Pergamon

Tetrahedron 56 (2000) 5353–5361

TETRAHEDRON

Efficient Synthesis of Resin-Bound α-TMSdiazoketones and Their Use in Solid-Phase Organic Synthesis

Yasuyoshi Iso,* Hirohisa Shindo and Hiroshi Hamana

Shionogi Research Laboratories, Shionogi & Co. Ltd., Fukushima-ku, Osaka 553-0002, Japan

Received 20 April 2000; accepted 22 May 2000

Abstract—α-TMSdiazoketones on a solid support could be simply and efficiently prepared by reaction of the corresponding resin-bound acid chlorides with excess TMSdiazomethane, without any bases. These α-TMSdiazoketones were used via carbenes or carbenoids for a variety of solid-phase reactions. These useful solid-phase reactions allow efficient construction of diverse compound libraries by use of combinatorial chemistry, due to the high reactivity and wide applications of the carbenes or carbenoids.

Introduction

Diazo compounds as precursors of carbenes or carbenoids, including α-diazoketones, have a long history of useful applications in organic chemistry[1] and have been an important and interesting theme for modern organic synthesis.[2] In solid-phase organic synthesis, some examples using diazo compounds were recently reported, such as cyclopropene synthesis,[3] furan synthesis via 1,3-dipolar cycloaddition,[4] OH-insertion reaction[5] and the 'diazo linker' method.[6] However, few synthetic methods for α-diazoketones on a solid support have been reported and the only synthesis required diazo formation of resin-bound 1,3-diketone with tosyl azide and subsequent deacylation of the 2-diazo-1,3-diketone with pyrrolidine.[5] In this route, the resin-bound 1,3-diketone must first be prepared as a starting material via a difficult procedure, and substances containing sensitive functional groups or protecting groups cannot be used because strong bases such as pyrrolidine must be used in deacylation.

We thus tried to develop a method which could directly give resin-bound α-diazoketones from resin-bound acid chlorides and diazomethane, as generally performed in solution reaction.[7] However, problems arise due to the highly toxic and explosive diazomethane used in the solid-phase reaction. The risk increases with a long reaction time and static electricity which can be generated by rubbing of polystyrene. To avoid this problem, we used TMSdiazomethane which is safer than diazomethane with respect to both toxicity and the possibility of explosion.[8] As a result, we found that TMSdiazomethane could successfully convert acid chlorides to α-TMSdiazoketones without any bases on a solid support and moreover, the molecular diversity could be increased by use of the C–Si bond remaining in a resin-bound substrate after subsequent reactions using α-TMSdiazoketone.

Results and Discussion

The preparation of resin-bound α-TMSdiazoketone **6** is shown in Scheme 1. After attachment of the Wang resin (**1**) and 4-hydroxy benzoic acid allyl ester (**2**) as a substrate under Mitsunobu conditions,[9] the allyl group was deprotected with $Pd(PPh_3)_4$ to give resin-bound carboxylic acid **4**.[10] The carboxyl group was converted into acid chloride **5** by oxalyl chloride under heating.[11] Next, resin **5** was reacted with TMSdiazomethane and triethylamine in the mixture solvent of THF/MeCN (1/1) at room temperature for 50 h to furnish resin-bound α-TMSdiazoketone **6**, which had IR absorption at 2102 cm^{-1} resulting from the formed diazo group. Another kind of resin-bound α-TMSdiazoketone **6′** containing an aliphatic substrate was also obtained without protection from azelaic acid (**2′**) instead of a phenol derivative, under the same reaction conditions as above. However, in order to use resin **6** in various reactions via a carbene or carbenoid, the yield of **6** must be as high as possible. We therefore optimized the reaction conditions from **5** to **6**.

The yield of **6** was determined by comparing the nitrogen content of **6** by elemental analysis with the calculated value and the result is shown in Table 1. The mixture of THF/MeCN (1/1) was better than only THF as the reaction solvent and 50 h was better than 24 h for the reaction time. With respect to the reagents, the quantity of triethylamine greatly affected the reaction yield, with the less used,

Keywords: diazo compound; carbene and carbenoid; solid-phase synthesis; combinatorial chemistry.

* Corresponding author. Tel.: +81-6-6458-5861; fax: +81-6-6458-0987; e-mail: yasuyoshi.isou@shionogi.co.jp

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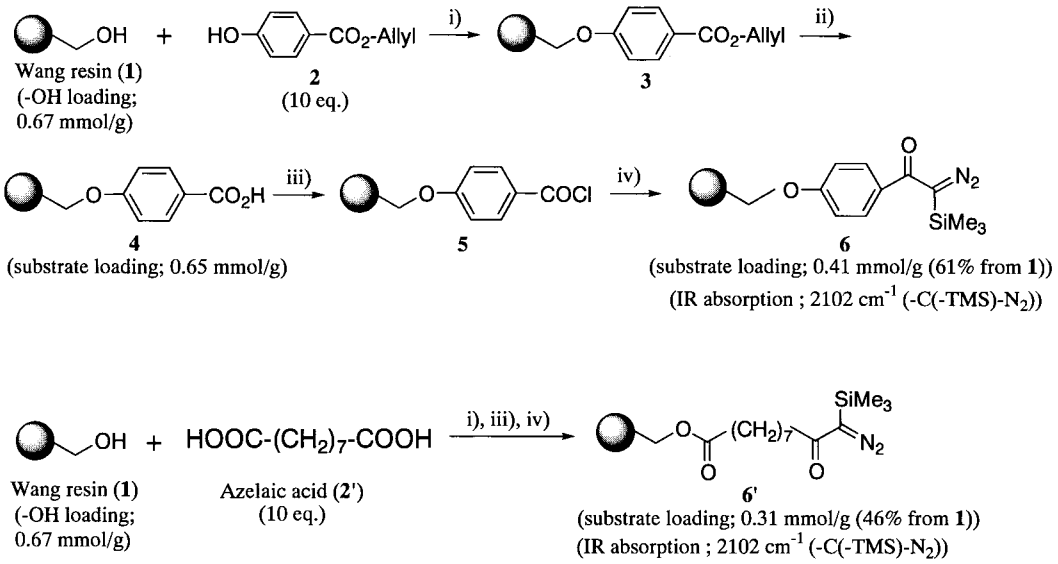
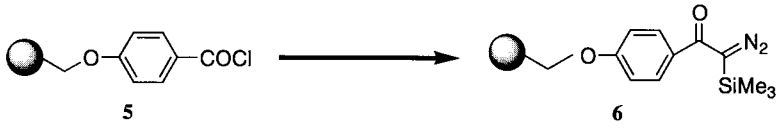
PII: S0040-4020(00)00440-3



Scheme 1. Synthetic route for preparation of resin-bound α-TMSdiazoketone (**6** or **6′**). (i) ADDP (5 equiv.), *n*-Bu_3P (5 equiv.) in THF, room temperature, 4 h. (ii) $Pd(PPh_3)_4$ (1 equiv.), AcOH (excess), 4-methylmorpholine (excess) in CH_3Cl_3, room temperature, 3 h. (iii) $(COCl)_2$ (10 equiv.), refluxed in benzene, 16 h. (iv) $TMSCHN_2$ (3 equiv.), Et_3N (1 equiv.) in THF/MeCN=1/1, room temperature, 50 h (this reaction condition is not optimized; see Table 1).

Table 1. Optimization of reaction conditions from **5** to **6** (all reactions were performed at room temperature)



5 **6**

Entry	Solvent	$TMSCHN_2$ (equiv.)	Et_3N (equiv.)	Time (h)	Yield (%)[a]
1	THF/MeCN=1/1	1.3	1.3	24	40.1
2	THF/MeCN=1/1	1.3	1.3	50	48.2
3	THF/MeCN=1/1	2	2	24	–
4	THF/MeCN=1/1	2	2	50	38.5
5	THF/MeCN=1/1	3	0	50	41.0
6	**THF/MeCN=1/1**	**3**	**0**	**50**	**80.5**
7	THF/MeCN=1/1	3	0.5	50	71.5
8	THF/MeCN=1/1	3	1	50	61.0
9	THF	2	2	50	25.7
10	THF	3	0	50	45.0

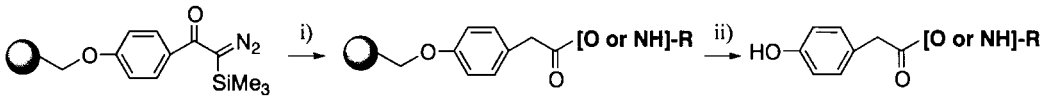
[a] The yield of **6** was determined by comparing the nitrogen content of **6** in elemental analysis with the calculated value.

leading to a higher yield. As a result, the conditions of entry 6 in the absence of triethylamine were the best even on further optimization of the reaction conditions. The advantage of entry 6 was also supported by both the strength of IR absorption at 2102 cm^{-1} and the yield after the subsequent Arndt–Eistert reaction[12] and cleavage. Comparing the above data about **6** and **6′** with time dependence, we found that resin-bound α-TMSdiazoketones were stable for at least a month in a desiccator shielded from light kept under reduced pressure, even at room temperature.

Next, we studied the various types of solid-phase reactions via carbenes or carbenoids, using resin-bound α-TMSdiazoketones **6** and **6′** prepared as above. First, we tried the Arndt–Eistert reaction, which is a classical and typical methylene insertion reaction via a carbene from α-diazoketones or α-TMSdiazoketones in solution reaction.[12] Table 2 shows that the solid-phase Arndt–Eistert reaction proceeded smoothly to give the corresponding methylene-inserted ester resin **7-1** or **7-2** in the reaction of resin **6** with alcohols **1** or **2** as a nucleophile, in the presence of 2,4,6-trimethylpyridine as an additive, without solvent at 180°C for 20 min. In this case, the TMS group would be removed by the action of a nucleophile on resin **6**.[12a] Resin **7-1** or **7-2** was cleaved with a 50% (v/v) solution of TFA in CH_2Cl_2 to furnish the expected **8-1** or **8-2** in 63 or 61% total yield from Wang resin (**1**), respectively (entry 1 and 2). Resin **6′** also gave methylene-inserted ester **8′-1** in 46% total yield by the same method as above (entry 4). Moreover, methylene-inserted amide **8-3** was obtained in 60% total yield, by the reaction of amine **3** with resin **6** in the absence of 2,4,6-trimethylpyridine under the same reaction conditions and the subsequent cleavage (entry 3). The above reactions did not proceed successfully under photochemical conditions.

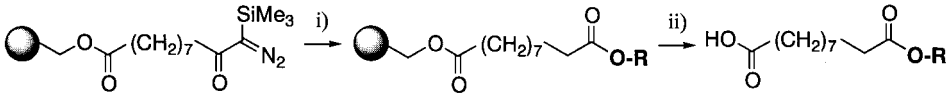
The results of the α-substitution reaction[2,5,13] using resin-bound α-TMSdiazoketones **6** and **6′** are shown in Table 3.

Table 2. Solid-phase Arndt–Eistert reaction



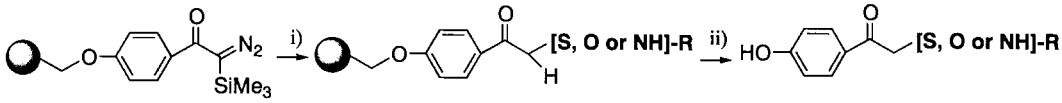
6 **7-(1, 2, 3)** **8-(1, 2, 3)**

i) **nucleophile** (**1**; HO-R (R=Bn) **2**; HO-R (R= -$(CH_2)_3$-⬡) **3**; H_2N-R (R=Ph)), ii) 50% TFA in CH_2Cl_2

Entry	Nucleophile (excess) (HO– or H_2N–R)	Additive	Reaction conditions	Total yield (%) of **8** or **8′** from Wang resin (**1**)
1	HO-CH_2-⬡ (**1**)		20 min, 180°C	63
2	HO-$(CH_2)_3$-⬡ (**2**)		20 min, 180°C	61
3	H_2N-⬡ (**3**)	–	20 min, 180°C	60
				
	6′ **7′-1** **8′-1**			
4	HO-CH_2-⬡ (**1**)		20 min, 180°C	46

The solid-phase α-substitution (SH-,[13a] OH-[5,13b] or NH-[13c] insertion) reaction via a carbenoid proceeded successfully by the reaction of resin **6** with thiol **1**, alcohol **2**, or amine **3**. After the reaction of resin **6** with thiol **1** or amine **3** using rhodium(II) acetate as a catalyst in benzene under heating and the subsequent cleavage, the expected α-substituted ketone **10-1** or **10-3** was obtained in 64 or 51% total yield from Wang resin (**1**), respectively (entry 1 and 3). α-Substituted ketone **10′-1** was also obtained in 41% total yield from resin **6′** and thiol **1** under the same reaction conditions as

Table 3. Solid-phase α-substitution (SH, OH or NH-insertion) reaction



6 **9-(1, 2, 3)** **10-(1, 2, 3)**

i) **$Rh_2(OAc)_4$ (cat.)** or **$BF_3 \cdot Et_2O$ (cat.)**, **reactant** (**1**; HS-R (R=Ph) **2**; HO-R (R=Et) **3**; H_2N-R (R=Ph))
ii) 50% TFA in CH_2Cl_2

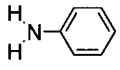
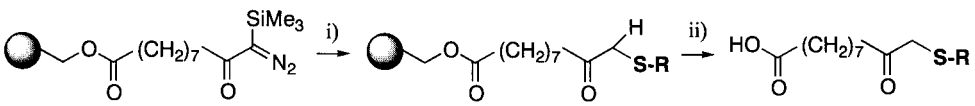
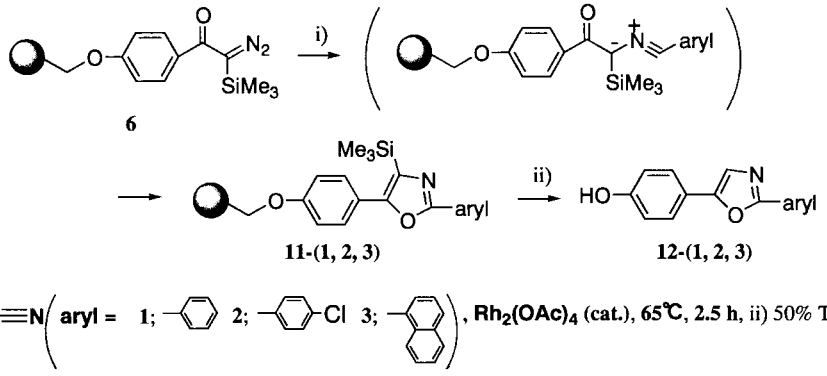
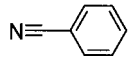
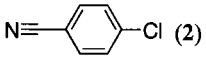
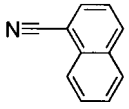
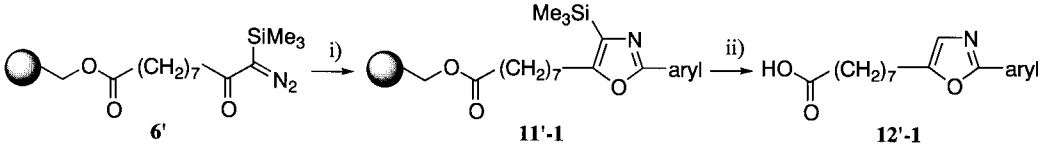
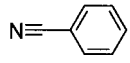
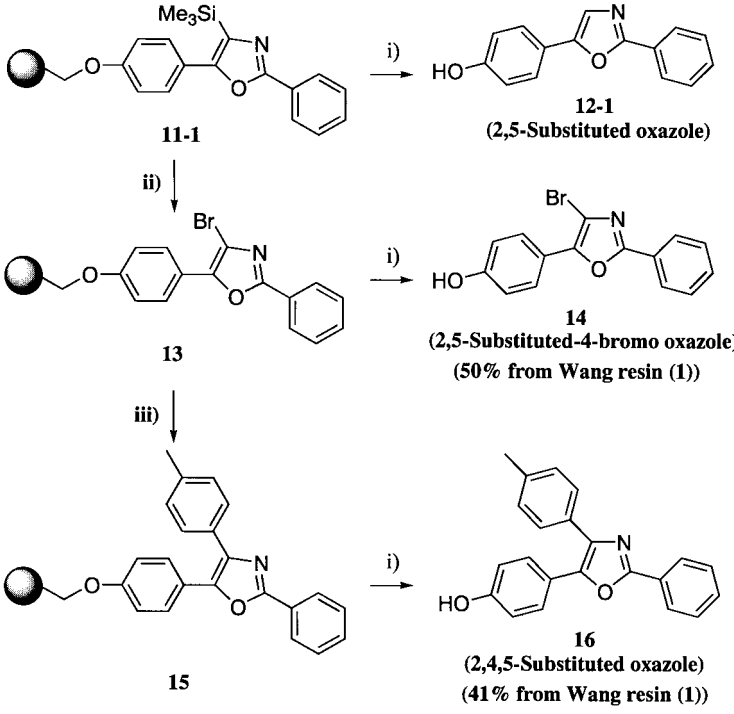
Entry	Reactant (excess)	Catalyst	Solvent	Reaction conditions	Total yield (%) of **10** or **10′** from Wang resin (**1**)
1	H-S-⬡ (**1**)	$Rh_2(OAc)_4$	Benzene	2 h, 50°C	64
2	H–O–Et (**2**)	$BF_3 \cdot Et_2O$	CH_2Cl_2	1 h, rt	52
3	 (**3**)	$Rh_2(OAc)_4$	Benzene	2 h, 85°C	51
					
	6′ **9′-1** **10′-1**				
4	H-S-⬡ (**1**)	$Rh_2(OAc)_4$	Benzene	2 h, 50°C	41

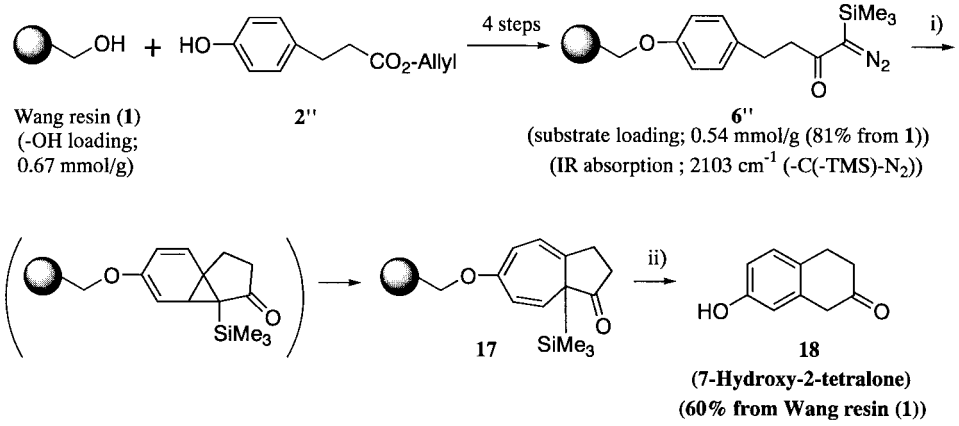
Table 4. Oxazole synthesis via ylide formation with aryl nitrile and subsequent 1,5-cyclization



Entry	Aryl nitrile (excess)	Solvent	Total yield (%) of **12** or **12′** from Wang resin (**1**)
1	 **(1)**	–	66
2	 **(2)**	Benzene	46
3	 **(3)**	Benzene	60
	 **6′** **11′-1** **12′-1**		
4	 **(1)**	–	48



Scheme 2. Further modifications using C–Si bond of resin (**11-1**): (i) 50% TFA in CH_2Cl_2; (ii) Br_2 (6 equiv.); Pyridine (3 equiv.) in CH_2Cl_2, 0°C; (iii) *p*-Tolylboronic acid (2.7 equiv.), $Pd(PPh_3)_4$ (cat.), aqueous Na_2CO_3 (2 M, 3.6 equiv.), refluxed in DME, 17 h.



Scheme 3. Solid-phase intramolecular Buchner reaction: (i) $Rh_2(OAc)_4$ (cat.), refluxed in $CHCl_3$, 40 min; (ii) 50% TFA in CH_2Cl_2.

entry 1 (entry 4). In the same way, alcohol **2** gave the corresponding α-alkoxy ketone **10-2** in 52% total yield using $BF_3{\cdot}Et_2O$ as a catalyst in CH_2Cl_2 at room temperature (entry 2).

Next, the ylide formation of resin-bound α-TMSdiazoketones with aryl nitriles via carbenoids and the subsequent 1,5-cyclization[14] proceeded successfully to give various oxazole derivatives on a solid support as shown in Table 4. After the reaction of resin **6** with aryl nitriles **1**, **2**, or **3** using rhodium(II) acetate as a catalyst in benzene or without solvent under heating for 2.5 h and the subsequent cleavage accompanied with desylilation, 2,5-substituted oxazole derivatives **12-1**, **12-2**, or **12-3** were obtained in 66, 46 or 60% total yield from Wang resin (**1**), respectively (entry 1, 2 and 3). Resin **6′** also furnished 2,5-substituted oxazole derivative **12′-1** in 48% total yield by the same method (entry 4). Moreover, we could perform further modifications using the C–Si[14b] bond of resin **11-1** (Scheme 2). Bromination of resin-bound oxazole derivative **11-1** at the position of the C–Si bond using bromine and pyridine[15] gave **13**, which furnished 2,5-substituted-4-bromo oxazole **14** in 50% total yield from Wang resin (**1**) after cleavage. Further Suzuki reaction[16] of resin **13** with *p*-tolylboronic acid and catalytic $Pd(PPh_3)_4$ furnished **15**, which also gave 2,4,5-substituted oxazole derivative **16** in 41% total yield from Wang resin (**1**) after cleavage. This means that a series of reactions allow a diverse substituent to be introduced at all carbons on the oxazole and the molecular diversity could be expanded more.

Formation of the fused ring system by intramolecular Buchner reaction[17] using resin-bound α-TMSdiazoketones **6″** proceeded successfully as shown in Scheme 3. At first, **6″** was synthesized as above from Wang resin (**1**) and 3-(4-hydroxyphenyl) propionic acid allyl ester (**2″**). Resin **6″** was refluxed with catalytic rhodium(II) acetate in $CHCl_3$ for 40 min to give **17** having the bicyclo[5.3.0]decane skeleton via a transient norcaradiene-like intermediate. Cleavage, rearrangement and desilylation of resin **17** occurred spontaneously with a 50% (v/v) solution of TFA in CH_2Cl_2 to furnish 7-hydroxy-2-tetralone (**18**) in 60% total yield from Wang resin (**1**).

Conclusion

We have developed a simple and efficient method for preparing α-TMSdiazoketones from carboxylic acid derivatives on a solid support under mild conditions. Using these resin-bound α-TMSdiazoketones which have diverse substrates including various kinds of phenols and aliphatic dicarboxylic acids, we successfully performed a variety of solid-phase reactions containing the Arndt–Eistert reaction, the α-substitution reaction, the oxazole synthesis via ylide formation with aryl nitrile and subsequent 1,5-cyclization, and the intramolecular Buchner reaction via carbenes or carbenoids. The use of these solid-phase reactions with combinatorial chemistry should contribute greatly to efficient construction of diverse compound libraries to search for interesting compounds for new drugs.

Experimental

General methods

Reagents were purchased from Aldrich, Tokyo Kasei (TCI-JP), and Kanto Chemical and used as received. Solvents were dried over appropriate molecular sieves. Particularly, THF was distilled under N_2 from lithium aluminum hydride, MeCN was dried by distillation from phosphorus pentoxide, and $CHCl_3$ was partitioned with conc. H_2SO_4 and water, dried over $CaCl_2$, and distilled, immediately prior to use. Wang resin was purchased from NovaBiochem. Compound purification by preparative TLC was carried out on plates (20 cm×20 cm, 0.5 mm thick) precoated with silica gel $60F_{254}$ (Merck).

A Barnes analytical/spectra-tech diffuse reflectance accessory was used for the infrared measurement of resins, and diffuse reflectance infrared Fourier transform (DRIFT) spectra of resins were obtained with a Nicolet 20SXB spectrometer with KBr optics.

4-Hydroxybenzoic acid allyl ester (2). THF (10 ml) was added to a suspension of 4-hydroxybenzoic acid (5.0 g, 36.2 mmol), thionyl chloride (3.95 ml, 54.3 mmol) and DMF (0.42 ml, 5.43 mmol) in CH_2Cl_2 (50 ml), and the reaction mixture was stirred for 30 min at room temperature.

After allyl alcohol (5.5 ml, 81.45 mmol) was added dropwise to the obtained clear solution containing the acid chloride, the reaction mixture was stirred for 2 h at room temperature. Then, saturated aqueous $NaHCO_3$ (150 ml) was added, and the reaction mixture was stirred for 30 min more. $CHCl_3$ (150 ml) and water (100 ml) were added, and the organic layer was taken, washed with water, dried ($MgSO_4$), evaporated in vacuo, and recrystallized from hexane to give **2** as white crystals (6.25 g, 97%). IR ($CHCl_3$): 3280, 1700, 1610 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.81 (dd, J=5.6 Hz, J=1.6 Hz, 2H), 5.28 (dd, J=10.2 Hz, J=1.8 Hz, 1H), 5.41 (dd, J=16.2 Hz, J=1.8 Hz, 1H), 5.93 (br s, 1H (–OH)), 5.94–6.14 (m, 1H), 6.88 (d, J=8.2 Hz, 2H), 7.99 (d, J=8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.1, 163.4, 137.0, 132.2, 122.0, 115.8, 115.5, 66.7. Anal calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.01; H, 5.60.

Preparation of resin 3. Tributylphosphine (0.834 ml, 3.35 mmol), **2** (1.2 g, 6.7 mmol), 1,1′-(Azodicarbonyl)dipiperidine (ADDP; 846 mg, 3.35 mmol) were added to a suspension of Wang resin (**1**) (0.67 mmol, i.e. 1.0 g of resin, hydroxy group loading 0.67 mmol/g) in anhydrous THF (50 ml), and the reaction mixture was agitated at room temperature for 4 h. The resin was filtered, washed with anhydrous THF (3×40 ml), DMF (3×40 ml), MeOH (3×40 ml), CH_2Cl_2 (3×40 ml), and ether (3×40 ml), and dried in vacuo (1.12 g).

Preparation of resin 4. Resin **3** (1.12 g, ~0.67 mmol) was suspended in anhydrous $CHCl_3$ (50 ml), and acetic acid (4 ml, 70 mmol), 4-methylmorpholine (2 ml, 18 mmol), and $Pd(PPh_3)_4$ (774 mg, 0.67 mmol) were added. The reaction mixture was agitated under N_2 at room temperature for 3 h. The resin was filtered, washed with 1% (w/v) diisopropylethylamine/DMF (3×40 ml), 1% (w/v) diethyldithiocarbamic acid sodium salt/DMF (3×40 ml), anhydrous DMF (3×40 ml), MeOH (3×40 ml), CH_2Cl_2 (3×40 ml), and ether (3×40 ml), and dried in vacuo (1.09 g). Generation of resin **4** and substrate loading of **4** were checked by cleavage of a part of the obtained resin.

After 50% (v/v) TFA/CH_2Cl_2 (2 ml) was added to the above resin (109 mg, ~0.67 mmol), and the reaction mixture was agitated at room temperature for 30 min, the resin was filtered and washed with CH_2Cl_2 (2 ml). The combined filtrates were concentrated and gave 4-hydroxybenzoic acid as a starting substrate after recrystallization from $CHCl_3$/ether, whose spectrum data were identical with those of an authentic sample (9.0 mg, 0.0652 mmol, 97%). Substrate loading of **4** was determined to be 0.65 mmol/g by the above result.

Preparation of resin 6 via resin 5 (entry 6). Oxalyl chloride (0.283 ml, 3.25 mmol) was added to a suspension of resin **4** (500 mg, ~0.325 mmol) in anhydrous benzene (30 ml), and the reaction mixture was agitated at 85°C for 16 h. Resin **5** was filtered, washed with anhydrous CH_2Cl_2 (3×30 ml), THF (3×30 ml), and ether (3×30 ml), and dried in vacuo (506 mg). TMSdiazomethane (ca. 10% solution in hexanes, 0.11 ml, ca. 0.098 mmol) was added to a suspension of resin **5** (50.6 mg, ~0.0325 mmol) in 1:1 (v/v) anhydrous THF/MeCN (2 ml), and the reaction mixture was agitated at room temperature for 50 h. The resin was filtered and washed with anhydrous THF (3×2 ml), MeCN (3×2 ml), CH_2Cl_2 (3×2 ml), and ether (3×2 ml) (52.0 mg). IR (KBr): 2102 (–C(–TMS)–N_2), 1720 (–CO–) cm^{-1}. Anal calcd for resin **6**: N, 1.59. Found: N, 1.28. Substrate loading of **6** was determined to be 0.54 mmol/g by the above result and total yield from Wang resin (**1**) was also determined to be 80.5%.

Preparation of resin 6′. Resin **6′** was prepared by the same method as above from commercially available azelaic acid (**2′**) as a starting material. IR (KBr): 2102 (–C(–TMS)–N_2), 1717 (–CO–) cm^{-1}. Anal calcd for resin **6′**: N, 1.54. Found: N, 0.95. Substrate loading of **6′** was determined to be 0.41 mmol/g by the above result and total yield from Wang resin (**1**) was also determined to be 61.7%.

4-Hydroxyphenylacetic acid benzyl ester (8-1). Resin **6** (52 mg, ~0.028 mmol) was suspended in 1:1 (v/v) anhydrous benzyl alcohol/2,4,6-trimethylpyridine (2 ml), and the reaction mixture was agitated at 180°C for 20 min. Resin **7-1** was filtered, washed with anhydrous CH_2Cl_2 (3×2 ml), THF (3×2 ml), and ether (3×2 ml), and dried in vacuo. A 50% (v/v) solution of TFA in CH_2Cl_2 (2 ml) was added to the above resin, and the reaction mixture was agitated at room temperature for 30 min. After the resin was filtered and washed with CH_2Cl_2 (2 ml), the combined filtrates were concentrated, and purified by preparative TLC (ethyl acetate/toluene) to give **8-1** (5.1 mg) in 63% yield from **1**. IR ($CHCl_3$): 3300, 1720, 1610 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.60 (s, 2H), 5.13 (s, 2H), 5.33 (br s, 1H (–OH)), 6.78 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 7.30–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 157.7, 130.6, 128.0, 125.7, 116.3, 66.2, 42.1. HR-FABMS: m/z calcd for MH^+ ($C_{15}H_{15}O_3$) 243.1021, found 243.1022.

4-Hydroxyphenylacetic acid 3-cyclohexylpropyl ester (8-2). Resin **6** (52 mg, ~0.028 mmol) was suspended in 1:1 (v/v) anhydrous 3-cyclohexyl-1-propanol/2,4,6-trimethylpyridine (2 ml), and the reaction mixture was agitated at 180°C for 20 min. The product (5.6 mg) was isolated as above in 61% yield from **1**. IR ($CHCl_3$): 3300, 1715 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.17–1.24 (m, 12H), 1.58–1.70 (m, 3H), 3.51 (s, 2H), 4.05 (t, J=6.6 Hz, 2H), 5.37 (br s, 1H (–OH)), 6.76 (d, J=8.4 Hz, 2H), 7.09 (d, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 157.8, 130.8, 125.4, 116.2, 64.8, 41.8, 35.8, 33.4, 33.1, 29.5, 27.3, 26.9. HR-FABMS: m/z calcd for MH^+ ($C_{17}H_{25}O_3$) 277.1804, found 277.1806.

2-(4-Hydroxyphenyl)*N*-phenylacetamide (8-3). Resin **6** (52 mg, ~0.028 mmol) was suspended in aniline (2.5 ml), and the reaction mixture was agitated at 180°C for 20 min. The product (4.6 mg) was isolated as above in 60% yield from **1**. IR ($CHCl_3$): 3500, 3300, 1710, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.67 (s, 2H), 5.38 (br s, 1H (–OH)), 6.87 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 7.11 (d, J=8.0 Hz, 1H), 7.24 (br s, 1H (–NH–)), 7.62 (t, J=8.4 Hz, 2H), 7.80 (d, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 157.3, 140.2, 130.5, 128.7, 127.3, 124.1, 119.6, 117.1, 44.9. HR-FABMS: m/z calcd for MH^+ ($C_{14}H_{14}NO_2$) 228.1025, found 228.1028.

Decanedioic acid monobenzyl ester (8′-1). Resin **6′** (57 mg, ~0.023 mmol) was suspended in 1:1 (v/v) anhydrous benzyl alcohol/2,4,6-trimethylpyridine (2 ml), and the reaction mixture was agitated at 180°C for 20 min. The product (4.5 mg) was isolated as above in 46% yield from **1**. IR ($CHCl_3$): 3400–2800, 1730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.22–1.30 (m, 12H), 2.35 (t, J=7.6 Hz, 4H), 5.12 (s, 2H), 7.27–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1, 173.3, 135.7, 128.6, 128.3, 128.2, 66.6, 34.2, 29.2, 29.0, 24.8. HR-FABMS: m/z calcd for MH^+ ($C_{17}H_{25}O_4$) 293.1753, found 293.1758.

1-(4-Hydroxyphenyl)-2-phenylthioethanone (10-1). Thiophenol (0.1 ml, 0.97 mmol) and $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) were added to a suspension of resin **6** (52 mg, ~0.028 mmol) in anhydrous benzene (2 ml), and the reaction mixture was agitated at 50°C for 2 h. Resin **9-1** was filtered, washed with anhydrous CH_2Cl_2 (3×2 ml), THF (3×2 ml), and ether (3×2 ml), and dried in vacuo. A 50% (v/v) solution of TFA in CH_2Cl_2 (2 ml) was added to the above resin, and the reaction mixture was agitated at room temperature for 30 min. After the resin was filtered, and washed with CH_2Cl_2 (2 ml), the combined filtrates were concentrated, and purified by preparative TLC (ethyl acetate/toluene) to give **10-1** (5.2 mg) in 64% yield from **1**. IR ($CHCl_3$): 3250, 1710, 1610 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.23 (s, 2H), 5.42 (br s, 1H (–OH)), 7.00 (d, J=8.8 Hz, 2H), 7.30–7.45 (m, 5H), 7.90 (d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3, 162.8, 135.5, 130.5, 129.2, 128.7, 127.0, 115.4, 37.8. HR-FABMS: m/z calcd for MH^+ ($C_{14}H_{13}O_2S$) 245.0636, found 245.0640.

2-Ethoxy-1-(4-hydroxyphenyl)ethanone (10-2). Ethanol (0.1 ml, 1.7 mmol) and $BF_3{\cdot}Et_2O$ (4 μl, 0.031 mmol) were added to a suspension of resin **6** (52 mg, ~0.028 mmol) in anhydrous CH_2Cl_2 (1 ml), and the reaction mixture was agitated at room temperature for 1 h. The product (3.1 mg) was isolated as above in 52% yield from **1**. IR ($CHCl_3$): 3260, 1710, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J=7.0 Hz, 3H), 3.63 (q, J=7.0 Hz, 2H), 4.67 (s, 2H), 5.40 (br s, 1H (–OH)), 6.88 (d, J=8.8 Hz, 2H), 7.92 (d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3, 163.4, 129.6, 126.1, 115.5, 73.7, 68.0, 14.8. HR-FABMS: m/z calcd for MH^+ ($C_{10}H_{13}O_3$) 181.0865, found 181.0869.

1-(4-Hydroxyphenyl)-2-phenylaminoethanone (10-3). Aniline (0.1 ml, 1.1 mmol) and $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) were added to a suspension of resin **6** (52 mg, ~0.028 mmol) in anhydrous benzene (1 ml), and the reaction mixture was agitated 85°C for 2 h. The product (3.9 mg) was isolated as above in 51% yield from **1**. IR ($CHCl_3$): 3480, 3290, 1710, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.68 (br s, 1H (–NH–)), 5.27 (s, 2H), 5.37 (br s, 1H (–OH)), 6.92 (d, J=8.8 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 7.37 (t, J=7.4 Hz, 1H), 7.62 (d, J=8.0 Hz, 2H), 7.81 (d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 161.8, 147.1, 132.4, 129.2, 127.9, 118.8, 115.5, 113.3, 47.8. HR-FABMS: m/z calcd for MH^+ ($C_{14}H_{14}NO_2$) 228.1025, found 228.1029.

9-Oxo-10-phenylthiodecanoic acid (10′-1). Thiophenol (0.1 ml, 0.97 mmol) and $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) were added to a suspension of resin **6′** (57 mg, ~0.023 mmol) in anhydrous benzene (2 ml), and the reaction mixture was agitated 50°C for 2 h. The product (4.0 mg) was isolated as above in 41% yield from **1**. IR ($CHCl_3$): 3350–2800, 1710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.23–1.54 (m, 10H), 2.28–2.39 (m, 4H), 3.62 (s, 2H), 7.10–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 179.2, 135.8, 129.2, 128.4, 126.0, 43.0, 42.1, 34.4, 29.3, 29.2, 24.9, 24.0. HR-FABMS: m/z calcd for MH^+ ($C_{16}H_{23}O_3S$) 295.1368, found 295.1372.

4-(2-Phenyloxazol-5-yl)phenol (12-1). $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) was added to a suspension of resin **6** (52 mg, ~0.028 mmol) in benzonitrile (1 ml, 9.8 mmol), and the reaction mixture was agitated at 65°C for 2.5 h. Resin **11-1** was filtered, washed with anhydrous CH_2Cl_2 (3×2 ml), THF (3×2 ml), and ether (3×2 ml), and dried in vacuo. A 50% (v/v) solution of TFA in CH_2Cl_2 (2 ml) was added to the above resin, and the reaction mixture was agitated at room temperature for 30 min. After the resin was filtered, and washed with CH_2Cl_2 (2 ml), the combined filtrates were concentrated, and purified by preparative TLC (ethyl acetate/toluene) to give **12-1** (5.2 mg) in 66% yield from **1**. IR ($CHCl_3$): 3290, 1730, 1610 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.10 (br s, 1H (–OH)), 6.93 (d, J=8.0 Hz, 2H), 7.33 (s, 1H), 7.40–7.60 (m, 3H), 7.63 (t, J=8.0 Hz, 2H), 8.10 (d, J=8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 157.2, 150.8, 131.9, 129.1, 127.8, 127.1, 126.7, 125.7, 121.7, 116.0. HR-FABMS: m/z calcd for MH^+ ($C_{15}H_{12}NO_2$) 238.0868, found 238.0869.

4-[2-(4-Chlorophenyl)oxazol-5-yl]phenol (12-2). *p*-Chlorobenzonitrile (0.1 g, 0.73 mmol) and $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) were added to a suspension of resin **6** (52 mg, ~0.028 mmol) in anhydrous benzene (2 ml), and the reaction mixture was agitated at 65°C for 2 h. The product (4.2 mg) was isolated as above in 46% yield from **1**. IR ($CHCl_3$): 3310, 1720, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.14 (br s, 1H (–OH)), 6.92 (d, J=8.2 Hz, 2H), 7.38 (s, 1H), 7.80 (d, J=8.2 Hz, 2H), 7.90–8.10 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 157.2, 150.8, 135.0, 130.6, 128.6, 127.1, 126.9, 125.6, 121.8, 116.2. HR-FABMS: m/z calcd for MH^+ ($C_{15}H_{11}ClNO_2$) 272.0478, found 272.0481.

4-(2-Naphthalen-1-yloxazol-5-yl)phenol (12-3). 1-Naphthonitrile (0.5 g, 3.26 mmol) and $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) were added to a suspension of resin **6** (52 mg, ~0.028 mmol) in anhydrous benzene (2 ml), and the reaction mixture was agitated at 65°C for 2 h. The product (5.8 mg) was isolated as above in 60% yield from **1**. IR ($CHCl_3$): 3290, 1710, 1610 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.11 (br s, 1H (–OH)), 6.87 (d, J=8.0 Hz, 2H), 6.96 (d, J=8.0 Hz, 2H), 7.48 (s, 1H), 7.55–7.62 (m, 2H), 7.69 (d, J=8.2 Hz, 2H), 7.97 (d, J=8.2 Hz, 2H), 8.29 (d, J=8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 150.9, 131.3, 131.1, 130.9, 130.5, 130.0, 128.5, 127.9, 127.1, 126.8, 125.6, 123.4, 122.8, 116.2. HR-FABMS: m/z calcd for MH^+ ($C_{19}H_{14}NO_2$) 288.1025, found 288.1029.

8-(2-Phenyloxazol-5-yl)octanoic acid (12′-1). $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) was added to a suspension of resin

6′ (57 mg, ~0.023 mmol) in benzonitrile (1 ml, 9.8 mmol), and the reaction mixture was agitated at 65°C for 2.5 h. The product (4.6 mg) was isolated as above in 48% yield from **1**. IR ($CHCl_3$): 3450–2850, 1730, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.18–1.51 (m, 10H), 2.37 (t, J=7.6 Hz, 2H), 2.76 (t, J=7.6 Hz, 2H), 7.36 (s, 1H), 7.35–7.46 (m, 3H), 7.98–8.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 155.0, 149.1, 131.8, 128.6, 127.0, 123.3, 34.1, 30.6, 30.5, 29.3, 28.1, 25.9, 24.8. HR-FABMS: m/z calcd for MH^+ ($C_{17}H_{22}NO_3$) 288.1600, found 288.1605.

4-(4-Bromo-2-phenyloxazol-5-yl)phenol (14). Bromine (8.6 μl, 0.168 mmol) and pyridine (6.8 μl, 0.084 mmol) were added to a suspension of resin **11-1** (54 mg, ~0.028 mmol) in CH_2Cl_2 (3 ml) under ice cooling, and the reaction mixture was agitated at 0°C for 2 h. Resin **13** was filtered, washed with anhydrous CH_2Cl_2 (5×2 ml), and dried in vacuo. A 50% (v/v) solution of TFA in CH_2Cl_2 (2 ml) was added to the above resin, and the reaction mixture was agitated at room temperature for 30 min. After the resin was filtered, and washed with CH_2Cl_2 (2 ml), the combined filtrates were concentrated, and purified by preparative TLC (ethyl acetate/toluene) to give **14** (5.3 mg) in 50% yield from **1**. IR ($CHCl_3$): 3280, 1720, 1605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.12 (br s, 1H (–OH)), 6.96 (d, J=8.4 Hz, 2H), 7.46–7.51 (m, 3H), 7.91 (d, J=8.4 Hz, 2H), 8.08 (d, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 158.2, 148.0, 131.1, 129.1, 128.2, 127.7, 126.7, 123.5, 116.8, 114.1. HR-FABMS: m/z calcd for MH^+ ($C_{15}H_{11}BrNO_2$) 316.0173, found 316.0178.

4-(2-Phenyl-4-*p*-tolyloxazol-5-yl)phenol (16). *p*-Tolylboronic acid (10.3 mg, 0.076 mmol), $Pd(PPh_3)_4$ (2.4 mg, 2.1 μmol), and aqueous Na_2CO_3 (2 M, 52 μl, 0.1 mmol) were successively added to a suspension of resin **13** (56 mg, ~0.028 mmol) in DME (6 ml), and the reaction mixture was refluxed for 17 h. After aqueous NH_4OAc (25%, w/v, 2 ml) was added and the reaction mixture was agitated for 5 min, resin **15** was filtered, washed with DME/H_2O (1:1, 3×2 ml), diluted HCl (0.2 N, 3×2 ml), water (3×2 ml), DME (3×2 ml), EtOAc (3×2 ml), EtOAc/MeOH (1:1, 3×2 ml), and MeOH (3×2 ml), and dried in vacuo. A 50% (v/v) solution of TFA in CH_2Cl_2 (2 ml) was added to the above resin, and the reaction mixture was agitated at room temperature for 30 min. After the resin was filtered, and washed with CH_2Cl_2 (2 ml), the combined filtrates were concentrated, and purified by preparative TLC (ethyl acetate/toluene) to give **16** (4.5 mg) in 41% yield from **1**. IR ($CHCl_3$): 3300, 1725, 1615 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 5.13 (br s, 1H (–OH)), 6.87 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 7.46–7.64 (m, 7H), 8.15 (d, J=8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 157.1, 145.5, 140.0, 134.9, 133.9, 133.3, 132.5, 130.2, 128.6, 127.6, 126.5, 126.4, 121.5, 116.3, 20.9. HR-FABMS: m/z calcd for MH^+ ($C_{22}H_{18}NO_2$) 328.1338, found 328.1341.

3-(4-Hydroxyphenyl) propionic acid allyl ester (2″). The product was obtained by the same method as the preparation of **2**, using 3-(4-hydroxyphenyl) propionic acid (6.02 g, 36.2 mmol) as a starting material (6.33 g, 85%). IR ($CHCl_3$): 3270, 1690, 1605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.62 (t, J=8.0 Hz, 2H), 2.90 (t, J=8.0 Hz, 2H), 4.57 (dd, J=5.6 Hz, J=1.8 Hz, 2H), 4.68 (br s, 1H (–OH)), 5.22 (dd, J=9.8 Hz, J=1.8 Hz, 1H), 5.28 (dd, J=16.2 Hz, J=1.8 Hz, 1H), 5.80–5.99 (m, 1H), 6.75 (d, J=8.8 Hz, 2H), 7.07 (d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 155.4, 132.7, 131.8, 129.5, 117.8, 115.5, 65.1, 35.8, 30.0. HR-FABMS: m/z calcd for MH^+ ($C_{12}H_{15}O_3$) 207.1021, found 207.1022.

Preparation of Resin 6″. Resin **6″** was synthesized by the same route and conditions as the preparation of resin **6**. IR (KBr): 2103 (–C(–TMS)–N_2), 1741 (–CO–) cm^{-1}. Anal calcd for resin **6″**: N, 1.56. Found: N, 1.26. Substrate loading of **6″** was determined to be 0.54 mmol/g by the above result and total yield from Wang resin (**1**) was also determined to be 80.6%.

7-Hydroxy-2-tetralone (18). $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol) was added to a suspension of resin **6″** (52 mg, ~0.028 mmol) in anhydrous $CHCl_3$ (4 ml), and the reaction mixture was refluxed for 40 min. Resin **17** was filtered, washed with anhydrous CH_2Cl_2 (3×2 ml), THF (3×2 ml), and ether (3×2 ml), and dried in vacuo. A 50% (v/v) solution of TFA in CH_2Cl_2 (2 ml) was added to the above resin, and the reaction mixture was agitated at room temperature for 30 min. After the resin was filtered, and washed with CH_2Cl_2 (2 ml), the combined filtrates were concentrated, and purified by preparative TLC (ethyl acetate/toluene) to give **18** (3.3 mg) in 60% yield from **1**: IR ($CHCl_3$) 3400–2800, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.54 (t, J=6.6 Hz, 2H), 2.99 (t, J=6.6 Hz, 2H), 3.53 (s, 2H), 5.00 (br s, 1H (–OH)), 6.75 (d, J=8.0 Hz, 1H), 7.03 (s, 1H), 7.10 (d, J=8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 154.3, 133.0, 129.6, 128.8, 115.7, 112.6, 44.9, 37.9, 27.7. HR-FABMS: m/z calcd for MH^+ ($C_{10}H_{11}O_2$) 163.0759, found 163.0762.

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