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NOVEL USE OF MESO-COMPOUND FOR THE PREPARATION OF OPTICALLY ACTIVE COMPOUNDS: SYNTHESIS OF OPTICALLY ACTIVE PROSTAGLANDIN INTERMEDIATES FROM CIS-2-CYCLOPENTENE-1,4-DIOL

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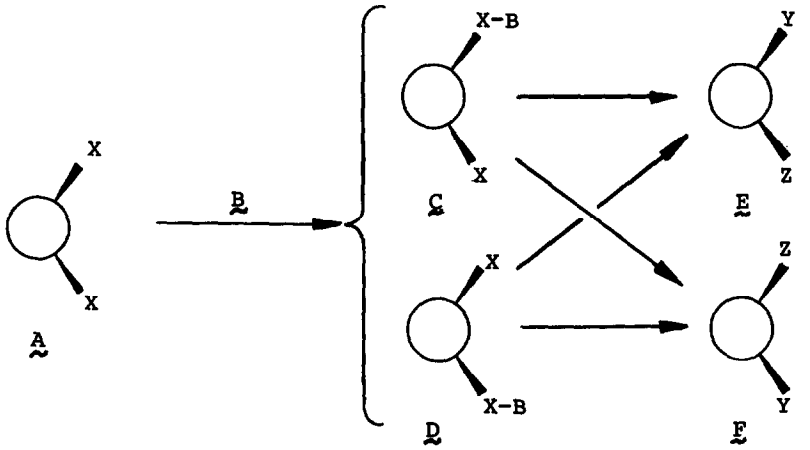
When preparation of optically active synthetic intermediates is examined by chemical resolution of racemic modification, two enantiomers are inevitably obtained. While one enantiomer having the desired absolute configuration is usable for further chemical elaboration, the other is completely useless for the synthetic scheme.

In order to avoid this problem which is always encountered in the usual chemical resolution, the use of symmetrically functionalized meso-compound as a resolution substrate in place of racemic modification is investigated. As shown in Scheme I, functionalization of the meso-compound(A) with an equimolar amount of the chiral compound(B) gives a mixture of the two diastereoisomers (C and D). Considering the structural characteristics of C or D which arise from the symmetric nature of A, it can reasonably be expected that preparation of the antipodal compounds(E and F) can be readily achieved from C or D by ordinary chemical transformations. Therefore, when C and D can be efficiently separated by the usual methods such as recrystallization and chromatography, it is considered theoretically possible to utilize the total amount of A for producing E or F.

We have now realized the concept shown in Scheme I[1] by cleanly separating C and D which are prepared from cis-2-cyclopentene-1,4-diol(1)[2] by using (S)-N-methanesulfonylphenylalanyl chloride(4)[3,4] as B, and have obtained several kinds of optically pure versatile prostaglandin intermediates.[1]

Acylation of 1 with 4(1.0 eq) in pyridine(rt, 15 hr), followed by extraction with ethyl acetate and simple separation by a silica gel column(chloro-

Scheme I

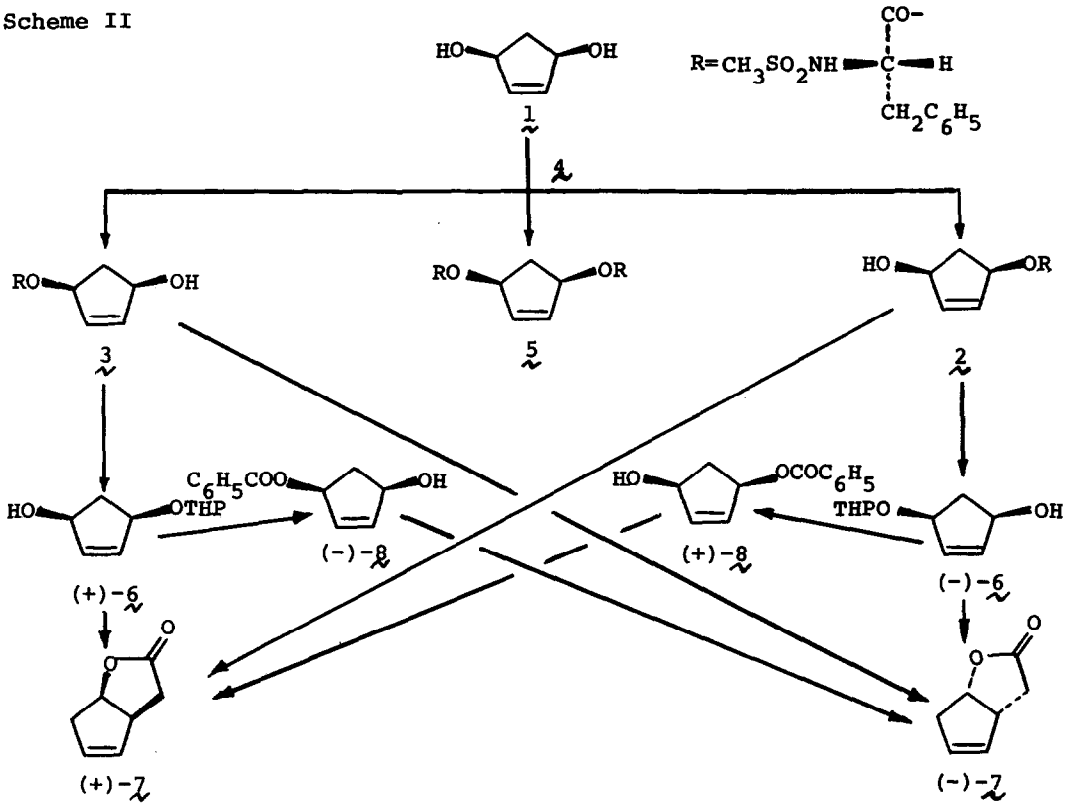


form), readily afforded an oily mixture of the monoesters(2 and 3; 9:10 by nmr analysis) and the oily diester(5),[4b,5] $[\alpha]_D^{20}$-51.3°(c=1.7, chloroform), in 51% and 24% yields, respectively. Trituration of the oily mixture(2 and 3) with ether effected a clean separation of the almost pure crystalline monoester(2) (19% from 1), mp 112-115°, $[\alpha]_D^{20}$+27.6°(c=2.3, chloroform), from the ether-soluble monoester(3). One recrystallization of almost pure 2 from a mixture of ether-chloroform afforded completely pure 2[4] (17% from 1), mp 118-119°, $[\alpha]_D^{20}$+30.5°(c=2.5, chloroform), as colorless plates. Evaporation of the original ethereal solution gave oily 3[4b] (32% from 1), $[\alpha]_D^{20}$-59.9°(c=1.7, chloroform), which was contaminated with a small amount of 2.[6]

Aiming to visualize the concept shown in Scheme I, preparation of the optically pure enantiomeric lactones((-)-7 and (+)-7) from 2 or 3 was examined as summarized in Scheme II.

Usual protection of the alcoholic function of 2 as tetrahydropyranyl(THP) ether, followed by hydrolysis of the chiral acyl group(KOH(1.5 eq)-aq. methanol, rt, 5 hr), gave the oily ether((-)-6)[4b] (81% from 2), $[\alpha]_D^{20}$-20.3°(c=1.3, chloroform), and 74% of (S)-N-methanesulfonylphenylalanine was recovered without racemization. According to the reported procedure,[7] (-)-6 was submitted to the Claisen rearrangement(triethyl orthoacetate-hydroquinone(catalytic amount), 160°, 10 hr), and the rearrangement product was treated under acidic condition(p-TsOH(catalytic amount)-methanol, 48 hr), giving optically pure (-)-7[8] (80% from (-)-6), mp 45-46°, $[\alpha]_D^{20}$-104°(c=1.1, methanol). On the other hand, when the Claisen rearrangement was directly attempted on 2 in a manner similar to that for (-)-6, and the rearrangement product was successively hydrolyzed(KOH(3.0 eq)-aq. methanol, rt, 5 hr) and lactonized(HCl(catalytic amount), rt, 24 hr), optically pure (+)-7[8] mp 45-46°, $[\alpha]_D^{20}$+104°(c=1.0, methanol), was obtained in 53% overall yield from 2. The same (+)-lactone ((+)-7) was also prepared from (-)-6 *via* (+)-benzoate((+)-8). Benzoylation

Scheme II



(benzoyl chloride(1.5 eq)-pyridine, rt, 15 hr) and cleavage of the THP ether (aq. acetic acid, rt, 24 hr) gave (+)-8[4] (85% from (-)-6), mp 62-63°, bp 143-145°(0.5 mmHg), $[\alpha]_D^{20}$+133°(c=1.7, chloroform). Successive Claisen rearrangement, alkaline hydrolysis, and lactonization similar to those for the preparation of (+)-7 from 2 afforded optically pure (+)-7(89% from (+)-8).

Application of the same reaction scheme as that for the preparation of (-)-7 from 2, to oily 3, afforded (+)-7, $[\alpha]_D^{20}$+75.8°(c=1.0, methanol), 72% optically pure[8] as a semisolid, via (+)-6,[4b] $[\alpha]_D^{20}$+16.0°(c=1.5, methanol). When preparation of (-)-7 from 3 was similarly attempted by the two different routes, (-)-7, $[\alpha]_D^{20}$-77.0°(c=1.7, methanol), 73% optically pure,[8] was obtained directly from 3 or via (-)-8,[4b] bp 143-146°(0.5 mmHg), $[\alpha]_D^{20}$-99.8°(c=2.0, chloroform). One recrystallization of partially optically active (-)-7 and (+)-7 from a mixture of ether and hexane gave optically pure samples showing mp 44.5-46°, $[\alpha]_D^{20}$-105°(c=1.0, methanol), and mp 45-46°, $[\alpha]_D^{20}$+104°(c=1.2, methanol), respectively.

The lactones((-)-7 and (+)-7) can be widely utilized as valuable intermediates for the synthesis of natural and unnatural prostaglandins,[10,11] and moreover, the antipodal pairs of optically active 4-alkoxy- or 4-acyloxy-2-

cyclopentene-1-ols((-)-6 and (+)-6 or (-)-8 and (+)-8) are also regarded as useful prostaglandin intermediates.[10,12]

The concept which has been realized by using 1, might be generally applicable to the synthesis of optically active compounds, and is considered one of the most useful methods due to its efficiency and operational simplicity.

References

1) The concept which is similar to ours, has been presented by Fischli, et al. They have prepared optically pure prostaglandin intermediates which are less versatile than those obtained by us. See, A. Fischli, M. Klaus, H. Mayer, P. Schönholzer, and R. Rüegg, Helv. Chim. Acta, 58, 564(1975).
2) C. Kaneko, A. Sugimoto, and S. Tanaka, Synthesis, 1974, 876.
3) Prepared from L-phenylalanine by successive treatments with methanesulfonyl chloride under the Schotten-Baumann condition and with phosphorous pentachloride in benzene.
4) Satisfactory a) analytical and b) infrared and nuclear magnetic resonance data have been obtained for this compound.
5) Hydrolysis of the useless diester(5) with barium hydroxide in aq. methanol (rt, 4 hr), recovered 1 and (S)-N-methanesulfonylphenylalanine in 68% and 85% yields.
6) This sample was found to contain 2 and 3 in a ratio of 14:86, since 72-73% optically active (-)- or (+)-7 could be prepared from this oily compound.
7) K. Kondo, M. Matsumoto, and F. Mori, Angew. Chem. Internat. Edit., 14, 103 (1975).
8) The lactone((-)-7) showing mp 46-47° and $[\alpha]_D^{25}$-106°(c=1, methanol), has the absolute configuration shown in Scheme II and is optically pure.[9]
9) J.J. Partridge, N.K. Chadha, and M.R. Uskoković, J. Am. Chem. Soc., 95, 7171 (1973).
10) a) S. Terashima, J. Syn. Org. Chem. Japan, 31, 353(1973); b) S. Terashima and S. Yamada, Metabolism and Disease, 12, 1489(1975).
11) For example: E.J. Corey, K.C. Nicolau, and D.J. Beams, Tetrahedron letters, 1974, 2439.
12) For example: J. Fried, J.C. Sih, C.H. Lin, and P. Dalven, J. Am. Chem. Soc., 94, 4343(1972)., and its preceding papers.