OBC
www.rsc.org/obc

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

Received 24th March 2005, Accepted 25th April 2005
First published as an Advance Article on the web 6th May 2005

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.

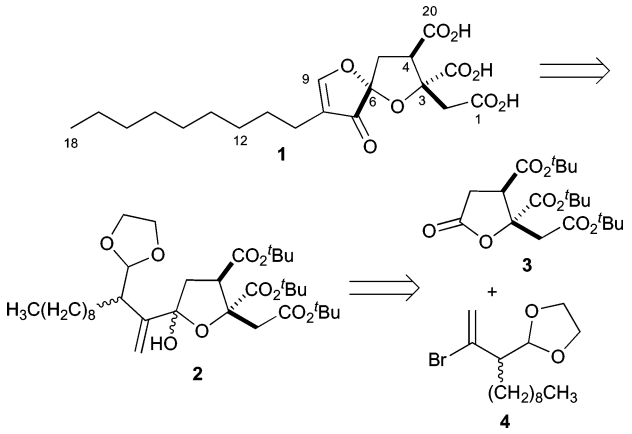
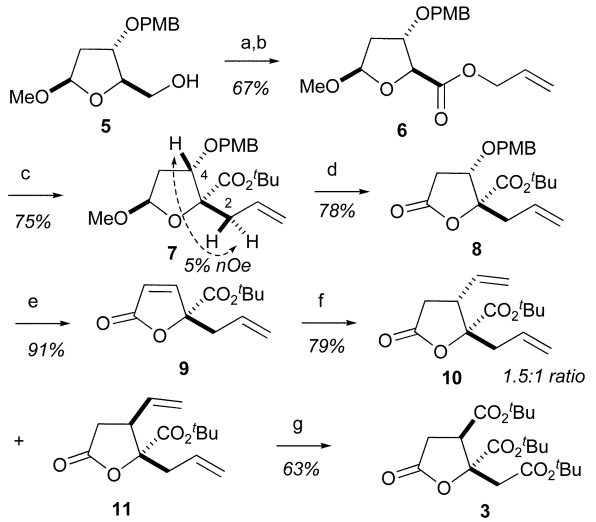


Fig. 1 Retrosynthetic analysis of trachyspic acid.

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) $TMSCl/NEt_3$, 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) O_3, DMS; (ii) $NaClO_2$, NaH_2PO_4; (iii) *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea.

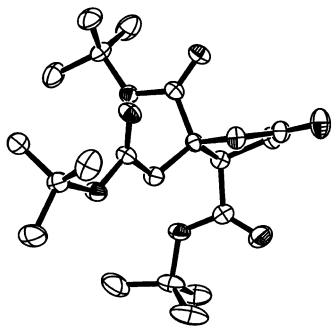


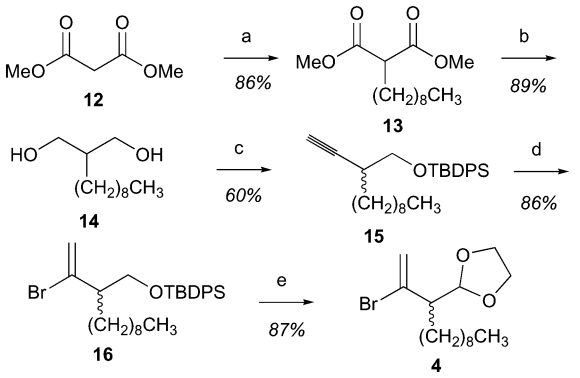
Fig. 2 X-Ray structure of lactone **3**.

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**.

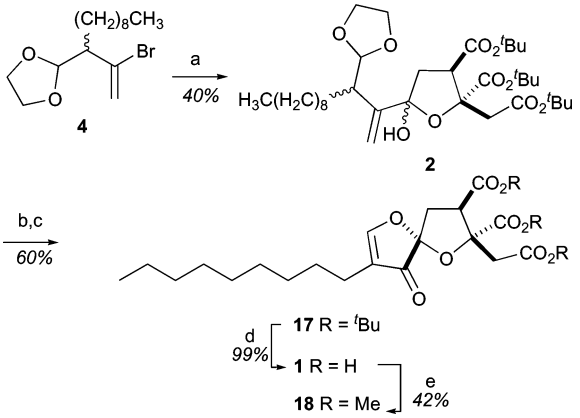
The bromide fragment **4** was synthesised as outlined in Scheme 2. Alkylation of the anion derived from dimethyl malonate (**12**) with nonyl bromide produced diester **13** which was reduced to diol **14** in excellent yield. Monoprotection and alkyne homologation using the Corey–Fuchs protocol[7] 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

DOI:10.1039/b504258e



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, $HOCH_2CH_2OH$, benzene, reflux.



Scheme 3 *Reagents and conditions*: (a) *t*-BuLi, Et_2O–hexane, −78 °C then lactone **3**; (b) 3M $HClO_4$, THF; (c) (i) Ac_2O, DMAP, pyridine; (ii) O_3, $NaHCO_3$, DMS; (d) TFA, CH_2Cl_2; (e) CH_2N_2, Et_2O.

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.

Acknowledgements

We thank Dr Hideyuki Shiozawa (Sankyo Co., Ltd.) for copies of the NMR spectra of natural trachyspic acid (**1**) and trachyspic acid trimethyl ester (**18**). This work was funded by the Australian Research Council-Discovery Projects Grants Scheme.

Notes and references

† X-Ray data for **3**: $C_{20}H_{32}O_8$ $M = 400.46$, $T = 295$ K, $\lambda = 0.71069$ Å, monoclinic, space group $P2_1$, $a = 11.267(1)$, $b = 19.608(2)$, $c = 12.035(1)$ Å, $\beta = 117.463°$, $V = 2359.2(3)$ 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 [$I > 2\sigma(I)$]. 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**: $[\alpha]_D^{21}$ −3.5 (*c* 0.213, MeOH); $[\alpha]_D^{23}$ −8.4 (*c* 0.350, CH_2Cl_2); Lit.[1] $[\alpha]_D^{21}$ +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 $C_{20}H_{28}O_9H$ $[M + H]^+$ 413.1812, found 413.1809.

§ Data for triester **18**: $[\alpha]_D^{23}$ −20.4 (*c* 0.130, CH_2Cl_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 (dd, $J = 12.8$, 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 $C_{23}H_{34}O_9Na$ $[M + Na]^+$ 477.2101, found 477.2093.

1 H. Shiozawa, M. Takahashi, T. Takatsu, T. Kinishita, K. Tanzawa, T. Hosoya, K. Furuya, S. Takahashi, K. Furihata and H. Seto, *J. Antibiot.*, 1995, **48**, 357.
2 K. Hirai, H. Ooi, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *Org. Lett.*, 2003, **5**, 857.
3 Compound **5** was synthesised from D-deoxyribose in an analogous fashion to that described for the corresponding benzyl compound see: R. M. Giuliano and F. J. Villani, Jr., *J. Org. Chem.*, 1995, **60**, 202; T. Suami, K. I. Tadano, Y. Iimura and H. Yokoo, *J. Carbohydr. Chem.*, 1986, **5**, 1.
4 M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski and P. J. Reider, *J. Org. Chem.*, 1999, **64**, 2564.
5 R. Di Florio and M. A. Rizzacasa, *J. Org. Chem.*, 1998, **63**, 8595; A. N. Cuzzupe, R. Di Florio and M. A. Rizzacasa, *J. Org. Chem.*, 2002, **67**, 4392; A. N. Cuzzupe, R. Di Florio, J. M. White and M. A. Rizzacasa, *Org. Biomol. Chem.*, 2003, **1**, 3572.
6 L. J. Mathias, *Synthesis*, 1979, 561.
7 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.
8 H. Shoji, D. Hedetaka, T. Satoru and S. Akira, *Tetrahedron Lett.*, 1983, 731.
9 W. F. Bailey and E. R. Punzalan, *J. Org. Chem.*, 1990, **55**, 5404.