Dioxabicyclooctanyl Naphthalenenitriles as Nonredox 5-Lipoxygenase Inhibitors: Structure−Activity Relationship Study Directed toward the Improvement of Metabolic Stability

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Naphthalenic lignan lactone **3a** (L-702,539), a potent and selective 5-lipoxygenase (5-LO) inhibitor, is extensively metabolized at two different sites: the tetrahydropyran and the lactone rings. Early knowledge of the metabolic pathways triggered and directed a structure−activity relationship study aimed toward the improvement of metabolic stability in this series. The best modifications discovered, *i.e.*, replacement of the lactone ring by a nitrile group, replacement of the tetrahydropyran ring by a 6,8-dioxabicyclo[3.2.1]octanyl moiety, and replacement of the pendant phenyl ring by a 3-furyl ring, were incorporated in a single molecule to produce inhibitor **9ac** (L-708,780). Compound **9ac** inhibits the oxidation of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid by 5-LO (IC_{50} = 190 nM) and the formation of leukotriene B_4 in human polymorphonuclear leukocytes (IC_{50} = 3 nM) as well as in human whole blood (IC_{50} = 150 nM). The good inhibitory profile shown by naphthalenenitrile **9ac** is accompanied by an improved resistance to oxidative metabolism. In addition, **9ac** is orally active in the functional model of antigen-induced bronchoconstriction in allergic squirrel monkeys (95% inhibition at 0.1 mg/kg).

Introduction

Leukotrienes are important biological mediators derived from arachidonic acid through the action of 5-lipoxygenase (5-LO).[1] Leukotriene B_4 (LTB_4) is a potent chemotactic agent and is involved in leukocyte activation.[2] The peptidoleukotrienes LTC_4, LTD_4, and LTE_4 are powerful spasmogenic agents and have been shown to be implicated in the pathology of several diseases.[3] Thus, selective inhibitors of 5-LO could form a new class of therapeutic agents for the treatment of disease states such as asthma[4] and rheumatoid arthritis.

Recently, we have reported a new class of selective and orally active inhibitors of 5-lipoxygenase, the naphthalenic lignan lactones.[5a] Compounds of this class interact with the arachidonic acid binding site of 5-LO and inhibit the enzymatic reaction by a nonredox mechanism.[5b] A representative example of this class is compound **2** (Chart 1) which exhibits excellent *in vitro* activity with an IC_{50} of 14 nM for the inhibition of arachidonic acid oxidation by human recombinant 5-LO and IC_{50}'s of 1.5 and 50 nM for the inhibition of LTB_4 production in human polymorphonuclear leukocytes and human whole blood, respectively. Carboxylate **1**, the open form of lactone **2**, is well absorbed in rats and readily converted *in vivo* to the active species **2**. Carboxylate **1** is orally active in inhibiting LTB_4 biosynthesis in a rat pleurisy model with an ED_{50} of 0.6 mg/kg. A functional model of antigen-induced bronchoconstriction in allergic squirrel monkeys also revealed the high potency of this inhibitor with 95% inhibition of the increase in airway resistance (R_L) at a dose of 0.3 mg/kg.

Unfortunately, compound **2** is extensively metabolized *in vivo*. In rats for example, methyl ether **2** is rapidly demethylated to the tertiary alcohol derivative **3a** (L-702,539) (Chart 1).[6] Furthermore, *in vivo*, the major metabolite **3a** is itself the subject of extensive oxidative metabolism occurring at two different sites:[7] first, on the lactone ring with the formation of the hydroxylactone **3b** and, second, on the tetrahydropyran ring with the formation of the hydroxypyran metabolite **3c** which undergoes further oxidation to the hydroxy acid **4**, a species in equilibrium with pyranone **5**. This extensive metabolism reduces the potential of development for this class of inhibitors. In this paper we will describe the synthesis and the biological activity of the different metabolites. We will also present the results of the structure−activity relationship (SAR) study that was directed toward the improvement of metabolic stability as well as the optimization of the *in vitro* potency.

Chemistry

The modifications on lead structure **2** were directed at three specific sites on the molecule: the lactone ring, the tetrahydropyran ring, and the pendant phenyl ring.

The majority of naphthalenic lactones **3a**−**v** (Table 1) were prepared by the alkylation of lactonic naphthols **7a**−**m** with the appropriate benzylic derivatives **6a**−**f** according to one of the three following methods: treatment with potassium carbonate in dimethylformamide (method A), treatment with cesium carbonate in dimethylformamide (method B), or Mitsunobu reaction (method C). Most substituted naphthalenes **9a**−**ac** (Table 2) were prepared by the treatment of naphthols **8a**−**w** with alkylating agents **6a,e** following the same methods. Saponification of naphthalenic lactones **3a,f,h,u** by ethanolic sodium hydroxide afforded the corresponding sodium carboxylates **10a,f,h,u** (Table 3).

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Chart 1. Metabolism of Tetrahydropyranyl Naphthalenic Lignan Lactones

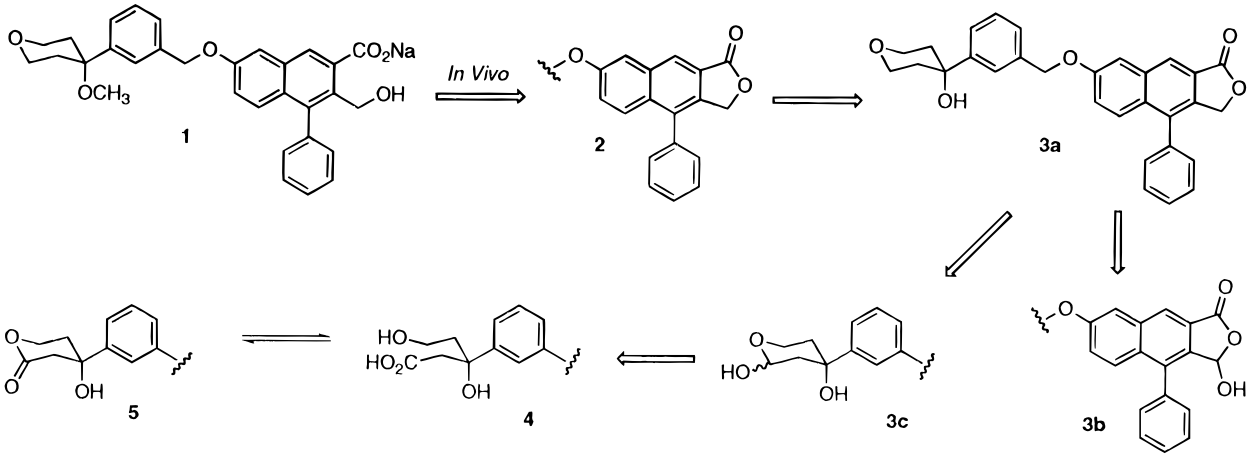
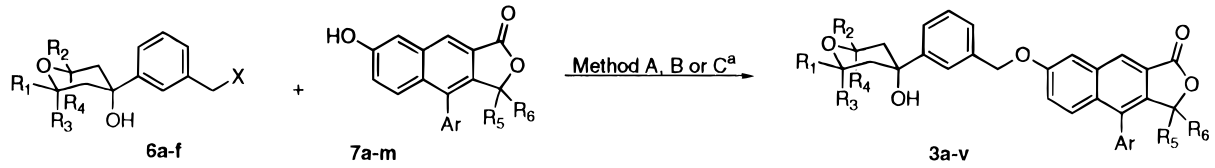


Table 1. Physical and Synthetic Data for Naphthalenic Lactones **3a**−**v**



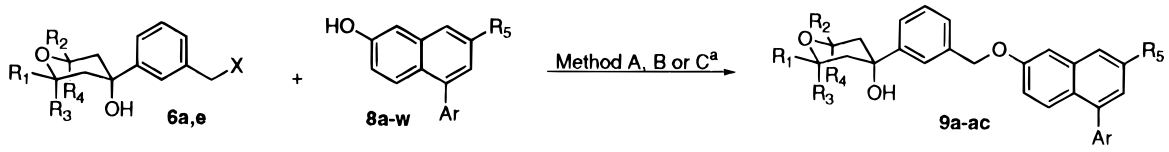
compd														
3	**6**	**7**	R_1	R_2	R_3	R_4	X	R_5	R_6	Ar	method[a]	formula	anal.[b]	yield (%)[c]
a	**a**	**a**	H	H	H	H	Br	H	H	Ph	A	$C_{30}H_{26}O_5 \cdot 0.2EtOAc$	C,H	75
b			H	H	H	H		OH	H	Ph		$C_{30}H_{26}O_6$	d	
c			H	H	OH	H		H	H	Ph		$C_{30}H_{26}O_6$	d	
d	**a**	**l**	H	H	H	H	Br	CH_3	H	Ph	B	$C_{31}H_{28}O_5 \cdot 0.5CH_2Cl_2$	C,H	34
e	**a**	**m**	H	H	H	H	Br	CH_3	CH_3	Ph	B	$C_{32}H_{30}O_5 \cdot 0.6CH_2Cl_2$	C,H	78
f	**c**	**a**	CH_3	CH_3	H	H	Br	H	H	Ph	B	$C_{32}H_{30}O_5$	d	16
g	**d**	**a**	H	H	HC=CH		Cl	H	H	Ph	A	$C_{32}H_{26}O_5 \cdot 1.2EtOAc$	C,H	77
h			H	H	H_2C-CH_2			H	H	Ph		$C_{32}H_{28}O_5$	C,H	
i	**b**	**a**	H	H	OCH_3	H	Br	H	H	Ph	A	$C_{31}H_{28}O_6 \cdot 0.1C_6H_{14}$	C,H	41
j	**e**	**a**	H	H	O−CH_2		OH	H	H	Ph	C	$C_{31}H_{26}O_6$	C,H,O	61
k	**a**	**g**	H	H	H	H	Br	H	H	4-FPh	B	$C_{30}H_{25}FO_5$	C,H,F	75
l	**a**	**h**	H	H	H	H	Br	H	H	4-ClPh	B	$C_{30}H_{25}ClO_5 \cdot 0.7EtOAc$	C,H	39
m	**a**	**i**	H	H	H	H	Br	H	H	4-MeOPh	B	$C_{31}H_{28}O_6$	C,H	42
n	**a**	**j**	H	H	H	H	Br	H	H	2-FPh	B	$C_{30}H_{25}FO_5 \cdot 0.4EtOAc$	C,H	56
o	**a**	**k**	H	H	H	H	Br	H	H	2-ClPh	B	$C_{30}H_{25}ClO_5$	C,H,Cl	45
p	**a**	**b**	H	H	H	H	Br	H	H	3-MeOPh	B	$C_{31}H_{28}O_6$	C,H	68
q	**a**	**c**	H	H	H	H	Br	H	H	3-Py	B	$C_{29}H_{25}NO_5$	d	26
r	**a**	**d**	H	H	H	H	Br	H	H	2-Fu	B	$C_{28}H_{24}O_6$	C,H	15
s	**a**	**e**	H	H	H	H	Br	H	H	3-Fu	B	$C_{28}H_{24}O_6 \cdot 0.2EtOAc$	C,H	51
t	**a**	**f**	H	H	H	H	Br	H	H	3-Th	B	$C_{28}H_{24}O_5S$	C,H,S	76
u	**e**	**e**	H	H	O−CH_2		OH	H	H	3-Fu	C	$C_{29}H_{24}O_7 \cdot 0.2EtOAc$	C,H	73
v	**f**	**e**	H	H	H_2C-O		OH	H	H	3-Fu	C	$C_{29}H_{24}O_7 \cdot 0.8EtOAc$	C,H	29

[a] Method A, K_2CO_3/DMF; method B, Cs_2CO_3/DMF; method C, Mitsunobu reaction. [b] Elemental analyses were within ±0.4% of the calculated value. [c] Isolated yield of the final step. [d] High-resolution mass spectrum was obtained for this compound.

The following compounds were prepared by different methods. The hydroxylactone metabolite **3b** was obtained by the pyridinium dichromate oxidation of sodium carboxylate **10a**. Acid-catalyzed hydrolysis of methyl glycoside **3i** afforded the hydroxypyran metabolite **3c**, which upon treatment with silver carbonate on Celite[8] afforded pyranone **5**. Bicyclic derivative **3h** was obtained by catalytic hydrogenation of unsaturated analog **3g**. Reduction of methyl ester **9h** with diisobutylaluminum hydride gave access to primary alcohol **9b** which was methylated (NaH, MeI) to deliver ether **9e**. Ester **9h** was also saponified with lithium hydroxide to afford carboxylic acid **9j**. Furthermore, treatment of methyl ester **9h** with methyllithium gave tertiary alcohol **9d**. Secondary alcohol **9c** was obtained by sodium borohydride reduction of acetyl derivative **9g**. Methylation of alcohol **9c** then provided ether **9f**. Treatment of chloromethyl derivative **9aa** with imidazole produced analog **9n**, while phenyl ketone **9u** was prepared by the addition of phenylmagnesium bromide to aldehyde **9ab** followed by pyridinium chlorochromate oxidation.

Benzylic Derivatives 6. The required benzyl halides and benzyl alcohols **6a**−**f** were prepared in the following ways. Radical bromination of toluene **11**[5a] yielded benzyl bromide **6a** (Scheme 1). The preparation of methyl glycoside **6b** involved *in situ* formation of 3-lithiotoluene (Scheme 2) by lithium−bromine exchange on 3-bromotoluene followed by the addition of 2,3-dihydro-4*H*-pyran-4-one[9] to afford tertiary alcohol **12**. Successive methoxybromination, tributyltin hydride-mediated reduction, and radical bromination com-

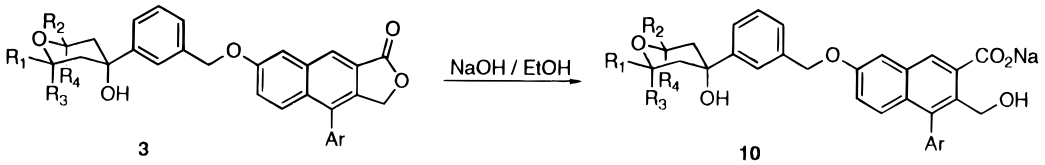
Table 2. Physical and Synthetic Data for Naphthalenes **9a**−**ac**



compd													
9	**6**	**8**	R_1	R_2	R_3	R_4	X	R_5	Ar	method[a]	formula	anal.[b]	yield (%)[c]
a	**a**	**f**	H	H	H	H	Br	CH_2CH_3	Ph	B	$C_{30}H_{30}O_3$·0.2EtOAc	C,H	94
b			H	H	H	H		CH_2OH	Ph		$C_{29}H_{28}O_4$·0.3$CHCl_3$	C,H	
c			H	H	H	H		$CH(CH_3)OH$	Ph		$C_{30}H_{30}O_4$	C,H	
d			H	H	H	H		$C(CH_3)_2OH$	Ph		$C_{31}H_{32}O_4$·0.35$CHCl_3$	C,H	
e			H	H	H	H		CH_2OCH_3	Ph		$C_{30}H_{30}O_4$·0.25$CHCl_3$	C,H	
f			H	H	H	H		$CH(CH_3)OCH_3$	Ph		$C_{31}H_{32}O_4$·0.3EtOAc	C,H	
g	**a**	**e**	H	H	H	H	Br	$COCH_3$	Ph	B	$C_{30}H_{28}O_4$·0.8EtOAc	C,H	74
h	**a**	**a**	H	H	H	H	Br	CO_2CH_3	Ph	B	$C_{30}H_{28}O_5$·0.5EtOAc	C,H	91
i	**a**	**b**	H	H	H	H	Br	CN	Ph	B	$C_{29}H_{25}NO_3$·0.1EtOAc	C,H,N	44
j			H	H	H	H		COOH	Ph		$C_{29}H_{26}O_5$·0.2$CHCl_3$	C,H	
k	**a**	**i**	H	H	H	H	Br	CN_4H	Ph	NaH/DMF	$C_{29}H_{26}N_4O_3$	d	10
l	**a**	**k**	H	H	H	H	Br	CN_4(3-CH_3)	Ph	B	$C_{30}H_{28}N_4O_3$·0.2EtOAc	C,H,N	64
m	**a**	**l**	H	H	H	H	Br	CN_4(2-CH_3)	Ph	B	$C_{30}H_{28}N_4O_3$·1.2H_2O	C,H,N	76
n			H	H	H	H		CH_2(1-imidazole)	Ph		$C_{32}H_{30}N_2O_3$·0.3EtOAc	C,H,N	
o	**a**	**g**	H	H	H	H	Br	CN	3-Fu	B	$C_{27}H_{23}NO_4$	C,H,N	73
p	**a**	**m**	H	H	H	H	Br	CN_4(3-CH_3)	3-Fu	B	$C_{28}H_{26}N_4O_4$·0.3EtOAc	C,H,N	54
q	**a**	**o**	H	H	H	H	Br	2-oxazoline	3-Fu	B	$C_{29}H_{27}NO_5$·0.8EtOAc	C,H,N	83
r	**a**	**q**	H	H	H	H	Br	2-thiazoline	3-Fu	B	$C_{29}H_{27}NO_4S$·0.3EtOAc	C,H,N	81
s	**a**	**p**	H	H	H	H	Br	2-(4,4-dimethyloxazoline)	3-Fu	B	$C_{31}H_{31}NO_5$·1.1EtOAc	C,H,N	87
t	**a**	**r**	H	H	H	H	Br	2-benzothiazole	3-Fu	B	$C_{33}H_{27}NO_4S$·0.5EtOAc	C,H,N	67
u			H	H	H	H		COPh	3-Fu		$C_{33}H_{28}O_5$·0.5CH_2Cl_2	C,H,N	
v	**a**	**s**	H	H	H	H	Br	CO(3-pyridine)	3-Fu	B	$C_{32}H_{27}NO_5$	d	52
w	**a**	**t**	H	H	H	H	Br	CO(2-thiazole)	3-Fu	B	$C_{30}H_{25}NO_5S$·0.9EtOAc	C,H,N	81
x	**a**	**u**	H	H	H	H	Br	CH_2(2-thiazole)	3-Fu	B	$C_{30}H_{27}NO_4S$·1.4EtOAc	C,H,N	81
y	**a**	**v**	H	H	H	H	Br	CO_2CH_3	$(CH_2)_3CH_3$	B	$C_{28}H_{32}O_5$·0.2EtOAc	C,H	64
z	**a**	**w**	H	H	H	H	Br	CO_2CH_3	CH_2Ph	B	$C_{31}H_{30}O_5$·0.4EtOAc	C,H	91
aa	**a**	**d**	H	H	H	H	Br	CH_2Cl	Ph	B			95
ab	**a**	**h**	H	H	H	H	Br	CHO	3-Fu	B			86
ac	**e**	**g**	H	H	O−CH_2		OH	CN	3-Fu	C	$C_{28}H_{23}NO_5$·0.4EtOAc	C,H,N	83

[a] Method A, K_2CO_3/DMF; method B, Cs_2CO_3/DMF; method C: Mitsunobu reaction. [b] Elemental analyses were within ±0.4% of the calculated value. [c] Isolated yield of the final step. [d] High-resolution mass spectrum was obtained for this compound.

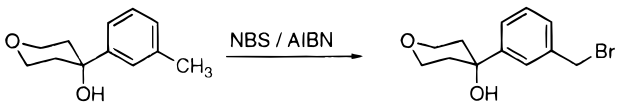
Table 3. Physical and Synthetic Data for Carboxylates **10a,f,h,u**



compd								
3	**10**	R_1	R_2	R_3	R_4	Ar	formula	anal.[a]
a	**a**	H	H	H	H	Ph	$C_{30}H_{27}O_6Na$·0.5NaOH	C,H
f	**f**	CH_3	CH_3	H	H	Ph	$C_{32}H_{31}O_6Na$·1.2NaOH	C,H
h	**h**	H	H	H_2C-CH_2		Ph	$C_{32}H_{29}O_6Na$·2.0NaOH	C,H
u	**u**	H	H	O−CH_2		3-Fu	$C_{29}H_{25}O_8Na$·0.6NaOH	C,H

[a] Elemental analyses were within ±0.4% of the calculated value.

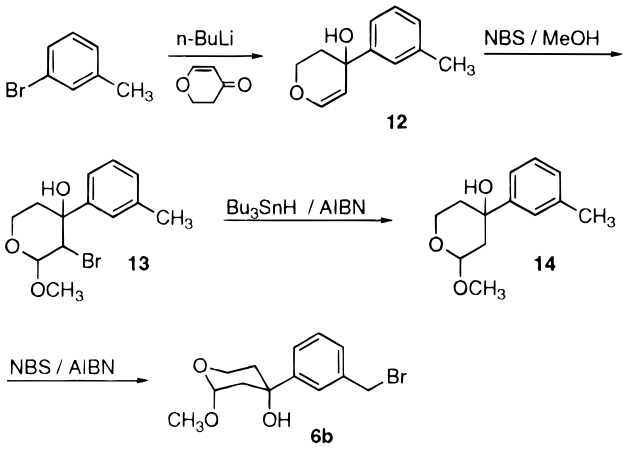
Scheme 1



pleted the synthetic sequence. A slightly modified approach was used to prepare benzylic derivatives **6c**−**f** (Table 4). Addition of protected 3-lithiobenzyl alcohols to tetrahydropyran-4-one derivatives **15c**,[10]**d**,[11]**e**,**f** gave access to tertiary alcohols **16c**−**f**. Alcohol deprotection and halogenation, if necessary, yielded the desired benzylic derivatives **6c**−**f**.

A practical procedure for the medium scale enantioselective synthesis of (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]-octan-3-one (**15e**) was elaborated by modifying already reported preparations[12] (Scheme 3). Sequential treatment of D-glucose in pyridine with *p*-toluenesulfonyl chloride (1 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2 equiv), and additional *p*-toluenesulfonyl chloride (2 equiv) delivered 2,4-bis(*O*-*p*-tolylsulfonyl)-1,6-anhydro-β-D-glucose (**17**) in a one-pot fashion. Reduction with lithium triethylborohydride followed by oxidation of the intermediate secondary alcohol with pyridinium chlorochromate yielded bicyclic ketone **15e**. The scarcity of L-glucose incited the search of a different

Scheme 2



approach for the stereoselective synthesis of enantiomeric (1*R*,5*S*)-6,8-dioxabicyclo[3.2.1]octan-3-one (**15f**). Thus, addition of the anion of 2-(2,2-dimethoxyethyl)-1,3-dithiane[13] to the *tert*-butyldimethylsilyl ether of (*S*)-(−)-glycidol[14] afforded secondary alcohol **18** (Scheme 4). Desilylation with tetrabutylammonium fluoride followed by acid-catalyzed cyclization gave glycoside **19**. Closure to the dioxabicyclo system **20** was effected by selective tosylation of the primary alcohol and DBU-promoted cyclization.[12a] Enantiomerically pure bicyclic ketone **15f** was finally obtained by mercury perchlorate cleavage of the 1,3-dithiane moiety.[15]

Lactonic Naphthols 7. The required lactonic naphthols **7a**−**f** bearing different aromatic rings were prepared according to the general method[16] shown in Scheme 5. Appropriate aryl carboxaldehydes were converted to thioacetals **21a**−**f** by treatment with thiophenol in the presence of boron trifluoride etherate. Conjugate addition of the anion of these thioacetals on 2(5*H*)-furanone followed by enolate trapping with 3-(benzyloxy)benzaldehyde yielded intermediates **22a**−**f** incorporating a completely assembled carbon framework. Treatment with boiling trifluoroacetic acid in the presence of thioanisole efficiently performed the cyclization to lactonic naphthols **7a**−**f** with concomitant debenzylation. (4-Fluorophenyl)naphthol **7g** was prepared by an intramolecular Diels−Alder reaction as described previously.[17]

Lactonic naphthols **7h**−**k** were prepared by the method presented in Scheme 6. Lithium−halogen exchange on aryl bromide **23**[18] followed by the addition of appropriate aromatic aldehydes gave benzyl alcohols **24a,h**−**k** which upon heating with maleic anhydride[19] yielded lignans **25a,h**−**k**. Reduction of the cyclic anhydrides by zinc borohydride followed by debenzylation afforded naphthols **7h**−**k**.

The syntheses of the 3-methylated naphthofuranones **7l**,**m** are highlighted in Scheme 7. Reduction of the anhydride moiety of compound **25a** with lithium aluminum hydride to the corresponding diol followed by selective silylation of the 3-hydroxymethyl function permitted side chain differentiation. Subsequent pyridinium chlorochromate oxidation and methylmagnesium bromide treatment afforded alcohol **26**. Protection of the secondary alcohol as an acetate was followed by fluoride desilylation and permanganate oxidation of the resulting primary alcohol to the corresponding carboxylic acid. Methanolysis of the acetate and acid treatment finally produced lactone **27**, which upon catalytic hydrogenation was debenzylated to the desired lactonic naphthol **7l**. Preparation of *gem*-dimethyllactone **7m** started with methyllithium addition on naphthofuranone **28**[17] followed by a permanganate oxidation to afford the intermediate 2-naphthoic acid derivative. Addition of methylmagnesium bromide followed by acid-catalyzed debenzylation gave access to dimethyllactone **7m**.

Naphthols 8. Naphthols **8a**−**f** were derived from 7-methoxy-4-phenyl-2-naphthoic acid[20] (**29**) (Scheme 8). Demethylation to naphthol **30** was accomplished by treatment with pyridine hydrochloride at 175 °C. Standard esterification gave methyl ester **8a** which in turn was converted to nitrile **8b** by the method of Weinreb.[21] Methyl ester **8a** was also reduced to primary alcohol **8c** which was transformed into chloromethyl derivative **8d.** Treatment of acid **30** with methyllithium gave access to acetylnaphthalene **8e**, which upon hydrogenation was transformed into ethyl derivative **8f**.

The synthesis of (3-furyl)naphthalenenitrile **8g** is presented in Scheme 9. Palladium-catalyzed coupling of 3-furoyl chloride with ethyl 3-iodopropionate followed by hydrolysis produced carboxylic acid **31.** Acetic anhydride-mediated conversion of acid **31** to the corresponding lactone and condensation with 3-methoxybenzaldehyde then yielded intermediate **32**, which upon acid treatment rearranged to naphthalene **33**.[20] The preparation of naphthol **8g** was completed by a Weinreb reaction to transform the ester into a nitrile[21] followed by a pyridine hydrochloride-promoted demethylation. Aldehyde **8h** was prepared by diisobutylaluminum hydride reduction of nitrile **8g**.

Reaction of nitriles **8b,g** with tributyltin azide afforded tetrazoles **8i,j** (Scheme 10), which after methylation were separated into their 2-methyl (**8k**,**m**) and 1-methyl (**8l,n**) isomers. Acid-catalyzed condensation of naphthalenenitrile **8g** with ethanolamines gave oxazoline derivatives **8o,p**; condensation with 2-aminoethanethiol gave thiazoline **8q**, and condensation with 2-aminothiophenol gave benzothiazole **8r** (Scheme 11). Addition of 3-lithiopyridine and 2-lithiothiazole to naphthalenenitrile **8g** afforded acylated naphthalenes **8s,t** respectively. Wolff−Kishner reduction of **8t** gave access to analog **8u** (Scheme 12).

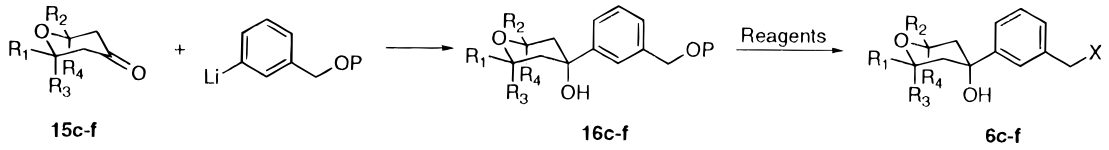
The preparation of naphthols **8v,w** bearing nonaromatic substituents in place of the pendant phenyl ring is presented in Scheme 13. The synthetic sequence involves addition of *n*-butyl or benzyl Grignard reagents on 3-carbethoxy-6-methoxy-1-tetralone[22] (**34**) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation, dehydration, pyridinium hydrochloride demethylation, and diazomethane esterification.

Structure−Activity Relationship

All of the compounds prepared were evaluated for their potency to inhibit (a) oxidation of arachidonic acid by recombinant human 5-LO (H5-LO),[5b] (b) production of LTB_4 in human peripheral blood polymorphonuclear leukocytes (HPMN),[23] and (c) production of LTB_4 in human whole blood (HWB).[23]

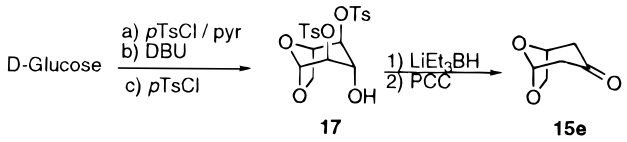
Metabolite Evaluation. As previously mentioned, naphthalenic lignan lactone **2** is extensively metabolized when administered orally to rats as its bioavailable carboxylate form **1**.[6] The major metabolite detected in

Table 4. Synthesis of Benzylic Derivatives **6c−f**

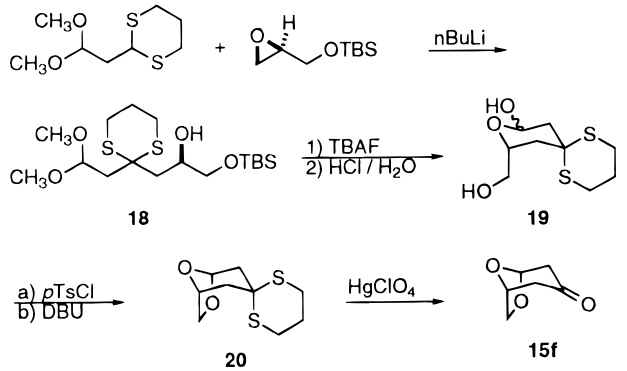


entry	R_1	R_2	R_3	R_4	P	reagents	X
c	CH_3	CH_3	H	H	THP	(1) *p*-TsOH, (2) DIPHOS/CBr_4	Br
d	H	H	HC=CH		THP	(1) *p*-TsOH, (2) PPh_3/CCl_4	Cl
e	H	H	O−CH_2		TBDPS	TBAF	OH
f	H	H	CH_2−O		TBDPS	TBAF	OH

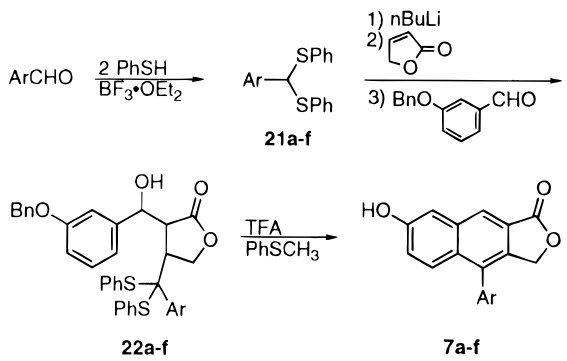
Scheme 3



Scheme 4

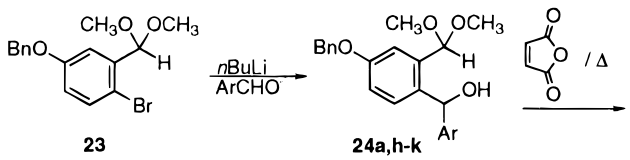


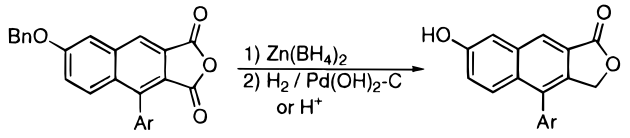
Scheme 5



	Ar
a	Ph
b	3-MeOPh
c	3-Pyr
d	2-Fu
e	3-Fu
f	3-Th

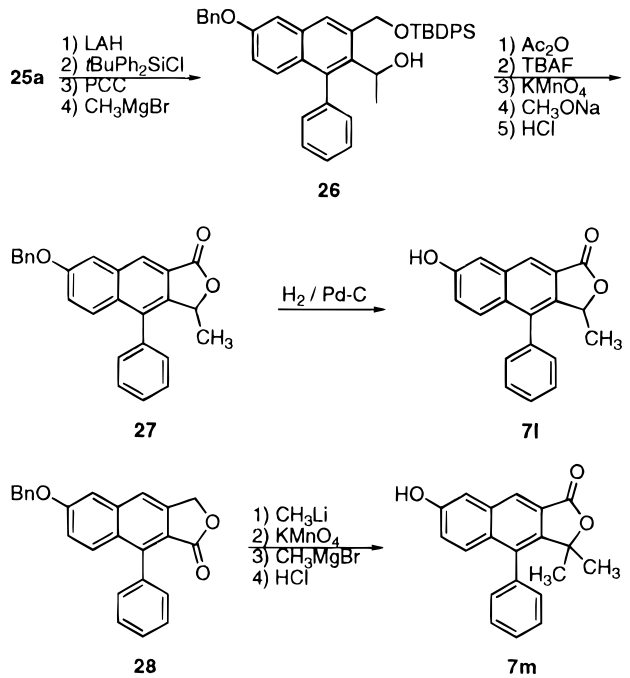
Scheme 6





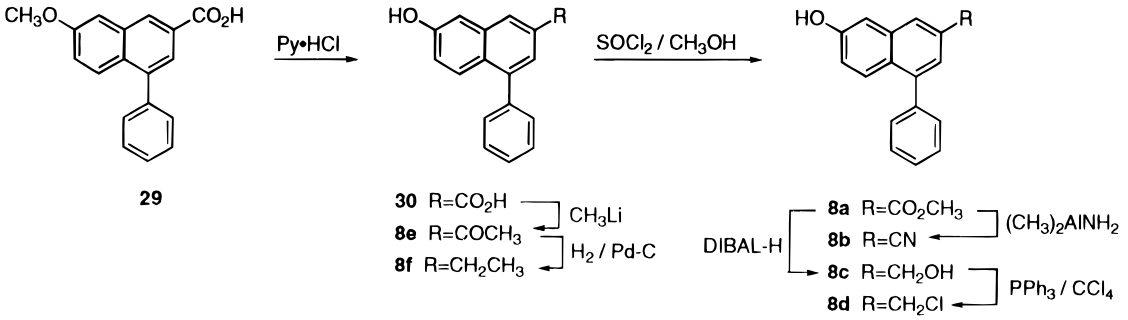
	Ar
a	Ph
h	4-ClPh
i	4-MeOPh
j	2-FPh
k	2-ClPh

Scheme 7

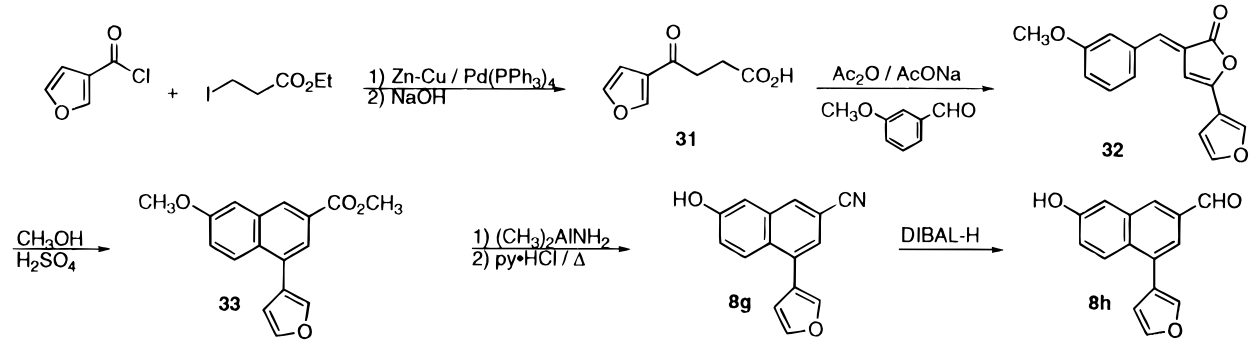


the plasma of dosed animals is demethylated lactone **3a**. The chemical synthesis of alcohol **3a** was performed and its biological activity evaluated *in vitro*. Despite a 8-fold loss of potency in the enzymatic H5-LO assay, alcohol **3a** was equipotent to methyl ether **2** in the cellular HPMN assay and only 3-fold less potent in the HWB assay (Table 5). Globally, **3a** presents a very good *in vitro* inhibitory profile. Unfortunately, this compound is also extensively metabolized when administered orally as its bioavailable carboxylate form **10a** in rats and rhesus monkeys. The metabolic pathway followed by lignan lactone **3a** (Chart 1) was elucidated with the help of *in vitro* studies using hepatic microsomes from rat, rhesus monkey, and human. A qualitative correlation between *in vitro* and *in vivo* biotransformations was established as reported by

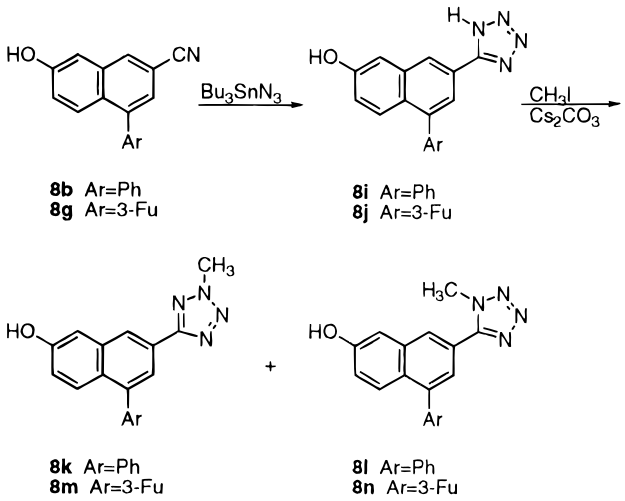
Scheme 8



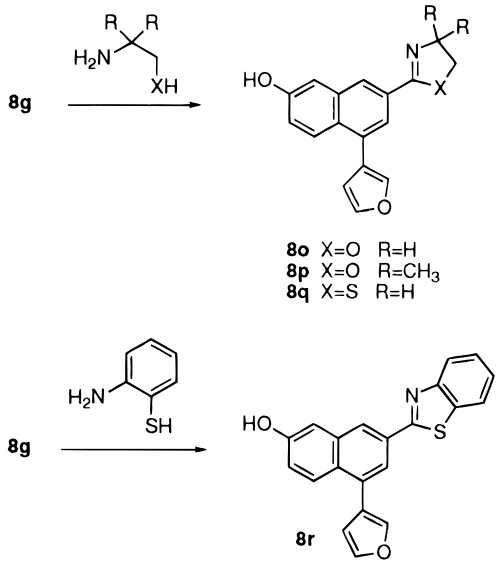
Scheme 9



Scheme 10



Scheme 11

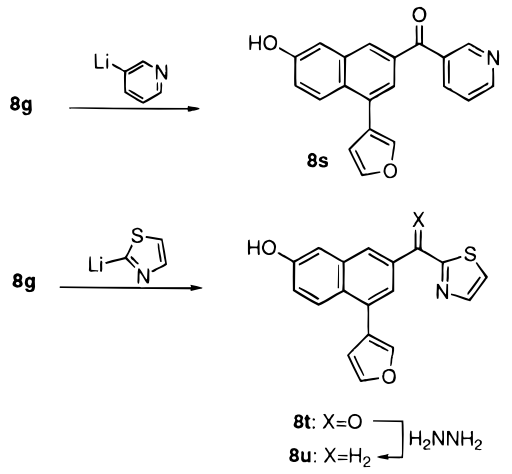


Chauret *et al.*[7a] The major metabolites, hydroxylactone **3b**, hydroxypyran **3c**, and pyranone **5**, were synthesized and evaluated *in vitro*. They all showed poor inhibitory activity or none at all. These results triggered our search for metabolically stable naphthalenic lignan lactone analogs. The elucidation of the metabolic pathway followed by lactone **3a** early in the drug discovery process proved to be extremely useful in directing our SAR studies to critical areas of the lead structure.

Lactone Ring Modifications. (a) Metabolism Blockade. In principle, oxidative metabolism on the lactone ring of compound **3a** could be prevented by substituting the benzylic methylene hydrogen atoms. In this respect, *gem*-dimethyllactone **3e** was prepared. Unfortunately, the introduction of two methyl groups on the lactone ring resulted in a major loss of *in vitro* activity (Table 6). In fact, even substitution by a single methyl unit also has a detrimental effect on the potency of analog **3d**. A possible explanation for this loss of activity involves the conformation of the pendant phenyl ring. The presence of substituents on the lactone ring forces the pendant phenyl ring to adopt an orthogonal position toward the naphthalene unit, and this conformation seems unfavorable for efficient enzyme binding. The fact that *ortho* substitution of the pendant phenyl ring also reduces potency (*vide infra*) is consistant with this hypothesis. Since metabolism blockade on the lactone ring did not prove to be promising, we next considered lactone replacement.

(b) Lactone Replacement. Replacement of the lactone ring of inhibitor **3a** by a simple ethyl (**9a**) or hydroxymethyl (**9b**) side chain results in compounds approximately 5 times less potent in the HPMN assay (Table 7), while replacement by a methoxymethyl (**9e**) side chain produces a nearly equipotent inhibitor. This result indicates the importance of incorporating a nonpolar binding site in the lactone surrogate side chain

Scheme 12



Scheme 13

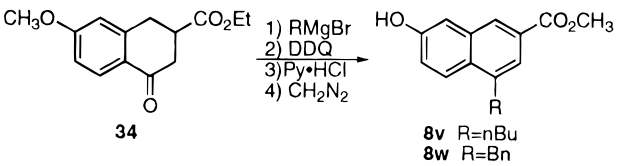
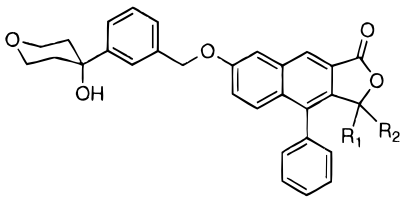


Table 5. *In Vitro* Potency of Naphthalenic Lignan Lactone **2** and Metabolites **3a**−**c** and **5**

	IC_{50} (nM)[a]		
	H5-LO	HPMN	HWB
2	14	1.5	50
3a	115	2	140
3b	>6000	>700	>3000
3c	810	15	1600
5	390	35	>3000

[a] Each IC_{50} value is an average of at least two independant determinations.

Table 6. *In Vitro* Potency of the Methylated Lactones **3d,e**

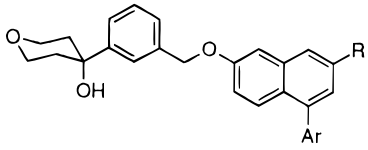


			IC_{50} (nM)[a]		
	R_1	R_2	H5-LO	HPMN	HWB
3d	CH_3	H	1300	150	>3000
3e	CH_3	CH_3	>6000	80	>3000

[a] Each IC_{50} value is an average of at least two independant determinations.

for efficient enzyme inhibition. Substitution on the hydroxymethyl (**9c,d**) or methoxymethyl (**9f**) side chains by methyl groups led to a reduction in activity. It is therefore apparent that increasing bulkiness in this region is unfavorable. In consequence, replacement of the lactone ring by planar functional groups was investigated. Naphthalene derivatives bearing an acetyl (**9g**), methoxycarbonyl (**9h**), or nitrile (**9i**) function were equipotent to lactone **3a**, while carboxylic acid **9j**, a potential metabolite of ester **9h**, and tetrazole **9k** were essentially inactive in the HPMN assay. Thus, non-acidic planar electron-withdrawing groups are efficient

Table 7. *In Vitro* Potency of Naphthalenes **9a**−**x**



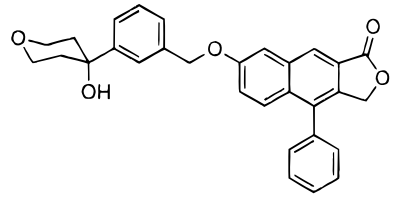
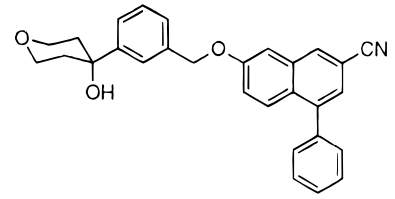
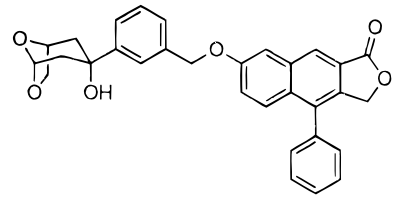
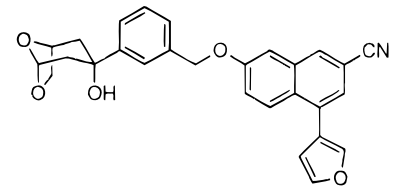
			IC_{50} (nM)[a]		
	R	Ar	H5-LO	HPMN	HWB
9a	CH_2CH_3	Ph	760	10*	>1000
9b	CH_2OH	Ph	260	9*	
9c	$CH(CH_3)OH$	Ph	520	28	675
9d	$C(CH_3)_2OH$	Ph	1500	59*	
9e	CH_2OCH_3	Ph	160	4*	200
9f	$CH(CH_3)OCH_3$	Ph	1200	41*	>1000
9g	$COCH_3$	Ph	130	2	90
9h	CO_2CH_3	Ph	70	3	100
9i	CN	Ph	120	3	100
9j	COOH	Ph		190*	
9k	CN_4H	Ph	>6000	>700*	>3000
9l	$CN_4(2\text{-}CH_3)$	Ph	120	4	310
9m	$CN_4(1\text{-}CH_3)$	Ph	3000	>67*	>10000*
9n	CH_2(1-imidazole)	Ph	640	40*	
9o	CN	3-Fu	30	2	10
9p	$CN_4(2\text{-}CH_3)$	3-Fu	80	2	80
9q	2-oxazoline	3-Fu	70	3	50
9r	2-thiazoline	3-Fu	50	2	75
9s	2-(4,4-dimethyloxazoline)	3-Fu	190	17	2900*
9t	2-benzothiazole	3-Fu	>6000	>62*	
9u	COPh	3-Fu	70	1	200*
9v	CO(3-pyridine)	3-Fu	120	7	370*
9w	CO(2-thiazole)	3-Fu	50	2	130
9x	CH_2(2-thiazole)	3-Fu	140	1	660*

[a] Each IC_{50} value corresponds to an average of at least two independant determinations, except those identified with an asterisk, which are the result of a single titration.

surrogates for the lactone ring. Furthermore, the drastic difference of potency between 1-methyltetrazole **9m** (IC_{50} = 3 μM in H5-LO assay) and 2-methyltetrazole **9l** (IC_{50} = 120 nM in H5-LO assay) indicates that the lactone surrogate needs to be coplanar to the naphthalene ring (a high-energy conformation for **9m**) for efficient enzyme binding. Other heterocycles may be used as surrogates. In the (3-furyl)naphthalene series, 2-oxazolyl (**9q**) and 2-thiazolyl (**9r**) analogs are equipotent to 2-methyltetrazole **9p**. Once again, increasing bulkiness by incorporating methyl substituents on the oxazoline ring (**9s**) results in a loss of potency. Heterocycles can be linked to the naphthalene ring by a carbonyl group (**9u**−**w**) or a methylene unit (**9x**) to produce analogs practically equipotent to 2-methyltetrazole **9p**. Therefore, the lactone ring of the naphthalenic lignan inhibitors can be efficiently replaced by a variety of planar functional groups and heterocycles without losing the *in vitro* activity.

There was nevertheless a potential drawback with the lactone replacement approach, and it concerned pharmacokinetics. Previous studies[5a] have shown that lactones such as **2** are not absorbed when administered orally to rats while their open carboxylate form (*e.g.*, **1**) are. By removing the lactone moiety, we obviously lose the ability to use this method for improving bioavailability. This concern was however alleviated when naphthalenenitrile **9i** was detected in rat plasma samples (0.7 μM at 6 h) after oral dosing at 20 mg/kg. Furthermore, naphthalenenitrile **9i** showed improved metabolic stability compared to lactone **3a** in an *in vitro* rat hepatic microsome assay. Under standard

Table 8. *In Vitro* Metabolism by Rat Hepatic Microsomes of Derivatives **3a,j** and **9i,ac**

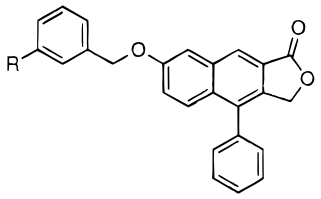
		Percentage of Parent Compound Metabolyzed[a]
3a		6-7%
9i		4-5%
3j		1-2%
9ac		0.4%

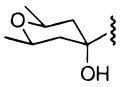
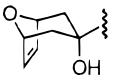
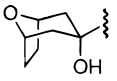
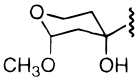
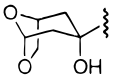
[a] Peak area$_{metabolites}$/(peak area$_{metabolites}$ + peak area$_{parent}$).

microsomal incubation conditions (see Experimental Section), lactone **3a** was transformed into four observable metabolites to the extent of 6−7%, while naphthalenenitrile **9i** was transformed into three observable metabolites to the extent of 4−5% (Table 8). For this encouraging pharmacokinetic behavior and owing to its improved metabolic stability, the nitrile moiety was selected as a preferred lactone surrogate for further SAR studies.

Tetrahydropyran Ring Modifications. Metabolism Blockade. To prevent the oxidative metabolism process leading from naphthalenic lignan lactone **3a** to hydroxypyran **3c**, a blockade approach similar to the one described previously for the lactone ring protection was undertaken on the tetrahydropyran ring. Introduction of two equatorial[24] methyl groups flanking the tetrahydropyran ring oxygen atom gave compound **3f** (Table 9). Despite a 6-fold loss of potency in the HWB assay, this analog is equipotent to **3a** in the enzymatic H5-LO and the cellular HPMN assays. However, HPLC analysis of plasma samples revealed the formation of at least four major metabolites when 2,6-dimethyltetrahydropyran **3f** was administered orally to rats as a solution of its carboxylate **10f**. The inability of equatorial substituents to significantly reduce metabolism suggests that enzymatic α-hydroxylation on the tetrahydropyran ring might occur in a stereospecific axial fashion. If that is the case, axial substituents would be expected to show a better ability to block metabolism. With this in mind, 8-oxabicyclo[3.2.1]octen-6-yl derivative **3g** and its saturated analog **3h** were prepared. While **3g** is 14-fold less potent than compound **3a** in the HPMN assay, saturated **3h** is only 3-fold less potent in the H5-LO and HPMN assays. The 8-oxabicyclo-[3.2.1]octanyl system showed improved efficacy in blocking metabolism. Only one major metabolite besides the expected hydroxylactone could be detected in plasma samples when oxabicyclo **3h** was administered orally to rats as a solution of its carboxylate **10h**.

Table 9. *In Vitro* Potency of Tetrahydropyran Derivatives **3f−j**

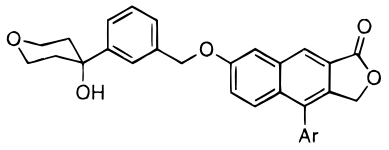


	R	IC_{50} (nM)[a] H5-LO	HPMN	HWB
3f		180	3	900
3g		400	27	>3000
3h		320	8	1000
3i		23	2	120
3j		240	6*	540

[a] Each IC_{50} value corresponds to an average of at least two independant determinations, except the one identified with an asterisk, which is the result of a single titration.

A further modification on the bicyclic ring system was inspired by the discovery that methyl glycoside **3i**, an intermediate in the synthesis of hydroxypyran metabolite **3c**, was remarquably active *in vitro* (IC_{50} = 23 nM in H5-LO assay). This observation suggested that the introduction of a second oxygen atom in the bicyclo-[3.2.1]octane ring system could increase the potency of the bicyclic inhibitors. The 6,8-dioxabicyclo[3.2.1]-octanyl analog **3j** was then prepared and showed indeed a 2-fold increase of potency in the HWB assay in comparison with monooxygenated **3h**. Even more significantly, the incorporation of a second oxygen atom in the bicyclic system improved further the metabolic stability as shown *in vitro* by the rat hepatic microsome assay. Following standard microsomal incubation, compound **3j** was metabolized to the extent of 1−2% only (Table 8). The 6,8-dioxabicyclo[3.2.1]octanyl ring system efficiently blocked oxidative metabolism and was selected as an efficient tetrahydropyranyl surrogate for further SAR studies.

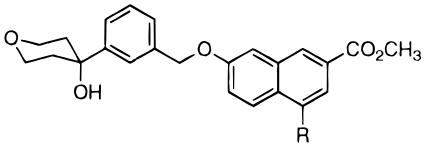
Table 10. *In Vitro* Potency of Naphthalenic Lactones **3k**−**t**



	Ar	IC_{50} (nM)[a] H5-LO	HPMN	HWB
3k	4-FPh	140	3	410
3l	4-ClPh	5500	26*	>3000
3m	4-MeOPh	6000	89*	
3n	2-FPh	360	18	1800
3o	2-ClPh	380	11*	1100
3p	3-MeOPh	80	4	260
3q	3-Py	720*	25	1200
3r	2-Fu	280	5*	450
3s	3-Fu	26	2	100
3t	3-Th	27	2	50

[a] Each IC_{50} value corresponds to an average of at least two independant determinations, except those identified with an asterisk, which are the result of a single titration.

Table 11. *In Vitro* Potency of Naphthalenes **9y,z**



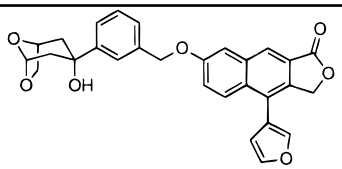
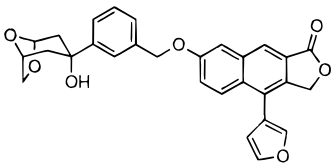
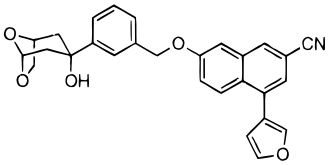
	R	IC_{50} (nM)[a] H5-LO	HPMN	HWB
9y	$(CH_2)_3CH_3$	2200	15*	
9z	CH_2Ph	>6000	>70*	

[a] Each IC_{50} value corresponds to an average of at least two independant determinations, except those identified with an asterisk, which are the result of a single titration.

Phenyl Ring Modifications: *In Vitro* Potency Optimization. A variety of analogs bearing differently substituted pendant phenyl rings was evaluated (Table 10). Substitution by a fluorine atom at the *para* position resulted in analog **3k**, an inhibitor equipotent to phenyl **3a** in the H5-LO assay. Larger substituents, either electron-withdrawing (chloro **3l**) or electron-donating (methoxy **3m**), were not tolerated at this position. *m*-Methoxyphenyl derivative **3p** is equipotent to compound **3a**. *Ortho* substitution by fluorine (**3n**) or chlorine (**3o**) atoms results in a 3−10-fold loss of activity. Replacement of the phenyl ring by a 6-membered heteroaromatic moiety was detrimental to activity as exemplified by 3-pyridyl analog **3q**. On the other hand, substitution by 5-membered heterocycles was favorable. Even though 2-furyl analog **3r** is 3-fold less active than phenyl substituted **3a**, 3-furyl derivative **3s** is more potent in each of the three assays used to evaluate the inhibitor potencies. The same trend was observed with the 3-thienyl analog **3t**. The requirement for an aromatic ring at this position is illustrated by the major loss of potency observed for naphthalenic esters **9y,z** bearing a butyl group and a benzyl group, respectively, in place of the pendant phenyl ring (Table 11).

Combination of the Best Modifications. Replacement of the pendant phenyl ring of dioxabicyclic analog **3j** by a 3-furyl moiety gave rise to compound **3u**, an inhibitor equipotent to tetrahydropyran **3a** in both H5-LO and HWB assays (Table 12) with an improved metabolic stability. After oral administration of the naphthalenic lactone analog **3u** in rats as a solution of its carboxylate **10u** (20 mg/kg), no major metabolites were detected in plasma samples besides the expected hydroxylactone. Compound **3u** is a chiral inhibitor, and since it was synthesized from D-glucose, it consists of a single enantiomer. In order to investigate the enantioselectivity of 5-LO inhibition[25] in the dioxabicyclo[3.2.1]-octanyl series, enantiomer **3v** was prepared. Enantiomer **3v** was 2−3-fold less potent than **3u** in the H5-LO and HPMN assays and more than 10-fold less active in the HWB assay.

Table 12. *In Vitro* Potency of 6,8-Dioxabicyclo[3.2.1]octanyl Derivatives **3u,v** and **9ac**

		IC_{50} (nM)[a] H5-LO	HPMN	HWB
3u		140	7	180
3v		340	21	2100*
9ac		190	3	150

[a] Each IC_{50} value corresponds to an average of at least two independant determinations, except the one identified with an asterisk, which is the result of a single titration.

The best modifications, *i.e.*, replacement of the lactone ring by a nitrile group, replacement of the tetrahydropyran ring by a 6,8-dioxabicyclo[3.2.1]octanyl moiety, and replacement of the pendant phenyl ring by a 3-furyl ring, were next incorporated in a single molecule to produce inhibitor **9ac**. This compound is equipotent to naphthalenic lignan lactone **3a** in the three *in vitro* assays. The good inhibitory profile shown by naphthalenenitrile **9ac** is accompanied by a strong resistance to oxidative metabolism. Under the standard rat microsomal incubation of compound **9ac**, a single metabolite was observed to the extent of only 0.4% (Table 8). This behavior was translated *in vivo* since no major metabolites were detected in rat plasma samples after oral dosing of naphthalenenitrile **9ac** (20 mg/kg), while the plasma concentration of the parent compound reached 2.5 μM 6 h after administration. Thus, the combination of the best modifications effectively resulted in the production of a potent and metabolically stable inhibitor with enhanced pharmacokinetic properties, naphthalenenitrile **9ac**.

Compound **9ac** (L-708,780) was found to be more potent *in vitro* than Zileuton[26] and MK-0591[23] (Table 13). When compared to Zeneca's inhibitor D2138,[27] inhibitor **9ac** is 2−3-fold more potent in the H5-LO and HPMN assays while it is 2-fold less potent in the HWB assay.

Table 13. Comparison of *in Vitro* Potency of Zileuton, MK-0591, D-2138, and **9ac**

	IC_{50} (nM)[a]		
	H5-LO	HPMN	HWB
Zileuton	3700	1100	2000
MK-0591	5000	3	500
D-2138	330	10	80
9ac	190	3	150

[a] Each IC_{50} value is an average of at least two independant determinations.

In Vivo Studies

In spite of its excellent *in vitro* potency, **9ac** showed only modest activity in inhibiting LTB_4 biosynthesis *in vivo* in a rat pleurisy model.[23] Using a 3 h oral pretreatment with a dose of 3 mg/kg, no inhibition was observed. For comparison, the FLAP inhibitor MK-0591[23] presents an ED_{50} of 0.5 mg/kg after a 2 h pretreatment in the same model. When rats were submitted to a longer pretreatment of 6 h, the same dose of **9ac** gave rise to 50% inhibition of the LTB_4 biosynthesis. This result correlates with the slow absorption of naphthalenenitrile **9ac** observed in rat after oral administration.

The effect of **9ac** on antigen-induced bronchoconstriction in allergic squirrel monkeys[23] was also measured. A 4 h pretreatment at 0.1 mg/kg oral dose followed by a challenge with an aerosol of *Ascaris* antigen produced a 95% inhibition of the increase in airway resistance (R_L) and a 100% inhibition of decrease in dynamic compliance (C_{dyn}). For MK-0591, the values obtained at a higher dose of 0.3 mg/kg were R_L= 44% and C_{dyn}= 46%.[23] Thus, **9ac** is more potent than MK-0591 in this functional model.

Conclusion

Elucidation of the metabolic pathways of naphthalenic lignan lactone **3a** early in the drug discovery process proved very useful in directing our SAR study toward critical areas of the lead structure. Replacement of the lactone and tetrahydropyran rings by a nitrile group and a 6,8-dioxabicyclo[3.2.1]octanyl moiety efficiently improves the metabolic stability of inhibitors in this series. Furthermore, replacing the pendant phenyl ring by a 3-furyl heterocycle leads to a major gain of *in vitro* activity. Combination of these three features in a single compound produces the highly potent 5-LO inhibitor **9ac.** Following oral administration of **9ac** in rats, no circulating metabolites were observed. Compound **9ac** is orally active in the functional model of antigen-induced bronchoconstriction in allergic squirrel monkeys. Thus, the further development of this series of nonredox inhibitors may result in the identification of novel antiasthma and antiinflammation agents.

Experimental Section

Biology. Generation of LTB_4 in Human Peripheral Blood Polymorphonuclear Leukocytes (HPMN) and Human Whole Blood (HWB). The generation of LTB_4 in human peripheral blood polymorphonuclear leukocytes and human whole blood was measured as previously described by Brideau *et al.*[23] Where more than two IC_{50} values have been determined, the 95% confidence limits (cl) were ±<120% of the mean value for HPMN and ±<90% of the mean value for HWB.

Activity of Human 5-Lipoxygenase (H5-LO). The activity of 5-LO was measured using a spectrophotometric assay and soluble extracts from sf9 cells overexpressing H5-LO as described by Falgueyret *et al.*[5b] Where more than two IC_{50} values have been determined, the 95% confidence limits were ±<80% of the mean value.

Leukotriene Biosynthesis in Rat Pleural Cavity. LTB_4 levels in rat pleural exudates following interpleural injection of carrageenan followed 16−20 h later by ionophore A23187 were determined as previously described.[23]

***Ascaris*-Induced Bronchoconstriction in Squirrel Monkeys.** Naturally sensitized male squirrel monkeys were challenged with an aerosol of *Ascaris* antigen. Changes in pulmonary mechanics (airway resistance, R_L, and dynamic compliance, C_{Dyn}) were monitored in conscious animals using airflow measurements from a face mask and measurements of pleural pressure as previously described.[23]

Rat Hepatic Microsomal Incubations. Incubations were conducted as described previously by Chauret *et al.*[7a] Briefly, the incubations were conducted with rat liver microsomal protein (1 mg in a 50 μL sucrose solution (0.25 M)), a premixed cofactor buffer containing 2.5 mM $MgCl_2$, 2.5 mM NADP, and 25 mM glucose-6-phosphate in a 125 mM phosphate buffer (pH 7.4 (400 μL)), and the drug candidate (12.5 μL of an 8 mM solution in DMSO). After a 2 min preincubation, 2 units of glucose-6-phosphate dehydrogenase (25 μL of a solution containing 80 units/mL in water) were added to give a total volume of 500 μL. The final drug concentration was 200 μM. Incubations were conducted at 37 °C for 1 h, and reactions were quenched by the addition of acetonitrile (500 μL). After centrifugation to remove precipitated proteins, the supernatant was analyzed by reverse phase HPLC. For analytical HPLC, the system consisted of Waters components: a 600-MS pump, a 715 Ultra WISP injector, a 994 photodiode array detector controlled by Powerline software, and a Nova Pak C18 column (3.9 × 150 mm). Eluent A was 20 mM ammonium acetate adjusted to pH 5.4 with acetic acid, and eluent B was methanol. A linear gradient was run from 47% to 87% methanol over 40 min. The detection wavelength was 245 nm.

Measurement of Plasma Level and Bioavailability. Male Sprague−Dawley rats (2) were starved overnight and dosed orally with the compound as a solution in 0.5% methocel (1 mL/100 g). Blood was taken from the jugular vein at 0, 0.5, 1, 2, 4, 6, and 8 h after dosing. In the intravenous studies, compounds were dissolved in 5% dextrose and injected intravenously in the jugular vein (dose volume = 0.1 mL/100 g). Blood was taken from the jugular vein at 0, 5, 15, and 30 min and 1, 2, 4, and 6 h after dosing. Blood was centrifuged and plasma collected. To 100 μL of each plasma sample was added an equal volume of acetonitrile to precipitate proteins. An aliquot (30 μL) of the supernatant after centrifugation was subjected to reverse phase HPLC. The parent compound was quantitated from the area of the corresponding peak, relative to the standard (plasma sample at time 0 min, spiked with varying concentrations of the compound).

Chemistry. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker AM 250 and 300 and AMX 300 spectrometers, and proton chemical shifts are reported relative to tetramethylsilane as internal standard. Infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer, and only the largest or most characteristic absorptions are reported. Melting points were obtained on either a Buchi 510 or Electrothermal 9100 apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN, Oneida Research Services, Whitesboro, NY, or Guelph Chemical Laboratories Ltd., Guelph, Ontario. Where reported only by symbols, the results were within 0.4% of theoretical values. High-resolution mass spectra were recorded at the Biomedical Mass Spectrometry Unit, McGill University, Montreal, Quebec.

Preparation of Benzylic Halides and Alcohols 6. 3-(4-Hydroxytetrahydro-2*H*-pyran-4-yl)benzyl Bromide (6a). A mixture of toluene **11**[5] (16 g, 77 mmol), *N*-bromosuccinimide (14.6 g, 82 mmol), and azoisobutyronitrile (AIBN) (127 mg, 0.8 mmol) in CCl_4 (250 mL) was refluxed for 1.5 h. Filtration and evaporation of the filtrate followed by chromatography on silica gel (hexane/EtOAc, 65:35) afforded the desired benzyl bromide as a yellow solid (19 g, 89%): ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.65 (m, 2H), 2.20 (m, 2H), 3.90 (m, 5H), 4.55 (s, 2H), 7.40 (m, 3H), 7.55 (br s, 1H).

3-(4-Hydroxy-2-methoxytetrahydro-2*H*-pyran-4-yl)benzyl Bromide (6b). Step 1: 3-(4-Hydroxy-3,4-dihydro-2*H*-pyran-4-yl)toluene (12). To a solution of 3-bromotoluene (12.2 g, 71.4 mmol) in THF (80 mL), cooled to −78 °C, was added *n*-butyllithium in hexane (2.2 M, 32.4 mL, 71.4 mmol). The resulting white suspension was stirred for 30 min; then there was added a solution of 2,3-dihydro-4*H*-pyran-4-one[9] (7.0 g, 71 mmol) in THF (40 mL). The resulting amber solution was stirred at −78 °C for 4 h and then allowed to warm up to room temperature, and the reaction was quenched with saturated aqueous NH_4Cl (250 mL), and the mixture was extracted three times with EtOAc. Extracts were washed twice with brine, dried, and evaporated to an oily residue which was chromatographed on silica gel (hexane/EtOAc, 85:15) to afford **12** as a yellow liquid (7.4 g, 54%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (m, 3H), 2.38 (s, 3H), 4.11 (m, 2H), 4.97 (d, 1H), 6.62 (d, 1H), 7.08 (dd, 1H), 7.19−7.35 (m, 3H).

Step 2: 3-(3-Bromo-4-hydroxy-2-methoxytetrahydro-2*H*-pyran-4-yl)toluene (13). To a solution of bromide **12** (4.03 g, 21.2 mmol) in methanol (30 mL) cooled to 0 °C was added slowly a suspension of *N*-bromosuccinimide (3.77 g, 21.2 mmol) in methanol (15 mL). After 1 h of stirring in the cold, the reaction was quenched with pH 7 phosphate buffer (100 mL) and the mixture extracted three times with CH_2Cl_2. The extracts were dried and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to afford the desired product as an amber oil (3.85 g, 60%) and as a mixture of diastereomers which was used as such.

Step 3: 3-(4-Hydroxy-2-methoxytetrahydro-2*H*-pyran-4-yl)toluene (14). A mixture of bromide **13** (3.85 g, 12.8 mmol), tributyltin hydride (3.72 g, 12.8 mmol), and AIBN (10 mg) in toluene (25 mL) was refluxed for 1.5 h and then evaporated. The residue was chromatographed on silica gel (hexane/EtOAc, 85:15) to afford the product as an oil (2.16 g, 76%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.72 (d, 1H), 1.96 (d, 1H), 2.13 (dd, 1H), 2,25 (m, 1H), 2.37 (s, 3H), 3.46 (s, 3H), 3.77 (m, 1H), 4.16 (m, 1H), 4.67 (s, 1H), 4.93 (d, 1H), 7.09 (m, 1H), 7.26 (m, 2H), 7.35 (s, 1H).

Step 4: 3-(4-Hydroxy-2-methoxytetrahydro-2*H*-pyran-4-yl)benzyl Bromide (6b). Following the radical bromination procedure described above in the preparation of **6a**, using the product from step 3 as starting material, the title product was obtained as an amber oil which was used crude: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.70 (d, 1H), 2.00 (d, 1H), 2.10 (dd, 1H), 2.25 (m, 1H), 3.45 (s, 3H), 3.80 (m, 1H), 4.15 (m, 1H), 4.50 (s, 2H), 4.75 (s, 1H), 4.95 (d, 1H), 7.30−7.45 (m, 3H), 7.60 (s, 1H).

3-(4α-Hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-4-yl)-benzyl Bromide (6c). Step 1: 2-[(3-Bromobenzyl)oxy]-tetrahydro-2*H*-pyran. To a solution of 3-bromobenzyl alcohol (11.5 g) and *p*-toluenesulfonic acid monohydrate (116 mg) in CH_2Cl_2 (100 mL) at 0 °C was added 3,4-dihydro-2*H*-pyran (6.2 mL). The resulting solution was stirred at room temperature for 3 h; then the reaction was quenched with aqueous NH_4OAc. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried, and evaporated. Chromatography on silica gel (hexane/EtOAc, 9:1) afforded the desired protected alcohol (72%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.5−2.0 (m, 6H), 3.55 (dt, 1H), 3.90 (dq, 1H), 4.70 (t, 1H), 4.75 (d, 1H), 7.20 (q, 2H), 7.40 (dd, 1H), 7.53 (s, 1H).

Step 2: 2-[[3-(4α-Hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-4-yl)phenyl]methyl]tetrahydro-2*H*-pyran (16c). Following the procedure of step 1 in the preparation of **6b**, but using 2,6-dimethyltetrahydro-4*H*-pyran-4-one (**15c**)[10] and the benzyl ether from step 1 as starting materials, **16c** was obtained (65%) as a mixture of α and β isomers. The isomers were separated by chromatography on silica gel (hexane/EtOAc, 6:4). The α isomer is the least polar isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (d, 6H), 1.59−1.95 (m, 10H), 3.50−3.60 (m, 2H), 3.90−4.20 (m, 3H), 4.50 (d, 1H), 4.70 (t, 1H), 4.80 (d, 1H), 7.20−7.45 (m, 3H), 7.50 (s, 1H).

Step 3: 3-(4α-Hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-4-yl)benzyl Alcohol. *p*-Toluenesulfonic acid monohydrate (12 mg, 63 mmol) was added to a solution of ether **16c** (400 mg, 1.25 mmol) in EtOH (5 mL). The reaction mixture was stirred at room temperature for 90 min before the volatiles were evaporated. The residue was then partitioned between water and ether, and the organic phase was dried ($MgSO_4$) and evaporated. Chromatography on silica gel (hexane/EtOAc, 1:1) afforded the desired alcohol (100 mg, 34%) which was used as such in the next step.

Step 4: 3-(4α-Hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-4-yl)benzyl Bromide (6c). To a solution of alcohol from step 3 (80 mg, 0.34 mmol) in CH_2Cl_2 (4 mL) was added CBr_4 (118 mg, 0.35 mmol). The mixture was cooled to −30 °C, and DIPHOS (124 mg, 0.34 mmol) was added. After 10 min, there was added a 1:10 mixture of EtOAc and hexane (10 mL), and the mixture was filtered. The filtrate was chromatographed on silica gel (EtOAc/hexane, 3:7) to afford the title product (83 mg, 82%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, 6H), 1.40−1.90 (m, 5H), 4.0 (m, 2H), 4.50 (s, 2H), 7.20−7.50 (m, 3H), 7.53 (s, 1H).

3-(3α-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)benzyl Chloride (6d). Step 1: 2-[[3-(3α-Hydroxy-8-oxabicyclo-[3.2.1]oct-6-en-3-yl)benzyl]oxy]tetrahydro-2*H*-pyran (16d). Following the procedure described in step 1 for the preparation of **6b**, but using ketone **15d**[11] and 2-[(3-bromobenzyl)oxy]-tetrahydro-2*H*-pyran as starting materials, the expected derivative **16d** was obtained in 52% yield as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50−1.75 (m, 6H), 1.90 (d, 2H), 2.50 (m, 2H), 3.03 (s, 1H), 3.55 (m, 1H), 3.90 (m, 1H), 4.49 (d, 1H), 4.72 (m, 1H), 4.80 (d, 1H), 4.93 (d, 2H), 6.59 (s, 2H) 7.25−7.45 (m, 3H), 7.48 (s, 1H).

Step 2: 3-(3α-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)benzyl Chloride (6d). A solution of tetrahydropyranyl ether **16d** (6.63 g, 21.0 mmol) and *p*-toluenesulfonic acid monohydrate (5.15 g, 27.1 mmol) in methanol (250 mL) was stirred at room temperature for 1 h. The mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 three times. The extracts were dried and evaporated, and the crude benzyl alcohol was dried by dissolving in benzene and evaporating twice. It was then dissolved in acetonitrile (100 mL), there were added triphenylphosphine (4.73 g, 18.0 mmol) and CCl_4 (18 mL, 166 mmol), and the mixture was stirred at room temperature for 4 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 65:35) to afford **6d** (2.42 g, 50%) as an amber oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.89 (d, 2H), 2.50 (dd, 2H), 3.07 (s, 1H), 4.60 (s, 2H), 4.93 (d, 2H), 6.60 (s, 2H), 7.26 (m, 1H), 7.34 (t, 1H), 7.43 (m, 1H), 7.53 (s, 1H).

(1*S*,5*R*)-3-(3α-Hydroxy-6,8-dioxabicyclo[3.2.1]octan-3-yl)benzyl Alcohol (6e). Step 1: 2,4-Bis(*O*-*p*-tolylsulfonyl)-1,6-anhydro-β-D-glucose (17). A solution of *p*-toluenesulfonyl chloride (233 g, 1.22 mol) in pyridine (350 mL) was added over 20 min to a cooled (0 °C) suspension of D-glucose (200 g, 1.11 mol) in pyridine (750 mL), and the resulting mixture was stirred at room temperature for 25 h. Dichloromethane (1.0 L) was added, and the mixture was cooled to 0 °C; then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (332 mL, 2.22 mol) was added over 15 min. After stirring at room temperature for 2 days, the mixture was again cooled to 0 °C and *p*-toluenesulfonyl chloride (448 g, 2.35 mol) was added. Stirring was continued at room temperature for 2 days; then the volatiles were evaporated, CH_2Cl_2 (1.5 L) was added, and the organic phase was washed with 1 N aqueous HCl (3 × 1.5 L) and then with brine, dried, and evaporated. The residue was chromatographed on silica gel (EtOAc) to afford ditosylate **17** (252 g, 48%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 6H), 2.75 (d, 1H), 3.70 (dd, 1H), 3.95 (m, 1H), 4.00 (d, 1H), 4.20 (d, 1H), 4.35 (d, 1H), 4.65 (d, 1H), 5.30 (s, 1H), 7.35 (m, 4H), 7.80 (m, 4H).

Step 2: (1*S*,3*S*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-3-ol. To a solution of ditosylate **17** (107 g, 0.228 mol) in THF (1.6 L) at −40 °C was added 1 M lithium triethylborohydride in THF (800 mL, 0.8 mol). The mixture was stirred at room temperature overnight and then cannulated into cold water (226 mL) with external cooling. There were added 3 N aqueous NaOH (640 mL, 1.92 mol) and then 30% H_2O_2 (490 mL, 4.3 mol). The reaction mixture was stirred at room temperature for 1 h, and the supernatant THF layer was collected and

concentrated. The resulting residue was recombined with the aqueous layer and extracted with CH_2Cl_2 using a continuous extractor for several hours. The organic layer was dried and evaporated, affording an oily residue which was chromatographed on silica gel (hexane/EtOAc, 1:1) to yield the desired product as an oil (25 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.80−2.40 (m, 4H), 3.73 (t, 1H), 4.05 (t, 1H), 4.33 (d, 1H), 4.55 (t, 1H), 5.65 (s, 1H).

Step 3: (1*S*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-3-one (15e). A solution of alcohol from step 2 (16.6 g, 89 mmol) in CH_2Cl_2 (200 mL) was added slowly to a suspension of pyridinium chlorochromate (38.4 g, 178 mmol) and Celite (22 g) in CH_2Cl_2 (400 mL), and the mixture was stirred at room temperature for 1 h. After dilution with ether (600 mL), the mixture was filtered through Celite and the filtrate evaporated. The residue was distilled using a Kügelrohr apparatus (100 °C, 1.8 mmHg) to afford the desired ketone as a colorless oil (8.2 g, 50%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 1H), 2.50 (d, 1H), 2.60 (s, 2H), 3.88 (s, 2H), 4.85 (t, 1H), 5.81 (s, 1H).

Step 4: (1*S*,5*R*)-3-(3α-Hydroxy-6,8-dioxabicyclo[3.2.1]-octan-3-yl)]benzyl Alcohol (6e). Following the procedure described in step 1 of the preparation of **6b**, but using ketone **15e** and 3-bromo-*O*-(*tert*-butyldiphenylsilyl)benzyl ether as starting materials, the expected silylated derivative **16e** was obtained. The crude product was treated with Bu_4NF in THF at room temperature for 1.5 h. After evaporation of the solvent, the crude product was chromatographed on silica gel (hexane/EtOAc, 4:1) to yield the alcohol **6e** as a colorless oil (92%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00 (dd, 2H), 2.22 (d, 1H), 2.40 (dd, 1H), 2.70 (br s, 1H), 3.75 (t, 1H), 3.95 (s, 1H), 4.45 (d, 1H), 4.65 (m, 3H), 5.70 (s, 1H), 7.30 (m, 2H), 7.50 (s, 1H).

(1*R*,5*S*)-3-(3α-Hydroxy-6,8-dioxabicyclo[3.2.1]octan-3-yl)benzyl Alcohol (6f). Step 1: Dithiane Silyl Ether 18. To a solution of 2-(2,2-dimethoxyethyl)-1,3-dithiane[13] (10.4 g, 50 mmol) in THF (50 mL) at −30 °C was added, over 30 min, *n*-butyllithium (1.3 M) in hexane (38.5 mL, 50 mmol). After 1 h, there was added a solution of (*S*)-(−)-glycidol *tert*-butyldimethylsilyl ether[14] (9.42 g, 50 mmol) in THF (10 mL) and stirring was continued at −30 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture partitioned between ether and water. The organic residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to yield **18** (16.0 g, 80%) as a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.97 (m, 2H), 2.08 (dd, 1H), 2.20 (dd, 1H), 2.30 (dd, 1H), 2.46 (dd, 1H), 2.85 (m, 4H), 3.29 (d, 1H), 3.34 (s, 3H), 3.38 (s, 3H), 3.53 (dd, 2H), 4.01 (m, 1H), 4.73 (dd, 1H).

Step 2: Dithiane 19. A solution of Bu_4NF (1 M) in THF (26.5 mL, 26.5 mmol) was added to a solution of dithiane silyl ether **18** (9.94 g, 25 mmol) in THF (50 mL). After 2 h at room temperature the mixture was evaporated and the residue chromatographed on silica gel (hexane/EtOAc, 1:3), affording the expected diol (6.64 g, 94%) as an amber oil. A portion of this material (3.11 g, 11.0 mmol) was dissolved in THF (40 mL), and 5% aqueous HCl (25 mL) was added. This mixture was stirred at 60 °C for 15 h and then refluxed for 3 h. After partitioning between water and EtOAc, the organic residue was evaporated to give **19** (2.05 g, 79%) as a mixture of α and β epimers which was used as such.

Step 3: Dioxabicyclo Dithiane 20. *p*-Toluenesulfonyl chloride (1.98 g, 10.4 mmol) was added to a cold (0 °C) solution of dithiane **19** in pyridine (10 mL). After stirring for 90 min at room temperature, methanol (1 mL) was added followed by chloroform (50 mL). The mixture was washed with water twice, dried, and evaporated to a residue which was chromatographed on silica gel (hexane/EtOAc, 3:2) to afford the expected primary tosylate (2.22 g, 65%) as an amber solid. A solution of this material (1.95 g, 5.0 mmol) in CH_2Cl_2 (30 mL) was treated with DBU (1.5 mL, 10 mmol) and the resulting mixture stirred at room temperature for 60 h. After evaporation of the volatiles, the residue was chromatographed on silica gel (hexane/EtOAc, 3:1) yielding dioxabicyclo dithiane **20** (0.77 g, 71%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90−2.10 (m, 2H), 2,10 (dd, 1H), 2.50 (m, 2H), 2.65 (d, 1H), 2.84 (m, 2H), 2.99 (m, 2H), 3.68 (m, 1H), 4.50 (d, 1H), 4.54 (m, 1H), 5.59 (s, 1H).

Step 4: (1*R*,5*S*)-6,8-Dioxabicyclo[3.2.1]octan-3-one (15e). A solution of mercury(II) perchlorate trihydrate (1.73 g, 3.81 mmol) in water (1 mL) was added over 10 min to a vigorously stirred mixture of **20** (757 mg, 3.47 mmol) and calcium carbonate (420 mg, 4.20 mmol) in THF (12 mL). After 40 min at room temperature more mercury perchlorate (0.56 g, 1.2 mmol) in water (0.2 mL) was added. After another 30 min at room temperature, ether was added, the mixture was stirred vigorously, and the ether phase was decanted, dried, and evaporated to deliver ketone **15f** (324 mg, 73%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (d, 1H), 2.60 (d, 2H), 2.80 (m, 1H), 3.88 (m, 2H), 4.86 (m, 1H), 5.83 (s, 1H).

Step 5: (1*R*,5*S*)-3-(3α-Hydroxy-6,8-dioxabicyclo[3.2.1]-octan-3-yl)benzyl Alcohol (6f). Following the procedure described in step 1 for the preparation of **6b**, but using ketone **15f** and 3-bromo-*O*-(*tert*-butyldiphenylsilyl)benzyl ether as starting materials, the expected silylated derivative **16f** was obtained in 43% yield. The crude product was treated with Bu_4NF in THF at room temperature for 1.5 h. After evaporation of the solvent, the crude product was chromatographed on silica gel (hexane/EtOAc, 4:1) to yield the alcohol **6f** as a colorless oil (93%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.80 (br s, 1H), 2.00 (m, 2H), 2.25 (d, 1H), 2.45 (dd, 1H), 3.80 (m, 1H), 3.85 (s, 1H), 4.50 (d, 1H), 4.70 (m, 3H), 5.75 (s, 1H), 7.25 (m, 1H), 7.30−7.45 (m, 2H), 7.55 (s, 1H).

Preparation of Lactonic Naphthols 7. 7-Hydroxy-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (7a). Step 1: Benzaldehyde Diphenyl Dithioacetal (21a). To a solution of benzaldehyde (31.8 g, 300 mmol) and thiophenol (69.2 g, 629 mmol) in isopropyl acetate (300 mL) cooled to 0 °C was added slowly boron trifluoride etherate (42.6 g, 300 mmol). The mixture was stirred in the cold for 1 h; then the reaction was quenched slowly with 10% aqueous K_2CO_3. The phases were separated, and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with aqueous carbonate and then three times with water, dried, and evaporated to an oil which solidified. The solid was triturated with pentane (250 mL) and filtered to afford the dithioacetal as a white solid (35.8 g). A further crop was obtained by crystallization of filtrate material (total 75.7 g, 82%).

Step 2: 7-Hydroxy-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (7a). To a solution of benzaldehyde diphenyl dithioacetal (23.5 g, 76 mmol) in THF (250 mL), cooled to −70 °C, was added slowly *n*-butyllithium in hexane (2.1 M, 37 mL, 77.7 mmol), and a yellow suspension resulted. After 20 min, there was added slowly 2(5*H*)-furanone (7.64 g, 91 mmol), and the mixture was stirred in the cold for 30 min, becoming a light yellow solution. There was added slowly a solution of 3-(benzyloxy)benzaldehyde (16.5 g, 77.7 mmol) in THF (75 mL), and stirring was continued at −70 °C for 1 h. Acetic acid (9 g, 150 mmol) was added slowly; then the mixture was allowed to warm up to room temperature. After dilution with an equal volume of ether, the mixture was washed four times with brine, dried, and evaporated to an oil which was the intermediate **22a**. This material was dissolved in thioanisole (75 mL), and there was added trifluoroacetic acid (190 mL). This mixture was heated at 60 °C for 1 h; then the trifluoroacetic acid was evaporated and the residual slurry was triturated with ether (200 mL) and filtered to afford the desired lactone **7a** as a cream-colored solid (12.7 g, 60%): mp >225 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.28 (s, 2H), 7.30 (dd, 1H), 7.47−7.64 (m, 6H), 7.68 (d, 1H), 8.31 (s, 1H), 9.08 (s, 1H); IR (KBr) 3240 (br), 1740, 1620, 1225 cm^{-1}.

The same method was followed, using the appropriate aromatic aldehyde as starting material, to prepare the following lactonic naphthols.

7-Hydroxy-4-(3-methoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7b): mp >225 °C; 30% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 5.32 (q, 2H), 7.03 (m, 3H), 7.25 (dd, 1H), 7.49 (m, 2H), 7.64 (d, 1H), 8.39 (s, 1H).

7-Hydroxy-4-(3-pyridyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7c). In this case, the product obtained after the TFA−thioanisole treatment was debenzylated but had not cyclized. This product (380 mg, 0.74 mmol) was stirred at room

temperature in TFA (3 mL) containing methanesulfonic acid (0.5 mL, 7.7 mmol) for 2 h. The TFA was evaporated and the residue diluted with ether and neutralized with 1 N aqueous NaOH. After several extractions with ether, the combined extracts were washed with brine, dried, and evaporated to a solid which was triturated with ether and filtered to afford the desired lactone **7c** (25% combined yield) as a pale yellow solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.50 (m, 2H), 6.45 (dd, 1H), 6.65−6.80 (m, 3H), 7.10 (d, 1H), 7.60 (s, 1H), 7.90 (m, 2H), 9.40 (s, 1H).

7-Hydroxy-4-(2-furyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7d): tan solid; mp 218 °C dec; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.55 (s, 2H), 6.73 (m, 1H), 6.98 (d, 1H), 7.40 (dd, 1H), 7.51 (d, 1H), 7.87 (s, 1H), 8.25 (s, 1H), 8.39 (d, 1H), 9.06 (br s, 1H).

7-Hydroxy-4-(3-furyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7e): tan solid; mp >225 °C; 37% yield; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.43 (s, 2H), 6.80 (d, 1H), 7.35 (dd, 1H), 7.51 (d, 1H), 7.86 (m, 1H), 7.98 (m, 1H), 8.03 (d, 1H), 8.28 (s, 1H), 9.25 (br s, 1H); IR (KBr) 3340 (br), 1740, 1622, 1225 cm^{-1}.

7-Hydroxy-4-(3-thienyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7f): yellow solid; mp >235 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.35 (s, 2H), 7.30 (m, 2H), 7.50 (d, 1H), 7.69 (m, 1H), 7.73 (m, 1H), 7.85 (d, 1H), 8.28 (s, 1H), 9.0 (br s, 1H).

7-Hydroxy-4-(2-fluorophenyl)-naphtho[2,3-*c*]furan-1(3*H*)-one (7j). Step 1: 5-(Benzyloxy)-2-(α-hydroxy-2-fluorobenzyl)benzaldehyde Dimethyl Acetal (24j). To a solution of 5-(benzyloxy)-2-bromobenzaldehyde dimethyl acetal (**23**)[18] (10.1 g, 30 mmol) in THF (150 mL) at −70 °C was added slowly *n*-butyllithium in hexane (2.1 M, 15 mL, 31.5 mmol). After 15 min, there was slowly added a solution of 2-fluorobenzaldehyde (3.97 g, 32 mmol) in THF (10 mL). The cooling bath was removed and the mixture allowed to warm up to 10 °C, whereupon the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the mixture extracted twice with ether. The extracts were washed three times with brine, dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 3:1) to afford **24j** as an oil (8.93 g, 78%).

Step 2: 7-(Benzyloxy)-4-(2-fluorophenyl)naphtho[2,3-*c*]furan-1,3-dione (25j). A mixture of acetal **24j** (8.9 g, 23.3 mmol), maleic anhydride (9.13 g, 93 mmol), and camphorsulfonic acid (1 g) in toluene (100 mL) was refluxed for 24 h. The solvent was evaporated and the residue diluted with ether (200 mL), stirred for 30 min, and filtered to afford the anhydride **25j** as an off-white solid (4.41 g, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 2H), 7.27−7.63 (m, 11H), 7.78 (d, 1H), 8.43 (s, 1H).

Step 3: 7-(Benzyloxy)-4-(2-fluorophenyl)naphtho[2,3-*c*]furan-1(3*H*)-one. To a solution of anhydride **25j** (1.19 g, 3 mmol) in DMF (20 mL) at 0 °C were added zinc chloride (820 mg, 6 mmol) and then, in portions, sodium borohydride (171 mg, 4.5 mmol). The mixture was warmed up to room temperature, more $NaBH_4$ was added (171 mg), and stirring was continued for 30 min. The mixture was diluted with water and acidified with 1 N aqueous HCl, and the precipitate was filtered (1.29 g). This solid was refluxed in benzene (50 mL) containing *p*-toluenesulfonic acid (50 mg) with azeotropic removal of water for 24 h. The solvent was evaporated and the residue boiled in EtOAc (25 mL) for 30 min, cooled, and filtered. The filtrate material was chromatographed on silica gel (hexane/EtOAc, 3:1) to afford the desired lactone as a white solid (438 mg, 38%): mp 179−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (dd, 2H), 7.29−7.53 (m, 11H), 7.63 (d, 1H), 8.42 (s, 1H).

Step 4: 7-Hydroxy-4-(2-fluorophenyl)naphtho[2,3-*c*]-furan-1(3*H*)-one (7j). A mixture of the lactone from step 3 (240 mg) and palladium hydroxide (20%) on carbon (80 mg) in EtOAc (40 mL) was stirred under an atmosphere of hydrogen at room temperature for 18 h. After filtration, evaporation of the filtrate afforded a solid residue which was triturated in ether to yield the desired naphthol **7j** as a white solid (162 mg, 88%): mp >230 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.27 (q, 2H), 7.33 (dd, 1H), 7.42 (m, 2H), 7.52−7.68 (m, 4H), 8.37 (s, 1H), 9.15 (br s, 1H).

The same method was followed, using the appropriately substituted benzaldehyde as starting material, to prepare the following naphthalenic lactones.

7-Hydroxy-4-(4-chlorophenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7h). In this case the final debenzylation was done as follows: The intermediate benzylated lactone (1.3 g) was heated in a mixture of acetic acid (20 mL) and 6 N aqueous HCl (5 mL) at 100 °C for 18 h. After cooling, the mixture was diluted with water and extracted with EtOAc, the extracts were washed with water, dried, and evaporated, and the residue was stirred with ether at room temperature for 1 h and filtered to afford **7h** (870 mg, 86%) as a white solid: mp >235 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 5.30 (d, 2H), 7.31 (dd, 1H), 7.50−7.58 (m, 3H), 7.60−7.66 (m, 2H), 7.70 (d, 1H), 8.33 (s, 1H), 9.05 (br s, 1H).

7-Hydroxy-4-(4-methoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7i). In this case the final debenzylation was done as follows: The intermediate benzylated lactone (225 mg) was stirred in a mixture of TFA (3 mL) and methanesulfonic acid (1 mL) at room temperature for 30 min. After evaporation of the TFA, the residue was dissolved in EtOAc, washed several times with water, dried, and evaporated. The residue was stirred with ether at room temperature for 30 min and filtered to yield **7i** (146 mg, 84%) as a beige solid.

7-Hydroxy-4-(2-chlorophenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (7k): obtained as a mixture of isomeric lactones which could not be separated; used as such in the coupling step.

7-Hydroxy-3-methyl-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (7l). Step 1: 6-(Benzyloxy)-2,3-bis(hydroxymethyl)-1-phenylnaphthalene. To a suspension of lithium aluminum hydride (2.5 g, 65.8 mmol) in THF (100 mL) at 0 °C was added anhydride **25a** (5.0 g, 13.1 mmol) in portions. The resulting mixture was refluxed for 2 h and then stirred at room temperature for 18 h. After cooling to 0 °C there was added slowly 6 N aqueous HCl until all the aluminum salts had dissolved. The mixture was diluted with EtOAc; the organic phase was washed several times with brine, dried, and evaporated. The residue was crystallized from EtOAc/hexane to afford the desired diol (1.4 g, 29%) as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.0 (br s, 1H), 4.60 (s, 2H), 4.95 (s, 2H), 5.20 (s, 2H), 7.10 (dd, 1H), 7.25−7.50 (m, 13H), 7.80 (s, 1H).

Step 2: 6-(Benzyloxy)-3-[[(*tert*-butyldiphenysilyl)oxy]-methyl]-2-(hydroxymethyl)-1-phenylnaphthalene. To a solution of diol from step 1 (1.02 g) in DMF (15 mL) was added imidazole (410 mg) and then *tert*-butylchlorodiphenylsilane (0.79 mL). After 1 h of stirring at room temperature, the mixure was diluted with ether, washed three times with water and then brine, dried, and evaporated. Chromatography on silica gel (hexane/EtOAc, 95:5) yielded the desired monosilylated compound as an oil (1.23 g, 73%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.03 (s, 9H), 3.30 (t, 1H), 4.55 (d, 2H), 5.0 (s, 2H), 5.20 (s, 2H), 7.10 (m, 2H), 7.40 (m, 18H), 7.75 (m, 4H).

Step 3: 6-(Benzyloxy)-3-[[(*tert*-butyldiphenysilyl)oxy]-methyl]-2-formyl-1-phenylnaphthalene. To a solution of alcohol from step 2 (1.2 g, 2 mmol) in CH_2Cl_2 (25 mL) was added dry powdered 4 Å molecular sieves (1 g) and pyridinium chlorochromate (1 g, 4.6 mmol). After stirring at room temperature for 1 h, the mixture was filtered through a short column of silica gel, eluting with ether. The eluate was evaporated to afford the desired aldehyde as an oil (1.1 g, 92%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.2 (s, 9H), 5.20 (s, 2H), 5.35 (s, 2H), 7.15 (dd, 1H), 7.35 (m, 18H), 7.75 (m, 4H), 8.35 (s, 1H), 9.80 (s, 1H).

Step 4: 6-(Benzyloxy)-3-[[(*tert*-butyldiphenysilyl)oxy]-methyl]-2-(1-hydroxyethyl)-1-phenylnaphthalene (26). To a solution of aldehyde from step 3 (1.1 g, 1.8 mmol) in THF (15 mL) at −78 °C was added dropwise 1.4 M methylmagnesium bromide in toluene−THF (2.8 mL, 3.9 mmol). After 10 min the cooling bath was removed and the reaction was quenched with saturated aqueous NH_4Cl. After dilution with ether, the organic phase was washed with water and brine, dried, and evaporated to afford the desired product as a foam (1.1 g, 98%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.35 (d, 3H), 3.25 (d, 1H), 4.45 (m, 1H), 5.00 (d, 1H), 5.20 (s, 2H), 5.40 (d, 1H), 7.00−7.50 (m, 19H), 7.75 (m, 5H).

Step 5: 2-(1-Acetoxyethyl)-6-(benzyloxy)-3-(hydroxymethyl)-1-phenylnaphthalene. To a solution of naphthalene **26** (300 mg, 0.5 mmol) in acetic anhydride (2 mL) were added pyridine (0.3 mL) and 4-(dimethylamino)pyridine (10 mg). After 2 h at room temperature, the mixture was diluted with ether, washed with water and then with aqueous $CuSO_4$, dried, and evaporated to afford a crude intermediate which was dissolved in THF (10 mL). At 0 °C there was added acetic acid (0.1 mL) followed by 1 M tetrabutylammonium fluoride in THF (1.4 mL). The mixture was stirred in the cold for 2 h, the reaction quenched with saturated aqueous NH_4Cl, and the mixture diluted with ether. The organic phase was washed with brine, dried, and evaporated and the residue chromatographed on silica gel (hexane/EtOAc, 7:3) to afford the desired alcohol as an oil (115 mg, 56% combined yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50 (d, 3H), 2.00 (s, 3H), 2.30 (s, 1H), 5.05 (m, 2H), 5.20 (s, 2H), 6.00 (q, 1H), 7.00−7.55 (m, 13H), 7.90 (s, 1H).

Step 6: 3-(1-Acetoxyethyl)-7-(benzyloxy)-4-phenyl-2-naphthoic Acid. To a solution of the alcohol from step 5 (110 mg, 0.26 mmol) in *tert*-butyl alcohol (6 mL) were added pH 7 aqueous phosphate buffer (4 mL) and a solution of $KMnO_4$ (90 mg, 0.57 mmol) in water (2 mL). After stirring for 3 h at room temperature, the mixture was diluted with EtOAc and aqueous sodium sulfite. It was then acidified to pH 2 with 10% aqueous HCl; the organic phase was collected, washed with water, dried, and evaporated to give the desired acid as an oil (104 mg, 91%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.60 (d, 3H), 2.00 (s, 3H), 5.10 (br s, 1H), 5.15 (s, 2H), 5.90 (q, 1H), 7.10−7.55 (m, 13H), 8.00 (s, 1H).

Step 7: 7-(Benzyloxy)-3-methyl-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (27). To a solution of acid from step 6 (100 mg, 0.23 mmol) in methanol (3 mL) was added sodium methoxide (5 mg), and the mixture was stirred at room temperature for 24 h and then evaporated. The residue was dissolved in EtOAc (3 mL), and 6 N aqueous HCl (2 drops) was added. After stirring at room temperature for 20 min, the mixture was washed three times with brine, dried, and evaporated to afford lactone **27** as a foam (86 mg, 100%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (s, 3H), 5.20 (s, 2H), 5.70 (q, 1H), 7.30−7.70 (m 13H), 8.30 (s, 1H).

Step 8: 7-Hydroxy-3-methyl-4-phenylnaphtho[2,3-*c*]-furan-1(3*H*)-one (7l). A solution of lactone **27** (86 mg) in EtOAc (3 mL) containing 10% palladium on carbon (26 mg) was stirred under an atmosphere of hydrogen at room temperature for 48 h. After filtration the filtrate was evaporated to afford lactonic naphthol **7l** as a solid (55 mg, 83%): ^{1}H NMR (250 MHz, CD_3OD) δ 1.15 (d, 3H), 5.70 (q, 1H), 7.20−7.70 (m, 8H), 8.30 (s,1H).

7-Hydroxy-3,3-dimethyl-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (7m). Step 1: 2-Acetyl-6-(benzyloxy)-3-(hydroxymethyl)-1-phenylnaphthalene. To a suspension of lactone **28**[17] (500 mg, 1.36 mmol) in THF (25 mL) at −78 °C there was added 1 M methyllithium in ether (2 mL, 2 mmol). The mixture was warmed slowly until a homogeneous solution was obtained; then the reaction was quenched with aqueous saturated NH_4Cl and the mixture partitioned between ether and water. Evaporation of the organic phase yielded the title compound as a foam which was used as such in the next step.

Step 2: 3-Acetyl-7-(benzyloxy)-4-phenyl-2-naphthoic Acid. To a solution of the alcohol from step 1 in *tert*-butyl alcohol (10 mL) were added pH 7 aqueous phosphate buffer (4 mL) and then a solution of potassium permanganate (500 mg, 3.16 mmol) in water (2 mL). After stirring at room temperature for 3 h, the mixture was diluted with EtOAc and aqueous sodium sulfite and acidified to pH 2 with 10% aqueous HCl. The organic phase was collected, washed with water, dried, and evaporated to give the desired acid (150 mg) as an oil.

Step 3: 7-(Benzyloxy)-3,3-dimethyl-4-phenylnaphtho-[2,3-*c*]furan-1(3*H*)-one. To a solution of acid from step 2 (150 mg) in THF (10 mL) at −8 °C was added dropwise 1.4 M methylmagnesium bromide in ether (0.8 mL). After 2 h at −8 °C, the reaction was quenched with 10% aqueous HCl and the mixture diluted with ether. After stirring for a further 2 h, the organic phase was collected, washed with water and then with brine, dried, and evaporated. Chromatography on silica gel (hexane/EtOAc/CH_2Cl_2, 85:15:30) afforded the desired lactone (76 mg, 14% for three steps) as a foam: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 6H), 5.20 (s, 2H), 7.20−7.55 (m, 13H), 8.35 (s, 1H).

Step 4: 7-Hydroxy-3,3-dimethyl-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (7m). A solution of benzyloxy lactone from step 3 (70 mg, 0.18 mmol) in acetic acid (2 mL) and 6 N aqueous HCl (0.8 mL) was heated at 120 °C for 4 h. After cooling, the mixture was diluted with EtOAc, and the organic phase was collected, washed with water and brine, dried, and evaporated to yield the phenol **7m** (52 mg, 97%) as a pale yellow foam.

Preparation of Naphthols 8. Methyl 7-Hydroxy-4-phenyl-2-naphthoate (8a). Step 1: 7-Hydroxy-4-phenyl-2-naphthoic Acid (30). A mixture of 7-methoxy-4-phenyl-2-naphthoic acid[20] (**29**) (55 g, 0.20 mol) and pyridine hydrochloride (400 g, 3.46 mol) was heated at 175 °C for 10 h. After cooling to room temperature, water (2 L) was added and after stirring for 15 min, the mixture was filtered. The solid was dissolved in water (1.5 L) containing 10 N aqueous NaOH (35 mL), and the solution was filtered. Acidification of the filtrate with 1 N aqueous HCl and filtration afforded the desired naphthol as a tan solid (28.5 g, 55%): mp >250 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.26 (dd, 1H), 7.43 (d, 1H), 7.48−7.58 (m, 5H), 7.78 (m, 2H), 8.46 (s, 1H).

Step 2: Methyl 7-Hydroxy-4-phenyl-2-naphthoate (8a). To a suspension of acid **30** (5 g) in methanol (60 mL) was added dropwise thionyl chloride (1.52 mL, 1.5 equiv). The mixture was stirred at room temperature for 18 h, and the solvent was evaporated. Chromatography of the residue on silica gel (hexane/EtOAc, 1:1) afforded the ester **8a** (4.51 g, 81%) as a tan solid: mp 192−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H), 5.32 (s, 1H), 7.18 (dd, 1H), 7.34 (d, 1H), 7.49 (m, 5H), 7.84 (m, 2H), 8.45 (s, 1H).

7-Hydroxy-4-phenyl-2-naphthalenenitrile (8b). To a suspension of naphthoate **8a** (890 mg, 2.19 mmol) in toluene (50 mL) was added 1 M dimethylaluminum amide in toluene[21] (9.59 mL), and the mixture was refluxed for 16 h. After cooling to 0 °C, there was added carefully 1 N aqueous HCl in excess, and after 15 min in the cold, the mixture was extracted four times with CH_2Cl_2. The extracts were washed three times with brine, dried, and evaporated to a solid which was chromatographed on silica gel (hexane/EtOAc, 3:7) to afford nitrile **8b** as a yellow solid (437 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H); 7.15 (d, 1H), 7.25 (d, 1H), 7.40−7.55 (m, 6H), 7.82 (d, 1H), 8.06 (s, 1H); IR (KBr) 3500−3200, 2200 cm^{-1}.

6-Hydroxy-3-(hydroxymethyl)-1-phenylnaphthalene (8c). To a solution of ester **8a** (2.5 g, 9.0 mmol) in THF (50 mL) at 0 °C was added diisobutylaluminum hydride (3.83 g, 26.9 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with methanol; then the mixture was evaporated to dryness and partitioned between 1 N aqueous HCl and EtOAC. The organic phase was washed three times with water, dried, and evaporated to a residue which was stirred in ether (20 mL) for 1 h and filtered to afford alcohol **8c** as a white solid (1.46 g, 65%).

3-(Chloromethyl)-6-hydroxy-1-phenylnaphthalene (8d). A mixture of alcohol **8c** (1.46 g, 5.84 mmol), triphenylphosphine (3.0 g, 11.7 mmol), and CCl_4 (10 g, 58.4 mmol) in CH_2Cl_2 was refluxed for 2 h. The mixture was evaporated and the residue chromatographed on silica gel (hexane/EtOAc, 4:1) to yield **8d** as a white solid (1.40 g, 89%): ^{1}H NMR (400 MHz, acetone-d_6) δ 4.88 (s, 2H), 7.13 (dd, 1H), 7.30 (m, 2H), 7.42−7.58 (m, 5H), 7.73 (d, 1H), 7.80 (s, 1H), 8.72 (s, 1H).

3-Acetyl-6-hydroxy-1-phenylnaphthalene (8e). To a solution of naphthoic acid **30** (12 g, 45.4 mmol) in ether (150 mL) at 0 °C was added slowly 1.4 M methyllithium in ether (160 mL, 224 mmol). The mixture was then stirred at room temperature for 24 h, the reaction quenched with chlorotrimethylsilane until pH 1, and the mixture diluted with water (100 mL). After 2 h of stirring, the organic phase was collected, washed with water, aqueous saturated K_2CO_3, and brine, dried, and evaporated. The residue was triturated in ether and filtered to afford ketone **8e** as a beige solid (6.76 g, 57%):

^{1}H NMR (250 MHz, $CDCl_3$) δ 2.75 (s, 3H), 5.61 (s, 1H), 7.15−7.85 (m, 9H), 8.30 (s, 1H).

3-Ethyl-6-hydroxy-1-phenylnaphthalene (8f). A mixture of ketone **8e** (167 mg) and palladium hydroxide (20%) on carbon (50 mg) in EtOAc (30 mL) was stirred under an atmosphere of hydrogen at room temperature for 24 h. After filtration, evaporation of the filtrate and chromatography on silica gel (hexane/EtOAc/CH_2Cl_2, 9:1:5) afforded the desired naphthol **8f** as a foamy solid (165 mg, 100%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (t, 3H), 2.80 (q, 2H), 5.40 (s, 1H), 6.95−7.80 (m, 10H).

4-(3-Furyl)-7-hydroxy-2-naphthalenenitrile (8g). Step 1: Ethyl 4-(3-Furyl)-3-oxobutanoate. To a solution of ethyl 3-iodopropanoate (96 g, 0.42 mol) in benzene (800 mL) and *N*,*N*-dimethylacetamide (80 mL), mechanically stirred, was added zinc−copper couple (50 g, 0.77 mol), and the mixture was stirred at 65 °C for 1.5 h. After cooling to 30 °C, there was added tetrakis(triphenylphosphine)palladium(0) (2 g), and then a solution of 3-furoyl chloride (50 g, 0.38 mol) in benzene (50 mL) was added at such a rate that the temperature did not exceed 55 °C. After the addition, the mixture was stirred until the temperature had dropped to 30 °C; then it was filtered. The filtrate was washed with 10% aqueous HCl (250 mL) and then three times with water, dried, and evaporated to an oil which solidified. The solid was triturated with hexane/ether (2:1) and filtered, affording the desired product (60.4 g, 80%): mp 55−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H), 2.72 (t, 2H), 3.09 (t, 2H), 4.15 (q, 2H), 6.78 (d, 1H), 7.44 (t, 1H), 8.07 (d, 1H).

Step 2: 4-(3-Furyl)-3-oxobutanoic Acid (31). To a suspension of ester from step 1 (60 g, 0.31 mol) in methanol (300 mL) and THF (70 mL) was added 2.5 N aqueous NaOH (130 mL), and the mixture was stirred at room temperature for 1 h. The resulting solution was diluted with water (250 mL) and then concentrated to a volume of 300 mL. Water was added (100 mL), and the mixture was filtered. The yellow filtrate was acidified with 6 N aqueous HCl and the resulting precipitate filtered to afford the desired acid **31** (47.2 g, 92%) as a tan solid: mp 148−149 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.64 (t, 2H), 3.10 (t, 2H), 6.78 (d, 1H), 7.65 (t, 1H), 8.42 (d, 1H).

Step 3: Furanone 32. A mixture of acid from step 2 (47 g, 0.28 mol), sodium acetate (25.4 g, 0.31 mol), *m*-anisaldehyde (42.2 g, 0.31 mol), and acetic anhydride (158 mL, 1.67 mol) was mechanically stirred and heated at 70 °C for 4.5 h. After cooling, the mixture was poured onto cold water (1 L), and after stirring for 20 min, the mixture was filtered. When dry, the solid was stirred in ether (300 mL) at room temperature for 30 min and filtered again affording furanone **32** as a gold-colored solid (43.8 g, 58%): mp 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.62 (s, 1H), 6.68 (d, 1H), 6.96 (dd, 1H), 7.11 (s, 1H), 7.21 (d, 1H), 7.40 (m, 2H), 7.53 (t, 1H), 7.88 (d, 1H).

Step 4: Methyl 4-(3-Furyl)-7-methoxy-2-naphthoate (33). To a suspension of furanone **32** (32.6 g, 0.122 mol) in methanol (250 mL), mechanically stirred, was slowly added sulfuric acid (24.5 g, 0.25 mol), and the resulting mixture was refluxed for 2 days. Some methanol was distilled off (100 mL), and the resulting suspension was cooled to room temperature and filtered, affording a solid (20.2 g) greatly enriched in the desired regioisomer. The solid was stirred in methanol (50 mL) at room temperature for 1 h and filtered, affording naphthoate **33** (19 g, 55%) as a grayish solid: mp 95−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.99 (s, 3H), 6.70 (s, 1H), 7.25 (m, 2H), 7.58 (s, 1H), 7.69 (s, 1H), 7.91 (s, 1H), 8.07 (d, 1H), 8.48 (s, 1H).

Step 5: 4-(3-Furyl)-7-methoxy-2-naphthalenenitrile. Following the procedure described above for the preparation of nitrile **8b**, using ester **33** as starting material and 2 equiv of dimethylaluminum amide, the desired nitrile was obtained in 75% yield as a light yellow solid: ^{1}H NMR (400 MHz, acetone-d_6) δ 3.98 (s, 3H), 6.86 (s, 1H), 7.37 (dd, 1H), 7.52 (d, 1H), 7.55 (s, 1H), 7.79 (s, 1H), 7.96 (s, 1H), 8.14 (d, 1H), 8.30 (s, 1H).

Step 6: 4-(3-Furyl)-7-hydroxy-2-naphthalenenitrile (8g). Following the demethylation procedure described above in the preparation of compound **30**, the desired naphthol **8g** was obtained in 57% yield as a light yellow solid: mp 198−199 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.84 (s, 1H), 7.34 (dd, 1H), 7.39 (s, 1H), 7.46 (s, 1H), 7.77 (s, 1H), 7.94 (s, 1H), 8.09 (d, 1H), 8.17 (s, 1H).

4-(3-Furyl)-7-hydroxy-2-naphthalenecarboxaldehyde (8h). To a solution of nitrile **8g** (1.5 g, 6.4 mmol) in THF (30 mL) at −78 °C was added dropwise 1.5 M diisobutylaluminum hydride in toluene (9.3 mL, 14 mmol). The mixture was stirred for 1 h at 0 °C and then at room temperature for 1 h and the reaction quenched with 10% aqueous HCl at 0 °C. The mixture was partitioned between EtOAc and water. The organic phase yielded aldehyde **8h** (1.35 g, 90%) as a pale yellow solid which was used as such: ^{1}H NMR (250 MHz, acetone-d_6) δ 6.80 (s, 1H), 7.35 (dd, 1H), 7.50 (s, 1H), 7.70 (s, 1H), 7.80 (s, 1H), 7.90 (s, 1H), 8.10 (d, 1H), 8.30 (s, 1H), 9.05 (s, 1H), 10.15 (s, 1H).

6-Hydroxy-1-phenyl-3-(tetrazol-5-yl)naphthalene (8i). Following the procedure for the preparation of **8j** but using nitrile **8b** as starting material, the desired tetrazole was obtained in 61% yield as a brown solid which was used as such.

1-(3-Furyl)-6-hydroxy-3-(tetrazol-5-yl)naphthalene (8j). To a solution of nitrile **8g** (134 mg, 0.57 mmol) in 1,2-dichlorobenzene (13 mL) was added tributyltin azide (663 mg, 1.7 mmol), and the mixture was stirred at 150 °C for 2 h. After cooling, the reaction was quenched with acetic acid (0.7 mL, 12 mmol), and 15 min later the insolubles were filtered to afford the expected tetrazole (158 mg) as a dark solid which was used as such.

6-Hydroxy-3-(2-methyltetrazol-5-yl)-1-phenylnaphthalene (8k) and 6-Hydroxy-3-(1-methyltetrazol-5-yl)-1-phenylnaphthalene (8l). Following the procedure for the preparation of **8m** but using tetrazole **8i** as starting material, a mixture of two methylated isomers was obtained and separated by chromatography on silica gel (hexane/EtOAc, 7:3). **8k**: beige solid (44%); ^{1}H NMR (250 MHz, acetone-d_6) δ 4.45 (s, 3H), 7.20 (dd, 1H), 7.40 (m, 1H), 7.50 (m, 5H), 7.75 (d, 1H), 7.90 (d, 1H), 8.45 (s, 1H), 9.00 (s, 1H). **8l**: beige solid (10%); ^{1}H NMR (250 MHz, acetone-d_6) δ 4.40 (s, 3H), 7.25 (dd, 1H), 7.40 (m, 1H), 7.50 (m, 5H), 7.60 (s, 1H), 7.80 (d, 1H), 8.20 (s, 1H), 9.05 (s, 1H).

1-(3-Furyl)-6-hydroxy-3-(2-methyltetrazol-5-yl)naphthalene (8m). To a solution of tetrazole **8j** (158 mg, 0.57 mmol) in DMF (3 mL) were added cesium carbonate (203 mg, 0.62 mmol) and iodomethane (0.039 mL, 0.62 mmol). The mixture was stirred at room temperature overnight, then the reaction was quenched with water, and the mixture was extracted with EtOAc. The product from the organic phase was chromatographed on silica gel (hexane/EtOAc, 7:3) to yield methyltetrazole **8m** (67 mg, 40%) as a cream-colored solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.45 (s, 3H), 6.75 (s, 1H), 7.30 (m, 2H), 7.60 (s, 1H), 7.70 (s, 1H), 8.10 (m, 2H), 8.50 (s, 1H).

6-Hydroxy-1-(3-furyl)-3-(2-oxazolinyl)naphthalene (8o). This compound was prepared in the same manner as **8p** using ethanolamine as starting material, in 51% yield: ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.00 (t, 2H), 4.45 (t, 2H), 6.80 (s, 1H), 7.20 (dd, 1H), 7.30 (d, 1H), 7.70 (d, 1H), 7.85 (s, 1H), 7.95 (d, 1H), 8.00 (s, 1H), 8.20 (s, 1H), 9.30 (br s, 1H).

6-Hydroxy-1-(3-furyl)-3-(4,4-dimethyl-2-oxazolinyl)naphthalene (8p). A mixture of nitrile **8g** (300 mg, 1.27 mmol), 2-amino-2,2-dimethylethanol (0.74 mL, 7.8 mmol), and zinc chloride (20 mg) was heated at reflux in chlorobenzene (20 mL) for 3 days. The mixture was concentrated and chromatographed on silica gel (hexane/EtOAc, 3:2) to yield naphthol **8p** (293 mg, 75%) as a white solid: ^{1}H NMR (250 MHz, acetone-d_6) δ 1.35 (s, 6H), 4.20 (s, 2H), 6.80 (d, 1H), 7.25 (dd, 1H), 7.35 (d, 1H), 7.75 (t, 1H), 7.80 (d, 1H), 7.90 (s, 1H), 8.05 (d, 1H), 8.20 (s, 1H), 8.90 (s, 1H).

6-Hydroxy-1-(3-furyl)-3-(2-thiazolinyl)naphthalene (8q). A mixture of nitrile **8g** (500 mg, 2.1 mmol) and 2-aminoethanethiol hydrochloride (1.2 g, 10 mmol) in chlorobenzene (30 mL) was refluxed for 24 h. After cooling, the mixture was diluted with EtOAc, washed twice with saturated $NaHCO_3$ and then with brine, dried, and evaporated. The solid residue was stirred vigorously with ether for 1 h at room temperature and filtered to afford naphthol **8q** (379 mg, 60%) as a pale yellow

solid: ^{1}H NMR (250 MHz, acetone-d_6) δ 3.50 (t, 2H), 4.45 (t, 2H), 6.70 (s, 1H), 7.25 (dd, 1H), 7.40 (d, 1H), 7.75 (t, 1H), 7.80 (d, 1H), 7.90 (s, 1H), 8.05 (m, 2H), 8.90 (s, 1H).

3-(2-Benzothiazolyl)-6-hydroxy-1-(3-furyl)naphthalene (8r). To a saturated solution of HCl in 1,2-dichlorobenzene (12 mL) was added 2-aminothiophenol (0.5 mL, 4.7 mmol). To the resulting suspension was added nitrile **8g** (200 mg, 0.85 mmol), and the mixture was refluxed for 3 days. The cooled mixture was chromatographed as such on silica gel (hexane/EtOAc, 9:1), affording a solid which was triturated in a small volume of ether at room temperature for 30 min and filtered to yield naphthol **8r** (115 mg, 39%) as a pale yellow solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 6.90 (s, 1H), 7.30 (dd, 1H), 7.45 (m, 2H), 7.55 (t, 1H), 7.80 (t, 1H), 8.00 (s, 1H), 8.10 (m, 4H), 8.45 (s, 1H).

6-Hydroxy-1-(3-furyl)-3-(3-pyridylcarbonyl)naphthalene (8s). To a solution of 3-bromopyridine (0.4 mL, 4.15 mmol) in ether (25 mL) at −78 °C was added dropwise 2.06 M *n*-butyllithium in hexane (2.0 mL, 4.12 mmol), and the resulting yellow mixture was stirred at −78 °C for 20 min. There was added a solution of nitrile **8g** (250 mg, 1.06 mmol) in THF (5 mL), and the mixture was warmed to 0 °C and stirred for 15 min. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was stirred at room temperature for 30 min and partitioned between EtOAc and water. Chromatography of the organic residue on silica gel (hexane/EtOAc, 1:9) afforded naphthol **8s** as a yellow solid (161 mg, 48%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.70 (m, 1H), 7.10 (d, 1H), 7.20 (dd, 1H), 7.45−7.70 (m, 5H), 8.05 (d, 1H), 8.15 (m, 1H), 8.75 (m, 1H), 8.85 (s, 1H).

6-Hydroxy-1-(3-furyl)-3-(2-thiazolylcarbonyl)naphthalene (8t). To a solution of thiazole (0.3 mL, 4.2 mmol) in THF (20 mL) at −78 °C was added 1.1 M *n*-butyllithium in hexane (3.8 mL, 4.2 mmol). After 30 min, there was added a solution of nitrile **8g** (250 mg, 1.06 mmol) in THF (5 mL). The reaction mixture was warmed to −20 °C and then the reaction quenched with 10% aqueous HCl. The mixture was stirred at room temperature for 1 h and extracted with ether. The extracts were washed with brine, dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 85:15) to afford ketone **8t** (195 mg, 57%) as an orange solid: ^{1}H NMR (250 MHz, acetone-d_6) δ 6.85 (s, 1H), 7.35 (dd, 1H), 7.50 (d, 1H), 7.80 (s, 1H), 7.95 (s, 1H), 8.15 (m, 5H), 9.10 (s, 1H).

6-Hydroxy-1-(3-furyl)-3-(2-thiazolylmethyl)naphthalene (8u). To a mixture of ketone **8t** (420 mg, 1.3 mmol) and potassium carbonate (1.4 g, 10 mmol) in diethylene glycol (10 mL) was added hydrazine (0.1 mL, 3.2 mmol). The mixture was stirred at 190 °C for 2 h, cooled down, and diluted with EtOAc and pH 7 buffer solution. The organic phase was washed with buffer and then with brine, dried, and evaporated. Chromatography on silica gel (hexane/EtOAc, 3:2) gave naphthol **8u** (221 mg, 55%) as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.50 (s, 2H), 6.65 (m, 1H), 7.05 (m, 2H), 7.15 (br s, 1H), 7.25 (m, 2H), 7.45 (s, 1H), 7.55 (t, 1H), 7.60 (s, 1H), 7.75 (d, 1H), 7.90 (d, 1H).

Methyl 4-*n*-Butyl-7-hydroxy-2-naphthoate (8v). Step 1: 4-*n*-Butyl-7-methoxy-1,2-dihydro-2-naphthoic Acid. To a suspension of anhydrous $CeCl_3$ (520 mg, 2.1 mmol) in THF (25 mL) at 0 °C was added tetralone **34**[22] (400 mg, 2.1 mmol) followed by *n*-butylmagnesium bromide (2.0 M) in ether (1.05 mL, 2.1 mmol). The mixture was stirred at 0 °C for 2 h; then the reaction was quenched with 1 N aqueous HCl and the mixture extracted with ether. The extracts were washed with 1 N HCl and then with brine, dried, and evaporated. Chromatography on silica gel (hexane/EtOAc, 4:1) yielded the dihydronaphthoic acid as an oil (263 mg, 72%).

Step 2: 4-*n*-Butyl-7-methoxy-2-naphthoic Acid. The acid from step 1 was dehydrogenated as described in step 2 of the preparation of naphthol **8w** to afford the desired naphthoic acid as a white solid (64%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (t, 3H), 1.50 (m, 2H), 1.75 (m, 2H), 3.10 (m, 2H), 3.95 (s, 3H), 7.30 (m, 2H), 7.80 (s, 1H), 8.00 (d, 1H), 8.50 (s, 1H).

Step 3: Methyl 4-*n*-Butyl-7-hydroxy-2-naphthoate (8v). The acid from step 2 was demethylated with pyridine hydrochloride as described in step 3 of the preparation of naphthol **8w** and the product esterified with diazomethane to afford naphthol **8v** (95%) as a brown oil.

Methyl 4-Benzyl-7-hydroxy-2-naphthoate (8w). Step 1: Methyl 4-Benzyl-7-methoxy-1,2-dihydro-2-naphthoate. To a solution of 3-carbethoxy-6-methoxy-1-tetralone (**34**)[22] (1.5 g) in THF (30 mL) at 0 °C was added 2.0 M benzylmagnesium chloride in THF until no more **34** remained, as monitored by TLC. The reaction was quenched with 10% aqueous HCl and extracted with ether. The extract was washed three times with water and brine, dried, and evaporated to afford a residue which was refluxed in benzene (30 mL) containing camphorsulfonic acid (20 mg) for 4 h with azeotropic removal of water. After evaporation of the solvent, the crude product (dihydronaphthoic acid) was esterified with ethereal diazomethane and the product chromatographed on silica gel (hexane/EtOAc, 95:5) to afford the desired methyl ester (1.29 g, 76%) as an oil which was used as such in the next step.

Step 2: Methyl 4-Benzyl-7-methoxy-2-naphthoate. A mixture of ester from step 1 (1.29 g, 4.2 mmol) and DDQ (950 mg, 4.2 mmol) in benzene (25 mL) was stirred at room temperature for 30 min. The mixture was diluted with ether, washed with aqueous NH_4Cl, water, and brine, dried, and evaporated. The residue was chromatographed on silica gel (hexane/EtOAc, 90:10) to afford the expected product as an oil (800 mg, 62%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.95 (s, 3H), 4.45 (s, 2H), 7.30 (m, 7H), 7.80 (d, 1H), 7.90 (d, 1H), 8.45 (s, 1H).

Step 3: Methyl 4-Benzyl-7-hydroxy-2-naphthoate (8w). A mixture of ester from step 2 (770 mg, 2.5 mmol) and pyridine·HCl (6.0 g, 52 mmol) was heated at 180−200 °C for 30 min. After cooling the mixture was partitioned between EtOAc (50 mL) and 3% aqueous HCl (10 mL). The organic phase was washed with water and then brine, dried, and evaporated to afford the naphthoic acid which was esterified with ethereal diazomethane. The ester was chromatographed on silica gel (hexane/EtOAc, 85:15) to afford naphthol **8w** as a foamy solid (456 mg, 62%): ^{1}H NMR (250 MHz, acetone-d_6) δ 3.90 (s, 3H), 4.45 (s, 2H), 7.25 (m, 6H), 7.40 (m, 1H), 7.70 (m, 1H), 8.00 (m, 1H), 8.30 (m, 1H), 8.90 (s, 1H).

Preparation of Final Products 3. Method A: 7-[[3-(4-Hydroxytetrahydro-2*H*-pyran-4-yl)phenyl]methoxy]-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (3a). A mixture of lactonic naphthol **7a** (800 mg, 2.89 mmol), benzylic halide **6a** (1.02 g, 3.76 mmol), and potassium carbonate (1.03 g, 7.44 mmol) in DMF (10 mL) was stirred at room temperature for 21 h. The mixture was diluted with water (50 mL) and extracted three times with EtOAc; the extracts were washed with 1 N NaOH and then twice with brine, dried, and evaporated. Chromatography on silica gel ($CHCl_3$/EtOAc, 1:1) afforded the desired product as a yellow solid (1.02 g, 75%): mp 191−192 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 3H), 2.20 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 5.25 (s, 2H), 7.35−7.60 (m, 10H), 7.65 (s, 1H), 7.75 (d, 1H), 8.45 (s, 1H).

Method B: 7-[[3-(4-Hydroxytetrahydro-2*H*-pyran-4-yl)-phenyl]methoxy]-4-(3-methoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (3p). A mixture of lactonic naphthol **7b** (204 mg, 0.67 mmol), benzylic halide **6a** (218 mg, 0.80 mmol), and cesium carbonate (343 mg, 1.33 mmol) in DMF (8 mL) was stirred at room temperature for 3 h. The mixture was diluted with water and acidified with 1 N aqueous HCl and the precipitate filtered. Purification by chromatography on silica gel (hexane/EtOAc) afforded the desired product as a white solid (225 mg, 68%): mp 182−184 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.71 (d, 2H), 2.22 (m, 2H), 3.86 (s, 3H), 3.90 (m, 4H), 5.24 (s, 2H), 5.26 (s, 2H), 6.92 (m, 2H), 7.03 (dd, 1H), 7.33 (dd, 1H), 7.45 (m, 5H), 7.67 (s, 1H), 7.77 (d, 1H), 8.38 (s, 1H).

Method C: 7-[[3-(1*R*,5*S*)-(3α-Hydroxy-6,8-dioxabicyclo-[3.2.1]octan-3-yl)phenyl]methoxy]-4-(3-furyl)naphtho-[2,3-*c*]furan-1(3*H*)-one (3v). Diethyl azodicarboxylate (0.052 mL, 0.33 mmol) was added to a solution of triphenylphosphine (87 mg, 0.33 mmol) in THF (2 mL). After 5 min, there were added naphthol **7e** (88 mg, 0.33 mmol) and, 5 min later, alcohol **6f** (71 mg, 0.30 mmol). The mixture was stirred at room temperature for 16 h, diluted with EtOAc (20 mL), and washed with 1 N aqueous NaOH, water, and brine, and the organic phase was evaporated. The residue was chromatographed

twice on silica gel ($CHCl_3$/EtOAc, 3:1, and then toluene/EtOAc, 4:1) to afford **3v** (42 mg, 29%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (m, 2H), 2.30 (d, 1H), 2.50 (dd, 1H), 3.80 (m, 1H), 3.91 (s, 1H), 4.50 (d, 1H), 4.70 (m, 1H), 5.22 (s, 2H), 5.33 (s, 2H), 5.78 (s, 1H), 6.60 (m, 1H), 7.35−7.50 (m, 5H), 7.65 (m, 3H), 8.01 (d, 1H), 8.33 (s, 1H).

The following compounds were prepared according to analogous procedures. Synthetic and physical data for final compounds **3a**−**v** are presented in Table 1.

3d: glassy solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (d, 3H), 1.70 (m, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 5.25 (s, 2H), 5.70 (q, 1H), 7.27−7.70 (m, 12H), 8.35 (s, 1H); HRMS ($C_{31}H_{28}O_5 + H^+$) calcd 481.2017, found 481.2015.

3e: white foamy solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 6H), 1.70 (m, 2H), 2.22 (m, 2H), 3.93 (m, 4H), 5.23 (s, 2H), 7.21−7.58 (m, 11H), 7.67 (s, 1H), 8.35 (s, 1H); HRMS ($C_{32}H_{30}O_5 + H^+$) calcd 495.2172, found 495.2172.

3f: white solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (d, 6H), 1.65−1.80 (m, 5H), 4.05 (m, 2H), 5.25 (m, 4H), 7.30−7.80 (m, 12H), 8.40 (s, 1H); HRMS ($C_{32}H_{30}O_5 + H^+$) calcd 495.2172, found 495.2170.

3g: white solid; mp 171−173 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90 (d, 2H), 2.55 (dd, 2H), 3.10 (s, 1H), 4.95 (d, 2H), 5.70 (s, 2H), 5.75 (s, 2H), 6.60 (s, 2H), 7.30−7.60 (m, 10H), 7.65 (s, 1H), 7.70 (d, 1H), 8.40 (s, 1H).

3i: white solid; mp 179−180 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.75 (d, 1H), 1.99 (d, 1H), 2.16 (dd, 1H), 2.27 (m, 1H), 3.47 (s, 3H), 3.79 (dd, 1H), 4.18 (m, 1H), 4.76 (s, 1H), 4.95 (d, 1H), 5.23 (s, 2H), 5.24 (s, 2H), 7.30−7.60 (m, 10H), 7.72 (m, 2H), 8.38 (s, 1H).

3j: white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (m, 2H), 2.30 (dd, 1H), 2.45 (dd, 1H), 3.80 (m, 1H), 3.90 (s, 1H), 4.50 (d, 1H), 4.70 (m, 1H), 5.20 (s, 2H), 5.25 (s, 2H), 5.75 (s, 1H), 7.25−7.70 (m, 12H), 8.35 (s, 1H).

3k: cream-colored solid; mp 167−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 1H), 1.72 (d, 2H), 2.23 (m, 2H), 3.94 (m, 4H), 5.23 (s, 4H), 7.18−7.52 (m, 9H), 7.67 (s, 1H), 7.70 (d, 1H), 8.38 (s, 1H).

3l: white solid; mp 125−127 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.64 (d, 2H), 2.10 (m, 2H), 3.74 (m, 2H), 3.90 (m, 2H), 4.08 (s, 1H), 5.33 (s, 6H), 7.36−7.46 (m, 3H), 7.55 (d, 3H), 7.66 (d, 2H), 7.72−7.82 (m, 3H), 8.41 (s, 1H).

3m: white solid; mp 220−223 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.63 (d, 2H), 2.11 (m, 2H), 3.74 (m, 2H), 3.88 (m, 2H), 3.92 (s, 1H), 5.30 (s, 2H), 5.34 (s, 2H), 7.15 (d, 2H), 7.38−7.45 (m, 5H), 7.55 (d, 1H), 7.78 (m, 3H), 8.38 (s, 1H).

3n: white solid; mp 194−196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 1H), 1.70 (d, 2H), 2.22 (m, 2H), 3.93 (m, 4H), 5.22 (s, 2H), 5.24 (s, 2H), 7.30−7.49 (m, 9H), 7.64 (d, 1H), 7.67 (s, 1H), 8.42 (s, 1H).

3o: lactonic naphthol used (**7k**) was a mixture of isomeric lactones; purification achieved on the mixture of coupled products by chromatography on silica gel (hexane/EtOAc, 1:1) to afford **3o** as a white solid; mp 198−200 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 1H), 1.72 (d, 2H), 2.22 (m, 2H), 3.93 (m, 4H), 5.18 (q, 2H), 5.24 (s, 2H), 7.30 (m, 2H), 7.39−7.55 (m, 7H), 7.62 (dd, 1H), 7.66 (s, 1H), 8.43 (s, 1H).

3q: yellow solid; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.55 (m, 2H), 2.00 (m, 2H), 3.75 (m, 4H), 5.10 (s, 1H), 5.30 (s, 2H), 5.40 (m, 2H), 7.40 (m, 4H), 7.65 (m, 3H), 7.90 (s, 1H), 8.00 (m, 1H), 8.55 (s, 1H), 8.75 (m, 2H); HRMS ($C_{29}H_{25}NO_5 + H^+$) calcd 468.1811, found 468.1812.

3r: white solid; mp 164−166 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.63 (d, 2H), 2.10 (m, 2H), 3.25 (m, 2H), 3.90 (m, 2H), 4.08 (s, 1H), 5.33 (s, 2H), 5.60 (s, 2H), 6.78 (m, 1H), 7.02 (m, 1H), 7.39−7.48 (m, 2H), 7.50−7.58 (m, 2H), 7.70 (m, 2H), 7.79 (s, 1H), 8.39 (s, 1H), 8.47 (d, 1H).

3s: cream-colored solid; mp 181−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 1H), 1.67 (d, 2H), 2.22 (m, 2H), 3.94 (m, 4H), 5.24 (s, 2H), 5.35 (s, 2H), 6.61 (d, 1H), 7.42 (m, 5H), 7.65 (m, 3H), 8.03 (d, 1H), 8.35 (s, 1H).

3t: white solid; mp 172−175 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.65 (d, 2H), 2.12 (m, 2H), 3.77 (m, 2H), 3.93 (m, 2H), 4.09 (s, 1H), 5.33 (s, 2H), 5.40 (s, 2H), 7.36 (m, 1H), 7.40−7.48 (m, 3H), 7.57 (d, 1H), 7.74 (m, 1H), 7.80 (m, 3H), 7.93 (d, 1H), 8.40 (s, 1H).

3u: white solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.06 (m, 1H), 2.12 (d, 1H), 2.34 (d, 1H), 2.50 (dd, 1H), 3.80 (dd, 1H), 3.95 (s, 1H), 4.52 (d, 1H), 4.72 (t, 1H), 5.22 (s, 2H), 5.36 (s, 2H), 5.80 (s, 1H), 6.60 (s, 1H), 7.30−7.50 (m, 5H), 7.60−7.70 (m, 3H), 8.00 (d, 1H), 8.36 (s, 1H).

7-[[3-(4-Hydroxytetrahydro-2*H*-pyran-4-yl)phenyl]-methoxy]-3-hydroxy-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (3b). A mixture of carboxylate **10a** (271 mg, 0.43 mmol) and pyridinium dichromate (487 mg, 1.3 mmol) in acetone (25 mL) was stirred at room temperature for 5 h and then filtered through Celite. The filtrate was evaporated and the residue chromatographed on silica gel ($CHCl_3$/MeOH, 9:1) to afford **3b** (40 mg, 19%) as a white solid: mp 219−220 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.60 (d, 2H), 2.10 (m, 2H), 3.75 (dd, 2H), 3.90 (m, 2H), 4.10 (s, 1H), 5.30 (s, 2H), 6.70 (s, 1H), 7.35−7.60 (m, 9H), 7.65 (d, 1H), 7.80 (m, 2H), 8.35 (s, 1H); HRMS ($C_{30}H_{26}O_6 + H^+$) calcd 483.1807, found 483.1809.

3c. To a solution of methyl glycoside **3i** (103 mg, 0.21 mmol) in THF (3 mL) was added 10% aqueous HCl (1.5 mL), and the mixture was stirred at room temperature for 24 h. Saturated aqueous $NaHCO_3$ (25 mL) was added, and the mixture was extracted with EtOAc. Chromatography of the organic residue on silica gel ($CHCl_3$/EtOAc, 1:1) gave **3c** (68 mg, 68%) as a colorless gum and as a mixture of α and β epimers**:** ^{1}H NMR (500 MHz, acetone-d_6) assignments done on mixture, α epimer δ 1.70 (d, 1H), 1.90 (d, 1H), 2.10 (dd, 1H), 2.25 (m, 1H), 3.65 (m, 1H), 4.35 (m, 1H), 5.30 (d, 1H), 5.30 (s, 2H), 5.35 (s, 2H), 5.90 (d, 1H), 7.35−7.45 (m, 3H), 7.45−7.55 (m, 4H), 7.58 (m, 2H), 7.72 (m, 2H), 7.80 (s, 1H), 8.40 (s, 1H); β-epimer, δ 1.60 (d, 1H), 1.80 (dd, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 3.80 (dd, 1H), 3.95 (d, 1H), 5.10 (dd, 1H), 5.30 (s, 2H), 5.35 (s, 2H), 7.35−7.45 (m, 3H), 7.45−7.55 (m, 4H), 7.58 (m, 2H), 7.72 (m, 2H), 7.80 (s, 1H), 8.40 (s, 1H); HRMS ($C_{30}H_{26}O_6 + H^+ - 2H_2O$) calcd 447.1596, found 447.1595.

3h. A mixture of alkene **3g** (52 mg, 1.1 mmol) and 10% palladium on carbon (22 mg) in EtOAc (3 mL) was stirred at room temperature under hydrogen for 45 min. After filtration, the filtrate was evaporated and the residue chromatographed on silica gel ($CHCl_3$/hexane, 4:1) to yield compound **3h** (38 mg, 73%) as a white solid: mp 125−127 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.80 (d, 2H), 2.00 (m, 2H), 2.40 (m, 4H), 4.50 (m, 2H), 5.65 (s, 2H), 5.70 (s, 2H), 7.25−7.60 (m, 10H), 7.65 (s, 1H), 7.70 (d, 1H), 8.35 (s, 1H).

7-[[3-(4-Hydroxy-2-oxotetrahydro-2*H*-pyran-4-yl)-phenyl]methoxy]-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (5). A mixture of hydroxypyran **3c** (152 mg, 0.31 mmol) and silver carbonate on Celite[8] (1.60 g) in benzene (25 mL) was refluxed for 4 h. The mixture was filtered and the filtrate evaporated. Chromatography on silica gel ($CHCl_3$/EtOAc, 3:2) yielded lactone **5** (59 mg, 39%) as a white solid: mp 192−195 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.15 (m, 1H), 2.40 (m, 1H), 2.95 (q, 2H), 4.40 (m, 1H), 4.75 (m, 1H), 5.25 (s, 4H), 7.30−7.55 (m, 10H), 7.60 (s, 1H), 7.75 (d, 1H), 8.40 (s, 1H). Anal. ($C_{30}H_{24}O_6$·0.4EtOAc) C,H.

Preparation of Final Products 9. The following compounds were prepared by one of the three methods described previously for the preparation of compounds **3.** Synthetic and physical data for final compounds **9a**−**ac** are presented in Table 2.

9a: white solid; mp 121−122.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (t, 3H), 1.60 (s, 1H), 1.70 (m, 2H), 2.20 (m, 2H), 2.80 (q, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 7.10−7.55 (m, 12H), 7.65 (s, 1H), 7.80 (d, 1H); HRMS ($C_{30}H_{30}O_3$+H^+) calcd 539.2274, found 539.2273.

9g: pale yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 3H), 2.20 (m, 2H), 2.70 (s, 3H), 3.90 (m, 4H), 5.20 (s, 2H), 7.25 (m, 1H), 7.40−7.50 (m, 10H), 7.65 (s, 1H), 7.85 (m, 2H), 8.35 (s, 1H); HRMS ($C_{30}H_{28}O_4 + H^+$) calcd 453.2065, found 453.2066.

9h: white solid; mp 98−100 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 3H), 2.20 (m, 2H), 3.90 (m, 4H), 3.95 (s, 3H), 5.20 (s, 2H), 7.25 (m, 1H), 7.35−7.50 (m, 9H), 7.65 (s, 1H), 7.85 (m, 2H), 8.50 (s, 1H); HRMS ($C_{30}H_{28}O_5 + H^+$) calcd 469.201 47, found 469.201 49.

9i: yellow solid; IR (KBr) 3600−3200, 2220, 1640, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.65 (dd, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 7.80−8.10 (m, 14H).

9l: white solid; mp 185 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 4.40 (s, 3H), 5.20 (s, 2H), 7.25 (dd, 1H), 7.35−7.60 (m, 9H), 7.65 (s, 1H), 7.85 (d, 1H), 8.00 (d, 1H), 8.55 (s, 1H).

9m: white solid; mp 209−210 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 2H), 1.80 (s, 1H), 2.20 (m, 2H), 3.90 (m, 4H), 4.25 (s, 3H), 5.20 (s, 2H), 7.30 (dd, 1H), 7.35−7.50 (m, 9H), 7.60 (d, 1H), 7.65 (s, 1H), 7.90 (d, 1H), 8.15 (s, 1H).

9o: cream-colored solid; mp 144−145 °C; IR (KBr) 3480, 2230, 1625, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (m, 2H), 2.18 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 6.65 (s, 1H), 7.28 (m, 2H), 7.34−7.55 (m, 5H), 7.65 (m, 2H), 8.08 (m, 2H).

9p: white solid; mp 155−157 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 2H), 1.85 (s, 1H), 2.20 (m, 2H), 3.90 (m, 4H), 4.45 (s, 3H), 5.20 (s, 2H), 6.75 (s, 1H), 7.25 (dd, 1H), 7.30−7.50 (m, 4H), 7.60 (t, 1H), 7.65 (s, 1H), 7.70 (s, 1H), 8.10 (m, 2H), 8.50 (s, 1H).

9q: pale yellow foam; ^1H NMR (250 MHz, DMSO-d_6) δ 1.55 (m, 2H), 2.00 (m, 2H), 3.75 (m, 4H), 4.15 (t, 2H), 4.80 (t, 2H), 5.30 (s, 2H), 6.90 (s, 1H), 7.40 (m, 4H), 7.65 (s, 1H), 7.75 (d, 1H), 7.90 (m, 2H), 8.10 (m, 2H), 8.50 (s, 1H).

9r: yellow solid; ^1H NMR (250 MHz, DMSO-d_6) δ 1.55 (m, 2H), 2.00 (m, 2H), 3.50 (t, 2H), 3.75 (m, 4H), 4.45 (t, 2H), 5.10 (s, 1H), 5.25 (s, 2H), 6.85 (s, 1H), 7.30−7.50 (m, 4H), 7.65 (s, 1H), 7.75 (m, 2H), 7.90 (t, 1H), 8.00 (m, 2H), 8.15 (s, 1H).

9s: yellow foam; ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 6H), 1.70 (m, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 4.20 (s, 2H), 5.20 (s, 2H), 6.70 (s, 2H), 7.30 (m, 2H), 7.45 (m, 3H), 7.55 (t, 1H), 7.65 (m, 2H), 7.90 (s, 1H), 8.05 (d, 1H), 8.30 (s, 1H).

9t: white solid; mp 165−167 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 3H), 2.20 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 6.75 (s, 1H), 7.25 (dd, 1H), 7.35−7.50 (m, 6H), 7.60 (t, 1H), 7.65 (s, 1H), 7.75 (s, 1H), 7.95 (d, 1H), 8.10 (m, 3H), 8.40 (s, 1H).

9v: pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (m, 3H), 2.20 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 6.70 (s, 1H), 7.25−7.80 (m, 11H), 8.10 (d, 1H), 8.75 (m, 1H), 8.85 (m, 1H); HRMS ($C_{32}H_{27}NO_5 + H^+$) calcd 506.1968, found 506.1970.

9w: yellow foam; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 5.25 (s, 2H), 6.75 (s, 1H), 7.35 (dd, 1H), 7.45 (m, 3H), 7.60 (t, 1H), 7.68 (s, 1H), 7.72 (s, 1H), 7.75 (d, 1H), 8.10 (m, 3H), 8.22 (d, 1H), 9.10 (s, 1H).

9x: pale yellow foam; ^1H NMR (250 MHz, $CDCl_3$) δ 1.65 (m, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 4.50 (s, 2H), 5.20 (s, 2H), 6.70 (s, 1H), 7.25 (m, 5H), 7.40−7.70 (m, 7H), 8.00 (d, 1H).

9y: yellow foam; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (t, 3H), 1.45 (m, 2H), 1.75 (m, 4H), 2.20 (m, 2H), 3.05 (m, 2H), 3.90 (m, 4H), 3.95 (s, 3H), 5.20 (s, 2H), 7.30−7.50 (m, 5H), 7.65 (s, 1H), 7.75 (s, 1H), 7.95 (d, 1H), 8.30 (s, 1H).

9z: pale yellow solid; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 2H), 1.75 (s, 1H), 2.20 (m, 2H), 3.90 (m, 4H), 3.95 (s, 3H), 4.45 (s, 2H), 5.20 (s, 2H), 7.15−7.50 (m, 10H), 7.60 (s, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.40 (s, 1H).

9aa: yellow solid; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 2H), 2.20 (m, 2H), 3.15−4.00 (m, 4H), 4.75 (s, 2H), 5.20 (s, 2H), 7.20 (dd, 1H), 7.25−7.85 (m, 13H).

9ab: yellow foam; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (m, 3H), 2.20 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 6.70 (s, 1H), 7.40 (m, 4H), 7.50 (m, 1H), 7.60 (t, 1H), 7.65 (s, 1H), 7.70 (s, 1H), 7.80 (s, 1H), 8.10 (d, 1H), 8.20 (s, 1H), 10.2 (s, 1H).

9ac: pale yellow solid; ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (dd, 2H), 2.30 (d, 1H), 2.50 (dd, 1H), 3.80 (m, 1H), 3.95 (s, 1H), 4.50 (d, 1H), 4.70 (m, 1H), 5.20 (m, 1H), 5.80 (s, 1H), 6.65 (s, 1H), 7.20−7.70 (m, 9H), 8.10 (m, 2H); HRMS ($C_{28}H_{23}NO_5 + H^+$) calcd 454.1654, found 454.1655.

9b. To a solution of ester **9h** (500 mg, 1.07 mmol) in THF (20 mL) at −78 °C was added 1 M diisobutylaluminum hydride in toluene (3.5 mL). The mixture was stirred at −78 °C for 1 h; then the reaction was quenched with 10% aqueous HCl and the mixture extracted with ether. The extracts were washed with aqueous HCl and then water, dried, and evaporated. Chromatography on silica gel (hexane/EtOAc, 2:3) gave **9b** as a white foam (385 mg, 82%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.90 (t, 1H), 2.20 (m, 2H), 3.90 (m, 4H), 4.85 (d, 2H), 5.20 (s, 2H), 7.15 (dd, 1H), 7.25 (d, 1H), 7.40−7.50 (m, 9H), 7.65 (s, 1H), 7.70 (s, 1H), 7.80 (d, 1H); HRMS ($C_{29}H_{28}O_4 + H^+$) calcd 441.2067, found 441.2066.

9c. To a solution of ketone **9g** (275 mg, 0.61 mmol) in ethanol (10 mL) was added $NaBH_4$ (45 mg, 1.2 mmol), and the mixture was stirred at room temperature for 3 h. After the reaction was quenched with 10% aqueous NaOH, the mixture was extracted with ether. After evaporation of the solvent, the crude product was stirred in a small volume of ether and filtered to afford **9c** (248 mg, 90%) as a white solid: mp 138.5−140.5 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.60 (d, 3H), 1.70 (m, 2H), 2.00 (d, 1H), 2.20 (m, 2H), 3.90 (m, 4H), 5.10 (m, 1H), 5.20 (s, 2H), 7.15 (dd, 1H), 7.30 (m, 2H), 7.45 (m, 8H), 7.65 (s, 1H), 7.75 (s, 1H), 7.80 (d, 1H); HRMS ($C_{30}H_{30}O_4 + H^+$) calcd 455.2224, found 455.2222.

9d. To a solution of ester **9h** (200 mg, 0.43 mmol) in THF (10 mL) at −78 °C was added 1.4 M methyllithium in ether (1.45 mL, 2.03 mmol). After 2 h at −78 °C. the reaction was quenched with saturated aqueous NH_4Cl and the mixture extracted with ether. The extracts were washed with brine, dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc/CH_2Cl_2, 1:1:1) to yield **9d** as a white foam (100 mg, 50%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.65−1.75 (m, 3H), 1.70 (s, 6H), 1.90 (s, 1H), 2.20 (m, 2H), 3.90 (m, 4H), 5,20 (s, 2H), 7.15 (dd, 1H), 7.30 (d, 1H), 7.35−7.50 (m, 9H), 7.65 (s, 1H), 7.80 (d, 1H), 7.85 (d, 1H); HRMS ($C_{31}H_{32}O_4 + H^+$) calcd 469.2379, found 469.2379.

9e. To a solution of alcohol **9b** (148 mg, 0.34 mmol) in THF (10 mL) at 0 °C were added NaH (10 mg, 0.417 mmol) and then iodomethane (30 mL, 0.48 mmol). The mixture was stirred at room temperature for 18 h; then the reaction was quenched with saturated aqueous NH_4Cl and the mixture extracted with ether. The crude product was chromatographed on silica gel (hexane/EtOAc, 3:2) to afford **9e** as a white foam (122 mg, 80%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.60 (s, 1H), 1.70 (m, 2H), 2.20 (m, 2H), 4.45 (s, 3H), 3.90 (m, 4H), 4.65 (s, 2H), 5.20 (s, 2H), 7.15 (dd, 1H), 7.25 (m, 1H), 7.40−7.50 (m, 9H), 7.65 (s, 1H), 7.70 (s, 1H), 7.80 (d, 1H); HRMS ($C_{30}H_{30}O_4 + H^+$) calcd 455.2224, found 455.2222.

9f. To a solution of alcohol **9c** (60 mg, 0.13 mmol) in THF (3 mL) were added 80% NaH dispersed in oil (10 mg, 0.33 mmol) followed by iodomethane (0.02 mL, 0.32 mmol). The mixture was stirred at room temperature for 24 h; the reaction was quenched with saturated aqueous NH_4Cl and the mixture partitioned between water and ether. The organic residue was chromatographed on silica gel (hexane/EtOAc/CH_2Cl_2, 3:2:2) to afford **9f** (50 mg, 81%) as a white foam: ^1H NMR (250 MHz, $CDCl_3$) δ 1.50 (d, 3H), 1.70 (m, 3H), 2.20 (m, 2H), 3.25 (s, 3H), 3.90 (m, 4H), 4.45 (q, 1H), 5.15 (s, 2H), 7.15 (dd, 1H), 7.30 (m, 2H), 7.45 (m, 8H), 7.65 (s, 2H), 7.85 (d, 1H).

9j. To a solution of ester **9h** (300 mg) in THF−methanol−water (3:1:1, 10 mL) was added $LiOH \cdot H_2O$ (50 mg). After stirring at room temperature for 18 h, the mixture was acidified to pH 3 with 10% aqueous HCl and extracted with ether. The extracts were washed with brine, dried, and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 9:1) to afford acid **9j** as a white solid (218 mg, 75%): mp 202−205 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (d, 2H), 2.22 (m, 2H), 3.50 (s, 1H), 3.75 (br s, 1H), 3.92 (m, 4H), 5.23 (s, 2H), 7.29 (dd, 1H), 7.37−7.54 (m, 9H), 7.67 (s, 1H), 7.88 (d, 1H), 7.93 (s, 1H), 8.59 (s, 1H); HRMS ($C_{29}H_{26}O_5 + H^+$) calcd 455.1860, found 455.1858.

9k. To a solution of tetrazole **8i** (175 mg, 0.61 mmol) in DMF (4 mL) were added 80% NaH dispersed in oil (38 mg, 1.5 mmol) and, 30 min later, benzylic halide **6a** (182 mg, 0.67 mmol), and the mixture was stirred at room temperature for 18 h. The mixture was partitioned between water and EtOAc and the mixture of alkylated products chromatographed on silica gel (hexane/EtOAc, 1:1, + 0.5% AcOH) to afford the desired **9k** (31 mg, 10%) as a white solid: mp 205−206 °C; ^1H NMR (250 MHz, acetone-d_6) δ 1.65 (m, 2H), 2.10 (m, 2H), 3.85 (m, 4H), 5.30 (s, 2H), 7.35 (dd, 1H), 7.40−7.60 (m, 8H), 7.65 (d, 1H), 7.75 (s, 1H), 7.85 (d, 1H), 7.95 (d, 1H), 8.60 (s, 1H); HRMS ($C_{29}H_{26}N_4O_3 + H^+$) calcd 479.2083, found 479.2082.

9n. To a suspension of 60% NaH dispersed in oil (218 mg, 5.45 mmol) in DMF (10 mL) were added (chloromethyl)-

naphthalene **9aa** (250 mg, 0.54 mmol) and imidazole (186 mg, 2.73 mmol). The mixture was stirred at room temperature for 18 h and then partitioned between water and EtOAc. The residue obtained from the organic phase was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to afford **9n** (171 mg, 64%) as a white solid: mp 172−174 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.64 (d, 2H), 2.10 (m, 2H), 3.76 (m, 2H), 3.90 (m, 2H), 4.10 (s, 1H), 5.29 (s, 2H), 5.44 (s, 2H), 6.95 (s, 1H), 7.17−7.27 (m, 3H), 7.37−7.56 (m, 9H), 7.66 (s, 1H), 7.75 (m, 3H).

9u. Step 1. To a solution of aldehyde **9ab** (250 mg, 0.58 mmol) in THF at −78 °C was added 2 M phenylmagnesium bromide in ether (0.8 mL, 1.6 mmol). The mixture was stirred at −78 °C for 20 min; then the reaction was quenched with saturated aqueous NH_4Cl and the mixture partitioned between ether and water. Chromatography of the organic residue on silica gel (hexane/EtOAc, 2:3) afforded the desired tertiary alcohol as an oil (244 mg, 82%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.6 (s, 1H), 1.70 (m, 2H), 2.20 (m, 2H), 2.35 (d, 1H), 3.90 (m, 4H), 5.20 (s, 2H), 6.00 (d, 1H), 6.65 (s, 1H), 7.20 (dd, 1H), 7.25−7.50 (m, 10H), 7.55 (t, 1H), 7.60 (s, 1H), 7.65 (s, 1H), 7.75 (s, 1H), 8.00 (d, 1H).

Step 2. To a solution of alcohol from step 1 (230 mg, 0.45 mmol) in CH_2Cl_2 (15 mL) at room temperature were added dry powdered 4 Å molecular sieves (500 mg) and pyridinium chlorochromate (300 mg, 1.4 mmol). After stirring for 30 min, the mixture was filtered through a short pad of silica gel, eluting with ether. The eluate was chromatographed on silica gel (hexane/EtOAc, 2:3) to afford **9u** as a pale yellow foam (180 mg, 78%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.6 (s, 1H), 1.70 (m, 2H), 2.20 (m, 2H), 3.90 (m, 4H), 5.20 (s, 2H), 6.70 (s, 1H), 7.35−7.65 (m, 10H), 7.70 (s, 1H), 7.80 (d, 1H), 7.90 (m, 2H), 8.10 (m, 2H).

Preparation of Sodium Carboxylates 10. 10a. A mixture of lactone **3a** (401 mg, 0.86 mmol) and 1 N aqueous sodium hydroxide (0.95 mL, 0.95 mmol) was refluxed in ethanol (7 mL) for 2 h. Evaporation of the resulting solution afforded a residue which was dissolved in water (5 mL). Lyophilization yielded the desired carboxylate **10a** (443 mg) as an off-white solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.56 (m, 2H), 1.98 (m, 2H), 3.75 (m, 4H), 4.17 (d, 2H), 5.09 (s, 1H), 5.21 (s, 2H), 7.0−7.6 (m, 11H), 7.65 (s, 1H), 7.95 (br s, 1H), 8.05 (s, 1H).

The following compounds were prepared according to an analogous procedure Synthetic and physical data for carboxylates **10** are presented in Table 3.

10f: white solid; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.1 (d, 6H), 1.4−1.7 (m, 4H), 3.8 (m, 2H), 4.2 (d, 2H), 5.1 (m, 1H), 5.2 (s, 2H), 7.1 (q, 1H), 7.2 (d, 1H), 7.3−7.7 (m, 8H), 7.9 (d, 1H), 8.0 (s, 1H), 8.5 (s, 1H).

10h: pale yellow solid; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.10 (dd, 2H), 2.33 (d, 2H), 4.17 (d, 2H), 4.37 (br s, 2H), 4.99 (s, 1H), 5.19 (s, 2H), 7.03−7.54 (m, 12H), 7.87 (t, 1H), 8.06 (s, 1H).

10u: white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.8 (d, 1H), 2.0 (dq, 2H), 2.2 (dd, 1H), 3.6 (t, 1H), 4.3 (br s, 2H), 4.4 (d, 1H), 4.6 (t, 1H), 5.1 (s, 1H), 5.2 (s, 2H), 5.6 (s, 1H), 6.6 (s, 1H), 7.1 (dd, 1H), 7.3−7.4 (m, 3H), 7.4 (d, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 7.7 (s, 1H), 7.9 (t, 1H), 8.0 (s, 1H).

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