Bull Soc Chim Fr (1997) 134, 809-815

Enantioselective synthesis of 3-substituted 4-aroyl-γ-lactones*

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(Received 1 August 1997; accepted 21 October 1997)

Summary — Michael addition of the lithiated chiral acyl equivalent **1** to 2-butenolide **2** afforded the (*1R*)-aroyl-γ-lactone **9** with an enantiomeric excess (ee) value of ≥ 99%. Michael addition of **1** to **2** and subsequent alkylation provided (3*S*)-substituted (*1R*)-aroyl-γ-lactones **12** and **14** with an ee value of 60 to 65% and enantiomerically pure lactones **10**, **11** and **13**. The absolute configuration of the Michael adduct **7** was unequivocally established by X-ray crystal analysis and consequently that of all γ-lactones **9**–**14** could be deduced.

asymmetric Michael addition–protonation / asymmetric Michael addition–α-alkylation / chiral acyl equivalent / functionalized γ-lactones

Résumé — Synthèse énantiosélective de 4-aroyl-γ-lactones substituées en 3. L'addition de Michael du dérivé lithié équivalent d'acyle chiral **1** sur le 2-butenolide **2** conduit à l'aroyl-γ-lactone **9** avec un ee ≥ 99%. L'addition de Michael de **1** sur **2** suivie d'alkylation permet d'obtenir les (3*S*)-substituées (*1R*)-aroyl-γ-lactones **12** et **14** avec un ee compris entre 60 et 65% ainsi que les lactones **10**, **11** et **13** énantiomériquement pures (ee ≥ 99%). La configuration absolue de l'adduit de Michael a été établie sans ambiguïté par une analyse aux rayons-X et par conséquent celle de toutes les γ-lactones **9**–**14**.

addition de Michael asymétrique–protonation / addition de Michael asymétrique α-alkylation / équivalent d'acyle chiral / γ-lactones fonctionnalisées

Introduction

Functionalized γ-lactones are useful building blocks leading to a wide variety of compounds which display interesting biological properties [1]. We have previously shown that Michael addition of lithiated 2-(dimethylamino)-2-arylacetonitrile to 2-butenolide and 2-pentenolide followed by the trapping of the intermediate enolates with various halides is a route of choice for the obtention of 3,4-disubstituted γ- and δ-lactones respectively [2]. Moreover, we have recently extended this approach to the enantioselective synthesis of functionalized δ-lactones [3] using as Michael donor a chiral masked acyl anion developed by Enders et al [4,5]. Enantiomerically enriched substituted γ-lactones have been obtained by different groups starting either from chiral 2-butenolides as Michael acceptors [6–8] or from chiral Michael donors [9]. However, the reaction of chiral aminonitriles with 2-butenolide has not been investigated up to now. We report herein the enantioselective synthesis of unsubstituted and 3-substituted 4-aroyl-γ-lactones following this approach.

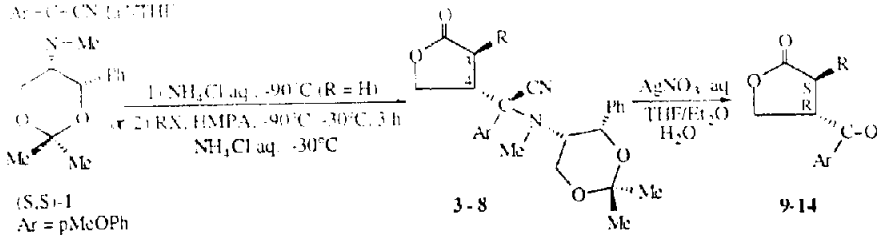
Results

Michael adducts **3**–**8** were obtained by conjugate addition of lithiated (*1S,5S,R/S*)-2-[*N*-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)*N*-methylamino]-2-(4-methoxyphenyl)acetonitrile **1** [5] to 2-butenolide **2** followed either by protonation or by alkylation with methyl bromoacetate, benzyl bromide, 3-bromo-2-methylpropene, bromo-2-methylbut-2-ene and [2-(iodomethyl)-2-propenyl] trimethylsilane [10] as outlined in scheme 1.

The lithiated reagent **1** was generated from the α-aminonitrile (*S,S,R/S*) in THF at −90 °C using 1.6 M *n*-BuLi in hexane. After addition of a stoichiometric amount of **2** the reaction was completed either (1) by leaving during 1 h at −90 °C then quenching at this temperature by a saturated aqueous NH_4Cl solution and subsequent usual work-up or (2) by adding a halide in HMPA solution at −90 °C, the temperature of the reaction medium being kept at −30 °C during 1 h. After hydrolysis and usual work-up as above, the crude products were analyzed by IR, ^1H and ^{13}C NMR spectroscopy. The results are presented in table I.

* Dedicated to Prof D Seebach on the occasion of his 60th birthday.

* Correspondence and reprints



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R	Predominant diastereomer Aminonitrile	Predominant enantiomer Aroyl lactone
H	**3**	**9**
CH_2CO_2Me	**4**	**10**
CH_2Ph	**5**	**11**
$CH_2-C(Me)=CH_2$	**6**	**12**
$CH_2-CH=CMe_2$	**7**	**13**
$CH_2-C(CH_2SiMe_3)=CH_2$	**8**	**14**

Scheme 1

Table I. Aminonitrile adducts **3**–**8** and aroyl lactones **9**–**14**.

R	*Michael adduct*			*Aroyl lactone*		
	Compound	*Yield (%)*[a]	*de (%)*[b]	*Compound*	*Yield (%)*[a,c,d]	*ee (%)*[d,e]
H	(*R,R,S,S*)-**3**[f]	90	⩾ 99	(*1R*)-**9**	70 (80)	⩾ 99 (95)
CH_2CO_2Me	(*S,R,R,S,S*)-**4**	85	⩾ 99	(*3S,1R*)-**10**	70 (75)	⩾ 99 (98)
CH_2Ph	(*S,R,R,S,S*)-**5**	90	⩾ 99	(*3S,1R*)-**11**	75 (80)	⩾ 99 (99)
$CH_2-C(Me)=CH_2$	(*S,R,R,S,S*)-**6**			(*3S,1R*)-**12**	(60)	(60)
$CH_2-CH=C(Me)_2$	(*S,R,R,S,S*)-**7**	95	⩾ 99	(*3S,1R*)-**13**	70 (80)	⩾ 99 (98)
$CH_2-C(CH_2SiMe_3)=CH_2$	(*S,R,R,S,S*)-**8**			(*3S,1R*)-**14**	(70)	(65)

[a] Yield (%) of isolated Michael adduct or aroyl lactone based on starting aminonitrile **1**. [b] determined by ^1H and ^{13}C NMR spectroscopy. [c] yield and ee (%) values refer to aroyl lactones obtained from crystallized Michael adducts; [d] yield and ee (%) values in brackets refer to aroyl lactones obtained from crude Michael adducts; [e] determined by ^1H NMR shift experiments with Eu(hfc)$_3$; [f] configuration given in the following order for **3**: $C_3C(CN)$, chiral auxiliary and for **4**–**8**: $C_1C_3C(CN)$, chiral auxiliary.

One predominant stereoisomer was characterized by ^1H NMR for the Michael adducts **3**–**8**. In the case of adducts **3**, **5** and **7** these stereoisomers were isolated after recrystallization of the corresponding crude products in 85 up to 95% yield (table I).

The stereochemistry of the Michael adducts was established by ^1H NMR study either on the pure stereoisomers **4**, **5** and **7** or on the crude products **6** and **8**. An unexpected *trans* quasi-diaxial relationship between the vicinal substituents was deduced from the $^3J(H_3,H_4)$ coupling constant values of 1.0 up to 4.4 Hz, the lactone ring adopting an envelope conformation as recently proposed by Jaime et al. [11].

The X-ray analysis of the Michael adduct **7**, shown in figure 1, supported the structural assignment deduced from ^1H NMR data: the $C_4C_3C_1C_{11}$ dihedral angle of −136° is in agreement with the two substituents occupying a *trans* quasi-diaxial position. Moreover, the envelope conformation is confirmed by the $C_5O_1C_2C_4$ dihedral angle of −0.18° as well as by the data presented in table II.

The general preference for such a conformation is certainly due to destabilizing gauche interactions involved in a quasi-diequatorial relationship. Similar favoured *trans* diaxial conformations were previously shown by us [2] and others [12].

The absolute configuration of the new chiral centers of **7** was unequivocally established from X-ray analysis: C_3: *S*, C_1: *R*, C_{11} (CN): *R*. We assumed that the Michael adducts **4**–**6** and **8** presented the same absolute configuration as **7** and that the absolute configuration of **3** is thus: C_1: *R*, C_{11} (CN): *R*.

The unmasking of the aminonitrile moiety of either the crude or the stereoisomerically pure Michael adducts was performed by aqueous silver nitrate treatment to prevent any isomerization according to Welvart et al. [13].

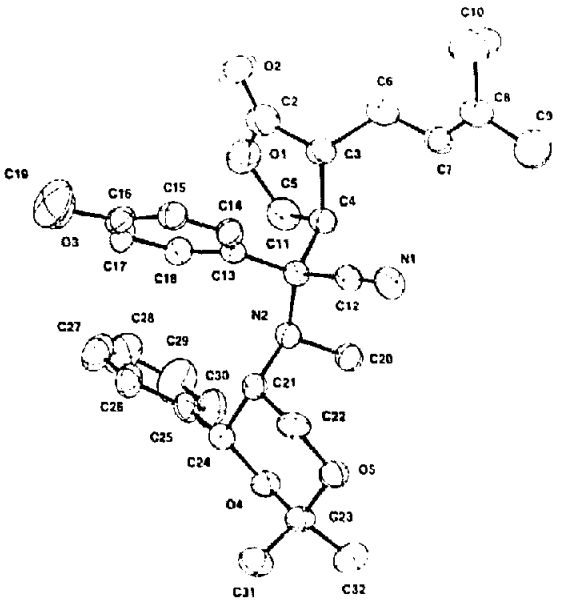

Fig 1. Perspective view of compound **7**.

Table II. Main X-ray data of **7** (selected torsional angles in degrees).

$C_6C_3C_1C_{11}$	= −136.85	$C_3O_1C_2C_3$	= −0.18
$C_{12}C_{11}C_4C_5$	= 169.91	$O_1C_2C_3C_4$	= −14.04
$C_{13}C_{11}C_4C_5$	= −71.94	$C_2C_3C_4C_5$	= 21.38
$N_2C_{11}C_4C_5$	= 51.60	$C_3C_4C_5O_1$	= −22.07
$N_2C_{21}C_4C_{25}$	= −42.81	$C_5C_7C_6C_3$	= −120.68
$C_{11}N_2C_{21}C_{24}$	= 153.72	$H_3C_3C_4H_4$	= −107.60

Crude aroyl-γ-lactones **9**–**14** obtained from crude Michael adducts were formed in a 60–80% yield with an enantiomeric excess varying from 60 to ⩾ 99% (table I).

Enantiomerically pure lactones **9**, **10**, **11** and **13** (ee ⩾ 99%) were isolated from the corresponding pure stereoisomer Michael adducts in a 70 to 75% yield (table I).

The enantiomeric excess values were measured by ^{1}H NMR using Eu(hfc)$_3$ and ensured by the study of the corresponding racemic lactones **9**–**14** prepared from 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile.

The expected *trans* stereochemistry of the 3-substituted 4-aroyl-γ-lactones **10**–**14** was evidenced by the $^3J(H_3,H_4)$ coupling constant values of 7.9 up to 9.3 Hz, the two substituents occupying a quasi-diequatorial position and the lactone ring lying in an envelope form. Such values are also in agreement with literature data [14]. We confirmed this *trans* relationship as well as the ring conformation by the X-ray analysis of the racemic γ-lactone **12** [15].

The absolute configuration of enantiomerically enriched γ-lactones was deduced from that of the corresponding Michael adducts: (4*R*) for **9** and (3*S*,4*R*) for **10**–**14**.

Discussion

The conjugate addition of **1** to 2-butenolide **2** is highly stereoselective as one stereoisomer is predominantly formed. In the same way one predominant stereoisomer is detected by conjugate addition followed by alkylation.

The obtention of enantiomerically pure γ-aroyllactones **9**–**11** and **13** after unmasking either the isolated stereoisomers of the Michael adducts **3**–**5** and **7** or the corresponding crude products suggests that the attack of the lithiated aminonitrile **1** takes place predominantly or exclusively on one face of **2**. This discrimination appears to be less efficient in the case of lactones **12** and **14**. Intermediate complexes between the lithiated ion-pair species and the carbonyl moiety of the lactone ring are probably involved [16,17]. The absolute configuration assigned to the Michael adducts **3**–**8** fits with a privileged attack of the Re face of the 2-butenolide. Such an observation is in line with our previous results related to δ-lactones [3] and to those of Enders et al concerning cyclohexanones [5].

Finally, the trapping of the intermediate enolates by the different halides occurs on the opposite side of the lactone ring leading to *trans* vicinal disubstituted Michael adducts.

We have thus demonstrated the efficiency of Michael addition of the chiral lithiated aminonitrile **1** to five-membered α,β-unsaturated lactone **2** followed either by protonation or by subsequent α-alkylation for the synthesis of enantiomerically enriched unsubstituted and 3-substituted 4-aroyl-γ-lactones **9**–**14**. Further investigation of this methodology is underway.

Experimental section

Reactions were performed in oven-dried glass under argon. Aminonitrile, 4*S*,5*S*,*R*/*S*-(+)-2[*N*-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-*N*-methylamino]-2-(4-methoxyphenyl) acetonitrile was prepared according to [1]; 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile was obtained according to [18]. Tetrahydrofuran was distilled from sodium-benzophenone before use; *n*-BuLi (1.6 M in hexane) was purchased from Aldrich. 3-bromo-2-methylpropene was prepared from the alcohol (Aldrich), [2-(iodomethyl)propenyl]-trimethylsilane was prepared according to [10]; benzyl bromide, 4-bromo-2-methylbut-2-ene and methyl bromoacetate were purchased from Acros. Melting points were uncorrected. Column chromatography was carried out using silica gel. IR spectra were recorded on a Perkin-Elmer 1310 instrument and were given in cm^{-1}. ^{1}H and ^{13}C NMR were recorded on Bruker AM200 and 250 spectrometers; chemical shifts are given in ppm (internal standard tetramethylsilane); *J* values were given in hertz and measured in some cases after irradiation of protons. Mass spectra were performed on a Nermag 10–10 mass spectrometer coupled with capillary chromatography (CPSil column, 25 m) or by chemical ionization with ammonia (CI, NH$_4$). Microanalyses were performed by the Service of Microanalysis of CNRS. Optical rotation values were obtained using a Perkin-Elmer P 341 polarimeter.

X-ray crystal structure determination for compound (S,R,R,S,S)-7

A suitable crystal, which belonged to the orthorhombic space group $P2_12_12_1$, with lattice constants a = 10.335(5),

[illegible] 18.3 [illegible] Å, V = 2887 [illegible] Å^3 and Z = [illegible]. Diffraction data were recorded at 295 K [illegible] Nonius CAD4 diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) in the range 2 < θ < 30° with the ω–2θ scan technique. Data were corrected for Lorentz-polarization effects and decay (loss of [illegible] in 18 h, linearly corrected) but not for absorption. 1141 reflections with $I > 3\sigma(I)$, out of 1782 unique reflections, were used. The structure was solved by direct methods 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 2.9 (R_w = 2.7).

The structure was solved by: (1) Data Collection CAD-4 PC Software (ENRAF-NONIUS, 1992) [19]; (2) Cell refinement: SET 4 and CELDIM (CAD-4 PC Software); (3) Data reduction: CRYSTALS [20].

Program(s) used to solve structure: SIR 92 [21]. Program(s) used to refine structure: CRYSTALS [20]. Molecular graphics: CAMERON [22].

A typical procedure for Michael addition: (R)-4-[(R)-cyano(N-(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N-methylamino(4-methoxyphenyl)-methyl]tetrahydrofuran-2-one **3**

A dry three-necked flask equipped with a mechanical stirrer, a thermometer and a rubber septum, under argon, was charged with 1.84 g (5 mmol) of (4S,5S,R,S)-2-(N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N-methylamino)-2-(4-methoxyphenyl)acetonitrile in 20 mL of anhydrous THF. The reaction mixture was cooled to −90 °C and after 10 min, [illegible] mL ([illegible] mmol) of 1.6 M *n*-butyllithium in hexane solution was added via a syringe. After 30 min, 420 mg (5 mmol) of 2(5*H*)-furanone **2** was added over a period of 5 min into the yellow solution of lithiated **1** 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 ^{1}H NMR and recrystallized from benzene giving the major isomer **3** (150 mg) as white crystals in a 70% yield. Mp 114 °C.

$[\alpha]_D^{25}$ = −19.8 (c = 1.00, THF).

IR (CCl_4): 2260, 1700 cm^{-1}.

^{1}H NMR (250 MHz, C_6D_6): [illegible]

^{13}C NMR (62.9 MHz, $CDCl_3$): 174.7, 160.2, 138.7, 128.8, 128.0, 127.8, 127.6, 124.4, 119.2, 114.2, 99.1, 75.8, 70.0, 66.0, 58.0, 55.2, 51.2, 42.9, 36.1, 32.0, 29.0, 18.9.

MS (CI, NH_3) m/z (relative intensity): [illegible]

Anal. calc. for [illegible] Found: C 68.84, H 6.60, N 6.01.

[illegible] 3'

Two diastereomers in a 70:30 ratio were obtained by addition of lithiated 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile on **2** and were characterized by ^{1}H NMR of the crude product.

IR (CCl_4): 2220, 1790 cm^{-1}.

Major isomer:

^{1}H NMR (200 MHz, $CDCl_3$): 7.45 (AB system, J = 7.9 Hz, 2H), 6.90 (AB system, J = 7.9, 2H), 4.20–4.30 (m, 1H), 3.95–4.18 (m, 1H), 3.75 (s, 3H), 3.25–3.50 (m, 1H), 2.75 (dd, J = 7.9 and 15.8 Hz, 1H), 2.48 (dd, J = 5.3 and 15.8 Hz, 1H), 2.25 (s, 6H).

MS (CI, NH_3) m/z (relative intensity): 292 (21), 275 (31), 248 (100).

Minor isomer characterized by the following ^{1}H NMR signals: 4.55–4.45 (m, 1H), 4.25–4.10 (m, 1H).

A typical procedure for Michael addition/α-alkylation: (3S,4R)-4-[(R)-cyano(N-(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N-methylamino(4-methoxyphenyl)methyl]-3-(methoxycarbonyl)methyl]tetrahydrofuran-2-one **4**

The intermediate enolate formed as described above by reaction of 840 mg (10 mmol) of **2** with 10 mmol of the lithiated derivative **1** in 40 mL of THF at −78 °C was trapped by adding via a syringe 1.88 g (11 mmol) of methyl bromoacetate in 10 mL of HMPA in 40 s. 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 ^{1}H NMR and either treated by 1 M aqueous $AgNO_3$ as above to give the aroyl lactone **10** with an ee value [illegible] 98% in a 85% yield or recrystallized from EtOH to give the diastereomer **4** in a 85% yield. Mp 105 °C.

$[\alpha]_D^{25}$ = [illegible] 63.5 (c = 1.00, THF).

IR (CCl_4): 1780 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): [illegible] 2.45 (m, 1H), 1.95 (q, J = 4.4 Hz, 1H), 1.45 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 176.5, 171.2, 160.3, 138.6, 129.0, 128.2, 127.7, 127.5, 124.2, 119.8, 114.5, 99.3, 75.6, 70.4, 66.2, 65.4, 58.8, 55.2, 51.3, 52.1, 46.9, 38.8, 36.4, 31.5, 29.0, 18.9.

MS (CI, NH_3) m/z (relative intensity): 523 (2), 196 (100).

Anal. calc. for [illegible] Found: C 66.27, H 6.64, N 5.87.

[illegible] tetrahydrofuran-2-one **4'**

4' was obtained as above by reaction of lithiated 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile with **2** followed by alkylation of the intermediate enolate with methyl bromoacetate. After crystallization of the crude product two diastereomers in a 70:30 ratio were obtained in a 75% yield.

Major isomer:

IR (CCl_4): 1790, 1740 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): 7.45 (AB system, J = 7.9 Hz, 2H), 6.95 (AB system, J = 7.9 Hz, 2H), 4.55–4.35 (m, 2H), [illegible] (s, 3H), 3.75 (s, 3H), 3.48 (q, J = 5.9 Hz, 1H), [illegible] (m, 2H), 2.60–2.45 (m, 1H), 2.30 (s, 6H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 176.4, 171.2, 160.3, 128.9, 128.4, [illegible], 75.3, 52.1, 45.2, 41.0, 38.7, [illegible].

MS (CI, NH_3) m/z (relative intensity) 347 (100).

Anal calc for $C_{?}H_{?}N_2O_{?}$: C 62.42 H 6.35 N 8.09. Found C 61.88, H 6.37, N 7.88.

Minor isomer characterized by the NMe_2 signal at 2.35 (s, 6H).

(3S,4R)-3-Benzyl-4-[(R)-cyano(N-((4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N-methylamino)(4-methoxyphenyl)methyl]-tetrahydrofuran-2-one **5**

The crude product was either deprotected leading to the aroyl lactone **11** with an ee value > 99% in a 80% yield or recrystallized from EtOH to give the diastereomer **5** in a 90% yield: Mp 110 °C.

$[\alpha]_D^{20}$ = −47.9 (c = 1.00, THF).

IR (CCl_4): 2940, 1780, 1610 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): 7.50–7.15 (m, 12H), 6.65 (AB system, J = 7.9 Hz, 2H), 4.96 (d, J = 4.4 Hz, 1H), 4.65 (dd, J = 2.4 and 12.6 Hz, 1H), 3.98 (dd, J = 4.2 and 12.6 Hz, 1H), 3.82 (dd, J = 3.4 and 10.5 Hz, 1H), 3.80 (s, 3H), 3.35 (dd, 8.4 and 10.5 Hz, 1H), 3.15–3.05 (m, J = 3.4 and 8.4 Hz, 1H), 3.05–2.85 (m, 2H), 2.90 (s, 3H), 2.70–2.60 (m, 1H), 2.40–2.38 (m, J = 5.2, 5.2 and 3.4 Hz, 1H), 1.60 (s, 3H), 1.55 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 177.4, 160.3, 138.7, 136.4, 129.3, 129.1, 128.8, 128.4, 127.7, 127.5, 127.3, 124.2, 119.6, 114.3, 99.3, 75.6, 70.5, 64.9, 58.7, 55.2, 51.2, 46.0, 44.4, 36.7, 35.9, 28.9, 18.9.

MS (CI, NH_3) m/z (relative intensity) 541 (60), 514 (100).

Anal calc for $C_{33}H_{36}N_2O_5$: C 73.33 H 6.66 N 5.18. Found C 73.09 H 6.54 N 5.12.

3-Benzyl-4-[cyano(dimethylamino)(4-methoxyphenyl)methyl]tetrahydrofuran-2-one **5′**

5′ was prepared as above by reaction of lithiated 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile with **2** followed by alkylation of the intermediate enolate by benzyl bromide. After crystallization of the crude product, two diastereomers in a 70:30 ratio were obtained in a 75% yield.

IR (CCl_4): 2960, 1780, 1610 cm^{-1}.

Major isomer:

^1H NMR (250 MHz, C_6D_6): 7.45 (AB system, J = 7.8 Hz, 2H), 7.25 (AB system, J = 7.8 Hz, 2H), 7.15–7.00 (m, 3H), 6.55 (AB system, J = 7.8 Hz, 2H), 4.05 (dd, J = 10.3 and 5.3 Hz, 1H), 3.30 (dd, J = 10.3 and 8.2 Hz, 1H), 3.15 (dd, J = 13.3 and 5.3 Hz, 1H), 3.15 (s, 3H), 3.00 (dd, J = 14.3 and 5.3 Hz, 1H), 3.15–2.80 (m, 1H), 2.65 (q, J = 5.3 Hz, 1H), 1.80 (s, 6H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 176.9, 160.3, 128.8, 128.7, 128.6, 128.5, 128.4, 127.2, 124.7, 116.6, 114.3, 71.7, 65.0, 55.2, 44.4, 40.9, 35.5.

MS (CI, NH_3) m/z (relative intensity) 254 (100), 365 (72).

Anal calc for $C_{22}H_{24}N_2O_3$: C 72.52 H 6.59 N 7.69. Found C 72.21 H 6.58 N 7.57.

Minor isomer characterized by the NMe_2 signal at 1.75 (s, 6H).

(3S,4R)-4-[(R)-Cyano(N-((4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N-methylamino)(4-methoxyphenyl)methyl]-3-(2-methylallyl)tetrahydrofuran-2-one **6**

Two diastereomers $\mathbf{6}_1$ and $\mathbf{6}_2$ were only detected in the crude product by the following signals due to the complexity of the ^1H NMR spectrum.

^1H NMR (250 MHz, C_6D_6): 4.50 (d, J = 5.5 Hz, 1H), 5.20 (d, J = 5.5 Hz, 1H), 3.22 (s, 3H $\mathbf{6}_1$), 3.20 (s, 3H $\mathbf{6}_2$), 2.75 (s, 3H $\mathbf{6}_1$), 2.70 (s, 3H $\mathbf{6}_2$).

MS (CI, NH_3) m/z (relative intensity) 207 (12), 208 (100).

4-[Cyano(dimethylamino)(4-methoxyphenyl)methyl]-3-(2-methylallyl)tetrahydrofuran-2-one **6′**

6′ was obtained by reaction of lithiated 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile with **2** followed by alkylation by 3-bromo-2-methylpropene. Two diastereomers, in a 70:30 ratio, were characterized by ^1H NMR (C_6D_6) of the crude product.

Major isomer:

IR (CCl_4): 2960, 1780 cm^{-1}.

^1H NMR (250 MHz, C_6D_6): 7.35 (AB system, J = 7.9 Hz, 2H), 6.65 (AB system, J = 7.9 Hz, 2H), 4.85 (s, 1H), 4.80 (s, 1H), 4.38 (dd, J = 3.0 and 10.1 Hz, 1H), 3.65 (dd, J = 7.1 and 10.1 Hz, 1H), 3.10 (s, 3H), 2.88–2.78 (m, J = 3.3 and 7.1 Hz, 1H), 2.65–2.55 (m, 1H), 2.45 (dd, J = 4.4 and 13.8 Hz, 1H), 2.15 (dd, J = 8.8 and 13.8 Hz, 1H), 1.90 (s, 6H), 1.78 (s, 3H).

MS (CI, NH_3) m/z (relative intensity) 316 (4), 329 (57), 302 (100).

Minor isomer characterized by the NMe_2 signal at 1.85 (s, 6H).

(3S,4R)-4-[(R)-Cyano(N-((4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-N-methylamino)(4-methoxyphenyl)methyl]-3-(3-methylbut-2-enyl)tetrahydrofuran-2-one **7**

The crude product crystallized spontaneously; pure **7** was obtained as white crystals after a simple washing by Et_2O in a 95% yield: Mp 121 °C.

$[\alpha]_D^{20}$ = −84.6 (c = 1.00, THF).

IR (CCl_4): 1780 cm^{-1}.

^1H NMR (250 MHz, C_6D_6): 7.30–7.00 (m, 7H), 6.52 (AB system, J = 7.9 Hz, 2H), 5.38–5.15 (broad s, 1H), 4.85 (dd, J = 4.8 and 11.5 Hz, 1H), 4.55 (d, J = 3.6 Hz, 1H), 3.95 (dd, J = 4.8 and 10.9 Hz, 1H), 3.60 (dd, J = 9.0 and 10.9 Hz, 1H), 3.50 (dd, J = 3.6 and 11.5 Hz, 1H), 3.65 (s, 3H), 2.85 (ddd, J = 9.0, 4.0 and 4.8 Hz, 1H), 2.80 (s, 3H), 2.50–2.48 (m, 1H), 2.48–2.15 (m, 3H), 1.65 (s, 3H), 1.50 (s, 6H), 1.15 (s, 3H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 177.2, 160.2, 138.7, 136.4, 128.2, 127.7, 127.5, 124.2, 119.6, 118.5, 99.3, 75.7, 70.6, 64.9, 58.7, 55.2, 51.1, 46.8, 44.2, 35.9, 29.4, 29.0, 25.7, 18.9, 17.9.

MS (CI, NH_3) m/z (relative intensity) 519 (48.1), 492 (100).

Anal calc for $C_{31}H_{38}N_2O_5$: C 71.81 H 7.33 N 5.40. Found C 71.51 H 7.56 N 5.47.

4-[Cyano(dimethylamino)(4-methoxyphenyl)methyl]-3-(3-methylbut-2-enyl)tetrahydrofuran-2-one **7′**

7′ was obtained by reaction of lithiated 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile with **2** followed by alkylation of the intermediate enolate by 1-bromo-3-methylbut-2-ene. One diastereomer **7′** was characterized in the crude product.

IR (CCl_4): 1780 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): 7.45 (AB system, J = 7.9 Hz, 2H), 6.95 (AB system, J = 7.9 Hz, 2H), 5.20–5.10 (m, 1H), 4.55 (dd, J = 10.8 and 3.6 Hz, 1H), 4.28 (dd, J = 10.8 and 4.3 Hz, 1H), 3.80 (s, 3H), 3.05–3.00 (m, J = 3.6, 7.4 and 3.6 Hz), 2.55–2.30 (m, 2H), 2.25 (s, 6H), 1.80–1.60 (m, 1H), 1.75 (broad s, 3H), 1.80 (broad s, 3H).

MS (CI, NH_3) m/z (relative intensity) 360 (3), 343 (67), 316 (100).

(3S,4R)-4-[(R)-Cyano(N-[illegible]-(2S,5S)-2,2-dimethyl-[illegible]-(dimethylamino)-(4-methoxyphenyl)methyl]-3-{2-[(trimethylsilyl)methyl]allyl}tetrahydrofuran-2-one **8**

8 was characterized in the ¹H NMR of the crude product next to unidentified compounds:

¹H NMR (250 MHz, $CDCl_3$): 7.40–7.00 (m, 7H), 6.55 (AB system, J = 7.9 Hz, 2H), 4.85 (dd, J = 4.6 and 12.6 Hz, 1H), 4.80 (s, 1H), 4.65 (s, 1H), 4.58 (d, J = 6.3 Hz, 1H), 4.00 (dd, J = 4.6 and 11.6 Hz, 1H), 3.62 (dd, J = 7.9 and 11.0 Hz, 1H), 3.50 (dd, J = 12.6 and 4.8 Hz, 1H), 3.48 (s, 3H), 2.90–3.0 (m, J = 4.6 Hz, 1H), 2.80 (s, 3H), 2.52–2.42 (m, 1H), 1.80 (d, J = 16.0 Hz, 1H), 1.58 (d, J = 16.0 Hz, 1H), 1.50 (s, 3H), 1.10 (s, 3H), 0.00 (s, 9H).

MS (CI, NH_3) m/z (relative intensity): 577 (5.15), 550 (8.81).

4-[Cyano(dimethylamino)(4-methoxyphenyl)methyl]-3-{2-[(trimethylsilyl)methyl]allyl}tetrahydrofuran-2-one **8'**

8' was obtained by reaction of lithiated 2-(dimethylamino)-2-(4-methoxyphenyl)acetonitrile with **2** followed by alkylation of the intermediate enolate by [2-(iodomethyl)-2-propenyl]trimethylsilane. The ¹H NMR spectrum of the crude product showed two diastereomers in a 70:30 ratio.

Major isomer

IR (CCl_4): 1780 cm^{-1}.

¹H NMR (250 MHz, $CDCl_3$): 7.45 (AB system, J = 7.9 Hz, 2H), 6.85 (AB system, J = 7.9 Hz, 2H), 4.78 (s, 1H), 4.75 (s, 1H), 4.72 (dd, J = 3.0 and 9.8 Hz, 1H), 4.38 (dd, J = 7.2 and 9.8 Hz, 1H), 3.80 (s, 3H), 3.70 (m, 3.0, 7.2 and 2.4 Hz, 1H), 2.60–2.50 (m, 1H), 2.40 (dd, J = 3.6 and 12.7 Hz, 1H), 2.30 (broad s, 6H), 2.30–2.10 (m, 1H), 1.70 (AB system, J = 12.7 Hz, 1H), 1.52 (AB system, J = 12.7 Hz, 1H), 0.5 (s, 9H).

MS (CI, NH_3) m/z (relative intensity): 418 (1), 401 (21), 374 (100).

Minor isomer characterized by a signal at 2.35 (s, 6H).

Typical general procedure for the obtention of aroyllactones

Crude or crystallized Michael adduct (5 mmol) was dissolved in 4 mL THF and 2 mL Et_2O and stirred with 6 mL of a 1 N aqueous solution of $AgNO_3$ for 6 h at room temperature. The precipitate was filtered and washed with Et_2O. The aqueous phase was extracted three times with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. Purification by column chromatography on silica gel gave the pure ketone (eluent, 60:40 Et_2O/petroleum ether). The ee value of the ketone was measured by ¹H NMR by addition of $Eu(hfc)_3$ on the signals corresponding to the aromatic protons for compounds **9**, **10**, **11**, **12**, to the methyl protons for compound **13** and to the vinylic protons for **14**.

(R)-4-(4-Methoxybenzoyl)tetrahydrofuran-2-one **9**

9 was obtained from pure isomer **3** after column chromatography in a 70% yield with an ee value ≥ 99%; oil.

$[\alpha]_D^{20}$ = –0.28 (c 1.00, THF).

IR (CCl_4): 1750, 1680 cm^{-1}.

¹H NMR (250 MHz, $CDCl_3$): 7.90 (AB system, J = 7.9 Hz, 2H), 7.00 (AB system, J = 7.9 Hz, 3H), 4.60 (t, J = 8.3 Hz, 1H), 4.55 (t, J = 8.3 Hz, 1H), 4.40–4.25 (m, 1H), 3.90 (s, 3H), 3.05 (dd, J = 8.3 and 16.6 Hz, 1H), 2.80 (dd, J = 8.3 and 16.6 Hz, 1H).

¹³C NMR (62.9 MHz, $CDCl_3$): 194.7, 175.5, 164.3, 130.8, 127.7, 114.2, 69.2, 55.5, 41.7, 30.9.

MS (CI, NH_3) m/z (relative intensity): 136 (55), 221 (24), 238 (100), 239 (17).

Anal calc for $C_{12}H_{12}O_4$: C, 65.45; H, 5.45. Found: C, 65.21; H, 5.69.

The crude aroyllactone obtained from the crude aminonitrile in a 80% yield exhibited an ee value of 85%. Racemic **9** obtained from **3'** was identified by ¹H NMR, ¹³C NMR and MS.

(3S,4R)-4-(4-Methoxybenzoyl)-3-[(methoxycarbonyl)methyl]tetrahydrofuran-2-one **10**

10 was obtained from **4** after column chromatography in a 70% yield with an ee value ≥ 99%; Mp 65 °C.

$[\alpha]_D^{20}$ = –66.8 (c 1.00, THF).

IR (CCl_4): 2680, 1790, 1740, 1680, 1600 cm^{-1}.

¹H NMR (200 MHz, $CDCl_3$): 7.95 (AB system, d, J = 7.9 Hz, 2H), 6.95 (AB system, d, J = 7.9 Hz, 2H), 4.70 (t, J = 9.2 Hz, 1H), 4.48 (q, J = 9.2 Hz, 1H), 4.15 (J = 9.2 Hz, 1H), 3.92 (s, 3H), 3.65 (s, 3H), 3.62–3.40 (m, 1H), 2.90 (dd, J = 5.5 and 16.7 Hz, 1H), 2.72 (dd, J = 5.5 and 16.7 Hz, 1H).

¹³C NMR (62.9 MHz, $CDCl_3$): 194.2, 176.6, 171.2, 164.4, 130.8, 128.4, 114.2, 68.0, 55.2, 51.9, 47.0, 38.4, 32.5.

MS (coupled with CPG) m/z (relative intensity): 292 (2), 135 (100).

Anal calc for $C_{15}H_{16}O_6$: C, 61.64; H, 5.47. Found: C, 61.39; H, 5.62.

The crude aroyllactone obtained from the crude aminonitrile in a 75% yield showed an ee value of 98%. Racemic **10** obtained from **4'** after column chromatography, in a 60% yield, was identified by ¹H NMR, ¹³C NMR and MS.

(3S,4R)-3-Benzyl-4-(4-methoxybenzoyl)tetrahydrofuran-2-one **11**

11 was obtained from the crude product **5** after column chromatography in a 80% yield with an ee value ≥ 99%; Mp 102 °C.

$[\alpha]_D^{20}$ = –29.4 (c 1.00, THF).

IR (CCl_4): 1790, 1680 cm^{-1}.

¹H NMR (250 MHz, $CDCl_3$): 7.65 (AB system, d, J = 7.9 Hz, 2H), 7.20–7.10 (m, 5H), 6.90 (AB system, J = 7.9 Hz, 2H), 4.35 (t, J = 7.9 Hz, 1H), 4.15 (t, J = 7.9 Hz, 1H), 4.05 (q, J = 7.9 Hz, 1H), 3.90 (s, 3H), 3.62–3.48 (m, 1H), 3.15 (dd, J = 4.9 and 13.8 Hz, 1H), 3.05 (dd, J = 7.5 and 13.8 Hz, 1H).

¹³C NMR (62.9 MHz, $CDCl_3$): 194.6, 177.4, 164.4, 137.0, 130.6, 129.3, 128.6, 128.2, 126.9, 114.0, 68.0, 55.5, 46.4, 44.1, 34.8.

MS (coupled with CPG) m/z (relative intensity): 310 (1), 411 (1).

Anal calc for $C_{19}H_{18}O_4$: C, 73.54; H, 5.80. Found: C, 73.26; H, 5.87.

The crude aroyllactone obtained from the crude aminonitrile in a 80% yield showed an ee value of 99%. Racemic **11** was obtained from **5'** in a 70% yield and identified by ¹H NMR, ¹³C NMR data and MS.

(3S,4R)-4-(4-Methoxybenzoyl)-3-(2-methylallyl)tetrahydrofuran-2-one **12**

12 obtained from the crude **6** after column chromatography in a 60% yield with an ee value of 60%; Mp 116 °C.

IR (CCl_4): 1770, 1680 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): 7.95 (AB system, J = 7.9 Hz, 2H), 7.00 (AB system, J = 7.9 Hz, 2H), 1.65 (s, 2H), 1.65–1.48 (m, 1H), 1.21–1.05 (m, 2H), 3.90 (s, 3H), 3.45 (dd, J = 10, 4.5 and 9.9 Hz, 1H), 2.65 (dd, J = 4.5 and 1 Hz, 1H), 2.52 (dd, J = 10 and 14 Hz, 1H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 193.3, 176.1, 163.3, 131.8, 113.2, 112.9, 66.8, 54.0, 47.1, 39.7, 38.0, 20.4.

MS (coupled with CPG) m/z (relative intensity): 274 (4), 135 (100).

Anal calc for $C_{16}H_{18}O_3$: C, 70.07; H, 5.83. Found: C, 69.83; H, 6.71.

Racemic **12** was obtained from **6'** in 70% yield and identified by ^1H NMR, ^{13}C NMR and MS data.

(4S,4R)-4-(4-Methoxybenzoyl)-4-(3-methylbut-2-enyl)-tetrahydrofuran-2-one ***13***

13 obtained from the crude product **7** after crystallization in 70% yield with an ee ≥ 99%; Mp 58 °C.

$[\alpha]_D^{20}$ = +33.2 (c = 1.00, THF).

IR (CCl_4): 1790, 1680 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): 7.90 (AB system, J = 7.9 Hz, 2H), 6.95 (AB system, J = 7.9 Hz, 2H), 5.0 (t, J = 9 Hz, 1H), 1.60–1.45 (m, 1H), 4.20–4.05 (m, 2H), 3.85 (s, 3H), 3.15 (m, J = 7.2 and 9.2 Hz, 1H), 2.55–2.30 (m, 2H), 1.53 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 195.0, 177.4, 164.2, 135.5, 130.7, 130.6, 128.6, 119.5, 114.0, 68.0, 55.1, 46.9, 43.1, 27.4, 25.5, 17.7.

MS (coupled with CPG) m/z (relative intensity): 288 (2), 289 (0.6), 135 (100).

Anal calc for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.57; H, 7.15.

The crude aroylactone was obtained from the crude aminonitrile in 80% yield with an ee value 98%. Racemic **13** was obtained from **7'** in 75% yield and identified by ^1H NMR, ^{13}C NMR data and MS.

(4S,4R)-4-(4-Methoxybenzoyl)-4-{2-[(trimethylsilyl)-methyl]allyl}tetrahydrofuran-2-one ***14***

14 obtained from the crude product **8** after column chromatography in 70% yield with an ee of 65%; oil.

$[\alpha]_D^{20}$ = +42.2 (c 1.00, THF).

IR (CCl_4): 1740, 1680 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): 7.90 (AB system, J = 7.9 Hz, 2H), 6.90 (AB system, J = 7.9 Hz, 2H), 1.65–1.50 (m, 2H), 1.15 (s, 1H), 1.25–1.05 (m, 2H), 3.90 (s, 3H), 3.50 (m, 3.6 and 10 Hz, 1H), 2.60 (dd, J = 3.6 and 13.6 Hz, 1H), 2.20 (dd, J = 4.0 and 13.6 Hz, 1H), 1.45 (s, 2H), 0.5 (s, 9H).

^{13}C NMR (62.9 MHz, $CDCl_3$): 194.8, 177.8, 164.1, 133.8, 130.7, 128.5, 114.0, 111.2, 68.3, 55.5, 47.6, 40.8, 39.0, 45.3, 1.5.

MS (coupled with CPG) m/z (relative intensity): 316 (0.5), 317 (0.2).

Anal calc for $C_{17}H_{24}O_4Si$: C, 65.89; H, 7.51. Found: C, 65.82; H, 7.65.

Racemic **14** was obtained from **8'** in 65% yield and identified by ^1H NMR, ^{13}C NMR data and MS.

Supplementary material

Tables of positional parameters and their esd, tables of refined displacement parameter expressions, bond angles, bond distances for **7** (29 pages) have been deposited as Supplementary Material with the British Library, Document Supply Centre at Boston Spa, Wetherby, West Yorkshire, LS23 7BQ, UK, as supplementary publication N° = SUP 90473 and are available on request from the Document Supply Centre.

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