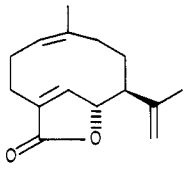
erization of 1 to yield pyroaristolactone (4). We have also demonstrated the value of ^{13}C NMR in readily determining the configuration of trisubstituted double bonds present in germacranolides. To emphasize this point, we have recorded in Table II the spectrum of one of our synthetic germacranolides (5)[2] referred to earlier, which was previ-



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ously reported to have a *cis*-1,10 double bond, and as expected the C-14 methyl resonance has a chemical shift greater than 20 ppm, specifically 23.2 ppm.

Experimental Section

IR spectra were obtained on a Beckman Acculab 6 spectrophotometer with chloroform as the solvent. ^1H and ^{13}C NMR spectra were recorded on a Bruker WH400 spectrometer with Me_4Si as an internal standard (δ 0.00) and deuteriochloroform as the solvent. The ^{13}C spectra were obtained in both the broad-band and off-resonance decoupled modes. Optical rotations were performed in chloroform solution by using a Bendix-NPL automatic polarimeter, Type 143, and UV spectra were recorded on a Beckman Model 24 spectrometer with 95% ethanol as the solvent. Melting points were determined on a Gallenkamp apparatus and are uncorrected. TLC analyses and separations were done with Fisher Redi-plate silica gel GF analytical plates (250 μm) or Analtech Uniplate silica gel GF preparative plates (1000 μm) with the solvent indicated. Accurate mass determinations were performed on a VG Micromass 7070F spectrometer. The aristolactone (1) used in these experiments was isolated from Virginia snake root (supplied by Indiana Botanicals, Hammond, IN) by using a previously reported procedure.[3]

Isoaristolactone (3). A procedure similar to one of those previously reported was followed.[4] To a solution of 143 mg (616 mmol) of aristolactone (1) in 8 mL of absolute ethanol was added 10 mL of 20% sulfuric acid in aqueous ethanol (1:1). The solution was stirred at room temperature under nitrogen for 6 h and then diluted with ether (100 mL). The ether phase was washed with saturated $NaHCO_3$ solution (3×) and with saturated NaCl solution (1×) and dried (anhydrous $MgSO_4$). The solvent was removed at reduced pressure, and the crude product was purified by preparative TLC (15% ethyl acetate/petroleum ether, R_f 0.43) to yield 98 mg (68%) of 3 as an oil: IR 3040, 2920, 2860, 1760, 1650, 910 cm^{-1}; NMR, see Tables I and II; $[\alpha]^{25}_D$ −37° (19 mg/mL) (lit.[4] $[\alpha]^{20}_D$ −42°).

Pyroaristolactone (4). A solution of 130 mg (560 mmol) of 1 in 3 mL of freshly distilled decane was heated to reflux under nitrogen for 10 h. The decane was removed in a Kugelrohr apparatus (70 °C, 20 torr), and the crude product was purified by preparative TLC (20% ethyl acetate/petroleum ether, R_f 0.48) to yield 54 mg (42%) of crystalline 4: mp 54–55 °C; IR 2960, 2930, 2860, 1755, 1650, 910 cm^{-1}; NMR, see Tables I and II; $[\alpha]^{25}_D$ −40° (12 mg/mL); UV λ_{max} = 218 nm (ϵ 6800); MS, Calcd for $C_{15}H_{20}O_2$ (M^+) *m/e* 232.1463, obsd 232.1463.

Attempted Isomerization of 4. To a solution of 19 mg of 4 in 1.2 mL of absolute ethanol was added 1.2 mL of 20% sulfuric acid in aqueous ethanol (1:1), and the solution was stirred under nitrogen for 6 h. The reaction was worked up as described for 3 to yield 19 mg of a product which was shown to be recovered 4 by TLC, IR, and NMR analysis.

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A New Synthesis of 3-Phenyl-1,2-benzisoxazoles: Sterically Constrained 3-Phenyl-1,2-benzisoxazoles by Intramolecular C=N Bond Formation at a Hindered Carbonyl Group

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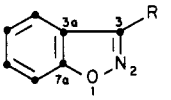
Recent reviews[1,2] list the following three primary ways of approaching the synthesis of 1,2-benzisoxazoles: (1)



formation of the 1–7a bond, represented by the cyclization of *o*-halo- or *o*-nitrobenzoyloximes; (2) formation of the 1–2 bond, represented by the cyclization of *o*-hydroxybenzoyloxime acetates or sulfonates; and (3) simultaneous formation of the 1–7a and 3–3a bonds, represented by the reaction of a benzyne with a nitrile oxide. We have previously reported on the use of the first and second methods in the synthesis of a number of 3-aryl-1,2-benzisoxazoles[3] and now report a new method for their synthesis—formation of the 2–3 bond—represented by the transoximation of 2-[(isopropylideneamino)oxy]benzophenones (Scheme I). This method not only represents a new method of 1,2-benzisoxazole synthesis but is also, in our hands, the only method for synthesizing 3-phenyl-1,2-benzisoxazoles that are substituted at both ortho positions of the 3-phenyl group.

We have been examining a number of the previously reported[3] 3-aryl-1,2-benzisoxazoles by ^{13}C NMR and required 3-(2,6-dimethylphenyl)-1,2-benzisoxazole (**3c**) as a model compound in which the 3-phenyl moiety should be orthogonal to the plane of the 1,2-benzisoxazole.[4] The initial approach to **3c** was along classical lines: it was planned to synthesize 2,6-dimethyl-2′-fluorobenzophenone (**1c**), to convert **1c** into its oxime, and to cyclize the *o*-fluorobenzophenone oxime under basic conditions. Compound **1c** was obtained smoothly by the method of Sato,[5] but it was found to resist oxime formation, presumably because of the sterically crowded environment around the carbonyl group. In other examples of such so-called "lethargic reactions", high pressures, strongly basic catalysts, or prolonged reaction times at room temperature have been recommended,[6,7] but in our case there was a competing reaction that made this approach impractical.

When **1c** was refluxed in pyridine for 48 h in the presence of excess hydroxylamine hydrochloride, **1c** was recovered mostly unchanged (see Experimental Section). The only other product that could be identified from the reaction mixture was the *o*-aminobenzophenone **4** isolated in 12% yield (Scheme II). Compound **4** presumably arises from the corresponding *o*-hydroxyaminobenzophenone,

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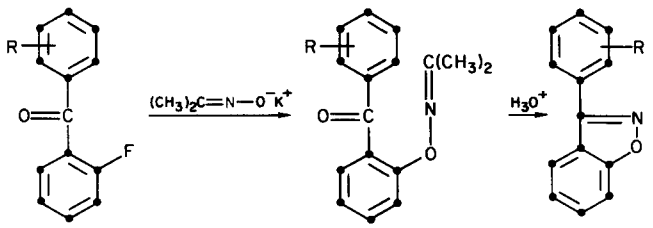
0022-3263/84/1949-0180$01.50/0

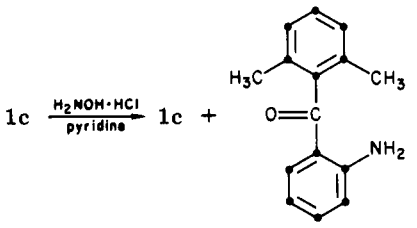
Scheme I[a]



1 2 3

[a] a, R = H; b, R = 2,3-Cl_2-4-OCH_3; c, R = 2,6-$(CH_3)_2$; d, R = 2,6-Cl_2.

Scheme II



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which is subsequently reduced in the presence of excess hydroxylamine. Such a reaction is analogous to the unexpected synthesis of 2,4,6-trinitroaniline (picramide) from picryl chloride and excess hydroxylamine hydrochloride through the intermediacy of the hydroxylamine.[8] Excess hydroxylamine functions as a reducing agent in the synthesis of β-amino-β-phenylpropionic acid[9] and β-amino-β-furylpropionic acid[10] from the corresponding α,β-unsaturated acids, again through the intermediacy of the hydroxylamines. Hydroxylamine *O*-sulfonic acid has been shown to be a source of diimide,[11,12] but the mechanism of reductions with hydroxylamine hydrochloride is largely unexplored.

The isolation of a small amount of **4** from the reaction of **1c** with hydroxylamine suggested a method of circumventing the remarkable lack of reactivity of the carbonyl group of **1c** toward oxime formation. It was reasoned that the fluorine of **1c** is less influenced by steric factors than the carbonyl group and that the oxygen anion of a suitably small oxime would displace the fluorine of **1c** in S_NAr fashion, giving a protected *O*-(2-benzoylphenyl)-hydroxylamine (Scheme I). In an acid-catalyzed reaction that would amount to a transoximation, the 2,3-bond of the desired 1,2-benzisoxazole **3c** could be formed in *intra*molecular fashion.

There was adequate literature precedent for this approach. The alkylation of acetone oxime to give *O*-alkylated derivatives without contamination by N-alkylated products (nitrones) is well documented.[13] Acid-catalyzed hydrolysis of the *O*-alkyl acetone oximes then yields *O*-alkylated hydroxylamines. O-Arylated acetone oximes have been obtained by the reaction of the metal salt of the oxime with activated nitrobenzenes[14] or with fluorobenzenes activated by nitro or trifluoromethyl groups.[15,16]

We have found that the potassium anion of acetone oxime reacts smoothly with 2-fluorobenzophenones in THF or dimethylacetamide to give 2-[(isopropylideneamino)-oxy]benzophenones, which are converted to 3-phenyl-1,2-benzisoxazoles upon acid-catalyzed transoximation.

In preliminary studies leading to the synthesis of **3c**, 2-fluorobenzophenone (**1a**) was converted to 2-[(isopropylideneamino)oxy]benzophenone (**2a**) in 68% yield after reaction with the potassium anion of acetone oxime for 1 h in refluxing tetrahydrofuran. Subsequent transoximation in aqueous, ethanolic hydrochloric acid gave 3-phenyl-1,2-benzisoxazole in an overall yield of 48% for the two steps. By eliminating the purification of **2a**, an overall yield of 65% was achieved.

Although S_NAr reactions proceed much faster at Ar–F bonds than at Ar–Cl bonds,[17] we had previously found that the cyclization of 2-chloro-2′-fluorobenzophenone oximes under basic conditions was not selective. That is to say, mixtures of 3-(2-chlorophenyl)- and 3-(2-fluorophenyl)-1,2-benzisoxazoles were obtained.[3] The new method is highly selective, however, giving 3-(2,3-dichloro-4-methoxyphenyl)-1,2-benzisoxazole (**3b**) in 73% overall yield from 2,3-dichloro-2′-fluoro-4-methoxybenzophenone (**1b**, Scheme I).

The use of *N,N*-dimethylacetamide was evaluated in the reaction of **1b** with the potassium anion of acetone oxime to give **2b**. *N,N*-dimethylacetamide was found not only to give a higher yield for the combined substitution–transoximation reactions (83% compared to 73% for THF) but also to allow the reaction with the anion to proceed rapidly at room temperature (see Experimental Section).

The synthesis of 3-(2,6-dimethylphenyl)-1,2-benzisoxazole (**3c**) and 3-(2,6-dichlorophenyl)-1,2-benzisoxazole (**3d**) in 54% and 70% yields, respectively, from the corresponding 2-fluorobenzophenones **1c** and **1d** demonstrated that the new method was indeed suitable for synthesizing the desired sterically constrained 3-phenyl-1,2-benzisoxazoles. In our hands this method represents the only practical way of using hindered 2-fluorobenzophenones as precursors of such compounds.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye Unicam SP3-200 grating spectrophotometer. Nuclear magnetic resonance spectra were taken on a JEOL C-60HL instrument. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. The mass spectra were obtained from a Finnigan Model 4000 spectrophotometer with an INCOS data system at 70 eV by direct insertion. Thin-layer chromatography (TLC) was performed on precoated glass plates (E. Merck 5.0 × 10.0 cm, silica gel 60, F-254). E. Merck 230–400 mesh silica gel was used for flash chromatography. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

Acetone oxime, 2-bromofluorobenzene, 1-bromo-2,6-dimethylbenzene, 2,6-dichlorobenzaldehyde, 2-fluorobenzoyl chloride, potassium *tert*-butoxide, and pyridinium chlorochromate were used directly as purchased from Aldrich Chemical Co. 2-Fluorobenzophenone (**1a**) was synthesized by the method of Bergmann et al.[18] and had a boiling point of 95–96 °C (0.05 torr) [lit.[18] bp 150 °C (16 torr)]. The synthesis of 2,3-dichloro-2′-fluoro-4-methoxybenzophenone (**1b**) has been reported previously.[3] *n*-Butyllithium in hexane was purchased from Alfa, and magnesium turnings were of 99.98% purity as supplied by Reade

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Manufacturing Co., Inc., in 25-g sealed bags. THF and *N,N*-dimethylacetamide were purchased from Aldrich and dried over freshly activated 3-Å molecular sieves before use.

2,6-Dimethyl-2′-fluorobenzophenone (1c). Magnesium turnings (1.25 g, 50 mmol) were placed in a flame-dried flask under an argon atmosphere. Enough dry THF was added to just cover the magnesium, and then a few drops of 1-bromo-2,6-dimethylbenzene were added from a dropping funnel containing 9.20 g (50 mmol). After about 5 min, the THF became light yellow and the flask was warm to the touch. At this point additional THF (50 mL) was added to the reaction flask, stirring was begun, and the remaining 1-bromo-2,6-dimethylbenzene was added at a rate so that an internal temperature of ca. 50 °C was maintained. Stirring was continued for 1.5 h after the addition was complete, and then the solution was titrated according to the method of Gilman[19] and determined to be 0.96 M.

To a solution of 2-fluorobenzoyl chloride (6.43 g, 40 mmol) in dry THF (100 mL) at −75 °C under an argon atmosphere was added 42 mL (40 mmol) of the Grignard solution. The reaction was allowed to come to room temperature overnight, and then distributed between ether and saturated aqueous ammonium chloride. The organic phase was separated, dried ($MgSO_4$), and evaporated to give an amorphous solid that was recrystallized from pentane to give 5.85 g (64%) of **1c**, mp 63–65 °C. An additional quantity of **1c** was obtained by flash chromatography of the pentane mother liquors (20% ethyl acetate–hexane). The appropriate fractions were evaporated and the residue triturated with a little cold pentane and filtered to give an additional 1.88 g (21%) of **1c**, mp 64–65 °C. The analytical sample was recrystallized once more from pentane and melted at 63–64 °C; IR ($CHCl_3$) 1670 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.16 (6 H, s, CH_3), 7.00–8.00 (7 H, m, Ar H); MS(EI), *m/e* (relative intensity) 228 (M^+, 93), 227 (M^+ − H, 100), 133 (2,6-dimethylbenzoyl, 51), 123 (2-fluorobenzoyl, 84). Anal. Calcd. for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 79.07; H, 5.77.

2,6-Dichloro-2′-fluorobenzophenone (1d). A solution of 2-bromofluorobenzene (5.83 g, 33.3 mmol) in dry THF (50 mL) was chilled in a dry ice–acetone bath to an internal temperature of −75 °C. A solution of *n*-butyllithium in hexane (26 mL of a 1.44 M solution, 37.4 mmol) was added dropwise so that the internal temperature of the reaction did not exceed −60 °C. After the addition was complete, the reaction mixture was allowed to stir at −75 °C for 15 min and then 5.8 g (33.3 mmol) of 2,6-dichlorobenzaldehyde in THF (20 mL) was added. After an additional 10 min, the reaction mixture was distributed between ether and saturated aqueous ammonium chloride. The organic layer was separated, dried, and concentrated under reduced pressure.

The resulting oil was purified by flash chromatography (5% ethyl acetate–hexane), and the fractions containing the major component were evaporated. This oil (6.21 g) was dissolved in CH_2Cl_2 (20 mL) and added to a suspension of pyridinium chlorochromate (7.2 g, 33 mmol) in CH_2Cl_2 (50 mL). After being stirred for 2.5 h, the reaction mixture was poured into ether (200 mL) and then this solution was passed through a pad of Florisil. The walls of the reaction flask and the Florisil pad were washed with additional ether (300 mL), and then the combined organic phases were concentrated under reduced pressure.

The resulting thick oil crystallized rapidly and was triturated with a little hexane to give 3.80 g (42%) of **1d** as a colorless solid, mp 85–86 °C. The analytical sample was recrystallized from hexane; mp 86–87 °C; IR ($CHCl_3$) 1680 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.00–8.20 (m, Ar H); MS(EI), *m/e* (relative intensity) 270 (M^+, ^{37}Cl, 50), 268 (M^+, 75), 175 (2,6-dichlorobenzoyl, ^{37}Cl, 58), 173 (2,6-dichlorobenzoyl, 80), 123 (2-fluorobenzoyl, 100). Anal. Calcd. for $C_{13}H_7Cl_2FO$: C, 58.02; H, 2.62. Found: C, 57.93; H, 2.65.

Reaction of 1c with Hydroxylamine Hydrochloride. A solution of **1c** (3.0 g, 13.3 mmol) and hydroxylamine hydrochloride (3.5 g, 50 mmol) was refluxed overnight in pyridine (50 mL). After 16 h additional $H_2NOH{\cdot}HCl$ (3.5 g) was added and reflux was continued. After a total of 40 h the pyridine was evaporated and the residue distributed between CH_2Cl_2 and 5% HCl. The organic phase was separated, dried ($MgSO_4$), and evaporated, and the resulting oil was purified by flash chromatography (20% EtOAc–hexane). Unreacted **1c** was the first material to elute from the column, amounting to 2.05 g (68% recovery) after the appropriate fractions were combined and the solvents removed. The recovered **1c** had a melting point of 62–64 °C without recrystallization and was identical with authentic **1c** by IR, MS, and NMR.

Following shortly after the unreacted **1c** was a product that was shown to be 2′-amino-2,6-dimethylbenzophenone (**4**): 0.36 g (12%); mp 121–122 °C after recrystallization from MeOH; IR ($CHCl_3$) 3500, 3350 (NH_2, asymmetrical and symmetrical N–H stretch), 1620 (C=O, vinylogous amide) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (6 H, s, CH_3), 6.36–6.90 (4 H, m, 3′-Ar H, 5′-Ar H and NH_2, 7.05–7.50 (5 H, m, Ar H); MS(EI), *m/e* (relative intensity) 225 (M^+, 100). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.96; H, 6.84; N, 6.08.

2-[(Isopropylideneamino)oxy]benzophenone (2a). Potassium *tert*-butoxide (1.23 g, 11 mmol) was added to a solution of acetone oxime (0.80 g, 11 mmol) in dry THF (15 mL). After stirring for 1 h, 2-fluorobenzophenone (**1a**, 2.0 g, 10 mmol) in THF (10 mL) was added, and the reaction was brought to reflux. After refluxing for 3 h, TLC showed that starting material had been consumed. The reaction mixture was cooled and distributed between ether and saturated aqueous ammonium chloride solution, after which the organic layer was separated, dried ($MgSO_4$), and evaporated. A thick oil was obtained, which crystallized rapidly and was recrystallized from hexane to give 1.71 g (68%) of **2a**: mp 77–79 °C; IR ($CHCl_3$) 1660 (C=O), 1600 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 1.40 (3 H, s, CH_3), 1.84 (3 H, s, CH_3), 7.00–7.65 (7 H, m, Ar H), 7.72–7.96 (2 H, m, *o*-Ar H); MS(EI), *m/e* (relative intensity) 253 (M^+, 3), 197 ($M^+ - (CH_3)_2C{=}N$, 4), 56 ($(CH_3)_2C{=}N^+$, 100). Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.20; H, 6.19; N, 5.54.

3-Phenyl-1,2-benzisoxazole (3a). To a solution prepared from 10 mL of 5% HCl and 10 mL of EtOH was added **2a** (0.51 g, 2.0 mmol). The reaction mixture was then refluxed for 1 h, at which time TLC showed no more starting material. The mixture was distributed between ether and water, and the organic phase was separated, dried ($MgSO_4$), and evaporated. The resulting amorphous material was crystallized from hexane to give 0.27 g (70%) of **3a**: mp 80–82 °C (lit.[20] mp 83–84 °C); IR ($CHCl_3$) 1610 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 7.10–7.95 (m, Ar H); MS(EI), *m/e* (relative intensity) 195 (M^+, 71), 167 (M^+ − CO, 50).

The above two steps were combined by taking the crude **2a** before recrystallization and reacting it in the EtOH–HCl mixture. In this way, 1.27 g (65%) of **3a** were obtained from 2.0 g (10 mmol) of **1a**, mp 80–82 °C.

3-(2,3-Dichloro-4-methoxyphenyl)-1,2-benzisoxazole (3b) from 1b. The potassium anion of acetone oxime (11 mmol) and 2,3-dichloro-2′-fluoro-4-methoxybenzophenone (**1b**, 3.0 g, 10 mmol) were reacted in THF, and the crude product was refluxed in 1:1 EtOH–5% HCl (150 mL) as for the sequence **1a** → **3a**. Purification by flash chromatography (CH_2Cl_2) and recrystallization from hexane gave 2.15 g (73%) of **3b** that melted at 144 °C, resolidified, and melted again at 151–153 °C; IR ($CHCl_3$) 1600 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 4.04 (3 H, s, OCH_3), 7.04 (1 H, d, J = 9 Hz, 5′-Ar H), 7.30–7.72 (5 H, m, Ar H, including d due to 6′-Ar H at 7.54, J = 9 Hz); MS(EI), *m/e* (relative intensity) 295 (M^+, ^{37}Cl, 59), 293 (M^+, 100), 267 (M^+ − CO, ^{37}Cl, 13), 265 (M^+ − CO, 30). Anal. Calcd for $C_{14}H_9Cl_2NO_2$: C, 57.16; H, 3.08; N, 4.76. Found: C, 57.09; N, 2.88; N, 4.74.

General Procedure for Reactions in *N,N*-Dimethylacetamide. Potassium *tert*-butoxide (1.23 g, 11 mmol) was added to a solution of acetone oxime (0.80 g, 11 mmol) in *N,N*-dimethylacetamide (30 mL). After stirring for 15 min, the *o*-fluorobenzophenone (10 mmol) was added in *N,N*-dimethylacetamide (15 mL). When TLC showed that the starting material had been consumed (30–45 min), the reaction mixture was distributed between ether and water and the organic phase was separated and evaporated. The resulting residue was refluxed for 2 h in 1:1 EtOH–5% HCl (150–200 mL), and then the reaction was allowed to cool. If the product did not crystallize, the reaction

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mixture was distributed between ether and water and then the organic phase was separated, dried ($MgSO_4$), and evaporated. The crude products were then purified by flash chromatography (20% EtOAc–hexane) and recrystallized from hexane or pentane.

3b: 83% from **1b**, crystallized directly from 1:1 EtOH–5% HCl; mp 143–144 °C; TLC, IR, NMR, and MS identical with those of **3b** isolated by the THF method. After recrystallization from hexane it exhibited the same melting behavior as in the THF method, melting at 144 °C, resolidifying, and melting again at 151–152 °C.

3c: 54% from **1c** (flash chromatography); mp 83–84 °C; IR ($CHCl_3$) 1600 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 2.14 (6 H, s, CH_3), 7.20–7.85 (7 H, m, Ar H); MS(EI), *m/e* (relative intensity) 223 (M^+, 100), 222 ($M^+ - H$, 62). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 81.09; H, 6.20; N, 6.25.

3d: 70% from **1d** (flash chromatography); mp 92–93 °C; IR ($CHCl_3$) 1610 (C=N), cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.75 (m, Ar H); MS(EI), *m/e* (relative intensity) 265 (M^+, ^{37}Cl, 63), 263 (M^+, 100), 237 ($M^+ - CO$, ^{37}Cl, 50), 235 ($M^+ - CO$, 78). Anal. Calcd for $C_{13}H_7Cl_2NO$: C, 59.11; H, 2.67; N, 5.30. Found: C, 58.96; H, 2.65; N, 5.26.

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Registry No. **1a**, 342-24-5; **1b**, 72498-53-4; **1c**, 87828-87-3; **1d**, 87828-88-4; **2a**, 87828-89-5; **3a**, 7007-67-2; **3b**, 87828-90-8; **3c**, 87828-91-9; **3d**, 87828-92-0; **4**, 87828-93-1; α-(2,6-dichlorophenyl)-*o*-fluorobenzyl alcohol, 87828-94-2; 1-bromo-2,6-dimethylbenzene, 576-22-7; 2-fluorobenzoyl chloride, 393-52-2; 2-bromofluorobenzene, 1072-85-1; 2,6-dichlorobenzaldehyde, 83-38-5.

[1,2]-Intramolecular Ene Reactions

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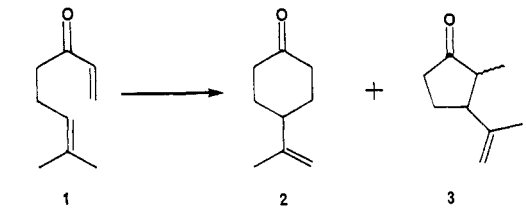
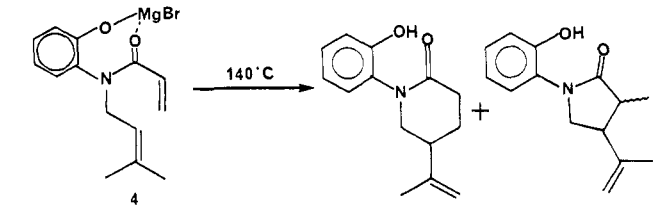
The intramolecular ene reaction has been elaborated into a versatile synthetic method. In a recent review,[1] Oppolzer and Snieckus enumerate three variants of the reaction in which the enophile is linked by a bridge to the olefinic terminal (type I), central atom (type II), or allylic terminal (type III) of the ene component. However, there are in principle six types of intramolecular ene reactions, since the bridge can be attached at either of two positions on the enophile as well as the three possible positions on the ene unit (see Scheme I). The type of intramolecular ene reaction can be specified by the attachment point of the bridge to the ene and enophile units, respectively. Using this terminology Oppolzer and Snieckus' type I becomes [1,1], type II becomes [2,1], and type III becomes [3,2]. [3,1]-Intramolecular ene reactions must result in the formation of a large ring and are therefore entropically unfavorable, but [1,2]- and [2,2]-intramolecular ene reactions are plausible (see Scheme II).

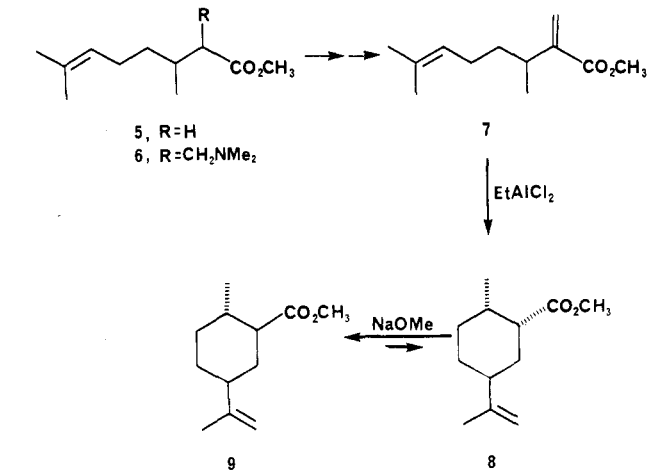
The electronically favored [1,2] adduct **2** has been obtained as the minor component of a mixture with the geometrically favored [1,1] adducts **3** in the thermal ene reaction of **1**.[2] Lewis acid catalysis of this reaction would be expected to enhance electronic effects and lead selectively to **2**, but a stepwise reaction leading to the formation





of 4-isopropyl-2-cyclohexenone via two 1,2-hydride shifts results.[3] [1,2] and [1,1] adducts have been obtained as mixtures from the $MgBr_2$-catalyzed intramolecular ene reaction of **4** at 140 °C.[4]

We set out to develop substrates that would undergo [1,2]- and [2,2]-intramolecular ene reactions selectively. Methyl 3,7-dimethyl-2-methylene-6-octenoate (**7**) was



chosen since Lewis acid catalysis should favor the [1,2] reaction and α,β-unsaturated esters are less susceptible to competing stepwise reactions than α,β-unsaturated ketones. Furthermore, the relative stereochemistry of the two chiral centers formed in the reaction should provide mechanistic information.

Condensation of the lithium enolate of methyl citronellate (**5**) with *N,N*-dimethylmethyleneammonium iodide gives a 66% yield (93% based on recovered **5**) of **6**, which is treated sequentially with methyl iodide and DBU to give a 63% yield of **7**.[5]

Treatment of **7** with 0.93 equiv of $EtAlCl_2$ in CH_2Cl_2 at 40 °C for 5 days gives an 82% yield of a single [1,2] adduct (**8**) as determined by GC and ^{13}C NMR analysis. The stereochemistry of **8** was established by spectroscopic analysis and chemical transformations. Epimerization of **8** with sodium methoxide in methanol for 5 days at reflux,[6] followed by reesterification with diazomethane, gives a

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