A Three-Step General Synthesis of 2-Azetidinones Bearing *N*-Dehydroamino Acid Side Chains[◇]

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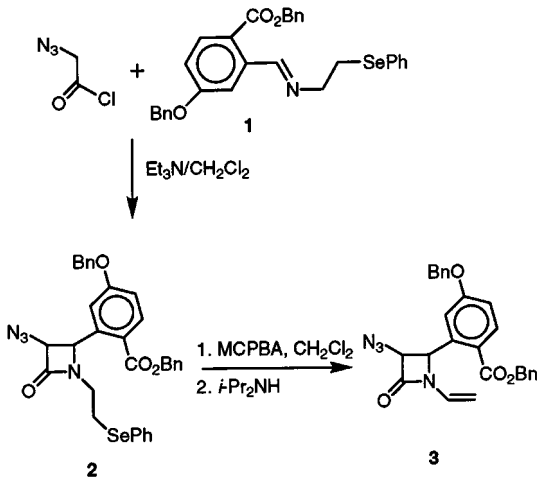
An efficient, three-step synthesis of *N*-vinyl-2-azetidinones **7** starting from α- or β-amino ester imines **4** has been developed. Staudinger reaction between imines **4** and a ketene precursor gave 2-azetidinones **5**. Enolate formation on the amino ester moiety of the 2-azetidinone **5**, selenylation, and finally *m*-CPBA treatment, afforded *N*-vinyl-2-azetidinones **7** in fair to excellent yields, with retention at the remaining stereocenters of the starting material. Two examples of the use of compounds **7** to prepare bi- and tricyclic 2-azetidinones are presented.

Introduction

The increasing resistance of bacteria to commonly used β-lactam antibiotics[1] and the ever-growing new applications of these products in fields ranging from enzyme inhibition[2] to the use of 2-azetidinones as raw materials for developing new synthetic methodologies[3] have triggered a renewed interest in developing new routes to polycyclic β-lactam systems. Our own interest in this field has resulted in new approaches to the synthesis of bi- and polycyclic 2-azetidinones.[4] In this context, a versatile, simple, and stereoselective route to *N*-vinyl-2-azetidinone derivatives was needed. Different approaches to this type of 2-azetidinone derivative are known. They are obtained mainly from penicillin derivatives by ring fission followed by basic isomerization.[5] Alternative routes to these compounds are the functionalization of 2-azetidinones having appropriate chains tethered to the lactam nitrogen. Examples are the intermolecular carbene insertion of β-oxodiazo esters into the NH lactam bond, as catalyzed by $Rh_2(OAc)_4$,[6] the enolization of *N*-1,3-acetal esters by TFA,[7] and the generation of transient *N*-vinyl-2-azetidinones from β-lactams derived from amino esters, especially serine[8] and threonine,[9] 2-amino-1,3-propanediols,[10] allylamine,[11] and β-hydroxyamines.[12] On the other hand, the *N*-vinyl moiety can be incorporated into the β-lactam nucleus by treating a ketene precursor with an appropriate 2-aza-1,3-diene derivative.[13] However, the major drawback of the existing routes for preparing *N*-vinyl-2-azetidinone derivatives is that they are designed to accomplish the synthesis of a defined product, and many of them lack the necessary versatility, especially in the introduction of the carboxy group contiguous to the lactam nitrogen, which is a characteristic of active β-lactam antibiotics.[14] We report herein the successful development of a three-step synthesis of *N*-vinyl-2-azetidinones, both in racemic and optically pure form, starting from imines derived from α- or β-amino esters. Our approach is based on the sequential Staudinger reaction between a ketene precursor and an amino ester imine, followed by α-selenylation of the amino ester moiety of the 2-azetidinone, and finally, oxidative deseleniation to produce the desired compounds. To the best of our knowledge, the sole precedent for the use of a seleno derivative to prepare an *N*-vinyl-2-azetidinone is the treatment of β-lactam **2**, prepared by cycloaddition of azidoacetyl chloride to the imine **1**, with *m*-CPBA/iPr$_2$NH to afford compound **3** (Scheme 1).[15]

Scheme 1



Results and Discussion

2-Azetidinones **5** were prepared by standard Staudinger reactions.[16] A series of imines **4a–g** derived from β-alanine, L-alanine, L-serine, and L-aspartic acid methyl esters, prepared in quantitative yield by condensation of various aldehydes with the corresponding amino ester in CH_2Cl_2 in the presence of $MgSO_4$,[17] were treated, without further purification, with the corresponding acid chloride in the

[◇] For a preliminary communication of a part of this work, see: B. Alcaide, C. Polanco, M. A. Sierra, *Synlett* **1998**, 416–418.

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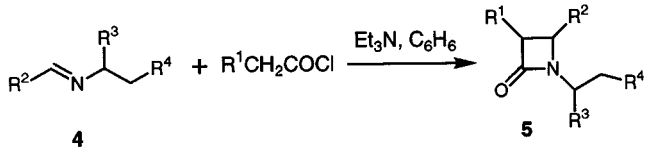
presence of Et_3N, except in the case of compound **4i**, where the acid/$Cl_2P(O)OPh$/Et_3N modification[18] of the Staudinger reaction was used (Scheme 2, Table 1). 2-Azetidinones **5a** and **5b** derived from β-alanine were obtained as single *cis* isomers, while 2-azetidinone **5c** was obtained as its *trans* isomer. L-Alanine-, L-serine-, and L-aspartic acid derived β-lactams, **5d**−**e**, **5g**, **5k**−**l**, were formed as diastereomeric mixtures of both *cis* diastereomers with low selectivity when the amino acid chiral center was the only one involved in the ring formation. In these cases, diastereomerically pure compounds **5** were easily obtained by flash chromatography. With the exception of compound **5f**, a single *cis* diastereomer was obtained when either a chiral ketene precursor (compounds **5h**−**i**) or an imine derived from D-glyceraldehyde acetonide (compounds **5b**, **5j**) was used.

Scheme 2



of the stereochemistry for compounds **5d**, **e**, **5g**, **5k**, **l** rather speculative.

With a diverse variety of compounds **5** at hand, their transformation into the desired *N*-vinyl-2-azetidinones was studied. Treatment of diastereomerically pure β-lactams **5** with LHMDS at −78°C (see Experimental Section for specific reaction conditions), generated the corresponding ester enolates, which were quenched with BrSePh to produce the α-seleniated derivatives **6** as diastereomeric mixtures. Although compounds **6** can be isolated, purified, and characterized (see Experimental Section for two examples), they were submitted to oxidation directly as obtained. Reaction of compounds **6** with *m*-CPBA at −78°C gave *N*-vinyl-2-azetidinones **7** in nearly quantitative yields (Scheme 3). The overall yields for the synthesis of compounds **7** range from fair to excellent (Table 2). Formation of the double bond in 2-azetidinone **7j** occurs upon simple treatment with base. This behavior has been observed previously in related systems.[24] While 2-azetidinones derived from β-alanine, **7a**−**c**, were obtained as single (*E*) isomers at the newly formed double bond, L-aspartic acid derivative **5l** yielded unselectively a mixture of (*E*/*Z*)-β-lactams, **7k**. In this case, the stereochemistry of the double bond was deter-

Table 1. Synthesis of 2-Azetidinones **5**

	R^1	R^2	R^3	R^4	Yield[a]	*cis/trans*	*d.r.*[b]
4a, 5a	BnO	Ph	H	CO_2Me	55	100:0	–
4b, 5b	BnO	Diox[c]	H	CO_2Me	88	100:0	100:0
4a, 5c	*i*-Pr	Ph	H	CO_2Me	80	0:100	–
4c, 5d	BnO	Ph	CO_2Me	H	81	100:0	60:40
4d, 5e	BnO	*o*-BrC_6H_4	CO_2Me	H	73	100:0	57:43
4e, 5f	BnO	Diox[c]	CO_2Me	H	72	100:0	84:16
4f, 5g	PhO	(*E*)-C(Me)=CHPh	CO_2Me	H	75	100:0	60/40
4c, 5h	Ox[d]	Ph	CO_2Me	H	51	100:0	100:0
4d, 5i	Ox[d]	*o*-BrC_6H_4	CO_2Me	H	70	100:0	100:0
4e, 5j	Pht[e]	Diox[c]	CO_2Me	H	75	100:0	100:0
4g, 5k	PhO	Ph	CO_2Me	TBDMSO	88	100:0	74:26
4h, 5l	BnO	Ph	CO_2Me	CO_2Me	87	100:0	57:43

[a] Yields are for pure, isolated material. For reactions forming diastereomeric mixtures, the listed yields are for the pure combined mixture of isomers. – [b] Determined by integration of well-resolved signals in the ^{1}H-NMR spectra of crude reaction mixtures prior to purification. – [c] Diox = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl. – [d] Ox = (*S*)-4-phenyl-2-oxooxazolidin-3-yl. – [e] Pht = phthalimido.

The assignment of (3*S*,4*R*) stereochemistry for the 2-azetidinones derived from Evans′ ketene (**5h**, **i**), and (3*R*,4*S*) to those derived from D-glyceraldehyde acetonide (**5b**, **5f** major isomer, and **5j**) is based on the current model for asymmetric induction in the Staudinger reaction.[19] The assignment of stereochemistry for the remaining 2-azetidinones is not straightforward. The stereochemistry of some related 2-azetidinones, derived from alanine *tert*-butyl ester and azidoacetyl chloride, has been determined by their conversion to peptides,[20] and it has been reported that D-threonine cinnamaldehyde imines induce the same stereochemistry as D-glyceraldehyde acetonide.[21] A similar observation has been reported for serine derivatives.[22] However, the lack of a reliable model for predicting the stereochemical outcome of the Staudinger reaction when the chiral center of the amino ester is the only one present[23] makes the assignment mined by NOE experiments and by comparison with related compounds.[24] 2-Azetidinone **5j** did not form the expected *N*-vinyl derivative under the standard conditions. A systematic variation of the reaction conditions was fruitless. Clearly, an imide group is not compatible with our approach. The stereochemical integrity of the chiral centers at the four-membered ring remains unaltered during the transformation of compounds **5** to products **7**.[25][26]

The results listed in Table 2 shown that our approach offers a versatile and efficient access to *N*-vinyl-2-azetidinone derivatives. It should be pointed out that compounds **7** represent α,β-dehydroamino acids bearing a 2-azetidinon-1-yl substituent. The role of α,β-dehydroamino acids as key intermediates in amino acid and peptide synthesis, and as constituents of naturally occurring antibiotics and phytotoxic peptides, is well known.[27]

Scheme 3

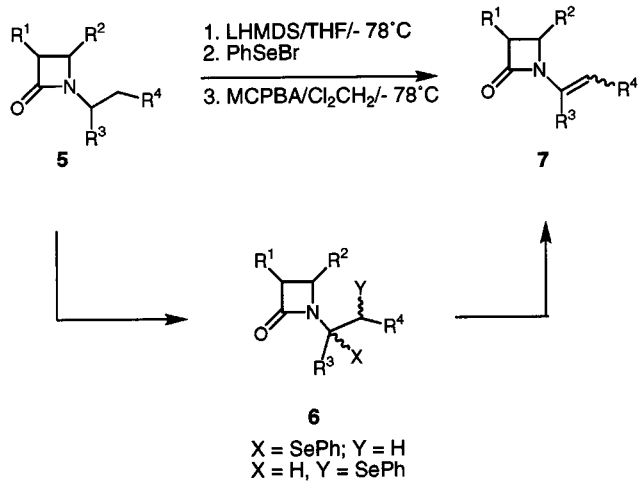


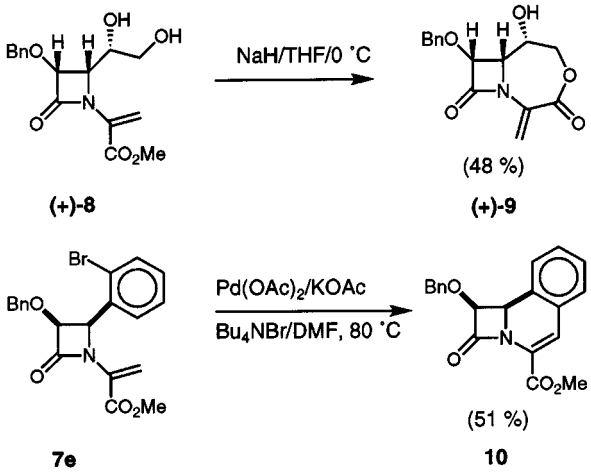
Table 2. Synthesis of *N*-vinyl-2-azetidinones **7**

	R^1	R^2	R^3	R^4	Yield[a]
7a	BnO	Ph	H	CO_2Me	89
7b	BnO	Diox[b]	H	CO_2Me	91
7c	*i*-Pr	Ph	H	CO_2Me	87
7d	BnO	Ph	CO_2Me	H	89
7e	BnO	*o*-BrC_6H_4	CO_2Me	H	91
7f	BnO	Diox[b]	CO_2Me	H	—[d]
7g	PhO	$C(CH_3)$=CHPh	CO_2Me	H	70
7h	Ox[c]	Ph	CO_2Me	H	55
7i	Ox[c]	*o*-BrC_6H_4	CO_2Me	H	85
7j	PhO	Ph	CO_2Me	H	66[e]
7k	BnO	Ph	CO_2Me	CO_2Me	83[f]

[a] Yields are for pure, isolated material. — [b] Diox = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl. — [c] Ox = (*S*)-4-phenyl-2-oxooxazolidin-3-yl. — [d] Compound **7f** was obtained in quantitative yield. However, extensive decomposition was observed during purification, hence the product was used as obtained in the synthesis of diol **8**; see text. — [e] Compound **7j** was obtained by base treatment of 2-azetidinone **5k**. — [f] Obtained as a 50:50 (*E*/*Z*) mixture.

Two preliminary examples of the application of these compounds to the synthesis of bi- and tricyclic β-lactam products are presented in Scheme 4. Diol (+)-**8** was prepared from compound (3*R*,4*S*)-**7f** by standard ketal deprotection with TsOH followed by purification by flash column chromatography. Several reaction conditions aimed at promoting the intramolecular Michael cyclization, including the use of NaOH in heterogeneous and homogeneous media, Triton B, and basic Amberlyst, all of which have proved efficient in promoting this reaction in related systems[28] were tested, but invariably led to extensive decomposition. Finally, treatment with NaH resulted in the instantaneous formation of seven-membered lactone (+)-**9** (48%, isolated pure material). On the other hand, heating of compound **7e** (80°C) in the presence of $Pd(AcO)_2$, KOAc, and Bu_4NBr in DMF solution resulted in its quantitative conversion to benzocarbacephem **10** (Scheme 4).[29][30] The stereochemistry remained unaltered during the formation of tricycle **10**, as confirmed by ^{1}H-NMR analysis in the presence of chiral shift reagents.[25] The cyclized product was isolated in 56% yield. These two examples are promising results with regard to our ultimate goal of developing compounds **7** as versatile intermediates for the synthesis of new bi- and polycyclic β-lactams.

Scheme 4



In conclusion, a three-step synthesis of 2-azetidinones bearing *N*-dehydroamino acid side chains has been developed. The process occurs without racemization when diastereomerically pure β-lactams are used. Preliminary cyclization studies involving the use of compounds **7** in preparing functionalized polycyclic β-lactam systems have yielded promising results. Efforts to develop an efficient synthesis of biologically active polycyclic β-lactam systems using the methodology reported here are currently in progress.

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Experimental Section

General: ^{1}H- (300 MHz) and ^{13}C-NMR (75.43 MHz) spectra were recorded in $CDCl_3$ solution, unless otherwise stated. Optical rotations were measured with a Perkin-Elmer 241 apparatus at room temperature (25°C) (λ = 5890 Å). Specific rotation values $[\alpha]_D$ are given in deg per dm, and the concentration (*c*) is expressed in g per 100 ml in $CHCl_3$. Elemental analyses were obtained at the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid). All solvents used in this work were purified by distillation. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. Benzene, CH_2Cl_2, and Et_3N were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. For purification of crude reaction mixtures by flash chromatography, Merck silica gel (230−400 mesh) was used as the stationary phase. Products were identified by TLC (Kieselgel 60F-254); UV light (λ = 254 nm) and 5% phosphomolybdic acid solution in 95% EtOH were used to develop the plates.

All commercially available compounds were used without further purification. The following chemicals were prepared according to literature procedures: phthalimidoacetyl chloride,[31] 2,3-*O*-(isopropylidene)-D-glyceraldehyde,[32] and (*S*)-(4-phenyl-2-oxooxazolidinyl)acetyl chloride.[33] Imines **4** were prepared by condensation of

the corresponding aldehyde and the amino ester hydrochloride in Et_2O solution in the presence of Et_3N, according to our reported procedure.[4c]

General Method for the Synthesis of the 2-Azetidinones **5a−l**. − *Method A:* The acid chloride (7.5 mmol) in anhydrous benzene (25 ml) was added dropwise by means of a syringe to a boiling solution of the imine (5 mmol) and Et_3N (10 mmol) in benzene (25 ml). The resulting mixture was refluxed until complete consumption of the imine (TLC). The crude mixture was diluted with CH_2Cl_2 (25 ml) and successively washed with saturated aqueous $NaHCO_3$ solution (2 × 40 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. Residues were purified by crystallization from the solvent indicated, or by flash chromatography (EtOAc/hexanes mixtures). Unless otherwise stated, when the reaction yielded diastereomeric mixtures, chromatographic separation allowed the isolation of the major isomer as a pure diastereomer. − *Method B:* This method was identical to Method A except that the reaction was carried out at room temperature.

cis-3-Benzyloxy-1-(2-methoxycarbonylethyl)-4-phenyl-2-azetidinone (**5a**): Method B. From 1.00 g (5 mmol) of imine **4a** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, 1.61 g (95%) of β-lactam **5a** was obtained as a colorless solid by crystallization from EtOAc/hexane; m.p. 137−138°C (EtOAc/hexane). − ^{1}H NMR: δ = 2.41−2.62 (m, 2 H), 3.23−3.34 (m, 1 H), 3.59 (s, 3 H), 3.60−3.75 (m, 1 H), 4.13 (d, *J* = 11.2 Hz, 1 H), 4.26 (d, *J* = 11.2 Hz, 1 H), 4.78 (d, *J* = 4.3 Hz, 1 H), 4.86 (d, *J* = 4.3 Hz, 1 H), 6.90−6.93 (m, 2 H), 7.19−7.26 (m, 3 H), 7.40−7.52 (m, 5 H). − ^{13}C NMR: δ = 171.6, 167.2, 136.4, 134.1, 128.8, 128.7, 128.6, 128.3, 128.2, 128.0, 83.7, 72.3, 62.9, 52.0, 36.3, 32.5. − IR (KBr): ṽ = 1760, 1740. − $C_{20}H_{21}NO_4$ (339.4): calcd. C 70.78, H 6.24, N 4.13; found C 71.00, H 6.45, N 4.51.

(+)-(3R,4S)-cis-3-Benzyloxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(2-methoxycarbonylethyl)-2-azetidinone (**5b**): Method B. From 1.08 g (5 mmol) of imine **4b** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, 1.60 g (88%) of β-lactam **5b** was obtained as a pale-yellow solid after purification by flash chromatography (EtOAc/hexane, 1:6); m.p. 66−67°C (EtOAc/hexane). − $[\alpha]_D$ = +59.2 (*c* = 0.05, $CHCl_3$). − ^{1}H NMR: δ = 1.33 (s, 3 H), 1.43 (s, 3 H), 2.60−2.72 (m, 2 H), 3.50−3.72 (m, 4 H), 3.68 (s, 3 H), 4.13 (dd, J_1 = 8.7 Hz, J_2 = 6.6 Hz, 1 H), 4.26−4.32 (m, 1 H), 4.59 (d, *J* = 5.1 Hz, 1 H), 4.61 (d, *J* = 11.7 Hz, 1 H), 4.88 (d, *J* = 11.7 Hz, 1 H), 7.22−7.38 (m, 5 H). − ^{13}C NMR: δ = 171.6, 167.5, 136.8, 128.4, 128.0, 127.7, 109.6, 80.2, 76.8, 72.8, 66.7, 60.6, 51.8, 37.2, 32.1, 26.8, 25.1. − IR ($CHCl_3$): ṽ = 1750, 1440. − $C_{19}H_{25}NO_6$ (363.4): calcd. C 62.80, H 6.93, N 3.85; found C 62.95, H 7.23, N 3.54.

trans-3-Isopropyl-1-(2-methoxycarbonylethyl)-4-phenyl-2-azetidinone (**5c**): Method A. From 1.00 g (5 mmol) of imine **4a** and 1.13 g (7.5 mmol) of isovaleryl chloride, 1.10 g (80%) of β-lactam **5c** was obtained as a pale-yellow oil after purification by flash chromatography (EtOAc/hexane, 1:6). − ^{1}H NMR: δ = 1.00 (d, *J* = 6.6 Hz, 3 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 2.02−2.20 (m, 1 H), 2.42−2.62 (m, 2 H), 2.80 (dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, 1 H), 3.10−3.20 (m, 1 H), 3.62 (s, 3 H), 3.68−3.77 (m, 1 H), 4.32 (d, *J* = 2.1 Hz, 1 H), 7.22−7.41 (m, 5 H). − ^{13}C NMR: δ = 171.6, 170.0, 138.4, 128.9, 128.2, 126.3, 67.3, 59.4, 51.8, 36.2, 32.7, 28.2, 20.1, 19.9. − IR ($CHCl_3$): ṽ = 1740. − $C_{16}H_{21}NO_3$ (275.3): calcd. C 69.79, H 7.69, N 5.09; found C 69.60, H 7.77, N 5.17.

cis-3-Benzyloxy-1-(1-methoxycarbonylethyl)-4-phenyl-2-azetidinone (**5d**): Method B. From 1.00 g (5 mmol) of imine **4c** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, a crude reaction mixture containing both *cis* diastereomers (60:40) was obtained. From this mixture, 0.44 g (26%) of the major isomer **5d** was separated as a pure compound after purification by flash chromatography (EtOAc/hexane, 1:4). Combined yield 81% (1.37 g). − *Major isomer:* White solid; m.p. 82−83°C (EtOAc). − $[\alpha]_D$ = +66.7 (*c* = 0.66, $CHCl_3$). − ^{1}H NMR: δ = 1.13 (d, *J* = 7.7 Hz, 3 H), 3.73 (s, 3 H), 4.12 (d, *J* = 11.1 Hz, 1 H), 4.26 (d, *J* = 11.1 Hz, 1 H), 4.61 (q, *J* = 7.7 Hz, 1 H), 4.94 (d, *J* = 4.8 Hz, 1 H), 5.03 (d, *J* = 4.8 Hz, 1 H), 6.91−6.95 (m, 2 H), 7.15−7.22 (m, 3 H), 7.35−7.44 (m, 5 H). − ^{13}C NMR: δ = 171.3, 167.6, 136.2, 135.2, 128.7, 128.5, 128.2, 128.2, 128.1, 127.9, 83.1, 72.3, 62.1, 52.5, 49.7, 16.0. − IR ($CHCl_3$): ṽ = 1770, 1745. − $C_{20}H_{21}NO_4$ (339.4): calcd. C 70.78, H 6.24, N 4.13; found C 70.41, H 6.30, N 4.06. − *Minor isomer* (from an enriched diastereomeric mixture): ^{1}H NMR: δ = 1.61 (d, *J* = 7.2 Hz, 3 H), 3.60 (s, 3 H), 4.02 (q, *J* = 7.2 Hz, 1 H), 4.13 (d, *J* = 11.1 Hz, 1 H), 4.28 (d, *J* = 11.1 Hz, 1 H), 4.83 (d, *J* = 4.5 Hz, 1 H), 4.90 (d, *J* = 4.5 Hz, 1 H), 6.91−6.94 (m, 2 H), 7.18−7.22 (m, 3 H), 7.35−7.44 (m, 5 H). − ^{13}C NMR: δ = 170.5, 166.7, 136.1, 133.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.7, 83.1, 72.1, 62.2, 52.2, 51.0, 15.2.

cis-3-Benzyloxy-4-(o-bromophenyl)-1-(1-methoxycarbonylethyl)-2-azetidinone (**5e**): Method B. From 1.35 g (5 mmol) of imine **4d** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, a crude reaction mixture containing both *cis* diastereomers (57:43) was obtained. From this mixture, 2.77 g (73%) of inseparable *cis* diastereomers **5e** was obtained as a pale-yellow oil after purification by flash chromatography (EtOAc/hexane, 1:4). From the diastereomeric mixture: *Major isomer:* ^{1}H NMR: δ = 1.21 (d, *J* = 7.3 Hz, 3 H), 3.75 (s, 3 H), 4.06 (q, *J* = 7.3 Hz, 1 H), 4.26−4.45 (m, 2 H), 5.02 (d, *J* = 4.7 Hz, 1 H), 5.53 (d, *J* = 4.7 Hz, 1 H), 6.75−6.78 (m, 2 H), 7.12−7.48 (m, 5 H), 7.51−7.60 (m, 2 H). − *Minor isomer:* ^{1}H NMR: δ = 1.68 (d, *J* = 7.5 Hz, 3 H), 3.67 (s, 3 H), 4.26−4.45 (m, 2 H), 4.69 (q, *J* = 7.5 Hz, 1 H), 4.97 (d, *J* = 4.6 Hz, 1 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 6.75−6.78 (m, 2 H), 7.12−7.48 (m, 5 H), 7.51−7.60 (m, 2 H). − ^{13}C NMR (from the diastereomeric mixture): δ = 171.1, 170.8, 168.1, 167.4, 136.4, 136.3, 134.7, 133.6, 133.0, 132.9, 130.4, 130.0, 129.9, 129.8, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 127.5, 127.3, 123.9, 123.7, 83.3, 83.1, 72.7, 72.7, 62.0, 61.4, 52.8, 52.7, 51.9, 50.3, 15.8, 15.7. − IR ($CHCl_3$): ṽ = 1760, 1740. − $C_{20}H_{20}BrNO_4$ (418.3): calcd. C 57.43, H 4.82, N 3.35; found C 57.68, H 4.99, N 3.16.

cis-3-Benzyloxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(1-methoxycarbonylethyl)-2-azetidinone (**5f**): Method B. From 1.08 g (5 mmol) of imine **4e** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, a crude reaction mixture containing both *cis* diastereomers (84:16) was obtained. From this mixture, 0.89 g (49%) of the major isomer **5f** was separated as a pure compound after purification by flash chromatography (EtOAc/hexane, 1:6). Combined yield 72% (2.61 g). − (+)-(3*R*,4*S*)-**5f**: Yellow oil; $[\alpha]_D$ = +89.8 (*c* = 1.98, $CHCl_3$). − ^{1}H NMR: δ = 1.23 (s, 3 H), 1.31 (s, 3 H), 1.52 (d, *J* = 7.4 Hz, 3 H), 3.55 (dd, J_1 = 8.7 Hz, J_2 = 6.1 H, 1 H), 3.67 (s, 3 H), 3.85 (dd, J_1 = 9.1 Hz, J_2 = 5.3 Hz, 1 H), 4.09 (dd, J_1 = 8.8 Hz, J_2 = 6.7 Hz, 1 H), 4.21−4.28 (m, 1 H), 4.40 (q, *J* = 7.41 Hz, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H), 4.60 (d, *J* = 5.3 Hz, 1 H), 4.85 (d, *J* = 11.8 Hz, 1 H), 7.22−7.32 (m, 5 H). − ^{13}C NMR: δ = 170.8, 167.5, 136.7, 128.3, 127.9, 127.7, 109.2, 80.0, 76.2, 72.8, 66.8, 61.2, 52.2, 50.2, 26.6, 25.0, 16.2. − IR ($CHCl_3$): ṽ = 1720, 1750. − $C_{19}H_{25}NO_6$ (363.4): calcd. C 62.78, H 6.94, N 3.86; found C 62.96, H 6.72, N 3.79. − *Minor isomer* (from an enriched diastereomeric mixture): ^{1}H NMR: δ = 1.28 (s, 3 H), 1.38 (s, 3 H), 1.63 (d, *J* = 7.7 Hz, 3 H), 3.72 (s, 3 H), 3.96 (d, *J* = 6.6 Hz, 1 H), 4.11−4.24 (m, 4 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 4.70 (d, *J* = 5.1 Hz, 1 H), 4.83 (d, *J* = 11.4 Hz, 1 H), 7.22−7.32 (m, 5 H).

– ^{13}C NMR: δ = 170.9, 167.4, 136.6, 128.4, 128.0, 127.9, 107.8, 80.5, 74.6, 73.2, 64.4, 58.4, 52.5, 50.2, 25.9, 23.7, 15.2.

cis-3-Benzyloxy-1-(1-methoxycarbonylethyl)-4-[(E)-1-methylstyryl]-2-azetidinone (**5g**): Method B. From 1.16 g (5 mmol) of imine **4f** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, a crude reaction mixture containing both *cis* diastereomers (60:40) was obtained. From this mixture, 0.46 g (24%) of the major isomer **5g** was separated as a pure compound after purification by flash chromatography (EtOAc/hexane, 1:8). Combined yield: 79% (1.50 g). – *Major isomer*: Yellow oil. $[\alpha]_D$ = +9.7 (*c* = 1.09, $CHCl_3$). – ^{1}H NMR: δ = 1.30 (d, *J* = 7.5 Hz, 3 H), 1.91 (s, 3 H), 3.65 (s, 3 H), 4.52–4.57 (m, 2 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.63 (d, *J* = 11.4 Hz, 1 H), 4.82 (d, *J* = 4.8 Hz, 1 H), 6.51 (s, 1 H), 7.15–7.21 (m, 10 H). – ^{13}C NMR: δ = 171.3, 167.9, 136.9, 136.8, 134.2, 130.7, 129.0, 128.6, 128.5, 128.2, 127.9, 126.9, 83.1, 73.8, 66.1, 52.5, 49.6, 15.3, 15.0. – IR ($CHCl_3$): $\tilde{\nu}$ = 1740. – $C_{23}H_{25}NO_4$ (379.5): calcd. C 72.80, H 6.64, N 3.69; found C 72.63, H 6.91, N 3.92. – *Minor isomer* (from an enriched diastereomeric mixture): ^{1}H NMR: δ = 1.56 (d, *J* = 7.5 Hz, 3 H), 1.86 (s, 3 H), 3.62 (s, 3 H), 3.97 (q, *J* = 7.5 Hz, 1 H), 4.31 (d, *J* = 5.1 Hz, 1 H), 4.57 (d, *J* = 11.4 Hz, 1 H), 4.66 (d, *J* = 11.4 Hz, 1 H), 4.73 (d, *J* = 5.1 Hz, 1 H), 6.43 (s, 1 H), 7.15–7.21 (m, 10 H). – ^{13}C NMR: δ = 170.9, 167.4, 137.1, 137.0, 133.0, 130.9, 129.2, 128.7, 128.5, 128.4, 128.1, 127.1, 83.3, 72.8, 66.3, 52.6, 51.6, 15.5, 15.2.

(+)-(3S,4R)-cis-1-(1-Methoxycarbonylethyl)-4-phenyl-3-[(S)-4-phenyl-2-oxooxazolidin-3-yl]-1-azetidinone (**5h**): A solution of Et_3N (6 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of (*S*)-(4-phenyl-2-oxooxazolidinyl)acetyl chloride (0.71 g, 3 mmol) in CH_2Cl_2 (10 ml) at –78°C under argon. The mixture was stirred for 30 min, and then a solution of the imine **4c** (0.38 g, 2 mmol) in CH_2Cl_2 (5 ml) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Then, MeOH (2 ml) followed by CH_2Cl_2 (20 ml) was added, and the mixture was washed with water and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 1:2) to afford 0.71 g (91%) of pure compound **5h** as a white solid; m.p. 177–178°C (EtOAc) (ref.[16d] 174–175°C). – $[\alpha]_D$ = +36.3 (*c* = 1.1, $CHCl_3$) [ref.[16d] +29.5 (*c* = 2.7, $CHCl_3$)]. – ^{1}H NMR: δ = 1.73 (d, *J* = 7.2 Hz, 3 H), 3.66 (s, 3 H), 3.91–3.97 (m, 2 H), 4.21 (t, *J* = 9.0 Hz, 1 H), 4.33 (dd, J_1 = 8.7 Hz, J_2 = 7.5 Hz, 1 H), 4.58 (d, *J* = 5.1 Hz, 1 H), 4.84 (d, *J* = 5.1 Hz, 1 H), 7.15–7.19 (m, 2 H), 7.23–7.25 (m, 2 H), 7.30–7.41 (m, 6 H). – ^{13}C NMR: δ = 171.0, 163.9, 136.6, 133.5, 129.5, 129.4, 129.0, 128.7, 127.8, 127.7, 70.4, 63.5, 62.2, 59.6, 52.7, 52.6, 15.7. – IR (KBr): $\tilde{\nu}$ = 1770. – $C_{22}H_{22}N_2O_5$ (394.4): calcd. C 66.99, H 5.62, N 7.10; found C 67.15, H 5.77, N 7.39.

(–)-(3S,4R)-cis-4-(2-Bromophenyl)-1-(1-methoxycarbonylethyl)-3-[(S)-4-phenyl-2-oxooxazolidin-3-yl]-1-azetidinone (**5i**): A solution of (*S*)-(4-phenyl-2-oxooxazolidinyl)acetic acid (0.33 g, 1.5 mmol) in CH_2Cl_2 (5 ml) was added to a solution of the imine **4d** (0.27 g, 1 mmol) in CH_2Cl_2 (5 ml). Then, Et_3N (3 mmol) followed by a solution of phenyl dichlorophosphate (0.36 g, 1.5 mmol) in CH_2Cl_2 (15 ml) were added. The mixture was stirred for about 12 h, then washed with saturated $NaHCO_3$ solution (2 × 10 ml) and water. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/hexane, 1:2) to afford 0.67 g (70%) of pure compound **5i** as a white solid; m.p. 144–145°C (EtOAc). – $[\alpha]_D$ = –79.8 (*c* = 1.05, $CHCl_3$). – ^{1}H NMR: δ = 1.85 (d, *J* = 7.5 Hz, 3 H), 3.67 (s, 3 H), 3.01–3.97 (m, 2 H), 4.23 (t, *J* = 8.7 Hz, 1 H), 4.37 (d, *J* = 5.4 Hz, 1 H), 4.60 (t, *J* = 8.1 Hz, 1 H), 5.07 (d, *J* = 5.4 Hz, 1 H), 7.22–7.24 (m, 2 H), 7.33–7.49 (m, 5 H), 7.58–7.61 (d, 2 H). – ^{13}C NMR: δ = 171.1, 164.7, 156.3, 136.6, 132.9, 132.6, 130.2, 130.1, 129.5, 129.4, 128.0, 127.4, 122.9, 70.3, 63.1, 62.6, 60.2, 53.0, 52.6, 15.9. – IR (KBr): $\tilde{\nu}$ = 1770, 1740, 1420. – $C_{22}H_{21}N_2O_5Br$ (473.3): calcd. C 55.92, H 4.48, N 5.93, Br 16.72; found C 56.14, H 4.67, N 6.24, Br 17.02.

(–)-(3R,4S)-cis-4-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(1-methoxycarbonylethyl)-3-phthalimido-2-azetidinone (**5j**): Method B. From 1.08 g (5 mmol) of imine **4e** and 1.68 g (7.5 mmol) of phthalimidylacetyl chloride, 1.53 g (79%) of β-lactam **5j** was obtained after purification by crystallization from EtOAc. White solid; m.p. 143–145°C (EtOAc). – $[\alpha]_D$ = –15.8 (*c* = 1.05, MeOH). – ^{1}H NMR ([D$_6$]DMSO): δ = 1.17 (s, 3 H), 1.27 (s, 3 H), 1.49 (d, *J* = 7.3 Hz, 3 H), 3.04–3.35 (m, 1 H), 3.61 (s, 3 H), 3.69–3.78 (m, 1 H), 4.05–4.22 (m, 2 H), 4.61 (q, *J* = 7.2 Hz, 1 H), 5.41 (d, *J* = 5.3 Hz, 1 H), 7.87–7.96 (m, 4 H). – ^{13}C NMR: ([D$_6$]DMSO): δ = 170.2, 166.9, 162.8, 135.1, 130.8, 123.7, 108.9, 74.6, 65.2, 61.0, 54.4, 52.2, 50.1, 26.3, 25.0, 16.0. – IR (KBr): $\tilde{\nu}$ = 1790, 1770, 1750, 1715. – $C_{20}H_{22}N_2O_7$ (402.4): calcd. C 59.70, H 5.51, N 6.96; found C 60.08, H 5.21, N 6.69.

1-[2-(tert-Butyldimethylsilyloxy)-1-(methoxycarbonyl)methyl]-cis-3-phenoxy-4-phenyl-2-azetidinone (**5k**): Method B. From 1.61 g (5 mmol) of imine **4g** and 1.28 g (7.5 mmol) of phenoxyacetyl chloride, a crude reaction mixture containing both *cis* diastereomers (74:26) was obtained. From this mixture, 2.00 g (88%) of both inseparable *cis* diastereomers of compound **5k** was obtained as a pale-yellow oil after purification by flash chromatography (EtOAc/hexane, 1:4). From the diastereomeric mixture: *Major isomer*: ^{1}H NMR: δ = –0.49 (s, 3 H), –0.35 (s, 3 H), 0.56 (s, 9 H), 3.47 (dd, J_1 = 10.2 Hz, J_2 = 2.7 Hz, 1 H), 3.57 (s, 3 H), 3.75 (dd, J_1 = 10.5 Hz, J_2 = 4.8 Hz, 1 H), 4.46 (dd, J_1 = 4.8 Hz, J_2 = 3.0 Hz, 1 H), 5.12 (d, *J* = 4.8 Hz, 1 H), 5.35 (d, *J* = 4.8 Hz, 1 H), 6.44–6.60 (m, 2 H), 6.82–6.90 (m, 2 H), 7.05–7.23 (m, 6 H). – ^{13}C NMR: δ = 169.0, 167.7, 82.2, 63.9, 61.0, 56.7, 52.6, 25.8, 18.7. – *Minor isomer*: ^{1}H NMR: δ = –0.09 (s, 3 H), –0.08 (s, 3 H), 0.72 (s, 9 H), 3.35 (s, 3 H), 3.91 (dd, J_1 = 10.5 Hz, J_2 = 5.4 Hz, 1 H), 4.01 (dd, J_1 = 8.1 Hz, J_2 = 10.5 Hz, 1 H), 4.10 (dd, J_1 = 8.1 Hz, J_2 = 5.4 Hz, 1 H), 4.90 (d, *J* = 4.5 Hz, 1 H), 5.25 (d, *J* = 4.5 Hz, 1 H), 6.64 (t, 2 H), 7.03–7.10 (m, 3 H), 7.14–7.27 (m, 5 H). – ^{13}C NMR: δ = 168.4, 166.2, 81.8, 62.6, 60.5, 57.7, 52.3, 25.8, 18.2. – For the mixture: IR ($CHCl_3$): $\tilde{\nu}$ = 1740, 1640. – $C_{25}H_{33}NO_5Si$ (455.6): calcd. C 65.90, H 7.31, N 3.08; found C 66.18, H 7.09, N 3.32.

cis-3-Benzyloxy-1-[1,2-bis(methoxycarbonylethyl)]-4-phenyl-2-azetidinone (**5l**): Method B. From 1.25 g (5 mmol) of imine **4h** and 1.38 g (7.5 mmol) of benzyloxyacetyl chloride, a crude reaction mixture containing both *cis* diastereomers (57:43) was obtained. From this mixture, 1.73 g (87%) of both inseparable *cis* diastereomers of compound **5l** was obtained as a pale-yellow oil after purification by flash chromatography (EtOAc/hexane, 1:4). The mixture was dispersed in Et_2O to afford 0.59 g (30%) of the analytically pure minor isomer. – *Major isomer* (from the diastereomeric mixture): ^{1}H NMR: δ = 2.56 (dd, J_1 = 4.9 Hz, J_2 = 17.5 Hz, 1 H), 2.79 (dd, J_1 = 17.5 Hz, J_2 = 6.8 Hz, 1 H), 3.37 (s, 3 H), 3.73 (s, 3 H), 4.10 (d, *J* = 11.2 Hz, 1 H), 4.19 (d, *J* = 11.2 Hz, 1 H), 4.81 (dd, J_1 = 6.8 Hz, J_2 = 4.9 Hz, 1 H), 4.94 (d, *J* = 4.7 Hz, 1 H), 4.98 (d, *J* = 4.7 Hz, 1 H), 6.89–6.92 (m, 2 H), 7.18–7.25 (m, 3 H), 7.32–7.38 (m, 5 H). – ^{13}C NMR: δ = 170.5, 169.2, 168.0, 136.3. 134.8, 129.0, 128.9, 128.8, 128.5, 128.3, 128.1, 83.7, 72.4, 63.3, 53.0, 52.0, 50.4, 34.4. – *Minor isomer*: White solid; m.p. 135–137°C (EtOAc). – $[\alpha]_D$ = –112.2 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR: δ = 3.07 (d, *J* = 6.3 Hz, 2 H), 3.59 (s, 3 H), 3.67 (s, 3 H),

4.13 (d, J = 11.7 Hz, 1 H), 4.26 (d, J = 11.7 Hz, 1 H), 4.40 (t, J = 7.3 Hz, 1 H), 4.62 (d, J = 4.6 Hz, 1 H), 4.88 (d, J = 4.6 Hz, 1 H), 6.89−6.93 (m, 2 H), 7.18−7.25 (m, 3 H), 8.44 (s, 5 H). − ^{13}C NMR: δ = 170.4, 169.9, 167.3, 136.3, 133.3, 129.0, 128.9, 128.5, 128.4, 128.3, 128.1, 83.5, 72.5, 62.9, 52.8, 52.3, 52.0, 34.2. − IR (KBr): ṽ = 1765, 1740. − $C_{22}H_{23}NO_6$ (397.4): calcd. C 66.49, H 5.83, N 3.52; found C 66.23, H 6.14, N 3.37.

General Method for the Synthesis of Compounds **7**. − *Method A:* BuLi (1.3 mmol, 1.6 M in hexanes) was added dropwise by means of a syringe to a cooled (−78°C) solution of hexamethyldisilazane (1.35 mmol) in anhydrous THF (5 ml) under argon. After 30 min, the resulting solution was transferred via a cannula to a cooled (−78°C) solution of the appropriate β-lactam (1 mmol) in anhydrous THF (5 ml) by applying a positive pressure of argon. After stirring for 1 h from −78°C to −60°C, PhSeBr (1.3 mmol) in THF (5 ml) was added rapidly to the enolate solution, resulting in instantaneous decolorization. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (7 ml) and extracted with ethyl acetate (10 × 3 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (15 ml) and brine (15 ml), and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound **6** thus obtained was used in the next step without further purification. − *Method B:* This method was identical to Method A except that the β-lactam was added dropwise to the solution of lithium hexamethyldisilazanide.

To a solution of the corresponding selenyl-β-lactam **6** (1 mmol) in CH_2Cl_2 (5 ml), cooled to −78°C, was added dropwise a solution of *m*-chloroperbenzoic acid (1.1 mmol, 55%) in 5 ml of CH_2Cl_2. Immediately after completion of the addition, TLC analysis indicated complete consumption of the starting material. The cold reaction mixture was then poured into a separatory funnel containing 30 ml of Et_2O and 30 ml of 10% aqueous Na_2SO_3 solution. The organic layer was separated, washed twice with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by crystallization or flash chromatography.

cis-3-Benzyloxy-1-(2-methoxycarbonyl-2-phenylselenylethyl)-4-phenyl-2-azetidinone (**6a**): Method A. From 0.17 g (0.5 mmol) of β-lactam **5a**, a crude reaction mixture was obtained containing both diastereomers (58:42) of compound **6a**. Diastereomerically pure compounds were obtained as yellow oils after flash chromatography (EtOAc/hexane, 1:3). Combined yield 83% (0.21 g). − *Major isomer:* Yield 39% (0.10 g). − ^{1}H NMR: δ = 3.42 (s, 3 H), 3.41 (dd, J_1 = 13.8 Hz, J_2 = 5.4 Hz, 1 H), 3.74−3.88 (m, 2 H), 4.10 (d, J = 11.1 Hz, 1 H), 4.23 (d, J = 11.1 Hz, 1 H), 4.82 (s, 2 H), 6.82−6.93 (m, 2 H), 7.15−7.48 (m, 13 H). − ^{13}C NMR: δ = 171.1, 167.2, 136.2, 135.8, 135.8, 133.5, 129.2, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 83.5, 72.1, 63.5, 52.4, 42.0, 40.2. − IR ($CHCl_3$): ṽ = 1760, 1730. − $C_{26}H_{25}NO_4Se$ (494.4): calcd. C 63.16, H 5.10, N 2.83; found C 63.30, H 5.30, N 2.95. − *Minor isomer:* Yield 20% (0.05 g). − ^{1}H NMR: δ = 3.27−3.33 (m, 1 H), 3.60 (s, 3 H), 3.82−3.91 (m, 2 H), 4.14 (d, J = 11.2 Hz, 1 H), 4.26 (d, J = 11.2 Hz, 1 H), 4.68 (d, J = 4.8 Hz, 1 H), 4.82 (d, J = 4.8 Hz, 1 H), 6.82−6.93 (m, 2 H), 7.18−7.38 (m, 11 H), 7.45−7.52 (m, 2 H). − ^{13}C NMR: δ = 171.2, 167.1, 136.2, 135.8, 135.8, 133.5, 129.2, 129.0, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 83.5, 72.1, 62.8, 52.4, 41.5, 40.2. − IR ($CHCl_3$): ṽ = 1760, 1740. − $C_{26}H_{25}NO_4Se$ (494.4): calcd. C 63.16, H 5.10, N 2.83; found C 63.38, H 5.01, N 2.91.

cis-3-Benzyloxy-4-(o-bromophenyl)-1-(1-methoxycarbonyl-1-phenylselenylethyl)-2-azetidinone (**6b**): Method B. From 0.19 g (0.5 mmol) of a diastereomeric mixture of **5e**, a crude reaction mixture was obtained containing both diastereomers (72:28) of **6b**. Diastereomerically pure compounds were obtained as yellow oils after flash chromatography (EtOAc/hexane, 1:6). Combined yield 61% (0.16 g). − *Major isomer:* Yield 30% (0.08 g). − ^{1}H NMR: δ = 1.78 (s, 3 H), 3.76 (s, 3 H), 4.10 (d, J = 11.4 Hz, 1 H), 4.20 (d, J = 11.4 Hz, 1 H), 4.55 (d, J = 4.8 Hz, 1 H), 4.71(d, J = 4.8 Hz, 1 H), 6.81−6.89 (m, 2 H), 7.23−7.81 (m, 12 H). − ^{13}C NMR: δ = 170.1, 165.6, 138.9, 136.2, 134.7, 132.8, 130.8, 130.3, 129.9, 129.2, 128.3, 128.1, 127.7, 127.4, 126.5, 123.3, 81.6, 72.6, 65.4, 63.4, 61.6, 60.5, 53.6, 25.8. − IR ($CHCl_3$): ṽ = 1760, 1735. − $C_{26}H_{24}NO_4SeBr$ (573.3): calcd. C 54.47, H 4.22, N 2.44, Br 13.94; found C 54.70, H 4.09, N 2.52, Br 14.25. − *Minor isomer:* Yield 15% (0.04 g). − ^{1}H NMR: δ = 2.05 (s, 3 H), 3.36 (s, 3 H), 4.12 (d, J = 11.5 Hz, 1 H), 4.22 (d, J = 11.4 Hz, 1 H), 4.61 (d, J = 4.9 Hz, 1 H), 5.11 (d, J = 4.9 Hz, 1 H), 6.81−6.89 (m, 2 H), 7.23−7.81 (m, 12 H). − ^{13}C NMR: δ = 168.9, 167.0, 139.0, 136.3. 134.8, 134.3, 133.8, 131.6, 130.3, 129.8, 129.7, 129.0, 128.1, 128.1, 128.0, 123.2, 82.3, 72.5, 64.8, 61.3, 52.7, 24.6. − IR ($CHCl_3$): ṽ = 1770, 1740.

cis-3-Benzyloxy-1-[(E)-(2-methoxycarbonyl)ethenyl]-4-phenyl-2-azetidinone (**7a**): Method A. From 0.17 g (0.5 mmol) of β-lactam **5a**, 0.15 g (89%) of pure compound **7a** was obtained as a white solid after purification by dispersion in Et_2O/hexane; m.p. 156−158°C (EtOAc/hexane). − ^{1}H NMR: δ = 3.58 (s, 3 H), 4.17 (d, J = 11.4 Hz, 1 H), 4.27 (d, J = 11.4 Hz, 1 H), 4.94 (AB, 2 H), 5.05 (d, J = 14.4 Hz, 1 H), 6.84−6.89 (m, 2 H), 7.13−7.16 (m, 3 H), 7.23−7.25 (m, 2 H), 7.30−7.34 (m, 3 H), 7.64 (d, J = 14.4 Hz, 1 H). − ^{13}C NMR: δ = 166.9, 164.6, 135.7, 133.4, 131.5, 128.9, 128.7, 128.3, 128.1, 128.0, 127.9, 102.8, 83.6, 72.6, 62.5, 51.4. − IR ($CHCl_3$): ṽ = 1780, 1710, 1640. − $C_{20}H_{19}NO_4$ (337.4): calcd. C 71.20, H 5.68, N 4.15; found C 71.03, H 5.93, N 4.42.

(+)-(3R,4S)-cis-3-Benzyloxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(E)-(2-methoxycarbonylethenyl)]-2-azetidinone (**7b**): Method A. From 0.18 g (0.5 mmol) of β-lactam **5b**, 0.17 g (91%) of compound **7b** was obtained as a pale-green oil after purification by flash chromatography (EtOAc/hexane, 1:6). − $[\alpha]_D$ = +116.3 (c = 1.16, $CHCl_3$). − ^{1}H NMR: δ = 1.35 (s, 3 H), 1.50 (s, 3 H), 3.62−3.73 (m, 1 H), 3.73 (s, 3 H), 3.97 (dd, J_1 = 9.0 Hz, J_2 = 5.7 Hz, 1 H), 4.21 (dd, J_1 = 9.0 Hz, J_2 = 6.9 Hz, 1 H), 4.31−4.42 (m, 1 H), 4.66 (d, J = 11.5 Hz, 1 H), 4.75 (d, J = 5.7 Hz, 1 H), 4.90 (d, J = 11.5 Hz, 1 H), 6.05 (d, J = 14.1 Hz, 1 H), 7.22−7.40 (m, 5 H), 7.48 (d, J = 14.1 Hz, 1 H). − ^{13}C NMR: δ = 167.6, 165.7, 136.8, 134.4, 128.7, 128.3, 128.4, 128.0, 110.1, 104.3, 80.5, 73.3, 66.7, 62.3, 51.5, 26.7, 25.0. − IR ($CHCl_3$): ṽ = 1780, 1710, 1640. − $C_{19}H_{23}NO_6$ (361.4): calcd. C 63.15, H 6.41, N 3.88; found C 63.36, H 6.67, N 4.04.

3-Isopropyl-trans-1-[(E)-(2-methoxycarbonyl)ethenyl]-4-phenyl-2-azetidinone (**7c**): Method A. From 0.14 g (0.5 mmol) of β-lactam **5c**, 0.12 g (87%) of compound **7c** was obtained as a white solid after purification by dispersion in Et_2O/hexane; m.p. 87−88°C (AcOEt/hexane). − ^{1}H NMR: δ = 1.05 (d, J = 6.7 Hz, 3 H), 1.11 (d, J = 6.7 Hz, 3 H), 2.17 (m, 1 H), 2.9 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1 H), 3.66 (s, 3 H), 4.59 (d, J = 2.0 Hz, 1 H), 5.01 (d, J = 14.2 Hz, 1 H), 7.23−7.44 (m, 5 H), 7.73 (d, J = 14.2 Hz, 1 H). − ^{13}C NMR: δ = 167.6, 167.5, 136.5, 134.1, 129.4, 128.9, 126.0, 101.0, 68.7, 60.2, 51.5, 28.8, 20.5, 20.1. − IR ($CHCl_3$): ṽ = 1770, 1710, 1640. − $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.12; found C 70.56, H 7.37, N 5.04.

(+)-cis-3-Benzyloxy-1-(1-methoxycarbonylethenyl)-4-phenyl-2-azetidinone (**7d**): Method B. From 0.17 g (0.5 mmol) of the major isomer of β-lactam **5d**, 0.14 g (89%) of compound **7d** was obtained as a yellow oil after purification by flash chromatography (EtOAc/

hexane). – $[\alpha]_D$ = +32.7 (*c* = 1.34, $CHCl_3$). – ^{1}H NMR: δ = 3.59 (s, 3 H), 4.15 (d, *J* = 11.4 Hz, 1 H), 4.27 (d, *J* = 11.4 Hz, 1 H), 4.93 (d, *J* = 4.8 Hz, 1 H), 5.44 (d, *J* = 4.8 Hz, 1 H), 5.91 (s, 1 H), 6.15 (s, 1 H), 6.84–6.88 (m, 2 H), 7.13–7.17 (m, 3 H), 7.24–7.32 (m, 5 H). – ^{13}C NMR: δ = 165.8, 162.3, 157.7, 136.2, 134.4, 131.0, 128.4, 128.3, 128.2, 128.1, 128.0, 115.5, 83.4, 72.3, 64.2, 52.3. – IR ($CHCl_3$): ṽ = 1760, 1730. – $C_{20}H_{19}NO_4$ (337.4): calcd. C 71.20, H 5.68, N 4.15; found C 71.47, H 5.55, N 4.03.

cis-3-Benzyloxy-4-(o-bromophenyl)-1-(1-methoxycarbonylethenyl)-2-azetidinone (**7e**): Method B. From 0.21 g (0.5 mmol) of a mixture of both *cis* diastereomers **5e**, 0.19 g (91%) of compound **7e** was obtained as a pale-yellow oil after purification by flash chromatography (EtOAc/hexane). – ^{1}H NMR: δ = 3.67 (s, 3 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 5.04 (d, *J* = 5.1 Hz, 1 H), 5.96 (d, *J* = 5.1 Hz, 1 H), 6.00 (s, 1 H), 6.24 (s, 1 H), 6.80–7.03 (m, 2 H), 7.13–7.40 (m, 5 H), 7.41–7.58 (m, 2 H). – ^{13}C NMR: δ = 165.7, 162.3, 136.4, 134.5, 133.0, 131.6, 131.3, 129.7, 128.7, 128.4, 128.1, 127.8, 123.2, 115.2, 83.5, 72.9, 64.1, 52.7. – IR ($CHCl_3$): ṽ = 1780, 1740, 1710. – $C_{20}H_{18}BrNO_4$ (416.3): calcd. C 57.71, H 4.36, N 3.36, Br 19.20; found C 57.42, H 4.05, N 3.64, Br 19.47.

(3R,4S)-cis-3-Benzyloxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(1-methoxycarbonylethenyl)-2-azetidinone (**7f**): Method B. From 0.36 g (1.0 mmol) of the major isomer of β-lactam **5f**, 0.36 g of crude compound **7f** was obtained as a yellow oil. This compound could not be obtained in analytically pure form and was used without further purification to obtain diol **8**. – ^{1}H NMR: δ = 1.19 (s, 3 H), 1.25 (s, 3 H), 3.56–3.65 (m, 1 H), 3.71 (s, 3 H), 4.02–4.41 (m, 1 H), 4.23–4.34 (m, 1 H), 4.31–4.42 (m, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H), 4.70 (d, *J* = 5.0 Hz, 1 H), 4.86 (d, *J* = 11.8 Hz, 1 H), 5.86 (s, 1 H), 5.99 (s, 1 H), 7.18–7.33 (m, 5 H). – ^{13}C NMR: δ = 166.5, 163.0, 136.6, 132.2, 128.6, 128.2, 127.8, 115.6, 109.7, 80.6, 76.1, 73.2, 66.6, 61.1, 52.2, 26.3, 25.0. – IR ($CHCl_3$): ṽ = 1780, 1710, 1640.

(+)-cis-3-Benzyloxy-1-(1-methoxycarbonylethenyl)-4-[(E)-1-methylstyryl]-2-azetidinone (**7g**): Method B. From 0.19 g (0.5 mmol) of the major isomer of β-lactam **5g**, 0.13 g (70%) of compound **7g** was obtained as a colorless oil after purification by flash chromatography (EtOAc/hexane, 4:1). – $[\alpha]_D$ = +2.6 (*c* = 0.9, $CHCl_3$). – ^{1}H NMR: δ = 1.82 (d, *J* = 1.2 Hz, 3 H), 3.70 (s, 3 H), 4.61 (d, *J* = 10.8 Hz, 1 H), 4.70 (d, *J* = 10.8 Hz, 1 H), 4.88 (d, *J* = 5.1 Hz, 1 H), 4.95 (d, *J* = 5.1 Hz, 1 H), 5.89 (s, 1 H), 6.10 (s, 1 H), 6.45 (s, 1 H), 7.23–7.35 (m, 10 H). – ^{13}C NMR: δ = 166.2, 162.5, 136.8, 136.7, 133.3, 131.8, 130.1, 129.0, 128.4, 128.1, 127.9, 127.8, 126.8, 114.5, 83.3, 73.1, 67.2, 52.4, 15.1. – IR ($CHCl_3$): ṽ = 1760, 1730, 1710. – $C_{23}H_{23}NO_4$ (377.4): calcd. C 73.19, H 6.14, N 3.71; found C 73.40, H 6.46, N 3.99.

(+)-(3S,4R)-cis-1-(1-Methoxycarbonylethenyl)-4-phenyl-3-[(S)-4-phenyl-2-oxooxazolidin-3-yl]-1-azetidinone (**7h**): Method B. From 0.20 g (0.5 mmol) of β-lactam **5h**, 0.11 g (55%) of compound **7h** was obtained as a yellow oil after purification by flash chromatography (EtOAc/hexane, 1:3). – $[\alpha]_D$ = +18.9 (*c* = 0.53, $CHCl_3$). – ^{1}H NMR: δ = 3.55 (s, 3 H), 3.83 (t, *J* = 8.0 Hz, 1 H), 4.18 (t, *J* = 8.7 Hz, 1 H), 4.69 (d, *J* = 5.4 Hz, 1 H), 4.74 (t, *J* = 8.1 Hz, 1 H), 5.90 (d, *J* = 5.4 Hz, 1 H), 6.02 (s, 1 H), 6.54 (s, 1 H), 7.06–7.62 (m, 8 H), 7.48 (d, 1 H), 7.57 (d, 1 H). – ^{13}C NMR: (the product decomposed during acquisition of the spectrum). – IR ($CHCl_3$): ν = 1780, 1700, 1640. – $C_{22}H_{20}N_2O_5$ (392.4): calcd. C 56.07, H 5.14, N 7.14; found C 56.44, H 4.76, N 6.77.

(–)-(3S,4R)-cis-4-(o-Bromophenyl)-1-(1-methoxycarbonylethenyl)-3-[(S)-4-phenyl-2-oxooxazolidin-3-yl]-1-azetidinone (**7i**): Method B. From 0.24 g (0.5 mmol) of β-lactam **5i**, 0.20 g (85%) of compound **7i** was obtained as a white solid after purification by flash chromatography (EtOAc/hexane, 1:4); m.p. 58–59°C (EtOAc/hexane). – $[\alpha]_D$ = –11.2 (*c* = 0.49, $CHCl_3$). – ^{1}H NMR: δ = 3.65 (s, 3 H), 4.01 (dd, J_1 = 8.7 Hz, J_2 = 7.0 Hz, 1 H), 4.31 (t, *J* = 8.8 Hz, 1 H), 4.57 (d, *J* = 5.4 Hz, 1 H), 4.81 (dd, J_1 = 8.7 Hz, J_2 = 7.1 Hz, 1 H), 5.85 (d, *J* = 5.4 Hz, 1 H), 6.10 (s, 1 H), 6.42 (s, 1 H), 7.22–7.63 (m, 9 H). – ^{13}C NMR: δ = 162.6, 162.4, 156.3, 136.9, 133.7, 132.3, 131.0, 129.9, 129.7, 129.6, 129.5, 127.8, 127.3, 122.0, 115.6, 70.5, 64.6, 62.9, 60.3, 52.4. – IR ($CHCl_3$): ṽ = 1785, 1770, 1740, 1620. – $C_{22}H_{19}N_2O_5Br$ (471.3): calcd. C 56.07, H 4.06, N 5.94, Br 16.95; found C 56.31, H 3.96, N 6.31, Br 16.81.

cis-1-(1-Methoxycarbonylethenyl)-3-phenoxy-4-phenyl-2-azetidinone (**7j**): BuLi (0.65 mmol, 1.6 M in hexane) was added dropwise by means of a syringe to a cooled (–78°C) solution of hexamethyldisilazane (0.70 mmol) in anhydrous THF (3 ml) under argon. After 30 min, the resulting solution was transferred via a cannula to a cooled solution (–78°C) of both *cis* diastereomers of β-lactam **5k** (0.23 g, 0.5 mmol) in anhydrous THF (3 ml) by applying a positive pressure of argon. After stirring for 30 min, the cold reaction mixture was quenched with saturated aqueous NH_4Cl solution (4 ml) and EtOAc (10 ml). The organic layer was washed with saturated $NaHCO_3$ solution and brine, and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified by dispersion in Et_2O to yield 0.11 g (66%) of analytically pure compound **7j** as a white solid; m.p. 93–95°C (EtOAc/hexane). – ^{1}H NMR: δ = 3.68 (s, 3 H), 5.56 (d, *J* = 4.9 Hz, 1 H), 5.72 (d, *J* = 4.9 Hz, 1 H), 6.04 (s, 1 H), 6.30 (s, 1 H), 6.70 (d, *J* = 8.9 Hz, 2 H), 6.87 (t, *J* = 7.5 Hz, 1 H), 7.11 (t, *J* = 7.5 Hz, 2 H), 7.13–7.17 (m, 5 H). – ^{13}C NMR: δ = 164.9, 162.4, 156.8, 133.6, 131.1, 129.4, 128.6, 128.3, 122.2, 116.1, 115.7, 82.1, 64.4, 52.6. – IR ($CHCl_3$): ṽ = 1760, 1730, 1610. – $C_{19}H_{17}NO_4$ (323.3): calcd. C 70.58, H 5.30, N 4.33; found C 70.73, H 5.53, N 4.17.

cis-3-Benzyloxy-1-[1,2-bis(methoxycarbonyl)ethenyl]-4-phenyl-2-azetidinone (**7k**): Method A. From 0.20 g (0.5 mmol) of the minor isomer of β-lactam **5l**, a mixture of (*Z*/*E*) diastereomers (50:50) was obtained, which could be separated by flash chromatography (EtOAc/hexane, 1:4). Combined yield 83% (0.164 mg). (–)-(*Z*)-**7k**: Colorless oil. – $[\alpha]_D$ = –134.5 (*c* = 2.0, $CHCl_3$). – ^{1}H NMR: δ = 3.71 (s, 3 H), 3.72 (s, 3 H), 4.19 (d, *J* = 11.4 Hz, 1 H), 4.28 (d, *J* = 11.4 Hz, 1 H), 4.91 (d, *J* = 5.1 Hz, 1 H), 5.67 (d, *J* = 5.1 Hz, 1 H), 6.33 (s, 1 H), 6.82–6.94 (m, 2 H), 7.12–7.19 (m, 3 H), 7.28–7.37 (m, 3 H), 7.41–7.49 (m, 2 H). – ^{13}C NMR: δ = 164.8, 164.5, 162.9, 136.4, 133.8, 131.5, 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 118.1, 83.6, 72.5, 65.0, 53.2, 52.3. – IR ($CHCl_3$): ṽ = 1740, 1640. – $C_{22}H_{21}NO_6$ (395.41): calcd. C 66.83, H 5.35, N 3.54; found C 67.12, H 5.21, N 3.37. – (–)-(*E*)-**7k**: White solid; m.p. 133–135°C. – $[\alpha]_D$ = –119.2 (*c* = 2.5, $CHCl_3$). – ^{1}H NMR: δ = 3.63 (s, 3 H), 3.79 (s, 3 H), 4.24 (d, *J* = 11.4 Hz, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 5.00 (d, *J* = 5.4 Hz, 1 H), 5.07 (d, *J* = 5.4 Hz, 1 H), 5.39 (s, 1 H), 6.82–6.90 (m, 2 H), 7.18–7.30 (m, 3 H), 7.31–7.45 (m, 5 H). – ^{13}C NMR: δ = 165.5, 164.0, 162.7, 139.9, 135.7, 131.3, 129.2, 128.7, 128.3, 128.2, 128.1, 128.0, 101.5, 83.2, 72.7, 62.9, 53.2, 51.8. – IR ($CHCl_3$): ṽ = 1790, 1750, 1715, 1630. – $C_{22}H_{21}NO_6$ (395.4): calcd. C 66.83, H 5.35, N 3.54; found C 66.97, H 5.23, N 3.49.

(+)-(3R,4S)-cis-3-Benzyloxy-4-[(S)-1,2-dihydroxyethyl]-1-(1-methoxycarbonylethenyl)-2-azetidinone (**8**): *p*-TsOH·H_2O (0.19 g, 1.1 mmol) was added to a solution of β-lactam **7f** (0.36 mg, 1.0 mmol) in THF/H_2O (1:1) (20 ml) and the mixture was refluxed until complete consumption of the starting material (TLC, ca. 3 h). The crude reaction mixture was then cooled to room temp., concentrated in vacuo, and the residue was neutralized with solid

$NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude compound was purified by flash chromatography (EtOAc/hexane, 1:2) to yield 0.25 g (82%) of **8** as a colorless oil. − $[\alpha]_D$ = +111.0 (*c* = 0.50, $CHCl_3$). − ^{1}H NMR: δ = 2.53 (br s, 1 H), 3.04 (br s, 1 H), 3.43−3.48 (br d, 1 H), 3.45−3.60 (br d, 1 H), 3.67 (s, 3 H), 3.87 (br s, 1 H), 4.53 (dd, J_1 = 5.4 Hz, J_2 = 3.9 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.75 (d, *J* = 5.44 Hz, 1 H), 4.88 (d, *J* = 11.6 Hz, 1 H), 5.96 (s, 1 H), 6.08 (s, 1 H), 7.23−7.32 (m, 5 H). − ^{13}C NMR: δ = 166.7, 163.6, 137.6, 131.7, 128.4, 128.1, 116.2, 81.1, 73.7, 70.4, 63.6, 60.4, 52.5. − IR ($CHCl_3$): ṽ = 3500, 1760, 1730, 1625. − $C_{16}H_{19}NO_6$ (321.33): calcd. C 59.81, H 5.96, N 4.36; found C 59.65, H 5.62, N 4.70.

Cyclization of Compound **8** *in the Presence of NaH:* A solution of β-lactam **8** (0.10 g, 0.31 mmol) in THF (3 ml) was added dropwise to a suspension of NaH (0.03 g, 0.79 mmol, 60% in paraffin, washed three times with hexane) in THF (1 ml) at 0°C (ice bath). The reaction mixture was stirred for 15 min at 0°C, then quenched with water (2 ml), and extracted with EtOAc (3 × 5 ml). The combined extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (EtOAc/hexane, 1:4) of the residue yielded 0.05 g (48%) of compound **9** as a colorless oil. − $[\alpha]_D$ = +56.3 (*c* = 0.48, $CHCl_3$). − ^{1}H NMR: δ = 3.73−3.87 (br m, 1 H), 3.99−4.13 (br m, 2 H), 4.66 (d, *J* = 11.6 Hz, 1 H), 4.63−4.70 (br m, 1 H), 4.78 (d, *J* = 5.4 Hz, 1 H), 4.92 (d, *J* = 11.6 Hz, 1 H), 4.90−5.15 (br m, 1 H), 5.93 (s, 1 H), 6.12 (s, 1 H), 7.19−7.34 (m, 5 H). − ^{1}H NMR ([D$_6$]DMSO): δ = 3.76 (d, *J* = 12.0 Hz, 1 H), 3.99 (br t, *J* = 9.9 Hz, 1 H), 4.74 (d, *J* = 11.7 Hz, 1 H), 4.83 (d, *J* = 11.7 Hz, 1 H), 4.96 (dd, J_1 = 10.2 Hz, J_2 = 5.4 Hz, 1 H), 5.03 (d, *J* = 5.4 Hz, 1 H), 5.11 (dd, J_1 = 12.0 Hz, J_2 = 3.0 Hz, 1 H), 5.83 (s, 1 H), 6.05 (s, 1 H), 6.22 (d, *J* = 8.4 Hz, 1 H), 7.15 (s, 5 H). − ^{13}C NMR: δ = 166.2, 162.6, 136.1, 131.9, 128.7, 128.5, 128.3, 116.3, 80.2, 73.4, 68.8, 65.0, 59.9. − ^{13}C NMR ([D$_6$]DMSO): δ = 166.5, 162.3, 137.1, 133.8, 128.5, 127.9, 127.7, 113.4, 80.9, 72.8, 68.1, 64.5, 59.8. − IR ($CHCl_3$): ṽ = 3370 (br), 1760, 1750, 1620, 1410. − FAB-MS: *m/z* (%): 290 (9), 262 (17), 232 (16), 91 (parent). − $C_{15}H_{15}NO_5$ (298.3): calcd. C 62.28, H 5.23, N 4.84; found C 62.52, H 5.00, N 4.47.

Cyclization of Compound **7e** *in the Presence of Pd(OAc)$_2$:* A mixture of β-lactam **7e** (0.05 g, 0.12 mmol), $Pd(OAc)_2$ (5 mol-%), KOAc (0.06 g, 0.6 mmol, 5 equiv.), and tetrabutylammonium bromide (0.04 g, 0.12 mmol) in DMF (1.0 ml) was stirred at 80°C for 48 h. After cooling to room temperature, H_2O (1 ml) was added and the resulting solution was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by chromatography (EtOAc/hexane, 1:1) to yield 0.02 mg (51%) of compound **10** as a white solid; m.p. 142−143°C (EtOAc/hexane). − ^{1}H NMR: δ = 3.83 (s, 3 H), 4.77 (d, *J* = 12.3 Hz, 1 H), 4.90 (d, *J* = 12.3 Hz, 1 H), 4.95 (d, *J* = 4.8 Hz, 1 H), 5.34 (d, *J* = 4.8 Hz, 1 H), 7.15 (s, 1 H), 7.18−7.31 (m, 9 H). − ^{13}C NMR: δ = 169.5, 162.4, 130.5, 130.1, 129.3, 128.5, 128.4, 128.2, 128.0, 127.9, 126.9, 126.8, 124.6, 86.4, 72.7, 54.2, 52.6. − IR ($CHCl_3$): ṽ = 1780, 1725, 1630. − $C_{20}H_{17}NO_4$ (335.4): calcd. C 71.63, H 5.11, N 4.18; found C 71.71, H 5.00, N 4.22.

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