Enantiospecific synthesis of (6*R*, 7*S*)-diastereoisomer of asperlin

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This paper is dedicated to Professor Arthur S. Perlin on the occasion of his 67th birthday

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An unambiguous synthesis of the (6*R*,7*S*)-diastereoisomer of asperlin from D-glucose involving a tandem epoxide formation/intramolecular Wadsworth–Emmons–Horner olefination has established the absolute configuration of the oxirane moiety in natural asperlin as (6*S*,7*R*).

Key words: asperlin, synthesis; Wadsworth–Emmons–Horner olefination; epoxide formation.

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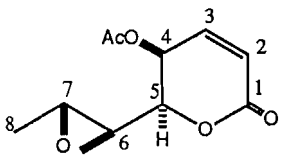
Grâce à une synthèse non ambiguë du diastéréoisomère (6*R*,7*S*) de l'asperline, à partir du D-glucose et faisant appel à un tandem de réactions impliquant la formation d'un époxyde et une oléfination intramoléculaire de Wadsworth–Emmons–Horner, on a pu établir que la configuration absolue de la portion oxirane de l'asperline naturelle est (6*S*,7*R*).

Mots clés : asperline, synthèse; oléfination Wadsworth–Emmons–Horner; formation d'un époxyde.

[Traduit par la revue]

Introduction

Asperlin, a fungal metabolite isolated (1) from cultures of *Aspergillus nidulans*, has been shown (2) to exhibit antibiotic and antitumour activity. Earlier nmr spectroscopic (3, 4) and synthetic studies (4, 5) of asperlin have demonstrated that the 4,5-substituents[2] of the lactone ring had the L-*threo* configuration and the exocyclic epoxypropyl moiety was *trans*; the absolute stereochemisty of the oxirane remained unsolved. These data have reduced the possible constitutions of asperlin to absolute configuration **1** or its 6,7-diastereoisomer **2.** Recently,



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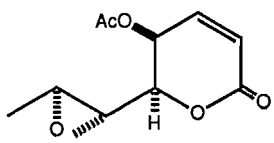

2

spin-lattice relaxation and nuclear Overhauser enhancement experiments were used to assign the (6*R*,7*S*)-diastereoisomer **2** to asperlin (6). However, a very recent synthesis (7) of D-asperlin indicated that natural asperlin was the (6*S*,7*R*)-diastereoisomer, i.e., **1.** This paper describes an unambiguous synthesis of **2**, which is diastereoisomeric to asperlin, thereby confirming by exclusion that the absolute configuration of the natural material is **1**. A preliminary account of this work has appeared (8).

Results and discussion

The strategy for the enantiospecific fabrication of **2**, illustrated in Scheme 1, involves a tandem oxirane formation/intramolecular Wadsworth–Emmons–Horner (9) olefination (this would guarantee the *Z*-geometry of the double bond) of the lactol **3**, which is readily derived from D-glucose.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-D-glucose **4** (10), readily affordable from D-glucose in two steps, was converted into the epoxy-lactone **2** in eight steps with an overall yield of 14%. Thus selective hydrolysis of the terminal isopropylidene group in **4** followed by esterification of the resultant diol with methanesulphonyl chloride as described previously (11) gave the dimethanesulphonate **5** in 73% overall yield. The primary methanesulphonate in **5** was displaced with lithium aluminium hydride (LAH) to provide the deoxy derivative **6** (91%), which then was debenzylated by palladium hydroxide catalysed hydrogenolysis to give the alcohol **7** in 94% yield. Esterification of **7** with dimethylphosphonoacetic acid in the presence of dicyclohexylcarbodiimide (DCCI) afforded the phosphonate **8** in 92% yield. Acetolysis of **8** with acetic anhydride mediated by boron trifluoride etherate gave smoothly the diacetate **9** (a mixture of anomers) in 97% yield. The anomeric acetoxy group in **9** was selectively (12) hydrolyzed ($SnCl_4$/MeCN followed by aqueous $HCONMe_2$) to the lactol **3** in 52% yield. The β-D-configuration of the anomeric hydroxy group in **3** was evident from the nmr spectrum ($J_{1,2} \approx 0.0$Hz). Transformation of the base labile **3** into the target epoxy-lactone **2** proved eventful. After considerable experimentation, treatment of **3** with mild base (13) (LiCl, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) gratifyingly produced the desired pyrone **2** in 47% yield. The epoxy-lactone **2** had mp 55–57°C, $[\alpha]_D$ +172° (*c* 1, EtOH), R_f 0.45 (silica gel tlc, diethyl ether), and spectroscopic data (mass, ir, ^{1}H nmr) similar to those of an authentic sample of asperlin. Since natural asperlin had mp 71–73°C, $[\alpha]_D$ +345° (*c* 0.5, EtOH) (1), R_f 0.50 (diethyl ether), **2** must be its diastereoisomer. The absolute configuration **1** is therefore assigned to asperlin.

Experimental

Melting points were recorded on a Kofler block. ^{1}H nuclear magnetic resonance (nmr) spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated. Mass spectra were recorded on a Kratos MS25 instrument. Infrared (ir) spectra were recorded on a Perkin–Elmer FT-IR 1710 spectrometer with samples as thin films; selected absorptions are reported in wave numbers (cm^{-1}). Optical rotations were measured on an AA-100 polarimeter using acetone as solvent unless otherwise stated. Thin-layer chromatography (tlc) was performed on glass plates precoated with Merck silica $60F_{254}$, and compounds were visualized with a spray of 5% v/v sulphuric acid in ethanol and subsequent heating. Tetrahydrofuran (THF) was distilled from sodium and benzophenone under dry nitrogen. Dichloromethane and acetonitrile were distilled from P_2O_5.

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[2]The numbering is indicated on structure **1**.

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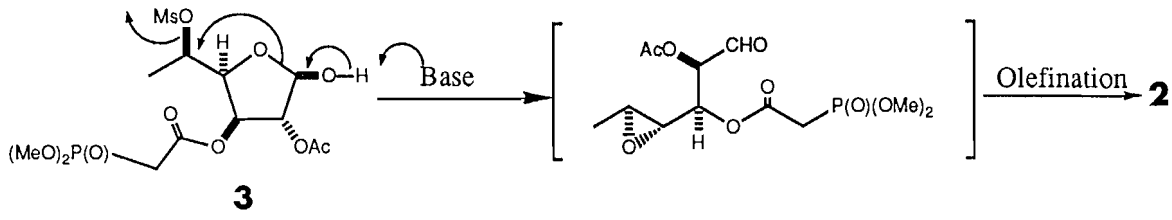

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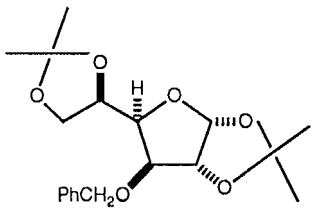
Ms = $MeSO_2$; Ac = MeCO

SCHEME 1



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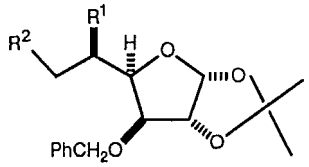
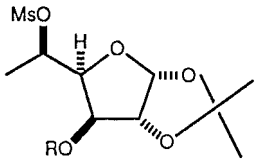


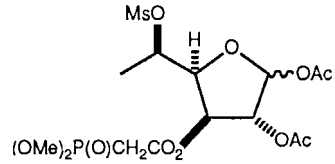
5 $R^1 = R^2 = MsO$

6 $R^1 = MsO$; $R^2 = H$



7 R = H

8 R = $(OMe)_2P(O)CH_2CO$



9

3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-5-O-methanesulphonyl-α-D-glucofuranose ***6***

To a stirred solution of the dimesylate **5** (11) (3.12 g, 6.69 mmol) in dry THF (95 mL) was added LAH (0.509 g, 13.39 mmol). The resultant solution was then heated at reflux under argon for 5 h. The reaction was quenched cautiously with water (3 mL), followed by the addition of aqueous ammonium chloride (15 mL), and extracted into chloroform (3 × 50 mL). The combined extracts were washed with water and aqueous ammonium chloride, dried (NA_2SO_4), and filtered. The filtrate was concentrated and the residue was chromatographed (ethyl acetate – hexane (1:2 v/v)) to give the 6-deoxy derivative **6** (2.25 g, 91%) as a colourless syrup that crystallized slowly. Recrystallization from diethyl ether – light petroleum (bp 40–60°C) afforded white crystals, mp 82–84°C; $[\alpha]_D^{20}$ −25.3° (*c* 4.4); R_f 0.50 (tlc, ethyl acetate – hexane (4:1 v/v)); ^{1}H nmr δ: 1.30 and 1.49 (2s, 6H, 2Me), 1.55 (d, 3H, $J_{6,5}$ 6.4 Hz, Me-6), 2.92 (s, 3H, CH_3SO_2), 4.05 (d, 1H, $J_{3,4}$ 2.9 Hz, H-3), 4.15 (d, 1H, $J_{4,5}$ 8.0 Hz, H-4), 4.61 (obscured by $PhCH_2$, 1H, H-2), 4.60 and 4.64 (2d, 2H J_{gem} 11.2 Hz, $PhCH_2$), 5.14 (m, 1H, H-5), 5.89 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 7.35 (br s, 5H, pH); ms *m/z* (CI, NH_3): 390 (92%, MNH_4^+). Anal. calcd. for $C_{17}H_{24}O_7S$: C 54.8, H 6.5, S 8.6; found: C54.4, H 6.6, S 8.8.

6-Deoxy-1,2-O-isopropylidene-5-O-methanesulphonyl-α-D-glucofuranose ***7***

A solution of **6** (3.03 g, 8.1 mmol) in ethanol (40 mL) was hydrogenated over $Pd(OH)_2$ (1.2 g) at room temperature and atmospheric pressure for 15 h. The catalyst was removed by filtration and the filtrate concentrated to give the alcohol **7** (2.18 g, 94%) as a white solid, which was recrystallized from diethyl ether–light petroleum (bp 40 – 60°C), mp 56–58°C; $[\alpha]_D^{20}$ −22.0° (*c* 2.9); R_f 0.24 (tlc, ethyl acetate – hexane (1:1 v/v)); ir: 3500 (OH); ^{1}H nmr δ: 1.30 and 1.49 (2s, 6H, 2Me), 155 (d, 3H, $J_{6,5}$ 6.5 Hz, Me-6), 3.07 (s, 3H, CH_3SO_2), 3.10 (d, 1H, $J_{OH,3}$ 4.2 Hz, OH-3), 4.02 (dd, 1H, $J_{4,3}$ 2.2, $J_{4,5}$ 9 Hz, H-4), 4.29 (dd, 1H, H-3), 4.55 (d, 1H, $J_{2,1}$ 3.7 Hz, H-2), 4.97 (dq, 1H, H-5), 5.89 (d, 1H, H-1); ms *m/z* (CI, NH_3): 300 (100%, MNH_4^+). Anal. calcd. for $C_{10}H_{18}O_6S$: C 42.5, H 6.4, S 11.3; found: C 42.5, H 6.4, S 11.4.

6-Deoxy-3-O-dimethylphosphonoacetyl-1,2-O-isopropylidene-5-O-methanesulphonyl-α-D-glucofuranose ***8***

Dicyclohexylcarbodiimide (3.60 g, 17.4 mmol) was added in one portion to a stirred solution of the alcohol **7** (3.07 g, 10.88 mmol) and dimethylphosphonoacetic acid (2.2 g, 13.06 mmol) in dry dichloromethane (60 mL) at 0°C. After 2 h, the reaction was quenched with ethanol (5 mL) and acetic acid (1 mL), and filtered. The filtrate was concentrated and the residue chromatographed (ethyl acetate) to give **8** (4.31 g, 92%) as a colourless syrup; $[\alpha]_D^{20}$ −8.3° (*c* 3.4); R_f 0.18 (tlc, ethyl acetate); ir: 1747 (ester C=O); ^{1}H nmr δ: 1.23 and 1.48 (2s, 6H, 2Me), 1.54 (d, 3H, $J_{6,5}$ 6.5 Hz, Me-6), 2.97 (s, 3H, CH_3SO_2), 3.02 (dd, 1H, $^2J_{PH'}$ 21.0, J_{gem} 15.0 Hz, PCH'), 3.12 (dd, 1H, $^2J_{PH}$ 21.0 Hz, PCH), 3.76 and 3.80 (2d, 6H, $^3J_{PH}$ 11.5 Hz, 2 MeO), 4.17 (dd, 1H, $J_{4,3}$ 2.8, $J_{4,5}$ 8.6 Hz, H-4), 4.52 (d, 1H, $J_{2,1}$ 3.5 Hz, H-2), 4.96 (dq, 1H, H-5), 5.32 (d, 1H, H-3), 5.89 (d, 1H, H-1); ms *m/z* (CI, NH_3): 433 (57%, MH^+). Exact mass calcd. for $C_{14}H_{26}O_{11}PS$ (MH^+): 433.0931; found: 433.0933.

1,2-Di-O-acetyl-6-deoxy-3-O-dimethylphosphonoacetyl-5-O-methanesulphonyl-D-glucofuranose ***9***

The acetonide **8** (5.7 g, 13.2 mmol) was dissolved in acetic anhydride (40 mL) and $BF_3 \cdot OEt_2$ (4 mL, 32.5 mmol) was introduced at 0°C with stirring. After 1 h, the reaction mixture was quenched with ice-water and extracted into ethyl acetate (3 × 120 mL). The combined extracts were washed successively with brine (2 × 80 mL), aqueous $NaHCO_3$ (2 × 70 mL), and brine (2 × 70 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated and the residue chromatographed to give **9** (6.1 g, 97%) as a pale yellow syrup; $[\alpha]_D^{22}$ +17.4° (*c* 9.3 ethanol); R_f 0.39 (tlc, chloroform–methanol (9:1 v/v)); ir: 1751 (ester C=O); ^{1}H nmr δ: inter alia 6.05 (s, 0.4H, αH-1), 6.40 (d, 0.6H, $J_{1,2}$ 4.4 Hz, βH-1); ms *m/z* (CI, NH_3): 494 (43% MNH_4^+). Exact mass calcd. for $C_{15}H_{21}NO_{13}PS$ (MH_4^+): 494.10951; found: 494.11429.

2-O-Acetyl-6-deoxy-3-O-dimethylphosphonoacetyl-5-O-methanesulphonyl-β-D-glucofuranose ***3***

Stannic chloride (0.869 mL, 7.41 mmol) was added to a solution of the diacetate **9** (1.17 g, 2.47 mmol) in acetonitrile (15 mL) with stirring at 0°C. After 2 h at room temperature, the reaction mixture was treated with acetonitrile (5 mL) containing water (4 M) and $HCONMe_2$ (0.4 M). After a further 20 h, the reaction was quenched with aqueous $NaHCO_3$ (3 mL) and extracted with chloroform (40 mL). The extract was dried (Na_2SO_4), filtered, and the filtrate concentrated. The residue was chromatographed to give the lactol **3** (0.407 g, 55% based on recovered starting material (0.35 g)) as a colourless syrup; $[\alpha]_D^{20}$ +13.26° (*c* 1.9); R_f 0.25 (tlc, chloroform–methanol (9:1 v/v)); ir: 3450 (OH), 1747 (ester C=O); ^{1}H nmr δ: 1.58 (d, 3H, $J_{6,5}$ 6.2 Hz, Me-6), 2.93 (s, 3H, CH_3SO_2), 3.24 (dd, 1H, $^2J_{PH'}$ 21.0, J_{gem} 14.5 Hz, PCH'), 3.32 (dd, 1H, $^2J_{PH}$ 21.0 Hz, PCH), 3.82 (d, 6H, $^3J_{PH}$ 11.5 Hz, 2 MeO), 4.12 (dd, 1H, $J_{4,3}$ 3.5, $J_{4,5}$ 8.7 Hz, H-4), 5.02 (s, 1H, H-1), 5.11 (dq, 1H, H-5), 5.21 (s, 1H, H-2), 5.28 (d, 1H, H-3); ms *m/z* (CI,

NH_3): 452 (11%, MH_4^+). Exact mass calcd. for $C_{13}H_{27}NO_{12}PS$ (MH_4^+): 452.0989; found: 452.0992.

(*6R,7S*)-*Diastereoisomer of asperlin* **2**

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.158 mL, 1.06 mmol) was added to a stirred solution of the lactol **3** (0.23 g, 0.53 mmol) in dry acetonitrile containing LiCl (0.024 g, 0.58 mmol) under nitrogen at room temperature. After 1 h, the reaction was quenched with aqueous NH_4Cl (1 mL) and extracted into chloroform (2 × 10 mL). The combined extracts were washed with water (2 × 5 mL), aqueous NH_4Cl (2 × 5 mL), dried (Na_2SO_4), and filtered. Solvent removal afforded a syrup that was chromatographed to give the epoxy-lactone **2** (0.058 g, 47%) as a colourless syrup, which crystallized with time, mp 56–57°C; $[\alpha]_D^{22}$ +172.0° (*c* 1, ethanol); R_f 0.45 (diethyl ether); ir: 1735 (ester C=O); ^{1}H nmr δ: 1.34 (d, 3H, $J_{8,7}$ 5.1 Hz, Me-8), 2.15 (s, 3H, CH_3CO), 3.00 (dd, 1H, $J_{6,7}$ 2.2, $J_{6,5}$ 4.9 Hz, H-6), 3.04 (dq, 1H, H-7), 4.35 (dd, 1H, $J_{5,4}$ 3.6 Hz, H-5), 5.50 (dd, 1H, $J_{4,3}$ 5.2 Hz, H-4), 6.22 (d, 1H, $J_{2,3}$ 9.8 Hz, H-2), 6.86 (d, 1H, H-3); ms *m/z* (CI, NH_3): 230 (100%, MH_4^+). Exact mass calcd. for $C_{10}H_{16}NO_5$ (MH_4^+): 230.10276; found: 230.10274.

For an authentic sample of asperlin, ^{1}H nmr data δ: 1.39 (d, 3H, $J_{8,7}$ 5.0 Hz, Me-8), 2.14 (s, 3H, CH_3CO), 3.04–3.10 (m, 2H, H-6,7), 4.10 (dd, 1H, $J_{5,6}$ 6.9, $J_{5,4}$ 2.8 Hz, H-5), 5.31 (dd, 1H, $J_{4,3}$ 5.7 Hz, H-4), 6.22 (d, 1H, $J_{2,3}$ 9.7 Hz, H-2), 7.07 (d, 1H, H-3).

Acknowledgments

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