Practical Partial Synthesis of Myriceric Acid A, an Endothelin Receptor Antagonist, from Oleanolic Acid

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Myriceric acid A (**1**) is an oleanane triterpene that is a potent and specific endothelin A receptor antagonist. A practical procedure for large-scale synthesis of myriceric acid A (**1**) has been developed starting from oleanolic acid **4**. The conversion of oleanolic acid **4** to the key intermediate myricerone **3** was achieved in an efficient manner employing a photochemical reaction (the Barton reaction) of nitrite **7**. Our synthetic procedure alleviated several difficulties of the original Barton's procedure with regard to yields and large-scale operation. Myricerone **3** afforded Horner−Wadsworth−Emmons (HWE) type phosphonate **2** which has proved to be a versatile precursor of **1**. The preparation of phosphonate **2** on a scale of several hundred grams is described. The synthesis was completed by condensation of **2** with 3,4-bis[(diphenylmethyl)oxy]benzaldehyde (**21**), giving α,*β*-unsaturated ester **22**, which was deprotected to afford **1**. The whole synthetic sequence is efficient (14 steps, 31% yield) and requires no chromatographic purification except to obtain the final product **1**.

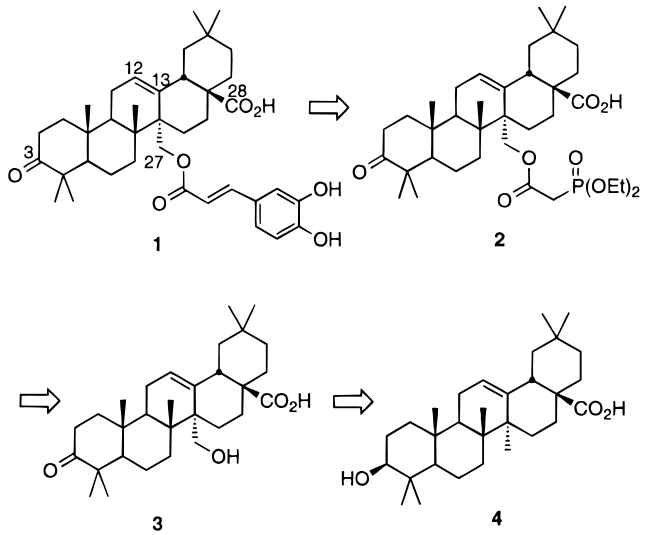
Introduction

Myriceric acid A (27-(caffeoyloxy)-3-oxoolean-12-en-28-oic acid) (**1**)[1] is a potent and specific endothelin A receptor antagonist[2] that was found by screening of the Shionogi natural product library and was isolated from a crude extract of twigs of the southern bayberry, *Myrica cerifera*. It is an oleanane triterpene that characteristically bears 3-oxo- and 27-caffeoyloxy-groups. It showed a promising hypotensive effect for therapeutic use in animal tests.[3] However, it was difficult to provide a sufficient amount of **1** for further pharmacological evaluation and study of structure−activity relationships of its derivatives, because of the scarcity of the plant in Japan and the low content of **1** in the plant (0.01%). To overcome this obstacle, we have developed a highly efficient and practical synthesis of **1** from naturally abundant oleanolic acid **4**. We herein report the details of this study.

Results and Discussion

The retrosynthetic analysis of **1** is illustrated in Scheme 1. We planned to prepare **1** via two key intermediates **2** and **3**. Our previous paper[1] described alkaline hydrolysis of the 27-caffeoyloxy group of **1** to give myricerone (**3**) and its subsequent acylation to 27-*O*-acylmyricerone. We prepared either the acetate or cinnamate of **3** in a moderate yield by acylation of **3** with acid chlorides or anhydrides, and 27-*O*-cinnamoylmyricerone was shown to be as potent as **1** among the synthetic 27-*O*-acyl derivatives. However, acylation of **3** was generally inefficient for several reasons. More than 3 equiv of acylating reagent was necessary to complete the 27-*O*-acylation owing to a concurrent formation of a mixed anhydride between the 28-carboxy group and an acylating reagent. Consequently, this required a mild alkaline workup to hydrolyze the mixed anhydride and chromatographic separation of the 27-*O*-acyloxy product from the excess acylating reagent. Moreover, we failed to prepare **1** by acylating **3** with 3,4-di-*O*-acetylcaffeic acid. In order to synthesize **1**, we developed a new synthetic procedure which employs a Horner−Wadsworth−Emmons (HWE) olefination[4] of crystalline 27-*O*-[(diethylphosphono)acetyl]myricerone (**2**) with a dihydroxybenzaldehyde derivative. HWE condensation of phosphonate **2** occurred with a variety of aldehydes to give α,*β*-unsaturated esters in good yields.

Scheme 1



As myricerone **3** was an apparent intermediate to **1**, we next focused on the synthesis of **3** from a readily available compound. Oleanolic acid (**4**)[5] has a very close

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

(1) Sakurawi, K.; Yasuda, F.; Tozyo, T.; Nakamura, M.; Sato, T.; Kikuchi, J.; Terui, Y.; Ikenishi, Y.; Iwata, T.; Takahashi, K.; Konoike, T.; Mihara, S.; Fujimoto, M. *Chem. Pharm. Bull.* **1996**, *44*, 343.

(2) For endothelins and their receptor antagonists, see Cheng, X.-M.; Nikam, S. S.; Doherty, A. M. *Curr. Med. Chem.* **1994**, *1*, 271. Doherty, A. M. *Drug Discovery Today* **1996**, *1*, 60. Ohlstein, E. H.; Elliott, J. D.; Feuerstein, G. Z.; Ruffolo, R. R. *Med. Res. Rev.* **1996**, *16*, 365.

(3) Fujimoto, M.; Mihara, S.; Nakajima, S.; Ueda, M.; Nakamura, M.; Sakurai, K. *FEBS Lett.* **1992**, *305*, 41. Mihara, S.; Fujimoto, M. *Eur. J. Pharmacol.* **1993**, *246*, 33. Mihara, S.; Sakurai, K.; Nakamura, M.; Konoike, T.; Fujimoto, M. *Eur. J. Pharmacol.* **1993**, *247*, 219.

(4) For a review, see Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(5) For a review of recent work on oleanane and related triterpenes, see Connolly, J. D.; Hill, R. A.; Ngadjui, B. T. *Nat. Prod. Rep.* **1994**, *11*, 467. For 27-caffeoyloxy oleananes, see Jiang, Z.-H.; Tanaka, T.; Kouno, I. *Tetrahedron Lett.* **1994**, *35*, 2031, Jiang, Z.-H.; Tanaka, T.; Kouno, I. *Chem. Pharm. Bull.* **1996**, *44*, 1669.

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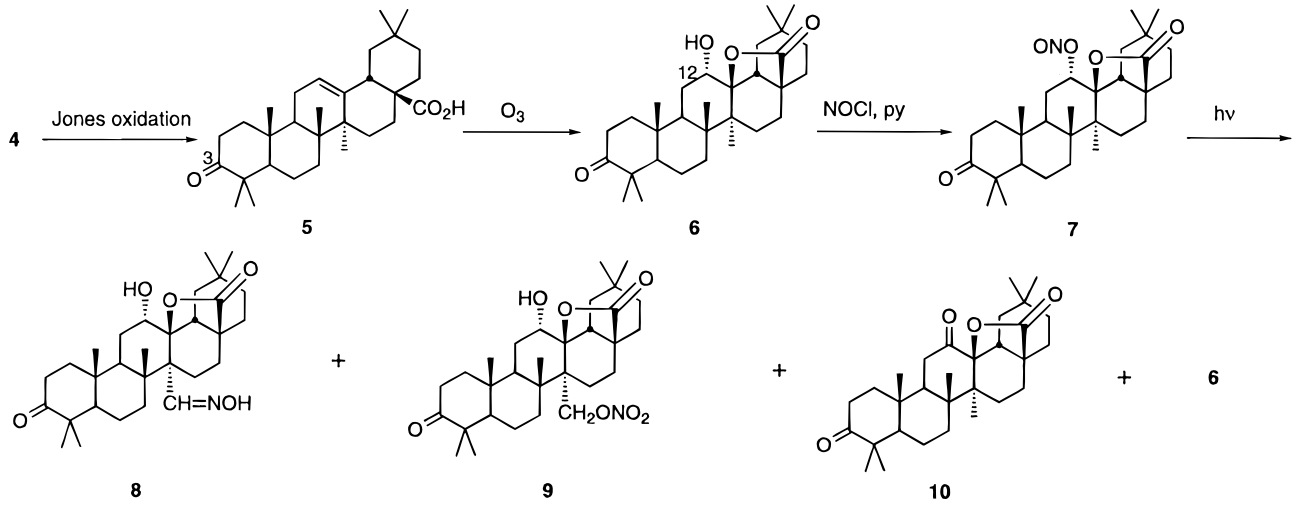
Scheme 2



structure to **3**, and all that is required to convert **4** to **3** is oxidation of the 3-hydroxy to the 3-oxo group and hydroxylation of the methyl group at the 27-position. Barton and co-workers[6] reported a synthesis of cincholic acid (3β-hydroxyolean-12-ene-27,28-dioic acid) three decades ago, which started from oleanolic acid (**4**) and introduced a hydroxy group at the 27-position by a photochemical reaction known as the Barton reaction.[7] Their method is in principle applicable to the synthesis of **3**, but it had some disadvantages including a number of low-yielding steps as well as the need for extensive chromatographic purification of the intermediates. Consequently, the overall yield of the final cincholic acid was much less than 1%. Thus, we modified the entire sequence of reactions and established a practical method suitable for large-scale synthesis of **1** without the need of chromatographic purification of the intermediates except for the final product **1**.

Our synthesis of **1** is shown in Schemes 2−4. Jones oxidation of oleanolic acid (**4**) gave oleanonic acid (**5**)[8] that has the same oxidation level at the 3-position as myricerone. The second oxidation, 27-hydroxylation, required a multistep conversion and began with introduction of the 12α-hydroxy group, a scaffold for the Barton reaction. Ozone was introduced to a solution of crude **5** to give 12α-hydroxy lactone **6**[9] as a major product with a small amount (6−7%) of 12-oxolactone **10**,[10] which can be removed by crystallization of **6**. Ozone oxidation[11] for generating 12α-hydroxy lactone **6** was more satisfactory than m-CPBA oxidation[6,12] that needs a large excess of m-CPBA, a longer reaction time, and chromatographic purification of **6**. This two-step oxidation of **4** to **6** also worked well for crude material **4** contaminated with isomeric ursolic acid (ca 2%), and **6** was obtained easily in a pure form by crystallization. Hydroxy lactone **6** was converted to nitrite **7** by treatment with nitrosyl chloride in pyridine, and the unstable nitrite **7** was isolated by conducting the workup and crystallization in a presence of pyridine.[13]

Table 1. Product Ratio of the Photochemical Reaction

solvent	concentration (mM)	pyridine (equiv to **7**)	product ratio (%)[a] **8**	**9**	**10**	**6**	others
acetone	67	0.2	69	1	2	22	5
toluene	67	0.2	53	1	4	18	24
CH_2Cl_2	67	0.2	59	0	1	25	11
THF	67	0.2	24	1	19	15	41
acetone	33	0.2	78	1	1	14	6
acetone	16	0.2	82	1	1	12	5
acetone	33	0	81	1	2	13	4
acetone	33	0.05	80	1	6	12	2
acetone	33	0.1	78	1	4	13	3
acetone	33	0.5	64	1	9	17	10
acetone	33	0.2 of NEt_3	72	2	10	10	7
acetone[b]	33	0.2	0	61	2	15	22

[a] Total peak area of the products is 100%. The ratio was calculated based on the UV absorbency (ϵ) at 197 nm of each product. [b] Reaction was carried out under an oxygen atmosphere.

Irradiation of nitrite **7** lead to several byproducts along with the desired oxime **8**.[14] They were identified as the parent hydroxy lactone **6**, its oxidized ketone **10**, and nitrate **9**.[15] We surveyed the conditions for the Barton reaction of **7** using a variety of solvents, temperature, concentration, additives, and wavelength, and the results are summarized in Table 1. The yields of the products were determined by HPLC after thermally decomposing the nitrosodimer to monomeric oxime **8**. The mechanism of the Barton reaction has been investigated extensively,[14,16,17] and most of our findings are in accord with the previous observations. However, we did not detect nitrimine **11**[6] or cyclic ether **12**[14] which are often observed as byproducts in the Barton reaction. Some significant observations of the photoreaction are as follows: acetone is the solvent of choice in terms of the yield of **8**. Starting material concentration is important, with the yield of **8**

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(11) Boar, R. B.; Knight, D. C.; McGhie, J. F.; Barton, D. H. R. *J. Chem. Soc. (C)* **1970**, 678. Boar, R. B.; Joukhadar, L.; Luque, M.; McGhie, J. F.; Barton, D. H. R.; Arigoni, D.; Brunner, H. G.; Giger, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2104.
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(14) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Smith, L. C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1159.
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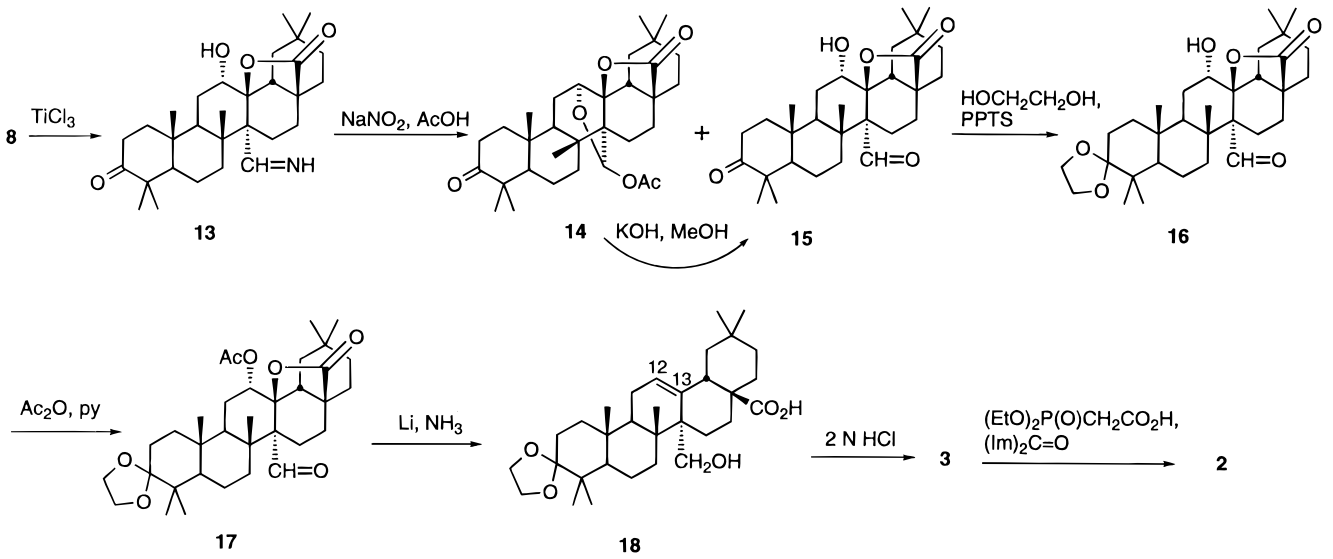
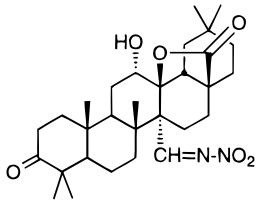
(16) Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* **1977**, *99*, 4518.
(17) Burke, S. D.; Silks, L. A.; Strickland, S. M. S. *Tetrahedron Lett.* **1988**, *29*, 2761.

Scheme 3



rising as the concentration decreased, and we chose the concentration of 67 mM as a compromise between the yield and operational practicality. Exclusion of oxygen is essential for preventing formation of nitrate **9**, with either an argon or nitrogen providing the best result. When the photoreaction was carried out in an oxygen atmosphere, nitrate **9** was obtained[15] in 61% yield instead of oxime **8**. An additive such as pyridine[13] was not essential for the Barton reaction itself; however, it prevented decomposition of **7** throughout the recrystallization and photoreaction. Addition of pyridine (0.05−0.2 equiv to **7**) was beneficial when the photoreaction period exceeded 1 h. Irradiation at 329−379 nm was most effective. The reaction temperature had no significant influence in the range of 0−30 °C, but **7** precipitated below 0 °C. On the basis of these results, we ran the photochemical reaction under the conditions where **7** was consumed in less than 1 h, and oxime **8** was obtained as a white crystalline powder in 69−85% yield (94−98% purity by HPLC) from **6** in a 20 g scale preparation.



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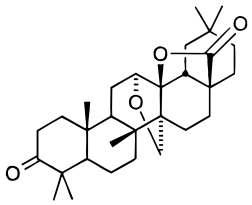

12

We tried another type of remote oxidation, the hypoiodite reaction,[18] often referred to as the Heusler reaction. Under typical conditions, **6** was treated with $Pb(OAc)_4$, I_2, and $CaCO_3$ under irradiation from a tungsten lamp at room temperature, and cyclic ether **12** was obtained in 70% yield. Unfortunately, the photoreaction was not amenable to large-scale. However, we discovered the reaction could be performed at room temperature with sonication, and ether **12** was obtained in 60% yield. Moreover, when the reaction was carried in toluene at reflux without irradiation, we found that there was a competing oxidation at the 2-position and the main product **12** was contaminated with a significant amount of 2-acetoxylated **6** and **12**. The resulting cyclic ether **12** was resistant to ring-opening reaction under a variety of conditions, and we did not pursue further conversion of **12**.

Barton *et al.* reported that a conversion of oxime **8** to aldehyde **15** was very difficult due to the extreme steric hindrance around the 27-position.[6] They proposed several methods for generating hydroxy aldehyde **15**, which were not practical for synthetic purposes. This led us to a new method of generating an aldehyde that utilizes an efficient three-step procedure via imine **13** (Scheme 3). Oxime **8** was reduced to imine **13** in the first step by treatment with $TiCl_3$,[19] and imine **13** was subsequently hydrolyzed to aldehyde in a two-step sequence. Upon treatment with $NaNO_2$ in aqueous dioxane−acetic acid, a 2:1 mixture of hydroxy aldehyde **15** and hemiacetal acetate **14** was obtained. Alkaline hydrolysis of the mixture provide aldehyde **15** as a sole product in 77% yield from oxime **8**. Imine **13** was stable under usual hydrolysis conditions, but underwent sodium cyanoborohydride reduction in acetic acid to give the 27-amino compound. A similar amine was reported to be generated from a nitrimine by catalytic hydrogenation or zinc−acetic acid reduction;[6] however, when we tried catalytic hydrogenation of nitrimine **11** prepared from oxime **8**, we obtained imine **13** quantitatively instead of the 27-amino compound.

The completion of the synthesis of myricerone **3** from **15** was accomplished as described in Scheme 3. The 3-oxo group of hydroxy aldehyde **15** was first protected as an ethylene ketal **16**, and then the 12-hydroxy group was acetylated to give acetoxy ketal **17** (96% from **15**). Reductive elimination of the acetoxy lactone moiety of **17** occurred efficiently under the lithium−liquid ammonia reduction to give quantitatively myricerone ethylene ketal **18**. Concomitant reduction of 27-aldehyde to an alcohol was convenient for synthesis of myricerone **3**. The ethylene ketal of **18** was deprotected by aqueous HCl, and myricerone **3** was obtained as a crystalline powder in 99% yield from **17**. Myricerone **3** thus obtained was sufficiently pure for practical synthesis, although it

(18) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525. Heusler, K.; Kalvoda, J. In *Organic Reaction in Steroid Chemistry;* Fried, J., Edward, J. A., Eds.; Van Noustrand Reinhold: New York, 1972; Vol. 2, chapter 12.

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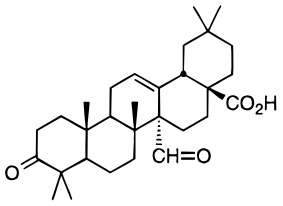
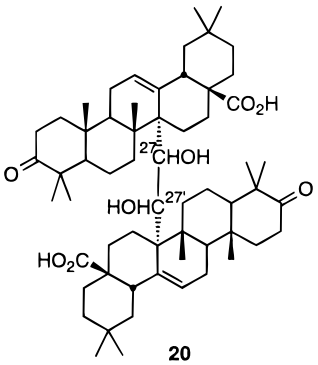
contained a small amount of incompletely reduced byproduct **19** (2%), which could be removed from **3** by recrystallization. Myricerone **3** prepared as above was identical with an authentic sample prepared by alkaline hydrolysis of natural **1**.[1]

Barton et al.[6] showed the regeneration of the 12,13 double bond of oleanolic acid derivatives was severely limited and low yielding. In contrast, the regeneration of the double bond from **17** was very facile, and we assumed that a substituent at the 27-position affected the efficiency of the olefin regeneration. In order to examine the substituent effect of the 27-position, we carried out the olefin regeneration using several related substrates bearing several 27- and 3-substituents. Our results as well as Barton's demonstrate that the reaction is sensitive to the substituent at the 27-position rather than the 3-position (Table 2). Efficient conversion of the substrates having the 27-aldehyde group was noteworthy. Our conjecture on the mechanism is as follows. The reductive elimination initially involves an electron transfer from lithium to the aldehyde group which is more electron-deficient than other groups. The resulting radical anion of the aldehyde effectively transfers an electron to the nearby 12α-acetoxy group, accelerating the reductive elimination of the acetoxy group and the lactone. The electron transfer mechanism is verified experimentally. Olefin aldehyde **19** was generally obtained as a byproduct after deketalization, and this implied that **19** was a primary product of the reduction. As an additional evidence, when the lithium−liquid ammonia reduction was done in a more concentrated solution, we obtained dimeric diol **20** together with myricerone (**3**) and aldehyde **19** after deketalization. The generation of diol **20** demonstrated the dimerization of a radical anion of the ethylene ketal of **19**. All these results suggest that the electron transfer to the aldehyde is a favorable process, and it facilitates the electron transfer to acetoxy group and the subsequent olefin regeneration.



19



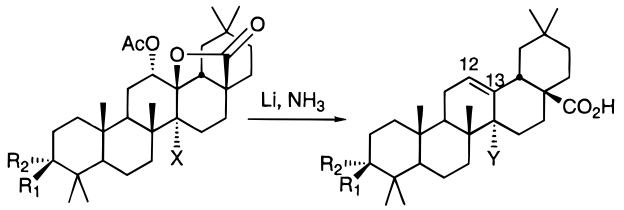
20

Acylation of myricerone **3** by 3,4-di-*O*-acetylcaffeoyl chloride only gave 27-*O*-acetylmyricerone and none of a caffeoyl derivative. We therefore devised an alternative HWE olefination employing phosphonate **2** for the preparation of myriceric acid A (**1**). Myricerone **3** was condensed with commercially available diethoxyphosphonoacetic acid by carbonyldiimidazole to give crystalline phosphonate **2**. The synthetic sequence from **4** was very efficient and phosphonate **2** could be prepared on a scale of several hundred grams (12 steps, 39% yield) without chromatographic purification of the intermediates.

To complete the partial synthesis of myriceric acid A (**1**), we attempted to condense **2** with 3,4-dihydroxybenzaldehyde under several basic conditions; however, myriceric acid A (**1**) was not obtained, and only starting materials were recovered. This was presumably because ionization of the phenolic OH group deactivated the aldehyde for HWE olefination. To prevent the inactivation we employed the diphenymethyl group as a protecting group of phenol,[20] and 3,4-bis[(diphenylmethyl)oxy]-benzaldehyde (**21**) was prepared by alkylating 3,4-dihydroxybenzaldehyde with bromodiphenylmethane (Scheme 4). Condensation[21] of **2** with **21** proceeded to give **22** quantitatively. Deprotection of the diphenymethyl group by trifluoroacetic acid−anisole gave myriceric acid A (**1**) which was identical to an authentic sample isolated from *M. cerifera*. The whole series of conversions gave high yields and **1** was obtained from oleanolic acid (**4**) in 14 steps in 31% yield.

Intermediate **2** is a more versatile intermediate than myricerone **3** for modification studies of **1** because it can be condensed with a variety of aldehydes to give α,β-unsaturated acyloxy derivatives in a single step. These derivatives enabled us to study their structure−activity relationships. From these studies, more potent and water-soluble derivatives were found. We have prepared several kilograms of **2** and a drug candidate[22] for further pharmacological evaluation.

Table 2. Effect of Substituents on 12,13-Olefin Regeneration



R_1, R_2	X	R_1, R_2	Y	yield (%)
ethylene ketal	-CH=O	ethylene ketal	$-CH_2OH$	90
ethylene ketal	$-CH_2ONO_2$	ethylene ketal	$-CH_2OH$	60
R_1=AcO- R_2=H-	-CH=O	R_1=HO- R_2=H-	$-CH_2OH$	97
	-CH=NOAc		$-CH_2NH_2$	48
	$-CH_2NHBoc$		$-CH_2NHBoc$	30
	$-CO_2Me$[a]		$-CO_2Me$	22
	-Me[a]		-Me	17-20
	-CN[a]		-CN	<3

[a]Ref 6.

Experimental Section

General. Reactions were carried out under a nitrogen atmosphere in anhydrous solvents (dried over molecular sieves type 4A). Organic extracts were dried over anhydrous $MgSO_4$. Solvent removal was accomplished under aspirator pressure using a rotary evaporator. TLC was performed with Merck precoated TLC plates silica gel 60 F_{254}, and compound visualization was effected with 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. Gravity chromatography was done with Merck silica gel 60 (70−230 mesh). HPLC analysis was performed under the conditions; column,

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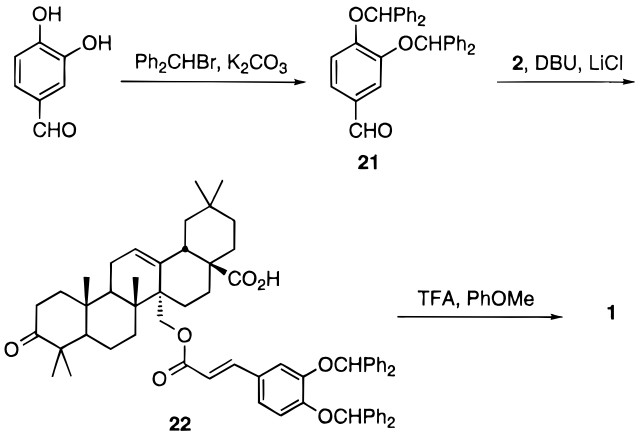
(21) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(22) Mihara, S.; Nakajima, S.; Matsumura, S.; Konoike, T.; Fujimoto, M. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1122.

Scheme 4



Cosmosil 5C18 AR 4.6 mm × 150 mm; guard column, Lichrospher 100 RP 18; solvent, MeCN/H_2O/AcOH (70/30/0.1) if not specified; flow rate, 1 mL/min; detection, 197 nm. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined as $CDCl_3$ solutions at 200 and 50.3 MHz. *J* values are given in hertz. High-resolution mass spectra (HR-LSIMS) were recorded on a Hitachi M-90 instrument.

Oleanonic Acid (3-Oxoolean-12-en-28-oic acid) (5). A suspension of oleanolic acid (**4**) isolated from olive leaves (200 g, 0.44 mol) in 2 L of CH_2Cl_2/acetone (1/1) was cooled to 5 °C, and a solution of Jones reagent (200 mL, 1.2 equiv) was added dropwise over 30 min maintaining the temperature at 5 °C, and the mixture was stirred for an additional 15 min. To the reaction mixture were added *i*-PrOH (100 mL) and H_2O (400 mL), and the resulting mixture was stirred at room temperature for 10 min. Water (3 L) and CH_2Cl_2 (2 L) were added to the mixture and the layers separated. The organic layer was washed with saturated NaCl (2 L), dried, and concentrated to 2.1 kg to give a CH_2Cl_2 solution of oleanonic acid **5**, which was ozonized in the next step. Pure oleanonic acid **5** was obtained by silica gel chromatography of a small aliquot of the extract and subsequent crystallization. Needles (MeOH), mp 178−179 °C. $[\alpha]^{24}_D$ +96.9° (*c* 1.506, $CHCl_3$) [lit.[8] mp 226−229 °C. $[\alpha]^{22}_D$ +98° (*c* 0.935, $CHCl_3$)]. TLC (hexane/EtOAc (2/1)) R_f 0.51. ^{1}H NMR: δ 0.81 (s, 3), 0.91 (s, 3), 0.93 (s, 3), 1.03 (s, 3), 1.05 (s, 3), 1.09 (s, 3), 1.15 (s, 3), 1.2−2.1 (m, 21), 2.3−2.7 (m, 2), 2.75−2.90 (br s, 1), 5.31 (br s, 1). ^{13}C NMR: δ 15.0, 17.0, 19.5, 21.4, 22.9, 23.5, 23.6, 25.8, 26.4, 27.7, 30.7, 32.2, 32.4, 33.1, 33.8, 34.1, 36.8, 39.1, 39.3, 41.0, 41.7, 45.8, 46.6, 46.9, 47.4, 55.3, 122.3, 143.7, 184.4, 217.5. Anal. Calcd for $C_{30}H_{46}O_3$: C, 79.25; H, 10.20. Found: C, 79.01; H, 10.21. LSIMS *m*/*z* 455 $[M + H]^+$.

12α-Hydroxy-3-oxooleanano-28,13-lactone 6. To the resulting solution of oleanonic acid (**5**) was added MeOH (200 mL), and ozone gas was introduced at −50 °C until **5** was not detected on TLC. After removing excess ozone by bubbling with N_2 stream, the solution was concentrated to 0.4 kg, and *i*-PrOH (150 mL) was added. The resulting crystalline product was collected by filtration and washed with *i*-PrOH to give **6** (163.3 g, 79%). Mp (MeOH) 283−285 °C dec. $[\alpha]^{23.5}_D$ +63.6° (*c* 1.001, $CHCl_3$) [lit.[9] mp 304−306 °C, $[\alpha]^{23.5}_D$ +60.4° (*c* 1.08, $CHCl_3$)]. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.34. HPLC t_R 10.5 min. IR ($CHCl_3$): 3619, 2955, 1760, 1699 cm^{-1}. ^{1}H NMR: δ 0.91 (s, 3), 0.99 (s, 6), 1.05 (s, 3), 1.10 (s, 3), 1.19 (s, 3), 1.32 (s, 3), 1.2−1.8 (m, 14), 1.8−2.2 (m, 8), 2.44−2.55 (m, 2), 3.91 (br s, 1). ^{13}C NMR: δ 16.3, 18.2, 18.4, 19.1, 21.1, 21,2, 23.9, 26.7, 27.5, 28.0, 29.2, 31.6, 33.3, 33.4, 34.0, 34.1, 36.2, 39.5, 39.6, 42.2, 43.8, 44.7, 47.4, 51.2, 54.8, 76.2, 90.6, 179.8, 217.7. Anal. Calcd for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.22; H, 9.81. LSIMS *m*/*z* 471 $[M + H]^+$.

3,12-Dioxooleanano-28,13-lactone 10. The title compound was isolated from the mother liquor of **6** by silica gel chromatography (6% yield), and the spectral data was identical with those of a synthetic sample.[10] Mp 273−275 °C (MeOH) [lit.[10] mp 268−270 °C]. TLC (CH_2Cl_2/EtOAc (10/1)) R_f 0.85. ^{1}H NMR: δ 0.97 (s, 3), 0.98 (s, 6), 1.04 (s, 3), 1.10 (s, 3), 1.38 (s, 3), 1.32 (s, 3), 1.2−1.8 (m, 14), 1.8−2.2 (m, 8), 2.39 (dd, 2, *J* = 11.9, 2.5), 2.4−2.55 (m, 2), 2.79 (t, 1, *J* = 14.2). Anal. Calcd for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 76.58; H, 9.28.

Lactone Nitrite 7. A stream of NOCl, generated from $NaNO_2$ (87.4 g) and 35% HCl (509 mL), was introduced to an ice-cold solution of **6** (298 g, 0.634 mol) in pyridine (3 L) at −40 °C over 30 min. The mixture was stirred at −40 °C for 30 min and poured into ice−water (4.4 L). The resulting precipitate was collected by filtration and washed with H_2O (2.5 L). The wet precipitate was dissolved in CH_2Cl_2/pyridine (2.9 L/52 mL), and the organic layer was separated and concentrated. The residue was triturated with hexane (1.2 L), and the white powder was filtered and washed with hexane (0.5 L) to give **7** as a white powder (296 g, 94%). Mp 254−258 °C dec. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.68. HPLC (MeCN/H_2O/AcOH (80/20/0.1)) t_R 27.1 min. IR ($CHCl_3$): 2955, 1760, 1699 cm^{-1}. ^{1}H NMR: δ 0.75 (s, 3), 0.93 (s, 3), 0.99 (s, 3), 1.04 (s, 3), 1.09 (s, 3), 1.16 (s, 3), 1.26 (s, 3), 1.2−1.7(m, 13), 1.7−2.3 (m, 8), 2.3−2.5 (m, 2), 5.64 (dd, 1, *J* = 3.5, 2.0). Anal. Calcd for $C_{30}H_{45}NO_5$: C, 72.11; H, 9.08; N, 2.80. Found: C, 72.06; H, 9.20; N, 2.85.

Photochemical Reaction of 7. The photoreaction conditions were surveyed using a variety of solvents, concentrations, temperatures, wavelengths, and additives. Each photoreaction mixture was heated under reflux in dichloroethane to decompose the primary photoproduct, nitroso dimer, and the composition of the products was monitored by TLC and HPLC. R_f and t_R of starting nitrite **7** and four major products are as follows: TLC (CH_2Cl_2/EtOAc (10/1)): R_f oxime **8** (0.1), nitrate **9** (0.6), hydroxy **6** (0.4), ketone **10** (0.7), nitrite **7** (0.85). HPLC: t_R (min), oxime **8** (3.6), nitrate **9** (7.7), hydroxy **6** (11.8), ketone **10** (12.9), nitrite **7** (27.1).

Twenty gram-scale preparation was performed by irradiating a solution of **7** (20 g, 40 mmol) in acetone (1.2 L) containing a small amount of pyridine (0.16 mL) with a high pressure Hg lamp (400 W) through a Pyrex filter under nitrogen atmosphere for 1 h. Fourteen batches of the photoreaction mixture were combined and concentrated (324 g). 1,2-Dichloroethane (1.4 L) was added to the residue, and the solution was refluxed for 1.5 h. The resulting slurry was collected by filtration and washed with dichloroethane (300 mL) to give **8** as white crystals (206 g, 74%). The filtrate was concentrated to 1.2 kg, and an additional amount of **8** (31 g, 11%, total yield 85%) was obtained as a crystalline powder: mp 285−289 °C dec. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.16. IR ($CHCl_3$): 3574, 3308, 3016, 2955, 2869, 1768, 1699 cm^{-1}. ^{1}H NMR: δ 0.90 (s, 3), 0.95 (s, 3), 0.98 (s, 3), 1.03 (s, 3), 1.07 (s, 3), 1.26 (s, 3), 1.2−1.8 (m, 13), 1.8−2.2 (m, 8), 2.2−2.4 (m, 2), 3.88 (d, 1, *J* = 6.0), 4.20 (d, 1, *J* = 6.0), 7.62 (s, 1), 8.12 (s, 1). ^{13}C NMR: δ 16.7, 18.1, 18.9, 21.0, 24.2, 24,6, 26.9, 27.1, 28.4, 31.4, 33.1, 33.8, 34.0, 35.4, 36.4, 39.0, 39.5, 42.9, 43.5, 44.2, 45.0, 47.3, 48.8, 50.2, 54.6, 75.1, 88.6, 156.8, 179.2, 218.1. $[\alpha]^{23.5}_D$ +48.9° (*c* 1.004, $CHCl_3$). Anal. Calcd for $C_{30}H_{45}NO_5$: C, 72.11; H, 9.08; N, 2.80. Found: C, 72.11; H, 9.08; N, 2.80. LSIMS *m*/*z* 500 $[M + H]^+$.

Nitrate 9. A solution of **7** (1 g, 2 mmol) and pyridine (0.032 mL, 0.4 mmol) in acetone (120 mL) was irradiated by high pressure Hg lamp under O_2 bubbling for 30 min. After condensing the mixture, *i*-PrOH (2 mL) was added, and the resulting precipitate was collected to give nitrate **9** (437 mg, 41%). Mp 221−222 °C. IR ($CHCl_3$): 3410, 1767, 1699, 1631, 1278 cm^{-1}. ^{1}H NMR: δ 0.92 (s, 3), 0.98 (s, 3), 1.00 (s, 3), 1.05 (s, 3), 1.10 (s, 3), 1.24 (s, 3), 1.2−2.0 (m, 20), 2.51 (m, 2), 3.95 (t, 1, *J* = 2.6), 4.96 (d, 2, *J* = 13.0), 5.07 (d, 2, *J* = 13.0). ^{13}C NMR: δ 16.7, 18.2, 18.9, 19.8, 20.9, 22.2, 23.8, 26.8, 27.1, 28.4, 31.7, 33.1, 33.8, 34.0, 36.3, 38.2, 39.6, 42.7, 44.4, 44.5, 45.8, 47.3, 51.1, 54.6, 71.6, 75.6, 88.3, 179.1, 217.2. $[\alpha]^{23}_D$ +54.6° (*c* 1.007, $CHCl_3$). HR-LSIMS *m*/*z* 532.3276 $[M + H]^+$ (calcd for $C_{30}H_{46}NO_7$, 532.3272).

Nitrimine 11. A solution of **8** (120 mg, 0.24 mmol) in dioxane (3 mL) and AcOH (8 mL) was treated with a 5% aqueous solution of $NaNO_2$ (6 mL) at room temperature for 24 h. The precipitate was collected, washed with water, and recrystallized from $CHCl_3$−MeOH to give nitrimine **11** (80 mg, 63%). Mp > 300 °C. IR (KBr): 3396, 2962, 1758, 1704, 1572,

1299, 970 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD): δ 0.89 (s, 3), 0.94 (s, 3), 0.98 (s, 3), 1.04 (s, 3), 1.08 (s, 3), 1.30 (s, 3), 1.2−2.6 (m, 24), 3.98 (br s, 1), 9.21 (s, 1). ^{13}C NMR ($CDCl_3$+CD_3OD): δ 17.6, 18.3, 19.3, 20.3, 20.7, 20.9, 24.3, 27.2, 27.3, 28.3, 31.5, 32.9, 33.9, 36.3, 36.7, 37.1, 39.3, 44.1, 45.1, 46.8, 47.4, 50.8, 51.3, 54.6, 74.7, 87.6, 179.2, 179.9, 219.2. Anal. Calcd for $C_{30}H_{44}N_2O_6$: C, 68.16; H, 8.39; N, 5.30. Found: C, 67.79; H, 8.33; N, 5.08. HR-LSIMS m/z 551.3090 $[M + Na]^+$ (calcd for $C_{30}H_{44}N_2O_6Na$, 551.3094).

Cyclic Ether 12. A mixture of **6** (106 mg, 0.226 mmol), $Pb(OAc)_4$ (416 mg, 0.939 mmol), I_2 (70.6 mg, 0.278 mmol), and $CaCO_3$ (161 mg, 1.61 mmol) in $CHCl_3$ (10 mL) was sonicated at 25−35 °C for 2 h. The mixture was poured into saturated $NaHCO_3$ (15 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 15 mL) and the combined fractions were dried and concentrated under reduced pressure. The residue was purified by silica gel chromatography (toluene/$CHCl_3$/EtOAc (20/6/3)) to give cyclic ether **12** (63 mg, 60%). Recrystallization from $CHCl_3$/EtOAc gave an analytically pure sample: mp > 300 °C. IR (KBr): 3435, 2945, 1770, 1708, 976 cm^{-1}. ^1H NMR: δ 0.95 (s, 3), 1.00 (s, 3), 1.01 (s, 3), 1.05 (s, 3), 1.09 (s, 3), 1.11 (s, 3), 1.2−1.9 (m, 19), 1.9−2.1 (m, 1), 2.16 (dd, 1, J = 13.4, 3.2), 2.4−2.6 (m, 2), 3.64 (d, 1, J = 9.3), 4.06 (d, 1, J = 4.5), 4.19 (d, 1, J = 9.3). ^{13}C NMR: δ 16.4, 18.2, 18.8, 19.7, 20.7, 22.1, 24.1, 25.6, 26.1, 26.3, 31.0, 33.1, 33.3, 33.8, 33.9, 36.4, 37.3, 38.9, 42.4, 42.5, 46.4, 47.3, 48.3, 49.1, 55.2, 74.5, 77.6, 90.5, 179.9, 217.2. $[\alpha]^{22}_D$ −15.7° (*c* 1.009, $CHCl_3$). Anal. Calcd for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.44. LSIMS m/z 469 $[M + H]^+$.

Imine 13. To a solution of oxime **8** (450 g, 0.90 mol) in dioxane (4.5 L) and AcOH (450 mL) was added 20% aqueous $TiCl_3$ (2.25 L) under ice cooling with the temperature maintained at 26 °C. Stirring was continued for 4 h, and the resulting solution was added to a mixture of EtOAc (13.5 L), Na_2CO_3 (1.66 kg, 17.4 mol), and H_2O (13.5 L) over 30 min with stirring and occasional addition of ice to keep the temperature below 40 °C. The organic layer was separated and washed with brine and water. The aqueous layer was extracted with two portions of EtOAc (10 L). The extracts were combined and concentrated to give crude imine **13** (480 g). The analytically pure sample was obtained by crystallization from hexane (88%) to provide a white powder: mp 263−266 °C dec. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.23. HPLC (MeCN/H_2O/AcOH (65/35/0.1)) t_R 3.77 min. IR ($CHCl_3$): 3017, 2953, 1766, 1699, 1636 cm^{-1}. ^1H NMR: δ 0.89 (s, 3), 0.92 (s, 3), 0.98 (s, 3), 1.02 (s, 3), 1.05 (s, 3), 1.1−1.7 (m, 16), 1.30 (s, 3), 1.8−2.3 (m, 6), 2.44−2.52 (m, 2), 3.76 (d, 1, J = 10.3), 6.99 (d, 1, J = 10.3), 8.11 (d, 1, J = 14.8). ^{13}C NMR: δ 16.6, 18.3, 18.9, 20.9, 21.2, 24,0, 25.7, 26.9, 27.0, 28.4, 31.6, 33.2, 33.8, 33.9, 35.0, 36.3, 39.4, 40.6, 43.1, 43.4, 44.7, 47.1, 50.0, 53.2, 54.6, 74.5, 89.0, 179.1, 182.6, 217.7. $[\alpha]^{23.5}_D$ +65.6° (*c* 1.008, $CHCl_3$). Anal. Calcd for $C_{30}H_{45}NO_4$: C, 74.50; H, 9.38; N, 2.90. Found: C, 74.33; H, 9.43; N, 2.90. LSIMS m/z 484 $[M + H]^+$.

12α-Hydroxy-3,27-dioxooleanano-28,13-lactone 15. The crude imine **13** (480 g) obtained above was dissolved in dioxane (4.36 L) and AcOH (436 mL) at 40 °C. To the solution was added an aqueous solution of $NaNO_2$ (186 g in 654 mL of H_2O) at 23 °C, and the resulting mixture was stirred for 1 h. HPLC of the reaction mixture showed the ratio of hemiacetal acetate **14** and **15** to be 1 to 2 (HPLC (MeCN/H_2O/AcOH (65/35/0.1) t_R **14** (12 min), **15** (9.0 min)). MeOH (2.83 L) and 2 N NaOH (4.0 L) were added to the resulting mixture maintaining the temperature between 14−26 °C, and the mixture was stirred for 2.5 h. The mixture was neutralized with 2 N HCl (1.0 L) and poured into a mixture of brine (8 L) and EtOAc (8 L). The organic layer was washed with brine, and the aqueous layer was extracted with EtOAc (6.5 L). The organic layers were combined, dried, and concentrated to 750 g. The residue was dissolved in EtOAc (2.6 L) and concentrated to 860 g. The resulting thick slurry was kept at 0 °C overnight, and the colorless crystalline powder was collected by filtration and washed with cold EtOAc (0.4 L) to give hydroxy aldehyde **15** (337 g, 77%). Mp 296−300 °C. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.60. IR ($CHCl_3$): 3018, 2957, 1771, 1703 cm^{-1}. ^1H NMR: δ 0.90 (s, 3), 0.94 (s, 3), 0.98 (s, 3), 1.02 (s, 3), 1.06 (s, 3), 1.26 (s, 3), 1.1−2.3 (m, 21), 2.46−2.53 (m, 2), 3.55 (br d, 1, J = 8.6), 3.94 (br d, 1, J = 8.6), 9.99 (s, 1). ^{13}C NMR: δ 17.1, 18.2, 18.9, 20.79, 20.84, 21,3, 24.4, 26.8, 27.0, 28.2, 31.6, 33.0, 33.6, 33.7, 35.5, 36.6, 37.7, 39.3, 43.2, 44.6, 44.2, 47.1, 49.8, 54.3, 58.3, 75.0, 87.1, 178.9, 210.1, 217.5. $[\alpha]^{23.5}_D$ +60.5° (*c* 1.003, $CHCl_3$). Anal. Calcd for $C_{30}H_{46}O_4$: C, 74.34; H, 9.15. Found: C, 74.18; H, 9.14. LSIMS m/z 485 $[M + H]^+$.

Ethylene Ketal 16. A suspension of hydroxy aldehyde **15** (267 g, 0.552 mol), toluene (2.67 L), ethylene glycol (308 mL), and PPTS (6.9 g, 28 mmol) was refluxed for 4 h with azeotropic removal of water with a Dean−Stark apparatus filled with molecular sieves. The resulting mixture was cooled and washed with H_2O (560 mL), and the aqueous layer was extracted with toluene−EtOAc (560 mL−280 mL). The organic layers were combined and concentrated to give crude **16** (320.3 g). A pure sample was obtained by silica gel chromatography. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.74. HPLC (MeCN/H_2O/AcOH (65/35/0.1) t_R 13.3 min. IR ($CHCl_3$): 3020, 3017, 2956, 1770, 1730, 1703 cm^{-1}. ^1H NMR: δ 0.79 (s, 3), 0.89 (s, 3), 0.90 (s, 3), 0.94 (s, 6), 1.21 (s, 3), 1.1−2.4 (m, 23), 3.21 (m, 1), 3.85−3.98 (m, 5), 10.02 (s, 1). ^{13}C NMR: δ 17.0, 17.7, 18.5, 20.0, 20.9, 21,1, 22.8, 24.5, 26.9, 26.9, 27.9, 31.5, 33.1, 33.7, 36.3, 36.9, 37.1, 37.5, 42.2, 43.4, 44.7, 45.9, 49.9, 53.2, 58.4, 64.9, 75.4, 87.2, 112.9, 179.2, 209.8 . $[\alpha]^{23.5}_D$ +3.5° (*c* 1.011, $CHCl_3$). LSIMS m/z 529 $[M + H]^+$.

Aldehyde Acetate 17. The crude **16** (320 g, 0.552 mol) was dissolved in CH_2Cl_2 (1.17 L), and to the solution were added pyridine (156 mL), acetic anhydride (130 mL, 1.38 mol), and DMAP (6.74 g, 55 mmol). After stirring the mixture at room temperature for 5 h, 2 N HCl (1.93 L) was added under ice cooling. The organic layer was separated and washed successively with H_2O (1.68 L), 10% $NaHCO_3$ (1.68 L), and H_2O (1.68 L), and the aqueous layers were extracted with CH_2Cl_2 (0.56 L). Combined organic layers were concentrated, and the residue was triturated with hexane (1.12 L) to give **17** as a white powder (303.7 g, 96%): mp 225−227 °C. TLC (hexane/EtOAc (1/1)) R_f 0.73. HPLC (MeCN/H_2O/AcOH (75/25/0.1) t_R 11.8 min. IR ($CHCl_3$): 3021, 2957, 1776, 1745, 1708, 1233 cm^{-1}. ^1H NMR: δ 0.81 (s, 6) 0.90 (s, 3), 0.92 (s, 3), 0.94 (s, 3), 1.21 (s, 3), 1.0−2.3 (m, 23), 2.12 (s, 3), 3.86−3.99 (m, 4), 5.27 (t, 1, J = 2.8), 10.24 (s, 1). ^{13}C NMR: δ 17.0, 17.7, 18.5, 19.0, 20.0, 20,7, 21.5, 22.9, 24.5, 24.8, 26.8, 31.4, 33.1, 33.4, 36.2, 36.4, 37.1, 37.2, 42.2, 42.3, 44.6, 48.1, 49.2, 53.4, 58.7, 64.9, 64.9, 76.8, 85.3, 112.8, 169.0, 178.3, 206.8 . $[\alpha]^{23.5}_D$ +4.5° (*c* 1.008, $CHCl_3$). Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.55; H, 8.83. Found: C, 71.21; H, 8.77. LSIMS m/z 571 $[M + H]^+$.

Reductive Olefin Regeneration and Myricerone Ketal 18. Lithium metal (11.1 g, 1.60 mol) was dissolved in liquid NH_3 (1.3 L), and to the solution was added a solution of **17** (152 g, 0.266 mol) in THF (1.3 L) over 1 h. After stirring for 45 min, EtOH (152 mL) was added, and the resulting solution was evaporated with gentle heating. 2 N HCl (2 L) was then added while keeping the temperature around 25 °C with occasional addition of ice, and 6 N HCl (200 mL) was added to bring the pH to 3. The mixture was extracted with CH_2Cl_2 (1.6 L) and H_2O (1.6 L), and the organic layer was washed with H_2O. The aqueous layer was extracted with CH_2Cl_2 (0.8 L), and the organic layers were combined and concentrated to give crude myricerone ketal **18** (187 g). Analytically pure **18** was obtained by chromatography (hexane−EtOAc, 90% yield) and subsequent crystallization from MeOH, mp 218−220 °C. TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.33. HPLC (MeCN/H_2O/AcOH (80/20/0.1)) t_R 5.2 min. IR ($CHCl_3$): 3016, 2952, 2882, 1695, 1210 cm^{-1}. ^1H NMR: δ 0.70 (s, 3), 0.83 (s, 3), 0.90 (s, 3), 0.91 (s, 3), 0.92 (s, 3), 0.96 (s, 3) , 1.1−2.0 (m, 24), 2.92 (dd, 1, J = 13.0, 4.0), 3.16 (d, 1, J = 11.8), 3.78 (d, 1, J = 11.8) 3.93 (br s, 4), 5.83 (br s, 1). ^{13}C NMR: δ 15.7, 18.3, 18.6, 20.1, 22.4, 23.0, 23.9, 24.2, 24.5, 26.6, 30.8, 32.3, 33.0, 33.5, 36.5, 37.0, 39.8, 40.3, 42.0, 44.9, 46.1, 47.5, 48.0, 52.9, 62.9, 64.8, 113.2, 129.5, 137.9, 184.0. $[\alpha]^{23.5}_D$ +42.4° (*c* 1.003, $CHCl_3$). Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.52; H, 9.82. LSIMS m/z 515 $[M + H]^+$.

Myricerone (27-hydroxy-3-oxoolean-12-en-28-oic Acid) (3). To a solution of crude **18** (187 g, obtained from 0.266 mol of **17**) in THF (685 mL) was added 2 N HCl (137 mL), and the resulting solution was refluxed for 75 min. After cooling to room temperature, the mixture was extracted with CH_2Cl_2/

H_2O (1.6 L/3.2 L). The organic layer was washed with H_2O (3.2 L), and the aqueous layer was extracted with CH_2Cl_2 (1.6 L). The combined organic extracts were concentrated, and triturated from CH_2Cl_2/hexane (0.2 L/1.26 L) to give **3** as a hygroscopic white powder (125 g, 99%). The spectral data (NMR, IR, $[\alpha]_D$) of the synthetic sample were identical to those of an authentic sample[1] obtained by alkaline hydrolysis of natural myriceric acid A (**1**). **3**: mp 211−213 °C (MeOH). TLC (CH_2Cl_2/EtOAc (8/1)) R_f 0.74. HPLC (MeCN/H_2O/AcOH (80/20/0.1)) t_R 3.3 min. IR ($CHCl_3$): 3010, 2945, 2867, 1697 cm^{-1}. ^1H NMR: δ 0.79 (s, 3), 0.94 (s, 3) 0.98 (s, 3), 1.03 (s, 6), 1.11 (s, 3), 1.1−2.1 (m, 22), 2.3−2.6 (m, 2), 2.97 (br d, 1, J = 12.8), 3.26 (d, 1, J = 11.8), 3.81 (d, 1, J = 12.2), 5.89 (br s, 1). ^{13}C NMR: δ 15.5, 18.3, 19.5, 21.4, 22.4, 23,8, 24.1, 24.4, 26.5, 36.8, 32.0, 32.2, 33.0, 33.5, 34.0, 36.8, 38.7, 39.7, 40.4, 44.9, 46.1, 47.3, 47.6, 54.7, 63.0, 129.3, 137.8, 183.7, 217.6. $[\alpha]^{23.5}_D$ +101.0° (*c* 1.003, $CHCl_3$). Anal. Calcd for $C_{30}H_{46}O_4 \cdot 0.2H_2O$: C, 75.97; H, 9.88. Found: C, 76.23; H, 10.18. HR-LSIMS *m/z* 493.3296 $[M + Na]^+$ (calcd for $C_{30}H_{46}O_4Na$, 493.3294).

Dimerization Product 20. Lithium metal (0.14 g, 20 mmol) was dissolved in liquid NH_3 (10 mL), and to the solution was added a solution of **17** (2.28 g, 0.266 mmol) in THF (23 mL) over 30 min. After stirring for 2.5 h, EtOH (3 mL) was added, and the resulting solution was evaporated with gentle heating. The remaining mixture was extracted as described above, and crude myricerone ketal **18** containing the two byproducts was obtained (1.92 g). The residue was deketalized as described above, and the remaining mixture was separated by silica gel chromatography (CH_2Cl_2−EtOAc) to give myricerone **3** (0.96 g, 46%), aldehyde **19** (0.1 g, 5%), and dimer **20** (0.4 g, 21%). HPLC: t_R (min), myricerone **4** (4.5), aldehyde **19** (5.7), dimer **20** (17.5). Aldehyde **19** was identical with an authentic sample prepared from PCC oxidation of **3**. **20**: mp 168−171 °C. TLC (hexane/EtOAc (2/1)) R_f 0.15. IR ($CHCl_3$): 3489, 1700, 1460, 1378 cm^{-1}. ^1H NMR and ^{13}C NMR spectrum were determined and assigned at 600 and 150 MHz, respectively, by Varian UNITY 600 instrument. Long range correlations were observed between C-27 and 27′-H in the HMBC (heteronuclear multiple bond connectivity) spectrum. ^1H NMR ($CDCl_3$−CD_3OD): δ 0.80 (s, 6), 0.87 (s, 6), 0.96 (s, 6), 1.01 (s, 6), 1.04 (s, 6), 1.05 (s, 6), 1.13 (dd, 2, J = 14.0, 4.3), 1.27 (m, 2), 1.29 (m, 2), 1.32 (m, 2), 1.33 (m, 2), 1.37 (m, 2), 1.42 (m, 2), 1.43 (m, 2), 1.52 (m, 2), 1.56 (m, 2), 1.69 (d, 2, J = 10.9), 1.69 (m, 2), 1.80 (m, 2), 1.85 (m, 2), 1.91 (m, 2), 1.93 (m, 2), 2.00 (m, 2), 2.03 (m, 2), 2.10 (ddd, 2, J = 18.8, 7.1, 3.3), 2.31 (ddd, 2, J = 15.8, 5.6, 2.8), 2.37 (dd, 2, J = 10.5, 7.2), 2.59 (ddd, 2, J = 15.8, 12.3, 6.9), 3.00 (dd, 2, J = 13.9, 4.3), 3.4−3.6 (br, 4), 4.02 (s, 2), 5.84 (t, 2, J = 3.3). ^{13}C NMR ($CDCl_3$−CD_3OD): δ 15.3, 19.8, 20.3, 21.8, 23.0, 23.4, 23.6, 24.8, 25.9, 30.7, 31.3, 32.5, 33.3, 33.7, 34.5, 37.4, 39.1, 41.2, 42.1, 45.0, 45.5, 46.6, 47.7, 52.7, 53.0, 69.3, 130.3, 140.0, 180.6, 219.4. LSIMS *m/z* 939 $[M + H]^+$. HR-LSIMS *m/z* 961.6521 $[M + Na]^+$ (calcd for $C_{60}H_{90}O_8Na$, 961.6528). Both the NMR spectrum and the HRMS supported the dimeric structure of **20**.

27-*O*-(Diethylphosphonoacetyl)myricerone (2). To a solution of diethylphosphonoacetic acid (230 g, 1.17 mol) in CH_2Cl_2 (2.2 L) was added carbonyldiimidazole (190 g, 1.17 mol) portionwise over 10 min, and subsequently myricerone **3** (220 g, 0.468 mol). After the mixture was stirred for 6 h at room temperature, 1 N HCl (2.2 L) was added to the mixture, and the organic layer was separated and washed with H_2O (2.2 L). The aqueous layer was extracted with CH_2Cl_2 (0.5 L), and the organic extracts were combined and concentrated to give crude **2** as a white foam (318 g). The foam was dissolved in EtOAc (340 mL) under reflux, and white crystals precipitated on cooling. The crystals were collected by filtration and washed with cold EtOAc (0.25 L) to give **2** which contained 7% of EtOAc (288 g, 84%). An analytically pure sample was obtained by recrystallization from MeCN: mp 109−112 °C. TLC (CH_2Cl_2/EtOAc (2/1)) R_f 0.21. HPLC (MeCN/H_2O/AcOH (65/35/0.1) t_R 5.3 min. IR ($CHCl_3$): 3027, 1730, 1697, 1261 cm^{-1}. ^1H NMR: δ 0.79 (s, 3), 0.89 (s, 3), 0.93 (s, 3), 1.02 (s, 3), 1.08 (s, 3), 1.11 (s, 3), 1.1−2.1 (m, 27), 2.3−2.6 (m, 2), 2.8−3.0 (m, 1), 2.93 (d, 2, J = 21.7), 4.05−4.36 (m, 6), 5.59 (br s, 1). ^{13}C NMR: δ 15.3, 16.4, 16.5, 18.0, 19.6, 21.4, 22.8, 23.5, 23.7, 26.6, 30.7, 32.4, 32.8, 33.0, 33.6, 33.7 34.0, 35.4, 37.0, 39.0, 39.9, 40.8, 45.0, 46.3, 46.4 (d, J = 151), 47.8, 55.1, 62.7 (d, J = 6.6), 62.8 (d, J = 6.6), 66.7, 127.3, 137.3, 165.6, 183.4, 217.3. $[\alpha]^{23}_D$ +85.6° (*c* 1.005, $CHCl_3$). Anal. Calcd for $C_{36}H_{57}O_8P$: C, 66.64; H, 8.85, P, 4.77. Found: C, 66.33; H, 8.83, P, 4.92. HR-LSIMS *m/z* 649.3863 $[M + H]^+$ (calcd for $C_{36}H_{57}O_8P$, 649.3866).

3,4-Bis[(diphenylmethyl)oxy]benzaldehyde 21. A mixture of 3,4-dihydroxybenzaldehyde (1.38 g, 10 mmol), bromodiphenylmethane (5.43 g, 22 mmol), pulverized K_2CO_3 (3.45 g, 25 mmol) in DMF (20 mL) was heated at 80 °C for 5 h. Additional portions of bromodiphenylmethane (5.43 g, 22 mmol), and pulverized K_2CO_3 (3.45 g, 25 mmol) were added, and the mixture was heated at 80 °C for 3 h. The mixture was extracted with EtOAc, and the organic layer was washed with 5% HCl and aqueous $NaHCO_3$. The extracts were concentrated and purified by chromatography (toluene/EtOAc (19/1)) to give 3,4-bis[(diphenylmethyl)oxy]benzaldehyde **21** (10.8 g, 23%) as a colorless oil. TLC (hexane/EtOAc = 2/1) R_f 0.35. IR (KBr): 3029, 1683, 1597, 1578, 1503, 1454, 1435, 1264 cm^{-1}. ^1H NMR: δ 6.35 (s, 2), 6.92 (d, 1, J = 8.4), 7.1−7.5 (m, 22), 9.67 (s, 1). ^{13}C NMR: δ 82.9, 83.1, 115.6, 115.8, 126.6, 126.9, 127.1, 128.1, 128.2, 128.9, 129.0, 130.5, 141.1, 141.5, 149.0, 154.4, 191.1. Anal. Calcd for $C_{33}H_{26}O_3$: C, 84.23; H, 5.57. Found: C, 84.42; H, 5.75.

***trans*-27-*O*-[3,4-bis[(diphenymethyl)oxy]cinnamoyl]-myricerone (22).** A mixture of **2** (390 mg, 0.6 mmol), 3,4-bis[(diphenylmethyl)oxy]benzaldehyde (**21**) (338 mg, 0.72 mmol), DBU (0.402 mL, 2.7 mmol), and LiCl (114 mg, 2.7 mmol) in DMF (4 mL) was stirred at room temperature for 5 h. The mixture was extracted with EtOAc, and the organic layer was washed with 5% HCl and aqueous $NaHCO_3$. The extracts were concentrated to give crude **22** as a white foam (648 mg). An analytically pure sample was obtained by chromatography (hexane/EtOAc (2/1)) in 95% yield. Mp 153−159 °C (MeOH). TLC (hexane/EtOAc (2/1)). R_f 0.55. $[\alpha]^{23}_D$ +88.3° (*c* 1.012, $CHCl_3$). IR (KBr): 3432, 2864, 1701, 1631, 1596, 1504, 1454 cm^{-1}. ^1H NMR: δ 0.83 (s, 6), 0.93 (s, 3), 1.03 (s, 3), 1.04 (s, 3), 1.07 (s, 3), 1.05−2.05 (m, 20), 2.1−2.6 (m, 2), 2.8−3.0 (m, 1), 4.10 (d, 1, J = 13.0), 4.32 (d, 1, J = 13.0), 5.62 (br s, 1), 6.00 (d, 1, J = 16.0), 6.26 (s, 1), 6.30 (s, 1), 6.84 (d, 1, J = 8.6), 6.9−7.0 (m, 2), 7.2−7.6 (m, 22). ^{13}C NMR: δ 14.1, 15.2, 18.1, 19.5, 21.4, 22.6, 22.6, 23.6, 24.0, 26.6, 30.5, 31.6, 32.3, 32.4, 32.9, 33.6, 33.9, 36.8, 38.8, 39.9, 40.8, 44.5, 45.2, 46.3, 47.2, 47.7, 54.9, 65.3, 82.8, 83.4, 116.1, 116.4, 116.7, 122.6, 126.7, 126.8, 127.7, 127.8, 128.5, 137.3, 141.1, 141.3, 144.4, 148.6, 150.9, 166.7, 184.3, 217.3. Anal. Calcd for $C_{65}H_{72}O_7$: C, 80.88; H, 7.52. Found: C, 80.51; H, 7.81. HR-LSIMS *m/z* 987.5180 $[M + Na]^+$ (calcd for $C_{65}H_{72}O_7Na$, 987.5172).

Myriceric Acid A 1. Trifluoroacetic acid (0.7 mL) was added to the solution of crude **22** (341 mg, 0.316 mmol) in anisole (2.0 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 1.5 h. The mixture was condensed under reduced pressure and purified by silica gel chromatography (toluene/EtOAc (2/1)) to give **1** (160 mg, 80% from **2**) as a white powder. The spectral data (NMR, IR, $[\alpha]_D$) of the synthetic sample were identical to those of the natural product.[1]

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Supporting Information Available: Copies of ^1H NMR spectra of compounds **9**, **16**, **19**, and **20** which lack elemental analyses (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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