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A novel efficient and stereoselective synthesis of *cis*- or *trans*-2,5-disubstituted tetrahydrofurans

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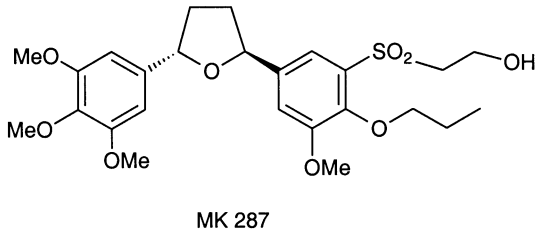
Abstract—A general route to either *cis*- or *trans*-2,5-alkyl or aryl disubstituted tetrahydrofurans is described, using the nucleophilic addition of organolithium derivatives to tricyclic lactones, followed by a highly stereocontrolled acid-assisted reduction with sodium cyanoborohydride of the hemiketals formed. The stereoselectivity observed can be rationalized by the preferential approach of the hydride on the less hindered face of an oxonium ion intermediate.

1. Introduction

Tetrahydrofurans rings are common structural patterns present in a variety of natural products, pharmaceutical and diverse synthetic intermediates and, due to their biological importance, there has been increasing interest in the synthesis of such ring systems.[1,2] Non natural tetrahydrofurans might also be of interest from a biological point of view and in particular 2,5-diaryltetrahydrofurans have been recently identified as competitive antagonists of platelet activating factor (PAF) receptor.[3] These compounds could then be good candidates for the therapy of asthma, inflammation, ischemia or acute allergy.

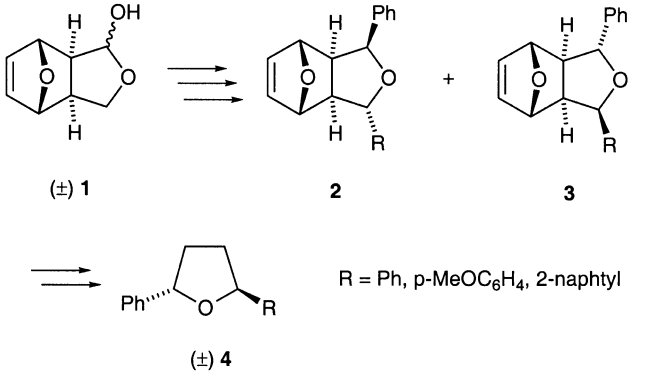
The more potent antagonists possess a 2,5-*trans*-disubstituted stereochemical relationship, the *cis* isomer being essentially biologically inactive[4] and, furthermore, one enantiomer could be considerably more active than the other one: for example the 2*S*,5*S* enantiomer of MK 287 (Fig. 1) is 20-fold more potent than the 2*R*,5*R* enantiomer.[5]



MK 287

Figure 1.

It seemed thus interesting to develop new synthetic ways affording pure stereomers and enantiomers of 2,5-disubstituted tetrahydrofurans. We had already described[6] that, starting from the lactol **1**, which can be easily obtained enantiomerically pure,[7] we were able to obtain a mixture of compounds **2** and **3** which, after retro-Diels–Alder reaction and hydrogenation, gives rise to stereoselectively pure tetrahydrofurans **4**. However, following this way, it was impossible to obtain enantiomerically pure compounds since we could not separate **2** and **3**. Furthermore we did not succeed to synthetize *cis*-2,5-disubstituted furans by this method.



(1)

We wish to report in this paper a novel route which could allow the stereoselective and enantioselective synthesis of *cis*- or *trans*-2,5-disubstituted tetrahydrofurans, starting from lactol **1**.

2. Results and discussion

We had shown[8] that, by appropriate choice of the metal and

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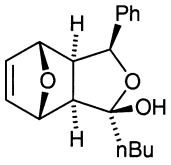
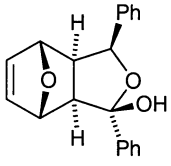
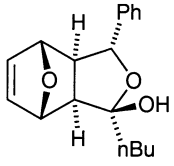
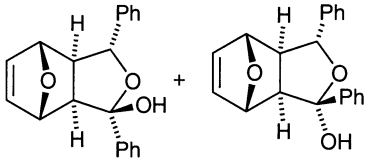
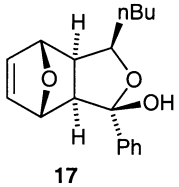
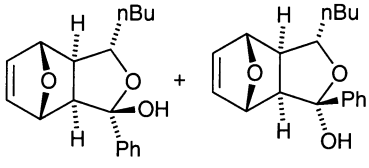
Table 1. Addition of organolithium reagents to the lactones **9**–**12**

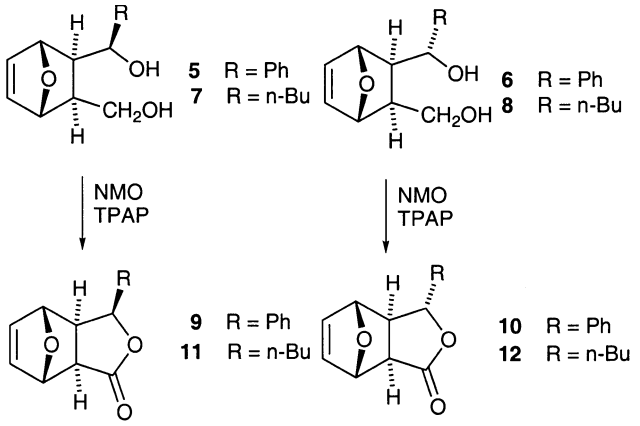
Lactone	Reagent	Product[a]	Yield (%)
9	*n*-BuLi	 **13**	82
859	PhLi	 **14**	85
10	nBuLi	 **15**	54
10	PhLi	 **16a** **16b**	68 (**16a**/**16b**=87/13)
11	PhLi	 **17**	71
12	PhLi	 **18a** **18b**	86 (**18a**/**18b**=72/28)

[a] The ratio of stereomers has been assigned by ^{1}H NMR. Stereomers **16a**, **16b** and **18a**, **18b** have not been isolated in pure form due to their instability.

of reaction conditions, organometallic compounds add with good to excellent selectivity on either one or the other diastereotopic face of the carbonyl group of the aldehyde which is the open form of the lactol **1**. Thus the diols **5**–**8** were obtained pure by action respectively of PhMgBr in THF, $PhTi(OiPr)_3$, *n*-BuMgBr in THF or *n*-BuMgCl in ether.

These diols were oxidized to the lactones **9**–**12** by reaction at room temperature with 4-methylmorpholine N-oxide (NMO) in the presence of tetrapropylammonium perruthenate (TPAP).[9]

The addition of organolithium compounds at −90°C to the lactones **9**–**12** proceeded with good to excellent yields (54–



(2)

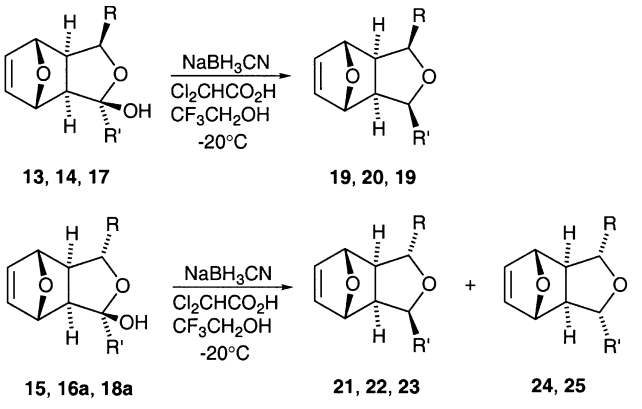
86%) and with high stereoselectivity to give the hemiketals **13**–**18** (Table 1). In most of the cases a unique anomeric stereomer was obtained. Only during the addition of phenyllithium to the lactones **10** and **12** a mixture of two stereomers was observed. The relative stereochemistry of the different substituents of the hemiketals formed has been tentatively assigned based on steric reasons: the geometry of the tricyclic lactones favoured an approach of the lithium reagent from the less hindered α-face of the C_5 lactone ring. This stereochemistry has not been confirmed at this stage since it is lost in the next step of our synthesis, which involves the reduction of a planar oxonium ion intermediate.

The conversion of lactones to cyclic ethers via deoxygenation of hemiketal intermediates has been studied in the carbohydrate area for the synthesis of C-glycosides but little is known for simple cyclic ethers. The reduction is usually carried out with triethylsilane in the presence of boron trifluoride etherate Et_3 $SiH/BF_3{\cdot}Et_2O$. Only one example of reduction by sodium cyanoborohydride in the presence of dichloroacetic acid in trifluoroethanol has been described.[10] In all the cases found in the literature, the reduction of six membered ring lactols afforded exclusively the β C-glycoside.[11] The stereochemical control was believed to be achieved by axial delivery of hydride on the oxonium ion intermediate.

The situation seems to be more complex for the deoxygenation of five membered ring lactols. A survey of the literature shows that the stereochemical course of this reaction depends on the nature, the position and the size of the ring substituents.[12] However some simple rules could be drawn from the published results. If the lactol possesses a vicinal oxygen substituent such as an acetate or a benzyloxy group, the incoming hydride approaches the presumed oxonium ion intermediate preferentially (and often exclusively) from the same face as the oxygen substituent.[13] In contrast if the oxygen bears a big protecting group such as OTBS[14] or is part of a 2,3-*O*-isopropylidene protecting group[15] a mixture of anomers is obtained. Finally if the substituent is not an hydroxyl or a protected hydroxyl group, the stereoselectivity of the lactol reduction is rationalized by steric reasons and it is suggested that the hydride adds to the oxonium ion on the less hindered face of the five membered ring. The role of the substituent position is not totally clear.[16]

In our case the reduction of lactols **13**–**18** could not be accomplished by Et_3SiH in the presence of a Lewis acid since these lactols are very sensitive to Lewis acid. But, as shown in Table 2, high levels of stereoselectivity have been obtained by reduction with sodium cyanoborohydride in the presence of dichloroacetic acid in trifluoroethanol at −20°C which are the best conditions we found.

The stereochemical outcome of the reduction is controlled by the steric hindrance of the bridge oxygen moiety. The stereochemistry of the γ-substituent plays a less important role on the course of the reaction. When the γ-substituent is on the same face of the five membered lactol ring than the oxygen bridge, a unique stereomer is obtained, arising from an approach of the hydride on the less hindered α-face.



(3)

Table 2. Reduction of lactols **13**–**18** by $NaBH_3CN$

Lactol	R	R′	Product(s)	Yield (%)	de[a]
13	Ph	nBu	**19**[b]	90	100
14	Ph	Ph	**20**	91	100
17	NBu	Ph	**19**[b]	71	100
15	Ph	nBu	**21**+**24**	76	70
16a	Ph	Ph	**22**+**25**	80	80
18a	NBu	Ph	**23**	67	100

[a] Determined by ^1H NMR.
[b] Since the starting lactol **1** was racemic, the products arising from reduction of **13** and **17** were identical.

In contrast two stereomers are generally obtained if the γ-substituent is on the opposite face and obstructs the approach of the reagent on the α-face (Fig. 2).

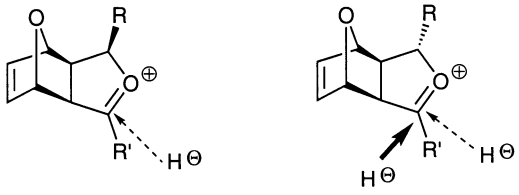


Figure 2.

The relative stereochemistry of the ethers **19**–**25** has been assigned by careful examination of their ^1H NMR spectra and in particular by the value of the coupling constants $J_{H_AH_C}$ and $J_{H_BH_D}$ (Fig. 3).[17]

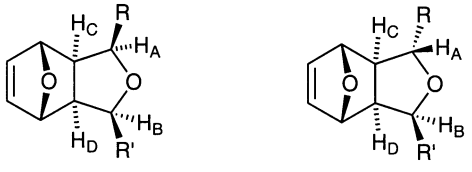
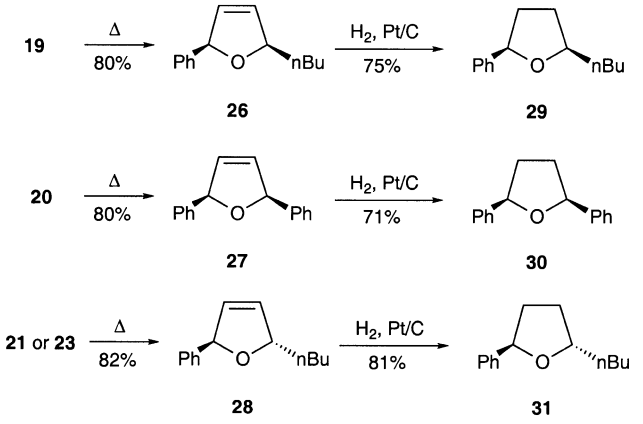


Figure 3.

When the substituents R and R′ are in *cis* position, the more stable conformation is the one where R and R′ adopt a pseudo equatorial position. The dihedral angles H_ACCH_C and H_BCCH_D are around 30° and $J_{H_AH_C} = J_{H_BH_D} \approx$ 7–8 Hz. If R and R′ are *trans*, the more stable conformation

involves R′ in pseudo equatorial and R in pseudo axial conformation. In this case the dihedral angle H_ACCH_C is around 90° and we found $J_{H_AH_C}$=1–3 Hz and $J_{H_BH_D}$=6–8 Hz (Fig. 3).

The stereochemistry has been confirmed by the transformation of compounds **19**–**23** into tetrahydrofurans. Flash thermolysis followed by a simple hydrogenation at atmospheric pressure over 5% Pt/C afforded with good yields the 2,5-disubstitued tetrahydrofurans **29**–**31**.



(4)

The transformation of **22** to *trans*-2,5-diphenyltetrahydrofuran has already been described.[6]

3. Conclusion

We have shown that *cis* and *trans* 2,5-disubstituted tetrahydrofurans can be obtained stereochemically pure from lactol **1**. Since the two enantiomers of **1** are available, this methodology can be used to synthetize the four diastereomers of 2,5-disubstituted tetrahydrofurans stereochemically and enantiomerically pure.

4. Experimental

4.1. Procedure for oxidation of diols 5, 6, 7, 8 to lactones 9, 10, 11, 12

To a solution of the diol (1 mmol) in CH_2Cl_2 (5 mL) were added activated 4 Å molecular sieves powder (500 mg) and tetrapropylammonium perruthenate (10 mg, 0,03 mmol). Then 4-methyl morpholin N-oxide (351 mg, 3 mmol) in CH_2Cl_2 (1 mL) was added dropwise at room temperature. The mixture was stirred for 3 h and then filtered through a pad of silica gel. The solid was washed with CH_2Cl_2 (10 mL) and EtOAc (30 mL). The solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt 60/40)

4.1.1. (1*S,2*R**,5*R**,6*S**,7*R**)-4,10-Dioxa-5-phenyltricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-one 9.** Yield 71%; colorless solid. mp 123–125°C. IR (KBr): 3075, 3061, 3014, 1761, 1493, 1454 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.84 (1H, dd, *J*=7.8, 7.5 Hz), 3.05 (1H, d, *J*=7.5 Hz), 4.38 (1H, d, *J*=1.5 Hz), 5.37 (1H, s), 5.74 (1H, d, *J*=8.0 Hz), 6.34 (1H, m), 6.48 (1H, m), 7.30–7.50 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 45.7, 48.7, 80.0, 81.2, 125.7, 128.0, 128.2, 135.9, 136.4, 137.4, 175.4. ESMS *m*/*z* (relative intensity): 479 (2MNa$^+$, 100), 251 (MNa$^+$, 83), 183 (91). Anal. calcd for $C_{14}H_{12}O_3$: C, 73.64; H, 5.30. Found: C, 73.23; H, 5.49.

4.1.2. (1*S,2*R**,5*S**,6*S**,7*R**)-4,10-Dioxa-5-phenyltricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-one 10.** Yield 60%; colorless solid. mp 97–99°C. IR (KBr): 3099, 3037, 3004, 2941, 1758, 1498, 1458 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.67 (1H, dd, *J*=7.7, 3.5 Hz), 3.00 (1H, d, *J*=7.7 Hz), 5.21 (1H, s), 5.35 (1H, d, *J*=3.5 Hz), 5.39 (1H, s), 6.40–6.54 (2H, m), 7.28–7.52 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 48.5, 50.6, 81.9, 83.7, 84.3, 125.2, 128.5, 128.9, 136.3, 136.7, 140.4, 175.1. ESMS *m*/*z* (relative intensity): 479 (2MNa$^+$, 100), 251 (MNa$^+$, 61), 183 (90). HRESMS: Calcd for $C_{14}H_{12}O_3Na^+$: 251.0684. Found: 251.0689. Anal. calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.26; H, 5.36.

4.1.3. (1*S,2*R**,5*R**,6*S**,7*R**)-4,10-Dioxa-5-butyltricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-one 11.** Yield 67%; colorless solid. mp 79–80°C. IR (KBr): 3076, 3013, 2963, 2931, 2871, 1764, 1463 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.95 (3H, t, *J*=7.0 Hz), 1.32–1.78 (5H, m), 1.85–1.99 (1H, m), 2.60 (1H, dd, *J*=7.7 Hz), 2.93 (1H, d, *J*=7.7 Hz), 4.57–4.66 (1H, m), 5.19 (1H, s), 5.29 (1H, s), 6.43–6.52 (2H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 13.8, 22.3, 28.1, 30.7, 43.9, 49.0, 79.3, 80.5, 81.4, 136.7, 137.3, 175.3. ESMS *m*/*z* (relative intensity): 439 (2MNa$^+$, 100), 263 (70), 231 (MNa$^+$, 54), 195 (51), 163 (54). Anal. calcd for $C_{12}H_{16}O_3$: C, 72.73; H, 9.09. Found: C, 72.81; H, 9.30.

4.1.4. (1*S,2*R**,5*S**,6*S**,7*R**)-4,10-Dioxa-5-butyltricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-one 12.** Yield 64%; colorless solid. mp 58°C. IR (KBr): 3024, 2994, 2955, 2934, 2872, 1755, 1470 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J*=6.8 Hz), 1.33–1.50 (4H, m), 1.64–1.79 (2H, m), 2.34 (1H, dd, *J*=7.7, 3.4 Hz), 2.84 (1H, d, *J*=7.7 Hz), 4.36 (1H, m), 4.97 (1H, s), 5.30 (1H, s), 6.42–6.50 (2H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 13.7, 22.1, 26.5, 36.2, 47.3, 48.5, 81.6, 83.5, 83.7, 136.3, 175.2. ESMS *m*/*z* (relative intensity): 439 (2MNa$^+$, 100), 263 (45), 231 (MNa$^+$, 34), 195 (33), 163 (33). Anal. calcd for $C_{12}H_{16}O_3$: C, 72.73; H, 9.09. Found: C, 72.83; H, 9.21.

4.2. General procedure for addition of organolithium compounds to lactones 9–12

To a solution of the lactone (1 mmol) in THF (10 mL) cooled at −90° was added dropwise a commercial solution of organolithium compound (1.1 mmol). The mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with ether (3×10 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt 80/20).

4.2.1. (1*S,2*R**,3*R**,5*R**,6*S**,7*R**)-4,10-Dioxa-3-butyl-5-phenyltricyclo[5.2.1.0^{2,6}]-dec-8-en-3-ol 13.** Prepared following the general procedure by addition of commercial butyllithium in hexane to lactone **9**. Yield 82%; colorless solid. mp 138–140°C. IR (KBr): 3380, 3005, 2969, 2859,

1605, 1497 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.99 (3H, t, J=6.9 Hz), 1.38–1.72 (4H, m), 1.90–2.05 (2H, m), 2.08 (1H, s), 2.46 (1H, d, J=6.9 Hz), 2.63 (1H, dd, J=6.9 Hz), 4.22 (1H, s), 5.00 (1H, s), 5.42 (1H, d, J=6.9 Hz), 6.30 (1H, m), 6.40 (1H, m), 7.29–7.43 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 13.9, 22.9, 26.0, 35.9, 49.4, 54.0, 78.5, 78.8, 105.2, 126.5, 127.3, 128.0, 137.3, 137.5, 138.2. ESMS *m/z* (relative intensity): 595 ($2MNa^+$, 28), 309 (MNa^+, 100). HRESMS: Calcd for $C_{18}H_{23}O_3Na^+$: 309.1467. Found: 309.1475. Anal. calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.23; H, 7.79.

4.2.2. (1*S,2*R**,3*R**,5*R**,6*S**,7*R**)-4,10-Dioxa-3,5-diphenyltricyclo[5.2.1.0^{2,6}]-dec-8-en-3-ol 14.** Prepared following the general procedure by addition of commercial phenyllithium in ether/cyclohexane to lactone **9**. Yield 85%; colorless solid. mp 133–135°C. IR (KBr): 3350, 3064, 3023, 3003, 2968, 1496, 1447 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 2.62–2.76 (2H, m), 4.11 (1H, s), 4.29 (1H, s), 5.53 (1H, d, J=6.7 Hz), 6.26 (2H, s), 7.31–7.59 (8H, m), 7.73–7.81 (2H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 49.6, 56.8, 78.8, 78.9, 79.9, 105.1, 126.5, 126.7, 127.4, 128.2, 137.5, 137.6, 138.2, 141.0. ESMS *m/z* (relative intensity): 329 (MNa^+, 100). HRESMS: Calcd for $C_{20}H_{18}O_3Na^+$: 329.1154. Found: 329.1153.

4.2.3. (1*S,2*R**,3*R**,5*S**,6*S**,7*R**)-4,10-Dioxa-3-butyl-5-phenyltricyclo[5.2.1.0^{2,6}]-dec-8-en-3-ol 15.** Prepared following the general procedure by addition of commercial butyllithium in hexane to lactone **10**. Yield 54%; colorless liquid. IR (film, NaCl): 3491, 3065, 3029, 2992, 2954, 2866, 1605, 1496 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.03 (3H, t, J=7.0 Hz), 1.24–1.68 (6H, m), 1.80–2.00 (2H, m), 2.52 (1H, dd, J=8.7, 7.7 Hz), 2.68 (1H, d, J=8.7 Hz), 4.69 (1H, d, J=7.6 Hz), 4.73 (1H, s), 4.86 (1H, s), 4.98 (1H, s), 6.40 (2H, s), 7.29–7.50 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.9, 22.8, 26.1, 39.1, 54.3, 57.1, 79.2, 80.3, 80.4, 104.0, 126.0, 127.7, 128.4, 135.7, 137.7, 141.0. ESMS *m/z* (relative intensity): 309 (MNa^+, 100). HRESMS: Calcd for $C_{18}H_{22}O_3Na^+$: 309.1467. Found: 309.1468. Anal. calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.46; H, 7.58.

4.2.4. (1*S,2*R**,3*R**,5*S**,6*S**,7*S**)-4,10-Dioxa-3,5-diphenyltricyclo[5.2.1.0^{2,6}]-dec-8-en-3-ol 16a.** Prepared following the general procedure by addition of commercial phenyllithium in ether/cycohexane to lactone **10**. Yield 68%; colorless liquid mixture of diastereomers (85/15). Major adduct: ^1H NMR (250 MHz, C_6D_6) δ: 2.21 (1H, dd, J=7.7 Hz, 2.48 (1H, d, J=7.7 Hz), 4.33 (1H, s), 4.74 (1H, d, J=7.7 Hz), 4.78 (1H, s), 5.32 (1H, s), 5.53 (1H, m), 5.64 (1H, m), 7.18–7.37 (8H, m), 7.95 (2H, m).

4.2.5. (1*S,2*R**,3*R**,5*R**,6*S**,7*R**)-4,10-Dioxa-3-phenyl-5-butyltricyclo[5.2.1.0^{2,6}]-dec-8-en-3-ol 17.** Prepared following the general procedure by addition of commercial phenyllithium in ether/cyclohexane to lactone **11**. Yield 71%; colorless liquid. IR (film, NaCl): 3273, 3085, 3070, 2999, 2934, 2874, 1687, 1606, 1492 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.98 (3H, t, J=6.9 Hz), 1.36–1.55 (4H, m), 1.70–2.00 (2H, m), 2.46–2.57 (2H, m), 4.03 (1H, d, J=1.3 Hz), 4.14 (1H, q, J=6.8 Hz), 5.01 (1H, s), 6.26 (1H, m), 6.37 (1H, m), 7.32–7.44 (3H, m), 7.57–7.66 (2H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.2, 23.0, 28.7, 29.7, 47.0, 55.1, 77.0, 77.8, 80.0, 104.6, 126.6, 128.0, 137.5, 137.6, 141.5. ESMS *m/z* (relative intensity): 309 (MNa^+, 100). HRESMS: Calcd for $C_{18}H_{22}O_3Na^+$: 309.1467. Found: 309.1465.

4.2.6. (1*S,2*R**,3*R**,5*S**,6*S**,7*R**)-4,10-Dioxa-3-phenyl-5-butyltricyclo[5.2.1.0^{2,6}]-dec-8-en-3-ol 18a.** Prepared following the general procedure by addition of commercial phenyllithium in ether/cyclohexane to lactone **12**. Yield 86%; colorless liquid mixture of diastereomers (85/15). Major product: ^1H NMR (200 MHz, C_6D_6) δ: 0.93 (3H, t, J=6.9 Hz), 1.15–1.56 (6H, m), 1.84 (1H, dd, J=7.7 Hz), 2.36 (1H, d, J=7.7 Hz), 3.71 (1H, q, J=6.8 Hz), 4.17 (1H, s), 4.77 (1H, d, J=1.3 Hz), 5.26 (1H, s), 5.57 (1H, m), 5.78 (1H, m), 7.07–7.29 (8H, m), 7.78–7.92 (2H, m). ^1H NMR (250 MHz, $CDCl_3$) δ: 0.96 (3H, t, J=6.9 Hz), 1.31–1.56 (4H, m), 1.64–1.93 (2H, m), 2.36 (1H, dd, J=7.7, 7.6 Hz), 2.67 (1H, d, J=7.7 Hz), 3.89 (1H, q, J=6.8 Hz), 4.75 (1H, s), 5.07 (1H, d, J=1.3 Hz), 5.11 (1H, s), 6.32 (1H, m), 6.48 (1H, m), 7.30–7.43 (6H, m), 7.60–7.68 (2H, m).

4.3. General procedure for the reduction of lactols 13–15, 16a, 17, 18a

To a solution of the lactol (1 mmol) in 1,1,1-trifluoroethanol (5 mL) at −20, −25°C was added $NaBH_3CN$ (3 mmol). The suspension was stirred for 5 min and was added dropwise dichloroacetic acid. The solution was stirred for 1 h. The mixture was quenched by a saturated solution of $NaHCO_3$ (5 ml), extracted with ether (3×10 mL). The organic phase was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt 90/10).

4.3.1. (1*S,2*R**,3*S**,5*R**,6*S**,7*R**)-4,10-Dioxa-3-butyl-5-phenyltricyclo[5.2.1.0^{2,6}]-dec-8-en 19.** Prepared from lactol **13**. Yield 90% or from lactol **17**. Yield 71%; colorless oil. IR (film, NaCl): 3005, 2955, 2858, 1607, 1494, 1454 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=6.9 Hz), 1.35–1.60 (4H, m), 1.70–2.04 (2H, m), 2.38 (1H, dd, J=6.8 Hz), 2.50 (1m, dd, J=6.8 Hz), 3.47 (1H, dt, J=7.0–6.3 Hz), 4.28 (1H, s), 4.93 (1H, d, J=6.6 Hz), 5.06 (1H, s), 6.27 (1H, m), 6.38 (1H, m), 7.28–7.44 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.0, 22.8, 28.9, 30.0, 48.7, 50.8, 77.8, 78.9, 79.2, 80.9, 126.6, 127.1, 128.0, 137.6, 138.9. ESMS *m/z* (relative intensity): 593 (100), 293 (MNa^+, 74). HRESMS: Calcd for $C_{18}H_{22}O_2Na^+$: 293.1518. Found: 293.1529.

4.3.2. (1*S,2*R**,3*S**,5*R**,6*S**,7*R**)-4,10-Dioxa-3,5-diphenyltricyclo[5.2.1.0^{2,6}]-dec-8-en 20.** Yield 90%; colorless solid. mp 134°C. IR (KBr): 3008, 2967, 2921, 2852, 1604, 1494, 1454 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 2.63 (2H, m), 4.35 (2H, s), 5.15 (2H, m), 6.26 (2H, s), 7.30–7.45 (6H, m), 7.57 (4H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 51.0, 78.9, 81.2, 126.7, 127.3, 128.2, 137.9, 138.8. ESMS *m/z* (relative intensity): 313 (MNa^+, 100). HRESMS: Calcd for $C_{20}H_{18}O_2Na^+$: 313.1204. Found: 313.1211. Anal. calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.49; H, 6.29.

4.3.3. (1*S, 2*R**, 3*S**, 5*S**, 6*S**, 7*R**)- and (1*S**, 2*R**, 3*R**, 5*S**, 6*S**, 7*R**)-4,10-Dioxa-3-butyl-5-phenyltricyclo-[5.2.1.0^{2,6}]-dec-8-en 21 and 24.** Following the general

procedure 91 mg of lactol **11** give 56 mg (65%) of **21** and 9 mg (11%) of **24** both as colorless oils.

21: IR (film, NaCl): 3080, 3061, 2955, 2858, 1603, 1494, 1454 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95 (3H, t, J=6.9 Hz), 1.36–1.70 (5H, m), 1.78–1.92 (1H, m), 2.44 (1H, dd, J=7.0, 7.2 Hz), 2.61 (1H, dd, J=3.3, 7.4 Hz), 4.08–4.20 (1H, m), 4.94 (1H, d, J=3.1 Hz), 5.03 (2H, s), 6.43 (2H, m), 7.36 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.0, 22.8, 28.9, 30.4, 49.5, 54.3, 78.2, 78.3, 82.0, 82.5, 125.5, 127.0, 128.3, 137.1, 137.3, 143.0. ESMS *m/z* (relative intensity): 563 ($2MNa^+$, 100), 293 (MNa^+, 67). HRESMS: Calcd for $C_{18}H_{22}O_2Na^+$: 293.1518. Found: 293.1521.

24: IR (film, NaCl): 3059, 3028, 2956, 2930, 2860, 1605, 1496, 1454 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95 (3H, t, J=6.9 Hz), 1.33–1.90 (6H, m), 2.26 (1H, dd, J=7.5, 8.4 Hz), 2.41 (1H, dd, J=7.5, 8.4 Hz), 3.77 (1H, dt, J= 7.0, 6.4 Hz), 4.57 (1H, d, J=7.5 Hz), 4.74 (1H, d, J= 1.4 Hz), 4.85 (1H, d, J=1.4 Hz), 6.36 (2H, m), 7.25–7.48 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.0, 22.9, 28.2, 34.6, 55.0, 57.6, 80.2, 80.7, 82.0, 83.3, 126.2, 127.6, 128.5, 136.3, 136.5, 141.9. ESMS *m/z* (relative intensity): 293 (MNa^+, 100). HRESMS: Calcd for $C_{18}H_{22}O_2Na^+$: 293.1518. Found: 293.1518.

4.3.4. ($1S^*, 2R^*, 3S^*, 5S^*, 6S^*, 7R^*$)- and ($1S^*, 2R^*, 3R^*, 5S^*, 6S^*, 7R^*$)-4,10-Dioxa-3,5-diphenyltricyclo[5.2.1.$0^{2,6}$]-dec-8-en 22 and 25. Following the general procedure 102 mg of lactol **16a** give 66 mg (68%) of **22** and 12 mg (12%) of **25** both as colorless solids.

22: mp 93–94°C. IR (KBr): 3082, 3059, 3028, 2998, 2978, 2920, 2851, 1602, 1493, 1457, 1450 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 2.60 (1H, dd, J=7.0 Hz), 2.73 (1H, dd, J=7.2, 2.4 Hz), 4.33 (1H, d, J=1.3 Hz), 5.12 (1H, s), 5.26 (1H, s), 5.27 (1H, d, J=10.9 Hz), 6.27 (1H, m), 6.43 (1H, m), 7.24–7.46 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 51.7, 53.9, 79.0, 80.5, 83.1, 83.3, 125.4, 126.6, 127.1, 127.3, 128.2, 128.5, 137.3, 137.4, 139.1, 143.0. ESMS *m/z* (relative intensity): 603 ($2MNa^+$, 31), 313 (MNa^+, 100). HRESMS: Calcd for $C_{20}H_{18}O_2Na^+$: 313.1204. Found: 313.1206.

25: mp 75–76°C. IR (KBr): 3025, 2953, 2850, 1603, 1493, 1452 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.59 (2H, dd, J=1.9, 5.2 Hz), 4.78 (2H, dd, J=1.8, 5.2 Hz), 4.95 (2H, s), 6.36 (2H, s), 7.33–7.60 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 58.0, 80.6, 83.8, 126.2, 127.8, 128.6, 136.4, 141.5. ESMS *m/z* (relative intensity): 313 (MNa^+, 100). HRESMS: Calcd for $C_{20}H_{18}O_2Na^+$: 313.1204. Found: 313.1208.

4.3.5. ($1S^*$,$2R^*$,$3S^*$,$5S^*$,$6S^*$,$7R^*$)-4,10-Dioxa-3-phenyl-5-butyltricyclo[5.2.1.$0^{2,6}$]-dec-8-en 23. Yield 67%; colorless solid. mp 78–79°C. IR (KBr): 3074, 3054, 3028, 3000, 2957, 2924, 2857, 1604, 1495, 1467, 1453 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=6.9 Hz), 1.32–1.58 (5H, m), 1.62–1.75 (1H, m), 2.26 (1H, dd, J=2.1, 7.1 Hz), 2.53 (1H, dd, J=7.0 Hz), 4.15 (1H, m), 4.28 (1H, s), 4.91 (1H, s), 5.14 (1H, d, J=6.9 Hz), 6.25 (1H, m), 6.41 (1H, m), 7.29–7.51 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.0, 22.6, 28.1, 34.9, 51.0, 51.8, 78.9, 79.3, 82.4, 82.8, 126.6, 127.1, 128.1, 137.1, 137.4, 139.4. ESMS *m/z* (relative intensity): 563 ($2MNa^+$, 40), 293 (MNa^+, 100). HRESMS: Calcd for $C_{18}H_{22}O_2Na^+$: 293.1518. Found: 293.1526. Anal. calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.13; H, 8.24.

4.4. General procedure for the flash thermolysis of 19, 20, 23

The tricyclic compounds **19**, **20**, **23** were evapored through an horizontal mullite tube (400°C, 10^{-3} Torr) and the thermolysate was collected on a finger cooled to liquid nitrogen temperature. After warming to room temperature, the finger was washed with ether and the resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ether 95:5).

4.4.1. *cis*-2-Phenyl-5-butyl-3,4-dihydrofuran 26. Yield 80%; colorless liquid. IR (film, NaCl): 3064, 3031, 2957, 2931, 2860, 1602, 1493 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz), 1.30–1.53 (4H, m), 1.61–1.77 (2H, m), 4.92 (1H, m), 5.77 (1H, m), 5.86 (1H, m), 5.96 (1H, m), 7.35 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.0, 22.7, 27.8, 36.5, 86.5, 87.5, 126.6, 127.6, 128.3, 130.0, 130.5, 142.0. ESMS *m/z* (relative intensity): 257 ($M{\cdot}MeOHNa^+$, 100), 473 ($2MNa^+$, 28).

4.4.2. *cis*-2,5-Diphenyl-3,4-dihydrofuran 27. Yield 78%; colorless liquid. IR (film, NaCl): 3059, 3030, 2845, 1604, 1494 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 5.93 (2H, d, J= 0.6 Hz), 6.08 (2H, d, J=0.8 Hz), 7.32–7.40 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 88.0, 127.0, 127.8, 128.4, 130.5, 141.2. ESMS *m/z* (relative intensity): 245 (MNa^+, 34), 277 ($M{\cdot}MeOHNa^+$, 100), 513 ($2MNa^+$, 22).

4.4.3. *trans*-2-Phenyl-5-butyl-3,4-dihydrofuran 28. Yield 82%; colorless liquid. IR (film, NaCl): 3059, 3031, 2957, 2931, 2860, 1601, 1492 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz), 1.33–1.50 (4H, m), 1.62–1.72 (2H, m), 5.10 (1H, m), 5.82 (1H, m), 5.88 (1H, m), 5.96 (1H, m), 7.33 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.0, 22.8, 27.5, 35.8, 86.6, 87.5, 126.4, 127.7, 128.4, 129.9, 130.2, 142.1. ESMS *m/z* (relative intensity): 257 ($M{\cdot}MeOHNa^+$, 100).

4.5. General procedure for the hydrogenation of dihydrofurans 26–28

A solution of the dihydrofuran (1 mmol) in ethylacetate (10 mL) was hydrogenated over 5% Pt/c (20 mg) at atmospheric pressure. After filtration, the catalyst was washed with ethylacetate (5 mL) and the filtrate was concentrated in vacuo. The oily mixture was purified by chromatography on silica gel (eluent: petroleum ether/dichloromethane 60:40).

4.5.1. *cis*-2-Phenyl-5-butyl tetrahydrofuran 29. Hydrogenation of 64 mg of **26** gives 46 mg (71%) of **29** as a coulourless liquid. IR (film, NaCl): 3064, 3029, 2930, 2859, 1604, 1494 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95 (3H, t, J=6.9 Hz), 1.30–1.90 (8H, m), 2.00–2.15 (1H, m), 2.23–2.48 (1H, m), 4.03 (1H, q, J=6.5 Hz), 4.89

(1H, dd, J=7.0, 7.3 Hz), 7.22–7.40 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.1, 22.8, 28.4, 31.3, 34.5, 35.7, 80.1, 80.7, 125.8, 127.0, 128.2, 143.6. ESMS m/z (relative intensity): 259 (100), 227 (MNa^+, 53). HRESMS: Calcd for $C_{14}H_{20}ONa^+$: 227.1412. Found: 227.1413. Anal. calcd for $C_{14}H_{02}O$: C, 82.30; H, 9.87. Found: C, 82.52; H, 9.68.

4.5.2. *cis*-2,5-Diphenyltetrahydrofuran 30. Hydrogenation of 82 mg of **27** gives 54 mg (65%) of **30** as a coulourless liquid. IR (film, NaCl): 3063, 3030, 2942, 2872, 1604, 1495 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.00 (2H, m), 2.45 (2H, m), 5.08 (2H, m), 7.30–7.50 (10H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 34.4, 81.2, 126.0, 127.3, 128.3, 142.9. ESMS m/z (relative intensity): 247 (MNa^+, 100). HRESMS: Calcd for $C_{16}H_{16}ONa^+$: 247.1099. Found: 247.1094. Anal. calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.13. Found: C, 85.81; H, 7.02.

4.5.3. *trans*-2-Phenyl-5-butyl tetrahydrofuran 31. Hydrogenation of 98 mg of **28** gives 80 mg (81%) of **31** as a colorless liquid. IR (film, NaCl): 3063, 3028, 2958, 2930, 2860, 1604, 1493 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.95 (3H, t, J=6.7 Hz), 1.34–1.95 (8H, m), 2.10–2.22 (1H, m), 2.34–2.45 (1H, m), 4.21 (1H, m), 5.02 (1H, dd, J=7.1, 7.4 Hz), 7.22–7.49 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.1, 22.8, 28.3, 32.4, 35.4, 35.8, 80.1, 125.6, 127.0, 128.2, 144. ESMS m/z (relative intensity): 227 (MNa^+, 100). HRESMS: Calcd for $C_{14}H_{20}ONa^+$: 227.1412. Found: 227.1411. Anal. calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.49; H, 9.61.

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