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Enantioselective Formal Synthesis of the Cytotoxic Topoisomerase II Inhibitor Deoxythysanone, Catalyzed by Chiral Spiroborate Ester

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Abstract—Bioactive pyranonaphthoquinone analogs, (1*R*,3*S*)-deoxythysanone, (1*R*,3*S*)-thysanone, and (1*R*,3*S*)-demethoxythysanone can be efficiently synthesized from a common intermediate product, (*S*)-3-methyl-3,4-dihydro-1*H*-isochromene-5,8-dione. We have developed a short synthetic route to pyranonaphthoquinone antibiotics, which involves enantioselective reduction of homobenzylic ketone in the presence of a chiral spiroborate catalyst with 87% enantiomeric excess as the key step. The subsequent oxa-Pectet–Spengler reaction, followed by oxidative demethylation, afforded deoxythysanone.

Keywords: homobenzylic ketone, spiroborate esters, asymmetric reduction, alcohol, deoxythysanone

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Compounds of the pyranonaphthoquinone family are of microbial origin and are used as antibiotics against pathogenic microorganisms like bacteria, fungi, yeasts, and viruses [1, 2]. Their basic skeleton consists of the naphtha[2,3-*c*]pyran-5,10-dione ring system in which the naphthoquinone moiety is fused to dihydropyran ring; an additional γ-lactone ring fused to the dihydropyran moiety is present in some members [3, 4]. Pyranonaphthoquinone skeleton is one of the most important pharmacophores constituting various bioactive natural products such as thysanone, deoxythysanone, ventiloquinone L, isoeleutherin, and eleutherin [5–9] (Fig. 1). Thysanone is a fungal isolate from *Thysanophora penicilloides*; it inhibits human rhinovirus 3C protease. Deoxythysanone showed *in vivo* growth inhibition of *Saccharomyces cerevisiae* with an IC_{50} value of 15 μM. Deoxythysanone also exhibited cytotoxicity against P388 murine leukemia cell lines with

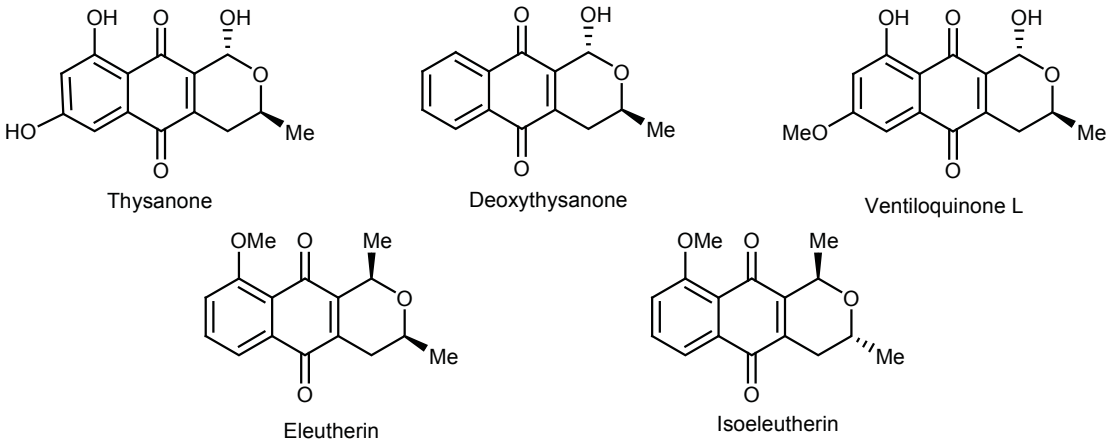
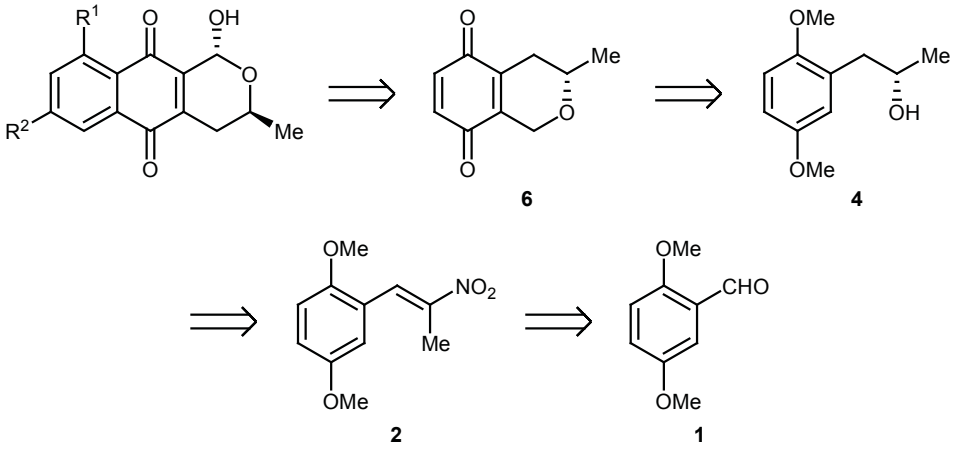


Fig. 1. Structures of some pyranonaphthoquinone antibiotics.

Scheme 1.

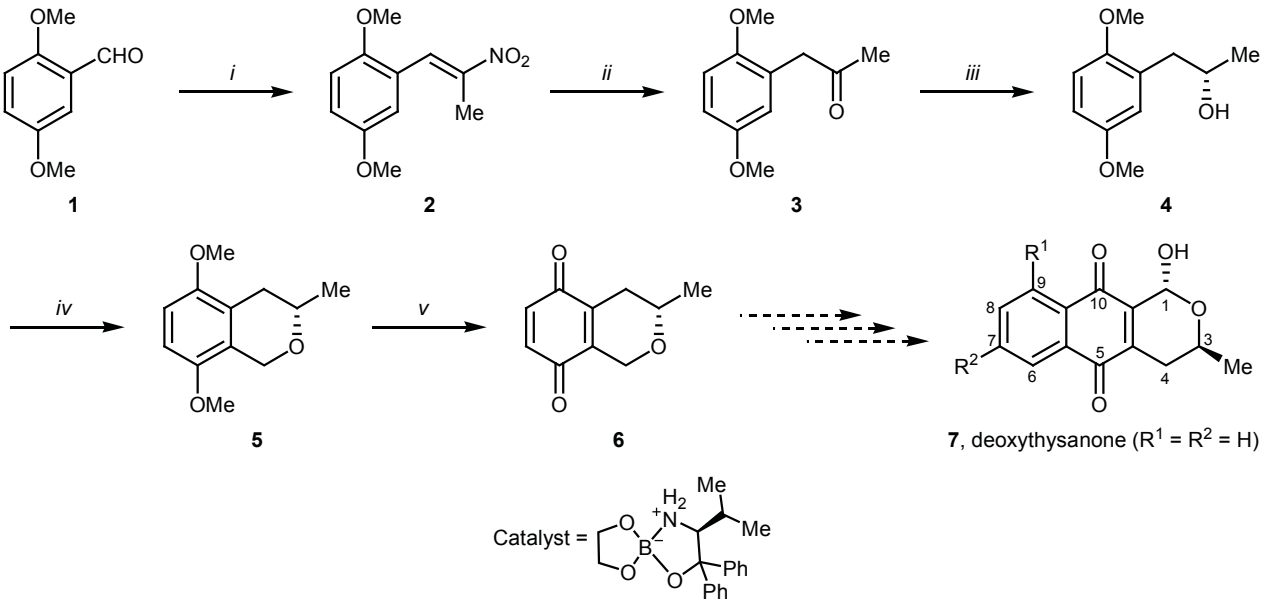


Deoxythysanone: $R^1 = R^2 = H$; thysanone: $R^1 = R^2 = OH$; demethoxythysanone: $R^1 = OH$, $R^2 = H$.

an IC_{50} value of 5–10 μM [10, 11]. The wide range of bioactivity of pyranonaphthoquinone antibiotics made them interesting synthetic targets. There have been several published reports on the synthesis of deoxythysanone and thysanone. The reported syntheses are based on the chiral pool approach [12], Sharpless asymmetric dihydroxylation [13], CBS reduction [14], enzymatic resolution [15], and asymmetric α-aminooxylation [16], but these protocols have drawbacks like several reaction steps, low yield, and low enantioselectivity. Hence, there is a need of a common synthetic approach that would combine efficient strategy with short time and high yield compared to the reported methods.

The objective of the present investigation is to develop a very short route for the synthesis of deoxythysanone via asymmetric reduction of intermediate ketone as the key stage. In addition, the syntheses of the ketone by modified Nef reaction are also described [17]. Retrosynthetic analysis of deoxythysanone (Scheme 1) showed that the creation of stereocenters at C^1 and C^3 is the main challenge [15]. Our synthetic strategy (Scheme 2) utilized 2,5-dimethoxybenzaldehyde (**1**) as a starting material for the synthesis of de-

Scheme 2.



Reagents and conditions: *i*: $EtNO_2$, *t*-$BuNH_2$, tolulene, reflux, 84%; *ii*: Fe, AcOH, 1h, 82%; *iii*: $BH_3 \cdot SMe_2$, catalyst, THF, 25°C, 30 min, 95%; *iv*: $ZnCl_2$ (30 mol %), $MeOCH_2Cl$, Et_2O, 0°C to r.t., 4 h, 82%; *v*: CAN, $MeCN/H_2O$, 0°C to r.t., 25 min.

oxythysanone. The nitroaldol condensation of 2,5-dimethoxybenzaldehyde (**1**) with nitroethane in the presence of *tert*-butylamine as a base gave (*E*)-1,4-dimethoxy-2-(2-nitroprop-1-en-1-yl)benzene (**2**) which was purified by column chromatography to isolate a yellow solid with 84% yield. The nitro group of **2** was subjected to modified Nef reaction with iron metal in acetic acid for 3 h at 60°C in order to obtain homobenzylic ketone **3** as a colorless liquid with 82% yield. Ketone **3** was reduced with oxazaborolidine catalyst at 25°C in 85% yield and 40% *ee*. Raising the temperature to 40°C increased enantiomeric excess to 50%, but the yield decreased to 80% [18]. Further reduction of **3** ketone was performed at 0°C using $BH_3 \cdot SMe_2$ in the presence of spiroborate ester catalyst prepared from chiral diphenylvalinol [19]; in this case, 60% *ee* and 90% yield were achieved. Optimization results showed that both enantiomeric excess and yield significantly increased (87% *ee*, 95% yield) when the reaction was carried out by slowly adding homobenzylic ketone **3** at a constant rate at room temperature.

The resulting chiral alcohol, (*S*)-1-(2,5-dimethoxyphenyl)propan-2-ol (**4)** was purified by flash chromatography. Alcohol **4** was then subjected to oxa-Pictet–Spengler cyclization with methoxymethyl chloride in the presence of $ZnCl_2$ (30 mol %) in anhydrous diethyl ether to afford *(S)*-5,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran (**5**) with 82% yield. Oxidative demethylation of **5** was carried out by the action of ceric ammonium nitrate (CAN) in aqueous acetonitrile to furnish the target quinone. Thus, we have successfully completed the synthesis of (+)-(*S*)-3-methyl-3,4-dihydro-1*H*-2-benzopyran-5,8-dione (**6**) in six steps with high optical purity (87% *ee*) and overall yield of 49.2%. The two-step conversion of **6** to (1*R*,3*S*)-deoxythysanone (**7a**) has been reported in [20]. Initially, quinone **6** reacted with 1-acetoxy-1,3-butadiene at room temperature in toluene for 48 h, followed by treatment with 1% aqueous solution of sodium carbonate in ethanol at room temperature for 5 h. Purification gave **7a** in 85% yield, and all its characteristics matched the reported data.

All isolated intermediate compounds were characterized by spectroscopic data (IR, ^1H and ^{13}C NMR). The enantiomeric excess of (*S*)-**4** was determined by HPLC analysis using a chiral AD-H column (250 mm×4.6 mm; particle size 5 μm) [21].

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer; the chemical shifts were measured relative to tetramethylsilane (^1H) or $CDCl_3$ (δ_C 77.00 ppm). The IR spectra were recorded on a Shimadzu FTIR-8400 spectrometer with samples loaded as thin films on KBr plates. The optical rotations were determined on a Jasco P-2000 polarimeter using 10-mm cells. Gas chromatographic/mass spectrometric analyses were run on an Agilent 5975 mass selective detector interfaced with an Agilent 7890 gas chromatograph (HP-5 capillary column, 30 m× 0.32 mm×0.25 μm, J & W Scientific). The LC/MS (ESI) data were obtained with a Waters H-Class HPLC system (Milford, MA) coupled to an ion trap mass spectrometer with an electrospray ionization source (Finnigan MAT, San Jose, CA). The melting points were taken with a Büchi 560 apparatus and are uncorrected. HPLC analysis was performed by using Waters HPLC system with an UV-Vis detector and an analytical X-Bridge C18 column (4.6×250 mm, 5 μm) at a flow rate of 1 mL/min. All reactions were carried out in dry solvents, unless otherwise stated. The reaction progress was monitored by TLC on silica gel plates (Kieselgel 60 F254, Merck). Visualization of spots on TLC plates was achieved either by UV light or by staining the plates in 2,4-dinitrophenylhydrazine/anisaldehyde and charring on a hot plate.

(*S*)-1-(2,5-Dimethoxyphenyl)propan-2-ol (4) [16]**.** A solution of BH_3–DMS complex (10 M, 0.5 mL, 5.0 mmol) was added with stirring over a period of 30 min at 25°C under argon to a mixture of chiral spiroborate ester (0.5 mmol) and anhydrous THF (15 mL). A solution of compound **3** (931 mg, 5.0 mmol) in anhydrous THF (5 mL) was than added over a period of 1 h using an infusion pump. After 30 min, compound **3** was completely consumed (TLC). The mixture was stirred at 25°C for an additional 1 h, cooled to 0°C, and slowly quenched with methanol (5 mL). After stirring for 1 h at room temperature, the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (20 mL), washed with a saturated solution of ammonium chloride (15 mL) and water (10 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography (15% EtOAc/hexane) to afford **4** (935 mg) as colorless oil.

1,4-Dimethoxy-2-(2-nitroprop-1-en-1-yl)benzene (2). Yield 84%, yellow solid. mp 64–62°C. IR spectrum (KBr), cm^{-1}: 2999, 2357, 2056, 1645, 1504, 1321, 1298, 1118, 1041, 860, 705, 482. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.21 s (1H), 7.91–6.82 m (3H), 3.82 s (3H, OCH_3), 3.78 s (3H, OCH_3) 2.38 s

(3H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 153.58, 153.17, 147.75, 129.61, 116.08, 115.84, 113.36, 110.44, 55.87, 56.07, 14.13. Mass spectrum: *m*/*z* 223.

1-(2,5-Dimethoxyphenyl)propan-2-one (3). Yield 82%, colorless liquid. IR spectrum (KBr), cm^{-1}: 3400, 3273, 2843, 1712, 1500, 1356, 1280, 1226, 1222, 1159, 810, 707, 526. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 6.79–6.70 m (3H), 3.76 s (3H, OCH_3), 3.75 s (3H, OCH_3) 3.64 s (2H, CH_2), 2.13 s (3H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 206.43, 153.13, 151.25, 124.30, 117.03, 112.40, 111.13, 55.70, 55.40, 45.44, 29.11. Mass spectrum: *m*/*z* 194.

1-(2,5-Dimethoxyphenyl)propan-2-ol (4). Yield 95%, white solid, mp 55–57°C, 96% *ee*, $[\alpha]_D^{25}$ = +11.21° (*c* = 1, MeOH) [16], $[\alpha]_D^{23}$ = +14.8° (*c* = 1.01, MeOH). IR spectrum (KBr), cm^{-1}: 3410, 2949, 1500, 1224, 1045. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 6.99–6.78 m (3H, H_{arom}), 4.03–3.99 m (1H, C**H**OH), 3.79 s (3H, OCH_3), 3.76 s (3H, OCH_3), 2.85 d.d (1H, *J* = 4.2, 13.2 Hz, CH_2), 2.65 d.d (1H, *J* = 8.1, 13.5 Hz, CH_2), 1.22 d (3H, *J* = 6.3 Hz, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 153.37, 151.69, 128.14, 117.49, 111.61, 111.25, 67.88, 55.76, 55.51, 40.41, 22.89. Mass spectrum: *m*/*z* 196.

(*S*)-5,8-Dimethoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran (5). Yield 82%, colorless solid, mp 49–51°C, 96% *ee*, $[\alpha]_D^{26}$ = +120.3° (*c* = 1.00, $CHCl_3$) [16], $[\alpha]_D^{26}$ = +149.9° (*c* = 1.00 $CHCl_3$). IR spectrum (KBr), cm^{-1}: 2935, 1604, 1485, 1257, 1072. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 6.63 d (1H, *J* = 8.7 Hz, H_{arom}), 6.58 d (1H, *J* = 8.7 Hz, H_{arom}), 4.92 d (1H, *J* = 16.3 Hz, CH), 4.59 d (1H, *J* = 15.7 Hz, CH), 3.76 s (3H, OCH_3), 3.74 s (3H, OCH_3), 3.65–3.72 m (1H, CH), 2.75 d.d (1H, *J* = 17.1, 3.3 Hz, CH), 2.39 d.d (1H, *J* = 16.5, 10.8 Hz, CH), 1.35 d (3H, *J* = 6.0 Hz, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 150.7, 149.3, 124.5, 123.8, 107.3, 106.6, 69.9, 64.4, 55.4, 55.3, 30.2, 21.6. Mass spectrum: *m*/*z* 208 $[M]^+$.

(+)-(*S*)-3-Methyl-3,4-dihydro-1*H*-2-benzopyran-5,8-dione (6). Yield 92%, yellow solid, mp 101–103°C, 87% *ee*, $[\alpha]_D^{26}$ = +245.4° (*c* = 0.5, $CHCl_3$) [16], $[\alpha]_D^{26}$ = +270.8° (*c* = 0.5, $CHCl_3$). IR spectrum (KBr), cm^{-1}: 2877, 1653, 1413, 1305, 1147, 837, 455. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 6.73 d (1H, *J* = 10.2 Hz, CH=), 6.68 d (1H, *J* = 10.2 Hz, CH=), 4.68 d.t (1H, *J* = 18.3, 2.7 Hz, OCH_2), 4.38 d.t (1H, *J* = 18.3, 2.7 Hz, OCH_2), 3.60–3.69 m (1H, OCH), 2.58 d (1H, *J* = 19.2, 2.7 Hz, CH_2), 2.12–2.24 m (1H, CH_2), 1.36 d (3H, *J* = 6.0 Hz, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 186.0, 185.7, 145.2, 139.5, 136.3, 136.0, 69.4, 62.7, 28.8, 21.1.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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