Tetrahedron. Asymmetry Vol. 3, No. 12, pp 1525-1528, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

A New Efficient Synthesis of the Biologically Potent PGD_2-Analogue ZK118182

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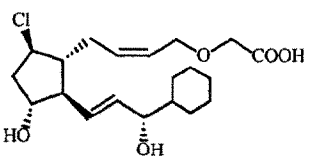
(*Received in UK* 12 *October* 1992)

Abstract : A highly stereoselective and practical synthetic method for ZK118182, which is chemically and metabolically stable and a biologically potent PGD_2-analogue developed by Schering AG, is reported.

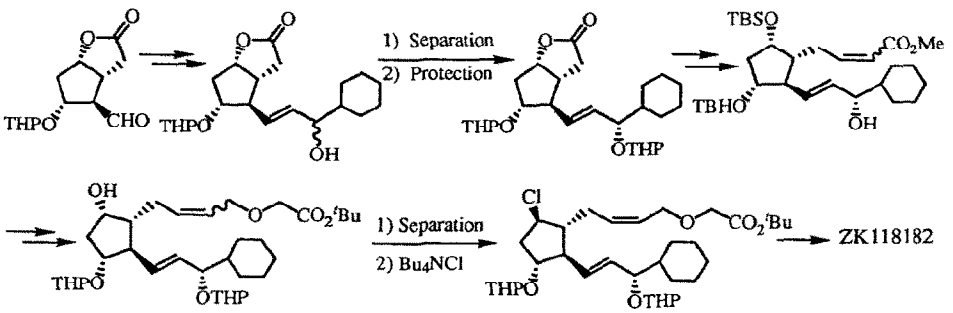
The development of chemically and metabolically stable analogues which mimic the activity of the natural PGD_2 in biological profile and potency has attracted much interest.[1] 3-Oxa-9-deoxy-9β-chloro-16,17,18,19,20-pentanor-15-cyclohexyl $PGF_{2\alpha}$ (ZK118182)[1c] developed by the scientists of Schering AG shows high affinity for the PGD_2-receptor and has interesting pharmacological properties such as high and long lasting blood pressure lowering activity on oral application in rats.[2]



ZK118182

The synthesis of ZK118182 has been carried out starting from the Corey lactone.[1c] The key steps of the synthetic method are shown in Scheme 1. This method, however, suffers from the following two major drawbacks ; 1) the need for separation of the two 15-hydroxy epimers after introducing the ω side-chain by a Wittig-Horner reaction and subsequent reduction with $NaBH_4$, and 2) the need for a tedious separation of the 5-*Z* and -*E* isomers after construction of the α side-chain by a Wittig-Horner reaction with $(RO)_2P(O)CH_2CO_2Me$ followed by reduction and etherification.

Scheme 1 : The key steps of Schering method for the synthesis of ZK118182



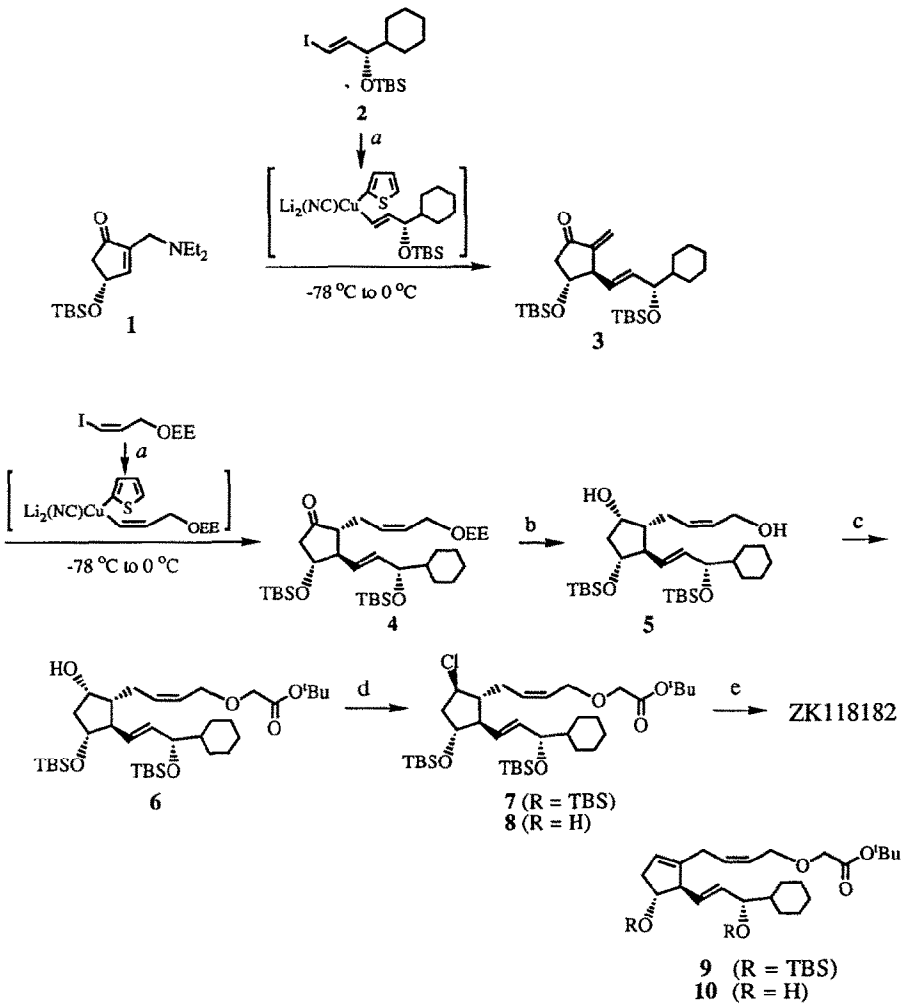
Herein we report an efficient route to ZK118182 which is free from these two problems. The method shown in Scheme 2 is based on the two-component coupling synthesis of PGs which we have developed recently as an industrially viable process.[3] Thus the conjugate addition reaction of 2-((diethylamino)methyl)-4-siloxy-2-cyclopentenone (**1**)[4] with the organocuprate derived from the ω side-chain unit **2**[5] afforded **3**[6] in 93% yield. The reaction of the enone **3** with the organocuprate prepared from (*Z*)-1-iodo-3-((1-ethoxyethyl)oxy)-1-propene via successive treatment with ^{t}BuLi and (2-thienyl)Cu(CN)Li afforded **4** in 68% yield. Reduction of **4** with L-Selectride and deprotection of the ethoxyethyl group by acid catalyzed hydrolysis provided the diol **5**[7] as a sole isomer in 60% yield. Treatment of **5** with $BrCH_2CO_2{}^tBu$ under phase-transfer conditions furnished the mono alkylated product **6**[8] in 81% yield without production of the dialkylated compound. The conversion of **6** into ZK118182 was carried out according to the Schering method. Thus tosylation of **6** and subsequent reaction with Bu4NCl afforded the 9-β-chloro compound **7** and $\Delta^{8,9}$-unsaturated by-product **9**. After removal of the 11- and 15-protecting groups, 9-β-chloro compound **8**[9] can be separated from $\Delta^{8,9}$-unsaturated product **10**. Saponification of **8** thus isolated with lithium hydroxide provided finally ZK118182, the spectroscopic data of which were in good agreement with the reported ones.[1c]

References and Notes

1) (a) U. Klar, A. Pletsch, W. Skuballa, H. Vorbrüggen, *BioMed. Chem. Lett.*, **2**, 445 (1992). (b) S. Seiler, C. L. Brassard, M. E. Federici, *Prostaglandins*, **40**, 119 (1990). (c) B. Buchmann, W. Skuballa, H. Vorbrüggen, *Tetrahedron Lett.*, **31**, 3425 (1990). (d) S. Ito, E. Okuda, K. Sugama, M. Negishi, O. Hayaishi, *Br. J. Pharmacol.*, **99**, 13 (1990). (e) P. Barraclough, A. G. Caldwell, C. J. Harris, W. P. Jackson, B. J. R. Whittle, *J. Chem. Soc., Perkin Trans I*, 1815 (1989). (f) K.-H. Thierauch, C.-St. Stuzebecher, E. Schillinger, H. Rehwinkel, B. Radüchel, W. Skuballa, H. Vorbruggen, *Prostaglandins*, **35**, 855 (1988), and the references cited therein.

2) B.-G. Schulz, R. Beckmann, B. Müller, G. Schröder, B. Maaß, K.-H. Thierauch, B. Buchmann, P. F. J. Verhallen, W. Fröhlich, *Abstracts of the VIIth International Conference of Prostaglandins and Related Compounds*, p.91, May 28-June 1, Florence, Italy (1990).

Scheme 2[a]



[a](a) ^{t}BuLi (2 eq), Et_2O, -78 °C, 30 min then (2-Thienyl)Cu(CN)Li (1.3 eq), THF, -78 °C, 15 min. (b) (1) L-Selectride (1.5 eq), THF, -78 °C, 1.5 h. (2) cat. PPTS, ^{i}PrOH, Et_2O, room temp., 20 h. (c) $BrCH_2CO_2{}^tBu$ (2.5 eq), cat. Bu_4NHSO_4, toluene-25% aq. NaOH, room temp., 4 h. (d) (1) p-TsCl (2.5 eq), DMAP (3 eq), CH_2Cl_2, room temp., 5 h. (2) Bu_4NCl (5 eq), DMF, 40 °C, 5 h. (e) (1) $(HF)_n$-pyridine, CH_3CN, room temp., 4 h, (2) LiOH, MeOH, room temp., 4 h.

3) Preparation of cyclopentenone intermediates and synthesis of natural PGs and their analogues : (a) S. Okamoto, Y. Kobayashi, H. Kato, K. Hori, T. Takahashi, J. Tsuji, F. Sato, *J. Org. Chem.*, **53**, 5590 (1988). (b) S. Okamoto, Y. Kobayashi, F. Sato, *Tetrahedron Lett.*, **30**, 4379 (1989). (c) H. Tsujiyama, N. Ono, T. Yoshino, S. Okamoto, F. Sato, *ibid*, **31**, 4481 (1990). (d) S. Okamoto, T. Yoshino, H. Tsujiyama, F. Sato, *ibid*, **32**, 5793 (1991). (e) S. Okamoto, T. Yoshino, F. Sato, *Tetrahedron : Asymmetry*, **2**, 35 (1991). (f) T. Yoshino S. Okamoto, F. Sato, *J. Org. Chem.*, **56**, 3205 (1991). Preparation of PGs ω side-chain units : (g) S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, *Tetrahedron Lett.*, **28**, 2033 (1987). (h) Y. Kitano, T. Matsumoto, S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, *Chem. Lett.*, 1523 (1987). (i) Y. Kitano, T. Matsumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, K. Miyaji, K. Arai, *Tetrahedron Lett.*, **28**, 6351 (1987). (j) Y. Kitano, T. Matsumoto, F. Sato, *Tetrahedron*, **44**, 4073 (1988).
4) Commercially available from Nissan Chemical Industries, Ltd. (Japan). See reference 3a.
5) Synthesized according to the procedure reported in reference 3i.
6) ^{1}H NMR ($CDCl_3$, 300 MHz) : δ -0.11, 0.04, 0.06 and 0.07 (4s, 12H), 0.87 and 0.89 (2s, 18H), 0.90-1.90 (m, 11H), 2.33 (dd, J = 6.3, 17.8 Hz, 1H), 2.64 (dd, J = 6.3, 17.8 Hz, 1H), 3.28-3.38 (m, 1H), 3.84-3.90 (m, 1H), 4.09-4.17 (m, 1H), 5.25 (d, J = 2.5 Hz, 1H), 5.47 (dd, J = 7.2, 15.4 Hz, 1H), 5.60 (dd, J = 5.4, 15.4 Hz, 1H), 6.12 (d, J = 2.9 Hz, 1H).
7) ^{1}H NMR ($CDCl_3$, 300 MHz) : δ -0.01, 0.03, 0.06 and 0.07 (4s, 12H), 0.88 and 0.89 (2s, 18H), 1.02-1.41 (m, 6H), 1.43-1.92 (m, 8H), 2.03 (dt, J = 13.7, 3.8 Hz, 1H), 2.20 (dt, J = 2.0, 7.1 Hz, 1H), 2.29 (t, J = 8.5 Hz, 1H), 2.52-2.80 (m, 3H), 3.73-3.90 (m, 2H), 4.10 (br s, 2H), 4.33-4.47 (m, 1H), 5.34 (dd, J = 8.7, 15.3 Hz, 1H), 5.45 (dd, J = 6.1, 15.3 Hz, 1H), 5.55 (dt, J = 4.9, 11.0 Hz, 1H), 5.70-5.89 (m, 1H).
8) ^{1}H NMR ($CDCl_3$, 300 MHz) : δ -0.01, 0.03, 0.05 and 0.06 (4s, 12H), 0.87 and 0.88 (2s, 18H), 1.48 (s, 9H), 1.10-1.98 (m, 14H), 2.15 (dt, J = 5.1, 14.1 Hz, 1H), 2.30 (dt, J = 2.7, 8.7 Hz, 1H), 2.35-2.52 (m, 1H), 3.74-3.81 (m, 1H), 3.95 (s, 2H), 3.98-4.50 (m, 2H), 4.12 (dd, J = 5.8, 11.6 Hz, 1H), 4.22 (dd, J = 6.3, 11.6 Hz, 1H), 5.32 (dd, J = 8.8, 15.2 Hz, 1H), 5.44 (dd, J = 6.0, 15.2 Hz, 1H), 5.50-5.74 (m, 2H).
9) Yield of **8** from **6** was 41%, and 18% yield of **10** was co-produced. The chlorination reaction has not been optimized.