Twisted Amides as Selective Acylating Agents for Hydroxyl Groups under Neutral Conditions: Models for Activated Peptides during Enzymatic Acyl Transfer Reaction

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The highly twisted amide **2** served as a selective acylating agent for diols under neutral conditions. The reaction of primary−secondary diols with **2** led to the corresponding primary alkyl monopivalates. For diols containing alcoholic and phenolic hydroxyl groups, alcoholic hydroxyl groups were selectively acylated under neutral conditions, whereas, the opposite selectivity was observed under basic conditions, similar to the cases using acyl halides or acid anhydrides. Although **1** and **3** were unreactive to alcohols, **5**−**10** having substituent groups at C-4 were reactive to alcohols to give the corresponding acetates or benzoates.

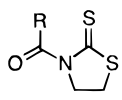
Introduction

It has been documented that amides are much less reactive toward nucleophiles than esters, and the hydrolysis of amides proceeds only under severe conditions.[1] Such properties of amides have been explained by means of the resonance of the nitrogen lone pair electron with the carbonyl group.[2] Nevertheless, enzymatically, the hydrolysis of amides readily proceeds under very mild conditions.[3] Although the exact mechanism of the enzyme-catalyzed hydrolysis of peptides has not yet been elucidated, it seems an attractive hypothesis that the C (O)−N bond of the peptides is twisted in the transition state[4] and the subsequent loss of resonance energy activates the carbonyl groups for hydrolysis. Recently, it has also been proposed that the orthogonal α-keto amide moiety of α-thrombin inhibitor cyclotheonamide B might function as an electrophilic mimic of the ArgX scissile amide bond of thrombin substrates.[5]

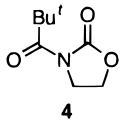
In the course of our research on the selective acylation of hydroxyl groups using active amides,[6] we have found that 3-pivaloyl-1,3-thiazolidine-2-thione (**2**)[6−8] has a high reactivity although it has the bukiest acyl group among them, furthermore, the high reactivity was ascribed to its highly twisted amide linkage, which was confirmed by ^{13}C NMR, IR, UV spectroscopic analysis and X-ray analysis.[9] Therefore, this compound is considered to be a transition state model for activated peptide during the enzymatic acyl transfer reaction.[10] Here we describe the selective acylation of diols using twisted amides as acylating agents under neutral conditions.

Results and Discussion[11]

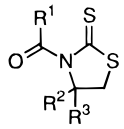
Compounds **1**−**3**[12] were readily prepared from the reaction of commercially available 1,3-thiazolidine-2-thione with corresponding acid chlorides in the presence of triethylamine. Similarly, 3-pivaloyloxazolidone (**4**),[7] which has a structure analogous to **2,** and amides **5**−**10** were also prepared by the acylation of the corresponding 1,3-oxazolidinone and 4-alkyl-1,3-thiazolidine-2-thiones, respectively.



1 R = Me
2 R = *t*-Bu
3 R = Ph



4



5 R^1 = Me, R^2 = Me, R^3 = Me
6 R^1 = Me, R^2 = *i*-Pr, R^3 = H
7 R^1 = Me, R^2 = *t*-Bu, R^3 = H
8 R^1 =Ph, R^2 = Me, R^3 = Me
9 R^1 =Ph, R^2 = *i*-Pr, R^3 = H
10 R^1 =Ph, R^2 = *t*-Bu, R^3 = H

To examine the reactivity of **1**−**4** under neutral conditions, the acylations of hexanol were studied. A mixture of hexanol and 1.1 equiv of **1** - **4** in toluene was heated at 80 °C for 18 h. Among the reagents **1**−**4**, **2** was the most reactive to quantitatively give hexyl pivalate,

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(1) For an example, see: Green, T. W.; Wuts, G. M. *Protective Groups in Organic Chemistry*, 2nd ed.; John Wiley & Sons, Inc.; New York, 1991.
(2) Pauling, L. *The Nature of the Chemical Bond*; Cornell University Press: Ithaca, NY, 1960. Robin, M. B.; Bovey, F. A.; Basch, H. In *The Chemistry of Amides*; Zabicky, J.,Ed.; Wiley-Interscience: London, 1970; pp 1−72.
(3) For an example, see: Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier Science Ltd.: Oxford, 1994.
(4) (a) Lumry, R. *The Enzymes;* Boyer, P. D.; Lardy, H.; Myrback, K., Eds.; Academic Press: New York, 1959; p 157. (b) Jencks, P. W. *Current Aspects of Biochemical Energetics*; Kaplan, N. O.; Kennedy, E. P., Eds.; Academic Press: New York, 1966; p 273. (c) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 282. (d) Lipscomb, W. N. *Tetrahedron* **1974**, *30*, 1725. (e) Walsh, C. *Enzymatic Reaction Mechanisms*; Freeman and Company: New York, 1979; Chapter 2, pp 24−48. (f) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman: New York, 1984; pp 331−344.
(5) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570.
(6) Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591.
(7) Yamada, S. *Tetrahedron Lett.* **1992**, *33*, 2171.
(8) Improved method for the synthesis of **2** was described in Experimental Section.
(9) Yamada, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1083.
(10) Brown and his co-workers have studied the hydrolysis of bicyclic distorted amides as models for activated peptide N−C═O units produced during enzyme-catalyzed hydrolysis, see: Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676. Wang, P. Q.; Bennet, A. J.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5757.
(11) For a preliminary communication, see: ref 7.
(12) Compound **1**: Chung-shi, L.; Yuen-hwa, Y.; Yao, L.; Yong-jun, L.; Ai-hsueh, L.; Chi-yi, H. *Tetrahedron Lett.*, **1981**, *22*, 3467. Compound **2**: see refs 6 and 8. Compound **3**: Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *53*, 555.

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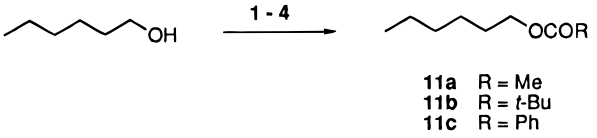
Table 1. Acylation of Hexanol with 3-Acyl-1,3-thiazolidine-2-thiones under Neutral Conditions



11a R = Me
11b R = *t*-Bu
11c R = Ph

reagent	product	yield/%[a]	recovery/%
1	**11a**	2	98
2	**11b**	97	3
3	**11c**	1	99
4	**11b**	1	99

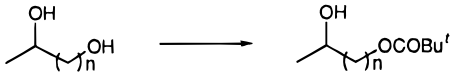
[a] Determined by GLC analysis.

although it has the bulkiest acyl group (Table 1). On the other hand, the other amides were unreactive under these reaction conditions. Since it has been known that distorted amides are more readily hydrolyzed than the planar ones,[13,14] the high reactivity of **2** should be attributed to its highly twisted amide structure. Thus, the carbonyl group of **2** is more electrophilic than those of **1** and **3** because of the loss of amide resonance. The quite low reactivity of **4**, whose structure is analogous to that of **2,** may be ascribed to the difference in the leaving property between the oxazolidinone and thiazolidine-2-thione groups.

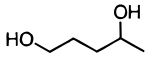
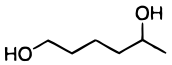
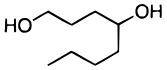
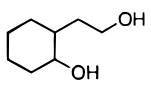
In order to explore the selectivity of **2** for the acylation of hydroxyl groups under neutral conditions, the diols containing primary and secondary hydroxyl groups were employed for the model substrates. A mixture of a diol and 1.1 equiv of **2** in toluene was stirred at 65−80 °C for 22−65 h, and the yields and products ratios were determined by GLC and ^{1}H NMR analyses. Table 2 shows these results and those for the reactions with pivaloyl chloride or pivalic anhydride to compare them with the selectivities.

The pivaloylation of 1,4-pentanediol (**12**) with **2** gave monoesters[6] in 84% yield with a small amount of the diester and the recovery of the diol (entry 1). The ratio of the primary to secondary pivalates was 27:1. On the other hand, the ratios in the reactions with pivaloyl chloride and pivalic anhydride were 3:1 and 8:1, respectively (entries 2 and 3). Similarly, diols **13**−**15** were also selectively acylated with **2** to give the corresponding primary alkyl pivalates[6] (entries 4−8). In particular, extremely high selectivity was observed in the case of 1,4-octanediol (**14**) (entry 6). Although the acylations of alcohols using the 3-acyl-1,3-thiazolidine-2-thiones have been performed by activation with a base[15] or Lewis acids such as $AgClO_4$[16] or CsF,[17] the acylations with the twisted amide **2** proceed even under neutral conditions because the amide has a torsional strain around C (O)−N bond, which reduces the activation energy for the acylation step. Compound **16** is in 1:2 equilibrium of a ring-opened alcohol **16a** having a primary hydroxyl group and an acetal **16b** having a secondary hydroxyl group in $CDCl_3$. The acylation of **16** with **2** in toluene at 80 °C for 24 h gave a 92:8 mixture of [(2-pivaloyloxy)methyl]benzaldehyde (**17**) and dimerized compound **18** (Scheme 1). On the other hand, employing pivaloyl chloride, the dimer **18** was produced as a major product. The dimer may be generated from the addition of ring-opened alcohol **16a** to an oxonium intermediate which is produced by dehydration from the acetal **16b**. Trost and Flygare have reported that similar chemoselective acylation of β-keto diols with the amide **2**, where the primary alkyl pivalates were selectively produced, during the synthesis of (−)-

Table 2. Selective Pivaloylation of Diols Containing Primary and Secondary Hydroxyl Groups

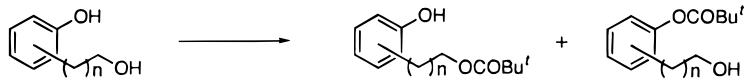


12-15 **12a-15a**

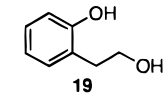
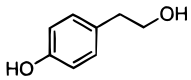
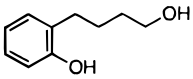
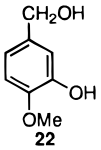
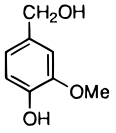
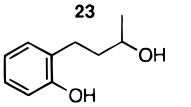
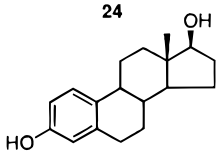
entry	diol	reagent[a)]	temp/°C	time/h	yield/%[b)] (recovery)	ratio[c)] prim. : sec.
1	 **12**	**2**	65	65	84(8)	27 : 1
2		Me_3CCOCl/Et_3N	r.t.	10	81(5)	3 : 1
3		$(Me_3CCO)_2O/Et_3N$	65	15	75(17)	8 : 1
4	 **13**	**2**	65	65	82(8)	20 : 1
5		Me_3CCOCl/Et_3N	r.t.	10	78(1)	7 : 1
6	 **14**	**2**	80	40	89(6)	44 : 1
7		Me_3CCOCl/Et_3N	r.t.	10	89(6)	4 : 1
8	 **15**	**2**	80	22	85(8)	27 : 1

a) 1.1 eq. of reagent was used. b) Yield of monoesters. GLC yield. c) Determined by GLC or ^{1}H NMR.

Table 3. Selective Pivaloylation of Diols Containing Alcoholic and Phenolic Hydroxyl Groups



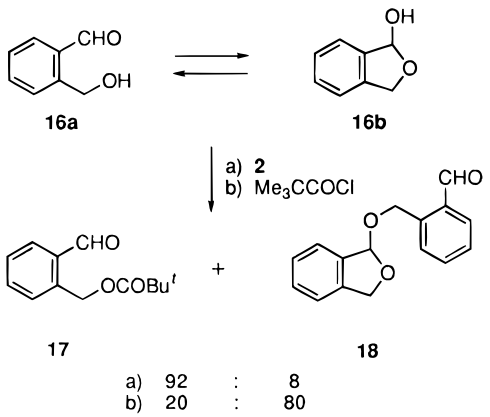
19-25 19a-25a 19b-25b

entry	diol	reagent[a]	temp/°C	time/h	yield/%[b]	ratio[c] (a : b)
1		2	65	48	91	99 : 1
2		2/Et$_3$N	65	24	85	40 : 60
3		Me$_3$CCOCl/Et$_3$N	r.t.	10	86	55 : 45
4		2	65	48	53	80 : 20
5		2/Et$_3$N	65	48	69	3 : 97
6		Me$_3$CCOCl/Et$_3$N	r.t.	10	92	5 : 95
7		2	80	18	79	98 : 2
8		Me$_3$CCOCl/Et$_3$N	r.t.	18	69	19 : 81
9		2	80	21	78	100 : 0
10		Me$_3$CCOCl/Et$_3$N	r.t.	4	77	2 : 98
11		2	80	21	76	99 : 1
12		Me$_3$CCOCl/Et$_3$N	r.t.	5	79	2 : 98
13		2	80	70	64	85 : 15
14		Me$_3$CCOCl/Et$_3$N	r.t.	24	78	0 : 100
15		2	60	90	61	67 : 33
16		Me$_3$CCOCl/Et$_3$N	r.t.	10	85	4 : 96

19 20 21 22 23 24 25

a) 1.1 eq. of reagent was used. b) Yield of monoesters. GLC yield. c) Determined by GLC and ^{1}H NMR.

Scheme 1



a) 92 : 8
b) 20 : 80

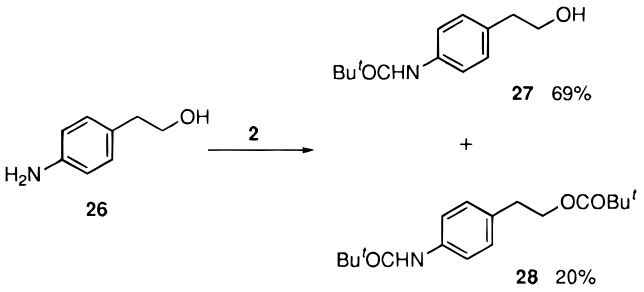
calyculin A[18] and rosefurane,[19] although the diols undergo cyclization and dehydration to give furans in the acylation with acid chlorides even in the presence of pyridine.

We then investigated the selectivity for the acylation of a variety of diols having phenolic and alcoholic hydroxyl groups. A mixture of the diols and **2** in toluene were heated at 60−80 °C for 20−60 h under neutral conditions. Table 3 shows the results and those of the reactions with pivaloyl chloride for the comparison. The alcoholic primary hydroxyl groups of **19**−**23** were acylated to yield alkyl esters exclusively (entries 1, 4, 7, 9, and 11). In contrast, the reactions with pivaloyl chloride selectively gave aryl pivalates (entries 3, 6, 8, 10, and 12). When the reactions with **2** were carried out in the

(13) Blackburn, G. M.; Plackett, J. D. *J. Chem. Soc. Perkin 2*, **1972**, 1366. *Idem. ibid.* **1973**, 981.
(14) Bennet, A. J.; Wang, Q-P. Slebocka-Tilk, H.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1990**, 112, 6383.
(15) Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E. *J. Org. Chem.* **1985**, *50*, 4072.
(16) Plusquellec, D.; Roulleau, F.; Bertho, F.; Lefeuvre, M.; Brown, E. *Tetrahedron* **1986**, *42*, 2457.
(17) Yamada, M.; Yahiro, S.; Yamano, T.; Nakatani. Y.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1990**, *127*, 824.
(18) Trost, B. M.; Flygare, J. A. *Tetrahedron Lett.* **1994**, *35*, 4059.
(19) Trost, B. M.; Flygare, J. A. *J. Org. Chem.* **1994**, *59*, 1078.

presence of triethylamine, the selectivity was reversed to give aryl pivalates similar to the reactions used pivaloyl chloride (entries 2 and 5). Even in the cases of **24** and **25**, which have secondary hydroxyl groups, the alcoholic hydroxyl groups were still predominantly acylated (entries 13 and 15). As can be seen from these results, the chemoselectivity of **2** for hydroxyl groups is on the order of primary > secondary > phenolic OH. Such selectivity is attributable to the difference in the nucleophilicities between the phenolic and alcoholic hydroxyl groups. Thus, the nucleophilicity of the phenolic hydroxyl group is less than that of the alcoholic one under neutral conditions, whereas, under basic conditions, the nucleophilicity of the latter is less than that of the former because the phenolate is more easily produced in basic media. In the case of 4-(hydroxyethyl)aniline (**26**), the amino group is selectively acylated to give an amide **27** in 69% yield together with 20% of a diacyl compound **28** (Scheme 2). The result is almost in agreement with that reported for the aminolysis of 3-hexadecanoylthiazolidine-2-thione with **26**.[20]

Scheme 2



We then turned our attention to selective acetylation and benzoylation. As described in Table 1, the reactivities of compound **1** and **3** to hexanol are quite lower than that of **2**. The low reactivity is ascribed to their planar C (O)−N geometry, which enables amide resonance and lowers the carbonyl reactivity. If alkyl substituents are introduced at C-4, the C (O)−N bond may rotate because of the steric repulsion between the acyl and the substituent groups. On the basis of this expectation, we made amides **5**−**10** and investigated their structures and reactivities.

Figure 1 shows the projections of the amide groups of **1**,**2** and **5**[21] down the C−N bonds and the values of the C (O)−N twist angles τ.[9,22] Comparing the projection of **5** with those of **1** and **2**, the C (O)−N bond of **5** is more twisted than that of **1**, though less than that of **2**. Therefore, it is clear that the introduction of a *gem*-dimethyl group at C-4 is effective for twisting the C (O)−N bond.

To elucidate the reactivity and selectivity of **5**-**10**, the acetylation and benzoylation of **19** and **22** were studied. The results are listed in Table 4. Reactions of **22** with **5**−**7** gave 3-hydroxy-4-methoxybenzyl acetate (**29a**)[23] as a major product with a small amount of 3-acetoxy-4-methoxybenzyl alcohol (**29b**)[23] and the diacetate[24] (entries 1−3). Since the reaction with **1** was very slow under the same reaction conditions, the introduction of a substituent group at C-4 is effective for accelerating the reactions. Benzoylations of **22** with **8** and **9** yielded **30a**[25] in high selectivity similar to the corresponding acetylations (entries 5 and 6). It is interesting to note that when **10** was employed for the benzoylation, the phenolic hydroxyl group was selectively acylated to give **30b** as a major product (entry 7) similar to the case used benzoyl chloride (entry 8). Details about the difference in the selectivity between **10** and the others are not clear, but following mechanistic sequence may be possible as shown in Scheme 3: generation of acyl cation by heterolysis of the C (O)−N bond, deprotonation of the phenolic hydroxyl group by the thiazolidine-2-thione anion, and the reaction of acyl cation with the phenoxide ion.

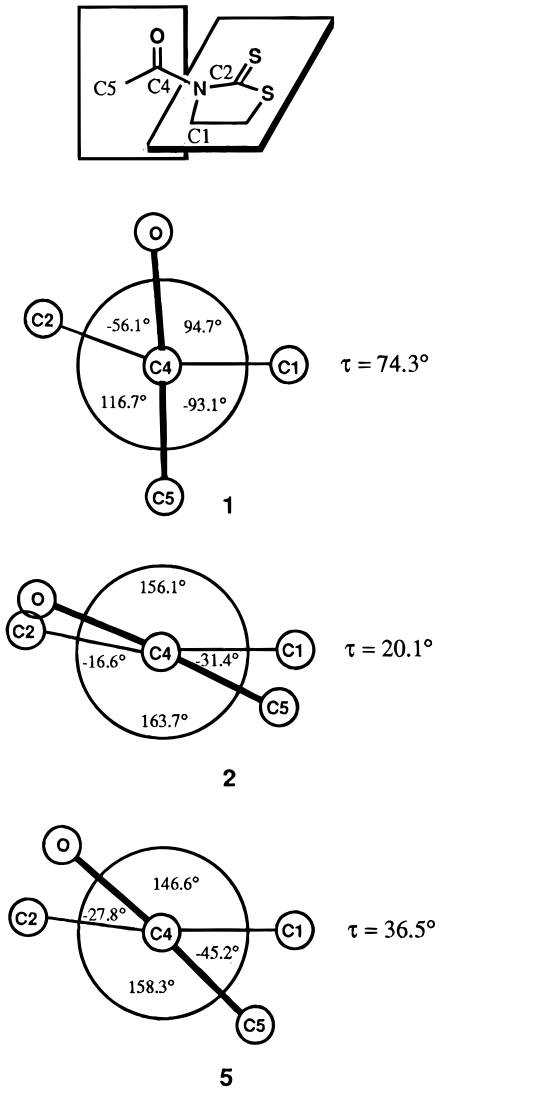
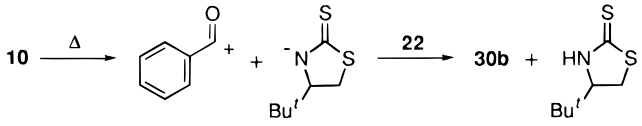


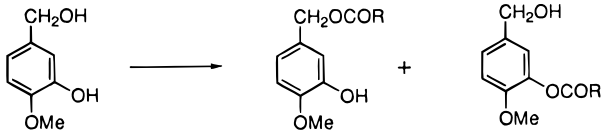
Figure 1. Projection of the amide groups of 1, 2 and 5 down the C−N bonds and the C (O)−N twist angle τ.

Scheme 3



(20) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 841.
(21) Yamada, S. *J. Org. Chem.* **1996**, *61*, 941.
(22) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169.
(23) Quick, J.; Crelling, J. K. *J. Org. Chem.* **1978**, *43*, 155.
(24) Ruderman, B. *J. Chem. Soc. India*, **1945**, *64*, 204.
(25) Yamato, M.; Hashigaki, K.; Honda, E.; Sato, K.; Koyama, T., *Chem. Pharm. Bull.* **1977**, *25*, 695.

Table 4. Selective Acetylation and Benzoylation of Diols Containing Alcoholic and Phenolic Hydroxyl Groups



22 **29a**: R = Me, **30a**: R = Ph **29b**: R = Me, **30b**: R = Ph

entry	reagent[a]	temp/°C	time/h	yield/%[b]	products	ratio (a : b)[c]
1	**5**	reflux	72	72	**29**	89 : 11
2	**6**	reflux	120	66	**29**	69 : 31
3	**7**	80	72	64	**29**	86 : 14
4	CH_3COCl/Et_3N	r.t.	24	70	**29**	20 : 80
5	**8**	reflux	72	79	**30**	98 : 2
6	**9**	reflux	72	76	**30**	97 : 3
7	**10**	80	72	69	**30**	7 : 93
8	$PhCOCl/Et_3N$	r.t.	24	89	**30**	3 : 97

a) 1.1 eq. of reagent was used. b) Yield of monoesters. GLC yield. c) Determined by GLC and/or ^1H NMR.

Summary

We have described selective acylations of hydroxyl groups using twisted amides under neutral conditions. The reaction of primary−secondary diols with **2** led to the corresponding primary monopivalates. For diols containing alcoholic and phenolic hydroxyl groups, the alcoholic hydroxyl groups were selectively acylated. Since the selectivity was completely opposite to that of the acyl halides or acid anhydrides, the present method is complimentary to the general ones. Another merit of the present method is that it will be applied to the compounds which are labile to acids or bases, because the reaction can be conducted under neutral conditions.

The present results indicate that it is possible to control the electrophilicity of an amide carbonyl by controlling the C (O)−N twist angle. Since it is postulated that the C (O)−N bond of peptide substrates are twisted and are activated during enzyme-catalyzed hydrolysis, the present twisted amides are considered to be models for the activated peptides.

Experimental Section

General. Melting points are uncorrected. Silica gel chromatography was carried out using Wakogel C-200 or Florisil (100−200 mesh). GLC was carried out using a 5% SE-30 or 10% DC-550 column (2 m x 3 mm). Infrared spectra were obtained as neat films between NaCl plates or as KBr pellets. ^1H NMR spectra were recorded at 270 and 400 MHz in $CDCl_3$, and the chemical shifts were reported relative to internal $SiMe_4$. ^{13}C NMR spectra were recorded at 100.4 MHz as 0.5 M solution in $CDCl_3$, and the chemical shifts were reported relative to internal $SiMe_4$. High- and low-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact.

Preparation of 3-Pivaloyl-1,3-thiazolidine-2-thione[6] (2). To a solution of 1,3-thiazolidine-2-thione (3.0 g, 25.2 mmol) and triethylamine (5.0 g, 50 mmol) in CH_2Cl_2 (60 mL) was added dropwise pivaloyl chloride (3.62 g, 30.2 mmol) at 0 °C. The solution was stirred for 2 h at 0 °C. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a solid. This was dissolved in hexane−ether, the insoluble precipitate was removed by filtration, and the filtrate was recrystallized from hexane-ether to yield 4.5 g of pure pale yellow plates in 88% yield.

Preparation of 3-Acetyl-4-isopropyl-1,3-thiazolidine-2-thione (6). To a solution of 4-isopropyl-1,3-thiazolidine-2-thione[26] (500 mg, 3.1 mmol) and triethylamine (0.7 mL) in dry CH_2Cl_2 (15 mL) was added dropwise acetyl chloride (290 mg, 3.7 mL) at 0 °C. The solution was stirred for 8 h at room temperature. The solution was washed with water and dried over anhydrous $MgSO_4$. After concentration *in vacuo* the residue was subjected to column chromatography (Florisil) using a 5:1 mixture of hexane−ethyl acetate as an eluent solvent to give 589 mg of an oily amide **6** in 93% yield: IR (neat) 2964, 1698, 1368, 1276, 1210, 1074 cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (d, J = 6.84 Hz, 3 H), 1.06 (d, J = 6.84 Hz, 3 H), 2.38 (dt, J = 6.3, 6.8 Hz, 1 H), 2.78 (s, 3 H), 3.03 (d, J = 11.2 Hz, 1 H), 3.51 (dd, J = 8.3, 11.2 Hz, 1 H), 5.15 (t, J = 6.8, 8.3 Hz, 1 H); ^{13}C NMR (400 MHz) δ 17.7, 19.0, 26.9, 30.4, 30.7, 71.2, 170.6, 203.2; MS *m/z* 203 (M^+, 79), 161 (17), 118 (100), 69 (24); HRMS calcd for $C_8H_{13}NOS_2$ 203.0439, found 203.0411.

Preparation of 3-Acetyl-4-*tert*-butyl-1,3-thiazolidine-2-thione (7). Concentrated sulfuric acid (7.5 g) was added dropwise to a round bottom flask containing *tert*-leucinol (3.0 g, 25.6 mmol) at 0 °C and the mixture was vigorously stirred for 2 h. Then, potassium *O*-ethyl dithiocarbonate in CH_2Cl_2 (6.1 g, 38.4 mmol), 2 N NaOH (100 mL), and ethanol (30 mL) were added to the reaction mixture, and the solution was heated at 80 °C for 2 h. After cooling to room temperature, the solution was acidified with 2 N HCl and extracted with three 50 mL portions of $CHCl_3$. The combined extracts were washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave crude mixture of compounds, which was subjected to column chromatography (silica gel) to give two crystalline compounds. The less polar fraction was 4-*tert*-butyl-1,3-thiazolidine-2-thione (**31**)(3.2 g): mp 143−144 °C; IR (KBr) 3154, 2957, 1506, 1293, 1042, 967, 663 cm^{-1}; ^1H NMR (270 MHz) δ 1.02 (s, 9 H), 3.42 (m, 2 H), 4.04 (t, J = 8.79 Hz, 1 H), 7.28 (br s, 1 H); ^{13}C NMR (400 MHz) δ 25.9, 34.4, 34.6, 73.6, 201.5; MS *m/z* 175 (M^+, 51), 132 (36), 118 (69), 73 (100); HRMS calcd for $C_7H_{13}NS_2$ 175.0490, found 175.0466. The polar fraction was 4-*tert*-butyl-1,3-oxazolidine-2-thione (**32**)(0.8 g): mp 153−156 °C; IR (KBr) 3183, 2962, 1534, 1285, 1183 cm^{-1}; ^1H NMR (270 MHz) δ 0.94 (s, 9 H), 3.78 (dd, J = 9.4, 6.2 Hz, 1 H), 4.47 (dd, J = 9.4, 6.2 Hz, 1 H); MS *m/z* 159 (M^+,

(26) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.

100), 131 (30); HRMS calcd for $C_7H_{13}NOS$ 159.0718, found 159.0737. To a solution of 4-*tert*-butyl-1,3-thiazolidine-2-thione (300 mg, 1,7 mmol) and triethylamine (1.0 mL) in dry CH_2Cl_2 (15 mL) was added dropwise acetyl chloride (175 mg, 2,2 mmol) at 0 °C, and the solution was stirred for 2 h at room temperature. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give an yellow oil. This was subjected to column chromatography (Florisil) to give amide **7** (350 mg, 94%): IR (neat) 2965, 1699, 1369, 1272, 1193, 1085, 1033 cm^{-1}; ^1H NMR (400 MHz) δ 1.04 (s, 9 H), 2.78 (s, 3 H), 3.10 (d, J = 12.7Hz, 1 H), 3.53 (dd, J = 8.3, 12.7 Hz, 1 H), 5.31 (d, J = 8.3, 1 H); ^{13}C NMR (400 MHz) δ 26.7, 26.8, 30.4, 38.0, 72.0, 170.3, 205.3; MS *m*/*z* 217 (M^+, 68), 161 (15), 118 (100), 55 (38); HRMS calcd for $C_9H_{15}NOS_2$ 217.0595, found 217.0549.

Preparation of 3-Benzoyl-4,4-dimethyl-1,3-thiazolidine-2-thione (8). To a solution of 4,4-dimethyl-1,3-thiazolidine-2-thione (2.0 g, 13.6 mmol) and triethylamine (3.0 mL) in 30 mL of dry CH_2Cl_2 was added dropwise benzoyl chloride (2.3 g, 16 mmol) at 0 °C. The solution was stirred for 20 h at room temperature. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give a yellow solid. This was recrystallized from ether to give pure amide **8** (2.8 g, 82%): mp 154−156 °C; IR (KBr) 1693, 1322, 1272, 1164, 998, 705 cm^{-1}; ^1H NMR (270 MHz) δ 1.72 (s, 6 H), 3.42 (s, 2 H), 7.43 (t, J = 7.3 Hz, 2 H), 7.56 (t, J = 7.3 Hz, 1 H), 7.78 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (400 MHz) δ 25.1, 25.2, 45.5, 73.7, 128.7, 129.8, 133.4, 134.3, 172.7, 200.8; MS *m*/*z* 251 (M^+, 14), 106 (6), 105 (100), 77 (40); HRMS calcd for $C_{12}H_{13}NOS_2$ 251.0439, found 251.0457.

Preparation of 3-Benzoyl-4-isopropyl-1,3-thiazolidine-2-thione (9). To a solution of 4-isopropyl-1,3-thiazolidine-2-thione (1.0 g, 6.2 mmol) and triethylamine (1.7 mL) in dry CH_2Cl_2 (50 mL) was added dropwise benzoyl chloride (1.05 g, 7.4 mmol) at 0 °C. The solution was stirred for 20 h at room temperature. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a yellow solid. This was recrystallized from hexane−ether to give pure amide **9** (1.42 g, 86%): mp 88−90 °C; IR (KBr) 1691, 1275, 1215, 1190, 1149, 1122, 1028, 973, 728, 692, 664 $cm^{-1;}$ ^1H NMR (400 MHz) δ 1.05 (d, J = 6.8 Hz, 6 H), 2.53 (dt, J = 4.4, 6.8 Hz, 1 H), 3.38 (dd, J = 7.8, 11.2 Hz, 1 H), 3.48 (dd, J = 7.8, 11.2 Hz, 1 H), 4.94 (dt, J = 4.9, 7.8 Hz, 1 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.54 (t, J = 7.3 Hz, 1 H), 7.90 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.3, 19.2, 29.5, 30.7, 73.1, 128.5, 129.9, 133.0, 133.9, 171.7, 203.0; MS *m*/*z* 265 (M^+, 17), 194 (2), 105 (100), 77 (38); HRMS calcd for $C_{13}H_{15}NOS_2$ 265.0595, found 265.0637.

Preparation of 3-Benzoyl-4-*tert*-butyl-1,3-thiazolidine-2-thione (10). To a solution of 4-*tert*-butyl-1,3-thiazolidine-2-thione (330, 1.89 mg) and triethylamine (0.5 mL) in dry CH_2Cl_2 (15 mL) was added dropwise benzoyl chloride (320 mg, 2.26 mmol) at 0 °C. The solution was stirred for 5 h at room temperature. The reaction mixture was washed with water, dried over anhydrous MgSO4, and concentrated to give a yellow solid. This was recrystallized from hexane−ether to give pure amide **10** (460 mg, 87%): mp 110−112 °C; IR (KBr) 1703, 1365, 1319, 1265, 1221, 1141, 802, 692, 667 cm^{-1}; ^1H NMR (400 MHz) δ 1.10 (s, 1 H), 3.30 (dd, J = 2.4, 11.7 Hz, 1 H), 3.73 (dd, J = 9.3, 11.7 Hz, 1 H), 5.15 (dd, J = 2.4, 9.3 Hz, 1 H), 7.41 (t, J = 7.3 Hz, 2 H), 7.54 (t, J = 7.3 Hz, 1 H), 7.80 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (400 MHz) δ 26.8, 31.3, 37.9, 75.0, 128.2, 130.3, 132.9, 133.8, 171.8, 203.1; MS *m*/*z* 279 (M^+, 21), 105 (100), 77 (16); HRMS calcd for $C_{14}H_{17}NOS_2$ 279.0751, found 279.0724.

General Procedure for the Selective Acylation of Diols with Twisted Amides 2, 5−10. A mixture of a diol (0.3 mmol) and an amide (0.33 mmol) in dry toluene (5 mL) was stirred at 60−80 °C or refluxing temperature for 18−90 h. The reaction mixture was concentrated and separated by preparative TLC using a 3:1 mixture of hexane and ethyl acetate as an eluent solvent to yield esters.

General Procedure for the Acylation of Diols with Acyl Halides. To a mixture of a diol (0.3 mmol) and triethylamine (0.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise acyl chloride (0.33 mmol) at 0 °C. The solution was stirred at room temperature for overnight. The reaction mixture was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent to give crude compounds, which was separated by preparative TLC using a 3:1 mixture of hexane and ethyl acetate as an eluent solvent to yield esters.

1-(Pivaloyloxy)octan-4-ol (14a): IR (neat) 3447, 2959, 1731, 1481, 1286, 1162 cm^{-1}; ^1H NMR (400 MHz) δ 0.91 (t, J = 7.1 Hz, 3 H), 1.20 (s, 9 H), 3.63 (br s, 1 H), 4.09 (t, J = 6.6 Hz, 2 H); MS *m*/*z* 231 (M^+ + 1, 1), 213 (1), 171 (3), 144 (8), 103 (60), 85 (38), 71 (100), 57 (98); HRMS calcd for $C_{13}H_{27}O_3$ (M^+ + 1) 231.1960, found 231.1955.

2-[(Pivaloyloxy)methyl]benzaldehyde (17): IR (neat) 1731, 1677, 1580, 1321, 1290, 1142, 911, 741 cm^{-1}; ^1H NMR (270 MHz) δ 1.25 (s, 9 H), 5.54 (s, 2 H), 7.51−7.89 (m, 4 H), 10.21 (s, 1 H); MS *m*/*z* 220 (M^+, 1), 205 (1), 151 (23), 135 (67), 118 (40), 105 (31), 77 (36), 57 (100); HRMS calcd for $C_{13}H_{16}O_3$ 220.1100, found 220.1067.

1,3-Dihydroisobenzofuranyl 2-formylbenzyl ether (18): IR (neat) 3055, 2890, 2750, 1695, 1602, 1465, 1370, 1192, 1076, 1003, 755 cm^{-1}; ^1H NMR (270 MHz) δ 5.06−5.41 (m, 4 H), 6.41 (d, J = 2.0 Hz, 1 H), 7.28−7.87 (m, 8 H), 10.27 (s, 1 H); MS *m*/*z* 135 (9), 118 (100), 105 (11), 89 (82); HRMS calcd for $C_8H_7O_2$ (M^+ − dihydrobenzofuranyl group) 135.0446, found 135.0425.

2-[2-(Pivaloyloxy)ethyl]phenol (19a): IR (neat) 3418, 1704, 1481, 1458, 1292 1233, 1170, 753 cm^{-1}; ^1H NMR (400 MHz) δ 1.19 (s, 9 H), 2.95 (t, J = 7.32 Hz, 2 H), 4.28 (t, J = 7.32 Hz, 2 H), 6.84 (t, J = 7.6 Hz, 2 H), 7.14 (t, J = 7.6 Hz, 2H); MS *m*/*z* 222 (M^+, 8), 138 (4), 120 (100), 107 (11), 55 (45); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1275.

2-(2-Hydroxyethyl)phenyl pivalate (19b): IR (neat) 3398, 2974, 1750, 1481, 1280, 1261, 1174, 1121, 1044, 750 cm^{-1}; ^1H NMR (270 MHz) δ 1.38 (s, 9 H), 2.79 (t, J = 6.4 Hz, 2 H), 3.81 (t, J = 6.4 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 1 H), 7.01 (d, J = 7.8 Hz, 1 H), 7.15−7.30 (m, 2 H); MS *m*/*z* 222 (M^+, 0.5), 138 (8), 120 (100), 107 (25), 55 (82); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1232.

4-[2-(Pivaloyloxy)ethyl]phenol (20a): IR (neat) 3403, 2973, 1704, 1517, 1292, 1225, 1169 cm^{-1}; ^1H NMR (270 MHz) δ 1.16 (s, 9 H), 2.86 (t, J = 6.8 Hz, 2 H), 4.23 (t, J = 6.8 HZ, 2 H), 5.02 (br s, 1 H), 6.75 (d, J = 8.8 Hz, 2 H), 7.08 (d, J = 8.8 Hz, 2 H); MS *m*/*z* 222 (M^+, 2), 138 (5), 120 (100), 107 (18); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1259.

4-(2-Hydroxyethyl)phenyl pivalate (20b): mp 46−48 °C; IR ($CHCl_3$) 3380, 2975, 1751, 1508, 1199, 1167, 1123, 1048 cm^{-1}; ^1H NMR (400 MHz) δ 1.35 (s, 9 H), 2.86 (t, J = 6.6 Hz, 2 H), 3.85 (t, J = 6.6 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H); MS *m*/*z* 222 (M^+, 28), 138 (63), 107 (100), 55 (80); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1240.

2-[4-(Pivaloyloxy)butyl]phenol (21a): IR (neat) 3422, 2960, 1703, 1457, 1293, 1173, 753 cm^{-1}; ^1H NMR (270 MHz) δ 1.20 (s, 9 H), 1.64−1.76 (m, 4 H), 2.65 (t, J = 7.3 Hz, 2 H), 4.12 (t, J = 6.1 Hz, 2 H), 5.04 (s, 1 H), 6.76 (d, J = 8.1 Hz, 1 H), 6.86 (t, J = 7.6 Hz, 1 H), 7.05−7.11 (m, 2 H); MS *m*/*z* 250 (M^+, 37), 166 (13), 148 (100), 133 (8), 120 (20), 107 (44); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1589.

2-(4-Hydroxybutyl)phenyl pivalate (21b): IR (neat) 3395, 2937, 1749, 1480, 1122 cm^{-1}; ^1H NMR (270 MHz) δ 1.38 (s, 9 H), 1.58−1.67 (m, 4 H), 2.54 (t, J = 7.3 Hz, 2 H), 3.63 (t, J = 5.7 Hz, 2 H), 6.96 (dd, J = 1.7, 7.8 Hz, 1 H), 7.11−7.26 (m, 3 H); MS *m*/*z* 250 (M^+, 64), 166 (15), 148 (100), 133 (11), 120 (18), 107 (52); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1593.

3-Hydroxy-4-methoxybenzyl pivalate (22a): IR (neat) 3448, 2972, 1725, 1515, 1280, 1159, 1131, 1032 cm^{-1}; ^1H NMR (270 MHz) δ 1.21 (s, 9 H), 3.89 (s, 3 H), 5.00 (s, 2 H), 5.18 (br s, 1 H), 6.82 (d, J = 0.7 Hz, 2 H), 6.92 (s, 1 H); MS *m*/*z* 238 (M^+, 24), 154 (7), 137 (100), 122 (14), 57 (54); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1196.

4-Methoxy-3-(pivaloyloxy)benzyl alcohol (22b): IR (neat) 3420, 2974, 1753, 1514, 1269, 1125, 1030 cm^{-1}; ^1H NMR (270 MHz) δ 1.36 (s, 9 H), 3.80 (s, 3 H), 4.58 (s, 2 H), 6.92 (d, J = 8.3 Hz, 1 H), 7.02 (d, J = 2.0 Hz, 1 H), 7.15 (dd, J = 2.2, 8.3 Hz, 1 H); MS *m/z* 238 (M^+, 4), 154 (21), 137 (4), 57 (100); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1180.

4-Hydroxy-3-methoxybenzyl pivalate (23a): IR (neat) 3520, 2970, 1725, 1515, 1280, 1157, 1131 cm^{-1}; ^1H NMR (270 MHz) δ 1.21 (s, 9 H), 3.89 (s, 3 H), 5.03 (s, 2 H), 6.85 (d, J = 5.9 Hz, 1 H), 6.86 (d, J = 5.9 Hz, 1 H), 6.88 (s, 1 H); MS *m/z* 238 (M^+, 54), 137 (77), 119 (100); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1176.

3-Methoxy-4-(pivaloyloxy)benzyl alcohol (23b): IR (neat) 3469, 2973, 1754, 1513, 1269, 1126, 1030 cm^{-1}; ^1H NMR (270 MHz) δ 1.37 (s, 9 H), 3.81 (s, 3 H), 4.66 (s, 2 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.90 (d, J = 8.1 Hz, 1 H), 6.97 (s, 1 H); MS *m/z* 238 (M^+, 71), 154 (100); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1221.

2-[3-(Pivaloyloxy)butyl]phenol (24a): IR (neat) 3447, 2977, 1699, 1457, 1184, 752 cm^{-1}; ^1H NMR (270 MHz) δ 1.22 (s, 9 H), 1.24 (d, J = 6.4 Hz, 3 H), 1.79−1.94 (m, 4 H), 2.65 (m, 2 H), 4.93 (m, 1 H), 5.35 (s, 1 H), 6.75 (d, J = 7.3 Hz, 1 H), 6.85 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.3 Hz, 2 H); MS *m/z* 250 (M^+, 65), 233 (3), 148 (100), 133 (30), 119 (11), 107 (44); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1523.

2-(3-Hydroxybutyl)phenyl pivalate (24b): IR (neat) 3395, 2969, 1749, 1123 cm^{-1}; ^1H NMR (270 MHz) δ 1.20 (d, J = 6.4 Hz, 3 H), 1.38 (s, 9 H), 1.44−1.76 (m, 2 H), 2.45−2.62 (m, 2 H), 3.54−3.68 (m, 1 H), 6.96 (dd, J = 2.0, 8.1 Hz, 1 H), 7.12−7.27 (m, 3 H); MS *m/z* 250 (M^+, 25), 233 (5), 217 (4), 148 (100), 133 (20), 107 (24); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1535.

17β-(Pivaloyloxy)estran-3-ol (25a): mp 232−234 °C; IR (KBr) 3464, 1713, 1501, 1303, 1187, 608 cm^{-1}; ^1H NMR (400 MHz) δ 0.84 (s, 3 H), 1.21 (s, 9 H), 4.66 (br t, J = 8.0 Hz, 1 H), 6.57 (d, J = 2.4, 1 H), 6.63 (dd, J = 2.4, 8.3 Hz, 1 H), 7.14 (d, J = 8.3 Hz, 1 H); MS *m/z* 356 (M^+, 17), 341 (5), 120 (35), 81 (64), 69 (100); HRMS calcd for $C_{23}H_{32}O_3$ 356.2351, found 356.2359.

3-(Pivaloyloxy)estran-17β-ol (25b): mp 183−185 °C; IR (KBr) 3554, 1742, 1483, 1149, 1130 cm^{-1}; ^1H NMR (270 MHz) δ 0.78 (s, 3 H), 1.27 (s, 9 H), 3.73 (t, J = 8.5 Hz, 1 H), 6.76 (br s, 1 H), 6.81 (dd, J = 2.4, 8.3 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 1 H); MS *m/z* 356 (M^+, 25), 341 (8), 272 (27), 86 (76), 69 (100); HRMS calcd for $C_{23}H_{32}O_3$ 356.2351, found 356.2323.

4-(2-Hydroxyethyl)trimethylpropionanilide (27): mp 112.5−114.5 °C; IR (KBr) 3440, 3320, 1659, 1608, 1538, 1413, 1326, 1245, 1163, 1069, 1021, 818, 602 cm^{-1}; ^1H NMR (400 MHz) δ 1.31 (s, 9 H), 2.82 (t, J = 6.6 Hz, 2 H), 3.81 (t, J = 6.6 Hz, 2 H), 7.16 (d, J = 8.5 Hz, 2 H), 7.45 (d, J = 8.5 Hz, 2 H); MS *m/z* 221 (M^+, 10), 190 (11), 106 (40), 57 (100); HRMS calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1431.

4-[2-(Pivaloyloxy)ethyl]trimethylpropionanilide (28): mp 151−152 °C; IR (KBr) 3448, 1726, 1659, 1604, 1526, 1163 cm^{-1}; ^1H NMR (400 MHz) δ 1.16 (s, 9 H), 1.31 (s, 9 H), 2.89 (d, J = 6.8 Hz, 2 H), 4.23 (d, J = 6.8 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.5 Hz, 2 H); MS *m/z* 305 (M^+, 2), 262 (1), 203 (22), 119 (17), 106 (8), 57 (100); HRMS calcd for $C_{18}H_{27}NO_3$ 305.1991, found 305.1973.

4-Methoxy-3-(benzoyloxy)benzyl alcohol (30b): IR (KBr) 3444, 2974, 1735, 1511, 1268, 1022 cm^{-1}; ^1H NMR (270 MHz) δ 3.82 (s, 3 H), 4.65 (s, 2 H), 6.99 (d, J = 8.3 Hz, 1 H), 7.19 (d, J = 2.1 Hz, 1 H), 7.24 (dd, J = 8.3, 2.1 Hz, 1 H), 7.51 (t, J = 8 Hz, 2 H), 7.63 (t, J = 8 Hz, 1 H), 8.21 (dd, J = 8, 1 Hz, 2 H) ; MS *m/z* 258 (M^+, 23), 136 (5), 105 (100); HRMS calcd for $C_{15}H_{14}O_4$ 258.0892, found 258.0874.

Supporting Information Available: ^1H NMR spectra of compounds **6**−**10**, **14a**, **17**, **18**, **19a**-**25a**, **19b**-**25b**, **27**, **28**, **30b**, **31**, and **32** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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