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Direct Synthesis of Esters and Amides from Unprotected Hydroxyaromatic and -aliphatic Carboxylic Acids

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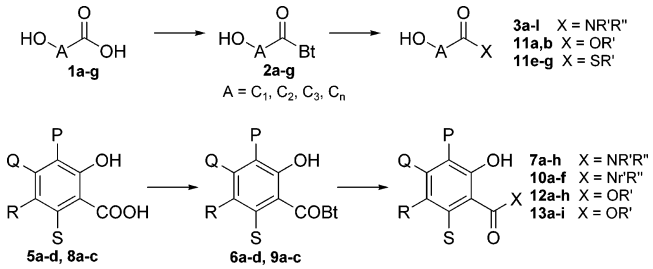

A facile method for the activation of hydroxy-substituted carboxylic acids using benzotriazole chemistry without prior protection of the hydroxy substituents is presented. The *N*-acylbenzotriazole intermediates **2a**−**g**, **6a**−**d**, and **9a**−**c** have been used for high-yielding synthesis of both aliphatic (**3a**−**l**) and aromatic (**7a**−**h**, **10a**−**f**) hydroxy carboxamides. High yields of aromatic hydroxy esters **12a**−**h** and **13a**−**i** were obtained using either neat alcohols in neutral microwave conditions or nucleophilic alkoxides and the intermediate *N*-(arylacyl)benzotriazoles. Moderate yields were obtained in the case of aliphatic hydroxy esters **11a**,**b** and thiolesters **11e**−**g** from the intermediates **2a**−**c**.

Introduction

The protection of an ancillary functional group while a transformation is being carried out at a different site in the molecule, followed by deprotection to regenerate the functionality, is frequently employed in organic synthesis. Various protecting groups are employed for a wide variety of functional groups.[1,2]

Esters, thiolesters, and amides of hydroxy carboxylic acids are important synthetic targets. Conventional methods for their preparation from the corresponding hydroxy acid requires initial protection of the hydroxy group (as an ester, ketal, or acetonide) conversion to the esters, thiolester or amide,[1,2] and subsequent deprotection. Conventional activation of a carboxyl group using, e.g., thionyl chloride or oxalyl chloride, cannot be safely employed in the presence of a free hydroxy group. The use of diazo compounds is limited by their explosive character, lack of generality, and toxicity.[3] Several peptide-coupling reagents (HATU,[4] HBTU,[5] BOP,[6] PyBOP,[7] DEPC,[8] EDC/BtOH[9,10]) enable direct coupling of free hydroxy *N*-protected amino acids with amino acids [HOR(NHP)COOH → HOR(NHP)CONHR′]. However, strictly anhydrous conditions are required and activated acid intermediates cannot usually be stored, handled in moist air, or even isolated. The carboxylic group of amino acid providing the NH for the coupling reaction frequently has to be esterified to make it soluble in a nonaqueous solvent.

Aromatic amides and esters have been synthesized by in situ activation of hydroxy acids using carbodiimide (EDC, DCC)/

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BtOH,[11] Mitsunobu[12,13] conditions (PPh_3/DEAD), or CDI-mediated coupling.[14] EDC/BtOH/base has been employed in the direct syntheses of simple amides from hydroxy acids.[15−17] Again, these reactions usually require strictly anhydrous conditions. A few reports describe transformation α-hydroxy acids into simple α-hydroxy esters using boric acid[18] or concentrated sulfuric acid,[19a] but require a large excess of the alcohol.

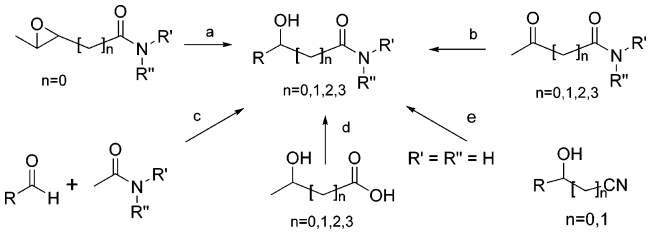
However, not all hydroxy acids on activation give the hydroxy ester or amide. Depending on the distance between the hydroxy and carboxyl groups within the molecule, the activated intermediate can form lactones, diolides,[19b] or polymers.

N-Acylbenzotriazoles are versatile synthetic equivalents of acyl halides.[20] They exist as stable solids at ambient conditions with moderate reactivity, which can be regulated. Appropriate *N*-acylbenzotriazoles effect formylation[21] and trifluoroacylation.[22] Regiospecific C-acylation of pyrrole and indoles[23] and the synthesis of oxamides,[24] 1,3-diketones,[25] polycyclic heteroaromatics,[26,27] Weinreb amides,[28] and N-protected dipeptides and tripeptides have been reported. In the case of peptides, protection of ancillary functional groups (hydroxy, thiol, imidazole-NH, indole-NH, amide, and carboxylic acid) in the amino acid monomers were not required.[29,30] Herein, we utilize benzotriazole chemistry in direct synthesis of simple esters, thiolesters, and amides from unprotected hydroxyaliphatic and -aromatic acids. The use of this methodology provides an economically viable alternative to the various peptide coupling agents.

Results and Discussion

Preparation of Hydroxy Carboxamides from Aliphatic Hydroxy Acids. Hydroxy amides are anti-convulsants[31] (α-hydroxy amides), thrombin inhibitors,[32] and RAR-γ specific retinoid agonists[33] (α-hydroxy amides). They are intermediates for the synthesis of oxazolidinediones,[34] oxindoles[35] (α-hydroxy amides), β-lactams[36] (β-hydroxy amides), and antidepressant drugs, e.g., (*R*)-fluoxetine (β-hydroxy amides), and building blocks for the synthesis of various natural products.[37]

SCHEME 1. Synthesis of Hydroxy Carboxamides



Common syntheses (Scheme 1) are from (a) epoxy amides,[38] (b) keto amides,[39−42] (c) a carbonyl and a nucleophile containing the amide,[43,44] (d) hydroxy acids,[33,45,47a] and (e) hydroxy nitriles.[47b]

Attempted one-pot conversions of α-hydroxy acids to hydroxy carboxamides, via the bis-trimethylsilyl derivative followed by conversion to acid chloride and treatment with the appropriate amine, frequently leads to α-chloro amide[33] formation. Other direct syntheses of the hydroxy amides have been achieved when the ancillary alcohol is sterically hindered.[32] *N*-Sulfinylanilines have been used to synthesize α-hydroxy *N*-aryl secondary amides from α-hydroxy acids.[33,45] The syntheses of two α-hydroxy *N*-arylamides using *N*-(1-methanesulfonyl)benzotriazole have been reported from our laboratories,[46] but there was no generalization of the methodology. With the in situ generation of Bt_2SO from a $SOCl_2$/BtH mixture for the synthesis of *N*-acylbenzotriazoles, we have now successfully expanded the method to include a wide variety of substrates.

The benzotriazole methodology was applied for direct synthesis of known and novel hydroxy amides **3a**−**l** from

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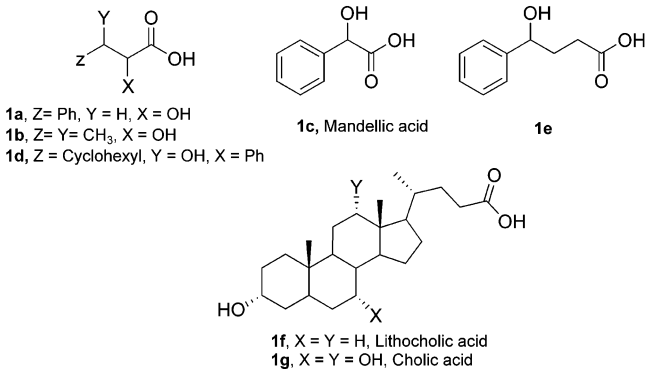


FIGURE 1. Hydroxy acids **1a**−**g**.

SCHEME 2

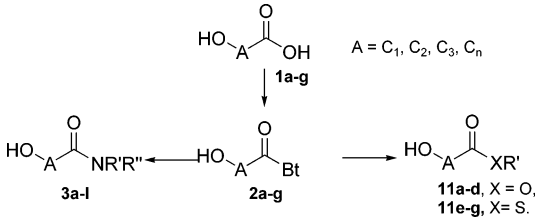


TABLE 1. Synthesis of Hydroxy Carboxamides 3a−l from Aliphatic Hydroxy Acids 1a−g

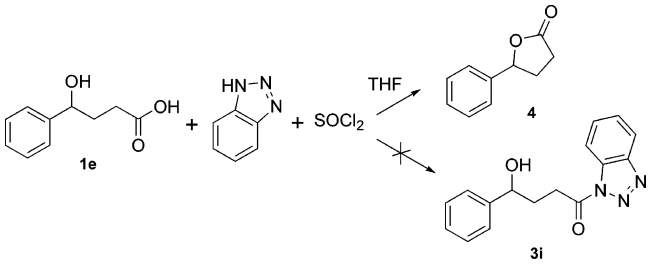
	compd	amine R′	utilized R″	product	yield (%)	mp (°C)
1	**1a**	$CH_3(CH_2)_2CH_2-$	H	**3a**	72	46−47
2	**1a**	$CH_3(CH_2)_6CH_2-$	CH_3-	**3b**	75	42−43
3	**1b**	$PhCH_2-$	H	**3c**	60 (96)[a]	84−85
4	**1b**	$-CH_2CH_2CH(Ph)CH_2CH_2-$		**3d**	61	103−104
5	**1c**	$PhCH_2CH_2-$	H	**3e**	68 (83)[b]	100−101
6	**1c**	$-CH_2(CH_2)_2CH_2-$		**3f**	77 (96)[c]	94−95
7	**1d**	$PhCH_2-$	H	**3g**	75	139−140
8	**1d**	$CH_2{:}CHCH_2-$	H	**3h**	62	97−98
9	**1e**	$-CH_2(CH_2)_2CH_2-$		**3i**	0[d]	
10	**1f**	$CH_3(CH_2)_3CH_2-$	H	**3j**	85	182−183
11	**1f**	$-CH_2(CH_2)_2CH_2-$		**3k**	93	167−168
12	**1g**	$PhCH_2CH(COOCH_3)-$	H	**3l**	66 (70)[e]	gel

[a] Using 3,4,5-trifluorobenzeneboronic acid.[47] [b] From the ethyl ester.[34] [c] From the methyl ester.[48] [d] Lactone **4** formed. [e] Using (DEPC).[8]

hydroxy acids **1a**−**g** (Figure 1, Scheme 2, and Table 1). Attempts to isolate and purify the intermediate *N*-(hydroxyacyl)-benzotriazoles **2a**−**g** showed that most are unstable, unlike nonfunctionalized *N*-acylbenzotriazoles. The *N*-acylbenzotriazole derivative **2c** of (±)-mandelic acid **1c** was isolated in 25% yields by flash column chromatography. The ^1H and ^{13}C spectra supported the structure, depicting the amide carbon at δ 171.8, but the compound was not stable enough for elemental analysis. Formation of the *N*-acylbenzotriazoles **2a**−**g** conducted in THF or dichloromethane is completed in 2 h and is accompanied by the formation of an insoluble solid. This water-soluble white solid is plausibly a mixture of benzotriazole hydrochloride and unreacted benzotriazole. However, the crude *N*-(hydroxyacyl)-benzotriazoles **2a**−**g** could be used directly. The supernatant containing *N*-(hydroxyacyl)benzotriazole was either syringed out or filtered to remove the accompanying solid and the filtrate used in further reactions.

The crude intermediate *N*-(hydroxyacyl)benzotriazoles **2a**−**g** were treated with primary and secondary amines and the amides **3a**−**l** obtained in varying yields (Scheme 2 and Table 1). The α-hydroxy acids **1a**−**c** gave high yields of secondary **3a**, **3c**, **3e** and tertiary **3b**, **3d**, **3f** amides. The use of aryl boronic acids[47a]

SCHEME 3



for the synthesis of **3c** has been reported for the case of α-hydroxy acids (entry 3, Table 1). The syntheses of compounds **3e** and **3f** have been reported from their alkyl esters; the conditions employed involved either high temperatures[34] (phenylethylamine reflux) or pressure[48] (8 kbar) (see entries 5 and 6, Table 1). The benzotriazole method was extended for the syntheses of secondary amides **3g** and **3h** (entries 7 and 8, Table 1) of β-hydroxy acid **1d**. However, the synthesis of tertiary amines from β-hydroxy acid presented difficulties, and mixtures were obtained. For γ-hydroxy acid **1e**, competitive intramolecular lactonization **4** was preferred over the formation of amide **3i** (Scheme 3). Conversions of mono- or polyhydroxyl bile acids such as lithocholic acid **1f** or cholic acid **1g** into their amides, which find application as gelating agents, presented no complications for our method. Use of this simple benzotriazole route was comparable to that of a peptide-coupling agent DEPC[8] (diethylphosphoryl cyanide) in the case of **3l** (entry 12, Table 1). The various amides synthesized are depicted in Table 1.

Preparation of Hydroxyaromatic Amides from Hydroxyaromatic Acids. Various amides of substituted salicyclic and naphthoic acids exhibit biological activity such as anthelmintic activity[49] and anti plaque agents.[50] The bis-naphthoic amides are used for the generation of chiral BINOL[51,52] reagents, and other hydroxy amides are important intermediates in synthetic organic chemistry.

Common approaches toward the synthesis of amides involve treatment of activated derivatives of acids, especially halides, acid anhydrides, or esters, with the corresponding amine. Phenyl esters of salicyclic acid have been effectively used;[53] however, their synthesis from salicylic acids requires harsh conditions.[54] Yet another indirect method for the synthesis of *o*-hydroxyaromatic amides would be via *o*-aminocarbonylation of the alkali metal salts of phenols[55,56] with isocyanates in high boiling solvents or under highly basic conditions at very low temperatures.[57,58]

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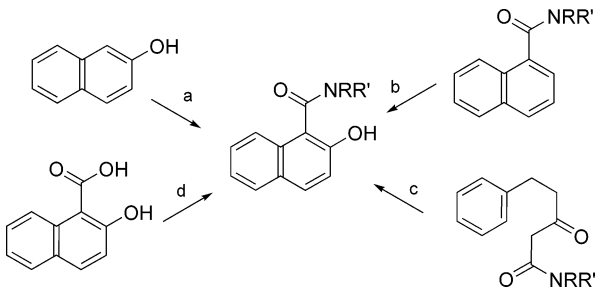
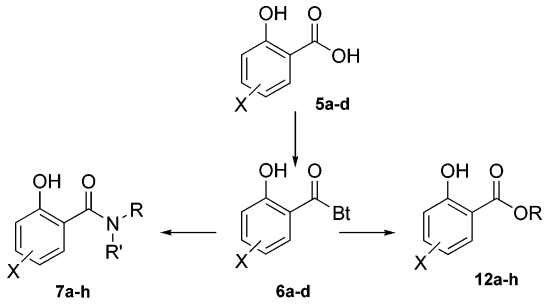
SCHEME 4



SCHEME 5



The various methods of synthesis of the *o*-hydroxynaphthyl amides (Scheme 4) are (a) from *o*-amino carbonylation of naphthols;[57−59] (b) from *o*-hydroxylations of naphthyl amides;[60,61] (c) 42% yielding metal-mediated oxidative cyclization of appropriately substituted aryl keto amides;[62] and (d) from *o*-hydroxynaphthoic acids using halogenating agents such as PCl_3,[63] $SOCl_2$[64] (used only in case of 2-hydroxy-3-naphthoic and 1-hydroxy-2-naphthoic acids), and diimides.[65] The indirect routes are harsh,[59] low yielding,[62] or require very low temperatures.[57,58,60,61] The limitations associated with these and other methods for the synthesis of amides have been discussed elsewhere.[46]

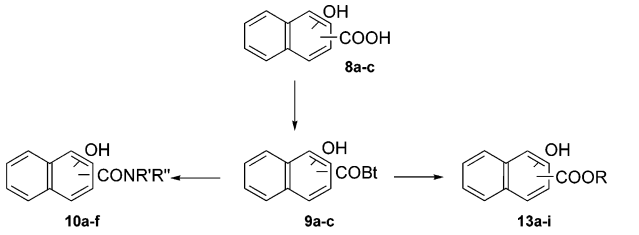
The salicyl amides **7a**−**h** were synthesized efficiently from the *N*-acylbenzotriazole derivatives **6a**−**d** of the corresponding salicylic acids **5a**−**d** (Scheme 5 and Table 2). Most of the intermediates **6a**−**d** could be isolated easily and were stable on silica gel at ambient conditions. They were characterized by ^{1}H and ^{13}C NMR spectra and elemental analysis. A similar attempt with 2-hydroxy-1-naphthoic acid **8a** (Scheme 6) gave a rather unstable *N*-acylbenzotriazole **9a** that reacted with atmospheric water forming the acid **8a**, and with methanol giving the methyl ester **13a**. Pure **9a** could, however, be isolated in about 25% yield by flash chromatography on silica gel and characterized spectrally and by elemental analyses (The singlet for the free hydroxyl group was observed at δ 10.72 in ^{1}H NMR, and the carbonyl was observed at δ 167.3 in the ^{13}C NMR spectra). Similarly, analytically pure samples of **9b** and **9c** were obtained by careful recrystallization from dichloromethane. These samples could be stored under refrigerated conditions without apparent decomposition. As for aliphatic acids, purification of the intermediate was not necessary. The supernatant layer containing the *N*-acylbenzotriazole could be used for further reactions.

TABLE 2. Synthesis of Substituted Salicylamides 7a−h (a, X = H; b, X = 5-Br; c, X = 4-OH; d, X = 3-Me)

	compd	R′	R″	method	product	yield (%)	mp (°C)
1	**5a**	furfuryl	H	A	**7a**	83 (97)[a]	109−110
2	**5a**	$-(CH_2)_5-$		A	**7b**	94 (69)[a]	142−143
3	**5b**	*n*-pentyl	H	A	**7c**	84	54−55
4	**5b**	*n*-octyl	CH_3	A	**7d**	82	92−93
5	**5c**	*n*-pentyl	H	A	**7e**	96	125−126
6	**5c**	phenyl	CH_3	B	**7f**	93	150−152
7	**5c**	$-(CH_2)_2O(CH_2)_2-$		B	**7g**	94	179−181
8	**5d**	$CH_3(CH_3)CH(CH_2)_2-$	H	A	**7h**	93	oil
9	**5d**	Cyclohexyl	CH_3	A	**7i**	0	

[a] Reported yield using phenyl salicylate.[53]

SCHEME 6



8a : 2-hydroxy-1-naphthoic acid, **8b** :1-hydroxy-2-naphthoic acid, **8c**: 2-hydroxy-3-naphthoic acid

TABLE 3. Synthesis of Amides 10a−f

	compd	R′	R″	method	product	yield (%)	mp (°C)
1	**8a**	Ph	H	B	**10a**	90	171−172
2	**8a**	$-(CH_2)_5-$		A	**10b**	93	242−243
3	**8b**	$PhCH_2CH_2-$	H	A	**10c**	94	125−126
4	**8b**	$-(CH_2)_4-$		A	**10d**	97	93−94
5	**8c**	CH_2:$CHCH_2-$	H	A	**10e**	75 (85)[a]	121−122
6	**8c**	$-(CH_2)_2O(CH_2)_2-$		A	**10f**	73	216−217

[a] Using thionyl chloride.[66]

Various primary and secondary amines (3 equiv) were treated with the *N*-acylbenzotriazoles **6a**−**d** (Scheme 5) in the presence of triethylamine (5 equiv) in THF (4 mL/mmol) (method A) to give a series of known and novel secondary and tertiary amides **7a**−**h** (Table 2). The reactions were very rapid, and the unprotected hydroxyl groups caused no complications. The products could be isolated in over 90% purity after the initial workup. Hardly surprisingly, a sterically demanding amine gave no yield (entry 9, Table 2) of the desired product, while the other amines gave very high yields. These compounds gave satisfactory proton and carbon NMR data and also elemental analysis. The various amides synthesized from derivatives of salicylic acid are presented in Table 2. This methodology could be extended to the *o*-hydroxynaphthoic acids **8a**−**c**. Various secondary and tertiary amides **10a**−**f** were synthesized (Scheme 6) from the corresponding *N*-acylbenzotriazole derivatives **9a**−**c** in good yields. In the case of synthesis of amides from poorly nucleophilic aromatic amines, microwave conditions (method B) were required to obtain good yields (see entry 6 in Table 2; see entry 1 in Table 3).

Preparation of Aliphatic α-Hydroxycarboxylic Esters and Thiolesters from α-Hydroxy Acids. α-Hydroxy esters are important building blocks for synthesis of natural products.

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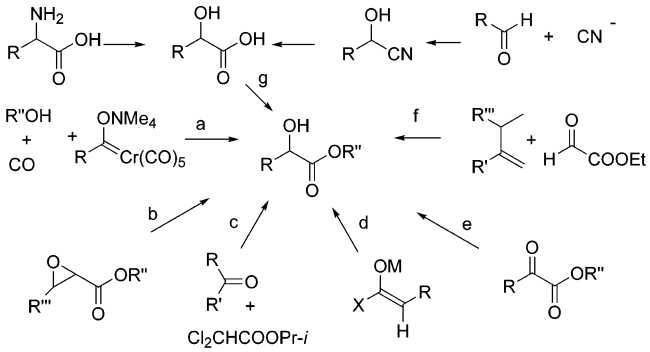
SCHEME 7. Synthesis of α-Hydroxy Carboxylic Esters



Common methods for their syntheses are (a) from hydroxy Fischer carbenes,[67] (b) selective opening of the epoxy esters,[68] (c) via α-chloroglycidic esters,[69] (d) oxidation of metal enolates,[70] (e) reduction of the appropriate keto esters,[71,72] (f) the glyoxalate-ene reaction,[73a] and (g) direct transformation of the α-hydroxy acid[18] (which can be obtained from α-amino acids[106,107] or cyanohydrins[73b]) as displayed in Scheme 7.

α-Hydroxycarboxylic thiolesters have received less attention, although they are amenable to several functional group transformations,[74,75] are bioactive in the areas of antitumor and glyoxalase I inhibitor,[76] and protect the unstable thio moiety while masking the undesired odor[77] of the free thiol.

Reported syntheses of α-hydroxythiolesters are (a) the Pinner reaction[78] (average yield: 62%, 13 examples), (b) from α-chloro thioesters[79] (average yield: 56%, 16 examples, restricted to 2-aminothiols derivatives of α,α-diaryl-α-chloro acids), (c) ozonolysis of thiophene substituted Henry adduct[80] (58%, one example), (d) rearrangement of the glyoxal−thiol adduct[81,82] (average yield: 63% for two steps, seven examples), (e) from organoaluminum reagents[83] (90%, one example), (f) via oxaborolidine-mediated reduction of α-phenyl thioenones followed by ozonolysis[84] (average yield: 44%, three steps, five examples), and (g) via Pummerer reaction of 1,3-dithiane 1,3-dioxide derivatives[74] (70% yield, three steps, enantioselective). The processes displayed in the scheme (Scheme 8) suffer from drawbacks. Some are restricted to thiophenol esters (paths c, f), some are very specific (path b: R = Ar, R′= Ar′, path e: R″ = SC(CH$_3$)$_3$), some involve the use of toxic/harsh conditions (paths a, c, f), while most are mutistep syntheses (paths a, c, d, f, g). Weinreb[83] has reported only one example of direct synthesis of α-hydroxy-*tert*-butyl thiol ester from mandelic acid using organoaluminum reagent, while the synthesis from α-halo thiolester salts (not commercially available) is not general as is discussed elsewhere.[79]

Visibly from the two schemes (Schemes 7 and 8), synthesis of α-hydroxy thiol esters does not analogously follow that of α-hydroxy esters. It should be noted that modified reducing agents cannot be employed in the case of hydroxy thiol esters due to the labile nature of the CO−S bond. A mild, direct, one-step procedure, devoid of protection/deprotection operations, to synthesize both the esters from a single starting material would be a useful tool in the syntheses of compound libraries.

As in the case with the synthesis of hydroxy amides, dropwise addition through a syringe of the supernatant benzotriazolating mixture and the hydroxy acid **1a**−**f** (Figure 1) to a mixture of the sodium salt of the alcohol or thiol (Scheme 2) at room temperature ensured the formation of the hydroxy carboxylic ester **11a**,**b** or thiolester **11e**−**g** (Table 4). Two known esters and three novel thiol esters were synthesized using this method. Attempts to increase the yield of esters by treating the *N*-(α-hydroxyacyl)benzotriazoles **1a**,**b** using more nucleophilic aromatic phenoxides failed. Use of neutral microwave conditions could not rectify this. Attempts to increase the yield of thiolesters by refluxing the *N*-(α-hydroxyacyl)benzotriazole **1a**−**c** with the sodium salt of thiol led to decomposition. Conducting the reactions at 0 °C also did not improve the yield. This method provides a mild protocol for the synthesis of both esters and thiolesters from one starting material, which is a desirable property for the synthesis of library compounds.

Preparation of Aromatic Esters from Substituted *o*-Hydroxy Aromatic Acids. Salicylihalamide,[12] lasiodiplodin,[13] and neocarzinostatin[86] are biologically active salicylic and hydroxy naphthoic esters. Salicylic acids have been esterified using DCC/DMAP,[87] large excesses of the alchohol and/or strong acid,[88] or bases.[89] Stereospecific Mitsunobu conditions[12,13,90] have been used extensively in total syntheses. A tertiary amine and the appropriate activated halide[91,92] esterify salicylic acids, but require high temperatures.

o-Hydroxynaphthoic esters are not common in the literature. The few reports which deal with their synthesis from the corresponding acids usually involve (a) strongly acidic conditions[93] for simple esters, (b) use of toxic diazomethane,[94] (c)

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SCHEME 8. Synthesis of Hydroxy Carboxylic Thiolesters.

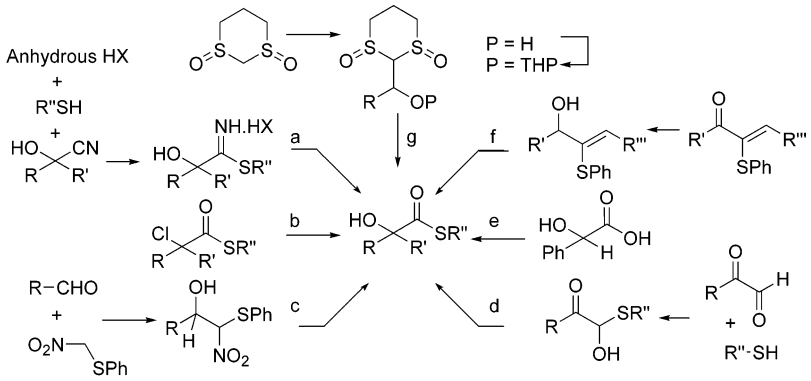

TABLE 4. Synthesis of Hydroxy Esters 11a,b and Thiolesters 11e−g

	compd	R′OH	X	product	yield (%)	mp (°C)
1	**1c**	MeOH	O	**11a**	40 (99)[a]	56−57
2	**1c**	EtOH	O	**11b**	72 (93)[b]	35−36
3	**1b**	PhOH	O	**11c**	mix	
4	**1a**	*p*-methoxyphenol	O	**11d**	mix	
5	**1a**	hexanethiol	S	**11e**	37	oil
6	**1c**	4-methoxythiophenol	S	**11f**	23	oil
7	**1b**	benzylthiol	S	**11g**	24	69−70

[a] Using boric acid.[18] [b] Using concd sulfuric acid.[85]

TABLE 5. Synthesis of Esters 12a−h

	compd	ROH	method	product	yield (%)	mp (°C)
1	**5a**	methanol	A	**12a**	94	oil
2	**5a**	cyclopentanol	A	**12b**	63	oil
3	**5a**	cyclopentanol	B	**12b**	92	oil
4	**5a**	1-penten-3-ol	B	**12c**	84	oil
5	**5b**	ethanol	B	**12d**	90	46−48
6	**5b**	cyclopentanol	B	**12e**	87	45−47
7	**5c**	*n*-propanol	B	**12f**	87	32−34
8	**5c**	cyclopentanol	B	**12g**	91	oil
9	**5d**	$CH_3(CH_2)_8CH_2OH$	B	**12h**	84	oil

TABLE 6. Synthesis of Esters 13a−i

	compd	ROH	method	product	yield (%)	mp (°C)
1	**8a**	methanol	A	**13a**	85 (90)[a]	79−80
2	**8a**	cyclopentanol	B	**13b**	85	oil
3	**8a**	4-pentyn-1-ol	B	**13c**	84	oil
4	**8a**	ethanol	B	**13d**	8 (62)[b]	56−58
5	**8b**	ethanol	B	**13e**	88	48−49
6	**8b**	cyclopentanol	B	**13f**	90	58−60
7	**8b**	4-pentyn-1-ol	B	**13g**	83	65−67
8	**8b**	1-penten-3-ol	B	**13h**	83	oil
9	**8c**	*n*-butanol	B	**13i**	84	oil

[a] Using *p*-TsOH·H_2O/DCC/Py.[100] [b] Oxidative cyclization.[62]

use of LiOH with DMS,[95] (d) use of carbodiimides[96−99] that gives the urea side product, or (e) multistep low-yielding oxidative cyclization using Mn(III) and Ce(IV)[62] to form the second aromatic ring. Zengin[100] esterified 2-hydroxy-1-naphthoic acid in 90% yield using DCC in pyridine with a catalytic amount of *p*-toulenesufonic acid in the presence of excess methanol, but the study dealt with only one example. The methods described above and other methods for the esterification of *o*-hydroxyaromatic acids usually lack generality,[95,101] involve sensitive reagents,[102,103] are low yielding,[104] or lead to intersubstrate esterification.[105] There is an obvious need for a general, efficient, gentle, and high-yielding process.

N-Acylbenzotriazoles **6a−d** of various salicylic acids **5a−d** were synthesized using the $SOCl_2$/BtH mixture Scheme 5. Esterification was achieved by the dropwise addition of the supernatant to sodium methoxide in methanol over 30 min (method A) to give the methyl ester **12a** and **13a** in 94 and 85% yield, respectively (Scheme 6).

Alternatively, avoiding basic conditions, the esters could be synthesized by heating the crude concentrated *N*-acylbenzotriazoles with 4 equiv of the appropriate neat alcohol for 10 min under microwave conditions (method B). The esters were obtained in good yields. Allyl alcohols (entry 4, Table 5, and entry 8, Table 6) or the presence of a triple bond (entries 3 and 7, Table 6) caused no concerns. Both primary and secondary alcohols were used. A series of mostly novel esters **12a−h** and **13a−i** were synthesized using the methods described above, and the results are presented in Tables 5 and 6. This method provides an alternative, mild, high-yielding method for the synthesis of *o*-hydroxy esters from *o*-hydroxyaryl carboxylic acids.

In conclusion, we have developed an economically viable alternative method for the activation of carboxylic acids in the presence of free hydroxy groups without their prior protection. The syntheses of amides in the case of both aliphatic and aromatic hydroxy acids were high yielding. The hydroxy aromatic esters were synthesized in high yields under both basic and neutral conditions (microwave), while yields for the synthesis of esters and thiolesters from the corresponding hydroxy acids were low. While in conventional direct synthesis the activation of the hydroxy acid is performed in situ, we have been able to separate the activation step from the nucleophilic substitution, thereby contributing to higher flexibility in reaction

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In conclusion, we have developed an economically viable alternative method for the activation of carboxylic acids in the presence of free hydroxy groups without their prior protection. The syntheses of amides in the case of both aliphatic and aromatic hydroxy acids were high yielding. The hydroxy aromatic esters were synthesized in high yields under both basic and neutral conditions (microwave), while yields for the synthesis of esters and thiolesters from the corresponding hydroxy acids were low. While in conventional direct synthesis the activation of the hydroxy acid is performed in situ, we have been able to separate the activation step from the nucleophilic substitution, thereby contributing to higher flexibility in reaction

conditions and substrates. The major advantage of this methodology lies in the synthesis of aromatic amides and esters wherein the intermediate *N*-(*o*-hydroxyaryl)benzotriazoles are stable isolable solids that can be treated under neutral conditions with the appropriate alcohol or amine.

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus and are uncorrected. All NMR spectra were recorded in $CDCl_3$ (unless specified as DMSO-d_6), with TMS as the internal standard for ^1H (300 MHz) or the solvent as the internal standard for ^{13}C (75 MHz). Microwave heating was carried out with a single-mode cavity Discoverer microwave synthesizer, producing continuous irradiation at 2455 MHz. THF was dried over sodium/benzophenone and used freshly distilled. Column chromatography was conducted on silica gel 200−425 meshes. The compounds **1a,**[106] **1b,**[107] **1d**,[108] and **1e**[109] were synthesized from reported procedures. Compounds **1c**, **1f**, **1g**, and salicylic acid/*o*-hydroxynaphthoic acid derivatives are available commercially.

General Procedure for the Synthesis of Hydroxy Carboxamides 3a−l from Hydroxy Acids 1a−g. To 6.3 mmol (750 mg) of benzotriazole in 12 mL of freshly dried THF or methylene chloride was added 2 mmol of $SOCl_2$ (0.148 mL) under an atmosphere of argon. The mixture was allowed to stir at room temperature for 45 min before the rapid addition of the hydroxy acids (**1a−f**, 2 mmol) in 8 mL of freshly dried THF/methylene chloride through a syringe while under inert atmosphere. The formation of a white solid was observed, and the reaction mixture was stirred for 2 h at room temperature. The supernatant contains the *N*-(hydroxyacyl)benzotriazole. The stirring was stopped after 2 h for the suspension to settle down for easy removal of the supernatant.

In a separate round-bottom flask, the appropriate amine (6 mmol) and triethylamine (6 mmol) were taken in 2 mL of freshly dried THF. The supernatant of the benzotriazolating mixture/hydroxy acid was carefully syringed out and added dropwise to this mixture while stirring under an inert atmosphere. The residual solid was washed with 5 mL of dry THF, and the washings were added to the amines. After 30 min, the reaction mixture was concentrated under vacuum to remove the solvent and triethylamine. The brown residue was taken in ether (25 mL) and the organic layer washed with 1 N HCl (2 × 25 mL), saturated sodium carbonate (until benzotriazole is not observed on TLC), and brine, dried over magnesium sulfate, and concentrated under vacuum. The residue was refined by flash chromatography over silica gel to give the respective hydroxy amides (**3a−l**).

***N*-Butyl-2-hydroxy-3-phenylpropionamide (3a):** white powder from ethyl acetate/hexanes (72%); mp 46−47 °C; IR (neat) ν = 3334, 2936, 2863, 1624, 1468 cm^{-1}; ^1H NMR δ 7.35−7.23 (m, 5H), 6.42 (br s, 1H), 4.28 (dt, J = 8.4, 4.4 Hz, 1H), 3.28−3.19 (m, 2H + H, A part of AB system $PhCH_2$), 2.90 (dd, J = 8.2, 6.9 Hz, 1H, B part of AB system), 2.56 (d, J = 4.7 Hz, 1H), 1.49−1.40 (m, 2H), 1.35−1.23 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 172.3, 136.8, 129.5, 128.7, 127.0, 72.8, 41.0, 38.8, 31.5, 20.0, 13.7. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.92; H, 9.01; N, 6.34.

2-Hydroxy-*N*-methyl-*N*-octyl-3-phenylpropionamide (3b): white plates from ethyl acetate/hexanes (75%); mixture of rotamers; mp 42−43 °C; IR (neat) ν = 3499, 2929, 2874, 1653, 1495 cm^{-1}; ^1H NMR δ 7.32−7.20 (m, 5H), 4.59−4.51 (m, 1H), 3.75 (d, J = 8.2 Hz, 0.5 H), 3.66 (d, J = 8.2 Hz, 0.5H), 3.49−3.11 (m, 2H), 2.96−2.77 (m, 3H), 2.94 (s, 1.5H, NCH_3), 2.95−2.84 (m, 2H), 2.80 (s, 1.5 H, NCH_3), 1.53−1.48 (m, 2H), 1.28−1.26 (m, 10H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 173.5, 173.3, 137.0, 136.9, 129.3, 129.2, 128.4, 128.3, 126.7 (2C), 69.0 (2C), 49.8, 48.5, 42.3, 41.8, 34.3, 33.4, 31.7(2C), 22.6, 22.5, 29.3, 29.2, 29.1 (2), 28.0, 26.9, 26.8, 26.6, 14.0 (2C). Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.49; H, 10.29; N, 4.72.

***N*-Benzyl-2-hydroxy-3-methylbutyramide**[47] **(3c):** white amorphous powder from hexanes/ethyl acetate (60%); mp 84−85 °C; IR (neat) ν = 3355, 2968, 2925, 1626, 1542, 1018 cm^{-1}; ^1H NMR δ 7.36−7.26 (m, 5H), 6.78 (br s, 1H), 4.50 (dd, J = 14.7, 8.7 Hz, 1H, A part of AB system), 4.45 (dd, J = 14.7, 8.7 Hz, 1H, B part of AB system), 4.03 (dd, J = 5.1, 3.2 Hz), 2.60 (br d, J = 5.2 Hz, 1H), 2.26−2.16 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 173.0, 138.0, 128.7, 127.8, 127.6, 76.4, 43.2, 31.9, 19.1, 15.4. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.62; H, 8.44; N, 6.92.

1-(4-Benzylpiperidin-1-yl)-2-hydroxy-3-methylbutan-1-one (3d): mixture of isomers; white amorphous powder from ethyl acetate/hexanes (61%); mp 103−104 °C; IR (neat) ν = 3417, 2962, 2870, 1634, 1494, 1022 cm^{-1}; ^1H NMR δ 7.32−7.26 (m, 2 H), 7.23−7.18 (m, 1H), 7.16−7.12 (m, 2H), 4.62−4.55 (m, 1H), 4.24−4.22 (m, 1H), 3.74−3.67 (m, 2H), 3.00−2.88 (m, 1H), 2.64−2.49 (m, 3H), 1.84−1.69 (m, 4H), 1.23−1.13 (m, 2H), 1.09−1.03 (m, 3H), 0.82−0.75 (m, 3H); ^{13}C NMR δ 172.2, 172.1, 139.7, 139.6, 129.0 (2C), 128.3 (2C), 126.1 (2C), 71.9, 71.8, 45.4, 45.0, 43.0, 42.9, 42.8 (2C), 38.2, 38.1, 32.5, 32.2, 31.9, 31.7, 31.6, 31.3, 19.8 (2C), 14.9, 14.7. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.31; H, 9.47; N, 5.05.

2-Hydroxy-*N*-phenethyl-2-phenylacetamide[34] **(3e):** white powder from ether (68%); mp 100−101 °C; IR (neat) ν = 3378, 1655, 1602, 1061 cm^{-1}; ^1H NMR δ 7.39−7.19 (m, 8H), 7.03−7.00 (m, 2H). 6.06 (br s, 1H), 4.95 (d, J = 3.3 Hz, 1H), 3.70 (d, J = 3.4 Hz, 1H), 3.56 (sextet, J = 6.6 Hz, 1H), 3.45 (sextet, J = 6.6 Hz, 1H), 2.82−2.66 (m, 2H); ^{13}C NMR δ 172.1, 139.4, 138.4, 128.8, 128.7, 128.6, 126.8, 126.5, 74.0, 40.7, 35.5. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.91; H, 6.75; N, 5.55.

2-Hydroxy-2-phenyl-1-pyrrolidin-1-ylethanone[110] **(3f):** white powder from ether (77%); mp 94−95 °C; IR (neat) ν = 3384, 2971, 2877, 1634, 1066 cm^{-1}; ^1H NMR δ 7.39−7.30 (m, 5H), 5.04 (d, J = 6.0 Hz, 1H), 4.76 (d, J = 6.0 Hz, 1H), 3.66−3.35 (m, 3H), 2.89−2.81 (m, 1H), 1.93−1.68 (m, 4H); ^{13}C NMR δ 170.6, 138.9, 128.9, 128.4, 127.7, 72.6, 46.5, 45.8, 25.9, 23.7.

***N*-Benzyl-3-cyclohexyl-3-hydroxy-2-phenylpropionamide (3g):** white amorphous powder from ethyl acetate/hexanes (75%); mp 139−140 °C; IR (neat) ν = 3287, 2925, 2851, 1640, 1545, 1030 cm^{-1}; ^1H NMR δ 7.37−7.23 (m, 8H), 7.14−7.11 (m 2H), 5.96 (br t, J = 6.2 Hz, 1H), 4.45 (dd, J = 15.0, 5.9 Hz, 1H, A part of AB system), 4.34 (dd, J = 15.0, 5.9 Hz, 1H, B part of AB system), 4.06 (br d, J = 4.4 Hz, 1H), 4.01−3.96 (m, 1H), 3.61 (d, J = 8.0 Hz, 1H), 1.71−0.98 (m, 11H); ^{13}C NMR δ 174.1, 137.8, 137.4, 129.0, 128.6, 128.4, 127.6, 127.4 (2C), 77.4, 55.2, 43.4, 39.8, 30.4, 26.3 (2C), 26.0, 25.8. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.28; H, 8.19; N, 4.22.

***N*-Allyl-3-cyclohexyl-3-hydroxy-2-phenylpropionamide (3h):** white needles from hexanes/ethyl acetate (62%); mp 97−98 °C; IR (neat) ν = 3301, 2926, 2852, 1640, 1544, 1033 cm^{-1}; ^1H NMR δ 7.39−7.27 (m, 5 H), 5.81−5.68 (m, 1H), 5.63 (br t, J = 5.3 Hz, 1H), 5.06 (dq, J = 8.0 Hz, 1.4 Hz, 1H), 5.01 (dq, J = 16.6, 1.6 Hz, 1H), 4.13 (br d, J = 4.0 Hz, 1H), 4.02−3.97 (m, 1H), 3.86−3. 82 (m, 2H), 3.59 (d, J = 8.2 Hz, 1H), 1.73−0.97 (m, 11 H); ^{13}C NMR δ 174.1, 137.5, 133.7, 129.1, 128.5, 127.6, 116.2, 77.3, 55.1, 41.7, 39.8, 30.5, 26.4, 26.3, 26.0, 25.6. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.57; H, 8.91; N, 5.00.

***N*-Lithocholyl-*n*-pentylamide (3j):** white needles from ether (85%); mp 182−183 °C; IR (neat) ν = 3288, 2929, 2863, 1646,

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1555, 1041 cm^{-1}; ^1H NMR δ 5.44 (br t, J = 6.5 Hz, 1H), 3.68−3.58 (m, 1H), 3.23 (q, J = 6.9 Hz, 2H), 2.28−2.18 (m, 1H), 2.10−0.84 (m, 43H), 0.64 (s, 3H); ^{13}C NMR δ 173.5, 71.8, 56.5, 56.0, 42.7, 42.0, 40.4, 40.1, 39.5, 36.4, 35.8, 35.5, 35.3, 34.5, 33.7, 31.8, 30.5, 29.4, 29.0, 28.2, 27.2, 26.4, 24.2, 23.3, 22.3, 20.8, 18.4, 14.0, 12.0. Anal. Calcd for $C_{29}H_{51}NO_2$: C, 78.14; H, 11.53; N, 3.14. Found: C, 77.85; H, 11.92; N, 3.07.

***N*-Lithocholylpyrrolidine amide**[111] **(3k):** white needles from ether (93%); mp 167−168 °C; IR (neat) ν = 3406, 2934, 2863, 1626, 1446, 1041 cm^{-1}; ^1H NMR δ 3.62 (m, 1H), 3.46 (t, J = 6.87 Hz, 2H), 3.42 (t, J = 6.73 Hz, 2H), 2.36−2.1 (m, 2H), 1.97−0.92 (m, 37H), 0.64 (s, 3H); ^{13}C NMR δ 172.2, 71.7, 56.4, 56.0, 46.5, 45.6, 42.7, 42.0, 40.4, 40.1, 36.4, 35.8, 35.5, 35.3, 34.5, 31.7, 30.9, 30.5, 28.2, 27.1, 26.4, 26.1, 24.4, 24.2, 23.3, 20.8, 18.5, 12.0. Anal. Calcd for $C_{28}H_{47}NO_2$: C, 78.27; H, 11.02; N, 3.26. Found: C, 77.90; H, 11.39; N, 3.28.

***N*-Cholyl-D-phenylglycine methyl ester**[8] **(3l):** white amorphous solid from methanol/dichloromethane (66%); IR (neat) ν = 3420, 2953, 2866, 1746, 1654, 1522 cm^{-1}; ^1H NMR δ 7.36−7.31 (m, 5H), 6.91 (d, J = 7.3 Hz, 1H), 5.58 (d, J = 7.1 Hz, 1H), 3. 93 (br s, 1H), 3.80−3.64 (m, 2H), 3.70 (s, 3H), 3.80 (br s, 3H, OH), 3.40 (br s, 1H), 2.39−0.74 (m, 25 H), 0.95 (d, J = 5.5 Hz, 3 H), 0.86 (s, 3H), 0.62 (s, 3H); ^{13}C NMR δ 173.3, 171.5, 136.5, 128.8, 128.3, 127.3, 73.0, 71.7, 68.4, 56.3, 53.4, 52.7, 46.5, 46.3, 41.5, 41.3, 39.3, 35.2, 34.6, 34.4, 32.7, 31.2, 30.1, 27.9, 27.5, 26.2, 23.2, 22.3, 17.3, 12.3.

General Procedure for the Synthesis of *o*-Hydroxyarylacylbenzotriazoles (6a−d, 9a−c). To 6.3 mmol (750 mg) of benzotriazole in 12 mL of freshly dried THF/dichloromethane was added 2 mmol of $SOCl_2$ (0.148 mL) under an atmosphere of argon. The mixture was allowed to stir at room temperature for 45 min before rapid addition of the substituted salicylic and *o*-hydroxynaphthoic acids (**5a**−**d**, **8a**−**c,** 2 mmol) in 8 mL of freshly dried THF through a syringe while under inert atmosphere. The formation of a white solid was observed and the reaction mixture stirred for 2 h at room temperature. The supernatant could be syringed out for subsequent operations. Alternatively, the solution was quickly filtered to remove the solid under an atmosphere of nitrogen and the filtrate concentrated under vacuum. The crude concentrated solid filtrate (usually >92% purity) could be used directly for the proceeding operations. Some of these derivatives were not stable to atmospheric water (**6c**, **9a**) and, therefore, had to be used immediately. Analytically pure samples were obtained by flash chromatography (**6c**, **9a**, low yields)/recrystallization.

Benzotriazol-1-yl(2-hydroxyphenyl)methanone (6a): pale yellow needles from diethyl ether (92%); mp 115−116 °C; IR (neat) ν = 3385 (br), 1648, 1479, 1449 cm^{-1}; ^1H NMR δ 10.81 (s, 1H), 8.61 (dd, J = 8.3, 1.5 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.72 (t, J = 7.3 Hz, 1H), 7.64−7.53 (m, 2 H), 7.13 (d, J = 8.5 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H); ^{13}C NMR δ 169.2, 163.6, 145.4, 137.1, 133.8, 132.4, 130.5, 126.5, 120.4, 119.6, 118.4, 114.9, 113.5. Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.51; H, 3.70; N, 17.51.

Benzotriazol-1-yl(5-bromo-2-hydroxyphenyl)methanone (6b): yellow needles from diethyl ether (87%); mp 108−109 °C; IR (neat) ν = 3122, 1651, 1483, 1451 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.67 (s, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.84 (s, 1H), 7.86−7.81 (m, 1H), 7.69−7.63 (m, 2H), 7.00 (d, J = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.3, 155.2, 145.5, 135.6, 132.1, 130.9, 130.8, 126.7, 123.0, 120.1, 118.6, 113.9, 109.6. Anal. Calcd for $C_{13}H_8BrN_3O_2$: C, 49.08; H, 2.53; N, 13.21. Found: C, 49.30; H, 2.35; N, 13.15.

Benzotriazol-1-yl(2,5-dihydroxyphenyl)methanone (6c): yellow needles from diethyl ether (40%); mp 182 °C (polymerizes); IR (KBr) ν = 3135, 1649, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.38 (s, 1H), 10.31 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 6.46−6.43 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.1, 163.3, 159.9, 145.3, 133.5, 131.3, 130.3, 126.2, 119.9, 113.8, 110.7, 107.4, 102.8. Anal. Calcd for $C_{13}H_9N_3O_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 61.09; H, 3.48; N, 16.32.

Benzotriazole-1-yl(3-methyl-2-hydroxyphenyl)methanone (6d): pale yellow needles from diethyl ether (92%); mp 124−126 °C; IR (neat) ν = 3384 (br w), 1659, 1483, 1454 cm^{-1}; ^1H NMR δ 10.0 (br s, 1H), 8.40 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 6.96 (t, J = 7.7 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR δ 169.7, 162.0, 145.4, 138.0, 132.5, 131.4, 130.4, 127.3, 126.4, 120.3, 118.9, 114.9, 112.7, 15.9. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.52; H, 4.27; N, 16.95.

Benzotriazol-1-yl(2-hydroxynaphthalen-1-yl)methanone (9a): white needles from diethyl ether; mp 138−140 °C; IR (neat) ν = 3384, 1718 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.9 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.0 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 167.3, 154.3, 145.8, 133.0, 131.5, 131.1, 130.8, 128.6, 128.1, 127.5, 126.9, 123.8, 122.7, 120.3, 118.3, 114.2, 113.9. Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.52. Found: C, 70.18; H, 3.81; N, 14.49.

Benzotriazol-1-yl(1-hydroxynaphthalen-2-yl)methanone (9b): yellow microcrystals from chloroform/hexanes; mp 150−151 °C; IR (neat) ν = 3444, 1632 cm^{-1}; ^1H NMR δ 12.58 (br s, 1H), 8.58 (d, J = 9.2 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.75−7.68 (m, 2H), 7.61−7.54 (m, 2H), 7.40 (d, J = 9.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 169.8, 164.9, 145.3, 137.4, 132.5, 130.9, 130.4, 127.4, 126.7, 126.3, 126.1, 124.8, 124.4, 120.3, 118.9, 115.0, 106.7. Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.52. Found: C, 70.25; H, 3.68; N, 14.90.

Benzotriazol-1-yl(3-hydroxynaphthalen-2-yl)methanone (9c): yellow microcrystals from dichloromethane; mp 157−158 °C; IR (neat) ν = 3198, 1659 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.34 (dt, J = 8.2, 1.0 Hz, 1H), 8.30 (dt, J = 8.2, 1.0 Hz, 1H), 8.30 (s, 1H), 7.94 (br d, J = 7.7 Hz, 1H), 7.86 (dt, J = 8.2, 1.0 Hz, 1H), 7.84 (br d, J = 7.7 Hz, 1H), 7.68 (dt, J = 8.2, 1.0 Hz, 1H), 7.56 (dt, J = 8.2, 1.0 Hz), 7.40 (dt, J = 8.2, 1.0, 1H), 7. 34 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 166.9, 152.6, 145.6, 136.0, 131.1, 131.0, 130.8, 128.7, 128.4, 126.9, 126.8, 126.3, 124.2, 124.1, 120.3, 114.1, 110.0. Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.52. Found: C, 70.25; H, 3.69; N, 14.86.

General Procedure for the Synthesis of Amides of Substituted Salicylic and *o*-Hydroxynaphthoic Acids (7a−h, 10a−f). Method A. In a 50 mL round-bottomed flask were stirred the appropriate primary or secondary amine (3 mmol) and triethylamine (3 mmol) in freshly dried THF. The supernatant (as described in the synthesis of **6a**−**d**, **9a**−**c**) was carefully syringed out and added rapidly to the mixture of amines under an inert atmosphere while being stirred. The stirring was continued for an additional 30 min. The reaction mixture was concentrated under vacuum to remove the solvent and excess triethylamine. The crude residue was taken up in ether (25 mL) and washed with water (25 mL), 1 N HCl (2 × 25 mL), and brine before being dried over magnesium sulfate. The concentrated organic layer was finally refined by column chromatography over silica gel to give the respective amides (**7a**−**e**,**h**, **10b**−**f**).

Method B. The appropriate crude acyl benzotriazole derivative **6a**−**d**, **9a**−**c** obtained from 1.2 mmol of salicylic/*o*-hydroxynaphthoic acids was taken in 1 equiv of the appropriate amine in a 50 mL round-bottom flask equipped with a stir bar. The flask was then exposed to microwave irradiation (120 W) at 120 °C for 10 min. The reaction mixture was diluted with $CHCl_3$ (10 mL) and the residue refined by column chromatography on silica gel to give the amides **7f**,**g** and **10a**.

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***N*-(Furan-2-ylmethyl)-2-hydroxybenzamide**[112] **(7a):** white needles from diethyl ether (83%); mp 109−110 °C; IR (neat) ν = 3364, 1645, 1592, 1546, 1496 cm^{-1}; ^{1}H NMR δ 12.20 (s, 1H), 7.42−7.34 (m, 3 H), 6.90 (dd, J = 8.24, 1.0 Hz, 1H), 6.84 (dt, J = 7.14, 1 Hz, 1H), 6.60 (br s, 1H), 6.35 (dd, J = 3.3, 1.8 Hz, 1H), 6.32 (d, J = 3.3 Hz, 1H), 4.63 (d, J = 5.94 Hz, 2H); ^{13}C NMR δ 169.7, 161.6, 150.4, 142.6, 142.5, 134.4, 125.4, 118.7, 114.0, 110.6, 108.1, 36.5. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.97; H, 5.18; N, 6.49.

(2-Hydroxyphenyl)piperidin-1-ylmethanone[53] **(7b):** white needles from methanol (94%); mp 142−143 °C; IR (neat) ν = 3153, 2939, 2856, 1591, 1475 cm^{-1}; ^{1}H NMR δ 9.67 (s, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.82 (t, J = 7.3 Hz, 1H), 3.65−3.61 (m, 4H), 1.70−1.62 (m, 6H); ^{13}C NMR δ 170.6, 158.7, 132.2, 128.1, 118.4, 117.8, 117.5, 46.7, 26.0, 24.4.

5-Bromo-2-hydroxy-*N*-pentylbenzamide (7c): pale yellow microcrystals from diethyl ether (84%); mp 54−55 °C; IR (neat) ν = 3374, 2930, 2859, 1635, 1591, 1543, 1475 cm^{-1}; ^{1}H NMR δ 12.36 (s, 1H), 7.46−7.43 (m, 2H), 6.88 (d, J = 9.3 Hz, 1H), 6.30 (br s, 1H), 3.43 (q, J = 6.3 Hz, 2H), 1.68−1.58 (m, 2H), 1.38−1.34 (m, 4H), 0.92 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 68.7, 160.5, 136.7, 127.8, 120.5, 115.9, 110.1, 39.9, 29.1, 29.0, 22.3, 13.9. Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64; N, 4.89. Found: C, 50.54; H, 5.57; N, 4.84.

5-Bromo-2-hydroxy-*N*-methyl-*N*-octylbenzamide (7d): cream microcrystals from ethyl acetate (82%); mp 92−93 °C; IR (neat) ν = 3125, 2927, 2855, 1612, 1490 cm^{-1}; ^{1}H NMR δ 9.74 (s, 1H), 7.40−7.37 (m, 2H), 6.87 (d, J = 9.5 Hz, 1H), 3.50−3.45 (m, 2H), 3.11 (s, 3H), 1.68−1.64 (m, 2H), 1.29 (br s, 10H). 0.88 (t, J = 6.2 Hz, 3H); ^{13}C NMR δ 170.2, 157.7, 134.9, 130.5, 119.8, 119.6, 110.1, 31.7, 29.2, 29.1, 27.3, 26.6, 22.6, 14.1. Anal. Calcd for $C_{16}H_{24}BrNO_2$: C, 56.15; H, 7.07; N, 4.09. Found: C, 56.46; H, 7.35; N, 4.10.

2,4-Dihydroxy-*N*-pentylbenzamide (7e): white microcrystals from ethyl acetate (96%); mp 104−105 °C; IR (neat) ν = 3385, 1637 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.06 (s, 1H), 10.03 (s, 1H), 8.51 (br t, J = 6.2 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 6.28 (dd, J = 8.8, 1.8 Hz, 1H), 6.22 (d, J = 1.8 Hz, 1H), 3.24 (q, J = 6.1 Hz, 2H), 1.54−1.50 (m, 2H), 1.29 (br s, 4H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 169.4, 162.7, 162.1, 128.8, 106.9, 106.6, 102.7, 39.5, 28.7, 21.9, 13.9. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56; H, 7.67; N, 6.27. Found: C, 64.77; H, 7.89; N, 6.28.

2,4-Dihydroxy-*N*-methyl-*N*-phenylbenzamide (7f): white microcrystals from chloroform (93%); mp 150.0−152.0 °C; IR (neat) ν = 3350, 1664, 1624, 1502 cm^{-1}; ^{1}H NMR δ 11.65 (s, 1H), 7.37−7.31 (m, 2H), 7.28−7.26 (m, 1H), 7.15−7.12 (m, 2H), 6.53 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 2.6 Hz, 1H), 5.88 (dd, J = 8.8, 2.6 Hz, 1H), 5.67 (br s, 1H), 3.46 (s, 3H); ^{13}C NMR δ 171.7, 162.9, 160.0, 145.3, 132.3, 129.7, 127.1, 126.6, 108.3, 106.3, 103.6, 39.5. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 68.77; H, 5.43; N, 5.77.

4-(Morpholin-4-ylcarbonyl)benzene-1,3-diol (7g): white microcrystals from chloroform (94%); mp 179.0−181.0 °C; IR (neat) ν = 3378, 1620, 1578 cm^{-1}; ^{1}H NMR δ 9.60 (s, 1H), 8.19 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.30 (dd, J = 8.4, 2.3 Hz, 1H), 3.68−3.65 (m, 8H); ^{13}C NMR δ 170.9, 160.0, 158.7, 129.9, 110.2, 107.4, 103.8, 66.7, 46.0. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.83; H, 5.99; N, 6.19.

2-Hydroxy-3-methyl-*N*-(3-methylbutyl)benzamide (7h): colorless oil (93%); IR (neat) ν = 3384, 2962, 2926, 2875, 1633, 1609, 1588, 1541 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.65 (s, 1H), 7.25 (d, J = 6.4 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 6.73 (t, J = 7.7 Hz, 1H), 6.39 (br s, 1H), 3.42−3.21 (m, 2H), 2.26 (s, 3H), 1.73−1.62 (m, 1H), 1.53−1.39 (m, 1H), 1.28−1.14 (m, 1H), 0.97−0.91 (m, 6H); ^{13}C NMR (DMSO-d_6): δ 170.6, 159.9, 134.8, 127.7, 122.6, 117.8, 113.5, 45.2, 34.8, 27.0, 17.1, 15.8, 11.2. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.77; H, 8.97; N, 6.63.

2-Hydroxy-*N*-phenyl-1-naphthamide (10a): white microcrystals from chloroform (95%); mp171.0−172.0 °C; IR (neat) ν = 3283 (br w), 1627, 1597, 1532, 1443 cm^{-1}; ^{1}H NMR δ 11.1 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.97 (br s, 1H), 7.85 (t, J = 8.2 Hz, 2H), 7.62 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.1 Hz, 1H) 7.45−7.38 (m, 3H), 7.26−7.19 (m, 2H); ^{13}C NMR δ 168.4, 159.8, 136.9, 134.4, 130.5, 129.7, 129.3, 128.8, 128.5, 125.3, 123.7, 122.3, 120.7, 119.4, 109.9. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.17; H, 4.94; N, 5.31.

(2-Hydroxynaphthalen-1-yl)piperidin-1-ylmethanone (10b): white needles from methanol (90%); mp 242−243 °C; IR (KBr) ν = 3175, 1606, 1514 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.93 (s, 1H), 7.83−7.77 (m, 2H), 7.51−7.41 (m, 2H), 7.33−7.28 (m, 1H), 7.19 (d, J = 8.9 Hz, 1H), 3.90 (br s, 1H), 3.56 (br s, 1H), 3.09 (s, 2H), 1.59 (s, 4H), 1.44 (br s, 1H), 1.24 (br s, 1H); ^{13}C NMR δ 165.9, 150.7, 131.2, 129.6, 128.2, 127.7, 126.9, 123.6, 123.1, 118.2, 117.1, 47.0, 24.3. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.34; H, 6.93; N, 5.15.

1-Hydroxynaphthalene-2-carboxylic acid *N*-phenethylamide (10c): pale yellow microcrystals from ethyl acetate (94%); mp 125−126 °C; IR (neat) ν = 3417, 1615, 1594, 1542, 1501 cm^{-1}; ^{1}H NMR δ 13.84 (s, 1H), 8.42 (d, J = 7.1 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.59−7.49 (m, 2H), 7.36−7.11 (m, 7H), 6.34 (br s, 1H), 3.75 (q, J = 6.6 Hz, 2H), 2.96 (t, J = 6.8 Hz, 1H); ^{13}C NMR δ 170.6, 160.6, 138.5, 136.2, 128.9, 128.8 (2C), 127.3, 126.8, 125.8, 125.6, 123.8, 120.6, 118.1, 106.6, 40.8, 35.6. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.94; H, 5.94; N, 4.86.

(1-Hydroxynaphthalen-2-yl)pyrrolidin-1-ylmethanone (10d): white microcrystals from ether (97%); mp 93−94 °C; IR (neat) ν = 3445 (br w), 2972, 2877, 1584, 1438 cm^{-1}; ^{1}H NMR δ 12.87 (s, 1H), 8.40 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.58−7.47 (m, 3H), 7.24 (d, J = 8.6 Hz, 1H), 3.77−3.73 (m, 4H), 1.97−1.92 (m, 4H); ^{13}C NMR δ 171.2, 159.4, 135.5, 128.5, 127.1, 125.5, 125.3, 123.9, 123.7, 116.9, 109.5, 48.9, 25.5. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.76; H, 6.27; N, 5.80. Found: C, 74.28; H, 6.30; N, 5.85.

3-Hydroxynaphthalene-2-carboxylic acid allylamide[66] **(10e):** pale yellow microcrystals from ethyl acetate (75%); mp 121−122 °C; IR (neat) ν = 3374, 1657, 1584, 1509 cm^{-1}; ^{1}H NMR δ 11.72 (s, 1H), 7.97 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.47 (dt, J = 6.9, 1.1 Hz, 1H), 7.31−7.26 (m, 2H), 6.70 (br s, 1H), 6.03−5.09 (m, 1H), 5.33 (dq, J = 17.0, 1.2 Hz, 1H), 5.25 (dq, J = 10.2 Hz, 1.2 Hz, 1H), 4.14 (tt, J = 5.8, 1.5 Hz, 2H); ^{13}C NMR δ 169.6, 156.6, 137.0, 133.3, 128.5, 128.4, 126.8, 126.7, 126.2, 123.9, 117.5, 116.8, 112.4, 42.2. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.69; H, 5.86; N, 6.17.

(3-Hydroxynaphthalen-2-yl)morpholin-4-ylmethanone[64] **(10f):** white needles from ethyl acetate (70%); mp 216−217 °C; IR (neat) ν = 3095, 2967, 2855, 1594, 1483 cm^{-1}; ^{1}H NMR δ 8.93 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.73 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.32 (s, 1H), 3.83−3.76 (m, 8H); ^{13}C NMR δ 170.2, 154.1, 135.8, 128.7, 128.3, 128.1, 126.9, 126.4, 124.1, 119.7, 112.3, 66.9 (2C). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.70; H, 5.95; N, 5.44.

General Procedure for the Synthesis of Hydroxy Aryl-/Alkyl- and Thio Esters (11a−g) from Hydroxy Acids. The (*N*-hydroxyacyl)benzotriazole was prepared as described in the synthesis of the hydroxy carboxamides.

The appropriate alcohol/thiol (6 mmol) was treated with NaH (60% dispersion in oil) (6.2 mmol) in 12 mL of anhydrous THF and stirred for 30 min. The supernatant of the benzotriazolating mixture/hydroxy acid was carefully syringed out and added dropwise to the sodium salt of the alchohol/thiol while under inert

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atmosphere. The residual solid was washed with 5 mL of dry THF, and the washings were added to the sodium salt of the alcohol. After 30 min, the reaction was concentrated under vacuum. Water (20 mL) and ether (20 mL) were added to the residue. The layers were separated, and the organic layer further washed with saturated sodium carbonate solution (to remove benzotriazole) and brine, dried over magnesium sulfate, and concentrated. The residue was refined by flash chromatography over silica gel to give the hydroxy aryl-/alkyl- and thio esters.

Methyl DL-mandelate[113] (11a): white powder from hexanes (40%); mp 56−57 °C; IR (neat) ν = 3468, 1735 cm^{-1}; ^{1}H NMR δ 7.43−7.32 (m, 5H), 5.18 (d, J = 5.6 Hz, 1H), 3.74 (s, 3H), 3.56 (d, J = 5.6 Hz, 1H); ^{13}C NMR δ 174.1, 138.2, 128.6, 128.5, 126.5, 72.8, 53.0.

Ethyl DL-mandelate[114] (11b): microcrystals from hexanes (72%); mp 35−36 °C; IR (neat) ν = 3469, 2983, 1735 cm^{-1}; ^{1}H NMR δ 7.44−7.28 (m, 5H), 5.15 (d, J = 5.8 Hz, 1H), 4.31−4.10 (m, 2H), 3.61 (d, J = 5.9 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.6, 138.4, 128.5, 128.3, 126.5, 72.8, 62.1, 13.9.

2-Hydroxy-3-phenylthiopropionic acid *S*-hexyl ester (11e): colorless oil (37%); IR (neat) ν = 3455, 2928, 2856, 1681 cm^{-1}; ^{1}H NMR δ 7.34−7.22 (m, 5H), 4.44 (ddd, J = 7.7, 6.5, 4.1 Hz, 1H), 3.17 (dd, J = 14.0, 4.1 Hz, 1H), 2.95 (dd, J = 14.0, 7.8 Hz, 1H), 2.9 (t, J = 7.3 Hz, 2H), 2.72 (d, J = 6.5 Hz, 1H), 1.62−1.52 (m, 2H), 1.4−1.21 (m, 6H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 203.2, 136.0, 129.5, 128.5, 126.9, 78.1, 41.1, 31.2, 29.2, 28.4, 22.4, 14.0. Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.80; H, 8.60.

Hydroxyphenylthioacetic acid *S*-(4-methoxyphenyl) ester (11f): colorless oil (23%); IR (neat) ν = 3462, 2940, 2837, 1698, 1592 cm^{-1}; ^{1}H NMR δ 7.48−7.36 (m, 5H), 7.24 (AA′BB′, J_{AB} = 8.8 Hz, 2H), 6.90 (AA′BB′, J_{AB} = 8.8 Hz, 2H), 5.31 (d, J = 3.9 Hz, 1H), 3.79 (s, 3H), 3.73 (d, J = 4.5 Hz, 1H); ^{13}C NMR δ 201.1, 160.7, 137.8, 136.1, 128.9, 128.8, 127.1, 117.0, 114.9, 79.8, 55.3. Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.42; H, 5.28.

2-Hydroxy-3-methylthiobutyric acid *S*-benzyl ester (11g): white needles from hexanes/ethyl acetate (24%); mp 69−70 °C; IR (neat) ν = 3406, 2926, 2855, 1638 cm^{-1}; ^{1}H NMR δ 7.31−7.23 (m, 5H), 4.17−4.10 (m, 3H), 2.82 (d, J = 6.2 Hz, 1H), 2.21−2.11 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 203.0, 137.2, 128.8, 128.6, 127.3, 81.7, 32.9, 32.7, 19.1, 15.1. Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19. Found: C, 64.47; H, 7.42.

General Procedure for the Synthesis of Esters of Substituted Salicylic and 12a−h and *o*-Hydroxynaphthoic Acids 13a−i. Method A. In a 50 mL round-bottomed flask, the appropriate alcohol (3 mmol) was treated with NaH (60% dispersion in oil) (3.2 mmol) in 6 mL of anhydrous THF and stirred for 0.5 h. The supernatant containing the acyl benzotriazole derivative (as described in the synthesis of **6a**−**d**, **9a**−**c**) was carefully syringed out and added dropwise to the sodium salt of the alcohol under an inert atmosphere. After 30 min, the reaction mixture was concentrated under vacuum. Water (20 mL) and ether (20 mL) were added to the concentrated residue. The layers were separated, and the organic layer was dried over magnesium sulfate, concentrated under vacuum, and refined by flash column chromatography to give the esters (**12a**,**b**, **13a**).

Method B. The crude acyl benzotriazole derivative **6a**−**d**, **9a**−**c** obtained from 1 mmol of salicylic/*o*-hydroxynaphthoic acids was taken in 3 equiv of the appropriate alcohol in a 50 mL round-bottom flask equipped with a stir bar. The flask was then exposed to microwave irradiation (120 W) at 120 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and the residue refined by column chromatography on silica gel with hexanes/ ethyl acetate (8/1) to give the respective ester **12b**−**h**, **13b**−**i**.

Methyl salicylate[115] (12a): colorless oil (94%); IR (neat) ν = 3188, 2955, 2853, 1681 cm^{-1}; ^{1}H NMR δ 10.77 (s, 1H), 7.83 (dd, J = 8.0, 1.7 Hz, 1H), 7.45 (ddd, J = 8.1, 6.9, 1.7 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.88 (td, J = 8.5, 1.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR δ 170.6, 161.5, 135.7, 129.9, 119.1, 117.5, 112.3, 52.2.

Cyclopentyl salicylate (12b): colorless oil (92%); IR (neat) ν = 3145, 2965, 2874, 1672 cm^{-1}; ^{1}H NMR δ 10.93 (s, 1H), 7.80 (dd, J = 7.9, 1.5 Hz, 1H), 7.44 (td, J = 8.0, 1.7 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.86 (t, J = 7.3 Hz, 1H), 5.40−5.46 (m, 1H), 1.65−2.01 (m, 8H); ^{13}C NMR δ 170.0, 161.6, 135.4, 129.8, 119.0, 117.5, 112.9, 32.7, 23.7. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.86; H, 7.03.

1-Ethylprop-2-enyl salicylate (12c): colorless oil (84%); IR (neat) ν = 3186, 2972, 2880, 1675, 1614 cm^{-1}; ^{1}H NMR δ 10.86 (s, 1H), 7.89 (dd, J = 8.0, 1.7 Hz, 1H), 7.45 (td, J = 7.8, 1.6 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 5.83−5.94 (m, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.24 (d, J = 10.6 Hz, 1H), 1.75−1.86 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 169.4, 161.7, 135.6, 135.5, 129.7, 119.0, 117.5, 117.2, 112.6, 77.0, 27.2, 9.3. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.87; H, 7.04.

Ethyl 5-bromo-2-hydroxybenzoate (12d): colorless microcrystals (90%); mp 46−48 °C; IR (neat) ν = 3143, 1681, 1608 cm^{-1}; ^{1}H NMR δ 10.80 (s, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.52 (dd, J = 8.9, 2.6 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 169.1, 160.6, 138.3, 132.2, 119.5, 114.1, 110.7, 61.9, 14.1. Anal. Calcd for $C_{12}H_{14}O_3$: C, 44.11; H, 3.70. Found: C, 44.29; H, 3.56.

Cyclopentyl 5-bromo-2-hydroxybenzoate (12e): colorless needles from chloroform/hexanes (87%); mp 45−47 °C; IR (neat) ν = 3412, 2966, 2873, 1674 cm^{-1}; ^{1}H NMR δ 10.90 (s, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.51 (dd, J = 9.0, 2.4 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 5.45−5.41 (m, 1H), 2.04−1.68 (m, 8H); ^{13}C NMR δ 168.9, 160.7, 138.2, 132.1, 119.5, 114.4, 110.6, 79.1, 32.7, 23.8. Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60. Found: C, 50.41; H, 4.52.

Propyl 2,4-dihydroxybenzoate (12f): colorless microcrystals from hexane/ethyl acetate (87%); mp 32−34 °C; IR (neat) ν = 3384, 1666, 1623 cm^{-1}; ^{1}H NMR δ 11.17 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 6.62 (br s, 1H), 6.42 (d, J = 2.1 Hz, 1H), 6.39 (dd, J = 8.5, 2.1 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 1.78 (sextet, J = 7.0 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 170.2, 163.3, 162.2, 131.9, 108.0, 105.8, 103.0, 66.7, 21.9, 10.4. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.30; H, 6.34.

Cyclopentyl 2,4-dihydroxybenzoate (12g): colorless oil (91%); IR (neat) ν = 3372, 1660 cm^{-1}; ^{1}H NMR δ 11.25 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.09 (br s, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.39 (dd, J = 8.6, 2.3 Hz, 1H), 5.41−5.36 (m, 1H), 2.00−1.59 (m, 8H); ^{13}C NMR δ 170.0, 163.1, 162.2, 131.9, 108.0, 106.0, 102.9, 78.3, 32.7, 23.7. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.58; H, 6.50.

Decyl 2-hydroxy-3-methylbenzoate (12h): pale yellow oil (84%); IR (neat) ν = 3165, 2926, 2855, 1671 cm^{-1}; ^{1}H NMR δ 7.69 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 6.77 (t, J = 7.6 Hz, 1H), 4.32 (t, J = 6.6 Hz, 2H), 2.26 (s, 3H), 1.81−1.72 (m, 2H), 1.81−1.27 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 170.7, 160.1, 136.3, 127.3, 126.5, 118.3, 111.8, 65.4, 31.9, 29.5, 29.3, 29.2, 28.5, 25.9, 22.6, 15.6, 14.1. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.65; H, 9.92.

2-Hydroxynaphthalene-1-carboxylic acid methyl ester[100] (13a): white needles from methanol (85%); mp 79−80 °C; IR (neat) ν = 3295 (br w), 1650 cm^{-1}; ^{1}H NMR δ 12.28 (s, 1H), 8.74 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.56 (ddd, J = 8.6, 7.9, 1.4 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H),

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7.17 (d, $J = 9.0$ Hz, 1H), 4.10 (s, 3H); ^{13}C NMR δ 172.8, 164.4, 136.9, 131.7, 129.1, 128.6, 128.4, 125.3, 123.6, 119.3, 104.6, 52.4.

Cyclopentyl 2-hydroxy-1-naphthoate (13b): pale yellow oil (85%); IR (neat) $\nu = 3345$ (br w), 2965, 2873, 1644 cm^{-1}; ^{1}H NMR δ 12.46 (s, 1H), 8.75 (d, $J = 8.9$ Hz, 1H), 7.86 (d, $J = 9.1$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.37−7.32 (m, 1H), 7.15 (d, $J = 8.9$ Hz, 1H), 5.65−5.59 (m, 1H), 2.09−1.69 (m, 8H); ^{13}C NMR δ 172.2, 164.3, 136.6, 131.9, 129.1, 128.6, 128.3, 125.0, 123.5, 119.3, 105.0, 79.3, 32.8, 23.8. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.88; H, 6.41.

Pent-4-ynyl 2-hydroxy-1-naphthoate (13c): colorless oil (84%); IR (neat) $\nu = 3296$, 1645 cm^{-1}; ^{1}H NMR δ 12.31 (s, 1H), 8.70 (d, $J = 8.7$ Hz, 1H), 7.85 (d, $J = 8.9$ Hz, 1H), 7.71 (d, $J = 7.1$ Hz, 1H), 7.56−7.51 (m, 1H), 7.34 (td, $J = 7.4$, 0.9 Hz, 1H), 7.14 (d, $J = 8.9$ Hz, 1H), 4.61 (t, $J = 6.4$ Hz, 2H), 2.43 (td, $J = 6.9$, 2.5 Hz, 2H), 2.14−2.02 (m, 3H); ^{13}C NMR δ 172.3, 164.4, 136.8, 131.7, 129.1, 128.5, 128.4, 125.1, 123.5, 119.2, 104.5, 82.5, 69.5, 64.3, 27.3, 15.4. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.32; H, 5.60.

Ethyl 2-hydroxy-1-naphthoate[62] (13d): colorless needles from chloroform/ hexanes (88%); mp 56−58 °C; IR (neat) $\nu = 3358$ (br w), 1644 cm^{-1}; ^{1}H NMR δ 12.4 (s, 1H), 8.77 (d, $J = 8.9$ Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.52 (td, $J = 6.1$ Hz, 1H), 7.34 (td, $J = 7.4$, 0.9 Hz, 1H), 7.14 (d, $J = 9.1$ Hz, 1H), 4.55 (q, $J = 4.2$ Hz, 2H), 1.51 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR δ 172.3, 164.3, 136.7, 131.8, 129.0, 128.6, 128.3, 125.2, 123.5, 119.2, 104.6, 61.9, 14.3.

Ethyl 1-hydroxy-2-naphthoate[116] (13e): colorless needles from chloroform/ hexanes (88%); mp 46−48 °C; IR (neat) $\nu = 2990$, 1656 cm^{-1}; ^{1}H NMR δ 12.1 (s, 1H), 8.38 (d, $J = 8.2$ Hz, 1H), 7.73−7.68 (m, 2H), 7.54 (td, $J = 8.1$, 1.4 Hz, 1H), 7.46 (td, $J = 7.0$, 1.2 Hz, 1H), 7.21 (d, $J = 8.7$ Hz, 1H), 4.38 (q, $J = 5.7$ Hz, 2H), 1.39 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR δ 171.0, 160.8, 137.0, 129.2, 127.3, 125.6, 124.7, 124.2, 123.7, 118.4, 105.7, 61.3, 14.1.

Cyclopentyl 1-hydroxy-2-naphthoate (13f): white microcrystals from chloroform/hexanes (90%); mp 58−60 °C; IR (neat) $\nu = 3385$, 2964, 2866, 1655 cm^{-1}; ^{1}H NMR δ 12.16 (s, 1H), 8.40 (d, $J = 8.2$ Hz, 1H), 7.75−7.71 (m, 2H), 7.58 (td, $J = 8.1$, 1.2 Hz, 1H), 7.50 (t, $J = 8.2$ Hz, 1H), 7.24 (d, $J = 8.8$ Hz, 1H), 5.50−5.45 (m, 1H), 2.05−1.65 (m, 8H); ^{13}C NMR δ 170.8, 160.9, 137.1, 129.2, 127.4, 125.6, 124.8, 124.3, 123.8, 118.3, 106.1, 78.4, 32.8, 23.8. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.80; H, 6.39.

Pent-4-ynyl 1-hydroxy-2-naphthoate (13g): white powder from chloroform/ hexanes (83%); mp 65−67 °C; IR (neat) $\nu = 3267$, 2975, 2844, 1650 cm^{-1}; ^{1}H NMR δ 12.0 (s, 1H), 8.40 (d, $J = 8.2$ Hz, 1H), 7.75−7.72 (m, 2H), 7.59 (td, $J = 8.2$, 1.4 Hz, 1H), 7.50 (td, $J = 8.1$, 1.1 Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 4.49 (t, $J = 6.3$ Hz, 2H), 2.40 (td, $J = 6.9$, 2.6 Hz, 2H), 2.07−1.99 (m, 3H); ^{13}C NMR δ 170.9, 161.0, 137.1, 129.3, 127.4, 125.7, 124.7, 124.1, 123.8, 118.5, 105.5, 82.8, 69.3, 63.7, 27.5, 15.3. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.39; H, 5.56.

1-Ethylprop-2-enyl 1-hydroxy-2-naphthoate (13h): colorless oil (83%); IR (neat) $\nu = 3408$, 2971, 2879, 1660, 1600 cm^{-1}; ^{1}H NMR δ 12.07 (s, 1H), 8.40 (d, $J = 8.2$ Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.57 (td, $J = 8.1$, 1.2 Hz, 1H), 7.49 (td, $J = 7.6$, 1.2 Hz, 1H), 7.26 (d, $J = 8.9$ Hz, 1H), 5.97−5.85 (m, 1H), 5.53−5.47 (m, 1H), 5.36 (d, $J = 18.3$ Hz, 1H), 5.25 (d, $J = 6.2$ Hz, 1H), 1.89−1.75 (m, 2H), 1.0 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR δ 170.4, 161.0, 137.1, 135.8, 129.3, 125.6, 127.4, 124.7, 124.2, 123.8, 118.4, 117.2, 105.8, 27.3, 9.4. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.89; H, 6.44.

Butyl 3-hydroxy-2-naphthoate (13i): yellow oil (84%); IR (neat) $\nu = 3226$, 2961, 2873, 1681 cm^{-1}; ^{1}H NMR δ 10.55 (s, 1H), 8.42 (s, 1H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.45 (td, $J = 8.1$, 1.0 Hz, 1H), 7.30−7.25 (m, 2H), 4.38 (t, $J = 6.6$ Hz, 2H), 1.84−1.75 (m, 2H), 1.56−1.44 (m, 2H), 1.0 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR δ 169.9, 156.3, 137.7, 132.1, 129.1, 129.0, 126.9, 126.2, 123.8, 114.3, 111.5, 103.3, 65.5, 30.5, 19.2, 13.7. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.64; H, 6.72.

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