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TOTAL SYNTHESIS OF (+)-SPATOL. A STEREOSPECIFIC CONSTRUCTION OF VICINAL DIEPOXIDES FROM 2,3-EPOXY-1,4-DIOLS

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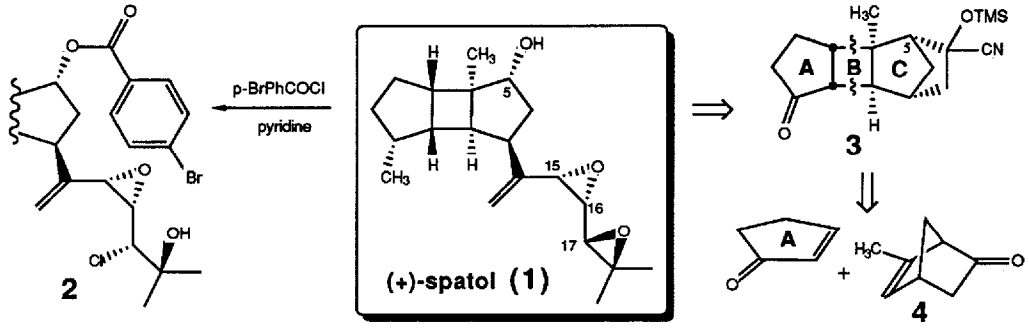
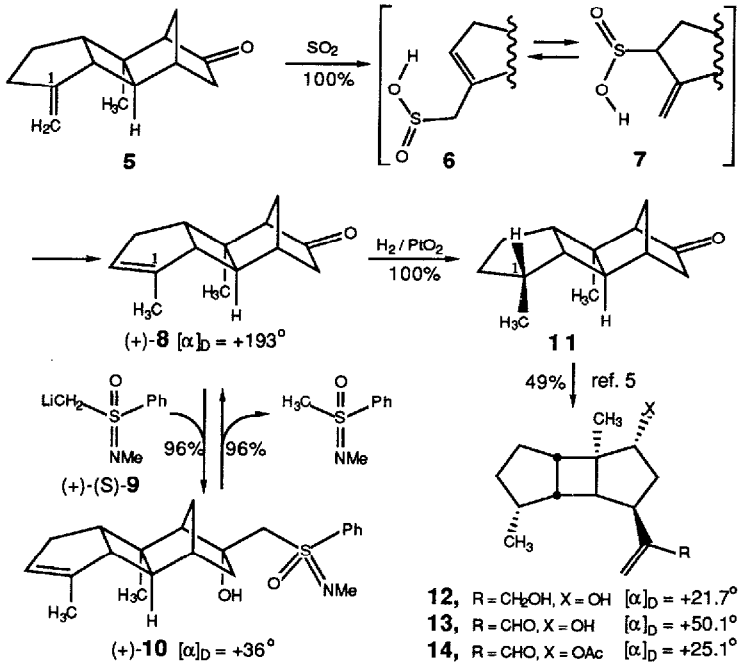
Summary: A total synthesis of (+)-spatol (1) was achieved which depends upon a novel stereospecific transformation of *trans*-2,3-epoxy-1,4-diols to generate the sensitive allylic vicinal *cis*-diepoxide in **1**.

Spatol (1), a structurally and functionally complex minor metabolite produced by a tropical marine alga,[1] shows potent cytotoxicity against skin and brain tumor cells, completely inhibiting cell division in human T242 Melanoma and 224C Astrocytoma neoplastic cell lines at 16 μg/mL. The unique allylic vicinal diepoxide in **1** constitutes by far the most challenging aspect of any synthetic approach to this target.[2] The high electrophilicity of this functional array is evidenced by the epoxide ring opening reaction with a chloride nucleophile which accompanies esterification upon treatment of **1** with p-bromobenzoyl chloride and pyridine producing **2**. This reactivity, almost certainly at the heart of spatol's biological activity, is reminiscent of the electrophilicity observed for the vicinal diepoxide in the cytotoxin crotepoxide[3] and the vicinal triepoxide in the antileukemic diterpenes triptolide and tripdiolide.[4] However, while the epoxy groups in these natural products are confined to rigid cyclohexane rings, those in spatol are located in a flexible acyclic side chain. We now report a total synthesis of spatol featuring a stereospecific epoxydiol rearrangement as the key step in a novel construction of the sensitive allylic diepoxide array.



Previously, we reported an effective strategy for stereocontrolled construction of the tricyclic spatane diterpene nucleus.[5] Photocycloaddition of 2-cyclopentenone with carbonyl-masked

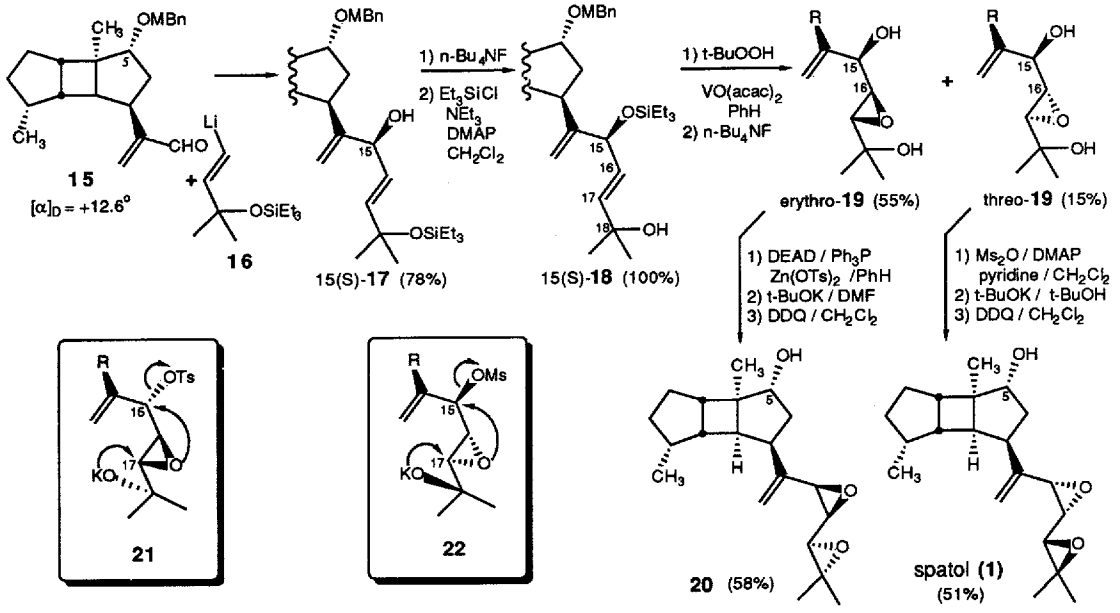
derivatives of 6-methylbicyclo[2.2.1]hept-5-en-2-one (**4**)[6] stereoselectively provides *exo* adducts, e. g. **3**, with the A-ring carbonyl remote from the B-ring methyl. Wittig methylenation of ketone **3** and hydrolysis delivers **5** in 89% yield. Catalytic hydrogenation of **5** is stereoselective favoring **11** over 1-epi-**11** by 10:1 owing to steric congestion of the α-face by a methyl group.[5]



However, isolation of epimerically pure **11** from the epimeric mixture requires a tedious fractional crystallization. Steric congestion of the α-face should more effectively control hydrogen delivery to the endocyclic alkene **8** in which the B-ring methyl group and C=C bond are in closer proximity than in the exocyclic alkene **5**. To improve selectivity during generation of the stereocenter at position 1, the exocyclic alkene **5** was isomerized to the endocyclic alkene **8**. Clean conversion of **5** to **8** occurs in liquid SO_2 presumably by an ene reaction producing **6**, [1.3] sigmatropic rearrangement to **7**, and retro ene elimination.[7] Evaporation of the SO_2 delivers pure crystalline **8**. Catalytic hydrogenation of **8** quantitatively delivers pure crystalline **11**, a major improvement over catalytic hydrogenation of **5**. Resolution[8] of ketone **8** was readily achieved by flash chromatography of the 1,2-adduct with chiral lithiosulfoximine (+)-(S)-**9**.[9] Retro ene elimination of the less soluble dextrorotatory diastereomer (+)-**10** delivers ketone (+)-**8**, mp 67-68 °C, which was correlated with natural spatol by conversion to acetate **14**[1] as described previously for racemic **8**.[5]

The spatane skeleton was completed by stereoselective addition of vinyllithium **16** to the 5-(p-methoxybenzyloxy)aldehyde **15** favoring the 15(S) over the 15(R) epimer of **17** by 13:1. This stereochemical assignment is established by stereospecific conversion of the major epimer into

(+)-spatol (*vide infra*). To ensure the requisite regioselectivity during monoepoxidation of the diene in 15(S)-**17**, the tertiary 18-hydroxyl was uncovered by desilylation and the secondary 15-hydroxyl was selectively masked by silylation. Vanadium-catalyzed epoxidation of 15(S)-**18** followed by desilylation favored the 15,16-erythro[10] diastereomer of epoxydiol **19** over the threo diastereomer by 4:1. Construction of the sensitive allylic diepoxide array was achieved by a novel stereospecific transformation of the epoxydiol erythro-**19**. Configurational inversion at the 15-position accompanied generation of a tosylate using the Still modification of the Mitsunobu reaction.[11] Subsequent t-BuOK catalyzed Payne rearrangement[12] and heterocyclization produced a *cis* diepoxide as summarized in **21**. Removal of the p-methoxybenzyl (MBn) protecting group upon treatment with DDQ[13] cleanly delivered an allylic *cis* diepoxide. Small chemical shift differences,[14] e.g. vinyl ^{1}H NMR resonances at δ5.14 and 5.09, showed that this diepoxide is **20**, epimeric at positions 15, 16, and 17 with (+)-spatol (**1**) which exhibits vinyl resonances at δ5.13 and 5.02. This conclusion is further supported by vinyl ^{13}C NMR resonances at δ141.8 and 112.9 for **20** but δ141.4 and 111.0 for **1**, and by $[\alpha]_D$ = -10.0° (c 0.7, $CHCl_3$) for **20** but $[\alpha]_D$ = +45.6° (c 1.56, $CHCl_3$)[1c] for **1**.



Stereospecific transformation of the epoxydiol threo-**19** into (+)-spatol (**1**) was accomplished by selective activation of the 15-hydroxyl as a mesylate followed by Payne rearrangement and heterocyclization, as summarized in **22**, and finally de-p-methoxybenzylation with DDQ. Each resonance in the ^{1}H NMR spectrum of synthetic **1** coincided within 0.01 ppm with a spectrum of an authentic sample of natural spatol.[14] The fact that this diepoxide is stable in the presence of t-BuOK contrasts with the ring cleaving formation of **2** from **1** by reaction with pyridinium chloride and suggests that the electrophilicity of the allylic diepoxide is amplified by the presence of an acid catalyst.

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14. All ^1H and ^{13}C NMR spectra of **20** and **1**, including those of an authentic sample of natural spatol were compared in $CDCl_3$ solutions on the same Brucker 9.4 Tesla MSL-400 FT-NMR spectrometer. **20**: mp 69-71 °C, $[\alpha]_D^{22}$ = -10.0° (c 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, 1 H, *J* = 1.3 Hz), 5.09 (s, 1 H), 3.74 (d, 1 H, *J* = 4.5 Hz), 3.50 (d, 1 H, *J* = 4.0 Hz), 3.09 (ddd, 1 H, *J* = 13.2, 5.5, 5.5 Hz), 2.90 (dd, 1 H, *J* = 7.5, 4.1 Hz), 2.52 (d, 1 H, *J* = 7.5), 2.25 (ddd, 1 H, *J* = 13.2, 13.2, 4.3 Hz), 2.15 (t, 1 H, *J* = 5.0 Hz), 2.08-2.02 (m, 1 H), 1.97 (t, 1 H, *J* = 7.4 Hz), 1.88-1.80 (2 H), 1.76-1.66 (2 H), 1.46-1.32 (6 H), 1.30 (s, 3 H), 0.98 (s, 3 H), 0.92 (d, 3 H, *J* = 6.7 Hz). ^{13}C NMR (100.607 MHz, $CDCl_3$, for APT a (+) indicates 0 or 2 attached protons, a (-) indicates 1 or 3 attached protons) δ 141.8 (+), 112.9 (+), 80.13 (-), 58.92 (-), 58.75 (+), 57.32 (-), 55.55 (-), 47.18 (+), 44.27 (-), 43.62 (-), 43.44 (-), 38.03 (-), 36.89 (+), 36.63 (-), 35.26 (+), 27.78 (+), 24.23 (-), 19.34 (-), 14.16 (-), 12.96 (-). **1**: $[\alpha]_D^{22}$ = +44.2° (c 0.66, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (dd, 1 H, *J* = 3.0, 1.5 Hz) 5.03, (s, 1 H), 3.74 (d, 1 H, *J* = 4.4 Hz), 3.44 (d, 1 H, *J* = 3.8 Hz), 3.03 (ddd, 1 H, *J* = 14.5, 5.5, 5.5 Hz), 2.87 (dd, 1 H, *J* = 7.9, 4.3 Hz), 2.49 (d, 1 H, *J* = 7. 9 Hz), 2.28 (ddd, 1 H, *J* = 13.2, 13.2, 4.3 Hz), 2.12-2.05 (2 H), 1.97 (t, 1 H, *J* = 6.8 Hz), 1.89-1.80 (2 H), 1.78-1.65 (2 H), 1.47-1.18 (3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 0.99 (s, 3 H), 0.91 (d, 3 H, *J* = 6.7 Hz). ^{13}C NMR (100.607 MHz, $CDCl_3$, for APT a (+) indicates 0 or 2 attached protons, a (-) indicates 1 or 3 attached protons) δ 141.5 (+), 111.0 (+), 79.96 (-), 58.42 (+), 58.12 (+), 57.06 (-), 55.14 (-), 47.21 (+), 43.79 (-), 43.40 (-), 43.25 (-), 37.82 (-), 36.87 (+), 36.56 (-), 35.18 (+), 27.87 (+), 24.23 (-), 19.26 (-), 14.47 (-), 12.97 (-).

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