A Facilitated Cyclic Ether Formation and Its Potential Application in Solid-Phase Peptide and Organic Synthesis

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A "trimethyl lock" system has been known to facilitate lactonization reactions through what has been termed a stereopopulation control mechanism. We have found that a similar trimethyl lock system can also facilitate cyclic ether formation with the concomitant release of a carboxylic acid in the presence of anhydrous tetrabutylammonium fluoride. To study this base-mediated trimethyl lock-facilitated cyclic ether formation, we synthesized fifteen model compounds. All model compounds underwent base-mediated cyclic ether formation in high yields at 0 °C to room temperature (r.t.) with the concomitant release of the attached carboxylate. Such a system potentially could be used for the development of a two-dimensional linker for solid phase peptide and organic synthesis.

Key words "trimethyl lock"; cyclization; linker; fluoride; quinone; hydroquinone

A "trimethyl lock" system has been known to facilitate lactonization reactions[2)] and cyclic ether formation in aqueous solutions.[3)] The mechanism through which such a trimethyl lock facilitates certain cyclization reactions has been thought to be due to the conformational restrictions imposed by the trimethyl lock (Chart 1).[2)] Such trimethyl lock-facilitated lactonization reactions have been used to develop redox-, esterase-, and phosphatase-sensitive prodrugs[4)] and redox-sensitive protecting groups for amines.[5,6)] In our studies of such trimethyl lock-facilitated cyclization reactions, we have found that facile base-mediated cyclic ether formation can be also accomplished at room temperature (r.t.) through treatment of the open-chain system **2** (R=CH_3) with tetrabutylammonium fluoride (TBAF) (Chart 1).

Recently, there has been a great deal of interest in developing linkers that are stable during synthetic reactions yet readily cleavable under mild reaction conditions for solid phase synthesis.[7)] Conceivably, this cyclization system could be used for the development of a two-dimensional linker for solid phase peptide and organic synthesis. In such a design, the quinone ester moiety **1** could be attached to an appropriate solid phase material, and the carboxylic acid moiety (R) could be either a protected amino acid for solid phase peptide synthesis or another organic acid, which would be modified through solid phase reactions. Such a linker, if successfully developed, would have the advantages of being cleavable with a mild reducing agent, such as $Na_2S_2O_4$, and TBAF, and of being more stable under acidic conditions than the commonly used benzyl ester linker.[8)] In addition, many amino acid side chain protections are expected to be stable under the cleavage conditions. Therefore, this type of resin linker will be particularly suitable for the synthesis of large peptides and small proteins using segment synthesis methods.[8)] The final cleavage is a two-step process: reduction followed by treatment with TBAF. This helps to minimize the stability problems of this linker (**1**) during any single chemical transformation.

To study the feasibility of such a system for the development of a novel two-dimensional linker for solid phase synthesis, we synthesized a series of esters **1** of acids with different structural features. These acids included protected amino acids and simple aliphatic and aromatic carboxylic acids. The cyclic ether formation with the concomitant release of the acid was studied after the reduction of the quinone moiety **1** to the hydroquinone **2** (Chart 1). We have found that such cyclizations could be accomplished with esters of acids with a variety of different structural features, indicating the general applicability of such a system in the development of a novel linker for solid phase synthesis.

Results and Discussion

For **1** to be used as a potential solid phase linker for peptide and organic syntheses, it was necessary to test the cyclization reactions of esters **2** with different structural features. First, we were interested in studying the cyclic ether formation of **2** with protected amino acids attached to the quinone moiety. Among the twenty natural amino acids, we chose nine representative ones (Chart 2). This group in-

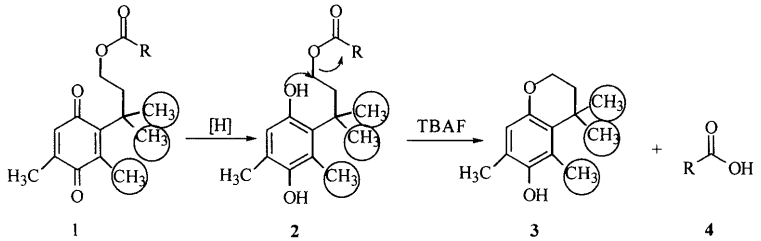

Chart 1. A "Trimethyl Lock"-Facilitated Cyclic Ether Formation

The methyl groups involved in the "trimethyl lock" are circled.

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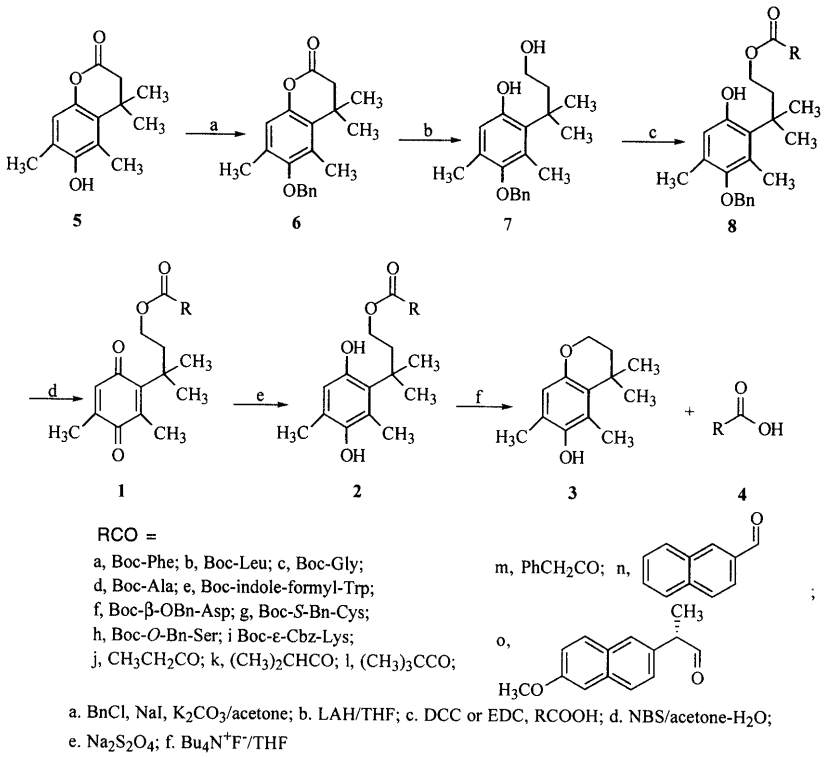

Chart 2. Synthesis and Cyclization Studies of Esters **2**

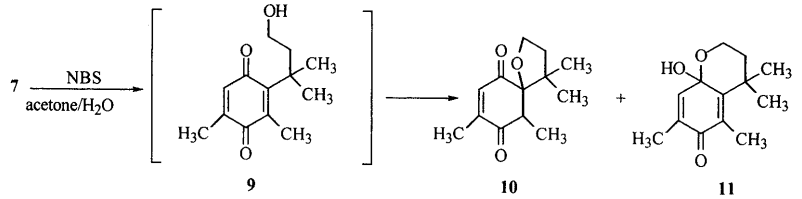

Chart 3. The Formation of Spiroether **10** and Hemiketal **11**

cluded amino acids bearing non-polar side chains (**2a**—**e**), aromatic side chains (**2a**, **e**), and protected side chain functional groups such as hydroxyl (**2h**), thiol (**2g**), amino (**2i**), and carboxyl groups (**2f**). We also synthesized the esters **2** of several other carboxylic acids with different structural features. Compounds **2j**—**m**, and **o** are all esters of aliphatic carboxylic acids with different steric hindrances and functional groups, and compound **2n** is an ester of an aromatic carboxylic acid.

Synthesis The synthesis of these esters **2** started with lactone **5**. The hydroxyl group of **5** was first protected as a benzyl ether to give **6**, which was then reduced using $LiAlH_4$ (LAH) to give the diol **7** (Chart 2).[3] It is known that without the benzyl protection of the phenol hydroxyl group, the reduction reaction is very slow due to the negative charge of the phenoxide.[3] Our initial plan was to oxidize the phenol **7** to quinone **9** (Chart 3), which would be followed by acylation of the primary hydroxyl group to give the desired products **1**. However, this approach did not lead to the formation of the desired product. Similar quinones in the presence of a trimethyl lock are known to undergo cyclizations to give a mixture of the spiroether **10** and a hemiketal **11** (Chart 3), which makes the acylation of the hydroxyl group of quinone **9** impossible.[9] Therefore, we studied the feasibility of selective acylation of the primary hydroxyl group of the diol intermediate **7** for the preparation of the desired product **1**. The selective acylation of the primary hydroxyl group of **7** was easily accomplished in high yields (about 90%) when the acids were protected amino acids (**8a**—**i**) activated with either dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC). Presumably due to the steric hindrance presented by the *gem*-dimethyl groups of **7** and the relative steric bulkiness of protected amino acids, the esterification occurred almost exclusively on the primary hydroxyl group to give the desired products **8** (Table 1).

Other acids bearing α-substituents also gave high yields of the monoester. Such was the case for **8k**, **o**. However, acids that did not have an α-substituent tended to give the diester as the side product. Such was the case for **8j**, **m**, and **n**. For 2,2-dimethylpropanoic acid (**8l**), the reaction using DCC as the activating agent was very slow, presumably because of the steric hindrance imposed by the *tert*-butyl group. Therefore, *N*,*N*-bis(2-oxo-3-oxozolidinyl)phosphinic chloride (Bop-Cl)[10] was used for the preparation of this compound (**8l**) in 67% yield. Oxalyl chloride was used as the activating reagent for the preparation of **8n**, **o**. The diester side product was found for the preparation of **8n**, which was the reason for the relatively low yield (73%).

For subsequent model studies, the hydroquinone was first

Table 1. Reaction Yields[a)]

RCO	Formation of **8**	Formation of **1**	Final release
a Boc–Phe	95	99	92
b Boc–Leu	99	97	93
c Boc–Gly	99	99	93
d Boc–Ala	93	97	94
e Boc–*N*-formyl–Trp	93	91	100 (80)
f Boc–*β*-OBn–Asp	100	98	88
g Boc–*S*-Bn–Cys	93	73	93
h Boc–*O*-Bn–Ser	95	95	100
i Boc–*ε*-Cbz–Lys	85	99	92
j $COCH_2CH_3$	72	99	95
k $COCH(CH_3)_2$	89	95	97
l $COC(CH_3)_3$	67	96	99
m $COCH_2C_6H_5$	80	96	95
n $CO–C_{10}H_7$	73	98	99
o (+)-$COCH(CH_3)–C_{10}H_6$–6-OMe	91	99	93 (93)

a) Yields for the formation of **8** and **1** were isolated yields. Yields for the final release were determined by HPLC, except for the yields in parentheses, which were isolated yields.

converted to the corresponding quinone compound **1** through oxidation with *N*-bromosuccinimide (NBS). The yields for this step of the reaction were generally close to quantitative, except for **8g**, the cysteine ester. It was suspected that the oxidation of the sulfur atom by NBS was the reason for this low yield. However, no detailed study was carried out to characterize the side product(s) from this oxidation reaction.

Final Cleavage The reduction of the quinone **1** to hydroquinone **2** was accomplished by shaking an ether solution of the quinone ester (**1a**—**o**) and an aqueous solution of $Na_2S_2O_4$ at r.t. The reaction color quickly changed from yellow to almost colorless, indicating the completion of the reduction. Approximately 20-fold $Na_2S_2O_4$ was employed. The yields were almost quantitative. The cyclization reaction was carried out by treatment of **2** with 1 M TBAF/tetrahydrofuran (THF) solution. These cyclization reactions were studied using reversed-phase HPLC by monitoring both the formation of the cyclic ether **3** and the disappearance of the starting material **2**. The formation of the acid **4** was also monitored when the acid had a chromophore. Figure 1 shows a typical HPLC reaction profile.

The quantitation of these compounds was carried out using the corresponding standard curves. The yields of these reactions were generally very high (Table 1). For two compounds (**2e**, **o**), the isolated yields were determined (Table 1). It should be noted that the cyclization was usually accompanied by a color change from yellow to orange and finally to blue/green. For the esters of protected amino acids, the cyclization was carried out at 0 °C under a nitrogen atmosphere with a TBAF/ester ratio of 3/1. However, the same reaction for the esters of the other carboxylic acids (**2j**—**n**) did not occur at 0 °C; instead the reactions were carried out at r.t. It should also be noted that for these non-amino acid esters, the reactions were carried out with a ratio of TBAF/ester of 8/1. Low reaction temperature (0 °C) and a lower ratio of TBAF/ester (3/1) led to lower yields. This indicated that the carboxylic acid moiety does influence the cyclization reaction. This is particularly relevant for the proper design of the reaction conditions in solid phase organic/peptide synthesis.

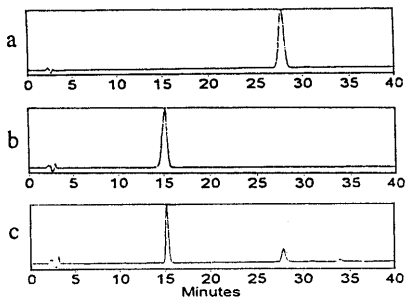

Fig. 1. HPLC Studies of the Deprotection of **1n**

Panel A, cycloether **3**; panel B, 2-naphthoic acid; panel C, **1n** after treatment with $Na_2S_2O_4$ in ether and water followed by Bu_4NF in THF for 1 h at r.t.

It suggests that peptides synthesized on this linker could probably be cleaved at 0 °C, whereas organic compounds could only be released from the solid phase at r.t.

It should be noted that TBAF is a very commonly used reagent, most notably for the cleavage of silyl protecting groups, and is known not to compromise the chiral integrity of protected amino acids, peptides, and other organic compounds.[11] However, we did not specifically examine the issue of racemization in this study. In a separate study, we have attached this linker to polystyrene resin beads. This linker was used for the successful synthesis of two short peptides [Boc–Trp–Ala–Gly–Gly–OH and Boc–Asn–Ala–Ser(OBn)–Gly–Glu(OBn)–OH],[12] further demonstrating the utility of such a linker system. However, because of the potential NBS oxidation problems associated with sulfur-containing amino acids, the application of this linker for the synthesis of peptides with the first amino acid being either protected cysteine or methionine may be problematic.

Conclusion

These model studies indicate that the base-mediated trimethyl lock-facilitated cyclic ether formation with concomitant release of a carboxylic acid generally gives high yields with esters of acids bearing different structural features. This makes it possible to use this trimethyl lock-based system for the development of a stable and readily cleavable linker for solid phase synthesis.

Experimental

General Melting points were determined using an electrothermal melting point apparatus and are uncorrected. NMR spectra were obtained on a 300 MHz Varian instrument. Chemical shifts are reported in parts per million (ppm) relative to Me_4Si as an internal standard. Unless stated otherwise commercial reagents were used without purification. Radial preparative layer chromatography (RPLC) was carried out on a Chromatotron (Harrison Research Co., Palo Alto, CA). Silica gel (200—400 mesh) was used for column chromatography. Solvent mixtures used for chromatography are expressed as v/v. Methylene chloride was distilled from CaH_2 under nitrogen. THF was distilled from sodium/benzophenone under nitrogen. TBAF–THF solution (1 M) was purchased from Aldrich Chemical Co. Sodium hydrosulfite (tech, *ca.* 85%) was used for the reduction reaction. All deprotection reactions were conducted in flame-dried glassware under a nitrogen atmosphere. HPLC analyses of the deprotection reaction were carried out using a Shimadzu HPLC system consisting of a SCL-10A system controller, two LC-10AS pumps, a SPD-10AV UV-VIS detector, and a SIL-10A auto injector (detection wavelength: 210 nm and 208 nm). The column was a C_{18} reversed phase analytical column from YMC (length=15 cm, i.d.=4.6 cm, particle size=5 mm). The solvent system was a gradient of 0.1% trifluoroacetic acid in acetonitrile and water. Abbreviations: Boc, *tert*-butoxycarbonyl; Bn, benzyl; Cbz, carbobenzyloxy.

6-Benzyloxy-4,4,5,7-tetramethylhydrocoumarin (6) The lactone **5**

(13.17 g, 59.9 mmol), benzyl chloride (15.16 g, 120 mmol), K_2CO_3 (16.52 g, 120 mmol), NaI (0.5 g, 13 mmol)) and 120 ml of acetone (dried on molecular sieves, 4Å) were mixed in a flask. The reaction mixture was refluxed for 20 h. Acetone was evaporated and the residue was mixed with 100 ml of water. This was extracted with methylene chloride (2×100 ml). The combined CH_2Cl_2 layers were washed with 100 ml of water and dried over $MgSO_4$. Solvent removal afforded a residue. Then 50 ml of hexanes was added to give a white precipitate (18.17 g, 98%): mp 95.5—96.5 °C; ^{1}H-NMR ($CDCl_3$) δ 7.50—7.40 (m, 5H), 6.78 (s, 1H), 4.75 (s, 2H), 2.58 (s, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 1.45 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 168.15, 152.71, 147.31, 137.21, 130.83, 129.60, 128.46, 128.01, 127.99, 117.36, 74.39, 45.81, 35.45, 27.57, 16.24, 14.87; IR (film) 1769, 1611, 1476, 1408, 1369, 1249, 1186, 1121, 981, 746, 699 cm^{-1}; FAB-MS *m/z*: 310.2 (M^+). *Anal.* Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.31; H, 7.16.

3-(5′-Benzyloxy-2′-hydroxy-4′,6′-dimethylphenyl)-3-methyl-1-butanol (7) To a $LiAlH_4$ (4.16 g, 109.6 mmol) suspension in 150 ml of dry THF cooled in an ice/water bath was added dropwise a solution of **6** (17.00 g, 54.8 mmol) in 80 ml of THF with stirring. After addition, the icy bath was removed and the reaction mixture was stirred at r.t. for 7 h. The reaction mixture was then slowly added to 300 g of ice containing 50 ml of concentrated HCl with stirring. This was followed by the addition of 50 ml of hexanes to separate the THF layer. The aqueous layer was extracted with ethyl acetate (4×150 ml). The combined organic layers were washed with water (2×100 ml) and dried over $MgSO_4$. After solvent evaporation, 100 ml of hexanes was added and the mixture was stored in a freezer for crystallization. A white solid product **7** (16.69 g, 97%) was obtained: mp 106.5—107.0 °C; ^{1}H-NMR ($CDCl_3$) δ 7.48—7.26 (m, 5H), 6.39 (s, 1H), 4.70 (s, 2H), 3.64 (t, J=6.8 Hz, 2H), 2.44 (s, 3H), 2.20 (s, 3H), 2.20 (t, J=6.8 Hz, 2H), 1.58 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 151.31, 150.12, 137.70, 131.57, 130.58, 129.18, 128.44, 127.84, 127.74, 117.42, 74.22, 61.45, 44.96, 39.94, 32.16, 16.27, 16.10; IR (film) 3384, 1601, 1452, 1400, 1368, 1227, 1023, 753, 696 cm^{-1}; MS *m/z* 314 (M^+). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.51; H, 8.42.

General Procedure for the Preparation of Amino Acid-diol Monoesters 8a—k, m Method A: DCC (1.0 equiv) was added to a solution of the diol **7** (1.0—2.0 eq), amino acid (1.0 equiv) and 4-(dimethylamino) pyridine (DMAP) (0.1—0.2 eq) in methylene chloride in an ice-water bath with stirring. After stirring for 10 min, the ice-water bath was withdrawn and stirring was continued overnight at r.t. The precipitates were filtered off. The filtrates were washed with 5% HCl solution, saturated $NaHCO_3$ solution, and water, and purified on a silica gel column.

Method B: EDC (2 equiv) was added to a solution of the diol **7** (1.0 eq), amino acid (2 eq) and DMAP (0.5 eq) in methylene chloride cooled in an ice-water bath with stirring. After the addition, the ice bath was removed and stirring was continued for 5 h at r.t. The reaction mixture was washed with 5% HCl solution, saturated $NaHCO_3$ solution and water, and dried over $MgSO_4$. Filtration and evaporation gave an oily residue which was purified on a silica gel column to afford the monoester **8**.

Diol-Phe Ester **8a**: To a solution of the diol **7** (1.450 g, 4.62 mmol), Boc–Phe–OH (1.224 g, 4.62 mmol) and DMAP (56 mg, 0.46 mmol) in 65 ml of CH_2Cl_2 in an ice-water bath was added DCC (952 mg, 4.62 mmol). After the addition the ice bath was removed. Stirring was continued overnight at r.t. The precipitates were filtered off. The filtrates were washed with 5% HCl solution (3×30 ml), saturated $NaHCO_3$ (3×30 ml) and water (3×40 ml) and dried over $MgSO_4$. Filtration and evaporation gave a residue, which was purified on a silica gel column (ethyl acetate : hexanes=1 : 5) to afford 2.57 g (99%) (**8a**) as a white foam: ^{1}H-NMR ($CDCl_3$) δ 7.50—7.05 (m, 10H), 6.40 (s, 1H), 4.69 (s, 2H), 4.38 (m, 1H), 4.20 (m, 1H), 4.00 (m, 1H), 3.04—2.90 (m, 2H), 2.44 (s, 3H), 2.20 (s, 3H), 2.15 (m, 2H), 1.55 (2s, 6H), 1.41 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 172.10, 155.62, 151.62, 150.23, 137.99, 136.33, 131.67, 130.16, 129.45, 129.25, 128.85, 128.64, 128.59, 127.96, 127.88, 127.07, 117.34, 80.30, 74.40, 64.43, 54.64, 41.39, 40.19, 38.31, 32.05, 28.47, 16.26; IR (film) 3377, 1736, 1713, 1689, 1603, 1497, 1400, 1366, 1227 1164 cm^{-1}; FAB-MS *m/z* 562 (M+H). *Anal.* Calcd for $C_{34}H_{43}NO_6$: C, 72.70; H, 7.72; N, 2.49. Found: C, 72.56; H, 7.99; N, 2.46.

Diol-Leu Ester **8b**: Diol **7** (126 mg, 0.4 mmol), Boc–Leu–OH (199 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B). A white foam product (216 mg, 100%) was obtained: ^{1}H-NMR ($CDCl_3$) δ 7.50—7.30 (m, 5H), 6.44 (s, 1H), 4.69 (s, 2H), 4.25 (m, 1H), 4.08 (m, 1H), 3.95 (m, 1H), 2.59 (m, 2H), 2.45 (s, 3H), 2.20 (s, 3H), 2.07 (m, 2H), 1.58, 1.53 (2s, 6H), 1.46 (s, 9H), 1.42 (m, 1H), 0.88 (d, J=6.6 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 173.80, 156.09, 151.89, 150.03, 137.99, 131.52, 130.22, 129.11, 128.59, 127.90, 117.31, 80.32, 74.39, 64.29, 52.26, 41.62, 41.44, 40.25, 32.23, 31.76, 28.51, 24.91, 22.99, 21.87, 16.30, 16.21; IR (film) 3365, 1713, 1686, 1604, 1400, 1367, 1228, 1163, 733, 697 cm^{-1}; FAB-MS *m/z* 528 (M+H). *Anal.* Calcd for $C_{31}H_{45}NO_6$: C, 70.56; H, 8.59; N, 2.65. Found: C, 70.52; H, 8.54; N 2.66.

Diol-Gly Ester **8c**: Diol **7** (126 mg, 0.4 mmol), Boc–Gly–OH (140 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B) to give a white foam (186 mg, 99%): ^{1}H-NMR ($CDCl_3$) δ 7.51—7.26 (m, 5H), 6.40 (s, 1H), 4.69 (s, 2H), 4.12 (t, J=6.9 Hz, 2H), 3.70 (d, J=5.7 Hz, 2H), 2.44 (s, 3H), 2.33 (t, J=6.9 Hz, 2H), 2.20 (s, 3H), 1.56 (s, 6H), 1.45 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 170.52, 156.29, 151.46, 150.43, 138.05, 131.85, 130.32, 129.41, 128.67, 128.04, 127.95, 117.39, 80.48, 74.46, 64.33, 42.60, 41.41, 40.27, 32.07, 29.92, 28.57, 16.29; FAB-MS *m/z* 472 (M+H). *Anal.* Calcd for $C_{27}H_{37}NO_6$: C, 68.77; H, 7.91; N, 2.97. Found: C, 68.63; H, 7.90; N, 2.99.

Diol-Ala Ester **8d**: Diol **7** (126 mg, 0.4 mmol), Boc–Ala–OH (151 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B). The reaction afforded a white foam (182 mg, 94%): ^{1}H-NMR ($CDCl_3$) δ 7.47—7.32 (m, 5H), 6.41 (s, 1H), 4.68 (s, 2H), 4.14 (t, J=7.2 Hz, 2H), 4.05 (m, 1H), 2.44 (s, 3H), 2.21 (m, 2H), 2.18 (s, 3H), 1.57, 1.55 (2s, 6H), 1.45 (s, 9H), 1.27 (d, J=6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.59, 155.62, 151.71, 150.10, 137.96, 131.59, 130.09, 129.22, 128.59, 127.93, 117.29, 80.29, 74.43, 64.51, 49.45, 41.36, 40.23, 32.03, 31.88, 28.52, 18.61, 16.27, 16.22; IR (film) 3377, 1736, 1713, 1689 1604, 1499, 1452, 1400, 1367, 1227, 1184 cm^{-1}; FAB-MS *m/z* 485 (M^+). *Anal.* Calcd for $C_{28}H_{39}NO_6$: C, 69.26; H, 8.09; N, 2.88. Found: C, 68.92; H, 8.11; N, 3.14.

Diol-Trp Ester **8e**: Diol **7** (126 mg, 0.4 mmol), Boc–Trp(For)–OH (266 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B). The reaction afforded a white foam (234 mg, 93%): ^{1}H-NMR ($CDCl_3$) δ 9.38, 9.00 (2s, 1H), 8.39—7.26 (m, 10H), 6.47, 6.38 (2s, 1H), 5.10 (m, 1H), 4.68 (s, 2H), 4.59 (m, 1H), 4.09 (m, 1H), 3.16 (m, 2H), 2.41 (s, 3H), 2.26 (m, 2H), 2.19 (s, 3H), 1.60, 1.53 (2s, 6H), 1.45 (s, 9H); FAB-MS *m/z* 628 (M^+). *Anal.* Calcd for $C_{37}H_{44}N_2O_7$: C, 70.67; H, 7.05; N, 4.46. Found: C, 70.51; H, 7.22; N, 4.43.

Diol-Asp Ester **8f**: Diol **7** (126 mg, 0.4 mmol), Boc–Asp(OBn)–OH (258 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the procedure (Method B). The reaction afforded a white foam (247 mg, 100%): ^{1}H-NMR ($CDCl_3$) δ 7.50—7.30 (m, 10H), 6.37 (s, 1H), 5.10 (s, 2H), 4.69 (s, 2H), 4.41 (m, 1H), 4.13 (m, 2H), 2.79 (m, 2H), 2.42 (s, 3H), 2.19 (s, 3H), 2.15 (m, 2H), 1.55, 1.54 (2s, 6H), 1.44 (s, 9H); FAB-MS *m/z* 620 (M+H). *Anal.* Calcd for $C_{36}H_{45}NO_8$: C, 69.76; H, 7.32; N, 2.26. Found: C, 69.70; H, 7.53; N, 2.54.

Diol-Cys Ester **8g**: Diol **7** (94 mg, 0.3 mmol), *S*-Bn–Boc–Cys–OH (93 mg, 0.3 mmol), DCC (62 mg, 0.3 mmol) and DMAP (7 mg, 0.06 mmol) were treated according to the general procedure (Method A). The reaction afforded **8g** (169 mg, 93%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.46—7.23 (m, 10H), 6.38 (s, 1H), 4.67 (s, 2H), 4.22 (m, 2H), 4.02 (m, 1H), 3.65 (s, 2H), 2.74 (m, 2H), 2.49 (m, 2H), 2.44 (s, 3H), 2.19 (s, 3H), 1.58, 1.54 (2s, 6H), 1.46 (s, 9H); FAB-MS *m/z* 608 (M+H). *Anal.* Calcd for $C_{35}H_{45}NO_6S$: C, 69.16; H, 7.46; N, 2.30. Found: C, 69.26; H, 7.56; N, 2.49.

Diol-Ser Ester **8h**: Diol **7** (94 mg, 0.3 mmol), *O*-Bn–Boc–Ser–OH (89 mg, 0.3 mmol), DCC (62 mg, 0.3 mmol) and DMAP (7 mg, 0.06 mmol) were treated according to the general procedure (Method A). The reaction afforded a white foam **8h** (166 mg, 94%): ^{1}H-NMR ($CDCl_3$) δ 7.44—7.30 (m, 10H), 6.34 (s, 1H), 4.68 (s, 2H), 4.49 (m, 2H), 4.24 (m, 2H), 4.01 (m, 1H), 3.73 (m, 2H), 2.55 (m, 2H), 2.43 (s, 3H), 2.18 (s, 3H), 1.56, 1.54 (2s, 6H), 1.46 (s, 9H); FAB-MS *m/z* 591 (M^+). *Anal.* Calcd for $C_{35}H_{45}NO_7$: C, 71.05; H, 7.67; N, 2.37. Found: C, 71.14; H, 7.78; N, 2.34.

Diol-Lys Ester **8i**: Diol **7** (94 mg, 0.3 mmol), Boc–ε-Cbz–Lys–OH (114 mg, 0.3 mmol), DCC (62 mg, 0.3 mmol) and DMAP (7 mg, 0.06 mmol) were treated according to the general procedure (Method A). The reaction afforded a white foam **8i** (173 mg, 85%): ^{1}H-NMR ($CDCl_3$) δ 7.47—7.26 (m, 10H), 6.46 (s, 1H), 5.12 (s, 2H), 4.69 (s, 2H), 4.16—4.03 (m, 3H), 3.17 (m, 2H), 2.56 (m, 2H), 2.43 (s, 3H), 2.19 (s, 3H), 1.62 (m, 4H), 1.57 (d, J=6.1 Hz, 6H), 1.43 (s, 9H), 1.26 (m, 2H); FAB-MS *m/z* 677 (M+H). *Anal.* Calcd for $C_{39}H_{52}N_2O_8$: C, 69.21; H, 7.74; N, 4.14. Found: C, 69.08; H, 8.00; N, 4.41.

Diol-Propionic Ester **8j**: DCC (104 mg, 0.5 mmol), propionic acid (37.3 ml, 0.5 mmol), diol **7** (314 mg, 1.0 mmol) and DMAP (6 mg, 0.05 mmol) in 12 ml methylene chloride were stirred for 72 h at r.t. The mixture was treated according to the general procedure (Method A) to give **8j** (133 mg, 72%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.44 (m, 5H), 6.34 (s, 1H), 4.68 (s, 2H), 4.01 (t, J=7.2 Hz, 2H), 2.44 (s, 3H), 2.29 (t, J=7.2 Hz, 2H), 2.24 (q, J=7.2 Hz, 2H), 2.20 (s, 3H), 1.58 (s, 6H), 1.08 (t, J=7.2 Hz, 3H); FAB-MS *m/z*

370 (M^+). *Anal.* Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.39; H, 7.98.

Diol-Isobutyric Ester **8k**: DCC (206 mg, 1.0 mmol), diol **7** (314 mg, 1.0 mmol), isobutyric acid (44 mg, 0.5 mmol) and DMAP (6 mg, 0.05 mmol) in 20 ml of CH_2Cl_2 were treated according to the general procedure (Method A) to afford **8k** (170 mg, 89%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.35 (m, 5H), 6.30 (s, 1H), 4.64 (s, 2H), 3.97 (t, J=7.2 Hz, 2H), 2.43 (m, 1H), 2.40 (s, 3H), 2.25 (t, J=7.2 Hz, 2H), 2.12 (s, 3H), 1.56 (s, 6H), 1.11 (d, J=7.2 Hz, 6H); FAB-MS *m/z*: 384 (M^+). *Anal.* Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.84; H, 8.41.

Diol-Trimethylacetic Ester **8l**: To a solution of the diol **7** (235 mg, 0.75 mmol), trimethylacetic acid (44 mg, 0.43 mmol) and TEA (76 mg, 0.75 mmol) in 10 ml of methylene chloride was added Bop–Cl (191 mg, 0.75 mmol). The reaction mixture was stirred for 24 h at r.t. Methylene chloride was evaporated. The residue was separated on a silica gel column (ethyl acetate : hexanes=1 : 4) to give **8l** (114 mg, 67%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.40 (m, 5H), 6.37 (s, 1H), 4.69 (s, 2H), 4.00 (t, J=7.2 Hz, 2H), 2.45 (s, 3H), 2.28 (t, J=7.2 Hz, 2H), 2.20 (s, 3H), 1.59 (s, 6H), 1.15 (s, 9H); FAB-MS *m/z* 398 (M^+). *Anal.* Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.04; H, 8.40.

Diol-Phenylacetic Ester **8m**: The diol **7** (314 mg, 1.0 mmol), phenylacetic acid (68 mg, 0.5 mmol), DCC (104 mg, 0.5 mmol) and DMAP (6 mg, 0.05 mmol) in 15 ml of methylene chloride were treated according to the general procedure (Method A) to give **8m** (172 mg, 80%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.46—7.17 (m, 10H), 6.27 (s, 1H), 4.63 (s, 2H), 4.00 (t, J=7.2 Hz, 2H), 3.48 (s, 2H), 2.37 (s, 3H), 2.25 (t, J=7.2 Hz, 2H), 2.13 (s, 3H), 1.51 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 172.04, 151.04, 150.61, 138.00, 131.99, 130.31, 129.49, 128.67, 128.04, 127.94, 127.20, 117.45, 74.46, 64.00, 41.69, 41.39, 40.28, 31.96, 16.29; FAB-MS *m/z* 432 (M^+). *Anal.* Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.51; H, 7.63.

Diol-Naphthoic Ester **8n**: Oxalyl chloride (191 mg, 1.5 mmol) was added to a solution of 2-naphthoic acid (86 mg, 0.5 mmol), and DMF (1 drop) in 20 ml of benzene at 45 °C. The mixture was stirred for 1 h and evaporated to dryness. The residue was then dissolved in 10 ml of methylene chloride. This mixture was added to a solution of the diol **7** (314 mg, 1.0 mmol) and triethylamine (TEA) (101 mg, 1.0 mmol) in 25 ml of methylene chloride. The mixture was stirred at r.t. for 72 h. After solvent evaporation, the product was purified on a silica gel column (ethyl acetate : hexanes=1 : 9, v/v) to give 170 mg (73%) of white solid product: ^{1}H-NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.96—7.79 (m, 4H), 7.60—7.47 (m, 2H), 7.42—7.30 (m, 5H), 6.35 (s, 1H), 4.57 (s, 2H), 4.37 (t, J=7.2 Hz, 2H), 2.51 (t, J=7.2 Hz, 2H), 2.47 (s, 3H), 2.11 (s, 3H), 1.66 (s, 6H); FAB-MS *m/z* 468.3 (M^+). *Anal.* Calcd for $C_{31}H_{32}O_4$: C, 79.46; H, 6.88. Found: C, 78.93; H, 7.02.

Diol-Methoxy-α-methylnaphthaleneacetic Ester **8o**: (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid (115 mg, 0.5 mmol), DMF (1 drop), benzene (20 ml), oxalyl chloride (190 mg, 131 ml, 1.5 mmol), the diol **7** (314 mg, 1.0 mmol), and TEA (101 mg, 139 ml, 1.0 mmol) were treated according to the method used for the product **8n** to afforded 240 mg (91%) of **8o** as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.68—7.08 (m, 11H), 6.27 (s, 1H), 4.63 (s, 2H), 4.01 (m, 2H), 3.89 (s, 3H), 3.75 (q, J=7.2, 1H), 2.35 (s, 3H), 2.23 (m, 2H), 2.15 (s, 3H), 1.52 (d, J=7.2 Hz, 3H), 1.50 (s, 6H); FAB-MS *m/z* 526 (M^+). *Anal.* Calcd for $C_{34}H_{38}O_5$: C, 77.54; H, 7.27. Found: C, 77.37; H, 7.37.

General Procedure for the Preparation of Quinone-Esters 1a—o

Monoester **8** (1 equiv) was dissolved in a mixture of acetone and water (5 : 1, v/v). Then solid NBS (0.98 equiv) was added in one portion. The reaction mixture was stirred for 15 min. After the acetone was evaporated, the aqueous phase was extracted with ether. The product was purified on a silica gel column (hexanes : ethyl acetate=3 : 1).

Quinone-Phe Ester **1a**: Diol-ester **8a** (2.425g, 4.37 mmol) and NBS (584 mg, 4.32 mmol) were treated according to the general procedure to give **1a** (2.03 g, 99%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.22 (m, 5H), 6.45 (m, 1H), 4.52 (m, 1H), 4.05 (m, 2H), 2.97 (m, 2H), 2.16 (s, 3H), 2.15 (m, 2H), 2.00 (s, 3H), 1.40 (s, 9H), 1.39 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.41, 188.28, 172.01, 155.14, 150.84, 144.06, 142.04, 136.20, 135.15, 129.77, 129.47, 128.70, 127.18, 80.05, 63.11, 54.67, 41.00, 39.43, 38.58, 30.39, 28.48, 15.57, 14.78; IR (film) 1731, 1717, 1648, 1497, 1365, 1168, 700 cm^{-1}; FAB-MS *m/z* 469 (M^+). *Anal.* Calcd for $C_{27}H_{35}NO_6$: C, 69.06; H, 7.51; N, 2.98. Found: C, 68.97; H, 7.52; N, 2.95.

Quinone-Leu Ester **1b**: Diol-ester **8b** (170 mg, 0.312 mmol) and NBS (55 mg, 0.312 mmol) were treated according to the general procedure to give **1a** (137 mg, 97%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.48 (q, J=1.35 Hz, 1H), 4.21 (m, 1H), 4.08 (m, 2H), 2.22 (m, 2H), 2.20 (s, 3H), 2.00 (d, J=1.35 Hz, 3H), 1.71 (m, 3H), 1.43 (s, 15), 0.93 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.44, 188.33, 173.63, 155.48, 150.82, 144.06, 142.05, 135.15, 79.92, 63.01, 52.27, 41.94, 41.03, 39.52, 30.48, 28.50, 24.92, 23.04, 22.02, 15.62, 14.78; IR (film) 1742, 1716, 1649, 1507, 1366, 1163 cm^{-1}; FAB-MS *m/z* 435 (M^+). *Anal.* Calcd for $C_{24}H_{37}NO_6$: C, 66.18; H, 8.56; N, 3.21. Found: C, 66.37; H, 8.73; N, 3.29.

Quinone-Gly Ester **1c**: Diol-ester **8c** (135 mg, 0.288 mmol) was treated with NBS (51 mg, 0.288 mmol) according to the general procedure to give **1b** (107 mg, 99%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.48 (q, J=1.8 Hz, 1H), 4.10 (t, J=7.2 Hz, 2H), 3.82 (d, J=5.4 Hz, 2H), 2.21 (t, J=7.2 Hz, 2H), 2.19 (s, 3H), 2.01 (d, J=1.8 Hz, 3H), 1.44 (s, 9H), 1.43 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.41, 188.27, 170.35, 155.74, 150.85, 144.02, 141.94, 135.13, 80.11, 63.12, 42.63, 41.07, 39.48, 30.42, 28.47, 15.53, 14.72; IR (film) 1742, 1717, 1649, 1513, 1366, 1166 cm^{-1}; FAB-MS *m/z* 379 (M^+). *Anal.* Calcd for $C_{20}H_{29}NO_6$: C, 63.31; H, 7.70; N, 3.69. Found: C, 63.18; H, 7.79; N, 3.58.

Quinone-Ala Ester **1d**: Diol-ester **8d** (124 mg, 0.256 mmol) was treated with NBS (45 mg, 0.256 mmol) according to the general procedure to give **1d** (98 mg, 97%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.48 (m, 1H), 4.23 (m, 1H), 4.09 (m, 2H), 2.21 (m, 2H), 2.20 (s, 3H), 2.00 (d, J=1.2 Hz, 3H), 1.44 (s, 9H), 1.43 (s, 6H), 1.33 (d, J=7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 189.48, 188.36, 173.47, 155.17, 150.93, 144.10, 142.07, 135.19, 80.05, 63.22, 49.47, 41.10, 39.58, 30.50, 28.55, 18.83, 15.60, 14.81; IR (film) 1736, 1715, 1648, 1508, 1453, 1366, 1244, 1166 cm^{-1}; FAB-MS *m/z* 393 (M^+). *Anal.* Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.24; H, 7.93; N, 3.61.

Quinone-Trp Ester **1e**: Diol-ester **8e** (159 mg, 0.253 mmol) was treated with NBS (45 mg, 0.253 mmol) according to the general procedure to give **1e** (123 mg, 91%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 9.40, 9.11 (2s, 1H), 8.04—7.19 (m, 5H), 6.45 (s, 1H), 4.60 (m, 1H), 4.03 (m, 2H), 3.24—3.12 (m, 2H), 2.30 (m, 2H), 2.20 (s, 3H), 1.98 (s, 3H), 1.43 (s, 6H), 1.37 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 189.48, 188.28, 171.84, 159.38, 155.21, 150.73, 144.18, 142.15, 135.16, 131.61, 125.65, 124.75, 123.40, 120.35, 119.33, 116.42, 109.91, 80.39, 63.44, 53.77, 41.02, 39.43, 30.39, 28.52, 28.31, 15.59, 14.81; IR (film) 1736, 1712, 1648, 1458, 1366, 1167, 793, 749 cm^{-1}; FAB-MS *m/z* 537 (M+H). *Anal.* Calcd for $C_{30}H_{36}N_2O_7$: C, 67.15; H, 6.75; N, 5.22. Found: C, 67.12; H, 6.82; N, 5.10.

Quinone-Asp Ester **1f**: Diol-ester **8f** (47 mg, 0.076 mmol) was treated with NBS (14 mg, 0.076 mmol) according to the general procedure to give **1f** (35 mg, 98%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.35 (m, 5H), 6.47 (d, J=1.3 Hz, 1H), 5.12 (s, 2H), 4.49 (m, 1H), 4.06 (m, J=7.0 Hz, 2H), 2.87 (m, 2H), 2.18 (s, 3H), 2.15 (m, 2H), 1.99 (d, J=1.2 Hz, 3H), 1.44 (s, 9H), 1.40 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.23, 188.13, 170.93, 170.62, 155.25, 150.58, 143.89, 141.98, 135.47, 134.97, 128.60, 128.39, 128.27, 80.14, 66.78, 63.47, 50.11, 40.73, 39.36, 36.86, 30.25, 28.32, 15.39, 14.60; IR (film) 1734, 1719, 1648, 1498, 1366, 1166, cm^{-1}; MS *m/z* 527 (M^+). *Anal.* Calcd for $C_{29}H_{37}NO_8$: C, 66.02; H, 7.07; N, 2.66. Found: C, 65.97; H, 7.17; N, 2.58.

Quinone-Cys Ester **1g**: Diol-ester **8g** (119 mg, 0.196 mmol) was treated with NBS (35 mg, 0.196 mmol) according to the general procedure to give **1g** (60 mg, 73%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.30 (m, 5H), 6.46 (s, 1H), 4.43 (m, 1H), 4.10 (m, 2H), 3.70 (s, 2H), 2.81 (m, 2H), 2.23 (m, 2H), 2.19 (s, 3H), 1.99 (s, 3H), 1.45 (s, 9H), 1.42 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.47, 188.35, 171.26, 155.64, 150.83, 144.16, 142.20, 137.94, 135.20, 129.17, 128.83, 127.47, 80.01, 63.60, 53.53, 41.08, 39.59, 37.03, 33.98, 30.50, 28.58, 15.63, 14.87; IR (film) 1742, 1714, 1649, 1495, 1167, 702 cm^{-1}; FAB-MS *m/z* 515 (M^+). *Anal.* Calcd for $C_{28}H_{37}NO_6S$: C, 65.22; H, 7.23; N, 2.72. Found: C, 65.28; H, 7.35; N, 2.98.

Quinone-Ser Ester **1h**: Diol-ester **8h** (118 mg, 0.200 mmol) was treated with NBS (36 mg, 0.2 mmol) according to the general procedure to give **1h** (95 mg, 95%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.30 (m, 5H), 6.46 (s, 1H), 4.50 (m, 2H), 4.35 (m, 1H), 4.09 (m, 2H), 3.79—3.63 (m, 2H), 2.19 (m, 2H), 2.17 (s, 3H), 1.99 (s, 3H), 1.44 (s, 9H), 1.41 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.47, 188.36, 170.84, 155.64, 150.93, 144.09, 142.15, 137.81, 135.21, 128.65, 128.04, 127.82, 80.19, 73.54, 70.26, 63.41, 54.33, 41.08, 39.58, 30.44, 28.57, 15.61, 14.81; IR (film) 1742, 1714, 1649, 1164 cm^{-1}; FAB-MS *m/z* 500 (M+H). *Anal.* Calcd for $C_{28}H_{37}NO_7$: C, 67.32; H, 7.46; N, 2.80. Found C, 67.26; H, 7.52; N, 2,91.

Quinone-Lys Ester **1i**: Diol-ester **8i** (68 mg, 0.1 mmol) was treated with NBS (18 mg, 0.1 mmol) according to the general procedure to give **1i** (60 mg, 99%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 5H), 6.48 (d, J=1.4 Hz, 1H), 5.09 (s, 2H), 4.18 (m, 1H), 4.08 (m, 2H), 3.19 (m, 2H), 2.22 (m, 2H), 2.19 (s, 3H), 1.99 (s, 3H), 1.50 (m, 6H), 1.42 (s, 15H); ^{13}C-NMR ($CDCl_3$) δ 189.54, 188.37, 172.87, 156.70, 150.88, 144.14, 142.14, 136.90, 135.22, 128.73, 128.29, 80.15, 66.87, 63.21, 53.48, 41.14, 39.57, 32.62,

30.48, 29.92, 29.66, 28.55, 22.64, 15.61, 14.95; IR (film) 1736, 1713, 1649, 1522, 1455, 1366, 1247, 1169 cm^{-1}; MS *m/z* 585 (M+H). *Anal.* Calcd for $C_{32}H_{44}N_2O_8$: C, 65.73; H, 7.59; N, 4.79. Found: C, 65.85; H, 7.58; N, 4.82.

Quinone-Propionic Ester **1j**: Diol-ester **8j** (133 mg, 0.36 mmol) and NBS (64 mg, 0.36 mmol) were treated according to the general procedure to give **1j** (99 mg, 99%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.47 (s, 1H), 4.02 (t, J=7.2 Hz, 2H), 2.26—2.16 (m, 7H), 2.00 (s, 3H), 1.43 (s, 6H), 1.08 (t, J=7.5 Hz, 3H); FAB-MS *m/z* 278 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.05; H, 7.97. Found: C, 69.18; H, 8.03.

Quinone-Isobutyric Ester **1k**: Diol-ester **8k** (166 mg, 0.43 mmol) and NBS (77 mg, 0.43 mmol) were treated according to the general procedure to give **1k** (120 mg, 95%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.48 (q, J=1.5 Hz, 1H), 4.02 (t, J=7.2 Hz, 2H), 2.43 (m, J=6.9 Hz, 1H), 2.20 (s, 3H), 2.19 (t, J=7.2 Hz, 2H), 2.00 (d, J=1.5 Hz, 3H), 1.43 (s, 6H), 1.10 (d, J=6.9 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.53, 188.48, 177.25, 151.30, 143.94, 141.91, 135.29, 62.21, 41.29, 39.69, 34.21, 30.56, 19.13, 15.60, 14.78; IR (film) 1733, 1648, 1576, 1470, 1239, 1190, 1156 cm^{-1}; FAB-MS *m/z* 292 (M^+). *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.90; H, 8.40.

Quinone-Trimethylacetic Ester **1l**: Diol-ester **8l** (60 mg, 0.151 mmol) and NBS (26 mg, 0.148 mmol) were treated according to the general procedure to give **1l** (44 mg, 96%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.50 (q, J=1.5 Hz, 1H), 4.01 (t, J=7.2 Hz, 2H), 2.20 (s, 3H), 2.19 (t, J=7.2 Hz, 2H), 2.00 (d, J=1.5 Hz, 3H), 1.43 (s, 6H), 1.14 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 189.55, 188.49, 178.76, 151.24, 143.98, 142.08, 135.31, 62.37, 41.19, 39.75, 38.84, 30.61, 27.39, 15.61, 14.82; IR (film) 1726, 1649, 1576, 1480, 1283, 1238, 1155 cm^{-1}; FAB-MS *m/z* 306 (M^+). *Anal.* Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.77; H, 8.43.

Quinone-Phenylacetic Ester **1m**: Diol-ester **8m** (93 mg, 0.215 mmol) and NBS (38 mg, 0.210 mmol) were treated according to the general procedure to give **1m** (70 mg, 96%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.31—7.20 (m, 5H), 6.46 (q, J=1.5 Hz, 1H), 4.04 (t, J=7.2 Hz, 2H), 3.53 (s, 2H), 2.18 (t, J=7.2 Hz, 2H), 2.15 (s, 3H), 1.99 (d, J=1.5 Hz, 3H), 1.39 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.41, 188.28, 171.64, 151.14, 143.94, 141.94, 135.25, 134.10, 129.38, 128.89, 128.78, 127.30, 62.83, 41.61, 41.14, 39.65, 30.50, 15.60, 14.74; IR (film) 1735, 1648, 1454, 1239, 1151 cm^{-1}; FAB-MS *m/z* 340 (M^+). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.97; H, 6.98.

Quinone-Naphthoic Ester **1n**: Diol-ester **8n** (115 mg, 0.245 mmol) and NBS 43 mg, 0.241 mmol) were treated according to the general procedure to give **1n** (90 mg, 98%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 8.49 (s, 1H), 7.96—7.82 (m, 4H), 7.62—7.52 (m, 2H), 6.35 (q, J=1.5 Hz, 1H), 4.41 (t, J=6.9 Hz, 2H), 2.41 (t, J=6.9 Hz, 2H), 2.22 (s, 3H), 1.73 (d, J=1.5 Hz, 3H), 1.51 (s, 6H); IR (film) 1715, 1647, 1283, 1227, 1195, 779, 762 cm^{-1}; FAB-MS *m/z* 376 (M^+). *Anal.* Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.60.

Quinone-(+)-methoxy-α-methylnaphthaleneacetic Ester **1o**: Diol-ester **8o** (254 mg, 0.480 mmol) and NBS (86 mg, 0.480 mmol) were treated according to the general procedure to give **1o** (208 mg, 99%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.70—7.05 (m, 6H), 6.39 (m, 1H), 4.00 (m, 2H), 3.91 (s, 3H), 3.72 (m, 1H), 2.13 (t, J=6.9 Hz, 2H), 2.05 (d, J=2.1 Hz, 3H), 1.95 (s, 3H), 1.52, 1.50 (d, J=6.9 Hz, 3H), 1.33 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.48, 188.37, 174.78, 157.91, 151.12, 143.87, 141.96, 135.80, 135.21, 133.94, 129.47, 129.18, 127.37, 126.36, 126.10, 119.19, 105.91, 62.77, 55.53, 45.71, 41.06, 39.65, 30.47, 18.76, 15.58, 14.69; IR (film) 1730, 1647, 1606, 1264, 1172 cm^{-1}; FAB-MS *m/z* 434 (M^+). *Anal.* Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.64; H, 6.94.

Reduction of Quinones 1a—o A solution of quinone **1a—o** in ethyl ether was shaken with 20 eq of aqueous sodium hydrosulfite solution at r.t. in a separatory funnel until the color of the reaction mixture changed from yellow to colorless. The ether layer was separated and the aqueous phase was extracted with ether. The combined ether layers were washed with saturated NaCl and then dried over $MgSO_4$. Solvent evaporation afforded the hydroquinone **2a—o**.

Release of the Carboxylic Acid a—i and o To a 7—8 mM solution of the hydroquinone **2a—i, o** (0.04—0.19 mmol) in THF was added dropwise TBAF (1.0 M in THF) (0.16—0.77 mmol) by a syringe with stirring under nitrogen at 0 °C. Five minutes after the addition, the ice-bath was removed and stirring was continued at r.t. The color of the mixture changed from colorless to yellow then to orange then to green, and finally to blue. After the disappearance of the starting material by TLC analysis (hexanes/ethyl acetate= 3/1, v/v), the mixture was diluted with acetonitrile and water (1/3) to 25.00 ml, from which 2.00 ml of solution was taken and diluted to 100.00 ml. This diluted solution was analyzed by HPLC.

Release of the carboxylic acids **j—n** were carried out following similar procedures with 18 mM solutions of hydroquinone **2j—n** (0.07—0.12 mmol) and 8-fold TBAF at r.t.

***N*-Boc-indole-formyl-tryptophan** A solution of quinone-trp ester **1e** (100 mg, 0.186 mmol) in 40 ml of ether was shaken with a solution of sodium hydrosulfite (2 g, 9.77 mmol) in 10 ml of water until the color of the reaction mixture changed from yellow to colorless. The organic layer was separated and the aqueous layer was extracted with ether (2×40 ml). The combined organic layers were washed with brine (2×10 ml) and dried over $MgSO_4$ for 3 h. Solvent evaporation afforded 99 mg of the hydroquinone monoester **2e**.

The hydroquinone **2e** was dissolved in freshly distilled THF (25 ml) which was chilled and stirred in an ice/water bath under a nitrogen atmosphere. To this solution 740 μl (0.74 mmol) of 1.0 M TBAF solution in THF was added dropwise. Five minutes after addition, the ice bath was withdrawn and stirring was continued for an additional 1.5 h at r.t. HPLC analysis of the reaction mixture showed 100% conversion to the cyclic ether and *N*-Boc-indole-formyl-tryptophan.

The reaction mixture was then concentrated and separated by RPLC (silica gel), gradient elution with methylene chloride/methanol (15/1 to 7/1), to give 28 mg (74%) of cyclic ether **3** and 49 mg (80%) of Boc-indole-formyl-tryptophan which was identified by ^{1}H-NMR.

6-Methoxy-α-methyl-2-naphthaleneacetic Acid A solution of compound **1o** (100 mg, 0.23 mmol) in 40 ml of ether was mixed with a solution of sodium hydrosulfite (2 g, 9.77 mmol) in 10 ml of water. The resulting mixture was shaken in a separatory funnel until the color of the reaction mixture changed from yellow to colorless. The organic layer was separated and the aqueous phase was extracted with ether (2×5 ml). The organic fraction was washed with brine (2×10 ml) and dried over $MgSO_4$ for 3 h. Solvent evaporation afforded the hydroquinone **2o** (97 mg).

To a solution of the hydroquinone **2o** (97 mg, 0.223 mmol) in freshly distilled THF (25 ml) cooled with an ice bath was slowly added dropwise TBAF (1.0 M in THF) (670 μl, 0.67 mmol) by a syringe with stirring under N_2. Five minutes after addition, the ice bath was removed and stirring was continued for an additional 2 h at r.t. The reaction solution was concentrated under reduced pressure to give the residue, to which 5 ml of 1 N NaOH was added. The aqueous solution was washed with ethyl ether (3×10 ml) and the combined organic layers were dried over $MgSO_4$. The residue after solvent removal was purified by column chromatography (hexanes : ethyl acetate= 3 : 1) to give cyclic ether **3** (38 mg) in 83% yield. The aqueous phase was acidified with 1 N HCl solution (10 ml) and a white precipitate was formed. The precipitate was extracted with ethyl ether (4×20 ml) and the combined organic extracts were dried over $MgSO_4$. Filtration and solvent evaporation gave a pale yellow solid (48 mg, 93%) which was identical to (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid according to ^{1}H-NMR.

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References and Notes

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