30 (each d, 3-, 4-, and Ph), 135.83, 139.60 (each s, Ph), 175.13, 175.89 (each s, CON), 196.18 (s, COPh); MS, *m/z* (rel intensity) 372 (M^+ – 68, 23), 371 (M^+ – 69, base peak), 230 (36), 229 (11), 144 (19), 118 (15), 105 (12), 77 (15). Anal. Calcd for $C_{26}H_{24}N_2O_5S$: C, 65.55; H, 5.04; N, 5.88. Found: C, 65.59; H, 5.12; N, 5.80.

6: colorless prisms (ethyl acetate); mp 284–285 °C; IR (KBr) 1772, 1708, 1665, 1515, 1380, 1200, 1190, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) 2.29, 2.39 (each 3 H, s, *p*-Me), 2.4–2.7 (2 H, m, 3-H), 2.98 (1 H, ddd, J_{3a-3} = 10.5 and 3.0, and J_{3a-3b} = 8.4 Hz, 3a-H), 3.51 (1 H, dd, J_{9a-9b} = 10.0 and J_{9a-6c} = 8.4 Hz, 9a-H), 3.53 (1 H, t, J_{3b-3a} = J_{3b-6a} = 8.4 Hz, 3b-H), 4.14 (1 H, br d, J_{9b-9a} = 10.0 Hz, 9b-H), 4.68 (1 H, d, J_{6c-9a} = 8.4 Hz, 6c-H), 5.07 (1 H, J_{6a-3b} = 8.4 Hz, 6a-H), 6.07 (2 H, br s, 1- and 2-H), 6.69 (2 H, d, *J* = 8.1 Hz, Ar), 7.0–7.6 (9 H, m, Ar), and 8.33 (2 H, d, *J* = 7.4 Hz, Ar); ^{13}C NMR ($CDCl_3$) 20.65 (*p*-Me x 2), 28.03 (3-C), 47.18, 48.02, 49.79, 51.88 (3b-, 6a-, 6c-, and 9a-C), 57.98 (3a-C), 61.48 (9b-C), 84.65 (6b-C), 124.02, 126.26, 126.35, 127.11, 128.32, 129.04, 129.08, 129.38, 129.44, 130.02, 133.04, 135.37, 137.89, 138.11 (1-C, 2-C, and Ar), 174.32, 174.48, 175.31, 177.11 (each CON), 195.44 (COPh); MS, *m/z* (rel intensity) 467 (M^+ – 104, 32), 466 (M^+ – 105, base peak), 188 (22), 144 (12), 118 (27), 105 (42), 76 (15). Anal. Calcd for $C_{35}H_{29}N_3O_5$: C; 73.54; H, 5.11; N, 7.35. Found: C; 73.69; H, 5.00; N, 7.34.

7: colorless prisms (ethyl acetate–hexane); mp 298 °C dec; IR (KBr) 2250, 1770, 1710–1690, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) 1.80 (3 H, br s, 2-Me), 2.16 (1 H, dd, J_{gem} = 15.5 and J_{3-3a} = 2.6 Hz, one of 3-H), 2.38 (1 H, br dd, J_{gem} = 15.5 and J_{3-3a} = 10.3 Hz, the other of 3-H), 2.51 (1 H, ddd, J_{3a-3} = 10.3, 2.6 and J_{3a-3b} = 7.0 Hz, 3a-H), 2.89, 3.06 (each 3 H, s, 5- and 8-Me), 3.24 (1 H, dd, J_{3b-6a} = 7.7 and J_{3b-3a} = 7.0 Hz, 3b-H), 3.69 (1 H, t, J_{9a-6c} = J_{9a-9b} = 8.4 Hz, 9a-H), 3.82 (1 H, d, J_{6c-9a} = 8.4 Hz, 6c-H), 4.31 (1 H, br d, J_{9b-9a} = 8.4 Hz, 9b-H), 4.67 (1 H, d, J_{6a-3b} = 7.7 Hz, 6a-H), 5.70 (1 H, br s, 1-H); ^{13}C NMR (DMSO-d_6) 22.77 (q, 2-Me), 24.88, 25.18 (each q, 5- and 8-Me), 32.36 (t, 3-C), 46.83, 47.36, 50.06, 53.53 (each d, 3b-, 6a-, 6c-, and 9a-C), 57.65 (d, 3a-C), 60.65 (d, 9b-C), 68.95 (s, 6b-C), 117.01 (d, 1-C), 117.71 (s, CN), 135.18 (s, 2-C), 174.66, 175.13, 175.36, 175.48 (each s, CON); MS, *m/z* (rel intensity) 354 (M^+, 3), 244 (15), 243 (base peak), 214 (43), 157 (48), 156 (16), 150 (17), 142 (21), 132 (11), 122 (11), 94 (82). Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.01; H, 5.15; N, 15.64.

8: colorless needles (ethyl acetate); mp 128–130 °C; IR (KBr) 2225, 1775, 1695, 1430, 1380, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) 2.22 (1 H, br dd, J_{gem} = 15.0 and J_{5-5a} = 5.9 Hz, one of 5-H), 2.4–2.6 (2 H, m, 1-H), 2.60 (1 H, dd, J_{gem} = 15.0 and J_{5-5a} = 1.8 Hz, the other of 5-H), 2.93 (3 H, s, 7-Me), 3.20 (1 H, ddd, J_{5a-5b} = 9.2, J_{5a-5} = 5.9, and 1.8 Hz, 5a-H), 3.48 (1 H, dd, J_{5b-5a} = 9.2 and J_{5b-8a} = 8.4 Hz, 5b-H), 3.62 (1 H, dd, J_{1-2} = 15.2 and J_{2-2a} = 9.0 Hz, 2-H), 4.13 (1 H, d, J_{8a-5b} = 8.4 Hz, 8a-H), 4.21 (1 H, br d, J_{2a-2} = 9.0 Hz, 2a-H), 5.98 (1 H, m, 3-H), 6.10 (1 H, m, 4-H), 7.51 (2 H, dd, Ph), 7.58 (1 H, d, Ph), 8.24 (1 H, d, Ph); ^{13}C NMR ($CDCl_3$) 25.33 (q, NMe), 28.94 (t, 5-C), 32.94 (t, 1-C), 33.05 (d, 2-C), 50.96, 51.20 (each d, 5b- and 8a-C), 58.39 (d, 2a-C), 60.96 (d, 5a-C), 81.26 (s, 8b-C), 119.11 (s, CN), 123.97, 125.66 (each d, 3- and 4-C), 128.71, 130.15, 133.04 (each d, Ph), 133.44 (s, Ph), 176.09, 177.79 (each s, CON), 196.63 (s, COPh); MS, *m/z* (rel intensity) 361 (M^+, 1), 257 (16), 256 (base peak), 118 (10), 43 (25). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 70.00; H, 5.56; N, 11.06.

9: colorless prisms (ethyl acetate–diethyl ether); mp 189 °C; IR (KBr) 2250, 1670, 1445, 1315, 1280, 1235, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) 1.6–2.9 (6 H, m, 2-, 4-, and 7-H), 3.1–4.0 (3 H, m, 1-, 4a-, and 7a-H), 4.89 (1 H, t, J_{3-4} = 9.3 Hz, 3-H), 5.67, 5.93 (each 1 H, m, 5- and 6-H), 7.3–7.7 (6 H, m, Ph), 7.8–8.0 (2 H, m, Ph), 8.2–8.4 (2 H, m, Ph); ^{13}C NMR ($CDCl_3$) 29.24 (t, 7-C), 32.53, 34.00 (each t, 2- and 4-C), 34.71 (d, 1-C), 56.18 (d, 7a-C), 58.77 (d, 4a-C), 68.18 (d, 3-C), 82.71 (s, 2a-C), 119.95 (s, CN), 126.01, 126.30 (each d, 5- and 6-C), 128.30, 128.60, 129.66, 130.54, 133.24, 134.13 (each d, Ph), 134.72, 140.13 (each s, Ph), 199.37 (s, COPh); MS, *m/z* (rel intensity) 313 (M^+ – 105, base peak), 172 (52), 171 (44), 118 (20), 105 (18), 76 (31). Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.90; H, 5.26; N, 6.70. Found: 68.89; H, 5.34; N, 6.62.

11: colorless prisms (ethyl acetate–hexane); mp 204–205 °C; IR (KBr) 2220, 1686, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 2.31 (1 H, ddd, J_{gem} = 13.6, J_{4-4a} = 9.1, and J_{4-3} = 7.0 Hz, one of 4-H), 2.66 (1 H, ddd, J_{gem} = 13.6, J_{4-3} = 9.5, and J_{4-4a} = 7.3 Hz, the other of 4-H), 2.90 (1 H, dd, J_{gem} = 17.1 and J_{5-4a} = 4.4 Hz, one of 5-H), 2.95 (1 H, dd, J_{gem} = 15.0 J_{2-1} = 1.1 Hz, 2-H (endo)), 3.32 (1 H, dd, J_{gem} = 15.0 and J_{2-1} = 8.0 Hz, 2-H (exo)), 3.42 (1 H, dd, J_{gem} = 17.1 and J_{5-4a} = 8.6 Hz, the other of 5-H), 3.67 (1 H, dddd, J_{4a-4} = 9.1, 7.3, J_{4a-5} = 8.6, and 4.4 Hz, 4a-H), 3.80 (1 H, ddd, J_{1-2} = 8.0, J_{1-9b} = 4.7, and J_{1-2} = 1.1 Hz, 1-H), 3.95 (1 H, dd, J_{3-4} = 9.5 and 7.0 Hz, 3-H), 4.16 (1 H, d, J_{9b-1} = 4.7 Hz, 9b-H), 7.2–7.6, 8.14 (10 H, m, Ar); ^{13}C NMR ($CDCl_3$) 31.41 (d, 3-C), 32.06 (t, 4-C), 36.41 (d, 1-C), 38.00, 38.77 (each t, 2- and 5-C), 55.47 (d, 4a-C), 60.06 (d, 9b-C), 81.30 (s, 2a-C), 119.36, 121.24 (each s, 1- and 3-CN), 123.89, 126.42, 128.07, 128.30, 128.89, 130.13, 133.71 (each d, Ar), 133.71, 134.66, 135.13 (each s, 9a-C), 197.90 (s, COPh); MS, *m/z*

(rel intensity) 353 (M^+, 12), 77 (base peak). Anal. Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.32; H, 5.46; N, 11.67.

12: colorless needles (ethyl acetate); mp 250–252 °C; IR (KBr) 2235, 2160, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) 2.50 (1 H, dd, J_{gem} = 13.6 and J_{3-4} = 8.8 Hz, one of 3-H), 2.87 (1 H, dd, J_{gem} = 14.3 and J_{2-1} = 7.3 Hz, 2-H (exo)), 3.00 (1 H, dd, J_{gem} = 14.3 and J_{2-1} = 1.1 Hz, 2-H (endo)), 3.15 (1 H, dd, J_{gem} = 13.6 and J_{3-4} = 8.8 Hz, the other of 3-H), 3.21 (1 H, dd, J_{gem} = 16.1 and J_{5-4} = 8.1 Hz, one of 5-H), 3.32 (1 H, q, J_{4a-5} = J_{4a-4} = 8.1 Hz, 4a-H), 3.35 (1 H, dd, J_{gem} = 16.1 and J_{5-4a} = 8.1 Hz, the other of 5-H), 3.69 (1 H, ddd, J_{1-2} = 7.3, 1.1, and J_{1-9b} = 4.4 Hz, 1-H), 3.95 (1 H, dt, J_{4-3} = 8.8 and J_{4-4a} = 8.1 Hz, 4-H), 4.15 (1 H, d, J_{9b-1} = 4.4 Hz, 9b-H), 7.3–7.6, 8.03 (9 H, m, Ar); ^{13}C NMR ($CDCl_3$) 30.05, 31.42, 34.47, 40.55 (1-, 2-, 3-, 4-, and 5-C) 55.85, 59.35 (5b- and 10b-C), 78.32 (9b-C), 120.25, 121.02 (each CN), 123.42, 125.67, 127.32, 127.50, 128.58, 129.35, 132.97, 135.33, 135.75 (each Ar), 198.01 (COPh); MS, *m/z* (rel intensity) 248 (M^+ – 105, 5), 84 (11), 83 (12), 69 (16), 44 (base peak). Anal. Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 77.93; H, 5.21; N, 11.57.

Synthesis and Rearrangement of Spiro[indan-2,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones]: A New Approach to Benzo[*b*]phenanthridinones

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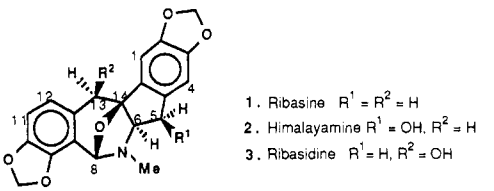
An efficient stereoselective synthesis of spiro[indan-2,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones] **4** based on the intramolecular aldol condensation of the dicarbonyl compound **11** is described. The potential of compounds of type **4** as starting materials for the preparation of various ring systems by acid-catalyzed rearrangement was also studied. The results clearly indicate the strong tendency to undergo rearrangement by migration of C-1, affording benzo[*b*]phenanthridinones **5** in very good yield. The course of the process proved to be independent of the stereochemistry at C-4′, as was evidenced by the formation of the same product, **15d**, from the C-4′ epimers **12** and **13**. However, all attempts to force rearrangement of C-4′ or the nitrogen atom to C-1 to form indanobenzazepinones (**6** or **7**) resulted only in substitution and epimerization at C-1.

Introduction

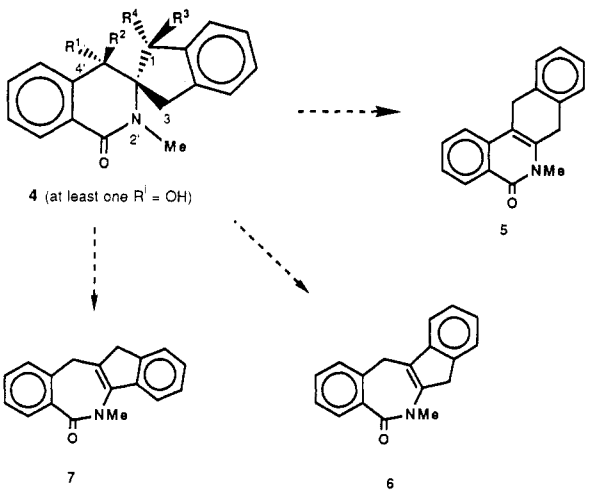
Ribasine (**1**)[1] was recently reported as the parent compound of a new class of alkaloids having the structure of 8,14-epoxy-indano[2,1-*c*][2]benzazepine. So far two other members, himalayamine (**2**)[2] and ribasidine (**3**),[3] both hydroxy derivatives of ribasine, are known (Scheme I).

The limited quantities of these alkaloids present in natural sources, together with the novelty of their skeleton and their potential pharmacological interest, make their synthetic preparation highly desirable.[4] We accordingly decided to explore the acid catalyzed rearrangement of spiro[indan-2,3′-1′,2′,3′,4′-tetrahydroisoquinolin-1′-ones] of the general type **4** (Scheme II). We reasoned that different ring systems could be obtained depending on the position of the hydroxyl group(s) and on the relative stereochemistry of the chiral centers in **4**. In particular, the migration of the carbon atoms C-1 or C-3 in 4′-hydroxy-substituted spiro compounds was expected to result in the formation of benzo[*b*]phenanthridinones **5**.[5] Alternatively, with a hydroxy group at C-1 in **4**, it was thought that indanobenzazepinones **6** (the basic nucleus of the ribasine alkaloids) or the isomeric **7** might be formed by migration of respectively C-4′[6] or the nitrogen atom[7] to C-1.

Scheme I



Scheme II



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