ORGANIC LETTERS

2005
Vol. 7, No. 19
4297−4300

A Stereocontrolled Synthesis of δ-*trans*-Tocotrienoloic Acid

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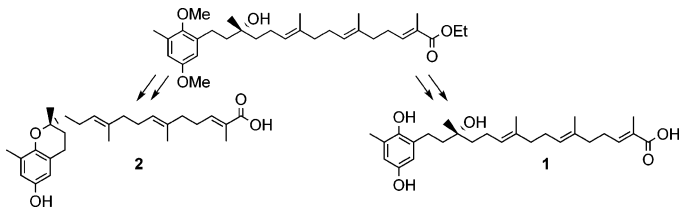
Received August 2, 2005

ABSTRACT



A consise stereoselective total synthesis of a naturally occurring polymerase β inhibitor, δ-*trans*-tocotrienoloic acid (2), is described. The key step in the synthesis is an acid-catalyzed cyclodehydration reaction. Additionally, this report corrects a previously reported structural assignment, defines the absolute stereochemistry of 2, and defines key structural requirements for polymerase β inhibition.

DNA polymerases play a central role in the replication, recombination, and repair of DNA.[1] In particular, DNA polymerase β (pol β) is a 39-kDa enzyme that participates in base excision repair, by both gap-filling polymerization and subsequent removal of the 5′-terminal deoxyribose phosphate residues from the incised apurinic and apyrimidinic sites. Importantly, it has been shown that pol β is involved in the repair of DNA lesions formed after exposure to DNA damaging agents such as cisplatin and bleomycin.[2] Consequently, the use of otherwise noncytotoxic pol β inhibitors in conjunction with these chemotherapeutic agents should logically potentiate their cytotoxicity, thus allowing for lower doses to be administered.

Our laboratory has studied the isolation and biological evaluation of naturally occurring pol β inhibitors; this has resulted in the discovery of several novel compounds with good inhibitory activity.[3] Recently, we reported the bioassay-guided isolation of a novel DNA polymerase β inhibitor, chrysochlamic acid (**1**, Figure 1), from the methyl ethyl ketone extract of *Chrysochlamys ulei*.[4] Compound **1** displayed good pol β inhibition (IC_{50} 4.3 μM), and was found to be unaffected by the presence of serum albumin, consistent with the possibility that **1** may be of utility in vivo. Given the interesting biological activity of **1**, its limited availability, and the need for structure confirmation, the total synthesis was deemed desirable.

Upon completion of the stereoselective synthesis of **1** it was determined that the previously reported structural assignment was incorrect. Accordingly, this report also details the first total synthesis of the correct structure, δ-*trans*-

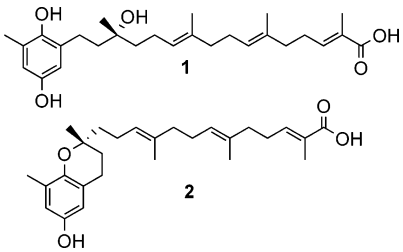


Figure 1. Structures of chrysochlamic acid (**1**) and δ-*trans*-tocotrienoloic acid (**2**).

(1) Kornbeg, A.; Baker. T. A. *DNA Replication*, 2nd ed.; W. H. Freeman and Co.: New York, 1992.

(2) (a) Chen, J.; Zhang, Y.-Z.; Wang, L.-K.; Sucheck, S. J.; Snow, A. M.; Hecht, S. M. *Chem. Commun*. **1998**, 2769. (b) Sun, D.-A.; Deng, J.-Z.; Starck, S. R.; Hecht, S. M. *J. Am. Chem. Soc*. **1999**, *121*, 6120. (c) Ma, J.; Starck, S. R.; Hecht, S. M. *J. Nat. Prod*. **1999**, *62*, 1660.

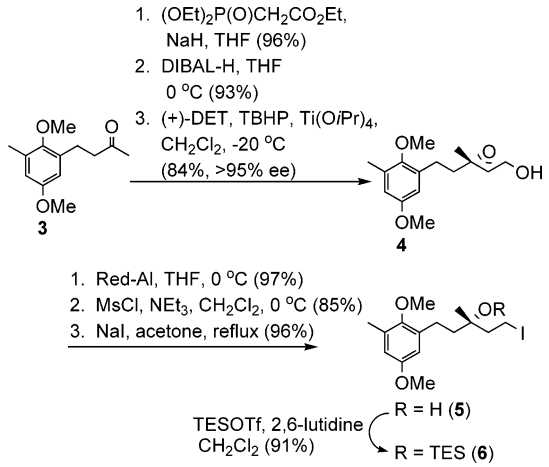
(3) Hecht, S. M. *Pharm. Biol*. **2003**, *41*, S68 and references therein.

10.1021/ol051849t CCC: $30.25
Published on Web 08/20/2005

tocotrienoloic acid (**2**),[5] via an acid-catalyzed cyclodehydration reaction of a late-stage intermediate utilized for the synthesis of **1**. The synthesis permitted facile access to both **1** and **2**, which permitted structure confirmation, as well as the determination of absolute stereochemistry.

Retrosynthetically, we envisioned the separate syntheses of both the requisite alkyl iodide **6** and vinyl iodide **11**, followed by an sp^3-sp^2 Suzuki coupling to assemble the molecule in a convergent and efficient manner, as shown below. The synthesis of alkyl iodide **6** is outlined in Scheme 1. Installation of the trisubstituted olefin was achieved in

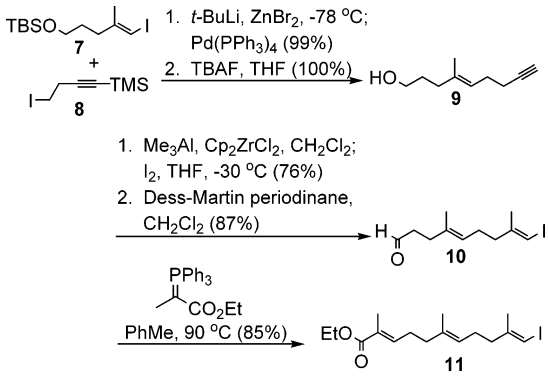
Scheme 1. Synthesis of Alkyl Iodide **6**[a]



96% yield via a Horner−Emmons reaction of **3**[6] with triethyl phosphonoacetate by the use of sodium hydride as the base.[7] The resulting α,β-unsaturated ethyl ester was reduced to the requisite allylic alcohol with DIBAL-H in good yield (93%). Asymmetric Sharpless epoxidation was accomplished by using the (+)-DET ligand to give the (*S*,*S*)-trisubstituted epoxide **4** in high yield (84%) and ee (95%).[8] Regioselective hydride delivery to the less substituted C of the epoxide was achieved with Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) in THF at 0 °C to give the desired 1,3-diol in 97% yield. Selective mesylation of the primary alcohol (methanesulfonyl chloride and NEt_3 in CH_2Cl_2 at 0 °C) gave the mesylate in 85% yield. Nucleophilic displacement of the mesylate with NaI-saturated acetone at reflux then gave alkyl iodide **5** in 96% yield.[9] Subsequent protection of the hindered tertiary alcohol was achieved using TESOTf with 2,6-lutidine in CH_2Cl_2 to afford the requisite alkyl iodide derivative **6** in 91% yield.

Several approaches to the vinyl iodide fragment **11** were explored; the most efficient route is outlined in Scheme 2.

Scheme 2. Synthesis of Vinyl Iodide **11**[a]



Construction of the silyl-protected enyne was accomplished in near quantitative yield via Negishi coupling of **7**[10] and **8**[11] by the use of methodology reported on similar systems.[11] Removal of the silyl groups with *tetra*-*n*-butylammonium fluoride (TBAF) in THF at 0 °C gave intermediate **9**[12] in quantitative yield. Zirconium-catalyzed carboalumination followed by iodination provided the (*E*,*E*)-vinyl iodide in 76% yield. The primary alcohol was then oxidized using Dess−Martin periodinane[13] to yield aldehyde **10** (87%). Wittig olefination with carbethoxyethylidene triphenylphosphorane in toluene at 90 °C gave the desired (*E*,*E*,*E*)-vinyl iodide **11** in 85% yield with a minor amount (~5%) of the undesired (*Z*)-isomer, which could be easily separated by column chromatography.

With both the alkyl iodide **6** and vinyl iodide **11** in hand, the Suzuki coupling was attempted using a variety of methods. The best results were obtained using 9-MeO-9-BBN, *t*-BuLi, K_3PO_4, Pd(dppf)Cl_2, and 1.5 equiv of **11** to give the desired coupled product in 65−81% yields (Scheme 3).[14] Deprotection of the TES-protected tertiary alcohol proceeded smoothly with 6 equiv of TBAF to afford key intermediate **12** in 92% yield. Saponification of the ethyl ester using K_2CO_3 in aqueous MeOH followed by mild

(4) Deng, J.-Z.; Sun, D.-A.; Starck, S. R.; Hecht, S. M.; Cerny, R. L.; Engen, J. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1147. Structural assignment was based on NMR (^1H, ^{13}C, 2D experiment) and HRMS [M − H_2O], and involved the assumption that the tertiary OH group had been lost during mass spectrometric analysis. In fact the mass spectrum of synthetic **1** did reflect some dehydration.

(5) (a) Monache, F. D.; Marta, M.; Mac-Quhae, M. M.; Nicoletti, *Gazz. Chim. Ital.* **1984**, *114*, 135. (b) Setzer, W. N.; Green, T. J.; Lawton, R. O.; Moriarity, D. M.; Bates, R. B.; Caldera, S.; Haber, W. A. *Planta Med.* **1995**, *61*, 275, from *Tovomitopsis psychotriifolia*. (c) Terashima, K.; Shimamura, T.; Tanabayashi, M.; Aqil, M.; Akinniyl, J. A.; Niwa, M. *Heterocycles* **1997**, *45*, 1559, from *Garcinia kola*.

(6) See Supporting Information for experimental procedures employed for the synthesis of **3**.

(7) The product was obtained in 6:1 (*E*/*Z*) ratio; attempts to improve this ratio were unsuccessful.

(8) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976. Percent ee was determined by analysis of the MTPA ester.

(9) While the 1,3-diol could be converted to the alkyl iodide directly using PPh_3, imidazole, and I_2, the yield was low.

(10) (a) Zheng, Y. F.; Oehlschlager, A. C.; Hartman, P. G. *J. Org. Chem.* **1994**, *59*, 5803. (b) Roush, W. R.; Barda, D. A.; Limberakis, C.; Roxanne, K. *Tetrahedron* **2002**, *58*, 6433. (c) Groth, U.; Richter, N.; Kalogerakis, A. *Eur. J. Org. Chem.* **2003**, *23*, 4034.

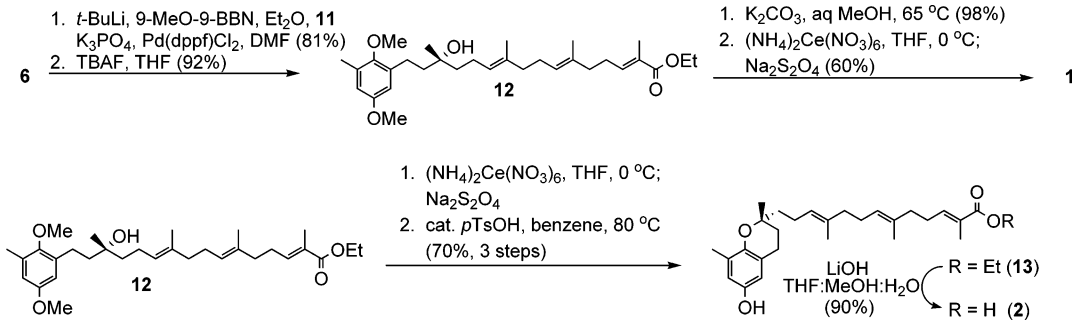
(11) (a) Foote, K. M.; Hayes, C. J.; John. M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917. (b) Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, T. A. *J. Am. Chem. Soc.* **1998**, *110*, 5383.

(12) Johnson, W. S.; Yarnell, T. M.; Myers, R. F.; Morton, D. R.; Boots, S. G. *J. Org. Chem.* **1980**, *45*, 1254.

(13) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

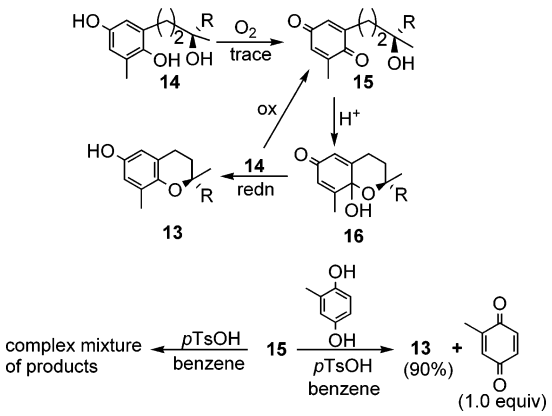
(14) (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. (b) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751.

Scheme 3. Suzuki Coupling and Synthesis of **1** and **2**[a]



demethylation via cerium ammonium nitrate (CAN) oxidation and reductive workup ($Na_2S_2O_4$) gave **1** as an air-sensitive yellow oil in 60% yield. Surprisingly, upon comparison of their NMR spectra, it was apparent that the spectrum of the synthetic compound differed slightly from that of the natural product. Examination of literature reports revealed that the NMR data from the natural product matched that of a previously reported natural product, *δ-trans*-tocotrienoloic acid (**2**), first isolated from the fruits of *Clusia grandiflora*.[5a] Since this compound has not been synthesized previously we sought to confirm the structural assignment and determine the absolute stereochemistry. We envisioned constructing **2** from previously synthesized intermediate **12** via an acid-catalyzed cyclodehydration reaction, thus allowing for rapid access to the natural product without major changes to the synthesis. Therefore, using the same oxidative demethylation procedure as described above, compound **12** was demethylated (Scheme 3) to give the air-sensitive hydroquinone derivative **14** shown in Scheme 4. Treatment

Scheme 4. Proposed Mechanism and Mechanistic Study of the Cyclodehydration Reaction



with catalytic *p*TsOH in benzene at reflux afforded the desired cyclization product **13**, presumably with *retention* of configuration as reported previously for similar systems (70% from **12**).[15] Saponification of the ethyl ester using K_2CO_3 and aqueous MeOH led to decomposition of the starting material; however, **2** was obtained in 90% yield using LiOH in THF−MeOH−H_2O. Synthetic **2** gave spectral data in full agreement with those of the natural product.[16] Interestingly, despite having a very similar structure, **1** displayed virtually no polymerase β inhibition even at concentrations >120 μM, compared to **2** (IC_{50} ~4 μM) in preliminary in vitro assays.

It may be noted that other approaches to the synthesis of tocotrienols have been reported,[17] although most of these have afforded racemic products. Considerable efforts have also been expended to define routes to optically pure chromans.[18]

While the cyclodehydration reaction has been reported previously for the synthesis of optically active chromans, we sought further mechanistic insight into this intriguing reaction. Cohen and co-workers[15c] had previously suggested a catalytic redox cycle similar to that shown in Scheme 4. In this case, hydroquinone **14** is oxidized in trace quantities to quinone **15** by O_2. Subsequent nucleophilic attack by the tertiary alcohol on the quinone forms hemiacetal **16**, which is reduced by the starting hydroquinone, generating additional **15**. To obtain further evidence for the proposed mechanism, quinone **15** was treated under the usual cyclodehydration conditions (*p*TsOH, benzene, 80 °C); as expected, formation of **13** was not observed due to the lack of the reducing hydroquinone, as shown in Scheme 4. Interestingly, admixture of quinone **15** and methylhydroquinone in the presence of *p*TsOH yielded **13** along with methyl 1,4-benzoquinone (1.0 equiv), arguing that the reaction must proceed through the previously proposed catalytic redox cycle shown in Scheme 4.

In summary, the stereoselective synthesis, structure confirmation, and absolute stereochemistry of (+)-*trans*-toco-

(15) (a) Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem.* **1987**, *52*, 5495. (b) Jung, M. E.; MacDougall, J. M. *Tetrahedron Lett.* **1999**, *40*, 6339. (c) Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445. (d) Mayer, H.; Vetter, W.; Metzger, J.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1967**, *50*, 1168.

(16) Synthetic **2** was identical by ^1H, ^{13}C NMR, and HRMS comparisons with the authentic sample. The optical rotation of synthetic **2**, $[\alpha]^{22}_D$ +19.6 (*c* 0.42, MeOH), had the same sign as that of the authentic sample, $[\alpha]^{23}_D$ +17.5 (*c* 0.18, MeOH). The somewhat lower $[\alpha]_D$ value originally recorded for the natural product (+6.7) undoubtedly reflected the low concentration used for the measurement. Optical rotations measured in $CHCl_3$ were found to give very low values, in agreement with an early report.[5c]

(17) (a) Pearce, B. C.; Parker, R. A.; Deason, M. E.; Qureshi, A. A.; Wright, J. J. *J. Med. Chem.* **1992**, *35*, 3595. (b) Terashima, K.; Takaya, Y.; Niwa, M. *Bioorg. Med. Chem.* **2002**, *10*, 1619.

(18) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966 and references therein.

trienoloic acid (**2**) via an acid-catalyzed cyclodehydration reaction has been accomplished. Additionally, this report corrects a previously reported structural assignment (i.e., **1**) and defines structural requirements for pol β inhibition. The route reported also provides access to analogues of **2** having potentially improved activity as DNA polymerase β inhibitors.

Acknowledgment. We thank Dr. James Ryan for the biochemical evaluation of **1** and **2**. This work was supported by NIH Research Grant 50771, awarded by the National Cancer Institute.

Supporting Information Available: Experimental procedures and characterization data for **1** and **2**, and synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051849T