Total Synthesis of S-(+)-Argentilactone

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Argentilactone, Carbohydrate Templates, Asymmetric Total Synthesis

Asymmetric total synthesis of *S*-(+)-argentilactone (**2**) was accomplished, using methyl-α-D-glucopyranoside (**3**) as carbohydrate template. Benzylidene acetal **5** was hydrolysed with ^{t}BuOOH/$AlCl_3$ and further manipulated to produce the aldehyde **10**. A Wittig reaction and subsequent oxidation of the anomeric position yielded the target argentilactone.

Introduction

Argentilactone (**1**), an α,β-unsaturated δ-lactone, was originally isolated in 1977 from the rhizomes of *Aristolochia argentina* Gris [1]. This compound is the major constituent of the essential oil and hexane extract of *Annona haematantha* [2] and also present in the methanolic extract of the leaves of *Chorisia crispiflora* [3]. The biological studies on **1** have revealed high antileishmanial [2] and cytotoxic activity against P-388 mouse leukaemia cells [3]. Moreover, it can also be used as starting material for the synthesis of interesting pheromones [4]. These features prompted us to undertake the total synthesis of this compound.

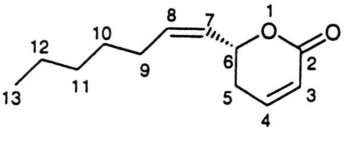
Although some racemic as well as enantiopure syntheses of natural argentilactone (**1**) have been reported [5–8], the enantiopure synthesis of non-natural argentilactone (**2**) did not appear in the literature so far. Herein we report on the first total synthesis of non-natural S-(+)-argentilactone (**2**).

In the past we have used carbohydrate templates [9] for the stereoselective synthesis of biologically interesting chiral building blocks that can be further elaborated to the syntheses of natural products [10]. Continuing our research in this context, we decided to design a strategy for the synthesis of α,β-unsaturated δ-lactones.

Results and Discussion

The stereochemistry at C-6 (pyran numbering) of **1** is *R* which requires a sugar from the L-series. Nevertheless, to confirm the absolute stereochemistry of **1** and to test its biological activity, we describe here an asymmetric total synthesis of *S*-(+)-argentilactone (**2**).

According to Holder and Fraser-Reid [11], **3** was efficiently converted into methyl-4,6-di-*O*-benzylidene-α-D-glucopyranoside (**4**) in 90% yield. The spectroscopic data were found to be exactly identical with those already reported [12]. The vicinal diol in **4** is now ready to undergo 2,3-dideoxygenation and we found iodoform/imidazole/ triphenyphosphine in toluene [13] to be an excellent reagent (87% yield) to produce **5** as white crystals. At this stage, we found that ^{t}BuOOH/$AlCl_3$ in dichloromethane can hydrolyse the



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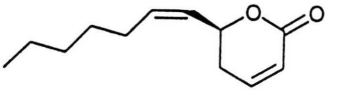

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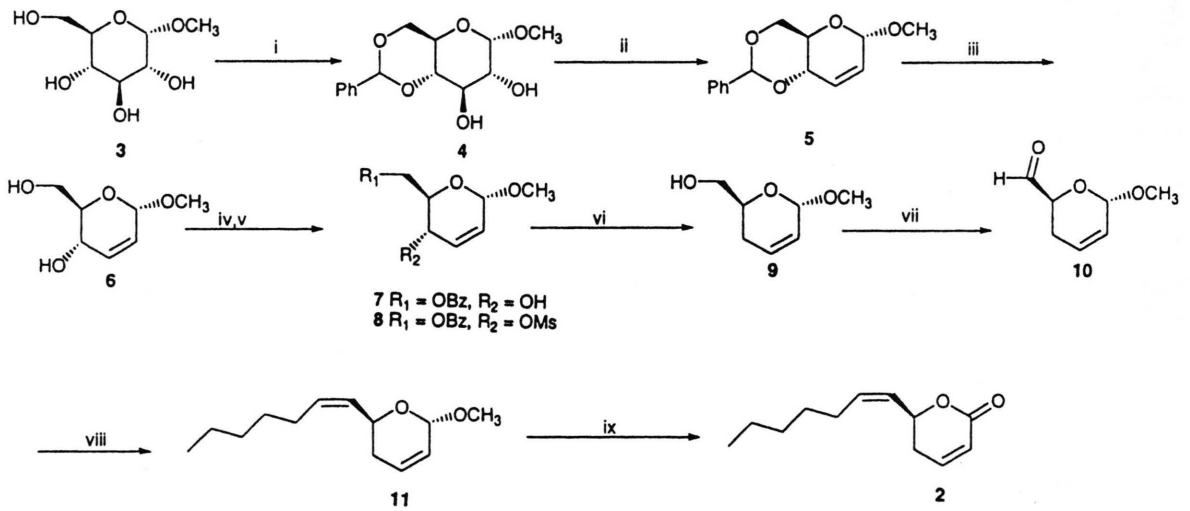
acetal function to produce **6** in good yield. Further reactions in this regard are still under investigation. Selective protection of the diol **6** at the primary position with benzoyl chloride at 0 °C and mesylation of the secondary alcohol generated **8** in 90% yield *via* two steps [14]. The mesyl group was displaced with superhydride® ($LiBHEt_3$) in THF. The presence of a CH_2 signal at δ = 26 ppm in the ^{13}C NMR spectrum (GASPE) and a multiplet around δ = 2.0 ppm in the ^1H NMR spectrum confirmed the deoxygenation at C-4 of the alcohol **9**. Swern oxidation of **9** generated the aldehyde **10,** and subsequent Wittig reaction of **10** with hexyltriphenylphosphonium bromide introduced the double bond between C-7 and C-8 in the final compound. The *cis* stereochemistry of the double bond is indicated by the low coupling constant (J = 10.3 Hz). Finally, **11** was oxidized at the anomeric position with aqueous H_2O_2 in the presence of a catalytic amount of MoO_3 [15] to generate the target argentilactone in ~30% overall yield from **3.** All spectroscopic data correlate with the reported natural product **1**, except the optical rotation, which is opposite to that reported for **1.**

Experimental

All chemicals and reagents were obtained from commercial suppliers and used as such without further purification. Compounds **4**[11], **5**[13], **7** and **8**[14] were prepared according to literature procedures. Solvents were dried and distilled according to standard methods. Column chromatography was performed on silica gel 60 (Merck, 0.063–0.200 mm) using the indicated solvent system. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 250 spectrometer with tetramethylsilane as internal standard. The chemical shifts are reported in parts per million (ppm). Mass spectra were recorded on a Finnigan MAT 312 mass spectrometer, connected to a PDO 11/34 (DEC) computer system. Optical rotations were obtained with an LEP AZ polarimeter (Zeiss, Jena) at 546 nm. All melting points are uncorrected.

Methyl 2,3-didehydro-2,3-dideoxy-α-D-erythro-hexoside (**6**)

To a stirred solution of **5** [13] (20 g, 0.08 mol) in absolute CH_2Cl_2 (100 ml) was added anhydrous ^{t}BuOOH (14.5 ml, 5.5 M in decane) under nitrogen. After 10 min was added $AlCl_3$ (10.7 g, 0.08 mol). Stirring was continued at the same temperature till TLC analysis showed no starting material. The reaction was quenched with slow addition of water and extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were dried (Na_2SO_4) and evaporated under low pressure to yield almost pure **5** (10.3 g, 0.06 mol) as a colourless oil, $[\alpha]_D^{24}$



Scheme 1. *Reagents and conditions*: i, $PhCH(OMe)_2$, *p*-TsOH, DMF, reflux under reduced pressure, 1h, 97% (ref. 11); ii, PPh_3, imidazole, CHI_3, toluene, reflux, 2 h, 87% (ref. 13); iii, $AlCl_3$, ^{t}BuOOH, CH_2Cl_2, −40 °C, 30 min, 80%; iv, PhCOCl, pyridine, 0 °C, 8 h, 90%; v, MsCl, pyridine, 5 °C, 4 h, 95% (ref. 14); vi, $LiBHEt_3$, THF, 12 h, 70%; vii, oxalyl chloride, DMSO, −40 °C, Et_3N, 1 h, 90%; viii, $C_6H_{13}PPh_3Br$, BuLi, 80%; ix, aq H_2O_2, MoO_3 and then Ac_2O, pyridine, 70%.

+104.3 (c = 1, methanol). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.00 (br s, 1 H , OH), 3.44 (s, 3 H, OMe), 3.64–3.72 (m, 1 H, 5-H), 3.86 (br s, 2 H, 6-H, 6′-H), 4.18 (m, 1 H, 4-H), 4.87 (br s, 1 H, 1-H), 5.74 (dt, J = 2.46, 10.2 Hz, 1 H, 3-H), 5.96 (d, J = 10.2 Hz, 1 H, 2-H). FAB-MS: m/z = 159.0 (18%) [M^+-1]. – $C_7H_{12}O_4$ (160.07): calcd. C 52.49, H 7.55; found C 52.31, H 7.40.

(2S)-Methoxy-(6S)-hydroxymethyl-5,6-dihydro-2H-pyran (**9**)

To a stirred solution of **8** [14] (19.5 g, 0.057 mol) in dry THF superhydride® (5 ml, 1M in THF) was added at 0 °C under nitrogen. The temperature was slowly raised to 40 °C. After 3 h the TLC showed no starting material. Excess hydride was destroyed with slow addition of water, then a 3 N NaOH solution (10 ml) was added, followed by the addition of a 30% aqueous H_2O_2 solution (10 ml). The mixture was than brought into a separatory funnel and the THF layer was collected. The aqueous layer was further extracted with ether, the combined organic layers were dried (Na_2SO_4) and the solvent was removed. After flash chromatography with 5% ethyl acetate in CH_2Cl_2 **9** (5.76 g, 70%) was obtained as a colourless oil, $[\alpha]_D^{25}$ –75.3° (c = 0.74, C_6H_6). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99–1.81 (m, 1 H, 4′-H), 2.25–2.04 (m, 1 H, 4-H), 2.29 (brs, 1 H, OH), 3.44 (s, 3 H, OMe), 3.82–3.54 (m, 2 H, 6′-H, 5-H), 4.01 (m, 1 H, 6-H), 4.90 (d, J = 2.0 Hz, 1 H, 1-H), 5.81–5.70 (m, 1 H, 3-H), 6.09–5.98 (m, 1 H, 2-H). EI-MS: m/z = 113 (100%) [M^+-OMe]. – $C_7H_{12}O_3$ (144.08): calcd. C 58.32, H 8.39; found C 58.25, H 8.35.

6-Methoxy-3,6-dihydro-2H-pyran-2-carbaldehyde (**10**)

A solution of oxalyl chloride (4 ml) in of CH_2Cl_2 (75 ml) was brought in a 250 ml three neck flask, equipped with two dropping funnels, containing DMSO (6.8 ml) in CH_2Cl_2 (20 ml) and alcohol **9** (5.76 g, 40 mmol) in CH_2Cl_2 (40 ml). At –78 °C DMSO was slowly added. The mixture was stirred for 2 min, then the alcohol was added within 5 min and stirring continued for 15 min. Triethylamine (30 ml) was added, the reaction mixture stirred for 5 min and then allowed to warm to rt. Water was added and the organic phase removed. The aqueous layer was further extracted with CH_2Cl_2 (50 ml), the organic layers were combined, dried, and evaporated. The compound was finally purified by flash chromatography using pure CH_2Cl_2 as solvent to afford **10** (5.11 g, 90%) as a colourless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.10–2.22 (m, 2 H, 4-H), 3.75 (s, 3 H, OMe), 4.40 (dd, J = 4.8, 10.1 Hz, 1H, 5-H), 5.19 (d, J = 2.6 Hz, 1 H, 1-H), 5.79–5.68 (m, 1 H, 3-H), 5.91–6.08 (m, 1H, 2-H), 9.71 (s, 1H, 6-H). – FAB-MS: m/z = 141.1 (40%) [M^+-1]. – $C_7H_{10}O_3$ (142.06): calcd. C 59.14, H 7.09; found C 59.07, H 7.00.

(2S)-Hept-1-enyl-(6S)-methoxy-3,6-dihydro-2H-pyran (**11**)

A solution of hexyltriphenylphosphonium bromide (15.34 g, 40 mmol) in THF-HMPA (2:1, 150 ml) was cooled to –50 °C and *n*-BuLi (25 ml, 1.6 M in hexane) was added *via* a syringe. After stirring several min at the same temperature, a solution of aldehyde **10** (5.0 g, 35.2 mmol) in THF (25 ml) was added to the reaction mixture *via* a syringe. The solution was allowed to warm to –10 °C over 45 min, petroleum ether was added, followed by extraction with water, aqueous $NaHCO_3$ and finally with water. The organic layer was separated, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2-hexane (80:20) to afford pure **11** (6.09 g, 80%) as colourless oil, $[\alpha]_D$ –50° (c = 0.74, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.9 Hz, 3H, CH_3), 1.34 (m, 6H, 3 × CH_2), 2.01–2.30 (m, 4H, 2 × CH_2), 3.38 (s, 3 H, OCH_3), 3.75 (m, 1H, 6-H), 4.88 (br s, 1H, 2-H), 5.48 (m, 1 H, 10-H), 5.76 (m, 2H, 3-H, 9-H), 6.08 (m, 1H, 4-H). – FAB-MS: m/z = 210 (5%) [M^+]. – $C_{13}H_{22}O_2$ (210.16): calcd. C 74.24, H 10.54; found C 74.13, H 10.44.

(S)-(+)-Argentilactone (**2**)

To a suspension of **10** (6.0 g, 22 mmol) in aqueous 30% H_2O_2 (250 ml) was added MoO_3 (0.6 g). The mixture was stirred at rt till completion of the reaction (TLC control). After disappearance of the substrate, water (250 ml) was added and the mixture extracted with CH_2Cl_2 (4× 50 ml). The combined extracts were washed with water, dried, and concentrated to dryness, to afford an anomeric mixture of peroxide which was dissolved in CH_2Cl_2 (25 ml) and added dropwise to a cooled and stirred mixture (1:1) of acetic anhydride and pyridine (50 ml) at <30 °C. The mixture was stored at rt for 2 h, then poured on crushed ice and extracted with CH_2Cl_2 (3×30 ml). The combined extracts were washed with sat. aq. $NaHCO_3$ and water, dried and concentrated to dryness, to afford **2** (2.99 g, 70% over two steps) as a yellow oil, $[\alpha]_D$ +19.1 (c = 0.5, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, Me), 1.3 (m, 6 H, 3×CH_2),

2.10 (m, 2 H, CH_2), 2.38 (m, 2 H, CH_2), 5.0–5.8 (m, 3 H, 5-H, 6-H, 7-H), 6.04 (ddd, J = 10.3, 1.8 Hz, 1H, 2-H), 6.91 (ddd, J = 10.3, 4.2 Hz, 1H, 3-H). – EI-MS: m/z = 194 (5%) [M^+]. – $C_{12}H_{18}O_2$ (194.27): calcd. C 79.19, H 9.34; found C 79.15, H 9.30.

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