Deprotection of Carboxylic Esters of β-Lactam Homologues. Cleavage of *p*-Methoxybenzyl, Diphenylmethyl, and *tert*-Butyl Esters Effected by a Phenolic Matrix

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p-Methoxybenzyl, diphenylmethyl, and *tert*-butyl esters were deprotected by gentle heating in phenol. This method of ester cleavage played an important role in β-lactam synthesis. The mechanism of the reaction is believed to involve a proton relay through a hydrogen-bonded phenolic matrix.

Introduction

The protection and deprotection of carboxyl groups often are the crucial steps in multistep syntheses of complex molecules. *p*-Methoxybenzyl (PMB), diphenylmethyl (BH), and *tert*-butyl (*t*-Bu) groups have been used to protect carboxyl groups. These protecting groups can be removed by treatment with protic acids,[1] e.g., trifluoroacetic acid (TFA),[2] formic acid,[3] or combinations of Lewis acids with anisole[4] or a thiol.[5] TFA is habitually used on the laboratory scale. In most cases, however, a stoichiometric amount, or even a large excess of acid is required to complete the reaction. This requirement frequently limits the use of esters as protecting groups for acid-labile compounds.

In the course of a study of the synthesis of β-lactam antibiotics,[6] PMB, BH, and *t*-Bu groups were advantageously employed to protect carboxyl groups. However, the application of conventional methods of ester cleavage often led to low yields of the desired β-lactam carboxylic acids, for the latter compounds are unstable under acidic conditions. However, we wish to report that this problem can be obviated by employing phenol as the reaction medium. Under such conditions, the cleavage of the esters involves an acid-catalyzed process that proceeds via a proton relay through a hydrogen-bonded phenolic matrix (Scheme I).

Results and Discussion

The cleavage of the cephalosporin PMB ester **1a** by treatment with TFA required more than 4 equiv of the acid dissolved in anisole. Treatment of **1a** with 3 equiv of the acid gave, after 2 h at 30 °C, the carboxylic acid **2** in only 55% yield, together with unchanged **1a** (39%). In contrast, when the solvent was phenol, treatment of **1a** with an equimolar amount of TFA at 45 °C for 1 h afforded the acid **2** in 91% yield (entry 1, Table I). *p*- and *m*-(*p*-Methoxybenzyl)phenol (**3a** and **4a**) were also isolated, in 57 and 15% yield, respectively. The amount of TFA that was required could be reduced to 0.5–0.1 equiv if slightly modified reaction conditions were employed (entries 2 and 3).[7] Other common acids, e.g., hydrochloric acid, sulfuric acid, potassium bisulfate, and *p*-toluenesulfonic acid (*p*-TsOH), could also be used (entries 4–7) in place of TFA.

Table I. Effect of Acid Catalysts on the Deprotection of PMB Ester 1a in Phenol

				yield[a] (%)	
entry	acid (equiv)	*T* (°C)	time (h)	**2**	recovered **1a**
1	TFA (1)	45	1.0	91[b]	0
2	TFA (0.5)	45	1.0	95	5
3	TFA (0.1)	60	1.2	96	3
4	HCl (0.03)	45	1.0	91	0
5	H_2SO_4 (0.05)	45	1.0	89	0
6	*p*-TsOH (0.05)	45	1.0	92	0
7	$KHSO_4$ (1.2)	45	1.0	86	0
8	none	45	1.0	30	69
9	none	60	1.0	77	23
10	none	60	3.0	96	1

[a] Determined by HPCL unless otherwise noted. The HPLC conditions were as follows: for **1a**, column ChemoPak Nucleosil 5C18 (4.0 Φ × 200 mm), mobile phase CH_3CN/H_2O, 47:53, flow rate 1.0 mL/min, detection UV at 254 nm; for **2**, column ChemcoPak Nucleosil 5C18 (4.0Φ × 200 mm), mobile phase CH_3CN/H_2O, 27:73 + 0.005 M PIC B-6, flow rate 0.9 mL/min, detection UV at 254 nm. [b] Isolated yield.

Table II. Deprotection of Carboxylic Esters 1 in Phenol

					yield[a] (%)	
entry	ester	acid (equiv)	*T* (°C)	time (h)	**2**	recovered **1**
1	**1b**	TFA (0.5)	45	1.0	92	0
2	**1c**	TFA (1)	45	2.0	38	45
3	**1c**	HCl (0.5)	45	2.0	64	29
4	**1d**	TFA (1)	45	1.0	0	100
5	**1e**	TFA (1)	45	1.0	0	100

[a] Determined by HPLC. The HPLC conditions were as follows: for **1b**, **1d**, and **1e**, same as described for **1a** in Table I; for **1c**, columnm YMC-Pack AM-312 ODS (6.0Φ × 150 mm), mobile phase CH_3CN/H_2O, 50:50 + 0.1% acetic acid, flow rate 2.0 mL/min, detection UV at 254 nm; for **2**, same as described in Table I.

(1) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; pp 152–192.
(2) Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.
(3) Kametani, T.; Sekine, H.; Honda, T. *Chem. Pharm. Bull.* **1982**, *30*, 4545.
(4) Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.* **1979**, 2793.
(5) Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett*, **1978**, 5211.
(6) Torii, S.; Tanaka, H.; Oshima, T.; Sasaoka, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3975.

(7) A precedent exists in the case of the hydrolysis of *N*-(benzyloxycarbonyl)-L-proline benzhydryl ester by TFA and phenol. However, a relatively large amount of TFA (1 mL) and phenol (0.2 g) were used to cleave 0.41 g (1 mmol) of the ester. See: Stelakatos, G. C.; Paganou, A.; Zervas, L. *J. Chem. Soc. C* **1966**, 1191.

0022-3263/91/1956-3633$02.50/0

Scheme I

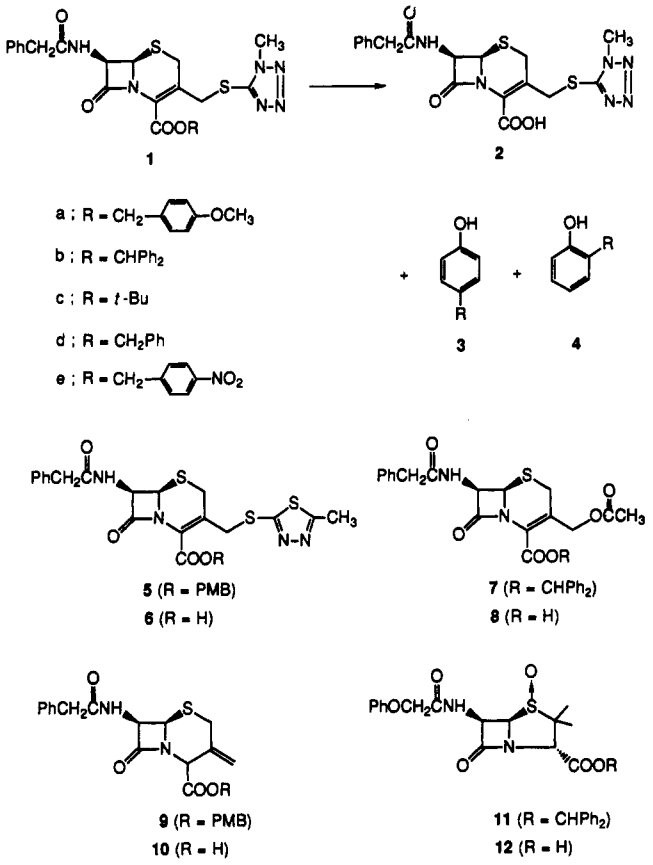


Table III. Deprotection of β-Lactam Carboxylic Esters in Phenol

entry	ester	acid (equiv)	T (°C)	time (h)	product	yield[a] (%)
1	5	TFA (1)	45	0.5	6	93
2	7	TFA (0.5)	45	1.0	8	93
3	9	HCl (0.25)	45	1.0	10	78
4	11	TFA (1)	45	1.0	12	91
5	13	HCl (1.1)	45	1.5	14	81
6	13	HCl (2.2)	45	1.5	15	92

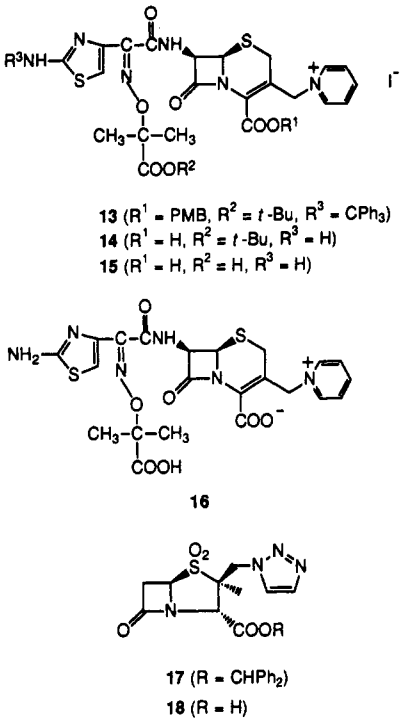
[a] Isolated yield.

Surprisingly, the reaction proceeded even in the absence of acid catalyst. Thus, when ester **1a** was heated in pure phenol at 45 °C for 1 h (entry 8), the carboxylic acid **2** was obtained in 30% yield. At 60 °C, the reaction was complete within 3 h and afforded **2** in 96% yield (entry 10).

The cleavage of the BH and *t*-Bu esters **1b** and **1c** in phenolic solution afforded the acid **2** in 92 and 64% yield, respectively (entries 1–3, Table II). However, the benzyl and *p*-nitrobenzyl esters **1d** and **1e** were recovered intact after 1 h of heating at 45 °C in phenol containing 1 equiv of TFA (entries 4 and 5). About 30% of the ester **1c** was recovered after 2 h of treatment with 0.5 equiv of hydrochloric acid in phenol. This result indicated that cleavage of *t*-Bu esters proceeds more slowly than that of PMB and BH esters (entry 3).

The versatility of the method was demonstrated by applying it to the cleavage of various β-lactam carboxylic esters. These included cephems and acid-labile penams. Some results are summarized in Table III. With *exo*-methylenecepham **9**, isomerization of the double bond to the endocyclic position to form a Δ^3-cephem did not accompany cleavage of the PMB ester (entry 3). The penicillin BH ester **11** was cleaved to the acid **12** in high yield (entry 4). The PMB, *t*-Bu, and *N*-trityl groups of compound **13** were all removed by treatement with 2.2 equiv of hydrochloric acid. However, partial cleavage of **13** upon exposure to 1.1 equiv of hydrochloric acid in phenol gave **14**, in which the *t*-Bu ester remained intact (entry 5). The *t*-Bu ester **14** could be cleaved by treatment with 2.2 equiv of hydrochloric acid in phenol to afford **15**. Compound **15** was eventually converted to ceftazidime **16**, a third generation cephalosporin antibiotic.[8]

Scheme II



It should be noted that the *N*-tritylamino group of **13** could also be deprotected and that the PMB ester could be cleaved while leaving the *t*-Bu ester intact. Also, syn–anti isomerization of the imino ether group of **13** was not observed (entries 5 and 6). These results clearly showed that the various functional groups of **13** could tolerate the reaction conditions employed (Scheme II).

The deprotection of the BH ester **17** to tazobactam **18**, a new β-lactamase inhibitor,[9] again demonstrated the versatility of the present method. Thus, the cleavage of the BH ester **17** in *m*-cresol afforded **18** in 90% yield. In contrast, the conventional methods (TFA/anisole,[2] HCO-OH,[3] or $AlCl_3$/anisole[4]) failed due to the instability of **18** under acidic conditions (Table IV).[10]

The formation of **3** and **4** during the cleavage of **1** (vide supra) suggested that phenol played an important role in the reaction by trapping benzyl or *tert*-butyl cations.

(8) (a) O'Callaghan, C. H.; Livermore, D. G. H.; Newall, C. E. *Ger. Pat.* 2921316 (*Chem. Abstr.* 1980, *92*, 198413c). (b) O'Callaghan, C. H.; Acred, P.; Harper, P. B.; Ryan, D. M.; Kirby, S. M.; Harding, S. M. *Antimicrob. Agents Chemother.* 1980, *17*, 876.

(9) (a) Hall, T. W.; Maiti, S. N.; Micetich, R. G.; Spevak, P.; Yamabe, S.; Ishida, N.; Kajitani, M.; Tanaka, M.; Yamasaki, T. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; Royal Society of Chemistry, Burlington House: London, 1985, pp 242–254. (b) Micetich, R. G.; Maitai, S. N.; Spevak, P.; Tanaka, M.; Yamazaki, T.; Ogawa, K. *Synthesis* 1986, 292.

(10) The benzhydryl group can be cleaved by catalytic hydrogenolysis.[11] In fact, hydrogenolysis of **17** with H_2 and Pd/C gave **18** in fair yield. However, the use of a large amount of Pd/C was needed to complete the reaction, and the use of extremely pure **17** was required to initiate the reaction. Otherwise, the reaction was sluggish, probably because a trace of unknown catalyst poison was present in the ester.

(11) Aboderin, A. A.; Delpierre, G. R.; Fruton, J. S. *J. Am. Chem. Soc.* 1965, *87*, 5469.

(12) Riddick, J. A.; Bungen, W. B. *Organic Solvents*; Wiley-Interscience: New York, 1970.

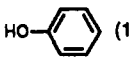
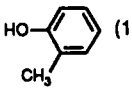
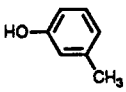
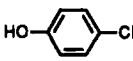
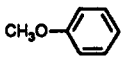
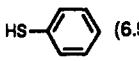
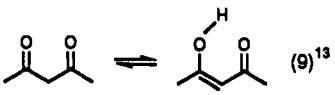
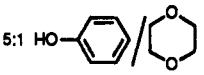
(13) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* 1953, *75*, 2439.

Table IV. Deprotection of Tazobactam Benzhydryl Ester (17)

entry	solvent	acid (equiv)	additive (equiv)	T (°C)	time (h)	yield (%) 18	yield (%) recovered 17
1	*m*-cresol			50	2.0	90[a]	0
2	$ClCH_2CH_2Cl$	TFA (7)	anisole (1)	20	0.5	46[b]	10[b]
3	99% HCOOH			40	0.5	21[b]	3[b]
4	50:50 $ClCH_2CH_2Cl/CH_3NO_2$	$AlCl_3$ (3)	anisole (1)	0	0.5	8[b]	3[b]

[a] Isolated yield. [b] Determined by HPLC (see Experimental Section).

Table V. Effect of Solvent on the Cleavage of PMB Ester 1a[a]

entry	solvent (pK_a)	yield[b] (%) 2	yield[b] (%) recovered 1a
1	 (10.02)[12]	77	23
2	 (10.29)[12]	22	78
3	 (10.09)[12]	45	52
4	 (10.26)[12]	39	59
5		0	100
6	 (6.5)[12]	1	84
7	 (9)[13]	0	100
8	5:1 	14	86

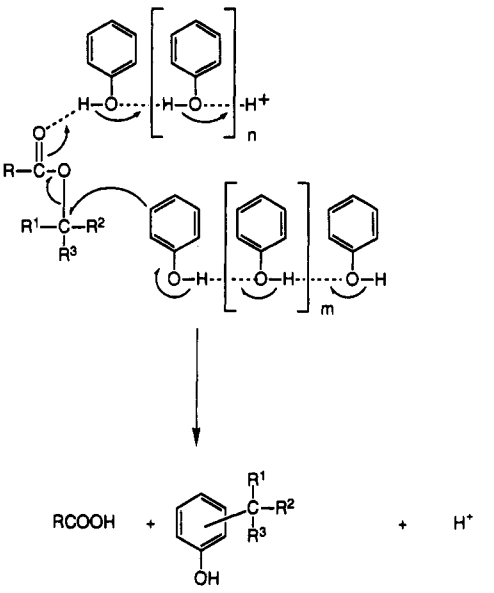
[a] Reaction conditions: 60 °C, 1 h, no added acid. [b] Determined by HPLC (see footnote in Table I).

Anisole was reported to promote the cleavage of benzyl esters to the corresponding acids.[4] However, in the absence of acid catalysts, treatment with anisole did not effect the deprotection of **1a** even at elevated temperatures. The unusual behavior of phenol may thus be due to the fact that it is an acid. In order to gain more information, the cleavage of **1a** was performed in various media. The results are summarized in Table V.

It is noteworthy that no reaction occurred in acetylacetone, which has a pK_a close to that of phenol (entry 7). On the other hand, thiophenol is more acidic than phenol and would be expected to have a cation-trapping ability similar to that of phenol. However, thiophenol exhibited almost no cleaving ability (entry 6). Only homologues of phenol, such as *o*-, *m*-, and *p*-cresol, proved, more or less, to be effective (entries 2–4). These observations suggested that ability of phenols to form hydrogen bonds probably is somehow responsible for the action observed. This conclusion is supported by the observation that the use of a mixed dioxane/phenol solvent inhibited the cleavage reaction significantly (entry 8).

The experimental results can be explained by postulating the existence of a hydrogen bonding network within a phenol matrix (Scheme III). The protons required for the cleavage can be supplied initially by added acids (vide supra) and, thereafter, catalytically via an SEAr process involving a nucleophile like anisole or phenol. Although the concentration of protons would be expected to be rather low under these conditions, protons could be efficiently relayed to the reaction center through the hydrogen bonding network of the phenolic matrix. Hence, the activation energy of this process may be small.[14] This proton relay phenomenon[16] is most probably responsible for the rate enhancement observed in phenolic media. A detailed study of the proton relay mechanism, based on semiempirical molecular orbital calculations, is currently underway. The results will be reported in due course.

Scheme III



Experimental Section

Melting points were determined with a Yamato melting point apparatus Model MP-21 and are uncorrected. IR spectra were recorded with a JEOL RFX-3002 FTIR spectrophotometer or a Shimadzu IR-440 IR spectrometer. Mass spectra were recorded with a Hitachi M-80 spectrometer. ^1H NMR spectra were recorded with a Varian VXR-300S spectrometer or a Varian FT-80A spectrometer. Elemental analyses were performed with a Yanaco CHN corder MT-3.

Cleavage of Cephem-4-carboxylic Esters in Phenol. General Procedure. The cleavage of **1a** is typical. A mixture of *p*-methoxybenzyl 7-(phenylacetamido)-3-(((1-methyl-1,2,3,4-tetrazol-5-yl)thio)methyl)-3-cephem-4-carboxylate[17] (**1a**; 2.0 g, 3.5 mmol) and phenol (7 g, 70 mmol) was heated at 45 °C. When the phenol had melted, TFA (270 mL, 3.5 μmol) was added and the mixture was stirred at 45 °C for 1 h. Then, the mixture was diluted with EtOAc (60 mL) and was extracted with saturated aqueous $NaHCO_3$ (22 mL). The aqueous extract was cooled in an ice bath, acidified to pH 1.0 with 10% aqueous HCl, and

(14) This phenolysis of an ester can be viewed as the alkylation of a phenol by an alkyl ester. The carboxylate acts as a leaving group. Hart[15] reported that phenol, but not anisole, could be alkylated by *tert*-butyl chloride in the absence of acid catalyst. "An amphoteric medium effect" was invoked to explain the reaction.

(15) Hart, H.; Simons, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 345.

(16) A proton relay mechanism is often invoked to explain enzyme reactions. See, for example: Merz, Jr., K. M.; Hoffmann, R.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1989**, *111*, 5636.

(17) The compound was prepared by a slight modification of the reported method. See: Torii, S.; Tanaka, H.; Sasaoka, M.; Saitoh, N.; Siroi, T.; Nokami, J. *Tetrahedron Lett.* **1982**, *23*, 2495.

extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo to afford the acid **2**[4,18] as a colorless solid. This was rinsed with CH_2Cl_2 and was dried in vacuo (1.43 g, 91%): IR (KBr) 3270, 3046, 2956, 1794, 1742, 1733, 1717, 1672, 1553, 1550, 1502, 1415, 1325, 1261, 1171, 1107, 1072, 1039, 1007, 738, 715 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.62 (d, J = 14.1 Hz, 1 H), 3.69 (d, J = 14.1 Hz, 1 H), 3.74 (d, J = 18.3 Hz, 1 H), 3.84 (d, J = 18.3 Hz, 1 H), 4.00 (s, 3 H), 4.37 (d, J = 13.5 Hz, 1 H), 4.45 (d, J = 13.5 Hz, 1 H), 5.10 (d, J = 4.8 Hz, 1 H), 5.83 (dd, J = 4.8, 9.3 Hz, 1 H), 7.20–7.40 (m, 5 H), 8.01 (d, J = 9.3 Hz, 1 H); MS (FD) m/e 447 (M^+ + 1). Anal. Calcd for $C_{18}H_{18}N_6O_4S_2$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.15; H, 4.14; N, 18.58.

The EtOAc solution remaining after the extraction with aqueous $NaHCO_3$ was washed several times with 10% aqueous NaOH and water, and this was concentrated in vacuo. The residue was purified by column chromatography on silica gel (benzene–EtOAc (10:1)) to give *p*-(*p*-methoxybenzyl)phenol (**3a**;[19] 0.43 g, 57%) and *o*-(*p*-methoxybenzyl)phenol (**4a**;[20] 0.11 g, 15%).

3a: IR (KBr) 3393, 1612, 1594, 1511, 1466, 1455, 1444, 1357, 1302, 1269, 1240, 1217, 1179, 1111, 1023, 858, 818, 773, 754, 673, 577, 530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 3.85 (s, 2 H), 6.74 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 8.4 Hz, 2 H), 7.03 (d, J = 8.4 Hz, 2 H), 7.08 (d, J = 8.4 Hz, 2 H); HREIMS m/e 214.0931 (214.0992 calcd for $C_{14}H_{14}O_2$).

4a: IR (KBr) 3382, 1613, 1594, 1515, 1456, 1350, 1302, 1270, 1239, 1226, 1179, 1114, 1090, 1021, 818, 753, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 3.93 (s, 2 H), 6.76–7.17 (m, 8 H); HREIMS m/e 214.0972 (214.0992 calcd for $C_{14}H_{14}O_2$).

The cleavage of various cephem-4-carboxylic esters 1 and other β-lactam carboxylic esters in phenol was performed in a manner similar to that described previously. The reaction conditions employed and the results are summarized in Tables II and III. The physical properties of the products and elemental analysis are reported in the following text.

7-(Phenylacetamido)-3-(((2-methyl-1,3,4-thiadiazol-5-yl)thio)methyl)-3-cephem-4-carboxylic acid (6) from ester 5: IR (KBr) 3302, 3046, 2943, 2898, 2795, 1787, 1723, 1665, 1620, 1550, 1502, 1441, 1405, 1376, 1360, 1309, 1242, 1197, 1107, 1068, 1007, 994, 959, 789, 776, 735, 702, 670 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.71 (s, 3 H), 3.62 (d, J = 14.1 Hz, 1 H), 3.69 (d, J = 14.1 Hz, 1 H), 3.70 (d, J = 18.6 Hz, 1 H), 3.84 (d, J = 18.6 Hz, 1 H), 4.33 (d, J = 13.5 Hz, 1 H), 4.58 (d, J = 13.5 Hz, 1 H), 5.12 (d, J = 5.1 Hz, 1 H), 5.83 (dd, J = 5.1, 9.0 Hz, 1 H), 7.20–7.40 (m, 5 H), 8.01 (d, J = 9.0 Hz, 1 H); MS(FD) m/e 463 (M^+ + 1). Anal. Calcd for $C_{19}H_{18}N_4O_4S_3$: C, 49.34; H, 3.92; N, 12.11. Found: C, 49.08; H, 3.98; N, 11.84.

7-(Phenylacetamido)-3-(acetoxymethyl)-3-cephem-4-carboxylic acid (8)[21] from ester 7: IR (KBr) 3283, 3219, 3065, 2981, 2603, 1791, 1755, 1723, 1698, 1665, 1547, 1502, 1466, 1421, 1386, 1351, 1235, 1200, 1161, 1120, 1078, 1039, 1007, 969, 728, 702 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.03 (s, 3 H), 3.51 (d, J = 18.6 Hz, 1 H), 3.69 (d, J = 18.6 Hz, 1 H), 3.62 (d, J = 14.4 Hz, 1 H), 3.72 (d, J = 14.4 Hz, 1 H), 4.81 (d, J = 13.2 Hz, 1 H), 5.10 (d, J = 13.2 Hz, 1 H), 5.13 (d, J = 4.8 Hz, 1 H), 5.84 (dd, J = 4.8, 9.6 Hz, 1 H), 7.20–7.40 (m, 6 H); MS(FD) m/e 391 (M^+ + 1). Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.08; H, 4.59; N, 6.95.

7-(Phenylacetamido)-3-*exo*-methylenecepham-4-carboxylic acid (10)[22] from ester 9: IR (KBr) 3302, 3046, 2962, 2673, 2609, 1771, 1742, 1659, 1524, 1412, 1240, 1219, 1197, 1176, 1165, 933, 850, 728 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.39 (d, J = 14.1 Hz, 1 H), 3.70 (d, J = 14.1 Hz, 1 H), 3.62 (d, J = 14.1 Hz, 1 H), 3.69 (d, J = 14.1 Hz, 1 H), 5.11 (s, 1 H), 5.30 (s, 1 H), 5.32 (s, 1 H), 5.35 (d, J = 4.5 Hz, 1 H), 5.58 (dd, J = 4.5, 9.0 Hz, 1 H), 7.20–7.40 (m, 5 H), 7.93 (d, J = 9.0 Hz, 1 H); MS(FD) m/e 333 (M^+ + 1). Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.68; H, 4.83; N, 8.14.

Penicillin V sulfoxide (12)[23] from ester 11: IR (KBr) 3540, 3386, 3309, 3213, 2988, 2744, 2551, 1803, 1778, 1759, 1739, 1672, 1604, 1534, 1508, 1444, 1348, 1296, 1277, 1261, 1242, 1222, 1091, 1072, 1036, 1023, 885, 844, 831, 760, 696, 584 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 1.34 (s, 3 H), 1.72 (s, 3 H), 4.56 (s, 1 H), 4.57 (d, J = 15.0 Hz, 1 H), 4.63 (d, J = 15.0 Hz, 1 H), 5.42 (d, J = 4.8 Hz, 1 H), 6.08 (dd, J = 4.8, 10.5 Hz, 1 H), 7.00–7.05 (m, 3 H), 7.30–7.40 (m, 2 H), 8.29 (d, J = 10.5 Hz, 1 H); MS(FD) m/e 366 (M^+).

Ceftazidime HI Salt (15). A mixture of the ceftazidime ester **13** (8.5 g, 8.1 mmol) and phenol (36 g, 387 mmol) was heated at 45 °C. When the phenol had melted, 35% aqueous HCl (1.6 mL, 18 mmol) was added and the mixture was stirred at 45 °C for 1.5 h. Then, the mixture was poured into stirred Et_2O (400 mL). The light yellow precipitate that formed was collected by suction filtration, rinsed with EtOAc, and dried in vacuo to give crude **15** (4.7 g, 92%): ^1H NMR (80 MHz, DMSO-d_6/D_2O) δ 1.45 (s, 6 H), 3.06 (d, J = 16 Hz, 1 H), 3.55 (d, J = 16 Hz, 1 H), 5.07 (d, J = 4 Hz, 1 H), 5.20 (d, J = 13 Hz, 1 H), 5.57 (d, J = 13 Hz, 1 H), 5.73 (d, J = 4 Hz, 1 H), 6.75 (s, 1 H), 8.08 (t, J = 6 Hz, 2 H), 8.54 (t, J = 6 Hz, 1 H), 9.12 (d, J = 6 Hz, 2 H).

Ceftazidime *tert*-Butyl Ester HI Salt (14). The cleavage of **13** (8.5 g) in phenol containing 1.1 equiv of HCl in a manner similar to that described previously gave crude **14** (4.5 g, 81%): ^1H NMR (80 MHz, DMSO-d_6) 1.37 (s, 9 H), 1.48 (s, 6 H), 3.52 (b s, 2 H), 5.22 (d, J = 6 Hz, 1 H), 5.60 (b s, 2 H), 5.90 (dd, J = 4, 8 Hz, 1 H), 6.85 (s, 1 H), 7.07 (d, J = 8 Hz, 1 H), 7.32 (b s, 2 H), 8.17 (t, J = 8 Hz, 2 H), 8.62 (t, J = 8 Hz, 1 H), 9.05 (d, J = 8 Hz, 2 H).

The cleavage of crude **14** in a similar manner gave **15**.

Ceftazidime (16). A mixture of 25% Amberlite LA-1 ion-exchange resin (acetate form),[24] methyl isobutyl ketone (110 mL), and a solution of crude **15** (4.8 g) and water (40 mL) was stirred for 20 min with ice cooling. The aqueous layer was drawn off, washed with EtOAc, and concentrated in vacuo. The aqueous concentrate was poured into *i*-PrOH, and the precipitate that formed was collected by suction filtration, rinsed with acetone, and dried in vacuo to give **16** (4.3 g, 64%): ^1H NMR (300 MHz, DMSO-d_6) 1.35 (s, 3 H), 1.38 (s, 3 H), 3.05 (d, J = 18.0 Hz, 1 H), 3.48 (d, J = 18.0 Hz, 1 H), 5.05 (d, J = 5.4 Hz, 1 H), 5.16 (d, J = 13.2 Hz, 1 H), 5.64 (d, J = 13.2 Hz, 1 H), 5.71 (dd, J = 5.4 8.1 Hz, 1 H), 6.66 (s, 1 H), 7.22 (s, 2 H), 8.11 (t, J = 5.7 Hz, 2 H), 8.54 (t, J = 5.7 Hz, 1 H), 9.42 (d, J = 5.7 Hz, 2 H). The ^1H NMR spectrum of **16** was identical with that of commercially available ceftazidime.

Cleavage of Tazobactam Diphenylmethyl Ester (17). Method A (by *m*-Cresol). To *m*-cresol (400 mL) was added **17** (50.0 g, 107 mmol) at 50 °C. The mixture was stirred for 2 h at 50 °C. The mixture was cooled in an ice bath and then methyl isobutyl ketone (1200 mL) was added. The mixture was extracted twice with saturated aqueous $NaHCO_3$ (250 mL). The combined aqueous extracts were washed with methyl isobutyl ketone. The aqueous solution was then cooled in an ice bath with stirring and was acidified to pH 1 with 10% aqueous HCl. Stirring was continued for 30 min with ice cooling. The colorless precipitate that formed was collected by suction filtration, rinsed with cold water, and dried in vacuo to give **18** (28.8 g, 90%): IR (KBr) 2800, 2440, 1815, 1797, 1705, 1458, 1430, 1329, 1315, 1190, 1139, 1118, 1085, 1020, 930, 790, 739, 714 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.32 (s, 3 H), 3.29 (d, J = 16.5 Hz, 1 H), 3.69 (dd, J = 4.5, 16.5 Hz, 1 H), 4.76 (s, 1 H), 4.89 (d, J = 15.6 Hz, 1 H), 5.16 (d, J = 4.5 Hz, 1 H), 5.21 (d, J = 15.6 Hz, 1 H), 7.77 (s, 1 H), 8.07 (s, 1 H); MS(FD) m/e 301 (M^+ + 1). Anal. Calcd for $C_{10}H_{12}N_4O_5S$: C, 40.00; H, 4.03; N, 18.66. Found: C, 39.72; H, 3.90; N, 18.60.

Method B (by TFA). To a mixture of $ClCH_2CH_2Cl$ (5 mL), anisole (0.11 mL, 1.02 mmol), and **17** (0.5 g, 1.02 mmol) was added TFA (0.54 mL, 7.14 mmol) at 20 °C. The reaction was monitored by HPLC until complete. The conditions of HLPC analysis were as follows: for **17**, column Unisil Q 10C18 (4.6 i.d. × 250 mm), mobile phase CH_3CN/H_2O, 75:25, flow rate 1.0 mL/min, detection UV at 220 nm; for **18**, column Unisil Q 10C18 (4.6 i.d. × 250 mm), mobile phase phosphate buffer/CH_3CN, 1000:25 (the phosphate

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buffer was prepared by dissolving 1.32 g of dibasic ammonium phosphate in 750 mL of distilled water, adjusting the pH to 2.5 with 85% aqueous H_3PO_4, and diluting the solution to 1000 mL with distilled water), flow rate 2.6 mL/min, detection UV at 210 nm. The yields of 18 and recovered 17 were determined by HPLC with an external standard. The results are summarized in Table IV.

Method C (by Formic Acid). A mixture of 99% HCOOH (2.5 mL) and 17 (0.5 g, 1.02 mmol) was heated at 40 °C. The reaction was monitored by HPLC until complete. The results are summarized in Table IV.

Method D (by $AlCl_3$). To a mixture of $ClCH_2CH_2Cl$ (2.5 mL), anisole (0.11 mL, 1.02 mmol), and 17 (0.5 g, 1.02 mmol) was added, drop by drop at 0 °C, a solution of $AlCl_3$ (0.41 g, 3.06 mmol) in CH_3NO_2 (2.5 mL). The reaction was monitored by HPLC until complete. The results are summarized in Table IV.

An Improved Synthesis of Dioxindole-3-propionic Acid and Some Transformations of the C-3 Hydroxyl Group[1]

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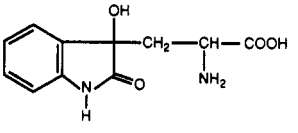
Dioxindole-3-propionic acid lactone (**3**) is obtained in 80% yield by oxidative cyclization of indole-3-propionic acid with t-BuBr/DMSO. In the presence of 18-crown-6 in DMSO, KCN opens the spirolactone ring of **3** at C-3 with the formation of 3-cyanooxindole-3-propionic acid (**4a**) in 14% yield. Methanolysis of the lactone is strongly promoted by DMAP, and the resulting 3-hydroxy ester (**5**) is converted into the 3-fluoro ester (**6**) with methyl DAST. Every attempt to isolate 3-fluorooxindole-3-propionic acid resulted in rapid intramolecular displacement of fluorine by the free carboxyl group to reform the spirolactone. The 3-hydroxy ester is converted into the 3-chloro ester (**9**) with $SOCl_2/Et_3N$. The halogen is readily displaced by nucleophiles (e.g., N_3^-, CN^-, NH_3, AcO^-, H_2O) to generate the corresponding methyl 3-X-oxindole-3-propionate. Saponification of the ester function provides the corresponding 3-X-oxindole-3-propionic acid. Acetylation of the 3-hydroxy ester provides a separable mixture of the *O*-acetyl (**16**) and *N*-acetyl (**17**) derivatives. As in the case of **3**, the *O*-acetyl derivative undergoes hydrogenolysis at C-3, while the 3-hydroxyl function is stable to removal by hydrogenolysis.

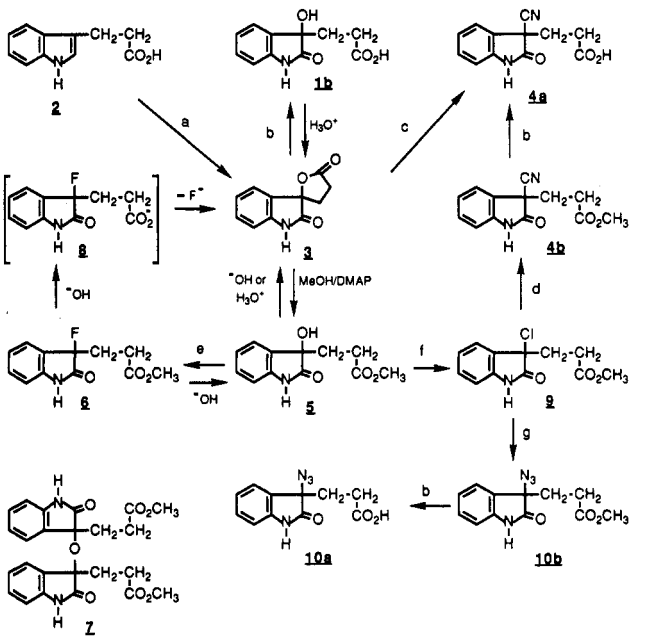
We have recently described the preparative separation of the diastereoisomers of dioxindolyl-L-alanine (**1a**) and the assignment of stereochemistry at C-3.[2] These diastereoisomers have the unique property of acting as "mirror-image enzyme inhibitors", since one isomer ($\alpha S,3R$) selectively inhibits the tryptophan-synthesizing enzyme, tryptophan synthase, while the other ($\alpha S,3S$) inhibits the tryptophan-degrading enzyme, tryptophanase.[3] Having found that these enzymes would tolerate not only hydrogen[4] but also hydroxyl[3] at C-3, we were drawn to extend the series of potential inhibitors to oxindolyl-L-alanines containing yet other substituents at C-3. Thus, we wished to evaluate the generality of the mirror-image phenomenon, the size limit of the C-3 substituents, and the possibility of creating both chemical affinity and photoaffinity labels for the enzymes through appropriate choice of substituents.



1a

Although dioxindolylalanine has been known since 1956,[5] we are unaware of any efforts to effect transformations of the C-3 hydroxyl group in the amino acid or its derivatives. Thus, we could only speculate on the possibility of effecting S_N2 displacements at the tertiary carbon or S_N1 displacements at this position adjacent to the carbocation-destabilizing oxindole carbonyl group;[6] furthermore, an N^{α}-acyl function may behave as a competitive internal nucleophile in displacing a leaving group at C-3.[7] In order to avoid the consumption of valuable dioxindolyl-L-alanine

Scheme I[a]



[a] a = *t*-BuBr/DMSO; b = ^-OH, followed by H_3O^+; c = KCN/18-crown-6, followed by H_3O^+; d = KCN/18-crown-6; e = Me DAST/$CHCl_3$; f = $SOCl_2/Et_3N/CH_2Cl_2$; g = NaN_3/15-crown-5.

(1) Taken in part from the Ph.D. dissertation (1990) of Rita B. Labroo, George Washington University, Washington, D.C.
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