

Synthetic Studies toward (–)-Cleistenolide: Highly Stereoselective Synthesis of New γ -Lactone Subunits

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This study describes the stereoselective synthesis of two new γ -lactones in 6 and 3 steps and 19 and 32% yield, respectively, directed toward the total synthesis of the natural product (–)-cleistenolide. The starting material was an enantiomerically pure diacetonide diol, derived from D-mannitol with the required stereocenters for (–)-cleistenolide synthesis. γ -Lactone syntheses were based on highly selective protection and deprotection of hydroxyls from D-mannitol. The formation of γ -lactone rings was the culmination of this approach, made possible by a Horner-Wadsworth-Emmons Z-olefination between diacetal aldehyde and ethyl 2-(bis(*o*-tolylxy)phosphoryl)acetate to produce an unsaturated ester. The *Z*-isomer ester was highly favored in relation to the *E*-isomer (*Z/E* ratio of 94:6), allowing the formation of the γ -lactone ring under acid catalysis. This strategy precluded the use of chiral auxiliaries or catalysts for the control of stereocenters in the novel γ -lactones.

Keywords: (–)-cleistenolide, γ -lactone, diacetonide diol, D-mannitol

Introduction

(–)-Cleistenolide (**1**) is an exponent of the class of 5,6-dihydro-2*H*-pyran-2-ones.¹⁻³ It contains a δ -lactone ring, a moiety found in the structure of several natural products with expressive antibiotic properties and anticancer activity against a broad spectrum of tumor cells.⁴⁻¹⁴ (–)-**1** and the polyoxygenated compound cleistodienol (Figure 1) were isolated by Samwel *et al.*¹⁵ in 2007 from *Cleistochlamys kirkii* (Benth.) Oliv. The plant species belongs to the family Annonaceae and originated from Tanzania and Mozambique. The use of *C. kirkii* extract in traditional medicine to treat infections, tuberculosis, and rheumatism^{1,15-21} motivated researchers to investigate the phytochemical properties of the plant. (–)-**1** showed *in vitro* antibacterial activity against *Bacillus anthracis* and *Staphylococcus aureus* and antifungal activity against *Candida albicans*.^{15,17}

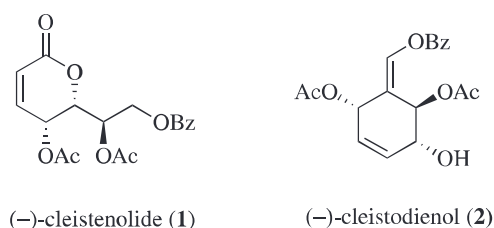


Figure 1. Chemical structures of (–)-cleistenolide and (–)-cleistodienol.

Because of the pharmacological potential of (–)-**1**, its interesting chemical architecture, and its low availability in nature (only 200 mg can be extracted from 1 kg dry weight of plant material),²² several researchers around the world have focused on its synthesis. Some studies^{17,23} indicated that the α,β -unsaturated δ -lactone ring of (–)-**1** can act as a Michael acceptor, which further enhances its biological action.

The first total synthesis of (–)-**1** was performed in 2010 by Schmidt *et al.*¹⁹ using a mannitol-derived compound as starting material. The researchers obtained

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(–)-**1** in an overall yield of 18% by applying a ring-closing metathesis protocol to prepare the basic component of the δ -lactone ring.¹⁹ In the same year, Cai *et al.*²² reported the stereoselective synthesis of (–)-**1** in eight steps and 49% overall yield. The reaction started from the natural sugar D-arabinose. The authors²² used Wittig olefination to form the α,β -unsaturated carbonyl unit, and Yamaguchi lactonization to afford the δ -lactone ring.

In the studies of Babu *et al.*,^{20,21} Ramesh and Meshram,²⁴ and Karier *et al.*,²⁵ the δ -lactone ring of (–)-**1** was also obtained by ring-closing metathesis. Ghogare *et al.*²⁶ and Reddy *et al.*^{1,27} used the Still-Gennari protocol to obtain *cis*-olefin, a key intermediate that facilitated obtaining the lactone ring of (–)-**1**. Benedekovic *et al.*²⁸ carried out Wittig olefination at a low temperature to favor the formation of *Z*-alkenes, followed by lactonization under acid catalysis to form the piran-2-one ring.

In the above-mentioned synthetic studies,^{19-21,24-28} several interesting conventional methodologies were applied, alone or in combination, to obtain the stereogenic centers found in the natural product. The current study reports an unprecedented approach for the stereoselective synthesis of two γ -lactones whose stereocenters originated from D-mannitol. The γ -lactones are considered advanced intermediates in the total synthesis of (–)-**1**. Their synthesis was made possible by using highly selective steps for protection and deprotection of hydroxyl groups in the starting material.

Experimental

General

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance spectrometer at 400 and 100 MHz, respectively, using CDCl₃ and CD₃OD as solvents. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. ¹H NMR chemical shifts are reported relative to tetramethylsilane (TMS) in CDCl₃ and using the residual signal of CD₂HOD (δ = 2.50 ppm) in CD₃OD as a reference. ¹³C NMR chemical shifts were recorded using CDCl₃ (δ = 77.2 ppm) and CD₃OD (δ = 49.2 ppm) signals as references. ¹H and ¹³C NMR spectra of compounds can be found in the Supplementary Information (SI) section. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analyses were performed on a Nexera UHPLC system (Shimadzu) hyphenated to a maXis ETD high-resolution (HR) electrospray ionization-quadrupole time-of-flight (ESI-QTOF) mass spectrometer (Bruker). Infrared (IR) spectra were recorded on a Varian 660 FTIR spectrometer equipped with a diamond

attenuated total reflectance (ATR) accessory as a thin film. Melting points were determined on an MQAPF-302 Microchemical apparatus and uncorrected. $[\alpha]_D$ values were measured using an Anton Paar MCP 300 polarimeter equipped with a 589 nm wavelength sodium vapor lamp at the Natural Products Laboratory 610 of the Oswaldo Cruz Foundation, Instituto René Rachou, Belo Horizonte City, Minas Gerais State, Brazil. Solution concentrations are denoted as *c* (g per 100 mL), followed by the solvent used. Purifications were performed by conventional or flash column chromatography on silica gel or neutral alumina. Tetrahydrofuran (THF) was distilled from sodium metal and benzophenone ketyl under nitrogen. Dimethylformamide (DMF) and dichloromethane were distilled from CaH₂. Acetonitrile was dried with anhydrous MgSO₄, distilled, and stored under 3 Å molecular sieves. Methanol and ethanol were dried over Mg⁰ and I₂ (cat.) under reflux until total consumption of Mg⁰, distilled, and stored under 3 Å molecular sieves. Thin layer chromatography (TLC) visualization was achieved under ultraviolet light (254 nm) or by spraying with KMnO₄ solution (1.0 g KMnO₄, 6.66 g K₂CO₃, and 1.66 mL 5% KOH in 100 mL distilled water) and heating and/or resublimed iodine. All chemicals were used as received unless otherwise stated.

Syntheses

(4*R*,4'*R*,4''*R*,5'*R*)-2,2,2',2'',2''-Hexamethyl-4,4',5',4''-tert-(1,3-dioxolane) (**10**)

To a mixture of acetone (75 mL) and sulfuric acid (0.5 mL) was added D-mannitol (5.052 g, 27.77 mmol) in portions and stirred for 18 h at room temperature. The mixture was neutralized by addition of aqueous NH₄OH (1.75 mL) and then Na₂CO₃ (3.125 g, 29.48 mmol). The residue was filtered, and the filtrate was concentrated to a volume of 20 mL under vacuum. Then, the solution was immersed in an ice bath to precipitate the product as a white solid. The solid product was collected and recrystallized from acetone to give **10** as crystals in 76% yield, mp 65.5-66.4 °C; Rf 0.68 (SiO₂, hexane/EtOAc 80:20); $[\alpha]_D^{25}$ +15.69 (*c* 1.02, CHCl₃); IR (ATR) $\bar{\nu}$ / cm⁻¹ 2990, 2957, 2880, 1368, 1211, 1064, 969, 844, 787, 508; ¹H NMR (400 MHz, CDCl₃) δ 4.25-4.15 (m, 2H), 4.12-4.05 (m, 2H), 4.03-3.90 (m, 4H), 1.43 (s, 6H), 1.39 (s, 6H), 1.36 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 110.2, 109.6, 79.4, 76.3, 66.3, 27.5, 26.5, 25.3; HRMS (ESI-TOF) *m/z*, calcd. for C₁₅H₂₇O₆ [M + H]⁺: 303.1808, found 303.1813.

(*R*)-1-((4*R*,4'*R*,5*S*)-2,2,2',2'-Tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethane-1,2-diol (**9**)

To a solution of triacetone **10** (1.958 g, 6.85 mmol) in

anhydrous methanol (78 mL) under an argon atmosphere and in an ice bath (0 °C) was added previously distilled acetyl chloride (28.03 mmol, 2.0 mL) dropwise. The mixture was stirred for 5 min at 0 °C, saturated aqueous K₂CO₃ (50 mL) was added, and the residue was extracted with EtOAc (3 × 80 mL). The combined EtOAc layers were washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **9** as a colorless oil in 29% yield and 41% (806.3 mg) of recovered starting material (**10**).

Study of the selective deprotection of triacetone **10** (Table 1)

Entries 1-9

Pyridinium *p*-toluenesulfonate (PPTS) (1.2 or 0.2 equiv) was added to a solution of triacetone **10** (3.795 g, 12.57 mmol) in anhydrous methanol (73 mL) and stirred under the time and temperature conditions specified in entries 1-9 of Table 1. The mixture was neutralized by addition of NaHCO₃ (15.14 mmol), filtered, and the filtrate

concentrated in vacuum. Then, water was added (70 mL), and the product extracted with EtOAc (3 × 70 mL). The combined EtOAc layers were washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **9** as a colorless oil in 39% and recover 47% of the starting material (**10**) (entry 8). R_f 0.31 (SiO₂, hexane/EtOAc 1:1); [α]_D²⁵ +21.18 (*c* 1.28, CH₃OH); IR (ATR) $\bar{\nu}$ / cm⁻¹ 3415, 2986, 2936, 2885, 1372, 1212, 1156, 1066, 843, 511; ¹H NMR (400 MHz, CDCl₃) δ 4.25-4.16 (m, 1H), 4.14-4.06 (m, 1H), 4.05-3.99 (m, 1H), 3.95-3.87 (m, 2H), 3.86-3.65 (m, 4H), 3.02 (s, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.37 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 110.3, 109.8, 80.6, 80.5, 76.6, 72.5, 67.8, 63.8, 27.0, 26.9, 26.4, 25.2; HRMS (ESI-TOF) *m/z*, calcd. for C₁₂H₂₃O₆ [M + H]⁺: 263.1495, found: 263.1491.

Entries 10-12

Iron(III) chloride hexahydrate (1 mol%) was added to a solution of triacetone **10** (2.014 g, 6.67 mmol) in anhydrous CH₂Cl₂ (100 mL) and stirred under the time and

Table 1. Studies of selective deprotection of triacetone **10**

entry	Reagent	Equiv	Solvent	Temperature / °C	time / h	Yield / %
1	PPTS	1.2	CH ₃ OH	rt	0.5	11 (21) ^a
2	PPTS	1.2	CH ₃ OH	rt	1	11 (20) ^a
3	PPTS	1.2	CH ₃ OH	rt	18	29 (32) ^a
4	PPTS	1.2	CH ₃ OH	35	1	27 (42) ^a
5	PPTS	1.2	CH ₃ OH	35	1.5	34 (41) ^a
6	PPTS	0.2	CH ₃ OH	rt	2.5	16 (28) ^a
7	PPTS	0.2	CH ₃ OH	rt	6	20 (29) ^a
8	PPTS	0.2	CH ₃ OH	35	3	39 (57) ^a
9	PPTS	0.2	CH ₃ OH	35	6	31 (41) ^a
10	FeCl ₃	0.01	CH ₂ Cl ₂	rt	0.1	NR
11	FeCl ₃	0.01	CH ₂ Cl ₂	rt	0.35	30 (43) ^a
12	FeCl ₃	0.01	CH ₂ Cl ₂	rt	1.2	15 (21) ^a
13	BiCl ₃	0.05	MeCN	rt	0.1	23 (24) ^a
14	Amberlite-IR120	0.02	acetone/H ₂ O	rt	6	NR
15	Amberlyst-15	0.02	acetone/H ₂ O	rt	48	15 (27) ^a

^aYield of **9** based on recovered starting material. PPTS: pyridinium *p*-toluenesulfonate; rt: room temperature; NR: did not react.

temperature conditions shown in entries 10–12 of Table 1. The mixture was neutralized by addition of saturated aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL), and the combined EtOAc layers dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **9** and recover the starting material (**10**).

Entry 13

Bismuth(III) chloride (5 mol%) was added to a solution of triacetoneide **10** (3.457 g, 11.45 mmol) in anhydrous CH₃CN (114 mL) and stirred for 10 min. The mixture was neutralized by addition of NaHCO₃ (1.145 mmol), filtered, and the filtrate was concentrated in vacuum. Then, water (60 mL) was added, and the product extracted with EtOAc (3 × 60 mL). The combined EtOAc layers were washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The yellowish residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **9** in 23% yield and recover 4% of the starting material **10**.

Ethyl 2-(bis(*o*-toluoyloxy)phosphoryl)acetate (**8**)

To a two-port flask containing 5 mol L⁻¹ PCl₃ (5 mL, 57.21 mmol), freshly distilled, in anhydrous CH₂Cl₂ (6.44 mL) at 0 °C was added 10 mol L⁻¹ *t*-BuOH (5.72 mL, 57.21 mmol) in anhydrous CH₂Cl₂ (0.29 mL), dropwise. The resulting mixture was stirred at 0 °C for 1 h, producing bubbles of HCl gas as a byproduct, which was purged (bubbling in water) at short intervals. Then, a 5 mol L⁻¹ solution of *o*-cresol (11.74 mL, 114 mmol) in anhydrous CH₂Cl₂ (11.06 mL) was added dropwise over 30 min. The mixture was stirred at 0 °C for 30 min and at ambient temperature for a further 12 h. The solvent was removed by rotary evaporation under vacuum, generating diphenylphosphite as a yellowish residue. It was used for the next step without previous purification.

To a solution containing 1 mol L⁻¹ diphenylphosphite (34.1 mmol) in anhydrous CH₂Cl₂ (34.1 mL) at 0 °C was added ethyl bromoacetate (3.77 mL, 34.1 mmol) and triethylamine (6.70 mL, 47.7 mmol). The mixture was stirred at 0 °C for 15 min and at ambient temperature for 1 h, and reaction completion was monitored by TLC. Water (30 mL) was added and the product extracted with a 3:1 (v/v) mixture of hexane/EtOAc (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum to obtain a yellowish residue. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 75:25) to provide phosphonate **8** as

a colorless oil in 27% yield. Rf 0.27 (SiO₂, hexane/EtOAc 75:25); IR (ATR) $\bar{\nu}$ / cm⁻¹ 2981, 2932, 2359, 2340, 1732, 1585, 1489, 1462, 1276, 1222, 1166, 1103, 928, 803, 756, 615; ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.27 (m, 2H), 7.19 (d, *J* 8.0 Hz, 2H), 7.16–7.05 (m, 4H), 4.22 (q, *J* 8.0 Hz, 2H), 3.33 (d, *J* 20.0 Hz, 2H), 2.25 (s, 3H), 1.26 (t, *J* 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.8, 148.8, 131.5, 129.5 (*J* 6.0 Hz), 127.1, 125.4, 120.4 (*J* 2.0 Hz), 62.0, 34.7 (*J* 137.0 Hz), 16.3, 14.0; HRMS (ESI-TOF) *m/z*, calcd. for C₁₈H₂₁NaO₅P [M + Na]⁺: 371.1019, found: 371.1026.

Ethyl (Z)-3-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)acetate (**6**)

Diol **9** (0.9655 g, 3.6851 mmol) was solubilized in ethyl ether (13.5 mL) and mixed with Bu₄NF (21.3 mg, 0.0812 mmol), water (7.0 mL), and NaIO₄ (1.7031 g, 7.37 mmol), added in small portions. The mixture was kept under stirring for 2 h at room temperature throughout the reaction, which was monitored by TLC using 2,4-dinitrophenylhydrazine solution as visualizing agent. The reaction was stopped by addition of saturated aqueous NaHCO₃ (50 mL), and the mixture extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum to give aldehyde (**5**) as a colorless oil. Rf 0.64 (SiO₂, hexane/EtOAc 1:1). The product (**5**) was subjected to the next step without previous purification. Triton B (1.6 mL, 40%, 4.054 mmol) was added dropwise to a solution of phosphonate **8** (1.415 g, 4.054 mmol) in anhydrous THF (48 mL) at –66 °C. The mixture was stirred at –66 °C for 15 min. Then, a solution of aldehyde **7** (3.69 mmol) in anhydrous THF (4 mL) was added slowly. The mixture was stirred at –66 °C for 2 h and at room temperature for 12 h. Saturated NH₄Cl solution (50 mL) was added, and the mixture extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (AlO₂, hexane/EtOAc 98:2) to give **6** as colorless oil in 89% yield (0.986 g). Rf 0.55 (AlO₂, hexane/EtOAc 90:10); [α]_D^{24.8} –29.51 (*c* 2.07, CHCl₃); IR (ATR) $\bar{\nu}$ / cm⁻¹ 2985, 2937, 2878, 2358, 2340, 1617, 1660, 1371, 1189, 1060, 1028, 878, 846, 824; ¹H NMR (400 MHz, CDCl₃) δ 6.15 (dd, *J* 11.6, 8.4 Hz, 1H), 5.94 (dd, *J* 11.6, 1.2 Hz, 1H), 5.45 (dt, *J* 8.4, 1.2 Hz, 1H), 4.25–4.10 (m, 4H), 4.01 (dd, *J* 8.0, 5.2 Hz, 1H), 3.81 (dd, *J* 8.0, 5.2 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.35–1.20 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 144.4, 123.5, 110.3, 109.5, 80.7, 76.0, 74.5, 66.1, 60.6, 27.3, 27.1, 26.7, 25.5, 14.4; HRMS (ESI-TOF) *m/z*, calcd. for C₁₅H₂₄NaO₆ [M + Na]⁺: 323.1465, found: 323.1462.

Ethyl (Z)-3-((4*R*,5*R*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**11**)

To a solution of diacetal ester **6** (0.256 g, 0.854 mmol) in anhydrous CH₃CN (48 mL) under an argon atmosphere was added BiCl₃ (14.0 mg, 0.427 mmol) and water (2 drops). The mixture was stirred for 2 h 20 min and neutralized by addition of NaHCO₃ (50 mg). The residue was concentrated under vacuum, mixed with water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **11** as a colorless oil in 57% yield (0.195 g) and recover 20% of the starting material (**6**).

Study of the selective deprotection of **6** (Table 2)

Entries 1-2

PPTS (0.2 equiv) was added to a solution of diacetal ester **6** (0.375 g, 1.25 mmol) in anhydrous methanol (7.3 mL) and stirred at 35 °C under the conditions described in entries 1 and 2 of Table 2. The mixture was neutralized by addition of NaHCO₃ (1.5 mmol), filtered, and the filtrate concentrated in vacuum. Then, water (15 mL) was added, and the product extracted with EtOAc (3 × 15 mL). The combined EtOAc layers were washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **11** and recover **6**.

Entry 3

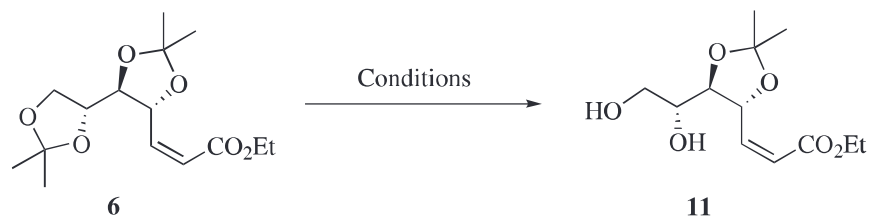
p-Toluenesulfonic acid (1 mol%) was added to a solution of diacetal ester **6** (0.552 g, 1.84 mmol) in anhydrous methanol

(5 mL) and stirred at room temperature for 16 h. The mixture was neutralized by addition of K₂CO₃ (0.20 mmol) and concentrated under vacuum. Then, water (30 mL) was added, and the product extracted with EtOAc (3 × 30 mL). The combined EtOAc layers were washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **11** in 33% yield and recover 16% of **6**.

Entries 4-5

To a solution of diacetal ester **6** (0.10 g, 0.33 mmol) in anhydrous ethanol (2 mL) was added 2 mol L⁻¹ HCl (3 drops). The mixture was stirred at room temperature for 6 h, neutralized by addition of triethylamine (3 drops), and concentrated under vacuum. Then, water (30 mL) was added, and the product extracted with EtOAc (3 × 30 mL). The combined EtOAc layers were washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 90:10 → 60:40) to give **11** in 60 and 68% yield and recover **6** in 24 and 21% yield for entries 4 and 5, respectively. R_f 0.21 (SiO₂, hexane/EtOAc 1:1); [α]_D²⁵ -70.62 (*c* 4.88, CHCl₃); IR (ATR) $\bar{\nu}$ /cm⁻¹ 3418, 2986, 2936, 2358, 2342, 1715, 1694, 1372, 1193, 1162, 1053, 1024, 872, 809; ¹H NMR (400 MHz, CDCl₃) δ 6.25 (dd, *J* 11.6, 8.8 Hz, 1H), 6.00 (dd, *J* 11.6, 1.2 Hz, 1H), 5.30 (t, *J* 8 Hz, 1H), 4.32 (d, *J* 3.2 Hz, 1H), 4.23 (q, *J* 8.0 Hz, 2H), 3.93-3.75 (m, 3H), 3.73-3.63 (m, 1H), 2.26 (t, *J* 4.0 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.31 (t, *J* 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.0, 146.9, 122.0, 110.5, 80.6, 76.3, 72.8, 64.2, 61.5, 27.0, 26.9, 14.1; HRMS (ESI-TOF) *m/z*, calcd. for C₁₂H₂₀NaO₆ [M + Na]⁺: 283.1152, found: 283.1149.

Table 2. Selective deprotection studies from diacetonide **6**



entry	Reagent	Equiv	Solvent	Temperature / °C	time / h	Yield / %
1	PPTS	0.2	CH ₃ OH	35	36	33 (41) ^a
2	PPTS	0.2	CH ₃ OH	35	24	47 (63) ^a
3	<i>p</i> -TsOH	0.01	CH ₃ OH	rt	16	33 (38) ^a
4	2 mol L ⁻¹ HCl	3 drops	EtOH	rt	6	60 (74) ^a
5	2 mol L ⁻¹ HCl	3 drops	EtOH	rt	9	68 (82) ^a

^aYield of **11** based on recovered starting material. PPTS: pyridinium *p*-toluenesulfonate; rt: room temperature.

(*Z*)-Ethyl-3-((4*R*,5*R*)-5-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**12**)

To a solution of diol acetal ester **11** (0.183 g, 0.704 mmol) and imidazole (96.86 mg, 1.41 mmol) in anhydrous CH₂Cl₂ (3 mL) was added *t*-butyldiphenylsilyl chloride (205 μL, 0.775 mmol) dropwise. The mixture was stirred at room temperature for 6 h and quenched by addition of water (10 mL). The product was extracted with CH₂Cl₂ (3 × 20 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by chromatography (SiO₂, hexane/EtOAc 90:10) to give **12** as a colorless oil in 78% yield (0.27 g). Rf 0.30 (SiO₂, hexane/EtOAc 80:20); [α]_D^{22.7} –31.11 (*c* 2.74, CHCl₃); IR (ATR) $\bar{\nu}$ / cm⁻¹ 3471, 2932, 2857, 2359, 2341, 1716, 1695, 1427, 1371, 1206, 1111, 1057, 875, 822, 700, 613; ¹H NMR (400 MHz, CDCl₃) δ 7.75–7.63 (m, 4H), 7.50–7.30 (m, 6H), 6.20 (dd, *J* 11.6, 8.8 Hz, 1H), 5.95 (dd, *J* 11.6, 0.8 Hz, 1H), 5.47 (t, *J* 8.0 Hz, 1H), 4.19 (q, *J* 8.0 Hz, 2H), 4.00–3.70 (m, 4H), 3.42 (d, *J* 4.0 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.28 (t, *J* 8.0 Hz, 3H), 1.06 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.7, 146.0, 135.6, 135.6, 133.5, 133.4, 129.6, 129.6, 127.7, 127.6, 122.5, 109.8, 80.0, 75.0, 73.0, 65.1, 60.9, 27.0, 26.8, 19.3, 14.1; HRMS (ESI-TOF) *m/z*, calcd. for C₂₈H₃₈NaO₆Si [M + Na]⁺: 521.2330, found: 521.2336.

(*Z*)-3-((4*R*,5*R*)-5-((*R*)-2-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid (**13**)

To a solution of monosilylated acetal ester **12** (0.171 g, 0.344 mmol) in 4:1 THF/H₂O (6.4 mL) was added LiOH (72.8 mg, 3.03 mmol) and the reaction mixture heated at 45 °C for 5 h. After this period, the mixture was cooled to room temperature and, after the addition of cold 0.5 mol L⁻¹ HCl (10 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to obtain a yellowish oil. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 80:20 → 70:30) to give **13** as a colorless oil in 90% yield (0.133 g). Rf 0.29 (SiO₂, hexane/EtOAc 70:30); [α]_D²³ –57.14 (*c* 3.29, CHCl₃); IR (ATR) $\bar{\nu}$ / cm⁻¹ 3075, 2931, 2857, 2359, 2340, 1694, 1428, 1372, 1211, 1111, 1058, 875, 822, 699, 614; ¹H NMR (400 MHz, CDCl₃) δ 7.75–7.62 (m, 4H), 7.50–7.30 (m, 6H), 6.27 (dd, *J* 12.0, 8.0 Hz, 1H), 5.98 (d, *J* 12.0 Hz, 1H), 5.43 (t, *J* 8.0 Hz, 1H), 4.00–3.70 (m, 4H), 1.41 (s, 3H), 1.34 (s, 3H), 1.06 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 169.7, 146.9, 135.6, 135.6, 133.2, 133.1, 129.8, 129.7, 127.7, 127.7, 122.2, 110.2, 79.9, 75.4, 73.2, 64.9, 27.0, 26.9, 26.8, 19.3; HRMS (ESI-TOF) *m/z*, calcd. for C₂₆H₃₄NaO₆Si [M + Na]⁺: 493.2017, found: 493.2022.

(*R*)-5-((1*R*,2*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1,2-dihydroxypropyl)furan-2(5*H*)-one (**3**)

To a solution of monosilylated acetal acid **13** (0.132 g, 0.28 mmol) in anhydrous CH₂Cl₂ (4 mL) was added FeCl₃·6H₂O (76.0 mg, 0.28 mmol). The mixture was stirred at room temperature for 15 min and quenched by the addition of saturated NaHCO₃ solution (6 mL). The mixture was extracted with EtOAc (3 × 10 mL), the organic layers dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to give a yellowish oil. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 80:20 → 70:30 → 60:40) to give **3** as a colorless oil in 78% yield (0.133 g). Rf 0.32 (SiO₂, hexane/EtOAc 1:1); [α]_D^{22.7} +22.76 (*c* 3.12, CHCl₃); IR (ATR) $\bar{\nu}$ / cm⁻¹ 3418, 3071, 2930, 2856, 2359, 1742, 1471, 1427, 1110, 822, 700, 610; ¹H NMR (400 MHz, CDCl₃) δ 7.70–7.60 (m, 4H), 7.54 (dd, *J* 5.6, 1.6 Hz, 1H), 7.48–7.33 (m, 6H), 6.15 (dd, *J* 5.6, 2.4 Hz, 1H), 5.40–5.30 (m, 1H), 3.92–3.88 (m, 2H), 3.87–3.70 (m, 2H), 2.73 (s, 1H), 2.54 (s, 1H), 1.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.0, 154.6, 135.5, 132.6, 130.1, 127.9, 122.2, 83.8, 72.2, 71.4, 64.9, 26.9, 19.3; HRMS (ESI-TOF) *m/z*, calcd. for C₂₆H₃₄NaO₆Si [M + H]⁺: 413.1784, found: 413.2682.

(*R*)-5-((1*R*,2*R*)-1,2,3-Trihydroxypropyl)furan-2(5*H*)-one (**14**) and (*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxymethyl)furan-2(5*H*)-one (**15**)

To a solution of diacetal ester **6** (0.559 g, 1.86 mmol) in acetone (7.4 mL) and water (0.1 mL) was added Amberlyst-15 (0.4 equiv, 123.7 mg, 0.3935 mmol), and the resulting mixture was stirred at room temperature for 24 h. Then, additional amounts of Amberlyst-15 (0.4 equiv) and water (0.2 equiv) were added, the mixture was stirred, and the reaction progress was monitored by TLC. After 72 h, the reaction mixture was filtered through Celite® and washed with dichloromethane, EtOAc, and acetone. The filtrate was concentrated under vacuum, giving a white solid. The residue was purified by column chromatography (SiO₂, hexane/EtOAc 80:20 → 60:40 → 0:100) to give **14** and **15** as white solids in 16% (0.053 g, 0.19 mmol) and 63% yield (0.25 g, 1.17 mmol), respectively.

Data for **14**

mp 108.0–108.5 °C; Rf 0.11 (SiO₂, hexane/EtOAc 1:1); [α]_D^{22.4} +71.43 (*c* 2.17, CH₃OH); IR (ATR) $\bar{\nu}$ / cm⁻¹ 3446, 3334, 2921, 2360, 2339, 1694, 1410, 1354, 1242, 1178, 1073, 1014, 868, 830, 640, 608; ¹H NMR (400 MHz, CD₃OD) δ 7.68 (dd, *J* 5.6, 1.2 Hz, 1H), 6.17 (dd, *J* 5.6, 2.0 Hz, 1H), 5.55–5.45 (m, 1H), 3.85–3.73 (m, 2H), 3.72–3.52 (m, 2H); ¹³C NMR (100 MHz, CD₃OD) δ 176.3, 157.9, 122.7, 85.6, 73.0, 71.5, 64.8; HRMS

(ESI-TOF) m/z , calcd. for $C_7H_{11}O_5$ $[M + H]^+$: 175.0601, found: 175.0601.

Data for 15

mp 121.2-122.2 °C; Rf 0.39 (SiO₂, hexane/EtOAc 1:1); $[\alpha]_D^{25} +30.89$ (c 3.14, CHCl₃); IR (ATR) $\bar{\nu}$ / cm⁻¹ 3341, 3110, 2989, 2906, 2863, 2359, 2341, 1715, 1377, 1210, 1177, 1065, 1026, 835, 663, 529; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, J 5.6, 1.2 Hz, 1H), 6.16 (dd, J 5.6, 2.0 Hz, 1H), 5.28-5.22 (m, 1H), 4.26-4.10 (m, 2H), 4.08-3.98 (m, 1H), 3.72-3.60 (m, 1H), 2.97 (d, J 4.0 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 154.5, 122.2, 109.9, 84.3, 75.6, 72.9, 67.2, 26.8, 25.1; HRMS (ESI-TOF) m/z , calcd. for $C_{10}H_{14}O_5$ $[M + H]^+$: 215.0914, found: 215.0915.

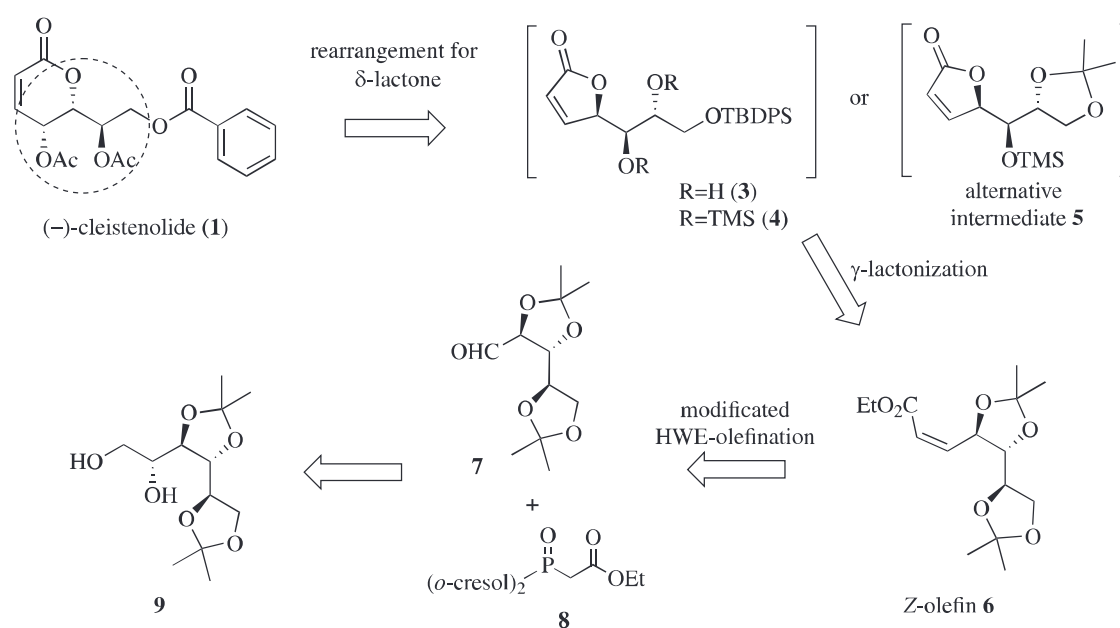
Results and Discussion

Retrosynthetic analysis²⁹ revealed that (–)-1 is derived from γ -lactone 4 or, alternatively, γ -lactone 5 (Scheme 1). Rearrangement of γ -lactone 4 to δ -lactone (–)-1 should be achieved by a three-step, one-pot sequence: reduction of the carbonyl with diisobutylaluminium hydride (DIBAL-H), treatment of the respective lactol with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and concomitant [1,4]-silyl transfer, and oxidation of the lactol, followed by disilylation and the respective esterifications. γ -Lactone 4 can be prepared from Z -olefin 6 by a five-step sequence. A Horner-Wadsworth-Emmons (HWE) olefination between aldehyde 7 and an Ando³⁰ phosphonate (8) should provide Z -olefin 6. Phosphonate 8

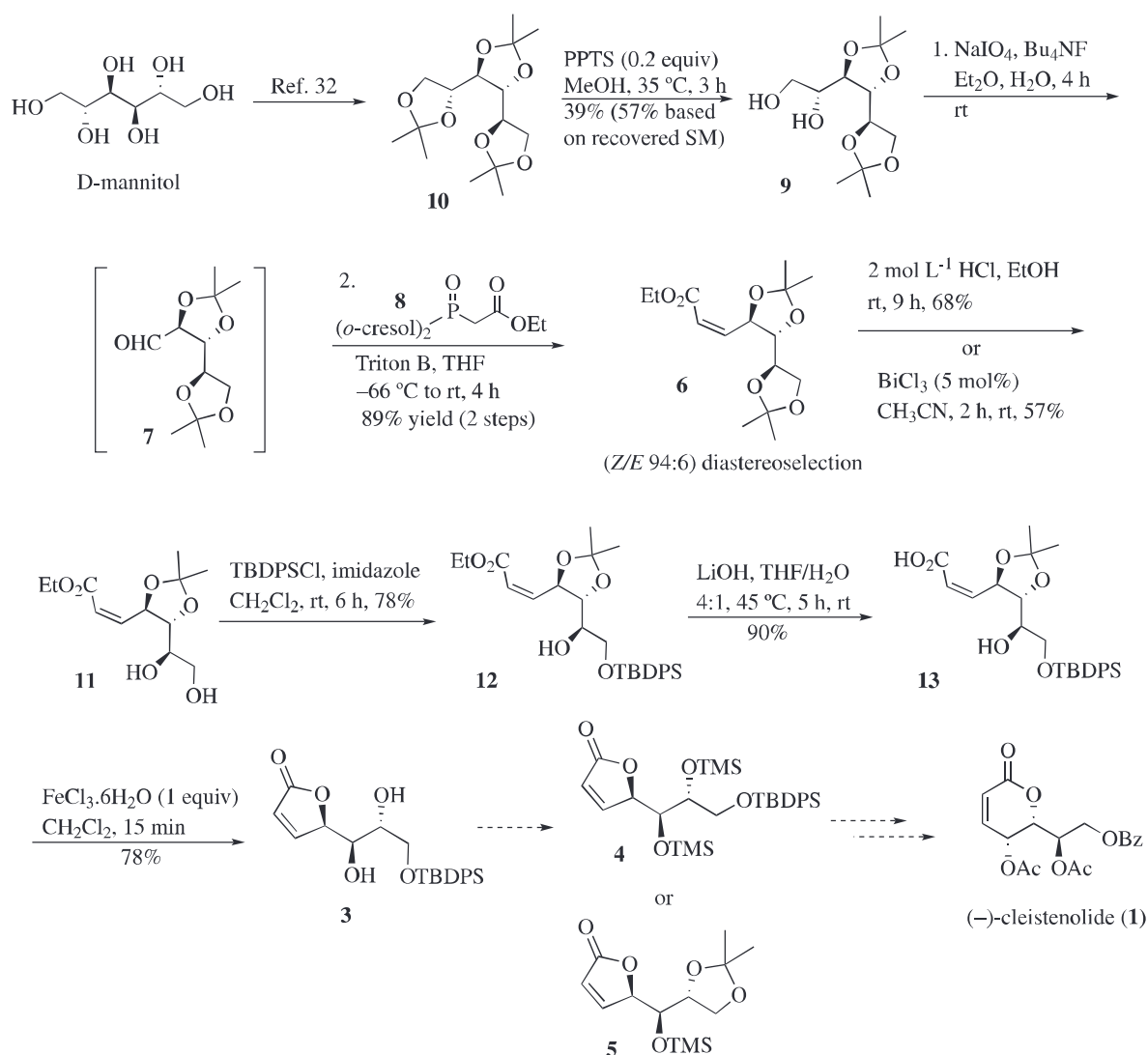
can be easily prepared at the laboratory. Oxidative cleavage of diol 9 should provide aldehyde 7. However, selective deacetylation of the D -mannitol-derived triacetone 10 should provide diol 9. Diol 9 would be the starting chiral precursor containing all required stereocenters for the synthesis of the target molecule.

In the present study, the synthesis of γ -lactone 3 began with the preparation of diol-diacetonide 9 as starting material. This compound (9) was synthesized for the first time from D -mannitol by L. F. Wiggins³¹ in 1946 (Scheme 2). Several attempts were made to obtain diacetal diol 9 by selective deprotection of triacetone 10 using the Wiggins method; however, results were unsatisfactory. Wiggins described obtaining a mixture of monoacetylated and diacetylated products in addition to the recovered starting material, which, in practice, constitutes a protocol that is difficult to reproduce, as evidenced by our results. Subsequently, we attempted an alternative procedure, described by Chandrasekhar *et al.*,³³ for the selective deacetylation of a benzyl ether diacetone using acetyl chloride (5 equiv and 5 min) in methanol at 0 °C. Acetal diol 9 was obtained in 29% yield after chromatographic purification, and 41% of the starting material was recovered. The method described by Reddy *et al.*,^{1,27} in which 60% AcOH is used, was also tested, but no satisfactory results were obtained.

Given the disappointing results of the preparation of diacetal diol 9, we found that additional studies with other deprotection reagents and different reaction conditions were necessary (Table 1). To the best of our knowledge, at present, there are no effective methods for obtaining diacetone 9 from its triacetone other than that reported by Wiggins.³¹



Scheme 1. Retrosynthetic analysis of (–)-cleistenolide (1) from γ -lactone 4 or 5.



Scheme 2. Stereoselective synthesis of γ -lactone **3**, a key intermediate in the total synthesis of (-)-cleistenolide (**1**).

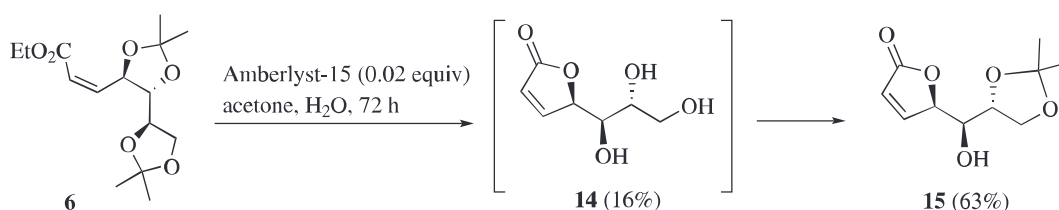
Investigations started with the use of pyridinium *p*-toluenesulfonate (PPTS)³⁴ (1.2 equiv) in methanol. Reactions were carried out at room temperature and 35 °C (entries 1-5, Table 1). The highest yield was 34% (entry 5). The use of PPTS (0.2 equiv) at room temperature did not improve the results (entries 6 and 7). When the reaction was carried out at 35 °C for 3 h (entry 8), **9** was obtained in 39% yield (57% based on the recovered starting material). However, when this same reaction was extended to 6 h (entry 9), the yield decreased to 31%. The use of FeCl₃·6H₂O³⁵ (entries 10-12), 5 mol% BiCl₃ (entry 13),³⁶ and Amberlyst-15 (entry 15)³⁷ at room temperature did not substantially improve the results. The conditions used to obtain **9** in 57% yield (entry 8) were selected as the most efficient, as the yield was much higher than that reported by Wiggins (28% yield based on recovered starting material).

After obtaining diol **9**, the compound was treated with sodium periodate to afford the corresponding

aldehyde (**7**) (Scheme 2). Compound **7** was then immediately subjected to HWE olefination with Ando³⁰ phosphonate **8** (ethyl 2-(bis(*o*-tolylxy)phosphoryl)acetate), prepared in our laboratory, affording the expected *Z*-olefin ester **6** with high diastereoselectivity (*Z/E*, 94:6), as verified by ¹H NMR spectroscopy of a crude aliquot of the reaction (Figure S10, SI section). After purification by neutral alumina column chromatography, diacetone ester **6** was subjected to another step of selective deprotection using BiCl₃ in catalytic quantity (5 mol%) in acetonitrile³⁴ to form diol ester **11** in 57% yield with 20% of recovered starting material.

For improvements in the yield of **7**, we carried out a new study of the selective deacetylation of substrate **6** (Table 2).

Table 2 shows that the best condition for selective deacetylation from **6** was the use of a 2 mol L⁻¹ HCl aqueous solution in ethanol at room temperature for 9 h, affording diol **11** in 68% yield (82% based on recovered starting material) (entry 5). This result was slightly higher than that



Scheme 3. Synthesis of γ -lactone **15** from diacetal ester **6**.

obtained with 5 mol% BiCl_3 in acetonitrile³⁶ (57% yield, Scheme 2), with the additional advantage of precluding the use of a toxic metal catalyst.

In possession of diol **11**, we subjected the compound to primary hydroxyl monosilylation by treatment with *tert*-butyl(chloro)diphenylsilane (TBDPSCI) in dichloromethane in the presence of imidazole.³⁸ Monosylated ester **12** was obtained in 78% yield (Scheme 2) and then hydrolyzed using LiOH in a mixture of THF/ H_2O (4:1) under heating at 45 °C,³⁹ resulting in the respective carboxylic acid **13**. The crude residue of the acid was subjected to further deacetylation using 1 equiv of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ^{34,40} for 15 min. The reaction generated, in a single step, the respective γ -lactone, (*R*)-5-((1*R*, 2*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-1,2-dihydroxypropyl)furan-2(5*H*)-one (**3**), in 70% yield (2 steps).

Unexpectedly, when diacetal **6** was treated with Amberlyst-15³⁷ (0.02 equiv) for 72 h in acetone/distilled water (6.6:3.4), it provided γ -lactone **15** in 63% yield (Scheme 3). We believe that total deacetylation of **6** and concomitant closure of the ring generated the intermediate γ -lactone triol **14**. Acetalization of **14** *in situ* was possible because of the presence of acetone (used as solvent) between the neighboring primary and secondary hydroxyls, thus forming the ketal γ -lactone **15** in a single step.

Subsequent steps in the total synthesis of (–)-**1** should be aimed at the silylation of hydroxyl groups in **3** and **15** to obtain the advanced trisilylated and monosilylated intermediates **4** and **5**, respectively (Scheme 1). Some attempts have already been made in this regard by using TMSCl and TMSOTf; however, the yields of the silylated products were very low and catalysts caused the degradation of the starting intermediates. Additional investigations of experimental procedures are necessary to assess the effects of changes in reaction temperature and reagent quantity and optimize reaction times. Further studies aimed at the total synthesis of δ -lactone (–)-**1** are ongoing in our laboratory.

Conclusions

A new approach to stereoselective synthesis allowed obtaining γ -lactones **3** and **15** in 19 and 32% overall yield, respectively. These lactones are key intermediates

in the total synthesis of (–)-**1** from diacetonide diol **9** (derived from D-mannitol, which is abundant in nature, commercially available, and low cost). The approach consisted of highly selective chemical manipulations that enabled the use of polyol **9** as a source of stereocenters for γ -lactones **3** and **15**, which can then be transferred to (–)-**1**. Studies in this direction are ongoing in our laboratory, and the results will be published later.

Supplementary Information

Supplementary data (¹H, ¹³C NMR, and mass spectra) are available free of charge at <http://jbc.sbq.org.br> as PDF file.

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Author Contributions

S. K. S., I. L. M., and D. A. M. were responsible for experimental syntheses and compound characterization; M. K. recorded HRMS spectra and analyzed HRMS data; M. A. N. D. analyzed the experimental results and revised the manuscript; G. D.-M. conceptualized the research, analyzed the results, and revised the manuscript. All authors contributed to the writing of the manuscript.

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