Novel Synthetic Oleanane and Ursane Triterpenoids with Various Enone Functionalities in Ring A as Inhibitors of Nitric Oxide Production in Mouse Macrophages†

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We initially randomly synthesized about 60 oleanane and ursane triterpenoids as potential anti-inflammatory and cancer chemopreventive agents. Preliminary screening of these derivatives for inhibition of production of nitric oxide induced by interferon-γ in mouse macrophages revealed that 3-oxooleana-1,12-dien-28-oic acid (**B-15**) showed significant activity (IC_{50} = 5.6 μM). On the basis of the structure of **B-15**, 19 novel olean- and urs-12-ene triterpenoids with a 1-en-3-one functionality having a substituent at C-2 in ring A have been designed and synthesized. Among them, 3-oxooleana-1,12-diene derivatives with carboxyl, methoxycarbonyl, and nitrile groups at C-2 showed higher activity than the lead compound **B-15**. In particular, 2-carboxy-3-oxooleana-1,12-dien-28-oic acid (**3**) had the highest activity (IC_{50} = 0.07 μM) in this group of triterpenoids. The potency of **3** was similar to that of hydrocortisone (IC_{50} = 0.01 μM), although **3** does not act through the glucocorticoid receptor. Interesting structure−activity relationships of these novel synthetic triterpenoids are also discussed.

Introduction

Oleanane and ursane triterpenoids are pentacyclic compounds with 30 carbon atoms, which are derived biosynthetically by the cyclization of squalene.[1] The group includes a very large number of naturally occurring members that cover an impressive variety of functional groups.[2] Many compounds of this group are reported to have interesting biological, pharmacological, or medicinal activities similar to those of retinoids and steroids, such as anti-inflammatory activity, suppression of tumor promotion, suppression of immunoglobulin synthesis, protection of the liver against toxic injury, induction of collagen synthesis, and induction of differentiation in leukemia or teratocarcinoma cells.[3] However, the potency of these triterpenoids is relatively weak. There are no systematic studies of structure−activity relationships based on chemical modification of oleanane and ursane triterpenoids.[4] We have therefore considered that bioassay-directed systematic drug design and synthesis of derivatives of oleanolic acid (**1**) and ursolic acid (**2**), which are commercially available, could be of great value in discovering novel structures with high biological potency.

The high output of nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS), which is expressed in activated macrophages, plays an important role in host defense. However, excessive production of NO also can destroy functional normal tissues during acute and chronic inflammation.[5] This phenomenon is also closely related mechanistically to carcinogenesis.[6] Thus, inhibitors of NO production in macrophages are potential anti-inflammatory and cancer chemopreventive drugs. Because oleanolic and ursolic acids are already known to have weak anti-inflammatory and anticarcinogenic activity,[3a,3b,3e,3f] we focused our attention on therapeutic agents of these diseases. For this purpose, we have adopted an assay system that measures inhibition of NO production induced by interferon-γ (IFN-γ) in mouse macrophages[7] as a preliminary screening assay system. We synthesized various oleanolic and ursolic acid derivatives and tested them as inhibitors of NO production. As a result, we have identified a series of novel olean-12-ene triterpenoids with a 1-en-3-one functionality having carboxyl, methoxycarbonyl, and nitrile groups at C-2 in ring A that show significant inhibitory activity (IC_{50} = 0.01−0.1 μM level) against production of NO induced by IFN-γ in mouse macrophages. In particular, 2-carboxy-3-oxooleana-1,12-dien-28-oic acid (**3**) had the highest activity (IC_{50} = 0.07 μM) in this group of compounds. The potency of **3** was similar to that of hydrocortisone (IC_{50} = 0.01 μM), although **3** does not act through the glucocorticoid receptor. We report here the synthesis, inhibitory activity, and structure−activity relationships of these novel triterpenoids in detail.

Chemistry

Discovery of Lead Compound. When we started this project, we had no information about a lead

† Part of this work has been reported in preliminary form: (a) Honda, T.; Finlay, H. J.; Gribble, G. W.; Suh, N.; Sporn, M. B. New enone derivatives of oleanolic acid and ursolic acid as inhibitors of nitric oxide production in mouse macrophages. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1623−1628. (b) Honda, T.; Rounds, B. V.; Bore, L.; Favaloro, F. G., Jr.; Gribble, G. W.; Suh, N.; Wang, Y.; Sporn, M. B. Novel synthetic oleanane triterpenoids: a series of highly active inhibitors of nitric oxide production in mouse macrophages. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3429−3434.

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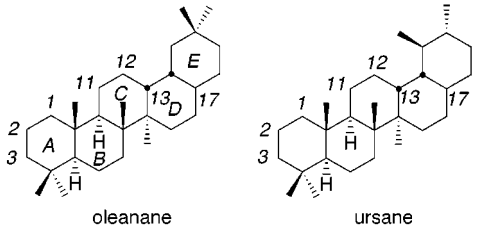
Table 1. Preliminary Screening Results of Synthetic Oleanane and Ursane Triterpenoids

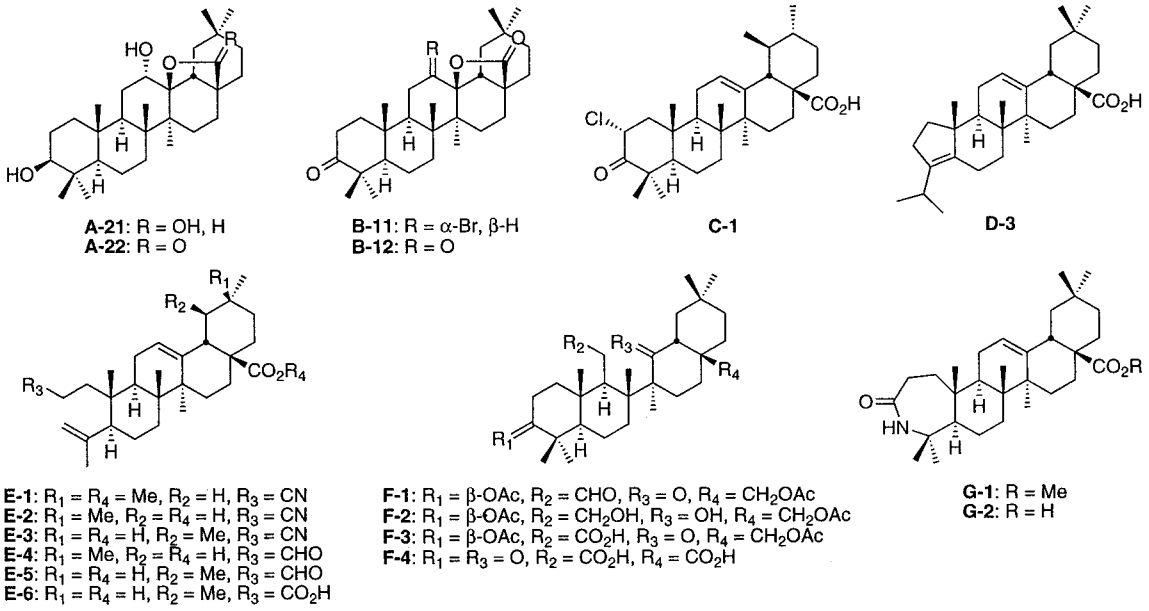


compd	skeleton	C-3	C-12	C-13	C-17	inhibition (%) at 10 μM[b]	ref
1	olean-12-ene	β-OH	H		CO_2H	38	10
2	urs-12-ene	β-OH	H		CO_2H	0	15
A-1	olean-12-ene	β-OH	H		CO_2Me	0	10
A-2	urs-12-ene	β-OH	H		CO_2Me	0	15
A-3	olean-12-ene	β-OAc	H		CO_2Me	10	10
A-4	urs-12-ene	β-OAc	H		CO_2Me	15	15
A-5	olean-12-ene	β-OAc	H		CO_2H	0	10
A-6	urs-12-ene	β-OAc	H		CO_2H	0	15
A-7	olean-12-ene	β-OH	H		CH_2OH	0	28
A-8	urs-12-ene	β-OH	H		CH_2OH	8	29
A-9	olean-12-ene	β-OAc	H		CH_2OAc	4	28
A-10	urs-12-ene	β-OAc	H		CH_2OAc	0	29
A-11	oleanane	β-OAc	α-OH	β-H	CO_2Me	0	*c*
A-12	oleanane	β-OAc	β-OH	β-H	CO_2Me	0	*c*
A-13	oleanane	β-OAc	β-OAc	β-H	CH_2OAc	0	*c*
A-14	oleanane	β-OAc	α-OH	β-H	CH_2OAc	0	*c*
A-15	oleanane	β-OH	α-OH	β-H	CH_2OH	48	*c*
A-16	oleanane	β-OH	β-OH	β-H	CH_2OH	20	*c*
A-17	oleanane	β-OH	=O	β-H	CO_2Me	0	10
A-18	oleanane	β-OAc	=O	β-H	CO_2Me	0	10
A-19	olean-12-ene	α-OH	H		CO_2H	18	30
A-20	urs-12-ene	α-OH	H		CO_2H	48	31
A-21[a]	oleanane	β-OH	α-OH	$-$O$-$	$-$CH(OH)$-$	21	32
A-22[a]	oleanane	β-OH	α-OH	$-$O$-$	$-$CO$-$	13	32
A-23	oleanane	β-OAc	12α,13α-epoxy-		CO_2Me	0	10
A-24	oleanane	β-OH	α-OH	β-OH	CH_2OH	22	32
B-1	olean-12-ene	=O	H		CO_2H	16	10
B-2	urs-12-ene	=O	H		CO_2H	22	33
B-3	olean-12-ene	=O	H		CO_2Me	24	10
B-4	urs-12-ene	=O	H		CO_2Me	16	15
B-5	olean-12-ene	=O	H		CHO	11	34
B-6	urs-12-ene	=O	H		CHO	21	34
B-7	oleana-11,13(18)-diene	=O	H		CO_2H	47	*c*
B-8	oleanane	=O	=O	β-H	CO_2Me	3	10
B-9	oleanane	=O	=O	β-H	CO_2H	37	*c*
B-10	oleanane	=O	=O	β-H	CHO	38	*c*
B-11[a]	oleanane	=O	α-Br	$-$O$-$	$-$CO$-$	4	10
B-12[a]	oleanane	=O	=O	$-$O$-$	$-$CO$-$	0	10
B-13	oleana-1,12-diene	=O	H		CO_2Me	19	9
B-14	ursa-1,12-diene	=O	H		CO_2Me	0	*d*
B-15	oleana-1,12-diene	=O	H		CO_2H	85	*d*
B-16	ursa-1,12-diene	=O	H		CO_2H	41	14
C-1[a]	urs-12-ene	=O	H		CO_2H	55	*c*
C-2	olean-12-ene	α-Cl	H		CO_2Me	2	*c*
C-3	olean-12-ene	α-Cl	H		CO_2H	0	*c*
D-1	oleana-2,12-diene	H	H		CO_2Me	3	35
D-2	oleana-2,12-diene	H	H		CO_2H	0	*c*
D-3[a]	olean-12-ene		H		CO_2H	0	*c*
E-1[a]	A-ring cleaved olean-12-ene		H		CO_2Me	21	36
E-2[a]	A-ring cleaved olean-12-ene		H		CO_2H	33	37
E-3[a]	A-ring cleaved urs-12-ene		H		CO_2H	39	37
E-4[a]	A-ring cleaved olean-12-ene		H		CO_2H	22	37
E-5[a]	A-ring cleaved urs-12-ene		H		CO_2H	55	37
E-6[a]	A-ring cleaved urs-12-ene		H		CO_2H	10	37
F-1[a]	C-ring cleaved oleanane	β-OAc			CH_2OAc	52	*c*
F-2[a]	C-ring cleaved oleanane	β-OAc			CH_2OAc	12	*c*
F-3[a]	C-ring cleaved oleanane	β-OAc			CH_2OAc	52	*c*
F-4[a]	C-ring cleaved oleanane	=O			CO_2H	28	*c*

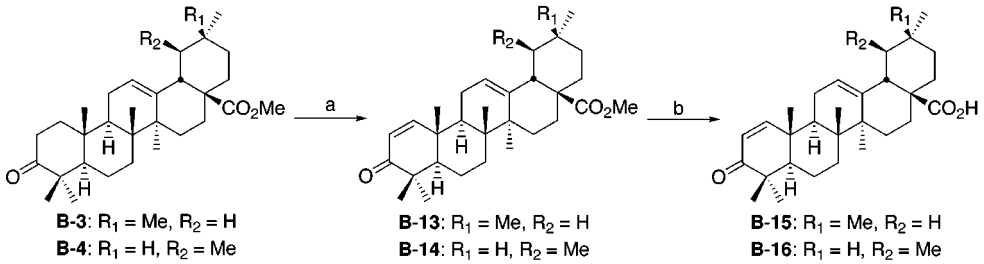
Table 1 (Continued)

compd	skeleton	C-3	C-12	C-13	C-17	inhibition (%) at 10 μM[b]	ref
G-1[a]	olean-12-ene		H		CO_2Me	0	36
G-2[a]	olean-12-ene		H		CO_2H	51	37
hydrocortisone						80	

[a] Structure shown below this table. [b] Details of the evaluation method are described in the Experimental Section. [c] Unknown compound (synthesis and spectral data will be published elsewhere). [d] Unknown compound (synthesis and spectral data are shown in this paper).



Scheme 1[a]



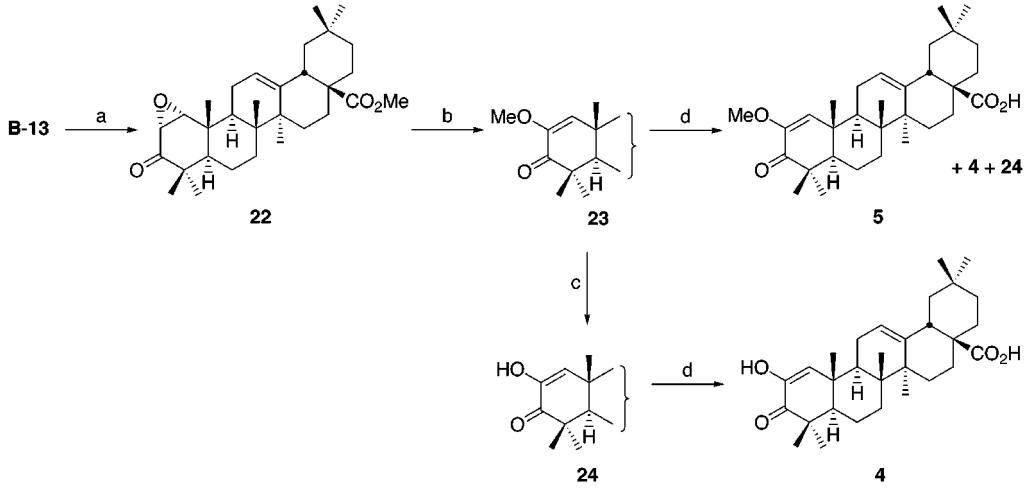
[a] Reagents: (a) PhSeCl, EtOAc; *m*CPBA, pyr, EtOAc; (b) LiI, DMF.

compound. Therefore, about 60 oleanolic and ursolic acid derivatives were initially randomly synthesized. They are divided into seven categories: 3-hydroxy derivatives, **A**; 3-oxo derivatives, **B**; chloro derivatives, **C**; dehydroxyoleanane derivatives, **D**; A-ring cleaved derivatives, **E**; C-ring cleaved oleanane derivatives, **F**; and lactams, **G** (see Table 1). In the preliminary screen of these derivatives for inhibition of production of NO induced by IFN-γ in mouse macrophages, 3-oxooleana-1,12-dien-28-oic acid (**B-15**) was found to show significant activity (inhibition: 85% at 10 μM, IC_{50} = 5.6 μM). (See Tables 1 and 2.)

Design and Synthesis of New Derivatives. When **B-15** is compared with the other derivatives, it has the following features: first, it is an oleanane; second, it has a 1-en-3-one functionality in ring A; third, it has a carboxyl group at C-17. We focused our attention on the 1-en-3-one functionality in ring A among these features. We therefore designed novel olean- and urs-12-ene triterpenoids with a 1-en-3-one functionality having a substituent at C-2 in ring A, **3**−**19**, and novel triterpenoid−steroid hybrid compounds, **20** and **21**[8] (see Table 2). The syntheses of these newly designed derivatives and compounds **B-13**−**B-16** are illustrated in Schemes 1−6.

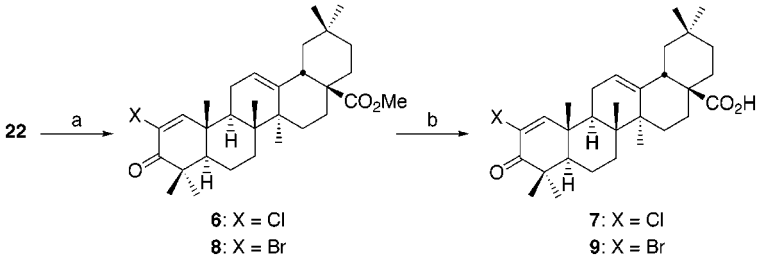
Ester **B-13**[9] was synthesized in 62% yield by introduction of a double bond at C-1 of methyl oleanonate (**B-3**)[10] with phenylselenenyl chloride (PhSeCl) in ethyl acetate and sequential addition of pyridine and *m*-chloroperbenzoic acid.[11,12] Acid **B-15** was synthesized in 85% yield by halogenolysis of **B-13** with lithium iodide in *N*,*N*-dimethylformamide (DMF).[13] Similarly, acid **B-16**[14] was synthesized in 58% yield via ester **B-14** from methyl ursonate (**B-4**).[15] Epoxide **22**[9] was prepared in 99% yield by epoxidation of **B-13** with alkaline hydrogen peroxide. Treatment of **22** with sodium methoxide[16] gave enone **23** (yield, 87%; 98% based on recovered **22**). Diosphenol **24** was synthesized by demethylation of the methyl enol ether at C-2 of **23** with hydrochloric acid in acetic acid (yield, 81%). Halogenolysis of **24** gave acid **4** (yield, 18%). Halogenolysis of **23** gave a desired partial demethylated product **5** in 28% (41% based on recovered

Scheme 2[a]



[a] Reagents: (a) 30% H_2O_2, NaOH(aq), THF; (b) NaOMe, MeOH; (c) HCl, AcOH; (d) LiI, DMF.

Scheme 3[a]



[a] Reagents: (a) HX, AcOH, $CHCl_3$; (b) LiI, DMF.

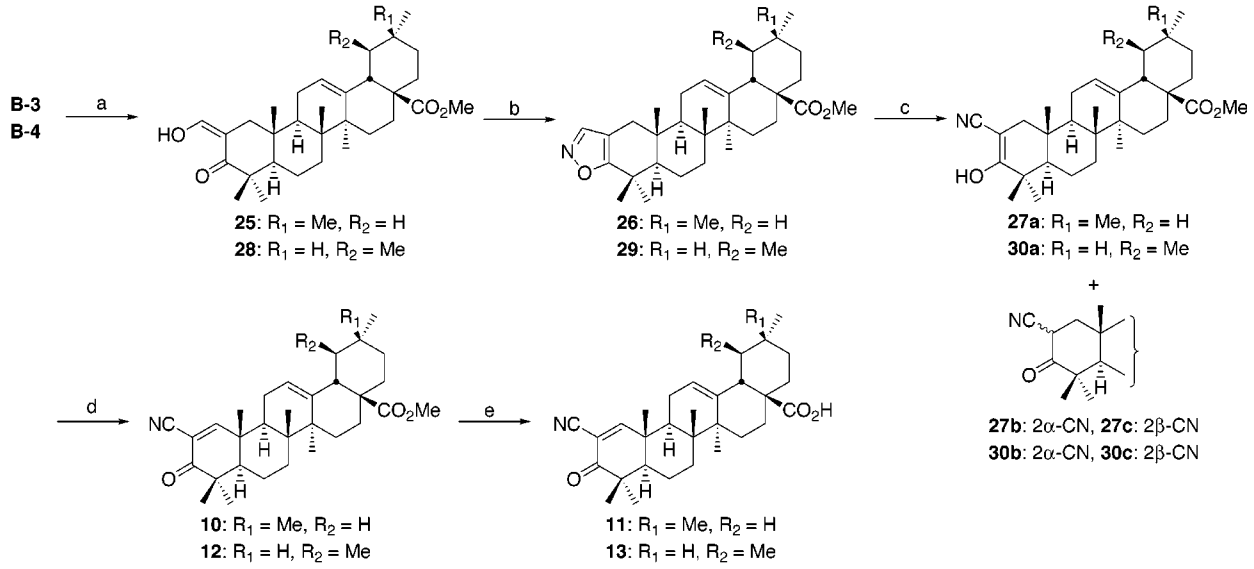
23) yield.[17] Chloride **6** was synthesized in 81% yield from **22** with hydrogen chloride in acetic acid and chloroform.[18] Halogenolysis of **6** gave chloride **7** in 77% yield. Similarly, bromides **8** and **9** were prepared from **22** and **8** (yield, 96% and 76%), respectively. Hydroxymethylene **25**[19,20] was prepared in 95% yield by formylation of **B-3** with ethyl formate in the presence of sodium methoxide in benzene.[21] Isoxazole **26** was prepared in 86% yield by condensation of **25** with hydroxylamine.[22] Cleavage of the isoxazole moiety of **26** with sodium methoxide gave nitrile **27** in 99% yield.[22] ^{1}H NMR showed that **27** is a mixture of three tautomers [**27a**, **27b** (2α-cyano), and **27c** (2β-cyano)] and that **27a** is the major one in $CDCl_3$. Enone **10** was prepared in 88% yield by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of **27** in benzene, although the same method as for **B-13** gave **10** in only 35% yield. Halogenolysis of **10** gave acid **11** in 71% (91% based on recovered **10**) yield. Similarly, ursane derivative **12** was synthesized in 52% yield via **28**,[20,23] **29**, and **30** from **B-4**. Acid **13** was prepared in 74% yield by halogenolysis of **12**. Enal **14** was prepared from **25** by PhSeCl−pyridine in methylene chloride and sequential addition of 30% hydrogen peroxide[24] (yield, 71%; 79% based on recovered **25**). Halogenolysis of **14** did not give acid **15** but a complex mixture. Therefore, the synthesis of acid **15** from oleanonic acid (**B-1**)[10] was attempted. Formylation of **B-1** with ethyl formate in the presence of sodium methoxide in tetrahydrofuran gave **32**[20] (yield, 45%; 66% based on recovered **B-1**). Acid **15** was prepared from **32** according to the same method as for **14** (yield, 71%; 84% based on recovered **32**). Jones oxidation of **14** gave acid **16** in 30% (39% based on recovered **14**) yield. Because this yield was not enough to synthesize derivatives **3** and **17**−**19** from **16**, an alternative route was adopted. Ester **31** was prepared in 74% (89% based on recovered **B-3**) yield from **B-3** by Stiles' reagent (methoxymagnesium methyl carbonate) in DMF,[25] followed by methylation with diazomethane. ^{1}H NMR showed that **31** is the single tautomer in $CDCl_3$ as depicted in Scheme 5. Enone **17** was prepared from **31** according to the same method as for **14** (yield, 83%; 90% based on recovered **31**). Hydrolysis of **17** with potassium hydroxide in aqueous methanol gave acid **16** selectively in 97% yield because the methoxycarbonyl group at C-17 of **17** is sterically hindered. Halogenolysis of **16** gave dicarboxylic acid **3** in 58% yield. Methylation of **3** with methanol under acidic conditions gave ester **18** selectively in 78% yield because of the steric hindrance of the carboxylic acid at C-17 of **3**. Amide **19** was prepared selectively in 96% yield from **17** with saturated ammonia−methanol.

Biological Results and Discussion

The inhibitory activities [IC_{50} (μM) value] of compounds **B-1**, **B-13**, **B-15**, **B-16**, **1**−**21**, and hydrocortisone (a positive control) on NO production induced by IFN-γ in mouse macrophages are shown in Table 2. These derivatives are arranged according to the strength of Taft's σ^* values[26] of substituents at C-2. These results provide the following interesting structure−activity relationships:

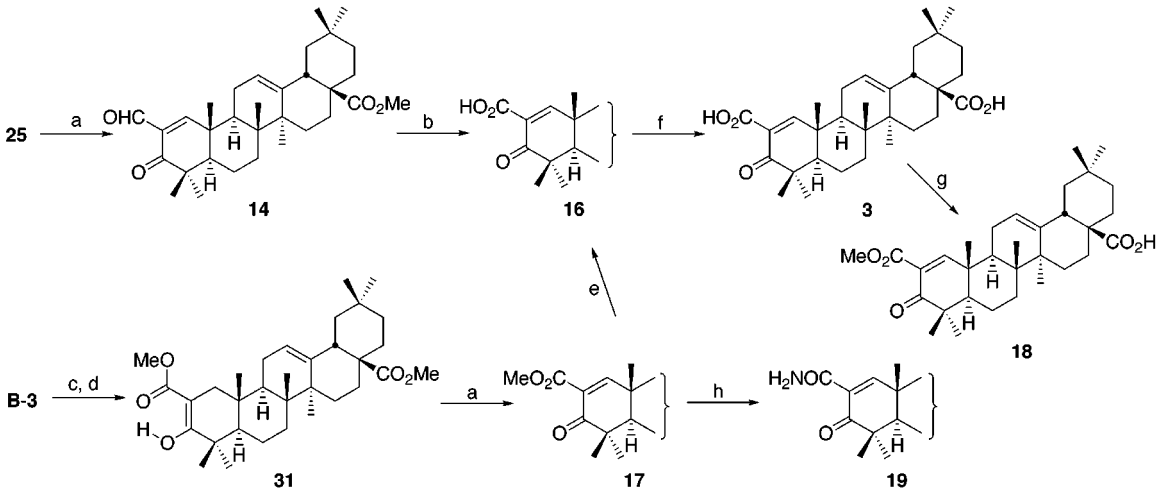
(1) In the A ring, a 1-en-3-one functionality is important for significant activity. The lead compound **B-15** is much more potent than the C-3 ketone **B-1** and the

Scheme 4[a]



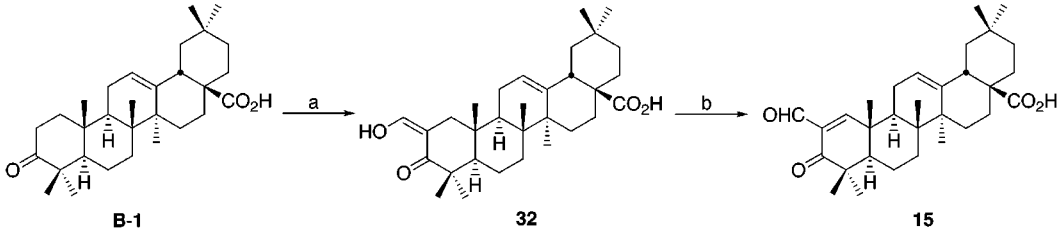
[a] Reagents: (a) HCO_2Et, NaOMe, PhH; (b) $NH_2OH{\cdot}HCl$, aq EtOH; (c) NaOMe, Et_2O, MeOH; (d) DDQ, PhH; (e) LiI, DMF.

Scheme 5[a]



[a] Reagents: (a) PhSeCl, pyr, CH_2Cl_2; 30% H_2O_2, CH_2Cl_2; (b) Jones; (c) Stiles' reagent, DMF; (d) CH_2N_2, Et_2O, THF; (e) KOH, aq MeOH; (f) LiI, DMF; (g) H_2SO_4, MeOH; (h) NH_3, MeOH.

Scheme 6[a]



[a] Reagents: (a) HCO_2Et, NaOMe, THF; (b) PhSeCl, pyr, CH_2Cl_2; 30% H_2O_2, CH_2Cl_2.

C-3 alcohol **1** (oleanolic acid). Also, the ursane derivative **B-16** is more potent than the C-3 alcohol **2** (ursolic acid).

(2) A correlation between Taft's σ^* values of substituents at C-2 and biological activity is not observed. This result shows that the activity does not depend on the strength of electron-withdrawing effect of a substituent at C-2.

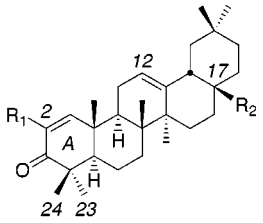
(3) Carboxyl, methoxycarbonyl, and nitrile groups at C-2 enhance activity. Compounds **3**, **10**, **11**, **16**, and **17** are about 10−100 times more potent than **B-15**. In particular, **3** showed the highest activity (IC_{50} = 0.07 μM) in this series of compounds. The potency of **3** was similar to that of hydrocortisone (IC_{50} = 0.01 μM).

(4) Hydroxyl, aminocarbonyl, methoxy, chloride, and bromide groups decrease activity. Compounds **4**−**9** and **19** are much less potent than **B-15**.

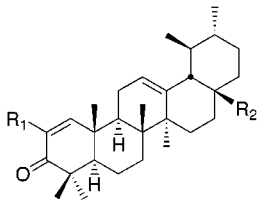
(5) A formyl group does not confer activity but only toxicity.

(6) 23,24-Dimethyl groups are important for signifi-

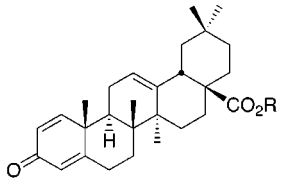
Table 2. Activity of Olean- and Urs-12-ene Triterpenoids with Various 1-En-3-one Functionalities



3-oxooleana-1,12-diene



3-oxoursa-1,12-diene



20: R = Me
21: R = H

compd	skeleton[a]	R_1 at C-2	R_2 at C-17	Taft's σ^* value of R_1	formula	analyses[b]	activity[c] IC_{50} (μM)
B-13	O	H	CO_2Me		$C_{31}H_{46}O_3$	ref 9	31
B-15	O	H	CO_2H		$C_{30}H_{44}O_3 \cdot 3/4H_2O$	C, H	5.6
20	D	H	CO_2Me		$C_{29}H_{40}O_3 \cdot 1/4H_2O$	C, H	>40
21	D	H	CO_2H		$C_{28}H_{38}O_3 \cdot 1/3H_2O$	C, H	13
B-16	U	H	CO_2H		$C_{30}H_{44}O_3$	ref 14	13
5	O	OH	CO_2H	1.34	$C_{30}H_{44}O_4 \cdot 1/2H_2O$	C, H	27
19	O	$CONH_2$	CO_2Me	1.68	$C_{32}H_{47}O_4N \cdot 3/4H_2O$	C, H, N	14
4	O	OMe	CO_2H	1.81	$C_{31}H_{46}O_4 \cdot 1/2H_2O$	C, H	30
17	O	CO_2Me	CO_2Me	2.00	$C_{33}H_{48}O_5$	C, H	0.9
18	O	CO_2Me	CO_2H	2.00	$C_{32}H_{46}O_5$	C, H	2.2
16	O	CO_2H	CO_2Me	2.08	$C_{32}H_{46}O_5 \cdot 1/2H_2O$	C, H	0.8
3	O	CO_2H	CO_2H	2.08	$C_{31}H_{44}O_5$	C, H	0.07
14	O	CHO	CO_2Me	2.15	$C_{32}H_{46}O_4$	C, H	toxic[d]
15	O	CHO	CO_2H	2.15	$C_{31}H_{44}O_4 \cdot 1/2H_2O$	C, H	toxic[d]
8	O	Br	CO_2Me	2.84	$C_{31}H_{45}O_3Br$	C, H	>40
9	O	Br	CO_2H	2.84	$C_{30}H_{43}O_3Br \cdot H_2O$	C, H	7.3
6	O	Cl	CO_2Me	2.96	$C_{31}H_{45}O_3Cl$	C, H	>40
7	O	Cl	CO_2H	2.96	$C_{30}H_{43}O_3Cl \cdot 1/4H_2O$	C, H	>40
10	O	CN	CO_2Me	3.30	$C_{32}H_{45}O_3N \cdot 1/4H_2O$	C, H, N	0.7
11	O	CN	CO_2H	3.30	$C_{31}H_{43}O_3N \cdot 1/2H_2O$	C, H, N	0.6
12	U	CN	CO_2Me	3.30	$C_{32}H_{45}O_3N \cdot 3/4H_2O$	C, H, N	5.1
13	U	CN	CO_2H	3.30	$C_{31}H_{43}O_3N \cdot H_2O$	C, H, N	6.2
B-1		oleanonic acid			$C_{30}H_{46}O_3$	ref 10	37
1		oleanolic acid			$C_{30}H_{48}O_3$	ref 10	>40
2		ursolic acid			$C_{30}H_{48}O_3$	ref 15	toxic[e]
		hydrocortisone					0.01

[a] O, 3-oxooleana-1,12-diene; D, 23,24-dinor-3-oxooleana-1,4,12-triene; U, 3-oxoursa-1,12-diene. [b] C, H, and N analyses were within ±0.4% of the theoretical values. [c] Details of the evaluation method are described in the Experimental Section. IC_{50} values of **3** and hydrocortisone were determined in the range of 0.1 pM−1 μM (10-fold dilutions). The other compounds were assayed in the range of 0.01−40 μM (4-fold dilutions). Values are an average of two separate experiments. [d] Compounds **14** and **15** were toxic to cells above 1 μM and were not active below 1 μM. [e] Ursolic acid (**2**) was toxic to cells above 10 μM and was not active below 10 μM.

cant activity. **B-15** is more potent than 23,24-dinor-olean-1-en-3-one derivative **21**.

(7) The oleanane skeleton is more potent than the ursane skeleton. **B-15**, **10**, and **11** are more potent than **B-16**, **12**, and **13**, respectively.

(8) The role of methoxycarbonyl and carboxyl groups at C-17 is ambiguous. In some analogues, the carboxyl group is more potent than the methoxycarbonyl group: acids **B-15**, **3**, **9**, and **21** are more potent than esters **B-13**, **16**, **8**, and **20**, respectively. For other analogues, the carboxyl and methoxycarbonyl groups show similar activity: acids **11** and **13** show similar activity to esters **10** and **12**, respectively. Lastly, acid **18** is less potent than ester **17**.

The inhibitory activity of new triterpenoids **3** and **11** was not blocked by the glucocorticoid antagonist, RU-486,[27] which reverses the action of hydrocortisone (see Figure 1). These data strongly suggest that the actions of these triterpenoids on the iNOS system are not mediated by their interaction with the glucocorticoid receptor.

On the basis of these structure−activity relationships, further lead optimization is in progress. Further biological evaluation and studies on the mechanism of action of **3** are also in progress.

Experimental Section

General Experimental Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-181 digital polarimeter. UV and IR spectra were recorded on a Hewlett-Packard 8451A UV/VIS spectrophotometer and a Perkin-Elmer 600 series FTIR spectrophotometer, respectively. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer. The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of C*H*Cl_3 (^1H NMR) and the δ 77.23 signal of *C*DCl_3 (^{13}C NMR) as internal standards. Low-resolution mass spectra and high-resolution MS data were obtained on a Micromass 70-VSE unless otherwise stated. Elemental microanalysis was performed by Atlantic Microlab Inc. TLC and preparative TLC (prep-TLC) were performed with Merck precoated TLC plates silica gel 60 F_{254}. Flash column chromatography was done with Select Scientific silica gel (230−400 mesh). The standard work up method was as follows: an organic extract was washed with saturated aqueous $NaHCO_3$ solution (three times) followed by saturated aqueous NaCl solution (three times), then dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated in vacuo.

Methyl 3-Oxooleana-1,12-dien-28-oate (**B-13**).[9] A solution of methyl oleanonate (**B-3**)[10] (2.00 g, 4.27 mmol) and phenylselenenyl chloride (98%) (1.00 g, 5.12 mmol) in EtOAc (85 mL) was stirred at room temperature for 3 h. To the stirred

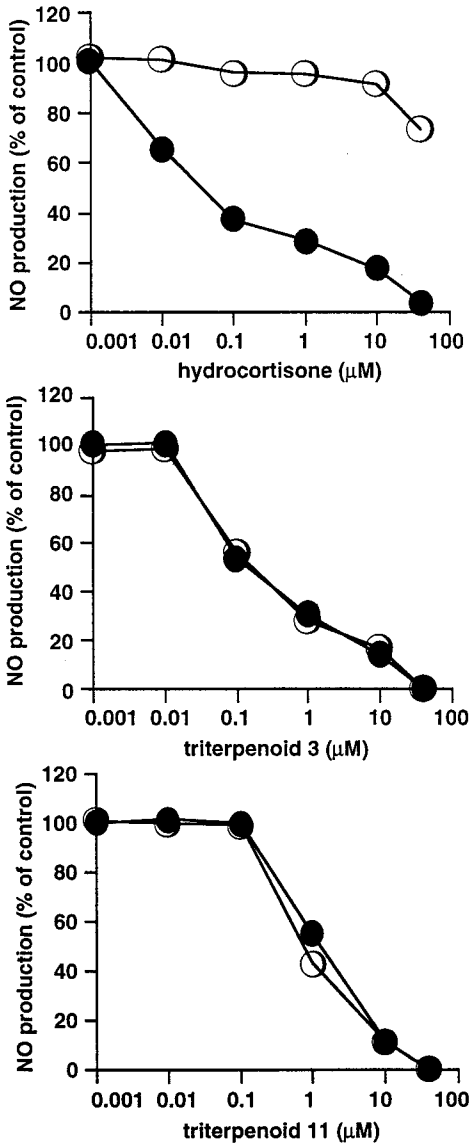


Figure 1. Blockage by glucocorticoid antagonist RU486 of hydrocortisone-inhibited NO production but not of triterpenoid (**3** and **11**) inhibited NO production in primary mouse macrophages. Macrophage cells were incubated with IFN-γ (20 ng/mL) together with hydrocortisone or triterpenoids without RU486 (●); in some cases RU486 (1 μM) was added simultaneously to both hydrocortisone- and triterpenoid-treated cell wells (○). RU486 itself does not interfere with NO production at the concentration tested.

mixture, saturated aqueous $NaHCO_3$ solution was added. After most of the aqueous layer was removed, pyridine (844 mg, 10.7 mmol) and *m*-chloroperbenzoic acid (50−60%) (3.68 g, 10.7 mmol) were added to the organic layer. The mixture was stirred at room temperature for 1 h. The mixture was washed with 5% aqueous NaOH solution (three times), saturated aqueous NH_4Cl solution (three times), and saturated aqueous NaCl solution (three times); dried over anhydrous $MgSO_4$; and filtered. The filtrate was evaporated in vacuo to give a solid. The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1)] to give **B-13** as a crystalline solid (1.23 g, 62%): mp 159−161 °C; $[\alpha]^{25}_D$ +103° (*c* 0.64, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 230 (3.92) nm. IR (KBr): 2946, 2867, 1728, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.04 (1H, d, J = 10.1 Hz), 5.81 (1H, d, J = 10.1 Hz), 5.36 (1H, t, J = 3.7 Hz), 3.64, (3H, s), 2.90 (1H, dd, J = 4.6, 13.9 Hz), 1.17 (3H, s), 1.16 (6H, s), 1.10, 0.94, 0.91, 0.83 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 205.5, 178.4, 159.3, 144.5, 125.2, 121.9, 53.6, 51.8, 47.0, 45.9, 44.7, 42.2, 42.0, 41.7, 40.3, 39.7, 34.1, 33.3, 32.7, 32.5, 30.9, 28.0, 27.9, 26.0, 23.8, 23.5, 23.2, 21.8, 19.1, 18.8, 17.5. EIMS (70 eV) *m*/*z*: 466 $[M]^+$ (73), 451 (11), 407 (31), 262 (57), 203 (100). HREIMS: Calcd for $C_{31}H_{46}O_3$: 466.3447. Found: 466.3446.

Methyl 3-Oxoursa-1,12-dien-28-oate (**B-14**). **B-14** was prepared from methyl ursonate (**B-4**)[15] according to the same method as for **B-13** to give an amorphous solid (66%): $[\alpha]^{26}_D$ +93° (*c* 0.77, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 232 (3.95) nm. IR (KBr): 2974, 2935, 2871, 1725, 1669 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.06 (1H, d, J = 10.1 Hz), 5.81 (1H, d, J = 10.1 Hz), 5.33 (1H, t, J = 3.8 Hz), 3.63 (3H, s), 2.28 (1H, d, J = 11.5 Hz), 1.17, 1.15 (each 3H, s), 1.10 (6H, s), 0.95 (3H, d, J = 5.4 Hz), 0.87 (3H, d, J = 6.3 Hz), 0.85 (3H, s). ^{13}C NMR ($CDCl_3$): δ 205.5, 178.2, 159.5, 139.0, 125.2, 125.0, 53.7, 53.3, 51.7, 48.4, 44.7, 42.6, 41.9, 40.5, 39.5, 39.2, 39.1, 36.8, 33.0, 30.8, 28.2, 28.1, 24.4, 23.7, 23.5, 21.8, 21.4, 19.1, 19.0, 17.7, 17.2. EIMS (70 eV) *m*/*z*: 466 $[M]^+$ (14), 406 (12), 262 (74), 203 (100). HREIMS: Calcd for $C_{31}H_{46}O_3$: 466.3447. Found: 466.3442.

3-Oxooleana-1,12-dien-28-oic Acid (**B-15**). A mixture of **B-13** (100 mg, 0.21 mmol) and LiI (500 mg) in dry DMF (2 mL) was heated under reflux for 6 h. The mixture was acidified with 5% aqueous HCl solution and then extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was worked up according to the standard method to give a solid (110 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1) followed by hexanes−EtOAc (2:1)] to give **B-15** as an amorphous solid (82 mg, 85%): $[\alpha]^{26}_D$ +103° (*c* 0.45, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 230 (3.75) nm. IR (KBr): 2941, 2866, 1732, 1695, 1671 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.04 (1H, d, J = 10.2 Hz), 5.81 (1H, d, J = 10.2 Hz), 5.35 (1H, t, J = 3.3 Hz), 2.86 (1H, dd, J = 4.2, 13.4 Hz), 1.16, 1.152, 1.147, 1.07, 0.94, 0.91, 0.84 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 205.5, 184.5, 159.2, 144.2, 125.3, 122.1, 53.5, 46.8, 45.8, 44.7, 42.1, 41.9, 41.3, 40.2, 39.7, 34.0, 33.3, 32.6, 32.5, 30.9, 28.0, 27.8, 26.0, 23.7, 23.5, 23.0, 21.8, 19.0, 18.9, 17.7. EIMS (70 eV) *m*/*z*: 452 $[M]^+$ (8.8), 437 (3.8), 406 (6.8), 248 (80), 233 (14), 203 (100). HREIMS: Calcd for $C_{30}H_{44}O_3$: 452.3290. Found: 452.3289. Anal. (Table 2).

3-Oxoursa-1,12-dien-28-oic Acid (**B-16**).[14] **B-16** was prepared from **B-14** according to the same method as for **B-15** to give an amorphous solid (88%): $[\alpha]^{26}_D$ +91° (*c* 0.84, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 230 (3.99) nm. IR (KBr): 3306, 2973, 2930, 2870, 1729, 1695, 1669 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (1H, d, J = 10.1 Hz), 5.82 (1H, d, J = 10.1 Hz), 5.33 (1H, t, J = 3.7 Hz), 2.24 (1H, d, J = 11.2 Hz), 1.18, 1.16, 1.11, 1.09 (each 3H, s), 0.96 (3H, d, J = 6.1 Hz), 0.88 (3H, d, J = 6.4 Hz), 0.88 (3H, s). ^{13}C NMR ($CDCl_3$): δ 205.5, 183.9, 159.4, 138.8, 125.3, 53.6, 52.9, 48.3, 44.7, 42.5, 41.9, 40.5, 39.6, 39.2, 39.0, 36.8, 32.9, 30.8, 28.2, 28.1, 24.2, 23.7, 23.4, 21.8, 21.3, 19.0, 17.8, 17.2. FABMS (NBA) *m*/*z*: 453 $[M + H]^+$ (100) (by a Micromass ZAB-SE). HRFABMS: Calcd for $C_{30}H_{44}O_3$ + H: 453.3369. Found: 453.3335 (by a Micromass 70-SE-4F).

2-Carboxy-3-oxooleana-1,12-dien-28-oic Acid (**3**). A mixture of **16** (109 mg, 0.21 mmol) and LiI (520 mg) in dry DMF (1.5 mL) was heated under reflux for 1 h. After 5% aqueous HCl solution was added, the acidic mixture was extracted with EtOAc three times. The extract was washed with water (three times) and saturated aqueous NaCl solution (three times), dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give a residue (108 mg). The residue was subjected to flash column chromatography [CH_2Cl_2−MeOH (15:1) followed by CH_2Cl_2−MeOH (10:1)] to afford **3** as a crystalline solid (61 mg, 58%): mp >250 °C dec; $[\alpha]^{26}_D$ +81° (*c* 0.53, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 234 (3.88) nm. IR (KBr): 3389, 2943, 2872, 1752, 1696, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (1H, s), 5.37 (1H, t, J = 3.5 Hz), 2.87 (1H, dd, J = 3.8, 13.9 Hz), 1.25, 1.22, 1.18, 1.15, 0.95, 0.93, 0.88 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 209.0, 183.9, 173.2, 165.2, 144.2, 123.4, 121.7, 52.4, 46.8, 45.7, 45.5, 42.3, 41.4, 41.1, 40.6, 40.4, 34.0, 33.2, 32.5, 32.3, 30.9, 28.4, 27.8, 26.0, 23.7, 23.5, 23.0, 22.0, 19.0, 18.4, 17.8. EIMS (70 eV) *m*/*z*: 496 $[M]^+$ (3.0), 478 (3.4), 452 (7.6), 248 (56), 231 (35), 203 (100). HREIMS: Calcd for $C_{31}H_{44}O_5$: 496.3189. Found: 496.3196. Anal. (Table 2).

2-Hydroxy-3-oxooleana-1,12-dien-28-oic Acid (**4**). **4** was prepared from **24** according to the same method as for **B-15**

except that the reaction time was 2 h. The reaction mixture was subjected to flash column chromatography [hexanes−EtOAc (5:1) followed by hexanes−EtOAc (4:1)] to give **4** as an amorphous solid (18%): $[\alpha]^{25}_D$ +99° (*c* 0.46, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 272 (3.71) nm. IR (KBr): 3434, 2938, 1698, 1667, 1649 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.35 (1H, s), 5.96 (1H, brs), 5.34 (1H, t, J = 3.5 Hz), 2.86 (1H, dd, J = 3.8, 13.9 Hz), 1.23, 1.22, 1.14, 1.11, 0.94, 0.92, 0.83 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 201.2, 184.0, 144.1, 143.9, 128.4, 122.3, 54.0, 46.8, 45.8, 44.1, 43.3, 42.2, 41.3, 40.2, 38.7, 34.0, 33.3, 32.6, 30.9, 27.8, 27.4, 26.1, 23.8, 23.6, 23.0, 22.0, 19.9, 18.9, 17.7. EIMS (70 eV) *m*/*z*: 468 $[M]^+$ (3.2), 248 (13), 203 (23), 149 (42), 84 (100). HREIMS: Calcd for $C_{30}H_{44}O_4$: 468.3240. Found: 468.3222. Anal. (Table 2).

2-Methoxy-3-oxooleana-1,12-dien-28-oic Acid (**5**). A mixture of **23** (230 mg, 0.46 mmol) and LiI (1045 mg) in dry DMF (3.5 mL) was heated under reflux for 4 h. The reaction mixture was worked up according to the same method as for **B-15** to give a solid (230 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (3:1) followed by hexanes−EtOAc (2:1), then hexanes−EtOAc (1:1)] to give **24** (35 mg; 16%, 23% based on recovered **23**), **23** (74 mg), **4** (27 mg; 12%, 18% based on recovered **23**), and **5** as an amorphous solid (63 mg; 28%, 41% based on recovered **23**): $[\alpha]^{26}_D$ +96° (*c* 0.29, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 266 (3.84) nm. IR (KBr): 3307, 2947, 2862, 1732, 1693, 1622 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.96 (1H, s), 5.36 (1H, t, J = 3.3 Hz), 3.56 (3H, s), 2.87 (1H, dd, J = 4.2, 13.9 Hz), 1.17 (9H, s), 1.11, 0.94, 0.91, 0.84 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 200.0, 184.4, 149.1, 144.4, 126.1, 122.1, 55.0, 53.2, 46.8, 45.9, 45.4, 43.3, 42.2, 41.3, 40.2, 38.5, 34.0, 33.3, 32.5, 30.9, 28.6, 27.8, 26.1, 23.8, 23.0, 22.0, 20.4, 19.2, 17.6. EIMS (70 eV) *m*/*z*: 482 $[M]^+$ (11), 415 (6.5), 245 (18), 203 (33), 157 (100). HREIMS: Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3375. Anal. (Table 2).

Methyl 2-Chloro-3-oxooleana-1,12-dien-28-oate (**6**). A solution of **22** (99 mg, 0.21 mmol) in AcOH including 1 M HCl (2.5 mL) and $CHCl_3$ (2.5 mL) was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2. After it was washed with water three times, it was worked up according to the standard method to give a solid (96 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (6:1)] to afford **6** as an amorphous solid (84 mg, 81%): $[\alpha]^{26}_D$ +98° (*c* 0.26, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 250 (3.91) nm. IR (KBr): 2943, 2866, 1727, 1689 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.22 (1H, s), 5.34 (1H, t, J = 3.5 Hz), 3.62 (3H, s), 2.89 (1H, dd, J = 4.2, 13.7 Hz), 1.203, 1.197 (each 3H, s), 1.14 (6H, s), 0.93, 0.90, 0.80 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 197.4, 178.3, 155.0, 144.5, 129.8, 121.5, 53.3, 51.8, 46.9, 46.3, 45.8, 42.2, 42.1, 41.64, 41.57, 40.3, 34.0, 33.3, 32.4, 30.9, 28.4, 27.8, 26.0, 23.8, 23.5, 23.1, 22.1, 19.1, 18.8, 17.5. EIMS (70 eV) *m*/*z*: 500 $[M]^+$ (21), 262 (27), 247 (96), 203 (100). HREIMS: Calcd for $C_{31}H_{45}O_3Cl$: 500.3057. Found: 500.3060. Anal. (Table 2).

2-Chloro-3-oxooleana-1,12-dien-28-oic Acid (**7**). **7** was prepared from **6** according to the same method as for **B-15** except that the reaction time was 4 h. The reaction mixture was subjected to flash column chromatography [hexanes−EtOAc (4:1) followed by hexanes−EtOAc (3:1)] to give **7** as an amorphous solid (77%): $[\alpha]^{26}_D$ +88° (*c* 0.50, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 252 (3.20) nm. IR (KBr): 3297, 2943, 2870, 1733, 1691, 1601 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.23 (1H, s), 5.35 (1H, t, J = 3.3 Hz), 2.86 (1H, dd, J = 4.3, 13.8 Hz), 1.22, 1.21, 1.16, 1.13, 0.94, 0.92, 0.84 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 197,4, 184.4, 154.9, 144.3, 129.9, 121.8, 53.2, 46.8, 46.4, 45.8, 42.21, 42.16, 41.6, 41.3, 40.3, 34.0, 33.3, 32.5, 32.4, 30.9, 28.5, 27.8, 26.0, 23.7, 23.5, 23.0, 22.1, 19.0, 18.9, 17.7. EIMS (70 eV) *m*/*z*: 486 $[M]^+$ (25), 248 (100), 203 (96). HREIMS: Calcd for $C_{30}H_{43}O_3Cl$: 486.2901. Found: 486.2898. Anal. (Table 2).

Methyl 2-Bromo-3-oxooleana-1,12-dien-28-oate (**8**). A solution of **22** (220 mg, 0.46 mmol) in AcOH including 1 M HBr (4.9 mL) and $CHCl_3$ (6.1 mL) was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2. After it was washed with water three times, it was worked up according to the standard method to give a solid (260 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (6:1)] to afford **8** as an amorphous solid (238 mg, 96%): $[\alpha]^{26}_D$ +88° (*c* 0.51, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 260 (3.69) nm. IR (KBr): 2943, 2870, 1733, 1691, 1601 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.49 (1H, s), 5.35 (1H, t, J = 3.5 Hz), 3.63 (3H, s), 2.90 (1H, dd, J = 4.0, 13.8 Hz), 1.20, 1.15 (each 6H, s), 0.94, 0.91, 0.81 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 197.3, 178.3, 159.5, 144.6, 121.8, 121.5, 53.3, 51.8, 46.9, 46.5, 45.8, 43.1, 42.3, 42.1, 41.7, 40.3, 34.0, 33.3, 32.4, 30.9, 28.7, 27.8, 26.0, 23.8, 23.6, 23.2, 22.3, 19.1, 18.7, 17.5. EIMS (70 eV) *m*/*z*: 546 (5.0) and 544 (5.2) $[M]^+$, 262 (8.5), 203 (24), 118 (100), 116 (100). HREIMS: Calcd for $C_{31}H_{45}O_3Br$: 544.2552. Found: 544.2553. Anal. (Table 2).

2-Bromo-3-oxooleana-1,12-dien-28-oic Acid (**9**). **9** was prepared from **8** according to the same method as for **B-15** except that the reaction time was 4 h. The reaction mixture was subjected to flash column chromatography [hexanes−EtOAc (4:1) followed by hexanes−EtOAc (3:1)] to give **9** as an amorphous solid (76%): $[\alpha]^{26}_D$ +82° (*c* 0.31, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 260 (3.52) nm. IR (KBr): 3434, 2939, 2870, 1727, 1686, 1601 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.49 (1H, s), 5.35 (1H, t, J = 3.4 Hz), 2.86 (1H, dd, J = 4.2, 13.7 Hz), 1.21 (6H, s), 1.16, 1.14, 0.94, 0.92, 0.83 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 197.2, 184.4, 159.3, 144.3, 121.84, 121.79, 53.3, 46.8, 46.5, 45.8, 43.1, 42.2, 42.0, 41.3, 40.3, 34.0, 33.2, 32.5, 32.4, 30.9, 28.7, 27.8, 26.0, 23.7, 23.5, 23.0, 22.2, 19.1, 18.7, 17.7. EIMS (70 eV) *m*/*z*: 532 (13) and 530 (14) $[M]^+$, 285 (5.6), 283 (6.2), 248 (100), 235 (10), 233 (11), 203 (84). HREIMS: Calcd for $C_{30}H_{43}O_3Br$: 530.2396. Found: 530.2383. Anal. (Table 2).

Methyl 2-Cyano-3-oxooleana-1,12-dien-28-oate (**10**). A solution of **27** (141 mg, 0.28 mmol) and DDQ (98%) (79 mg, 0.34 mmol) in benzene (10 mL) was heated under reflux for 4 h. After insoluble matter was removed by filtration, the filtrate was evaporated in vacuo to give a solid. The solid was subjected to flash column chromatography [benzene−acetone (20:1)] to give a crystalline solid (123 mg, 88%): mp 201−202 °C; $[\alpha]^{26}_D$ +67° (*c* 0.53, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (3.65) nm. IR (KBr): 2945, 2874, 2232, 1724, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75 (1H, s), 5.36 (1H, t, J = 3.5 Hz), 3.64 (3H, s), 2.91 (1H, dd, J = 3.9, 13.9 Hz), 1.22, 1.21, 1.15, 1.14, 0.94, 0.92, 0.83 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 198.3, 178.3, 170.2, 144.8, 121.1, 115.2, 114.0, 52.8, 51.8, 46.9, 45.8, 45.1, 42.3, 41.7, 41.3, 40.8, 40.5, 34.0, 33.3, 32.4, 32.3, 30.9, 27.9, 27.8, 26.0, 23.8, 23.4, 23.1, 21.8, 18.9, 18.1, 17.6. EIMS (70 eV) *m*/*z*: 491 $[M]^+$ (35), 459 (13), 432 (27), 262 (22), 247 (24), 203 (100). HREIMS: Calcd for $C_{32}H_{45}O_3N$: 491.3399. Found: 491.3391. Anal. (Table 2).

2-Cyano-3-oxooleana-1,12-dien-28-oic Acid (**11**). **11** was prepared from **10** according to the same method as for **B-15** except that the reaction time was 3 h. The reaction mixture was subjected to flash column chromatography [hexanes−EtOAc (3:1) followed by hexanes−EtOAc (2:1), then hexanes−EtOAc (1:1)] to give **11** as an amorphous solid (71%, 91% based on recovered **10**): $[\alpha]^{26}_D$ +61° (*c* 0.66, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 238 (3.87) nm. IR (KBr): 3387, 2947, 2870, 2233, 1729, 1691, 1609 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75 (1H, s), 5.35 (1H, t, J = 3.3 Hz), 2.86 (1H, dd, J = 4.0, 13.6 Hz), 1.22, 1.21, 1.15, 1.12, 0.94, 0.92, 0.85 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 198.2, 184.3, 170.1, 144.4, 121.4, 115.1, 114.1, 52.7, 46.8, 45.7, 45.0, 42.2, 41.3, 40.8, 40.5, 33.9, 33.2, 32.5, 32.2, 30.9, 27.9, 27.7, 25.9, 23.7, 23.4, 22.9, 21.8, 18.9, 18.1, 17.7. EIMS (70 eV) *m*/*z*: 477 $[M]^+$ (18), 462 (5.6), 431 (16), 416 (10), 248 (76), 235 (25), 203 (100). HREIMS: Calcd for $C_{31}H_{43}O_3N$: 477.3243. Found: 477.3240. Anal. (Table 2).

Methyl 2-Cyano-3-oxoursa-1,12-dien-28-oate (**12**). **12** was prepared from **30** according to the same method as for **10** to give an amorphous solid (62%): $[\alpha]^{26}_D$ +53° (*c* 0.35, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (3.74) nm. IR (KBr): 2973, 2926, 2870, 2229, 1723, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.77 (1H, s), 5.33 (1H, t, J = 3.7 Hz), 3.62 (3H, s), 2.29 (1H, d, J = 11.2 Hz), 1.23, 1.21, 1.14, 1.11 (each 3H, s), 0.96, 0.88 (each 3H, d, J = 6.3 Hz), 0.86 (3H, s). ^{13}C NMR ($CDCl_3$): δ 198.3, 178.1, 170.4, 139.3, 124.2, 115.2, 114.0, 53.2, 52.8, 51.7, 48.3, 45.1, 42.7, 41.2, 40.70, 40.65, 39.1, 39.0, 36.7, 32.6, 30.8, 28.1, 28.0, 24.3, 23.6, 23.4, 21.8, 21.3, 18.9, 18.2, 17.8, 17.2. EIMS (70

eV) *m/z*: 491 $[M]^+$ (38), 431 (35), 262 (46), 249 (82), 203 (65), 84 (100). HREIMS: Calcd for $C_{32}H_{45}O_3N$: 491.3399. Found: 491.3395. Anal. (Table 2).

2-Cyano-3-oxoursa-1,12-dien-28-oic Acid (**13**). **13** was prepared from **12** according to the same method as for **B-15** except that the reaction time was 4 h. The reaction mixture was subjected to prep-TLC [hexanes−EtOAc (1.5:1)] to give **13** as an amorphous solid (74%): $[\alpha]^{26}_D$ +48° (*c* 0.50, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 238 (3.86) nm. IR (KBr): 3417, 2973, 2926, 2870, 2233, 1731, 1689 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.77 (1H, s), 5.31 (1H, t, J = 3.2 Hz), 2.24 (1H, d, J = 11.0 Hz), 1.22, 1.20, 1.12, 1.11 (each 3H, s), 0.95, 0.88 (each 3H, d, J = 5.7 Hz), 0.87 (3H, s). ^{13}C NMR ($CDCl_3$): δ 198.2, 184.2, 170.2, 139.0, 124.4, 115.1, 114.1, 52.8, 52.7, 48.2, 45.0, 42.6, 41.2, 40.68, 40.65, 39.1, 39.0, 36.7, 32.5, 30.7, 28.1, 28.0, 24.1, 23.6, 23.3, 21.8, 21.3, 18.9, 18.2, 17.7, 17.2. EIMS (70 eV) *m/z*: 477 $[M]^+$ (22), 431 (23), 248 (100), 203 (48). HREIMS: Calcd for $C_{31}H_{43}O_3N$: 477.3243. Found: 477.3240. Anal. (Table 2).

Methyl 2-Formyl-3-oxooleana-1,12-dien-28-oate (**14**). To a stirred solution of phenylselenenyl chloride (98%) (161 mg, 0.82 mmol) in CH_2Cl_2 (7.2 mL) was added a solution of pyridine (75 mg, 0.95 mmol) in CH_2Cl_2 (1.0 mL) in an ice bath. After 15 min, a solution of **25** (204 mg, 0.41 mmol) in CH_2Cl_2 (2.0 mL) was added, and the mixture was stirred an additional 1 h. After the mixture was washed with 10% aqueous HCl solution (3 mL) twice, 30% H_2O_2 (0.4 mL) was added to the stirred mixture in the ice bath. After an additional 40 min, the mixture was worked up according to the standard method to give a solid (199 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1)] to afford **25** (20 mg) and **14** as an amorphous solid (144 mg; 71%, 79% based on recovered **25**): $[\alpha]^{26}_D$ +12° (*c* 0.60, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 238 (3.85) nm. IR (KBr): 2946, 2867, 1724, 1703, 1673, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.00 (1H, s), 7.79 (1H, s), 5.37 (1H, t, J = 3.6 Hz), 3.63 (3H, s), 2.90 (1H, dd, J = 4.2, 13.9 Hz), 1.18, 1.17, 1.16, 1.14, 0.94, 0.91, 0.85 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 203.7, 190.7, 178.3, 165.2, 144.5, 131.2, 121.6, 52.8, 51.8, 47.0, 45.8, 45.1, 42.3, 41.7, 41.3, 40.5, 39.8, 34.0, 33.3, 32.44, 32.38, 30.9, 28.2, 27.8, 26.0, 23.8, 23.5, 23.2, 21.7, 19.2, 18.2, 17.6. EIMS (70 eV) *m/z*: 494 $[M]^+$ (95), 435 (87), 262 (40), 203 (100). HREIMS: Calcd for $C_{32}H_{46}O_4$: 494.3396. Found: 494.3398. Anal. (Table 2).

2-Formyl-3-oxooleana-1,12-dien-28-oic Acid (**15**). **15** was prepared from **32** according to the same method as for **14**. The reaction mixture was subjected to flash column chromatography [hexanes−EtOAc (3:1) followed by hexanes−EtOAc (2:1)] to give **15** as an amorphous solid (71%, 84% based on recovered **32**): $[\alpha]^{26}_D$ +26° (*c* 0.95, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (3.82) nm. IR (KBr): 2948, 2866, 1725, 1701, 1674, 1608 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.00 (1H, s), 7.79 (1H, s), 5.36 (1H, t, J = 3.3 Hz), 2.86 (1H, dd, J = 3.8, 13.9 Hz), 1.18, 1.17, 1.15, 1.14, 0.94, 0.92, 0.87 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 203.7, 190.7, 184.3, 165.0, 144.2, 131.2, 121.8, 52.8, 46.8, 45.7, 45.1, 42.3, 41.4, 41.3, 40.5, 39.8, 34.0, 33.2, 32.5, 32.3, 30.9, 28.2, 27.8, 26.0, 23.7, 23.5, 23.0, 21.6, 19.2, 18.2, 17.8. EIMS (70 eV) *m/z*: 480 $[M]^+$ (5.5), 434 (3.1), 419 (3.4), 248 (56), 233 (27), 203 (100). HREIMS: Calcd for $C_{31}H_{44}O_4$: 480.3240. Found: 480.3237. Anal. (Table 2).

Methyl 2-Carboxy-3-oxooleana-1,12-dien-28-oate (**16**). **(1) From 14**: To a solution of **14** (357 mg, 0.72 mmol) in acetone (71 mL) was added Jones reagent (0.5 mL) dropwise in an ice bath. The mixture was stirred in the ice bath for 20 min. After excess Jones reagent was decomposed with MeOH, the acetone was evaporated in vacuo. After water was added to the resultant mixture, the aqueous mixture was extracted with EtOAc three times. The extract was washed with water (three times) and saturated aqueous NaCl solution (three times), dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give a residue (294 mg). The residue was subjected to flash column chromatography [hexanes−EtOAc (1:1) followed by EtOAc] to afford **14** (89 mg) and **16** as a crystalline solid (109 mg; 30%, 39% based on recovered **14**): mp 230−231 °C; $[\alpha]^{26}_D$ +85° (*c* 0.61, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 234 (3.78) nm. IR (KBr): 3436, 2946, 2876, 1756, 1722, 1633 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (1H, s), 5.36 (1H, t, J = 3.5 Hz), 3.64 (3H, s), 2.90 (1H, dd, J = 3.9, 13.7 Hz), 1.24, 1.21, 1.19, 1.13, 0.94, 0.91, 0.85 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 209.2, 178.4, 173.4, 165.2, 144.5, 123.3, 121.4, 52.4, 51.8, 47.0, 45.7, 45.5, 42.3, 41.7, 41.1, 40.6, 40.4, 34.0, 33.3, 32.4, 32.3, 30.9, 28.3, 27.8, 26.0, 23.8, 23.5, 23.1, 22.0, 19.0, 18.3, 17.7. EIMS (70 eV) *m/z*: 510 $[M]^+$ (16), 492 (15), 451 (14), 433 (14), 262 (27), 203 (100). HREIMS: Calcd for $C_{32}H_{46}O_5$: 510.3345. Found: 510.3347. Anal. (Table 2).

(2) From 17: A solution of **17** (500 mg, 0.95 mmol) in MeOH (29 mL) and aqueous KOH solution (KOH, 2.9 g; water, 10 mL) was heated under reflux for 15 min. After removal of MeOH in vacuo, the mixture was acidified with 5% aqueous HCl solution. It was extracted with EtOAc (three times). The extract was washed with water and saturated aqueous NaCl solution (each three times), dried over $MgSO_4$, and filtered. The filtrate gave **16** as a crystalline solid (470 mg, 97%). It was used for the next reaction without further purification.

Methyl 2-Methoxycarbonyl-3-oxooleana-1,12-dien-28-oate (**17**). **17** was prepared from **31** by the similar method as for **14**. The reaction mixture was subjected to flash column chromatography [hexanes−EtOAc (4:1)] to give **17** as an amorphous solid (83%, 90% based on recovered **31**): $[\alpha]^{26}_D$ +63° (*c* 0.78, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 230 (3.97) nm. IR (KBr): 2947, 2866, 1727, 1684, 1624 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.73 (1H, s), 5.37 (1H, t, J = 3.5 Hz), 3.79, 3.64 (each 3H, s), 2.90 (1H, dd, J = 3.9, 13.7 Hz), 1.16 (6H, s), 1.15, 1.12, 0.94, 0.91, 0.84 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 201.2, 178.4, 166.0, 164.3, 144.5, 129.2, 121.7, 52.7, 52.4, 51.8, 47.0, 45.9, 45.8, 42.3, 41.8, 41.5, 40.3, 39.5, 34.1, 33.3, 32.4, 32.3, 30.9, 28.7, 27.8, 25.9, 23.8, 23.6, 23.2, 21.5, 19.4, 18.0, 17.5. EIMS (70 eV) *m/z*: 524 $[M]^+$ (24), 492 (23), 465 (13), 262 (35), 203 (100). HREIMS: Calcd for $C_{33}H_{48}O_5$: 524.3502. Found: 524.3494. Anal. (Table 2).

2-Methoxycarbonyl-3-oxooleana-1,12-dien-28-oic Acid (**18**). A solution of **3** (52 mg, 0.10 mmol) in MeOH (5.2 mL) containing concentrated H_2SO_4 (0.15 mL) was heated under reflux for 30 min. After saturated aqueous NaCl solution was added to the mixture, it was extracted with EtOAc three times. The extract was worked up according to the standard method to give a residue (53 mg). The residue was subjected to flash column chromatography [hexanes−EtOAc (2:1)] to give **18** as an amorphous solid (42 mg, 78%): $[\alpha]^{26}_D$ +61° (*c* 0.56, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 230 (3.83) nm. IR (KBr): 3323, 2947, 2866, 1733, 1695, 1622 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.73 (1H, s), 5.37 (1H, t, J = 3.4 Hz), 3.79 (3H, s), 2.86 (1H, dd, J = 4.1, 13.7 Hz), 1.16, 1.15, 1.14, 1.12, 0.94, 0.92, 0.86 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 201.1, 184.2, 166.0, 164.2, 144.2, 129.2, 122.0, 52.7, 52.4, 46.9, 45.9, 45.8, 42.2, 41.5, 41.4, 40.3, 39.5, 34.0, 33.3, 32.5, 32.3, 30.9, 28.7, 27.8, 26.0, 23.7, 23.6, 23.0, 21.4, 19.4, 18.0, 17.7. EIMS (70 eV) *m/z*: 510 $[M]^+$ (2.6), 495 (2.0), 478 (2.5), 432 (3.0), 263 (29), 248 (58), 231 (37), 203 (100). HREIMS: Calcd for $C_{32}H_{46}O_5$: 510.3345. Found: 510.3344. Anal. (Table 2).

Methyl 2-Aminocarbonyl-3-oxooleana-1,12-dien-28-oate (**19**). A solution of **17** (100 mg, 0.19 mmol) in saturated ammonia MeOH (10 mL) was kept at room temperature overnight. The mixture was evaporated in vacuo to give a solid (108 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (1.5:1)] to give **19** as an amorphous solid (94 mg, 96%): $[\alpha]^{26}_D$ +77° (*c* 0.60, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 236 (3.91) nm. IR (KBr): 3413, 2943, 2866, 1727, 1689 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.45 (1H, brs), 8.27 (1H, s), 5.72 (1H, brs), 5.37 (1H, t, J = 3.4 Hz), 3.64 (3H, s), 2.90 (1H, dd, J = 4.2, 13.9 Hz), 1.17, 1.16, 1.15, 1.14, 0.94, 0.92, 0.84 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 205.8, 178.4, 169.0, 165.8, 144.3, 121.8, 52.2, 51.8, 47.0, 46.0, 45.7, 42.3, 41.8, 41.2, 40.4, 39.6, 34.1, 33.3, 32.5, 32.3, 30.9, 29.1, 27.8, 26.0, 23.8, 23.6, 23.2, 21.9, 19.4, 18.6, 17.6. EIMS (70 eV) *m/z*: 509 $[M]^+$ (34), 492 (23), 450 (100), 262 (19), 203 (56). HREIMS: Calcd for $C_{32}H_{47}O_4N$: 509.3505. Found: 509.3500. Anal. (Table 2).

Methyl 1α,2α-Epoxy-3-oxoolean-12-en-28-oate (**22**).[9] To a solution of **B-13** (223 mg, 0.48 mmol) in 2 N aqueous NaOH solution (1.7 mL) and THF (11 mL) was added a solution of

30% H_2O_2 (1.4 mL) in MeOH (2.8 mL) in an ice bath. The mixture was stirred at room temperature for 4 h. To the mixture were added saturated aqueous $NaHSO_3$ and 5% aqueous NaOH solutions, successively. After removal of THF and MeOH, the resultant mixture was acidified with 6 M aqueous HCl solution. The acidic layer was extracted with CH_2Cl_2 three times. The extract was worked up according to the standard method to give **22** as a crystalline solid (228 mg, 99%). This material was used for the next reaction without further purification. An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 212−213 °C; $[\alpha]^{26}_D$ +157° (*c* 0.80, $CHCl_3$). IR (KBr): 2943, 2866, 1727, 1699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.36 (1H, t, $J = 3.3$ Hz), 3.64 (3H, s), 3.50 (1H, d, $J = 4.5$ Hz), 3.37 (1H, d, $J = 4.5$ Hz), 2.90 (1H, dd, $J = 4.2$, 13.9 Hz), 1.21, 1.11, 1.01, 0.97, 0.94, 0.92, 0.80 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 213.0, 178.4, 144.5, 121.8, 64.1, 57.1, 51.8, 47.0, 46.3, 45.9, 45.0, 42.1, 41.7, 40.8, 39.7, 38.8, 34.1, 33.3, 32.5, 32.3, 30.9, 28.2, 28.0, 26.0, 24.0, 23.8, 23.3, 21.1, 19.1, 17.4, 15.1. EIMS (70 eV) *m*/*z*: 482 $[M]^+$ (7.7), 422 (13), 262 (31), 249 (11), 203 (100). HREIMS: Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3391.

Methyl 2-Methoxy-3-oxooleana-1,12-dien-28-oate (**23**). A mixture of **22** (300 mg, 0.62 mmol) and Na (360 mg) in MeOH (36 mL) was heated under reflux for 48 h. After removal of MeOH in vacuo, the resultant mixture was diluted with water and then acidified with 6 M aqueous HCl solution. The aqueous mixture was extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was worked up according to the standard method to give a solid (320 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (4:1)] to afford **22** (31 mg) and **23** as an amorphous solid (270 mg; 87%, 98% based on recovered **22**): UV (EtOH) λ_{max} (log ϵ): 266 (3.77) nm. IR (KBr): 2946, 2866, 1727, 1682, 1621 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.96 (1H, s), 5.36 (1H, t, $J = 3.5$ Hz), 3.64, 3.55 (each 3H, s), 2.90 (1H, dd, $J = 4.1$, 13.7 Hz), 1.17 (6H, s), 1.16, 1.13, 0.93, 0.90, 0.81 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 200.1, 178.4, 149.0, 144.6, 126.3, 121.9, 54.9, 53.2, 51.8, 47.0, 45.9, 45.4, 43.3, 42.3, 41.7, 40.2, 38.4, 34.0, 33.3, 32.6, 32.5, 30.9, 28.5, 27.8, 26.0, 23.81, 23.76, 23.2, 22.0, 20.4, 19.2, 17.4. EIMS (70 eV) *m*/*z*: 496 $[M]^+$ (80), 436 (21), 328 (19), 262 (36), 203 (100). HREIMS: Calcd for $C_{32}H_{48}O_4$: 496.3553. Found: 496.3544.

Methyl 2-Hydroxy-3-oxooleana-1,12-dien-28-oate (**24**). A suspension of **23** (100 mg, 0.20 mmol) in 3 M aqueous HCl solution (3 mL) and AcOH (3 mL) was heated under reflux for 5 h. The mixture was neutralized with saturated aqueous Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 three times. The extract was worked up according to the standard method to give a solid (90 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1)] to afford **24** as an amorphous solid (78 mg, 81%): UV (EtOH) λ_{max} (log ϵ): 272 (3.63) nm. IR (KBr): 3426, 2939, 2870, 1725, 1667, 1648 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.35 (1H, s), 5.93 (1H, brs), 5.34 (1H, t, $J = 3.5$ Hz), 3.63 (3H, s), 2.89 (1H, dd, $J = 4.0$, 13.7 Hz), 1.22 (6H, s), 1.13, 1.12, 0.94, 0.91, 0.80 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 201.3, 178.4, 144.4, 143.9, 128.4, 122.0, 54.1, 51.8, 47.0, 45.9, 44.1, 43.3, 42.2, 41.6, 40.2, 38.7, 34.1, 33.3, 32.7, 32.5, 30.9, 27.8, 27.4, 26.1, 23.8, 23.6, 23.2, 22.0, 19.8, 18.9, 17.5. EIMS (70 eV) *m*/*z*: 482 $[M]^+$ (26), 446 (68), 422 (25), 262 (35), 203 (100). HREIMS: Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3387.

Methyl 2-Hydroxymethylene-3-oxoolean-12-en-28-oate (**25**).[19] To a stirred mixture of **B-3** (1084 mg, 2.31 mmol) and ethyl formate (97%) (707 mg, 9.26 mmol) in benzene (12 mL) was added NaOMe (501 mg, 9.27 mmol). The mixture was stirred at room temperature for 1 h. After the mixture was washed with 5% aqueous HCl solution twice, it was worked up according to the standard method to give **25** as an amorphous solid (1095 mg, 95%). This material was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes−EtOAc (7:1)] and subsequent recrystallization from MeOH as colorless needles: mp 199−201 °C. UV (EtOH) λ_{max} (log ϵ): 296 (3.94) nm. IR (KBr): 3426, 2943, 2862, 1725, 1637, 1588 cm^{-1}. ^1H NMR ($CDCl_3$): δ 14.92 (1H, d, $J = 3.1$ Hz), 8.58 (1H, d, $J = 3.1$ Hz), 5.35 (1H, t, $J = 3.7$ Hz), 3.64 (3H, s), 2.90 (1H, dd, $J = 4.2$, 13.6 Hz), 2.29 (1H, d, $J = 14.4$ Hz), 1.92 (1H, d, $J = 14.4$ Hz), 1.20, 1.16, 1.12, 0.94 (each 3H, s), 0.91 (6H, s), 0.80 (3H, s). ^{13}C NMR ($CDCl_3$): δ 190.9, 188.6, 178.4, 144.0, 122.3, 106.0, 52.3, 51.8, 47.0, 46.0, 45.9, 42.0, 41.6, 40.3, 39.4, 39.3, 36.5, 34.1, 33.3, 32.5, 32.1, 30.9, 28.6, 27.9, 25.9, 23.8, 23.6, 23.3, 21.1, 19.7, 16.8, 14.7. EIMS (70 eV) *m*/*z*: 496 $[M]^+$ (4.4), 437 (23), 262 (38), 233 (20), 203 (100). HREIMS: Calcd for $C_{32}H_{48}O_4$: 496.3553. Found: 496.3550.

Methyl Isoxazolo[4,5-*b*]olean-12-en-28-oate (**26**). A mixture of **25** (994 mg, 2.0 mmol), hydroxylamine hydrochloride (1391 mg, 20 mmol) in water (1.8 mL) and EtOH (48 mL) was heated under reflux for 1 h. After EtOH was removed in vacuo, EtOAc was added to the resultant mixture. The EtOAc layer was washed with water (three times) and saturated aqueous NaCl solution (three times), dried over $MgSO_4$, and filtered. The filtrate gave a solid (1086 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (6:1) followed by hexanes−EtOAc (5:1)] to give **26** as an amorphous solid (934 mg, 86%): UV (EtOH) λ_{max} (log ϵ): 228 (3.65) nm. IR (KBr): 2940, 2864, 1725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.98 (1H, s), 5.34 (1H, t, $J = 3.5$ Hz), 3.63 (3H, s), 2.89 (1H, dd, $J = 4.4$, 13.7 Hz), 2.42 (1H, d, $J = 15.1$ Hz), 1.30, 1.21, 1.15, 0.93, 0.90, 0.88, 0.79 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 178.4, 173.2, 150.4, 144.0, 122.3, 109.0, 53.7, 51.7, 46.9, 46.3, 46.0, 42.0, 41.6, 39.5, 38.9, 35.5, 34.9, 34.0, 33.3, 32.5, 32.1, 30.9, 29.0, 27.9, 25.9, 23.8, 23.5, 23.2, 21.6, 19.0, 16.7, 15.4. EIMS (70 eV) *m*/*z*: 493 $[M]^+$ (11), 434 (18), 262 (28), 249 (16), 203 (100). HREIMS: Calcd for $C_{32}H_{47}O_3N$: 493.3556. Found: 493.3556.

Methyl 2-Cyano-3-oxoolean-12-en-28-oate (**27**). To a stirred solution of **26** (887 mg, 1.80 mmol) in Et_2O (50 mL) and MeOH (25 mL) was added NaOMe (3.2 g) in an ice bath. The mixture was stirred at room temperature for 1 h. The mixture was diluted with a mixture of CH_2Cl_2 and Et_2O (1:2) (50 mL). After the extract was washed with 5% aqueous HCl solution, it was worked up according to the standard method to afford **27** as an amorphous solid (879 mg, 99%). This material was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes−EtOAc (5:1)] as an amorphous solid: UV (EtOH) λ_{max} (log ϵ): 238 (3.88) nm. IR (KBr): 2946, 2870, 2202, 1724, 1633 cm^{-1}. ^1H NMR of major tautomer **27a** ($CDCl_3$): δ 6.15 (1H, brs), 5.31 (1H, t, $J = 3.6$ Hz), 3.63 (3H, s), 2.88 (1H, dd, $J = 4.0$, 13.6 Hz), 2.09 (1H, d, $J = 15.0$ Hz), 1.16, 1.13, 1.07, 0.95, 0.93, 0.90, 0.76 (each 3H, s). EIMS (70 eV) *m*/*z*: 493 $[M]^+$ (6.3), 434 (17), 262 (19), 249 (20), 203 (100). HREIMS: Calcd for $C_{32}H_{47}O_3N$: 493.3556. Found: 493.3548.

Methyl 2-Hydroxymethylene-3-oxours-12-en-28-oate (**28**).[23] **28** was prepared from **B-4** according to the same method as for **25** to give an amorphous solid (quantitative). This material was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes−EtOAc (7:1)] and subsequent recrystallization from MeOH as colorless needles: mp 170−171 °C. UV (EtOH) λ_{max} (log ϵ): 294 (3.86) nm. IR (KBr): 3426, 2947, 2921, 2866, 1727, 1637, 1590 cm^{-1}. ^1H NMR ($CDCl_3$): δ 14.91 (1H, brs), 8.57 (1H, s), 5.31 (1H, t, $J = 3.7$ Hz), 3.62 (3H, s), 2.31 (1H, d, $J = 14.4$ Hz), 2.27 (1H, d, $J = 12.5$ Hz), 1.95 (1H, d, $J = 14.4$ Hz), 1.19, 1.12, 1.10 (each 3H, s), 0.96 (3H, d, $J = 6.0$ Hz), 0.92 (3H, s), 0.87 (3H, d, $J = 6.6$ Hz), 0.81 (3H, s). ^{13}C NMR ($CDCl_3$): δ 191.0, 188.5, 178.2, 138.4, 125.6, 106.0, 53.2, 52.3, 51.7, 48.4, 45.7, 42.4, 40.3, 39.7, 39.5, 39.3, 39.1, 36.8, 36.4, 32.4, 30.9, 28.7, 28.2, 24.4, 23.7, 23.6, 21.4, 21.1, 19.7, 17.2, 17.0, 14.8. EIMS (70 eV) *m*/*z*: 496 $[M]^+$ (11), 437 (15), 262 (80), 233 (41), 203 (100). HREIMS: Calcd for $C_{32}H_{48}O_4$: 496.3553. Found: 496.3547.

Methyl Isoxazolo[4,5-*b*]urs-12-en-28-oate (**29**). **29** was prepared from **28** according to the same method as for **26** to give an amorphous solid (84%): UV (EtOH) λ_{max} (log ϵ): 228 (3.70) nm. IR (KBr): 2969, 2922, 2870, 1725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.98 (1H, s), 5.31 (1H, t, $J = 3.4$ Hz), 3.62 (3H, s), 2.46 (1H, d, $J = 15.0$ Hz), 2.27 (1H, d, $J = 11.1$ Hz), 1.31, 1.22,

1.10 (each 3H, s), 0.96 (3H, d, $J = 6.3$ Hz), 0.90 (3H, s), 0.88 (3H, d, $J = 6.3$ Hz), 0.81 (3H, s). ^{13}C NMR ($CDCl_3$): δ 178.2, 173.2, 150.4, 138.4, 125.5, 109.1, 53.7, 53.2, 51.7, 48.3, 46.3, 42.3, 39.7, 39.3, 39.1, 38.8, 36.8, 35.8, 34.9, 32.4, 30.9, 29.1, 28.3, 24.4, 23.7, 23.5, 21.6, 21.4, 19.0, 17.2, 16.9, 15.6. EIMS (70 eV) *m/z*: 493 $[M]^+$ (9.1), 434 (20), 262 (65), 249 (33), 203 (100). HREIMS: Calcd for $C_{32}H_{47}O_3N$: 493.3556. Found: 493.3547.

Methyl 2-Cyano-3-oxours-12-en-28-oate (**30**). **30** was prepared from **29** according to the same method as for **27** to give an amorphous solid (quantitative). This material was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes−EtOAc (5:1)] as an amorphous solid: UV (EtOH) λ_{max} (log ϵ): 238 (3.93) nm. IR (KBr): 2947, 2870, 2203, 1724, 1631 cm^{-1}. ^{1}H NMR of major tautomer **30a** ($CDCl_3$): δ 5.92 (1H, brs), 5.28 (1H, t, $J = 3.5$ Hz), 3.61 (3H, s), 2.26 (1H, d, $J = 11.0$ Hz), 2.13 (1H, d, $J = 15.0$ Hz), 1.16, 1.13, 1.08, 1.07, 0.96 (each 3H, s), 0.95, 0.77 (each 3H, d, $J = 6.3$ Hz). EIMS (70 eV) *m/z*: 493 $[M]^+$ (6.8), 434 (19), 262 (62), 249 (44), 203 (100). HREIMS: Calcd for $C_{32}H_{47}O_3N$: 493.3556. Found: 493.3558.

Methyl 3-Hydroxy-2-methoxycarbonyloleana-2,12-dien-28-oate (**31**). A mixture of **B-3** (2.0 g, 4.27 mmol) and 1.8 M DMF solution of methoxymagnesium methyl carbonate (Stiles' reagent) (20 mL, 36 mmol) was heated under reflux for 2 h while a slow stream of N_2 was bubbled through the mixture with a pipet. To the mixture were added 5% aqueous HCl solution and EtOAc. The aqueous layer was extracted with EtOAc (three times). The combined organic layers were washed with water (three times) and saturated aqueous NaCl solution (three times), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give a solid (2.26 g). To a solution of the solid in THF (30 mL) was added excessive amount of ethereal diazomethane. The mixture was kept at room temperature for 10 min. The mixture was evaporated in vacuo to give a solid (2.38 g). The solid was subjected to flash column chromatography [hexanes−EtOAc (7:1)] to give **B-3** (330 mg) and **31** as crystals (1.66 g; 74%, 89% based on recovered **B-3**): mp 160−162 °C. UV (EtOH) λ_{max} (log ϵ): 262 (4.01) nm. IR (KBr): 2948, 2858, 1737, 1660, 1615 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 12.51 (1H, s), 5.33 (1H, t, $J = 3.7$ Hz), 3.74, 3.63 (each 3H, s), 2.89 (1H, dd, $J = 4.2$, 13.9 Hz), 2.35 (1H, d, $J = 15.7$ Hz), 1.18, 1.14, 1.10, 0.94 (each 3H, s), 0.91 (6H, s), 0.78 (3H, s). ^{13}C NMR ($CDCl_3$): δ 178.5, 177.9, 174.2, 143.8, 122.6, 94.3, 52.5, 51.8, 51.7, 47.0, 46.13, 46.09, 42.0, 41.7, 39.4, 38.6, 38.4, 35.7, 34.1, 33.3, 32.6, 32.1, 31.0, 28.8, 27.9, 26.0, 23.8, 23.6, 23.3, 20.4, 19.8, 16.8, 15.1. EIMS (70 eV) *m/z*: 526 $[M]^+$ (0.6), 494 (5.6), 479 (2.5), 466 (1.6), 435 (13), 262 (28), 203 (100). HREIMS: Calcd for $C_{33}H_{50}O_5$: 526.3658. Found: 526.3658.

2-Hydroxymethylene-3-oxoolean-12-en-28-oic Acid (**32**). To a stirred mixture of oleanonic acid (**B-1**)[10] (540 mg, 1.19 mmol) and ethyl formate (97%) (357 mg, 4.66 mmol) in THF (12 mL) was added NaOMe (258 mg, 4.78 mmol). The mixture was stirred at room temperature overnight. The mixture was acidified with 10% aqueous HCl solution. The mixture was extracted with EtOAc three times. The extract was worked up according to the standard method to give a solid (600 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1) followed by hexanes−EtOAc (4:1)] to afford **B-1** (168 mg) and **32** as a crystalline solid (260 mg; 45%, 66% based on recovered **B-1**): mp 200−203 °C dec. UV (EtOH) λ_{max} (log ϵ): 292 (3.93) nm. IR (KBr): 2946, 2654, 1732, 1694, 1644, 1587 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 14.91 (1H, brs), 8.59 (1H, s), 5.34 (1H, t, $J = 3.5$ Hz), 2.86 (1H, dd, $J = 4.5$, 13.9 Hz), 2.29 (1H, d, $J = 14.6$ Hz), 1.93 (1H, d, $J = 14.6$ Hz), 1.19, 1.16, 1.10, 0.94, 0.92, 0.91, 0.82 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 190.7, 188.8, 184.7, 143.8, 122.6, 105.9, 52.2, 46.8, 46.0, 45.9, 41.9, 41.2, 40.2, 39.34, 39.30, 36.5, 34.0, 33.3, 32.6, 32.0, 30.9, 28.6, 27.8, 25.9, 23.7, 23.5, 23.1, 21.0, 19.6, 17.0, 14.6. EIMS (70 eV) *m/z*: 482 $[M]^+$ (1.8), 438 (2.7), 436 (3.6), 248 (77), 203 (100). HREIMS: Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3392.

Evaluation Methods. 1. Reagents. Recombinant mouse IFN-γ (LPS content, <10 pg/mL) was purchased from Genzyme (Cambridge, MA). All other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO). Inhibitory test compounds were dissolved in DMSO before addition to cell cultures; final concentrations of DMSO were 0.1% or less. Controls with DMSO alone were run in all cases.

2. Cell Culture. To obtain primary macrophages, female CD-1 mice, 5−10 weeks of age (Charles River Breeding Laboratories, Wilmington, MA), were injected intraperitoneally with 2 mL of 4% thioglycollate broth (Difco Laboratories, Detroit, MI). Four days after injection, peritoneal macrophages were harvested and processed according to Nathan's procedure.[7b] Cells were seeded in 96-well plates at 2×10^5 cells/well and incubated for 48 h with 20 ng/mL IFN-γ in the presence or absence of inhibitory test compounds.

3. Measurement of NO Production in Mouse Macrophages. Nitrite accumulation was used as an indicator of NO production in the medium and was assayed by the Griess reaction.[7a] Griess reagent (100 μL) was added to 100 μL of each supernatant from IFN-γ or inhibitory test compound-treated cells in triplicate. The protein determination was performed by Bradford protein assay. The plates were read at 550 nm against a standard curve of sodium nitrite.

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