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Enantioselective synthesis of *cis*-1,2-dialkyl substituted cyclopentanoid and isoprostane building blocks via 6-*exo*-trigonal radical cyclizations

Giuseppe Zanoni, Savino Re, Alessia Meriggi, Francesca Castronovo and Giovanni Vidari*

Dipartimento di Chimica Organica, Università di Pavia, Viale Taramelli 10, 27100 Pavia, Italy

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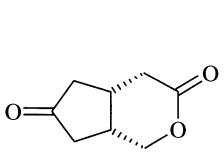
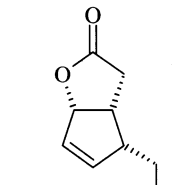
Abstract—Two different 6-*exo*-trigonal cyclizations of enantiomerically enriched 6-heptenyl radicals readily afforded versatile synthetic precursors of *cis*-1,2-dialkyl substituted cyclopentane derivatives. Starting from one of these intermediates, we accomplished an enantiospecific formal synthesis of two important isoprostanes, namely 15-F_{2c}-IsoP and *ent*-15-F_{2c}-IsoP.

1. Introduction

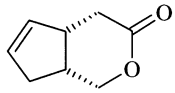
Over the last few years our interest has focused on the synthesis of lactones **1**[1] and **2a**,[2,3] which are attractive building blocks for the synthesis of *cis*-1,2-dialkyl substituted cyclopentane derivatives. In fact, the three oxygenated functional groups of **1** and **2a** are all different in character, thus allowing for chemo- and regioselective transformations; in addition, the *cis* fusion between the two rings allows predictable stereocontrol in addition reactions to the carbon atoms of the ring systems. The synthetic utility of compounds **1** and **2a**, and the *O*-benzyl ether **2b**[4–6] has been demonstrated in the syntheses of iridoids[1,3–5] and compounds of the 12-oxophytodienoic cascade.[2] In the preceding paper of this series[3] we have described the kinetic resolution of (±)-**2a** through an irreversible enantioselective transacylation promoted by *Pseudomonas cepacia* lipase, which led to enantiomerically enriched (+)-**2c** along with slow reacting (+)-**2a**. Herein we report two complementary asymmetric approaches to lactones (+)-**2a** and (−)-**2a** based on two different stereoselective 6-*exo*-trigonal cyclizations of chiral heptenyl radicals. En route to **2a**, both enantiomers of lactones **1** and **3** were also obtained in enantiomerically pure form. The enantiomers (+)-**2a** and (−)-**2a** were then separately converted into diols (−)-**4a** and (+)-**4a**, respectively, thus accomplishing a formal synthesis of isoprostanes 15-F_{2c}-IsoP and *ent*-15-F_{2c}-IsoP, respectively.



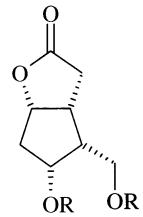
(+)-**1**



(+)-**2a** R=H
2b R=Bn
(-)-**2c** R=Ac



(+)-**3**



(-)- **4a** R=H
(-)- **4b** R=Ac

* Corresponding author. Tel.: +39 0382507322; fax: +39 0382507323; e-mail: vidari@chifis.unipv.it

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2. Results and discussion

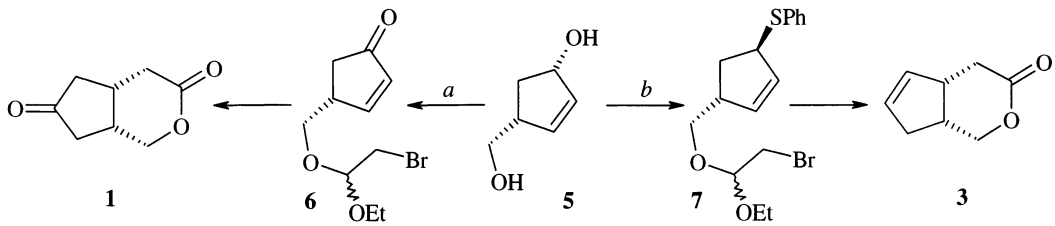
Heptenyl radicals can cyclize in a 6-*exo* or 7-*endo* fashion.[7] Although a fair number of 7-*endo* cyclizations are known, 6-*exo*-trigonal cyclizations are more common, and most examples of stereoselective heptenyl radical cyclizations fall into this class.[7] In particular, Stork[8] and others[9] have demonstrated that radical cyclization of bromoacetals can lead, in a highly stereoselective fashion, to six-membered acetal rings *cis*-annulated to rings of different size. We sought to employ this strategy with the aim of constructing the δ-lactone ring of compounds **1** and **3**, respectively, using the 6-*exo*-trigonal radical cyclizations of bromoacetals **6** and **7**, respectively (Scheme 1, routes *a* and *b*, respectively).

In essence, the two reactions differ in the tactics used for accelerating the radical cyclization; in route *a* the alkene acceptor is activated with an electron-withdrawing group,[8] while in route *b* the intermediate cyclopentyl radical would be trapped by a rapid elimination of a thiophenyl radical.[10] We envisaged diol **5** as a suitable starting material for the synthesis of acetals **6** and **7** in either enantiomeric series. In fact, Hodgson has recently reported an efficient enantioselective base-induced rearrangement of the achiral epoxy-alcohol **8**, which can afford either diol (−)-**5** or (+)-**5**, e.e. ≥95%, depending on the configuration of dilithiated norephedrine used as a base (Scheme 2).[5,11]

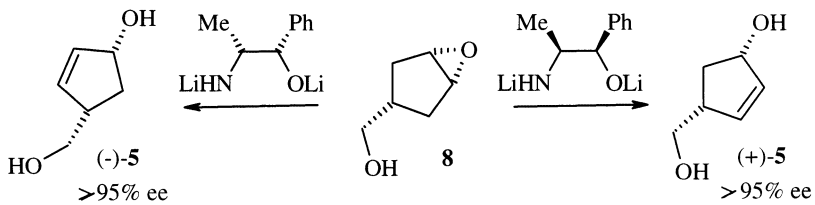
For convenience, Schemes 1, 3 and 4 and the experimental section describe the reactions performed in one enantiomeric series; actually, both antipodes of lactones **1**, **2a** and **3** were obtained according to an identical sequence of reactions starting from either (−)-**5** or from (+)-**5**.

2.1. Asymmetric synthesis of lactones 1, 2a and 3

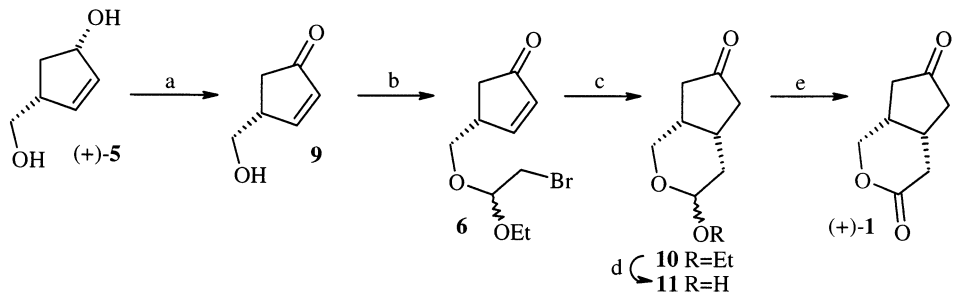
Selective oxidation of the allylic hydroxy group of diol (+)-**5**, $[\alpha]_D^{20}$ +43.4 (*c* 1.0, CH_2Cl_2) [lit.[11] $[\alpha]_D^{20}$ +46.7 (*c* 1.55, CH_2Cl_2)], with PCC readily afforded the keto-alcohol **9**, which was converted under standard conditions to bromoderivative **6** as a mixture of epimeric acetals. Exposure of **6** to tributyltin hydride cleanly afforded the desired annulated product **10**, which was converted to lactone (+)-**1** in two additional simple steps (Scheme 3). Comparison of the spectroscopic data of (+)-**1** with an authentic sample of the racemic compound[1] confirmed the *cis* stereochemistry at the ring fusion, whereas the absolute configuration and the enantiomeric excess, up to 95%, was verified by conversion to (+)-**2a**[2] and subsequent enantioselective GC analysis.[3]



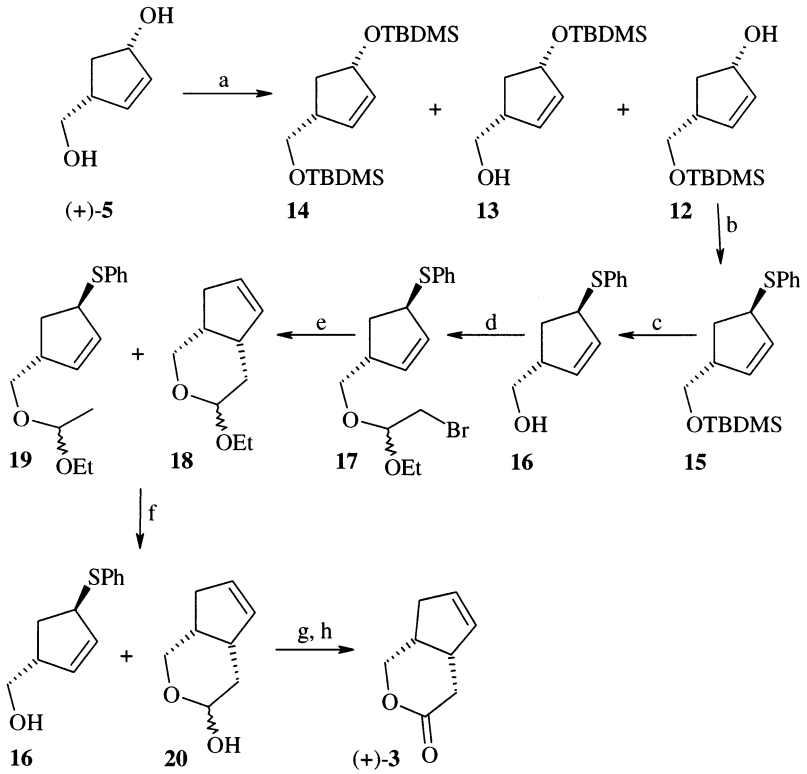
Scheme 1.



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) DMAPCC, CH_2Cl_2, 20°C, 12 h, 70%; (b) NBS, ethyl vinyl ether, CH_2Cl_2, −40→20°C, 23 h, 76%; (c) nBu$_3$SnH, cat. AIBN, toluene, reflux, 6 h, 95%; (d) THF, 0.25N HCl, 0→20°C, 4 h, 94%; (e) PCC, CH_2Cl_2, 20°C, 3 h, 85%.



Scheme 4. *Reagents and conditions*: (a) TBDSMCl, imidazole, DMAP, CH_2Cl_2, 20°C, 3 h, 40% of **12**; (b) *N*-(phenylthio)phthalimide, $n$$Bu_3P$, benzene, 20°C, 4 h, 97%; (c) Bu_4NF, 20°C, 10 h, 98%; (d) NBS, ethyl vinyl ether, CH_2Cl_2, −40→20°C, 24 h, 98%; (e) $Me_3SnSnMe_3$, Ph_2CO, 320 nm, 4 h; (f) THF, 0.25N HCl, 0→20°C, 5 h; (g) chromatographic separation, 56% of compound **20** from acetal **17**; (h) PCC, CH_2Cl_2, 20°C, 3 h, 85%.

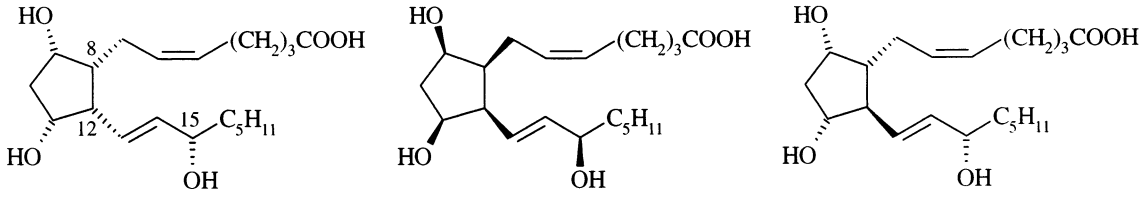
In order to perform pathway *b* of Scheme 1, at first we needed to mask the primary hydroxy group of diol (+)-**5**. Using standard methods, the desired monoprotected silyl ether **12** was obtained in 40% yield along with the regioisomeric derivative **13** and the diprotected ether **14**; the latter compounds were easily separated from **12** by flash column chromatography on silica gel and recycled (Bu_4NF) to starting diol **5**. The allyl phenyl sulphide **15** was then introduced with a Mitsunobu-type reaction[12] and a bromoacetal group was subsequently installed on the deprotected primary alcohol **16**. This reaction sequence readily afforded the key intermediate **17** on gram scale in reproducible high yields (ca. 90% over three steps).

Tandem photoinduced radical 6-*exo*-trigonal cyclization and phenylthio radical expulsion allowed the clean conversion of bromoacetal **17** into the bicyclic olefin **18** as a mixture of acetal epimers. They were accompanied by variable amounts of the hydrodebrominated product **19**. The mixture of compounds **18** and **19** could not be efficiently separated at this stage and was therefore directly submitted to hydrolysis of the acetal group. At this stage hemiacetals **20** were easily separated from alcohol **16** by flash column chromatography and were then readily oxidized to the expected lactone (+)-**3**. NMR data confirmed the structure, while the absolute configuration and the enantiomeric excess, up to 95%, were verified by conversion[†] of (+)-**3** into (+)-**2a** and (−)-**2c** and enantioselective GC analysis of the latter compounds.[3]

2.2. Stereoselective synthesis of isoprostane and prostaglandin building blocks

As stated in the introduction, enantiomerically enriched lactones **1** and **2a** are valuable starting materials for the enantioselective synthesis of iridoids and compounds of the 12-oxophytodienoic cascade.[1–3] To further exploit the synthetic potential of **2a**, we decided to explore its conversion into the *endo* Corey-like lactone **4a**, which would constitute a practical entry to F-prostaglandins and F-isoprostanes. Isoprostanes are a new class of reactive compounds that are formed in mammalian cells as products of free radical-induced peroxidation of arachidononoyl lipids. They exert unique biological actions relevant to the pathobiology of oxidative stress.[13–15] In contrast to the *cyclo*-oxygenase mediated process leading to prostaglandins, the non-enzymatic radical mechanism results in the formation of prostanoids with a *cis*-arrangement of the 8- and 12-sidechains (compare compounds **21** and **22** with **23**).

[†] The conversion was executed according to the procedure described for (±)-**3** in Ref. 2.



21 15-F_{2c}-IsoP (12-*epi*-$PGF_{2\alpha}$)

22 *ent*-15-F_{2c}-IsoP (*ent*-12-*epi*-$PGF_{2\alpha}$)

23 $PGF_{2\alpha}$

Isoprostanes are generated in racemic form, which is consistent with a non-enzymatic pathway; however, both enantiomers of the compounds are necessary for biological evaluation. 15-F_{2c}-Isop **21**[16–18] and its enantiomer **22**[19,20] are among the most synthetically targeted isoprostanes.[21] Moreover, compound **21** possesses biological activity similar to that of $PGF_{2\alpha}$ and was shown to activate the $PGF_{2\alpha}$ human receptor in the eye.[22]

Following the pioneering work of the Rockach group, diols (−)-**4a**[15,23] and (+)-**4a**,[19,24] and derivatives,[20,25,26] have been widely used as starting materials in the asymmetric syntheses of F_{2c}- and *ent*-F_{2c} isoprostanes, respectively. Notably, so far all these cyclopentane derivatives have been obtained by annulating an endocyclic radical to a butenolide acceptor double bond (a radical 12→8 5-*exo*-trigonal cyclization, according to the proposed IsoP numbering[27]) and their chirality have been derived from members of the sugar chiral pool.

With both (+)-**2a** and (−)-**2a** readily available either by enzymatic kinetic resolution[3] or asymmetric synthesis (this paper), we envisaged their straightforward conversion into diols (−)-**4a** and (+)-**4a**, respectively, through the intermediacy of iododerivatives of type **26**. However, we met no success in attempts to install a iodohydrin across the double bond of the acetate of (+)-**2a** using conventional methods.[28] In contrast, we discovered that exposure of (−)-**2c** to ICl in MeCN–H_2O (8:1) gave rise to a mixture (ratio 7:3) of acetoxy-iodohydrins **26** and **27** in 96% isolated yield. The reaction occurred rapidly at room temperature and proceeded with a complete stereocontrol of the installed stereocenters at C(10) and C(11). Formation of the two regioisomeric monoacetates **26** and **27** could be explained by assuming that the iodonium ion **24**, installed on the less hindered convex side of the bicyclic structure **2c**, was rapidly intercepted by the proximate acetoxy group giving rise to the resonance stabilized cation **25** which, in the presence of H_2O, finally collapsed to the two acetates (Scheme 5).

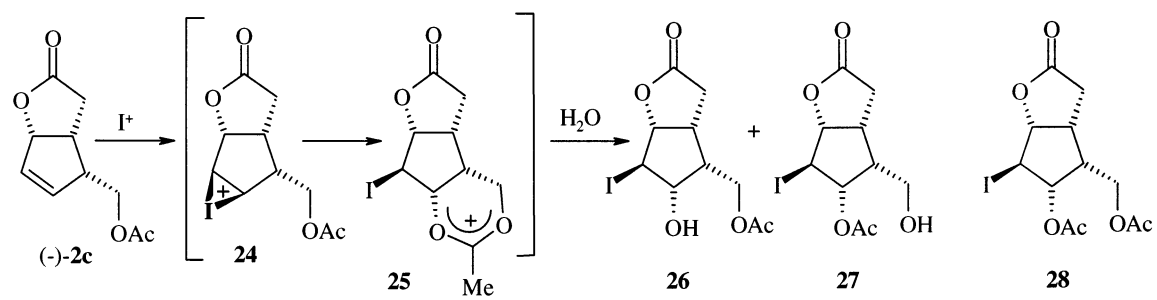
To our knowledge, this simple method for the 1,3-functionalization of a homoallylic acetate has no precedent in the literature. The stereochemistry of compounds **26** and **27** was assigned by inspection of the vicinal coupling constants in the ^1H NMR spectra and proton correlations in NOESY experiments; moreover, both monoacetates gave a single diacetate **28** upon acetylation under standard conditions. Hydrodeiodination (*n*-Bu_3SnH) of compound **28**, followed by removal of both acetyl groups of **4b** using an anionic exchange resin, readily afforded diol (−)-**4a** in 86% yield over two steps. The synthesized **4a** had mp 126–127°C and $[\alpha]_D^{20}$ −13.5 (*c* 0.5, $CHCl_3$), identical with the literature.[15,23] As mentioned earlier in the article, all the reactions of (−)-**2c** have been duplicated with (+)-**2c**. Consequently, we also prepared diol (+)-**4a** ($[\alpha]_D^{20}$ +12 (*c* 0.6, $CHCl_3$), identical with the literature.[19,24])

3. Conclusion

In conclusion, we have described the first asymmetric synthesis of both enantiomers of building block lactones **1** and **3** using two different 6-*exo*-trigonal radical cyclizations of 6-heptenyl radicals. Each enantiomer of these compounds was then separately converted, in a completely stereocontrolled fashion, into diols (−)-**4a** and (+)-**4a**, respectively, thus accomplishing an enantiospecific formal synthesis of 15-F_{2c}-IsoP **21** and *ent*-15-F_{2c}-IsoP **22**, respectively. Our synthesis of diols (−)-**4a** and (+)-**4a** describes an innovative approach with respect to existing methods and compares favorably with the literature in terms of stereoselectivity and yield.

4. Experimental

Melting points were determined on a Fisher–Johns hot plate and are uncorrected. IR spectra were recorded as



Scheme 5.

thin films on a Perkin–Elmer FT-IR Paragon 100 PC spectrometer ^{1}H NMR (300 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$ solution unless indicated otherwise with a Bruker CXP 300 spectrometer. Chemical shifts are reported in δ units relative to $CHCl_3$ [δ_H 7.26, δ_C (central line of t) 77.0]; the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, qu = quintuplet, m = multiplet, and br = broad are used throughout. Coupling constants (J) are given in Hz. The multiplicity (in parentheses) of each carbon atom was determined by DEPT experiments. Mass spectra (direct inlet system) were recorded at 70 eV (0.5 mA) with a Finnigan MAT 8222 instrument. Syringes and needles for the transfer of reagents were dried at 140°C and allowed to cool in a desiccator over P_2O_5 before use. Analytical TLC was carried out on glass-backed plates, pre-coated with a 0.25 mm layer of silica gel, and visualization was effected with short-wavelength UV light (254 nm) or with 0.5% vanillin solution in H_2SO_4–EtOH (4:1) followed by heating. Flash column chromatography was accomplished with Kieselgel 60 (40–63 μm). E.e. values were determined by HRGC using a Hewlett–Packard mod. 5890II instrument, equipped with a EASY-SEP capillary column purchased from Analytical Technology (25m× 0.32 mm id and 0.25 μm film thickness); injector (split splitless, split ratio 1:36) temperature 250°C, detector (FID) temperature 280°C, carrier gas He, 1.27 mL min^{-1}. Retention times (t_R) are given in min. Optical activity was measured with a Perkin–Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. All commercial reagent grade solvents were dried and degassed by standard techniques directly before use. Yields are reported for chromatographically and spectroscopically pure isolated compounds.

4.1. (4*R*)-4-Hydroxymethyl-cyclopent-2-enone (+)-9

4-(Dimethylamino)pyridinium chlorochromate (5.6 g, 21.6 mmol) was added in one portion to a solution of diol (+)-**5**, e.e. ≥95%,[5,11] $[\alpha]_D^{20}$ +43.4 (*c* 1.0, CH_2Cl_2) [lit.[11] $[\alpha]_D^{20}$ +46.7 (*c* 1.55, CH_2Cl_2)], (0.5 g, 4.38 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 12 h at 20°C, diluted with Et_2O and filtered on a Celite pad. Evaporation of the solvent gave a residue which was purified by flash chromatography on silica gel (15 g). Elution with Et_2O gave ketone (+)-**9** (320 mg, 65%), as a pale yellow oil; $[\alpha]_D^{20}$ +159 (*c* 0.5, CH_2Cl_2); IR (neat): 3400, 2930, 2880, 1710, 1590, 1195, 1070, 1030, 945, 790 cm^{-1}; ^{1}H NMR: δ 1.89 (1H, s), 2.18 (1H, dd, J = 18 and 2), 2.51 (1H, dd, J = 18 and 7), 3.15–3.24 (1H, m), 3.65–3.85 (2H, m), 6.24 (1H, dd, J = 5.5 and 2), 7.70 (1H, dd, J = 5.5 and 2); ^{13}C NMR: δ 37.4 (2), 43.8 (1), 64.4 (2), 135.3 (1), 164.9 (1), 209.2 (0); EIMS *m*/*z* (rel. intensity): 112 [M$^+$] (34), 97 (19), 94 (15), 82 (85), 67 (22), 66 (21), 53 (100), 31 (41). Anal. calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.35; H, 7.11%.

4.2. (1′*RS*,4*R*)-4-(2-Bromo-1-ethoxy-ethoxymethyl)-cyclopent-2-enone 6

Freshly recrystallized (H_2O) NBS (184 mg, 1.03 mmol) was added in one portion to a solution of (+)-**9** (100 mg, 0.89 mmol) in dry CH_2Cl_2 (4 mL) under an argon atmosphere. The mixture, cooled to −40°C, was treated with ethyl vinyl ether (120 μL, 1.26 mmol), stirred for 2 h, allowed to warm to 20°C, and stirred for an additional 21 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), extracted with H_2O, and the aqueous phase re-extracted with CH_2Cl_2 (3×5 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue purified by flash chromatography on silica gel (5 g). Elution with hexane–EtOAc (4:1) gave an inseparable mixture of diastereomeric bromoacetals **6** as a pale yellow oil (178 mg, 76%); IR (neat): 3050, 2980, 2925, 1713, 1588, 1425, 1348, 1187, 1127, 1058, 785 cm^{-1}; ^{1}H NMR: δ 1.22 (3H, t, J = 7.0), 2.15 (1H, dd, J = 18.8 and 2), 2.51 (1H, dd, J = 18.8 and 7.5), 3.25 (1H, m), 3.38 (2H, d, J = 7.0), 3.50–3.80 (4H, m), 4.68 (1H, t, J = 7.0), 6.24 (1H, dd, J = 5.5 and 2.0), 7.72 (1H, m); ^{13}C NMR: δ 15.1 (3), 37.8 (2), 38.0 (2), 41.7 (1), 41.9 (1), 60.9 (2), 62.7 (2), 66.5 (2), 66.6 (2), 68.0 (2), 68.1 (2), 99.5 (1), 99.6 (1), 134.9 (1), 135.1 (1), 164.8 (1), 165.3 (1), 206.4 (0).

4.3. (4a*S*,7a*R*)-3-Ethoxy-hexahydro-cyclopenta[*c*]pyran-6-one 10

A catalytic amount of AIBN and a solution of tributyltin hydride (280 μL, 1.04 mmol) in dry benzene (20 mL) were added to a solution of bromoacetals **6** (200 mg, 0.76 mmol) in dry benzene (8 mL) under an argon atmosphere. The mixture was heated under reflux for 6 h, allowed to warm to rt, concentrated, and the residue purified by flash chromatography on silica gel (5 g). Elution with hexane–EtOAc (2:1) gave an inseparable mixture of diastereomeric acetals **10** as a colorless oil (133 mg, 95%); IR (neat): 2960, 2920, 2888, 1740, 1440, 1405, 1380, 1335, 1205, 1146, 1123, 1060, 1010, 970, 950, 860 cm^{-1}; ^{1}H NMR: δ 1.2–2.8 (11H, m), 3.4–4.1 (4H, m), 4.65–4.8 (1H, m). CIMS (CH_4): *m*/*z* 185 [M+H$^+$].

4.4. (4a*S*,7a*R*)-3-Hydroxy-hexahydro-cyclopenta[*c*]-pyran-6-one 11

To a solution of acetals **10** (100 mg, 0.54 mmol) in THF (2 mL) at 0°C was added aqueous HCl (0.25N, 1 mL). The solution was stirred at 0°C for 1 h, then at rt for 4 h, diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3×5 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue purified by flash chromatography on silica gel (8 g). Elution with hexane–EtOAc (35:65) gave an inseparable mixture of diastereomeric lactols **11** as a colorless oil (80 mg, 94%); IR (neat): 3404, 2950, 2855, 1735, 1403, 1162, 1087, 1059, 1017, 945, 875, 855 cm^{-1}; ^{1}H NMR: δ 2–2.6 (8H, m), 2.9 (0.5H, brs, OH), 3.2 (0.5H, brs, OH), 3.55 (0.5H, dd, J = 14.0 and 3.4), 3.80 (0.5H, dd, J = 14.0 and 3.4), 3.96 (0.5H, dd, J = 14.0 and 3.4), 4.30 (0.5H, dd, J = 14.0 and 3.4), 4.88 (0.5H, brd, J = 10.5), 5.20 (0.5H, brs); EIMS *m*/*z* (rel. intensity): 156 [M$^+$] (9), 128 (3), 110 (30), 95 (20), 82 (30), 69 (48), 67 (65), 54 (43), 41 (100).

4.5. (+)-(4a*R*,7a*R*)-Tetrahydro-cyclopenta[*c*]pyran-3,6-dione (+)-1

Solid pyridinium chlorochromate (PCC) (276 mg, 1.28 mmol) and NaOAc (20 mg) were added to a solution of lactols **11** (100 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) at rt After stirring for 3 h, Et_2O (10 mL) was added and the reaction mixture was filtered on a pad of Celite, and concentrated. The residue was purified by flash chromatography on silica gel (8 g). Elution with hexane–EtOAc (1:1) gave lactone (+)-**1** (84 mg, 85%), $[\alpha]_D^{20}$ +17.0 (*c* 0.3, CH_2Cl_2), identical (^1H, ^{13}C NMR, and MS spectra) with an authentic sample of (±)-**1**.[1]

4.6. (1*S*,4*R*)-(+)-4-(*tert*-Butyldimethylsilanyloxymethyl)-cyclopent-2-enol (+)-12

To a solution of diol (+)-**5**, e.e. ≥95%,[5,11] $[\alpha]_D^{20}$ +43.4 (*c* 1.0, CH_2Cl_2) [lit.[11] $[\alpha]_D^{20}$ +46.7 (*c* 1.55, CH_2Cl_2)], (300 mg, 2.63 mmol) in dry CH_2Cl_2 (5 mL) at 0°C under an argon atmosphere, was added sequentially imidazole (353 mg, 5.2 mmol), 4-dimethylaminopyridine (DMAP) (10 mg), and a solution of *tert*-$BuMe_2SiCl$ (356 mg, 2.36 mmol) in dry CH_2Cl_2 (9 mL). The mixture was stirred at 0°C for 3 h, then filtered and evaporated to dryness under vacuum. The residue was separated by flash chromatography on silica gel (35 g). Elution with hexane–EtOAc (85:15) gave, in addition to **13** (90 mg, 15%), **14** (45 mg, 5%) and recovered **5** (75 mg, 20%), monoprotected diol (+)-**12** as a colorless oil (242 mg, 40%), $[\alpha]_D^{20}$ +58.6 (*c* 0.6, CH_2Cl_2); IR (neat): 3405, 3050, 2955, 2857, 1614, 1361, 1256, 1177, 1083,1041, 1007 cm^{-1}; ^1H NMR: δ 0.05 (6H, s), 0.90 (9H, s), 1.55 (1H, brd, $J=14.0$), 2.28 (1H, ddd, $J=14.0$, 8.5, and 7.0), 2.70–2.85 (2H, m), 3.56 (2H, m), 4.60 (1H, m), 5.75 (1H, dd, $J=7.0$ and 2.0), 5.95 (1H, brd, $J=7.0$); ^{13}C NMR: δ −5.6 (2×3), 18.4 (0), 25.9 (3×3), 36.9 (2), 46.2 (1), 64.4 (2), 75.5 (1), 134.8 (1), 135.2 (1).

4.7. (1′*R*,4′*R*)-*tert*-Butyldimethyl-(4-phenylsulfanyl-cyclopent-2-enylmethoxy)-silane 15

To a solution of *N*-(phenylthio)phthalimide (134.2 mg, 0.53 mmol) in dry benzene (3 mL) at rt under an argon atmosphere, was added *n*-Bu_3P (130 μL, 0.53 mmol) and, after stirring for 5 min, a solution of compound **12** (100 mg, 0.44 mmol) in dry benzene (1 mL). The mixture was stirred for 4 h at rt and then evaporated to dryness. The residue was taken up in hexane and the organic layer was washed with H_2O and dried ($MgSO_4$). Evaporation under vacuum gave an oily residue which was purified by flash chromatography on silica gel (8 g). Elution with hexane–EtOAc (49:1) gave sulphide **15** as a colorless oil (136 mg, 97%), IR (neat): 3059, 2955, 2856, 1584, 1465, 1379, 1255, 1097, 837, 777 cm^{-1}; ^1H NMR: δ 0.05 (6H, s), 0.95 (9H, s), 2.0–2.1 (2H, m), 2.90–3.0 (1H, m), 3.4–3.6 (2H, m), 4.25–4.35 (1H, m), 5.80 (2H, brs), 7.15–7.40 (5H, m); EIMS *m*/*z* (rel. intensity): 320 [M^+] (8), 263 (35), 204 (30), 197 (19), 188 (10), 167 (25), 153 (32), 145 (16), 115 (16), 89 (100), 79 (39), 75 (54), 73 (81).

4.8. (1′*R*,4′*R*)-(+)-(4-Phenylsulfanyl-cyclopent-2-enyl)-methanol (+)-16

To a solution of sulphide **15** (100 mg, 0.31 mmol) in THF (3 mL) at rt, was added tetrabutylammonium fluoride (1.0 M in THF, 1 mL). The mixture was stirred at rt for 10 h, then evaporated to dryness, and the residue purified by flash chromatography on silica gel (8 g). Elution with hexane–EtOAc (7:3) gave sulphide **16** as a colorless oil (63 mg, 98%), $[\alpha]_D^{20}$ +184.1 (*c* 1.1, CH_2Cl_2); IR (neat): 3374, 3056, 2927, 1584, 1479, 1439, 1379, 1027, 791, 691 cm^{-1}; ^1H NMR: δ 2.10–2.20 (2H, m), 2.90–3.05 (1H, m), 3.50–3.70 (2H, m), 4.30–4.40 (1H, m), 5.82 (1H, brd, $J=6.5$), 5.90 (1H, brd, $J=6.5$), 7.15–7.50 (5H, m); ^{13}C NMR: δ 34.5 (2), 47.5 (1), 52.3 (1), 65.5 (2), 126.5 (1), 128.6 (2×1), 131.2 (2×1), 133.2 (1), 134.3 (1), 135.5 (0); EIMS *m*/*z* (rel. intensity): 206 [M^+] (39), 142 (6), 110 (75), 97 (50), 96 (45), 79 (100), 67 (75), 41 (22).

4.9. (1″*RS*,1′*R*,4′*R*)-[4-(2-Bromo-1-ethoxy-ethoxymethyl)-cyclopent-2-enylsulfanyl]-benzene 17

Freshly recrystallized (H_2O) NBS (96 mg, 0.54 mmol) was added in one portion to a solution of compound (+)-**16** (100 mg, 0.48 mmol) in dry CH_2Cl_2 (4 mL) under an argon atmosphere. The mixture, cooled to −40°C, was treated with ethyl vinyl ether (86 μL, 0.90 mmol), stirred for 2 h, allowed to warm to rt and stirred for an additional 22 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), extracted with H_2O (8 mL), and the aqueous phase re-extracted with CH_2Cl_2 (3×5 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue purified by flash chromatography on silica gel (8 g). Elution with hexane–EtOAc (19:1) gave an inseparable mixture of diastereomeric bromoacetals **17** as a pale yellow oil (170 mg, 98%); IR (neat): 3050, 2973, 2924, 1584, 1479, 1438, 1376, 1265, 1130, 738, 691 cm^{-1}; ^1H NMR: δ 1.10–1.30 (3H, m), 2.05–2.25 (2H, m), 2.95–3.10 (1H, m), 3.30–3.70 (6H, m), 4.25–4.35 (1H, m), 4.60–4.72 (1H, m), 5.85 (2H, brs), 7.15–7.50 (5H, m); ^{13}C NMR: δ 15.0 (3), 34.5 (2), 35.1 (2), 45.1 (1), 47.6 (1), 52.2 (1), 52.4 (1), 62.5 (2), 65.6 (2), 69.5 (2), 101.4 (1), 101.5 (1), 126.5 (1), 128.7 (2×1), 131.2 (2×1), 132.5 (1), 133.3 (1), 134.3 (1), 134.8 (1), 135.6 (0); EIMS *m*/*z* (rel. intensity): 358 [$M^+(^{81}Br)$] (2), 356 [$M^+(^{79}Br)$] (2), 232 (10), 205 (25), 189 (11), 153 (34), 151 (35), 149 (18), 147 (15), 125 (22), 123 (27), 109 (23), 79 (100), 73 (91), 45 (54).

4.10. (3*RS*,4a*S*,7a*R*)-1,3,4,4a,7,7a-Hexaydro-cyclopenta[*c*]pyran-3-ol 20

A solution of bromoacetals **17** (100 mg, 0.28 mmol), $Me_3SnSnMe_3$ (105 mg, 0.32 mmol), and benzophenone (51 mg, 0.28 mmol) in degassed, dry benzene (6 mL) in a quartz tube was irradiated at 320 nm in a Rayonet photoreactor. After 4 h, the reaction mixture was concentrated and the oily residue purified by flash chromatography on silica gel (8 g). Elution with hexane–CH_2Cl_2 (2:3) gave an inseparable mixture of acetals **18** and **19**, which were immediately submitted

to hydrolysis of the acetal group. A solution of **18** and **19** in THF (2 mL) was treated with HCl (0.25N, 4 mL) and stirred at rt for 5 h. The reaction mixture was then quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give a residue which purified by flash chromatography on silica gel (8 g). Elution with CH_2Cl_2–hexane (4:1), followed by Et_2O–hexane (1:1), gave recovered alcohol **16** (10 mg, 17%) and lactols **20** (22 mg, 56% from **17**), as an inseparable mixture of epimers in the ratio of 1.3:1; IR (neat): 3380, 3050, 2925, 2843, 1600, 1505, 1352, 1265, 1060, 1050 cm^{-1}; ^1H NMR: δ 1.70–2.10 (6.9H, m), 2.15 (1.3, m), 2.30–2.50 (5.6H, m), 2.75 (1H, m), 3.05 (1.3H, m), 3.41 (1.3H, dd, $J=11.6$ and.7.5), 3.74 (1H, dd, $J=12.0$ and 5.0), 3.85 (1H, dd, $J=12.0$ and 6.5), 3.93 (1.3H, dd, $J=11.6$ and 5.5), 4.95 (1.3H, m), 5.05 (1H, m), 5.62 (1.3H, dq, $J=5.5$ and 2.0), 5.73 (1.3H, dq, $J=5.5$ and 2.0), 5.76 (2H, brs); CIMS (CH_4): m/z 141 [M+H$^+$], 123, 111, 97, 79.

4.11. (4aS,7aR)-(+)-4,4a,7,7a-Tetrahydro-1*H*-cyclopenta-[*c*]pyran-3-one (+)-3

Solid PCC (154 mg, 0.71 mmol) and NaOAc (10 mg) were added to a solution of lactols **20** (50 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at rt. After stirring for 3 h, Et_2O (10 mL) was added and the reaction mixture was filtered on a pad of Celite, and concentrated. The residue was purified by flash chromatography on silica gel (5 g). Elution with Et_2O–hexane (4:1) gave lactone (+)-**3** (42 mg, 85%) as a low melting point solid, $[\alpha]_D^{20}$ +42.0 (*c* 0.3, CH_2Cl_2); IR (KBr): 3058, 2917, 1747, 1480, 1427, 1380, 1260, 1135, 1083, 992 cm^{-1}; ^1H NMR: δ 2.27 (1H, ddt, $J=17.0$, 2.5, and 3.0), 2.35 (1H, dd, $J=15.0$ and 6.5), 2.62–2.87 (2H, m), 2.73 (1H, dd, $J=15.0$ and 7.0), 3.30–3.40 (1H, m), 4.05 (1H, dd, $J=11.5$ and 7.0), 4.30 (1H, dd, $J=11.5$ and 4.5), 5.55 (1H, dq, $J=6.0$ and 2.0), 5.75 (1H, dq, $J=6.0$ and 2.0); ^{13}C NMR: δ 33.8 (2), 33.9 (1), 36.1 (2), 41.9 (1), 70.2 (2), 130.8 (1), 131.8 (1), 173.1 (0); EIMS m/z (rel. intensity): 138 [M$^+$] (3), 120 (3), 96 (57), 79 (89), 77 (31), 67 (43), 66 (100), 60 (99), 51 (10), 39 (35). Anal. calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.65; H, 7.12.

4.12. (3a*R*,4*R*,5*S*,6*S*,6a*R*)-Acetic acid 4-acetoxymethyl-6-iodo-2-oxo-hexahydro-cyclopenta[*b*]furan-5-yl ester 28

To a solution of acetate (–)-**2c**[3] (290 mg, 1.48 mmol) in MeCN–H_2O (4:1, 5 mL) at rt in the dark, was added solid ICl (264 mg, 1.63 mmol) in one portion. The mixture was stirred at rt for 4 h, concentrated to remove MeCN, quenched with aqueous $NaHCO_3$ and extracted with Et_2O (4×10 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography on silica gel (20 g). Elution with EtOAc–hexane (4:6) gave 478 mg of iodolactones **26** and **27** in the ratio of 7:3 and in 95% overall yield. A sample of the mixture was separated on silica gel to afford pure acetate **26** as a pale yellow oil; IR (neat): 3428, 2960, 2924, 1740, 1368, 1241, 1176, 1016 cm^{-1}; ^1H NMR: δ 2.1 (3H, s), 2.59 (1H, dd, $J=19.0$ and 11.0), 2.72 (1H, dd, $J=19.0$ and 4.3), 3.0 (brs, OH), 3.11 (1H, m), 3.24 (1H, m), 4.22 (1H, dd, $J=11.5$ and 6.8), 4.41 (1H, d, $J=5.2$), 4.41 (1H, s), 4.49 (1H, dd, $J=11.5$ and 8.1), 5.37 (1H, d, $J=8.0$); ^{13}C NMR: δ 20.7 (3), 29.9 (2), 31.1 (1), 37.4 (1), 42.7 (1), 60.8 (2), 79.8 (1), 91.7 (1), 171.2 (0), 176.1 (0); EIMS m/z (rel. intensity): 340 [M$^+$] (1), 280 (31), 262 (28), 153 (75), 125 (21), 109 (9), 107 (25), 79 (28), 54 (52), 43 (100). To a solution of the two acetates **26** and **27** (200 mg, 0.59 mmol) in CH_2Cl_2 (4 mL) at rt under an argon atmosphere, were added, in the order, pyridine (48 μL, 0.59 mmol), cat. DMAP, and Ac_2O (56 μL, 0.59 mmol). The mixture was stirred at rt for 30 min and then quenched with MeOH. After diluting with CH_2Cl_2 (10 mL), the organic layer was washed with saturated aqueous $NaHSO_4$ to remove pyridine, dried ($MgSO_4$) and taken to dryness. The solid residue (200 mg, 89%) was constituted by iododiacetate **28**, mp 123–125°C, $[\alpha]_D^{20}$ +30.6 (*c* 0.8, CH_2Cl_2), which did not need further purification; IR (KBr): 2925, 2853, 1783, 1744, 1370, 1221, 1171 cm^{-1}; ^1H NMR: δ 2.05 (3H, s), 2.10 (3H, s), 2.60–2.75 (2H, m), 3.30–3.40 (2H, m), 4.20 (1H, dd, $J=12.0$ and 6.7), 4.31 (1H, dd, $J=12.0$ and 7.2), 4.47 (1H, s), 5.24 (1H, brs), 5.36 (1H, d, $J=6.1$); ^{13}C NMR: δ 20.6 (3), 20.7 (3), 26.5 (1), 29.5 (2), 37.3 (1), 41.1 (1), 59.9 (2), 81.1 (1), 91.0 (1), 169.5 (0), 170.5 (0), 175.2 (0); EIMS m/z (rel. intensity): 382 [M$^+$] (1), 322 (5), 262 (85), 213 (22), 195 (13), 171 (18), 153 (67), 135 (35), 125 (16), 111 (16), 107 (36), 79 (25), 43 (100).

4.13. (3a*R*,4*R*,5*R*,6a*S*)-(–)-Acetic acid 5-acetoxy-2-oxo-hexahydro-cyclopenta[*b*]furan-4-ylmethyl ester (–)-4b

A catalytic amount of AIBN and tributyltin hydride (295 μL, 1.1 mmol) were added to a solution of iododiacetate **28** (350 mg, 0.92 mmol) in dry THF (5 mL) under an argon atmosphere. The mixture was heated under reflux for 3 h, allowed to cool to rt, concentrated, and the residue partitioned between MeCN and hexane (3×10 mL). The MeCN layer was concentrated and purified by flash chromatography on silica gel (18 g). Elution with a gradient of EtOAc in hexane gave diacetate **4b** (213 mg, 91%), $[\alpha]_D^{20}$ –49.1 (*c* 1.2, CH_2Cl_2); IR (neat): 2960, 2890, 1740, 1720, 1378, 1227, 1185, 1120, 1070 cm^{-1}; ^1H NMR: δ 2.0–2.10 (1H, m), 2.03 (3H, s), 2.07 (3H, s), 2.38 (1H, d, $J=15.9$), 2.49 (1H, ddd, $J=12.0$, 7.0, and 3.6), 2.60–2.72 (2H, m), 3.27 (1H, qu, $J=7.5$), 4.17 (1H, dd, $J=11.6$ and 7.7), 4.31 (1H, dd, $J=11.6$ and 7.7), 5.17 (1H, t, $J=7.0$), 5.24 (1H, t, $J=3.6$); ^{13}C NMR: δ 20.4 (3), 20.6 (3), 29.5 (2), 38.1 (1), 39.0 (2), 44.4 (1), 59.9 (2), 75.0 (1), 83.5 (1), 169.6 (0), 170.3 (0), 176.4 (0). Anal. calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.35; H, 6.33.

4.14. (3a*R*,4*R*,5*R*,6a*S*)-(–)-5-Hydroxy-4-hydroxy-methyl-hexahydro-cyclopenta[*b*]furan-2-one (–)-4a

Dowex® 1X8-200 ion-exchange resin (Cl^- form, 1 g) was added to aqueous NaOH (0.1 M, 15 mL); the mixture was stirred at rt for 2 h, filtered and the resin washed with 0.1 M NaOH and H_2O. The collected resin was resuspended in NaOH (0.1 M, 15 mL), stirred for

1 h, filtered, washed with H_2O and dried overnight under vacuum (0.01 mmHg). A solution of diacetate **4b** (30 mg, 0.12 mmol) in MeOH (2 mL) was treated with the ion-exchange resin (OH^- form) (220 mg) at rt for 30 min. The reaction mixture was then filtered, concentrated and the residue crystallized from EtOH to give white crystals of diol (–)-**4a** (19 mg, 95%), mp 126–127°C (lit.[15,23] 126–127°C), $[\alpha]_D^{20}$ −13.5 (*c* 0.5, $CHCl_3$) [lit.[24] $[\alpha]_D$ +12 (*c* 1.5 10^{-2}, $CDCl_3$) for (+)-**4a**]; IR (KBr): 3420, 3000, 1750, 1368, 1224, 1175, 1120, 1030 cm^{-1}; ^1H NMR: δ 1.96 (1H, ddd, $J=15.5$, 7.0, and 3.7), 2.08–2.22 (1H, m), 2.26 (1H, d, $J=15.5$), 2.59 (1H, dd, $J=19.0$ and 11.5), 2.77 (1 OH, brs), 2.88 (1H, dd, $J=19.0$ and 4.0), 3.15 (1H, ddt, $J=11.5$, 4.0, and 7.0), 3.50 (1 OH, d, $J=3.7$), 3.90 (1H, dd, $J=11.0$ and 6.9), 4.00 (1H, dd, $J=11.0$ and 7.6), 4.45 (1H, t, $J=3.7$), 5.17 (1H, t, $J=7.0$); ^{13}C NMR (MeOH-d_4): δ 31.9 (2), 40.1 (1), 43.0 (2), 51.1 (1), 60.2 (2), 74.0 (1), 87.7 (1), 181.5 (0); CIMS (NH_3): m/z 190 [M+NH_4^+]. The spectroscopic data were consistent with the literature.[15,19,23,24]

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