Pergamon

Tetrahedron Letters, Vol 35, No. 20, pp 3413-3416, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6 00+0.00

0040-4039(94)E0536-7

Isolation and Synthesis of Siphonarienal, a New Polypropionate From *Siphonaria grisea*

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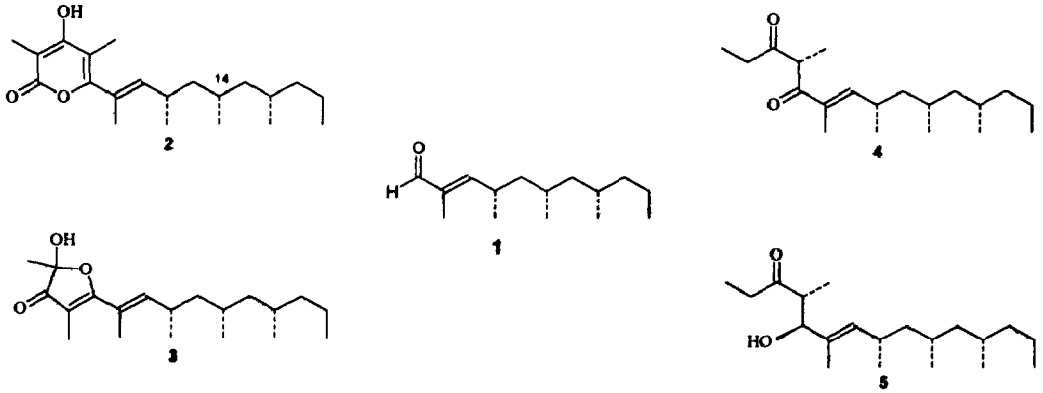
Abstract: Siphonarienal **1**, a pentapropionate derivative, was isolated from the marine pulmonate mollusk *Siphonaria grisea*. Its structure was established on the basis of its spectroscopic data and its absolute configuration was assured by its enantioselective synthesis.

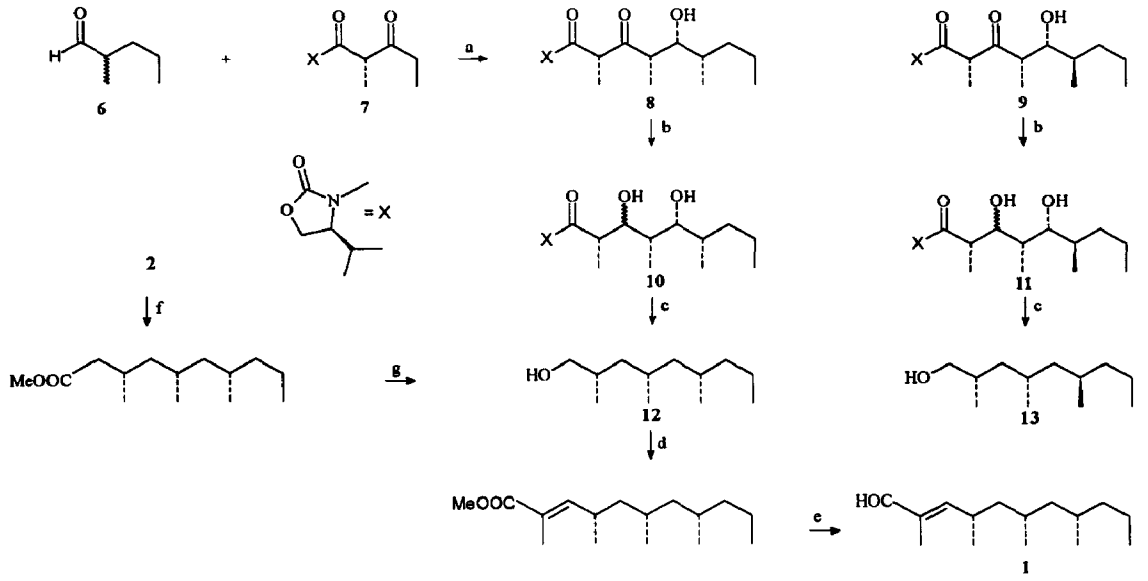
Polypropionates have been reported from a number of marine pulmonate mollusks belonging to the genera *Siphonaria*[1], *Tridachia*[2] and *Onchidium*[3] In our research on *Siphonaria grisea* collected at the Canary Islands, we have isolated three stereochemically homologous polypropionates **3-5**, all of them containing three methyl groups in the side chain with an S configuration[4]. During that research we also established an identical absolute configuration for the side chain of pectinatone **2**, which was assured by X-ray diffraction analysis and chemical correlations. Thus, this study has established that the absolute configuration at C-14 in pectinatone was S and not R as previously reported, which was reinforced by identical results published by Garson et al. in an independent work[5].



During another study of a collection of *S. grisea* from Dakar (Senegal) we found, together with the metabolites obtained in the Canary Islands collection, a very unstable minor compound **1**[6]. Its structure was impossible to assure in the light of the available spectroscopic data, although the NMR data suggested that the new metabolite was an α,β-unsaturated aldehyde with a linear side chain similar to those observed for compounds **2-5**. Due to the small amount of compound combined with its instability, it was impossible to confirm its absolute configuration. However, taking into account that it is biosynthetically unlikely that *S. grisea* would generate related metabolites differing in chirality in the same side chain, we had decided to carry out the enantioselective synthesis of compound **1** with all the side-chain methyl groups having an S configuration.

The synthesis of siphonarienal **1** began with the construction of the C_3-C_{11} subunit. It was achieved, following the methodology developed by Evans[7], through a combined aldol-reduction sequence which mimics in the laboratory the enzymatic acylation and reduction that occur in polypropionate biosynthesis. Thus, the aldol union of the aldehyde **6** with the titanium enolate of the β-keto imide **7** gave the mixture of the syn adduct in high yield, which was chromatographed by silica gel to obtain pure diastereomers **8** and **9**. Each aldol adduct diastereomer was treated with sodium triacetoxyborohydride to give the 1,3 diols **10** and **11** in a 1:1 mixture of epimers, which were mesylated. The reductive removal of the mesyl group and the auxilary chiral group was accomplished by treatment with $LiAlH_4$, yielding the alcohols **12** and **13** with the desired deoxypolypropionate side chain. The correct diastereomer was then identified by comparison of the spectroscopical and physical properties of **12** and **13**[8] with those observed for the alcohol obtained by the chemical degradation of pectinatone **2**[4] (Scheme 1).

Scheme 1



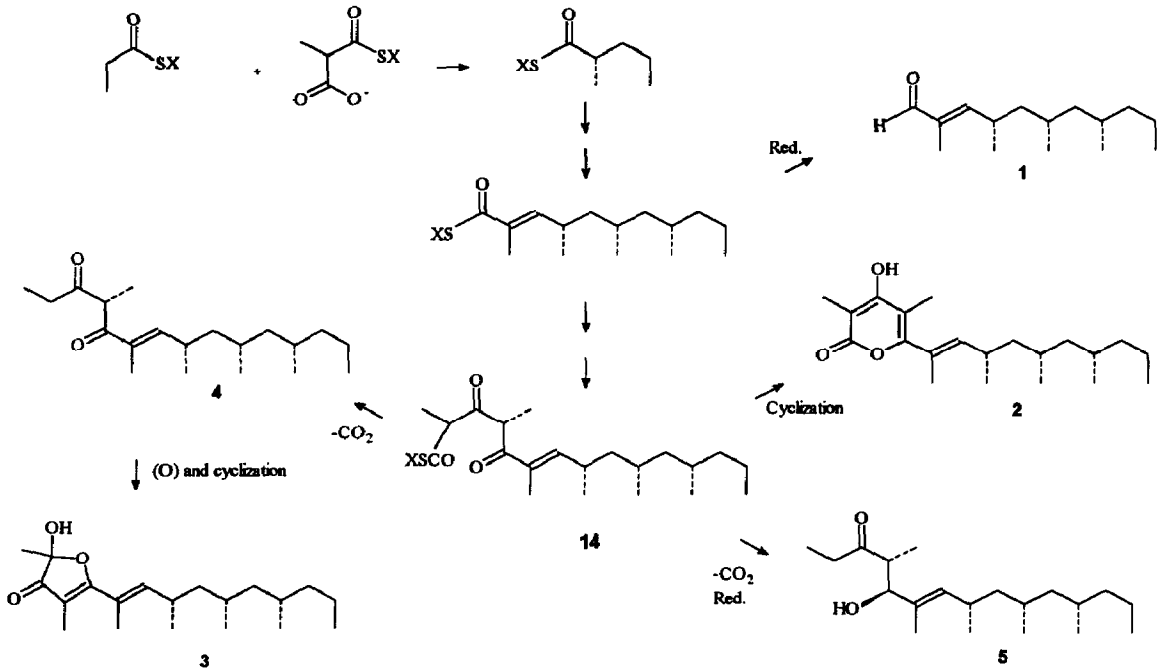
a) $TiCl_4$, CH_2Cl_2, $(iPr)_2NEt$, -78°→ 40°, 86%, **b)** $Na(AcO)_3BH$, AcOH, r.t., 90%; **c)** i) MsCl, Py, DMAP, r.t.; ii) $LiAlH_4$, Et_2O, -78°→ 0°, 53%; **d)** i) $Py.SO_3$, DMSO, Et_3N, r.t.; ii) $EtO_2CC(Me)=PPh_3$, C_6H_5Me, 80°, 64%; **e)** i) DIBAL, CH_2Cl_2, -78°→ 0°C; ii) MnO_2, CH_2Cl_2, r.t., 65%; **f)** i) HIO_4, $RuCl_3.3H_2O$, r.t.; ii) CH_2N_2, Et_2O, r.t., 92%; **g)** $LiAlH_4$, Et_2O, r.t., 92%.

Starting from **12**, a four-steps sequence consisting of Moffat oxidation and condensation with (carbomethoxymethylidene)tryphenylphosphorane followed by reduction with DIBAL and oxidation with MnO_2 provided a compound which was identical in all aspects with siphonarienal **1**.

The polypropionate origin of these natural compounds has been demonstrated by the incorporation of [1-^{14}C] sodium propionate in denticulatins A and B[9], thus establishing that these compounds share a common

biosynthetic origin to actinomycete metabolites such as erythromycin. In this case, it has been established that the

Scheme 2



erythromycin aglycone, 6-deoxyerythronolide B, is biosynthesized from propionyl-CoA starter unit followed by iterative methylmalonyl-CoA condensations[10]. The β-keto functionalities are either left unmodified or are appropriately reduced to their final status after each condensation. A similar biosynthetic pathway could be proposed for the metabolites isolated from *S. grisea* (Scheme 2).The isolation of siphonarienal **1** with a pentapropionate nature, reinforces this proposal as iterative condensations of propionyl units. The biosynthesis of the major metabolites from *S. grisea* could be rationalized as directly derived from the heptapropionate **14**, after obvious metabolic reactions.

Acknowledgements

M.N. acknowledges financial support from the Plan Nacional de Investigaciones Farmacéuticas Far 91-0827. A. P. thanks M.E.C. for a fellowship.

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6.- 1: oil; $[\alpha]_D$= +7.5° (c, 0.2, $CHCl_3$); HRMS: m/z 223.2047 (calc. $C_{15}H_{27}O$ 223.2062). EIMS: m/z, 223 $(M-H)^+$; 154 $(M-C_4H_6O)$; 123; 111; I.R. ν_{max} cm^{-1}: 1650; UV (λ^{EtOH}_{max}) : 240 nm (ε 5880); ^{1}H-NMR (δ, $CDCl_3$): 0.81 (d, J= 6.5 Hz, 3H), 0.84 (d, J= 6.3 Hz, 3H), 0.88 (t, J= 7.4 Hz, 3H), 1.05 (d, J= 6.3 Hz, 3H), 1.77 (s, 3H), 2.83 (m, 1H), 6.22 (d, J= 10 Hz, 1H), 9.39 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$): 9.75 (q), 14.75 (q), 20.37 (t), 20.42 (q), 20.72 (q), 20.91 (q), 28.63 (d), 30.02 (d), 31.63 (d), 39.63 (t), 44.61 (t), 45 96 (t), 138.35 (s), 161.19 (d), 196 0 (d).

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8.- **12:** oil, $[\alpha]_D$= +3.84° (c, 0.39, $CHCl_3$); ^{1}H-NMR (δ, $CDCl_3$): 0.84 (d, J= 6.3 Hz, 3H), 0.87 (d, J= 6.5 Hz, 3H), 0.89 (t, J= 7.1 Hz, 3H), 0.93 (d, J= 6.7 Hz, 3H), 3.33 (dd, J= 6.7 and 10.4 Hz, 1H), 3.52 (dd, J= 5.3 and J=10.4 Hz, 1H), ^{13}C-NMR (δ, $CDCl_3$): 14 67 (q), 17 93 (q), 20.34 (t), 20.83 (q), 21.31 (q), 27.96 (d), 30.15 (d), 33.51 (d), 39.25 (t), 41.70 (t), 45.59 (t), 68.61 (t).
13: oil, $[\alpha]_D$= +15.2° (c, 0 25, $CHCl_3$); ^{1}H-NMR (δ, $CDCl_3$): 0.82 (d, J=6.4 Hz), 0.86 (d, J=6 Hz), 0.89 (t, J=8 Hz), 0.93 (d, J=6.5 Hz), 3.38 (dd, J=5.3 and 10.6 Hz), 3.53 (dd, J=6.9 and 10.6 Hz); ^{13}C-NMR (δ,$CDCl_3$): 14.13 (q), 17.06 (q), 19.28 (q), 20.07 (t), 20 27 (q), 27 37 (d), 29.72 (d), 33.01 (d), 40.49 (t), 41.94 (t), 44.34 (t), 68.44 (t).

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(*Received in UK* 2 *February* 1994; *revised* 16 *March* 1994; *accepted* 17 *March* 1994)