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Synthesis of a novel prostaglandin containing heteroatoms in the ring cyclopentane

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Abstract—A novel prostaglandin analogue, *n*-heptyl-4-(3-hydroxy-*trans*-1-octenyl)-1,3-thiazolidin-2-thione, containing heteroatoms in the ring has been synthesized. The key step in the synthesis was the preparation of the five-membered ring starting from of L-cysteine ethyl ester hydrochloride.

Many prostaglandins derivatives have been synthesized in recent years in an attempt to develop therapeutic agents.[1,2] Prostaglandins analogues containing heteroatoms in the ring have received a great deal of attention in view of their potential biological properties,[3–7] and also due to the diversified biological activity and the rapid metabolism of the naturally occurring prostaglandins. Particularly interesting is that these prostaglandins containing heteroatoms into the ring can act as both gastric-acid secretion and platelet-aggregation inhibitors. In this paper, we report a total synthesis of a new prostaglandin analogue in which the oxygen carbonyl at C-9 was substituted by a sulfur atom and the carboxylic acid at C-1 in the α-side chain was substituted by the methyl group.[7]

The route for the synthesis of this new azathia-PG_1 is shown in Scheme 1.

Reaction of L-cysteine ethyl ester hydrochloride with carbon disulfide in the presence of triethyl amine in CH_2Cl_2 at room temperature, and subsequent chromatography on silica gel G with chloroform, afforded the appropriately functionalized intermediate **2**.[8] Reduction of the thiazolidine ester **2** with an excess of sodium borohydride in boiling methanol in the presence of *t*-butanol,[9] followed by chromatography on silica gel G with chloroform–methanol (98:2), afforded the thiazolidine alcohol **3**. No racemization was observed for compound **4** according to X-ray crystallographic data.

The protection of the primary hydroxy group present in **3** accomplished by using dihydropyran in the presence of a catalytic amount of *p*-toluenesulfonic acid in methylene chloride–tetrahydrofuran,[10] followed by chromatography of the thiazolidine ether **4** on silica gel G with chloroform–methanol (99:1).

N-Alkylation of the thiazolidine ether **4** was carried out by using the procedure described by Zoretic and Soja.[11] Reaction of the sodium salt of **4** with 1-iodoheptane in THF at 50°C under nitrogen atmosphere and subsequent chromatography on silica gel G with hexane–acetone (8:2), afforded the *N*-alkylated thiazolidine ether **5**. The *N*-heptyl derivative **5** so obtained was treated with pyridinium *p*-toluenesulfonate (PPTS) followed by chromatography on silica gel G with chloroform–methanol (8:2), affording the deprotected *N*-heptyl thiazolidine alcohol **6**. Oxidation of **6** with Swern reagent[12] in methylene chloride at −60°C under nitrogen atmosphere followed by addition of water, solvent evaporation and a rapid filtration of the reaction mixture on silica gel G, afforded the aldehyde **7** in approximately 55% yield.

Reaction of the *N*-heptyl thiazolidine aldehyde **7** with the lithium salt of dimethyl-(2-oxoheptyl)phosphonate in tetrahydrofuran at 0°C for 3 h and subsequent chromatography on silica gel G with hexane–acetone (8:2), gave the enone **8**.[11] Reduction of the enone **8** with an ethanolic sodium borohydride at room temperature

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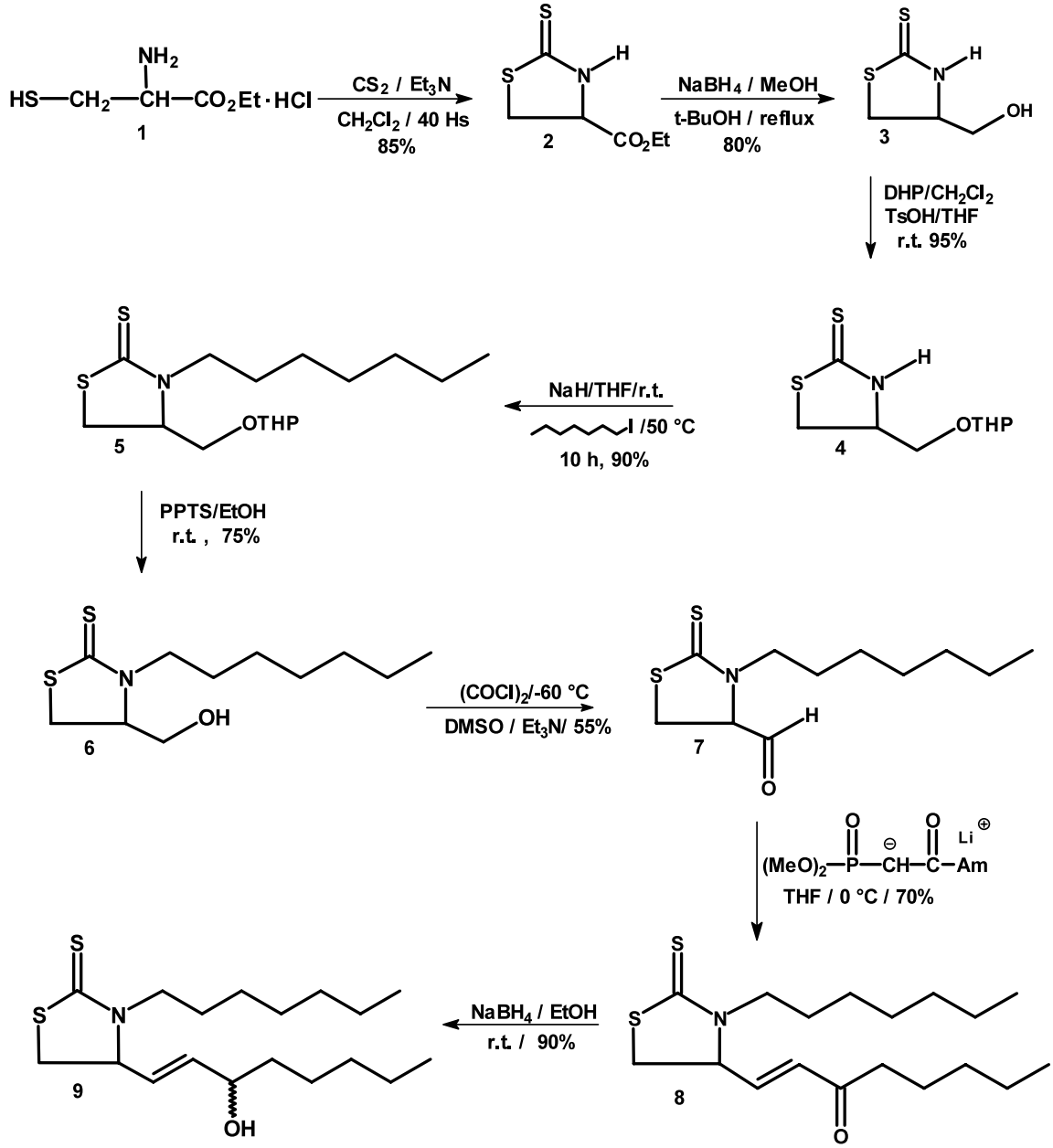

Scheme 1.

and destruction of the excess of sodium borohydride with an ethanolic hydrochloric acid solution at 0°C, followed by chromatography on silica gel G with hexane–acetone (8:2), afforded the novel prostaglandin *n*-heptyl-4-(3-hydroxy-*trans*-1-octenyl)-1,3-thiazolidin-2-thione **9** as a mixture (2:1) of the two corresponding diastereomeric allyl alcohols.

In summary, the synthetic sequence developed in this work for obtaining azathia-PG analogues starting from an easily accessible compound has been described. An easy five-membered ring formation from L-cysteine ethyl ester hydrochloride serves as a key of further interconvertions of functional groups.

Other azathia-PG analogues of **9** with modified α-side chains[6,13] and possessing bulk groups at C-15 are still in course in our laboratory. Details of pharmacological studies of **9** are now under investigation.

The novel compounds obtained in the synthesis were fully characterized by ^{1}H NMR (200 MHz) and microanalyses.[14]

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14. All compounds resulting from the synthesis were fully characterized by ^{1}H NMR (200 MHz) and microanalyses, but only the data of the novel compounds are given as follows. Compound **3**: ^{1}H NMR ($CDCl_3$): δ 4.34–4.44 (m, 1H); 3.63–3.81 (m, 3H); 3.47–3.52 (dd, 1H, $J=6.6$ e 5.9 Hz); 2.89 (sl, 2H). Microanalyses: C, 32.3; H, 4.70; N, 9.52%. Compound **4**: ^{1}H NMR ($CDCl_3$): δ 8.32 (sl, 1H); 4.63–4.67 (m, 1H); 4.46–4.50 (m, 2H); 3.77–3.91 (m, 2H); 3.50–3.69 (m, 3H); 1.25–1.85 (m, 6H). Microanalyses: C, 45.97; H, 6.39; N, 5.45%. Compound **5**: ^{1}H NMR ($CDCl_3$): δ 4.63–4.95 (m, 1H); 3.78–3.97 (m, 2H); 3.35–3.56 (m, 5H); 2.95–3.18 (m, 2H); 1.27–1.84 (m, 16H); 0.88 (t, 3H, $J=6$ Hz). Microanalyses: C, 58.53; H, 8.66; N, 4.22%. Compound **6**: ^{1}H NMR ($CDCl_3$): δ 4.50–4.63 (m, 1H); 3.67–3.79 (m, 2H); 3.29–3.64 (m, 2H); 3.04–3.14 (t, 3H, $J=6$ Hz); 1.61–1.75 (m, 2H); 1.20–1.50 (m, 8H); 0.89 (t, 3H, $J=7$ Hz). Microanalyses: C, 53.60; H, 8.43; N, 5.66%. Compound **7**: ^{1}H NMR ($CDCl_3$): δ 9.93 (s, 1H); 4.99–5.04 (dd, 1H, $J=6$ e 8.8 Hz); 3.65–3.77 (m, 1H); 3.25–3.51 (m, 1H); 3.29 (t, 2H, $J=7.4$ Hz); 1.15–1.78 (m, 10H); 0.88 (t, 3H, $J=6.6$ Hz). Compound **8**: ^{1}H NMR ($CDCl_3$): δ 7.27–7.47 (m, 1H); 6.82–7.14 (m, 1H); 3.25 (t, 2H, $J=7.3$ Hz); 3.03–3.10 (dd, 1H, $J=7.3$ e 14 Hz); 2.73–2.80 (dd, 1H, $J=7$ e 14 Hz); 2.63 (t, 2H, $J=7.3$ Hz); 1.13–1.83 (m, 16H); 0.88 (t, 6H, $J=7$ Hz). Microanalyses: C, 60.31; H, 8.18; N, 3.66%. Compound **9**: ^{1}H NMR ($CDCl_3$): δ 6.90–6.94 (m, 1H); 6.52–6.65 (m, 2H); 5.29 (sl, 1H); 4.13–4.31 (m, 2H); 3.20 (t, 2H, $J=7.3$ Hz); 2.05–2.11 (m, 1H); 1.25–1.84 (m, 18H); 0.88 (t, 6H, $J=6.6$ Hz). Microanalyses: C, 63.06; H, 09.20; N, 03.70%.