

# Synthesis of a Dicyano Abietane, a Key Intermediate for the Antiinflammatory Agent TBE-31

Evans O. Onyango,<sup>†</sup> Liangfeng Fu,<sup>†</sup> and Gordon W. Gribble\*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States

Supporting Information

**ABSTRACT:** The synthesis of dicyano abietane 11, a potential precursor to the biologically active tricyclic biscyano enone 6 (TBE-31), was accomplished in eight steps from epoxide 13. The synthesis features a Lewis acid promoted stereoselective cyclization of epoxide 13 to generate the tricyclic ring system 12 in one step.



O leanolic acid (1), ursolic acid (2), and betulinic acid (3), the most common pentacyclic triterpenoids, exhibit modest biological activity.<sup>1</sup> Over the past 15 years, our triterpenoid research program entailed the modification of the ring-A C-3 hydroxy, ring-C double bond, and the C-28 carboxylic acid of both oleanolic and ursolic acid.<sup>2,3</sup> This led to the syntheses of several highly biologically active oleanolic acid derivatives, such as CDDO methyl ester (2-cyano-3,12dioxooleana-1,9(11)-dien-28-oic acid methyl ester) (Bardoxolone Methyl) (4), CDDU methyl ester, and their derivatives (Figure 1).<sup>4–8</sup> For example, 4 completed successful phase 1 and 2 clinical trials for some cancers and chronic kidney disease.<sup>1,5</sup>



Figure 1. Pentacyclic triterpenoids.

The ring-A cyano enone and ring-C enone moieties are essential for the biological activity of 4. To this end, we synthesized a series of tricyclic analogues having these same functionalities in rings A and C (i.e., the A–B–C ring pharmacophore) and tested their biological activity.<sup>9</sup> Thus, the inhibitory activity of 11 against the production of nitric oxide in RAW 264.7 cells stimulated with interferon- $\gamma$  (IFN $\gamma$ ) was found to be twice that of hydrocortisone, a well-known antiinflammatory drug.<sup>10</sup> This promising biological activity of 11 ultimately led to the discovery of TBE-31 (6), which is 10 times more active than CDDO-Me (4) (Figure 2).<sup>11</sup> The higher potency and lower molecular weight of TBE-31 (6) make it especially attractive for further biological studies.



Figure 2. Synthetic design of tricyclic bis-enones.

Our previous synthesis<sup>12</sup> of TBE-31 (6) was adopted in part from that of 11 and featured a 12-step synthesis from commercially available 2-carbomethoxycyclohexanone  $(7)^{13}$ (Scheme 1). We described a second synthesis of 6,<sup>14</sup> but the





key steps were impractical for further customization. Thus, excess lithium in liquid ammonia and carefully controlled conditions were necessary for the reductive methylation of enone 8 to a mixture of ketones 9a, 9b, and 9c. Nine additional steps were required to convert 9 to TBE-31 (6).

Retrosynthetically, abietane-type diterpenoid 11 is involved as the key intermediate to furnish TBE-31, while 11 can be obtained from alcohol 12 through the installation of a cyano enone in ring A and a cyano group in ring C. A Lewis acid catalyzed cyclization reactions would afford alcohol 12, from readily available epoxide 13 (Scheme 2).

Received:November 14, 2013Published:December 4, 2013

# Scheme 2. Retrosynthetic Analysis



We now describe an efficient synthesis of tricycle 11, which we view as viable for the synthesis of TBE-31 (6). The synthesis of epoxide 13 began with thioacetalization of isovanillin tri-isopropylsilyl  $16^{15}$  to yield dithiane 14 in 98% yield, using silica gel treated with thionyl chloride (SOCl<sub>2</sub>-SiO<sub>2</sub>) (Scheme 3).<sup>16</sup> Lithiation of dithiane 14 under standard



conditions<sup>17,18</sup> followed by alkylation of the resultant anion with the known chiral epoxy geranyl bromide  $15^{19}$  gave the S<sub>N</sub>2 substitution product 17 in 89% yield, with no evidence of nucleophilic epoxide ring opening by the organolithium. That allylic substitution was achieved by employing only the organolithium is noteworthy; in previously reported reactions of this kind sequential transmetalation of organolithium to the corresponding organocuprate was invariably required.<sup>20-22</sup> We had originally intended to cyclize 17 in order to allow for further functionalization of ring B and therefore gain access to recently isolated abietane-type diterpenoids,<sup>23</sup> bearing a hydroxyl or carbonyl moiety at C-7 (abietane skeleton numbering, Scheme 2). However, attempted cyclization of 17 gave mainly monocyclization product and only a trace of the desired product along with several unidentified byproducts. We thus moved on with reductive desulfurization using *n*-butyltin hydride<sup>18</sup> to give the epoxy derivative 13 in 82% yield. After removal of the dithiane protecting group, there was a significant improvement in the yield of cyclized tricyclic products. Initial cyclization of 13 performed with dialkyl aluminum catalysts (Et<sub>2</sub>AlCl and Me<sub>2</sub>AlCl), MeAICl<sub>2</sub>, and InBr<sub>3</sub> gave 1:1 mixtures of 12 and 18 in 40-60% yield.

Gratifyingly,  $BF_3 \cdot OEt_2^{24}$  at -78 °C promoted the diastereoselective (*trans* only product) cyclization of the dethiolated epoxy olefin 13 to give 69% of a 2:1 regioisomeric mixture of 12 and 18. The regioisomers, easily separable by column chromatography, were identified on the basis of their <sup>1</sup>H NMR spectra: alcohol 12 has the aromatic protons appear as two singlets, whereas in 18 they are doublets (AX pattern). The relative stereochemistry (*trans* geometry of the AB ring juncture) was later determined by X-ray crystallography of an advanced intermediate (*vide infra*). The observed diastereoselectivity can be attributed to the preorganized chair-chair conformation as postulated by Stork and Eschenmosher.<sup>25</sup> We also examined and were encouraged by the fact that the reactions leading to 13 led to the preparation of its trifluoromethanesulfonate analogue (Tf replacing TIPS in 13, not shown), a sequence with a potential of reducing the number of steps required to reach 11. Unfortunately, attempted cyclization of this trifluoromethanesulfonate analogue under the same conditions gave an intractable mixture.

Oxidation of alcohol **12** using 4 equiv of iodobenzoic acid  $(IBX)^3$  in DMSO at 85 °C furnished the enone **19** in 90% yield (Scheme 4). TBAF removal of the silyl group followed by

# Scheme 4. Synthesis of Enone 21



reaction of the resultant phenol with triflic anhydride in methylene chloride in the presence of pyridine gave the triflate **20** in 87% yield (2 steps). Slight modification of the cyanation conditions  $(Zn(CN)_2/Pd_2(dba)_3/dppf/DMF/110 \ ^{\circ}C)$  reported by Treston and co-workers<sup>26</sup> gave the carbonitrile **21** in 95% yield. A crystal of compound **21** was analyzed by X-ray crystallography and confirmed the *trans* stereochemistry between the AB ring junction methyl and hydrogen.

Halogenolysis of enone 21 with iodine in pyridine at ambient temperature gave  $\alpha$ -iodo enone 22 in 92% yield (Scheme 5).



Treatment of **22** with CuCN in DMF at 140 °C facilitated the Rosenmund–von Braun type reaction to give 88% of cyano enone **23**.<sup>27</sup> Finally, demethylation to **11**<sup>10</sup> was achieved in 80% yield by exposure of **23** to BBr<sub>3</sub>. The reaction required 4 days at room temperature, but complete consumption of the starting material was achieved after 8 h in refluxing CH<sub>2</sub>Cl<sub>2</sub>.<sup>28</sup> Furthermore, the **11** was also obtained in good yield (75%) by demethylation in molten pyridinium chloride.<sup>29</sup> In both cases the product **11** was identical (spectral data) to that reported earlier.<sup>10</sup>

In summary, an efficient and convenient synthesis of tricycle 11 was accomplished in five steps from readily accessible epoxide 13. The synthesis features an epoxide-initiated polycyclization for the installation of the tricyclic skeleton in a single step. Synthetic efforts for the conversion of 11 to TBE- 31 (6) and other potentially bioactive cyano enones are currently underway and will be reported in due course.

# ASSOCIATED CONTENT

## **Supporting Information**

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

# AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: ggribble@dartmouth.edu.

#### **Author Contributions**

<sup>†</sup>These authors contributed equally to this work.

## Notes

The authors declare no competing financial interest.

# ACKNOWLEDGMENTS

We acknowledge general support from Reata Pharmaceuticals and thank Michael Sporn (Geisel School of Medicine) for his interest in our work.

## REFERENCES

(1) Sporn, M. B.; Liby, K. T.; Yore, M. M.; Fu, L.; Lopchuk, J. M.; Gribble, G. W. J. Nat. Prod. 2011, 74, 537.

(2) Honda, T.; Rounds, B. V.; Bore, L.; Finlay, H. J.; Favaloro, F. J., Jr.; Suh, N.; Wang, Y.; Sporn, M. B.; Gribble, G. W. J. Med. Chem. **2000**, 43, 4233.

(3) Fu, L.; Gribble, G. W. Org. Lett. 2013, 15, 1622.

(4) Honda, T.; Honda, Y.; Favaloro, F. G., Jr.; Gribble, G. W.; Suh, N.; Place, A. E.; Rendi, M. H.; Sporn, M. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1027.

(5) Liby, K. T.; Sporn, M. B. Pharmacol. Rev. 2013, 64, 972.

(6) Petronelli, A.; Pannitteri, G.; Testa, U. Anti-Cancer Drugs 2009, 20, 880.

(7) Sporn, M. B.; Liby, K. T.; Yore, M. M.; Suh, N.; Albini, A.; Honda, T.; Sundararajan, C.; Gribble, G. W. *Drug Dev. Res.* **2007**, *68*, 174.

(8) Fu, L.; Lin, Q.-X.; Gribble, G. W. Chem. Commun., submitted for publication.

(9) Liby, K. T.; Yore, M. M.; Roebuck, B. D.; Baumgartner, K. J.; Honda, T.; Sundararajan, C.; Yoshizawa, H.; Gribble, G. W.; Williams, C. R.; Risingsong, R.; Royce, D. B.; Dinkova-Kostova, A. T.; Stephenson, K. K.; Egner, P. A.; Yates, M. S.; Groopman, J. D.; Kensler, T. W.; Sporn, M. B. *Cancer Res.* **2008**, *68*, 6727.

(10) Honda, T.; Yoshizawa, H.; Sundararajan, C.; Gribble, G. W. J. Org. Chem. 2006, 71, 3314.

(11) Favaloro, F. G., Jr.; Honda, T.; Honda, Y.; Gribble, G. W.; Suh, N.; Risingsong, R.; Sporn, M. B. J. Med. Chem. **2002**, 45, 4801.

(12) Honda, T.; Sundararajan, C.; Yoshizawa, H.; Su, X.; Honda, Y.; Liby, K. T.; Sporn, M. B.; Gribble, G. W. J. Med. Chem. 2007, 50, 1731.

(13) Honda, T.; Honda, Y.; Yoshizawa, H.; Gribble, G. W. Org. Prep.
Proced. Int. 2005, 37, 546.

(14) Honda, T.; Yoshizawa, H.; Sundararajan, C.; David, E.; Lajoie, M.; Favaloro, F. G., Jr.; Janosik, T.; Su, X.; Honda, Y.; Roebuck, B. D.; Gribble, G. W. J. Med. Chem. **2011**, *54*, 1762.

(15) Ramacciotti, A.; Fiaschi, R.; Napolitano, E. J. Org. Chem. 1996, 61, 5371.

(16) Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. J. Org. Chem. 1986, 51, 1427.

(17) Topczewski, J. J.; Callahan, M. P.; Kodet, J. G.; Inbarasu, J. D.; Mente, N. R.; Beutler, J. A.; Wiemer, D. F. *Bioorg. Med. Chem.* **2011**, *19*, 7570.

(18) Kim, M. B.; Shaw, J. T. Org. Lett. 2010, 12, 3324.

(19) Corey, E. J.; Noe, M. C.; Wen-Chung, S. Tetrahedron Lett. 1993, 34, 5995.

(20) Gansäuer, A.; Justicia, J.; Rosales, A.; Worgull, D.; Rinker, B.; Cuerva, J. M.; Oltra, J. E. *Eur. J. Org. Chem.* **2006**, 4115.

(21) Neighbors, J. D.; Topczewski, J. J.; Swenson, D. C.; Wiemer, D. F. Tetrahedron Lett. 2009, 50, 3881.

(22) Gansaeuer, A.; Justicia, J.; Rosales, A.; Rinker, B. Synlett 2005, 2005, 1954.

(23) Yang, L.; Qiao, L.; Ji, C.; Xie, D.; Gong, N.; Lu, Y.; Zhang, J.; Dai, J.; Guo, S. J. Nat. Prod. 2013, 76, 216.

(24) Isaka, T.; Hasegawa, M.; Toshima, H. Biosci. Biotechnol. Biochem. 2011, 75, 2213.

(25) Zhao, J.; Zhao, Y.; Loh, T. Chem. Commun. 2008, 1353.

(26) Suwandi, L. S.; Agoston, G. E.; Shah, J. H.; Hanson, A. D.; Zhan, X. H.; LaVallee, T. M.; Treston, A. M. Bioorg. Med. Chem. Lett. 2009,

19, 6459.

(27) You, R.; Long, W.; Lai, Z.; Sha, L.; Wu, K.; Yu, X.; Lai, Y.; Ji, H.; Huang, Z.; Zhang, Y. J. Med. Chem. **2013**, 56, 1984.

(28) Wilson, M. PCT Patent WO/1980/000841,1980.

(29) Schmid, C. R.; Beck, C. A.; Cronin, J. S.; Staszak, M. A. Org. Process Res. Dev. 2004, 8, 670.