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Synthesis of Taurospongin A

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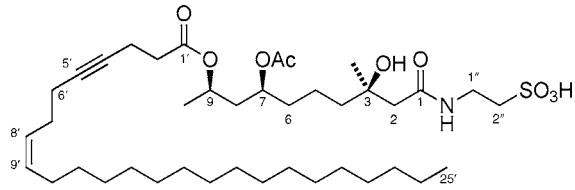
ABSTRACT



taurospongin A

Two new routes to the C(1−10) carboxylic acid core of taurospongin A are presented. In the first route, overall asymmetric hydration of a C(2)−C(3) alkene is achieved by Sharpless AD and selective deoxygenation at C(2); in the second route, the C(3) stereogenic center is set by Tietze asymmetric allylation. A short synthesis of the C(1′−25′) fatty acid combines with the product from the first route to complete the total synthesis of taurospongin A.

Kobayashi reported the isolation and structural elucidation of taurospongin A (**1**, Scheme 1) from the sponge *Hippospongia* sp. and described its inhibitory activity against DNA polymerase β ($IC_{50} = 7.0\ \mu M$, $K_i = 1.7\ \mu M$) and HIV reverse transcriptase ($IC_{50} = 6.5\ \mu M$, $K_i = 1.3\ \mu M$).[1] Assignment of the stereochemistry in the natural product was supported by a synthesis of the enantiomer of the C(1−10) core in which the C(3) stereogenic center was imported as (*R*)-mevalonolactone and the C(7,9) diol was created without stereocontrol. In subsequent synthetic work,[2a,3] the C(3) and C(7,9) centers were treated as essentially separate stereochemical problems. Ley's total synthesis[2b,c] differs in this respect by the use of π-allyltricarbonyl lactone complexes to direct stereoselective delivery of hydride (to generate the *syn*-C(7,9) diol) or methyl (to generate the C(3) center).

We became interested in taurospongin A as a starting point for identifying selective inhibitors of proteins associated with cellular repair mechanisms and their potential to synergize with cancer chemotherapeutic drugs. Accordingly, we required a synthesis of the C(1−10) core that is practical, amenable to reasonable scale-up, and sufficiently flexible to allow a variety of stereoisomers and derivatives to be prepared. In this paper, we describe two candidate solutions to this problem and carry one of these through to a new total synthesis of the natural product.

In our original plan, summarized in Scheme 1, we aimed to achieve, in a single fluoride-mediated step, deprotection of the C(9) hydroxyl group (in **4**), its esterification with acyl fluoride **2**, and release of the C(1) carboxylic acid group. This guided our choice to protect the carboxylic acid as a 2-(trimethylsilyl)ethyl ester. A second guiding feature was based on functionalization of α,β-unsaturated ester **5** by asymmetric dihydroxylation in both enantiomeric series, and subsequent selective α-deoxygenation for the total synthesis. We had in mind the possibility of retaining the α-hydroxyl group for the preparation of analogues or using asymmetric aminohydroxylation for access to 3-amino analogues.

This analysis identified ketone **6** as a key intermediate, and this was prepared in an efficient seven-step sequence

(1) Ishiyama, H.; Ishibashi, M.; Ogawa, A.; Yoshida, S.; Kobayashi, J. *J. Org. Chem.* **1997**, *62*, 3831–3836.

(2) Total syntheses: (a) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624–9625. (b) Hollowood, C. J.; Ley, S. V.; Yamanoi, S. *Chem. Commun.* **2002**, 1624–1625. (c) Hollowood, C. J.; Yamanoi, S.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 1664–1675.

(3) Formal syntheses: (a) Zheng, G. R.; Lu, W.; Cai, J. C. *Chin. Chem. Lett.* **2001**, *12*, 961–964. (b) Ghosh, A. K.; Lei, H. *Tetrahedron: Asymmetry* **2003**, *14*, 629–634. (c) Moreau, X.; Bazan-Tejeda, B.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 7288–7289. (d) Fujino, A.; Sugai, T. *Adv. Synth. Catal.* **2008**, *350*, 1712–1716. (e) See also: Zheng, G. R.; Lu, W.; Cai, J. C. *Chin. Chem. Lett.* **2000**, *11*, 663–664.

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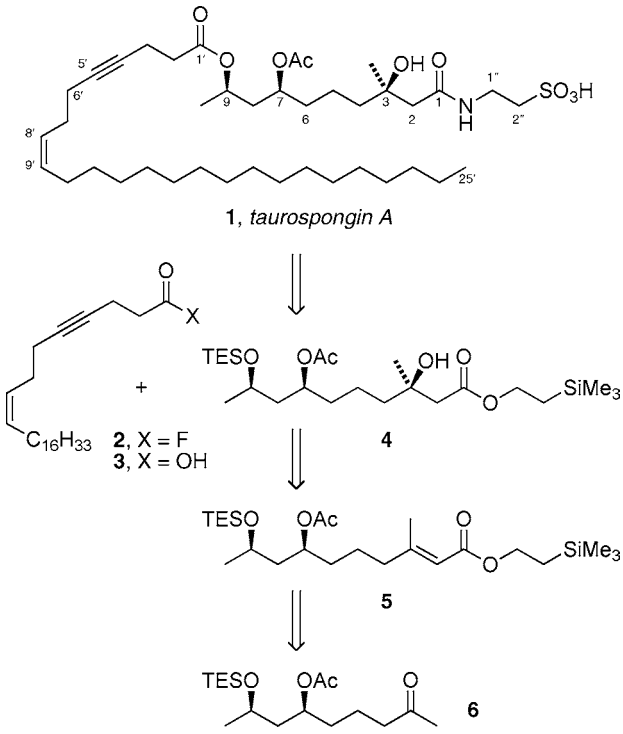
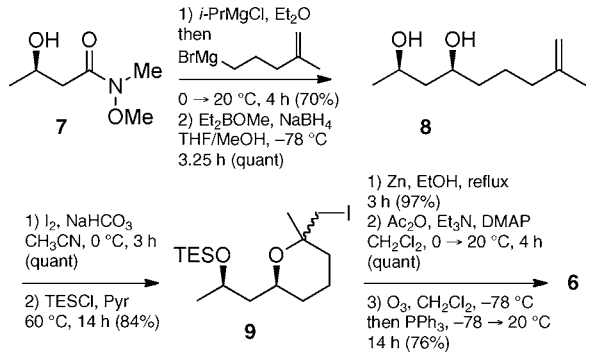
Scheme 1. Retrosynthetic Strategy



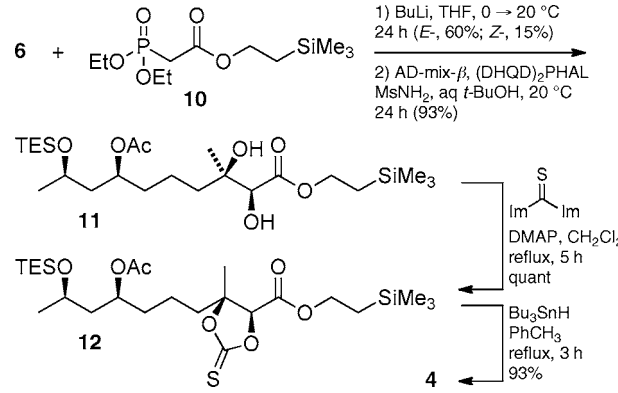
from Weinreb amide **7**[4] (Scheme 2). Key steps include the *syn*-stereoselective reduction[5] to give diol **8** whose hydroxyl groups were differentiated by selective iodoetherification and subsequent zinc-mediated ring-opening (from **9**).

Scheme 2. Synthesis of Protected Keto-Diol **6** (First Route)



This ketone was elaborated straightforwardly (→ **5**, *E*-/*Z*-, 4:1) by HWE reaction[6] and asymmetric dihydroxylation of the separated *E*-isomer (→ **11**, Scheme 3).[7] We then faced the issue of selective α-deoxygenation and, in the absence of suitable precedent for this transformation with *β*,*β*-disubstituted substrates, we surveyed many methods to achieve this, without success.[8] Eventually, homolytic reduction[9] of cyclic thionocarbonate derivative **12** was found to be reliable, affording the desired C(1−10) unit (**4**) in good yield along with a small amount of eliminated material (**5**).

Scheme 3. Completion of the C(1−10) Core (First Route)



A second route to the C(1−10) core was based on a more convenient access to analogues of ketone **6** using Wacker oxidation to install the carbonyl group (Scheme 4). This employed commercially available 5-bromo-1-pentene in the first step in place of 5-bromo-2-methyl-1-pentene, the synthesis of which is somewhat tedious and temperamental.[10] The efficiency of the Wacker oxidation depended on the protecting groups; in the C(7,9)-differentiated diol **15**, the $PdCl_2/Cu(OAc)_2$ conditions[11] shown were most reliable. However, with model compounds **19** and **20** the mild $Pd(OAc)_2$/pyridine conditions[12] were more successful (→ **22** and **23**) but this was a poor reaction for di-*O*-benzyl substrate **21** for which the classical conditions[13] were effective (→ **24**).

(4) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782–10783.

(5) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.

(6) Phosphonate **10** was prepared according to the procedure described in: Cushman, M.; Casimiro-Garcia, A.; Hejchman, E.; Ruell, J. A.; Huang, M.; Schaeffer, C. A.; Williamson, K.; Rice, W. G.; Buckheit, R. W., Jr. *J. Med. Chem.* **1998**, *41*, 2076–2089.

(7) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(8) For example: borohydride reduction of the cyclic sulfite/sulfate: (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539. (b) Upadhya, T. T.; Nikalje, M. D.; Sudalai, A. *Tetrahedron Lett.* **2001**, *42*, 4891–4893. Iodide-mediated reduction of the α-triflate: (c) Elliott, R. P.; Fleet, G. W. J.; Gyoung, Y. S.; Ramsden, N. G.; Smith, C. *Tetrahedron Lett.* **1990**, *31*, 3785–3788. Reduction of the α-mesylate: (d) [Na(Hg)]: Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565. (e) [Zn/NaI]: Ueki, T.; Kinoshita, T. *Org. Biomol. Chem.* **2004**, *2*, 2777–2785. Selenide reduction of the α,*β*-epoxide: (f) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469–12486.

(9) Rho, H.-S. *Synth. Commun.* **1997**, *27*, 3887–3893.

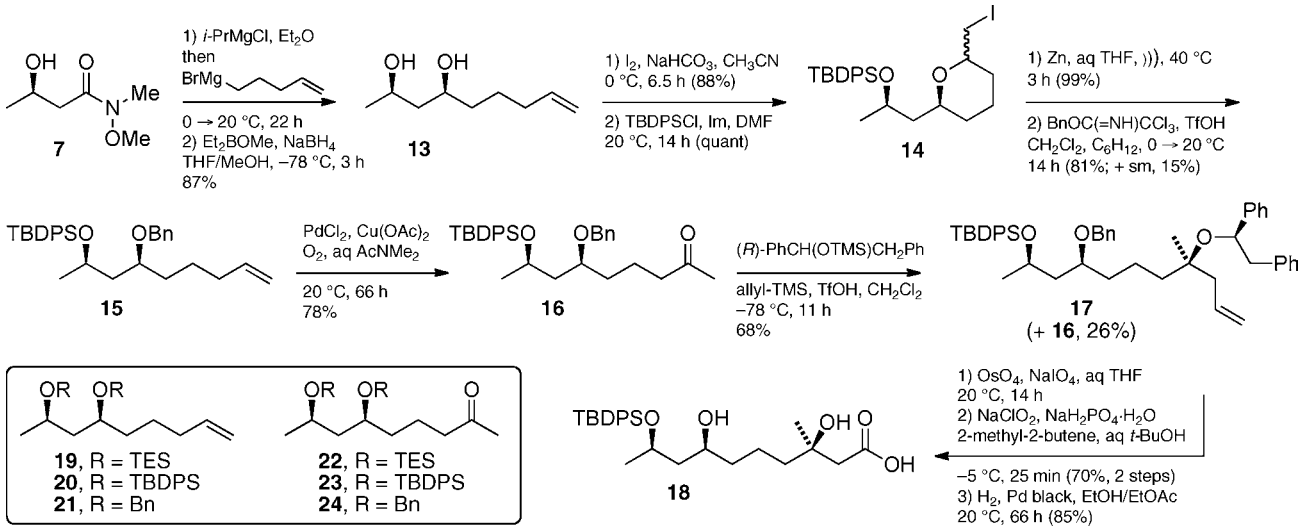
(10) From methallyl alcohol: (a) $CH_3C(OEt)_3$, cat. CH_3CO_2H, 140 °C; (b) $LiAlH_4$, Et_2O; (c) TsCl, pyridine; (d) LiBr, acetone (38% overall); step (d) has to be performed with care to avoid alkene isomerization and loss of the volatile product during isolation.

(11) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765–8768.

(12) Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1915–1918.

(13) Tsuji, J.; Nagashima, H.; Nemoto, H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 137−139.

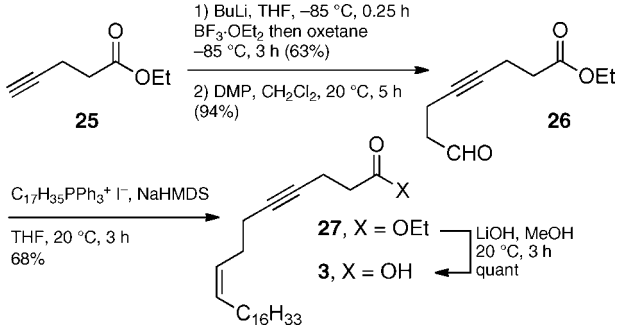
Scheme 4. Second Route to the C(1−10) Core



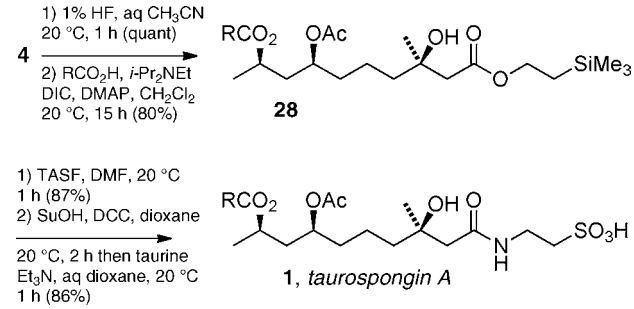
From this ketone (**16**) an alternative to the HWE/AD/deoxygenation procedure was developed. Grignard allylation of methyl ketone **22** was completely nonstereoselective but application of Tietze's procedure,[14] that employs (*R*)-1,2-diphenylethanol as a chiral auxiliary, showed very high reagent control[15] to establish the C(3) center in **17**. Alkene oxidation and hydrogenolysis revealed both the C(7) hydroxyl and carboxylic acid groups to complete the second C(1−10) synthesis.

From intermediate **4** it then remained to deprotect and acylate at C(9) and release the carboxylic acid. To date, we have been unable to effect clean formation of acyl fluoride **2** and our trials with this approach have been inconclusive.[16] However, stepwise deprotection and esterification with acid **3**, prepared as shown in Scheme 5, was successful following Jacobsen's procedure (Scheme 6). Removal of the 2-(trimethylsilyl)ethyl group proceeded poorly with TBAF, but TASF[17] produced the acid very cleanly. In our hands, the mixed anhydride method described by Jacobsen[2a] for the coupling with taurine was not satisfactory; fortunately, the *N*-hydroxysuccinimide method used by Ley,[2b,c] following Kobayashi,[1] worked very well to complete the total synthesis.

Scheme 5. Synthesis of C(1′−25′) Fatty Acid



Scheme 6. Completion of the Synthesis (RCO$_2$H = **3**)



Interestingly, although the ^{13}C NMR data in $CDCl_3$ matched those reported,[2c] some of the peaks were weak and broadened, and we suggest that in the nonpolar solvent, aggregation, such as reverse micelle formation, may be responsible. In this context, we note that the ^{13}C data listed by Kobayashi[1] are missing many of the resonances reported by Ley. In CD_3OD, all ^{13}C and ^{1}H NMR resonances are sharp, presumably because the polar, protic solvent is effective at solvating taurospongin A fully.

Our total synthesis of taurospongin A requires 15 steps from Weinreb amide **7** and was achieved in ca. 13.5% overall

(14) Tietze, L. F.; Kinzel, T.; Wolfram, T. *Chem.—Eur. J.* **2009**, *15*, 6199–6210. We are very grateful to Professor Tietze and his group for their invaluable advice in relation to this procedure.

(15) The stereochemistry at C(3) in compound **17** was assumed on the basis of Tietze's model (ref 14). None of the resonances in the ^{13}C NMR spectrum for **17** were doubled, including that at 34.6 ppm, which was sensitive to stereochemical change (34.4 ppm in the adduct generated using the (*S*)-configured auxiliary).

(16) We will report further details in a full description of this work.

yield (average ca. 88% per step). The original aim of developing a *practical* synthesis has been met, and with two routes to the C(1−10) core in hand, we are in a position to survey broad structure−activity relationships through analogue testing.

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Supporting Information Available: Procedures and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.

(18) Reynolds, L. Chemistry Part II Thesis, Oxford, 2008.