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CONVENIENT SYNTHESIS OF (±)- AND (*S*)-ANTIPODE OF (4*E*,7*S*)-7-METHOXYTETRADEC-4-ENOIC ACID, THE ANTIMICROBIAL PRINCIPLE OF MARINE CYANOPHYTE

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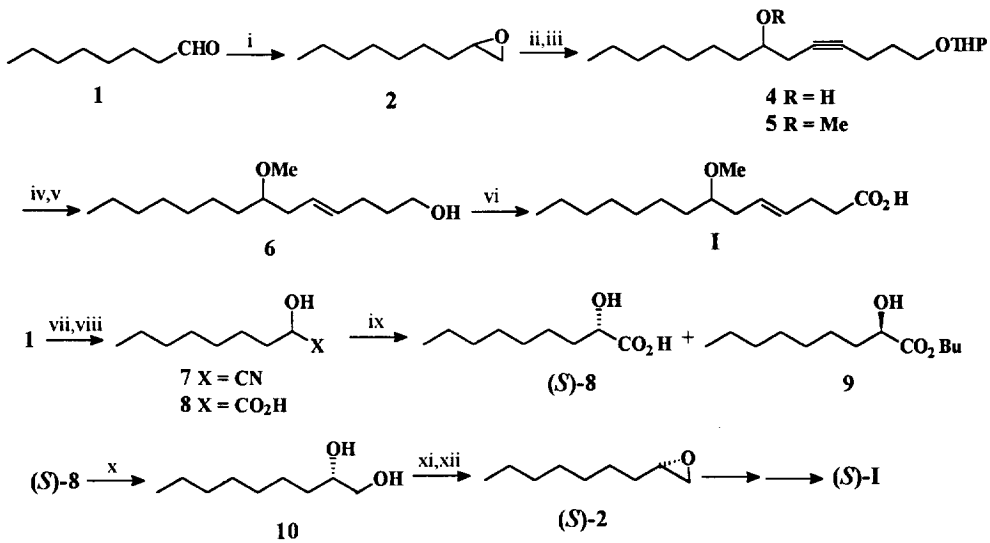
Abstract : The (±)- and (*S*)-isomers of title compound **I** were prepared *via* a short and efficient route. The key features of the synthesis were the use of easily accessible materials, operationally simple reaction protocol and highly enantioselective lipase catalyzed esterification for the generation of the required chiron. Copyright © 1996 Published by Elsevier Science Ltd

Marine chemistry has of late attracted great attention due to the possibility of obtaining safer and more potent bioactive compounds[1]. In addition, the structural diversity of marine metabolites often promises involvement of novel biosynthetic pathways akin to terrestrial kingdom. The title compound, (4*E*,7*S*)-7-methoxytetradec-4-enoic acid, **I** is one such metabolite, isolated[2] from the blue green alga, *Lyngbya majascula*. In addition, this is also amenable[3] from the lipid fraction of the shallow water *Lyngbya* species. Several bioactive amides including the fish antifeedant, malyngamide A[4] are also derived from the above novel fatty acid. Compound **I** is reported[5] to possess antimicrobial activity against gram-positive bacteria, *Staphylococus aureus and Bacillus subtilis*. The (*S*)-configuration of naturally occurring **I** has been confirmed by its first enantioselective synthesis reported[6] during the course of this work. In continuation of our recent works on marine chemicals[7] and antimicrobial compounds[8], we devised a convenient synthesis of both (±)- and (*S*)-**I** to study the activity-stereochemistry relationship. Both the earlier syntheses of racemic[9] and (*S*)-**I**[6] involved multiple steps. In addition the latter route employed rather inaccessible synthons and even the chiron utilized was difficult to prepare. The present highly enantioselective route is devoid of all these drawbacks and hence more efficient.

For the synthesis of the title compound, first we tested the suitability of our proposed route by preparing (±)-**I**. Thus, 1-octanal **1** was converted to the epoxy compound **2** by Corey's procedure[10]. This was then reacted with the 4-pentynol derivative, **3** to furnish the diol derivative **4**. Attempted methylation of **4** with MeI/NaH/THF produced the desired methyl ether **5** in poor yield, the reason for which was not studied. Consequently, compound **4** was methylated using *n*-BuLi as the base to afford **5** in excellent yield. Its depyranylation followed by stereoselective *E*-reduction with Li-metal in NH_3 gave the alcohol **6**. This was then oxidized with PDC in DMF to furnish (±)-**I**.

After establishing the synthetic scheme, we proceeded with the preparation of (*S*)-**I**. This required availability of the key epoxide **2** in homochiral form. We envisaged that the best precursors for chiral epoxides would be the corresponding α-hydroxy acids which in turn can be easily prepared by lipase catalyzed esterification[11]. Hence, we first prepared the required C_9-hydroxy acid **8** from the aldehyde **1**. Chemical cyanohydrination of **1** smoothly afforded **7** which on acidic hydrolysis led to the hydroxy acid **8** in excellent yield. It was then subjected to esterification with 1-butanol in toluene using *Candida rugosa* lipase (CRL) as the

catalyst. In the presence of freshly activated molecular sieve 4A° powder, the reaction proceeded smoothly to furnish (*S*)-**8** and (*R*)-butyrate **9**. The absolute configuration of the former was determined by comparing the sign of its specific rotation with those reported[12].



Scheme

i) Dimsyl ion/Me_3SI/DMSO, ii) $HC{\equiv}C(CH_2)_3OTHP$ (**3**)/*n*-BuLi/THF, iii) *n*-BuLi/THF/MeI; iv) MeOH/PTS; v) Li/NH_3; vi) PDC/DMF; vii) $NaHSO_3$/KCN/CH_2Cl_2/H_2O; viii) HCl/Δ; ix) CRL/*n*-BuOH/Toluene/mol. sieve; x) LAH/ether; xi) HBr-HAc; xii) K_2CO_3/MeOH.

The ee of (*S*)-**8** was assayed to be >97% by its esterification and subsequent derivatization to the MTPA ester followed by PMR analysis. The acid was then reduced with LAH to the (*S*)-diol **10**. Its bromoacetylation with HBr-HAc and subsequent base treatment led to the (*S*)-epoxide **2**. This was then converted to the target compound **I** following identical procedure as described above for the synthesis of the racemic sample.

Based on the enantiomeric purity of the starting chiron, (*S*)-**8**, the synthetic compound **I** should also be >97% enatiomerically pure. This was also corroborated from the chiroptical data of our sample with the reported values[6].

EXPERIMENTAL:

All the boiling points are uncorrected. The IR spectra were scanned with a Perkin-Elmer spectrophotometer model 837. The ^1H NMR spectra were recorded in $CDCl_3$ with a Bruker AC-200 (200 MHz) instrument. The optical rotations were measured with a Jasco DIP 360 polarimeter. Anhydrous reactions were carried out under Ar using freshly dried solvents. The organic extracts were dried over anhydrous Na_2SO_4. For enzymatic resolution CRL (Sigma, sp. act. 904 units/mg) was used as obtained.

1-Epoxynonane 2 : To a stirred solution of dimsyl anion [prepared from NaH (1.44 g, 0.03 mol, 50% suspension in oil) and DMSO (40 ml) at 55-60°C] was added trimethylsulphonium iodide[10] (4.08 g, 0.02 mol) in DMSO (10 ml) in such a way as to maintain the internal temperature <5 °C. After 15 min, the aldehyde **1** (2.4 g, 0.019 mol) in THF (30 ml) was introduced into it at 0 °C, the mixture stirred for 30 min at 0 °C and 1.5 h at

room temperature. Ice cold water (200 ml) was added in the flask and the mixture extracted with hexane. The hexane layer was washed with water and brine and finally dried. Removal of solvent followed by column chromatography of the residue over silica gel (0-10% ether/ hexane) afforded pure **2**. yield : 2.03 g (75%); b.p. 70-71° C/10 mm (lit[12]. b.p. 77-79° C/15 mm); IR : 1200, 1170 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.4-1.7 (m, 12H), 2.1-2.3 (m, 2H).

1-Tetrahydropyranyloxytetradec-4-yn-7-ol 4 : To a stirred and cooled (-20 °C) solution of 1-tetrahydropyranyloxy-pent-4-yne **3** (1.7 g, 0.01 mol) in THF (30 ml) was added *n*-BuLi (6.3 ml, 0.01 mol, 1.6 M solution in hexane). After 30 min, the mixture was cooled to -40 °C and HMPA (5 ml) was added into the mixture followed by the epoxide **2** (1.2 g, 8.5 mmol) in THF (10 ml). After stirring for 4 h at -40 °C and 24 h at room temperature, the reaction was quenched with aqueous saturated NH_4Cl. The organic portion was separated, the aqueous layer extracted with ether and the combined organic extract washed with water and brine. After drying and solvent removal, the residue was purified by column chromatography (silica gel, 0-20% EtOAc/hexane) to give **4**. yield: 2.14 g (81%); IR: 3380, 870, 810 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.29 (br. s, 14H), 1.4-1.6 (m, 6H), 1.9-2.2 (m, 4H), 2.41 (br. s, D_2O exchangeable, 1H), 3.6-3.9 (m, 5H), 4.5 (s, 1H). Anal. Calcd. for $C_{19}H_{34}O_3$: C, 73.5; H, 11.04. Found: C, 73.75; H, 11.12.

1-Tetrahydropyranyloxy-7-methoxytetradec-4-yne 5 : To a cooled (0 °C) and stirred suspension of **4** (2.1 g, 6.8 mmol) in THF (30 ml) was added *n*-BuLi solution (6.4 ml, 10.5 mmol, 1.6 M in hexane). After 0.5 h, MeI (4.3 g, 30.0 mmol) was slowly added to it and stirring continued for 48 h. The mixture was poured in ice-water, extracted with ether, the ether layer washed with water and brine and dried. Removal of solvent in vacuo gave **5** which was purified by column chromatography (silica gel, 0-10% EtOAc/hexane). yield : 1.89 g (86%); IR : 1200, 870, 810 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.32 (br. s, 14H), 1.5-1.7 (m, 6H), 2.0-2.2 (m, 4H), 3.51 (s, 3H), 3.6-3.9 (m, 5H), 4.5 (s, 1H). Anal. Calcd. for $C_{20}H_{36}O_3$: C, 74.02; H, 11.18. Found: C, 73.81; H, 11.06.

(*E*)-7-Methoxytetradec-4-en-1-ol 6 : A mixture of the above compound (1.85 g, 5.7 mmol) and PTS (0.1 g) in MeOH (20 ml) was refluxed till depyranylation was complete (4 h, *cf.* TLC). Most of the solvent was removed under reduced pressure and the residue extracted with ether. The ether extract was washed with aqueous 10% $NaHCO_3$, water and brine and finally dried. Solvent removal and column chromatography over silica gel (0-20% EtOAc/hexane) gave the depyranylated product. yield : 1.2 g (88%); IR : 3400, 1200, 1060 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.32 (br. s, 14H), 1.9-2.2 (m, 4H), 2.6 (s, D_2O exchangeable, 1H), 3.51 (s, 3H), 3.68 (t, J = 7 Hz, 2H), 3.9-4.0 (m, 1H). Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.18; H, 11.68.

To a solution of the above compound (2.0 g, 8.3 mmol) in NH_3 (30 ml) was added Li-metal (0.469 g, 0.067 mol) in pieces till the blue colour persisted for 1 h. The mixture was treated with NH_4Cl (s) (2.0 g) and NH_3 was allowed to evaporate. It was cautiously diluted with ice-water and extracted with ether. The ether layer was washed with saturated NH_4Cl solution, dried and concentrated in vacuo. The residue was chromatographed over silica gel (0-20% EtOAc/hexane) to furnish pure **6**. yield : 1.87 g (93%); IR : 3410, 1200, 980 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.32 (br. s, 14H), 2.0-2.2 (m, 4H), 2.4 (s, D_2O exchangeable, 1H), 3.5 (s, 3H), 3.6-3.9 (m, 3H), 5.3-5.5 (m, 2H). Anal. Calcd. for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48. Found: C, 74.14; H, 12.4.

(*E*)-7-Methoxytetradec-4-enoic Acid I : To a stirred suspension of PDC (7.14 g, 0.019 mol) in DMF (40 ml) was added compound **6** (1.2 g, 4.96 mmol) in DMF (5 ml). After stirring for 30 h at room temperature, the mixture was poured in ice-water (500 ml) and extracted with ether. The ether layer was thoroughly washed with water, brine and dried. The residue obtained on concentration was purified by column chromatography (silica

gel, 0-10% MeOH/$CHCl_3$) to give **I**. yield : 0.926 g (73%); IR : 3700-3500, 1710, 1200, 980 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.30 (br. s, 12H), 2.0-2.2 (m, 4H), 2.34 (t, *J* = 7 Hz, 2H), 3.54 (s, 3H), 3.8-4.0 (m, 1H), 5.3-5.5 (m, 2H), 8.71 (s, D_2O exchangeable, 1H). Anal. Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.56; H, 11.12.

2-Hydroxyoctanonitrile 7 : To a solution of 1-octanal (1) (10.0 g, 0.08 mol) in CH_2Cl_2 (100 ml) was added $NaHSO_3$ (12.2 g, 0.117 mol) in water (20 ml). Immediately a white solid separated which was dissolved in water (80 ml). A solution of KCN (7.61 g, 0.117 mol) in water (20 ml) was added to it over a period of 3 h keeping the reaction temperature below 5 °C. After stirring for 16 h at room temperature, the organic layer was separated and the aqueous portion extracted with $CHCl_3$. The combined organic extract was washed with water, brine and dried. Removal of solvent followed by column chromatography over silica gel (0-15% EtOAc/hexane) gave pure **7**. yield : 9.55 g (77%); IR : 3380, 2200, 810 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.30 (br. s, 12H), 1.8 (s, D_2O exchangeable, 1H), 4.3 (t, J = 6 Hz, 1H). Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.81; H, 11.22; N, 8.77.

2-Hydroxynonanoic Acid 8 : A mixture of compound **7** (9.0 g, 0.058 mol) and conc. HCl (145 ml) was stirred for 16 h at room temperature and subsequently at 80 °C for 6 h. The mixture was extracted with $CHCl_3$, the organic extract washed with water, brine and dried. After concentration, the residue was chromatographed over silica gel (0-5% $CHCl_3$/MeOH) to furnish pure **8** as a white solid which was recrystallized from hexane. yield : 9.6 g (95%); mp : 69-69 °C; IR : 3700-3500, 3340, 1710 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.29 (br. s, 12H), 4.5 (t, *J* = 6 Hz, 1H), 8.8 (s, D_2O exchangeable, 1H). Anal. Calcd. for $C_9H_{18}O_3$: C, 62.03; H, 10.41. Found: C, 62.2; H, 10.63.

Butyl (*R*)-2-Hydroxynonanoate 9 : A mixture of (±)-**8** (5.2, 0.03 mol), *n*-butanol (8.2 ml, 0.09 mol), powdered molecular sieve 4A° and CRL (2.0 g) in toluene (40 ml) was stirred till 46% conversion (34 h). The mixture was filtered, the solid residue washed thoroughly with EtOAc and the combined organic extract concentrated under reduced pressure. The residue obtained was chromatographed over silica gel (0-20% EtOAc/hexane) to furnish pure **9** and (*S*)-**8**. (*R*)-**9** : yield : 2.75 g (40%); $[\alpha]_D^{24}$ +14.1 (c 2.1, $CHCl_3$); IR : 3340, 1740 cm^{-1}; PMR : δ 0.9-1.0 (m, 6H), 1.32 (br. s, 16H), 2.4 (s, D_2O exchangeable, 1H), 3.9-4.2 (m, 3H). Anal, Calcd. for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found: C, 67.89; H, 11.21. (*S*)-**8** : yield : 2.65 g (51%); $[\alpha]_D^{24}$ -3.48 (c 3.16, $CHCl_3$). The spectral data were identical to those with the racemic sample.

(*S*)-Nonane-1,2-diol 10 : To a stirred suspension of LAH (0.655 g, 17.2 mmol) in ether (30 ml) was added (*S*)-**8** (2.0 g, 11.5 mmol) in ether (20 ml) at room temperature. Stirring was continued for 16 h at the same temperature, excess LAH was decomposed by dropwise addition of aqueous saturated Na_2SO_4 solution and the solution filtered. The solid precipitate was washed with EtOAc and the organic extract concentrated in vacuo and the residue chromatographed over silica gel (0-20% EtOAc/hexane) to furnish pure **10**. yield : 1.55 g (84%); $[\alpha]_D^{24}$ -2.8 (c 1.21, $CHCl_3$); IR : 3480, 1610 cm^{-1}; PMR : δ 0.9 (dist. t, 3H), 1.29 (br. s, 12H), 2.8 (s, D_2O exchangeable, 2H), 3.68 (d, *J* = 7 Hz, 2H), 3.8-3.9 (m, 1H). Anal. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.68; H, 12.34.

(*S*)-1-Epoxynonane 2 : HBr in acetic acid (3.0 ml, 33%) was added to **10** (1.2 g, 7.5 mmol) at 0-10° C. After stirring for 1 h at room temperature, it was cooled to 0° C and K_2CO_3 (7.5 g, 54.0 mmol) in H_2O (9 ml) was added to it. The mixture was extracted with ether, the combined extract washed with aqueous K_2CO_3, water, brine and dried. After concentration, the product was used as such for the next step.

A solution of KOH in MeOH (2.6 ml, 2.0 M) was slowly added to the above compound in MeOH (10 ml) at 0° C. Immediately a white precipitate formed which was removed by filtration, the filtrate concentrated in vacuo and residue extracted with ether. The ether layer was washed with water, brine and finally dried. Removal of solvent and column chromatography of the residue afforded pure (*S*)-**2**. yield : 0.862 g (81%); $[\alpha]_D^{24}$ -8.9 (c 1.14, $CHCl_3$), (lit[6]. $[\alpha]_D^{20}$ -8.6 (c 1, $CHCl_3$)). Its spectral data were identical with those of the racemic sample.

(7*S*)-1-Tetrahydropyranyloxytetradec-4-yn-7-ol 4 : $[\alpha]_D^{22}$ -1.9 (c 2.2, $CHCl_3$).

(7*S*)-1-Tetrahydopyranyloxy-7-methoxytetradec-4-yne 5 : $[\alpha]_D^{22}$ -3.7 (c 1.47, $CHCl_3$).

(7*S*,4*E*)-7-Methoxytetradec-4-en-1-ol 6 : $[\alpha]_D^{22}$ -3.1 (c 1.88, $CHCl_3$).

(7*S*,4*E*)-7-Methoxytetradec-4-enoic Acid I : $[\alpha]_D^{22}$ -10.86 (c 2.4, $CHCl_3$), (lit[3]. $[\alpha]_D^{20}$ -11.1 (c 3.9, $CHCl_3$)).

The spectral data of (*S*)-**4** to (*S*)-**6** and (*S*)-**I** were identical with those of the respective racemic samples.

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REFERENCES

1. Moore, R. E., in "*Marine Natural Products: Chemical and Biological Perspectives*", Vol. IV, ed. Scheuer, P. J., Academic Press, New York, pp. 1-52.
2. Wright, A. D.; Coll, J. C., *J. Nat. Prod.*, **1990**, *53*, 845.
3. Cardellina II, J. H.; Dalietos, D.; Marner, F. -J.; Mynderse, J. S.; Moore, R. E., *Phytochemistry*, **1978**, *17*, 2091.
4. Wyile, C. R.; Paul, V. J., *Marine Ecology Progress Series*, **1988**, *45*, 23.
5. Gerwick, W. H.; Reyes, S., Alvarado, B., *Phytochemistry*, **1987**, *26*, 1701.
6. Muller, C.; Voss, G.; Gerlach, H., *Liebigs Ann. Chem.*, **1995**, 673.
7. Kulkarni, B. A.; Chattopadhyay, S.; Chattopadhyay, A.; Mamdapur, V. R., *J. Org. Chem.*, **1993**, *58*, 5223.
8. Sharma, A.; Chattopadhyay, S., *Liebigs Ann. Chem.*, (in press).
9. Fryhle, C. B.; Williard, P. G.; Rybak, C. M., *Tetrahedron Lett.*, **1992**, *33*, 2327.
10. Corey, E. J., Chaykovsky, M., *J. Am. Chem. Soc.*, **1965**, *87*, 1353.
11. Parida, S.; Dordick, J. S., *J. Am. Chem. Soc.*, **1991**, *113*, 2253.
12. Haase, B.; Schneider, M. P., *Tetrahedron Asymm.*, **1993**, *4*, 1017.

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