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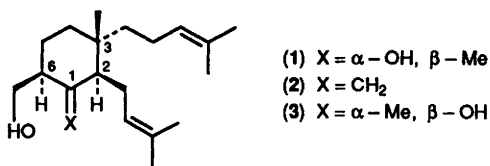
A New Synthetic Route to (\pm)-Magydardienediol via a Radical Cyclisation-trapping Reaction

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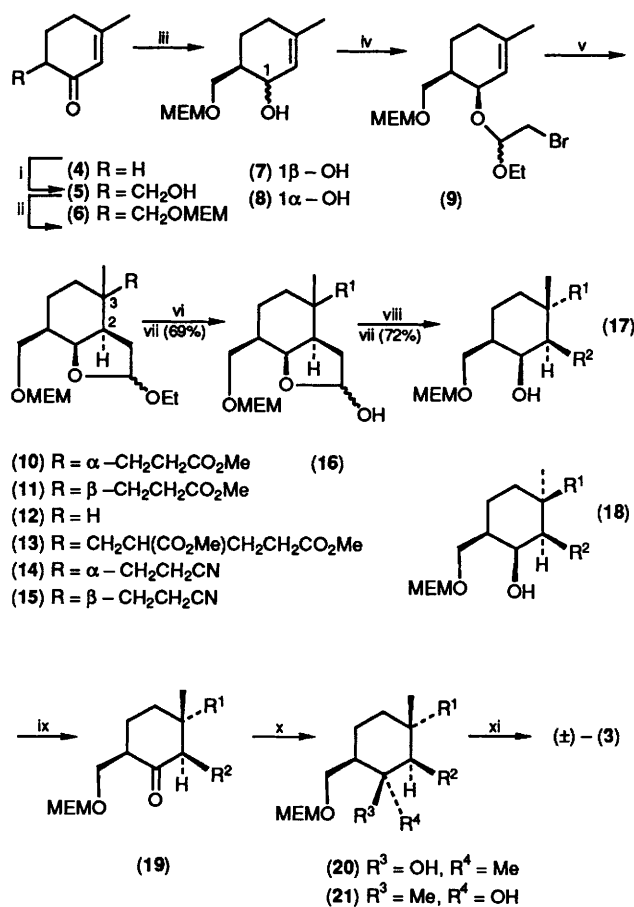
(\pm)-1-*epi*-Magydardienediol, an intermediate for the synthesis of (\pm)-magydardienediol, has been synthesised stereoselectively from 3-methylcyclohex-2-enone in 12 steps via a sequential intra- and inter-molecular radical C–C bond-forming reaction.

(+)-Magydardienediol and (+)-magydartrienol are diterpenes isolated from *Magydaris panacifolia* (Vahl) Lange (Umbelliferae)¹ and the previously reported structures for these diterpenes have recently been revised to (1) and (2),



respectively.² Structure (1) has also been assigned to bonandiol, which was isolated from *Bonannia graeca* (L.) Halacsy (Umbelliferae).³ These diterpenes have an irregular carbon skeleton which may be formed by the head-to-head condensation of two monoterpene units. The total synthesis of the diterpenes (\pm)-(1) and (\pm)-(2) has been reported by J. de Pascual Teresa and co-workers.⁴ We now report the first stereocontrolled synthesis of (\pm)-1-*epi*-magydardienediol (3), which has already been transformed into (\pm)-magydardienediol (1) via (\pm)-magydartrienol (2).⁴

The synthetic route from 3-methylcyclohex-2-enone (4) to (\pm)-*epi*-magydardienediol (3) via a sequential intra- and inter-molecular radical C–C bond-forming reaction⁵ as the key step is shown in the Scheme. Condensation of the kinetic enolate of the enone (4) with a large excess of gaseous formaldehyde at -78°C gave the β -hydroxy ketone (5).† After protection of the primary hydroxy group as its 2-methoxyethoxymethyl (MEM) ether the enone (6) was reduced with lithium tri-*n*-butylborohydride (L-Selectride) at -78°C to give the *cis*-allylic alcohol (7) [δ 4.20 (1 H, m, $W_{1/2}$ ca. 10 Hz, 1-H) and 5.63 (1 H, m, 2-H)] along with a small amount (<3%) of the inseparable *trans*-allylic alcohol (8) [δ 4.13 (1 H, d, J 7.7 Hz, 1-H) and 5.36 (1 H, br s, 2-H)].⁶ The allylic alcohol (7) was then treated with *N*-bromosuccinimide (NBS) in a large excess of ethyl vinyl ether at -20°C for 3 days to give the bromo acetal (9) as a mixture of diastereoisomers in 56% yield along with the starting material (7) (25%). A solution of the bromo acetal (9) in *t*-butyl alcohol containing methyl acrylate (25 equiv.), tributyltin chloride (0.3 equiv.), sodium cyanoborohydride (7 equiv.), and azoisobutyronitrile (AIBN) (0.5 equiv.) was heated at 80°C under an argon atmosphere to give a mixture of the bicyclic esters (10) and (11) in a ratio of 4:1 and 56% yield along with the product of reductive debromination (12) (15%) and that of



Scheme. Reagents and conditions: i, LiNPr¹, H₂C=O, THF, -78°C , 65%; ii, MEMCl, Pr²NEt, CH₂Cl₂, room temp., 87%; iii, L-Selectride, THF, -78°C , 61%; iv, NBS, EtOCH=CH₂, -20°C , 57%; v, AIBN, NaBH₃CN, Bu₃SnCl, CH₂=CHCO₂Me, Bu¹OH, 80°C , 56%; vi, Bu¹AlH, toluene, -78°C , 77%; vii, Ph₃P⁺CH(Me)₂Br⁻, BuLi, ether, room temp.; viii, AcOH–H₂O (3:1), room temp., 86%; ix, CrO₃·2pyridine, CH₂Cl₂, room temp., 96%; x, MeLi, ether, 0°C , 71%; xi, 1% HCl–acetone, room temp., 51%.

trapping of two molecules of the ester (13) (20%). The *cis*-ring fused structure having newly introduced *trans*-substituents at C-2 and C-3 was assigned, on precedent,⁵ to the major diastereoisomers (10). When the radical reaction was performed

† All the compounds reported herein were obtained as oils and gave satisfactory spectral data [IR, ¹H NMR (270 MHz, CDCl₃, Me₄Si), and MS].

using acrylonitrile instead of methyl acrylate the yield of the cyclisation-trapping reaction products (14) and (15) increased to 69%, but the ratio decreased to 2:1.

The inseparable mixture of the diastereoisomers (10) and (11) was then transformed into the dienes (17) and (18) in 4 steps *via* the hemiacetals (16). The mixture of dienes (17) [m/z 382 (M^+ , 0.1%)] and (18) [δ 0.92 (3 H, s, 3-Me); m/z 382 (M^+ , 0.1%)] was carefully separated by silica gel column chromatography with benzene-ethyl acetate (10:1) as eluant. The stereochemistry of compound (17) was confirmed on the basis of the pyridine induced ^1H NMR solvent shift of the 3-methyl signal [δ ($[\text{C}_2\text{H}_5]\text{-pyridine}$) 1.31 and $\delta(\text{CDCl}_3)$ 0.99] due to the hydroxy group in a 1,3-diaxial relationship⁷ and the axial methyl singlet at δ 0.71 in the ^1H NMR spectrum of the ketone (19)[†] which was obtained by the oxidation of the alcohol (17). Addition of methyl-lithium to the ketone (19) gave solely the tertiary alcohol (20), none of the desired alcohol (21) being obtained

[†] Alkyl (R^1) copper conjugate addition to the enone (6) followed by trapping of the resulting enolate with an electrophile R^2 -halogen may give in one pot a mixture of the ketone (19) and its diastereoisomers. Equilibration of the mixture by treatment with base may increase the proportion of the ketone (19), but the equilibration is not adequate for preparation of the ketone (19) in optically active form because of its racemisation.

[‡] Although we were unable to compare directly the spectra of the diol (3) with those of an authentic sample, the ^{13}C NMR spectral data were in complete accord with those reported in ref. 4. All the ^1H NMR signals were lower and shifted by 0.08 ppm and the IR absorptions (ν_{max} 3 375, 1 135, 1 105, 1 085, and 1 045 cm^{-1}) were also slightly shifted from the reported values.

even in the presence of methylaluminium bis(2,6-di-*t*-butyl-4-methylphenoxide).⁸ Finally, the tertiary alcohol (20) was hydrolysed with 1% HCl in acetone to give (\pm)-1-*epi*-magydar-dienediol (3),[‡] thus completing our formal total synthesis of (\pm)-magydar-dienediol and (\pm)-magydar-trienol.

References

- 1 J. de Pascual Teresa, C. Grande, and M. Grande, *Tetrahedron Lett.*, 1978, 4563.
- 2 H. Nagano, M. Tori, M. Shiota, and J. de Pascual Teresa, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2971; J. de Pascual Teresa, C. Grande, J. R. Moran, M. Grande, *Chem. Lett.*, 1984, 247.
- 3 M. Bruno, L. Lamartina, F. Lentini, C. Pascual, and G. Savona, *Tetrahedron Lett.*, 1984, **25**, 4287.
- 4 J. de Pascual Teresa, J. R. Moran, J. J. B. Lopez, A. F. Mateos, and M. G. Benito, *An. Quim.*, 1986, **82**, 183.
- 5 G. Stork and P. M. Sher, *J. Am. Chem. Soc.*, 1983, **105**, 6765; 1986, **108**, 303; G. Stork, P. M. Sher, and H.-L. Chen, *ibid.*, 1986, **108**, 6384; R. J. Ferrier, P. M. Petersen, and M. A. Taylor, *J. Chem. Soc., Chem. Commun.*, 1989, 1247.
- 6 A. Amann, G. Ourisson, and B. Luu, *Synthesis*, 1987, 1002; V. Kumar, A. Amann, G. Ourisson, and B. Luu, *Synth. Commun.*, 1987, **17**, 1279.
- 7 P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, 1978, **90**, 5480.
- 8 K. Maruoka, T. Itoh, and H. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 4573.

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