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Asymmetric Synthesis of Unusual Fused Tricyclic β-Lactam Structures via Aza-Cycloadditions/Ring Closing Metathesis

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Conveniently substituted bis-β-lactams, pyrrolidinyl-β-lactams, and piperidinyl-β-lactams undergo ring-closing methatesis using Grubbs' carbene, $Cl_2(Cy_3P)_2Ru{=}CHPh$, to give medium-sized rings fused to bis-2-azetidinone, pyrrolidinyl-2-azetidinone, or piperidinyl-2-azetidinone systems. The diolefinic cyclization precursors can be obtained from optically pure 4-oxoazetidine-2-carbaldehydes bearing an extra alkene tether at position 1 or 3 of the β-lactam ring via [2 + 2] cycloaddition of imino 2-azetidinones, N-metalated azometine ylide [3 + 2] cycloaddition, and subsequent N-acylation of the pyrrolidinyl nitrogen atom, or through aza-Diels−Alder cycloaddition of 2-azetidinone-tethered imines. Under standard reaction conditions, the combination of cycloaddition reactions of 2-azetidinone-tethered imines with ring-closing methatesis offers an asymmetric entry to a variety of unusual fused tricyclic 2-azetidinones bearing two bridgehead nitrogen atoms.

Introduction

β-Lactam antibiotics account for 50% of the total antibiotic market of the world. The extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer.[1] There has, therefore, been much effort expended in recent years to prepare new structural types having the 2-azetidinone ring as a common feature, which will overcome the defense mechanisms of the bacteria. Tricyclic β-lactam antibiotics, generally referred to as trinems, are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases.[2] In addition, the ever-growing new applications of 2-azetidinones in fields ranging from enzyme inhibition[3] to the use of these products as starting materials to develop new synthetic methodologies[4] has triggered a renewed interest in the building of new polycyclic β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures.[5] On the other hand, ring-closing metathesis (RCM) has recently emerged as a powerful tool for the formation of a variety of ring systems.[6] Ring sizes from five through to complex macrocycles have been synthesized. However, the complexity and functional group tolerance of substrates in this process need to be further investigated to expand its applicability in organic syntheses. Although many investigations have been made in this field into various types of dienes, there are a limited number of reports on the use of β-lactam building blocks for the metathesis, with only Barret, Holmes, and

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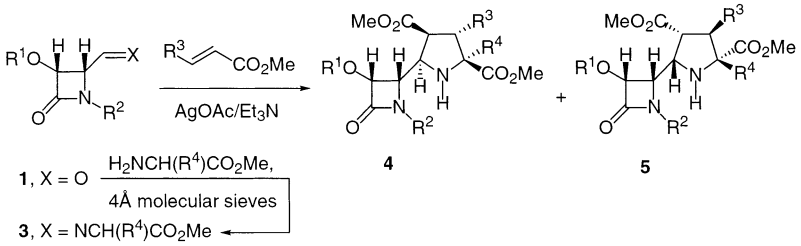
TABLE 1. Synthesis of Pyrrolidinyl-β-lactams 4 and 5



aldehyde	R^1	R^2	R^3	R^4	products	**4**/**5** ratio[a]	yield **4**/**5**[b] (%)
(+)-**1a**	Me	2-propenyl	H	H	(+)-**4a**/(+)-**5a**	65:35	34/18
(+)-**1a**	Me	2-propenyl	H	Me	(+)-**4b**/(+)-**5b**	66:34	49/25
(+)-**1a**	Me	2-propenyl	CO_2Me	Me	(+)-**4c**/(+)-**5c**	60:40	45/30
(+)-**1b**	Me	3-butenyl	H	H	(+)-**4d**/(+)-**5d**	69:31	36/16
(+)-**1b**	Me	3-butenyl	H	Me	(+)-**4e**/(+)-**5e**	64:36	42/24
(+)-**1c**	Me	4-pentenyl	H	Me	(+)-**4f**/(+)-**5f**	59:41	47/33
(+)-**1d**	2-propenyl	PMP	H	Me	(+)-**4g**[c]	*c*	51[d]

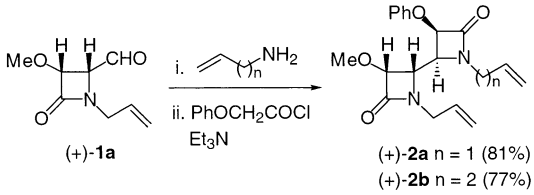
[a] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification.PMP = 4-$MeOC_6H_4$. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] The ^{1}H NMR spectrum of the crude mixture showed mainly (+)-**4g** together with two other minor isomers accounting, respectively, for 9% and 4% of the products formed. [d] Additional fractions containing the major cycloadduct together with traces of the minor isomers were isolated after column chromatography, accounting for an overall 69% yield.

Genet having recently reported the construction of bicyclic β-lactams, mainly in racemic form.[7] However, no efforts have been published to construct the tricyclic β-lactam skeleton via RCM. In connection with our ongoing project directed toward the synthesis of potentially bioactive products through β-lactams,[8] in this paper, we present a novel concept for the asymmetric synthesis of unusual fused tricyclic 2-azetidinones, which is based on a [2 + 2], [3 + 2], or [4 + 2] aza-cycloaddition reaction and a ring-closing metathesis sequence.[9]

Results and Discussion

Cycloaddition precursors, alkenyl-4-oxoazetidine-2-carbaldehydes **1a**−**d**, were prepared using standard methodology.[8] The diolefinic metathesis precursors were obtained in optically pure form in a straightforward fashion from 2-azetidinone-tethered imines. Depending on the desired ring size of the central ring, our approach required the introduction of alkene functionality at either the β-lactam ring or at the nitrogen atom of the four-, five-, and six-membered heterocycles. In addition, this small-sized heterocycle, incorporation should be facilitated by aza-cycloadditions. Thus, C4,C4′-bis-β-lactams (+)-**2a** and (+)-**2b** were prepared from aldehyde (+)-**1a** by a two-step route.[10] Treatment with allylamine followed by ketene−imine cyclization directly provided the diene bis-β-lactam (+)-**2a** (81%) as a single diastereoisomer. Similarly, the bis-β-lactam (+)-**2b** was achieved in 77% yield using homoallylamine and further methoxyacetyl chloride-triethylamine treatment (Scheme 1).

SCHEME 1



The requisite dienes **6** should be again available from alkenyl-4-oxoazetidine-2-carbaldehydes **1**. Treatment of aldehydes **1** with various α-amino esters in the presence of 4 Å molecular sieves provided the corresponding aliphatic aldimines **3**. These were obtained in quantitative yields and were used in the next step without further purification. 1,3-Dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides was achieved at room temperature via metal ion catalysis to afford with moderate diastereoselectivity and in useful to good yields (80−52%) mixtures of cycloadducts **4** and **5** (see Table 1) having an alkene tether at the C3 or N1 positions of the 2-azetidinone ring, as we previously reported for alanine (glycine)-derived iminoesters bearing a *N*-(4-methoxyphenyl) unit at the β-lactam ring.[11] Fortunately, in all cases

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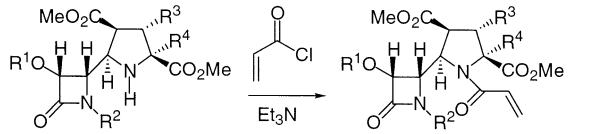
the major isomers **4** could be easily separated by flash chromatography from the diastereomeric cycloadducts **5**. Finally, the N-acylation reaction of the pyrrolidinyl nitrogen atom on cycloadducts **4** was effective to obtain dienic substrates **6** in good yields (Scheme 2).

SCHEME 2

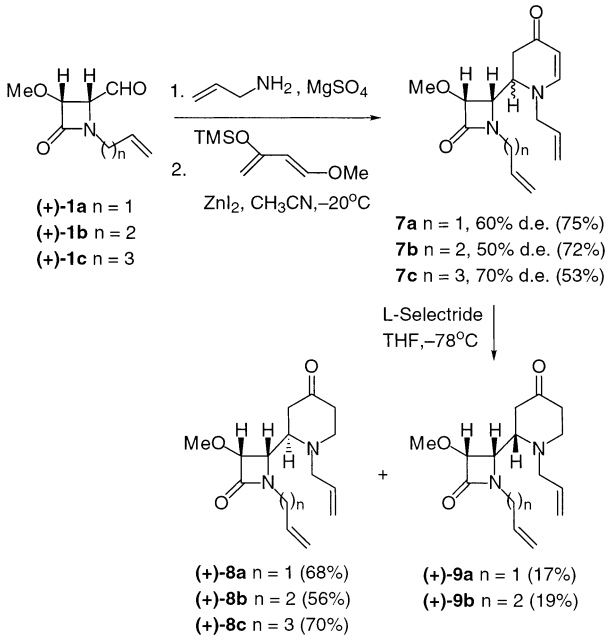


(+)-4a R^1 = Me, R^2 = 2-propenyl
(+)-4b R^1 = Me, R^2 = 2-propenyl
(+)-4c R^1 = Me, R^2 = 2-propenyl
(+)-4d R^1 = Me, R^2 = 3-butenyl
(+)-4e R^1 = Me, R^2 = 3-butenyl
(+)-4f R^1 = Me, R^2 = 4-pentenyl
(+)-4g R^1 = 2-propenyl, R^2 = PMP

(+)-6a R^3 = H, R^4 = H (100%)
(+)-6b R^3 = H, R^4 = Me (100%)
(–)-6c R^3 = CO_2Me, R^4 = Me (57%)
(+)-6d R^3 = H, R^4 = H (90%)
(+)-6e R^3 = H, R^4 = Me (89%)
(+)-6f R^3 = H, R^4 = Me (97%)
(+)-6g R^3 = H, R^4 = Me (88%)

To further expand the scope of substrates to submit to RCM, we thought of the piperidine-β-lactam moiety, in which the four- or five-membered azaheterocycle is replaced by a piperidine residue. The aza Diels−Alder reaction of *N*-alkenyl-2-azetidinone-tethered propenylimines with Danishefsky's diene provided the required precursors.[12] To activate the imine, we used 20% molar zinc iodide as Lewis acid catalyst. Cycloaddition took place at low temperature to give mixtures of diastereoisomers **7** with modest diastereoselectivity in favor of the anti isomer, but it could not be separated from the minor syn isomer. Fortunately, L-Selectride reduction of the alkene moiety at the six-membered ring is a convenient way to obtain the desired dienes. Thus, the diastereomeric adducts **8** and **9** were easily separated by gravity flow chromatography after L-Selectride treatment (Scheme 3).

SCHEME 3



(+)-1a n = 1
(+)-1b n = 2
(+)-1c n = 3

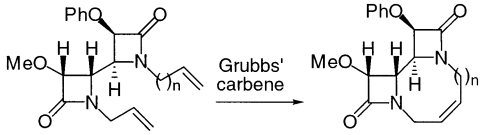
7a n = 1, 60% d.e. (75%)
7b n = 2, 50% d.e. (72%)
7c n = 3, 70% d.e. (53%)

(+)-8a n = 1 (68%)
(+)-8b n = 2 (56%)
(+)-8c n = 3 (70%)

(+)-9a n = 1 (17%)
(+)-9b n = 2 (19%)

In view of the particular disposition of a variety of dienes to undergo ring-closing metathesis reactions, we sought to apply this methodology to our novel 2-azetidinone-tethered diene substrates **2**, **6**, and **8** for the synthesis of unusual fused tricyclic β-lactams bearing two bridgehead nitrogen atoms. The use of this approach in the synthesis of tricyclic 2-azetidinones has not been hitherto applied. The extraordinary functional group tolerance of the ruthenium-based catalyst $Cl_2(Cy_3P)_2Ru{=}CHPh$ coupled with its commercial availability makes it the catalyst of choice. Our objective was the synthesis of tricyclic β-lactam structures containing various medium-sized central rings and four-, five- and six-membered distal rings. Treatment of dienes **2**, **6**, and **8** with Grubbs' catalyst under smooth ring-closing metathesis conditions (5 mol %, CH_2Cl_2, 25 °C), analogous to those described for bicyclic β-lactams,[7] did not furnish the desired tricycles. The majority of the reaction mixture was composed of unreacted dienes. While the reasons for this lack of cyclization were not definitively established, we attributed the low reactivity of the structures **2**, **6**, and **8** to either the ring strain inherent to the fused tricyclic products or kinetic problems associated with its formation. Finally, we found that dienic substrates **2**, **6**, and **8** require more vigorous conditions for ring closure. It is believed that high temperature is favorable for rotation about the single bond connecting the two rings, and a "cis"-like conformation is probably necessary for cyclization. Among the various solvents and conditions tested, we found that toluene at reflux temperature gave the best yields of tricyclic-β-lactams containing medium-sized central rings. Grubbs' catalyst is known to be moderately thermally unstable, and the decomposition would inhibit productive metathesis.[13] To circumvent this problem, Grubbs' carbene was added in small portions every 20 min (5 mol % is the overall amount of all the portions). Thus, the catalytic species is continuously being renewed by fresh Grubbs' carbene. Exposure of dienes **2**, **6**, and **8** to the ruthenium catalyst $Cl_2(Cy_3P)_2Ru{=}CHPh$ under our standard cyclization conditions (5 mol % catalyst, 0.03 M, toluene, 110 °C) resulted in clean formation of the tricycles **10**−**12** in moderate to good yields (31−69%) (Schemes 4−6). It should be mentioned that minor

SCHEME 4



(+)-**2a** n = 1
(+)-**2b** n = 2

(+)-**10a** n = 1 (69%)
(+)-**10b** n = 2 (54%)

cycloadducts **9** as well as the N-acylated derivatives of minor cycloadducts **5** did not undergo RCM. Thus, for a successful RCM a structural condition must be satisfied in the starting dienes, namely, a relative anti stereochemistry at the single bond connecting the two heterocyclic rings. As has been outlined recently, ligand modification in Grubbs' carbene improves their excellent application profile even further.[14] Metathesis of some compounds **2**, **6**, and **8** was effected with the second-

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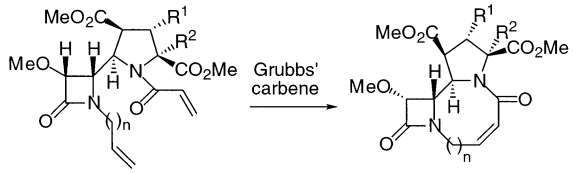
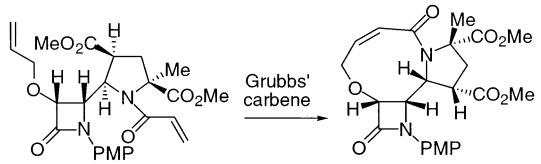
(13) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

SCHEME 5

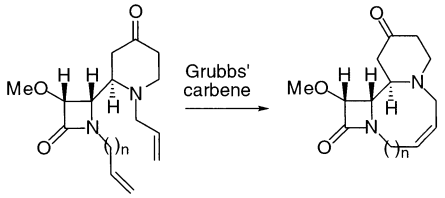


(+)-6a **(+)-11a** R^1 = H, R^2 = H, n = 1 (62%)
(+)-6b **(+)-11b** R^1 = H, R^2 = Me, n = 1 (67%)
(−)-6c **(+)-11c** R^1 = CO_2Me, R^2 = Me, n = 1 (57%)
(+)-6d **(+)-11d** R^1 = H, R^2 = H, n = 2 (58%)
(+)-6e **(+)-11e** R^1 = H, R^2 = Me, n = 2 (58%)
(+)-6f **(+)-11f** R^1 = H, R^2 = Me, n = 3 (35%)



(+)-6g **(+)-11g** (35%)

SCHEME 6



(+)-8a **(+)-12a** n = 1 (53%)
(+)-8b **(+)-12b** n = 2 (31%)
(+)-8c **(+)-12c** n = 3 (33%)

generation 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (Im)-substituted ruthenium-based catalyst $ImCl_2Cy_3$-PRu=CHPh, obtaining results similar to those observed with Grubbs' carbene. Because the second-generation Grubbs' catalyst neither accelerated the reaction rate or improved the yield of tricycles **10**−**12**, we chose the less expensive first-generation Grubbs' carbene for our study. Interestingly, in the Grubbs' carbene promoted reaction of compounds (+)-**8b** and (+)-**8c** together with the RCM products (+)-**12b** and (+)-**12c** we isolated N-deallylation products. Results of this novel method toward catalytic N-deallylation of tertiary amines by using Grubbs' carbene will be published independently.[8e]

^{1}H NMR analysis of the reaction mixtures showed a single isomer for compounds **10**−**12** in all cases. Not unexpectedly, only the *cis*-olefin was formed for eight- and nine-membered rings (compounds **10a**−**b**, **11a**−**e**, (+)-**11g**, and **12a**,**b**), while for the 10-membered diazoninones (+)-**11f** and (+)-**12c** only the *trans*-olefin was obtained.[15] Importantly, the stereochemical integrity of the stereogenic centers at the four-, five-, and six-membered rings remained unaltered during the transformation of dienic compounds **2**, **6**, and **8** into tricyclic products **10**−**12**. The stereochemistry of fused tricyclic 2-azetidinones **10**−**12** was deduced by qualitative homonuclear NOE difference spectra. Taking into account that dienes **2**, **6**, and **8** could be cyclized, the stereochemistry for compounds **2**, **6**, and **8** was inmediately deduced by comparison with the NOE results of the tricyclic systems. Furthermore, the stereochemistry of metathesis precursors **2**, **6**, and **8** was assigned on the basis of our previous results for related cycloaddition products.[10−12]

Conclusions

The combination of [2 + 2], [3 + 2], or [4 + 2] cycloaddition of imines and ring-closing metathesis has been shown as a useful synthetic tool for the asymmetric synthesis of unusual fused tricyclic 2-azetidinones bearing two bridgehead nitrogen atoms. A range of substrates was examined, and tricyclic β-lactams containing eight, nine, and 10 medium-sized central rings and four-, five-, and six-membered distal rings were prepared. In addition to the novelty of this sequential strategy, this methodology is very versatile with the possibility of obtaining a variety of conveniently functionalized tricyclic β-lactams just by changing the substituents in readily available starting materials. The method offers the possibility of a future application to different chiral building blocks other than 2-azetidinones, and we believe this finding could open a new way for the design and asymmetric synthesis of fused heterocycles. Other aspects of this chemistry are currently under investigation in our laboratory.

Experimental Section

General Methods. General experimental data and procedures have been previously reported.[8] NMR spectra were recorded in $CDCl_3$ solutions, except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Specific rotation $[\alpha]_D$ is given in deg per dm at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General Procedure for the Synthesis of C4,C4′-Bis-β-lactams 2. A suspension of 4-oxoazetidine-2-carbaldehyde (+)-**1a** (308 mg, 1.82 mmol), the appropriate amine (2.73 mmol), and $MgSO_4$ (1.75 g, 14.6 mmol) in anhydrous dichloromethane (25 mL) was stirred at room temperature overnight. Then, the mixture was filtered, and the solvent was removed under reduced pressure. Further purification was not necessary, and the resulting imino β-lactams were used as such. Phenoxyacetyl chloride (469 mg, 2.75 mmol) in anhydrous dichloromethane (5 mL) was added dropwise via syringe to a solution of the corresponding imine and Et_3N (555 mg, 5.49 mmol) in dichloromethane (30 mL), at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and was stirred for 16 h. The crude mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (2 × 5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **2**. Spectroscopic and analytical data for some representative forms of **2** follow.[16]

(14) (a) Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67. (b) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811. (c) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236. (d) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. *J. Org. Chem.* **2000**, *65*, 2204.

(15) Since it is known that the *J* value for *trans*-olefins is approximately 12−18 Hz while for *cis*-olefins its is approximately 7−11 Hz, the geometry of the double bond could be determined. In addition, NOE experiments were performed to confirm these assignments.

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

C4,C4′-Bis-2-azetidinone (+)-2a. From 156 mg (2.73 mmol) of allylamine, after column chromatography eluting with ethyl acetate/hexanes (1:1), 500 mg (81%) of the compound (+)-**2a** was obtained: colorless oil; $[\alpha]_D = +15.5$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 3.52 (s, 3H), 3.86 (m, 2H), 4.18 (m, 4H), 4.59 (d, 1H, $J = 5.1$ Hz), 5.16 (m, 4H), 5.31 (d, 1H, $J = 5.1$ Hz), 5.77 (m, 2H), 7.04 (m, 2H), 7.31 (m, 3H); ^{13}C NMR δ 167.6, 165.9, 157.2, 131.5, 129.8, 122.7, 118.3, 118.1, 115.7, 83.5, 80.5, 59.3, 56.5, 56.2, 44.4, 44.0; IR ($CHCl_3$, cm^{-1}) ν 1765, 1750; MS (CI), *m/z* 343 ($M^+ + 1$, 100), 342 (M^+, 11). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.72; H, 6.44; N, 8.16.

General Procedure for the Synthesis of Cycloadducts 4 and 5. A solution of the appropriate 4-azetidinone-2-carbaldehyde **1** (1.00 mmol) in anhydrous dichloromethane (7 mL) was added dropwise to a stirred solution of 4 Å molecular sieves (2.0 g) and the corresponding α-amino ester (1.50 mmol) in dichloromethane (3 mL) at room temperature. After being stirred for 2 h at room temperature, the mixture was filtered through a plug of Celite. The solvent was removed under reduced pressure giving in quantitative yield imines **3**. The crude product was used for the next step without any further purification.

To a solution of the appropriate imine **3** (1.00 mmol) in anhydrous toluene (6 mL) were sequentially added silver acetate (1.20 mmol), the corresponding dipolarophile (1.50 mmol), and triethylamine (1.20 mmol), and the reaction mixture was stirred at room temperature for 40 h. Saturated aqueous NH_4Cl (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/hexanes/triethylamine mixtures gave analytically pure compounds **4** and **5**.

Preparation of Cycloadducts (+)-4b and (+)-5b. From 400 mg (2.35 mmol) of the aldehyde (+)-**1a** and 364 mg (3.53 mmol) of alanine methyl ester, after column chromatography eluting with ethyl acetate/hexanes (10:1 containing 10% of triethylamine), were obtained 396 mg (49%) of the less polar compound (+)-**4b** and 202 mg (25%) of the more polar compound (+)-**5b**.

Cycloadduct (+)-4b: colorless oil; $[\alpha]_D = +30.6$ (*c* 0.7, $CHCl_3$); ^1H NMR (C_6D_6) δ 1.18 (s, 3H), 1.49 (dd, 1H, $J = 13.8$, 7.8 Hz), 2.56 (dd, 1H, $J = 13.8$, 3.9 Hz), 3.04 (m, 1H), 3.20 (s, 3H), 3.32 (m, 4H), 3.40 (s, 3H), 3.53 (dd, 1H, $J = 8.4$, 4.8 Hz), 3.82 (dd, 1H, $J = 15.6$, 7.2 Hz), 4.05 (m, 2H), 5.10 (m, 2H), 5.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.5, 173.6, 167.5, 131.9, 118.4, 83.6, 65.5, 62.0, 59.3, 58.9, 52.4, 51.5, 46.3, 43.6, 41.1, 27.4; IR ($CHCl_3$, cm^{-1}) ν 3334, 1736; MS (CI), *m/z* 341 ($M^+ + 1$, 100), 340 (M^+, 25). Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.50; H, 7.07; N, 8.20.

Cycloadduct (+)-5b: colorless oil; $[\alpha]_D = +56.8$ (*c* 0.8, $CHCl_3$); ^1H NMR (CD_3OD) δ 1.29 (s, 3H), 1.85 (dd, 1H, $J = 13.8$, 7.5 Hz), 2.63 (dd, 1H, $J = 13.8$, 1.5 Hz), 3.02 (td, 1H, $J = 8.1$, 2.1 Hz), 3.49 (s, 3H), 3.54 (m, 4H), 3.65 (m, 4H), 3.93 (m, 2H), 4.53 (d, 1H, $J = 5.1$ Hz), 5.12 (m, 2H), 5.72 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.6, 173.5, 168.0, 132.6, 117.6, 84.2, 64.1, 61.6, 59.4, 58.6, 52.6, 51.9, 46.5, 43.5, 40.6, 28.1; IR ($CHCl_3$, cm^{-1}) ν 3339, 1740; MS (CI), *m/z* 341 ($M^+ + 1$, 100), 340 (M^+, 17). Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.39; H, 7.08; N, 8.27.

Preparation of Cycloadducts (+)-4c and (+)-5c. From 274 mg (1.64 mmol) of the aldehyde (+)-**1a** and 253 mg (2.45 mmol) of alanine methyl ester, after column chromatography eluting with ethyl acetate/hexanes (7:1 containing 10% of triethylamine), were obtained 290 mg (45%) of the less polar compound (+)-**4c** and 193 mg (30%) of the more polar compound (+)-**5c**.

Cycloadduct (+)-4c: colorless oil; $[\alpha]_D = +34.1$ (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3H), 3.19 (d, 1H, $J = 10.2$ Hz), 3.35 (dd, 1H, $J = 10.8$, 9.3 Hz), 3.54 and 3.65 (s, each 3H), 3.67 (m, 1H), 3.68 and 3.78 (s, each 3H), 3.90 (m, 1H), 4.08 (m, 2H), 4.30 (d, 1H, $J = 4.8$ Hz), 5.18 (m, 4H), 5.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.5, 177.3, 174.0, 167.8, 132.2, 117.8, 83.3, 66.9, 60.5, 59.1, 58.3, 55.2, 52.8, 52.1, 52.0, 49.0, 43.8, 21.5; IR ($CHCl_3$, cm^{-1}) ν 3336, 1734; MS (CI), *m/z* 399 ($M^+ + 1$, 100), 398 (M^+, 33). Anal. Calcd for $C_{18}H_{26}N_2O_8$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.19; H, 6.59; N, 7.01.

Cycloadduct (+)-5c: colorless oil; $[\alpha]_D = +24.1$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 3.57 (m, 4H), 3.66 (s, 3H), 3.71 (m, 4H), 3.79 (s, 3H), 3.85 (d, 1H, $J = 5.1$ Hz), 4.02 (m, 3H), 4.46 (d, 1H, $J = 4.9$ Hz), 5.22 (m, 2H), 5.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.1, 171.9, 171.5, 167.2, 131.9, 117.9, 84.2, 66.7, 59.1, 59.0, 57.1, 54.5, 52.8, 52.1, 51.9, 48.9, 43.0, 20.7; IR ($CHCl_3$, cm^{-1}) ν 3332, 1735; MS (CI), *m/z* 399 ($M^+ + 1$, 100), 398 (M^+, 21). Anal. Calcd for $C_{18}H_{26}N_2O_8$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.34; H, 6.56; N, 7.02.

Preparation of Cycloadducts (+)-4d and (+)-5d. From 274 mg (1.64 mmol) of the aldehyde (+)-**1b** and 221 mg (2.45 mmol) of glycine methyl ester, after column chromatography eluting with ethyl acetate/hexanes (3:1 containing 10% of triethylamine), were obtained 162 mg (36%) of the less polar compound (+)-**4d** and 71 mg (16%) of the more polar compound (+)-**5d**.

Cycloadduct (+)-4d: colorless oil; $[\alpha]_D = +40.7$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.30 (m, 4H), 3.17 (m, 1H), 3.35 (m, 2H), 3.53 (m, 1H), 3.58 (s, 3H), 3.69 (m, 4H), 3.79 (m, 4H), 4.36 (d, 1H, $J = 4.9$ Hz), 5.07 (m, 2H), 5.77 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.9, 173.8, 167.9, 135.2, 117.1, 83.5, 63.8, 59.8, 59.5, 59.4, 52.3, 51.8, 45.6, 40.7, 34.4, 32.1; IR ($CHCl_3$, cm^{-1}) ν 3338, 1735; MS (CI), *m/z* 341 ($M^+ + 1$, 100), 340 (M^+, 25). Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.52; H, 7.09; N, 8.24.

Cycloadduct (+)-5d: colorless oil; $[\alpha]_D = +75.0$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.35 (m, 4H), 3.02 (m, 1H), 3.13 (dd, 1H, $J = 7.3$, 5.8 Hz), 3.39 (dd, 1H, $J = 8.5$, 5.8 Hz), 3.52 (m, 1H), 3.58 (s, 3H), 3.68 and 3.75 (s, each 3H), 3.90 (m, 2H), 4.48 (d, 1H, $J = 5.1$ Hz), 5.08 (m, 2H), 5.73 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.7, 173.2, 168.1, 134.7, 117.3, 83.7, 62.9, 59.2, 57.9, 57.7, 52.2, 51.9, 44.9, 40.2, 32.7, 32.3; IR ($CHCl_3$, cm^{-1}) ν 3340, 1737; MS (CI), *m/z* 341 ($M^+ + 1$, 100), 340 (M^+, 18). Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.38; H, 7.08; N, 8.25.

General Procedure for the N-Acylation of Cycloadducts 4. Synthesis of Dienes 6. Acryloyl chloride (1.3 mmol) and triethylamine (1.3 mmol) were sequentially added dropwise to a stirred solution of the corresponding pyrrolidinyl-β-lactam **4** (1.0 mmol), in dichloromethane (17 mL) at 0 °C, and the mixture was stirred for 3 h. The organic phase was washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. In some cases, chromatography of the residue eluting with hexanes/ethyl acetate mixtures was necessary to obtain analytically pure compounds **6**. Spectroscopic and analytical data for some representative pure forms of **6** follow.

Compound (+)-6a: pale yellow oil (100%); $[\alpha]_D = +20.2$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.44 (m, 2H), 3.02 (m, 1H), 3.54 (s, 3H), 3.64 (m, 4H), 3.71 (s, 3H), 3.89 (dd, 1H, $J = 15.8$, 5.7 Hz), 4.12 (dd, 1H, $J = 10.3$, 5.2 Hz), 4.28 (d, 1H, $J = 5.2$ Hz), 4.55 (dd, 1H, $J = 10.5$, 8.3 Hz), 4.67 (dd, 1H, $J = 10.3$, 6.9 Hz), 5.11 (m, 2H), 5.71 (m, 2H), 6.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.3, 170.8, 169.3, 165.4, 131.5, 130.7, 127.0, 117.8, 83.3, 59.7, 59.3, 58.5, 55.9, 52.7, 52.3, 45.9, 44.7, 31.1; IR ($CHCl_3$, cm^{-1}) ν 1735, 1650; MS (CI), *m/z* 381 ($M^+ + 1$, 100), 380 (M^+, 17). Anal. Calcd for $C_{18}H_{24}N_2O_7$: C, 56.83; H, 6.36; N, 7.36. Found: C, 56.90; H, 6.37; N, 7.34.

Compound (+)-6b: pale yellow oil (100%); $[\alpha]_D = +20.1$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.56 (s, 3H), 2.06 (dd, 1H, $J = 12.7$, 6.0 Hz), 2.57 (dd, 1H, $J = 13.1$, 12.9 Hz), 3.35 (m, 1H), 3.50 (s, 3H), 3.65 (m, 4H), 3.69 (s, 3H), 3.77 (m, 1H), 4.22 (m, 2H), 4.74 (dd, 1H, $J = 9.7$, 6.9 Hz), 5.01 (m, 2H), 5.67 (m, 2H), 6.31 (m, 2H); ^{13}C NMR δ 173.4, 170.6, 169.3, 164.1, 131.3, 128.9, 127.8, 117.1, 83.0, 65.8, 59.3, 59.1, 56.1, 52.7, 52.1, 44.4, 44.2, 39.7, 21.3; IR ($CHCl_3$, cm^{-1}) ν 1748, 1651; MS (CI), *m/z*

395 ($M^+ + 1$, 100), 391 (M^+, 21). Anal. Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.92; H, 6.68; N, 7.06.

Compound (+)-6g: pale yellow oil (88%); $[\alpha]_D = +14.2$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H), 2.14 (dd, 1H, J = 12.7, 5.9 Hz), 2.77 (t, 1H, J = 13.2 Hz), 3.44 (m, 1H), 3.68 and 3.72 (s, each 3H), 3.85 (s, 3H), 4.01 (m, 2H), 4.48 (dd, 1H, J = 12.2, 5.4 Hz), 4.57 (d, 1H, J = 5.4 Hz), 4.85 (dd, 1H, J = 10.3, 7.3 Hz), 4.96 (dd, 1H, J = 10.8, 5.4 Hz), 5.26 (m, 3H), 5.72 (dd, 1H, J = 16.6, 1.9 Hz), 5.83 (m, 1H), 7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 171.6, 166.2, 164.8, 156.7, 133.3, 131.1, 128.6, 127.3, 119.8, 117.8, 113.9, 80.9, 72.2, 66.7, 60.4, 58.6, 55.4, 52.8, 52.2, 45.2, 40.9, 21.1; IR ($CHCl_3$, cm^{-1}) ν 3336, 1735; MS (CI), *m*/*z* 486 ($M^+ + 1$, 100), 485 (M^+, 19). Anal. Calcd for $C_{25}H_{29}N_2O_8$: C, 61.85; H, 6.02; N, 5.77. Found: C, 61.92; H, 6.01; N, 5.76.

General Procedure for the Synthesis of Cycloadducts 7. A solution of allylamine (1.10 mmol) in dichloromethane (4 mL) was added dropwise to a stirred suspension of the appropriate 4-azetidinone-2-carbaldehyde **1** (1.0 mmol) and magnesium sulfate (1.50 mmol) in dichloromethane (100 mL) at room temperature. After being stirred for 16 h at room temperature, the mixture was filtered and the solvent was removed under reduced pressure. The solvent was removed under reduced pressure giving in quantitative yield the corresponding imines. The crude product was used for next step without any further purification.

A solution of the appropriate imine (1.0 mmol) in acetonitrile (5 mL) was added dropwise to a stirred suspension of zinc iodide (1.10 mmol) in acetonitrile (13 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 15 min, and then Danishefsky's diene (1.20 mmol) was added. After disappearance of the imine (TLC), saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures (containing 1% of triethylamine) gave compounds **7**. Spectroscopic and analytical data for some representative forms of **7** follow.

Cycloadduct 7a. From the allyl imine of aldehyde (+)-**1a** (250 mg, 1.20 mmol), 248 mg (75%) of cycloadduct **7a**, containing ca. 20% of its syn epimer, was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.21 and 2.83 (m, each 1H), 3.49 (s, 2.4H), 3.57 (s, 0.6H), 3.96 (m, 4H), 4.21 (m, 1H), 4.43 (m, 1H), 4.93 (m, 1H), 5.19 (m, 4H), 5.69 (m, 2H), 6.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 190.5 (M), 189.9 (m), 168.5 (M), 168.4 (m), 152.1 (M + m), 133.4 (m), 133.0 (M), 130.8 (m), 130.5 (M), 119.7 (M), 119.3 (m), 118.7 (m), 118.6 (M), 98.5 (M + m), 82.9 (M), 82.6 (m), 59.4 (M), 58.6 (m), 58.3 (M), 56.5 (m), 56.1 (m), 54.9 (M), 54.3 (m), 53.1 (M), 44.9 (m), 44.4 (M), 37.6 (M), 37.2 (m); IR ($CHCl_3$, cm^{-1}) ν 1740, 1705; MS (CI), *m*/*z* 277 ($M^+ + 1$, 100), 276 (M^+, 12).

General Procedure for the Synthesis of Dienes 8. A cooled solution of L-Selectride (49 mg, 0.259 mmol) in tetrahydrofuran (0.259 mL) was added dropwise to a stirred solution of the appropriate cycloadduct **7** (0.236 mmol) in tetrahydrofuran (3.5 mL) at −78 °C, and the mixture was stirred for 1 h at −78 °C. Saturated aqueous sodium hydrogen carbonate (0.5 mL) was added, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures (containing 1% of triethylamine) gave analytically pure compounds **8** and **9**.

Preparation of Compounds (+)-8a and (+)-9a. From 100 mg (0.36 mmol) of the cycloadduct **7a**, after column chromatography eluting with ethyl acetate/hexanes (2:1 containing 1% of triethylamine), 60 mg (68%) of the less polar compound (+)-**8a** and 14 mg (16%) of the more polar compound (+)-**9a** were obtained.

Compound (+)-8a: colorless oil; $[\alpha]_D = +141.0$ (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.25 and 2.57 (m, each 2H), 3.17 and 3.43 (m, each 2H), 3.56 (m, 4H), 3.72 (dd, 1H, J = 10.5, 4.6 Hz), 3.86 (dd, 1H, J = 15.4, 7.3 Hz), 4.20 (ddt, 1H, J = 15.4, 4.4. 1.7 Hz), 4.45 (d, 1H, J = 4.9 Hz), 5.18 (m, 4H), 5.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.7, 167.9, 135.7, 132.5, 118.3, 118.1, 83.2, 62.0, 59.3, 56.0, 55.9, 46.6, 43.8, 39.3, 37.4; IR ($CHCl_3$, cm^{-1}) ν 1742, 1715; MS (CI), *m*/*z* 279 ($M^+ + 1$, 100), 278 (M^+, 9). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.79; H, 7.96; N, 10.08.

Compound (+)-9a: colorless oil; $[\alpha]_D = +33.5$ (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.35 and 2.81 (m, each 2H), 3.28 (m, 5H), 3.49 (m, 4H), 3.91 (t, 1H, J = 5.3 Hz), 4.14 (m, 1H), 4.43 (t, 1H, J = 5.2 Hz), 5.19 (m, 4H), 5.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.0, 168.4, 134.9, 131.5, 118.9, 118.2, 83.8, 59.7, 59.6, 58.1, 56.2, 48.7, 44.6, 41.2, 39.3; IR ($CHCl_3$, cm^{-1}) ν 1741, 1716; MS (CI), *m*/*z* 279 ($M^+ + 1$, 100), 278 (M^+, 12). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.65; H, 7.96; N, 10.04.

General Procedure for the RCM Reaction. To a solution protected from the sunlight of the corresponding dienes **2**, **6**, and **8** (0.20 mmol) in anhydrous toluene (6 mL) was added in portions $Cl_2(Cy_3P)_2Ru{=}CHPh$ (0.01 mmol) under argon. The resulting mixture was heated at reflux until complete disappearance of the starting material (TLC) and was concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **10**−**12**.

Tricyclic 2-Azetidinone (+)-10b. From 80 mg (0.223 mmol) of diene (+)-**2b** was obtained 40 mg (54%) of compound (+)-**10b** as a pale yellow oil: $[\alpha]_D = +36.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.36 (m, 2H), 3.09 (m, 1H), 3.39 (s, 3H), 3.73 (m, 2H), 4.12 (m, 3H), 4.56 (d, 1H, J = 4.4 Hz), 5.30 (d, 1H, J = 4.3 Hz), 5.71 (m, 2H), 7.05 (m, 3H), 7.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.2, 164.7, 157.5, 129.7, 129.6, 129.2, 122.6, 115.9, 83.2, 80.0, 59.7, 58.6, 58.3, 36.3, 36.1; IR ($CHCl_3$, cm^{-1}) ν 1762, 1753; MS (CI), *m*/*z* 329 ($M^+ + 1$, 100), 328 (M^+, 9). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.92; H, 6.15; N, 8.51).

Tricyclic 2-Azetidinone (+)-11c. From 60 mg (0.135 mmol) of diene (−)-**6c** was obtained 32 mg (57%) of compound (+)-**11c** as a yellow oil: $[\alpha]_D = +210.8$ (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H), 3.33 (m, 2H), 3.72 (s, 3H), 3.77 and 3.78 (s, each 3H), 4.11 (m, 2H), 4.22 (dd, 1H, J = 10.2, 4.8 Hz), 4.60 (d, 1H, J = 4.8 Hz), 4.84 (d, 1H, J = 10.1 Hz), 6.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.6, 170.8, 166.9, 166.8, 165.6, 129.3, 128.2, 83.1, 70.9, 62.5, 58.9, 58.4, 57.1, 52.9, 52.8, 52.7, 47.1, 36.5, 23.8; IR ($CHCl_3$, cm^{-1}) ν 1743, 1661; MS (CI), *m*/*z* 425 ($M^+ + 1$, 100), 426 (M^+, 15). Anal. Calcd for $C_{19}H_{24}N_2O_9$: C, 53.77; H, 5.70; N, 6.60. Found: C, 53.85; H, 5.71; N, 6.59.

Tricyclic 2-Azetidinone (+)-11d. From 80 mg (0.221 mmol) of diene (+)-**6d** was obtained 43 mg (58%) of compound (+)-**11d** as a pale brown oil: $[\alpha]_D = +145.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.39 (m, 4H), 3.08 (m, 1H), 3.49 (s, 3H), 3.64 (m, 5H), 3.79 (s, 3H), 4.13 (dd, 1H, J = 10.2, 4.6 Hz), 4.25 (d, 1H, J = 4.9 Hz), 4.55 (dd, 1H, J = 10.5, 7.1 Hz), 4.64 (dd, 1H, J = 10.0, 8.5 Hz), 5.89 and 6.35 (m, each 1H); ^{13}C NMR ($CDCl_3$) δ 172.5, 170.8, 168.8, 168.3, 132.9, 125.7, 83.0, 61.3, 58.7, 56.9, 52.6, 52.1, 45.6, 38.7, 31.5, 27.3; IR ($CHCl_3$, cm^{-1}) ν 1742, 1662; MS (CI), *m*/*z* 367 ($M^+ + 1$, 100), 366 (M^+, 11). Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.80; H, 6.04; N, 7.63.

Tricyclic 2-Azetidinone (+)-11f. From 67 mg (0.158 mmol) of diene (+)-**6f** was obtained 22 mg (35%) of compound (+)-**11f** as a pale brown oil: $[\alpha]_D = +92.1$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H), 2.13 (dd, 1H, J = 12.7, 6.4 Hz), 2.33 (m, 2H), 2.65 (t, 1H, J = 13.2 Hz), 2.83 (m, 1H), 3.32 (m, 2H), 3.56 (s, 3H), 3.72 and 3.79 (s, each 3H), 4.24 (m, 1H), 4.76 (dd, 1H, J = 9.3, 6.8 Hz), 5.35 (m, 1H), 5.48 (m, 1H), 5.69 (m, 1H), 6.42 (d, 1H, J = 17.1 Hz), 6.57 (dd, 1H, J = 17.1, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 173.8, 171.2, 169.8, 164.2, 128.4, 127.9, 83.2, 66.7, 59.95, 59.6, 56.9, 53.2, 52.6, 44.7, 42.4, 40.2,

31.1, 21.8, 18.4; IR ($CHCl_3$, cm^{-1}) ν 1744, 1664; MS (CI), *m/z* 395 ($M^+ + 1$, 100), 394 (M^+, 14). Anal. Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.94; H, 6.66; N, 7.08.

Tricyclic 2-Azetidinone (+)-11g. From 45 mg (0.093 mmol) of diene (+)-**6g** was obtained 15 mg (35%) of compound (+)-**11g** as a pale yellow oil: $[\alpha]_D = +214.1$ (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48 (s, 3H), 2.09 (dd, 1H, $J = 12.5$, 4.6 Hz), 2.71 (dd, 1H, $J = 13.2$, 12.9 Hz), 3.48 (m, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 3.78 (s, 3H), 4.09 (m, 1H), 4.38 (m, 1H), 4.54 (d, 1H, $J = 4.1$ Hz), 4.91 (m, 2H), 5.67 (d, 1H, $J = 16.7$ Hz), 6.31 (dd, 1H, $J = 16.4$, 10.1 Hz); ^{13}C NMR ($CDCl_3$) δ 174.6, 173.0, 166.8, 165.1, 157.0, 132.7, 128.1, 127.0, 120.1, 114.2, 82.3, 77.4, 67.0, 60.9, 58.8, 55.8, 53.2, 52.6, 45.5, 41.8, 22.2; IR ($CHCl_3$, cm^{-1}) ν 1744, 1660; MS (CI), *m/z* 459 ($M^+ + 1$, 100), 458 (M^+, 11). Anal. Calcd for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.34; H, 5.70; N, 6.14.

Tricyclic 2-Azetidinone (+)-12a. From 60 mg (0.216 mmol) of diene (+)-**8a** was obtained 28 mg (53%) of compound (+)-**12a** as a pale brown oil: $[\alpha]_D = +96.7$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.55 (dd, 1H, $J = 14.6$, 10.2 Hz), 1.70 (m, 2H), 2.10 and 2.30 (m, each 2H), 2.71 (m, 3H), 3.02 (s, 3H), 3.23 (dd, 1H, $J = 14.2$, 6.8 Hz), 3.57 (d, 1H, $J = 4.4$ Hz), 3.69 (dd, 1H, $J = 14.2$, 6.4 Hz), 5.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 207.7, 166.4, 132.2, 123.8, 82.0, 61.1, 59.8, 58.9, 53.5, 51.3, 40.6, 39.7, 36.6; IR ($CHCl_3$, cm^{-1}) ν 1744, 1716; MS (CI), *m/z* 251 ($M^+ + 1$, 100), 250 (M^+, 9). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.31; H, 7.24; N, 11.21.

Tricyclic 2-Azetidinone (+)-12c. From 50 mg (0.171 mmol) of diene (+)-**8c** were obtained 15 mg (33%) of the less polar compound (+)-**12c** and the corresponding more polar N-deallylation product: colorless oil; $[\alpha]_D = +191.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.26 (m, 8H), 3.05 (m, 4H), 3.34 (m, 1H), 3.48 (s, 3H),3.49 (m, 3H), 4.35 (d, 1H, $J = 5.0$ Hz), 5.61 and 5.79 (m, each 1H); ^{13}C NMR ($CDCl_3$) δ 211.0, 170.8, 137.1, 128.8, 83.2, 77.0, 62.9, 59.6, 59.2, 47.3, 41.3, 37.9, 30.1, 28.1, 25.7; IR ($CHCl_3$, cm^{-1}) ν 1740, 1712; MS (CI), *m/z* 279 ($M^+ + 1$, 100), 278 (M^+, 10). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.80; H, 7.98; N, 10.04.

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Supporting Information Available: Spectroscopic and analytical data for compounds (+)-**2b**, (+)-**4a**, (+)-**4e**−**g**, (+)-**5a**, (+)-**5e**, (+)-**5f**, (−)-**6c**, (+)-**6d**−**f**, **7b**, **7c**, (+)-**8b**, (+)-**8c**, (+)-**9b**, (+)-**10a**, (+)-**11a**, (+)-**11b**, (+)-**11e**, and (+)-**12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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