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Expeditious Entry to Enantiopure Mono- and Bis(Tricyclic) β-Lactams by Single or Double [2+2] Cycloaddition of Allenynes

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A thermal methodology for the expeditious preparation of structurally novel strained tricyclic β-lactams containing a cyclobutene ring has been developed. Besides, the first examples accounting for the intramolecular double [2+2] cycloaddition of bis(allenyne)s have been achieved through thermolysis of C_2-symmetric or unsymmetric bis(β-lactam–allenyne)s, which have been prepared by copper-promoted alkyne homo- or cross-coupling reactions. The bis(tricyclic) ring structures bearing a central seven-membered ring arise from the regioselective cyclization of the alkyne with the distal bond of the allene, most likely via a radical intermediate.

Introduction

The importance of cyclobutane-containing compounds both as target molecules as well as useful building blocks for the construction of more complex structures has been widely demonstrated.[1] However, relatively few methods for the preparation of four-membered carbocycles are available in comparison with superior cyclohomologues. In particular, the [2+2] cycloaddition of allenes with alkynes represents an important strategy for the preparation of cyclobutene derivatives with high atom economy.[2] Unfortunately, this process has suffered from low stereo- and positional selectivity (considering the intramolecular [2+2] cycloaddition of allenynes, two regioisomers can be formed, the proximal cycloadduct by reaction of the alkyne with the internal 2π component, and the distal cycloadduct by reaction with the external 2π component of the allene moiety). On the other hand, the enormous interest in β-lactams in medicinal chemistry, as key structural features of many antibiotics and serine protease inhibitors, and as valuable synthetic intermediates in organic chemistry, has triggered considerable research efforts toward the enantioselective synthesis of these compounds.[3] The appealing properties of intramolecular cycloaddition reactions would seem to recommend their application to the preparation of functionalized tricyclic β-lactams.[4] Our combined interest in the area of β-lactams and the synthetic use of allenes[5] led us to explore single and double [2+2] allenyne cyclization strategies for developing a versatile entry to novel fused tricyclic and attached-ring bis(tricyclic) β-lactams containing cyclobutene rings.[6]

Results and Discussion

Starting substrates, enantiopure acetonide-2-azetidinones **1a** and **1b**, were obtained as single *cis* enantiomers through ketene–imine cyclization following our previous procedure.[7] Terminal alkynes **1** were functionalized as their corresponding phenyl, 2-thiophenyl, 2-pyridyl, and propynylphenyl derivatives **2a**–**g** by treatment with the appropriate iodoarene or phenylacetylene under Sonogashira or Cadiot–Chodkiewicz conditions (Scheme 1). Standard acetonide hydrolysis of compounds **1** and **2** followed by oxidative cleavage of the resulting diols smoothly provided 4-oxoazetidine-2-carbaldehydes **4a**–**i** (Scheme 1).[8] Cyclization precursors, allenynes **5a**–**k**, were readily obtained beginning from the appropriate 4-oxoazetidine-2-carbaldehydes **4** through regio- and stereocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media, adopting our methodology (Scheme 2).[9]

Although, in theory, an intramolecular cycloaddition of β-lactam–enynes could be used to prepare tricycles, there is no report in the literature involving [2+2] cycloaddition reaction of 2-azetidinone-tethered alkynes. Because of the inherent instability imparted by the cumulated double bond in allenes, cycloaddition reactions take place easily in comparison with an isolated double bond. Having obtained allenynols **5**, the next stage was set the key [2+2] process on

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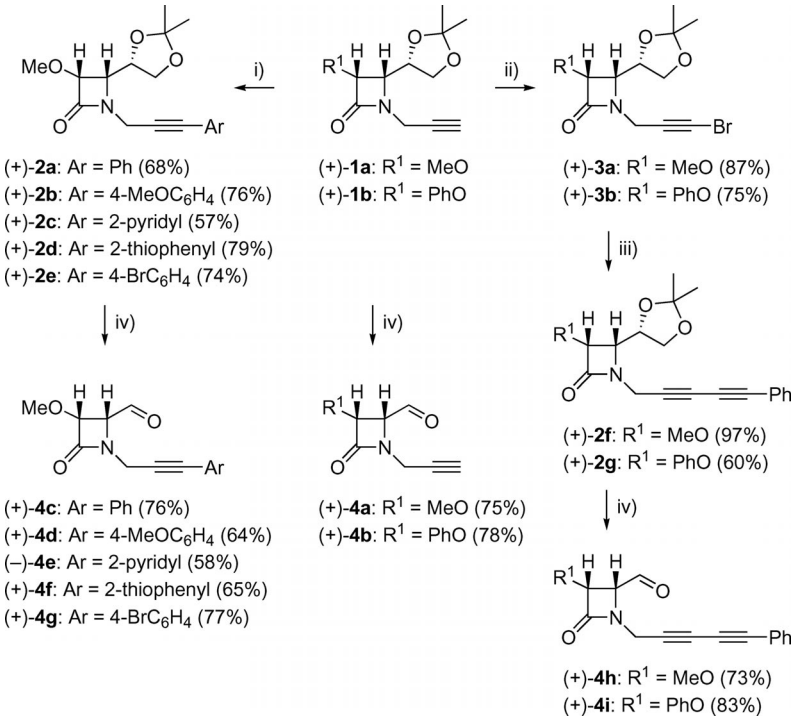
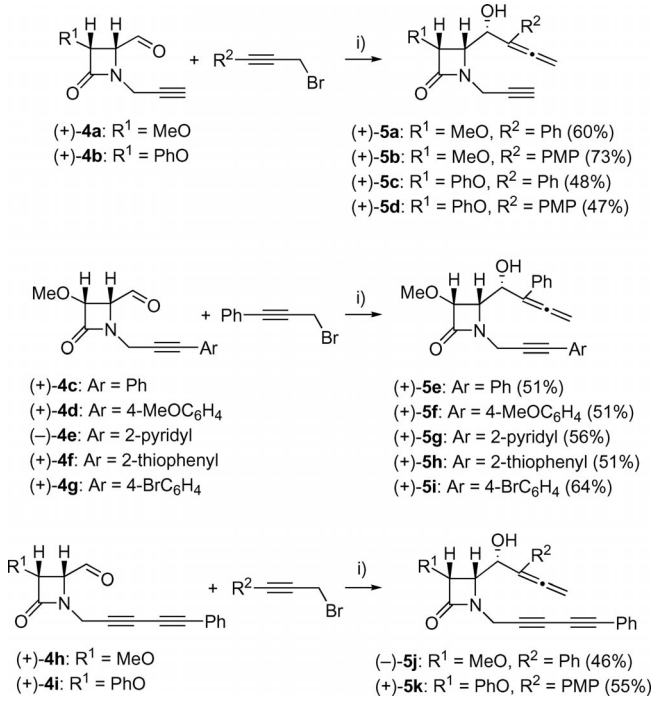
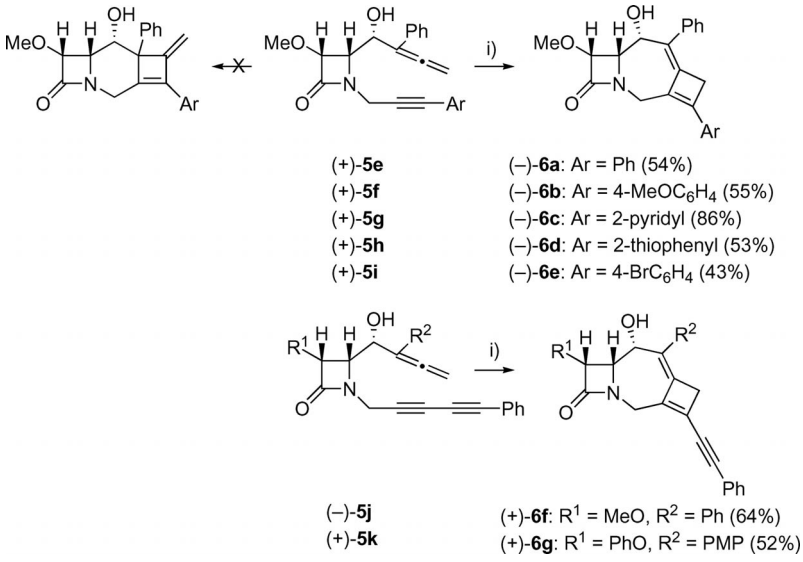


Scheme 1. Preparation of 4-oxoazetidine-2-carbaldehydes **4**. Reagents and conditions: (i) ArI (1 mol-%), $Pd(PPh_3)_2Cl_2$ (2 mol-%), CuI, Et_3N, DMSO, 50 °C, 4 h; **2a**: ArI = iodobenzene; **2b**: ArI = 1-iodo-4-methoxybenzene; **2c**: ArI = 2-iodopyridine; **2d**: ArI = 2-iodothiophene; **2e**: ArI = 1-bromo-4-iodobenzene. (ii) NBS, AgOAc, acetone, darkness, r.t., 4 h. (iii) Phenylacetylene, $MeOH/CH_2Cl_2$, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, 0 °C, 18 h. (iv) (a) PTSA, THF/H_2O, Δ, 2 h; (b) $NaIO_4$, $NaHCO_3$ (aq. sat.), CH_2Cl_2, r.t., **4a**: 2 h; **4b**: 2 h; **4c**: 24 h; **4d**: 24 h; **4e**: 72 h; **4f**: 18 h; **4g**: 18 h; **4h**: 24 h; **4i**: 24 h. PTSA = *p*-toluenesulfonic acid.



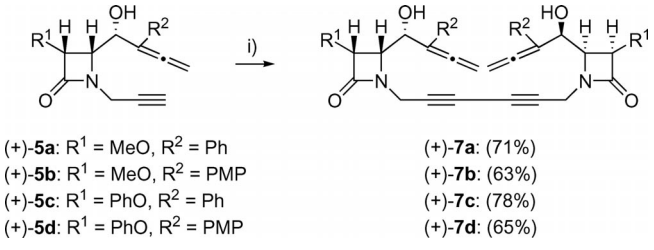
Scheme 2. Preparation of allenynes **5**. Reagents and conditions: (i) In, THF/NH_4Cl (aq. sat.), r.t., 18 h. PMP = 4-$MeOC_6H_4$.

reacting the allene group as a 2π-electron donor. A model thermal cyclization of allenynes **5** was carried out by heating a solution of α-allenol **5a** in toluene at 110 °C in a sealed tube. Unfortunately, no conversion was found. A variety of experimental variables, such as the temperature and solvent, were systematically examined, but not even a trace amount of the expected tricycle was detected in the crude reaction mixtures. We therefore speculated how the presence of a substituent at the alkyne moiety may influence the reactivity. Thus, a range of alkynyl-substituted building blocks **5** was exposed to thermal reaction conditions. Thermolysis of allenynes **5e**–**k** bearing an aryl, heteroaryl, or alkynyl group on the alkyne side afforded strained tricyclic β-lactams **6a**–**g** in reasonable yields and complete regioselectivity (Scheme 3). It is of note that allenynes **5j** and **5k** containing a 1,3-diyne functionality reacted with the phenylacetylene group remaining intact. Thus, the mildness of the method allowed the incorporation of a 1,3-diyne moiety as a reactive partner, displaying exquisite chemoselectivity towards the internal alkynic moiety, directing the cyclization to the exclusive formation of fused tricyclic cyclobutene **6g**. The tricyclic ring structures **6a**–**g** bearing a central seven-membered ring arise from the formal [2+2] cycloaddition of the alkyne with the distal bond of the allene, most likely via a diradical intermediate. The regioselectivity of the process is not affected by the substituent at the alkyne carbon atom. No trace amount of the exocyclic methylene regioisomer through cycloaddition, with six-membered central ring formation could be detected (Scheme 3), despite the fact that, according to Baldwin's rules for ring formation, the ease of cyclization increases with decreasing ring size ($5 > 6 > 7$).[10]



Scheme 3. Preparation of tricyclic β-lactams **6**. Reagents and conditions: (i) toluene, sealed tube, 110 °C, **6a**: 4 h; **6b**: 5 h; **6c**: 4 h; **6d**: 3 h; **6e**: 6 h; **6f**: 1.5 h; **6g**: 2 h. PMP = 4-$MeOC_6H_4$.

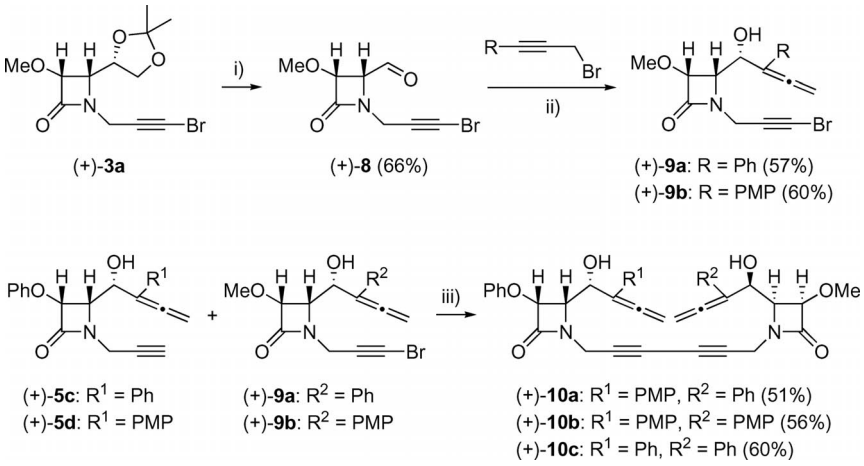
Because the presence of a 1,3-diyne moiety at the allenyne fragment had no effect upon the selectivity of the cyclization, we decided to explore the double [2+2] cycloaddition in the hitherto difficult to prepare diyne–diallene functionality. To screen the reactivity of the bis(allenyne) moiety, homodimerization of allenynes **5a**–**d** was studied in the presence of a copper promoter. The homodimerization reaction proceeded smoothly to afford desired diyne–diallenes **7a**–**d** by using modified classical copper-promoted conditions (Scheme 4).[11] Copper(II) acetate in combination with potassium carbonate in acetonitrile gave the best performance.



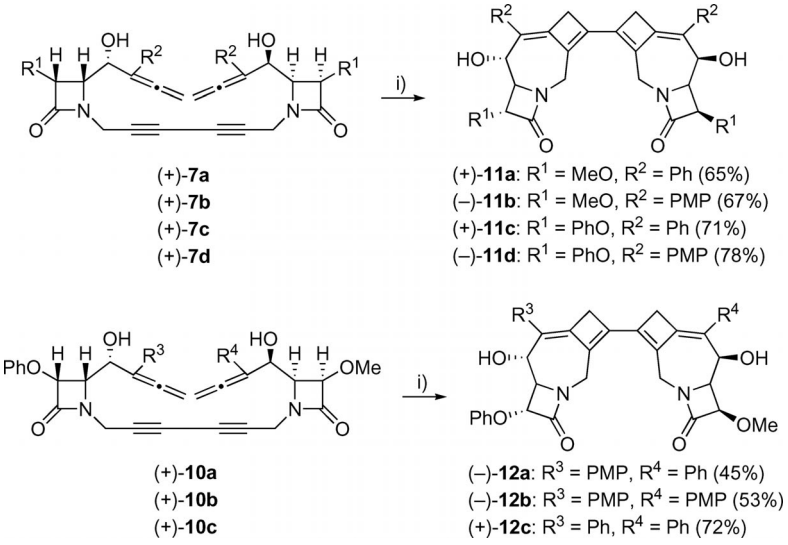
Scheme 4. Copper-promoted preparation of C_2-symmetric bis(allenyne)s **7a**–**d**. Reagents and conditions: (i) $Cu(OAc)_2$, K_2CO_3, MeCN, r.t., 4 h. PMP = 4-$MeOC_6H_4$.

Having obtained C_2-symmetric bis(β-lactam–allenyne)s, the next stage was to determine selective heterocoupling conditions to achieve unsymmetrical bis(β-lactam–allenyne)s. We envisioned that the target unsymmetrical allenynes could come from the copper-catalyzed Cadiot–Chodkiewicz cross-coupling reaction of a bromoallenynyl–β-lactam with a terminal allenyne–β-lactam. Heterocoupling precursors, bromoallenynes **9**, were smoothly prepared from bromoalkyne **3a** by aldehyde unmasking followed by allenylation reaction of bromoalkynyl carbaldehyde **8** (Scheme 5). Cross-coupling reactions using the Cadiot–Chodkiewicz protocol[12] between bromoallenynes **9a** and **9b** and allenynes **5c** and **5d** catalyzed by CuCl and $NH_2OH{\cdot}HCl$ in 70% ethylamine in water solvent produced the corresponding unsymmetrical bis(β-lactam–allenyne)s **10** in good yields (Scheme 5).

Because it is known that dimers exhibit greater biological activity in comparison with their monomeric components,[13] and despite the lack of reports on double [2+2] cycloaddition of bis(allenyne)s, the availability of bis(allenyne)s **7** and **10** prompted us to test their reactivity. IR spectroscopic analysis was undertaken on the crude reaction mixtures after heating at 110 °C. From the IR data, it is observed that the vibrational frequencies at ca. 2220 and 1940 cm^{-1}, characteristic of C≡C and C=C=C bond stretching, respectively, completely vanished after thermal treatment. The disappearance of the C≡C and C=C=C bands indicates that the thermal reactions involve every single acetylenic and allenic unit. We observed the formation of C_2-symmetric attached-ring bis(tricyclic) β-lactams **11a**–**d** by a double [2+2] allenyne cyclization. As shown in Scheme 6, unsymmetrical bis(β-lactam–allenyne)s **10a**–**c** also participate in this chemistry, leading to bis(tricycle)s **12a**–**c** upon thermal treatment. The reactions were so regioselective that the signal for the alkenyl cyclobutene protons (corresponding to the internal isomers) were not observed in the ^1H NMR spectra of the unpurified reaction mixtures. Compounds **11** and **12** are remarkable, as they bear a challenging dimeric tricyclic 2-azetidinone structure having both a strained cyclobutene as well as a seven-membered ring. No detectable erosion of the stereochemical integrity at the stereogenic centers under the thermal conditions was observed. The depicted distal cycloadducts were the only isolated isomers; allenynes **5**, **7**, and **10** showed the same regiochemical preference. In order to see if products



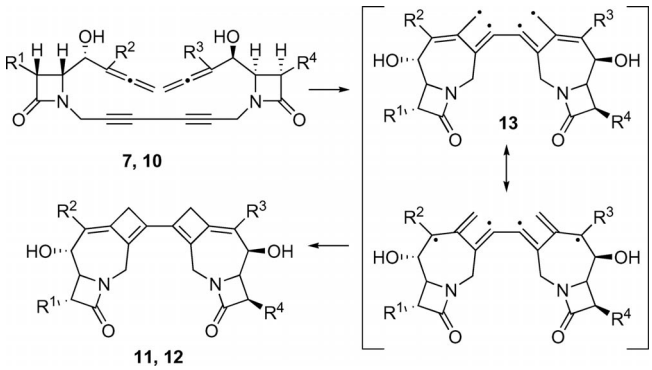
Scheme 5. Copper-promoted preparation of unsymmetrical bis(allenyne)s **10a**–**c**. Reagents and conditions: (i) (a) PTSA, THF/H_2O, Δ, 2 h; (b) $NaIO_4$, $NaHCO_3$ (aq. sat.), CH_2Cl_2, r.t., 8 h. (ii) In, THF/NH_4Cl (aq. sat.), r.t., 18 h. (iii) MeOH/CH_2Cl_2, CuCl, NH_2OH·HCl, $EtNH_2$, 0 °C, 18 h. PMP = 4-$MeOC_6H_4$.



Scheme 6. Synthesis of enantiopure C_2-symmetric and unsymmetrical attached-ring bis(tricyclic) β-lactams **11** and **12**. Reagents and conditions: (i) toluene, sealed tube, 110 °C, **11a**: 1.5 h; **11b**: 2 h; **11c**: 1 h; **11d**: 3 h; **12a**: 1 h; **12b**: 1 h; **12c**: 1 h. PMP = 4-$MeOC_6H_4$.

from a single [2+2] allenyne cyclization could be isolated at short reaction times, we stopped the reaction of bis(β-lactam–allenyne) **7a** prematurely (30 min). In the event, the only detectable products were the starting material and bis(cyclization) adduct **11a**, which may point that both cyclizations occur simultaneously.

A conceivable mechanism for the preparation of bis(tricycle)s **11** and **12** from bis(β-lactam–allenyne)s **7** and **10** may initially involve the formation of tetraradical intermediates. 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 involvement of a radical mechanism. The formation of fused strained bis(tricycle)s **11** and **12** can be rationalized by a mechanism that includes exocyclic tetraradical intermediate **13** through initial double carbon–carbon bond formation, involving the central allene and the proximal alkyne carbon atoms (Scheme 7). For this pathway, the final step must involve a rapid double ring closure of the tetraradical intermediates, before bond rotation can occur.



Scheme 7. A conceivable mechanistic explanation for the thermal double [2+2] allenyne cyclization.

Conclusions

In conclusion, we have developed a convenient methodology for the synthesis of strained tricyclic β-lactams containing a cyclobutene ring through a totally regioselective [2+2] cycloaddition reaction of 2-azetidinone-tethered allenynols. Besides, the first examples accounting for the intramolecular double [2+2] cycloaddition of bis(allenyne)s have been achieved by thermolysis of C_2-symmetric or unsymmetric bis(β-lactam–allenyne)s. A conceivable mechanism for the achievement of bis(tricycle)s from bis(β-lactam–allenyne)s may imply the formation of tetraradical intermediates involving the distal allene bonds.

Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken with an Agilent 6520 Accurate-Mass QTOF LC–MS spectrometer using the electronic impact (EI) or electrospray modes (ESI) unless otherwise stated. IR spectra were recorded with a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

Preparation of Fused Tricyclic and Attached-Ring Bis(tricyclic) β-Lactams 6, 11, and 12 as a General Procedure for the Thermal Cyclization of Mono- and Bis(allenyne)s 5, 7, and 10: A solution of the appropriate allenyne **5**, **7**, or **10** (0.15 mmol) in toluene (5 mL) was heated at 110 °C in a sealed tube. After disappearance (1–5 h) of the starting material (TLC), the mixture was cooled down to room temperature and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate/hexanes) gave analytically pure compounds. Spectroscopic and analytical data for pure forms of **6**, **11**, and **12** follow.

Tricyclic β-Lactam (–)-6a: From allenyne (+)-**5e** (45 mg, 0.12 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave (–)-**6a** (25 mg, 54%) as a colorless oil. $[\alpha]_D^{20} = -72.3$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.57 (m, 2 H, Ar-*H*), 7.34 (m, 8 H, Ar-*H*), 4.96 (dt, J = 18.5, 3.7 Hz, 1 H, NC*H*H), 4.82 (br. s, 1 H, C*H*OH), 4.63 (d, J = 4.6 Hz, 1 H, CH), 4.42 (d, J = 18.5 Hz, 1 H, NCH*H*), 4.30 (d, J = 4.6 Hz, 1 H, CH), 3.71 (s, 3 H, OCH_3), 3.51 (dt, J = 13.8, 3.6 Hz, 1 H, C*H*H), 3.35 (br. s, 1 H, OH), 3.17 (ddd, J = 13.8, 4.0, 2.3 Hz, 1 H, CH*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.6 (NC=O), 145.1 (Cq), 139.9 (Cq), 139.8 (Cq), 134.3 (Cq), 133.5 (Cq), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.2 (CH), 126.7 (CH), 126.6 (CH), 125.9 (Cq), 83.7 (CH), 71.9 (CH), 61.5 (CH), 59.8 (OCH_3), 41.2 (CH_2), 35.5 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1745, 1646 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{22}NO_3$ $[M + H]^+$ 360.1600; found 360.1604.

Tricyclic β-Lactam (–)-6c: From allenyne (+)-**5g** (35 mg, 0.097 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave compound (–)-**6c** (30 mg, 86%) as a colorless oil. $[\alpha]_D^{20} = -39.2$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.68 (m, 2 H, Ar-*H*), 7.56 (m, 2 H, Ar-*H*), 7.47 (m, 1 H, Ar-*H*), 7.37 (m, 2 H, Ar-*H*), 7.21 (m, 1 H, Ar-*H*), 5.02 (dt, J = 19.9, 3.8 Hz, 1 H, NC*H*H), 4.83 (br. s, 1 H, C*H*OH), 4.65 (m, 1 H, NCH*H*), 4.62 (d, J = 3.7 Hz, 1 H, CH), 4.27 (d, J = 4.8 Hz, 1 H, CH), 3.69 (s, 3 H, CH_3), 3.54 (dt, J = 13.9, 3.5 Hz, 1 H, C*H*H), 3.38 (br. s, 1 H, OH), 3.23 (dq, J = 13.9, 2.0 Hz, 1 H, CH*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.4 (NC=O), 152.4 (Cq), 150.2 (CH), 143.9 (Cq), 139.9 (Cq), 139.7 (Cq), 139.5 (Cq), 136.1 (Cq), 132.1 (CH), 131.9 (CH), 128.3 (CH), 127.2 (CH), 122.1 (CH), 121.4 (CH), 83.6 (CH), 72.9 (CH), 62.1 (CH), 60.8 (CH), 42.8 (CH_2), 36.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 1744, 1643 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{21}N_2O_3$ $[M + H]^+$ 361.1552; found 361.1585.

Tricyclic β-Lactam (+)-6f: From allenyne (–)-**5j** (50 mg, 0.13 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave compound (+)-**6f** (32 mg, 64%) as a pale-yellow oil. $[\alpha]_D^{20} = +6.3$ (c = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.49 (m, 5 H, Ar-*H*), 7.36 (m, 4 H, Ar-*H*), 7.28 (m, 1 H, Ar-*H*), 4.81 (br. s, 1 H, C*H*OH), 4.74 (dt, J = 19.0, 4.0 Hz, 1 H, NC*H*H), 4.60 (d, J = 4.5 Hz, 1 H, CH), 4.27 (d, J = 19.0 Hz, 1 H, NCH*H*), 4.23 (d, J = 4.6 Hz, 1 H, CH), 3.69 (s, 3 H, CH_3), 3.44 (dt, J = 13.7, 3.2 Hz, 1 H, C*H*H), 3.34 (br. s, 1 H, OH), 3.18 (dq, J = 13.7, 2.0 Hz, 1 H, CH*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.5 (NC=O), 145.4 (Cq), 140.3 (Cq), 139.3 (Cq), 131.6 (CH), 128.9 (Cq), 128.5 (CH), 128.4 (CH), 127.9 (Cq), 127.1 (CH), 126.9 (Cq), 122.4 (Cq), 102.1 (Cq), 83.5 (CH), 83.3 (Cq), 71.9 (CH), 61.2 (CH), 59.7 (OCH_3), 40.8 (CH_2), 39.6 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3433, 2232, 1746, 1643 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{22}NO_3$ $[M + H]^+$ 384.1600; found 384.1595.

Bis(tricyclic) β-Lactam (+)-11a: From bis(allenyne) (+)-**7a** (30 mg, 0.052 mmol). Chromatography (hexanes/ethyl acetate, 1:3) of the residue gave compound (+)-**11a** (20 mg, 65%) as a colorless oil. $[\alpha]_D^{20} = +66.6$ (c = 0.5, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 7.50 (m, 4 H, Ar-*H*), 7.33 (m, 6 H, Ar-*H*), 4.82 (m, 2 H, 2 C*H*OH), 4.70 and 4.22 (d, J = 18.2 Hz, each 2 H, 2 NC*H*H, 2 NCH*H*), 4.59 (dd, J = 4.8, 1.2 Hz, 2 H, 2 CH), 4.22 (d, J = 4.8 Hz, 2 H, 2 CH), 3.69 (s, 6 H, 2 CH_3), 3.35 (dt, J = 13.6, 2.9 Hz, 2 H, 2 C*H*H), 3.28 (br. s, 2 H, 2 OH), 3.12 (m, 2 H, 2 CH*H*) ppm. ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 166.6 (NC=O), 140.9 (Cq), 139.2 (Cq), 138.6 (Cq), 137.4 (Cq), 128.6 (CH), 128.5 (CH), 127.2 (Cq), 127.0 (CH), 83.6 (CH), 71.7 (CH), 61.3 (CH), 59.8 (CH_3), 40.4 (CH_2), 36.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3426, 1748, 1645 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{33}N_2O_6$ $[M + H]^+$ 565.2339; found 565.2342.

Bis(tricyclic) β-Lactam (–)-11b: From bis(allenyne) (+)-**7b** (30 mg, 0.048 mmol). Chromatography (hexanes/ethyl acetate, 1:20) of the residue gave compound (–)-**11b** (20 mg, 67%) as a colorless oil. $[\alpha]_D^{20} = -95.7$ (c = 0.3, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 7.44 and 6.89 (d, J = 8.8 Hz, each 4 H, Ar-*H*), 4.79 (s, 2 H, C*H*OH), 4.68 and 4.21 (d, J = 15.7 Hz, each 2 H, 2 NC*H*H, 2 NCH*H*), 4.58 (d, J = 4.8 Hz, 2 H, 2 CH), 4.20 (d, J = 4.8 Hz, 2 H, 2 CH), 3.83 (s, 6 H, 2 CH_3), 3.69 (s, 6 H, 2 CH_3), 3.31 (dt, J = 13.6, 2.8 Hz, 2 H, 2 C*H*H), 3.26 (br. s, 2 H, 2 CH*H*), 3.12 (d, J = 15.1 Hz, 2 H, 2 OH) ppm. ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 166.5 (NC=O), 158.8 (Cq), 139.7 (Cq), 138.3 (Cq), 136.7 (Cq), 131.8 (Cq), 128.2 (CH), 127.9 (CH), 113.9 (CH), 83.5 (CH), 71.7 (CH), 61.2 (CH), 59.8 (CH_3), 55.3 (CH_3), 40.4 (CH_2), 36.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1747, 1650 cm^{-1}. HRMS (ESI): calcd. for $C_{36}H_{37}N_2O_8$ $[M + H]^+$ 625.2550; found 625.2542.

Bis(tricyclic) β-Lactam (+)-11c: From bis(allenyne) (+)-**7c** (40 mg, 0.058 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave compound (+)-**11c** (28 mg, 71%) as a colorless oil. $[\alpha]_D^{20} = +29.4$ (c = 0.4, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 7.41 (m, 12 H, Ar-*H*), 7.12 (m, 8 H, Ar-*H*), 5.31 (d, J = 4.8 Hz, 2 H, 2 CH), 4.96 (br. s, 2 H, 2 C*H*OH), 4.78 and 4.29 (d, J = 18.0 Hz, each 2 H, 2 NC*H*H, 2 NCH*H*), 4.43 (d, J = 4.8 Hz, 2 H, 2 CH), 3.37 (d, J = 13.8 Hz, 2 H, 2 C*H*H), 3.15 (d, J =

13.8 Hz, 2 H, 2 CH*H*) ppm. ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 165.2 (NC=O), 157.1 (Cq), 140.9 (Cq), 139.1 (Cq), 138.6 (Cq), 137.5 (Cq), 129.8 (CH), 128.8 (C), 128.5 (CH), 127.4 (CH), 127.1 (CH), 123.3 (CH), 116.1 (CH), 80.9 (CH), 71.6 (CH), 61.8 (CH), 40.6 (CH_2), 36.2 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3428, 1746, 1647 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{37}N_2O_6$ $[M + H]^+$ 689.2652; found 689.2657.

Bis(tricyclic) β-Lactam (–)-11d: From bis(allenyne) (+)-**7d** (60 mg, 0.08 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave compound (–)-**11d** (46 mg, 78%) as a colorless oil. $[\alpha]_D^{20}$ = –7.8 (*c* = 2.2, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 7.39 (m, 6 H, Ar-*H*), 7.04 (m, 12 H, Ar-*H*), 5.31 (d, *J* = 4.5 Hz, 2 H, 2 CH), 4.94 (br. s, 2 H, 2 C*H*OH), 4.79 and 4.28 (m, each 2 H, 2 NC*H*H, 2 NCH*H*), 4.42 (d, *J* = 4.5 Hz, 2 H, 2 CH), 3.84 (s, 6 H, 2 OCH_3), 3.35 (m, 2 H, 2 C*H*H), 3.12 (m, 2 H, 2 CH*H*) ppm. ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 165.2 (NC=O), 158.9 (Cq), 157.0 (Cq), 139.8 (Cq), 138.2 (Cq), 136.9 (Cq), 131.6 (CH), 129.8 (CH), 128.3 (CH), 128.1 (Cq), 123.2 (CH), 116.0 (CH), 113.9 (CH), 80.8 (CH), 71.5 (CH), 61.6 (CH), 55.3 (CH_3), 40.6 (CH_2), 36.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1749, 1644 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{41}N_2O_8$ $[M + H]^+$ 749.2863; found 749.2869.

Bis(tricyclic) β-Lactam (–)-12a: From bis(allenyne) (+)-**10a** (20 mg, 0.03 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave compound (–)-**12a** (9 mg, 45%) as a colorless oil. $[\alpha]_D^{20}$ = –263.4 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (m, 9 H, Ar-*H*), 7.17 (d, *J* = 7.8 Hz, 2 H, Ar-*H*), 7.09 (t, *J* = 7.3 Hz, 1 H, Ar-*H*), 6.91 (d, *J* = 9.8 Hz, 2 H, Ar-*H*), 5.31 (d, *J* = 3.7 Hz, 2 H, 2 CH), 4.94 and 4.83 (br. s, each 1 H, 2 C*H*OH), 4.70 (m, 2 H, NC*H*H, NCH*H*), 4.59 (d, *J* = 3.7 Hz, 1 H, CH), 4.41 (d, *J* = 4.7 Hz, 1 H, CH), 4.23 (d, *J* = 4.6 Hz, 1 H, CH), 4.26 (m, 2 H, NC*H*H, NCH*H*), 3.84 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.34 (m, 2 H, C*H*H, CH*H*), 3.09 (m, 2 H, C*H*H, CH*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.8 (NC=O), 165.1 (NC=O), 158.9 (Cq), 157.0 (Cq), 140.9 (Cq), 139.8 (Cq), 139.3 (Cq), 138.4 (Cq), 138.3 (Cq), 137.3 (Cq), 136.9 (Cq), 132.9 (Cq), 129.8 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 127.0 (CH), 123.2 (CH), 116.0 (CH), 113.9 (CH), 83.5 (CH), 80.9 (CH), 71.7 (CH), 71.6 (CH), 61.6 (CH), 61.3 (CH_3), 59.8 (CH_3), 55.3 (CH), 40.6 (CH_2), 40.4 (CH_2), 36.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3434, 1746, 1648 cm^{-1}. HRMS (ESI): calcd. for $C_{40}H_{37}N_2O_7$ $[M + H]^+$ 657.2601; found 657.2607.

Bis(tricyclic) β-Lactam (–)-12b: From bis(allenyne) (+)-**10b** (30 mg, 0.04 mmol). Chromatography (hexanes/ethyl acetate, 1:1) of the residue gave compound (–)-**12b** (16 mg, 53%) as a yellow oil. $[\alpha]_D^{20}$ = –22.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.45 (m, 3 H, Ar-*H*), 7.34 (m, 2 H, Ar-*H*), 7.17 (m, 3 H, Ar-*H*), 6.90 (m, 5 H, Ar-*H*), 5.31 (d, *J* = 5.7 Hz, 1 H, CH), 4.93 and 4.80 (br. s, each 1 H, 2 C*H*OH), 4.73 (m, 2 H, NC*H*H, NCH*H*), 4.59 (d, *J* = 4.1 Hz, 1 H, CH), 4.41 (d, *J* = 4.8 Hz, 1 H, CH), 4.25 (m, 2 H, NCH*H*, NC*H*H), 4.21 (d, *J* = 4.8 Hz, 1 H, CH), 3.84 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 3.69 (s, 3 H, CH_3), 3.33 (m, 2 H, C*H*H, CH*H*), 3.14 (m, 2 H, CH*H*, C*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.6 (NC=O), 165.2 (NC=O), 159.0 (Cq), 158.9 (Cq), 157.1 (Cq), 139.9 (Cq), 139.7 (Cq), 138.5 (Cq), 137.9 (Cq), 136.9 (Cq), 136.6 (Cq), 131.8 (Cq), 131.6 (Cq), 129.8 (CH), 128.3 (CH), 128.1 (Cq), 127.9 (Cq), 123.2 (CH), 116.1 (CH), 114.0 (CH), 113.9 (CH), 83.5 (CH), 80.9 (CH), 71.7 (CH), 71.6 (CH), 61.7 (CH), 61.2 (CH), 59.8 (CH), 40.6 (CH_2), 40.4 (CH_2), 36.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3435, 1748, 1646 cm^{-1}. HRMS (ESI): calcd. for $C_{41}H_{39}N_2O_8$ $[M + H]^+$ 687.2706; found 687.2701.

Bis(tricyclic) β-Lactam (+)-12c: From bis(allenyne) (+)-**10c** (48 mg, 0.08 mmol). Chromatography (hexanes/ethyl acetate, 1:2) of the residue gave compound (+)-**12c** (35 mg, 72%) as a colorless oil. $[\alpha]_D^{20}$ = +123.5 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.52 (m, 4 H, Ar-*H*), 7.34 (m, 8 H, Ar-*H*), 7.18 (m, 2 H, Ar-*H*), 7.10 (m, 1 H, Ar-*H*), 5.32 (d, *J* = 4.5 Hz, 1 H, CH), 4.97 and 4.84 (br. s, each 1 H, C*H*OH), 4.78 and 4.72 (d, *J* = 19.0 Hz, each 1 H, NC*H*H, NCH*H*), 4.61 (d, *J* = 4.5 Hz, 1 H, CH), 4.44 (d, *J* = 4.5 Hz, 1 H, CH), 4.31 and 4.25 (d, *J* = 14.3 Hz, each 1 H, NC*H*H, NCH*H*), 4.24 (d, *J* = 4.5 Hz, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.37 and 3.16 (t, *J* = 13.4 Hz, each 2 H, 2 C*H*H, 2 CH*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.6 (NC=O), 165.1 (NC=O), 157.0 (Cq), 140.9 (Cq), 140.8 (Cq), 139.2 (Cq), 139.0 (Cq), 138.9 (Cq), 138.3 (Cq), 137.6 (Cq), 137.2 (Cq), 133.1 (Cq), 131.6 (Cq), 129.8 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 123.1 (CH), 116.1 (CH), 83.5 (CH), 71.7 (CH), 71.5 (CH), 61.7 (CH), 61.2 (CH), 59.7 (CH_3), 40.6 (CH_2), 40.3 (CH_2), 36.3 (CH_2), 36.2 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 1747, 1650 cm^{-1}. HRMS (ESI): calcd. for $C_{39}H_{34}N_2NaO_6$ $[M + Na]^+$ 649.2315; found 649.2305.

Supporting Information (see footnote on the first page of this article): Compound characterization data and experimental procedures for compounds **2a**–**g**, **3a**, **3b**, **4c**–**i**, **5a**–**k**, **6b**, **6d**, **6e**, **6g**, **7a**–**d**, **9a**, **9b**, and **10a**–**c**, in addition to copies of the NMR spectra of all new compounds.

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[1] For recent reviews, see: a) V. M. Dembitsky, *J. Nat. Med.* **2008**, *62*, 1; b) Z. Rappoport, J. F. Liebman (Eds.), *The Chemistry of Cyclobutanes*, John Wiley & Sons, Ltd., Chichester, UK, **2005**, vol. 1, pp. 357–440; c) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449; d) J. C. Namyslo, D. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485; e) A. K. Sadana, R. K. Saini, W. E. Billups, *Chem. Rev.* **2003**, *103*, 1539; for a selected reference, see: f) J. M. Um, H. Xu, K. N. Houk, W. Tang, *J. Am. Chem. Soc.* **2009**, *131*, 6664.

[2] For a review on the [2+2] cycloaddition chemistry of allenes, see: a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783; for allene/alkyne [2+2] cycloadditions, see: b) D. J. Pasto, W. Kong, *J. Org. Chem.* **1988**, *53*, 4807; c) D. J. Pasto, K. D. Sugi, *J. Org. Chem.* **1992**, *57*, 1146; d) Q. Shen, G. B. Hammond, *J. Am. Chem. Soc.* **2002**, *124*, 6534; e) Y. Horino, M. Kimura, S. Tanaka, T. Okajima, Y. Tamaru, *Chem. Eur. J.* **2003**, *9*, 2419; f) Y. Yang, J. L. Petersen, K. K. Wang, *J. Org. Chem.* **2003**, *68*, 5832; g) H. Ohno, T. Mizutani, Y. Fado, K. Miyamura, T. Tanaka, *Angew. Chem. Int. Ed.* **2005**, *44*, 5113; h) K. M. Brummond, D. Chen, *Org. Lett.* **2005**, *7*, 3473; i) C. H. Oh, A. K. Gupta, D. I. Park, N. Kim, *Chem. Commun.* **2005**, 5670; j) C. Mukai, Y. Hara, Y. Miyashita, F. Inagaki, *J. Org. Chem.* **2007**, *72*, 4454; k) X. Jiang, S. Ma, *Tetrahedron* **2007**, *63*, 7589; l) T. V. Ovaska, R. E. Kyne, *Tetrahedron Lett.* **2008**, *49*, 376; m) N. Saito, Y. Tanaka, Y. Sato, *Org. Lett.* **2009**, *11*, 4124; n) M. R. Siebert, J. M. Osbourn, K. M. Brummond, D. J. Tantillo, *J. Am. Chem. Soc.* **2010**, *132*, 11952.

[3] For selected reviews and leading papers, see: a) J. Mulchande, R. Oliveira, M. Carrasco, L. Gouveia, R. C. Guedes, J. Iley, R. Moreira, *J. Med. Chem.* **2010**, *53*, 241; b) B. Alcaide, P. Al-

mendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437; c) F. Von Nussbaum, M. Brands, B. Hinzen, S. Weigan, D. Häbich, *Angew. Chem. Int. Ed.* **2006**, *45*, 5072; *Angew. Chem.* **2006**, *118*, 5194; d) J. D. Rothstein, S. Patel, M. R. Regan, C. Haenggeli, Y. H. Huang, D. E. Bergles, L. Jin, M. D. Hoberg, S. Vidensky, D. S. Chung, S. V. Toan, L. I. Bruijn, Z.-z. Su, P. Gupta, P. B. Fisher, *Nature* **2005**, *433*, 73; e) L. Kvaerno, T. Ritter, M. Werder, H. Hauser, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 4653; *Angew. Chem.* **2004**, *116*, 4753; f) D. A. Burnett, *Curr. Med. Chem.* **2004**, *11*, 1873; g) B. Alcaide, P. Almendros, *Curr. Med. Chem.* **2004**, *11*, 1921; h) G. Veinberg, M. Vorona, I. Shestakova, I. Kanepe, E. Lukevics, *Curr. Med. Chem.* **2003**, *10*, 1741; i) D. Niccolai, L. Tarsi, R. J. Thomas, *Chem. Commun.* **1997**, 2333; j) R. B. Morin, M. Gorman (Eds.), *Chemistry and Biology of β-Lactam Antibiotics*, Academic, New York, **1982**, vols. 1–3.

[4] Tricyclic β-lactam antibiotics that are generally referred to as trinems are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases: a) O. Kanno, I. Kawamoto, *Tetrahedron* **2000**, *56*, 5639; b) S. Hanessian, B. Reddy, *Tetrahedron* **1999**, *55*, 3427; c) C. Ghiron, T. Rossi "The Chemistry of Trinems" in *Targets in Heterocyclic Systems-Chemistry and Properties* (Eds.: O. A. Attanasi, D. Spinelli), Societa Chimica Italiana, Rome, **1997**, vol. 1, pp. 161–186; for a review on tricyclic β-lactams, see: d) B. Alcaide, P. Almendros, *Curr. Org. Chem.* **2002**, *6*, 245.

[5] See, for instance: a) B. Alcaide, P. Almendros, A. Luna, M. R. Torres, *Adv. Synth. Catal.* **2010**, *352*, 621; b) B. Alcaide, P. Almendros, T. Martínez del Campo, M. T. Quirós, *Chem. Eur. J.* **2009**, *15*, 3344; c) B. Alcaide, P. Almendros, R. Carrascosa, T. Martínez del Campo, *Chem. Eur. J.* **2009**, *15*, 2496; d) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 1901; e) B. Alcaide, P. Almendros, R. Carrascosa, M. C. Redondo, *Chem. Eur. J.* **2008**, *14*, 637; f) B. Alcaide, P. Almendros, T. Martínez del Campo, *Angew. Chem. Int. Ed.* **2007**, *46*, 6684; *Angew. Chem.* **2007**, *119*, 6804; g) B. Alcaide, P. Almendros, T. Martínez del Campo, *Angew. Chem.* **2006**, *118*, 4613; *Angew. Chem. Int. Ed.* **2006**, *45*, 4501.

[6] For a report on the thermal [2+2] cyclization of enallenes, see: a) B. Alcaide, P. Almendros, C. Aragoncillo, *Org. Lett.* **2003**, *5*, 3795; b) B. Alcaide, P. Almendros, C. Aragoncillo, M. C. Redondo, M. R. Torres, *Chem. Eur. J.* **2006**, *12*, 1539.

[7] a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Commun.* **1999**, 1913; b) B. Alcaide, P. Almendros, C. Aragoncillo, *J. Org. Chem.* **2001**, *66*, 1612; c) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, C. Pardo, E. Sáez, M. R. Torres, *J. Org. Chem.* **2002**, *67*, 7004.

[8] B. Alcaide, P. Almendros, N. Rodríguez-Salgado, *J. Org. Chem.* **2000**, *65*, 3310.

[9] B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Eur. J.* **2002**, *8*, 1719.

[10] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[11] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; b) G. Eglinton, A. R. Galbrait, *Chem. Ind. (London)* **1956**, 737; c) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320.

[12] a) P. Cadiot, W. Chodkiewicz in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Marcel Dekker, New York, **1969**, pp. 597; b) S. Kim, *Angew. Chem.* **2009**, *121*, 7876; *Angew. Chem. Int. Ed.* **2009**, *48*, 7740.

[13] For a report describing that tanikolide dimer is a more potent inhibitor of cytoplasmic proteins than its monomer, see: a) M. Gutiérrez, E. H. Andrianasolo, W. K. Shin, D. E. Goeger, A. Yokochi, J. Schemies, M. Jung, D. France, S. Cornell-Kennon, E. Lee, W. H. Gerwick, *J. Org. Chem.* **2009**, *74*, 5267; similarly, the increased antibacterial activity of β-lactam heterodimers in comparison with their monomeric components has been reported: b) D. D. Long, J. B. Aggen, B. G. Christensen, J. K. Judice, S. S. Hegde, K. Kaniga, K. M. Krause, M. S. Linsell, E. J. Moran, J. L. Pace, *J. Antibiot.* **2008**, *61*, 595.

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