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A New Synthetic Route to (±)-Magydardienediol *via* a Radical Cyclisation-trapping Reaction

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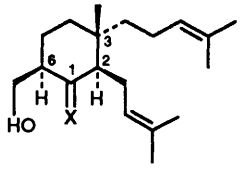
(±)-1-*epi*-Magydardienediol, an intermediate for the synthesis of (±)-magydardienediol, has been synthesised stereoselectively from 3-methylcyclohex-2-enone in 12 steps *via* a sequential intra- and inter-molecular radical C–C bond-forming reaction.

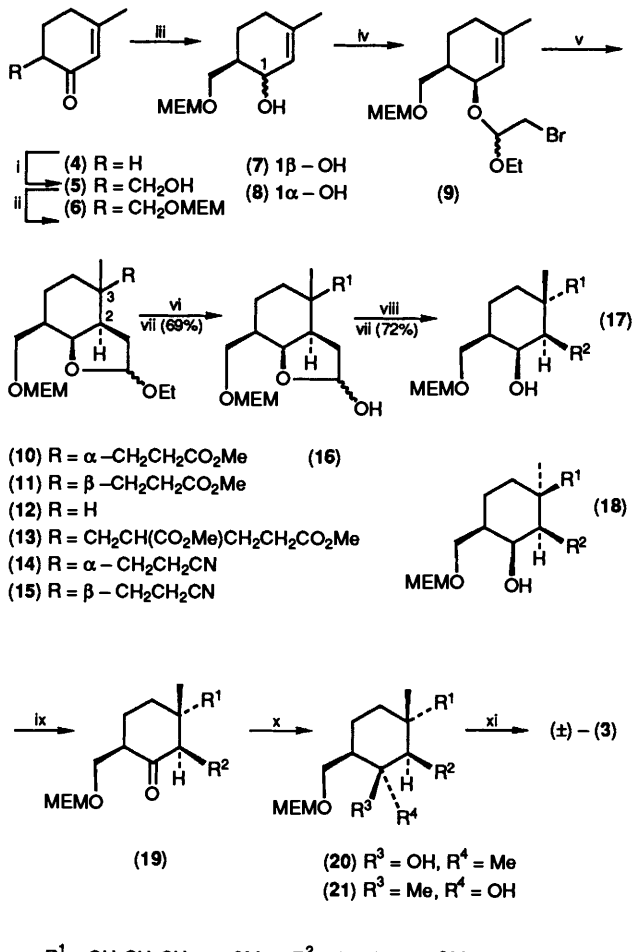
(+)-Magydardienediol and (+)-magydartrienol are diterpenes isolated from *Magydaris panacifolia* (Vahl) Lange (Umbelliferae)[1] and the previously reported structures for these diterpenes have recently been revised to (**1**) and (**2**),



(**1**) X = α-OH, β-Me
(**2**) X = CH_2
(**3**) X = α-Me, β-OH

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 (±)-(**1**) and (±)-(**2**) has been reported by J. de Pascual Teresa and co-workers.[4] We now report the first stereocontrolled synthesis of (±)-1-*epi*-magydardienediol (**3**), which has already been transformed into (±)-magydardienediol (**1**) *via* (±)-magydartrienol (**2**).[4]

The synthetic route from 3-methylcyclohex-2-enone (**4**) to (±)-*epi*-magydardienediol (**3**) *via* a sequential intra- and intermolecular radical C–C bond-forming reaction[5] 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-s-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



(**4**) R = H
(**5**) R = CH_2OH
(**6**) R = CH_2OMEM
(**7**) 1β-OH
(**8**) 1α-OH
(**9**)
(**10**) R = α-$CH_2CH_2CO_2Me$
(**11**) R = β-$CH_2CH_2CO_2Me$
(**12**) R = H
(**13**) R = $CH_2CH(CO_2Me)CH_2CH_2CO_2Me$
(**14**) R = α-CH_2CH_2CN
(**15**) R = β-CH_2CH_2CN
(**16**)
(**17**)
(**18**)
(**19**)
(**20**) R^3 = OH, R^4 = Me
(**21**) R^3 = Me, R^4 = OH
R^1 = $CH_2CH_2CH{=}CMe_2$, R^2 = $CH_2CH{=}CMe_2$

Scheme. *Reagents and conditions:* i, $LiNPr^i_2$, $H_2C{=}O$, THF, −78 °C, 65%; ii, MEMCl, Pr^i_2NEt, CH_2Cl_2, room temp., 87%; iii, L-Selectride, THF, −78 °C, 61%; iv, NBS, $EtOCH{=}CH_2$, −20 °C, 57%; v, AIBN, $NaBH_3CN$, Bu_3SnCl, $CH_2{=}CHCO_2Me$, Bu^tOH, 80 °C, 56%; vi, Bu^i_2AlH, toluene, −78 °C, 77%; vii, $Ph_3P^+CH(Me)Br^-$, BuLi, ether, room temp.; viii, AcOH–H_2O (3:1), room temp., 86%; ix, CrO_3·2pyridine, CH_2CCl_2, 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, $CDCl_3$, Me_4Si), 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 ^{1}H NMR solvent shift of the 3-methyl signal [δ($[^2H_5]$-pyridine) 1.31 and δ($CDCl_3$) 0.99] due to the hydroxy group in a 1,3-diaxial relationship [7] and the axial methyl singlet at δ 0.71 in the ^{1}H 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 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 (±)-1-*epi*-magydardienediol (**3**),‡ thus completing our formal total synthesis of (±)-magydardienediol and (±)-magydartrienol.

† 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 ^{1}H 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.

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