Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1345–1350

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of a cytotoxic amide of *Telesto riisei*

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Received 29 December 1997; accepted 2 March 1998

Abstract

An efficient synthesis of both the enantiomers of *N*-(2-phenylethyl)-8-hydroxypentadecacarboxamide using the cytotoxic principles of *Telesto riisei* has been formulated using cyclohexylideneglyceraldehyde **1** as the chiral template. A non-stereoselective Grignard addition to the aldehyde **1** gave the C-3 epimers of the required chiron, 3-alkylglycerol which were converted to the title compound *via* a standard sequence of reactions. © 1998 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

The search for new bioactive organic compounds has led to an explosive growth of marine chemistry in the last decade.[1] This has also provided compounds with novel structural features which probably owe their origin to several factors in the marine kingdom such as the salty environment, unusual metabolisms and involvement of symbiotic relationships acting individually or in combination. To this end, numerous species of soft corals and gorgonians which abound in tropical reefs have been the major focus of attention leading to a vast array of secondary metabolites.[2] In contrast, the octocoral order, *Telestaceae* contains few members and their chemical investigation is also rather scarce. Only one of these *viz*. *Telesto riisei* has so far been investigated leading to the isolation of two new pregnane derivatives[3] and several highly functionalized prostanoids.[4,5] The chemical constituents of the octocoral were found to be totally environment dependent and varied according to their habitation. Recently, from *T*. *riisei*, collected at Chuuk Atoll, Federated States of Micronesia, two new bioactive amides were isolated.[6] These were identified as *N*-(2-phenylethyl)-8-hydroxypentadecacarboxamide **I** and the corresponding 8-oxo compound. Both compounds showed cytotoxicity to murine leukemia cells (P-388) with ED50 (μg/ml) values 2.2 and 2.1 respectively. Although, the amide **I** was optically active, the stereochemistry of its C-8 centre is still obscure.

In view of the promising bioassay result, compound **I** seems to be a good candidate in cancer therapy research. At the same time, the importance of chirality on bioactivity warrants availability of

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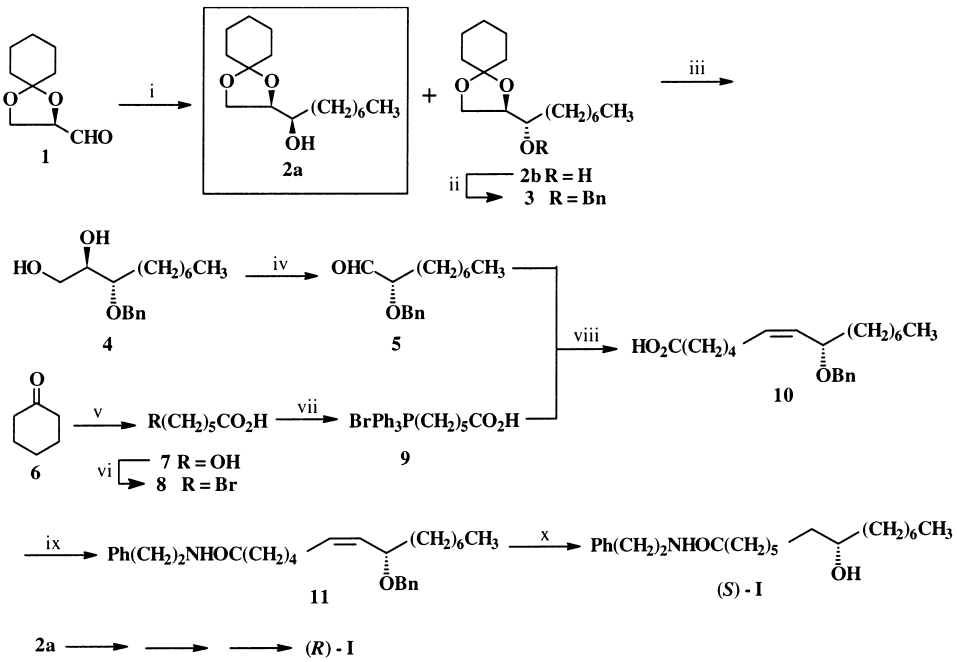
PII: S0957-4166(98)00091-3

its enantiomers in homochiral forms. This would not only provide an insight into its mechanism of action but also lead to better therapeutic formulation. In addition, the hitherto unknown configuration of the natural compound could also be determined by its synthesis. With this aim, we developed the first enantiomeric synthesis of **I** in its antipodal forms.

The synthetic strategy (Scheme 1) was based on an asymmetric strategy recently developed[7] from our laboratory for the preparation of chiral 3-alkylglycerols. Reaction of various organo–metallic reagents to various glyceraldehyde derivatives is known to proceed with modest to poor enantioselectivity. However, it was found[7] that using cyclohexylideneglyceraldehyde[8] **1** as the chiral template, the resultant carbinol enantiomers obtained by Grignard addition could be separated easily by normal column chromatography. Owing to their homochirality and varied functionality, the resultant triol derivatives are suitable for the asymmetric syntheses of a diverse array of complex natural products. In spite of modest enantioselectivity, the above process thus provides the epimeric 3-alkylglycerols in homochiral forms. This aspect seemed attractive in the present case, as we were interested in the synthesis of both the enantiomers of **I**.



i) $CH_3(CH_2)_6MgBr$/THF, ii) NaH/BnBr/Bu_4NI/THF/Δ, iii) Aq. Trifluoroacetic acid, iv) $NaIO_4/CH_3CN$-H_2O, v) HCO_3H; N vi) HBr/H_2SO_4/Δ, vii) Ph_3P/CH_3CN/Δ, viii) *n*-BuLi/THF, ix) $Ph(CH_2)_2NH_2$/DCC/DMAP/CH_2Cl_2, x) H_2/10% Pd-C/EtOH.

Scheme 1.

2. Results and discussion

Consequently, for the synthesis, the aldehyde **1** was reacted with *n*-heptylmagnesium bromide to furnish the epimeric alcohols **2a** and **2b** which were individually isolated by normal column chromatography over silica gel. Their *syn*- and *anti*-stereochemistry were confirmed by comparing the ^1H NMR resonances of the $–CH_2O$ and –CHO groups with those reported in the literature.[9a,b] In contrast

to the three multiplets shown for the above protons in the high field (500 MHz) ^{1}H NMR spectrum of **2a**, compound **2b** exhibited four well separated multiplets at δ 3.77–3.83 (1H), 3.86–3.89 (1H), 3.93–3.96 (1H) and 3.98–4.04 (1H) respectively. Both the synthons were tailor-made for the synthesis of **I** antipodes. For the synthesis of (*S*)-**I**, **2b** was benzylated to furnish **3** which on acidic hydrolysis gave the triol derivative **4**. Cleavage of its diol function with $NaIO_4$ afforded the desired chiron **5**.

The other component **9** required for the synthesis, was prepared from cyclohexanone **6**. Thus, compound **6** was subjected to a Baeyer–Villiger oxidation[10] with performic acid to give the hydroxy acid **7**. Its bromination furnished the known compound **8**[11] which was converted to the phosphonium salt **9** by heating with Ph_3P. A Wittig reaction[12] between the aldehyde **5** and **9** in the presence of *n*-BuLi as the base afforded the acid **10**. Since the olefin geometry was of no consequence to the synthesis, we did not analyze its composition. To check if there was any racemisation during the Wittig reaction, the acid **10** was converted to its methyl ester with diazomethane and subjected to HPLC analysis on CHIRALCEL OJ (Daicel Chemical Industries) column using 15% 2-propanol/hexane as the eluent and a flow rate of 0.5 ml/min. Two peaks with retention times of 45 min (99%) and 48 min (1%) established its ee to be 98%. The acid was then converted to the amide **11** by reacting with 2-phenylethylamine in the presence of DCC-DMAP. This on catalytic hydrogenation over 10% Pd–C in EtOH led to (*S*)-**I**.

Following an identical procedure, (*R*)-**I** was also synthesized starting from the *syn*-triol derivative **2a**. Their spectral data were in conformity with those reported.[6] Both the antipodes of synthetic **I** should be enantiomerically pure as their respective precursors *viz*. **2a** and **2b** were homochiral as suggested by their high field ^{1}H NMR spectra. Since the natural compound showed a negative specific rotation similar to that of (*R*)-**I**, prepared by us, its configuration also must be (*R*).

3. Experimental

All the boiling points were uncorrected. The IR spectra were scanned with a Perkin–Elmer spectrophotometer model 837 and only the pertinent bands are mentioned. The ^{1}H 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.

*3.1. 1,2-Cyclohexylidenedecane-3-ol **2b***

To a stirred solution of *n*-heptylmagnesium bromide [prepared from 1-bromoheptane (10.74 g, 0.06 mol) and Mg (1.75 g, 0.072 mol)] in anhydrous THF (60 ml) was added **1** (5.1 g, 0.03 mol) in THF (15 ml) at 0°C. After 3 h, the reaction was quenched with aqueous saturated NH_4Cl and the mixture extracted with ether. The ether layer was washed with water and brine and finally dried. Removal of the solvent under reduced pressure followed by column chromatography of the residue over silica gel gave pure **2a** (with 8% EtOAc/hexane) followed by a mid-fraction of the diastereomeric mixture (with 8–10% EtOAc/hexane) and finally pure **2b** (with 12% EtOAc/hexane). The mid-fraction was again column chromatographed, as above, to obtain the second batch of **2a** and **2b**. **2a**: Yield: 2.35 g (29%); $[\alpha]_D^{22}$ +9.76 (c 0.41, $CHCl_3$); IR: 3380, 1030, 880, 810 cm^{-1}; ^{1}H NMR: δ 0.87 (dist. t, 3H), 1.24–1.38 (m, 12H), 1.4–1.6 (m, 10H), 2.3 (br. s, D_2O exchangeable, 1H), 3.44–3.47 (m, 1H), 3.68–3.71 (m, 1H), 3.93–4.0 (m, 2H). Anal. calcd for $C_{16}H_{30}O_3$: C 71.07, H 11.18; found: C 70.88, H 11.48. **2b**: Yield: 4.1 g (50.6%); $[\alpha]_D^{22}$ +8.75 (c 0.32, $CHCl_3$); IR: 3400, 1030, 880, 810 cm^{-1}; ^{1}H NMR: δ 0.88 (dist.

t, 3H), 1.2–1.39 (m, 12H), 1.41–1.65 (m, 10H), 2.84 (br. s, D_2O exchangeable, 1H), 3.77–3.83 (m, 1H), 3.86–3.89 (m, 1H), 3.93–3.96 (m, 1H), 3.98–4.04 (m, 1H).

*3.2. (2*R*,3*S*)-1,2-Cyclohexylidene-3-benzyloxydecane **3***

A solution of **2b** (2.0 g, 7.4 mmol) in THF (20 ml) was added dropwise to a magnetically stirred suspension of hexane washed NaH (0.391 g, 8.15 mmol, 50% dispersion in oil) in THF (20 ml) at room temperature. The mixture was heated to 60°C for 1 h to ensure complete anion generation. After cooling to room temperature, BnBr (1.4 g, 8.15 mmol) in THF (10 ml) was added and stirring continued for 18 h. The mixture was then poured into cold water and extracted with ether. The ether extract was washed with water and brine and dried. Removal of solvent followed by column chromatography (silica gel, 0–10% EtOAc/hexane) of the residue gave pure **3**. Yield: 2.39 g (90%); $[\alpha]_D^{22}$ +7.48 (c 1.47, $CHCl_3$); IR: 3065, 3030, 1600, 1440, 700 cm^{-1}; ^1H NMR: δ 0.88 (dist. t, 3H), 1.24–1.38 (m, 12H), 1.4–1.62 (m, 10H), 3.75–3.81 (m, 1H), 3.93–3.96 (m, 1H), 4.01–4.1 (m, 2H), 4.55 (s, 1H), 4.63 (s, 1H), 7.35 (s, 5H). Anal. calcd for $C_{23}H_{36}O_3$: C 76.62, H 10.07; found: C 76.57, H 10.16.

*3.3. (2*R*,3*S*)-3-Benzyloxydecane-1,2-diol **4***

A solution of **3** (2.3 g, 6.4 mmol) in trifluoroacetic acid (10 ml) and water (1 ml) was stirred at room temperature for 72 h. Most of the solvent was removed in vacuo, the residue suspended in $CHCl_3$ and washed successively with water, 10% aqueous $NaHCO_3$, water and brine. After drying, the extract was concentrated in vacuo and the residue chromatographed (silica gel, 0–5% MeOH/$CHCl_3$) to furnish **4**. Yield: 1.5 g (83.7%); $[\alpha]_D^{22}$ +8.95 (c 0.38, $CHCl_3$); IR: 3390, 3065, 3030, 1650, 1020, 697 cm^{-1}; ^1H NMR: δ 0.88 (dist. t, 3H), 1.3–1.6 (m containing a br. s at δ 1.32, 12H), 3.1 (br. s, D_2O exchangeable, 2H), 3.45–3.55 (m, 2H), 3.6–3.8 (m, 1H), 4.05–4.2 (m, 1H), 4.55 (s, 1H), 4.63 (s, 1H), 7.35 (s, 5H). Anal. calcd for $C_{17}H_{28}O_3$: C 72.82, H 10.07; found: C 72.77, H 10.31.

*3.4. (2*S*)-2-Benzyloxynonanal **5***

To a cooled (0°C) and stirred solution of **4** (1.5 g, 5.36 mmol) in CH_3CN:H_2O (50 ml, 3:2) was added $NaIO_4$ (2.2 g, 10.3 mmol) in portions. After stirring for 1.5 h, the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in ether, the ether layer washed successively with water, aqueous Na_2SO_3, water, aqueous $Na_2S_2O_3$, water and brine and finally dried. Removal of solvent gave pure **5** (*cf.* TLC) which was used as such for the next step. Yield: 1.12 g (84%); IR: 3065, 3030, 2715, 1735, 1030 cm^{-1}; ^1H NMR: δ 0.9 (dist. t, 3H), 1.25–1.6 (m containing a br. s at δ 1.3, 12H), 4.5 (s, 2H), 4.6–4.9 (m, 1H), 7.35 (s, 5H), 9.8 (d, *J*=1.5 Hz, 1H).

*3.5. 6-Bromohexanoic acid **8***

To a stirred solution of HCO_3H [prepared from H_2O_2 (120 ml, 30%) and HCO_2H (360 ml)] was added cyclohexanone **6** (31 ml) over a period of 1 h. After stirring for 24 h, water (200 ml) was added and the mixture extracted with $CHCl_3$ by continuous liquid–liquid solvent extraction. The solvent and excess HCO_2H was removed first at normal pressure and subsequently under reduced pressure (0.1 mmHg) to furnish the hydroxy acid **7**. Yield: 30.2 g (75%); IR: 3500–2500, 1710, 1420 cm^{-1}; ^1H NMR: δ 1.45 (br. s, partially D_2O exchangeable, 7H), 2.4 (t, *J*=6 Hz, 2H), 3.6 (t, *J*=6 Hz, 2H), 10.2 (br. s, D_2O exchangeable, 1H).

To a stirred and cooled (0°C) aqueous solution 48% HBr (37.0 g) was slowly added conc. H_2SO_4 (12 ml). Subsequently, compound **7** (30.2 g, 0.23 mol) was carefully introduced to the above acid mixture. The mixture was then refluxed for 8 h, brought to room temperature, diluted with water and extracted with ether. The organic extract was washed with water and brine, dried and concentrated. The crude product was purified by vacuum distillation to give **8**. Yield: 28.7 g (64%); bp: 104–106°C/0.2 mmHg (lit.[11] bp: 142–143°C/11 mmHg); IR: 3500–2500, 1710 cm^{-1}; ^1H NMR: δ 1.3–1.9 (m, 6H), 2.4 (t, *J*=6 Hz, 2H), 3.43 (t, *J*=6 Hz, 2H), 11.3 (br. s, D_2O exchangeable, 1H). Anal. calcd for $C_6H_{11}O_2Br$: C 36.96, H 5.68; found: C 36.77, H 5.59.

*3.6. 5-Carboxypentyltriphenylphosphonium bromide **9***

A mixture of **8** (27.7 g, 0.142 mol) and Ph_3P (38.0 g, 0.144 mol) in CH_3CN (150 ml) was refluxed for 48 h. Most of the solvent was removed in vacuo and the residue titurated with solvent ether. The precipitated pale yellow solid was filtered, washed thoroughly with ether and dried in vacuo over P_2O_5 to get **9**. Yield: 61.4 g (94%); mp: 205°C, (lit.[10] mp: 200–203°C).

*3.7. (8S)-(6E/Z)-8-Benzyloxypentadec-6-enoic acid **10***

To a stirred suspension of **9** (2.23 g, 4.88 mmol) in THF (20 ml) at −25°C was added *n*-BuLi (6.1 ml, 1.6 M in hexane, 9.77 mmol). After stirring for 1 h at the same temperature, it was cooled to −30°C and the aldehyde **5** (1.1 g, 4.4 mmol) in THF (20 ml) was added to it. Stirring was continued for 4 h at −30°C and 12 h at room temperature. It was treated with aqueous saturated NH_4Cl, the organic part separated and the aqueous portion extracted with ether. The combined organic extract was washed with water and brine and finally dried. Removal of solvent and subsequent column chromatography of the product over silica gel (0–5% MeOH/$CHCl_3$) gave **10** as a mixture of geometrical isomers. Yield: 0.96 g (63%); $[\alpha]_D^{22}$ +3.71 (c 1.54, $CHCl_3$); IR: 3550–3250, 3065, 3030, 1710 cm^{-1}; ^1H NMR: δ 0.9 (dist. t, 3H), 1.2–1.7 (m, 16H), 2.0–2.4 (m, 4H), 4.5 (s, 2H), 4.6–4.8 (m, 1H), 5.5–5.6 (m, 2H), 7.16 (br. s, 5H), 9.1 (br. s, D_2O exchangeable, 1H). Anal. calcd for $C_{22}H_{34}O_3$: C 76.26, H 9.89; found: C 76.42, H 10.12.

*3.8. (8S)-8-Hydroxypentadecanoic acid 2-phenylethyl amide **I***

A solution of compound **10** (0.24 g, 0.7 mmol), 2-phenylethylamine (0.085 g, 0.7 mmol), DCC (0.144 g, 0.7 mmol) and DMAP (0.05 g) in CH_2Cl_2 (10 ml) was stirred for 16 h. The precipitated solid was removed by filtration, the filtrate washed with aqueous dil. HCl (2 N), water and brine and dried. Solvent removal followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) gave **11**. Yield: 0.14 g (45%); $[\alpha]_D^{22}$ +2.56 (c 0.52, $CHCl_3$); IR: 3335, 1690 cm^{-1}; ^1H NMR: δ 0.88 (dist. t, 3H), 1.2–1.6 (m, 14H), 1.7–2.0 (m, 4H), 2.55 (t, *J*=7 Hz, 2H), 3.3 (t, *J*=7 Hz, 2H), 4.51 (br. s, 1H), 4.6–4.7 (m containing an s at δ 4.62, 3H), 5.3–5.5 (m, 2H), 7.16 (s, 10H).

A mixture of **11** (0.14 g, 0.31 mmol) and 10% Pd–C (0.05 g) in EtOH (10 ml) was shaken under a slight a positive pressure of hydrogen until the required uptake of H_2. The reaction mixture was diluted with EtOAc and the supernatant passed through a pad (2 inches) of silica gel. The eluent was concentrated in vacuo and the residue purified by preparative TLC (silica gel, 15% EtOAc/hexane) to furnish **I**. Yield: 0.089 g (79%); mp: 77°C (lit.[6] mp: 78°C); $[\alpha]_D^{22}$ +3.68 (c 0.46, $CHCl_3$), (lit.[6] $[\alpha]_D^{25}$ −2.68 (c 0.41, $CHCl_3$)); IR: 3335, 1690 cm^{-1}; ^1H NMR: δ 0.88 (dist. t, 3H), 1.32 (br. s, 22H), 1.7–1.8 (m, 2H), 2.55 (t, *J*=7 Hz, 2H), 3.3–3.35 (m, 2H), 3.45–3.59 (m, 1H), 4.51 (br. s, 1H), 7.35 (s, 5H). Anal. calcd for $C_{23}H_{39}O_2N$: C 76.40, H 10.87; found: C 76.22, H 10.62.

3.9. (2R,3R)-1,2-Cyclohexylidene-3-benzyloxydecane **3**

$[\alpha]_D^{22}$ +4.32 (c 0.78, $CHCl_3$); IR: 3065, 3030, 1610, 1460, 720 cm^{-1}; ^1H NMR: δ 0.86 (dist. t, 3H), 1.22–1.35 (m, 12H), 1.4–1.6 (m, 10H), 3.48–3.56 (m, 1H), 3.78–3.84 (m, 1H), 3.88–3.96 (m, 2H), 4.55 (s, 1H), 4.6 (s, 1H), 7.35 (s, 5H).

3.10. (2R,3R)-3-Benzyloxydecane-1,2-diol **4**

$[\alpha]_D^{22}$ +3.88 (c 0.68, $CHCl_3$); IR: 3440, 3065, 3030, 1630, 1010, 700 cm^{-1}; ^1H NMR: δ 0.9 (dist. t, 3H), 1.32 (br. s, 12H), 2.68 (br. s, D_2O exchangeable, 2H), 3.51–3.55 (m, 2H), 3.63–3.72 (m, 1H), 4.1–4.6 (m, 3H), 7.35 (s, 5H).

3.11. (8R)-(6Z)-8-Benzyloxypentadec-6-enoic acid **10**

$[\alpha]_D^{22}$ −3.34 (c 1.4, $CHCl_3$); IR: 3500–3200, 3065, 3030, 1715 cm^{-1}; ^1H NMR: δ 0.9 (dist. t, 3H), 1.2–1.63 (m, 16H), 2.1–2.45 (m, 4H), 4.55 (s, 2H), 4.64–4.78 (m, 1H), 5.5–5.6 (m, 2H), 7.26 (br. s, 5H), 8.9 (br. s, D_2O exchangeable, 1H).

3.12. (8R)-8-Hydroxypentadecanoic acid 2-phenylethyl amide **I**

$[\alpha]_D^{24}$ −3.36 (c 0.88, $CHCl_3$), (lit.[6] $[\alpha]_D^{25}$ −2.68 (c 0.41, $CHCl_3$)); mp: 73°C (lit.[6] mp: 78°C); IR: 3340, 1685 cm^{-1}; ^1H NMR: δ 0.87 (dist. t, 3H), 1.30 (br. s, 22H), 1.74–1.83 (m, 2H), 2.59 (t, *J*=7 Hz, 2H), 3.31–3.39 (m, 2H), 3.4–3.51 (m, 1H), 4.48 (br. s, 1H), 7.35 (s, 5H).

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