Tetrahedron: *Asymmetry* 19 (2008) 2546–2554

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis and spectroscopic correlation of the diastereoisomers of 2,3-dihydroxy-2,6,8-trimethyldeca-(4*Z*,6*E*)-dienoic acid: implications for the structures of papuamides A–D and mirabamides A–D

Gurusankar Ramamoorthy, Cristina M. Acevedo, Edgardo Alvira, Mark A. Lipton *

Department of Chemistry, Purdue University, West Lafayette, IN 47907-1392, USA

ARTICLE INFO

Article history:
Received 30 July 2008
Accepted 24 September 2008

ABSTRACT

All 4 diastereomeric possibilities for the 2,3-dihydroxy-2,6,8-trimethyldeca-(4*Z*,6*E*)-dienoic acid (Dhtda) residue, found in the cyclic depsipeptide natural products papuamides A–D and mirabamides A–D, were stereoselectively synthesized using a *Z*-selective Wittig reaction of both enantiomers of 2,4-dimethylhex-2-enyl-triphenylphosphonium bromide with all four diastereoisomers of ethyl-3-formyl-2-methyl-1,4-dioxaspiro[4,4]nonane-2-carboxylate. To elucidate the configuration of Dhtda, the ^{1}H and ^{13}C NMR spectra of the synthetic isomers were compared to those of the natural residue. On the basis of that comparison, it is suggested that the likely configuration of the diastereomer present in Dhtda residue is either (2*R*,3*S*,8*S*) or (2*S*,3*R*,8*S*) in the papuamides and mirabimides.

1. Introduction

Papuamides **1a**–**d**, cytotoxic, antiviral cyclic depsipeptides isolated from marine sponges *Theonella mirabilis* and *swinhoei*, are the first marine-derived peptides reported to contain a 2,3-dihydroxy-2,6,8-trimethyldeca-(4*Z*,6*E*)-dienoic acid moiety.[1] More recently, four new cyclic depsipeptides called mirabamides A–D **2a**–**d** were isolated from the marine sponge *Siliquariaspongia mirabilis* and found to have *anti*-HIV activity and structural similarities with papuamides, differing only in the chlorination of the homoproline residue and the glycosylation of the *β*-methoxytyrosine residue.[2] Although nearly all of the stereochemistry of papuamides A–D **1a**–**d** has been elucidated, that of the 2,3-dihydroxy-2,6,8-trimethyldeca-(4*Z*,6*E*)-dienoic acid (Dhtda) residue remained undefined (Fig. 1).

As part of our efforts directed toward the synthesis and structural elucidation of papuamide A **1a**, we herein report the syntheses of all four diastereomers of Dhtda using a *Z*-selective Wittig reaction between (*S*)-isomer of triphenylphosphonium bromide **7** and all four diastereomers of the aldehyde obtained from the commercially available diethyl tartrate **8**. It was reasoned that comparison of the spectroscopic data of the four synthetic isomers with those of the natural residue would permit the assignment of the relative configuration of the Dhtda fragment.[3]

2. Results and discussion

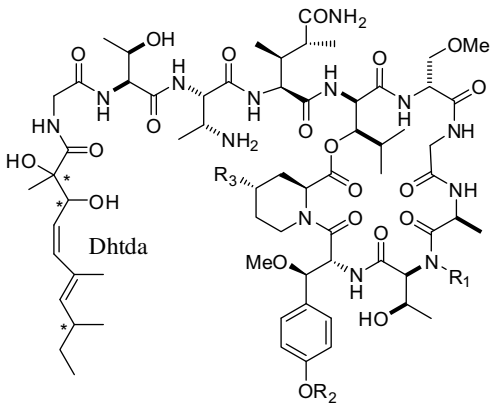
The synthetic pathway for the *S*-phosphonium bromide **7** (Scheme 1) is a modification of the procedure reported by Miki in the synthesis of Probetaenone I.[4] The synthesis began with the oxidation of commercially available *S*-(−)-2-methyl-1-butanol (**3**) to an aldehyde using TEMPO and iodobenzene diacetate (BIAB). Owing to the high volatility of the intermediate aldehyde, it was subjected to an in situ Horner–Wadsworth–Emmons reaction with triethyl 2-phosphonopropionate (**4**) under Masamune–Roush conditions[5] using LiCl and DBU. The product was a 9:1 mixture of *E* and *Z* olefins that was separated by column chromatography to afford the *E* isomer **5** in 70% yield.[6]

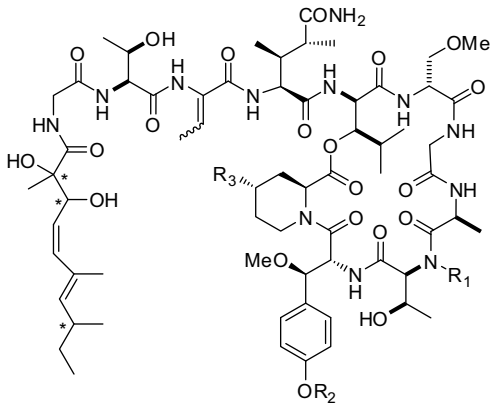
The α,β-unsaturated ester **5** was then reduced to alcohol **6** using DIBAL-H in toluene at −78 °C with no sign of reduction or isomerization of the double bond.[6] Finally, enantiomerically pure triphenyl-phosphonium bromide **7** was obtained from alcohol **6** in one step and without any sign of alkene isomerization using the PPh_3·HBr complex in acetonitrile.

The synthesis of the other half of Dhtda (Scheme 2) started with the protection of diethyl-L-tartrate **8** as its ketal **9**. Treatment of **9** with LHMDS and CH_3I in the presence of LiCl at −78 °C gave the monoalkylated product **10** as a single diastereomer, whereas in Seebach's work using the acetonide analogue of **9** (LDA/HMPA/CH_3I) both diastereomers were obtained in an 86:14 ratio and 79% yield, with 15% of the dimethylated product and 6% of starting material.[7,8] The configuration of the two diastereomers was established by NOE experiments. Intriguingly, product **10** results from methylation of what would appear to be the more hindered face

* Corresponding author.
E-mail address: lipton@purdue.edu (M. A. Lipton).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.09.031

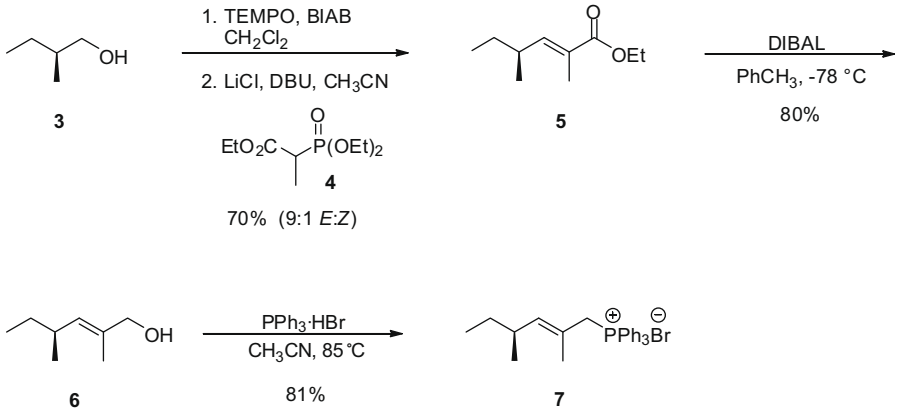




1a. Papuamide A: R_1=CH_3, R_2=R_3=H
1b. Papuamide B: R_1=R_2= R_3=H
2a. Mirabamide A: R_1=CH_3, R_2=α-rhamnose, R_3=Cl
2c. Mirabamide C: R_1=CH_3, R_2=H, R_3=Cl
2d. Mirabamide D: R_1=CH_3, R_2= α-rhamnose, R_2=H

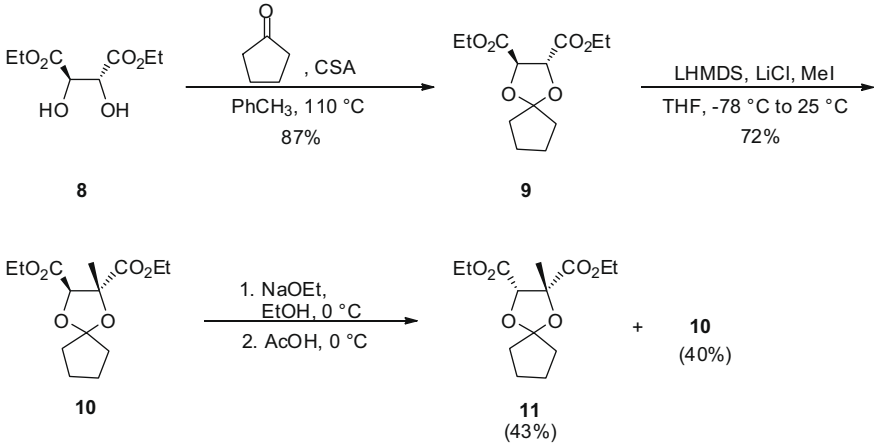
1c. Papuamide C: R_1=CH_3, R_2=R_3=H
1d. Papuamide D: R_1=R_2=R_3=H
2b. Mirabamide B: R_1=CH_3, R_2=α-rhamnose, R_3=Cl

Figure 1. Structures of papuamides A–D and mirabamides A–D. Undefined stereogenic carbons are marked with an asterisk.



3 **4** **5** **6** **7**

Scheme 1.

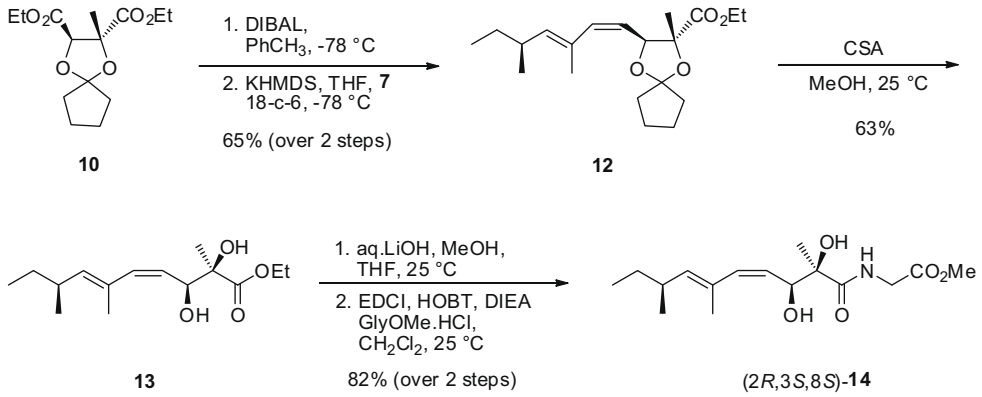


8 **9** **10** **11**

Scheme 2.

of the enolate intermediate. Treatment of **10** with LHMDS and quenching it with NH_4Cl resulted in retention of configuration with only the starting material being returned. When the base was changed to sodium ethoxide and the reaction was quenched with HOAc at 0 °C, a 1:1 mixture of diastereomers **10** and **11** was obtained and separated by column chromatography.

Selective monoreduction of the diastereomeric ethyl esters **10** and **11** using DIBAL-H in toluene at −78 °C (Scheme 3) resulted



Scheme 3.

in a complex mixture. Unreacted starting material was recovered by filtration through silica gel and the remaining mixture of products was carried onto the next step without further purification. Other sterically hindered hydride sources were tested with no improvement in yield or selectivity and selective saponification proved no more successful. The 'salt free' *Z*-Selective Wittig reaction[9] of phosphonium salt **7** with both diastereomers **10** and **11** in the presence of KHMDS and 18-crown-6 afforded the protected Dhtda ethyl esters (2*R*,3*R*,8*S*)-**12** and (2*R*,3*S*,8*S*)-**12**, respectively, in good yield. The same synthetic pathway was applied to diethyl-D-tartrate *ent*-**8** to obtain protected Dhtda esters (2*S*,3*S*,8*S*)-**12** and (2*S*,3*R*,8*S*)-**12**.

Deprotection of the ketal in **12** was carried out using CSA in methanol to obtain Dhtda ethyl ester **13**. Ester **13** was hydrolyzed and the resultant carboxylic acid was converted into its glycine amide (2*R*,3*S*,8*S*)-**14**. The other diastereomeric amides (2*R*,3*R*,8*S*)-**14**, (2*S*,3*S*,8*S*)-**14**, and (2*S*,3*R*,8*S*)-**14** were also obtained using the same procedure.

With the four unique diastereomers in hand, ^{1}H and ^{13}C NMR spectra of the four isomers of **14** were compared with the values reported for the Dhtda fragment in the papuamides and mirabamides using the universal NMR database approach developed by Kishi.[10] The ^{1}H and ^{13}C NMR of all the diastereomers of Dhtda were recorded in CD_3OD, 4:1—CD_3CN–H_2O, and DMSO-d_6.[1] Figures 2 and 3 show the differences in ^{13}C and ^{1}H NMR data in CD_3OD between the different diastereomers of **14** and the authentic Dhtda fragment in papuamide B.

As can be seen in Figure 2, the carbon chemical shifts differ substantially between the different diastereomers of **14**. The spectra of the diastereomeric glycine amides of Dhtda **14** were recorded to

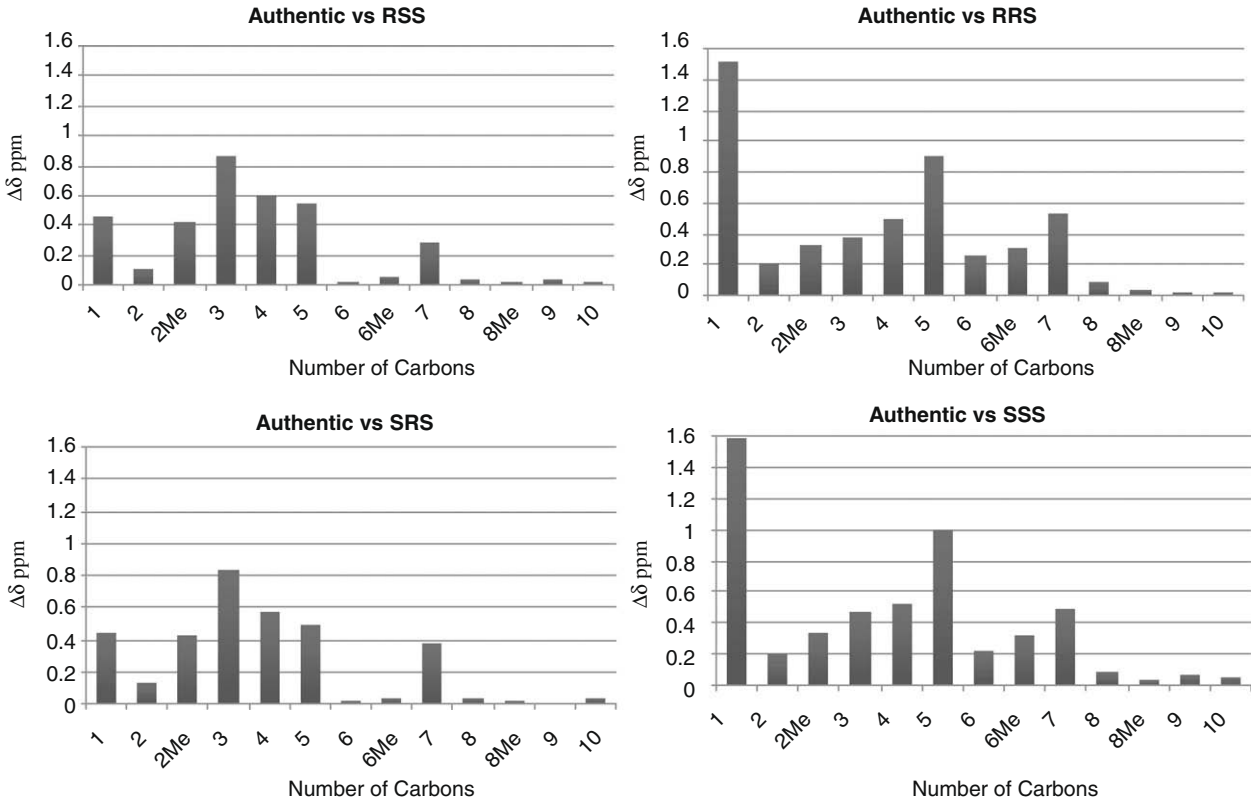


Figure 2. ^{13}C NMR differences between isomers (*RSS*)-, (*SRS*)-, (*RRS*)-, and (*SSS*)-**14** in CD_3OD and the authentic Dhtda fragment in papuamide B. The numbering scheme used was that employed in the original publication on the isolation of papuamide.

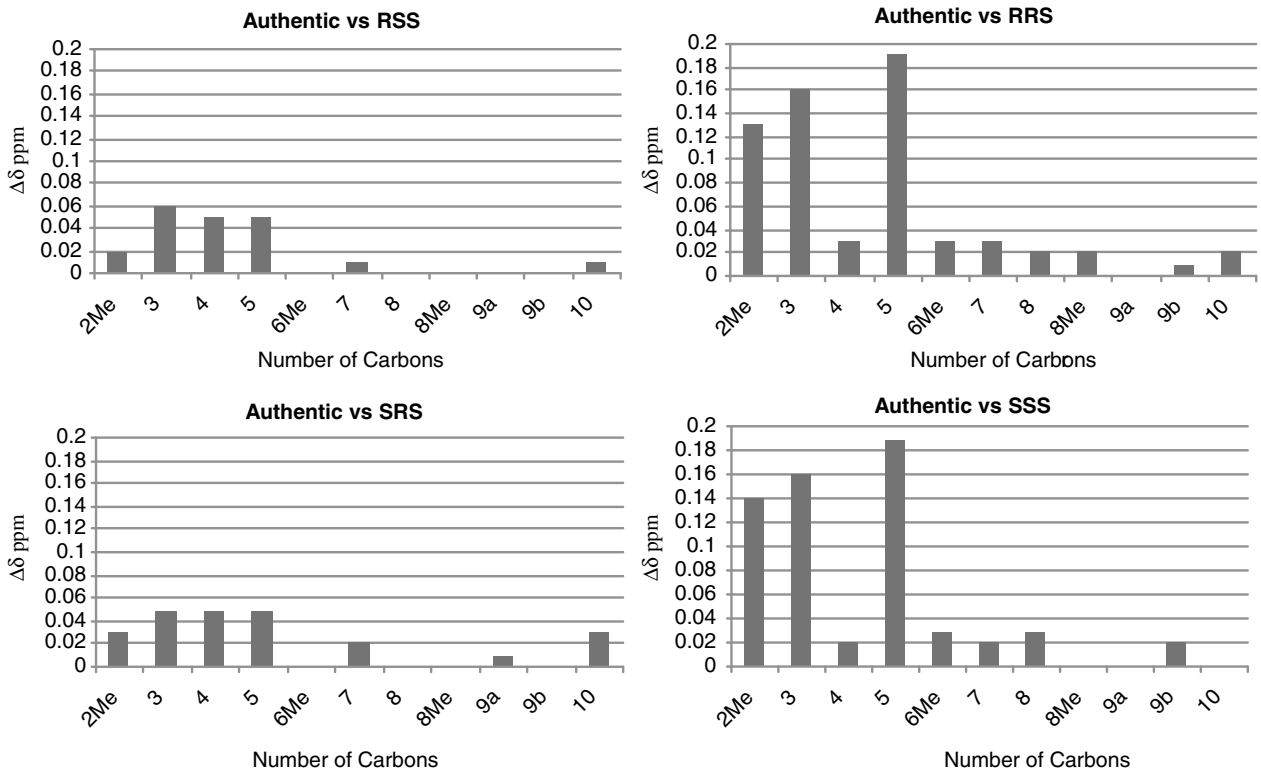
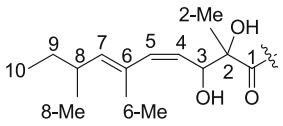


Figure 3. ^{1}H NMR differences between isomers (*RSS*)-, (*SRS*)-, (*RRS*)-, and (*SSS*)-**14** and the Dhtda fragment in papuamide B in CD_3OD. The numbering scheme used in the plots is the same as in the original publication.



mimic as closely as possible the environment within the natural products. There is a good general agreement in the ^{13}C NMR spectra between the various isomers of **14** and the authentic Dhtda residue. The isomers (*RRS*)-**14** and (*SSS*)-**14** show larger deviations from the natural product ($\sum\sigma = 5.08$ and 5.36 ppm, respectively), whereas the other diastereomers (*RSS*)-**14** and (*SRS*)-**14** have smaller deviations ($\sum\sigma = 3.43$ and 3.40 ppm, respectively).

In the case of the ^{1}H NMR differences (Fig. 3), it was observed that diastereomers (*RRS*)-**14** and (*SSS*)-**14** have the larger deviations ($\sum\sigma = 0.64$ and 0.61, respectively) from authentic Dhtda, which implies a *syn*-relationship between the C-2 and C-3 hydroxyl substituents in Dhtda.

The deviation of the ^{1}H NMR chemical shifts of the two *syn*-diastereomers (*RSS*)-**14** ($\sum\sigma = 0.20$ ppm) and (*SRS*)-**14** ($\sum\sigma =$ 0.24 ppm) was roughly comparable. To distinguish between these two possibilities, we next turned to the vicinal coupling constants in the ^{1}H NMR spectrum. It was found that both diastereomers (*RSS*)-**14** ($\sum J = 2.6$ Hz) and (*SRS*)-**16** ($\sum J = 2.4$ Hz) had the closest values of coupling constants for protons H_4, H_5, H_7, and H_{13}, and a much lower cumulative deviation from those of the authentic residue.

The original publication on the isolation of the papuamides also reported ^{1}H NMR spectra in 4:1 CD_3CN–H_2O.[1] To distinguish between the two *syn*-diastereomers, their ^{1}H NMR spectra were recorded in the same solvent mixture for comparison to authentic Dhtda (Fig. 4). The two *anti*-diastereomers (*RRS*)-**14** and (*SSS*)-**14** once again showed larger deviations ($\sum\sigma = 0.76$ and 0.78 ppm), and both (*RSS*)-**14** and (*SRS*)-**14** showed similar small deviations ($\sum\sigma = 0.38$ and 0.39 ppm). Even with these additional data, the ^{1}H coupling constants and ^{13}C chemical shifts values were still indistinguishable for the *syn*-diastereomers.

The ^{1}H NMR of authentic Dhtda was also reported in DMSO-d_6 as a tripeptide in the original publication.[1] Therefore, the ^{1}H NMR spectra of all four diastereomers of **14** were taken in DMSO-d_6 (Fig. 5) and consistently the two *anti*-diastereomers (*RRS*)-**14** and (*SSS*)-**14** showed cumulatively larger deviations ($\sum\sigma = 0.54$ and 0.54 ppm, respectively). The two *syn*-diastereomers (*RSS*)-**14** and (*SRS*)-**14** showed smaller deviations ($\sum\sigma = 0.15$ and 0.17 ppm, respectively), while the coupling constant data did not yield any further distinction. It should be noted that the substantial difference in chemical shifts seen between the *syn*- and *anti*-diastereomeric pairs in CD_3OD was consistently observed in the other NMR solvents. When the combined deviation of both ^{1}H NMR chemical shifts values in all solvents is taken into consideration, the NMR database suggests that diastereomer (*RSS*)-**14** or its enantiomer (*SRR*)-**14** best matches the natural product. It is therefore suggested that the configuration of the Dhtda residue in the papuamides is either (2*R*,3*S*,8*S*) or (2*S*,3*R*,8*R*).

The ^{1}H NMR of chemical shifts of all four diastereomers of Dhtda in 4:1-CD_3CN–H_2O were also compared with the recently reported authentic Dhtda of mirabamides A-D in 5:1—CD_3CN–H_2O[2] (Fig. 6). The *syn*-diastereomers (*RSS*)- and (*SRS*)-**14** showed lesser deviations from the authentic Dhtda than the corresponding *anti*-diastereomers (*RRS*)-and (*SSS*)-**14**. Between the *syn*-diastereomers (*RSS*)-**14** ($\sum\sigma = 0.25$) showed smaller cumulative deviation than (*SRS*)-**14** ($\sum\sigma = 0.28$) as in the papuamides. This further proves and supports that the configuration of Dhtda fragment that is present in both papuamides A–D and mirbamides A–D is either (2*R*,3*S*,8*S*) or (2*S*,3*R*,8*R*).

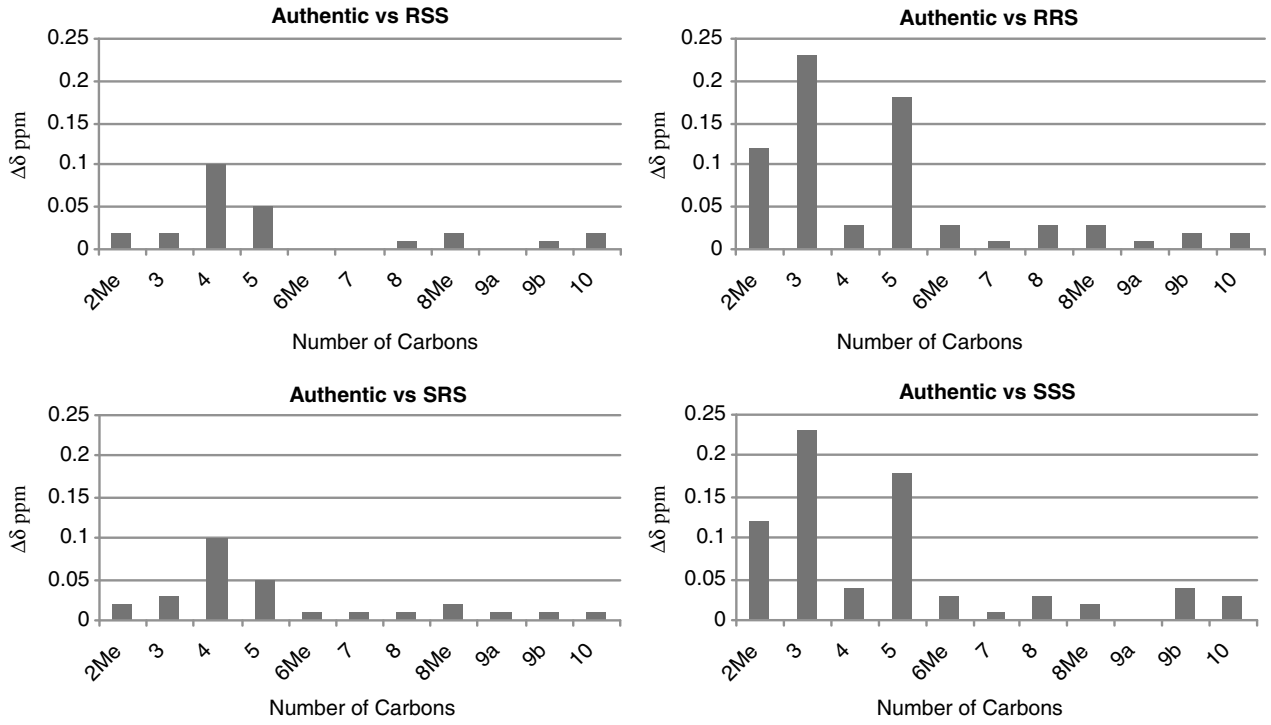


Figure 4. [1]H NMR chemical shift differences between isomers (*RSS*)-, (*SRS*)-, (*RRS*)-, and (*SSS*)-**14** and the authentic Dhtda fragment in papuamide A in 4:1—CD_3CN–H_2O.[1] The numbering scheme used in the plots is the same as in the original publication.

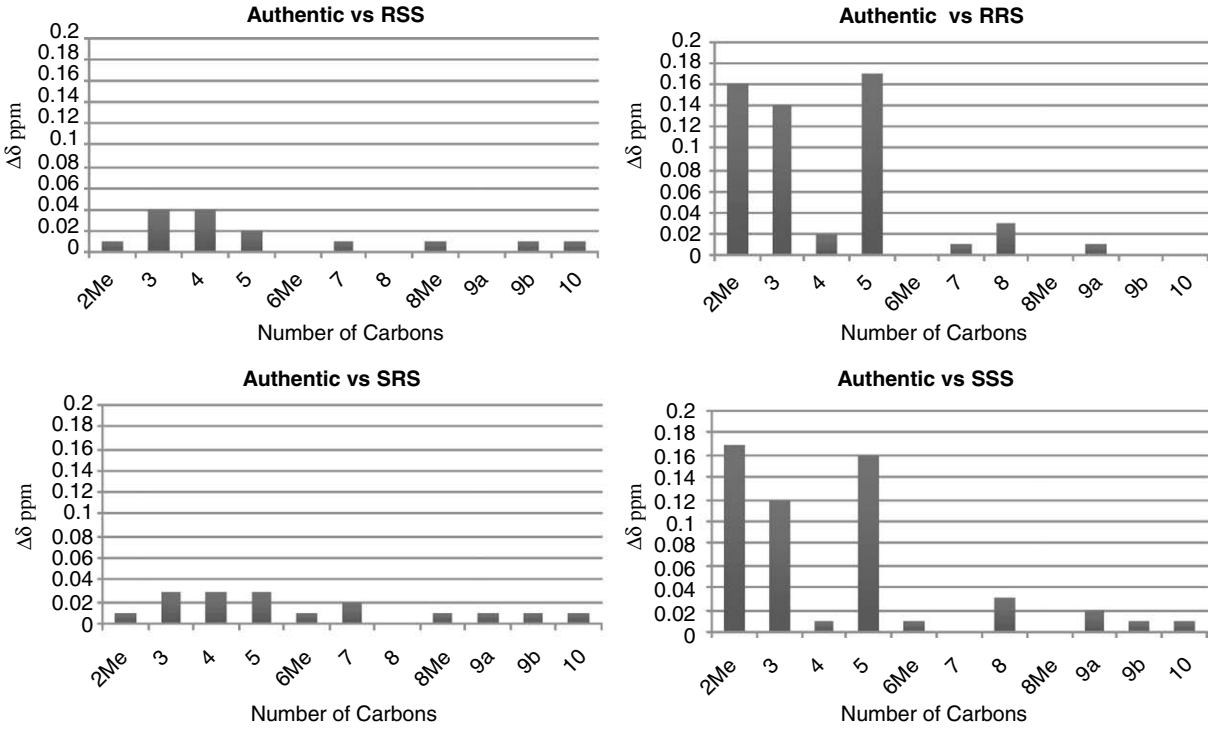


Figure 5. [1]H NMR differences between isomers (*RSS*)-, (*SRS*)-, (*RRS*)-, and (*SSS*)-**14** and the authentic Dhtda fragment in papuamide A in DMSO-D_6. The numbering scheme used in the plots is the same as in the original publication.

3. Conclusion

The synthesis of all four diastereomers of the fatty acid Dhtda has been accomplished, starting from both enantiomers of diethyl tartrate and (*S*)-(−)-2-methylbutane-1-ol, in 11–12 steps and 9% overall yield. Using [1]H NMR and [13]C NMR data in various solvents, we were able to conclude that the enantiomeric pair of (*RSS*)- and (*SRR*)-**14** best matches the spectroscopic data of Dhtda in the papuamides and mirabamides. It is therefore suggested that the configuration of Dhtda in the papuamides and mirabamides is either (2*R*,3*S*,8*S*) or (2*S*,3*R*,8*R*), a conclusion supported by the recent total synthesis of papuamide B.[3]

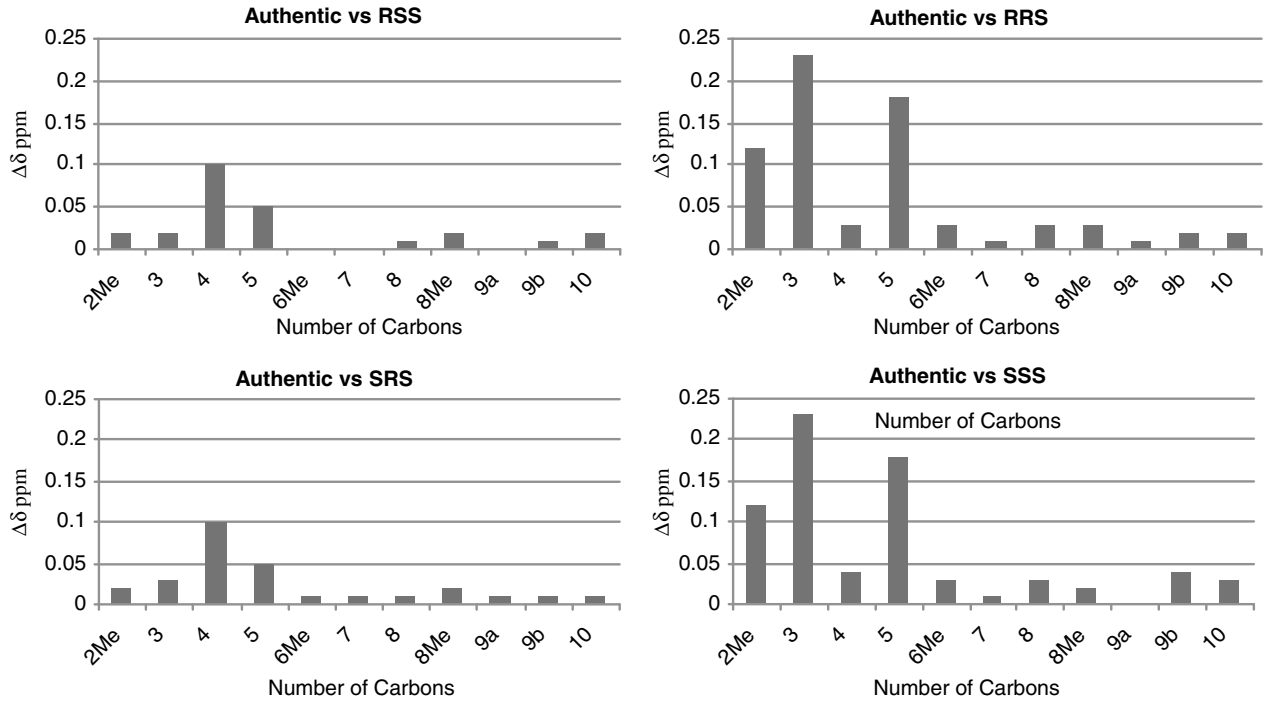


Figure 6. ^{1}H NMR differences between isomers (*RSS*)-, (*SRS*)-, (*RRS*)- and (*SSS*)-**14** and the authentic Dhtda fragment in mirabamide A in 4:1—CD_3CN–H_2O. The numbering scheme used in the plots is the same as in the original publication.

4. Experimental

4.1. General information

4.1.1. Ethyl (2*E*,4*S*)-2,4-dimethyl-2-hexenoate 5

To a solution of (*S*)-2-methyl-1-butanol **3** (1.20 mL, 11.4 mmol) in CH_2Cl_2 (8 mL), TEMPO (180 mg, 1.2 mmol) and iodobenzene diacetate (4.40 g, 13.7 mmol) were added at 25 °C, and the mixture was stirred for 4 h under a N_2 atmosphere. The reaction mixture was washed with satd $Na_2S_2O_{3(aq)}$, satd $NaHCO_{3(aq)}$, water (2×) and brine, and dried over Na_2SO_4. The organic layer containing the crude aldehyde was diluted with CH_2Cl_2 to a volume of 15 mL and used in the next step without further purification.

To a slurry of LiCl (2.93 g, 68.2 mmol) in CH_3CN (10 mL) were added triethyl 2-phosphonopropionate **4** (2.7 mL, 12.5 mmol) and DBU (1.2 mL, 11.9 mmol), and the resultant mixture was stirred for 15 min at 25 °C. The solution of the crude aldehyde in CH_2Cl_2 was added to the reaction mixture at 25 °C and stirred for 12 h under a N_2 atmosphere. The reaction mixture was diluted with diethyl ether (20 mL) and washed with water (2×) and satd $NaCl_{(aq)}$, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (5% Et_2O/hexanes) to afford the ester **5** (1.35 g, 70%) as a colorless liquid. $[\alpha]_D^{25} = +20.0$ (*c* 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.19 (q, *J* = 7.2, 14.4 Hz, 2H), 2.4 (m, 1H), 1.83 (s, 3H), 1.40–1.20 (m, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 147.8, 126.5, 60.3, 34.9, 29.6, 19.7, 14.3, 12.5, 11.9; HRMS calcd 170.1307, found 170.1300; IR ($CHCl_3$) ν_{max} 2960, 2937, 1710, 1479, 1274, 1227, 1177, 1095, 1027 cm^{-1}.

4.2. (2*E*,4*S*)-2,4-Dimethyl-2-hexen-1-ol 6

To a cooled solution of ester **5** (800 mg, 4.71 mmol) in CH_2Cl_2 (5 mL), DIBAL in toluene (1.0 M, 11.8 mL, 11.8 mmol) was slowly added at −78 °C and the mixture was stirred for 2 h at −78 °C. The reaction mixture was quenched with 2 M HCl (10 mL) at −78 °C and allowed to warm to room temperature with vigorous stirring until the suspended solid was fully dissolved. The reaction mixture was extracted with EtOAc (3×) and the combined organic layer was washed with water (1×), satd $NaCl_{(aq)}$ (2×), dried over Na_2SO_4, and concentrated in vacuo. The crude alcohol was purified by flash column chromatography (25% EtOAc/hexanes) to furnish **6** (500 mg, 83%) as a colorless liquid. $[\alpha]_D^{25} = +22.5$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.00 (s, 2H), 2.28 (m, 1H), 1.68 (s, 3H), 1.58 (br s, 1H), 1.42–1.22 (m, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 132.7, 69.0, 33.7, 30.2, 20.6, 13.8, 11.9; HRMS calcd 128.1201, found 128.1202; IR ($CHCl_3$) ν_{max} 3432 (br), 2962, 2873, 1459, 1382, 1074, 1037 cm^{-1}.

4.3. (2*E*,4*S*)-2,4-Dimethyl-2-hexenyltriphenylphosphonium bromide 7

To a solution of alcohol **6** (500 mg, 3.91 mmol) in CH_3CN (8 mL) was added triphenylphosphonium bromide (1.61 g, 4.69 mmol) at 25 °C and the reaction mixture was stirred for 6 h at 95 °C. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford **7** (1.45 g, 81%) as a tan solid. $[\alpha]_D^{25} = +12.4$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.55 (m, 15H), 4.92 (q, *J* = 5.7, 3.1 Hz, 1H), 4.26 (m, 2H), 2.00 (m, 1H), 1.39 (d, *J* = 2.4 Hz, 3H), 0.88 (m, 2H), 0.55 (d, *J* = 6.6 Hz, 3H), 0.50 (t, *J* = 7.32, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 142.9, 135.3, 135.2, 134.2, 134.1, 130.6, 130.4, 121.0, 120.9, 119.0, 117.9, 34.7, 34.6, 34.6, 34.1, 29.7, 29.6, 19.9, 19.8, 18.8, 18.8, 11.8; IR (CH_2Cl_2) ν_{max} 2968, 2943, 2925, 2293, 2252, 1440, 1375, 1112, 1039, 918, 752, 720, 692 cm^{-1}.

4.4. Diethyl (2*R*,3*R*)-1,4-dioxaspiro[4,4]nonane-2,3-dicarboxylate 9

A solution of (+)-diethyl-L-tartrate **8** (5.0 g, 24.3 mmol), cyclopentanone (10.7 mL, 121 mmol), and 10-camphorsulfonic acid

(560 g, 2.43 mmol) in toluene (60 mL) was heated in a Dean-Stark apparatus at 150 °C for 24 h. The reaction mixture was diluted with EtOAc (20 mL) and washed using satd $NaHCO_{3(aq)}$ (1×), water (2×), satd $NaCl_{(aq)}$ (1×) then dried over Na_2SO_4, and concentrated in vacuo. The crude acetal was purified by flash column chromatography (10% EtOAc/hexanes) to give **9** (5.80 g, 87%) as a colorless liquid. $[\alpha]_D^{25} = -32.5$ (*c* 3.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.18 (q, 4H, *J* = 6.9 Hz), 1.83 (m, 2H), 1.77 (m, 2H), 1.60 (m, 4H), 1.22 (t, 6H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 123.3, 76.9, 61.8, 36.8, 23.4, 14.1; MS(EI-CI) 273 (M+1); IR (CH_2Cl_2) ν_{max} 2976, 2878, 1757, 1739, 1336, 1199, 1124, 1026 cm^{-1}.

4.5. Diethyl (2*R*,3*R*)-2-methyl-1,4-dioxaspiro[4,4]nonane-2,3-dicarboxylate 10

To a cooled mixture of ester **9** (2.2 g, 8.09 mmol), anhydrous LiCl (2.1 g, 48.5 mmol), and methyl iodide (1.5 mL, 24.3 mmol) in THF (8 mL) was added a solution of LHMDS in THF (1.0 M, 9.7 mL, 9.71 mmol) slowly at −78 °C. The mixture was slowly warmed to 25 °C and stirred for 16 h. The reaction mixture was poured into EtOAc (20 mL) and washed with water (3×), satd $NaCl_{(aq)}$ (1×), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/hexanes) to afford **10** (1.66 g, 72%) as a colorless oil. $[\alpha]_D^{25} = -56.1$ (*c* 1.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.26 (m, 4H), 2.18 (m, 1H), 1.98 (m, 1H), 1.69 (m, 6H), 1.42 (s, 3H), 1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 169.1, 122.3, 83.1, 79.8, 62.3, 61.7, 37.5, 37.3, 24.2, 23.3, 20.4, 14.5, 14.4; HRMS calcd 286.1416, found 286.1418; IR (CH_2Cl_2) ν_{max} 2989, 2873, 1754, 1736, 1336, 1243, 1199, 1119, 1023 cm^{-1}.

4.6. Diethyl (2*R*,3*S*)-2-methyl-1,4-dioxaspiro[4,4]nonane-2,3-dicarboxylate 11

To a stirred mixture of flame dried and powdered 4 Å molecular sieves in absolute ethanol (2 mL) was added a solution of **10** (1.0 g, 3.50 mmol) in absolute ethanol (2 mL) and the mixture stirred for 10 min, then cooled to 0 °C and a solution of sodium ethoxide in ethanol (2.7 M, 1.6 mL, 4.20 mmol) was added. The reaction was stirred for 1 h and quenched with glacial acetic acid (250 μL) at 0 °C. The mixture was filtered through Celite™ and concentrated in vacuo. The residue was dissolved in EtOAc (10 mL), washed with water (1×) and satd $NaCl_{(aq)}$ (1×), and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The mixture of **10** and **11** was separated by flash column chromatography (10% EtOAc/hexanes) to furnish **10** (400 mg, 40%) and **11** (430 mg, 43%) as colorless oils. $[\alpha]_D^{25} = -24.4$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (s, 1H), 4.21 (m, 4H), 2.06 (m, 2H), 1.82 (m, 2H), 1.470 (m, 6H), 1.67 (s, 3H), 1.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 167.6, 121.4, 83.2, 82.6, 61.9, 61.8, 38.3, 36.9, 23.9, 23.6, 22.7, 14.4; HRMS calcd 286.1416, found 286.1412; IR (CH_2Cl_2) ν_{max} 2977, 2873, 1762, 1739, 1374, 1197, 1124, 1026 cm^{-1}.

4.7. Ethyl (2*R*,3*S*)-3-[(1*Z*,3*E*,5*S*)-3,5-dimethylhepta-1,3-dienyl]-2-methyl-1,4-dioxaspiro[4.4]nonane-2-carboxylate (*RSS*)-12

To a solution of **10** (1.0 g, 3.50 mmol) in toluene (10 mL) at −78 °C was slowly added DIBAL in toluene (1.0 M, 4.2 mL, 4.20 mmol), and the resultant mixture was stirred for 1 h. The reaction was quenched with MeOH (8 mL) at −78 °C and warmed to 25 °C. The slurry thus produced was diluted with ethyl acetate (15 mL) and satd aqueous sodium potassium tartrate (15 mL), stirred for 45 min, and the two phases separated. The aqueous phase was extracted with ethyl acetate (3×) and the combined organic layer was washed with water (2×) and satd $NaCl_{(aq)}$, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was filtered through silica gel to afford the crude aldehyde (300 mg) as a clear liquid that was used for the next reaction without further purification.

To a stirred suspension of the phosphonium ion **7** (618 mg, 1.36 mmol) in THF (5 mL) was slowly added KHMDS in THF (0.91 M, 1.6 mL, 1.50 mmol) at −78 °C, and the resultant mixture was stirred for 15 min whereupon a solution of 18-crown-6 in THF (0.5 mL) was added and the stirring continued for another 15 min. A solution of the crude aldehyde (300 mg) in THF (3 mL) was added to the reaction mixture at −78 °C and stirred for 8 h at −78 °C. The reaction was quenched by the addition of satd $NH_4Cl_{(aq)}$ (1×5 mL) and extracted with diethyl ether (3×). The combined organic layers were washed with water (3×) and satd $NaCl_{(aq)}$, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (5% Et_2O/hexanes) to give (*RSS*)-**12** (270 mg, 65% based on recovered SM) as a colorless liquid. $[\alpha]_D^{25} = +15.9$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, *J* = 11.7 Hz, 1H), 5.39 (t, 1H, *J* = 9.9 Hz), 5.21 (d, 1H, *J* = 9.3 Hz), 4.19 (d, 1H, *J* = 9.3 Hz), 4.19 (m, 2H), 2.30 (m, 1H), 1.94 (m, 3H), 1.75 (d, 3H, *J* = 1.2 Hz), 1.69 (m, 5H), 1.39 (s, 3H), 1.32 (m, 2H), 1.27 (t, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.85 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 140.2, 138.7, 130.0, 121.5, 119.4, 82.8, 76.6, 61.3, 37.9, 37.0, 34.5, 30.3, 24.0, 23.2, 20.6, 20.0, 16.7, 14.1, 12.1; HRMS calcd 336.2301, found 336.2306; IR ($CHCl_3$) ν_{max} 2961, 2868, 1735, 1453, 1336, 1264, 1109, 1024 cm^{-1}.

4.8. Ethyl (2*R*,3*R*)-3-[(1*Z*,3*E*,5*S*)-3,5-dimethylhepta-1,3-dienyl]-2-methyl-1,4-dioxaspiro[4.4]nonane-2-carboxylate (*RRS*)-12

Prepared by the same procedure used to make (*RSS*)-**12**. $[\alpha]_D^{25} = +18.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, 1H, *J* = 11.7 Hz), 5.25 (d, 1H, *J* = 9.9 Hz), 5.18 (dd, 1H, *J* = 9.9, 11.4 Hz) 4.77 (d, 1H, *J* = 9.9 Hz), 4.19 (m, 2H), 2.33 (m, 1H), 2.15 (m, 1H), 1.99 (m, 1H), 1.80 (m, 3H), 1.75 (d, 3H, *J* = 1.2 Hz), 1.69 (m, 6H), 1.49 (s, 3H), 1.39 (m, 1H), 1.30 (t, 3H, *J* = 7.2 Hz), 1.26 (m, 1H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.87 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 141.0, 138.5, 129.9, 121.2, 119.8, 83.5, 80.5, 61.2, 38.2, 36.9, 34.7, 30.3, 23.9, 23.2, 22.1, 20.8, 16.8, 14.2, 12.2; HRMS calcd 336.2301, found 336.2309; IR ($CHCl_3$) ν_{max} 2961, 2925, 2868, 1749, 1732, 1456, 1336, 1232, 1106, 1024 cm^{-1}.

4.9. Ethyl (2*S*,3*R*)-3-[(1*Z*,3*E*,5*S*)-3,5-dimethylhepta-1,3-dienyl]-2-methyl-1,4-dioxaspiro[4.4]nonane-2-carboxylate (*SRS*)-12

Prepared by the same procedure used to make (*RSS*)-**12**. $[\alpha]_D^{25} = +28.0$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, 1H, *J* = 11.7 Hz), 5.38 (dd, 1H, *J* = 10.2, 11.4 Hz), 5.22 (d, 1H, *J* = 9.6 Hz), 5.19 (dd, 1H, *J* = 9.9Hz), 4.19 (m, 2H), 2.31 (m, 1H), 1.92 (m, 3H), 1.74 (d, 3H, *J* = 1.2 Hz), 1.67 (m, 5H), 1.39 (s, 3H), 1.36 (m, 1H), 1.27 (t, 3H, *J* = 7.2 Hz), 1.26 (m, 1H), 0.96 (d, 3H, *J* = 6.6 Hz), 0.85 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 140.5, 139.0, 121.8, 119.6, 83.1, 61.6, 38.2, 37.3, 34.8, 30.5, 24.2, 23.4, 20.9, 20.3, 16.9, 14.4, 12.4; HRMS calcd 336.2379, found 336.2380; IR ($CHCl_3$) ν_{max} 2961, 2873, 1734, 1453, 1374, 1336, 1267, 1108, 1024 cm^{-1}.

4.10. Ethyl (2*S*,3*S*)-3-[(1*Z*,3*E*,5*S*)-3,5-dimethylhepta-1,3-dienyl]-2-methyl-1,4-dioxaspiro[4.4]nonane-2-carboxylate (*SSS*)-12

Prepared by the same procedure used to make (*RSS*)-**12**. $[\alpha]_D^{25} = +13.7$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, 1H, *J* = 11.7 Hz), 5.26 (d, 1H, *J* = 9.6 Hz), 5.18 (dd, 1H, *J* = 9.9, 11.4 Hz), 4.77 (d, 1H, *J* = 9.9 Hz), 4.19 (m, 2H), 2.33 (m, 1H), 2.15 (m, 1H), 1.99 (m, 1H), 1.80 (m, 3H), 1.75 (d, 3H, *J* = 1.2 Hz), 1.69

(m, 6H), 1.49 (s, 3H), 1.39 (m, 1H), 1.30 (t, 3H, J = 7.2 Hz), 1.26 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 0.87 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.3, 138.7, 130.1, 121.4, 120.0, 83.7, 80.7, 61.4, 38.4, 37.2, 34.8, 30.5, 24.1, 23.4, 22.3, 21.0, 17.0, 14.5, 12.4; HRMS calcd 336.2301, found 336.2306; IR ($CHCl_3$) ν_{max} 2960, 2868, 1749, 1732, 1456, 1374, 1337, 1233, 1106, 1024 cm^{-1}.

4.11. Ethyl (2*R*,3*S*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienylcarboxylate (*RSS*)-13

To a solution of **12** (150 mg, 0.45 mmol) in 1:1 MeOH–CH_2Cl_2 (2 mL) was added 10-camphorsulfonic acid (20 mg, 0.09 mmol) and the reaction mixture was stirred for 24 h at 25 °C. The reaction was concentrated in vacuo and diluted with EtOAc (5 mL). The organic layer was washed with satd $NaHCO_{3(aq)}$ (1×), water (2×) and brine (1×), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (25% EtOAc/hexanes) to afford **13** (75 mg, 63%) as a colorless oil. $[\alpha]_D^{25} = -80.1$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, 1H, J = 11.7 Hz), 5.43 (dd, 1H, J = 9.9, 11.7 Hz), 5.24 (d, 1H, J = 9.9 Hz), 4.79 (d, 1H, J = 9.9 Hz), 4.38 (m, 2H), 3.46 (br s, 1H), 2.33 (m, 1H), 1.76 (d, 3H, J = 0.9 Hz), 1.38 (m, 1H), 1.28 (t, 3H, J = 7.2 Hz), 1.27 (s, 3H), 1.25 (m, 1H), 0.95 (d, 3H, J = 6.6 Hz), 0.85 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 139.0, 138.6, 124.7, 77.3, 62.5, 34.7, 30.5, 22.6, 20.9, 17.0, 14.4, 12.4; HRMS calcd 270.1831, found 270.1828; IR (CH_2Cl_2) ν_{max} 3489, 2962, 2925, 2855, 1736, 1456, 1377, 1251, 1118, 1019 cm^{-1}.

4.12. Ethyl (2*R*,3*R*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienylcarboxylate (*RRS*)-13

Prepared by the same procedure used to make (*RSS*)-**13**. $[\alpha]_D^{25} = +44.7$ (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, 1H, J = 11.7 Hz), 5.38 (d, 1H, J = 10.2 Hz), 5.32 (dd, 1H, J = 10.2, 12.6 Hz), 4.62 (d, 1H, J = 9.9 Hz), 4.20 (m, 2H), 3.46 (br s, 1H), 2.32 (m, 1H), 1.79 (d, 3H, J = 1.2 Hz), 1.46 (s, 3H), 1.36 (m, 1H), 1.28 (m, 1H), 1.26 (t, 3H, J = 7.2 Hz), 0.95 (d, 3H, J = 6.6 Hz), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 139.9, 138.8, 130.9, 124.3, 77.1, 72.2, 62.5, 34.7, 30.6, 22.8, 20.9, 16.8, 14.4, 12.4; HRMS calcd 270.1831, found 270.1830; IR (CH_2Cl_2) ν_{max} 3438, 2962, 2927, 2866, 1729, 1599, 1452, 1247, 1119, 1018 cm^{-1}.

4.13. Ethyl (2*S*,3*R*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienylcarboxylate (*SRS*)-13

Prepared by the same procedure used to make (*RSS*)-**13**. $[\alpha]_D^{25} = +110.4$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, 1H, J = 11.7 Hz), 5.46 (dd, 1H, J = 9.9, 11.7 Hz), 5.26 (d, 1H, J = 9.9 Hz), 4.79 (d, 1H, J = 9.9 Hz), 4.26 (q, 2H, 7.5 Hz), 3.46 (br s, 1H), 2.34 (m, 1H), 1.76 (d, 3H, J = 1.2 Hz), 1.38 (m, 1H), 1.29 (t, 3H, J = 7.2 Hz), 1.27 (s, 3H), 1.26 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 0.87 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 139.2, 138.4, 130.7, 124.7, 77.2, 71.9, 62.5, 34.7, 30.6, 22.6, 21.0, 17.0, 14.4, 12.4; HRMS calcd 270.1831, found 270.1834; IR (CH_2Cl_2) ν_{max} 3467, 2961, 2925, 2868, 1735, 1456, 1375, 1250, 1176, 1117, 1018 cm^{-1}.

4.14. Ethyl (2*S*,3*S*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienylcarboxylate (*SSS*)-13

Prepared by the same procedure used to make (*RSS*)-**13**. $[\alpha]_D^{25} = +3.4$ (c 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, 1H, J = 11.7 Hz), 5.37 (d, 1H, J = 10.2 Hz), 5.32 (d, 1H, J = 10.5 Hz), 4.63 (d, 1H, J = 9.9 Hz), 4.20 (m, 2H), 3.46 (br s, 1H), 2.32 (m, 1H), 1.80 (d, 3H, J = 1.2 Hz), 1.45 (s, 3H), 1.35 (m, 1H), 1.26 (m, 1H), 1.25 (t, 3H, J = 7.2 Hz), 0.97 (d, 3H, J = 6.6 Hz), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 140.2, 138.7, 131.0, 124.2, 77.2, 72.1, 62.5, 34.7, 30.5, 22.8, 20.9, 16.7, 14.4, 12.3; HRMS calcd 270.1831, found 270.1832; IR (CH_2Cl_2) ν_{max} 3466, 2962, 2925, 2873, 1731, 1455, 1375, 1247, 1117, 1018 cm^{-1}.

4.15. Methyl *N*-[(2*R*,3*S*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienoyl]glycinate (*RSS*)-14

To a solution of **13** (65 mg, 0.24 mmol) in 1:1 MeOH–THF (700 μL) was added a solution of LiOH (65 mg, 1.53 mmol) in water (300 μL) at 25 °C and the reaction mixture was stirred for 3 h. (*Note*: The (2*R*,3*R*,8*S*)- and (2*S*,3*S*,8*S*)-isomers needed 24 h for consumption of the starting material). The reaction mixture was concentrated in vacuo, diluted with water and acidified to pH 2 with 2 M HCl. The aqueous solution was extracted with EtOAc (3×) and the combined organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude acid was carried on to the next step without further purification.

To a stirred solution of the crude acid, HOBt (48 mg, 0.31 mmol), glycine methyl ester hydrochloride (47 mg, 0.37 mmol), and diisopropylethylamine (430 μL, 3.10 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added EDCI (71 mg, 0.37 mmol) at 25 °C and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with 0.5 M HCl (2×), water (1×), and brine (1×). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (60% EtOAc/hexanes) to afford **14** (62 mg, 82%) as a colorless, viscous oil. $[\alpha]_D^{25} = -16.8$ (c 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 6.11 (d, 1H, J = 11.9 Hz), 5.44 (dd, 1H, J = 10.4, 11.6 Hz), 5.27 (d, 1H, J = 9.6 Hz), 4.85 (d, 1H, J = 10.3 Hz), 3.98 (AB, 2H, J_{AB} = 17.8 Hz, ΔAB = 68.6 Hz), 3.72 (s, 3H), 2.36 (m, 1H), 1.80 (br s, 3H), 1.39 (m, 1H), 1.28 (m, 1H), 1.24 (s, 3H), 0.97 (d, 3H, J = 6.8 Hz), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 178.9, 171.8, 139.4, 138.5, 132.2, 126.5, 78.6, 72.2, 52.6, 41.8, 35.6, 31.4, 23.2, 21.1, 17.0, 12.5; HRMS calcd 314.1967, found 314.1965; IR (CH_2Cl_2) ν_{max} 3379, 2959, 2929, 2872, 1744, 1655, 1528, 1451, 1439, 1370, 1214, 1020 cm^{-1}.

4.16. Methyl *N*-[(2*R*,3*R*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienoyl]glycinate (*RRS*)-14

The procedure for making (*RSS*)-**14** was followed, except that the saponification required 12 h to reach completion. $[\alpha]_D^{25} = +38.5$ (c 3.75, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (br s, 1H), 5.97 (d, 1H, J = 11.8 Hz), 5.52 (dd, 1H, J = 10.1, 11.8 Hz), 5.27 (d, 1H, J = 9.5 Hz), 4.63 (d, 1H, J = 10.1 Hz), 3.97 (m, 1H), 3.71 (m, 1H), 3.71 (s, 3H), 2.34 (m, 1H), 1.77 (br s, 3H), 1.39 (s, 3H), 1.38 (m, 1H), 1.28 (m, 1H), 0.97 (d, 3H, J = 6.5 Hz), 0.88 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.8, 171.7, 139.1, 138.2, 132.4, 126.4, 78.5, 72.7, 52.6, 41.6, 35.5, 31.5, 23.1, 21.0, 16.7, 12.5; HRMS calcd 314.1967, found 314.1968; IR (CH_2Cl_2) ν_{max} 3395, 2956, 2925, 2873, 1747, 1656, 1530, 1450, 1439, 1367, 1210, 1183, 1013 cm^{-1}.

4.17. Methyl *N*-[(2*S*,3*R*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienoyl]glycinate (*SRS*)-14

The procedure for making (*RSS*)-**14** was followed. $[\alpha]_D^{25} = +55.0$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 6.11 (d, 1H, J = 11.8 Hz), 5.44 (dd, 1H, J = 10.4, 11.6 Hz), 5.28 (d, 1H, J = 9.6 Hz), 4.84 (d, 1H, J = 10.3 Hz), 4.00 (AB, 3H, J_{AB} = 17.8 Hz, Δ AB = 68.6 Hz), 3.72 (s, 3H), 2.36 (m, 1H), 1.80 (br s, 3H), 1.39 (m, 1H), 1.29 (m, 1H), 1.23 (s, 3H), 0.97 (d, 3H, J = 6.6 Hz), 0.89 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 178.9, 171.8, 139.3, 138.6, 132.1, 126.5, 78.6, 72.3, 52.6, 41.8, 35.6, 31.4, 23.2, 21.1, 16.9, 12.5; HRMS calcd 314.1967, found 314.1966; IR (CH_2Cl_2) ν_{max} 3395, 2959, 2930, 2873, 1746, 1657, 1530, 1452, 1439, 1370, 1215, 1020 cm^{-1}.

4.18. Methyl *N*-[(2*S*,3*S*,4*Z*,6*E*,8*S*)-2,3-dihydroxy-2,6,8-trimethyldeca-4,6-dienoyl]glycinate (*SSS*)-14

The procedure for making (RRS)-**14** was followed. $[\alpha]_D^{25} = -3.2$ (*c* 2.5, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 5.97 (d, 1H, $J = 11.9$ Hz), 5.51 (dd, 1H, $J = 10.5$, 11.9 Hz), 5.27 (d, 1H, $J = 9.6$ Hz), 4.63 (d, 1H, $J = 9.9$ Hz), 3.91 (AB, 3H, $J_{AB} = 17.7$ Hz, $\Delta AB = 48.1$ Hz), 3.71 (s, 3H), 2.33 (m, 1H), 1.77 (br s, 3H), 1.40 (s, 3H), 1.37 (m, 1H), 1.28 (m, 1H), 0.97 (d, 3H, $J = 6.7$ Hz), 0.86 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.8, 171.7, 139.1, 138.2, 132.4, 126.4, 78.5, 72.7, 52.6, 41.6, 35.5, 31.5, 23.1, 21.0, 16.7, 12.5; HRMS calcd 314.1967, found 314.1965; IR (CH_2Cl_2) ν_{max} 3395, 2956, 2930, 2868, 1747, 1654, 1527, 1452, 1436, 1367, 1212, 1016 cm^{-1}.

Acknowledgments

We are grateful to the NIH (AI50888) for financial support of this work. C.M.A. also thanks the Sloan Foundation and the NIH for graduate research assistantships.

References

1. Ford, P. W.; Gustafson, K. R.; McKee, T. C.; Shigematsu, N.; Maurizi, L. K.; Pannell, L. K.; Williams, D. E.; Dilip de Silva, E.; Lassota, P.; Allen, T. M.; Van Soest, R.; Anderson, R. J.; Boyd, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 5899.
2. Alberto, P.; Elena, G.; Heather, L. B.; Michelle, K.; Carole, A. B. *J. Nat. Prod.* **2007**, *70*, 1753.
3. During the preparation of this manuscript, a total synthesis of papuamide B appeared that arrived at similar conclusions as our own: Xie, W.; Ding, D.; Zi, W.; Li, G.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1.
4. Miki, S.; Sato, Y.; Tabuchi, Y.; Oikawa, H.; Ichihara, A.; Sakamura, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1228.
5. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
6. Ley, S. V.; Armstrong, A.; Diez-Martin, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 667.
7. Seebach, D.; Abei, J. D.; Gander-Coquoz, M.; Naef, R. *Chem. Acta* **1987**, *70*, 1192.
8. (a) Crich, D.; Hao, X. *J. Org. Chem.* **1998**, *63*, 3796; (b) Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016.
9. Bruce, E. M.; Allen, B. R. *Chem. Rev.* **1989**, *89*, 863.
10. Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *13*, 2177.