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Lewis Acid-Promoted Intermolecular Carbonyl-ene Reaction of Enantiopure 4-Oxoazetidine-2-carbaldehydes. Rapid Entry to Novel Fused Polycyclic β-Lactams

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Lewis acid-promoted carbonyl-ene reaction of enantiomerically pure 4-oxoazetidine-2-carbaldehydes with various activated alkenes gives 4-[(1′-hydroxy)homoallyl]-β-lactams with a very high level of syn diastereofacial selectivity. The above homoallylic alcohols are used for the diastereoselective preparation of fused bicyclic, tricyclic, and tetracyclic β-lactams of nonconventional structure using tandem one-pot radical addition/cyclization or elimination−intramolecular Diels−Alder sequences. In addition, a novel domino process was discovered, the C4−N1 β-lactam bond breakage/intramolecular Diels−Alder reaction.

Introduction

The Lewis acid-promoted ene reaction of a carbonyl compound (enophile) with an alkene having an allylic hydrogen (an "ene") represents a powerful method for selective carbon−carbon bond formation.[1] Although synthetically very useful, the carbonyl-ene reaction is severely substrate limited and only intramolecular ene reactions[1,2] or intermolecular reactions with either electron-deficient carbonyl compounds[3] or electron-rich olefins[4] have been reported. The use of Lewis acid is crucial to activate the carbonyl group due to the inherent low nucleophilicity of the olefin. Simple aliphatic or aromatic aldehydes are usually unreactive. However, electron-deficient aldehydes such as glyoxylate esters, formaldehyde, chloral, etc. have been successfully used in carbonyl-ene reactions. Among different reported examples, only a very few papers refer to the asymmetric version of this reaction using chiral aminoaldehydes.[5]

The development of new approaches to the stereocontrolled synthesis of β-lactam systems is a subject of great interest in the context of their possible use as biologically active compounds[6] or as versatile chiral building blocks.[7] On the other hand, the chiral β-amino alcohol moiety is present in many biologically important molecules such as dipeptide isosteres and statine and its analogues, and therefore, its stereocontrolled synthesis remains an intensive research area.[8] Our interest in the use of

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(2) See, for instance: (a) Williams, J. T.; Bahia, P. S.; Snaith, J. S. *Org. Lett.* **2002**, *4*, 3727. (b) Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* **2001**, *3*, 4205. (c) Srikrishna, A.; Dinesh, C.; Anebouselvy, K. *Tetrahedron Lett.* **1999**, *40*, 1031. (d) Aggarwal, V. K.; Vennall, G. P.; Davey, P. N.; Newman, Ch. *Tetrahedron Lett.* **1998**, *39*, 1997. (e) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403.

(3) *Glyoxylates:* (a) Gathergood, N.; Jorgensen, K. A. *Chem. Commun.* **1999**, 1869. (b) Nakai, T.; Mikami, K.; Terada, M. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. *Formaldehyde:* (d) Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667. (e) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 464. *Chloral:* (f) Benner, J. P.; Gill, G. B.; Parrot, S. J.; Wallace, B.; Begley, M. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 315. *Fluoral:* (g) Mikami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, *34*, 7591. (h) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85.

(4) (a) Milles, W. H.; Berreth, C. L.; Anderton, C. A. *Tetrahedron Lett.* **1996**, *37*, 7893. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426 and references therein. (c) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 555. (d) Mikami, K.; Loh, T.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 6737. (e) Mikami, K.; Ohmura, H. *Chem. Commun.* **2002**, 2626.

(5) (a) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Synlett* **1998**, 1187. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (c) Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron: Asymmetry* **1990**, *1*, 13. (d) Mikami, K.; Knaeko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909.

(6) See, for example: (a) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (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) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, **1992**.

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(8) See, for example: (a) Enders, D.; Reinhold: U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219. (b) Rich, D. H. Peptidase Inhibitors in *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed; Pergamon Press: Oxford, 1990; Vol. 2, p 391. (c) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. (d) Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976.

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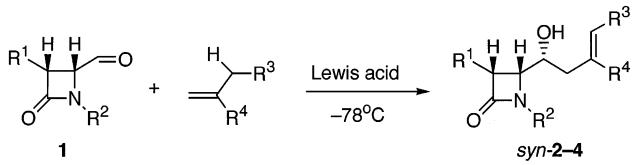
TABLE 1. Lewis Acid-Promoted Intermolecular Carbonyl-ene Reaction of 4-Oxoazetidine-2-carbaldehydes 1 with Olefins[a]



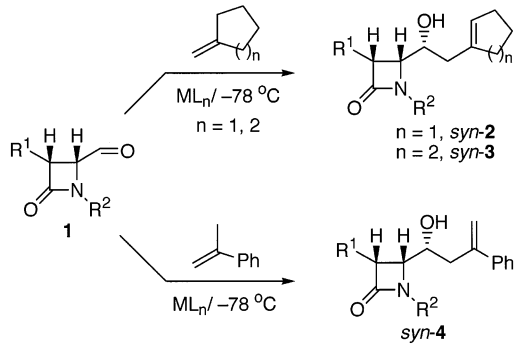
1 *syn*-**2–4**

aldehyde	R^1	R^2	R^3, R^4	Lewis acid	*t* (h)	product[b]	yield (%)[c]
(+)-**1a**	OMe	PMP	$-(CH_2)_3-$	$SnCl_4$	5	(+)-*syn*-**2a**	45
(+)-**1a**	OMe	PMP	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	5	(+)-*syn*-**2a**	65
(+)-**1b**	OPh	PMP	$-(CH_2)_3-$	$SnCl_4$	3	(+)-*syn*-**2b**	60
(+)-**1b**	OPh	PMP	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	3	(+)-*syn*-**2b**	40
(+)-**1c**	OBn	2-propenyl	$-(CH_2)_3-$	$SnCl_4$	3	(+)-*syn*-**2c**	41
(+)-**1c**	OBn	2-propenyl	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	1	(+)-*syn*-**2c**	60
(+)-**1d**	OBn	3-butenyl	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	26	(+)-*syn*-**2d**	61
(+)-**1e**	OMe	2-propynyl	$-(CH_2)_3-$	$SnCl_4$	6	(+)-*syn*-**2e**	40
(+)-**1e**	OMe	2-propynyl	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	6	(+)-*syn*-**2e**	51
(+)-**1f**	OMe	3-butynyl	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	3	(+)-*syn*-**2f**	45
(+)-**1g**	O-allyl	PMP	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	2	(+)-*syn*-**2g**	83[d]
(+)-**1h**	O-propargyl	PMP	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	2	(+)-*syn*-**2h**	85[d]
(−)-**1i**	Pht[e]	3-butenyl	$-(CH_2)_3-$	$BF_3{\cdot}Et_2O$	18	(−)-*syn*-**2i**	51[f]
(+)-**1b**	OPh	PMP	$-(CH_2)_4-$	$SnCl_4$	5	(+)-*syn*-**3a**	70
(+)-**1b**	OPh	PMP	$-(CH_2)_4-$	$BF_3{\cdot}Et_2O$	5	(+)-*syn*-**3a**	33
(+)-**1c**	OBn	2-propenyl	$-(CH_2)_4-$	$SnCl_4$	5	(+)-*syn*-**3b**	37
(+)-**1c**	OBn	2-propenyl	$-(CH_2)_4-$	$BF_3{\cdot}Et_2O$	5	(+)-*syn*-**3b**	15
(+)-**1a**	OMe	PMP	H, Ph	$BF_3{\cdot}Et_2O$	5	(+)-*syn*-**4a**	66
(+)-**1d**	OBn	3-butenyl	H, Ph	$BF_3{\cdot}Et_2O$	26	(+)-*syn*-**4b**	60
(+)-**1e**	OMe	2-propynyl	H, Ph	$BF_3{\cdot}Et_2O$	4	(+)-*syn*-**4c**	64
(+)-**1f**	OMe	3-butynyl	H, Ph	$BF_3{\cdot}Et_2O$	17	(+)-*syn*-**4d**	52
(+)-**1g**	O-allyl	PMP	H, Ph	$BF_3{\cdot}Et_2O$	5	(+)-*syn*-**4e**	42[g]
(+)-**1h**	O-propargyl	PMP	H, Ph	$BF_3{\cdot}Et_2O$	4	(+)-*syn*-**4f**	66[g]
(−)-**1i**	Pht[e]	3-butenyl	H, Ph	$BF_3{\cdot}Et_2O$	26	(−)-*syn*-**4g**	46[f]

[a] All reactions were run at −78 °C in dichloromethane in a molar ratio of aldehyde/alkene/Lewis acid = 1:2:1.2 unless otherwise noted. PMP = 4-methoxyphenyl. [b] Isomer shown was the only product detected in the crude mixture by 300 MHz ^1H NMR spectroscopy. [c] Yields are for pure products purified by column chromatography with correct analytical and spectroscopic data. [d] Reaction was run at −40 °C. [e] Pht = phthalimido. [f] Reaction was run at 0 °C. [g] Reaction was run at −25 °C.

4-oxoazetidine-2-carbaldehydes **1** as substrates for addition reactions and cyclization processes[9] prompted us to evaluate their ene reactions with activated alkenes as a route to unusual, functionalized monocyclic and polycyclic 2-azetidinones.[10] We wish to report here the use of enantiomerically pure 4-oxoazetidine-2-carbaldehydes **1** as novel enophiles for Lewis acid-catalyzed carbonyl-ene reactions, to give β-lactam homoallylic alcohols **2**−**4** with extremely high syn diastereofacial selectivity (Scheme 1), together with further interesting synthetic transformations to structurally novel fused bicyclic, tricyclic, and tetracyclic β-lactams.

SCHEME 1



Results and Discussion

Starting substrates, enantiopure 4-oxoazetidine-2-carbaldehydes **1a**−**i**, were obtained as single cis enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde through Staudinger reaction with the appropriate acid chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[9]

A model reaction of aldehyde (+)-**1a** with methylenecyclopentane in the presence of tin(IV) chloride in dichloromethane at −78 °C for 5 h gave homoallylic alcohol (+)-**2a** in moderate yield and essentially complete syn diastereoselectivity (>99%) (Table 1). This preliminary result encouraged us to screen other Lewis acids for the above reaction for better yield. We were pleased to find that use of $BF_3{\cdot}Et_2O$ under similar conditions also gave (+)-**2a** but with much improved results in terms of yield. The stereochemical outcome of the process is not affected by the different coordinative abilities of the Lewis acid ($BF_3{\cdot}Et_2O$ has only one coordination site). In addition, other tested Lewis acid such as Me_2AlCl, Et_2AlCl, $TiCl_4$, or $Sc(OTf)_3$ were less effective for the ene process, even after longer times.[11] From the above results we focused our attention on $SnCl_4$ and $BF_3.Et_2O$ as catalysts to explore the scope of this process with different enantiopure β-lactam aldehydes **1** and alkenes. All ene reac-

(9) See, for instance: (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (b) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719. (d) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781. (e) Alcaide, B.; Pardo, C.; Sáez, E. *Synlett* **2002**, 85.

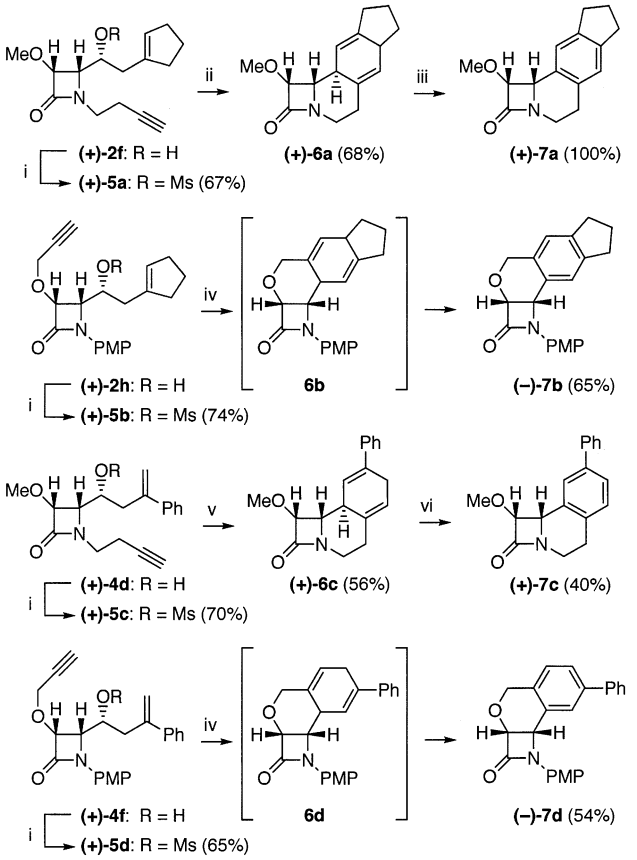
(10) For a recent review on the synthesis and biological properties of polycyclic-β-lactams with nonclassical structures, see: Alcaide, B.; Almendros, P. *Curr. Org. Chem.* **2002**, *6*, 245.

tions afforded syn products **2**−**4** exclusively in moderate to good yields independently of the catalyst used (Table 1). Tin(IV) chloride gave a superior yield for the methylenecyclohexane carbonyl-ene reaction. Interestingly, reactions of aldehydes **1** with α-methylstyrene only occurred in the presence of $BF_3{\cdot}Et_2O$ to furnish products **3** in reasonable yields. α-Methylstyrene was not so prone to afford the carbonyl-ene product under tin(IV) chloride catalysis because a competing event took place, namely, the polymerization of the alkene.[12] Probably, $BF_3{\cdot}Et_2O$ can activate the carbonyl group of 4-oxoazetidine-2-carbaldehydes and effectively scavenge the acidic proton of the ene adduct.

Configuration at the carbinolic chiral center of the above alcohols was established by comparison of the ^{1}H NMR chemical shifts of the (*R*)- and (*S*)-acetylmandelates of compound (+)-**2b**.[13] It should be noted that the observed syn selectivity is even higher than that obtained by us in a related reaction of some compounds **1** with different propenylmetal reagents under Lewis acid catalysis.[14] Moreover, in contrast to our previous report on addition reactions,[15] the stereoselectivity of the ene reaction was not dependent on the bulkiness of substituents on the β-lactam ring. As in previous Lewis acid-promoted reactions with allylmetal reagents, the observed syn diastereoselectivity can be explained by invoking the Felkin−Anh model.[14]

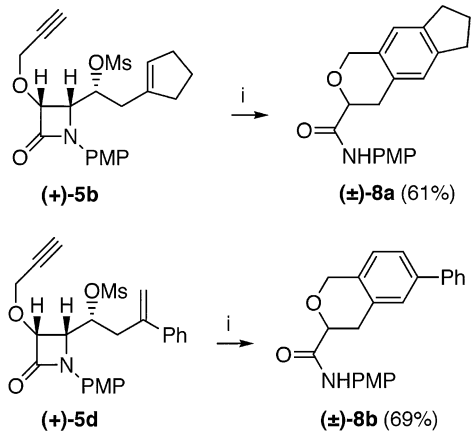
Among different ene products **2**−**4**, enyne derivatives are of particular interest due to their propensity to undergo different cyclization processes using various methodologies involving both radicals and transition metal-catalyzed reactions. Moreover, the presence of the homoallylic alcohol moiety in all these compounds led us to consider alternative cycloaddition methods mainly based on the IMDA reaction. Thus, we turned our attention to the synthesis of fused β-lactams, which may have antibacterial potential because they are novel polycyclic-2-azetidinones with nonclassical structures.[10] Mesylates **5** possessing a pendant alkyne at position 1 or 3 of the β-lactam ring, on heating in a sealed tube with 1.0 equiv of DBU in benzene, afforded the corresponding Diels−Alder cycloadducts **6** in a completely stereoselective fashion.[16] 1,4-Cyclohexadienes **6** are prone to undergo aromatization as illustrated in Scheme 2. In fact, when mesylates (+)-**5b** and (+)-**5d** were heated in the presence

SCHEME 2[a]



[a] Key: (i) MsCl, Et_3N, rt. (ii) DBU, benzene, 190 °C, 96 h. (iii) $CDCl_3$, rt, 24 h. (iv) DBU, benzene, 170 °C, 72 h. (v) DBU, benzene, 140 °C, 44 h. (vi) Pd−C, benzene, 150 °C, 24 h.

SCHEME 3[a]



[a] Key: (i) DBU, benzene, 80 °C, 70 h.

of DBU for a prolonged time, the tetracyclic β-lactams (−)-**7b** and (−)-**7d** containing a benzene ring were the only isolated products in reasonable yields.

Interestingly, the treatment of enantiomerically pure mesylates (+)-**5b** and (+)-**5d** with a slight excess of DBU (1.5 equiv) in benzene at reflux temperature gave rise to unexpected products, the racemic amides (±)-**8a** and (±)-**8b** (Scheme 3). The formation of compounds **8** could be rationalized in terms of an unprecedented domino C4−N1 β-lactam bond breakage/intramolecular Diels−Alder

(11) Recently, $Sc(OTf)_3$ has been reported to be a highly efficient catalyst for reaction of aromatic aldehydes and methylenecyclohexane. See ref 2b.

(12) This is partly because the homoallylic alcohol product (ene adduct) forms a complex with the Lewis acid promoter to generate a strongly acidic proton. This acidic proton migrates intramolecularly to a double bond of the ene adduct or intermolecularly to a starting styrene derivative to produce a labile cationic intermediate, which triggers various side reactions.

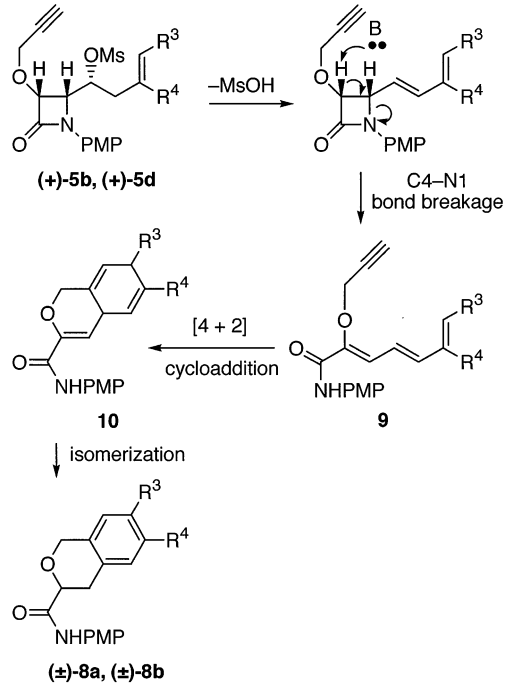
(13) (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovic, J. M.; Balwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (b) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877. (c) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2002**, *67*, 4579.

(14) Alcaide, B.; Almendros, P.; Salgado, N. R. *J. Org. Chem.* **2000**, *65*, 3310.

(15) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **1999**, 1913.

(16) Alternatively, the transformation of ene adducts **2**−**4** into polycyclic 2-azetidinones **6** can be achieved in one pot upon heating in a sealed tube the homoallylic alcohols in the presence of mesyl chloride and DBU.

SCHEME 4



reaction.[9b,17] The driving force of the reaction may be the formation of the highly conjugate trienes **9** under the reaction conditions (excess of base). Amides **8** presumably arise from the isomerization of the initially formed [4 + 2] cycloadducts **10** (Scheme 4). However, it is not clear whether the first step of the domino reaction is the cleavage of the β-lactam ring or the Diels−Alder cycloaddition.

Although construction of medium-sized rings[18] using free radical methodology is difficult to achieve and the synthesis of eight- and nine-membered rings fused to β-lactams has been virtually ignored,[19] we planned to investigate this strategy in ene adducts **4** bearing an extra alkyne tether. The tin-promoted radical cyclization proceeded elegantly in enynes (+)-**4c** and (+)-**4d** to provide the desired nonconventional bicyclic β-lactams **11** as single isomers in moderate yields (Scheme 3). Treatment of vinylic stannane (+)-**11a** with PTSA in CH_2Cl_2 yielded the destannylated eight-membered fused adduct (+)-**12**.

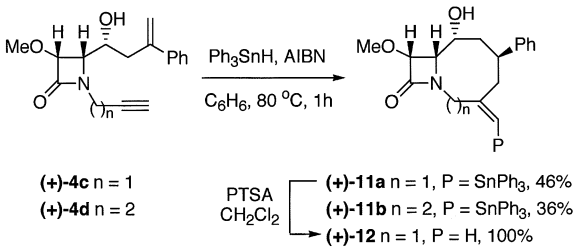
The structure and stereochemistry of compounds **6**, **7**, **11**, and **12** were assigned by NMR studies. The cis stereochemistry of the four-membered ring was set during the cyclization step to form the 2-azetidinone ring,

(17) There is in the literature a precedent, described some time ago in our group, for opening β-lactams in the presence of base by a related mechanism. See: Alcaide, B.; Domínguez, G.; Martín-Domenech, A.; Plumet, J.; Monge, A.; Pérez-García, V. *Heterocycles* **1987**, *26*, 1461.

(18) Synthesis of medium-sized rings, notably eight- and nine-membered ring systems, has usually been hampered by entropic/enthalpic factors and transannular interactions between the methylene groups. For reviews, see: (a) Galli, L.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. In view of these difficulties, the synthesis of these structures still remains a partially unsolved problem. For selected reviews on medium-sized ring preparation, see: (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (d) Molander, G. *Acc. Chem. Res.* **1998**, *31*, 603. (e) Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

(19) Only examples available have been recently reported by us. See ref 15.

SCHEME 5



and it was transferred unaltered during the further synthetic steps. The polycyclic structures (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of fused β-lactams **6**, **7**, **11**, and **12** were established by NMR one- and two-dimensional techniques.[20]

Conclusions

In conclusion, the present study provides the first insight into the manner in which 4-oxoazetidine-2-carbaldehydes and activated alkenes undergo coupling under Lewis acid catalysis. In addition, we have shown that combination of carbonyl-ene reaction and IMDA or radical cyclization is a useful methodology for the preparation of enantiopure fused bicyclic, tricyclic, and tetracyclic β-lactams of nonconventional structure. In addition, a novel domino process, the C4−N1 β-lactam bond breakage/intramolecular Diels−Alder reaction, was discovered.

Experimental Section

General. General experimental data and procedures have been previously reported.[9c,15] NMR spectra were recorded in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are given in parts per million relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). All commercially available compounds were used without further purification.

General Procedure for the Lewis Acid-Promoted Ene Reaction of 4-Oxoazetidine-2-carbaldehydes 1. Synthesis of Homoallylic Alcohol Derivatives 2−4. To a stirred solution of the appropriate aldehyde **1** (1 mmol) and methylenecyclopentane, methylenecyclohexane, or α-methylstyrene (2 mmol) in dry dichloromethane (10 mL) at −78 °C was added $SnCl_4$ or $BF_3{\cdot}OEt_2$ (1.2 mmol) dropwise, and the mixture was stirred at this temperature for the time indicated in Table 1. Saturated aqueous sodium hydrogen carbonate (3 mL) was added, and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure followed by flash chromatography (SiO_2; hexanes/ethyl acetate mixtures) yielded the corresponding ene adducts **2**−**4** in analytically pure form. Spectroscopic and analytical data for some representative pure forms of **2**−**4** follow.[21]

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-(1-cyclopentenyl)-ethyl]-3-methoxy-1-(3-butynyl)-2-azetidinone, (+)-2f. From 157 mg (0.87 mmol) of aldehyde (+)-**1f** was obtained 100 mg (45%) of compound (+)-**2f** as a colorless oil. $[\alpha]_D = +39.6$ (*c* 1.6, $CHCl_3$).

(20) Compounds **6**, **7**, **11**, and **12** showed values of coupling constants and NOE enhancements in good agreement with those reported for analogous systems. See refs 14 and 15.

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

^{1}H NMR: δ 1.88 (m, 2H), 1.99 (t, 1H, J = 2.7 Hz), 2.34 (m, 7H), 2.52 (m, 2H), 3.37 (m, 1H), 3.59 (s, 3H), 3.65 (m, 1H), 3.74 (t, 1H, J = 4.8 Hz), 4.00 (m, 1H), 4.48 (d, 1H, J = 4.8 Hz), 5.52 (br s, 1H). ^{13}C NMR: δ 167.8, 140.0, 127.6, 83.0, 81.0, 70.1, 68.9, 61.0, 59.3, 40.3, 35.9, 35.0, 32.5, 23.3, 17.7. IR ($CHCl_3$, cm^{-1}): ν 3420, 1747. MS (EI), m/z: 264 (M^+ + 1, 7), 263 (M^+, 100). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.51; H, 8.08; N, 5.30.

(3*R*,4*S*)-3-Propargyloxy-4-[(*R*)-1-hydroxy-2-(1-cyclopentenyl)-ethyl]-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-2h. From 111 mg (0.43 mmol) of aldehyde (+)-**1h** was obtained 123 mg (85%) of compound (+)-**2h** as a yellow solid. Mp: 88−89 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +78.6 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 1.87 (m, 2H), 2.31 (m, 6H), 2.36 (d, 1H, J = 3.4 Hz), 2.55 (t, 1H, J = 2.4 Hz), 3.79 (s, 3H), 4.24 (m, 1H), 4.33 (t, 1H, J = 5.0 Hz), 4.52 (m, 2H), 4.96 (d, 1H, J = 5.1 Hz), 5.50 (br s, 1H), 6.86 (m, 2H), 7.44 (m, 2H). ^{13}C NMR: δ 164.7, 156.8, 140.3, 130.8, 127.2, 120.4, 114.1, 79.7, 78.4, 76.0, 69.2, 60.7, 59.0, 55.5, 35.7, 35.0, 32.5, 23.3. IR (KBr, cm^{-1}): ν 3420, 1741. MS (CI), m/z: 342 (M^+ + 1, 100), 341 (M^+, 19). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.28; H, 6.75; N, 4.12.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-(1-cyclohexenyl)-ethyl]-1-(*p*-methoxyphenyl)-3-phenoxy-2-azetidinone, (+)-3a. From 100 mg (0.34 mmol) of aldehyde (+)-**1b** was obtained 93 mg (70%) of compound (+)-**3a** as a colorless solid. Mp: 150−151 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +178.6 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 1.60 (m, 4H), 2.14 (m, 5H), 2.43 (m, 1H), 3.80 (s, 3H), 4.27 (m, 1H), 4.40 (dd, 1H, J = 7.0, 5.3 Hz), 5.38 (d, 1H, J = 5.4 Hz), 5.57 (br s, 1H), 6.88 (m, 2H), 7.11 (m, 3H), 7.35 (m, 2H), 7.56 (m, 2H). ^{13}C NMR: δ 163.7, 157.4, 156.7, 133.5, 130.8, 129.6, 125.6, 122.5, 120.3, 115.8, 113.9, 79.3, 69.2, 61.2, 55.3, 42.6, 28.0, 25.2, 22.7, 22.1. IR (KBr, cm^{-1}): ν 3489, 1757. MS (EI), m/z: 394 (M^+ + 1, 14), 393 (M^+, 100). Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.37; H, 6.89; N, 3.54.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-phenyl-3-butenyl]-3-methoxy-1-(3-butynyl)-2-azetidinone, (+)-4d. From 100 mg (0.55 mmol) of aldehyde (+)-**1f** was obtained 87 mg (52%) of compound (+)-**4d** as a colorless solid. Mp: 91−92 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +2.3 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 1.97 (t, 1H, J = 2.7 Hz), 2.24 (d, 1H, J = 2.9 Hz), 2.52 (m, 3H), 3.03 (ddd, 1H, J = 13.9, 3.4, 1.2 Hz), 3.38 (m, 1H), 3.62 (s, 3H), 3.63 (m, 1H), 3.76 (dd, 1H, J = 6.8, 5.1 Hz), 3.94 (ddd, 1H, J = 12.7, 6.6, 3.2 Hz), 4.47 (d, 1H, J = 4.9 Hz), 5.21 (br s, 1H), 5.52 (d, 1H, J = 1.2 Hz), 7.40 (m, 5H). ^{13}C NMR: δ 167.8, 144.0, 139.5, 128.5, 128.0, 126.0, 115.8, 82.8, 81.1, 70.0, 69.6, 61.0, 59.2, 40.3, 40.0, 17.8. IR (KBr, cm^{-1}): ν 3402, 1743. MS (CI), m/z: 300 (M^+ + 1, 100), 299 (M^+, 16). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.32; H, 7.04; N, 4.65.

(3*R*,4*S*)-3-Propargyloxy-4-[(*R*)-1-hydroxy-3-phenyl-3-butenyl]-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-4f. From 120 mg (0.46 mmol) of aldehyde (+)-**1h** was obtained 116 mg (66%) of compound (+)-**4f** as a colorless oil. $[\alpha]_D$ = +77.6 (c 1.8, $CHCl_3$). ^{1}H NMR: δ 2.25 (d, 1H, J = 3.7 Hz), 2.45 (t, 1H, J = 2.3 Hz), 2.62 (dd, 1H, J = 14.2, 9.3 Hz), 3.04 (dd, 1H, J = 14.2, 3.2 Hz), 3.79 (s, 3H), 4.14 (m, 1H), 4.32 (t, 1H, J = 5.7 Hz), 4.52 (dd, 2H, J = 15.6, 2.4 Hz), 4.92 (d, 1H, J = 5.4 Hz), 5.17 (br s, 1H), 5.45 (d, 1H, J = 1.0 Hz), 6.85 (m, 2H), 7.37 (m, 7H). ^{13}C NMR: δ 164.6, 156.8, 144.4, 139.8, 130.7, 128.4, 127.8, 126.3, 120.6, 115.8, 114.1, 79.8, 78.4, 76.0, 69.5, 60.9, 58.9, 55.4, 39.6. IR ($CHCl_3$, cm^{-1}): ν 3306, 1747. MS (CI), m/z: 378 (M^+ + 1, 100), 377 (M^+, 9). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.30; H, 6.11; N, 3.74.

General Procedure for the Preparation of Methanesulfonates (+)-5a−d. Methanesulfonyl chloride (138 mg, 1.20 mmol) and triethylamine (243 mg, 2.40 mmol) were sequentially added dropwise to a stirred solution of the corresponding homoallylic alcohol (1.0 mmol), in dichloromethane (10 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The organic phase was washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure methanesulfonates **5**. Spectroscopic and analytical data for some representative pure forms of **5** follow.

Methanesulfonate of (3*R*,4*S*)-4-[(*R*)-1-Hydroxy-2-(1-cyclopentenyl)-ethyl]-3-methoxy-1-(3-butynyl)-2-azetidinone, (+)-5a. From 37 mg (0.14 mmol) of alcohol (+)-**2f** was obtained 33 mg (67%) of compound (+)-**5a** as a colorless oil. $[\alpha]_D$ = +42.7 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 1.90 (m, 2H), 1.99 (t, 1H, J = 2.7 Hz), 2.37 (m, 8H), 3.00 (s, 3H), 3.38 (dt, 1H, J = 14.2, 6.2 Hz), 3.58 (s, 3H), 3.75 (m, 1H), 4.02 (dd, 1H, J = 8.0, 5.1 Hz), 4.52 (d, 1H, J = 5.1 Hz), 5.06 (ddd, 1H, J = 8.0, 6.6, 4.3 Hz), 5.55 (br s, 1H). ^{13}C NMR: δ 167.6, 138.5, 129.1, 82.7, 81.0, 80.7, 70.4, 59.2, 58.4, 39.7, 39.3, 35.2, 34.3, 32.4, 23.4, 17.2. IR ($CHCl_3$, cm^{-1}): ν 1749. MS (CI), m/z: 342 (M^+ + 1, 100), 343 (M^+, 11). Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10. Found: C, 56.38; H, 6.76; N, 4.06.

Methanesulfonate of (3*R*,4*S*)-3-Propargyloxy-4-[(*R*)-1-hydroxy-3-phenyl-3-butenyl]-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-5d. From 116 mg (0.31 mmol) of aldehyde (+)-**4f** was obtained 91 mg (65%) of compound (+)-**5d** as a colorless oil. $[\alpha]_D$ = +49.1 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 2.48 (t, 1H, J = 2.4 Hz), 2.57 (s, 3H), 3.10 (ddd, 1H, J = 15.1, 4.6, 1.0 Hz), 3.22 (dd, 1H, J = 15.1, 6.9 Hz), 3.80 (s, 3H), 4.46 (m, 3H), 4.90 (d, 1H, J = 5.4 Hz), 5.15 (dt, 2H, J = 6.9, 4.6 Hz), 5.27 (d, 1H, J = 1.0 Hz), 5.51 (d, 1H, J = 1.2 Hz), 6.87 (m, 2H), 7.33 (m, 7H). ^{13}C NMR: δ 164.0, 157.0, 142.4, 139.5, 129.9, 128.6, 127.9, 126.3, 119.8, 117.8, 114.4, 79.9, 79.6, 78.1, 76.2, 58.8, 57.7, 55.5, 38.0, 37.1. IR ($CHCl_3$, cm^{-1}): ν 1748. MS (EI), m/z: 456 (M^+ + 1, 15), 455 (M^+, 100). Anal. Calcd for $C_{24}H_{25}NSO_6$: C, 63.28; H, 5.53; N, 3.07. Found: C, 63.36; H, 5.56; N, 3.05.

General Procedure for the Preparation of Diels−Alder Cycloadducts 6 or Trycycles 7. DBU (1.50 mmol) was added dropwise to a solution of the corresponding methanesulfonate **5** (1.0 mmol) and hydroquinone (cat.) in benzene (10 mL). The resulting solution was heated in a sealed tube at the appropriate temperature (140−190 °C). The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with dichloromethane/ethyl acetate/hexanes mixtures gave analytically pure adducts **6** or **7**.

Cycloadduct (+)-6a. From 31 mg (0.09 mmol) of methanesulfonate (+)-**5a** and after heating at 190 °C for 96 h was obtained 15 mg (68%) of compound (+)-**6a** as a colorless oil. $[\alpha]_D$ = +44.2 (c 0.5, $CHCl_3$). ^{1}H NMR: δ 1.71 (m, 2H), 2.18 (m, 5H), 2.85 (m, 5H), 3.14 (dd, 1H, J = 9.5, 3.9 Hz), 3.61 (s, 3H), 3.88 (m, 1H), 4.58 (dd, 1H, J = 3.9, 1.2 Hz), 5.19 (br s, 1H), 5.76 (br s, 1H). ^{13}C NMR: δ 166.8, 143.6, 132.0, 125.0, 114.6, 85.1, 59.4, 59.2, 40.8, 39.0, 36.9, 33.6, 32.5, 29.0, 21.9. IR ($CHCl_3$, cm^{-1}): ν 1751. MS (ES), m/z: 269 (M^+ + 23, 22), 246 (M^+ + 1, 100), 245 (M^+, 11). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.53; H, 7.78; N, 5.69.

Tricyclic β-Lactam (−)-7b. From 52 mg (0.12 mmol) of methanesulfonate (+)-**5b** and after heating at 170 °C for 22 h was obtained 26 mg (65%) of compound (−)-**7b** as a colorless oil. $[\alpha]_D$ = −174.9 (c 1.0, $CHCl_3$). ^{1}H NMR: δ 2.09 (m, 2H), 2.92 (m, 4H), 3.76 (s, 3H), 4.71 and 4.87 (d, each 1H, J = 14.2 Hz), 5.13 (d, 1H, J = 4.9 Hz), 5.32 (d, 1H, J = 4.9 Hz), 6.85 (m, 2H), 7.07 (s, 1H), 7.41 (s, 1H), 7.49 (m, 2H). ^{13}C NMR: δ 164.6, 156.6, 145.4, 144.0, 134.0, 130.7, 127.6, 127.0, 122.5, 119.1, 114.3, 80.4, 66.2, 55.5, 54.6, 32.7, 32.6, 25.3. IR ($CHCl_3$, cm^{-1}): ν 1748. MS (CI), m/z: 322 (M^+ + 1, 100), 321 (M^+, 11). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.63; H, 6.00; N, 4.33.

Tricyclic β-Lactam (−)-7d. From 52 mg (0.11 mmol) of methanesulfonate (+)-**5d** and after heating at 170 °C for 22 h was obtained 22 mg (54%) of compound (−)-**7d** as a colorless oil. $[\alpha]_D$ = −267.7 (c 0.5, $CHCl_3$). ^{1}H NMR: δ 3.76 (s, 3H), 4.82 and 4.95 (d, each 1H, J = 14.2 Hz), 5.23 (d, 1H, J = 4.9 Hz), 5.41 (d, 1H, J = 5.1 Hz), 6.85 (m, 2H), 7.30 (d, 1H, J = 8.1 Hz), 7.52 (m, 8H), 7.75 (d, 1H, J = 1.9 Hz). ^{13}C NMR: δ 164.4,

157.0, 142.1, 141.6, 141.1, 135.1, 130.6, 129.8, 129.0, 127.7, 127.2, 127.0, 119.1, 114.5, 80.6, 65.7, 55.5, 54.3. IR ($CHCl_3$, cm^{-1}): ν 1743. MS (CI), *m*/*z*: 358 ($M^+ + 1$, 100), 357 (M^+, 9). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.40; H, 5.33; N, 3.90.

Preparation of Tricyclic β-Lactam (+)-7c. Pd−C (cat.) was added to a solution of the Diels−Alder cycloadduct (+)-**6c** (20 mg, 0.08 mmol) in benzene (6 mL). The resulting suspension was heated in a sealed tube at 150 °C for 24 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with 7/0.5/7 hexane/ethyl acetate/dichloromethane gave 8 mg (40%) of analytically pure adduct (+)-**7c**.

Tricyclic β-Lactam (+)-7c. $[\alpha]_D = +63.0$ (*c* 0.4, $CHCl_3$). ^1H NMR: δ 2.76 (m, 1H), 3.11 (m, 2H), 3.51 (s, 3H), 4.12 (m, 1H), 4.83 (d, 1H, $J = 4.2$ Hz), 4.86 (d, 1H, $J = 4.4$ Hz) 7.42 (m, 8H). ^{13}C NMR: δ 169.1, 149.9, 140.7, 133.5, 131.1, 130.2, 128.8, 127.3, 127.0, 126.2, 126.1, 85.3, 58.9, 54.2, 37.0, 29.7. IR ($CHCl_3$, cm^{-1}): ν 1745. MS (CI), *m*/*z*: 358 ($M^+ + 1$, 100), 357 (M^+, 9). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.50; H, 6.16; N, 4.99.

General Procedure for the Synthesis of Bicyclic Amides 8. DBU (1.50 mmol) was added dropwise to a solution of the corresponding methanesulfonate (1.0 mmol) in benzene (10 mL). The resulting solution was heated under reflux for 70 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with hexane/ethyl acetate mixtures gave analytically pure amides **8**.

Bicyclic Amide (±)-8a. From 50 mg (0.11 mmol) of methanesulfonate (+)-**5b** was obtained 24 mg (61%) of bicycle (±)-**8a** as a colorless solid. Mp: 180−181 °C (hexane/ethyl acetate). ^1H NMR: δ 2.08 (m, 2H), 2.89 (m, 4H), 2.98 (dd, 1H, $J = 16.3$, 11.2 Hz), 3.26 (dd, 1H, $J = 16.3$, 3.9 Hz), 3.81 (s, 3H), 4.29 (dd, 1H, $J = 11.2$, 3.9 Hz), 4.90 (d, 1H, $J = 15.4$ Hz), 5.00 (d, 1H, $J = 14.7$ Hz), 6.89 (m, 3H), 7.07 (s, 1H), 7.54 (m, 2H), 8.38 (br s, 1H). ^{13}C NMR: δ 169.2, 156.6, 143.4, 142.8, 131.2, 130.6, 130.1, 124.9, 121.5, 120.0, 114.3, 74.8, 68.7, 55.6, 32.6, 31.4, 25.7. IR (KBr, cm^{-1}): ν 3320, 1665. MS (CI), *m*/*z*: 324 ($M^+ + 1$, 100), 323 (M^+, 10). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.38; H, 6.58; N, 4.31.

General Procedure for the Synthesis of Vinylic Stannanes 11. A solution of the appropriate enyne **4** (0.40 mmol), triphenyltin hydride (0.60 mmol), and AIBN (cat.) in benzene (35 mL) was heated at reflux temperature until complete disappearance (typically 1 h) of starting material (TLC). The reaction mixture was allowed to cool to room temperature; the solvent was removed under reduced pressure, and vinylstannanes **11** were obtained after purification by flash chromatography on silica gel using hexane/ethyl acetate/triethylamine mixtures.

Bicyclic β-Lactam (+)-11a. From 50 mg (0.17 mmol) of ene adduct (+)-**4c** was obtained 50 mg (46%) of compound (+)-**11a** as a colorless oil. $[\alpha]_D = +69.5$ (*c* 2.0, $CHCl_3$). ^1H NMR: δ 1.84 (dd, 1H, $J = 14.4$, 7.2 Hz), 2.28 (dd, 1H, $J = 14.4$, 6.6 Hz), 2.65 (t, 1H, $J = 13.2$ Hz), 2.85 (d, 1H, $J = 13.5$ Hz), 2.91 (d, 1H, $J = 5.0$ Hz), 3.17 (s, 1H), 3.25 (d, 1H, $J = 5.0$ Hz), 3.37 (s, 3H), 3.51 (m, 1H), 3.91 (d, 1H, $J = 5.7$ Hz), 3.97 (d, 1H, $J = 12.9$ Hz), 4.03 (d, 1H, $J = 12.9$ Hz), 6.50 (br s, 1H), 7.28 (m, 5H), 7.45 (m, 15H). ^{13}C NMR: δ 166.7, 153.0, 148.5, 137.4, 136.7, 131.1, 129.1, 128.8, 128.4, 126.8, 125.7, 81.7, 66.5, 60.3, 59.2, 51.0, 47.8, 39.4, 34.5. IR ($CHCl_3$, cm^{-1}): ν 1749. MS (EI), *m*/*z*: 636 (M^+, 7), 560 ($M^+ - 76$, 100). Anal. Calcd for $C_{35}H_{35}NO_3Sn$: C, 66.06; H, 5.54; N, 2.20. Found: C, 66.76; H, 5.58; N, 2.18.

Preparation of Bicyclic β-Lactam (+)-12. To a solution of adduct (+)-**11a** (37 mg, 0.06 mmol) in dichloromethane (5 mL) was added solid *p*-TsOH·H_2O (14 mg, 0.07 mmol) in a single portion. The resulting clear solution was stirred at room temperature for 3 h and then neutralized with solid $NaHCO_3$. The mixture was washed with water (2 × 3 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Chromatography of the residue eluting with hexane/ethyl acetate (2:1) gave 16 mg (100%) of analytically pure bicycle (+)-**12**.

Bicyclic β-Lactam (+)-12. $[\alpha]_D = +72.5$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.83 (dd, 1H, $J = 14.7$, 7.8 Hz), 2.32 (dd, 1H, $J = 14.7$, 6.9 Hz), 2.50 (m, 2H), 3.26 (s, 1H), 3.49 (m, 1H), 3.65 (s, 3H), 3.77 (dd, 1H, $J = 5.1$, 1.3 Hz), 3.87 (d, 1H, $J = 12.7$ Hz), 4.01 (d, 1H, $J = 12.7$ Hz), 4.12 (d, 1H, $J = 5.5$ Hz), 4.52 (d, 1H, $J = 5.5$ Hz), 5.08 (br s, 1H), 5.24 (br s, 1H), 7.27 (m, 5H). ^{13}C NMR: δ 167.0, 148.7, 140.6, 128.5, 126.8, 125.9, 119.7, 83.1, 66.6, 59.9, 59.5, 45.8, 45.5, 40.0, 34.9. IR ($CHCl_3$, cm^{-1}): ν 1748. MS (EI), *m*/*z*: 287 (M^+, 1), 87 (100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.16; H, 7.31; N, 4.85.

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Supporting Information Available: Compound characterization data for isomerically pure compounds (+)-**2a**−**e**, (+)-**2g**, (−)-**2i**, (+)-**3b**, (+)-**4a**−**c**, (+)-**4e**, (−)-**4g**, (+)-**5b**, (+)-**5c**, (+)-**6c**, (+)-**7a**, (±)-**8b**, (+)-**11b**, and (*R*)- and (*S*)-acetylmandelates of compound (+)-**2b**, as well as experimental procedures for (*R*)- and (*S*)-acetylmandelates of compound (+)-**2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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