(+)-13-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (1). A solution of 29 mg (0.1 mmol) of diol **18** in 3 mL of dry methylene chloride containing 30 μL (0.30 mmol) of dihydropyran and 2 mg of pyridinium *p*-toluenesulfonate was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of an aqueous sodium bicarbonate solution. The reaction mixture was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was chromatographed on 8 g of silica gel. Elution with hexane–ether (1:1) gave 45 mg (98%) of the corresponding bis(tetrahydropyranyl) ether [R_f 0.46 (1:3 hexane-ether); IR ($CHCl_3$) 2920, 2850, 2830, 1750, 1695, 1455, 1445, 1430, 1370, 1340, 1315, 1275, 1250, 1215, 1190, 1175, 1160, 1145, 1120, 1105, 1065, 1025, 1010, 965, 905, 900, 860 cm^{-1}], which was employed directly in the next reaction.

To a solution of 45 mg (0.099 mmol) of the above tetrahydropyranylated lactone in 1.0 mL of dry toluene, cooled to −78 °C, was added dropwise 0.19 mL (0.30 mmol) of diisobutylaluminum hydride (1.6 M in toluene). After 1 h at −78 °C and 1 h at −60 °C, the reaction was quenched by the careful addition of methanol. The reaction mixture was warmed to room temperature and diluted with ethyl acetate and water. After 1.5 h at room temperature anhydrous magnesium sulfate was added. The resulting mixture was filtered and concentrated under reduced pressure. The crude lactol was chromatographed on 8 g of silica gel. Elution with hexane–ether (1:2) provided 43.5 mg (96%) of pure lactol [R_f 0.34 (1:3 hexane-ether); IR ($CHCl_3$) 3590, 3380 (br), 2990, 2920, 2840, 1695, 1460, 1445, 1435, 1370, 1340, 1315, 1270, 1225, 1170, 1145, 1120, 1065, 1010, 970, 905, 895, 840 cm^{-1}], which was used directly in the next reaction.

A suspension of 59 mg (1.39 mmol) of 56.9 sodium hydride dispersion in 0.65 mL of dry dimethyl sulfoxide was stirred at 50–55 °C for ca. 3 h. To the above solution of dimsyl sodium, cooled to room temperature, was added 308 mg (0.695 mmol) of (4-carboxylbutyl)triphenylphosphonium bromide [dried for 2 h at 100 °C under vacuum prior to use] in 0.8 mL of dry dimethyl sulfoxide. After 30 min, a solution of 43.5 mg (0.095 mmol) of the above lactol in 0.65 mL of dry dimethyl sulfoxide was added to the red ylide solution in one portion. After 20 min at room temperature, the reaction was quenched with water and acidified to pH 4.5–5.0 with a sodium bisulfate solution. The resulting solution was extracted exhaustively with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was esterified with ethereal diazomethane. The crude product was chromatographed on 8 g of silica gel. Elution with hexane–ether (1:3) yielded 47 mg (89%) of ester **19** [R_f 0.46 (1:3 hexane–ether); IR ($CHCl_3$) 3520 (br), 2995, 2940, 2825, 1720, 1700, 1450, 1430, 1375, 1350, 1335, 1315, 1270, 1220, 1195, 1165, 1145, 1125, 1070, 1030, 1015, 990, 900, 875, 865, 710, 655 cm^{-1}], which was used in the next reaction.

A solution of 28 mg (0.051 mmol) of ester **19** in 3 mL of absolute ethanol containing 8 mg of pyridinium *p*-toluenesulfonate was heated at 50–55 °C under argon. After ca. 5 h the cooled (25 °C) reaction mixture was quenched with solid sodium bicarbonate and concentrated under reduced pressure. The residue was chromatographed on 8 g of silica gel. Elution with ether–ethyl acetate (2:1) afforded 17.8 mg (91%) of pure 13-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**): R_f 0.24 (ethyl acetate); $[\alpha]^{26}_D$ +30° (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 3600, 3400 (br), 2990, 2940, 2920, 2850, 1720, 1700, 1450, 1430, 1360, 1310, 1275, 1220, 1160, 1150, 1105, 1090, 1080, 1040, 1020, 1000, 960, 880 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.2–1.9 (m, 12 H), 2.0–2.4 (m, 5.5 H), 2.31 (t, 2 H, J = 7 Hz, $CH_2CO_2CH_3$), 2.47 (m, 0.5 H, C-12 H), 3.01 (d, 1 H, J = 4 Hz, OH), 3.30 (br s, 1 H, OH), 3.63 (s, 3H, CO_2CH_3), 4.20 (3 H, 2CHOH, OH), 4.57 (m, 1 H, CHOH), 4.74 (dd, 1 H, J_{HF} = 36 Hz, J = 9 Hz, CH=CF), 5.39 (m, 2 H, CH=CH). Anal. Calcd for $C_{21}H_{35}FO_5$: C, 65.26; H, 9.13. Found: C, 65.01; H, 9.21.

Acknowledgment. Generous support for this work from the National Institute of Child Health and Human Development, National Institutes of Health (Grant HD 14646), and G.D. Searle & Co. is gratefully acknowledged.

Registry No. **1**, 97211-24-0; **2**, 97211-25-1; **3**, 97211-26-2; **4**, 97211-27-3; **4** (phosphonium intermediate), 97211-40-0; **4** (phosphoranylidene intermediate), 97211-41-1; **5** (R = H), 52437-21-5; **5** (R = CH_3), 97211-28-4; **5** (R = CH_3) (*t*-$BuMe_2Si$), 97211-29-5; **6**, 71155-12-9; **6**-o1, 74778-89-5; **7**, 57820-77-6; **7** (tosylate), 97211-39-7; **8**, 97211-30-8; **9**, 97211-31-9; **10**, 97211-32-0; **11** (R = *t*-$BuMe_2Si$), 97275-90-6; **11** (R = H), 97275-91-7; **12**, 97211-33-1; (±)-**13**, 97211-34-2; (±)-**14**, 97211-35-3; (±)-**15**, 97275-93-9; (±)-**15** ethylene ketal), 97275-94-0; **16**, 97211-36-4; (±)-**16**, 97275-92-8; **17**, 97234-63-4; **18**, 97211-37-5; **18** (2THP), 97211-42-2; **19**, 97211-38-6; **19** (lactol), 97211-43-3; **19** (acid), 97211-44-4; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.

Diastereofacial Selectivity in the Reaction of Allylic Organometallic Compounds with Imines. Stereoelectronic Effect of Imine Group

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Received December 11, 1984

The diasterofacial selectivity in the reaction of crotyl organometallic compounds (**4**) (M = Li^+, Mg, B, and Sn) with imines (**3**) is investigated. The reaction of ordinary imines produces the erythro isomer (**5**) predominantly regardless of the metal (M). With increase of the steric bulk of the R group or with aryl substituent in the R′ group, the threo isomer (**6**) predominates in the reaction of crotyl-9-BBN. The ratio of erythro (**11**)/threo (**12**) in the reaction of pent-3-en-2-yl-9-BBN (**9**) is higher than the ratio of erythro (**5**)/threo (**6**) in the reaction of crotyl-9-BBN itself. On the basis of these observations, the transition-state geometry is discussed.

Although the diastereofacial selectivity in the reaction of allylic organometallic compounds with aldehydes has been intensely investigated during the last few years,[1] no attempts have yet been made to elucidate such selectivity with imines.[2] If high diastereofacial selectivity is realized with imines, such reactions may be practically useful for the synthesis of nitrogen-containing natural products, e.g., amino sugars,[3] sphingolipid bases, amino acids,[4] and β-

(1) (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) The literatures before December, 1981 are listed in the above two reviews. For the recent literatures, see *Tetrahedron* symp.-in-print No 16, **1984**, *40*, No 12, and references sited therein.

(2) The Cran/anti-Cram problem of imines is reported: (a) Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031.

(3) For allylic organometallic approach, see: (a) Goto, Y.; Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1983**, 671. (b) Fuganti, C.; Grasselli, P.; P-Fantoni, G. *J. Org. Chem.* **1983**, *48*, 909.

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Table I. Diastereofacial Selectivity in the Reaction of 3 with 4

entry	imine (3) R	imine (3) R′	compd	4 (M)	product ratio, %[a] 5 (erythro):6 (threo)	total yield, %[b]
1	Ph	Ph	**3a**	Li	60:40	50
2				MgCl	74:26	95
3				9-BBN[c]	0:100	93
4				$SnBu_3/BF_3$	75:25	80
5	Ph	*p*-tolyl	**3b**	MgCl	72:28	92
6				9-BBN	0:100	95
7				$SnBu_3/BF_3$	79:21	85
8	Ph	*n*-Pr	**3c**	MgCl	63:37	95
9				9-BBN	85:15	95
10	Ph	*i*-Pr	**3d**	9-BBN	65:35	79
11	*n*-Pr	*n*-Pr	**3e**	9-BBN	75:25	90
12	*n*-Pr	*i*-Pr	**3f**	9-BBN	100:0	97
13	*i*-Pr	*n*-Pr	**3g**	9-BBN	34:66	95
14	*i*-Pr	*i*-Pr	**3h**	9-BBN	30:70	60

[a] By ^1H and ^{13}C NMR and GLPC analyses. [b] Isolated yield. [c] 9-BBN = 9-borabicyclo[3.3.1]nonyl.

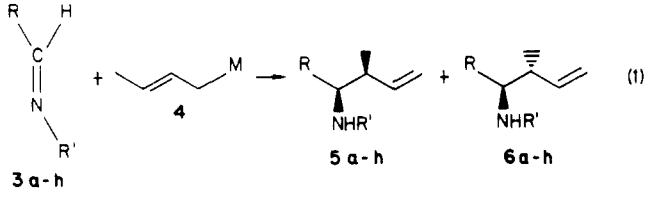
lactams.[4] Further, the reaction of imines is theoretically interesting, since the trans geometry[5] of aldimines necessarily forces the electrophile (El, Lewis acids or metals) to coordinate the nitrogen atom syn to the R group (**1**).

1 **2**

On the other hand, it is usually believed that the complexation at aldehydes occurs anti to the R group (**2**).[6] Therefore, it is expected that the reaction of imines may exhibit a different stereoselectivity from the reaction of aldehydes.[7] We now report a systematic investigation on the diastereofacial selectivity in the reaction of imines (**3**) with allylic organometallic compounds (M = Li, Mg, B, and Sn).

Results and Discussion

Reactions of Crotyl Organometallic Compounds (4). We examined the reaction of **3** with **4** and investigated the product ratio of **5** (erythro, syn) and **6** (threo, anti). The results are summarized in Table I.

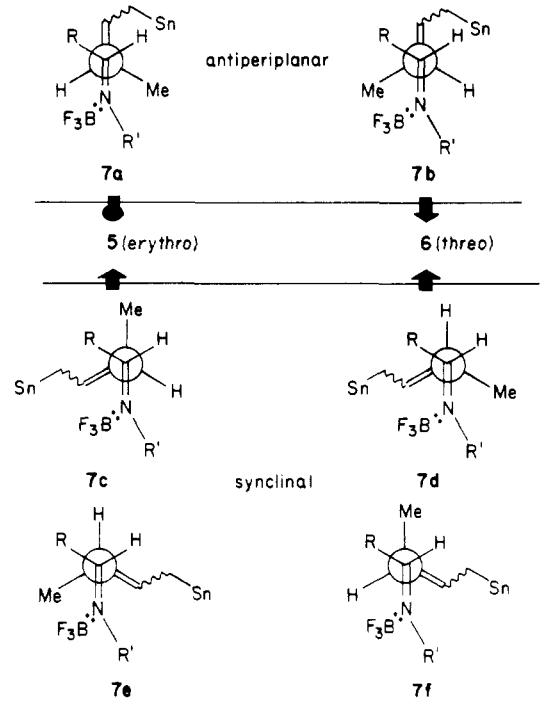


3a-h **4** **5a-h** **6a-h** (1)

M = Li, Mg, B, Sn

Generally speaking, the erythro isomer (**5**) is produced predominantly irrespective of the metal (M), *except entries 3, 6, 13, and 14.* The erythro selectivity of crotyltributylstannane (entries 4 and 7) can be understood via the acyclic antiperiplanar transition state (Scheme I) in a similar manner as described in the reaction of aldehydes.[6a,,] Without BF_3, the reaction with crotyltin did not occur even at high pressure[6a] and high temperature, in contrast with the reaction of aldehydes. Therefore, the coordination of BF_3 is essential to induce the reaction, and it is reasonable to propose the acyclic mechanism. Among six possible geometries, the steric crowding increases in the order of **7a < 7d < 7b,c,e,f.** Consequently, the predominant formation of **5** is anticipated, and this proved to be the case. To further confirm this mechanism, we examined the reaction of other imines. Unfortunately, however, the reaction proceeded only with the imines bearing an aryl group in the R′ substituent, and the preparation of imines like (alkyl)CH=N(aryl) was difficult.

Scheme I. Acyclic Transition-State Geometry



The erythro selectivity of crotyl-9-BBN (entries 9–12), as well as crotyllithium and crotylmagnesium chloride (entries 1, 2, 5, and 8), can be explained via the six-mem-

(4) High enantio- and diastereoselective synthesis of certain amino acids and β-lactams is realized. The results will be published in due course: Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.*, in press.

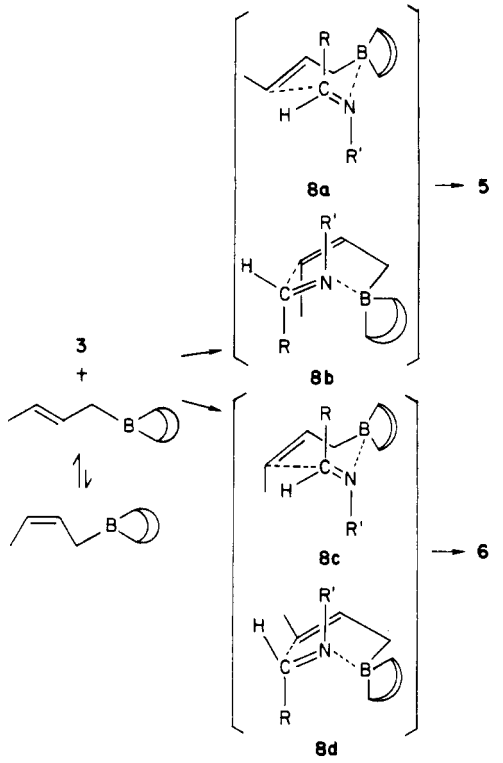
(5) It is known that aldimines normally takes the trans configuration: McCarty, C. G. In "The Chemistry of the Carbon-Nitrogen Double Bond"; Patai, S., Ed., Interscience: London, 1970; p 363.

(6) (a) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K., *Tetrahedron*, **1984**, *40*, 2239. (b) Reetz, M. T.; Sauerwald, M. *J. Org. Chem.* **1984**, *40*, 2292. (c) For a synclinal transition state in the reaction of aldehydes, see: Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.

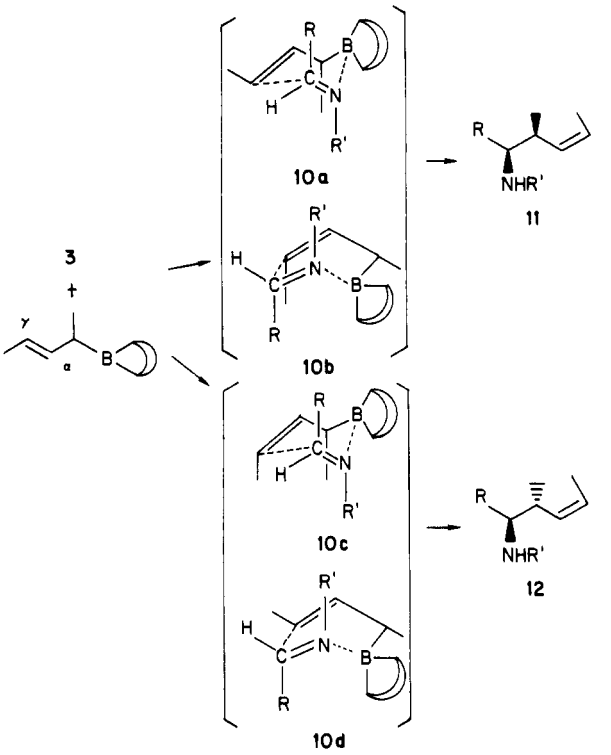
(7) For the reaction of imines with enolates and related compounds, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1 and references cited therein. (b) Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946. (c) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. (d) Broadley, K.; Davies, S. G. *Tetrahedron Lett.* **19848** 1743. (e) Dubois, J.; Axiotis, G. *Ibid.* **1984**, 2143. (f) For the reaction with allylstannanes: Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 147.

(8) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

Scheme II. Cyclic Transition-State Geometry



Scheme III. Cyclic Transition-State Geometry



bered chair transition state (Scheme II). The reaction with lithium crotyl-*n*-butyl-9-BBN ate complex was quite sluggish in comparison with the reaction with crotyl-9-BBN itself. Therefore, the coordination of boron to the nitrogen atom is essential to induce the allylation reaction, and hence it is reasonable to propose the cyclic transition state.[9] The erythro isomer is produced through either **8a** or **8b**, and the threo isomer is afforded via either **8c** or **8d**. Since the (*E*)-isomer of crotyl-9-BBN is thermodynamically more stable than the (*Z*)-isomer[10] and the ratio of *E*/*Z* increases with the coordination of nucleophiles to boron,[11] mainly the (*E*)-isomer must participate in the transition state. Therefore, **5** is presumably produced through **8a**. The reaction of cortyllithium and -magnesium compounds also proceeds via **8a** (entries 1, 2, 5, and 8).

The erythro selectivity does not so much depend upon the steric bulk of the R′ group (entries 9–12), but that of the R group exerts a strong influence upon the selectivity (entries 13 and 14). The 1,3-diaxial interaction between the R group and the bridgehead proton of the 9-BBN ring[2b] and the 1,2 axial–equatorial interaction between the R group and the Me group in **8a** increase with the steric bulk of R group. Under such circumstances, **8d** is more stable than **8a**, leading to the predominant formation of **6**.

The exclusive formation of **6** in entries 3 and 6 should be noted. Two factors are essential for the high threo selectivity: (i) the use of 9-BBN (cf. entries 1, 2, 4 vs. 3, and 5, 7 vs. 6) and (ii) the presence of an aryl group as the R′ substituent (cf. entries 3 and 6 vs. 8–10). Boron-promoted isomerization of benzylideneaniline from the *E* form to the *Z* form may be responsible for the threo selectivity.

Table II. Diastereofacial Selectivity in the Reaction of 3 with 9

entry	imine (3) R	imine (3) R′	imine (3) compd	11 (erythro): 12 (threo)	total yield, %[b]
1	Ph	Ph	**3a**	8:92	90
2	Ph	*n*-Pr	**3c**	100:0	84
3	Ph	*i*-Pr	**3d**		no reaction
4	*n*-Pr	*i*-Pr	**3f**	100:0	75
5	*i*-Pr	*n*-Pr	**3g**	85:15	78

[a] By ^{1}H NMR and GLPC. [b] Isolated yield.

n-Bu-9-BBN or BF_3·OEt_2 was added to an ether solution of benzylideneaniline at −78 °C, and the ^{1}H and ^{13}C NMR spectra were investigated at −78, −50, −30, −10, and 0 °C and room temperature. However, such isomerization could not be detected. Therefore, here also, the boatlike transition state **8d** may be involved, though the reason why aryl groups favor the boatlike geometry is not clear.[12]

Reactions of Pent-3-en-2-yl-9-BBN (9). To further confirm the transition-state geometry, we examined the reaction of **9** with **3** (Scheme III), are the results are summarized in Table II. Since the α-substituent of crotyl-9-BBN derivatives goes to the axial position of the six-membered chair transition state,[13] **10c** may be destabilized owing to three 1,3-diaxial interactions at the R′ side. Although it is not clear whether the methyl group at the α-position goes to either the axial or equatorial position in the boatlike geometries (**10b** and **10d**), introduction of the methyl group destabilizes the boat transition state itself in comparison with the chair transition state, owing to the steric repulsion between the methyl group and 9-BBN ring protons. Therefore, the relative stability of **10a** vs. other geometries must be enhanced in comparison with the relative stability of **8a** vs. **8b**, **8c**, and **8d**. This proved to

(9) For boron containing six-membered chair transition state in the reaction of aldehydes, see: (a) ref 1 and references cited therein. (b) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236. (c) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330.

(10) Kramer, G. W.; Brown, H. C. *J. Organometal. Chem.* **1977**, *132*, 9.

(11) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969.

(12) A boatlike transition state is proposed in the reaction of B-3-pinanyl-9-BBN with aldehydes: Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1317.

(13) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229 See also ref 9b and 9c.

be the case as indicated in Table II. The ratio of erythro isomer (11)/threo isomer (12) increases in comparison with the ratio of 5/6 (cf. entries 2, 4, and 5 of Table II vs. 9, 12, and 13 of Table I, respectively). Even in the reaction of benzylideneaniline, a small amount of 11 is obtained (entry 1 of Table II vs. entry 3 of Table I). Further, formation of the cis isomers (11 and 12) again confirms the axial orientation of the α-substituent. The result of entry 3 indicates that ease of the reaction strongly depends upon the steric factors of both the reactant and the reagent.

In conclusion, the reaction of ordinary imines with allylic organometallic compounds (M = Li, Mg, and B) proceeds primarily through a six-membered chairlike transition state, in which the imine R group occupies an axial position owing to the stereoelectronic effect of imines. With increase of the steric bulk of R or with aryl substituent in R′, the chairlike transition state is destabilized, and the boatlike transition state may predominate.[14] The BF_3-mediated reaction with crotyltributylstannane proceeds through an acyclic transition state similar to that described for the reaction of aldehydes, resulting in the predominant formation of the erythro isomer.

Experimental Section

General information concerning instrumentation and materials is described previously.[6a,11] Imines were prepared according to the reported procedure.[15]

***N*-Benzylideneaniline**: mp 52–53 °C (lit.[16] 52 °C); ^{1}H NMR (CCl_4) δ 7.1–7.6 (m, 8)f 7.8–8.0 (m, 2); 8.40 (s, 1).

***N*-Benzylidene-*p*-toluidine**: mp 33–34 °C (lit.[16] 33–35 °C); ^{1}H NMR (CCl_4) δ 2.25 (s, 3), 7.0–7.2 (m, 2), 7.3–7.5 (m, 2), 7.5–7.7 (m, 3), 7.8–8.0 (m, 2), 8.60 (s, 1).

***N*-Benzylidene-*n*-propylamine**: bp 102–104 °C/18 mmHg; ^{1}H NMR (CCl_4) δ 0.98 (t, J = 7.5 Hz, 3), 1.71 (sextet, J = 7.0 Hz, 2), 3.53 (t, J = 7.0 Hz, 2), 7.3–7.5 (m, 3), 7.6–7.8 (m, 2), 8.19 (s, 1).

***N*-Benzylideneisopropylamine**: bp 89–93 °C/17 mmHg; ^{1}H NMR (CCl_4) δ 1.20 (d, J = 7.0 Hz, 6), 3.45 (septet, J = 6.5 Hz, 1), 7.3–7.5 (m, 3), 7.6–7.8 (m, 2), 8.21 (s, 1).

***N*-Butylidene-*n*-propylamine**: bp 71 °C/108 mmHg (lit.[15a] 120–124 °C); ^{1}H NMR (CCl_4) δ 0.88 (t, J = 7.0 Hz, 3), 0.95 (t, J = 7.0 Hz, 3), 1.57 (sextet, J = 7.0 Hz, 4), 2.18 (q, J = 6.5 Hz, 2), 3.27 (t, J = 6.5 Hz, 2), 7.63 (t, J = 4.5 Hz, 1).

***N*-Butylideneisopropylamine**: bp 61–63 °C/130 mmHg (lit.[15a] 100–111 °C); ^{1}H NMR (CCl_4) δ 0.92 (t, J = 7.5 Hz, 3), 1.05 (d, J = 7.0 Hz, 6), 1.55 (sextet, J = 7.0 Hz, 2), 2.0–2.3 (m, 2), 3.18 (septet, J = 6.0 Hz, 1), 7.37 (t, J = 4.5 Hz, 1).

***N*-Isobutylidene-*n*-propylamine**: bp 64–65 °C/130 mmHg (lit.[15a] 108–114 °C); ^{1}H NMR (CCl_4) δ 0.87 (t, J = 6.5 Hz, 3); 1.01 (d, J = 7.0 Hz, 6), 1.54 (sextet, J = 7.0 Hz, 2), 2.35 (m, 1), 3.22 (t, J = 6.5 Hz, 2), 7.48 (d, J = 5.0 Hz, 1).

***N*-Isobutylideneisopropylamine**: bp 56–58 °C/165 mmHg; ^{1}H NMR (CCl_4) δ 0.99 (d, J = 6.0 Hz, 6), 1.04 (d, J = 6.0 Hz, 6), 2.23 (sp-d, J = 6.5 and 5.0 Hz, 1), 3.14 (sp, J = 6.0 Hz, 1), 7.49 (d, J = 4.5 Hz, 1). The preparation of alkylideneaniline was difficult due to formation of by-products.[17]

Reactions of 4 with 3. The reaction was carried out in a similar manner as described previously.[6a,11] To an ether solution of **3** (1 mmol) was added **4** (1.1 mmol) at −78 °C. In the case of crotylstannane, BF_3·OEt_2 (1.1 mmol) was added prior to the addition of the reagent. The reaction of Li, Mg, and Sn was quenched at room temperature with sat. $NaHCO_3$ solution. The product from the reaction of Li and Mg was isolated through Kugelrohr distillation. The product from Sn was filtered through a short column of silica gel to remove the Bu_3Sn residue and then distilled. The reaction of B was quenched at 0 °C with several drops of concentrated HCl. The mixture was stirred overnight at room temperature, and aqueous NaOH solution (3 N) was added at 0 °C to make the solution basic. The mixture was extracted twice with ether, dried, condensed, and filtered through a short column of silica gel (hexane:ether = 10:1) to remove the 9-BBN residue.

***N*-Phenyl-2-methyl-1-phenyl-3-butenylamine**: bp 130–135 °C/0.1 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ of erythro isomer 0.98 (d, J = 7.5 Hz, 3), 2.4–2.8 (m, 1), 4.0 (br, 1), 4.30 (t, J = 5.0 Hz, 1), 5.0–5.3 (m, 2), 5.6–6.0 (m, 1), 6.3–6.6 (m, 3), 6.8–7.1 (m, 2) 7.19 (s, 5); δ of threo isomer 0.95 (d, J = 7.5 Hz, 3), 2.2–2.6 (m, 1), 4.0 (br, 1), 4.0 (d, J = 6.5 Hz, 1), 4.9–5.2 (m, 2), 5.5–5.9 (m, 1), 6.2–6.6 (m, 3), 6.8–7.0 (m, 2), 7.0–7. (m, 5); MS; m/e (M^+) 237. Anal. ($C_{17}H_{19}N$) C, H.

***N*-*p*-Tolyl-2-methyl-1-phenyl-3-butenylamine**: bp 135 °C/0.1 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ of erythro isomer 0.99 (d, J = 7.5 Hz, 3), 2.35 (s, 3), 2.4–2.8 (m, 1), 4.0 (br, 1), 4.35 (d, J = 5.0 Hz, 1), 5.0–5.3 (m, 2), 5.6–6.0 (m, 1), 6.5–7.2 (m, 4), 7.20 (s, 5); δ of threo isomer 0.95 (d, J = 7.5 Hz, 3), 2.35 (s, 3), 2.4–2.8 (m, 1), 4.0 (br, 1), 4.1 (d, J = 6.5 Hz, 1), 4.9–5.2 (m, 2), 5.5–5.9 (m, 1), 6.5–7.2 (m, 4), 7.25 (s, 5); MS, m/e (M^+) 251. Anal. ($C_{18}H_{21}HN$) C, H.

***N*-Propyl-2-methyl-1-phenyl-3-butenylamine**: bp 120–125 °C/1 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ of erythro isomer 0.84 (t, J = 7.0 Hz, 3), 0.91 (d, J = 7.5 Hz, 3), 1.12 (br, 1), 1.20–1.60 (m, 2), 2.31 (t, J = 7.0 Hz, 2), 2.10–2.60 (m, 1), 3.50 (d, J = 5.5 Hz, 1), 4.80–5.10 (m, 2), 5.60–6.00 (m, 1), 7.16 (s, 5); δ of threo isomer 0.80 (t, J = 7.0 Hz, 3), 0.89 (d, J = 7.5 Hz, 3), 1.20 (br, 1), 1.20–1.60 (m, 2), 2.26 (t, J = 7.0 Hz, 2), 2.00–2.50 (m, 1), 3.20 (d, J = 7.5 Hz, 1), 4.90–5.10 (m, 2), 5.60–6.00 (m, 1), 7.15 (s, 5); MS, m/e (M^+) 203. Anal. ($C_{14}H_{21}N$) C, H.

***N*-Isopropyl-2-methyl-1-phenyl-3-butenylamine**: bp 120–135 °C/1 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ of erythro isomer 0.92 (d, J = 6.0 Hz, 9), 1.02 (br, 1), 2.2–2.7 (m, 2), 3.59 (d, J = 5.5 Hz, 1), 4.8–5.1 (m, 2), 5.5–5.9 (m, 1), 7.1–7.3 (m, 5); δ of threo isomer 0.74 (d, J = 7.5 Hz, 3), 0.89 (t, J = 6.0 Hz, 6), 1.06 (br, 1), 2.1–2.4 (m, 1), 2.4–2.6 (m, 1), 3.33 (d, J = 8.0 Hz, 1), 4.9–5.2 (m, 2), 5.5–5.9 (m, 1), 7.1–7.3 (m, 5); MS, m/e (M^+) 203. Anal. ($C_{14}H_{21}N$) C, H.

***N*-Propyl-3-methyl-1-hepten-4-ylamine**: bp 150–155 °C/15 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ 0.74 (s, 1), 0.8–1.1 (m, 9), 1,2–1.6 (m, 6), 2.2–2.4 (m, 1), 2.4–2.6 (m, 3), 4.9–5.1 (m, 2), 5.6–6.0 (m, 1) (discrimination of both isomers with ^{1}H NMR was difficult); ^{13}C NMR ($CDCl_3$) δ of erythro isomer 11.63, 14.10, 15.15, 19.62, 23.37, 33.34, 39.81, 49.56, 61.53, 113.92, 141.74; δ of threo isomer 11.63, 14.18, 15.35, 19.05, 23.32, 33.21, 40.48, 49.73, 61.43, 114.14, 142.08; MS, m/e (M^+) 169. Anal. ($C_{11}H_{23}N$) C, H.

***N*-Isopropyl-3-methyl-1-hepten-4-ylamine**: bp 150–155 °C/15 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ 0.56 (br, 1), 0.8–1.0 (m, 12), 1.1–1.4 (m, 4), 2.2–2.5 (m, 2), 2.84 (sp, J = 6.5 Hz, 1), 4.8–5.1 (m, 2), 5.5–6.0 (m, 1); ^{13}C NMR ($CDCl_3$) δ of erythro isomer 14.13, 15.73, 19.64, 23.21, 23.60, 33.85, 40.37, 45.81, 58.76, 114, 16, 141.63; MS, m/e (M^+) 169. Anal. ($C_{11}H_{23}N$) C, H.

***N*-Propyl-2,4-dimethyl-5-hexen-3-ylamine**: bp 150–155 °C/15 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ of erythro isomer 0.52 (s, 1), 0.8–1.1 (m, 12), 1.2–1.6 (m, 2), 1.6–1.9 (m, 1), 2.01 (t, J = 5.5 Hz, 1), 2.1–2.5 (m, 1), 2.58 (t, J = 6.5 Hz, 2), 4.8–5.1 (m, 2), 5.6–6.0 (m, 1); δ of threo isomer 0.52 (s, 1), 0.8–1.1 (m, 12), 1.2–1.6 (m, 2), 1.6–1.8 (m, 1), 1.93 (t, J = 5.5 Hz, 1), 2.1–2.4 (m, 1), 2.53 (t, J = 7.0 Hz, 2), 4.8–5.1 (m, 2), 5.6–6.0 (m, 1); ^{13}C NMR ($CDCl_3$) δ of erythro isomer 11.72, 15.41, 17.75, 20.83, 23.77, 30.61, 40.95, 53.42, 67.66, 113.00, 143.43; δ of threo isomer 11.72, 17.97, 18.07, 20.52, 23.71, 30.73, 40.78, 53.42, 67.99, 114.01, 142.09; MS, m/e (M^+) 169. Anal. ($C_{11}H_{23}N$) C, H.

***N*-Isopropyl-2,4-dimethyl-5-hexen-3-ylamine**: bp 150–155 °C/15 mmHg (Kugelrohr); ^{1}H NMR (CCl_4) δ 0.44 (br, 1), 0.8–1.1 (m, 15), 1.5–1.9 (m, 1), 2.0–2.4 (m, 2), 2.78 (sp, J = 6.0 Hz, 1), 4.9–5.1 (m, 2), 5.6–6.1 (m, 1); ^{13}C NMR ($CDCl_3$) δ of erythro isomer 14.14, 17.64, 18.42, 21.08, 23.68, 32.94, 41.44, 47.98, 64.11, 112.88, 143.60; δ of threo isomer 16.00, 18.11, 18.19, 23.36, 23.57, 30.89, 41.13, 48.13, 64.56, 113.79, 142.25; MS, m/e (M^+) 169. Anal. ($C_{11}H_{23}N$) C, H.

Structure Determination of 5 and 6. Aminomercuration. The aminomercuration of homoallylamines (**5** and **6**) was carried

(14) For the reaction of allenic organometallic compounds with imines, see: Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1004.

(15) (a) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82. (b) Castello, J. A.; Goldmacher, J. E.; Barton, L. A.; Kane, J. S. *J. Org. Chem.* **1968**, *33*, 3501.

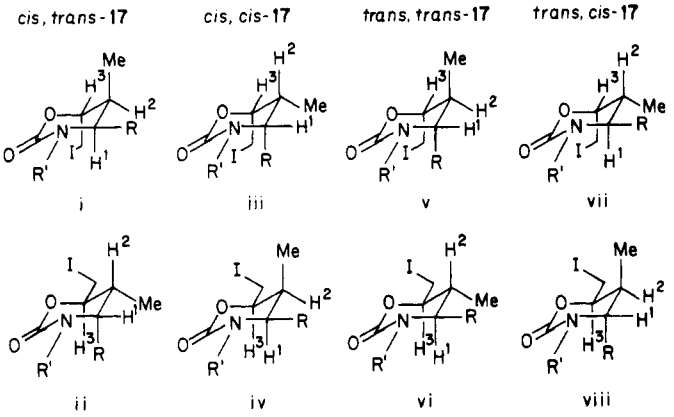
(16) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.

(17) Karasch, M. S.; Richlin, I.; Mayo, F. R. *J. Am. Chem. Soc.* **1940**, *62*, 494.

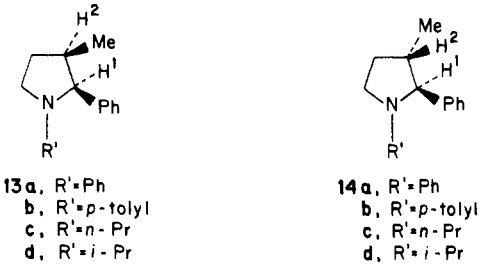
Table III. Selected NMR Data of 13 and 14

	$J_{H^1-H^2}$, Hz	δ_{H^1}	δ_{Me}
13a	8	4.52	0.68
14a	4	4.12	1.11
13b	8	4.55	0.70
14b	4	4.16	1.15
13c	8	3.36	0.51
14c	8	2.66	0.92
13d	8	3.77	0.49
14d	6.5	3.00	0.84

Chart I. Possible Conformations of 17



out according to the reported procedure.[18] The cis pyrrolidine (**13**) was obtained from **5**, while the trans isomer (**14**) was obtained



from **6**. The vicinal coupling constant of various five-membered ring compounds is in the range of 0–11 Hz for the trans isomer and of 4.5–10 Hz for the cis isomer.[19] Therefore, generally speaking, the stereochemistry of five-membered ring compounds cannot be definitely determined by the coupling constant. However, the methyl protons of **13** must be shielded by the phenyl group, and H^1 of **14** must be shielded by the methyl group. Actually, as indicated in Table III, the methyl protons of **13** and H^1 of **14** appeared at higher field than those of **14** and H^1 of **13**, respectively. Although we could determine the structures of certain amines via the aminomercuration reaction, this method was limited to the phenyl-substituted compounds (entries 1–10 of Table I).

Structure Determination of 5 and 6. Iodolactonization.[20] The homoallylamines were treated with benzyl chloroformate (1.1 equiv) in aqueous Na_2CO_3 solution at room temperature. The mixture was stirred for 10 h. The usual workup gave the carbamates (**15** and **16**) in nearly quantitative yield except **5a** and **6a**, in which the conversion was only 30%. To a solution of the carbamate dissolved in CH_2Cl_2 were added 3 equiv of I_2 at room temperature, and the mixture was stirred for 24 h. The reaction was quenched with aqueous sodium hyposulfate solution. The usual workup, followed by filtration through the short column of silica gel ($CHCl_3$ as an eluent) to separate benzyl iodide, gave the cyclic iodocarbamate **17** (Scheme IV). The yield of **17** from

(18) Perie, J. J.; Laval, J. P.; Roussel, J.; Lattes, A. *Tetrahedron* **1972**, *28*, 675.
(19) Gaudemer, A. "Stereochemistry, Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol 1, p 44.
(20) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465.

Table IV. Selected Coupling Constants of 17 (Hz)

		from 5		from 6	
		cis,trans-**17**	*cis,cis*-**17**	*trans,trans*-**17**	*trans,cis*-**17**
a	$J_{H^1-H^2}$			*a*	2
	$J_{H^2-H^3}$				2.3
c	$J_{H^1-H^2}$	5.49	*a*	*a*	6
	$J_{H^2-H^3}$	10.38			1.8
e	$J_{H^1-H^2}$	3.85	*b*	*a*	*b*
	$J_{H^2-H^3}$	10.38			
f	$J_{H^1-H^2}$	4.64	*a*	*a*	*a*
	$J_{H^2-H^3}$	10.50			
g	$J_{H^1-H^2}$	4.27	4.88	*a*	10.01
	$J_{H^2-H^3}$	10.68	1.83		2.93
h	$J_{H^1-H^2}$	3.97	*a*	*a*	1.25
	$J_{H^2-H^3}$	10.68			3.00

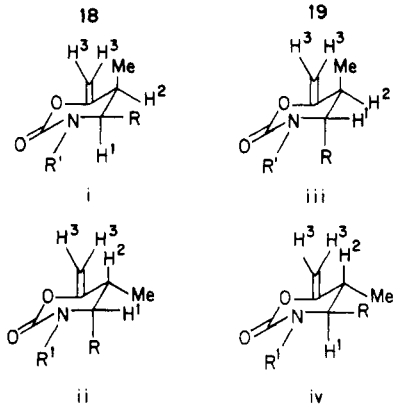
[a] This isomer was not produced. [b] The coupling constant was not clear.

Table V. Selected Coupling Constants of 18 and 19 (Hz)

	18		19	
	$J_{H^1-H^2}$	$J_{H^2-H^3}$	$H_{H^1-H^2}$	$J_{H^2-H^3}$
a			3.5	0
c	6.0	1.8	3.0	0
e	4.0	2.0	*a*	0
f	4.7	1.8		
g	4.0	2.0	*a*	0
h	5.0	1.8	1.5	0

[a] The coupling constant was not clear.

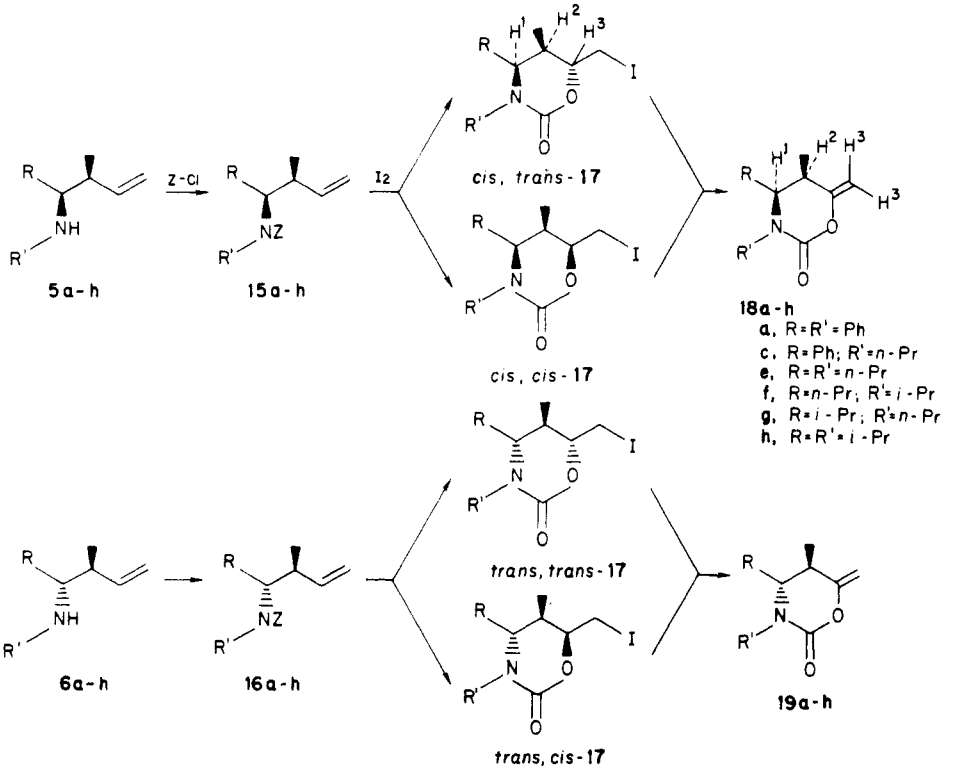
Chart II. Possible Conformations of 18 and 19



5 and **6** was in the range of 64–83%. There is a possibility that the iodolactonization produces totally four diastereomers as indicated in Scheme IV. Fortunately, however, *trans,cis*-**17** was formed as a single product from **6**, and *cis,trans*-**17** was produced either exclusively or predominantly from **5**. Since **17** presumably takes chair conformation, the vicinal coupling constant ($^3J_{H-H}$) should be 0–6 Hz for the eq–eq or eq–ax protons and 8–16 Hz for the ax–ax protons.[19] If both $^3J_{H^1-H^2}$ and $^3J_{H^2-H^3}$ exhibit the coupling constant for ax–ax protons, the compound corresponds to vi in Chart I. However, as indicated in Table IV, such isomer could not be detected. If $^3J_{H^2-H^3}$ exhibits the ax–ax coupling constant, it corresponds to ii. Actually, the major isomer obtained from **5** showed such a coupling constant (Table IV); the *cis,trans*-**17** takes the conformation of ii rather than that of i. Therefore, the minor isomer from **5** can be attributed to *cis,cis*-**17** (conformation iv). Among 8 possible conformations, iii and v may be eliminated due to the presence of 1,3-diaxial substituents. Consequently, the single isomer from **6** must be *trans,cis*-**17**. The stereochemistry of **5a** and **5c** determined by the iodolactonization was in agreement with the stereochemistry by the aminomercuration, and hence the iodolactonization of **5b** and **5d** was not carried out.

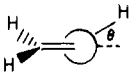
Structure Determination. Dehydroiodination of 17. To further confirm the stereochemistry of **17**, the dehydroiodination with 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) was carried out

Scheme IV. Determination of Stereochemistry[a]



[a] Z = CO_2CH_2Ph.

according to the reported procedure.[21] To a solution of **17** dissolved in dry benzene was added 2 equiv of DBU. The mixture was refluxed for 24 h, and the reaction was monitored by TLC ($CHCl_3$). The solvent was removed under reduced pressure, and the residue was purified by the short column of silica gel (ether:hexane = 1:1). Under these conditions, **18** and **19** were obtained in 60–72% yield and **17** was recovered in 20–30% yield. The selected coupling constants of **18** and **19** are summarized in Table V. It is known that the allyl type long-range coupling constant ($^4J_{H-H}$) is about 0 Hz for dihedral angle $\theta = \sim 0°$ and 1–2 Hz for $\theta = \sim 90°$.[19] (see A). Among four possible conformations in Chart



A

II, iv can be eliminated because of lack of the ax–ax coupling in **19** (Table V). The long-range coupling constant (1.5–2.0 Hz) corresponds to ii, and the zero coupling corresponds to iii.

Reactions of 9 with 3. **9** was prepared in a similar manner as described previously.[22] The reaction was carried out as described above. The homoallylamine was obtained in nearly quantitative yield, except entry 3. Products were purified by column chromatography on silica gel.

***N*-Phenyl-2-methyl-1-phenyl-3-pentenylamine (12a)**: bp 140–145 °C/0.1 mmHg (Kugelrohr); ^1H NMR (CCl_4) δ 0.83 (d, J = 7.5 Hz, 3), 1.56 (dd, J = 1, and 5 Hz, 3), 2.5–2.9 (m, 1), 3.88 (dd, J = 8 and 2 Hz, 1), 4.10 (br, 1), 5.0–6.0 (m, 2), 6.3–6.7 (m, 3), 6.9–7.1 (m, 2), 7.1–7.6 (m, 5); IR (CCl_4) 680, 1260, 1310, 1420, 1445, 1490, 1590, 2865, 3020, 3385 cm^{-1}; MS, m/e (M^+) 251. Anal. ($C_{18}H_{21}N$) C, H. The erythro isomer could not be isolated in pure form, but the aminomercuration indicated the presence of the isomer as mentioned later.

***N*-Propyl-2-methyl-1-phenyl-3-pentenylamine (11c)**: bp 130 °C/1 mmHg (Kugelrohr); ^1H NMR (CCl_4) δ 0.85 (t, J = 8 Hz, 3), 0.93 (d, J = 7.5 Hz, 3), 1.13 (br, 1), 1.1–1.6 (m, 2), 1.48 (dd, J = 1 and 6.5 Hz, 3), 2.2–2.5 (m, 2), 2.6–2.9 (m, 1), 3.46 (d, J = 6 Hz, 1), 5.0–5.5 (m, 2), 7.25 (s, 5); IR (CCl_4) 1600, 3390 cm^{-1}; MS, m/e (M^+) 217. Anal. ($C_{15}H_{23}N$) C, H.

***N*-Isopropyl-5-methyl-6-octen-4-ylamine (11f)**: bp 160–165 °C/15 mmHg (Kugelrohr); ^1H NMR (CCl_4) δ 0.43 (br, 1), 0.8–1.1 (m, 12);, 1.1–1.6 (m, 4), 1.59 (d, J = 5.5 Hz, 3), 2.1–3.0 (m, 3), 5.1–5.6 (m, 2); IR (CCl_4) 3400 cm^{-1}; MS, m/e (M^+) 183. Anal. ($C_{12}H_{25}N$) C, H. The double bond geometry of the above three products was determined by irradiation of the CH and CH_3 bonded to the double bond; $^3J_{H-H}$ = 10–11 Hz. Further, the absence of 960 cm^{-1} in the IR spectra indicated the cis geometry.

***N*-Propyl-2,4-dimethyl-5-hepten-3-ylamine (11g and 12g)**: bp 160–165 °C/15 mmHg (Kugelrohr); ^1H NMR (400 MHz,[23] $CDCl_3$) δ of erythro-cis isomer 0.831 (d, J = 6.714 Hz, 3), 0.917 (t, J = 7.324 Hz, 3), 0.934 (d, J = 6.714 Hz, 3), 0.983 (d, J = 6.714 Hz, 3), 1.1 (br, 1), 1.42–1.52 (m, 2), 1.613 (dd, J = 1.641 and 6.714 Hz, 3), 1.73–1.84 (m, 1), 1.991 (dd, J = 3.968 and 7.314 Hz, 1), 2.51–2.64 (m, 3), 5.252 (qdd, J = 1.641, 10.07, and 10.37 Hz, 1), 5.361 (m, 1); δ of threo isomer 0.8–1.1 (m, 13), 1.46–1.56 (m, 2), 1.642 (dd, J = 1.526 and 6.714 Hz, 3), 1.8 (m, 1), 2.1 (m, 1), 2.5–2.7 (m, 3), 5.363 (qdd, J = 1.526, 9.76, 10.99 Hz, 1), 5.469 (qd, J = 6.714 and 10.98 Hz, 1); IR (CCl_4) 3400 cm^{-1}; MS, m/e (M^+) 183. Anal. ($C_{12}H_{25}N$) C, H. The retention time of **12** in GLPC (PEG 6000, 5%, 2 m) was shorter than that of **11**.

Structure Determination of 11 and 12. The stereochemistry of **12a** was determined by aminomercuation (48 h). **3,5-Dimethyl-1,2-diphenylpyrrolidine** was obtained in 70% yield: bp 140–145 °C/0.1 mmHg (Kugelrohr); ^1H NMR (CCl_4) δ 1.12 (d, J = 6.5 Hz, 3), 1.49 (d, J = 7 Hz, 3), 1.7–1.9 (m, 2), 2.1–2.3 (m, 1), 3.5–4.0 (m, 1), 4.09 (d, J = 7.5 Hz, 1), 6.4–6.8 (m, 3), 7.0–7.6 (m, 7); MS, m/e (M^+) 251. The chemical shift (1.12) of the methyl protons clearly indicates the trans geometry (cf. Table III). A small peak (d, J = 7 Hz) at 0.70 ppm was also observed, which was ascribed to the *cis*-pyrrolidine. Diastereomer ratio was determined by comparison of the peak height. The stereochemistry of **11c** was determined by the iodolactonization.

6-(α-Iodoethyl)-5-methyl-4-phenyl-3-propylperhydro-1,3-oxazine-2-one was produced in 67% yield from **11c**: mp 115–116

(21) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114.

(22) Yatagai, H.; Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 4548.

(23) Unless otherwise indicated a 100-MHz NMR instrument was used.

°C (colorless prism); ^{1}H NMR (CCl_4) δ 0.72 (d, J = 7.5 Hz, 3), 0.93 (t, J = 7 Hz, 3), 1.3–1.8 (m, 2), 2.05 (d, J = 7.5 Hz, 3), 2.38 (qdd, J = 7.5, 5, and 10 Hz, 1 H at C-5), 2.5–2.9 (m, 1), 2.99 (dd, J = 1.5 and 10 Hz, 1 H at C-6), 3.1–3.7 (m, 1), 4.16 (qd, J = 7.5 and 1.5 Hz, 1), 4.51 (d, J = 5 Hz, 1 H at C-4), 7.2–7.5 (m, 5); $^3J_{H^4-H^5}$ = 5 Hz and $^3J_{H^5-H^6}$ = 10 Hz indicate the cis,trans form (cf. Table IV); MS, m/e (M$^+$) 387. The stereochemistry of **11f** was not able to be determined by the iodolactonization.

6-(α-Iodoethyl)-3-isopropyl-5-methyl-4-propylperhydro-1,3-oxazin-2-one was produced in 70% yield; ^{1}H (400 MHz, $CDCl_3$) δ 0.964 (t, J = 7.019 Hz, 3), 0.984 (d, J = 6.714 Hz, 3), 1.264 (d, J = 6.714 Hz, 3), 1.309 (d, J = 6.713 Hz, 3), 1.2–1.7 (m, 4), 2.073 (d, J = 7.019 Hz, 3), 3.07–3.13 (m, 3), 4.013 (sp, J = 6.714 Hz, 1), 4.264 (q, J = 7.019 Hz, 1); MS, m/e (M$^+$) 353.

The dehydroiodination produced **6-ethylidene-3-isopropyl-5-methyl-4-propylperhydro-1,3-oxazin-2-one** in 75% yield: ^{1}H NMR (CCl_4) δ 0.92 (br, 3), 1.09 (d, J = 7 Hz, 3), 1,26 (d, J = 7.5 Hz, 3), 1.29 (d, J = 7.5 Hz, 3), 1.1–1.5 (m, 4), 1.66 (dd, J = 2.0 and 7.5 Hz, 3), 2.4–2.7 (m, 1), 3.0–3.2 (m, 1), 3.82 (sp, J = 7.5 Hz, 1), 4.46 (qd, J = 7.5 and 2.0 Hz, 1 H at the sp^2 carbon); the long-range coupling constant (J = 2 Hz) indicates the cis geometry (cf. Table V); MS, m/e (M$^+$) 225. The stereochemistry of **11g** was determined by the iodolactonization.

6-(α-Iodoethyl)-4-isopropyl-5-methyl-3-propylperhydro-1,3-oxazin-2-one was produced in 65% yield: mp 68.5–6.95 °C (colorless plate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.932 (t, J = 7.325 Hz, 3), 0.960 (d, J = 7.019 Hz, 3), 1.000 (d, J = 7.019 Hz, 3), 1.104 (d, J = 7.104 Hz, 3), 1.6–1.7 (m, 2), 1.9–2.1 (m, 1), 2.069 (d, J = 7.019 Hz, 3), 2.17–2.25 (, 1), 2.688 (m, 1), 3.053 (t, J = 4.273 Hz, 1), 3.022 (dd, J = 6.304 and 7.524 Hz, 1 H at C-4), 3.0921 (dd, J = 1.526 and 10.681 Hz, 1 H at C-6), 4.253 (qd, J = 7.019 and 1.526 Hz, 1); $^3J_{H^5-H^6}$ = 10.681 and $^3J_{H^4-H^5}$ = 6.304 or 7.524 indicate the cis,trans isomer; MS, m/e (M$^+$) 353. Consequently, the structure of the minor isomer **12g** was determined to be threo.

Supplementary Material Available: Spectroscopic data for **13**, **14**, **15**, **16**, **17**, **18**, and **19** (8 pages). Ordering information is given on any current masthead page.

A Regioselective Route to Gossypol Analogues: The Synthesis of Gossypol and 5,5′-Didesisopropyl-5,5′-diethylgossypol

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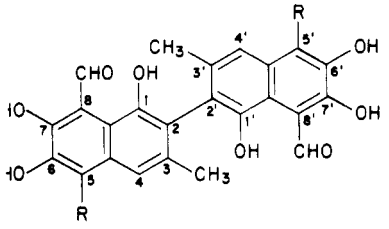
Received December 7, 1984

The synthesis of 5,5′-diethyl-1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-[2,2′-binaphthalene]-8,8′-dicarboxaldehyde is described. The synthetic route developed utilizes the regioselective bisformylation of a precursor obtained from gossypol. The route provides access to 5,5′-disubstituted gossypol analogues as well as completing a total synthesis of gossypol itself.

The search for a male antifertility agent has been hampered by the absence of a lead compound. Consequently, the 1978 Chinese report[1] that the cotton seed pigment gossypol (1) was an effective male antifertility agent



1, R = CH(CH$_3$)$_2$
2, R = CH$_2$CH$_3$

spawned enormous interest. We initiated a program designed to explore the molecular determinants of biological activity of gossypol. In the course of these studies we learned that minor molecular manipulation of the phenolic and aldehydic groups led to substantial loss of in vivo activity. However, the role of the isopropyl moieties in biological activity was unexplored. Herein we describe a synthesis of the diethyl analogue of gossypol, 5,5′-didesisopropyl-5,5′-diethylgossypol (2).

The structure of gossypol had been formulated by Adams et al.[6] as early as 1938. The first conclusive proof by total synthesis was presented 20 years later by Edwards.[2] Venuti,[3] in 1981, published a synthesis of a precursor to gossypol and relied on the earlier work for formal completion of his synthesis. In none of the above reports, however, were details of the introduction of the 8,8′-formyl groups presented. We now also describe a means of obtaining gossypol from apogossypol (3).

The synthetic route reported here is expected to be of general applicability in regard to the introduction of functionality in the 5,5′-positions.

We chose to approach the synthesis of 5,5′-didesisopropyl-5,5′-diethylgossypol (2) by manipulation of a biphenyl precursor available from gossypol itself (Scheme I). Thus gossypol[4] (1) was treated with base to provide apogossypol (3), which was readily methylated to furnish the hexamethyl ether 4.[5-8] Didesisopropylapogossypol hexamethyl ether 5 was subsequently obtained on acid treatment of 4.[9] The known compounds 4 and 5 served as starting materials for our synthesis.

It was necessary to introduce the ethyl group in the

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