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Synthesis and biological evaluation of new cross-conjugated dienone marine prostanoid analogues †

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The synthesis of a series of brominated cross-conjugated dienones, marine prostanoid analogues, was considered using two cyclopentannelation processes, from enamine (by a domino 3-aza Claisen/Mannich reaction) and from dioxolane ester alkylation followed by intramolecular Wittig reaction. All the compounds synthesized featured the same cross-conjugated dienone system, with a vicinal *syn* or *anti* diol on the ω-chain. The replacement of the ω-side-chain of the natural prostanoids with a 1-hydroxyphenyl-butyl moiety gave new prostanoids (**32**–**34**) with good cytotoxicities. In a second series of products, the possibility of a shorter α-side-chain bearing a simple phenyl ester was investigated. The results indicated a dramatic increase in the cytotoxicity (**39**, **40**, **43**, **44**). Finally, in a third series, the ω-1-hydroxyphenyl-butyl was replaced by a 1-hydroxymethyloxybenzyl chain. These simpler compounds (**45**, **46**, **47**, **48**, **60**) are still highly cytotoxic, in the medium range of 60 nM, close to the value of natural punaglandins.

Introduction

Marine prostaglandins[1] such as clavulone II,[2] naturally halogenated halovulone[3] and punaglandin IV[4] isolated from corals are characterised by an alkylidene cyclopentenone structure. Their cytotoxic and antitumour activities[5] have been demonstrated, both *in vitro* and *in vivo*. Although many syntheses of naturally occurring alkylidene cyclopentenone prostaglandins have been described,[6] only limited structure–activity relationships have been reported in the literature concerning simplified analogues[7] in spite of the potential therapeutic opportunities presented by these compounds.[8] In contrast, considerable progress has been made towards understanding both the mechanism of action and the diverse biological activities of mammalian-derived antitumour Δ^7-PGA$_1$- and Δ^{12}-PGJ$_2$-prostaglandins.[9] The latter exert potent action *via* direct interaction with putative nuclear proteins, resulting in cell arrest and growth inhibition, cell differentiation,[10] induction of cellular defence mechanisms against viral infection,[11] modulation of gene and protein functions.[12] In particular, it has been recently shown that their cytotoxic activities are associated with induction of p21,[13] induction of heat-shock protein,[14] selective inhibition of cyclin D1 gene transcription in breast cancer cell lines,[15] and inhibition of NFkB.[16] More recently, it has been reported that prostaglandins which promote neurite outgrowth could be designed (Fig. 1).[17]

As part of ongoing studies on the synthesis of cyclopentenone prostaglandin analogues,[18] we were interested in exploring the biological activities of simplified analogues of antitumour marine prostaglandins, punaglandins and clavulones. For this task, we focused on the synthesis of chiral 2-halogeno-4,5-dihydroxy cyclopentenone analogues with modified α and ω chains. The presence of a diol functionality on the ω side-chain should enhance the chemical stability of the cyclopentenone ring by avoiding a possible isomerisation of a stereogenic centre bearing a tertiary alcohol[19] and, at the same time, increased water solubility, which appeared to be a important problem in the development of related compounds.[20]

Chemistry

The synthesis of the targeted cross-conjugated dienone **1** bearing a 5-phenylpentanol or a 2-benzyloxy-ethanol Rω side-chain, could be envisioned by alkylation of the 4-spiro-1,3-dioxolanyl-2-cyclopentenone **2** with various Rα aldehydes. As regards the synthesis of cyclopentenone **2**, we envisioned two possible annelation strategies: the first one from enamine **3** by an intramolecular Wittig reaction as we already reported.[18] Compound **3** could be obtained from chiral aldehydes **10** or **15** (Scheme 1) and compound **4** from chiral ester **51**, all of them derived from the natural pool of chirality.

† Electronic supplementary information (ESI) available: ^{1}H NMR, COSY and NOESY spectra. See http://www.rsc.org/suppdata/ob/b4/b404016c/

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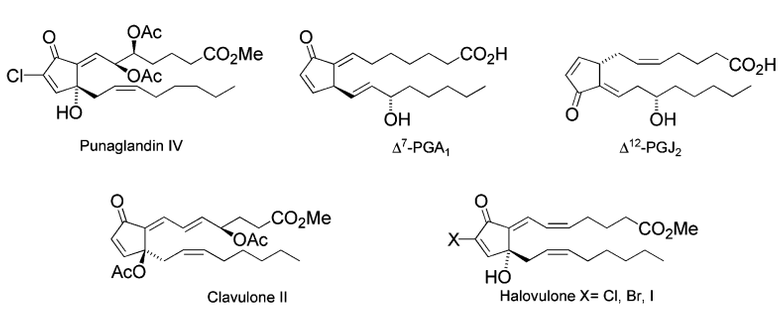

Fig. 1 Cyclopentenone prostaglandins (PGs).

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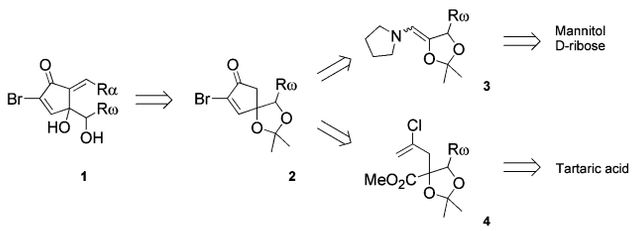
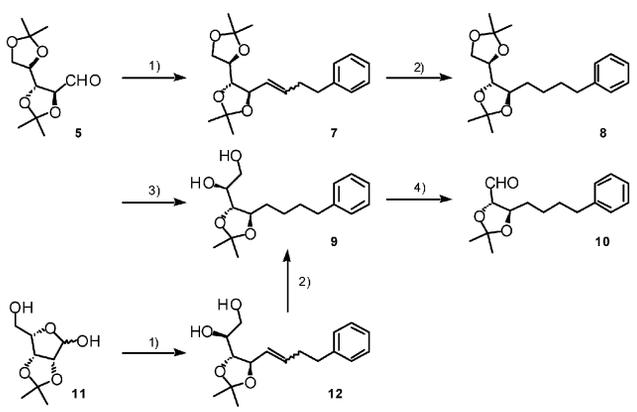


Scheme 1 Retrosynthetic analysis.

Synthesis of aldehydes 10 and 15

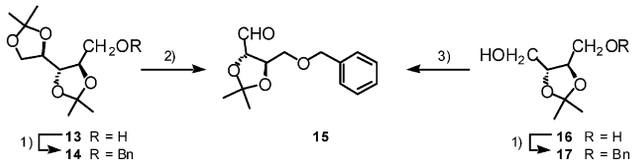
The aldehyde **10** was synthesised in 34% yield from aldehyde **5**, readily accessible in 2 steps from D-mannitol.[21] Thus, a Wittig reaction, at room temperature, with the ylide derived from triphenylphosphine 3-phenylpropyl bromide **6**, was realized giving the alkene **7** as an *E*/*Z* (1/9) mixture (66%). After catalytic hydrogenation of the double bond (10% Pd/C in EtOAc) the bis-dioxolanyl compound **8** was obtained (60% from **5**). Selective acidic hydrolysis of the terminal acetal (AcOH–H_2O, 20 °C, 3/1) gave the diol **9** (68%) and recovered starting material **8** (32%). Oxidative cleavage of the glycol with $NaIO_4$ furnished the aldehyde **10** (82%), but a more direct route to **10** was found from 2,3-*O*-isopropylidene α-D-ribose **11**.[22] The synthetic route was based on the epimerisation of the C-2 atom of the 2,3-dioxolane-ribose,[23] which occurred using harsh basic conditions (50 °C in DMSO) necessary to complete the Wittig reaction with the ylide derived from **6** (Scheme 2).[24]



Scheme 2 *Reagents and conditions*: 1) $Br^-Ph_3P^+(CH_2)_3C_6H_5$ **6**, NaH, DMSO, 20 °C; 2) H_2, Pd/C, AcOEt; 3) AcOH–H_2O, 20 °C, 3 h; 4) $NaIO_4$, MeOH–H_2, 20 °C, 1 h.

The Wittig product **12** was obtained as a *E*/*Z* mixture, which was hydrogenated (H_2, C/Pd in EtOAc) giving the diol **9** (97%). The latter compound possessed the characteristic NMR value of $\Delta\delta^1$H (0.02 ppm) and $\Delta\delta^{13}$C (0.31 ppm) for the acetal methyl group of *threo* configuration in accordance with Allevi's observations.[25] The diol **9** obtained was subsequently oxidized with $NaIO_4$ to furnish the aldehyde **10** (82%).

For its part, the benzyloxymethyl aldehyde **15** was readily prepared following two routes. The first started from the 2,3;4,5-di-*O*-isopropylidene D-arabinitol **13**[26] easily synthesized by reduction of the aldehyde **5**. Benzylation of **13** (NaH, BnCl, DMF) gave compound **14** (59%) and recovered alcohol **13** (24%). Selective cleavage of the terminal acetal was accomplished by treatment with periodic acid in Et_2O at 0 °C,[21] furnishing the aldehyde **15** in moderate yield (32%), along with the unreacted starting material **14** (52%). A shorter way to this aldehyde was followed from the readily accessible *erythro*-2,3-dioxolanyl butanetriol **16**, obtained in 2 steps from tartaric acid.[27] Selective benzylation of **16** furnished the alcohol **17** (88%). The aldehyde **14** was obtained after Swern oxidation[28] (Scheme 3).



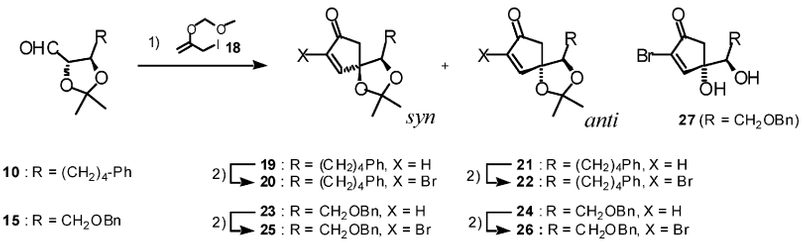
Scheme 3 *Reagents and conditions*: 1) NaH, BnCl, DMF, 0 °C, 1 h; 2) H_5IO_6, Et_2O, 0 °C, 4 h; 3) NaH, BnBr, DMF, 0 °C, 1 h; 3) $(CICO)_2$, DMSO, −78 °C, Et_3N.

Synthesis of (*syn* 4*R*,5*R*), (*anti* 4*R*, 5*S*), (*syn* 4*R*, 5*R*) and (*anti*4*R*, 5*S*) bromo-cyclopentenones 20,22,25 and 26. The synthesis of a series of cyclopentenones was readily achieved from enamines derived from aldehydes using a domino 3-aza-Claisen/Mannich reaction.[18d] Thus, treatment of aldehyde **10** with pyrrolidine in CH_3CN/toluene, at 50 °C in the presence of molecular sieves, furnished an *E*/*Z* mixture of enamine intermediates immediately alkylated with 2-methoxymethyloxy-3-iodopropene at reflux for 19 h to give the cyclopentenone diastereoisomers **19** and **21** (37%) in a 1/1 mixture. After treatment with Br_2 in CH_2Cl_2, the bromocyclopentenones **20** and **22** were obtained (41%). It is noteworthy that, owing to the smaller reactivity of diastereoisomer **19** during the bromination step, the pure recovered cyclopentenone **19** could be isolated (30%). In the same manner, cyclopentenones **23** + **24** were obtained (36%) from aldehyde **15** and, after bromination, the pure unreacted diastereoisomer (4*R*,5*R*) **23** was isolated (8.5%) along with the bromo derivatives **25** + **26** (44%). Moreover, in this case, the (4*S*,5*R*) isomer **26** was slightly unstable and partially decomposed *in situ* into diol **27** (20%) (Scheme 4).

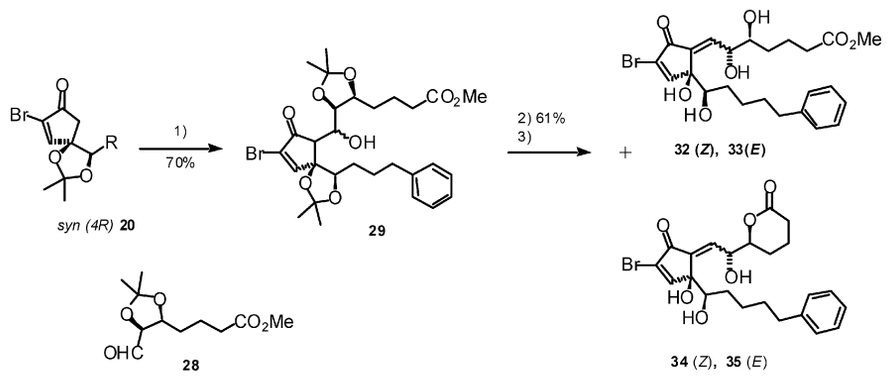
Synthesis of alkylidene cyclopentenone. Starting from the *syn*-(4*R*,5*R*) 2-bromo-4-alkyl-4-hydroxy-2-cyclopentenone **20** bearing the modified hydroxylated ω side-chain, we introduced the α side-chain. We first chose the natural α side-chain, as present in the marine punaglandins. Thus, compound **20** was condensed, *via* its lithium enolate, with the aldehyde **28** easily prepared in 4 steps from 2-deoxy-glucose following the Corey procedure.[29] An inseparable mixture of aldol diastereoisomers products **29** was obtained (41.6%) along with the starting material **20** (19%). Compound **29** was further transformed into alkylidene cyclopentenones by elimination of the alcohol. This proceeded upon treatment with Ac_2O and 4-DMAP in pyridine at 60 °C, furnishing the two diastereoisomers (*Z*) **30** and (*E*) **31** easily separated by chromatography. Then, hydrolysis of the dioxolane rings with TFA in THF at 20 °C for 1 h afforded the tetraols **32** (16.5%) and **33** (19%) along with the corresponding cyclised δ-lactone products (*Z*) **34** (56%) and (*E*) **35** (58%), respectively (Scheme 5). After neutralisation, treatment of lactones **34** and **35** with K_2CO_3 in MeOH afforded esters **32** and **33**, respectively (100%).

In order to make new and simpler analogues, we introduced a shorter aromatic α-side-chain bearing a terminal methyl ester function, selecting 4-formyl methylbenzoate for aldolisation. In this way, when the *syn*-(4*R*,5*R*) cyclopentenone **20** was condensed with aldehyde **36** using the same conditions as previously described, the alkylidene cyclopentenones (*Z*) **37** and (*E*) **38**, difficult to separate (10/1 ratio, 60%), were obtained. Fortunately, after hydrolysis of the acetal ring, the diols (*Z*) **39** (60%) and (*E*) **40** (23%) were easily isolated and characterised. The same sequence of reaction from the *anti* diol (4*R*,5*S*) **22** gave a mixture of diastereoisomers (*Z*) **41** + (*E*) **42**, and the diols (*Z*) **43** and (*E*) **44** after hydrolysis of the acetal ring (Scheme 6).

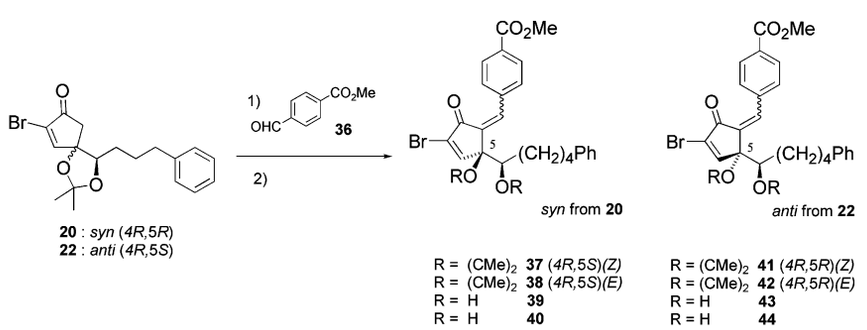
In the case of benzyloxymethyl cyclopentenones **25** and **26**, we directly adopted the solution of purifying at the ultimate alkylidene cyclopentenone step. By this procedure a series of compounds was obtained after column chromatography: (*Z*, 2*S*) **45** (30%), (*E*, 2*S*) **46** (17%), (*Z*, 2*R*) **47** (26%), (*E*, 2*R*) **48** (12%) (Scheme 7).



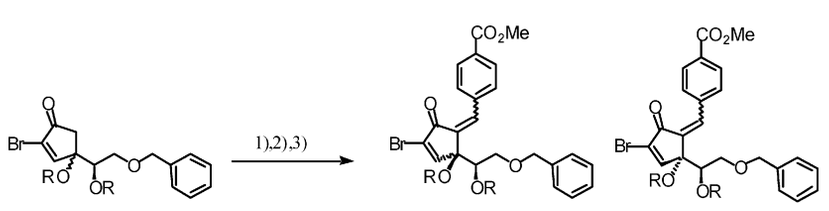
Scheme 4 *Reagents and conditions*: 1) pyrrolidine, CH_3CN–toluene, then **18**; 2) Br_2, CH_2Cl_2, NEt_3.



Scheme 5 *Reagents and conditions*: 1) LDA, THF, −78 °C, 0.5 h, **28**; 2) Ac_2O, 4,4-DMAP, pyridine, 60 °C, 4 h; 3) TFA, THF, 20 °C, 1 h.



Scheme 6 *Reagents and conditions*: 1) LDA, THF, −78 °C, 0.5 h; 2) Ac_2O, 4,4-DMAP, pyridine, 60 °C, 4 h; 3) TFA, THF, 20 °C, 1 h.



Scheme 7 *Reagents and conditions*: 1) LDA, THF, −78 °C, 0.5 h; 2) Ac_2O, 4,4-DMAP, pyridine, 60 °C, 4 h; 3) TFA, THF, 20 °C, 1 h.

The results of preliminary biological testing concerning these compounds (Fig. 2) were sufficiently good to prompt us to develop a more efficient route to the synthesis of alkylidene cyclopentenone having a *syn* diol stereochemistry. For this task, we adopted the synthesis of chiral cyclopentenone involving diastereoselective alkylation of dioxolane ester, followed by an annelation using an intramolecular Wittig reaction, recently reported by our group.[18d]

Stereoselective synthesis of the alkylidene cyclopentenone 60 by C-alkylation of the dioxolane ester followed by intramolecular Wittig reaction (Scheme 8). Starting from *erythro*-2,3-dioxolanyl butanetriol **16** we prepared the 4-fluorobenzyl ether derivative **49**.[30] After Swern oxidation, the aldehyde **50** was obtained (85%), and transformed into the methyl ester **51** using the Lichtenthaler[31] procedure (Br_2, MeOH/H_2O, $NaHCO_3$, 97%). Then, treatment of this ester with KHMDS (1.1 eq) in THF at −78 °C, followed by addition of 2-chloro-3-iodo-propene[32] afforded by expected contrasteric alkylation[18b] the major alkylated ester product (4*S*) **52**, along with its diastereoisomer (4*R*) **53** as an inseparable mixture (87%, ratio 8/2). However, after reduction of the ester function with $LiAlH_4$ in THF at 20 °C, the two diastereoisomers: *major* **54** (4*R*) and *minor* **55** (4*S*), were easily separated. Oxidation of **54** by PCC afforded the aldehyde **56** (94%). The chloroallyl chain was transformed into the uncharacterised bromomethyl ketone intermediately by action of NBS with a catalytic amount of HBr in CH_3CN. Then, the crude α-bromoketone was treated with triphenylphosphine in refluxing dichloromethane to perform an intramolecular Wittig reaction, furnishing the cyclopentenone **57**. The stereochemistry of the quaternary centre formed was unambiguously determined from ^1H NMR NOESY experiments matching with computer calculated energy minimisation (MM2 in Chem3D) with both diastereoisomers. Transformation into the targeted cyclopentenone was performed by careful bromination of cyclopentenone with Br_2 in CH_2Cl_2 (73%), followed by aldol condensation at −78 °C between the lithium enolate of ketone **58** and aldehyde **36**. Then the

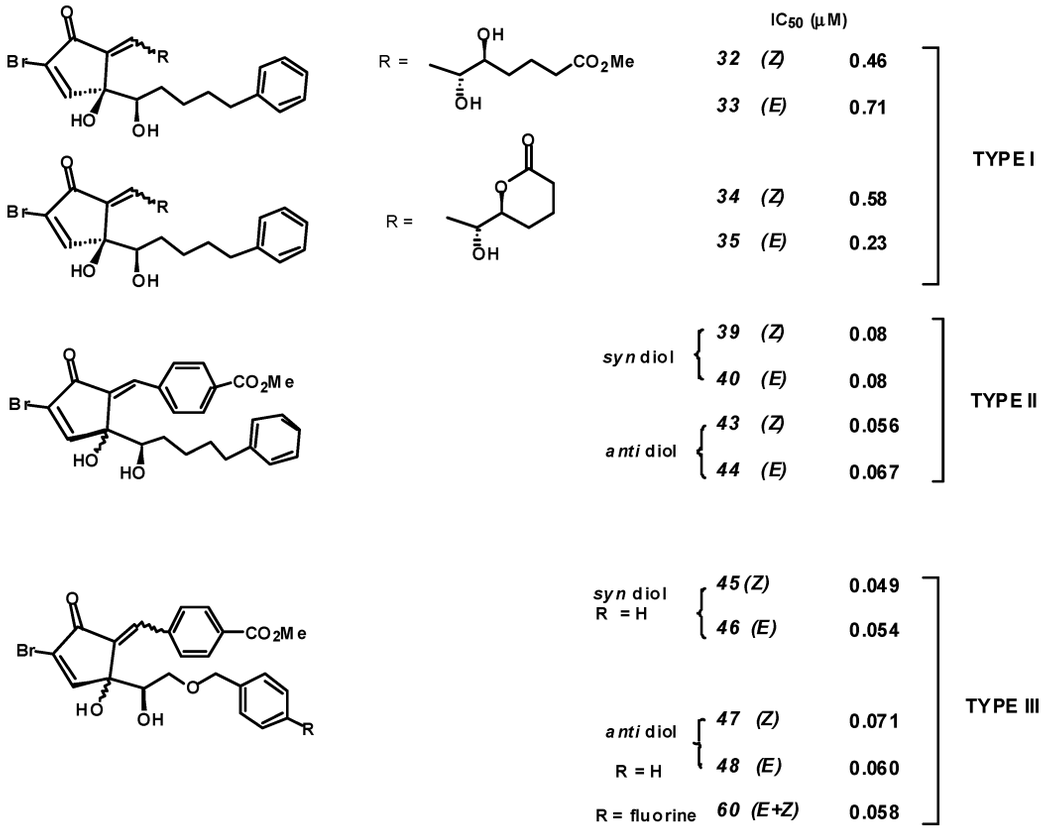
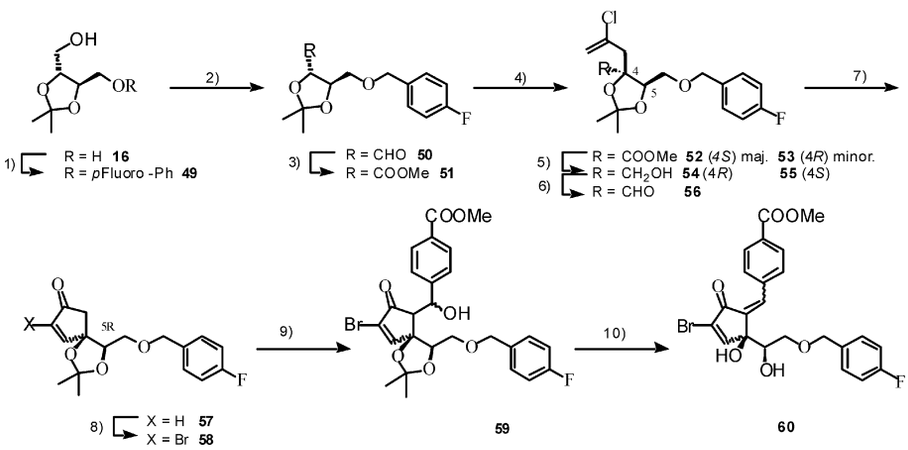


Fig. 2 Cytotoxicity of cyclopentenone prostaglandins (PGs) on B16 melanoma cells lines and L1210 for compound **60**.



Scheme 8 *Reagents and conditions*: 1) *p*-fluorobenzyl bromide, DMF, NaH, *n*-Bu_4NI, r.t.; 2) Cl_2CO_2, DMSO, NEt_3, CH_2Cl_2, −78 °C (85%); 3) Br_2, $MeOH/H_2O$, $NaHCO_3$ (97%); 4) KHMDS (1.1 eq.), THF, −78 °C, 0.5 h then CH_2=C(Cl)CH_2I, (87%), diaster. ratio 4/1; 5) $LiAlH_4$ in THF, r.t. (82%); 6) PCC, CH_2Cl_2, r.t. (94%); 7) NBS, HBr cat., CH_3CN/H_2O, 4/1, r.t., then Ph_3P, dioxane, propylene oxide; 8) Br_2, CH_2Cl_2 then Et_3N; 9) LDA, THF, −78 °C then methyl-4-formyl-benzoate **36**; 10) (a) Ac_2O, pyridine, r.t., (b) TFA, CH_2Cl_2.

same protocol as previously described (*vide supra*), involving elimination of the hydroxyl and hydrolysis of the acetal ring, furnished the cyclopentenone **60** with high diastereoselectivity.

Conclusion

A new series of simplified analogues of natural cyclopentadienone prostaglandins have been prepared.[33] These bromo cross-conjugated dienones displayed good cytotoxicities that could be compared with the cytotoxicity of the natural oxylipins. The use of the tandem 3-aza-Cope/Mannich annelation reaction allowed rapid access to all the possible stereoisomers in order to evaluate their structure–activity relationships. From these results we selected one compound, which was stereoselectively synthesized using a different, efficient route.

Experimental

Biological activities

In vitro cytotoxicity

The cellular test of colony forming was realised on B16 melanoma mouse cell line C57B46. The cells were grown in MEM (Eagle's minimum essential medium, GIBCO) enriched with 10% bovine foetal serum, vitamins, sodium pyruvate, essential amino acids, L-glutamine and gentamycin. The cells were grown in a humidified atmosphere containing 5% CO_2 at 37 °C.

Test of colony forming: 200 cells were plated in Petri boxes (60 mm diameter) in 5 mL of medium. After 20 h, the medium was replaced with a new medium containing various concentrations of drug. After 24 h, the medium was replaced by fresh medium. After growing for 11 days, the boxes were washed with

PBS (saline phosphate buffer), the colony forming cells were fixed with MeOH, stained with a 0.2% crystal violet solution. Only the colonies of more than 50 cells were considered. In the control, cells were grown in the same conditions. The data of the following 3 parameters were collected: "colony-forming efficacy" – determined as the ratio of the number of colonies formed upon number of harvest cells × 100; "survival cell fraction" – determined as the ratio of number of colonies formed upon the number of harvest cells treated × 100; "survival level" – determined as the ratio of survival cell fraction upon colony forming efficacy × 100. From the response curves, the IC_{50} was determined as the concentration of drug inducing 50% inhibition.

Biological results

All the compounds synthesized featured the same cross-conjugated dienone system along with a vicinal *syn* or *anti* diol on the ω chain. In the first series, we investigated replacement of the ω side-chain of the natural prostanoids by a 1-hydroxy-phenyl-butyl moiety, giving a *syn* diol. As seen in Fig. 2 (**33**,**32**), we soon observed that these potentially more polar compounds were still very active. No difference was observed irregardless of whether the α side-chain was lactonised or not (**34**, **35**). The double bond *E*/*Z* geometry appeared as unimportant. In the second series of products, the possibility of a shorter α side-chain bearing a simple aromatic ester was investigated as well as the configuration *syn* or *anti* of the diol on the ω side-chain. The results indicated an order of magnitude increase in cytotoxicity, which could only be attributed to this new α side-chain (**39**, **40**, **43**, **44**). Finally, in the third series, the ω-1-hydroxy-phenyl-butyl 1-hydroxy-5-phenylpentyl was replaced by a 1-hydroxymethyl-oxybenzyl chain. These more simplified compounds (**45**, **46**, **47**, **48**, **60**) were still highly cytotoxic and in the medium range of 60 nM, close to the value of natural punaglandins (PUG III, IC_{50} on L1210 = 40 nM).[4b]

Chemistry

General

Measurements of ^1H NMR spectra (300 or 400 MHz) were made in $CDCl_3$ (which also provided the lock signal at $\delta = 7.26$ ppm) in a Bruker 300 spectrometer; *J* values are given in Hz. Mass spectra were determined with CI (NH_3 or CH_4). Melting points are uncorrected. Optical rotations in 10^{-1} deg cm^2 g^{-1} were measured in a Perkin-Elmer 241 polarimeter at 20 °C and shown in the form $[\alpha]_D^{20}$ +22 (*c* 1, $CHCl_3$), *i.e.* concentration and solvent in parentheses. Silica gel 60 (35–70 nm) was used for flash chromatography and distilled cyclohexane, ethyl acetate and dichloromethane were used as eluents. Analytical plates (Merk 60 F_{254} aluminium sheets) were rendered visible by spraying with *p*-anisaldehyde–H_2SO_4–AcOH–EtOH or with phosphomolybdic acid (5% in ethanol), followed by heating. Prior to use, THF was distilled from sodium/benzophenone, and CH_2Cl_2 from P_2O_5. DMF was stored over 4 Å molecular sieves under dry argon atmosphere. Triethylamine was stored under argon atmosphere.

2,2,2′,2′-Tetramethyl-5-(4-phenyl-butyl)-[4,4′]bi[[1,3]dioxolanyl] (8)

To a suspension of NaH (3.3 g, 143 mmol) in anhydrous DMSO (250 mL) was added in 0.5 h, at room temperature, a solution of phosphonium salt **6** (1.1 eq, 44.6 g, 96,7 mmol) in DMSO (100 mL), prepared by treating 1.1 eq. of PPh_3 with commercial Br-$(CH_2)_3$-Ph in xylene at reflux. After reflux and cooling, the crystals were collected (mp 215 °C). The red-orange solution was stirred for 1 h, then a solution of aldehyde **5**[21] (9.5 g, 41.3 mmol) in DMSO (50 mL) was added, and the mixture was stirred for 2 h. The reaction was stopped by addition of ice/H_2O (500 mL) and extracted with Et_2O (3 × 300 mL). The organic layers were washed with H_2O (3 × 200 mL), with a saturated aq. solution of NaCl (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (cyclohexane/EtOAc, 8/1). Compound **7** was obtained as a mixture of diastereoisomers (*Z*/*E* ratio: 9/1, from NMR) (9.1 g, 66%), which were directly engaged in the next step. This mixture was dissolved in EtOAc (200 mL), and 10% Pd/C (90 mg) was added. The reaction was stirred under hydrogen (1 atm) for 2 h. After filtration on a celite pad, the filtrate was evaporated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 6/1 to 1/1), to give **8** (5.5 g, 60%). $[\alpha]_D^{20}$ +14° (*c* 1.2, $CHCl_3$); Found: C, 71.90; H, 8.96. Calc. for $C_{20}H_{30}O_4$ (334.46): C, 71.82; H, 9.04%; δ_H (300 MHz, $CDCl_3$) 7.31–7.19 (m, 5H), 4.12 (m, 1H), 3.97 (m, 3H), 3.56 (dd, 1H, *J* 7 and 7.5), 2.64 (t, 2H, *J* 7), 1.64 (m, 6H), 1.40 (s, 6H), 1.36 (s, 3H), 1.35 (s, 3H); δ_C (75 MHz, $CDCl_3$) 142.5, 128.3, 128.3, 125.5, 109.5, 108.8, 81.0, 80.3, 77.1, 67.6, 35.8, 33.4, 31.4, 27.3, 26.9, 26.6, 25.5; *m*/*z* (Cl, NH_3) 352 $[M + NH_4]^+$, 335 $[M + H]^+$.

1-[2,2-Dimethyl-5-(4-phenyl-butyl)-[1,3]dioxolan-4-yl]-ethane-1,2-diol (9)

By hydrolysis of compound 8. Compound **8** (500 mg, 1.5 mmol) was dissolved in a AcOH/H_2O mixture (3/1, v/v, 50 ml), and stirred for 3 h at room temperature. The reaction mixture was neutralised by addition of a saturated aqueous $KHCO_3$ solution. The reaction mixture was then extracted with EtOAc (3 × 30 mL) and washed with brine. The collected organic layers were evaporated under reduced pressure and the residue obtained was purified by flash column chromatography (cyclohexane/EtOAc, 6/1 to 1/1) to give compound **9** (300 mg, 68%) as well as the recovered compound **8** (160 mg, 32%).

From 2,3-*O*-isopropylidene-D-ribose 11. BuLi (2.5 M in hexane, 40.5 mL) was slowly added to anhydrous DMSO (150 mL) at r.t., in 0.5 h, then a solution of phosphonium salt, **6** in DMSO (150 mL, 47.55 g, 103.1 mmol) was added. To the red-orange solution obtained was added a solution of 2,3-*O*-isopropylidene ribose **11**[22] (19.5 g, 102 mmol) in DMSO (200 mL). The reaction mixture was stirred for 18 h at 50 °C. After addition of an ice–water mixture, the reaction was stopped and extracted with Et_2O (3 × 250 mL). The collected organic layers were then washed with water, brine, and dried ($MgSO_4$). After filtration and evaporation of the filtrate under reduced pressure, a residue was obtained. The remaining Ph_3P was removed by crystallisation from boiling Et_2O, followed by cooling. Finally, the Et_2O solution was concentrated and the residue obtained was purified by flash column chromatography (cyclohexane–Et_2O, 1/1 to pure Et_2O) giving compound **12** as a mixture of diastereoisomers (10.1 g, 34%) which was directly engaged in the next step (Compound **12** (*E*/*Z* mixture of diastereoisomers): δ_H (300 MHz, $CDCl_3$) 7.32–7.16 (m, 5H, arom-H), 5.90–5.70 (m, 1H), 5.55–5.39 (m, 1H), 4.96 and 4.67 (2 dd, *E*/*Z*), 3.75–3.54 (m, 4H), 2.76–2.68 (m, 2H), 2.56–2.43 (m, 2H), 1.45 (s, 3H, isopr.), 1.41 (s, 3H, isopr.); *m*/*z* (Cl/NH_3) 310 $[M + NH_4]^+$). To a solution of **12** (10 g, 34 mmol) in EtOAc (200 mL) was added 1 g of catalyst (10% Pd/C). The suspension was stirred under hydrogen (1 atm). The reaction mixture was then filtered on celite and the filtrate was evaporated under reduced pressure to give compound **9** (9.8 g, 97%) as a syrup. $[\alpha]_D^{20}$ +22 (*c* 1, $CHCl_3$); Found C, 69.27; H, 8.68. Calc. for $C_{17}H_{26}O_4$ (294.39) C, 69.36; H, 8.90%; δ_H (300 MHz, $CDCl_3$) 7.30–7.16 (m, 5H, arom-H), 3.97 (dt, 1H, *J* 3 and 7.7, H-4), 3.71 (m, 4H), 2.75 (br s, 1H, OH), 3.00 (br s, 1H, OH), 2.63 (t, 2H, *J* 7.2), 1.64 (m, 6H), 1.40 (s, 3H, isopr.), 1.38 (s, 3H, isopr.); δ_C (75 MHz, $CDCl_3$) 142.5, 128.3, 128.1, 125.5, 108.8, 80.8, 79.3, 72.8, 63.8, 35.8, 33.9, 31.4, 27.3, 27.0, 25.8; *m*/*z* (CI, NH_3) 312 $[M + NH_4]^+$, 295 $[M + H]^+$.

2,2-Dimethyl-5-(4-phenyl-butyl)-[1,3]dioxolane-4-carbaldehyde (10)

To a solution of compound **9** (0.3 g, 1.02 mmol) in a MeOH/H_2O mixture (2/1, 30 mL), $NaIO_4$ (0.22 g, 1.03 mmol) was added. After 1 h, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure, and co-evaporated with toluene (2 × 50 mL). Compound **10**, obtained as a hydrate (0.22 g, 82%), was directly engaged in the next step [δ_H (300 MHz, $CDCl_3$) 9.83 (d, 0.7H, *J* 3, CHO), 7.30–7.18 (m, 5H, arom-H), 4.90 (m, 0.3H) 3.95 (m, 2H), 2.62 (t, 2H, *J* 7.5), 1.66 (m, 6H), 1.46 (s, 3H, isopr.), 1.41 (s, 3H, isopr.); δ_C (75 MHz, $CDCl_3$) 201, 142.3, 128.2, 125.5, 84.7, 76.9, 35.7, 33.5, 31.3, 27.0, 26.0, 25.2; *m/z* (Cl/NH_3) 280 $[M + NH_4]^+$, 263 $[M + H]^+$.

1-*O*-Benzyl-2,3:4,5-di-*O*-isopropylidene-D-arabinitol (14)

NaH (60% in oil, 390 mg, 9.75 mmol) was added to a solution of di-isopropylidene mannitol **13** (1.84 g, 7.9 mmol)[26] in DMF (30 mL) at 0 °C. The suspension was stirred for 1 h, then benzyl chloride (1 mL, 8.68 mmol) was added. The reaction was stirred for 18 h at r.t. then quenched by addition of an ice–H_2O mixture (100 mL). After extraction with Et_2O, the collected organic layers were washed with H_2O, with brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure a residue was obtained, which was purified by flash column chromatography (cyclohexane–EtOAc, 6/1 to 3/1) to furnish compound **14** (1.52 g, 59%) and the starting compound **13** (450, 24%). δ_H (250 MHz, $CDCl_3$) 7.47 (m, 5H, arom-H), 4.70 (s, 2H, CH_2Ph), 4.32–4.00 (m, 4H), 3.98–3.54 (m, 3H), 1.42 (s, 6H, isopr.), 1.35 (s, 6H, isopr.); δ_C (62.5 MHz, $CDCl_3$) 138, 128, 127.4, 127.2, 109.5,109.3, 79.4, 77.4, 76.8, 73.1, 70.3, 67.3, 26.7, 26.3, 24.9.

4-*O*-Benzyl-2,3-*O*-isopropylidene-D-threose (15)

From 14. A solution of compound **14** (1.52 g, 4.72 mmol) in Et_2O (20 mL) was dropwise added to a solution of H_5IO_6 (1.61 g, 7.1 mmol) in anhydrous Et_2O (80 mL) under argon at 0 °C. The reaction mixture was stirred for 4 h at r.t. The reaction was then filtered on celite and the filtrate was washed with a saturated aqueous solution of $NaHCO_3$, and with brine. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (cyclohexane–EtOAc, 6/1 to 1/1), giving compound **15** (380 mg, 32%) and starting compound **14** (790 mg, 52%).

From 16. Anhydrous DMSO (3 g, 38.5 mmol) in CH_2Cl_2 (10 mL) was added to a solution of oxalyl chloride (2 mL, 23.5 mmol) in CH_2Cl_2 (30 ml) at −78 °C under argon. The reaction mixture was stirred for 0.3 h. Then a solution of compound **17** (4 g, 15.9 mmol) in CH_2Cl_2 (10 ml) was added. After 2 h, a solution of Et_3N (12 mL) in CH_2Cl_2 (10 mL) was added, and the solution was stirred for 0.5 h, then diluted with CH_2Cl_2 (100 mL). The organic layer was washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give compound **15** (2.5 g) as an amorphous solid, which was directly engaged in the next step. δ_H (90 MHz, $CDCl_3$) 9.70 (br s, 1H, CHO), 7.26 (br s, 5H, arom-H), 4.60 (m, 2H, O-CH_2-Ph), 4.16 (m, 1H), 3.83 (m, 1H), 3.47 (m, 2H), 1.50 (s, 3H, isopr.), 1.42 (s, 3H, isopr.).

1-*O*-Benzyl-2,3-*O*-isopropylidene-D-threitol (17)

NaH (60%, 1.6 g, 40.1 mmol) was added to a solution of **16**[27] (5.9 g, 36.4 mmol) in anhydrous DMF (65 mL) at −15 °C. The reaction mixture was stirred for 0.5 h, then benzyl bromide (6.9 g, 40 mmol) in solution in DMF (50 mL) was added. After stirring for 1 h at r.t., the reaction mixture was poured into an ice–H_2O mixture (150 mL). The reaction mixture was then extracted with Et_2O (4 × 40 mL), and the collected organic layers were washed with H_2O, with brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure, the residue obtained was purified by flash column chromatography (cyclohexane–EtOAc, 8/1 to 3/1), giving compound **17** (8 g, 88%); $[a]_D^{20}$ −9 (*c* 1, $CHCl_3$), [lit.[34] $[a]_D^{20}$ −8 (*c* 1, $CHCl_3$)]. δ_H (90 MHz, $CDCl_3$) 7.33 (br s, 5H, arom-H), 4.58 (s, 2H), 4.16–3.45 (m, 6H), 2.25–2.10 (br s, 1H, OH), 1.43 (s, 6H).

(5*R*) and (5*S*)-2,2-Dimethyl-4(*R*)-(4-phenyl-butyl)-1,3-dioxa-spiro[4.4]non-8-en-7-one (19) and (21)

Pyrolidine (5.17 mL, 61.9 mmol) was added to a solution of compound **10** (9 g, 34.4 mmol) in CH_3CN–toluene (1/1, v/v, 100 mL). The reaction was stirred at 50 °C for 1.5 h, then evaporated under reduced pressure. The residue obtained was dissolved in CH_3CN (200 mL), then 2-iodomethyl-3,5-dioxa-hex-1-ene **18**[35] (12.9 mL, 85.5 mmol) was added and the mixture was heated for 18 h at 80 °C. After evaporation under reduced pressure, a residue was obtained which was purified by flash column chromatography (cyclohexane–EtOAc 10/1) to give a mixture of diastereoisomers **19** and **21** (3.85 g, 37%).

Compound (5*R*) 19. This compound was isolated by flash column chromatography, as recovered starting material, from the bromination reaction of the mixture (4*R* + 4*S*) of cyclopentenones. $[a]_D^{20}$ +101 (*c* 1, $CHCl_3$); Found C, 76.12; H, 8.27. Calc for $C_{19}H_{24}O_3$ (300.40): C, 75.97; H, 8.05%; ν_{max} (cm^{-1}, $CDCl_3$) 1719 (C=O); δ_H (300 MHz, $CDCl_3$) 7.20 (d, 1H, *J* 5.5), 7.14 (m, 5H, arom-H), 5.90 (d, 1H, *J* 5.5), 3.80 (dd, 1H, *J* 5.5 and 5.5), 2.47 (t, 2H), 2.53 and 2.15 (2d, 2H, AB syst., *J* 15), 1.50 (m, 6H), 1.37 (s, 3H, isopr.), 1.32 (s, 3H, isopr.); δ_C (75 MHz, $CDCl_3$) 205.0, 160.9, 142.1, 134.4, 128.3, 125.6, 108.4, 86.9, 81.1, 44.0, 35.5, 31.1, 29.5, 29.3, 28.5, 26.1; *m/z* (Cl/NH_3) 318 $[M + NH_4]^+$, 301 $[M + H]^+$.

Compound (5S) 21. ν_{max} (cm^{-1}, $CDCl_3$) 1723 (C=O); δ_H (250 MHz, $CDCl_3$/C_6D_6, 1/1) 7.11 (m, 5H, arom-H), 6.88 (d, 1H, *J* 5.70, H-3), 5.96 (d, 1H, *J* 5.70, H-2), 3.72 (dd, 1H, *J* 3 and 8.5, H-6), 2.57 and 2.15 (2d, 2H, AB syst., *J* 17, H-5 and H-5′), 2.47 (t, 2H, *J* 7, H-10), 1.46 (m, 6H), 1.30 (s, 3H, isopr.), 1.29 (s, 3H, isopr.); *m/z* (Cl/NH_3) 318 $[M + NH_4]^+$, 301 $[M + H]^+$.

(5*R*) and (5*S*)-8-Bromo-2,2-dimethyl-4(*R*)-(4-phenyl-butyl)-1,3-dioxa-spiro[4.4]-non-8-en-7-one (20) and (22)

A solution of bromine (0.17 mL of Br_2 in 5 mL of CH_2Cl_2) was dropwise added to a solution of **19** + **21** (1 g, 3.33 mmol) in CH_2Cl_2 (50 mL). The orange solution obtained was stirred for 0.4 h, then Et_3N was added (0.91 mL, 6.6 mmol). After addition of water and extraction with CH_2Cl_2 the organic layers were collected, washed with water, with brine, and dried ($MgSO_4$). The residue obtained after filtration and evaporation under reduced pressure was purified by flash column chromatography (cyclohexane–EtOAc, 10/1), giving bromo compounds **20** (300 mg) and **22** (220 mg) in 41% overall yield as well as starting compound **19** (155 mg, 15.5%).

Compound (5*R*) 20. $[a]_D^{20}$ −51 (*c* 0.83, $CHCl_3$); Found C 60.41; H 6.28. Calc. for $C_{19}H_{23}BrO_3$ (379,29) C, 60.17; H, 6.11%; ν_{max} (cm^{-1}, $CDCl_3$) 1733 (C=O); δ_H (300 MHz, $CDCl_3$) 7.37 (s, 1H, H-3), 7.27–7.11 (m, 5H, arom-H), 3.95 (dd, 1H, *J* 8.8 and 6.15, H-6), 2.87 and 2.42 (2d, 2H, AB syst., *J* 18.5), 2.57 (t, 2H, *J* 7.5), 1.58 (m, 6H), 1.39 (s, 6H, isopr.), δ_C (75 MHz, $CDCl_3$) 197.3, 158.9, 142.0, 128.2, 125.74, 109.1, 85.0, 80.5, 42.5, 35.6, 31.2, 28.8, 26.4, 27.7, 26.4; *m/z* (Cl/NH_3) 398 $[M + NH_4]^+$, 396 $[M + NH_4]^+$, 381 $[M + H]^+$, 379 $[M + H]^+$.

Compound (5*S*) 22. $[a]_D^{20}$ +41 (*c* 0.83, $CHCl_3$); Found C, 60.37; H, 6.22. Calc. for $C_{19}H_{23}BrO_3$ (379.29) C, 60.17; H, 6.11%; ν_{max} (cm^{-1}, $CDCl_3$) 1733 (C=O); δ_H (250 MHz, $CDCl_3$)

7.50 (s, 1H, H-3), 7.23–7.10 (m, 5H, arom-H), 4.04 (dd, 1H, *J* 3.6 and 9.3), 2.81 and 2.54 (2d, 2H, AB syst., *J* 18.5) 2.61 (t, 2H, *J* 7.12), 1.61 (m, 6H), 1.50 (s, 3H, isopr.), 1.40 (s, 3H, isopr.); *m/z* (Cl/NH_3) 398 $[M + NH_4]^+$, 396 $[M + NH_4]^+$, 381 $[M + H]^+$, 379 $[M + H]^+$.

(5*R*) and (5*S*)-4(*R*)-Benzyloxymethyl-2,2-dimethyl-1,3-dioxa-spiro[4.4]non-8-en-7-one (23) and (24)

Obtained in 36% yield from **15** (4.3 g, 17.2 mmol) using the same procedure as for the synthesis of **19** + **21**; ν_{max} (cm^{-1}, $CDCl_3$) 1723 (C=O). Compounds **23** + **24**: Found C, 70.77; H, 7.19. Calc. for $C_{17}H_{20}O_4$ (288.34): C, 70.81; H, 6.99%; δ_H (250 MHz, $CDCl_3$) 7.40–7.10 (m, 6H, arom-H), 6.14 (d, 0.5H, *J* 5.85), 6.04 (d, 0.5H, *J* 5.0), 4.52 and 4.44 (dd, 1H, AB syst., *J* 11.9), 4.45 (d, 1H, AB syst., *J* 11.9), 4.40–4.00 (m, 1H), 3.80–3.20 (m, 2H), 2.70, 2.58 (2d, 1H, AB syst., *J* 18.4), 2.57 (d, 1H, AB syst.), 1.52, 1.47, 1.44, 1.40, (s, 6H, isopr.); *m/z* (DCI/NH_3) 306 $[M + NH_4]^+$, 289 $[M + H]^+$.

(5*R*) and (5*S*)-4(*R*)-Benzyloxymethyl-8-bromo-2,2-dimethyl-1,3-dioxa-spiro[4.4]non-8-en-7-one (25) and (26)

Obtained by bromination of the **23** + **24** mixture as described for **19** + **21**. After reaction, the residue obtained after evaporation under reduced pressure was purified by flash column chromatography (cyclohexane–EtOAc, 10/1 to 2/1) to give a mixture of **25** + **26** (740 mg, 44%), starting compounds **23** + **24** (110 mg, 8.5%), and diol **27** as a mixture of diastereoisomers (300 mg, 20%). After another purification, the pure compound **25** was obtained as well as the enriched **26**.

Compound (5*R*) 25. $[a]_D^{20}$ +33 (*c* 1, $CHCl_3$); Found C, 55.37, H, 5.33. Calc. for $C_{17}H_{19}O_4Br$ (367.24) C, 55.60; H, 5.21%; ν_{max} (cm^{-1}, $CDCl_3$) 1734; δ_H (300 MHz, $CDCl_3$) 7.44 (s, 1H), 7.39–7.22 (m, 5H, arom.), 4.49 and 4.44 (2d, 2H, AB syst., *J* 10.5), 4.28 (t, 1H, *J* 5.5 and 5.5), 3.72 (dd, 1H, *J* 5.5 and 9.7), 3.46 (dd, 1H, *J* 5.5 and 9.7), 2.88 and 2.46 (2d, 2H, *J* 18.4), 1.45 (s, 3H, isopr.), 1.44 (s, 3H, isopr.); δ_C (75 MHz, $CDCl_3$) 197.2, 158.9, 136.8, 128.4, 128.2, 127.9, 127.8, 128.1, 109.9, 84.8, 78.2, 73.8, 68.2, 42.2, 27.6, 26.5; *m/z* (DCI/NH_3) 386 and 384 $[M + NH_4]^+$.

Compound (5*S*) 26. Found C, 55.42; H, 5.45. Calc. for $C_{17}H_{19}O_4Br$ (367.24) C, 55.60; H, 5.21%; ν_{max} (cm^{-1}, $CDCl_3$) 1734; δ_H (300 MHz, $CDCl_3$) 7.50 (s, 1H), 7.35–7.21 (m, 5H, arom-H), 4.49 and 4.42 (2d, 2H, AB syst., *J* 11.9), 4.29 (dd, 1H, ABX syst., *J* 5.2 and 7.25), 3.67 (dd, 1H, AB syst., *J* 2 and 9.7), 3.39 (dd, 1H, ABX syst., *J* 7.25 and 9.7), 2.82 and 2.73 (2d, 2H, AB syst., *J* 20), 1.51 (s, 3H, isopr.), 1.43 (s, 3H, isopr.); δ_C (75 MHz, $CDCl_3$) 196.8, 157.4, 136.9, 128.4, 127.9, 127.4, 109.7, 85.35, 79.4, 73.9, 67.2, 43.5, 28.8, 26.12.

(4*S*)-(2-Benzyloxy-1(*R*)-hydroxy ethyl)-4-hydroxy-cyclopent-2-enone (27)

ν_{max} (cm^{-1}) 1729 C=O), 3449 (OH); δ_H (250 MHz, $CDCl_3$) 7.47 (s, 1H), 7.38–7.28 (m, 5H, arom-H), 4.56 and 4.50 (2d, 2H, AB syst., *J* 11.6), 3.73 (m, 2H), 3.62 (m, 2H), 3.16 (br s, 1H, OH), 2.84, 2.50 (d, 1H, AB syst., *J* 18.4); *m/z* (DCI/NH_3) 346 and 344 $[M + NH_4]^+$.

(4*R*)-{5(*S*)-[8-Bromo-2,2-dimethyl-7-oxo-4(*R*)-(4-phenyl-butyl)-1,3-dioxa-spiro[4.4]non-8-en-6(*Z*)-ylidenemethyl]-(2,2-dimethyl-[1,3]dioxolan-(3*R*)-(4*S*)-yl}-butyric acid methyl ester (30) and (4*R*)-{5(*S*)-[8-bromo-2,2-dimethyl-7-oxo-4(*R*)-(4-phenyl-butyl)-1,3-dioxa-spiro[4.4]non-8-en-6(*E*)-ylidenemethyl]-(2,2-dimethyl-[1,3]dioxolan-(3*R*)-(4*S*)-yl}-butyric acid methyl ester (31)

Aldolisation step. A solution of LDA (2 M, 0.33 ml, 0.66 mmol) was added to a solution of compound **20** (210 mg, 0.55 mmol) in dry THF (20 mL) at −78 °C. The reaction was stirred for 0.25 h, then a solution of compound **28**[29] (255 mg, 1.1 mmol) in THF (2 mL) was added. The reaction was quenched after 0.5 h by addition of an aqueous saturated solution of NH_4Cl. H_2O (10 mL) was then added and the reaction mixture was extracted with EtOAc (3 × 30 mL). The collected organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (cyclohexane/EtOAc, 15/1 to 4/1) to give the aldol product **29** (140 mg, 41.6%), as a mixture of diastereoisomers, and starting compound **20** (40 mg, 19%).

Elimination step. Ac_2O (0.22 mL) and cat. 4-DMAP were successively added to a solution of the crude compound **29** (100 mg, 0.16 mmol) in anhydrous pyridine (6 mL). The reaction mixture was stirred for 4 h at 60 °C. After evaporation under reduced pressure, and co-evaporation with toluene (2 × 50 mL) a residue was obtained which was purified by flash column chromatography (cyclohexane/EtOAc, 12/1 to 8/1), giving compounds (*Z*) **30** (20 mg, 20%) and (*E*) **31** (60 mg, 62%).

Compound (*Z*) 30. $[a]_D^{20}$ −91 (*c* 1, $CHCl_3$); Found C, 60.80; H, 6.93. Calc. for $C_{30}H_{39}O_7Br$ (591.54) C, 60.91; H, 6.65%; δ_H (250 MHz, $CDCl_3$) 7.34 (s, 1H), 7.29–7.12 (m, 5H, arom-H), 6.18 (d, 1H, *J* 7.75), 5.61 (t, 1H, *J* 7.75 and *J* 6.8), 4.43 (ddd, 1H, *J* 6.8 and 9.5), 4.15 (dd, 1H, *J* 3 and 8.8), 3.61 (s, 3H, COOMe), 2.58 (t, 2H, *J* 7.3), 2.29 (t, 2H, *J* 7.6), 1.75 (m, 10H), 1.55 (s, 3H, isopr.), 1.50 (s, 3H, isopr.), 1.46 (3H, isopr.), 1.37 (3H, isopr.); δ_C (62.5 MHz, $CDCl_3$) 187.0, 172.8, 155.4, 142.0, 139.6, 135.5, 130.0, 128.0, 125.4, 109.2, 108.5, 85.9, 80.4, 78.1, 74.4, 51.1, 35.4, 33.4, 30.8, 30.2, 30.2, 26.2, 21.7, 27.9, 26.8, 25.2; *m/z* (Cl/NH_3) 610 and 608 $[M + NH_4]^+$.

Compound (*E*) 31. $[a]_D^{20}$ −37 (*c* 1, $CHCl_3$); Found C, 60.67; H, 6.86. Calc. for $C_{30}H_{39}O_7Br$ (591.54) C, 60.91; H, 6.65%; ν_{max} (cm^{-1}, $CDCl_3$) 1718 (C=O); δ_H (250 MHz, $CDCl_3$) 7.43 (s, 1H, H-3), 7.29–7.14 (m, 5H, arom-H), 6.64 (d, 1H, *J* 10.5), 5.14 (dd, 1H, *J* 10.5 and *J* 6.2), 4.20 (m, 2H), 3.65 (s, 3H, COOMe), 2.58 (t, 2H, *J* 7.5), 2.32 (t, 2H, *J* 7), 1.69 (m, 10H), 1.53 (s, 6H, isopr.), 1.49 (s, 3H, isopr.), 1.37 (3H, isopr.); δ_C (62.5 MHz, $CDCl_3$) 187.0, 173.8, 157.3, 142.3, 135.2, 134.2, 129.5, 128.3, 128.2, 125.6, 109.4, 86.0, 81.1, 78.4 and 74.2, 59.3, 35.4, 33.6, 31.0, 30.3, 29.0, 27.0, 22.1, 28.3, 26.2, 25.8, 25.0; *m/z* (Cl/NH_3) 310 $[M + NH_4]^+$, 308 $[M + NH_4]^+$.

6(*Z*)-[4-Bromo-2(*S*)-hydroxy-2-(1(*R*)-hydroxy-5(*S*)-phenyl-pentyl)-5-oxo-cyclopent-3-enylidene]-(5*R*),(6*R*)-dihydroxy-heptanoic acid methyl ester (32) and 6(*S*)-{2(*Z*)-[4-bromo-2(*S*)-hydroxy-2-(1(*R*)-hydroxy-5-phenyl-pentyl)-5-oxo-cyclopent-3-enylidene]-1(*R*)-hydroxy-ethyl}-tetrahydro-pyran-2-one (34)

To an aqueous solution of TFA in H_2O (2 mL, 1/1) at 0 °C was added a solution of compound **30** (63 mg, 0.1 mmol) in THF (0.5 mL). The reaction mixture was stirred for 1 h at r.t. After evaporation under reduced pressure, the residue obtained was purified by flash column chromatography (cyclohexane/MeOH, 40/1) to give compound **32** (9 mg, 16.5%) and lactone **34** (28.5 mg, 56%). Treatment of the lactone **34** (9 mg, 0.02 mmol) for 4 h at r.t. in dry MeOH (1 mL) with a (0.1 M) solution of K_2CO_3 in MeOH (30 µL) followed by neutralisation (stirring with 50S (H^+) resin), filtration and evaporation, afforded compound **32** (9 mg).

Compound 32. $[a]_D^{20}$ −38 (*c* 1, $CHCl_3$); Found C, 56.21; H, 6.02. Calc. for $C_{30}H_{39}O_7Br$ (591.54) C, 56.37; H, 6.11%; ν_{max} (cm^{-1}, $CDCl_3$) 1718 (C=O), 3414 (OH); δ_H (300 MHz, $CDCl_3$) 7.31–7.14 (m, 6H, arom-H), 6.44 (d, 1H, *J* 7.5), 5.30 (br s, 1H, OH), 5.27 (d, 1H, *J* 7.5), 4.80 (br s, 1H, OH), 4.10 (br s, 2H,

OH), 3.79 (m, 1H), 3.63 (m, 1H), 3.58 (s, 3H, COOMe), 2.58 (t, 2H, *J* 6.5), 2.29 (t, 2H, *J* 7), 1.58 (m), 1.29 (m, 10H); δ_C (75 MHz, $CDCl_3$) 188.6, 174.3, 156.7, 142.1, 139.3, 137.3, 129.9, 128.2, 125.6, 80.4, 75.3, 74.8, 69.8, 51.5, 35.7, 33.3, 31.4, 31.0, 29.5, 25.9, 21.0; *m/z* (Cl/NH_3) 530 and 528 $[M + NH_4]^+$.

Compound 34. $[a]_D^{20}$ −42 (*c* 1, $CHCl_3$), −54 (*c* 1, MeOH); ν_{max} (cm^{-1}, $CDCl_3$) 3398 (OH), 1712 (C=O); δ_H (250 MHz, $CDCl_3$) 7.40 (s, 1H), 7.29–7.13 (m, 5H, arom-H), 6.42 (d, 1H, *J* 7.8), 5.36 (dd, 1H, *J* 7.8 and 3.6), 4.65 (br s, 2H, OH), 4.48 (m 1H), 3.80 (dd, 1H, *J* 2 and 10), 3.22 (br s, 1H, OH), 2.58 (t, 2H, *J* 6.5), 2.41 (m, 2H), 1.96–1.48 (m, 10H); δ_C (62,5 MHz, $CDCl_3$) 188.6, 172.2, 156.9, 142.0, 138.1, 137.3, 129.6, 128.1, 128.0, 125.4, 82.7, 80.2, 75.0, 68.0, 35.5, 33.4, 31.4, 30.9, 29.4, 25.6, 22.8, 17.7; *m/z* (Cl/NH_3) 498 and 496 $[M + NH_4]^+$.

6(*E*)-[4-Bromo-2(*S*)-hydroxy-2-(1(*R*)-hydroxy-5(*S*)-phenyl-pentyl)-5-oxo-cyclopent-3-enylidene]-(5*R*),(6*R*)-dihydroxy-heptanoic acid methyl ester (33) and 6(*S*)-{2(*Z*)-[4-bromo-2(*S*)-hydroxy-2-(1(*R*)-hydroxy-5-phenyl-pentyl)-5-oxo-cyclopent-3-enylidene]-1(*R*)-hydroxy-ethyl}-tetrahydro-pyran-2-one) (35)

Treatment of compound **31** (130 mg, 0.22 mmol) following the same protocol as for compound **30**, furnished compound **33** (21 mg, 19%) and lactone **35** (561 mg, 58%). Similarly, treatment of lactone (*E*) **35** (31 mg, 0.06 mmol) in the same conditions as for lactone **34** afforded compound **33** (33 mg, 100%).

Compound 33. $[a]_D^{20}$ −43 (*c* 1, MeOH); Found C, 56.13; H, 5.97. Calc. for $C_{24}H_{31}O_7Br$ (511.41) C, 56.37; H, 6.11%; ν_{max} (cm^{-1}, $CDCl_3$) 3406 (OH), 1718 (C=O); δ_H (250 MHz, $CDCl_3$) 7.41 (s, 1H), 7.30–7.14 (m, 5H, arom-H), 6.75 (d, 1H, *J* 7.8), 5.40 (br s, 1H, OH), 4.73 (dd, 1H, *J* 7.8 and 4.3), 3.93 (dd, 1H, *J* 2 and 10), 3.81 (dt, 1H, *J* 4.3 and 6.5), 3.63 (s, 3H, COOMe), 2.59 (t, 2H, *J* 6), 2.35 (m, 2H), 1.72–1.16 (m, 10H); δ_C (62.5 MHz, $CDCl_3$) 188.7, 175.1, 157.75, 142.3, 138.3, 134.8, 128.7, 128.3, 128.2, 125.6, 81.5, 75.3, 73.3, 70.4, 51.8, 35.7, 33.3, 32.0, 31.2, 31.1, 26.1, 20.3; *m/z* (Cl/NH_3) 530 and 528 $[M + NH_4]^+$.

Compound 35. $[a]_D^{20}$ +6 (*c* 1, $CHCl_3$); ν_{max} (cm^{-1}, $CDCl_3$) 3445 (OH), 1723 (C=O); δ_H (250 MHz, $CDCl_3$) 7.41 (s, 1H), 7.30–7.15 (m, 5H, arom-H), 6.64 (d, 1H, *J* 7.1), 4.77 (dd, 1H, *J* 7.1 and 6.9), 4.73 (br s, 1H, OH), 4.52 (br s, 1H, OH), 4.44 (m, 1H), 3.96 (dd, 1H, *J* 2, *J* 10), 3.40 (br s, 1H, OH), 2.60 (m, 2H), 2.53 (m, 2H), 2.11–1.51 (m, 10H); δ_C (62.5 MHz, $CDCl_3$) 188.1, 171.5, 156.8, 142, 138.7, 132.8, 128.9, 128.0, 125.4, 82.2, 81.4, 75.0, 69.2, 35.4, 30.7, 30.1, 29.4, 25.6, 22.9, 17.7; *m/z* (Cl/NH_3) 498 and 496 $[M + NH_4]^+$. HRMS. Calc for M- $C_{11}H_{14}O$: 315.99463, found 315.99442.

4-[8-Bromo-2,2-dimethyl-7-oxo-4(*R*)-(4-phenyl-butyl)-1,3-dioxa-spiro[4.4]-5(*S*)non-8-en-6-(*Z*)-ylidenemethyl]-benzoic acid methyl ester (37)

Treatment of compound **20** (120 mg, 0.32 mmol) following the same procedure as for compound **29**, with the aldehyde **36** furnished the intermediary, not characterized aldol (12 mg, 70%). The latter compound was treated with Ac_2O (2.5 mL) and pyridine (10 mL) and 4-DMAP for 1.5 h at 80 °C. After evaporation and purification of the residue by flash column chromatography, a *Z*/*E* mixture of compounds **37** + **38** was obtained (10/1 ratio, 70 mg, 61%). A second purification allowed isolation of pure compound **37**.

Major compound (*Z*) 37. $[a]_D^{20}$ −38 (*c* 0.66, $CHCl_3$); Found C, 64.21; H, 5.89. Calc. for $C_{28}H_{29}O_5$ Br *M* 525.44 $C_{24}H_{31}O_7Br$ (511.41) C, 64.01; H, 5.56%; ν_{max} (cm^{-1}, $CDCl_3$) 1718 (C=O conjugate), 1631 (C=O ester); δ_H (250 MHz, $CDCl_3$) 8.05 (br d, 2H, *J* 8.4), 7.98 (br d, 2H, *J* 8.4), 7.35 (s, 1H), 7.26–7.10 (m, 5H, arom-H), 6.96 (s, 1H), 4.22 (dd, 1H, *J* 2.4 and *J* 9), 3.93 (s, 3H, COOMe), 2.56 (t, 2H, *J* 7.3), 1.65 (s, 3H, isopr.), 1.55–1.44 (m, 6H), 1.53 (s, 3H, isopr.); δ_C (62.5 MHz, $CDCl_3$) 185.4, 166.2, 153.9, 141.8, 137.9, 137.0, 134.3, 131.4, 131.3, 130.7,129.0, 128.0, 128.0, 125.4, 109.2, 86.5, 81.2, 51.9, 35.4, 30.8, 30, 26.1, 26.8, 25.1; *m/z* (Cl/NH_3) 544 and 542 $[M + NH_4]^+$, 527 and 525 $[M + H]^+$.

(*Z*) and (*E*)-[4-Bromo-2(*S*)-hydroxy-2-(1(*R*)-hydroxy-5-phenyl-pentyl)-5-oxo-cyclopent-3-enylidenemethyl]-benzoic acid methyl ester (39) and (40)

Treatment of a mixture of compounds **37** + **38** (70 mg, 0.16 mmol) following the same procedure as for compounds **30** + **31** furnished the major compound (*Z*) **39** (18 mg, 23%) and compound (*E*) **40** (46 mg, 60%).

Major compound (*Z*) 39. $[a]_D^{20}$ −28 (*c* 0.5, $CHCl_3$); Found C, 62.03; H, 5.43. Calc. for $C_{25}H_{25}BrO_5$ (484.09) C, 61.86; H, 5.19%; ν_{max} (cm^{-1}, $CDCl_3$) 3589 (OH), 1718 (C=O), 1627 (C=O ester); δ_H (250 MHz, $CDCl_3$) 8.06 (br d, 2H, *J* 3), 8.00 (br d, 2H, *J* 3), 7.41 (s, 1H), 7.34–7.14 (m, 6H, arom-H), 3.93 (s, 3H, COOMe), 3.91 (m, 1H), 2.79 (s, 1H, OH), 2.62 (t, 2H, *J* 6.5), 2.30 (d, 1H, *J* 4.4, OH), 1.61–1.25 (m, 6H); δ_C (62.5 MHz, $CDCl_3$) 186.0, 166.4, 154.3, 142.1, 137.5, 137.2, 136.4, 132,1, 131.0, 129.2, 128.2, 125.6, 81.1, 75.9, 52.2, 35.7, 31.3, 31.0, 25.8; *m/z* (Cl/NH_3) 504 and 502 $[M + NH_4]^+$, 487 and 485 $[M + H]^+$.

Minor compound (*E*) 40. $[a]_D^{20}$ +32 (*c* 0.23, $CHCl_3$); Found C, 61.98; H, 5.37. Calc. for $C_{25}H_{25}BrO_5$ (484.09) C, 61.86; H, 5.19%; ν_{max} (cm^{-1}, $CDCl_3$) 3582 (OH), 1718 (C=O), 1635 (C=O ester); δ_H (300 MHz, $CDCl_3$) 8.07 (br d, 2H, *J* 8.3), 8.00 (br d, 2H), 7.61 (s, 1H), 7.59 (s, 1H), 7.29–7.12 (m, 5H, arom-H), 4.08 (m, 1H), 3.94 (s, 3H, COOMe), 2.68 (s, 1H, OH), 2.59 (t, 2H, *J* 7.4), 1.97 (br s, 1H, OH), 1.60–1.25 (m, 6H); δ_C (75 MHz, $CDCl_3$) 188.1, 166.1, 155.6, 141.9, 137.0, 135.8, 134.4, 131.4, 131.1, 129.9 and 129.5, 128.1 and 128.0, 125.4, 81.8, 72.4, 52.8, 35.4, 30.9, 29.4, 25.6; *m/z* (Cl/NH_3) 504 and 502 $[M + NH_4]^+$, 487 and 485 $[M + H]^+$.

(*Z*) and (*E*)-4-[8-Bromo-2,2-dimethyl-7-oxo-4(*R*)-(4-phenyl-butyl)-1,3-dioxa-spiro[4.4]-5(*S*)non-8-en-6-(*Z*)-ylidenemethyl]-benzoic acid methyl ester (41) and (42)

Obtained in 43% overall yield from compound (4*R*, 5*S*) **22** (130 mg, 0.34 mmol) by the aldolisation/elimination sequence with aldehyde **36**, following the same procedure as for compound **20**.

Compounds 41 (*Z*) + 42 (*E*). δ_H (300 MHz, $CDCl_3$) 8.10 and 8.00 (2m, 4H, arom-H), 7.78 (s, 0.5H), 7.64 (s, 0.5H, 7.46 (s, 0.5H), 7.28–7.06 (m, 5H, arom-H), 7.00 (s, 1H), 4.14 (dd, 1H), 3.97 (dd, 1H), 3.95 (s, 1.5H, COOMe), 3.94 (s, 1.5H, COOMe), 2.57 (t, 2H), 2.49 (t, 1H), 1.59, 1.58, 1.54, 1.30 (4s, 6H, 1.64–1.18 (m, 6H); δ_C (75 MHz, $CDCl_3$) 187.5, 185.6, 166.3, 155.3, 152.4, 141.9, 141.9, 138.1, 137.7, 137.4, 137.0, 132.4, 131.4, 131.0, 130.9, 130.7, 129.8, 129.4, 129.2, 128.5, 128,2, 125.7, 109.7, 109.2, 87.4, 86.9, 82.9, 78.8, 52.2, 35.6, 35.4, 31.0, 30.8, 29.6, 29.3, 29.2, 28.6, 27.1, 26.5, 25.9, 25.5; *m/z* (DCI/NH_3) 542 and 544 $[M + NH_4]^+$, 527 and 525 $[M + H]^+$.

4(*Z*) and 4(*E*)-[4-Bromo-2(*R*)-hydroxy-2-(1(*R*)-hydroxy-5-phenyl-pentyl)-5-oxo-cyclopent-3-enylidenemethyl]-benzoic acid methyl ester (43) and (44)

Obtained by hydrolysis of the mixture **41** + **42** (50 mg, 0.95 mmol) using the same condition as for compounds **37** + **38** and furnished **43** (*Z*) (22 mg, 48%) and **44** (*E*) (21 mg, 46%).

Compound (*Z*) 43. $[a]_D^{20}$ +5 (*c* 1, $CHCl_3$); Found C, 61.74; H, 5.27. Calc. for $C_{25}H_{25}O_5Br$ (485.38): C, 61.86; H, 5.19%; ν_{max} (cm^{-1}, $CDCl_3$) 3850 (OH), 1718 (C=O conj.), 1627 (C=O ester); δ_H (300 MHz, $CDCl_3$) 8.10 (br d, 2H, *J* 8.5), 8.00 (br d, 2H,

J 8.5), 7.56 (s, 1H), 7.26–7.10 (m, 5H, arom-H), 7.05 (s, 1H), 3.92 (s, 3H, COOMe), 3.91 (m, 1H), 2.58 (t, 2H, *J* 6.5), 1.66–1.50 (m, 2H, OH), 1.35–1.15 (m, 6H); δ_C (75 MHz, $CDCl_3$) 186.0, 166.5, 153.8, 142.0, 137.1, 136.8, 136.1, 131.3, 129.6, 131.4, 129.3, 128.2, 125.6, 81.8, 76.8, 52.3, 35.6, 31.2, 30.8, 25.8; *m*/*z* (DCI/NH_3) 502 and 504 $[M + NH_4]^+$, 465 and 487 $[M + H]^+$.

Compound (*E*) 44. $[\alpha]_D^{20}$ −29 (*c* 1, $CHCl_3$); Found C, 62.13; H, 5.42. Calc. for $C_{25}H_{25}O_5Br$ (485.38): C, 61.86; H, 5.19%; ν_{max} (cm^{-1}, $CDCl_3$) 3585 (OH), 1718 (CO), 1636 (CO ester); δ_H (300 MHz, $CDCl_3$) 8.02 (br d, 2H, *J* 8), 7.98 (br d, 2H, *J* 8), 7.76 (s, 1H), 7.53 (s, 1H), 7.22–7.12 (m, 3H), 6.99–6.96 (m, 2H), 4.16 (d, 1H, *J* 8.5), 3.94 (s, 3H, COOMe), 3.85 (br s, 1H, OH), 2.86 (br s, 1H, OH), 2.39 (t, 2H), 1.40–1.10 (m, 6H); δ_C (75 MHz, $CDCl_3$) 188.6, 166.4, 156.5, 141.9, 137.4, 135.3, 134.3, 131.5, 129.6 and 128.1, 131.0 and 129.0, 125.57, 81.97, 72.09, 52.32, 35.31, 31.71, 30.4 and 25.4; *m*/*z* (DCI/NH_3) 504 and 502 $[M + NH_4]^+$, 487 and 485 $[M + H]^+$.

Z-(2*S*,1*R*), *E*-(2*S*,1*R*), *Z*-(2*R*,1*R*) and *E*-(2*R*,1*R*) 4-[2-(2-Benzyloxy-1-hydroxy-ethyl)-4-bromo-2-hydroxy-5-oxo-cyclopent-3-enylidenemethyl]-benzoic acid (45), (46), (47) and (48)

A mixture of compound **25** + **26** (750 mg, 2 mmol) in THF (50 mL) was treated at −78 °C with LDA (1.66 M, 1.7 mL). After 1 h, *p*-methoxybenzaldehyde **36** (410 mg, 2.18 eq.) was added as described. Extraction and purification (cyclohexane–EtOAc, 10/1) gave a mixture of aldol product diastereoisomers (510 mg) which was directly treated with pyridine (12 mL), Ac_2O (2 mL), and 4-DMAP. After co-evaporation (×3) with toluene, the product obtained was purified (cyclohexane–EtOAc, 6/1), furnishing a residue (460 mg, 93%), which was dissolved in a mixture of THF/H_2O/TFA (2/2/1, 10 mL) and heated at 80 °C for 1.5 h. After evaporation of the solvent and successive co-evaporations with toluene (3 × 50 mL), a residue was obtained. The cyclopentadienone diastereoisomers were separated by chromatography on a silica gel column (cyclohexane–EtOAc, 6/1 to 3/1), successively giving compounds **48** (52 mg, 12%), **47** (110 mg, 26%), **46** (72 mg, 17%) and **45** (130 mg, 30%).

Compound *Z*,2*S*,1*R* 45. $[\alpha]_D^{20}$ +62 (*c* 0.4, $CHCl_3$); Found C, 58.54; H, 4.69. Calc for $C_{23}H_{21}BrO_6$ (473.31) C, 58.37; H, 4.47%; δ_H (300 MHz, $CDCl_3$) 8.05 (2d, 2H, *J* 7), 7.99 (2d, 2H, *J* 7), 7.63 (s, 1H), 7.50 (s, 1H), 7.45–7.30 (m, 5H, arom-H), 4.58 and 4.56 (2d, 2H, AB syst., *J* 12), 4.27 (dd, 1H, ABX syst., *J* 5.1 and 5.6), 3.94 (s, 3H, COOMe), 3.92 (s, 1H, OH), 3.83 (dd, 1H, ABX syst., *J* 5.1 and 9.7), 3.67 (dd, 1H, ABX syst., *J* 5.6 and 9.7), 3.60 (s, 1H, OH); *m*/*z* (DCI/NH_3) 492 and 490 $[M + NH_4]^+$, 475 and 473 ($[M + H]^+$.

Compound *E*,2*S*,1*R* 46. $[\alpha]_D^{20}$ −28 (*c* 0.75, $CHCl_3$); Found C, 58.62; H, 4.71. Calc for $C_{23}H_{21}BrO_6$ (473.31) C, 58.37; H, 4.47%; δ_H (300 MHz, $CDCl_3$) 8.03 (2d, 2H, *J* 8.5), 7.98 (2d, 2H, *J* 8.5), 7.51 (s, 1H), 7.39–7.31 (m, 5H, arom-H), 7.05 (s, 1H), 4.61 and 4.56 (2d, 2H, *J* 12.7), 4.04 (dd, 1H, *J* 5.2 and 4.6), 3.93 (s, 3H, COOMe), 3.92 (s, 1H, OH), 3.80 (dd, 1H, *J* 5.2 and 9.6, H-7), 3.68 (dd, 1H, *J* 4.6 and 9.6), 3.57 (s, 1H, OH); *m*/*z* (DCI/NH_3) 492 and 490 $[M + NH_4]^+$.

Compound *Z*,2*R*,1*R* 47. $[\alpha]_D^{20}$ −46 (*c* 1, $CHCl_3$); Found C, 58.23; H, 4.61. Calc for $C_{23}H_{21}BrO_6$ (473.31) C, 58.37; H, 4.47%; ν_{max} (cm^{-1}, $CDCl_3$) 1718, 3537 (OH); δ_H (300 MHz, $CDCl_3$) 8.04 (2d, 2H, syst., *J* 8.5), 7.98 (2d, 2H, syst., *J* 8.5), 7.72 (s, 1H, H-3), 7.56 (s, 1H), 7.30–7.27 (m, 3H, arom-H), 7.15–7.12 (m, 2H, arom-H), 4.31 (m, 3H), 4.01 (br s, 1H, OH), 3.93 (s, 3H, COOMe), 3.24 (dd, 1H, *J* 4.0 and 10.1), 3.10 (dd, 1H, *J* 6.0 and 10.1), 3.00 (br s, 1H, OH); δ_C (75 MHz, $CDCl_3$) 188.3, 166.4, 156.6, 137.3, 136.7, 135.6, 133.6, 131.6, 130.9, 129.6, 129.1, 128.3, 128.0, 127.9, 127.6, 80.0, 73.3, 69.5, 71.2, 52.3; *m*/*z* (DCI/NH_3) 475 and 473 $[M + H]^+$, 492 and 490 $[M + NH_4]^+$.

Compound *E*,2*R*,1*R* 48. $[\alpha]_D^{20}$ +26 (*c* 1, $CHCl_3$); Found C, 58.53; H, 4.28. Calc for $C_{23}H_{21}BrO_6$ (473.31) C, 58.37; H, 4.47%; ν_{max} (cm^{-1}, $CDCl_3$) 1718, 3538 (OH); δ_H (300 MHz, $CDCl_3$) 8.04 (br d, 2H, *J* 8.5), 7.98 (br d, 2H, *J* 8.5), 7.52 (s, 1H), 7.36–7.25 (m, 5H, arom-H), 7.09 (s, 1H), 4.47 (s, 2H), 4.06 (dd, 1H, *J* 3.8, *J* 5.7), 3.93 (s, 3H, COOMe), 3.77 (br s, 1H, OH), 3.54 (dd, 1H, *J* 3.8 and 10.1), 3.41 (dd, 1H, *J* 5.7 and 10.1), 3.21 (br s, 1H, OH); δ_C (75 MHz, $CDCl_3$) 185.7, 166.6, 153.8, 137.4, 137.4, 136.7, 135.4, 131.0, 129.2, 128.5, 128.1, 127.9, 80.1, 74.9, 73.7, 69.9, 52.3; *m*/*z* (DCI/NH_3) 492 and 490 $[M + NH_4]^+$, 475 and 473 $[M + H]^+$.

[5(*R*)-(4(*R*)-Fluoro-benzyloxymethyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-methanol (49)

To a solution of diol **16** (13.0 g, 78.9 mmol) in anhydrous DMF (150 mL) were added sodium hydride (3.79 g, 60% in oil, 94.7 mmol), a catalytic amount of tetrabutylammonium iodide (291 mg, 0.79 mmol) and 4-fluorobenzyl bromide (10.33 mL, 82.8 mmol) at room temperature under argon. After stirring for 18 h, the reaction mixture was poured into water (500 mL). The organic phase was extracted with ether (3 × 200 mL), dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. $[\alpha]_D^{20}$ +5° (*c* 1, $CHCl_3$); Found C, 61.10; H, 6.98. Calc. for $C_{14}H_{19}FO_4$ (270.30) C, 62.21; H, 7.09%; ν_{max} (cm^{-1}, $CHCl_3$ solution) 3606, 3460, 2990, 2934, 2878; δ_H (300 MHz, $CDCl_3$) 7.28 (m, 2H), 7.04 (m, 2H), 4.54 (s, 2H), 4.05 (m, 1H), 3.92 (dd, 1H), 3.77 (m, 1H), 3.65 (m, 1H, J 4.3 and 11.8), 3.64 (dd, 1H, *J* 5.5), 3.54 (dd, 1H, *J* 5.5 and 9.9), 2.20 (dd, 1H), 1.42 and 1.41 (2 s, 6H); *m*/*z* (CI, NH_3) 288 $[M+NH_4]^+$.

4-*O*-*p*-Fluoro-benzyl-2,3-*O*-isopropylidene-D-threose (50)

Dimethylsulfoxide (2.64 mL, 37.2 mmol) was dropwise added to a solution of oxalyl chloride (9.3 mL of a 2 M CH_2Cl_2 solution, 18.6 mmol) in dry CH_2Cl_2 at −78 °C under argon. After stirring for 1 h, a solution of the alcohol **49** (3.9 g, 14.3 mmol) in 65 mL of CH_2Cl_2 was added dropwise. Then, two hours later, triethylamine (9.9 mL, 71.45 mmol) was added and, after 30 min under stirring, the flask was removed from the dry ice-bath and allowed to reach room temperature. The reaction was then quenched by addition of brine (200 mL) and the organic phase was extracted and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 4/1 to 2/1), to give the aldehyde **50** (3.10 g, 81%) as a pale yellow oil. $[\alpha]_D^{20}$ +19° (*c* 1.5, $CHCl_3$); Found C, 61.34; H, 6.72. Calc for $C_{14}H_{17}FO_4$ (270.30) C, 62.68; H, 6.39%; ν_{max} (cm^{-1}, $CHCl_3$ solution) 2869, 1734; δ_H (300 MHz, $CDCl_3$) 9.77 (s, 1H), 7.30 (m, 2H), 7.03 (t, 2H), 4.57 (s, 2H), 4.25 (m, 2H), 3.68 (dd, 1H, *J* 10.5 and 3.8), 3.63 (dd, 1H, *J* 10.5 and 3.9), 1.45 and 1.43 (s, 6H); *m*/*z* (CI, NH_3) 286 $[M + NH_4]^+$.

5(*S*)-((4*R*)-Fluoro-benzyloxymethyl)-2,2-dimethyl-[1,3]-dioxolane-4(*S*)-carboxylic acid methyl ester (51)

Sodium hydrogenocarbonate (16.2 g, 193 mmol) was added to a solution of aldehyde **50** (3.24 g, 12.07 mmol) in a (9/1) MeOH/H_2O mixture (95 mL). Bromine (2.01 mL, 39 mmol) was then added dropwise at room temperature. After stirring the orange reaction mixture for 2 h, a 10% sodium hydrogenosulfite solution was added until the medium turned colourless. The organic layer was extracted with CH_2Cl_2 (2 × 200 mL), dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue obtained was purified by

flash column chromatography on silica gel (cyclohexane/EtOAc, 6/1 to 4/1), to give ester **51** (2.75 g, 76 %) as a colourless oil. $[\alpha]_D^{20}$ −19 (*c* 1.7, $CHCl_3$); ν_{max} (cm^{-1}, $CHCl_3$) 2994, 2956, 1757; δ_H (300 MHz, $CDCl_3$) 7.32 (t, 2H), 7.03 (t, 2H), 4.59 (s, 2H), 4.39 (d, 1H, *J* 7.5), 4.36 (m, 1H), 3.78 (s, 3H), 3.76 (dd, 1H, *J* 10.5 and 2.8), 3.67 (dd, 1H, *J* 10.5 and 5.0), 1.50 (s, 3H), 1.46 (s, 3H); *m*/*z* (CI, NH_3) 316 $[M + NH_4]^+$, 299 $[M + H]^+$.

(4*S*) and (4*R*)-(2-Chloro-allyl)-5(*R*)-(4-fluoro-benzyloxymethyl)-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (52) and (53)

Ester **51** (2.08 g, 6.96 mmol) was dissolved in dry THF (130 mL) under argon and the solution was cooled down to −78 °C. KHMDS was then dropwise added (15.3 mL of a 0.5 M toluene solution, 7.65 mmol), followed 10 min later by a cyclohexane solution (17.7 mL, 0.59 M) of 2-chloro-3-iodopropene (10.44 mmol). After stirring for 30 min at −78 °C, the reaction was quenched by addition of a 1 M aq. HCl solution (15 mL) and the flask was removed from the dry ice-bath. Then, 1 g of sodium hydrogenosulfite was added and, after extraction with CH_2Cl_2 (2 × 200 mL), the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 4/1 to 2/1), to give pure ester **53** (major product) and the enriched compound **53** (2.59 g, 87%, 80/20 from NMR, de 60%) as a colourless oil. A second purification allowed isolation of the pure compounds.

Compound (4*S*)(5*R*) (52). $[\alpha]_D^{20}$ +13 (*c* 1.3, $CHCl_3$); Found: C, 56.64; H, 5.84. Calc. $C_{18}H_{22}ClFO_5$ (372.11) C, 57.99; H, 5.95%; ν_{max} (cm^{-1}, $CHCl_3$) 2927, 2955, 2995, 1733; δ_H (300 MHz, $CDCl_3$) 7.33 (t, 2H), 7.05 (t, 2H), 5.31 (d, 1H, *J* 1.3), 5.24 (s, 1H), 4.62 (dd, 1H, *J* 11.9), 4.52 (dd, 1H, *J* 11.9), 4.32 (dd, 1H, *J* 7.9 and 2.7), 3.82 (dd, 1H, *J* 10.3 and 2.8), 3.78 (s, 3H),3.65 (dd, 1H, *J* 10.3 and 8.0), 2.80 (dd, 1H, *J* 14.4), 2.64 (dd, 1H, *J* 14.4), 1.55 (s, 3H), 1.47 (s, 3H); *m*/*z* (CI, NH_3) 390 $[M + NH_4]^+$.

Compound (4*R*)(5*R*) (53). $[\alpha]_D^{20}$ +6° (*c* 1.5, $CHCl_3$); Found: C, 50.38; H, 5.16. Calc. for $C_{18}H_{22}ClFO_5$ (372.11) C, 57.99; H, 5.95%; ν_{max} (cm^{-1}, $CHCl_3$) 2873, 2928, 2991, 1733; δ_H (300 MHz, $CDCl_3$) 7.31 (t, 2H), 7.03 (t, 2H), 5.35 (d, 1H, *J* 1.0), 5.30 (s, 1H, *J* 1.0), 4.57 (dd, 1H, *J* 12.0), 4.48 (d, *J* 12.0), 4.27 (dd, 1H, *J* 6.7 and 3.6), 3.71 (dd, 1H, *J* 3.6), 3.69 (s, 3H), 3.52 (dd, 1H, *J* 10.9 and 6.7), 3.08 (d, 1H, *J* 15.2), 2.73 (d, 1H, *J* 15.2), 1.62 (s, 3H), 1.44 (s, 3H); *m*/*z* (CI, NH_3) 390 $[M + NH_4]^+$.

[(4*R*)-(2-Chloro-allyl)-5(*R*)-(4-fluoro-benzyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (54) and [(4*S*)(2-chloro-allyl)-5(*R*)-(4-fluoro-benzyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (55)

A mixture of esters **52** + **53** (3.59 g, 9.62 mmol) was dissolved in 96 mL of anhydrous THF. Then, $LiAlH_4$ (474.5 mg, 12.50 mmol) was added at room temperature and the reaction mixture was stirred for 45 min at r.t. under argon. The mixture was then cautiously transferred into a beaker containing water (400 mL) and CH_2Cl_2 (400 mL), then 12 M hydrochloric acid was added until the white precipitate was dissolved. After extraction with CH_2Cl_2 the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 10/1 to 7/1), to give alcohols **54** (1.7 g, 51.5%) and **55** (0.428 g, 13 %) as a colourless oil.

Compound (4*R*)-(5*R*) 54. $[\alpha]_D^{20}$ +61 (*c* 1.3, $CHCl_3$); Found: C, 59.17; H, 6.45. Calc. for $C_{18}H_{22}ClFO_5$ (344.81) C, 59.22; H, 6.43%; ν_{max} (cm^{-1}, $CHCl_3$): 3466, 2876, 2937, 2991; δ_H (300 MHz, $CDCl_3$) 7.29 (t, 2H), 7.04 (t, 2H), 5.39 (d, 1H), 5.28 (s, 1H), 4.58 (dd, 1H, *J* 11.6), 4.49 (dd, 1H, *J* 11.6), 4.33 (dd, 1H, *J* 7.0 and 6.0), 3.72 (dd, 2H, *J* 7.8), 3.67 (dd, 1H, *J* 9.5 and 6.0), 3.51 (dd, 1H, *J* 9.5 and 7.2), 2.59 (dd, 1H), 2.47 (dd, 1H), 2.40 (m, 1H), 1.52 (s, 3H), 1.38 (s, 3H); *m*/*z* (CI, NH_3) 362 $[M + NH_4]^+$.

Compound (4*S*)-(5*R*) 55. $[\alpha]_D^{20}$ +6 (*c* 1, $CHCl_3$); Found: C, 60.62; H, 6.44. Calc. for $C_{18}H_{22}ClFO_5$ (344.81) C, 59.22; H, 6.43%; ν_{max} (cm^{-1}, $CHCl_3$): 2934, 2991; δ_H (300 MHz, $CDCl_3$) 7.30 (m, 2H), 7.04 (m, 2H), 5.37 (d, 1H, *J* 1.0), 5.28 (s, 1H), 4.57 (dd, H, *J* 11.9), 4.32 (t, 1H, *J* 5.1), 3.73 (m, 2H), 3.54 (d, 2H, *J* 6.7), 2.77 (dd, 2H, *J* 14.7), 2.33 (t, 1H, *J* 6.7), 1.48 (s, 3H), 1.41 (s, 3H); *m*/*z* 362 (CI, NH_3) $[M + NH_4]^+$.

4(*S*)-(2-Chloro-allyl)-5(*R*)-(4-fluoro-benzyloxymethyl)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (56)

The alcohol **54** (2.55 g, 7.39 mmol) was dissolved in 123 mL of dry CH_2Cl_2 under argon. Then pyridinium chlorochromate (3.19 g, 14.78 mmol) was introduced at room temperature. After stirring for 21 h, pyridinium chlorochromate (1.59 g, 7.39 mmol) was added. After reacting for 24 h, the reaction medium was transferred into a flask containing 200 mL of ether. The solution was filtered through a short silica pad and the solvent was evaporated under reduced pressure, giving the aldehyde **56** (2.4 g, 94%) as a pale yellow oil, $[\alpha]_D^{20}$ +60 (*c* 1.5, $CHCl_3$); Found: C, 58.08; H, 5.51. Calc. for $C_{17}H_{20}ClFO_4$ (342.79) C, 59.56; H, 5.88%; ν_{max} (cm^{-1}, $CHCl_3$ solution) 2924, 2994, 1733; δ_H (300 MHz, $CDCl_3$) 9.67 (s, 1H), 7.29 (t, 2H), 7.03 (t, 2H), 5.36 (d, 1H), 5.26 (s, 1H), 4.47 (dd, 2H), 4.33 (dd, 1H, *J* 5.0 and 4.2), 3.66 (dd, 1H, *J* 10.4 and 4.2), 3.55 (dd, 1H, *J* 10.9 and 5.3), 3.02 (d, 1H, *J* 15.0), 2.75 (d, 1H, *J* 15.0), 1.62 (s, 3H), 1.49 (s, 3H); *m*/*z* (CI, NH_3) 360 $[M + NH_4]^+$.

(5*R*),4(*R*)-Fluoro-benzyloxymethyl-2,2-dimethyl-1,3-dioxa-spiro[4.4]non-8-en-7-one (57)

The aldehyde **56** (1.00 g, 2.92 mmol) was dissolved in MeCN/H_2O (30 mL, 4/1). To this solution, at 0 °C, was added *N*-bromosuccinimide (530 mg, 2.98 mmol) and one drop of a 0.1 M hydrobromic acid solution in water. The medium took on a bright yellow colour. After stirring for 30 min, the reaction mixture was poured into a separatory funnel and extracted by 3 × 50 mL of CH_2Cl_2. The solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude α-bromoketone intermediate was then dissolved in anhydrous CH_2Cl_2 (25 mL) under argon. Triphenylphosphine (1.68 g, 6.40 mmol) and triethylamine (0.45 ml, 3.21 mmol) were successively added to this solution, and the reaction medium was stirred for 24 h. The reaction was then quenched with pouring the mixture into a separatory funnel containing 100 mL of water. After extraction, the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 6/1 to 4/1), to give cyclopentenone **57** (313 mg, 35%) a colourless oil, $[\alpha]_D^{20}$ +70 (*c* 1.4, $CHCl_3$); Found: C, 66.80; H, 6.43. Calc. for $C_{17}H_{19}FO_4$ (306.33) C, 66.65; H, 6.25%; ν_{max} (cm^{-1}, $CHCl_3$ solution) 2927, 2991, 1723; δ_H (300 MHz, $CDCl_3$) 7.32 (d, 1H, *J* 5.4), 7.23 (m, 2H), 7.02 (m, 2H), 6.21 (d, 1H, *J* 5.9), 4.43 (dd, 2H, *J* 11.0), 4.27 (t, 1H, *J* 6.0), 3.64 (dd, 1H, *J* 10.0 and 6.0), 3.39 (dd, 1H, *J* 10.0 and 5.8), 2.64 (d, 1H, *J* 18.3), 2.30 (dd, 1H, *J* 18.3), 1.45 (s, 3H), 1.43 (s, 3H); δ_C (100 MHz, $CDCl_3$) 206, 162, 160, 136, 130, 114, 110, 86, 79, 73, 68, 43, 7; *m*/*z* (CI, NH_3) 324 $[M + NH_4]^+$.

(5*R*)-8-Bromo-4(*R*)-(4-fluoro-benzyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro[4.4]non-8-en-7-one (58)

Cyclopentenone **57** (166.6 mg, 543 μmol) was dissolved in anhydrous CH_2Cl_2 (1.9 mL) under argon. After cooling to 0 °C,

a 3 M solution of bromine in CH_2Cl_2 (0.18 mL, 0.5 μmol) was slowly added until the orange colour persisted. Once all the bromine was added, (0.151 mL, 1.09 mmol) the reaction was stirred for 10 min and poured into a separatory funnel containing water (10 mL). After extraction with CH_2Cl_2, the organic layers were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 6/1 to 4/1), to give bromo-cyclopentenone **58** (153.4 mg, 73%) as a yellow oil, $[a]_D^{20}$ +15° (*c* 1, $CHCl_3$).

Compound 58. ν_{max} (cm^{-1}, $CHCl_3$ solution) 2871, 2929, 2992, 1733; δ_H (300 MHz, $CDCl_3$) 7.44 (s, 1H), 7.19 (m, 2H), 7.03 (m, 2H), 4.37 (dd, 2H, *J* 11.0), 4.25 (t, 1H, *J* 6.2), 3.69 (dd, 1H, *J* 9.7 and 5.7), 3.43 (dd, 1H, *J* 9.7 and 6.8), 2.85 (d, 1H, *J* 18.3), 2.44 (d, 1H, *J* 18.3), 1.45 (s, 3H), 1.44 (s, 3H); *m/z* (CI,NH_3) 404 (^{81}Br) and 402 (^{79}Br) $[M + NH_4]^+$.

(5*R*) 4-{8-Bromo-4(*R*)-(4-fluoro-benzyloxymethyl)-2,2-dimethyl-7-oxo-1,3-dioxa-spiro[4.4]non-8-en-6-yl]-hydroxy-methyl}-benzoic acid methyl ester (59)

The bromo-cyclopentenone **58** (94.5 mg, 0.245 mmol) was dissolved in 8.7 mL of anhydrous THF under argon. The solution was cooled to −78 °C, then 0.54 μL (0.27 mmol) of a 0.5 M solution of KHMDS in toluene was added. After stirring for 10 min, methyl 4-formylbenzoate (80 mg, 0.49 μmol) dissolved in 1 mL of anhydrous THF was added dropwise. After 45 min, the reaction was quenched by addition of water and allowed to reach room temperature. The organic layers were extracted with CH_2Cl_2, dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure giving a residue containing a mixture of inseparable diastereoisomeric aldol products **59**. Compound **59**: δ_H (300 MHz, $CDCl_3$) 8.00 (m, 2H), 7.53 (s, 0.5 H), 7.47 (s, 0.5 H), 7.31 (t, 2H), 7.20 (m, 2H), 7.15–6.96 (m, 2H), 5.25 (m, 1H), 4.43 (m, 2H), 4.29–2.98 (m, 4H), 3.93 (s, 3H), 1.58 (t, 6H); *m/z* (CI, NH_3) 568 (^{81}Br) and 566 (^{79}Br) $[M + NH_4]^+$.

{4-Bromo-2(*S*)-[2-(4-fluoro-benzyloxy)-1(*R*)-hydroxy-ethyl]-2-hydroxy-5-oxo-cyclopent-3-enylidenemethyl}-benzoic acid methyl ester (60)

The mixture of aldols **59** (35.7 mg, 65 μmol) was dissolved into anhydrous pyridine (1 mL) under argon. To this solution were introduced acetic anhydride (55 μL) and a catalytic amount of 4-DMAP. The reaction medium was then heated at 80 °C for 1.25 h and the reaction was quenched by pouring it into a separatory funnel containing a saturated $CuSO_4$ solution (10 mL). After extraction with CH_2Cl_2, the organic phase was washed with a saturated solution of $CuSO_4$, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue obtained was dissolved into a H_2O/THF/TFA mixture (1 mL, 2/2/1) and stirred for 3 h under argon at 80 °C. The reaction medium was then transferred into a separatory funnel containing brine (10 mL). After extraction by CH_2Cl_2, the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 4/1 to 3/1), to give bromo-cyclopentadienone **60** (12.8 mg, 40% from **59**, 1/4 *E*/*Z* mixture) as a yellow oil. Compound **60**: δ_H (300 MHz, $CDCl_3$) 8.00 (m, 3H), 7.72 (m, 0.4H), 7.63 (s, 0.2H), 7.54 (s, 0.2H), 7.50 (m, 0.4H), 7.49 (s, 0.8H), 7.29 (m, 2H), 7.06 (m, 2.25H), 4.52 (t, 2H), 4.06 (m, 1H, *J* 3.9), 3.92 (s, 3H), 3.75 (dd, 1H, *J* 9.8 and 5.1), 3.65 (dd, 1H, *J* 9.7 and 4.6), 3.54 (s, 1H), 2.79 (br d, 1H); Cl-HRMS (CH_4) *m/z* Calc. for $C_{23}H_{21}(^{79}Br)FO_6$ 491.0506, and for $C_{23}H_{21}(^{81}Br)FO_6$ 493.0485, found 491.0495 (^{79}Br), 493.0478 (^{81}Br) $[M + H]^+$.

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