Synthetic Oleanane and Ursane Triterpenoids with Modified Rings A and C: A Series of Highly Active Inhibitors of Nitric Oxide Production in Mouse Macrophages†

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We have designed and synthesized 16 new olean- and urs-1-en-3-one triterpenoids with various modified rings C as potential antiinflammatory and cancer chemopreventive agents and evaluated their inhibitory activities against production of nitric oxide induced by interferon-γ in mouse macrophages. This investigation revealed that 9(11)-en-12-one and 12-en-11-one functionalities in ring C increase the potency by about 2−10 times compared with the original 12-ene. Subsequently, we have designed and synthesized novel olean- and urs-1-en-3-one derivatives with nitrile and carboxyl groups at C-2 in ring A and with 9(11)-en-12-one and 12-en-11-one functionalities in ring C. Among them, we have found that methyl 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate (**25**), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (**26**), and methyl 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate (**29**) have extremely high potency (IC_{50} = 0.1 nM level). Their potency is similar to that of dexamethasone although they do not act through the glucocorticoid receptor. Overall, the combination of modified rings A and C increases the potency by about 10 000 times compared with the lead compound, 3-oxooleana-1,12-dien-28-oic acid (**8**) (IC_{50} = 1 μM level). The selected oleanane triterpenoid, CDDO (**26**), was found to be a potent, multifunctional agent in various in vitro assays and to show antiinflammatory activity against thioglycollate−interferon-γ-induced mouse peritonitis.

Introduction

Oleanane and ursane triterpenoids are pentacyclic compounds with 30 carbon atoms, biosynthetically derived from the cyclization of squalene.[1] This is a vast class of natural products whose structural diversity includes a wide array of functional groups.[2] Many compounds of this group are reported to have various interesting biological, pharmacological, or medicinal activities including antiinflammatory and anticarcinogenic activities.[3] However, in many cases, the potency of these triterpenoids is relatively weak. Therefore, anticipating highly potent novel structures, we began bioassay-directed systematic drug design and synthesis of derivatives of commercially available oleanolic acid (**1**) and ursolic acid (**2**) (cf. Scheme 1).

To discover antiinflammatory and cancer chemopreventive drugs from these derivatives, we have adopted an assay system that measures inhibition of nitric oxide (NO) production induced by interferon-γ (IFN-γ) in mouse macrophages[4] as a preliminary screening assay system. In a previous paper,[5] we reported that olean-12-ene triterpenoids with a 1-en-3-one functionality having nitrile, methoxycarbonyl, and carboxyl groups at C-2 in ring A, **3**−**7**, show significant potency [IC_{50} = 0.01−0.1 μM level, about 10−100 times more potent than the lead compound **8** (IC_{50} = 1 μM level)] in this assay. As a continuation of this work, we have synthesized 16 new olean- and urs-1-en-3-one derivatives with various modified rings C, **9**−**24**, and evaluated their inhibitory activities in the above assay. This investigation revealed that 9(11)-en-12-one, 12-en-11-one, and 13-(18)-en-11-one functionalities in ring C increase the potency by about 2−10 times compared with the original 12-ene. Subsequently, we have designed and synthesized novel olean- and urs-1-en-3-one derivatives with nitrile, methoxycarbonyl, and carboxyl groups at C-2 in ring A and with 9(11)-en-12-one, 12-en-11-one, and 13-(18)-en-11-one functionalities in ring C, **25**−**35**. Among them, we have found that methyl 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate (**25**), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (**26**), and methyl 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate (**29**) have extremely high potency (IC_{50} = 0.1 nM level). We report here the synthesis, inhibitory activity, and

† 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.; Gribble, G. W.; Suh, N.; Wang, Y.; Sporn, M. B. Design and synthesis of 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2711−2714. (c) 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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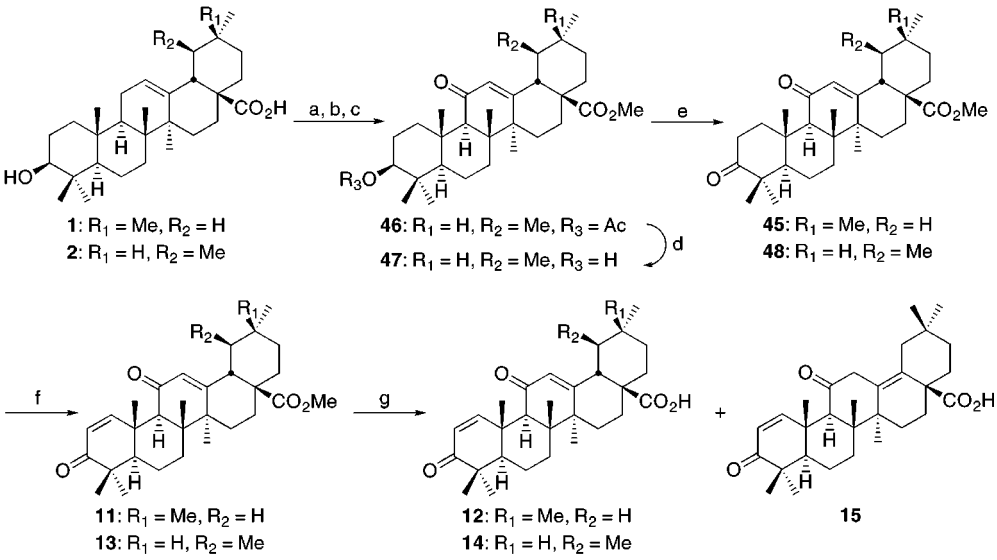
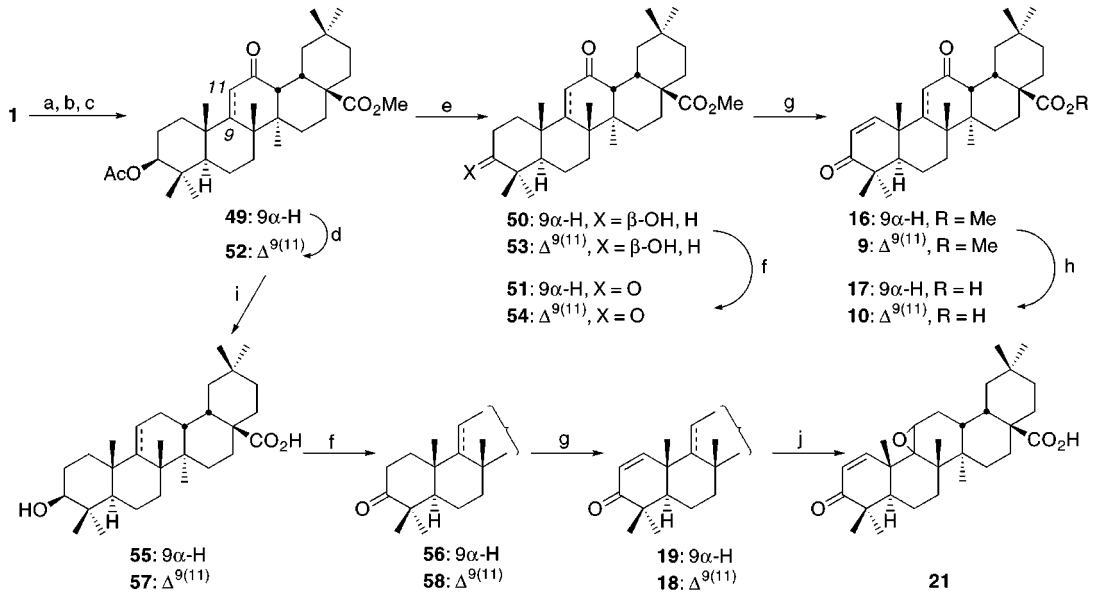
Scheme 1[a]



[a] Reagents: (a) CH_2N_2, Et_2O, THF; (b) Ac_2O, pyr; (c) CrO_3, pyr, CH_2Cl_2; (d) KOH, aq MeOH; (e) Jones; (f) PhSeCl, EtOAc, 30% H_2O_2, THF; (g) LiI, DMF.

Scheme 2[a]



[a] Reagents: (a) CH_2N_2, Et_2O, THF; (b) Ac_2O, pyr; (c) 30% H_2O_2, AcOH; (d) Br_2, HBr, AcOH; (e) KOH, aq MeOH; (f) Jones; (g) PhSeCl, EtOAc, 30% H_2O_2, THF; (h) LiI, DMF; (i) NH_2NH_2, KOH, diethylene glycol; (j) *m*CPBA, CH_2Cl_2.

structure−activity relationships (SARs) of these novel triterpenoids in detail.

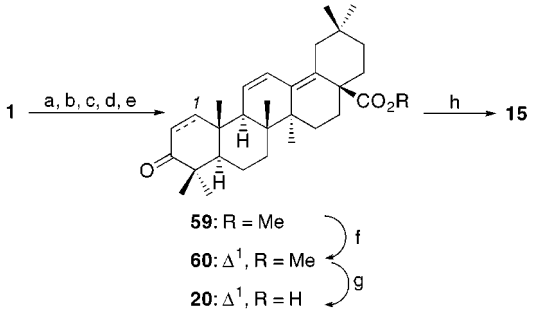
Chemistry

Modification of Ring C and Carboxyl Group at C-17. Enones **9**−**21** were designed and synthesized to discover what structures of ring C enhance potency in comparison with the original 12-ene, i.e., the lead compound **8**[5] (Schemes 1−3).[6] In addition, enones **22**−**24** were designed and synthesized to learn which functionality at C-17 is most appropriate (Scheme 4).

Enone **11** was prepared by introduction of a double bond at C-1 of known C-3 ketone **45**,[7] which was prepared in five steps from oleanolic acid (**1**), with phenylselenenyl chloride in ethyl acetate and sequential addition of 30% hydrogen peroxide (PhSeCl−H_2O_2) (yield, 97%).[8] Halogenolysis of **11** with lithium iodide (LiI) in *N*,*N*-dimethylformamide (DMF)[9] gave α,*β*- and *β*,*γ*-unsaturated ketones **12** and **15** in 43% and 22% yield, respectively. C-3 alcohol **47** was obtained quantitatively by alkaline hydrolysis (reflux) of known acetate **46**,[10] which was prepared in three steps from ursolic acid (**2**). Jones oxidation of **47** gave C-3 ketone **48** in 89% yield. Enone **13** was prepared in 93% yield from **48** by the same method as for **11**. Halogenolysis of **13** gave acid **14** in 58% yield.[11]

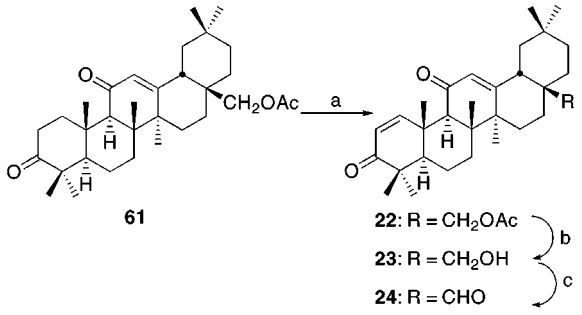
Similarly, enone **16** was synthesized in 74% yield via **50** and **51** from C-12 ketone **49**, which was prepared in three steps from **1** according to a known method,[12,13] and enone **9** was also synthesized in 60% yield via **53** and **54** from known C-12 ketone **52** which was prepared from **49** with bromine and hydrobromic acid in acetic acid.[14] Halogenolysis of enones **16** and **9** gave acids **17** and **10** in 62% and 68% yield, respectively. Enone **19**

Scheme 3[a]



[a] Reagents: (a) CH_2N_2, Et_2O, THF; (b) Ac_2O, pyr; (c) SeO_2, AcOH; (d) KOH, aq MeOH; (e) CrO_3, pyr, CH_2Cl_2; (f) PhSeCl, EtOAc, 30% H_2O_2, THF; (g) LiI, DMF; (h) Jones.

Scheme 4[a]



[a] Reagents: (a) PhSeCl, EtOAc, 30% H_2O_2, THF; (b) KOH, aq MeOH; (c) CrO_3, pyr, CH_2Cl_2.

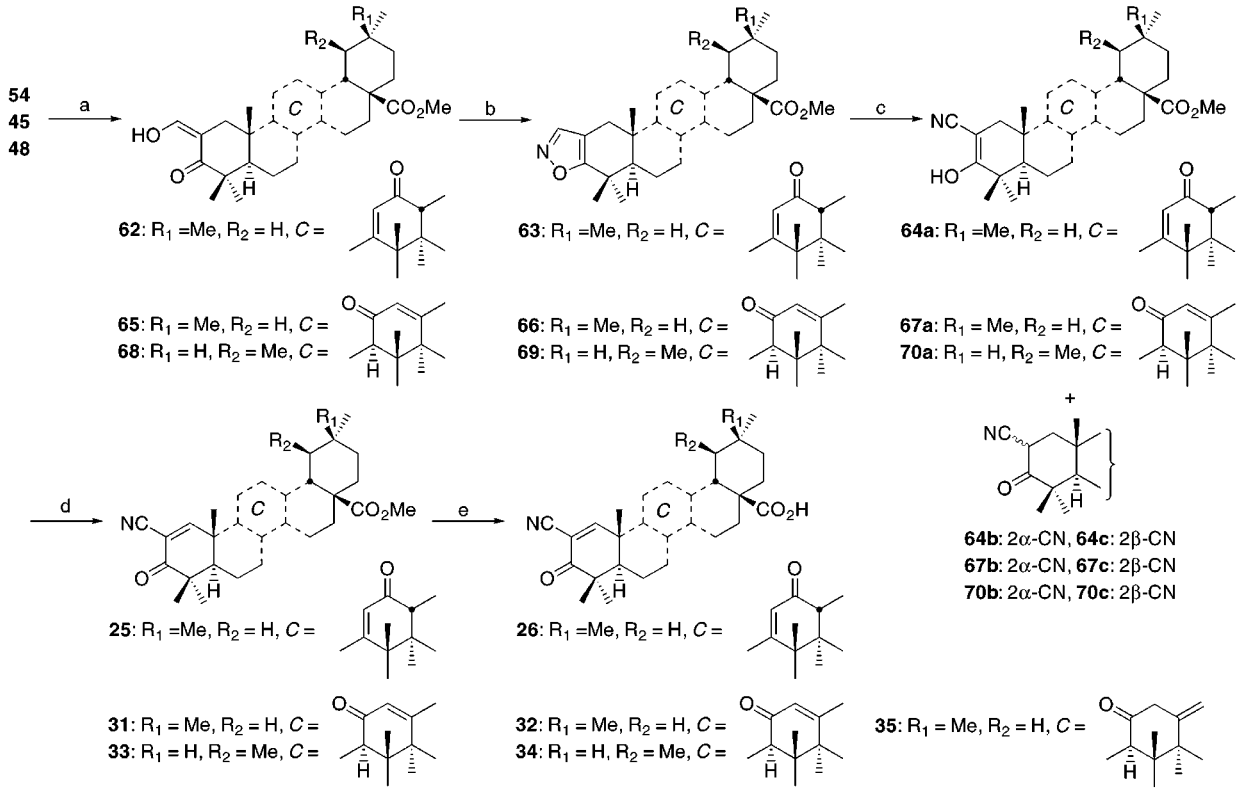
was obtained in 68% yield from known C-3 ketone **56**[15] which was synthesized via **55** from **49**. Enone **18** was obtained in 76% yield via **58** from acid **57**, which was prepared in 53% yield from **52** by Wolff−Kishner reduction. Epoxide **21**[16] was prepared in 46% yield by oxidation of **18** with *m*-chloroperbenzoic acid (*m*CPBA) in methylene chloride (CH_2Cl_2). Enone **20** was synthesized in 37% yield via **60** from known diene **59**[17] which was prepared in five steps from **1**. Interestingly, Jones oxidation of **20** afforded the same deconjugated enone **15** (yield, 28%) as halogenolysis of **11**. Enone **22** was prepared in 83% yield from krukovine A acetate (**61**), which was previously synthesized in our laboratory.[18] Alkaline hydrolysis (at room temperature)[19] of **22** gave enone **23** in 78% yield. Ratcliffe oxidation[20] of **23** with chromium trioxide and pyridine in CH_2Cl_2 afforded aldehyde **24** in 89% yield.

Among these new synthetic enones, **9**−**12** and **15** showed more inhibitory activity than the lead compound **8** on production of NO-induced IFN-γ in mouse macrophages (see Table 1). Overall, 9(11)-en-12-one, 12-en-11-one, and 13(18)-en-11-one functionalities in ring C increase the potency by about 2−10 times compared with the original 12-ene.

Combination of Modified Ring A with Ring C. On the basis of our previous results,[5] in which olean-12-ene triterpenoids with a 1-en-3-one functionality having nitrile, methoxycarbonyl, and carboxyl groups at C-2 in ring A, **3**−**7**, are about 10−100 times more potent than **8** (see Table 1), and the above results, we have designed and synthesized novel oleanane and ursane triterpenoids with modified rings A and C, **25**−**35**. In addition, to further discern SARs, amide **36** and enal **37** were designed and synthesized because amide **41** and enal **42** showed low potency and toxicity, respectively, in our previous evaluation (see Table 1).[5] The syntheses of these newly designed triterpenoids are illustrated in Schemes 5−7.

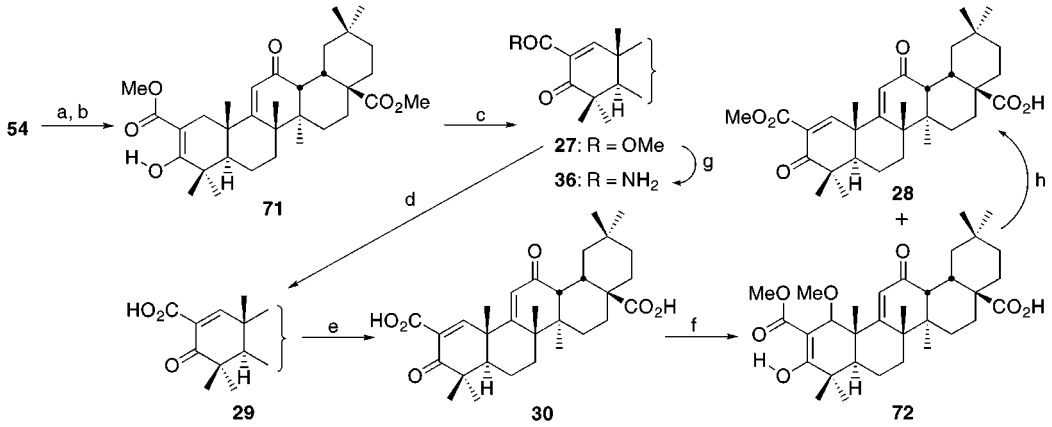
Hydroxymethylene **62**[21] was prepared in 99% yield by formylation of **54** with ethyl formate in the presence

Scheme 5[a]



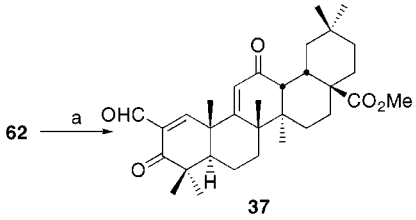
[a] Reagents: (a) HCO_2Et, NaOMe, PhH; (b) $NH_2OH{\cdot}HCl$, aq EtOH; (c) NaOMe, Et_2O, MeOH; (d) DDQ, PhH; (e) LiI, DMF.

Scheme 6[a]



[a] Reagents: (a) Stiles' reagent, DMF; (b) CH_2N_2, Et_2O, THF; (c) PhSeCl, pyr, CH_2Cl_2, 30% H_2O_2, CH_2Cl_2; (d) KOH, aq MeOH; (e) LiI, DMF; (f) H_2SO_4, MeOH; (g) NH_3, MeOH; (h) SiO_2.

Scheme 7[a]



[a] Reagents: (a) PhSeCl, pyr, CH_2Cl_2, 30% H_2O_2, CH_2Cl_2.

of sodium methoxide in benzene.[22] Isoxazole **63** was obtained in 66% yield from **62** by the addition of hydroxylamine.[23] Cleavage of the isoxazole moiety of **63** with sodium methoxide gave nitrile **64** quantitatively.[23,24] CDDO methyl ester (**25**) was prepared in 92% yield by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of **64** in benzene, although PhSeCl−H_2O_2 gave **25** in only 40% yield. Halogenolysis of **25** gave CDDO (**26**) in 68% yield. Similarly, olean-12-en-11-one derivative **31** was synthesized in 53% yield via **65**,[21] **66**, and **67**[24] from **45**. Halogenolysis of **31** gave α,β- and β,γ-unsaturated ketones **32** and **35** in 37% and 16% yield, respectively. Urs-12-en-11-one derivative **33** was also synthesized in 61% yield via **68**,[21] **69**, and **70**[24] from **48**. Halogenolysis of **33** gave acid **34** in 60% yield.[11]

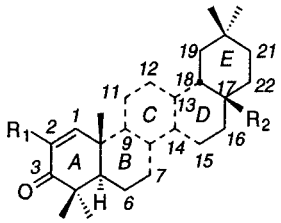
Ester **71** was prepared in 78% yield from C-3 ketone **54** by Stiles' reagent (methoxymagnesium methyl carbonate) in DMF,[25] followed by methylation with diazomethane. ^{1}H NMR showed that **71** in $CDCl_3$ is the single tautomer depicted in Scheme 6. Enone **27** was prepared from **71** by PhSeCl−pyridine in CH_2Cl_2 and sequential addition of 30% H_2O_2[26] (yield, 71%; 88% based on recovered **71**). Hydrolysis (reflux) of **27** with potassium hydroxide in aqueous methanol (MeOH) gave C-2 carboxylic acid **29** and decarboxylated enone **9** in 78% and 8% yield, respectively. Because of the steric hindrance of the methoxycarbonyl group at C-17 of **27**, the above conditions gave monoesters **29** and **9** selectively. Halogenolysis of **29** gave dicarboxylic acid **30** and decarboxylated enone **10** in 47% and 24% yield, respectively. Interestingly, methylation of **30** with MeOH under acidic conditions gave a mixture of desired monoester **28** and Michael adduct **72**.[27] The ratio of **28** to **72** was determined to be 4:5 by ^{1}H NMR. Because the adduct **72** was readily transformed into **28** under purification conditions (see Experimental Section), **28** was finally obtained in 82% yield from **30**. Amide **36** was prepared selectively from **27** with saturated ammonia−MeOH (yield, 49%; 88% based on recovered **27**). Enal **37** was synthesized from **62** according to the same method as for **27** (yield, 62%; 74% based on recovered **62**).

Biological Results and Discussion

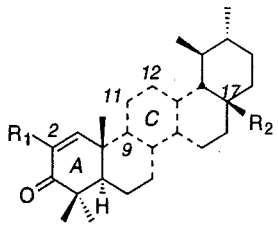
The inhibitory activities [IC_{50} (μM) value] of synthetic triterpenoids **3**−**44**, oleanolic acid (**1**), ursolic acid (**2**), hydrocortisone, and dexamethasone (both glucocoriticoids are used as positive controls) on NO production induced by IFN-γ in mouse macrophages are shown in Table 1. These derivatives are arranged categorically in order of the amplification of potency due to the structure of ring C. Among novel synthetic oleanane and ursane triterpenoids, **25**, CDDO (**26**), and **29** showed extremely high potency (IC_{50} = 0.1 nM level). Their potency is equivalent to that of dexamethasone although their inhibitory activity is not blocked by the glucocorticoid antagonist, RU-486,[28] which reverses the action of dexamethasone (data not shown).

This series of synthetic triterpenoids showed the following interesting SARs: (1) A 9(11)-en-12-one functionality is the strongest enhancer of potency among structures of ring C. Oleanane triterpenoids **10** and **9** (IC_{50} = 0.1 μM level) are about 10−100 times more potent than the lead compounds **8** (IC_{50} = 1 μM level) and **43** (IC_{50} = 10 μM level), respectively. (2) 12-En-11-one, 13(18)-en-11-one, and 12-one functionalities also enhance potency. Oleanane triterpenoids **11**, **12**, **15**, and **17** are more potent than **8**. Also, ursane triterpenoids **13** and **14** are more potent than **44**. (3) A 9(11)-ene functionality shows similar potency to the original 12-ene (compare **18** with **8**). (4) The saturated ring C, 11,-13(18)-diene, and 9,11-epoxide are less potent than the original 12-ene (compare **19**−**21** with **8**). (5) Carboxyl, methoxycarbonyl, and nitrile groups at C-2 enhance potency.[5] Oleanane triterpenoids **3**−**7** (IC_{50} = 0.01−0.1 μM level) are about 10−100 times more potent than **8**. Ursane triterpenoids **38** and **39** are more potent than **44**. (6) The combination of a 9(11)-en-12-one functionality with nitrile and carboxyl groups at C-2 enhances the potency synergistically. Oleanane triterpenoids **25**, CDDO (**26**), and **29** (IC_{50} = 0.1 nM level) are about 10 000 times more potent than **8** (see Figure 1). (7) Although compounds **27** and **30** were also expected to show similar

Table 1. Activity of Olean-1-en-3-one and Urs-1-en-3-one Triterpenoids



olean-1-en-3-one



urs-1-en-3-one

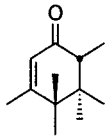
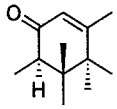
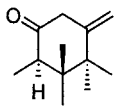
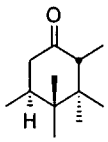
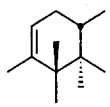
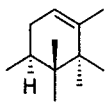
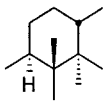
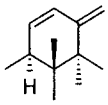
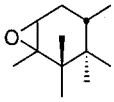
compd	skeleton[a]	structure of ring C	R_1 at C-2	R_2 at C-17	formula	analyses[b]	activity[c] IC_{50}(μM)
9	O		H	CO_2Me	$C_{31}H_{44}O_4 \cdot 1/3H_2O$	C,H	0.7
10	O		H	CO_2H	$C_{30}H_{42}O_4 \cdot 1/3H_2O$	C,H	0.2
25	O		CN	CO_2Me	$C_{32}H_{43}O_4N$	C,H,N	0.0001
26	O		CN	CO_2H	$C_{31}H_{41}O_4N$	C,H,N	0.0002
27	O		CO_2Me	CO_2Me	$C_{33}H_{46}O_6$	C,H	toxic[d]
28	O		CO_2Me	CO_2H	$C_{32}H_{44}O_6 \cdot 1/3H_2O$	C,H	0.1
29	O		CO_2H	CO_2Me	$C_{32}H_{44}O_6 \cdot 1/2H_2O$	C,H	0.0008
30	O		CO_2H	CO_2H	$C_{31}H_{42}O_6 \cdot 1/2H_2O$	C,H	0.2
36	O		$CONH_2$	CO_2Me	$C_{32}H_{45}O_5N \cdot 1/3H_2O$	C,H,N	0.1
37	O		CHO	CO_2Me	$C_{32}H_{44}O_5 \cdot 5/4H_2O$	C,H	0.1
11	O		H	CO_2Me	$C_{31}H_{44}O_4$	C,H	2.8
12	O		H	CO_2H	$C_{30}H_{42}O_4 \cdot 1/4H_2O$	C,H	1.1
13	U		H	CO_2Me	$C_{31}H_{44}O_4 \cdot 1/4H_2O$	C,H	8.9
14	U		H	CO_2H	$C_{30}H_{42}O_4 \cdot 1/4H_2O$	C,H	5.1
22	O		H	CH_2OAc	$C_{32}H_{46}O_4$	C,H	>40
23	O		H	CH_2OH	$C_{30}H_{44}O_3 \cdot 1/2H_2O$	C,H	3.0
24	O		H	CHO	$C_{30}H_{42}O_3 \cdot 1/2H_2O$	C,H	3.8
31	O		CN	CO_2Me	$C_{32}H_{43}O_4N \cdot 1/3H_2O$	C,H,N	0.02
32	O		CN	CO_2H	$C_{31}H_{41}O_4N \cdot 1/3H_2O$	C,H,N	0.04
33	U		CN	CO_2Me	$C_{32}H_{43}O_4N$	C,H,N	0.1
34	U		CN	CO_2H	$C_{31}H_{41}O_4N \cdot H_2O$	C,H,N	0.8
15	O		H	CO_2H	$C_{30}H_{42}O_4 \cdot 3/4H_2O$	C,H	2.6
35	O		CN	CO_2H	$C_{31}H_{41}O_4N \cdot 1/2H_2O$	C,H,N	0.07
16	O		H	CO_2Me	$C_{31}H_{46}O_4$	C,H	14
17	O		H	CO_2H	$C_{30}H_{44}O_4 \cdot 2/3H_2O$	C,H	3.3
18	O		H	CO_2H	$C_{30}H_{44}O_3 \cdot 1/2H_2O$	C,H	5.2
43	O		H	CO_2Me	$C_{31}H_{46}O_3$	ref 32	31
8	O		H	CO_2H	$C_{30}H_{44}O_3 \cdot 3/4H_2O$	ref 5	5.6
44	U		H	CO_2H	$C_{30}H_{44}O_3$	ref 33	13
3	O		CN	CO_2Me	$C_{32}H_{45}O_3N \cdot 1/4H_2O$	ref 5	0.7
4	O		CN	CO_2H	$C_{31}H_{43}O_3N \cdot 1/2H_2O$	ref 5	0.6
38	U		CN	CO_2Me	$C_{32}H_{45}O_3N \cdot 3/4H_2O$	ref 5	5.1
39	U		CN	CO_2H	$C_{31}H_{43}O_3N \cdot H_2O$	ref 5	6.2
5	O		CO_2Me	CO_2Me	$C_{33}H_{48}O_5$	ref 5	0.9
40	O		CO_2Me	CO_2H	$C_{32}H_{46}O_5$	ref 5	2.2
6	O		CO_2H	CO_2Me	$C_{32}H_{46}O_5 \cdot 1/2H_2O$	ref 5	0.8
7	O		CO_2H	CO_2H	$C_{31}H_{44}O_5$	ref 5	0.07
41	O		$CONH_2$	CO_2Me	$C_{32}H_{47}O_4N \cdot 3/4H_2O$	ref 5	14
42	O		CHO	CO_2Me	$C_{32}H_{46}O_4$	ref 5	toxic[d]

Table 1 (Continued)

compd	skeleton[a]	structure of ring C	R_1 at C-2	R_2 at C-17	formula	analyses[b]	activity[c] IC_{50}(μM)
19	O		H	CO_2H	$C_{30}H_{46}O_3 \cdot 2/3H_2O$	C,H	8.5
20	O		H	CO_2H	$C_{30}H_{42}O_3 \cdot H_2O$	C,H	9.7
21	O		H	CO_2H	$C_{30}H_{44}O_4 \cdot 1/2H_2O$	C,H	36
1	oleanolic acid						>40
2	ursolic acid						toxic[e]
	hydrocortisone						0.01
	dexamethasone						0.0001

[a] O, olean-1-en-3-one; U, urs-1-en-3-one. [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 compounds **7**, **25**, **26**, **29**, **31**, **32**, **35**, hydrocortisone, and dexamethasone 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 **27** and **42** 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.

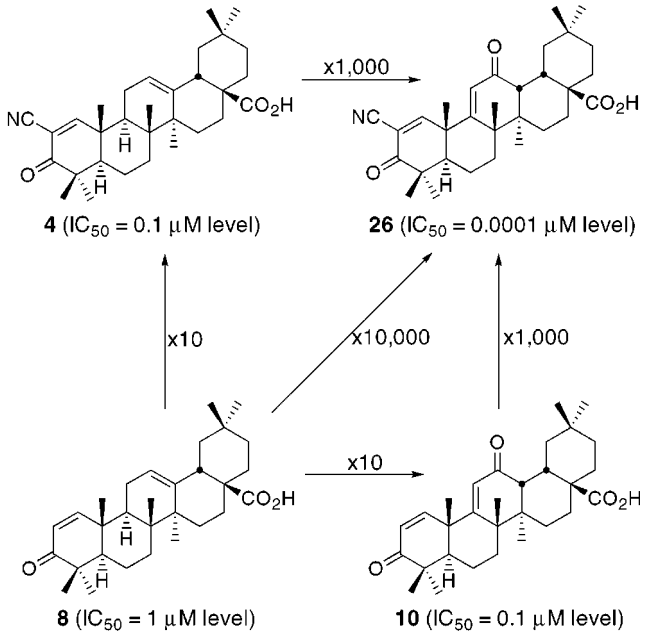


Figure 1. SARs between CDDO (**26**) and its lead compounds **4**, **8**, and **10**.

high potency to CDDO from the perspective of SARs, they did not (compare them with **5** and **7**). The reason diacid **30** did not show high potency might be that the higher polarity than that of monoacids **26** and **29** influences the bioavailability and permeability toward macrophages. (8) The combination of a 9(11)-en-12-one functionality with amide and formyl groups at C-2 does not enhance potency as strongly as a nitrile or carboxyl group as expected from the consideration of the activity of oleana-1,12-dien-3-one with amide and formyl groups at C-2 (compare **36** and **37** with **41** and **42**, respectively). (9) The combination of 12-en-11-one and 13(18)-en-11-one functionalities with a nitrile group at C-2 also strongly enhances the potency. Oleanane triterpenoids **31**, **32**, and **35** (IC_{50} = 0.01 μM level) are about 100 times more potent than **8**. Also, ursane triterpenoids **33** and **34** (IC_{50} = 0.1 μM level) are about 100 times more potent than **44** (IC_{50} = 10 μM level). (10) The oleanane skeleton is more potent than the ursane skeleton. Oleanane derivatives **3**, **4**, **8**, **11**, **12**, **31**, and **32** are more potent than ursane derivatives **38**, **39**, **44**, **13**, **14**, **33**, and **34**, respectively. (11) Acetoxymethyl, hydroxymethyl, and formyl groups at C-17 decrease potency compared with the carboxyl group at C-17 (compare **22**−**24** with **12**). (12) 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 **7**, **8**, **17**, and **28** are more potent than esters **6**, **43**, **16**, and **27**, respectively. For other analogues, the carboxyl and methoxycarbonyl groups show similar potency: acids **4**, **26**, **32**, and **39** show similar potency to esters **3**, **25**, **31**, and **38**, respectively. Acids and esters with a nitrile group at C-2 seem to show this tendency although the reason is unknown. Lastly, acids **30** and **40** are less potent than esters **29** and **5**, respectively.

The selected oleanane triterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (**26**), was found to be a potent, multifunctional agent in various in vitro assays.[29] For example, CDDO induces monocytic differentiation of human myeloid leukemia cells and adipogenic differentiation of mouse 3T3-L1 fibroblasts.[30] CDDO inhibits proliferation of many human tumor cell lines. CDDO blocks de novo synthesis of inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2) in mouse macrophages. CDDO will protect rat brain hippocampal neurons from cell death induced by β-amyloid. The above potencies have been found at concentrations ranging from 10^{-6} to 10^{-9} M in cell culture. In addition, CDDO shows antiinflammatory activity against thioglycollate−IFN-γ-induced mouse peritonitis (0.1 μmol of CDDO/mouse, ip: a complete

suppression of both NO production and iNOS protein synthesis; 0.01 μmol of CDDO/mouse, ip: more than 50% suppression in these measurements).[31] CDDO may be a potential drug candidate for inflammatory diseases and chemoprevention of cancer.

Currently, further biological evaluation of CDDO, **25**, and **29** in vitro and in vivo for both antiinflammation and chemoprevention is in progress. Further studies on the mechanism of action of these compounds also are 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. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer unless otherwise stated. The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of C*H*Cl$_3$ (^{1}H NMR) and δ 77.23 signal of *C*DCl$_3$ (^{13}C NMR) as an internal standard unless otherwise stated. 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 workup 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 3,12-Dioxooleana-1,9(11)-dien-28-oate (9). A solution of **54** (145 mg, 0.30 mmol) and phenylselenenyl chloride (98%) (69 mg, 0.35 mmol) in EtOAc (7 mL) was stirred at room temperature for 2.5 h. To the stirred mixture was added water (1.5 mL). After most of the aqueous layer was removed, THF (2.7 mL) and 30% H_2O_2 (0.24 mL) were added to the organic layer. The mixture was stirred at room temperature for 1 h. The mixture was worked up according to the standard method to give a crude solid (134 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1)] to give **9** as an amorphous solid (96 mg, 67%): $[\alpha]^{23}_D$ +58° (*c* 0.64, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (4.20) nm. IR (KBr): 2948, 2872, 1723, 1666, 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33 (1H, d, J = 10.5 Hz), 6.00 (1H, s), 5.92 (1H, d, J = 10.5 Hz), 3.69 (3H, s), 3.04 (1H, ddd, J = 3.4, 4.6, 13.4 Hz), 2.91 (1H, d, J = 4.6 Hz), 1.41, 1.31, 1.19, 1.12, 1.01, 1.00, 0.89 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 203.7, 199.8, 178.4, 171.6, 155.0, 126.1, 123.8, 52.1, 49.8, 48.5, 47.4, 45.8, 44.9, 42.2, 42.0, 36.0, 34.7, 33.5, 33.0, 32.3, 31.7, 30.8, 28.2, 27.3, 27.1, 24.7, 23.3, 22.8, 21.84, 21.81, 18.6. EIMS (70 eV) *m*/*z*: 480 [M]$^+$ (99), 465 (100), 446 (42), 405 (27), 315 (41), 244 (44). HREIMS Calcd for $C_{31}H_{44}O_4$: 480.3240. Found: 480.3238. Anal. (Table 1).

3,12-Dioxooleana-1,9(11)-dien-28-oic Acid (10). A mixture of **9** (82 mg, 0.17 mmol) and LiI (405 mg) in dry DMF (2 mL) was heated under reflux for 7.5 h. To the mixture were added water and 5% aqueous HCl solution. The 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 an amorphous solid (78 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (1:1)] to give **10** as a crystalline solid (54 mg, 68%). An analytically pure sample was obtained by recrystallization from a mixture of hexanes and EtOAc (2:1) as colorless needles: mp >270 °C dec; $[\alpha]^{23}_D$ +63° (*c* 0.42, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (4.14) nm. IR (KBr): 3117, 2973, 2941, 2867, 1734, 1710, 1671, 1639, 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33 (1H, d, J = 10.6 Hz), 6.02 (1H, s), 5.93 (1H, d, J = 10.6 Hz), 3.02 (1H, ddd, J = 3.4, 4.9, 13.7 Hz), 2.96 (1H, d, J = 4.9 Hz), 1.41, 1.32, 1.19, 1.11, 1.02, 1.00, 0.90 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 203.8, 199.6, 183.9, 171.7, 155.0, 126.1, 123.8, 49.9, 48.4, 47.2, 45.8, 44.8, 42.2, 41.9, 35.9, 34.6, 33.4, 33.1, 32.3, 31.6, 30.8, 28.2, 27.3, 27.1, 24.8, 23.2, 22.7, 21.83, 21.75, 18.5. EIMS (70 eV) *m*/*z*: 466 [M]$^+$ (100), 451 (42), 301 (17), 244 (45). HREIMS Calcd for $C_{30}H_{42}O_4$: 466.3083. Found: 466.3064. Anal. (Table 1).

Methyl 3,11-Dioxooleana-1,12-dien-28-oate (11). 11 was prepared from methyl 3,11-dioxoolean-12-en-28-oate (**45**)[7] according to the same method as for **9** to give a crystalline solid (97%). This material was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes−EtOAc (3:1)], followed by recrystallization from a mixture of hexanes and EtOAc (3:1) as crystals: mp 189−191 °C; $[\alpha]^{24}_D$ +152° (*c* 0.34, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 248 (4.26) nm. IR (KBr): 2942, 2861, 1725, 1666, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.79 (1H, d, J = 10.3 Hz), 5.81 (1H, d, J = 10.3 Hz), 5.74 (1H, s), 3.66 (3H, s), 3.05 (1H, dd, J = 4.6, 14.9 Hz), 2.67 (1H, s), 2.08 (1H, ddd, J = 4.0, 13.7, 13.7 Hz), 1.39 (6H, s), 1.16, 1.11, 0.97, 0.96, 0.95 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 204.7, 199.3, 177.6, 170.4, 161.8, 127.6, 124.8, 55.7, 52.9, 52.1, 46.3, 45.3, 44.9, 44.4, 43.9, 42.0, 39.1, 33.8, 33.0, 32.3, 31.7, 30.9, 28.0, 27.8, 23.8, 23.6, 23.0, 21.7, 20.1, 19.4, 18.3. EIMS (70 eV) *m*/*z*: 480 [M]$^+$ (88), 465 (15), 421 (24), 397 (52), 276 (36), 257 (47), 217 (100). HREIMS Calcd for $C_{31}H_{44}O_4$: 480.3240. Found: 480.3231. Anal. (Table 1).

3,11-Dioxooleana-1,12-dien-28-oic Acid (12) and 3,11-Dioxooleana-1,13(18)-dien-28-oic Acid (15). 12 and **15** were prepared from **11** by the similar method as for **10** except that the reaction time was 2 h. The reaction mixture was subjected to prep-TLC [hexanes−EtOAc (3:5)] to give **12** as an amorphous solid (43%) and **15** as a crystalline solid (22%). **12**: $[\alpha]^{24}_D$ +161° (*c* 0.51, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 248 (4.35) nm. IR (KBr): 3154, 2948, 2869, 1732, 1652, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.77 (1H, d, J = 10.3 Hz), 5.81 (1H, d, J = 10.3 Hz), 5.74 (1H, s), 3.02 (1H, dd, J = 4.3, 13.6 Hz), 2.67 (1H, s), 2.09 (1H, ddd, J = 5.2, 14.3, 14.3 Hz), 1.39, 1.38, 1.15, 1.08, 0.97, 0.96, 0.95 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 204.8, 199.4, 183.2, 170.1, 161.8, 127.9, 124.9, 55.7, 52.9, 46.2, 45.4, 44.9, 44.3, 44.0, 41.8, 39.1, 33.8, 33.0, 32.4, 31.7, 30.9, 28.0, 27.9, 23.8, 23.6, 22.7, 21.7, 20.2, 19.7, 18.2. FABMS (NBA, by a VG analytical ZAB 2SE) *m*/*z*: 467 [M + H]$^+$. HRFABMS (by a VG analytical ZAB 2SE) Calcd for $C_{30}H_{42}O_4$ + H: 467.3161. Found: 467.3161. Anal. (Table 1). **15**: mp >190 °C dec; $[\alpha]^{25}_D$ −16° (*c* 0.26, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 210 (4.16), 226 (4.15), 300 (3.16) nm. IR (KBr): 3200, 2946, 2866, 1692 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.46 (1H, d, J = 10.1 Hz), 5.82 (1H, d, J = 10.1 Hz), 3.56 (1H, d, J = 17.8 Hz), 2.88 (1H, d, J = 17.8 Hz), 2.65 (1H, s), 2.31 (2H, m), 2.09 (1H, m), 1.44, 1.31, 1.16, 1.10, 0.96, 0.93, 0.76 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 208.6, 204.8, 181.9, 160.8, 133.8, 129.9, 125.1, 58.0, 52.9, 48.1, 44.8, 44.3, 44.1, 43.4, 41.1, 39.1, 36.7, 35.7, 33.03, 32.95, 32,8, 32.2, 27.7, 26.6, 24.2, 21.8, 20.2, 20.1, 19.2, 18.8. FABMS (NBA, by a VG analytical ZAB 2SE) *m*/*z*: 467 [M + H]$^+$. HRFABMS (by a VG analytical ZAB 2SE) Calcd for $C_{30}H_{42}O_4$ + H: 467.3161. Found: 467.3187. Anal. (Table 1).

Methyl 3,11-Dioxoursa-1,12-dien-28-oate (13). 13 was prepared from **48** according to the same method as for **9** to give a crystalline solid (93%). An analytically pure sample was obtained by recrystallization from a mixture of hexanes and EtOAc (3:1) as crystals: mp 172−174 °C; $[\alpha]^{24}_D$ +150° (*c* 0.49, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 248 (4.26) nm. IR (KBr): 2973, 2948, 2866, 1726, 1670, 1655, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.75 (1H, d, J = 10.3 Hz), 5.82 (1H, d, J = 10.3 Hz), 5.71 (1H, s), 3.63 (3H, s), 2.64 (1H, s), 2.47 (1H, d, J = 11.7 Hz), 2.11 (1H, ddd, J = 4.6, 14.7, 14.7 Hz), 1.41, 1.33, 1.16, 1.11 (each 3H, s), 0.98 (3H, d, J = 7.2 Hz), 0.97 (3H, s), 0.89 (3H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 204.7, 198.8, 177.3, 164.5, 161.8, 130.4, 124.8, 55.5, 53.1, 53.0, 52.1, 47.9, 45.0, 44.9, 44.2, 39.0, 38.82, 38.79, 36.1, 32.5, 30.5, 28.7, 27.8, 24.0, 21.8, 21.3, 21.2, 20.1, 19.4, 18.3, 17.3. EIMS (70 eV) *m*/*z*: 480 [M]$^+$ (84), 465

(19), 421 (15), 397 (100), 257 (38), 217 (39). HREIMS Calcd for $C_{31}H_{44}O_4$: 480.3240. Found: 480.3239. Anal. (Table 1).

3,11-Dioxoursa-1,12-dien-28-oic Acid (14). 14 was prepared from **13** by the similar method as for **10** except that the reaction time was 1.25 h. The reaction mixture was crystallized from a mixture of hexanes and EtOAc (2:1) to give **14** as crystals (58%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp >275 °C dec; $[\alpha]^{24}_D$ +157° (*c* 0.29, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 247 (4.17) nm. IR (KBr): 3116, 2983, 2950, 2930, 1720, 1668, 1628 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.74 (1H, d, J = 10.3 Hz), 5.82 (1H, d, J = 10.3 Hz), 5.71 (1H, s), 2.65 (1H, s), 2.44 (1H, d, J = 11.2 Hz), 2.13 (1H, m), 1.41, 1.34, 1.15, 1.08 (each 3H, s), 0.99 (3H, d, J = 7.2 Hz), 0.97 (3H, s), 0.89 (3H, d, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 204.8, 199.0, 183.1, 164.3, 161.7, 130.6, 124.8, 55.4, 52.9, 52.8, 47.7, 45.0, 44.9, 44.2, 39.0, 38.8, 38.7, 36.2, 32.5, 30.4, 28.6, 27.8, 23.7, 21.7, 21.3, 21.1, 20.2, 19.6, 18.2, 17.2. FABMS (NBA, by a VG analytical ZAB 2SE) *m*/*z*: 467 $[M + H]^+$. HRFABMS (by a VG analytical ZAB 2SE) Calcd for $C_{30}H_{42}O_4$ + H: 467.3161. Found: 467.3202. Anal. (Table 1).

3,11-Dioxooleana-1,13(18)-dien-28-oic Acid (15). To a solution of **20** (106 mg, 0.24 mmol) in acetone (6.5 mL) was added Jones reagent (0.36 mL) dropwise in an ice bath. The mixture was stirred at room temperature for 30 min. After removal of acetone, water was added to the resultant mixture. The aqueous mixture was extracted with CH_2Cl_2 (three times). The extract was worked up according to the standard method to give a solid (80 mg). The solid was subjected to prep-TLC [hexanes−EtOAc (1.2:1.0)] to give **15** as a crystalline solid (31 mg, 28%).

Methyl 3,12-Dioxoolean-1-en-28-oate (16). 16 was prepared from **51** according to the same method as for **9**. The crude solid was subjected to flash column chromatography [hexanes−EtOAc (3:1) followed by hexanes−EtOAc (2:1)] to give **16** as an amorphous solid (75%): $[\alpha]^{24}_D$ +2.1° (*c* 0.39, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 234 (3.85) nm. IR (KBr): 2946, 2867, 1724, 1700, 1671 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.95 (1H, d, J = 10.3 Hz), 5.84 (1H, d, J = 10.3 Hz), 3.70 (3H, s), 2.82 (1H, ddd, J = 3.5, 4.2, 13.4 Hz), 2.68 (1H, d, J = 4.2 Hz), 2.49 (1H, dd, J = 4.6, 16.4 Hz), 2.33 (1H, dd, J = 13.3, 16.4 Hz), 1.16, 1.11, 1.10, 1.06, 0.99, 0.97, 0.91 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 210.4, 204.8, 178.5, 157.2, 126.0, 53.4, 52.2, 52.1, 47.5, 44.8, 44.2, 42.4, 42.3, 39.5, 38.6, 36.4, 34.6, 33.5, 33.0, 32.2, 31.6, 30.8, 27.82, 27.76, 23.3, 22.9, 21.6, 20.8, 19.1, 18.5, 16.6. EIMS (70 eV) *m*/*z*: 482 $[M]^+$ (5.5), 467 (42), 407 (100), 278 (25), 218 (64). HREIMS Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3387. Anal. (Table 1).

3,12-Dioxoolean-1-en-28-oic Acid (17). 17 was prepared from **16** by the similar method as for **10** except that the reaction time was 4.5 h. The crude material was subjected to prep-TLC [hexanes−EtOAc (1:2)] to give **17** as a crystalline solid (62%): mp 243−245 °C dec; $[\alpha]^{24}_D$ +2.3° (*c* 0.27, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 234 (3.89) nm. IR (KBr): 3166, 2946, 2866, 1722, 1696, 1668, 1651 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.96 (1H, d, J = 10.4 Hz), 5.84 (1H, d, J = 10.4 Hz), 2.79 (2H, m), 2.51 (1H, dd, J = 4.9, 15.9 Hz), 2.35 (1H, dd, J = 13.2, 15.9 Hz), 1.17, 1.11 (each 3H, s), 1.10 (6H, s), 1.00, 0.98, 0.93 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 210.2, 204.9, 184.2, 157.2, 126.0, 53.3, 52.2, 47.4, 44.8, 44.1, 42.4, 42.3, 39.5, 38.6, 36.2, 34.6, 33.5, 33.2, 32.0, 31.6, 30.8, 27.8, 23.3, 22.8, 21.6, 20.7, 19.1, 18.5, 16.7. EIMS (70 eV) *m*/*z*: 468 $[M]^+$ (9.7), 453 (15), 407 (39), 218 (19), 83 (100). HREIMS Calcd for $C_{30}H_{44}O_4$: 468.3240. Found: 468.3221. Anal. (Table 1).

3-Oxooleana-1,9(11)-dien-28-oic Acid (18). 18 was prepared from **58** according to the same method as for **9**. The crude solid was subjected to prep-TLC [hexanes−EtOAc (2:1)] to give **18** as a crystalline solid (80%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp >240 °C dec; $[\alpha]^{24}_D$ +55° (*c* 0.28, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 234 (3.93) nm. IR (KBr): 3138, 3053, 2959, 2930, 2869, 1727, 1693, 1645 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.42 (1H, d, J = 10.4 Hz), 5.85 (1H, d, J = 10.4 Hz), 5.63 (1H, t, J = 3.4 Hz), 1.35, (3H, s), 1.16 (6H, s), 1.07, 0.94 (each 3H, s), 0.90 (6H, s). ^{13}C NMR ($CDCl_3$): δ 205.0, 185.0, 157.9, 147.7, 124.4, 118.6, 49.9, 48.1, 44.7, 44.1, 41.3, 38.6, 36.2, 35.6, 34.4, 33.7, 33.6, 33.2, 31.8, 30.8, 28.5, 28.0, 27.2, 26.9, 26.3, 23.6, 23.4, 21.7, 18.8, 18.7. FABMS (NBA, by a VG analytical ZAB 2SE) *m*/*z*: 453 $[M + H]^+$. HRFABMS (by a VG analytical ZAB 2SE) Calcd for $C_{30}H_{44}O_3$ + H: 453.3369. Found: 453.3390. Anal. (Table 1).

3-Oxoolean-1-en-28-oic Acid (19). 19 was prepared from 3-oxoolean-28-oic acid (**56**)[15] according to the same method as for **9**. The crude solid was subjected to flash column chromatography [hexanes−EtOAc (3:1)] to give **19** as an amorphous solid (68%): $[\alpha]^{24}_D$ +30° (*c* 0.55, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 236 (3.90) nm. IR (KBr): 3200, 2944, 2866, 1729, 1692, 1672 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.11 (1H, d, J = 10.2 Hz), 5.82 (1H, d, J = 10.2 Hz), 2.22 (1H, m), 1.13, 1.06, 1.04, 0.99, 0.96, 0.92, 0.88 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 205.7, 184.9, 159.8, 125.4, 53.5, 48.1, 44.8, 44.7, 42.9, 40.8, 39.7, 37.4, 36.7, 36.5, 34.5, 33.6, 33.4, 32.5, 30.6, 28.5, 28.0, 26.9, 23.6, 23.3, 21.6, 19.2, 17.2, 16.9. FABMS (NBA, by a Micromass ZAB-SE) *m*/*z*: 455 $[M + H]^+$. HRFABMS (by a Micromass 70-SE-4F) Calcd for $C_{30}H_{46}O_3$ + H: 455.3525. Found: 455.3518. Anal. (Table 1).

3-Oxooleana-1,11,13(18)-trien-28-oic Acid (20). 20 was prepared from **60** by the similar method as for **10** except that the reaction time was 4 h. The crude solid was subjected to prep-TLC [hexanes−EtOAc (2.5:1)] to give **20** as an amorphous solid (56%): $[\alpha]^{24}_D$ −88° (*c* 0.44, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 246 (4.35), 252 (4.35) nm. IR (KBr): 3167, 3036, 2944, 2863, 1727, 1695, 1672 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.27 (1H, d, J = 10.1 Hz), 6.57 (1H, dd, J = 2.9, 10.5 Hz), 5.89 (1H, d, J = 10.1 Hz), 5.81 (1H, dd, J = 1.5, 10.5 Hz), 2.57 (1H, d, J = 14.2 Hz), 2.29 (2H, m), 1.174, 1.170, 1.10, 1.00, 0.98, 0.86, 0.82 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 205.7, 182.8, 159.1, 136.6, 132.5, 126.5, 125.7, 125.4, 53.4, 48.4, 48.3, 45.0, 42.4, 41.6, 40.8, 39.3, 37.0, 35.6, 32.9, 32.7, 32.4, 31.9, 27.7, 25.1, 24.3, 21.32, 21.27, 20.0, 19.2, 16.9. FABMS (NBA, by a VG analytical ZAB 2SE) *m*/*z*: 451 $[M + H]^+$. HRFABMS (by a VG analytical ZAB 2SE) Calcd for $C_{30}H_{42}O_3$ + H: 451.3212. Found: 451.3240. Anal. (Table 1).

9,11-Epoxy-3-oxoolean-1-en-28-oic Acid (21). A mixture of **18** (57 mg, 0.13 mmol) and *m*CPBA (60%) (43 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature overnight. After the mixture was diluted with a mixture of CH_2Cl_2 and Et_2O (1:2), it was worked up according to the standard method to give a solid (65 mg). The solid was subjected to prep-TLC [hexanes−EtOAc (1.5:1)] to give **21** as a crystalline solid (27 mg, 46%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 253−254 °C; $[\alpha]^{24}_D$ −14° (*c* 0.25, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 236 (3.88) nm. IR (KBr): 2970, 2945, 1688 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.55 (1H, d, J = 10.4 Hz), 5.85 (1H, d, J = 10.4 Hz), 3.02 (1H, s), 1.39 (3H, s), 1.07 (6H, s), 1.04, 0.96, 0.92, 0.87 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 204.5, 184.4, 154.4, 125.2, 67.8, 60.2, 47.9, 45.3, 44.9, 42.3, 41.5, 38.4, 37.3, 35.7, 34.3, 33.6, 33.3, 30.8, 30.0, 28.2, 27.9, 26.9, 24.9, 23.6, 23.3, 21.1, 20.6, 18.7, 18.6. FABMS (NBA, by a VG analytical ZAB 2SE) *m*/*z*: 469 $[M + H]^+$. HRFABMS (by a VG analytical ZAB 2SE) Calcd for $C_{30}H_{44}O_4$ + H: 469.3318. Found: 469.3314. Anal. (Table 1).

3,11-Dioxooleana-1,12-dien-28-yl Acetate (22). 22 was prepared from 3,11-dioxoolean-12-en-28-yl acetate (**61**)[18] according to the same method as for **9**. The crude solid was subjected to prep-TLC [hexanes−EtOAc (3:1)] to give **22** as an amorphous solid (83%): $[\alpha]^{24}_D$ +131° (*c* 0.45, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 246 (4.31) nm. IR (KBr): 2949, 2868, 1742, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.72 (1H, d, J = 10.1 Hz), 5.79 (1H, d, J = 10.1 Hz), 5.67 (1H, s), 3.97 (1H, d, J = 11.2 Hz), 3.71 (1H, d, J = 11.2 Hz), 2.66 (1H, s), 2.29 (1H, dd, J = 4.2, 13.2 Hz), 2.07 (3H, s), 2.03 (1H, ddd, J = 4.4, 13.9, 13.9 Hz), 1.404, 1.397, 1.18, 1.15, 1.11, 0.93, 0.91 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 204.7, 198.9, 171.2, 170.2, 161.7, 128.3, 124.8, 70.3, 55.8, 53.0, 45.7, 44.99, 44.96, 43.8, 42.9, 39.0, 36.0, 33.9, 33.0, 32.1, 31.2, 31.0, 27.8, 26.1, 23.7, 23.5, 22.1, 21.7, 21.1, 20.2, 19.0, 18.3. EIMS (70 eV) *m*/*z*: 494 $[M]^+$ (100), 446 (92), 411

(41), 406 (37), 351 (19). HREIMS Calcd for $C_{32}H_{46}O_4$: 494.3396. Found: 494.3396. Anal. (Table 1).

28-Hydroxyoleana-1,12-diene-3,11-dione (23). A solution of **22** (47 mg, 0.095 mmol) and KOH (300 mg) in MeOH (3 mL) was stirred at room temperature for 20 min. The mixture was acidified with 5% 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 an amorphous solid (42 mg). The solid was subjected to prep-TLC [hexanes−EtOAc (1.7:1)] to give **23** as an amorphous solid (34 mg, 78%): $[\alpha]^{24}_D$ +145° (*c* 0.50, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 250 (4.13) nm. IR (KBr): 3477, 2947, 2865, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.72 (1H, d, J = 10.3 Hz), 5.80 (1H, d, J = 10.3 Hz), 5.67 (1H, s), 3.48 (1H, d, J = 11.0 Hz), 3.25 (1H, d, J = 11.0 Hz), 2.67 (1H, s), 2.21 (1H, dd, J = 3.8, 13.6 Hz), 1.97 (1H, ddd, J = 4.4, 13.7, 13.7 Hz), 1.41, 1.40 (each 3H, s), 1.16 (6H, s), 1.11, 0.93, 0.91 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 204.8, 199.1, 171.4, 161.8, 128.0, 124.8, 69.8, 55.7, 53.0, 45.8, 45.1, 45.0, 43.9, 43.0, 39.0, 37.2, 34.0, 33.1, 32.2, 31.3, 30.8, 27.8, 26.1, 23.6, 21.8, 21.7, 20.3, 19.0, 18.4. EIMS (70 eV) *m/z*: 452 $[M]^+$ (100), 437 (15), 434 (16), 383 (16), 364 (50), 248 (46). HREIMS Calcd for $C_{30}H_{44}O_3$: 452.3290. Found: 452.3292. Anal. (Table 1).

Oleana-1,12-diene-3,11,28-trione (24). To a stirred mixture of CrO_3 (70 mg, 0.70 mmol) and pyridine (110 mg, 1.39 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of **23** (53 mg, 0.12 mmol) in dry CH_2Cl_2 (1.5 mL). The mixture was stirred at room temperature for 15 min. The mixture was worked up according to Ratcliffe's procedure[20] to give a crude solid of **24** (47 mg, 89%). The solid was recrystallized from a mixture of hexanes and EtOAc (2:1) to give **24** as colorless needles (31 mg, 59%): mp >267 °C dec; $[\alpha]^{24}_D$ +160° (*c* 0.27, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 248 (4.15) nm. IR (KBr): 2944, 2864, 1719, 1674, 1644 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.40 (1H, s), 7.76 (1H, d, J = 10.3 Hz), 5.80 (1H, d, J = 10.3 Hz), 5.77 (1H, s), 2.84 (1H, dd, J = 4.3, 13.6 Hz), 2.64 (1H, s), 2.10 (1H, ddd, J = 3.9, 14.3, 14.3 Hz), 1.38 (6H, s), 1.15, 1.10 (each 3H, s), 0.96 (6H, s), 0.93 (3H, s). ^{13}C NMR ($CDCl_3$): δ 205.4, 204.7, 199.0, 169.1, 161.7, 128.0, 124.8, 55.7, 53.0, 49.1, 45.4, 44.9, 44.3, 43.9, 40.1, 39.1, 33.2, 32.9, 32.4, 30.9, 27.9, 27.30, 27.26, 23.5, 23.3, 21.7, 21.6, 20.1, 19.6, 18.3. EIMS (70 eV) *m/z*: 450 $[M]^+$ (100), 446 (64), 367 (45), 362 (31), 246 (36). HREIMS Calcd for $C_{30}H_{42}O_3$: 450.3134. Found: 450.3129. Anal. (Table 1).

Methyl 2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oate (25). A mixture of **64** (1.51 g, 2.97 mmol) and DDQ (98%) (0.77 g, 3.32 mmol) in dry benzene (80 mL) was heated under reflux for 30 min. 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 (10:1)] to give **25** as an amorphous solid (1.38 g, 92%): $[\alpha]^{23}_D$ +33° (*c* 0.68, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 244 (4.07) nm. IR (KBr): 2950, 2872, 2233, 1722, 1690, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.04 (1H, s), 5.96 (1H, s), 3.68 (3H, s), 3.02 (1H, ddd, J = 3.4, 4.9, 13.4 Hz), 2.92 (1H, d, J = 4.9 Hz), 1.47, 1.31, 1.24, 1.15, 0.99, 0.98, 0.88 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 199.0, 196.8, 178.3, 168.6, 165.9, 124.2, 114.7, 114.6, 52.1, 49.8, 47.8, 47.3, 45.9, 45.2, 42.7, 42.2, 35.9, 34.6, 33.4, 32.9, 31.8, 31.6, 30.8, 28.1, 27.1, 26.8, 24.7, 23.2, 22.7, 21.8, 21.7, 18.4. EIMS (70 eV) *m/z*: 505 $[M]^+$ (100), 490 (81), 430 (42), 315 (47), 269 (40). HREIMS Calcd for $C_{32}H_{43}O_4N$: 505.3192. Found: 505.3187. Anal. (Table 1).

2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic Acid (26). A mixture of **25** (612 mg, 1.21 mmol) and LiI (3.0 g) in dry DMF (10 mL) was heated under reflux for 4 h. To the mixture were added water and 5% aqueous HCl solution. The mixture was extracted with EtOAc (three times). The extract was 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 an amorphous solid. The solid was subjected to flash column chromatography [hexanes−EtOAc (1:1) followed by CH_2Cl_2−MeOH (15:1)] to give crude **26** (530 mg). The crude product was purified by recrystallization from benzene to give crystals. To remove benzene completely, the crystals were dissolved in CH_2Cl_2 (20 mL) and the solvent was evaporated in vacuo to give benzene-free **26** as an amorphous solid (405 mg, 68%): $[\alpha]^{22}_D$ +33 ° (*c* 0.28, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (4.21) nm. IR (KBr): 2950, 2867, 2235, 1692, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.05 (1H, s), 6.00 (1H, s), 3.06−2.98 (2H, m), 1.48, 1.34, 1.25, 1.16, 1.02, 1.00, 0.90 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 199.0, 196.8, 183.7, 168.8, 165.9, 124.2, 114.7, 114.5, 49.8, 47.8, 47.1, 45.9, 45.2, 42.7, 42.3, 35.8, 34.5, 33.3, 33.0, 31.8, 31.5, 30.8, 28.1, 27.1, 26.8, 24.8, 23.2, 22.6, 21.72, 21.71, 18.4. EIMS (70 eV) *m/z*: 491 $[M]^+$ (100), 476 (62), 445 (29), 430 (27), 269 (94). HREIMS Calcd for $C_{31}H_{41}O_4N$: 491.3036. Found: 491.3020. Anal. (Table 1).

Methyl 2-Methoxycarbonyl-3,12-dioxooleana-1,9(11)-dien-28-oate (27). To a solution of phenylselenenyl chloride (98%) (78 mg, 0.40 mmol) in CH_2Cl_2 (3.2 mL) in an ice bath was added a solution of pyridine (35 mg, 0.44 mmol) in CH_2Cl_2 (0.8 mL). After 15 min, a solution of **71** (108 mg, 0.20 mmol) in CH_2Cl_2 (1.4 mL) was added and the mixture was stirred an additional 1 h. After the mixture was washed with 10% aqueous HCl solution (1.6 mL) twice, 30% H_2O_2 (0.2 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 (108 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (2:1)] to afford **71** (21 mg) and **27** as colorless needles (76 mg; 71%, 88% based on recovered **71**): mp 187−188 °C; $[\alpha]^{23}_D$ +35° (*c* 0.38, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 246 (4.06) nm. IR (KBr): 2944, 2867, 1722, 1664, 1597 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.05 (1H, s), 6.09 (1H, s), 3.79, 3.69 (each 3H, s), 3.04 (1H, ddd, J = 3.5, 4.5, 13.9 Hz), 2.94 (1H, d, J = 4.5 Hz), 1.37, 1.30, 1.18, 1.17, 1.01, 0.99, 0.88 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 199.6, 199.4, 178.3, 170.8, 165.0, 160.7, 129.9, 125.2, 52.5, 52.1, 50.0, 48.3, 47.4, 46.0, 45.8, 42.3, 42.0, 36.0, 34.6, 33.4, 32.9, 31.7, 30.8, 28.2, 28.1, 27.3, 24.6, 23.3, 22.8, 21.7, 21.4, 18.8. EIMS (70 eV) *m/z*: 538 $[M]^+$ (20), 523 (40), 506 (100), 315 (47). HREIMS Calcd for $C_{33}H_{46}O_6$: 538.3294. Found: 538.3289. Anal. (Table 1).

2-Methoxycarbonyl-3,12-dioxooleana-1,9(11)-dien-28-oic Acid (28). A solution of **30** (33 mg, 0.064 mmol) in MeOH (3.1 mL) containing concentrated H_2SO_4 (0.09 mL) was heated under reflux for 25 min. After water 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 solid (31 mg). The solid was a mixture of **28** and 3-hydroxy-1-methoxy-2-methoxycarbonyl-12-oxooleana-2,9(11)-dien-28-oic acid (**72**). The solid was subjected to prep-TLC [hexanes−EtOAc (1:1)] to give only **28** as a crystalline solid (27 mg, 82%). An analytically pure sample was obtained by recrystallization from a mixture of hexanes and EtOAc (2:1) as colorless needles: mp >265 °C dec; $[\alpha]^{23}_D$ +34° (*c* 0.42, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 240 (4.09) nm. IR (KBr): 3118, 2977, 2940, 2869, 1718, 1692, 1636 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.06 (1H, s), 6.11 (1H, s), 3.81 (3H, s), 3.09−2.98 (2H, m), 1.38, 1.34, 1.20, 1.19, 1.04, 1.02, 0.91 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 199.7, 199.2, 183.5, 170.9, 165.1, 160.7, 130.0, 125.3, 52.6, 50.0, 48.3, 47.2, 46.0, 45.9, 42.3, 42.0, 35.9, 34.6, 33.4, 33.1, 31.7, 31.6, 30.8, 28.2, 28.1, 27.3, 24.7, 23.2, 22.7, 21.7, 21.4, 18.8. EIMS (70 eV) *m/z*: 524 $[M]^+$ (17), 509 (24), 492 (100), 446 (38), 302 (31). HREIMS Calcd for $C_{32}H_{44}O_6$: 524.3138. Found: 524.3142. Anal. (Table 1). **72**:[34] ^1H NMR ($CDCl_3$): δ 13.06 (1H, s), 5.93 (1H, s), 4.46 (1H, s), 3.82 (3H, s), 3.21 (3H, s), 3.03 (2H, m), 2.12 (1H, dd, J = 3.8, 10.4 Hz), 1.26, 1.22, 1.13, 1.07, 1.05, 1.02, 0.92 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 200.2, 184.1, 182.1, 174.8, 174.0, 124.4, 96.9, 57.3, 51.9, 50.1, 47.4, 46.0, 45.7, 44.7, 42.8, 41.5, 39.5, 36.1, 34.7, 33.4, 33.2, 31.7, 31.2, 30.9, 28.5, 24.3, 23.8, 23.3, 23.2, 22.8, 21.2, 20.9, 18.5. EIMS (70 eV) *m/z*: 556 $[M]^+$ (3.0), 538 (54), 524 (61), 509 (35), 492 (96), 446 (86), 315 (100). HREIMS Calcd for $C_{33}H_{48}O_7$: 556.3400. Found: 556.3410.

Methyl 2-Carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate (29). A mixture of **27** (273 mg, 0.51 mmol) and KOH (1.6 g) in water (5.3 mL) and MeOH (16 mL) was heated under reflux for 15 min. After the mixture was acidified with 10% aqueous HCl solution, it was extracted with EtOAc (three

times). The extract was 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 (264 mg). The solid was recrystallized from MeOH to afford **29** as colorless needles (174 mg). The solid (75 mg) which was obtained from the mother liquid was subjected to flash column chromatography [hexanes−EtOAc (1:1)] to give **9** (19 mg, 8%) and **29** as colorless needles (33 mg, total 78%): mp 155−156 °C dec; $[\alpha]^{23}_D$ +50° (*c* 0.30, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 254 (4.14) nm. IR (KBr): 2950, 2872, 1756, 1722, 1664 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.77 (1H, s), 6.17 (1H, s), 3.70 (3H, s), 3.04 (1H, ddd, J = 3.6, 4.5, 13.2 Hz), 2.92 (1H, d, J = 4.5 Hz), 1.48, 1.34, 1.29, 1.22 (each 3H, s), 1.00 (6H, s), 0.90 (3H, s). ^{13}C NMR ($CDCl_3$): δ 207.6, 199.1, 178.4, 169.1, 168.5, 164.3, 124.5, 123.8, 52.1, 49.9, 47.7, 47.4, 45.9, 45.7, 42.5, 42.2, 35.9, 34.6, 33.4, 32.9, 31.8, 31.7, 30.8, 28.2, 27.5, 27.1, 24.8, 23.2, 22.8, 22.0, 21.8, 18.5. EIMS (70 eV) *m*/*z*: 524 $[M]^+$ (12), 509 (31), 506 (74), 480 (52), 465 (83), 405 (56), 315 (66), 175 (100). HREIMS Calcd for $C_{32}H_{44}O_6$: 524.3138. Found: 524.3138. Anal. (Table 1).

2-Carboxy-3,12-dioxooleana-1,9(11)-dien-28-oic Acid (30).[35] A mixture of **29** (120 mg, 0.23 mmol) and LiI (545 mg) in dry DMF (1.6 mL) was heated under reflux for 30 min. The reaction mixture was worked up according to the same method as for **26** to give a solid (125 mg). The solid was recrystallized from a mixture of hexanes and EtOAc (1:2) to afford **30** as colorless needles (36 mg). The solid which was obtained from the mother liquid was subjected to flash column chromatography [hexanes−EtOAc (1:2)] to give **10** (26 mg, 24%) and **30** as colorless needles (19 mg, total 47%): mp >260 °C dec; $[\alpha]^{24}_D$ +52° (*c* 0.28, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 256 (4.17) nm. IR (KBr): 3269, 2956, 2928, 1750, 1728, 1658, 1631, 1595 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.77 (1H, s), 6.18 (1H, s), 3.04 (1H, ddd, J = 3.5, 4.9, 13.6 Hz), 2.98 (1H, d, J = 4.9 Hz), 1.48, 1.36, 1.30, 1.23 (each 3H, s), 1.02 (6H, s), 0.91 (3H, s). EIMS (70 eV) *m*/*z*: 510 $[M]^+$ (12), 492 (100), 466 (71), 451 (75), 405 (48), 301 (37). HREIMS Calcd for $C_{31}H_{42}O_6$: 510.2981. Found: 510.2979. Anal. (Table 1).

Methyl 2-Cyano-3,11-dioxooleana-1,12-dien-28-oate (31). **31** was prepared from **67** according to the same method as for **25** to give an amorphous solid (80%): $[\alpha]^{24}_D$ +97° (*c* 0.49, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 250 (4.24) nm. IR (KBr): 2944, 2867, 2233, 1726, 1686, 1656, 1617 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.59 (1H, s), 5.77 (1H, s), 3.65 (3H, s), 3.06 (1H, dd, J = 4.0, 13.7 Hz), 2.69 (1H, s), 2.08 (1H, ddd, J = 4.1, 13.6, 13.6 Hz), 1.41, 1.38, 1.21, 1.15, 0.97, 0.96, 0.95 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 198.4, 197.8, 177.5, 173.0, 171.5, 127.3, 115.1, 113.5, 54.5, 52.2, 52.0, 46.3, 45.5, 45.3, 44.4, 44.1, 42.1, 40.0, 33.8, 33.0, 31.9, 31.6, 30.9, 28.0, 27.8, 23.8, 23.6, 23.0, 21.7, 19.6, 19.4, 18.2. EIMS (70 eV) *m*/*z*: 505 $[M]^+$ (100), 445 (22), 417 (27), 370 (20). HREIMS Calcd for $C_{32}H_{43}O_4N$: 505.3192. Found: 505.3200. Anal. (Table 1).

2-Cyano-3,11-dioxooleana-1,12-dien-28-oic Acid (32)[35] and 2-Cyano-3,11-dioxooleana-1,13(18)-dien-28-oic Acid (35). **32** and **35** were prepared from **31** by the similar method as for **26**. The reaction mixture was subjected to prep-TLC [hexanes−EtOAc−MeOH (50:100:1.5)] to give **32** as a crystalline solid (37%) and **35** as an amorphous solid (16%). **32**: mp >270 °C dec; $[\alpha]^{24}_D$ +101° (*c* 0.28, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 250 (4.23) nm. IR (KBr): 3228, 2944, 2867, 2233, 1732, 1689, 1656 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.58 (1H, s), 5.78 (1H, s), 3.04 (1H, dd, J = 3.7, 13.9 Hz), 2.69 (1H, s), 2.11 (1H, ddd, J = 3.9, 13.7, 13.7 Hz), 1.42, 1.40, 1.22, 1.14, 1.00, 0.973, 0.968 (each 3H, s). EIMS (70 eV) *m*/*z*: 491 $[M]^+$ (34), 445 (31), 397 (26), 257 (36), 189 (59), 95 (100). HREIMS Calcd for $C_{31}H_{41}O_4N$: 491.3036. Found: 491.3034. Anal. (Table 1). **35**: $[\alpha]^{25}_D$ −1.7° (*c* 0.47, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 210 (3.94), 240 (4.02), 304 (2.89) nm. IR (KBr): 3178, 2948, 2867, 2234, 1726, 1694, 1611 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.25 (1H, s), 3.60 (1H, d, J = 19.2 Hz), 2.91 (1H, d, J = 19.2 Hz), 2.68 (1H, s), 1.47, 1.30, 1.22, 1.15, 0.97, 0.94, 0.77 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 208.2, 197.7, 182.0, 171.8, 133.0, 130.5, 115.1, 113.9, 56.9, 52.0, 48.1, 45.2, 44.2, 44.0, 43.5, 41.1, 40.0, 36.7, 35.7, 33.1, 32.8, 32.4, 32.2, 27.6, 26.5, 24.2, 21.8, 20.1, 19.6, 19.3, 18.7. EIMS (70 eV) *m*/*z*: 491 $[M]^+$ (5.3), 461 (55), 445 (100), 351 (38), 310 (29), 257 (50). HREIMS Calcd for $C_{32}H_{41}O_4N$: 491.3036. Found: 491.3040. Anal. (Table 1).

Methyl 2-Cyano-3,11-dioxoursa-1,12-dien-28-oate (33). **33** was prepared from **70** according to the same method as for **25** to give a crystalline solid (90%): mp >275 °C dec; $[\alpha]^{25}_D$ +91° (*c* 0.36, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 250 (4.22) nm. IR (KBr): 2984, 2937, 2866, 2232, 1725, 1687, 1658, 1614 cm^{-1}. ^1H NMR (500 MHz, by a Varian Unityplus, $CDCl_3$): δ 8.55 (1H, s), 5.74 (1H, s), 3.63 (3H, s), 2.68 (1H, s), 2.49 (1H, d, J = 11.5 Hz), 2.12 (1H, m), 1.44, 1.34, 1.21, 1.15 (each 3H, s), 0.99 (3H, d, J = 6.4 Hz), 0.97 (3H, s), 0.89 (3H, d, J = 6.4 Hz). ^{13}C NMR (125.705 MHz, by a Varian Unityplus, $CDCl_3$): δ 197.9, 197.8, 177.2, 172.9, 165.6, 130.1, 115.1, 113.5, 54.2, 53.1, 52.1, 52.0, 47.8, 45.2, 45.1, 44.4, 39.9, 38.8, 36.0, 32.1, 30.4, 28.6, 27.8, 24.0, 21.7, 21.2, 21.1, 19.6, 19.4, 18.2, 17.3. EIMS (70 eV) *m*/*z*: 505 $[M]^+$ (62), 490 (15), 446 (19), 445 (19), 430 (23), 411 (47), 256 (37), 217 (37), 189 (69), 119 (100). HREIMS Calcd for $C_{32}H_{43}O_4N$: 505.3192. Found: 505.3200. Anal. (Table 1).

2-Cyano-3,11-dioxoursa-1,12-dien-28-oic Acid (34).[35] A mixture of **33** (155 mg, 0.31 mmol) and LiI (750 mg) in dry DMF (2.4 mL) was heated under reflux for 1.5 h. The reaction mixture was poured into water to give a solid. The solid was filtered and washed with water (several times). The crude solid (140 mg) was crystallized from a mixture of hexanes and EtOAc (2:1) to give **34** as crystals (90 mg, 60%). An analytically pure sample was obtained by crystallization from a mixture of CH_2Cl_2 and MeOH as crystals: mp >285 °C dec; $[\alpha]^{25}_D$ +119° (*c* 0.25, DMSO). UV (DMSO) λ_{max} (log ϵ): 264 (4.16) nm. IR (KBr): 3117, 3050, 2983, 2951, 2930, 2873, 2231, 1719, 1685, 1624 cm^{-1}. ^1H NMR [DMSO-d_6, internal standard: δ 2.50 (CD_2HSOCD_3)]: δ 8.49 (1H, s), 5.54 (1H, s), 2.95 (1H, s), 2.33 (1H, d, J = 11.2 Hz), 2.11 (1H, dd, J = 3.9, 13.2, 13.2 Hz), 1.35, 1.30, 1.13, 1.06 (each 3H, s), 0.942 (3H, d, J = 4.2 Hz), 0.935 (3H, s), 0.84 (3H, d, J = 6.4 Hz). EIMS (70 eV) *m*/*z*: 465 $[M - CN]^+$ (36), 446 $[M - CO_2H]^+$ (100), 420 (4.0), 405 (11), 315 (17), 244 (19). HREIMS Calcd for $C_{31}H_{41}O_4N - CN$: 465.3005. Found: 465.3010. Calcd for $C_{31}H_{41}O_4N - CO_2H$: 446.3059. Found: 446.3060. Anal. (Table 1).

Methyl 2-Aminocarbonyl-3,12-dioxooleana-1,9(11)-dien-28-oate (36). A solution of **27** (41.5 mg, 0.78 mmol) in saturated ammonia MeOH (4 mL) was kept at room temperature overnight. The mixture was evaporated in vacuo to give a residue (41 mg). The residue was subjected to flash column chromatography [hexanes−EtOAc (1:1.5)] to give **27** (18.5 mg) and **36** as an amorphous solid (19.6 mg; 49%, 88% based on recovered **27**): $[\alpha]^{24}_D$ +42° (*c* 0.36, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 242 (4.23) nm. IR (KBr): 3433, 3334, 2949, 2871, 1725, 1692, 1666 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.64 (1H, s), 8.35 (1H, d, J = 3.3 Hz), 6.22 (1H, s), 5.73 (1H, d, J = 3.3 Hz), 3.69 (3H, s), 3.05 (1H, ddd, J = 3.7, 4.5, 13.2 Hz), 2.92 (1H, d, J = 4.5 Hz), 1.41, 1.32 (each 3H, s), 1.20, 1.01 (each 6H, s), 0.90 (3H, s). ^{13}C NMR ($CDCl_3$): δ 204.4, 199.2, 178.5, 169.9, 165.3, 164.8, 127.8, 125.1, 52.1, 50.0, 47.8, 47.4, 46.2, 45.8, 42.2, 42.0, 35.9, 34.7, 33.4, 33.0, 31.73, 31.70, 30.8, 28.4, 28.2, 27.7, 24.7, 23.3, 22.9, 21.9, 21.8, 18.8. EIMS (70 eV) *m*/*z*: 523 $[M]^+$ (2.2), 508 (9.1), 506 (21), 446 (9.6), 315 (6.9), 84 (100). HREIMS Calcd for $C_{32}H_{45}O_5N$: 523.3298. Found: 523.3292. Anal. (Table 1).

Methyl 2-Formyl-3,12-dioxooleana-1,9(11)-dien-28-oate (37). **37** was prepared from **62** according to the same method as for **27** to give an amorphous solid (62%, 74% based on recovered **62**): $[\alpha]^{24}_D$ −3.7° (*c* 0.39, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ): 254 (4.05) nm. IR (KBr): 2944, 2867, 1722, 1704, 1668, 1611 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.02 (1H, s), 8.11 (1H, s), 6.14 (1H, s), 3.70 (3H, s), 3.05 (1H, ddd, J = 3.7, 4.5, 13.2 Hz), 2.93 (1H, d, J = 4.5 Hz), 1.44, 1.33, 1.23, 1.19 (each 3H, s), 1.00 (6H, s), 0.89 (3H, s). ^{13}C NMR ($CDCl_3$): δ 202.2, 199.3, 189.8, 178.4, 169.9, 161.4, 131.5, 124.7, 52.1, 49.9, 48.2, 47.4, 46.0, 45.4, 42.3, 42.1, 36.0, 34.7, 33.4, 33.0, 31.9, 31.7, 30.8, 28.2, 27.5, 27.2, 24.7, 23.3, 22.8, 21.8, 21.6, 18.7. EIMS (70 eV) *m*/*z*: 508 $[M]^+$ (37), 493 (35), 446 (44), 315 (28), 84 (100). HREIMS Calcd for $C_{32}H_{44}O_5$: 508.3189. Found: 508.3183. Anal. (Table 1).

Methyl 3β-Hydroxy-11-oxours-12-en-28-oate (47). A solution of methyl 3β-acetoxy-11-oxours-12-en-28-oate (**46**)[10] (150 mg, 0.29 mmol) and KOH (1.0 g) in MeOH (10 mL) was heated under reflux for 30 min. After removal of MeOH in vacuo, the resultant mixture was acidified with 6 M aqueous HCl solution. The aqueous layer 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 **47** as an amorphous solid (138 mg, quantitative): UV (EtOH) λ_{max} (log ϵ): 250 (4.17) nm. IR (KBr): 3494, 2928, 2869, 1728, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.59 (1H, s), 3.60 (3H, s), 3.21 (1H, dd, J = 5.9, 10.6 Hz), 2.78 (1H, ddd, J = 3.5, 3.5, 13.6 Hz), 2.41 (1H, d, J = 11.4 Hz), 2.29 (1H, s), 2.07 (1H, m), 1.29, 1.11, 0.99 (each 3H, s), 0.96 (3H, d, J = 6.2 Hz), 0.90 (3H, s), 0.86 (3H, d, J = 6.2 Hz), 0.79 (3H, s). ^{13}C NMR ($CDCl_3$): δ 200.1, 177.4, 163.0, 130.9, 78.9, 61.7, 55.2, 52.9, 52.0, 47.9, 44.8, 43.9, 39.34, 39.28, 38.82, 38.77, 37.3, 36.2, 33.2, 30.5, 28.6, 28.3, 27.5, 24.1, 21.3, 21.2, 19.0, 17.6, 17.3, 16.4, 15.8. EIMS (70 eV) m/z: 484 $[M]^+$ (40), 317 (100), 276 (48), 257 (34). HREIMS Calcd for $C_{31}H_{48}O_4$: 484.3553. Found: 484.3552. This material was used for the next reaction without further purification.

Methyl 3,11-Dioxours-12-en-28-oate (48). To a solution of **47** (144 mg, 0.30 mmol) in acetone (14 mL) in an ice bath was added Jones reagent dropwise until the color of the solution changed to pale brown from green. The mixture was stirred at room temperature for 10 min. After removal of acetone, water was added to the resultant mixture. 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 **48** as an amorphous solid (128 mg, 89%): UV (EtOH) λ_{max} (log ϵ): 252 (4.11) nm. IR (KBr): 2949, 2869, 1726, 1709, 1654 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.65 (1H, s), 3.63 (3H, s), 2.96 (1H, ddd, J = 4.2, 7.1, 13.4 Hz), 2.65 (1H, ddd, J = 7.1, 11.2, 15.9 Hz), 2.45 (1H, d, J = 11.5 Hz), 2.40 (1H, s), 2.37 (1H, ddd, J = 4.2, 6.5, 15.9 Hz), 2.10 (1H, ddd, J = 4.6, 14.7, 14.7 Hz), 1.31, 1.26, 1.10, 1.06 (each 3H, s), 0.98 (3H, d, J = 6.3 Hz), 0.95 (3H, s), 0.88 (3H, d, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 217.5, 199.3, 177.4, 163.6, 130.7, 60.9, 55.6, 52.9, 52.1, 47.9, 47.8, 44.7, 44.0, 39.9, 38.8, 36.9, 36.1, 34.4, 32.6, 30.5, 28.6, 26.6, 24.1, 21.6, 21.2, 21.1, 18.9, 17.3, 15.7. EIMS (70 eV) m/z: 482 $[M]^+$ (25), 467 (20), 423 (10), 317 (100), 276 (47), 257 (74). HREIMS Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3400. This material was used for the next reaction without further purification.

Methyl 3β-Hydroxy-12-oxooleanan-28-oate (50). 50 was prepared from methyl 3β-acetoxy-12-oxooleanan-28-oate (**49**)[12] according to the same method as for **47** to give a crystalline solid (quantitative): mp 133−135 °C. IR (KBr): 3540, 2945, 2866, 1725, 1698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.67 (3H, s), 3.18 (1H, dd, J = 5.0, 10.9 Hz), 2.77 (1H, ddd, J = 3.4, 4.2, 13.4 Hz), 2.60 (1H, d, J = 4.2 Hz), 2.14 (2H, m), 1.84 (2H, m), 0.98, 0.96, 0.95, 0.93, 0.89, 0.84, 0.77 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 212.0, 178.6, 78.8, 55.3, 52.0, 49.9, 47.5, 42.1, 41.4, 39.0, 38.7, 38.1, 37.1, 36.4, 34.6, 33.6, 33.1, 32.1, 32.0, 30.8, 28.1, 27.7, 27.2, 23.3, 22.9, 20.7, 18.5, 16.3, 15.5, 15.4. EIMS (70 eV) m/z: 486 $[M]^+$ (37), 471 (100), 411 (65), 278 (68), 218 (65). HREIMS Calcd for $C_{31}H_{50}O_4$: 486.3709. Found: 486.3701.

Methyl 3,12-Dioxooleanan-28-oate (51). 51 was prepared from **50** according to the same method as for **48** to give an amorphous solid (98%): IR (KBr): 2948, 2866, 1723, 1702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.69 (3H, s), 2.80 (1H, ddd, J = 3.7, 4.4, 13.7 Hz), 2.64 (1H, d, J = 4.4 Hz), 2.53 (1H, ddd, J = 7.2, 10.9, 15.9 Hz), 2.40 (1H, ddd, J = 3.8, 7.0, 15.9 Hz), 2.23 (2H, m), 1.09, 1.05, 1.01, 0.983, 0.976, 0.95, 0.90 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 217.1, 211.4, 178.6, 55.1, 52.0, 49.4, 47.6, 47.5, 42.2, 41.4, 38.8, 36.8, 36.4, 34.6, 34.1, 33.6, 33.1, 32.2, 31.3, 30.8, 27.8, 26.4, 23.3, 22.9, 21.4, 20.7, 19.7, 16.1, 15.0. EIMS (70 eV) m/z: 484 $[M]^+$ (4.2), 469 (39), 409 (100), 357 (6.7), 278 (25), 218 (72). HREIMS Calcd for $C_{31}H_{48}O_4$: 484.3553. Found: 484.3544.

Methyl 3β-Hydroxy-12-oxoolean-9(11)-en-28-oate (53). 53 was prepared from methyl 3β-acetoxy-12-oxoolean-9(11)-en-28-oate (**52**)[14] according to the same method as for **47** to give an amorphous solid (97%): UV (EtOH) λ_{max} (log ϵ): 250 (4.03) nm. IR (KBr): 3549, 3382, 2941, 2865, 1717, 1706, 1654, 1644, 1595 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.75 (1H, s), 3.68 (3H, s), 3.21 (1H, dd, J = 4.8, 11.4 Hz), 3.02 (1H, ddd, J = 3.5, 4.6, 13.4 Hz), 2.84 (1H, d, J = 4.6 Hz), 1.23, 1.18, 1.03 (each 3H, s), 0.99 (6H, s), 0.89, 0.83 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 200.8, 178.6, 178.5, 122.9, 78.2, 52.0, 50.4, 49.6, 47.5, 45.5, 41.9, 40.2, 39.4, 36.6, 36.0, 34.7, 33.5, 33.1, 33.0, 31.7, 30.8, 28.3, 27.7, 24.0, 23.9, 23.3, 22.9, 22.0, 18.2, 15.8. EIMS (70 eV) m/z: 484 $[M]^+$ (4.7), 469 (33), 409 (61), 407 (85), 315 (16), 278 (36), 218 (100). HREIMS Calcd for $C_{31}H_{48}O_4$: 484.3553. Found: 484.3553.

Methyl 3,12-Dioxoolean-9(11)-en-28-oate (54). 54 was prepared from **53** according to the same method as for **48** to give an amorphous solid (92%). An analytically pure sample was obtained by flash column chromatography [hexanes−EtOAc (3:1)]: UV (EtOH) λ_{max} (log ϵ): 250 (3.74) nm. IR (KBr): 2944, 2867, 1722, 1708, 1661, 1594 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.80 (1H, s), 3.70 (3H, s), 3.04 (1H, ddd, J = 3.3, 4.9, 13.2 Hz), 2.89 (1H, d, J = 4.9 Hz), 2.66 (1H, ddd, J = 7.2, 10.9, 15.7 Hz), 2.49 (1H, ddd, J = 3.8, 7.1, 15.7 Hz), 2.22 (1H, ddd, J = 3.9, 7.1, 13.4 Hz), 1.31, 1.28, 1.13, 1.09, 1.010, 1.005, 0.90 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 216.1, 200.3, 178.5, 176.8, 124.2, 52.0, 51.1, 49.7, 47.7, 47.5, 45.6, 42.0, 39.6, 37.2, 36.0, 34.7, 34.3, 33.5, 33.0, 32.2, 31.7, 30.8, 28.3, 26.4, 24.0, 23.8, 23.3, 22.9, 21.8, 21.6, 19.3. EIMS (70 eV) m/z: 482 $[M]^+$ (16), 467 (56), 423 (13), 407 (23), 315 (100), 255 (62), 246 (63). HREIMS Calcd for $C_{31}H_{46}O_4$: 482.3396. Found: 482.3392.

3β-Hydroxyolean-9(11)-en-28-oic Acid (57).[35] A mixture of **52** (2.27 g, 4.31 mmol), KOH (22 g), and anhydrous hydrazine (98%) (25 mL) in diethylene glycol (200 mL) was heated under reflux (inside temperature, 165 °C) for 1.5 h. Excess hydrazine was distilled off from the mixture until the inside temperature rose to 215 °C. Then, the mixture was heated under reflux (inside temperature, 215−220 °C) for 6 h. The mixture was poured into water (500 mL). Aqueous HCl solution (6 M) was added to give a precipitate. The precipitate (dry weight, 1.76 g) was filtered and washed with water (several times). The filtrate 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 (0.36 g). The combined solids were crystallized from a mixture of CH_2Cl_2 and MeOH (1:1) to afford **57** as colorless crystals (first crop, 670 mg; second crop, 180 mg). The solid obtained from the mother liquid was subjected to flash column chromatography [hexanes−EtOAc (2:1)] to give **57** as crystalline solid (200 mg, total weight: 1050 mg; 53%): mp >275 °C dec. IR (KBr): 3467, 3305, 2947, 2875, 1692 cm^{-1}. ^1H NMR [acetone-d_6, internal standard: δ 2.05 (CD_2HCOCD_3)]: δ 5.35 (1H, t, J = 3.7 Hz), 3.11 (1H, dd, J = 6.8, 9.0 Hz), 1.14, 1.11, 0.98, 0.94, 0.93, 0.89, 0.78 (each 3H, s). EIMS (70 eV) m/z: 456 $[M]^+$ (32), 446 (26), 441 (15), 302 (16), 248 (100). HREIMS Calcd for $C_{30}H_{48}O_3$: 456.3603. Found: 456.3603.

3-Oxoolean-9(11)-en-28-oic Acid (58). 58 was prepared from **57** according to the same method as for **48** to give an amorphous solid (95%): IR (KBr): 2947, 2870, 1708, 1694 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.38 (1H, t, J = 3.4 Hz), 2.63 (1H, ddd, J = 7.1, 11.5, 15.9 Hz), 2.42 (1H, ddd, J = 3.7, 6.8, 15.9 Hz), 1.25, 1.13, 1.09, 0.97, 0.94 (each 3H, s), 0.90 (6H, s). ^{13}C NMR ($CDCl_3$): δ 217.9, 185.2, 152.5, 118.7, 52.8, 48.1, 47.7, 43.8, 38.7, 38.6, 38.4, 36.2, 35.7, 34.9, 34.4, 33.7, 33.6, 33.2, 31.8, 30.8, 28.6, 27.3, 26.3, 25.5, 24.9, 23.6, 23.5, 21.5, 19.6, 18.7. EIMS (70 eV) m/z: 454 $[M]^+$ (32), 439 (13), 408 (26), 248 (65), 235 (100). HREIMS Calcd for $C_{30}H_{46}O_3$: 454.3447. Found: 454.3439.

Methyl 3-Oxooleana-1,11,13(18)-trien-28-oate (60). 60 was prepared from methyl 3-oxooleana-11,13(18)-dien-28-oate (**59**)[17] according to the same method as for **9**. The crude solid was subjected to flash column chromatography [hexanes−EtOAc (6:1)] to give **60** as a crystalline solid (66%): mp 131−133 °C. UV (EtOH) λ_{max} (log ϵ): 246 (4.54), 252 (4.54) nm. IR (KBr): 3029, 2944, 2859, 1726, 1674 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.27 (1H, d, J = 10.3 Hz), 6.57 (1H, dd, J = 2.9, 10.5 Hz), 5.89 (1H, d, J = 10.3 Hz), 5.79 (1H, dd, J = 1.7, 10.5 Hz), 3.68 (3H, s), 2.54 (1H, d, J = 14.4 Hz), 2.28 (2H, m), 1.91 (1H, m),

1.18, 1.17, 1.10, 0.98, 0.95, 0.86, 0.81 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 205.5, 177.1, 159.1, 136.2, 133.2, 126.7, 125.7, 125.0, 53.4, 52.0, 48.6, 48.4, 45.0, 42.4, 41.7, 40.8, 39.3, 37.0, 35.6, 32.8, 32.4, 32.0, 27.7, 25.2, 24.3, 21.32, 21.27, 20.0, 19.2, 16.7. EIMS (70 eV) *m/z*: 464 $[M]^+$ (84), 449 (13), 405 (100), 327 (14), 267 (19), 239 (29). HREIMS Calcd for $C_{31}H_{44}O_3$: 464.3290. Found: 464.3293.

Methyl 2-Hydroxymethylene-3,12-dioxoolean-9(11)-en-28-oate (62). To a solution of **54** (4.00 g, 8.29 mmol) in dry benzene (90 mL) was added ethyl formate (97%) (3.0 mL) and NaOMe (2.68 g, 50 mmol). The mixture was stirred at room temperature for 2 h. Then the mixture was diluted with a mixture of CH_2Cl_2 and Et_2O (1:2) and washed with 5% aqueous HCl solution (three times). The washings were reextracted with a mixture of CH_2Cl_2 and Et_2O (1:2) and the combined organic layers were worked up according to the standard method to give **62** as an amorphous solid (4.19 g, 99%): UV (EtOH) λ_{max} (log ϵ): 252 (3.66), 294 (3.53) nm. IR (KBr): 3461, 2950, 2867, 1724, 1661, 1596 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 14.86 (1H, d, J = 2.8 Hz), 8.77 (1H, d, J = 2.8 Hz), 5.90 (1H, s), 3.70 (3H, s), 3.05 (1H, ddd, J = 3.1, 4.5, 13.6 Hz), 2.92 (1H, d, J = 4.5 Hz), 2.62 (1H, d, J = 14.4 Hz), 2.30 (1H, d, J = 14.4 Hz), 1.28, 1.24, 1.18, 1.17, 1.02, 1.01, 0.91 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 200.3, 190.2, 188.3, 178.5, 175.8, 124.4, 105.1, 52.1, 49.7, 48.4, 47.5, 45.6, 42.0, 40.6, 39.3, 37.2, 36.0, 34.7, 33.5, 33.0, 31.7, 31.5, 30.8, 28.5, 28.4, 23.6, 23.3, 23.2, 22.9, 21.8, 21.0, 19.1. EIMS (70 eV) *m/z*: 510 $[M]^+$ (11), 495 (39), 435 (38), 315 (100), 255 (55). HREIMS Calcd for $C_{32}H_{46}O_5$: 510.3345. Found: 510.3351. This material was used for the next reaction without further purification.

Methyl 12-Oxoisoxazolo[4,5-*b*]olean-9(11)-en-28-oate (63). To a solution of **62** (4.00 g, 7.83 mmol) in EtOH (110 mL) and water (11 mL) was added hydroxylamine hydrochloride (5.44 g, 78 mmol). The mixture was heated under reflux for 1 h. The mixture was concentrated in vacuo and water (50 mL) was added. The mixture 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. The solid was subjected to flash column chromatography [hexanes−EtOAc (3:1)] to give **63** as an amorphous solid (2.63 g, 66%): UV (EtOH) λ_{max} (log ϵ): 238 (3.63) nm. IR (KBr): 2944, 2867, 1724, 1660, 1596 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.07 (1H, s), 5.89 (1H, s), 3.70 (3H, s), 3.05 (1H, ddd, J = 3.7, 4.6, 13.4 Hz), 2.93 (1H, d, J = 4.6 Hz), 2.79 (1H, d, J = 15.1 Hz), 2.40 (1H, d, J = 15.1 Hz), 1.35, 1.29, 1.27, 1.16, 1.03, 1.01, 0.90 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 200.2, 178.5, 176.3, 172.3, 150.4, 124.7, 108.7, 52.1, 49.9, 49.7, 47.5, 45.8, 42.0, 41.5, 36.1, 35.4, 34.7, 33.8, 33.5, 33.0, 31.7, 31.5, 30.9, 29.0, 28.4, 24.8, 23.29, 23.25, 22.9, 21.8, 21.6, 18.5. EIMS (70 eV) *m/z*: 507 $[M]^+$ (14), 492 (51), 446 (25), 432 (49), 315 (100). HREIMS Calcd for $C_{32}H_{45}O_4N$: 507.3349. Found: 507.3354.

Methyl 2-Cyano-3,12-dioxoolean-9(11)-en-28-oate (64). To a solution of **63** (2.00 g, 3.94 mmol) in MeOH (60 mL) and Et_2O (125 mL) in an ice bath was added NaOMe (7.25 g, 134 mmol). The mixture was stirred at room temperature for 45 min and then diluted with a mixture of CH_2Cl_2 and Et_2O (1:2). It was washed with 5% aqueous HCl solution (three times) and the acidic washings were reextracted with a mixture of CH_2Cl_2 and Et_2O (1:2). The combined organic layers were worked up according to the standard method to give **64** as an amorphous solid (2.00 g, quantitative): UV (EtOH) λ_{max} (log ϵ): 242 (4.16) nm. IR (KBr): 3411, 2944, 2867, 2206, 1722, 1661, 1636, 1597 cm^{-1}. ^{1}H NMR of major tautomer **64a** ($CDCl_3$): δ 7.08 (1H, brs), 5.75 (1H, s), 3.67 (3H, s), 3.01 (1H, ddd, J = 3.7, 4.6, 13.7 Hz), 2.89 (1H, d, J = 4.6 Hz), 2.40 (1H, d, J = 15.3 Hz), 2.23 (1H, d, J = 15.3 Hz), 1.24, 1.21, 1.19, 1.11 (each 3H, s), 0.98 (6H, s), 0.88 (3H, s). EIMS (70 eV) *m/z*: 507 $[M]^+$ (84), 492 (99), 432 (58), 315 (100). HREIMS Calcd for $C_{32}H_{45}O_4N$: 507.3349. Found: 507.3340. This material was used for the next reaction without further purification.

Methyl 2-Hydroxymethylene-3,11-dioxoolean-12-en-28-oate (65). 65 was prepared from **45** according to the same method as for **62** to give a crystalline solid (98%): mp 232−234 °C. UV (EtOH) λ_{max} (log ϵ): 254 (4.15), 296 (3.91) nm. IR (KBr): 3456, 2944, 2867, 1728, 1656, 1589 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 14.87 (1H, d, J = 2.7 Hz), 8.62 (1H, d, J = 2.7 Hz), 5.69 (1H, s), 3.64 (3H, s), 3.49 (1H, d, J = 14.8 Hz), 3.03 (1H, dd, J = 3.6, 13.9 Hz), 2.40 (1H, s), 2.05 (1H, ddd, J = 4.1, 13.7, 13.7 Hz), 1.93 (1H, d, J = 14.8 Hz), 1.36, 1.18, 1.12, 1.08, 0.95, 0.94, 0.93 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 199.9, 189.6, 189.2, 177.6, 169.6, 128.0, 106.0, 59.8, 52.4, 52.1, 46.4, 44.8, 44.5, 43.8, 41.8, 40.2, 39.9, 36.5, 33.8, 33.0, 32.0, 31.7, 30.9, 28.6, 28.0, 23.64, 23.59, 23.1, 21.1, 18.8, 18.7, 14.8. EIMS (70 eV) *m/z*: 510 $[M]^+$ (14), 495 (21), 451 (22), 446 (42), 435 (22), 317 (31), 257 (100). HREIMS Calcd for $C_{32}H_{46}O_5$: 510.3345. Found: 510.3348.

Methyl 11-Oxoisoxazolo[4,5-*b*]olean-12-en-28-oate (66). 66 was prepared from **65** according to the same method as for **63** to give an amorphous solid (74%): UV (EtOH) λ_{max} (log ϵ): 250 (4.10) nm. IR (KBr): 2944, 2867, 1728, 1657, 1624 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.99 (1H, s), 5.71 (1H, s), 3.67 (1H, d, J = 15.5 Hz), 3.64 (3H, s), 3.04 (1H, dd, J = 3.8, 13.6 Hz), 2.51 (1H, s), 2.06 (1H, ddd, J = 4.2, 13.9, 13.9 Hz), 2.03 (1H, d, J = 15.5 Hz), 1.37, 1.31, 1.22, 1.06, 0.96, 0.94, 0.93 (each 3H, s). ^{13}C NMR ($CDCl_3$): δ 199.8, 177.6, 172.4, 169.6, 150.5, 128.1, 109.2, 60.3, 53.5, 52.1, 46.4, 45.1, 44.5, 43.8, 41.8, 38.7, 36.2, 34.9, 33.9, 33.1, 32.1, 31.7, 30.9, 29.1, 28.1, 23.7, 23.6, 23.1, 21.7, 18.7, 18.2, 15.8. EIMS (70 eV) *m/z*: 507 $[M]^+$ (31), 492 (30), 448 (20), 432 (28), 257 (72), 217 (100). HREIMS Calcd for $C_{32}H_{45}O_4N$: 507.3349. Found: 507.3345.

Methyl 2-Cyano-3,11-dioxoolean-12-en-28-oate (67). 67 was prepared from **66** by the similar method as for **64**. The crude solid was subjected to flash column chromatography [hexanes−EtOAc (2:1)] to give **67** as an amorphous solid (92%): UV (EtOH) λ_{max} (log ϵ): 246 (4.18) nm. IR (KBr): 3411, 2944, 2867, 2200, 1725, 1656 cm^{-1}. ^{1}H NMR of major tautomer **67a** ($CDCl_3$): δ 6.40 (1H, brs), 5.67 (1H, s), 3.62 (3H, s), 3.33 (1H, d, J = 15.9 Hz), 3.02 (1H, dd, J = 3.7, 13.7 Hz), 2.53 (1H, s), 2.36 (1H, d, J = 15.9 Hz), 1.33, 1.15, 1.11, 1.08 (each 3H, s), 0.92 (6H, s), 0.87 (3H, s). EIMS (70 eV) *m/z*: 507 $[M]^+$ (3.7), 492 (5.2), 447 (5.8), 432 (8.4), 276 (7.0), 257 (21), 217 (31), 84 (100). HREIMS Calcd for $C_{32}H_{45}O_4N$: 507.3349. Found: 507.3349.

Methyl 2-Hydroxymethylene-3,11-dioxours-12-en-28-oate (68). 68 was prepared from **48** according to the same method as for **62** to give an amorphous solid (89%): UV (EtOH) λ_{max} (log ϵ): 254 (4.06), 298 (3.84) nm. IR (KBr): 3454, 2978, 2931, 2866, 1728, 1659, 1619, 1590 cm^{-1}. ^{1}H NMR (500 MHz, by a Varian Unityplus, $CDCl_3$): δ 14.87 (1H, d, J = 3.2 Hz), 8.63 (1H, d, J = 3.2 Hz), 5.67 (1H, s), 3.63 (3H, s), 3.46 (1H, d, J = 14.9 Hz), 2.46 (1H, d, J = 11.2 Hz), 2.40 (1H, s), 2.10 (1H, m), 1.98 (1H, d, J = 14.9 Hz), 1.31, 1.20, 1.13, 1.12 (each 3H, s), 0.98 (1H, d, J = 6.3 Hz), 0.96 (3H, s), 0.88 (3H, d, J = 6.6 Hz). ^{13}C NMR (125.705 MHz, by a Varian Unityplus, $CDCl_3$): δ 199.4, 189.7, 189.2, 177.4, 163.7, 130.9, 106.0, 59.5, 53.0, 52.4, 52.1, 47.9, 44.4, 44.0, 40.2, 40.0, 38.9, 38.8, 36.5, 36.1, 32.2, 30.5, 28.7, 28.6, 24.1, 21.2, 21.1, 18.9, 18.7, 17.3, 14.9. EIMS (70 eV) *m/z*: 510 $[M]^+$ (15), 495 (48), 435 (42), 315 (100), 274 (22), 255 (57). HREIMS Calcd for $C_{32}H_{46}O_5$: 510.3345. Found: 510.3347.

Methyl 11-Oxoisoxazolo[4,5-*b*]urs-12-en-28-oate (69). 69 was prepared from **68** according to the same method as for **63** to give an amorphous solid (81%): UV (EtOH) λ_{max} (log ϵ): 248 (4.09) nm. IR (KBr): 2973, 2937, 2866, 1727, 1658, 1619 cm^{-1}. ^{1}H NMR (500 MHz, by a Varian Unityplus, $CDCl_3$): δ 7.99 (1H, s), 5.68 (1H, s), 3.64 (1H, d, J = 15.6 Hz), 3.63 (3H, s), 2.50 (1H, s), 2.46 (1H, d, J = 11.5 Hz), 2.11 (1H, m), 2.07 (1H, d, J = 15.6 Hz), 1.33, 1.31, 1.23, 1.09 (each 3H, s), 0.98 (3H, d, J = 6.6 Hz), 0.97 (3H, s), 0.89 (3H, d, J = 6.6 Hz). ^{13}C NMR (125.705 MHz, by a Varian Unityplus, $CDCl_3$): δ 199.2, 177.3, 172.4, 163.7, 150.5, 130.8, 109.2, 60.0, 53.5, 52.9, 52.1, 47.8, 44.7, 44.0, 38.9, 38.8, 38.6, 36.2, 36.1, 34.9, 32.3, 30.5, 29.1, 28.7, 24.1, 21.7, 21.2, 21.1, 18.7, 18.2, 17.3, 15.8. EIMS (70 eV) *m/z*: 507 $[M]^+$ (9.3), 492 (13), 317 (13), 257 (24), 217 (12), 84 (100). HREIMS Calcd for $C_{32}H_{45}O_4N$: 507.3349. Found: 507.3351.

Methyl 2-Cyano-3,11-dioxours-12-en-28-oate (70). 70 was prepared from **69** by the similar method as for **64**. The crude solid was subjected to flash column chromatography [hexanes−EtOAc (2:1)] to give **70** as a crystalline solid (94%): mp 169−171 °C. UV (EtOH) λ_{max} (log ϵ): 246 (4.17) nm. IR (KBr): 3401, 2978, 2937, 2866, 2202, 1725, 1668 cm^{-1}. ^1H NMR of major tautomer **70a** (500 MHz, by a Varian Unityplus, $CDCl_3$): δ 5.86 (1H, brs), 5.66 (1H, s), 3.62 (3H, s), 3.33 (1H, d, J = 15.7 Hz), 2.45 (1H, d, J = 10.3 Hz), 2.33 (1H, s), 2.10 (1H, m), 1.92 (1H, d, J = 15.7 Hz), 1.29, 1.17, 1.15, 1.09 (each 3H, s), 0.97 (3H, d, J = 6.4 Hz), 0.93 (3H, s), 0.87 (3H, d, J = 6.6 Hz). EIMS (70 eV) m/z: 507 $[M]^+$ (25), 492 (31), 467 (45), 446 (54), 317 (34), 276 (26), 257 (85), 217 (100). HREIMS Calcd for $C_{32}H_{45}O_4N$: 507.3349. Found: 507.3351.

Methyl 3-Hydroxy-2-methoxycarbonyl-12-oxooleana-2,9(11)-dien-28-oate (71). A mixture of **54** (258 mg, 0.53 mmol) and 1.8 M DMF solution of methoxymagnesium methyl carbonate (Stiles' reagent) (2.5 mL, 4.5 mmol) was heated at 110 °C for 1 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 (305 mg). To a solution of the solid in THF (6 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 (310 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (4:1)] to give **71** as crystals (225 mg, 78%): mp 210−211 °C. UV (EtOH) λ_{max} (log ϵ): 252 (4.20) nm. IR (KBr): 2944, 2867, 1725, 1661, 1618 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.49 (1H, s), 5.94 (1H, s), 3.76, 3.69 (each 3H, s), 3.04 (1H, ddd, J = 3.1, 4.9, 13.2 Hz), 2.90 (1H, d, J = 4.9 Hz), 2.70 (1H, d, J = 15.3 Hz), 2.06 (1H, d, J = 15.3 Hz), 1.26, 1.20, 1.17, 1.14 (each 3H, s), 1.00 (6H, s), 0.89 (3H, s). ^{13}C NMR ($CDCl_3$): δ 200.5, 178.5, 176.9, 176.7, 173.9, 124.5, 94.1, 52.0, 51.8, 49.7, 48.6, 47.5, 45.6, 42.0, 39.3, 38.6, 36.3, 36.1, 34.7, 33.5, 33.1, 31.7, 31.5, 30.8, 28.6, 28.4, 24.3, 23.3, 23.2, 22.9, 21.8, 20.4, 19.1. EIMS (70 eV) m/z: 540 $[M]^+$ (3.9), 525 (5.7), 508 (23), 493 (54), 433 (35), 315 (100). HREIMS Calcd for $C_{33}H_{48}O_6$: 540.3451. Found: 540.3454.

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.[4b] 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.[4a] 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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