Stereoselective Allylation of 4-Oxoazetidine-2-carbaldehydes. Application to the Stereocontrolled Synthesis of Fused Tricyclic β-Lactams via Intramolecular Diels−Alder Reaction of 2-Azetidinone-Tethered Trienes†

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Allylation reactions of racemic and optically pure 4-oxoazetidine-2-carbaldehydes were investigated both under anhydrous conditions and in aqueous media. Different Lewis acid or metal mediators showed varied diastereoselectivities on product formation during allylation reactions of the above aldehydes with allyltrimethylsilane, allyltributylstannane, or allyl bromide. Under standard reaction conditions, tin(IV) chloride-promoted addition of allyltrimethylsilane to 4-oxoazetidine-2-carbaldehydes provided the highest diastereoselectivity and the best yield. Boron trifluoride−diethyl ether-promoted reaction of allyltributylstannane provided slightly lower diastereoselectivity with the same facial preference. Indium-promoted allylation showed a reverse diastereofacial preference, although the observed selectivity is not synthetically useful. The mesylates of these homoallylic alcohols were used for the stereoselective preparation of *cis*-4-butadienyl-2-azetidinones. Interestingly, mesylates having an extra alkene or alkyne tether at position 1 or 3 of the β-lactam ring, on heating in a sealed tube with equimolecular amounts of DBU in toluene, yielded fused tricyclic 2-azetidinones through a tandem one-pot elimination−intramolecular Diels−Alder reaction.

Introduction

The reactions of propenylmetal reagents with chiral carbonyl compounds are of great interest in the context of acyclic diastereoselective synthesis.[1] Lewis acid-promoted addition of allylsilanes and allylstannanes to carbonyl compounds is now a well-established methodology and an important synthetic tool.[2] Although many investigations have been made in this field into various types of chiral α-substituted aldehydes, no information is available regarding the stereochemistry of reactions involving 4-oxoazetidine-2-carbaldehydes with allylmetals. There are a limited number of reports on the use of β-lactams as chiral building blocks for the allylation reaction, just Bose and Paquette having recently reported the allylindation of 2,3-azetidinediones in aqueous tetrahydrofuran.[3] On the other hand, the Diels−Alder reaction has been developed to provide a valuable vehicle for asymmetric synthesis. An attractive feature of this reaction resides in the possibility, in principle, of generating up to four contiguous stereocenters in one step. The intramolecular version (IMDA) is a powerful method for the construction of bicyclic and polycyclic systems.[4] At the outset of the present study,[5] it was known that racemic *trans*-3-butadienyl-2-azetidinones react with some dienophiles on heating,[6] but there is no report involving IMDA reaction of 2-azetidinone-tethered trienes.

The importance and structural diversity of biologically active β-lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted 2-azetidinones with attendant control of functional groups and stereochemistry. In addition, the increased resistance of bacteria to classical antibiotics has

† Dedicated to Prof. Jose L. Soto on the occasion of his 70th birthday.

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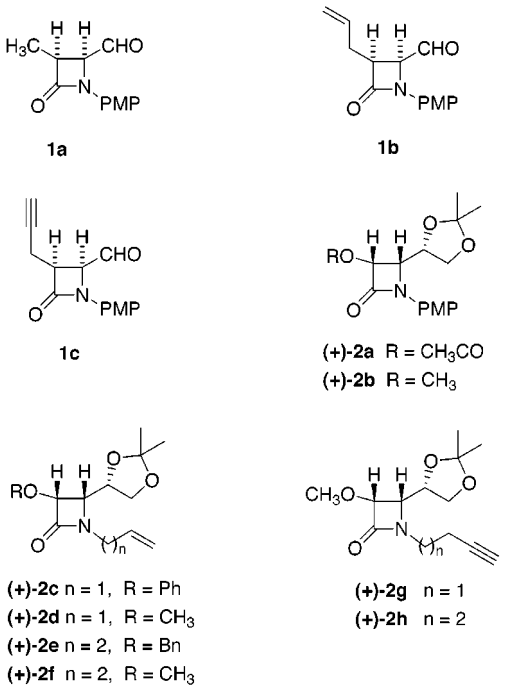
triggered a renewed interest in the building of new polycyclic systems having the 2-azetidinone ring as a common feature.[7] Recently, trinem antibiotics have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to β-lactamases, and stability to renal dehydropeptidases.[8] As a result of their impressive biological activity, polycyclic β-lactams have become interesting targets for synthesis.[9] Continuing with our work on the synthesis and synthetic applications of chiral, functionalized 2-azetidinones,[10] we now report full details of a straightforward synthesis of different types of fused tricyclic β-lactams which involves the use of both stereoselective allylation of β-lactam aldehydes and IMDA reaction. In addition, a study on the stereoselectivity of reactions between 4-oxoazetidine-2-carbaldehydes and allylic organometallics is also described.

Results and Discussion

The starting substrates, 4-oxoazetidine-2-carbaldehydes **1**, were prepared both in racemic and in optically pure forms using standard methodology. Racemic compounds **1a**−**c** were obtained as single *cis*-diastereoisomers, following our one-pot method from *N*,*N*-di(*p*-methoxyphenyl)glyoxal diimine.[10d,11] Enantiomerically pure 2-azetidinones (+)-**2a**−**h** 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 (Chart 1).[12] Transesterification of 3-acetoxy-2-azetidinone (+)-**2a** with sodium methoxide in methanol gave alcohol (+)-**3**, which

Chart 1



by treatment either with allyl bromide or methyl propiolate, under different basic conditions, gave the 2-azetidinones (+)-**4** and (+)-**5**, respectively (Scheme 1). Standard acetonide hydrolysis to provide diols **6**, followed by oxidative cleavage ($NaIO_4/CH_2Cl_2/NaHCO_3$),[13] smoothly formed 4-oxoazetidine-2-carbaldehydes (+)-**1d**−**j** in excellent yields (Scheme 2). Compound (+)-**2d** required further manipulation to obtain the desired 4-oxoazetidine-2-carbaldehydes (+)-**1k** and (+)-**1l** (see later; Schemes 4, 6).

First, we studied the allylation reactions of 4-oxoazetidine-2-carbaldehyde **1a** with some propenylmetal reagents derived from a number of metallic elements (e.g., Bi, In, Mg, Si, Sn, and Zn). Chemical yields were generally good in all cases, but the diastereoselectivity of the process was a function of the nature of both the allylmetal reagent and the Lewis acid (Table 1).

The results in Table 1 crearly show that tin(IV) chloride-promoted reaction of allyltrimethylsilane (Table 1, entry 1) and boron trifluoride−diethyl ether-promoted reaction of allyltributylstannane (Table 1, entry 3) are the best methods for the stereoselective addition to

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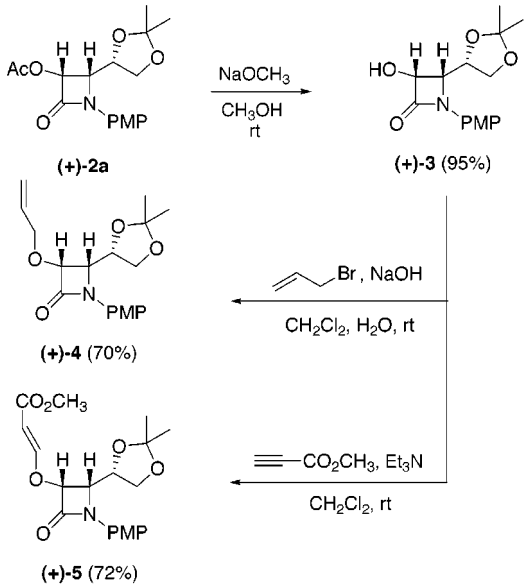
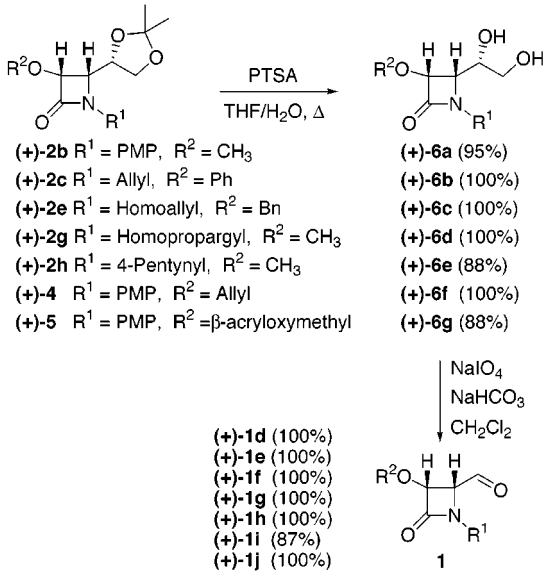
(13) The system ($NaIO_4/CH_2Cl_2/NaHCO_3$) is more convenient that our previously reported method involving the reagent ($NaIO_4$/MeOH/H_2O), avoiding the formation of a diastereomeric mixture of methoxy hemiacetals, which requires an azeotropic distillation using a Dean−Stark apparatus to give the free aldehyde.

Scheme 1

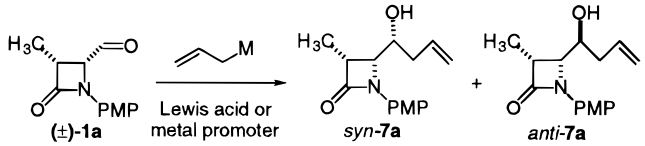


Scheme 2



4-oxoazetidine-2-carbaldehyde **1a**. Boron trifluoride−diethyl ether-promoted reaction of allyltributylstannane provided slightly lower diastereoselectivity with the same facial preference. Reaction with allyltin trichloride[14] (Table 1, entry 2) or allylzinc bromide[15] (Table 1, entry 6) further lowered the diastereoselectivity. Allylation with allyl bromide using the bimetal system magnesium/bismuth trichloride[16] (Table 1, entry 4) or tin(II) chloride[17] (Table 1, entry 7) as the mediators provided a low diastereoselectivity. With allylindium reagent in aqueous medium,[18] the diastereofacial preference is reversed,[19] although the observed selectivity is not synthetically useful (Table 1, entry 5). From these results, we chose the inexpensive, nontoxic allyltrimethylsilane rather than its counterpart, allyltributylstannane, for allylation in our study with different substituted 4-oxoazetidine-2-carbaldehydes **1**. Reaction of 4-oxoazetidine-2-carbaldehydes **1** with allyltrimethylsilane in the presence of tin(IV) chloride, at −78 °C for 45 min, gave homoallylic alcohols **7** with good to excellent *syn*-stereoselectivities (de 80−100%, by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification) (Table 2). Additionally, ketones were found to be completely unreactive under these conditions, and it was possible to chemoselectively add allyltrimethylsilane to 4-oxoazetidine-2-carbaldehyde (+)-**1k** bearing an α,β-unsaturated ketone. None of the allylated ketone was obtained, giving exclusively the product (+)-**7k** by stereoselective addition to the aldehyde moiety (see Scheme 4). Configuration at the carbinolic chiral center of the major isomers for products (+)-**7d** and (+)-**7i** was established by comparison of the ^{1}H NMR chemical shifts of their acetylmandelates (+)-**8d**, (+)-**9d** and (+)-**8i**, (+)-**9i**[20] and was assumed to be the same for the rest of the β-lactams **7**. It should be noted that the relative ^{1}H NMR chemical shifts of the β-lactamic and alcoholic protons were diagnostic for the **7**-*syn*- and **7**-*anti*-homoallylic alcohols for the relative stereochemistry. For any pair of *syn*- and *anti*-diastereomers, the β-lactamic (3-H) and alcoholic hydrogens of the **7**-*syn*-isomers were ca. 0.1 ppm

Table 1. Effect of Organometallic Reagents on the Stereoselective Allylation of 4-Oxazetidine-2-carbaldehyde 1a[a]



entry	M	Lewis acid or metal	*T* (°C)/*t* (h)	solvent	*syn*:*anti* ratio[b]	yield (%)[c]
1	$SiMe_3$	$SnCl_4$	−78/0.75	CH_2Cl_2	92:8	79
2	$SnCl_3$		−78/1	CH_2Cl_2	75:25	80
3	$SnBu_3$	$BF_3.Et_2O$	−78/1	CH_2Cl_2	91:9	75
4	Br	$Mg/BiCl_3$	20/18	THF/H_2O	72:28	50
5	Br	In	20/5	THF/H_2O	46:54	75
6	ZnBr		−78/3	THF	62:38	73
7	Br	$NaI/SnCl_2$	20/20	DMF	61:39	51

[a] All reactions were carried out on a 1 mmol scale. PMP = 4-$MeOC_6H_4$. [b] The ratio based on ^{1}H NMR. [c] Yield of pure, isolated product with correct analytical and spectral data.

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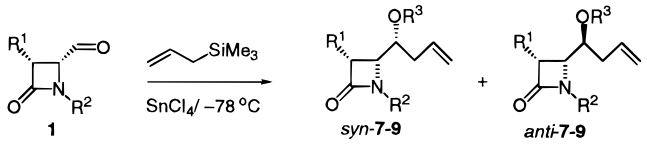
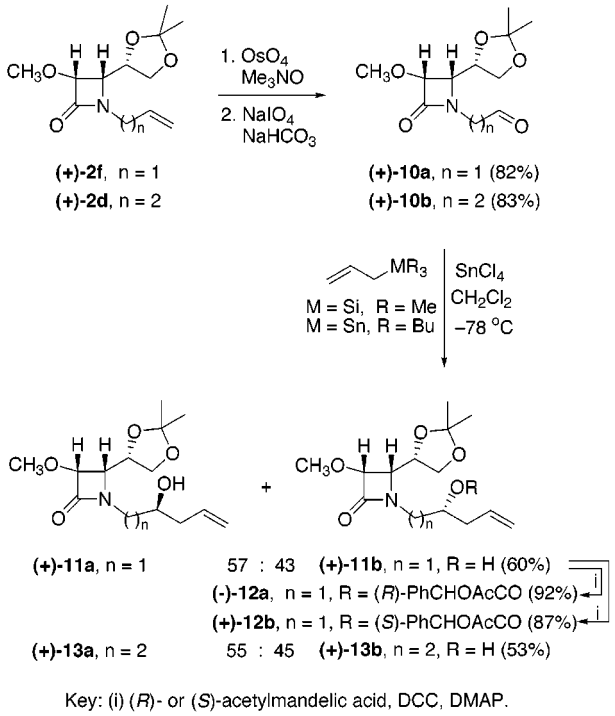
Table 2. Tin(IV) Chloride-Mediated Allylation of 4-Oxoazetidine-2-carbaldehydes 1 with Allyltrimethylsilane



entry	product	R^1	R^2	R^3	*syn:anti* ratio	yield (%)[a]
1	(±)-**7a**	CH_3	PMP[b]	H	92:8	79
2	(±)-**7b**	allyl	PMP	H	100:0	60
3	(±)-**7c**	propargyl	PMP	H	95:5	66
4	(+)-**7d**	OCH_3	PMP	H	90:10	85
5	(+)-**8d**	OCH_3	PMP	(*R*)-PhCH(OAc)CO		88[c]
6	(+)-**9d**	OCH_3	PMP	(*S*)-PhCH(OAc)CO		79[c]
7	(+)-**7e**	OPh	allyl	H	90:10	57
8	(+)-**7f**	OBn	homoallyl	H	100:0	54
9	(+)-**7g**	OCH_3	homopropargyl	H	95:5	83
10	(+)-**7h**	OCH_3	4-pentynyl	H	95:5	71
11	(+)-**7i**	*O*-allyl	PMP	H	95:5	71
12	(+)-**8i**	*O*-allyl	PMP	(*R*)-PhCH(OAc)CO		77[c]
13	(+)-**9i**	*O*-allyl	PMP	(*S*)-PhCH(OAc)CO		68[c]
14	(+)-**7j**	*O*-(*β*-acryloxymethyl)	PMP	H	93:7	55
15	(+)-**7k**	OCH_3	2-oxo-3-pentenyl	H	100:0	50
16	(+)-**7l**	OCH_3	2,4-pentadienyl	H	100:0	74

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] PMP = 4-$MeOC_6H_4$. [c] Yield refers to the *O*-acetylmandelate (**8** or **9**) starting from the corresponding alcohol **7**.

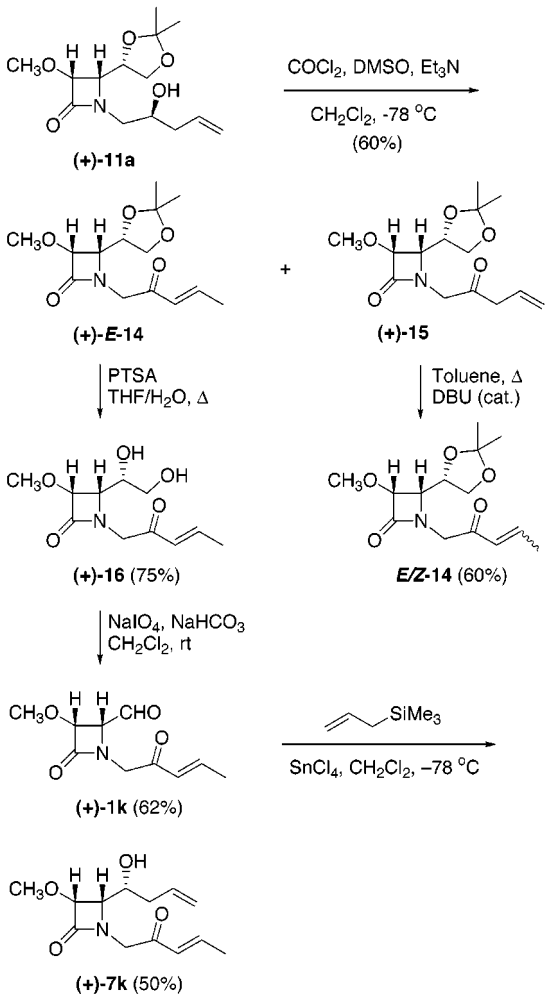
Scheme 3



Key: (i) (*R*)- or (*S*)-acetylmandelic acid, DCC, DMAP.

upfield of the analogous hydrogens of the **7**-*anti*-isomers. The stereochemical result can be tentatively interpreted by the transition state model as proposed by Felkin et al.[21] and modified by Anh (see Figure 1).[22] This model neglects the coordinating action of M^+ and stresses nonbonding interactions of approaching atoms. In our case it could explain that the stereochemical sense of the process is not affected by the Lewis acid or by the different coordinative abilities of the substituents at C3 in the *β*-lactam ring.

Scheme 4



In contrast to the stereoselectivity observed in allylation with 4-oxoazetidine-2-carbaldehydes **1**, aldehydes (+)-**10a** and (+)-**10b** were found to react with propenylmetal reagents with useless stereoselectivity (Scheme 3).

(21) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199.
(22) Anh, N. *Top. Curr. Chem.* **1980**, *88*, 114.

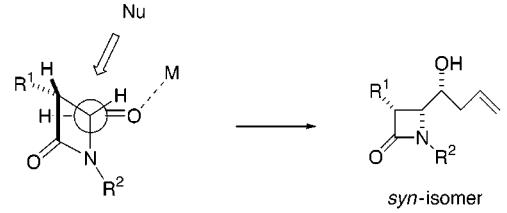


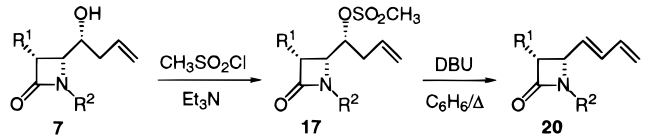
Figure 1.

The diastereomeric alcohols (+)-**11a** and (+)-**11b** could be separated by bench chromatography. The absolute configuration of the minor alkenol (+)-**11b** was assigned by comparison of the ^{1}H NMR chemical shifts of its (*R*)- and (*S*)-acetylmandelates (−)-**12a** and (+)-**12b**. Products (+)-**13a** and (+)-**13b** could not be separated and were characterized as mixture (Scheme 3). Swern oxidation of homoallylic alcohol (+)-**11a** or (+)-**11b**, generated from aldehyde (+)-**10a** and allyltrimethylsilane, gave an equimolecular mixture of α,*β*- and *β*,*γ*-unsaturated ketones (+)-***E*-14** and (+)-**15**. Exposure of *β*,*γ*-unsaturated ketone (+)-**15** to an excess of triethylamine was not efficient to promote isomerization to (+)-***E*-14**.[23] However, treatment of ketone (+)-**15** with a catalytic DBU in toluene at reflux temperature resulted in complete conversion to the α,*β*-unsaturated ketone **14**, but as a mixture of *E*/*Z* isomers (60:40). To our delight, Swern oxidation of homoallylic alcohols (+)-**11a** and (+)-**11b**, generated from the aldehyde (+)-**10a** and allyltin trichloride, provided the α,*β*-unsaturated ketone (+)-***E*-14** as the only product. This difference in behavior to Swern conditions of alcohols (+)-**11**, generated from either allyltrimethylsilane or allyltributylstannane, may be due to the very small amount of tin compounds that may still remain after chromatographic purification on homoallylic alcohols (+)-**11**, working as a catalyst for the isomerization.[24] Product (+)-***E*-14** after acidic treatment gave dihydroxyketone (+)-**16**, which was cleaved using sodium periodate to give keto aldehyde (+)-**1k**. This aldehyde was chemo- and stereoselectively allylated, yielding the homoallylic alcohol (+)-**7k** (Scheme 4).

Next, we investigated the dehydration of hydroxy-*β*-lactams **7**, **11**, and **13** to give 4-butadienyl, 1-pentadienyl, and 1-hexadienyl derivatives **20**, **21**, and **22**, respectively (Table 3 and Scheme 5). Compounds **7**, **11**, and **13** were transformed, in very good yields, into mesylates **17**, **18**, and **19** by treatment with mesyl chloride and Et_3N. Finally, mesylates **17**, **18**, and **19** stereoselectively gave the novel conjugated dienes **20**, **21**, and **22** by gentle heating in benzene or toluene in the presence of DBU. The *trans*-geometry of the internal double bond in these compounds was consistent with vinylic coupling constants of ca. 16.5 Hz in their ^{1}H NMR spectra.

Elimination of mesylate (+)-**18** gave the 1,3-diene (−)-**21** as a major product, which was easily separated by flash chromatography from a minor 1,4-diene (+)-**23**. Conjugation of the new double bond with the lone pair of the nitrogen atom is believed to promote the formation of (+)-**23**. However, in the case of (+)-**19**, 1,3-diene (+)-**22** was the only product from the elimination (Scheme 5).

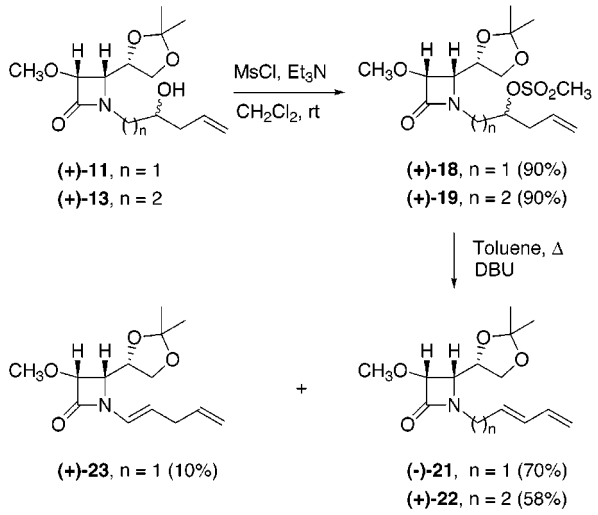
Table 3. Stereoselective Preparation of Mesylates 17 and Conjugated Dienes 20



entry	product	R^1	R^2	ratio *E*:*Z*	yield (%)[a]
1	(±)-**17a**	CH_3	PMP[b]		97
2	(±)-**17b**	allyl	PMP		82
3	(±)-**17c**	propargyl	PMP		83
4	(+)-**17d**	*O*-allyl	PMP		92
5	(+)-**17e**	OPh	allyl		79
6	(+)-**17f**	OBn	homoallyl		89
7	(+)-**17g**	OCH_3	homopropargyl		88
8	(+)-**17h**	OCH_3	4-pentynyl		83
9	(±)-**20a**	CH_3	PMP	100:0	75
10	(±)-**20b**	allyl	PMP	75:25	74
11	(±)-**20c**	propargyl	PMP	100:0	58
12	(+)-**20d**	*O*-allyl	PMP	100:0	89
13	(+)-**20e**	OPh	allyl	90:10	66
14	(+)-**20f**	OBn	homoallyl	95:5	66
15	(+)-**20g**	OCH_3	homopropargyl	95:5	71
16	(+)-**20h**	OCH_3	4-pentynyl	95:5	92

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] PMP = 4-$MeOC_6H_4$.

Scheme 5



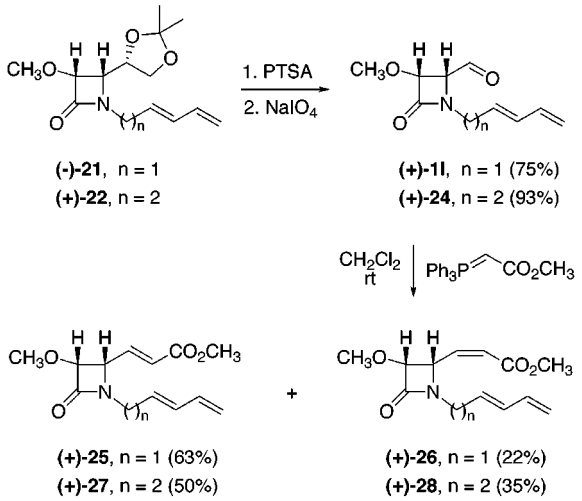
This methodology for the preparation of chiral dienes is superior in yield and stereoselectivity to Wittig reaction between the semistabilized allylidenetriphenylphosphorane and chiral aldehydes.[25] In fact, when allylidenetriphenylphosphorane, generated from allyltriphenylphosphonium bromide and BuLi in THF, was allowed to react with 4-oxoazetidine-2-carbaldehyde **1a**, the diene **20a** was obtained in a 10% overall yield and low *E*/*Z* selectivity (isomeric ratio 60:40). Reaction between stabilized carboxymethylentriphenylphosphorane and 4-oxoazetidine-2-carbaldehyde (+)-**1l** gave two major products, which were separated and identified as the isomeric products (+)-**25** and (+)-**26**. A similar result was obtained when the aldehyde (+)-**24** was used instead of (+)-**1l**, giving olefins (+)-**27** and (+)-**28**. Trienes (+)-**25** and (+)-**27** showed a *trans*-geometry on the new double bonds

(23) For a similar transformation, see: Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170.

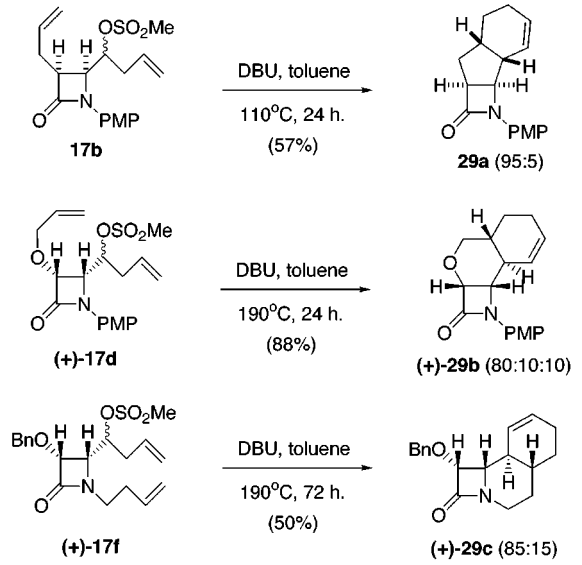
(24) This experiment was carried out several times on a 1 mmol scale, reproducing the same result every single attempt.

(25) (a) Lubineau, A.; Augé, J.; Lubin, N. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3011. (b) Maryanoff, B. E.; Reitz B. A. *Chem. Rev.* **1989**, *89*, 863.

Scheme 6



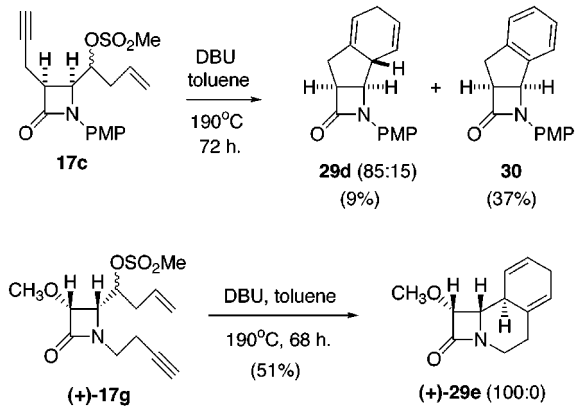
Scheme 7



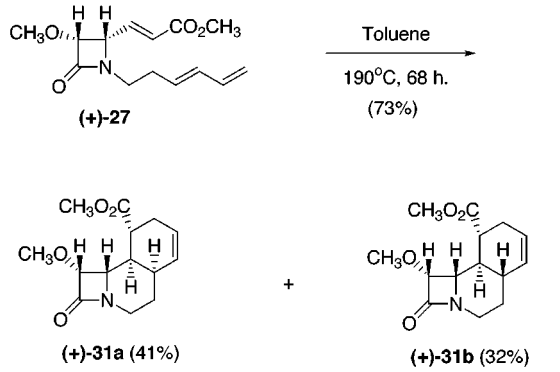
(vinylic coupling constants of ca. 16.0 Hz in their ^{1}H NMR spectra) (Scheme 6).

Interestingly, mesylates **17** having an extra alkene or alkyne tether at position 1 or 3 of the β-lactam ring, on heating in a sealed tube with 1 equiv of DBU in toluene, yielded the corresponding Diels−Alder cycloadducts **29**. These adducts were obtained in good yields (50−88%) with reasonable levels of stereoselectivity (Schemes 7 and 8; only major isomers for adducts **29** are represented). Thus, for example, adduct **29e** was obtained as a single diastereomer, and the tricycle **29a** accounted for an excellent (95%) yield of the products formed. This stereoselectivity is not affected significantly by the nature of the substituents on the β-lactam ring. When mesylate **17c** was heated in the presence of DBU, product **30** was obtained as a major component, along with a minor Diels−Alder cycloadduct **29d** (dr = 85:15) (Scheme 8). Tricycle **30** presumably arises from the aromatization of the initially formed adduct **29d**. Cycloadducts were characterized as mixtures of diastereomers, except for **29e** (obtained as a single diastereomer) and **29a**, which could be separated by flash chromatography. By contrast, treatment of some dienes **20** with Lewis acids (Et_2AlCl, $SnCl_4$, and ZnI_2) under different experimental conditions

Scheme 8



Scheme 9

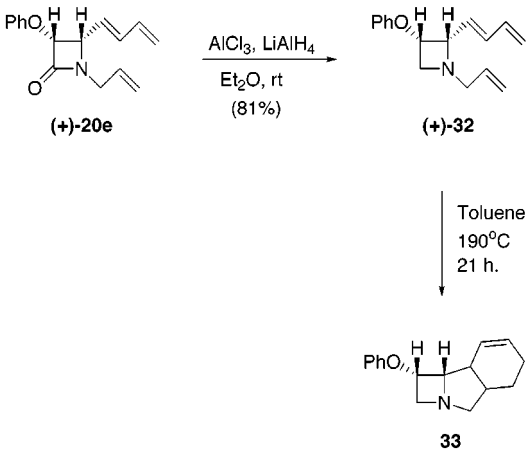


failed to give the corresponding IMDA compounds, unreacted starting material being recovered in all cases.

Triene (+)-**27** was heated in a sealed tube in toluene at 190 °C to give a mixture of cycloadducts (+)-**31a** and (+)-**31b** in good yield (73%) with modest stereoselectivity (65:35) in favor of the epimer (+)-**31a**. Both isomers (+)-**31a** and (+)-**31b** could be separated by flash chromatography (Scheme 9). Exposure of trienes (+)-**20e** and (+)-**25** to standard Diels−Alder conditions afforded none of the desired adducts. The results above show that the IMDA reaction is a simple and, most of the time, an efficient entry to different tricyclic 2-azetidinones with a five- or six-membered ring fused to the β-lactam nucleus. Exceptions are those monocyclic 2-azetidinone-tethered trienes having an *N*-allyl moiety. The sharp contrast in reactivity between (+)-**20e** and (+)-**20f** or (+)-**25** and (+)-**27** may have its origin in the instability of the 2-azetidinone ring with a pyramidalized lactam nitrogen.[26] Transition states leading to fused tricyclic β-lactams from 2-azetidinone-tethered trienes are expected to have highly pyramidalized β-lactam nitrogens. To confirm that this effect was responsible for the failure of compounds (+)-**20e** and (+)-**25** to form cyclized derivatives, azetidine (+)-**32** was prepared. The planarity of the

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

Scheme 10



amide nitrogen, imposed by the amide resonance, is excluded in azetidines.[27] Azetidine (+)-**32** was smoothly obtained by reduction of *β*-lactam (+)-**20e** with monochloroalane (AlH_2Cl), generated in situ from $LiAlH_4/AlCl_3$, following the procedure reported by Ojima.[28] The reaction was instantaneous at room temperature, and the stereochemistry of the starting monolactam remained unaltered during the process. Azetidine (+)-**32** was further heated in a sealed tube in toluene at 190 °C for 21 h to give a mixture of tricyclic azetidines **33**, analyzed by the ^{1}H NMR spectrum of the crude reaction mixture. Unfortunately these cycloadducts could not be fully characterized because of their instability to chromatographic conditions applied (Scheme 10).

The stereochemical outcome of the IMDA reactions in 2-azetidinone-tethered trienes producing compounds **29**−**31** may be explained through the transition states depicted in Scheme 11. In all cases the sense of diastereoselectivity seems to be controlled by the C4 stereogenic center in the *β*-lactam ring.

Configurational Assignment for Tricyclic Systems. The structure and stereochemistry of compounds **29** and **31** 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, and it was transferred unaltered during the further synthetic steps. Compounds **29a** and **29d** showed values of coupling constant $J_{2,3}$ in good agreement with those reported for analogous systems.[29,30] Thus, an *anti*-relative disposition between H2 and H3 was assigned for compounds **29a** and **29d** with a $J_{2,3} = 0$ Hz. Furthermore, NOE irradiation of H2 on compound **29a** resulted in 2% enhancement of the signal corresponding to H3, which is in agreement with the proposed *anti*-stereochemistry

Scheme 11

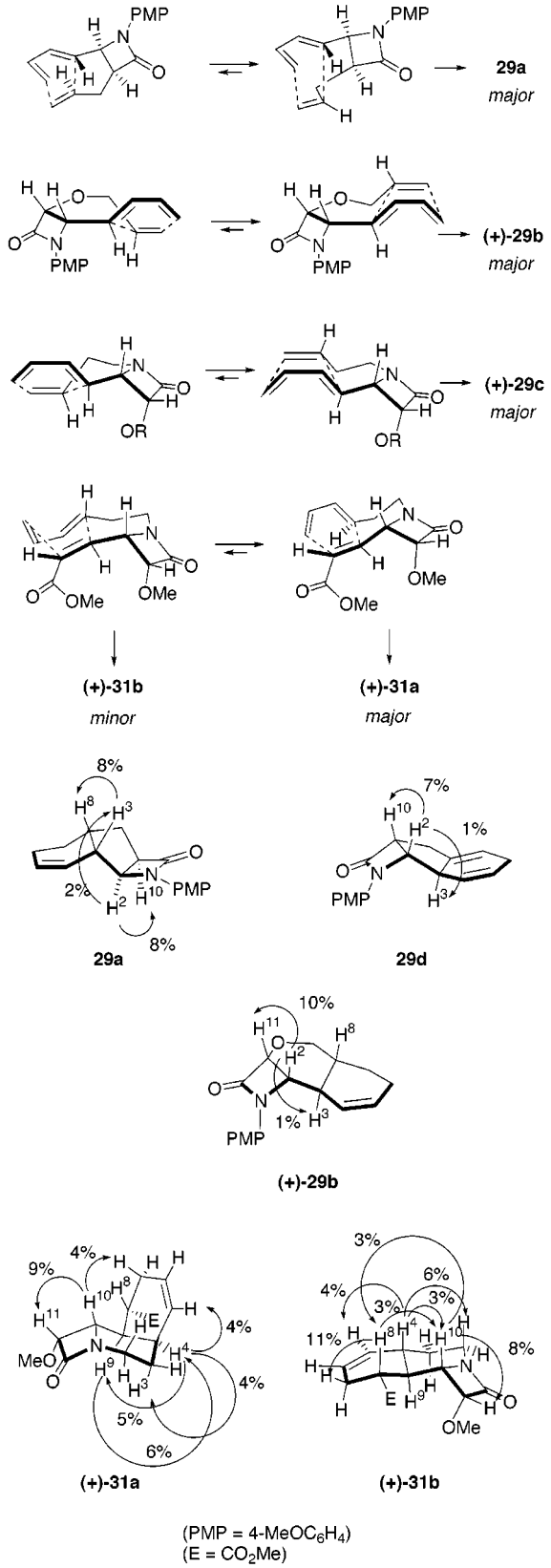


Figure 2. Selected NOE effects and stereochemistry of fused tricyclic *β*-lactams **29a**, (+)-**29b**, **29d**, (+)-**31a**, and (+)-**31b**.

(Figure 2), while irradiation of H3 resulted in an 8% enhancement of the signal corresponding to H8. Thus, a *syn*-stereochemistry was established for this moiety. Irradiation of H2 on compound **29d** gave an NOE

(27) Reviews on the synthesis and chemistry of azetidines: (a) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*, Padwa, A., Eds.; Elsevier: Oxford, U.K., 1996; Vol 1B, Chapter 1.18, p 507. (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds—Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 3, p 1. (c) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331.

(28) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263.

(29) For clarity through this work, tricyclic 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 carbonyl group (for 2-azetidinones).

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

enhancement of 1% on H3, being assigned an *anti*-relative disposition between H2 and H3.

Azetidinones **29b**,**c**,**e** and **31a**,**b** have a six-membered ring fused to the β-lactam. The absence of NOE enhancement was observed on H2 and H8 for compound **29b** upon irradiation of H3. NOE enhancement lower than 1% was observed on H3 when H2 was irradiated, which is consistent with an *anti* H2−H3/*anti* H3−H8 stereochemistry. NOE irradiation on H9 of compound **29c** resulted in values lower than 1% enhancements on the signals corresponding to H4 and H10. The value of $J_{9,10} = 10.3$ Hz, typical for *trans*-diaxial disposition, and the absence of NOE enhancement on H9 upon irradiation of H10 ensure an *anti* H4−H9/*anti* H9−H10 stereochemistry. The *anti* H9−H10 stereochemistry for compound **29e** was obvious on the basis of the value of $J_{9,10} = 9.8$ Hz and the absence of NOE enhancement on H9 upon irradiation of H10. The assignment of the stereochemistry for compounds **31a**,**b** was deduced by comparison with the above results. Thus, values of $J_{9,10} = 9.6$ and 10.2 Hz for compounds **31a** and **31b**, respectively, ensure an *anti* H9−H10 stereochemistry. The absence of NOE enhancements on H8 for compound **31a** upon irradiation of H9 and on H9 for compound **31b** on irradiating the signal corresponding to H8 is in good agreement with an *anti*-relative disposition between H8 and H9. The absence of NOE enhancement on H9 upon irradiation of H4 for compound **31b** and a NOE enhancement of 6% on H4 upon irradiation of H9 for compound **31a** showed that compounds **31a** and **31b** are epimers at C4 (Figure 2).

Conclusions

The present study provides the first insight into the manner in which 4-oxoazetidine-2-carbaldehydes and a variety of allylmetal reagents undergo coupling in both anhydrous and aqueous environments. Tin(IV) chloride-promoted reaction of allyltrimethylsilane and boron trifluoride−diethyl ether-promoted addition of allyltributylstannane, both in anhydrous conditions, are the best methods for the stereoselective addition to 4-oxoazetidine-2-carbaldehydes. These results show that both the allylation of β-lactam aldehydes and tandem elimination/intramolecular Diels−Alder reaction are highly diastereoselective processes which can be used for the functionalization of monocyclic 2-azetidinones and for the preparation of fused tricyclic 2-azetidinones from simple monocyclic precursors. Furthermore, as far as we know, these are the first examples of stereoselective allylation of 4-oxoazetidine-2-carbaldehydes, as well as the first intramolecular Diels−Alder reaction of 2-azetidinone-tethered trienes. Other aspects of this chemistry are under investigation.

Experimental Section

General Procedures. General experimental data and procedures have been previously reported.[10b] NMR spectra were recorded in $CDCl_3$ solutions, except as otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 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. The following chemicals were prepared according to literature procedures: 3-butenamine,[31] 3-butynamine,[32] *N*,*N*-di(*p*-methoxyphenyl)diimine,[33] 2,3-*O*-(isopropylidene)-D-glyceraldehyde.[34] 4-Pentynamine was prepared following the procedure of Taylor for 3-butynamine.[32]

Tin(IV) Chloride-Promoted Reactions between Allyltrimethylsilane and 4-Oxoazetidine-2-carbaldehydes. General Procedure for the Synthesis of Homoallylics Alcohols 7a−l, 11a,b, and 13a,b. A solution of the corresponding aldehyde (1.0 mmol) in dichloromethane (3.5 mL) was added dropwise to a stirred solution of tin(IV) chloride (1.0 mmol) in dichloromethane (5 mL) at −78 °C. After 5 min, allyltrimethylsilane (1.5 mmol) was added, and the mixture was stirred for 45 min at −78 °C. Saturated aqueous sodium hydrogen carbonate (10 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, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave analytically pure compounds. Spectroscopic and analytical data for some representative pure forms of **7** follow.[35]

(3*SR*,4*SR*)-4-[(*RS*)-1-Hydroxy-3-butenyl]-3-methyl-1-(*p*-methoxyphenyl)-2-azetidinone, 7a. From 219 mg (1 mmol) of aldehyde **1a**, 206 mg (79%) of compound **7a** was obtained as a white solid. Mp: 107−108 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 1.28 (dd, 3H, J = 7.5, 2.0 Hz), 1.92 (d, 1H, J = 4.5 Hz), 2.17 and 2.31 (m, each 1H), 3.33 (m, 1H), 3.70 (s, 3H), 3.89 (m, 1H), 4.08 (qd, 1H, J = 7.7, 5.8 Hz), 5.09 (dd, 1H, J = 8.8, 1.5 Hz), 5.13 (s, 1H), 5.79 (m, 1H), 6.77 and 7.37 (dt, each 2H, J = 8.8, 2.5 Hz). ^{13}C NMR: δ 169.0, 156.3, 133.5, 131.4, 120.5, 118.9, 114.0, 71.3, 58.6, 55.5, 45.6, 39.5, 9.5. IR (KBr, cm^{-1}): ν 3330, 1718. MS (EI), *m*/*z*: 262 (M^+ + 1, 21), 261 (M^+, 100), 163 (78). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.97; H, 7.30; N, 5.37.

(3*SR*,4*SR*)-4-[(*RS*)-1-Hydroxy-3-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propenyl)-2-azetidinone, 7b. From 245 mg (1 mmol) of aldehyde **1b**, 172 mg (60%) of compound **7b** was obtained as a white solid. Mp: 85−86 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 1.87 (d, 1H, J = 5.4 Hz), 2.25 and 2.42 (m, each 1H), 2.65 (m, 2H), 3.46 (m, 1H), 3.79 (s, 3H), 4.00 (m, 1H), 4.23 (t, 1H, J = 5.5 Hz), 5.14 (dq, 2H, J = 17.0, 1.5 Hz), 5.15 and 5.20 (d, each 1H, J = 1.5 Hz), 5.82 (m, 1H), 5.97 (m, 1H), 6.87 and 7.40 (dd, each 2H, J = 9.0, 2.5 Hz). ^{13}C NMR: δ 168.0, 156.5, 135.6, 133.7, 131.2, 120.7, 118.8, 116.5, 114.1, 70.3, 58.5, 55.5, 50.3, 40.1, 29.1. IR (KBr, cm^{-1}): ν 3335, 1707. MS (EI), *m*/*z*: 288 (M^+ + 1, 22), 287 (M^+, 100), 189 (44). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.07; H, 7.35; N, 4.87.

(3*SR*,4*SR*)-4-[(*RS*)-1-Hydroxy-3-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propynyl)-2-azetidinone, 7c. From 243 mg (1 mmol) of aldehyde **1c**, 199 mg (66%) of compound **7c** was obtained as a pale green solid. Mp: 83−84 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 1.95 (d, 1H, J = 4.1 Hz), 2.14 (t, 1H, J = 2.6 Hz), 2.35 and 2.56 (m, each 1H), 2.81 (dd, 1H, J = 4.7, 2.6 Hz), 2.86 (dd, 1H, J = 9.9, 2.6 Hz), 3.62 (q, 1H, J = 5.1 Hz), 3.85 (s, 3H), 4.28 (m, 1H), 4.36 (dd, 1H, J = 5.5, 4.2 Hz), 5.22 (m, 2H), 5.89 (m, 1H), 6.93 and 7.44 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 166.3, 156.7, 133.7, 130.9, 121.0, 118.9, 114.2, 81.4, 70.3, 69.6, 58.3, 55.5, 50.0, 40.5, 14.6. IR (KBr, cm^{-1}): ν 3300, 1741. MS (EI), *m*/*z*: 286 (M^+ + 1, 24), 285 (M^+, 100). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.55; H, 6.70; N, 4.95.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butenyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-7d. From 236 mg (1 mmol) of aldehyde (+)-**1d**, 236 mg (85%) of compound (+)-**7d** was obtained as a colorless oil. $[\alpha]_D = +150.4$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 2.40 (m, 2H), 2.66 (d, 1H, J = 3.9 Hz), 3.76 (s,

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3H), 3.87 (s, 3H), 4.16 (m, 1H), 4.38 (t, 1H, J = 4.8 Hz), 4.71 (d, 1H, J = 5.1 Hz), 5.18 (dd, 1H, J = 8.5, 1.5 Hz), 5.23 (s, 1H), 5.94 (m, 1H), 6.95 and 7.49 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 165.1, 156.8, 134.4, 130.7, 120.5, 118.0, 114.2, 82.7, 70.4, 60.1, 59.7, 55.5, 38.3. IR (KBr, cm^{-1}): ν 3489, 1736. MS (EI), *m*/*z*: 278 (M^+ + 1, 11), 277 (M^+, 58), 149 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.02; H, 6.90; N, 5.03.

(3*R*,4*S*)-3-Benzyloxy-1-(3-butenyl)-4-[(*R*)-1-hydroxy-3-butenyl]-2-azetidinone, (+)-7f. From 259 mg (1 mmol) of aldehyde (+)-**1f**, 163 mg (54%) of compound (+)-**7f** was obtained as a colorless oil. $[\alpha]_D$ = +57.1 (*c* 1.5, CH_2Cl_2). ^{1}H NMR: δ 2.33 (m, 4H), 2.48 (d, 1H, J = 3.0 Hz), 3.22 and 3.63 (dd, each 1H, J = 14.0, 7.0 Hz), 3.67 (dd, 1H, J = 8.0, 5.1 Hz), 3.90 (m, 1H), 4.61 (d, 1H, J = 5.1 Hz), 4.68 and 4.95 (d, each 1H, J = 11.7 Hz), 5.10 (m, 4H), 5.77 (m, 2H), 7.33 (m, 5H). ^{13}C NMR: δ 167.8, 136.8, 134.9, 134.0, 128.6, 128.2, 127.9, 118.5, 117.1, 80.6, 73.2, 70.1, 60.0, 40.9, 38.8, 31.8. IR ($CHCl_3$, cm^{-1}): ν 3480, 1735. MS (EI), *m*/*z*: 302 (M^+ + 1, 3), 301 (M^+, 7), 91 (100). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.70; H, 7.71; N, 4.70.

(3*R*,4*S*)-1-(3-Butynyl)-4-[(*R*)-1-hydroxy-3-butenyl]-3-methoxy-2-azetidinone, (+)-7g. From 181 mg (1 mmol) of aldehyde (+)-**1 g**, 185 mg (83%) of compound (+)-**7 g** was obtained as a colorless oil. $[\alpha]_D$ = +62.3 (*c* 2.5, CH_2Cl_2). ^{1}H NMR: δ 1.98 (t, 1H, J = 2.7 Hz), 2.49 (d, 1H, J = 3.2 Hz), 2.50 (dt, 2H, J = 7.0, 2.7 Hz), 3.33 (ddd, 1H, J = 13.7, 13.0, 6.6 Hz), 3.57 (s, 3H), 3.66 (td, 1H, J = 13.7, 13.0, 7.0 Hz), 3.76 (dd, 1H, J = 5.6, 4.9 Hz), 3.88 (m, 1H), 4.46 (d, 1H, J = 4.9 Hz), 5.15 (m, 2H), 5.81 (m, 1H). ^{13}C NMR: δ 167.7, 133.8, 118.4, 82.9, 80.9, 70.1, 70.0, 60.6, 59.2, 40.2, 38.5, 17.7. IR ($CHCl_3$, cm^{-1}): ν 3430, 3290, 1740. MS (EI), *m*/*z*: 224 (M^+ + 1, 20), 223 (M^+, 100). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.43; H, 7.77; N, 6.17.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propenyloxy)-2-azetidinone, (+)-7i. From 261 mg (1 mmol) of aldehyde (+)-**1i**, 215 mg (71%) of compound (+)-**7i** was obtained as a pale green solid. Mp: 76−77 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +135.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 2.27 (m, 2H), 2.54 (d, 1H, J = 3.8 Hz), 3.72 (s, 3H), 4.05 (m, 1H), 4.18 (dd, 1H, J = 5.1, 4.4 Hz), 4.19 (ddt, 1H, J = 12.9, 6.6, 1.5 Hz), 4.39 (ddt, 1H, J = 12.9, 5.1, 1.5 Hz), 4.71 (d, 1H, J = 5.3 Hz), 5.03 (dd, 1H, J = 8.5, 1.5 Hz), 5.08 (d, 1H, J = 0.8 Hz), 5.22 (dq, 1H, J = 9.0, 1.5 Hz), 5.29 (dq, 1H, J = 17.2, 1.5 Hz), 5.83 (m, 2H), 6.80 and 7.33 (dd, each 2H, J = 8.8, 2.5 Hz). ^{13}C NMR: δ 165.2, 156.8, 134.4, 133.1, 130.7, 120.5, 118.5, 118.0, 114.2, 80.5, 72.7, 70.5, 60.2, 55.5, 38.3. IR (KBr, cm^{-1}): ν 3300, 1716. MS (EI), *m*/*z*: 304 (M^+ + 1, 14), 303 (M^+, 64), 149 (100). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.32; H, 7.00; N, 4.61.

(3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butenyl]-3-methoxy-1-(2-oxo-3-pentenyl)-2-azetidinone, (+)-7k. From 211 mg (1 mmol) of compound (+)-**1k**, 127 mg (50%) of compound (+)-**7k** was obtained as a colorless oil. $[\alpha]_D$ = +75.0 (*c* 3.8, CH_2Cl_2). ^{1}H NMR: δ 1.92 (dd, 3H, J = 6.9, 1.5 Hz), 2.14 and 2.30 (m, each 1H), 2.73 (d, 1H, J = 3.0 Hz), 3.60 (s, 3H), 3.91 (m, 2H), 4.26 and 4.47 (d, each 1H, J = 18.5 Hz), 4.59 (d, 1H, J = 4.9 Hz), 5.07 (m, 1H), 5.15 (s, 1H), 5.82 (m, 1H), 6.13 (dq, 1H, J = 15.9, 1.7 Hz), 6.95 (qd, 1H, J = 15.9, 6.9 Hz). ^{13}C NMR: δ 193.6, 168.5, 145.2, 133.9, 129.0, 118.4, 83.6, 70.2, 61.7, 59.5, 48.6, 38.6, 18.6. IR ($CHCl_3$, cm^{-1}): ν 3447, 1753, 1701. MS (EI), *m*/*z*: 254 (M^+ + 1, 25), 253 (M^+, 100). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.60; H, 7.59; N, 5.57.

Tin(IV) Chloride-Promoted Reaction between Allyltributyltin and 4-Oxoazetidine-2-carbaldehyde 1a. A cooled solution of tin(IV) chloride (313 mg, 1.2 mmol) in dichloromethane (1.2 mL) was added dropwise to a stirred solution of allyltributyltin (397 mg, 1.2 mmol) in dichloromethane (4.5 mL) at −78 °C. After 5 min, a solution of the aldehyde **1a** (219 mg, 1.0 mmol) in dichloromethane (1 mL) was added dropwise, and the mixture was stirred for 1 h at −78 °C. Saturated aqueous sodium hydrogen carbonate (10 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, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1 containing 1% of triethylamine) as an eluent gave 209 mg (80%) of compound *syn*-**7a**, containing ca. 25% of its *anti*-**7a** epimer. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.99; H, 7.27; N, 5.32.

Boron Trifluoride Diethyl Etherate-Promoted Reaction between Allyltributyltin and 4-Oxoazetidine-2-carbaldehyde 1a. A solution of the aldehyde **1a** (219 mg, 1.0 mmol) in dichloromethane (1 mL) was added dropwise to a stirred solution of boron trifluoride diethyl etherate (213 mg, 1.5 mmol) in dichloromethane (4 mL) at −78 °C. After 5 min, allyltributyltin (397 mg, 1.2 mmol) was added, and the mixture was stirred for 1 h at −78 °C. Saturated aqueous sodium hydrogen carbonate (10 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, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1 containing 1% of triethylamine) as an eluent gave 196 mg (75%) of compound *syn*-**7a**, containing ca. 9% of its *anti*-**7a** epimer. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.87; H, 7.25; N, 5.30.

Magnesium/Bismuth(III) Chloride-Promoted Reaction between Allylbromide and 4-Oxoazetidine-2-carbaldehyde 1a. Allyl bromide (187 mg, 1.54 mmol) was added to a well-stirred suspension of bismuth(III) chloride (501 mg, 1.59 mmol) and metallic magnesium (57 mg, 2.36 mmol) in THF/water (4:1, 4 mL) at room temperature. After 20 min, a solution of the aldehyde **1a** (219 mg, 1.0 mmol) in tetrahydrofuran (1 mL) was added dropwise, and the mixture was stirred for 18 h at room temperature. Hydrochloric acid (1 M, 10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with dichloromethane (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave 131 mg (50%) of compound *syn*-**7a**, containing ca. 28% of its *anti*-**7a** epimer. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.81; H, 7.20; N, 5.26.

Indium-Promoted Reaction between Allylbromide and 4-Oxoazetidine-2-carbaldehyde 1a. Allyl bromide (242 mg, 2.0 mmol) was added to a well-stirred solution of the aldehyde **1a** (219 mg, 1.0 mmol) and indium powder (229 mg, 1.99 mmol) in THF/water (1:1, 5 mL) at room temperature. After 5 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with dichloromethane (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave 196 mg (75%) of compound *syn*-**7a**, containing ca. 54% of its *anti*-**7a** epimer. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.79; H, 7.22; N, 5.26.

Zinc-Promoted Reaction between Allylbromide and 4-Oxoazetidine-2-carbaldehyde 1a. Allyl bromide (76 mg, 0.584 mmol) was added dropwise to a stirred solution of zinc dust in tetrahydrofuran (730 μL) at room temperature. The reaction was activated by a gentle heating, for a few seconds. When the ebullition calmed down, the mixture was cooled at 5 °C, allyl bromide (303 mg, 2.50 mmol) was added dropwise, and the mixture was stirred at 5 °C for 30 min. The resulting allylzinc bromide was recooled to −78 °C, and a solution of the aldehyde **1a** (219 mg, 1.0 mmol) in tetrahydrofuran (1 mL) was added. After 3 h at −78 °C, saturated aqueous sodium hydrogen carbonate (10 mL) was added, and the mixture was allowed to warm to room temperature, before being extracted with dichloromethane (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave 191 mg (73%) of compound *syn*-**7a**, containing ca. 38% of its *anti*-**7a** epimer.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.04; H, 7.39; N, 5.28.

Tin(II) Chloride-Promoted Reaction between Allyl-bromide and 4-Oxoazetidine-2-carbaldehyde 1a. Tin(II) chloride monohydrate (462 mg, 2.05 mmol) and sodium iodide (307 mg, 2.05 mmol) were sequentially added to a stirred solution of the aldehyde **1a** (219 mg, 1.0 mmol) and allyl bromide (182 mg, 1.5 mmol) in DMF (2 mL) at room temperature. After 20 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with dichloromethane (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave 133 mg (51%) of compound *syn*-**7a**, containing ca. 39% of its *anti*-**7a** epimer. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.78; H, 7.42; N, 5.18.

General Procedure for the Preparation of *O*-Acetyl-mandelates 8d,i, 9d,i, and 12a,b. (*R*)-*O*-Acetylmandelic acid (20 mg, 0.10 mmol) and 4-(dimethylamino)pyridine (DMAP) (cat.) were added to a solution of the corresponding homoallylic alcohol (0.09 mmol) in dichloromethane (1.0 mL) followed by a solution of dicyclohexylcarbodiimide (DCC) (37 mg, 0.18 mmol) in dichloromethane (500 μL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure, and diethyl ether was added. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue eluting with dichloromethane/ethyl acetate mixtures gave analytically pure *O*-acetylmandelates **8**, **9**, and **12**. Spectroscopic and analytical data for some representative pure forms of **8** follow.

(*R*)-*O*-Acetylmandelate of (3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butenyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-8d. From 25 mg (0.09 mmol) of compound (+)-**7d**, 36 mg (88%) of compound (+)-**8d** was obtained as a colorless oil. $[\alpha]_D = +50.4$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 2.09 (s, 3H), 2.46 (t, 2H, J = 6.6 Hz), 3.29 (s, 3H), 3.72 (s, 3H), 4.27 (t, 1H, J = 5.5 Hz), 4.38 (d, 1H, J = 5.2 Hz), 5.03 (dd, 1H, J = 6.6, 1.1 Hz), 5.07 (s, 1H), 5.28 (q, 1H, J = 5.9 Hz), 5.70 (m, 1H), 5.71 (s, 1H), 6.71 and 7.18 (dd, each 2H, J = 7.0, 2.2 Hz), 7.22 (m, 5H). ^{13}C NMR: δ 170.3, 168.1, 164.8, 156.7, 133.0, 132.4, 130.2, 129.2, 128.7, 127.7, 119.7, 118.8, 114.2, 82.6, 74.6, 72.7, 59.2, 57.0, 55.4, 35.4, 20.7. IR ($CHCl_3$, cm^{-1}): ν 1747, 1647. MS (EI), *m*/*z*: 454 (M^+ + 1, 9), 453 (M^+, 29), 149 (100). Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.25; H, 5.97; N, 3.04.

(*S*)-*O*-Acetylmandelate of (3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butenyl]-3-methoxy-1-(*p*-methoxyphenyl)-2-azetidinone, 9d. From 25 mg (0.09 mmol) of compound (+)-**7d**, 32 mg (79%) of compound (+)-**9d** was obtained as a colorless oil. $[\alpha]_D = +133.0$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 2.03 (s, 3H), 2.27 (m, 2H), 3.53 (s, 3H), 3.73 (s, 3H), 4.30 (dd, 1H, J = 7.0, 5.1 Hz), 4.54 (d, 1H, J = 5.1 Hz), 4.69 (dd, 1H, J = 17.0, 1.5 Hz), 4.77 (dd, 1H, J = 10.3, 1.5 Hz), 5.33 (m, 2H), 5.59 (s, 1H), 6.82 (dd, 2H, J = 7.0, 2.2 Hz), 7.27 (m, 7H). ^{13}C NMR: δ 169.7, 167.8, 164.8, 156.8, 133.8, 131.9, 130.1, 129.1, 128.6, 127.8, 120.2, 118.6, 114.3, 82.6, 74.0, 73.3, 59.4, 57.5, 55.5, 35.3, 20.7. IR ($CHCl_3$, cm^{-1}): ν 1751, 1645. MS (EI), *m*/*z*: 454 (M^+ + 1, 8), 453 (M^+, 28), 149 (100). Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.29; H, 6.06; N, 3.15.

Swern Oxidation of Homoallylic Alcohols 11a,b. A solution of dimethyl sulfoxide (67 mg, 0.856 mmol) in dichloromethane (280 μL) was added dropwise to a stirred solution of oxalyl chloride (54 mg, 0.423 mmol) in dichloromethane (468 μL) at −78 °C. After 20 min, a solution of the alcohol (+)-**11** (from allyltributyltin) (100 mg, 0.351 mmol) in dichloromethane (300 μL) was added, and the mixture was stirred for 1 h at −78 °C. Triethylamine (270 μL) was added at −78 °C, and the mixture was allowed to warm to room temperature. Water (1 mL) 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/hexane (2:1 containing 1% of triethylamine) gave 60 mg (60%) of α,β-unsaturated ketone (+)-***E*-14** as a pale yellow oil.

(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-[2-oxo-3-pentenyl]-3-methoxy-2-azetidinone, (+)-*E*-14. Pale yellow oil: $[\alpha]_D = +69.1$ (*c* 2.0, CH_2Cl_2). ^{1}H NMR: δ 1.29 and 1.32 (s, each 3H), 1.87 (dd, 3H, J = 6.9, 1.7 Hz), 3.38 (m, 1H), 3.48 (s, 3H), 3.57 (dd, 1H, J = 8.8, 5.4 Hz), 3.83 (dd, 1H, J = 9.2, 5.1 Hz), 4.02 (dd, 1H, J = 8.8, 6.3 Hz), 4.09 (d, 1H, J = 18.0 Hz), 4.22 (m, 1H), 4.45 (d, 1H, J = 18.0 Hz), 4.53 (d, 1H, J = 5.1 Hz), 6.06 (dq, 1H, J = 15.9, 1.5 Hz), 6.86 (qd, 1H, J = 15.9, 6.9 Hz). ^{13}C NMR: δ 192.6, 168.2, 144.4, 129.0, 109.5, 83.3, 76.9, 66.7, 60.6, 59.2, 48.0, 26.8, 25.2, 18.5. IR ($CHCl_3$, cm^{-1}): ν 1755, 1705. MS (EI), *m*/*z*: 284 (M^+ + 1, 20), 283 (M^+, 100). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.29; H, 7.35; N, 4.91.

General Procedure for the Preparation of Methanesulfonates 17a−h, 18, and 19. 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 dichloromethane/ethyl acetate or hexanes/ethyl acetate mixtures gave analytically pure methanesulfonates **17**, **18**, or **19**. Spectroscopic and analytical data for some representative pure forms of **17** follow.

Methanesulfonate of (3*SR*,4*SR*)-4-[(*RS*)-1-Hydroxy-3-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propenyl)-2-azetidinone, 17b. From 100 mg (0.348 mmol) of homoallylic alcohol **7b**, 103 mg (82%) of compound **17b** was obtained as a colorless solid after purification by flash chromatography (dichloromethane/ethyl acetate, 9.5/0.5): colorless solid. Mp: 99−101 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 2.33 (s, 3H), 2.46 (m, 2H), 2.64 (m, 2H), 3.47 (dt, 1H, J = 7.7, 5.9 Hz), 3.71 (s, 3H), 4.38 (dd, 1H, J = 9.2, 5.9 Hz), 4.97 (m, 1H), 5.13 (dq, 2H, J = 8.8, 1.8 Hz), 5.21 (d, 2H, J = 8.8 Hz), 5.89 (m, 2H), 6.81 and 7.24 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 166.8, 156.6, 134.5, 130.9, 130.6, 120.3, 117.6, 114.1, 80.8, 55.5, 55.0, 50.4, 38.0, 37.3, 31.5, 29.3. IR (KBr, cm^{-1}): ν 1753, 1348, 1169. MS (EI), *m*/*z*: 366 (M^+ + 1, 23), 365 (M^+, 100). Anal. Calcd for $C_{18}H_{23}NSO_5$: C, 59.16; H, 6.34; N, 3.83. Found: C, 59.10; H, 6.36; N, 3.85.

Methanesulfonate of (3*SR*,4*SR*)-4-[(*RS*)-1-Hydroxy-3-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propynyl)-2-azetidinone, 17c. From 342 mg (1.13 mmol) of homoallylic alcohol **7c**, 358 mg (83%) of compound **17c** was obtained as a green pale oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.5/0.5): pale green oil. ^{1}H NMR: δ 2.20 (t, 1H, J = 2.5 Hz), 2.39 (s, 3H), 2.74 (m, 4H), 3.61 (td, 1H, J = 8.8, 5.5 Hz), 3.78 (s, 3H), 4.50 (dd, 1H, J = 9.2, 5.5 Hz), 5.28 (m, 3H), 5.98 (m, 1H), 6.87 and 7.29 (dd, each 2H, J = 6.9, 2.2 Hz). ^{13}C NMR: δ 165.1, 156.8, 130.8, 130.3, 120.5, 120.4, 114.1, 80.3, 71.9, 55.5, 55.2, 49.8, 37.9, 37.6, 31.5, 14.7. IR ($CHCl_3$, cm^{-1}): ν 3310, 1753, 1360, 1175. MS (EI), *m*/*z*: 364 (M^+ + 1, 24), 363 (M^+, 100). Anal. Calcd for $C_{18}H_{21}NSO_5$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.40; H, 5.84; N, 3.87.

Methanesulfonate of (3*R*,4*S*)-4-[(*R*)-1-Hydroxy-3-butenyl]-1-(*p*-methoxyphenyl)-3-(2-propenyloxy)-2-azetidinone, (+)-17d. From 277 mg (0.913 mmol) of homoallylic alcohol (+)-**7i**, 319 mg (92%) of compound (+)-**17d** was obtained as a pale green solid after purification by flash chromatography (dichloromethane/ethyl acetate, 9.5/0.5): pale green solid. Mp: 64−66 °C (hexanes/ethyl acetate). $[\alpha]_D = +79.9$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR: δ 2.53 (s, 3H), 2.65 (m, 2H), 3.79 (s, 3H), 4.27 and 4.42 (ddt, each 1H, J = 12.9, 5.5, 1.5 Hz), 4.51 (dd, 1H, J = 8.5, 5.2 Hz), 4.80 (d, 1H, J = 5.2 Hz), 5.10 (m, 1H), 5.23 (dq, 1H, J = 17.0, 1.5 Hz), 5.28 (2H, m), 5.38 (dq, 1H, J = 17.0, 1.5 Hz), 5.94 (m, 2H), 6.88 and 7.37 (dd, each 2H, J = 8.8, 2.2 Hz). ^{13}C NMR: δ 164.9, 156.8, 133.0, 131.5, 130.2, 119.9, 119.7, 118.6, 114.3, 81.3, 80.1, 72.6, 57.3, 55.5, 38.0, 36.8, 31.5. IR (KBr, cm^{-1}): ν 1749, 1362, 1177. MS (EI), *m*/*z*: 382 (M^+ + 1, 14), 381 (M^+, 63), 149 (100). Anal. Calcd

for $C_{18}H_{23}NSO_6$: C, 56.68; H, 6.08; N, 3.67. Found: C, 56.70; H, 6.11; N, 3.66.

Methanesulfonate of (3*R*,4*S*)-3-Benzyloxy-1-(3-butenyl)-4-[(*R*)-1-hydroxy-3-butenyl]-2-azetidinone, (+)-17f. From 192 mg (0.638 mmol) of homoallylic alcohol (+)-**7f**, 216 mg (89%) of compound (+)-**17f** was obtained as a pale green oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.5/0.5): pale green oil. $[\alpha]_D = +46.2$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR: δ 2.33 (m, 2H), 2.54 and 2.67 (m, each 1H), 3.02 (s, 3H), 3.20 and 3.68 (dd, each 1H, J = 14.0, 7.0 Hz), 3.88 (dd, 1H, J = 8.0, 5.1 Hz), 4.62 (d, 1H, J = 5.1 Hz), 4.69 and 4.92 (d, each 1H, J = 11.7 Hz), 5.11 (m, 5H), 5.76 (m, 2H), 7.35 (m, 5H). ^{13}C NMR: δ 167.6, 136.5, 134.7, 131.7, 128.6, 128.2, 128.1, 119.9, 117.4, 81.5, 80.1, 73.1, 57.5, 40.3, 39.4, 36.9, 31.4. IR ($CHCl_3$, cm^{-1}): ν 1745, 1365, 1175. MS (EI), *m*/*z*: 380 (M^+ + 1, 2), 379 (M^+, 6), 91 (100). Anal. Calcd for $C_{19}H_{25}NSO_5$: C, 60.14; H, 6.64; N, 3.69. Found: C, 60.10; H, 6.65; N, 3.66.

Methanesulfonate of (3*R*,4*S*)-1-(3-Butynyl)-4-[(*R*)-1-hydroxy-3-butenyl]-3-methoxy-2-azetidinone, (+)-17g. From 550 mg (2.47 mmol) of homoallylic alcohol (+)-**7g**, 650 mg (88%) of compound (+)-**17g** was obtained as a colorless oil after purification by flash chromatography (ethyl acetate/hexane, 4/6): colorless oil. $[\alpha]_D = +36.3$ (*c* 3.0, CH_2Cl_2). ^{1}H NMR: δ 1.98 (t, 1H, J = 2.7 Hz), 2.53 (m, 4H), 3.04 (s, 3H), 3.27 (td, 1H, J = 14.0, 6.1 Hz), 3.56 (s, 3H), 3.73 (ddd, 1H, J = 14.1, 7.5, 6.6 Hz), 4.02 (dd, 1H, J = 8.3, 5.1 Hz), 4.51 (d, 1H, J = 5.1 Hz), 4.99 (m, 1H), 5.16 (dq, 1H, J = 5.1, 1.2 Hz), 5.23 (q, 1H, J = 1.2 Hz), 5.84 (m, 1H). ^{13}C NMR: δ 167.6, 131.8, 119.8, 82.7, 81.5, 80.7, 70.5, 59.2, 58.0, 39.7, 39.4, 36.8, 17.3. IR ($CHCl_3$, cm^{-1}): ν 3308, 1755, 1360, 1175. MS (EI), *m*/*z*: 302 (M^+ + 1, 10), 301 (M^+, 65), 149 (100). Anal. Calcd for $C_{13}H_{19}NSO_5$: C, 51.81; H, 6.35; N, 4.65. Found: C, 51.87; H, 6.25; N, 4.53.

General Procedure for the Preparation of Dienes 20a, 21−23, Trienes 20b,d−f, and Dienynes 20c,g,h. DBU (1.10 mmol) was added dropwise to a solution of the corresponding methanesulfonate (1.0 mmol) in benzene or toluene (10 mL). The resulting solution was heated under reflux for 16 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 dichloromethane/ethyl acetate or hexanes/ethyl acetate mixtures gave analytically pure polyenes **20**−**23**.

(3*SR*,4*SR*)-4-[(1*E*)-1,3-Butadienyl]-1-(*p*-methoxyphenyl)-3-(2-propenyl)-2-azetidinone, 20b. From 100 mg (0.274 mmol) of methanesulfonate **17b**, 40 mg (74%) of compound **20b** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): colorless oil. ^{1}H NMR: δ 2.29 and 2.45 (m, each 1H), 3.44 (td, 1H, J = 9.2, 5.9 Hz), 3.70 (s, 3H), 4.55 (dd, 1H, J = 7.5, 5.9 Hz), 5.11 (m, 4H), 5.73 (m, 2H), 6.29 (m, 2H), 6.77 and 7.27 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 166.5, 155.9, 136.0, 135.5, 134.9, 131.6, 128.1, 118.9, 118.2, 116.7, 114.3, 56.5, 55.5, 53.4, 29.4. IR ($CHCl_3$, cm^{-1}): ν 1734. MS (EI), *m*/*z*: 270 (M^+ + 1, 2), 269 (M^+, 8), 149 (100). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.86; H, 7.11; N, 5.17.

(3*SR*,4*SR*)-4-[(1*E*)-1,3-Butadienyl]-1-(*p*-methoxyphenyl)-3-(2-propynyl)-2-azetidinone, 20c. From 120 mg (0.33 mmol) of methanesulfonate **17c**, 54 mg (58%) of compound **20c** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): colorless oil. ^{1}H NMR: δ 1.96 (t, 1H, J = 3.0 Hz), 2.63 (m, 2H), 3.10 (dt, 1H, J = 5.1, 3.0 Hz), 3.71 (s, 3H), 4.34 (dd, 1H, J = 8.1, 2.2 Hz), 5.12 (dd, 1H, J = 9.2, 1.8 Hz), 5.22 (dd, 1H, J = 15.0, 1.8 Hz), 5.73 (dd, 1H, J = 15.0, 8.5 Hz), 6.29 (td, 1H, J = 16.5, 10.5 Hz), 6.40 (dd, 1H, J = 14.5, 10.5 Hz), 6.78 and 7.28 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 164.4, 156.1, 135.5, 135.0, 131.4, 130.4, 119.2, 118.3, 114.3, 79.4, 70.7, 58.6, 55.5, 55.0, 17.3. IR ($CHCl_3$, cm^{-1}): ν 3308, 1747. MS (EI), *m*/*z*: 268 (M^+ + 1, 5), 267 (M^+, 23), 149 (100). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.30; H, 6.40; N, 5.25.

(3*R*,4*S*)-4-[(1*E*)-1,3-Butadienyl]-1-(*p*-methoxyphenyl)-3-(2-propenyloxy)-2-azetidinone, (+)-20d. From 96 mg (0.252 mmol) of methanesulfonate (+)-**17d**, 64 mg (89%) of compound (+)-**20d** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): colorless oil. $[\alpha]_D = +47.4$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 3.78 (s, 3H), 4.17 (m, 2H), 4.64 (dd, 1H, J = 9.0, 4.8 Hz), 4.83 (d, 1H, J = 4.8 Hz), 5.27 (m, 4H), 5.83 (dd, 1H, J = 14.7, 8.8 Hz), 5.94 (m, 1H), 6.41 (td, 1H, J = 16.5, 10.3 Hz), 6.51 (dd, 1H, J = 14.5, 10.3 Hz), 6.85 and 7.37 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 163.7, 156.3, 137.2, 135.7, 133.5, 131.1, 127.6, 119.1, 118.6, 118.3, 114.3, 82.6, 72,0, 60.5, 55.5. IR ($CHCl_3$, cm^{-1}): ν 1746. MS (EI), *m*/*z*: 286 (M^+ + 1, 5), 285 (M^+, 23), 67 (100). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.55; H, 6.75; N, 4.91.

(3*R*,4*S*)-3-Benzyloxy-4-[(1*E*)-1,3-butadienyl]-1-(3-butenyl)-2-azetidinone, (+)-20f. From 120 mg (0.316 mmol) of methanesulfonate (+)-**17f**, 51 mg (66%) of compound (+)-**20f** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): colorless oil. $[\alpha]_D = +64.4$ (*c* 1.8, CH_2Cl_2). ^{1}H NMR: δ 2.25 (m, 2H), 3.07 and 3.41 (ddd, each 1H, J = 14.0, 7.0, 2.0 Hz), 4.15 (dd, 1H, J = 9.2, 4.4 Hz), 4.58 and 4.61 (d, each 1H, J = 11.4 Hz), 4.72 (d, 1H, J = 4.4 Hz), 5.07 and 5.25 (m, each 2H), 5.72 (m, 2H), 6.32 (dd, 1H, J = 14.7, 10.7 Hz), 6.38 (td, 1H, J = 16.5, 9.9 Hz), 7.32 (m, 5H). ^{13}C NMR: δ 166.8, 136.9, 135.8, 134.8, 128.4, 128.2, 128.0, 127.7, 127.6, 119.0, 117.2, 83.1, 72.6, 60.6, 39.4, 32.0. IR ($CHCl_3$, cm^{-1}): ν 1745. MS (EI), *m*/*z*: 284 (M^+ + 1, 3), 283 (M^+, 10), 91 (100). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.47; N, 4.94. Found: C, 76.23; H, 7.49; N, 4.90.

(3*R*,4*S*)-4-[(1*E*)-1,3-Butadienyl]-1-(3-butynyl)-3-methoxy-2-azetidinone, (+)-20g. From 100 mg (0.332 mmol) of methanesulfonate (+)-**17g**, 48 mg (71%) of compound (+)-**20g** was obtained as a colorless oil after purification by flash chromatography (ethyl acetate/hexane, 4/6): colorless oil. $[\alpha]_D = +44.0$ (*c* 2.1, CH_2Cl_2). ^{1}H NMR: δ 1.95 (t, 1H, J = 2.7 Hz), 2.35 (dt, 2H, J = 7.0, 2.7 Hz), 3.11 (td, 1H, J = 14.0, 6.9 Hz), 3.38 (s, 3H), 3.46 (dd, 1H, J = 14.0, 7.0 Hz), 4.25 (dd, 1H, J = 9.3, 4.8 Hz), 4.52 (d, 1H, J = 4.8 Hz), 5.19 (m, 2H), 5.66 (m, 1H), 6.31 (dd, 1H, J = 14.5, 10.0 Hz), 6.35 (td, 1H, J = 16.5, 10.0 Hz). ^{13}C NMR: δ 167.7, 137.4, 135.7, 126.9, 119.1, 85.3, 80.8, 70.2, 60.7, 58.6, 38.7, 18.1. IR ($CHCl_3$, cm^{-1}) ν: 3310, 1750. MS (EI), *m*/*z*: 206 (M^+ + 1, 15), 205 (M^+, 100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.30; H, 7.27; N, 6.74.

General Procedure for the Preparation of Diels−Alder Cycloadducts 29a−e and Tricycle 30. DBU (1.10 mmol) was added dropwise to a solution of the corresponding methanesulfonate **17b**−**e**,**g** (1.0 mmol) and hydroquinone (cat.) in toluene (10 mL). The resulting solution was heated in a sealed tube at 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 or hexanes/ethyl acetate mixtures gave analytically pure adducts **29** and **30**.

Tricyclic 2-Azetidinone 29a. From 70 mg (0.192 mmol) of methanesulfonate **17b** and after heating at 110 °C for 24 h, 30 mg (57%) of compound **29a** was obtained as a white solid after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): white solid. Mp: 131−132 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 1.57 (1H, m), 1.66 (2H, m), 1.86 (dd, 1H, J = 13.0, 7.0 Hz), 1.96 (m, 2H), 2.39 (1H, m), 2.77 (td, 1H, J = 6.3, 3.0 Hz), 3.52 (dd, 1H, J = 8.5, 3.8 Hz), 3.72 (s, 3H), 4.07 (d, 1H, J = 3.8 Hz), 5.36 (dt, 1H, J = 10.3, 3.0 Hz), 5.73 (m, 1H), 6.81 and 7.28 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 166.8, 155.9, 131.0, 129.4, 125.3, 118.0, 114.4, 61.6, 55.5, 53.9, 38.6, 34.1, 25.5, 21.2, 20.6. IR (KBr, cm^{-1}): ν 1740. MS (EI), *m*/*z*: 270 (M^+ + 1, 10), 269 (M^+, 51), 149 (100). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.82; H, 7.12; N, 5.15.

Tricyclic 2-Azetidinone (+)-29b. From 100 mg (0.262 mmol) of methanesulfonate (+)-**17d** and after heating at 190 °C for 24 h, 66 mg (88%) of compound (+)-**29b** was obtained as a white solid after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): white solid. Mp: 102−103 °C (hexanes/ethyl acetate). $[\alpha]_D = +54.9$ (*c* 1.0, CH_2-

Cl_2). ^{1}H NMR: δ 1.29 (1H, m), 1.65 (1H, m), 1.72 (1H, m), 2.14 (2H, m), 2.36 (dd, 1H, J = 11.0, 7.1 Hz), 3.53 (t, 1H, J = 11.0 Hz), 3.81 (s, 3H), 3.87 (dd, 1H, J = 11.0, 4.5 Hz), 3.96 (dd, 1H, J = 7.1, 5.3 Hz), 4.94 (d, 1H, J = 5.3 Hz), 5.77 (m, 1H), 5.89 (dd, 1H, J = 10.3, 1.9 Hz), 6.90 and 7.40 (dd, each 2H, J = 7.0, 2.2 Hz). ^{13}C NMR: δ 165.0, 156.5, 130.5, 129.0, 128.3, 119.8, 119.4, 114.5, 113.9, 69.7, 56.6, 55.4, 42.3, 34.4, 24.8. IR (KBr, cm^{-1}): ν 1736. MS (EI), *m*/*z*: 286 (M^+ + 1, 10), 285 (M^+, 100). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.57; H, 6.65; N, 4.92.

Tricyclic 2-Azetidinone (+)-29c. From 120 mg (0.316 mmol) of methanesulfonate (+)-**17f** and after heating at 190 °C for 72 h, 44 mg (50%) of compound (+)-**29c** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.8/0.2): colorless oil. $[\alpha]_D$ = +83.4 (*c* 1.7, $CHCl_3$). ^{1}H NMR: δ 1.32 (3H, m), 1.50 (dd, 1H, J = 10.0, 4.0 Hz), 1.64 (1H, m), 2.16 (3H, m), 2.79 (1H, m), 3.21 (dd, 1H, J = 10.3, 5.1 Hz), 3.91 (dd, 1H, J = 14.0, 5.5 Hz), 4.73 (d, 1H, J = 11.8 Hz), 4.74 (d, 1H, J = 5.1 Hz), 4.92 (d, 1H, J = 11.8 Hz), 5.50 (d, 1H, J = 9.6 Hz), 5.77 (dd, 1H, J = 9.5, 3.0 Hz), 7.35 (m, 5H). ^{13}C NMR: δ 167.7, 137.4, 128.8, 128.4, 127.7, 127.6, 125.9, 82.5, 72.7, 57.6, 40.1, 38.4, 35.7, 31.5, 28.9, 25.4. IR ($CHCl_3$, cm^{-1}) ν: 1741. MS (EI), *m*/*z*: 283 (M^+, 8), 91 (100). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.28; H, 7.51; N, 4.95.

Tricyclic 2-Azetidinone (+)-29e. From 125 mg (0.415 mmol) of methanesulfonate (+)-**17g** and after heating at 190 °C for 68 h, 43 mg (51%) of compound (+)-**29e** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 9.6/0.4): pale brown oil. $[\alpha]_D$ = +122.7 (*c* 3.0, CH_2Cl_2). ^{1}H NMR: δ 2.10 (2H, m), 2.66 (3H, m), 2.87 (1H, m), 3.19 (dd, 1H, J = 9.8, 4.2 Hz), 3.54 (s, 3H), 3.84 (ddd, 1H, J = 13.0, 5.5, 2.0 Hz), 4.48 (dd, 1H, J = 4.2, 1.5 Hz), 5.51 (m, 2H), 5.72 (m, 1H). ^{13}C NMR: δ 167.3, 132.1, 125.7, 124.2, 121.4, 85.3, 59.5, 59.4, 39.9, 36.7, 34.1, 26.8. IR ($CHCl_3$, cm^{-1}): ν 1745. MS (EI), *m*/*z*: 206 (M^+ + 1, 92), 205 (M^+, 33), 91 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.32; H, 7.31; N, 6.74.

Thermal Treatment of Compound 17c. From 110 mg (0.302 mmol) of methanesulfonate **17c**, after heating at 190 °C for 72 h, and after flash chromatography eluting with dichloromethane/ethyl acetate (9.8:0.2), 8 mg (9%) of the less polar compound **29d** and 30 mg (37%) of the more polar compound **30** were obtained.

Tricyclic 2-Azetidinone 29d: colorless oil. ^{1}H NMR: δ 2.16 (2H, s), 2.43 (dd, 1H, J = 18.8, 10.3 Hz), 2.75 (dd, 1H, J = 18.8, 8.2 Hz), 3.23 (m, 1H), 3.67 (dd, 1H, J = 4.4, 1.8 Hz), 3.72 (s, 3H), 3.81 (ddd, 1H, J = 10.3, 4.8, 2.2 Hz), 4.79 (m, 1H), 5.64 (m, 1H), 6.06 (d, 1H, J = 9.6 Hz), 6.79 and 7.29 (dd, each 2H, J = 7.0, 2.2 Hz). IR ($CHCl_3$, cm^{-1}): ν 1740. MS (EI), *m*/*z*: 268 (M^++ 1, 11), 267 (M^+, 53), 118 (100). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.42; H, 6.41; N, 5.32.

Tricyclic 2-Azetidinone 30: colorless oil. ^{1}H NMR (DMSO-d_6): δ 3.12 (s, 1H), 3.15 (s, 2H), 3.35 (s, 1H), 3.70 (s, 3H), 6.87 (d, 2H, J = 8.8 Hz), 7.13 and 7.20 (m, each 2H), 7.53 (d, 2H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6): δ 172.6, 155.1, 141.9, 132.5, 126.4, 124.2, 120.7, 113.8, 55.1 (2C), 44.9, 36.4. IR ($CHCl_3$, cm^{-1}): ν 1742. MS (EI), *m*/*z*: 267 (M^+ + 2, 77), 265 (M^+, 3), 123 (100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.91; H, 5.75; N, 5.30.

Preparation of Diels−Alder Cycloadducts 31a,b. A solution of the triene (+)-**27** (48 mg, 0.181 mmol) and hydroquinone (cat.) in toluene (5 mL) was heated in a sealed tube at 190 °C for 96 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and after flash chromatography eluting with hexanes/ethyl acetate (1:1), 23 mg (41%) of the less polar compound (+)-**31a** and 12 mg (32%) of the more polar compound (+)-**31b** were obtained.

Tricyclic 2-Azetidinone (+)-31a: colorless oil. $[\alpha]_D$ = +59.7 (*c* 1.9, CH_2Cl_2). ^{1}H NMR (C_6D_6): δ 0.92 (dd, 1H, J = 13.4, 1.9 Hz), 1.25 (1H, m), 1.74 (ddd, 1H, J = 18.5, 7.3, 4.4 Hz), 2.20 (td, 1H, J = 12.2, 3.4 Hz), 2.37 (1H, brs), 2.42 (1H, m), 2.51 (1H, brs), 2.70 (1H, m), 2.90 (dd, 1H, J = 10.3, 4.9 Hz), 3.27 (s, 3H), 3.34 (dd, 1H, J = 5.9, 3.9 Hz), 3.40 (s, 3H), 4.10 (dd, 1H, J = 4.9, 1.5 Hz), 5.14 (d, 1H, J = 9.8 Hz), 5.52 (dd, 1H, J = 9.8, 2.5 Hz). ^{13}C NMR: δ 174.4, 167.2, 128.3, 126.9, 85.0, 59.3, 52.0, 51.6, 39.4, 34.3, 31.9, 29.2, 29.1, 23.5. IR ($CHCl_3$, cm^{-1}): ν 1745, 1740. MS (EI), *m*/*z*: 266 (M^+, 30), 265 (M^+, 100). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.31; H, 7.25; N, 5.24.

Tricyclic 2-Azetidinone (+)-31b: white solid. Mp: 103−104 °C (hexanes/ethyl acetate). $[\alpha]_D$ = +250.2 (*c* 1.4, CH_2Cl_2). ^{1}H NMR: δ 1.26 (dq, 1H, J = 13.0, 5.7 Hz), 1.67 (2H, m), 2.09 (2H, m), 2.38 (dt, 1H, J = 10.5, 4.5 Hz), 2.50 (1H, m), 2.71 (ddt, 1H, J = 14.0, 4.5, 1.5 Hz), 3.48 (s, 3H), 3.58 (s, 3H), 3.62 (dd, 1H, J = 10.2, 4.8 Hz), 3.81 (dd, 1H, J = 14.0, 5.5 Hz), 4.32 (d, 1H, J = 4.8 Hz), 5.36 (dd, 1H, J = 10.0, 2.2 Hz), 5.64 (m, 1H). ^{13}C NMR: δ 173.6, 167.1, 129.2, 125.9, 84.7, 58.6, 57.0, 51.5, 42.5, 39.9, 38.3, 38.0, 31.3, 27.3. IR (KBr, cm^{-1}): ν 1745, 1741. MS (EI), *m*/*z*: 266 (M^+, 41), 265 (M^+, 100). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.32; H, 7.20; N, 5.31.

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Supporting Information Available: Spectroscopic and analytical data as well as experimental procedures for compounds (+)-**1d**−**l**, (+)-**2a**−**h**, (+)-**3**, (+)-**4**, (+)-**5**, (+)-**6a**, (+)-**6c**, (+)-**6e**, (+)-**6g**, **7a,** (+)-**7f**, (+)-**7h**, (+)-**7j**, (+)-**7l**, (+)-**8i**, (+)-**9i**, (+)-**10a**,**b**, (+)-**11a**,**b**, (−)-**12a**, (+)-**12b**, (+)-**13a**,**b**, (+)-**16**, **17a**, (+)-**17f**, (+)-**17h**, **18**, **19**, **20a**, (+)-**20f**, (+)-**20h**, (−)-**21**, (+)-**22**−**28**, and (+)-**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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