Pergamon

Tetrahedron, Vol. 52, No. 30, pp. 10083-10094, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00542-X

Enantioselective Synthesis of Unsubstituted and 3-Substituted-4-Aroyl-δ-Lactones. Easy Way to Enantiopure Bicyclic Lactone Systems.

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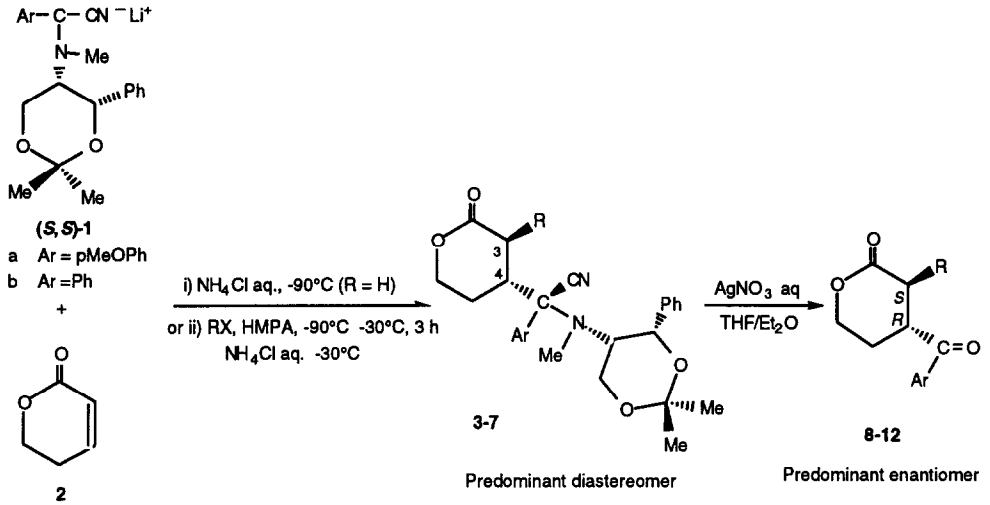
Abstract : Michael addition of lithiated chiral aminonitriles **1a,b** to α,β-unsaturated lactone **2** afforded (4*R*)-aroyl-δ-lactones **8a,b** with a ee value ≥ 99%. Michael addition / subsequent α alkylation process gave the corresponding (3*S*)-substituted-(4*R*)-aroyl-δ-lactones **9-10a**, **9b** with a ee value of 66 up to 87% and **11-12a** with high enantiomeric purity the ee being ≥ 99%. The absolute configuration of the Michael adduct **7a** was established by X-ray analysis and as a result that of all the other compounds was assigned. Lewis acid catalyzed cyclization of (3*S*,4*R*)-**12a** provided the enantiomerically pure hydroxy bicyclic lactone (4a*R*,5*S*,8a*S*)-**13a**.

Functionalized bicyclic lactones are useful key intermediates in the synthesis of many natural products particularly in the sesquiterpenes field.[1,2] We recently reported that Lewis acid catalyzed cyclization of lactones bearing *trans* vicinal aroyl and allylic moieties provided stereoselectively highly functionalized *trans* fused ring bicyclic lactones.[3] The starting aroyl-δ-lactones were readily available by conjugate addition of masked acyl anions such as lithiated (N,N-dimethylamino)phenylacetonitrile to α,β-unsaturated lactone followed by C-allylation of the intermediate enolate and by the unmasking of the Michael adduct.[4,5,6] The next challenge was to develop an asymmetric route to monocyclic and bicyclic aroyllactones. Asymmetric conjugate addition by reaction of a chiral reagent to a prochiral substrate has been shown to be a powerful strategy for enantioselective synthesis.[7a,b] Moreover, recent literature results were encouraging for this target: Enders and coworkers published a very efficient enantioselective synthesis of unsubstituted and 2-substituted-cyclohexanones using chiral equivalents of acyl anions.[8,9]

Herein, we describe first the enantioselective synthesis of unsubstituted and 3-substituted-4-aroyl-δ-lactones and second that of a bicyclic hydroxy lactone.

Synthesis and identification of (4R) and (3S,4R) substituted-δ-lactones.

Compounds **3-4a,b**, **5-7a** were obtained by conjugate addition of lithiated (*4S,5S*)-[N-(2,2-dimethyl-1,2-dioxane-5-yl)-N-methylamino](4-aryl)acetonitriles **1a,b** to 5,6-dihydro-2H-pyran-2-one **2** followed by protonation or α-alkylation with various halides: methyl iodide, benzyl bromide, 1-bromo-2-methyl-2-propene, [2-(iodomethyl)-2-propenyl] trimethylsilane as outlined in scheme 1.



R	Aminonitrile	Aroyllactone
H	**3a,b**	**8a,b**
$CH_2-C(Me)=CH_2$	**4a,b**	**9a,b**
Me	**5a**	**10a**
CH_2Ph	**6a**	**11a**
$CH_2-C(CH_2SiMe_3)=CH_2$	**7a**	**12a**

Scheme 1

α-Aminonitriles *S,S,S/R* **1a** (Ar = pMeOPh) and **1b** (Ar = Ph) were prepared according to [8]. The lithiated reagents were generated from **1a,b** in THF at -90°C by using 1.6M nBuLi as base. After addition of equimolecular amount of **2** the reactions were either i) run at -90°C, 1 h and quenched by a saturated aqueous NH_4Cl solution and treated as usual or ii) THF/HMPA (80/20) solutions of the halides were added to the reaction medium whose temperature was kept at -30°C during 3 h ; after hydrolysis by a saturated aqueous NH_4Cl solution and usual workup, the crude products were analyzed by IR and ^1H and ^{13}C NMR spectroscopy. The results are summarized in Table I.

Table 1. Aminonitriles adducts 3-7 and aroyllactones 8-12

Ar	R	Michael addition			Aroyl lactone				
			Yield %[a]	de %[b,c]		Yield % [a,c]		ee % [c,d]	
pMeOPh	H	**(*R*,*R*,*S*,*S*)-3a**[e]	70	≥99	**(4*R*)-8a**	65	(80)	≥99	(87)
Ph	H	**(*R*,*R*,*S*,*S*)-3b**	50	≥99	**(4*R*)-8b**	45	(75)	≥99	(70)
pMeOPh	CH_2-C=CH_2 Me	**(*S*,*R*,*R*,*S*,*S*)-4a**[f]	g		**(3*S*,4*R*)-9a**		(65)		(83)
Ph	CH_2-C=CH_2 Me	**(*S*,*R*,*R*,*S*,*S*)-4b**	g		**(3*S*,4*R*)-9b**		(55)		(66)
pMeOPh	Me	**(*S*,*R*,*R*,*S*,*S*)-5a**	g		**(3*S*,4*R*)-10a**		(60)		(87)
pMeOPh	CH_2Ph	**(*S*,*R*,*R*,*S*,*S*)-6a**	60	≥99	**(3*S*,4*R*)-11a**	55	(63)	≥99	(80)
pMeOPh	CH_2-C=CH_2 CH_2SiMe_3	**(*S*,*R*,*R*,*S*,*S*)-7a**	75	≥99	**(3*S*,4*R*)-12a**	70	(85)	≥99	(99)

[a] Yield based on aminonitrile **1a,b**. [b] Determined by ^1H and ^{13}C NMR spectroscopy. [c] Values in brackets refer to syntheses without crystallization of Michael adducts **3 - 7**. [d] Determined by ^1H NMR shift experiments with Eu(hfc)$_3$. [e] Configuration given in the following order C_4,C(CN), chiral auxiliary.[f] Configuration given in the following order C_3,C_4,C(CN), chiral auxiliary. [g] Michael adduct did not crystallize, the yields are given on the crude aroyllactones

In all cases the presence of one predominant diastereomer was clearly shown. Crude Michael adducts have been recrystallized providing one pure diastereomer in the case of **3a**, **3b**, **6a** and **7a** (de ≥ 99%) in a 50-75% yield (Table I). No X-ray analysis could be obtained for monosubstituted lactones **3a,b** the crystals exhibiting a twin structure. As a consequence, the absolute configuration could not be established at this stage. The ^1H NMR study of crude or pure diastereomers of 3,4-disubstituted lactones carried out in $CDCl_3$ and C_6D_6 indicated that the signals corresponding to H_3 and H_4 protons were not separated except for **6a** ($^3J_{H3H4}$ = 5.4 Hz in C_6D_6). The X-ray analysis of **7a** [10] showed that the lactone ring adopted a twist conformation having the two substituents in a *trans* quasi-diequatorial position, the dihedral angle $C_7C_3C_4C_{14}$ value being 106.36° (Table II). The conformation of **6a** is probably similar. The X-ray analysis of **7a** based on the known configuration (*S*,*S*) of the chiral auxiliary gave the absolute configuration of the three new chiral centers: C_3S, C_4R, C(CN)*R*. The same absolute configuration was deduced for aminonitriles **4a,b**, **5-6a**, for **3a,b** the absolute configuration is the following: (C_4R, C(CN)*R*).

Treatment of the crude aminonitriles **3-7a**, **3-4b** by aqueous silver nitrate, which is known to occur without any isomerization [6] afforded the corresponding crude aroyllactones **8-12a**, **8-9b** in a 55 up to 85% yield respectively (Table I).

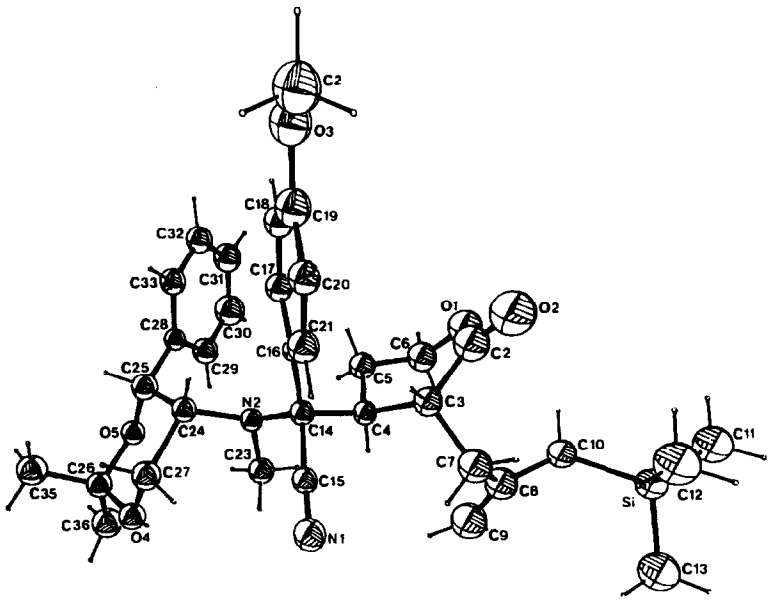


Fig. 1 : ORTEP [10] drawing of compound **7a**.

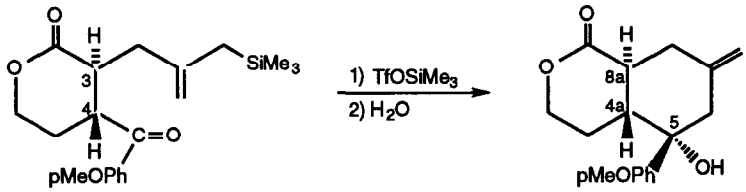
Table 2. Main X-ray Data of 7a (selected torsional angles in deg.)

$C_7C_3C_4C_{14}$ =	106.36	$C_6O_1C_2C_3$ =	2.42
$C_{15}C_{14}C_4C_5$ =	-165.86	$O_1C_2C_3C_4$ =	-25.99
$C_{21}C_{16}C_{14}C_4$ =	100.50	$C_2C_3C_4C_5$ =	1.90
$N_2C_{14}C_4C_5$ =	53.38	$C_3C_4C_5C_6$ =	38.54
$C_{14}N_2C_{24}C_{27}$ =	-90.33	$C_4C_5C_6O_1$ =	-64.68
$C_{27}C_{24}C_{25}C_{28}$ =	-171.29	$C_5C_6O_1C_2$ =	-44.31

The enantiomeric excess value determined by $Eu(hfc)_3$ is 66 up to 99% (Table I). The synthesis of the racemic form of **12a**, starting from lithiated (N,N-dimethylamino) p-methoxyphenylacetonitrile **1c** was performed in order to ensure the 99% value. In the same way the unmasking of the keto moiety was carried out on diastereomerically pure aminonitriles **3a,b** and **6-7a** providing the pure aroyllactones in a 45 to 70% yield, the enantiomeric excess being ≥ 99% (Table I). A *trans* diequatorial relationship between the two substituents was assigned to the aroyllactones **10a**, **11a** and **12a**, the $^3J_{H3H4}$ coupling constant value being 10.2, 10.5 and 8.5 Hz respectively. A similar *trans* relationship has been previously established for the racemic form of **9a** and **9b**.[3,6] Moreover the lactone ring lies probably in a boat conformation as we had previously shown for **9a** by X-ray analysis.[11] The absolute configuration of pure aroyllactones is thus the following (4*R*) for **3a,b** and (3*S*,4*R*) for **9a,b**, **10-12a** (see discussion).

Synthesis and identification of bicyclic lactone

Ring closure of (3*S*,4*R*)-**12a** bearing an allylsilane moiety was carried out in CH_2Cl_2 at -78°C during 3 h in the presence of catalytic amount of trimethylsilyl triflate (Scheme 2).[12,13] After usual workup the crude product was isolated as crystals. ^1H NMR analysis showed that a single diasteromer **13a** was formed. The $^3J_{H4aH8a}$ coupling constant value of 11.9 Hz confirmed as expected the *trans* ring junction. The presence of an exomethylene moiety was evidenced by two singlets (5.06 and 4.90 ppm) in the ^1H NMR spectrum.



(*3S,4R*)-**12a** (*4aR,5S,8aS*)-**13a**

Scheme 2

In order to determine the ee value of **13a**, the corresponding racemic form was prepared starting from the aminonitrile **1c**. A splitting of aromatic protons and of the pMeO moiety was observed for the racemic compound by addition of $Eu(hfc)_3$. Such a splitting was not detected for **13a** which was thus synthesized with a ee ≥ 99% in a 80% yield. The absolute configuration is the following (*4aR,5S,8aS*) (see discussion).

Discussion

Several points of this study are worthy of comments:

a) A high diastereoselectivity is evidenced for the conjugate addition of **1a,b** to the α,β-unsaturated lactone **2**, one diastereomer being formed predominantly. However we noted that the replacement of a phenyl group by a paramethoxy one improved the diastereoselectivity : actually, the crude aroyllactone (4*R*)-**8a** was obtained with a ee value of 87% instead of 70% for (4*R*)-**8b**, the yield being 75-80% (Table 1). Such effect could be due to a different structure of the lithiated species in THF medium.[14,15] Similar increase of the diastereoselectivity was also shown for **9a** and **9b**, the conjugate addition and subsequent α-alkylation being performed in THF/HMPA medium. These observations are in line with those of Enders and coworkers related to cyclohexenone.[8,9]

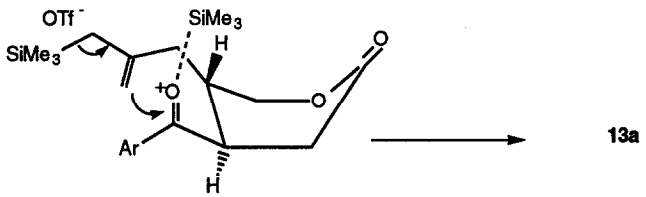
b) Aroyllactones **8a, 8b, 11a, 12a** were obtained with high ee value (≥ 99%) by the unmasking of pure aminonitrile diastereomers ; however such a high ee value was also observed for the crude lactone **12a**.

c) Equilibration of the pure aminonitrile diastereomer **7a** in $CDCl_3$ was evidenced by ^1H NMR study : after four weaks 25% of a diastereomer whose aminonitrile center is inverted was characterized. Iminium intermediates which have been previously postulated might be involved in this epimerization.[9,16] The absolute configuration of the Michael adducts was easily deduced from that of **7a** established by X-ray analysis. In the same way the absolute configuration of the corresponding aroyllactones was given.

d) These results suggest that the attack of lithiated reagents **1a,b** takes place predominantly or exclusively on the Re face of the α,β-unsaturated lactone **2**, a intermediate complex between the lithiated ion-

pair species and the carbonyl moiety of **2** being probably involved. As expected, the enolate trapping by the various halides on the opposite side of the lactone is evidenced.

e) The absolute configuration (*4aR,5S,8aS*) of the single diastereomer **13a** obtained by Lewis acid catalyzed cyclization of (3*S*,4*R*)-**12a** was assigned by taking into account the relative configuration deduced by X-ray analysis of a racemic analogous bicyclic compound **13b** (bearing a phenyl group instead of a pMeOPh) group prepared previously.[3] A transition state via a complex involving a carbonyl Lewis acid moiety in a pre-axial position, the aryl group lying in a pre-equatorial position can be considered (Fig. 2).



Complex

Fig. 2

Conclusion

The use of chiral aminonitriles **1a,b** in Michael addition / protonation or subsequent α-alkylation processes with α,β-unsaturated lactone **2** has proved to be a powerful way for the enantioselective synthesis of (4*R*)-aroyllactones **8a,b** and (3*S*)-substituted-(4*R*)-aroyl ones **11-12a**. A privileged attack of the Re face of the unsaturated lactone by the lithiated aminonitrile **1a,b** was envisionned to explain the high enantioselectivity observed. It was also shown that TMSOTf catalyzes the ring closure of (3*S*,4*R*)-**12a** affording the enantiomerically pure hydroxy bicyclic lactone bearing three chiral centers (4a*R*,5*S*,8a*S*)-**13a**. This stategy will be applied to the enantioselective synthesis of similar type of building blocks.

Experimental section

Reactions were performed in oven-dried glass under argon. Aminonitriles 4*S*,5*S*,*R*/*S*-(+)-[N-(2,2-dimethyl-4-phenyl-1,2-dioxan-5-yl)-N-methylamino](4-methoxyphenyl)acetonitrile **1a** and phenylacetonitrile **1b** were prepared according to reference [9] ; (N,N-dimethylaminophenyl)acetonitrile **1c** was obtained according to reference [5]. Tetrahydrofuran was distilled from sodium-benzophenone before use, nBuLi (1.6M in hexane) was purchased from Aldrich, 1-bromo-2-methyl-2-propene was prepared from the alcohol (Aldrich), [2-(iodomethyl)-2-propenyl]trimethylsilane was prepared according to reference [17], benzylbromide and methyl iodide were purchased from Across. Melting points are uncorrected. Column chromatography was carried out using silica gel. IR spectra were recorded on a Perkin-Elmer 1310 and are given in cm^{-1}. ^1H and ^{13}C NMR were recorded on a Brucker AM200 and 250 MHz spectrometers ; chemical shifts 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 (CP Sil column 25 m) or by chemical ionization (CI) with ammonia. Microanalyses were done by the Service of Microanalysis of CNRS. Optical rotation values were obtained using a Perkin-Elmer P.241 polarimeter.

*X-ray crystal structure determination for compound (S,R,R,S,S)-***7a**. A suitable crystal, which belonged to the orthorhombic space group $P2_12_12_1$, with lattice constants of a = 11.762(5), b = 15.399(8), c = 18.356(9) Å, V = 3325(5)Å^3 and Z = 4 was selected. Diffraction data were recorded at 243°K on an Enraf-Nonius CAD4 diffractometer using graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å) in the range 2°<2θ<40° with the ω-2θ scan technique. Data were corrected for Lorentz-polarization effects and decay (loss of 4% in 18 hours, linearly corrected) but not for absorption. 1196 reflections with I>3σ(I), out of 1782 unique reflections, were used. The structure was solved by direct method [18] and refined by full-matrix least squares (F) with isotropic thermal parameters. H atoms were introduced at calculated positions and constrained to ride on their parent C atoms. The final R value was 0.083 (Rw = 0.102). All calculations were performed on a Vax 4000-200 computer with the Enraf-Nonius MolEN system.[19]

A typical procedure for Michael addition follows : ***(4R)-4-[(R)-Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino)(4-methoxyphenyl)methyl]tetrahydropyran-2-one*** **3a** : A dry three neck flask equipped with a mechanical stirrer, a thermometer and a rubber septum, under argon was charged with 3.66 g (10 mmol) of (4*S*,5*S*,*R*/*S*)-(+)-[N-(2,2-dimethyl-4-phenyl-1,2-dioxan-5-yl)-N-methylamino](4-methoxyphenyl)acetonitrile **1a** in 40 mL of THF. The reaction mixture was cooled to -78°C and after 30 min 8 mL (12 mmol) of 1.6N n-butyllithium was added via a syringe. After 30 min 980 mg (10 mmol) of 5,6-dihydro-2H-pyran-2-one **2** was added over a period of 10 min into the yellow solution of lithiated **1a** kept at -90°C. After 1 h at this temperature 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 and dried over $MgSO_4$. After filtration and solvent evaporation the crude product was analyzed by ^1H NMR and either treated by 1M aqueous $AgNO_3$ in THF/Et_2O : 1/1 to give the crude aroyl lactone **8a** with a ee value of 87% in a 80% (3.70 g) yield or recrystallized from EtOH affording the major diastereomer **3a** (3.24 g) as white crystals in a 70% yield: mp 148°C; $[\alpha]_D^{20}$ = -6.9° (c = 1.00, THF); IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR 250 MHz (C_6D_6) 7.30 - 7.00 (m, 5H), 6.50 - 6.40 (m, 4H), 4.92 (dd, J = 14.5 and 1.8 Hz, 1H), 4.50 (d, J = 3.6 Hz, 1H), 3.50 (dd, J = 14.5 and 3.8 Hz, 1H), 3.31 - 3.20 (m, 2H), 3.15 (s, 3H), 2.85 (s, 3H), 2.60 (ddd, J = 16.3, 7.2 and 1.8 Hz, 1H), 2.45 - 2.35 (m, 1H), 2.08 - 1.90 (m, 1H), 1.50 (s, 3H), 1.35 (dd, J = 16.3 and 10.8 Hz, 1H), 1.15 (s, 3H), 1.15 - 0.95 (m, 1H), 0.75 - 0.55 (m, 1H); ^{13}C NMR 63 MHz ($CDCl_3$) 168.1, 160.3, 139.6, 124.9, 119.9, 114.0, 99.2, 76.0, 71.6, 67.1, 66.9, 58.9, 54.9, 54.6, 38.5, 35.8, 33.8, 29.4, 22.4, 18.8; CIMS m/z (relative intensity) : 465 (12.5), 464 (0.7), 438 (100). Analysis calcd for $C_{27}H_{32}N_2O_5$: C, 69.82; H, 6.89; N, 6.03. Found : C, 70.02; H, 7.09; N, 6.02.

(4R)-4-[(R)-Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino)(phenyl) methyl]tetrahydropyran-2-one **3b** : the deprotection of the crude Michael adduct product gave the aroyl lactone **8b** with a ee value of 70% in a 75% yield. After recrystallisation of the crude Michael adduct from EtOH the major diastereomer was obtained as white crystals in a 50% yield : mp 168°C; $[\alpha]_D^{20}$ = +22.6° (c 1.00, THF); IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR 250 MHz (C_6D_6) 7.20 - 6.70 (m, 10H), 4.90 (dd, J = 14.7 Hz, 1H), 4.45 (dd, J = 4.7 Hz, 1H), 3.40 (dd, J = 14.7 and 4.7 Hz), 3.30 - 3.15 (m, 1H), 3.12 (td, J = 14.7 and 4.7 Hz, 1H), 2.85 (s, 3H), 2.62 - 2.48 (m, 1H), 2.30 - 2.22 (m, 1H), 2.05 - 1.85 (m, 1H), 1.51 (s, 3H), 1.30 - 1.15 (m, 1H), 1.10 (s, 3H), 1.10 - 0.90 (m, 1H), 0.70 - 0.45 (m, 1H); ^{13}C NMR 50.4 MHz ($CDCl_3$) δ 169.3, 138.8, 132.3, 129.4, 129.0, 128.6, 128.3, 128.0, 127.9, 127.6, 127.2, 125.6, 125.0,

119.3, 99.4, 75.8, 73.2, 72.1, 67.8, 61.9, 58.8, 57.0, 54.7, 54.4, 38.7, 36.0, 35.5, 34.2, 33.2, 29.9, 29.5, 28.9, 22.3, 19.0, 18.7; CIMS m/z (relative intensity) : 435 (85.2), 434 (63), 408 (100). Analysis calcd for $C_{26}H_{30}N_2O_4$: C, 71.88; H, 6.91; N, 6.45. Found : C, 71.42; H, 6.79; N, 6.21.

A typical Michael addition/α alkylation procedure follows : ***(3S,4R)-4-[Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino)(4-methoxyphenyl)methyl]-3-[(trimethylsilylmethyl)allyl]tetrahydropyran-2-one*** **7a** : the intermediate enolate formed as described above by reaction of 980 mg (10 mmol) of **2** with 10 mmol of the lithiated derivative of **1a** in 40 mL of THF at -78°C was trapped by adding via a syringe 2.80 g (11 mmol) of [2-(iodomethyl)-2-propenyl]trimethylsilane in 12 mL of HMPA in 40 sec. The reaction mixture was then 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 Michael adduct was analyzed by ^1H NMR and either treated by 1M aqueous $AgNO_3$ as above to give the aroyl lactone **12a** with a ee value ≥ 99% in a 85% yield or recrystallized from EtOH to give the diastereomer **7a** in a 75% yield : mp 190°C; $[\alpha]_D^{20}$ = -79.9° (c = 1.00, THF); IR ($CHCl_3$) 1755 cm^{-1}; ^1H NMR 250 MHz (C_6D_6) 7.25 - 7.05 (m, 7H), 6.58 (dd, J = 8.4 Hz, 2H), 4.94 (d, J = 13.0 Hz, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 4.56 (d, J = 3.3 Hz, 1H), 3.60 - 3.30 (m, 3H), 3.20 (s, 3H), 3.02 (s, 3H), 2.80 - 2.60 (m, 2H), 2.60 - 2.50 (m, 1H), 2.50 - 2.40 (m, 2H), 1.88 (d, J = 13.0 Hz, 1H), 1.76 (d, J = 13.0 Hz, 1H), 1.55 - 1.40 (m, 1H), 1.50 (s, 3H), 1.42 - 1.28 (m, 1H), 1.15 (s, 3H), 1.15 - 1.10 (m, 1H), 0.05 (s, 9H); ^{13}C NMR 50.4 MHz ($CDCl_3$) 170.2, 160.6, 143.9, 139.7, 130.2, 125.2, 121.0, 114.2, 111.6, 99.2, 76.0, 72.0, 66.2, 64.4, 58.8, 54.8, 54.3, 43.0, 42.8, 42.4, 35.9, 29.4, 26.3, 21.7, 18.9; CIMS m/z (relative intensity) : 590 (14), 436 (100). Analysis calcd for $C_{34}H_{46}N_2O_5Si$: C, 69.15; H, 7.79; N, 4.74. Found : C, 68.91; H, 7.64; N, 4.74.

7c obtained as above by reaction of lithiated (N,N-dimethylamino)phenylacetonitrile with **2** followed by alkylation of the intermediate enolate by [2-(iodomethyl)-2-propenyl]trimethylsilane. After crystallization of the crude product one diastereomer was obtained in a 75% yield : mp 142°C; IR ($CHCl_3$) cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) 7.48 (dd, J = 8.4 Hz, 2H), 6.91 (dd, J = 8.4 Hz, 2H), 4.79 (s, 1H), 4.72 (s, 1H), 4.21 - 4.07 (m, 2H), 3.82 (s, 3H), 2.99 - 2.82 (m, J = 3.3 Hz, 1H), 2.82 - 2.75 (m, J = 3.3 Hz, 1H), 2.59 - 2.49 (m, 2H), 2.28 (broad s, 6H), 2.10 - 1.90 (m, 2H), 1.65 - 1.55 (m, 2H), 0.05 (s, 9H); ^{13}C NMR 62.9 MHz ($CDCl_3$) 171.9, 160.0, 143.1, 129.3, 124.8, 117.1, 113.8, 111.8, 73.3, 63.3, 55.1, 42.29, 41.6, 40.8, 40.7, 26.0, 22.0, 1.57; CIMS m/z (relative intensity) : 414 (10), 415 (100). Analysis calcd for $C_{23}H_{34}O_3N_2Si$: C, 66.66; H, 8.21; N, 6.76. Found : C, 66.09; H, 8.19; N, 6.61.

(3S,4R)-4-[(R)-Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino)(4-methoxyphenyl)methyl]-3-(2-methylallyl)tetrahydropyran-2-one **4a** : the deprotection of the crude product gave the aroyl lactone **9a** with a ee value of 83% in a 65% yield. **5a** was characterized in the ^1H NMR of the crude product by the following signals : ^1H NMR 250 MHz (C_6D_6) 7.20 - 7.05 (m, 7H), 6.52 (d, J = 8.4 Hz, 2H), 4.90 (dd, J = 14.8 and 2.0 Hz, 1H), 4.85 (s, 1H), 4.75 (s, 1H), 4.52 (d, J = 5.9 Hz, 1H), 3.60 - 3.10 (m, 3H), 3.22 (s, 3H), 2.92 (s, 3H), 2.70 - 2.55 (m, 1H), 2.50 - 2.42 (m, 2H), 2.40 - 2.28 (m, 2H), 1.82 (s, 3H), 1.50 (s, 3H), 1.30 - 1.00 (m, 1H), 1.10 (s, 3H), 0.95 - 0.75 (m, 1H); CIMS for $C_{31}H_{38}N_2O_5$ m/z (relative intensity) : 519 (11), 492 (100).

(3S,4)-4-[(R)-Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino) phenylmethyl]-3-(2-methylallyl)tetrahydropyran-2-one **4b** : the deprotection of the crude product gave the aroyl lactone **9b** with a ee value of 66% in a 55% yield. **4b** was characterized in the ^1H NMR of the crude product by the following signals : ^1H NMR 250 MHz (C_6D_6) 7.30 - 7.15 (m, 10H), 4.90 (d, J = 13.1 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.50 (d, J = 4.7 Hz, 1H), 3.45 - 3.28 (m, 3H), 2.97 (s, 3H), 1.82 (s, 3H), 1.50 (s, 3H), 1.10 (s, 3H); CIMS for $C_{30}H_{36}N_2O_4$ m/z (relative intensity) : 468 (16), 462 (76), 222 (100).

(3S,4R)-4-[(R)-Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino)(4-methoxyphenyl)methyl]-3-(methyl)tetrahydropyran-2-one **5a** : the deprotection of the crude product gave the aroyl lactone **10a** with a ee value of 87% in a 60% yield. The diastereomer **5a** was characterized in the ^1H NMR of the crude product by the following signals : ^1H NMR 250 MHz (C_6D_6) 7.30 - 7.00 (m, 7H), 6.55 (d, J = 8.5 Hz, 2H), 4.95 (d, J = 14.7 Hz, 1H), 4.55 (d, J = 4.7 Hz, 1H), 3.60 - 3.40 (m, 3H), 3.25 (s, 3H), 2.82 (s, 3H), 2.48 - 2.41 (m, 1H); CIMS for $C_{28}H_{34}N_2O_5$ m/z (relative intensity) : 479 (15), 452 (100).

(3S,4R)-3-[Benzyl]-[(R)-Cyano(N-(2,2-dimethyl-4-(S)-phenyl-1,2-dioxan-5-(S)-yl)-N-methylamino)(4-methoxyphenyl)methyl]tetrahydropyran-2-one **6a** : the deprotection of the crude product gave the aroyl lactone **11a** with a ee value of 80% in a 63% yield. After recrystallization from EtOH **6a** was obtained as white crystals in a 60% yield : mp 194°C; $[\alpha]_D^{20}$ = +19.9° (c = 1.00, THF); ^1H NMR 250 MHz (C_6D_6) 7.38 (dd, J = 7.9 Hz, 2H), 7.20 - 7.00 (m, 5H), 6.51 (dd, J = 7.9 Hz, 1H), 5.00 (d, J = 14.0 and 1.5 Hz, 1H), 4.55 (d, J = 3.6 Hz, 1H), 3.50 (dd, J = 14.0 and 3.6 Hz, 1H), 3.45 - 3.35 (m, 2H), 3.35 - 3.25 (m, 1H), 3.20 (s, 3H), 3.00 - 2.70 (m, 1H), 2.95 (s, 3H), 2.79 (q, J = 5.4 Hz, 1H), 2.75 - 2.60 (m, 1H), 2.55 - 2.48 (m, 1H), 1.55 (s, 3H), 1.20 (s, 3H), 1.20 - 0.99 (m, 2H); ^{13}C NMR 62 MHz ($CDCl_3$) 159.8, 138.6, 136.8, 129.7, 129.5, 128.4, 127.8, 127.7, 127.3, 126.9, 125.0, 120.7, 113.5, 99.1, 71.0, 66.1, 66.5, 65.3, 58.5, 55.0, 54.2, 44.3, 40.75, 38.6, 35.4, 28.8, 22.0, 21.8, 18.8, 15.0, 13.6; CIMS for $C_{34}H_{38}N_2O_5$ m/z (relative intensity) : 528 (100).

Typical general procedure for aroyllactones follows : Crude or crystallized Michael adducts (5 mmol) dissolved in 4 mL THF and 2 mL Et_2O and stirred with 6 mL of a 1N aqueous solution of $AgNO_3$ for 6 h at room temperature. The precipitate was filtered and washed with Et_2O and H_2O. The aqueous phase was extracted by Et_2O (three times) and the combined organic layers were washed with brine and dried over $MgSO_4$. Purification by column chromatography on silica gel gave the pure ketones (eluent 60/40 : Et_2O/hexane). The ee values of the ketones was measured by ^1H NMR study by addition of Eu(hfc)$_3$ inducing a large shift either of the aromatic protons for compounds **8** - **11a**, **8** - **9b** of the vinylic ones for **12a** and of the protons of the 4-methoxy moiety for **13a**.

(4R)-4-(-Methoxy)benzoyl-tetrahydropyran-2-one **8a** obtained from isomer **3a** after column chromatography in a 65% yield with a ee value ≥ 99% : mp 108°C; $[\alpha]_D^{20}$ = +4.5° (c 1.00, THF); IR ($CDCl_3$) 1685, 1750 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) 7.95 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 4.45 - 4.30 (m, 1H), 4.03 - 3.80 (m, 1H), 3.91 (s, 3H), 3.00 (dd, J = 16.0 and 8.5 Hz, 1H), 2.70 (dd, J = 16.0 and 6.0 Hz, 1H), 2.32 - 2.15 (m, 1H), 2.15 - 1.91 (m, 1H); ^{13}C NMR 50.4 MHz ($CDCl_3$) 197.4, 170.8, 164.1, 130.8, 127.7, 114.2, 66.8, 55.5, 37.4, 31.5, 26.1; MS (coupled with CPG) m/z (relative intensity) : 235 (1), 234 (5), 135 (100). Analysis calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 5.98. Found: C, 66.53; H, 6.03.

(4R)-4-Benzoyl-tetrahydropyran-2-one **8b** obtained from isomer **3b** after column chromatography in a 45% yield with a ee value ≥ 99% : mp 85°C; $[\alpha]_D^{20}$ = +10.8° (c 1.00, THF); IR ($CDCl_3$) 1690, 1740 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) 8.10 - 7.92 (m, 2H), 7.72 - 7.48 (m, 3H), 4.50 - 4.30 (m, 2H), 4.08 - 3.90 (m, 1H), 3.00 (dd, J = 16.8 and 8.4 Hz, 1H), 2.70 (dd, 16.8 and 5.6 Hz, 1H), 2.35 - 2.26 (m, 1H), 2.24 - 1.98 (m, 1H); ^{13}C NMR 50.4 MHz ($CDCl_3$) 199.9, 170.5, 134.6, 133.8, 128.9, 128.4, 66.7, 66.0, 37.7, 31.2, 25.9; MS (coupled with CPG) m/z (relative intensity) : 264 (0.4), 105 (100). Analysis calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found : C, 70.53; H, 6.09.

(3S,4R)-4-(4-Methoxy)benzoyl-3-(2-methylallyl)tetrahydropyran-2-one **9a** obtained by column chromatography of the Michael adduct in a 65% yield with a ee value of 83% : mp 104°C. The racemic **9a** was previously described.[3]

(3S,4R)-4-Benzoyl-3-(2-methylallyl)tetrahydropyran-2-one **9b** obtained by chromatography of the crude Michael adduct in a 55% yield with a ee value of 66% : mp 80.2°C. The racemic **9b** was described in reference [3].

(3S,4R)-4-(4-Methoxy)benzoyl-3-methyl-tetrahydropyran-2-one **10a** obtained by column chromatography of the Michael adduct in a 60% yield with a ee value of 87% : mp 96°C; IR ($CDCl_3$) 1680, 1745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.95 (d, J = 5.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 4.40 - 4.20 (m, 2H), 3.88 (s, 3H), 3.62 - 3.46 (m, 1H), 3.40 - 3.20 (m, J = 10.2 Hz, 1H), 2.35 - 2.15 (m, 1H), 1.90 (dq, J = 14.1 and 4.3 Hz, 1H), 1.15 (d, J = 7.6 Hz, 3H); ^{13}C NMR 50.4 MHz ($CDCl_3$) 197.5, 174.9, 163.9, 130.6, 128.2, 114.0, 65.6, 55.4, 43.7, 35.1, 27.4, 15.1; MS (coupled with CPG) m/z (relative intensity) : 248 (1.4), 135 (100). Analysis calcd for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found : C, 67.51; H, 6.62.

(3S,4R)-3-Benzyl)-4-(4-methoxy)benzoyl tetrahydropyran-2-one **11a** obtained by deprotection of **6a** and column chromatography with a ee ≥ 99% in a 55%: mp 115°C; $[\alpha]_D^{20}$ = +19.9° (c = 1.00, THF); IR ($CDCl_3$) 1745, 1680 cm^{-1}; ^1H NMR 250 MHz (C_6D_6) 7.60 (d, J = 8.4 Hz, 2H), 7.40 - 7.30 (m, 2H), 7.10 - 6.90 (m, 3H), 6.60 (d, J = 8.4 Hz, 2H), 3.71 - 3.60 (m, 1H), 3.58 - 3.46 (m, J = 10.5, 10.5 and 2.6 Hz, 1H), 3.38 (td, J = 3.9 and 11.8 Hz, 1H), 3.20 - 3.03 (m, J = 6.5 Hz, 1H), 3.12 (broad s, 3H), 2.96 (dd, J = 15.7 and 3.9 Hz, 1H), 1.42 - 1.20 (m, 1H), 1.12 - 0.90 (qd, J = 3.9 and 14.4 Hz, 1H); ^{13}C NMR 62.9 MHz ($CDCl_3$) δ 197.2, 163.9, 138.2, 130.6, 129.6, 128.2, 127.8, 126.5, 113.9, 65.7, 55.0, 41.7, 41.2, 33.5, 27.4; MS (coupled with CPG) m/z (relative intensity) : 324 (2), 189 (100). Analysis calcd for $C_{20}H_{20}O_4$: C, 74.07; H, 6.17. Found : C, 73.94; H, 6.30.

(3S,4R)-4-(4-Methoxy)benzoyl-3[2-[(trimethylsilyl)methyl]allyl]tetrahydropyran-2-one **12a** obtained by deprotection of the isomer **7a** and column chromatography as an oil with a ee ≥ 99% in a 70% yield (eluting solvent ether/hexane : 50/40); $[\alpha]_D^{20}$ = -11° (c 1.00, THF); ^1H NMR 250 MHz ($CDCl_3$) 7.91 (dd, J = 8.4 Hz, 2H), 6.98 (dd, J = 8.4 Hz, 2H), 4.49 (broad s, 1H), 4.40 - 4.20 (m, 2H), 4.37 (broad s, 1H), 3.90 (s, 3H), 3.78 - 3.66 (m, 1H), 3.66 - 3.53 (m, J = 8.5, 5.3 and 1.0 Hz, 1H), 2.58 (dd, J = 14.5 and 5.3 Hz, 1H), 2.31 - 2.10 (m, 1H), 2.19 (dd, J = 14.5 and 8.5 Hz, 1H), 1.90 - 1.75 (m, J = 14.5 and 4.0 Hz, 1H), 1.40 (broad s, 2H), 0.05 (broad s, 9H); ^{13}C NMR 62 MHz ($CDCl_3$) 196.9, 174.1, 163.7, 143.9, 130.6, 128.0, 113.9, 111.4, 65.6, 55.4, 42.0, 39.6, 38.2, 27.3, 25.4, -1.5; MS (coupled with CPG) m/z (relative intensity) : 360 (13), 361 (100). Analysis calcd for $C_{20}H_{28}O_4Si$: C, 66.66; H, 7.77. Found : C, 66.45; H, 7.89.

(4aR,5S,8aS)-5-Hydroxy-7-methylidene-5-(4-methoxyphenyl)-3,4,4a,5,6,7,8,8a-octahydroisocoumarin **13a** : 0.15 eq. TMSOTf (22 µl) was added via a syringe to **12a** 172 mg (0.47 mmol) in 3 mL of CH_2Cl_2 at -78°C under argon and stirred 3 h at this temperature. The reaction mixture was diluted with Et_2O (2 mL) and then quenched with H_2O (1 mL). The organic layer was separated. The aqueous layer was extracted twice with Et_2O (10 mL). The combined layers were washed with brine and dried over $MgSO_4$ filtered and concentrated in vacuo to give a white solid with a ee value ≥ 99% in a 80% yield : mp 143.8°C after recrystallization from EtOH; $[\alpha]_D^{20}$ = 101° (c 1.00, THF); IR ($CDCl_3$) 3550, 2910, 1750, 1650 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) 7.40 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.4 Hz, 2H), 5.06 (s, 1H), 4.90 (s, 1H), 4.30 - 4.10 (m, 2H), 3.85 (s, 3H), 3.00 - 2.82 (m, 1H), 2.80 - 2.65 (m, 2H), 2.40 - 2.15 (m, 3H), 1.90 (s, 1H), 1.70 - 1.50 (m, 2H); ^1H NMR 250 MHz C_6D_6) 7.10 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 4.78 (d, J = 1.7 Hz, 1H), 4.52 (s, 1H), 3.62 - 3.48 (m, 2H), 2.83 - 2.70 (m, 1H), 2.25 - 2.05 (m, 3H), 2.15 (s, 3H), 1.82 (dd, J = 13.9 and 1.7 Hz, 1H), 1.56 (dt, J = 11.9 and 8.2 Hz, 1H), 1.38 (s, 1H), 1.31 - 1.18 (m, 1H), 1.15 - 0.95 (m, 1H); ^{13}C NMR 62 MHz (C_6D_6) 174.6, 158.5, 142.6, 136.7, 125.8, 114.0, 113.7, 66.9, 66.7, 65.8, 55.2, 49.7, 43.2, 40.5, 34.8, 23.0, 15.2; MS m/z (relative intensity) : 289 (100). Analysis calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found : C, 71.21; H, 7.08.

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(*Received in Belgium* 19 *April* 1996; *accepted* 4 *June* 1996)