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Azedaralide: total synthesis, relative and absolute stereochemical assignment

Luke A. Baker,[a] Craig M. Williams,[a,*] Paul V. Bernhardt[a] and Gary W. Yanik[b]

[a]*School of Molecular and Microbial Sciences, University of Queensland, Brisbane, 4072 Queensland, Australia*
[b]*PDR-Chiral Inc., 1331A South Killian Drive, Lake Park, FL 33403, USA*

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Abstract—Azedaralide, a potentially advanced intermediate for the total synthesis of various tetranortriterpenes, was constructed utilising the Fernández-Mateos protocol and assigned both relative and absolute stereochemistries. Both asymmetric aldol and classical chiral resolution attempts failed to deliver pure enantiomers whereas preparative chiral chromatography resolved racemic azedaralide with ease.

1. Introduction

Azedaralide **1**, isolated from *Melia azedarach* (1.7 mg from 1.5 kg root bark) by Nakatani et al.,[1] displays antifeedant and ichthyotoxic properties, and is to date the only δ-lactone degraded limonoid isolated from *M. azedarach*.[1] In addition, azedaralide **1** appears to have the required connectivity to act as an advanced intermediate for total syntheses studies of the tetranortriterpenes (limonoids) andirobin **2** and mexicanolide **3** (Fig. 1).[2] In this regard two distinctly different approaches to viable quantities of azedaralide **1** were investigated, the results of which are described herein.

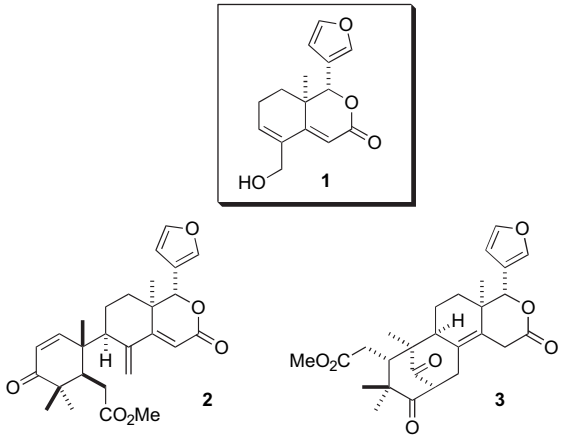

Figure 1.

2. Results and discussion

Due to the large amount of work already conducted on the total synthesis of *dl*-pyroangolensolide[3–7] **4**, the most simplistic, yet logically direct approach to azedaralide **1**, that being exocyclic allylic oxidation was examined in the first instance. Numerous methods to effect allylic oxidation were exhaustively investigated, for example, SeO_2/*t*-BuO_2H,[8] $Pd(OAc)_2$[9] and $Hg(OAc)_2$,[10] but in all cases these procedures provided epoxide **5** and/or starting material **4**. However, selenium dioxide or selenious acid in dioxane[11] afforded azedaralide **1**[12] in 17% yield along with the corresponding aldehyde **6** (28%), resulting from over oxidation (Fig. 2).

Although access to **1** using the selenium dioxide protocol was rapid, the disappointing yield and purity indicated that an alternative strategy was required. Of the procedures

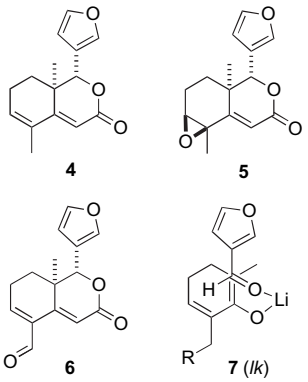

Figure 2.

* Corresponding author. Tel.: +61 7 3365 3530; fax: +61 7 3365 4299; e-mail: c.williams3@uq.edu.au

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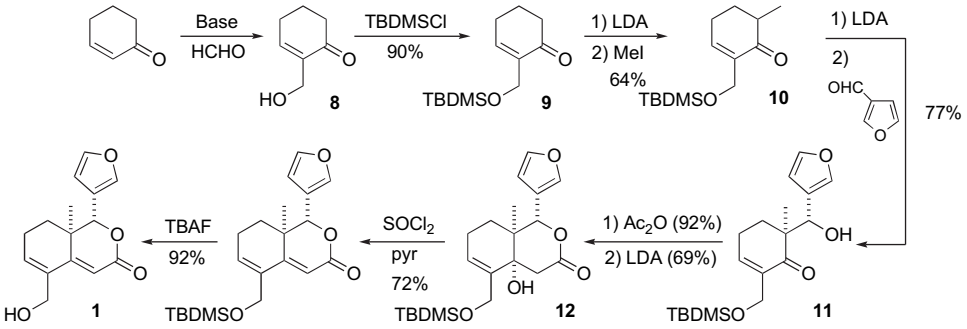

Scheme 1.

available for the construction of *dl*-pyroangolensolide[3–7] **4**, Fernández-Mateos[7] maintains an unrivalled sequence (stereospecific, four steps, 62% overall yield). On closer inspection of the proposed transition state[13] [*lk* approach, **7** (R=H)] the allylic methyl group seems not to play a role in the stereochemical outcome of the reaction, hence, additional functionality, for example, an ether unit (**7**, R=OR′) should be easily accommodated without transition state disruption (Fig. 2).

Installation of the oxygen functionality was best achieved using the El Gaïed (DMAP or imidazole)[14] Baylis–Hillman variants (Scheme 1). Alcohol **8** was then protected as a *t*-BDMS ether (i.e., **9**) (90%) and methylated (i.e., **10**) (64%). The Fernández-Mateos stereospecific aldol proceeded without incident, as predicted, giving **11** in 77% yield, which was routinely acetylated (92%) and cyclised affording the hydroxylactone **12** (69%). Elimination (72%) and deprotection (92%) revealed azedaralide **1** [19% overall yield, eight steps], as confirmed by X-ray crystal structure analysis of the racemate (Fig. 3).

In an attempt to introduce asymmetry into the racemic sequence seen in Scheme 1, both asymmetric aldol and classical chiral resolution type protocols were investigated. For example, asymmetric aldol reactions with **10** and 3-furaldehyde failed (e.g., DIP-Cl[15]), and difficulties were also encountered in converting **10** into the SAMP derivative.[16] Classical chiral resolution using covalent chiral auxiliaries was attempted by converting **11** to the (–)-menthoxy acetate

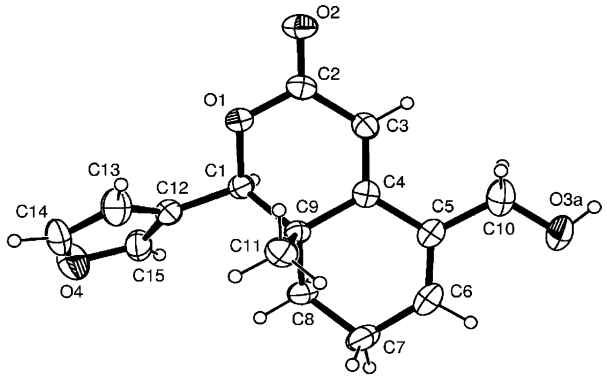

Figure 3. ORTEP3 view of **1** crystallised as a racemate (30% probability ellipsoids).

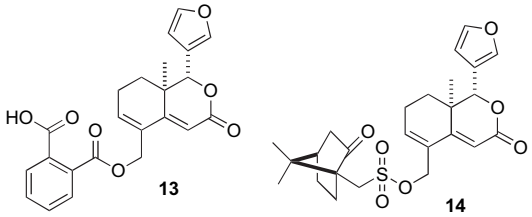

Figure 4.

and (+)-Mosher's ester[17] derivatives. Although the diastereomers could be easily seen by NMR analysis separation was not achieved. Non-covalent methods, for example, treating the phthalate derivative **13** with α-methylbenzylamine[18] (and brucine) did not yield crystals (Fig. 4). Lipases, both acetylase (lipase PS) and deacetylase (lipase PS)[19,20] protocols failed to react with either the alcohol **11** or corresponding acetate.

Preparative chiral chromatography on the other hand completely resolved the mixture of azedaralide enantiomers. This task including transpacific transportation required only days in comparison to months investigating failed asymmetric and classical protocols described above. The (+)-enantiomer was then converted to the crystalline sulfonate **14** (Fig. 4) using 1*S*-(+)-10-camphorsulfonyl chloride,[21] which gave the X-ray crystal structure shown in Figure 5. Considering the predetermined absolute stereochemistry of the camphorsulfonyl chloride [via the sulfonic acid (*R*,*S*)] the absolute stereochemistry of the (+)-enantiomer, as demonstrated in the X-ray crystal structure, must be *R*,*R*. The (+)-enantiomer has a rotation of +385.0, which is at variance with that reported rotation (+165)[1] for the isolated natural product. Considering that only 1.7 mg of the isolated natural product were obtained and that the ^{1}H NMR of the material revealed impurities,[12] we are inclined to accept our optical rotation value as more accurate.

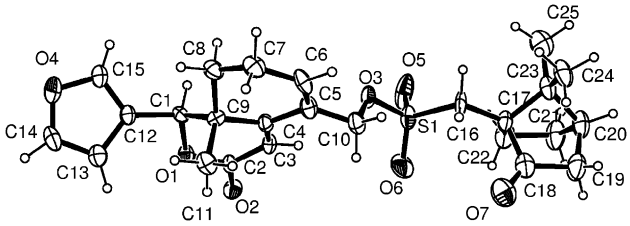

Figure 5. ORTEP3 view of **14** (30% probability ellipsoids shown).

3. Conclusion

In conclusion, capitalising on the ingenious stereospecific Fernández-Mateos protocol has allowed a direct synthesis of azedaralide **1** in viable quantities. Furthermore, the current sequence (eight steps, 19% overall yield) is a near 70 fold improvement in overall yield on the only tetranortriterpene advanced intermediate **15** reported[5] so far (15 steps, 0.27% overall yield) (Fig. 6). Chiral chromatography in conjunction with X-ray crystal structure analysis was paramount for elucidating and confirming Nakatani's proposed configuration of azedaralide **1**.

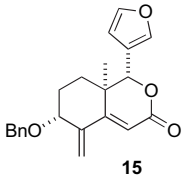

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Figure 6.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV400 (400.13 MHz; 100.62 MHz), AV300 (300.13 MHz; 75.47 MHz) and DRX (or AV) 500 (500.13 MHz; 125.77 MHz) instruments in deuteriochloroform ($CDCl_3$). Coupling constants are given in Hertz and chemical shifts are expressed as δ values in parts per million. High and low resolution EI mass spectral data were obtained on a KRATOS MS 25 RFA. Electrospray mass spectrometry was performed on a Finnigan MAT 900 XL-Trap. Microanalyses were performed by the University of Queensland Microanalytical Service. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Chiral chromatography was performed on a Berger Multigram SFC (Mettler–Toledo) using a Chiralpak AS-H-SFC column 2.1 dia×25 cm long (Chiral Technologies) and a K-2501 UV detector (Knauer) with an eluent mixture of CO_2/MeOH 80/20 flowing at 25 mL/min. Injection, detection and collection were controlled by AutoPrep software (PDR-Chiral). IR spectra were obtained on a Perkin Elmer FTIR Spectrometer, Spectrum 2000.

4.2. X-ray crystallography

Data for all compounds were collected at 293 K on an Enraf–Nonius CAD4 diffractometer. Data reduction, direct methods structure solution and full least squares refinement (SHELX97[22]) were performed with the WINGX package.[23] Drawings of all molecules were created with ORTEP3.[24] Data in CIF format have been deposited with the Cambridge Crystallographic Data Centre (CCDC deposition numbers 601060 and 601061). Copies of the data can be obtained free of charge upon request to deposit@ccdc.cam.ac.uk.

4.2.1. Reaction of pyroangolensolide 4 with selenium dioxide. *dl*-Pyroangolensolide **4** (500 mg, 2.05 mmol) and freshly sublimed selenium dioxide (341 mg, 3.07 mmol) were heated at reflux in 1,4-dioxane (34 mL) for 20 h. A colour change from pale yellow to dark brown was observed after 5–10 min. On cooling the solvent was removed under high vacuum and the residue was redissolved in dichloromethane and filtered. The filtrate was washed with 2 M hydrochloric acid, water and brine followed by drying (Na_2SO_4) and evaporation in vacuo. The residue was then reacted under the same conditions as above and after work up was subjected to column chromatography (2:1 diethyl ether/petroleum spirit) which afforded two fractions.

Fraction 1 afforded aldehyde **6** (148 mg, 28%) as white crystals. mp 147–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (s, 3H), 1.42–1.51 (m, 1H), 1.56–1.62 (m, 1H), 2.47–2.58 (m, 1H), 2.62–2.75 (m, 1H), 5.14 (s, 1H), 6.43–6.44 (m, 1H), 7.17–7.19 (m, 1H), 7.21 (s, 1H), 7.41–7.42 (m, 1H), 7.46–7.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 23.5, 29.1, 36.9, 80.2, 109.9, 115.1, 120.0, 133.1, 141.2, 143.1, 151.4, 158.4, 165.1, 191.7; MS (EI) *m*/*z* (%): 258 ($M^{+\bullet}$, 2), 214 (1), 178 (1), 162 (100), 147 (14), 134 (27), 119 (21), 105 (16), 91 (25). Anal. Calcd for $C_{15}H_{14}O_4$: C, 70.03; H, 5.09. Found: C, 70.08; H, 5.45%.

Fraction 2 afforded azedaralide **1**, which contained an unidentified impurity (<10%) (92 mg, 17%). Characterisation data below.

4.2.2. 2-[(*tert*-Butyldimethylsilyloxy)methyl]-2-cyclohexenone 9. 2-Hydroxymethyl-2-cyclohexenone **8** (5 g, 40.32 mmol) was dissolved in anhydrous dichloromethane (100 mL) and anhydrous triethylamine (13.25 mL) under an argon atmosphere. To this was added in one portion, *tert*-butyldimethylsilyl chloride (7.17 g, 47.56 mmol) and the mixture was allowed to stir for 24 h at room temperature. The reaction mixture was poured into a separatory funnel containing saturated sodium hydrogen carbonate (25 mL), and the organic layer partitioned. The aqueous layer was extracted with dichloromethane (3×30 mL) and the combined organic phases were washed with water, dried (Na_2SO_4), evaporated and the residue subjected to column chromatography (2:1 petroleum spirit/diethyl ether), yielding the titled compound **9** as a pale yellow oil (8.56 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.05 (s, 6H), 0.90 (s, 9H), 1.98 (p, J=6.3 Hz, 2H), 2.37–2.41 (m, 4H), 4.33 (AB, 2H), 6.97–6.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.5, −3.6, 18.3, 22.9, 25.55, 25.6, 25.9, 38.3, 60.0, 138.3, 143.9, 199.0; Near IR (Neat) ν (cm^{-1}) 1671, 1461, 1399; MS (EI) *m*/*z* (%): 240 ($M^{+\bullet}$, 1), 225 (4), 193 (3), 183 (100), 167 (1), 151 (9), 142 (1), 127 (2), 117 (1), 109 (1), 101 (1), 91 (3); HRMS calcd for $C_{13}H_{24}O_2Si$ 240.1545, Found 240.1548.

4.2.3. 2-[(*tert*-Butyldimethylsilyloxy)methyl]-6-methyl-2-cyclohexenone 10. To a cold (0 °C) stirring solution of diisopropylamine (6.16 mL, 43.7 mmol) in anhydrous tetrahydrofuran (50 mL) under an argon atmosphere, was added *n*-butyl lithium (1 M in hexanes, 31.5 mL, 41.6 mmol) over a period of 10 min. After a further 45 min, 2-[(*tert*-butyldimethylsilyloxy)methyl]-2-cyclohexenone **9** (10 g, 41.6 mmol) in tetrahydrofuran (50 mL) was added dropwise via

cannula. The reaction was stirred at 0 °C for a further 60 min, before dropwise addition of iodomethane (7.8 mL, 125 mmol). Saturated sodium hydrogen carbonate (40 mL) was added to the cold solution after 30 min, and the suspension was allowed to warm to room temperature (2 h). Extraction with petroleum spirit (4×100 mL), followed by washing with brine, drying (Na_2SO_4) and evaporation resulted in an oily residue. Column chromatography (5:1 petroleum spirit/diethyl ether) afforded **10** as an orange-brown oil (6.8 g, 64%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.05 (s, 6H), 0.90 (s, 9H), 1.11 (d, J=6.83 Hz, 3H), 1.66–1.74 (m, 1H), 2.00–2.06 (m, 1H), 2.37–2.41 (m, 2H), 4.29–4.35 (m, 2H), 6.91–6.92 (br m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.4, 1.0, 15.0, 18.4, 25.0, 25.9, 29.7, 31.0, 41.7, 60.2, 137.7, 143.0, 201.6; MS (EI) m/z (%): 254 ($M^{+\bullet}$, 1), 239 (4), 225 (5), 211 (2), 207 (6), 197 (99), 193 (6), 183 (100), 167 (6), 155 (7), 153 (9), 151 (12), 127 (5), 117 (2), 105 (7), 91 (8); HRMS calcd for $C_{14}H_{26}O_2Si$ 254.1702, Found 254.1699.

4.2.4. 2-[(*tert*-Butyldimethylsilyloxy)methyl]-6-[(furan-3-yl)hydroxymethyl]-6-methyl-2-cyclohexenone 11. To a stirred solution of diisopropylamine (5 mL, 35.7 mmol) in anhydrous tetrahydrofuran (100 mL) at 0 °C under an argon atmosphere, was added *n*-butyl lithium (1.32 M in hexanes, 25.8 mL, 34.1 mmol) dropwise over a period of 5 min. After 25 min at 0 °C, the solution was cooled to −78 °C and a solution of 2-[(*tert*-butyldimethylsilyloxy)methyl]-6-methyl-2-cyclohexenone **10** (5 g, 19.7 mmol) in anhydrous tetrahydrofuran (25 mL) was added via cannula (3 min). The reaction was stirred for 3 h at −78 °C before quenching with saturated ammonium chloride solution (30 mL) and slow warming to room temperature (12 h). The organic layer was partitioned and the aqueous layer extracted with dichloromethane (4×50 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. Column chromatography of the residue (5:1 petroleum spirit/diethyl ether) afforded the desired product **11** as a pale yellow oil (5.3 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.90 (s, 9H), 1.17 (s, 3H), 1.49–1.53 (m, 1H), 1.69–1.75 (m, 1H), 2.37–2.41 (br m, 2H), 4.25–4.39 (m, 2H), 4.89 (s, 1H), 6.36 (s, 1H), 6.97 (br s, 1H), 7.35 (d, J=1.5 Hz, 1H), 7.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.5, 14.5, 18.3, 22.3, 25.9, 31.1, 47.5, 60.1, 71.5, 110.1, 123.9, 136.6, 140.5, 142.5, 144.1, 206.2; Near IR (Neat) ν (cm^{-1}) 3444, 1651, 1503, 1461; HRMS ESI calcd for $C_{19}H_{30}O_4NaSi$ 373.1811, Found 373.1809.

4.2.5. 2-[(*tert*-Butyldimethylsilyloxy)methyl]-6-[(furan-3-yl)acetoxymethyl]-6-methyl-2-cyclohexenone. Acetic anhydride (8.7 mL) was added dropwise to a cold (0 °C) solution of **11** (2.5 g, 7.14 mmol) in pyridine (8.7 mL) under an argon atmosphere. The cold bath was removed and stirring continued at room temperature for 4 h, followed by addition of iced water (20 mL). On warming to room temperature, the mixture was transferred to a separatory funnel and extracted with dichloromethane (4×20 mL). The combined extracts were washed successively with sodium hydrogen carbonate, water and brine, dried (Na_2SO_4) and evaporated. Excess pyridine was removed in vacuo prior to column chromatography (2:1 petroleum spirit/diethyl ether) affording the titled compound as a yellow oil (2.59 g, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.05 (s, 6H), 0.89 (s, 9H), 1.16 (s, 3H), 1.79–1.91 (m, 2H), 2.05 (s, 3H), 2.39 (br s, 2H), 4.21–4.32 (m, 2H), 6.28 (s, 1H), 6.33 (s, 1H), 6.87 (br s, 1H), 7.28 (s, 1H), 7.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.53, −5.49, 18.3, 18.6, 20.9, 22.1, 25.9, 29.2, 48.9, 60.1, 71.6, 110.1, 122.2, 137.0, 140.6, 142.0, 142.5, 169.7, 200.4; HRMS calcd for $C_{21}H_{32}O_5NaSi$ 415.1916, Found 415.1923.

4.2.6. 5-[(*tert*-Butyldimethylsilyloxy)methyl]-1-(furan-3-yl)-4a-hydroxy-8a-methyl-4,4a,8,8a-tetrahydro-1*H*-isochromen-3(7*H*)-one 12. To a stirred solution of diisopropylamine (8.67 mL, 6.18 mmol) in anhydrous tetrahydrofuran (15 mL) at 0 °C under an argon atmosphere, was added *n*-butyl lithium (1.32 M in hexanes, 4.46 mL) dropwise over a period of 4 min. After 30 min at 0 °C, the solution was cooled to −78 °C and a solution of 2-[(*tert*-butyldimethylsilyloxy)methyl]-6-[(furan-3-yl)-acetoxymethyl]-6-methyl-2-cyclohexenone (2 g, 5.10 mmol) in tetrahydrofuran (15 mL) was added dropwise. The reaction was stirred at −78 °C for 5 h, before quenching with saturated ammonium chloride solution (15 mL). After warming to room temperature (12 h), the mixture was transferred to a separatory funnel, extracted with dichloromethane (4×20 mL) and washed successively with water and brine. The extracts were then dried (Na_2SO_4), evaporated and subjected to column chromatography (2:1 diethyl ether/petroleum spirit) affording the titled compound **12** (1.37 g, 69%) as a white, crystalline solid.

Mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.01 (s, 3H), 1.31–1.36 (m, 1H), 1.88–1.93 (m, 1H), 2.09–2.16 (m, 2H), 3.02 (AB, 2H), 3.69 (br s, 1H), 4.10 (d, J=11.6 Hz, 1H), 4.47 (d, J=11.6 Hz, 1H), 5.21 (s, 1H), 5.87 (br s, 1H), 6.43 (s, 1H), 7.40 (d, J=1.6 Hz, 1H), 7.43 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.57, −5.58, 15.0, 18.0, 21.8, 25.8, 27.3, 39.5, 39.9, 66.4, 71.5, 77.7, 109.8, 121.2, 128.5, 137.0, 140.6, 143.0, 170.3; HRMS calcd for $C_{21}H_{32}O_5NaSi$ 415.1916, Found 415.1919.

4.2.7. 5-[(*tert*-Butyldimethylsilyloxy)methyl]-1-(furan-3-yl)-8a-methyl-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one. To a solution of **12** (1.00 g, 2.55 mmol) in anhydrous dichloromethane (15 mL), was added anhydrous pyridine (825 μL, 10.2 mmol) under an argon atmosphere. The reaction flask was cooled in an ice-bath, and thionyl chloride (372 μL, 5.10 mmol) added dropwise. After 20 min, water (10 mL) was added and the mixture was allowed to warm to room temperature over 1 h. The reaction mixture was extracted with dichloromethane (2×30 ml), washed with saturated sodium hydrogen carbonate and brine then dried (Na_2SO_4). Evaporation followed by column chromatography of the residue (1:1 petroleum spirit/diethyl ether) gave the titled compound as a white, crystalline solid (690 mg, 72%).

Mp 93.5–94.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.07 (s, 6H), 0.90 (s, 9H), 1.01 (s, 3H), 1.41–1.50 (m, 2H), 2.28–2.37 (m, 2H), 4.30 (AB, 2H), 5.11 (s, 1H), 5.79 (s, 1H),

6.43 (br s, 2H), 7.40 (d, J=1.5 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.38, −5.35, 15.9, 18.3, 22.0, 25.9, 29.9, 37.1, 62.4, 80.7, 109.3, 110.1, 120.2, 132.2, 134.7, 141.1, 142.9, 157.3, 165.8; Near IR (Neat) ν (cm^{-1}) 1704, 1635, 1597; HRMS calcd for $C_{21}H_{30}O_4NaSi$ 397.1811, Found 397.1817; Anal. Calcd for $C_{21}H_{30}O_4Si$: C, 67.34; H, 8.07. Found: C, 67.37; H, 8.26%.

4.2.8. 1-(Furan-3-yl)-5-hydroxymethyl-8a-methyl-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one (azedaralide) 1. Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 2.67 mL, 2.67 mmol) was added dropwise to a 0 °C solution of 5-[(*tert*-butyldimethylsilyloxy)methyl]-1-(furan-3-yl)-8a-methyl-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one (500 mg, 1.34 mmol) in anhydrous tetrahydrofuran (25 mL). The solution was stirred at this temperature for 20 min, before dilution with ethyl acetate (10 mL) and hydrochloric acid (1 M, 10 mL). The reaction was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with brine (40 mL) and dried (Na_2SO_4). Evaporation and column chromatography of the residue (diethyl ether) afforded azedaralide (**1**) as a pale yellow, crystalline solid (320 mg, 92%). After chiral chromatography (+)-azedaralide $[\alpha]_D$ +385.0 (*c* 1.59, MeOH) and (−)-azedaralide $[\alpha]_D$ −391.9 (*c* 1.47, MeOH) at 27 °C.

Mp 108–108.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.02 (s, 3H), 1.41–1.51 (m, 3H), 2.25–2.39 (m, 2H), 4.33 (q, J=12.8 Hz, 2H), 5.13 (s, 1H), 5.94 (s, 1H), 6.43 (br s, 1H), 7.41 (t, J=1.5 Hz, 1H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.0, 22.0, 29.7, 37.1, 62.8, 80.7, 110.0, 110.2, 120.1, 132.5, 136.7, 141.2, 143.0, 157.3, 165.8; MS (EI) *m/z* (%): 260 ($M^{+\bullet}$, 2), 216 (1), 183 (2), 173 (2), 164 (100), 149 (15), 135 (3), 119 (38), 105 (11), 99 (13), 91 (14); Near IR [(+)-azedaralide] (Neat) ν (cm^{-1}) 3429, 1676, 1629, 1591; HRMS calcd for $C_{15}H_{16}O_4$ 260.1049, Found 260.1050; Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.37; H, 6.32%.

4.2.9. [(1*R*,8a*R*)-1-(furan-3-yl)-8a-methyl-3-oxo-3,7,8,8a-tetrahydro-1*H*-isochromen-5-yl]methyl (1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl methanesulfonate 14. (+)-Azedaralide (20 mg, 0.077 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) under an atmosphere of argon. Anhydrous triethylamine (25 μL, 0.18 mmol) was added and the reaction vessel cooled in an ice-bath, prior to dropwise addition of (+)-camphorsulfonyl chloride (29 mg, 0.12 mmol). The solution was then allowed to warm slowly to room temperature. After 21 h the solvent was removed in vacuo, and the residue taken up into dichloromethane (10 mL), before washing with hydrochloric acid (2 M), and water. The organic phase was dried (Na_2SO_4), and evaporated. The residue was subjected to column chromatography (diethyl ether) to yield the desired sulfonate (32 mg, 88%) as an amorphous solid, which was recrystallised (ethyl acetate) affording white needles. $[\alpha]_D$ +260.1 (*c* 1.45, $CDCl_3$) at 27 °C.

Mp 160.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (s, 3H), 1.03 (s, 3H), 1.09 (s, 3H), 1.43–1.50 (m, 3H), 1.60–1.65 (m, 1H), 1.92–2.12 (m, 3H), 2.34–2.44 (m, 4H), 3.01 (d, 1H, J=15 Hz), 3.57 (dd, 1H, J=15, 1 Hz), 4.93 (AB, m, 2H), 5.14 (s, 1H), 5.95 (s, 1H), 6.43 (s, 1H), 6.59–6.60 (m, 1H), 7.41–7.42 (m, 1H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 19.7, 19.8, 22.4, 24.9, 26.9, 29.3, 37.2, 42.5, 42.7, 48.0, 48.1, 58.0, 69.4, 80.5, 110.0, 111.3, 119.9, 127.8, 141.2, 142.5, 143.0, 156.0, 165.1, 214.5; MS (EI) *m/z* (%): 474 ($M^{+\bullet}$, 2), 410 (1), 378 (1), 294 (1), 260 (9), 242 (3), 215 (15), 178 (3), 164 (85), 146 (46), 118 (100), 109 (34), 91 (29); HRMS calcd for $C_{25}H_{33}O_7S$ 474.1712, Found 474.1712.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.030.

References and notes

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12. The ^{1}H NMR spectrum of azedaralide **1** provided by M. Nakatani, et al.[1] is identical in all respects to our data. The ^{13}C NMR spectrum is in slight disagreement; we observed an additional peak at 110.0 ppm, whereas M. Nakatani, et al.[1] reports overlapping peaks at 157.2 ppm. A visual comparison of the ^{1}H NMR spectra can be made from the supporting information.

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