Asymmetric Total Synthesis of the Antileukaemic Lignans (+)-*trans*-Burseran and (−)-Isostegane

By KIYOSHI TOMIOKA, TSUNEO ISHIGURO, and KENJI KOGA*

(*Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo* 113, *Japan*)

Summary (−)-Isostegane and (+)-*trans*-burseran were synthesized by a highly specific asymmetric pathway from a chiral butenolide.

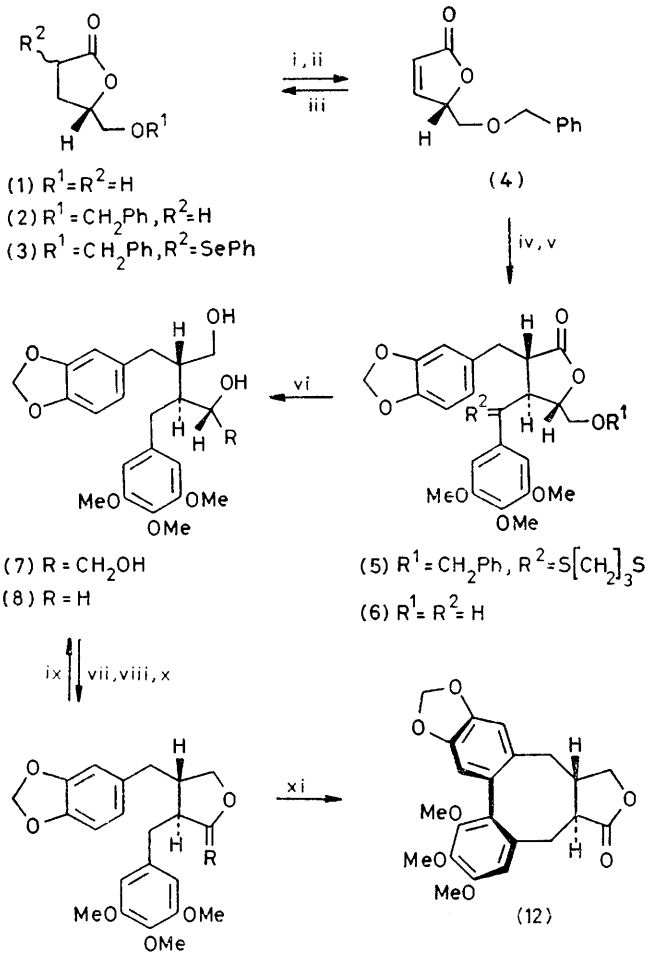
As part of a continuing study directed towards the asymmetric total synthesis of antileukaemic lignan lactones,[1] we describe here the total synthesis of the antileukaemic lignans (+)-*trans*-burseran (**9**)[2] and (−)-isostegane (**12**) having the steganacin skeleton[3] by a highly specific asymmetric pathway from the easily available chiral butyrolactone (**2**) as shown in the Scheme.

The key intermediate, the chiral butenolide (**4**) {$[\alpha]_D^{20}$ −107° (ethanol)} was prepared in two steps from (**2**) in 50% yield.† Compound (**4**) was confirmed to be optically pure by its catalytic hydrogenation into (**1**),[4] whose optical rotation value showed that no racemization had occurred. Conjugate addition[5] of the trimethoxybenzaldehyde dithioacetal anion to (**4**) followed by quenching with piperonyl bromide gave (**5**) {$[\alpha]_D^{20}$ +1·78° (chloroform), *ca.* 95% pure} in 96% yield. Reduction of (**5**) with Raney nickel afforded, after careful chromatography (SiO_2, ether), the optically pure lactone (**6**) {$[\alpha]_D^{20}$ +63·5° (ethanol), 57%} and an isomer {$[\alpha]_D^{20}$ −12·2° (ethanol), 1%}. Although the structure of this isomer has not been determined as yet, comparison of ^{13}C n.m.r. spectra shows that this compound is a stereoisomer of (**6**). The structure and optical purity of (**6**) were confirmed by its conversion into (+)-deoxypodorhizon (**11**) the optical antipode of the naturally occurring (−)-compound.[6] This means that conjugate addition of the anion to (**4**) proceeds in a highly specific asymmetric manner from the β-side of (**4**) without any base induced racemization of (**4**).

Reduction of (**6**) with $LiAlH_4$ followed by oxidation with sodium metaperiodate to remove the original chiral centre and to transfer the position of the carbonyl group gave the hemiacetal (**10**) {$[\alpha]_D^{20}$ +48·1° (ethanol)} in good yield. Collins oxidation of (**10**) gave optically pure (+)-deoxypodorhizon (**11**) {$[\alpha]_D^{25}$ +21·3° (chloroform)} in 95% yield. I.r., ^1H n.m.r., ^{13}C n.m.r. spectra and the absolute optical rotation value of (**11**) were identical with those of natural (−)-deoxypodorhizon.[6]

Non-phenolic oxidative coupling of (**11**) afforded (−)-isostegane (**12**) {m.p. 169—170 °C, $[\alpha]_D^{23}$ −161° (chloroform)} which was optically pure. ^1H and ^{13}C n.m.r. spectra of optically active (**12**) were identical with those of the racemic material prepared by the reported method.[6]

Reduction of (**11**) with $LiAlH_4$ gave the *trans* diol (**8**) {m.p. 94·5—95·5 °C, $[\alpha]_D^{20}$ +31·6° (chloroform)} in 77% yield. Treatment of (**8**) with toluene-*p*-sulphonyl chloride in pyridine afforded (+)-*trans*-burseran (**9**) {$[\alpha]_D^{20}$ +37·5° (chloroform)} in 84% yield. I.r. and mass spectra of synthetic (**9**) were not distinguishable from those reported for natural burseran.[2]



SCHEME. Reagents: i, Lithium di-isopropylamide, $(PhSe)_2$ tetrahydrofuran (THF), 59%. ii, $NaIO_4$, aq. MeOH, 85%. iii, 5% Pd-C, H_2, EtOH, 84%. iv, Lithio trimethoxybenzaldehyde dithioacetal, piperonyl bromide, THF, 96%. v, Raney nickel, EtOH, 57%. vi, $LiAlH_4$, THF, 98%. vii, $NaIO_4$, aq. Bu^tOH, 85%. viii, CrO_3, 2 C_5H_5N, CH_2Cl_2, 95%. ix, $LiAlH_4$, THF, 77%. x, *p*-$MeC_6H_4SO_2Cl$, pyridine, 84%. xi, VOF_3, CH_2Cl_2–CF_3CO_2H, 41%.

† Satisfactory spectral and analytical data were obtained for all new compounds.

The first successful, highly specific asymmetric total synthesis of (−)-isostegane and (+)-*trans*-burseran indicates that the syntheses of other pharmacologically active lignans in optically pure states can be achieved.

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