STEREOSELECTIVE TOTAL SYNTHESIS OF OPTICALLY ACTIVE TRANS- AND CIS-BURSERAN. DETERMINATION OF THE STEREOCHEMISTRY OF NATURAL ANTITUMOR BURSERAN

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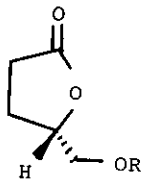
Abstract —— Optically pure trans- and cis-burseran were synthesized stereoselectively from (R)-(+)-β-piperonyl-γ-butyrolactone (2). Both compounds gave satisfactory ^{13}C NMR spectra. By comparing their behavior on gas chromatography, the naturally occurring burseran characterized as an antitumor agent was determined to be the trans-isomer.

As part of continuing studies directed towards the asymmetric total synthesis of antileukemic lignan lactones based on the novel approach to use easily available optically active γ-butyrolactone derivative (1) as a chiral synthon, we have reported the successful syntheses of optically active key intermediates (R)-(+)- and (S)-(-)-2 and their application to the total syntheses of some optically active lignan lactones including, for example, (-)- and (+)-podorhizon, (-)- and (+)-deoxypodorhizon, (-)-hinokinin, (-)-isodeoxypodophyllotoxin, and (-)-isostegane.[1~4]

Burseran was isolated as an antitumor compound from Bursera Microphylla (Burseraceae) and has been characterized as a lignan, 3-(3,4-methylenedioxybenzyl)-4-(3',4',5'-trimethoxybenzyl)tetrahydrofuran.[5] Although the synthetic study in order to determine the stereochemistry of burseran has been undertaken, the synthetic burseran obtained was a mixture of the trans- and cis-isomer (3 and 4). Gas



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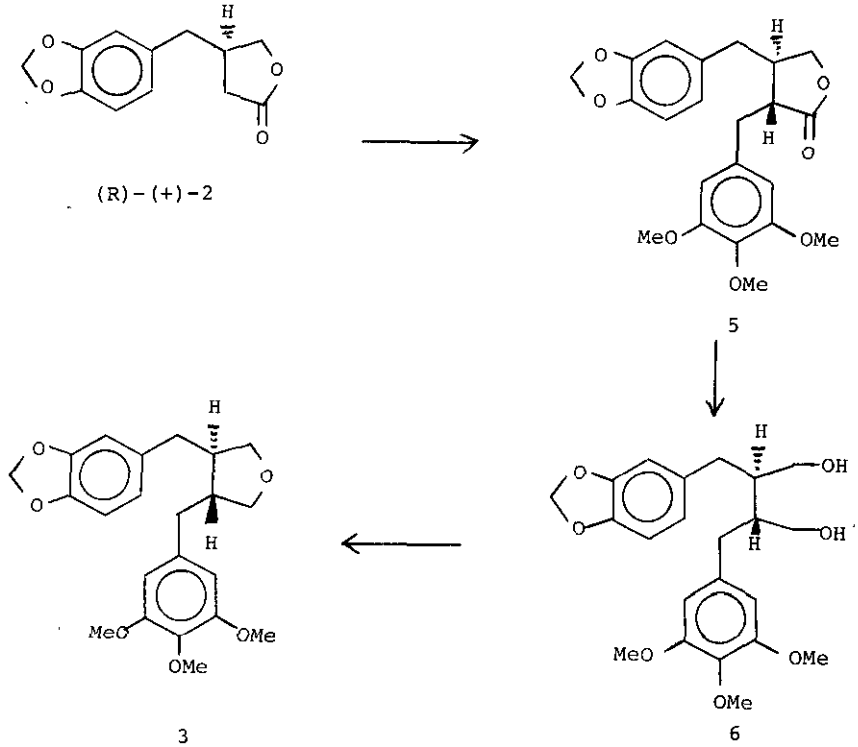
chromatographic analysis, however, showed that the natural product had a retention time identical to that component of the synthetic mixture which moved faster.[6]

As this gas chromatographic behavior is the only available data to determine the diastereomeric configuration of natural burseran, it is highly necessary to achieve a new synthetic route to obtain trans- as well as cis-isomer in unequivocal way.

In the present study, we describe the stereoselective total synthesis of (-)-trans- and (+)-cis-burseran from the key intermediate (R)-(+)-2 and also the determination of the stereochemistry of the naturally occurring antitumor burseran to be the trans-isomer based on the gas chromatographic analysis.

(-)-trans-Burseran (3) was synthesized as shown in Cahrt I. The key intermediate (R)-(+)-2 was alkylated with 3,4,5-trimethoxybenzyl bromide (LDA, THF, -78°C) to give stereoselectively (-)-deoxypodorhizon (5) in 83% yield,[7] which was reduced with lithium aluminum hydride (THF) to afford the trans-diol (6) ($[\alpha]_D^{20}$ -29.9° ($CHCl_3$), mp 95~96°C) in 84% yield. Treatment of 6 with p-TsCl in pyridine

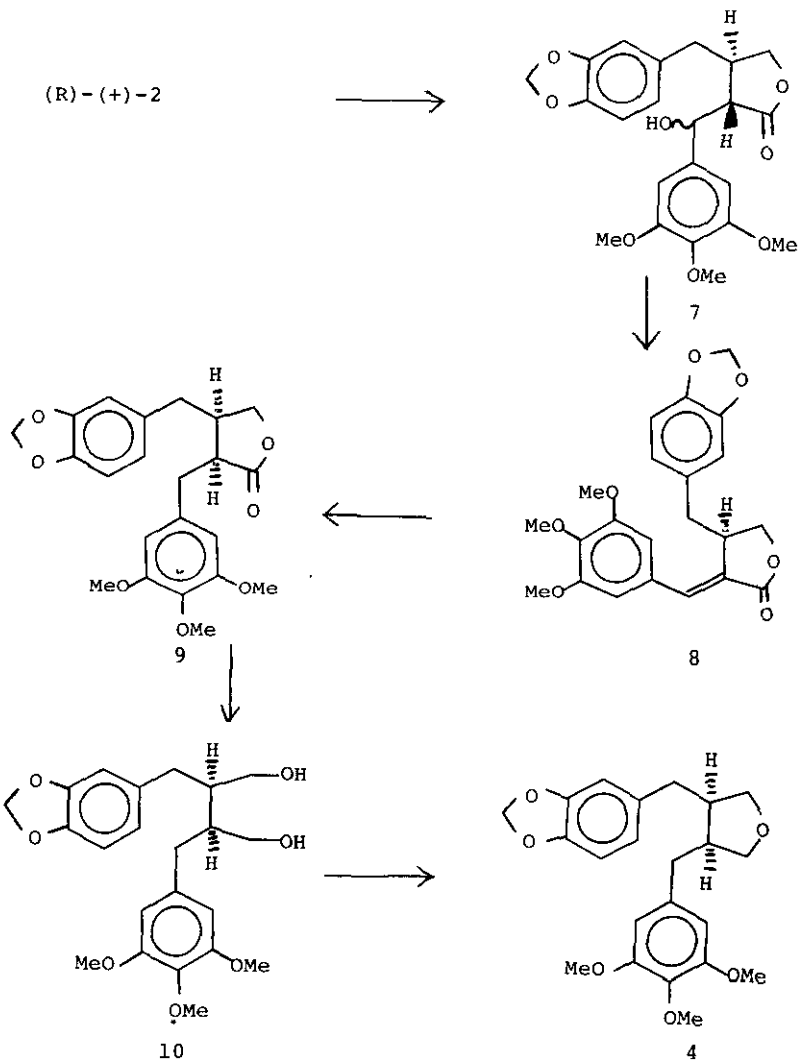
Chart I



(-23°C, 4 h; reflux 1.5 h) gave, after column chromatography (SiO_2, $Et_2O/CHCl_3$ =1/4), (-)-trans-burseran (3) ($[\alpha]_D^{20}$ -34.8° ($CHCl_3$)) in 72% yield. IR and MASS spectra of this synthetic 3 are identical with the reported spectra of natural burseran.[5,8]

(+)-cis-Burseran (4) was synthesized stereoselectively as shown in Chart II. The mixture of the crude hydroxyalkylation products (7) prepared from (R)-(+)-2,[4]

Chart II

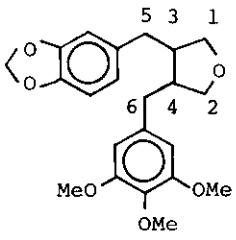


was tosylated (n-BuLi, p-TsCl, THF, -78~25°C, 3 h) followed by the treatment with $KOBu^t$ in methanol to give (-)-anhydropodorhizol (8) ($[\alpha]_D^{21}$ -54.1° ($CHCl_3$), lit.,[9] $[\alpha]_D^{21}$ -55.2° ($CHCl_3$)) in 80% overall yield. Catalytic hydrogenation of 8 over 5% Pd-C in acetic acid gave, after column chromatography (SiO_2, $Et_2O/CHCl_3$=1/99), (+)-cis-dihydroanhydropodorhizol (9) containing trans-isomer (5) (ca. 30%) in 63% yield. Lithium aluminum hydride reduction of the mixture in THF gave, after careful separation using PTLC (SiO_2, $Et_2O/CHCl_3$=1/1), the pure cis-diol (10) ($[\alpha]_D^{20}$ +9.65° ($CHCl_3$)) and the trans-diol (6), in 50 and 15% yields respectively. By the same way with that of the preparation of the trans isomer, the cis-diol (10) was converted to (+)-cis-burseran (4) ($[\alpha]_D^{20}$ +5.4° ($CHCl_3$)) in 60% yield. IR and MASS spectra of this synthetic (+)-cis-burseran are also identical with the reported spectra of the natural burseran.[5]

These trans- and cis-burseran gave the satisfactory ^{13}C NMR spectra as shown in Table. It was expectedly shown that the peaks of the cis-compound were in higher field than those of the trans-isomer.

Table. ^{13}C NMR of 3 and 4

Carbon	3(trans)ppm	4(cis)ppm
1(or2)	73.2(T)	72.0(T)
2(or1)	73.2(T)	71.9(T)
3(or4)	46.6(D)	43.8(D)
4(or3)	46.3(D)	43.6(D)
5(or6)	39.9(T)	33.9(T)
6(or5)	39.2(T)	33.4(T)



JEOL FX100. TMS as an internal standard. $CDCl_3$ as a solvent. The figures in parenthesis are the multiplicities in the case of off resonance.

Finally it became clear from the gas chromatographic analysis using the same type column as reported before[6,11] that the synthetic trans-isomer moved faster than the cis-isomer.[12] Therefore it is concluded that the natural antitumor burseran is trans-burseran (3).[6] However, since the optical rotation value of the natural burseran is not available,[13] the absolute stereochemistry of burseran still remains unknown.

The successful stereoselective total synthesis of (-)-trans- and (+)-cis-burseran from (R)-(+)-2, as well as the reported synthesis of (S)-(-)-2,[1] holds promise for the asymmetric total synthesis of natural burseran from the chiral synthon (1).

Biological activities of synthetic burserans will be reported in future.[14]

Acknowledgement

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References and Notes

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5. J. R. Cole, E. Bianchi, and E. R. Trumbull, J. Pharm. Sci., 58, 175 (1969).
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7. Satisfactory spectral (NMR, IR, and MASS) or analytical data were obtained for all compounds.
8. These spectra are also identical with those of the antipodal (+)-trans-burseran, which was previously synthesized applying the new method from the chiral butenolide. See reference 3.
9. M. Kuhn and A. von Wartburg, Helv. Chim. Acta, 50, 1546 (1967).
10. Isomerization of the initial cis-product into the trans-isomer would occurred during the hydrogenation, or during the removal of acetic acid. See reference 9.
11. Stainless column, 1 m, 15% QF 1 on diasolid A, 258°C, carrier gas N_2 1 Kg/cm^2.
12. Under the condition cited in reference 11, the retention times of the trans- and cis-burseran were 1.5 and 2.2 min respectively.
13. More information of natural burseran from Drs. J. R. Cole and E. R. Trumbull was not available. See references 5 and 6.
14. Studies are now in progress by Professor Den-ichi Mizuno and his coworkers of Faculty of Pharmaceutical Sciences, University of Tokyo.

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