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# STEREOSELECTIVE SYNTHESIS OF (9S,12R,13S)-TRIHYDROXYOCTADECA(10E,15Z)-DIENOIC ACID

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**Summary:** The stereoselective synthesis of the title natural product is described.

Unsaturated $C_{18}$ hydroxy fatty acids are valuable natural products[1] endowed with numerous biological profiles. Synthesis of these fatty acids is being relentlessly pursued in these[2a] as well as other[2b] laboratories. We now describe the first synthesis of (9S, 12R, 13S)-trihydroxy-octadeca-(10E,15Z)-dienoic acid (malyngic acid) (**1**), isolated as a major fatty acid[3] component from shallow and deep water varieties of Lyngbya majuscula[3a]. The absolute stereostructure of **1** was unambiguously established by spectral and chemical degradation studies[3a].

The known precursor (**2**)[4] was subjected to the Sharpless asymmetric epoxidation[5] with (+)-di-isopropyl tartrate as a chiral auxiliary to give the 2,3-epoxy alcohol (**3**) (70%). Treatment of **3** with phenylisocyanate in the presence of triethylamine gave the urethane (**4**) which on successive reaction with borontrifluoride-etherate[6] and methanolic sodium methoxide afforded the triol (**5**) (50%). After selectively generating the tert.butyldimethylsilyl (TBS) derivative (**6**), the product was protected as an acetonide, followed by desilylation, to give **7** (80%). Partial reduction of the triple bond in **7** over Lindlar's catalyst, furnished **8** which on Swern oxidation afforded the aldehyde **9** (93%). Compound **9** was subjected to the Wittig reaction with ethyl 10-(triphenylphosphorylidine)-9-oxodeconoate[7] to give the (E)-unsaturated ketone (**10**) (80%). Compound **10** was treated with sodium borohydride[2b] in methanol to furnish a mixture of diastereomers (**11** and **12**) separated, in almost equal amounts, by chromatography. The stereochemical assignment at C-9 of compound **12** was established[8] by chemical transformation to the well defined natural product (**1**). Thus, compound **12** was hydrolysed to the acid **13** in the presence of potassium carbonate in aqueous methanol. The $^1$H NMR spectrum of **13** was concurrent with the reported data[3a]. Subsequent removal of acetonide group with p-toluenesulfonic acid in THF completed the sequence to afford **1** [$[\alpha]_D$ 7.7°(MeOH), lit.[3] $[\alpha]_D$ 7.5° (MeOH)].

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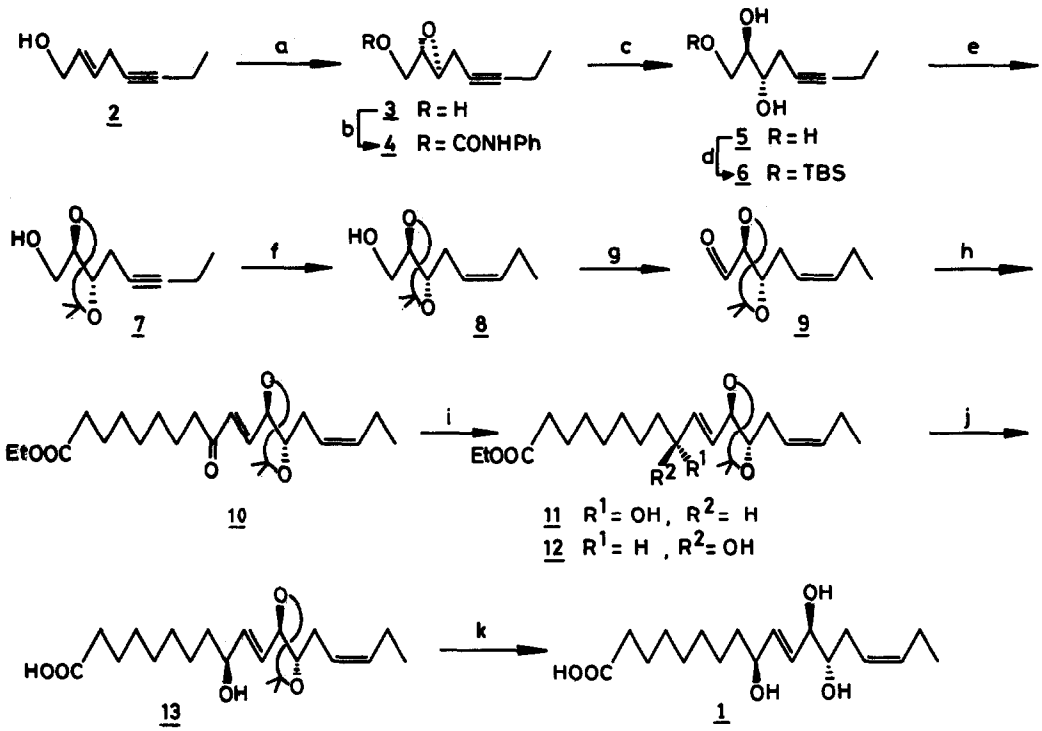


a) (+)DIPT, TBHP, $Ti(iOPr)_4$, $CH_2Cl_2$, -20°C, 18 h; b) PhNCO, $Et_3N$, $CH_2Cl_2$, RT, 18 h; c) i $BF_3$:$Et_2O$, $Et_2O$, 0°C, 2 h; ii NaOMe, MeOH, RT, 15 min; d) TBS-Cl, Imid., $CH_2Cl_2$, RT, 18 h; e) i $Me_2C(OMe)_2$, $CH_3COCH_3$, PPTS, RT, 18 h; ii $Bu_4NF$, THF, RT, 4 h; f) Lindlar's cat, $H_2$, 3 h; g) $(COCl)_2$, DMSO, $NEt_3$, -78°C, 1 h; h) $EtOOC-(CH_2)_7-COCH=PPh_3$, $CH_3CN$, 80°C, 2 h; i) $NaBH_4$, MeOH, RT, 15 min; j) $K_2CO_3$, MeOH, RT, 18 h; k) PTSA, THF, RT, 18 h.

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8. Compound **11** on deesterification and de-ketalation gave the C-9 epimer of **1**.

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