

EFFICIENT SYNTHESIS OF NATURAL (+)-COLLINUSIN USING CATALYTIC ASYMMETRIC HYDROGENATION WITH A CHIRAL BISPHOSPHINE-RHODIUM(I) COMPLEX¹⁾Toshiaki MORIMOTO,^a Mitsuo CHIBA,^b and Kazuo ACHIWA^{*,a}

School of Pharmaceutical Sciences, University of Shizuoka,^a 395 Yada, Shizuoka 422, Japan and Research Center, Toyotama Perfumery Co. Ltd.,^b Kyodo Building (Showa), 1-3-8 Honcho, Nihonbashi Chuo-ku, Tokyo 103, Japan

(+)-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 phenylpropionate.³⁾ However, the absolute configuration of C-3 was not clarified.

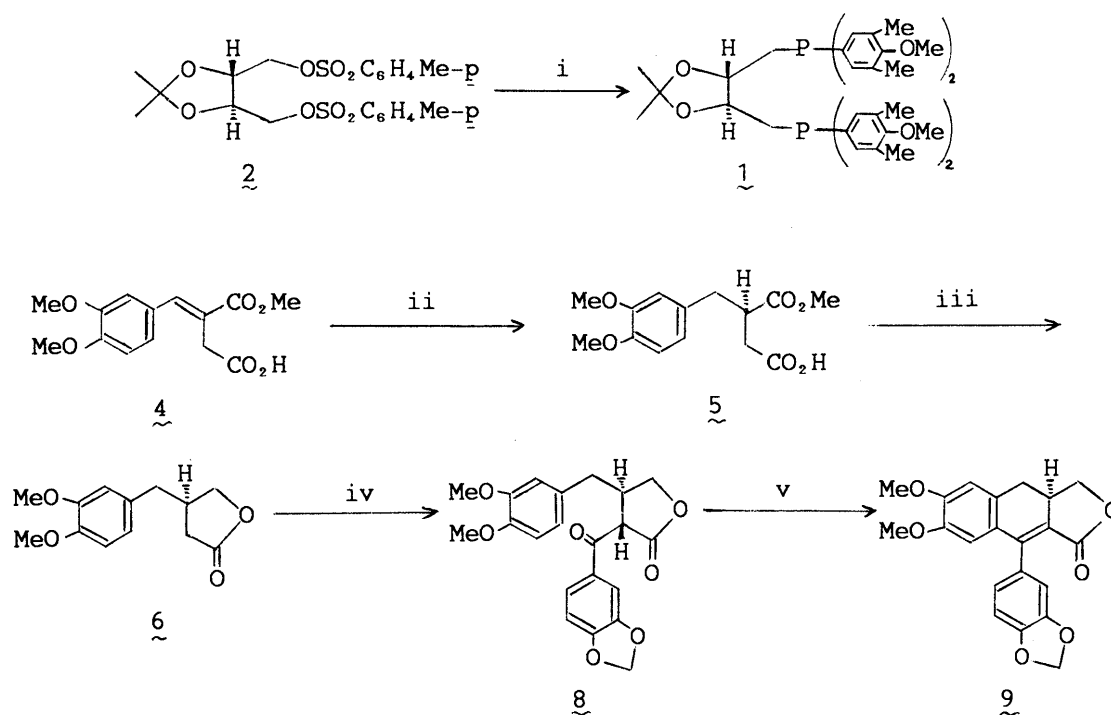
In connection with natural lignan synthesis, Brown⁴⁾ and Koga⁵⁾ reported the synthesis of many optically active lignans via the tedious optical resolution of α -arylmethylsuccinic acid half esters and via many reaction steps from L-glutamic acid.

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 DIOPs⁹⁾ 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 synthesis 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 ($[\text{Rh}(\text{COD})\text{Cl}]_2$) (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'-Me₂C₆H₂)₂PH (3), n-BuLi, THF. ii) (S,S)-MOD-DIOP (1), [Rh(COD)Cl]₂, NEt₃, H₂, MeOH. iii) KOH, CaCl₂, NaBH₄, 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), [α]_D²¹ +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 [α]_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 morpholine 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), [α]_D²³ +26.1° (c 1.23, EtOH), $\geq$ 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 (SiO₂, toluene-ethyl acetate (4:1)). Recrystallization from ethanol gave needles, mp 122–123°C, [α]_D²⁴ +73.4° (c 1.08, CHCl₃). 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 ([α]_D²⁵ +134.2° (c 1.01, chloroform)) were in good agreement with those of the reported natural (+)-collinusin²⁾ (mp 196°C, [α]_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 lignans¹⁰⁾ in optically pure forms.

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