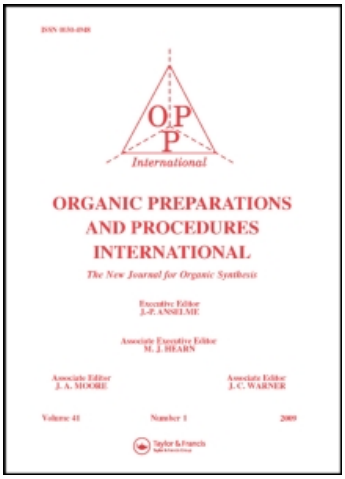

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EXPEDIENT SYNTHESES OF ESPINTANOL, *p*-METHOXYCARVACROL AND THYMOQUTNOL DIMETHYL ETHER

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661 (1991).

3. A. Prashant, G. L. D. Krupadanam and G. Srimannarayana, *Bull. Chem. Soc. Jpn*, **65**, 1191 (1992).

4. S. S. Mathur and S. Hans, *J. Chem. Soc. Perkin Trans I*, 2479 (**1975**).

5. S. Tomio, H. Yoshiyuki, K. Yoshitaka and To Kazuhiro, *Bull. Chem. Soc. Jpn*, **55**, 2450 (1982).

6. B. L. Dale and C. L. Wendy, *J. Org. Chem.*, **58**, 2068 (1993).

7. M. Black, J. I. G. Cadogan, G. A. Cartwright, H. McNab and A. D. Macpherson, *Chem. Commun.*, 959 (**1993**).

8. M. Kuchar, B. Kakac, O. Nemecek, E. Kraus and J. Holubeck, *Coll. Czech. Chem. Commun.*, **38**, 447 (1973).

9. R. S. Mali, S. G. Tilve, S. N. Yeola and A. R. Manekar, *Heterocycles*, **26**, 121 (1987).

10. N. Britto, V. G. Gore, R. S. Mali and A. C. Ranade, *Synth. Commun.*, **19**, 1899 (1989).

11. E. Pretsch, T. Clerc, J. Seibl and W. Simon, *Tabellen Zur Strukturaufklarung Organischer Verbindungen mit Spektrokopischen Methoden*, Springer, Berlin, 1976.

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EXPEDIENT SYNTHESES OF ESPINTANOL, *p*-METHOXYCARVACROL AND THYMOQUINOL DIMETHYL ETHER

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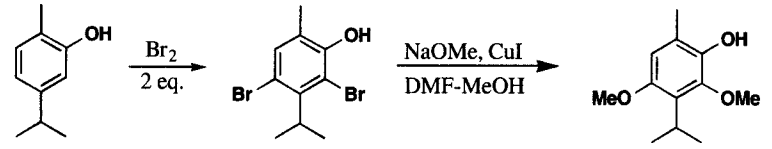
A substantial number of oxygenated p-cymene derivatives have been isolated from a variety of plant sources especially from trees. The title compounds, for example, were first isolated from the spruce tree *Oxandra espintata* (espintanol),[1] from the incense-cedar heartwood *Libocedrus decurrens* (p-methoxycarvacrol)[2] and from *Eupatorium triplinere* (thymoquinol dimethylether).[3] p-Cymene derivatives of this type were shown early on by Erdtman and Rennerfelt to exhibit varying degrees of toxicity toward wood-destroying fungi.[4] In addition, espintanol has been shown to have antiparasitic activity against a number of strains of *Trypanosoma cruzi* and *Leishmania*, the latter responsible for

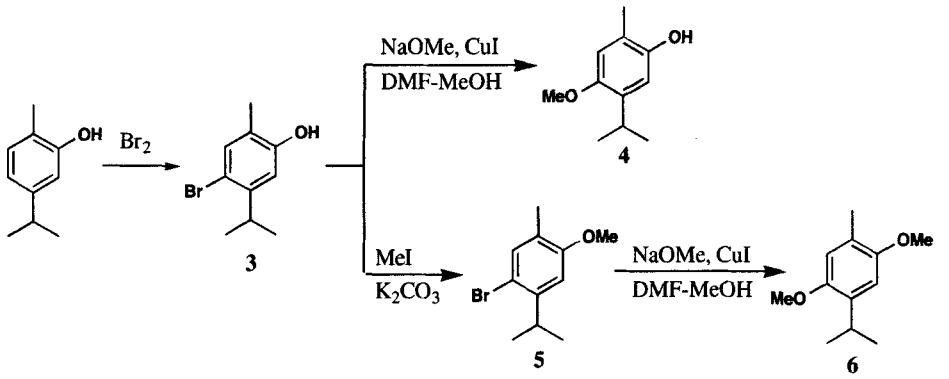
certain types of Leichmanioses. Small amounts of these physiologically active compounds are usually obtained from their natural sources; thus, it is important to synthesize gram quantities in order to further examine their physiological activity.

Two synthetic routes to espintanol have been reported in the literature, the first by Hocquemiller *et al.* in nine steps[1, 8] and the second by Wadsworth and Losch in seven steps[5] in *ca.* 2% and 11% overall yield respectively. We envisioned a substantially shorter two-step route to espintanol starting from the commercially available monoterpene carvacrol, introducing two leaving groups in the appropriate positions followed by a double copper(I) mediated nucleophilic substitution as the key step.[6] Thus, carvacrol was first dibrominated affording **1** in 78% yield after chromatography, a reaction reported as early as 1891 (Scheme 1).[7] Treatment of **1** with 11 equivalents of sodium methoxide and 3.5 equivalents of copper(I) iodide in a 2.5:1 methanol-DMF mixture at 70° for 48 hrs gave, after chromatography on silica (hexanes:EtOAc, 95:5), espintanol in 72% yield.[8] The high yield was gratifying in that polysubstituted aromatic compounds, especially those with alkoxy and hydroxy functionalities, frequently afford low yield of substitution products with dehalogenation as a competing side-reaction.[9] Reductive debromination of **1** was not observed. This also constitutes a formal total synthesis of O-methylespintanol which has previously been prepared from espintanol using diazomethane.[1, 10] This route can most likely be expanded to other oxygenated p-cymene derivatives and two other natural products were prepared accordingly as shown below.



Carvacrol **1** **2**

p-Methoxycarvacrol (**4**) was prepared by bromination of carvacrol[11] followed by reaction of the monobromide **3** with sodium methoxide in the presence of copper(I) iodide, producing the desired product **4** in 82% yield (Scheme 2). Thymoquinol dimethyl ether was prepared starting from the monobromide **3** via the methylated bromide**5** (77%)[12] and again a copper(I) mediated nucleophilic substitution (Scheme 2). In the latter case, the rate of reaction of **5** was substantially lower compared to the alcohols **1** and **3**, and a 66% yield was realized after 48 h at reflux. In addition to the desired product, 32% of the starting material **5** was recovered. Complete conversion of **3** to **4** could not be realized; prolonged heating only resulted in a lower yield.



EXPERIMENTAL SECTION

High-field ^{1}H NMR spectra recorded on a JEOL Eclipse 270 using $CDCl_3$ as solvent has been included to update existing spectral data. Melting points (uncorrected) were determined on a MEL-TEMP.

2,4-Dibromocarvacrol (1).- To a solution of carvacrol (4.50 g, 30.0 mmol) in glacial acetic acid (25 mL) cooled to 0° was added Br_2 (3.40 mL, 66.3 mmol) over 20 min. After complete addition, the reddish-brown reaction mixture was removed from the cold bath and stirred overnight at ambient temperature. The mixture was poured out on ice (100 mL), the ice was allowed to melt, and the aqueous solution was extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and the solvent was removed, *in vacuo*, to give a brown semi-solid. The crude product was purified by column chromatography using hexanes-EtOAc (9:1) as eluent affording **1** (7.22 g, 78%) as a pale yellow oil, bp. 140-142°/10 mm, lit.[7a] 175-177°/25-30 mm. ^{1}H NMR: δ 7.05 (br s, 1H), 5.83 (br s, 1H), 3.78 (septet, J = 8 Hz, 1H), 2.19 (s, 3H), 1.37 (d, J = 8 Hz, 6H).

Espintanol (2).- Small pieces of sodium (1.61 g, 70.0 mmol) were added to a round-bottomed flask containing methanol (25 mL, freshly distilled from CaH_2). After all sodium was consumed, copper (I) iodide (3.82 g, 20.0 mmol), **1** (1.98 g, 6.42 mmol), and DMF (10 mL) was added and the resulting slurry was heated to 110° (external bath temperature) for 48 hrs. The mixture was cooled to ambient temperature followed by addition of diethyl ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The phases were separated, the blue aqueous phase was extracted with diethyl ether (50 mL), and the combined organic phase was washed with saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium chloride (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography using hexanes-EtOAc (19:1) as eluent affording **2** (0.97 g, 72%) as a pale yellow oil, bp. 148°/10 mm, no lit. bp. available. Espintanol crystallizes as colorless needles upon storage at -20°, mp 42-43°, lit.[5] 43.3-44°. ^{1}H NMR: δ 6.45 (s, 1H), 5.40 (br s, 1H), 3.74 (s, 6H), 3.33 (septet, J = 6.9 Hz, 1H), 2.23 (s, 3H), 1.33 (d, J = 6.7 Hz, 6H).

4-Bromocarvacrol (3).- To a solution of carvacrol (9.01 g, 60.0 mmol) in glacial acetic acid (50 mL) cooled to 0° was added Br_2 (3.40 mL, 66.4 mmol) over 20 min. After complete addition, the reddish-

brown reaction mixture was removed from the cold bath and stirred for 3 hrs at ambient temperature. The mixture was poured out on ice (200 mL), the ice was allowed to melt, and the aqueous solution was extracted with dichloromethane (2 x 75 mL). The combined organic phase was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo* to give a pale yellow oil. The crude product was purified by column chromatography using hexanes-EtOAc (19:1) as eluent affording **3** (11.06 g, 80%) as a pale yellow oil that solidifies into pale yellow crystals upon storage at -20°, mp. 44-46°, lit.[11] 46° . ^{1}H NMR: δ 7.26 (s, 1H), 6.69 (s, 1H), 5.46 (br s, 1H), 3.23 (septet, J = 7.0 Hz, 1H), 2.18 (s, 3H), 1.43 (d, J = 7.0 Hz, 6H).

p-Methoxycarvacrol (4).- Small pieces of sodium (0.77 g, 33.4 mmol) was added to a round-bottomed flask containing methanol (15 mL, freshly distilled from CaH_2). After all sodium was consumed, copper (I) iodide (1.91 g, 10.0 mmol), **3** (1.16 g, 5.06 mmol), and DMF (10 mL) was added and the resulting slurry was heated to 110° (external bath temperature) for 48 hrs. The mixture was cooled to ambient temperature followed by addition of diethyl ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The phases were separated and the blue aqueous phase was extracted with diethyl ether (50 mL) and the combined organic phases was with saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium chloride (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography using hexanes-EtOAc (19:1) as eluent affording **4** (0.75 g, 82%) as white crystals, mp. 64°, lit.[2] 67-67.5°. ^{1}H NMR: δ 6.64 (m, 2H), 4.78 (br s, 1H), 3.77 (s, 3H), 3.23 (septet, J = 6.8 Hz, 1H), 2.17 (s, 3H), 1.14 (d, J = 6.8 Hz, 6H).

4-Bromocarvacrol Methyl Ether (5).- A solution of potassium hydroxide (1.04 g, 85%, 15.7 mmol), **4** (2.75 g, 12.0 mmol), and iodomethane (2.28 g, 24.1 mmol) in DMSO (20 mL) was stirred at ambient temperature for 72 hrs. The mixture was diluted with water (50 mL) and the resulting solution was extracted with diethyl ether (4 x 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography using hexanes-EtOAc (19:1) as eluent affording **5** (2.26 g, 77%) as a pale yellow oil, bp 143-144°/10 mm, lit.[12] 164-166°/12 mm. ^{1}H NMR: δ 7.26 (s, 1H), 6.70 (s, 1H), 3.81 (s, 3H), 3.31 (septet, J = 6.9 Hz, 1H), 2.14 (s, 3H), 1.22 (d, J = 6.9 Hz, 6H).

Thymoquinol Dimethyl Ether (6).- Small pieces of sodium (1.22 g, 52.9 mmol) were added to a round-bottomed flask containing methanol (30 mL). After all sodium was consumed, copper (I) iodide (3.06 g, 16.0 mmol), **5** (1.95 g, 8.02 mmol), and DMF (12 mL) was added and the resulting slurry was heated to 110° (external bath temperature) for 48 hrs. The mixture was cooled to ambient temperature followed by addition of diethyl ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The phases were separated and the blue aqueous phase was extracted with diethyl ether (50 mL) and the combined organic phase was washed with saturated aqueous sodium hydrogen carbonate (50 mL) and saturated aqueous sodium chloride (50 mL). The organic phases was dried ($MgSO_4$), filtered, and the solvents were removed in vacuo. The crude product was purified by column chromatography using hexanes-EtOAc (19:1) as eluent affording **6** (0.42 g, 27%) as a pale yellow oil. A mixed fraction

containing **5** and **6** was rechromatographed to afford, in order of elution , **5** (0.62 g) and **6** (0.60 g, 39%), bp 114°/10 mm, lit.[3] 118°/12 mm. ^{1}H NMR: δ 7.25 (s, 1H), 6.71 (s, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.31 (septet, J = 6.9 Hz, 1H), 2.20 (s, 3H), 1.24 (d, J = 6.9 Hz, 6H.

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REFERENCES

† Undergraduate Research Participant

1. R. Hocqmiller, D. Cortes, G. J. Arango, S. H. Myint, A. Cave, A. Angelo, V. Munos and A. Fournet, *J. Nat. Prod.*, **54**, 445 (1991).

2. E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **20**, 443 (1955).

3. F. W. Semmler, *Ber.*, **41**, 509 (1908).

4. H. Erdtman and E. Rennerfelt, *Acta Chem. Scand.*, **3**, 906 (1949), see also A. B. Anderson, E. Zavarin and T. Scheffer, *Nature*, **181**, 1275 (1958).

5. D. J. Wadsworth and S. Losch, *Tetrahedron*, **50**, 8673 (1994).

6. For a review of related copper mediated reactions, see J. Lindley, *ibid.*, **40**, 1433 (1984). For a recent applications in synthesis, see: K. Noda, N. Hosoya, R. Irie, Y. Yamashita and T. Katsuki, *ibid.*, **50**, 9609 (1994).

7. a) G. Mazzara and G. Planchen, *Gazz. Chim. Ital.* **21**, 471 (1891); b) G. Dahmer, *Ann.*, **333**, 346 (1904); c) For an alternative synthesis see: B. Miller and J. G. Haggerty, *J. Org. Chem.*, **51**, 174 (1986).

8. It should be noted that the first total synthesis of espintanol also used carvacrol as starting material.

9. R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc. (C)*, 312 (1969).

10. For isolation of O-methyl espintanol, see ref 1.

11. G. Mazzara, *Gazz. Chim. Ital.*, **16**, 195 (1886).

12. O. Wallach and F. Neuman, *Ber.*, **28**, 1662 (1895). The literature bp. value is different from our compound. Since both the starting material, bromocarvacrol, and the final product thymoquinol dimethyl ether has the correct mp and bp and the ^{1}H NMR is in complete accordance with the structure for 4-bromocarvacrol methyl ether, we believe that the literature bp. is incorrect.

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