Enantioselective Total Synthesis of Taurospongin A

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Enantioselective Total Synthesis of Taurospongin A

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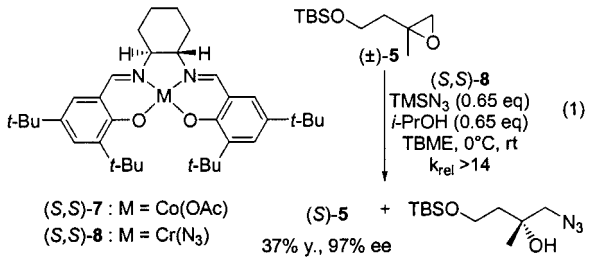
Taurospongin A (**1**) is a structurally interesting fatty acid derivative isolated recently from the Okinawan marine sponge *Hippospongia* sp. and found to exhibit remarkable dual activity as a potent inhibitor of both DNA polymerase β and HIV reverse transcriptase.[1] As a synthetic target, taurospongin A displays several structurally interesting elements including a stereochemically defined tertiary alcohol at C3 and differentially acylated secondary alcohols at C7 and C9. We describe herein the first total synthesis of **1** by an approach that features the use of highly effective asymmetric catalytic reactions to set each stereocenter independently.

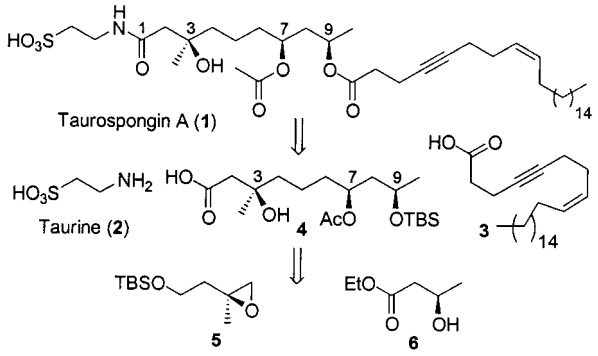
The synthetic plan is outlined in Scheme 1. After disconnection of taurine (**2**) and fatty acid **3**, fragment **4** remains as the only chiral component. We envisioned tertiary alcohol construction by alkylation of 2,2-disubstituted epoxide **5**, a substrate that would serve not only the purposes of this synthesis but also as an interesting test for recently developed epoxide kinetic resolution protocols. To attain maximum flexibility in the synthesis of taurospongin A and its diastereomers, we anticipated establishing the 1,3-diol relationship at C7−C9 by means of distinct asymmetric carbonyl reduction reactions.

Recently, our laboratories have identified highly effective methods for the kinetic resolution of terminal epoxides catalyzed by cobalt complex **7** and chromium complex **8**.[2,3] While the hydrolytic kinetic resolution (HKR) with catalyst **7** has been used with success with a wide variety of monosubstituted terminal epoxides, 2,2-disubstituted epoxide (±)-**5**[4,5] failed to react under HKR conditions. In contrast, kinetic resolution with (salen)Cr catalyst **8** and $TMSN_3$ proved successful, providing the desired enantioenriched epoxide (*S*)-**5** with a $k_{rel} > 14$ (eq 1).[6] Thus, by



employing 0.65 equiv of $TMSN_3$ and 0.65 equiv of 2-propanol, chiral epoxide **5** was isolated in 37% yield and 97% ee. The use of 2-propanol was found to be essential for the attainment of reasonable reaction rates in the kinetic resolution of **5**. This additive effects the stoichiometric conversion of $TMSN_3$ to HN_3, the latter having been shown previously to be the active reagent in the catalytic cycle.[7] The good selectivity observed in the kinetic resolution of **5** is particularly notable given the small degree of steric differentiation between the substituents in this 2,2-disubstituted epoxide.

Scheme 1



Reaction of **5** with lithium acetylide/$BF_3{\cdot}OEt_2$ proceeded cleanly to provide the desired tertiary alcohol, which was next protected as a triethyl silyl ether to complete the synthesis of chiral building block **9** (Scheme 2). β-Hydroxy ester **6** was prepared in 99% ee by the asymmetric catalytic hydrogenation of methyl acetoacetate as reported by Noyori and co-workers.[8] Protection as the TBS ether provided the requisite second chiral building block, **10**. The lithium acetylide derivative of **9** was coupled with the Weinreb amide derived from **10** to afford ynone **11** in 72% yield.[9,10]

With the fragment **11** in hand, only the stereocenter at C7 remained to be set. Although a variety of methods exist for the stereocontrolled reduction of β-alkoxy ketones, modest diastereoselectivities are often observed, especially in substrates lacking α-substituents.[11] The asymmetric catalytic transfer hydrogenation of ynones disclosed recently by Noyori was considered as a particularly attractive alternative.[12] In the context of our synthesis, the successful implementation of the Noyori reduction would allow preparation of either C7 epimer by selection of the appropriate enantiomer of the chiral catalyst. Treatment of propargylic

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

(2) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.

(3) (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420−7421. (b) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937−7940. (c) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898.

(4) Racemic epoxide **5** was prepared in two steps and 85% yield from commercially available 3-methyl-3-buten-1-ol (see the Supporting Information).

(5) For selected examples of kinetic resolution of 2,2-disubstituted epoxides, see: (a) Orru, R. V. A.; Mayer, S. F.; Kroutil, W.; Faber, K. *Tetrahedron* **1998**, *54*, 859−874. (b) Osprian, I.; Kroutil, W.; Mischitz, M.; Faber, K. *Tetrahedron: Asymmetry* **1997**, *8*, 65−71. (c) Lakner, F. J.; Hager, L. P. *J. Org. Chem.* **1996**, *61*, 3923−3925.

(6) The stereochemical assignment was made by comparison with literature data: Gill, M.; Smrdel, A. F. *Tetrahedron: Asymmetry* **1990**, *1*, 453−464.

(7) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924−10925. In the kinetic resolution of terminal epoxides, the secondary alcohol that is generated upon ring opening reacts readily with $TMSN_3$ to generate HN_3 and the corresponding silyl ether. As a result, only a catalytic amount of Brønsted acid is needed for the reaction, and adventitious water is generally sufficient. In contrast, the tertiary alcohol generated in the ring opening of **5** is unreactive toward $TMSN_3$, so a stoichiometric amount of Brønsted acid is needed.

(8) (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163−4166. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1−13.

(9) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

(10) The starting terminal alkyne **9** was also recovered in 24% yield.

(11) For selected examples of diastereoselective reduction of β-alkoxy ketones to give syn-1,3-monoprotected diols, see: (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419−5422. (b) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396−1408. (c) Yoshimatsu, M.; Naito, M.; Shimizu, H.; Muraoka, O.; Tanabe, G.; Kataoka, T. *J. Org. Chem.* **1996**, *61*, 8200−8206.

(12) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739.

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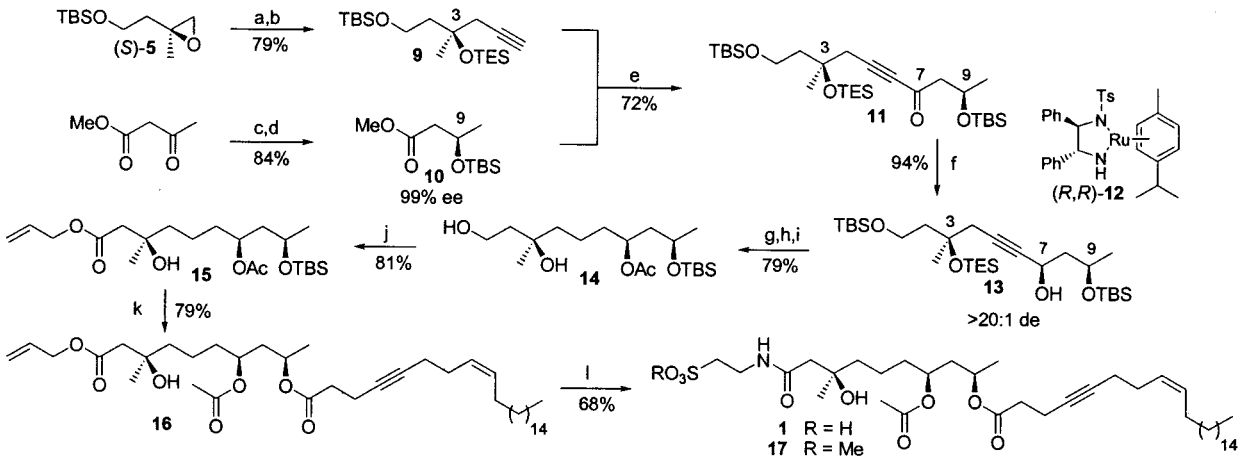
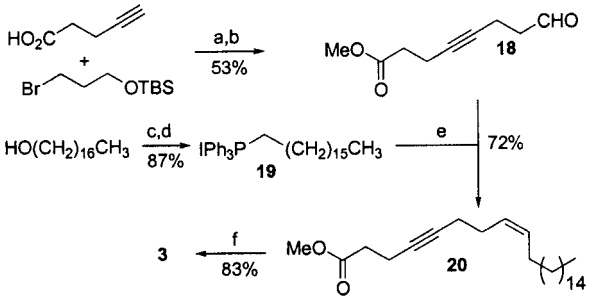
Scheme 2[a]



[a] Reagents: (a) acetylene, *n*-BuLi, BF_3·OEt_2, THF, −78 °C, rt, 81%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 97%; (c) (*R*)-BINAP-Ru(II), H_2 (100 atm), MeOH, 92%, 99% ee; (d) TBSCl, imidazole, CH_2Cl_2, 91%; (e) (i) Me(MeO)NH·HCl, *i*-PrMgCl, THF, −10 °C, (ii) *t*-BuLi, THF, −78 °C, (iii) −10 °C, 60 °C, 72% (+24% of **9**); (f) 2 mol % (*R*,*R*)-**12**, 2-propanol, 94%, >90% de; (g) $Pd(OH)_2$, Et_3N, EtOAc, H_2, 93%; (h) Ac_2O, DMAP, pyridine, 99%; (i) TBAF, HOAc, THF, 86%; (j) (i) cat. TEMPO, Aliquat 336, KBr, NaOCl, H_2O, CH_2Cl_2; (ii) allyl bromide, *i*-Pr_2NEt, CH_2Cl_2, 81% (two steps); (k) (i) HF·pyridine, THF; (ii) **3**, DIC, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 79% (two steps); (l) (i) $Pd(PPh_3)_4$, pyrrolidine, CH_2Cl_2; (ii) EtO_2CCl, Et_3N, THF; (iii) taurine, MeCN, H_2O, 68% (three steps).

Scheme 3[a]



[a] Reagents: (a) (i) *n*-BuLi, THF, HMPA, −45 °C; (ii) cat *p*-TsOH, MeOH, reflux, 78%; (b) PDC, MS 4A, Celite, CH_2Cl_2, 74%; (c) $(PhO)_3P$, I_2, 94%; (d) Ph_3P, MeCN, reflux, 93%; (e) NaHMDS, THF, −20 °C, rt, 72%; (f) LiOH, MeOH, THF, H_2O, 83%.

ketone **11** with ruthenium catalyst **12** in 2-propanol provided the desired propargylic alcohol (**13**) in 94% yield and ≥20:1 diastereoselectivity.[13] Reduction using the opposite enantiomer of catalyst **12** gave the anti diastereoisomer with similarly high diastereoselectivity (≥20:1), confirming that the stereoselectivity of ynone reduction is indeed completely under catalyst control in this instance.

Hydrogenation of the triple bond, followed by acetylation of the free secondary alcohol and selective deprotection of both primary TBS and tertiary TES groups with TBAF and acetic acid, provided diol **14** in 79% yield from **13**. The primary alcohol was then oxidized by means of TEMPO-catalyzed reaction with hypochlorite[14] to afford the core structure **4** (see Scheme 1), and this was prepared for the final side-chain attachment steps by protection as the allyl ester derivative **15**.

The synthesis of unconjugated *Z*-enyne acid **3** is outlined in Scheme 3. Reaction of the dianion derived from 5-pentynoic acid with (3-bromopropoxy)-*tert*-butyldimethylsilane provided the corresponding disubstituted alkynyl carboxylic acid,[15] which was converted to aldehyde **18** by treatment with *p*-toluenesulfonic acid in methanol followed by PDC oxidation. Wittig precursor **19** was prepared in two steps from commercially available 1-heptadecanol. Condensation of the derived ylide with aldehyde **18** provided the desired *Z*-enyne ester **20** in 72% yield as a single isomer within both ^1H and ^{13}C NMR detection limits. Saponification of the ester **20** with lithium hydroxide gave desired acid **3** in 34% overall yield for the five-step sequence.

Deprotection of the TBS ether of intermediate **15** with HF·pyridine in THF was followed by immediate esterification of the crude hydroxy acetate with **3** in order to suppress unwanted migration of the C7 acetate group. Following deprotection of the allyl ester, the resulting acid was converted to the corresponding mixed anhydride in preparation for taurine coupling. It was found that the optimal solvent for the amide bond construction was a mixture of water and acetonitrile, allowing good taurine solubility while avoiding hydrolysis of the mixed anhydride. Taurospongin A was obtained in 68% yield overall yield from **16**. The sulfonic acid was subsequently converted into methyl ester **17** for charactization purposes and comparison with the analogous natural product derivative. The synthetic and natural material were found to be identical in all respects (^1H and ^{13}C NMR, $[\alpha]_D$, HRMS).

The synthesis of taurospongin A was accomplished in 14 steps from epoxide **5** in 6% overall yield, including the kinetic resolution. The route highlights the power of modern asymmetric catalytic methods in natural product synthesis, both for accessing useful chiral building blocks and also for achieving complete diastereocontrol in reactions of a relatively complex substrate. The fact that all three stereocenters in taurospongin A were set independently by enantioselective reactions allows ready access to all eight stereoisomers of the core structure by the same basic synthetic strategy.

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Supporting Information Available: Complete experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all key intermediates (56 pages).

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(13) Diastereoselectivities were evaluated by analysis of the crude ^1H NMR spectrum. Both diastereoisomers were separable by flash chromatography.

(14) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562.

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