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Preparation of enantiopure 3,5,5-trialkyl-γ-butyrolactones by diastereospecific 5-*endo* halo lactonizations

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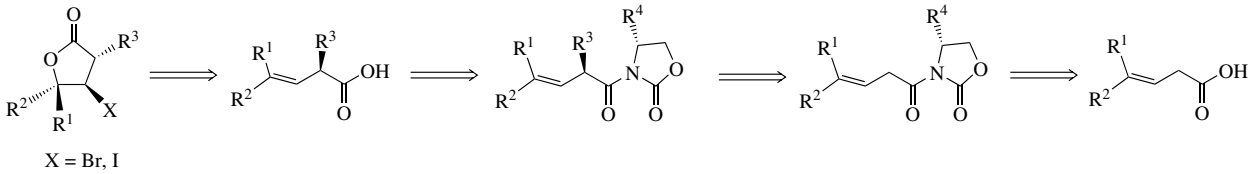
Abstract—A new preparation of 3,5,5-trialkyl-γ-butyrolactones of defined absolute configuration is reported. This method involves the diastereoselective alkylation of 3,4-ethylenic acids after incorporation of a chiral Evans auxiliary, and then after separation of the two diastereomers and hydrolysis of the auxiliary, stereospecific halo lactonizations. This method was applied to the preparation of a natural product, present in a sponge.

1. Introduction

The formation of γ-butyrolactones by 5-*endo* halo lactonizations has been the subject of numerous reports since the pioneering work of Fittig.[1] The diastereoselectivity of these reactions has also been studied for the preparation of 3,4,5-trisubtituted-γ-butyrolactones.[2] We started a new program concerning the synthesis of optically active γ-butyrolactones by 5-*endo* halo lactonizations. With this objective, we recently found that such an aim could be reached by enantioselective halo lactonizations using chiral halo reagents.[3] Herein we report our results concerning the formation of enantiomerically pure 3,5,5-trialkyl-γ-butyrolactones by diastereospecific halo lactonizations. Access to such enantiomerically enriched or pure γ-butyrolactones, is rather rare,[4] but shows the interest to find new methods to synthesize this interesting family of compounds.

2. Results and discussion

The approach we decided to examine involved the diastereospecific lactonization of enantiopure 2-substituted 3,4-ethylenic acids, using Evans methodology (Scheme 1).[5] We first examined this methodology starting from (*E*)-4-phenylpent-3-enoic acid **1** (Scheme 1).[6] The corresponding oxazolidinone **2** was prepared using a standard procedure by reaction of the mixed anhydride obtained by reaction of the acid with pivaloyl chloride, with the anion formed from (*R*)-phenyloxazolidinone. The subsequent methylation of compound **2** led to a mixture (60:40) of the two diastereomers **3a** and **3b** (Scheme 2). After separation of these diastereomers by liquid chromatography over silica gel, the (*R*)-stereochemistry of the major isomer **3a** was established from its NMR spectra, and secured by X-ray crystallography. After hydrolysis of its chiral auxiliary,



Scheme 1.

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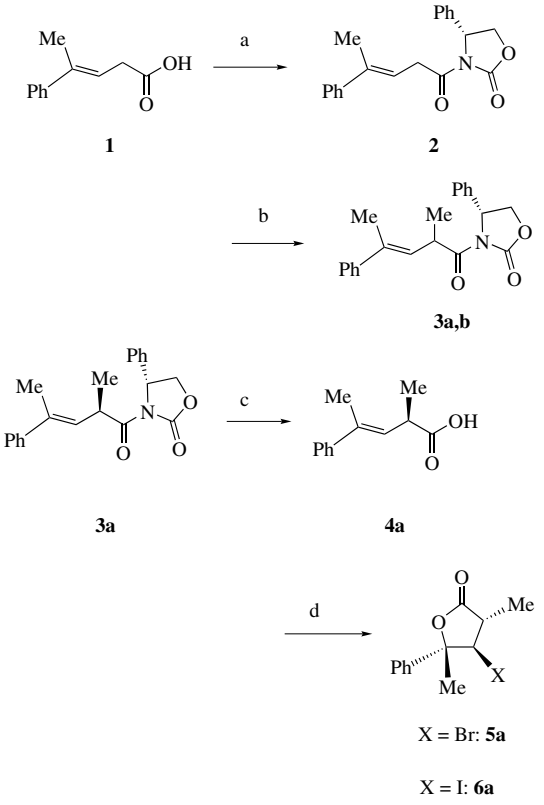
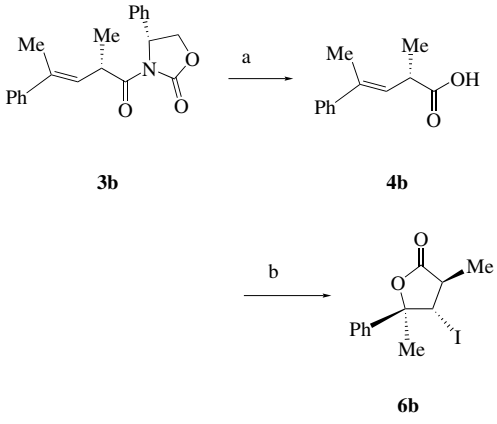


Scheme 2. (a) (i) PivCl, Et_3N, THF, 0 °C; (ii) (*R*)-phenyl-oxazolidinone, *n*BuLi, THF, −78 °C to rt (85%); (b) LDA, HMPA, THF, −78 °C then MeI, THF, −78 °C (60%: dr: 60:40); (c) LiOH, H_2O_2, THF, H_2O (90%); (d) $X^+(coll)_2\ PF_6^-$, DCM (X = I; 93%. X = Br; 70%).

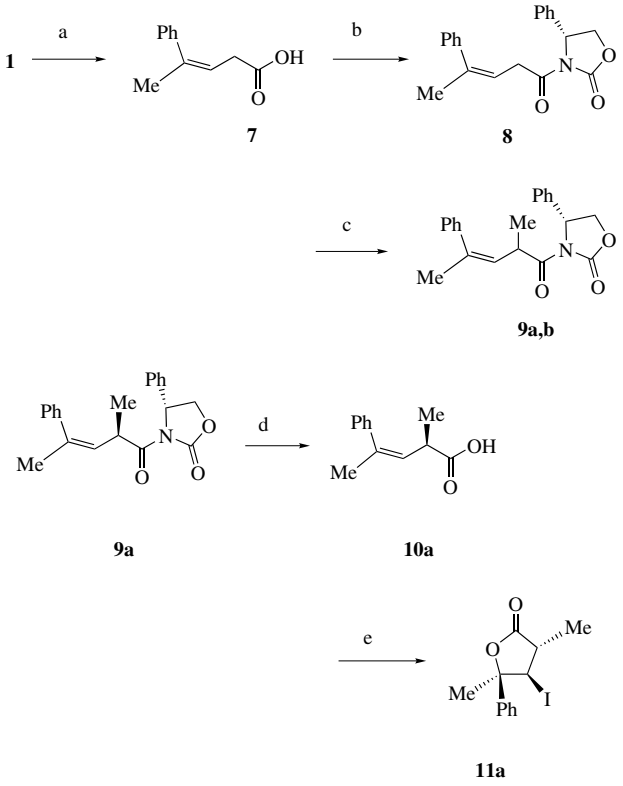
the corresponding enantiomerically pure acid (*R*)-**4a** was submitted to halo lactonizations in dichloromethane using halo(*bis*-collidine) hexafluorophosphate, to give the desired halo lactones **5a** and **6a**. With both the bromo and iodo reagents, only one diastereomer was isolated.

The structure of halo lactones **5a** and **6a** was established from their spectral data. The structure of iodo lactone **6a** was also secured by X-ray crystallography. The configuration of these lactones was found to be (3*S*,4*R*,5*S*). Similarly, the hydrolysis of the minor diastereomer (*S*)-**3b** led to the corresponding acid (*S*)-**4b**, which upon iodo lactonization allowed the preparation of lactone **6b** of (3*R*,4*S*,5*R*)-configuration (Scheme 3). The comparable absolute values measured for the $[\alpha]_D$ of iodo lactones **6a** and **6b** show that these two lactones are the two enantiomers of the same diastereomer.

We next examined, the preparation of the diastereomer of iodo lactone **6a**. This preparation was initially started from (*Z*)-4-phenyl-3-pentenoic acid. This acid was obtained by photochemical isomerization of its (*E*)-isomer.[3] The subsequent formation of the enantiomerically pure acid (*R*)-**10a** was then accomplished by the same procedure reported for the preparation of lactones **5a** and **6a** (Scheme 4). The preparation of iodo lactone **11a** was then carried out from (*R*)-acid **10a** using iodo(*bis*-collidine) hexafluorophosphate as an electrophile. In this case, only one lactone was isolated: iodo lactone **11a** of (3*R*,4*S*,5*R*)-configuration. The



Scheme 3. (a) LiOH, H_2O_2, THF, H_2O (62%); (b) $I^+(coll)_2\ PF_6^-$, DCM (91%).

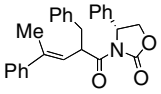
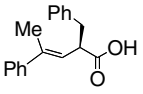
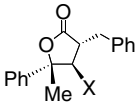
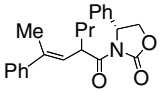
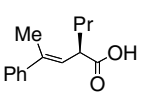
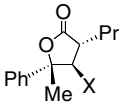
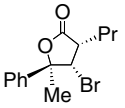
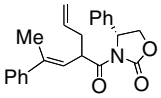
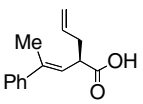
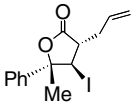
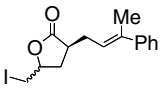
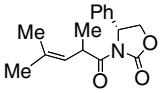
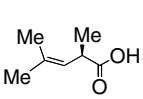
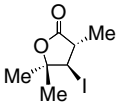


Scheme 4. (a) *hv*, heptane, rt (70%); (b) (i) PivCl, Et_3N, THF, 0 °C; (ii) (*R*)-phenyl-oxazolidinone, *n*BuLi, THF, −78 °C to rt (70%); (c) LDA, HMPA, THF, −78 °C then MeI, THF, −78 °C (33%: dr: 70:30); (d) LiOH, H_2O_2, THF, H_2O (85%); (e) $I^+(coll)_2\ PF_6^-$, DCM (89%).

reaction with the minor diastereomer should lead, in the same way, to the enantiomer of lactone **11a**. Having established that this methodology allows the preparation of the four diastereomers of 3,5,5-trialkyl γ-butyrolactones, we decided to examine its scope. Oxazolidinone **2** was thus alkylated using various alkyl halides. These alkylations were carried out in THF at −78 °C, using LDA as base. Our results are reported in Table 1.

This type of 3,4-unsaturated oxazolidinone was found to be less reactive than the saturated ones.[5] With the excep-

Table 1.

Entry	Alkylating agent	Oxazolidinone (yield; %; dr)	Acid[a]	Halo lactone (yield; %)	Other product(s), (yield; %)
a	$PhCH_2Br$	 **12** (70%; 88:12)	 **13**	 **14** X = I (91%) **15** X = Br (80%)	
b	PrI	 **16** (36%; 77:23)	 **17**	 **18** X = I (92%) **19** X = Br (67%)	 **20** (17%)
c		 **21** (55%; 70:30)	 **22**	 **23** (27%)	 **24** (54%; 45:55[b])
d	MeI	 **25** (60%; 80:20)	 **26**	 **27** (76%)	

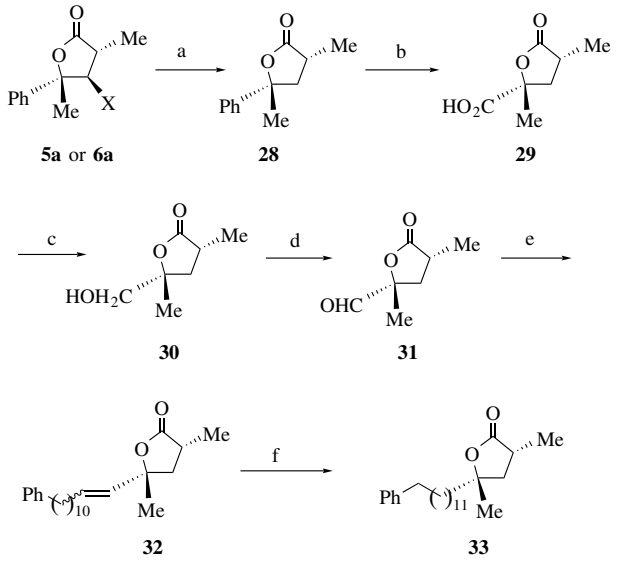
[a] Major diastereomer isolated after separation of the two diastereoisomeric oxazolidinones and hydrolysis.
[b] Proportion of the two diastereomers.

tion of benzyl bromine (entry a), for which we observed a good yield in the alkylation of ozaxolidinone **2**, with other alkylating agents moderate yields were obtained (entries b–d). However, only products corresponding to the alkylation at the 2-position were isolated. After separation of the two diastereomers, cyclization of the major diastereomer of the acids, obtained by hydrolysis of the corresponding oxazolidinones, led to the halo lactones in high yields. With iodo(*bis*-collidine) hexafluorophosphate, the cyclizations were always diastereospecific. With the bromo reagent, as in the case of acid **17**, a mixture of the two diastereomers was isolated (entry b). In the case of acid **22** issued from the major diastereomer of oxazolidinone **21**, a competition between the 5-*endo* and the 5-*exo* iodo lactonizations was observed. It is interesting to note that the 5-*exo* lactonization was not diastereospecific, since a mixture of the two diastereomers **24** was isolated. This result shows than when the stereogenic center is at the β-position of the carbon–carbon double bond, approach of the iodo reagent is not stereochemically controlled. The same diastereospecific 5-*endo* iodo lactonization was observed for the iodo lactonization of (*R*)-2,4-dimethylpent-3-enoic acid **26** (entry d). This result shows that this methodology can be also used for the formation of enantiopure lactones in which the two substituents in 4-position are two alkyl groups. A stereospecific preparation of such 3,4-unsaturated carboxylic esters has recently been reported.[7]

The low reactivity of the anion formed from oxazolidinone **2** was confirmed by the fact that the desired alkylations were not observed with $ClSiPh_2Me$, $PhSeCH_2Br$, Me_3SiCH_2I, HCO_2Et, CO_2, trioxane or CH_2ClI.

3. Application

Two γ-lactones possessing a dialkylated carbon at the 4-position have recently been isolated from the dark brown sponge *Plakortis nigra*.[8] The absolute configurations of these lactones were not assigned. We decided to apply our methodology to the synthesis of one of these compounds (compound **33** in Scheme 5). The first steps of this synthesis involve the dehalogenation of lactone **5a** or **6a** followed by oxidative degradation of the phenyl group (Scheme 5). The next reaction involves the preparation of aldehyde **31**, which was obtained after reduction of acid **29** into alcohol **30** using borane, followed by Dess–Martin oxidation. The carbon chain was then introduced by a Wittig reaction, and the desired lactone was obtained by hydrogenation over palladium. The yields corresponding to the preparation of compounds **32** and **33** have not been optimized. The spectra of lactone **33** are in agreement with those reported for the natural product.[8] The rotatory power found for this compound was $[\alpha]_D = -8.5$ (*c* 0.2, MeOH), comparable to the $[\alpha]_D = -7.1$ (*c* 0.13, MeOH) reported.[8] This negative value allows us to



Scheme 5. (a) Bu_3SnH, AIBN, benzene (92% from **6a**; 87% from **5a**); (b) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O, 70 °C, 3 h; (c) BH_3–THF, 16 h, 0 °C (56% from **28**; *E*/*Z*: 77–23); (d) Dess–Martin periodinane, DCM, 1 h, rt; (e) $Ph(CH_2)_{11}PPh_3^+ Br^-$, THF, *n*-BuLi, 15 h, −78 °C to rt (53%; *E*/*Z*: 77–23); (f) H_2, AcOEt, $Pd(OH)_2$ (31%).

conclude that the natural product **33** has a (3*R*,5*S*)-absolute configuration.

4. Conclusion

We have reported a methodology, which allows the preparation of 3,5,5-trialkyl-γ-butyrolactones of defined absolute configuration. This method involves the diastereoselective alkylation of 3,4-ethylenic acids after incorporation of an Evan's chiral auxiliary, followed after separation of the two diastereomers and hydrolysis of the auxiliary, and stereospecific halo lactonizations. This method was applied to the preparation of a natural product, present in a sponge. The absolute configuration of this natural product was also established.

5. Experimental

(*E*)-4-Phenylpent-3-enoic acid **1**,[3,6] (*R*)-4-phenyloxazolidin-2-one,[9] (*Z*)-4-phenylpent-3-enoic acid **7**,[3] iodo- and bromo(*bis*-collidine) hexafluorophosphates[10] have been prepared as previously reported. Purification of compounds has been carried out by column flash chromatography on silica gel.

5.1. (*R*)-3-((*E*)-4-Phenylpent-3-enoyl)-4-phenyloxazolidin-2-one 2

To acid **1** (0.50 g, 2.84 mmol) in solution in THF (45 mL) cooled at −78 °C was added successively NEt_3 (0.478 mL, 3.41 mmol) and pivaloyl chloride (0.382 mL, 3.12 mmol). This mixture was stirred 15 min at this temperature, warmed at 0 °C for 45 min, and cooled again at −78 °C. This cold solution was cannulated to a second flask, cooled at the same temperature, and containing the lithium salt (*R*)-4-phenyloxazolidin-2-one in THF (5 mL), which was prepared by dropwise addition of butyl lithium (1.78 mL of a 1.6 M solution in hexane, 2.84 mmol) to oxazolidine (0.463 g, 2.84 mmol). After 20 min at −78 °C, the flask was warmed at room temperature. After 2 h, an ammonium chloride solution (20 mL) was added, and the solvents removed under vacuum. The residue was then purified by liquid chromatography (pentane/diethyl ether: 80–20), to give compound **2** (0.463 g, 85%) as a solid (mp: 105 °C), $[\alpha]_D^{20} = -85.9$ (*c* 1.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.38–7.22 (m, 10H), 5.98 (t, $J = 6.8$ Hz, 1H), 5.45 (dd, $J = 8.6$ and 4.0 Hz, 1H), 4.71 (dd, $J = 8.6$ Hz and 8.6 Hz, 1H), 4.30 (dd, $J = 9.0$ and 3.6 Hz, 1H), 3.88 (d, $J = 6.8$ Hz, 1H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 169.9, 153.2, 142.4, 138.8, 138.0, 128.6, 128.0, 127.7, 126.6, 125.4, 125.2, 118.1, 69.5, 57.0, 35.2, 15.9. IR (film) *v* (cm^{-1}): 3056, 2985, 2920, 2360, 2340, 1782, 1708. ES MS: 344.1 (M+Na). ES HRMS (M+Na) for $C_{20}H_{19}O_3NNa$: 344.1263. Found: 344.1281.

5.2. (*R*)-3-((*E*)-2-Methyl-4-phenylpent-3-enoyl)-4-phenyl-oxa-zolidin-2-one 3a and 3b

To diisopropylamine (0.270 mL, 1.925 mmol) in THF (4.5 mL) was added at 0 °C butyl lithium (0.456 mL of a 1.6 M solution in hexane, 1.95 mmol) and HMPA (0.45 mL). After stirring for 30 min at 0 °C, the solution was cooled to −78 °C and a THF solution (4 mL) of oxazolidinone **2** (0.515 g, 1.61 mmol) was added. After 1 h at this temperature, methyl iodide (0.30 mL, 4.83 mmol) was added, and after 30 min of stirring, the solution was warmed at −40 °C. After 1 h at this temperature, the solution was warmed at −10 °C, and a saturated solution of ammonium chloride (10 mL) was added. The solvents were removed under vacuum, and the aqueous phase extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed successively with 0.5 M HCl (3 mL), H_2O (3 mL), and a saturated NaCl solution (3 mL). After drying over $MgSO_4$, the solvents were removed under vacuum and the residue purified by liquid chromatography (pentane/diethyl ether: 85–15) to give 0.195 mg of the major diastereomer **3a** (36%) and 0.130 mg of the minor diastereomer **3b** (24%).

5.3. (*R*)-3-((*R*,*E*)-2-Methyl-4-phenylpent-3-enoyl)-4-phenyl-oxazolidin-2-one 3a

White solid mp = 138 °C, $[\alpha]_D^{20} = -149.0$ (*c* 0.96, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ ppm: 7.41–7.23 (m, 10H), 5,88 (d, $J = 9.4$ Hz, 1H), 5.43 (dd, $J = 8.6$ and 3.6 Hz, 1H), 4.90 (m, 1H), 4.68 (dd, $J = 9.0$ Hz, $J = 9.0$ Hz, 1H), 4.27 (dd, $J = 9.0$ and 3.9 Hz, 1H), 2.12 (s, 3H), 1.27 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$; 62.9 MHz) δ ppm: 174.7, 153.2, 142.8, 139.0, 136.7, 129.0, 128.7, 128.5, 128.0, 126.9, 126.2, 125.6, 69.6, 57.6, 37.7, 18.3, 16.1. IR (solution) *v* (cm^{-1}): 3054, 2987, 2305, 1781, 1705. MS ES^+: 358,2 $(M+Na)^+$. ES HRMS (M+Na) calculated for pour $C_{21}H_{21}O_3NNa$: 358.1419. Found: 358.1424.

5.4. (4*R*)-3-((2*S*,3*E*)-2-Methyl-4-phenylpent-3-enoyl)-4-phenyl-1,3oxazolidine-2-one 3b

Oil. ^{1}H NMR ($CDCl_3$, 360 MHz) δ ppm: 7.38–7.23 (m, 5H), 5.96 (d, $J = 6.8$ Hz, 1H), 5.47 (dd, $J = 9.0$ and 4.7 Hz, 1H), 4.90 (m, 1H), 4.70 (dd, $J = 8.7$ Hz, $J = 8.7$ Hz, 1H), 4.23 (dd, $J = 8.7$ and 4.3 Hz, 1H), 2.11 (s, 3H), 1.28 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 174.6, 153.2, 142.7, 138.7, 137.6, 128.9, 128.4, 127.9, 126.9, 126.1, 125.6, 69.5, 57.6, 38.1, 17.1, 16.1. IR (film) ν (cm^{-1}): 3052, 2986, 2304, 1780, 1707. ES MS: 358.2 $(M+Na)^+$. ES HRMS (M+Na) for $C_{21}H_{21}O_3NNa$: 358.1419. Found: 358.1418.

5.5. (*R*,*E*)-2-Methyl-4-phenylpent-3-enoic acid 4a

To ozaxolidinone **3a** (0.190 g, 1 mmol) in solution in a mixture of THF–H_2O (10 mL, 3:1) was added dropwise 30% hydrogen peroxide (0.364 mL, 6 mmol) and an aqueous solution (2 mL) of lithium hydroxide (0.064 g, 2.5 mmol). After 2 h at 0 °C, a 1.3 M sodium sulfite solution (12 mL) was added, and the solution was stirred 30 min at rt. The organic phase was removed under vacuum, and the aqueous phase extracted with dichloromethane (3×20 mL), and acidified (pH 1). The resulting aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic phases were dried over $MgSO_4$, and concentrated under vacuum. Acid **4a**, isolated as a white solid (mp 81 °C), was pure enough to be used without further purification. Oxazolidinone **3a** was quantitatively recovered in the first dichloromethane phase. $[\alpha]_D^{20} = -53.1$ (*c* 1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.40–7.24 (m, 5H), 5.76 (d, $J = 9.2$ Hz, 1H), 3.54 (dq, $J = 9.2$ and 7.0 Hz, 1H), 1.82 (s, 3H), 1.36 (d, $J = 7$ Hz, 3H).

5.6. (*S*,*E*)-2-Methyl-4-phenylpent-3-enoic acid 4b

White solid: mp 81 °C, $[\alpha]_D^{20} = +54.0$ (*c* 1.20, CH_2Cl_2).

5.7. (3*S*,4*R*,5*S*)-4-Bromo-3,5-dimethyl-5-phenyldihydrofuran-2(3*H*)-one 5a

To a dichloromethane solution (20 mL) of acid **3a** (0.142 g, 0.748 mmol) was added bromo(I)(bis-collidine) hexafluorophosphate (0.420 g, 0.822 mmol). After stirring for 2 h at rt, the mixture was concentrated under vacuum, and the residue purified by liquid chromatography (pentane/diethyl ether: 90–10), to give 0.136 g of lactone **5a** (68%). White solid: mp = 76.2 °C (CH_2Cl_2), $[\alpha]_D^{20} = -25.4$ (*c* 3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ ppm: 7.55–7.53 (m, 2H), 7.41–7.32 (m, 3H), 4.07 (d, $J = 11.2$ Hz, 1H), 3.01 (dq, $J = 11.2$ and 6.8 Hz), 1.86 (s, 3H), 1.36 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$; 62.9 MHz) δ ppm: 174.0, 142.1, 128.6, 128.3, 124.1, 86.1, 57.4, 44.3, 24.9, 12.5. IR ($CDCl_3$) ν cm^{-1}: 3155, 3065, 2984, 2938, 1778.

5.8. (3*S*,4*R*,5*S*)-4-Iodo-3,5-dimethyl-5-phenyldihydrofuran-2(3*H*)-one 6a

This iodo lactone was obtained using the protocol used for the preparation of bromo lactone **5a** (93%). White solid: mp 100.5 °C, $[\alpha]_D^{20} = -45.9$ (*c* 0.90, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ ppm: 7.57–7.54 (m, 2H), 7.41–7.34 (m, 3H), 4.02 (d, $J = 11.9$ Hz, 1H), 2.96 (dq, $J = 11.9$ Hz, $J = 7.2$ Hz, 1H), 1.96 (s, 3H), 1.36 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$; 62.9 MHz) δ ppm: 174.2, 141.5, 128.4, 128.1, 124.1, 85.4, 45.4, 34.6, 26.6, 12.3. IR ($CDCl_3$) ν cm^{-1}: 3155, 2984, 2937, 1774. MS ES$^+$: 339.0 $(M+Na)^+$. An X-ray crystal structure of this iodo lactone has been carried out.

5.9. (3*R*,4*S*,5*R*)-4-Iodo-3,5-dimethyl-5-phenyldihydrofuran-2(3*H*)-one 6b

This lactone was obtained using the method described for the preparation of lactone **5a**. $[\alpha]_D^{20} = +47.0$ (*c* 0.95, CH_2Cl_2). White solid: mp 100.5 °C. Its spectra were identical to those of lactone **6a**.

5.10. (*R*)-3-((*Z*)-4-Phenylpent-3-enoyl)-4-phenyloxazolidin-2-one 8

This compound was obtained using the method reported for the preparation of compound **2**, as a yellow oil (85%). $[\alpha]_D^{20} = -30.7$ (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.37–7.19 (m, 8H), 7.11–7.09 (m, 2H), 5.61 (t, $J = 7.2$ Hz, 1H), 5.34 (dd, $J = 8.6$ and 3.6 Hz, 1H), 4.57 (dd, $J = 9.0$ Hz, $J = 9.0$ Hz, 1H), 4.16 (dd, $J = 9.0$ and 3.6 Hz, 1H), 3.59 (m, 2H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 170.8, 152.4, 142.9, 138.7, 135.0, 129.3, 128.8, 128.0, 127.1, 127.0, 125.7, 118.4, 66.0, 55.0, 37.6, 16.3. IR (film) ν (cm^{-1}): 3057, 3034, 2973, 2916, 1780, 1705, 1600, 1575, 1493, 1456. MS ES$^+$: 344.1 $(M+Na)^+$. ES HRMS (M+Na) calculated for $C_{20}H_{19}O_3NNa$: 344.1263. Found: 344.1262.

5.11. (*R*)-3-((*R*,*Z*)-2-Methyl-4-phenylpent-3-enoyl)-4-phenyl-oxazolidin-2-one 9a

This compound has been obtained using the method reported for the preparation of compound **3a** as a mixture of two diastereomers (70:30), 33% yield. After liquid chromatography, the major diastereomer **9a** was obtained in a pure form. Oil, $[\alpha]_D^{20} = -100.3$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.38–7.10 (m, 10H), 5.59 (d, $J = 9.0$ Hz, 1H), 5.28 (dd, $J = 8.7$ and 3.6 Hz, 1H), 4.56 (dd, $J = 8.7$ Hz, $J = 8.7$ Hz, 1H), 4.46 (m, 1H), 4.17 (dd, $J = 8.7$ and 3.6 Hz, 1H), 2.04 (s, 3H), 1.18 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 174.3, 152.4, 139.1, 138.8, 136.7, 129.0, 128.5, 127.9, 127.4, 125.7, 125.6, 125.5, 69.6, 57.5, 37.7, 25.8, 19.1. IR (film) ν (cm^{-1}), 3055, 2988, 1783, 1701. MS ES$^+$: 358.1 $(M+Na)^+$. ES HRMS (M+Na) calculated for $C_{21}H_{21}O_3NNa$: 358.1419. Found: 358.1418.

5.12. (*R*,*Z*)-2-Methyl-4-phenylpent-3-enoic acid 10a

This acid was prepared using the procedure reported for acid **4a**. Oil, $[\alpha]_D^{20} = -252.8$ (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.36–7.32 (m, 2H), 7.28–7.25 (m, 1H), 7.21–7.19 (m, 2H), 5.49 (d, $J = 10.0$ Hz, 1H), 3.20 (dq, $J = 10.0$ and 7.2 Hz, 1H), 2.05 (s, 3 H), 1.19 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ ppm: 181.6, 141.2, 139.3, 128.3, 127.7, 127.0, 125.4, 39.6, 25.8,

18.3. IR (film) ν (cm^{-1}): 3054, 2987, 1707, 1601, 1551, 1494, 1421.

5.13. (3*S*,4*R*,5*R*)-4-Iodo-3,5-dimethyl-5-phenyldihydrofuran-2(3*H*)-one 11a

This lactone was obtained from acid **10a**, using the procedure reported for the preparation of lactone **5a**. $[\alpha]_D^{20} = -66.3$ (*c* 0.9, CH_2Cl_2). White solid: mp 99 °C (CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.43-7.32 (m, 5H), 4.16 (d, $J = 12.6$ Hz, 1H), 2.71 (dq, $J = 12.6$ and 6.8 Hz, 1H), 1.89 (s, 3H), 1.33 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$; 62.9 MHz) δ ppm: 175.9, 139.4, 128.5, 127.9, 126.5, 86.5, 44.0, 35.2, 26.3, 12.4. IR ($CDCl_3$) ν cm^{-1}: 3054, 2986, 1781, 1600, 1551, 1498, 1438. Anal. Calcd for $C_{12}H_{13}IO_2$: C, 45.59; H, 4.14. Found: C 45.45; H 4.15.

5.14. (*R*)-3-((*E*)-2-Benzyl-4-phenylpent-3-enoyl)-4-phenyloxazolidin-2-one 12

This compound has been obtained using the method reported for the preparation of compound **3a** as a mixture of two diastereomers (88:12), 70% yield. Only the major diastereomer **12a** could be isolated in a pure form. White solid: mp 140.1 °C (CH_2Cl_2), $[\alpha]_D^{20} = -196.8$ (*c* 1.33, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.30–7.03 (m, 15H), 5.82 (d, $J = 9.7$ Hz, 1H), 5.40 (dd, $J = 8.6$ and 3.6 Hz, 1H), 5.28 (ddd, $J = 9.7$, 7.9 and 6.8 Hz, 1H), 4.64 (dd, $J = 8.6$ Hz, $J = 8.6$Hz, 1H), 4.21 (dd, $J = 8.6$ and 3.6 Hz, 1H), 3.13 (dd, $J = 12.9$ and 6.8 Hz, 1H), 2.73 (dd, $J = 13.0$ and 7.9 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 173.5, 153.2, 142.9, 138.8, 138.7, 138.0, 129.4, 129.0, 128.2, 128.1, 128.0, 127.0, 126.2, 125.7, 125.5, 124.3, 69.5, 57.6, 44.8, 39.4, 16.2. IR (film) ν cm^{-1}: 3054, 2986, 2922, 2305, 1781, 1702. MS ES^+: 434.2 $[M+Na]^+$. ES HRMS (M+Na) calculated for $C_{27}H_{25}O_3NNa$: 434.1732. Found: 434.1730.

5.15. (*R*,*E*)-2-Benzyl-4-phenylpent-3-enoic acid 13

This acid was obtained using the method used for the preparation of acid **4a**. White solid: mp 81.2 °C (CH_2Cl_2), $[\alpha]_D^{20} = -154.1$ (*c* 1.08, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 11.50 (br, 1H, COOH), 7.31–7.17 (m, 10H), 5.75 (d, $J = 9.7$ Hz, 1H), 3.68 (ddd, $J = 9.7$, 7.9 and $J = 6.5$ Hz, 1H), 3.20 (dd, $J = 13.3$ Hz and 6.5 Hz, 1H), 2.87 (dd, $J = 13.3$ and 7.9 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 180.3, 142.9, 138.9, 138.4, 129.1, 128.3, 127.2, 126.5, 125.8, 124.0, 47.4, 38.7, 16.2. IR ($CDCl_3$) ν cm^{-1}: 3085, 3064, 3030, 2926, 2861, 1706. MS ES^+: 553.2 2[(M−H)+Na]$^+$. ES HRMS (M+Na) calculated for $C_{36}H_{34}O_4Na$: 553.2355. Found: 553.2379.

5.16. (*R*)-3-((*E*)-4-Phenyl-2-propylpent-3-enoyl)-4-phenyloxazolidin-2-one

The alkylation of compound **2** with 1-iodopropane has been carried using the method reported for the preparation of compound **3**. A mixture of two diastereomers (77:23) was obtained (36% yield). Only the major diastereomer (*R*)-3-((*R*,*E*)-4-phenyl-2-propylpent-3-enoyl)-4-phenyloxazolidin-2-one **16a** was isolated in a pure form. Oil, $[\alpha]_D^{20} = -128.1$ (*c* 0.99, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.39–7.19 (m, 10H), 5.80 (d, $J = 9.7$ Hz, 1H), 5.41 (dd, $J = 9.0$ and 3.8 Hz, 1H), 4.94 (m, 1H), 4.64 (dd, $J = 9.0$ Hz, $J = 9.0$ Hz, 1H), 4.24 (dd, $J = 9.0$ and 3.8 Hz, 1H), 2.12 (s, 3H), 1.75 (m, 2H), 1.46 (m, 2H), 0.86 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 174.5, 153.3, 143.1, 139.2, 137.7, 129.1, 128.6, 128.1, 127.0, 125.8, 125.6, 117.9, 69.6, 57.8, 42.8, 35.7, 20.0, 16.6, 13.9. IR (film) ν cm^{-1}: 2958, 2930, 2872, 1779, 1702. MS ES^+: 386.1 $(M+Na)^+$. ES HRMS (M+Na) calculated for $C_{23}H_{25}O_3NNa$: 386.1732. Found: 386.1739.

5.17. (*R*,*E*)-4-Phenyl-2-propylpent-3-enoic acid 17

This acid was obtained using the method used for the preparation of acid **4a**. Oil, $[\alpha]_D^{20} = -54.8$ (*c* 1.98, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 11.22 (br, 1H, COOH), 7.41–7.21 (m, 5H), 5.73 (d, $J = 9.8$ Hz, 1H), 3.45 (m, 1H), 2.10 (s, 3H), 1.87 (m, 1H), 1.63 (m, 1H), 1.40 (m, 2H), 0.90 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 181.0, 143.0, 137.9, 128.2, 127.1, 125.8, 125.3, 45.1, 35.0, 20.3, 16.4, 13.9. IR (film) ν (cm^{-1}): 3054, 2961, 2933, 2874, 1705. MS ES^+: 457.2 2(M−H+Na)$^+$. ES HRMS (M+Na) calculated for $C_{28}H_{34}O_4Na$: 457.2355. Found: 457.2352.

5.18. (*R*)-3-(2-((*E*)-2-Phenylprop-1-enyl)pent-4-enoyl)-4-phenyloxazolidin-2-one 21

The alkylation of compound **2** with allyl bromide was carried using the method reported for the preparation of compound **3**. A mixture of two diastereomers (70:30) was obtained (55% yield). Only the major diastereomer (*R*)-3-((*R*)-2-((*E*)-2-phenylprop-1-enyl)pent-4-enoyl)-4-phenyloxazolidin-2-one) **21a** was isolated in a pure form as an oil, $[\alpha]_D^{20} = -151.0$ (*c* 1.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 7.40–7.25 (m, 10H), 5.80 (d, $J = 9.8$ Hz, 1H), 5.71 (m, 1H), 5.42 (dd, $J = 8.8$ and 3.8 Hz, 1H), 5.06 (m, 1H), 4.88 (m, 2H), 4.63 (dd, $J = 8.8$ Hz, $J = 8.8$ Hz, 1H), 4.27 (dd, $J = 8.8$ and 3.7 Hz, 1H), 2.52 (m, 1H), 2.26 (m, 1H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 173.7, 153.3, 142.9, 139.0, 138.0, 134.2, 128.9, 128.6, 128.1, 127.0, 126.0, 125.7, 124.7, 117.4, 69.6, 57.8, 42.7, 37.7, 16.6. IR (film) ν cm^{-1}: 3054, 2987, 1780, 1702, 1602, 1551, 1494, 1421. MS ES^+: 384.1 $(M+Na)^+$. ES HRMS (M+Na) calculated for $C_{23}H_{23}O_3NNa$: 384.1576. Found: 384.1576.

5.19. (*R*)-2-((*E*)-2-Phenylprop-1-enyl)pent-4-enoic acid 22

This acid was obtained using the method used for the preparation of acid **4a**. Oil, $[\alpha]_D^{20} = -80.2$ (*c* 2.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 10.95 (br, 1H, COOH), 7.39–7.22 (m, 5H), 5.83 (m, 1H), 5.72 (d, $J = 11.2$ Hz, 1H), 5.13 (dd, $J = 17.0$ and 1.2 Hz, 1H), 5.06 (dd, $J = 10.0$ and 1.2 Hz, 1H), 3.51 (m, 1H), 2.60 (ddd, $J = 14.2$ Hz, $J = 7.1$ Hz, $J = 7.1$ Hz, 1H), 2.40 (ddd, $J = 14.1$ Hz, $J = 7.1$ Hz, $J = 7.1$ Hz, 1H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ ppm: 180.0, 142.9,

138.5, 128.2, 127.2, 125.9, 124.4, 117.3, 45.2, 39.6, 16.5. IR (film) ν cm^{-1}: 3054, 2987, 1708, 1600, 1551, 1494, 1421. MS ES$^+$: 453.1 2(M−H+Na)$^+$.

5.20. (*R*)-3-(2,4-Dimethylpent-3-enoyl)-4-phenyloxazolidin-2-one 25

The alkylation of compound **2** with methyl iodide has been carried using the method reported for the preparation of compound **3**. A mixture of two diastereomers (85:15) was obtained (60% yield). Only the major diastereomer (*R*)-3-((*R*)-2,4-dimethylpent-3-enoyl)-4-phenyloxazolidin-2-one **25a** was isolated in a pure form as an oil, $[\alpha]_D^{20} = -157.0$ (*c* 2.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.36–7.26 (m, 5H), 5.38 (dd, $J = 8.6$ Hz, $J = 3.6$ Hz, 1H), 5.21 (d, $J = 9.4$ Hz, 1H), 4.70 (m, 1H), 4.63 (dd, $J = 8.6$ Hz, $J = 8.6$ Hz, 1H), 4.22 (dd, $J = 9.0$ and 3.6 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.14 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 175.4, 153.2, 139.2, 134.2, 128.5, 125.6, 123.0, 69.6, 57.6, 37.0, 25.6, 18.3, 18.1. IR (film) ν (cm^{-1}): 3054, 2986, 1781, 1704. MS ES$^+$: 296.1 (M+Na)$^+$. ES HRMS (M+Na) calculated for $C_{16}H_{19}O_3NNa$: 296.1263. Found: 296.1261.

5.21. (*R*)-2,4-Dimethylpent-3-enoic acid 26

This acid was obtained using the method used for the preparation of acid **4a** (86%). Oil, $[\alpha]_D^{20} = -310.0$ (*c* 2.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 11.70 (br, 1H, COOH), 5.14 (d, $J = 13.3$ Hz, 1H), 3.45 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.22 (d, $J = 10.0$ Hz). ^{13}C NMR ($CDCl_3$; 62.9 MHz) δ ppm: 182.0, 134.7, 123.1, 38.8, 25.6, 17.9, 17.7. IR (film) ν cm^{-1}: 3054, 2985, 1707.

5.22. (3*S*,4*R*,5*S*)-3-Benzyl-4-iodo-5-methyl-5-phenyldihydrofuran-2(3*H*)-one 14

This iodo lactone was obtained using the method reported for the preparation of lactone **5a** (91% yield). White solid: mp 85.8 °C, $[\alpha]_D^{20} = +4.2$ (*c* 1.25, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.29–7.23 (m, 10H), 3.91 (d, $J = 11.2$ Hz, 1H), 3.30 (dd, $J = 14.0$ and 4.0 Hz, 1H), 3.24 (ddd, $J = 11.2$, 5.5 and 4.0 Hz, 1H), 3.03 (dd, $J = 14.0$ and 5.5 Hz, 1H), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 173.7, 141.4, 136.0, 129.5, 128.7, 128.6, 128.3, 127.2, 124.6, 85.9, 51.9, 32.0, 31.1, 27.2. IR (CH_2Cl_2) ν cm^{-1}: 3066, 3031, 2929, 1774. MS ES$^+$: 414.9 (M+Na)$^+$. ES HRMS (M+Na) calculated for $C_{18}H_{17}O_2INa$: 415.0171. Found: 415.0177.

5.23. (3*S*,4*R*,5*S*)-3-Benzyl-4-bromo-5-methyl-5-phenyldihydrofuran-2(3*H*)-one 15

This bromo lactone was obtained using the method reported for the preparation of lactone **5a** (84% yield). White solid: mp 93.0 °C, $[\alpha]_D^{20} = -11.0$ (*c* 1.07, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.31–7.19 (m, 10H), 4.03 (d, $J = 10.8$ Hz, 1H), 3.32 (ddd, $J = 10.8$, 5.8 and 5.0 Hz, 1H), 3.18 (dd, $J = 14.1$ and 5.0 Hz, 1H), 3.06 (dd, $J = 14.1$ and 5.8 Hz, 1H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 173.7, 141.4, 136.0, 129.5, 128.7, 128.6, 127.2, 125.5, 85.9, 51.9, 32.0, 31.1, 27.2. IR (CH_2Cl_2) ν cm^{-1}: 3066, 3032, 1778. MS ES$^+$: 367.0, 369.0 (M+Na)$^+$.

5.24. (3*S*,4*R*,5*S*)-4-Iodo-5-methyl-5-phenyl-3-propyldihydrofuran-2(3*H*)-one 18

This iodo lactone was obtained using the method reported for the preparation of lactone **5a** (92% yield). White solid: mp 109.9 °C (CH_2Cl_2), $[\alpha]_D^{20} = -18.9$ (*c* 0.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 7.55–7.53 (m, 2H), 7.41–7.35 (m, 3H), 4.15 (d, $J = 11.5$ Hz, 1H), 2.96 (m, 1H), 1.96 (s, 3H), 1.76 (m, 2H), 1.57 (m, 1H), 1.45 (m, 1H), 0.95 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 174.4, 142.0, 128.7, 128.3, 124.4, 85.6, 50.1, 32.4, 29.6, 27.6, 19.2, 14.0. IR (CH_2Cl_2) ν cm^{-1}: 3054, 2987, 1775, 1604, 1551, 1496, 1421. MS ES$^+$: 367.0 (M+Na)$^+$. ES HRMS (M+Na) calculated for $C_{14}H_{17}O_2Na$: 367.0171. Found: 367.0170.

5.25. 4-Bromo-5-methyl-5-phenyl-3-propyldihydrofuran-2(3*H*)-ones 19 and 20

These bromo lactones were obtained using the method reported for the preparation of lactone **5a** (67% yield). An inseparable mixture (80:20) of two diastereomers was isolated. (3*S*,4*R*,5*S*)-4-Bromo-5-methyl-5-phenyl-3-propyldihydrofuran-2(3*H*)-one **19**. (major diastereomer) Oil. ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.53–7.51 (m, 2H), 7.43–7.32 (m, 3H), 4.20 (d, $J = 10.8$ Hz, 1H), 3.02, (dt, $J = 10.6$ and 6 Hz, 1H), 1.86 (s, 3H), 1.76–1.49 (m, 4H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 173.9, 142.3, 128.7, 128.3, 124.1, 86.0, 55.4, 48.7, 29.9, 25.5, 19.4, 13.9. IR (CH_2Cl_2) ν cm^{-1}: 2964, 2935, 2876, 1778. (3*S*,4*S*,5*R*)-4-Bromo-5-methyl-5-phenyl-3-propyldihydrofuran-2(3*H*)-one **20**. (minor diastereomer), oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 7.53–7.51 (m, 2H), 7.43–7.32 (m, 3H), 4.91 (d, $J = 5.4$ Hz, 1H), 2.62, (dt, $J = 9.4$ and 5.2 Hz, 1H), 1.86 (s, 3H), 1.76–1.49 (m, 4H), 0.88 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 174.0, 142.3, 129.0, 128.3, 124.1, 88.1, 62.3, 45.5, 29.8, 29.2, 20.2, 13.7.

5.26. (3*S*,4*R*,5*S*)-3-Allyl-4-iodo-5-methyl-5-phenyldihydrofuran-2(3*H*)-one 23

The iodo lactonization of the corresponding acid **22** led to a mixture of three iodo lactones: (3*S*,4*R*,5*S*)-3-Allyl-4-iodo-5-methyl-5-phenyldihydrofuran-2(3*H*)-one 23 and 5-iodomethyl-3-(3-phenylbut-2-en-1-yl)dihydrofuran-2-ones **24**. Lactone **23**. Oil, $[\alpha]_D^{20} = -30.1$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 7.54–7.50 (m, 2H), 7.40–7.36 (m, 3H), 5.71 (m, 1H), 5.18 (d, $J = 9.2$ Hz, 1H), 5.14 (d, $J = 9.2$ Hz, 1H), 4.15 (d, $J = 11.8$ Hz, 1H), 3.06 (m, 1H), 2.72 (m, 1H), 2.46 (m, 1H), 1.97 (s, 3H).^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 173.6, 141.8, 132.1, 128.7, 128.4, 124.5, 120.0, 86.0, 50.1, 31.0, 30.6, 27.4. IR (film) ν cm^{-1}: 3155, 2983, 1776. MS ES$^+$: 365.1 (M+Na)$^+$. ES HRMS (M+Na) calculated for $C_{14}H_{15}O_2I$-Na: 365.0014. Found: 365.0021. Lactone **24**. Isolated as a mixture of two diastereomers (45:55). Oil. Main diastereomer: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 7.42–7.26 (m,

5H), 5.71 (d, $J = 8.3$ Hz, 1H), 4.49 (m, 1H), 3.80 (m, 1H), 3.47 (m, 1H), 3.33 (m, 1H), 2.83 (ddd, $J = 13.0$, 9.0 and 5.7 Hz, 1H), 2.43 (m, 1H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 176.4, 142.2, 140.5 (2C), 128.2, 127.3, 125.7, 76.5, 41.5, 36.7, 16.6, 6.7. Minor diastereomer: ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 7.42–7.26 (m, 5H), 5.66 (d, $J = 8.7$ Hz, 1H), 4.68, (m, 1H), 3.80 (m, 1H), 3.47 (m, 1H), 3.33 (m, 1H), 2.41 (m, 1H), 2.16 (s, 3H), 1.83 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 176.4, 142.2, 140.5 (2C), 128.1, 127.4, 125.2, 76.5, 39.8, 35.0, 16.5, 7.3.

5.27. (3*S*,4*R*)-4-Iodo-3,5,5-trimethyldihydrofuran-2(3*H*)-one 27

This iodo lactone was obtained using the method reported for the preparation of lactone **5a**. White solid. $[\alpha]_D^{20} = -16.7$ (*c* 2.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 3.87 (d, $J = 12.2$ Hz, 1H), 2.80 (m, 1H), 1.59 (s, 3H), 1.50 (s, 3H), 1.31 (d, $J = 6.8$ Hz). ^{13}C NMR ($CDCl_3$, 90 MHz) δ ppm: 174.6, 84.3, 44.8, 32.8, 26.0, 25.7, 12.4. IR ($CDCl_3$) ν cm^{-1}: 3054, 2987, 1775. Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36. Found: C, 33.14; H, 4.31.

5.28. (3*S*,5*S*)-3,5-Dimethyl-5-phenyldihydrofuran-2(3*H*)-one 28

To iodo lactone **5a** (0.18 g, 0.57 mmol) in solution in benzene (7 mL) was added azabisisobutyronitrile (3 mg) and tributyltin hydride (0.1657 mg, 0.57 mmol). The solution was heated at 80 °C for 15 h. After cooling, acetonitrile (10 mL) was added, and the resulting solution washed with pentane (3 × 5 mL), and concentrated under vacuum. The residue was purified by liquid chromatography, to give 0.100 g of lactone **28** as an oil (92% yield). $[\alpha]_D^{20} = -32.0$ (*c* 0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.37–7.26 (m, 5H), 2.77 (dd, $J = 12.2$ and 8.3 Hz, 1H), 2.53 (ddq, $J = 6.8$ Hz, 8.3 and 12.2 Hz, 1H), 2.00 (dd, $J = 12.2$ Hz, $J = 12.2$ Hz, 1H), 1.73 (s, 3H), 1.25 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ ppm: 179.2, 143.8, 128.5, 127.6, 124.1, 84.4, 45.0, 34.9, 30.3, 14.6. IR (film) ν cm^{-1}: 3064, 3029, 2982, 2934, 2876, 1767, 1496, 1448. MS ES$^+$: 213.1 (M+Na)$^+$. ES HRMS (M+Na) calculated for $C_{12}H_{14}O_2Na$: 213.0891. Found: 213.0898.

5.29. (2*R*,4*R*)-2,4-Dimethyl-5-oxotetrahydrofuran-2-carboxylic acid 29

To lactone **28** (0.200 g, 1.05 mmol) in solution in a mixture acetonitrile/water/tetrachloromethane (7:3.5:3.5 mL) was added at rt sodium periodate (4.50 g, 21 mmol) and $RuCl_3{\cdot}nH_2O$ (0.0216 g, 0.105 mmol). After heating for 3 h at 70 °C, the cooled solution was filtered over Celite. The filtrate was extracted with diethyl ether (3 × 5 mL). The solid was well washed with diethyl ether, and the combined ether phases dried over $MgSO_4$, and concentrated under vacuum, to give acid **29** (0.116 g, 70%), which was used for the next step without purification.

5.30. (3*R*,5*R*)-5-(Hydroxymethyl)-3,5-dimethyldihydrofuran-2(3*H*)-one 30

The crude acid **29** was dissolved in THF (4 mL), and cooled at 0 °C. A borane solution (0.734 mL of a 1 M solution in THF, 0.734 mmol) was added, and the solution was stirred 16 h at 0 °C. After hydrolysis by the addition of a saturated solution of NH_4Cl (10 mL), the THF was removed under vacuum. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined ether phases were then washed with 0.5 M HCl solution (5 mL), saturated NaCl solution (5 mL), and dried over $MgSO_4$. The organic phase was concentrated under vacuum, to give alcohol **30**, which was purified by liquid chromatography (pentane/diethyl ether: 75–25). Yield: 0.085 g, 56% (from **28**). Oil, $[\alpha]_D^{20} = -4.9$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 3.71 (d, $J = 12.2$ Hz, 1H), 3.46 (d, $J = 12.2$ Hz, 1H), 2.86 (m, 1H), 2.13 (bs, 1H), 2.08 (m, 2H), 1.35 (s, 3H), 1.29 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ ppm: 172.3, 84.1, 67.7, 36.7, 35.0, 22.3, 15.4. IR (film) ν cm^{-1}: 3450, 3054, 2986, 1766. MS ES$^+$: 167.1 (M+Na)$^+$.

5.31. (2*R*,4*R*)-2,4-Dimethyl-5-oxotetrahydrofuran-2-carbaldehyde 31

To hydroxy lactone **30** (80 mg, 0.555 mmol) in dichloromethane solution (3 mL) was added a Dess–Martin periodinane (35.3 mg, 0.833 mmol), and the solution was stirred at rt for 1 h. Saturated $NaHCO_3$ (3 mL) and saturated $Na_2S_2O_3$ solutions (3 mL) were added, and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, and concentrated under vacuum, to give aldehyde **31** (73 mg, 92% yield). This aldehyde was unstable over silica gel and was used without purification for the next step. ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 10.0 (s, 1H), 2.06 (m, 2H), 1.60 (m, 1H), 1.55 (s, 3H), 1.22 (d, $J = 7.5$ Hz, 3H).

5.32. Triphenyl(11-phenylundecyl)phosphonium bromide

A mixture of the commercially available (11-bromoundecyl)-benzene (0.50 g, 1.73 mmol) and triphenylphosphine (2.27 g, 8.65 mmol) in acetonitrile (20 mL) was heated overnight at reflux. After cooling, the solvent was removed under vacuum, and the solid washed with diethyl ether (5 × 5 mL). The resulting solid was used without further purification. ^{1}H NMR (MeOH-d_4, 360 MHz) δ (ppm): 7.90–7.72 (m, 15H), 7.26–7.12 (m, 5H), 3.48 (m, 2H), 2.58 (t, $J = 7.6$ Hz, 2H), 1.67–1.52 (m, 6H), 1.30–1.26 (m, 12H). ^{13}C NMR (MeOH-d_4, 90 MHz) δ (ppm): 143.9, 136.2, 134.8, 134.7, 134.5, 131.6, 131.4, 130.0, 129.7, 129.6, 129.4, 129.2, 126.2, 120.6, 119.2 (2C), 36.9, 32.7, 31.7, 31.4, 30.5, 30.3, 29.9, 23.6, 23.5, 23.1, 22.3. ES HRMS (M−Br) calculated for $C_{35}H_{42}P^+$: 493.3019. Found: 493.3023.

5.33. (3*R*,5*R*)-3,5-Dimethyl-5-(13-phenyldodec-1-enyl)dihydrofuran-2(3*H*)-one 32

To a suspension of triphenyl(11-phenylundecyl)phosphonium bromide (0.231 g, 0.422 mmol) in THF (1 mL) cooled

at −78 °C was added butyl lithium (0.281 mL of a 1.5 M sol. in hexane, 0.422 mmol). The mixture was stirred 30 min at −78 °C then warmed at 0 °C. A solution of aldehyde **31** in THF (1 mL) was added dropwise, and the solution was stirred overnight at rt. A saturated solution of NH_4Cl was added and the organic solvents removed under vacuum. The aqueous phase was extracted with diethyl ether (3 × 1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by liquid chromatography to give 0.043 g (53%) of compound **32** (*E*/*Z*: 77–23). *E*-isomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.27–7.29 (m, 2H), 7.19–7.16 (m, 3H), 5.36 (m, 2H), 2.59 (t, $J = 7.3$, 2H), 2.27 (m, 1H), 2.00 (m, 2H), 1.60 (m, 3H), 1.43 (s, 3H), 1.31–1.26 (m, 18H). *Z*-isomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.27–7.29 (m, 2H), 7.19–7.16 (m, 3H), 6.39 (d, $J = 11$ Hz, 1H), 5.66 (dt, $J = 11.6$ and 7.3, 1H), 2.59 (t, $J = 7.3$, 2H), 2.27 (m, 1H), 2.00 (m, 2H), 1.60 (m, 3H), 1.42 (s, 3H), 1.31–1.26 (m, 18H).

5.34. (3*R*,5*S*)-3,5-Dimethyl-5-(12-phenyldodecyl)dihydrofuran-2(3*H*)-one 33

An ethyl acetate solution (2 mL) of unsaturated lactone **32** (35 mg, 0.098 mmol) containing $Pd(OH)_2$ (3 mg) was stirred under a hydrogen atmosphere for 15 h. After filtration, the filtrate was concentrated under vacuum, and the residue was purified by liquid chromatography (pentane/diethyl ether: 95–5) to give lactone **33** (11 mg, 31%) as an oil. $[\alpha]_D^{20} = -8.5$ (*c* 0.20, MeOH). ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.27–7.29 (m, 2H), 7.19–7.16 (m, 3H), 2.60 (t, $J = 7.50$ Hz, 1H), 2.27 (m, 1H), 1.72 (m, 1H), 1.67 (m, 2H), 1.59 (m, 2H), 1.34 (s, 3H), 1.31–1.22 (m, 21H). ^{13}C NMR (MeOD, 90 MHz) δ ppm: 181.6, 143.8, 129.2, 126.4, 86.1, 42.6, 42.4, 36.8, 31.0, 30.6–30.5 (6C), 30.1, 24.9, 24.8, 15.5. IR (film) ν cm^{-1}: 3054, 2986, 1767. ES HRMS (M+Na) calculated for $C_{24}H_{38}O_2Na$ 381.2770. Found 381.2772.

6. X-ray-structures

CCDC-643270 and CCDC-643271 contain the supplementary crystallographic data for compounds **3a** and **6a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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