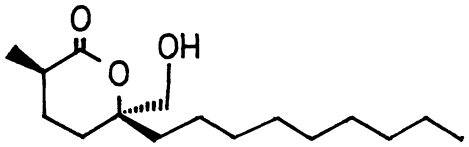
CHEMISTRY LETTERS, pp. 1223-1226, 1980.

AN ASYMMETRIC TOTAL SYNTHESIS OF A NEW MARINE ANTIBIOTIC-MALYNGOLIDE

Yoji SAKITO, Shin TANAKA, Masatoshi ASAMI,
and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

(-)-Malyngolide was synthesized from (S)-2-hydroxy-2-nonyl-6-heptenal, prepared in high optical yield by an asymmetric synthesis using (S)-2-(anilinomethyl)pyrrolidine as a chiral auxiliary.

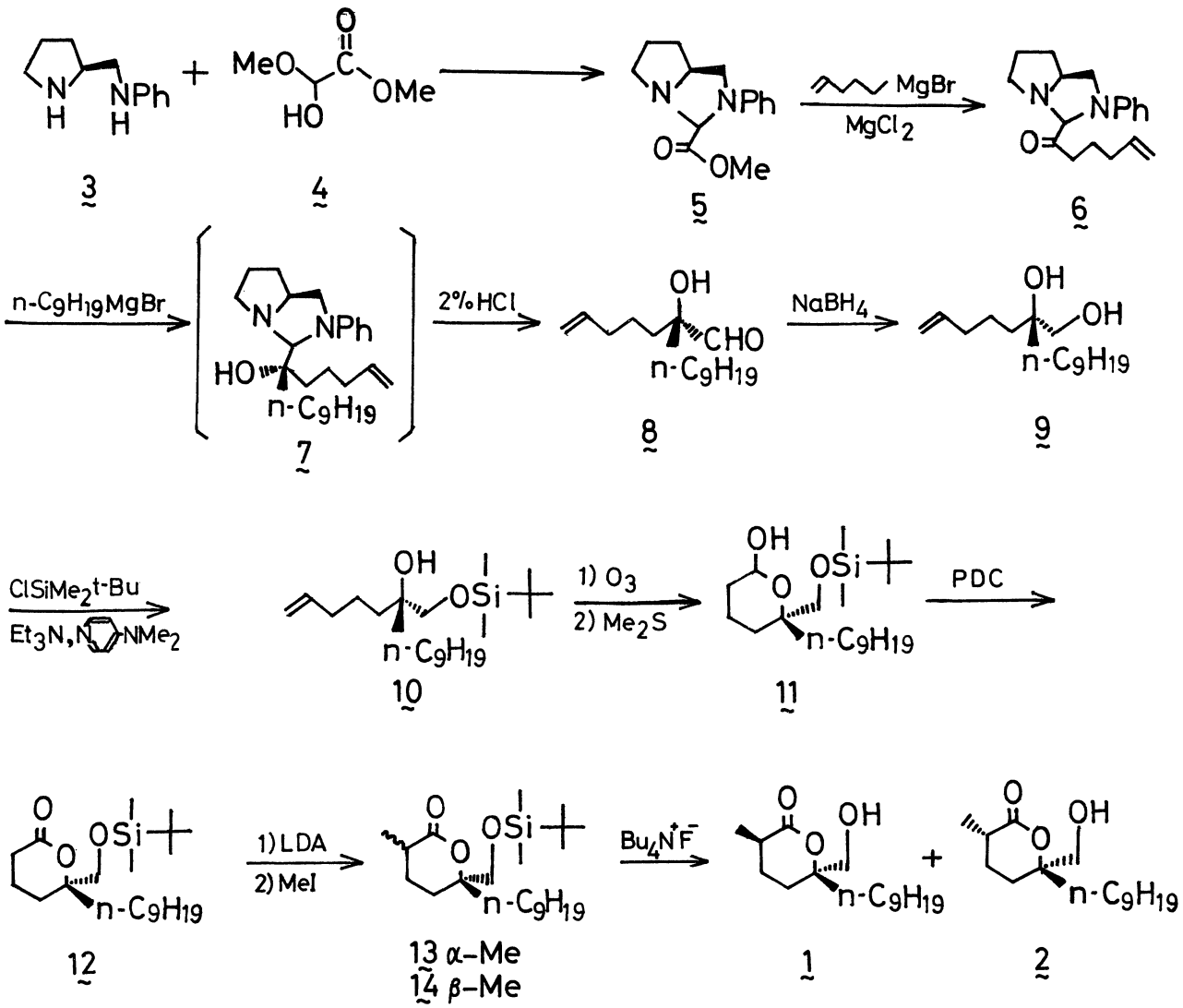
We recently reported an asymmetric synthesis of α-hydroxy aldehydes with high optical yields using (S)-2-(anilinomethyl)pyrrolidine as a chiral auxiliary.[1),2)] (S)-Frontalin and its antipode were separately synthesized in high optical yields by this method.[3)] In this communication we wish to report an asymmetric total synthesis of (2R,5S)-(-)-malyngolide 1, a recently discovered antibiotic from the marine blue-green alga *Lyngbya majuscula* Gomont[4)], by employing a chiral α-hydroxy aldehyde as a key intermediate.



1

The synthetic route to (-)-malyngolide is illustrated in the scheme.

Keto aminal 6[5)] was prepared by the reaction of methoxycarbonyl aminal 5[2)] with 4-pentenylmagnesium bromide in the presence of magnesium chloride at -100°C. The aminal 6 was treated with nonylmagnesium bromide at -100°C and the resulting hydroxy aminal 7 was hydrolyzed to yield α-hydroxy aldehyde 8[6)], which was immediately reduced with sodium borohydride at room temperature. Diol 9[7)] was obtained in 52% overall yield from 5 after purification by silica gel column



scheme

chromatography. The protection of the primary hydroxyl group of 9 was accomplished in 98% yield by treatment with t-butyldimethylsilyl chloride, triethylamine and a catalytic amount of 4-dimethylaminopyridine. Ozonolysis of the resulting silyl ether 10[8] at -78°C in methanol followed by reductive work up with dimethyl sulfide at room temperature afforded lactol 11[9] in 69% yield after purification by silica gel column chromatography. The lactol 11 was oxidized to lactone 12[10] with pyridinium dichromate[11] in N,N-dimethylformamide at room temperature in almost quantitative yield. The lactone 12 was treated with lithium diisopropylamide at -78°C in the presence of HMPA, and alkylated with methyl iodide to afford a diastereomeric mixture of methyl lactones 13 and 14 in 74% yield. These methyl

lactones were desilylated by treatment with tetrabutylammonium fluoride to yield a diastereomeric mixture of malyngolide 1[12] and its C-2 epimer 2[13] in 58% and 29% yield respectively. When the methylation was carried out in the absence of HMPA, an approx. 4:6 ratio of 1:2 was obtained. The diastereomers 1 and 2 could be easily separated by silica gel column chromatography. The specific rotation of 1 was $[\alpha]_D^{22}$ -12.3° (c 1.07, $CHCl_3$) and its optical purity was 95% based on $[\alpha]_D$ -13°(c 2, $CHCl_3$) reported in reference 4). The IR and NMR spectra of 1 were identical with those of the natural product.[4] On the other hand, the separated C-2 epimer 2 was easily epimerized to an approx. 1:1 mixture of 1 and 2 by treatment with $KOBu^t$ in DMSO. Therefore 1 could be obtained from 12 in high overall yield after one equilibration.

Acknowledgment

We thank Dr. R. E. Moore of the University of Hawaii, for providing the analytical data of malyngolide.

References and Notes

1) T. Mukaiyama, Y. Sakito, and M. Asami, Chem. Lett., 1978, 1253.

2) T. Mukaiyama, Y. Sakito, and M. Asami, ibid., 1979, 705.

3) Y. Sakito and T. Mukaiyama, ibid., 1979, 1027.

4) J. H. Cardellina II, R. E. Moore, E. V. Arnold, and J. Clardy, J. Org. Chem., 44, 4039 (1979).

5) IR (neat) ν=1720, 1640, 995, and 910 cm^{-1}. NMR (CCl_4) δ=1.30-2.60(10H,m), 2.70-3.30(3H,m), 3.50-4.00(2H,m), 4.20(1H,s), 4.60-5.10(2H,m), 5.20-6.00(1H,m), 6.10-7.20(5H,m).

6) IR (neat) ν=3500, 1720, and 1640 cm^{-1}. NMR (CCl_4) δ=0.87(3H,brt), 1.23(16H,br), 1.50-2.20(6H,m), 2.95(1H,s), 4.70-5.10(2H,m), 5.30-6.00(1H,m), 9.22(1H,s).

7) IR (neat) ν=3400 and 1640 cm^{-1}. NMR (CCl_4) δ=0.87(3H,brt), 1.23(20H,br), 1.80-2.20(2H,m), 3.10(1H,br), 3.23(2H,br), 3.57(1H,br), 4.70-5.10(2H,m), 5.30-6.00(1H,m). $[\alpha]_D^{23}$-0.35° (neat).

8) IR (neat) ν=3450, 1640, and 1100 cm^{-1}. NMR (CCl_4) δ=0.03(6H,s), 0.90(12H,s), 1.23(20H,br), 1.70-2.10(3H,m), 3.30(2H,s), 4.60-5.10(2H,m), 5.30-6.00(1H,m). $[\alpha]_D^{23}$-0.25° (neat).

9) IR (neat) ν=3400, 1100, and 835 cm^{-1}. NMR (CCl_4) δ=0.03(6H,s), 0.90(12H,s), 1.10-2.00(22H,br), 3.20-3.50(3H,br), 4.83(1H,br).

10) IR (neat) ν=1735, 1255, and 1115 cm^{-1}. NMR (CCl_4) δ=0.03(6H,s), 0.87(12H,s), 1.23(16H,br), 1.60-2.00(4H,m), 2.00-2.40(2H,m), 3.43(2H,s). $[\alpha]_D^{25}$-0.89°(c 1.57, $CHCl_3$).

11) E. J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.

12) IR(CCl_4) ν=3420, 1730 and 1720 cm^{-1}. NMR($CDCl_3$, 90 MHz) δ=0.87(3H,brt), 1.30 (19H,br), 1.50-2.20(4H,m), 2.40(1H,m), 3.47(1H,d,J=12Hz), 3.70(1H,d,J=12Hz).

13) IR(CCl_4) ν=3400, 1730 and 1715 cm^{-1}. NMR($CDCl_3$) δ=0.87(3H,brt), 1.27(19H,br), 1.50-2.20(4H,m), 2.30-2.70(1H,m), 3.50(2H,br). $[\alpha]_D^{25}$ +19.1°(c 1.13, $CHCl_3$).

(Received July 29, 1980)