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Total Synthesis of (±)-Parvifoline

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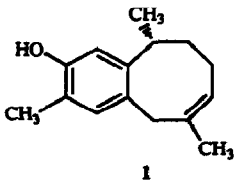
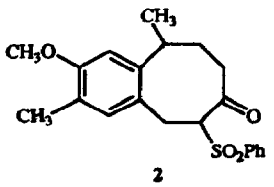
Abstract: (±) -Parvifoline (**1**) has been synthesized via intramolecular cyclization of a sulfone-stabilized carbanion.

Parvifoline (**1**) is a bicyclic sesquiterpene found as a constituent of *Coreopsis parvifolia*, [1] *Perezia carpholepsis*,[2] *and Perezia alamani var. oolepsis* (Asteraceae).[3] Its structure and absolute configuration were deduced from spectral comparisons and chemical transformations to the known curcuquinone.[4] An interesting structural feature of **1** is the fused benzocyclooctene carbon frame-work embedding a deconjugated double bond which readily migrates into conjugation under acidic conditions.[4] In this communication, we describe the first synthesis of (±)-**1** using a route that involves eight-membered ring construction via intramolecular ketosulfone cyclization. [5,6,7,8]

We envisaged that ketosulfone **2** would be a suitable intermediate for the delayed introduction of the olefin moiety. The synthetic plan called for the preparation of sulfone ester **3** followed by intramolecular cyclization to give **2**.



1



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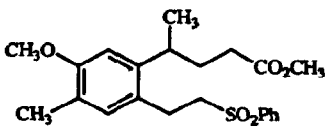
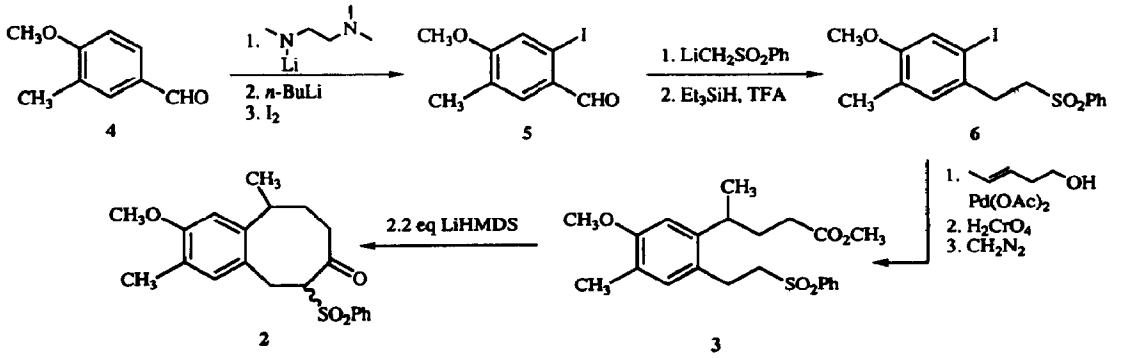


3

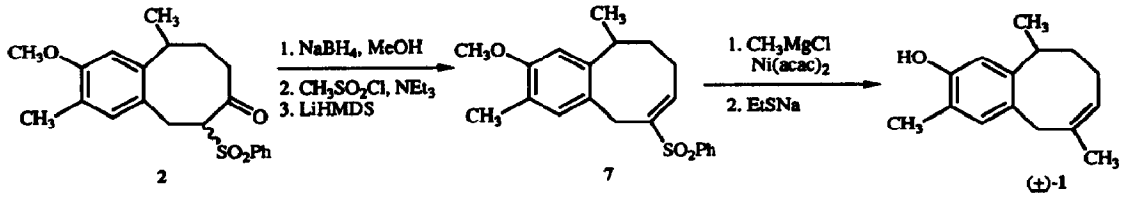
The sulfone ester **3** was easily obtained starting with commercially available 3-methyl-*p*-anisaldehyde (**4**) as shown in Scheme 1. α-Amino alkoxide directed lithiation[9] of **4** followed by reaction with iodine provided aldehyde **5**[10] in 53% isolated yield, together with unreacted starting material. Treatment of **5** with the anion of methyl phenyl sulfone followed by reduction of the crude product with triethylsilane and trifluoroacetic acid in dichloromethane afforded iodosulfone **6**[11] in 80% overall yield. Introduction of the ester side chain was readily accomplished using Larock's palladium-catalyzed coupling protocol.[12] Thus reaction of aryl iodide **6** with

trans-3-penten-1-ol,[13] subsequent Jones oxidation of the resultant aldehyde and esterification with diazomethane yielded **3** (44% overall) as light yellow crystals.[14,15]



Scheme 1

The critical ring closure was achieved by slow addition of 2.2 equiv. of lithium bis(trimethylsilyl)amide (LiHMDS, 1.0*M* in THF) to a solution of **3** ($5 \cdot 10^{-3}$*M* in THF) at 0°C followed by stirring the reaction mixture at this temperature for 2 h. After extractive isolation and chromatography on silica gel, ketosulfone **2**[16] was obtained in 67% yield as a 9:1 mixture of diasteromers.[17]



Scheme 2

The stage was now set for the introduction of the deconjugated olefin (Scheme 2). Thus reduction of **2** with $NaBH_4$ in MeOH (94%), mesylation of the alcohol (CH_3SO_2Cl, NEt_3) and immediate elimination with LiHMDS gave vinylsulfone **7**[18] in 75% overall yield. Transition-metal-catalyzed introduction of the methyl group was achieved by treating **7** with MeMgCl in the presence of $Ni(acac)_2$ (75%).[19] Smooth demethylation of the protected phenol was then accomplished without migration of the double bond under basic conditions (EtSNa, DMF, 150°C, 12h, 90%). ^1H and ^{13}C NMR, IR and MS data of synthetic (±)-**1** were in complete agreement with an authentic sample of natural parvifoline provided by Professor Joseph-Nathan.[20]

The ability to use carbanions derived from phenyl sulfones in medium ring construction further underlines their generally accepted premier position amongst carbanion-stabilizing groups.[21] We will report shortly on the extension of this chemistry to other ring systems.

Acknowledgement: We wish to thank C. Li for mass spectroscopic analysis, NSERC for undergraduate student research awards to MLC (Co-op student, McGill University) and SL (Co-op student, Université de Sherbrooke), and Professor Joseph-Nathan for a sample of natural parvifoline.

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9. (a) Comins, D.L.; Brown, J.D. *J. Org. Chem.* **1984,** *49*, 1078. (b) For a review of α-amino alkoxide directed lithiations, see: Comins, D.L. Synlett **1992**, 615.

10. **5**: colourless crystals, mp 102-103°C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.86 (s, 1H), 7.62 (s, 1H), 3.99 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz), acetone-d_6) δ 194.35, 163.65, 131.98, 129.07, 128.50, 122.42, 99.89, 56.73, 15.97; IR (KBr) υ 2835, 1680, 1590 cm^{-1}; MS (DCI, CH_4) *m/z* 277 $(M+H)^+$; anal. calcd for $C_9H_9IO_2$: C, 39.16; H, 3.29; found: C, 39.10; H, 3.27.

11. **6**: colourless crystals, mp 126-128°C; ^{1}H NMR (200 MHz, acetone-d_6) δ 7.98 (d, 2H), 7.72 (m, 3H), 7.23 (s, 1H), 7.07 (s, 1H), 3.80 (s, 3H), 3.41-3.36 (m, 2H), 3.05-2.90 (m, 2H), 2.05 (s, 3H), ^{13}C NMR (100 MHz, acetone-d_6) δ 157.95, 140.24, 134.60, 132.73, 132.15, 130.24, 129.03, 128.01, 121.53, 96.37, 56.19, 56.06, 33.92, 15.91; IR (KBr) υ 1595, 1490, 1440, 1300, 1140 cm^{-1}; MS (DCI, CH_4) *m/z* 417 $(M+H)^+$; anal. calcd for $C_{16}H_{17}IO_3S$: C, 46.17; H, 4.12; S, 7.70; found: C, 45.99; H, 4.06; S, 7.83.

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14. **3**: light yellow crystals, mp 90-91°C; ^{1}H NMR (200 MHz acetone-d_6) δ 7.98 (d, 2H), 7.77 (t, 1H), 7.69 (t, 2H), 6.87 (s, 1H), 6.76 (s, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.45-3.24 (m, 2H), 3.02-2.70 (m, 3H), 2.25-2.08 (m, 2H), 1.88-1.79 (m, 2H), 1.15 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.97, 158.01, 143.83, 140.55, 134.49, 132.54, 130.18, 128.95, 127.56, 124.79, 108.34, 57.60, 55.61, 51.58, 34.29, 33.37, 32.50, 25.93, 22.54, 15.74; IR (KBr) υ 3010, 1725, 1440 cm^{-1}; MS (CI, CH_4) *m/z* 405 $(M+H)^+$; anal. calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98; found: C, 65.44; H, 7.05.

15. The initially formed aldehyde (60%) was obtained as a 2.8:1 mixture of 4-arylation vs. 3-arylation on *trans*-3-penten-1-ol in favour of the desired product. The mixture was separated at the acid stage. For a similar product distribution using iodobenzene and 2-buten-1-ol, see: (a) Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* **1976**, *41*, 265. (b) Chalk, A.J.; Magennis, S.A. *J. Org. Chem.* **1976**, *41*, 273.

16. **2**: colourless solid, mp 150-156°C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.96 (d, 2H), 7.77 (t, 1H), 7.66 (t, 2H), 6.88 (s, 1H), 6.78 (s, 1H), 4.08 (X part of ABX, 1H, *J*=12.6, 3.99 Hz), 3.78 (s, 3H), 3.63 (A part of ABX, 1H, *J*=13.2, 13.2 Hz), 3.20-3.05 (m, 3H), 2.18-1.89 (m, 2H), 1.36 (d, 3H, *J*=7.0 Hz), 1.40-1.25 (m, 1H); IR (KBr) υ 1705, 1610, 1500, 1440 cm^{-1}; MS (CI, CH_4) *m/z* 373 $(M+H)^+$; anal. calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49; found: C, 67.04; H, 6.53.

17. For related strategies leading to macrocycles and seven-membered ketosulfones, see: (a) Fehr, C. *Helv. Chim. Acta.* **1983**, *66*, 2512; (b) Jones, D.N.; Maybury, M.W.J.; Swallow, S.; Tomkinson, N.C.O. *Tetrahedron Lett.* **1993**, *34*, 8553.

18. **7**: colourless solid, mp 142-145°C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.94 (d, 2H), 7.75 (t, 1H), 7.68 (t, 2H), 7.15 (t, 1H, *J*=8.0 Hz), 3.81 (s, 3H), 3.69 (A part of ABq, 1H, *J*=18.5 Hz), 3.42 (B part of ABq, 1H, *J*=18.5 Hz), 2.94 (m, 1H) 2.05-1.92 (m, 2H), 2.06 (s, 3H), 1.72-1.68 (m, 1H), 1.45-1.25 (m, 1H), 1.32 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.72, 143.73, 143.54, 141.02, 140.23, 134.14, 132.61, 130.20, 128.77, 126.22, 124.37, 107.38, 55.59, 38.46, 34.64, 34.22, 24.01, 19.28, 15.66; IR ($CHCl_3$) υ 3010, 1510, 1415 cm^{-1}; HRMS calcd for $C_{21}H_{24}O_3S + NH_4^+$ 374.1790, found 374.1790.

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20. Demethylation under Lewis acid conditions, e.g. BBr_3, CH_2Cl_2, -78°C occurred readily but with complete conjugation of the olefin.

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