mass spectrometer (EBEB) with a 6 keV Xe^0 primary beam. Accelerating voltage was 10 kV. CID took place in a cell located between MS-1 and MS-2, which was held at 3 kV above ground, so that the CID energy was 7 kV. Helium was used as the collision gas, at a pressure sufficient to reduce the MH^+ abundance to 20% of its initial value.

Biological Studies. Thymic Hormones. Synthetic $T\alpha_1$ was endotoxin free and was provided by Alpha 1 Biomedicals, Inc., Washington, D.C., as a gift from Dr. A. L. Goldstein, Department of Biochemistry, The George Washington University School of Medicine and Health Sciences, Washington, D.C. Synthetic TP5 was purchased from Sigma Chemical Co.

Purification of Human T Lymphocytes. Human T lymphocytes were purified from whole blood as previously described.[15] In brief, peripheral blood mononuclear cells were incubated for 1 h at room temperature on plastic petri dishes in order to remove the macrophages. The T lymphocytes were then purified from the nonadherent cell population by rosetting for 1 h at 4 °C with neuraminidase-treated sheep erythrocytes. The rosetted T cells were separated from B cells on Ficoll-Hypaque gradients. The rosetted cells (pellet) were treated with a 0.8% solution of Tris-ammonium chloride, pH 7.4, to lyse the sheep erythrocytes. Following lysis, the T cells were washed well and examined for purity by using fluorescein-conjugated CD2, CD3 monoclonal antibodies for T cells (Ortho Diagnostic Systems, Raritan, NJ), CD20 for B cells (Coulter Corp., Hialeh, FL), and CD11 and CD14 for monocytes/macrophages (Becton-Dickinson, Mountain View, CA). The B cells were removed from the interface, washed well, and examined for purity as T lymphocytes. These purification procedures normally result in T lymphocytes of greater than 90% purity. For optimal response of T lymphocytes, 5–10% macrophages are added to T cell suspensions.

Effect of Peptides on T Lymphocytes. Human T cell cultures were incubated in microtiter plates at 37 °C and 5% CO_2 in a humidified atmosphere. The mixtures were composed of 2×10^5 T cells per well, 0.5% (v/v) PHA (GIBCO), and peptides at 1 μg/mL concentration, in a total volume of 200 μL. For RNA synthesis, 1 μCi of [^{3}H]uridine (ICN Radiochemicals) was added initially and the cultures were incubated for 18–24 h. In some experiments a specific activation signal anti-T3 receptor monoclonal antibody (OKT3, Ortho), at 1.56 ng/mL, was used instead of PHA. For DNA synthesis, the cultures were incubated for a total of 72 h with the final 16 h being in the presence of 1 μCi of [^{3}H]thymidine (6.7 Ci/mmol, ICN Radiochemicals). Following incubation, the cells were harvested and counted in a liquid-scintillation counter. The degree of incorporation of radiolabeled uridine or thymidine was used as a measure of the effect of the peptides on the T lymphocytes.

Acknowledgment. Mass spectra were provided by the MIT Mass Spectrometry Facility, which is supported by a grant from the NIH Division of Research Resources (Grant No. RR00317, to K. Biemann). We thank Dr. Chen-hui Zeng for the LSIMS spectra, Dr. Daniel Kassel for the CID MS/MS data, and Dr. Catherine Costello for arranging the mass spectral study and interpretating the data. We especially want to thank Dr. Abraham Patchornik, The Weizmann Institute of Science, Rehovot, Israel, for a generous supply of PHBT and for many helpful discussions. This research was supported, in part, by a grant from the University of Pittsburgh, Office of Research, Research Development Fund.

Registry No. 1, 123167-50-0; 2, 123167-51-1; 3, 123167-52-2; 4, 123167-53-3; BOC-deblocked 4·TFA, 123167-87-3; 5, 123167-54-4; BOC-deblocked 5·TFA, 123167-83-9; 6, 123167-55-5; 7, 123167-56-6; 8, 123167-57-7; BOC-deblocked 8·TFA, 123167-85-1; 9, 123167-58-8; 10, 123167-59-9; 10 (free acid), 123167-88-4; 11, 123167-60-2; BOC-deblocked 11·TFA, 123183-56-2; 12, 123167-61-3; BOC-deblocked 12·TFA, 123167-71-5; 13, 123167-62-4; BOC-deblocked 13·TFA, 123183-58-4; 14, 123183-53-9; BOC-deblocked 14·TFA, 123183-60-8; 15, 123167-63-5; BOC-deblocked 15·TFA, 123167-73-7; 16, 123167-64-6; BOC-deblocked 16·TFA, 123167-75-9; 17, 123167-65-7; BOC-deblocked 17·TFA, 123183-62-0; 18, 123167-66-8; BOC-deblocked 18·TFA, 123167-77-1; 19, 123183-54-0; BOC-deblocked 19·TFA, 12316.-79-3; 20, 123167-67-9; BOC-deblocked 20·TFA, 123167-81-7; 21, 123167-68-0; BOC-Tyr(2Br-Z)-OH, 47689-67-8; BOC-Tyr(2Br-Z)-OCs, 123167-69-1; $PhCOCH_2Br$, 70-11-1; H-Asn-OBzl·HCl, 69863-43-0; BOC-Glu(OcHex)-OH, 73821-97-3; thymosin, 61512-21-8.

2-Substituted-1-naphthols as Potent 5-Lipoxygenase Inhibitors with Topical Antiinflammatory Activity

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The synthesis, biological evaluation, and structure–activity relationships of a series of 1-naphthols bearing carbon substituents at the 2-position are described. These compounds are potent inhibitors of the 5-lipoxygenase from RBL-1 cells and also inhibit bovine seminal vesicle cyclooxygenase. Structure–activity relationships for these two enzymes are different, implying specific enzyme inhibition rather than a nonspecific antioxidant effect. 2-(Arylmethyl)-1-naphthols are among the most potent 5-lipoxygenase inhibitors reported (IC_{50} values generally 0.01–0.2 μM) and show excellent antiinflammatory potency in the mouse arachidonic acid ear edema model. To study the effects of structure on in vitro and in vivo activity, four general features of the molecules were varied: the 2-substituent, the 1-hydroxyl group, substitution on the naphthalene rings, and the 1,2-disubstituted naphthalene unit itself. 2-Benzyl-1-naphthol (**5a**, DuP 654) shows a very attractive profile of topical antiinflammatory activity and is currently in clinical trials as a topically applied antipsoriatic agent.

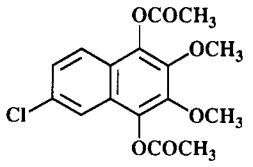
The enzyme 5-lipoxygenase (5-LO) catalyzes the first step in the oxidation of arachidonic acid to leukotrienes. Leukotrienes elicit a variety of biological responses such as smooth muscle contraction, increased vascular permeability, and leukocyte chemotaxis.[1,2] The importance of these phenomena to the inflammatory response implicates the leukotrienes in the pathology of a variety of inflammatory and allergic diseases. The widely used nonsteroidal antiinflammatory drugs such as indomethacin, which show

(1) Sirois, P. *Adv. Lipid Res.* **1985**, *21*, 79.

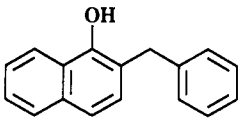
(2) Ford-Hutchinson, A. W. *ISI Atlas Sci.: Pharmacol.* **1987**, *1*, 25.

0022-2623/90/1833-0360$02.50/0

Chart I



Lonapalene



DuP 654 (5a)

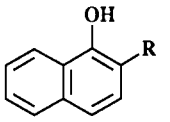
palliative effects in some diseases (rheumatoid arthritis and osteoarthritis, for example), do not greatly affect the biosynthesis of the leukotrienes. Instead, these drugs inhibit cyclooxygenase (CO), the primary enzyme responsible for the generation of prostaglandins and thromboxanes.[3]

Inflammatory skin diseases, such as psoriasis and contact dermatitis, are not significantly improved by CO inhibitors. These diseases display a marked involvement of leukotrienes in their pathological processes.[4,5] For example, psoriatic skin contains elevated levels of leukotrienes, and intradermal injection or topical application of leukotriene B_4 to normal skin produces an erythematous response with neutrophil influx, reminiscent of the inflammation seen in psoriasis and other dermatoses. There is an unmet need for drugs effective in the treatment of inflammatory skin diseases, since the current therapies (glucocorticosteroids, anthralin, and psoralin with UV-A irradiation) possess significant toxic effects, are inconvenient or cosmetically unacceptable, or are only partially efficacious.[6]

Over the past decade, extensive research efforts have identified selective 5-LO and mixed 5-LO/CO inhibitors, many of which have demonstrated antiinflammatory properties. These compounds generally fall into one or more of three categories:[7-9] substrate or product analogues, antioxidants, and iron chelating agents such as hydroxamic acids.[10] Recently, 5-LO inhibition has emerged as an attractive approach to the treatment of inflammatory skin diseases; in particular, the selective agent lonapalene[11] (Chart I) has been reported to show clinical efficacy as an antipsoriatic agent.

In this paper we describe studies of 1-naphthols, bearing carbon-linked substituents in the 2-position, which are very potent inhibitors of 5-LO and also inhibit CO. These compounds possess activity in several animal models of skin inflammation; 2-(arylmethyl)-1-naphthols are particularly interesting as topical antiinflammatory agents. One example from this series, DuP 654 (2-benzyl-1-naphthol, **5a**), has been selected for clinical evaluation as a topical antipsoriatic agent on the basis of its complete pharmacological profile.[12] The synthesis and biological activity of these compounds are described, and the structure–activity relationships (SARs) are discussed with respect to four features of the molecules: the nature of the 2-substituent [particularly variation in the 2-(arylmethyl) group], substitution on the naphthalene rings, the presence of the phenolic hydroxyl group, and variation in the 1,2-disubstituted naphthalene unit itself.

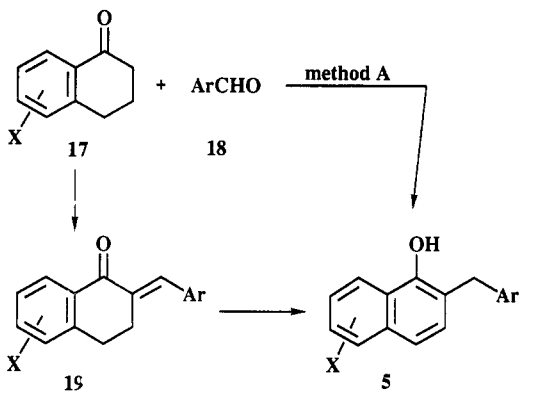
Table I. Inhibition of 5-LO, CO, and Ear Edema by 2-Substituted-1-naphthols



no.	R[a]	RBL-1 50-LO IC_{50}, μM[b]	BSV CO IC_{50}, μM[b]	AA ear edema, % inhibition[c]
1	H[d]	3.6	2.0	59
2	CH_3[d]	0.13	3.0	73
3	$C(CH_3)_3$[e]	0.18	37	67
4	$CH_2CH{=}CH_2$[f]	0.056	18	91
5a	$CH_2C_6H_5$[g]	0.019	3.4	82
6	$CH(CH_3)C_6H_5$	0.070	8.7	45
7	$C(=O)C_6H_5$[h]	20	(26% at 75)	30
8	$CH{=}CHC_6H_5$	0.16	13	65
9	$CH_2CH_2C_6H_5$	0.14	nd	69
10	$COOC_2H_5$[i]	25	(0% at 75)	0
11	$CH{=}CHCOOC_2H_5$	0.045	11	0
12	$CH_2CH_2COOC_2H_5$	0.058	13	69
13	$C(=O)(CH_2)_3COOC_2H_5$	(23% at 25)	(12% at 75)	13
14	$C(=NOH)(CH_2)_3COOC_2H_5$	2.7	(27% at 75)	29
15	$(CH_2)_4COOC_2H_5$	0.011	18	74
16	$(CH_2)_4COOH$	4.2	720	9

[a] Synthesis detailed in the Experimental Section unless otherwise indicated. [b] Averages of two or more IC_{50} determinations; the standard errors average 11% of the values shown; nd = not determined. Values in parentheses are percent inhibition at the concentration shown (μM) where IC_{50} values were not determined. [c] Dose of 100 μg/ear; the standard errors average 9% of the values shown. Inhibition greater than 22% is considered significant ($p < 0.05$). [d] Ref 27. [e] Ref 29. [f] Ref 30. [g] Ref 16. [h] Ref 31. [i] Ref 32.

Scheme I. Synthesis of 2-(Arylmethyl)-1-naphthols



Chemistry

A number of methods exist for attaching carbon substituents to the 2-position of 1-naphthol, and many 1-naphthols bearing such substituents are known in the literature. A selection of compounds possessing a variety of 2-substituents was desired in order to broadly define the SAR for this portion of the molecule. These compounds, shown in Table I, either were known in the literature or were prepared according to well-established synthetic methods: Friedel–Crafts acylation of 1-naphthol[13] or selective 2-lithiation of a 1-naphthyl ether.[14,15]

(3) Shen, T. Y. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; Chapter 62.
(4) Greaves, M. W. In *The Leukotrienes: Their Biological Significance*; Piper, P. J., Ed.; Raven: New York, 1986; p 175.
(5) Greaves, M. W. *J. Am. Acad. Dermatol.* **1987**, *16*, 751.
(6) Farber, E. M.; Nall, L. *Drugs* **1984**, *28*, 324.
(7) Bach, M. K. In *The Leukotrienes*; Academic: New York, 1984; Chapter 6.
(8) Cashman, J. R. *Pharm. Res.* **1985**, 253.
(9) Gillard, J. W.; Guindon, Y. *Drugs Future* **1987**, *12*, 453.
(10) For example: Summers, J. B.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Dyer, R. D.; Carter, G. W. *J. Med. Chem.* **1987**, *30*, 574.
(11) Jones, G. H., et al. *J. Med. Chem.* **1986**, *29*, 1504; and references cited therein.
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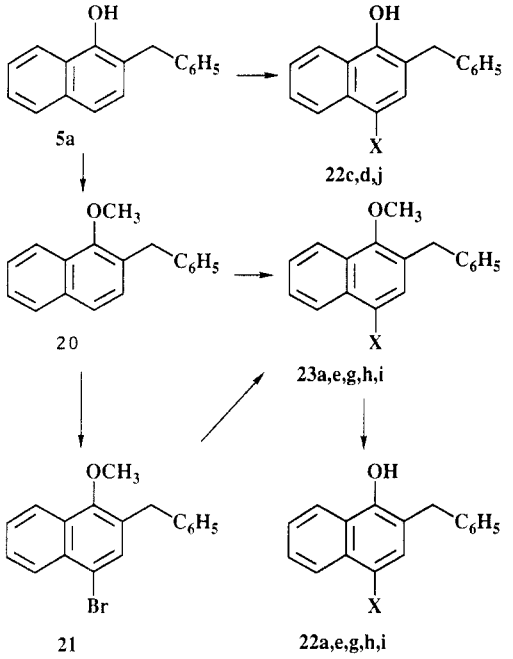
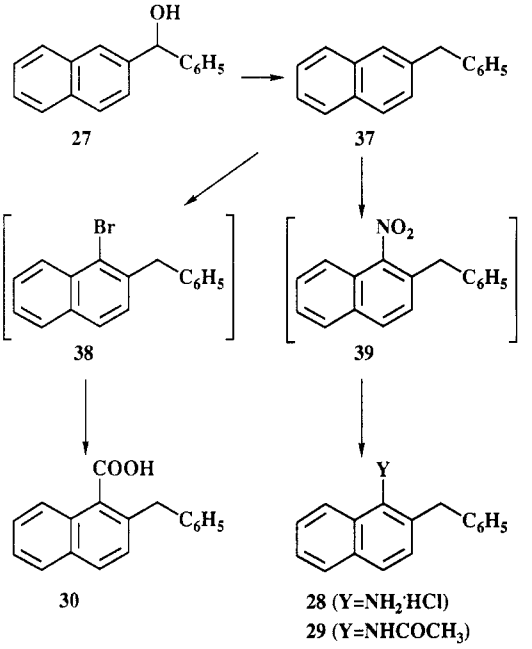
(14) Shirley, D. A.; Cheng, C. F. *J. Organomet. Chem.* **1969**, *20*, 251.
(15) Narasimhan, N. S.; Mali, R. S.; Barve, M. V. *Synthesis* **1979**, 906.

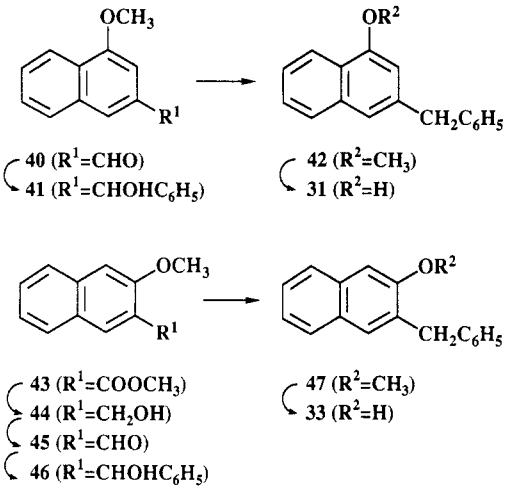
Scheme II. Synthesis of 4-Substituted 2-Benzyl-1-naphthols



Scheme III. Synthesis of Other 2-Benzylnaphthalene Derivatives



Scheme IV. Synthesis of Benzylnaphthol Positional Isomers



Details are given in the Experimental Section.

Because of the interesting antiinflammatory profile of 2-benzyl-1-naphthol (**5a**), this structure was chosen as the basis for further variation. Compound **5a** was first prepared in 1925 by alkylation of sodium 1-naphthoxide;[16] only a few other examples of simple 2-(arylmethyl)-1-naphthols had been previously reported in the literature.[17-20] An attractive method for the preparation of analogues involves the base-catalyzed condensation of a 1-tetralone **17** with an aromatic aldehyde **18** to provide the benzylidene ketone **19** (Scheme I). These materials are surprisingly resistant to isomerization to the naphthol;[21] rhodium and iridium catalysts, as well as strong base, have been used for this purpose.[17,18,22]

We found it most convenient to perform the crossed aldol condensation and aromatization in one step (method A), by heating a mixture of the appropriate tetralone and aldehyde in *tert*-butyl alcohol with 2 equiv of potassium *tert*-butoxide (Scheme I). Acidification and extractive workup provided the desired naphthols **5** in fair to good yields, as shown in Table II. This method provided rapid access to compounds with a variety of substituents on both the pendent ring and the naphthalene ring. In the case of the nitro-substituted analogue **5v** the two-step process, using isomerization of **19v** (X = H, Ar = 4-$NO_2C_6H_4$) by rhodium chloride catalysis,[22] was preferable. Preparation of the methyl sulfone **5u** required phenolic hydroxyl protection of the thioether analogue **51**, followed by oxidation and deprotection.

Substitution at the 4-position of the naphthol was of special interest, since the electronic characteristics of groups at that position should strongly influence the phenolic hydroxyl group. Most compounds with 4-substituents (included in Table II) were prepared by direct electrophilic substitution of **5a** or of the corresponding methyl ether **20**, or by manipulations of 4-bromo-2-benzyl-1-methoxynaphthalene (**21**) followed by demethylation with boron tribromide (method B) or with pyridine hydrochloride. (Scheme II summarizes these transformations, which are detailed in the Experimental Section.) Friedel–Crafts benzoylation of 4-methoxy-1-naphthol followed by reduction of the ketone provided the 4-methoxy analogue **22b**. 4-Methyl derivative **5kk** was obtained by the tetralone route shown in Scheme I.

A number of structurally diverse compounds were also prepared to further define the SARs (Table III). Since 5-LO is an oxidase, phenols can inhibit the enzyme as reducing agents. Nonphenolic analogues were prepared to determine whether hydrogen bonding or acidic properties are more important than redox properties. These were prepared from **5a** by oxidation to the quinone **26**,[23] alkylation (**20**, **24**), or acetylation (**25**) or were prepared

(16) Claisen, L.; Kremers, F.; Roth, F.; Tietze, E. *Liebigs Ann. Chem.* **1925**, *442*, 210.
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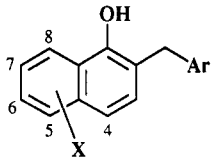
Table II. Preparation of and Inhibition of 5-LO and Ear Edema by 2-(Arylmethyl)-1-naphthols



no.	Ar	X	yield,[a] %	crystn solvent[b]	mp, °C	anal.	RBL-1 5-LO IC_{50}, μM[c]	AA ear edema, % inhibition[d]
5a	C_6H_5	H	60	H/B	73–74	*e*	0.019	82
5b	4-$CH_3C_6H_4$	H	40	H	69–70	*f*	0.024	79
5c	2-$CH_3C_6H_4$	H	65	H	81–82	C, H	0.12	66
5d	4-$CH_3OC_6H_4$	H	57	H/B	80–81	C, H	0.075	85
5e	3-$CH_3OC_6H_4$	H	36	H	55–57	C, H	0.11	72
5f	4-$C_2H_5OC_6H_4$	H	62	H	72–74	C, H	0.062	68
5g	2-$C_2H_5OC_6H_4$	H	71	H	69–70	C, H	0.57	51
5h	3,4-$(CH_3O)_2C_6H_3$	H	59	H/B	106–108	C, H	0.051	60
5i	3,4-$(OCH_2O)C_6H_3$	H	64	H/B	94–95	C, H	0.040	78
5j	3-$C_6H_5OC_6H_4$	H	50	H	50–52	C, H	0.083	60
5k	4-$C_6H_5CH_2OC_6H_4$	H	35	H	88–89	C, H	0.072	12
5l	4-$CH_3SC_6H_4$	H	71	H	81–82	C, H, S	0.048	76
5m	4-$(CH_3)_2NC_6H_4$	H	12	H/B	127–129	C, H, N	0.14	67
5n	4-FC_6H_4	H	56	H/B	75–77	C, H, F	0.13	76
5o	4-ClC_6H_4	H	51	H/B	97–98	C, H, Cl	0.039	66
5p	3-ClC_6H_4	H	58	H/B	75–76	C, H, Cl	0.052	67
5q	4-BrC_6H_4	H	40	B	101–103	C, H, Br	0.068	50
5r	3-BrC_6H_4	H	55	H	81–83	C, H	0.088	55
5s	3,4-$Cl_2C_6H_3$	H	54	H/B	89–90	C, H, Cl	0.18	58
5t	3-$CF_3C_6H_4$	H	52	H/B	85–87	C, H, F	0.27	67
5u	4-$(CH_3SO_2)C_6H_4$	H	exp	Bz/C	144–145	C, H, S	0.24	0
5v	4-$NO_2C_6H_4$	H	exp	H/B	91–92	C, H, N	0.048	58
5w	2-naphthyl	H	52	H	90–92	C, H	0.058	52
5x	2-thienyl	H	50	H/B	56–58	C, H	0.060	84
5y	2-furyl	H	55	H	74–76	C, H	0.037	84
5z	*N*-CH_3-2-pyrryl	H	59	H/B	86–88	C, H, N	0.14	72
5aa	*N*-CH_3-2-imidazolyl	H	52	H/B	118–120	C, H, N	3.5	9
5bb	2-pyridyl	H	23	H/B	67–68	C, H, N	0.39	56
5cc	3-pyridyl	H	51	T	172–174	C, H, N	0.23	46
5dd	4-pyridyl	H	50	B/E	159–161	C, H, N	0.14	62
5ee	C_6H_4	5-CH_3O	78	H/C	116–117	C, H	0.10	69
5ff	C_6H_4	6-CH_3O	68	H/B	91–92	C, H	1.9	76
5gg	C_6H_4	7-CH_3O	44	H/B	54–55	C, H	3.5	52
5hh	C_6H_4	6,7-$(CH_3O)_2$	73	H/B	165–167	C, H	1.7	33
5ii	C_6H_4	5,7-$(CH_3)_2$	44	T/C	101–102	C, H	0.062	44
5jj	C_6H_4	5,8-$(CH_3)_2$	44		90–92	C, H	0.12	52
5kk	C_6H_4	4-CH_3	63	H	75–77	C, H	0.020	62
22a	C_6H_4	4-C_6H_4	exp	M	132–134	C, H	0.056	26
22b	C_6H_4	4-OCH_3	exp		75–77	*g*	0.031	69
22c	C_6H_4	4-$COCH_3$	exp	M	140–141	C, H	0.51	16
22d	C_6H_4	4-COC_6H_4	exp	T	152–155	C, H	0.054	41
22e	C_6H_4	4-COOH	exp	T	205 dec	C, H	5.8	3
22f	C_6H_4	4-$COOC_2H_5$	exp	H	79–80	C, H	0.16	16
22g	C_6H_4	4-SO_2CH_3	exp	B	163–165	C, H, S	40	15
22h	C_6H_4	4-SO_2NH_2	exp	T	167–169	C, H, N, S	9.4	3
22i	C_6H_4	4-NO_2	exp	B	119 dec	C, H, N	48	28
22j	C_6H_4	4-Br	exp	C	126–128	C, H, Br	0.077	33

[a] Yields for purified products prepared by method A. exp: see Experimental Section for details. [b] B = *n*-butyl chloride; Bz = benzene; C = cyclohexane; E = ethanol; H = hexanes; M = methylcyclohexane; T = toluene. [c] Averages of two or more IC_{50} determinations; the standard errors average 11% of the values shown. [d] Dose of 100 μg/ear; averages of two or more determinations; the standard errors average 9% of the values shown. Inhibition greater than 22% is considered significant ($p < 0.05$). [e] Lit.[16] mp 73.5–74 °C. [f] Lit.[17] mp 66–67 °C. [g] HRMS: calcd 264.1150; found, 264.1150.

from the carbinol **27**[24] as outlined in Scheme III. Bromination and nitration of **37** were not regioselective, but the desired 1-substituted isomer could be isolated in each case after further transformations of **38** and **39**.

The naphthalene ring might be considered as a "core" upon which the hydroxyl and benzyl group are anchored. To examine the effects of altered arrangements of these moieties, several positional isomers were prepared. (These are also included in Table III.) 3-Benzyl-1-naphthol (**31**) was prepared from the aldehyde **40** by using straightforward transformations (Scheme IV). 3-Benzyl-2-naphthol (**33**) was prepared by the same reaction sequence from the isomeric starting material. The other positional isomers **32**[25] and **34**[26] are known compounds, as are the two phenols lacking the fused naphthalene rings, **35**[27] and **36**.[28]

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Table III. Inhibition of 5-LO, CO, and Ear Edema by Miscellaneous Compounds Related to 2-(Arylmethyl)-1-Naphthols

no.	compound[a]	RBL-1 5-LO IC_{50}, μM[b]	BSV CO IC_{50}, μM[b]	AA ear edema, % inhibition[c]
20	2-benzyl-1-methoxynaphthalene	55	(0% at 75)	5
24	2-benzyl-1-(hydroxyethoxy)naphthalene	40	(28% at 75)	12
25	2-benzyl-1-acetoxynaphthalene	0.14	240	63
26	2-benzyl-1,4-naphthoquinone[d]	0.29	(16% at 75)	59
27	phenyl 2-naphthylcarbinol[e]	40	nd	16
28	2-benzyl-1-naphthylamine hydrochloride	9.1	18	35
29	*N*-(2-benzyl-1-naphthyl)acetamide	(13% at 25)	nd	8
30	2-benzyl-1-naphthoic acid	(2% at 25)	(15% at 75)	0
31	3-benzyl-1-naphthol	0.69	2.7	28
32	4-benzyl-1-naphthol[f]	0.82	5.9	42
33	3-benzyl-2-naphthol	7.2	35	33
34	1-benzyl-2-naphthol[g]	3.9	16	23
35	2-benzylphenol[h]	63	(22% at 75)	32
36	2,6-dibenzylphenol[i]	8.8	52	21

[a] Synthesis detailed in the Experimental Section unless otherwise indicated. [b] Averages of two or more IC_{50} determinations; the standard errors average 11% of the values shown; nd = not determined. Values in parentheses are percent inhibition at the concentration shown (μM) where IC_{50} values were not determined. [c] Dose of 100 μg/ear; averages of two or more determinations; the standard errors average 9% of the values shown. Inhibition greater than 22% is considered significant ($p < 0.05$). [d] Ref 23. [e] Ref 24. [f] Ref 25. [g] Ref 26. [h] Ref 27. [i] Ref 28.

Biological Evaluation

The 5-LO-inhibitory activities of the naphthols and related compounds were evaluated by using a crude preparation of the cytosolic enzyme from the rat basophilic leukemia (RBL-1) cell line, as described by Jakschik et al.[33-35] Each test was run in duplicate, and each IC_{50} determination was performed at least twice in separate experiments. CO inhibitory activity was determined by using the bovine seminal vesicle enzyme assay,[36,37] with at least two IC_{50} determinations per compound. In both cases, the standard error of the mean of these multiple determinations averaged 11% of the IC_{50} value. A 3-fold difference in average IC_{50} values between analogues was found to be much greater than two standard errors.

The mouse arachidonic acid induced ear edema assay (AA ear) of Young et al.[38] served as a measure of topical antiinflammatory activity. (Both leukotrienes and prostaglandins are involved in the observed swelling and leukocyte influx, but 5-LO inhibitors have been reported to be better inhibitors of this model.[39,40]) Compounds were tested at least twice in separate experiments involving groups of 10 animals. The standard error of the mean for these determinations averaged 9%.

Results obtained from the enzyme and in vivo tests are given in Tables I–III. Data for several standard drugs are shown in Table IV. Indomethacin was chosen as a representative CO inhibitor; phenidone and nordihydroguaiaretic acid (NDGA) are examples of 5-LO inhibitors.

Table IV. Biological Data for Standard Drugs and Selected 1-Naphthols

compound	RBL-1 5-LO IC_{50}, μM[a]	BSV CO IC_{50}, μM[a]	AA ear edema % inhibn[b]	AA ear edema ED_{50}, μg/ear[c]
indomethacin	(47% at 25)	1.8	20	780 (50)
phenidone	0.57	(31% at 75)	58	41 (8)
NDGA	0.15	14	25	nd
lonapalene[11]	0.70	(0% at 75)	50	100 (5)
L-651,896[42]	0.25	57	52	55 (7)
4	0.056	18	91	4.4 (2)
5a	0.019	3.4	82	9.4 (3)
15	0.011	18	74	40 (10)

[a] Averages of two or more IC_{50} determinations. The standard errors average 11% of the values shown. Values in parentheses are percent inhibition at the concentration shown (μM) where IC_{50} values were not determined. [b] Dose of 100 μg/ear; averages of two or more determinations; the standard errors average 9% of the values. Inhibition greater than 22% is considered significant ($p < 0.05$). [c] Averages of two or more determinations; the value in parentheses is the standard error; nd = not determined.

Lonapalene is a selective 5-LO inhibitor which has shown clinical efficacy as an antipsoriatic agent,[11] and L-651,896 is an experimental antioxidant 5-LO inhibitor which also displays topical antiinflammatory activity.[41]

Discussion

The effects of 1-naphthol itself on enzymatic arachidonic acid oxidation have been previously reported by several workers. This antioxidant inhibited both bovine seminal vesicle CO and soybean lipoxygenase 1 in cell-free systems at concentrations of 0.4–100 μM.[43] In intact human platelets, micromolar concentrations of 1-naphthol inhibited CO while enhancing 12-lipoxygenase activity.[44] The 12-lipoxygenase from mouse epidermal cytosol was also inhibited (IC_{50} about 10 μM).[45] (Substituted naphthols have not been well investigated. Wurm et al.[46] reported that 2-alkyl-5-methoxy-1-naphthols inhibited the CO from rat renal medullary microsomes with micromolar potency, but no effects on lipoxygenases were studied.)

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As shown in Table I, we found that 1-naphthol (1) inhibits both 5-LO and CO. Substitution at the 2-position by a methyl group (2) leaves the CO potency unchanged but enhances the 5-LO activity significantly. Examination of the enzyme inhibition data in Table I shows this lack of correlation between 5-LO and CO potency to be general, suggesting that a simple antioxidant effect does not explain the activity of these compounds. In addition to the oxidation potential, other factors such as steric, electronic, or lipophilic effects probably contribute to the interaction of the inhibitors with the enzymes.

The effect of gross changes in the 2-substituent on 5-LO and antiinflammatory activity can be seen in Table I. In general, an acyl (7, 13), oxime (14), or ester group (10) at this position results in a much less active compound, both in vitro and in vivo. Variation of the substituent while maintaining high lipophilicity (compare **5a** and **9**, for instance) can lead to significant changes in potency, but good inhibitory activity is retained. An unexpected observation is the much weaker activity of the carboxylic acid **16** in light of the potency of the corresponding ethyl ester **15**. The natural substrates of 5-LO (arachidonic acid and other polyunsaturated fatty acids) are metabolized as free carboxylates, so **16** might be expected to display greater efficacy as an inhibitor. However, others have also reported that esters and other nonionized functional groups confer more potency than free carboxylic acids in various series of 5-LO inhibitors, including close analogues of substrates or products.[47-49] These findings also suggest a requirement for overall high lipophilicity in potent 5-LO inhibitors.

The quantitative correlation between 5-LO inhibition and topical antiinflammatory activity is limited, but the data indicate that 5-LO activity is required for potency in vivo. In general, the best 5-LO inhibitors (with IC_{50} values below 0.1 μM) also display the best topical antiinflammatory activity (greater than 50% inhibition at 100 μg/ear). The acrylate ester derivative **11**, which is very potent in vitro but is inactive topically, is an exception. A lack of direct correlation between in vitro and in vivo potency is not unexpected, since many additional factors such as skin penetration, differential water/lipid solubility, and modes and rates of metabolism undoubtedly affect in vivo activity.

Table IV compares the three most potent naphthols from Table I (**4**, **5a**, and **15**) with several standard drugs. Indomethacin, a selective CO inhibitor, had very limited activity in the AA ear edema assay. In contrast, the prototypic antioxidant 5-LO inhibitors phenidone and NDGA did show topical antiinflammatory effects. Lonapalene (a selective 5-LO inhibitor) and L-651,896 (a mixed inhibitor), both of which have been reported to display topical antiinflammatory activity, had ED_{50} values of 100 and 55 μg/ear, respectively. 2-Allyl-1-naphthol (**4**) and 2-benzyl-1-naphthol (**5a**), two of the most potent 5-LO inhibitory naphthols, are extremely potent antiinflammatory agents, with AA ear edema ED_{50} values below 10 μg/ear.

Although **4** was the most potent topical antiinflammatory, this naphthol is unstable toward autoxidation, decomposing significantly in a few days unless precautions are taken to exclude air. We therefore chose to examine analogues of the 2-benzyl derivative **5a** to explore the effects of structure on 5-LO inhibition and antiinflammatory activity. Compounds in which substitution on the benzyl moiety and on the naphthol ring are varied are shown in Table II.

Examination of entries **5a–dd** shows that most changes in the pendent aromatic ring affect the 5-LO inhibitory potency over a 20-fold range in a rather unpredictable manner. However, most of these compounds retain IC_{50} values well below 0.5 μM, which is usually sufficient potency for good in vivo activity. Ortho substitution seems to be slightly disfavored (**5a** > **5c** > **5g**), and less lipophilic groups are also less potent (**5u**, **5bb**, **5cc**, **5dd**). The *N*-methylimidazolyl group (**5aa**) is particularly disfavored, possibly due to the more hydrophilic nature of this ring. Electronic factors seem to be relatively unimportant; electron-rich rings have little effect on activity (compare **5a** with **5h** and **5x**), and electron-poor ones are less potent (**5s**, **5v**) but still quite active. All these trends are reflected and somewhat accentuated in the topical antiinflammatory potency, with the added constraint that extreme lipophilicity or large size (**5k**, for example) reduces activity, probably due to poor bioavailability. The wide range of substituents tolerated on the pendent ring implies that this moiety makes a relatively minor contribution to the activity, as long as it is not too hydrophilic.

Substitution on the fused (nonphenolic) ring of the naphthol reduces in vitro potency, this effect being more severe for substitution in the 6- and 7-positions of the naphthol (see entries **5ee–jj**). This may reflect a steric barrier in the enzyme. The topical activity does not correlate well with enzyme inhibition for these ring-substituted analogues.

Substitution at the 4-position of the naphthol gives interesting differences in activity. Increased polarity or hydrophilicity is detrimental to enzyme inhibition (**5a** > **22f** > **22e**), but large size is well tolerated (**22a**, **22d**). Increasing electron-withdrawing ability in 4-substituents generally reduces 5-LO inhibitory activity (**5a** > **22j** > **22c** > **22i**). This result supports the antioxidant nature of the enzyme inhibition, since electron-withdrawing substituents should increase the oxidation potential of the naphthol. (Several of these naphthols have been shown by EPR spectroscopy to reduce the iron in the active site of soybean lipoxygenase 1. The inhibition of this enzyme appears to be competitive, with the trend in K_i values paralleling the RBL-1 5-LO IC_{50} values.[50]) Notably, all 4-substituents except for small, relatively electroneutral groups (**5kk**, **22b**) reduce antiinflammatory activity, possibly due to decreased topical bioavailability.

Further support for an antioxidant mechanism comes from data for compounds in which the naphthol hydroxyl is replaced by another functional group (entries **20–30** in Table III). The reducing capability of the phenolic hydroxyl is required for both in vitro and in vivo activity; replacement by a nonphenolic hydroxyl (**24**, **27**) causes total loss of activity, as does alkylation (**20**) or replacement by another acidic (**30**) or polar (**28**, **29**) but less redox-active group. The acetate (**25**) and quinone (**26**) retain some of the activity of the parent naphthol, although the potency is reduced. (These compounds could act as prodrugs, since the acetate may undergo hydrolysis and the quinone may be reduced to the hydroquinone, either in the crude RBL-1 cell preparation or in the skin. Analogously, lonapalene and its analogues were suggested to be ester prodrugs for an active phenolic 5-LO inhibitor.[11])

Two compounds were examined in which the ortho relationship between the hydroxyl and benzyl groups was

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changed (Table III). When the benzyl group is moved from the 2-position (**5a**) to the 3- or 4-position (**31** or **32**, respectively), both 5-LO inhibition and topical activity are retained but potency is reduced. Interestingly, the CO potency is almost unchanged, suggesting that the position of the benzyl group plays a role in enzyme selectivity.

The requirement for the 1-naphthol ring system was examined by testing two 2-naphthols (**33** and **34**) and two lipophilic nonfused phenols (**35** and **36**). All are much less potent as 5-LO inhibitors and are virtually inactive as antiinflammatory agents. This might reflect either reduced enzyme binding for steric or hydrophobic reasons or differences in oxidation potential. The parallel decreases in CO inhibitory activity suggest the latter reason.

Conclusions

2-Substituted-1-naphthols are potent mixed 5-LO/CO inhibitors which show some selectivity for 5-LO inhibition in vitro and also possess interesting topical antiinflammatory activity. The biological activity appears to be due to an antioxidant mechanism, with potency and selectivity resulting from the nature and position of the substituents on the naphthol nucleus. The identity of the 2-substituent is relatively unimportant for good activity, as long as it is lipophilic and linked to the naphthol through a nonoxidized carbon atom, but arylmethyl groups at this position have the best pharmacological profile.

Compound **5a** (DuP 654) is an extremely potent 5-LO inhibitor, which also inhibits CO. It is a very potent, efficacious antiinflammatory agent when administered topically in the mouse AA ear edema model, in which it has been shown to lower the increased levels of 5-HETE in AA-challenged skin.[51] Because of this activity, and because of its potency in other skin inflammation models[12] (notably delayed-type hypersensitivity to 2,4-dinitrofluorobenzene in the mouse[40]), this compound is currently under clinical evaluation as a topical antiinflammatory drug.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Spectra were recorded for all compounds and intermediates and were consistent with assigned structures. NMR spectra were recorded with a Varian T-60 (60 MHz), a Varian Gemini 200 (200 MHz), or an IBM 200SY (200 MHz) spectrometer, using Me_4Si as an internal standard. Infrared spectra were recorded on a Beckman Acculab 8 grating spectrometer or a Perkin-Elmer 1710 FTIR spectrometer, as mineral oil mulls unless otherwise indicated. Mass spectra were recorded on a Du Pont DP-1 (EI) or a Finnigan-MAT 8230 (CI) spectrometer. Microanalyses were performed by Micro-Analysis Inc., Wilmington, DE, or by Spang Microanalytical Laboratory, Eagle Harbor, MI, and were within 0.4% of the calculated values. All organic phases were dried over anhydrous $MgSO_4$ and concentrated on a Buchi rotary evaporator at aspirator pressure. Chromatography was done by using the medium-pressure flash method.[52] [^{14}C]Arachidonic acid was obtained from Du Pont NEN Products, Boston, MA; unlabeled arachidonic acid was obtained from NuChekPrep, Eden Prairie, MN. A Packard Prias liquid scintillation counter was used to measure radioactivity of labeled enzyme reaction products and was programmed to convert cpm to dpm to account for variable quenching by solvents.

2-(1-Phenylethyl)-1-naphthol (6). Following the procedure of Shirley and Cheng,[14] 1-methoxynaphthalene (7.90 g, 50.0 mmol) in cyclohexane (20 mL) was added at room temperature to a solution of *n*-butyllithium (1.6 M; 31 mL, 50.0 mmol) and TMEDA (5.80 g, 50.0 mmol) in cyclohexane (10 mL). The mixture was stirred at room temperature for 2 h and then was treated dropwise with acetophenone (6.00 g, 50.0 mmol). After 3 h, water was added. The mixture was extracted with ether, dried, and concentrated. Chromatography (10% ethyl acetate/hexane) and trituration (petroleum ether) gave 2.50 g (18%) of 1-methoxy-2-(1-phenyl-1-hydroxyethyl)naphthalene (**48**): mp 89–91 °C; NMR (60 MHz, $CDCl_3$) δ 8.0–7.1 (11 H), 5.1 (bs, 1 H), 3.2 (s, 3 H), 2.0 (s, 3 H); IR 3500 cm^{-1} (OH); high-resolution (HR) MS ($C_{19}H_{18}O_2$) calcd 278.1307, found 278.1300. A solution of this material (2.25 g, 8.08 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C to a stirred mixture of triethylsilane (10.2 g, 87.7 mmol) and BF_3 etherate (4.04 g, 28.5 mmol) and stirred for 30 min. The solution was poured into aqueous K_2CO_3 and extracted with ether. The organic phase was dried and concentrated. Chromatography (5% ethyl acetate/hexane) gave 2.05 g (98%) of 1-methoxy-2-(1-phenylethyl)-naphthalene (**49**): mp 54–56 °C; NMR (60 MHz, $CDCl_3$) δ 8.2–7.1 (11 H), 4.85 (q, J = 7 Hz, 1 H), 3.90 (s, 3 H), 1.65 (d, J = 7 Hz, 1 H); HR MS ($C_{19}H_{18}O$) calcd 262.1358, found 262.1355. A solution of this material (1.95 g, 7.43 mmol) in CH_2Cl_2 (10 mL) was added to a −78 °C solution of BBr_3 (1.0 M in CH_2Cl_2; 10.0 mL, 10.0 mmol) in CH_2Cl_2 (75 mL). The mixture was allowed to slowly warm to room temperature and was stirred for a total of 6 h. Water was carefully added dropwise, and the mixture was extracted with ether. The organic phase was dried and concentrated. Chromatography (10% ethyl acetate/hexane) gave 1.56 g (85%) of **6**: oil; NMR (60 MHz, $CDCl_3$) δ 8.2–7.2 (11 H), 5.1 (s, 1 H), 4.45 (q, J = 7 Hz, 1 H), 1.70 (d, J = 7 Hz, 3 H); IR 3515 cm^{-1} (OH); MS (EI) m/z 248 (100%). Anal. ($C_{18}H_{16}O$) C, H.

2-Cinnamyl-1-naphthol (8). 1-(Methoxymethoxy)-naphthalene[53,54] (3.76 g, 20.0 mmol) in dry ether (40 mL) was treated dropwise at room temperature with *n*-butyllithium (1.6 M in hexane; 25.0 mL, 40.0 mmol). The mixture was stirred for 1.5 h and then was treated dropwise with phenylacetaldehyde (6.00 g, 50.0 mmol) in ether (15 mL). After 2 h, the reaction was quenched with saturated aqueous NH_4Cl, and the organic phase was dried and concentrated to give a viscous oil. This was dissolved in ethanol (100 mL), and 1 N HCl (100 mL) was added. The mixture was heated at reflux for 60 min and then was cooled and concentrated. The aqueous residue was extracted with ethyl acetate, and the organic phase was dried and concentrated. Chromatography (5% ethyl acetate/hexane) and recrystallization (hexane) gave 1.36 g (28%) of **8**: mp 155–156 °C; NMR (200 MHz, $CDCl_3$) δ 8.13 (m, 1 H), 7.80 (m, 1 H), 7.7–7.1 (11 H), 5.63 (s, 1 H); IR 3520 cm^{-1} (OH), 1560 (C=C); MS (EI) m/z 246 (100%). Anal. ($C_{18}H_{14}O$) C, H.

2-(2-Phenylethyl)-1-naphthol (9). **8** (0.75 g, 3.0 mmol) in ethanol (25 mL) was hydrogenated (48 psig) over 10% Pd/C (0.08 g) at room temperature. The mixture was filtered and concentrated to give, after recrystallization (cyclohexane/hexane), 0.55 g (74%) of **9**: mp 84–86 °C; NMR (200 MHz, $CDCl_3$) δ 8.03 (m, 1 H), 7.78 (m, 1 H), 7.42 (m, 3 H), 7.23 (m, 6 H), 4.83 (s, 1 H), 3.02 (m, 4 H); IR 3570 cm^{-1} (OH); MS (EI) m/z 248 (32%), 157 (100%). Anal. ($C_{18}H_{16}O$) C, H.

Ethyl 2-(1-Hydroxy-2-naphthyl)acrylate (11). Sodium hydride (60% in mineral oil; 0.48 g, 12.0 mmol) in dry THF (10 mL) was treated with triethyl phosphonoacetate (2.69 g, 12.0 mmol) in THF (5 mL) over 10 min, followed by stirring for 15 min more. 1-(Methoxymethoxy)-2-naphthaldehyde[15,55] (2.16 g, 10.0 mmol) in THF (5 mL) was added over 5 min. The mixture was heated at reflux for 18 h and then was cooled and quenched with 1 N HCl. The mixture was extracted with ethyl acetate, and the organic phase was dried and concentrated. Chromatography provided an oil which was heated at reflux in ethanol (25 mL) with concentrated H_2SO_4 (2 drops) for 3 h. The solution was cooled, diluted with water, and extracted with ethyl acetate. The organic phase was dried and concentrated to give, after recrystallization (CCl_4), 1.67 g (69%) of **11**: mp 157–158 °C; NMR (200 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 8.40 (d, J = 14 Hz, 1 H), 8.32 (m,

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1 H), 7.73 (m, 1 H), 7.56 (d, J = 7 Hz, 1 H), 7.46 (m, 2 H), 7.33 (d, J = 7 Hz, 1 H), 6.46 (d, J = 14 Hz, 1 H), 4.24 (q, J = 7 Hz, 2 H), 1.35 (t, J = 7 Hz, 3 H); IR 3300 (OH), 1685 (C=C), 1195 cm^{-1} (COC); MS (EI) m/z 242 (36%), 196 (100%). Anal. ($C_{15}H_{14}O_3$) C, H.

Ethyl 3-(1-Hydroxy-2-naphthyl)propionate (12). **11** (2.25 g, 9.30 mmol) was hydrogenated (50 psig) over 10% Pd/C (0.16 g) in ethanol (65 mL) at room temperature. The mixture was filtered and concentrated. Chromatography (15% ether/petroleum ether) and recrystallization (hexane) gave 1.58 g (70%) of **12**: mp 62–65 °C; NMR (200 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 8.30 (m, 1 H), 7.72 (m, 1 H), 7.42 (m, 2 H), 7.36 (d, J = 6 Hz, 1 H), 7.13 (d, J = 6 Hz, 1 H), 4.15 (q, J = 7 Hz, 2 H), 3.02 (t, J = 6 Hz, 2 H), 2.77 (t, J = 6 Hz, 2 H), 1.58 (t, J = 7 Hz, 3 H); IR 3200 (OH), 1750 cm^{-1} (C=O); MS (EI) m/z 244 (43%), 198 (100%). Anal. ($C_{15}H_{16}O_3$) C, H.

Ethyl 5-(1-Hydroxy-2-naphthyl)-5-ketovalerate (13). According to the procedure of Fawaz and Fieser,[13] glutaric acid (147 g, 1.11 mol) was melted on an oil bath at 125 °C. $ZnCl_2$ (163.8 g, 1.20 mol) and 1-naphthol (121.2 g, 0.84 mol) were added, and the mixture was stirred for 30 min. The semiliquid mass was poured into water and stirred vigorously until a powder resulted, which was collected by filtration and dissolved in 10% NaOH. The resulting slurry was filtered, and the filtrate was acidified to give a tan solid. After filtration and drying, this was recrystallized (toluene) to give 59.3 g (27%) of 5-(1-hydroxy-2-naphthyl)-5-ketovaleric acid (**50**):[56] mp 192–194.5 °C; NMR (60 MHz, DMSO-d_6) δ 14.0 (bs, 1 H), 12.5 (bs, 1 H), 8.3 (m, 1 H), 8.0–7.1 (5 H), 3.2 (t, J = 7 Hz, 2 H), 2.4 (t, J = 7 Hz, 2 H), 2.0 (q, J = 7 Hz, 2 H); IR 2700 (OH), 1730 cm^{-1} (C=O); MS (EI) m/z 258 (100%). Anal. ($C_{15}H_{14}O_4$) C, H. This ketoacid (24.77 g, 95.9 mmol) was heated at reflux in ethanol (200 mL) with concentrated H_2SO_4 (1 mL) for 16 h. The solution was cooled, diluted with water, and concentrated. The aqueous residue was extracted with ethyl acetate, and the organic phase was dried and concentrated. Recrystallization (hexane) gave 18.43 g (70%) of **13**: mp 94–96 °C; NMR (60 MHz, $CDCl_3$) 13.95 (s, 1 H), 8.40 (m, 1 H), 7.8–7.2 (5 H), 4.12 (q, J = 7 Hz, 2 H), 3.05 (t, J = 7 Hz, 2 H), 2.7–2.0 (4 H), 1.25 (t, J = 7 Hz, 3 H); IR 1745, 1640 cm^{-1} (C=O); MS (CI) m/z 287 (100%). Anal. ($C_{17}H_{18}O_4$) C, H.

Ethyl 5-(1-Hydroxy-2-naphthyl)-5-ketovalerate Oxime (14). **13** (5.00 g, 17.6 mmol), hydroxylamine hydrochloride (3.67 g, 52.8 mmol), and K_2CO_3 (3.65 g, 26.4 mmol) were heated at reflux in ethanol (170 mL) for 16 h. The cooled mixture was poured into water and the precipitate collected by filtration. Recrystallization (cyclohexane) gave 2.94 g (55%) of **14**: mp 87–88 °C; NMR (200 MHz, $CDCl_3$) δ 12.26 (s, 1 H), 8.40 (m, 1 H), 7.75 (m, 1 H), 7.6–7.1 (5 H), 4.17 (q, J = 7 Hz, 2 H), 3.05 (t, J = 7 Hz, 2 H), 2.48 (t, J = 7 Hz, 2 H), 2.05 (m, 2 H), 1.27 (t, J = 7 Hz, 3 H); IR 3310 (OH), 1705 cm^{-1} (C=O); MS (EI) m/z 301 (73%), 196 (100%). Anal. ($C_{17}H_{19}NO_4$) C, H, N.

Ethyl 5-(1-Hydroxy-2-naphthyl)valerate (15). According to the method of Fawaz and Fieser,[13] **13** (15.00 g, 52.0 mmol) was reduced with zinc amalgam (prepared from 17.0 g of Zn) in ethanol/HCl. Chromatography (10% ethyl acetate/hexane) and recrystallization (n-butyl chloride/hexane) gave 3.61 g (25%) of **15**:[56] mp 55–57 °C; NMR (200 MHz, $CDCl_3$) δ 8.13 (m, 1 H), 7.60 (m, 1 H), 7.43 (m, 2 H), 7.37 (d, J = 7 Hz, 1 H), 7.21 (d, J = 7 Hz, 1 H), 5.84 (s, 1 H), 4.13 (q, J = 7 Hz, 2 H), 2.76 (bt, 2 H), 2.37 (bt, 2 H), 1.70 (bm, 4 H), 1.23 (t, J = 7 Hz, 3 H); IR 3460 (OH), 1720 cm^{-1} (C=O); MS (CI) m/z 273 (100%). Anal. ($C_{17}H_{20}O_3$) C, H.

5-(1-Hydroxy-2-naphthyl)valeric Acid (16). **15** (2.72 g, 10.0 mmol) was boiled in 5% aqueous NaOH (50 mL) for 60 min under N_2. The cooled solution was acidified with HCl, and the precipitate was isolated by filtration to give 2.43 g (100%) of **16**: mp 112–114 °C; NMR (60 MHz, DMSO-d_6) δ 12.0 (bs, 1 H), 8.2 (m, 1 H), 7.8 (m, 1 H), 7.43 (m, 2 H), 7.35 (d, J = 8 Hz, 1 H), 7.25 (d, J = 8 Hz, 1 H), 3.3 (b, 1 H), 2.76 (bt, 2 H), 2.25 (bt, 2 H), 1.58 (m, 4 H); IR 3570 (OH), 1710 cm^{-1} (C=O); MS (CI) m/z 245 (100%). Anal. ($C_{15}H_{16}O_3$) C, H.

Method A. 2-Benzyl-1-naphthol (5a). A solution of 1-tetralone (5.85 g, 40.0 mmol) and benzaldehyde (4.25 g, 40.0 mol) in tert-butyl alcohol (400 mL) was treated with potassium tert-butoxide (8.80 g, 80.0 mmol) and heated at reflux under nitrogen for 16 h. The mixture was cooled, acidified with 1 N HCl, and concentrated to remove the tert-butyl alcohol. The aqueous residue was extracted with ethyl acetate, and the organic phase was dried and concentrated. Chromatography (10% ether/petroleum ether) and recrystallization (n-butyl chloride/hexane) gave 6.25 g (67%) of **5a**: mp 73–74 °C (lit.[16] 73.5–74 °C).

According to method A, compounds **5b–t** and **5w–kk** were prepared, as summarized in Table II. The corresponding 1-tetralones are available commercially, except for 6,7-dimethoxy-1-tetralone (used to prepare **5hh**).[57]

2-[[4-(Methylsulfonyl)phenyl]methyl]-1-naphthol (5u). According to the procedure of Corey et al.,[58] the naphthol sulfide **5l** was converted in quantitative yield to the tert-butyldimethylsilyl ether **51**, isolated as a colorless oil: NMR (60 mHz, $CDCl_3$) δ 8.4–7.0 (10 H), 4.1 (s, 2 H), 2.4 (s, 3 H), 1.1 (s, 9 H), 0.2 (s, 6 H); MS (CI) m/z 395 (100%). Anal. ($C_{24}H_{30}OSSi$) C, H, S, Si. This material (2.00 g, 5.10 mmol) was stirred with sodium perborate (1.81 g, 11.0 mmol) in acetic acid (25 mL) at room temperature for 20 h. The mixture was diluted with water, extracted with ether, dried, and concentrated. Chromatography (30% ether/petroleum ether) gave 1.38 g (63%) of the sulfone **52**: mp 108.5–109.5 °C; NMR (60 MHz, $CDCl_3$) δ 8.3–7.0 (10 H), 4.3 (s, 2 H), 3.0 (s, 3 H), 1.1 (s, 9 H), 0.2 (s, 6 H); IR 1305, 1155 cm^{-1} (SO_2); MS (EI) m/z 426 (40%), 369 (100%). Anal. ($C_{24}H_{30}O_3SSi$) C, H, S. The silyl ether was cleaved by heating at reflux in 1:1 1 N HCl/ethanol for 3 h. The solution was extracted with ethyl acetate, dried, concentrated, and recrystallized (cyclohexane/benzene) to give 0.75 g (80%) of **5u**: mp 144–145 °C; NMR (200 MHz, $CDCl_3$) δ 8.80 (s, 1 H), 8.27 (m, 1 H), 7.80 (m, 3 H), 7.6–7.1 (6 H), 4.30 (s, 2 H), 3.03 (s, 3 H); IR 3490 (OH), 1212, 1155 cm^{-1} (SO_2); MS (EI) m/z 312 (100%). Anal. ($C_{18}H_{16}O_3S$) C, H, S.

2-[(4-Nitrophenyl)methyl]-1-naphthol (5v). A mixture of 1-tetralone (10.00 g, 68.4 mmol) and 4-nitrobenzaldehyde (10.34 g, 68.4 mmol) was stirred at room temperature and treated with a solution of KOH (4.60 g, 82.1 mmol) in ethanol (200 mL). After 6 h, the mixture was poured into water, and the isolated solid was recrystallized (ethanol) to give 16.89 g (89%) of **19v** (X = H, Ar = 4-nitrophenyl): mp 187–189 °C; NMR (200 MHz, $CDCl_3$) δ 8.4–8.1 (3 H), 7.88 (s, 1 H), 7.7–7.2 (5 H), 3.2–2.9 (4 H); IR 1680 cm^{-1} (C=O); MS (CI) m/z 280 (100%). Anal. ($C_{17}H_{13}NO_3$) C, H, N. This material (2.00 g, 7.16 mmol) and rhodium trichloride trihydrate (0.19 g, 0.7 mmol) was heated at reflux in ethanol (200 mL) for 24 h. After concentration, the residue was partitioned between water and ethyl acetate, and the organic phase was dried and concentrated. Chromatography (10% ether/petroleum ether) and recrystallization (n-butyl chloride/hexane) gave 1.05 g (53%) of **5v**: NMR (200 MHz, $CDCl_3$) δ 8.15 (d, J = 7 Hz, 2 H), 7.96 (m, 1 H), 7.83 (m, 1 H), 7.55–7.30 (5 H), 7.23 (d, J = 7 Hz, 1 H), 5.22 (s, 1 H), 4.25 (s, 2 H); IR 3544 cm^{-1} (OH); MS (CI) m/z 280 (100%). Anal. ($C_{17}H_{13}NO_3$) C, H, N.

1-Methoxy-2-benzylnaphthalene (20). **5a** (10.00 g, 43.0 mmol), CH_3I (9.08 g, 64.0 mmol), and K_2CO_3 (8.85 g, 64.0 mmol) were stirred in refluxing acetone for 18 h. The cooled suspension was filtered, and the filtrate was diluted with CH_2Cl_2 and washed with water. After drying and concentration, the resulting oil was distilled on a Kugelrohr apparatus (150–175 °C, 0.3 Torr) to provide a solid. Recrystallization (hexane) gave 7.80 g (73%) of **20**: mp 57–59 °C (lit.[19] mp 50–52 °C); NMR (200 MHz, $CDCl_3$) δ 8.12 (d, J = 7 Hz, 1 H), 7.82 (d, J = 7 Hz, 1 H), 7.6–7.3 (3 H), 7.25 (6 H), 4.20 (s, 2 H), 3.88 (s, 3 H); IR (neat film) 1258 cm^{-1} (COC); MS (EI) m/z 248 (100%). Anal. ($C_{18}H_{16}O$) C, H.

1-Methoxy-2-benzyl-4-bromonaphthalene (21). A solution of **20** (8.48 g, 34.0 mmol) in acetic acid (220 mL) was treated dropwise at room temperature with a solution of Br_2 (5.45 g, 34.0 mmol) in acetic acid (50 mL). The solution was poured into water, extracted with CH_2Cl_2, dried, and concentrated. Kugelrohr

(56) This compound was reported, with no characterization, by Xi, G.; Guo, X.; Chen, R. *Yao Hsueh Hsueh Pao* **1980**, *15*, 548; *Chem. Abstr.* **1981**, *94*, 191985y.

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distillation of the residue (190–200 °C, 0.3 Torr) gave 10.97 g (99%) of **21**: mp 57–59 °C; NMR (200 MHz, $CDCl_3$) δ 8.10 (m, 2 H), 7.53 (m, 3 H), 7.20 (m, 5 H), 4.10 (s, 2 H), 3.85 (s, 3 H); IR (neat film) 1265 cm^{-1} (COC); MS (EI) *m/z* 328 (75%), 326 (89%). Anal. ($C_{18}H_{15}BrO$) C, H, Br.

1-Methoxy-2-benzyl-4-phenylnaphthalene (23a). A solution of **21** (5.00 g, 15.3 mmol) and [1,3-bis(diphenylphosphino)-propane]nickel(II) chloride (0.40 g, 0.74 mmol) in dry ether (50 mL) was treated dropwise at 0 °C with phenylmagnesium chloride (2.0 M solution in THF; 9.50 mL, 19.0 mmol). The mixture was stirred for 2 h at room temperature, quenched with 1 N HCl, and extracted with CH_2Cl_2. The organic phase was dried and concentrated, and the residue was chromatographed (10% CH_2Cl_2/hexane) to give 4.26 g (86%) of **23a**: mp 103–105 °C (hexane); NMR (200 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7 Hz, 1 H), 7.85 (d, *J* = 7 Hz, 1 H), 7.51 (m, 1 H), 7.40 (m, 6 H), 7.22 (m, 6 H), 4.21 (s, 2 H), 3.92 (s, 3 H); IR 1260 cm^{-1} (COC); MS (EI) *m/z* 324 (100%). Anal. ($C_{24}H_{20}O$) C, H.

Method B. 4-Phenyl-2-benzyl-1-naphthol (22a). A solution of **23a** (3.00 g, 9.24 mmol) in CH_2Cl_2 (90 mL) was stirred at −78 °C and treated dropwise with BBr_3 (1.0 M solution in CH_2Cl_2; 27.7 mL, 27.7 mmol). The mixture was allowed to warm to room temperature and stirred for 18 h. HCl (1 N) was carefully added, and the mixture was extracted with additional CH_2Cl_2. The organic phase was dried and concentrated, and the residue was recrystallized from methylcyclohexane to give 2.1 g (73%) of **22a**: mp 132–134 °C; NMR (200 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8 Hz, 1 H), 7.83 (d, *J* = 8 Hz, 1 H), 7.43 (m, 7 H), 7.25 (m, 6 H), 5.13 (s, 1 H), 4.17 (s, 2 H); IR 3500 cm^{-1} (OH); MS (EI) *m/z* 310 (100%). Anal. ($C_{23}H_{18}O$) C, H.

4-Methoxy-2-benzyl-1-naphthol (22b). $AlCl_3$ (3.50 g, 26.2 mmol) was added to a solution of 4-methoxy-1-naphthol (5.00 g, 28.7 mmol) and benzoyl chloride (5.00 g, 35.6 mmol) in CH_2Cl_2 (200 mL) at room temperature. The mixture was stirred for 18 h and poured into water. It was extracted with ether, and the organic phase was dried and concentrated. Chromatography (10% ethyl acetate/hexane) gave 1.71 g (22%) of 4-methoxy-2-benzoyl-1-naphthol (**53**): mp 109–112 °C; NMR (60 MHz, $CDCl_3$) δ 13.6 (s, 1 H), 8.5–6.7 (10 H), 3.8 (s, 3 H); IR (1631 cm^{-1} (C=O); MS (EI) *m/z* 278 (100%). Anal. ($C_{18}H_{14}O_3$) C, H. This material (1.50 g, 5.4 mmol) was reduced with zinc amalgam (prepared from 3.8 g of Zn) in methanol/HCl according to the method of Fawaz and Fieser.[13] Chromatography (30% ethyl acetate/hexane) gave 0.22 g (15%) of **22b**: mp 75–77 °C; NMR (200 MHz, $CDCl_3$) δ 8.3–7.0 (m, 9 H), 6.6 (s, 1 H), 4.7 (s, 1 H), 4.1 (s, 2 H), 3.9 (s, 3 H); IR 3370 cm^{-1} (OH); MS (CI) *m/z* 265 (100%); HR MS ($C_{18}H_{16}O_2$) calcd 264.1150, found 264.1150.

4-Acetyl-2-benzyl-1-naphthol (22c). Acetyl chloride (11.78 g, 0.150 mol) was added dropwise to a suspension of $AlCl_3$ (20.08 g, 0.150 mol) in CH_2Cl_2 (200 mL) at 0 °C. The mixture was stirred for 10 min and then treated dropwise with a solution of **5a** (12.00 g, 0.051 mol) in CH_2Cl_2 (60 mL). After 4 h at 0 °C and 18 h at room temperature, the mixture was treated with 1 N HCl and extracted with CH_2Cl_2, and the extracts were dried and concentrated. Chromatography (10% ethyl acetate/toluene) gave a white solid, which was boiled in ethanol (150 mL) with H_2SO_4 (1 mL) for 40 min. The solution was cooled and poured into water, and the isolated solid was recrystallized (toluene) to give 1.40 g (10%) of **22c**: mp 139–140.5 °C; NMR (200 MHz, $CDCl_3$) δ 8.96 (m, 1 H), 8.18 (m, 1 H), 7.84 (s, 1 H), 7.52 (m, 2 H), 7.25 (m, 5 H), 6.23 (s, 1 H), 4.20 (s, 2 H), 2.66 (s, 3 H); IR 3300 (OH), 1645 cm^{-1} (C=O); MS (EI) *m/z* 276 (83%), 261 (100%). Anal. ($C_{19}H_{16}O_2$) C, H.

Using the same method, **4-benzoyl-2-benzyl-1-naphthol (22d)** was prepared from **5a** and benzoyl chloride in 40% yield: mp 152–155 °C (toluene); NMR (200 MHz, $CDCl_3$) δ 8.30 (m, 1 H), 8.20 (m, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.50 (m, 6 H), 7.25 (m, 5 H), 5.73 (s, 1 H), 4.14 (s, 2 H); IR 3220 (OH), 1640 cm^{-1} (C=O); MS (EI) *m/z* 338 (100%). Anal. ($C_{24}H_{18}O_2$) C, H.

1-Methoxy-2-benzyl-4-naphthoic acid (23e). A solution of **21** (5.00 g, 15.3 mmol) in THF (50 mL) was cooled to −78 °C and treated dropwise with *n*-butyllithium (1.55 M in hexane; 10.9 mL, 16.9 mmol). The mixture was stirred for 60 min at −78 °C, and then CO_2(g) was blown onto the surface of the solution at this temperature for 10 min. The solution was warmed to room temperature, poured into 1 N HCl, and extracted with CH_2Cl_2. After the solution was dried and concentrated, the residue was recrystallized (methylcyclohexane) to give 4.00 g (90%) of **23e**: mp 146–148 °C; NMR (200 MHz, $CDCl_3$) δ 9.18 (d, *J* = 7 Hz, 1 H), 8.26 (s, 1 H), 8.20 (d, *J* = 7 Hz, 1 H), 7.60 (m, 2 H), 7.24 (m, 5 H), 4.23 (s, 2 H), 3.91 (s, 3 H); IR 3200–2600 (OH), 1700 cm^{-1} (C=O); MS (EI) *m/z* 292 (100%). Anal. ($C_{19}H_{16}O_3$) C, H.

1-Hydroxy-2-benzyl-4-naphthoic Acid (22e). According to method B, **23e** was converted into **22e** in 68% yield: mp 203–206 °C dec; NMR (200 MHz, DMSO-d_6) δ 9.15 (bs, 1 H), 9.09 (d, *J* = 7 Hz, 1 H), 8.39 (d, *J* = 7 Hz, 1 H), 8.16 (s, 1 H), 7.50 (m, 2 H), 7.41 (s, 1 H), 7.23 (m, 5 H), 4.22 (s, 2 H); IR 3400 (OH), 3200–2600 (COOH), 1580 cm^{-1} (C=O); MS (EI) *m/z* 278 (100%). Anal. ($C_{18}H_{14}O_3$) C, H.

Ethyl 1-Hydroxy-2-benzyl-4-naphthoate (22f). 22e (2.55 g, 9.20 mmol) was heated at reflux for 3 days in ethanol (125 mL) containing 3 drops of concentrated H_2SO_4. The cooled solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with $NaHCO_3$ and water and then was dried and concentrated. Chromatography (10% ethyl acetate/hexane) and recrystallization (hexane) gave 1.74 g (62%) of **22f**: mp 79–80 °C; NMR (200 MHz, $CDCl_3$) δ 9.00 (d, *J* = 7 Hz, 1 H), 8.16 (d, *J* = 7 Hz, 1 H), 8.13 (s, 1 H), 7.52 (m, 2 H), 7.25 (m, 5 H), 5.67 (s, 1 H), 4.43 (q, *J* = 6 Hz, 2 H), 4.18 (s, 2 H), 1.43 (t, *J* = 6 Hz, 3 H); IR 3400 (OH), 1680 (C=O), 1220, 1190 cm^{-1} (COC); MS (EI) *m/z* 306 (100%). Anal. ($C_{20}H_{18}O_3$) C, H.

1-Methoxy-2-benzyl-4-(methylsulfonyl)naphthalene (23g). A solution of **21** (2.00 g, 6.11 mmol) in dry THF (50 mL) was cooled to −78 °C and treated with *n*-butyllithium (1.55 M in hexane; 4.35 mL, 6.74 mmol) over 5 min. After stirring for 20 min at −78 °C, the lithio derivative was treated with methyl disulfide (0.86 g, 9.17 mmol) and the solution was stirred for an additional 30 min. It was poured into water and extracted with CH_2Cl_2. The extract was dried and concentrated, and the sulfide **54** thus obtained was used without further purification: NMR (200 MHz, $CDCl_3$) δ 8.27 (m, 1 H), 8.13 (m, 1 H), 7.53 (m, 2 H), 7.21 (m, 6 H), 4.18 (s, 2 H), 3.86 (s, 3 H), 2.43 (s, 3 H); MS (EI) *m/z* 294 (100%). Anal. ($C_{19}H_{18}OS$) C, H, S. The residue was dissolved in CH_2Cl_2 (25 mL) and treated dropwise with *m*-chloroperoxybenzoic acid (80%; 3.06 g, 14.2 mmol) in CH_2Cl_2 (25 mL) at room temperature. After 15 min, the mixture was filtered, and the filtrate was washed with $NaHCO_3$ and NaCl, dried, and concentrated. Chromatography (50% ethyl acetate/hexane) and recrystallization (*n*-butyl chloride) gave 1.19 g (57%) of **23g**: mp 124.5–126 °C; NMR (200 MHz, $CDCl_3$) δ 8.66 (m, 1 H), 8.23 (m, 1 H), 8.18 (s, 1 H), 7.65 (m, 2 H), 7.23 (m, 5 H), 4.21 (s, 2 H), 3.90 (s, 3 H), 3.16 (s, 3 H); MS (EI) *m/z* 326 (100%). Anal. ($C_{19}H_{18}O_3S$) C, H, S.

4-(Methylsulfonyl)-2-benzyl-1-naphthol (22g). According to method B, **23g** was converted into **22g** in 71% yield: mp 163–164.5 °C (*n*-butyl chloride); NMR (200 MHz, $CDCl_3$) δ 8.63 (m, 1 H), 8.27 (m, 1 H), 8.21 (s, 1 H), 7.64 (m, 2 H), 7.4–7.2 (m, 5 H), 5.87 (s, 1 H), 4.22 (s, 2 H), 3.20 (s, 3 H); IR 3362 (OH), 1381, 1288, 1129 cm^{-1} (SO_2); MS (EI) *m/z* 312 (100%). Anal. ($C_{18}H_{16}O_3S$) C, H, S.

1-Methoxy-2-benzyl-4-naphthalenesulfonamide (23h). 20 (3.00 g, 12.1 mmol) was added in portions to concentrated sulfuric acid (10 mL) at −10 °C. The resulting solution was stirred for 1.5 h, poured into ice–water, and extracted with ethyl acetate. The extract was dried, silica gel (100 g) was added, and the solvent was removed. The solid was eluted with 50% ethyl acetate/hexane (to remove remaining **20**), and then with methanol. The methanol eluent was concentrated, and the residue was boiled with thionyl chloride (10 mL) for 1 h. Concentration provided a brown oil, which was dissolved in THF and added dropwise to concentrated NH_4OH (125 mL) at 10 °C. After 10 min, the mixture was acidified with HCl and extracted with ethyl acetate. Drying and concentration of the extract provided a glass, which was chromatographed (50% ethyl acetate/hexane) and recrystallized (*n*-butyl chloride) to give 1.00 g (25%) of **23h**: mp 159–161 °C; NMR (200 MHz, $CDCl_3$) δ 8.55 (m, 1 H), 8.22 (m, 1 H), 8.13 (s, 1 H), 7.65 (m, 2 H), 7.23 (5 H), 4.92 (s, 2 H), 4.20 (s, 2 H), 3.92 (s, 3 H); IR 3323, 3237 (NH), 1326, 1140 cm^{-1} (SO_2); MS (EI) *m/z* 327 (100%). Anal. ($C_{18}H_{17}NO_3S$) C, H, N, S.

1-Hydroxy-2-benzyl-4-naphthalenesulfonamide (22h). According to method B, **23h** was converted in 55% yield (after chromatography) to **22h**: mp 167–168 °C (toluene); NMR (200

MHz, DMSO-d_6) δ 10.2 (bs, 1 H), 8.50 (m, 1 H), 8.37 (m, 1 H), 7.90 (s, 1 H), 7.60 (m, 2 H), 7.42 (s, 2 H), 7.24 (5 H), 4.18 (s, 2 H); IR 3446, 3392, 3272 (OH, NH), 1313, 1140 cm^{-1} (SO_2); MS (EI) m/z 313 (100%). Anal. ($C_{17}H_{15}NO_3S$) C, H, N, S.

1-Methoxy-2-benzyl-4-nitronaphthalene (23i). A solution of **20** (21.0 g, 85.0 mmol) in acetic acid (200 mL) was treated at room temperature over 5 min with fuming HNO_3 (42 mL) and then was stirred for 2 h and poured into water. The precipitate was isolated and chromatographed (5% ethyl acetate/hexane) to give 14.7 g (59%) of **23i**: mp 76–78 °C (hexane); NMR (200 MHz, $CDCl_3$) δ 8.60 (dd, J = 7, 2 Hz, 1 H), 8.21 (dd, J = 7, 2 Hz, 1 H), 8.10 (s, 1 H), 7.65 (m, 2 H), 7.25 (m, 5 H), 4.22 (s, 2 H), 3.93 (s, 3 H); IR 1530 (NO_2), 1350 cm^{-1} (COC); MS (EI) m/z 293 (100%). Anal. ($C_{18}H_{15}NO_3$) C, H, N.

4-Nitro-2-benzyl-1-naphthol (22i). A mixture of **23i** (1.00 g, 3.40 mmol) and pyridine hydrochloride (3.94 g, 34.0 mmol) was heated at 210 °C for 5 min. The cooled mass was partitioned between 0.5 N HCl and CH_2Cl_2, and the organic phase was dried and concentrated. Chromatography (30% ethyl acetate/hexane) and recrystallization (*n*-butyl chloride) gave 0.58 g (61%) of **22i**: mp 119 °C dec; NMR (200 MHz, $CDCl_3$) δ 8.78 (d, J = 9 Hz, 1 H), 8.33 (s, 1 H), 8.24 (d, J = 9 Hz, 1 H), 7.66 (m, 2 H), 7.30 (m, 5 H), 6.00 (s, 1 H), 4.20 (s, 2 H); IR 3440 (OH), 1460 cm^{-1} (NO_2); MS (CI) m/z 280 (100%). Anal. ($C_{17}H_{13}NO_3$) C, H, N.

4-Bromo-2-(phenylmethyl)-1-naphthol (22j). A solution of **20** (1.00 g, 4.27 mmol) in acetic acid (20 mL) was treated dropwise at room temperature with Br_2 (0.68 g, 4.27 mmol) in acetic acid (6 mL). The solution was stirred for 5 min and then poured into water. The precipitate was collected and dried to give, after recrystallization (cyclohexane), 1.21 g (88%) of **22j**: mp 123–125 °C; NMR (200 MHz, $CDCl_3$) δ 8.14 (m, 1 H), 7.61 (s, 1 H), 7.55 (m, 2 H), 7.26 (m, 6 H), 5.13 (s, 1 H), 4.13 (s, 2 H); IR 3440 cm^{-1} (OH); MS (EI) m/z 314 (99%), 312 (100%). Anal. ($C_{17}H_{13}BrO$) C, H, Br.

2-[(2-Benzyl-1-naphthyl)oxy]ethanol (24). A mixture of **5a** (2.00 g, 8.54 mmol), 2-bromoethanol (4.27 g, 34.2 mmol), K_2CO_3 (4.72 g, 34.2 mmol), and acetone (25 mL) was heated at reflux for 18 h. The cooled mixture was filtered and concentrated. Chromatography (3% ethyl acetate/toluene) and trituration (hexane) gave 1.96 g (82%) of **24**: mp 65–68 °C; NMR (200 MHz, $CDCl_3$) δ 8.16 (d, J = 7 Hz, 1 H), 7.83 (d, J = 7 Hz, 1 H), 7.6–7.4 (m, 3 H), 7.23 (m, 6 H), 4.23 (s, 2 H), 4.07 (m, 4 H), 2.30 (bs, 1 H); IR 3550, 3350 cm^{-1} (OH); MS (EI) m/z 278 (100%). Anal. ($C_{19}H_{18}O_2$) C, H.

2-Benzyl-1-acetoxynaphthalene (25). A solution of **5a** (5.00 g, 21.0 mmol) and acetic anhydride (3.25 g, 31.8 mmol) in pyridine (50 mL) was stirred at room temperature for 18 h. It was diluted with water and extracted with ether, and the extracts were washed with 1 N HCl until the washes were acidic. Drying and concentration gave a light yellow liquid, which was chromatographed (5% ethyl acetate/hexane) to give a colorless solid. Recrystallization (hexane) gave 4.75 g (82%) of **25**: mp 67–69 °C; NMR (200 MHz, $CDCl_3$) δ 7.9–7.6 (3 H), 7.45 (m, 2 H), 7.20 (6 H), 4.01 (s, 2 H), 2.40 (s, 3 H); IR 1760 cm^{-1} (C=O); MS (EI) m/z 276 (9%), 234 (100%). Anal. ($C_{19}H_{16}O_2$) C, H.

2-Benzylnaphthalene (37). A solution of **27**[24] (48.8 g, 0.208 mol) in CH_2Cl_2 (500 mL) at 0 °C was treated with triethylsilane (72.6 g, 0.624 mol), then with BF_3 etherate (100 mL, 0.611 mol), and stirred for 15 min. The solution was poured into ice-cold aqueous $NaHCO_3$ and extracted with ether. The organic phase was washed with $NaHCO_3$ and NaCl, dried, and concentrated. The residual oil was distilled in a Kugelrohr apparatus (135–137 °C, 0.25 Torr) to give 44.1 g (97%) of **37**: mp 53–55 °C; NMR (200 MHz, $CDCl_3$) δ 7.80 (m, 3 H), 7.65 (s, 1 H), 7.46 (m, 2 H), 7.4–7.2 (6 H), 4.16 (s, 2 H); MS (EI) m/z 218 (100%). Anal. ($C_{17}H_{14}$) C, H.

2-Benzyl-1-naphthylamine Hydrochloride (28). A solution of **37** (15.00 g, 59.8 mmol) in acetic acid (100 mL) at 15 °C was treated dropwise with a solution of fuming nitric acid (3.54 mL, 77.7 mmol) in acetic acid (10 mL). The solution was stirred at room temperature for 6 h and then was treated with additional fuming nitric acid (2.0 mL). It was warmed to 60 °C for 2 h and then stirred at room temperature for 18 h. The mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with $NaHCO_3$, water, and NaCl and then was dried and concentrated to give an oily mixture of nitro compounds (18.4 g). Without purification, this material was mixed with iron filings (8.5 g), acetic acid (25 mL), and ethanol (100 mL) and was heated at reflux for 24 h. The solvents were removed under vacuum, and the residue was dissolved in ethyl acetate and water. The aqueous phase was made basic with sodium carbonate and extracted with ethyl acetate. The organic layers were dried and concentrated. Chromatography (25% ethyl acetate/hexane) provided a brown oily solid, which was dissolved in ether and treated with HCl/ether. The precipitate was recrystallized (ethanol/hexane) to give 1.98 g (13%) of **28**: mp 208–210 °C dec; NMR (200 MHz, DMSO-d_6) δ 8.30 (b, 3 H), 8.24 (d, J = 8 Hz, 1 H), 7.92 (d, J = 8 Hz, 1 H), 7.70 (d, J = 8 Hz, 1 H), 7.59 (t, J = 8 Hz, 2 H), 7.3 (m, 6 H), 4.32 (s, 2 H); IR 2900 cm^{-1} (NH_3^+); MS (CI) m/z 233 (100%). Anal. ($C_{17}H_{15}N\cdot HCl$) C, H, Cl, N.

***N*-(2-Benzyl-1-naphthyl)acetamide (29).** A solution of **28** (0.80 g, 3.0 mmol) in triethylamine (20 mL) was treated dropwise at 0 °C with acetic anhydride (5 mL). After 3 h, additional acetic anhydride (5 mL) was added, and the reaction was stirred at room temperature for 18 h. The mixture was concentrated and the residue was diluted with ethyl acetate, washed with 1 N HCl, water, and NaCl, dried, and concentrated. Recrystallization (ethanol) gave 0.24 g (29%) of **29**: mp 196–197 °C; NMR (200 MHz, DMSO-d_6) δ 9.83 (s, 1 H), 7.90 (m, 2 H), 7.80 (d, J = 8 Hz, 1 H), 7.51 (m, 2 H), 7.4–7.1 (6 H), 4.08 (s, 2 H), 2.23 (s, 3 H); IR 3279 (NH), 1646 cm^{-1} (C=O); MS (EI) m/z 275 (100%). Anal. ($C_{19}H_{17}NO$) C, H, N.

2-Benzyl-1-naphthoic Acid (30). A solution of **37** (10.00 g, 42.7 mmol) in acetic acid (70 mL) was treated at room temperature with a solution of Br_2 in acetic acid (0.60 M; 75 mL, 45 mmol) and heated at 60 °C for 6 h. The solution was concentrated, and the residue was dissolved in ethyl acetate, washed with $NaHCO_3$, Na_2SO_3, and NaCl, dried, and concentrated to provide a yellow oil (13.0 g), used without further purification. This mixture of bromo derivatives (6.00 g, nominally 20 mmol) was converted to a mixture of isomeric carboxylic acids by the procedure used to prepare **23e**. Chromatography (33% ethyl acetate/hexane + 1% acetic acid) and recrystallization (heptane) gave 0.83 g (16%) of **30**: mp 133–136 °C; NMR (200 MHz, $CDCl_3$) δ 8.13 (d, J = 7 Hz, 1 H), 7.87 (d, J = 8 Hz, 2 H), 7.56 (m, 2 H), 7.28 (6 H), 4.35 (s, 2 H); IR 3200–2400 (OH), 1681 cm^{-1} (C=O); MS (EI) m/z 262 (100%). Anal. ($C_{18}H_{14}O_2$) C, H.

1-Methoxy-3-naphthaldehyde (40). 1-Methoxy-3-(hydroxymethyl)naphthalene[59] (7.40 g, 40.0 mmol) and pyridinium chlorochromate (21.40 g, 99.0 mmol) were stirred in CH_2Cl_2 (265 mL) for 3 h at room temperature. The mixture was filtered through Florisil, and the effluent was concentrated. Recrystallization (hexane) gave 5.33 g (72%) of **40**: mp 67–69 °C; NMR (200 MHz, $CDCl_3$) δ 10.08 (s, 1 H), 8.32 (m, 1 H), 7.94 (m, 2 H), 7.63 (m, 2 H), 7.28 (s, 1 H), 4.06 (s, 3 H); IR 1695 cm^{-1} (C=O); MS (EI) m/z 186 (100%). Anal. ($C_{12}H_{10}O_2$) C, H.

Using the same method, **2-methoxy-3-naphthaldehyde (45)** was prepared from the corresponding carbinol **43** (made from the commercially available 2-hydroxy-3-naphthoic acid, via the ether–ester **44**, by the procedures of ref 58) in 76% yield: mp 89–91 °C; NMR (200 MHz, $CDCl_3$) δ 10.58 (s, 1 H), 8.33 (s, 1 H), 7.87 (d, J = 8 Hz, 1 H), 7.73 (d, J = 8 Hz, 1 H), 7.53 (t, J = 8 Hz, 1 H), 7.37 (t, J = 8 Hz, 1 H), 7.16 (s, 1 H), 3.98 (s, 3 H); IR 1700 cm^{-1} (C=O); MS (EI) m/z 186 (100%). Anal. ($C_{12}H_{10}O_2$) C, H.

Phenyl(1-methoxy-3-naphthyl)carbinol (41). A solution of phenylmagnesium chloride (2.0 M in THF; 14.5 mL, 29.0 mmol) and ether (45 mL) was stirred at 0 °C and treated dropwise with a solution of **40** (4.50 g, 24.0 mmol) in ether (45 mL). After 15 min, the reaction was quenched with saturated NH_4Cl. The ether layer was removed, dried, and concentrated. Chromatography (5% ethyl acetate/toluene) and recrystallization (hexane) gave 5.80 g (91%) of **41**: mp 92–94.5 °C; NMR (200 MHz, $CDCl_3$) δ 8.20 (m, 1 H), 7.73 (m, 1 H), 7.5–7.3 (8 H), 6.74 (s, 1 H), 5.90 (bs, 1 H), 3.90 (s, 3 H), 2.46 (d, J = 3 Hz, 1 H); IR 3410 cm^{-1} (OH); MS (EI) m/z 264 (100%). Anal. ($C_{18}H_{16}O_2$) C, H.

Using the same method, **45** was converted to **phenyl(2-methoxy-3-naphthyl)carbinol (46)** in 87% yield: mp 81–83.5 °C; NMR (200 MHz, $CDCl_3$) δ 7.72 (m, 3 H), 7.5–7.2 (7 H), 7.12

(59) Horii, Z.; Matsumoto, Y.; Momose, T. *Chem. Pharm. Bull.* **1971**, *19*, 1215.

(s, 1 H), 6.13 (d, J = 6 Hz, 1 H), 3.85 (s, 3 H), 3.16 (d, J = 6 Hz, 1 H); IR 3420 cm^{-1} (OH); MS (EI) m/z 264 (100%). Anal. ($C_{18}H_{16}O_2$) C, H.

3-Benzyl-1-methoxynaphthalene (42). A solution of **41** (5.75 g, 22.0 mmol) and triethylsilane (3.31 g, 28.5 mmol) in CH_2Cl_2 (70 mL) was stirred at 0 °C and treated dropwise with BF_3 etherate (9.41 g, 66.3 mmol). The mixture was stirred at 0 °C for 2 h, and then at room temperature overnight. The mixture was then diluted with water and extracted with CH_2Cl_2. The organic phase was dried and concentrated to give 5.4 g (98%) of **42**: mp 43–45 °C; NMR (200 MHz, $CDCl_3$) δ 8.20 (m, 1 H), 7.71 (m, 1 H), 7.43 (m, 2 H), 7.25 (m, 6 H), 6.62 (s, 1 H), 4.10 (s, 2 H), 3.92 (s, 3 H); IR 1232, 1278 cm^{-1} (COC); MS (EI) m/z 248 (100%). Anal. ($C_{18}H_{16}O$) C, H.

Likewise, **46** was converted into **3-benzyl-2-methoxynaphthalene (47)** in quantitative yield: oil; NMR (200 MHz, $CDCl_3$) δ 7.68 (t, J = 8 Hz, 2 H), 7.48 (s, 1 H), 7.4–7.2 (7 H), 7.10 (s, 1 H), 4.12 (s, 2 H), 3.88 (s, 3 H); IR 1255 cm^{-1} (COC); MS (EI) m/z 248 (100%). Anal. ($C_{18}H_{16}O$) C, H.

3-Benzyl-1-naphthol (31). According to method B, **42** was converted to **31** in 57% yield: mp 68–69 °C (hexane); NMR (200 MHz, $CDCl_3$) δ 8.08 (m, 1 H), 7.73 (m, 1 H), 7.43 (m, 2 H), 7.25 (m, 6 H), 6.54 (s, 1 H), 5.15 (s, 1 H), 4.03 (s, 2 H); IR 3330 cm^{-1} (OH); MS (EI) m/z 234 (100%). Anal. ($C_{17}H_{14}O$) C, H.

3-Benzyl-2-naphthol (33). According to method B, **46** was converted to **33** in 73% yield. Alternatively, condensation of 2-tetralone with benzaldehyde, according to method A, provided **33** in 58% yield: mp 90–92 °C (hexane); NMR (200 MHz, $CDCl_3$) δ 7.70 (m, 2 H), 7.60 (s, 1 H), 7.30 (m, 7 H), 7.10 (s, 1 H), 4.93 (s, 1 H), 4.17 (s, 2 H); IR 3530 cm^{-1} (OH); MS (EI) m/z 234 (100%). Anal. ($C_{17}H_{14}O$) C, H.

RBL-1 5-Lipoxygenase Assay. The procedure of Jakschik et al. was used.[33-35] The enzyme was prepared as a 10000g supernatant from homogenized RBL-1 cells. Because of variability in the enzyme content from culture to culture, an amount of supernatant was chosen to give a net production of 3300–3800 dpm of 5-HETE under the assay conditions (total cell protein 9–20 μg/assay). All reactions were run in duplicate. In a total volume of 100 μL, the appropriate amount of enzyme was incubated with test compound (prepared in 5% DMSO, 95% 0.2 M Tris, pH 8.5) in a phosphate buffer (45 mM sodium phosphate, 0.83 mM EDTA, 0.083% gelatin, 0.1 mM glutathione, 0.83 mM calcium chloride, 0.012 mM indomethacin) at pH 7.0 and 37 °C for 5 min. The reaction was initiated by the addition of 20 μL of a solution of arachidonic acid in phosphate buffer. The final concentration of substrate in the assay solution was 0.042 mM, including 0.167 μCi of [^{14}C]arachidonic acid (specific activity 50 mCi/mmol). The reaction was terminated after 2 min by freezing in CO_2/ethanol. 5-LO products were separated from unreacted arachidonic acid on silica gel columns with hexane/ethyl acetate/acetic acid (82:17:1). 5-HETE was eluted with hexane/THF/ethyl acetate/acetic acid (65:30:10:1). Remaining products were eluted with methanol/water/acetic acid (70:30:1). Activity was measured as the total radioactivity in the 5-LO products, and inhibition was calculated as $(1 - D/C) \times 100\%$, where D is the activity in the presence of the test compound and C is the control activity. IC_{50} values were calculated by linear regression analysis using three concentrations of drug, spanning the 50% inhibition point.

Bovine Seminal Vesicle CO Assay. The method of White and Glassman[36] as modified by Vigdahl and Tukey[37] was used. All reactions were run in duplicate. Solutions of the enzyme (40 μg in 10 μL of 0.25 M sucrose, 0.005 M KH_2PO_4, pH 7.4), buffer (20 μL; 0.2 M Tris, pH 8.5), and cofactor mixture (25 μL; 8.5 mM glutathione, 2.5 mM epinephrine, 0.35 mM EDTA) were mixed and cooled on ice. The test compound (in DMSO, diluted to 25 μL with 0.2 M Tris buffer, pH 8.5) was added, and the mixture was incubated at 37 °C for 2 min. [^{14}C]Arachidonic acid (25 μL, 0.2 μCi/mL in 0.1 mM sodium arachidonate) was added, and the reaction was incubated for 10 min. The reaction was stopped by freezing (CO_2/ethanol). The mixture was separated on silica gel columns, using hexane/THF/acetic acid (70:30:1) to remove unreacted arachidonate. The prostaglandin products were eluted with ethyl acetate/ethanol (85:15). IC_{50} values were determined as described for the 5-LO assay.

Arachidonic Acid Induced Ear Edema Assay. The procedure of Young et al.[38] was used. Groups of 10 male CF_1 mice (18–20 g) were used. Arachidonic acid solution (100 μg/mL in acetone) was prepared fresh daily. Solutions of test compounds were prepared in acetone and were applied to both ears just prior to challenge with 1 mg of arachidonic acid (10 μL of solution), applied to the inner surface of one ear. The unchallenged ear served as the negative control. The animals were sacrificed by cervical dislocation 60 min after challenge. Disks (6-mm diameter) were removed from each ear with a skin biopsy punch, and the weights were determined. The swelling was measured as the difference in weight between punches from the challenged and unchallenged ears; this value varied less than 10% between repeat experiments. Percent inhibition was calculated by using $[(C - T)/C] \times 100\%$, where C is the positive control swelling and T is the drug-tested swelling. Statistical significance was determined by Student's t test. The standard errors of the values reported averaged (for a large selection of the compounds) less than 9% of these values. ED_{50} values were obtained in selected cases by using three doses as described for the 5-LO assay.

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Registry No. **1**, 90-15-3; **2**, 7469-77-4; **3**, 27286-81-3; **4**, 28164-58-1; **5**, 36441-32-4; **5b**, 62085-40-9; **5c**, 109381-15-9; **5d**, 109380-82-7; **5e**, 109380-85-0; **5f**, 109381-07-9; **5g**, 109381-14-8; **5h**, 109380-96-3; **5i**, 123239-52-1; **5j**, 109380-94-1; **5k**, 109380-84-9; **5l**, 109380-90-7; **5l** (*tert*-butyldimethylsilyl ether), 109381-38-6; **5m**, 109381-01-3; **5n**, 109381-12-6; **5o**, 62085-41-0; **5p**, 109381-06-8; **5q**, 109381-13-7; **5r**, 109380-86-1; **5s**, 109381-04-6; **5t**, 109381-02-4; **5u**, 109381-37-5; **5v**, 123239-53-2; **5w**, 109381-22-8; **5x**, 109380-98-5; **5y**, 92496-36-1; **5z**, 109380-99-6; **5aa**, 123239-54-3; **5bb**, 109381-00-2; **5cc**, 109380-80-5; **5dd**, 109381-05-7; **5ee**, 109381-26-2; **5ff**, 62085-42-1; **5gg**, 109381-27-3; **5hh**, 25298-23-1; **5ii**, 123239-55-4; **5jj**, 109381-28-4; **5kk**, 109381-24-0; **6**, 4398-16-7; **7**, 21009-99-4; **8**, 123239-44-1; **9**, 79387-90-9; **10**, 33950-71-9; **11**, 123239-45-2; **12**, 67881-35-0; **13**, 123239-46-3; **14**, 123239-47-4; **15**, 77634-41-4; **16**, 123239-48-5; **17** (X = H), 529-34-0; **17** (X = 5-MeO), 33892-75-0; **17** (X = 6-MeO), 1078-19-9; **17** (X = 7-MeO), 6836-19-7; **17** (X = 6,7-$(MeO)_2$), 13575-75-2; **17** (X = 5,7-Me_2), 13621-25-5; **17** (X = 5,8-Me_2), 5037-63-8; **17** (X = 4-Me), 19832-98-5; **18** (Ar = Ph), 100-52-7; **18** (Ar = 4-MeC_6H_4), 104-87-0; **18** (Ar = 2-MeC_6H_4), 529-20-4; **18** (Ar = 4-$MeOC_6H_4$), 123-11-5; **18** (Ar = 3-$MeOC_6H_4$), 591-31-1; **18** (Ar = 4-$EtOC_6H_4$), 10031-82-0; **18** (Ar = 2-$EtOC_6H_4$), 613-69-4; **18** (Ar = 3,4-$(MeO)_2C_6H_3$), 120-14-9; **18** (Ar = 3,4-$(OCH_2O)C_6H_3$), 120-57-0; **18** (Ar = 3-$PhOC_6H_4$), 39515-51-0; **18** (Ar = 4-$PhCH_2OC_6H_4$), 4397-53-9; **18** (Ar = 4-$MeSC_6H_4$), 3446-89-7; **18** (Ar = 4-$Me_2NC_6H_4$), 28602-27-9; **18** (Ar = 4-FC_6H_4), 459-57-4; **18** (Ar = 4-ClC_6H_4), 104-88-1; **18** (Ar = 3-ClC_6H_4), 587-04-2; **18** (Ar = 4-BrC_6H_4), 1122-91-4; **18** (Ar = 3-BrC_6H_4), 3132-99-8; **18** (Ar = 3,4-$Cl_2C_6H_3$), 6287-38-3; **18** (Ar = 3-$CF_3C_6H_4$), 454-89-7; **18** (Ar = 2-naphthyl), 66-99-9; **18** (Ar = 2-thienyl), 98-03-3; **18** (Ar = 2-furyl), 98-01-1; **18** (Ar = *N*-Me-2-pyrryl), 1192-58-1; **18** (Ar = *N*-Me-2-imidazolyl), 13750-81-7; **18** (Ar = 2-pyridyl), 1121-60-4; **18** (Ar = 3-pyridyl), 500-22-1; **18** (Ar = 4-pyridyl), 872-85-5; **19v**, 49545-72-4; **20**, 68707-66-4; **21**, 109381-44-4; **22a**, 109381-54-6; **22b**, 68707-63-1; **22c**, 109381-43-3; **22d**, 109381-41-1; **22e**, 109381-49-9; **22f**, 109381-50-2; **22g**, 123239-50-9; **22h**, 109381-58-0; **22i**, 123239-51-0; **22j**, 109381-40-0; **23a**, 109381-53-5; **23e**, 109381-48-8; **23g**, 123239-58-7; **23h**, 109381-57-9; **23i**, 68707-67-5; **24**, 123239-59-8; **25**, 123239-60-1; **27**, 35060-38-9; **28**, 123239-61-2; **29**, 123239-62-3; **30**, 123239-63-4; **31**, 123239-69-0; **33**, 123239-70-3; **37**, 613-59-2; **40**, 123239-64-5; **41**, 123239-65-6; **42**, 123239-67-8; **44**, 39110-92-4; **45**, 56679-88-0; **46**, 123239-66-7; **47**, 123239-68-9; **48**, 123263-84-3; **49**, 123239-49-6; **50**, 77634-37-8; **52**, 109381-39-7; **53**, 123239-56-5; **54**, 123239-57-6; $PhCOCH_3$, 98-86-2; $PhCH_2CHO$, 122-78-1; $HO_2C(CH_2)_3CO_2H$, 110-94-1; *p*-$NO_2C_6H_4CHO$, 555-16-8; 1-methoxynaphthalene, 2216-69-5; 1-(methoxymethoxy)naphthalene, 7382-37-8; triethyl phosphonoacetate, 867-13-0; 1-(methoxymethoxy)-2-naphthaldehyde, 73220-21-0; 4-methoxy-1-naphthol, 84-85-5; 1-methoxy-3-(hydroxymethyl)naphthalene, 33295-48-6.