Straightforward Asymmetric Entry to Highly Functionalized Medium-Sized Rings Fused to β-Lactams via Chemo- and Stereocontrolled Divergent Radical Cyclization of Baylis−Hillman Adducts Derived from 4-Oxoazetidine-2-carbaldehydes†

Benito Alcaide,* Pedro Almendros, and Cristina Aragoncillo

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense 28040-Madrid, Spain

alcaideb@eucmax.sim.ucm.es

Received November 2, 2000

DABCO promoted reactions of various activated vinyl systems with optically pure 4-oxoazetidine-2-carbaldehydes **1** gave rise to Baylis−Hillman adducts **3** with excellent *syn* stereoselectivities, without detectable racemization. Products **3** are used for the asymmetric preparation of unusual 2-azetidinones fused to medium-sized rings via chemo- and stereocontrolled divergent radical cyclization. The formation of bicyclic β-lactams **4**−**6** could be rationalized through a tandem radical Michael addition/*endo* cyclization or a tandem radical addition/Michael addition, depending on the electronic nature of the radical promoter.

Introduction

The Baylis−Hillman reaction, an emerging carbon−carbon bond forming reaction for the preparation of a β-hydroxy-α-methylene ketone, nitrile, ester, etc., involves an activated alkene and a carbon electrophile in the presence of a suitable catalyst (particularly a tertiary amine).[1] This fascinating reaction has many of the basic properties that an efficient synthetic method should have, e.g., it is selective, economical in atom count, requires mild conditions, and provides densely funtionalized products.[2] However, the reaction suffers from two major drawbacks, namely, its slow reaction rate and limited scope of substrates. On the other hand, the interest in free radical reactions applied to synthetic problems continues to advance, and these reactions have been used successfully for a growing number of synthetic targets, being a powerful tool in the synthesis of five- and six-membered carbocycles and heterocycles.[3] This wide research has been fostered by its operational simplicity and its tolerance to substrate functionalization. Furthermore, by a combination of stereoelectronic and molecular orbital effects, radical cyclizations occur, in general, with high degrees of both regio- and stereocontrol.

Due to the increased resistance of bacteria to common β-lactam antibiotics,[4] there has been much effort expended in recent years to prepare new structural types having the 2-azetidinone ring as common feature, which will both target the PBPs and overcome the defense mechanisms of the bacteria.[5] Besides, the ever-growing new applications of 2-azetidinones in fields ranging from enzyme inhibition[6] to the use of these products as starting materials to develop new synthetic methodologies, has triggered a renewed interest in the building of new bi- and polycyclic β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures.[7]

* To whom correspondence should be addressed.

† Dedicated to Prof. José Elguero on the occasion of his 65th birthday.

(1) For reviews, see: (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (d) Drewes, S. E.; Roos, G. H. P.; Thomas, R. J. *Tetrahedron* **1988**, *44*, 4653. (e) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 4653.

(2) For very recent, selected examples, see: (a) Trost, B. T.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534. (b) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729. (c) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343. (d) Mikami, K.; Okubo, Y. *Synlett* **2000**, 491. (e) Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis* **2000**, 545. (f) Basavaiah, D.; Hyma, R. S.; Muthukumaran, K.; Kumaragurubaran, N. *Synthesis* **2000**, 217. (g) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1. (h) Kaye, P. T.; Nokanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1331.

(3) For leading references, see: (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Pekin Trans. 1* **2000**, 1. (b) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155. (c) Aldabbagh, F.; Bowman, W. R. *Contemp. Org. Synth.* **1997**, 261. (d) Rousseau, G.; Homsi, F. *Chem. Soc. Rev.* **1997**, *26*, 453. (e) Fallis, A. B.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (f) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions*; VCH Publishers: New York, 1996. (g) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (h) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (i) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: New York, 1995. (j) Barton, D. H. R.; Parekh, S. I. *Half a Century of Free Radical Chemistry*; Cambridge University Press: Cambridge, 1993. (k) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. (l) Curran, D. P. In *Comprehesive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1992; Vol 4, Chapter 4.2. (m) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (n) Curran, D. P. M. *Synthesis* **1988**, 417 and 489.

(4) See, for example: (a) Díaz, N.; Suárez, D.; Merz, K. M. M., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4197. (b) Page, M. I. *Chem. Commun.* **1998**, 1609. (c) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (d) Hook, V. *Chem. Br.* **1997**, *33*, 34. (e) Spratt, B. G. *Science* **1994**, *264*, 388. (f) Davies, J. *Science* **1994**, *264*, 375.

(5) For reviews on this subject, see: (a) Lednicer, D. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1995; Vol. 5. (b) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (c) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (d) Ojima, I. *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993, 197. (e) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992. (f) Marchand-Brynaert, J.; Ghosez, L. *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukas, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; p.727. (g) Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer: Vienna, 1985; Vol. 47, p1. (h) Manhas, M. S.; Bose, A. K. *β-Lactams: Natural and Synthetic*; Wiley: New York, 1971; Part 1.

10.1021/jo005715z CCC: $20.00
Published on Web 02/02/2001

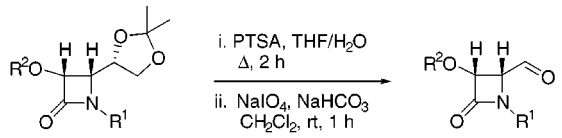
Continuing with our work on the synthesis and synthetic applications of chiral, functionalized 2-azetidinones,[8] we wish to report now full details of a straightforward synthesis of unusual, chiral nonracemic bicyclic β-lactams via combination of Baylis−Hillman reaction of 4-oxoazetidine-2-carbaldehydes with free-radical chemistry.[9]

Results and Discussion

The starting substrates, 4-oxoazetidine-2-carbaldehydes **1**, were prepared in optically pure form using standard methodology.[8a] Enantiopure 2-azetidinones **2** were obtained from imines of (*R*)-2,3-*O*-isopropylidenepropanal, through Staudinger reaction with the corresponding acid chlorides in the presence of Et_3N as single *cis* enantiomers.[10] Standard acetonide hydrolysis to provide diols, followed by oxidative cleavage, smoothly formed 4-oxoazetidine-2-carbaldehydes **1** in excellent yields (Scheme 1).

The Baylis−Hillman reaction using nonracemic protected α-amino aldehydes has been attempted with limited success, due to partial racemization of the chiral aldehyde by DABCO after prolongate exposure times[11a] or due to poor diastereoselection.[11b,c] To our delight,

Scheme 1



(+)-2a R^1 = 2-Propenyl, R^2 = Ph	**(+)-1a** (91%)
(+)-2b R^1 = 3-Butenyl, R^2 = Ph	**(+)-1b** (94%)
(+)-2c R^1 = 2-Propynyl, R^2 = Ph	**(+)-1c** (70%)
(+)-2d R^1 = 3-Butynyl, R^2 = Ph	**(+)-1d** (72%)
(+)-2e R^1 = 4-Pentynyl, R^2 = Ph	**(+)-1e** (86%)
(+)-2f R^1 = 5-Hexynyl, R^2 = Ph	**(+)-1f** (98%)
(+)-2g R^1 = 2-Propenyl, R^2 = CH_3	**(+)-1g** (96%)

Baylis−Hillman adducts **3a**−**i** can be prepared, almost as single diastereoisomers, by the DABCO promoted reaction of various activated vinyl systems with the appropriate 4-oxoazetidine-2-carbaldehyde **1**, and performing the experiment in acetonitrile at −20 °C. However, when the reaction was carried out at ambient temperature maintaining the molar ratio of reagents (aldehyde/DABCO/alkene = 1:1:10), partial epimerization together with some unreacted aldehyde were observed. We carried out a study in order to test the effect of the amount of catalyst on the conversion rate, finding that the process can be significantly accelerated on increasing the amount of catalyst (DABCO), without detectable racemization (see Table). There is not a significant solvent (acetonitrile, tetrahydrofuran or dichloromethane) effect in the observed diastereoselectivity. High diastereoselectivity was generally observed when different aldehydes were used. However, enhancing solvent polarity slightly improved the yield, with the best yield obtained in acetonitrile, which became the solvent of choice.

Placing a bulky group, such as *p*-methoxyphenyl at N1, decreased the efficiency of the addition, making now the C4-epimerization of the β-lactam a competitive process with the Baylis−Hillman reaction. It is possible that the carbaldehyde moiety is now less accessible to the activated olefin due to steric effects. However, the bulkiness of the 3-phenoxy substituent on the β-lactam ring may play a role in ensuring the high selectivity of this process, while less demanding groups dropped the diastereoselectivity. In fact, when a methoxy group was used instead, the stereoselectivity was lowered (entry 12, Table 1). Fortunately, diastereomeric Baylis−Hillman adducts *syn*-**3** and *anti*-**3** could be separated by flash chromatography. The observed stereochemistry might be tentatively explained by the Felkin−Anh model, through an *anti*-Felkin addition. The large substituent (the aminogroup of the four-membered ring) is assumed to be arranged perpendicularly to the carbonyl group. The activated olefin may attack the C=O bond in the most favored conformation, explaining the preference for the *syn*-configured products (Figure 1).

In view of the importance of ring structures in essentially all classes of natural products, numerous combinations of reactions have therefore been exploited to construct mono- and polycyclic derivatives. Among the various available options, such as cycloaddition reactions,

(6) For selected references, see: (a) Mascaretti, O. A.; Boschetti, C. E.; Danelon, G. O.; Mata, E. G.; Roveri, O. A. *Curr. Med. Chem.* **1995**, *1*, 441. (b) Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127. (c) Vaccaro, W. D.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313. (d) Vaccaro, W. D.; Sher, R.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 35. (e) Burnett, D. A. *Tetrahedron Lett.* **1994**, *35*, 7339. (f) Borthwick, A. D.; Weingarte, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365. (g) Ogilvie, W.; Bailey, M.; Poupart, M.-A.; Abraham, A.; Bhavsar, P.; Bonneau, P.; Bordeleau, J.; Bousquet, Y.; Chabot, C.; Duceppe, J.-S.; Fazal, G.; Goulet, S.; Grand-Maitre, C.; Guse, I.; Halmos, T.; Lavallee, P.; Leach, M.; Malefant, E.; O'Meara, J.; Plante, R.; Plouffe, C.; Poirier, M.; Soucy, F.; Yoakim, C.; Deziel, R. *J. Med. Chem.* **1997**, *40*, 4113.

(7) For an exhaustive revision of 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: New York, 1993; Chapter 3. For selected recent examples building bicyclic β-lactams, see: (b) Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377. (c) Hwu, J. R.; Hakimelahi, S.; Moosavi-Movahedi, A. A.; Tsay, S.-C. *Chem.—Eur. J.* **1999**, *5*, 2705. (d) Maison, W.; Kosten, M.; Charpy, A.; Kintscher-Langenhagen, J.; Schlemminger, I.; Lützen, A.; Westerhoff, O.; Martens, J. *Eur. J. Org. Chem.* **1999**, 2433. (e) Banfi, L.; Guanti, G.; Basso, A. *Eur. J. Org. Chem.* **2000**, 939. (f) Jensen, M. S.; Yang, C.; Hsiao, Y.; Rivera, N.; Wells, K. M.; Chung, J. Y. L.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *2*, 1081.

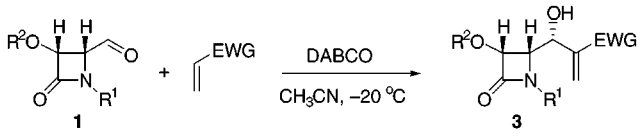
(8) (a) Alcaide, B.; Almendros, P.; Salgado, N. R. *J. Org. Chem.* **2000**, *65*, 3310. (b) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Commun.* **2000**, 485. (c) Alcaide, B.; Sáez, E. *Tetrahedron Lett.* **2000**, *41*, 1647. (d) Alcaide, B.; Almendros, P.; Salgado, N. R.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 4453. (e) Alcaide, B.; Aly, M. F.; Rodríguez, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 3453. (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2000**, *2*, 1411. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **2000**, 757.

(9) For a preliminary communication of a part of this work, see: Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **1999**, 1913.

(10) The *cis*-selectivity observed for compounds **2** was expected according to the current model for the Staudinger reaction. (a) Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 5869. (b) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. (c) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (d) 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: (e) Niu, Ch.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 497. (f) Hubschwerelen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206. (g) Welch, J. T.; Araki, K.; Kawecki, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454. (h) 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.

(11) (a) Drewes, S. E.; Khan, A. A.; Rowland, K. *Synth. Commun.* **1993**, *23*, 183. (b) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981. (c) Manickum, T.; Roos, G. *Synth. Commun.* **1991**, *21*, 2269.

Table 1. Stereoselective Baylis−Hillman Reaction of 4-oxoazetidine-2-carbaldehydes 1[a]



entry	aldehyde	R^1	R^2	EWG	DABCO (mol %)	t (h)	adduct	d.r.[b]	yield (%)[c]
1	**(+)-1a**	2-propenyl	Ph	$COCH_3$	10	96	**(+)-3a**	99:1	80
2	**(+)-1a**	2-propenyl	Ph	$COCH_3$	20	32	**(+)-3a**	99:1	80
3	**(+)-1a**	2-propenyl	Ph	$COCH_3$	50	24	**(+)-3a**	99:1	80
4	**(+)-1a**	2-propenyl	Ph	$COCH_3$	100	17	**(+)-3a**	99:1	80
5	**(+)-1a**	2-propenyl	Ph	CN	100	192	**(+)-3b**	93:7	84
6	**(+)-1a**	2-propenyl	Ph	$COOCH_3$	100	120	**(+)-3c**	99:1	58
7	**(+)-1b**	3-butenyl	Ph	$COCH_3$	100	72	**(+)-3d**	99:1	72
8	**(+)-1c**	2-propynyl	Ph	$COCH_3$	100	72	**(+)-3e**	96:4	78
9	**(+)-1d**	3-butynyl	Ph	$COCH_3$	100	24	**(+)-3f**	99:1	67
10	**(+)-1e**	4-pentynyl	Ph	$COCH_3$	100	48	**(+)-3g**	99:1	60
11	**(+)-1f**	5-hexynyl	Ph	$COCH_3$	100	24	**(+)-3h**	99:1	60
12	**(+)-1g**	2-propenyl	Me	$COCH_3$	100	144	**(+)-3i**	81:19	71

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data.

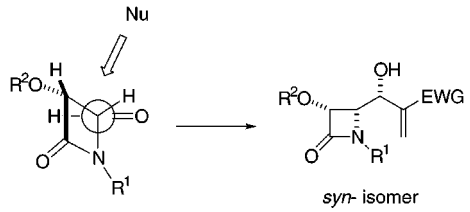


Figure 1. Model to explain the observed stereochemistry by delivery of the activated olefin to the less hindered face.

ring transformations, and cyclization reactions, the latter are probably the most commonly used because of the number of possible initiators and terminators. But not every ring size is accessible with the same ease. Cyclization processes generally fail when applied to the construction of medium-sized rings, because of enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain ends meeting).[12] However there are a few notable exceptions, such as the rapidly emerging metathesis reaction.[13] Indirect routes (ionic- and radical-based ring expansions and fragmentations) are often needed to access such structures.[14]

Unlike intermolecular C−C bond formation involving radical additions to activated (usually electrophilic) olefins, clean bimolecular additions to simple alkenes are not generally easy to accomplish using common radical processes. Although construction of five- and six-membered rings has received much attention, problems associated with the formation of medium-sized rings using free radical methodology are widely appreciated. Even the formation of seven-membered rings in the 7-*exo*-*trig* mode is likely to be unsuccessful in most cases (at 25 °C, $k_{7exo} < 7 \times 10^{-1}$ s^{-1}). However, several authors were able to prepare seven-membered rings by radical cyclization on substrates having only a limited degree of freedom, including β-lactam-tethered haloalkenes or alkynes[15,16] and arylbridged compounds.[17] The formation of rings with more than seven atoms have unfavorable rates because the addition step is often too slow to allow it to compete successfully with other pathways open to the radical intermediate. In stannane-based chemistry for example, premature hydrogen abstraction from the organotin hydride is difficult to avoid. Nevertheless, Gibson has reported the radical cyclization of aryl radicals onto α,β-unsaturated amino esters to give eight- and nine-membered ring benzocyclic α-aminoesters which have the nitrogen atom in the ring,[18a] and Pattenden has studied this methodology of cyclization for the synthesis of eight-membered bicyclic lactones.[18b]

Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with dissociation energies from 20 to 40 Kcal mol^{-1}, cleavage can be caused in the liquid phase. The dissociation energy of the $PhCH_2-H$ bond is 88 Kcal mol^{-1}, so the generation of the benzylic radical is an unexpected process via heating at usual temperatures.[19] To our surprise, Baylis−Hillman adduct (+)-**3a**, on heating in toluene, *p*-xylene, or mesitylene in a sealed tube at 210 °C,[20] formed as single isomers the bicyclic products **4a**−**c**, which were

(12) (a) Galli, L.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(13) For some recent reviews on olefin metathesis, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (c) Fürstner, A. *Synlett* **1999**, 1523. (d) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Shuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (g) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(14) For selected references, see: (a) Kirsch, V.; Wolff, C.; Näther, C.; Tochtermann, W. *Eur. J. Org. Chem.* **2000**, *99*, 1741. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (c) Boivin, J.; Pothier, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 9239. (d) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. (e) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (f) Wovkulich, P. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 1, pp 843−899. (g) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

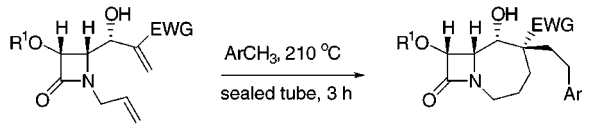
(15) (a) Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1237. (b) Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun. 1* **1986**, 78.

(16) (a) Bachi, M. D. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Bentley, P. H., Southgate, R., Eds.; Special Publication No. 70; Royal Society of Chemistry: London, 1989; Ch. 6. (b) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841.

(17) (a) Beck, A. L.; Mascal, M.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J.; Coates, W. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 797. (b) Mathvink, R.; Boger, D. L. *J. Org. Chem.* **1988**, *53*, 3377.

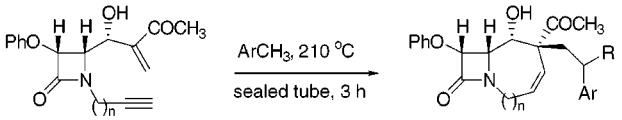
(18) (a) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Chem. Commun. 1* **1997**, 637. (b) Blake, A. J.; Hollingworth, G. J.; Pattenden, G. *Synlett* **1996**, 643.

Scheme 2



(+)-3a R^1 = Ph, EWG = $COCH_3$	**(+)-4a** Ar = Ph, 37%, dr = 99 : 1
(+)-3a R^1 = Ph, EWG = $COCH_3$	**(+)-4b** Ar = 4-MeC_6H_4, 45%, dr = 99 : 1
(+)-3a R^1 = Ph, EWG = $COCH_3$	**(+)-4c** Ar = 3,5-diMeC_6H_4, 38%, dr = 99 : 1
(+)-3b R^1 = Ph, EWG = CN	**(+)-4d** Ar = Ph, 37%, dr = 85 : 15
(+)-3c R^1 = Ph, EWG = $COOCH_3$	**(+)-4e** Ar = Ph, 56%, dr = 80 : 20
(+)-3i R^1 = CH_3, EWG = $COCH_3$	**(+)-4f** Ar = Ph, 43%, dr = 99 : 1
(+)-3i R^1 = CH_3, EWG = $COCH_3$	**(+)-4g** Ar = 4-MeC_6H_4, 38%, dr = 99 : 1

Scheme 3

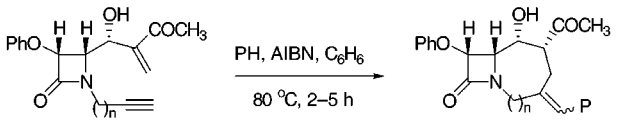


(+)-3e n = 1	**(+)-5a** R = H, Ar = Ph, 40%, dr = 99 : 1
(+)-3e n = 1	**(+)-5b** R = OH, Ar = Ph, 20%, dr = 99 : 1
(+)-3e n = 1	**(+)-5c** R = CH_3, Ar = Ph, 45%, dr = 50 : 50
(+)-3e n = 1	**(+)-5d** R = H, Ar = 4-MeC_6H_4, 60%, dr = 99 : 1
(+)-3f n = 2	**(+)-5e** R = H, Ar = Ph, 50%, dr = 99 : 1
(+)-3f n = 2	**(+)-5f** R = H, Ar = 4-MeC_6H_4, 53%, dr = 99 : 1

isolated in modest yields (37−45%); the use of chlorobenzene or anisole as solvents gave unaltered starting material. Variation of Baylis−Hillman adduct was examined. Dienes **3b**, **3c**, and **3i** by heating in toluene or *p*-xylene suffer as well this novel thermally induced reaction (Scheme 2). The COMe substituent gave the best match of diastereoselectivity. Changing the EWG to COOMe saw the lowest diastereoselectivity.

When enyne (+)-**3e** was used instead of diene (+)-**3a** the reaction proceeded in the same manner, giving product (+)-**5d** in good yield (60%). Furthermore, thermal treatment of enyne (+)-**3f** with toluene or *p*-xylene gave the eight-membered cycles (+)-**5e** and (+)-**5f** in reasonable yields. Interestingly, the use of benzyl alcohol allowed us to obtain the hemicetal derivative (+)-**5b** (Scheme 3). Although this latter compound was isolated in low yield (20%), this is an interesting case because three new chiral centers are generated in a straightforward and highly stereoselective manner. The use of ethyl benzene instead of benzyl alcohol furnished a mixture of two products (+)-**5c** (50:50) which were identified as epimers at the benzylic carbon center. Compounds **5** were obtained as single diastereomers except (+)-**5c**, derived from ethylbenzene. However, attempts to promote such a thermal reaction on substrate (+)-**3g** failed, and complex reaction mixtures were isolated in all cases. When a catalytic amount of hydroquinone was added, the reaction rate was considerably reduced and the product yield fell dramatically. This fact confirms that a radical reaction is involved. Also, together with compounds **4** and

Scheme 4



(+)-3e n = 1	**(+)-6a** n = 1, P = $SnPh_3$, 85%, *Z*:*E* = 99 : 1
(+)-3f n = 2	**(+)-6b** n = 2, P = $SnPh_3$, 90%, *Z*:*E* = 99 : 1
(+)-3g n = 3	**(+)-6c** n = 3, P = $SnPh_3$, 80%, *Z*:*E* = 1 : 99
(+)-3e n = 1	**6d** n = 1, P = SPh, 65%, *Z*:*E* = 60 : 40
(+)-3f n = 2	**6e** n = 2, P = SPh, 70%, *Z*:*E* = 70 : 30
(+)-3g n = 3	**6f** n = 3, P = SPh, 64%, *Z*:*E* = 30 : 70

5, 1,2-diarylethanes were isolated as byproducts in all cases. These products may be formed by recombination of the initially generated benzylic radicals.

In view of the particular disposition of 1,5- and 1,6-enyne-2-azetidinones to undergo 5-*exo* and 6-*exo* tin-promoted radical cyclization,[21] we examined the applicability of this methodology to our novel Baylis−Hillman 1,ω-enyne substrates **3e**−**h** for the synthesis of less common bicyclic β-lactams. This approach in the preparation of seven-membered or larger sized rings has not been hitherto applied.[22] The extraordinary synthetic potential of Baylis−Hillman adducts **3** is illustrated by a dramatic change in the chemoselectivity when the bicyclic β-lactam (+)-**6a** was smoothly formed as the exclusive product from compound (+)-**3e**, in nearly quantitative yield as crude product. The tin-promoted radical reaction was also useful in the conversion of the homologous 1,4-tethered enynes (+)-**3f** and (+)-**3g** into the corresponding bicyclic systems (+)-**6b** and (+)-**6c** with similar efficiency and selectivity. Compounds **6a**−**c** were exclusively obtained as single *Z*- or *E*-isomers. The triphenyltin group in the final products represents a very useful handle since it provides an entry into the exceptionally rich chemistry of tin. In addition, PhSH reacted in boiling benzene with β-lactams **3e**−**g** in the presence of a catalitic amount of AIBN as initiator under an inert atmosphere, delivering in good yields the corresponding phenylthiovinyl derivatives **6d**−**f** as mixtures of *Z*/*E*-isomers (Scheme 4). Fortunately, in all cases the isomeric products *Z*-**6d**−**f** and *E*-**6d**−**f** could be easily separated by gravity flow chromatography, wherein the major isomer was usually the less polar compound. It should be noted that reactions were carried out under standard dilution conditions and did not require the use of high dilution techniques. Efforts to promote this process on substrate (+)-**3h** failed, even by conducting the experiment with very low concentrations of both the Baylis−Hillman adduct (+)-**3h** and Bu_3SnH and slow addition of reagents, such as syringe pump addition. In this case the radical addition to the triple bond occurs, but the rate of hydrogen-atom transfer to unclyclized radicals is faster than the further Michael addition required for achieving the then-membered fused bicycle.

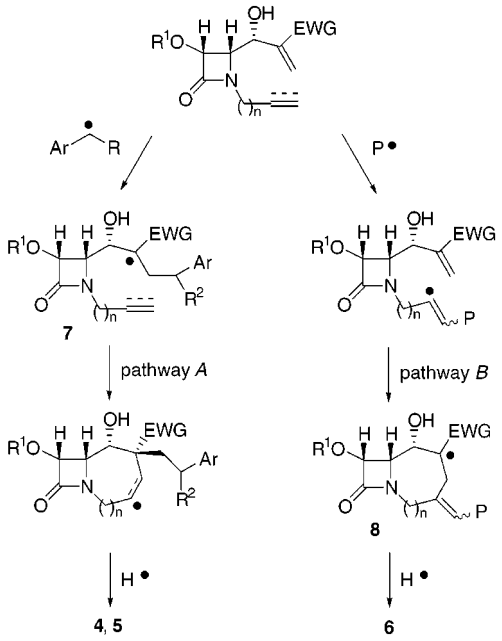
Formation of bicyclic β-lactams **4**, **5**, and **6** can be explained in terms of a competition between a tandem radical Michael addition/*endo* cyclization and a tandem radical addition/Michael addition, depending on the

(19) For a review on formation of free radicals by thermal cleavage, see: (a) Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York, 1980; pp. 44−61. For a summary of methods of radical formation, see: (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Elmsford, New York, 1986; pp 267−281.

(20) One of the reviewers has suggested that the generation of a benzylic radical is unlikely by simple heating in toluene or other aromatic compounds. For this reviewer, a much more likely scenario is that traces of oxygen serve to generate the benzylic radicals.

(21) Representative examples: Cyclizations using R_3SnH: Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829. Janardhanam, S.; Balakumar, A.; Rajagopalan, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 551. Cyclizations using sulfur- and phosphorus-centered radicals: Brumwell, J. E.; Simpkins, N. S.; Terret, N. K. *Tetrahedron* **1994**, *50*, 13533.

Scheme 5. Mechanistic explanation for the formation of bicyclic β-lactams 4−6



electronic nature of the radical promoter (Scheme 5). It is known that nucleophilic radicals react more rapidly with electron poor alkenes than with electron rich alkenes or alkynes, and conversely, electrophilic radicals react more rapidly with electron rich alkenes than electron poor alkenes.[31] In our case, Baylis−Hillman adducts **3** may react through two different pathways to give the bicyclic systems. The more nucleophilic benzylic radical would favor formation of compounds **4** and **5** through pathway *A*, while the more electrophilic radicals, such as PhS• and Ph_3Sn•, should promote formation of compounds **6** through pathway *B*. Alternatively, the differences in reactivity between the benzylic and the thiyl and stannyl radicals, respectively, could be explained by other considerations. Thus, for the thiyl and stannyl radicals the initial addition to the double bond is fast but reversible. Since the cyclization is a slow reaction, it cannot compete with fragmentation. However, the addition to the triple bond is irreversible, and therefore only products deriving from addition to the triple bond are isolated. Addition of the benzylic radical to the double bond of course is not reversible.

The α-substituted *β*-oxy-radicals (types **7** and **8** in Scheme 5) react preferentially via the transition states **I** and **II** which minimize the steric repulsive interactions between the *β*-lactam ring and the bulky aryl moiety. We should like to note that the 1,2-asymmetric induction observed during the radical process is favored by steric reasons and it is consistent with the attack in the enolate radicals occurring *anti* to the *β*-lactam ring attached to the C-2 stereogenic center (Figure 2).[23] The difference in behavior between ethylbenzene and benzyl alcohol may be due to the extent of coordination in the radical involved in the reaction. It is possible that internal hydrogen bonding between the ketonic oxygen atom and the hydroxylic hydrogen atom from the benzylic moiety gives rise to a rotationally restricted transition state, generating a preferred conformation.[24] The methyl group from ethylbenzene does not have this ability of coordination with the ketone, involving two conformations with the same energy.

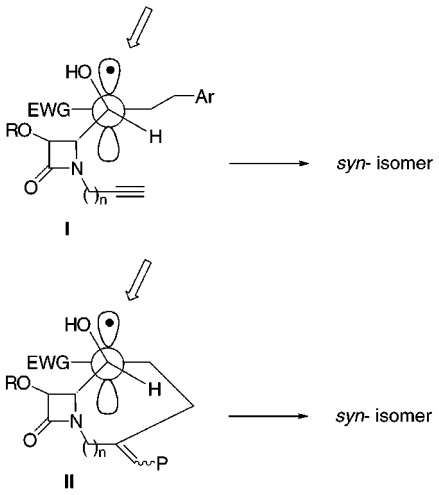
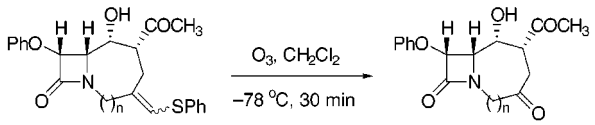


Figure 2. Model to rationalize the 1,2-stereoinduction on radical reactions.

Scheme 6



6d n = 1
6e n = 2
6f n = 3

(+)-9a n = 1, 60%
(+)-9b n = 2, 70%
(+)-9c n = 3, 52%

To illustrate the value of these substrates, exocyclic double bond thioderivatives **6d−f** were ozonolyzed to give seven-, eight- and nine-membered[25] ketones **9a−c** (Scheme 6).

To test the reactivity of these polyfunctionalized substrates, Swern oxidation was carried out in bicycle (+)-**5d** providing diketone (−)-**10a**. Treatment of *β*-dicarbonylic compound (−)-**10a** with hydrazine hydrate formed product (+)-**11a** as single isomer (Scheme 7). This transformation could be rationalized through a retroaldol reaction followed by a stereoselective protonation of the enolate to the less hindered face.

Configurational Assignment for Bicyclic Systems. The bicyclic structure (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **4**, **5**, **6**, and **11** were established by NMR mono- and two-dimensional techniques. Taking into account that optically pure Baylis−Hillman adducts **3** could be obtained and cyclized,[26] the stereochemistry for compounds **3** was inmediately deduced by comparison with the NOE results of

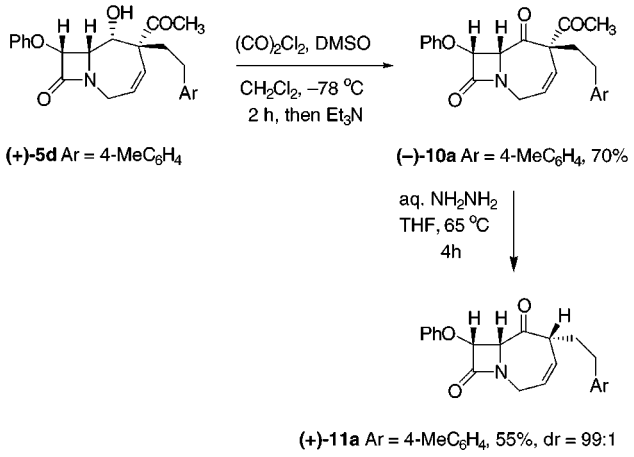
(22) The only related example is by Parsons et al. and refers to the cyclization of *N*-(2-bromo-2-propen-1-yl)-4-allyl-2-azetidinone to yield a homocarbacephem derivative. See ref 15.

(23) For selected references on 1,2-asymmetric induction in radical reactions, see for example: (a) Giese, B.; Damm, W.; Dickhaut, J.; Wetterich, F.; Sun, S.; Curran, D. P. *Tetrahedron Lett.* **1991**, *32*, 6097. (b) Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* **1993**, *34*, 431. (c) Renaud, P.; Bourquard, T. *Synlett* **1995**, 1021. (d) Giese, B.; Bulliard, M.; Dickhaut, J.; Halbach, R.; Hassler, C.; Hoffmann, U.; Hinzen, B.; Senn, M. *Synlett* **1995**, 116.

(24) For the role of intramolecular hydrogen bonding in the stereocontrol of α-sulfinylated *β*-hydroxy-radicals see: Mase, N.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 2797.

(25) The generation of nine-membered nitrogen heterocycles (azonines) bearing defined constitutions and configurations is still a challenge in organic synthesis. Furthermore, azonines are found as subunits in natural and pharmaceutically important products. See: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131.

Scheme 7



(+)-5d Ar = 4-MeC_6H_4 **(−)-10a** Ar = 4-MeC_6H_4, 70%

(+)-11a Ar = 4-MeC_6H_4, 55%, dr = 99:1

the bicyclic systems. Besides, the *cis*-stereochemistry 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.[27] NOE irradiation of H6 (carbinolic hydrogen) on compound (+)-**4f** resulted in enhancement of the signals corresponding to H7 and C*H*HBn (12% and 9%, respectively), which is consistent with a *syn* H6−H7/*syn* H6−CH_2Bn relative stereochemistry. Conversely, NOE enhancement (10%) was observed on H6 upon irradiation of C*H*HBn. NOE enhancements of 7% and 10% were observed on H6 and H8, respectively, upon irradiation of H7, so confirming this pattern. The *syn* H7−H8/*syn* H7−CH_2CH_2Ar relative stereochemistry for compound (+)-**5e** was obvious on the basis of NOE enhancements of the signals corresponding to H8 and C*H*HCH_2Ar (8% and 9%, respectively) upon irradiation of H7. Furthermore, NOE irradiation of H8 resulted in a 7% enhancement of the signal corresponding to H7. A NOE enhancement of 2% on H5 for compound (+)-**11b** on irradiating the signal corresponding to H7 is in good agreement with a *syn*-relative disposition between H5 and H7 (Figure 3). Analogous NOE enhancements were observed for remaining compounds **4** and **5**.

Azetidinones **6** have a medium-sized ring bearing an exocyclic double bond fused to the *β*-lactam. The stereochemistry at the stereocenters in compounds **6** was stablished by NOE studies, as shown in Figure 3 for compounds (+)-***Z*-6a**, (−)-***Z*-6d**, and (+)-***E*-6d**. The geometry of the exocyclic double bond was assigned by qualitative homonuclear NOE difference spectra as depicted in Figure 3 for compounds (+)-***Z*-6a**, (−)-***Z*-6d**, and (+)-***E*-6d**. Similar values of NOE enhancements for compounds **6b**−**f** were observed, in agreement with the proposed stereochemistries.

In conclusion, we have shown that combination of Baylis−Hillman reaction and tandem radical addition/cyclization sequences is an extremely useful synthetic tool for the asymmetric synthesis of densely functionalized

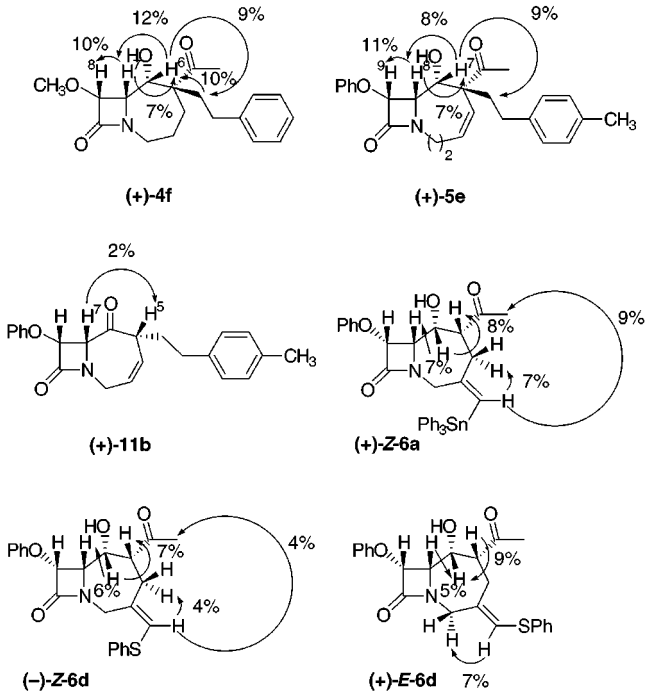


Figure 3. Selected NOE effects and stereochemistry of some fused bicyclic *β*-lactams **4**−**6**.

monocyclic *β*-lactams and a number of unusual bicyclic *β*-lactams fused to medium rings. This methodology is very versatile offering the possibility to obtain a variety of conveniently functionalized bicyclic *β*-lactams just by changing the substituents in readily available 4-oxoazetidine-2-carbaldehydes, activated alkenes, or radical precursors. In addition to the novelty of this strategy, the method proved to be general and highly diastereoselective for the preparation up to nine-membered fused rings, offering the possibility of a future application to different chiral building blocks other than 2-azetidinones. Other aspects of this chemistry are currently under investigation in our laboratory.

Experimental Section

General. General experimental data and procedures have been previously reported.[8a] 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. All commercially available compounds were used without further purification. 4-Oxoazetidine-2-carbaldehydes (+)-**1a** and (+)-**1c** and 2-azetidinones (+)-**2a**, (+)-**2c**, and (+)-**2g** were prepared according to our previously reported procedures.[8a]

General Procedure for the Synthesis of Compounds 3a−i. A solution of the appropriate 4-oxoazetidine-2-carbaldehyde **1** (0.20 mmol) in acetonitrile (2 mL) was added dropwise to a stirred solution of DABCO (22.4 mg, 0.20 mmol) in acetonitrile (2 mL) at −20 °C. After 15 min, an activated olefin (2.00 mmol) was added at −20 °C and the reaction mixture was placed in a −20 °C freezer until complete disappearance of the aldehyde (TLC). The mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or ethyl acetate/dichloromethane mixtures gave analytically pure compounds **3**. Spectroscopic and analytical data for some representative forms of **3** follow.[28]

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-methylidene-3-oxo-butyl]-3-phenoxy-1-(2-propenyl)-2-azetidinone, (+)-3a. From 249

(26) Derivatizing the hydroxyesters **3** with (*R*)- and (*S*)-*O*-acetylmandelic acids would allow assignment of the configuration at the carbinolic stereocenter. However, sluggish and low yielding reactions were observed. This behavior of the *β*-lactamic Baylis−Hillman adducts is in sharp contrast with the good yields observed by us for related *O*-acetylmandelates derived from homoallylic alcohols. See ref 8a.

(27) For clarity throughout this work, bicyclic systems have been numbered according to 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 amide carbonyl group.

mg (1.08 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and after 17 h at −20 °C, 260 mg (80%) of compound (+)-**3a** was obtained as a colorless solid after purification by flash chromatography (dichloromethane/ethyl acetate, 9/1). Colorless solid. Mp: 114−116 °C (hexanes/ethyl acetate). $[\alpha]_D = +58.1$ (*c* 0.9, $CHCl_3$). ^1H NMR: δ 2.35 (s, 3H), 3.14 (d, 1H, $J = 4.6$ Hz), 3.65 (dd, 1H, $J = 15.4$, 7.5 Hz), 4.24 (m, 1H), 4.31 (d, 1H, $J = 4.9$ Hz), 4.86 (m, 1H), 5.19 (m, 2H), 5.23 (d, 1H, $J = 4.9$ Hz), 5.70 (m, 1H), 6.26 (s, 1H), 6.37 (d, 1H, $J = 1.5$ Hz), 7.05 (m, 3H), 7.31 (m, 2H). ^{13}C NMR: δ 199.6, 165.7, 157.2, 146.6, 131.3, 129.7, 128.6, 122.8, 119.0, 115.8, 80.7, 68.5, 58.9, 44.1, 26.2. IR (KBr, cm^{-1}): ν 3431, 1763, 1665. MS (EI), *m*/*z*: 302 ($M^+ + 1$, 54), 301 (M^+, 6), 60 (100). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.50; H, 6.55; N, 4.55.

(3*R*,4*S*)-4-[(*R*)-2-Cyano-1-hydroxy-2-propenyl]-3-phenoxy-1-(2-propenyl)-2-azetidinone, (+)-*syn*-3b. From 341 mg (1.47 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and after 192 h at −20 °C, 327 mg (78%) of compound (+)-syn-**3b** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 3/2). Colorless solid. Mp: 78−80 °C (hexanes/ethyl acetate). $[\alpha]_D = +68.3$ (*c* 0.7, $CHCl_3$). ^1H NMR: δ 3.15 (d, 1H, $J = 3.4$ Hz), 3.71 (dd, 1H, $J = 15.4$, 7.0 Hz), 4.20 (dd, 1H, $J = 15.9$, 4.9 Hz), 4.32 (t, 1H, $J = 4.4$ Hz), 4.65 (bs, 1H), 5.29 (m, 2H), 5.32 (d, 1H, $J = 4.4$ Hz), 5.79 (m, 1H), 6.12 (s, 1H), 6.29 (d, 1H, $J = 1.5$ Hz), 7.08 (m, 3H), 7.33 (m, 2H). ^{13}C NMR: δ 165.5, 156.9, 132.5, 130.9, 129.8, 123.1, 122.6, 119.7, 116.6, 115.9, 80.7, 69.6, 58.6, 44.4. IR (KBr, cm^{-1}): ν 3430, 2230, 1759. MS (CI), *m*/*z*: 285 ($M^+ + 1$, 100), 284 (M^+, 36). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.69; H, 5.67; N, 9.85. Found: C, 67.59; H, 5.81; N, 9.73.

(3*R*,4*S*)-4-[(*R*)-2-Carboxymethyl-1-hydroxy-2-propenyl]-3-phenoxy-1-(2-propenyl)-2-azetidinone, (+)-3c. From 362 mg (1.56 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and after 120 h at −20 °C, 289 mg (58%) of compound (+)-**3c** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 2/1). Colorless solid. Mp: 120−122 °C (hexanes/ethyl acetate). $[\alpha]_D = +71.5$ (*c* 0.8, $CHCl_3$). ^1H NMR: δ 3.14 (d, 1H, $J = 4.6$ Hz), 3.65 (dd, 1H, $J = 15.4$, 7.8 Hz), 3.78 (s, 3H), 4.22 (ddt, 1H, $J = 15.4$, 4.9, 1.5 Hz), 4.36 (dd, 1H, $J = 4.9$, 3.4 Hz), 4.83 (m, 1H), 5.15 (dq, 1H, $J = 10.9$, 1.5 Hz), 5.22 (m, 1H), 5.23 (d, 1H, $J = 4.9$ Hz), 5.69 (m, 1H), 6.15 (t, 1H, $J = 1.7$ Hz), 6.39 (t, 1H, $J = 1.5$ Hz), 7.06 (m, 3H), 7.31 (m, 2H). ^{13}C NMR: δ 166.4, 165.8, 157.3, 138.6, 131.2, 129.8, 127.9, 122.9, 119.4, 116.0, 80.9, 69.1, 58.7, 52.1, 44.3. IR (KBr, cm^{-1}): ν 3428, 1759, 1672. MS (EI), *m*/*z*: 317 ($M^+ + 1$, 100), 316 (M^+, 17). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.40; H, 5.91; N, 4.51.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-methylidene-3-oxo-butyl]-3-phenoxy-1-(2-propynyl)-2-azetidinone, (+)-*syn*-3e. From 109.8 mg (0.48 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1c** and after 72 h at −20 °C, 107 mg (75%) of compound (+)-syn-**3e** was obtained as a colorless solid after purification by flash chromatography (dichloromethane/ethyl acetate, 9/1). Colorless solid. Mp: 116−118 °C (hexanes/ethyl acetate). $[\alpha]_D = +89.1$ (*c* 0.8, $CHCl_3$). ^1H NMR: δ 2.26 (t, 1H, $J = 2.5$ Hz), 2.40 (s, 3H), 3.22 (d, 1H, $J = 4.4$ Hz), 3.78 and 4.45 (dd, each 1H, $J = 17.6$, 2.5 Hz), 4.42 (dd, 1H, $J = 4.9$, 2.9 Hz), 4.91 (m, 1H), 5.23 (d, 1H, $J = 5.1$ Hz), 6.29 and 6.37 (d, each 1H, $J = 1.5$ Hz), 7.06 (m, 3H), 7.31 (m, 2H). ^{13}C NMR: δ 199.4, 164.9, 157.0, 146.4, 129.6, 128.2, 122.8, 115.7, 80.8, 75.9, 73.1, 68.1, 58.4, 31.2. IR (KBr, cm^{-1}): ν 3393, 3292, 1755, 1665. MS (CI), *m*/*z*: 301 ($M^+ + 2$, 17), 300 ($M^+ + 1$, 100). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.12; H, 7.83; N, 4.76.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-methylidene-3-oxo-butyl]-1-(4-pentynyl)-3-phenoxy-2-azetidinone, (+)-3g. From 123 mg (0.478 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1e** and after 48 h at −20 °C, 93 mg (60%) of compound (+)-**3g** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9/1). $[\alpha]_D = +71.8$ (*c* 0.4, $CHCl_3$). ^1H NMR: δ 1.79 (td, 2H, $J = 12.4$, 6.8 Hz), 1.98 (t, 1H, $J = 2.7$ Hz), 2.24 (td, 2H, $J = 6.8$, 2.7 Hz), 2.39 (s, 3H), 3.15 (d, 1H, $J = 4.6$ Hz), 3.27 and 3.56 (td, each 1H, $J = 14.0$, 7.8 Hz), 4.31 (dd, 1H, $J = 4.6$, 3.7 Hz), 4.86 (m, 1H), 5.21 (d, 1H, $J = 4.9$ Hz), 6.29 and 6.38 (d, each 1H, $J = 1.5$ Hz), 7.05 (m, 3H), 7.31 (m, 2H). ^{13}C NMR: δ 199.8, 165.9, 157.3, 146.4, 129.7, 128.9, 122.8, 115.8, 82.9, 80.6, 69.2, 68.8, 59.6, 41.1, 26.3, 26.1, 16.2. IR ($CHCl_3$, cm^{-1}): ν 3395, 3291, 1756, 1666. MS (CI), *m*/*z*: 329 ($M^+ + 2$, 10), 328 ($M^+ + 1$, 100). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.82; H, 6.32; N, 4.36.

Thermally-Induced Reactions between Baylis−Hillman Adducts 3 and Reagents bearing a Benzylic-Type Hydrogen. General Procedure for the Synthesis of Bicycles 4a−g and 5a−f. A solution of the corresponding Baylis−Hillman adduct **3** (0.20 mmol) in the appropriate benzylic solvent (10 mL) was heated in a sealed tube at 210 °C for 3 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and after purification by flash chromatography bicycles **4** and **5** were obtained.

Bicycle (+)-4b. From 111.3 mg (0.368 mmol) of Baylis−Hillman adduct (+)-**3a**, 68 mg (45%) of compound (+)-**4b** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 4/6). Colorless solid. Mp: 83−85 °C (hexanes/ethyl acetate). $[\alpha]_D = +50.9$ (*c* 1.6, $CHCl_3$). ^1H NMR: δ 1.33 (m, 1H), 1.68 (td, 1H, $J = 13.2$, 3.7 Hz), 2.02 (m, 3 H), 2.19 (td, 1H, $J = 12.7$, 3.7 Hz), 2.22 (s, 3H), 2.31 (s, 3H), 2.36 (td, 1H, $J = 13.4$, 5.0 Hz), 2.57 (td, 1H, $J = 12.2$, 5.2 Hz), 2.69 (s, 1H), 3.45 (m, 2H), 4.31 (d, 1H, $J = 4.6$ Hz), 4.52 (m, 1 H), 5.19 (d, 1H, $J = 4.6$ Hz), 7.06 (m, 5 H), 7.17 (d, 2H, $J = 8.5$ Hz), 7.35 (t, 2H, $J = 8.5$ Hz). ^{13}C NMR: δ 211.9, 165.2, 157.2, 138.3, 135.6, 129.8, 129.2, 128.1, 123.1, 116.2, 80.4, 66.7, 60.1, 57.6, 42.8, 38.2, 32.8, 30.2, 25.6, 22.6, 21.0. IR (KBr, cm^{-1}): ν 3332, 1753, 1709. MS (EI), *m*/*z*: 409 ($M^+ + 2$, 36), 408 ($M^+ + 1$, 100). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.56; H, 7.13; N, 3.51.

Bicycle (+)-4c. From 53.7 mg (0.178 mmol) of Baylis−Hillman adduct (+)-**3a**, 28 mg (38%) of compound (+)-**4c** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 1/1). Colorless solid. Mp: 116−117 °C (hexanes/ethyl acetate). $[\alpha]_D = +55.3$ (*c* 0.6, $CHCl_3$). ^1H NMR: δ 1.35 (m, 3H), 1.67 (td, 1H, $J = 12.9$, 3.9 Hz), 1.99 (m, 3H), 2.13 (td, 1H, $J = 13.2$, 3.7 Hz), 2.24 (s, 3H), 2.28 (s, 6H), 2.73 (d, 1H, $J = 2.2$ Hz), 3.45 (m, 2H), 4.32 (d, 1H, $J = 4.4$ Hz), 4.52 (d, 1H, $J = 2.9$ Hz), 5.21 (d, 1H, $J = 4.4$ Hz), 6.79 (m, 3H), 7.11 (m, 3H), 7.34 (m, 2H). ^{13}C NMR: δ 211.9, 165.1, 157.2, 141.3, 137.9, 129.8, 127.7, 126.0, 123.1, 116.2, 80.4, 66.7, 60.0, 57.5, 42.7, 38.1, 32.8, 30.4, 25.6, 22.6, 21.2. IR (KBr, cm^{-1}): ν 3330, 1750, 1704. MS (CI), *m*/*z*: 422 ($M^+ + 1$, 100), 421 ($M^+ + 1$, 50). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.16; H, 7.33; N, 3.48.

Bicycle (+)-4d. From 55.8 mg (0.196 mmol) of Baylis−Hillman adduct (+)-*syn*-**3b**, 27 mg (37%) of compound *syn*-**4d**, containing ca. 15% of its *anti*-**4d** epimer, was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 3/1). Colorless solid. Mp: 145−147 °C (hexanes/ethyl acetate). $[\alpha]_D = +62.3$ (*c* 0.7, $CHCl_3$). ^1H NMR: δ 1.99 (m, 4H), 2.22 (m, 2H), 2.77 (d, 1H, $J = 2.9$ Hz), 2.85 (t, 2H, $J = 8.0$ Hz), 3.49 (m, 2H), 4.18 (d, 1H, $J = 2.9$ Hz), 4.48 (d, 1H, $J = 4.9$ Hz), 5.28 (d, 1H, $J = 4.9$ Hz), 7.15 (m, 7H), 7.34 (m, 3H). ^{13}C NMR: δ 164.9, 156.8, 140.4, 129.9, 128.6, 128.4, 126.4, 123.4, 121.4, 116.1, 80.1, 69.4, 57.5, 46.9, 42.7, 38.5, 32.3, 31.6, 22.3. IR (KBr, cm^{-1}): ν 3340, 2250, 1746. MS (EI), *m*/*z*: 377 ($M^+ + 1$, 36), 421 ($M^+ + 1$, 100). Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.48; H, 6.35; N, 7.38.

Bicycle (+)-4e. From 60 mg (0.189 mmol) of Baylis−Hillman adduct (+)-**3c**, 43 mg (56%) of compound *syn*-**4e**, containing ca. 15% of its *anti*-**4e** epimer was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/2). Colorless oil. $[\alpha]_D = +71.7$ (*c* 0.6, $CHCl_3$). ^1H NMR: δ 1.57 (m, 2H), 1.87 (m, 2H), 2.23 (m, 2H), 2.43 (td, 1H, $J = 11.5$, 4.9 Hz), 2.60 (td, 1H, $J = 11.5$, 5.5 Hz), 2.84 (d, 1H, $J = 2.7$ Hz), 3.41 (dd, 2H, $J = 9.8$, 2.5 Hz), 3.74

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

(s, 3H), 4.31 (d, 1H, J = 4.6 Hz), 4.47 (d, 1H, J = 2.7 Hz), 5.20 (d, 1H, J = 4.6 Hz), 7.15 (m, 7H), 7.29 (m, 3H). ^{13}C NMR: δ 175.0, 165.1, 157.2, 141.4, 129.8, 128.4, 128.3, 125.9, 123.1, 116.1, 80.1, 68.2, 57.6, 54.9, 51.9, 42.9, 39.3, 32.2, 31.1, 22.6. IR ($CHCl_3$, cm^{-1}): ν 3336, 1747, 1710. MS (CI), m/z: 410 (M^+ + 1, 26), 409 (M^+ + 1, 26). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.26; H, 6.55; N, 3.48.

Bicycle (+)-4f. From 57.9 mg (0.242 mmol) of Baylis−Hillman adduct (+)-*syn*-**3i**, 54 mg (43%) of compound (+)-**4f** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/2). $[\alpha]_D$ = +66.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.26 (m, 1H), 1.66 (td, 1H, J = 13.4, 3.9 Hz), 1.96 (m, 3H), 2.21 (s, 3H, CH3), 2.24 (m, 1H), 2.36 (td, 1H, J = 13.9, 5.4 Hz), 2.68 (td, 1H, J = 12.2, 4.8 Hz), 3.07 (d, 1H, J = 2.2 Hz), 3.38 (m, 2H), 3.67 (s, 3H), 4.13 (d, 1H, J = 4.6 Hz), 4.42 (s, 1H), 4.51 (d, 1H, J = 4.6 Hz), 7.19 (m, 5H). ^{13}C NMR: δ 211.9, 166.6, 141.5, 128.5, 128.3, 126.0, 82.9, 66.7, 59.9, 59.7, 57.1, 42.4, 38.1, 32.8, 30.7, 29.7, 25.5, 22.6. IR ($CHCl_3$, cm^{-1}): ν 3336, 1752, 1708. MS (CI), m/z: 332 (M^+ + 1, 100), 331 (M^+, 36). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.85; H, 7.61; N, 4.23. Found: C, 68.97; H, 7.43; N, 4.13.

Bicycle (+)-5a. From 56.6 mg (0.189 mmol) of Baylis−Hillman adduct (+)-*syn*-**3e**, 30 mg (40%) of compound (+)-**5a** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 1/1). Colorless solid. Mp: 130−132 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +60.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.96 (td, 1H, J = 13.2, 3.7 Hz), 2.25 (s, 3H), 2.42 (dd, 1H, J = 12.2, 3.7 Hz), 2.50 (dd, 1H, J = 13.4, 4.9 Hz), 2.60 (d, 1H, J = 1.5 Hz), 2.66 (td, 1H, J = 12.5, 4.6 Hz), 3.71 (dd, 1H, J = 19.3, 1.5 Hz), 4.29 (d, 1H, J = 4.6 Hz), 4.55 (dd, 1H, J = 19.3, 5.1 Hz), 4.64 (s, 1H), 5.29 (dd, 1H, J = 4.4, 1.5 Hz), 5.59 (d, 1H, J = 12.7 Hz), 5.71 (ddd, 1H, J = 12.9, 4.9, 2.7 Hz). ^{13}C NMR: δ 209.0, 164.7, 157.1, 141.0, 130.3, 129.8, 128.5, 128.3, 126.2, 125.4, 123.2, 116.2, 82.2, 68.1, 62.2, 58.6, 41.2, 39.7, 30.4, 27.8. IR (KBr, cm^{-1}): ν 3332, 1745, 1704. MS (EI), m/z: 392 (M^+ + 1, 11), 391 (M^+, 100). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.76; H, 6.60; N, 3.50.

Bicycle (+)-5b. From 52 mg (0.173 mmol) of Baylis−Hillman adduct (+)-*syn*-**3e**, 14 mg (20%) of compound (+)-**5b** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/1). $[\alpha]_D$ = +62.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.71 (s, 3H), 2.59 (dd, 1H, J = 12.9, 10.5 Hz), 2.75 (dd, 1H, J = 12.9, 6.6 Hz), 3.60 (m, 1H), 4.49 (d, 1H, J = 4.4 Hz), 4.66 (m, 4H), 5.24 (dd, 1H, J = 10.5, 6.6 Hz), 5.29 (dd, 1H, J = 4.4, 1.5 Hz), 5.61 (m, 1H), 5.77 (ddd, 1H, J = 12.9, 5.4, 2.2 Hz), 7.01 (m, 3H), 7.17 (m, 3H), 7.24 (m, 1H), 7.32 (m, 3H). ^{13}C NMR: δ 164.9, 157.1, 141.7, 130.4, 129.8, 128.4, 127.6, 127.3, 127.2, 126.7, 125.3, 122.9, 115.7, 81.9, 79.8, 77.2, 71.9, 63.5, 62.0, 58.5, 46.9, 41.8, 20.7. IR ($CHCl_3$, cm^{-1}): ν 3330, 1743. MS (CI), m/z: 408 (M^+ + 1, 100), 407 (M^+, 22). Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.63; H, 6.23; N, 3.46.

Bicycle (+)-5d. From 60 mg (0.20 mmol) of Baylis−Hillman adduct (+)-syn-**3e**, 49 mg (60%) of compound **(+)-5d** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/1). $[\alpha]_D$ = +52.4 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 1.93 (m, 1H), 2.24 (s, 3H), 2.31 (s, 3H), 2.36 (dd, 1H, J = 11.9, 4.2 Hz), 2.48 (dd, 1H, J = 13.4, 4.9 Hz), 2.60 (td, 1H, J = 16.1, 4.9 Hz), 2.68 (bs, 1H), 3.70 (dq, 1H, J = 19.0, 2.0 Hz), 4.29 (d, 1H, J = 4.6 Hz), 4.54 (dq, 1H, J = 19.0, 5.0 Hz), 4.63 (s, 1 H), 5.28 (dd, 1H, J = 4.6, 1.5 Hz), 5.58 (d, 1H, J = 13.0 Hz), 5.70 (ddd, 1H, J = 13.0, 5.1, 2.9 Hz), 7.10 (m, 7 H), 7.36 (m, 2 H). ^{13}C NMR: δ 209.2, 164.9, 157.3, 138.1, 135.8, 130.5, 130.0, 129.4, 128.3, 125.5, 123.3, 116.4, 82.3, 68.2, 62.4, 58.7, 41.4, 40.0, 30.1, 28.0, 21.1. IR ($CHCl_3$, cm^{-1}): ν 3328, 1770, 1760. MS (CI), m/z: 406 (M^+ + 1, 100), 405 (M^+, 42). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.36; H, 6.57; N, 3.74.

Bicycle (+)-5f. From 64 mg (0.205 mmol) of Baylis−Hillman adduct **(+)-3f**, 46 mg (53%) of compound **(+)-5f** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate, 4/6). Colorless solid. Mp: 142−143 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +62.3 (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 1.41 (m, 2H), 1.96 (m, 2H), 2.23 (s, 3H), 2.32 (s, 3H), 2.59 (m, 2H), 2.82 (s, 1H), 3.30 (dt, 1H, J = 13.2, 3.4 Hz), 3.64 (td, 1H, J = 13.2, 2.4 Hz), 4.53 (s, 1 H), 4.70 (d, 1H, J = 5.4 Hz), 5.19 (d, 1H, J = 5.4 Hz), 5.65 (d, 1H, J = 11.5 Hz), 5.88 (dt, 1H, J = 11.5, 7.3 Hz), 7.07 (m, 5 H), 7.15 (d, 2H, J = 7.8 Hz), 7.34 (dd, 2H, J = 8.3, 7.3 Hz). ^{13}C NMR: δ 211.1, 167.3, 157.2, 137.8, 135.7, 134.7, 129.9, 129.7, 129.2, 128.1, 123.1, 116.3, 79.6, 70.5, 59.7, 57.9, 43.2, 39.5, 29.7, 26.8, 25.3, 20.9. IR (KBr, cm^{-1}): ν 3421, 1751, 1711. MS (EI), m/z: 420 (M^+ + 1, 34), 419 (M^+, 100). Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.56; H, 7.09; N, 3.24.

General Procedure for the Synthesis of Compounds 6a−c. A solution of the appropriate Baylis−Hillman adduct **3** (0.40 mmol), triphenyltin hydride (0.60 mmol), and AIBN (cat.) in benzene (35 mL) was heated at reflux temperature until complete disappearance of starting material (TLC). The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and vinylstannanes **6a−c** were obtained. The crude product can be purified by flash chromatography on deactivated silica gel using hexanes/ethyl acetate (1:1 containing 1% of triethylamine) as an eluent.

Bicycle (+)-*Z*-6b. From 54 mg (0.172 mmol) of Baylis−Hillman adduct (+)-**3f**, 103 mg (90%) of compound (+)-***Z*-6b** was obtained as a colorless oil. $[\alpha]_D$ = + 25.4 (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ 2.36 (s, 3H), 2.52 (m, 1H), 2.64 (bs, 1H), 2.87 (m, 2H), 3.24 (m, 2H), 3.62 (m, 2H), 4.35 (bs, 1H), 4.36 (d, 1H, J = 4.6 Hz), 5.07 (d, 1H, J = 4.6 Hz), 6.05 (s, 1H), 7.09 (m, 6H), 7.35 (m, 8H), 7.60 (m, 6H). ^{13}C NMR: δ 209.4, 165.4, 157.1, 156.3, 138.2, 136.7, 136.4, 129.6, 129.1, 128.6, 122.7, 115.7, 81.0, 66.6, 58.7, 56.5, 39.2, 37.1, 33.9, 29.5. IR ($CHCl_3$, cm^{-1}): ν 3522, 1771, 1756. MS (EI), m/z: 587 (M^+ - 77, 24), 77 (100). Anal. Calcd for $C_{36}H_{35}NO_4Sn$: C, 65.08; H, 5.31; N, 2.11; Sn, 17.86. Found: C, 65.20; H, 5.39; N, 2.14; Sn, 17.76.

Bicycle (+)-*Z*-6c. From 81 mg (0.1247 mmol) of Baylis−Hillman adduct (+)-**3g**, 134 mg (80%) of compound (+)-***Z*-6c** was obtained as a colorless solid. Colorless solid. Mp: 72−74 °C (hexanes/ethyl acetate). $[\alpha]_D$ = + 88.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ 1.68 and 1.98 (m, each 1H), 2.32 (s, 3H), 2.69 (m, 3H), 2.95 (d, 1H, J = 2.5 Hz), 2.99 (dd, 1H, J = 14.4, 11.0 Hz), 3.22 (td, 1H, J = 10.7, 3.4 Hz), 3.97 (dd, 1H, J = 15.6, 6.8 Hz), 4.43 (d, 1H, J = 9.3 Hz), 4.59 (d, 1H, J = 5.0 Hz), 5.19 (d, 1H, J = 5.0 Hz), 6.35 (s, 1H), 7.09 (m, 3H), 7.37 (m, 11H), 7.56 (m, 6H). ^{13}C NMR: δ 209.5, 165.6, 161.7, 157.1, 138.3, 136.8, 129.8, 129.3, 128.8, 126.0, 123.2, 116.2, 81.8, 71.3, 59.6, 42.7, 41.5, 34.3, 31.1, 30.6. IR ($CHCl_3$, cm^{-1}): ν 3520, 1770, 1755. MS (EI), m/z: 601 (M^+ - 77, 42), 77 (100). Anal. Calcd for $C_{37}H_{37}NO_4Sn$: C, 65.61; H, 5.50; N, 2.06; Sn, 17.50. Found: C, 65.73; H, 5.43; N, 2.10; Sn, 17.42.

General Procedure for the Synthesis of Compounds 6d−f. A solution of the appropriate Baylis−Hillman adduct **3** (0.40 mmol), benzenethiol (0.60 mmol), and AIBN (cat.) in benzene (35 mL) was heated at reflux temperature until complete disappearance of starting material (TLC). The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and after purification by gravity flow chromatography, bicycles **6d−f** were obtained as isomerically pure products.

Reaction of Enyne (+)-*syn*-3e and Benzenethiol. From 130 mg (0.434 mmol) of Baylis−Hillman adduct (+)-*syn*-**3e**, and after chromatography eluting with ethyl acetate/hexanes (3.5:6.5), 47 mg (26%) of the less polar compound (+)-***E*-6d** and 68 mg (39%) of the more polar compound (−)-***Z*-6d** were obtained.

Bicycle (+)-*E*-6d. Colorless solid. Mp: 120−122 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +9.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 2.40 (s, 3H), 2.87 (dd, 1H, J = 14.2, 5.6 Hz), 2.89 (d, 1H, J = 2.4 Hz), 3.05 (dd, 1H, J = 14.2, 5.6 Hz), 3.29 (td, 1H, J = 5.6, 2.4 Hz), 3.82 (d, 1H, J = 13.7 Hz), 4.30 (s, 1 H), 4.34 (dd, 1H, J = 14.1, 1.5 Hz), 4.62 (d, 1H, J = 4.9 Hz), 5.27 (dd, 1H, J = 4.6, 1.5 Hz), 6.31 (s, 1 H), 7.10 (m, 4H), 7.31 (m, 6H). ^{13}C NMR: δ 208.9, 164.8, 156.9, 134.6, 131.4, 129.9, 129.8, 129.2, 127.2, 123.2, 115.9, 80.8, 66.9, 58.9, 54.5, 50.1, 30.4, 28.9. IR (KBr, cm^{-1}): ν 3431, 1747, 1712. MS (CI), m/z: 410 (M^+ + 1, 100), 409 (M^+, 50). Anal. Calcd for $C_{23}H_{23}NSO_4$: C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.57; H, 5.56; N, 3.38; S, 7.90.

Bicycle (−)-*Z*-6d. Colorless solid. Mp: 128−130 °C (hexanes/ethyl acetate). $[\alpha]_D = -190.6$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 2.26 (s, 3H), 2.90 (dd, 1H, J = 14.6, 4.6 Hz), 3.06 (dd, 1H, J = 14.6, 4.1 Hz), 3.11 (bs, 1H) 3.18 (dd, 1H, J = 7.8, 4.4 Hz), 4.16 (dd, 1H, J = 15.6, 1.5 Hz), 4.32 (d, 1H, J = 15.6 Hz), 4.41 (d, 1H, J = 2.9 Hz), 4.52 (dd, 1H, J = 4.9, 1.0 Hz), 5.29 (dd, 1H, J = 4.9, 1.5 Hz), 6.18 (d, 1H, J = 1.0 Hz), 7.11 (m, 3H), 7.32 (m, 7H). ^{13}C NMR: δ 208.2, 165.2, 156.9, 135.1, 132.9, 129.9, 129.4, 129.2, 127.0, 126.2, 123.3, 116.0, 81.0, 66.4, 59.1, 56.2, 43.9, 32.2, 29.2. IR (KBr, cm^{-1}): ν 3436, 1750, 1710. MS (CI), *m*/*z*: 410 (M^+ + 1, 100), 409 (M^+, 42). Anal. Calcd for $C_{23}H_{23}NSO_4$: C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.58; H, 5.78; N, 3.30; S, 7.73.

Reaction of Enyne (+)-3g and Benzenethiol. From 82 mg (0.250 mmol) of Baylis−Hillman adduct (+)-**3g**, and after chromatography eluting with ethyl acetate/hexanes (1:1), 45 mg (45%) of the less polar compound (+)-***E*-6f** and 19 mg (19%) of the more polar compound (+)-***Z*-6f** were obtained.

Bicycle (+)-*E*-6f. Colorless solid. Mp: 114−116 °C (hexanes/ethyl acetate). $[\alpha]_D = +111.6$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.85 (m, 1H), 2.11 (m, 2H), 2.34 (s, 3H), 2.45 (d, 2H, J = 7.6 Hz), 2.87 (m, 1H), 3.03 (bs, 1H), 3.13 (dd, 1H, J = 14.9, 11.0 Hz), 3.22 (m, 1H), 4.23 (dd, 1H, J = 14.9, 5.4 Hz), 4.34 (m, 1H), 4.37 (d, 1H, J = 4.9 Hz), 5.26 (d, 1H, J = 4.9 Hz), 6.26 (s, 1H), 7.07 (t, 1H, J = 7.3 Hz), 7.11 (d, 2H, J = 7.8 Hz), 7.31 (m, 7H). ^{13}C NMR: δ 209.7, 165.7, 157.0, 140.6, 135.4, 129.8, 129.2, 126.9, 123.2, 123.1, 116.2, 82.0, 71.4, 59.3, 52.9, 41.8, 38.2, 31.4, 31.0, 28.0. IR ($CHCl_3$, cm^{-1}): ν 3426, 1740, 1706. MS (CI), *m*/*z*: 438 (M^+ + 1, 100), 437 (M^+, 38). Anal. Calcd for $C_{25}H_{27}NSO_4$: C, 68.63; H, 6.22; N, 3.20; S, 7.33. Found: C, 68.53; H, 6.14; N, 3.12; S, 7.23.

Bicycle (+)-*Z*-6f. Colorless solid. Mp: 124−125 °C (hexanes/ethyl acetate). $[\alpha]_D = +144.1$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.69 (m, 3H), 2.16 (m, 2H), 2.36 (s, 3H), 2.83 (dd, 1H, J = 15.6, 12.3 Hz), 2.92 (bs, 1H), 3.25 (m, 2H), 4.11 (m, 1H), 4.14 (d, 1H, J = 4.9 Hz), 4.38 (d, 1H, J = 9.5 Hz), 5.14 (d, 1H, J = 4.9 Hz), 6.21 (s, 1H), 7.05 (m, 3H), 7.30 (m, 7H). ^{13}C NMR: δ 209.6, 165.9, 156.9, 141.5, 135.6, 129.7, 129.3, 128.5, 126.7, 123.1, 123.0, 116.0, 81.7, 71.0, 59.5, 52.3, 41.3, 33.7, 32.2, 30.7, 29.7. IR ($CHCl_3$, cm^{-1}): ν 3432, 1738, 1708. MS (CI), *m*/*z*: 438 (M^+ + 1, 100), 437 (M^+, 44). Anal. Calcd for $C_{25}H_{27}NSO_4$: C, 68.63; H, 6.22; N, 3.20; S, 7.33. Found: C, 68.76; H, 6.12; N, 3.26; S, 7.41.

Ozonolysis of Phenylthiovinyl Derivatives 6d−f. General Procedure. Ozonolyzed air was bubbled through a solution of the bicycles **6d−f** (0.18 mmol) in dichloromethane (3 mL) at −78 °C for 30 min. Air was then blown through the solution for 10 min, and dimethyl sulfide (112 mg, 1.80 mmol) was added. The reaction was allowed to warm to room temperature, and the solvent was removed under reduced pressure and after purification by flash chromatography, ketones **9a−c** were obtained.

Compound (+)-9b. From 77 mg (0.182 mmol) of phenylthiovinyl derivative **6e**, 40 mg (70%) of compound (+)-**9b** was obtained as a colorless solid after purification by chromatography (ethyl acetate/hexanes, 2/1). Mp: 218−219 °C (hexanes/ethyl acetate). $[\alpha]_D = +50.1$ (*c* 1.0, CH_3COCH_3). ^1H NMR: δ 2.20 (s, 3H), 2.44 (m, 1H), 2.64 (dd, 1H, J = 14.1, 10.7 Hz), 3.05 (m, 1H), 3.86 (m, 4H), 4.72 (m, 2H), 5.35 (d, 1H, J = 4.9 Hz), 5.49 (bs, 1H), 7.07 (m, 3H), 7.34 (m, 2H). ^{13}C NMR: δ 205.8, 190.2, 166.3, 158.4, 130.4, 122.7, 116.1, 81.4, 73.3, 59.8, 55.6, 39.4, 37.0, 34.9, 30.1. IR ($CHCl_3$, cm^{-1}): ν 3442, 1750, 1722, 1710. MS (CI), *m*/*z*: 318 (M^+ + 1, 100), 317 (M^+, 20). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.48; H, 6.13; N, 4.35.

Compound (+)-9c. From 41 mg (0.101 mmol) of phenylthiovinyl derivative **6f**, 17 mg (50%) of compound (+)-**9c** was obtained as a colorless solid after purification by chromatography (ethyl acetate/hexanes, 3/1). Colorless solid. Mp: 113−114 °C (hexanes/ethyl acetate). $[\alpha]_D = +101.4$ (*c* 1.1, $CHCl_3$). ^1H NMR: δ 1.90 (m, 5H), 1.98 (s, 3H), 2.42 (m, 2H), 3.46 (dd, 1H, J = 13.7, 10.3 Hz), 3.65 (m, 1H), 3.78 (dd, 1H, J = 13.2, 7.3 Hz), 3.91 (dd, 1H, J = 7.8, 4.9 Hz), 5.05 (d, 1H, J = 4.9 Hz), 5.19 (t, 1H, J = 6.4 Hz), 7.07 (t, 1H, J = 7.3 Hz), 7.2 (d, 1H, J = 7.8 Hz, PhO), 7.31 (m, 3H, PhO). ^{13}C NMR: δ 205.6, 165.8, 157.3, 129.7, 122.9, 116.7, 114.0, 79.0, 74.7, 55.0, 54.5, 34.1, 32.4, 30.6, 19.8. IR ($CHCl_3$, cm^{-1}): ν 3440, 1750, 1714, 1710. MS (CI), *m*/*z*: 332 (M^+ + 1, 100), 332 (M^+, 20). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.44; H, 6.49; N, 4.21.

Swern Oxidation of Alcohols (+)-5d. Procedure for the Preparation of β-Diketone (−)-10a. A solution of dimethyl sulfoxide (23.1 mg, 0.296 mmol) in dichloromethane (100 μL) was added dropwise to a stirred solution of oxalyl chloride (18.7 mg, 0.147 mmol) in dichloromethane (165 μL) at −78 °C. After 20 min, a solution of the alcohol (+)-**5d** (0.123 mmol) in dichloromethane (300 μL) was added and the mixture was stirred for 3 h at −78 °C. Triethylamine (95 μL) was added at −78 °C, and the mixture was allowed to warm to room temperature. Water (350 μL) was added and the mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave diketone (−)-**10a**.

Compound (−)-10a. From 50 mg (0.123 mmol) of alcohol **(+)-5d**, 35 mg (70%) of diketone **(−)-10a** was obtained as a pale yellow oil after purification by chromatography (ethyl acetate/hexanes, 2/1). $[\alpha]_D = -3.5$ (*c* 0.6, $CHCl_3$). ^1H NMR: δ 2.20 (s, 3H), 2.29 (s, 3H), 2.32 (m, 2H), 2.56 (m, 2H) 3.79 (dd, 1H, J = 19.3, 2.9 Hz), 4.66 (d, 1H, J = 5.1 Hz), 4.68 (dt, 1H, J = 19.5, 2.7 Hz), 5.54 (dd, 1H, J = 7.7, 1.8 Hz), 5.83 (ddd, 1H, J = 12.2, 4.0, 2.7 Hz), 6.16 (ddd, 1H, J = 12.2, 2.7, 1.7 Hz), 7.05 (m, 6H), 7.29 (m, 3H). ^{13}C NMR: δ 203.9, 202.2, 164.5, 156.9, 137.4, 135.7, 129.6, 129.2, 128.0, 126.5, 125.0, 123.1, 116.1, 84.3, 70.2, 65.3, 40.9, 36.3, 30.3, 27.6, 20.9. IR ($CHCl_3$, cm^{-1}): ν 1770, 1760, 1745. MS (CI), *m*/*z*: 404 (M^+ + 1, 100), 403 (M^+, 44). Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.32; H, 6.37; N, 3.55.

Retro-Aldol Reaction of β-Diketone (−)-10a. Procedure for the Preparation of Compound (+)-11a. Hydrazine hydrate (5.1 mg, 0.16 mmol) was added to a stirred solution of diketone (−)-**10a** (58 mg, 0.144 mmol) in tetrahydrofuran (750 μL), and the mixture was refluxed for 4 h. The reaction mixture was allowed to cool to room temperature, then water (400 μL) was added and the mixture was extracted with ethyl acetate (3 × 2 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue gave compound (+)-**11a**.

Compound (+)-11a. From 58 mg (0.144 mmol) of diketone (−)-**10a**, 29 mg (55%) of compound (+)-**11a** was obtained as a colorless oil after purification by chromatography (ethyl acetate/hexanes, 1/1). $[\alpha]_D = +280.3$ (*c* 0.9, $CHCl_3$). ^1H NMR: δ 1.92 (m, 1H), 2.43 (m, 1H), 2.50 (s, 3H), 2.73 (m, 2H) 3.87 (m, 1H), 4.37 (m, 1H), 4.79 (d, 1H, J = 4.9 Hz), 4.96 (dq, 1H, J = 18.5, 2.9 Hz), 5.43 (m, 1H), 5.69 (dd, 1H, J = 4.9, 1.0 Hz), 5.81 (m, 1H), 7.23 (m, 6H), 7.49 (m, 3H). ^{13}C NMR: δ 201.7, 165.2, 156.9, 138.7, 135.4, 129.6, 129.0, 128.2, 127.2, 125.7, 122.9, 115.8, 83.7, 65.2, 47.5, 41.0, 32.8, 31.7, 20.9. IR ($CHCl_3$, cm^{-1}): ν 1768, 1750. MS (EI), *m*/*z*: 362 (M^+ + 1, 18), 361 (M^+, 100). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.31; H, 6.37; N, 3.96.

Acknowledgment. Support for this work by the DGI-MCYT (Project BQU2000−0645) is gratefully acknowledged. C. Aragoncillo thanks the Comunidad Autónoma de Madrid for a fellowship.

Supporting Information Available: Spectroscopic and analytical data for compounds (+)-**1b**, (+)-**1d−g**, (+)-**2b**, (+)-**2d−f**, (+)-**3d**, (+)-**3f**, (+)-**3h**, (+)-*syn*-**3i**, (+)-*anti*-**3i**, (+)-**4a**, (+)-**4g**, (+)-**5c**, (+)-**5e**, (+)-**6a**, (+)-**6e**, and (+)-**9a**, as well as general experimental procedures for compounds **1a−g** and **2a−g**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005715Z