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Dialkylzinc mediated radical additions to chiral *N*-enoyloxazolidinones in the presence of benzaldehyde. Mechanistic investigation, structural characterization of the resulting γ-lactones☆

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Abstract—Diethylzinc was used in the presence of oxygen to mediate radical additions to chiral *N*-enoyloxazolidinones derived from fumaric acid. The synthesis of sterically crowded trisubstituted γ-lactones was achieved through a multicomponent reaction involving *t*-butyl iodide and benzaldehyde in addition to the above mentioned reagents. The domino process includes successively: iodine atom transfer, radical addition, homolytic substitution at zinc, aldol condensation, and lactonization. The diastereoselectivity of the reaction and the structural features of the resulting lactones were investigated. A tentative rationalization is discussed. Comparative experiments carried out with diisopropylzinc were performed.

1. Introduction

In 1998, Ryu demonstrated that the reaction of diethylzinc with oxygen could be used to initiate the reduction of alkyl halides by tributyltin hydride.[1] Since then, our group has been investigating the ability of diethylzinc to mediate radical-polar crossover reactions. We first studied the reactivity of glyoxylic imines,[2] and then we extended our investigations to radical additions to enones.[3] In these reactions, the ethyl radical generated through the reaction of diethylzinc with oxygen acts as the chain carrier. More recently, we have shown that, owing to spin delocalization on the oxygen atom in the intermediate radical, conjugate additions to *N*-enoyloxazolidinones proceeded like additions to enones, that is, they were immediately followed by homolytic substitution at zinc, which generated zinc enolates. The latter were trapped with benzaldehyde to give the corresponding aldols.[4,5] Whereas with enones, the addition/homolytic substitution sequence could be carried out indifferently with Et_2Zn or Et_3B,[6] in the case of *N*-enoyloxazolidinones it required exclusively zinc-mediated conditions.[4,7] It seems that in the presence of Et_3B, homolytic substitution at boron did not occurred.

To extend the domino process to the formation of γ-lactones according to the mechanism depicted in Scheme 1,[8] we selected fumaric acid derived chiral oxazolidinones **1** and **2** (Fig. 1) as substrates.

Sibi and co-workers had previously demonstrated that high regio- and stereo-selectivity could be reached when radical additions to substrates of type **2** were carried out in the presence of Lewis acids.[9,10] However, to avoid problems with the regioselectivity, the symmetrical substrate **1**, with a C_2 axis in the conformation shown in Figure 1, was selected first. For the sake of comparison, and to better understand the mechanism, we also investigated the reactivity of compound **2**.

2. Results and discussion

2.1. Diethylzinc mediated addition of *t*-butyl radical

All the reactions were carried out at −10 °C.[11] Two

☆ See Refs. 27 and 28.

Keywords: Diethylzinc; *N*-Enoyloxazolidinones; γ-Lactones; Radical-polar crossover reaction.
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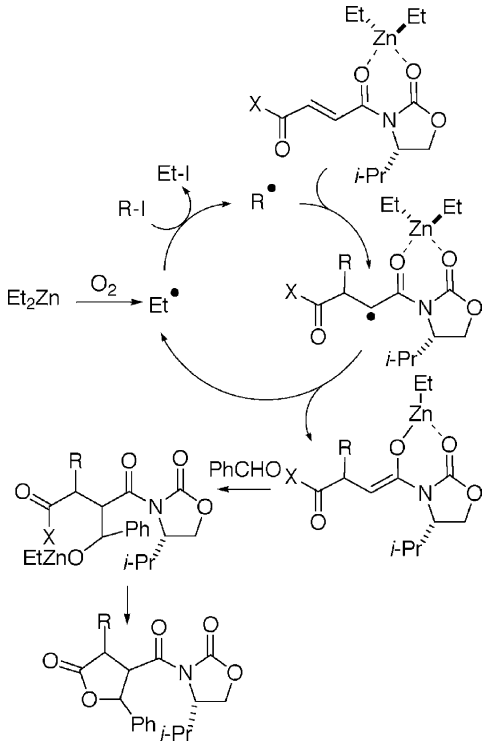


Scheme 1.

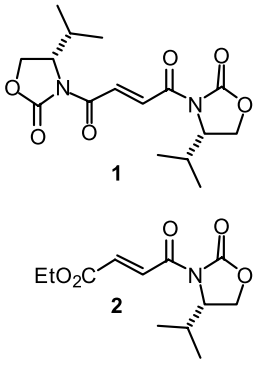
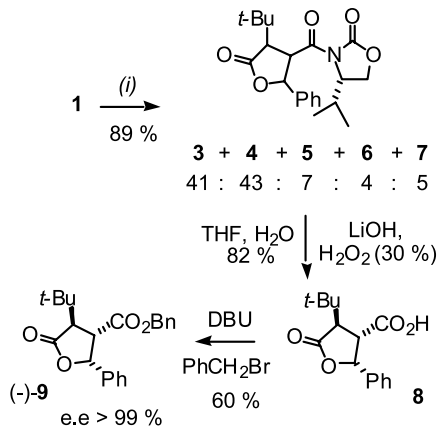


Figure 1.

equivalents of Et_2Zn (1 M solution in hexane) were added to a 0.2 M solution containing either **1** or **2** (1 equiv), benzaldehyde (1.1 equiv) and *t*-BuI (10 or 45 equiv) in dichloromethane. The solution was stirred for 1 h while being injected with 20 mL of air (0.2–0.3 equiv of O_2),[12] and was then allowed to warm up to room temperature before being quenched with aqueous NH_4Cl.

Since a zinc/iodine exchange can be excluded in the case of a tertiary alkyl iodide,[13] *t*-butyl iodide was selected in order to ensure that the process started with a radical pathway. As expected, the use of fumaric derivatives resulted in the stereoselective synthesis of trisubstituted γ-lactones (Scheme 2, Fig. 2 for stereochemical assignments).

It must be noted that when the reaction was carried out with only 10 equiv of *t*-BuI, the lactones resulting from the competitive addition of ethyl radical—7 detectable diastereomers—accounted for approximately 15–18% of the



Scheme 2. (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

reaction products. Their total amount was reduced to traces in the presence of a very large excess of the tertiary iodide. The doubly activated double bond was reactive enough with respect to ethyl radical for the radical addition to compete with the fast iodine atom transfer from the tertiary iodide.

Theoretically, eight diastereomers could result from the whole process. Substrate **1** led to a mixture of mainly two diastereomers, **3** and **4**, in nearly equal amounts (Scheme 2, Fig. 2). These two isomers were isolated as pure samples and fully characterized by X-ray spectroscopy.[28] Three minor isomeric lactones (**5**–**7**) were detected from the ^1H NMR spectrum of the mixture. The stereochemistry of **5** was securely determined since it was later isolated as a pure sample when using **2** as starting material (vide infra). The

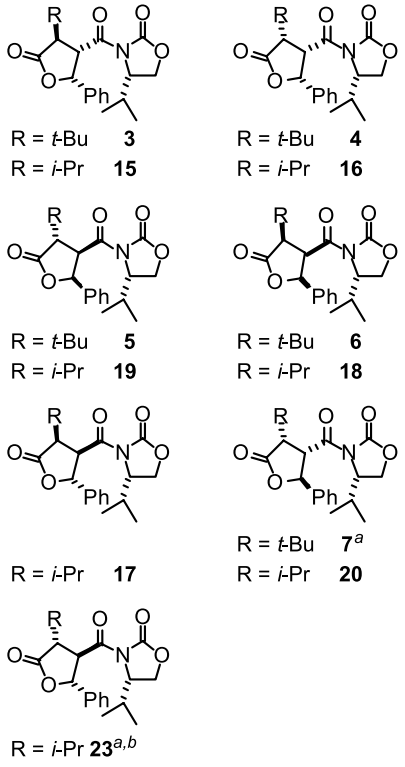
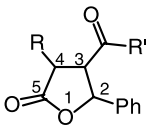


Figure 2. [a]Tentative assignment, based on spectral similarities. [b]The absolute configurations at the lactone ring might be reversed.

stereochemistry of **6** followed from spectral analogies with **4** (characteristic ^{1}H NMR signals were deduced from the analysis of enriched chromatographic fractions). We tentatively assigned the 2,3-*trans*, 3,4-*cis* configuration to **7** (cf. Fig. 2 and Table 1).

Table 1. Chemical shifts and coupling constants of the lactone ring protons in **3**–**11**, **15**–**23**, **25**

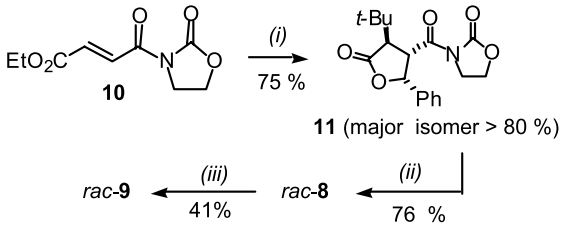


γ-Lactone	δH4 (ppm)	δH3 (ppm)	δH2 (ppm)	J_{34} (Hz)	J_{23} (Hz)
3	3.39	5.07	5.73	6.6	9.4
4	2.89	5.40	5.54	6.4	5.4
5	3.42	4.79	5.89	7.7	9.6
6	2.91	5.45	5.61	6.4	5.2
7	3.19	4.37	5.82	8.5	8.3
8	3.01	3.64	5.65	8.1	9.2
9	3.12	3.70	5.65	7.7	9.2
11[a]	3.36	5.02	5.75	6.4	9.4
15	3.50	4.95	5.78	6.8	9.4
16	2.61	5.36	5.56	6.6	5.7
17	2.97	4.56	5.82	8.7	7
18	2.64	5.39	5.63	6.6	5.6
19	3.56	4.67	5.96	8.3	9.3
20	3.16	4.44	5.84	8.9	7.4
21[a]	3.12	3.61	5.70	8.3	8.9
22	3.23	3.65	5.68	8.1	8.9
23	3.31	5.18	5.29	10.9	9.4
25[a]	3.48	4.88	5.83	6.8	9.2

[a] Major isomer.

The preparative interest of the method was further improved through the cleavage of the remaining auxiliary, carried out on the crude mixture, which, much to our surprise, led to **8** as a single isomer. To determine its optical purity, **8** was transformed via esterification into the corresponding benzylic ester **9** (the yield of the esterification was modest, 41–42% under standard conditions; it reached 60% when using benzylbromide as the solvent, cf. Section 4).

The enantiomeric excess was higher than 99% according to analytic chiral HPLC (Chiralcel OD-H, cf. Supporting Information[27]) by reference to a racemic sample prepared according to Scheme 3.



Scheme 3. (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C; (ii) LiOH, H_2O_2 (30%); (iii) DIC, DMAP, $PhCH_2OH$.

It is worth noting that attempts to assign the stereochemistries of **3**, **4**, **5**, **8** and **9**, based on the vicinal coupling constants analysis referring to literature data, led to erroneous structures. The compounds taken as references were closely related lactones, including natural products such as nephromopsinic, pertusarinic and nephrosteranic acids.[14] It seems that, compared to these natural products, our lactones contain bulkier substituents which induce significant conformational changes in the five-membered ring. The characteristic chemical shifts and coupling constants of the protons in the lactone ring are summarized in Table 1.[15] The absolute configurations of the ring carbons in lactones **3**, **4** and **5** were unambiguously confirmed by X-ray analysis. In the case of lactones **8** and **9**, the 2,3-*cis*, 3,4-*trans* relative configuration was confirmed by NOESY (cf. Supporting Information[27]).

Pure samples of **3** and **4** were isolated and treated separately with $LiOH/H_2O_2$, and both led to the same enantiomer of **8**. This means that epimerization at C4 occurred prior to the cleavage of the auxiliary. Apparently, although there was no control of the facial selectivity during the addition of *t*-butyl radical (55:45), the condensation of both diastereomeric zinc enolates with benzaldehyde resulted in a good level of control of the absolute configuration at both C3 (89:11) and C2 (84:12). Once the configuration at C2 has been controlled, then the configurations at C4 and C3, are determined via the base-catalyzed epimerization that occurs under thermodynamic control during the cleavage step.

A sequence involving ring opening and subsequent ring closure of the resulting carboxylate via Michael addition, that would induce epimerization at C2 before the auxiliary is cleaved, might be considered to explain the high enantioselectivity. We rather believe that, owing to steric hindrance, the reaction of HOO^- with lactones **5**, **6**, and probably **7** (provided the presumed stereochemical assignment is correct) resulted in the cleavage of the oxazolidinone ring.[16]

We were able to isolate from the non-acidic fraction, the presumed amide-alcohol **12a** that could issue from the opening of the oxazolidinone ring of **6**, or **7** (Fig. 3).[17] Unfortunately **12a** could not be quantified nor fully separated from the oxazolidinone auxiliary.

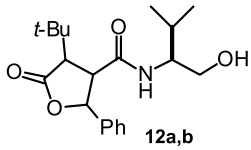


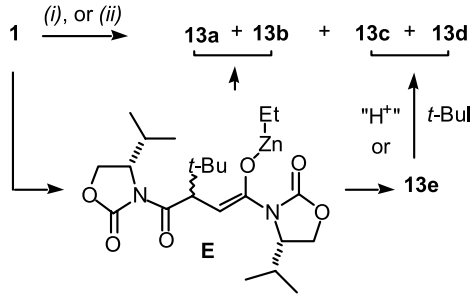
Figure 3.

Additional experiments were conducted on the isolated mixture of lactones resulting from **1** to get evidence of the epimerization process. Treatment with DBU (1 equiv) clearly showed that **4** isomerized into **3**. Because of their low initial amount, we could not ascertain whether lactones **6** or **7** were converted to **5**.

The lack of facial selectivity in the addition of *t*-Bu˙ leads us to recall the results reported by Sibi, who designed a large space demanding substituent on the auxiliary to reach total diastereoselectivity in the radical additions to simple *N*-enoyloxazolidinones carried out in the presence of chelating Lewis acids.[9,10] This lack of selectivity clearly

means that in the presence of diethylzinc the substrates do not keep the conformation shown in Figure 1, which should lead to total control. Thus, in our case, increasing the bulk of the substituent on the auxiliary might be useless.

In order to determine the diastereomeric ratio of the intermediate zinc enolates, «blank» experiments were performed. Compound **1** was allowed to react with diethylzinc and *t*-butyl iodide (45 equiv) in the absence of benzaldehyde.[18] The diastereoselectivity was compared to that observed for the addition of *t*-butyl radical mediated with tributyltin hydride at −10 °C, in the presence of 2 equiv of $ZnCl_2$ (Scheme 4, Fig. 4).[19]



Scheme 4. (i) **13a** (39%)+**13b** (3%)+**13c** (6.5%)+**13d** (24%) (relative ratio=54:5:8:33); (ii) 63% **13a**:**13b**=60:40. (i) $ZnEt_2$ (2 equiv), *t*-BuI (45 equiv), air (20 mL), CH_2Cl_2, 1 h, the yields refer to isolated products; (ii) Bu_3SnH (2 equiv), $ZnCl_2$ (2 equiv), *t*-BuI (5 equiv), BEt_3 (cat), −78 °C.

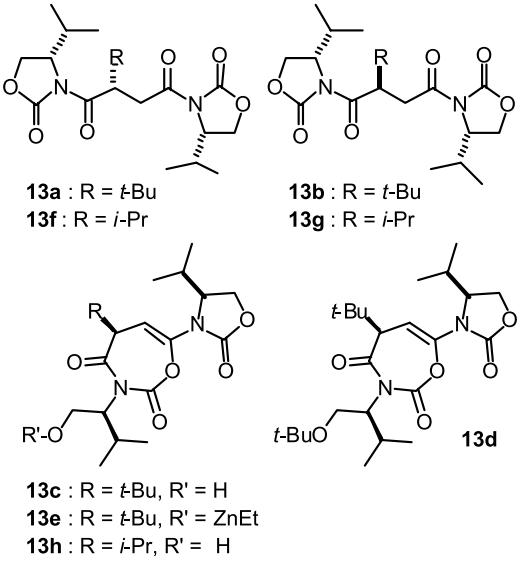
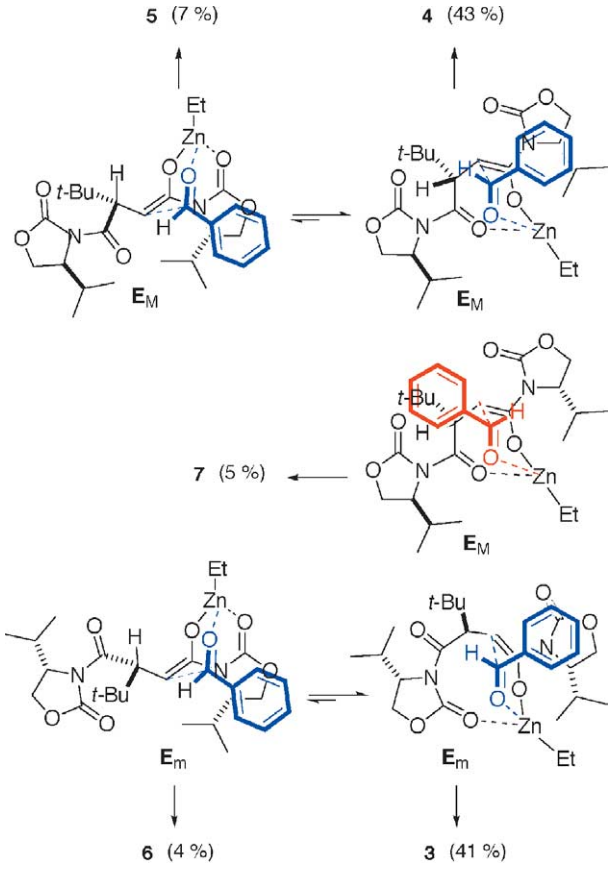


Figure 4.

It was difficult to determine accurately the diastereomeric ratio from the ^1H NMR spectrum of the crude mixture because of overlapping characteristic signals. The ratio was determined after semi-preparative HPLC from the yields in isolated products. Besides one largely predominant diastereomer, which was assigned structure **13a** (**13b** was only detected as trace amount), two unexpected products were formed. Their signals overlapped with the AB part of the ABX pattern characteristic of the methylene α to the carbonyl group in **13a** and **13b** (Scheme 4, Fig. 4). These products, identified as **13c** and **13d** after they were isolated as pure samples, resulted from the same zinc-enolate as **13b** did, via intramolecular nucleophilic displacement. The resulting primary alkoxide **13e** could react slowly with *t*-BuI via either elimination or substitution to give **13c** and **13d**. **13c** also originates from the protonation of **13e** upon treatment with aqueous NH_4Cl. The rearrangement would be prevented in the presence of benzaldehyde, which is more electrophilic than the carbamate.

All these results could be rationalized according to Scheme 5. As shown in Scheme 1, whatever the conformation around the N–C(=O) bond, owing to steric interactions, the preferred conformation around the CH–C(=O) bonds should be *s-cis*, and therefore diastereomeric *Z* enolates should be expected.



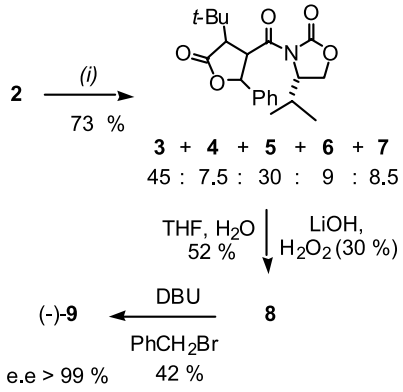
Scheme 5.

The major enolate (E_M) resulting from the attack of *t*-Bu˙ at the *re* face of the double bond would rather adopt a seven-membered chelate structure, than a six-membered chelate one. A similar conformation could not be adopted by the minor enolate (E_m), resulting from the attack of *t*-Bu˙ at the *si* face. The conformational change around the exocyclic N–C(=O) bond would explain why, in the absence of benzaldehyde, this enolate rearranged through nucleophilic displacement at the endocyclic carbonyl group to give **13e** (Fig. 4).

In the presence of benzaldehyde, the preferential approach of the electrophile would be controlled at C3 by the auxiliary attached to the enolate moiety. The control at C2 would be the consequence of the steric bulk and of the

spatial arrangement of the substituents at C4. This arrangement would explain the preference for the Zimmerman–Traxler transition structures shown in Scheme 5, with the phenyl group in a pseudo-axial position rather than for those with the phenyl group in a pseudo-equatorial position. The former structures lead to **3**, **4**, **5** and **6**, while the latter lead to **7**.

As shown in Scheme 6, the comparative reaction conducted on oxazolidinone **2** was less selective, particularly regarding the facial selectivity in the aldol condensation. It led mostly to a mixture of **3** and **5**, and also to minor amounts of the three other diastereomers previously detected when starting from **1**. The exact balance for stereocontrol was 54:46 at C4, 52.5:47.5 at C3, and 61:39 at C2. However, the radical addition was totally regioselective, only the carbon bearing the ethoxycarbonyl group was attacked by *t*-Bu˙.

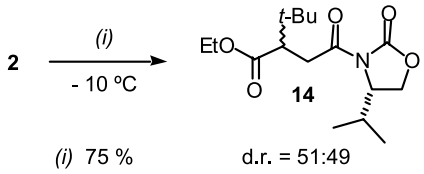


Scheme 6. (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

As previously mentioned, the structure of **5** (that could be isolated as a pure sample from this experiment), in which the lactone moiety is the mirror image of the lactone moiety in **3**, could be determined by comparing the chemical shifts and vicinal coupling constants of both lactones, which were quite similar (Table 1). It was unambiguously confirmed by X-ray spectroscopy.[28]

We observed that the cleavage of the remaining auxiliary, followed by the acid-basic extraction performed on the mixture of **3**–**7**, led to **8** (the same enantiomer as that obtained from **1**) but in only 52% yield. As previously, the enantiomeric excess of the corresponding benzylic ester was higher than 99%. Again, owing to epimerization at C4, lactone **4** was converted to **3**. The total amount of **3** and **4** accounted for the lower yield in acid **8**. This indirectly confirmed that the cleavage of lactones **5**, **6** and **7**, that were formed in much larger amounts from **2** than from **1**, led to non-acidic products through the cleavage of the oxazolidinone ring. This is probably due to the sterically hindered exocyclic cleavage, connected to an unfavourable conformation of the auxiliary around the C(O)–N bond.[20] The cleavage of a pure sample of **5** led to a mixture of products: **12b** (Fig. 3), unreacted **5**, and unidentified products.

Again, the selectivity of the reaction is in agreement with the low diastereoselectivity in the addition of *t*-butyl radical (51:49), as witnessed through the experiment described in Scheme 7. It can be noted that the overall diastereomeric ratio in Scheme 6 (**3**+**6**/**4**+**5**+**7**=54:46) supported the configuration assigned to C4 in **7** that would result from the attack of *t*-Bu˙ from the rear.

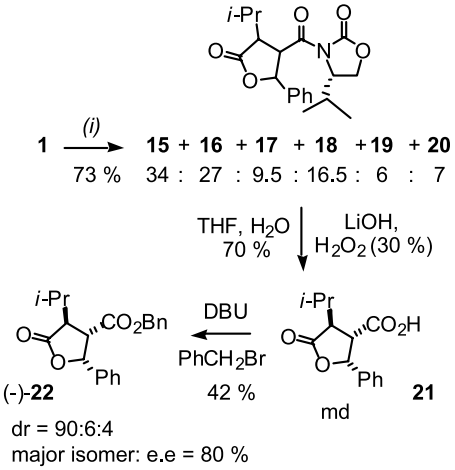


Scheme 7. (i) $ZnEt_2$ (2 equiv), *t*-BuI (45 equiv), air (20 mL), CH_2Cl_2,1 h.

We also investigated the diastereoselectivity of the process when using Et_2Zn alone, in the absence of any alkyl iodide. Due to the presence of oxygen, the radical-polar crossover mechanism is likely, but the contribution of a polar pathway could not be conclusively ruled out. When **1** was used as the substrate, seven lactones resulted from the addition of Et˙.[21] As it was difficult to chromatographically separate pure samples, and as the cleavage of the auxiliary led to a mixture of diastereomeric acids, the investigation of this reaction was not carried further.

2.2. Addition of diisopropylzinc

Attempted addition of *i*-Pr˙ performed by reacting **1** with diethylzinc in the presence of *i*-PrI led to complex mixtures of lactones resulting from both the addition of Et˙ and that of *i*-Pr˙. The diastereoselectivity of the addition of the secondary radical was therefore investigated by reacting **1** and **2** directly with diisopropylzinc and oxygen, in the presence of benzaldehyde. Even though the reaction of dialkylzinc with oxygen is quite fast, the contribution of a polar addition could not be totally ruled out in this case. The results are summarized in Scheme 8.



Scheme 8. (i) Zn(*i*-Pr_2) (2 equiv), PhCHO (1.1 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

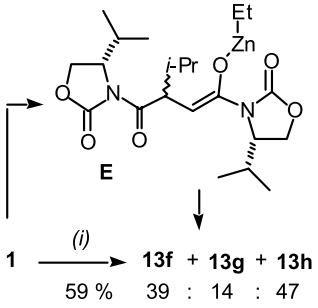
A mixture of six diastereomeric lactones **15**–**20** was isolated (cf. Fig. 2 for stereochemical assignments). Since a complete separation could be achieved in this case through purification by semi-preparative chiral HPLC, yields refer to the isolated products. The two major isomers are likely to have structures similar to those of **3** and **4**. Stereochemical

assignments were made possible by comparing the chemical shifts and coupling constants of H2, H3 and H4 to those of the same protons in **3**–**7** (Table 1). Lactone **19** is likely to have the same structure as **5**. The analysis of the NMR parameters in Table 1 also allowed us to establish structural similitudes between **6** and **18**, and between **7** and **20**. **17** has no structural similitudes with lactones **3**–**7** (the most significant correlations established from the corresponding NOESY spectra are reported in the Supporting Information[27]). The structure of **18** was confirmed by X-ray spectroscopy. The diastereoselectivity reflects an overall 60:40 ratio for *i*-Pr˙ approaching from the front and from the rear, respectively. This ratio is close to that registered for the addition of *t*-Bu˙. However, the secondary radical attacked preferentially the *si* face of the conjugate double bond.

The cleavage of the auxiliary led to **21** (as a mixture of 3 detectable diastereomers). The diastereomeric ratio was confirmed, and the optical purity of the major isomer was determined after esterification. According to ^{1}H NMR, **22** would be a mixture of three diastereomers in a 90:6:4 ratio. The analysis of **22** by chiral HPLC was made by comparing it with a racemic sample prepared from **10** according to a procedure similar to that described for the synthesis of racemic **9**.[22]

We speculate that the lactones bearing an *i*-propyl substituent are less hindered than those bearing a *t*-butyl group, and might well all be cleaved by nucleophilic attack at the exocyclic carbonyl. This would explain why **21** is obtained as a mixture of diastereomers. The epimerization of **16**, and presumably that of **17**, into **15** prior to cleavage would still occur. However, the exocyclic cleavage of **19** would lead to the mirror image of the acid resulting from **15** and this would account for the lower ee (80%) determined after esterification. The exocyclic cleavage of **18** and **20** would contribute to the minor diastereomers of **21**.

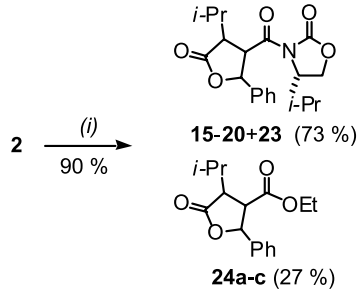
The facial selectivity in the addition of *i*-Pr˙ was confirmed by adding diisopropylzinc alone to **1**. As in the case of the addition of *t*-Bu˙, the zinc enolate precursor of **13g** rearranged via cyclization (Scheme 9) and led to **13h** (Fig. 4) after acid treatment.



Scheme 9. (i) Zn(*i*-Pr$_2$) (2 equiv), air (20 mL), CH_2Cl_2, 2 h, (yields refer to isolated products).

The reaction led to a mixture of diastereomeric adducts, **13g** and **13f**, and to **13h**[23] (Fig. 4) in 59% overall yield. The observed diastereomeric ratio (61:39) corroborated quite well again the 60:40 ratio determined from the mixture of lactones **15**–**20** reported in Scheme 8.

The reaction of **2** with diisopropylzinc led to a complex mixture (Scheme 10). The analysis of the ^{1}H NMR spectrum of the mixture enabled us to identify lactones **15**–**20** and an additional diastereomer **23**.[24] In addition, three regioisomeric lactones **24a**–**c** resulting from the attack of *i*-Pr˙ at the position α to the ethoxycarbonyl group and accounting for approximately 27% of the mixture were also formed.[25]



Scheme 10. Zn(*i*-Pr$_2$) (2 equiv), PhCHO (1.1 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

The spectral identification is based on the analysis by ^{1}H NMR of enriched fractions of these new products isolated by semi-preparative HPLC. A complete stereochemical assignment could not be achieved for **24a**–**c** which could result from the contribution of a polar mechanism.

3. Conclusion

The dialkylzinc mediated radical additions to fumaric acid derived oxazolidinones carried out in the presence of benzaldehyde led to sterically crowded γ-lactones. The diastereoselectivity is sensitive to the nature of both the substrate and the radical. Regarding asymmetric synthesis, the preparative interest of the method is restricted to the introduction of tertiary alkyl groups. Further investigations of the scope and limitations of the reaction with regard to the nature of the electrophile will be reported in due course.

4. Experimental

4.1. General

NMR, and DEPT spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ as the solvent. The *J* values are given in Hz. Melting point are uncorrected. Column chromatographies were performed on silica gel 60. The solvents for chiral chromatography (*n*-hexane, 2-PrOH, EtOH) are HPLC grade. They were degassed and filtered on Millipore membrane 0.45 μm before use. Cellulose tris(3,5-dimethylphenylcarbamate) chiral stationary phases, CHIRALCEL OD-H (250×4.6 mm) and CHIRALCEL OD (250×10 mm) DAICEL columns are available from Merck-Eurolab. The chiral HPLC analyses were performed on a screening unit composed of Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV detector and

on-line chiroptical detectors: Jasco OR-1590 polarimeter or Jasco CD-1595 circular dichroism. The semi-preparative HPLC separations were performed with Merck-Hitachi LiChrograph L-6000 pump, Merck-Hitachi L-4000 UV detector and Merck D-7000 system manager. Detailed chromatographic conditions are reported in the Supporting Information. The optical rotatory powers were measured on a 241 MC Perkin–Elmer polarimeter with a sodium lamp and a double-jacketed cell at 25 °C.

4.1.1. 1,4-Bis-(4(*S*)-*i*-propyl-2-oxo-oxazolidin-3-yl)-but-2-ene-1,4-dione (1). The substrates were prepared according to literature procedures.[26] Methylmagnesium bromide (0.58 mL, 1.7 mmol, 1.1 equiv, 3 M in ether) was added to a solution of 4-isopropyl-oxazolidin-2-one (200 mg, 1.55 mmol) and hydroquinone (2 mg, 0.02 mmol) in 10 mL of anhydrous THF at 0 °C. After stirring for 20 mn at 0 °C, fumaryl chloride (84 μL, 0.78 mmol, 0.5 equiv) was added. The mixture was stirred for 30 mn at room temperature, diluted with 20 mL of ether (peroxide free), and finally washed first with saturated aqueous ammonium chloride, and then with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduce pressure. The crude product was purified by FC (10% EtOAc–pentane) leading to **1** as a crystalline solid (382 mg, 1.13 mmol, 73%). Mp 119 °C. ^{1}H NMR (300 MHz): δ 0.83 (d, 6H, J=7.0 Hz), 0.89 (d, 6H, J=7.0 Hz), 2.36 (dsept, 2H, J=4.0, 7.0 Hz), 4.22 (dd, 2H, J=3.2, 9.0 Hz), 4.32 (t, 2H, J=9.0 Hz), 4.47 (m, 2H), 8.12 (s, 2H). ^{13}C NMR (75 MHz): δ 14.6 (CH_3), 17.9 (CH_3), 28.2 (CH), 58.6 (CH), 63.7 (CH_2), 132.9 (CH), 153.7 (C=O), 163.6 (C=O). $[\alpha]_D^{25}=+152$ (c 1.03, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 57.00; H, 6.57; N, 8.28.

4.1.2. 4-(4(*S*)-*i*-Propyl-2-oxo-oxazolidin-3-yl)-4-oxo-but-2-enoic acid ethyl ester (2). Methylmagnesium bromide (0.61 mL, 1.7 mmol, 1.1 equiv, 3 M in ether) was added to a solution of 4-isopropyl-oxazolidin-2-one (212 mg, 1.64 mmol) and hydroquinone (2 mg, 0.02 mmol) in 11 mL of anhydrous THF at 0 °C. After stirring for 20 mn at 0 °C, fumaric ethyl ester mono chloride (267 mg, 1.64 mmol, 1 equiv) was added. The mixture was stirred for 30 mn at room temperature, diluted with 21 mL of ether (peroxide free), and finally washed first with saturated aqueous ammmonium chloride, and then with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduce pressure. The crude product was purified by FC (10% EtOAc–pentane) to give **2** (217 mg, 0.85 mmol, 52%) as a yellow oil. ^{1}H NMR (300 MHz): δ 0.89 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 1.33 (t, 3H, J=7.2 Hz), 2.43 (dsept, 1H, J=3.4, 7.0 Hz), 4.27 (q, 2H, J=7.2 Hz), 4.28 (dd, 1H, J=3.4, 8.3 Hz), 4.36 (t, 1H, J=8.3 Hz), 4.44 (dt, 1H, J=8.3, 3.4 Hz), 6.85 (d, 1H, J=15.5 Hz), 8.09 (d, 1H, J=15.5 Hz). ^{13}C NMR (75 MHz): δ 14.0 (CH_3), 14.5 (CH_3), 17.8 (CH_3), 28.2 (CH), 58.5 (CH), 61.2 (CH_2), 63.6 (CH_2), 132.3 (CH), 134.0 (CH), 153.5 (C=O), 163.6 (C=O), 164.8 (C=O). $[\alpha]_D^{25}=+89$ (c 1.02, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.39; H, 6.71; N, 5.44.

4.2. General procedure for the synthesis of lactones

Method A. Benzaldehyde (1.1 equiv) and *t*-BuI (none, 10, or 45 equiv) were added under argon at −10 °C, to a 0.2 M solution of substrate, in dichloromethane. Diethylzinc (2 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at the same temperature while air (20 mL) was injected through a needle into the solution over 1 h. After stirring overnight at room temperature, the reaction was quenched by aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC. All the reactions were repeated several times giving each time similar yields and reproducible diastereomeric ratios.

Method B. Benzaldehyde (1.1 equiv) was added under argon at −10 °C, to a 0.2 M solution of substrate, in dichloromethane. Diisopropylzinc (2 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at the same temperature while air (20 mL) was injected through a needle into the solution over 1 h. After completion, the reaction was quenched by aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC.

4.2.1. 3-(4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (3 and 4). Treating **1** (50 mg, 0.148 mmol) according to method A, in the presence of *t*-butyl iodide (45 equiv, 795 μL), led to **3** and **4** together with small amounts of three other diastereomers (**5**, **6**, **7**) (49 mg, 0.13 mmol, 89%) isolated after purification by FC (5–20%, EtOAc–pentane). The diastereomeric ratio (41:43:7:4:5) was determined from ^{1}H NMR. A second chromatography on silica gel (15–25 μmesh; 2% EtOAc–pentane) allowed the isolation of pure samples of **3** and **4** (order of elution **3**, **4**, **5**, **6**, **7**). Anal. Calcd for $C_{21}H_{27}NO_5$ (mixture of **3**+**4**): C, 67.54; H, 7.29; N, 3.75. Found: C, 67.50; H, 7.54; N, 3.60.

4.2.2. [3*S*-(4*R*-2*R*)-4*S*] (3). Mp 96 °C. ^{1}H NMR (300 MHz): δ 0.74 (d, 3H, J=6.8 Hz), 0.77 (d, 3H, J=6.8 Hz), 1.14 (s, 9H), 2.12 (dsept, 1H, J=4.0, 6.8 Hz), 3.39 (d, 1H, J=6.6 Hz), 3.51 (t, 1H, J=8.3 Hz), 3.58 (ddd, 1H, J=1.7, 4.0, 8.3 Hz), 3.95 (dd, 1H, J=1.7, 8.3 Hz), 5.07 (dd, 1H, J=6.6, 9.4 Hz), 5.73 (d, 1H, J=9.4 Hz), 7.17–7.23 (m, 2H), 7.30–7.37 (m, 3H). ^{13}C NMR (75 MHz): δ 14.7 (CH_3), 17.7 (CH_3), 27.4 (CH_3), 28.6 (CH), 33.4 (C), 47.9 (CH), 51.2 (CH), 58.7 (CH), 63.5 (CH_2), 78.7 (CH), 126.5 (CH), 128.3 (CH), 129.1 (CH), 136.0 (C), 153.8 (C=O), 169.8 (C=O), 176.1 (C=O). $[\alpha]_D^{25}=+15$ (c 1.04, $CHCl_3$).

4.2.3. [3*S*-(4*S*-2*R*)-4*S*] (4). Mp 271–273 °C. ^{1}H NMR (300 MHz): δ 0.76 (d, 3H, J=7.0 Hz), 0.79 (d, 3H, J=7.0 Hz), 1.15 (s, 9H), 2.14 (dsept, 1H, J=4.0, 7.0 Hz), 2.89 (d, 1H, J=6.4 Hz), 3.29 (t, 1H, J=8.5 Hz), 3.60 (ddd, 1H, J=2.1, 4.0, 8.5 Hz), 3.87 (dd, 1H, J=2.1, 8.5 Hz), 5.40 (dd, 1H, J=6.4, 5.4 Hz), 5.54 (d, 1H, J=5.4 Hz), 7.30–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 14.6 (CH_3), 17.8 (CH_3), 28.7 (CH), 29.3 (CH_3), 31.2 (C), 47.8 (CH), 54.9 (CH), 58.5 (CH), 63.3 (CH_2), 79.2 (CH), 125.5 (CH), 128.2 (CH), 128.4

(CH), 134.8 (C), 153.6 (C=O), 169.1 (C=O), 173.9 (C=O). $[\alpha]_D^{25} = +62$ (*c* 0.59, $CHCl_3$).

4.2.4. (2*R*-3*S*-4*R*) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (8). H_2O_2 (30%) (141 μL, 1.4 mmol) and $LiOH.H_2O$ (22 mg, 0.52 mmol) were added at 0 °C to a solution of the isomeric mixture of **3–7** obtained from **1** (129 mg, 0.346 mmol) in THF (2.3 mL) and H_2O (0.6 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of $Na_2S_2O_3$ (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×5). The combined organic phases were dried over $MgSO_4$, concentrated and purified by semi-preparative HPLC. This led to isolate a mixture of **12a** and the auxiliary oxazolidinone. The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give **8** (74 mg, 0.282 mmol, 82%) mp 223 °C. $[\alpha]_D^{25} = -19.6$ (*c* 0.57, $CHCl_3$).^{1}H NMR (300 MHz): δ 1.10 (s, 9H), 3.01 (d, 1H, J=8.0 Hz), 3.64 (dd, 1H, J=8.0, 9.2 Hz), 5.65 (d, 1H, J=9.2 Hz), 7.19–7.27 (m, 5H). ^{13}C NMR (75 MHz): δ 27.4 (CH_3), 33.2 (C), 49.2 (CH), 51.4 (CH), 78.2 (CH), 125.8 (CH), 128.3 (CH), 128.8 (CH), 135.8 (C), 174.0 (C=O), 175.8 (C=O). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.82; H, 6.79.

4.2.5. 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ((*S*)-1-hydroxymethyl-2-methyl-propyl-amide (12a). ^{1}H NMR (300 MHz): δ 0.80 (d, 3H, J=6.8 Hz), 0.81 (d, 3H, J=6.6 Hz), 1.15 (s, 9H), 1.69 (m, 1H), 2.86 (m, 1H), 3.20–3.36 (m, 2H), 3.23 (superimposed d, 1H, J=5.5 Hz), 3.43 (dd, 1H, J=8.9, 5.5 Hz), 5.56 (br s, 1H), 5.59 (d, 1H, J=8.9 Hz), 5.71 (br d, 1H, J=8.5 Hz).

^{13}C NMR (75 MHz): δ 17.6 (CH_3), 18.0 (CH_3), 27.6 (3× CH_3), 28.7 (CH), 33.6 (C), 50.4 (CH), 52.7 (CH), 56.6 (CH), 62.4 (CH_2), 79.9 (CH), 126.6 (CH), 128.2 (CH), 128.8 (CH), 136.4 (C), 169.4 (C=O), 176.5 (C=O). HRMS calcd for $C_{20}H_{29}NO_4Na$ [MNa^+]: 370.1994; found: 370.1988.

4.2.6. (2*R*-3*S*-4*R*) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (9). A mixture of **8** (53 mg, 0.20 mmol, 1 equiv), benzyl bromide (47 μL, 0.39 mmol, 2 equiv) and DBU (45 μL, 0.30 mmol, 1.5 equiv) in benzene (1 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduce pressure. The residue was purified on silica gel (10% EtOAc–pentane) to give **9** (30 mg, 42%).

In an alternative procedure, a mixture containing **8** (15 mg, 0.06 mmol, 1 equiv), benzyl bromide (1 mL) and DBU (13 μL, 0.09 mmol, 1.5 equiv) was stirred at room temperature for 7 days. The mixture was directly purified by chromatography on silica gel (100% pentane, then 5% AcOEt–pentane) to give **9** (12 mg, 60%). The enantiomeric excess was determined by chiral HPLC on CHIRALCEL OD-H (250×4.6 mm): hexane–2-PrOH (90:10), 1 mL/min, 25 °C, UV and circular dichroïsm detection at 254 nm, Rt(−)=6.88 min, Rt(+)=7.45 min, $k(-)$=1.28, $k(+)$=1.48, α=1.15 and Rs=1.17.

^{1}H NMR (300 MHz): δ 1.09 (s, 9H), 3.12 (d, 1H, J=7.7 Hz), 3.70 (dd, 1H, J=7.7, 9.2 Hz), 4.62 (AB pattern, 2H, J=12.1 Hz, $\Delta\nu$=61.9), 5.65 (d, 1H, J=9.2 Hz), 7.06–7.36 (m, 10H). ^{13}C NMR (75 MHz): δ 27.4 (CH_3), 33.2 (C), 49.5 (CH), 51.3 (CH), 67.3 (CH_2), 78.5 (CH), 125.8 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 134.6 (C), 136.0 (C), 169.9 (C=O), 175.9 (C=O). $[\alpha]_D^{25} = -20$ (*c* 1.03, $CHCl_3$). HRMS calcd for $C_{22}O_4H_{25}$ [MH^+]: 353.1753; found: 353.1769.

4.2.7. 3-(4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (5). Treating **2** (67 mg, 0.26 mmol) according to method A, in the presence of *t*-butyl iodide (45 equiv, 1.4 mL), led to a mixture of **3–7** (76 mg, 0.20 mmol, 73%) isolated after purification by FC (2–10% EtOAc–pentane). The diastereomeric ratio was determined by ^{1}H NMR. A second chromatography allowed the isolation of a pure sample of **5**. Anal. Calcd for $C_{21}H_{27}NO_5$ (mixture): C, 67.53; H, 7.29; N, 3.75. Found: C, 67.41; H, 7.41; N, 3.67.

4.2.8. [3*R*-(4*S*-2*S*)-4*S*] (5). Mp 139–141 °C. ^{1}H NMR (300 MHz): δ 0.24 (d, 3H, J=6.8 Hz), 0.66 (d, 3H, J=6.8 Hz), 1.09 (s, 9H), 1.53 (dsept, 1H, J=2.0, 6.8 Hz), 3.42 (d, 1H, J=7.7 Hz), 4.08–4.23 (m, 3H), 4.79 (dd, 1H, J=7.7, 9.6 Hz), 5.89 (d, 1H, J=9.6 Hz), 7.22–7.35 (m, 5H). ^{13}C NMR (75 MHz): δ 14.3 (CH_3), 18.0 (CH_3), 27.4 (CH_3), 28.3 (CH), 33.4 (C), 47.8 (CH), 51.7 (CH), 59.1 (CH), 63.7 (CH_2), 79.0 (CH), 127.2 (CH), 128.6 (CH), 129.1 (CH), 135.9 (C), 153.8 (C=O), 169.5 (C=O), 175.9 (C=O). $[\alpha]_D^{25} = +85$ (*c* 0.59, $CHCl_3$).

4.2.9. 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ((*S*)-1-hydroxymethyl-2-methyl-propyl-amide (12b). Treating **5** (16 mg, 0.043 mmol) with LiOH (1.5 equiv, 0.064 mmol, 3 mg) and H_2O_2 (4 equiv, 0.172 mmol, 18 μL) in THF (500 μL) and H_2O_2 (125 μL), led after acid-basic extraction and purification by liquid chromatography on silicagel (95:5 to 60:40, pentane–EtOAc) to 10 mg of a mixture of products containing unreacted starting material, unidentified products, and **12b**. Unfortunately, **12b** could not be fully separated from the other products. The structure was assigned from the ^{1}H NMR of an enriched chromatographic fraction.

^{1}H NMR (300 MHz) characteristic signals of **12b**: δ 0.65 (d, 3H, J=7.0 Hz), 0.70 (d, 3H, J=6.8 Hz), 1.14 (s, 9H), 1.90–2.02 (m, 2H), 3.13 (d, 1H, J=6.4 Hz), 3.20–3.28 (m, 1H), 3.30–3.50 (m, 2H), 3.42 (superimposed dd, 1H, J=6.4, 8.9 Hz), 5.42 (br d, 1H, J=7.7 Hz), 5.60 (d, 1H, J=8.9 Hz), 7.25–7.40 (m, 5H).

4.2.10. 4-(2-Oxo-oxazolidin-3-yl)-4-oxo-but-2-enoic acid ethyl ester (10). Methylmagnesium bromide (4.34 mL, 12.3 mmol, 1.1 equiv, 3 M in ether) was added to a solution of oxazolidin-2-one (1 g, 11.5 mmol) and hydroquinone (15 mg, 0.02 mmol) in 73 mL of anhydrous THF at 0 °C. After stirring for 20 mn at 0 °C, fumaric ethyl ester mono chloride (1.87 g, 11.5 mmol, 1 equiv) was added. The mixture was stirred for 30 mn at room temperature, diluted

with 150 mL of ether (peroxide free), and finally washed first with saturated aqueous ammmonium chloride, and then with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduce pressure. The crude product was purified by FC (20% EtOAc–pentane) to give **10** (1.08 g, 5.1 mmol, 45%) as a solid. Mp 62–63 °C. ^{1}H NMR (300 MHz): δ 1.27 (t, 3H, J=7.2 Hz), 4.07 (t, 2H, J=8.1 Hz), 4.20 (q, 2H, J=7.2 Hz), 4.46 (t, 2H, J=8.1 Hz), 6.85 (d, 1H, J=15.7 Hz), 8.05 (d, 1H, J=15.7 Hz). ^{13}C NMR (75 MHz): δ 13.8 (CH_3), 42.3 (CH_2), 61.1 (CH_2), 62.3 (CH_2), 131.7 (CH), 133.6 (CH), 153.0 (C=O), 163.4 (C=O), 164.5 (C=O). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.60; H, 5.23; N, 6.46.

4.2.11. 3-(4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-oxazolidin-2-one (11). Treating **10** (43 mg, 0.20 mmol) according to method A, in the presence of *t*-butyl iodide (1.1 mL, 9 mmol), led to **11** (50 mg, 0.15 mmol, 75%) isolated as a mixture of isomers (major isomer >80%) after purification by FC (5–20% EtOAc–pentane). The stereochemistry was assigned according to the analogy of the coupling constants with those observed in **3**. ^{1}H NMR (300 MHz) of major isomer: δ 1.13 (s, 9H), 3.07 (ddd, 1H, J=6.4, 9.3, 10.8 Hz), 3.36 (d, 1H, J=6.4 Hz), 3.72 (ddd, 1H, J=7.0, 9.3, 10.9 Hz), 3.91 (dt, 1H, J=7.0, 9.1 Hz), 4.20 (dt, 1H, J=6.4, 9.1 Hz), 5.02 (dd, 1H, J=6.4, 9.4 Hz), 5.75 (d, 1H, J=9.4 Hz), 7.19–7.23 (m, 2H), 7.30–7.38 (m, 3H). ^{13}C NMR (75 MHz): δ 27.5 (CH_3), 33.4 (C), 42.4 (CH_2), 47.9 (CH), 51.02 (CH) 62.0 (CH_2), 78.8 (CH), 126.3 (CH), 128.4 (CH), 129.0 (CH), 136.0 (C), 153.1 (C=O), 169.9 (C=O), 176.0 (C=O). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.27; H, 6.45; N, 4.17.

4.2.12. (2*R-3*S**-4*R**) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (*rac*-8).** H_2O_2 (30%) (62 μL, 0.60 mmol, 4 equiv) and $LiOH.H_2O$ (9.5 mg, 0.23 mmol, 1.5 equiv) were added at 0 °C to a solution of **11** (50 mg, 0.15 mmol) in THF (2 mL) and H_2O (0.50 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of $Na_2S_2O_3$ (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×5). The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give racemic **8** (30 mg, 0.114 mmol, 76%). The spectrocopic data were identical to those of the optically pure sample previously described.

4.2.13. (2*R-3*S**-4*R**) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (*rac*-9).** Diisopropylcarbodiimide (51 μL, 0.33 mmol, 1.64 equiv) was added to a solution of racemic **8** (52 mg, 0.20 mmol, 1 equiv), DMAP (3.77 mg, 0.03 mmol, 0.15 equiv), benzylic alcohol (31 μL, 0.3 mmol, 1.5 equiv) and triethylamine (58 μL, 0.42 mmol, 2.1 equiv) in dichloromethane (760 μL) at 0 °C. The mixture was stirred for 17 h at room temperature. After addition of ethyl acetate to the mixture, the insoluble materials were filtered off through Celite. The filtrate was evaporated to give racemic **9** (23 mg, 0.08 mmol) in 41% yield, as attested by its NMR spectra the crude product was pure enough for analytic purpose. The spectroscopic data were identical to those of the enantiopure sample previously described.

4.2.14. 2-*tert*-Butyl-1,4-bis-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-butane-1,4-dione (13a,b). *t*-BuI (795 μL, 6.67 mmol, 45 equiv) was added under argon at −10 °C, to a 0.2 M solution of substrate **1** (50 mg, 0.15 mmol), in dichloromethane. Diethylzinc (270 μL, 0.27 mmol, 1.8 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at −10 °C while air (20 mL) was injected through a needle into the solution over 1 h. After completion (1 night), the reaction was quenched by aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC to give a mixture **13a**,**b** and **13d** (together with trace amount of **13c** resulting from the partial protonation of **13e**). Separation by semi-preparative HPLC (CHIRALCEL OD (250×10 mm), hexane–ethanol (90:10), 4.5 mL/min, UV detection at 220 nm) led to the isolation of **13d** (4.12 min, 16 mg), a fraction containing **13b** (5.86 min) and what we assumed to be **13c** (6.90 min) in a 32:68 ratio (5.5 mg), **13a** (8.64 min, 22.9 mg). The yields determined from the above chromatographic separation were: **13a** (39%), **13d** (24%), **13c** (6.5%), **13b** (3%). This would correspond to a 54:46 rear to front selectivity for the addition of *t*-Bu$^{\cdot}$.

Compound **13a**. Mp 219 °C. ^{1}H NMR (300 MHz): δ 0.84 (d, 3H, J=6.8 Hz), 0.86 (d, 3H, J=6.6 Hz), 0.91 (d, 3H, J=7.2 Hz), 0.95 (d, 3H, J=7.0 Hz), 1.01 (s, 9H), 2.22 (septd, 1H, J=6.8, 4.3 Hz), 2.37 (septd, 1H, J=7.0, 3.6 Hz), 3.27 (dd, 1H, J=3.2, 18.3 Hz), 3.45 (dd, 1H, J=11.9, 18.3 Hz), 4.15–4.23 (m, 3H), 4.27 (pseudot, 1H, J=8.9 Hz), 4.35–4.46 (m, 3H). ^{13}C NMR (75 MHz): δ 14.5 (CH_3), 15.1 (CH_3), 17.8 (CH_3), 18.1 (CH_3), 27.5 (CH_3), 28.1 (CH), 28.7 (CH), 33.3 (CH_2), 36.0 (C), 45.4 (CH), 58.4 (CH), 59.2 (CH), 62.7 (CH_2), 63.9 (CH_2), 154.0 (C=O), 154.1 (C=O), 172.3 (C=O), 175.3 (C=O). $[\alpha]_D^{25}=+106.5$ (c 1.01, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}N_2O_6$: C, 60.59; H, 8.14; N, 7.07. Found: C, 60.61; H, 8.16; N, 6.96.

4.2.15. (*R*)-3-((*S*)-1-*tert*-Butoxymethyl-2-methyl-propyl)-5-*tert*-butyl-7-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-5*H*-[1,3]-oxazepine-2,4-dione (13d). ^{1}H NMR (300 MHz): δ 0.79 (d, 3H, J=6.6 Hz), 0.88 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=6.6 Hz), 1.09 (2×s, 18H), 2.18–2.29 (m, 1H), 2.37 (septd, 1H, J=7.0, 4.0 Hz), 3.27 (d, 1H, J=6.4 Hz), 3.52 (dd, 1H, J=8.1, 3.8 Hz), 3.78 (dd, 1H, J=10.5, 8.1 Hz), 3.85 (td, 1H, J=10.5, 4.1 Hz), 4.26 (dd, 1H, J=8.9, 2.3 Hz), 4.37 (dd, 1H, J=8.9, 7.9 Hz), 4.48 (ddd, 1H, J=7.9, 4.0, 2.3 Hz), 5.52 (br d, 1H, J=6.0 Hz). ^{13}C NMR (75 MHz): δ 14.9 (CH_3), 17.9 (CH_3), 19.9 (CH_3), 20.3 (CH_3), 27.1 (CH), 27.3 (CH_3), 27.4 (CH_3), 28.9 (CH), 33.1 (C), 47.1 (=CH), 53.2 (CH), 58.5 (CH_2), 59.4 (2× CH), 63.6 (CH_2), 73.0 (C), 153.9 (C=O), 168.2 (C=), 172.1 (C=O), 177.3 (C=O). Anal. Calcd for $C_{24}H_{40}N_2O_6$: C, 63.69; H, 8.91; N, 6.19. Found: C, 62.92; H, 8.92; N, 5.76. HRMS calcd for $C_{24}H_{40}N_2O_6Na$ [MNa^+]: 475.2784; found: 475.2764.

Characteristic ^{1}H NMR signals of **13c** were deduced from

an enriched chromatographic fraction: δ 1.10 (s, 9H), 2.80 (br s, 1H, OH), 5.6 (br, s, 1H, C═CH).

4.2.16. 2-*tert*-Butyl-1,4-bis-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-butane-1,4-dione (13a,b). To a solution containing **1** (50 mg, 0.148 mmol) and $ZnCl_2$ (40 mg, 0.3 mmol) in a 4:1 mixture of CH_2Cl_2 (3 mL) and THF (740 μL), were added *t*-BuI (0.74 mmol, 89 μL) and Bu_3SnH (0.3 mmol, 80 μL, 2 equiv) at −78 °C. Et_3B (1 M in hexane, 0.3 mmol, 300 μL) was then added via syringe, and then air (7.4 mL) was added with a syringe pump over 15 min. The reaction was stirred for 1 h at −78 °C, then the reaction mixture was diluted with Et_2O (22 mL), washed with 1 M HCl (2× 3 mL) and concentrated. The residue dissolved in CH_2Cl_2 was washed with saturated $Na_2S_2O_3$, the organic phase was dried over $MgSO_4$ and concentrated. After dilution with Et_2O, the solution was stirred with KF (5 equiv) overnight, filtered, concentrated and the residue was purified by flash chromatography (0–50%, EtOAc–pentane) to give **13a** and **13b** in a 60:40 ratio (37 mg, 0.093 mmol, 63%).

4.2.17. 2-[2-((*S*)-4-*i*-Propyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-3,3-dimethyl-butyric acid ethyl ester (14). Treating **2** (50 mg, 0.196 mmol) with Et_2Zn (0.35 mmol, 353 μL) and *t*-BuI (8.82 mmol, 1.1 mL) according to the procedure already described for the preparation of **13**, led after purification by FC (5–30%, EtOAc–pentane) to **14** (46 mg, 0.147 mmol, 75%) as a nearly 1:1 mixture of diastereomers.

^{1}H NMR (300 MHz): δ 0.87 (d, 6H, J=6.8 Hz), 0.88 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=6.8 Hz), 1.00 (s, 9H), 1.01 (s, 9H), 1.26 (t, 3H, J=7.0 Hz), 1.28 (t, 3H, J=7.2 Hz), 2.22–2.42 (m, 2H), 2.65 (dd, 1H, J=12.1, 2.9 Hz), 2.68 (dd, 1H, J=12.1, 2.9 Hz), 3.10 (dd, 1H, J=18.5, 2.9 Hz), 3.14 (dd, 1H, J=18.3, 2.9 Hz), 3.35 (dd, 1H, J=18.9, 12.1 Hz), 3.42 (dd, 1H, J=18.5, 12.1 Hz), 4.04–4.30 (m, 8H), 4.35–4.45 (m, 2H). ^{13}C NMR (75 MHz): δ 14.2 (CH_3), 14.3 (CH_3), 14.6 (CH_3), 14.7 (CH_3), 17.8 (CH_3), 17.9 (CH_3), 28.0 (2× CH_3), 28.3 (CH), 28.4 (CH), 32.5 (C), 32.6 (C), 34.7 (2× CH_2), 50.6 (CH), 50.8 (CH), 58.3 (CH), 58.4 (CH), 60.1 (CH_2), 60.2 (CH_2), 63.4 (CH_2), 63.5 (CH_2), 154.1 (2× C═O), 172.3 (C═O), 172.5 (C═O), 174 (C═O), 174.4 (C═O). HRMS calcd for $C_{16}H_{28}NO_5$ [MH^+]: 314.1967; found: 314.1968.

4.2.18. 3-(4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (15–20). Treating **1** (100 mg, 0.29 mmol) according to method B led to a mixture of isomeric lactones **15**–**20** (76 mg, 0.215 mmol, 73%) isolated after purification by FC (5–20%, EtOAc–pentane). The diastereomeric ratio (34:9.5:27:16.5:6:7), given by order of elution, was determined on the isolated products after having achieved a complete separation of the mixture by chiral HPLC (CHIRALCEL OD (250×10 mm), hexane–ethanol (80:20), 4.5 mL/min, UV detection at 220 nm). This led by order of elution to **15** (4.90 min, 26.2 mg, 34%), **17** (5.90 min, 7.3 mg, 9.5%), **16** (6.79 min, 20.6 mg, 27%), **18** (9.06 min, 12.7 mg, 16.5%), **19** (10.10 min, 4.6 mg, 6%), **20** (11.45 min, 5.1 mg, 7%). Anal. Calcd for $C_{20}H_{25}NO_5$ (mixture of isomers): C, 66.84; H, 7.01; N, 3.90. Found: C, 66.90; H, 6.95; N, 3.81.

Compound **15**. Mp 125–126 °C. ^{1}H NMR (300 MHz): δ 0.76 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.8 Hz), 1.04 (d, 3H, J=7.0 Hz), 1.07 (d, 3H, J=7.0 Hz), 2.14 (dsept, 1H, J=4.2, 7.0 Hz), 2.33 (oct, 1H, J=6.8 Hz), 3.47–3.56 (m, 2H), 3.57–3.63 (m, 1H), 3.96 (dd, 1H, J=1.7, 8.5 Hz), 4.95 (dd, 1H, J=6.8, 9.4 Hz), 5.78 (d, 1H, J=9.4 Hz), 7.17–7.25 (m, 2H), 7.31–7.38 (m, 3H). ^{13}C NMR (75 MHz): δ 14.7 (CH_3), 17.7 (CH_3), 18.9 (CH_3), 20.2 (CH_3), 28.5 (CH), 28.8 (CH), 47.3 (CH), 47.5 (CH), 58.8 (CH), 63.5 (CH_2), 79.3 (CH), 127.4 (CH), 128.4 (CH), 129.1 (CH), 135.9 (C), 153.8 (C), 169.5 (C), 177.1 (C). $[\alpha]_D^{25}$ = +4 (*c* 1.02, $CHCl_3$).

Compound **17**. ^{1}H NMR (300 MHz): δ 0.74 (d, 3H, J=6.8 Hz), 0.88 (d, 3H, J=6.8 Hz), 1.04 (d, 3H, J=6.8 Hz), 1.14 (d, 3H, J=6.8 Hz), 2.02 (oct, 1H, J=6.8 Hz), 2.38 (dsept, 1H, J=4.1, 6.9 Hz), 2.97 (dd, 1H, J=5.9, 8.7 Hz), 4.24 (dd, 1H, J=9.3, 3.4 Hz), 4.34 (dd, 1H, J=9.3, 8.3 Hz), 4.35–4.40 (superimposed m, 1H), 4.56 (dd, 1H, J=8.5, 7.0 Hz), 5.82 (d, 1H, J=7.0 Hz), 7.29–7.46 (m, 5H). ^{13}C NMR (75 MHz): δ 14.4 (CH_3), 17.8 (CH_3), 19.7 (CH_3), 21.9 (CH_3), 27.7 (CH), 28.0 (CH), 48.2 (CH), 52.7 (CH), 58.6 (CH), 63.6 (CH_2), 80.1 (CH), 125.4 (CH), 128.8 (CH), 128.6 (CH), 138.0 (C), 153.5 (C═O), 169.5 (C═O), 175.4 (C═O). $[\alpha]_D^{25}$ = −16 (*c* 1.04, $CHCl_3$).

Compound **16**. ^{1}H NMR (300 MHz): δ 0.74 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.8 Hz), 0.89 (d, 3H, J=6.8 Hz), 1.31 (d, 3H, J=6.8 Hz), 2.11 (dsept, 1H, J=4.3, 6.8 Hz), 2.24 (dsept, 1H, J=10.2, 6.8 Hz), 2.61 (dd, 1H, J=6.6, 10.2 Hz), 3.20 (dd, 1H, J=8.1, 8.9 Hz), 3.64 (ddd, 1H, J=2.1, 4.3, 8.1 Hz), 3.84 (dd, 1H, J=2.1, 8.9 Hz), 5.36 (dd, 1H, J=5.7, 6.6 Hz), 5.56 (d, 1H, J=5.7 Hz), 7.31–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 15.0 (CH_3), 17.7 (CH_3), 21.3 (CH_3), 21.7 (CH_3), 25.4 (CH), 29.0 (CH), 48.2 (CH), 51.4 (CH), 58.6 (CH), 63.6 (CH_2), 79.0 (CH), 125.6 (CH), 128.3 (CH), 128.4 (CH), 134.9 (C), 153.4 (C═O), 169.0 (C═O), 175.7 (C═O). $[\alpha]_D^{25}$ = +109.4 (*c* 1.02, $CHCl_3$).

Compound **18**. Mp 181 °C. ^{1}H NMR (300 MHz): δ −0.01 (d, 3H, J=7.0 Hz) (the shielding indicates that the protons are held above the aromatic ring as confirmed by X-ray spectroscopy[28]), 0.67 (d, 3H, J=7.0 Hz), 0.84 (d, 3H, J=6.6 Hz), 1.30 (d, 3H, J=6.6 Hz), 1.64 (dsept, 1H, J=2.7, 7.0 Hz), 2.06 (dsept, 1H, J=10.6, 6.6 Hz), 2.64 (dd, 1H, J=6.6, 10.6 Hz), 4.03 (dd, 1H, J=2.7, 9.3 Hz), 4.10 (t, 1H, J=9.3 Hz), 4.25 (dt, 1H, J=9.3, 2.7 Hz), 5.39 (dd, 1H, J=5.6, 6.6 Hz), 5.63 (d, 1H, J=5.6 Hz), 7.24–7.37 (m, 3H), 7.38–7.45 (m, 2H). ^{13}C NMR (75 MHz): δ 13.6 (CH_3), 18.0 (CH_3), 21.2 (CH_3), 21.9 (CH_3), 25.8 (CH), 28.3 (CH), 47.3 (CH), 52.4 (CH), 58.5 (CH), 63.0 (CH_2), 79.3 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 134.4 (C), 153.5 (C═O), 169.1 (C═O), 175.4 (C═O). $[\alpha]_D^{25}$ = +54 (*c* 1.01, $CHCl_3$).

Compound **19**. ^{1}H NMR (300 MHz): δ 0.25 (d, 3H, J=7.0 Hz), 0.66 (d, 3H, J=7.0 Hz), 1.01 (d, 3H, J=7.0 Hz), 1.05 (d, 3H, J=7.0 Hz), 1.51–1.62 (m, 1H), 2.28 (dsept, 1H, J=5.1, 7.0 Hz), 3.56 (dd, 1H, J=5.1, 8.3 Hz), 4.08–4.25 (m, 3H), 4.67 (dd, 1H, J=8.3, 9.3 Hz), 5.96 (d, 1H, J=9.3 Hz), 7.23–7.34 (m, 5H). ^{13}C NMR (75 MHz): δ 14.3 (CH_3), 18.1 (CH_3), 19.0 (CH_3), 20.0 (CH_3), 28.3 (CH), 28.7 (CH), 47.3 (CH), 47.9 (CH), 59.0 (CH), 63.7 (CH_2), 79.6 (CH), 127.2 (CH), 128.6 (CH), 129.2 (CH), 135.8 (C), 153.8 (C═O), 169.0 (C═O), 176.8 (C═O). $[\alpha]_D^{25}$ = +156 (*c* 0.98, $CHCl_3$).

Compound **20**. ^{1}H NMR (300 MHz): δ 0.92 (d, 3H, J= 6.8 Hz), 0.96 (d, 3H, J=6.8 Hz), 1.11 (d, 3H, J=6.8 Hz), 1.15 (d, 3H, J=6.8 Hz), 2.00 (oct, 1H, J=6.8 Hz), 2.39 (dsept, 1H, J=3.6, 6.8 Hz), 3.16 (dd, 1H, J=5.1, 8.9 Hz), 4.22–4.34 (m, 2H), 4.44 (dd, 1H, J=8.9, 7.4 Hz), 4.44 (superimposed pseudo t, 1H, J=8.9 Hz), 5.84 (d, H, J= 7.4 Hz), 7.31–7.45 (m, 5H). ^{13}C NMR (75 MHz): δ 14.6 (CH_3), 18.1 (CH_3), 19.2 (CH_3), 22.2 (CH_3), 28.0 (CH), 29.7 (CH), 48.6 (CH), 53.0 (CH), 58.7 (CH), 63.6 (CH_2), 80.0 (CH), 125.9 (CH), 128.7 (CH), 128.8 (CH), 138.1 (C), 153.5 (C=O), 168.9 (C=O), 175.2 (C=O).

4.2.19. 3-(4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (15–20+23+ 24a–c). Treating **2** (97 mg, 0.38 mmol) according to method B led to a mixture of lactones that was separated by semi-preparative HPLC (CHIRALCEL OD (250×10 mm), hexane–ethanol (80:20), 4.5 mL/min, UV detection at 220 nm). The separation led, by order of elution to: a first fraction containing **15** and **24a–c** in a 21:79 ratio (27.6 mg); **17** (27 mg); **16** and **23** in a 52:48 ratio (11.7 mg); **18** and **19** in a 90:10 ratio (8 mg); **18** and **19** in a 25:75 ratio (6.1 mg); **19** (23.3 mg), **20** (4.7 mg). The intermediate chromatographic fractions (6.3 mg) remixed together contained **24a–c** (65%), **18** (9%), **19** (16%), **20** (10%). A second separation of the very first fraction allowed to analyze the NMR spectra of **24a–c** (CHIRALCEL OD (250×10 mm), hexane–ethanol (95:5), 4.5 mL/min, UV detection at 220 nm, **24a** (5.79 min), **24b** (6.83 min), **24c** (10.48 min)).

Compound **23**. ^{1}H NMR (300 MHz): δ 0.55 (d, 3H, J= 7.0 Hz), 0.87 (d, 3H, J=7.0 Hz), 0.98 (d, 3H, J=7.0 Hz), 1.06 (d, 3H, J=7.0 Hz), 2.20–2.40 (m, 2H), 3.31 (dd, 1H, J=10.9, 4.2 Hz), 4.12 (dd, 1H, J=9.3, 2.9 Hz), 4.21 (pseudot, 1H, J=9.1 Hz), 4.48 (pseudo dt, 1H, J=8.3, 3.2 Hz), 5.18 (dd, 1H J=10.9, 9.4 Hz), 5.29 (d, 1H, J= 9.4 Hz), 7.32–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 14.0 (CH_3), 17.9 (CH_3), 18.3 (CH_3), 20.2 (CH_3), 27.6 (CH), 28.3 (CH), 30.9 (CH), 47.8 (CH), 53.0 (CH), 62.9 (CH_2), 83.0 (CH), 126.6 (CH), 128.8 (CH), 129.5 (CH), 135.9 (C), 152.9 (C=O), 171.8 (C=O), 175.2 (C=O).

4.2.20. Ethyl 4-*i*-propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylate (24a–c). *Compound* **24a**. ^{1}H NMR (300 MHz): δ 1.00 (d, 3H, J=6.8 Hz), 1.02 (d, 3H, J= 7.2 Hz), 1.25 (t, 3H, J=7.2 Hz), 2.34 (m, 1H), 3.10 (dd, 1H, J=10.8, 8.3 Hz), 3.17 (dd, 1H, J=10.8, 4.2 Hz), 4.22 (m, 2H), 5.43 (d, 1H, J=8.3 Hz), 7.28–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 14.9 (CH_3), 19.1 (CH_3), 20.6 (CH_3), 28.6 (CH), 52.0 (CH), 52.3 (CH), 62.5 (CH_2), 81.3 (CH), 126.3 (CH), 129.6 (CH), 129.7 (CH), 138.8 (C), 172.3 (C=O), 176.1 (C=O).

Compound **24b**. ^{1}H NMR (300 MHz): δ 0.91 (t, 3H, J= 7.2 Hz), 1.04 (d, 6H, J=7.0 Hz), 2.30 (m, 1H), 3.21 (dd, 1H, J=7.8, 5.1 Hz), 3.59 (pseudot, 1H, J=8.7 Hz), 3.71 (ABX_3 pattern, 2H), 5.68 (d, 1H, J=9.1 Hz), 7.19–7.42 (m, 5H). ^{13}C NMR (75 MHz): δ 13.6 (CH_3), 18.9 (CH_3), 20.0 (CH_3), 28.4 (CH), 47.5 (CH), 48.7 (CH), 61.2 (CH_2), 79.2 (CH), 125.9 (CH), 128.4 (CH), 128.8 (CH), 135.9 (C), 169.6 (C=O), 176.9 (C=O).

Compound **24c**. ^{1}H NMR (300 MHz): δ 0.85 (t, 3H, J= 7.2 Hz), 0.93 (d, 3H, J=6.8 Hz), 1.31 (d, 3H, J=6.6 Hz), 2.15 (m, 1H), 2.58 (dd, 1H, J=10.2, 6.8 Hz), 3.61 (dd, 1H, J=6.8, 5.7 Hz), 3.75 (ABX_3 pattern, 2H), 5.53 (d, 1H, J= 5.7 Hz), 7.29–7.37 (m, 5H). ^{13}C NMR (75 MHz): δ 13.6 (CH_3), 21.3 (CH_3), 21.7 (CH_3), 26.2 (CH), 51.6 (CH), 52.0 (CH), 60.8 (CH_2), 78.7 (CH), 125.4 (CH), 128.3 (CH), 128.4 (CH), 135.0 (C), carbonyl quaternary carbons were not detected under the registration conditions. HRMS calcd for $C_{16}H_{21}O_4$ [MH^+]: 277.1440; found: 277.1436.

4.2.21. (2*R*-3*S*-4*S*) 4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (21). H_2O_2 (30%) (117 μL, 1.14 mmol) and $LiOH.H_2O$ (18 mg, 0.43 mmol) were added at 0 °C to a solution of **15–20** obtained from **1** (86 mg, 0.24 mmol) in THF (2 mL) and H_2O (0.5 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of $Na_2S_2O_3$ (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×3). The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give **21** as a white solid (42 mg, 0.169 mmol, 70%).

^{1}H NMR (300 MHz), major isomer: δ 1.03 (d, 3H, J= 6.8 Hz), 2.26 (dsept, 1H, J=5.3, 6.8 Hz), 3.12 (dd, 1H, J=5.3, 8.3 Hz), 3.61 (dd, 1H, J=8.3, 8.9 Hz), 5.70 (d, 1H, J=8.9 Hz), 7.19–7.40 (m, 5H), 8.24 (br s, 1H). ^{13}C NMR (75 MHz): δ 19.4 (CH_3), 20.4 (CH_3), 28.8 (CH), 48.2 (CH), 49.1 (CH), 79.5 (CH), 126.3 (CH), 128.8 (CH), 128.9 (CH), 136.1 (C), 173.7 (C=O), 177.5 (C=O). HRMS calcd for $C_{14}H_{15}O_4$ [$(M-H)^-$]: 247.0970; found: 247.0977.

4.2.22. (2*R*-3*S*-4*S*) 4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (22). A mixture of **21** (42 mg, 0.17 mmol, 1 equiv), benzyl bromide (39 μL, 0.33 mmol, 2 equiv) and DBU (38 μL, 0.25 mmol, 1.5 equiv) in benzene (1 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduce pressure. The residue was purified on silica gel (10% EtOAc–pentane) to give 24 mg (42%) of ester **22** as a 90:6:4 ratio of diastereomers. The enantiomeric excess of the major isomer (80%) was determined from chiral HPLC (CHIRALCEL OD-H (250×4.6 mm), hexane–2-PrOH (90:10), 1 mL/min, 25 °C, UV and circular dichroïsm detection at 254 nm, Rt(−)=8.16 min, Rt(+)=9.76, k(−)=1.64, k(+)=2.16, α=1.32 and Rs=2.49).

^{1}H NMR (300 MHz): δ 1.02 (d, 3H, J=7.0 Hz), 1.03 (d, 3H, J=7.0 Hz), 2.29 (dsept, 1H, J=5.1, 7.0 Hz), 3.23 (dd, 1H, J=5.1, 8.1 Hz), 3.65 (dd, 1H, J=8.1, 8.9 Hz), 4.65 (AB pattern, 2H, J=12.1 Hz, $\Delta\nu$=53.4), 5.68 (d, 1H, J= 8.9 Hz), 7.05–7.11 (m, 2H), 7.15–7.23 (m, 2H), 7.27–7.35 (m, 6H). ^{13}C NMR (75 MHz): δ 18.8 (CH_3), 20.0 (CH_3), 28.3 (CH), 47.5 (CH), 48.6 (CH), 67.2 (CH_2), 79.0 (CH), 125.8 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 134.6 (C), 135.7 (C), 169.5 (C=O), 176.7 (C=O). HRMS calcd for $C_{21}H_{23}O_4$ [MH^+]: 339.1596; found: 339.1594.

4.2.23. 3-(4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-isopropyl-oxazolidin-2-one (25). Treating **10** (200 mg, 0.94 mmol) according to method B led to 215 mg of a mixture containing lactones **25** (4 stereoisomers), together with lactones bearing a carbethoxy group (resulting from the transfer of the isopropyl group to the carbon α to the carbonyl bearing the auxiliary), in a 70:30 ratio (rough estimate based on the NMR signals of the protons α to the phenyl group), isolated after purification by FC (5–20%, EtOAc–pentane).

^{1}H NMR (300 MHz) of the major isomer: (**25**): ^{1}H NMR (300 MHz): δ 1.03 (d, 3H, J=7.0 Hz), 1.07 (d, 3H, J=6.8 Hz), 2.31 (m, 1H), 3.12 (ddd, 1H, J=10.9, 9.2, 6.6 Hz), 3.48 (dd, 1H, J=6.8, 5.7 Hz), 3.67–3.79 (m, 1H), 3.98 (dt, 1H, J=7.2, 9.2 Hz), 4.23 (dt, 1H, J=6.6, 9.2 Hz), 4.88 (dd, 1H, J=9.2, 6.8 Hz), 5.83 (d, 1H, J=9.2 Hz), 7.17–7.25 (m, 2H), 7.30–7.37 (m, 3H). ^{13}C NMR (75 MHz): δ 19.0 (CH_3), 20.1 (CH_3), 28.8 (CH), 42.4 (CH_2), 47.2 (CH), 47.3 (CH), 62.1 (CH2), 79.3 (CH), 126.2 (CH), 128.4 (CH), 129.0 (CH), 135.9 (C), 153.1 (C=O), 169.5 (C=O), 177.0 (C=O). HRMS calcd for C17H19NO5Na [MNa+]: 340.1161; found: 340.1157.

4.2.24. (2*R-3*S**-4*S**) 4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (*rac*-21).** H_2O_2 (30%) (266 μL, 2.60 mmol) and LiOH.H_2O (41 mg, 0.98 mmol) were added at 0 °C to a solution of the preceding mixture of lactones (206 mg, 0.65 mmol) in THF (4.3 mL) and H_2O (1.1 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of NaS_2O_3 (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×3). The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give racemic **21** as a white solid (131 mg).

4.2.25. (2*R-3*S**-4*S**)4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (*rac*-22).** A mixture of *rac*-**21** (131 mg, 0.53 mmol, 1 equiv), benzyl bromide (122 μL, 1.03 mmol, 2 equiv) and DBU (118 μL, 0.79 mmol, 1.5 equiv) in benzene (1.8 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduce pressure. The residue was purified on silica gel (10% EtOAc–pentane) to give racemic **22** (105 mg, 0.31 mmol, 58%) of as a 90:6:4 mixture of diastereomers. The spectral data were identical to those already described for the optically active compound.

4.2.26. 2-*i*-Propyl-1,4-bis-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-butane-1,4-dione (13f,g). Zn(*i*-Pr)$_2$ (266 μL, 0.266 mmol, 2 equiv) was added to a solution of **1** (45 mg, 0.133 mmol) in dichloromethane (650 μL). The reaction was stirred at −10 °C while air was injected in the solution. After completion the reaction was quenched with aqueous NH_4Cl, and the aqueous phase was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated. The crude product was purified by semi-preparative chromatography (CHIRALCEL OD (250×10 mm), hexane–ethanol (90:10), 4.5 mL/min, UV detection at 220 nm). This led, by order of elution, to **13g** (8.21 min, 3.9 mg, 8%), **13h** (9.12 min, 14.1 mg, 28%), **13f** (10.46 min, 11.7 mg, 23%).

Compound **13f**. Mp 144–145 °C. ^{1}H NMR (300 MHz): δ 0.86 (d, 3H, J=6.8 Hz), 0.87 (d, 3H, J=7.0 Hz), 0.91 (d, 3H, J=7.0 Hz), 0.95 (d, 6H, J=7.0 Hz), 1.01 (d, 3H, J=6.8 Hz), 1.99 (pseudo oct, 1H, J=6.8 Hz), 2.23 (dsept, 1H, J=4.3, 6.8 Hz), 2.37 (dsept, 1H, J=3.8, 7.0 Hz), 3.13 (dd, 1H, J=3.0, 18.3 Hz), 3.46 (dd, 1H, J=11.9, 18.3 Hz), 4.16–4.31 (m, 5H), 4.35–4.45 (m, 2H). ^{13}C NMR (75 MHz): δ 14.5 (CH_3), 15.1 (CH_3), 17.8 (CH_3), 18.0 (CH_3), 18.5 (CH_3), 20.6 (CH_3), 28.1 (CH), 28.7 (CH), 29.8 (CH), 34.9 (CH_2), 43.8 (CH), 58.4 (CH), 58.9 (CH), 62.9 (CH_2), 63.9 (CH_2), 153.8 (C=O), 154.1 (C=O), 172.3 (C=O), 175.4 (C=O). HRMS calcd for $C_{19}H_{30}N_2O_6Na$ [MNa^+]: 405.2002; found: 405.2003.

Compound **13g**. ^{1}H NMR (300 MHz): δ 0.86 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=7.0 Hz), 0.89 (d, 3H, J=7.0 Hz), 0.92 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 1.08 (d, 3H, J=7.0 Hz), 2.09–2.20 (m, 1H), 2.25–2.40 (m, 2H), 3.08 (dd, 1H, J=3.0, 18.5 Hz), 3.42 (dd, 1H, J=11.7, 18.7 Hz), 4.12–4.36 (m, 6H), 4.42–4.50 (m, 1H). ^{13}C NMR (75 MHz): δ 14.5 (CH_3), 14.7 (CH_3), 18.0 (2×CH_3), 18.1 (CH_3), 20.8 (CH_3), 28.3 (CH), 28.7 (CH), 29.9 (CH), 33.7 (CH_2), 43.7 (CH), 58.4 (CH), 58.5 (CH), 63.2 (CH_2), 63.4 (CH_2), 153.9 (C=O), 154.0 (C=O), 172.3 (C=O), 175.5 (C=O). HRMS calcd for $C_{19}H_{31}N_2O_6$ [MH^+]: 383.2182; found: 383.2196.

4.2.27. (*S*)-3-((*S*)-1-Hydroxymethyl-2-methyl-propyl)-5-*i*-propyl-7-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-5*H*-[1,3]-oxazepine-2,4-dione (13h). ^{1}H NMR (300 MHz): δ 0.82 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=6.5 Hz), 1.01 (d, 3H, J=6.8 Hz), 1.02 (d, 3H, J=6.8 Hz), 2.29–2.51 (m, 3H), 3.34 (pseudo t, 1H, J=5.1 Hz), 3.75–3.88 (m, 2H), 4.03 (m, 1H), 4.28 (dd, 1H, J=8.9, 2.5 Hz), 4.39 (pseudo t, 1H, J=8.5 Hz), 4.49 (ddd, 1H, J=7.9, 3.8, 2.5 Hz), 5.45 (br s, 1H). ^{13}C NMR (75 MHz): δ 14.8 (CH_3), 17.7 (CH_3), 17.9 (CH_3), 19.6 (CH_3), 19.8 (CH_3), 20.1 (CH_3), 26.1 (CH), 27.8 (CH), 28.7 (CH), 45.0 (=CH), 50.53 (CH), 59.3 (CH), 61.2 (CH), 61.4 (CH_2), 63.8 (CH_2), 153.9 (C=O), 167.9 (C=), 173.6 (C=O), 178.7 (C=O). HRMS calcd for $C_{19}H_{31}N_2O_6$ [MH^+]: 383.2182; found: 383.2181.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.042.

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17. The cleavage of a pure sample of **5**, later obtained from substrate **2**, confirmed that **5** did not lead to acid **8**, but to a mixture of products containing another amide-alcohol **12b**.
18. The reaction conducted with 10 equivalents of *t*-BuI gave also a clear evidence for the competition between the addition of *t*-Bu$^{\cdot}$ and Et$^{\cdot}$.
19. The diastereomeric ratio was roughly estimated by ^{1}H NMR from the integration of the overlapping AB parts of the ABX systems in each diastereomer.
20. The tridimensional structure of **5** clearly reveals that both faces of the exocyclic carbonyl group are hindered and none can be attacked by the nucleophile.
21. All seven lactones exhibited characteristic doublets for the proton α to the phenyl group at: 6.03 ppm (J=9.1 Hz), 16%; 5.86 ppm (J=7.5 Hz), 16%; 5.84 ppm (J=7.4 Hz), 24%; 5.83 ppm (J=8.9 Hz), 5%; 5.69 ppm (J=5.7 Hz), 28%; 5.63 ppm (J=5.9 Hz), 5%; 5.44 ppm (J=9.1 Hz). The relative ratio were grossly estimated from the ^{1}H NMR spectrum of the mixture after elimination of unreacted benzaldehyde by liquid chromatography.
22. The racemic lactone **25** was prepared via the addition of *i*-Pr$^{\cdot}$ to **10**. The addition of Zn(*i*-Pr)$_2$ to **10** in the presence of benzaldehyde led to a mixture of regioisomers (26% of isomeric lactones resulted from the attack of *i*-Pr$^{\cdot}$ at the vinylic carbon α to the carbonyl bearing the auxiliary). The saponification led to the crude acid in 81% yield. The corresponding benzylic ester was isolated in 59% overall yield as a mixture of 3 quantifiable diastereomers (dr=90:6:4). The major isomer showed ^{1}H NMR signals very close to those of **9** (cf. Table 1).
23. It must be noted that in the NMR spectra of **13h** (and **13c**) and to a lesser extent the spectrum of **13d**, the doublet corresponding to the vinylic proton and the signal of the corresponding carbon are broadened. This phenomenon is probably related to the rate of rotation around the C–N bond. Lowering the temperature at -10 °C afforded well resolved spectra and allowed to unambiguously establish the correlation between the protons and the corresponding carbons by HMQC.
24. The relative ratio of **15**–**20** and **23** was determined both from the ^{1}H NMR spectrum of the mixture and from the chromatographic separation: **15** (6.5%), **17** (30%), **16** (7%),

23 (6.5%), **18** (11%), **19** (33%), **20** (6%). The characteristic ^{1}H and ^{13}C NMR signals of **23** could be determined from an isolated mixture of **23** and **16**. **23** might have a *trans*, *trans* relative configuration according to the coupling constants ($J_{23}=9.4$, $J_{34}=10.9$ Hz) very similar to those reported by Sibi in Ref. 9 for nephrosteranic acid ($J_{23}=9.4$ Hz, $J_{34}=11.3$ Hz) and roccelaric acid ($J_{23}=9.4$ Hz, $J_{34}=11.4$ Hz).

25. The ^{1}H NMR spectrum of enriched chromatographic fractions clearly show the characteristic signals of the ethoxycarbonyl groups and the absence of the oxazolidinone protons (cf. Section 4.2.20).
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27. Supporting Information content: Chiral HPLC analyses of racemic and optically pure lactones **9** and **22** (S2–S5), of lactones **15**, **16**, **17**, **18**, **19** and **20** (S6), detailed chiral HPLC conditions (S7). Significant NOESY correlations for lactones **9** and **15**–**20** (S8).
28. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 257463 for lactone **3**, 257464 for lactone **4**, 257465 for lactone **5**, and 257466 for lactone **18**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].