A New Route to Optically Active (4*R*)-2-Substituted 4-Hydroxycyclopent-2-enones from D-Glucose

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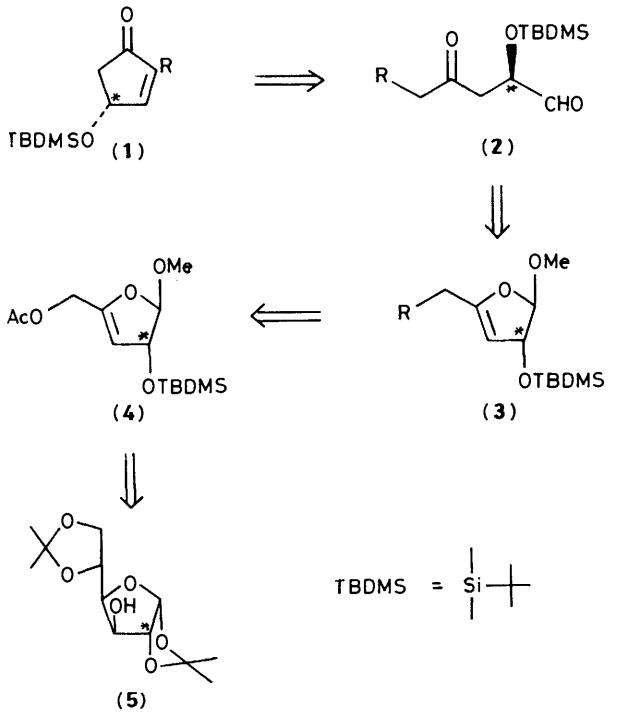
A synthetic sequence, starting from diacetoneglucose, is developed for optically active (4*R*)-2-(dimethyl-t-butylsilyloxy)-4-oxo aldehyde (**2**). The key step is the regioselective palladium-catalysed allylation of malonate with the allylic acetate (**4**). The 4-oxo aldehyde (**2**) undergoes $Ba(OH)_2$ cyclization to the optically active (4*R*)-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enone derivative (**1**).

Chiral compounds containing the 4-hydroxycyclopent-2-enone entity are important as key intermediates for the synthesis of different classes of biologically active products, namely prostaglandins,[1] pyrethroids,[2] and antibiotics of the pentenomycin series.[3] Here we outline a general route to (4*R*)-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enones (**1**) starting from the commercially available diacetoneglucose (1,2;5,6-di-isopropylidene-D-glucose) (**5**) and based on the use of the allylic acetate (**4**) as a key intermediate (Scheme 1). This compound displays the following features: (*a*) it is readily accessible from diacetoneglucose using routine chemistry; (*b*) a functionalized chain R can be connected to the C-5 centre by palladium-catalysed allylic substitution reactions; (*c*) the functionalities present on the dihydrofuran ring make it a synthetic equivalent of a 2-hydroxy-4-oxo aldehyde; (*d*) the starred stereogenic centre with *R*-configuration can be carried through the whole sequence to the target cyclopentenone (**1**) unchanged.



Scheme 1.

Results and Discussion

Our aim was to prepare *O*-protected 4-oxo aldehydes (**2**) in order to carry out an intramolecular aldol reaction to the target (**1**). The corresponding cyclization on oxo aldehydes containing a free hydroxy group was unsuccessful, affording only intractable mixtures of products.‡

The synthetic plan is depicted in Scheme 2. The starting acid (**6**) was readily obtained from the diacetoneglucose (**5**) by traditional methods.[4] In order to obtain the necessary differential protection at C-1 and C-2, the acid (**6**) was treated with methanol and catalytic H_2SO_4 at reflux to give the ester glycosides as an anomeric mixture containing mainly the β-anomer (**7**) (α:β = 1:2). Hydroxy silylation and toluene-*p*-sulphonate elimination with DBU gave the unsaturated ester (**8**).§

The reduction of the ester function of (**8**) was achieved with $LiAlH_4$ in THF, and the corresponding alcohol was extracted with chloroform after quenching the reaction mixture. Since solvent evaporation under vacuum led to complete decomposition of the product, we added the dried chloroform phase containing the crude alcohol directly to a mixture of acetic anhydride, triethylamine, and 4-dimethylaminopyridine. The acetate (**4**) was so isolated in 75% yield.

The key step is the malonic ester reaction on acetate (**4**); the reaction was carried out using tetrakis(triphenylphosphine)-palladium as the catalyst (10% mol) in refluxing THF and forming *in situ* the malonate anion by means of potassium carbonate under heterogeneous conditions;[5] compound (**9**) was obtained regioselectively in 85% yield. Decarboxylation[6] afforded the monoester (**10**) in 83% yield. The alcohol obtained in the successive reduction step was unstable in the pure state since it spontaneously cyclized, even under neutral conditions,

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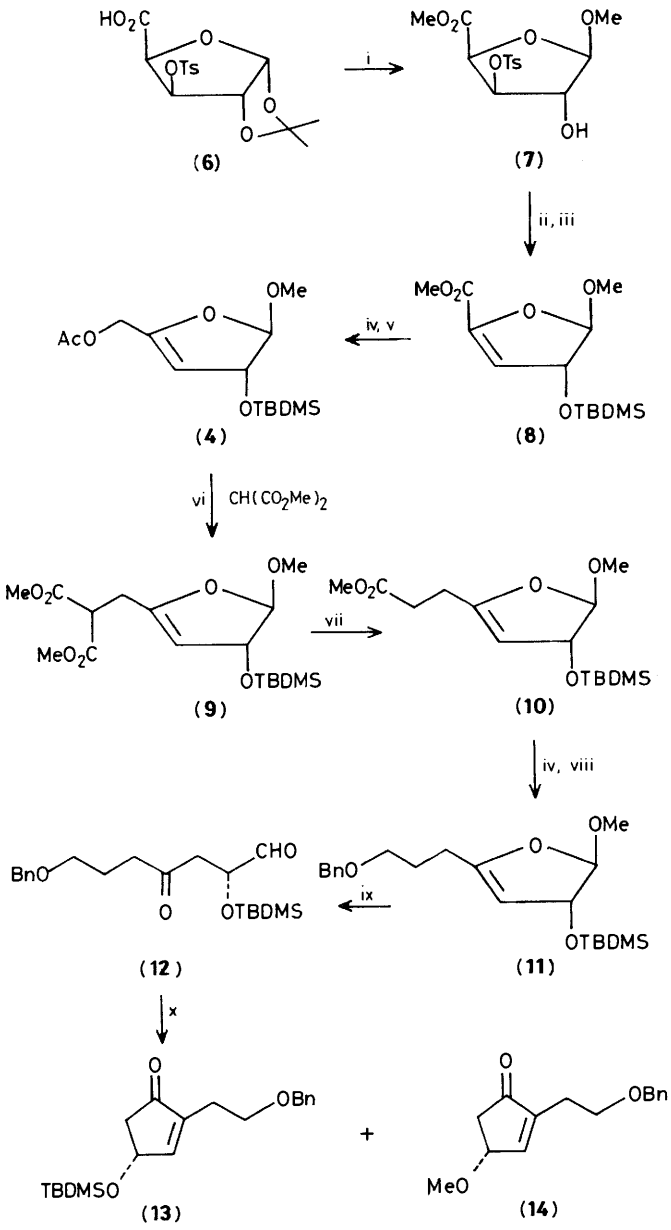
‡ The cyclization of closely related 2-hydroxy-4-oxo aldehydes has been reported: S. Achab and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1983, 391; S. Achab, J. P. Cosson, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1984, 1040; in spite of several attempts we were unable to obtain similar results.

§ The α- and β-isomers were easily separated by flash chromatography. Here the use of the most abundant isomer is described; the other isomer goes through a parallel synthetic sequence but with slightly lower yields.



Scheme 2. *Reagents:* i, MeOH, H^+; ii, TBDMSCl; iii, DBU; iv, LAH, v, Ac_2O; vi, $Pd(PPh_3)_4$cat.; vii, KOH, 18-crown-6-ether; viii, NaH, BnBr; ix, H^+; x, $Ba(OH_2)$, MeOH

to spirofuran derivatives;* the ethereal extracts of the crude alcohol were, therefore, directly treated with NaH and benzyl bromide to give (**11**) in 73% yield.

The ring opening of (**11**) was performed by simple acidic hydrolysis with 2×10^{-2}M HCl in THF–H_2O at room temperature, affording the desired 4-oxo aldehyde (**12**) in high yield after column chromatography, as a stable compound having the appropriate spectroscopic properties.

The critical cyclization step† gave good results only when methanolic $Ba(OH)_2$ was used.[7] Treatment of compound (**12**) with a 10^{-2}M solution of $Ba(OH)_2$ (1.2 equiv.) in methanol at room temperature for 5 h afforded a mixture of the two cyclized products (**13**) and (**14**) in 66% overall yield (1:1 ratio) which were easily separated by chromatography on silica gel.

Compound (**13**) appeared optically pure on the basis of the 300 MHz ^{1}H n.m.r. spectrum in the presence of the chiral shift reagent Eu(hfc)$_3$. Furthermore (**13**) was desilylated and then converted into the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate.[8] The spectrum of the latter compound confirmed the enantiomeric purity of (**13**). The methoxy derivative (**14**) showed optical activity $\{[\alpha]^{25} +1.7°$ (*c* 1.18 in MeOH$\}$. In the ^{1}H n.m.r. spectrum the vinylic proton signal at δ 7.3 p.p.m. was split into two signals at δ 9.42 and 9.47 p.p.m. upon addition of Eu(hfc)$_3$; integration furnished a 7:3 ratio corresponding to a 40% e.e. By comparison with known optical rotations of 4-hydroxy- and 4-alkoxycyclopent-2-enone derivatives,[9] we tentatively assigned the *R*-configuration to the major enantiomers.

An explanation for the mechanism by which (**14**) was produced can be drawn from the recently reported work by Novak *et al.*,[9] which examined the reaction of optically active 4-hydroxy- and 4-silyloxy-2-alkylcyclopent-2-enones with sodium methoxide in methanol and sodium ethoxide in ethanol. They found that partially racemized 4-methoxy- or 4-ethoxycyclopent-2-enones were always formed through the initial conjugate addition of alkoxides to the enone moiety followed by the elimination of the 4-hydroxy (or silyloxy) substituent. The final product was formed by the further addition of alkoxide to the 4,5 double bond or by the [1,5] sigmatropic rearrangement of the intermediate enolate.

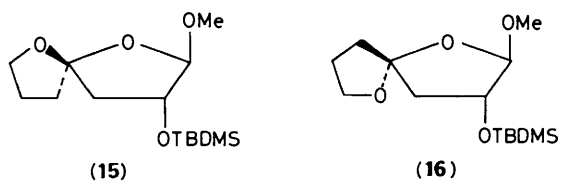
We have shown that cyclopentenone (**13**), a potential chiral intermediate for prostaglandin synthesis‡ may be prepared from the cheap, readily available diacetoneglucose. This strategy also appears to be a versatile route to other natural cyclopentanone derivatives by introducing different side chains in (**3**) using palladium-catalysed allylic substitution reactions.

Experimental

General.—Optical rotations were obtained with a Perkin-Elmer 241 polarimeter equipped with a sodium lamp. I.r. spectra were recorded with a Perkin-Elmer 682 instrument. Unless otherwise stated ^{1}H n.m.r. analyses were performed on a Varian EM390 spectrometer at 90 MHz in $CDCl_3$ and chemical shifts were measured as δ values using TMS as internal standard. For 300 MHz ^{1}H n.m.r. spectra a Brüker CXP instrument was employed. ^{13}C N.m.r. spectra were recorded with a Varian FT80A spectrometer at 20 MHz. A VG 7070 double focussing (70 eV) mass spectrometer was used for both normal m.s. analysis and exact mass measurements.

T.l.c. analyses were performed on Kieselgel 60 F_{254} plates and flash column chromatography with Kieselgel 60 (230—400

* Diastereoisomeric spirofurans (**15**) and (**16**) were isolated in one experiment. The i.r. spectrum showed no OH band; in the ^{13}C n.m.r. spectrum a quarternary dioxygenated carbon at 115.8 p.p.m. was present together with the usual dioxygenated CH at 110 p.p.m.; in the ^{1}H n.m.r. spectrum a clear ABX pattern at 2.35 p.p.m. was observed. Other spectroscopic data are in agreement with the following structures.



† We screened a large spectrum of reagents, both basic (including NaOH in MeOH–H_2O, K_2CO_3 in H_2O, Pr^i_2EtN, and DBU in $CHCl_3$) and acidic (including CF_3CO_2H in THF, BF_3·Et_2O, anhydrous $ZnCl_2$, and $TiCl_4$ in CH_2Cl_2), but we invariably obtained complex mixtures.

‡ The cyclopentenone (**13**) can easily be converted into PGEs through debenzylation, oxidation of the side chain alcohol to aldehyde, Wittig reaction, and final conjugate addition of an R_ω chain-containing synthon.

mesh) purchased from Merck. In both cases cyclohexane–ethyl acetate or cyclohexane–ether mixtures were used as eluants.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl and benzene from $LiAlH_4$, while methanol was dried by refluxing over magnesium. Commercial $Ba(OH)_2 \cdot 8H_2O$ and K_2CO_3 were heated at 120 °C at 0.1 mmHg for 10 h. All other chemicals were pure commercial products and were used as purchased.

Methyl (*Methyl* 3-O-*Tosyl*-β-D-*xylofuranosid*)*uronate* (**7**).—Conc. H_2SO_4 (4 drops) was added to a solution of compound (**6**) (15 g, 41.9 mmol) in dry methanol (100 ml) and the mixture was refluxed under argon until t.l.c. analysis indicated complete conversion of the acid (2—3 h) into (**7**) and its anomer (small amounts of by products at low R_F were also present). After being cooled the reaction mixture was quenched with 10% aqueous $NaHCO_3$ (10 ml). After methanol distillation and extraction with EtOAc, the dried (Na_2SO_4) organic phase was concentrated and the residue flash chromatographed (cyclohexane–EtOAc, 8:2) to afford a mixture of (**7**) and its anomer as an oil (12.33 g, 85% overall) (Found: C, 48.6; H, 5.2. $C_{14}H_{18}O_8S$ requires C, 48.55; H, 5.2%).

Methyl (4R,5R)-4-(*Dimethyl-t-butylsilyloxy*)-4,5-*dihydro*-5-*methoxyfuran*-2-*carboxylate* (**8**).—The mixture of compound (**7**) and its anomer (12.33 g, 35.6 mmol) was dissolved in *N*,*N*-dimethylformamide (80 ml). Imidazole (6.05 g, 89 mmol) and dimethyl-t-butylsilyl chloride (TBDMSCl) (6.70 g, 44.5 mmol) were added and the reaction mixture was maintained at room temperature for 20 h. Water (50 ml) was added and after extraction with ether, drying (Na_2SO_4), and solvent evaporation, the crude product, in $CHCl_3$ (80 ml) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.58 ml, 37.4 mmol) at room temperature for 24 h. Evaporation of the solvent followed by column chromatography (cyclohexane–EtOAc, 95:5) afforded compound (**8**) (5.47 g, 53%) as an oil (Found: C, 54.1; H, 8.4. $C_{13}H_{24}O_5Si$ requires C, 54.2; H, 8.4%); $\nu_{max.}$(neat) 2 930, 2 850, 1 740, 1 635, 1 450, 1 320, 1 270, 1 230, 1 130, 1 100, 950, 860, and 800 cm^{-1}; δ_H 5.93 (1 H, d, $J_{3,4}$ 3 Hz, 3-H), 5.2 (1 H, d, $J_{4,5}$ 1.5 Hz, 5-H), 4.77 (1 H, m, 4-H), 3.83 (3 H, s, CH_3OCO), 3.53 (3 H, s, CH_3O), 0.9 (9 H, s, CH_3C), and 0.13 (6 H, s, CH_3Si); δ_C 160.3, 149.0, 113.2, 111.8, 79.4, 56.5, 52.0, 25.5, 17.8, −4.3, and −4.7; and the (4R,5S)-*isomer* (2.37 g, 23%) as an oil (Found: C, 54.3; H, 8.3); $\nu_{max.}$(neat) 2 930, 2 850, 1 740, 1 635, 1 450, 1 320, 1 270, 1 230, 1 130, 1 100, 950, 860, and 800 cm^{-1}; δ_H 5.9 (1 H, d, $J_{3,4}$ 3 Hz, 3-H), 5.3 (1 H, d, $J_{4,5}$ 6 Hz, 5-H), 5.0 (1 H, dd, $J_{4,5}$ 6 Hz, $J_{3,4}$ 3 Hz, 4-H), 3.8 (3 H, s, CH_3OCO), 3.57 (3 H, s, CH_3O), 0.9 (9 H, s, CH_3C), and 0.13 (6 H, s, CH_3Si); δ_C 160.8, 146.8, 113.0, 105.7, 73.7, 56.8, 52.1, 25.6, 18.3, −4.5, and −5.0.

(4R,5R)-4-(*Dimethyl-t-butylsilyloxy*)-4,5-*dihydro*-5-*methoxyfuran*-2-*ylmethyl Acetate* (**4**).—Compound (**8**) (5 g, 17.4 mmol) in THF (20 ml) in dry, argon flushed apparatus was cooled at 0 °C. $LiAlH_4$ (1M in ether, 8.7 ml) was added dropwise with stirring during 5 min. After a further 20 min at 0 °C the reaction was quenched by the addition of a saturated solution of sodium potassium tartrate (15 ml). The resulting heterogeneous mixture was filtered, extracted with chloroform (5 × 20 ml), and the combined extracts were dried ($MgSO_4$) for 3 h. The solution was added dropwise to a mixture of acetic anhydride (18 ml), triethylamine (16 ml), and 4-dimethylaminopyridine (0.21 g, 1.7 mmol) with stirring at room temperature. After 1 h acetylation was complete; the volatile materials were evaporated off under reduced pressure and acetic anhydride was taken off by heating at 35 °C at 0.1 mmHg for 3 h. The residue was chromatographed using cyclohexane–EtOAc (9:1) as eluant to afford compound (**4**) as an oil (3.94 g, 75%) (Found: C, 55.7; H, 8.65. $C_{14}H_{26}O_5Si$ requires C, 55.6; H, 8.7%); $[\alpha]_D^{25}$ −206° (*c* 1.25 in MeOH); $\nu_{max.}$(neat) 2 950, 2 930, 2 850, 1 745, 1 670, 1 230, 1 115, 1 080, 855, 835, and 775 cm^{-1}; δ_H 5.1 (1 H, d, 5-H), 5.03 (1 H, m, 3-H), 4.65 (1 H, m, 4-H), 4.6 (2 H, s, CH_2O), 3.43 (3 H, s, CH_3O), 2.03 (3 H, s, CH_3CO), 0.9 (9 H, s, CH_3C), and 0.13 (6 H, s, CH_3Si); δ_C 170.0, 155.3, 113.0, 102.1, 79.7, 58.7, 56.1, 25.6, 20.5, 17.9, −4.5, and −4.8; *m*/*z* 271 (M^+ − CH_3O, 2%), 245 (6), 213 (13), 185 (7), 143 (25), 117 (100), 89 (15), 75 (36), 73 (31), and 43 (37).

Dimethyl 2-[(4R,5R)-4-(*Dimethyl-t-butylsilyloxy*)-4,5-*dihydro*-5-*methoxyfuran*-2-*ylmethyl*]*propanedioate* (**9**).—In a dry flask connected to an argon line through a water condenser, compound (**4**) (3.94 g, 13.05 mmol) was mixed with THF (40 ml), $Pd(PPh_3)_4$ (1.5 g, 1.3 mmol), and K_2CO_3 (5.5 g, 40 mmol); dimethyl malonate (4.57 ml, 40 mmol) was then added and the reaction mixture heated at reflux for 15 h. After addition of water (10 ml), extraction with ether, drying (Na_2SO_4), and concentration, column chromatography of the residue (cyclohexane–EtOAc, 92:8) afforded (**9**) as an oil (4.15 g, 85%) (Found: C, 54.4; H, 8.1. $C_{17}H_{30}O_7Si$ requires C, 54.4; H, 8.1%); $[\alpha]_D^{25}$ +118° (*c* 1.3 in MeOH); $\nu_{max.}$ 2 960, 2 930, 2 860, 1 755, 1 740, 1 665, 1 430, 1 250, 1 110, 1 070, 865, 835, and 775 cm^{-1}; δ_H 5.07 (1 H, d, 5-H), 4.87 (1 H, d, 3-H), 4.63 (1 H, m, 4-H), 3.77 (6 H, s, CH_3OCO), 3.73 [1 H, t, $CH(COO)_2$], 3.47 (3 H, s, CH_3O), 2.87 (2 H, d, CH_2), 0.9 (9 H, s, CH_3C), and 0.1 (6 H, s, CH_3Si); δ_C 168.7, 157.4, 112.5, 100.4, 79.9, 55.9, 52.5, 49.0, 27.7, 25.6, 17.9, −4.6, and −4.8; *m*/*z* 359 (M^+ − CH_3, 4%), 343 (23), 317 (100), 299 (79), 285 (66), 257 (87), 111 (57), 89 (90), 73 (98), and 59 (49).

Methyl [(4R,5R)-4-(*Dimethyl-t-butylsilyloxy*)-4,5-*dihydro*-5-*methoxyfuran*-2-*yl*]*propanoate* (**10**).—A solution of KOH in dry methanol (0.8M; 15.3 ml) was added dropwise to a stirred solution of (**9**) (4.15 g, 11.1 mmol) and 18-crown-6 ether (3.22 g, 12.2 mmol) in anhydrous benzene (100 ml) previously cooled at 10 °C. The resulting pale yellow mixture was kept at room temperature for *ca.* 8 h. T.l.c. showed complete disappearance of (**9**), the product being obtained as a salt with $R_F = 0$. The methanol was distilled off as an azeotropic mixture with benzene to a temperature of 80 °C. An additional 1 h reflux resulted in complete decarboxylation (disappearance of the $R_F = 0$ spot in t.l.c.). Water (20 ml) was added upon cooling, the benzene layer was separated, the aqueous phase was extracted with ether, and the combined extracts were dried (Na_2SO_4). Evaporation of the solvent followed by chromatography (cyclohexane–EtOAc, 92:8) gave (**10**) as an oil (2.91 g, 83%) (Found: C, 57.0; H, 8.9. $C_{15}H_{28}O_5Si$ requires C, 56.9; H, 8.9%); $[\alpha]_D^{25}$ −202° (*c* 1.09 in MeOH); $\nu_{max.}$(neat) 2 950, 2 930, 2 860, 1 740, 1 665, 1 435, 1 255, 1 110, 1 070, 860, 835, and 775 cm^{-1}; δ_H 5.1 (1 H, d, 5-H), 4.83 (1 H, m, 3-H), 4.67 (1 H, m, 4-H), 3.7 (3 H, s, CH_3OCO), 3.5 (3 H, s, CH_3O), 2.57 (4 H, s, CH_2CH_2), 0.9 (9 H, s, CH_3C), and 0.1 (6 H, s, CH_3Si); δ_C 167.6, 160.0, 112.5, 98.8, 80.1, 55.9, 51.5, 30.7, 25.6, 23.7, 17.9, −4.6, and −4.7; *m*/*z* 301 (M^+ − CH_3, 4%), 285 (12), 259 (100), 241 (45), 199 (31), 185 (18), 153 (27), 125 (18), 111 (67), 89 (69), 75 (41), and 73 (95).

(4R,5R)-2-(3-*Benzyloxypropyl*)-4-(*dimethyl-t-butylsilyloxy*)-4,5-*dihydro*-5-*methoxyfuran* (**11**).—$LiAlH_4$ (1M in ether, 4.7 ml) was added dropwise with stirring to compound (**10**) (2.91 g, 9.21 mmol) in THF (20 ml) in an argon flushed apparatus at 0 °C. After completion of the reduction (20 min), water (10 ml) was added to quench the reaction. The resulting mixture was filtered, extracted with ether (5 × 15 ml), and the combined extracts were dried ($MgSO_4$) for 4 h. In a separate flask, under argon, NaH (60% dispersion in oil; 1.84 g, 46 mmol), previously washed with dry pentane, was suspended in THF (10 ml). The alcohol-containing solution, filtered free from $MgSO_4$, was added dropwise, while the temperature was maintained at 0 °C. After 20 min benzyl bromide (1.32 ml, 11 mmol) and $Bu_4N^+I^-$ (0.17 g, 0.46 mmol) were added. After 5 h t.l.c. analysis was

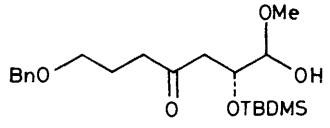
performed to ascertain whether complete conversion of the intermediate alcohol to the benzyl ether had occurred. If necessary, additional NaH was added portionwise and the procedure described above repeated. Finally, after addition of water and extraction with ether, the organic solution was dried (Na_2SO_4) and evaporated. Flash chromatography (cyclohexane–ether, 9:1) afforded (**11**) as an oil (2.54 g, 73%) (Found: C, 66.7; H, 9.0. $C_{21}H_{34}O_4Si$ requires C, 66.6; H, 9.0%); $[\alpha]_D^{25}$ −161° (*c* 1.0 in MeOH); $\nu_{max.}$(neat) 3 030, 2 950, 2 930, 2 860, 1 665, 1 460, 1 450, 1 360, 1 255, 1 110, 1 070, 855, 840, 775, 700, and 650 cm^{-1}; δ_H 7.25 (5 H, s, Ph), 5.0 (1 H, d, 5-H), 4.7 (1 H, m, 3-H), 4.6 (1 H, m, 4-H), 4.4 (2 H, s, PhCH_2O), 3.43 (2 H, t, CH_2OBn), 3.4 (3 H, s, CH_3O), 2.25 (2 H, m, CH_2CH_2CH_2O), 1.83 (2 H, m, $CH_2CH_2CH_2O$), 0.9 (9 H, s, CH_3C), and 0.1 (6 H, s, CH_3Si); δ_C 161.5, 128.2, 127.4, 127.2, 112.4, 110.4, 98.5, 80.2, 72.7, 69.2, 55.9, 26.4, 25.7, 25.0, 17.9, −4.5, and −4.65; *m/z* 347 (M^+ − CH_3O, 1%), 321 (2), 289 (2), 227 (21), 199 (7), 173 (5), 147 (21), 92 (31), 91 (100), 75 (19), and 73 (21).

(2R)-7-*Benzyloxy*-2-(*dimethyl-t-butylsilyloxy*)-4-*oxoheptanal* (**12**).—Aqueous HCl (1M; 4 drops) was added to a solution of compound (**11**) (2.54 g, 6.72 mmol) in THF (15 ml) and the mixture was kept at room temperature for 20 min. The solution was diluted with water (10 ml) and the organic product was extracted with ether and dried (Na_2SO_4). Flash chromatography (cyclohexane–ether, 8:2) gave compound (**12**) as an oil (2.20 g, 90%) (Found: C, 66.0; H, 8.8. $C_{20}H_{32}O_4Si$ requires C, 65.9; H, 8.85%); $[\alpha]_D^{25}$ +18.5° (*c* 1.3 in MeOH); $\nu_{max.}$(neat) 3 030, 2 950, 2 930, 2 860, 1 735, 1 715, 1 470, 1 460, 1 450, 1 360, 1 250, 1 110, 840, 780, 735, and 695 cm^{-1}; δ_H 9.6 (1 H, s, 1-H), 7.25 (5 H, s, Ph), 4.45 (2 H, s, PhCH_2O), 4.42 (1 H, t, 2-H), 3.45 (2 H, t, 7-H), 2.73 (2 H, d, 3-H), 2.53 (2 H, t, 5-H), 1.85 (2 H, quint., 6-H), 0.9 (9 H, s, CH_3C), 0.15 (3 H, s, CH_3Si), and 0.1 (3 H, s, CH_3Si); δ_C 205.5, 202.9, 128.4, 127.6, 74.0, 72.9, 69.2, 46.0, 40.5, 25.7, 23.8, 17.9, −4.5, and −4.65; *m/z* 335 (M^+ − CHO, 8%), 307 (7), 221 (10), 199 (30), 129 (8), 125 (8), 92 (27), 91 (100), 75 (27), and 73 (32); *m/z* at 335 has exact mass 335.205 18 corresponding to the formula $C_{19}H_{31}O_3Si$ (Calc. 335.204 24).

Cyclization of Aldehyde (**12**).—$Ba(OH)_2$ (0.31 g, 1.82 mmol) was dissolved in anhydrous methanol (160 ml) under argon. The oxo aldehyde (**12**) (1.1 g, 3.02 mmol) as a solution in methanol (20 ml) was added with stirring at room temperature. The reaction was continued for 5 h to ensure a good conversion into the cyclized products.* HCl (1M; 3.6 ml) was added while checking the pH for neutrality; the methanol was then evaporated under reduced pressure, the organic material was extracted with ether, and the extract dried (Na_2SO_4), and concentrated. Column chromatography of the residue (cyclohexane–ether, 87:13) gave (4R)-2-(2-*benzyloxyethyl*)-4-(*dimethyl-t-butylsilyloxy*)*cyclopent*-2-*enone* (**13**), as an oil (0.34 g, 33%) (Found: C, 69.4; H, 8.7. $C_{20}H_{30}O_3Si$ requires C, 69.3; H, 8.7%); $[\alpha]_D^{25}$ +23.2° (*c* 0.5 in MeOH); $\nu_{max.}$(neat) 3 030, 2 950, 2 930, 2 870, 1 710, 1 470, 1 460, 1 450, 1 360, 1 260, 1 095, 1 070, 910, 835, 780, and 700 cm^{-1}; δ_H 7.3 (5 H, s, Ph), 7.17 (1 H, m, 3-H), 4.9 (1 H, m, 4-H), 4.5 (2 H, s, PhCH_2O), 3.65 (2 H, t, CH_2OBn), 2.7 (1 H, dd, $J_{5,5}$ 18 Hz, $J_{4,5}$ 6 Hz, 5-H), 2.47 (2 H, m, CH_2CH_2O), 2.25 (1 H, 18 Hz, $J_{4,5}$ 6 Hz, 5-H), 2.47 (2 H, m, CH_2CH_2O), 2.25 (1 H, dd, $J_{5,5}$ 18 Hz, $J_{4,5}$ 2.5 Hz, 5-H), 0.9 (9 H, s, CH_3C), and 0.13 (6 H, s, CH_3Si); δ_C 205.5, 158.1, 144.1, 128.2, 127.5, 72.7, 69.0, 67.5, 45.1, 25.7, 24.9, 18.0, and −4.8; *m/z* 289 (M^+ − C_4H_9, 14%), 259 (7), 255 (5), 195 (5), 183 (13), 149 (4), 123 (3), 92 (28), 91 (100), 75 (33), and 73 (23); *m/z* at 289 showed an exact mass measurement, 289.126 42, corresponding to the formula $C_{16}H_{21}O_3Si$ (Calc. 289.125 99); and 2-(2-*benzyloxyethyl*)-4-*methoxycyclopent*-2-*enone* (**14**) as an oil (0.25 g, 33%) (Found: C, 73.0; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.1; H, 7.4%); $[\alpha]_D^{25}$ +1.7° (*c* 1.18 in MeOH); $\nu_{max.}$(neat) 3 020, 2 980, 2 860, 1 710, 1 095, 740, and 695 cm^{-1}; δ_H 7.33 (5 H, s, Ph), 7.3 (1 H, m, 3-H), 4.4—4.6 (3 H, s and m, PhCH_2O and 4-H), 3.65 (2 H, t, CH_2OBn), 3.43 (3 H, s, CH_3O), 2.4—2.9 (3 H, m, CH_2CH_2O and 5-H), and 2.3 (1 H, dd, $J_{5,5}$ 18 Hz, $J_{4,5}$ 2.5 Hz, 5-H); δ_C 205.5, 155.1, 145.4, 128.4, 127.7, 77.0, 72.9, 67.6, 56.9, 41.4, and 25.1; *m/z* 246 (M^+, traces), 214 (2%), 155 (10), 125 (10), 123 (10), 112 (20), 97 (10), 95 (30), 91 (100), and 79 (14).

Determination of the Enantiomeric Purity of (**13**).—300 MHz ^1H N.m.r. spectra of the product were recorded at increasing concentrations of Eu(hfc)$_3$ until the chemical shift of the vinylic proton from the initial 7.17 p.p.m. value increased to 9.81 p.p.m.; no splitting was observed. A sample of (**13**) (0.1 g) was dissolved in methanol (5 ml) and a few drops of 1M HCl were added to pH 1; the solution was kept at room temperature for 2 h, when t.l.c. indicated complete conversion into the desilylated alcohol. A saturated solution of $NaHCO_3$ (3 ml) was added, methanol was evaporated off under reduced pressure, and the residue was extracted with ethyl acetate. The crude alcohol, dissolved in dichloromethane (5 ml), was treated with pyridine (0.05 ml) and α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) (0.13 g) for 6 h at room temperature.[8] The reaction was quenched with water (3 ml), extracted with ethyl acetate, and the extracts dried and evaporated. Chromatography of the residue (cyclohexane–ether, 50:50) gave the MTPA ester: δ_H(300 MHz in $CDCl_3$) 7.49 (1 H, m, 3-H), 7.4—7.25 (10 H, m, Ph), 5.98 (1 H, m, 4-H), 4.48 (2 H, s, PhCH_2O), 3.62 (2 H, t, CH_2OBn), 3.52 (3 H, s, CH_3O), 2.88 (1 H, dd, 5-H), 2.53 (2 H, m, CH_2CH_2O), and 2.31 (1 H, dd, 5-H). A partially racemized sample of the same alcohol was obtained from an attempted cyclization of (**12**) with $Ba(OH)_2$ in water–acetonitrile and was submitted to the same esterification procedure with MTPACl; in the 300 MHz ^1H n.m.r. spectrum of this ester it was possible to observe four dd signals: two, at 2.88 and 2.31 p.p.m., corresponding to those observed in the spectrum of the enantiomerically pure compound; the other two at 2.90 and 2.40 p.p.m. being attributed to the epimeric ester.

* In an early phase the aldehyde is in equilibrium with the hemiacetal (**17**) which can be isolated by quenching the reaction after 0.5 h. This compound showed the following ^1H n.m.r. data, in agreement with the supposed structure: 7.3 (5 H, s, Ph), 4.67 (1 H, d, 1-H), 4.47 (2 H, s, PhCH_2O), 3.97 (1 H, m, 2-H), 3.5 (2 H, t, 7-H), 3.35 (3 H, s, CH_3O), 2.7 (2 H, d, 3-H), 2.57 (2 H, t, 5-H), 1.87 (2 H, quint., 6-H), 0.9 (9 H, s, CH_3C), 0.15 (3 H, s, CH_3Si), and 0.1 (3 H, s, CH_3Si). This compound, resubjected to the same condensation conditions [$Ba(OH)_2$ in MeOH], gave rise to the same products (**13**) and (**14**) obtained from the 4-oxo aldehyde (**12**).



(**17**)

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