Improved Synthesis of an Ascaroside Pheromone Controlling Dauer Larva Development in *Caenorhabditis elegans*

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Abstract: Using an efficient Wacker oxidation as a key step, we describe a significantly improved synthesis of the dauer-promoting ascaroside **2** for biological studies of the novel sterol ring methylase STRM-1.

Key words: carbohydrates, natural products, pheromones, stereoselective synthesis, Wacker reactions

The life cycle of the nematode *Caenorhabditis elegans* has been extensively studied over the last decade. Under unfavorable conditions, such as scarcity of food or overcrowding, *C. elegans* enters diapause and forms so-called dauer larvae.[1] The dauer larva represents a stress-resistant and non-aging arrested developmental stage. Steroidal hormones, the dafachronic (cholesten-26-oic) acids, are required to bypass dauer larva formation and to enter reproductive development.[2] In the course of our studies,[3] we achieved efficient and stereoselective syntheses of the (25*R*)-cholesten-26-oic acids[4] as well as the more active (25*S*)-cholesten-26-oic acids.[5] In the presence of these ligands, the hormonal receptor DAF-12 is inactivated and the worms enter reproductive development. In the absence of dafachronic acid ligands, DAF-12 is activated and *C. elegans* enters the so-called diapause generating dauer larvae.[2]

Recently, several pheromones that induce dauer larva formation of *C. elegans* have been isolated and synthesized.[6–8] As common structural feature, these pheromones represent glycosides of the dideoxy sugar ascarylose (Figure 1). In 2005, Paik et al. described the isolation and synthesis of the first compound in this series and called it daumone (**1**).[6] In the same year, O'Doherty and Guo reported the second synthesis of daumone (**1**) using a palladium-catalyzed glycosylation.[7] This pheromone initiates diapause entry of *C. elegans*. More recently, the identification and synthesis of a series of different ascarosides **2**–**4** has been reported (Figure 1).[8] It has been demonstrated, that the ascarosides **2**–**4** exhibit a significantly stronger dauer-promoting activity than daumone (**1**) itself.[8] Moreover, the blend of ascarosides **2**–**4** regulates formation of dauer larvae and attraction of male larvae. At concentrations (pM) more than 10,000 times lower than required for dauer induction (nM–μM), ascarosides **2**–**4** function as male attractants. At higher concentrations (nM–μM), the male attractant effect is lost and they deter hermaphrodites.[8]

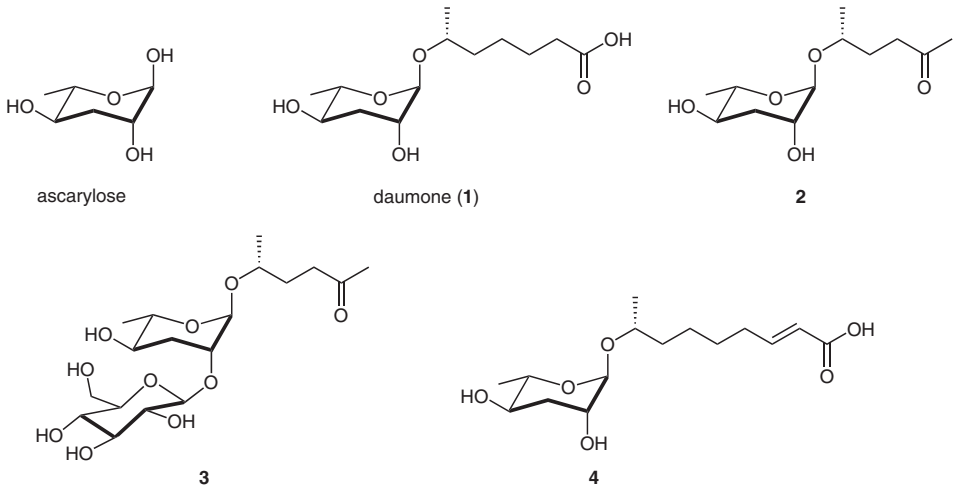

Figure 1 Ascarylose, daumone (**1**), and the ascarosides **2**–**4**

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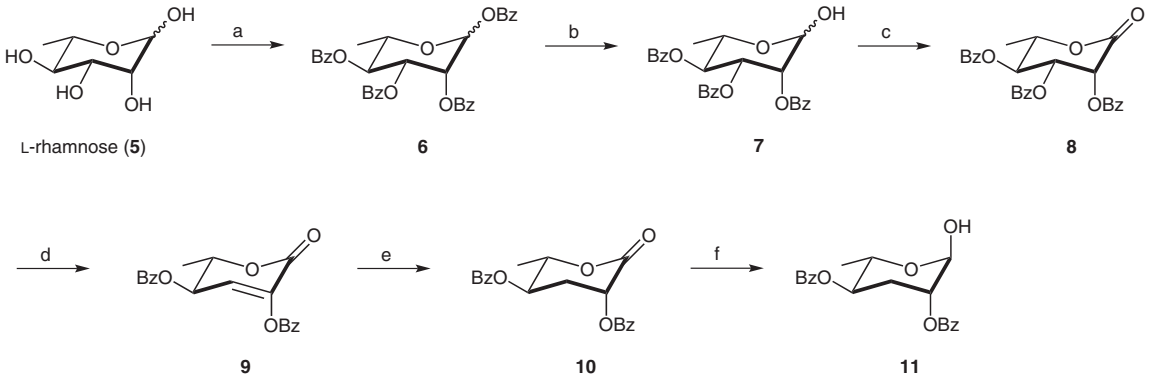


Scheme 1 Improved transformation of L-rhamnose (**5**) into 2,4-di-*O*-benzoylascarylose (**11**). *Reagents and conditions:* (a) BzCl, pyridine, 0 °C to r.t., 16 h, 95%; (b) NH_3(g), MeOH–THF (3:7), 0 °C to r.t., 12 h, 87%; (c) PCC, 4 Å molecular sieves, CH_2Cl_2, 0 °C to r.t., 4 h, 85%; (d) Et_3N–$CHCl_3$ (1:4), r.t., 16 h, 81%; (e) 10% Pd/C, H_2, EtOAc, r.t., 24 h, 96%; (f) disiamylborane, THF, 0 °C to r.t., 20 h, 94%, β/α = 4.6:1.

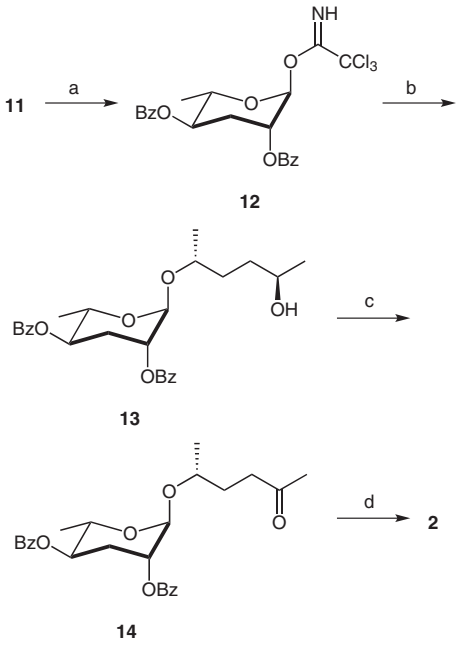
Recently, we identified the novel sterol methylating enzyme STRM-1, which regulates the in vivo concentration of dafachronic acids by methylating the biosynthetic precursors of dafachronic acids.[9] Thus, *strm-1* mutant worms have elevated in vivo concentrations of dafachronic acids. In order to study the biological function of STRM-1 in the dauer-formation process, we prepared the ascaroside **2** to test the response to this pheromone in *strm-1* mutant worms.[9] The ascaroside **2** has been obtained previously in 10 steps and 13% overall yield starting from L-rhamnose (**5**) (Schemes 1 and 2).[8a] Conversion of L-rhamnose (**5**) into the dideoxysugar ascarylose was described in 1977 by Monneret et al.[10,11] 2,4-Di-*O*-benzoylascarylose (**11**), the crucial intermediate for the ascarosides **1**–**4**, was prepared from L-rhamnose (**5**) as originally reported in 1979 (Scheme 1).[6,11]

Treatment of **5** with benzoyl chloride in pyridine led to the fully protected rhamnose **6** (Scheme 1). Selective deprotection of the anomeric hydroxy group with ammonia to the lactol **7** followed by pyridinium chlorochromate oxidation afforded the lactone **8**. By using dry triethylamine and dry chloroform for the elimination of benzoic acid from **8**, we have been able to improve the yield of the unsaturated lactone **9** from 65%[6] to 81%. Increasing the reaction time for the catalytic hydrogenation of **9** also provided a better access to the lactone **10** (24 h, 96% yield instead of 3 h, 85% yield).[6] Reduction of the lactone with disiamylborane provided 2,4-di-*O*-benzoylascarylose (**11**) (6 steps, 51% overall yield) as an anomeric mixture (β/α 4.6:1).[6,12] Compound **11** is the central intermediate for the synthesis of daumone (**1**) and the ascarosides **2**–**4**.[6,8]

Clardy et al. used a four-step sequence for the transformation of **11** into the ascaroside **2** (Scheme 2).[8a] Conversion into the trichloroacetimidate **12**, followed by stereoselective glycosidation with (2*R*,5*R*)-hexane-2,5-diol to **13**, pyridinium dichromate oxidation to **14**, and final saponification afforded the ascaroside **2** in 36% overall yield based on **11**.[8a]

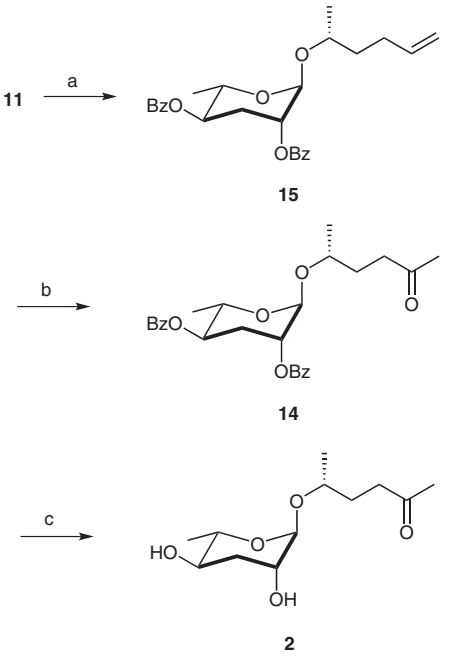
We have developed an optimized route for the synthesis of the ascaroside **2** from 2,4-di-*O*-benzoylascarylose (**11**) (Scheme 3). Key steps of our approach are glycosidation of the anomeric hydroxy group with commercial (2*R*)-hex-5-en-2-ol followed by Wacker oxidation of the terminal double bond to generate the methyl ketone.

Glycosidation of **11** with (2*R*)-hex-5-en-2-ol was achieved in the presence of boron trifluoride–diethyl ether complex, following a well-known literature protocol.[6,13,14] Treatment of **11** with (2*R*)-hex-5-en-2-ol in the presence of 3.0 equivalents of boron trifluoride–diethyl ether afforded compound **15** in only 61% yield. However, using 1.5 equivalents of boron trifluoride–diethyl ether led to a significant improvement of the yield for compound **15** (93%). Wacker oxidation of **15** in a mixture of *N*,*N*-dimethylformamide and water (7:1) using catalytic amounts of palladium(II) acetate and copper(I) chloride in the presence of air afforded the methyl ketone **14** in 89% yield.[15]



Scheme 2 Previously reported synthesis of the ascaroside **2**.[8a] *Reagents and conditions:* (a) cat. DBU, $Cl_3CC{\equiv}N$, CH_2Cl_2, r.t., 30 min, 81%; (b) cat. TMSOTf, (2*R*,5*R*)-hexane-2,5-diol, CH_2Cl_2, 0 °C, 30 min, 64%; (c) PDC, 4 Å molecular sieves, CH_2Cl_2, r.t., 2 h, 89%; (d) 1 M KOH in MeOH, r.t., 3 h, 78%.

Finally, saponification of **14** with potassium hydroxide in methanol provided quantitatively the ascaroside **2**.



Scheme 3 Efficient three-step synthesis of the ascaroside **2** from intermediate **11**. *Reagents and conditions:* (a) $BF_3{\cdot}OEt_2$, (2*R*)-hex-5-en-2-ol, CH_2Cl_2, 0 °C to r.t., 16 h, then Et_3N, 20 min, 93%; (b) cat. $Pd(OAc)_2$, cat. CuCl, DMF–H_2O (7:1), air, r.t., 18 h, 89%; (c) 1 M KOH in MeOH, r.t., 3 h, 99%.

Clardy et al. described an assay for testing the biological activity of ascarosides.[8a] This original protocol results in large variation of the number of dauer larvae which are formed. Reproducible results in dauer larva formation were obtained only at high concentrations of the ascaroside **2** and daumone (**1**).[9] Thus, we have developed robust assay conditions for effective induction of dauer larva formation in wild-type worms (increase of the percentage of dauer larvae which have been formed: 73% to 89%).[9] Exposing *strm-1* mutant worms to these conditions resulted in 0% to 10% induction of dauer larva formation. Our observations indicated that *strm-1* mutant worms have significantly reduced ability of dauer larva formation. Under conditions supporting normal growth, the concentration of pheromone in the surrounding medium is directly proportional to the number of worms. High pheromone concentrations are the signal for worms to enter diapause in order to avoid overcrowding and starvation. In consequence of their low sensitivity to natural pheromones, *strm-1* mutant worms generate dauer larvae only under super-crowded conditions leading to very high concentrations of pheromones. Our findings emphasize that STRM-1 is a major component in regulation of dauer larva formation.

In conclusion, the present synthesis provides the ascaroside **2** in only three steps and an excellent overall yield of 82% based on 2,4-di-*O*-benzoylascarylose (**11**) (previous work:[8a] 4 steps, 36% overall yield). The highly efficient Wacker oxidation at the olefinic side chain of intermediate **15** represents the key step of our approach. Moreover, two key steps of the synthesis of **11** starting from L-rhamnose (**5**) have been significantly improved. Thus, the approach to the ascaroside **2** starting from L-rhamnose (**5**) has been improved from 10 steps and 13% overall yield[6,8a] to 9 steps and 42% overall yield. The procedure described in the present work provides access to the ascarosides **1**–**4** in gram quantities. Moreover, the olefinic side chain at the stage of intermediate **15** opens up the access to further ascaroside derivatives, e.g. via olefin metathesis, cycloaddition, hydroboration, or dihydroxylation. Using the ascaroside **2**, we have developed efficient conditions to induce dauer larva formation.[9] The assay for diapause shows that STRM-1 activity plays a major role in regulating dauer larva formation. Moreover, investigation of other mutant worms using the present assay would potentially lead to the identification of further genes involved in regulation of dauer larva formation.

All reactions were carried out using anhyd solvents in oven-dried glassware under an argon atmosphere. THF, EtOAc, and CH_2Cl_2 were dried using a solvent purification system (MBraun-SPS). Pyridine was obtained from Fluka (H_2O content less than 50 ppm). Et_3N was heated under reflux with CaH_2 for 48 h and stored over 3 Å molecular sieves. Anhyd $CHCl_3$ was obtained by passing through a column of alumina and stored over 3 Å molecular sieves. All other chemicals were used as received from commercial sources. Flash chromatography was performed using silica gel from Acros Organics (0.063–0.200 mm). TLC was performed with TLC plates from Merck (60 F_{254}) using $Ce(SO_4)_2$/phosphomolybdic acid reagent for visualization. PE = petroleum ether. Specific rotation values were measured on a Perkin Elmer 341 polarimeter. IR spectra were recorded on a Thermo Nicolet Avatar 360 FT-IR spectrophotometer using the ATR method. NMR spectra were recorded on Bruker Avance II 300, DRX 500 and Avance III 600 NMR spectrometers with the deuterated solvent as internal standard. ESI-MS spectra were recorded on an Esquire LC with an ion trap detector from Bruker. Positive and negative ions were detected.

2,4-Di-*O*-benzoyl-3,6-dideoxy-L-*erythro*-hex-2-enono-1,5-lactone (9)

Anhyd Et_3N (75 mL) was added to a soln of **8** (9.6 g, 20.2 mmol) in anhyd $CHCl_3$ (300 mL) and the mixture was stirred at r.t. for 16 h. After addition of H_2O (100 mL), the layers were separated. The organic layer was washed with H_2O (2 × 100 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (silica gel, toluene–EtOAc, 10:1) afforded **9** as a light yellow oil; yield: 5.81 g (81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 6.7 Hz, 3 H), 4.95 (m, 1 H), 5.69 (t, *J* = 4.7 Hz, 1 H), 6.70 (d, *J* = 4.7 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.63 (t, *J* = 7.6 Hz, 1 H), 8.06 (d, *J* = 7.6 Hz, 2 H), 8.11 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (DEPT, 75 MHz, $CDCl_3$): δ = 18.33 (CH_3), 68.52 (CH), 77.35 (CH), 125.48 (CH), 127.89 (C), 128.62 (2 CH), 128.65 (2 CH), 128.71 (C), 129.90 (2 CH), 130.41 (2 CH), 133.85 (CH), 134.18 (CH), 140.78 (C), 157.91 (C=O), 164.24 (C=O), 165.45 (C=O).

MS (ESI): *m*/*z* = 353.1 [$(M + H)^+$], 370.1 [$(M + NH_4)^+$], 375.0 [$(M + Na)^+$].

2,4-Di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,5-lactone (10)

A soln of **9** (5.99 g, 17.0 mmol) in EtOAc (100 mL) was added to a Schlenk flask loaded with 10% Pd/C (397 mg). The resulting mixture was stirred under an H_2 atmosphere at r.t. for 24 h and then filtered through a short pad of Celite (EtOAc, 250 mL). Removal of the solvent and purification of the residue by flash chromatography (silica gel, toluene–EtOAc, 10:1) provided **10** as a light yellow syrup which slowly solidified on standing; yield: 5.76 g (96%).

MS (ESI): *m*/*z* = 355.1 [(M + H)$^+$], 372.1 [(M + NH_4)$^+$], 377.1 [(M + Na)$^+$].

Further spectroscopic data are available in the literature.[6]

(2*R*)-1-(Hex-5-en-2-yl)-2,4-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexopyranoside (15)

BF_3·OEt_2 (0.15 mL, 884 μmol) was slowly added to a mixture of (2*R*)-hex-5-en-2-ol (100 μL, 83 mg, 827 μmol), **11** (201 mg, 564 μmol) and powdered 4Å molecular sieves (24 mg) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at r.t. for 16 h. After addition of Et_3N (0.5 mL), the mixture was stirred for a further 20 min. Removal of the solvent and purification of the residue by flash chromatography (silica gel, PE–Et_2O, 20:1) provided **15** as a light yellow oil; yield: 230 mg (93%).

IR (ATR): 3065, 2975, 2934, 1720, 1685, 1652, 1602, 1451, 1377, 1315, 1262, 1215, 1176, 1151, 1100, 1065, 1022, 998, 944, 910, 708, 685 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.1 Hz, 3 H), 1.27 (d, *J* = 6.3 Hz, 3 H), 1.57–1.64 (m, 1 H), 1.72–1.79 (m, 1 H), 2.16–2.27 (m, 3 H), 2.41 (dt, *J* = 13.5, 3.7 Hz, 1 H), 3.87 (sext, *J* = 6.1 Hz, 1 H), 4.12 (dq, *J* = 3.6, 6.3 Hz, 1 H), 4.95 (s, 1 H), 5.00 (ddd, *J* = 10.2, 3.0, 1.2 Hz, 1 H), 5.08 (m, 1 H), 5.14 (m, 1 H), 5.18 (ddd, *J* = 14.5, 10.0, 4.6 Hz, 1 H), 5.87 (m, 1 H), 7.44–7.48 (m, 4 H), 7.56–7.60 (m, 2 H), 8.04 (m, 2 H), 8.11 (m, 2 H).

^{13}C NMR (DEPT, 125 MHz, $CDCl_3$): δ = 17.85 (CH_3), 19.08 (CH_3), 29.71 (CH_2), 29.96 (CH_2), 36.33 (CH_2), 66.99 (CH), 70.62 (CH), 71.21 (CH), 71.95 (CH), 93.69 (CH), 114.75 (CH_2), 128.43 (4 CH), 129.61 (2 CH), 129.83 (C), 129.85 (2 CH), 129.97 (C), 133.17 (CH), 133.24 (CH), 138.39 (CH), 165.66 (C=O), 165.79 (C=O).

MS (ESI): *m*/*z* = 339.1 [(M – $C_6H_{11}O$)$^+$], 456.2 [(M + NH_4)$^+$], 461.2 [(M + Na)$^+$].

(5*R*)-5-(2,4-Di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexopyranosyl)hexan-2-one (14)

$Pd(OAc)_2$ (8 mg, 36 μmol) and CuCl (4 mg, 40 μmol) were added to a soln of **15** (90 mg, 205 μmol) in DMF (7 mL) and H_2O (1 mL). The mixture was stirred in an open flask at r.t. for 18 h. After addition of sat. NH_4Cl soln (20 mL) and Et_2O (20 mL) the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed and the residue was purified by flash chromatography (silica gel, PE–Et_2O, 3:1 to 2:1) to provide **14** as a light yellow oil; yield: 83 mg (89%).

IR (ATR): 2975, 2929, 1714, 1686, 1652, 1635, 1602, 1451, 1316, 1263, 1216, 1176, 1153, 1100, 1066, 1021, 942, 893, 853, 808, 709, 686 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.1 Hz, 3 H), 1.28 (d, *J* = 6.3 Hz, 3 H), 1.84–1.89 (m, 2 H), 2.14–2.20 (m, 1 H), 2.20 (s, 3 H), 2.41 (dt, *J* = 13.5, 3.7 Hz, 1 H), 2.60 (t, *J* = 7.5 Hz, 2 H), 3.88 (sext, *J* = 6.1 Hz, 1 H), 4.05 (dq, *J* = 3.6, 6.3 Hz, 1 H), 4.93 (s, 1 H), 5.12 (m, 1 H), 5.17 (ddd, *J* = 14.5, 9.9, 4.6 Hz, 1 H), 7.44–7.48 (m, 4 H), 7.56–7.59 (m, 2 H), 8.03–8.05 (m, 2 H), 8.09–8.11 (m, 2 H).

^{13}C NMR (DEPT, 125 MHz, $CDCl_3$): δ = 17.85 (CH_3), 18.86 (CH_3), 29.66 (CH_2), 29.95 (CH_3), 30.82 (CH_2), 39.65 (CH_2), 67.11 (CH), 70.53 (CH), 71.06 (CH), 71.44 (CH), 93.55 (CH), 128.44 (4 CH), 129.61 (2 CH), 129.75 (C), 129.85 (2 CH), 129.92 (C), 133.21 (CH), 133.28 (CH), 165.64 (C=O), 165.78 (C=O), 208.42 (C=O).

MS (ESI): *m*/*z* = 339.1 [(M – $C_6H_{11}O_2$)$^+$], 472.1 [(M + NH_4)$^+$], 477.2 [(M + Na)$^+$].

(–)-(5*R*)-5-(3,6-Dideoxy-α-L-*arabino*-hexopyranosyl)hexan-2-one (2)

A 1 M soln KOH in MeOH (11 mL) was added to **14** (520 mg, 1.14 mmol) and the resulting mixture was stirred at r.t. for 3 h. After addition of solid $NaHCO_3$ (370 mg), the solvent was evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 12:1) to afford the ascaroside **2** as a colourless oil; yield: 280 mg (99%).

$[\alpha]_D^{23}$ –68.0 (*c* 1.17, CH_2Cl_2) [Lit.[8a] $[\alpha]_D^{23}$ –78.4 (*c* 1.2, CH_2Cl_2)].

IR (ATR): 3405, 2969, 2930, 1709, 1652, 1376, 1261, 1202, 1126, 1099, 1024, 982, 950, 882, 852, 838, 782, 734 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 1.13 (d, *J* = 6.1 Hz, 3 H), 1.21 (d, *J* = 5.8 Hz, 3 H), 1.68–1.82 (m, 3 H), 1.97 (dt, *J* = 13.0, 3.1 Hz, 1 H), 2.14 (s, 3 H), 2.62 (t, *J* = 7.4 Hz, 2 H), 3.56–3.61 (m, 2 H), 3.73 (m, 1 H), 3.79–3.83 (m, 1 H), 4.66 (s, 1 H).

^{1}H NMR (600 MHz, CD_3OD): δ = 1.20 (d, *J* = 6.1 Hz, 3 H), 1.29 (d, *J* = 6.0 Hz, 3 H), 1.75–1.88 (m, 3 H), 2.02 (ddt, *J* = 13.1, 0.6, 3.4 Hz, 1 H), 2.23 (s, 3 H), 2.69 (dt, *J* = 2.5, 7.4 Hz, 2 H), 3.59 (ddd, *J* = 11.0, 9.4, 4.4 Hz, 1 H), 3.63 (dq, *J* = 9.4, 6.0 Hz, 1 H), 3.78 (m, 1 H), 3.84–3.88 (m, 1 H), 4.71 (s, 1 H).

^{13}C NMR (DEPT, 125 MHz, acetone-d_6): δ = 18.22 (CH_3), 19.10 (CH_3), 29.74 (CH_3), 31.80 (CH_2), 36.36 (CH_2), 39.94 (CH_2), 67.68 (CH), 69.44 (CH), 70.48 (CH), 70.92 (CH), 97.00 (CH), 207.88 (C=O).

^{13}C NMR (DEPT, 150 MHz, CD_3OD): δ = 18.06 (CH_3), 19.08 (CH_3), 29.85 (CH_3), 32.10 (CH_2), 35.96 (CH_2), 40.44 (CH_2), 68.28 (CH), 69.85 (CH), 71.29 (CH), 71.51 (CH), 97.32 (CH), 211.45 (C=O).

MS (ESI): *m*/*z* = 247.2 [(M + H)$^+$], 264.1 [(M + NH_4)$^+$], 269.1 [(M + Na)$^+$].

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