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Synthesis of Podophyllotoxin and its Derivatives *via* $NiCl_2/NaBH_4$ Reduction of Isoxazoline Ring

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A novel synthesis of podophyllotoxin was carried out in four steps. The key step was reduction of isoxazoline ring followed by diazotization and the resultant alkene was treated with $Mn(OAc)_3/CH_3COOK$ to form podophyllotoxin.

Key Words: Nickel chloride, Isoxazoline, Podophyllotoxin, Manganese acetate.

INTRODUCTION

Podophyllotoxin (Fig. 1)[1], a natural lignan that is currently used as a precursor to semi synthetic anticancer drugs like etoposide, teniposide, etopophos, *etc*. Podophyllotoxin has been extracted from two important medicinal plants named *Podophyllum emodi* an Indian species and *Podophyllum peltatum*, a North American species which belongs to the family of berbideracea[2]. It has also been extracted from other medicinal plants called *Podophyllum pleianthum* by Jackson *et al.*[3]. The dried roots and rhizomes of these plants are known as podophyllum, which on extraction from alcohol and after drying gives a resin termed podophyllin.

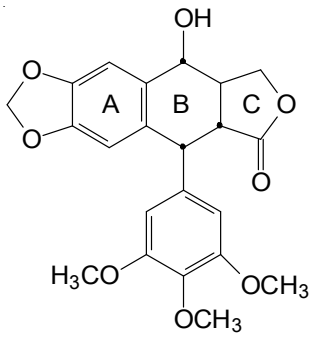


Fig. 1. Podophyllotoxin

Four general approaches to the synthesis of podophyllotoxin derivatives[4] have so far been developed although several variations and innovations have been introduced within each of these overall schemes; namely (i) the oxoester route[5], (ii) dihydroxy acid route[6], (iii) Diels-Alder approach[7], (iv) tandem conjugate addition[8].

Only five approaches to the asymmetric synthesis of podophyllotoxin or analogues have been achieved using asymmetric conjugate addition or Diels-Alder reactions. The key step in the first route was reported by Ward *et al.*[8b] involves asymmetric conjugate addition of anion to chiral butenolide to yield adduct which has been further elaborated to (-) deoxy-iso-podophyllotoxin.

Meyers *et al.*[9] achieved asymmetric synthesis of (-) podophyllotoxin in 24 steps. The key step in the asymmetric conjugate addition of a trimethoxyphenyl anion to chiral oxazoline to yield chiral adduct.

EXPERIMENTAL

Melting points were taken in open capillaries using Thomus Hoover melting point apparatus and are uncorrected. The compounds were routinely checked for their purity by TLC using silica gel G. IR spectra were recorded on a nujol mull on Shimadzu 8300 spectrometer. ^1H NMR were recorded either on a Bruker 300 MHz or Bruker 200 MHZ or Jeol 60 MHZ Hitachi Perkin Elmer spectrometer in $CDCl_3$ solution. Tetramethyl silane (TMS) was used as an internal standard and the chemical shifts are expressed in ppm (δ). The ^{13}C NMR spectra were measured either on Jeol GSX 400(100 MHz) or 75 MHz instrument and the values are in parts per million downfield from the tetramethyl silane. Mass spectra were obtained either on Maspec MSW 9629 or Fennigen 4021 spectrometer and the important fragments are given with the relative intensities in the bracket.

Thin layer chromatograms were obtained on a silica gel (HF, 254, Sd Fine Chem) coated on glass slides. Silica gel-G (TLC grade) slurry was prepared by dissolving 50 g of silica

gel in 100 mL of the solvent mixture (chloroform:methanol-2:1) and the TLC plates prepared as per the methods of Piefer[10]. Visualization of the spots on the chromatogram was relied on adsorption of iodine. Chromatographic separations were carried out on a silica gel (70-230 mesh, Merck) column. The proportion of the solvents for the chromatography was given as volume/volume.

Typical experimental procedure for compound (6d): The required aldoximes **(2)** were prepared by standard method by warming a solution of aromatic aldehydes in ethanol with hydroxylamine hydrochloride in presence of sodium acetate. Mixture of safrole (**1**, 0.810 g, 5 mmol) and benzaldoxime (**2d**, 0.605 g, 5 mmol) were taken in alcohol in presence of chloramines-T (1.43 g, 5.1 mmol) and refluxed for 3 h and the progress of the reaction was monitered by TLC. After the completion of the reaction, alcohol was evaporated under vaccum. The reaction mixture was extracted with diethyl ether (25 mL) and the organic layer was washed with 10 % NaOH solution (25 mL × 2). The organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum to get required 5-benzo[1,3]dioxol-5-ylmethyl-3-phenyl-4,5-dihydro-isoxazole **(3d)** (1.25 g, 90 %), m.p. 170-71 ºC; IR (Nujol): ν 1690 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.65 (d, 2H, CH_2), 2.83 (d, 2H, CH_2), 3.6 (m, 1H, CH), 5.91 (s, 2H, OCH_2O), 6.51-6.62 (m, 3*H*, Ar'H), 7.2-7.65 (m, 5H, ArH).

Mixture of 5-benzo[1,3]dioxol-5-ylmethyl-3-phenyl-4,5-dihydro-isoxazole (**3d**, 1.40 g, 5 mmol) and $NiCl_2{\cdot}6H_2O$ (2.37 g, 10 mmol) were taken in methanol and cooled to -10 ºC. Sodium borohydride (0.74 g, 20 mmol) was added in small quantities for 0.5 h by maintaining the same temperature. It was then kept at -10 ºC for further 0.5 h to complete the reaction. After completion of the reaction, the reaction mixture was filtered through celite bed. The TLC of the organic layer showed a major spot with R_f value 0.54 and one minor spot with R_f value 0.72. The organic layer after drying over anhydrous sodium sulphate was concentrated under vacuum to get a oily mass. It was then subjected to column chromatography using chloroform and acetone (9:1) as eluent. The major fraction was then evaporated under vacuum to gave 4-amino-1-benzo[1,3]dioxol-5-yl-4-phenyl-butan-2-ol **(4d)** as pale brown solid (0.993 g, 70 %). m.p. 154-55 ºC; IR (Nujol): ν 3650 (broad OH), 3350 (sharp NH), 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.98 (m, 2H, CH_2), 2.72 (d, 2H, CH_2), 3.62 (m, 1H, OCH), 3.85 (t, 1H, NCH), 5.92 (s, 2H, OCH_2O), 6.51-6.62 (m, 3H, Ar'H), 7.10-7.22 (m, 5H, ArH).

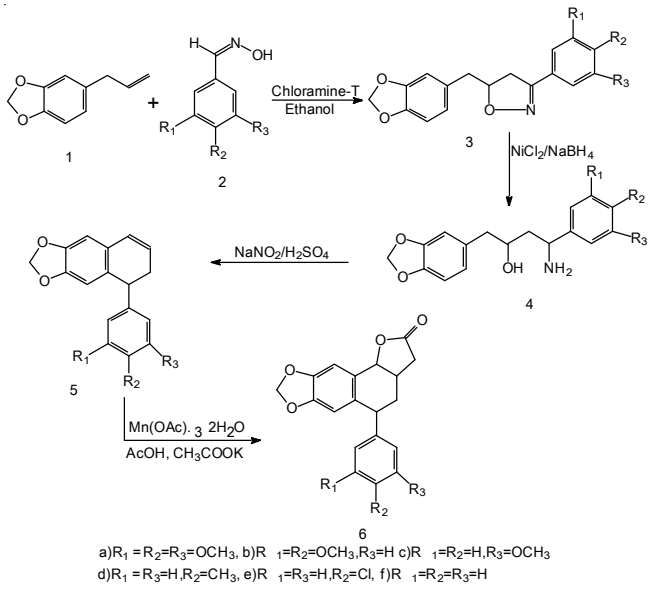
Solution of 4-amino-1-benzo[1,3]dioxol-5-yl-4-phenyl-butan-2-ol (**4d**, 1.42 g, 5 mmol) in 5 % aqueous sulphuric acid (50 mL) was cooled to 0 ºC. Sodium nitrite (0.35 g, 5.2 mmol) was added in small quantities for 0.5 h by maintaining the same temperature. It was then kept at 0 ºC for further 0.5 h to complete the reaction. After completion of the reaction, the reaction mass was extracted with diethylether (25 mL). The organic layer was washed with distilled water (10 mL), dried over anhydrous sodium sulphate and evaporated under vacuum to get a oily mass. TLC of this shows a major spot at R_f value 0.5 in chloroform:acetone (7:1) as eluent. It was then passed through a column packed with silica gel using chloroform:acetone (7:1) as eluting solvent. The required fraction was pooled together, evaporated to dryness under reduced pressure gave 5-phenyl-5,6-dihydro-naphtho[2,3-d][1,3]dioxole **(5d)** as colourless oily mass (0.93 g, 75 %), b.p. 174-175 ºC; IR (Nujol): ν 1600 cm^{-1} (-C=C-); ^1H NMR ($CDCl_3$): δ 2.58 (m, 2H, CH_2), 4.07 (d, 1H, CH), 5.70 (m, 1H, CH), 5.92 (s, 2H, OCH_2O), 6.61 (d, 1H, CH), 6.75-7.02 (m, 2H, Ar'H), 7.30-7.60 (m, 5H, ArH); MS (relative abundance) m/z: for $C_{17}H_{14}O_2$, 250 (M^+, 18), 174(100), 173(40), 144(30), 130 (35), 78(25).

A mixture of 5-phenyl-5,6-dihydronaphtho[2,3-d][1,3]-dioxol (**5d**, 1.25 g, 5 mmol), Mn(III) acetate dihydrate (1.34 g, 5 mmol) and potassium acetate (0.58 g, 6 mmol) in glacial acetic acid (15 mL) were refluxed under nitrogen atmosphere till the brown colour was disappeared. The resulting reaction mixture was cooled and diluted with water (15 mL). It was then extracted in diethyl ether, washed with water (2 × 20 mL), 10 % sodium bicarbonate solution (2 × 20 mL) and finally with water (20 mL). Ether layer after drying over anhydrous sodium sulphate was completely evacuated to get thick residue. The pure lactone was isolated by passing through column packed with 70-320 mesh silica gel using petroleum ether:ethyl acetate mixture (8:2) as eluent. Evaporation of major fraction yields 5-phenyl-3a,4,5,10b-tetrahydro-3*H*-1,7,9-trioxa-dicyclo-penta[a,g]naphthalene-2-one **(6d)** (0.61 g, 40 %) as an oily liquid, b.p. 143-44 ºC. IR (Nujol): ν 1750 cm^{-1} (lactone C=O); ^1H NMR ($CDCl_3$): δ 1.85 (m, 2H, CH_2), 2.26 (d, 2H, CH_2), 2.82 (m, 1H, CH), 4.13 (t, 1H, CH), 5.31 (d, 1H, CH), 5.92 (s, 2H, OCH_2O), 6.43 (s, 2H, Ar'H), 7.3-7.59 (s, 5H, ArH); MS (relative abundance) m/z: for $C_{19}H_{16}O_4$, 308 (M^+, 35), 264(100), 232(40), 231(35), 202 (26), 188(48), 78(25).

RESULTS AND DISCUSSION

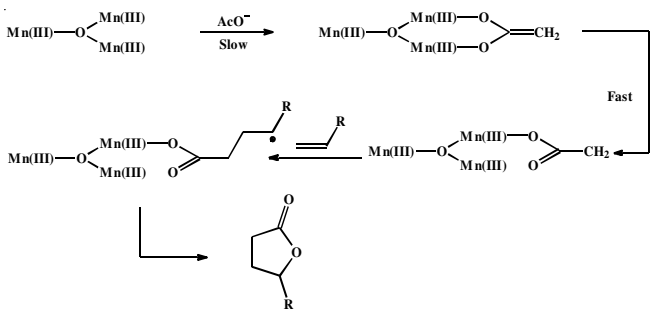
We report herein a short and convenient synthesis of (-) podophyllotoxin in 4 steps (**Scheme-I**) through 1,3-dipolar cycloaddition of safrole with substituted benzaldoxoime in presence of chloramine-T, followed by reduction of isoxazoline ring with $NiCl_2/NaBH_4$ in presence of methanol as a solvent. The β-amino alcohols produced on diazotization with acid catalyst cyclizes the ring and on the elimination of water on the ring to form a tetraline. Here we observed that the isomers produced and they were separated by column chromatography. This tetraline on reaction with $Mn(OAc)_3/CH_3COOK$ in acetic acid as a solvent form the lignan lactone ring which resembles the podophyllotoxin.

Most commonly employed method for the synthesis of isoxazolines involving 1,3-dipolar cycloaddition reaction of nitrile oxides to olefin. Rai *et al.*[11-13] and others[14] did considerable work on 1,3-dipolar cycloaddition using chloramine-T as oxidant for generating 1,3-dipoles. The production of β-amino alcohols requires that both the C=N and N-O bond of the isoxazoline be reduced. This can be achieved through reduction of isoxazoline either with $Me_3OBF_4/NaBH_4$ or LAH[15]. Annuziata *et al.*[16] synthesized optically active amino alcohols by stereoselective reduction of isoxazoline derivatives by using $NiCl_2$ and $NaBH_4$ at low temperature. It is well known that reaction of primary aliphatic amines with nitrous acid liberate corresponding primary alcohols[17]. During this process nitrogen is evolved. When nature of the alkyl permits it, the products are mixture of isomeric alcohols, isomeric alkanes



Scheme-I

and cyclized structures. This prompted us to treat β-amino alcohols prepared by the isoxazoline with nitrous acid with a view to get the cyclized product *via* the tandem cyclization of the intermediate carbocation. The oxidative addition of acetic acid to alkenes reported by Heiba *et al.*[18] and Bush and Finkbeiner[19] in provides the basis for a general approach to oxidative free radical cyclizations. Radical cyclization of alkenes has become a valuable method for the synthesis of cyclic compounds[20]. The application of Mn(III) oxidative free-radical cyclizations was initially investigated by Corey and Kang[21], Ernst and Fristad[22] and Snider *et al.*[23]. Heating the one electron oxidant, Mn(III) acetate in acetic acid at reflux temperature 115 ºC generates the α-carboxymethyl radical. This radical adds to double bonds of the alkenes with the formation of 3-caboxy alkyl radical, which is oxidized by second equivalent of Mn(III) acetate affords γ-lactone (**Scheme-II**).



Scheme-II

Conclusion

This is a new and modified route for the synthesis of podophyllotoxin via reduction of isoxazoline ring with $NiCl_2$ and $NaBH_4$ reagent.

REFERENCES

1. V. Podwyssotzki, *Arch. Exp. Pathol. Pharmakol*., **13**, 29 (1880).
2. J.L. Hartwell and A.W. Schrecker, *Fortschr. Chem. Org. Naturst*., **13**, 83 (1958).
3. E.D. Jakson and M.P. Dewick, *Phytochemistry,* **24**, 2407 (1985).
4. R.S. Ward, *Synthesis,* 719 (1992).
5. W.J. Gensler and C.D. Gatasoni, *J. Org. Chem*., **31**, 4004 (1966) and reference cited therein; A.S. Kende, M.L. King and D.P. Kurran, *J. Org. Chem*., **46**, 2826 (1981) and references cited therein; W.S. Murphy and Wattansasin, *J.C.S. Perkin Trans-1*, 271 (1882); J.R. Peterson, H.D. Do and R.D. Rogers, *Synthesis,* 275 (1991); D.M. Vyas, P.M. Skonezny, T.A. Jenkins and T.W. Doyle, *Tetrahedron Lett*., **27**, 3099 (1986).
6. S.P. Forsey, D. Rajapaksha, N.J. Taylor and R. Rodrigo, *J. Org. Chem*., **54**, 4280 (1989); D.W. Jones and A.M. Thomson, *J. Chem. Soc. Chem. Commun*., 1330 (1988) and references cited therein; D.I. Macdonald and T. Durst, *J. Org. Chem*., **53**, 3663 (1988); J. Van der Eycken, P. de Clercq and M. Vandewalle, *Tetrahedron,* **42**, 4297 (1986).
7. J. Mann, L.T.F. Wong and A.R. Beard, *Tetrahedron Lett*., **26**, 1667 (1985); W. Choy, *Tetrahedron,* **46**, 2281 (1990); L.H. Klemm, D.R. Olson and D.V. White, *J. Org. Chem*., **36**, 3740 (1971); J.L. Charlton, G.L. Plourde, K. Koh and A.S. Secco, *Can. J. Chem*., **68**, 2022 (1990); T. Marimoto, M. Chiba and K. Achiwa, *Tetrahedron Lett*., **31**, 261 (1990).
8. (a) F.E. Ziegler and J.A. Schwarz, *J. Org. Chem*., **43**, 985 (1978); (b) A. Pelter, R.S. Ward, M.C. Pritchard and T. Kay, *J. Chem. Soc., Perkin Trans* 1, 1603 (1988); A. Pelter, R.S. Ward, D.M. Jones and P. Maddocks, *Tetrahedron Asymm.,* **3**, 239 (1992) and references cited therein; A.G. Gonzalez, J.P. Perez and J.M. Trujillo, *Tetrahedron,* **34**, 1011 (1987); A.P. Ganeshpure and R. Stevenson, *J. Chem. Soc., Perkin Trans. I*, 1681 (1981); E. Brown and A. Dugan, *Tetrahedron,* **45**, 141 (1989); J.P. Kutney, *Synlett,* 11 (1991).
9. A.I. Meyers, R.A. Andrews and S.J. Teague, *J. Am. Chem. Soc*., **110**, 7854 (1988).
10. J.J. Peifer, *Microchim. Acta*, **3**, 529 (1962).
11. K.M.L. Rai and A. Hassner, *Indian J. Chem.*, **36B**, 242 (1997).
12. K.M.L. Rai and A. Hassner, *Synth. Commun*., **27**, 467 (1997).
13. K.M.L. Rai, A. Hassner and Wim Dahean, *Synth. Commun*., **24**, 1669 (1994).
14. A.P. Kozikowski and H. Ishida, *J. Am. Chem. Soc*., **102**, 4265 (1980).
15. G. Just and K. Dhal, *Tetrahedron*, **24**, 5251 (1968).
16. R. Annuaziata, M. Cinquini, F. Cozzi, A. Gilardi and A. Restelli, *J. Chem. Soc. Perkin Trans. I*, 2289 (1985).
17. I.L. Finar, Organic Chemistry, ELBS Low Priced edn., Vol. 1, p. 376 (1975).
18. E.I. Heiba, R.M. Dessau and W.J. Koehl Jr., *J. Am. Chem. Soc*., **90**, 5905 (1968).
19. J.B. Bush Jr. and H. Finkbeiner, *J. Am. Chem. Soc*., **90**, 5903 (1968).
20. B.B. Snider, *Chem. Rev*., 339 (1996).
21. E.J. Corey and M.C. Kang, *J. Am. Chem. Soc*., **106**, 5384 (1984).
22. A.B. Ernst and W.E. Fristad, *Tetrahedron Lett*., **26**, 3761 (1985).
23. B.B. Snider, R.M. Mohan and S.A. Kates, *J. Org. Chem*., **50**, 3659 (1985).