Development of a Novel Redox-Sensitive Protecting Group for Amines Which Utilizes a Facilitated Lactonization Reaction†

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Selective protection and deprotection of functional groups are essential components of modern organic and peptide synthesis. To cope with the demand for the synthesis of organic molecules and peptides with increasing complexity, there has been a need to develop novel protecting groups which are readily cleavable under fundamentally different conditions to ensure selective modifications of specified functional groups. This report is focused on the development of a redox-sensitive amine protecting group using a substituted quinone propionic acid (**1a**). The key feature of this protecting group is that upon reduction of the quinone **1** to the hydroquinone **2**, it undergoes a spontaneous lactonization to release the functional group attached to the carboxyl group (HXR). High yields were achieved for both the protection and deprotection reactions, and the reduction conditions required for the deprotection are very mild ($Na_2S_2O_4$ or electrochemically) and thus very compatible with most functional groups encountered in organic molecules and peptides.

Introduction

Selective protection and deprotection of functional groups are essential components of modern organic and peptide synthesis. Significant progress has been made in the development of suitable protecting groups for a great number of functional groups. Although a variety of protecting groups are available for the protection of amines, the most commonly used ones require similar acid/base conditions for their cleavage. Some of the amino protecting groups which do not require acid/base conditions for cleavage, however, are cleaved under relatively harsh conditions, such as in the case for the removal of toluenesulfonyl and phthalimide protection of amines.[1-3] To cope with the demand for the synthesis of organic molecules and peptides with increasing complexity, there has been a need to develop novel protecting groups which are readily cleavable under fundamentally different conditions to ensure selective modifications of specified functional groups. This report is focused on the development of a redox-sensitive amine protecting group using a substituted quinone propionic acid.

Substituted quinone propionic acid derivatives of **1a**, upon reduction, undergo a facile spontaneous intramolecular cyclization to release the moieties (XR) attached to the carboxyl functional group (Scheme 1).[4-8] The facile cyclization reaction is the result of the "trimethyl lock system" (as shown in Scheme 1), which was shown earlier to increase the rate of the cyclization reaction by the order of 10^{5-7}.[4-8] The result of such a facilitation is that the dihydroquinone intermediate **2** only has a half-life of approximately 100 s at room temperature in aqueous solution.[9-11] Such systems have been used to develop prodrugs of amines and alcohols.[9-12] However, the facile release of amines from this system also makes it an attractive target for the development of a unique amine protecting strategy. Furthermore, the reduction can be accomplished under mild conditions ($Na_2S_2O_4$ or electrochemically),[4-12] which is compatible with most functional groups encountered in organic molecules and peptides. Therefore, using this method, an amine can be protected as an amide and readily released when needed through mild reduction.

One essential requirement for the development of a practical protecting group is that the protection and deprotection must be carried out in high yields under mild conditions. The studies focused on the search for conditions that would give high yields for both the protection (to form the amide) and deprotection (release) reactions.

Results

Synthesis of the Quinone Acid 1a. The quinone propionic acid **1a** was synthesized in three steps starting from commercially available 2,6-dimethylbenzoquinone.[5,10,12] Each step affords over 90% yield without the need for chromatographic purification of the intermediates. Furthermore, the lactone **3** generated upon reduction of **1a–c** can be converted back to the acid **1a** in one step in over 90% yield, therefore allowing the recycling of the protecting group.[10]

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Scheme 1

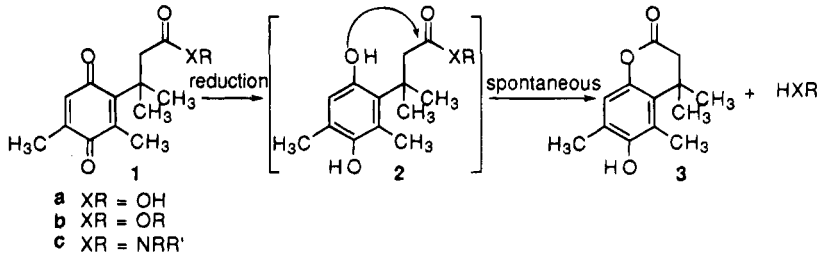
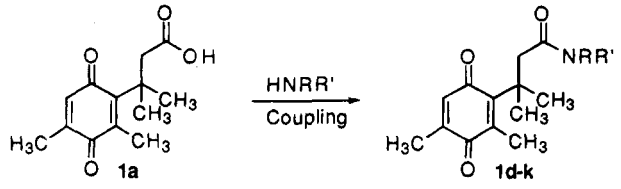


Table 1. Protection of Amines (HNRR') with Quinone Propionic Acid



	R	R'	method[a]	yield (%)	release yield[b]
1d	CH_2Ph	H	I	93	quantitative
1e	$CH_2CH_2CH_2Ph$	H	I	94	quantitative
1f	C_6H_{11}	H	I	95	quantitative
1g	CH_2Ph	CH_3	I	94	quantitative
1h	$(CH_2)_4OH$	H	I	92	quantitative
1h	$(CH_2)_4OH$	H	II	95	quantitative
1h	$(CH_2)_4OH$	H	III	92	quantitative
1i	$CH(CH_2Ph)COOEt$	H	I	97	quantitative[c]
1j	Ph	H	I	70	slow
1j	Ph	H	II	50	slow
1k	$PhOCH_3$-p	H	I	17	slow

[a] Method I: DCC/HOBt/CH_2Cl_2, 0 °C. Method II: TEA/IBCF/CH_2Cl_2(DMF)/−25 °C. Method III: BOP/TEA/CH_2Cl_2, 0 °C to rt. [b] Analyzed with HPLC. [c] Isolated yield over 90%.

Amide Preparations. To evaluate the idea of using this substituted quinone propionic acid **1a** as an amine protecting group, we have studied the conversion of **1a** to amides using a series of amines and methodologies commonly used for the formation of peptide bonds.[13,14] These methodologies include dicyclohexylcarbodiimide (DCC) activation in the presence of hydroxybenzotriazole (HOBt), BOP activation, and activation using isobutyl chloroformate (IBCF). The results are listed in Table 1. The amines studied include primary amines with the nitrogen attached to a primary carbon (**1d**, **1e**) or a secondary carbon (**1f**), secondary amines (**1g**), an amine in the presence of a hydroxyl functional group (**1h**), and an amino acid ester (phenylalanine ethyl ester, **1i**) (Table 1). In all cases, the yield for the amide formation is about 90%. Furthermore, an amine functional group can be selectively protected in the presence of other nucleophiles such as a hydroxyl functional group in over 90% yield (**1h**). However, the reaction of the quinone acid **1a** with aromatic amines gave much lower yields (**1j**, **1k**). The reaction of aniline with quinone acid **1a** gave a 70% yield of the desired amide when the DCC−HOBt method was used and a 50% yield when isobutyl chloroformate method was used. In an attempt to study the effect of increased nucleophilicity of the aromatic amine on the coupling yield, anisidine was used to couple with the quinone acid **1a**. Unexpectedly, the yield of the amide formation was much lower (17%) than that of aniline. One unique feature of this particular reaction is that as soon as anisidine was added to the reaction solution containing quinone acid **1a**, a dark black color appeared. Analysis of the reaction mixture showed the formation of lactone **3** in the reaction. The lactone **3** was isolated in 13% yield. Therefore, the method worked well for aliphatic amines, however not very well for aromatic amines. It should be noted that there is no stability problem with the amides prepared at room temperature upon being exposed to light for extended period of time (1 to 2 weeks).

Deprotection and Release Studies. The deprotections were accomplished by simply shaking a solution of the amides **1d−k** and $Na_2S_2O_4$ in a mixture of methanol and water at room temperature. The reduction of the quinone to dihydroquinone is accompanied by a color change from yellow to colorless. However, a biphasic reaction by shaking an organic solution of the amides **1c** with the aqueous solution of $Na_2S_2O_4$ achieves the same results. To study the practicality of using this protecting group in organic synthesis, **1i** was dissolved in a mixture of methanol water solution (1:1). Approximately a 20-fold excess of $Na_2S_2O_4$ was added to the solution. After the reaction was stirred for about 5 h, the free amine (phenylalanine ethyl ester) was recovered in 90% yield through acid−base extraction without the need for chromatographic purification. Also recovered was the lactone **3** in 95% yield, which can be reconverted to the acid **1a** in over 90% yield.[10] HPLC was used to monitor the deprotection of the other amides (**1d−k**) in a methanol−water mixture at room temperature. When $Na_2S_2O_4$ was used as the reducing agent, the deprotection was mostly complete within a few minutes. However, the deprotection of the residual amount of the amides (**1d−i**) may take slightly longer. In all cases described, 100% deprotection was achieve within a few hours for the amides **1d−i** of aliphatic amines. A representative HPLC profile is shown in Figure 1. It can be seen that within 8.5 h all of the amide **1i** disappeared. The situation for the amides of aromatic amines **1j,k** is somewhat different. Upon being dissolved in the methanol−water mixture in the absence of any other reagents, the aromatic amides **1j,k** would show up as two peaks, indicating the rapid conversion of the amide to another compound, which will be discussed in the following section. Furthermore, complete release of the aromatic amines was not achieved even after the treatment of **1j,k** with $Na_2S_2O_4$ for 1 day.

Discussion

One of the most important requirements for a practical protecting group is that the protection and deprotection can be carried out in high yields. We were interested in studying the applicability of developing this protecting

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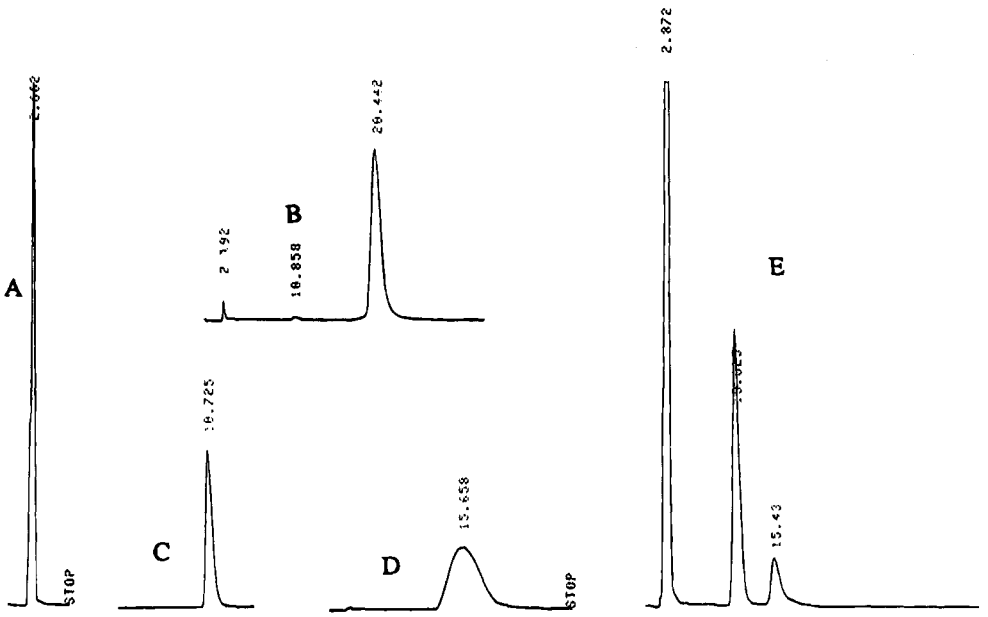

Figure 1. HPLC studies of the deprotection of **1i**: panel A, $Na_2S_2O_4$ in methanol–water; panel B, **1i** standard; panel C, **3** standard; panel D, phenylalanine ethyl ester standard; panel E, **1i** after treatment with $Na_2S_2O_4$ for 8.5 h in methanol–water solution. Detailed experimental conditions are described in the Experimental Section.

group for the protection of a variety of different amines and whether amines can be selectively protected in the presence of other nucleophiles such as a hydroxyl group. One thing that was an initial concern was whether the steric hindrance of the quinone propionic acid (**1a**) would affect the coupling of this acid to somewhat hindered amines. In a related study, we examined the crystal structures of the quinone acid **1a** and the benzylamide **1d**.[15] It was shown that due to the presence of the trimethyl lock, the side chain was forced to fold back in such a way that the side-chain carbonyl carbon is positioned about 3.2 Å away from the quinone carbonyl oxygen. Because of the close proximity of the side-chain carboxyl group and the quinone system, there was the question of whether coupling of sterically hindered amines would be difficult due to steric congestion. Therefore, we studied the coupling of the quinone acid **1a** with amines of different steric bulkiness. The coupling yields were high for all aliphatic amines, regardless of whether they are primary or secondary. This indicates that the steric congestion of the system does not itself affect the coupling of the acid **1a** with an amine. In addition, with all the coupling methods studied, similar yields were obtained. Furthermore, the deprotections of the amides of the aliphatic amines were achieved essentially quantitatively. All of these demonstrated the practicality of using this agent as a protecting group for the protection of aliphatic amines.

The attempt to develop this as a protecting group for aromatic amines did not have as much success. First the coupling reaction between the quinone acid **1a** and aniline gave low yields using two different methods. In an attempt to study the effect of increased nucleophilicity of aromatic amines on the coupling yield, anisidine was used to couple with quinone propionic acid **1a**. However, unexpectedly, the addition of anisidine to the quinone propionic acid solution in the presence of the coupling agents resulted in a dark-colored solution, which did not happen with any other coupling reactions studied. This reaction gave only a 17% yield of the desired amide **1k**. Also isolated from the reaction mixture was lactone **3** (13%). The most logical explanation is that anisidine is a strong enough reducing agent that under the coupling conditions the reduction of the quinone acid **1a** or the amide **1k** formed could occur. The dihydroquinone intermediate formed (**2**) can subsequently undergo a cyclization to give the lactone **3** as shown in Scheme 1. Consequently, anisidine is oxidized, which might be the reason for the dark color of the reaction solution. The easy oxidation of anisidines is well documented in the literature.[16,17] It has been shown that upon oxidation, anisidine can be converted to azobenzene derivatives, among other products. The complication with aromatic amines does not stop with the low yield and potential oxidative chemistry problem. During the deprotection step, upon coming in contact with aqueous solution, amides **1j,k** of aromatic amines would show up as two peaks in the HPLC chromatogram. Earlier studies from our group have shown that the amides of aromatic amines can undergo a spontaneous spirocyclization in aqueous solution to give spirolactam **4**. The structure of such a spirocyclization product has been confirmed by NMR studies.[18] Attempts were made to study the mechanistic aspect of the reaction.[19] It seems that the ease with which the amides of aromatic amines undergo base-promoted deprotonation is responsible for the spirocyclization reaction which occurs only with aromatic amides. The result of such a spirocyclization is that a significant portion of this compound stays in the nonreactive spirolactam **4**, therefore resulting in a slow rate

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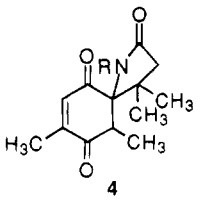
of deprotection. Both factors limit the application of the this reagent being used as a protecting group for aromatic amines.



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Therefore, the method can be efficiently used for the protection of aliphatic amines. However, the protection of aromatic amines using this reagent is not as practical.

Conclusions

In conclusion, the substituted quinone propionic acid system **1a** (Scheme 1) can be used as a stable, and yet readily cleavable under mild conditions, protecting group for aliphatic amines. This new protecting group has the advantage of using fundamentally different cleavage methods as compared to the commonly used acid/base deprotection conditions and will add to the diversities of protecting groups available. It will be particularly useful for the synthesis and modifications of compounds with multifunctional groups, where selective protection and deprotection are of utmost importance. In the area of peptide synthesis, side-chain manipulations are often desired[20] but are difficult to accomplish due to the lack of variety in protecting groups.[13,14] The introduction of this new type of protection for the side-chain functional groups of amino acids would greatly facilitate synthesis of peptides with side-chain modifications including cyclizations, due to the unique conditions required for its cleavage. With the availability of a variety of coupling methods for the preparation of amides, this new type of redox-sensitive amine protecting group will find wide applications in organic and peptide synthesis.

Further work is underway to extend the application of this type of redox-sensitive protecting group to peptide synthesis and modification, as well as hydroxyl and thiol protections.

Experimental Section

Melting points were determined on a Thomas-Hoover or an Electrothermal melting point apparatus and are uncorrected. NMR spectra were obtained on either a Varian XL-300 or a Bruker AM-500 spectrophotometer. All ^1H chemical shifts are reported in ppm relative to the internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (center of triplet, δ 77.0). Mass spectra were recorded on a Ribermag R10-10 quadruple spectrometer. Elemental analyses were conducted at The University of Kansas. Column chromatography was accomplished with 70–230 mesh silica gel (Aldrich Chemical Co.). All starting materials and chemical agents, unless otherwise specified, were obtained commercially from Aldrich Chemical Co. The sodium hydrosulfite is technical grade and 85% pure. The HOBt from Aldrich was that of the hydrate form.

HPLC Studies. The HPLC study of the deprotection reaction was carried out using a Shimatzu HPLC system equipped with a UV detector (detection wavelength: 260 nm). The column was a C_{18} reverse phase analytical column from AllTech (length: 250 mm, i.d. 4.6 mm). The solvent systems are a gradient of 30% to 75% acetonitrile in water.

General Method I for Coupling Reaction. 3-(3′,6′-Dioxo-2′,4′-dimethyl cyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic acid (**1a**, 1–2 equiv) was dissolved in CH_2Cl_2 followed by the addition of the amine (1.0 equiv) and HOBt (1–2 equiv). After the solution was cooled to 0 °C in an ice bath, dicyclohexylcarbodiimide (DCC, 1–2 equiv) was added followed by (dimethylamino)pyridine (DMAP, 0–0.2 equiv). The reaction solution was stirred at 0 °C for 1 h and warmed to room temperature. After stirring at room temperature for about 2 h, the reaction solution was cooled in an ice bath and then filtered and washed with CH_2Cl_2. The CH_2Cl_2 solution was extracted with saturated $NaHCO_3$ (four times) and then citric acid (three times) followed by water (one time). The organic phase was dried over Na_2SO_4. After filtration and evaporation, the residue was purified through silica gel chromatography (CH_3OH:Et_3N:CH_2Cl_2 = 2:1:97) and then recrystallized from EtOAc/hexane.

General Method II for Coupling Reaction. 3-(3′,6′-Dioxo-2′,4′-dimethyl cyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic acid (**1a**, 1.0 equiv) was dissolved in DMF, and then triethylamine (2.0 equiv) was added. After the solution was cooled in an ice bath, 4-hydroxylbutylamine (1.0 equiv) was added followed by the addition of BOP (1.5 equiv). Then the solution was stirred at 0 °C under argon for 3 h. Methylene chloride was added, and the solution was washed with citric acid (10%, 3 times), saturated $NaHCO_3$ (3 times), and H_2O (2 times) and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel chromatography (CH_3OH:Et_3N:CH_2Cl_2 = 2.5:1.5:96).

General Method III for Coupling Reaction. 3-(3′,6′-Dioxo-2′,4′-dimethyl cyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic acid (**1a**, 1.0 equiv) was dissolved in DMF, and then triethylamine (2.0 equiv) was added. After the solution was cooled to −25 °C, isobutylchloroformate (1.0 equiv) was added followed by 4-hydroxylbutylamine (1.0 equiv). Then the solution was stirred at −20 to −30 °C for 2.5 h. Methylene chloride was added, and the solution was washed with citric acid (10%, 3 times), saturated $NaHCO_3$ (3 times), and H_2O (2 times) and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel chromatography (CH_3OH:Et_3N:CH_2Cl_2 = 2:1:97).

3-(3′,6′-Dioxo-2′,4′-dimethyl cyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic acid *N*-Benzylamide[10] (1d). Acid **1a** (248 mg, 1.05 mmol), benzylamine (98%, 110.2 μL, 1 mmol), DCC (216 mg, 1.05 mmol), and HOBt (142 mg, 1.05 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow crystalline solid (218 mg, 98%): mp 142–143.5 °C; ^1H NMR ($CDCl_3$) δ 7.20 (5 H, m), 6.41 (1 H, d, J = 1.41 Hz), 6.01 (1 H, b), 4.28 (2 H, d, J = 5.73 Hz), 2.84 (2 H, s), 2.11 (3 H, s), 1.92 (3 H, s), 1.40 (6 H, s); ^{13}C NMR ($CDCl_3$), δ 190.1, 188.2, 171.6, 152.2, 143.4, 139.1, 138.2, 135.2, 128.6, 127.7, 127.4, 49.2, 43.3, 38.9, 29.3, 15.6, 14.3; HRMS (EI, m/e) 325.1660 (MH^+, calcd 325.1678); MS (EI) m/e 325 (M^+), 282, 234, 220, 191, 91, 79.

3-(3′,6′-Dioxo-2′,4′-dimethyl cyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-(3-Phenyl-1-propyl)amide (1e). Acid **1a** (472 mg, 2 mmol), 3-phenyl-1-propylamine (98%, 145 μL, 1 mmol), DCC (412 mg, 2 mmol), and HOBt (306 mg, 2 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow crystalline solid (328 mg, 93%): mp 83–84.5 °C; ^1H NMR ($CDCl_3$) δ 7.30–7.12 (5 H, m), 6.50 (1 H, d, J = 1.5 Hz), 5.40 (1 H, b), 3.19 (2 H, m), 2.80 (2 H, s), 2.59 (2 H, m), 2.15 (3 H, s), 1.97 (3 H, d, J = 1.53 Hz), 1.75 (2 H, m), 1.42 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 190.0, 188.2, 171.6, 152.3, 143.4, 141.3, 138.8, 135.2, 128.4, 128.3, 126.0, 49.4, 38.9, 38.6, 33.2, 31.2, 29.2, 15.6, 14.3; MS (EI) m/e 317 (M^+), 353, 220, 177, 117, 105, 91, 77. Anal. Calcd for $C_{22}H_{27}NO_3$: C,74.76; H, 7.70; N, 3.96. Found: C, 74.90; H, 8.09; N, 3.80.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-Cyclohexylamide (1f). Acid **1a** (472 mg, 2 mmol), cyclohexylamine (117 μL, 1 mmol), DCC (412 mg, 2 mmol), and HOBt (306 mg, 2 mmol) were treated according to the general coupling procedure I. The reaction

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afforded a yellow crystalline solid (301 mg, 95%): mp 153–154 °C; ^{1}H NMR ($CDCl_3$) δ 6.46 (1 H, d, J = 1.5 Hz), 6.50 (1 H, d, J = 8.31 Hz), 3.59 (1 H, m), 2.73 (2 H, s), 2.08 (3 H, s), 1.91 (3 H, d, J = 1.53 Hz), 0.95–1.75 (11 H, m), 1.36 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 189.8, 188.1, 170.6, 152.5, 143.1, 138.4, 135.2, 49.3, 47.7, 38.6, 33.0, 28.9, 25.3, 24.7, 15.5, 14.1; MS (EI) m/e 317 (M^+), 274, 235, 219, 191, 98, 83. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.73; H, 8.90; N, 4.80.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-Methyl-*N*′-benzylamide (1g). Acid **1a** (472 mg, 2 mmol), *N*-methyl-*N*′-benzylamine (97%, 133 μL, 1 mmol), DCC (433 mg, 2.1 mmol), HOBt (321 mg, 2.1 mmol), and DMAP (26 mg, 0.2 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow crystalline solid (318 mg, 94%): mp 85–86.5 °C; ^{1}H NMR ($CDCl_3$) rotomer A δ 7.3–7.0 (5 H, m), 6.4 (1 H, b), 4.43 (2 H, s), 3.04 (2 H, s), 2.75 (3 H, s), 2.07 (3 H, s), 1.89 (3 H, s), 1.32 (6 H, s); rotomer B δ 7.3–7.0 (5 H, m), 6.3 (1 H, b), 4.42 (2 H, s), 3.02 (2 H, s), 2.81 (3 H, s), 2.08 (3 H, s), 1.87 (3 H, s), 1.39 (6 H, s); ^{13}C NMR ($CDCl_3$), δ rotomer A 189.7, 188.1, 172.0, 153.6, 143.2, 137.0, 136.3, 134.9, 128.7, 127.4, 127.0, 53.1, 46.9, 37.9, 33.4, 28.6, 15.5, 14.2; rotomer B 189.9, 188.1, 171.9, 153.7, 143.3, 137.1, 136.3, 134.8, 128.3, 127.4, 126.1, 50.4, 47.7, 37.7, 34.7, 28.8, 15.5, 14.2; MS (EI) m/e 340 (MH^+), 339 (M^+), 296, 248, 220, 191, 120, 91. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.68; H, 7.18; N, 3.99.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl-3,3-dimethylpropanoic Acid *N*-(4-Hydroxyl)-butylamide (1h). Acid **1a** (98 mg, 0.42 mmol), 4-hydroxylbutylamine (37 mg, 0.42 mmol), DCC (86 mg, 0.42 mmol), HOBt (95%, 59 mg, 0.42 mmol), and triethylamine (115 μL, 1.0 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow crystalline solid (120 mg, 92%): mp 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 6.52 (1 H, d, J = 1.56 Hz), 5.60 (1 H, b), 3.64 (2 H, m), 3.19 (2 H, m), 2.83 (2 H, s), 2.16 (3 H, s), 2.04 (3 H, s), 1.99 (3 H, d, J = 1.41 Hz), 1.62 (1 H, b), 1.51–1.55 (4 H, m), 1.44 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 189.9, 188.2, 171.9, 152.5, 143.2, 138.6, 135.2, 61.9, 49.1, 38.9, 38.5, 29.6, 29.0, 26.0, 15.5, 14.2; MS (EI) m/e 307 (M^+) 292, 264, 220, 149, 135, 121. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.40; H, 8.20; N, 4.56. Found: C, 66.39; H, 8.00; N, 4.54.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-(4-Hydroxyl)butylamide (1h). Acid **1a** (100 mg, 0.42 mmol), 4-hydroxylbutylamine (39 μL, 0.42 mmol), BOP (281 mg, 0.63 mmol), and triethylamine (118 μL, 0.85 mmol) were treated according to the general coupling procedure II. The reaction afforded a yellow crystalline solid (120 mg, 92%).

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-diene)-3,3-dimethylpropanoic Acid *N*-(4-Hydroxyl)butylamide (1h). Acid **1a** (100 mg, 0.42 mmol), 4-hydroxylbutylamine (39 μL, 0.42 mmol), isobutyl chloroformate (IBCF, 55 μL, 0.42 mmol), and triethylamine (115 μL, 0.85 mmol) were treated according to the general coupling procedure III. The reaction afforded a yellow crystalline solid (127 mg, 97%).

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-(1(*R*)-(Ethoxylcarbonyl)-2-phenylethylamide (1i). Acid **1a** (260 mg, 1.1 mmol), L-phenylalanine ethyl ester·HCl (230 mg, 1 mmol), DCC (227 mg, 1.1 mmol), HOBt (95%, 177 mg, 1.1 mmol), and NMM (110 μL, 1.0 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow oily product (407 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.2–7.0 (5 H, m), 6.40 (1 H, d, J = 1.41 Hz), 6.0 (1 H, d, J = 8.19 Hz), 4.70 (1 H, m), 4.05 (2 H, q, J = 7.1 Hz), 2.95 (2 H, m), 2.79 (2 H, d, J = 2.9 Hz), 2.04 (3 H, s), 1.89 (3 H, s), 1.33 (3 H, s), 1.29 (3 H, s), 1.14 (3 H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 189.7, 188.0, 171.4, 171.2, 152.0, 143.2, 138.8, 135.7, 135.0, 129.1, 128.3, 126.8, 53.1, 61.3, 52.6, 48.9, 38.4, 37.8, 28.94, 28.88, 15.4, 14.1, 13.9; HRMS (EI, m/e) 411.2060 (M^+, calcd 411.2046); MS (EI) m/e 411 (M^+), 396, 368, 235, 219, 191, 120, 91.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-Phenylamide (1j). Acid (472 mg, 2 mmol), aniline (96 μL, 1 mmol), DCC (412 mg, 2 mmol), and HOBt (306 mg, 2 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow crystalline solid (216.4 mg, 70%): mp 152–152.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (5 H, m), 7.1 (1 H, t, J = 7.3 Hz), 6.50 (1 H, d, J = 1.6 Hz), 3.04 (2 H, s), 2.18 (3 H, s), 1.97 (3 H, s), 1.49 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 190.2, 188.2, 170.1, 151.8, 143.7, 139.4, 137.5, 135.0, 128.9, 124.3, 120.0, 50.4, 38.8, 29.3, 15.6, 14.4; MS (EI) m/e 311 (M^+, 56), 219 (M – aniline, 75), 191 (100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.03; H, 6.51; N, 4.40.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-Phenylamide (1j). Acid (260 mg, 1.1 mmol), aniline (96 μL, 1 mmol), triethylamine (155 μL, 1.1 mmol), and IBCF (145 μL, 1.1 mmol) were treated according to the general coupling procedure II. The reaction afforded a yellow crystalline solid (154 mg, 50%), which is identical to that obtained according to the general procedure I.

3-(3′,6′-Dioxo-2′,4′-dimethylcyclohexa-1′,4′-dienyl)-3,3-dimethylpropanoic Acid *N*-(*p*-Methoxyphenyl)amide (1k). Acid (472 mg, 2 mmol), *p*-methoxyaniline (124 mg, 1 mmol), DCC (412 mg, 2 mmol), and HOBt (306 mg, 2 mmol) were treated according to the general coupling procedure I. The reaction afforded a yellow crystalline solid (59 mg, 17%): mp 152 °C (sublimation); ^{1}H NMR of the product is identical to that reported in the literature.[10] Also recovered from the reaction is 58 mg (13%) of the lactone **3**.

Deprotection of 1i. The solution of the amide **1i** (309 mg) in 20 mL of methanol was added to the solution of 4 g of $Na_2S_2O_4$ in 30 mL of water. The yellow color of the amide disappeared immediately. The solution was kept stirring for 6 h. Then methanol was evaporated, and Na_2CO_3 was added to bring the pH of the solution to >10. The products were extracted with ethyl acetate (50 mL × 4). The combined organic extracts were washed with 1% HCl (10 mL × 5) and then dried over $MgSO_4$ overnight. Solvent evaporation gave 157 mg of a white solid (95%), which was identical to **3** as judged by ^{1}H and ^{13}C NMR. To the combined 1% HCl washings was then added Na_2CO_3 to bring the pH to over 10. This solution was then extracted with ethyl acetate (15 mL × 3). The combined organic extracts were dried over $MgSO_4$ for 1 h. Solvent evaporation gave a white oily solid (132 mg, 91%), which is identical to standard phenylalanine ethyl ester as judged by ^{1}H and ^{13}C NMR.

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Supplementary Material Available: A copy of the ^{1}H NMR spectrum of **1i** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

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