Tetrahedron Letters No. 36, pp 3379 - 3382.

0040-4039/78/0901-3379$02.00/0

SYNTHESIS OF OPTICALLY PURE STEROID INTERMEDIATE BY THE NOVEL USE OF MESO-COMPOUND

Shiro Terashima,[a)]* Munehiko Nara,[b)] and Shun-ichi Yamada[c)]

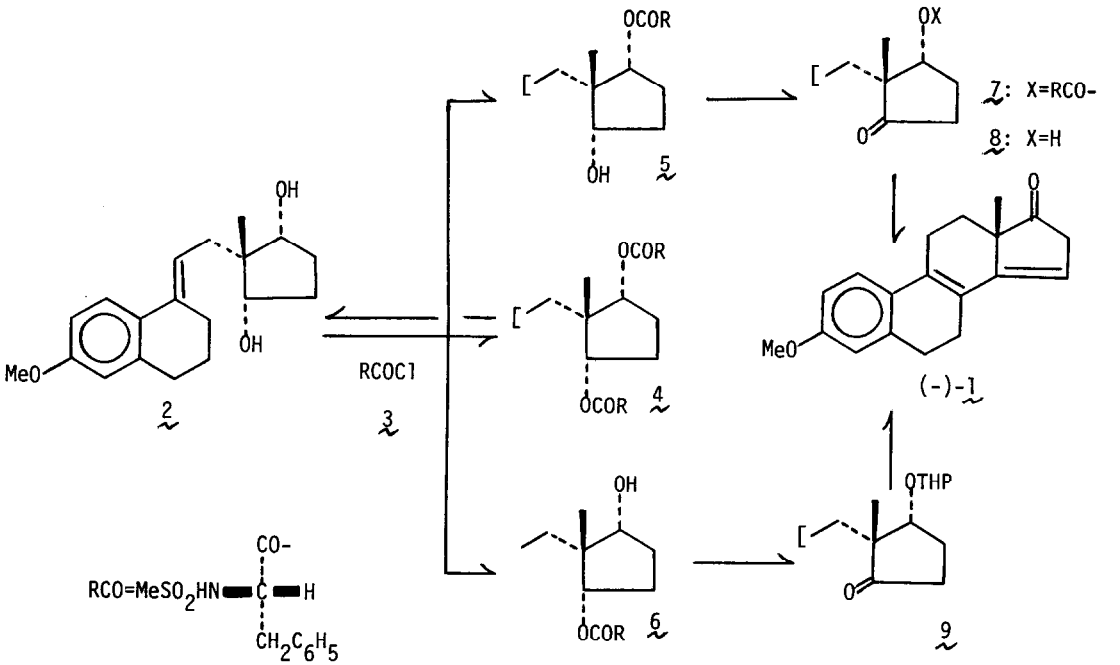
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan;[a)] Tokyo Research Laboratories, Kowa Co. Ltd., 2-17-43. Noguchicho, Higashimurayama, Tokyo 189, Japan;[b)] Faculty of Pharmaceutical Sciences, Josai University, 1-1, Keyakidai, Sakadoshi, Saitama 350-02, Japan[c)]

When preparation of optically active synthetic intermediate is attempted by ordinary chemical resolution of racemic compound, maximum 50% of the resolution substrate can only be utilized for further synthetic scheme. Aiming to overcome this inefficiency, the authors have developed the new methodology[1,2)] which recommends utilization of symmetrically functionalized meso-compound as a resolution substrate in place of racemic modification. Thus, when meso-compound is monofunctionalized by a chiral compound and each of the formed diastereomers, separable by fractional recrystallization or chromatography, is submitted to further chemical elaboration including protective group transposition, it is theoretically possible to convert the total amount of the starting material into one requisite optically pure synthetic intermediate.[3)]

Although two structural types of optically pure prostaglandin intermediates have already been prepared by employing our novel methodology,[1,2)] synthesis of optically pure steroid intermediate(1) from which the synthetic route to natural (+)-estrone has been established,[4)] is examined to explore the generality of this new concept. This report describes our successful synthesis of optically pure 1 from the meso-diol(2)[5)] using (S)-N-methanesulfonylphenylalanyl chloride(3)[1)] as a chiral agent.

As shown in Scheme I, acylation of 2 with 3(1.6 eq) in a mixture of pyridine and tetrahydrofuran(rt, 16 h), followed by extractive isolation with ethyl acetate and separation by preparative tlc(silica gel, solvent:ethyl acetate-hexane 1:1, 3 developments), affords the

Scheme I



unreacted 2(26%), the oily diester(4)[9b](23%), $[\alpha]_D^{20}$-89.5°(c=1.1, chloroform), the oily less polar monoester(5)[9b](22%), $[\alpha]_D^{20}$-50.8°(c=1.2, chloroform), and the crystalline more polar monoester(6)[9](19%), mp 120-121.5°C(fine needles from ethyl acetate-hexane), $[\alpha]_D^{20}$+22.6°(c=1.1, chloroform). Since alkaline hydrolysis(KOH(4.0 eq) in aq. methanol, rt, 48 h) of the useless 4 readily gives 2(96%), the yield of 5 and 6 can be calculated as 42% and 36%, respectively, when corrected for the total amount of the recovered 2. Separation of 5 and 6 can also be accomplished more simply by fractional recrystallization. Thus, after removal of 2 and 4 by column chromatography(alumina, solvent:chloroform), an oily mixture of 5 and 6, $[\alpha]_D^{20}$-22.8°(c=1.6, chloroform), which is obtained by evaporation of the combined chloroform eluates from the column, is triturated with a small amount of ethyl acetate-hexane to give the crude crystalline 6(54%),[10] $[\alpha]_D^{20}$-18.0°(c=2.4, chloroform), as a semisolid. Recrystallization of the semisolid from ethyl acetate-hexane affords the pure 6[9](16%),[10] $[\alpha]_D^{20}$+22.4°(c=1.4, chloroform), as colorless needles. Two lots of the mother liquor from

trituration and recrystallization are combined and evaporated in vacuo to yield the crude oily 5[9b](59%),[10] which is contaminated with 6.

Pfitzner-Moffatt oxidation[11] of the pure 5 separated by preparative tlc, gives the ketone(7)[9](95%), mp 116.5-118°C(needles from methanol), $[\alpha]_D^{20}$-106°(c=1.4, chloroform). When the same oxidation is carried out using the crude oily 5(vide supra) and the crude 7 thus obtained is twice recrystallized from methanol, the pure 7,[9] mp 116-118°C, $[\alpha]_D^{20}$ -106°(c=1.6, chloroform), is also obtained as colorless needles in 36% yield based on 5 (19% based on 2[10]). The chiral acyl group of 7 is then cleaved by alkaline hydrolysis (KOH(2.5 eq) in methanol-tetrahydrofuran, rt, 16 h), giving the known hydroxy ketone(8)[9b] (86%), mp 103.5-104°C(fine needles from methanol), $[\alpha]_D^{20}$-89.6°(c=1.2, chloroform)(lit.,[12] mp 102-103°C, $[\alpha]_D^{24}$-83.6°(c=1.0, chloroform)). The hydroxy ketone(8) can readily be converted into the optically pure (-)-1[9](two steps 70%), mp 141-142.5°C(plates from ethanol), $[\alpha]_D^{20}$-102°(c=1.0, chloroform)(lit.,[13] mp 143°C, $[\alpha]_D$-103°(c=0.6, chloroform); lit.,[14] mp 141-142°C, $[\alpha]_D$-102°(c=1, chloroform)), by successive acidic cyclization under the established condition[12] and Pfitzner-Moffatt oxidation.[11]

On the other hand, successive protection of the alcoholic function of the crystalline monoester(6) as tetrahydropyranyl(THP) ether, hydrolytic removal of the chiral acyl group under alkaline condition(KOH(4.0 eq) in aq. methanol, rt, 16 h), and Pfitzner-Moffatt oxidation,[11] yields the protected ketone(9)[9b](three steps 88%), $[\alpha]_D^{20}$-27.3°(c=1.0, chloroform), as an oil. Simultaneous acidic cleavage of the protecting THP group of 9 and ring closure(aq. HCl-methanol, reflux, 2 h), followed by oxidation under Pfitzner-Moffatt condition,[11] furnished the optically pure (-)-1[9](two steps 65%), mp 141-142.5°C (plates from ethanol), $[\alpha]_D^{20}$-102°(c=0.9, chloroform)(vide supra).

Summarizing the above results, the preparation of optically pure (-)-1 can be accomplished in 45%[10] or 21%[10] yield from 2, by separating 5 and 6 by preparative tlc or recrystallization.

Further attempts to prepare optically pure synthetic intermediates which are important for the synthesis of complex natural products, by employing our novel methodology, are under progress in these laboratories.

References and Notes

1) S. Terashima, S. Yamada, and M. Nara, Tetrahedron Letters, 1977, 1001.

2) S. Terashima, M. Nara, and S. Yamada, Tetrahedron Letters, 1978, 1487.

3) For a detailed discussion on the concept of the new methodology, see ref. 1.

4) D. Taub,"The Total Synthesis of Natural Products" ed. by J. ApSimon, A Wiley-Interscience Publication, John-Wiley & Sons, New York, London, Sydney, Toronto, Vol. 2, pp 693-703.

5) This was prepared from the corresponding dione[6] by successive reduction with lithium tri-t-butoxyaluminum hydride[7] and lithium aluminum hydride in tetrahydrofuran(-70°C). The sample obtained as colorless prisms(59%)(recrystallized from ethyl acetate-hexane) showed mp 100-103°C(lit.,[8] mp 99-105°C).

6) C.H. Kuo, D. Taub, and N.L. Wendler, J. Org. Chem., 33, 3126(1968).

7) H.C. Brown and R.F. McFarlin, J. Am. Chem. Soc., 80, 5372(1958).

8) E. Tömörkény, N. Makk, G. Tóth, A. Szabó, and A. Szentirmai, Acta Chim. Acad. Sci. Hung., 91, 81(1976).

9) Satisfactory a) analytical and b) infrared and nuclear magnetic resonance data have been obtained for this compound.

10) Corrected for the total amount of the recovered 2.

11) K.E. Pfitzner and J.G. Moffatt, J. Am. Chem. Soc., 87, 5661 and 5670(1965).

12) T. Asako, H. Hiraga, and T. Miki, Chem. Pharm. Bull.(Tokyo), 21, 107(1973).

13) R. Bucourt, L. Nédélec, J-C. Gasc, and J. Weill-Raynal, Bull. Soc. Chim. Fr., 1967, 561.

14) R. Pappo, R.B. Garland, C.J. Jung, and R.T. Nicholson, Tetrahedron Letters, 1973, 1827.

(Received in Japan 5 June 1978; received in UK for publication 4 July 1978)