Base-Promoted Isomerization of *cis*-4-Formyl-2-azetidinones: Chemoselective *C*4-Epimerization vs Rearrangement to Cyclic Enaminones

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Two simple, efficient, and complementary methods for the regiospecific C4-epimerization of *cis*-4-formyl-2-azetidinones **1**−**3** are described. The first method uses 40% aqueous dimethylamine as reagent in heterogeneous medium with benzene at room temperature, in the presence of benzyltributylammonium bromide (3−4 mol %) as the phase-transfer catalyst. This transformation tolerates alkyl, alkenyl, alkynyl, aryl, and alkoxy substituents at the C3 of the 2-azetidinone ring. However, limitations of this isomerization are as follows: (i) only *N*-(*p*-methoxyphenyl)-*β*-lactams can be used, and (ii) transformation is less compatible with heteroatomic substituents bonded to the C3 position of the 2-azetidinone ring. A highly general solution to these problems relies on the use of sodium carbonate as the isomerization reagent in different solvents. We also describe a novel base-promoted rearrangement of the *β*-lactam ring to cyclic enaminones **6** and **21**, involving an E1cB-elimination reaction in *cis*-4-formyl-2-azetidinones.

Introduction

4-Formyl-2-azetidinones are versatile building blocks that can serve not only for the synthesis of *β*-lactam antibiotics, including monobactams, carbapenems, carbacephems, and isooxacephems,[2] but also for the preparation of other useful non-*β*-lactam synthetic targets such as *β*-substituted aspartic acid derivatives and isoserines.[3] Among the different methods for the synthesis of this particular type of monocyclic *β*-lactams, the Staudinger reaction on appropriately functionalized imines is probably the most used approach.[4,5] However, regarding the stereochemical outcome of the reported routes, a very strong preference for *cis*-*β*-lactam formation is observed. Work from our group has resulted in a general, totally stereoselective one-pot synthesis of *cis*-4-formyl-*β*-lactams based on the reaction of acid chlorides and 1,4-bis(4-methoxyphenyl)-1,4-diazabuta-1,3-diene wherein the later serves as a synthon of the corresponding α-formylimine.[6] Consequently, the development of stereocontrolled methods for the synthesis of *trans*-4-formyl-*β*-lactams becomes of great interest in *β*-lactam chemistry. In connection with our investigations on the synthesis and synthetic applications of chiral, functionalized 2-azetidinones,[7] we also required a facile access to these compounds. We found that typical reagents used for epimerization on related systems[4f,8] failed to give the expected trans isomers. Instead, complex mixtures of products were

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(2) Selected examples: (a) Thomas, R. C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Springer-Verlag: Berlin−Heidelberg, 1990; p 533. (b) Georg, G. I. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 4, p 431. (c) Bodurow, Ch.; Carr, M. A. *Tetrahedron Lett.* **1989**, *30*, 4081. (d) Georg, G. I.; Kant, J. *J. Org. Chem.* **1988**, *53*, 692. (e) Mastalerz, H.; Menard, M.; Vinet, V.; Desiderio, 3.; Fung-Tomc, T.; Kessler, R.; Tsai, Y. *J. Med. Chem.* **1988,** *31*, 1190. (f) Mastalerz, H.; Vinet, H. *Chem. Commun.* **1987**, 1283. (g) Cainelli, G.; Panunzio; M., Basile, T.; Bargini, A.; Giacomini, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2637. (h) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *19*, 1129. (i) Hart, D. J.; Ha, D.-Ch. *Tetrahedron Lett.* **1985**, *26*, 5493.

(3) For an excellent review on the synthesis of *β*-amino acids and their derivatives from *β*-lactams, see: (a) Palomo, C.; Aizpurua, J. M.; Gamboa, I. in *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; Chapter 14, p 279. Selected examples: (b) Duhamel, P.; Goument, B.; Plaquevent, J. Ch. *Tetrahedron Lett.* **1987**, *28*, 2595. (c) Broady, S. D.; Rexhausen, J. E.; Thomas, E. J. *Chem. Commun.* **1991**, 708. (d) Bose, A. K.; Womelsdorf, J. F.; Krishnan, L.; Urbanczyk-Lipkowska, Z.; Shelly, D. C.; Manhas, M. *Tetrahedron* **1991**, *47*, 5379. (e) Robinson, R. P.; Donahue, K. M. *J. Org. Chem.* **1992**, *57*, 7309. (f) Palomo, C.; Cabre, F.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4819. (g) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746. (h) Kende, A. S.; Koch, K.; Dorey, G.; Kaldor, I.; Liu, K. *J. Am. Chem. Soc.* **1993**, *115*, 9842. (i) Palomo, C.; Aizpurua, J. M.; Gamboa, I.; Maneiro, E.; Odriozola, B. *Chem. Commun.* **1994**, 1505.

(4) See, for example: (a) Niu, Ch.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 497. (b) Jarayaman, M.; Deshmukh, A. R.-A. S.; Bhawal, B. M. *J. Org. Chem.* **1994**, *59*, 5921. (c) Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martínez-Ripoll, M. *J. Am. Chem. Soc.* **1992,** *114*, 9360. (d) Palomo, C.; Ontoria, J. M.; Odriozola, J. M.; Aizpurua, J. M.; Gamboa, I. *Chem. Commun.* **1990**, 503. (e) Thomas, R. C. *Tetrahedron Lett.* **1989**, *30*, 5239. (f) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227. (g) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065. (h) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.

(5) (a) Palomo, C.; Aizpurua, J. M.; Gamboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, *3223*, 3. (b) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers, Inc.: New York, 1993; Chapter 6, p 295.

(6) (a) Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Sierra, M. A. *Tetrahedron Lett.* **1991**, *32*, 803. (b) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.

(7) See, for instance: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **1999**, 1913. (b) Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377. (c) Alcaide, B.; Alonso, J. M.; Aly, M. F.; Sáez, E.; Martínez-Alcázar, M. P.; Hernández-Cano, F. *Tetrahedron Lett.* **1999**, *40*, 5391. (d) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786. (e) Alcaide, B.; Rodríguez-Vicente, A.; Sierra, M. A. *Tetrahedron Lett.* **1998**, *39*, 163. (f) Alcaide, B.; Aly, M. F.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 8819. (g) Alcaide, B.; Martín-Cantalejo, Y.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 9156.

(8) Epimerization at C3 and/or C4 is effected by: (a) DBN: Bose, A. K.; Narayanan, C. S.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1970**, 975. (b) DBU: Hart, D. J.; Ha, D.-Ch. *Tetrahedron Lett.* **1985**, *26*, 5493. (c) Me_3SiOTf: Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647. (d) NaOH and n-BuLi: Alcaide, B.; Domínguez, G.; Escobar, G.; Parreño, U.; Plumet, J. *Heterocycles* **1986**, *24*, 1579. (e) Kawabata, T.; Itoh, K.; Hiyam, T. *Tetrahedron Lett.* **1989**, *30*, 4837.

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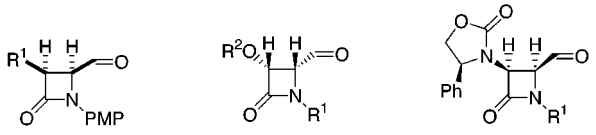
Chart 1



1a: R^1 = Et
1b: R^1 = allyl
1c: R^1 = propargyl
1d: R^1 = *i*-Pr
1e: R^1 = *t*-Bu
1f: R^1 = Ph
1g: R^1 = OBn
1h: R^1 = OPh
1i: R^1 = Phtalimido

(+)-2a: R^1 = PMP, R^2 = Bn
(+)-2b: R^1 = Bn, R^2 = Bn
(+)-2c: R^1 = allyl, R^2 = Ph
(+)-2d: R^1 = propargyl, R^2 = Ph
(+)-2e: R^1 = PMP, R^2 = Ph

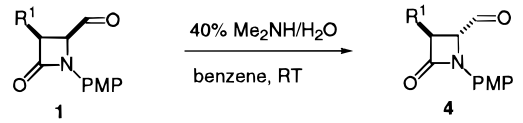
(+)-3a: R^1 = PMP
(+)-3b: R^1 = Bn

obtained in all cases. This is probably due to the high instability of the compound to the usual isomerization conditions. We report here two simple, efficient, and complementary methods for the synthesis of *trans*-4-formyl-*β*-lactams through chemoselective C4-epimerization of the corresponding cis isomers using both aqueous solution of dimethylamine in heterogeneous phase and sodium carbonate as isomerization reagents. On the other hand, enaminones are valuable synthetic intermediates for the construction of biologically active nitrogen heterocycles through aza-annulation reactions with acrylate derivatives.[9] In this context, we also describe a novel base-catalyzed rearrangement of the *β*-lactam ring to cyclic enaminones related to tetronic acid,[10] involving an E1cB-elimination reaction in *cis*-3-alkoxy-4-formyl-2-azetidinones.

Results and Discussion

Racemic and enantiomerically pure *cis*-4-formyl-*β*-lactams **1**−**3** were selected as starting materials since they cover a representative variety of substituents with different steric and electronic characteristics at positions N1 and C3 of the *β*-lactam ring. All compounds **1**−**3** (Chart 1) were prepared using previously reported standard methodologies.[6b,7f−g]Due to the instability of the *β*-lactam aldehydes to the previously reported reagents and experimental conditions we thought in dimethylamine, easily available as a 40% aqueous solution, as the reagent of choice. After several experiments in various solvents, we found the best results in benzene at room temperature in heterogeneous medium. Furthermore, we observed that the use of benzyltributylammonium bromide as a phase-transfer catalyst notably shorthened reaction times required for isomerization (compare methods A and B in Table 1).[11] Thus, in a typical experiment, a 40% aqueous solution of dimethylamine (1 mL) was added to a solution of the *cis*-formyl-*β*-lactam **1** (0.4 mmol) in benzene (5 mL) containing benzyltributylammonium bromide (3−4 mol %), and the mixture was stirred at room temperature. The reaction mixture was subjected to an extractive workup to yield essentially pure trans isomer **4**, as shown in Table 1. This transformation tolerates alkyl, alkenyl, alkynyl, aryl, and alkoxy substituents at the C3 of the 2-azetidinone ring. Compounds **4a** and **4d** are of particular interest because they are closely related to intermediates used in the synthesis of PS-5 and PS-6 *trans*-carbapenem antibiotics.[2a−b] The size of the C3 substituent on the 2-azetidinone influences the conversion rate, sterically more demanding groups decreasing the reaction time required for the isomerization. However, compound **1h** having a phenoxy group at C3 fails to give the expected trans isomer; intractable reaction mixtures with considerable loss of material were obtained instead. *cis*-3-Phthalimido-*β*-lactam **1i** also failed to give the corresponding trans isomer. In this case, reaction of dimethylamine with phthalimido group may be responsible for this failure.[12] However, two major drawbacks in this isomerization are as follows: (i) only *N*-(*p*-methoxyphenyl)-*β*-lactams can be used, and (ii) transformation is not compatible with amino (and in some cases oxygenated) substituents bonded to the *C*3 position of the 2-azetidinone ring.

Table 1. Synthesis of *trans*-4-Formyl-*β*-lactams 4



1 **4**

substrate[a,b]	R^1	reaction time (h) A[c]	reaction time (h) B[d]	product	trans/cis ratio[e]	yield[f] (%)
1a	Et	65	168	**4a**	95:5	83
1b	allyl	36	72	**4b**	95:5	80
1c	propargyl	36	72	**4c**	95:5	82
1d	*i*-Pr	21	24	**4d**	100:0	87
1e	*t*-Bu	3	6	**4e**	100:0	90
1f	Ph	15	24	**4f**	100:0	85
1g	BnO	16	16	**4g**	100:0	7a

[a] Starting substrates **1** were in all cases racemic. [b] PMP = 4-methoxyphenyl. [c] Method A: reaction time in the presence of benzyltributylammonium bromide. [d] Method B: reaction time without benzyltributylammonium bromide. [e] Determined from integration in the ^{1}H NMR (300 MHz) of the crude reaction mixtures. [f] Yield of pure, isolated product with correct analytical and spectral data.

The reaction course for this isomerization may be rationalized according to two different pathways, involving either the enolate or the enamino-*β*-lactam as the intermediates (Scheme 1). To confirm participation of enamines **5** as intermediates in the isomerization process we prepared compounds **5a**,**b** by reaction of *cis*-*β*-lactam **1d**,**e** with pyrrolidine[13] in the presence of the $ZnCl_2$/α-phenylethylamine complex as catalyst, using benzene as solvent and a Dean−Stark apparatus to remove the water formed during the reaction.[14] After 1 h in refluxing

(9) See, for example: (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (b) Murphy, J. P.; Hadden, M.; Stevenson, P. J. *Tetrahedron* **1997**, *53*, 11827. (c) Campos, P. J.; Arranz, J.; Rodriguez, M. A. *Tetrahedron Lett.* **1997**, *38*, 8397. (d) Cavé, C.; LePorhiel-Castellon, Y.; Daley, V.; Riche, C.; Chiaroni, A.; d'Angelo, J. *Tetrahedron Lett.* **1997**, *38*, 8703. (e) Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493. (f) Fustero, S.; de la Torre, M. G.; Jofre, V.; Carlon, R. P.; Navarro, A.; Fuentes, A. S.; Carrio, J. S. *J. Org. Chem.* **1998**, *63*, 8825. (g) Fustero, S.; de la Torre, M. G.; Pina, B.; Fuentes, A. S. *J. Org. Chem.* **1999**, *64*, 5551.

(10) For a general review on enaminones, see: Greenhill, J. V. *Chem. Rev.* **1977**, *6*, 277.

(11) Similar rate acceleration was observed for other catalysts, such as $Bu_4N^+I^-$, $Bu_4N^+HSO_4^-$, $BnEt_3N^+Cl^-$. Complexation of R_4N^+ with the formyl oxygen could be responsible for this catalytic effect on the isomerization.

(12) The use of methylamine as deprotecting phthalimido group has been reported. See, for example: Motawia, M. S.; Wengel, J.; Abdel-Megid, A. E.-S.; Pedersen, E. B. *Synthesis* **1989**, 384.

(13) Due to the difficulties to obtain enamines from dimethylamine, we used pyrrolidine as a model amine to prepare pure, isolable enamines.

(14) Reaction conditions typically used for the synthesis of imines when either the amine or the carbonyl compound are less reactive. See, for example: Alcaide, B.; Moreno, A. M.; Rodríguez-Vicente; Sierra, M. A. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2203.

Scheme 1

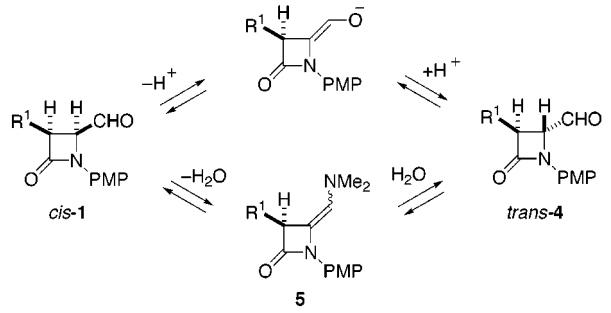
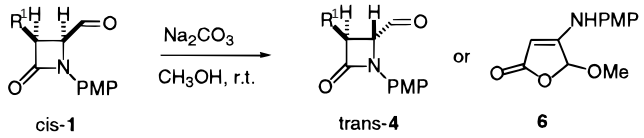


Table 2. Reaction of *cis*-4-Formyl-β-lactams 1 with Na_2CO_3 in Methanol[a]

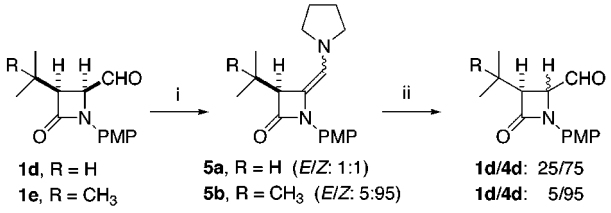


entry	substrate[b,c]	R^1	reaction time (h)	product	trans/cis ratio[d]	yield[e] (%)
1	**1a**	Et	4	**4a**	100:0	>95
2	**1b**	*i*-Pr	4	**4b**	100:0	>95
3	**1c**	*t*-Bu	2	**4c**	100:0	>95
4	**1d**	Ph	4	**4d**	100:0	>95
5	**1g**	BnO	3	**6**		80[f]
6	**1h**	PhO	3	**6**		80[f]

[a] Compound **1** (1 mmol), Na_2CO_3 (2 mmol), and methanol (30 mL) were used. [b] Starting substrates **1** were in all cases racemic. [c] PMP = 4-methoxyphenyl. [d] Determined from integration in the ^{1}H NMR (300 MHz) of the crude reaction mixtures. [e] >95% conversion by ^{1}H NMR observed in all cases (No further purification needed). [f] Isolated yield after column chromatography.

benzene, compounds **5** were obtained as mixtures of *E*/*Z* isomers [(1:1) for **5a** and (95:5) for **5b**]. Crude enamines were stirred with water in benzene at room temperature to give trans/cis mixtures of the corresponding 4-formyl-β-lactams [(75:25) for **5a** and (95:5) for **5b**, after 48 and 72 h, respectively] (Scheme 2). Although not conclusive at all, these experiments suggest that enamines are not the actual intermediates in the isomerization since their hydrolysis requires longer reaction times for a lower cis/trans stereoselectivity to be obtained.

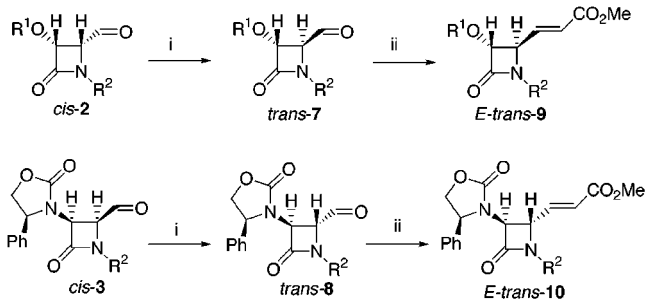
Scheme 2[a]



[a] Key: (i) pyrrolidine, benzene, $ZnCl_2$·α-phenylethylamine complex (cat.), Δ; (ii) water−benzene.

To overcome limitations of the above method, we used sodium carbonate as isomerization reagent. First, we tested isomerization of 3-alkyl and 3-arylderivatives **1a** and **1d**−**f** using sodium carbonate in methanol at room temperature, to check the utility of this reagent in comparison with the previously used dimethylamine. Essentially pure trans isomers **4** were obtained in almost quantitative yields in all cases (Table 2, entries 1−4). As shown in Table 2, better yields and stereoselectivities were obtained, and shorter reactions times were required

Scheme 3[a]



[a] Key: (i) Na_2CO_3, acetonitrile−water (1:1); (ii) $Ph_3P{=}CHCO_2Me$, Et_2O, Δ.

for isomerization. Next, we investigated epimerization of derivatives *cis*-**1g**,**h** having alkoxy substituents at position *C*3. To our surprise, a clean transformation to cyclic enaminone **6** was observed in both cases, instead of the expected C4-epimerization (entries 5 and 6). Enantiomerically pure 3-alkoxyderivative *cis*-**2b**, having an *N*-benzyl group, behaves in similar way, although in this case the product was unstable and quickly evolved to a complex reaction mixture of unidentified products. When compound *cis*-**3a**, having a nitrogenated substituent at C3 was used, neither the corresponding *trans*-4-formyl derivative nor the cyclic enaminone was obtained, and as in the previous case a complex reaction was observed. This new reaction, which involves a tandem E1cB-elimination−rearrangement process of the intermediate enolate, will be studied later in this paper.[15]

Due to participation of methanol in the above reactions, we used other different solvents in order to prevent rearrangement process and to get the desired C4-isomerization in substrates having heteroatomic substituents on C3. We found that a homogeneous mixture of sodium carbonate in acetonitrile−water gave the best results (Scheme 3, Table 3).[16] Reaction times shown in Table 3 were the optimum for each compound. Longer reaction times gave complex crude mixtures and lower yields. Because of the considerable loss of yield during chromatographic purification, the crude trans/cis mixtures of β-lactam aldehydes were transformed by Wittig olefination into the corresponding trans/cis mixtures of α,β-unsaturated esters *E*-**9** and *E*-**10**, stereoselectively.[3a,17] In this way, good yields of compounds *E-trans*-**9** and *E-trans*-**10** were obtained, better than that of the corresponding *trans*-formyl-β-lactams **7** and **8**, when these compounds were isolated by chromatography (see, for example, entries 1 and 5). It is important to note that the small amount of cis isomers **9** and **10** arising from unreactive minor cis stereoisomers **2** and **3** were easily removed at this point by column chromatography.

(15) Access to diverse structural types of natural or synthetic compounds lacking the β-lactam ring have been reported by cleavage of the 2-azetidinone ring through any of the four possibilities. See, for example: (a) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755. (b) Alcaide, B.; Martín-Cantalejo, Y.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 9156 and references therein.

(16) Very recently, a related cis/trans isomerization of *N*-Boc-2,2-dimethyloxazolidine-5-carbaldehydes using K_2CO_3 in methanol has been reported. See: Pastó, M.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron Lett.* **1998**, *39*, 1233.

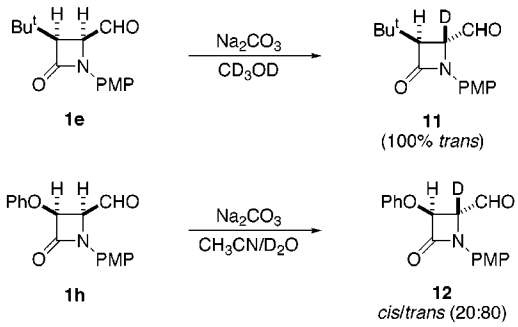
(17) Wittig reaction involving 4-formyl-β-lactams is a versatile methodology frequently used for the synthesis of different functionalized β-amino acids. See, for example: (a) Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429. See also refs 3i and 7b.

Table 3. Reaction of *cis*-4-Formyl-*β*-lactams 2 and 3 with Na_2CO_3 in Acetonitrile−Water[a] and Subsequent Wittig Olefination with $Ph_3P{=}CHCO_2Me$

entry	substrate[b]	R^1	R^2	isomerization time (h)	trans/cis ratio[c]	yield (%)[d] *trans*-**7**/**8**	yield (%)[d] *E-trans*-**9**/**10**
1	(+)-**2a**	Bn	PMP	16	85:15	(−)-**7a** (60)	(−)-**9a** (85)
2	(+)-**2b**	Bn	Bn	48	85:15	(+)-**7b** (45)	(+)-**9b** (60)
3	(+)-**2c**	Ph	allyl	24	80:20	(+)-**7c** (60)	
4	(+)-**2d**	Ph	propargyl	24	75:25		(+)-**9d** (50)
5	(+)-**2e**	Ph	PMP	3	80:20	(−)-**7e** (55)	(−)-**9e** (65)
6	(+)-**3a**	-	PMP	24	95:5[e]		(+)-**10a** (67)
7	(+)-**3b**	-	Bn	96	93:7		(+)-**10b** (70)

[a] Substrate **1**−**3** (1 mmol), Na_2CO_3 (2 mmol), and acetonitrile−water (1/1, 30 mL) were used. [b] Starting substrates **2** and **3** were used as enantiopure cis isomers. [c] Determined from integration in the ^1H NMR (300 MHz) of the crude reaction mixtures. [d] Yields refer to isolated products after column chromatography starting from the corresponding cis isomers. [e] Percentage (95%) of trans isomer **8a** refers to a mixture of both trans C4- and C3-epimers (80% and 15%, respectively).

Scheme 4

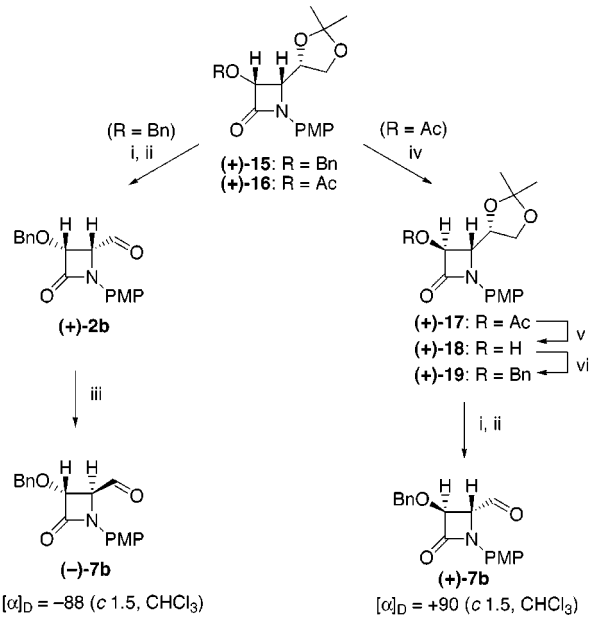


Chemoselective C4-epimerization was observed in all cases except for compound *cis*-**3a**, in which minor C3-isomerization was also observed (see Table 3, footnote d).[18]

Finally, two sets of experiments were carried out in order to demonstrate the C4-chemoselective epimerization. First, isomerization of compound *cis*-**1e** by treatment with Na_2CO_3 in deuterated methanol gave *trans*-4-deutero derivative **11** in almost quantitative yield. Also, treatment of compound *cis*-**1h** with Na_2CO_3 in CH_3CN-D_2O yielded a trans/cis mixture (80/20) of deuterated compounds, from which *trans*-4-deutero compound **12** was easily obtained (50% as pure product) after column chromatography (Scheme 4). Compounds **11** and **12** were unambiguously identified by ^1H and ^{13}C NMR through comparison with the corresponding spectra for trans isomers **4e** and **4h**, respectively (see Figures 1 and 2 in the Supporting Information).

In a second experiment, absolute configuration of *β*-lactam aldehyde (−)-**7b** ($[\alpha]_D = -88$, *c* 1.5 $CHCl_3$) [obtained through isomerization of (+)-*cis*-(3*R*,4*R*)-4-formyl-*β*-lactam **2b** following the above methods] was determined by comparison with (+)-*trans*-(3*S*,4*R*)-4-formyl-*β*-lactam, *ent*-**7b**, prepared from acetal *β*-lactam (+)-**16**. Compound (+)-**16** and its C3-epimer (+)-**17** were prepared through a well-established protocol reported by Bose[4f] (Scheme 5). Reaction of compound (+)-**17** with sodium methoxide in methanol gave the corresponding *trans*-3-hydroxy derivative (+)-**18**, which was transformed into the (+)-*trans*-3-benzyloxy-2-azetidinone **19** by benzylation under phase-transfer conditions. Standard acetonide hydrolysis, followed by cleavage of the resulting diol ($NaIO_4$/MeOH/H_2O), yielded (3*S*,4*S*)-*trans*-4-formyl-2-azetidinone *ent*-**7b** ($[\alpha]_D = +90$, *c* 1.5 $CHCl_3$). Compounds (−)-**7b** and *ent*-**7b** had identical physical and spectroscopic properties except for optical rotations, which were of the same value, but of opposite sign as corresponds to enantiomers. Thus, the 3*R*,4*R* configuration can be assigned to (−)-**7b**. Therefore, these results clearly demonstrate that C4-epimerization was the only stereochemical outcome of the base-promoted reactions reported herein.

Scheme 5[a]

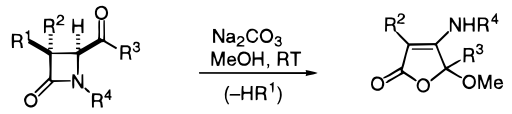


[a] Key: (i) PTSA, THF/H_2O (1:1), Δ; (ii) $NaIO_4$, CH_2Cl_2/water (100:1), rt; (iii) DMA or Na_2CO_3 isomerization; (iv) see ref 4f; (v) NaOMe, MeOH, rt; (vi) BnBr, CH_2Cl_2/NaOH(50%), $Bu_3BnN^+Br^-$.

As we have previously stated, reaction of compounds **1g** and **1h** with Na_2CO_3 in methanol smoothly gave cyclic enaminone **6**. This compound is closely related to enaminones derived from tetronic acid, valuable synthetic intermediates for the construction of biologically active nitrogen heterocycles through aza-annulation reactions with acrylate derivatives.[10] To explore the scope of this new reaction, we prepared a set of different substituted 2-azetidinones **20**, having as structural requirement both an acyl group at position 4 and at least one leaving group on position 3 of the *β*-lactam ring. Compounds **20** were obtained following previously reported methods (see the Experimental Section). Thus, reaction of compounds **20** with Na_2CO_3 in methanol at room temperature for the reaction times indicated in Table 4, smoothly gave the corresponding substituted cyclic enaminones **21**. Pure

(18) Partial epimerization at C3 in a 3-amino-substituted *β*-lactam has been reported using a mixture of $NaHCO_3$ and Na_2CO_3. See, for instance: Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432.

Table 4. Synthesis of Cyclic Enaminones 21

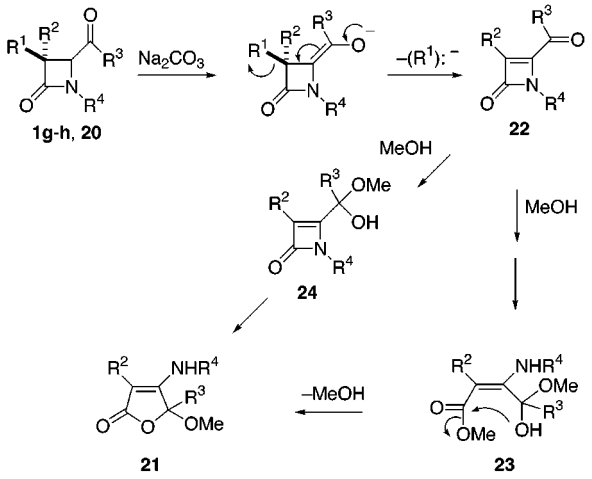


20 **21**

susbtrate[a]	R^1	R^2	R^3	R^4	*t* (h)	product	yield[b] (%)
20a	Br	Et	H	PMP	3	**21a**	85
20b	Cl	Me	H	PMP	3	**21b**	76
20c	Cl	Cl	H	PMP	3	**21c**	80
20d	BnO	H	Me	Propargyl	1.5	**21d**	32[c]
20e	PhO	H	Me	PMP	6	**21e**	80
20f	PhO	H	Ph	PMP	48	**21f**	70

[a] Starting compounds **20** were in all cases racemic. [b] Yields are for pure products purified by column chromatography. [c] Considerable loss of material was observed in this case after chromatographic purification.

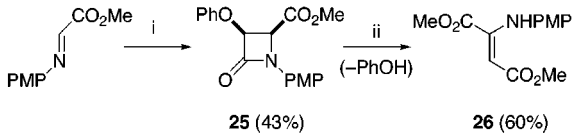
Scheme 6



compounds **21** were isolated in good to excellent yields (70−85%) by flash chromatography, but some decomposition was observed for the sensitive *N*-propargylenaminone **21d** during purification. The above results strongly suggest that an acyl group able to stabilize a negative charge at C4 position, and a good leaving group on C3, are necessary for the process to occur. Formation of compounds **21** may be rationalized through a tandem E1cB-elimination−rearrangement process of the enolate generated initially, followed by ring opening of the resulting highly strained 2-azetinones **22**,[19,20] as shown in Scheme 6. Further intramolecular transesterification of the resulting hemiacetal enaminoester **23** gives final enamine lactone **21**. One of the reviewers has suggested an alternative reaction pathway involving addition of methanol to intermediate **22** and further lactonization of the resulting hemiacetal **24** to give enaminone **21**.

To achieve more information of the process, we used as substrate the 3-phenoxy-4-methoxycarbonyl-β-lactam **25**,[4d] with an ester group on C4 instead of the aldehyde or ketone moieties present in related compounds **20**. Thus, treatment of compound **25** with Na_2CO_3 in methanol at room temperature for 3 h gave enaminodiester **26**, along with phenol (Scheme 7). Spectral data for compound **26** were identical to those reported in the literature for the *Z*-isomer, obtained by an independent route.[21] In this case, the final product is the enaminodiester **26** since this open compound (type **23**) is unable to yield the intermediate hemiacetal (type **24**) and, hence, final lactonization to the corresponding cyclic enaminone.

Scheme 7[a]



[a] Key: (i) $PhCH_2COCl$, Et_3N, rt; (ii) Na_2CO_3, MeOH.

In conclusion, we have demonstrated that both aqueous solution of dimethylamine in heterogeneous phase and sodium carbonate in different solvents promote the regiospecific C4-epimerization of cis-3-substituted 4-formyl-2-azetidinones. The former is particularly effective for *N*-(*p*-methoxyphenyl)-2-azetidinones having alkyl or aryl substituents at C3, while the latter is more general and advangeous independently of the type of substituents at positions N1 and C3 of the β-lactam ring. Hence, these two methods complements each other and enable the regiospecific C4-epimerization of a wide variety of *cis*-4-formyl β-lactams. In addition, a novel base-promoted rearrangement of the β-lactam ring to cyclic enaminones related to tetronic acid, involving an E1cB-elimination reaction in *cis*-3-alkoxy-4-formyl-2-azetidinones, has been uncovered. We have also demonstrated the generality of this process for other structurally related compounds having acyl groups on C4 and a good leaving group on C3 of the β-lactam ring. Studies concerning further applications of these new processes are now in progress.

Experimental Section

General Methods. General experimental data and procedures have been previously reported.[7b] NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Specific rotation $[\alpha]_D$ is given in deg per dm at 20 °C, and the concentration (*c*) is expressed in g per 100 mL in $CHCl_3$. All commercially available compounds were used without further purification. The following starting materials were prepared according to reported procedures: *cis*-1-(*p*-methoxyphenyl)-3-isopropyl-4-formyl-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-4-formyl-3-phenyl-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-4-formyl-3-phenoxy-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-3-benzyloxy-4-formyl-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-3-ethyl-4-formyl-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-3-bromo-3-ethyl-4-formyl-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-3-chloro-4-formyl-3-methyl-2-azetidinone,[6b] *cis*-1-(*p*-methoxyphenyl)-3,3-dichloro-4-formyl-2-azetidinone,[6b] (+)-(3*R*,4*S*)-*cis*-1-(*p*-methoxyphenyl)-3-benzyloxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone,[4f] (+)-(3*R*,4*S*)-*cis*-3-acetoxy-1-(*p*-methoxyphenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone,[4f] (+)-(3*R*,4*S*)-*cis*-1-(*p*-methoxyphenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-azetidinone,[4f] (+)-(3*R*,4*S*)-*cis*-1-(*p*-methoxyphenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-mesyloxy-2-azetidinone,[4f] (+)-(3*S*,4*S*)-*trans*-3-acetoxy-1-(*p*-methoxyphenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone,[4f] (+)-*cis*-(1-benzyl)-3-[(*S*)-4-phenyl-2-oxooxazolidin-3-yl]-4-formyl-2-azetidinone,[4h] (+)-(3*R*,4*S*)-*cis*-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(2-propynyl)-3-phenoxy-2-azetidinone,[7b] *cis*-3-benzyloxy-4-(α-methylstyryl)-1-(2-propyn-

(19) For a review on the chemistry of azetines, see: De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, 1996; Vol. 1, Chapter 1.18.4, p 575.

(20) The synthesis of 1-acyl-4-oxo-2-azetines has been reported. See, for example: Arbuzov, B. A.; Zobova, N. N. *Synthesis* **1974**, 461.

(21) (a) Huisgen, R.; Herbig, K.; Siegl, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2526. (b) Greenhill, J. V.; Ramli, M.; Tomassini, Th. *J. Chem. Soc., Perkin Trans. 1* **1975**, 588.

yl)-2-azetidin-one,[7b] *cis*-3-allyl-1-(*p*-methoxyphenyl)-4-formyl-2-azetidinone,[7d] *cis*-1-(*p*-methoxyphenyl)-4-formyl-3-(2-propynyl)-2-azetidinone,[7d] (+)−(3*R*,4*S*)-*cis*-4-formyl-3-phenoxy-1-(2-propenyl)-2-azetidinone,[7d] (+)-*cis*-(1-*p*-methoxyphenyl)-4-formyl-3-[(*S*)-4-phenyl-2-oxooxazolidin-3-yl]-2-azetidinone,[7g] *cis*-1-(*p*-methoxyphenyl)-3-phenoxy-4-benzoyl-2-azetidin-one,[22] and methyl glyoxalate hydrate.[23]

General Procedure for the Synthesis of *trans*-β-Lactams 4, 7, 9, 10, 11, and 12. Method A. A mixture of the starting *cis*-β-lactam (1 mmol) and dimethylamine (40% aq, 1 mL) in benzene (10 mL) was stirred at room temperature until complete disappearance of the starting material (TLC). The organic layer was extracted, and the crude material was purified by flash chromatography (silica gel, hexane/AcOEt mixtures). **Method B.** A mixture of the starting *cis*-β-lactam (1 mmol), benzyltributylammonium bromide (0.05 mmol), and dimethylamine (40% aq, 1 mL) in benzene (10 mL) was stirred at room temperature until complete disappearance of the starting material (TLC).Then, the organic layer was extracted and the crude material was purified by flash chromatography (silica gel, hexane/AcOEt mixtures). **Method C.** A mixture of the starting *cis*-β-lactam (1 mmol) and sodium carbonate (2 mmol) in methanol (10 mL) was stirred at room temperature until complete disappearance of the starting material (TLC). The mixture was concentrated, extracted with CH_2Cl_2, and dried ($MgSO_4$). After removal of the solvent, the desired product was obtained without further purification. **Method D.** A solution of the starting *cis*-β-lactam (1 mmol) and sodium carbonate (2 mmol) in a mixture of acetonitrile/water (1:1, 30 mL) was stirred at room temperature. The organic layer was extracted with AcOEt (×5) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude mixture was purified by flash chromatography (silica gel, hexane/AcOEt mixtures). **Method E.** The crude product obtained using method C (1 mmol of starting cis β-lactam) was dissolved in ether (10 mL), and $Ph_3P{=}CHCO_2Me$ (1.2 mmol) was added. The mixture was stirred and heated at reflux until complete disappearance of the starting material (TLC). After removal of the solvent under reduced pressure, the product was purified by column chromatography (silica gel, hexane/AcOEt mixtures) to yield *E* isomer exclusively. Spectroscopic and analytical data for some representative pure forms of compounds **4**, **7**, **9**, **10**, **11**, and **12** follow.[24]

(±)-*trans*-4-Formyl-3-isopropyl-1-(*p*-methoxyphenyl)-2-azetidinone (4d). Method A. Reaction time: 24 h. **Method B.** Reaction time: 21 h. From 0.20 g (0.81 mmol) of (±)-**1d**, 0.17 g (87%) of (±)-**4d** was obtained after purification by flash chromatography (hexane/AcOEt 3/1). Colorless oil. (**Method C.** Reaction time: 4 h, quantitative yield). ^{1}H NMR ($CDCl_3$) δ: 0.98 (d, 3H, J = 6.9 Hz), 1.07 (d, 3H, J = 6.9 Hz), 2.05 (m, 1H), 3.05 (dd, 1H, J = 2.7, 8.1 Hz), 3.75 (s, 3H), 4.08 (dd, 1H, J = 2.7, 4.2 Hz), 6.79 (d, 2H, J = 6.9 Hz), 7.18 (d, 2H, J = 6.9 Hz), 9.65 (d, 1H, J = 4.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 198.8, 167.7, 156.4, 131.1, 117.4, 114.4, 60.9, 59.4, 55.4, 27.9, 20.0, 19.8. IR ($CHCl_3$) ν: 1760, 1740. MS *m*/*z*: 247 (M^+, 71), 218 (8), 190 (58), 149 (28), 134 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.24; H, 7.12; N, 5.60.

(±)-*trans*-3-*tert*-Butyl-4-formyl-1-(*p*-methoxyphenyl)-2-azetidinone (4e). Method A. Reaction time: 6 h. **Method B.** Reaction time: 3 h. From 0.20 g (0.77 mmol) of (±)-**1e**, 0.18 g (90%) of (±)-**4e** was obtained after purification by flash chromatography (hexane/AcOEt 3/1). White solid. Mp: 120−122 °C (AcOEt/hexane). (**Method C.** Reaction time: 2 h, quantitative yield). ^{1}H NMR ($CDCl_3$) δ: 1.03 (s, 9H), 3.06 (d, 1H, J = 2.7 Hz), 3.71 (s, 3H), 4.10 (dd, 1H, J = 2.7, 4.4 Hz), 6.79 (d, 2H, J = 9.1 Hz), 7.18 (dd, 2H, J = 9.1 Hz), 9.66 (d, 1H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 199.2, 164.3, 156.5, 131.1, 117.5, 114.5, 63.5, 59.7, 55.5, 31.5, 27.1. IR (KBr) ν: 1760, 1740. MS *m*/*z*: 261 (M^+, 84), 232 (8), 204 (70), 149 (28), 134 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.74; H, 7.06; N, 5.12.

(−)-(3*R*,4*S*)-*trans*-3-Benzyloxy-4-formyl-1-(*p*-methoxyphenyl)-2-azetidinone (7a). Following method B or C starting from (+)-**2a**, as described for the above product (±)-**4g**. This compound was found to be identical with the one described above on the basis of their spectral data. Yield: 60% (either method). White solid. Mp: 146−148 °C (AcOEt/hexane). $[\alpha]_D$ = −88 (*c* 1.5, $CHCl_3$).

(+)-(3*R*,4*S*)-1-Benzyl-3-benzyloxy-4-formyl-2-azetidinone (7b). Method D. Reaction time: 48 h. From 0.10 g (0.34 mmol) of (+)-**2b**, 0.05 g (45%) of (+)-**7b** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. $[\alpha]_D$ = +44.9 (*c* 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.85 (t, 1H, J = 1.5 Hz), 4.21 (d, 1H, J = 14.7 Hz), 4.58 (d, 1H, J = 11.8 Hz), 4.58 (d, 1H, J = 1.5 Hz), 4.74 (d, 1H, J = 14.7 Hz), 4.79 (d, 1H, J = 11.8 Hz), 7.1−7.4 (m, 10H), 9.08 (d, 1H, J = 1.5 Hz). IR ($CHCl_3$) ν: 1760. MS *m*/*z*: 296 (M^+ + 1, 3), 163 (8), 133 (7), 91 (100). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C,73.39; H, 5.99; N, 4.44.

(+)-(3*R*,4*S*)-1-Allyl-4-formyl-3-phenoxy-2-azetidinone (7c). Method D. Reaction time: 3 h. From 0.10 g (0.43 mmol) of (+)-**2c**, 0.06 g (60%) of (+)-**7c** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. $[\alpha]_D$ = +29 (*c* 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.81 (dd, 1H, J = 7.2, 15.4 Hz), 4.12 (dd, 1H, J = 5.7, 15.4 Hz), 4.23 (t, 1H, J = 1.8 Hz), 5.18 (m, 3H), 5.81 (m, 1H), 6.96 (m, 3H), 7.20 (m, 2H), 9.81 (d, 1H, J = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 196.7, 164.2, 156.9, 130.6, 130.0, 123.2, 120.7, 115.8, 82.2, 65.6, 44.7. IR ($CHCl_3$) ν: 1760. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.22; H, 5.43; N, 6.20.

(−)-(3*R*,4*S*)-4-Formyl-1-(*p*-methoxyphenyl)-3-phenoxy-2-azetidinone (7e). Method D. Reaction time: 3 h. From 0.20 g (0.67 mmol) of (+)-**2e**, 0.11 g (56%) of (−)-**7e** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. $[\alpha]_D$ = −30 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3H), 4.62 (dd, 1H, J = 1.8, 3.3 Hz), 5.34 (d, 1H, J = 1.8 Hz), 6.92 (d, 2H, J = 7.0 Hz), 7.06 (m, 3H), 7.25−7.4 (m, 4H), 9.93 (d, 3.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 196.8, 160.8, 157.1, 156.6, 129.9, 123.1, 118.4, 115.6, 115.8, 114.6, 81.4, 65.6, 55.5. IR ($CHCl_3$) ν: 1760. MS *m*/*z*: 297 (M^+, 90), 241 (15), 176 (42). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.08; N, 4.71. Found: C, 68.87; H, 5.31; N, 4.86.

(−)-(3*R*,4*R*)-3-Benzyloxy-4-(2-methoxycarbonyl)ethenyl-1-(*p*-methoxyphenyl)-2-azetidinone (9a). Method E. From (+)-**2a** (0.1 g, 0.32 mmol), 0.1 g (85%) of (−)-**9a** was obtained as a colorless oil. $[\alpha]_D$ = −60 (*c* 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.65 (s, 3H), 3.70 (s, 3H), 4.28 (dc, 1H, J = 1.0, 1.7, 4.0, 7.1), 4.45 (d, 1H, J = 1.7 Hz), 4.53 (d, 1H, J = 11.7 Hz), 4.84 (d, 1H, J = 11.7 Hz), 5.76 (dd, 1H, J = 1.0, 15.9 Hz), 6.64 (dd, 1H, J = 7.1, 15.9 Hz), 6.76 (d, 2H, J = 9.0 Hz), 7.16 (d, 2H, J = 9.0 Hz), 7.30 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 165.8, 162.7, 156.8, 142.4, 136.7, 130.5, 128.9, 128.8, 128.7, 128.5, 118.9, 114.7, 87.6, 72.7, 61.1, 55.6, 52.0. IR (KBr) ν: 1755, 1724, 1510. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.43; H, 5.65; N, 4.02.

(+)-(3*R*,4*R*)-1-Benzyl-3-benzyloxy-4-(2-methoxycarbonyl)ethenyl-2-azetidinone (9b). Method E. From 0.20 g (0.68 mmol) of (+)-**2b**, 0.12 g (60%) of (+)-**9b** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. $[\alpha]_D$ = +7.5 (*c* 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.74 (s, 3H), 3.82 (ddd, 1H, J = 0.7, 1.5, 8.1 Hz), 3.95 (d, 1H, J = 15.0 Hz), 4.45 (d, 1H, J = 1.5 Hz), 4.54 (d, 1H, J = 11.6 Hz), 4.73 (d, 1H, J = 15.0 Hz), 4.79 (d, 1H, J = 11.6 Hz), 5.74 (dd, 1H, J = 0.7, 15.8 Hz), 6.56 (dd, 1H, J = 8.1, 15.8 Hz), 7.2−7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 166.0, 165.6, 142.4, 136.4, 134.6, 128.9, 128.7, 128.6, 128.5, 128.5, 128.1, 124.1, 87.7, 73.2, 60.2, 51.9, 44.8. IR ($CHCl_3$) ν: 1760, 1724. MS *m*/*z*: 352 (M^+ + 1, 2), 218 (10), 91 (100). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.89; H, 5.87; N, 3.65.

(+)-(3*S*,4*S*)-4-(2-Methoxycarbonyl)ethenyl-1-(*p*-methoxyphenyl)-3-[(*S*)-4-phenyl-2-oxo-oxazolidin-3-yl]-2-azetidinone (10a). Method E. From 0.20 g (0.55 mmol) of (+)-

(22) Alcaide, B.; Domínguez, G.; Escobar, G.; Parreño, U.; Plumet, J. *Heterocycles* **1986**, *24*, 1579.

(23) Fernández, F.; García, G.; Rodríguez, J. E. *Synth. Commun.* **1990**, *20*, 2837 and references therein.

(24) Full spectroscopy and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

3a, 0.15 g (67%) of (+)-**10a** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. $[\alpha]_D = +183$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 3.61 (m, 1H), 3.64 (s, 3H), 3.72 (s, 3H), 4.31 (dd, 1H, $J = 6.3, 8.7$ Hz), 4.69 (t, 1H, $J = 8.7$ Hz), 4.82 (d, 1H, $J = 2.4$ Hz), 4.97 (dd, 1H, $J = 6.3, 8.7$ Hz), 5.81 (dd, 1H, $J = 0.9, 15.6$ Hz), 6.72 (d, 2H, $J = 9.3$ Hz), 6.8 (dd, 1H, $J = 8.1, 15.6$ Hz), 6.89 (d, 2H, $J = 9.3$ Hz), 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 165.4, 160.2, 157.0, 156.8, 141.9, 137.5, 129.8, 129.5, 127.6, 124.5, 118.9, 114.3, 70.2, 66.0, 58.8, 57.9, 55.5, 51.9. IR ($CHCl_3$) ν: 1757, 1710. MS *m*/*z*: 422 (M^+, 69), 362 (69), 273 (66), 219 (100). Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.40; H, 5.25; N, 6.63. Found: C, 65.62; H, 5.36; N, 6.91.

(+)-(3*S*,4*S*)-1-Benzyl-3-[(*S*)-4-phenyl-2-oxo-oxazolidin-3-yl]-4-(2-methoxycarbonyl)ethenyl-2-azetidinone (10b). Method E. From 0.20 g (0.57 mmol) of (+)-**3b**, 0.15 g (70%) of (+)-**10b** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. $[\alpha]_D = +24.8$ (*c* 4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 3.46 (dd, 1H, $J = 2.2, 8.1$ Hz), 3.64 (s, 3H), 3.82 (d, 1H, $J = 15.1$ Hz), 4.11 (dd, 1H, $J = 6.6, 8.8$ Hz), 4.45 (d, 1H, $J = 15.1$ Hz), 4.61 (t, 1H, $J = 8.8$ Hz), 4.65 (d, 1H, $J = 2.2$ Hz), 4.83 (dd, 1H, $J = 6.6, 8.8$ Hz), 5.66 (d, 1H, $J = 15.8$ Hz), 6.57 (dd, 1H, $J = 8.1, 15.8$ Hz), 6.9 (m, 2H), 7.2 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 165.4, 163.6, 157.2, 142.1, 137.8, 137.0, 134.0, 129.5, 128.8, 128.0, 127.7, 127.1, 125.0, 70.7, 66.0, 59.0, 57.6, 51.9, 45.1. IR ($CHCl_3$) ν: 1763, 1718. MS (*m*/*z*): 407 ($M^+ + 1$, 8), 406 (M^+, 6), 346 (65), 273 (100). Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 68.20; H, 5.62; N, 7.10.

(±)-*trans*-3-*tert*-Butyl-4-formyl-4-deutero-1-(*p*-methoxyphenyl)-2-azetidinone (11). Method C (using CD_3OD as solvent). Reaction time: 3 h. Yield: 85%. ^1H NMR ($CDCl_3$) δ: 1.02 (s, 9H), 3.06 (d, 1H, $J = 2.7$ Hz), 3.71 (s, 3H), 6.79 (d, 2H, $J = 9.1$ Hz), 7.18 (dd, 2H, $J = 9.1$ Hz), 9.66 (d, 1H, $J = 4.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 199.2, 164.4, 156.5, 131.1, 117.5, 114.5, 63.5, 59.3 (t, $J = 95$ Hz), 55.5, 31.5, 27.1. IR ($CHCl_3$) ν: 1760, 1730.

Enamine 5b. A solution of 4-formyl-β-lactam **1e** (1 mmol), pyrrolidine (1 mmol), and α-phenylethylamine/$ZnCl_2$ as catalyst (0.05 mmol) in benzene (20 mL) was heated at reflux for 2 h using a Dean−Stark apparatus. Then the solvent was removed under reduced pressure, and the product was characterized without further purification. Colorless oil. ^1H NMR ($CDCl_3$) δ: 1.09 (s, 9H), 1.63 (m, 4H), 2.66 (m, 4H), 3.42 (s, 1H), 3.80 (s, 3H), 5.35 (s, 1H), 6.8 (d, 2H, $J = 8.7$ Hz), 7.5 (dd, 2H, $J = 8.7$ Hz). ^{13}C NMR ($CDCl_3$) δ: 168.9, 156.9, 128.6, 123.1, 122.2, 115.1, 113.3, 64.6, 55.4, 54.7, 32.2, 27.1, 24.7. IR ($CHCl_3$) ν: 2960, 1736, 1510.

General Procedure for the Synthesis of Enaminones 6, 21, and 26. A mixture of the starting *cis*-4-formyl- or *cis*-4-acyl-β-lactam (1 mmol) and sodium carbonate (2 mmol) in methanol (10 mL) was stirred at room temperature until complete disappearance of the starting material (TLC). The mixture was then concentrated, extracted with CH_2Cl_2, and dried ($MgSO_4$). After removal of the solvent, the crude mixture was purified by column chromatography (silica gel, hexane/AcOEt mixtures) to yield enaminones **6**, **21,** and **26**. Spectroscopic and analytical data for some representative pure forms of compounds **6**, **21**, and **26** follow.

Compound (±)-6. Reaction time: 3 h. From 0.10 g (0.34 mmol) of (±)-**1g** or 0.11 g (0.34 mmol) of (±)-**1h**, 0.06 g (80%) of (±)-**6** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). White solid. Mp: 130−132 °C (AcOEt/hexane). ^1H NMR ($CDCl_3$) δ: 3.56 (s, 3H), 3.81 (s, 3H), 5.16 (s, 1H), 5.77 (s, 1H), 6.90 (d, 2H, $J = 8.9$ Hz), 7.10 (d, 2H, $J = 8.9$ Hz), 7.16 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 172.8, 160.5, 157.0, 131.9, 121.8, 114.8, 99.8, 85.0, 55.5, 55.4. IR (KBr) ν: 1720, 1630. MS *m*/*z*: 236 ($M^+ + 1$, 7), 235 (M^+, 29), 204 (18), 203 (61), 174 (100). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.36; H, 5.68; N, 6.25.

Compound (±)-21a. Reaction time: 3 h. From 0.23 g (0.82 mmol) of (±)-**20a**, 0.20 g (95%) of (±)-**21a** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. ^1H NMR ($CDCl_3$) δ: 0.74 (t, 3H, $J = 7.2$ Hz), 1.88 (m, 2H), 3.42 (s, 3H), 3.75 (s, 3H), 5.56 (s, 1H), 6.10 (br s, 1H), 6.81 (d, 2H, $J = 8.8$ Hz), 7.03 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 170.0, 157.9, 155.1, 130.8, 126.0, 114.2, 101.0, 98.4, 55.5, 55.2, 16.0, 12.8. IR ($CHCl_3$) ν: 1745, 1654, 1514. MS *m*/*z*: 263 (M^+, 46), 231 (57), 202 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.99; H, 6.27; N, 5.11.

Compound (±)-21c. Reaction time: 3 h. From 0.60 g (2.19 mmol) of (±)-**20c**, 0.47 g (80%) of (±)-**21c** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). Colorless oil. ^1H NMR ($CDCl_3$) δ: 3.44 (s, 3H), 3.84 (s, 3H), 5.78 (s, 1H), 6.55 (br s, 1H), 6.91 (d, 2H, $J = 8.8$ Hz), 7.1 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 167.0, 158.3, 154.0, 129.1, 126.0, 114.3, 98.0, 90.7, 55.5, 55.5. IR ($CHCl_3$) ν: 1757, 1654. MS *m*/*z*: 271 (M^+ ^{37}Cl, 19), 270 (10), 269 (M^+ ^{35}Cl, 52), 209 (100). Anal. Calcd for $C_{12}H_{12}NO_4$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.26; H, 4.20; N, 4.92.

Compound (±)-26. Reaction time: 3 h. From 0.22 g (0.67 mmol) of (±)-**25**, 0.11 g (60%) of (±)-**26** was obtained after purification by flash chromatography (hexane/AcOEt 2/1). ^1H NMR ($CDCl_3$) δ: 3.68 (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 5.32 (s, 1H), 6.83 (d, 2H, $J = 9.3$ Hz), 6.89 (d, 2H, $J = 9.3$ Hz).

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Supporting Information Available: Compound characterization data and experimental procedures for products **1e**, (+)-**2b**, (+)-**2d**, **4a**−**c**,**f**−**h**, (+)-**7b**, (+)-**9d**, (−)-**9e**, **12**, (+)-**18**, **(+)-19**, **20d**,**e**, **21b**,**d**−**f**, **25**, and **27**−**30**, and Figures 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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