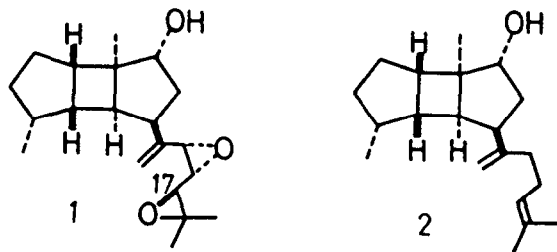


THE FIRST TOTAL SYNTHESIS OF (+)-SPATOL WITH NATURAL CONFIGURATION

Masahide Tanaka, Kiyoshi Tomioka, and Kenji Koga*
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary: The first total synthesis of (+)-spatol (**1**) with natural configuration is described. The important step utilizes the carbon-carbon bond formation with simultaneous epoxide formation by the reaction of optically pure sulfonium ylide (**4**) and optically pure epoxy aldehyde (**5**).

Spatol (**1**) is a member of the novel spatane diterpenes isolated from brown marine algae of the family Dictyotaceae.^{1,3)} Spatol is also known to be endowed with remarkable biological properties including a potent inhibition of cell replication.¹⁾ X-ray crystallographic analysis of its derivative revealed the unique structure of **1**, which is characterized by the presence of linear vinylic diepoxide sidechain attached to the cis, anti, cis-tricyclo[5.3.0.0^{2,6}]decane skeleton.^{1,4)} Quite recently Salomon⁵⁾ and we⁶⁾ have reported independent synthesis of racemic⁵⁾ and optically pure⁶⁾ stoechospermol (**2**), a representative of the spatane diterpenes of the lower oxidation level. We describe herein the first total synthesis of (+)-spatol in an optically pure form with natural configuration. The synthesis provides the direct evidence for the C-17 stereochemistry to be S-configuration in natural (+)-spatol (**1**).¹⁾



Our general idea for the synthesis of **1** is the coupling of two optically pure units, sulfonium ylide (**4**) derived from **3**⁶⁾ and epoxy aldehyde (**5**),⁷⁾ with a simultaneous epoxide

formation. Since the synthetic methods for the linear vinylic diepoxide systems are quite few,^{8,9)} we started our investigations with a model study. Three sulfonium salts (**6a,b,c**)¹⁰⁾ were prepared from 2-cyclohexylprop-2-en-1-ol.¹¹⁾ Treatment of **6a** (R=Me) with LDA or BuLi in DME followed by the addition of racemic **5** however, resulted in the formation of **10** (R=Me, R'=H) as a major product, which is considered to be arisen from the deprotonation at the MeS group of **6a** and following [2,3] sigmatropic rearrangement.¹²⁾ Attempted reaction by the use of diphenyl sulfonium salt (**6b**: R=Ph) was also unsatisfactory to give rise to a mixture of diepoxides in low yield as shown in the Table I. Fortunately, it was found that, when the diethyl sulfonium salt (**6c**: R=Et) was treated with methyl lithium in the presence of 1 eq. of HMPA in DME and then with **5**, the desired vinylic diepoxide (**7**) was obtained as a major isomer in 25% yield, accompanied by the formation of three epoxide isomers (**8**, **9**)¹³⁾ and the rearranged product (**10**: R=Et, R'=Me). The structure of **7** was assigned by the following experiments. The syn, syn-alcohol (**11**: $J_{\text{Ha,Hb}}=8$ Hz),¹⁴⁾ prepared by the reaction of the corresponding allyl stannane with **5** according to the chemistry of Yamamoto, Maruyama, and Keck,¹⁵⁾ was treated with Me_3OBF_4 in CH_2Cl_2 and then with methyl lithium in DME-HMPA to afford the *cis*-diepoxide (**8**: $J_{\text{Ha,Hb}}=4$ Hz)¹⁶⁾ having the undesired relative configuration. Coupling constant between the protons of the newly created epoxide of **7** is 4 Hz and this indicates that **7** has the desired relative configuration identical with that of **1**.

Application of the method to our goal provided (+)-spatol as described below. The allylic alcohol (**3**: $[\alpha]_{\text{D}}^{20} -60^\circ$ (CHCl_3))⁶⁾ was converted to the crystalline sulfonium salt (**12**: $[\alpha]_{\text{D}}^{24} +84.2^\circ$ (CHCl_3), mp 123-126°C) in 79% overall yield in four steps (i. MsCl , NEt_3 - CH_2Cl_2 ; ii. NaSEt -DMF; iii. 10% H_2SO_4 -acetone; iv. Et_3OBF_4 - CH_2Cl_2). Treatment of **12** with methyl lithium in the presence of 1 eq. of HMPA in DME at -70°C for 60 min and then with optically active **5**⁷⁾ at -70°C for 60 min and then at room temperature for 60 min afforded, after careful separation by HPLC (silica gel, acetone-hexane/1:6), (+)-spatol (**1**) and two isomers (**13**, **14**)¹⁷⁾ in a ratio of 24:12:64 in 13% yield and the rearranged product (**15**) in 35% yield.^{18,19)} Optical rotation, melting point, tlc behavior, and spectroscopic data of the synthetic spatol (**1**) ($[\alpha]_{\text{D}}^{23} +45.5^\circ$ (CHCl_3), mp 100-101°C, mixed mp 100-102°C) were completely identical with those of the natural spatol ($[\alpha]_{\text{D}} +45.6^\circ$ (CHCl_3), mp 100-102°C). Since the optically pure epoxy aldehyde (**5**) with definite configuration was incorporated in **1**, the C-17 stereochemistry in natural spatol was firmly established.¹⁾

Evaluation of the cytotoxic activity of spatol and its isomers, and further efforts for the improvement of the coupling step are the subjects of the current studies.

Acknowledgments The authors are grateful to Dr. W. Fenical for providing natural spatol. This work was supported by a grant-in-aid from the Ministry of Education, Science and Culture, Japan.

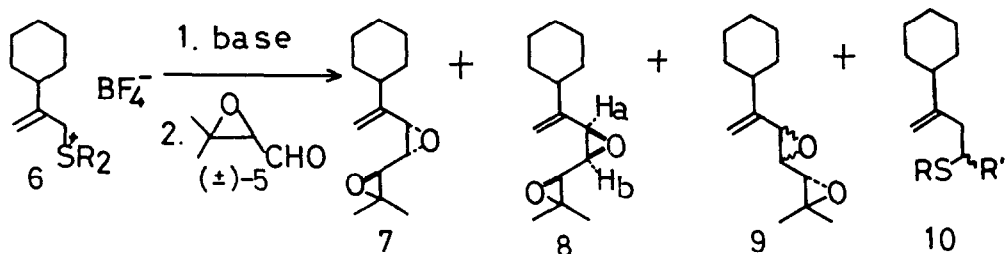
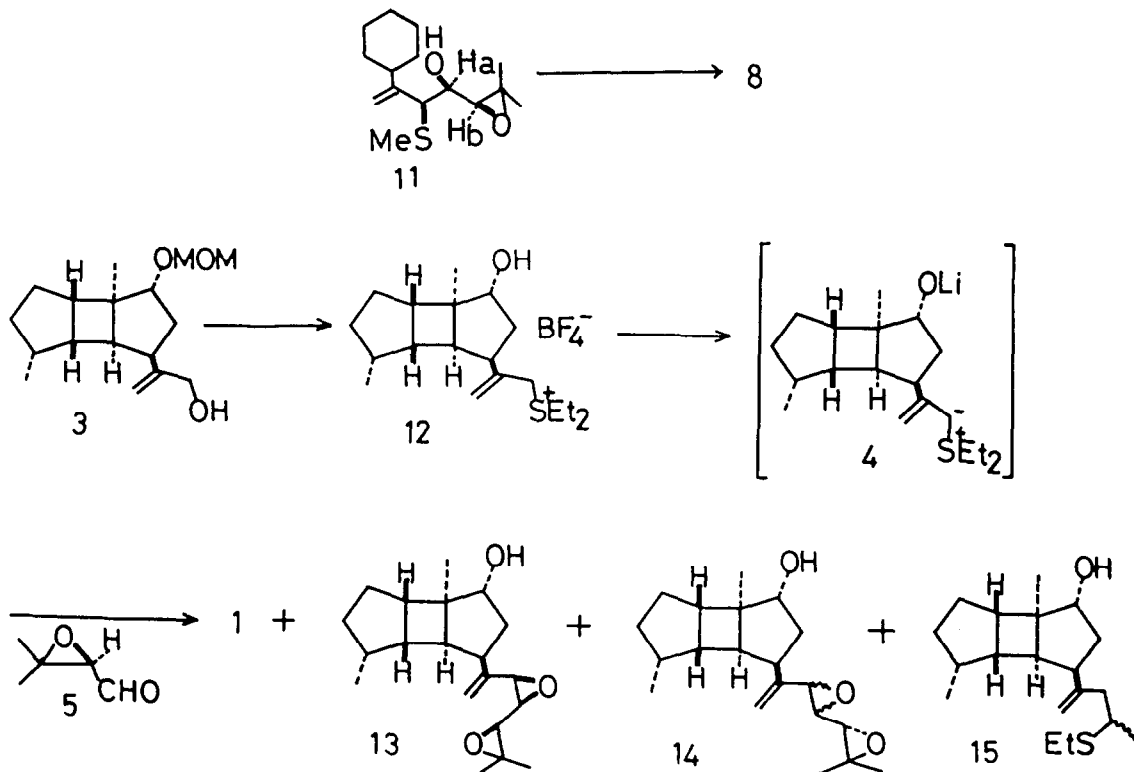


Table I

	R	Base	7%	8%	9 ^a %	10%
6a	Me	LDA	0	0	0	74 ^b
		<i>n</i> -BuLi	4	0	5	40 ^b
6b	Ph	LDA	3	0	2	-
		<i>n</i> -BuLi	3	2	4	-
6c	Et	<i>n</i> -BuLi	11	5	17	19 ^c
		MeLi	20	5	19	7 ^c
		MeLi+HMPA(1eq)	25	4	22	11 ^c

a) A mixture of two *trans*-diastereomers. The ratio was around 5:1. b) $\text{R}'=\text{H}$. c) $\text{R}'=\text{Me}$.



References and Notes

- 1) W. H. Gerwick, W. Fenical, D. V. Engen, and J. Clardy, J. Am. Chem. Soc., 102, 7991 (1980); W. H. Gerwick, W. Fenical, and M. U. S. Sultanbawa, J. Org. Chem., 46, 2233 (1981); W. H. Gerwick and W. Fenical, ibid., 48, 3325 (1983).
- 2) B. N. Ravi and R. J. Wells, Aust. J. Chem., 35, 129 (1982).
- 3) S. L. Fernandes, S. Y. Kamat, and S. K. Paknikar, Tetrahedron Lett., 21, 2249 (1980).
- 4) J. Krepinsky, Z. Samek, F. Sorm, D. Lamparsky, P. Ochsner, and Y.-R. Navas, Tetrahedron, S8, 53 (1967).
- 5) R. G. Salomon, N. D. Sachinvala, S. R. Raychaudhuri, and D. B. Miller, J. Am. Chem. Soc., 106, 2211 (1984).
- 6) a) M. Tanaka, K. Tomioka, and K. Koga, Tetrahedron Lett., 25, 3035 (1985); b) K. Tomioka, M. Tanaka, and K. Koga, ibid., 23, 3401 (1982).
- 7) Prepared from (2S)-2,3-epoxy-3-methylbutanol (S. Yamada, M. Shiraishi, M. Ohmori, and H. Takayama, Tetrahedron Lett., 25, 3347 (1984)) by Collins oxidation.
- 8) For the linear vinylic diepoxide (Hedamycin), see: M. Ceroni and U. Seuin, Tetrahedron Lett., 1979, 3703.
- 9) For the cyclic diepoxide (Coriamyrtin), see: K. Tanaka, F. Uchiyama, K. Sakamoto, and Y. Inubushi, J. Am. Chem. Soc., 104, 4965 (1982); H. Niwa, K. Wakamatsu, T. Hida, K. Niiyama, H. Kigoshi, M. Yamada, H. Nagase, M. Suzuki, and K. Yamada, ibid., 106, 4547 (1984).
- 10) All new compounds gave satisfactory analytical and spectroscopic data.
- 11) Details will be reported in a full account.
- 12) B. M. Trost and L. S. Martin, Jr., "Sulfur Ylides", Academic Press, New York, 1975; E. J. Corey, Y. Arai, and C. Mioskowski, J. Am. Chem. Soc., 101, 6748 (1979).
- 13) A mixture of two trans-diepoxides (the ratio is about 5:1).
- 14) E. D. Mihelich, Tetrahedron Lett., 1979, 4729.
- 15) Y. Yamamoto, Y. Saito, and K. Maruyama, J. Chem. Soc., Chem. Commun., 1326 (1982); G. E. Keck, D. E. Abbott, E. P. Boden, and E. J. Enholm, Tetrahedron Lett., 25, 3927 (1984).
- 16) M. Shimagaki, Y. Matsuzaki, I. Hori, T. Nakata, and T. Oishi, Tetrahedron Lett., 25, 4779 (1984).
- 17) The trans-isomer was produced as a single isomer (the relative configuration is unknown).
- 18) The formation of lithium alkoxide would be responsible for the low yield and low selectivity compared to the results of the model study. Protection of the hydroxyl group of **12** is not yet successful.
- 19) **13**: oil, $[\alpha]_D^{24} +11^\circ$ (CHCl₃), ¹H NMR (CDCl₃) δ: 2.94 (1H, dd, J=4, 7 Hz), 3.51 (1H, dd, J=1, 4 Hz); **14**: oil, $[\alpha]_D^{23} +24^\circ$ (CHCl₃), ¹H NMR (CDCl₃) δ: 2.83 (1H, dd, J=2, 7 Hz), 3.34 (1H, d, J=2 Hz); **15**: An oil of a 2:1 mixture of two diastereomers. $[\alpha]_D^{24} +30^\circ$ (CHCl₃).

(Received in Japan 12 September 1985)