Scope of [1 + 2 + 3] Annulations Using Aminonitriles as Michael Donors

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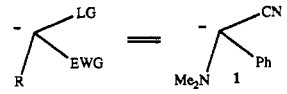
Received November 3, 1992

The reaction of (*N*,*N*-dimethylamino)phenylacetonitrile anion (1) as a one-carbon atom Michael donor toward α,β-unsaturated lactones and ketones followed by allylation of the intermediate enolates provided in a one-pot procedure *trans* α-monoallylated β-substituted lactones and cyclanones **4a–d**, **5**, and **6b**. Attempts at cyclization of compounds **4a–d** and **5b**, with the cyano moiety being the leaving group, were unsuccessful. The only successful [1 + 2 + 3] hexannulation giving *N*,*N*-dimethylamino *trans* ring-fused bicyclic lactone **12b** was run with **6b** bearing an allylic silane moiety.

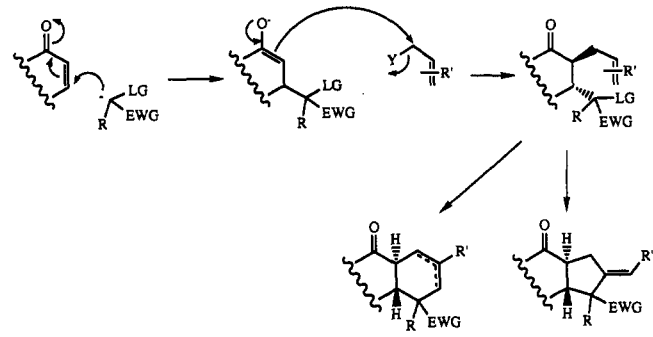
Posner et al. have recently developed convergent and flexible [1 + 2 + 2] and [1 + 2 + 3] annulations (Scheme I) allowing the synthesis of polycyclic systems.[1] The use of tris(phenylthio)methyllithium as the one-carbon Michael donor led to compounds bearing phenylthio moieties. We planned thus to extend this methodology in order to introduce other functional groups on bicyclic systems, more particularly amino substituents which are present in numerous synthetic targets.

Lithiated (*N*,*N*-dimethylamino)phenylacetonitrile (1) was selected for its ability to act in the first step as a Michael donor toward unsaturated lactones **2a,b** and cyclenones **2c,d**, the intermediate enolates being trapped by allylic halides in a tandem fashion; in the final step, ring closure could likely occur via cationic intermediates, with the cyano being easily removable as an anionic leaving group.



The conjugate addition of reagent 1 to cyclenones **2c–d**[2a] as well as the alkylation by methyl iodide in a one-pot fashion has been described by our group;[2b] however, to our knowledge there are few literature data on this one-pot process concerning unsaturated six-membered lactones.[3] On the other hand, it is well-known that aminonitriles lead easily to the corresponding iminium salts, with the cyano group being the leaving group.[4] Moreover, iminium intermediates have been involved in many

Scheme I



cyclization processes.[5] All these literature results were encouraging ones for such a project.

We report herein first the synthesis of the precursors of the iminium salts, which are the lactones **4a,b**, **5**, and **6b** and cyclic ketones **4c,d**, bearing in a vicinal position (*N*,*N*-dimethylamino)phenylacetonitrile and allylic moieties, and second the ring closure attempts.

Synthesis and Identification of α-Monoallylated β-Substituted Lactones and Cyclanones. The conjugate addition of aminonitrile 1 to 2-pentenolide (**2a**), 2-hexenolide (**2b**), cyclopentenone (**2c**), and cyclohexenone (**2d**) has been carried out followed by trapping the intermediate enolates with the allylic halides 1-bromo-2-methyl-2-propene (**3a**), 1-bromo-3,3-dimethyl-2-propene (**3b**), and [2-(iodomethyl)-2-propenyl]trimethylsilane (**3c**, Scheme II).

Several potential experimental problems were avoided as follows: (i) retro-Michael reactions were avoided by using polar media such as THF–HMPA mixtures in which enolate C-allylation takes place with satisfactory yields; (ii), α,α′-enolate isomerization when using cyclenones, inducing trapping in the undesired α′ position, was ruled

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(2) (a) Zervos, M.; Wartski, L. *Tetrahedron Lett.* **1984**, *25*, 4441. (b) Zervos, M.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1986**, *42*, 4963. For a recent asymmetric synthesis example, see: Enders, D.; Mannes, D.; Raabe, G. *Synlett* **1992**, 837.

(3) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 227.

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(5) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 2, Chapter 4.5. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (c) Yue, C.; Royer, J.; Husson, H. P. *J. Org. Chem.* **1992**, *57*, 4211.

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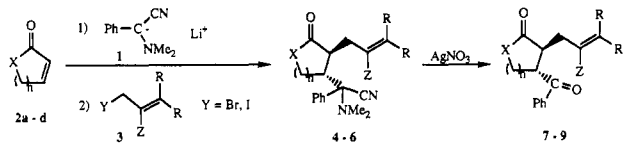
Scheme II



R	Z	X	n	Product Aminonitrile	Product Arylketone
H	Me	O	1	4a	7a
H	Me	O	2	4b	7b
H	Me	CH_2	1	4c	7c
H	Me	CH_2	2	4d	7d
Me	H	O	2	5b	8b
H	CH_2SiMe_3	O	2	6b	9b

out by starting with lactones; (iii) polyalkylations often observed with allylic halides,[6] (iii) possible acylation reactions were avoided by using lactones.[7]

The conjugate addition of **1** to **2a–d** was therefore performed in a THF–HMPA mixture (80/20, v/v) at −78 °C; the intermediate enolates were allylated by using 1.5 equiv of allylic halides **3a–c**, the temperature of the reaction medium being kept between −30 and 0 °C during 3–4 h. After hydrolysis by an aqueous NH_4Cl solution and usual workup, the crude products were analyzed by IR and ^1H NMR spectroscopy.

Lactones **4a–d** and cyclanones **5**, **6b** bearing the aminonitrile moiety were obtained as mixtures of diastereomers, in a 50/50 to 70/30 ratio, which was determined by ^1H NMR. Besides these compounds, nonallylated Michael adducts and products resulting from allylation of **1** were characterized by ^1H NMR and mass spectra analysis of the crude products. Thin-layer chromatography on silica gel or column chromatography on neutral alumina allowed us to obtain either pure diastereomers or mixtures of the two diastereomers plus the corresponding aryl ketones **7a–d**, **8b**, and **9b**. On one hand, the stereochemistry of pure diastereomer aminonitriles $\mathbf{4a_1}$, $\mathbf{4d_1}$, and $\mathbf{5b_1}$ was assigned by ^1H NMR analysis and for $\mathbf{4d_1}$ by X-ray crystal structure determination. An unexpected *trans* diaxial relationship between the two substituents of six membered ketone $\mathbf{4d_1}$ was deduced from the following coupling constant values ($CDCl_3$): $^3J_{H2H3}$ = 2.5 Hz; $^3J_{H3H4}$ = 4.0 Hz, and $^3J_{H3H4'}$ = 6.4 Hz. These values as well as small long-range couplings detected in the 2D NMR COSY contour plots[10a] and assigned to $^4J_{H2H4}$ or $^4J_{H2H6'}$ are in good agreement with a cyclohexyl ring lying in a chair conformation. The X-ray analysis confirmed the chair conformation adopted by the cyclohexyl ring as well as the *trans* diaxial relationship between the C_2–C_7 and C_3–C_{11} bonds. The solid-state structure is shown in Figure 1; the principal angles are listed in Table I. The 2.5-Hz coupling constant value of $^3J_{H2H3}$ perfectly fits with the dihedral angle $C_7C_2C_3C_{11}$ = 150.82° determined in the crystal structure showing thus a similarity of the preferred conformations in the solid state and in solution.

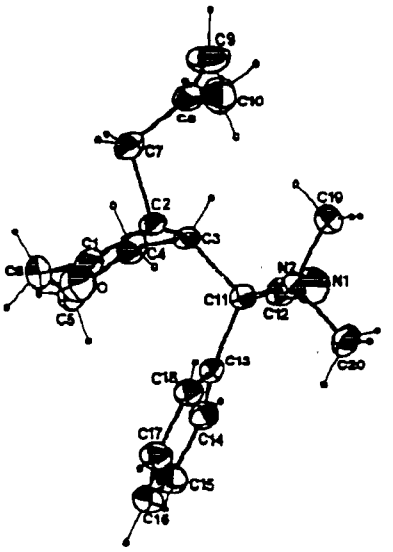


Figure 1.

Table I. Main X-ray Data of $\mathbf{4d_1}$ (Selected Dihedral Angles in deg)

$C_2C_7C_8C_9$	107.18	$H_{42}C_4C_5H_{51}$	170.06
$C_3C_2C_7C_8$	−74.95	$H_{51}C_5C_6H_{61}$	−170.11
$C_7C_2C_3C_{11}$	150.82	$C_2C_3C_{11}C_{12}$	−166.96
$C_{11}C_3C_4H_{42}$	−155.28	$C_3C_{11}C_{13}C_{18}$	−77.36

MM_2 calculations using the MM_2-like force field (MAD version 2.0)[10b] have shown that this *trans* diaxial conformer is by far the more favored (8–9 kcal) as compared either to a twist boat bearing the two substituents in axial position or a chair one having the two substituents in equatorial position. In the latter case, strong gauche interactions between the two bulky substituents lying in the equatorial position are probably highly destabilizing.

Surprisingly, the ^1H NMR data of five-membered lactone $\mathbf{4a_1}$, especially the $^3J_{H3H4}$ value of 3 Hz ($CDCl_3$), are also in agreement with a *trans* quasidiaxial relationship between the two C_3 and C_4 substituents. As in the recent paper of Jaime[11a] two envelope conformations can be considered for substituted γ-lactones. Once again, the *trans* quasidiaxial conformer seems to be favored, as a consequence of gauche interactions developed in the diequatorial conformer. Such *trans* diaxial preferred conformations have been carried out in a few cases both for six- and five-membered rings.[10a,11] The ^1H NMR spectrum of the six-membered lactone aminonitrile $\mathbf{5b_1}$ carried out in $CDCl_3$ shows that the signals corresponding to H_3 and H_4 protons are not separated. The X-ray analysis of $\mathbf{5b_1}$ indicates that the lactone ring adopts a quasiboat conformation having the C_3 and C_4 substituents in a *trans* diaxial relationship, the dihedral angle $H_3C_3C_4H_4$ being −104.28°. The solid-state structure is shown in Figure 2; the principal angles are listed in Table II.

The ^1H NMR data in C_6D_6 are in agreement with a quasi-boat conformation, having the two substituents in the quasiaxial position, which is nevertheless different from that observed in the solid state probably due to the solvent effect and the known flexibility of the lactone ring; the $^3J_{H3H4}$ coupling constant value of 6.7 Hz corresponds only to a difference of 30° compared to the solid state.[10c,d]

(6) House, H. O.; Prabhu, A. V.; Philips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.
(7) Casey, M.; Manage, A. C.; Nezhat, L. *Tetrahedron Lett.* **1988**, *29*, 5821.
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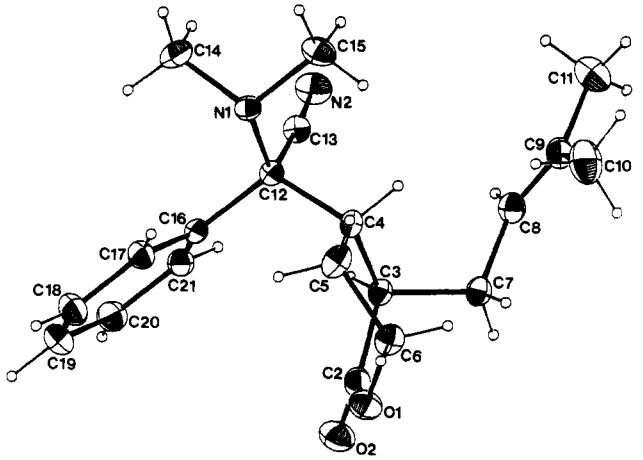


Figure 2.

Table II. Main X-ray Data of $5b_1$ (Selected Dihedral Angles in deg)

$C_3C_7C_8C_9$	110.10	$H_4C_4C_5H_{51}$	152.60
$C_4C_3C_7C_8$	-58.26	$H_4C_4C_5H_{52}$	33.43
$H_3C_3C_4H_4$	-104.28	$H_{51}C_5C_6C_{61}$	176.69
$C_{12}C_4C_3C_7$	133.61	$C_4C_{12}C_{16}C_{17}$	85.13

On the other hand, as the ^1H NMR analysis of mixtures of diastereomer aminonitriles was too complicated, configurational assignments were deduced in these cases from those of the aryl ketones obtained by aqueous silver nitrate treatment[8] of the corresponding aminonitriles, which is known to occur without any isomerization around the two vicinal bonds.[2,9] However, no information about conformation of the starting aminonitriles was thus available.

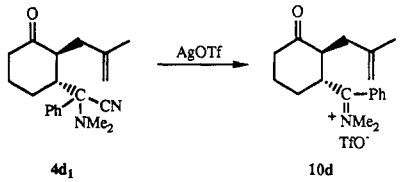
The ^1H NMR data of five-membered tetrahydrofuranone **7a** and cyclopentanone **7c** derivatives, particularly the coupling constant values, respectively, $^3J_{H3H4}$ = 9.0 Hz and $^3J_{H2H3}$ = 10.0 Hz, are in agreement with a *trans* relationship of the two substituents lying in a quasi-diequatorial position. For the six-membered ones **7–9b** and **7d** the same *trans* relationship could be deduced from the coupling constant values, respectively, $^3J_{H3H4}$ = 9.0–9.2 Hz for tetrahydropyranones and $^3J_{H2H3}$ = 10.0 Hz for cyclohexanone.

Therefore, all these reactions involving conjugate addition/enolate trapping by allylic halides take place as previously shown in other cases[1-3] on each side of the mean plane of the Michael acceptor (α,β-unsaturated lactone or ketone).

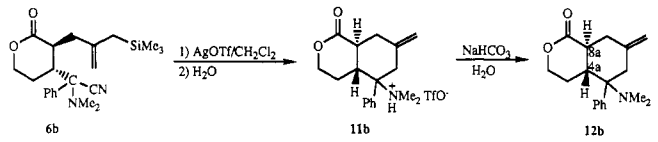
Ring Closure Attempts. Aminonitriles **4a–d** and **5b** were treated with 1.1 equiv of copper or silver triflate, silver fluoroborate, and silver acetate in C_6D_6 or CH_2Cl_2 at room temperature for various times. Precipitation of copper or silver cyanide occurred immediately, showing the formation of the iminium salts. After hydrolysis by a saturated aqueous ammonium chloride solution followed by usual workup, the ^1H NMR of the crude products only indicated the presence of the corresponding ketones **6a–d** even when the reactions were run in the presence of 4-Å molecular sieves.[12]

At first sight this lack of ring closure might be due to an unfavorable conformation of the iminium salts at least for $\mathbf{4a_1}$ and $\mathbf{4d_1}$ as the *trans* diaxial conformation of these aminonitriles could be retained after the loss of the cyano group. Such is not the case: the ^1H NMR spectrum of the

Scheme III



Scheme IV



CD_2Cl_2 solution obtained after silver triflate treatment of $\mathbf{4d_1}$ (vide supra) followed by AgCN filtration shows that the iminium triflate **10d**, characterized by two NMe singlets at δ 3.68 and 3.20 ppm, exhibits a *trans* diequatorial conformation according to the $^3J_{H2H3}$ coupling constant value of 10.5 Hz (Scheme III).

The only successful ring closure experiment was performed with aminonitrile **6b** bearing an allylic silane moiety, known to favor intramolecular cyclization processes.[4,5] After silver triflate treatment followed by extraction by diethyl ether, solid **11b** was isolated in a 47% yield plus nonidentified polymeric materials (Scheme IV).

The ^1H NMR data of **11b** show that a single diastereomer of an ammonium triflate of bicyclic lactone bearing an exocyclic double bond is formed as confirmed by the presence of a broad singlet at 5.25 ppm (2H) and two doublets of H^+NMe at 3.15 ppm and 2.70 ppm in $CDCl_3$ solution.

Treatment of **11b** by a 0.1 M aqueous sodium bicarbonate solution followed by extraction with diethyl ether gave a single diastereomer **12b** of the corresponding *N,N*-dimethylamine quantitatively. The *trans* ring junction has been assigned by ^1H NMR analysis (C_6D_6) as the value of $^3J_{H4aH8a}$ = 14.0 Hz. Presumably, the phenyl group adopts an equatorial position by taking into account the H_4 and $H_{4'}$ shielding just as in the 7-chloro-5-hydroxy-7-methyl-5-phenyloctahydroisocoumarin, whose structure has been determined by X-ray analysis.[13]

In conclusion, a suitable choice of the third component allows the successful [1 + 2 + 3] annulation. This result indicates that double bonds bearing a methyl or a dimethyl moiety as in compounds **4a–d** and **5b** are not sufficiently nucleophilic toward the *N,N*-dimethyliminium salts examined. The cyano group appears to be a good leaving group to induce Michael–ring closure (MIRC) reactions but the nucleophilicity of the double bond has to be adjusted to perform ring closure. Nethertheless, cyclization of the corresponding aryl ketones **7a,b**, **8b**, and **9b** in the presence of Lewis acids, giving alcohols, takes place whatever the double bond substituents.[13]

Experimental Section

Reactions were performed in oven-dried glassware under argon. Melting points are uncorrected. Tetrahydrofuran was distilled from sodium benzophenone before use; dichloromethane and hexamethylphosphoramide were distilled from calcium hydride under argon. α,β-Unsaturated lactones **2a,b** and α-enones **2c,d** are commercial (Aldrich) as well as 1-bromo-3,3-dimethyl-2-

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propene (**3b**) (Fluka); 1-bromo-2-methyl-2-propene (**3a**) was prepared from the alcohol (Aldrich); [2-(iodomethyl)-2-propenyl]-trimethylsilane was prepared according to ref 14 and (*N,N*-dimethylamino)phenylacetonitrile according to ref 15. Column chromatography was carried out using neutral alumina and thin-layer chromatography using Merck Kieselgel 60 silica gel. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer and are given in cm^{-1}. ^1H NMR spectra were recorded on a Brücker AM 200 and AM 250 MHz spectrometers; chemical shifts δ are given in ppm (internal standard $CHCl_3$); J values are given in Hz and measured in some cases after irradiation of protons. Mass spectra were performed on a Nermag 10-10 mass spectrometer coupled with a capillary chromatography (CPSil column 25 m) or by chemical ionization with NH_3. Microanalyses were done by the Service of Microanalysis of CNRS.

X-ray crystal structure determination for **4d$_1$**: a suitable crystal, which belonged to the monoclinic space group $P2_1/n$, with lattice constants of a = 12.284(7) Å, b = 8.699(3) Å, c = 17.826(9) Å, β = 108.87(6)°, and Z = 4, was selected. Data were collected using an Enraf-Nonius CAD-4 diffractometer (Mo Kα radiation, λ = 0.710 73 Å) in the range $1<\theta>25°$. 2085 reflections with $I > 3\,\sigma(I)$ were used after Lorentz-polarisation corrections. The structure was solved by using direct method (MULTAN[16a]) and refined by full-matrix least-squares (F) and all non-H atoms constrained to ride on their parent carbon atoms. For **5b$_1$**: a suitable crystal, which belonged to the triclinic space group P-1, with lattice constants of a = 8.871(2) Å, b = 10.152(3) Å, c = 10.611(4) Å, α = 95.02(3)°, β = 102.63(2)°, γ = 101.98(2)°, and Z = 2, was selected. Data were collected using an Enraf-Nonius CAD-4 diffractometer (Mo, Kα radiation, λ = 0.710 73 Å) in the range $1<\theta<25°$. 2027 reflections with $I > 3\sigma(I)$ were used after Lorentz-polarization corrections. The structure was solved by using direct method (SIR88[16b]) and refined by full-matrix least-squares (F) with atoms refined anisotropically. Hydrogen atoms were included at calculated positions and constrained to ride on their parent carbon atoms. The final R value was R = 0.057. All calculations were performed on a Vax 4200 computer with the Enraf-Nonius MolEN Package.[17,18]

A typical procedure for Michael addition followed by α alkylation follows. **3-[Cyano(dimethylamino)phenylmethyl]-2-(2-methylallyl)cyclohexan-1-one (4d).** A dry three-neck flask equipped with a mechanical stirrer, a thermometer, and a rubber septum, under argon, was charged with 800 mg (5 mmol) of (*N,N*-dimethylamino)phenylacetonitrile (**1**) and 20 mL of THF. The reaction mixture was cooled to −78 °C, and after 10 min 3.7 mL of 1.6 N *n*-butyllithium in hexane (5.5 mmol) was added via a syringe. After 30 min, 480 mg (5 mmol) of 2-cyclohexen-1-one (Aldrich) was added over a period of 10 min into the yellow solution of lithiated (*N,N*-dimethylamino)phenylacetonitrile kept at −78 °C. After 30 min, 1.2 g (5.5 mmol) of 1-bromo-2-methyl-2-propene in 6 mL of HMPA was added via a syringe, and the reaction mixture was warmed to −30 °C and stirred at this temperature for 4 h. Aqueous NH_4Cl was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. Combined organic layers were washed three times with water and brine to remove HMPA and dried over $MgSO_4$. After filtration and solvent evaporation, the crude product (1.35 g) was analyzed by ^1H NMR indicating the presence of two diastereomers **4d$_1$** and **4d$_2$** in a 70/30 ratio plus 3-(1-cyano-1-(*N,N*-dimethylamino)-1,1-phenyl-2-methylbut-1-ene. Purification by column chromatography led to a mixture of **4d$_1$** and **4d$_2$** (80% yield) plus the corresponding ketone **7d**; one diastereomer **4d$_1$** was recrystallized from hexane.

Isomer **4d$_1$**: mp 102.5 °C; IR (CH_2Cl_2) 2220, 1710; ^1H NMR 200 MHz ($CDCl_3$) 7.60–7.50 (m, 2H), 7.40–7.30 (m, 3H), 4.80 (s, 1H), 4.65 (s, 1H), 3.10 (broad t, J = 2.5 Hz, 1H), 2.70 (m, J = 2.5, 4.0 and 6.4 Hz, 1H), 2.55 (dd, J = 13.1 and 6.4 Hz, 1H), 2.40 (dd, J = 13.1 and 8.9 Hz, 1H), 2.30–2.05 (m, 2H), 2.25 (s, 6H), 1.82 (s, 3H), 1.80–1.60 (m, 2H), 1.60–1.40 (m, 1H), 0.70–0.55 (m, 1H). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.41; H, 8.38; N, 9.03. Found: C, 77.37; H, 8.36; N, 8.93. Isomer **4d$_2$** was characterized from the **4d$_1$** + **4d$_2$** mixture: 200 MHz ($CDCl_3$) 4.80 (s, 1H), 4.62 (s, 1H), 2.29 (s, 6H). MS of **4d$_1$** and **4d$_2$** mixture (*m/z* chem ionization) 311 (M + 1).

4-[Cyano(dimethylamino)phenylmethyl]-3-(2-methylallyl)tetrahydrofuran-2-one (4a). Two diastereomers, **4a$_1$** and **4a$_2$**, in a 70/30 ratio were characterized by ^1H NMR of the crude product. By washing the crude product with hexane the diastereomer **4a$_1$** crystallized: mp 53 °C; IR (CH_2Cl_2) 1770, 1650; ^1H NMR 200 MHz ($CDCl_3$) 7.65–7.50 (m, 2H), 7.50–7.35 (m, 3H), 4.92 (t, J = 1.0 Hz, 1H), 4.80 (s, 1H), 4.65 (dd, J = 10.0 and 3.0 Hz, 1H), 4.22 (dd, J = 10.0 and 7.0 Hz, 1H), 3.08 (dt, J = 7.0 and 3.0 Hz, 1H), 2.60–2.20 (m, 3H), 2.25 (s, 6H), 1.78 (s, 3H); ^1H NMR, 200 MHz (C_6D_6) 7.05–6.90 (m, 2H), 6.62–6.48 (m, 3H), 4.45 (t, J = 1.0 Hz, 1H), 4.31 (s, 1H), 3.82 (dd, J = 10.0 and 3.7 Hz, 1H), 3.17 (dd, J = 10.0 and 8.0 Hz, 1H), 2.36 (dt, J = 8.0 and 3.7 Hz, 1H), 2.15–2.01 (m, 1H), 1.95 (dd, J = 14.0 and 4.0 Hz, 1H), 1.65 (dd, J = 14.0 and 9.0 Hz, 1H), 1.40 (s, 6H), 1.25 (s, 3H). Anal. Calcd $C_{18}H_{22}N_2O_2$: C, 72.48; H, 7.38; N, 9.39. Found: C, 71.97; H, 7.31; N, 9.23. Isomer **4a$_2$** characterized in the **4a$_1$** + **4a$_2$** mixture: 200 MHz ($CDCl_3$) δ 4.88 (s, 1H), 4.79 (s, 1H), 2.23 (s, 6H), 1.73 (s, 3H). MS (*m/z* chem ionization) 299 (M + 1).

4-[Cyano(dimethylamino)phenylmethyl]-3-(2-methylallyl)tetrahydropyran-2-one (4b): IR (neat) 2210, 1790, 1650. After purification by column chromatography **4b$_1$** and **4b$_2$** in a 75/25 ratio were characterized by ^1H NMR: 200 MHz (C6D6) **4b$_1$** 7.60–7.45 (m, 2H), 7.15–6.90 (m, 3H), 4.88 (s, 1H), 4.85 (s, 1H), 3.50–3.30 (m, 2H), 2.85 (ddd, J = 8.2, 5.2 and 4.9 Hz, 1H), 2.60–2.48 (m, 2H), 2.48–2.32 (m, J = 7.4, 9.3 and 4.9 Hz, 1H), 1.91 (s, 6H), 1.90 (s, 3H), 1.70–1.45 (m, 1H), 1.40–1.15 (m, 1H); **4b$_2$** 7.60–7.50 (m, 2H), 7.15–6.90 (m, 3H), 4.80 (s, 1H), 4.69 (s, 1H), 1.95 (s, 6H), 1.75 (s, 3H); **4b$_1$** + **4b$_2$** MS (*m/z* chem ionization) 330 (M + 1).

3-[Cyano(dimethylamino)phenylmethyl]-2-(2-methylallyl)cyclopentanone (4c): IR (neat) 2210, 1790, 1650. Attempts of purification by column chromatography gave only ketone **7c**. After the crude product was washed with hexane two diastereomers **4c$_1$** and **4c$_2$** in a 50/50 ratio were characterized plus ketone **7c** by the following ^1H NMR signals. **4c$_1$** + **4c$_2$**: ^1H NMR 250 MHz ($CDCl_3$) 7.50–7.30 (m, 5H), 4.95 (s, 0.5H), 4.92 (s, 0.5H), 4.80 (s, 0.5H), 4.78 (s, 0.5H), 2.30 (s, 1.5H), 2.24 (s, 1.5H), 1.90 (s, 1.5H), 1.89 (s, 1.5H); MS *m/z* 296 (M^+).

4-[Cyano(dimethylamino)phenylmethyl]-3-(2-methylpent-3-enyl)tetrahydropyran-2-one (5b). Only one diastereomer **5b$_1$** has been characterized in the crude product; **5b$_1$** was recrystallized from EtOH: mp 101.3 °C; IR (CH_2Cl_2) 2220, 1740; ^1H NMR 200 MHz ($CDCl_3$) 7.60–7.50 (m, 2H), 7.50–7.32 (m, 3H), 5.15 (broad t, J = 6.2 and 1.0 Hz, 1H), 4.20–4.09 (m, 2H), 2.90–2.55 (m, 4H), 2.32 (s, 6H), 2.15–1.75 (m, 2H), 1.78 (s, 3H), 1.72 (s, 3H); ^1H NMR 250 MHz (C_6D_6) 7.48–7.25 (m, 2H), 7.05–6.90 (m, 3H), 5.30 (broad t, J = 5.6 Hz, 1H), 3.60–3.38 (m, J = 11.2 and 2.5 Hz, 2H), 2.80–2.65 (m, 3H), 2.50–2.35 (m, J = 10.0, 6.9 and 6.7 Hz, 1H), 1.90 (s, 6H), 1.70 (s, 3H), 1.65 (s, 3H), 1.60–1.40 (m, J = 14.9 and 10.0 Hz, 1H), 1.40–1.22 (m, J = 14.9, 6.9, 3.8 and 2.7 Hz, 1H); MS (*m/z* chem ionization) 327 (M + 1). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.61; H, 7.97, N, 8.58. Found: C, 73.19; H, 7.94; N, 7.99.

4-[Cyano(dimethylamino)phenylmethyl]-3-[[(trimethylsilyl)methyl]allyl]tetrahydropyran-2-one (6b). After column chromatography **6b$_1$** and **6b$_2$** (70% yield) in a 70/30 ratio were characterized by the following ^1H NMR signals: ^1H NMR 250 MHz ($CDCl_3$) 7.65–7.50 (m, 2H), 7.50–7.30 (m, 3H), 4.72 (s, 0.7H), 4.69 (s, 0.3H), 4.25–4.08 (m, 2H), 3.02–2.98 (m, 1H), 2.98–2.75 (m, 1H), 2.60–2.40 (m, 2H), 2.29 (s, 4.2H, **b$_1$**), 2.28 (s, 1.8H, **b$_2$**), 2.12–1.98 (m, 2H), 1.68 (s, 1.4H, **b$_1$**), 1.66 (s, 0.6H, **b$_2$**), 0.15–0.0 (broad, s, 9H); MS (*m/z* chem ionization) 385 (M + 1).

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General Procedure for the Synthesis of Benzoyl Cyclanones and Lactones: 3-Benzoyl-2-(2-methylallyl)cyclohexanone (7d). To 1.5 g (5 mmol) of crude product placed in a flask and dissolved in 2 mL of THF and 2 mL of Et_2O were added 5 mL (5.5 mmol) of 1 M $AgNO_3$ aqueous solution. After the reaction mixture was stirred for 4 h, the organic layer was filtered and the precipitate was washed three times with CH_2Cl_2. Combined CH_2Cl_2 layers were washed with water and brine and dried over $MgSO_4$. Filtration and solvent evaporation gave a yellow oil which was purified by TLC (eluting solvent ether/hexane = 7/3) to give **7d** in a 70% yield (896 mg); oil; R_f 0.3 eluting solvent; ether/hexane = 7/3; IR (neat) 1710, 1680; ^{1}H NMR 200 MHz ($CDCl_3$) 8.10–7.80 (m, 2H), 7.70–7.30 (m, 3H), 4.62 (s, 1H), 4.55 (s, 1H), 3.65 (tdd J = 10.0, 4.0, and 1.0 Hz, 1H), 3.18 (dt, J = 7.0 and 10.0 Hz, 1H), 2.70–2.25 (m, 3H), 2.25–1.50 (m, 5H), 1.68 (s, 3H); ^{1}H NMR, 250 MHz (C_6D_6) 7.81–7.71 (m, 2H), 7.10–6.98 (m, 3H), 4.71 (s, 1H), 4.68 (s, 1H), 3.30–3.18 (m, $\omega_{1/2}$ = 10.9 Hz, 2H), 2.68 (dd, J = 13.7 and 5.5 Hz, 1H), 2.20 (dtd, J = 12.1, 3.4, and 1.5 Hz, 1H), 1.95–1.80 (m, J = 12.1 and 6.8 Hz, 2H), 1.70 (s, 3H), 1.65–1.15 (m, 4H); MS (m/z) 256 (M^+). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.60; H, 7.80. Found: C, 79.06; H, 8.09.

4-Benzoyl-3-(2-methylallyl)tetrahydrofuran-2-one (7a). Purified by TLC (eluting solvent hexane/ether = 7/3) and recrystallized from EtOH (75% yield): mp 92.1 °C; IR (CH_2Cl_2) 1790, 1680; ^{1}H NMR 250 MHz ($CDCl_3$) 7.98–7.90 (m, 2H), 7.68–7.45 (m, 3H), 4.67 (broad s, 2H) 4.65–4.55 (m, 1H), 4.25–4.08 (m, 2H), 3.52–3.40 (m, J = 10.4, 3.9, and 9.1 Hz, 1H), 2.69 (dd, J = 13.0 and 3.9 Hz, 1H), 2.28 (dd, J = 13.0 and 10.4 Hz, 1H), 1.68 (s, 3H); MS (m/z) 244. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.77; H, 6.55. Found: C, 73.58; H, 6.43.

4-Benzoyl-3-(2-methylallyl)tetrahydropyran-2-one (7b). Purified by TLC and recrystallized from EtOH (80% yield): mp 62.8 °C; IR (CH_2Cl_2) 1790, 1680; ^{1}H NMR 250 MHz ($CDCl_3$) 7.98–7.88 (m, 2H), 7.60–7.38 (m, 3H), 4.55 (s, 2H), 4.35–4.20 (m, 2H), 3.70 (td, J = 9.1 and 5.2 Hz, 1H), 3.50 (td, J = 9.1 and 5.2 Hz, 1H), 2.55 (dd, J = 13.1 and 5.2 Hz, 1H), 2.28–2.12 (m, J = 13.1 Hz, 2H), 1.85–1.70 (m, J = 14.4, 5.2, and 3.9 Hz, 2H), 1.62 (s, 3H); ^{1}H NMR 250 MHz (C_6D_6) 7.80–7.70 (m, 2H), 7.25–7.02 (m, 3H), 4.55 (s, 1H), 4.44 (s, 1H), 3.81 (td, J = 10.9 and 3.7 Hz, 1H), 3.64 (dt, J = 10.9 and 3.7 Hz, 1H), 3.52 (td, J = 8.5 and 4.8 Hz, 1H), 3.29 (td, J = 8.5 and 4.8 Hz, 1H), 2.68 (dd, J = 13.3 and 4.8 Hz, 1H), 2.16 (dd, J = 13.3 and 8.5 Hz, 1H), 1.70–1.45 (m, 1H), 1.60 (s, 3H), 1.17–1.03 (m, J = 14.5 and 3.7 Hz, 1H); MS (m/z chem ionization) 259 (M + 1). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.41; H, 6.97. Found: C, 74.22; H, 6.85.

3-Benzoyl-2-(2-methylallyl)cyclopentanone (7c). Purified by TLC (eluting solvent ether/hexane = 7/3); R_f 0.2 eluting solvent ether/hexane = 7/3; mp 28 °C; IR (neat) 1740, 1675; ^{1}H NMR, 200 MHz ($CDCl_3$) 8.00–7.89 (m, 2H), 7.62–7.38 (m, 3H), 4.55 (s, 2H), 3.82 (td, J = 10.0 and 7.0 Hz, 1H), 3.08 (tdd, J = 10.0, 5.0, and 1.5 Hz, 1H), 2.65–2.20 (m, 4H), 2.08 (dd, J = 14.0 and 10.0 Hz, 1H), 2.00–1.80 (m, 1H), 1.62 (s, 3H); MS (m/z) 242 (M^+).

4-Benzoyl-3-(2-methylpent-3-enyl)tetrahydropyran-2-one (8b). Purified by TLC (eluting solvent ether/hexane = 1/1): oil; R_f 0.4 eluting solvent ether/hexane = 1/1; IR (neat) 1780, 1680; ^{1}H NMR 250 MHz ($CDCl_3$) 7.98–7.88 (m, 2H), 7.65–7.42 (m, 3H), 5.00 (tt, J = 7.0 and 1.0 Hz, 1H), 4.10 (m, 2H), 3.68 (td, J = 9.2 and 5.2 Hz, 1H), 3.45 (dt, J = 9.2 and 5.2 Hz, 1H), 2.40 (m, 2H), 2.31–2.22 (m, J = 14.4 and 7.8 Hz, 1H), 1.90–1.79 (m, J = 14.4, 5.2, and 2.6 Hz, 1H), 1.42 (s, 3H), 1.35 (s, 3H); MS (m/z) 273 (M^+). Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35. Found: C, 74.88; H, 7.45.

4-Benzoyl-3-[2-[(trimethylsilyl)methyl]allyl]tetrahydropyran-2-one (9b). Purified by TLC (eluting solvent ether/hexane = 7/3): mp 61 °C; ^{1}H NMR 200 MHz ($CDCl_3$) 8.05–7.90 (m, 2H), 7.70–7.40 (m, 3H), 4.52 (s, 1H), 4.40–4.20 (m, 3H), 3.80–3.68 (m, 1H), 3.60 (broad t, J = 9.1 and 5.3 Hz, 1H), 2.60 (ddd, J = 14.5, 5.3 and 0.5 Hz, 1H), 2.40–2.18 (m, J = 14.5 and 7.9 Hz, 2H), 1.92–1.75 (m, J = 14.8, 4.0 and 2.5 Hz, 1H), 1.41 (s, 2H), 0.00 (broad s, 9H); MS (m/z chem ionization) 331 (M + 1). Anal. Calcd for $C_{19}H_{26}O_3Si$: C, 69.09; H, 7.97. Found: C, 69.25; H, 7.96.

Ring Closure. General Procedure. 5×10^{-4} mol of purified **4a–d**, **5b**, or **6b** in 1 mL of CH_2Cl_2 or C_6H_6 was added via a syringe to 5×10^{-4} mol of silver triflate dissolved in 1 mL of CH_2Cl_2 or C_6H_6 with 4-Å molecular sieves[12] placed in a two-neck flask under argon and stirred at room temperature. A precipitate was immediately formed; stirring was continued for 6 h. After hydrolysis with water, the precipitate was filtered and washed with CH_2Cl_2 or C_6H_6. Combined organic layers were washed with water and brine and dried over $MgSO_4$. After filtration the solvent was evaporated. The ^{1}H NMR analysis of the crude product obtained from **4d** showed either a mixture of iminium salt **10d** and ketone **7d** or only **7d** depending upon hydrolysis duration; with **4a–c** or **5b** only ketones **7a–c** or **8b** were characterized. When starting from **6b**, a gray solid **11b** was obtained (47% yield).

5-Dimethylammonio-5-phenyl-7-methylidene-3,4,4a,5,6,7,-8a-octahydroisocoumarin trifluoromethanesulfonate (11b): mp 204 °C; IR (CH_2Cl_2) 3100–3000, 2920, 2760, 1740, 1650; ^{1}H NMR 200 MHz ($CDCl_3$) 9.20 (broad s, 1H), 7.88–7.78 (m, 2H), 7.58–7.45 (m, 3H), 5.25 (broad s, 2H), 4.40–4.18 (m, 2H), 3.25–3.08 (m, 3H), 3.15 (d, J = 6.0 Hz, 3H), 2.70 (d, J = 6.0 Hz, 3H), 2.60–2.40 (m, 3H), 2.10–1.90 (m, 2H); ^{1}H NMR 250 MHz (pyridine) 14.20 (broad s, 1H), 7.92–7.89 (m, 2H), 7.42–7.30 (m, 3H), 5.02 (s, 1H), 4.97 (s, 1H), 4.10–4.06 (m, 1H), 3.69–3.65 (m, 1H), 3.11 (dd, J = 14.0 and 1.0 Hz, 1H), 2.63 (d, J = 14.0 Hz, 1H), 2.40 (dd, J = 14.0 and 1.0 Hz, 1H), 2.31 (dd, J = 14.0 and 10.0 Hz, 1H), 2.20 (m, 2H), 2.14 (s, 6H), 2.00–1.89 (m, 1H), 1.70–1.67 (m, 1H); ^{13}C NMR (pyridine) 23.55, 34.37, 36.75, 38.58, 40.34, 41.60, 65.44, 67.84, 111.97, 127.66, 128.16, 130.28, 143.74, 146.62, 173.42. Anal. Calcd for $C_{19}H_{24}F_3NO_5S$: C, 52.40; H, 5.51; N, 3.30. Found: C, 52.05; H, 5.33; N, 3.07.

5-(Dimethylamino)-5-phenyl-7-methylidene-3,4,4a,5,6,7,-8a-octahydroisocoumarin (12b). **11b** was dissolved in 0.1 M aqueous HCO_3Na solution. After extraction by Et_2O, drying over $MgSO_4$, and evaporation of the solvent a white solid was obtained: mp 114.6 °C; IR ($CHCl_2$) 2960, 2910, 2880, 2840, 2790, 1740, 1650; ^{1}H NMR 250 MHz ($CDCl_3$) 7.80–7.70 (m, 2H), 7.28–7.10 (m, 3H), 5.05–4.92 (m, 2H), 4.10–3.96 (m, 1H), 3.68–3.55 (m, 1H), 2.98 (d, J = 14 Hz, 1H), 2.62 (d, J = 14.0 Hz, 1H), 2.42 (dd, J = 14.0 and 2.9 Hz, 1H), 2.30–1.90 (m, 10H), 1.83–1.65 (m, 1H); ^{1}H NMR 250 MHz (C6D6) 7.80–7.65 (m, 2H), 7.20–6.95 (m, 3H), 4.87 (d, J = 1.5 Hz, 1H), 4.82 (d, J = 1.5 Hz, 1H), 3.50–3.35 (m, J = 12.2 Hz, 1H), 3.17–2.99 (m, 2H), 2.40 (d, J = 14.9 Hz, 1H), 2.25–2.02 (m, 2H), 1.98 (td, J = 12.2 and 2.5 Hz, 1H), 1.80 (broad s, 6H), 1.65–1.47 (m, J = 12.2 Hz, 1H), 1.42–1.28 (m, 2H); MS (m/z chem ionization) 286 (M + 1).

3-[(Dimethylphenyliminio)methyl]-3-(2-methylallyl)cyclohexan-1-one trifluoromethanesulfonate (10d). 5×10^{-4} mol of **4d** dissolved into 1 mL of CD_2Cl_2 was added to 5×10^{-4} silver triflate dissolved in 1 mL of CD_2Cl_2 placed in a two-neck flask and stirred at room temperature for 5 min. After filtration of the precipitate and evaporation of CD_2Cl_2 the ^{1}H NMR of the crude product was performed in C_6D_6: ^{1}H NMR 250 MHz (C_6D_6) 7.70–7.00 (m, 5H), 4.72 (s, 1H), 4.30 (s, 1H), 3.68 (s, 3H), 3.38 (td, J = 10.5 and 2.0 Hz, 1H), 3.20 (s, 3H).

Acknowledgment. We thank Prof. Y. Lallemand, Dr. L. Blanco, and Mrs. M. Bertrand for NMR assignments and the NSF and the CNRS for an international award (87-N-920053).