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Efficient and Scalable Synthesis of Bardoxolone Methyl (CDDO-methyl Ester)

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ABSTRACT

Bardoxolone methyl (2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oic acid methyl ester; CDDO-Me) (1), a synthetic oleanane triterpenoid with highly potent anti-inflammatory activity (levels below 1 nM), has completed a successful phase I clinical trial for the treatment of cancer and a successful phase II trial for the treatment of chronic kidney disease in type 2 diabetes patients. Our synthesis of bardoxolone methyl (1) proceeds in ~50% overall yield in five steps from oleanolic acid (2), requires only one to two chromatographic purifications, and can provide gram quantities of 1.

The biological importance of naturally occurring triterpenoids has long been recognized. The annual reviews in *Natural Product Reports* is ample testimony to the widespread distribution and biologial activity of these compounds, which includes squalenes, lanostanes, fusidanes, dammaranes, euphanes, and others. Within each class is a dazzling array of structural diversity and a wide range of biological activity.[1]

Oleanolic acid (**2**) and ursolic acid (**3**) (Scheme 1), the most commonly studied triterpenoids, exhibit modest biological activity, although **2** has been marketed in China as an oral drug for the treatment of liver disorders in humans.[2] Our synthetic plan entailed modifying the C-3 hydroxyl, the ring-C double bond, and the C-28 carboxylic acid.[3] This led to syntheses of several highly biologically active oleanolic acid derivatives, CDDO-methyl ester (2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid methyl ester) (**1**), ethyl amide **4**, trifluoroethyl amide **5**, and imidazolide **6** (Figure 1).[4] Details of their biological properties are described in recent reviews.[5−7]

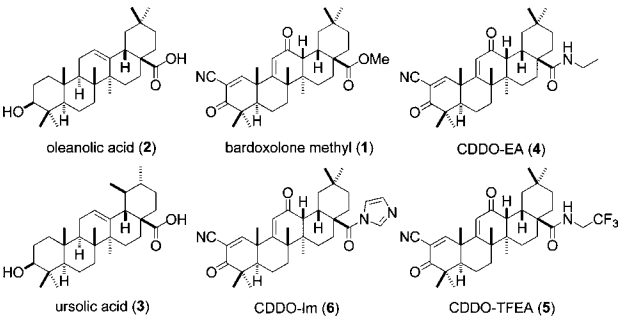

Figure 1. OA (**1**), UA (**2**), and our synthetic analogues.

Our initial synthesis of bardoxolone methyl (**1**), although reasonably efficient, involves 10 steps, the final DDQ-mediated oxidation of cyano enol **7** is not cost−effective and is only practical for a laboratory synthesis (Scheme 1).[3] Thus, a more efficient and scalable synthesis is highly desirable for further clinical development of these triterpenoid analogues.

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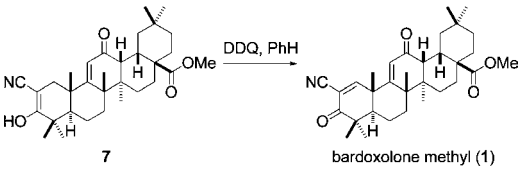
Scheme 1. DDQ-Mediated Oxidation for Synthesis of **1**



In this paper, we present a gram-scale synthesis of bardoxolone methyl (**1**) in a minimum of five steps in an overall 50% yield, requiring only one or two flash column chromatographic purifications.

Scheme 2. Strategic Analysis for Conversion from OA (**2**) to **1**

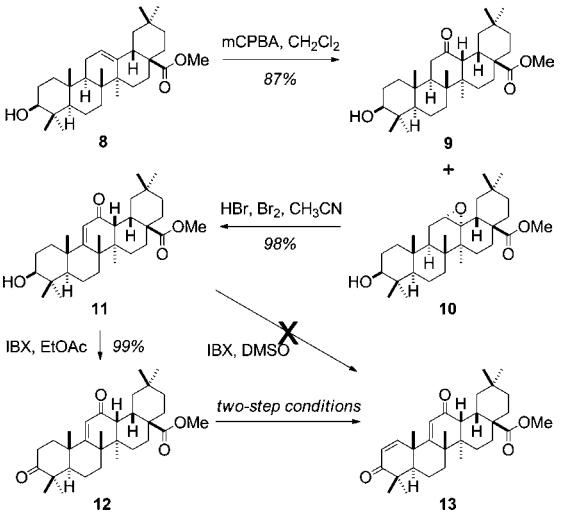
Our goal was to achieve the synthesis of bardoxolone methyl (**1**) within five steps (minimum number of steps possible to obtain **1** from oleanolic acid **2**) as shown in Scheme 2. Initially, we envisioned that generation of the ring-C enone be performed before formation of ring-A cyano enone. In this event, ring-C enone **11** was obtained in three steps from oleanolic acid, and our two-step planned sequence from **11** to **1** failed (Scheme 3). Ideally, a one-step oxidation from alcohol **11** to bis-enone **13** followed by a direct regioselective C−H cyanation would afford **1** in two steps. However, both a Saegusa oxidation[8] and a selenation/oxidation/elimination protocol resulted in bis-enone **13** in more than two steps; moreover, $Pd(OAc)_2$ and PhSeCl are not ideal reagents for large-scale synthesis. While the IBX oxidation introduced by Nicolaou and coworkers[9] could accomplish a one-step oxidation from alcohols to α,β-unsaturated ketones, this reaction failed in our system.

Believing that the ring-C enone in **11** is the main reason for the failure of the IBX oxidation, we turned our attention to methyl oleanoate **8**. Fortuitously, the IBX oxidation of **8** smoothly afforded ring-A enone **14** in excellent yield. *m*-CPBA epoxidation of enone **14** gave a mixture of C-ring epoxidized **15** and **16**, without affecting the ring-A enone double bond. Direct treatment of the mixture of **15** and **16** with hydrogen bromide and bromine in acetonitrile did not give the desired bis-enone **13**. Instead, the corresponding ring-A bromoenone **17** was obtained in 70%

(8) Kürti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Oxford, 2005; pp 390−391.

(9) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

Scheme 3. Approach to **1** via Prior C-Ring Enone Formation



overall yield from **14**; the ring-C enone remained unbrominated (Scheme 4). A solvent study for this oxidation and regioselective bromination sequence revealed that acetic acid is the best solvent for this transformation (Table 1).

Scheme 4. Synthetic Generation of Ring-A Bromo Bisenone **17**

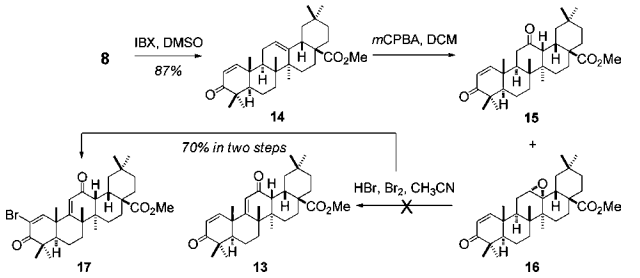
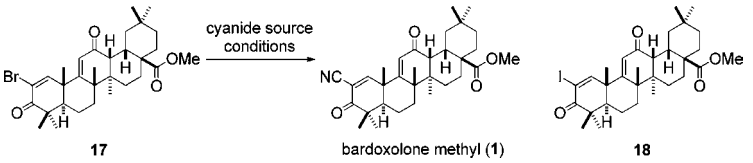


Table 1. Optimization of Bromo Enone **17** Formation

entry	solvent	yield (%)	entry	solvent	yield (%)
1	THF	57	5	$(CH_2)_2Cl_2$	55
2	**AcOH**	**79**	6	CH_2Cl_2	53
3	MeOH	25	7	toluene	64
4	dioxane	64	8	acetone	57

With bromo enone **17** in hand, our final task was to install the C-2 cyano group (Table 2). Our initial attempt using copper(I) cyanide in dimethylformamide at 140 °C for 3 h resulted in the complete consumption of **17**, but only about 25% yield of the desired cyano enone **1** was obtained (entry 1). To our delight, reducing the temperature to 120 °C did afford 49% yield of **1**, but about 20% of **17** was recovered (entry 2). Potassium iodide is believed to be the ideal reagent for catalytic conversion of bromide to iodide upon heating,[10] and iodo enone **18** is considered to

Table 2. Optimization of the Cyanation of Bromo Enone **17**

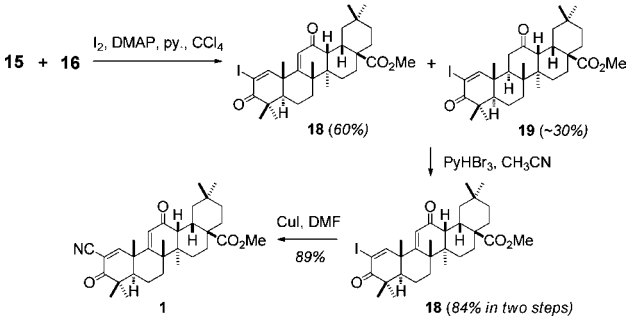


entry	catalyst	CN source	temp (°C)	time (h)	additive	conversion (%)	yield (%)
1		CuCN	140	3		100	25
2		CuCN	120	24		~80	49
3		**CuCN**	**120**	**24**	**KI (20%)**	**100**	**66**
4	$CuBr_2$	DMF, NH_4OAc	120	24	TMEDA	100	0
5		$K_3Fe(CN)_6$	140	24		~30	19
6	CuI	$K_3Fe(CN)_6$	140	24		~30	21
7	$CuBr_2$	$K_3Fe(CN)_6$	120	24		trace	trace
8	$Pd(dppf)_2$	$K_3Fe(CN)_6$	140	24			0

be much more reactive than **17**. Promisingly, a 20% introduction of potassium iodide afforded bardoxolone methyl (**1**) in 66% yield with no recovery of **17** (entry 3, Table 2). Further attempts to employ other cyanide sources instead of copper(I) cyanide were also performed. Recently, a concoction of an ammonium salt and dimethylformamide as the cyanide source has been applied in cyanation coupling reactions.[11] However, in our hands, while no starting bromo enone was recovered, none of the desired bardoxolone methyl (**1**) was isolated, probably due to the nucleophilicity of ammonia, especially under the high reaction temperature (entry 1). Although potassium ferricyanide is also a potential cyanide source, no conditions we tried afforded **1** in decent yields (entry 5–8). In most cases, the starting bromo enone was recovered.

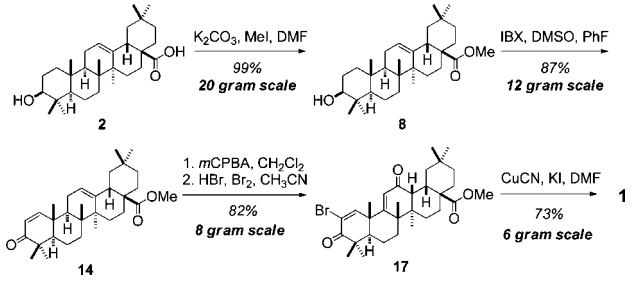
To further confirm the much higher reactivity of iodo enone toward cyanation compared to bromo enone, an efficient and scalable synthesis of iodo enone **18** was developed (Scheme 5). Starting from enone **15** or **16**, iodo enone **19** could be generated under mild iodination conditions. Surprisingly, a mixture of iodo enone **19** and **18** was obtained in 30% and 60% yields, respectively, together with a trace amount of bis-enone **13**. A subsequent treatment of the mixture of **18** and **19** with pyridinium tribromide in acetonitrile afforded iodo enone **18** in an overall 84% yield from enone **15** or **16**. This is the first reported ring−C enone formation of pentacyclic triterpenoids under presumably nonacidic conditions, which has potential applications for acid sensitive substrates. Final cyanide formation by treatment with copper(I) cyanide in dimethylformamide at 120 °C afforded bardoxolone methyl (**1**) in 89% yield, which improved our overall synthetic efficiency by more than 10%. This is additional evidence that iodo enone **18** is indeed a superior substrate to bromo enone **17** in cyanation.

Scheme 5. Scalable Synthesis of **18** and Further Conversion to **1**



As summarized in Scheme 6, our multigram-scale five-step synthesis of bardoxolone methyl (**1**) is more effective than a smaller scale operation. Thus, the *m*-CPBA epoxidation followed by oxidative bromination gave the corresponding bromo enone **17** in an 82% yield in an 8-g-scale reaction, compared to 79% on a 0.5-g scale. And cyanide displacement resulted in a 73% yield of **1** in a 6-g scale compared to 66% in a 0.2-g scale.

Scheme 6. Gram-Scale Synthesis of Bardoxolone Methyl (**1**)



(10) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.

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In summary, we have synthesized bardoxolone methyl (**1**) in five steps in 50% overall yield from commercially available oleanolic acid. This route should provide facile access to other bardoxolone methyl analogues in fewer than 10 steps. Our synthesis features a bromide−hydrogen bromide mediated enone formation together with regioselective enone bromination, followed by an efficient cyanide displacement to furnish bardoxolone methyl (**1**). The iodine-mediated ring-C enone formation accompanied by a regioselective ring-A enone iodination features the first reported ring-C enone formation under nonacidic conditions, which should be valuable for future investigations based on acid-sensitive substrates. Cross-coupling cyanation reactions with iodo enone **18** using potassium ferricyanide as the cyanide source are currently undergoing in the laboratory.

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Supporting Information Available. 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.

The authors declare no competing financial interest.