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Studies Directed toward the Synthesis of Terreulactone A: Rapid Construction of the A, B, C Rings

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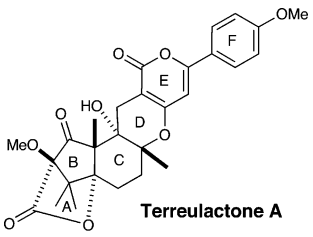
ABSTRACT



An efficient, rapid synthesis of the A, B, C rings of terreulactone A is described. Key steps in the synthesis include a diastereoselective benzylic acid rearrangement to create the desired quaternary center at C_2 and a mild bromolactonization to assemble the lactonic ring A.

Acetylcholine is a neurotransmitter that plays an essential role in memory and learning. Markedly decreased levels of acetylcholine are a hallmark of Alzheimer's disease.[1] Acetylcholinesterase (AChE), the enzyme that degrades acetylcholine to its inactive form (choline), has thus emerged as a promising molecular target in the treatment of Alzheimer's disease.[2] Presumably, inhibition of AChE would result in increased levels of acetylcholine, which could lead to improved neural functioning in Alzheimer's patients. Needless to say, while this approach certainly seems reasonable, Alzheimer's is a complex disease and the drugs currently available which were developed on the basis of this premise have not yet been established as clinically viable agents.

Terreulactones A−D, microbial metabolites isolated from solid-state fermentation of *Aspergillus terreus* F000501, are potent and highly selective inhibitors of AChE, with IC_{50} values ranging from 0.06 to 0.42 μM.[3] Terreulactone A (**1**) is a sesquiterpene lactone type meroterpenoid (Figure 1). The

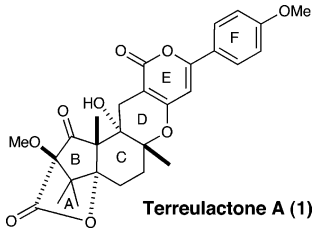


Figure 1. Structure of terreulactone A.

structural complexity of terreulactone A (**1**), combined with its promising biological profile (IC_{50} of 0.23 μM), prompted us to launch a program toward its total synthesis.

Our strategy toward the synthesis of terreulactone A (**1**) is outlined in Scheme 1. Thus, intermediate **3**, itself obtained from the readily available Wieland−Miescher ketone (**2**),

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(1) (a) Davies, P.; Maloney, A. J. F. *Lancet* **1976**, *2*, 1403. (b) Whitehouse, P. J.; Price, D. L.; Struble, R. G.; Clarke, A. W.; Coyle, J. T.; DeLong, M. R. *Science* **1982**, *215*, 1237.

(2) (a) Davis, K. L.; Mohs, R. C. *Am. J. Psychiatry* **1982**, *139*, 1421. (b) Thal, L. J.; Fuld, P. A.; Masur, D. M.; Sharpless, N. S. *Ann. Neurol.* **1983**, *13*, 491.

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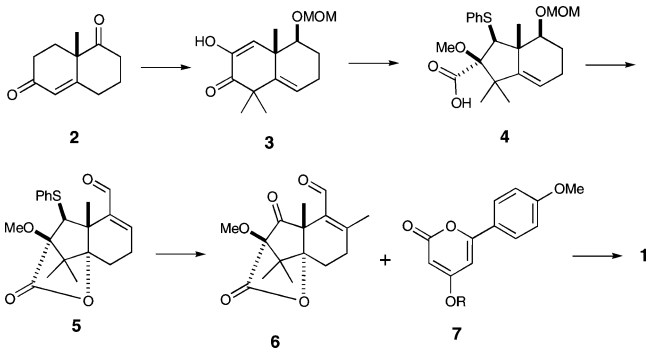
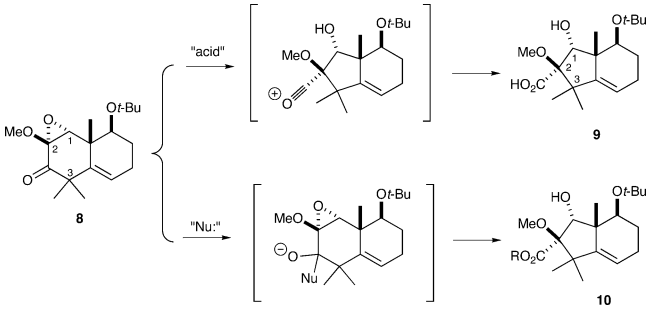
would be subjected to a stereoselective ring contraction protocol to afford **4**.[4] Lactonization followed by appropriate functional group management could ultimately provide intermediate **5**, which we expected would be amenable to conversion to **6** in a fairly straightforward fashion. Finally, we hoped to couple **6** with a suitable E,F progenitor, **7** (for instance, according to the [3 + 3] annulation strategy developed by Hsung).[5]

Scheme 1



We originally hoped that an epoxide of the type **8** might be induced to undergo ring contraction to afford the 6,5-fused bicyclic framework possessing the requisite functionalization at C_2 and C_1.[6] Thus, under acidic conditions, we anticipated that C_3 would migrate to open the epoxide, affording an oxonium intermediate which would subsequently be trapped to afford **9** (Scheme 2). Alternatively,

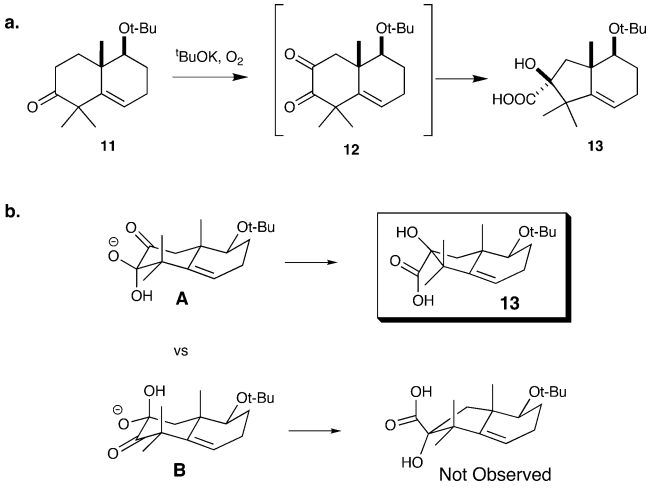
Scheme 2



under nucleophilic conditions, a tetrahedral intermediate could be envisioned which, upon collapse, might afford the ring contracted intermediate **10**. Unfortunately, extensive attempts to bring about the desired rearrangement in any experimental mode were unsuccessful, resulting only in decomposition or unproductive side reactions.

Fortunately, in the course of preparing intermediate **8**, we had serendipitously discovered that an attempted one-step oxidation of **11** to **12** proceeded smoothly to provide the ring-contracted intermediate **13** as a single diastereomer (Scheme 3a). NOE analysis of the reduced diol congener of **13** revealed that the newly generated C_2 stereocenter possessed the configuration required for the natural product. A rationale for this stereochemical outcome is provided in Scheme 3b. Thus, migration of the *gem*-dimethyl bearing carbon (through intermediate **A**) is favored on the basis of general considerations of migratory aptitude, which is sensitive to stability of cationoid character. Moreover, intermediate **B** would presumably be destabilized by 1,3,5-triaxial abutments. Encouraged by this unexpected result, we set out to modify the substrate to incorporate the requisite C_1 functionality.

Scheme 3



Our synthesis commenced with the chemo- and stereoselective reduction of the Wieland−Miescher ketone (**2**) followed by protection of the resultant alcohol to afford **14** (Scheme 4). Dimethylation of **14** provided **15**, which was then subjected to a two-step oxidation sequence to afford the enol intermediate **3**. The next task would be the introduction of the C_1 functionality. We elected to install a sulfur group, which would eventually be unmasked through a Pummerer rearrangement to afford the requisite C_1 carbonyl. Thus, treatment of **3** with the electrophilic sulfurizing reagent $PhSO_2SPh$ led to installation of the thiophenyl group at C_1. The crude intermediate was heated to 110 °C in degassed aqueous KOH solution[4] and then treated with MeI and NaH to afford the ring-contracted intermediate **16** in 45% overall yield for the three steps. The carboxylic acid was then liberated under Gassman's conditions[7] to provide

(3) (a) Kim, W.-G.; Cho, K.-M.; Lee, C.-K.; Yoo, I.-D. *Tetrahedron Lett.* **2002**, *43*, 3197. (b) Cho, K.-M.; Kim, W.-G.; Lee, C.-K.; Yoo, I.-D. *J. Antibiot.* **2003**, *56*, 344. (c) Kim, W.-G.; Cho, K.-M.; Lee, C.-K.; Yoo, I.-D. *J. Antibiot.* **2003**, *56*, 351.

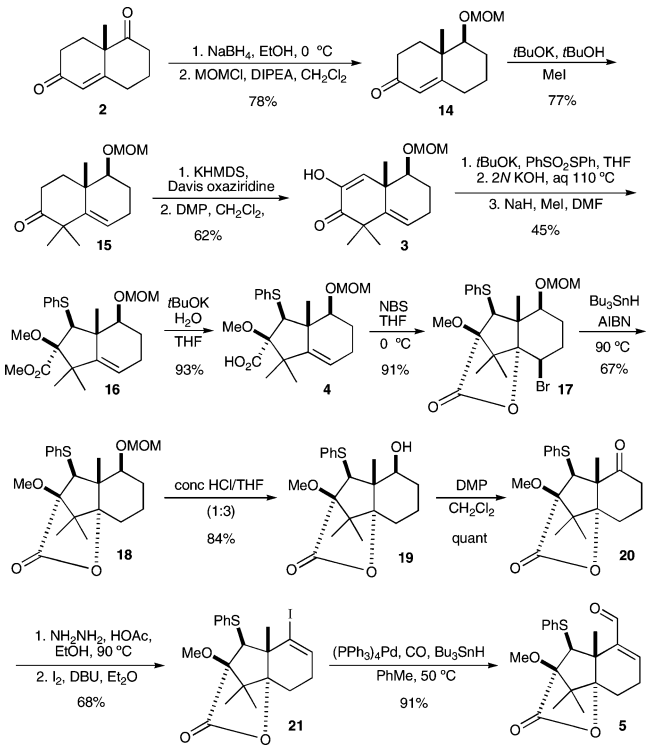
(4) Georgian, V.; Kundu, N. *Tetrahedron* **1963**, *19*, 1037.

(5) (a) Zehnder, L. R.; Hsung, R. P.; Wang, J. S.; Golding, G. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3876. (b) Cole, K. P.; Hsung, R. P.; Yang, X.-F. *Tetrahedron Lett.* **2002**, *43*, 3341. (c) Cole, K. P.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 8791.

(6) (a) Matoba, K.; Karibe, N.; Yamazaki, T. *Chem. Pharm. Bull.* **1984**, *32*, 2639. (b) Grant, P. K.; Lynch, G. P.; Simpson, J.; Wong, G. *Aust. J. Chem.* **1993**, *46*, 1125.

(7) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

Scheme 4



intermediate **4**. Upon examination of a number of lactonization conditions, we found that treatment of **4** with NBS at 0 °C afforded the bromolactone **17** in 91% yield. Attempts to reduce the bromide were complicated by a competition reaction involving regeneration of the alkene; however, this problem was circumvented through recourse to neat $SnBu_3H$ reaction conditions. We note, parenthetically, that when the reaction was allowed to proceed for longer than approximately 5 min, significant amounts of sulfur-reduced side product were observed. The structure of intermediate **18** has been confirmed through X-ray crystallography (Figure 2).

Intermediate **18** was subjected to MOM deprotection conditions followed by oxidation of the resultant alcohol to afford ketone **20**. The latter was converted to the vinyl iodide **21** according to the Barton protocol.[8] Finally, **21** was advanced to the key coupling partner, enal **8**, through palladium-mediated carbonylation.[9]

(8) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147.

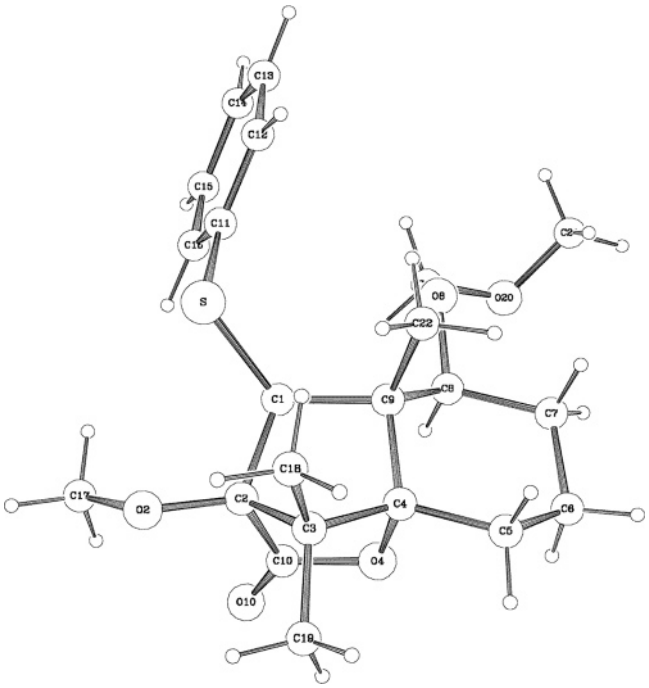


Figure 2. ORTEP representation of the X-ray crystal structure of **18**.

In conclusion, the synthesis of the fully functionalized A,B,C ring system of terreulactone A has been accomplished. A key transformation involves a distereoselective ring contraction of the diketone (**3**) to afford a 6,5-fused bicyclic system.[10] Studies toward the completion of the synthesis of terreulactone A (**1**) are under investigation.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, including X-ray data for intermediate **18** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

(10) For previous instances of ring contractions based on processes mechanistically related to the benzylic acid rearrangement, see: (a) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1996**, *37*, 3929 (b) Grieco, P. A.; Collins, J. L.; Huffman, J. C. *J. Org. Chem.* **1998**, *63*, 9576.