Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 24, pp. 4101–4110, 1997

Printed in Great Britain
PII: S0957-4166(97)00597-1 0957-4166/97 $17.00 + 0.00

Bicyclic γ-butyrolactones. Relation between conformation of the lactone ring and chiroptical properties

Cristina Forzato, Patrizia Nitti and Giuliana Pitacco *
Dipartimento di Scienze Chimiche, Università di Trieste, via Licio Giorgieri 1, I-34127 Trieste, Italy

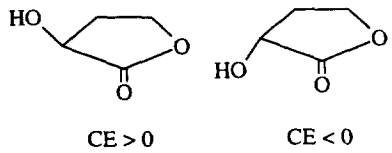
Abstract: The CD curves of a set of condensed γ-butyrolactones have been investigated. A simple correlation between the sign of the Cotton effect (CE) and the configuration of C_α can be deduced from the resulting data. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Introduction

Since the beginning of the study of optically active compounds, many attempts have been made to correlate the sign of the Cotton effect with the absolute configuration, with the aim of establishing a general rule for the prediction of the absolute configuration.[1] In particular for γ-lactones, several empirical rules have been proposed based on the Cotton effect due to the $n \rightarrow \pi^*$ transition of the carbonyl group.

A lactone sector rule was proposed by Klyne *et al.*[2] and successively by Snatzke *et al.*,[3] while for aldono-γ-lactones independent rules were proposed by Okuda *et al.*[4] and Beecham[5] to predict the configuration at C_α and the ring conformation respectively. The rule formulated by Okuda *et al.*[4] says that the sign of the CE is determined by the orientation of the hydroxy group at the α-position, being positive when the OH group is above the plane of the lactone ring and negative when it is below, whatever is the conformation of the lactone ring (Scheme 1). In ribono-γ-lactones the Okuda rule has been found to be valid also when the hydroxy group at C_α is substituted for a methyl group.[6]

Okuda rule



CE > 0 CE < 0

Scheme 1.

On the other hand, Beecham[5] stated that the sign of the CE depends on the conformation of the lactone ring, being negative when the β-carbon is below the plane of the ester group (conformation **A**) and positive when it is above (conformation **B**) (Scheme 2). The conformation of the lactone ring was the determining factor also for Legrand and Bucourt[7] who stated a general rule for 5-, 6- and 7-membered lactones based on the sign of the O–CO–C_α–C_β torsional angle. A negative CE is expected for a positive torsional angle (conformation **A**) and a positive CE for a negative torsional angle (conformation **B**) (Scheme 2). These rules however are valid only if the carboxylic chromophore is coplanar and, therefore, inherently achiral. X-Ray studies have shown that this is approximately the case for most lactones investigated.[8] Apparently, at least for monocyclic γ-lactones, the configurations at C_β and C_γ have no influence on the sign of the Cotton effect.[9]

* Corresponding author. Email: pitacco@dschsun3.univ.trieste.it

Beecham rule

conformation A **conformation B**

CE < 0 CE > 0

Legrand-Bucourt rule

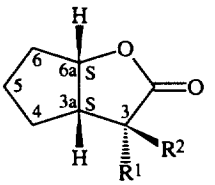
Scheme 2.

In Scheme 2 two different views for each conformation are drawn, to allow an easier comparison with the following condensed γ-lactones.

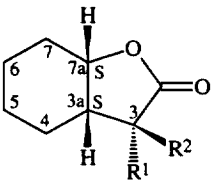
Results and discussion

In the present work we describe the ^{1}H-NMR and CD studies of bicyclic lactones **1–8** of known absolute configuration. In particular, the configuration of C-6a in compounds **1** and that of C-7a in compouds **2–8** is always S (Scheme 3).

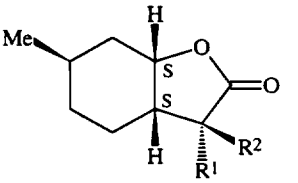
Cis-*fused γ-Lactones*



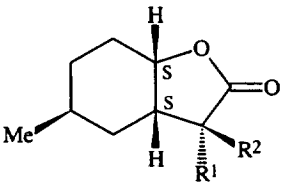
1a,b,c



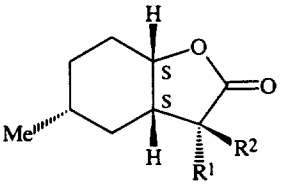
2a,b,c



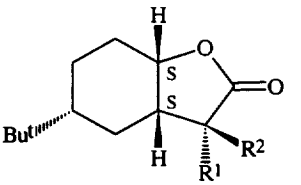
3a,b,c



4a,b,c

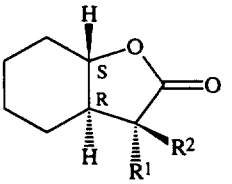


5a,b,c

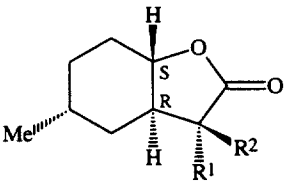


6a,b

Trans-*fused γ-Lactones*



7a,b,c



8a,b

a: $R^1 = R^2 = H$

b: $R^1 = H$, $R^2 = Me$

c: $R^1 = Me$, $R^2 = H$

Scheme 3.

Synthesis of the condensed γ-lactones

Compounds **1a–8a** were prepared according to literature methods,[10–14] as indicated in Table 1.

Compounds **1b–8b** were prepared by stereoselective α-methylation of the respective lithium enolate, in accordance with the method by Grieco and Miyashita.[15] Introduction of the methyl group occurred from the same side as H-3a in the *cis*-fused systems and from the opposite side in the *trans*-fused ones.

Compounds **1c**, **3c–5c** and **7c** were obtained from **1b**, **3b–5b** and **7b** respectively, by inversion of configuration at C-3, by stereoselective protonation of the corresponding lithium enolate. Obtainment of the lactones **6c** and **8c** by inversion of configuration at C-3 of **6b** and **8b** was not possible for steric reasons. Scheme 4 illustrates the above processes. Compound **2c** was prepared according to the literature.[12]

Molecular geometry and chiroptical properties of the condensed γ-lactones

In a recent paper,[16] the authors reported on the relation between the conformation of the γ-lactone ring and the optical rotation sign. The conformational assignments were based on the values of the chemical shift of the protons α to the carbonyl group. The *quasi* axial proton was assigned the lowfield signal and the *quasi* equatorial proton the highfield signal. Hence the conformation of the lactone ring of reported compounds was easily determined.[16] Since the method was promising also in view of a possible correlation with the sign of the Cotton effect, we analyzed the ^{1}H-NMR spectra of our condensed γ-lactones, taking into account not only the signals of the protons at C-3 but also that at C-6a (in compounds **1**) or C-7a (in compounds **2–8**).

The results of our investigations are summarized in Table 1, which lists the main spectroscopic data for lactones **1–8**.

As to the protons α to the carbonyl group (H-3), the most striking feature is that in the *trans* fused lactones **7** and **8** the axial proton resonates at higher field than the equatorial one, in contrast to what was found for the *cis*-fused lactones **1–5**. These latter compounds follow the trend already observed,[16] as it is evident from a comparison of the value of their chemical shifts with those found for the conformationally locked *cis*-fused system **6a** (Scheme 5). For a comparison with the *trans*-fused derivatives we referred to compound **9**.

These assignments were confirmed by DIFNOE measurements, carried out on a few significant compounds, whose results are reported in the experimental section. From these data it can be deduced that when the lactone ring is fused to a five-membered ring (**1a,b,c**), $^3J_{ax-eq}$ is around 10 Hz, $^3J_{eq-eq}$ is 0–4 Hz, while when it is condensed with a six-membered ring and the fusion is *trans*, $^3J_{ax-ax}$ is around 13 Hz and $^3J_{ax-eq}$ is 6–8 Hz. In a blocked *cis*-fused structure such as **6**, $^3J_{ax-eq}$ is still 6–7 Hz, while $^3J_{eq-eq}$ is 0 Hz. All compounds are laevorotatory, with the exception of **4a**. As a consequence, on the basis of the sole optical rotation sign, all lactones but **4a** should adopt the same conformation. This was the case for most lactones, but not for all of them. For the *cis*-fused systems **2–5** in fact, a conformational equilibrium between the two forms **A** and **B** (Scheme 2) should be considered. Actually, in a few cases (Entries 4, 5 and 10), the existence of an equilibrium is evident from the values of the chemical shift of H-3, as is the fact that compound **4b** (Entry 11) is in conformation **B**. This results from a comparison of the coupling constants for **2a**, **2b** and **4a** with those found for the anancomeric derivative **6a** whose lactone ring is in conformation **A** (Scheme 6).

The same conclusions are reached by taking into account the pattern of H-7a. The conformation **A** or **B** of the lactone ring is determined by the conformation of the condensed carbocyclic ring, in which H-7a is either equatorial or axial respectively (Scheme 5), if one ignores distortions and flattening of the carbocyclic ring due to the fusion.

To establish whether H-7a was equatorial or axial, we referred to the values of the coupling constants found for **6a**[12] for a typical equatorial proton (Table 1) and to those for **9** (H-3_{ax}: dd, 13.4, 16.1 Hz; H-3_{eq}: dd, 6.4, 16.1 Hz; H-7a: dt, 11.0, 11.0, 3.9 Hz) for an axial one (Scheme 5). From this comparison, it can be deduced that lactone **4b** (Entry 11) is surely in conformation **B**, while **2b** (Entry 5) and **4a**

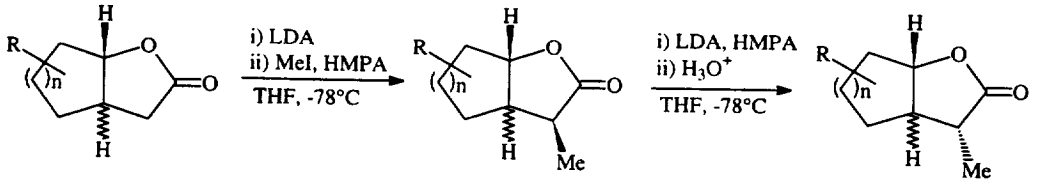
Table 1. Spectroscopic and chiroptical data

Entry	Compd	^{1}H-NMR ($CDCl_3$)						Conf. of the lactone ring	% ee	UV (MeOH)		$[\alpha]_D^{25}$ (MeOH)	CD (MeOH)	
		H-3				CH-O[a]								
		H-3ax δ, ppm	H-3eq δ, ppm	J_{3ax-3a} (Hz)	J_{3eq-3a} (Hz)	δ, ppm	multipl., ^3J (Hz)			λ, nm	ε		λ, nm	[θ]
1	(-)-**1a**[10]	2.80	2.24	10.0	0.0	5.01	t, 5.1	A	>99	212	93	-36.0 (c 0.48)	212	-2019
2	(-)-**1b**[11]	-	2.37	-	3.9	4.98	t, 5.5	A	>99	216	220	-66.4 (c 0.28)	218	+1567
3	(-)-**1c**[11]	2.85	-	8.8	-	4.86	dt, 5.4, 5.4, 1.7[11]	A	>99	219	74	-31.2 (c 0.16)	215	-2173
4	(-)-**2a**[12]	2.61	2.24	6.7	2.7	4.51	q, 4.2	A--B	94	225	70	-40.0 (c 1.0)	213	+1243
5	(-)-**2b**[12]	2.38		8.8		4.44	dt, 8.3, 6.1, 6.1	A=B	>99	219	129	-44.0 (c 0.15)	222	+2658
6	(-)-**2c**[12]	2.70	-	6.8	-	4.35	q, 2.9	A	>99	217	135	-38.0 (c 0.15)	222	-804
7	(-)-**3a**[12]	2.64	2.16	6.6	0.0	4.45	q, 3.4	A	94	221	342	-64.0 (c 0.14)[b]	212	+269
8	(-)-**3b**[12]	-	2.33	-	0.0	4.68	q, 3.9	A	94	220	438	-63.0 (c 0.03)	215	+4615
9	(-)-**3c**	2.79	-	7.0	-	4.45	q, 3.4	A	94[c]	216	111	-56.3 (c 0.12)	220	-1949
10	(+)-**4a**[13]	2.43		-	-	4.50	dt, 8.8, 6.1, 6.1	A=B	98	220	110	+3.9 (c 0.18)	213	+2125
11	(-)-**4b**[13]	2.46	-	6.8		4.41	dt, 10.7, 6.8, 6.8	B	98	223	74	-35.0 (c 0.16)	217	+4231
12	(-)-**4c**	2.79	-	7.3		4.42	q, 3.9	A	98[c]	225	330	-44.0 (c 0.20)	220	-2089
13	(-)-**5a**[12]	2.68	2.19	6.3	0.0	4.49	q, 3.1	A	96	220	246	-41.0 (c 0.3)[b]	209	+343
14	(-)-**5b**[12]	-	2.21	-	0.0	4.53	q, 2.6	A	96	218	160	-58.0 (c 0.3)	215	+4824
15	(-)-**5c**	2.79	-	7.3	-	4.39	dt, 3.3, 3.2, 3.2	A	96[c]	217	307	-29.9 (c 0.10)	219	-1687
16	(-)-**6a**[12]	2.71	2.21	6.6	0.0	4.48	q, 3.0	A	96	222	314	-30.8 (c 0.12)[b]	225	-281
17	(-)-**6b**[12]	-	2.32	-	0.0	4.60	q, 2.7	A	96	218	257	-33.6 (c 0.14)	216	+4265
18	(-)-**7a**[14]	2.22	2.51	13.0	6.3	3.78	ddd, 11.1, 10.4, 3.8	A	94	215	85	-75.0 (c 0.2)	217	-2970
19	(-)-**7b**	-	2.56	-	7.3	3.90	dt, 11.4, 11.4, 3.9	A	>99[c]	220	54	-48.8 (c 0.31)	215	+922
20	(-)-**7c**	2.24	-	12.7	-	3.74	dt, 10.7, 10.7, 3.9	A	>99[c]	218	116	-13.2 (c 0.14)	219	-4778
21	(-)-**8a**[13]	2.18	2.46	-	-	3.79	dt, 10.6, 10.6, 3.9	A	99	-	-	-91.1 (c 0.09)	218	-3819
22	(-)-**8b**[13]	-	2.59	-	7.8	3.94	dt, 11.2, 11.2, 3.9	A	99	-	-	-99.6 (c 0.05)	212	+800

[a] H-6a for lactones **1**, H-7a for lactones **2-8**

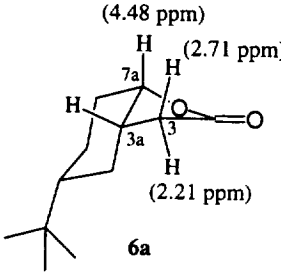
[b] measured for chloroform solutions

[c] e.e. of the parent lactone

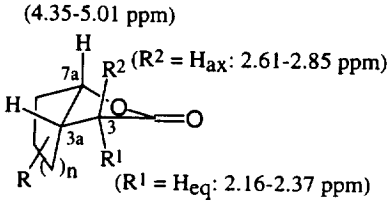


n = 1,2
R = Me, ^{t}Bu

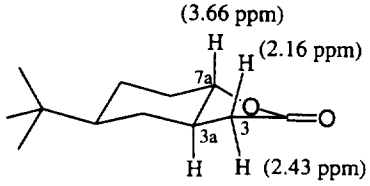
Scheme 4.



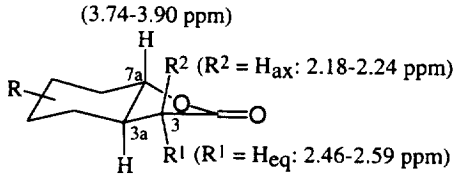
6a



1a,3a,5a
1b,3b,5b,6b
1c,2c,3c,4c,5c



9

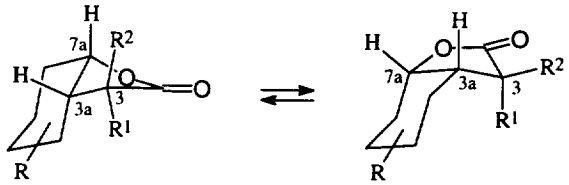


7a,7b,7c,8a,8b

Scheme 5.

Conformation A **Conformation B**

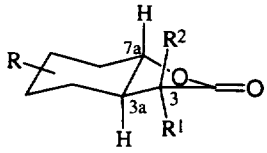
***Cis*-fused condensed γ-lactones**



5a,6a
3b,5b,6b
2c,3c,4c,5c

2a,2b,4a **4b**

***Trans*-fused condensed γ-lactones**



7a,7b,7c,8a,8b

Scheme 6.

(Entry 10) are in conformational equilibrium, as is **2a** (Entry 4), although the equilibrium is shifted to the left.

Once the preferred conformation of the lactone ring in these condensed γ-lactones had been established, it was interesting to correlate it to the sign of the CD curves.

trans-*Fused condensed γ-lactones*

In the *trans*-fused derivatives **7a** and **8a**, which bear no substituent at C-3 and are blocked in conformation **A**, the Cotton effect is strongly negative ($-3000<[\Theta]<-4000$), in accordance with Beecham[5] and Legrand–Bucourt[7] rules. As expected,[3a] the creation of a stereogenic centre adjacent to the chromophore has a strong influence on the sign of the CD curve, overwhelming the effect of the chirality of the lactone ring and the Okuda rule can be applied successfully. Actually, compounds **7b** and **8b**, in which the methyl group is above the plane of the ring, show a positive molar ellipticity (+922 and +800 respectively). The situation is reversed for **7c** in which the methyl group is below the plane of the ring thus determining a negative Cotton effect. A comparison of the intensity of the CD curve of **7a** ([Θ] −2970) with that of **7c** ([Θ] −4778) confirm that the two effects, conformation of the ring and presence of a chiral centre at C-3, are additive.

cis-*Fused condensed γ-lactones*

The *cis*-fused lactones **1a** and **6a**, which are locked in conformation **A**, show a negative Cotton effect ([Θ] −2019 and −281 respectively), in agreement with Beecham[5] and Legrand–Bucourt[7] rules. Once again, introduction of a methyl group above the plane of the ring changes the sign of the Cotton effect ([Θ] +1567 and +4824 respectively), while inversion of configuration at C-3 (methyl group below the plane) inverts the sign of the Cotton effect too ([Θ] −2173 for **1c**).

The other *cis*-fused lactones **2a**, **3a**, **4a** and **5a** show a positive Cotton effect. Lactones **2a** and **4a** are likely to receive some contribution from the conformation **B**, as indicated by the values of coupling constants of their protons (Table 1), while the low intensity of the $n\rightarrow\pi^*$ band observed for **3a** and **5a** (+269 and +343 respectively) would suggest that some counter-balancing factor is operating. It could be attributed either to a contribution from non-chair conformations of the carbocyclic ring or to the configuration of the β-carbon atom, although, at least for monocyclic lactones, the β- and γ-carbon atoms seem to have no influence on the CE.

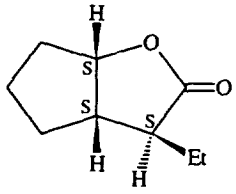
When these lactones are α-methylated, the resulting compounds **2b–5b** show a strong positive Cotton effect due to the fact that the methyl group is located above the lactone ring. Inversion of configuration at C-3 leads to the corresponding diastereoisomers **2c–5c**, whose Cotton effect is negative, in accordance with the Okuda rule.

Therefore, the Okuda rule seems to be valid also for α-methyl-γ-lactones as already observed.[6]

A substitution of the methyl group at C-3 for an ethyl group does not affect the sign of the CE. For instance, when (−)-**1a** was ethylated under the usual conditions,[15] two diastereoisomers were obtained, namely (−)-**10b** and (−)-**10c** (Scheme 7), owing to the fact that ethylation was no longer diastereoselective. The isomers were separated and fully characterized by HC COSY and DIFNOE experiments. They showed a positive CE and negative CE respectively, in agreement with the Okuda rule.

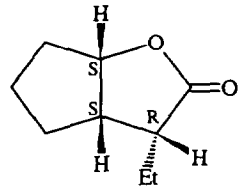
Experimental section

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded as a film, unless otherwise stated, on a Jasco FTIR 200 spectrophotometer. ^{1}H-NMR spectra were run on a Jeol EX-400 (400 MHz) spectrometer, using deuteriochloroform as solvent and tetramethylsilane as an internal standard, unless otherwise stated. ^{13}C-NMR spectra were recorded on a Jeol EX-400 (100.4 MHz) instrument. Optical rotations were determined on a Perkin–Elmer Model 241 polarimeter. CD spectra were obtained on a Jasco J-700A spectropolarimeter (0.1 cm cell) in methanol. UV spectra were recorded on Perkin–Elmer Lambda 2 and Jasco V-550 spectrophotometers (1 cm cell)



(-)-**10b**

$[\Theta]_{218} = +1600$



(-)-**10c**

$[\Theta]_{216} = -2275$

Scheme 7.

in methanol. GLC analyses were obtained on a Carlo–Erba GC 8000 instrument, the capillary column being OV 1701 (25 m×0.32 mm) (carrier gas He, 40 KPa); Chiraldex® type G-TA, trifluoroacetyl γ-cyclodextrin (40 m×0.25 mm); mass spectra were run by the electron-impact mode (70 eV) on a Hewlett–Packard 5971A GC–MS instrument and a VG 7070 (70 eV). TLCs were performed on Whatman K6F silica gel plates (eluent: light petroleum/ethyl acetate). Flash chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). Light petroleum refers to the fraction with b.p. 40–70°C and ether to diethyl ether. Compound (−)-(1S,5R)-2-oxabicyclo[3.3.0]oct-6-en-3-one was purchased from Aldrich.

(−)-(3aS,6aS)-2H-Hexahydrocyclopenta[b]furan-2-one ***1a***

According to the literature,[10] 1 g of (−)-(1S,5R)-2-oxabicyclo[3.3.0]oct-6-en-3-one was hydrogenated with hydrogen on Pd(C) (5%) (1 g) in 170 ml of ethyl acetate for 24 h. The catalyst was removed by filtration and the product purified by flash-chromatography. DIFNOE experiments: irradiation of H-4 at 1.55 ppm enhanced the following signals: H-6a at 5.01 ppm (2%), H-3a at 2.90 ppm (3%), and H-3_{eq} at 2.24 ppm (3%).

(−)-(3aR,7aS)-trans-*Hexahydro-2(3H)-benzofuranone* ***7a***[14]

^{1}H-NMR ($CDCl_3$:C_6D_6 in ratio 6:1), δ, ppm: 3.51 (1H, dt, J_1=J_2 11.0, J_3 3.9, H-7a), 2.29 (1H, dd, J_1 16.1, J_2 6.4, H-3_{eq}), 2.16 (1H, dq, H-7_{eq}), 1.96 (1H, dd, J_1 16.1, J_2 13.2, H-3_{ax}), 1.73 (2H, m, H-4_{eq}+H-5_{eq}), 1.62 (2H, m, H-3a+H-6_{eq}), 1.37 (1H, dq, H-7_{ax}), 1.20 (1H, qt, H-5_{ax}), 1.13 (1H, qt, H-6_{ax}), 1.03 (1H, qd, H-5_{ax}). DIFNOE experiments: irradiation of H-3_{eq} at 2.29 ppm enhanced H-3a at 1.62 ppm (10%).

Synthesis of α-alkylated lactones

Lactones **1b–8b** were obtained by α-methylation of **1a–8a** respectively, following the procedure by Grieco.[15] This reaction does not lower the e.e. of the parent lactone, as it has been proved several times.[13] Lactones (−)-**10b** and (−)-**10c** were obtained in the ratio 78:22 by α-ethylation with EtI of (−)-**1a** following the same procedure and were separated by flash-chromatography.

(−)-(3S,3aS,6aS)-2H-Hexahydro-3-methylcyclopenta[b]furan-2-one ***1b***

Spectroscopic data according to Smith *et al.*[11]; e.e. >99%; $[\alpha]_D^{25}$=−66.4 (c 0.28, CH_3OH); CD: $[\Theta]_{218}$=+1567 (CH_3OH); UV: ε_{216}=220, M^{-1} cm^{-1} (CH_3OH).

(−)-(3S,3aR,7aS)-trans-*Hexahydro-3-methyl-2(3H)-benzofuranone* ***7b***

Oil, IR (film): 1780 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 3.90 (1H, dt, J_1=J_2 11.4, J_3 3.9, H-7a), 2.56 (1H, dq, J_1=J_2=J_3 7.8, J_4 7.3, H-3), 2.18 (1H, m, H-7_{eq}), 1.88 (2H, m, H-3a+H-6_{eq}), 1.72 (2H, m, H-4+H-5), 1.46 (1H, dq, J_1=J_2=J_3 11.4, J_4 3.9, H-7_{ax}), 1.36–1.11 (3H, m, H-6_{ax}+H-4′+H-5′), 1.08 (3H, d, J 7.8, CH_3); ^{13}C-NMR, δ, ppm: 179.2 (s), 82.7 (d), 51.6 (d), 41.2 (d), 30.0 (t), 27.2 (t), 25.1 (t), 24.0 (t), 12.3 (q); MS, m/z: 154 ($M^{+\bullet}$, 8), 110 (20), 95 (30), 82 (22), 81 (49), 69 (22), 68 (53), 67 (100), 66 (28), 55 (16); e.e. >99%; $[\alpha]_D^{25}$=−48.8 (c 0.31, CH_3OH); $[\Theta]_{215}$=+922; UV: ε_{220}=54,

M^{-1} cm^{-1} (CH_3OH). DIFNOE experiments: irradiation of CH_3 at 1.08 ppm enhanced H-7a at 3.90 ppm (5%); irradiation of H-3 at 2.56 ppm enhanced H-3a at 1.88 ppm (3%).

(−)-(3S,3aS,6aS)-2H-Hexahydro-3-ethylcyclopenta[b]furan-2-one ***10b***

Oil, IR (film): 1770 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 4.90 (1H, dt, J_1=J_2 5.4, J_3 2.0, H-6a), 2.56 (1H, m, H-3a), 2.21 (1H, ddd, J_1 5.4, J_2 3.9, J_3 8.8, H-3), 1.97 (1H, m), 1.84–1.51 (7H, m), 1.00 (3H, d, J 7.6, CH_3); ^{13}C-NMR, δ, ppm: 177.8 (s), 82.3 (d), 46.8 (d), 41.7 (d), 31.2 (t), 31.1 (t), 22.9 (t), 21.0 (t), 9.1 (q); MS, m/z: 154 ($M^{+\bullet}$, 0.04), 126 (82), 125 (15), 98 (14), 97 (28), 95 (29), 83 (12), 82 (43), 81 (57), 79 (19), 68 (33), 67 (100), 66 (12), 55 (33), 53 (16); e.e. >99%; $[\alpha]_D^{25}$=−38.1 (c 0.16, CH_3OH); CD: $[\Theta]_{218}$=+1600 (CH_3OH); UV: ε_{217}=253, M^{-1} cm^{-1} (CH_3OH).

(−)-(3R,3aS,6aS)-2H-Hexahydro-3-ethylcyclopenta[b]furan-2-one ***10c***

Oil, IR (film): 1770 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 4.78 (1H, t, J 5.1, H-6a), 2.73 (1H, quintet, J 7.8, H-3a), 2.57 (1H, ddd, J_1 4.9, J_2 7.8, J_3 10.3, H-3), 1.86 (3H, m), 1.73–1.32 (5H, m), 0.96 (3H, d, J 7.3, CH_3); ^{13}C-NMR, δ, ppm: 178.7 (s), 84.5 (d), 45.5 (d), 42.9 (d), 32.6 (t), 25.2 (t), 24.3 (t), 19.8 (t), 12.5 (q); MS, m/z: 154 ($M^{+\bullet}$, 2), 126 (71), 108 (10), 98 (12), 97 (29), 95 (27), 84 (10), 82 (32), 81 (40), 79 (18), 69 (14), 68 (26), 67 (100), 66 (12), 55 (23), 53 (14); e.e. >99%; $[\alpha]_D^{25}$=−44.5 (c 0.22, CH_3OH); CD: $[\Theta]_{216}$= −2275 (CH_3OH); UV: ε_{218}=346, M^{-1} cm^{-1} (CH_3OH). DIFNOE experiments: irradiation of H-6a at 4.78 ppm enhanced the following signals: H-3a at 2.73 ppm (3%) and H-3 at 2.57 ppm (1%).

General procedure for the inversion at the C_α

To a solution of LDA (2.4 mmol in 3 ml of anhydrous THF) was added a solution of lactone (2 mmol) in 1 ml of THF, over a period of 30 min. The reaction was stirred at −78°C for 2 h, 1 equiv. of HMPA was added and after 5 min the reaction was quenched with HCl 1:4. The usual workup followed.

The optically active lactones **1c**, **3c–5c** and **7c** were obtained from the corresponding optically active lactones **1b**, **3b–5b** and **7b** in accordance with the above procedure. All products were purified by flash-chromatography. This reaction does not lower the e.e. of the parent lactone, as it has been proved several times.

(−)-(3R,3aS,6aS)-2H-Hexahydro-3-methylcyclopenta[b]furan-2-one ***1c***

Spectroscopic data according to Smith *et al.*[11]; e.e. >99%; $[\alpha]_D^{25}$=−31.2 (c 0.16, CH_3OH); CD: $[\Theta]_{215}$=− 2173 (CH_3OH); UV: ε_{219}=74 M^{-1} cm^{-1} (CH_3OH).

(−)-(3R,3aS,6R,7aS)-cis-*Hexahydro-3,6-dimethyl-2(3H)-benzofuranone* ***3c***

Oil, IR (film): 1770 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 4.45 (1H, *pseudo*q, J 3.4, H-7a), 2.79 (1H, quintet, J 7.0, H-3), 2.22 (2H, m, H-3a+H-7_{eq}), 1.68 (2H, m, H-5_{eq}+H-4_{eq}), 1.56 (1H, m, H-6), 1.21 (1H, m, H-7_{ax}), 1.15 (3H, d, J 7.3, CH_3), 1.07 (1H, m, H-4_{ax}), 0.92 (3H, d, J 6.3, CH_3), 0.89 (1H, m, H-5_{ax}); ^{13}C-NMR, δ, ppm: 179.7 (s), 78.1 (d, C-7a), 42.1 (d, C-3), 38.9 (d, C-3a), 36.0 (t, C-7), 31.9 (t, C-5), 26.1 (d, C-6), 23.0 (t, C-4), 21.8 (q), 9.0 (q); MS, m/z: 168 ($M^{+\bullet}$, 2), 167 (5), 124 (11), 109 (10), 96 (14), 95 (100), 81 (17), 68 (24), 67 (30), 55 (18); e.e. 94%; $[\alpha]_D^{21}$=−56.3 (c 0.12, CH_3OH); $[\Theta]_{220}$=−1949; UV: ε_{216}=111, M^{-1} cm^{-1} (CH_3OH). DIFNOE experiments: irradiation of H-7a at 4.45 ppm enhanced the following signals: H-3a at 2.22 ppm (6%) and H-3 at 2.79 ppm (4%); irradiation of H-3 at 2.79 ppm enhanced H-3a at 2.22 ppm (6%).

(−)-(3R,3aS,5S,7aS)-cis-*Hexahydro-3,5-dimethyl-2(3H)-benzofuranone* ***4c***

M.p. 34°C (from light petroleum); IR (film): 1780 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 4.42 (1H, *pseudo*q, J 3.9, H-7a), 2.79 (1H, quintet, J 7.3, H-3), 2.45 (1H, m, H-3a), 2.00 (2H, m), 1.84 (1H, m), 1.67 (1H, tt, J_1=J_2 4.4, J_3 13.7, J_4 26.9), 1.44 (1H, m), 1.29 (2H, m), 1.13 (3H, d, J 7.3, CH_3), 0.98 (3H, d, J 7.3, CH_3); ^{13}C-NMR, δ, ppm: 179.8 (s), 77.2 (d), 41.8 (d), 34.5 (d), 27.9 (t), 25.3 (d), 24.8 (t), 21.7 (t), 16.5 (q), 9.1 (q); MS, m/z: 168 ($M^{+\bullet}$, 0.1), 124 (8), 109 (12), 96 (13), 95 (100), 82 (14),

81 (23), 69 (11), 68 (23), 67 (39), 55 (24); e.e. 98%; $[\alpha]_D^{21}=-44.0$ (c 0.20, CH_3OH); $[\Theta]_{220}=-2089$; UV: $\varepsilon_{225}=330$, M^{-1} cm^{-1} (CH_3OH). DIFNOE experiments: irradiation of H-7a at 4.42 ppm enhanced the following signals: H-3a at 2.45 ppm (3%) and H-3 at 2.79 ppm (3%); irradiation of H-3 at 2.79 ppm enhanced H-3a at 2.45 (5%).

(−)-(3R,3aS,5R,7aS)-cis-*Hexahydro-3,5-dimethyl-2(3H)-benzofuranone* ***5c***

Oil, IR (film): 1770 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 4.39 (1H, dt, $J_1=J_2$ 3.2, $J_3=3.3$, H-7a), 2.79 (1H, dq, $J_1=J_2$ 7.0, J_3 7.3, H-3), 2.32 (1H, ddt, $J_1=J_2$ 6.1, J_3 12.2, J_4 4.0, H-3a), 2.24 (1H, m, H-7), 1.60 (2H, m, H-7′+H-4), 1.50 (1H, m, H-6), 1.33 (1H, m, H-5), 1.15 (3H, d, J 7.0, CH_3), 1.09 (1H, ddd, J_1 4.0, J_2 12.7, J_3 17.4, H-6′), 0.93 (3H, d, J 6.7, CH_3), 0.70 (1H, q, J 12.6, H-4′); ^{13}C-NMR, δ, ppm: 179.9 (s), 76.9 (d), 42.3 (d), 40.1 (d), 31.6 (t), 29.9 (d), 28.2 (t), 27.8 (t), 22.4 (q), 9.0 (q); MS, m/z: 168 ($M^{+\bullet}$, 2), 167 (M-H, 5), 124 (11), 109 (10), 96 (14), 95 (100), 81 (17), 68 (24), 67 (30), 55 (18); e.e. 96%; $[\alpha]_D^{21}=-29.9$ (c 0.10, CH_3OH); $[\Theta]_{219}=-1687$; UV: $\varepsilon_{217}=307$, M^{-1} cm^{-1} (CH_3OH). DIFNOE experiments: irradiation of H-7a at 4.39 ppm enhanced the following signals: H-3a at 2.32 ppm (5%) and H-3 at 2.79 ppm (3%); irradiation of H-3 at 2.79 ppm enhanced H-3a at 2.32 ppm (4%).

(−)-(3R,3aR,7aS)-trans-*Hexahydro-3-methyl-2(3H)-benzofuranone* ***7c***

M.p. 60–62°C (from light petroleum). IR (film): 1790 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 3.74 (1H, dt, $J_1=J_2$ 10.7, J_3 3.9, H-7a), 2.26 (1H, dq, J_1 6.8, J_2 12.7, H-3), 2.23 (1H, m), 1.94 (2H, m), 1.82 (1H, m), 1.55–1.23 (5H, m), 1.21 (3H, d, J 6.8, CH_3); ^{13}C-NMR, δ, ppm: 179.2 (s), 82.7 (d), 51.6 (d), 41.2 (d), 30.0 (t), 27.2 (t), 25.1 (t), 24.0 (t), 12.3 (q); MS, m/z: 154 ($M^{+\bullet}$, 1), 110 (20), 95 (30), 82 (22), 81 (49), 69 (22), 68 (53), 67 (100), 66 (22), 55 (38); e.e. >99%; $[\alpha]_D^{25}=-13.2$ (c 0.14, CH_3OH); $[\Theta]_{219}=-4778$; UV: $\varepsilon_{218}=116$, M^{-1} cm^{-1} (CH_3OH).

*(3aR,5R,7aS)**-trans-*5*-t-*Butyl-hexahydro-2(3H)-benzofuranone* ***9***

Compound **9** was obtained from *trans*-2-(2-nitroethyl)-4-*t*-butylcyclohexanol[14] by Nef reaction occurring on the nitro group, followed by lactonization: oil, IR (film): 1775 cm^{-1} (O–C=O); ^{1}H-NMR, δ, ppm: 3.66 (1H, dt, $J_1=J_2$ 11.0, J_3 3.9, H-7a), 2.44 (1H, dd, J_1 6.4, J_2 16.1, H-3), 2.16 (2H, m), 1.90 (3H, m), 1.47 (1H, m), 1.16 (2H, m), 1.01 (1H, q, J 11.6), 0.81 (9H, d, J 1.0, $C(CH_3)_3$); ^{13}C-NMR, δ, ppm: 177.0 (s), 85.4 (d), 47.7 (d), 44.8 (d), 36.3 (t), 32.7 (s), 30.0 (t), 29.2 (t), 27.8 (q), 25.1 (t); MS, m/z: 196 ($M^{+\bullet}$, 1), 181 (10), 141 (15), 140 (16), 122 (13), 95 (12), 81 (18), 80 (35), 67 (15), 57 (100), 56 (30), 55 (18).

Acknowledgements

The authors thank the M.U.R.S.T., C.N.R., Rome, and the University of Trieste for their financial support.

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(*Received in UK 24 October 1997*)