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# Easy Access to Highly Functionalized Bicyclic Lactones and Ketones.

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**Abstract** : Lewis acid catalyzed cyclization of lactones **1** - **4** or cyclohexanone **5** bearing trans vicinal aroyl and allylic moieties provided stereoselectively functionalized trans fused ring lactones and cyclohexanones as well as aromatic analogues in high yields. Cyclization of **1** leads to a single stereomer of 7-chloro-5-hydroxy octahydroisocoumarin **6** exclusively or 5-hydroxy isocoumarin **9** predominantly depending on the Lewis acid nature while **4** gives exclusively methylene octahydroisocoumarin **10** or dihydroisocoumarin **11** according to the quantity of TMSOTf used. Similar results are obtained with **5** leading either to **12** or **15** exclusively or to a mixture of **13** and **14** depending on reaction conditions.

Obtention of highly functionalized bicyclic compounds constitutes the key step of the total synthesis of many natural products.[1,2] Carbonyl-ene reactions have been widely studied for the construction of such classes of compounds especially intramolecular Lewis acid mediated reactions of unsaturated aldehydes and methyl ketones, the former being more reactive.[3,4,5] Recently, it was pointed out that trifluoromethyl ketones are good enophiles.[6] In order to synthesize functionalized bicyclic lactones and cyclohexanones bearing aromatic groups, we report herein the study of intramolecular ring forming processes under Lewis acid catalysis of readily available tetrahydropyranones **1** - **4** and cyclohexanone **5** having aroyl and allylic moities in a trans vicinal position. To our knowledge, the reactivity of ω-unsaturated aryl ketones has not been examined yet. Furthermore, Snider et al. reported that attempts to synthesize six-membered rings by Lewis acid catalyzed intramolecular reaction of a cyclohexanone bearing a methylbutenyl substituent in the α-position were unsuccessful ; nevertheless, the introduction of a carbethoxy group in the α position led to the desired ene adduct.[7] All those literature results were encouraging for such a project.

***Synthesis and identification of bicyclic lactones and cyclohexanones***

Starting materials were easily obtained by unmasking the carbonyl function[8] of Michael adducts formed in a one-pot fashion by conjugate addition of masked benzoyl anions to α,β-unsaturated lactones or cyclic enones followed by C-allylation of the intermediate enolates.[9] As for compounds **1**, **4** and **5**,[9] as previously described a trans diequatorial relationship of the two vicinal substituents has been assigned to lactone **2**, the $^3J_{H3H4}$ coupling constant value being 9.2 Hz. The $^1H$ NMR spectrum of **3** carried out in various solvents shows that the signals corresponding to $H_3$ and $H_4$ protons are not separate; on the other hand, the

single-crystal X-ray analysis of **3** indicates that the $C_3$ and $C_4$ substituents lie in a trans quasi-diequatorial relationship, the lactone ring exhibiting a boat conformation.[10]

Ring closure of compounds **1** - **5** have been carried out in $CH_2Cl_2$ solutions generally for 2 h. at -78°C (except for a few cases) in the presence of various Lewis acids. Water or 0.1M aqueous $NaHCO_3$ was added to the reaction mixture obtained from lactone or cyclohexanone derivatives respectively. After the usual work-up, the crude reaction mixtures have been analyzed by IR and $^1H$ NMR spectroscopy. Crystallization from ethanol or thin layer chromatography (TLC) on silica gel allowed the isolation of the bicyclic products except for the unstable chloroalcohols **13** and **14**. The results are summarized in Table I.

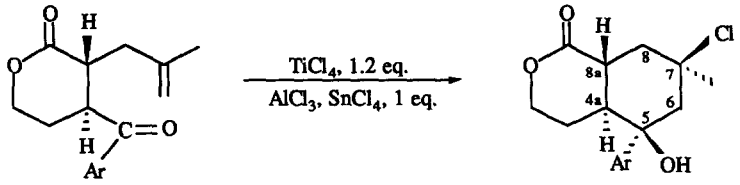
Table 1

Cyclization of six-membered ring compounds **1** - **5** in the presence of Lewis Acids in $CH_2Cl_2$, 2 hours at -78°C

| Run | Compound | X | Z | Ar | Lewis acid (eq.) | Products | Yield [a] | |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | O | Me | $C_6H_5$ | $AlCl_3$ (1) | **6** | 80 | (50) |
| 2 | 1 | O | Me | $C_6H_5$ | $Et_2AlCl$ [b] (1) | SM | | |
| 3 | 1 | O | Me | $C_6H_5$ | $Me_2AlCl$ [b] (1) | SM | | |
| 4 | 1 | O | Me | $C_6H_5$ | $TiCl_4$ (1.2) | **6** | 85 | (75) |
| 5 | 1 | O | Me | $C_6H_5$ | $Ti(OiPr)_4$ (1.2) | SM | | |
| 6 | 1 | O | Me | $C_6H_5$ | $TiCl_4$ (0.1) | SM | | |
| 7 | 1 | O | Me | $C_6H_5$ | $SnCl_4$ [b] (1) | **6**[c] | 80 | |
| 8 | 1 | O | Me | $C_6H_5$ | $ZrCl_4$ [b] (1) | SM | | |
| 9 | 1 | O | Me | $C_6H_5$ | TMSOTf (1) | **9/10** : 9/1 | 90 | |
| 10 | 1 | O | Me | $C_6H_5$ | TMSOTf (10) | **9/10** : 9/1 | 60 | |
| 11 | 2 | O | Me | $pClC_6H_4$ | $TiCl_4$ (1.2) | **7** | 84 | (75)[d] |
| 12 | 3 | O | Me | $pCH_3OC_6H_4$ | $TiCl_4$ (1.2) | **8** | 80 | (75) |
| 13 | 4 | O | $CH_2SiMe_3$ | $C_6H_5$ | $TiCl_4$ (1.2) | **6/10** : 1/1 | 90 | |
| 14 | 4 | O | $CH_2SiMe_3$ | $C_6H_5$ | TMSOTf (1) | **10** | 90 | (80) |
| 15 | 4 | O | $CH_2SiMe_3$ | $C_6H_5$ | TMSOTf (10) | **11** | 90 | (65) |
| 16 | 5 | $CH_2$ | Me | $C_6H_5$ | $TiCl_4$ (1.2) | **12** | 90 | (75) |
| 17 | 5 | $CH_2$ | Me | $C_6H_5$ | TMSOTf (1) | **13/14** : 75/25 | 30[e] | |
| 18 | 5 | $CH_2$ | Me | $C_6H_5$ | TMSOTf (10) | **15** | 80[e] | (60) |

a) Yields % and ratios are determined by $^1H$ NMR analysis of the crude products, starting materials (SM) being the complement to 100%. () Yield % of isolated products.b) Reaction was carried out at 20°C, 2 hours c). Traces of **9** + **10** mixture.d) Yield of 9. e) Complement to 100% being polymers.

Treatment of tetrahydropyranones **1** - **3** bearing a methylpropenyl group with 1. 2 eq. of $TiCl_4$, 1 eq. of $AlCl_3$ (Table 1, runs 1, 4, 11 and 12) or 1 eq. of $SnCl_4$ (Table 1, run 7) gave 7-chloro-5-hydroxy bicyclic lactones **6** - **8** as single products which have been isolated in 50 - 75% yield (eq. 1).

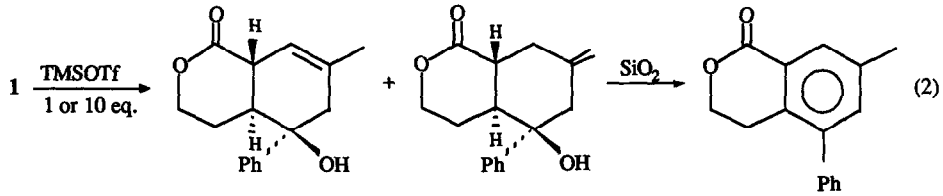



(1)

| | | |
|---|---|---|
| Ar = Ph | **1** | **6** |
| Ar = pCl-$C_6H_4$ | **2** | **7** |
| Ar = pMeO-$C_6H_4$ | **3** | **8** |

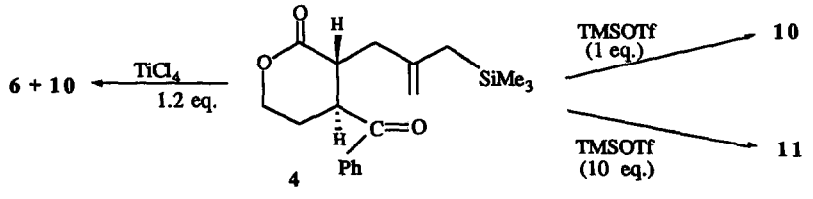
This cyclization did not take place using either 1 eq. of $Et_2AlCl$, $Me_2AlCl$, $Ti(OiPr)_4$, $ZrCl_4$ or 0.1 eq. of $TiCl_4$ (Table 1, runs 2, 3, 5, 6, 8), starting material being recovered.

1 eq. of TMSOTf induced cyclization of **1** to give a mixture of bicyclic hydroxy compounds **9** and **10** in a 9/1 ratio (Table 1, run 9) (eq. 2) from which **9** was isolated in 70% yield by crystallization. The use of 10 eq. of TMSOTf led to the same ratio of **9** and **10**, the yield being lower (Table 1, run 10). TLC on silica gel of the **9** + **10** mixture provided the aromatic lactone **11** in 65% yield.



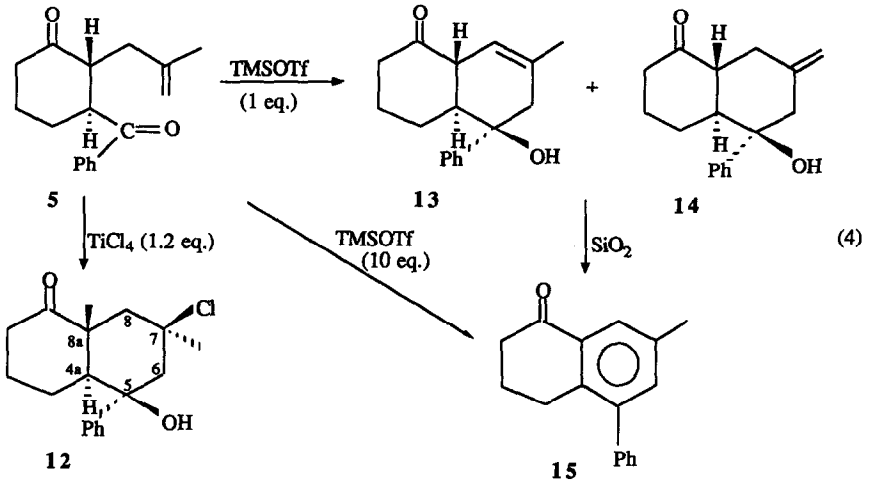

**9** **10** **11** (2)

On the other hand, reaction of **4** bearing an allylsilane moiety carried out with 1.2 eq. of $TiCl_4$ provided a mixture of **6** and **10** in a 1/1 ratio (Table 1, run 13) while using 1 eq. of TMSOTf (Table I, run 14) afforded only **10** which was obtained in 80% isolated yield. With 10 eq. of TMSOTf, only compound **11** was obtained (Table 1, run 15) (eq. 3) in 65% isolated yield.




4 (3)

1.2 eq. of $TiCl_4$ induced cyclization of cyclohexanone **5** to give 7-chloro-5-hydroxy bicyclic compound **12** (Table 1, run 16) in 75% isolated yield after purification by crystallization. With 1 eq. of TMSOTf (Table 1, run 17) bicyclic hydroxy ketones **13** and **14** in a 75/25 ratio were present in the crude product, in addition to other compounds which are probably isomers; the estimated yield is 30%, the remaining 70% being polymers. TLC on silica gel of the crude product did not allow purification of these unstable alcohols but led to **15** in 20% isolated yield. Using 10 eq. of the same Lewis acid afforded only the aromatic ketone **15** in 60% isolated yield (Table 1, run 18 ) (eq. 4).




(4)

Structural assignments of bicyclic compounds **6** - **15** have been based upon IR, $^1H$ and $^{13}C$ NMR spectroscopy, elemental analysis or mass spectra and single-crystal X-ray analysis in the case of **6**, **10** and **12**.

$^1H$ NMR studies indicated that compounds **6** - **8** are obtained as single stereoisomers. The trans ring junction was deduced from the $^3J_{H4aH8a}$ coupling constant values of 11.5 to 12.0 Hz. The presence of a methyl group α to the chlorine substituent was confirmed by the presence of a singlet at 1.75 ppm. Moreover, the $^4J_{H6H8}$ coupling constant value of 2.6 Hz suggested that the cyclohexyl ring adopts a chair conformation. Structure of **6** was unambiguously established by single-crystal X-ray analysis (Table 2, Fig. 1) which indicated : i) a cis relationship between $C_{8a}$ - $H_{8a}$, $C_7$ - Cl, $C_5$ - OH bonds the Cl, $H_{8a}$ and O (OH) atoms being respectively located at -1.972, - 1.233 and 1.624Å from the pseudo mean plane of the cyclohexyl ring ; ii) an equatorial position of the phenyl substituent bissecting the cyclohexyl ring ; iii) a boat conformation of the lactone ring, the $C_{8a}C_1O_2C_3$ and $C_{8a}$ $C_{4a}C_4C_3$ torsional angle values being 4.86 and 4.16° respectively. It appears from the $^1H$ NMR study that the shielding of $H_4$ and $H_{4'}$ protons is well accounted by an equatorial position of the phenyl ring, the lactone ring lying in a boat conformation. The trans ring junction as well as the chair conformation of the cyclohexyl ring deduced from $^1H$ NMR data have been thus confirmed. Therefore the preferred conformation in solution is similar to the one observed in solid state. The relative configuration of **6** is the following (4aS,5R,7S,8aR) or (4aR,5S,7R,8aS).

Table 2

Main X-ray data of compounds **6, 10, 12**
(Selected Dihedral Angles in degrees)

| | **6** | **10** | **12** |
|---|---|---|---|
| $H_4\ C_{4a}\ C_{8a}\ H_{8a}$ | 172.94 | 173.4 | -178.25 |
| $C_3\ O_2\ C_1\ C_{8a}$ | 4.86 | 3.04 | |
| $C_3\ C_4\ C_{4a}\ C_{8a}$ | 4.16 | 1.13 | -56.21 |
| $C_{4a}\ C_{8a}\ C_8\ C_7$ | 59.61 | 53.55 | -54.84 |
| $C_{4a}\ C_5\ C_6\ C_7$ | -47.68 | -55.33 | 48.34 |
| $H_{4a}\ C_{4a}\ C_5\ O_3$ | 174.88 | 179.59 | -172.69 |
| $H_4\ C_{4a}\ C_5\ C_{10}$ | 56.20 | 60.12 | -54.36 |
| $O_3\ C_5\ C_{10}\ C_{11}$ | -76.62 | -167.54 | 178.44 |
| $H_{62}\ C_6\ C_7\ C_9$ | 49.12 | 108.40 | 67.09 |
| $C_3\ C_2\ C_1\ C_8$ | | | 55.02 |

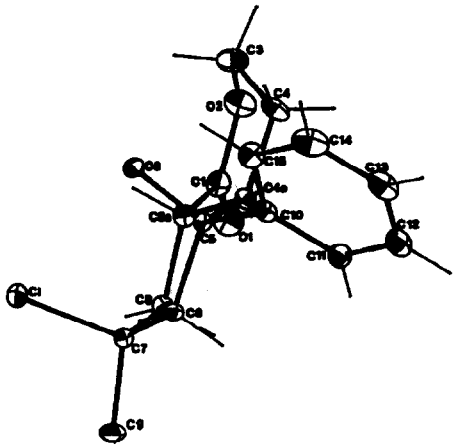


Fig. 1 ORTEP [11] drawing of **6**

Compounds **7** and **8** exhibiting $^1H$ NMR data analogous to those of **6**, similar conformations and relative configurations at $C_{4a}$,$C_5$,$C_7$ and $C_{8a}$ positions can be deduced.

$^1H$ NMR spectra of **9** and **10** clearly showed that these compounds are obtained as single stereomers bearing either a methyl group or an exomethylene one respectively ; the trans ring junction was established by the $^3J_{H8aH4a}$ coupling constant values of 12.5 and 12.0 Hz respectively. The single-crystal X-ray analysis of **10** indicated that the relative configuration at $C_{4a}$, $C_5$ and $C_{8a}$, atoms is similar to that of **6** (Table II, Fig. 2). The conformation adopted by the lactone ring is also a boat, the $C_3O_2C_1C_{8a}$ and $C_3C_4C_{4a}C_{8a}$ torsional angle values being 3.14 and 1.13° respectively ; the cyclohexyl ring lies in a chair conformation, the phenyl ring being located in equatorial position.

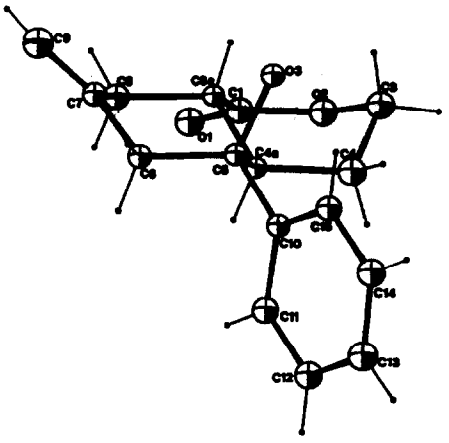


Fig. 2 ORTEP drawing of **10**

Dehydrohalogenation of **6** with silver triflate (AgOTf) in $CH_2Cl_2$ affording a mixture of **9**, **10** and **11** in a 8/1/1 ratio unambigously proved that **9** exhibits the same relative configuration at $C_{4a}$, $C_5$ and $C_{8a}$ carbon atoms as both compounds **6** and **10**.

Finally, the structure of lactone **11** was confirmed by $^1H$ NMR study showing characteristic signals of aromatic protons and methyl ones.

Bicyclic ketone **12** is obtained as a single stereoisomer as indicated by the $^1H$ NMR data; the ring junction is in a trans relationship according to the $^3J_{H2H3}$ coupling constant value of 12.0 Hz. The single crystal X-ray analysis has been performed for **12** showing that the relative configuration at $C_{4a}$, $C_5$, $C_7$ and $C_{8a}$ carbon centers is identical to that observed for **6**, the $C_7$-Cl, $C_{8a}$-$H_{8a}$, $C_5$-OH bonds being in a cis relationship. As expected, both the cyclohexanone and the cyclohexane rings adopt chair conformations the $C_3C_2C_1C_{8a}$, $C_3C_4C_{4a}C_{8a}$ and $C_{4a}C_5C_6C_7$ dihedral angle values being 55.02, -56.21 and 48.34° respectively. In the same way, the phenyl ring is located in equatorial position (Table 2, Fig. 3).

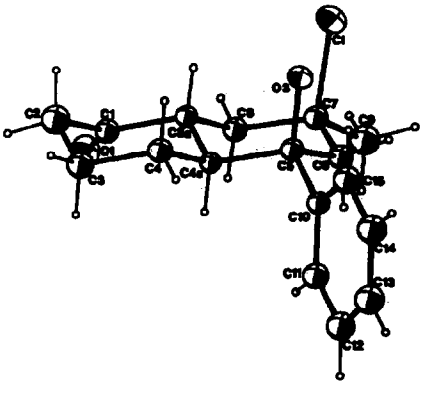


Fig. 3 ORTEP drawing of **12**

Alcohols **13** and **14** could not be fully characterized, however their $^1H$ NMR spectroscopic data are similar to those of **9** and **10** respectively. In order to strengthen these structural assignments **12** was treated by AgOTf in $CH_2Cl_2$ at 0°C for 1 h.: only the aromatic ketone **15** was obtained and consequently, no information about **13** and **14** can be drawn. However when performing this treatment for 15 min. at -5°C and quenching the reaction mixture by 0.1M aqueous $NaHCO_3$, it was possible to avoid such an aromatization process and the $^1H$ NMR spectra of the crude product indicates the presence of compounds **13** and **14** and in addition regioisomers and polymers. Thus, it can be assumed that compounds **13** and **14** exhibit the same relative configuration at $C_{4a}$ and $C_5$ centers as observed in the related ketone **12**.

The structure of **15** was established by the $^1H$ NMR data indicating the presence of one methyl and aromatic groups.

### *Discussion*

Several points observed during this study are worthy of comment : i) whatever the nature of the Lewis acid and the number of equivalents used no lactone ring opening reaction occurred with lactones **1 - 4** ; in the same way, cyclisation of cyclohexanone **5** in the presence of $TiCl_4$ or excess of TMSOTf is regioselective since only compounds resulting from the attack of the aryl ketone group have been observed. ii) cyclisation of lactones **1 - 4** and cyclohexanone **5** proceeded with a high stereoselectivity leading to a single stereomer of trans fused lactones and ketones. The most important fact is that in the case of bicyclic 7-chloro-5-hydroxy compounds **6 - 8** as well as **12**, a similar relative configuration at the four asymmetric centers $C_{4a}$, $C_5$, $C_7$, $C_{8a}$ has been evidenced, the $C_5$-OH, $C_7$-Cl and $C_{8a}$-$H_{8a}$ bonds being in a cis relationship. Moreover, the same relative configuration at $C_{4a}$, $C_5$, $C_{8a}$ has been assigned to both hydroxy lactones **9** and **10** and to hydroxy ketones **13** and **14**.

The stereoselective obtention of chlorobicyclic lactones **6 - 8** suggests that a six-center transition state (TS) involving a carbonyl - Lewis acid complex A lying in pre-axial position, the phenyl group being located in pre-equatorial one can be considered (Fig. 4) ; transfer of a chloride ion can be favored by a positive charge developed in the $C_7$ position.[12] A six-center TS having the carbonyl - Lewis acid complex B in pre-equatorial position as proposed by Yamamoto[13] in the case of aldehydes is strongly disfavored with the ketones **1 - 3** (Fig. 5) : the good overlap between the carbonyl and ene $\pi$ bonds which could take place in the TS is counterbalanced both by steric interactions due to the position of the phenyl group and by the inability of the chlorine atom to stabilize the too far located positive charge developed in the $C_7$ center.

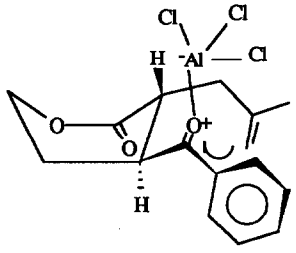



Figure 4 : complex A

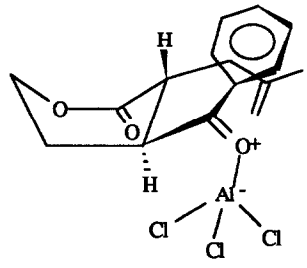



Figure 5 : complex B

Cyclization of **1** in the presence of TMSOTf leading predominantly to **9** can be interpreted by a six-center TS via a complex C (Fig. 6) providing a good overlap between the two $\pi$ systems and allowing the allylic hydrogen at $C_8$ center to be removed . Analogous TS have been previously proposed by Snider and Begue for ring closure reactions of methyl and trifluoromethyl ketones respectively.[3,6]

A TS via the complex D (Fig. 7) takes into account the cyclization process of **4**, the positive charge developed at the $C_7$ center being highly stabilized by the silicon-carbon bond in $\beta$ position ; this intermediate carbenium provided either compound **10** or a mixture of **10** and **6** depending on the selected Lewis acid TMSOTf and $TiCl_4$ respectively (Fig. 7).[14]

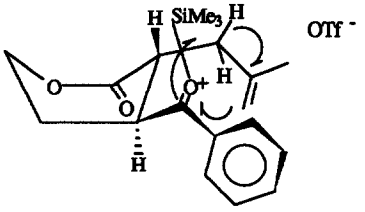



Figure 6 : complex C

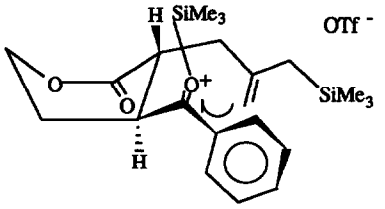



Figure 7 : complex D

Finally, six-center TS which involves an A-like complex is considered for the cyclization of cyclohexanone **5** catalyzed by $TiCl_4$, since the stereoselectivity of this process is the same as the previously observed with lactones **1** - **3**.[15]

The bicyclic tertiary-alcohols have been isolated in most cases by crystallization. Nevertheless simple TLC on silicagel of hydroxy lactones **9** and **10** or hydroxy ketones **13** and **14** provided the corresponding aromatic compounds **11** or **15** respectively.

## CONCLUSION

It has been shown that arylketones are by far more reactive in the presence of various Lewis acids than the methyl ones studied by Snider ; this different behaviour could be interpreted by steric hindrance effects in the case of the methyl ketones; indeed, molecular orbital energy calculations indicated that Lewis acid complexation by either aryl ketones or methyl ones induced a levelling of their LUMO energies levels.[16]

The ring closure of easily available lactones and cyclanone **1** - **5** bearing trans vicinal aroyl and allylic moieties has proved to be synthetically useful allowing a facile entry to highly functionalized bicyclic lactones and ketones with stereoselective formation of quaternary carbon centers and to aromatic systems.

## ACKNOWLEDGEMENTS

We thank for helpful discussions Dr J. SEYDEN, Professor G.H. POSNER and Dr NGUYEN TRONG ANH.

## EXPERIMENTAL SECTION

Melting points are uncorrected. Dichloromethane was distilled from calcium hydride under argon. Lewis acids are used pure ($AlCl_3$, $Et_2AlCl$, $Me_2AlCl$, $SnCl_4$, $ZrCl_4$, TMSOTf) or in $CH_2Cl_2$ solution ($TiCl_4$). TLC was carried out using Merck Kieselgel 60 silicagel. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer and are given in $cm^{-1}$. $^1H$ NMR and $^{13}C$ 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 Hertz. Mass spectra were performed on a Nermag 10-10 mass spectrometer coupled with a capillary chromatography (CPSil column 25 m) or by chemical ionization (CI) with ammonia. Microanalyses were done by the Service of Microanalysis of CNRS.

**X-ray Crystal Structure Determination** : Data were collected at room temperature on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator (λ = 0.71073 Å). The cell parameters were obtained by a least-squares refinement of the setting angles of 25 reflections with θ between 8 and 12°. Three standard reflections were measured after each hour and no decay was observed the data were corrected for Lorentz polarization effects. The structures were solved by using direct method MULTAN[17] for $ClO_3C_{16}H_{19}$ and $O_3C_{16}H_{18}$, SIR 88[18] for $ClO_2C_{17}H_{21}$ and refined by full-matrix least-squares (F). Hydrogen atoms were included at calculated positions and constrained to ride on their parent carbon atoms. All calculations were performed on a Vax 4200 computer with the Enraf-Nonius MolEN Package.[19]

***X-ray crystal data for 6*** : monoclinic, space groupe Cc, a = 18.908(12) Å, b = 7.721(1) Å, c = 11.541(2) Å, β = 118.23(3)°, V = 1485(1) $Å^3$, Z = 4, θmax = 25°. 1221 reflections with I > 3 σ(I) were considered observed out of 1300 unique data collected. All atoms were refined with anisotropic thermal parameters. Current final residuals are R = 0.034, Rw = 0.044.

***X-ray crystal data for 10*** : orthorhombic, space groupe Pbca, a = 7.506(3) Å, b = 24.407(6) Å, c = 14.732(4) Å, V = 2699(2) $Å^3$, Z = 8, θmax = 22°. 412 reflections with I > 3 σ(I) were considered observed out of 1642 unique data collected. All atoms were refined with anisotropic thermal parameters. Current final residuals are R = 0.054, Rw = 0.058.

***X-ray crystal data for 12*** : monoclinic, space groupe $P2_1/n$, a = 11.308(3) Å, b = 8.886(3) Å, c = 15.380(4) Å, β = 93.90(3)°, V = 1542(1) $Å^3$, Z = 4, θmax = 25°. 735 reflections with I > 3 σ(I) were considered observed out of 2708 unique data collected. Cl and O atoms were refined with anisotropic thermal parameters. Current final residuals are R = 0.053, Rw = 0.056.

Compounds **1, 4, 5** prepared by Michael addition of lithiated N,N-dimethylaminophenyl acetonitrile to α,β-unsaturated lactone or cyclohexen-2-one followed by alkylation were described previously. [9] Compounds **2** and **3** were obtained in the same way using respectively N,N-dimethylamino-4-chloro or 4-methoxyphenylacetonitriles.

*4-(4-chloro)benzoyl-3-(2-methylallyl)tetrahydropyran-2-one* **2**. Crystallized from ethanol : mp : 112°C. IR ($CH_2Cl_2$) : 2990 , 2910 , 1750 , 1680 , 1600 , 1575 , 1400 , 1100 . $^1H$ NMR 200 MHz ($C_6D_6$) : 7.45 - 7.35 (m, 2H) ; 7.05 - 6.95 (m, 2H) ; 4.48 (br s, 1H) ; 4.46 (br s, 1H) ; 3.68 (td, J = 10.5, 2.5 Hz ,1H) ; 3.38 - 3.55 (m, 2H) ; 2.91 (td, J = 9.2, 3.4 Hz, 1H) ; 2.72 (dd ,J = 13.8, 3.4 Hz ,1H) ; 2.11 (dd ,J = 13.8, 9.2 Hz ,1H) ; 1.56 (s, 3H) ; 1.45 - 1.25 (m ,1H) ; 0.95 - 0.80 (m ,J = 13.8 ,3.4, 1.5 Hz ,1H) . $^{13}C$ NMR 75 MHz ($CDCl_3$) : 21.6 ; 27.2 ; 38.0 ; 39.3 ; 42.5 ; 65.5 ; 66.8 ; 114.7 ; 129.2 ; 129.7 ; 133.4 ; 140.1 ; 142.2 ; 173.6 ; 197.3. Analysis calcd for $C_{16}H_{17}O_3Cl$ : C, 65.64 ; H, 5.81 ; Cl, 12.13. Found : C, 66.05 ; H, 5.69 ; Cl, 11.86 .

*4-(4-methoxy)benzoyl-3-(2-methylallyl)tetrahydropyran-2-one* **3**. Crystallized from ethanol : mp : 104 °C . IR ($CH_2Cl_2$) : 2920 , 1745 , 1680 , 1610 , 1580 , 1510 , 1180 . $^1H$ NMR 200 MHz ($C_6D_6$) : 7.80 - 7.60 (m ,2H) ; 6.70 - 6.50 (m, 2H) ; 4.60 (s, 1H) ; 4.55 (d, J = 0.5 Hz, 1H) ; 3.80 (td, J = 13.8, 4.6 Hz, 1H) ; 3.70 - 3.50 (m, 2H) ; 3.25 - 3.05 (m, 4H) ; 2.78 (dd, J = 13.8, 4.6 Hz, 1H) ; 2.22 (dd, J = 13.8, 8.8 Hz, 1H) ; 1.65 (s, 3H) ; 1.62 - 1.40 (m, 1H) ; 1.15 - 0.95 (m, J = 13.8, 3.5 Hz, 1H). $^{13}C$ NMR 75 MHz

($CDCl_3$) : 21.7 ; 27.3 ; 38.0 ; 39.0 ; 42.0 ; 55.1 ; 65.7 ; 113.9 ; 127.9 ; 130.6 ; 142.1 ; 150.3 ; 163.8 ; 173.9 ; 179.1. Analysis calcd. for $C_{17}H_{20}O_4$ : C, 70.83 ; H , 6.94. Found : C , 71.19, H, 6.99 .

**Typical cyclization procedure.** *7-chloro-5-hydroxy-7-methyl-5-phenyl-3,4,4a,5,6,7,8,8a-octahydroisocoumarin* **6**. 1.2 eq. TiCl4 (0.2 mL 3M solution of $TiCl_4$ in $CH_2Cl_2$) was added via a syringe to **1** (129 mg, 0.5 mmol) in 3 mL of $CH_2Cl_2$ at -78°C under argon and stirred 2 h. at this temperature. The reaction mixture was diluted with diethyl ether (2 mL) and then quenched with water (1 mL). The organic layer was separated. The aqueous layer was extracted twice with $CH_2Cl_2$ (2 mL). The combined organic layers were washed with brine (2 mL), dried on $MgSO_4$ filtered and concentrated in vacuo to a yellow solid. Recrystallization from ethanol gave the title lactone as white crystals (110 mg, 75% yield) : mp : 129.4°C. IR ($CDCl_3$) : 3560, 2980, 2920, 1740, 1450, 1265, 1050 $cm^{-1}$ ; $^1H$ NMR 250 MHz ($CDCl_3$) : 7.50 - 7.25 (m, 5H) ; 4.40 - 4.15 (m, 2H) ; 3.90 (s, 1H) ; 3.25 (td , J = 12.0, 3.2 Hz, 1H) ; 2.77 (dt ,J = 14.2, 2.6 Hz , 1H) ; 2.33 (dd ,J = 15.2, 2.6 Hz ,1H) ; 2.25 - 2.10 (m, 1H) ; 2.05 (d, J = 15.2 Hz , 1H) ; 1.85 (dd, J = 14.2, 12.0 Hz ,1H) ; 1.80 - 1.75 (m, 1H) ; 1.75 (s, 3H) ; 1.70 - 1.50 (m, 1H). $^{13}C$ NMR 75 MHz ($CDCl_3$) : 22.6 ; 34.7 ; 36.2 ; 42.2 ; 43.1 ; 52.4 ; 67.0 ; 71.1 ; 125.0 ; 127.2 ; 128.5 ; 144.9 ; 174.2. MS (m/z CI) : 312 (M +1) 90.24% ; 314 (M +1) 30.49%. Analysis calcd. for $C_{16}H_{19}O_3Cl$ : C, 65.19 ; H, 6.45 ; Cl, 12.05. Found : C, 64.85 ; H, 6.41 ; Cl, 11.78.

*7-Chloro-5-hydroxy-5-(4-chlorophenyl)-7-methyl-3,4,4a,5,6,7,8,8a-octahydroisocoumarin* **7.** Crystallized from ethanol as white crystals ; mp : 127.7°C. IR ($CDCl_3$) : 3560, 2980, 2920, 1740, 1490, 1280 $cm^{-1}$ ; $^1H$ NMR 200 MHz ($CDCl_3$) : 7.55 - 7.27 (m, 4H) ; 4.40 - 4.05 (m, 2H) ; 3.95 (s, 1H) ; 3.20 (td, J = 11.5, 3.2 Hz ,1H) ; 2.72(dt, J = 14.2, 2.6 Hz ,1H) ; 2.28 (dd, 15.2, 2.6 Hz, 1H) ; 2.25 - 2.02 (m, 1H) ; 2.02 (d, J = 15.2 Hz ,1H) ; 1.85 (dd, J = 14.2, 12.0 Hz, 1H) ; 1.75 (s, 3H) ; 1.70 - 1.50 (m, 2H). MS (m/z CI) : 346 (M +1) 100% ; 348 (M +1) 38%.Analysis calcd. for $C_{16}H_{18}O_3Cl_2$ : C, 58.35 ; H, 5.47 ; Cl, 21.58. Found : C, 58.33 ; H, 5.45 ; Cl, 21.76.

*7-Chloro-5-hydroxy-5-(4-methoxyphenyl)-7-methyl-3,4,4a,5,6,7,8,8a-octahydroisocoumarin* **8.** Crystallized from ethanol as white crystals ; mp : 138.4°C. IR ($CDCl_3$) : 3560, 2980, 2920, 1740, 1510, 1250 $cm^{-1}$ ; $^1H$ NMR 200 MHz ($CDCl_3$ ) : 7.40 - 6.90 (AA'BB' system, 4H) ; 4.40 - 4.20 (m, 2H) ; 3.90 (s, 1H) ; 3.80 (s, 3H) ; 3.22 (td,J = 11.5,2.6 Hz, 1H) ; 2.75 (dt,J = 16.3, 2.6 Hz, 1H) ; 2.30, (dd, J = 16.3, 2.6 Hz ,1H) ; 2.25 - 2.10 (m, 1H) ; 2.05 (d, J = 16.3 Hz, 1H) ; 1.85 (dd, J = 16.3, 12.5 Hz, 1H) ; 1.80 - 1.50 (m, 2H) ; 1.75 (s, 3H). MS (m/z CI) : 342 (M +1) 100% ; 344 (M +1) 30.81%. Analysis calcd. for $C_{17}H_{21}O_4Cl$ : C, 62.86 ; H, 6.47 ; Cl, 10.93. Found : C, 62.47 ; H, 6.64 ; Cl, 11.19.

*5-Hydroxy-7-methyl-5-phenyl-3,4,4a,5,6,7,8,8a-hexahydroisocoumarin* **9**. Crystallized from ethanol as white crystals ; mp : 130.7°C .IR (neat) : 3420, 2960, 2920, 1740, 1600, 1450, 1110 $cm^{-1}$ ; $^1H$ NMR 250 MHz ($CDCl_3$) : 7.50 - 7.20 (m, 5H) ; 6.00 (s, 1H) ; 4.30 - 4.10 (m, 2H) ; 3.40 (br d, J = 12 Hz, 1H) ; 2.70 (d,J = 17.3 Hz, 1H) ; 2.35 - 2.20 (m, 1H) ; 2.15 (d, J = 17.3 Hz, 1H) ; 1.90 (br s, 1H) ; 1.80 (s, 3H) ; 1.65 - 1.40 (m, 2H). $^{13}C$ NMR 75 MHz ($CDCl_3$) : 22.5 ; 23.2 ; 39.8 ; 40.3 ; 47.1 ; 66.8 ; 74.2 ; 117.2 ; 124.7 ; 128.5 ; 133.5 ; 144.8 ; 174.1. MS (coupled with CPG) : 258 (M) 10.79%. Analysis calcd. for $C_{16}H_{18}O_3$ : C, 74.47 ; H, 6.99. Found : C, 74.41 ; H, 6.97.

*5-Hydroxy-7-methylidene-5-phenyl-3,4,4a,5,6,7,8,8a-octahydroisocoumarin* **10.** Crystallised from ethanol as white crystals : mp : 163°C . IR ($CH_2Cl_2$) 3550, 2910 , 1750 , 1650 , 1610 , 1390 . $^1H$ NMR 250 MHz ($C_6D_6$) : 7.20 - 7.00 (m,5 H) ; 4.73 (d, J = 0.5 Hz, 1H) ; 4.49 (d, J = 0.5 Hz, 1H) ; 3.60 - 3.42 (m, 2H) ; 2.78 (dd, J = 10.7, 1.7 Hz, 1H) ; 2.23 - 2.00 (m, 3H) ; 1.85 (dd, J = 12.5, 1.7 Hz, 1H) ; 1.55 (dt , J =

12.5, 7.0 Hz, 1H) ; 1.38 (s, 1H) ; 1.25 - 1.08 (m, J = 12.5, 8.9 Hz,1H) ; 1.02 - 0.90 (m, J = 12.5, 7.1 Hz,1H). $^{13}C$ NMR 75 MHz ($CDCl_3$) : 22.9 ; 34.7 ; 40.4 ; 43.1 ; 49.5 ; 66.5 ; 66.9 ; 114.2 ; 124.6 ; 125.5 ; 127.1 ; 128.4 ; 142.5 ; 174.6. MS (m/z CI) : 276 (M+1) 100% .Analysis calcd. for $C_{16}H_{18}O_3$ : C, 74.41 ; H, 6.97. Found : 74.25 ; H, 7.04.

*4-Methyl-6-phenyl-7,8-dihydroisocoumarin* **11.** Pale yellow oil obtained by TLC on silicagel of the **9** + **10** mixture : Rf = 0.9 eluting solvent : hexane/ether : 7/3 . IR (neat) : 2915, 1720, 1610, 1340, 1290 $cm^{-1}$ ; $^1H$ NMR 200 MHz ($CDCl_3$ ) : 7.98 (s, 1H) ; 7.60 - 7.10 (m, 6H) ; 4.48 (t, J = 5.7 Hz, 2H) ; 2.99 (t, J = 5.7 Hz ,2H) ; 2.48 (s, 3H). $^{13}C$ NMR 75 MHz ($CDCl_3$) : 20.9 ; 26.1 ; 67.2 ; 125.6 ; 127.6 ; 128.2 ; 128.4 ; 129.0 ; 129.9 ; 134.2 ; 135.5 ; 137.2 ; 139.3 ; 140.4 ; 165.7. MS (coupled with CPG) : 238 (M) 100%.

*7-Chloro-5-hydroxy-7-methyl-5-phenyl-3,4,4a,5,6,7,8,8a - octahydronaphtalen - 1(2H)-one* **12.** Crystallized from ethanol as white crystals : mp : 131°C. IR (neat) : 3560, 2900, 2920, 1715, 1600, 1500 $cm^{-1}$ ; $^1H$ NMR 250 MHz ($C_6D_6$) : 7.40 - 7.00 (m, 5H) ; 3.80 (s, 1H) ; 2.78 (td, J = 12.0, 2.8 Hz, 1 H) ; 2.50 (dt, J = 15.0, 2.8 Hz ,1H) ; 2.25 - 2.10 (m, 1H) ; 1.90 (dd,J = 15.0, 2.8 Hz ,1H) ; 1.85 - 1.70 (m, 1H) ; 1.60 - 1.35 (m, 5H) ; 1.25 (s, 3H) ; 1.25 - 1.00 (m, 2H). $^{13}C$ NMR 75 MHz ($CDCl_3$) : 24.3 ; 25.9 ; 41.0 ; 41.8 ; 46.8 ; 51.4 ; 52.1 ; 52.6 ; 67.2 ; 71.7 ; 76.2 ; 125.0 ; 127.0 ; 128.4 ; 128.7 ; 145.9. MS (m/z CI) : 310 (M +1) 100% ; 312 (M +1) 33.17%. Analysis calcd. for $C_{17}H_{21}O_2Cl$ : C, 69.74 ; H, 7.17 ; Cl, 12.13. Found : C, 70.13 ; H, 7.45 ; Cl, 11.53.

*5-Hydroxy-7-methyl-5-phenyl-3,4,4a,5,6,8a -octahydronaphtalen -1(2H)-one* **13** *and 5-Hydroxy-7-methylidene-5-phenyl-3,4,4a,5,6,7,8,8a-octahydronaphtalen-1(2H)-one* **14** characterized in the crude product : IR (neat) : 3420, 2920, 1710, 1600, 1450, 910 $cm^{-1}$. $^1H$ NMR 250 MHz ($CDCl_3$) characteristic signals of **13** : 6.00 (br s, 1H) ; 3.30 (br d, 1H) ; 1.70 (s, emerging from a massif) ; characteristic signals of exomethylene protons of **14** : 4.9 (br s, 1H) and 5.1 (br s, 1H). MS (coupled with CPG) : 256 (M) 19%. TLC on silicagel of the crude product led to **15** in a 25% yield.

*7-Methyl-5-phenyl-3,4-dihydronaphtalen-1(2H)-one* **15.** Pale yellow oil obtained by TLC on silicagel : Rf = 0.3 eluting solvent : hexane/ether 7/3.IR (neat) : 2920, 1680, 1600, 1330, 1250, 1170 $cm^{-1}$ ; $^1H$ NMR 250 MHz ($CDCl_3$) : 7.92 (s, 1H) ; 7.50 - 7.10 (m, 6H) ; 2.81 (t, J = 6.0 Hz ,2H) ; 2.66 (t, J = 6.0 Hz ,2H) ; 2.40 (s, 3H) ; 2.02 (qt, J = 6.0 Hz, 2H). $^{13}C$ NMR 75 MHz ($CDCl_3$) : 20.8 ; 23.3 ; 27.8 ; 39.0 ; 127.0 ; 127.2 ; 128.2 ; 128.3 ; 129.1 ; 132.8 ; 135.6 ; 139.0 ; 140.6 ; 141.8 ; 151.3 ; 198.9. MS (coupled with CPG) : 236 (M) 100%.

***Treatment of chloride 6 by AgOTf.*** A solution of **6** (148 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was stirred 1 h. at room temperature with AgOTf (130 mg, 0.5 mmol). After addition of water followed by usual work-up, the crude product was analyzed by $^1H$ NMR indicating the formation of **9**, **10** and **11** in a 8/1/1 ratio.

***Treatment of chloride 12 by AgOTf.*** A solution of **12** (147 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was stirred 1.30 h. at various temperatures with AgOTf (130 mg, 0.5 mmol). After treatment by 0.1M aqueous $NaHCO_3$ and usual work-up, the crude product was analyzed by $^1H$ NMR and mass spectroscopy coupled with CPG : at 0°C, 1 h. **15** was only formed while at -5°C, 15 min. **13** and **14** were characterized in the crude product next to compounds which are probably regioisomers ($^1H$ NMR 200 MHz, $CDCl_3$ : 5.60 (br s) ; 5.65 - 5.75 (m)).

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