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Synthesis of taurospongin A: a potent inhibitor of DNA polymerase and HIV reverse transcriptase, using π-allyltricarbonyliron lactone complexes

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Received (in Cambridge, UK) 22nd May 2002, Accepted 5th June 2002
First published as an Advance Article on the web 1st July 2002

The synthesis of taurospongin A has been achieved using, as a key step, a π-allyltricarbonyliron lactone complex to control a highly stereoselective addition of a methyl group to a carbonyl unit located in the side chain of the complex.

Taurospongin A (**1**) (Fig. 1) is an unusual acetylene containing natural product consisting of two fatty acid residues and a taurine unit. This compound was isolated from a purple coloured sponge *Hippospongia sp.* in 1997 and shown to be a potent inhibitor of DNA polymerase β and HIV reverse transcriptase.[1]

One elegant synthesis of **1** has already been reported in which the three stereogenic centres were created in three separate reagent controlled processes.[2] Here we report a conceptually different approach whereby a π-allyltricarbonyliron lactone complex[3] is used to transfer chiral information, through tethering, to achieve a highly stereoselective addition of a methyl group to a carbonyl unit appended to the side-chain of the complex. This general process had been established earlier by our group to install 1,5-, 1,7- and 1,5,7-hydroxylated stereogenic centres in alkyl chains.[4]

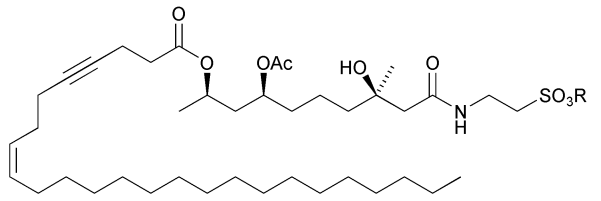
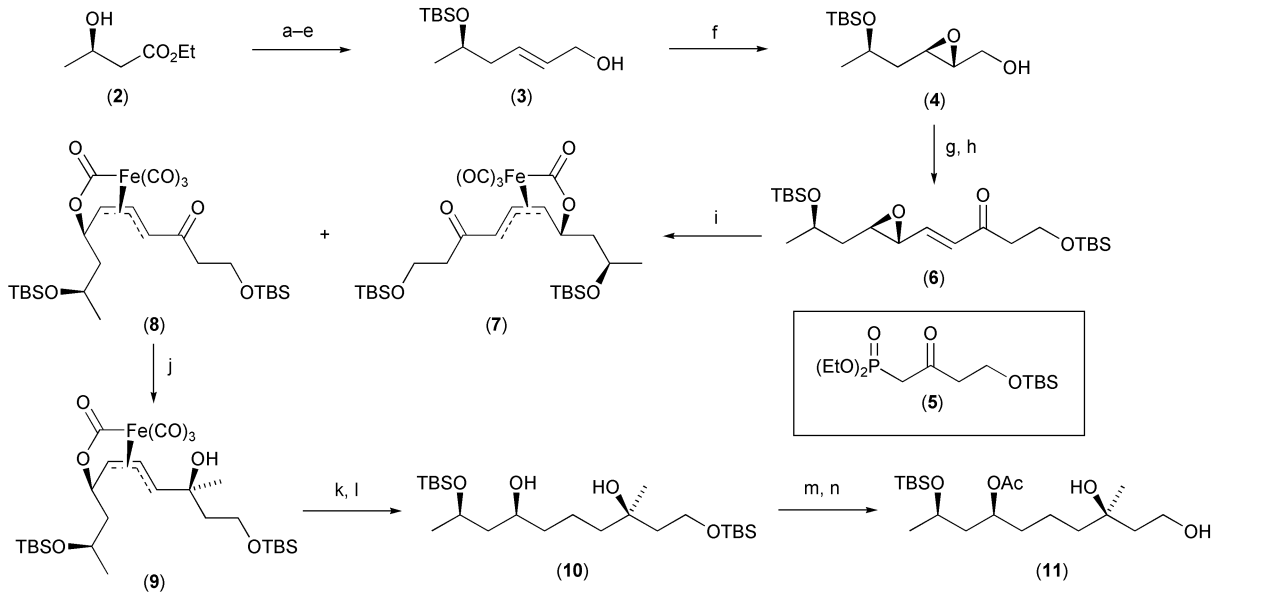


Fig. 1 Taurospongin A (**1**): R = H. Taurospongin A methyl ester (**20**): R = Me.

The synthesis begins from ethyl (3*R*)-hydroxybutanoate **2** by a known sequence[5] of reactions comprising *tert*-butyldimethylsilyl protection, DIBAL reduction, Swern oxidation, Wittig coupling and then a further reduction to afford the allylic alcohol **3** in good overall yield. Compound **3** was subjected to the Sharpless asymmetric epoxidation procedure,[6] which gave **4** with 93% d.e. again in good yield (Scheme 1). Following oxidation of **4**, to an intermediate aldehyde, reaction with the diethyl phosphonate derivative **5** gave **6** as the precursor for the iron carbonyl chemistry. The phosphonate **5**, in turn, was prepared from β-propiolactone by ring opening with methoxide followed by protection with *tert*-butyldimethylsilyl chloride and coupling with diethylmethylphosphonate in the usual way.

Next the alkenyl epoxide **6** was reacted with diiron nonacarbonyl in THF[7] to give the π-allyltricarbonyliron lactone complexes **7** and **8** in 14 and 48% yields respectively. These complexes were readily separated by silica gel chromatography.

The major *endo*-complex **8** was then reacted with trimethylaluminium to give the tertiary alcohol **9** in 81% yield and excellent stereocontrol owing to the preferred s-*cis* conformation of the carbonyl group in the appended side chain.[4b] Following our previously established reductive decomplexation protocol[8] using sodium acetoxyborohydride followed by hydrogenation, **9** was smoothly converted to the protected polyol **10**



Scheme 1 *Reagents and conditions*: (a) TBSCl, imidazole, DMF, 0 °C, 100%; (b) DIBAL-H, PhMe, 0 °C, 83%; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (d) Ph_3PCHCO_2Me, CH_2Cl_2, rt, 78% for two steps; (e) DIBAL-H, PhMe, 0 °C, 82%; (f) $Ti(O\textit{i}\text{-}Pr)_4$, D-diisopropyl tartrate, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −20 °C, 82%; (g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 88%; (h) **5**, NaH, THF, 76%; (i) $Fe_2(CO)_9$, THF, rt, **7** 14%, **8** 48%; (j) $AlMe_3$, CH_2Cl_2, 0 °C, 81%; (k) $NaBH(OAc)_3$, THF, rt; (l) H_2, Pd/C, EtOAc, rt, 81% for two steps; (m) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 0 °C, 98%; (n) TBAF, AcOH, THF, 0 °C, 81%.

DOI: 10.1039/b204994p

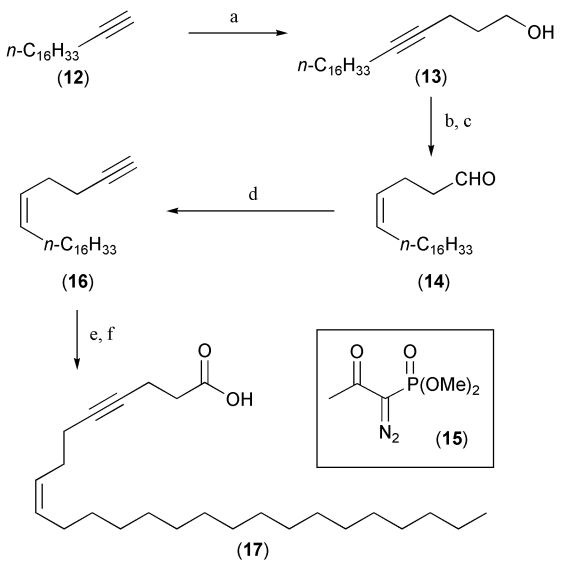
in 81% overall yield. Lastly this was acetylated using acetic anhydride and 4-dimethylaminopyridine (DMAP) and deprotected selectively using buffered tetra(*n*-butyl)ammonium fluoride (TBAF) to give the known[2] taurospongin fragment **11** (Scheme 1). The spectral and optical rotational data were identical to the sample previously synthesised by Jacobsen *et al*.[2]

For the synthesis of the other fatty acid side chain (Scheme 2), octadec-1-yne **12** was deprotonated with *n*-butyllithium and coupled with 2-(3-bromopropoxy)tetrahydro-2*H*-pyran followed by acidic work-up to give the alcohol **13**. This compound was selectively hydrogenated with the Lindlar catalyst and oxidised with periodinane[9] to the aldehyde **14**, which was homologated with the Ohira reagent **15**[10] to give the enyne **16** in 84% yield over three steps. This compound was extended further by deprotonation with *n*-butyllithium and alkylation with 2-(3-bromopropoxy)tetrahydro-2*H*-pyran to give a product (82% yield) which, upon direct oxidation with Jones reagent, gave the required acid **17** in 92% yield (46% overall yield from the acetylene **12**).

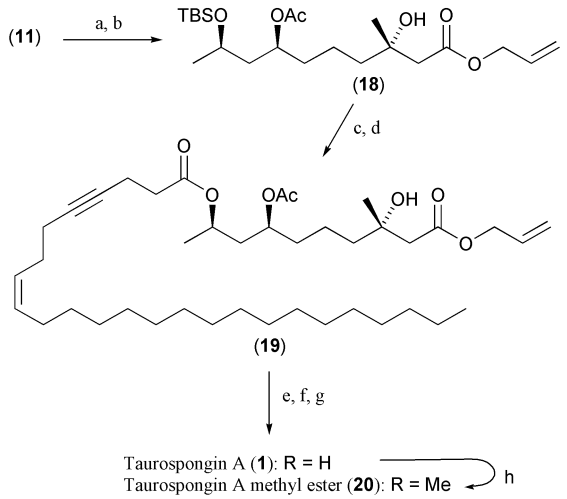
The final steps of the synthesis were achieved by a modification of the literature route.[2] Diol **11** was transformed to the corresponding acid *via* oxidation with TEMPO, KBr, $NaHCO_3$ and NaOCl, and converted to the allyl ester **18** by alkylation with allyl bromide in the presence of Hünigs' base (*i*-Pr_2NEt). Removal of the *tert*-butyldimethylsilyl protecting group from **18** using HF–pyridine was successful and the product was then coupled directly with the acid **17** using 1,3-diisopropylcarbodiimide (DIC), Hünigs' base and DMAP to give **19**.

Lastly, removal of the allyl protecting group using standard procedures with $Pd(PPh_3)_4$ and pyrrolidine gave an intermediate carboxylic acid that was activated by forming *N*-hydroxysuccinic ester with DCC and finally coupled with taurine ($H_2NCH_2CH_2SO_3H$) to give natural product taurospongin A **1** (Scheme 3).[1] The NMR data for **1** was consistent with the previously synthesised material.[2]† For full characterization, our synthetic sample was treated with diazomethane to give the corresponding methyl ester **20**,[1] which turned out to be in complete agreement with previously reported data of the samples derived either from isolated or synthetic natural products.[1,2]

In summary, we report new syntheses of the two fatty acid components that are then used to construct taurospongin A, an inhibitor of DNA polymerase β and HIV reverse transcriptase.



Scheme 2 *Reagents and conditions*: (a) *n*-BuLi, *n*-$C_{16}H_{33}I$, HMPA, THF, −20 °C → rt, then 6 M H_2SO_4, 0 °C, 73%; (b) H_2, Lindlar cat., quinoline; (c) Dess–Martin periodinane, CH_2Cl_2, rt; (d) **15**, K_2CO_3, MeOH, 84% for three steps; (e) *n*-BuLi, 2-(3-bromopropoxy)tetrahydro-2*H*-pyran, HMPA, THF, −20 → 0 °C , 82%; (f) Jones reagent, acetone, 0 °C → rt, 92%.



Scheme 3 *Reagents and conditions*: (a) cat. TEMPO, Aliquat® 336, KBr, aq. NaOCl, aq. $NaHCO_3$, CH_2Cl_2; (b) allyl bromide, *i*-Pr_2NEt, CH_2Cl_2, 87% for two steps; (c) HF·py, THF; (d) **17**, DIC, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 63% for two steps; (e) $Pd(PPh_3)_4$, pyrrolidine, CH_2Cl_2; (f) *N*-hydroxysuccinimide, DCC, 1,4-dioxane; (g) taurine, NEt_3, 1,4-dioxane, H_2O, 97% for three steps; (h) CH_2N_2, ether, 75%.

We gratefully acknowledge the financial support from the BP endowment and the Novartis Research Fellowship (to SVL), Uehara Foundation for a Postdoctoral Fellowship (to SY).

Notes and references

† The NMR data for **1**: δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0 Hz), 1.18 (3H, br s), 1.23–1.33 (33H, m), 1.42–1.60 (4H, m), 1.67–1.68 (1H, m), 1.91–1.95 (1H, m), 1.99–2.04 (2H, m), 2.05 (3H, s), 2.14–2.22 (4H, m), 2.31 (2H, br s), 2.44–2.46 (4H, m), 3.13 (2H, br s), 3.66 (2H, br s), 4.70 (1H, br s), 4.91–4.95 (2H, m), 5.35–5.44 (2H, m), 7.74 (1H, br s); δ_C (150 MHz, $CDCl_3$) 14.1, 14.8, 19.1, 19.6, 20.0, 21.2, 22.7, 26.1, 26.8, 27.3, 29.3–31.9, 34.3, 34.9, 35.2, 40.4, 42.2, 46.5, 50.0, 68.5, 71.1, 71.8, 78.2, 80.7, 127.8, 131.2, 171.0, 171.6, 173.2. Measured α_D of synthetic product **1**, $[\alpha]_D^{25}$ −3.5 (*c* 0.37, $CHCl_3$) has opposite sign to the reported data, $[\alpha]_D^{27}$ +2.4 (*c* 0.2), although the α_D of methyl ester 20, $[\alpha]_D^{25}$ −1.4 (*c* 0.49, $CHCl_3$) is consistent with the reported data, $[\alpha]_D^{27}$ −1.4 (*c* 0.78, $CHCl_3$, ref. 1) and $[\alpha]_D$ −3.00 (*c* 0.53, $CHCl_3$, ref. 2).

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