

ACYCLIC STEREOSELECTION USING RELATIVE 1,2-ASYMMETRIC INDUCTION.
SELECTIVE SYNTHESIS OF (+)-BLASTMYCINONE

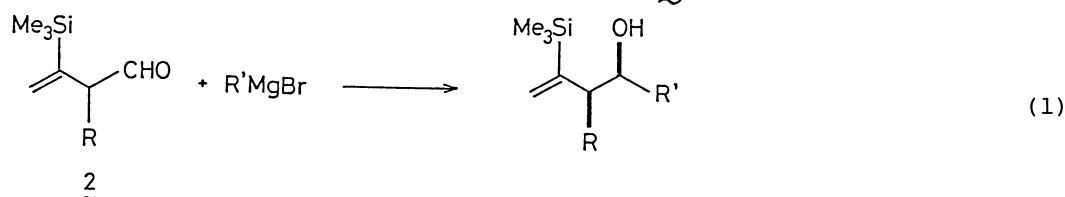
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(+)-Blastmycinone has been synthesized based on the stereo-selective addition reaction of 1-trimethylsilylmagnesium bromide with (-)-(R)-2-butyl-3-trimethylsilylbut-3-enal.

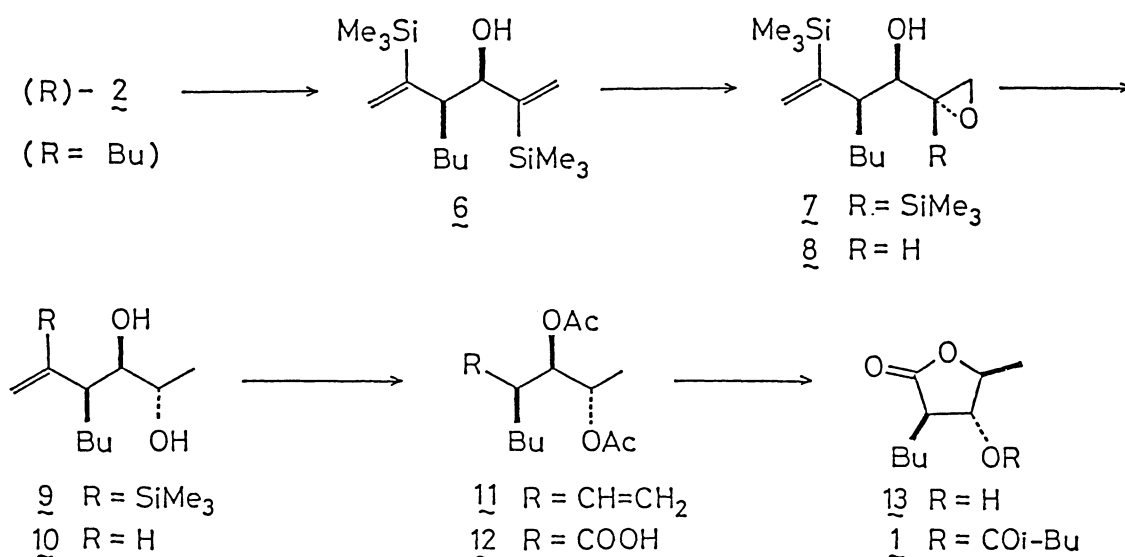
(+)-Blastmycinone (1) is a degradation product of antimycin A₃, an antifungal antibiotic¹⁾ and has been synthesized in both racemic and optically active forms by several groups.²⁾ Herein, we report the synthesis of (+)-1 by a method of the stereocontrolled construction of acyclic systems.^{3,4)}

Recently, we have shown that 2-methyl-3-trimethylsilylbut-3-enal (2) (R = Me) reacts with Grignard reagents highly selectively affording syn addition products with more than 99% diastereoselectivity (Eq. 1).⁵⁾ We also reported the convenient method for preparation of both (R)- and (S)-2 (R = Me), which was based



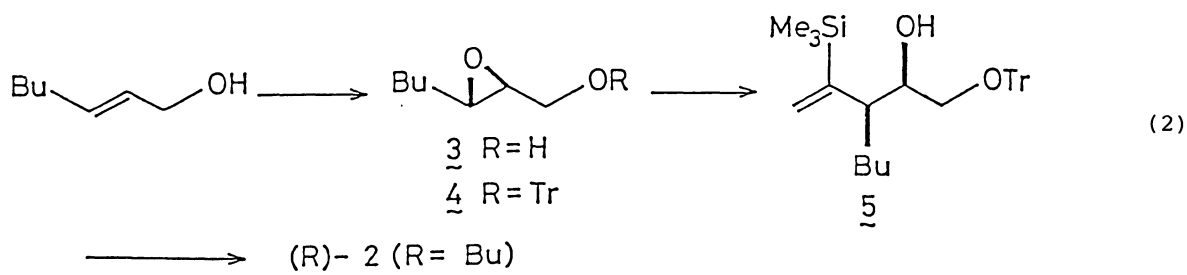
on the regiospecific ring opening of the epoxide obtained by Sharpless asymmetric epoxidation of trans-crotyl alcohol.⁶⁾ Based on these findings, we have prepared (+)-1 starting with the optically active aldehyde (R)-2 (R = Bu). Our method is shown in Scheme 1.

The aldehyde (R)-2 (R = Bu) was prepared according to Eq. 2 as described in the previous paper.⁶⁾ Thus, (E)-2-hexen-1-ol, prepared from propargyl alcohol and butyl bromide,⁷⁾ was epoxidized to 3⁸⁾ in 70% yield using (L)-(+)-diisopropyl tartrate and TBHP.⁹⁾ After protection of 3 as trityl ether (TrCl, Et₃N,



Scheme 1.

DMAP, CH₂Cl₂), the resulting $\underline{4}$ was treated with 1-trimethylsilylvinylmagnesium bromide in THF in the presence of CuI to afford the alcohol $\underline{5}$.¹⁰⁾ Deprotection of crude $\underline{5}$ (Cl₂CHCOOH, H₂O), purification by column chromatography on silica gel, and subsequent treatment with NaIO₄ afforded (R)- $\underline{2}$ (R = Bu), [α]_D²⁵ -16.7° (c 1.04, CHCl₃). The yield of (R)- $\underline{2}$ from $\underline{3}$ was 68%.



Reaction of (R)- $\underline{2}$ (R = Bu) thus prepared with 1-trimethylsilylvinylmagnesium bromide in THF (-78 °C → r.t.) yielded $\underline{6}$ exclusively in 91% yield.⁵⁾ Epoxidation of $\underline{6}$ with TBHP and Ti(Oi-Pr)₄ in CH₂Cl₂ gave $\underline{7}$ (73%) and its regioisomer (3%) which could be separated by column chromatography on silica gel.^{9,11)} Noteworthy is the fact that V⁵⁺-catalyzed epoxidation of $\underline{6}$ resulted in low yield (10-30%) of $\underline{7}$.¹²⁾ Treatment of $\underline{7}$ with t-BuOK and then with Bu₄NF in THF resulted in regio-specific protodesilylation¹³⁾ yielding $\underline{8}$ (96%), which was changed to the diol $\underline{9}$ (92%) by treatment with LiAlH₄ in ether (0 °C → r.t.). Protodesilylation of $\underline{9}$ with KH-HMPA (r.t., 10 h)¹⁴⁾ and acetylation with Ac₂O-pyridine afforded $\underline{11}$ (75%). Ozonolysis of $\underline{11}$ in MeOH (-78 °C, 30 min), treatment with Me₂S and oxidation (CrO₃-H₂SO₄) gave $\underline{12}$ in 70% yield. The compound $\underline{12}$ was converted to blast-

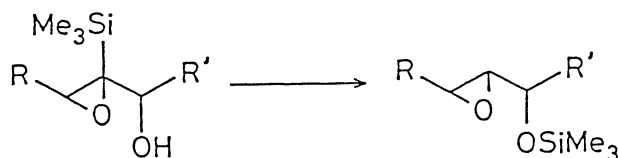
mycinolactol (13) (95%), mp 49.0-49.5 °C (lit^{2d}) mp 50-51 °C), $[\alpha]_D^{22}$ -18.7° (c 1.55, MeOH) (lit^{2d}) -18° (c 1.61, MeOH), by treatment with K₂CO₃ in MeOH-H₂O (4:1) followed by addition of aqueous HCl. Finally, treatment of 13 with isovaleryl chloride afforded (+)-blastmycinone (1) (80%), $[\alpha]_D^{23}$ +11.0° (c 1.16, CHCl₃) (lit^{2d}) +10° (c 1.50, CHCl₃). ¹H NMR spectral data were in accord with values reported in the literature.^{2e,15}

In conclusion, we succeeded in a highly stereoselective synthesis of (+)-1. The present method can be effectively used for controlling three consecutive asymmetric centers of α, β -dihydroxy- γ -methyl compounds.

References

- 1) E. E. van Tamelen, J. P. Dickie, M. E. Loomans, R. S. Dewey, and F. M. Strong, *J. Am. Chem. Soc.*, **83**, 1639 (1961); A. J. Birch, D. W. Cameron, Y. Harada, and R. W. Rickards, *J. Chem. Soc.*, **1961**, 889; H. Yonehara and S. Takeuchi, *J. Antibiot., Ser. A*, **11**, 254 (1958); M. Kinoshita, S. Aburaki, and S. Umezawa, *J. Antibiot.*, **25**, 373 (1972).
- 2) a) M. Kinoshita, M. Wada, and S. Umezawa, *J. Antibiot.*, **22**, 580 (1969); b) M. Kinoshita, M. Wada, S. Aburaki, and S. Umezawa, *ibid.*, **24**, 724 (1971); c) H. Koyama, K. Kogure, K. Mori, and M. Matsui, *Agric. Biol. Chem.*, **37**, 915 (1973); d) M. Kinoshita, S. Aburaki, M. Wada, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **46**, 1279 (1973); e) S. Aburaki, N. Konishi, and M. Kinoshita, *ibid.*, **48**, 1254 (1975); f) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, *J. Org. Chem.*, **46**, 2290 (1981); g) T. Nakata, M. Fukui, and T. Oishi, *Tetrahedron Lett.*, **24**, 2657 (1983); h) T. Fujisawa, H. Kohama, K. Tajima, and T. Sato, *ibid.*, **25**, 5155 (1984); i) A. P. Kozikowski and A. K. Ghosh, *J. Org. Chem.*, **49**, 2762 (1984); j) N. Sayo, E. Nakai, and T. Nakai, The 48th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1984, *Abstr.*, 1W 44.
- 3) Part of this report was presented at the 31st Symposium on Organometallic Chemistry, Tsukuba, October 1984, *Abstr.*, B123.
- 4) Recently, Fujisawa et al. reported preparation of (+)-1 using the ester enolate Claisen rearrangement as a key step. See ref. 2h.
- 5) F. Sato, M. Kusakabe, and Y. Kobayashi, *J. Chem. Soc., Chem. Commun.*, **1984**, 1130.
- 6) Y. Kobayashi, Y. Kitano, and F. Sato, *J. Chem. Soc., Chem. Commun.*, **1984**, 1329.

- 7) D. E. Ames, A. N. Covell, and T. G. Goodburn, *J. Chem. Soc.*, 1963, 5889.
- 8) Since asymmetric epoxidation of this type of trans-allyl alcohols is known to proceed with high enantiomeric excess (over 95%), the optical purities of 3 and other intermediates used here were not confirmed.
- 9) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, 103, 6237 (1981).
- 10) To a solution of CuI (2.5 mmol) in THF (2 ml) and Me₂S (0.4 ml) was added a THF solution of 1-trimethylsilylvinylmagnesium bromide (46 ml, 0.55 M, 25 mmol) and then 3 (15 mmol) dissolved in THF (20 ml) at 0 °C. The reaction mixture was stirred for 24 h at 0 °C and usual work up afforded 5, which was used for the next step without purification.
- 11) To a solution of 6 (4.7 mmol) in CH₂Cl₂ (45 ml) was added Ti(Oi-Pr)₄ (4.7 mmol) and the mixture was stirred for 20 min at 0 °C. Anhydrous TBHP (7.1 mmol) in CH₂Cl₂ (2.5 ml) was added to the reaction mixture. After 12 h at 0 °C, usual work up gave 7, which was purified by column chromatography on silica gel.
- 12) For the V⁵⁺-catalyzed stereoselective epoxidation of allylic alcohols having trimethylsilyl group on the double bonds, see the following reports: H. Tomioka, T. Suzuki, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 23, 3387 (1982); A. S. Narula, *ibid.*, 23, 5579 (1982).
- 13) NaH in HMPA or t-BuOK in THF was found to be effective for facile shift of the 1,3-trimethylsilyl group in β '-hydroxy- α,β -epoxysilanes giving silyloxy epoxides at room temperature (unpublished results).



- 14) F. Sato, Y. Tanaka, and M. Sato, *J. Chem. Soc., Chem. Commun.*, 1983, 165.
- 15) The ¹³C NMR (CDCl₃) spectra of 1 and 13 are as follows: 1, δ 13.5, 19.1, 22.1, 25.4, 28.7, 42.9, 46.2, 78.2, 78.9, 172.0, 175.3; 13, δ 13.8, 18.2, 22.5, 28.1, 28.7, 48.5, 78.6, 80.6, 177.2.

(Received January 7, 1985)