Tetrahedron Letters, Vol.32, No.51, pp 7567-7570, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Enantioselective Synthesis of (+)-Magydardienediol

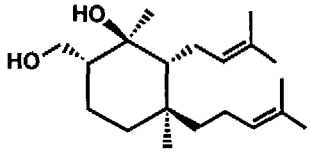
Morio Asaoka,* Masahito Sakurai, and Hisashi Takei

Department of Life Chemistry, Tokyo Institute of Technology,
Midoriku, Yokohama 227 Japan

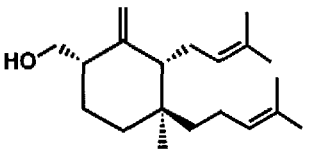
Key Words: (+)-magydardienediol; diterpene; asymmetric synthesis;
diastereoselective synthesis; (+)-magydartrienol.

Abstract: *The first enantioselective total synthesis of the title compound is described.*

(+)-Magydardienediol and (+)-magydartrienol were isolated from *Magydaris panacifolia* (Vahl) Lange (Umbelliferae) in 1978,[1] and initial assignment of their structures was amended, on the basis of their spectral data, to those shown below in 1984.[2a,b] In the same year, bonandiol was isolated from *Bonannia graeca* (L.) Halacsy (Umbelliferae), and the same structure as (+)-magydardienediol was assigned to it.[2c] A total and a formal syntheses of the racemate have been reported.[3] In this communication we will describe the first enantioselective synthesis of (+)-magydardienediol.

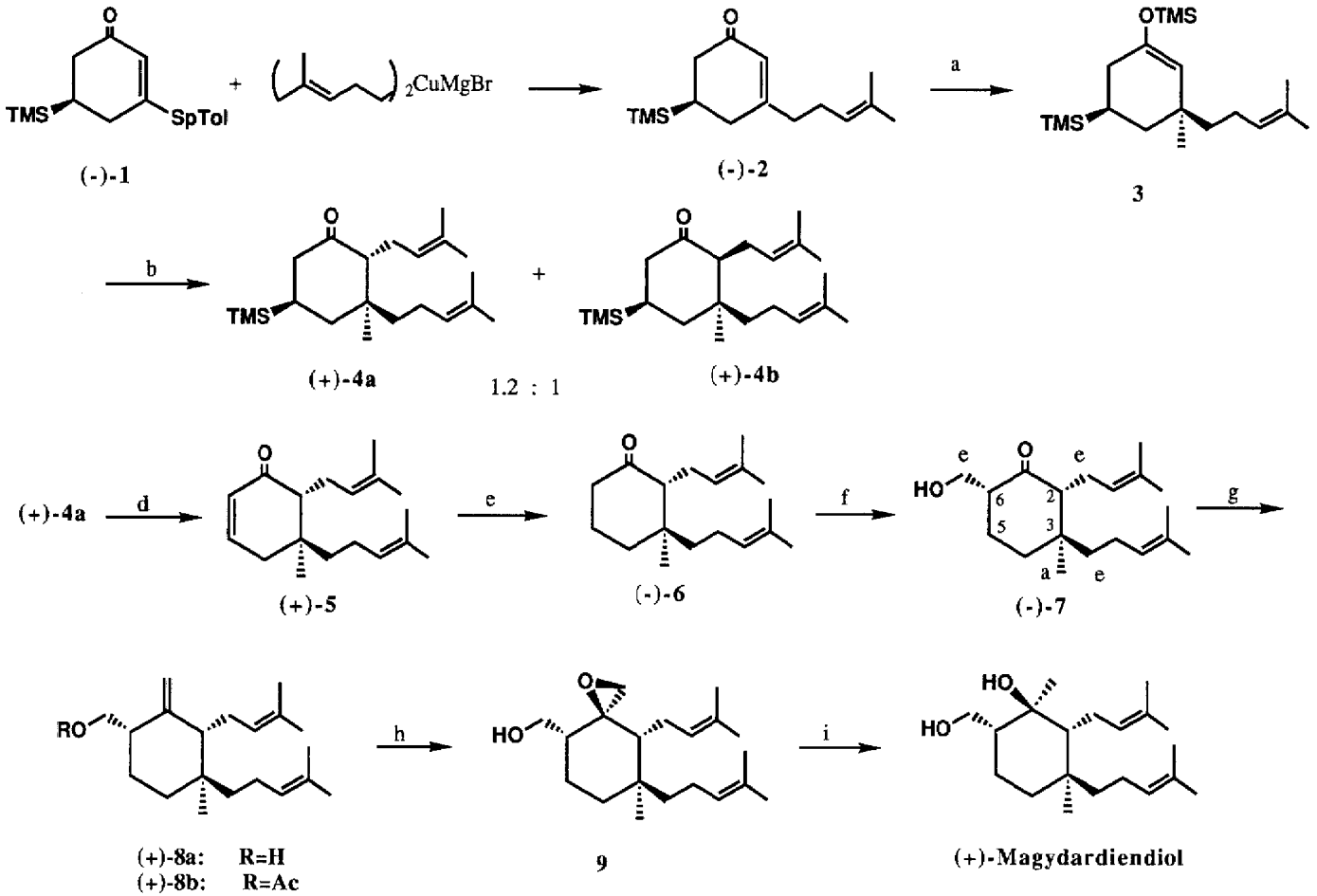


(+)-magydardienediol



(+)-magydartrienol

We recently reported a highly enantioselective construction of chiral quaternary carbon center at a 3 position of cyclohexanone ring starting from the enantiomeric enone (-)-**1**,[4] and the method was conveniently applied to this synthesis. Thus, the enone (-)-**2** [$[\alpha]_D^{22}$-56.4°(c 1.9, $CHCl_3$)] was prepared from (-)-**1** in 77% yield by the addition-elimination reaction with $R_2CuMgBr$ (R=4-methyl-3-pentenyl, -78°C, 40 min). Our trials for direct conversion of (-)-**2** into the tetrasubstituted cyclohexanone **4a** or **4b** by 1,4-addition of dimethylcuprate and subsequent quenching of the intermediary enolate with prenyl halide resulted in failure. Therefore, (-)-**2** was first converted to the enol silyl ether **3** with MeMgI and chlorotrimethylsilane in the presence of catalytic CuBr-Me_2S (THF, 2 equiv HMPA, -78°C, 0.5 h, quantitative yield).[5] The diastereohomogeneity of **3** was confirmed by ^{13}C-NMR after hydrolysis of the enol silyl ether moiety with KF-MeOH. For the conversion of the enol silyl ether to the 2-prenyl ketones (**4a** and/or **4b**), while the Pd(0) catalyzed reaction with prenyl carbonate,[6]



Scheme 1. a) MeMgI, cat. CuBr, TMSCl; b) MeLi, prenyl-I; c) 1.5M NaOH, MeOH; d) i) LDA, TMSCl, ii) NBS, iii) TBAF; e) L-selectride; f) LDA, HCHO; g) $TiCl_4$-Zn-CH_2Br_2; h) t-BuOOH, $VO(acac)_2$; i) LAH.

fluoride-[7] or Lewis acid-[8] promoted reactions with prenyl bromide gave poor results, prenylation via lithium enolate gave satisfactory results. Treatment of **3** with methyllithium[9] at 0°C for 1 h and then with prenyl iodide (2 equiv) in THF solution at 0°C for 2 h furnished a mixture of easily separable two diastereoisomers [(+)-**4a**:(+)-**4b**=1.2:1] in 66% combined yield.[10] Treatment with base (typical conditions: 1.5M NaOH-MeOH, rt, 3 h) of the minor isomer (**4b**) afforded 3.3:1-2.5:1 mixture of (+)-**4a** and (+)-**4b** in 78-99% recovery. On the basis of these results, the stereostructures of (+)-**4a** and (+)-**4b** were tentatively assigned as shown in Scheme 1, since, in the structure of (+)-**4a**, all of the three large substituents can adopt equatorial positions.

Removal of the trimethylsilyl group from (+)-**4a** was carried out via bromination (N-bromosuccinimide, -78°C, THF, 0.5 h) of regioselectively formed enol silyl ether and subsequent desilylbromination with tetrabutylammonium fluoride (-78°C-rt, 1 h) to give (+)-**5** in 86% overall yield. Conjugate reduction of the enone (+)-**5** with L-selectride[11] in THF at -78°C gave the ketone (-)-**6**,[12] in 95% yield. Hydroxymethylation of (-)-**6** in THF at -78°C with LDA and gaseous formaldehyde gave (-)-**7** (77%) as a major diastereoisomer (diastereopurity: ≥90%).

To determine the structure of (-)-**7**, analysis of its relative configuration and conformation was carried out by ^{1}H-NMR (500 MHz), and the results were in good accordance with the depicted structure.[13] Since the absolute stereochemistry of the quaternary carbon center, C(3), is clear, the absolute structure of (-)-**7** was unambiguously established. By direct comparison of the ^{13}C- and ^{1}H-NMR spectra, (±)-**7**, synthesized by Teresa et al.,[3a] and (-)-**7** were proved to have the same relative configuration.

Though some trials for the direct methylenation of this sterically hindered ketone were reported to be unsuccessful,[3a] the methylenation proceeded smoothly by the use of $TiCl_4$-Zn-CH_2Br_2 system[14] (rt, 4 h) to give (+)-**8a** in 45% yield. Since this product still contained a small amount of diastereoisomer and a trace amount of unidentified by-product, further purification by careful column chromatography was carried out on the acetate (+)-**8b**,[12] whose ^{1}H- and ^{13}C-NMR spectral properties were identical with those of natural one.[1] Regeneration of hydroxy moiety with LiOH in methanol (rt, 2 h) gave almost pure (+)-**8a** [$[\alpha]_D^{21}$+33.6°(c 1.8, $CHCl_3$), cf. (+)-magydartrienol: $[\alpha]_D$+43.1°($CHCl_3$)[1]]. Though the ^{1}H-NMR spectrum of (+)-**8a** (270 MHz) and that of (+)-magydartrienol at 200 MHz were in good agreement, their ^{13}C-NMR spectra were apparently different.[12] These results suggest that the structure of (+)-magydartrienol might be a diastereo isomer of (+)-**8a**. The conversion of (+)-**8a** to (+)-magydardienediol was achieved by the method of Teresa et al.[3a] under slightly modified conditions, i.e., treatment of the trienol with anhydrous t-BuOOH in toluene and $VO(acac)_2$ at rt for 1.5 h afforded the epoxyalcohol **9** in 79% yield. Reduction of the epoxide with $LiAlH_4$ at rt for 1 h gave (+)-magydardienediol [$[\alpha]_D^{20}$+20.8°(c 1.7, $CHCl_3$), lit.[1] $[\alpha]_D$+24.4°(c 1, $CHCl_3$)], which gave satisfactory ^{13}C- and ^{1}H-NMR spectra, in 74% yield.

Acknowledgement: We are grateful to Profs. J. de Pascual Teresa, J. R. Moran, and M. Grande for providing the spectra of (+)-magydardienediol, (+)-magydartrienol, (+)-magydartrienol acetate, and synthetic intermediates [(±)-**7** and (±)-**9**] and for their helpful information. We would like to thank Dr. Yoshiyuki Nakamura, of this Institute, for measurement of some NMR spectra.

REFERENCES

1. J. de Pascual Teresa, C. Grande, and M. Grande, *Tetrahedron Lett.*, **1978**, 4563.
2. a) J. de Pascual Teresa, C. Grande, J. R. Moran, and M. Grande, *Chem. Lett.*, **1984**, 247; b) H. Nagano, M. Tori, M. Shiota, and J. de Pascual Teresa, *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 2971;

c) M. Bruno, L. Lamartina, F. Lentini, C. Pascual, and G. Savona, *Tetrahedron Lett.*, **1984**, *25*, 4287.

3. a) J. de Pascual Teresa J. R. Moran, J. J. Lopez, A. F. Mateos, and M. Grande, *An. Quim.*, **1986**, *82*, 183; b) H. Nagano, Y. Seko, and K. Nakai, *J. Chem. Soc., Parkin Trans. 1*, **1991**, 1291.
4. M. Asaoka, K. Takenouchi, and H. Takei, *Tetrahedron Lett.*, **1988**, *29*, 325.
5. Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, **1986**, *27*, 4025.
6. J. Tsuji, I. Minami, and I. Shimizu, *Chem. Lett.*, **1983**, 1325.
7. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **1982**, *104*, 1025.
8. M. T. Reetz, S. Hüttenhain, P. Walz, and U. Löwe, *Tetrahedron Lett.*, **1979**, 4971.
9. E. W. Colvin, "*Silicon Reagents in Organic Synthesis*," Academic Press Ltd., London (1988) p. 106.
10. In this alkylation step, use of prenyl bromide instead of iodide or use of 1,2-dimethoxyethane as a solvent caused the contamination of (+)-**4a** with regioisomer [prenylation at C(6)].
11. J. M. Fortunato and B. Ganem, *J. Org. Chem.*, **1976**, *41*, 2194.
12. Spectral data and specific rotation of some intermediates are shown below.
    (+)-**4a**: oil; $[\alpha]_D^{22}$+45.4°(c 1.5, $CHCl_3$); ^{1}H-NMR(60 MHz, $CDCl_3$): δ=0.0(9H, s), 0.74(3H, s), 1.61(12H, s), 1.08-2.47(12H, m), 4.95(2H, m) ppm; IR(neat): 1710 (C=O) cm^{-1}.
    (+)-**4b**: mp 67° (MeOH); $[\alpha]_D^{25}$+79.1°(c 1.5, $CHCl_3$); ^{1}H-NMR(60 MHz, $CDCl_3$): δ=0.0(9H, s), 0.92(3H, s), 1.60(12H, s), 1.0-2.77(12H, m), 4.87(2H, m) ppm; IR(KBr): 1710 (C=O) cm^{-1}.
    (+)-**5**: oil; $[\alpha]_D^{20}$+57.0°(c 8.3, $CHCl_3$); ^{1}H-NMR(90 MHz, $CDCl_3$): δ=0.98(3H, s), 1.2-1.52(3H, m), 1.60(6H, s), 1.68(6H, s), 1.77-2.14(2H, m), 2.28(4H, m), 5.10(2H, m) 5.96(1H, dt, J=2 and 11 Hz), 6.97(1H, dt, J=3.6 and 11 Hz) ppm; IR(neat): 1680 (C=O) cm^{-1}.
    (-)-**6**: oil; $[\alpha]_D^{20}$-24.4°(c 2.1, $CHCl_3$); ^{1}H-NMR(270 MHz, $CDCl_3$): δ=0.79(3H, s), 1.61(3H, s), 1.63(3H, s), 1.64(3H, s), 1.69(3H, s), 1.29-2.05(9H, m), 2.17-2.37(4H, m), 4.98-5.11(2H, m) ppm; IR(neat): 1710 (C=O) cm^{-1}.
    (+)-**8a**: oil; ^{1}H-NMR(270 MHz, $CDCl_3$): δ=0.74(3H, s), 1.60(3H, s), 1.63(3H, s), 1.66(3H, s), 1.68(3H, s), 1.20-2.17(13H, m), 3.57(1H, dd, J=6.3 and 10.8 Hz), 3.82(1H, dd, J=7.6 and 10.8 Hz), 4.69 (1H, s), 4.83(1H, s), 5.02(1H, m), 5.10(1H, m) ppm. ^{13}C-NMR(67.5 MHz, $CDCl_3$): δ=148.6, 131.1, 131.0, 125.0, 124.5, 107.6, 64.8, 51.6, 46.7, 41.4, 38.5, 35.4, 29.7, 26.9, 25.7, 24.1, 22.0, 20.4, 18.0, 17.6 ppm.
    (+)-**8b**: oil; $[\alpha]_D^{21}$+45.9°(c 2.0, $CHCl_3$), lit.[1] $[\alpha]_D$+23.9°($CHCl_3$); ^{1}H-NMR(270 MHz, $CDCl_3$): δ=0.71(3H, s), 1.60(3H, s), 1.62(3H, s), 1.66(3H, s), 1.69(3H, s), 2.06(3H, s), 1.90-2.24(12H, m), 4.07(1H, dd, J=7.5 and 11.0 Hz), 4.30(1H, dd, J=5.7 and 11.0 Hz), 4.63(1H, s), 4.74(1H, s), 5.00(1H, m), 5.10(1H, m) ppm. ^{13}C-NMR(67.5 MHz, $CDCl_3$): δ=171.3, 148.0, 131.1, 130.8, 125.0, 124.6, 106.7, 66.6, 51.4, 43.3, 41.9, 38.6, 36.4, 27.7, 25.7, 25.7, 23.7, 22.0, 21.0, 19.8, 18.0, 17.6 ppm.
13. The relative configuration and conformation were determined based on the following features: (1) The shielding of C(3)-Me (δ=0.72 ppm) can be explained by its axial arrangement. (2) An axial configuration for C(6)-H was confirmed by the coupling constants with C(5)-H_2 (J= 13 and 6 Hz). (3) The cis relationship of C(2)-H and C(6)-H was ascertained from the NOE enhancement.
14. L. Lombardo, *Org. Synth.*, **1987**, *65*, 81; K. Takai, Y. Hotta, K. Oshima, and H. Nozaki., *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 1698.

(Received in Japan 19 September 1991)