Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 341–345
Tetrahedron

The absolute stereochemistry of grenadamide

Juma'a R. Al Dulayymi, Mark S. Baird* and Keith Jones

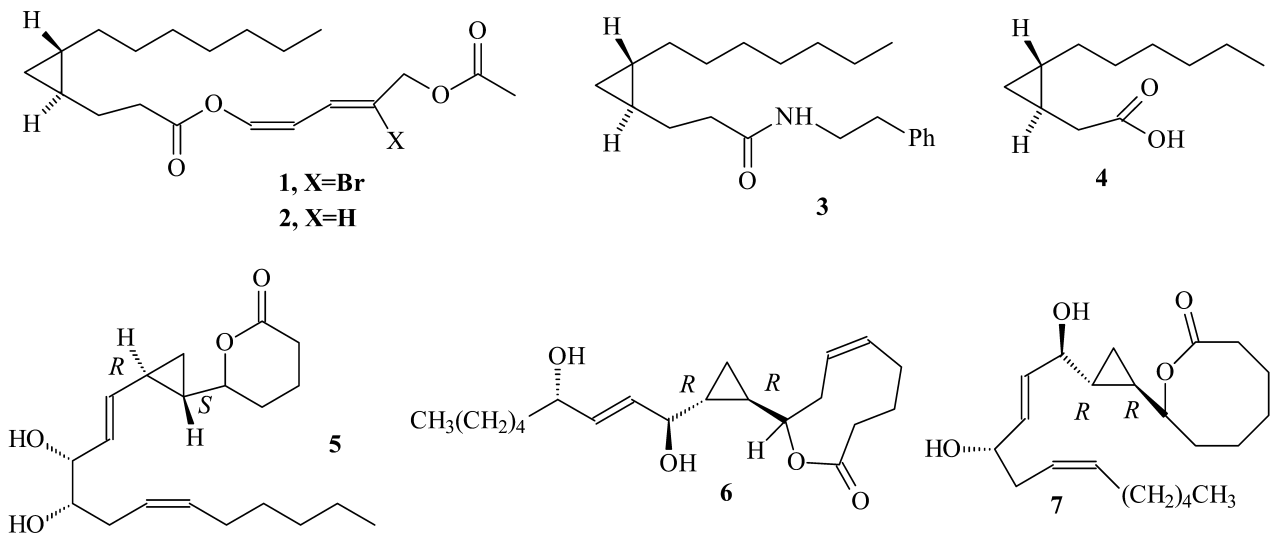
Department of Chemistry, University of Wales, Bangor, Gwynedd Wales LL57 2UW, UK

Received 20 September 2003; revised 15 October 2003; accepted 6 November 2003

Abstract—3-(2*S*-Heptylcycloprop-1*S*-yl)propanoic acid 2-phenylethanamide was synthesised from *cis*-cyclopropan-1,2-dimethanol via enzymatic desymmetrisation of the dibutyrate; it gave identical NMR spectroscopic data to those reported for grenadamide but had an equal and opposite absolute rotation, indicating that the latter is the 2*R*,1*R*-enantiomer.

Sitachitta and Gerwick have reported the isolation of three cyclopropane containing metabolites, grenadadiene (**1**), debromogrenadadiene (**2**) and grenadamide (**3**) from the organic extracts of the marine cyanobacterium *Lyngyba majuscule*, and established their *trans*-cyclopropane relative stereochemistry (Scheme 1).[1] Although the racemic esters (**1**) and (**2**) have been synthesised,[2] there appears to be no information concerning the absolute stereochemistry of these three molecules. Related simple *trans*-cyclopropane fatty acids have been isolated from other species, such as cascarillic acid (**4**) from cascarilla bark, again of unreported absolute stereochemistry.[3] More complex derivatives such as the costanolactones are of known stereochemistry, as shown for costanolactone E (**5**).[4] The reverse absolute stereochemistry of the cyclopropane is reported for the acid and alkyl derived side chains of related halicholactones such as (**6**),[5] and in solandelactones such as (**7**).[6]

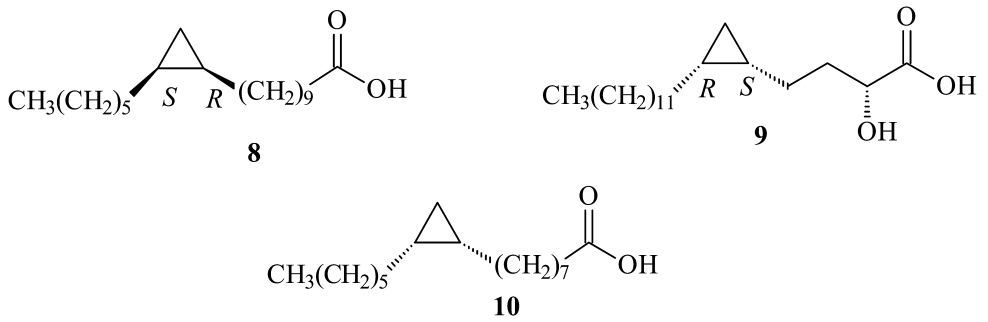
The related *cis*-cyclopropane fatty acids, lactobacillic acid (**8**)[7] is reported to have the 9*R*,10*S*-configuration. On the other hand, cepaciamide, a derivative of the acid (**9**),[8] the corresponding hydroxy acid chain of plakoside A,[9] and a derivative of the acid (**10**) isolated from the slime mould *Pyhysarum polycephalum*,[10] all have *S,R*-configuration of fatty acid and alkyl chains respectively (Scheme 2). A number of other natural *cis*-cyclopropane fatty acids are of unknown absolute stereochemistry.[11]



Scheme 1.

Keywords: Grenadamide; Stereochemistry; Synthesis.
* Corresponding author. Tel.: +44-124-838-2374; fax: +44-124-837-0528; e-mail address: chs028@bangor.ac.uk

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.11.006



Scheme 2.

As part of a study designed to complete the assignment of absolute stereochemistry to the full range of natural cyclopropane fatty acids, we now establish the absolute stereochemistry of granadamide through the synthesis of its enantiomer.

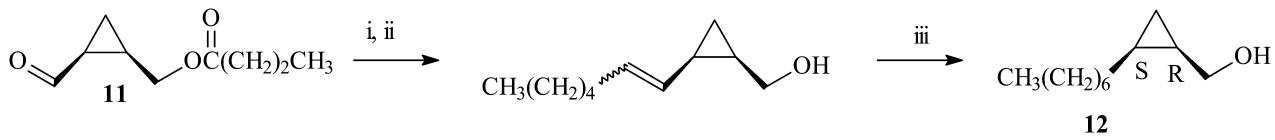
The alcohol (**12**) was prepared from aldehyde (**11**)[7c,12] (Scheme 3), following a procedure applied to a lower homologue,[7c] and closely related to that developed by Grandjean et al.[12] The aldehyde was obtained as before by selective enzymatic hydrolysis of *cis*-cyclopropane-1,2-dimethanol di-*n*-butyrate to (2*R*-*n*-butyryloxymethyl-cycloprop-1*S*-yl)methanol, followed by oxidation and gave an optical rotation consistent with an ee of >95% as established through the use of chiral lanthanide shift reagents,[12] and the formation of diastereomeric esters in earlier work.[7c]

Oxidation to (**13**) and epimerisation using sodium methoxide in methanol,[13] gave a 19:1 mixture of (**14**) and (**13**); reaction of the mixture with ethoxycarbonyl triphenylphosphorane in toluene gave after chromatography the *trans*-ester (**15**). The double bond was removed by reaction with di-potassium azodicarboxylate and ethanoic acid in methanol at room temperature to give the ester (**16**).[14] This was hydrolysed, converted into the corresponding acid chloride and treated with 2-phenylethylamine to give the amide (**18**) (Scheme 4).

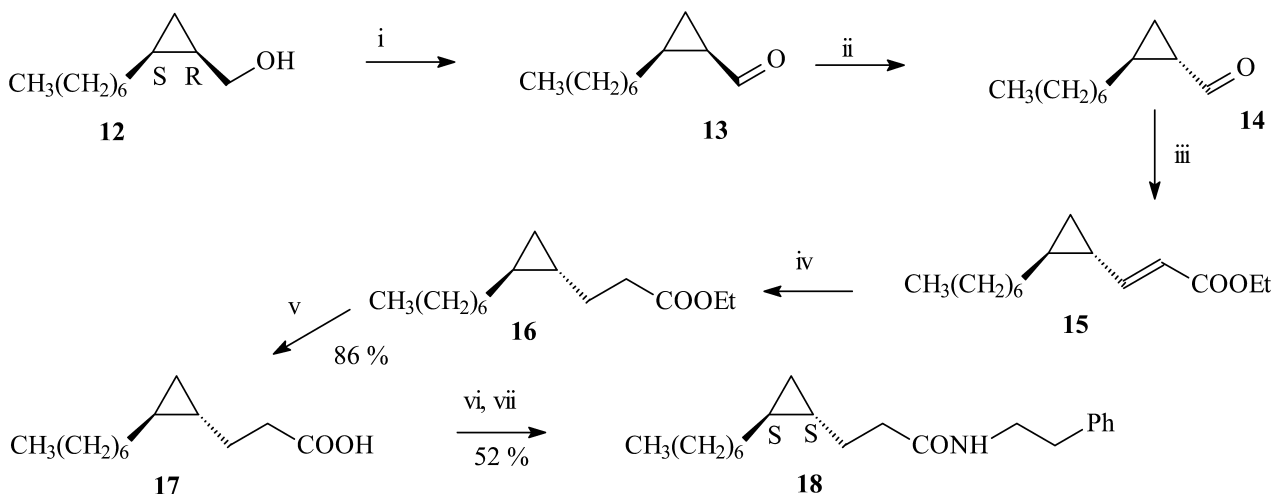
The amide gave a ^{1}H NMR spectrum that was identical to that reported for granadamide;[1] however, its $[\alpha_D]^{22}$ was+12.6 (*c* 0.84, $CHCl_3$) whereas, that for the natural product is reported to be −11.0 (*c* 0.1, $CHCl_3$).[1] The natural material is therefore characterised as the *R*,*R*-enantiomer (**19**) (Scheme 5).[15]

1. Experimental

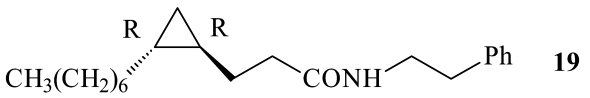
Ether and tetrahydrofuran were dried over sodium wire. Petroleum ether was of boiling point 40–60 °C. Reactions which had to be carried under inert conditions, were carried out under a slow stream of dry nitrogen. Silica (Merck 7736 silica gel) and silica plates used for thin layer and column



Scheme 3. (i) $BrPh_3P(CH_2)_5CH_3$, *n*BuLi, THF, −78 °C (55%; *Z*:*E* 4.6:1); (ii) k_2CO_3, MeOH (86%); (iii) aq. $CuSO_4$, hydrazine hydrate, $NaIO_4$, iPrOH, AcOH (86%).



Scheme 4. (i) PCC, CH_2Cl_2 (91%); (ii) NaOMe, MeOH, reflux, 48 h (84%; 19:1 *trans*:*cis*); (iii) $Ph_3PCHCOOEt$, toluene (71%); (iv) $KO_2CN{=}NCO_2K$, AcOH, MeOH, rt, 48 h (83%); (v) KOH, EtOH, water, rt (86%); (vi) $SOCl_2$; (vii) $PhCH_2CH_2NH_2$ (52%).



19

Scheme 5.

chromatography were obtained from Aldrich. GLC was carried out on the Perkin–Elmer Model 8410 on a capillary column (15 m×0.53 mm). Unless otherwise stated products were one spot on TLC or one peak on GLC. IR spectra were carried out on the Perkin–Elmer 1600 FTIR spectrometer as liquid films. NMR spectra were recorded in $CDCl_3$ on the Bruker AC250 at a frequency of 250 MHz for protons. $[\alpha]_D$ values were recorded in $CHCl_3$ on the POLAAR 2001 Optical Activity polarimeter. (1*S*,2*R*)-2-*n*-butyryloxymethyl-1-formylcyclopropane $[\alpha]_D^{22}$+61.1 (*c* 1.42, $CHCl_3$) [lit. $[\alpha]_D^{22}$+59.8 (*c* 2.68, CH_2Cl_2), corresponding to >95% ee],[12]was prepared as described earlier and gave identical ^1H and ^{13}C NMR and IR spectra to those reported.[7c,12]

1.1. (1*R*,2*S*)-2-(Heptylcycloprop-1-yl)methanol (12)

n-Butyl lithium (27.5 mL, 44 mmol, 1.6 M, in hexane) was added dropwise to a suspension of 1-hexyl-triphenylphosphonium bromide (16.4 g, 38 mmol, 1.3 mol.eq.) in dry THF (120 mL) at −78 °C under nitrogen. The reaction was allowed to reach room temperature for 1 h when a deep orange colour appeared, then cooled again to −78 °C when (1*S*,2*R*)-2-butyryloxymethyl-1-formylcyclopropane (5 g, 0.03 mol) in dry THF (10 mL) was added slowly by syringe. The reaction was stirred overnight at room temperature, then quenched with sat.aq. ammonium chloride (50 mL) and extracted with ether (3×100 mL). The combined organic layers were washed with water (50 mL), dried and evaporated to give a residue which was stirred with petroleum/ether (50 mL) for 10 min. The resulting precipitate was filtered off and the filtrate was evaporated to give an oil. Chromatography on silica eluting with petrol/ether (5:1) gave a colourless oil, *(1R,2R)-1-butyryloxymethyl-2-[Z/E-hept-1-en-1-yl]cyclopropane* (3.65 g, 55%) as a mixture of two isomers in ratio 4.6:1; (major *Z*-isomer) [Found M^+: 238.1923, $C_{15}H_{26}O_2$ requires: 238.1933]; δ_H: 5.45 (1H, dtd, *J*=0.9, 7.0, 11.5 Hz), 5.03 (1H, br.dd, *J*=9.1, 11.5 Hz), 4.15 (1H, dd, *J*=7.0, 11.6 Hz), 3.9 (1H, dd, *J*=8.0, 11.6 Hz), 2.27 (2H, t, *J*=7.3 Hz), 2.21 (2H, br.m), 1.8–1.5 (3H, m, including a pentet, *J* ca. 7 Hz), 1.4–1.2 (7H, m), 1.05 (1H, dt, *J*=4.8, 8.5 Hz), 0.95–0.8 (6H, m, including a triplet, *J* ca. 7 Hz), 0.38 (1H, br.q, *J*=5.8); δ_H (minor E-isomer): 5.58 (1H, m), 5.2 (1H, br.d, *J* ca. 15 Hz), the remaining signals were obscured by the major isomer, IR (film) 2960, 2930, 1736 cm^{-1}. Anhydrous potassium carbonate (2.4 g, 0.017 mol) was added to a stirred solution of the cyclopropane (4.13 g, 0.16 mol) in methanol (30 mL). After 4 h, TLC showed no starting material remained. The K_2CO_3 was then filtered and washed with ether (2×20 mL). The filtrate was evaporated to give a yellow oil, (1*R*, 2*R*)-2-((Z/E-hept-1-en-1-yl)-1-cycloprop-1-yl)methanol (2.5 g, 86%). This was used for the next stage without purification.

To the crude product (2.5 g, 0.015 mol) in isopropyl alcohol (100 mL) was added sat.aq. $CuSO_4$ (2 mL), acetic acid (2 mL) and hydrazine hydrate (20 mL), and the mixture was heated to 56 °C. Sodium periodate (31.8 g, 0.15 mol) in hot water (100 mL) was added dropwise over 1.5 h. The mixture was stirred for 2 h, allowed to reach room temperature, then diluted with ether (150 mL). The organic layer was separated and the aqueous layer extracted with ether (2×50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography on silica eluting with petrol/ether (5:2) gave *(1R, 2S)-(2-heptylcycloprop-1-yl)methanol* (2.2 g, 86%) (**12**) as a colourless oil [Found M^+-H_2O:152.1581, $C_{11}H_{20}$ requires: 152.1565], $[\alpha]_D^{25}$+23.6 (*c* 1.14, $CHCl_3$); δ_H: 3.65 (1H, dd, *J*=7.9, 11.3 Hz), 3.55 (1H, dd, *J*=11.3, 7.9 Hz), 1.8 (1H, br.s), 1.5–1.2 (13H, m), 1.1 (1H, m), 0.87 (3H, t, *J*=7.3 Hz), 0.7 (1H, dt, *J*=4.2, 8.2 Hz), −0.03 (1H, br.q, *J*=5.2 Hz); δ_C: 64.8, 33.4, 31.7, 31.1, 30.8, 30.0, 24.1, 19.6, 17.6, 15.6, 10.9; IR (film) 3430 cm^{-1}.

1.2. *cis*-(1*R*,2*S*)-2-Heptyl-1-formylcyclopropane (13)

(1*R*,2*S*)-2-Heptylcycloprop-1-ylmethanol (2 g, 0.012 mol) in dichloromethane (10 mL) was added to a stirred suspension of PCC (5.1 g, 0.023 mol) in dichloromethane (100 mL) at room temperature. The reaction was stirred for 2 h, when a black precipitate had formed. The mixture was poured into ether (100 mL) and filtered on a bed of celite with silica gel and washed with ether. This was then evaporated to yield the crude product as a yellow oil. Chromatography on silica eluting with petrol/ether (5:2), gave *cis-(1R,2S)-2-heptyl-1-formylcyclo-propane* (**13**) (1.8 g, 91%) as a colourless oil [Found M^+:168.1539, $C_{11}H_{20}O$ requires: 168.1514], $[\alpha]_D^{24}$+14.7 (*c* 0.95, $CHCl_3$); δ_H: 9.34 (1H, d, *J*=5.5 Hz), 1.87 (1H, m), 1.7–1.1 (15H, m), 0.88 (3H, t, *J*=7 Hz); δ_C: 203.3, 33.3, 31.5, 30.6, 29.7, 29.3, 26.3, 24.1, 16.2, 15.6; IR (film) 2925, 2855, 1705 cm^{-1}.

1.3. *trans*-(1*R*,2*S*)-2-Heptyl-1-formylcyclopropane (14)

cis-(1*R*,2*S*)-2-Heptyl-1-formylcyclopropane (1.7 g, 0.01 mol) was to added to a stirred solution of sodium methoxide (0.6 g, 0.011 mol) in methanol (130 mL) and refluxed for 48 h. The mixture was quenched with sat.aq. ammonium chloride (20 mL), and extracted with ether (2×50 mL). The combined organic layers were dried and evaporated to yield a yellow oil. Chromatography on silica gel eluting with petrol/ether (5:1) gave *(1R,2S)-2-heptyl-1-formylcyclopropane* (**14**) as a colourless oil containing ca. 5% of the *cis*-isomer (1.43 g, 84%) [Found M^+: 168.1510, $C_{11}H_{20}O$ requires: 168.1514], $[\alpha]_D^{22}$+41.4 (*c* 1.45, $CHCl_3$); δ_H: 9.00 (1H, d, *J*=5.5 Hz), 1.61 (1H, m), 1.51–1.22 (14H, m), 0.97–0.86 (4H, m, including 3H, t, *J*=7 Hz at 0.88); δ_C: 202.5, 34.1, 33.3, 32.0, 30.7, 30.6, 24.2, 24.1, 16.3, 15.5; IR (film) 2925, 2855, 1709 cm^{-1}.

1.4. (*E*)-3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)acrylic acid ethyl ester (15)

The above *trans*-(1*R*,2*S*)-2-heptyl-1-formylcyclopropane (0.43 g, 0.0025 mol) in toluene (2 mL) was added to a stirred solution of (ethoxycarbonylmethylene)triphenyl phosphorane (1.13 g, 0.0032 mol) in toluene (10 mL) and stirred at room temperature for 24 h. The toluene was rotary evaporated, and the residue was treated with petrol/ether (5:2) (30 mL) and refluxed for 10 min. The solid residual phosphonium oxide was filtered off and washed with

petrol/ether (2×15 mL) and the filtrate was rotary evaporated. The crude product was then columned on silica gel eluting with petrol/ether (5:1) to give *(E)-3-((1S, 2S)-(2-heptylcycloprop-1-yl)acrylic acid ethyl ester* (**15**) (0.43 g, 71%) as a colourless oil [Found M^+: 238.1945, $C_{15}H_{26}O_2$ requires: 238.1933], $[\alpha]_D^{24}$+66.8 (*c* 1.28, $CHCl_3$); δ_H: 6.49 (1H, dd, *J*=10.4, 15.4 Hz), 5.89 (1H, d, *J*=15.4), 4.17 (2H, q, *J*=7.3 Hz), 1.4–1.2 (16H, br.m), 1.0 (1H, m). 0.86 (3H, t, *J*=6.7 Hz), 0.85–0.74 (2H, m); IR (film) 2923, 2854, 1718, 1644, 1465 cm^{-1}. Less than 5% of the *cis*-isomer could be detected by NMR.

1.5. 3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)propionic acid ethyl ester (16)

Freshly distilled acetic acid (1.13 g, 0.019 mol) in methanol (3 mL) was add slowly to a stirred solution of (*E*)-3-((1*S*, 2*S*)-2-heptylcycloprop-1-yl)acrylic acid ethyl ester (0.3 g, 0.0012 mol) and dipotassium azodicarboxylate (2.4 g, 0.012 mol) at room temperature. The mixture was stirred for 24 h then additional dipotassium azo-dicarboxylate (2.4 g) and acetic acid (1.2 g) were added. After a further 24 h, the mixture was diluted with water (15 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with sat.aq. sodium bicarbonate (15 mL), dried and evaporated, to give a residue which was columned on silica gel eluting with petrol/ether (10: 0.5) to give *3-((1S,2S)-(2-heptylcycloprop-1-yl)propionic acid ethyl ester* (**16**) (0.25 g, 83%) as a colourless oil [Found M^+: 240.2096, $C_{15}H_{28}O_2$ requires: 240.2089], $[\alpha]_D^{24}$+12.5 (*c* 0.69, $CHCl_3$); δ_H: 4.14 (2H, q, *J*=7 Hz), 2.37 (2H, t, *J*=7.6 Hz), 1.6–1.1 (17H, m), 0.89 (3H, t, *J*=7 Hz), 0.43 (2H, m), 0.2 (2H, m); δ_C: 173.8, 61.5, 34.5, 34.1, 31.9, 29.7, 29.6, 29.5, 29.3, 22.7, 18.8, 18.1, 14.2, 14.1, 11.8; IR (film) 2923, 2854, 1736, 1178 cm^{-1}.

1.6. 3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)propionic acid (17)

3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)propionic acid ethyl ester (0.2 g, 0.83 mmol) was added to a stirred solution of potassium hydroxide (0.46 g, 8.3 mmol) in ethanol (3 mL) and water (0.5 mL). The mixture was stirred for 1 h when TLC showed no starting remained, then diluted with water (6 mL), ether (15 mL) and acidified to pH 2 with sulphuric acid (5%). The organic layer was separated and the aqueous layer was re-extracted with ether (2×10 mL). The combined organic layers were dried and evaporated to give *3-((1S, 2S)-(2-heptylcyclo-prop-1-yl)propionic acid* (**17**) as a thick yellow oil (0.152 g, 86%) [Found M^+: 212.1777, $C_{13}H_{24}O_2$ requires: 212.1776], $[\alpha]_D^{24}$+14.8 (*c* 1.05, $CHCl_3$); δ_H: 2.45 (2H, t, *J*=7.25 Hz), 1.63–1.5 (2H, m), 1.4–1.21 (12H, m), 1.15 (1H, m), 0.91 (3H, t, *J*=6.6 Hz), 0.47 (2H, m), 0.24 (2H, m); δ_C: 179.6, 34.2, 34.1, 31.9, 29.6, 29.5, 29.4, 29.3, 22.7, 18.9, 18.1, 14.1, 11.8; IR (film) 3397, 2923, 2854, 1709, 1178 cm^{-1}.

1.7. 3-((1*S*,2*S*)-2-Heptylcycloprop-1-yl)-*N*-phenethylpropionamide (18)

3-((1*S*, 2*S*)-2-Heptylcycloprop-1-yl)propionic acid (0.15 g, 0.71 mmol) was treated with thionyl chloride (3 mL) and refluxed for 2 h. The excess of thionyl chloride was distilled off to give a residue of 3-((1*S*,2*S*)-(2-heptylcyclopropyl)-propionyl chloride which showed δ_H: 2.9 (2H, t, *J*=7.3 Hz), 1.7 (2H, m), 1.5–1.16 (11H, m), 1.02–0.8 (4H, m, including a triplet with coupling constant 6.7 Hz), 0.47 (2H, m), 0.26 (2H, m); δ_C: 173.7, 47.3, 34.0, 31.9, 29.8, 29.6, 29.5, 29.3, 22.7, 19.0, 17.5, 14.2, 11.9; the residue was cooled to 5 °C and treated with phenylethyl amine (0.85 g, 7.1 mmol) under nitrogen. A white precipitates was formed and the reaction was stirred for 2 h. The mixture was diluted with water and the product was extracted with ether (2×10 mL). The combined organic layers were washed with brine, dried and evaporated to give a crude product which was purified by chromatography on silica eluting with petrol/ethyl acetate (1:1) to give *3-((1S,2S)-(2-heptyl-cycloprop-1-yl)-N-phenethylpropionamide* (**18**) (0.115 g, 52.3%) as a pale yellow solid [Found M^+: 315.2561, $C_{21}H_{33}NO$, requires: 315.2562] $[\alpha]_D^{22}$+12.6 (*c* 0.82, $CHCl_3$) (lit. $[\alpha]_D$-11.0 (*c* 0.1, $CHCl_3$))[1]; δ_H: 7.35–7.2 (5H, m), 5.6 (1H, br.s), 3.54 (2H, q, *J*=6.4 Hz), 2.83 (2H, t, *J*=6.7 Hz), 2.21 (2H, t, *J*=7.6 Hz), 1.52 (2H, m), 1.4–1.25 (10H, m), 1.15 (2H, m), 0.89 (3H, t, *J*=6.7 Hz), 0.4 (2H, m), 0.182 (2H, m); δ_C 173.0, 138.9, 128.75, 128.6, 126.5, 40.5, 36.9, 35.7, 34.1, 31.9, 30.4, 29.6, 29.5, 29.4, 22.7, 18.9, 18.2, 14.1, 11.8; IR (film) 3310, 2918, 2850, 1637 cm^{-1}.

References and notes

1. Sitachitta, N.; Gerwick, W. H. *J. Nat. Prod.* **1998**, *61*, 681–684.
2. He, R.; Deng, M.-Z. *Org. Lett.* **2002**, *4*, 2759–2762.
3. (a) Hiyama, T.; Yamamoto, H.; Nishio, K.; Kitatani, K.; Nozaki, H. *Bull. Chem. Soc. Jpn* **1979**, *52*, 3632–3637. (b) Wilson, S. R.; Prodan, K. A. *Tetrahedron Lett.* **1976**, *17*, 4231–4234.
4. (a) Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett.* **1990**, *31*, 2995–2998. (b) Nagle, D. G.; Gerwick, W. H. *J. Org. Chem.* **1994**, *59*, 7227–7237. (c) Miyaoka, H.; Shigemoto, T.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7407–7408. (d) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81–88.
5. (a) Critcher, D. J.; Connolly, S.; Wills, M. *J. Chem. Soc., Chem. Comm.* **1995**, 139–140. (b) Critcher, D. J.; Connolly, S.; Wills, M. *Tetrahedron Lett.* **1997**, 3763–3766. (c) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638–6657.
6. Seo, Y.; Cho, K. I.; Rho, J.-R.; Shin, J. *Tetrahedron* **1996**, *52*, 10583–10596.
7. (a) Buist, P. H.; Pon, R. A. *J. Org. Chem.* **1990**, *26*, 6240–6241. (b) Coxon, G. D.; Knobl, S.; Roberts, E.; Baird, M. S.; Al Dulayymi, J. R.; Besra, G. S.; Brennan, P. J.; Minnikin, D. E. *Tetrahedron Lett.* **1999**, *40*, 6689–6692. (c) Coxon, G. D.; Al Dulayymi, J. R.; Baird, M. S.; Knobl, S.; Roberts, E.; Minnikin, D. E. *Tetrahedron: Asymmetry* **2003**, *14*, 1211–1222.
8. Jiao, Y.; Yoshihara, T.; Ishikuri, S.; Uchino, H.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 1039–1042.
9. Mori, K.; Tashiro, T.; Akasaka, K.; Ohrui, H.; Fattorusso, E. *Tetrahedron Lett.* **2002**, *43*, 3719–3722.
10. (a) Kobayashi, S.; Tokunoh, R.; Shibasaki, M.; Shinigawa, R.; Murakami-Murofushi, K. *Tetrahedron Lett.* **1993**, *34*,

4047–4050. (b) Liliom, K.; Bittman, R.; Swords, B.; Tibor, G. *Mol. Pharmacol.* **1996**, *50*, 616–623.
11. (a) See e.g. Jie, L. K. *J. Chem. Soc., Chem. Comm.* **1977**, 78. (b) Grondin, I.; Smadja, J.; Farines, M.; Soulier, J. *Oleagineux Corps Gras Lipides* **1997**, *4*, 459–463. (c) Fenical, W.; Howard, S. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865–1874. (d) Shin, B. A.; Kim, Y. R.; Lee, I-S.; Sung, C. K.; Hong, J.; Sim, C. J.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **1999**, *62*, 1554–1557.
12. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1991**, *47*, 1215–1230.
13. Barloy-Da Silva, C.; Benkouider, A.; Pale, P. *Tetrahedron Lett.* **2000**, *41*, 3077–3081.
14. Jorgensen, M. J. *J. Am. Chem. Soc.* **1969**, *91*, 6430–6443.
15. This could readily be prepared from the enantiomer of (**11**), prepared by enzyme catalysed monobutyration of cis-cyclopropan-1,2-dimethanol,[7b] using the same sequence as described above.