N-Trimethylsilyl Imines: Applications to the Synthesis of β-Lactams

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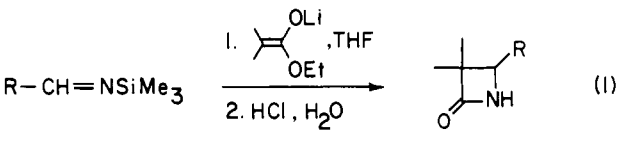
Abstract: Ester enolates and *N*-trimethylsilyl imines react to afford *N*-protio-β-lactams. The stereochemical course of the reaction depends on the ester enolate geometry. Therefore (*E*)-enolates give mainly cis β-lactams while (*Z*)-enolates give nearly equal mixtures of cis and trans β-lactams. The use of ethyl β-hydroxybutyrate as the ester component allows the preparation of β-lactams of potential use in carbapenem synthesis. The differences in the behavior of *N*-trimethylsilyl and *N*-aryl imines in ester–imine condensations are also discussed,

The reaction between Reformatsky reagents and imines to afford β-lactams was first reported by Gilman and Speeter close to 40 years ago.[1] Since the initial report, several research groups have investigated this reaction,[2-4] Most notably, a series of studies from the laboratores of Kagan[2] and Gaudemar[3] delineated some of the mechanistic and stereochemical features of the reaction. Recently, Bergbreiter and Newcomb introduced a potentially useful variant of this reaction in which lithium enolates of esters replace Reformatsky reagents,[5-7]

The recent discovery of carbapenems and related antibiotics has stimulated enormous activity in the area of β-lactam synthesis.[8] Thus, it is surprising that the ester–imine condensation route to β-lactams has not been explored within the context of carbapenem synthesis.[9] It is possible that the apparent neglect of this reaction is due to implications in the early work that only limited types of esters and imines could be used in this process. We recently introduced a variant of the ester–imine condensation which affords N-unsubstituted β-lactams, useful substructures in carbapenem synthesis.[10a] At the time of that report, however, the prospects for using esters and imines which introduce C-3 and C-4 substituents appropriate for carbapenem synthesis were uncertain, We have now found that a number of suitable esters and imines can be used and the details are presented herein.[10b]

Results and Discussion

Survey of Esters. Our initial studies showed that *N*-trimethylsilyl imines derived from benzaldehyde, cinnamaldehyde, and (trimethylsilyl)propargaldehyde reacted with the lithium enolate of ethyl isobutyrate to afford good yields of β-lactams (eq 1).[10a] It was also found that ethyl α-thiophenoxyacetate (**1a**)



(1)

69–79%

R = Ph, CH=CHPh, C≡CSiMe3

and ethyl α-thiophenoxypropionate (**1b**) reacted with *N*-(trimethylsilyl)benzaldimine (**2**) to afford mixtures of stereoisomeric β-lactams (Table I). We subsequently found, however, that the yields of β-lactams decreased drastically when the corresponding butyrate (**1c**) and isovalerate (**1d**) were used (Table I, entries 3 and 4).

To test the hypothesis that steric hindrance was the primary cause of decreased yields, the reactions documented in Table II were performed. These results indicate that steric effects are truly important. Both small and large substituents at the α-position of the ester depress the yields (entries 1, 2, and 5), From a practical standpoint, however, it is noted that entries 3 and 4 afford the C-3 substituents appearing in the carbapenem antibiotics PS-7 and PS-6, respectively,[12]

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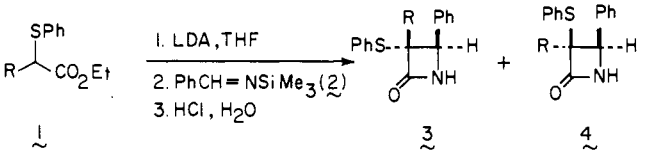
Table I. β-Lactams from α-Thiophenoxy Ester Enolates[11]



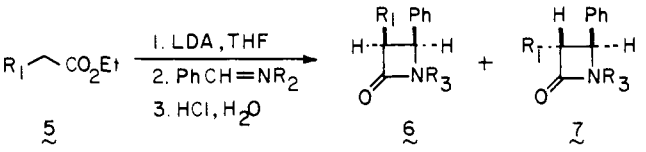
1 3 4

a R = H, b R = Me, c R = Et, d R = i-Pr

entry	R[a]	procedure[b]	%3[c,d]	%4[c,d]
1	H	A (3)	48	5
2	Me	A (36)	18	41
3	Et	A (40)	2	6
4	*i*-Pr	B (15)	0	0

[a] The esters were prepared from the corresponding acids. [b] See the Experimental Section for a detailed procedure. The number in parentheses refers to the reaction time in hours after mixing of the enolate and imine. [c] Isolated yields. [d] The stereochemical assignments are based on coupling constants (H_3–H_4) and difference NOE experiments.

Table II. β-Lactams from Nonfunctionalized Ester Enolates in THF



5 6 7

a R_1 = H, b R_1 = Me, c R_1 = Et, d R_1 = i-Pr, e R_1 = t-Bu

entry	R_1[a]	R_2	R_3	procedure	%6[c,d]	%7[c,d]
1	H	$SiMe_3$	H	A (2)	14	0
2	Me	$SiMe_3$	H	A (3)	41	3
3	Et	$SiMe_3$	H	A (2)	72	0
4	*i*-Pr	$SiMe_3$	H	A (1)	80	1
5	*t*-Bu	$SiMe_3$	H	B (2)	40	0
6	Me	Ph	Ph	B (2)	45	2
7	*i*-Pr	Ph	Ph	B (2)	87	1

[a] The esters were commercially available or prepared from the corresponding acids. [b] See footnote b of Table I. [c] Isolated yields. [d] The stereochemical assignments are based on H_3–H_4 coupling constants (J_{cis} = 5–6 Hz and J_{trans} = 2–3 Hz).

(1) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255.
(2) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941. Kagan, H. B.; Luche, J. L. *Bull. Soc. Chim. Fr.* **1969**, 3500. Kagan, H. B.; Luche, J. L. *Ibid.* **1971**, 2260.
(3) Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *268*, 2228. Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Ibid.* **1970**, *270*, 233. Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1972**, 3841. Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Ibid.* **1973**, 1668.

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Table III. Effect of Enolate Geometry and Solvent on β-Lactam Stereochemistry

$$\mathbf{5} \xrightarrow[2.\ PhCH{=}NR_2]{1.\ LDA} \mathbf{6} + \mathbf{7}$$

b, R_1 = Me; **c**, R_1 = Et; **d**, R_1 = *i*-Pr

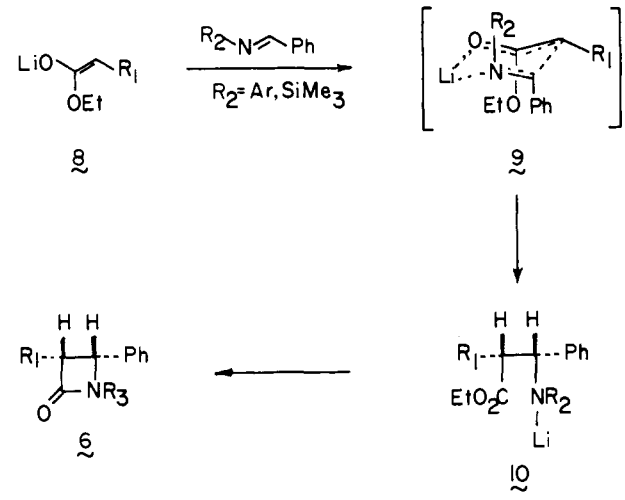
entry[a]	R_1	R_2	R_3	procedure[b]	%6	%7
1	Me	$SiMe_3$	H	A (*E*, 3)	41	3
2	Me	$SiMe_3$	H	C (*Z*, 2)	19	25
3	Me	$SiMe_3$	H	D (*E*, 2)	29	9
4	Me	Ph	Ph	B (*E*, 2)	45	2
5	Me	Ph	Ph	C (*Z*, 2)	12	19
6	Me	Ph	Ph	D (*E*, 2)	10	20
7	Et	$SiMe_3$	H	A (*E*, 2)	72	0
8	Et	$SiMe_3$	H	C (*Z*, 2)	28	38
9	Et	$SiMe_3$	H	D (*E*, 2)[c]	40	16
10	Et	Ph	Ph	B (*E*, 2)[c]	69	17
11	Et	Ph	Ph	C (*Z*, 2)	5	42
12	Et	Ph	Ph	D (*E*, 2)	5	41
13	*i*-Pr	$SiMe_3$	H	A (*E*, 1)	80	1
14	*i*-Pr	$SiMe_3$	H	C (*Z*, 2)	43	43
15	*i*-Pr	$SiMe_3$	H	D (*E*, 2)	83	1
17	*i*-Pr	Ph	Ph	B (*E*, 2)	87	1
18	*i*-Pr	Ph	Ph	C (*Z*, 2)	5	87
19	*i*-Pr	Ph	Ph	D (*E*, 2)	5	86
20	*i*-Pr	*p*-MeOPh	*p*-MeOPh	B (*E*, 2)	82	2
21	*i*-Pr	*p*-MeOPh	*p*-MeOPh	C (*Z*, 2)[d]	41	32
22	*i*-Pr	*p*-MeOPh	*p*-MeOPh	C (*Z*, 2)[e]	4	80
23	*i*-Pr	*p*-MeOPh	*p*-MeOPh	D (*E*, 2)	5	79

[a] The experiments are organized in groups of three. Each group refers to results with a common ester–imine pair by using the three fundamentally different reaction conditions described in the text (procedures A or B, C, and D). [b] See the Experimental Section for detailed procedures. The letter and numbers in parentheses refer to major enolate geometry and reaction time in hours, respectively. [c] See ref 19 for further discussion of these experiments. [d] Reaction temperature kept at 0 °C. [e] Reaction temperature kept at room temperature.

We were surprised that any of the esters shown in Table II gave β-lactams since it had been reported that ethyl acetate (**5a**) and ethyl propionate (**5b**) failed to afford β-lactams upon treatment with benzylidene aniline under similar conditions.[5] In fact, we found that both **5b** and **5d** react smoothly with benzylidene aniline to afford β-lactams as shown in Table II (entries 6 and 7). Thus, there seems to be little difference in the behavior of *N*-trimethylsilyl and *N*-aryl imines.

One interesting feature of the reactions documented in Table II is the cis stereoselectivity. This can be explained by a transition-state model similar to that frequently used to rationalize the stereochemical course of aldol condensations (Scheme I).[13]

Scheme I



Ample literature precedence suggests that treatment of esters **5** with lithium diisopropylamide affords (*E*)-enolate **8**,[14] We imagine that **8** adds to imines via a tightly coordinated transition state **9** to afford the erythro adduct **10** which cyclizes to cis β-lactam **6**.[15] Of course, this model assumes that the imines exist

(4) Deshpande, S. M.; Mukerjee, A. K.; Dey, P. M. *Ind. J. Chem.* **1968**, *6*, 238. Cuingnet, E.; Poulain, D.; Tarterat-Adalberon, M. *Bull. Soc. Chim. Fr.* **1969**, 514. Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 259.

(5) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

(6) For other relevant studies see: Simora, E.; Mladenova, M.; Kurtev, B. I. *Izvest. Otol. Khim. Nauk.* (*Bulg. Akad. Nauk.*) **1970**, *3*, 497. Bose, A. K.; Khajavi, M. S.; Manhas, M. S. *Synthesis*, **1982**, 407. Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946.

(7) For the acid-catalyzed variant of this strategy see: Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643.

(8) For an overview of β-lactam chemistry see: "Chemistry and Biology of β-Lactam Antibiotics", Morin, R. B., Goldman, M., Eds.; Academic Press: New York, 1982; Vol. 1–3. For a review of carbapenem synthesis see: Ratcliffe, R. W.; Albers-Schönberg, G. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Goldman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 227–313.

(9) For recent reviews of β-lactam synthesis see: Isaacs, N. S. *Chem. Soc. Rev.* **1976**, 181. Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731.

(10) (a) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289. (b) Taken in part from: Yang, T.-K. Ph.D. thesis, The Ohio State University, 1983.

(11) Esters **1a–d** were prepared by Fischer esterification of the corresponding acids which were commercially available or prepared via known procedures: Grieco, P. A.; Wang, C.-L. *J. Chem. Soc., Chem, Commun.* **1975**, 714. Iwai, K.; Kawai, M.; Kosugi, H.; Uda, H. *Chem. Lett.* **1974**, 385.

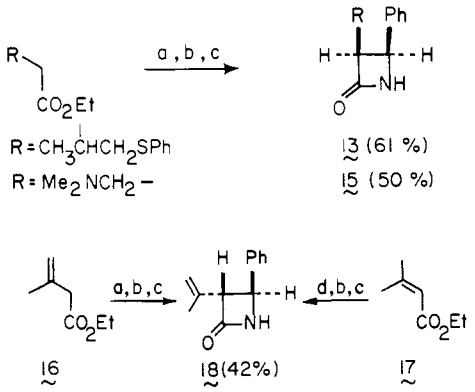
(12) Shibamoto, N.; Kori, A.; Nishino, M.; Nakamura, K.; Kiyoshima, K.; Okamura, K.; Okabe, M.; Okamoto, R.; Fukagawa, Y.; Shimauchi, Y.; Ishikura, T.; Lein, J. *J. Antibiot.* **1980**, *33*, 1128.

(13) Evans, D. A.; Nelson, J. V.; Taber, T. R. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Academic Press: New York, 1982; Vol. 13, pp 1–115. Heathcock, C. A. *Science* (*Washington*, D. C.) **1981**, *214*, 395. Although Scheme I has been the working hypothesis on which we have based some experiments, it is undoubtedly an oversimplification.

(14) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. See also: Heathcock, C. A.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. A.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(15) The cyclization of β-(trimethylsilyl)amino esters is known: Birkofer, L.; Schramm, J. *Liebigs Ann. Chem.* **1975**, 2195. In addition, the stereochemical result of entry 6 in Table II has some mechanistic significance. Since it has been reported that methylketene and benzylidene aniline undergo cycloaddition to give the trans β-lactam, it is unlikely that ketenes are intermediates in the studies presented here: Tschamber, T.; Streith, J. *Tetrahedron Lett.* **1980**, 4503.

Scheme II



(a) LDA, THF (b) PhCH=NSiMe$_3$ (c) HCl, H_2O (d) LDA, THF – HMPA

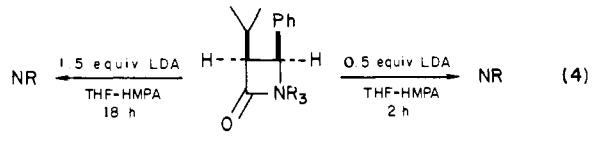
predominantly as trans geometrical isomers.[15,16]

In an attempt to determine the affect of enolate geometry on the stereochemical course of ester–imine condensations, the experiments shown in Table III were performed. Solutions containing predominantly (*E*)- or (*Z*)-enolates were prepared according to Ireland's procedures.[14] Thus, procedures A and B afford mainly (*E*)-enolates in tetrahydrofuran. Procedure C gives predominantly (*Z*)-enolates in tetrahydrofuran–hexamethylphosphoramide. Finally, procedure D gives (*E*)-enolate in tetrahydrofuran–hexamethylphosphoramide.[17,18] Entries 1, 4, 7, 10, 13, 16, and 20 reiterate that cis β-lactams are obtained when (*E*)-enolates are used in tetrahydrofuran. Entries 2, 8, and 14 show that roughly equal mixtures of stereoisomers are obtained when *N*-trimethylsilyl imines are treated with (*Z*)-enolates. Entries 3, 9, and 15 are important control experiments which show that hexamethylphosphoramide only affects the *N*-trimethylsilyl imine reactions at the stage of enolate generation, Entries 5, 11, 18, 21, and 22 show that enolate geometry also effects the stereochemical course of *N*-aryl imine condensations. Entries 6, 12, 19, and 23, however, suggest that hexamethylphosphoramide also exerts an effect at some stage of the reaction beyond enolate formation. In subsequent experiments, it was shown that *N*-aryl-β-lactam **6d** (R_3 = Ph) isomerizes easily upon treatment with a strong base in tetrahydrofuran–hexamethylphosphoramide (eq 2) or under the condensation conditions (eq 3). In addition,

$$\textbf{6d}\ (R_3 = \text{Ph})\ \text{or}\ \textbf{7d}\ (R_3 = \text{Ph}) \xrightarrow[\text{THF-HMPA}]{\text{0.5 equiv LDA}}_{\text{2 h}} \textbf{6d}\ (4\%) + \textbf{7d}\ (81\%) \quad (2)$$

$$\textbf{5d} \xrightarrow[\text{2. PhCH=NPh}]{\text{1. LDA, THF-HMPA}}_{\text{3. 0.5 equiv 6d } (R_3 = \text{Ph})} \textbf{6d}\ (R_3 = \text{Ph},\ 5\%) + \textbf{7d}\ (R_3 = \text{Ph},\ 89\%) \quad (3)$$

N-protio-β-lactam **6d** (R_3 = H) and *N*-(trialkylsilyl)-β-lactam **11** resist isomerization under similar conditions (eq 4).[19,20] Thus,



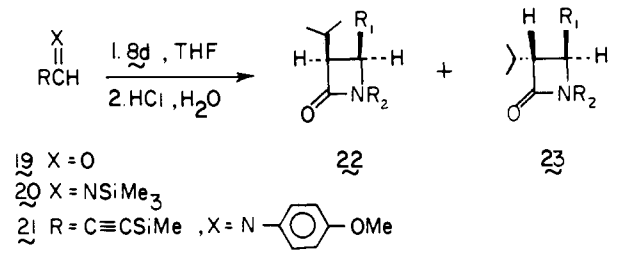
6d, R_3 = H
11, R_3 = *t*-BuMe$_2$Si

(16) Kagan has noted cis selectivity in Reformatsky reagent–imine condensations under certain conditions.[2] Enolate geometry was uncertain in these studies.

(17) For reference, methyl propanoate, *tert*-butyl propanoate, methyl butanoate, *tert*-butyl butanoate, and methyl β,β-dimethylbutanoate afford *E*/*Z* ratios of 95:5, 95:5, 91:9, 95:5, and 97:3, respectively, by using procedure A.[14]

(18) For reference, methyl butanoate, *tert*-butyl butanoate, and methyl β,β-dimethylbutanoate afford *E*/*Z* ratios of 16:84, 23:77, and 9:91, respectively, by using procedure C.[14]

Table IV. β-Lactams from Ethyl Isovalerate and Imines



a R_1 = CH=CH$_2$ b R_1 = C≡CSiMe$_3$ c R_1 = CH=CHSPh

d R_1 = 2-furyl e R_1 = C≡CPhpOMe

entry	imine	procedure[a]	%22[b]	%23[b]
1	**20a**	A (1.5)	11	0
2	**20b**	A (2.5)	52	5
3	**20c**	A (10)	71	5
4	**20d**	A (2.5)	84	1
5	**20e**	A (3)	81[c]	0
6	**21**	A (2)	65[d]	6

[a] The stoichiometry of ester to imine (aldehyde in the case of imines **20**) was 1:1. See the Experimental Section for a detailed procedure. The numbers in parentheses refer to reaction times in hours after mixing of the enolate and imine and warming to room temperature. [b] See Table II, footnotes c and d. [c] Reaction performed on 70 mmol scale; see Experimental Section. [d] Desilylated **22** was also obtained in a 6% yield.

the difference in behavior between *N*-trimethylsilyl and *N*-aryl imines in hexamethylphosphoramide arises from differences in the ease with which the product β-lactams isomerize. Finally, although the yields of several entries are lower than desirable and isomerization causes some interpretive problems,[19] these experiments suggest that (*Z*)-enolates do not add to imines exclusively via a coordinated chairlike transition state similar to **9**.

Several esters carrying additional functionality were also examined (Scheme II), For example, ester **12** behaves much like ethyl isovalerate, giving cis β-lactam **13** as a nearly equal mixture of diastereomers along with only traces of the trans β-lactam.[21] β-Amino ester **14** also reacts smoothly with *N*-(trimethylsilyl)-benzaldimine to afford **15**.[22] Finally, the dienolate derived from esters **16** and **17** affords trans β-lactam **18** in either tetrahydrofuran or tetrahydrofuran–hexamethylphosphoramide. The reasons for this selectivity are not clear at this point.

Survey of Imines. The results presented above indicated that a variety of esters could be used in the ester–imine condensation. All of these reactions, however, were performed with benzaldimines, To be useful in carbapenem synthesis, it was clear that this reaction would also have to accommodate a variety of imines. The imines which were surveyed are shown in Table IV. Imines

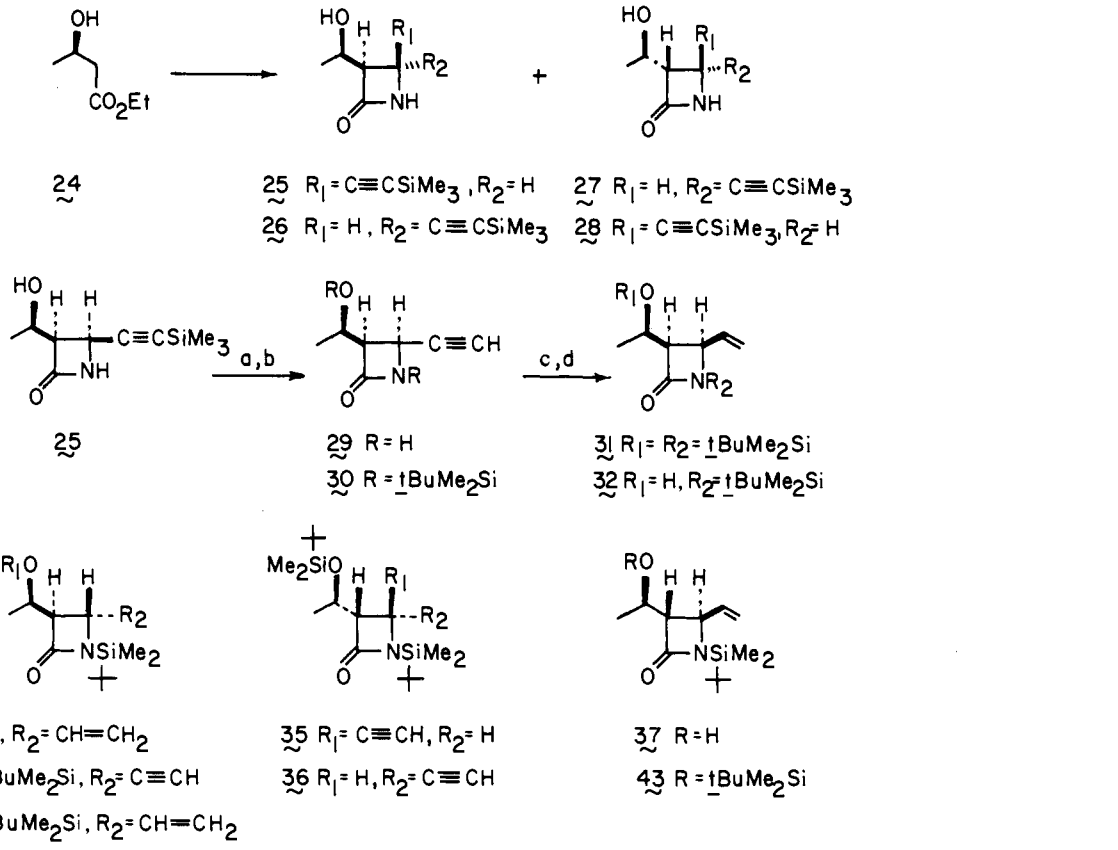
(19) We have found that **11** is converted to a mixture of the corresponding trans isomer, **7d** (R_3 = H), **11**, and **6d** (R_3 = H) in 54%, 17%, 13%, and 10% yields, respectively, upon treatment with 0.2 equiv of lithium hexamethyldisilazide in PhH–HMPA at room temperature for 4 h. When the experiment shown in entry 9 was performed at −25 °C (2 h), **6** and **7** were formed in 45% and 6% yields, respectively. Furthermore, it was shown that **6c** (R_3 = *t*-BuMe$_2$Si) isomerizes upon treatment with LDA in HMPA–THF by using conditions under which **6d** (R_3 = *t*-BuMe$_2$Si, **11**) is stable (eq 4). Thus, we suspect that the **6**:**7** ratio shown in Table III (entry 9) is low due to partial isomerization of **6** to **7**. When the experiment shown in entry 10 was performed at −25 °C (2 h), **6** and **7** were obtained in 53% and 7% yields, respectively. We suspect that isomerization may be occurring here as well as in the experiment shown in entry 3. Finally, in entries 5, 6, 11, and 12, some products derived from enolization of **6** (**7**) and addition to a second equivalent of imine were obtained.

(20) For other relevant isomerization studies see: Luche, J. L.; Kagan, H. B.; Parthasarathy, R.; Tsoucaris, G.; DeRango, C.; Zelwer, C. *Tetrahedron* **1968**, *24*, 1275.

(21) Ester **12** was prepared from 3-methyl-2-buten-1-ol in three steps via Jones oxidation, radical addition of thiphenol to the terminal double bond, and esterification of the resulting acid.

(22) This reaction was kept at −20 °C for 4 h prior to workup. The trans β-lactam was also obtained in a 7% yield. Ester **14** was prepared from ethyl acrylate and dimethylamine.

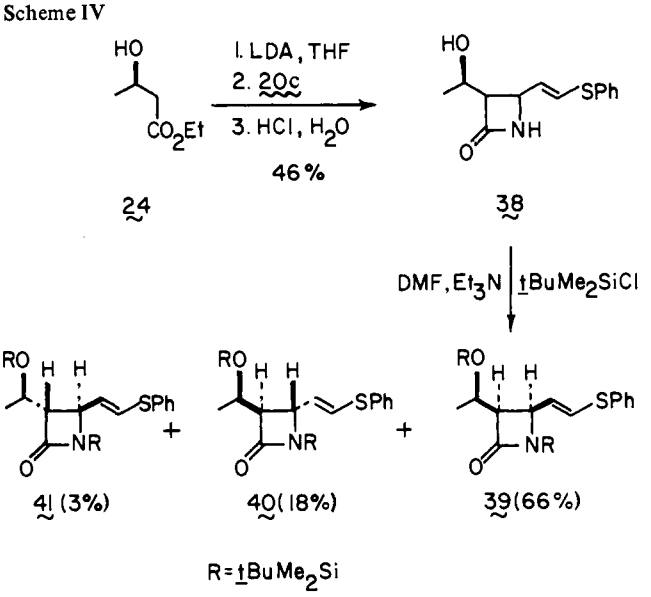
Scheme III



20a–20e were simply generated in situ by treating the corresponding aldehydes **19** with lithium bis(trimethylsilyl)amide in tetrahydrofuran in a modification of the Rochow–Wannagat procedure.[23,24] Solutions of imines generated in this manner were used directly in subsequent reactions, Imine **21** was prepared from *p*-anisidine and (trimethylsilyl)propargaldehyde in a 48% yield, The results of reactions between ethyl isovalerate (**5d**) and imines **20** and **21** are also documented in Table IV, It was encouraging to find that, with the exception of acrolein (**19a**), all of the aldehydes (imines) shown in Table IV could be efficiently converted to β-lactams **22** and **23** in a *single operation*! Once again, high stereoselectivity was observed, We anticipate that all of the C-4 substituents introduced via imines **20** and **21** will be suitable for completing the synthesis of the carbapenem nucleus and such efforts are currently under way, In summary, Table IV shows that the ester–imine condensation is very promising in terms of substituent placement at C-4 of the β-lactam.

Reactions with Ethyl β-Hydroxybutyrate. In many carbapenem antibiotics, an α-hydroxyethyl group resides at C-3 of the β-lactam nucleus,[25] Therefore we examined the possibility of using β-hydroxybutyrates as the ester component of the reaction, Some of our initial results are shown in Scheme III. Treatment of ethyl β-hydroxybutyrate with imine **20b** gave a partially separable mixture of β-lactams **25–28**, Pure samples of **25** and **26** could be isolated in 44% and 5% yields, respectively. In addition, a diastereomeric mixture of **26–28** was isolated in a 17% yield, The structure of **25** was proven by conversion to the known β-lactam **32**.[26] Thus, treatment of **25** with tetra-*n*-butylammonium fluoride[27] gave **29** (90%) which was silylated to afford **30** (94%).[28] Catalytic hydrogenation of alkyne **30** over palladium on barium

Scheme IV



(23) Krüger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132.
(24) Aldehydes **19a** and **19e** were purchased. Aldehydes **19b** and **19c** were prepared by known procedures: Komarov, N. V.; Yarosh, O. G.; Astaf'eva, L. N. *J. Gen. Chem. USSR* (*Engl. Transl.*) **1966**, *36*, 920. Engelhard, N.; Kolb, A., *Ann. Chem.* **1964**, *673*, 136. Aldehyde **19e** was prepared by Swern oxidation (Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480) of the appropriate alcohol (Bohlman, F.; Enkelmann, R.; Plettner, W. *Chem. Ber.* **1964**, *97*, 2118). Imine **21** was prepared from **19b** and *p*-anisidine in a 48% yield.
(25) A specific example is thienamycin: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6163. See also ref 8.
(26) Bouffard, F. A., Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. We thank F. A. Bouffard for providing 300-MHz ^{1}H NMR spectra of **6a–d** in their work for comparison with our samples of **32**, **33**, and **37**.
(27) Nakamura, E.; Kuwajima, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 498.
(28) Birkofer, L.; Ritter, A. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 417.

sulfate in pyridine gave olefin **31** (91%),[29] Treatment of **31** with 1 N hydrochloric acid in aqueous methanol gave a mixture of desilylated products from which pure **32** could be isolated,[30] The spectral properties of this material compared favorably with those reported elsewhere.[26] The structure of **26** was proven by conversion to the known β-lactam **33** via an identical reaction sequence.[26] Finally, sequential treatment of the aforementioned mixture of lactams **26–28** with tetra-*n*-butylammonium fluoride and *tert*-butyldimethylsilyl chloride gave a separable mixture of β-lactams **34–36** in 57%, 36%, and 0.8% yields, respectively. The structures of **34** and **35** were proven by conversion to the known lactams **33** and **37**, respectively.[26] The structure of **36** was assigned on the basis of spectral data ($J_{H_3-H_4}$ = 6 Hz).

Scheme IV shows that ester **24** and imine **20c** afford a mixture of β-lactams **38** (46%) which could only be partially separated with difficulty, Silylation of the mixture, however, gave separable β-lactams **39–41** in 66%, 18%, and 3% yields, respectively. The structures of **39** and **40** were established by conversion to **31** (57%) and **42** (33%), respectively, upon treatment with W-2 Raney nickel in ethanol.[31]

Two aspects of the reactions shown in Schemes III and IV are notable. First, although the ester–imine condensation allows the construction of complicated β-lactams in a remarkably straightforward manner, the stereocontrol of the process is not totally satisfactory at present. It is possible that the origin of the stereochemical problem lies in a lack of clean enolate geometry.[32a] Although it is possible to develop models which are consistent with the formation of **25** (**39**) and **26** (**40**) as the major stereoisomers, we defer speculation until more data regarding enolate geometry are available,[32b] Second, it is noted that both (*R*)- and (*S*)-**24** are readily available. Therefore this strategy, in principle, could afford highly functionalized β-lactams in an enantioselective manner.

Summary and Conclusions

We are now confident that the ester–imine condensation will be valuable in the synthesis of carbapenems and other β-lactam antibiotics, β-Lactams with potentially useful substituents at C-3, C-4, and nitrogen can be prepared in a straightforward manner. Furthermore, the stereochemical relationship between C-3 and C-4 can frequently be controlled by selecting appropriate imines ($SiMe_3$ vs. aryl) and reaction conditions (LDA–THF vs. LDA–THF–HMPA). Studies directed toward incorporating asymmetry and enolizable imines into this scheme as well as its use in natural product synthesis will be the subjects of future reports.

Experimental Section

All melting points are uncorrected. ^1H nuclear magnetic resonance spectra are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, integration, interpretation]. Mass spectra were recorded at an ionization energy of 70 eV.

Solvents and reagents were purified prior to use. All reactions were carried out under a blanket of either nitrogen or argon in flame-dried flasks. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh) or LoBar columns (medium pressure).

General procedures for the preparation of β-lactams are presented below along with selected specific examples. Table I–IV should provide the reader with the additional information needed to repeat other examples. Data characterizing new β-lactams prepared via the ester–imine condensation are also presented below. β-Lactams **3a**,[10a] **3b**,[10a] **4a**,[10a] **4b**,[10b] **6a** (R_3 = H),[33] **6b** (R_3 = H),[34] **6b** (R_3 = Ph),[35] **6c** (R_3 = Ph),[35] **6d** (R_3 = Ph),[35] **7b** (R_3 = H),[34] **7b** (R_3 = Ph),[35] **7c** (R_3 = Ph),[35] and **7d** (R_3 = Ph)[35] have been previously reported. The spectral data and melting points of these compounds were consistent with the assigned structures (available in supplementary material). Experimental procedures for the reactions outlined in eq 2–4 and Schemes II–IV are available in the supplementary material.

Preparation of β-Lactams from Esters and Imines: Procedure A. To 689 mg (4.12 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 3.0 mL of anhydrous tetrahydrofuran was added 3.96 mmol of *n*-butyllithium in hexane (1.4–1.6 M) at −70 °C in one portion. The solution was stirred for 15 min and 3.75 mmol of the appropriate aldehyde in 1.0 mL of tetrahydrofuran was added at a rate such that the temperature did not exceed −60 °C. The mixture was stirred for 50 min, and the resulting cold solution of *N*-trimethylsilyl imine was used directly in the following reaction.

To a solution of 433 mg (4.30 mmol) of diisopropylamine in 3.0 mL of tetrahydrofuran was added 4.36 mmol of *n*-butyllithium in hexane (1.4–1.6 M) at −70 °C. The solution was stirred for 10 min followed by the addition of 3.74 mmol of the appropriate ester in 2.0 mL of tetrahydrofuran at a rate such that the temperature did not exceed −60 °C. The solution was stirred for 50 min followed by the addition of the silyl imine solution via cannula over a 5 min period. The mixture was stirred at −70 °C for 1 h, the cold bath was removed, and the mixture was allowed to warm to room temperature followed by stirring for the indicated time period (see tables). The resulting solution was diluted with 100 mL of diethyl ether and washed sequentially with 50 mL of 1 N aqueous hydrochloric acid and 50 mL of water. The combined aqueous washes were extracted with three 100-mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by recrystallization and chromatography over silica gel (eluted with an appropriate ethyl acetate–hexane mixture).

Procedure B. To a solution of the ester enolate at −70 °C, prepared as outlined in procedure A, was added the appropriate *pure imine* in 2.0 mL of tetrahydrofuran over a 5-min period. Procedure A was followed for the remainder of the reaction.

Procedure C. All operations were identical with procedure B except 2.0 mL of hexamethylphosphoramide was added *prior* to addition of the ester.

Procedure D. All operations were identical with procedure B except 2.0 mL of hexamethylphosphoramide was added 30–50 min *after* preparation of the ester.

***trans*-3-Isopropenyl-4-phenyl-2-azetidinone (18).** To a solution of 3.46 g (34.3 mmol) of diisopropylamine in 35 mL of tetrahydrofuran was added 22.4 mL (34.2 mmol) of 1.52 M *n*-butyllithium in hexane over a 5-min period at −70 °C. The mixture was stirred for 10 min and 7.0 mL of hexamethylphosphoramide was added. To the solution was added 3.82 g (29.9 mmol) of ethyl 3-methyl-2-butenoate (**17**) in 10 mL of tetrahydrofuran over a 5-min period. The cold solution was stirred for 20 min followed by addition of 5.31 g (30.0 mmol) of *N*-(trimethylsilyl)benzaldimine (**2**) in 10 mL of tetrahydrofuran over a 5-min period. The resulting mixture was stirred at −70 °C for 1 h, warmed to room temperature, stirred for 2 h, and diluted with 200 mL of ether. The solution was washed with two 50-mL portions of 1 N aqueous hydrochloric acid. The washes were extracted with two 200-mL portions of ether. The ethereal solutions were dried ($MgSO_4$) and concentrated in vacuo to give 6.01 g of a yellow oil. The oil was chromatographed over 50 g of silica gel (ethyl acetate–hexane, 1:4) to give 1.97 g of β-lactam **18**. Rechromatography of fractions containing impure **18** gave an additional 0.39 g (42% total) of pure **18**: IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.82 (d, *J* = 1 Hz, 3 H, CH_3), 3.57 (d, *J* = 2.5 Hz, 1 H, CH), 4.52 (d, *J* = 2.5 Hz, 1 H, CHN), 4.82–5.00 (m, 2 H, $=CH_2$), 6.92 (br s, 1 H, NH), 7.30 (s, 5 H, ArH); exact mass calcd for $C_{12}H_{13}NO$ *m/e* 187.0997, found *m/e* 187.1004.

***cis*-3-Isopropyl-4-((*p*-methoxyphenyl)ethynyl)-2-azetidinone (22, R_1 = C≡CPh-*p*-OMe, R_2 = H).** To a cooled solution of lithium hexamethyldisilazide [prepared from 12.75 g (76.2 mmol) of hexamethyldisilazane and 44.5 mL (72.4 mmol) of 1.63 M *n*-butyllithium in hexane according to procedure A] in 60 mL of tetrahydrofuran was added 11.0 g (68.7 mmol) of aldehyde **19e**[24] in 20 mL of tetrahydrofuran at a rate such that the temperature did not exceed −60 °C. The resulting solution was stirred at −70 °C for 40 min and added via cannula to a solution of

(29) Swaminathan, S.; John, J. P.; Ramachandran, S. *Tetrahedron Lett.* **1962**, 729.

(30) The major products of this reaction resulted from N-desilylation and N,O-bisdesilylation.

(31) Autrey, R. L.; Scullard, P. W. *J. Am. Chem. Soc.* **1968**, *90*, 4917. The stereochemical assignment for **41** is based on spectral data and is only tentative. ^1H NMR data indicate that **41** may be a trans β-lactam with a cis olefin geometry.

(32) (a) For pertinent references see Kraus, G. A.; Taschner, M. J. *Tetrahedron Lett.* **1977**, 4575. Fráter, G. *Helv. Chim. Acta.* **1979**, *62*, 2825, 2829. Seebach, D.; Wasmuth, D. *Helv. Chim. Acta.* **1980**, *63*, 197. The stereochemical results presented in these papers can be rationalized on the basis of either (*E*)- or (*Z*)-enolate formation. (b) Deol, B. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459. Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495.

(33) Durst, T.; Van Den Elzen, R.; Legault, R. *Can. J. Chem.* **1974**, *52*, 3206.

(34) Moriconi, E. J.; Kelly, J. F. *Tetrahedron Lett.* **1968**, *1435*.

(35) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941.

the enolate prepared from ethyl isovalerate according to procedure A [8.01 g (79.3 mmol) of diisopropylamine, 48.0 mL (78.1 mmol) of 1.63 M *n*-butyllithium in hexane, and 9.0 g (69.2 mmol) of ethyl isovalerate (**5d**) in 90 mL of tetrahydrofuran]. The mixture was allowed to warm to room temperature over a period of 3 h, diluted with 100 mL of ether, and washed with two 100-mL portions of 1 N aqueous hydrochloric acid. The washes were extracted with three 200-mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting residual solid was recrystallized from ethyl acetate–hexane (1:2) to give 9.9 g of **22** as pale yellow crystals (mp 128–129 °C). The mother liquor was chromatographed over 120 g of silica gel (eluted with ethyl acetate–hexane, 1:3) to give an additional 3.58 g (81% total) of product: mp 128–129 °C; IR (CH_2Cl_2) 3590, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d, J = 6 Hz, 3 H, CH_3), 1.16 (d, J = 6 Hz, 3 H, CH_3), 1.90–2.60 (m, 1 H, CH), 3.03 (ddd, J = 10, 5, 1 Hz, 1 H, CHC=O), 3.76 (s, 3 H, OCH_3), 4.46 (d, J = 5 Hz, CHN), 6.75 (d, J = 9 Hz, with underlying br s, 3 H, ArH and NH), 7.27 (d, J = 9 Hz, 2 H, ArH); exact mass calcd for $C_{15}H_{17}NO_2$ m/e 243.1259, found m/e 243.1244.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.99; H, 6.86.

3-(α-Hydroxyethyl)-4-((trimethylsilyl)ethynyl)-2-azetidinone (25–28). To a cooled solution of lithium hexamethyldisilazide [prepared from 6.12 g (37.9 mmol) of hexamethyldisilazane and 21.0 mL (34.4 mmol) of 1.64 M *n*-butyllithium] was added 4.20 g (33.3 mmol) of aldehyde **19b**[24] in 10 mL of tetrahydrofuran at a rate such that the temperature did not exceed −65 °C. The resulting solution was stirred at −70 °C for 30 min and added via cannula to a solution of the dianion prepared from ethyl β-hydroxybutyrate (**24**) according to procedure A [7.01 g (69.4 mmol) of diisopropylamine, 42.0 mL (68.8 mmol) of 1.64 M *n*-butyllithium in hexane, and 4.38 g (33.1 mmol) of **24** in 70 mL of tetrahydrofuran]. The mixture was stirred at −70 °C for 1 h, allowed to warm to room temperature, and stirred for an additional hour. The mixture was diluted with 100 mL of ether and washed with two 100-mL portions of saturated aqueous ammonium chloride. The aqueous washes were extracted with three 150-mL portions of ether and the combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed twice over silica gel (LoBar size C column, eluted with ethyl acetate–dichloromethane, 2:3) to give 2.74 g (44%) of β-lactam **25**, 1.15 g (17%) of a mixture of diastereomeric β-lactams **26–28**, and 317 mg (5%) of β-lactam **26** as crystalline solids. Lactam **25**: mp 131–132 °C; IR (CH_2Cl_2) 3550, 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9 H, $SiMe_3$), 1.38 (d, J = 6 Hz, 3 H, CH_3), 2.80 (br s, 1 H, OH), 3.33 (t, J = 5.4 Hz, 1 H, CHCO), 4.20–4.40 (m with d, J = 5.4, at δ 4.37, 2 H, NCH and OCH), 6.05 (br s, 1 H, NH); exact mass calcd for $C_{10}H_{17}NO_2Si - H_2O$ m/e 193.0923, found m/e 193.0871. Lactam **26**: mp 108–109 °C; IR (CH_2Cl_2) 3420, 1770 cm^{-1}; NMR ($CDCl_3$) δ 0.19 (s, 9 H, $SiMe_3$), 1.38 (d, J = 6 Hz, 3 H, CH_3), 2.21 (br s, 1 H, OH), 3.35 (m, 1 H, CHCO), 4.08–4.24 (m with d, J = 2.5 Hz, at δ 4.15, 2 H, NCH and OCH), 6.27 (br s, 1 H, NH); exact mass calcd for $C_{10}H_{17}NO_2Si - H_2O$ m/e 193.0923, found m/e 193.0871.

3-(α-Hydroxyethyl)-4-(2-(phenylthio)ethenyl)-2-azetidinone (38) and *N*,*O*-Bis(*tert*-butyldimethylsilyl)-3-(α-hydroxyethyl)-4-(2-(phenylthio)-ethenyl)-2-azetidinone (39–41). A sample of 497 mg (3.74 mmol) of ester **24** and 615 mg (3.75 mmol) of aldehyde **19c** were allowed to react according to procedure A (7.5 mmol of LDA was used and the mixture was stirred for 20 h after reaching room temperature). The crude mixture of products was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 3:2) to give 425 mg (46%) of three diasteriomeric β-lactams **38**. A pure sample of the β-lactam corresponding to **39** (R = H) could be obtained by recrystallization: mp 170–171 °C; IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR (Me_2SO-d_6) δ 1.08 (d, J = 6 Hz, 3 H, CH_3), 3.10–3.40 (m, 1 H, CHCO), 3.65–3.85 (m, 1 H, CHO), 4.29 (dd, J = 8, 6 Hz, 1 H, CHN), 4.57 (d, J = 4 Hz, 1 H, OH), 6.15 (dd, J = 15, 8 Hz, 1 H, =CH), 6.56 (d, J = 15 Hz, 1 H, =CHS), 7.33 (s, 5 H, ArH), 8.00 (br s, 1 H, NH); exact mass calcd for $C_{13}H_{15}NO_2S$ m/e 249.0823, found m/e 249.0838.

To a solution of 200 mg (0.80 mmol) of the lactams **38** prepared above in 5.0 mL of *N*,*N*-dimethylformamide were added 500 mg (3.33 mmol) of *tert*-butyldimethylsilyl chloride and 250 mg (2.47 mmol) of triethylamine at room temperature. The mixture was stirred for 5 h, diluted with 50 mL of ether, and washed with two 10-mL portions of water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was carefully chromatographed three times over a LoBar size B column (eluted with ethyl acetate–hexane, 1:24) to give 251 mg (66%) of **39**, 67 mg (18%) of **40**, and 10 mg (3%) of **41**. Lactam **39**: IR (CH_2Cl_2) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.23 (s, 6 H, $SiMe_2$), 0.93 (s, 9 H, *t*-Bu), 0.97 (s, 9 H, *t*-Bu), 1.30 (d, J = 6 Hz, 3 H, CH_3), 3.25–3.50 (m, 1 H, CHCO), 3.90–4.30 (m, 2 H, NCH and OCH), 6.03 (dd, J = 15, 8 Hz, 1 H, =CH), 6.46 (d, J = 15 Hz, 1 H, =CHS), 7.35 (s, 5 H, ArH); exact mass calcd for $C_{25}H_{43}NO_2Si_2S - C_4H_9$ m/e 420.1849, found m/e 420.1864. Lactam **40**: IR (CH_2Cl_2) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.07 (s, 6 H, $SiMe_2$), 0.18 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, *t*-Bu), 0.93 (s, 9 H, *t*-Bu), 1.27 (d, J = 6 Hz, 3 H, CH_3), 2.95 (dd, J = 4, 2.5 Hz, 1 H, CHCO), 3.90–4.30 (m, 2 H, CHO and CHN), 5.62 (dd, J = 15, 8 Hz, 1 H, =CH), 6.38 (d, J = 15 Hz, 1 H, =CHS), 7.30 (s, 5 H, ArH); exact mass calcd for $C_{25}H_{43}NO_2Si_2S - C_4H_9$ m/e 420.1849, found m/e 420.1831. Lactam **41**: IR (CH_2Cl_2) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.21 (s, 3 H, $SiCH_3$), 0.24 (s, 3 H, $SiCH_3$), 0.92 (s, 3 H, *t*-Bu), 1.11 (s, 9 H, *t*-Bu), 1.34 (d, J = 6 Hz, 3 H, CH_3), 3.07 (dd, J = 4, 2.5 Hz, 1 H, CHCO), 4.17–4.28 (m, 1 H, CHO), 4.52 (dd, J = 10, 2.5 Hz, 1 H, CHN), 5.84 (t, J = 11 Hz, 1 H, =CH), 6.39 (d, J = 11 Hz, 1 H, =CHS), 7.30 (m, 5 H, ArH); exact mass calcd for $C_{25}H_{43}NO_2Si_2S - CH_3$ m/e 462.2318, found 462.2307.

***rel*-(3*S*,4*R*)-3-Ethyl-4-phenyl-3-(phenylthio)-2-azetidinone (4c) and *rel*-(3*R*,4*R*)-3-Ethyl-4-phenyl-3-(phenylthio)-2-azetidinone (3c).** Lactam **4c**: mp 127–128 °C; IR (CH_2Cl_2) 3400, 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, J = 7 Hz, 3 H, CH_3), 1.70–2.10 (m, 2 H, CH_2), 4.73 (s, 1 H, CHN), 6.70 (br s, 1 H, NH), 7.07–7.70 (m, 10 H, ArH); exact mass calcd for $C_{17}H_{17}NOS$ m/e 283.0976, found m/e 283.1010.

Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05. Found: C, 71.34; H, 5.74.

Lactam **3c**: mp 127–128.5 °C; IR (CH_2Cl_2) 3400, 1770 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (t, J = 7 Hz, 3 H, CH_3), 1.00–2.00 (m, 2 H, CH_2), 4.66 (s, 1 H, CHN), 6.00 (br s, 1 H, NH), 7.00–7.60 (m, 8 H, ArH), 7.60 (m, 2 H, ArH); exact mass calcd for $C_{17}H_{17}NOS$ m/e 283.0976, found m/e 283.1010.

***cis*-3-Ethyl-4-phenyl-2-azetidinone (6c, R_3 = H) and *trans*-3-Ethyl-4-phenyl-2-azetidinone (7c, R_3 = H).** Lactam **6c** (R_3 = H): mp 123–124 °C; IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 0.50–1.55 (m, 5 H, CH_2CH_3), 3.32 (ddt, J = 10, 6, 2 Hz, 1 H, CHCO), 4.80 (d, J = 5 Hz, 1 H, CHN), 6.70 (br s, 1 H, NH), 7.27 (s, 5 H, ArH); exact mass calcd for $C_{11}H_{13}NO$ m/e 175.0997, found m/e 175.0953.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.86; H, 7,53.

Lactam **7c** (R_3 = H): mp 77–78.5 °C; IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (t, J = 7 Hz, 3 H, CH_3), 1.65–2.02 (m, 2 H, CH_2), 2.78–3.02 (m, 1 H, CHCO), 4,31 (d, J = 2 Hz, 1 H, CHN), 6.85 (br s, 1 H, NH), 7.30 (s, 5 H, ArH); exact mass calcd for $C_{11}H_{13}NO$ m/e 175,0997, found m/e 175.0968.

***cis*-3-Isopropyl-4-phenyl-2-azetidinone (6d, R_3 = H) and *trans*-3-Isopropyl-4-phenyl-2-azetidinone (7d, R_3 = H).** Lactam **6d** (R_3 = H): mp 129–130 °C; IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 0.44 (d, J = 6 Hz, 3 H, CH_3), 1.04 (d, J = 6 Hz, 3 H, CH_3), 1.44–1.90 (m, 1 H, CH), 3.13 (ddd, J = 12, 6, 1 Hz, 1 H, CHCO), 4.80 (d, J = 6 Hz, 1 H, CHN), 6.60 (br s, 1 H, NH), 7.20 (s, 5 H, ArH); exact mass calcd for $C_{12}H_{15}NO$ m/e 189,1154, found m/e 189.1173.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 76.02; H, 8.02.

Lactam **7d** (R_3 = H): mp 112–113 °C; IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3 H, CH_3), 1.05 (d, J = 6 Hz, 3 H, CH_3), 1.65–2.40 (m, 1 H, CH), 2.73 (dd, J = 8, 2 Hz, 1 H, CHCO), 4.32 (d, J = 2 Hz, 1 H, CHN), 6.80 (br s, 1 H, NH), 7.20 (s, 5 H, ArH); exact mass calcd for $C_{12}H_{15}NO$ m/e 189.1154, found m/e 189.1159.

***cis*-3-*tert*-Butyl-4-phenyl-2-azetidinone (6e, R_3 = H):** mp 151–152 °C; IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (s, 9 H, *t*-Bu), 3.40 (dd, J = 6, 1 Hz, 1 H, CHCO), 4.88 (d, J = 6 Hz, 1 H, CHN), 6.67 (br s, 1 H, NH), 7.35 (s, 5 H, ArH); exact mass calcd for $C_{13}H_{17}NO$ m/e 203.1310, found m/e 203.1349.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.06; H, 8.70.

***cis*-3-Isopropyl-1-(*p*-methoxyphenyl)-4-phenyl-2-azetidinone (6d, R_3 = *p*-MeOPh) and *trans*-3-Isopropyl-1-(*p*-methoxyphenyl)-4-phenyl-2-azetidinone (7d, R_3 = *p*-MeOPh).** Lactam **6d** (R_3 = *p*-MeOPh): mp 164–165 °C; IR (CH_2Cl_2) 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.41 (d, J = 6 Hz, 3 H, CH_3), 1.11 (d, J = 6 Hz, 3 H, CH_3), 1.40–2.00 (m, 1 H, CH), 3.18 (dd, J = 11, 6 Hz, 1 H, CHCO), 3.67 (s, 3 H, OCH_3), 5.05 (d, J = 6 Hz, 1 H, CHN), 6.70 (d, J = 9 Hz, 2 H, ArH), 7.20 (d, J = 9 Hz, 2 H, ArH), 7.29 (s, 5 H, ArH); exact mass calcd for $C_{19}H_{21}NO_2$ m/e 295.1668, found m/e 295.1620.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.02; H, 7.15.

Lactam **7d** (R_3 = *p*-MeOPh): mp 115–116 °C; IR (CH_2Cl_2) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (d, J = 6 Hz, 3 H, CH_3), 1.13 (d, J = 6 Hz, 3 H, CH_3), 1.90–2.50 (m, 1 H, CH), 2.83 (dd, J = 9, 2 Hz, 1 H, CHCO), 3.68 (s, 3 H, OCH_3), 4.63 (d, J = 2 Hz, 1 H, CHN), 6.70 (d, J = 9 Hz, 2 H, ArH), 7.20 (d, J = 9 Hz, 2 H, ArH), 7.29 (s, 5 H, ArH); exact mass calcd for $C_{19}H_{21}NO_2$ m/e 295.1668, found m/e 295.1675.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.55; H, 7.28.

***cis*-4-Phenyl-3-(1-(phenylthio)prop-2-yl)-2-azetidinone (13).** Isolated as a mixture of diastereomers: mp 130–131 °C; IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 0.55 (d, J = 6 Hz, 3 H, CH_3), 1.50–2.10 (m, 1 H, CH), 2.65 (dd, J = 12, 10 Hz, 1 H, CHS), 3.31 (ddd, J = 12, 6, 1 Hz, 1 H, CHCO), 3.57 (dd, J = 12, 3 Hz, 1 H, CHS), 4.70 and 4.75 (two d, J = 6 Hz, 1 H, CHN), 6.67 (br s, 1 H, NH), 6.80–7.40 (m, 10 H, ArH); exact mass calcd for $C_{18}H_{19}NOS$ m/e 297.1188, found m/e 297.1202.

***cis*-3-((Dimethylamino)methyl)-4-phenyl-2-azetidinone (15)**: IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 6 H, NMe_2), 2.18 (m, 2 H, CH_2N), 3.64 (q, J = 6 Hz, 1 H, CHCO), 4.82 (d, J = 6 Hz, 1 H, CHN), 7.30 (m, 6 H, ArH and NH); exact mass calcd for $C_{12}H_{16}N_2O$ m/e 204.1273, found m/e 204,1304.

***cis*-4-Ethenyl-3-isopropyl-2-azetidinone (22a, R_2 = H)**: mp 129–130.5 °C; IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (d, J = 6 Hz, 3 H, CH_3), 1.10 (d, J = 6 Hz, 3 H, CH_3), 1.50–2.25 (m, 1 H, CH), 2.93 (ddd, J = 10, 6, 1 Hz, 1 H, CHCO), 4.13 (t, J = 6 Hz, 1 H, CHN), 5.10–5.47 (m, 2 H, $=CH_2$), 5.65–6.20 (m, 1 H, =CH), 6.48 (br s, 1 H, NH); exact mass calcd for $C_8H_{13}NO - C_3H_7$ m/e 96.0450, found m/e 96.0424.

***cis*-3-Isopropyl-4-((trimethylsilyl)ethynyl)-2-azetidinone (22b, R_2 = H) and *trans*-3-Isopropyl-4-((trimethylsilyl)ethynyl)-2-azetidinone (23b, R_2 = H).** Lactam **22b**: mp 81–82 °C; IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 0.17 (s, 9 H, $SiMe_3$), 1.01 (d, J = 6 Hz, 3 H, CH_3), 1.16 (d, J = 6 Hz, 3 H, CH_3), 1,80–2.40 (m, 1 H, CH), 2.96 (ddd, J = 10, 5.5, 1 Hz, 1 H, CHCO), 4.25 (d, J = 5.5 Hz, 1 H, CHN), 7.00 (br s, 1 H, NH); exact mass calcd for $C_{11}H_{19}NOSi - CH_3$ m/e 194.1127, found m/e 194.1106.

Anal. Calcd for $C_{11}H_{19}NOSi$: C, 63.10; H, 9.15. Found: C, 63.24; H, 9.07.

Lactam **23b**: mp 72–73 °C; IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 0.17 (s, 9 H, $SiMe_3$), 1.00 (d, J = 6 Hz, 3 H, CH_3), 1.06 (d, J = 6 Hz, 3 H, CH_3), 1.70–2.35 (m, 1 H, CH), 3.03 (ddd, J = 8, 3, 1.5 Hz, 1 H, CHO), 3.90 (d, J = 3 Hz, 1 H, CHN), 6.40 (br s, 1 H, NH); exact mass calcd for $C_{11}H_{19}NOSi - CH_3$ m/e 194.1127, found m/e 194.1130.

***cis*-3-Isopropyl-4-(*trans*-2-(thiophenoxy)ethenyl)-2-azetidinone (22c, R_2 = H)**: mp 93–94.5 °C; IR (CH_2Cl_2) 3400, 1760 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3 H, CH_3), 1.08 (d, J = 6 Hz, 3 H, CH_3), 1.50–2.20 (m, 1 H, CH), 2.90 (ddd, J = 10, 5.5, 1 Hz, 1 H, CHCO), 4.15 (dd, J = 7, 5.5 Hz, 1 H, CHN), 5.67 (dd, J = 15, 7 Hz, 1 H, =CH), 6.43 (d, J = 15 Hz, 1 H, =CHS), 6.85 (br s, 1 H, NH), 7.28 (s, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NOS$ m/e 247.1031, found m/e 247.1037.

Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.26; H, 6.93. Found: C, 67.97; H, 7.00.

***cis*-4-(2-Furyl)-3-isopropyl-2-azetidinone (22d, R_2 = H)**; mp 146–147 °C; IR (CH_2Cl_2) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 0.56 (d, J = 6 Hz, 3 H, CH_3), 1.10 (d, J = 6 Hz, 3 H, CH_3), 1.65–2.10 (m, 1 H, CH), 3.10 (ddd, J = 12, 5.5, 1 Hz, 1 H, CHCO), 4.76 (d, J = 5.5 Hz, 1 H, CHN), 6.25–6.40 (m, 2 H, ArH), 6.65 (br s, 1 H, NH), 7.30–7.40 (m, 1 H, ArH); exact mass calcd for $C_{10}H_{13}NO_2$ m/e 179.0920, found m/e 179.0993.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 67.37; H, 7.21.

***cis*-3-Isopropyl-1-(*p*-methoxyphenyl)-4-((trimethylsilyl)ethynyl)-2-azetidinone (22, R_1 = C≡CSiMe$_3$, R_2 = *p*-MeOPh)**: mp 102–103 °C; IR (CH_2Cl_2) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.17 (s, 9 H, $SiMe_3$), 1.9–2.5 (m, 1 H, CH), 3.06 (dd, J = 10, 6 Hz, 1 H, CHCO), 3.73 (s, 3 H, OCH_3), 4.56 (d, J = 6 Hz, 1 H, CHCN), 6,83 (d, J = 9 Hz, 2 H, ArH), 7.45 (d, J = 9 Hz, 2 H, ArH).

Anal. Calcd for $C_{18}H_{25}NO_2Si$: C, 68.53; H, 7.99. Found: C, 68.36; H, 7.48.

***cis*-4-Ethynyl-3-isopropyl-1-(*p*-methoxyphenyl)-2-azetidinone (22, R_1 = C≡CH, R_2 = *p*-MeOPh)**: mp 111–112 °C; IR (CH_2Cl_2) 3300, 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, J = 7 Hz, 3 H, CH_3), 1.30 (d, J = 7 Hz, 3 H, CH_3), 2.35 (m, 1 H, CH), 2.60 (d, J = 1.5 Hz, 1 H, ≡CH), 3.15 (dd, J = 9, 5 Hz, 1 H CHCO), 3.85 (s, 3 H, OCH_3), 4.70 (dd, J = 6, 1.5 Hz, 1 H, CHN), 6.90 (d, J = 9 Hz, 2 H, ArH), 7.50 (d, J = 9 Hz, 2 H, ArH).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.95; H, 6.78.

***trans*-3-Isopropyl-1-(*p*-methoxyphenyl)-4-((trimethylsilyl)ethynyl)-2-azetidinone (23, R = C≡CSiMe$_3$, R_2 = *p*-MeOPh)**, IR (CH_2Cl_2) 1745 cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9 H, $SiMe_3$), 1.06 (d, J = 7 Hz, 3 H, CH_3), 1.11 (d, J = 7 Hz, 3 H, CH_3), 1.7–2.3 (m, 1 H, CH), 3.15 (dd, J = 8, 3 Hz, 1 H, CHCO), 3.73 (s, 3 H, OCH_3), 4.19 (d, J = 3 Hz, 1 H, CHN), 6.83 (d, J = 9 Hz, 2 H, ArH), 7,45 (d, J = 9 Hz, 2 H, ArH); exact mass calcd for $C_{18}H_{25}NO_2Si$ m/e 305.1655, found m/e 305.1682.

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Registry No. 1c, 61829-56-9; **2**, 17599-61-0; **3c**, 90696-08-5; **4c**, 90696-09-6; **5a**, 141-78-6; **5b**, 105-37-3; **5c**, 105-54-4; **5d**, 108-64-5; **5d** (lithium enolate), 90696-39-2; **5e**, 5340-78-3; **6a** (R_3 = H), 5661-55-2; **6b** (R_3 = H), 16934-12-6; **6b** (R_3 = Ph), 22628-31-5; **6c** (R_3 = H), 90696-10-9; **6c** (R_3 = Ph), 17324-18-4; **6c** (R_3 = *t*-BuMe$_2$Si), 90696-40-5; **6d** (R_3 = H), 90696-11-0; **6d** (R_3 = Ph), 17324-20-8; **6d** (R_3 = *p*-MeOPh), 90696-12-1; **6e** (R_3 = H), 90696-13-2; **7b** (R_3 = H), 16934-13-7; **7b** (R_3 = Ph), 17324-17-3; **7c** (R_3 = H), 90696-14-3; **7c** (R_3 = Ph), 17324-19-5; **7d** (R_3 = H), 90718-41-5; **7d** (R_3 = Ph), 17324-21-9; **7d** (R_3 = *p*-MeOPh), 90696-15-4; **11**, 90696-16-5; **12**, 90696-17-6; **13** (isomer 1), 90696-18-7; **13** (isomer 2), 90761-51-6; **14**, 20120-21-2; **15**, 90696-19-8; **16**, 1617-19-2; **16** (acid), 1617-31-8; **17**, 638-10-8; **18**, 90696-20-1; **19a**, 107-02-8; **19b**, 2975-46-4; **19c**, 80227-71-0; **19d**, 98-01-1; **19e**, 90696-21-2; **19e** (alcohol), 37614-59-8; **20a**, 90696-22-3; **20b**, 83948-31-6; **20c**, 90696-23-4; **20d**, 83948-29-2; **20e**, 90718-42-6; **21**, 90696-41-6; **22a** (R_2 = H), 90696-24-5; **22b** (R_2 = H), 90696-25-6; **22c** (R_2 = H), 90696-26-7; **22d** (R_2 = H), 90696-27-8; **22e** (R_2 = H), 90696-28-9; **22** (R_1 = C≡CSiMe$_3$; R_2 = *p*-MeOPh), 90696-29-0; **22** (R_1 = C≡CH; R_2 = *p*-MeOPh), 90696-30-3; **23b** (R_2 = H), 90696-31-4; **23** (R_1 = C≡CSiMe$_3$; R_2 = *p*-MeOPh), 90696-32-5; **24**, 5405-41-4; **25**, 90696-33-6; **26**, 90761-39-0; **27**, 90761-40-3; **28**, 90819-96-8; **29**, 90696-34-7; **30**, 90696-35-8; **31**, 90696-36-9; **32**, 90761-41-4; **33**, 84276-68-6; **34**, 90761-42-5; **35**, 90761-43-6; **36**, 90761-44-7; **37**, 84276-67-5; **38** (isomer 1), 90696-37-0; **38** (isomer 2), 90761-45-8; **38** (isomer 3), 90761-46-9; **39**, 90696-38-1; **40**, 90761-47-0; **41**, 90761-48-1; **42**, 90761-49-2; **43**, 90761-50-5; PhCH=NPh, 538-51-2; PhCH=N-*p*-MeOPh, 783-08-4; PhSH, 108-98-5; 4-iodoanisole, 696-62-8; propargyl alcohol, 107-19-7; *p*-anisidine, 104-94-9.

Supplementary Material Available: Experimental procedures for reactions outlined in eq 2–4 and Schemes II–IV and spectral data characterizing all compounds not described in the experimental section (11 pages), Ordering information is given on any current masthead page,