Articles

Alkyne−$Co_2(CO)_6$ Complexes in the Synthesis of Fused Tricyclic *β*-Lactam and Azetidine Systems[†,1]

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A synthetic approach to racemic and enantiomerically pure, fused tricyclic 2-azetidinones and azetidines has been developed by using a Pauson−Khand (P−K) reaction on monocyclic enyne−*β*-lactams as the key synthetic step. The access to cyclization precursors, monocyclic *β*-lactams **1**−**7**, was achieved by Staüdinger reaction of enyne imines **8** and **9** and D-glyceraldehyde imines **10** and (benzyloxy)- or phenoxyacetyl chlorides. Enyne imines **8** and **9** formed *cis*-2-azetidinones **1** and **2** having the required enyne moiety. *cis*-2-Azetidinones **11** were obtained as single diastereomers and transformed to enyne-2-azetidinones **3** and **5** by standard methodology. Alternatively, 4-formyl-2-azetidinones **14** were prepared by cyclization of *p*-anisyl glyoxal diimine and (benzyloxy)acetyl chloride and converted to racemic enyne-*β*-lactams **4** and **6** by standard reactions. Enyne-2-azetidinones **1**−**7** were reacted with $Co_2(CO)_8$ to quantitatively yield the corresponding alkyne−$Co_2(CO)_6$ complexes. Reaction of such complexes with different promoters, especially heat and TMANO, formed tricyclic 2-azetidinones **15**−**19** with the ring system fused to the C3−C4 and C4−N1 lactam bonds. Yields were usually high, and the processes were highly diastereoselective. The exceptions were enyne-2-azetidinones **2** and **3a** bearing *N*-propargyl moieties. These products decomposed to mixtures of unidentifiable products. Inhibition of the amide resonance was postulated as responsible for the failure of *β*-lactams **2** and **3a** to form tricyclic systems. In fact, the analogous enyne−azetidines **20a,b** smoothly cyclized to form the corresponding tricyclic systems. This approach to tricyclic azetidines was extended to prepare different products. A new, unprecedented, N1−C2 bond breakage was also observed in the azetidine ring. The results described show that the P−K reaction is a suitable approach to tricyclic 2-azetidinones and azetidines. These are the first examples reported for a P−K reaction in with the enyne system is tethered to a strained heterocyclic four-membered ring.

Introduction

Recent trends in *β*-lactam chemistry focus on the preparation of structures far away from the classical penem, cefem, and even carbapenem series.[2] The increased resistance of bacteria to the commonly used *β*-lactam antibiotics[3] and the evergrowing new applications of these products in fields ranging from enzyme inhibition[4] to the use of 2-azetidinones as starting materials to develop new synthetic methodologies[5] has triggered a renewed interest in the building of new polycyclic systems having the 2-azetidinone ring as common feature. Starting from the trinem nucleus (formerly known as tribactam and, in terms of antibiotic activity, still an unsurpassed reference),[6] different polycyclic 2-azetidinone systems have been recently reported.[7] Most of the approaches to these compounds rest in the stepwise preparation of a functionalized 2-azetidinone, followed by the central ring closure by methods that have been used for many years in the preparation of bicyclic *β*-lactams.[8] A dramatically different and impressive approach to trinem-related tricyclic structures has been recently disclosed.[9] In this route, an in situ generated azometine ylide reacted with a six-membered dipolaro-

[†] This work is respectfully dedicated to the memory of Juan Francisco de Andrés, a teacher.

(1) For a preliminary communication of a part of this work, see: Alcaide, B.; Polanco, C.; Sierra, M. A. *Tetrahedron Lett.* **1996**, *37*, 6901.

(2) Biodi, S. In *Anti-Infectives: Recent Advances in Chemistry and Structure Activity Relationship*; Bentley, P. H., O'Hanlon, P. J., Eds.; Special Publication No. 198; RSC: Cambridge, U.K., 1997; pp 86−100.

(3) For excellent articles on the bacterian resistance to the common use antibiotics, see: (a) Hook, V. *Chem. Br.* **1997**, *33*, 34. (b) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333.

(4) Recent examples: (a) Wu, G.; Tormos, W. *J. Org. Chem.* **1997**, *62*, 6412. (b) Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B.; Davis, H. R. *J. Med. Chem.* **1996**, *39*, 3684 and references therein.

(5) See, for example: Ojima, I. *Adv. Asymmetric Synth.* **1995**, *1*, 95.

(6) (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Andreotti, D.; Gaviraghi, G.; Carlesso, R.; Bismara, C. Eur. Pat. Appl. EP0416953 A2, 1991; *Chem. Abstr.* **1992**, *116*, 235337t. (b) Perboni, A.; Rossi, T.; Gaviraghi, G.; Ursini, A.; Tarzia, G. WO 9203437, 1992; *Chem. Abstr.* **1992**, *117*, 7735m.

(7) Recent examples: (a) Sakya, S. M.; Strohmeyer, T. W.; Lang, S. A.; Lin, Y.-I *Tetrahedron Lett.* **1997**, *38*, 5913. (b) Annibalc, A. D.; Pesce, A.; Resta, S.; Irogolo, C. T. *Tetrahedron* **1997**, *53*, 13129. (c) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125. (d) Alcaide, B.; Rodríguez-Vicente, A.; Sierra, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2203. (e) Banik, B. K.; Gottumukkala, V.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1996**, *37*, 1363. (f) Chuansheng, N.; Pettersson, T.; Miller, M. J. *J. Org. Chem.* **1996**, *61*, 1014. (g) Crocker, P. J.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 6176. (h) Gilchrist, T. L.; Graham, K. *Tetrahedron Lett.* **1995**, *47*, 8693. (i) Hanessian, S.; Reddy, B. G. *BioMed. Chem. Lett.* **1994**, *19*, 2285.

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phile to form the tricyclic [4.5.6] skeleton in a single step. Except for the polycyclic β-lactams built onto the penem or cefem nuclei,[10] the synthesis of other polycyclic 2-azetidinones has been less investigated. Most of the research in this field has focused onto benzo-fused carbapenem or carbacefem derivatives,[11] as they are potential suicide β-lactamase inhibitors. Other polycyclic systems have been prepared by multistep synthesis directed toward each specific type of compounds.[7]

The simultaneous construction of two of the three rings of a tricyclic β-lactam system, on a preformed monocyclic 2-azetidinone, was at the beginning of this work a conceptually different, straightforward, approach to this type of compounds. Following this idea we devised the Pauson−Khand (P−K) cyclization[12] of enyne−2-azetidinones to access to tricyclic β-lactams. This reaction was chosen because it ranks among the best methods to increase molecular complexity in a single synthetic step. The idea of our original project was to gain access to all possible modes of fusion on the four-membered ring, starting from easily available precursors. In this paper we report in full[1] the scope of this approach to new tricyclic β-lactam systems, as well as the extension of the P−K cyclization to prepare new tricyclic azetidines. Furthermore, the structural requisites for the P−K reaction on a four-membered 2-azetidinone ring, to the best of our knowledge unprecedented, will be also discussed.

Results and Discussion

A series of enyne−2-azetidinones **1**−**7** (Figure 1) were prepared to build tricyclic β-lactams by using the P−K reaction, to study the scope of the approach and its regio- and stereochemistry. Enyne imines **8** and **9** and D-glyceraldehyde acetonide imines **10**, prepared by standard aldehyde−amine condensation, were reacted with alkoxyacetyl chlorides in the presence of Et_3N to yield 2-azetidinones **1a**,**b**, **2**, and **11a**−**d**, in good to excellent yields and exclusively as *cis*-diastereomers. Compounds **11a**−**d** was also single *cis*-enantiomers (ee > 95%).[13] 2-Azetidinones **1a**,**b** and **2** have the enyne moiety required carrying out the P−K reaction. However, compounds **11a**−**d** required further manipulation to obtain the enyne functionality. Standard acetonide hydrolysis to yield diols **12**, followed by reaction with thiocarbonyldiimidazole (TCDI) in boiling THF[14,15] and $(MeO)_3P$[15] yielded optically pure enyne−2-azetidinones **3a**−**d**

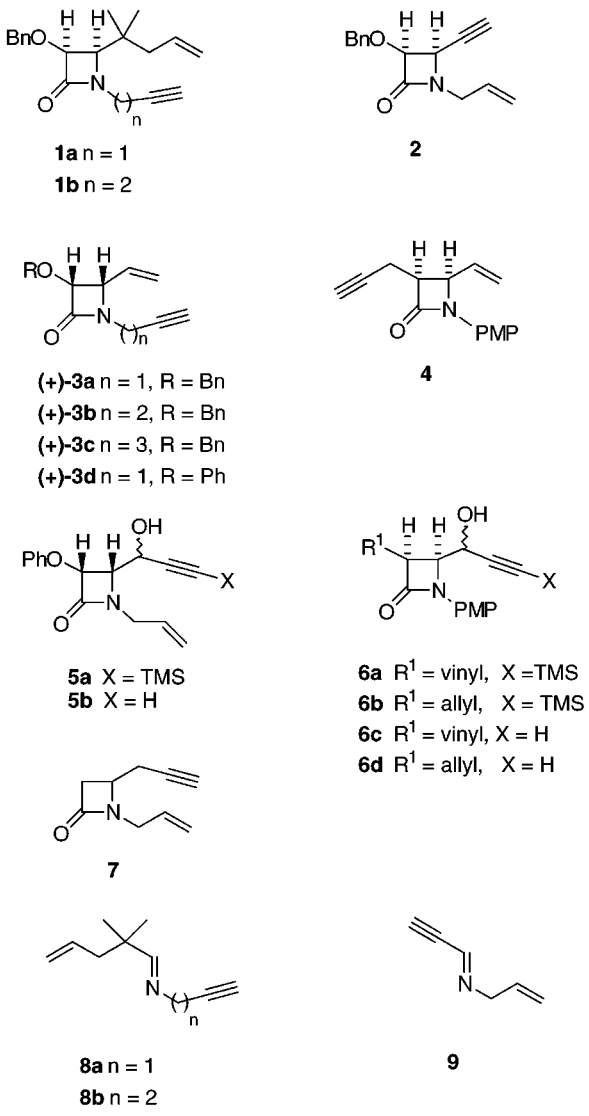

Figure 1.

(8) For an exhaustive revision on cyclization methodologies to prepare bicyclic β-lactams, see: (a) Kant, J.; Walker, D. G. In *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993; Chapter 3. Recent examples on the application of cyclization reactions to trinem and trinem derivatives synthesis: (b) Camerini, R.; Donati, D.; Marchioro, C.; Mazzoni, A.; Pachera, R.; Panunzio, M. *Tetrahedron: Asymmetry* **1997**, *8*, 15. (d) Di Fabio, R.; Rossi, T.; Thomas, R. J.; Thomas, R. J. *Tetrahedron Lett.* **1997**, *38*, 3587. (e) Marchioro, C.; Pentassuglia, G.; Perboni, A.; Donati, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 463. (f) Rossi, T.; Marchiro, C.; Paio, A.; Thomas, R. J.; Zarantonello, P. *J. Org. Chem.* **1997**, *62*, 1653. (d) Hanessian, S.; Griffin, A. M.; Rozema, M. J. *BioMed. Chem. Lett.* **1997**, *7*, 1857. (e) Guiron, C.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1997**, *20*, 3569. (f) Hanessian, S.; Rozema, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 9884.

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(11) (a) Joyeau, R.; Yadav, L. D. S.; Wakselman, M. *J. Chem. Soc., Perkin Trans 1* **1987**, 1899. (b) Finkelstein, J.; Holden, K. G.; Perchonock, C. D. *Tetrahedron Lett.* **1978**, 1629. (c) Hakimelahi, G. H.; Just, G. *Can. J. Chem.* **1979**, *57*, 1939. (d) Bose, A. K.; Ram, B.; Hoffman, N. A.; Hutchinson, A. J.; Manhas, M. S. *J. Heterocycl. Chem.* **1979**, *16*, 1313. (e) Miyake, H.; Tokutake, N.; Kirisawa, M. *Synthesis* **1983**, 833. (f) Bachi, M. D.; Klein, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1925. (g) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680. (h) Ongania, K. H.; Wallnoefer, M. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 2.

(12) For reviews on the P−K reaction, see: (a) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 12, p 703. (b) Schore, N. E. *Org. React.* **1991**, *40*, 1. (c) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.

(13) The *cis*-selectivity observed for compounds **1a**,**b**, **2**, and **11a**−**d** was expected according to the current model for the Staüdinger reaction. (a) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. (b) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (c) Palomo, C.; Aizpurua, J. M.; Mielgo, A.; Linden, A. *J. Org. Chem.* **1996**, *61*, 9186. This model accounts for a *3R,4S* stereochemistry for D-glyceraldehyde-derived 2-azetidinones. For an experimental study on the synthesis of 2-azetidinones derived from D- and L-glyceraldehyde acetonide imines, see: (d) Hubschwerelen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206. (e) Welch, J. T.; Araki, K.; Kawecki, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454. (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 and references therein.

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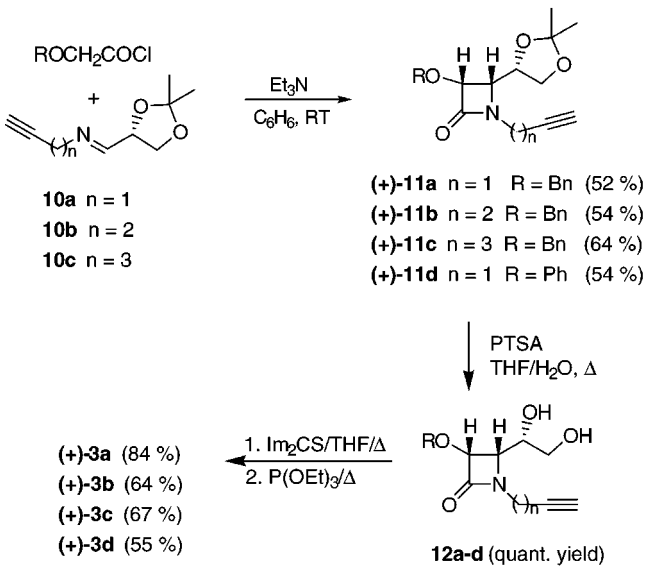
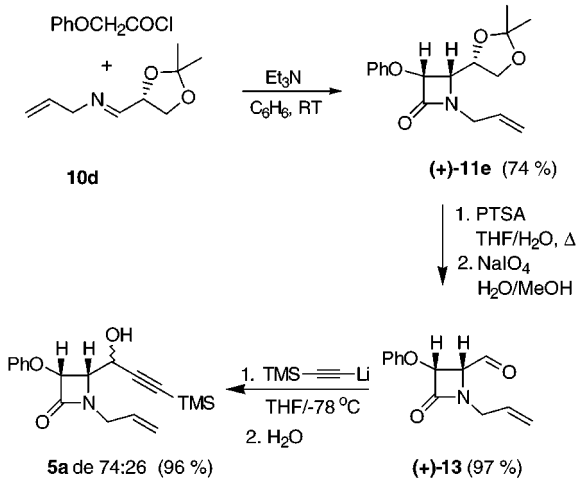
(15) Horton, D.; Turner, W. N. *Tetrahedron Lett.* **1964**, *36*, 2531.

Scheme 1



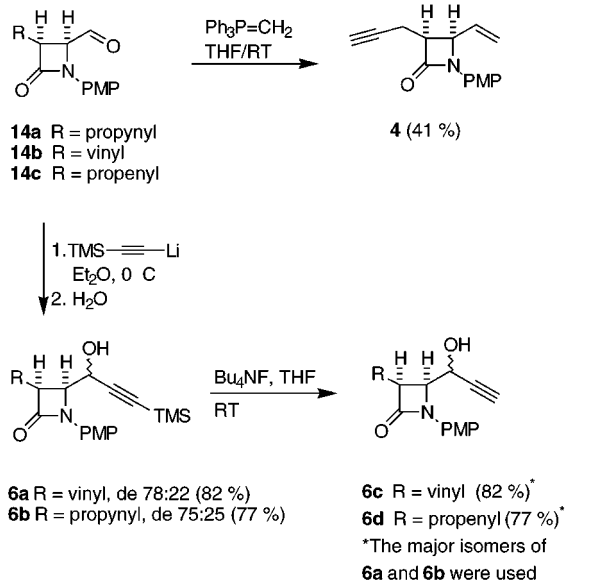
(Scheme 1). Alternatively, oxidative cleavage of diol **12e** ($NaIO_4$/MeOH/H_2O)[16] obtained from **11e**, formed 4-formyl-2-azetidinone **13**. Compound **13** was obtained as a diasteromeric mixture of methoxy hemiacetals, which were easily transformed to the free aldehyde by azeotropic distillation using a Dean−Stark apparatus. Optically pure aldehyde **13** was converted to the diastereomeric mixture of enyne alcohols **5a** by reaction with lithium (trimethylsilyl)acetylide (THF, −78 °C) (Scheme 2). 2-Azetidinone **5b** having a terminal alkyne was prepared by desilylation of compound **5a** with Bu_4NF.[17]

Scheme 2



Reaction of D-glyceraldehyde acetonide imines **10** with crotonyl, 4-pentenoyl, and 4-pentinoyl chloride produced sluggish reaction mixtures on the different reaction conditions tested. Access to substrates **4** and **6** was achieved from racemic aldehydes **14**, prepared by reaction of *p*-anisyl glyoxal diimine and the above acid chlorides, following our previously reported procedure.[18] Wittig

Scheme 3



reaction of aldehyde **14a** with methylenetriphenylphosphonium ylide formed *β*-lactam **4** (41%). Addition of lithium (trimethylsilyl)acetylide to aldehydes **14b**,**c** yielded hydroxypropargyl derivatives **6a**,**b** in excellent yields and as diastereomeric mixtures in the exocyclic stereogenic center (Scheme 3). Treatment of compounds **6a**,**b** with Bu_4NF yielded 2-azetidinones **6c**,**d**. Finally, racemic 2-azetidinone **7** was prepared from *NH*-4-acetoxy-2-azetidinone and propargylmagnesium bromide, followed by alkylation with allyl bromide according to the reported procedure.[19]

With a variety of enyne−2-azetidinones in hand the P−K reaction was tested next. Previous work from our laboratories[20] has shown that 2-azetidinones having a *N*-propargyl−$Co_2(CO)_6$ moiety lost the propargyl group when heated in the presence of wet DMSO. With these results in mind, the behavior of $Co_2(CO)_6$−alkyne complexes derived from compounds **2** and **3a** with a *N*-propargyl moiety attached to the lactam nitrogen or with the triple bond directly bonded to the ring C4 position, was tested. Reaction of compounds **2** and **3a** with $Co_2(CO)_8$ at room temperature formed the corresponding alkyne-$Co_2(CO)_6$ complexes quantitatively.[21] These complexes were reacted with the different promoters of the P−K reaction, including heat (boiling toluene or benzene),[12] *N*-methylmorfoline *N*-oxide (NMO),[22] trimethylamine *N*-oxide (TMANO),[23] and DMSO.[24] Very complex reaction mixtures were obtained in all cases. The sole identifiable, trace products were the corresponding *NH*-2-azetidinones. These results shown that the presence

(16) Alcaide, B.; Esteban, G.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1994**, *59*, 7994.

(17) Corey, E. J.; Snider, D. B. *J. Am. Chem. Soc.* **1972**, *94*, 2459.

(18) 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.

(19) (a) Nishida, A.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1981**, *22*, 4819. (b) Ziegler, C. B.; Curran, W. V.; Keigelson, G. B.; Bitha, P.; Fabio, P.; Strohmeyer, T.; Short, K.; Liu, Y.-i. *Tetrahedron* **1994**, *50*, 12085.

(20) Alcaide, B.; Pérez-Castells, J.; Sánchez-Vigo, B.; Sierra, M. A. *Chem. Commun.* **1994**, 587.

(21) 2-Azetidinone−alkyne−$Co_2(CO)_6$ complexes can be isolated and characterized. See the Supporting Information for one example.

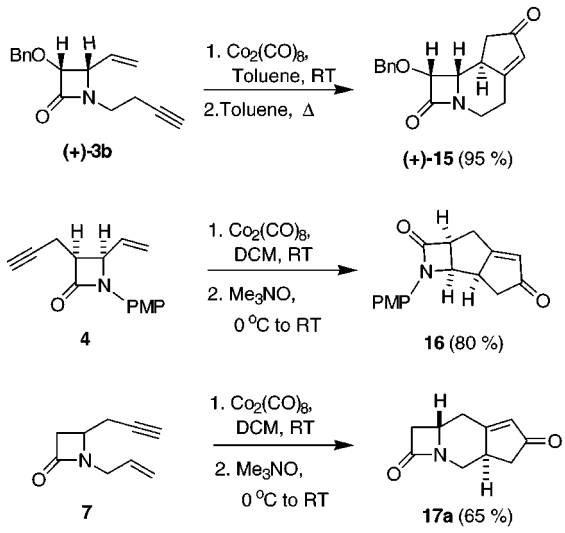
(22) Examples: (a) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396−1406. (b) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220−223.

(23) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990** *31*, 5289.

(24) (a) DMSO: Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220. (b) DMS: Stumpf, A.; Jeong, N.; Sunghee, H *Synlett* **1997**, 205.

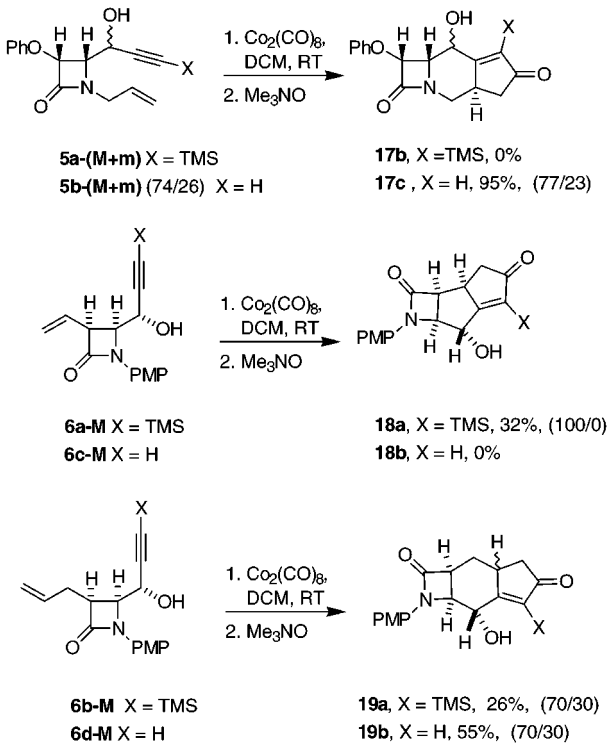
of *N*-propargyl groups is not compatible with our approach. Compounds **3b**, **4**, and **7**, lacking a propargyl moiety, were tested next. Formation of the alkyne−$Co_2(CO)_6$ complexes occurred in quantitatively yield. Treatment of such complexes with TMNO gave extremely clean reaction mixtures, containing the desired tricyclic products **15**−**17a**, as single diastereomers, and compound **15**, as a single enantiomer.[25] Pure compounds **15**−**17a** were obtained by flash chromatography (Scheme 4). Other promoters, such as boiling toluene, wet silica gel,[26] and NMO gave analogous results. Best yields were obtained for compound **15** in boiling toluene while TMANO was superior for compounds **16** and **17a**. It should be pointed out the exquisite selectivity of these reactions (see below for configurational assignment). Compound **3c** quantitatively gave the corresponding alkyne−$Co_2(CO)_6$ complex, which was unreactive in the different conditions tested.

Scheme 4



To extend this approach to the synthesis of many other types of fused tricyclic 2-azetidinones, as well as to determine its compatibility with the presence in the molecule of a versatile functional group, compounds **5** and **6** having an hydroxypropargyl moiety were tested next. Monocyclic TMS derivatives **5a-(M + m)** (as a mixture of both isomers: M, major isomer; m, minor isomer) and the separated major isomers of 2-azetidinones **6a-M** and **6b-M** were reacted first. In both cases the corresponding alkyne-$Co_2(CO)_6$ complexes were obtained again without novelty. Treatment of the complexes derived from **6a-M** and **6b-M** with TMANO formed tricyclic derivatives **18a** and **19a**, in low yields. In both cases considerable amounts of decomplexed starting material were recovered. The complex derived from **5a** yielded only the decomplexed starting 2-azetidinone **5a** upon treatment with TMANO. The hindered triple bond should be responsible for the low yields obtained, a fact documented in the literature.[27] Furthermore, while TMS derivative **6a-M** gave a single diastereomer of the tricycle **18a**, a diastereomeric mixture (70:30) of compound **19a** was obtained from **6b-M**. The analogous reaction of complexes derived from terminal alkynes **5b-(M + m)** (as a diastereomer mixture) and **6d-M** (major diastereomer) gave tricycles **17c** and **19b**. Surprisingly, the complex derived from compound **6c-M** was unreactive toward cyclization and decomplexed **6c-M** was recovered unchanged. Other reaction conditions were tested to promote the cyclization of compound **6c-M**, always with negative results. The selectivity of the cyclizations of compounds **5b-(M + m)** and **6d-M** depends, again, on the structure of the substrate. Thus, compound **5b-(M + m)** cyclized in almost quantitative yield, to give the mixture of diastereomeric tricycles **17c**, without changes in the starting diastereomer ratio. Tricycles **17c** were now easily separated by flash chromatography, to give both diastereomers of **17c** as optically pure compounds differing, exclusively, in the configuration of the carbon bearing the hydroxyl group. Cyclization of azetidinone **6d-M** gave a mixture of diastereomeric tricycles **19b** (70:30), with a selectivity analogous to the TMS derivative **6b-M**. It appears to be that the selectivity is intrinsic to the cyclization mode.

Scheme 5



Finally, although the difficulty to obtain ring sizes higher than five or six by a P−K reaction is well-known,[12] we tested this possibility on the complexes derived from β-lactams **1a**,**b**. As expected, complex reaction mixtures were obtained in the diverse conditions used. The sole identifiable material was derived from the reduction of the triple bond to the olefin on azetidinones **1a**,**b**, and it was isolated in very low yield (8% and 17%, respectively).

(25) In all cases the diastereomer ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification.

(26) (a) Smit, W. D.; Kireev, S. L.; Nefedov, O. M.; Tarasov, V. A. *Tetrahedron Lett.* **1989**, *30*, 4021−4024. (b) Gybin, A. S.; Smit, W. A.; Caple, R.; Veretenov, A. L.; Shashkov, A. S.; Vorontsova. L. G.; Kurella, M. G.; Chertkov, V. S.; Carapetyan, A. A.; Kosnikov, A. Y.; Alexanyan, M. S.; Lindeman, S. V.; Panov, V. N.; Maleev, A. V.; Struchkov, Y. T.; Sharpe, S. M. *J. Am. Chem. Soc.* **1992**, *114*, 5555.

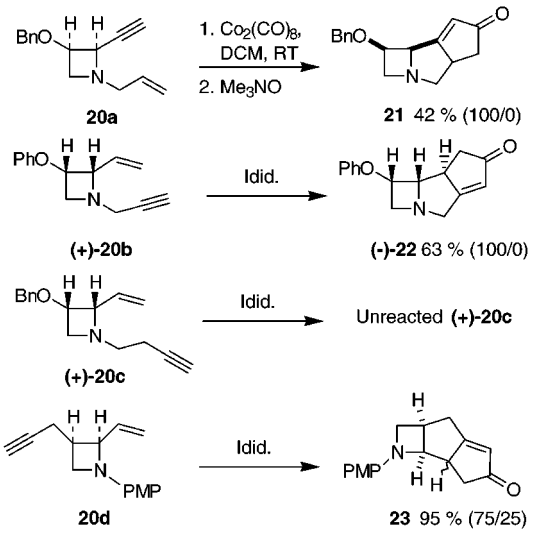
(27) Mukai, C.; Uchiyama, U.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761.

Although unusual, the reduction of a triple bond under P−K reaction conditions has been reported.[28]

Results above show that the P−K reaction is a simple and, most of the times, an efficient entry to different tricyclic 2-azetidinones with a five- or six-membered ring fused to the *β*-lactam nucleus. Exceptions are those monocyclic 2-azetidinones having an *N*-propargyl moiety. These results are significative since amides having a propargyl group form P−K derived products.[29] It is well-known that the 2-azetidinone ring with a pyramidalized lactam nitrogen is unstable.[30] Transition states leading to tricyclic 2-azetidinones from alkyne−$Co_2(CO)_6$ complexes are expected to have highly pyramidalized *β*-lactam nitrogens. To test if this effect was responsible for the failure of compounds **2** and **3a** to form cyclized derivatives, azetidines **20a**,**b** were prepared. The planarity of the amide nitrogen, imposed by the amide resonance, is excluded in azetidines. Additionally, due to the interesting biological activity of some related tricyclic azetidines,[31] the study was extended to azetidines **20c**,**d**, derived from 2-azetidinones reactive toward P−K cyclization. Azetidines **20** were easily prepared by reduction of the corresponding *β*-lactams with excess of AlH_2Cl (generated in situ from $LiAlH_4/AlCl_3$) following the procedure reported by Ojima.[32] The reaction was instantaneous at room temperature, and the stereochemistry of the starting monolactams remained unaltered during the process.

Azetidines **20** were reacted with $Co_2(CO)_8$ in solution of DCM forming the corresponding complexes in quantitative yields. These complexes were submitted, without isolation, to TMANO treatment at room temperature, yielding, with the exception of azetidine **20c**, the expected tricyclic derivatives **21**−**23** (Scheme 6). The unstability of both the azetidines **20**, and of the final products, precluded heating as a promoter for the P−K reaction. Pure tricyclic azetidines **22** and **23** were obtained by flash chromatography (hexane/Et_3N mixtures). Compound **21** was unseparable from a new product lacking the azetidine nucleus (see below). Azetidines **20a**,**b** yielded exclusively a single diastereomer of the corresponding

Scheme 6



tricyclic products, but compound **20d** formed a 75:25 mixture of compound **23**. Formation of compounds **21** and **22** from azetidines **20a**,**b** clearly demonstrated that the lactam nitrogen is the responsible for the failure of *β*-lactams **2** and **3a** to form tricyclic 2-azetidinones. It can be concluded that, for *N*-propargyl derivatives, the amide resonance should both decrease the mobility on the P−K intermediate and also force a planarity which is not compatible with the cyclization process. A surprising result is the inertia of compound **20c** toward cyclization. The different reaction conditions tested either resulted in recovering of starting decomplexed material or in formation of intractable reaction mixtures. A hypothesis to explain these results may be the anchorage of the basic nitrogen to the coordination site to be filled by the olefin double bond. This coordination should inhibit the cyclization. The presence on compound **20c** of an additional methylene group, with respect to the reactive azetidine **20b**, may ensure an appropriate geometry by placing the basic nitrogen close to the unsaturated cobalt cluster. An analogous result was obtained for the complex of TMS derivative of **20c**. In this case, standard TMNO treatment resulted in the recovering of decomplexed starting material.

The reactivity of azetidine **20a** deserves a special comment. Sequential reaction of compound **20a** with $Co_2(CO)_8$ and TMANO formed the desired tricycle **21**. However, a new product lacking the azetidine ring was obtained (47% yield, pure material) together with azetidine **21**. NMR and analytical data for this new compound were compatible with the bicyclic structure **24**. To ensure that compound **21** was not the precursor of bicycle **24**, the reaction mixture obtained from **20a** was submitted to the reaction conditions above. The composition of the mixture remained unaltered through the process. Formation of compound **24** by azetidine ring breakage has no precedents in the literature, except for our recent report[33] of an analogous process on azetidines having an acetal or thiocetal attached to C2. These compounds smoothly rearranged by N1−C2 bond breakage to bicyclic pyrrolidines, upon treatment with $AlEt_2Cl$. Azepine **24** may arise from a similar process. It is well-known the

(28) (a) Chisato, M.; Masahiko, U.; Miyoji, H. *Chem. Commun.* **1992**, 1014. (b) Montaña, A. M.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *An. Quim.* **1987**, *84*, 82 and references therein.

(29) See, for example: (a) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396. (b) Brown, S. W.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1205. (d) Becker, D. P.; Flynn, D. L. *Tetrahedron Lett.* **1993**, *34*, 2087. (c) Yoo, S.-e.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968.

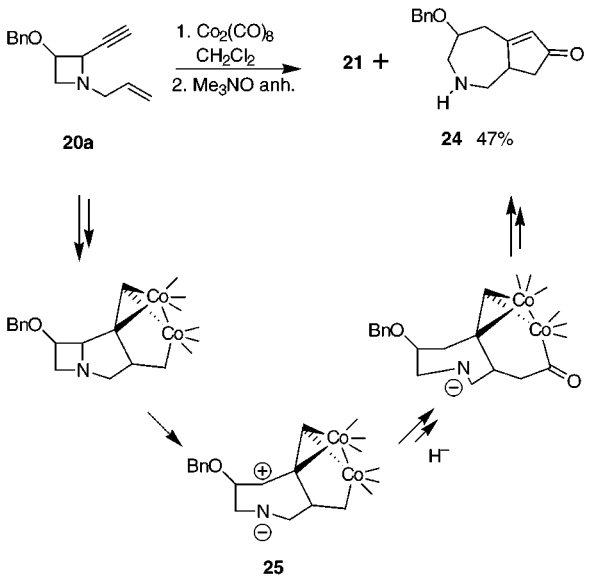
(30) For some selected examples reporting the bizarre effects caused by the inhibition of NC=O resonance in amides, especially in the so-called anti-Bredt amides, see: (a) Alcaide, B.; Casarrubios, L.; Domínguez, G.; Sierra, M. A.; Monge, A. *J. Am. Chem. Soc.* **1995**, *117*, 5604. (b) Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113. (c) Collins, T. J.; Coots, R. J.; Furutani, T. T.; Keech, J. T.; Peake, G. T.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1986**, *108*, 5333. (d) Somayaji, V.; Brown, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 4738. (e) Somayaji, V.; Skorey, K. I.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 4866. Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1987**, *52*, 805. (f) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073.

(31) Reviews on the synthesis and chemistry of azetidines: (a) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Eds.; Elsevier: Oxford, U.K., 1996; Vol. 1, Chapter 1.21.3. (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds-Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 3, pp 1−217. (c) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331. To the best of our knowledge, the sole precedent on the multistep synthesis of tricyclic azetidines and their role as serotoninergic agents is by Becker and Flynn: (d) Becker, D. P.; Flynn, D. L. *Tetrahedron* **1993**, *49*, 5047.

(32) Ojima, M.; Zhao, T.; Yamato, K.; Nakahashi *J. Org. Chem.* **1991**, *56*, 5263.

(33) Alcaide, B.; Salgado, N. R.; Sierra, M. A. *Tetrahedron Lett.* **1998**, *39*, 467.

Scheme 7



ability of Co clusters to stabilize carbocations on the carbon contiguous to the metal.[34] Intermediate **25** would be formed after N1−C2 bond rupture, a process which would relieve the steric energy of the crowded previous intermediate. Formation of azepine **24** would end by hydride capture from the reaction medium (Scheme 7).[28] An alternative reaction pathway involving the interaction of the basic azetidine nitrogen with the organometallic cluster to promote the azetidine ring breakage has been proposed by a reviewer. This is an appealing possibility which cannot be disregarded with data in hand, since formation of compound **24** would be closely related with the azetidine ring breakage induced by $AlEt_2Cl$. Although much research will be necessary before ensuring the generality of this process, it seems clear that the presence of a *N*-propargyl moiety endows the azetidine and 2-azetidinone nuclei with a special reactivity.

Configurational Assignment. The structure and stereochemistry of compounds **15**−**19** and **21**−**23** have been assigned by NMR techniques. The *cis*-stereochemisty of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring, and it is transferred unaltered during the further synthetic steps. Compounds **16** and **18a** showed values of $J_{2,3}$ and $J_{8,9}$ in good agreement with those reported for analogous systems.[35,36] Thus, a *syn*-stereochemistry for the hydrogens of the central five-membered ring was assigned for compound **16** with $J_{2,3} = 4.8$ Hz, while an *anti*-relative disposition between H2 and H3 was assigned for compound **18a** with a $J_{2,3} = 0$ Hz. Furthermore, NOE-irradiation of H2 on compound **16** resulted on 11% enhancement on the signal corresponding to H3, which is in agreement with the proposed *cis*-stereochemistry (Figure 2). For compound **18a** the analogous measurement resulted in 3% enhancement, while irradiation of H9 ($J_{8,9} = 9.3$ Hz) resulted in a 11% enhancement on the signal corresponding to H8. Thus, a *syn*-stereochemisty was established for this moiety.

Azetidinones **15**, and **17a**,**c** have a six-membered ring fused to the β-lactam. In these cases the stereochemisty

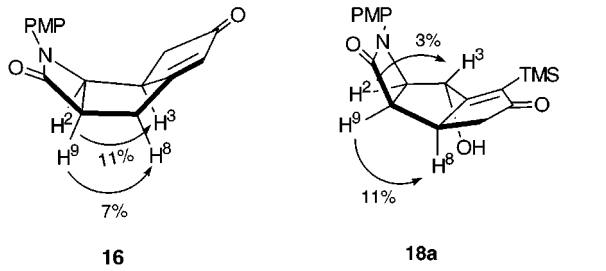


Figure 2.

was assigned from compounds **17c**, which are epimers at the carbinol center. ^{1}H NMR spectra were similar in both epimers except, as expected, in the signals associated with H8. Thus, values of $J_{8,9} = 1.7$ Hz for **17c-M** and 4.7 Hz for **17c-m** were measured, which are congruent respectively with syn and anti stereochemistry between both hydrogens.[37][36] NOE irradiation on H8 resulted in complementary results for both isomers. Thus, NOE enhancements of 4% were observed on H9 and H6 for **17c-M**, while a 6% enhancement was observed on H3 for compound **17c-m**. It can be concluded that compound **17c-M** has a syn H8−H9/anti H8−H3 stereochemistry, while compound **17c-m** has an anti H8−H9/syn H8−H3 stereochemistry. On the basis of analogous data, an anti H3−H9 stereochemistry was established for compound **17a**. Stereochemistry for compound **15** was immediate by comparison with the above results. Thus, the value of $J_{8,9} = 7.5$ Hz and a NOE enhancement of 8% on H3 and the absence of NOE enhancement on H9 upon irradiation of H8 ensure an anti H8−H9/syn H8−H3 stereochemisty for this compound (Figure 3). It is noteworthy that, for the epimers of **17c**, the additional carbinolic stereocenter has no influence in the stereochemistry of the six−five ring junction.

The assignment of the stereochemistry of compounds **19a**,**b**, having the six-membered ring fused to the C3−C4 bond of the β-lactam ring, was based on the major isomer of compound **19b**. Again, NOE irradiation of H3 resulted on enhancement of the signals corresponding to H2, H5, and H8 (3, 4, and 4%, respectively), which is consistent with an anti H3−H2/syn H3−H8 relative stereochemistry. The $J_{2,3} = 2.5$ Hz is also consistent with an anti H2−H3 stereochemistry in a pseudo-boat conformation. Analogous NOE enhancements were observed between H2 and H3 in both isomers of compound **19a**; $J_{2,3}$ was in the same range for both isomers, which pointed to their nature of epimers at C8. However, NOE enhancement was not observed for H8 in either isomer of compound **19a** when H3 was irradiated (Figure 4). It may be concluded then that both isomers of compound **19a** have an opposite stereochemistry at C8. The sense of diastereoselectivity may be controlled by the stereocenter contiguous to the olefin bond. However, these are the sole cases in which a total diastereoselectivity was not observed.

(34) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 12, p 685.

(35) For clarity through this work tricyclic systems has been numbered according with the numeration used for trinems. Thus, the four-membered ring nitrogen has been assigned the locator 1 and the remaining positions have been numbered to place the higher number on the carbonyl group (for 2-azetidinones) or former carbonyl carbon (for azetidines).

(36) (a) Galluci, J. C.; Ha, D.-C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283. (b) Alcaide, B.; Esteban, G.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J. *J. Org. Chem.* **1994**, *59*, 7994.

(37) Günther, H. *NMR Spectroscopy*; John Wiley and Sons: Chichester, U.K., 1995.

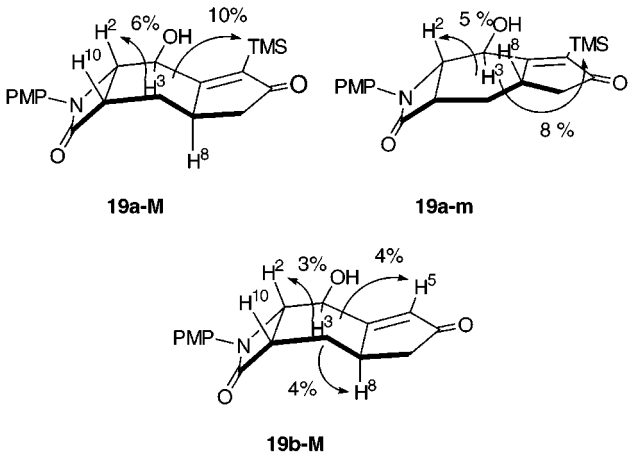


Figure 4.

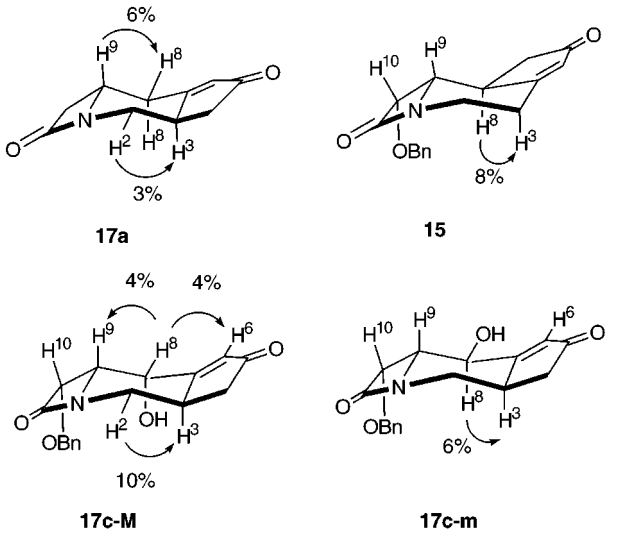


Figure 3.

The stereochemistry of tricyclic azetidines **22** and **23** was determined on the same basis (Figure 5). The complexity of the spectra in these compounds required the unambiguous elucidation of every proton, which was done by two-dimensional techniques (COSY and/or HETCOR). For compound **23**, $J_{2,3} = 5.8$ Hz is in agreement with a syn stereochemistry, by comparison with reported data for related derivatives.[31d] NOE irradiation of H3 on compound **23** resulted in an 11% enhancement of the signal corresponding to H2, which allows us to assign a syn H2−H3 stereochemistry. Irradiation of H7 on compound **22** did not produced any enhancement on H8, which pointed to an anti relationship between both hydrogens. Finally, the stereochemistry of compound **21** could not be determined due to the overlapping of the significative signals with those of bicyclic azepine **24**.

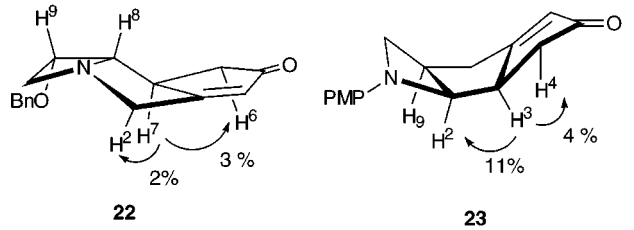


Figure 5.

In conclusion, a synthetic approach to both racemic and enantiomerically pure fused tricyclic 2-azetidinones and azetidines has been developed by using a P−K reaction as the key step. The process is highly diastereoselective and allows one to prepare all the possible modes of ring fusion. The exclusive limitation of this process is the presence of an *N*-propargyl moiety attached to the 2-azetidinone ring. This structural feature is compatible with azetidine cyclization, showing that the planarity imposed by the amide group is responsible for the failure of *N*-propargyl-2-azetidinones to cyclize. A potentially interesting azetidine bond breakage has been disclosed. To our knowledge this is the first time that a P−K cyclization was studied with both the alkyne and the alkene tethered to a heterocyclic four-membered ring. Efforts to develop other cyclization approaches to fused β-lactam and azetidine systems using 2-azetidinone alkyne−$Co_2(CO)_6$ complexes are now underway.

Experimental Section

General Methods. General experimental data and procedures have been previously reported.[7c] 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 chemicals were prepared according to literature procedures: 2,2-Dimethyl-5-pentenal,[38] 4-butynamine,[39] *N*,*N*-bis(*p*-methoxyphenyl)diimine,[40] 2,3-*O*-(isopropylidene)-D-glyceraldehyde,[41] propynal,[42] 3-ethenyl-4-formyl-1-(*p*-methoxyphenyl)-2-azetidinone.[18]

General Procedure for the Synthesis of Compounds 1a,b, and 11a,e. The corresponding alkoxyacetyl chloride (15 mmol) in anhydrous benzene (30 mL) was added dropwise via syringe to a solution of the corresponding imine (10 mmol) and Et_3N (20 mmol) in benzene (30 mL) under argon. The resulting mixture was stirred at room temperature until complete disappearance of the imine (TLC). The crude mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuo. The crude compound was purified by flash chromatography (EtOAc/hexanes mixtures) to yield analytically pure compounds **1** or **11**. Spectroscopic and analytical data for some representative forms of **1** and **11** follow.[43]

***cis*-3-(Benzyloxy)-4-(1,1-dimethyl-3-butenyl)-1-(2-propynyl)-2-azetidinone, 1a.** From 2.98 g (2.0 mmol) of imine **8a** and 5.47 g (3.0 mmol) of (benzyloxy)acetyl chloride, 5.64 g (95%) of compound **1a** was obtained as a colorless oil after purification by flash chromatography (1/6 hexane/AcOEt). ^{1}H NMR: δ 1.07 (s, 6 H), 2.25 (dd, 1 H, J = 13.5, 7.7 Hz), 2.27 (s, 1 H), 2.30 (dd, 1 H, J = 13.5, 7.7 Hz), 3.65 (d, 1 H, J = 5.3 Hz), 3.79 (dd, 1 H, J = 17.7, 2.1 Hz), 4.39 (dd, 1 H, J = 17.7, 2.1 Hz), 4.69 (d, 1 H, J = 5.3 Hz), 4.68 (d, 1 H, J = 11.9 Hz), 4.95 (d, 1 H, J = 11.9 Hz), 4.94−5.09 (m, 2 H), 5.76−5.94 (m,

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(39) Dumont, J. L.; Chodkiewicz, W.; Cadiot, P *Bull. Soc. Chim. Fr.* **1967**, *2*, 588.
(40) (a) Kliegman, J. M.; Barnes, R. K. *J. Org. Chem.* **1970**, *35*, 3140−3143. (b) Barnes, R. K.; Kliegman, J. M. *Tetrahedron* **1970**, *26*, 2555.
(41) Schmid, C.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J.; Prather, D. E. Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.
(42) Sauer, J. C. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. IV, p 813.
(43) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

1 H), 7.26−7.36 (m, 5 H). ^{13}C NMR: δ 168.8, 137.4, 134.5, 128.5, 127.9, 127.7, 118.2, 82.4, 76.7, 73.3, 73.2, 65.9, 43.8, 36.3, 31.4, 24.9, 23.4. IR ($CHCl_3$): ν 3300, 1750, 1640. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.53; H, 8.03; N, 4.50.

(+)-(3*R*,4*S*)-3-(Benzyloxy)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(2-propynyl)-2-azetidinone, (+)-11a. From 3.34 g (2.0 mmol) of imine **10a** and 5.47 g (3.0 mmol) of (benzyloxy)acetyl chloride, 3.28 g (52%) of compound **(+)-11a** was obtained as a colorless crystalline solid after purification by flash chromatography (1/6 EtOAc/hexane). Mp: 64−65 °C (AcOEt/hexanes). $[\alpha]_D = +76.3$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR: δ 1.32 (s, 3 H), 1.46 (s, 3 H), 2.22 (t, 1 H, $J = 2.4$ Hz), 3.68 (dd,1 H, $J = 4.8$, 8.7 Hz), 3.79 (dd, 1 H, $J = 9.3$, 5.4 Hz), 3.87 (dd, 1 H, $J = 17.4$, 2.4 Hz), 4.10 (dd, 1 H, $J = 6.6$, 8.7 Hz), 4.38 (dd, 1 H, $J = 17.4$, 2.4 Hz), 4.33−4.47 (m, 1 H), 4.61 (d, 1 H, $J = 11.7$ Hz), 4.61 (d, 1 H, $J = 5.4$ Hz), 4.89 (d, 1 H, $J = 11.7$ Hz), 7.28−7.30 (m, 5 H). ^{13}C NMR: δ 167.0, 136.9, 128.6, 128.2, 127.9, 117.6, 109.9, 80.7, 76.9, 73.1, 72.2, 66.8, 59.3, 30.7, 27.0, 25.3. IR ($CHCl_3$): ν 3230, 1770. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.77; H, 6.42; N, 4.71.

(+)-(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-phenoxy-1-(2-propen-yl)-2-azetidinone, (+)-11e. From 3.38 g (2.0 mmol) of imine **10d** and 5.12 g (3.0 mmol) of phenoxyacetyl chloride, 4.48 g (74 %) of compound **(+)-11e** was obtained as a pale yellow oil after purification by flash chromatography (1/6 EtOAc/hexane). Mp: 63−65 °C (AcOEt/hexanes). $[\alpha]_D = +100.9$ ($c = 1.1$, $CHCl_3$). ^{1}H NMR: δ 1.37, (s, 3 H), 1.44 (s, 3 H), 3.38 (dd, 1 H, $J = 8.8$, 5.9 Hz), 3.77−3.87 (m, 2 H), 4.12−4.24 (m, 2 H), 4.41−4.48 (m, 1 H), 5.20 (d, 1 H, $J = 5.2$ Hz), 5.22−5.28 (m, 2 H), 5.68−5.82 (m, 1 H), 6.98−7.07 (m, 3 H), 7.26−7.33 (m, 2 H) . ^{13}C NMR: δ 165.6, 157.3, 131.2, 129.6, 129.5, 122.5, 118.9, 109.7, 79.9, 77.1, 66.9, 59.8, 44.0, 26.8, 25.2. IR (KBr): ν 1760, 1600. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.65; H, 6.51; N, 4.33.

General Procedure for the Synthesis of Compounds 3a−d. To a solution of the corresponding β-lactam **11** (10 mmol) in THF/H_2O (1:1, 200 mL) was added solid *p*-TsOH·H_2O (12 mmol) in a single portion. The resulting clear solution was refluxed until complete disappearance of the starting material. The reaction mixture was allowed to cool to room temperature, the THF was removed under vacuo, and the aqueous residue was neutralized with solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layer was dried ($MgSO_4$). The solvent was removed under vacuo, and the residue was dissolved in 150 mL of THF. 1,1-Thiocarbonyldiimidazole (12 mmol) was added to this solution, and the mixture was refluxed until the starting material disappeared (TLC). The reaction mixture was diluted with CH_2Cl_2 and dried ($MgSO_4$). After removal of the solvent under vacuo, the obtained thiocarbonate was used in the next step without purification. A solution of thiocarbonate in $(MeO)_3P$ (30 mL) was refluxed until the starting product was consumed (TLC). The solvent was then evaporated under vacuo and the reaction crude was purified by flash chromatography (4:1 hexanes/EtOAc) affording the expected, analytically pure, 4-vinyl-2-azetidinones **3a**−**d** as pale yellow oils.

(+)-(3*R*,4*S*)-3-Benzyloxy-1-(2-propynyl)-4-vinyl-2-azetidinone, (+)-3a. From 3.28 g (10.0 mmol) of compound **11a**, 2.02 g (84%) of compound **(+)-3a** was obtained as a colorless oil after purification by flash chromatography (6/1 hexane/EtOAc). $[\alpha]_D = +54.1$ ($c = 3.0$, $CHCl_3$).^{1}H NMR: δ 2.23 (t, 1 H, $J = 2.7$ Hz), 3.69 (dd, 1 H, $J = 17.4$, 2.7 Hz), 4.26 (m, 2 H), 4.56 (d, 1 H, $J = 15.6$ Hz), 4.60 (d, 1 H, $J = 15.6$ Hz), 4.76 (d, 1 H, $J = 4.8$ Hz), 5.43−5.48 (m, 2 H), 5.90−5.97 (m, 1 H), 7.26−7.35 (m, 5 H). ^{13}C NMR: δ 166.2, 136.7, 131.9, 128.5, 128.2, 128.18, 122.5, 83.1, 76.4, 72.73, 72.70, 60.6, 29.3. IR ($CHCl_3$): ν 3000, 1750. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.32; H, 6.06: N, 6.11.

(+)-(3*R*,4*S*)-3-(Benzyloxy)-1-(3-butynyl)-4-vinyl-2-azetidinone, (+)-3b. From 3.56 g (10.4 mmol) of compound **11b**, 1.70 g (64%) of compound **(+)-3b** was obtained as a colorless oil after purification by flash chromatography (6/1 hexane/EtOAc). $[\alpha]_D = +23.8$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR: δ 1.99 (td, 1 H, $J = 2.7$, 0.6 Hz), 2.37−2.45 (m, 2 H), 3.16 (dt, 1 H, $J = 13.9$, 7.0 Hz), 3.49 (dt, 1 H, $J = 13.9$, 7.0 Hz), 4.26 (dd, 1 H, $J = 8.7$, 4.5 Hz), 4.63 (d, 1 H, $J = 11.4$ Hz), 4.65 (d, 1 H, $J = 11,4$ Hz), 4.75 (d, 1 H, $J = 4.5$ Hz), 5.38−5.46 (m, 2 H), 5.86−5.95 (m, 1 H), 7.23−7.32 (m, 5 H). ^{13}C NMR: δ 166.9, 136.8, 132.7, 128.5, 128.2, 128.1, 122.3, 83.0, 81.0, 72.6, 70.4, 61.7, 38.9, 18.3. IR ($CHCl_3$): ν 3320, 1760, 1710. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.31; H, 6.54; N, 5.27.

(+)-(3*R*,4*S*)-3-(Benzyloxy)-1-(4-pentynyl)-4-vinyl-2-azetidinone, (+)-3c. From 1.72 g (5.0 mmol) of compound **11c**, 0.86 g (67%) of compound **(+)-3c** was obtained as a colorless oil after purification by flash chromatography (5/1 hexane/EtOAc). $[\alpha]_D = +22.8$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR: δ 1.56−1.77 (m, 2 H), 1.90 (t, 1 H, $J = 2.6$ Hz), 2.11−2.16 (m, 2 H), 3.04−3.26 (m, 1 H), 3.28−3.42 (m, 1 H), 4.05 (dd, 1 H, $J = 8.8$, 4.4 Hz), 4.52−4.61 (AB, 2 H, $J = 14.7$ Hz), 4.66 (d, 1 H, $J = 4.4$ Hz), 5.22−5.39 (m, 2 H), 5.38−5.89 (m, 1 H), 7.21−7.27 (5 H). ^{13}C NMR: δ 167.1, 136.9, 132.9, 128.5, 128.2, 128.1, 122.1, 82.9, 82.8, 72.6, 69.3, 61.6, 39.5, 26.6, 16.3. IR ($CHCl_3$): ν 3315, 1760, 1715. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.15; H, 6.74; N, 5.41.

(+)-(3*R*,4*S*)-3-Phenoxy-(1-propynyl)-4-vinyl-2-azetidinone, (+)-3d. From 1.52 g (5.0 mmol) of compound **11d**, 0.63 g (55%) of compound **(+)-3c** was obtained as a colorless oil after purification by flash chromatography (6/1 hexane/EtOAc). $[\alpha]_D = +10.1$ ($c = 0.1$, $CHCl_3$). ^{1}H NMR: δ 2.26 (t, 1 H, $J = 2.7$ Hz), 3.73 (dd, 1 H, $J = 2.7$, 17.7 Hz), 4.33 (dd, 1 H, $J = 2.7$, 17.7 Hz), 4.50 (dd, 1 H, $J = 4.5$, 8.7 Hz), 5.29 (d, 1 H, $J = 4.5$ Hz), 5.35−5.51 (m, 2 H), 5.81−5.93 (m, 1 H), 6.9−7.3 (m, 5 H). ^{13}C NMR: δ 164.7, 157.3, 130.86, 129.62, 123.2, 122.4, 115.6, 81.8, 76.2, 73.0, 60.8, 29.6. IR ($CHCl_3$): ν 3290, 1760. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.77; N, 6.16. Found: C, 73.78; H, 5.51; N, 6.00.

(+)-*(3R,4S)*-4-Formyl-3-phenoxy-1-(2-propenyl)-2-azetidinone, (+)-13. To a solution of the β-lactam **11e** (4.02 g, 13.0 mmol) in THF/H_2O (1/1, 200 mL) was added solid *p*-TsOH·H_2O (1,83g, 14.3 mmol) in a single portion. The resulting solution was then refluxed until complete disappearance of the starting material. The reaction mixture was allowed to cool to room temperature, the THF was removed under vacuo, and the aqueous residue was neutralized with solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layer was dried ($MgSO_4$). The solvent was removed under vacuo, and the resulting oil was dissolved in 150 mL of 1/1 MeOH/H_2O. $NaIO_4$ (20 mmol) was added to this solution, and the mixture was maintained below 20 °C and stirred vigorously until total disappearance of the starting material (TLC). The reaction mixture was diluted with water and extrated with CH_2Cl_2 (3 × 50 mL) and dried ($MgSO_4$). After removal of the solvent under vacuo the crude was dissolved in benzene and refluxed with a Dean−Stark apparatus for 2 h. Evaporation of the solvent under vacuo yielded 2.97 g (97%) of pure aldehyde **(+)-13** as a colorless oil. $[\alpha]_D = +59.4$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR: δ 3.87 (dd, 1 H, $J = 15.3$, 7.2 Hz), 3.97 (dd, 1 H, $J = 14.8$, 6.0 Hz), 4.30 (dd, 1 H, $J = 5.1$, 2.4 Hz), 5.13−5.19 (m, 2 H), 5.36 (d, 1 H, $J = 5.1$ Hz), 5.63−5.72 (m, 1 H), 6.83−6.98 (m, 2 H), 7.17−7.22 (m, 3 H), 9.59 (d, 1 H, $J = 2.4$ Hz). ^{13}C NMR: δ 197.2, 164.3, 156.7, 130.3, 129.6, 122.9, 120.4, 115.4, 82.0, 63.2, 44.4. IR ($CHCl_3$): ν 1780, 1740, 1600. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.87; H, 5.35; N, 6.38.

***cis*-1-(*p*-Methoxyphenyl)-3-(2-propynyl)-4-vinyl-2-azetidinone, 4.** BuLi (1.5 mL, 1.6 M in hexanes) was added to a slurry of PPh_3CH_2I (0.85 g, 2.1 mmol) in anhydrous THF (6 mL) under argon. The resulting mixture was stirred at room temperature during 0.5 h, and 2-azetidinone **14a** (0.32 g, 1 mmol) in anhydrous THF (5 mL) was added dropwise via syringe. The mixture was stirred at room temperature for 2 h. The reaction was then quenched with NH_4Cl (3 mL, saturated solution) and extracted with AcOEt (4 × 10 mL). The organic layers were dried ($MgSO_4$), and the solvent was removed under vacuo. The residue was chromatographied (EtOAc/hexanes) to yield 0.13 g (41%) of pure compound **4** as a colorless crystalline solid. Mp: 73−75 °C (EtOAc/hexanes).

^{1}H NMR: δ 1.94 (t, 1 H, J = 2.5 Hz), 2.35−2.45 (m, 1 H), 2.52−2.62 (m, 1 H), 3.49−3.57 (m, 1 H), 3.69 (s, 3 H), 4.57 (t, 1 H, J = 5.9 Hz), 5.29−5.45 (m, 2 H), 5.89−6.01 (m, 1 H), 6.76 (d, 2 H, J = 8.4 Hz), 7.25 (d, 2 H, J = 8.4 Hz). ^{13}C NMR: δ 164.8, 156.2, 132.0, 131.4, 121.2, 118.4, 114.3, 80.9, 70.2, 56.8, 55.6, 52.3, 15.0. IR ($CHCl_3$): ν 3300, 1740, 1700, 1510. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.65; H, 6.27; N, 5.81. Found: C, 74.48; H,6.53; N, 5.67.

Synthesis of 4-(1-hydroxy-3-trimethylsilyl-2-propynyl)-2-azetidinones, 5a and 6a−b. BuLi (1.3 mmol, 1.6 M in hexane) was added dropwise via syringe to a cooled (0 °C) solution of (trimethylsilyl)acetylene (1.3 mmol) in anhydrous THF (5 mL) under argon. After 15 min, the resulting solution was transferred *via* cannula to a cooled solution (−78 or 0 °C) of the corresponding β-lactam (1 mmol) in anhydrous THF (5 mL) by using argon pressure. The resulting mixture was stirred until complete disappearance of the starting material (TLC). The crude mixture was quenched with saturated aqueous NH_4Cl solution and dried ($MgSO_4$). Solvent was removed in vacuo, and the crude compound was purified by flash chromatography.

***cis*-4-(1-Hydroxy-3-(trimethylsilyl)-2-propynyl)-3-phenoxy-1-(2-propenyl)-2-azetidinone, 5a.** From 0.46 g (2.0 mmol) of aldehyde **(+)-13** cooled to 0 °C after 15 min a crude mixture containing both *cis*-diastereomers (75/25) was obtained. From this mixture, 0.63 g (96%) of an inseparable mixture of both diastereomers was obtained as colorless oil after purification by flash chromatography (1/4 EtOAc/hexane).

Major Isomer. ^{1}H NMR: δ −0.06 (s, 9 H), 2.59 (d, 1 H, J = 4.8 Hz), 3.80 (dd, 1 H, J = 15.6, 6.9 Hz), 4.05 (t, 1 H, J = 4.8 Hz), 4.20 (ddt, 1 H, J = 15.6, 5.4, 1.5 Hz), 4.70 (t, 1 H, J = 4.5 Hz), 5.16−5.26 (m, 3 H), 5.70−5.87 (m, 1 H), 6.92−7.05 (m, 3 H), 7.18−7.30 (m, 2 H). ^{13}C NMR: δ 165.7, 157.4, 131.4, 129.6, 122.8, 118.9, 116.0, 102.6, 92.1, 81.5, 61.7, 60.7, 44.0, −0.4.

Minor Isomer. ^{1}H NMR: δ −0.08 (s, 9 H), 2.76 (d, 1 H, J = 8.1 Hz), 3.87 (dd, 1 H, J = 15.3, 6.9 Hz), 3.97 (t, 1 H, J = 5.0 Hz), 4.10 (ddt, 1 H, J = 15.3, 5.1, 1.5 Hz), 4.68 (dd, 1 H, J = 8.1, 5.0 Hz), 5.16−5.26 (m, 3 H), 5.70−5.87 (m, 1 H), 6.92−7.05 (m, 3 H), 7.18−7.30 (m, 2 H). ^{13}C NMR: δ 165.7, 157.4, 131.2, 129.7, 122.9, 119.3, 116.3, 102.5, 92.6, 81.6, 61.1, 60.2, 43.3, −0.4. IR ($CHCl_3$): ν 3560, 2410, 1760, 1600, 1500. Anal. Calcd for $C_{18}H_{23}NO_3Si$: C, 65.62; H, 7.04; N, 4.25. Found: C, 65.90; H, 6.88; N, 4.01.

***cis*-4-(1-Hydroxy-3-(trimethylsilyl)-2-propynyl)-1-(*p*-methoxyphenyl)-3-vinyl-2-azetidinone, 6a.** From 0.90 g (1.5 mmol) of compound **14b** at −78 °C after 2 h a crude mixture containing both *cis*-diastereomers (78/22) was obtained. Both isomers were separated as pure compounds after chromatography (1/6 EtOAc/hexane). Combined yield: 0.79 g (82%).

Major Isomer. White solid: Mp 94−96 °C (EtOAc/hexane). ^{1}H NMR: δ 0.1 (s, 9 H), 2.72 (d, 1 H, J = 6.3 Hz), 3.92 (s, 3 H), 3.96 (dd, 1 H, J = 6.0, 6.9 Hz), 4.31 (t, 1 H, J = 5.9 Hz), 4.53 (t, 1 H, J = 6.1 Hz), 5.26−5.43 (m, 2 H), 5.94−6.08 (m, 1 H), 6.62−6.78 (d, 2 H), 7.38−7.47 (d, 2 H). ^{13}C NMR: δ 165.7, 156.4, 132.8, 129.1, 121.9, 119.8, 114.9, 103.3, 93.0, 62.8, 59.4, 55.5, 55.1, −0.5. IR ($CHCl_3$): ν 3400 (broad), 1750, 1520. Anal. Calcd for $C_{18}H_{23}NO_3Si$: C, 65.62; H, 7.04; N, 4.25. Found: C, 65.97; H, 6.88; N, 4.49.

Minor Isomer. White solid: Mp 79−81 °C (EtOAc/hexane). ^{1}H NMR: δ 0.0 (s, 9 H), 2.21 (s broad, 1 H), 3.69 (s, 3 H), 4.02 (dd, 1 H, J = 7.8, 5.8 Hz), 4.27 (dd, 1 H, J = 5.8, 3.5 Hz), 4.68 (d, 1 H, J = 3.0 Hz), 5.29 (d, 1 H, J = 10.3 Hz), 5.43 (d, 1 H, J = 17.2 Hz), 6.09 (ddd, 1 H, J = 17.2, 10.3, 7.8 Hz), 6.75−6.79 (d, 2 H), 7.33−7.38 (d, 2 H). ^{13}C NMR: δ 165.1, 156.3, 130.7, 129.0, 121.8, 119.7, 114.2, 102.1, 94.3, 61.5, 59.1, 55.4, 55, −0.6. IR ($CHCl_3$): ν 3600, 3400, 2405, 1750. Anal. Calcd for $C_{18}H_{23}NO_3Si$: C, 65.62; H, 7.04; N, 4.25. Found: C, 65.31; H, 7.27; N, 4.39.

***cis*-4-(1-Hydroxy-3-(trimethylsilyl)-2-propynyl)-1-(*p*-methoxyphenyl)-3-(2-propenyl)-2-azetidinone, 6b.** From 0.37 g (1.5 mmol) of compound **14c** at −78 °C after 90 min a crude mixture containing both *cis*-diastereomers (75/25) was obtained. From this mixture, both diastereomers were obtained as white solids after purification by flash chromatography (1/6 EtOAc/hexane). Combined yield: 0.38 g (75%). The major isomer was obtained as a pure compound after crystalization (EtOAc/hexane).

Major Isomer. White solid. Mp 74−75 °C. Yield: 0.30 g (59%). ^{1}H NMR: δ 0.15 (s, 9 H), 2.43 (d, 1 H, J = 7.1 Hz), 2.60−2.81 (m, 2 H), 3.45 (td, 1 H, J = 7.4, 5.9 Hz), 3.75 (s, 3 H), 4.34 (t, 1 H, J = 5.3 Hz), 4.73 (dd, 1 H, J = 7.1, 5.3 Hz), 5.09 (dd, 1 H, J = 10.3, 1.1 Hz), 5.17 (dd, 1 H, J = 17.2, 1.5 Hz), 5.89−6.02 (m, 1 H), 6.78−6.83 (d, 2 H), 7.41−7.51 (d, 2 H). ^{13}C NMR: δ 167.5, 156.4, 135.9, 131.1, 120.1, 116.8, 114.1, 103.8, 93.2, 61.8, 58.7, 55.6, 51.0, 29.0, −0.3. IR (KBr): ν 3360 (broad), 1720, 1640. Anal. Calcd for $C_{19}H_{25}NO_3Si$: C, 66.44; H, 7.34; N, 4.08. Found: C, 66.79; H, 7.12; N, 4.17.

1-(2-Propenyl)-4-(2-propynyl)-2-azetidinone, 7. NaH (0.2 g ca 5 mmol, 60% dispersion in mineral oil) was placed in a round botton flask and washed three times with anhydrous hexane under argon. Anhydrous THF (5 mL) was added via syringe, and the resulting slurry was cooled to 0 °C (ice bath). 4-Propargyl-2-azetidinone (0.22 g, 2 mmol) in THF (3 mL) and allyl bromide (0.29 g, 2.4 mmol) in THF (3 mL) were added sequentially to this slurry dropwise via syringe. The reaction mixture was stirred 20 min at 0 °C, and anhydrous DMF (0.4 mL) was added via syringe. The cooling bath was removed, and the reaction was stirred 12 h at room temperature. The resulting mixture was quenched with 1 N HCl (2 mL) and water (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed under vacuo, and the residue was purified by chromatography to yield 0.23 g (77%) of pure compound **7** as a viscous colorless oil. ^{1}H NMR: δ 2.07 (t, 1 H, J = 2.7 Hz), 2.53−2.57 (m, 2 H), 2.80 (dd, 1 H, J = 14, 2.0 Hz), 3.07 (dd, 1 H, J = 14.7, 4.8 Hz), 3.67−3.78 (m, 2 H), 4.02 (ddt, 1 H, J = 15.6, 5.4, 1.2 Hz), 5.17−5.89 (m, 2 H), 5.70−5.87 (m, 1 H). ^{13}C NMR: δ 166.5, 132.1, 118.6, 81.1, 71.5, 49.2, 44.3, 41.9, 22.6. IR ($CHCl_3$): ν 3300, 1740, 1660, 1640. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.58; H, 7.32; N, 9.65.

General Procedure for the Synthesis of Tricyclic 2-Azetidinones 15−19. Method A. Solid $Co_2(CO)_8$ (0.21 g, 0.6 mmol) was added to a solution of the corresponding 2-azetidinone (0.12 g, 0.5 mmol) in anhydrous CH_2Cl_2 (7 mL) under argon. The dark solution thus obtained was stirred at room temperature until complete complex formation by TLC (ca. 1 h) The resulting solution of $Co_2(CO)_6$−alkyne complex was cooled to 0 °C, and solid anhydrous TMANO (0.08 g, 1 mmol) was added. The reaction flask was open to the air and warmed to room temperature by immediate removal of the ice bath. After 30 min, the reaction was again cooled to 0 °C, 0.08 g (1 mmol) of solid anhydrous TMANO was added, and the solution was warmed again to room temperature by immediate removal of the ice bath. This sequence was repeated until a total of 3 mmol (0.24 g) of anhydrous TMANO was added. After that the solution was stirred for 1 h at room temperature. During this period a purple precipitate was formed. TLC analysis indicated the complete consumption of the starting material and the formation of a more polar, UV active spot. The crude mixture was diluted with AcOEt (20 mL) and filtrated through a short path of Celite. The solvent was removed under vacuo, and a colorless solid was obtained. The cyclic compounds were purified by chromatography or crystallization, as indicated in each case.

Method B. Solid $Co_2(CO)_8$ (0.21 g, 0.6 mmol) was added to a solution of the corresponding 2-azetidinone (0.5 mmol) in anhydrous toluene (7 mL) under argon. The dark solution was stirred at room temperature until complete complex formation by TLC (ca. 1 h). The resulting solution of $Co_2(CO)_6$−alkyne complex was refluxed for 2 h. The solution was diluted with AcOEt (20 mL), filtered through Celite, and concentrated under reduced pressure. The solid residue was crystallized (AcOEt).

Tricyclic 2-Azetidinone (+)-15. Method B. From 0.13 g of 2-azetidinone **(+)-3b** (0.5 mmol), 0.14 g (95%) of **(+)-15** was obtained as a colorless solid after crystallization (AcOEt). Mp: 108−110 °C. $[\alpha]_D$ = +83.6 (c = 1.0, $CHCl_3$). ^{1}H NMR:

δ 1.97 (dd, 1 H, J = 19.2, 2.1 Hz), 2.47 (dd, 1 H, J = 18.7, 6.6 Hz), 2.46−2.58 (m, 1 H), 2.75−2.89 (m, 2 H), 3.09 (t, 1 H, J = 7.2 Hz), 3.31 (dd, 1 H, J = 9.1, 3.9 Hz), 4.07−4.15 (m, 1 H), 4.60 (d, 1 H, J = 11.7 Hz), 4.81 (d, 1 H, J = 11.7 Hz), 4.80 (d, 1 H, J = 9.1 Hz), 6.05 (s, 1 H), 7.22−7.35 (m, 5 H). ^{13}C NMR: δ 207.4, 177.1, 165.3, 136.9, 130.9, 129.0, 128.8, 128.4, 83.7, 73.7, 61.5, 39.9, 39.5, 38.1, 29.8. IR ($CHCl_3$): ν 1760, 1710, 1400. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.29; H, 6.24; N, 5.14. EIMS: m/z 283 (parent), 254, 192, 164, 136, 108, 91, 65.

Tricyclic 2-Azetidinone 16. Method A. From 0.12 g of 2-azetidinone **4** (0.5 mmol), 0.11 g (80%) of **15** was obtained as colorless solid after crystallization (EtOAc/hexanes). Mp: 159−160 °C. ^{1}H NMR: δ 2.15 (dd, 1 H, J = 17.7, 3.9 Hz), 2.46 (dd, 1 H, J = 17.7, 6.6 Hz), 2.61 (dd, 1 H J = 16.5, 9.9 Hz), 3.08−3.14 (d, 2 H), 3.69 (s, 3 H), 3.92 (dd, 1 H, J = 9.6, 3.9 Hz), 4.53 (t, 1 H, J = 4.8 Hz), 6.04 (s broad, 1 H), 6.74 (d, 2 H, J = 9.5), 7.17 (d, 2 H, J = 9.5 Hz). ^{1}H NMR(DMSO-d_6): δ 1.86 (dd, 1 H, J = 17.8, 3.7 Hz), 2.43−2.53 (m, 1 H), 2.78 (dd, 1 H, J = 16.2, 9.7 Hz), 2.90 (d, 1 H, J = 16.3 Hz), 3.30−3.38 (m, 1 H), 3.71 (s, 3 H), 4.01 (dd, 1 H, J = 8.5, 4.3 Hz), 4.75 (t, 1 H, J = 4.6 Hz), 6.11 (s, 1 H), 6.91 (d, 2 H), 7.28 (d, 2 H). ^{13}C NMR: δ 209.7, 181.8, 165.2, 156.6, 131.4, 129.3, 118.3, 114.7, 55.6, 55.0, 54.3, 46.8, 38.6, 28.4. IR ($CHCl_3$): ν 1740, 1705, 1640. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.49; H, 5.50; N, 4.98. EIMS: m/z 269, 240, 213, 212, 149, 134, 91 (parent), 65.

Tricyclic 2-Azetidinone 17a. Method A. From 0.15 g (1.0 mmol) of 2-azetidinone **7**, 0.11 g (65%) of compound **17** was obtained as a colorless solid after crystallization (EtOAc/hexane). Mp: 154−155 °C. ^{1}H NMR: δ 1.88 (dd, 1 H, J = 18.9, 1.8 Hz), 2.18 (t., 1 H, J = 12.0 Hz), 2.34−2.45 (m, 2 H), 2.66 (dd, 1 H, J = 15.0, 1.8 Hz), 2.73−2.76 (m, 1 H), 3.05−3.16 (m, 2 H), 3.35−3.42 (m, 1 H), 4.16 (dd, 1 H, J = 13.2, 7.5 Hz), 6.05 (s, 1 H). ^{13}C NMR: δ 206.9, 176.7, 165.1, 130.2, 47.6, 45.6, 45.5, 39.7, 39.1, 37.8. IR ($CHCl_3$): ν 1740, 1710, 1620. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.91; H, 6.54; N, 7.73.

Tricyclic 2-Azetidinone 17c. Method A. From 0.06 g (0.2 mmol) of a mixture of both diastereomers of **5b** (74/26), a crude reaction mixture containing both tricyclic β-lactams **17c** (77/23) was obtained as a white solid after filtration through a short path of Celite. Combined yield: 95%. The major diastereomer was separated as pure compound by chromatography (2/1 EtOAc/hexane) in a 30% yield.

Major Isomer. ^{1}H NMR: δ 1.97 (dd, 1 H, J = 19.0, 1.4 Hz), 2.49−2.58 (m, 2 H), 3.49−3.57 (m, 1 H), 3.60 (s, 1 H), 3.70 (dd, 1 H, J = 4.4, 1.7 Hz), 4.37 (dd, 1 H, J = 13.1, 7.8 Hz), 5.13 (d, 1 H, J = 1.7 Hz), 5.34 (dd, 1 H, J = 4.5, 1.6 Hz), 6.14 (s, 1 H), 6.99−7.11 (m, 3 H), 7.24−7.33 (m, 2 H). ^{13}C NMR: δ 207.0, 174.7, 164.8, 156.6, 130.1, 129.6, 123.8, 116.1, 83.0, 66.2, 57.2, 45.8, 39.0, 34.5. IR (KBr): ν 3540 (broad), 1770, 1715, 1645, 1600. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.69; H, 5.08; N, 5.16.

Minor Isomer. ^{1}H NMR: δ 2.05 (dd, 1 H, J = 18.9, 2.1 Hz), 2.41−2.58 (m, 2 H), 3.48−3.54 (m, 1 H), 3.68 (s, 1 H), 3.69−3.72 (m, 1 H), 4.21 (dd, 1 H, J = 12.9, 7.2 Hz), 4.71 (d, 1 H, J = 7.8 Hz), 5.37 (dd, 1 H, J = 3.8, 1.1 Hz), 6.28 (s, 1 H), 6.97−7.11 (m, 3 H), 7.24−7.33 (m, 2 H). ^{13}C NMR: δ 205.6, 179.1, 164.1, 157.0, 129.8, 128.9, 122.9, 115.6, 81.5, 67.0, 60.2, 44.5, 39.9, 39.0. IR (KBr): ν 3330 (broad), 1760, 1700, 1675, 1630.

Tricyclic 2-Azetidinone, 18a. Method A. From 0.11 g (0.3 mmol) of compound **6a-M**, 0.04 g (32%) of tricyclic compound **18a** was obtained as a white solid and 0.07 g (64%) of starting material **6a-M** was recovered unchanged. Mp: 159−160 °C. ^{1}H NMR: δ 0.05 (s, 9 H), 2.56 (dd, 1 H, J = 18.6, 6.9 Hz), 2.74 (dd, 1 H, J = 18.6, 3.7 Hz), 2.86 (s broad, 1 H), 3.42−3.50 (m, 1 H), 3.75 (s, 3 H), 3.78 (dd, 1 H, J = 9.3, 3.7 Hz), 4.43 (d, 1 H, J = 3.7 Hz), 4.93 (d, 1 H, J = 1.5 Hz), 6.76−6.79 (d, 2 H), 7.17−7.20 (d, 2 H). ^{13}C NMR: δ 214.0, 186.2, 162.9, 156.4, 144.4, 129.8, 118.0, 114.4, 66.3, 61.8, 55.4, 52.9, 41.5, 38.9, −1.4. IR (KBr): ν 3350 (broad), 1745, 1680, 1630. Anal. Calcd for $C_{19}H_{23}NO_4Si$: C, 63.84; H, 6.49; N, 3.92. Found: C, 64.09; H, 6.61; N, 3.70.

Tricyclic 2-Azetidinone, 19a. Method A. From 0.10 g (0.3 mmol) of compound **6b-M**, a crude reaction mixture containing both diastereomers of compound **19a** (70/30) was obtained. From this mixture, 0.03 g (26%) of inseparable diastereomers **19a** was obtained as pale yellow oil after purification by flash chromatography (1/2 EtOAc/hexane), and 0.05 g (51%) of starting material was recovered unchanged.

Major Isomer. ^{1}H NMR: δ 0.23 (s, 9 H), 1.74 (ddd, 1 H, J = 13.8, 13.5, 5.4 Hz), 2.09 (dd, 1 H, J = 18.3, 3.4 Hz), 2.44−2.57 (m, 1 H), 2.65 (dd, 1 H, J = 18.3, 6.6 Hz), 3.03−3.12 (m, 1 H), 3.68 (td, 1 H, J = 5.4, 2.0 Hz), 3.80 (s, 3 H), 4.37 (dd, 1 H, J = 5.4, 1.2 Hz), 5.14 (s broad, 1 H), 6.89−6.92 (d, 2 H), 7.35−7.38 (d, 2 H). ^{13}C NMR: δ 210, 184.9, 166.6, 156.5, 144.5, 130.1, 118.4, 114.7, 62.9, 55.5, 55.0, 47.7, 42.2, 36.8, 26.4, −0.9.

Minor Isomer. ^{1}H NMR: δ −0.1 (s, 9 H), 1.98 (dt, 1 H, J = 14.7, 5.1 Hz), 2.26 (dd, 1 H, J = 18.4, 3.7 Hz), 2.54−2.57 (m, 1 H), 2.50 (dd, 1 H, J = 18.4, 7.1 Hz), 3.23−3.28 (m, 1 H), 3.55 (ddd, 1 H, J = 8.4, 5.4, 3.7 Hz), 3.79 (s, 3 H), 4.47 (dd, 1 H, J = 5.4, 2.4 Hz), 5.33 (d, 1 H, J = 2.4 Hz), 6.86−6.92 (d, 2 H), 7.30−7.38 (d, 2 H). ^{13}C NMR: δ 205, 182.6, 166.1, 156.4, 144.5, 130.0, 118.3, 114.6, 64.9, 56.4, 55.0, 45.8, 45.2, 35.6, 25.3, −1.0. IR ($CHCl_3$): ν 3400 (broad), 1745, 1710, 1595. Anal. Calcd for $C_{20}H_{25}NO_4Si$: C, 64.66; H, 6.78; N, 3.77. Found: C, 64.95; H, 6.49; N, 3.98.

Tricyclic 2-Azetidinone, 19b. Method A. From 0.10 g (0.4 mmol) of compound **6d-M**, a crude reaction mixture containing both tricyclic β-lactams **19b** (70/30) was obtained. From this mixture, both diastereomers of 2-azetidinone **19b** were obtained as pale yellow oils after purification by flash chromatography (2/1 EtOAc/hexane). Combined yield: 0.06 g (55%).

Major Isomer. Yellow oil: yield 0.03 g (30%). ^{1}H NMR: δ 1.42 (td, 1 H, J = 13.7, 7.2 Hz), 1.63 (s broad, 1 H), 2.07 (dd, 1 H, J = 18.9, 1.4 Hz), 2.57 (ddd, 1 H, J = 12.5, 5.1, 1.5 Hz), 2.62 (dd, 1 H, J = 18.9, 7.0 Hz), 2.89−2.97 (m, 1 H), 3.64 (t, 1 H, J = 5.6 Hz), 3.73 (s, 3 H), 4.25 (dd, 1 H, J = 5.6, 1.3 Hz), 4.82 (s broad, 1 H), 6.16 (s, 1 H), 6.82−6.87 (d, 2 H), 7.30−7.41 (d, 2 H). IR ($CHCl_3$): ν 3400 (broad), 1745, 1710, 1625, 1515. ^{13}C NMR: δ 207.1, 174.9, 164.9, 156.7, 130.0, 129.5, 123.7, 116.1, 82.9, 66.1, 57.2, 45.7, 39.7, 34.5.

Minor Isomer. Yellow oil: yield 0.01 g (10%). ^{1}H NMR: δ 1.83−1.90 (m, 1 H), 2.16 (dd, 1 H, J = 18.2, 2.9 Hz), 2.28−2.19 (m, 1 H), 2.64 (dd, 1 H, J = 18.2, 6.6 Hz), 2.82−2.89 (m, 1 H), 3.21 (d, 1 H, J = 14.3 Hz), 3.46−3.53 (m, 1 H), 3.73 (s, 3 H), 3.81−3.90 (m, 1 H), 4.47 (td, 1 H, J = 5.8, 2.5 Hz), 5.78 (s, 1 H), 6.86−6.92 (d, 2 H), 7.30−7.38 (d, 2 H). ^{13}C NMR: δ 205.6, 179.2, 164.1, 157.0, 129.8, 128.9, 122.9, 115.6, 81.5, 67.0, 60.3, 44.5, 39.9, 39.0. IR ($CHCl_3$): ν 3400 (broad), 1750, 1715, 1630. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 67.95; H, 5.89; N, 4.99.

General Procedure for the Synthesis of Azetidines 20. To a suspension of $LiAlH_4$ (3 mmol) in anhydrous Et_2O (5 mL) was added *via* cannula a solution of $AlCl_3$ (3 mmol) in Et_2O (5 mL) under argon pressure, and the mixture was refluxed for 30 min. The resulting AlH_2Cl suspension was added dropwise to a solution of corresponding azetidinone (1 mmol) dissolved in Et_2O (5 mL). The reaction was refluxed until complete transformation of the starting material (TLC, ca. 15 min). Then, the mixture was allowed to reach room temperature, quenched with water (5 mL), and diluted with Et_2O. The organic layer was successively washed with water and brine and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude was purified by flash chromatography. Spectroscopic and analytical data for some representative forms of **20** follow.[43]

***cis*-3-(Benzyloxy)-2-ethynyl-*N*-(2-propenyl)azetidine, 20a.** From 0.30 g (1.2 mmol) of β-lactam **2**, 0.24 g (86%) of azetidine **20a** was obtained as a colorless oil after purification by flash chromatography (6/1 hexane/AcOEt). ^{1}H NMR: δ 2.61 (d, 1 H, J = 2.1 Hz), 3.15−3.22 (m, 3 H), 3.40 (td, 1 H, J = 6.3, 1.2 Hz), 4.24−4.31 (m, 2 H), 4.42 (d, 1 H, J = 11.7 Hz), 4.65 (d, 1 H, J = 11.7 Hz), 5.09 (d broad, 1 H, J = 10.2 Hz), 5.17 (d broad, 1 H, J = 19.2 Hz), 5.70−5.82 (m 1 H), 7.20−7.38 (m, 5 H). ^{13}C NMR: δ 137.3, 134.2, 128.2, 128.0, 127.8, 117.3, 77.9, 77.8, 71.3, 69.2, 59.8, 59.3, 56.6. IR ($CHCl_3$): ν 3310, 3100,

2940, 2885, 1730. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.48; H, 7.39; N, 6.07.

(+)-(*2S,3S*)-3-Phenoxy-*N*-(2-propynyl)-2-vinylazetidine, (+)-20b. From 0.45 g (2.0 mmol) of *β*-lactam, **(+)-3d** 0.38 g (89%) of azetidine **(+)-20b** was obtained as a colorless oil after purification by flash chromatography (6/1 hexane/AcOEt). $[\alpha]_D = +107.8$ ($c = 1.0$). ^{1}H NMR: δ 2.21 (t, 1 H, J = 2.4 Hz), 3.31−3.37 (m, 3 H), 3.58 (dd, 1 H, J = 8.7, 5.4 Hz), 4.07 (t broad, 1 H, J = 6.9 Hz), 4.76 (td, 1 H, J = 5.8, 1.6 Hz), 5.12 (dd, 1 H, J = 9.9, 1.8 Hz), 5.25 (dd , 1 H, J = 17.4, 1.8 Hz), 5.92−6.04 (m, 1 H), 6.71−6.75 (d, 2 H), 6.84−6.88 (t, 1 H), 7.14−7.20 (m, 2 H). ^{13}C NMR: δ 157.6, 133.5, 129.3, 120.9, 119.2, 115.0, 78.1, 73.3, 71.4, 68.5, 54.7, 41.7. IR ($CHCl_3$): ν 3310, 3020, 2970, 2860, 2410, 1715, 1605, 1595. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.18; H, 7.39; N, 6.27.

General Synthesis of Tricyclic Azetidines 21−23, and the Azepine 24. The experimental procedures were identical to those used for the synthesis of tricyclic 2-azetidinones.

Reaction of compound 20a. Method A. From 0.09 g (0.4 mmol) of compound **20a** was obtained a crude containing a mixture of compounds **24** and **21** (66/33). From this mixture 0.04 g (47%) of compound **24** was obtained by chromatography (13/1 AcOEt/Et_3N), and 0.05 g (42%) of a mixture containing compound **21** and azepine **24**.

Azepine 24. ^{1}H NMR: δ 1.93 (dd, 1 H, J = 18.4, 2.9 Hz), 2.48 (dd, 1 H, J = 9.9, 8.1 Hz), 2.53 (dd, 1 H, J = 13.3, 6.3 Hz), 2.76 (dd, 1 H, J = 14.3, 2.6 Hz), 2.90−2.93 (m, 2 H), 3.14 (m, 1 H), 3.09−3.19 (m, 2 H), 3.51−3.58 (m, 1 H), 4.48 (d_{AB}, 1 H, J = 11.8 Hz), 4.54 (d_{AB}, 1 H, J = 11.8 Hz), 5.87 (d, 1 H, J = 1.5 Hz), 7.08−7.5 (m, 5 H). ^{13}C NMR: δ 208.3, 181.4, 138.2, 131.6, 128.5, 127.8, 127.6, 76.0, 70.9, 54.1, 53.9, 47.7, 41.4, 36.4. IR ($CHCl_3$): ν. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.95; H, 7.22; N, 5.71.

Tricyclic Azetidine 21a. ^{1}H NMR: δ 2.10 (ddd, 1 H, J = 17.5, 3.0, 0.8 Hz), 2.44 (t, 1 H, J = 12.0 Hz), 2.73 (dd, 1 H, J = 17.5, 6.6 Hz), 3.10 (dd, 1 H, J = 12.0, 7.5 Hz), 3.11−3.40 (m, 1 H), 3.68−3.82 (m, 1 H), 4.02 (dd, 1 H, 9.6, 6.6 Hz), 4.38 (d, 1 H, J = 11.7 Hz), 4.46 (d, 1 H, J = 11.7 Hz), 4.75 (d, 1 H, J = 6.6 Hz), 6.09 (d, 1 H, J = 2.4 Hz), 7.20−7.30 (m, 5 H). ^{13}C NMR: δ 209.8, 184.9, 137.0, 128.5, 128.4, 128.0, 127.8, 71.6, 69.2, 68.9, 60.2, 59.2, 43.4, 40.9.

Tricyclic Azetidine (−)-22. Method A. From 0.23 g (1.0 mmol) of compound **(+)-20b**, 0.16 g (66%) of **(−)-22** was obtained as a colorless solid after flash chromatography (10/1 EtOAc/Et_3N). Mp: = 116−118 °C. $[\alpha]_D = -94.4$ (c = 1.0, $CHCl_3$) ^{1}H NMR: δ 1.90 (dd, 1 H, J = 1.17.6, 3.9 Hz), 2.26 (dd, 1 H, J = 17.6, 6.4 Hz), 3.34−3.43 (m, 2 H), 3.68−3.73 (m, 1 H), 4.21 (dd, 1 H, J = 8.8, 7.0 Hz), 4.96 (dd, 1 H, J = 11.8, 6.3 Hz), 5.97 (s, 1 H), 6.71 (d, 2 H, J = 8.1 Hz), 6.91 (t, 2 H, J = 7.4 Hz), 7.17−7.24 (m, 3 H). ^{13}C NMR: δ 209.5, 186.8, 156.4, 129.7, 125.9, 121.7, 114.7, 74.7, 66.6, 64.6, 56.4, 43.3, 41.6. IR ($CHCl_3$): ν 3010, 1715, 1610. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.30; H, 6.55; N, 5.63.

Tricyclic Azetidine 23. Method A. From 0.18 g (0.7 mmol) of compound **20d** was obtained 0.20 g (95%) of a mixture of both diastereomers **23** (75/25).

Major Isomer. ^{1}H NMR: δ 2.19 (dd, 1 H, J = 17.1, 3.9 Hz), 2.46 (dd, 1 H, J = 17.1, 6.3 Hz), 2.68−2.89 (m, 2 H), 2.98−3.02 (m, 1 H), 3.26−3.59 (m, 1 H), 3.42 (dd, 1 H, J = 7.2, 2.7 Hz), 3.67 (s, 3 H), 3.769 (t, 1 H, J = 7.8 Hz), 4.36 (t, 1 H, J = 5.4−6.0 Hz), 6.06 (s broad, 1 H), 6.217 (d, 2 H), 6.72 (d, 2 H). ^{13}C NMR: δ 211.6, 186.8, 152.1, 145.8, 127.3, 114.7, 111.9, 67.6, 57.7, 55.8, 49.9, 38.1, 35.5, 33.4.

Minor Isomer. ^{1}H NMR: δ 2.26 (dd, 1 H, J = 17.4, 3.9 Hz), 2.65 (dd, 1 H, J = 17.4, 6.3 Hz), 2.68−2.89 (m, 2 H), 2.92 (t, 1 H, J = 8.6 Hz), 3.18−3.25 (m, 1 H), 3.62 (dd, 1 H, J = 7.1, 4.6 Hz), 3.69 (s, 3 H), 3.98 (t, 1 H, J = 7.4 Hz), 4.07 (dd, 1 H, J = 7.8, 4.5 Hz), 5.81 (t broad, 1 H, J = 1.8 Hz), 6.28 (d, 2 H), 6.75 (d, 2 H). ^{13}C NMR: δ 209.9, 188.6, 152.0, 143.6, 125.3, 114.9, 112.8, 71.4, 57.4, 55.8, 50.0, 42.3, 36.1, 33.7. IR ($CHCl_3$): ν 1710, 1640, 1510. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.61; H, 6.55; N, 5.73.

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Supporting Information Available: Spectroscopic and analytical data for compounds **1b**, **8a**,**b**, **10a**−**d**, **11b**−**d**, **14a**,**c**, **5b**, **6c**,**d**, and **20c**−**d**, as well as procedures for the isolation of reduced 2-azetidinones and an example of characterization of the cobalt complex derived from 2-azetidinone **1a** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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