Organic LETTERS

Letter

pubs.acs.org/OrgLett

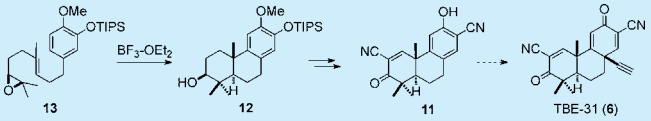
Synthesis of a Dicyano Abietane, a Key Intermediate for the Anti-inflammatory Agent TBE-31

Evans O. Onyango,† Liangfeng Fu,† 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 bis-cyano 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.



Oleanolic acid (**1**), ursolic acid (**2**), and betulinic acid (**3**), the most common pentacyclic triterpenoids, exhibit modest biological activity.[1] 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.[2,3] This led to the syntheses of several highly biologically active oleanolic acid derivatives, such as CDDO methyl ester (2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid methyl ester) (Bardoxolone Methyl) (**4**), CDDU methyl ester, and their derivatives (Figure 1).[4−8] For example, **4** completed successful phase 1 and 2 clinical trials for some cancers and chronic kidney disease.[1,5]

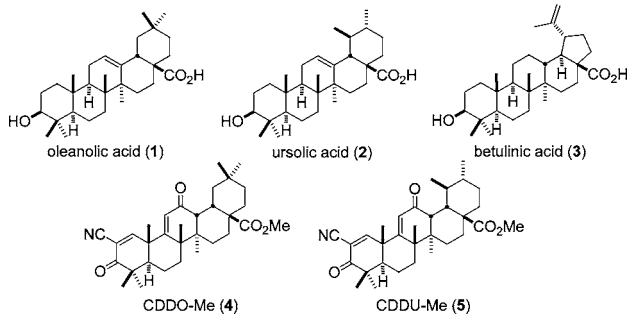


Figure 1. Pentacyclic triterpenoids.

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.[9] Thus, the inhibitory activity of **11** against the production of nitric oxide in RAW 264.7 cells stimulated with interferon-γ (IFNγ) was found to be twice that of hydrocortisone, a well-known anti-inflammatory drug.[10] 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).[11] The higher potency and lower molecular weight of TBE-31 (**6**) make it especially attractive for further biological studies.

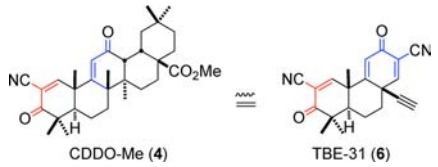
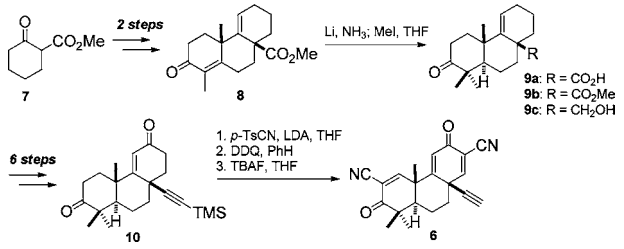


Figure 2. Synthetic design of tricyclic bis-enones.

Our previous synthesis[12] 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**,[14] 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**).

Scheme 1. Reported Synthesis of TBE-31 (6)

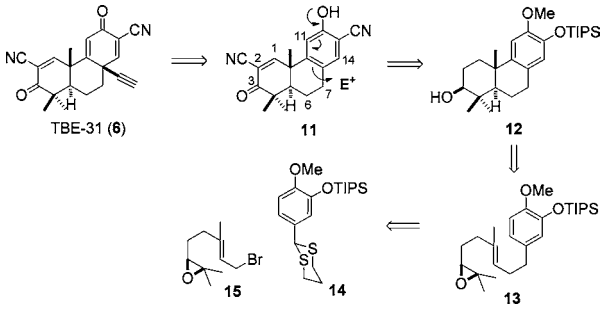


Retrosynthetically, abietane-type diterpenoid **11** is involved as the key intermediate to furnish TBE-31, while **11** can be obtained from alcohol **12** through the installation of a cyano enone in ring A and a cyano group in ring C. A Lewis acid catalyzed cyclization reactions would afford alcohol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

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

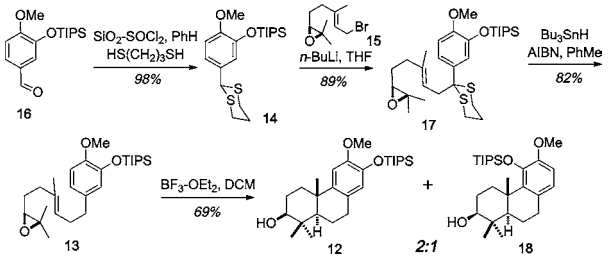
   dx.doi.org/10.1021/ol403289y | *Org. Lett.* 2014, 16, 322−324

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 ($SOCl_2$-SiO_2) (Scheme 3).[16] Lithiation of dithiane **14** under standard

Scheme 3. Synthesis and Epoxyolefin Cyclization of 13

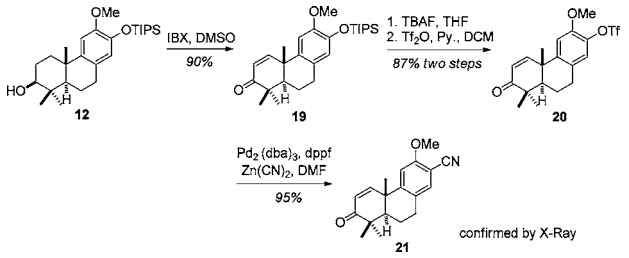


conditions[17,18] followed by alkylation of the resultant anion with the known chiral epoxy geranyl bromide **15**[19] gave the S_N2 substitution product **17** in 89% yield, with no evidence of nucleophilic epoxide ring opening by the organolithium. That allylic substitution was achieved by employing only the organolithium is noteworthy; in previously reported reactions of this kind sequential transmetalation of organolithium to the corresponding organocuprate was invariably required.[20−22] 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,[23] 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[18] 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_2AlCl and Me_2AlCl), $MeAlCl_2$, and $InBr_3$ 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 ^1H 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.[25] 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

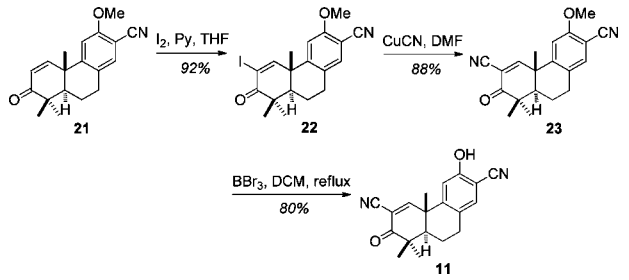
Scheme 4. Synthesis of Enone 21



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 °C) reported by Treston and co-workers[26] 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 α-iodo enone **22** in 92% yield (Scheme 5).

Scheme 5. Synthesis of Abietane Analogue 11



Treatment of **22** with CuCN in DMF at 140 °C facilitated the Rosenmund−von Braun type reaction to give 88% of cyano enone **23**.[27] Finally, demethylation to **11**[10] was achieved in 80% yield by exposure of **23** to BBr_3. The reaction required 4 days at room temperature, but complete consumption of the starting material was achieved after 8 h in refluxing CH_2Cl_2.[28] Furthermore, the **11** was also obtained in good yield (75%) by demethylation in molten pyridinium chloride.[29] In both cases the product **11** was identical (spectral data) to that reported earlier.[10]

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-

dx.doi.org/10.1021/ol403289y | Org. Lett. 2014, 16, 322−324

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

†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.