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A Novel Orally Active Inhibitor of IL-1 Generation: Synthesis and Structure–Activity Relationships of 3-(4-Hydroxy-1-naphthalenyl)-2-propenoic Acid Derivatives

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A new series of 3-(4-hydroxy-1-naphthalenyl)-2-propenoic acids was prepared and the inhibitory activities of its members on IL-1 generation were evaluated both by in vitro systems using human monocytes and/or rat exudated macrophages stimulated with LPS, and by an in vivo system using the rat CMC-LPS air-pouch model. Many compounds in this series were found to be potent inhibitors of IL-1 generation both in vitro and in vivo. Structure–activity relationships indicated that in the rat CMC-LPS air-pouch model by oral administration the (*Z*)-2-substituted propenoic acids with 3-alkoxy, 5-alkyl, and 4-hydroxy substituents on the naphthalene ring exhibit optimal inhibition. Among the compounds evaluated, (*Z*)-3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic acid (**20a**), which inhibited IL-1 generation from human monocytes with an IC_{50} value of 3.0 μM and had an IC_{50} value of 1.4 μM for rat exudated macrophages, showed the most potent inhibitory activity in the rat CMC-LPS model by oral administration. Compound **20a** also showed antiinflammatory effects in animal models of inflammation.

Inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) have recently become a center of attention in the study of the pathology and development of inflammatory response. In particular, because of its multiple biological activities, IL-1, a polypeptide produced by activated macrophages and other cell types, is thought to be an essential mediator of inflammation. For example, IL-1 induces fever and the production of the acute phase proteins by hepatocytes, and it also stimulates prostaglandins and collagenase production by synovial cells.[1]

In clinical study, the importance of IL-1 in rheumatoid arthritis (RA) has been reported by various investigators. RA is a chronic inflammatory disease characterized by marked inflammation in the synovium. IL-1 activity has been detected in the synovial fluid of RA patients[2,3] and in culture supernatants from RA synovial tissues.[4] IL-1 production by RA synovium correlated with the degree of inflammation.[4] On the basis of these facts, it is thought that an inhibitor of IL-1 generation could be a useful therapeutic agent in the treatment of RA.

Some compounds such as SK&F86002,[5] CP66,248,[6] E5110,[7] and SK&F105561[8] have been reported to be inhibitors of IL-1 generation. These compounds inhibit the IL-1 generation from human monocytes in in vitro studies, but no inhibitory effects in in vivo studies have been reported for them so far.

In the course of developing an orally active inhibitor of IL-1 generation, we have discovered a new series of 3-(4-hydroxy-1-naphthalenyl)-2-propenoic acid derivatives. We investigated the structure–activity relationships of these compounds as inhibitors of IL-1 generation with respect to the substituents on the naphthalene ring and the *E*–*Z* isomers of the 2-propenoic acids using the in vitro systems and the in vivo rat air-pouch inflammatory model. Among the compounds evaluated, (*Z*)-3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic acid (**20a**) was one of the most potent orally active inhibitors of IL-1 generation.

In the present paper, we describe the synthesis and the structure-activity relationships of 3-(4-hydroxy-1-naphthalenyl)-2-propenoic acid derivatives.

Chemistry

The requisite intermediate aldehydes or ketones for the synthesis of a series of 3-(4-hydroxy-1-naphthalenyl)-2-propenoic acids were prepared as shown in Scheme I. Lactone 1[9] was treated with alkyllithium or Grignard reagent to give the ketones **2a,b**. Compounds **2a,b** were reduced with $NaBH_4$, treated with trifluoroacetic anhydride in the presence of pyridine, hydrogenated over 10% palladium on carbon, and then protected with the methoxymethoxy group to give the 8-alkyl-4-(methoxymethoxy)naphthalenes **2c,d**. Reduction of **2a,b** can also be achieved by the Wolff–Kishner reaction in reasonable yield. Compound **2g** was prepared in four steps from

(1) Oppenheim, J. J.; Kovacs, E. J.; Matsushima, K.; Durum, S. K. There is more than one interleukin 1. *Immunol. Today* 1986, *7*, 45–56.
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Scheme I. Preparation of the Intermediate Aldehydes and Ketones

1)

1

2a: R^1 = COMe, R^2 = H
b: R^1 = COEt, R^2 = H
c: R^1 = Et, R^2 = MOM
d: R^1 = n-Pr, R^2 = MOM
e: R^1 = C(OH)(Me)$_2$, R^2 = H
f: R^1 = C(=CH$_2$)Me, R^2 = Ac
g: R^1 = i-Pr, R^2 = MOM

3a: R^1 = Et, R^2 = Me
b: R^1 = Et, R^2 = Et
c: R^1 = Et, R^2 = (CH$_2$)$_4$Me
d: R^1 = Et, R^2 = (CH$_2$)$_2$OMe
e: R^1 = n-Pr, R^2 = Me
f: R^1 = i-Pr, R^2 = Me

4a - f (R^3 = H)
R^1 and R^2 are the same as **3a - f**
4g: R^1 = Et, R^2 = Me, R^3 = Me
h: R^1 = Et, R^2 = Me, R^3 = n-Bu

2)

5

6a: R^1 = H, R^2 = CHO
b: R^1 = MOM, R^2 = CHO
c: R^1 = MOM, R^2 = CH$_2$OTBDMS

7a: R^1 = OCH$_2$Ph, R^2 = CH$_2$OTBDMS
b: R^1 = OCH$_2$Ph, R^2 = CHO
c: R^1 = Cl, R^2 = CHO

3)

8a: R^1 = 8-CH$_2$OH
b: R^1 = 5-Br

9a: R^1 = 8-CHO
b: R^1 = 8-CH=CHCOOEt
c: R^1 = 8-(CH$_2$)$_3$OMe
d: R^1 = 5-Et

10a: R^1 = 5-(CH$_2$)$_3$OMe
b: R^1 = 8-Et

4)

11

12a: R^1 = OH
b: R^1 = OPO(OEt)$_2$
c: R^1 = Et

13a: R^1 = CHO
b: R^1 = OH

14

5)

3a → 15 → 16

lactone 1. Formylation of **2c,d,g** with BuLi and DMF[10] gave the 2-naphthalenecarboxaldehyde derivatives, which were oxidized with *m*-CPBA, hydrolyzed under alkaline conditions (KOH/aqueous MeOH), and then alkylated with an alkyl halide in the presence of anhydrous K_2CO_3 to give the 2-alkoxynaphthalene derivatives **3a–f**. Deprotection of the phenolic hydroxy group of **3a–f** with HCl followed by formylation of the ring with $TiCl_4$ and $CHCl_2OCH_3$[11] gave the aldehydes, which were then treated with

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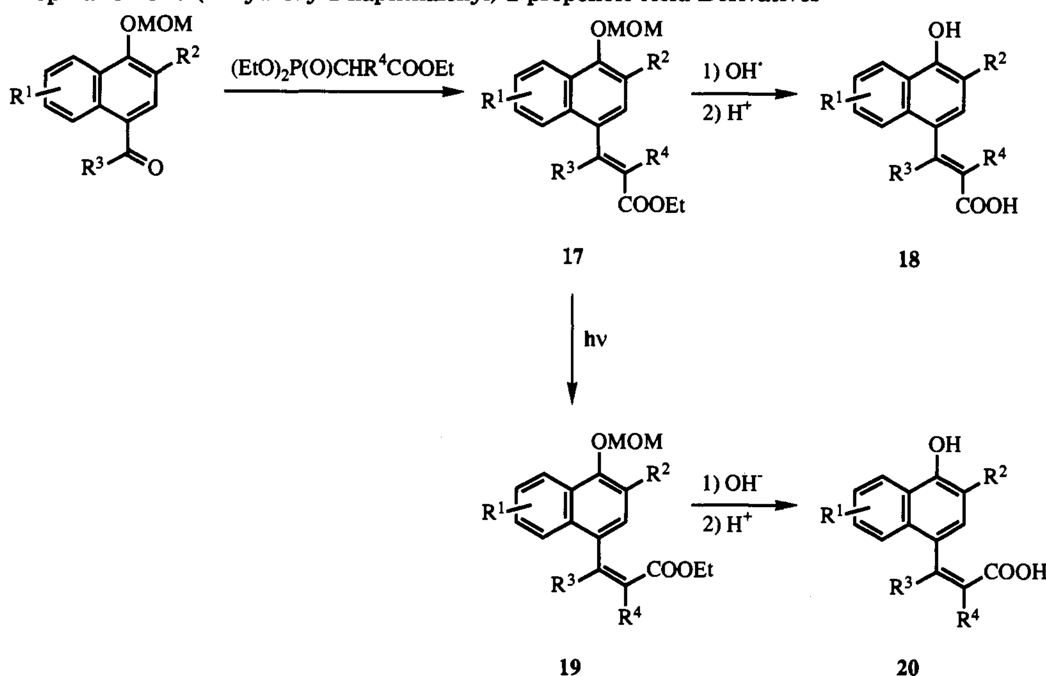
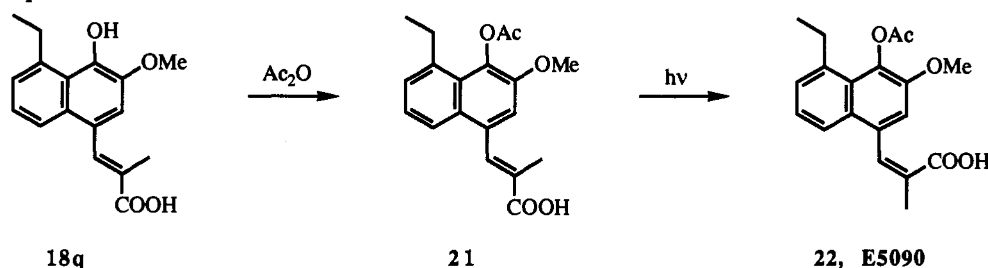
Scheme II. Preparation of 3-(4-Hydroxy-1-naphthalenyl)-2-propenoic Acid Derivatives



Scheme III. Preparation of E5090



NaH and CH_3OCH_2Cl to yield the desired aldehydes **4a–f**. Aldehydes **4a** were treated with alkyllithium or Grignard reagent followed by oxidation with MnO_2 to yield the desired ketones **4g,h**.

In the case of R^2 = benzyl in Scheme I-1), formylation of the ring could not be achieved, because debenzylation occurred. Therefore, 5-ethyl-4-(methoxymethoxy)-3-(phenylmethoxy)-1-naphthalenecarboxaldehyde (**7b**) was prepared by another route as shown in Scheme I-2). Formylation of **5** with $TiCl_4$ and $CHCl_2OCH_3$ followed by protection of the phenolic hydroxy group with methoxymethoxy group gave the aldehyde **6b**. Reduction of **6b** with $NaBH_4$ followed by protection with the TBDMS group[12] gave the silyl ether **6c**, which was then treated with the same procedure described in the preparation of **3a** with use of benzyl bromide instead of iodomethane to give the 2-(phenylmethoxy)naphthalene derivative **7a**. Desilylation of **7a** with tetra-*n*-butylammonium fluoride followed by oxidation with MnO_2 gave the desired aldehye **7b**.

Other aldehydes were prepared as shown in Scheme I-3–5. Details are given in the Experimental Section.

3-(4-Hydroxy-1-naphthalenyl)-2-propenoic acids **18** and **20** were prepared as shown in Scheme II. The Wadsworth–Emmons reaction between suitable aldehydes or ketones and phosphonates gave the (*E*)-propenoic acid ethyl esters **17**, which were then hydrolyzed under alkaline conditions (KOH/aqueous EtOH) followed by deprotection of the phenolic hydroxy group with HCl to yield the (*E*)-3-(4-hydroxy-1-naphthalenyl)-2-propenoic acids **18**. Photochemical *E*–*Z* isomerization of **17** was performed with a high-pressure Hg lamp in acetone to give the *Z* isomers **19**,[13] which were then hydrolyzed under alkaline conditions (KOH/aqueous EtOH) followed by deprotection of the phenolic hydroxy group with HCl to yield the (*Z*)-3-(4-hydroxy-1-naphthalenyl)-2-propenoic acids **20**. However, in the case of $R^3 = R^4$ = H, deprotection of the phenolic hydroxy group of the *Z* isomers resulted in conversion to the *E* isomers. The *E* and *Z* configurations of the compounds were assigned on the basis of ^1H NMR analysis.

The synthetic route to (*Z*)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid (**22**) (E5090) is shown in Scheme III. Compound **18q** was acetylated with acetic anhydride in the presence of pyridine to give the (*E*)-acetate **21**, which was then photoisomerized in acetone with a high-pressure Hg lamp to yield **22**.[13] Acetylation of (*Z*)-3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic acid (**20a**) gave the (*E*)-acetate **21**.

Results and Discussion

The inhibitory activities on IL-1 generation were evaluated both by the in vitro systems using human

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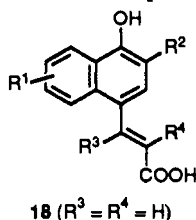
(12) Corey, E. J.; Venkateswarlu, A. Protection of hydroxy groups as *tert*-butyldimethylsilyl derivatives. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(13) Compounds 17 and 21 were photoisomerized to yield the *E,Z* mixtures (ca. E/Z = 2/3), which were separated by flash column chromatography.

Table I. Effects of the Substituents at the 3- and 5-Positions on the Naphthalene Ring against IL-1 Generation



compd	R^1	R^2	mp, °C dec	anal.[c]	IL-1 IC_{50},[a] μM HM[d]	IL-1 IC_{50},[a] μM RM[e]	in vivo air-pouch model: % inhibition[b] (100 μM[f])
a	5-Et	Cl	200	C, H, Cl	5.4 (5.3, 5.4)	6.0	Ia[g]
b	5-Et	OMe	185	C, H	2.4 (1.5–3.5)	1.5	88 (±3)
c	5-Et	OEt	179–180	C, H		1.4	75 (±10)
d	5-Et	$O(CH_2)_4Me$	137–138	C, H	5.3 (4.8–5.7)	2.5	33 (±5)
e	5-Et	OCH_2Ph	172–174	C, H	6.7[h]	1.9	39 (±12)
f	5-Et	$O(CH_2)_2OMe$	142–143	C, H	>10	3.5	34 (±11)
g	5-H	OMe	178–180	C;[i] H[j]	1.9 (1.8–2.0)	1.4	Ia
h	5-Me	OMe	194–195	H; C[k]	2.5[h]	<1	Ia
i	5-*n*-Pr	OMe	187–189	C, H	2.3 (2.0, 2.6)	<1	91 (±1)
j	5-*i*-Pr	OMe	188–189	C, H	1.4 (1.3, 1.6)	1.0	73 (±2)
k	$5\text{-}(CH_2)_3OMe$	OMe	186–188	C, H		6.3	Ia

[a] Concentration of drug inhibiting IL-1 generation by 50% of control value. IC_{50} values were calculated by the least-squares method. [b] Percent inhibition (% ± SEM) of IL-1 generation in rat CMC-LPS air-pouch model. Values are the mean of five animals. [c] Analyses for the elements indicated were within 0.4% of the calculated values. [d] Human monocyte. Values are the mean of two or more experiments. [e] Rat macrophage. Values are the mean of duplicate experiments. [f] Local administration. [g] Inactive (Ia) is defined as <25% inhibition at a screening dose. [h] One experiment. [i] C: calcd, 68.84; found, 68.12. [j] H: calcd, 4.95; found, 5.06. [k] C: calcd, 69.75; found, 68.29.

monocytes[14] and/or rat exudated macrophages[15] stimulated with LPS, and by the in vivo system using rat CMC-LPS air pouch model.[15,16] The relative potencies are expressed as the IC_{50} values for the in vitro studies and as the inhibitory percentages after local administration (100 μM) and/or after oral administration (50 and 200 mg/kg) for the in vivo studies.

The effects of the substituents at the 3- and 5-positions of the naphthalene ring are summarized in Table I. Compounds **18b,c,i,j** substituted with a small alkoxy group at the 3-positions showed high inhibitory activities both in the in vitro and in vivo systems. On the other hand, compounds **18d–f** with a large alkoxy substituent were slightly less active in vivo. Changing the methoxy to a chloro substituent, as in **18a**, resulted in loss of the in vivo activity, while the in vitro activities were retained. Of the 5-substituted compounds, nonsubstituted **18g** and methyl-substituted **18h** inhibited IL-1 generation in vitro, but were inactive in the rat CMC-LPS air-pouch model. 5-Ethyl- or 5-propyl-substituted compounds **18b,c,i,j** showed high inhibitory activities both in in vitro and in in vivo systems.

In order to examine the importance of the ethyl substituent at the 5-position of the naphthalene ring, compounds **18l–p** were evaluated. These results are summarized in Table II. Compounds **18l–n** retained in vitro potency, but were inactive in the in vivo system. The discrepancy between the in vitro and the in vivo activity may be due to differences in the cell population or serum concentration between the in vitro and the in vivo studies.

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(15) Tanaka, M.; Chiba, K.; Okita, M.; Kaneko, T.; Tagami, K.; Hibi, S.; Okamoto, Y.; Shirota, H.; Goto, M.; Sakurai, H.; Machida, Y.; Yamatsu, I. 3-(5-Alkyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic acids as orally active inhibitors of IL-1 generation. *J. Med. Chem.* **1991**, *34*, 2647–2649.

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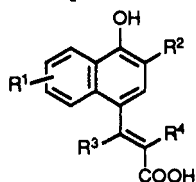
Compounds **18o,p** were significantly less active both in in vitro and in in vivo systems. These results indicated that the steric bulk of an ethyl substituent in the 2-position of the naphthalene ring reduces activity and that an alkyl substituent is suitable for the 5-position of the ring. From the results of Tables I and II, the combination of 3-methoxy and 5-ethyl or 5-propyl substituents on the naphthalene ring appeared to yield the most potent inhibitors of IL-1 generation.

Placement of the various substituents at the 2- and 3-positions of the propenoic acid side chain affected the inhibitory effects on IL-1 generation (Table III). The results show that the 2-substituted compounds **18q–u,x–z** are more potent inhibitors of IL-1 generation than the 3-substituted compounds **18v,w** in vitro. After local administration, the compounds **18q–s,x–z** with substituents in the 2-position showed activities comparable to those of the corresponding unsubstituted compounds **18b,i,j**. However, after oral administration, only a few compounds **18i,q,r,x,y** slightly inhibited IL-1 generation at 200 mg/kg.

The configurational effects of the double bond of the propenoic acids on activity are summarized in Table IV. The (*Z*)-2-substituted compounds generally have higher inhibitory activities than the (*E*)-2-substituted compounds in the CMC-LPS air-pouch model by oral administration and exhibit higher plasma concentrations and AUC values than the *E* isomers.[15] The compounds with a benzyl group **20c,g** at the 2-position of the propenoic acid strongly inhibited IL-1 generation in the in vivo system after local administration, but after oral administration, only compound **20g** slightly inhibited IL-1 generation at 200 mg/kg. The 3-substituted compound **20d** was inactive even as the *Z* form, both in the in vitro and in vivo systems. The most efficacious compounds were those with a methyl or an ethyl substituent at the 2-position of the propenoic acid.

Among the compounds evaluated, (*Z*)-3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-prope-

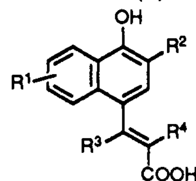
Table II. Positional Effects of the Ethyl Substituent on the Naphthalene Ring against IL-1 Generation



compd	R^1	mp, °C dec	anal.[c]	IL-1 IC_{50},[a] μM: HM[d]	IL-1 IC_{50},[a] μM: RM[e]	in vivo air-pouch model: % inhibition[b]: 100 μM[f]
b	5-Et	185	C, H	2.4 (1.5–3.5)	1.5	88 (±3)
l	6-Et	180–182	H; C[g]	4.0[h]	4.1	Ia[i]
m	7-Et	161–162	H; C[j]	3.9 (3.5, 4.2)	4.0	Ia
n	8-Et	168–169	C, H	1.8[h]	5.5	26 (±15)
o	2-Et	168–170	C, H	>10	>10	Ia
p	2,5-$(Et)_2$	167–169	C; H[k]	>10	~10	Ia

[a] Concentration of drug inhibiting IL-1 generation by 50% of control value. IC_{50} values were calculated by the least-squares method. [b] Percent inhibition (% ± SEM) of IL-1 generation in rat CMC-LPS air-pouch model. Values are the mean of five animals. [c] Analyses for the elements indicated were within 0.4% of the calculated values. [d] Human monocyte. Values are the mean of two or more experiments. [e] Rat macrophage. Values are the mean of duplicate experiments. [f] Local administration. [g] C: calcd, 70.57; found, 69.82. [h] One experiment. [i] Inactive (Ia) is defined as <25% inhibition at a screening dose. [j] C: calcd, 70.57; found, 69.96. [k] H: calcd, 6.71; found, 6.66.

Table III. Effects of the Substituents at the 2- and 3-Positions of the (*E*)-Propenoic Acids against IL-1 Generation



compd	R^1	R^3	R^4	mp, °C dec	anal.[c]	IL-1 IC_{50},[a] μM: HM[d]	IL-1 IC_{50},[a] μM: RM[e]	in vivo air-pouch model: % inhibition[b]: 100 μM[f]	200 mg/kg[g]	50 mg/kg[g]
b	5-Et	H	H	185	C, H	2.4 (1.5–3.5)	1.5	88 (±3)	Ia[h]	
q	5-Et	H	Me	196	C, H	4.8 (4.4–5.1)	2.0	85 (±4)	36 (±9)	
r	5-Et	H	Et	171–173	C, H		1.4	72 (±4)	41 (±4)	
s	5-Et	H	CH_2Ph	174–176	H; C[i]		2.3	79 (±3)	Ia	
t	5-Et	H	S	160–163	C, S; H[j]		6.5	44 (±9)		
u	5-Et	H	Ph	180–181	C; H[k]		2.5	42 (±11)	Ia	
v	5-Et	Me	H	148–150	C, H		>10	Ia		
w	5-Et	n-Bu	H	139–140	C, H	5.8[l]	>10	52 (±4)		
i	5-*n*-Pr	H	H	187–189	C, H	2.3 (2.0, 2.6)	<1	91 (±1)	32 (±3)	Ia
x	5-*n*-Pr	H	Me	170	C, H	~1	1.0	91 (±1)	67 (±11)	Ia
y	5-*n*-Pr	H	Et	175–176	C, H	3.7[l]	<1	91 (±1)	62 (±5)	
j	5-*i*-Pr	H	H	188–189	C, H	1.4 (1.3, 1.6)	1.0	73 (±2)	Ia	
z	5-*i*-Pr	H	Me	198–200	C, H	<1	1.0	70 (±7)	Ia	

[a] Concentration of drug inhibiting IL-1 generation by 50% of control value. IC_{50} values were calculated by the least-squares method. [b] Percent inhibition (% ± SEM) of IL-1 generation in rat CMC-LPS air-pouch model. Values are the mean of five animals. [c] Analyses for the elements indicated were within 0.4% of the calculated values. [d] Human monocyte. Values are the mean of two or more experiments. [e] Rat macrophage. Values are the mean of duplicate experiments. [f] Local administration. [g] Oral administration. [h] Inactive (Ia) is defined as <25% inhibition at a screening dose. [i] C: calcd, 76.22; found, 75.66. [j] H: calcd, 5.47; found, 5.54. [k] H: calcd, 5.79; found, 5.86. [l] One experiment.

noic acid (**20a**) showed the most potent inhibitory activity on IL-1 generation in the rat air-pouch inflammatory model by oral administration.

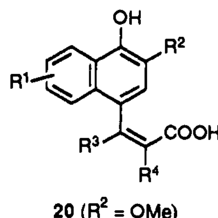
However, compound **20a** was slightly unstable.[17] This physical instability of **20a** suggested that the development of a stable formulation would be difficult. The best way to achieve such a formulation would be to protect the 4-hydroxy substituent. Fortunately, we found that the 4-acetyloxy compound **22** (E5090) was quite stable.[18] Compound **22** itself had little or no inhibitory effect on IL-1 generation in vitro (IC_{50} > 30 μM both for human monocytes and rat exudated macrophages), but orally administered **22** was rapidly adsorbed and immediately transformed to the deacetylated form **20a**, which was pharmacologically active. The effectiveness of compound **22** was almost equal to that of compound **20a** in the rat air-pouch model (MED, 25 mg/kg, po).[19]

Overall, (*Z*)-3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic acid (**20a**) was chosen as the most potent orally active inhibitor of IL-1 generation.

(17) This compound was isomerized to the *E* form **18q** by irradiation by light (1000 lux, 1 week, ca. *Z*/*E* = 4/1) and mainly converted to the *E* form **18q** in acidic solutions or in organic solvents such as EtOH.

(18) This compound was stable to heat (55 °C, 3 months, no change) and irradiation by light (1000 lux, 1 month, *Z*/*E* = 30/1).

Table IV. Effects of the Substituents at the 2- and 3-Positions of the (Z)-Propenoic Acids against IL-1 Generation



compd	R^1	R^3	R^4	mp, °C dec	anal.[c]	IL-1 IC_{50},[a] μM: HM[d]	IL-1 IC_{50},[a] μM: RM[e]	in vivo air-pouch model: % inhibition[b]: 100 μM[f]	200 mg/kg[g]	50 mg/kg[g]
a	5-Et	H	Me	193	C, H	3.0 (2.1–4.0)	1.4	94 (±1)	91 (±2)	65 (±8)
b	5-Et	H	Et	134–136	C, H		2.1	90 (±4)	71 (±5)	43 (±8)
c	5-Et	H	CH_2Ph	129–131	C, H		2.1	94 (±3)	Ia[h]	Ia
d	5-Et	Me	H	185–188	C, H		>10	Ia		
e	5-n-Pr	H	Me	155	C, H	~1	1.1	87 (±2)	86 (±3)	33 (±12)
f	5-n-Pr	H	Et	134–136	C, H	<1[i]	<1	90 (±2)	78 (±2)	47 (±8)
g	5-n-Pr	H	CH_2Ph	104–106	C; H[j]		1.6	91 (±1)	51 (±7)	
h	5-i-Pr	H	Me	195–196	C, H	2.1[i]	1.4	87 (±6)	79 (±2)	29 (±17)

[a] Concentration of drug inhibiting IL-1 generation by 50% of control value. IC_{50} values were calculated by the least-squares method. [b] Percent inhibition (% ± SEM) of IL-1 generation in rat CMC-LPS air-pouch model. Values are the mean of five animals. [c] Analyses for the elements indicated were within 0.4% of the calculated values. [d] Human monocyte. Values are the mean of two or more experiments. [e] Rat macrophage. Values are the mean of duplicate experiments. [f] Local administration. [g] Oral administration. [h] Inactive (Ia) is defined as <25% inhibition at a screening dose. [i] One experiment. [j] H: calcd, 6.43; found, 6.49.

Table V. Effects of Compound **20a**, Prednisolone, and Indomethacin on the CMC-LPS Air-Pouch Model[a]

compound	mg/kg[b]	IL-1 units/mL	IL-1 % inhibn	PGE_2 ng/mL	PGE_2 % inhibn	Granuloma wet weight, g	Granuloma % inhibn
Experiment 1							
control		1715.1 ± 208.8		9.1 ± 1.3		1.94 ± 0.07	
20a	12.5	1288.9 ± 232.2	Ia[c]	5.9 ± 0.5	35	1.93 ± 0.10	Ia
	25	1026.7 ± 221.5	40	5.2 ± 1.3	43	1.61 ± 0.09*	37
	50	596.2 ± 128.9*	65	2.9 ± 1.1*	68	1.49 ± 0.15*	49
	100	275.2 ± 54.4***	84	0.8 ± 0.2***	91	1.25 ± 0.10***	76
	200	157.3 ± 32.3***	91	0.9 ± 0.4***	90	1.16 ± 0.10***	87
LPS (−)		ND[d]		ND		1.04 ± 0.08	
Experiment 2							
control		903.7 ± 103.0		20.3 ± 5.1		2.16 ± 0.08	
prednisolone	2.5	596.1 ± 112.0	34	6.2 ± 0.8*	69	1.72 ± 0.12*	48
	10	327.6 ± 84.6*	64	2.8 ± 0.7*	86	1.36 ± 0.11***	88
indomethacin	3	994.7 ± 243.9	Ia	0.7 ± 0.4***	97	2.08 ± 0.13	Ia
LPS (−)		ND		ND		1.25 ± 0.06	

[a] Values are the mean of five animals. [b] Oral administration. [c] Inactive (Ia) is defined as <25% inhibition at a screening dose. [d] Not detected. Significant difference from control: (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

Characterization of Compound 20a

The inhibitory effects of compound **20a** on IL-1 generation were observed to be common to several in vitro systems, using not only human monocytes but also rat and mouse exudated macrophages with various stimuli such as LPS, opsonized zymosan, and immune complexes.[20] This universality of the in vitro inhibitory effects of compound **20a** on IL-1 generation was also found in a steroidal antiinflammatory drug, prednisolone. These inhibitory effects may be due to the inhibition of IL-1α and β mRNA expression, as suggested by northern blotting analysis.[20] However, the precise details of this mechanism are unknown and are now under investigation.

The effects of compound **20a**, prednisolone, and indomethacin on the CMC-LPS air-pouch model were examined (Table V). Compound **20a** and prednisolone dose-dependently inhibited the generation of IL-1 and PGE_2. Moreover, both compounds suppressed granuloma formation in parallel with the inhibition of IL-1 generation. The inhibitory activity of compound **20a** in this model was estimated to be between $^1/_5$ and $^1/_{20}$ that of prednisolone according to the parameter measured. On the other hand, indomethacin did not show any effect on IL-1 generation and granuloma formation, in spite of its complete inhibition of PGE_2 generation.

The antiinflammatory activity of these three compounds was also examined (Table VI). Compound **20a** dose-dependently inhibited the paw swelling of adjuvant arthritis. In this model, prostaglandins are usually accepted to be one of the important mediators involved. However, compound **20a** exhibited no inhibitory effects on cyclooxygenase activity in sheep seminal vesicles even at 300 μM. The antiinflammatory activity in this model of arthritis suggests that the compound **20a** may exert its effects by a novel mechanism of action.

Conclusion

A new series of 3-(4-hydroxy-1-naphthalenyl)-2-propenoic acid derivatives was synthesized and the inhibitory

(19) This compound dose-dependently inhibited IL-1 generation by oral administration. The inhibition percents were 41%** (25 mg/kg), 56%** (50 mg/kg), and 95%*** (200 mg/kg). Significant difference from control: (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

(20) Goto, M.; Chiba, K.; Hashida, R.; Shirota, H. A novel inhibitor of IL-1 generation, E5090: In vitro inhibitory effects on the generation of IL-1 by human monocytes. Agents Actions 1991, 32, Suppl. 225–229.

Table VI. Inhibitory Effects of Compound **20a**, Prednisolone, and Indomethacin on the Adjuvant Arthritis in Rats[a]

		adjuvant-untreated paw	
compound	dose, mg/kg	swelling (%)	inhibition (%)
control		55.2 ± 5.5	
20a	12.5	44.1 ± 6.3	20.1
	25	36.4 ± 4.0*	34.1
	50	33.8 ± 4.9*	38.8
	100	26.8 ± 2.8***	51.4
prednisolone	5	30.7 ± 3.9**	44.4
indomethacin	1	28.8 ± 4.0**	47.8

[a] The test drugs were orally administered once daily from the first day of the adjuvant treatment. The swelling of the adjuvant-untreated paw (mean ± SEM of 6–10 animals) was evaluated by using a plethysmometer at the 15th day after adjuvant treatment. Significant difference from control: (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

activities of its members on IL-1 generation were evaluated by in vitro and in vivo systems. For the substituents on the naphthalene ring, structure–activity relationships indicated that an ethyl or propyl substituent in the 5-position and a small alkoxy substituent such as methoxy in the 3-position are important for activity and that steric bulk in the 2-position appears to reduce activity. The compounds with 3-methoxy, 4-hydroxy, and 5-ethyl substituents on the naphthalene ring showed potent inhibitory effects on IL-1 generation in in vivo studies. The 2-substituted compounds of the propenoic acid series had higher inhibitory activities on IL-1 generation than the 3-substituted compounds both in vitro and in vivo studies. In particular, the (*Z*)-2-substituted propenoic acid derivatives showed strong inhibitory activities not only after local administration to the air pouch but also after oral administration in the CMC-LPS air-pouch model.

On the basis of these results, (*Z*)-3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic acid (**20a**), which inhibited IL-1 generation from human monocytes with an IC_{50} value of 3.0 μM and had an IC_{50} value of 1.4 μM for rat exudated macrophages, was chosen as the most potent orally active inhibitor of IL-1 generation. Similarly to prednisolone, compound **20a** dose-dependently inhibited IL-1 generation and granuloma formation over the dose range 25–200 mg/kg in the rat CMC-LPS air-pouch model by oral administration. This compound exhibited no inhibitory effects on cyclooxygenase activity in sheep seminal vesicles even at 300 μM, unlike the NSAIDs. However, orally administered **20a** inhibited PGE_2 generation by inflammatory tissue in the rat air-pouch model in parallel with its inhibition of IL-1 generation. Moreover, compound **20a** inhibited the paw-swelling of adjuvant arthritis. Because of these inhibitory effects on IL-1 generation in in vitro and in vivo systems and its efficacy in animal models of inflammation, it is expected that compound **20a** will greatly contribute to investigations of the role of IL-1 in inflammation, especially to its study in vivo.

Experimental Section

Chemistry. All melting points were determined on a YAZAWA BY-10 melting point apparatus in open capillary tubes and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX-90Q or a Varian UNITY 400 spectrometer with tetramethylsilane as an internal standard. Photochemical *E–Z* isomerization was performed with a high-pressure Hg lamp (100 W, Pyrex vessel). All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure. Merck silica gel 60, 70–230 mesh or 230–400 mesh, was used for flash column chromatography. Thin layer chromatography (TLC) was developed using Merck silica gel 60F-254 precoated glass plates. Compounds were detected on TLC by UV light (254 nm).

1-(8-Hydroxy-1-naphthalenyl)ethanone (2a). To a solution of 2*H*-naphtho[1,8-*bc*]furan-2-one (1)[9] (200 g, 1.18 mol) in anhydrous THF (2000 mL) at −75 °C under a nitrogen atmosphere was added dropwise MeLi (1.12 M in Et_2O; 1200 mL, 1.34 mol) over a period of 3 h. After stirring at the same temperature for 1 h, the reaction mixture was quenched with a saturated aqueous ammonium chloride (100 mL) at −75 °C, acidified with aqueous HCl (concentrated HCl 160 mL/H_2O 1000 mL), and then extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (15:85) to afford **2a** (135 g, 62%) as a yellow solid: mp 98–100 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 2.80 (s, 3 H), 7.00–7.22 (m, 1 H), 7.32–7.60 (m, 3 H), 7.84–8.12 (m, 2 H), 9.70 (br s, 1 H).

1-(8-Hydroxy-1-naphthalenyl)-1-propanone (2b). To a solution of 1 (460 g, 2.70 mol) in anhydrous THF (4.2 L) at −78 °C under a nitrogen atmosphere was added dropwise EtMgBr (3.0 M in Et_2O; 900 mL, 2.70 mol) over a period of 2 h. After warming of the reaction to 0 °C, a saturated aqueous ammonium chloride was added and the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (15:85) to afford **2b** (176 g, 33%) as a yellow solid: mp 114–117 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (t, 3 H, *J* = 7 Hz), 3.00 (q, 2 H, *J* = 7 Hz), 7.92 (dd, 1 H, *J* = 3.6 Hz, 6 Hz), 7.12–7.68 (m, 4 H), 7.82 (dd, 1 H, *J* = 1.8 Hz, 7 Hz), 8.66 (br s, 1 H).

8-Ethyl-1-(methoxymethoxy)naphthalene (2c). To a solution of **2a** (1040 g, 5.58 mol) in EtOH (8.5 L) at 0 °C was added in portions $NaBH_4$ (131 g, 3.46 mol) over a period of 1 h. After stirring of the reaction mixture at room temperature for 30 min, the excess reducing agent was decomposed by addition of acetone (1000 mL) at 0 °C and the solvent was then evaporated. HCl (1 N, 4.0 L) was added to the residue and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. Hexane was added to the residue for crystallization. The crystalline precipitate was collected by filtration to afford 8-hydroxy-α-methyl-1-naphthalenemethanol (1000 g, 95%) as a pale brown solid: mp 89–90 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.64 (d, 3 H, *J* = 7.2 Hz), 3.70 (br s, 1 H), 5.31 (q, 1 H, *J* = 7.2 Hz), 6.94–7.83 (m, 6 H), 10.40 (br s, 1 H).

To a mixture of this naphthalenemethanol (270 g, 1.43 mol) and pyridine (170 mL, 2.20 mol) in THF (500 mL) at 0 °C was added trifluoroacetic anhydride (357 g, 1.70 mol) over a period of 45 min. After stirring of the reaction mixture for 30 min, AcOEt (2000 mL) was added and then the mixture was washed successively with brine, 1 N HCl, and a saturated aqueous $NaHCO_3$, dried, and filtered. THF (3750 mL) was added to the filtrate, and this solution was hydrogenated over 10% palladium on carbon (water content ~50%; 37.5 g) at 1 atm for 6 h. The catalyst was filtered off and the filtrate was evaporated to about 3000 mL. The resulting solution was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated to give 348 g of crude 8-ethyl-1-naphthalenol as a brown oil, which was used in the next step without further purification: ^1H NMR (90 MHz, $CDCl_3$) δ 1.34 (t, 3 H, *J* = 7 Hz), 3.30 (q, 2 H, *J* = 7 Hz), 5.30 (br s, 1 H), 6.60 (dd, 1 H, *J* = 1.8 Hz, 7 Hz), 7.02–7.42 (m, 4 H), 7.58 (dd, 1 H, *J* = 1.8 Hz, 7 Hz).

To a solution of this crude naphthalenol in DMF (1000 mL) at 0 °C was added in portions sodium hydride (60% dispersion in mineral oil; 69 g, 1.72 mol) over a period of 1 h, followed by addition of chloromethyl methyl ether (160 g, 1.99 mol) at the same temperature. After stirring at room temperature for 30 min, the mixture was poured into ice water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with hexane to afford **2c** (259 g, 83%) as a pale yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, 3 H, *J* = 7 Hz), 3.28 (q, 2 H, *J* = 7 Hz), 3.46 (s, 3 H), 5.24 (s, 2 H), 6.90–7.60 (m, 6 H).

8-Hydroxy-α,α-dimethyl-1-naphthalenemethanol (2e). To a solution of 1 (20.2 g, 0.117 mol) in anhydrous THF (200 mL) at -60 °C under a nitrogen atmosphere was added MeMgBr (3.0 M in Et_2O; 140 mL, 0.42 mol) over a period of 30 min. After stirring of the reaction mixture at -30 °C for 1 h, a saturated aqueous ammonium chloride was added and the mixture was extracted with AcOEt. The organic extract was washed with water, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford **2e** (14.3 g, 60%) as a colorless solid: mp 76–77 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.81 (s, 6 H), 5.00 (br s, 2 H), 6.91–7.42 (m, 5 H), 7.66 (dd, 1 H, J = 1.8 Hz, 7.7 Hz).

8-(1-Methylethenyl)-1-naphthalenol Acetate (2f). To a solution of **2e** (11.3 g, 56 mmol) in pyridine (24 mL) at room temperature was added acetic anhydride (12 mL, 127 mmol), and this mixture was then heated at 60 °C for 6 h. Water was added and the mixture was extracted with AcOEt. The organic extract was washed successively with 2 N HCl, water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford **2f** (3.6 g, 29%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 2.16 (t, 3 H, J = 0.6 Hz), 2.27 (s, 3 H), 4.81 (m, 1 H), 5.06 (m, 1 H), 6.98–7.80 (m, 6 H).

1-(Methoxymethoxy)-8-(1-methylethyl)naphthalene (2g). A solution of **2f** (3.6 g, 15.9 mmol) in EtOH (100 mL) was hydrogenated over 10% palladium on carbon (water content ~50%; 0.2 g) at 1 atm for 20 h. The catalyst was filtered off and the filtrate was evaporated to give the crude product, which was purified by column chromatography on silica gel eluting with AcOEt/hexane (3:97) to afford 8-(1-methylethyl)-1-naphthalenol acetate (1.72 g, 47%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (d, 6 H, J = 6.7 Hz), 2.40 (s, 3 H), 3.85–4.16 (m, 1 H), 7.00–7.80 (m, 6 H).

To a solution of this acetate (8.4 g, 36.8 mmol) in MeOH (50 mL) at room temperature was added sodium methoxide (2.2 g, 40.7 mmol). After stirring of the reaction mixture for 10 min, water was added, and the mixture was acidified with 1 N HCl and then extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. This residue was treated with the same procedure described in the preparation of **2c** (in part) to afford **2g** (8.13 g, 96%) as a pale yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (d, 6 H, J = 6.7 Hz), 3.54 (s, 3 H), 4.29–4.65 (m, 1 H), 5.32 (s, 2 H), 7.00–7.64 (m, 6 H).

8-Ethyl-2-methoxy-1-(methoxymethoxy)naphthalene (3a). To a solution of **2c** (300 g, 1.39 mol) in anhydrous Et_2O (2200 mL) at -20 °C under a nitrogen atmosphere was added n-BuLi (1.6 M in hexane; 1300 mL, 2.08 mol) over a period of 1.5 h. The mixture was allowed to warm to room temperature and stirring was continued for 2 h. The mixture was recooled to -40 °C and treated dropwise with DMF (215 mL). After stirring of the reaction mixture for 30 min, water (100 mL) was added and the organic layer was dried and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford 8-ethyl-1-(methoxymethoxy)-2-naphthalenecarboxaldehyde (253 g, 75%) as a colorless solid: mp 41.5–42.5 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7 Hz), 3.30 (q, 2 H, J = 7 Hz), 3.53 (s, 3 H), 5.09 (s, 2 H), 7.21–7.87 (m, 5 H), 10.46 (s, 1 H).

To a solution of this aldehyde (220 g, 0.90 mol) in CH_2Cl_2 (1540 mL) was added in portions m-CPBA (85%; 186 g, 0.90 mol) over a period of 1 h, and this mixture was then refluxed for 30 min. After cooling of the reaction mixture to 0 °C, a saturated aqueous sodium thiosulfate solution (200 mL) was added and the resulting precipitate was filtered off. The filtrate was washed successively with water, a saturated aqueous sodium bicarbonate solution, and brine, dried, and evaporated. To a solution of this residue in MeOH (500 mL) was added a solution of KOH (89 g, 1.59 mol) in H_2O (200 mL), and this mixture was then refluxed for 20 min. After cooling of the reaction mixture to room temperature, the mixture was poured into ice-cooled 2 N HCl (700 mL) and extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. A mixture of this residue, iodomethane (256 g, 1.80 mol) and anhydrous K_2CO_3 (500 g, 3.6 mol) in DMF (600 mL) was stirred at 60 °C for 2 h. Water was added and the mixture was extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (3:97) to afford **3a** (166 g, 75%) as a yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz), 3.36 (q, 2 H, J = 7 Hz), 3.58 (s, 3 H), 3.95 (s, 3 H), 5.16 (s, 2 H), 7.16–7.70 (m, 5 H).

5-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (4a). To a solution of **3a** (200 g, 0.81 mol) in acetone (1000 mL) at 0 °C was added 3.5 N HCl (280 mL). After stirring at room temperature for 5 h, the mixture was poured into ice water and extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated to give 178 g of crude 8-ethyl-2-methoxy-1-naphthalenol as a brown oil, which was used in the next step without further purification: ^1H NMR (90 MHz, $CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz), 3.32 (q, 2 H, J = 7 Hz), 3.96 (s, 3 H), 6.30 (s, 1 H), 7.06–7.32 (m, 4 H), 7.36–7.58 (m, 1 H).

To a solution of this crude naphthalenol in CH_2Cl_2 (1000 mL) at 0 °C were added titanium(IV)chloride (178 mL, 1.62 mol) and dichloromethyl methyl ether (121 mL, 1.34 mol). After stirring for 30 min, the mixture was poured into ice water and extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. The resulting solid residue was washed with hexane/isopropyl ether (1:1) to afford 5-ethyl-4-hydroxy-3-methoxy-1-naphthalenecarboxaldehyde (110 g, 59%) as a yellow solid: mp 114–115 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7 Hz), 3.37 (q, 2 H, J = 7 Hz), 4.09 (s, 3 H), 7.05 (s, 1 H), 7.20–7.56 (m, 2 H), 7.77 (s, 1 H), 8.97 (dd, 1 H, J = 1.6 Hz, 8 Hz), 10.39 (s, 1 H).

To a solution of this aldehyde (324 g, 1.41 mol) in DMF (1000 mL) at 0 °C was added in portions sodium hydride (60% dispersion in mineral oil; 68 g, 1.70 mol) over a period of 1 h, followed by addition of chloromethyl methyl ether (129 mL, 1.70 mol) at the same temperature. After stirring at room temperature for 20 min, the mixture was poured into ice water and extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:19) to afford **4a** (288 g, 75%) as a yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz), 3.36 (q, 2 H, J = 7 Hz), 3.55 (s, 3 H), 4.00 (s, 3 H), 5.31 (s, 2 H), 7.20–7.50 (m, 2 H), 7.76 (s, 1 H), 8.90 (dd, 1 H, J = 2.6 Hz, 7 Hz), 10.36 (s, 1 H).

3-Ethoxy-5-ethyl-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (4b). Compound **2c** was treated with the same procedure described in the preparation of **3a** and **4a** with use of iodoethane instead of iodomethane to afford **4b** as a brown oil in 48% total yield: ^1H NMR (90 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7.7 Hz), 1.50 (t, 3 H, J = 7.7 Hz), 3.36 (q, 2 H, J = 7.7 Hz), 3.52 (s, 3 H), 4.20 (q, 2 H, J = 7.7 Hz), 5.32 (s, 2 H), 7.18–7.48 (m, 2 H), 7.72 (s, 1 H), 8.88 (dd, 1 H, J = 2.6 Hz, 7.7 Hz), 10.30 (s, 1 H).

5-Ethyl-4-(methoxymethoxy)-3-(pentyloxy)-1-naphthalenecarboxaldehyde (4c). Compound **2c** was treated with the same procedure described in the preparation of **3a** and **4a** with use of 1-bromopentane instead of iodomethane to afford **4c** as a brown oil in 40% total yield: ^1H NMR (90 MHz, $CDCl_3$) δ 0.80–1.10 (m, 3 H), 1.14–1.62 (m, 7 H), 1.68–2.04 (m, 2 H), 3.38 (q, 2 H, J = 7 Hz), 3.54 (s, 3 H), 4.14 (t, 2 H, J = 7 Hz), 5.32 (s, 2 H), 7.18–7.50 (m, 2 H), 7.74 (s, 1 H), 8.90 (dd, 1 H, J = 2.6 Hz, 7 Hz), 10.44 (s, 1 H).

5-Ethyl-3-(2-methoxyethoxy)-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (4d). Compound **2c** was treated with the same procedure described in the preparation of **3a** and **4a** with use of 2-bromoethyl methyl ether instead of iodomethane to afford **4d** as a brown oil in 34% total yield: ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz), 3.38 (q, 2 H, J = 7 Hz), 3.42 (s, 3 H), 3.52 (s, 3 H), 3.68–3.86 (m, 2 H), 4.16–4.34 (m, 2 H), 5.36 (s, 2 H), 7.20–7.52 (m, 2 H), 7.76 (s, 1 H), 8.92 (dd, 1 H, J = 2.6 Hz, 7 Hz), 10.32 (s, 1 H).

3-Methoxy-4-(methoxymethoxy)-5-propyl-1-naphthalenecarboxaldehyde (4e). Compound **2b** was treated with the same procedure described in the preparation of **2c**, **3a**, and **4a** to afford **4e** as a brown oil in 13% total yield: ^1H NMR (90 MHz, $CDCl_3$) δ 0.96 (t, 3 H, J = 7 Hz), 1.42–1.90 (m, 2 H), 3.12–3.42

(m, 2 H), 3.54 (s, 3 H), 4.00 (s, 3 H), 5.28 (s, 2 H), 7.14–7.48 (m, 2 H), 7.76 (s, 1 H), 8.89 (dd, 1 H, J = 1.8 Hz, 7 Hz), 10.45 (s, 1 H).

3-Methoxy-4-(methoxymethoxy)-5-(1-methylethyl)-1-naphthalenecarboxaldehyde (4f). Compound **2g** was treated with the same procedure described in the preparation of **3a** and **4a** to afford **4f** as a pale yellow oil in 40% total yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.34 (d, 6 H, J = 6.7 Hz), 3.53 (s, 3 H), 3.98 (s, 3 H), 4.43–4.77 (m, 1 H), 5.26 (s, 2 H), 7.30–7.57 (m, 2 H), 7.76 (s, 1 H), 8.93 (dd, 1 H, J = 2.0 Hz, 6.9 Hz), 10.45 (s, 1 H).

1-[5-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenyl]ethanone (4g). To a solution of **4a** (2.0 g, 7.3 mmol) in anhydrous THF (20 mL) at −78 °C under a nitrogen atmosphere was added MeLi (1.12 M in Et_2O; 11.5 mL, 12.9 mmol). After stirring of the reaction mixture for 30 min, a saturated aqueous ammonium chloride was added and the mixture was then extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. To a solution of this residue in CH_2Cl_2 (20 mL) was added MnO_2 (30 g), and this mixture was then stirred at room temperature for 20 h. The oxidizing agent was filtered off and the filtrate was evaporated to give the crude product, which was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford **4a** (1.3 g, 62%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz), 2.70 (s, 3 H), 3.34 (q, 2 H, J = 7 Hz), 3.53 (s, 3 H), 3.96 (s, 3 H), 5.21 (s, 2 H), 7.20–7.31 (m, 2 H), 7.55 (s, 1 H), 8.21–8.37 (m, 1 H).

1-[5-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenyl]-1-pentanone (4h). Compound **4a** (2.0 g, 7.3 mmol) was treated with the same procedure described in the preparation of **4g** with use of *n*-BuLi instead of MeLi to afford **4h** (1.18 g, 49%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.80–1.06 (m, 3 H), 1.12–1.92 (m, 7 H), 2.96 (t, 2 H, J = 7 Hz), 3.34 (q, 2 H, J = 7 Hz), 3.54 (s, 3 H), 3.96 (s, 3 H), 5.18 (s, 2 H), 7.16–7.32 (m, 2 H), 7.42 (s, 1 H), 7.92–8.10 (m, 1 H).

5-Ethyl-4-hydroxy-1-naphthalenecarboxaldehyde (6a). 8-Ethyl-1-naphthalenol (**5**) (24.0 g, 0.14 mol) was treated with the same procedure described in the preparation of **4a** (in part) to afford **6a** (15.9 g, 57%) as a pale brown solid: mp 193–194 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz), 3.32 (q, 2 H, J = 7 Hz), 7.04 (d, 1 H, J = 8 Hz), 7.33 (dd, 1 H, J = 1.4 Hz, 8 Hz), 7.56 (t, 1 H, J = 8 Hz), 7.94 (d, 1 H, J = 8 Hz), 9.17 (dd, 1 H, J = 1.4 Hz, 8 Hz), 10.07 (s, 1 H), 11.40 (s, 1 H).

5-Ethyl-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (6b). Compound **6a** (15.9 g, 79 mmol) was treated with the same procedure described in the preparation of **4a** (in part) to afford **6b** (15.4 g, 79%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz), 3.34 (q, 2 H, J = 7 Hz), 3.60 (s, 3 H), 5.46 (s, 2 H), 7.20 (d, 1 H, J = 7 Hz), 7.22–7.70 (m, 2 H), 7.88 (d, 1 H, J = 7 Hz), 9.32 (dd, 1 H, J = 1.4 Hz, 7 Hz), 10.70 (s, 1 H).

(1,1-Dimethylethyl)[[5-ethyl-4-(methoxymethoxy)-1-naphthalenyl]methoxy]dimethylsilane (6c). To a solution of **6b** (41.2 g, 169 mmol) in EtOH (200 mL) at 0 °C was added in portions $NaBH_4$ (4.5 g, 119 mmol) over a period of 20 min. After stirring of the reaction mixture for 30 min, water was added and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. To a mixture of this residue and *tert*-butyldimethylsilyl chloride (30.0 g, 0.20 mol) in DMF (140 mL) at room temperature was added imidazole (28.5 g, 0.42 mol). After stirring of the reaction mixture for 5 h, water was added and the mixture was extracted with AcOEt. The organic extract was washed with water, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (2:98) to afford **6c** (55.3 g, 91%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.12 (s, 6 H), 0.94 (s, 9 H), 1.32 (t, 3 H, J = 7 Hz), 3.30 (q, 2 H, J = 7 Hz), 3.52 (s, 3 H), 5.04 (s, 2 H), 5.28 (s, 2 H), 7.00 (d, 1 H, J = 7 Hz), 7.10–7.40 (m, 3 H), 7.72 (dd, 1 H, J = 2.6 Hz, 7 Hz).

(1,1-Dimethylethyl)[[5-ethyl-4-(methoxymethoxy)-3-(phenylmethoxy)-1-naphthalenyl]methoxy]dimethylsilane (7a). **Compound 6c** (4.9 g, 13.5 mmol) was treated with the same procedure described in the preparation of **3a** with use of benzyl bromide instead of iodomethane to afford **7a** (1.03 g, 16%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.10 (s, 6 H), 0.94 (s, 9 H), 1.28 (t, 3 H, J = 7 Hz), 3.38 (q, 2 H, J = 7 Hz), 3.46 (s, 3 H), 5.08 (s, 2 H), 5.12 (s, 2 H), 5.18 (s, 2 H), 7.10–7.60 (m, 9 H).

5-Ethyl-4-(methoxymethoxy)-3-(phenylmethoxy)-1-naphthalenecarboxaldehyde (7b). To a solution of **7a** (1.03 g, 2.2 mmol) in THF (20 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.0 M in THF; 2.65 mL, 2.65 mmol). After stirring of the reaction mixture for 30 min, water was added and the mixture was extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. To a solution of this residue in CH_2Cl_2 (30 mL) was added MnO_2 (11 g), and this mixture was then stirred at room temperature for 12 h. The oxidizing agent was filtered off and the filtrate was evaporated to give the crude product, which was purified by column chromatography on silica gel eluting with AcOEt/hexane (3:97) to afford **7b** (620 mg, 80%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz), 3.38 (q, 2 H, J = 7 Hz), 3.46 (s, 3 H), 5.20 (s, 2 H), 5.32 (s, 2 H), 7.18–7.54 (m, 7 H), 7.80 (s, 1 H), 8.92 (dd, 1 H, J = 2.6 Hz, 7 Hz), 10.28 (s, 1 H).

3-Chloro-5-ethyl-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (7c). To a solution of **6a** (0.81 g, 4.0 mmol) in benzene (30 mL) was added sulfuryl chloride (0.49 mL, 6.0 mmol), and this mixture was then refluxed for 30 min. After cooling of the reaction mixture to room temperature, the mixture was poured into water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid residue was washed with isopropyl ether to afford 3-chloro-5-ethyl-4-hydroxy-1-naphthalenecarboxaldehyde (0.8 g, 84%) as a yellowish brown solid: mp 139–142 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.28 (t, 3 H, J = 7 Hz), 3.36 (q, 2 H, J = 7 Hz), 7.40 (dd, 1 H, J = 1.8 Hz, 7 Hz), 7.60 (t, 1 H, J = 7 Hz), 8.12 (s, 1 H), 9.11 (dd, 1 H, J = 1.8 Hz, 7 Hz), 10.12 (s, 1 H).

This aldehyde (2.6 g, 11.1 mmol) was treated with the same procedure described in the preparation of **4a** (in part) to afford **7c** (2.5 g, 81%) as a brown oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz), 3.34 (q, 2 H, J = 7 Hz), 3.60 (s, 3 H), 5.24 (s, 2 H), 7.20–7.64 (m, 2 H), 7.88 (s, 1 H), 9.02 (dd, 1 H, J = 1.8 Hz, 10.8 Hz), 10.20 (s, 1 H).

8-(Methoxymethoxy)-1-naphthalenecarboxaldehyde (9a). A mixture of 8-hydroxy-1-naphthalenemethanol (**8a**)[21] (9.5 g, 54.5 mmol), anhydrous K_2CO_3 (22.7 g, 164 mmol), and chloromethyl methyl ether (5.43 mL, 71.0 mmol) in acetone (210 mL) was refluxed for 1 h. The solid was filtered off and the filtrate was evaporated. To a solution of this residue in CH_2Cl_2 (250 mL) were added pyridinium trifluoroacetate (4.3 g, 22.2 mmol) and pyridinium dichromate (18.3 g, 48.6 mmol), and this mixture was then stirred at room temperature for 12 h. The oxidizing agent was filtered off and the filtrate was evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford **9a** (5.1 g, 43%) as a colorless solid: mp 56–57 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.50 (s, 3 H), 5.35 (s, 3 H), 7.16–8.00 (m, 6 H), 11.11 (s, 1 H).

3-[8-(Methoxymethoxy)-1-naphthalenyl]-2-propenoic Acid Ethyl Ester (9b). To a suspension of sodium hydride (60% dispersion in mineral oil; 1.36 g, 34 mmol) in 1,2-dimethoxyethane (500 mL) at 0 °C was added triethyl phosphonoacetate (7.63 g, 34 mmol). After stirring of the mixture for 5 min, a solution of **9a** (4.9 g, 22.7 mmol) in 1,2-dimethoxyethane (30 mL) was added and stirring was continued for 10 min. Water was added and the mixture was extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford **9b** (6.4 g, 99%) as a pale brown oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz), 3.54 (s, 3 H), 4.28 (q, 2 H, J = 7 Hz), 5.32 (s, 2 H), 6.14 (d, 1 H, J = 15 Hz), 7.08–7.87 (m, 6 H), 8.93 (d, 1 H, J = 15 Hz).

1-(Methoxymethoxy)-8-(3-methoxypropyl)naphthalene (9c). A solution of **9b** (6.4 g, 22.3 mmol) in THF (60 mL) was hydrogenated over 10% palladium on carbon (water content ~50%; 0.6 g) at 1 atm for 4 h. The catalyst was filtered off and the filtrate was evaporated. To a suspension of $LiAlH_4$ (0.62 g,

(21) Packer, R. J.; Smith, D. C. C. 8-Hydroxy-1-naphthoyl compounds. *J. Chem. Soc. C* 1967, 2194–2201.

16.3 mmol) in THF (20 mL) at 0 °C was added a solution of this residue in THF (20 mL) and this mixture was stirred at room temperature for 1 h. After cooling of the reaction mixture to 0 °C, 1 N HCl was added and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (3:7) to afford 8-(methoxymethoxy)-1-naphthalenepropanol (5.2 g, 94%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.51 (br s, 1 H), 1.82–2.15 (m, 2 H), 3.37 (m, 2 H), 3.56 (s, 3 H), 3.72 (t, 2 H, J = 7 Hz), 5.34 (s, 2 H), 7.03–7.72 (m, 6 H).

This naphthalenepropanol (5.1 g, 20.7 mmol) was treated with the same procedure described in the preparation of **4a** (in part) with use of iodomethane instead of chloromethyl methyl ether to afford **9c** (5.3 g, 98%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.89–2.13 (m, 2 H), 3.22–3.54 (m, 4 H), 3.35 (s, 3 H), 3.54 (s, 3 H), 5.34 (s, 2 H), 7.04–7.72 (m, 6 H).

5-Ethyl-1-(methoxymethoxy)naphthalene (9d). 5-Bromo-1-naphthalenol (**8b**) (6.9 g, 30 mmol) was treated with the same procedure described in the preparation of **4a** (in part) to afford 5-bromo-1-(methoxymethoxy)naphthalene (7.2 g, 90%) as a red solid: mp 49–50 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.51 (s, 3 H), 5.34 (s, 2 H), 7.09 (br d, 1 H, J = 7 Hz), 7.20–7.36 (m, 1 H), 7.42 (t, 1 H, J = 7 Hz), 7.73 (br d, 1 H, J = 7 Hz), 7.78 (t, 1 H, J = 7 Hz), 8.21 (br d, 1 H, J = 7 Hz).

To a solution of this naphthalene (6.9 g, 26 mmol) in anhydrous THF (1000 mL) at –60 °C under a nitrogen atmosphere was added n-BuLi (1.6 M in hexane; 21.3 mL, 34 mmol). After stirring at –60 °C to –40 °C for 1 h, the mixture was then treated with iodoethane (4.2 mL, 52 mmol). The mixture was allowed to warm to room temperature, poured into water, and extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (7:93) to afford **9d** (5.5 g, 98%) as a pale yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.35 (t, 3 H, J = 7 Hz), 3.06 (q, 2 H, J = 7 Hz), 3.51 (s, 3 H), 5.33 (s, 2 H), 6.92–7.08 (m, 1 H), 7.11–7.47 (m, 3 H), 7.51–7.61 (m, 1 H), 7.92–8.40 (m, 1 H).

3-Methoxy-4-(methoxymethoxy)-5-(3-methoxypropyl)-1-naphthalenecarboxaldehyde (10a). Compound **9c** was treated with the same procedure described in the preparation of **3a** and **4a** to afford **10a** as a pale yellow oil in 43% total yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.85–2.11 (m, 2 H), 3.28–3.57 (m, 4 H), 3.34 (s, 3 H), 3.55 (s, 3 H), 4.02 (s, 3 H), 5.34 (s, 2 H), 7.30–7.54 (m, 2 H), 7.82 (s, 1 H), 8.98 (dd, 1 H, J = 2.6 Hz, 7 Hz), 10.44 (s, 1 H).

8-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (10b). Compound **9d** was treated with the same procedure described in the preparation of **3a** and **4a** to afford **10b** as a colorless oil in 13% total yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.38 (t, 3 H, J = 7 Hz), 3.08 (q, 2 H, J = 7 Hz), 3.58 (s, 3 H), 3.93 (s, 3 H), 5.36 (s, 2 H), 7.30–7.58 (m, 2 H), 7.82 (s, 1 H), 8.17 (dd, 1 H, J = 3.6 Hz, 7 Hz), 10.75 (s, 1 H).

Phosphoric Acid Diethyl 7-Methoxy-2-naphthalenyl Ester (12b). A mixture of 2,7-dihydroxynaphthalene (**11**) (25 g, 156 mmol), iodomethane (9.7 mL, 156 mmol), and anhydrous K_2CO_3 (32.3 g, 234 mmol) in acetone (300 mL) was stirred at room temperature for 5 h. The solid was filtered off and the filtrate was evaporated. The residue was chromatographed on a short silica gel column to give 14 g of crude 7-hydroxy-2-methoxynaphthalene (**12a**) as a pale brown solid, which was used in the next step without further purification. To a solution of this crude **12a** in THF (200 mL) at 0 °C was added sodium hydride (55% dispersion in mineral oil; 3.5 g, 80 mmol). After stirring of the mixture for 20 min, diethyl phosphorodichloridate (12.7 mL, 88 mmol) was added and stirring was continued for 5 min. Water was added and the mixture was extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:1) to afford **12b** (14.4 g, 30%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 6 H), 3.90 (s, 3 H), 4.25 (m, 4 H), 7.09 (m, 2 H), 7.19 (m, 1 H), 7.59 (m, 1 H), 7.71 (m, 2 H).

7-Ethyl-2-methoxynaphthalene (12c). To a mixture of dichloro[1,3-bis(diphenylphosphino)propane]nickel(II)[22] (0.65 g, 1.2 mmol) and EtMgCl (2.0 M in THF; 36 mL, 72 mmol) was added a solution of **12b** (7.4 g, 23.8 mmol) in THF (10 mL), and this mixture was then stirred at room temperature for 14 h.[23] The mixture was poured into ice water and extracted with AcOEt. The organic extract was washed successively with 1 N HCl and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (2:98) to afford **12c** (3.6 g, 81%) as a colorless solid: mp 51–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3 H, J = 7.5 Hz), 2.79 (q, 2 H, J = 7.5 Hz), 3.91 (s, 3 H), 7.06–7.09 (m, 2 H), 7.20 (dd, 1 H, J = 1.6 Hz, 8.4 Hz), 7.53 (br s, 1 H), 7.67–7.70 (m, 2 H).

7-Ethyl-2-methoxy-1-naphthalenecarboxaldehyde (13a). Phosphorus oxychloride (0.8 mL, 8.4 mmol) was added dropwise to DMF (8.0 mL) at 0 °C. After stirring of the mixture for 30 min, **12c** (1.3 g, 7 mmol) was added and the reaction mixture was stirred at 60 °C for 7 h. After cooling of the reaction mixture to room temperature, 5 N NaOH (30 mL) was added and the mixture was extracted with AcOEt. The organic extract was washed successively with water and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:4) to afford **13a** (0.6 g, 40%) as a pale brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7.5 Hz), 2.84 (q, 2 H, J = 7.5 Hz), 4.40 (s, 3 H), 7.22 (d, 1 H, J = 9.2 Hz), 7.29 (dd, 1 H, J = 1.6 Hz, 8.4 Hz), 7.70 (d, 1 H, J = 8.4 Hz), 8.02 (d, 1 H, J = 9.2 Hz), 9.12 (m, 1 H), 10.89 (s, 1 H).

7-Ethyl-2-methoxy-1-naphthalenol (13b). To a solution of **13a** (0.6 g, 2.8 mmol) in MeOH (12 mL) at room temperature were added H_2O_2 (31%; 0.33 mL, 3.3 mmol) and catalytic amount of concentrated H_2SO_4. After stirring of the reaction mixture for 1 h, water was added and the mixture was extracted with AcOEt. The organic extract was washed with a saturated aqueous sodium thiosulfate solution and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (3:17) to afford **13b** (0.5 g, 88%) as a pale brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7.5 Hz), 2.82 (q, 2 H, J = 7.5 Hz), 3.99 (s, 3 H), 5.98 (br s, 1 H), 7.19 (d, 1 H, J = 9.0 Hz), 7.23 (dd, 1 H, J = 1.6 Hz, 8.4 Hz), 7.36 (d, 1 H, J = 9.0 Hz), 7.67 (d, 1 H, J = 8.4 Hz), 7.92 (m, 1 H).

6-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (14). Compound **13b** was treated with the same procedure described in the preparation of **4a** to afford **14** as a colorless solid in 41% yield: mp 89–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3 H, J = 7.5 Hz), 2.85 (q, 2 H, J = 7.5 Hz), 3.63 (s, 3 H), 4.03 (s, 3 H), 5.44 (s, 2 H), 7.45 (dd, 1 H, J = 1.8 Hz, 8.8 Hz), 7.77 (s, 1 H), 8.09 (m, 1 H), 8.99 (d, 1 H, J = 8.8 Hz), 10.41 (s, 1 H).

3,8-Diethyl-2-methoxy-1-(methoxymethoxy)naphthalene (15). To a mixture of **3a** (2.2 g, 8.9 mmol) and TMEDA (1.7 mL, 11.2 mmol) in anhydrous Et_2O (20 mL) at 0 °C under a nitrogen atmosphere was added dropwise n-BuLi (1.6 M in hexane; 8.4 mL, 13.4 mmol). After stirring of the mixture at room temperature for 3 h, iodoethane (1.1 mL, 13.7 mmol) was added and then stirring was continued for 12 h. Water was added and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1.5:98.5) to afford **15** (2.0 g, 82%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7.5 Hz), 1.34 (t, 3 H, J = 7.5 Hz), 2.83 (q, 2 H, J = 7.5 Hz), 3.38 (q, 2 H, J = 7.5 Hz), 3.60 (s, 3 H), 3.93 (s, 3 H), 5.22 (s, 2 H), 7.23–7.31 (m, 2 H), 7.43 (s, 1 H), 7.59 (m, 1 H).

2,5-Diethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenecarboxaldehyde (16). Compound **15** was treated with the same procedure described in the preparation of **4a** to afford **16** as a pale brown oil in 21% yield: ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7.5 Hz), 1.32 (t, 3 H, J = 7.5 Hz), 3.16 (q, 2 H, J =

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7.5 Hz), 3.39 (q, 2 H, J = 7.5 Hz), 3.55 (s, 3 H), 3.93 (s, 3 H), 5.28 (s, 2 H), 7.33 (dd, 1 H, J = 1.1 Hz, 7.0 Hz), 7.44 (dd, 1 H, J = 7.0 Hz, 8.6 Hz), 8.77 (dd, 1 H, J = 1.1 Hz, 8.6 Hz), 10.80 (s, 1 H).

(*E*)-3-[5-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenyl]-2-methyl-2-propenoic Acid Ethyl Ester (17q). To a suspension of sodium hydride (60% dispersion in mineral oil; 36 g, 0.90 mol) in dry DMF (500 mL) at 0 °C was added triethyl 2-phosphonopropionate (268 g, 1.12 mol) over a period of 1 h. After stirring of the mixture at room temperature for 1 h, a solution of **4a** (206 g, 0.75 mol) in dry DMF (250 mL) was added and stirring was continued for 15 min. Water was added and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (1:9) to afford **17q** (262.4 g, 98%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz), 1.38 (t, 3 H, J = 7 Hz), 1.96 (d, 3 H, J = 1.3 Hz), 3.34 (q, 2 H, J = 7 Hz), 3.57 (s, 3 H), 3.91 (s, 3 H), 4.28 (q, 2 H, J = 7 Hz), 5.17 (s, 2 H), 7.04–7.31 (m, 3 H), 7.60 (m, 1 H), 8.03 (br s, 1 H).

(*E*)-3-(5-Ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic Acid (18q). To a solution of **17q** (28 g, 78 mmol) in EtOH (240 mL) was added a solution of KOH (28 g, 0.5 mol) in H_2O (55 mL) and this mixture was then refluxed for 1 h. The cooled solution was acidified with 2 N HCl and extracted with AcOEt. The organic extract was washed with water, dried, and evaporated to afford (*E*)-3-[5-ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenyl]-2-methyl-2-propenoic acid (23 g, 89%) as a pale yellow solid: mp 127–128 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 2.00 (d, 3 H, J = 1.8 Hz), 3.35 (q, 2 H, J = 7 Hz), 3.56 (s, 3 H), 3.93 (s, 3 H), 5.19 (s, 2 H), 7.17–7.29 (m, 3 H), 7.61–7.71 (m, 1 H), 8.26 (s, 1 H).

To a solution of this acid (23 g, 70 mmol) in acetone (250 mL) at room temperature was added concentrated HCl (15 mL). After stirring for 1.5 h, the mixture was poured into water (3.5 L), the resulting precipitate was collected by filtration and then washed with water to afford **18q** (19 g, 95%) as a pale yellow solid: mp 196 °C dec; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7 Hz), 2.04 (d, 3 H, J = 1.3 Hz), 3.34 (q, 2 H, J = 7 Hz), 3.97 (s, 3 H), 6.47 (s, 1 H), 7.12–7.35 (m, 3 H), 7.52–7.75 (m, 1 H), 8.27 (s, 1 H).

(*Z*)-3-[5-Ethyl-3-methoxy-4-(methoxymethoxy)-1-naphthalenyl]-2-methyl-2-propenoic Acid Ethyl Ester (19a). A solution of **17q** (15.6 g, 43.5 mmol) in acetone (300 mL) was irradiated at room temperature for 2 h with a high-pressure Hg lamp. The solvent was evaporated and the resulting residue was purified by column chromatography on silica gel eluting with AcOEt/hexane (3:97) to afford **19a** (6.6 g, 42%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.75 (t, 3 H, J = 7 Hz), 1.28 (t, 3 H, J = 7 Hz), 2.19 (d, 3 H, J = 1.8 Hz), 3.34 (q, 2 H, J = 7 Hz), 3.57 (s, 3 H), 3.83 (q, 2 H, J = 7 Hz), 3.89 (s, 3 H), 5.13 (s, 2 H), 7.01–7.31 (m, 4 H), 7.53–7.74 (m, 1 H).

(*Z*)-3-(5-Ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic Acid (20a). Compound **19a** (71.2 g, 0.20 mol) was treated with the same procedure described in the preparation of **18q** in a stream of nitrogen under light-shielding conditions to afford **20a** (50 g, 87%) as a yellow solid: mp 193 °C dec; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7 Hz), 2.16 (d, 3 H, J = 1.5 Hz), 3.31 (q, 2 H, J = 7 Hz), 3.76 (s, 3 H), 6.34 (br s, 1 H), 7.04–7.32 (m, 4 H), 7.42–7.64 (m, 1 H).

(*E*)-3-[4-(Acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic Acid (21). To a solution of **18q** (440 mg, 1.5 mmol) in pyridine (2.4 mL, 30 mmol) at room temperature was added acetic anhydride (0.42 mL, 4.5 mmol). After stirring at the same temperature for 1 h, the mixture was poured into water and extracted with AcOEt. The organic extract was washed successively with diluted HCl and water, dried, and evaporated. The resulting solid residue was washed with hexane to afford **21** (390 mg, 78%) as a colorless solid: mp 195–196 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.34 (t, 3 H, J = 7 Hz), 2.01 (d, 3 H, J = 1.5 Hz), 2.41 (s, 3 H), 3.12 (q, 2 H, J = 7 Hz), 3.91 (s, 3 H), 7.14–7.36 (m, 3 H), 7.56–7.73 (m, 1 H), 8.22 (m, 1 H).

(*Z*)-3-[4-(Acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic Acid (22, E5090). Compound **21** (1.15 g, 3.5 mmol) was treated with the same procedure described in the preparation of **19a** to afford **22** (470 mg, 41%) as a colorless solid: mp 148–150 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7 Hz), 2.16 (d, 3 H, J = 1.5 Hz), 2.39 (s, 3 H), 3.08 (q, 2 H, J = 7 Hz), 3.80 (s, 3 H), 7.08–7.32 (m, 4 H), 7.50–7.69 (m, 1 H), 8.60 (br s, 1 H).

Pharmacology. In Vitro IL-1 Generation Using Human Monocytes. Human peripheral mononuclear cells obtained from healthy volunteers were suspended in RPMI 1640 containing 10% heat-inactivated autologous serum and seeded into 48-well plastic culture plates (1–2 × 10^6 cells/0.5 mL per well). The cells were cultured for 1.5 h, and nonadherent cells were removed by rinsing, and the remaining cells were used as the monocytes preparation. The monocytes were cultured in RPMI 1640 containing 1% heat-inactivated autologous serum and 0.1% ethanol with 1 μg/mL of LPS in the presence or absence of test drugs for 16–18 h. After the cultivation, both the extra- and intracellular IL-1 activities were determined by the standard LAF assay.[14] The amounts of IL-1 in the test samples were calculated by a titration curve prepared with standard human recombinant IL-1β (Genzyme). The IL-1 levels of LPS treated and untreated control were 24–194 and 2–16 units/mL, respectively.

In Vitro IL-1 Generation Using Rat Exudated Macrophages. Exudated macrophages of rats (Fisher) were prepared by the intraperitoneal injection of 2.5% glycogen solution. After 4 days, peritoneal exudated cells were collected. The cells suspended in RPMI 1640 containing 1% heat-inactivated serum derived from normal rats were seeded to 48-well culture plates (0.5 × 10^6 cells/0.5 mL) and incubated at 37 °C for 1.5 h. Nonadherent cells were removed by rinsing, and the remaining cells were used as the exudated macrophage preparation. The macrophages were cultured with LPS (1 ng/mL) for 4 h in the presence or absence of test compounds. After the cultivation, the intracellular IL-1 activity was determined by the standard LAF assay.[14] The amounts of IL-1 in the test samples were calculated by a titration curve prepared with standard human recombinant IL-1α (Genzyme). The IL-1 levels of LPS-treated control were 105–618 units/mL, and the levels of untreated control were negligible.

Rat CMC-LPS Air-Pouch Inflammation Model. A volume of 10 mL of air was injected subcutaneously into the dorsum of rats. At 24 h after the injection of air, 6 mL of a sterilized 2% (w/v) sodium carboxymethyl cellulose (CMC-Na, Cellogen F-3H, Dai-ichikogyo Seiyaku Co.) in saline was injected into the air-pouch. Inflammation was induced by injecting 5 ng of lipopolysaccharide (LPS, Sigma) dissolved in 0.5 mL of saline 24 h after the CMC injection. The test compounds were administered either orally, suspended in 0.5% methyl cellulose solution, or locally, dissolved in 5% EtOH-RPMI 1640 medium containing 30% heat-inactivated autologous serum at a final concentration in the exudate of 100 μM.[24] Five animals were used in each group. Oral administration was performed at 2 h before the LPS injection, and local administration was performed at 30 min and just before the LPS injection. At 4 h after the LPS injection, 50 μL of inflammatory exudate was collected from the air-pouch for measurements of IL-1 activity. The extra- and intracellular IL-1 activities were determined by the standard LAF assay.[14] The amounts of IL-1 in the test samples were calculated by a titration curve prepared with standard human recombinant IL-1α (Genzyme). The IL-1 levels of LPS-treated control were 903–4856 units/mL, and the levels of untreated control were negligible. The amounts of PGE_2 in the exudate supernatant were determined by using a radioimmunoassay kit (New England Nuclear). Granuloma wet weights were determined at 5 days after the LPS injection.

Supplementary Material Available: A listing of NMR data for compounds 18, 20, and 22 (8 pages). Ordering information is given on any current masthead page.

(24) The exudate volumes at the time of drug administration were about 5 mL.