Enantiospecific synthesis of (−)-trachyspic acid

Steven C. Zammit, Jonathan M. White and Mark A. Rizzacasa*

School of Chemistry, Bio21 Institute, 30 Flemington Rd, The University of Melbourne, 3010, Victoria, Australia. E-mail: masr@unimelb.edu.au; Fax: 61 3 9347 8396; Tel: 61 3 8344 2397

The enantiospecific synthesis of (−)-trachyspic acid (1) is presented. This has allowed for the assignment of the absolute configuration of natural (+)-trachyspic acid as 3*S*,4*S*,6*S*.

In the course of screening for heparanase inhibitors, a new metabolite named trachyspic acid (**1**) (Fig. 1) was isolated from the culture broth of *Talaromyces trachyspermus*.[1] Trachyspic acid inhibited heparananse with an IC_{50} of 36 μM and its structure was deduced by NMR techniques and chemical analysis.[1] Recently, Hatakeyama and coworkers[2] reported a synthesis of (±)-**1** which served to confirm the relative configuration. Herein, we report the first enantiospecific synthesis of (−)-**1** which allowed for the determination of the absolute configuration of this natural product.
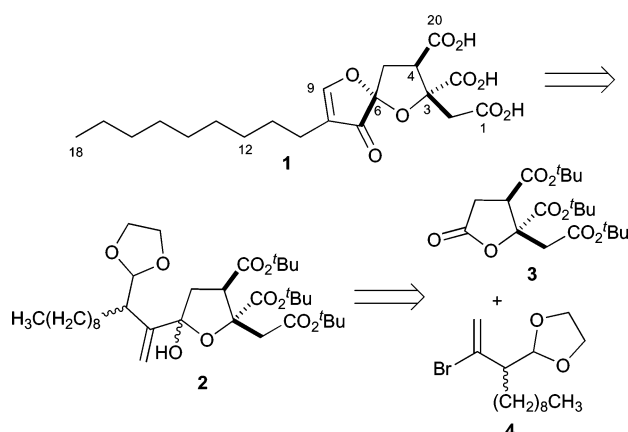

Fig. 1 Retrosynthetic analysis of trachyspic acid.

Our approach to trachyspic acid (**1**) is shown in Fig. 1. We envisaged that **1** could be secured from intermediate acetal **2** by acid induced deprotection–spiroketalisation followed by oxidative alkene cleavage and elimination in a manner similar to that utilised for the synthesis of racemic **1**.[2] Compound **2** in turn could be synthesised *via* addition of the anion derived from vinyl bromide **4** to the chiral lactone **3**.

The synthesis of key chiral lactone **3** is outlined in Scheme 1. The D-deoxyribose derived alcohol **5**[3] was oxidised[4] in one step to the acid and esterification with allyl alcohol provided ester **6**. Ireland–Claisen rearrangement of ester **6** under conditions previously described by us[5] proceeded in a stereoselective manner (ds > 95%) without any β-elimination to afford *tert*-butyl ester **7** in good yield after esterification[6] following the rearrangement. The stereochemistry of **7** was confirmed by an NOE observed between the H4 and H2 protons (numbering as for **1**). Acetal hydrolysis followed by oxidation afforded lactone **8** which upon PMB group removal and elimination gave α,β-unsaturated lactone **9**. Conjugate addition afforded alkenes **10** and **11** in a good yield but with poor stereoselectivity. The stereochemistry of isomer **11** was assigned on the basis of a single crystal X-ray structure (Fig. 2)† determined on the derived tri-*tert*-butyl ester **3** (see below). It should be noted that at the
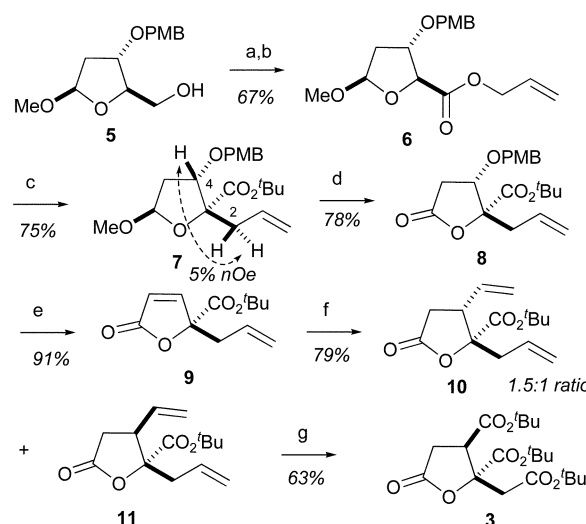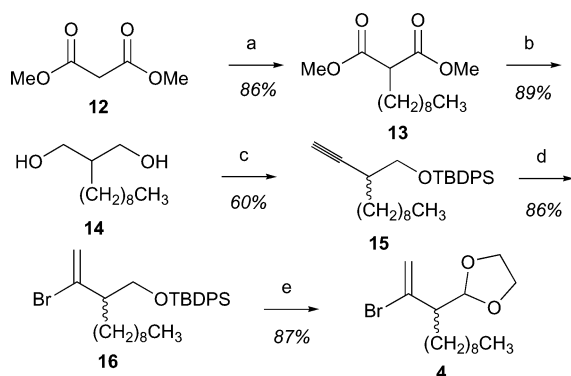

Scheme 1 *Reagents and conditions*: (a) NaOCl, $NaClO_2$, TEMPO; (b) DCC, DMAP, allyl alcohol; (c) (i) TMSCl/NEt₃, LDA, THF/HMPA, −95 °C; (ii) aq. NaOH; (iii) *N*,*N'*-diisopropyl-*O-tert*-butylisourea; (d) (i) 10% HCl; (ii) PCC; (e) (i) DDQ; (ii) MsCl, pyridine; (f) CuI, vinylMgBr, DMS, −45 °C; (g) (i) O₃, DMS; (ii) $NaClO_2$, NaH_2PO_4; (iii) *N*,*N'*-diisopropyl-*O-tert*-butylisourea.
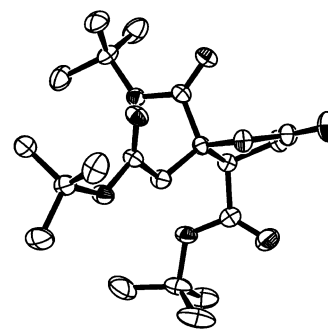
**Fig. 2** X-Ray structure of lactone **3**.

inception of this study, the relative configuration between C3 and C4 of **1** was not confirmed so access to both diastereoisomers was desirable. In any event, the correct isomer **11** was subjected to ozonolysis and subsequent oxidation and protection to yield the required lactone fragment **3**.

The bromide fragment **4** was synthesised as outlined in Scheme 2. Alkylation of the anion derived from dimethyl malonate (**12**) with nonyl bromide produced diester **13** which was reduced to diol **14** in excellent yield. Monoprotection and alkyne homologation using the Corey–Fuchs protocol[7] afforded alkyne **15**. Bromoboration and acid induced deboronation[8] gave vinyl bromide **16** which was deprotected, oxidised and converted into the dioxolane fragment **4**.

The final steps to (−)-trachyspic acid (**1**) are detailed in Scheme 3. Treatment of the vinyl bromide **4** with *t*-BuLi resulted in halogen–metal exchange[9] and the resultant anion added selectively to the lactone carbonyl group in compound **3** to

Scheme 2 *Reagents and conditions*: (a) NaOMe, nonyl bromide, MeOH, reflux; (b) LiAlH$_4$, 0 °C; (c) (i) NaH, TBDPSCl; (ii) Dess Martin reagent; (iii) PPh$_3$, CBr$_4$, 0 °C; (iv) BuLi, −78 °C; (d) *B*-Br-9-BBN, AcOH, 0 °C; (e) (i) TBAF; (ii) Dess Martin reagent; (iii) *p*-TsOH, HOCH$_2$CH$_2$OH, benzene, reflux.
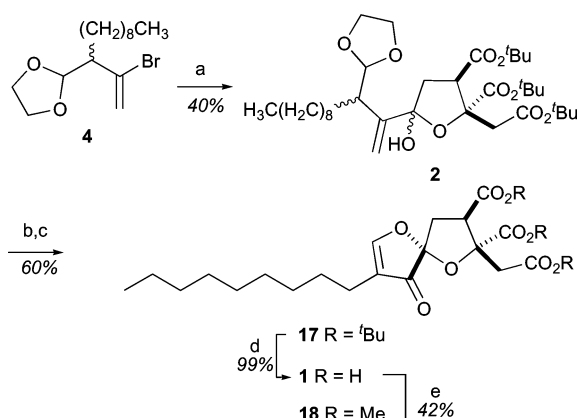
Scheme 3 *Reagents and conditions*: (a) *t*-BuLi, Et$_2$O–hexane, −78 °C then lactone **3**; (b) 3M HClO$_4$, THF; (c) (i) Ac$_2$O, DMAP, pyridine; (ii) O$_3$, NaHCO$_3$, DMS; (d) TFA, CH$_2$Cl$_2$; (e) CH$_2$N$_2$, Et$_2$O.

provide the acetal **2** as a mixture of isomers at the anomeric centre. Acid induced deprotection of the dioxolane resulted in concomitant spirocyclisation which upon acetylation and subsequent ozonolysis–elimination[2] provided spiroacetal **17** as a ∼4 : 1 mixture of spiroisomers favouring the desired compound **17**. TFA induced deprotection then gave (−)-(3*R*,4*R*,6*R*)-trachyspic acid (**1**) which was identical to natural **1** in all respects except for the sign of optical rotation.‡ Synthetic **1** was also further characterised by conversion into the known trimethyl ester derivative **18**.§ This confirms that natural (+)-trachyspic acid has the absolute configuration opposite to that shown in Fig. 1, namely 3*S*,4*S*,6*S*.

In conclusion, we have achieved an enantiospecific synthesis of the unnatural enantiomer of trachyspic acid, confirming the absolute configuration of this compound. A synthesis of natural

(+)-trachyspic acid using the methodology described herein is underway in our laboratories and will be reported in due course.

Notes and references

† X-Ray data for **3**: C$_{20}$H$_{32}$O$_8$ M = 400.46, T = 295 K, λ = 0.71069 Å, monoclinic, space group $P2_1$, a = 11.267(1), b = 19.608(2), c = 12.035(1) Å, β = 117.463°, V = 2359.2(3) Å^3, Z = 4, D_c = 1.127 Mg m^{-3}, μ(Mo-Kα) 0.086 mm^{-1}, F(000) 864, crystal size 0.5 × 0.25, 0.05 mm. 12556 reflections measured, 6113 independent (R_{int} 0.629) the final wR (F^2 all data) was 0.0979 and final R was 0.0457 for 3200 data with [I > 2σ(I)]. Flack parameter = 0.0(10). CCDC reference number 268561. See http://www.rsc.org/suppdata/ob/b5/b504258e for crystallographic data in cif format.

‡ Data for synthetic (−)-**1**: $[a]_D^{21}$ −3.5 (*c* 0.213, MeOH); $[a]_D^{23}$ −8.4 (*c* 0.350, CH$_2$Cl$_2$); Lit.[1] $[a]_D^{21}$ +3.1 (*c* 1.0, MeOH); ν_{max} (thin film) 3425, 2927, 2856, 1724, 1611, 1370, 1139, 1000 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.84 (t, J = 6.6 Hz, 3H), 1.23 (br s, 12H), 1.39 (m, 2H), 2.02 (t, J = 7.8 Hz, 1H), 2.36 (m, 2H), 2.67 (d, J = 16.8 Hz, 1H), 2.85 (d, J = 16.8 Hz, 1H), 3.56 (dd, J = 7.8, 11.8 Hz, 1H), 8.45 (s, 1H); δ_C (100 MHz, DMSO-d_6) 14.0, 20.5, 22.1, 27.5, 28.6, 28.7, 28.9, 31.3, 37.6, 38.7, 48.4, 86.5, 108.1, 116.7, 170.1, 170.6, 171.3, 174.5, 198.2 HRMS (ESI): Calcd for C$_{20}$H$_{28}$O$_9$H [M + H]$^+$ 413.1812, found 413.1809.

§ Data for triester **18**: $[a]_D^{23}$ −20.4 (*c* 0.130, CH$_2$Cl$_2$); ν_{max} (thin film) 2926, 2854, 1742, 1612, 1367, 1135, 1007 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.84 (t, J = 6.8 Hz, 3H), 1.23 (br s, 12H), 1.38 (m, 2H), 2.02 (t, J = 7.6 Hz, 1H), 2.39 (d, J = 12.8, 13.2 Hz, 1H), 2.47 (dd, J = 7.2, 13.2 Hz, 1H), 2.87 (d, J = 16.8 Hz, 1H), 2.93 (d, J = 16.8 Hz, 1H), 3.55 (s, 3H), 3.64 (s, 3H), 3.70 (s, 3H), 3.80 (dd, J = 7.6, 12.6 Hz, 1H), 8.47 (s, 1H); δ_C (100 MHz, DMSO-d_6) 14.0, 20.5, 22.2, 27.5, 28.7, 28.8, 29.0, 31.4, 37.3, 38.5, 47.7, 51.9, 52.6, 53.0, 86.5, 107.7, 117.0, 169.1, 169.5, 169.8, 174.7, 197.7 HRMS (ESI): Calcd for C$_{23}$H$_{34}$O$_9$Na [M + Na]$^+$ 477.2101, found 477.2093.

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