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A SHORT SYNTHESIS OF THE ANTIMITOTIC ALLYLIC DIEPOXIDE FUNCTIONAL ARRAY OF SPATOL

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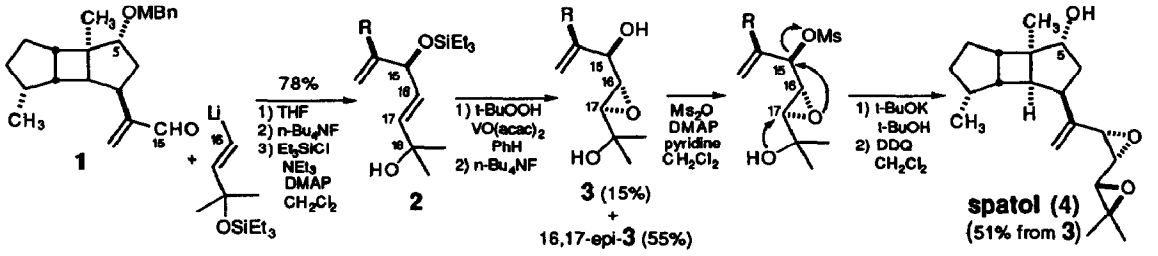
Summary: An α-lithio epoxide intermediate provides a highly stereocontrolled synthesis of the spatol allylic diepoxide, a functional array that is uniquely effective at inhibiting mitosis.

Spatol (**4**), a marine diterpene, is cytotoxic toward human skin and brain cancer cells.[1] However, limited availability from natural sources is hampering studies of spatol's medicinal potential. Total synthesis could not only ameliorate the supply problem, but could also allow investigation of relationships between structure and biological activity by providing access to structural analogues. The chemically sensitive[2] allylic diepoxide array of spatol is undoubtedly of paramount importance for its biological activity.[3] This moiety is a redoubtable synthetic challenge because it contains both densely packed reactive functionality and three contiguous stereocenters that are isolated from those of the tricyclic nucleus. The two methods reported previously for generating the spatol diepoxide gave poor yields.[4,5] We now find that a novel α-lithio epoxide can be used as a key intermediate in an efficient construction of such allylic diepoxides.

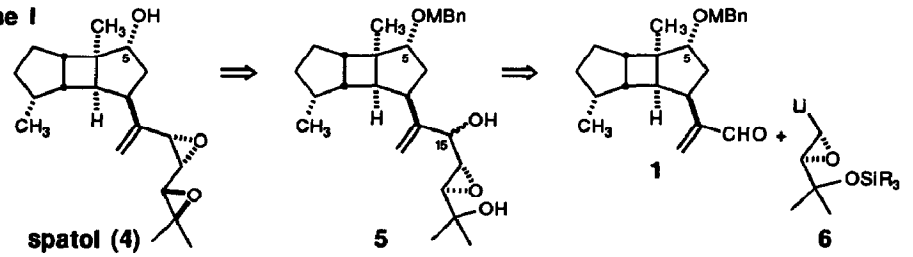
Our recent total synthesis of spatol (**4**), demonstrated that the allylic diepoxide functional array can be generated from epoxydiol **3** or its C15 epimer by Payne rearrangement-heterocyc-



lization of sulfonate mono ester derivatives.[4] Establishing the correct relationships between the stereocenters of the tricyclic nucleus and those in the allylic diepoxide side chain required selective generation of the correct configurations at C16 and C17. Therefore, the unfavorable diastereoselectivity encountered in the epoxidation of **2** limited the efficacy of this approach.

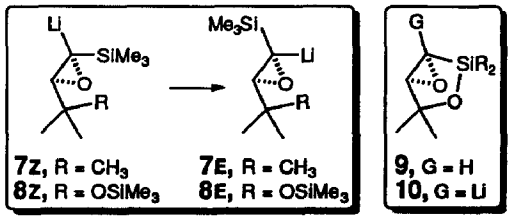
Now we are exploring a different, more convergent,[6] synthetic strategy involving the union of chiral nonracemic building blocks **1** and **6** with the correct absolute configurations (Scheme I),

Scheme I

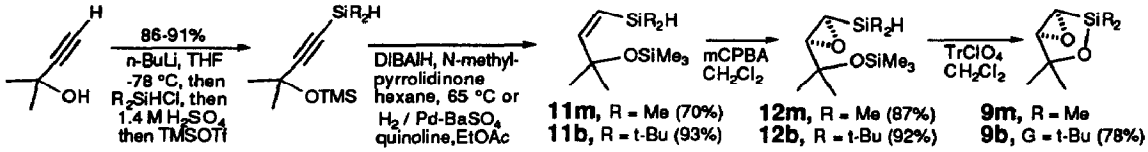


an "absolute asymmetric synthesis".[7] Generation of either configuration at position 15 in **5** is satisfactory because such epoxy diols can be selectively converted in one step, with or without inversion of configuration, into suitable sulfonate ester precursors of spatol (**4**).[4]

Pioneering studies by Eisch and Galle showed that α-lithio epoxides, stabilized with a trialkylsilyl reactivity control element, are readily available by metallation of the corresponding α-silyl epoxides.[8] Unfortunately, a proclivity toward isomerization to **7E** was found for the α-lithio-α-silyl epoxide **7Z**.[8] A similar epimerization of **8Z** into **8E** would compromise its utility as a synthetic equivalent of α-lithio epoxide synthon **6**. However, anchoring the anion-stabilizing silyl substituent by a temporary bridge to the tertiary hydroxyl group precludes configurational instability. We now find that the alkoxy dialkylsilyl groups in α-silyl epoxides **9** provide adequate stabilization to permit generation of the key α-lithio epoxides **10**, and that these intermediates can serve as stereochemically defined synthetic equivalents of α-lithio epoxide synthon **6** (see Scheme I).

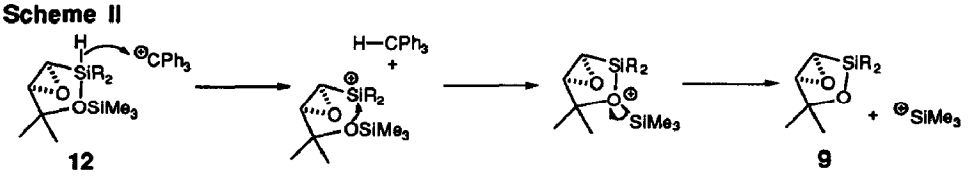


In one route to the requisite α-silyl epoxides **9**, hydroalumination-hydrolysis[8] provided vinylsilane **11m**. The di-t-butyl analogue **11b** was generated by partial hydrogenation in the presence of Lindlar catalyst. The syntheses of **9b** and **9m** were completed by a novel heterocyclization of the epoxides **12b** and **12m** that was promoted by trityl perchlorate.[9] This reaction

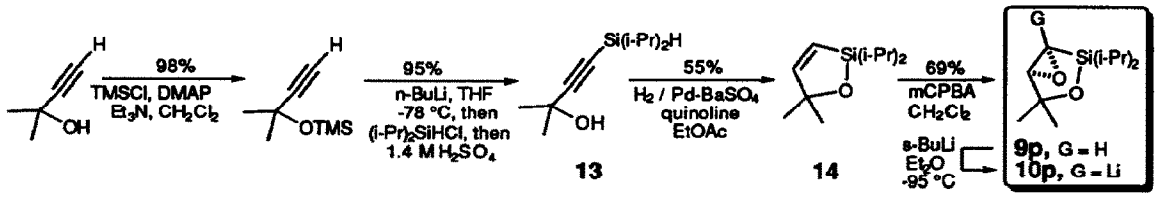


presumably involves preliminary abstraction of hydride by the trityl cation. Subsequent intramolecular O-silylation followed by expulsion of a trialkylsilyl cation delivers **9** (Scheme II).

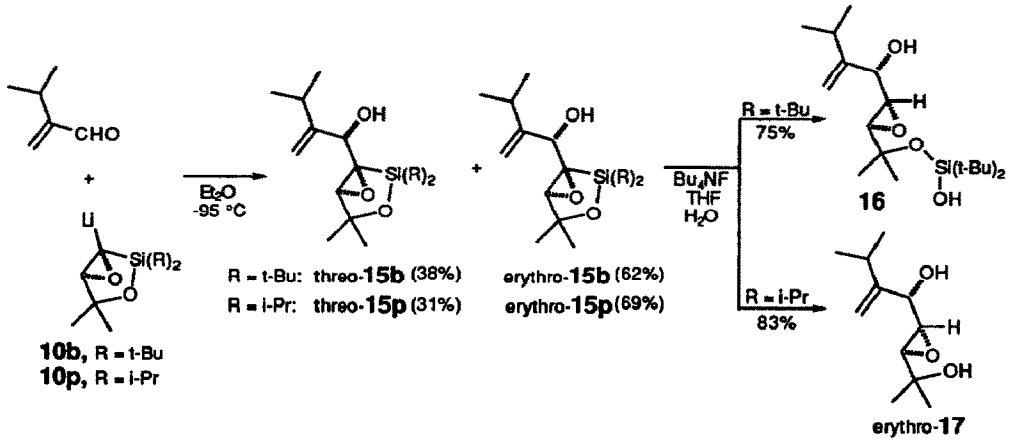
Scheme II



A different approach was developed for preparing the di-i-propyl analogue **9p**. A noteworthy feature of this route is a novel partial hydrogenation-dehydrogenative heterocyclization that delivers vinyl siloxane **14** in one step from hydroxy alkynylsilane **13**. Most importantly, metallation of **9b** or **9p** produced an α-lithio epoxide **10b** or **10p** respectively.



The α-epoxy dimethylsiloxane **9m**, that was readily prepared from chloro(dimethyl)silane, exhibited inconveniently high hydrolytic instability. Thus, **9m** decomposed upon attempted purification by chromatography on silica gel. To increase hydrolytic stability, we turned to the di-t-butyl analogue **9b**, a stable, nicely crystalline solid. Conjunction of the derived α-lithio epoxide **10b** with 2-(i-propyl)acrolein delivered a 6:4 epimeric mixture of adducts **15b**. The major adduct is presumed to be the erythro diastereomer by analogy with the corresponding adducts **15p** (vide infra). However, the hydrolytic stability provided by the t-butyl substituents was too great. Thus, treatment of the major adduct with Bu_4NF in moist THF delivered a silyl ether **16**.



As a compromise, racemic **10p** was prepared. Reaction with 2-(i-propyl)acrolein delivered an epimeric mixture of adducts **15p** favoring the erythro diastereomer by 7:3. The structures of these isomeric epoxides were established by desilylation.[10] Thus, erythro-**17**, generated by the new two-step synthesis, was identical with a sample prepared previously by a different route.[4]

The racemic intermediate **10p** described above provides ready access to spatol analogues for structure-activity studies. However, only conjunction of aldehyde **1** with the correct enantiomer of **10p** will provide the correct absolute configurations at positions 16 and 17 in **5** that are required to accomplish the efficient construction of natural spatol (**4**) envisioned in Scheme I. A route to optically pure epoxide **10p** must now be found.

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REFERENCES AND NOTES

1. (a) Gerwick, W. H.; Fenical, W.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7991. (b) Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233. (c) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 3325.

2. A novel ring opening of spatol (**4**) that produces **i** is promoted by mild acid (Py•HCl) catalysis. Even the simple analogue **ii** exhibits similar reactivity. Thus, the acid-catalyzed hydrolysis of **ii** is presumably mechanistically related generating diol **iii**.

4 i ii iii

3. Even the simple analogue **ii** is antimitotic. Thus, it inhibits the first synchronous cell division of fertilized sea urchin eggs (ED_{50} = 100μM) albeit less effectively than spatol (ED_{50} = 4 μM).[1] Interestingly, although **iii** does not prevent cell division, it induces unsymmetrical cell division as seen by the generation of abnormal zygotes in a dose dependent fashion. For assay method see: Murthi, K.; Salomon, R. G.; Sternlicht, H.; *Prostaglandins* **1990**, *39*, 611.

Sample	[iii] (μM)	Cells (per 100 eggs) single	double	abnormal
1	0	6	92	1
2	88	17	68	15
3	176	15	55	30
4	265	20	55	25
5	350	18	40	42

4. Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, *113*, 3096.

5. Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 6109.

6. Velleux, L.; Valls, J.; Mathieu, *Angew. Chem., Int. Ed.* **1967**, *6*, 778.

7. This strategic category was formulated by Woodward in connection with the total synthesis of cobyric acid: Woodward, R. B.; *Pure Appl. Chem.* **1973**, *33*, 145.

8. (a) Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646. (b) Eisch, J. J.; J. J.; Galle, J. E. *J. Organomet. Chem.* **1976**, *121*, C10. (c) Eisch, J. J.; J. J.; Galle, J. E. *J. Organomet. Chem.* **1976**, *41*, 2615. (d) Eisch, J. J.; J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293.

9. Chen, Y. L.; Barton, T. J. *Organometallics*, **1987**, *6*, 2590.

10. Such desilylations proceed with retention of configuration at the epoxy carbon: Chan, T. H.; Lau, P. W. K.; Li, M. P. *Tetrahedron Lett.* **1976**, 2667.

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