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STUDIES DIRECTED TOWARDS THE ASYMMETRIC TOTAL SYNTHESIS OF ANTILEUKEMIC LIGNAN LACTONES. SYNTHESIS OF OPTICALLY PURE KEY INTERMEDIATE AND ITS UTILITY

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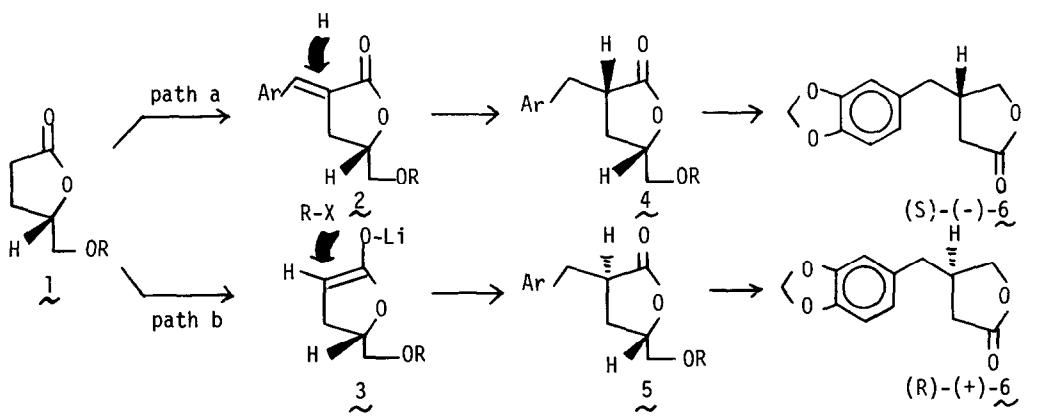
Summary: By the self-immolative asymmetric synthesis, optically pure key intermediate β-piperonyl-γ-lactone (R)-(+)-6 was found to be prepared in reasonable yield from the easily available chiral γ-lactone synthon (1) which had been also reported to give an antipode (S)-(-)-6. The optically pure (R)-(+)-6 was shown to be converted successfully into several optically pure natural lignan lactones.

We have recently described a new self-immolative[1] asymmetric synthesis leading to optically active lignan lactone (-)-podorhizon (an antipode of natural 10) based on the use of easily available chiral γ-lactone (1) as a chiral synthon.[2] The key intermediate (S)-(-)-6 for the above synthesis has the same configuration with steganacin type lignan lactone.[3] On the other hand, the antipode (R)-(+)-6 is required as the key intermediate for the synthesis of numerous naturally occurring lignan lactones such as podophyllotoxin[4] and hinokinin[5]. Because of the reason cited above, it is highly desirable for the synthesis of pharmacologically potent lignan lactones to devise a method by which both enantiomers (S)-(-)- and (R)-(+)-6 can be obtained selectively from the same chiral synthon (1) which is easily available from L-glutamic acid.

Our previous publication[2] shows clearly that palladium catalysed hydrogenation of 2 (R=CH_2Ph) took place preferentially from the opposite side to the benzyloxymethyl group to afford 4 (R=H) as a major product, which was successfully converted to (S)-(-)-6 (path a). Assuming



that alkylation of 1 with piperonyl bromide would also occur preferentially from β side as shown in 3 as in the case of stereoselective hydrogenation of 2, it is highly probable that the major product would be 5 which could be converted to (R)-(+)-6, an antipode of (S)-(-)-6 (path b). We now describe our results on this approach to (R)-(+)-6 and its usefulness as a key intermediate for the synthesis of optically active natural lignan lactones.

The chiral lactone 1 ($R=CPh_3$)[6] having more bulky trityloxymethyl group which is anticipated to give better stereoselectivity in the alkylation step than benzyloxymethyl group, prepared from 1 (R=H)[7] and trityl chloride in pyridine, was alkylated (LDA, piperonyl bromide, THF, -78°C) to give 5 ($R=CPh_3$)[6a] as a diastereomeric mixture. Lithium aluminum hydride reduction of 5 followed by hydrogenation (5% Pd-carbon, $PdCl_2$, EtOH) gave the crystalline triol (8)[6a] (mp 82-85°C, $[\alpha]_D^{20}$ -18.1° (c=0.930, EtOH)) as a diastereomeric mixture. According to the previously reported procedure,[2] this triol (8) was converted to (+)-podorhizon (10) ($[\alpha]_D^{21}$ +45.7° (c=0.60, $CHCl_3$), lit.,[8] $[\alpha]_D^{21}$ +79.5° (c=0.588, $CHCl_3$))[6a] via 9 and 6 in order to analyze the stereochemistry of the alkylation step. From the optical rotation value of the above 10, it became clear that 6 obtained above had R-configuration and was 58% optically pure. It means that, as was expected, alkylation of 1 ($R=CPh_3$) with piperonyl bromide took place preferentially from β side to give 5 ($R=CPh_3$) and 4 ($R=CPh_3$) in the ratio of 79 to 21. Enantioenrichment of 10 obtained above in 58% optically pure state was successfully achieved by recrystallization from MeOH to give optically pure 10 of mp 128-130°C (lit.,[8] 129-130°C), $[\alpha]_D^{21}$ +78.5° (c=0.560, $CHCl_3$).

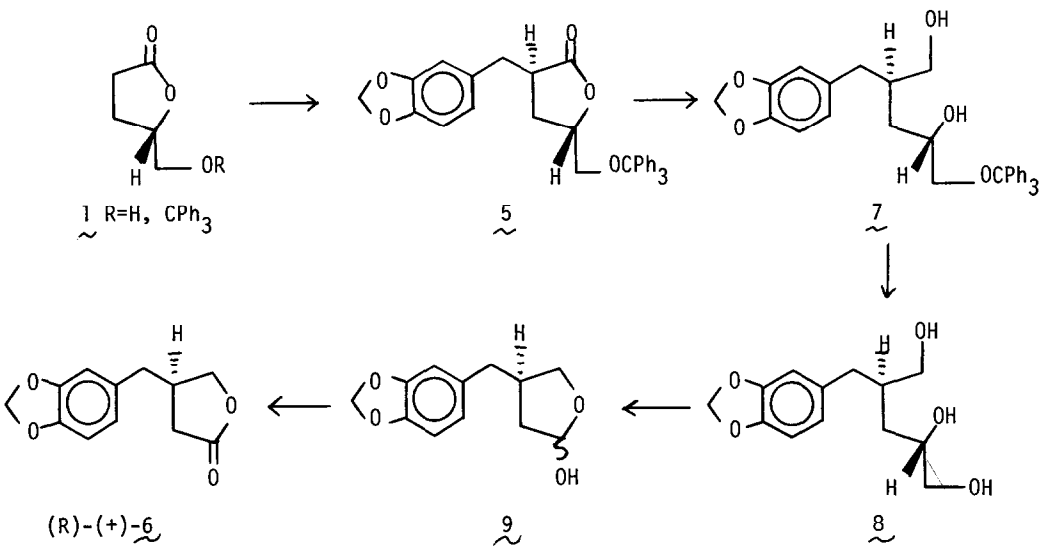
Further studies to obtain the optically pure key intermediate (R)-(+)-6 were also undertaken. Recrystallization of the triol (8), obtained above as a diastereomeric mixture, from $CHCl_3$ is found to give the diastereomerically pure triol (8)[6] of mp 90.5-91.5°C, $[\alpha]_D^{20}$ -20.9° (c=0.412, EtOH), which was confirmed to be optically pure by the conversion into natural lignan lactones via the intermediate (R)-(+)-6 as described below. Practically the pure triol (8) was found to be synthesized in 60% overall yield from the chiral synthon (1, $R=CPh_3$) by simply recrystallizing the crude material obtained in three steps without any purification of every intermediates (5 and 7). The pure triol (8) was treated with $NaIO_4$ in aqueous tert-BuOH at room temperature, in order to remove the original chiral center and to transfer the carbonyl position, to give the hemiacetal (9) ($[\alpha]_D^{20}$ +20.3° (c=1.258, $CHCl_3$))[6a] in 98% yield. Collins oxidation of 9 gave the optically pure key intermediate (R)-(+)-6 ($[\alpha]_D^{20}$ +5.22° (c=1.13, $CHCl_3$), lit.,[8] $[\alpha]_D^{20}$ +4.8° (c=1.142, $CHCl_3$))[6a] in 89% yield, whose physical data were in good agreement with those of the reported degradation product (6) of natural (+)-podorhizon (10).[8]

Simple treatment of the optically pure (R)-(+)-6 with LDA in THF at -78°C for 20 min followed by addition of piperonyl bromide (-78°C, 4 hr) gave, after usual work-up and silica gel column chromatographic purification (2% Et_2O-$CHCl_3$), optically pure natural (-)-hinokinin (14) ($[\alpha]_D^{20}$ -35.1° (c=0.701, $CHCl_3$), lit.,[5] $[\alpha]_D^{20}$ -35° (c=1.00, $CHCl_3$))[6a] in 71% yield. By the same way, (R)-(+)-6 was converted to optically pure natural (-)-deoxypodorhizon (13)[9] ($[\alpha]_D^{25}$ -22.2° (c=0.410, $CHCl_3$), lit.,[10] $[\alpha]_D^{25}$ -21.6° (c=0.4, $CHCl_3$))[6a] in 83% yield.

Treatment of the anion of optically pure (R)-(+)-6, prepared above, with trimethoxybenzaldehyde at - 78°C for 2 hr gave, after PTLC (silica gel, 0.5% iso-PrOH-$CHCl_3$), (-)-podorhizol (11) ($[\alpha]_D^{21}$ -51.7° (c=0.944, $CHCl_3$), lit.,[8,11] $[\alpha]_D^{21}$ -51.8° (c=1.046, $CHCl_3$))[6a] and

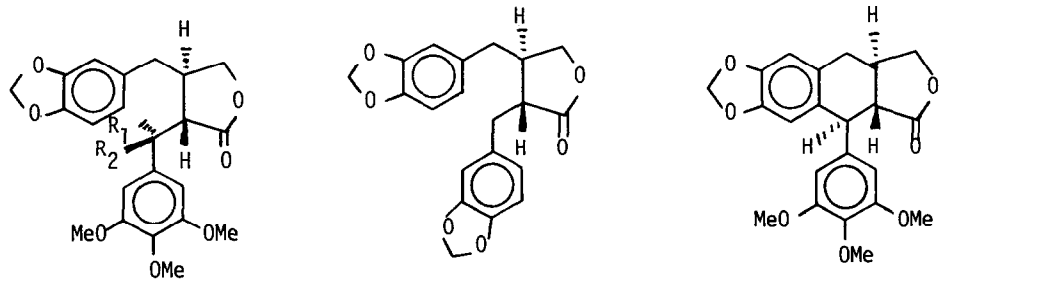
(-)-epipodorhizol (12) ($[\alpha]_D^{21}$ -32.3° (c=0.600, $CHCl_3$), lit.,[8] $[\alpha]_D^{21}$ -32.6° (c=0.628, $CHCl_3$))[6a] in 41 and 42% yields, respectively.

Optically pure (R)-(+)-6 was also converted (-)-isodeoxypodophyllotoxin (15) (mp 250-253°C, $[\alpha]_D^{21}$ -80.8° (c=0.624, $CHCl_3$), lit.,[8] mp 252-254°C, $[\alpha]_D^{21}$ -84.6° (c=0.614, $CHCl_3$))[6] via trifluoroacetic acid treatment of the crude hydroxyalkylation products (11 and 12) in 96% yield.[12]



1 R=H, CPh_3 5 7

(R)-(+)-6 9 8



10 R_1=R_2=O
11 R_1=H, R_2=OH
12 R_1=OH, R_2=H
13 R_1=R_2=H

14 15

Since Brown reported very recently the total synthesis of (±)-attenuol from the racemic 6,[13] our present synthesis of optically pure (R)-(+)-6 constitutes the formal total synthesis of naturally occurring (-)-attenuol.[14]

Further studies along this line towards the asymmetric total synthesis of antileukemic lignan lactones are now in progress in our laboratory.

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References and Notes

1. A special group of asymmetric syntheses are those in which a new asymmetric center is created by the transfer of asymmetry within the molecule. Such processes usually involve destruction of the original chiral center and have thus been termed "self-immolative" originally by Mislow. We are using this term when the original chiral center is destroyed after playing its role to create a new asymmetric center. cf. K. Mislow, Introduction to Stereochemistry, Benjamin, New York, 1966, p. 131.
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