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A synthesis of (4*S*)-2-(acetoxymethyl)-4-(*tert*-butyl-diphenylsilyloxy)-2-cyclopenten-1-one

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Abstract—We describe here a synthesis of (4*S*)-2-(acetoxymethyl)-4-(*tert*-butyldiphenylsilyloxy)-2-cyclopenten-1-one **1** from L-malic acid in seven steps via an intramolecular aldolization–dehydration cyclization reaction of the acyclic 1,6-dialdehyde **10**. The conditions of the intramolecular aldolization–dehydration cyclization reaction were also optimized. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Both racemic and enantiomerically pure 4-hydroxy-2-(hydroxymethyl)-2-cyclopenten-1-one are versatile synthetic intermediates in the syntheses of a number of cyclopentanoid natural products.[1–5] The racemic 4-hydroxy-2-(hydroxymethyl)-2-cyclopenten-1-one was synthesized from 2-methyl-3-(hydroxymethyl)furan.[6] The (4*R*)-enantiomer of the compound and its derivatives were synthesized from (−)-quinic acid.[7–9] Recently, the (4*S*)-enantiomer of the compound and its derivatives became valuable to us because of their use in the total syntheses of prostanoid natural products. But, to the best of our knowledge, synthesis of the (4*S*)-enantiomer of the compound has not been reported in the literature. Now we would like to report a synthesis of (4*S*)-2-(acetoxymethyl)-4-(*tert*-butyldiphenylsilyloxy)-2-cyclopenten-1-one **1** namely a protected form of (4*S*)-4-hydroxy-2-(hydroxymethyl)-2-cyclopenten-1-one.

2. Results and discussion

As outlined in Scheme 1, the title compound **1** was synthesized in six steps starting from compound **2**, which is readily available by a one-pot reaction with L-malic acid according to a known procedure.[10] Compound **2** was treated with excess thionyl chloride to produce an acyl chloride which was immediately exposed to 6 equiv. of fresh Grignard reagent **3** (Scheme 2)[11] in THF to give the ketodiester **4** in 75% yield. With compound **4** in hand, we first tried Dieckmann cyclization in order to get a useful cyclic compound **5**, however, the reaction failed to give the desired product **5**, and only an elimination product **6** was observed. We then turned to protect the carbonyl group of **4** with 1.2 equiv. of 1,3-propanedithiol and 1.5 equiv. of boron trifluoride etherate to afford the dithiane **7** in 85% yield. Methanolysis of compound **7** in the presence of catalytic K_2CO_3 gave **8**, the temperature here should be kept at around −5°C in order to avoid marked racemization. Without purification, the crude compound **8** was directly treated with 2 equiv. of *tert*-butylchlorodiphenylsilane and 4 equiv. of imidazole to yield silyl ether **9** in 84% yield from **7**. It was observed that hydroxy diester **8** underwent gradual lactonization and polymerization. So immediate use of the crude **8** was imperative. Reduction of compound **9** with 3 equiv. of DIBAL-H at −78°C produced dialdehyde **10** which underwent an intramolecular aldolization–dehydration cyclization reaction to give the cyclic enal **11** in a moderate yield. The dialdehyde **10** could not be purified and stored due to polymerization. But, it was stable enough in dilute solution to be further used to perform the intramolecular aldolization–dehydration cyclization reaction. The yield of this cyclization reaction depended on the concentration of the

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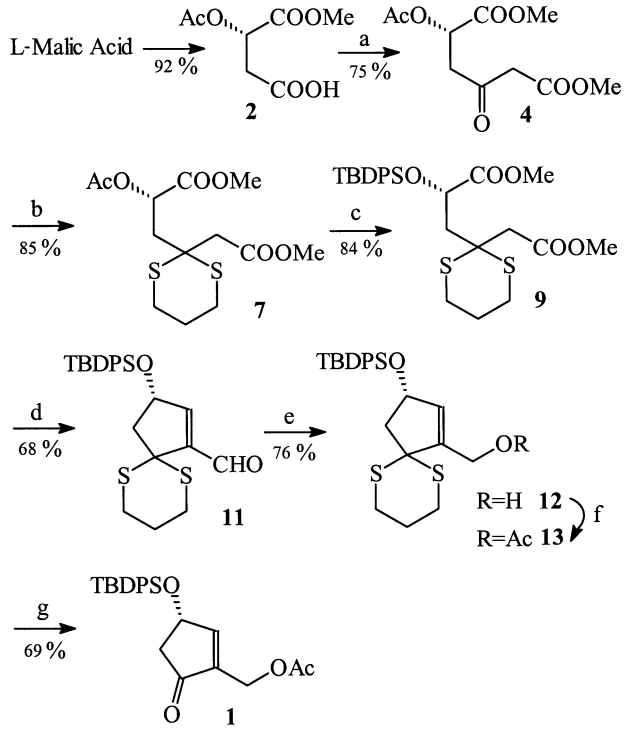
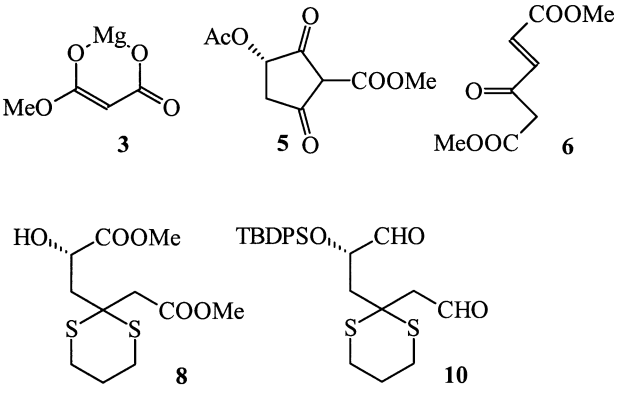


Scheme 1. (a) $SOCl_2$ (excess), 40°C, 3 h then 6 equiv. of **3**, in THF, rt, 12 h; (b) 1,3-propanedithiol (1.2 equiv.), $BF_3{\cdot}OEt_2$ (1.5 equiv.) CH_2Cl_2, −10°C, 4 h; (c) cat. K_2CO_3, in methanol, −5°C, 5 h; then 2 equiv. of *tert*-butylchlorodiphenylsilane, 4 equiv. of imidazole, in CH_2Cl_2, rt, overnight; (d) DIBAL-H (3 equiv.), CH_2Cl_2, −78°C, 0.5 h; then cat. PPTS, toluene, 0°C, 18 h; (e) $NaBH_3CN$ (1.5 equiv.), methanol, rt 2 h; (f) Ac_2O (excess), triethylamine (3 equiv.), rt, overnight; (g) H_5IO_6 (3 equiv. of), THF, 10°C, 3 min.



Scheme 2.

dialdehyde solution, solvents, temperature and catalyses. Optimization of the reaction conditions was carried out in order to avoid racemization and to get the best yield. A catalyst was necessary for the intramolecular aldolization–dehydration cyclization. As shown in Table 1, bases and strong acids were poor catalysts for the reaction: when strong acids such as HCl and *p*-toluenesulfonic acid were used as catalysts, obvious racemization occurred during the reaction. When amines such as triethylamine and pyridine were used as catalysts, almost no racemization was observed, but these amines only gave low yields. Fortunately, ammonium salts turned to be good catalyses. Thus, ammonium salts such as pyrrolidinium acetate and pyridinium *p*-toluenesulfonate gave acceptable yields and excellent ee values. Toluene and dichloromethane were suitable solvents. Reduction of enal compound **11** with sodium cyanoborohydride gave the allyl alchol **12**. Protection of the hydroxy group of **12** with excess acetic anhydride then afforded the allyl ether **13** in 76% yield from **11** and removal of the dithiane group of **13** with 3 equiv. of periodic acid[12–14] produced the desired cyclic enone **1** in 69% yield. It was confirmed that the enantiomeric purity of the final compound **1** is >98% by HPLC analysis on a chiralcel OD column.

In summary, the work described in this article provides an approach to the useful chiron **1**. The title compound **1** can be obtained from L-malic acid in around 17% overall yield from this seven-step synthesis. The reaction conditions of the intramolecular aldolization–dehydration cyclization were also optimized. It is worth pointing out that the enal **11** could also be a useful synthon for total syntheses of prostanoid compounds.

3. Experimental

3.1. General methods

NMR spectra were acquired on Bruker AM-300 in $CDCl_3$ using TMS as internal standard. Proton and carbon chemical shifts are reported on the delta scale as parts per million (ppm). Mass spectra were recorded on Finnigan 4021. IR spectra were recorded on Schimadzu IR-400. In particular, methylene chloride was distilled over CaH_2. THF was distilled from sodium prior to use. All chemicals were analytically pure and were used as received without purification. Compound **2** was prepared according to a known procedure.[10]

3.2. (2*S*)-Dimethyl-2-acetoxy-4-oxoadipate 4

Compound **2** (4.2 g, 22.1 mmol) was dissolved in thionyl chloride (15 mL). The solution was warmed to 40°C and stirred for 3 h. Excess thionyl chloride was removed by distillation in a vacuum with a dry ice trap. Residue was immediately used as such without purification.

To a rapidly stirred suspension of magnesium turning (3.22 g, 132.5 mmol) in anhydrous THF (100 mL) were added 1,2-dibromoethane (1.87 g, 10.0 mmol) and 2-bromopropane (16.6 g, 135.0 mmol). Warming was continued until magnesium disappeared. Then the solution was diluted with THF (250 mL) and cooled to room temperature. A solution of monomethyl malonate (7.83 g, 66.3 mmol) in THF (20 mL) was dropwise added within 10 min. After addition, the temperature was maintained at 45°C for 1.5 h then cooled down to room temperature. The above fresh acyl chloride was added and stirring was continued overnight. THF was removed on a rotavapor, and the residue was dissolved

Table 1. Intramolecular aldolization–dehydration cyclization of **10**

Entry	Solvent	Catalysis	Temp. (°C)	Time (h)	Yield (%)	Ee (%)[a]
1	Toluene	HCl	Rt	8	15	85
2	Toluene	Et_3N	Rt	10	21	98
3	Toluene	Py	Rt	10	24	98
4	Toluene	PTS[b]	Rt	12	18	87
5	Toluene	PDA[c]	Rt	12	58	98
6	Toluene	PPTS[d]	Rt	12	66	98
7	Toluene	PPTS	0	18	68	98
8	Benzene	PPTS	Rt	12	61	98
9	DCM[e]	PPTS	0	18	65	98
10	THF	PPTS	0	18	32	–

[a] The ee value was determined by HPLC with Chiral OD column.
[b] *p*-Toluenesulfonic acid.
[c] Pyrrolidinium acetate.
[d] Pyridinium *p*-toluenesulfonate.
[e] Dichloromethane.

in a cooled 1N aqueous HCl (150 mL) solution. The aqueous solution was extracted twice by ethyl acetate (2×150 mL). Combined extracts was washed successively with water (50 mL) and brine (50 mL) and then dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude oil, which was purified by chromatography on silica gel to give (2*S*)-dimethyl-2-acetoxy-4-oxoadipate **4** (4.1 g, 16.7 mmol, 75%). ^{1}H NMR δ 2.12 (s, 3H), 3.14 (d, $J=6.0$ Hz, 2H), 3.52 (s, 2H), 3.757 (s, 3H), 3.763 (s, 3H), 5.51 (t, $J=6.0$ Hz, 1H). ^{13}C NMR δ 197.69, 169.80, 169.61, 166.93, 67.24, 52.64, 52.45, 49.06, 43.41, 20.45. MS (*m*/*z*) 248 (M^++2). IR (neat) 2957, 1747 (br), 1231 (br) cm^{-1}.

3.3. (2*S*)-Dimethyl-2-acetoxy-4,4-(propylenedithio)-adipate 7

A solution of compound **4** (2.95 g, 12.0 mmol) in CH_2Cl_2 (20 mL) was cooled to −10°C, 1,3-propanedithiol (1.55 g, 14.3 mmol) and $BF_3{\cdot}OEt_2$ (2.55 g, 18.0 mmol) were added in turn. The mixture was stirred at −10°C for about 4 h, and the reaction was monitored by TLC. After the reaction was complete, it was quenched at once with saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated, and aqueous layer was extracted twice with CH_2Cl_2 (2×30 mL). The extracts were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a crude product which was purified by chromatography to afford (2*S*)-dimethyl-2-acetoxy-4,4-(propylenedithio)-adipate **7** (3.42 g, 10.2 mmol, 85%). $[\alpha]_D$ −158 (*c* 0.5, CH_2Cl_2). ^{1}H NMR δ 1.90–2.00 (m, 2H), 2.13 (s, 3H), 2.75 (d, $J=4.7$ Hz, 1H), 2.76 (d, $J=6.8$ Hz, 1H), 2.81–2.93 (m, 4H), 3.03 (s, 2H), 3.72 (s, 3H), 3.77 (s, 3H), 5.47 (dd, $J=4.7$ Hz; 6.7 Hz, 1H). ^{13}C NMR δ 170.32, 170.04, 168.90, 69.80, 52.63, 51.78, 48.57, 43.72, 39.17, 26.50, 26.30, 24.32, 20.80. MS (*m*/*z*) 336 (M^+). IR (neat) 2960, 1766, 1739, 1376, 1225 cm^{-1}. Anal. calcd for $C_{13}H_{20}O_6S_2$: C, 46.41; H, 5.99. Found: C, 46.31; H, 5.92%.

3.4. (2*S*)-Dimethyl-2-(*tert*-butyldiphenylsilyloxy)-4,4-(propylenedithio)adipate 9

To a stirred and cooled solution of compound **7** (3.03 g, 9.0 mmol) in anhydrous methanol (30 mL), added was catalytic K_2CO_3 (124 mg, 0.9 mmol). The temperature of the mixture was maintained around –5°C with a ice-salt bath. The reaction was continued and monitored by TLC. After compound **7** disappeared as shown by TLC, solvent was immediately removed by a rotavapor. The residue was dissolved in CH_2Cl_2 (30 mL), *tert*-butylchlorodiphenylsilane (4.95 g, 18.0 mmol) and imidazole (2.45 g, 36.0 mmol) were added. The solution was stirred overnight, and then the reaction was quenched by 1N HCl (30 mL) aqueous solution. Organic layer was separated and aqueous layer was extracted once more with CH_2Cl_2 (30 mL). Extracts were combined and dried over anhydrous $MgSO_4$. Removal of solvent gave a crude oil which was purified by chromatography to produce (2*S*)-dimethyl-2-(*tert*-butyldiphenylsilyloxy)-4,4-(propylenedithio)adipate **9** (3.73 g, 7.0 mmol, 78%). $[\alpha]_D$ −226 (*c* 0.6, CH_2Cl_2). ^{1}H NMR δ 1.07 (s, 9H), 1.88–1.95 (m, 2H), 2.71 (dd, $J=5.5$ Hz; 14.9 Hz, 1H), 2.76–2.82 (m, 4H), 2.83 (dd, $J=5.9$ Hz; 14.9 Hz, 1H), 3.02 (d, $J=15.1$ Hz, 1H), 3.07 (d, $J=15.1$ Hz, 1H), 3.26 (s, 3H), 3.62 (s, 3H), 4.62 (t, $J=5.9$ Hz, 1H), 7.33–7.45 (m, 6H), 7.66–7.71 (m, 4H). ^{13}C NMR δ 172.73, 168.95, 135.90, 133.09, 132.86, 129.71, 129.59, 127.49, 127.34, 71.09, 51.56, 51.37, 47.98, 43.58, 43.03, 26.88, 26.40, 24.27, 19.31. MS (*m*/*z*) 502 (M^+–OMe). IR (neat) 2951 (br), 1741 (br), 1429, 1113, 703, 508 cm^{-1}. Anal. calcd for $C_{27}H_{36}O_5S_2Si$: C, 60.87; H, 6.81. Found: C, 60.98; H, 6.90%.

3.5. (9*S*)-9-(*tert*-Butyldiphenylsilyloxy)-7-formyl-1,5-dithiaspiro[5,4]dec-7-ene 11

A solution of compound **9** (3.08 g, 5.78 mmol) in CH_2Cl_2 (60 mL) was cooled to −78°C, 1 M DIBAL-H solution (17.5 mL) in hexanes was added slowly within 5 min, then the solution was stirred at −78°C for 0.5 h. The reaction was quenched with methanol (2 mL), and the temperature was allowed to rise to 0°C. Aqueous

2N HCl solution (20 mL) was added, the organic layer was separated and dried with anhydrous Na_2SO_4. Removal of solvent by a rotavapor gave crude dialdehyde **10** which cannot be stored without decomposition and should be immediately dissolved in toluene (60 mL). The catalyst (1.2 mmol) indicated in Table 1 was added, and the solution was stirred overnight. The organic phase was washed in turn with water (10 mL) and brine (10 mL). After drying over anhydrous $MgSO_4$, the solvent was removed to produce a residue which was purified by flash chromatography on silica gel to afford (9*S*)-9-(*tert*-butyldiphenylsilyloxy)-7-formyl-1,5-dithiaspiro[5,4]dec-7-ene **11** in the yield as shown in Table 1. $[\alpha]_D$ −112 (*c* 1.0, CH_2Cl_2). ^1H NMR δ 1.12 (s, 9H), 1.49–1.56 (m, 2H), 2.24–2.40 (m, 2H), 2.62 (dd, $J=5.8$ Hz; 13.7 Hz, 1H), 2.75–2.85 (m, 1H), 2.87 (dd, $J=6.9$ Hz; 13.7 Hz, 1H), 3.08–3.18 (m, 1H), 4.97–5.02 (m, 1H), 6.29 (d, $J=2$ Hz, 1H), 7.16–7.26 (m, 6H), 7.66–7.73 (m, 4H), 9.54 (s, 1H). ^{13}C NMR δ 188.10, 148.92, 135.83, 135.79, 133.54, 133.46, 130.06, 128.11, 127.96, 127.79, 127.47, 74.76, 54.23, 28.31, 27.96, 26.77, 23.76, 19.04.

3.6. (9*S*)-7-(Acetoxymethyl)-9-(*tert*-butyldiphenylsilyloxy)-1,5-dithiaspiro[5,4]dec-7-ene 13

To a solution of compound **11** (1.81 g, 3.98 mmol) in methanol (10 mL) was added $NaBH_3CN$ (375 mg, 5.96 mmol). After the reaction was complete, water (50 mL) was added. The aqueous solution was extracted with ethyl acetate (2×30 mL). The extracts were combined and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude oil. Acetic anhydride (6 mL) and triethylamine (1.21 g, 12.0 mmol) were added. The mixture was stirred overnight. The reaction was quenched by water (30 mL), then the aqueous solution was twice extracted with hexanes (2×30 mL). Extracts were combined and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a residue which was chromatographed to afford (9*S*)-7-(acetoxymethyl)-9-(*tert*-butyldiphenylsilyloxy)-1,5-dithiaspiro[5,4]dec-7-ene **13** (1.51 g, 3.03 mmol, 76%). $[\alpha]_D$ –92 (*c* 1.1, CH_2Cl_2). ^1H NMR δ 1.07 (s, 9H), 1.75–1.92 (m, 1H), 2.00–2.10 (m, 1H), 2.07 (s, 3H), 2.51 (dd, $J=5.6$ Hz; 13.1 Hz, 1H), 2.70–2.82 (m, 2H), 2.90–3.05 (m, 2H), 3.05 (dd, $J=6.8$ Hz; 13.1 Hz, 1H), 4.70–4.95 (m, 3H), 5.78 (d, $J=1.6$ Hz, 1H), 7.35–7.50 (m, 6H), 7.65–7.80 (m, 4H). ^{13}C NMR δ 170.33, 142.49, 135.73, 134.24, 133.90, 133.84, 129.70, 127.64, 75.73, 60.23, 58.94, 52.89, 28.84, 27.59, 26.86, 24.30, 20.92, 19.06. MS (*m*/*z*) 498 (M^+). IR (neat) 2956, 1746, 1218, 702 cm^{-1}. Anal. calcd for $C_{27}H_{34}O_3S_2Si$: C, 65.02; H, 6.87. Found: C, 65.23; H, 6.71%.

3.7. (4*S*)-2-(Acetoxymethyl)-4-(*tert*-butyldiphenylsilyloxy)-2-cyclopenten-1-one 1

To a well stirred solution of compound **13** (910 mg, 1.82 mmol) in anhydrous THF (5 mL) was added a fresh solution of H_5IO_6 (1.25 g, 5.48 mmol) in anhydrous THF (5 mL). After addition, stirring was continued at 10°C for 3 min. Then ethyl acetate (60 mL) and water (20 mL) was immediately added. Organic layer was separated and washed with saturated aqueous solution (15 mL) of Na_2SO_3 and brine (10 mL). The extract was dried over anhydrous $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography on silica gel to afford the desired cyclic enone (4*S*)-2-(acetoxymethyl)-4-(*tert*-butyldiphenylsilyloxy)-2-cyclopenten-1-one **1** (513 mg, 1.26 mmol, 69%). $[\alpha]_D$ –67 (*c* 0.8, CH_2Cl_2). ^1H NMR (C_6D_6) δ 1.07 (s, 9H), 1.59 (s, 3H), 2.15–2.32 (m, 2H), 4.41–4.52 (m, 1H), 4.63 (d, $J=15.5$ Hz, 1H), 4.69 (d, $J=15.4$ Hz, 1H), 6.92 (d, $J=2$ Hz, 1H), 7.13–7.25 (m, 6H), 7.55–7.70 (m, 4H). MS (*m*/*z*) 409 (M^++1). IR (neat) 2987, 1749, 1702, 1418, 1212, 736 cm^{-1}. Anal. calcd for $C_{24}H_{28}O_4Si$: C, 70.55; H, 6.91. Found: C, 70.31; H, 6.88%.

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