AN EFFICIENT SYNTHESIS OF NATURAL (+)-NEOISOSTEGANE USING ASYMMETRIC HYDROGENATION CATALYZED BY A CHIRAL BISPHOSPHINE-RHODIUM(I) COMPLEX[1]

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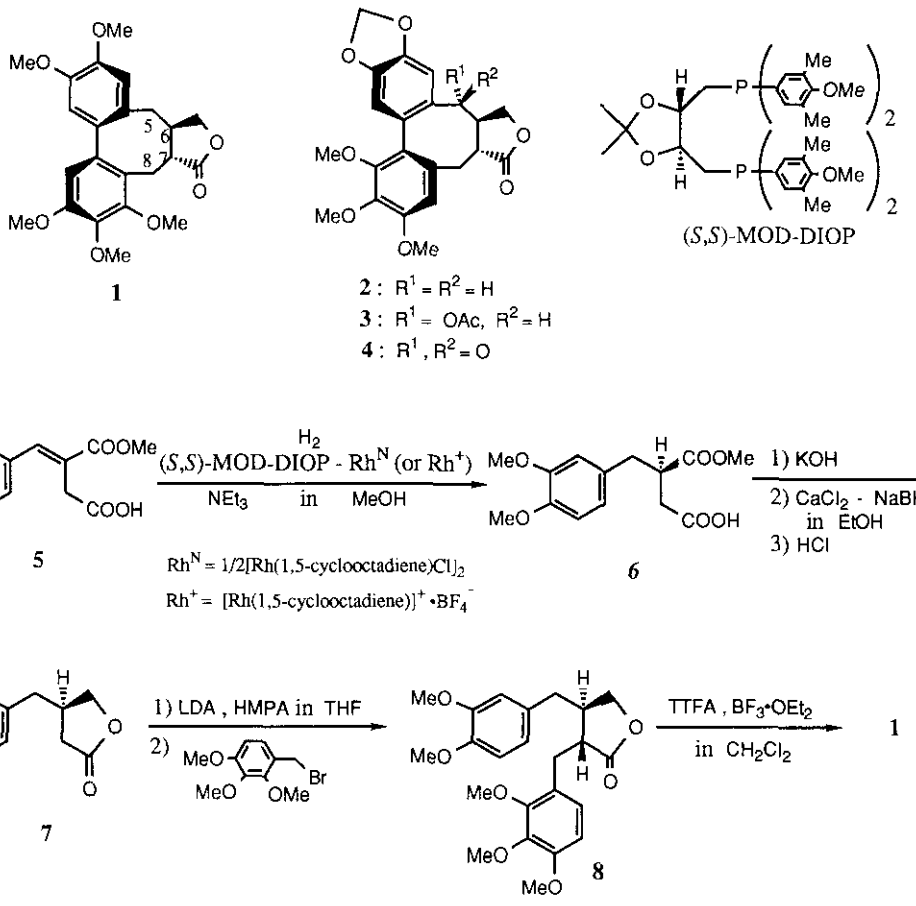
Abstract —— (+)-Neoisostegane, a natural lignan lactone was synthesized by utilizing a catalytic asymmetric hydrogenation of α-veratrylidenesuccinic acid half-ester with a (S,S)-MOD-DIOP-rhodium(I) as a key step, and the absolute configuration was determined to be (M,6R,7R).

(+)-Neoisostegane (1) was isolated by Robin[2] and Sneden[3] from Steganotaenia araliacea (Apiaceae) as one of the chemical constituents having some cytotoxity, and the structure was elucidated to be a new type of a bisbenzocyclooctadiene lignan lactone from its ^1H and ^{13}C nmr spectra and by chemical correlation with known steganes. However, the absolute configuration was not reported.
The total synthesis of racemic 1 and its analogues was recently reported by Robin[4] via intramolecular non-phenolic oxidative biaryl coupling of dibenzylbutanolides with ruthenium(IV) tetrakis(trifluoroacetate). In connection with natural bisbenzocyclooctadiene lignan synthesis, the syntheses of optically active stegane (2), steganacin (3), and steganone (4) were reported by Koga et al.[5,6] or Meyers[7] via many reaction steps from L-glutamic acid or via a biaryl coupling of a chiral aromatic oxazoline.
This communication describes a simple and efficient synthesis of natural (+)-neoisostegane (1) using the catalytic asymmetric hydrogenation of α-veratrylidenesuccinic acid half-ester (5) with a rhodium(I) complex of (4S,5S)-(-)-4,5-bis[bis-(4'-methoxy-3',5'-dimethylphenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane ((S,S)-MOD-DIOP) as a key reaction.



Scheme 1

The present synthetic route of natural neoisostegane (1) is outlined in Scheme 1. The key asymmetric hydrogenation of α-veratrylidenesuccinic acid half-methyl ester (5) was carried out in methanol in the presence of triethylamine at 30 °C under 1 atm of hydrogen using a neutral rhodium(I) complex (Rh^N=1/2[Rh(1,5-cyclooctadiene)Cl]$_2$) of (S,S)-MOD-DIOP (0.2 mol% to the substrate) as a catalyst in the manner reported previously.[8] The chemical yield of the product (6) was quantitative and the optical yield was 94% ee (determined by hplc of its mono-morpholine amide derivative). When the asymmetric hydrogenation was carried out at 50 °C under 5 atm of hydrogen in the presence of a cationic rhodium(I) complex (Rh^+= [Rh(1,5-cyclooctadiene)]$^+$•BF_4^-) of (S,S)-MOD-DIOP (0.05 mol% to the substrate), the product (6) was obtained quantitatively in 96% ee. Single recrystallization

from isopropyl ether gave the pure (R)-enantiomer (6) (≥ 99% ee) in about 80% isolated yield. After conversion of the half-ester (6) to β-veratryl-γ-butyrolactone (7) by calcium borohydride reduction,[8] the lactone (7) was lithiated with lithium diisopropylamide (LDA) at -60 °C in tetrahydrofurane (THF) in the presence of hexamethylphosphoric triamide (HMPA), and allowed to react with 2,3,4-trimethoxybenzyl bromide, affording a dibenzylated lactone (8) as a syrup, $[\alpha]_D^{22}$ -48.6° (c 1.23, $CHCl_3$), in 96% yield after purification by column chromatography (SiO_2, toluene-AcOEt(3:1)). Non-oxidative coupling of the lactone (8) with thalium(III) trifluoroacetate (TTFA) in the presence of boron trifluoride etherate, followed by chromatography (SiO_2, toluene-ethyl acetate (4:1)) and recrystallization (isopropyl ether) gave (+)-neoisostegane (1) as pure prisms, mp 156-157 °C, $[\alpha]_D^{19}$ +107.7° (c 0.51, $CHCl_3$) in 48% yield. Although the product showed a melting point and an optical rotation value different from the repoted values (mp 71-74 °C,[2] mp 107-108 °C,[3] $[\alpha]_D^{20}$ +65°±5 (c 0.35, $CHCl_3$)[2]), its ir (KBr, 1776 cm^{-1}), ^1H nmr (270 MHz, $CDCl_3$ δ: 1.91 (dd, 1H, J=13.2, 9.2 Hz), 2.02 (dd, 1H, J=12.8, 9.2 Hz), 2.22 (dddd, 1H, J=12.8, 11.4, 9.9, 6.6 Hz), 2.41 (dd, 1H, J=13.2, 9.9 Hz), 2.67 (d, 1H, J=13.2 Hz), 3.68 (d, 1H, J=13.2 Hz), 3.78 (dd, 1H, J=11.4, 8.4 Hz), 3.85 (s, 3H), 3.88 (s, 3H), 3.93 (s, 6H), 3.96 (s, 3H), 4.38 (dd, 1H, J=8.4, 6.6 Hz), 6.51 (s, 1H), 6.69 (s, 1H), 6.72 (s, 1H)), and ^{13}C nmr spectral data (67.8 MHz, $CDCl_3$ δ: 24.1, 34.2, 46.8, 49.7, 56.1, 60.8, 61.1, 69.9, 109.7, 112.1, 114.0, 126.6, 130.9, 132.4, 136.1, 141.9, 147.3, 148.9, 150.6, 151.5, 176.2) were in fair agreement with the reported values[2,3] for natural neoisostegane (1). Since the elemental analysis of our product also established the molecular formular which was well consistent with 1 (Anal. Calcd for $C_{23}H_{26}O_7$: C,66.65; H,6.32. Found: C,66.50; H,6.43), the natural product previously isolated was regarded as being optically or chemically impure. By inquiry to Prof. Robin, we were informed that the natural sample obtained in a very small quantity contained fatty materials as impurities. Thus, the physical data of our product could be regarded as the true ones of natural (+)-neoisostegane (1), and the absolute configuration was determined to be (M,6R,7R).

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