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A CONVERGENT SYNTHESIS OF OPTICALLY ACTIVE ASPYRONE.

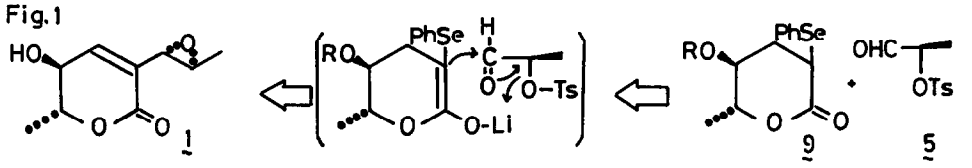
Takeyoshi Sugiyama,* Tetsuya Murayama and Kyohei Yamashita.
Department of Agricultural Chemistry, Faculty of Agriculture,
Tohoku University, Aoba-ku Sendai 981, Japan.

Abstract: Aspyrone (1) was elabolated in an optically pure form by the key reaction involving a nucleophilic addition of δ-lactone enolate to 2-tosyloxy-aldehyde and a subsequent in situ formation of epoxide.

Through the recent works on the biologically active 5-oxygenated dihydropyran-2-ones,[1] our interests were directed toward the chiral synthesis of the more complicated congener aspyrone (1), one of antibiotics isolated from the culture broth of Aspergillus species.[2] 1 has a characteristic structural feature arising from the skeletal rearrangement on its biosynthetic pathway.[3] Its absolute stereochemistry was determined as 5S,6R,1'S,2'S by the X-ray crystallographic and degradative works.[4]

In this paper, we wish to report the first total synthesis of optically active aspyrone (1). As illustrated in Fig. 1, we anticipated a tandem nucleophilic addition of δ-lactone enolate to 2-tosyloxypropanal and subsequent ring closure to epoxide as a key step for building up the target skeleton. Then the most preferable intermediates would be (R)-1-formylethyl p-toluenesulfonate (5) and (5S,6R)-5-t-butyldimethylsiloxy-6-methyl-3-phenylselenotetrahydro-2H-pyran-2-one (9).

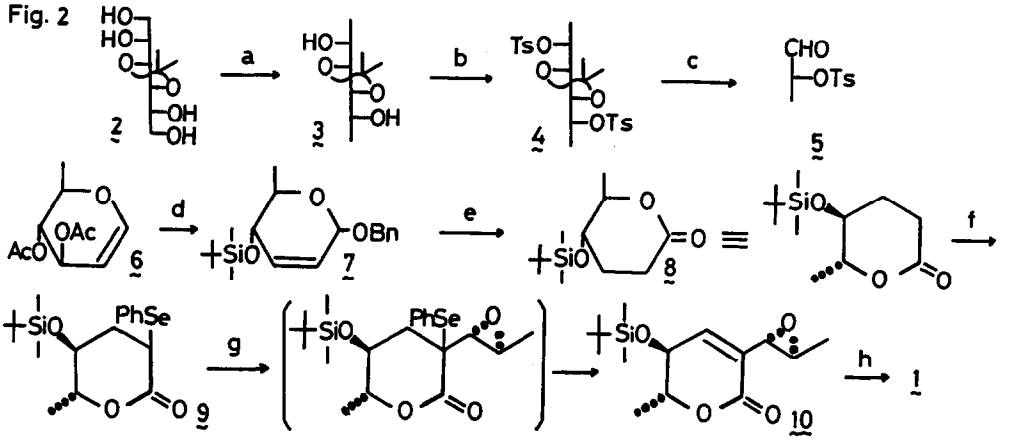
Fig.1



As shown in Fig. 2, 5 was derived from 3,4-O-isopropylidene-D-mannitol (2).[5] Tosylation of terminal hydroxyl groups and reduction with lithium aluminum hydride gave 3, which was re-esterified with tosyl chloride to 4 (mp 91.5℃). Deprotection of 4 and oxidation with sodium periodate gave a labile 5.[6] For the another chiral segment 9, D-rhamnal diacetate (6)[7] was utilized as a readily available precursor. Ferrier reaction[8] on 6 afforded 2,3-unsaturated glycoside, which was saponified and re-protected as t-butyldimethylsilyl ether (7). Successive hydrogenation and debenzylation of 7, followed by oxidation with pyridinium dichromate gave δ-lactone (8, mp 68-69℃, $[\alpha]_D$ +74.6° ($CHCl_3$)). Phenylselenylation on 8 afforded diastereomeric mixture of 9. At the convergent step, α-phenylseleno-δ-lactone (9) was successively treated with lithium hexamethyldisilazide and then with 5 at -78℃. The crude reaction product was oxidized with hydrogen peroxide and shaken with aqueous sodium hydrogen carbonate to yield 5-protected aspyrone (10, mp 71-71℃, $[\alpha]_D$ +40° ($CHCl_3$)) bearing the desired trans-epoxide in a 61 % yield in 3 steps. Careful investigation

of the mother liquor of 10 revealed the presence of less than 0.2 % of an isomeric cis-eoxide as barely detected by NMR spectroscopy.[9] Deprotection of 10 with fluoride anion provided the pure aspyrone (1, mp 112-112.5℃ (lit.[3b] 110-112℃), $[\alpha]_D$ -10.1° (lit.[3b] -10.5° ($CHCl_3$)). Its spectral properties were quite identical with those of natural one.

Fig. 2



(a)i)TsCl/py,ii)LAH(89%); (b)TsCl-Et_3N (93%); (c)i)TFAaq.(82%),ii)$NaIO_4$(86%); (d)i) $PhCH_2OH$-$SnCl_4$(95%),ii)K_2CO_3,iii)TBDMSCl-imidazole(98%);(e)i)H_2/Pd-C(84%),ii)PDC(85%); (f)LDA,PhSeCl(60%); (g)i)Li-HMDS,5,ii)H_2O_2,iii)$NaHCO_3$aq.(61%); (h)TBAF-PhCOOH(50%).

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References and notes.

1) T. Murayama, T. Sugiyama, and K. Yamashita, Agric. Biol. Chem., 51, 2055 (1987), and references cited therein. 2) (a) S. D. Mills and W. B. Turner, J. Chem. Soc. (C), 1967, 2242. (b) S. Natori, S. Sasaki, H. Kurata, S. Udagawa, M. Ichinoe, M. Saito, and M. Umeda, Chem. Pharm. Bull., 18, 2259 (1970). (c) W. Rosenbrook, Jr. and R. E. Carney, Tetrahedron Lett., 1970, 1867. (d) J. H. Moore, T. P. Murray, and M. E. Marks, J. Agric. Food Chem., 22, 697 (1974). 3) (a) T. Simpson and J. S. E. Holker, Tetrahedron Lett., 1975, 4693. (b) R. J. Copeland, R. A. Hill, D. J. Hinchcliffe, and J. Staunton, J. Chem. Soc. Perkin Trans. I, 1984, 1013. (c) R. G. Bereton, M. J. Garson, and J. Staunton, J. Chem. Soc. Perkin Trans. I, 1984, 1027. 4) M. J. Garson, J. Staunton, and P. G. Jones, J. Chem. Soc. Perkin Trans. I, 1984, 1021. 5) L. Wiggins, J. Chem. Soc., 1945, 13. 6) On standing in the air, 5 changes readily to its hydrate form. 7) D. B. Tulshian and B. Fraser-Reid, J. Am. Chem. Soc., 103, 474 (1984). 8) P. Bhate, D. Horton, and W. Priebe, Carbohyd. Res., 144, 331 (1985). 9) Recovered product (ca. 0.4 %) was deprotected, acetylated and analyzed by NMR (270 MHz). It contained about 40 % of cis-epoxide ($\delta_{2'H}$ 3.37, $J_{1'-2'}$ =4.1 Hz). For trans-epoxide (aspyrone acetate): $\delta_{2'H}$ 2.80, $J_{1'-2'}$ =1.8 Hz.

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