SYNTHESIS OF BOTH ENANTIOMERS OF 8-AZA-11-DEOXY-10-THIAPROSTAGLANDIN E_1

Noboru Kubodera,* Hiroyuki Nagano, Michiro Takagi, and Isao Matsunaga
New Drug Research Laboratories, Chugai Pharmaceutical Co., Ltd.
3-41-8 Takada, Toshima-ku, Tokyo 171, Japan

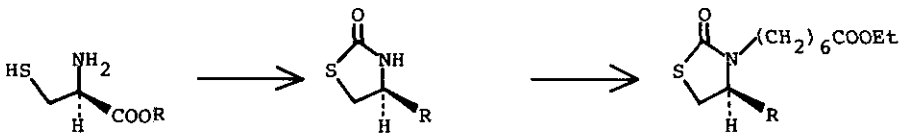
Abstract----Synthesis of both enantiomers of 8-aza-11-deoxy-10-thiaprostaglandin E_1 has been achieved starting from D- and L-cysteine, respectively.

In recent years, a variety of prostaglandin analogs has been synthesized with considerable chemical and biological interest. Particularly, an intense interest has been focused on the synthesis of heterocyclic prostaglandin analogs containing hetero-atoms in the five-membered ring,[1] such as 8,10-diaza,[2] 8,11-diaza,[3] 8,12-diaza,[4] 9,11-diaza,[2b] 9,12-diaza,[5] 10,12-diaza,[2b,6] 9-aza-11-oxa,[7] 11-aza-9-oxa,[7b] 8-aza-9-thia,[8] 8-aza-11-thia,[2a,9] 9-aza-11-thia,[7a,10] 11-aza-8-thia,[11] 12-aza-9-thia,[12] 9,11-dioxa,[13] and 9,11-dithia[13b] derivatives. In this paper, we describe the synthesis of another type of the dihetero-analog, 8-aza-11-deoxy-10-thiaprostaglandin E_1, in both enantiomeric forms starting from the corresponding optically active amino acids, D- and L-cystene, respectively.

Hydrochloride of the amino-ester(2), prepared from D-cysteine(1), was treated with phosgene in the presence of sodium bicarbonate to give methyl (S)-(+)-2-oxothiazolidine-4-carboxylate(3)[14] in 78.7% yield as a practically pure oil, ν_{max}^{neat} 3270, 1740, 1680, 1210, $\delta(CDCl_3)$ 3.66(2H, m), 3.81(3H, s), 4.51(1H, dd, J= 7.2, 5 Hz), 7.05(1H, s, disappeared with D_2O), m/e 161(M^+), 102(base peak), $[\alpha]_D^{27}$ +49.8°(c=2.0, EtOH). The ester group of 3 was selectively reduced with sodium borohydride to give (S)-(+)-2-oxothiazolidine-4-methanol(4) in 76.7% yield as colorless prisms, mp 103.5-104.5°, ν_{max}^{KBr} 3250, 1640, $\delta(CD_3OD)$ 3.1-4.1(5H, m), 4.74 (2H, s), m/e 133(M^+), 102(base peak), $[\alpha]_D^{28}$ +0.8°(c=1.0, EtOH). After protection of the primary hydroxy group by ether formation, the resulting (S)-(+)-4-(1-ethoxyethoxy)methyl-2-oxothiazolidine(5), ν_{max}^{neat} 3250, 1680, $\delta(CDCl_3)$ 1.20(3H, t), 1.31(3H, t), 3.0-3.9(5H, m), 4.03(2H, q), 4.76(1H, q), 6.59(1H, s, disappeared with D_2O), was treated with ethyl 7-iodoheptanoate in the presence of sodium

hydride to give ethyl (S)-(+)-7-[4-(1-ethoxyethoxy)methyl-2-oxo-3-thiazolidine]-heptanoate(6) in 93.0% yield as a pale yellow oil, ν_{max}^{neat} 1730, 1680, δ($CDCl_3$) 1.21 (3H, t), 1.26(3H, t), 1.33(3H, d), 1.4(8H, br), 2.30(2H, t), 2.9-3.9(9H, m), 4.15 (2H, q), 4.76(1H, q). Deprotection of 6 with *p*-toluenesulfonic acid in ethanol afforded ethyl (S)-(+)-7-(4-hydroxymethyl-2-oxo-3-thiazolidine)heptanoate(7) almost quantitatively as a practically pure oil, ν_{max}^{neat} 3450, 1730, 1680(shoulder), 1650, δ($CDCl_3$) 1.26(3H, t), 1.4(8H, br), 2.30(2H, t), 2.9-3.9(8H, m, 1H disappeared with D_2O), 4.14(2H, q), m/e 289(M^+), 212(base peak), $[\alpha]_D^{27}$ +42.5°(c=2.0, EtOH), which on the Pfitzner-Moffatt oxidation gave ethyl (S)-(+)-7-(4-formyl-2-oxo-3-thiazolidine)heptanoate(8), ν_{max}^{neat} 1730, 1675, δ($CDCl_3$) 1.26(3H, t), 1.4(8H, br), 2.31(2H, t), 3.0-3.9(4H, m), 4.15(2H, q), 4.80(1H, br), 9.78(1H, s), m/e 287 (M^+), 212(base peak), $[\alpha]_D^{27}$ +26.2°(c=1.0, EtOH), in 53.2% yield as a pale yellow oil.

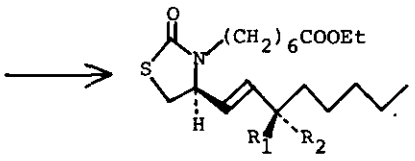
The Wittig reaction of 8 with dimethyl sodio-2-oxoheptylphosphonate provided ethyl (S)-(+)-7-[4-(3-oxo-*trans*-1-octenyl)-2-oxo-3-thiazolidine]heptanoate(9), ν_{max}^{neat} 1730, 1680, δ($CDCl_3$) 0.89(3H, t), 1.24(3H, t), 1.4(14H, br), 2.29(2H, t), 2.59(2H, t), 3.05(2H, m), 3.50(2H, t), 4.13(2H, q), 4.35(1H, m), 6.25(1H, d, J= 16 Hz), 6.76(1H, dd, J=16, 7 Hz), m/e 383(M^+), 238(base peak), $[\alpha]_D^{28}$ +55.2°(c=1.0, EtOH), exclusively, in 55.8% yield. The stereochemistry of the double bond formed was readily deduced to be E configuration based on PMR coupling constant(16 Hz). Although the conversion could not be carried out stereoselectively, 9, upon reduction with sodium borohydride, furnished 42.6% yield of (12S,15S)-(+)-8-aza-11-deoxy-10-thiaprostaglandin E_1 ethyl ester(10), ν_{max}^{neat} 3450, 1730, 1670, δ($CDCl_3$) 0.88(3H, t), 1.23(3H, t), 1.4(16H, br), 2.27(2H, t), 2.35(1H, s, disappeared with D_2O), 2.76-3.56(5H, m), 4.10(2H, q), 4.25(1H, br), 5.38-5.82(2H, m), m/e 385(M^+), 212(base peak), $[\alpha]_D^{28}$ +45.3°(c=1.0, EtOH), as the more polar component, accompanied by 41.8% yield of its C-15 epimer(11), ν_{max}^{neat} 3450, 1730, 1660, δ($CDCl_3$) 0.90(3H, t), 1.25(3H, t), 1.4(16H, br), 2.30(2H, t), 2.45(1H, s, disappeared with D_2O), 2.80-3.60(5H, m), 4.12(2H, q), 4.30(1H, br), 5.41-5.86(2H, m), m/e 385(M^+), 367(base peak), $[\alpha]_D^{28}$ +21.2°(c=1.0, EtOH), as the less polar component after purification using silica gel plates. For the confirmation of the configuration at C-15 center, 10 was converted into the known (S)-(-)-2-acetoxyheptanal(13) via a two-step sequence. Thus, 10 was acetylated to give the corresponding acetate (12), ν_{max}^{neat} 1730, 1680, δ($CDCl_3$) 0.90(3H, t), 1.25(3H, t), 1.4(16H, br), 2.06(3H, s), 2.29(2H, t), 2.75-3.17(2H, m), 3.38(2H, t), 4.12(2H, q), 4.30(1H, br),

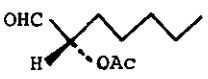


1, R=H
2, R=Et

3, R=COOEt
4, R=CH_2OH
5, R=$CH_2OCH(Me)OEt$

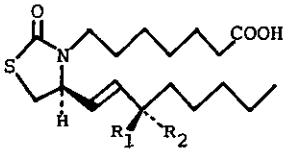
6, R=$CH_2OCH(Me)OEt$
7, R=CH_2OH
8, R=CHO

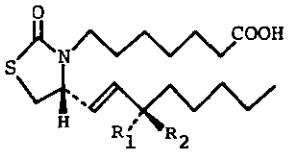




13

9, $R_1=R_2=O$
10, $R_1=H$, $R_2=OH$
11, $R_1=OH$, $R_2=H$
12, $R_1=H$, $R_2=OAc$





14, $R_1=H$, $R_2=OH$
15, $R_1=OH$, $R_2=H$

16, $R_1=H$, $R_2=OH$
17, $R_1=OH$, $R_2=H$

5.16-5.79(3H, m), which on ozonolysis afforded 13 ($[\alpha]_D^{25}$ -32.5°(c=1.0, $CHCl_3$) (lit.[15] $[\alpha]_D^{21}$ -33.2°(c=2.0, $CHCl_3$)) and the aldehyde(8) in overall yields of 83.0% and 75.0%, respectively, after purification using silica gel plates. It is interesting that the behavior of 10 and 11, each epimer at C-15 center, on a silica gel plate was well correspond to that of natural prostaglandins and their C-15 epimers.[16] Hydrolysis of 10 with sodium hydroxide in aqueous ethanol gave (12S,15S)-(+)-8-aza-11-deoxy-10-thiaprostaglandin E_1(14) in 98.5% yield as colorless needles, mp 93-94° ν_{max}^{KBr} 3600-2400, 1730, 1640, $\delta(CDCl_3)$ 0.89(3H, t), 1.4(16H, br), 2.32(2H, t), 2.72-3.62(4H, m), 4.04-4.36(2H, m), 5.64-5.89(2H, m), 6.09(2H, s, disappeared with D_2O), m/e 357(M^+), 86(base peak), $[\alpha]_D^{28}$ +48.6°(c=1.0, EtOH). Similarly, 11 was transformed into (12S,15R)-(+)-8-aza-11-deoxy-10-thiaprostaglandin E_1(15) in 97.4% yield as colorless needles, mp 70-71° ν_{max}^{KBr} 3600-2400, 1730, 1640, $\delta(CDCl_3)$ 0.90(3H, t), 1.4(16H, br), 2.33(2H, t), 2.70-3.60(4H, m), 4.04-4.38 (2H, m), 5.65-5.90(2H, m), 5.98(2H, s, disappeared with D_2O), m/e 357(M^+), 86(base peak), $[\alpha]_D^{28}$ +23.5°(c-1.0, EtOH).

In the same manner, the enantiomers of these prostaglandin analogs, (12R, 15R)-(-)-8-aza-11-deoxy-10-thiaprostaglandin E_1(16), mp 90-91°, $[\alpha]_D^{27}$ -46.5°(c= 1.0, EtOH), and (12R,15S)-(-)-8-aza-11-deoxy-10-thiaprostaglandin E_1(17), mp 72-73°, $[\alpha]_D^{27}$ -22.3°(c=1.0, EtOH), were prepared in comparable yields using L-cysteine as starting material.

Among four thiazolidine prostanoids synthesized, 14, which possessed the same configuration as that of naturally occurring prostaglandin E_1, had the most potent branchodilatory activity in anesthetized dogs at a dose of 10^{-5} g/kg, while its C-15 epimer(15) had almost no effect. Interestingly, both enantiomers, (16) and (17), exhibited the same activity at the same dose though moderate. The inducing effect of rabbit platelet aggregation was also shown in 17. Details of pharmacological studies are now under investigation.

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