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SYNTHESIS OF AN OPTICALLY PURE PROSTAGLANDIN INTERMEDIATE FROM CIS-2-CYCLOHEXENE-1,4-DIOL

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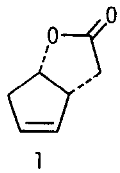
As an efficient method for producing optically active compound, the use of symmetrically functionalized *meso*-compound as a resolution substrate is considered most desirable because it is theoretically possible to utilize the total amount of *meso*-compound for synthesizing one requisite enantiomer usable for synthetic scheme.[1,2] Although this concept has been realized by preparing optically pure lactone(**1**) from *cis*-2-cyclopentene-1,4-diol,[1] preparation of another optically pure prostaglandin intermediate(**2**)[3] is attempted to explore the generality of this novel methodology, by using *cis*-2-cyclohexene-1,4-diol(**3**)[4] as a resolution substrate and (S)-N-phthaloylphenylalanyl chloride(**4**)[5] as a chiral compound.



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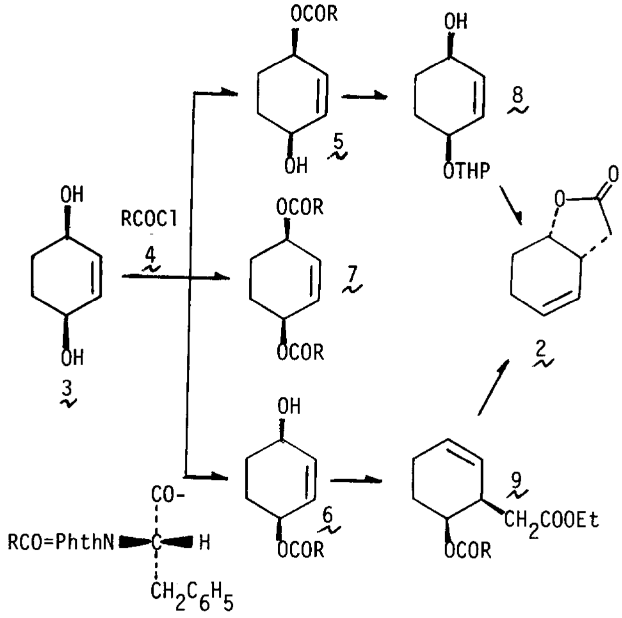
As shown in the scheme, acylation of **3** with **4**(1.5 eq)(anhyd. $KHCO_3$(10 eq) in THF, rt, 3.5 days), followed by extraction with ether and separation by a silica gel column($CHCl_3$), gave a mixture of the monoesters(**5** and **6**)[6b] as an oil(54%), $[\alpha]_D^{20}$-124°(c=1.8, $CHCl_3$), and the crystalline diester(**7**)[6](7.8%), mp 182.5-183°C, $[\alpha]_D^{20}$-154°(c=1.2, $CHCl_3$). The mixture of **5** and **6** was dissolved in ether, and the ethereal solution was cooled in an ice bath. This operation yielded a mixture of **5** and **6** as colorless needles[6b](34% from **3**) in which **5** was predominant, mp 94-98°C, $[\alpha]_D^{20}$-106°(c=1.5, $CHCl_3$). Further recrystallization of this substance from ether afforded a mixture of **5** and **6**(*ca*.3:1)[7,8] as colorless needles[6b](17% from **3**), mp 97.5-100°C, $[\alpha]_D^{20}$-75.3°(c=1.1, $CHCl_3$). Concentration of the original ethereal mother liquor gave a mixture of **5** and **6**(*ca*. 1:5)[7] as colorless needles[6b] (19% from **3**), mp 69-71°C, $[\alpha]_D^{20}$-162°(c=1.3, $CHCl_3$).

Protection of the alcoholic function of the mixture of **5** and **6**(*ca*. 3:1) as tetrahydropyranyl(THP) ether, followed by hydrolysis of the chiral acyl group(KOH(2.0 eq)-aq. MeOH, rt, 5 hr), gave oily **8**[6b] in a quantitative yield, $[\alpha]_D^{20}$-17.3°(c=1.2, $CHCl_3$). The alcohol(**8**) was submitted to Claisen rearrangement(triethyl orthoacetate-hydroquinone (catalytic amount), 160°C, 24 hr), and the rearrangement product was hydrolyzed(KOH(2.0 eq)-aq. MeOH), then simultaneously deprotected and lactonized(aq. AcOH, rt, 2 days), giving the desired lactone(**2**) as a semisolid[6b](79% from **8**), bp 96-97°C(4 mmHg), $[\alpha]_D^{20}$-15.0°(c=1.3,



MeOH), 50% optically pure.9) Two repeated recrystallizations from ether-hexane gave optically pure 2 as colorless prisms6)(53% from 8), mp 68.5-69.5°C, $[\alpha]_D^{20}$-29.8°(c=0.9, MeOH).

On the other hand, when a mixture of 5 and 6(ca. 1:5) was directly treated under the condition of Claisen rearrangement similar to that for 8, and the rearrangement product(9) was successively hydrolyzed(KOH(4.0 eq)-aq. MeOH, rt, 5 hr) and lactonized(HCl(catalytic amount), rt, 24 hr), the lactone(2),6b) $[\alpha]_D^{20}$ -20.2°(c=1.2, MeOH), 67% optically pure,9) was obtained as a colorless semisolid(87% from 6). Recrystallization from ether-hexane readily gave optically pure 2 as colorless prisms6b)(53% from 6), mp 68-69.5°C, $[\alpha]_D^{20}$-30.0°(c=1.0, MeOH).

As described above, the preparation of optically pure 2 could be accomplished in 15% overall yield from 3. Further studies on applicability of the novel method to preparation of optically pure key intermediate for natural product synthesis are under progress in these laboratories.

References and Notes

1) S. Terashima, S. Yamada, and M. Nara, Tetrahedron Letters, 1977, 1001.
2) For a detailed discussion on the concept, see ref. 1.
3) a) E.J. Corey and T. Ravindranathan, Tetrahedron Letters, 1971, 4753. b) E.J. Corey and B.B. Snider, Ibid., 1973, 3091. c) Idem., J. Org. Chem., 39, 256(1974).
4) C. Kaneko, A. Sugimoto, and S. Tanaka, Synthesis, 1974, 876.
5) J.C. Sheehan, D.W. Chapman, and R.W. Roth, J. Am. Chem. Soc., 74, 3822(1952).
6) Satisfactory a) analytical and b) infrared and nuclear magnetic resonance data have been obtained for this compound.
7) This was calculated from the optical purity of 2 derived from this compound.
8) Although repeated recrystallizations increased the ratio of 5 to 6 upto 94:6, effort to prepare completely pure 5 seemed useless because it was found that partially optically active 2 could readily give optically pure sample when recrystallized from ether-hexane.
9) The lactone(2) showing $[\alpha]_D^{20}$-30.0°(c=1.0, MeOH), was assumed to be optically pure(lit.,3c) $[\alpha]_D^{27}$-28°(c=0.83, MeOH)).