EFFICIENT SYNTHESIS OF NATURAL (+)-COLLINUSIN USING CATALYTIC ASYMMETRIC HYDROGENATION WITH A CHIRAL BISPHOSPHINE-RHODIUM(I) COMPLEX[1)]

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(+)-Collinusin, a natural lignan lactone, has been synthesized by using the asymmetric hydrogenation of a α-veratrylidenesuccinic acid half ester with a (S,S)-MOD-DIOP-rhodium(I) complex catalyst as a key reaction, and the absolute configuration of the C-3 has been determined to be R.

KEYWORDS collinusin; lignan lactone; asymmetric hydrogenation; catalyst; bisphosphine-rhodium(I) complex; enantioselective total synthesis

(+)-Collinusin[2a)] is one of the chemical constituents of Cleistanthus collinus (Roxb.), a highly poisonous plant. The structure was determined to be 2 by its chemical transformations and spectral data,[2)] and furthermore, by a synthesis of a racemic compound involving cyclization of a cinnamyl phenylpropiolate.[3)] However, the absolute configuration of C-3 was not clarified.

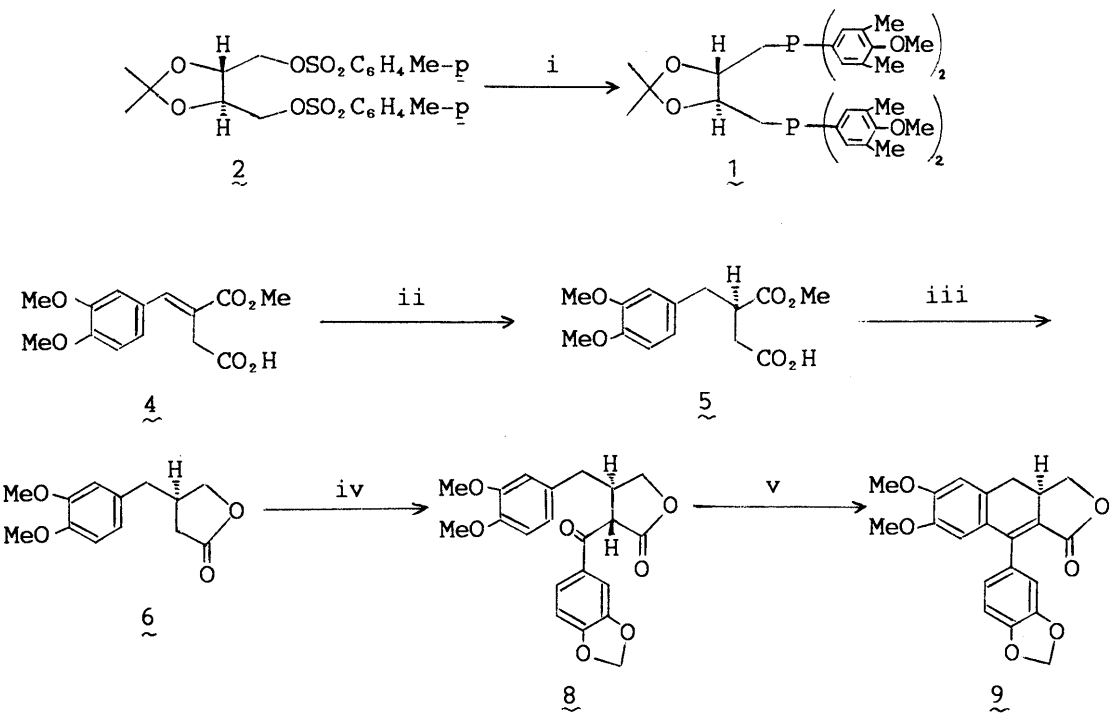
In connection with natural lignan synthesis, Brown[4)] and Koga[5)] reported the synthesis of many optically active lignans via the tedious optical resolution of α-arylmethylsuccinic acid half esters and via many reaction steps from L-glutamic acid.

We report here a very efficient synthesis of natural (+)-collinusin using the catalytic asymmetric hydrogenation of α-veratrylidenesuccinic acid half-ester (4) with a rhodium(I) complex of (4S,5S)-(-)-4,5-bis[bis(4′-methoxy-3′,5′-dimethyl-phenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane ((S,S)-MOD-DIOP, 1) as a key reaction.

In the previous papers, we reported the development of several chiral bisphosphine ligands, BCPMs,[6)] DIOCP,[7)] BPPMs,[8)] and DIOPs[9)] for efficient asymmetric hydrogenation. Among them, a modified DIOP, (R,R)-MOD-DIOP,[9a)] was found to show very high enantioselectivity in the hydrogenation of itaconic acid and its derivatives bearing β-aryl groups. The hydrogenation products were (S)-succinic acid derivatives which were useful intermediates for the non-natural antipode of lignans.

In order to synthesize natural lignans (R-form), we first prepared (S,S)-MOD-DIOP (1), mp 128.5-129.5°C, $[\alpha]_D^{20}$ -14.4° (c 1.02, benzene), in 65% yield by the reaction of (S,S)-ditosylate (2) with the lithium salt of diarylphosphine (3) under the conditions reported previously.[9a)]

Our present synthsis route of natural collinusin is outlined in Chart 1. The key asymmetric hydrogenation of 4 was carried out in the following manner. A mixture of (S,S)-MOD-DIOP (1) (2.4×10^{-2} mmol) and rhodium cyclooctadiene chloride dimer ($[Rh(COD)Cl]_2$) (10^{-2} mmol) in degassed methanol (5 ml) was stirred under an argon atmosphere for 0.5 h, giving a clear yellow solution of the neutral rhodium complex. The solution of the catalyst prepared was added to a mixture of 4 (10 mmol) and triethylamine (10 mmol) in degassed methanol (15 ml). The mixture was stirred at 30°C for 40 h under a



i) (p-MeO-m,m'-$Me_2C_6H_2)_2PH$ (3), n-BuLi, THF. ii) (S,S)-MOD-DIOP (1), $[Rh(COD)Cl]_2$, NEt_3, H_2, MeOH. iii) KOH, $CaCl_2$, $NaBH_4$, EtOH. iv) LDA, HMPA, ethyl carbonic-piperonylic anhydride (7), THF. v) HCl, MeOH.

Chart 1

hydrogen pressure of 1 atm. The usual work-up gave (R)-α-veratrylsuccinic acid monomethyl ester (5), $[\alpha]_D^{21}$ +23.8° (c 1.47, EtOH) in 97% yield. The optical yield was calculated as 88% ee on the basis of the maximum optical rotation $[\alpha]_D$ +27° (c 1.2, EtOH) for the pure (R)-enantiomer.[4a] The correct optical yield was determined to be 94% ee by high pressure liquid chromatography (HPLC) of its monomorpholine amide derivative on a chiral column, Chiralcel OC (Daicel), using isopropyl alcohol-hexane (1:1) as an eluent. Single recrystallization of the product from isopropyl ether gave the pure (R)-enantiomer (5), mp 99-100°C (lit.,[4a] mp 99-101.5 °C), $[\alpha]_D^{23}$ +26.1° (c 1.23, EtOH), ≥ 99% ee (by HPLC of its morpholine amide derivative). The potassium salt of the half-ester (5) was converted to β-veratryllactone (6) in 95% yield by reduction with calcium borohydride.[4a] The lactone (6) was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) in the presence of hexamethylphosphoramide (HMPA) at -60 °C, yielding the lithium enolate, which was allowed to react with a mixed anhydride (7). After quenching the reaction mixture with aqueous ammonium chloride, α-piperonyloylated lactone (8) was isolated in 70% yield by column chromatography (SiO_2, toluene-ethyl acetate (4:1)). Recrystallization from ethanol gave needles, mp 122-123°C, $[\alpha]_D^{24}$ +73.4° (c 1.08, $CHCl_3$). Dehydrative ring-closure of 8 was achieved by heating with methanolic hydrogen chloride, affording (+)-collinusin (9) (63% yield) which was purified by recrystallization from acetone. Its IR and ^1H NMR spectra, melting point (192.5-193.5°C), and optical rotation value ($[\alpha]_D^{25}$ +134.2° (c 1.01, chloroform)) were in good agreement with those of the reported natural (+)-collinusin[2] (mp 196°C, $[\alpha]_D$ +132.48° (c 2.04, chloroform)). Thus, the absolute configuration of C-3 of natural (+)-collinusin was determined to be R.

This is the first highly enantioselective total synthesis of a natural lignan such as (+)-collinusin by use of catalytic asymmetric hydrogenation in a key step. The present methodology using the catalytic asymmetric hydrogenation with (S,S)-MOD-DIOP-rhodium(I) complex can provide a very efficient synthesis route to other physiologically active lignans[10] in optically pure forms.

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