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Synthesis of thio analogues of *myo*-inositol-1-monophosphate, as possible inhibitors of *myo*-inositol-1-monophosphatase

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Summary — 2-Deoxy-2-thio-*myo*-inositol 1-phosphate **2** and, 2-deoxy-2-thio-*scyllo*-inositol 1-phosphate **3** were prepared from *myo*-inositol.

inositol / inositol-phosphate / synthesis

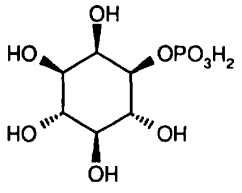
Résumé — Synthèse d'analogues soufrés du *myo*-inositol 1-monophosphate comme éventuels inhibiteurs de la *myo*-inositol 1-monophosphatase. *Les 2-déoxy-2-thio-*myo*-inositol 1-phosphate **2** et, 2-deoxy-2-thio-*scyllo*-inositol 1-phosphate **3** ont été préparés à partir du* myo*-inositol.*

inositol / inositol-phosphate / synthèse

Introduction

A treatment of manic depression uses lithium salts [1]. These salts seem to act as uncompetitive inhibitors of the *myo*-inositol monophosphatase [2-4]. The difficulties in balancing such a treatment and its accompanying side effects [5, 6] has prompted the search for new treatments. Particularly, different workers have tried to establish the structural requirements for affinity towards *myo*-inositol 1-monophosphatase [6, 7-14]. These structure–activity relationships led to a first pharmacophore model associated with *myo*-inositol-1-monophosphate **1** [10] confering an affinity and a mechanistic importance to the hydroxyls in positions 2 and 6, respectively. More recently, X-ray analyses of the monophosphatase have been published and proposed three-dimensional structures for the affinity site of the 1-monophosphate [15-18]. Taking into account these results, it seemed interesting to prepare analogues of **1**, with thio substituents in position 2.

We report, here, the synthesis of 2-deoxy-2-thio-*myo*-inositol 1-phosphate **2** and 2-deoxy-2-thio-*scyllo*-inositol 1-phosphate **3**; the latter bears an inverted configuration at position 2 and thus has an equatorial instead of an axial thiol group.



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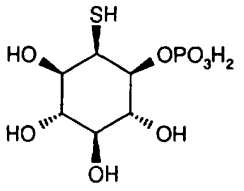

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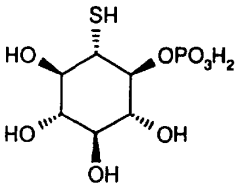

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Syntheses

The synthesis of 2-deoxy-2-thio-*myo*-inositol 1-monophosphate **2** is shown in scheme 1. The starting compound was 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol **4**. This was prepared from *myo*-inositol by means of well-established procedures [19]. A two-step, one-pot procedure transformed compound **4** into the crotyl (or but-2-enyl) ether **6**. Thus, the two remaining hydroxyls were reacted with dibutyltin oxide in acetonitrile in the presence of tetrabutylammonium bromide yielding the cyclic intermediate **5** [20], which was opened without isolation by means of crotyl bromide (CrBr), giving selectively the expected product **6**. The axial hydroxyl in position 2 was reacted with triphenylphosphine, imidazole and iodide in toluene to yield the 2-iodo derivative **7**, bearing an inverted configuration at this position

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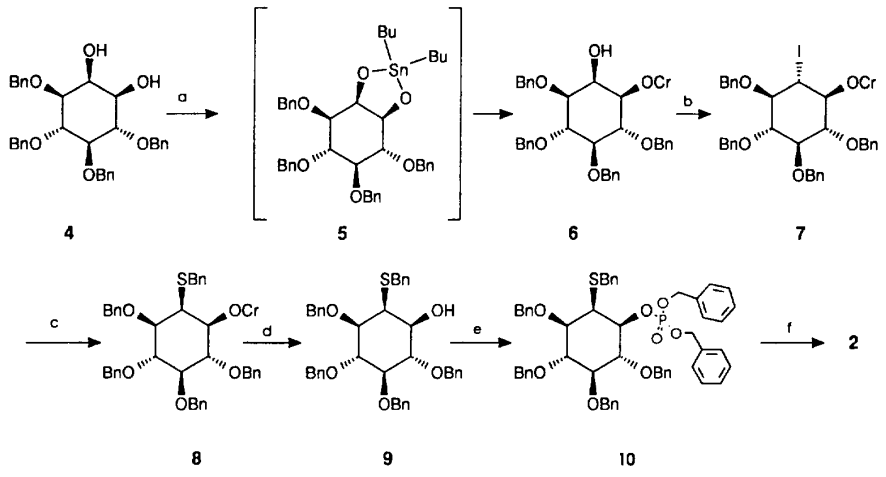
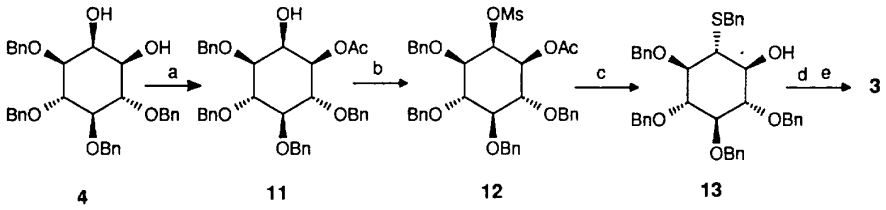


Scheme 1. Synthesis of 2-deoxy-2-thio-*myo*-inositol 1-monophosphate **3**: a: Bu_2SNO, CrBr, CH_3CN, Bu_4NBr, b: $P(C_6H_5)_3,I_2$, imidazole, c: $C_6H_5CH_2SNa$, DMSO, d: *t*BuOK, e: TBPP, DMF, NaH, f: Na/NH_3, then Amberlist $77H^+$.



Scheme 2. Synthesis of 2-deoxy-2-thio-*scyllo*-inositol 1-monophosphate **4**: a: AcCl, pyridine, b: MsCl, pyridine, c: $C_6H_5CH_2SNa$, DMSO, d: TBPP, DMF, NaH, e: Na/NH_3, then Amberlist $77H^+$.

[10, 21]. This iodide was substituted in an SN_2 procedure using the sodium salt of benzylic thiol to yield the thio analogue **8**, which also has the *myo*-inositol configuration. The next steps concerned the selective removal of the crotyl ether in position 1 by means of potassium *tert*-butoxide in dimethyl sulfoxide and hydrolysis, yielding the alcohol **9** [22, 23]. The synthesis of this compound was previously reported by Guidot et al by means of a different reaction scheme [24]. Position 1 was phosphorylated by means of tetrabenzyl pyrophosphate (TBPP) using the procedure published by Kozikowski [25]. Total deprotection of the molecule was achieved by treatment with sodium in liquid ammonia, giving the expected product **2**. This was stabilized as the cyclohexylammonium salt.

For the synthesis of the 2-deoxy-2-thio-*scyllo*-inositol 1-monophosphate **3**, we have also used the tetrabenzyl protected *myo*-inositol **4** as a starting material (scheme 2). This compound was transformed in the corresponding 1-monoacetate **11** by means of acetyl chloride and pyridine in methylene chloride without having to use a tin ketal intermediate. Such selectivity between the axial hydroxyl in position 2 and the neighboring equatorial hydroxyl was observed in numerous cases in the field of *myo*-inositol derivatives [26-29]. The hydroxyl group in position 2 was then transformed into the mesylate **12** using mesyl chloride in pyridine [21]. The *cis* configuration of positions 1 and 2 avoids the formation of an acetyloxonium intermediate. Such anchimeric assistance was observed by using benzoate, acetate or benzyl ether vicinal groups, but required a *trans* configuration between the groups concerned [30-32]. The treatment with the salt of benzylic thiol induces a direct SN_2 substitution of the mesylate, yielding a thio analogue **13** with the *scyllo*-inositol configuration with all the substituents in an equatorial orientation. The substitution conditions also removed the acetate in position 1. The final steps concerned the phosphorylation, deprotection and stabilization of the molecule, as described above, leading to 2-deoxy-2-thio-*scyllo*-inositol 1-monophosphate **3**.

Unfortunately, these thio analogues showed a poor activity against *myo*-inositol 1-monophosphatase.

Experimental section

General methods

Melting points were measured on a Mettler PF 62 apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC 200 spectrometer using the δ scale. Coupling constants are given in Hz.

3,4,5,6-Tetra-O-benzyl-1-O-(but-2-enyl)-myo-inositol **6**

The diol **4** (11.0 g, 2.03×10^{-2} mol), tetrabutylammonium bromide (9.84 g, 3.04×10^{-2} mol), and dibutyltin oxide (7.85 g, 3.04×10^{-2} mol) were dissolved in acetonitrile (300 mL). Crotyl bromide was added (4.17 mL, 4.06×10^{-2} mol) and the reaction mixture was refluxed over

molecular sieves (4 Å) for 20 h. The solvent was removed under reduced pressure and the residue was dissolved in ether (300 mL) and washed with water (300 mL). The organic layer was stirred with a saturated solution of sodium bicarbonate (200 mL) for 2 h. The ether phase was filtered through a Celite pad and dried over sodium sulfate. After evaporation of the solvent the crude material was recrystallized from ether/hexane giving 8.0 g (66%) of white crystals melting at 77 °C.

^{1}H NMR ($CDCl_3$): 7.4–7.0 (m, 20H, $(C_6H_5)_4$), 5.7–5.4(m, 2H, C*H*=C*H*-CH_3), 4.9–4.7 (m, 8H, $(CH_2C_6H_5)_4$), 4.21 (t, J = 2.6, 1H, H_2), 4.08 (d, J = 4.7, 2H, CH_2–CH=CH), 3.97 (t, J = 9.5, 1H, H_6), 3.91 (t, J = 9.5, 1H, H_4), 3.5–3.2 (m, 3H, H_1, H_3, H_5), 2.44 (broad s, 1H, exchangeable with D_2O, O*H*), 1.68 (d, J = 5.1, 3H, CH=CH-CH_3).

Anal calc for $C_{38}H_{42}O_6$: C: 76.74, H: 7.12; Found: C: 76.71, H: 6.99.

3,4,5,6-Tetra-O-*benzyl-1*-O-*(but-2-enyl)-2-deoxy-2-iodo*-scyllo-*inositol* **7**

Alcohol **6**, (2.0 g, 3.36×10^{-3} mol), imidazole (915 mg, 1.34×10^{-2} mol) and triphenylphosphine (3.52 g, 1.34×10^{-2} mol) were dried under vacuum and then dissolved in anhydrous toluene (50 mL). Iodine (3.75 g, 1.48×10^{-2} mol) was added and the mixture was refluxed for 18 h. After dilution with ethyl acetate (100 mL) and washing with a 10% solution of $Na_2S_2O_5$ (5 × 200 mL), the organic layer was dried over sodium sulfate, and, filtered. After removal of the solvent, the crude material was chromatographed on a silica gel column eluted with a hexane/ether 3:1 mixture leading to **7** (1.6 g, 67%) as crystals melting at 100 °C.

^{1}H NMR ($CDCl_3$): 7.5–7.2 (m, 20H, $(C_6H_5)_4$), 5.8–5.6 (m, 2H, CH_2-C*H*=C*H*), 5.0–4.8 (m, 8H, $(CH_2C_6H_5)_4$), 4.34 (d, J = 2.0, 2H, CH_2-CH=CH), 4.01 (t, J = 10.6, 1H, H_2), 3.7–3.4 (m, 5H, H_1, H_3, H_4, H_5, H_6), 1.73 (d, J = 4.4, 3H, CH=CH-CH_3).

Anal calc for $C_{38}H_{41}IO_5$: C: 64.77, H: 5.86, I: 18.00. Found: C: 65.40, H: 6.21, I: 17.73.

3,4,5,6-Tetra-O-*benzyl-2*-S-*benzyl-1*-O-*(but-2-enyl)-2-deoxy-2-thio*-myo-*inositol* **8**

The iodo *scyllo*-inositol derivative **7** (1.4 g, 1.99×10^{-3} mol) and the sodium salt of benzylic thiol (1.4 g) were dried in vacuum, dissolved in anhydrous dimethylformamide (50 mL) and, heated at 100 °C for 18 h. The crude material was hydrolyzed with water (200 mL) and extracted with ether (2 × 200 mL). The organic phase was washed with a saturated solution of ammonium chloride and dried over sodium sulfate. The residue obtained after evaporation of the solvents was chromatographed on a silica-gel column eluted with a hexane/ether 4:1 mixture leading to **8** (561 mg, 40%) as crystals melting at 251 °C.

^{1}H NMR (C_6D_6): 7.4–6.9 (m, 25H, $(C_6H_5)_5$), 5.5–5.4 (m, 2H, CH_2-C*H*=C*H*), 5.1–4.8 (m, 6H, containing at 4.23 (t, J = 9.5, 1H, H_6), 3.96 (AB system, J_{AB} = 13.9 $\Delta\delta$ = 0.13, 2H, SCH_2) 3.89 (t, J = 3.2, 1H, H_2) and CH_2–CH=CH)), 3.5–3.2 (m, 4H, H_1, H_3, H_4, H_5), 1.53 (d, J = 3.6, 3H, CH=CH-CH_3).

Anal calc for $C_{45}H_{48}O_5S$: C: 77.11, H: 6.90, S: 4.57. Found: C: 76.83, H: 6.85, S: 5.35.

3,4,5,6-Tetra-O-*benzyl-2*-S-*benzyl-2-deoxy-2-thio*-myo-*inositol* **9**

The crotyl ether **8** (300 mg, 4.28×10^{-4} mol), was dissolved in anhydrous dimethyl sulfoxide (10 mL). Sublimated potassium *tert*-butoxide (600 mg) was added and the mixture was heated at 50 °C for 2 h. After addition of a half-saturated potassium chloride solution (50 mL) at 0 °C, the product was extracted with ether (3 × 50 mL). The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness giving a crude product which was purified by column chromatography on silica gel eluted with hexane/ether 1:1. The alcohol **9** was obtained as an oil (100 mg, 36%).

^{1}H NMR ($CDCl_3$): 7.5–7.1 (m, 25H, $(C_6H_5)_5$), 5.1–4.4 (m, 10H, $(CH_2C_6H_5)_5$), 4.2–3.3 (m, 8H, containing at 3.97 (AB system, J_{AB} = 11.3, $\Delta\delta$ = 0.26, 2H, SCH_2) and H_1, H_2, H_3, H_4, H_5, H_6), 2.48 (d, J = 5.5, 1H, exchangeable with D_2O, O*H*).

Anal calc for $C_{41}H_{42}O_5S$: C: 76.13, H: 6.55, S: 4.96. Found: C: 75.87, H: 6.60, S: 4.68.

2-Deoxy-2-thio-myo-*inositol 1-monophosphate* **2**

The alcohol **9** (80 mg, 1.24×10^{-5} mol) and tetrabenzyl pyrophosphate (133 mg, 2.84×10^{-4} mol) were dissolved in anhydrous dimethylformamide (3 mL). After 30 min the reaction mixture was cooled to 0 °C and sodium hydride (15 mg, 60% suspension, 3.72×10^{-4} mol) was added. The reaction vessel was then kept between 0 and 4 °C for 18 h. The solvent was evaporated in vacuum. The residue was dissolved in dichloromethane and stirred for 15 min, then filtered through a Celite pad. The filtrate was evaporated to dryness and the crude product purified by chromatography on a silica-gel column eluted with hexane/ether 1:2. The di-*O*-benzyl phosphate was obtained as a yellow oil (90 mg, 80%).

^{1}H NMR ($CDCl_3$): 7.5–6.8 (m, 35H, $(C_6H_5)_7$), 5.1–4.7 (m, 13H, $(CH_2C_6H_5)_6$ and, H_1), 4.2–3.7 (m, 4H, 4.04 (t, J = 10.2, 1H, H_6), 3.74 (t, J = 4.0, 1H, H_2) and, S-CH_2), 3.53 (dd, J = 6.9, J = 4.0, 1H, H_3), 3.49 (t, J = 5.5, 1H, H_4), 3.41 (t, J = 9.1, 1H, H_5).

Liquid ammonia was condensed at −78 °C (20 mL). Small pieces of metallic sodium were added (approximatively 30 mg). The dibenzyl phosphate (50 mg, 5.51 × 10^{-5} mol) dissolved in 2 mL anhydrous tetrahydrofuran was injected into the mixture. Additional small pieces of sodium (in total 100 mg) were added to maintain the blue color for 3 h. Excess of sodium was hydrolyzed with water. Ammonia was evaporated at room temperature overnight. The residue was treated with ether and water. The water layer was washed several times with ether. The water layer was concentrated and chromatographed on an Amberlite 77 H^+ ion exchanger resin. The acidic fractions were lyophilized and the residue treated with cyclohexylamine (1 mL) and evaporated to dryness. The crude product was dissolved in water and washed several times with ether. The water solution was lyophilized yielding the stabilized monophosphate **3** (30 mg, 91%).

^{31}P NMR (D_2O): 2.86.

Anal calc for $C_6H_{13}O_8PS$, 3 $NH_2C_6H_{11}$, H_2O: C: 48.70, H: 9.20, N: 7.10, S: 5.41, P: 5.24. Found: C: 48.68, H: 8.77, N: 7.44, S: 4.87, P: 4.75.

1-O-*Acetyl-3,4,5,6-tetra*-O-*benzyl*-myo-*inositol* **11**

The diol **4** (5.0 g, 9.3×10^{-3} mol) was dissolved in methylene chloride (50 mL). Anhydrous pyridine (1.86 mL, 2.31×10^{-2} mol) and acetyl chloride (1.0 mL, 1.4×10^{-2} mol) were added at 0 °C. The reaction vessel was then kept at room temperature overnight. Ethyl acetate (200 mL) was added to precipitate the pyridinium salts. The reaction mixture was filtered and the solvents removed under reduced pressure. The crude product was purified on a silica-gel chromatography column eluted with hexane/ether 1:2. White crystals (3.7 g, 68%) melting at 113 °C were obtained.

^{1}H NMR ($CDCl_3$): 7.3–7.2 (m, 20H, $(C_6H_5)_4$), 4.9–4.7 (m, 9H, $(CH_2C_6H_5)_4$ and H_1), 4.30 (t, $J = 2.3$, 1H, H_2), 4.09 (t, $J = 9.6$, 1H, H_6), 3.97 (t, $J = 9.4$, 1H, H_4), 3.57 (dd, $J = 9.3$, $J = 2.8$, 1H, H_3) 3.56 (t, $J = 9.3$, 1H, H_5), 2.49 (broad s, 1H, exchangeable with D_2O, O*H*), 2.07 (s, 3H, $OCOCH_3$).

1-O-*Acetyl-3,4,5,6-tetra*-O-*benzyl-2*-O-*mesyl*-myo-*inositol* **12**

The alcohol **11** (3.25 g, 5.58×10^{-3} mol) was dissolved in anhydrous pyridine (100 mL). The reaction vessel was cooled to 0 °C and mesyl chloride (0.9 mL, 1.12×10^{-2} mol) was added. The reaction mixture was kept at room temperature overnight. Ethyl acetate was added (200 mL), the organic phase was washed with water (2×200 mL), dried over sodium sulfate, filtered and evaporated to dryness. The product was used as such for the next step.

^{1}H NMR ($CDCl_3$): 7.4–7.3 (m, 20H, $(C_6H_5)_4$), 5.25 (t, $J = 2.4$, 1H, H_2), 4.9–4.7 (m, 9H, $(CH_2C_6H_5)_4$, and H_1), 4.00 (t, $J = 9.7$, 1H, H_6), 3.90 (t, $J = 9.6$, 1H, H_4), 3.64 (dd, $J = 8.4$, $J = 2.4$, 1H, H_3), 3.58 (t, $J = 9.0$, 1H, H_5), 2.97 (s, 3H, OSO_2CH_3), 2.08 (s, 3H, $OCOCH_3$).

2-S-*Benzyl-3,4,5,6-tetra*-O-*benzyl-2-deoxy-2-thio*-scyllo-*inositol* **13**

The mesylate **12** (1.0 g, 1.51×10^{-3} mol) was dissolved in a mixture of 2-methoxyethanol/water 9:1 (50 mL) and the sodium salt of benzylic thiol (860 mg, 7.55×10^{-3} mol) was added. The mixture was refluxed for 20 h and then, extracted with ether (100 mL). The organic layer was washed with water and dried over sodium sulfate. The crude product obtained after filtration and solvent evaporation was chromatographed on a silica-gel column eluted with hexane/ether 2:1 giving white crystals (530 mg, 54%) melting at 81 °C.

^{1}H NMR ($CDCl_3$): 7.4–7.3 (m, 25H, $(C_6H_5)_5$), 5.0–4.8 (m, 8H, $(CH_2C_6H_5)_4$), 3.92 (AB system, $J_{AB} = 12.4$, $\Delta\delta = 0.06$, 2H, SCH_2), 3.6–3.4 (m, 5H, H_1, H_3, H_4, H_5, H_6), 2.91 (s, 1H, exchangeable with D_2O, O*H*), 2.63 (t, $J = 12.0$, 1H, H_2).

Anal calc for $C_{41}H_{42}O_5S$: C: 76.13, H: 6.54, S: 4.95. Found: C: 76.20, H: 6.44; S: 5.21.

2-Deoxy-2-thio-scyllo-*inositol 1-monophosphate* **3**

The alcohol **13** (200 mg, 3.10×10^{-4} mol) was phosphorylated using the same procedure as that described for **9** yielding the protected phosphate **14** as a yellow oil (200 mg, 71%).

^{1}H NMR ($CDCl_3$): 7.4–7.0 (m, 35H, $(C_6H_5)_7$), 5.1–4.6 (m, 12H, $(CH_2C_6H_5)_6$), 3.96 (AB system, $J_{AB} = 11.7$, $\Delta\delta = 0.15$, 2H, SCH_2), 3.6–3.5 (m, 5H, H_1, H_3, H_4, H_5, H_6), 2.82 (t, $J = 10.5$, 1H, H_2).

Deprotection of **14** as described for **10** gave compound **3** (67 mg) as a powder.

^{31}P NMR (D_2O): 1.04.

Anal calc for $C_6H_{13}O_8PS$, 1.5 $C_6H_{11}NH_2$, H_2O: C: 40.71, H: 7.75, N: 4.75, S: 7.23, P: 7.00. Found: C: 40.67, H: 7.53, N: 5.52, S: 7.64, P: 5.37.

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