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COMMUNICATION

SYNTHESIS OF ENANTIOPURE FIVE-CARBON, STEREODIADS APPLICABLE FOR THE PREPARATION OF THE MYCOLACTONES

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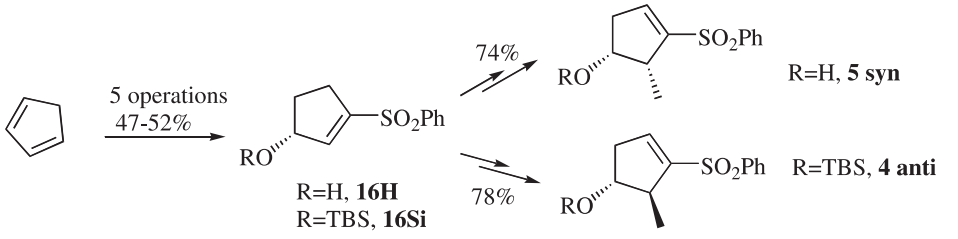
Synthesis of enantiopure γ-hydroxycyclopentenyl sulfones **16H**, **16Si** from cyclopentadiene is accomplished using the Trost palladium-mediated protocol. Conversion of these substrates into stereodiads **4anti** and **5syn** is described.



Keywords: Vinyl sulfone; Enantiopure; Five-carbon stereodiads

Mycolactones A, B (**1Z,1E**) have been isolated from *M. ulcerans* by the research group of P.L.C. Small. The materials were purified by HPLC and shown to rapidly regenerate an equilibrium population of approximately 3 : 2. These compounds are the first toxins isolated from a mycobacterium [1]. Their relative and absolute stereochemistry have been described by Kishi (Figure 1) [2].

To probe the mycolactone SAR profile we elected to undertake its synthesis by preparing a smorgasbord of interchangeable fragments. The initial targets were **4anti** and **5syn** as we felt these materials could be efficiently prepared from cyclopentadiene, thus extending our research with termini-differentiated enantiopure 5–7 carbon segments (Scheme 1) [3].

We have previously shown that enantiopure vinyl sulfone **12** is a useful intermediate for the synthesis of carbacyclin [4] and its analogs, which continue to elicit substantial pharmaceutical interest [5]. Our previous synthesis of **12** involved 11 operations and included a classical resolution, factors that are unattractive to organic chemists in the new millennium (Scheme 2).

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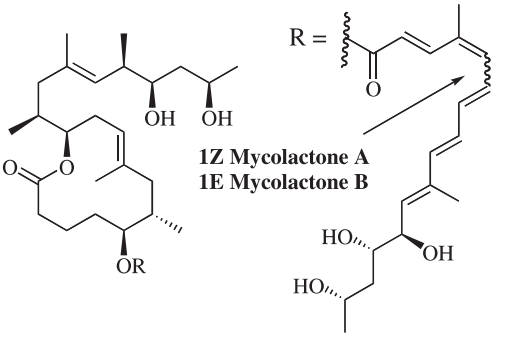
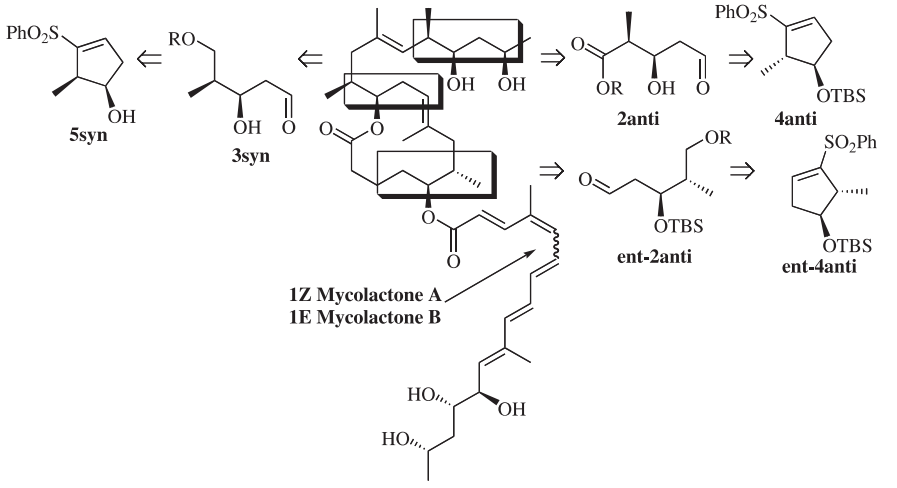
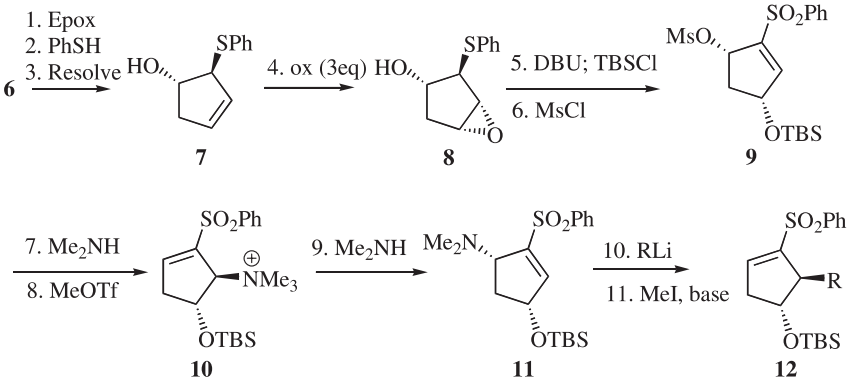


FIGURE 1 Mycolactone synthetic analysis.

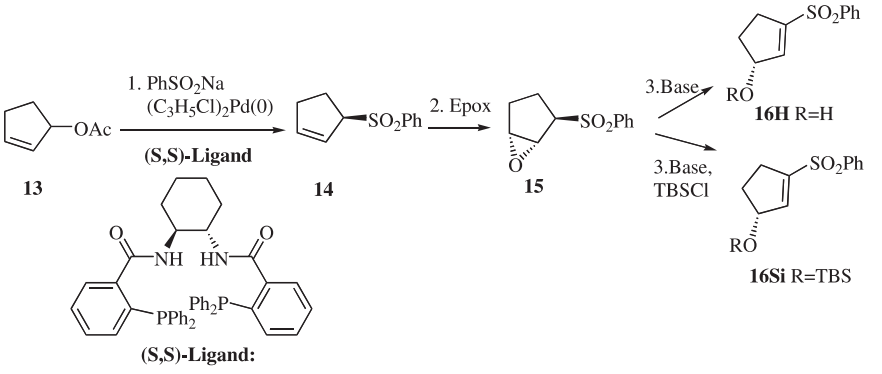


SCHEME 1

A more satisfactory synthesis of the key enantiopure starting materials was accomplished on a large scale with minimal financial expenditure. Following the *Organic Synthesis* protocol [6], hydrogen chloride gas was added to neat cyclopentadiene **6** to generate 3-chlorocyclopent-1-ene. Immediate treatment of this exceptionally reactive allylic halide (not shown) with sodium



SCHEME 2



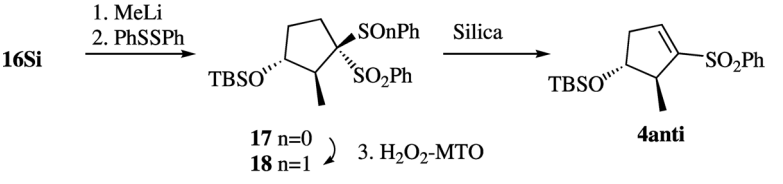
SCHEME 3

acetate provided racemic allylic acetate **13** in 60% yield. Application of the Trost catalytic asymmetric sulfonylation protocol [7] gives the known allylic sulfone **14** in >90% yield and >95% ee (Scheme 3). As previously demonstrated [7, 8] epoxidation of this key material with MCPBA followed by treatment with base provides an efficient synthesis of both alcohol **16H** (97%) and TBS ether **16Si** (85%).

Compounds **16H** and **16Si** are attractive enantiopure intermediates for stereoselective synthesis of termini-differentiated five-carbon fragments. For example, treatment of **16Si** with methyllithium in THF at −78 °C, warming to −25 °C over 2.5 h followed by addition of diphenyl disulfide and warming to 25 °C for 1 h provides sulfide **17** in 78% yield. This material need not routinely be isolated, but oxidized directly to sulfoxide **18** [9] after the sulfenylation reaction. Attempted chromatography on silica gel affords the desired vinyl sulfone **4anti** in quantitative yield (Scheme 4).

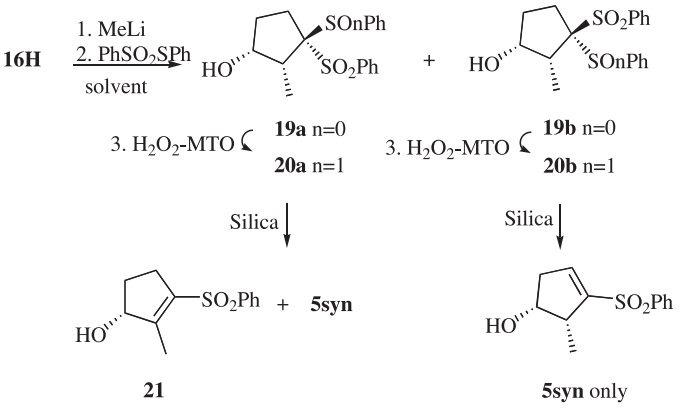
Alcohol **16H** provides access to the complementary stereochemical series. We have previously demonstrated that treatment of γ-hydroxy vinyl sulfones with two equivalents of organolithium reagents results in *syn* delivery of the organolithium moiety, presumably *via* coordination of the second equivalent of RLi to the initially formed lithium alkoxide (Scheme 5) [8].

Although the *syn* stereochemistry of methyl and alcohol moieties was faithfully set in the addition reaction, *in situ* sulfenylation generated **19a/19b** as a separable pair of diastereomeric α-sulfenylsulfones. Oxidation–elimination of these pure materials with MTO-catalyzed hydrogen peroxide oxidation generated unstable sulfoxides **20a** and **20b** as evidenced by TLC. These compounds were not isolated but allowed to undergo elimination to the corresponding vinyl sulfones. While *syn*-elimination of **20b** regiospecifically provided the desired alcohol **5syn** (99%), isomer **20a** strongly favored formation of unwanted **21**. Fortunately, addition of 1 equiv of HMPA at the sulfenylation stage gave a 1:6 mixture of **19a/19b** which could be routinely processed to afford a 74% yield of **5syn**.



SCHEME 4

To conclude, stereodiads **4anti** and **5syn** are efficiently synthesized from enantiopure γ-hydroxycyclopentenyl sulfones **16H**, **16Si**.



Solvent	**19a** : **19b**
Toluene	100:0
THF	1:1
THF–20%HMPA	1:6

SCHEME 5

EXPERIMENTAL

((*1R*,*2S*)-3-Benzenesulfonyl-2-methylcyclopent-3-enyloxy)-*t*-butyldimethylsilane (4anti)

Solid **17** (539 mg, 1.17 mmol) was dissolved in ethanolic H_2O_2 (2.6 mL, 1.28 mmol, 0.5 M), and a catalytic amount of MTO (methyltrioxorhenium) was added to the solution, resulting in a mild exotherm, which subsided after 10 min. After formation of the more polar sulfoxide **18** appeared complete by TLC analysis, SiO_2 was added to the solution, which was stirred for an additional 3 h to complete elimination of the phenylsulfinic acid. The mixture was poured into aqueous $NaHSO_3$ to decompose the excess H_2O_2. The aqueous solution was extracted with CH_2Cl_2, and washed with brine. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography on silica gel to afford vinylsulfone **4 anti** (410 mg, 99%).

4 anti R_f 0.55 (20% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.88 (m, 2H), 7.58 (m, 3H), 6.74 (t 1H), 4.03 (m, 1H), 2.78 (m, 1H), 2.57 (m, 1H), 2.34 (m, 1H), 1.12 (d, 3H, $J = 7.3$ Hz), 0.75 (s, 9H), −0.02 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 146.4, 140.8, 133.2, 129.1, 127.8, 80.3, 48.8, 40.7, 25.7, 17.8, 16.5, −4.77.

(*1R*,*2R*,*3S*)-3-Benzenesulfonyl-2-methyl-3-phenylthiocyclopentanol (19a) and (*1R*,*2R*,*3R*)-3-Benzenesulfonyl-2-methyl-3-phenylthio-cyclopentanol (19b)

MeLi (7.6 mL, 8.34 mmol, 1.10 M) was added dropwise to a solution (15 mL, THF) of **16H** (849 mg, 3.79 mmol) at −78 °C. The reaction was then slowly warmed to −30 °C over 2–3 h while monitoring the disappearance of **16H** and the appearance of the conjugate addition products. The reaction was quenched with PhSSPh (2.07 g, 9.48 mmol). The mixture was diluted

with Et_2O, and washed with saturated NH_4Cl, water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford **19a** (280 mg, 22%) and **19b** (293 mg, 23%).

19a: R_f 0.55 (50% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (m, 2H), 7.74 (m, 3H), 7.64 (m, 2H), 7.43 (m, 3H), 4.17 (t, 1H, $J = 7.0$ Hz), 3.42 (bs, 1H), 2.76 (m, 1H), 2.55 (m, 1H), 2.03 (m, 2H), 1.52 (m, 1H), 1.32 (d, 3H, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.78, 136.55, 134.01, 131.69, 130.39, 129.52, 128.96, 128.51, 80.30, 76.35, 52.86, 36.91, 33.66, 10.88.

19b: R_f 0.50 (50% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.07 (m, 2H), 7.60 (m, 5H), 7.33 (m, 3H), 4.21 (m, 1H), 2.72 (m, 2H), 2.01 (m, 3H), 1.77 (m, 1H), 1.11 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.50, 136.28, 134.19, 131.51, 129.17, 129.11, 129.02, 82.80, 76.85.

Experiments with HMPA as cosolvent (**19a**:**19b** < 1:6): MeLi (0.4 mL, 0.56 mmol, 1.4 M) was added dropwise to a solution THF–HMPA (0.6 and 0.15 mL) of **16H** (56 mg, 0.25 mmol) at −78 °C. The reaction was then slowly warmed to −35 °C over 3.5 h while monitoring the disappearance of **16H** and the appearance of the conjugate addition products. The reaction was quenched with a solution of THF–HMPA (0.6 and 0.15 mL) $PhSO_2SPh$ (0.31 g, 1.24 mmol), then slowly warmed to 0 °C. Subsequently, the reaction mixture was diluted with diethyl ether and washed with saturated NH_4Cl, water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford **19b** (64 mg, 74%).

(*1R*,*2R*)-3-Benzenesulfonyl-2-methylcyclopent-3-enol (5syn)

19b (25 mg, 0.718 mmol) was dissolved in ethanolic H_2O_2 (1.72 mL, 0.86 mmol, 0.5 M), and a catalytic amount of MTO was added to the solution. The same procedure as for **4anti** was then followed to afford vinylsulfone **5syn** (17 mg, 99%).

5syn R_f 0.25 (50% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.92 (m, 2H), 7.62 (m, 1H), 7.59 (m, 2H), 6.74 (d, 1H), 4.49 (q, 1H), 2.93 (m, 1H), 2.76 (m, 1H), 2.52 (m, 1H), 1.12 (d, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 147.12, 140.58, 140.06, 133.48, 129.22, 127.91, 74.14, 42.86, 39.48, 11.25; MS (EI): 238 (M^+), 125 (base peak), 221 ($M^+ - OH$). MS (CI): 239 (M + H, base peak), 221 (M + H − H_2O).

((*R*)-3-Benzensulfonylcyclopent-2-enyloxy)-*t*-butyldimethylsilane (16Si)

Allyl sulfone **15** (4.03 g, 19.4 mmol) was dissolved in CH_2Cl_2 (125 mL). To this solution was added MCPBA (4.01 g, 23.2 mmol) portionwise at 0 °C. The reaction mixture was allowed to warm to room temperature and vigorously stirred for 36 h. The reaction mixture was then diluted with CH_2Cl_2, washed with saturated Na_2CO_3, $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude oil was then purified by flash column chromatography on silica gel to afford epoxy sulfone (3.7 g, 86%) which is directly used in the next reaction. To a solution of epoxy sulfone (7.21 g, 32.2 mmol) in THF (50 mL) was added DBU (496 mg, 3.22 mmol, 0.1 eq.) at room temperature. The resulting mixture was heated at 67 °C for 18 h and then cooled to room temperature. Subsequently, the reaction mixture was concentrated *in vacuo* and the resulting crude oil was purified by flash column chromatography on silica gel to afford γ-hydroxylvinyl sulfone **16H** (7.0 g, 97%). **16H** was dissolved in THF (110 mL), to which was added TBSCl (5.31 g, 35.4 mmol), imidazole (3.38 g, 48.3 mmol), followed by a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 24 h, and the reaction was then quenched with saturated $NaHCO_3$ and diluted with Et_2O. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*.

The resulting crude oil was purified by flash column chromatography on silica gel to afford of γ-silyloxyvinyl sulfone **16Si** (10.9 g, 85%) as a colorless oil.

16H R_f 0.50 (50% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.88 (m, 2H), 7.58 (m, 3H), 6.65 (s, 1H), 4.96 (m, 1H), 2.63 (m, 1H), 2.50 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 146.9, 142.8, 138.6, 133.9, 129.4, 128.1, 76.2, 33.9, 29.3. $[\alpha]_D^{25} = +72.7°$ (*c*, 2.25, CH_2Cl_2). MS (EI): 224 (M^+), 55 (base peak). MS (CI):225 (M + H, base peak). HRMS (EI): calculated for $C_{11}H_{12}O_3S$ 224.0507, found 224.0502.

16Si R_f 0.65 (20% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (m, 2H), 7.71 (m, 3H), 6.60 (m, 1H), 4.96 (m, 1H), 2.45 (m, 3H), 1.82 (m, 1H), 0.87 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 145.9, 143.4, 138.9, 133.6, 129.2, 128.2, 76.8, 34.6, 29.1, 25.8, 18.1, −4.68, −4.72.

((*1R*,*2S*,*3R*)-3-Benzensulfonyl-2-methyl-3-phenylthiocyclopentyl-oxy)-*t*-butyldimethylsilane (17)

MeLi (4.84 mL, 6.79 mmol) was added at −78 °C to a solution of copper iodide (645 mg, 3.38 mmol) in Et_2O (5 mL). The resultant mixture was stirred for 15 min, then warmed to 0 °C for 5 min, at which point the reaction mixture became a clear solution. The reaction was cooled to −78 °C, then transferred to a solution of **16Si** (1.04 g, 3.07 mmol) in THF (20 mL) at −78 °C. The resulting yellow mixture was allowed to warm to −25 °C over 2–3 h, then quenched with PhSSPh (2.02 g, 9.22 mmol). The reaction mixture was diluted with Et_2O, washed with water and brine. The organic layer was dried with anhydrous $MgSO_4$ filtered, concentrated *in vacuo* and purified by flash column chromatography on silica gel to afford α-phenylthiosulfone **17** (1.03 g, 78%).

17 R_f 0.80 (20% EtOAc in hexanes), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.03 (m, 2H), 7.72 (m, 5H), 7.34 (m, 3H), 4.01 (q, 1H, $J = 7.4$ Hz), 2.42 (m, 2H), 1.83 (m, 1H), 1.64 (m, 1H), 1.50 (m, 1H), 1.03 (d, 3H, $J = 6.8$ Hz), 0.87 (s, 9H), 0.04 (d, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.4, 136.1, 133.8, 131.2, 129.7, 129.4, 128.8, 128.7, 81.2, 78.4, 48.9, 31.7, 29.4, 25.8, 18.0, 12.0, −4.41, −4.71.

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