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ASYMMETRIC TOTAL SYNTHESIS OF (-)-DEOXYPODOPHYLLOTOXIN[1]

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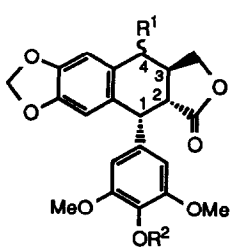
Abstract: An efficient total synthesis of (-)-deoxypodophyllotoxin has been achieved by employing the asymmetric hydrogenation of α-piperonylidene-succinic acid half ester with a rhodium(I) complex of (S,S)-MOD-DIOP as a key step.

Podophyllotoxin (1) and its analogues such as epipodophyllotoxin (2) and deoxypodophyllotoxin (3) are naturally occurring or modified, cytotoxic lignans,[2] and can serve as precursors to clinical antitumor agents, etoposide (4) and teniposide (5).[3] Although there have been many elegant syntheses of racemic podophyllotoxin (1) and its derivatives,[4] very few asymmetric total synthesis of these compounds has been reported.[5]

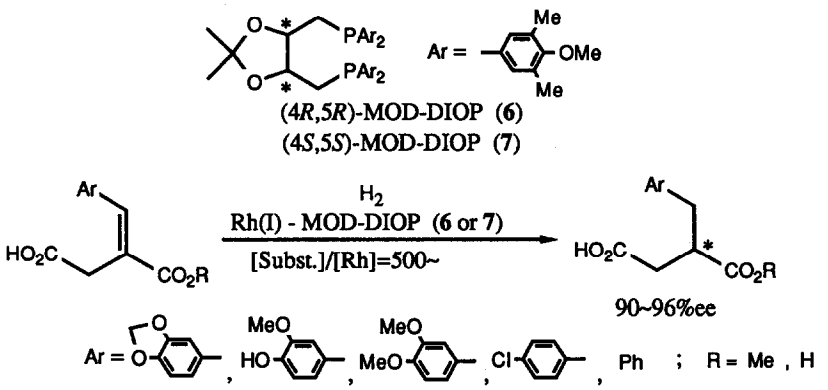
This communication describes an efficient total synthesis of (-)-deoxy-podophyllotoxin (3)[6] using an asymmetric hydrogenation of α-piperonylidene-succinic acid half-methyl ester (8) catalyzed by a rhodium(I) complex of (S,S)-MOD-DIOP (7).

In previous papers,[7,8] we reported that the rhodium(I) complex of a chiral bisphosphine, (R,R)- or (S,S)-MOD-DIOP (6 or 7) was a very efficient catalyst for the asymmetric hydrogenation of itaconic acid and its derivatives bearing β-aryl groups (Scheme 1). The optically active succinic acid derivatives thus obtained have been shown to be useful intermediates for the asymmetric synthesis of several types of lignans.[8,9] Then, these results prompted us to develop a new practical method for the synthesis of optically active podophyllum lignans.

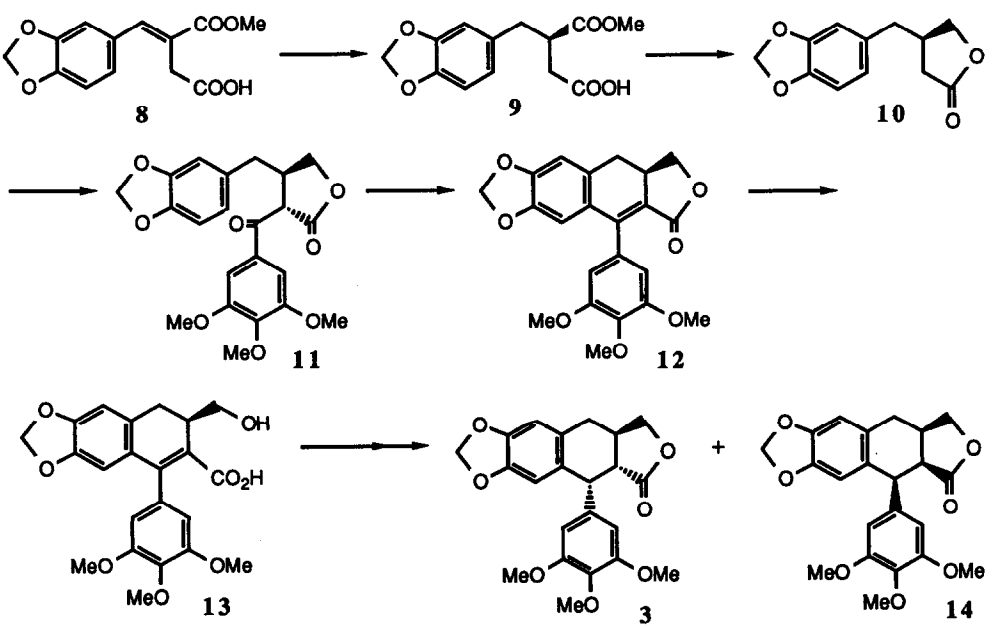


1: R^1 = α-OH, R^2 = Me
2: R^1 = β-OH, R^2 = Me
3: R^1 = H, R^2 = Me
4: R^1 = 4:6-O-ethylidene-β-D-glucopyranosyl-, R^2 = H
5: R^1 = 4:6-O-(2'-thenylidene)-β-D-glucopyranosyl-, R^2 = H

Our synthetic strategy of (-)-deoxypodophyllotoxin (3) was based on the asymmetric hydrogenation, followed by reductive lactonization, acylation, and dehydrative ring-closure to afford α-apopicropodophyllin (12). The catalytic hydrogenation of racemic 12 was well-known to yield the racemic product (14) of all-cis configurations,[10] and a modified method involving electroreduction of racemic 12 was reported to afford rac-deoxypicropodophyllin,[11] which would be convertible to 3 by metal enolation and succeeding kinetic controlled protonation.[12] Recently, Yamaguchi et al.[13] developed another convenient method for construction of 1,2-cis and 2,3-trans



Scheme 1



Scheme 2

configurations involving saponification of racemic 3,4-dihydronaphthalene lactones, followed by catalytic hydrogenation.

Our present synthetic route is shown in Scheme 2. The asymmetric hydrogenation of α-piperonylidenesuccinic acid half-methyl ester (8) was carried out at 30 °C for 40 h in methanol in the presence of triethylamine under 1 atm of hydrogen using the neutral rhodium(I) complex (0.2 mol% to the substrate) of (S,S)-MOD-DIOP (7) prepared just prior to use by mixing 1/2 [Rh(1,5-cyclooctadiene)Cl]$_2$ and 7 in methanol. Usual work-up gave (R)-α-piperonylsuccinic acid half-ester (9), $[\alpha]_D^{28}$ +27.1° (c 2.03, MeOH) in a quantitative yield. The optical yield was calculated as 89% ee on the basis of the maximum optical rotation value $[\alpha]_D^{20}$ +30.4° (c 2, MeOH).[9a] The correct optical yield was determined to be 93% ee by HPLC of its monomorpholine amide derivative on a chiral column, Chiralcel OC (Daicel), using isopropyl alcohol-hexane (1:1) as an eluent. Single recrystallization from isopropyl ether gave the pure (R)-enantiomer (9), mp 101-102 °C (lit.,[9a] 102-104 °C), $[\alpha]_D^{25}$ +28.5° (c 2.01, MeOH), 99% ee (determined by HPLC of its morpholine amide derivative). The half-ester (9) was converted by calcium borohydride-reduction[9a] to (R)-β-piperonyl-γ-lactone (10), bp 230-235 °C (bath temp.)/3 mmHg, $[\alpha]_D^{25}$ +4.8° (c 1.19, $CHCl_3$) (lit.,[9a] $[\alpha]_D^{20}$ +4.87° (c 0.87, $CHCl_3$)), in 97% yield. The lactone (10) was acylated with 3,4,5-trimethoxybenzoyl chloride in THF at -60 °C in the presence of HMPA after lithiation with LDA, affording (+)-podorhizon (11), mp 129-130 °C, $[\alpha]_D^{23}$ +79.6° (c 0.68, $CHCl_3$), 100% ee by HPLC (lit.,[14] mp 129-130°C, $[\alpha]_D^{21}$ +79.5° (c 0.588, $CHCl_3$)) in 53% yield after purification by chromatography and recrystallization. Dehydrative ring-closure of 11 by heating with methanolic hydrogen chloride gave (+)-γ-apopicropodophyllin (12), mp 285-286 °C, $[\alpha]_D^{27}$ +112.8° (c 0.63, $CHCl_3$), in 80% yield. Saponification of 12 with potassium hydroxide followed by acidification gave (-)-apopodophyllic acid (13), mp 284-285 °C, $[\alpha]_D^{24}$ -24.7° (c 0.65, $CHCl_3$), in 64% yield. Catalytic hydrogenation of 13 using 5% Pd on carbon under an initial hydrogen pressure of 20 atm gave an oily product, which was directly lactonized with DCC in chloroform, affording a mixture of lactones, 3 and 14. The mixture was separated by PTLC (silica gel, toluene : ethyl acetate= 4:1), followed by recrystallization from ethanol, giving pure (-)-deoxypodophyllotoxin (3) and (+)-isodeoxypicropodophyllin (14) in 37% and 25% yield, respectively. (-)-Deoxypodophyllotoxin (3) thus obtained showed a melting point 168-170 °C and an optical rotation value $[\alpha]_D^{25}$ -113.4° (c 0.50, $CHCl_3$), both of which were in good agreement with those of natural doxypodophyllotoxin (lit.,[6] mp 168-169 °C, $[\alpha]_D^{20}$ -115° (c 0.50, $CHCl_3$). Its IR and ^{1}H NMR spectral data were also in fair agreement with those of natural one. (+)-Isodeoxypicropodophyllin (14) showed a melting point 203.5-205.5 °C and an optical rotation value $[\alpha]_D^{27}$ +117.0° (c 0.53, $CHCl_3$).[15]

This is the first successful asymmetric total synthesis of (-)-deoxypodophyllotoxin (3). Since it has been recently reported that 3 is microbially convertible to epipodophyllotoxin (2)[16] which is a key intermediate for the synthesis of etoposide (4) and teniposide (5), the present method using the catalytic hydrogenation with (S,S)-MOD-DIOP-rhodium(I) complex can provide a simple and efficient synthetic route to various optically active podophyllum lignans.

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References and Notes

1) Asymmetric Reactions Catalyzed by Chiral Metal Complexes XXXVII.
2) For reviews: I. Jardin, in "Anticancer Agents Based on Natural Product Models", ed. by J. M. Cassady and J. D. Douros, Academic Press, Inc., New York, 1980, p 319; W. D. MacRae and G. H. N. Towers, Phytochemistry, 23, 1207 (1984); W. M. Hearon and W. S. MacGregor, Chem. Rev. 55, 957 (1955).
3) For a review: B. F. Issell, Cancer Chemother. Pharmacol., 7, 73 (1982).
4) a) For a review: R. S. Ward, Chem. Soc. Rev., 11, 75 (1982); b) D. I. Macdonald and T. Durst, J. Org. Chem., 53, 3663 (1988); 51, 4749 (1986); D. W. Jones and A. M. Thompson, J. Chem. Soc., Chem. Commun., 1987, 1797; D. M. Vyas, P. M. Skonezny, T. A. Jenks, and T. W. Doyel, Tetrahedron Lett., 27, 3099 (1986); T. Kaneko and H. Wong, Tetrahedron Lett., 28, 517 (1987); M. E. Jung and G. T. Lowen, Tetrahedron Lett., 27, 5319 (1986); W. S. Murphy and S. Wattanasin, J. Chem. Soc., Perkin I., 1982, 271; D. Rajapaka and R. Rodorigo, J. Am. Chem. Soc, 103, 6208 (1981); J. Van der Eycken, P. DeClerqu, and M. Vanderwalle, Tetrahedron Lett., 26, 3871 (1985).
5) R. C. Andrews, S. J. Teague, and A. I. Meyers, J. Am. Chem. Soc., 110, 7854 (1988).
6) J. L. Hartwell and A. W. Schrecker, J. Am. Chem. Soc., 76, 4034 (1954); J. L. Hartwell, A. W. Schrecker, and J. M. Johnson, J. Am. Chem. Soc., 75, 2138 (1953).
7) T. Morimoto, M. Chiba, and K. Achiwa, Tetrahedron Lett., 30, 735 (1989).
8) T. Morimoto, M. Chiba, and K. Achiwa, Chem. Pharm. Bull., in press; Heterocycles, in press.
9) a) E. Brown and A. Daugan, Tetrahedron Lett., 26, 3997 (1985); b) E. Brown and A. Daugan, Tetrahedron Lett., 27, 3719 (1986); Heterocycles, 26, 1169 (1987); K. Khamlach, R. Dhal, and E. Brown, Tetrahedron Lett., 30, 2221 (1989).
10) L. H. Klemm, K. W. Gopinath, D. Hsu Lee, F. W. Kelly, E. Trod, and T. M. McGuire, Tetrahedron, 22, 1797 (1966).
11) L. H. Klemm, D. R. Olson, and D. V. White, J. Org. Chem., 36, 3740 (1971).
12) W. J. Gensler and C. D. Gatsonis, J. Org. Chem., 31, 4004 (1966); A. S. Kende, M. L. King, and D. P. Curran, J. Org. Chem., 46, 2826 (1981).
13) M. Tanoguchi, T. Kashima, H. Saika, T. Inoue, M. Arimoto, and H. Yamaguchi, Chem. Pharm. Bull. (Tokyo), 37, 68 (1989).
14) M. Kuhn and A. von Wartburg, Helv. Chem. Acta., 50, 1546 (1967).
15) The antipode, (-)-isodeoxypicropodophyllin, mp 202.3-203.2 °C, $[\alpha]_D^{20}$ -114° (c 0.51, $CHCl_3$), was derived from (-)-podophyllotoxin [A. W. Schreker and J. L. Hartwell, J. Am. Chem. Soc., 75, 5916 (1953)].
16) K. Kondo, M. Ogura, Y. Midorikawa, M. Kozawa, H. Tsujibo, K. Baba, and Y. Inamori, Agri. Biol. Chem., 53, 777 (1989).

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