

Synthesis of Strained Tricyclic β -Lactams by Intramolecular [2+2] Cycloaddition Reactions of 2-Azetidinone-Tethered Enallenols: Control of Regioselectivity by Selective Alkene Substitution

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Abstract: A convenient metal-free methodology for the preparation of structurally novel, strained tricyclic β -lactams containing a cyclobutane ring has been developed. The first examples accounting for the intramolecular [2+2] cycloaddition reactions in β -lactams have been achieved by the ther-

molysis of 2-azetidinone-tethered enallenols, which have been prepared in aqueous media by regio- and diastereoselective indium-mediated carbonyl al-

lenylation of 4-oxoazetidine-2-carbaldehydes. Notably, the regioselectivity of the cycloaddition can be tuned in the allene component just by a subtle variation in the substitution pattern of the alkene component.

Keywords: allenes • cyclization • cycloaddition • lactams • radicals

Introduction

The importance of the stereoselective synthesis of chiral β -lactams is ever increasing in light of structure-activity relationship studies and the development of new derivatives of the β -lactam antibiotics and inhibitors of β -lactamases.^[1] Due to increased bacterial resistance,^[2] the discovery of tri-

cyclic β -lactam antibiotics, which are a new class of synthetic antibacterial agents featuring good resistance to β -lactamases and dehydropeptidases,^[3] 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.^[4] In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition,^[5] to the use of these products as starting materials for the development of new synthetic methodologies.^[6]

During the past decades the allene moiety has developed from almost a rarity to an established member of the weaponry utilized in modern organic synthetic chemistry.^[7] In particular, the [2+2] cycloaddition reaction of allenes with alkenes has been of special interest, because of the synthetic importance of the methylenecyclobutane products produced.^[8] However, this process has suffered from low stereo- and positional selectivity. Intramolecularization of the reactions, usually by placing the reacting group at a distance that produces five- or six-membered rings, should solve the regioselectivity problems as larger rings are unfavored.

In our ongoing project, directed towards the preparation of nitrogen-containing products of biological interest,^[9] we have initiated a study into the use of allenols in organic synthesis. In this contribution, we present full details of the formal [2+2] cycloaddition of the alkene partner with the distal bond of the allene moiety in 2-azetidinone-tethered enallenols,^[10] together with a reversal of regioselectivity in

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 Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author. It contains compound characterization data and experimental procedures for compounds **2a–m**, **(+)-3a**, **(+)-3b**, **(+)-4a**, **(+)-4b**, **(-)-4c**, **(±)-5a**, **(±)-5b**, **(+)-6a**, **(+)-7b**, **(+)-7c**, **(±)-9c**, **(±)-10**, and **(±)-11**.

the allene component just by a subtle variation of the substitution pattern of the alkene to give cyclobutane fused β -lactams.

Results and Discussion

The starting substrates, 4-oxoazetidine-2-carbaldehydes **1a–f** (Table 1), were prepared both in the racemic form and in

Table 1. Regio- and stereoselective allenylation of 4-oxoazetidine-2-carbaldehydes **1** in aqueous media.

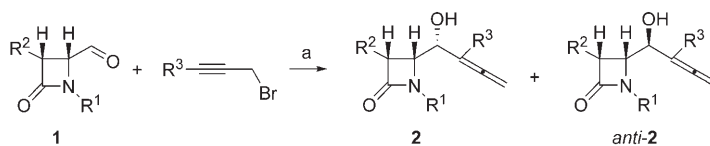
Aldehyde	R ¹	R ²	R ³	Product	syn/anti ratio ^[a]	Yield [%] ^[b]
(+)- 1a	allyl	MeO	Me	(+)- 2a	95:5	75
(+)- 1a	allyl	MeO	Ph	(+)- 2b	100:0	64
(+)- 1b	3-methyl-but-2-enyl	MeO	Me	(+)- 2c	85:15	68
(+)- 1b	3-methyl-but-2-enyl	MeO	Ph	(+)- 2d	100:0	61
(+)- 1c	methallyl	MeO	Ph	(+)- 2e	100:0	51
(+)- 1d	methallyl	PhO	Me	(+)- 2f	90:10	79
(+)- 1d	methallyl	PhO	Ph	(+)- 2g	100:0	58
(±)- 1e	PMP	vinyl	Me	anti-(±)- 2h	10:90	60
(±)- 1e	PMP	vinyl	Ph	(±)- 2i	70:30	89
(±)- 1f	PMP	isopropenyl	Me	anti-(±)- 2j	10:90	72
(±)- 1f	PMP	isopropenyl	Ph	(±)- 2k	65:35	63

[a] The ratio was determined from the integration of well-resolved signals in the ¹H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [b] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-MeOC₆H₄.

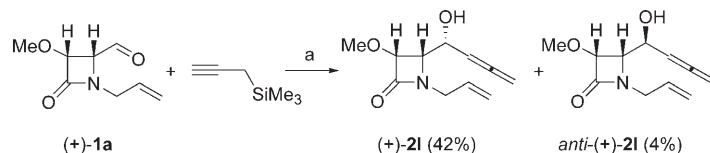
optically pure form by using standard methodology. Enantiopure 2-azetidinones (+)-**1a–d** were obtained as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylidene-glyceraldehyde, by means of a Staudinger reaction with methoxy- or phenoxyacetyl chloride in the presence of Et₃N, followed by sequential acidic acetone hydrolysis and oxidative cleavage.^[11] Racemic compounds (±)-**1e** and (±)-**1f** were obtained as single *cis*-diastereoisomers, following our one-pot method from *N,N*-di-(*p*-methoxyphenyl)glyoxal diimine.^[12] 2-Azetidinone-tethered allenols **2a–k** (Table 1) were obtained by a metal-mediated Barbier-type carbonyl-allenylation reaction of β -lactam aldehydes **1a–f** in aqueous media by using our previously described methodologies (Scheme 1, Table 1).^[9d,e] α -Allenyl alcohol (+)-**2l** was prepared by boron trifluoride diethyl etherate-induced condensation of 4-oxoazetidine-2-carbaldehydes (+)-**1a** with propargyltrimethylsilane (Scheme 2). When total diastereocontrol

was not achieved for the indium-mediated allenylation of aldehydes **1**, the diastereomeric α -allenols **2** and *anti*-**2** were easily separated by gravity flow chromatography.

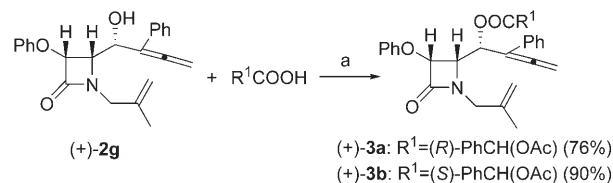
Derivatization of the enantiopure 3-phenoxy α -allenol (+)-**2g** with (*R*)- and (*S*)-acetylmandelic acids to give mandelates **3** enabled the assignment of the configuration at the carbinolic stereocenter (Scheme 3). The configuration at the carbinolic chiral center of the product (+)-**2g** was established by using Trost's method, which involved a comparison of the ¹H NMR chemical shifts of the acetylmandelates (+)-**3a** and (+)-**3b**,^[13] and was assumed to be the same for the rest of enantiopure β -lactams **2**. The configurational assignment for the racemic series was confirmed by X-ray crystallography of the C3-alkenyl adduct *anti*-(±)-**2j** (Figure 1).^[14] It should be noted that the relative ¹H NMR chemical shifts of the β -lactamic and carbinolic protons could be a diagnostic tool for the determination of the relative stereochemistries of *2-syn*-



Scheme 1. Regioselective preparation of α -allenic alcohols **2** in aqueous media. Reagents and conditions: a) In, THF, NH₄Cl (aq sat.), RT, 3–16 h.



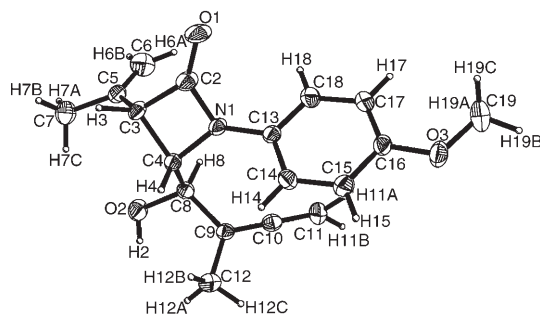
Scheme 2. Regioselective preparation of α -allenic alcohol (+)-**2l** in anhydrous media. Reagents and conditions: a) BF₃·Et₂O, CH₂Cl₂, –78 °C, 1 h.



Scheme 3. Preparation of (*R*)- and (*S*)-acetylmandelates **3**. Reagents and conditions: a) DCC, DMAP (cat), CH₂Cl₂, RT, 16 h (DCC = *N,N*-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine).

and *2-anti*-allenols. For any pair of *syn*- and *anti*-diastereomers, the β -lactamic (H3) and carbinolic hydrogens of the *2-syn*-isomers were approximately δ = 0.05–0.2 ppm upfield of

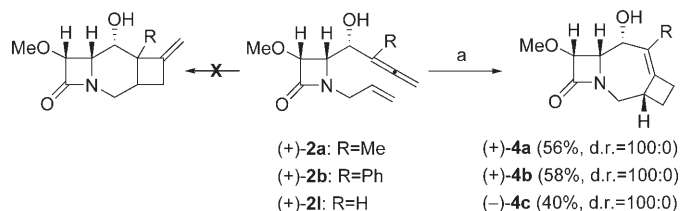
Abstract in Spanish: Se ha descubierto una metodología para la preparación de β -lactamas tricíclicas tensionadas estructuralmente novedosas sin la intervención de metales. La pirólisis de alenoles- β -lactámicos, que se prepararon en medio acuoso mediante la alenilación carbonílica de 4-oxoazetidín-2-carbaldehídos, constituye el primer ejemplo de cicloadición intramolecular [2+2] en β -lactamas. Mención especial merece la regioselectividad observada, pudiéndose controlar y modular con un simple cambio en la sustitución del alqueno.

Figure 1. X-ray diffraction analysis of α -allenol *anti*-($\pm$)-**2j**.

the analogous hydrogens of the **2-anti**-isomers, whilst opposite behavior was observed for the other β -lactamic proton (H4). For the stereoselective addition of the organometallic reagents to β -alkoxyaldehydes **1a–d**, 1,5-metal chelation between the C3-alkoxy substituent and the oxygen aldehyde should preferentially orient towards a 1,2-*anti* selectivity. The lack of 1,5-chelation in 4-oxoazetidine-2-carbaldehydes **1a–f**, can favor either 1,2-*syn* (Cram–Felkin–Ahn control, β -alkoxyaldehydes **1a–d**) or 1,2-*anti* addition (*anti*-Cram–Felkin–Ahn control, β -alkenylaldehydes ($\pm$)-**1e** and ($\pm$)-**1f**), depending on the nature of the C3-group and the nucleophile; these results demonstrate that controlling the stereoselectivity of these reactions is not a trivial matter.

Although, in theory, intramolecular cycloaddition reactions of β -lactam-dienes could be used to prepare tricycles, such reactions involving 2-azetidinone-tethered alkenes have not been reported in the literature. Because of the inherent instability imparted by the cumulated double bond in allenes, cycloaddition reactions take place easily relative to an isolated double bond. Having obtained the enallenols **2**, the next stage was to react the allene group as a 2π -electron donor in the [2+2] process.

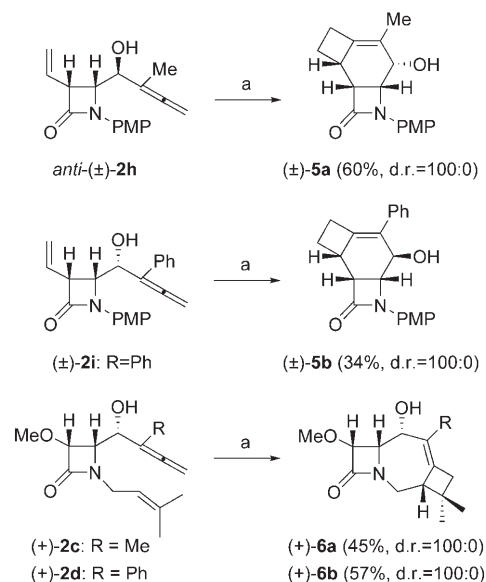
A model thermal cyclization reaction for the enallenols **2** was carried out by heating a solution of *N*-allyl α -allenol (**+)-2a** in toluene at 220 °C in a sealed tube. The thermolysis afforded, in reasonable yield and complete regio- and diastereoselectivity, the tricyclic β -lactam (**+)-4a**, which bears a cyclobutane ring (Scheme 4).^[15] Enallenols (**+)-2b** and

Scheme 4. Regio- and diastereoselective preparation of tricyclic β -lactams **4**. Reagents and conditions: a) toluene, 220 °C, sealed tube, (**+)-4a**: 5 h, (**+)-4b**: 3 h, (**-)-4c**: 10 h.

(**+)-2l** also efficiently undergo [2+2] thermal cyclization to afford the corresponding tricycles (**+)-4b** and (**-)-4c**. The tricyclic ring structures **4a–c** arise from the

formal [2+2] cycloaddition of the alkene with the distal bond of the allene, most likely via a diradical intermediate. The regioselectivity of the process is not affected by the substitution at the allene carbon. The cyclization of the allene (**+)-2l** results in a somewhat slower rate of reaction, but with similar regioselectivity.^[16] Substitution patterns in enallenols (**+)-2a**, (**+)-2b**, and (**+)-2l** were selected in order to direct the regioselectivity of the cycloaddition to the six-membered central-ring formation. However, it was found that the thermal reaction produced tricycles **4**, which bear a central seven-membered ring. No traces of the exocyclic methylene regioisomer were detected.

In a similar manner, 3-vinyl allenols *anti*-($\pm$)-**2h** and ($\pm$)-**2i** produced the C3–C4 fused tricyclic 2-azetidinones ($\pm$)-**5a** and ($\pm$)-**5b**. The present reaction was successfully extended to the enallenols (**+)-2c** and (**+)-2d**, terminally disubstituted at the alkene moieties, producing the tricycles (**+)-6a** and (**+)-6b** (Scheme 5). No other isomers or side

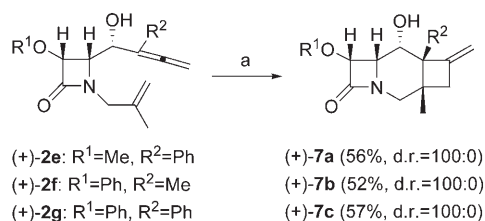
Scheme 5. Regio- and diastereoselective preparation of tricyclic β -lactams **5** and **6**. Reagents and conditions: a) toluene, 220 °C, sealed tube, ($\pm$)-**5a**: 4.5 h, ($\pm$)-**5b**: 3.5 h, (**+)-6a**: 14 h, (**+)-6b**: 8 h.

products were detected. Although complete conversion was observed by TLC and ^1H NMR spectroscopic analysis of the crude reaction mixtures, some decomposition of the sensitive tricycles **5** and **6** was detected during purification by flash chromatography; this may be responsible for the moderate isolated yields obtained in some cases.

Our observed regioselectivity for the thermal [2+2] cycloaddition is remarkable as it contrasts previously reported related examples in which the 2π -component was the internal double bond of the allene moiety.^[17] Only Padwa et al. have reported a similar regioselectivity in their study of intramolecular [2+2] cycloaddition reactions of (phenylsulfonyl)-enallenols, which were used for the preparation of bicyclo-[4.2.0]octene systems,^[18] related to compounds **5**. However,

these authors were not able to prepare bicyclo-[5.2.0]nonenes, related to compounds **4** and **6**, obtaining instead monocyclic-substituted cyclooctenes.^[18]

As substitution at every position of the alkene moiety in 2-azetidinone-tethered enallenols is possible, the effect of a substituent at the internal position of the alkene double bond was studied. Exposure of *N*-methallyl allenols (+)-**2e–g** to the above thermal treatment afforded methylenecyclobutane 2-azetidinones (+)-**7a–c** as the only products (Scheme 6). No other isomer was detected in the ¹H NMR



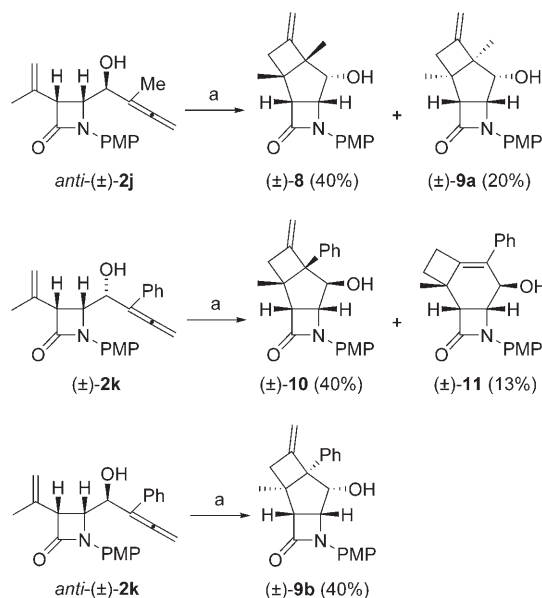
Scheme 6. Regio- and diastereoselective preparation of tricyclic β-lactams **7**. Reagents and conditions: a) toluene, 220 °C, sealed tube, (+)-**7a**: 5 h, (+)-**7b**: 8 h, (+)-**7c**: 7 h.

spectrum of the crude reaction mixtures. The regioselective assignment is based on the ¹H NMR pattern of the vinylic protons. Of the possible regioisomers, only compounds **7** were formed, as is apparent from the ¹H NMR spectra in which the vinylic groups appear as two sharp singlets at δ = 4.95–4.99 and 4.97–5.01 ppm. Additional signals for compounds **7** appeared as a multiplet or doublets at δ = 2.54–2.82 ppm, suggesting the presence of only a methylene group on the cyclobutane ring. Vinylic proton signals were not detected by ¹H NMR spectroscopy for tricycles **4–6**. In fact, adducts **4** and **5** produced several multiplets (δ = 1.61–3.58 ppm) in the ¹H NMR spectra corresponding to two methylene groups on the cyclobutane ring. However, the ¹³C NMR spectra for compounds **7** produced one signal at δ = 113.6–113.7 ppm, characteristic of the C=CH₂ vinylic carbon atom of compounds **7**.

Notably, the presence of an internal substituent on the alkene moiety switched the regioselectivity. The successful reversal of regioselectivity in the allene component, just by a subtle variation in the substitution of the alkene moiety, is an important development. In our case, it allowed for the preparation of a diverse array of structurally novel strained tricyclic β-lactams. For example, enantiopure compounds **7a–c** are remarkable as they bear two quaternary stereogenic centers.^[19] As a result of steric congestion, the stereocontrolled construction of carbon atoms containing four carbon ligands, all-carbon quaternary centers, is a formidable challenge for chemical synthesis. This challenge is magnified when the central carbon is stereogenic.^[20]

To further explore the regio- and diastereoselectivity of the present formal [2+2] cycloaddition, the reactions of 2-azetidinones *anti*-(±)-**2j**, (±)-**2k**, and *anti*-(±)-**2k**, bearing an isopropenyl group on one side (C3) and the allenol moiety on the other side (C4), were investigated

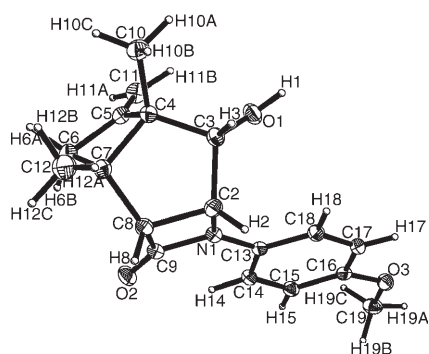
(Scheme 7). There are several interesting features that are noteworthy from this study. First, the regioselectivity. Upon use of enallenol (±)-**2k**, both the [2+2] cycloaddition prod-



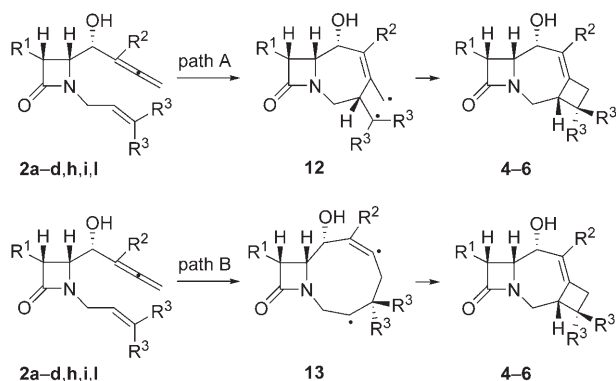
Scheme 7. Preparation of strained tricyclic β-lactams **8–11**. Reagents and conditions: a) toluene, 220 °C, sealed tube, (±)-**8**, (±)-**9a**: 2 h; (±)-**10**, (±)-**11**: 1.5 h; (±)-**9b**: 2 h.

uct at the internal double bond (±)-**10** and the unexpected distal cycloadduct (±)-**11** were obtained in 40% and 13% yields, respectively. Full regiocontrol was achieved for enallenols *anti*-(±)-**2j** and *anti*-(±)-**2k**. Second, the diastereoselectivity. The C3-isopropenyl α-allenols employed in Scheme 7 are structurally equivalent to the *N*-methallyl α-allenols of Scheme 6. However, the thermal treatment of enallene *anti*-(±)-**2j** resulted in a mixture of two separable diastereomers. The intramolecular cycloaddition of *anti*-(±)-**2k** provided the tricycle (±)-**9b** in 40% yield as a single regio- and diastereomer. The stereochemical relationship of tricycle (±)-**8** was established by X-ray diffraction analysis (Figure 2).^[21] To see if the [2+2] cycloaddition reaction is reversible, the separated cycloadducts (±)-**8**, (±)-**9a**, (±)-**9b**, (±)-**10**, and (±)-**11** were subjected to the reaction conditions again. However, after heating a solution of the separated cycloadducts **8–11** in toluene at 220 °C in a sealed tube for 8 h, they remained unaltered.

Thermal [2+2] cycloaddition reactions,^[22] normally helped by Lewis acids, are much less common than photochemical ones,^[23] and usually they are assumed to occur through the participation of dipolar or diradical intermediates. In our case, when a catalytic amount of hydroquinone was added, the reaction rate was considerably reduced and the product yield fell dramatically. This fact is consistent with the involvement of a radical mechanism. The formation of fused, strained tricycles **4–6** can be rationalized by a mechanism that includes an exocyclic diradical intermediate **12** through

Figure 2. X-ray diffraction analysis of tricyclic β -lactam ($\pm$)-**8**.

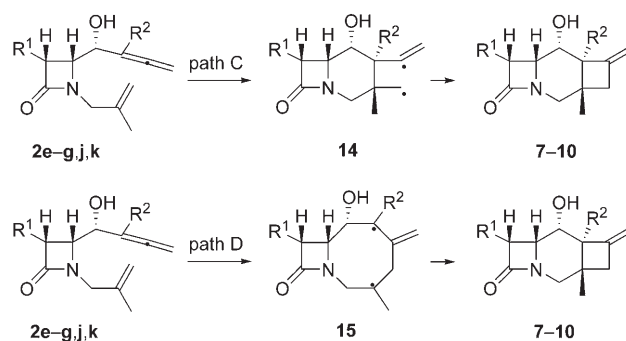
initial carbon–carbon bond formation involving the central allene and proximal alkene carbon atoms (path A, Scheme 8). An alternative mechanism for the thermal reac-

Scheme 8. Rationalization for the thermal preparation of strained tricyclic β -lactams **4–6**.

tion, which leads to tricyclic 2-azetidinones **4–6** is proposed in path B (Scheme 8). This pathway involves an endocyclic diradical intermediate **13**, arising from the initial attack of the terminal olefinic carbon onto the distal allene carbon. For both pathways, the final step must involve a rapid ring-closure of the diradical intermediates, before bond rotation can occur.

Analogously, the thermal formation of fused, strained tricycles **7–10** can be rationalized by a mechanism which includes an exocyclic diradical intermediate **14** through initial carbon–carbon bond formation involving the proximal allene and internal alkene carbon atoms (path C, Scheme 9). An alternative pathway leading to tricyclic 2-azetidinones **7–10** is proposed in path D (Scheme 9). This proposal involves an endocyclic diradical intermediate **15**, arising from the initial attack of the terminal olefinic carbon onto the central allene carbon. The final ring-closing step of the diradical intermediates accounts for the cyclobutane formation.

It seems that the regioselectivity in this type of [2+2] cycloaddition reaction is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom, as the enallenes **2a–d,h,i,l** that are lacking a methyl

Scheme 9. Rationalization for the thermal preparation of strained tricyclic β -lactams **7–10**.

group exclusively produced addition at the β,γ -double bond, while the enallenes **2e–g,j,k**, which bear a methyl group at the internal olefinic carbon underwent a formal [2+2] cycloaddition reaction at the α,β -double bond. Path A (Scheme 8) looks valid for the formation of products **4–6**. For this case, the Me group at R^3 stabilizes the exocyclic diradical, and the presence of the double bond promotes the allylic radical **12** over the alternate endocyclic vinylic radical **13** in path B. However, it could be presumed that for the formation of compounds **7–10**, path D (Scheme 9) is more reasonable. The simultaneous stabilization of the endocyclic diradical **15** by the presence of a methyl substituent and allylic stabilization makes this radical favored over the exocyclic diradical **14**. Substitution on the allene moiety affects the rate of the reaction, presumably by influencing the stability of the allylic portion of the resulting exocyclic diradical intermediate **12**. Thus, for example, cyclization of the enallenol (+)-**2l** requires 10 h for completion, whereas the reaction of substituted analogues (+)-**2a** and (+)-**2b** is complete in 5 h and 3 h, respectively.

The structures and stereochemistries of compounds **4–11** were assigned by NMR spectroscopic studies. The *cis*-stereochemistry of the four-membered β -lactam ring was set during the cyclization step to form the 2-azetidinone nucleus, and it was transferred unaltered during the following synthetic steps. The tricyclic structures (by DEPT, HMQC, HMBC, and COSY) and the stereochemical relationships (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of fused cyclobutane β -lactams **4–11** were established by NMR spectroscopic one- and two-dimensional techniques. This structural and configurational assignment was confirmed by an X-ray diffraction analysis of the cycloadduct ($\pm$)-**8**, which is the major product from the cyclization of enallenol ($\pm$)-**2j**.^[24]

Selected NOE enhancements which are in agreement with the proposed stereochemistries are shown in Figure 3. As an example, NOE irradiation of the less shielded proton of the C2 methylene group (trinem numbering) in compound (+)-**6b** gave an increment both on the H3 proton (7%) and the H8 proton (4%). Irradiation of the more shielded proton of the C2 methylene group in compound (+)-**6b** resulted in a 4% increment on the signal corre-

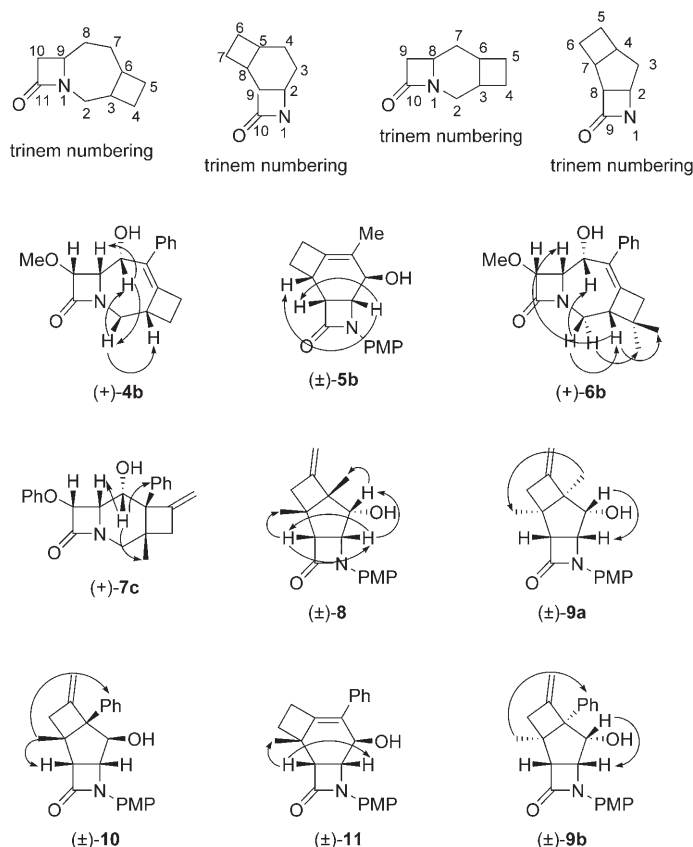


Figure 3. Selected NOE spectroscopic data for tricyclic β -lactams 4–11.

sponding to one of the C4 methyl groups. Irradiation of the H3 proton in compound (+)-6b gave a NOE enhancement on the other C4 methyl hydrogens (5%), together with a 4% increment on the signal of the H8 proton. As another example, irradiation of the H3 hydrogen (trinem numbering) in compound (±)-9b resulted in a 6% increment on the H2 proton and an absence of NOE enhancement on the phenyl signals. NOE irradiation of the protons on the methyl group in compound (±)-9b gave a 4% increment on the phenyl hydrogens, but no enhancement was observed on the H8 proton. Similar figures were observed on performing NOE experiments for the rest of tricycles 4–11.

Conclusion

In conclusion, we have presented a convenient metal-free methodology for the synthesis of racemic and enantiopure strained tricyclic β -lactams containing a cyclobutane ring by means of intramolecular formal [2+2] cycloaddition reactions in 2-azetidinone-tethered enallenols. Interestingly, the regioselectivity of this thermal cyclization is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom. Enallenols lacking a methyl group exclusively produced addition at the β,γ -double bond, while enallenols bearing a methyl group at the internal olefinic carbon underwent a formal [2+2] cycloaddition reaction at

the α,β -double bond. Taking both of these observations together, this cyclization reaction has the potential to significantly extend the utility of the allenol moiety in synthesis.

Experimental Section

General methods: ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in CDCl_3 , except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H , $\delta = 0.0$ ppm), or CDCl_3 (^{13}C , $\delta = 76.9$ ppm). Low and high resolution mass spectra were taken on a HP5989A spectrometer by using the electronic impact (EI) or electrospray (ES) modes, unless otherwise stated. Specific rotation $[\alpha]_D$ is given in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ at 20°C , and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. Aldehydes (+)-1a,^[11a] (+)-1d,^[11b] (±)-1e,^[12b] and (±)-1f,^[12b] were prepared according to our previously reported procedures. Data for α -allenols (+)-2a, (+)-2b, (±)-2h, (±)-2i, and (+)-2l can be found in reference [9e], whilst data for tricycles (+)-4a, (+)-4b, and (±)-5a can be found in the Supporting Information of the preliminary communication for this paper.^[10]

General procedure for the preparation of strained tricyclic β -lactams 4–11: A solution of the corresponding enallenol 2 (0.20 mmol) in toluene (10 mL) was heated in a sealed tube at 220°C until the starting material had been consumed (determined by TLC analysis). The reaction mixture was allowed to cool to room temperature, and then the solvent was removed under reduced pressure. After purification by flash chromatography tricycles 4–11 were obtained. Spectroscopic and analytical data for some representative forms of compounds 4–11 follow.^[25]

Tricyclic (+)-6b: By starting from enallenol (70 mg, 0.22 mmol) (+)-2d, followed by chromatography of the product residue (hexanes/EtOAc 3:1), compound (+)-6b (40 mg, 57%) was produced as a colorless oil; $R_f = 0.30$ (hexanes/EtOAc 3:1); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.31$ (m, 5H; ArH), 4.66 (d, $J = 0.8$ Hz, 1H; H8), 4.53 (dd, $J = 4.6$, 1.2 Hz, 1H; H10), 4.01 (dd, $J = 12.7$, 5.6 Hz, 1H; NCHH), 3.86 (dd, $J = 4.6$, 1.0 Hz, 1H; H9), 3.64 (s, 3H, OMe), 3.40 (m, 1H, NCHH), 2.98 (m, 1H; H3), 2.63 (m, 2H, H5+H5'), 1.70 (d, $J = 1.7$ Hz, 1H; OH), 1.19 and 1.09 ppm (s, each 3H; Me ($\times 2$)); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 165.9$ (C11), 142.7, 139.8, 135.1, 128.2 (Ar), 127.9, 126.5 (Ar), 84.5 (C10), 72.6 (C8), 59.6 (C9), 59.5 (OMe), 49.9 (C3), 43.3 (C5), 39.8, 32.9, 29.7 (Me), 23.9 ppm (Me); IR (CHCl_3): $\tilde{\nu} = 3215$, 1742 cm^{-1} ; MS (ES): m/z (%): 314 (100) $[M+H]^+$, 313 (12) $[M]^+$; elemental analysis (%) calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_3$ (313.4): C 72.82, H 7.40, N 4.47; found C 72.95, H 7.36, N 4.44.

Tricyclic (+)-7a: By starting from enallenol (58 mg, 0.19 mmol) (+)-2e, followed by chromatography of the product residue (hexanes/EtOAc 3:1), compound (+)-7a (32 mg, 56%) was produced as a colorless oil; $R_f = 0.32$ (hexanes/EtOAc 3:1); $[\alpha]_D = +21.5$ ($c = 0.8$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.31$ (m, 5H; ArH), 4.97 and 4.95 (s, each 1H; $=\text{CH}_2$), 4.57 (d, $J = 5.1$ Hz, 1H; H9), 4.03 (m, 3H; NCHH, H7+H8), 3.82 (d, $J = 15.5$ Hz, 1H; NCHH), 3.64 (s, 3H; OMe), 2.76 (s, 1H; H4), 2.74 (s, 1H; H4'), 1.75 ppm (s, 3H; Me); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 167.8$ (C10), 139.9 ($\text{C}=\text{CH}_2$), 131.6 (Ar), 128.3 (Ar), 128.1, 123.1, 113.7 ($\text{C}=\text{CH}_2$), 84.9, 83.1 (C9), 75.7, 69.2 (C7), 59.7, 59.5, 47.8 (NCH₂), 25.0 (C4); 20.3 (Me); IR (CHCl_3): $\tilde{\nu} = 3223$, 1750 cm^{-1} ; MS (ES): m/z (%): 300 (100) $[M+H]^+$, 299 (9) $[M]^+$; elemental analysis (%) calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$ (299.4): C 72.22, H 7.07, N 4.68; found C 72.19, H 7.04, N 4.71.

Preparation of tricycles (±)-8 and (±)-9a: By starting from α -allenol alcohol (75 mg, 0.25 mmol) (±)-2j, followed by chromatography of the product residue (hexanes/EtOAc 5:1), the less polar compound (±)-8 (30 mg, 40%) and the more polar compound (±)-9a (15 mg, 20%) were obtained.

Tricyclic (±)-8: Colorless solid; m.p. $113\text{--}115^\circ\text{C}$; $R_f = 0.23$ (hexanes/EtOAc 5:1); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.45$ and 6.85 (d, $J =$

9.0 Hz, each 2H; ArH), 4.85 (t, $J=2.2$ Hz, 2H; $=CH_2$), 4.57 (dd, $J=5.8$, 4.6 Hz, 1H; H2), 4.07 (brs, 1H; H3), 3.78 (s, 3H; OMe), 3.38 (d, $J=4.6$ Hz, 1H; H8), 3.19 (dt, $J=16.0$, 1.9 Hz, 1H; H6), 2.51 (dt, $J=16.0$, 2.9 Hz, 1H; H6'), 1.75 (brs, 1H; OH), 1.26 (s, 3H; Me), 1.15 ppm (s, 3H; Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta=165.8$ (C9), 156.1, 151.2 ($C=CH_2$), 131.6, 118.6 (Ar), 114.2 (Ar), 106.9 ($C=CH_2$), 82.5 (C2), 62.8, 61.2, 61.1, 55.4 (OMe), 41.3, 37.8 (C6), 21.9 (Me), 20.5 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}=3310$, 1734 cm^{-1} ; MS (EI): m/z (%): 300 (20) $[M+H]^+$, 299 (100) $[M]^+$; elemental analysis (%) calcd for $C_{18}H_{21}NO_3$ (299.4): C 72.22, H 7.07, N 4.68; found C 72.09, H 7.03, N 4.70.

Tricycle ($\pm$)-9a: Colorless solid; m.p. 120–122°C; $R_f=0.12$ (hexanes/EtOAc 5:1); 1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=7.48$ and 6.85 (d, $J=9.0$ Hz, each 2H; ArH), 4.85 (t, $J=2.7$ Hz, 1H; $=CHH$), 4.79 (t, $J=1.7$ Hz, 1H; $=CHH$), 4.72 (t, $J=4.4$ Hz, 1H; H2), 4.51 (d, $J=5.1$ Hz, 1H; H3), 3.71 (s, 3H; MeO), 3.43 (d, $J=4.1$ Hz, 1H; H8), 2.54 (dt, $J=15.0$, 2.7 Hz, 1H; H6), 2.35 (dt, $J=15.0$, 1.7 Hz, 1H; H6'), 1.59 (brs, 1H; OH), 1.36 (s, 3H; Me), 1.06 ppm (s, 3H; Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta=166.1$ (C9), 156.0, 151.9 ($C=CH_2$), 120.3, 118.5 (Ar), 114.1 (Ar), 103.9 ($C=CH_2$), 80.2 (C2), 62.2, 61.1, 59.5, 55.3 (OMe), 44.3, 42.9 (C6), 18.0 (Me), 13.1 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}=3312$, 1738 cm^{-1} ; MS (EI): m/z (%): 300 (21) $[M+H]^+$, 299 (100) $[M]^+$; elemental analysis (%) calcd for $C_{18}H_{21}NO_3$ (299.4): C 72.22, H 7.07, N 4.68; found C 72.33, H 7.10, N 4.66.

Tricycle ($\pm$)-9b: By starting from enallenol *anti*-($\pm$)-2k (40 mg, 0.11 mmol), followed by chromatography of the product residue (hexanes/EtOAc 2:1), compound ($\pm$)-9b (16 mg, 40%) was produced as a colorless oil; $R_f=0.30$ (hexanes/EtOAc 2:1); 1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=7.25$ (m, 7H; ArH), 6.82 (d, $J=9.0$ Hz, 2H; ArH), 5.20 (t, $J=2.5$ Hz, 1H; $=CHH$), 5.13 (brs, 1H; $=CHH$), 4.81 (t, $J=5.3$ Hz, 1H; H2), 4.61 (d, $J=5.5$ Hz, 1H; H3), 3.71 (s, 3H; OMe), 3.56 (d, $J=4.5$ Hz, 1H; H8), 2.48 and 2.61 (dt, $J=10.2$, 1.5 Hz, each H; H6+H6'), 1.68 (brs, 1H; OH), 1.91 ppm (s, 3H; Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta=165.1$ (C9), 155.9, 149.2, 134.9 ($C=CH_2$), 132.1, 129.1 (Ar), 128.3 (Ar), 127.0 (Ar), 118.3 (Ar), 114.0 (Ar), 109.1 ($C=CH_2$), 80.3 (C2), 70.8, 63.2, 62.3, 55.3 (OMe), 47.1 (C7), 43.5 (C6), 20.7 ppm (Me); IR ($CHCl_3$): $\tilde{\nu}=3240$, 1733 cm^{-1} ; MS (EI): m/z (%): 362 (25) $[M+H]^+$, 361 (100) $[M]^+$; elemental analysis (%) calcd for $C_{23}H_{25}NO_3$ (361.4): C 76.43, H 6.41, N 3.88; found C 76.30, H 6.37, N 3.91.

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