Synthesis of Nitrogen-Containing Heterocycles 9 [1]. Preparation and Carbon-Carbon Bond Cleavage of Spiro[cycloalkane[1',2',4']-triazolo[1',5'-*a*][1',3',5']triazine] Derivatives and Related Compounds

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Diaminomethylenehydrazones of cyclic ketones **1-5** reacted with ethyl *N*-cyanoimidate (**I**) at room temperature or with bis(methylthio)methylenecyanamide (**II**) under brief heating to give directly the corresponding spiro[cycloalkane[1',2',4']triazolo[1',5'-*a*][1',3',5']triazine] derivatives **7-12** in moderate to high yields. Ring-opening reaction of the spiro[cycloalkanetriazolotriazine] derivatives occurred at the cycloalkane moiety upon heating in solution to give 2-alkyl-5-amino[1,2,4]triazolotriazines **13-16**. Diaminomethylenehydrazones **17-19**, of hindered acyclic ketones, gave 2-methyl-7-methylthio[1,2,4]-triazolo[1,5-*a*][1,3,5]triazines **21-23** by the reaction with **II** as the main products with apparent loss of 2-methylpropane from the potential precursor, 2-*tert*-butyl-2-methyl-7-methylthio[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazines **20**, in good yields. In general, bis(methylthio)methylenecyanamide **II** was found to be a favorable reagent to the one-step synthesis of the spiro[cycloalkanetriazolotriazine] derivatives from the diaminomethylenehydrazones. The spectral data and structural assignments of the fused triazine products are discussed.

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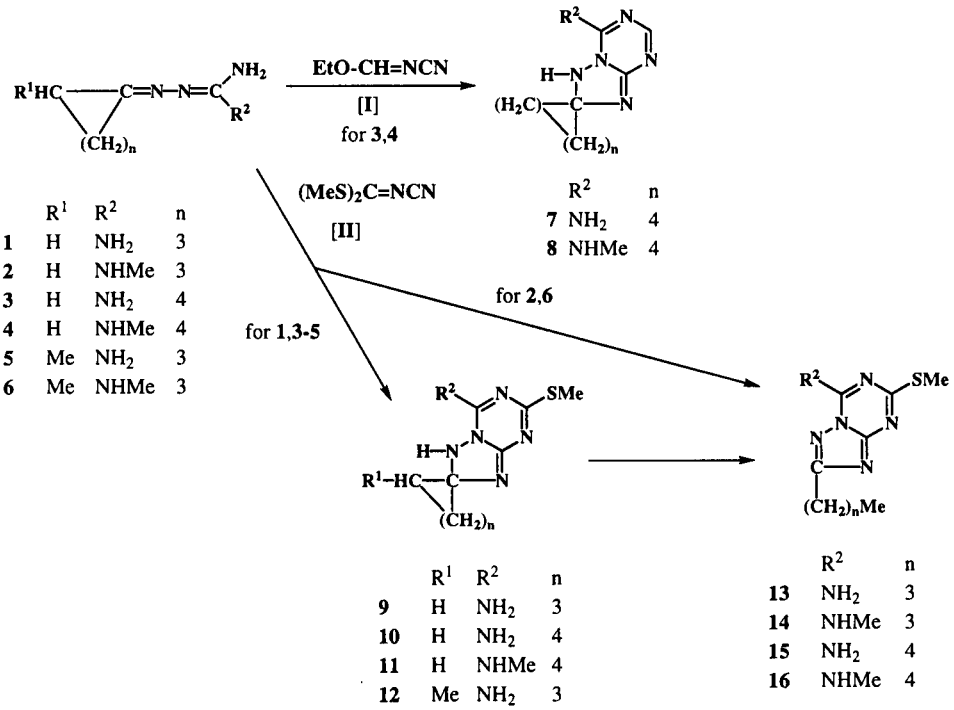
The author has previously reported preparation of spiro[cycloalkane[1',2',4']triazolo[1',5'-*c*]pyrimidine derivatives from cycloalkylidenehydrazones and ethoxymethylenemalononitrile as well as their ring-opening reactions [1]. The author has also reported that treatment of certain diaminomethylenehydrazones of aromatic carbonyl compounds with ethyl *N*-cyanoimidate successfully gave the corresponding 5-amino[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazine derivatives [2]. On the basis of these studies, I have now attempted to perform the one-step synthesis of spiro[cycloalkane[1',2',4']triazolo[1',5'-*a*]-[1',3',5']triazine derivatives through the electrocyclic reaction of the initial condensation products between diaminomethylenehydrazones of cyclic ketones and ethyl *N*-cyanoimidate (**I**) or bis(methylthio)methylenecyanamide (**II**) as shown in Scheme 1.

Scheme 1



	R^1	R^2	n
1	H	NH_2	3
2	H	NHMe	3
3	H	NH_2	4
4	H	NHMe	4
5	Me	NH_2	3
6	Me	NHMe	3

	R^2	n
7	NH_2	4
8	NHMe	4

	R^1	R^2	n
9	H	NH_2	3
10	H	NH_2	4
11	H	NHMe	4
12	Me	NH_2	3

	R^2	n
13	NH_2	3
14	NHMe	3
15	NH_2	4
16	NHMe	4

Scheme 2

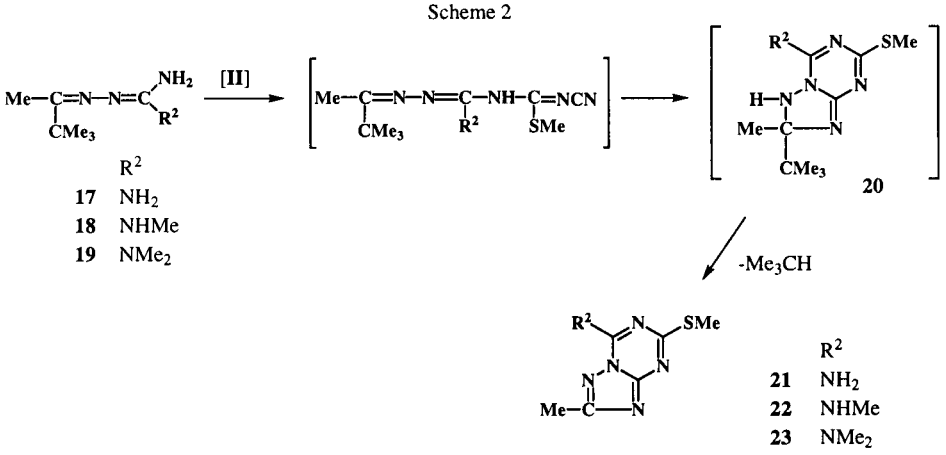


Table 1

Analytical and Physical Data for Spiro[cycloalkane-1,2'-[1',2',4']triazolo[1',5'-*a*][1',3',5']triazines

Compound No.	Yield (%)	Mp °C [4]	Formula	Calcd./Found C	H	N	MS, m/z (Rel. Int.)	^{1}H NMR Spectral Data
10	75	195-230	$C_{10}H_{16}N_6S$	47.60 47.55	6.39 6.43	33.30 33.51	252 (M^+, 19), 196 (100)	1.52 (m,10H, 5xCH_2), 2.30 (s, 3H, SCH_3), 5.74 (s, 1H, H-3), 7.17 (bs, 1H, NH), 7.80 (bs, 1H, NH)
11	52	135-155	$C_{11}H_{18}N_6S$	49.60 49.62	6.81 6.82	31.55 31.09	266 (M^+, 23), 210 (100)	1.38 (m, 6H, 3x CH_2),1.55 (m, 4H, 2xCH_2), 2.32 (s, 3H, SCH_3), 2.76 (d, J = 3.4,3H, $NHCH_3$), 5.69 (s, 1H, H-3), 7.49 (bs, 1H, NH)
12[5]	64	107-155	$C_{10}H_{16}N_6S$	47.60 47.46	6.39 6.10	33.30 33.18	252 (M^+, 12), 196 (100)	0.76 and 0.84 (each d, J = 6.3, 3H, $CHCH_3$), 1.57-1.78 (m, 6H, 3x CH_2), 2.31 (s, 3H, SCH_3), 2.48 and 2.51 (each m, 1H, $CHCH_3$), 5.71 and 5.98 (s, 1H, H-3),7.21 (bs, 1H, NH), 7.81(bs, 1H, NH)

When diaminomethylenehydrazone **1** was reacted with ethyl *N*-Cyanoimidate **I** in acetonitrile at room temperature, a complex mixture resulted, from which isolation of the triazine product expected was unsuccessful. In contrast, the six-membered homolog **3** gave the corresponding spiro compound **7** in 44% yield under similar reaction conditions. An even higher yield (80%) could be obtained when the reaction was performed by dropwise-addition of a solution of **I** in chloroform into **3** in the same solvent at room temperature. The *N*-methylated homolog **4** was possible to cyclize to **8** but in poor yield (10%) and proved to have the same tendency as less reactivity toward ethoxymethylenemalononitrile [1]. Consequently, the one-step synthesis of spirotriazolotriazines through the reaction using **I** seemed to be restricted to preparation of the spiro[cyclohexanetriazolotriazines](n=4) only.

The spiro[cycloalkanetriazolotriazines] in which the cycloalkane moieties are both five- and six-membered rings, however, could successfully be synthesized in a one step reaction, when **II** was used in place of **I**. Thus, the reaction of **1** with **II** in acetonitrile at the reflux temperature(80°) for 10 minutes gave **9** in 74% yield after chromatographic purification. As expected, the six-membered homolog **3** gave the corresponding spiro compound **10** in comparable yield under similar conditions. Typically, unreactive diaminomethylenehydrazone **4** also gave the spiro compound **11** in 52% yield under similar conditions. However, the reaction of *N*-monomethylated, five-membered compound **2** with **II** under similar conditions resulted in a complex mixture, from which separation of the desired product was unsuccessful. When the reaction of **2** with **II** was performed in acetonitrile at 65-70° for 1 hour, the ring-cleaved compound **14** was obtained. It is reasonable to consider that the spiro compound was formed as an intermediate from **6** under the reaction conditions to give **16** as the final product.

Unexpectedly, the diaminomethylenehydrazone of highly hindered ketone **17** successfully reacted with **II** in hot acetonitrile to produce 5-amino-2-methyl-7-methylthio[1,2,4]triazolo[1,5-*a*][1,3,5]triazine **21** as the only product isolated (92% yield) with spontaneous loss of the *tert*-butyl group from the potential precursor, 5-amino-2-*tert*-butyl-2-methyl-7-methylthio[1,2,4]triazolo[1,5-*a*]-

Table 2
Analytical and Physical Data for 2-Alkyl-5-amino-7-methylthio[1,2,4]triazolo[1,5-*a*][1,3,5]triazines

Compound No.	Yield (%)	Mp °C	Formula	Calcd./Found C	H	N	MS, m/z (Rel. Int.)	^{1}H NMR Spectral Data
14	23	101-103	$C_{10}H_{16}N_6S$	47.60 47.88	6.39 6.19	33.30 33.15	252 (M^+, 5), 210 (100)	0.90 (t, J = 7.3, 3H, CH_3),1.34 (sext, J = 7.3, 1H, CH_2), 1.71 (quin, J = 7.2, 2H, CH_2), 2.51 (s, 3H, SCH_3), 2.72 (t, J = 7.3, 2H, CH_2), 2.97 (bs, 3H, $NHCH_3$), 8.97 (bs, 1H, NH)
15	69	135-138	$C_{10}H_{16}N_6S$	47.60 47.55	6.39 6.44	33.30 33.41	252 (M^+, 18), 196 (100)	0.90 (t, J = 7.3, 3H, CH_3), 1.37 (m, 4H, 2xCH_2), 1.84 (quin, J = 7.3,2H, CH_2), 2.60 (s, 3H, SCH_3), 2.82 (t, J = 7.3, 2H, CH_2), 6.36 (bs, 2H, NH_2)
22	61	251-252	$C_7H_{10}N_6S$	39.99 39.79	4.79 4.70	39.97 39.71	210 (M^+, 100)	2.40 (s, 3H, CH_3), 2.51(s, 3H, SCH_3), 2.97 (d, J = 4.9, 3H, CH_3), 9.00 (d, J = 4.9, 1H, NH)
23	53	222-223	$C_8H_{12}N_6S$	42.84 42.73	5.39 5.24	37.47 37.27	224 (M^+, 100)	2.36 (s, 3H, CH_3), 2.49 (s, 3H, SCH_3), 3.33 (s, 6H, $N(CH_3)_2$)

[1,3,5]triazine **20** (Scheme 2). The moderate to good yields of the cleaved triazolotriazines **21** and **22** from the hindered ketone aminomethylenehydrazones suggests that the initial condensation between the aminomethylenehydrazone and the reagent **II** should readily proceed in spite of the unfavorable structure. Furthermore, **II** can react with **19** which, in general, is found to be less reactive toward cyclization due to the *N,N*-disubstituted structure on the terminal nitrogen, to produce the corresponding triazolotriazine **23**.

In view of the above discussion, **II** would be the highly applicable reagent for syntheses of the [1,2,4]triazolo-[1,5-*a*][1,3,5]triazine ring system through the electrocyclic reaction starting with diaminomethylenehydrazones. Analytical and spectral data on the spiro[cycloalkane-[1',2',4']triazolo[1,5-*a*][1',3',5']triazine] derivatives **7-12** thus obtained are presented in the Experimental section and Tables 1 and 3.

The ring-opening reaction of the spiro[cycloalkanetriazolotriazines] at the cycloalkane moiety could be performed by heating the substrate in acetonitrile or methanol, except for compounds **7** and **8** which did not give rise to the cleaved product reproducibly. Certain of cleaved products were obtained directly from the reaction between diaminomethylenehydrazones and **II** if the reaction was subjected to prolonged heating or the reaction medium contained some amine base. The cleavage of compound **12** occurred to produce 2-(straight-alkyl)-triazolotriazine **15** in a similar manner as reported in the reaction of the triazolopyrimidine system [1]. The spectral data for the isolated compounds **13-16**, **21**, **22** and **23** are shown in the Experimemtal section and Tables 2 and 3.

EXPERIMENTAL

Melting points were determined in open capillary tubes and uncorrected. ^{1}H and ^{13}C nmr spectra were obtained with a JNM EX-400 (400 MHz) or a JNM FX-90Q (90 MHz) spectrometer.

Table 3
^{13}C NMR Chemical Shifts of Ring Carbons in theTriazolotriazines

Compound No.	C-2	C-5	C-7	C-9
10	85.0	151.7	176.4	150.9
11	85.4	150.9	176.4	150.8
12	94.1	151.7	176.3	151.0
	94.3	151.5	176.4	151.3
14	167.1	147.8	174.5	156.5
15	169.5	148.9	174.0	157.2
22	147.8	172.6	163.6	156.6
23	148.2	171.6	162.6	158.6

The chemical shift values were recorded in parts per million (ppm) on the δ scale with tetramethylsilane as the internal reference. The mass spectra (75 eV) were obtained on a JEOL JMS-D100 mass spectrometer. Preparative high-performance liquid chromatography (hplc) was carried out in a Kusano Kagaku KHLC-201 instrument with a 300 X 22 mm glass column packed with silica gel. Microanalyses were performed with a Perkin-Elmer 240D elemental analyzer at the Microanalytical Laboratory of Kitasato University.

The diaminomethlylenehydrazones **1-6**, **17-19** used were known compounds and prepared according to literatures [1-3].

Preparation of Spiro[cycloalkane-1,2'-(5'-substituted)[1',2',4']-triazolo[1',5'-*a*][1',3',5']triazine].

Spiro[cyclohexane-1,2'-(5'-amino)[1',2',4']triazolo[1',5'-*a*]-[1',3',5']triazine] (**7**).

A solution of diaminomethylenehydrazone (**3**) (0.46 g, 3 mmoles) and **I** (0.34 g, 3.5 mmoles) in acetonitrile (5 ml) was allowed to stand at room temperature. After 3 hours, crystals gradually deposited from the solution, and were collected by filtration to give the spiro compound **7** as colorless needles (0.27 g, 44%), mp 163-167°; ^{1}H nmr (DMSO-d_6): δ 1.38 (m, 4H, 2 x CH_2), 1.53 (m, 6H, 3 x CH_2), 5.80 (s, 1H, H-3), 7.18 and 7.84 (each bs, 1H, NH), 7.49 (s, 1H, H-7); ^{13}C nmr (DMSO-d_6): δ 22.1 (t), 24.7 (t), 37.2 (t), 84.8 (s), 151.9 (s), 153.7 (s), 163.6 (d); ms: m/z (relative intensity) 206 (M^+, 14), 163 (93), 150 (100).

Anal. Calcd. for $C_9H_{14}N_6$: C, 52.41; H, 6.84; N, 40.75. Found: C, 52.64; H, 6.60; N, 40.74.

Spiro[cyclohexane-1,2'-(5'-monomethylamino)[1',2',4']-triazolo[1',5'-*a*][1',3',5']triazine] (**8**).

In a similar manner as described for **7**, treatment of **4** (0.67 g, 4 mmoles) with **I** (0.47 g, 4.8 mmoles) in acetonitrile (5 ml) gave the title compound as colorless needles, yield 0.09 g (10%), mp 162-180°; ^{1}H nmr (DMSO-d_6): δ 1.39 (m, 4H, 2 x CH_2), 1.54 (m, 6H, 3 x CH_2), 2.80 (s, 3H, NCH_3), 5.79 (s, 1H, H-3), 7.60 (s, 1H, H-7); ^{13}C nmr (DMSO-d_6): δ 22.2 (t), 24.8 (t), 26.8 (q), 37.1 (t), 85.2 (s), 151.9 (s), 152.8 (s), 163.5 (d); ms: m/z (relative intensity) 220 (M^+, 12), 177 (78), 164 (100).

Anal. Calcd. for $C_{10}H_{16}N_6$: C, 54.53; H, 7.32; N, 38.15. Found: C, 54.72; H, 7.35; N, 38.16.

Spiro[cyclopentane-1,2'-(5'-amino)-7'-methylthio[1',2',4']-triazolo[1',5'-*a*][1',3',5']triazine] (**9**).

A solution of diaminomethylenehydrazone (**1**) (0.4 g, 1 mmole) and **II** (0.15 g, 1 mmole) in acetonitrile (2 ml) was heated under reflux for 10 minutes during which time the starting materials went into solution and then the desired product rapidly separated. The crystals were collected by filtration and washed with acetonitrile to give the spiro compound as colorless needles (0.18 g, 74 %), mp 177-181°; ^{1}H nmr (DMSO-d_6): δ 1.66 (m, 8H, 4 x CH_2), 2.30 (s, 3H, SCH_3), 5.96 (s, 1H, H-3), 7.26 and 7.84 (each bs, 1H, NH); ^{13}C nmr: δ 13.1 (q), 23.3 (t), 38.8 (t), 93.3 (s), 151.3 (s), 151.5 (s), 176.5 (s); ms: m/z(relative intensity) 238 (M^+, 7), 209 (37), 196 (100).

Anal. Calcd. for $C_9H_{14}N_6S$: C, 45.36; H, 5.92; N, 35.25. Found: C, 45.88; H, 5.87, N, 35.15.

The spiro compounds **10-12** were similarly obtained and their analytical data are shown in Table 1.

Ring-opening of Spiro[cycloalkane-1,2'-(5'-substituted)[1',2',4']-triazolo[1',5'-*a*][1',3',5']triazine.

Ring-opening of Spiro Compound **9**. Formation of 5-Amino-2-butyl-7-methylthio[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**13**).

A 0.1 gram portion of the product **9** was dissolved in methanol (3 ml) and the solution was boiled for 5 hours. After evaporation of the solvent, the residue was subjected to hplc on silica gel with chloroform as the eluent to give the cleaved product **13** (0.08 g, 80%) as white crystals. Recrystallization from acetonitrile gave the analytical sample of 5-amino-2-butyl-7-methylthio[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**13**) as colorless needles, mp 149-150°; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, J = 7.3, 3H, CCH_3), 1.42 (sext, J = 7.33, 2H, CH_2), 1.80 (quin, J = 7.32, 2H, CH_2), 2.51 (s, 3H, SCH_3), 2.72 (t, J = 7.33, 2H, CH_2), 2.97 (bs, 3H, $NHCH_3$), 8.97 (bs, 1H, $NHCH_3$); ^{13}C nmr (deuteriochloroform): δ 13.8 (q), 14.3 (q), 22.4 (t), 28.9 (t), 29.8 (t), 148.9 (s), 157.3 (s), 169.6 (s), 174.1 (s); ms: m/z (relative intensity) 238 (M^+, 7), 196 (100).

Anal. Calcd. for $C_9H_{14}N_6S$: C, 45.36; H, 5.92; N, 35.25. Found: C, 45.03; H, 6.01: N, 35.49.

Ring-opening of Spiro Compound **11**. Formation of 5-Amino-2-pentyl-7-methylthio[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**16**).

A solution of spiro compound **11** (0.1 g) in methanol (1 ml) was heated under reflux for 5 hours and evaporated. The residue which contained about 85% of the cleaved product was subjected to hplc on silica gel using chloroform as the eluent to give the desired product **16** (0.07 g, 70%) as colorless prisms, mp 84-89°; ^{1}H nmr (deuteriochoroform): δ 0.89 (t, J = 7.33, 3H, CH_3), 1.34 (m, 4H, 2 x CH_2), 1.80 (quin, J = 7.32, 2H, CH_2), 2.59 (s, 3H, SCH_3), 2.79 (t, J = 7.33, CH_2), 3.22 (d, J = 4.88, 3H, $NHCH_3$), 6.52 (bs, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.0 (q), 14.4 (q), 22.4 (t), 27.4 (t), 27.6 (q), 29.0 (t), 31.4 (t), 148.2 (s), 157.0 (s), 168.7 (s), 174.5 (s); ms: m/z (relative intensity) 266 (M^+, 24), 210 (100).

Anal. Cacd. for $C_{11}H_{18}N_6S$: C, 49.60; H, 6.81; N, 31.55. Found: C, 49.48; H, 6.75; N, 31.67.

Direct Formation of Cleaved Compound **16**.

A solution of 2-methylpentanone *N*-methylaminoamino-methylenehydrazone **6** (0.17 g, 1 mmole) and **II** (0.15 g, 1 mmole) in acetonitrile (2 ml) was heated at 55-60° for 1 hour and then evaporated under reduced pressure. The residue was subjected to preparative hplc on silica gel using chloroform as the eluent to collect homogeneous fractions from which the title compound **16** (0.06 g, 24%) was obtained as colorless prisms, mp 83-89°.

5-Amino-2-methyl-7-methylthio[1,2,4]triazolo[1,5-*a*][1,3,5]-triazine (**21**).

A solution of diaminomethylenehydrazone (**17**) (0.16 g, 1 mmole) and **II** (0.15 g, 1 mmole) in acetonitrile (2 ml) was heated under reflux for 1 hour during which time the starting materials went into solution and then the desired product rapidly deposited. The crystals were collected by filtration and washed with acetonitrile to give compound **21** (0.17 g, 92%), mp 228-229°; ^{1}H nmr (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 2.49 (s, 3H, SCH_3), 8.59 (bs, 1H, NH), 8.85 (bs, 1H, NH); ^{13}C nmr (DMSO-d_6); δ 13.4 (q), 14.5 (q), 149.2 (s), 157.0 (s), 163.7 (s), 172.6 (s); ms: m/z (relative intensity) 196 (M^+, 100).

Anal. Calcd. for $C_6H_8N_6S$: C, 36.72; H, 4.11; N, 42.83. Found: C, 36.90; H, 4.10; N, 43.03.

REFERENCES AND NOTES

[1] Part 8: Y. Miyamoto and C. Yamazaki, *J. Heterocyclic Chem.*, **34**, 871 (1997).

[2] Y. Miyamoto, C. Yamazaki and M. Matzui, *J. Heterocyclic Chem.*, **27**, 1553 (1990).

[3] Y. Miyamoto and C. Yamazaki, *J. Heterocyclic Chem.*, **26**, 763 (1989).

[4] The broad melting range may probably be due to partial ring-opening of the spiro compounds in the course of heating.

[5] The duplicated values for the ^{1}H and ^{13}C resonances indicate that compound **12** exists as a diastereomeric mixture.