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Asymmetric Kinugasa reaction involving six-membered cyclic nitrones

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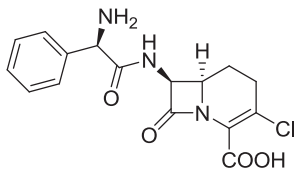
ABSTRACT

Kinugasa reactions between terminal acetylenes and six-membered ring nitrones when one or both components are chiral, proceed in a low to moderate yield and with a high diastereoselectivity affording mostly one, dominant β-lactam product. The first step of the reaction is controlled by the configuration of the nitrone, whereas the protonation of the C-7 center of the carbacepham skeleton in the second step depends on: a) the configuration of the bridgehead carbon atom formed in the first step, b) epimerization process in the presence of a base, and c) on the configuration of the stereogenic center in the acetylenic partner. In the case of the nitrone derived from dihydroisoquinoline, the reaction proceeds in a more complex way affording not only β-lactams, but also products derived from the alternative regio-1,3-cycloaddition, or nucleophilic addition of the acetylene to the double bond of the nitrone.

1. Introduction

The carba-analogs of penicillins and cephalosporins, which are found to be relatively resistant to β-lactamase enzymes, represent a powerful tool against bacterial infections.[1–3]

Although the former ones—carbapenems—are more popular, the latter—carbacephem antibiotics—like Loracarbef (**1**) have also found a proper place in modern therapy.[4,5]



Loracarbef (**1**)

Recently,[6] we have reported an application of diastereoselective version of copper(I)-mediated reaction between nitrones and terminal acetylenes, discovered in 1972 by Kinugasa and Hashimoto,[7,8] for direct and simple formation of the basic skeleton of carbapenem antibiotics. As a reactants for these reactions the non-racemic cyclic nitrones, derived from malic acid,[6a–c] tartaric acid,[6a–c] and pentofuranoses[6d,9] and simple acetylenes have been used, which open an easy access to side chains present in carbapenem antibiotics. Reactions displayed the high diastereoselectivity leading to one dominant product. The addition was controlled by the substituent present in the nitrone, whereas the protonation of intermediate enolate in the second step occurred from the less-shielded side of carbapenam skeleton.[6a] Consequently, the major product displayed the relative cis-orientation of protons in the four-membered β-lactam ring. Kinugasa reaction involving six-membered ring nitrones is the logic continuation of our earlier studies. It should be noted, however, that the six-membered ring nitrones are less stable[10] than their five-membered congeners, therefore extension of the reaction time may lead to the formation of decomposition products.

2. Results and discussion

For the present study we selected three different nitrones, two nonchiral, **2** and **3**, and one chiral **4**, which after the Kinugasa reaction should provide carbacepham skeletons. As acetylenes we selected representative nonchiral compounds **5**, **6** and chiral ones derived from D- and L-glyceraldehyde **7**,[6b] **7ent**,[11] which are known to provide products in a relatively good yield.[6b,c] Except commercially available acetylenes **5** and **6** other substrates **2**,[12] **3**,[13] **4**[14] and **7**,[6b] **7ent**[11] were obtained following the known procedures.

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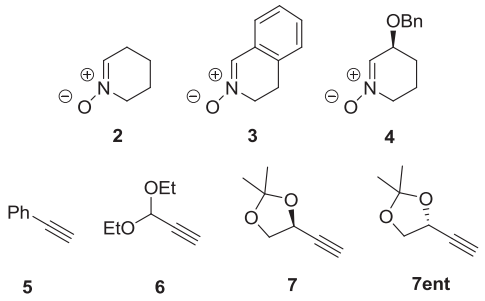
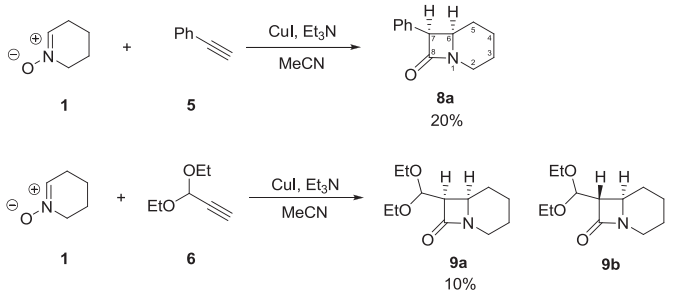


Reactions between nitrone **2** and the non-chiral acetylenes **5** and **6** proceeded with a relatively good diastereoselectivity, affording the corresponding racemic carbacephams **8a** and **9a** in a very low yield, 20% and 10%, respectively (Scheme 1). The accompanying isomer **9b** was not isolated, only noticed in ^{1}H NMR spectra of crude post reaction mixtures. The relative configuration of H-6 and H-7 protons in both products **8a** and **9a** were established analyzing the $^3J_{H6-H7}$ coupling constants and was found to be cis for both compounds.

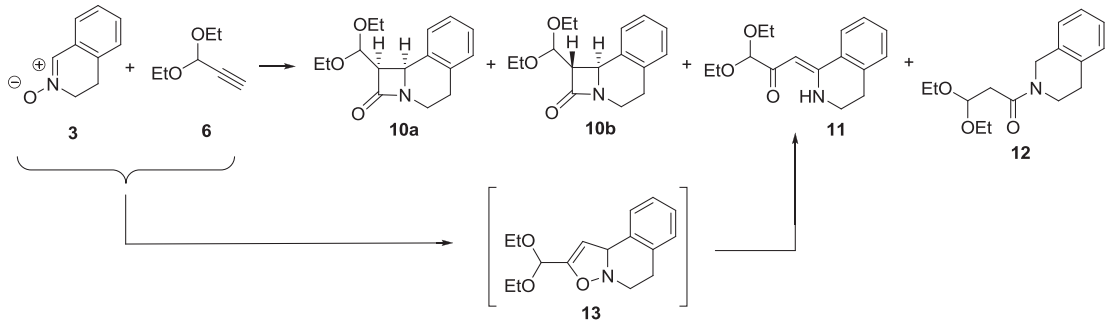


Scheme 1.

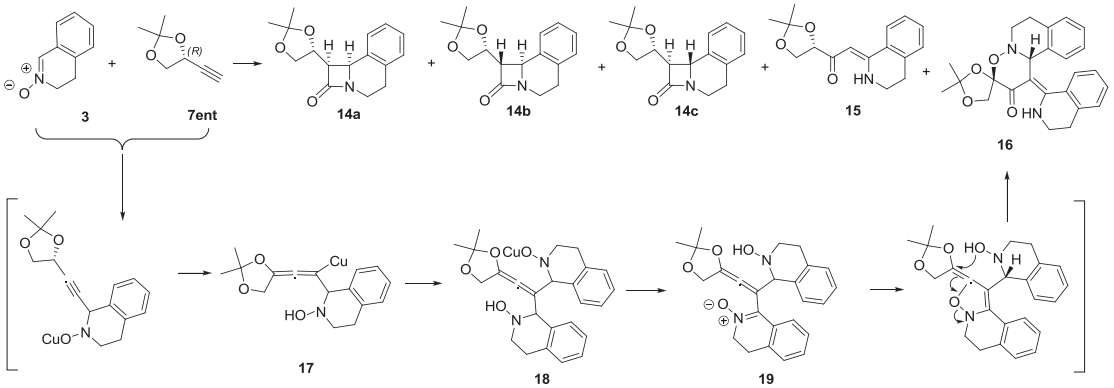
Compound **3**, derived from dihydroisoquinoline, showed different reactivity than previously investigated cyclic nitrones. Acetylene **5** did not afford any defined product, whereas more reactive compound **6** gave expected β-lactams **10a** and **10b** in a ratio of about 2:1, respectively, accompanied by adduct **11** originated from the opposite regiochemistry of the first 1,3-dipolar cycloaddition step of the reaction (intermediate **13**). In addition, occasionally a minute amount of *N*-acyl-tetrahydroisoquinoline **12** was also isolated, which is probably formed as a result of a redox reaction involving copper acetylide and the nitrone. (Scheme 2).

Even more convoluted reaction pathway was found for nitrone **3** and acetylene **7ent**. Enamino-ketone **15**, the main component of the reaction mixture, was obtained in 25.5% yield. Expected Kinugasa products **14a**, **14b**, **14c**, and racemic product **16** consisting of two molecules of the nitrone and one acetylene, were obtained in 29.3% yield and a ratio of about 5:7:1:2, respectively (Scheme 3, Fig. 1). The mixture of **14a**, **14b**, **14c**, and **16** was separated into individual pure components by HPLC chromatography. The configuration of β-lactam products **14a**, **14b**, and **14c** were assigned using ^{1}H NMR and CD spectroscopy. Structure of **16** was established by the crystal structure analysis (Fig. 1).

The plausible reaction pathway leading to **16** involves known alkylation of the nitrone by cooper acetylide[10,15] followed by rearrangement of the triple bond to the cooper salt of allene **17** and subsequently alkylation of the second molecule of the nitrone. The intermediate **18** underwent oxidation of one hydroxylamine fragment to nitrone **19**, which was followed by the rapid intramolecular 1,3-dipolar cycloaddition. The final step involves intramolecular addition of the free *N*-hydroxy group to the vinyl ether double bond, followed by the cleavage of the N–O bond to afford compound **16** (Scheme 3). The control of absolute configuration of the final molecule is lost, leading consequently racemate **16**, owed to either the presence of plane of symmetry in allene **18**, or to the possible oxidation of enantiotopic hydroxylamine fragments in nitrone **19**.



Scheme 2.



Scheme 3.

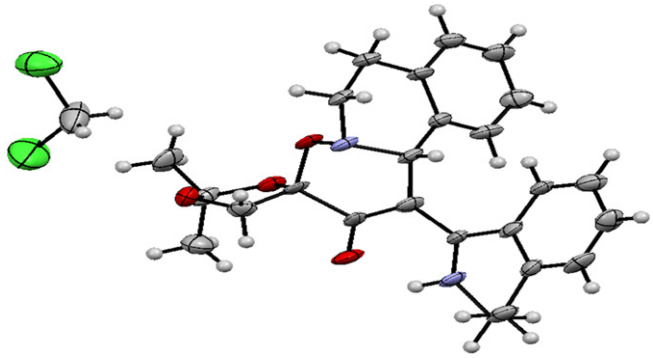


Fig. 1. X-ray structure of compound **16** (with inclusion of solvent—dichloromethane).[17]

Reactions of nitrone **4** with acetylenes **5**–**7**/**7ent** under standard conditions followed a typical pathway for the Kinugasa process (Scheme 4). β-Lactam products were obtained in a low to moderate yield. In the case of acetylene **5**, one cis product **20** was obtained. Acetal **6** afforded two products: *cis* **21a** and *trans* **21b** in a ratio of about 2:1, respectively, both of them had the same configuration at the bridgehead carbon atom as a result of *anti* addition to the benzyloxy group of the nitrone. Formation of trans isomer could be attributed to the base catalyzed epimerization at the carbon atom next to the carbonyl group.

In the case of both chiral substrates, mixtures of isomeric products were obtained. Bearing in mind our earlier findings,[6] compounds **4** and **7** constitute the matched pair, whereas compounds **4** and **7ent** constitute the mismatched pair. In both cases, domination of the nitrone stereogenic center was observed. Acetylene **4** and nitrone **7** afforded two products **22a** and **22b** in a ratio of about 2:1, respectively. Both products had the same configuration at the bridgehead carbon atom, as a result of *anti* addition to the benzyloxy group in the nitrone. The structure and configuration of both products were established by the ^{1}H NMR, and, in the case of **22a**, was corroborated also by the X-ray (Fig. 2). In the case of the mismatched pair **4** and **7ent**, the main product **23a** was accompanied by the trace amount of the other isomer **23b**, which was not

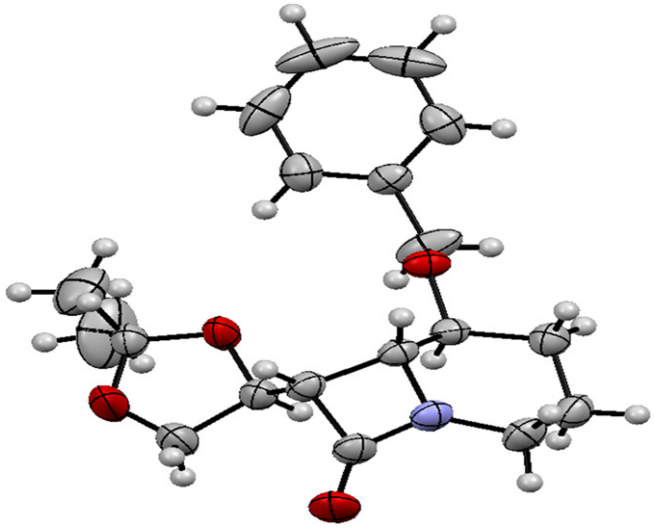
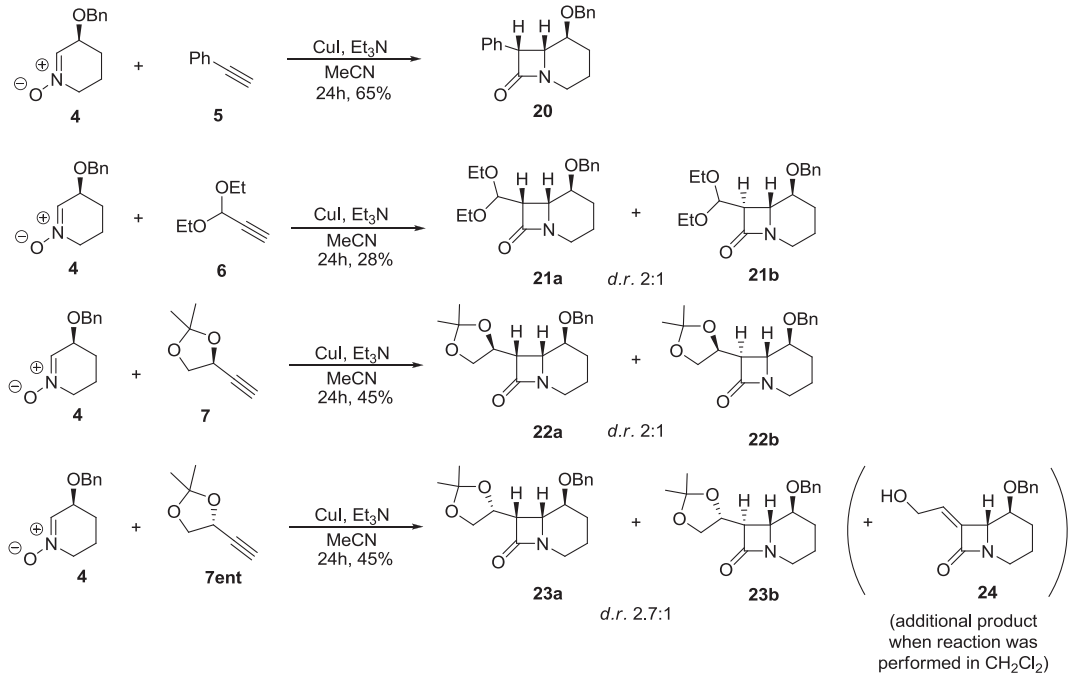


Fig. 2. X-ray structure of compound **22a**.[17]

isolated in a pure form. When, however, the reaction was performed in methylene chloride, the β-lactams **23a** and **23b** were accompanied by the product **24**, which, plausibly, results from the acid promoted deprotection of the diol moiety followed by elimination of water molecule.

2.1. Determination of absolute configuration at C6

Our previous studies on the structure—chiroptical properties of penicillin and cephalosporin analogs have shown that the absolute configuration at the bridgehead carbon can be easily determined by application of simple β-lactam helicity rule.[16] This rule, originally developed for the bicyclic β-lactams with nonplanar amide chromophore, correlates the sign of Cotton effect (CE) of amide n→π* transition with the absolute stereochemistry at the ring junction. According to this rule, the bicyclic β-lactams belong to the D series (or, alternatively to the L series) when in their CD spectra the positive (or negative) sign of CE is present (Fig. 3).



Scheme 4.

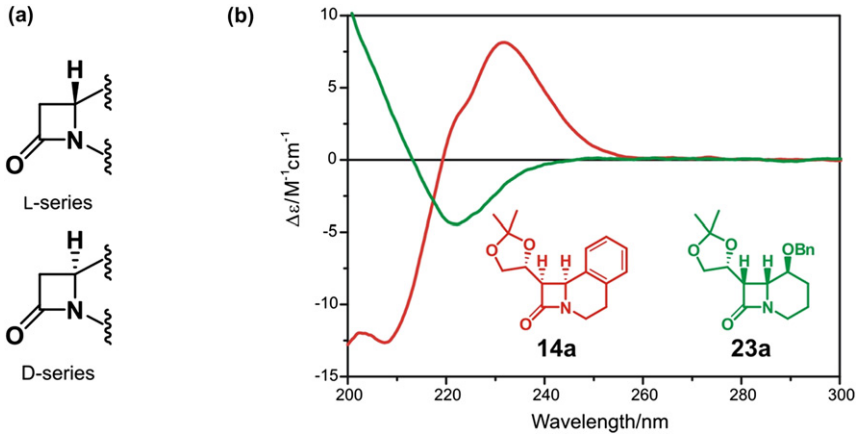


Fig. 3. (a) Definition of D- and L-series, (b) CD spectra of compounds **14a** and **23a** recorded in acetonitrile.

Since the amide chromophore in studied compounds is twisted (X-ray data of compound **22a**, the angle O=C8–N1–C2 equals to 15.7°, Fig. 2)[17] the β-lactam helicity rule can be applied for the absolute configuration assignment at C6. According to the rule, compounds that displayed the positive sign at 220–230 nm were assigned as belonging to the D series, and the negative sign was characteristic for compounds from the L series (Fig. 3).

3. Conclusions

We have shown that the diastereoselective Kinugasa reaction involving six-membered nitrones proceeds in a lower yield but with a similar diastereoselectivity to the reactions involving five-membered congeners, very likely resulting from the lower stability of dipole components. Based on the known mechanism, it is possible to rationalize the stereochemical pathway of the reaction and to predict the geometry of synthesized products. The first step of Kinugasa reaction, the 1,3-dipolar cycloaddition, is controlled predominantly by the configuration of the nitrone. The protonation of the intermediate enolate in the second step depends mostly on the configuration at the bridgehead carbon atom formed in the first step. As a result, the reaction is leading to the cis substituted carbacepham as the main diastereoisomer, except for the reactions involving nitrones derived from the dihydro-isoquinoline.

In the case of latter, the reaction pathway is more complicated owing to the influence of the rigid aromatic ring coupled with the nitrone double bond. The flat geometry of the dipole molecule causes that the carbon atom of the C=N double bond is more electrophilic than the corresponding one in the other investigated nitrones. Consequently, the nucleophilic terminal of the copper acetylide has the tendency to be added to the electrophilic center of the nitrone. This attractive force is manifested by formation of side products originated from the opposite regiochemistry of 1,3-dipolar cycloaddition step, as well as, products derived from addition of acetylide to the nitrone double bond.

In all cases, formation of trans isomer should be assigned to the base catalyzed epimerization at the carbon atom next to the β-lactam carbonyl group.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on Varian VN MRS Spectrometer at 600 MHz and 150 MHz, respectively, in $CDCl_3$ or C_6D_6. TMS was used as an internal standard. Chemical shifts are reported as δ values in parts per million, and coupling constants are in hertz. The proton assignment was done based on COSY experiments. Infrared spectra were recorded on a FTIR-1600 Perkin–Elmer spectrophotometer. CD spectra were recorded on Jasco J-815 spectropolarimeter. Optical rotation was recorded on Jasco P-2000 polarimeter. High-resolution mass spectra were recorded on ESI-TOF Mariner Spectrometer (Perspective Biosystem) or Synapt G2-S Waters Spectrometer for electrospray ionization. Thin layer chromatography was performed on Merck aluminum sheet Silica Gel 60 F254. Column chromatography was carried out using Merck silica gel (230–400 mesh), zones were detected visually by ultraviolet irradiation (254 nm) or spraying with $H_2MoO_4 \cdot H_2O$/$Ce(SO_4)_2 \cdot 4H_2O$ in 15% H_2SO_4, followed by heating at 100 °C. All reactions were performed under argon in pre-dried glassware. All solvents were purified by standard techniques. Diastereomeric ratios of cephams obtained were determined for the crude post reaction mixtures by ^{1}H NMR or HPLC.

Nitrones **2**,[12] **3**,[13] and **4**[14] were obtained according known procedures. Acetylenes **5** and **6** were purchased from Aldrich, whereas acetylenes **7**[6b] and **7ent**[11] were obtained following our protocols.

4.2. Reaction of nitrones with acetylenes. General procedure

To a suspension of CuI (190 mg, 1 mmol) in dry, degassed MeCN (5 mL) were added 0.56 mL (4.0 mmol) of Et_3N and acetylene (1 mmol) and the mixture was cooled to 0 °C. After 15 min, a solution of nitrone (2 mmol) in MeCN (5 mL) was added slowly, and the mixture was kept at 0 °C for an additional 15 min. After that time the cooling bath was removed, and the reaction mixture was stirred at room temperature under argon atmosphere. The progress of the reaction was monitored by TLC. Subsequently, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel. The diastereoisomeric ratio was assigned by HPLC or ^{1}H NMR.

*4.2.1. Compound **8**.* Compound **8** was obtained from **2** and **5** in 20% yield.

4.2.1.1. (6R,7S*)-7-Phenyl-1-azabicyclo[4.2.0]octan-8-one (**8**).* Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.23 (m, 5H), 4.61 (1H, d, *J* 5.1, 1.1 Hz), 3.92 (1H, dd, *J* 13.5, 5.2 Hz), 3.69 (1H, m, *J* 11.0, 5.1, 4.6 Hz), 2.80–2.72 (1H, m), 1.86–1.77 (1H, m), 1.67–1.61 (1H, m), 1.52–1.34 (3H, m), 0.95–0.84 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 133.6, 128.5(2×), 128.4(2×), 127.1, 58.3, 52.6, 38.7, 26.9, 24.9, 21.8; IR (film) ν: 1743 cm^{-1}; HRMS (ESI) *m/z* calcd for $[M+Na]^+$ $C_{13}H_{15}NONa$ 224.1051; found 224.1048.

*4.2.2. Compound **9a**.* Compound **9a** was obtained from **2** and **6** in 10% yield.

4.2.2.1. (6R,7R*)-7-(Diethoxymethyl)-1-azabicyclo[4.2.0]octan-8-one (**9a**/**9b**).* A mixture of diastereomers in a ratio of about 4.6:1, respectively; isomer **9a**: oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.82 (1H, d, *J* 7.4 Hz), 3.7 (1H, dd, *J* 13.4, 5.3 Hz), 3.7–3.49 (4H, m), 3.47 (1H, ddd, *J* 7.4, 5.0, 1.8 Hz), 3.42 (1H, m), 2.67 (1H, m), 1.9–1.3 (6H, m), 1.21 (3H, t), 1.17 (3H, t); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{21}NO_3Na$ $[M+Na]^+$: 250.1419; found 250.1414; IR (film) ν: 1748 cm^{-1}; Compound **9b**: oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: selected signals taken from the spectrum of **9a**: 4.78 (d, *J* 4.5 Hz), 3.06 (d, *J* 4.5, 1.6 Hz).

*4.2.3. Compounds **10a**, **10b**, **11** and **12**.* Compounds **10a**, **10b**, **11** and **12** were obtained following general procedure, from **6** and nitrone **3**. The **10a**/**10b** ratio was assigned by HPLC (LiChrosorb® Si60 250×4.6, 5 μm, 10% *i*-PrOH in hexane, 1 mL/min, 226 nm; retention times: 7.2 min (**10b**), 8.6 min (**10a**)). Preliminary separation of **11** (6.5%) was made using 40% AcOEt in hexane, subsequently **10a** and **10b** (58%) in a ratio of about 2:1 were separated by preparative HPLC using 2.5% *i*-PrOH in hexane (preparative LiChrosorb® Si60 column, 5 μm); a minute amount of **12** was found to accompany the mixture of **10a** and **10b**.

4.2.3.1. (1R,9bS*)-1-Diethoxymethyl-1,4,5,9b-tetrahydro-azeto[2,1-a]isoquinolin-2-one (**10a**).* Oil ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30–7.10 (4H, Ar), 4.69 (1H, d, *J* 5.4 Hz), 4.27 (1H, d, *J* 5.3 Hz), 4.08 (1H, ddd, *J* 13.5, 5.7, 0.6 Hz), 3.81 (1H, dt, *J* 5.3, 0.6 Hz), 3.62 (1H, m, CH*H*CH_3), 3.41 (1H, m, CH*H*CH_3), 3.30 (1H, m, CH*H*CH_3), 3.07 (1H, m), 2.96 (1H, m, CH*H*CH_3), 2.90 (1H, m), 2.63 (1H, dd, *J* 15.7, 3.8 Hz), 1.14 (3H, t, *J* 7.1 Hz, CH_2CH_3), 0.89 (3H, t, *J* 7.1 Hz, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.3, 135.4, 132.0, 129.5, 127.6, 127.1, 126.1, 98.5, 62.1, 61.2, 58.0, 50.7, 37.3, 29.3, 15.2, 14.7; IR (film) ν: 2974, 1759, 1357, 1060, 753 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $[M+Na]^+$ $C_{16}H_{21}NO_3Na$ 298.1414; found 298.1428.

4.2.3.2. (1S, 9bS*)-1-Diethoxymethyl-1,4,5,9b-tetrahydro-azeto[2,1-a]isoquinolin-2-one (**10b**).* Oil ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30–7.10 (4H, m), 4.90 (1H, d, *J* 4.4 Hz), 4.60 (1H, bs), 3.93 (1H, ddd, *J* 12.9, 6.6, 4.1 Hz), 3.29 (1H, dd, *J* 4.4, 2.3 Hz), 3.83 (1H, m, CH*H*CH_3), 3.75 (1H, m CH*H*CH_3), 3.67 (1H, m CH*H*CH_3), 3.62 (1H, m CH*H*CH_3), 3.14 (1H, ddd, *J* 13.0, 9.3, 5.2 Hz), 3.02 (1H, ddd, *J* 15.7, 9.1, 6.7 Hz), 2.74 (1H, dt, *J* 15.6, 4.4 Hz), 1.272 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.266 (3H, t, *J* 7.0 Hz, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.9, 135.3, 133.8, 129.2, 127.2, 126.9, 126.4, 99.80, 63.9, 63.0, 62.5, 49.7, 37.7, 28.2, 15.31, 15.29; IR (film) ν: 2975, 1755, 1371, 1061, 746 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $[M+Na]^+$ $C_{16}H_{21}NO_3Na$ 298.1414 found 298.1413.

*4.2.3.3. (3Z)-3-(3,4-Dihydroisoquinolin-1(2H)-ylidene)-1,1-diethoxypropan-2-one (**11**).* Oil ^{1}H NMR (600 MHz, $CDCl_3$) δ: 11.40 (1H, s), 7.80–7.15 (4H, m), 6.04 (1H,s), 4.73 (1H,s), 3.76–3.70 (2H, m, CH_2CH_3), 3.66–3.60 (2H, m, CH_2CH_3), 3.51–3.47 (2H, m), 2.92 (2H, dd, *J* 6.6, 6.5 Hz), 1.26 (6H, 2× t, *J* 7.1 Hz 2× CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.7, 159.3, 136.6, 131.3, 129.0, 128.2, 127.1, 126.0, 102.6, 85.9, 62.4 (2×), 38.6, 28.2, 15.3 (2×); IR (film) ν: 2974, 1727, 1618, 1561, 1309, 1103, 1061, 757 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $[M+Na]^+$ $C_{16}H_{21}NO_3Na$ 298.1414 found 298.1408.

*4.2.3.4. 3,3-Diethoxy-N-(1,2,3,4-tetrahydroizoquinoline)propioamide (**12**).* A mixture of rotamers: IR (film) ν_{max}: 1640, 1060 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.20–7.00 (4H, m), 4.95 (1H, m), 4.74 (1H, s), 4.66 (1H, s), 3.82 (1H, m), 3.78–3.54 (5H, m), 2.90–2.74 (4H, m), 1.22–1.09 (6H, m); LR MS (ESI) *m*/*z* 300.16 $[M+Na]^+$

*4.2.4. Compounds **14a**, **14b**, **14c**, **15**, and **16**.* Compounds **14a**, **14b**, **14c**, **15**, and **16** were obtained according to the general procedure from **3** and **7ent**. Their ratio was assigned by HPLC (LiChrosorb® Si60 250×4.6, 5 μm, 10% Et_2O in CH_2Cl_2, 1 mL/min, 254 nm; retention times: 7.9 min (**16**), 12.0 min (**14a**), 13.23 min (**14b**), 14.05 (**14c**)). Preliminary separation of **15** (25.5%) was done using 40% AcOEt in hexane. Subsequently compound **16** and β-lactams **14a**, **14b**, **14c** (29%) in a ratio of about 5:7:1:2, respectively, were separated by preparative HPLC using 10% diethyl ether in CH_2Cl_2 (2× Nucleosil Si60 10×250, 5 μm, 6 mL/min, 254 nm).

*4.2.4.1. (1R,9bS)-1-[(4R)-2,2-Dimethyl-1,3-dioxolan-4yl]-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**14a**).* Oil; $[\alpha]_D^{20}$ −154 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.25–6.60 (4H, m), 4.20 (1H, d, *J* 5.2 Hz), 3.98 (1H, dd, *J* 8.5, 6.9 Hz), 3.85 (1H, dd, *J* 8.5, 6.1 Hz), 3.66–3.61 (2H, m), 3.38 (1H, dd, *J* 9.7, 5.2 Hz), 2.61 (1H, ddd, *J* 16.8, 11.3, 7.0 Hz), 2.26 (1H, ddd, *J* 13.4, 11.3, 4.5 Hz), 1.94 (1H, dd, *J* 16.0, 4.2 Hz), 1.03 (3H, s), 1.33 (3H, s); ^{13}C NMR (150 MHz, C_6D_6) δ: 167.9, 134.6, 132.2, 129.3, 128.2, 127.0, 126.1, 108.4, 71.5, 67.5, 58.1, 51.4, 36.7, 28.6, 26.8, 25.3; IR (film) ν: 2934, 1751, 1370, 1218, 1062, 838, 752 cm^{-1}; HRMS (EI) *m*/*z* calcd for [M] $C_{16}H_{19}O_3$ N 273.1365 found 273.1357.

*4.2.4.2. (1S,9bS)-1-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**14b**).* Oil; $[\alpha]_D^{20}$ −58 (*c* 0.94, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6) δ: 7.20–6.60 (4H, m), 4.31 (1H, bs), 4.18 (1H, ddd, *J* 7.5, 6.4, 3.6 Hz), 4.06 (1H, dd, *J* 8.4, 7.5 Hz), 3.73 (1H, dd, *J* 8.4, 6.4 Hz), 3.56 (1H, m), 2.79 (1H, dd, *J* 3.6, 2.4 Hz), 2.51–2.42 (2H, m), 1.95 (1H, m), 1.46 (3H, s), 1.29 (3H, s); ^{13}C NMR (150 MHz, C_6D_6) δ: 167.3, 135.5, 134.0, 129.2, 126.8, 126.5, 126.0, 109.4, 72.6, 66.1, 60.5, 50.3, 37.2, 27.8, 26.4, 25.5; IR (film) ν: 2936, 1751, 1370, 1218, 1061, 847, 745 cm^{-1}; HRMS (EI) *m*/*z* calcd for [M] $C_{16}H_{19}O_3$ N 273.1365 found 273.1353.

*4.2.4.3. (1R,9bR)-1-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**14c**).* Oil; $[\alpha]_D^{22}$ +27 (*c* 0.16, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6) δ: 7.23–6.68 (4H, m), 4.22 (1H, bs), 4.16 (1H, dt, *J* 7.5 and 6.2 Hz) 3.87 (1H, dd, *J* 8.5, 6.2 Hz), 3.79 (1H, dd, *J* 8.5, 6.2 Hz), 3.55 (1H, ddd, *J* 12.8, 6.6, 3.8 Hz), 2.73 (1H, dd, *J* 7.5, 2.1 Hz), 2.48 (1H, m), 2.46 (1H, m), 1.97 (1H, m), 1.33 (3H, s), 1.22 (3H, s); ^{13}C NMR (150 MHz, C_6D_6) δ: 167.1, 135.3, 133.9, 129.2, 126.9, 126.6, 126.3, 108.9, 74.0, 67.7, 62.2, 51.4, 37.1, 27.8, 26.7, 25.2; IR (film) ν: 2936, 1751, 1370, 1218, 1061, 847, 745 cm^{-1}; HRMS (EI) *m*/*z* calcd for [M] $C_{16}H_{19}O_3$ N 273.1365 found 273.1362.

*4.2.4.4. (2Z)-2-(3.4-Dihydroisoquinolin-1(2H)-ylidene)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)-ethanone (**15**).* Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 11.4 (1H, s), 7.80–7.19 (4H, m), 6.09 (1H, s), 4.54 (1H, dd, *J* 6.9, 6.4 Hz), 4.31 (1H, dd, *J* 8.1, 7.5 Hz), 4.04 (1H, dd, *J* 8.1, 6.4 Hz), 3.51 (2H, ddd, *J* 6.9, 6.4, 3.5 Hz), 2.96–2.92 (2H, m), 1.54 (3H, s), 1.45 (3H, s); ^{1}H NMR (600 MHz, C_6D_6) δ: 11.6 (1H, s), 7.70–6.58 (4H, Ar), 6.46 (1H, s), 4.69 (1H, dd, *J* 7.4, 6.2 Hz), 4.35 (1H, dd, *J* 8.2, 6.0 Hz), 4.25 (1H, dd, *J* 8.2, 7.5 Hz), 2.54–2.45 (2H, m), 2.07–1.98 (2H, m), 1.54 (3H, s), 1.34 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.3, 158.9, 136.7, 131.4, 128.9, 128.3, 127.2, 125.8, 110.3, 85.3, 79.3, 68.3, 38.6, 28.2, 26.3, 25.6; IR (film) ν: 2984, 1751, 1635, 1557, 1445, 1370, 1220, 1061, 856 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $[M+Na]^+$ $C_{16}H_{19}NO_3Na$ 296.1257 found 296.1249.

*4.2.4.5. (1′Z)-1′-(3,4-Dihydroisoquinolin-1(2H)-ylidene)-2,2-dimethyl-1′,6′,7′,11b′-tetrahydro-2′H-spiro[1,3]dioxolane-4,3′-[1,2]oxazino[3,2-a]isoquinolin]-2′-one (**16**).* Colorless crystals; 179–182 °C; ^{1}H NMR (600 MHz, C_6D_6) δ: 13.4 (1H, s), 7.66–6.40 (8H, m), 4.96 (1H, s), 4.80 (1H, d, *J* 8.4 Hz), 4.62 (1H, d, *J* 8.4 Hz), 3.29 (1H, ddd, *J* 13.9, 7.3, 3.7 Hz), 3.01 (1H, m), 2.96 (1H, m), 2.60–2.50 (2H, m), 2.23 (1H, ddd, *J* 16.4, 7.3, 4.0 Hz), 2.11 (1H, m), 1.84 (1H, dt, *J* 15.0, 3.1 Hz), 1.67 (3H, s), 1.45 (3H, s); ^{13}C NMR (150 MHz, C_6D_6) δ: 189.7, 157.0, 138.9, 138.6, 134.7, 130.0, 129.0, 128.6, 128.2, 126.8, 126.2, 125.9,

(two aromatic carbons are shielded by C_6D_6 signals) δ: 113.1, 107.3, 101.1, 75.3, 61.4, 51.5, 38.3, 29.5, 27.4, 25.3, 24.5; IR (film) ν: 2929, 1726, 1608, 1576, 1552, 1466, 1257, 1098, 1044, 1019, 839, 763 cm^{-1}; HRMS (ESI) m/z calcd for $[M+Na]^+$ $C_{25}H_{26}N_2O_4Na$ 441.1785 found 441.1785.

*4.2.5. (5S,6R,7R)-5-(Benzyloxy)-7-phenyl-1-azabicyclo[4.2.0]octan-8-one (**20**).* Yield 65%; $[\alpha]_D^{20}$ +1.9 (*c* 1.1, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ: 7.36–724 (8H, m), 7.03 (2H, m), 4.69 (1H, dd, *J* 5.0, 1.7 Hz), 3.97 (1H, d, *J* 10.8 Hz), 3.84 (1H, dd, *J* 13.2, 5.5 Hz), 3.62 (1H, d, *J* 8.6, 5.0 Hz), 3.60 (1H, d, *J* 10.8 Hz), 3.02 (1H, ddd, *J* 11.3, 8.6, 4.1 Hz), 2.69–2.61 (1H, m), 2.15–2.09 (1H, m), 1.79–1.74 (1H, m), 1.52–1.48 (1H, m), 1.41–1.33 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.6, 137.8, 133.1, 129.1(×2), 128.5, 128.3(×2), 127.7(×2), 127.6(×2), 127.5, 74.5, 70.6, 58.6, 57.7, 37.8, 28.1, 24.6; IR (film) ν: 1748 cm^{-1}; HRMS (ESI) m/z calcd for $[M+Na]^+$ $C_{20}H_{21}NO_2Na$ 330.1465; found: 330.1470.

*4.2.6. Compounds **21a** and **21b**.* Compounds **21a** and **21b** were obtained according from **4** and **6** following the general procedure. Products were separated by chromatography using 10% acetone in CH_2Cl_2. Yield **21a** 19% and **21b** 9%. The diastereoisomeric ratio assigned by ^1H NMR **21a**:**21b**=2:1.

*4.2.6.1. (5S,6R,7S)-5-(Benzyloxy)-7-(diethoxymethyl)-1–azabicyclo[4.2.0]octan-8-one (**21a**).* Oil; $[\alpha]_D^{20}$ +98 (*c* 1.1, CH_2Cl_2); ^1H NMR (600 MHz, C_6D_6) δ: 7.00–7.30 (5H, m), 4.86 (1H, d, *J* 3.8 Hz), 4.39 (1H, d, *J* 11.6 Hz), 4.34 (1H, d, *J* 11.6 Hz), 3.74 (1H, ddd, *J* 11.0, 8.5, 4.2 Hz), 3.43 (1H, m), 3.71–3.53 (3H, m, 3× CH*H*CH_3), 3.38 (1H, ddd, *J* 5.0, 3.8, 1.7 Hz), 3.25 (1H, m, 1× CH*H*CH_3), 3.08 (1H, dd, *J* 8.5, 5.0 Hz), 1.96 (1H, m), 1.65 (1H, m), 1.06 (3H, t, *J* 7.1 Hz), 1.03 (3H, t, *J* 7.1 Hz), 0.89–0.81 (2H, m), 1.04 (1H, m); ^{13}C NMR (150 MHz, C_6D_6) δ: 163.4, 139.1, 128.2, 128.1, 127.9, 127.3(2×), 98.9, 73.9, 70.1, 62.4, 60.9, 57.8, 55.0, 37.2, 37.1, 28.3, 15.3, 15.1; IR (film) ν: 2928, 1753, 1454, 1057, 698 cm^{-1}; HRMS (ESI) m/z calcd for $[M+Na]^+$ $C_{19}H_{27}NO_4Na$ 356.1836 found 356.1838.

*4.2.6.2. (5S,6R,7R)-5-(Benzyloxy)-7-(diethoxymethyl)-1–azabicyclo [4.2.0] octan-8-one (**21b**).* Oil; $[\alpha]_D^{20}$ +14 (*c* 0.95, CH_2Cl_2); ^1H NMR (600 MHz, C_6D_6) δ: 7.35–7.00 (5H, m), 4.71 (1H, d, *J* 4.4 Hz), 4.63 (1H, d, *J* 11.9 Hz, CH*H*Ph), 4.36 (1H, d, *J* 11.9 Hz, CH*H*Ph), 3.62 (1H, m, CH*H*CH_3), 3.56 (1H, m, CH*H*CH_3), 3.44–3.38 (2H, m, 2× CH*H*CH_3) 3.37–3.31 (2H, m) 3.23 (1H, dd, *J* 4.4, 1.6 Hz), 2.87 (1H, ddd, *J* 11.3, 8.4, 3.9 Hz), 1.96 (1H, dt, *J* 12.6, 4.4 Hz); 1.66 (1H, m), 1.05 (3H, t, *J* 7.0 Hz CH_2CH_3); 1.04 (3H, t, *J* 7.0 Hz CH_2CH_3); 1.00 (1H, m), 0.94–0.81 (2H, m); ^{13}C NMR (150 MHz, C_6D_6) δ: 163.5, 139.0, 128.2(2×), 128.1, 127.6, 127.3, 100.4, 77.6, 70.1, 63.5, 62.7, 62.2, 55.0, 37.2, 29.1, 24.0, 15.1, 15.1; IR (film) ν: 2929, 1751, 1454, 1058, 698 cm^{-1}; HRMS (ESI) m/z calcd for $[M+Na]^+$ $C_{19}H_{27}NO_4Na$ 356.1836 found 356.1837.

*4.2.7. Compounds **22a**, **22b**.* Compounds **22a**, **22b** were obtained according to the general procedure, using **7**. Solvent for chromatography 10% acetone in CH_2Cl_2 Yield **22a** and **22b** 45% The diastereoisomeric ratio assigned by ^1H NMR **22a**:**22b** 2.5:1.

*4.2.7.1. (5S,6R,7R,4′S)-5-benzyloxy-7-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-aza-bicyclo[4.2.0]octan-8-one (**22a**).* Mp 98–100 °C; $[\alpha]_D^{25}$ +75 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ: 7.40–7.27 (5H, m), 4.64 (1H, d, *J* 10.9 Hz), 4.58 (1H, d, *J* 10.9 Hz), 4.37 (1H, m), 4.19 (1H, dd, *J* 8.5, 6.3 Hz), 3.93 (1H, dd, *J* 8.5, 7.0 Hz), 3.70 (1H, bdd, *J* 13.3, 5.3 Hz), 3.60 (1H, ddd, *J* 10.6, 8.7, 4.1 Hz), 3.50 (1H, dd, *J* 8.7, 4.6 Hz), 3.45 (1H, ddd, *J* 9.7, 4.6, 1.7 Hz), 2.60 (1H, m), 2.28 (1H, m), 1.77 (1H, m) 1.49 (1H, m), 1.38 (1H, m), 1.43 (3H, s), 1.36 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.8, 138.2, 128.3(2×), 128.0, 127.9, 127.8, 109.1, 74.2, 71.3, 71.1, 68.2, 57.1, 55.7, 37.7, 28.5, 26.8, 25.6, 24.1; IR (film) ν: 2936, 1749, 1370, 1104, 1066, 699 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{25}NO_4$ 331.1784; found: 331.1799.

*4.2.7.2. (5S,6R,7S,4′S)-5-Benzyloxy-7-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-aza-bicyclo[4.2.0]octan-8-one (**22b**).* ^1H NMR (600 MHz, $CDCl_3$, signals was taken from the spectrum of crude **22a**) δ: 4.62 (1H, d, *J* 11.6 Hz), 4.58 (1H, d, *J* 11.6 Hz), 4.38 (1H, m, *J* 7.0, 6.3, 4.1 Hz), 4.02 (1H, dd, *J* 8.3, 6.3 Hz), 3.93 (1H, dd, *J* 8.3, 7.0 Hz), 3.71 (1H, m), 3.27 (1H, dd, *J* 8.5, 1.0 Hz), 3.25 (1H, dd, *J* 8.5, 3.3 Hz), 3.09 (1H, dd, *J* 4.1, 1.0 Hz), 2.60 (1H, m), 2.16 (1H, m), 1.78 (1H, m), 1.40 (2H, m), 1.41 (3H, s), 1.37 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.0, 138.0, 128.5, 127.9, 127.8, 127.6, 109.8, 77.9, 72.6, 70.8, 66.3, 59.5, 55.5, 37.8, 28.8, 26.4, 25.5, 24.5.

*4.2.8. Compounds **23a**, **23b**.* Compounds **23a**, **23b** were obtained according to the general procedure, using acetylene **7ent**. The post reaction mixture was separated by chromatography using 5% acetone in CH_2Cl_2 to provide pure **23a** in 33% yield and a mixture of **23a** and **23b** (12%).

*4.2.8.1. (5S,6R,7R,4′R)-5-benzyloxy-7-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-aza-bicyclo[4.2.0]octan-8-one (**23a**).* Oil; $[\alpha]_D^{20}$ +145 (*c* 1.6, CH_2Cl_2); ^1H NMR (600 MHz, C_6D_6) δ: 7.25–7.05 (5H, m), 4.40 (1H, d, *J* 11.5 Hz), 4.28 (1H, d, *J* 11.5 Hz), 4.14–4.10 (2H, m), 3.93 (1H, ddd *J* 11.3, 8.6, 4.0 Hz), 3.65 (1H, m), 3.43 (1H, dd, *J* 13.1, 5.5 Hz), 2.97 (1H, dd, *J* 8.6, 5.0 Hz), 2.78 (1H, dt, *J* 5.0, 1.4 Hz); 1.96 (1H, m), 1.78 (1H, m), 1.51 (3H, s), 1.31 (3H, s), 1.10 (1H, m), 1.00 (1H, m), 0.86 (1H, m); ^{13}C NMR (150 MHz, C_6D_6) δ: 164.0, 138.9, 128.2, 127.9, 127.7, 127.6 (one aromatic carbon was shielded by C_6D_6 signals) 110.0, 74.9, 72.3, 70.2, 67.7, 55.5, 54.2, 37.1, 26.2, 26.8, 26.2, 23.9; IR (film) ν: 2934, 1751, 1370, 1061, 699 cm^{-1}; HRMS (ESI) m/z calcd for $[M+Na]^+$ $C_{19}H_{25}NO_4Na$ 354.1681; found 354.1680.

*4.2.8.2. (5S,6R,7S,4′R)-5-Benzyloxy-7-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-aza-bicyclo[4.2.0]octan-8-one (**23b**).* ^1H NMR (600 MHz, $CDCl_3$, selected signals taken from the spectrum of crude **23a**) δ: 4.54 (1H, d, *J* 11.7 Hz), 4.30 (1H, d, *J* 11.7 Hz), 4.08 (1H, m, *J* 8.0, 6.7, 6.2 Hz), 3.97 (1H, dd *J* 8.4, 6.2 Hz), 3.93 (1H, dd, *J* 8.4, 6.7 Hz), 3.04 (1H, dd, *J* 8.2, 1.5 Hz), 2.82 (1H, dd, *J* 8.0, 1.5 Hz), 1.33 (3H, s), 1.20 (3H, s).

*4.2.9. Compounds **23a**, **23b**, and **24**.* Compounds **23a**, **23b**, and **24** were obtained in the similar reaction perform in dichloromethane according to the general procedure, using acetylene **7ent**. The post reaction mixture was separated by chromatography using 5% acetone in CH_2Cl_2 to provide pure **23a** in 17.5% yield and a mixture of **23a** and **23b** (14%), and **24** (15%).

*4.2.9.1. (5S)-5-Benzyloxy-7-(2-hydroxy-ethylidene)-1–azabicyclo [4.2.0] octan-8-one (**24**).* Oil; $[\alpha]_D^{21}$ +61 (*c* 0.4, CH_2Cl_2); ^1H NMR (600 MHz, C_6D_6) δ: 7.25–7.00 (5H, m), 5.99 (br t, 1H, *J* 3.4 Hz), 4.14 (1H, d, *J* 11.5 Hz), 3.96 (2H, m), 3.93 (1H, d, *J* 11.5 Hz), 3.73 (1H, d, *J* 8.5 Hz), 3.56 (1H, br s), 3.45 (1H, dd, *J* 13.5, 5.7 Hz), 2.84 (1H, ddd *J* 11.2, 8.5, 3.5 Hz), 2.03 (1H, dt, *J* 13.0, 4.5 Hz), 1.51 (1H, m), 0.90 (1H, m), 0.83 (1H, m), 0.66 (1H, m); ^{13}C NMR (150 MHz, C_6D_6) δ: 161.7, 141.4, 137.1, 128.4, 127.9(×2), 127.6, 126.1, 78.7, 69.8, 60.2, 58.8, 37.2, 26.4, 24.3; IR (film) ν: 3425, 2928, 1744, 1715, 1386, 1090, 700 cm^{-1}; HRMS (ESI) m/z calcd for $[M+Na]^+$ $C_{16}H_{19}NO_3Na$ 296.1263 found 296.1263.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.031. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Chemistry and Biology of β-Lactam Antibiotics; Academic: New York, NY, 1982; (b) Georg, G. I. *Organic Chemistry of Beta-lactams*; VCH: 1993.
2. Bonfiglio, G.; Russo, G.; Nicoletti, G. *Expert Opin. Invest. Drugs* **2002**, *11*, 529–544.
3. Moellering, R. C. J.; Eliopoulos, G. M.; Sentochnik, D. E. *J. Antimicrob. Chemother.* **1989**, *24*, 1–7.
4. (a) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787–3790; (b) Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321–2324; (c) Zmijewski, M. J., Jr.; Briggs, B. S.; Thompson, A. R.; Wright, I. G. *Tetrahedron Lett.* **1991**, *32*, 1621–1622; (d) Bodurow, C. C.; Levy, J. N.; Wiitala, K. W. *Tetrahedron Lett.* **1992**, *33*, 4283–4286; (e) Frazier, J. W.; Staszak, M. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 857–860; (f) Deeter, J. B.; Hall, D. A.; Jordan, C. L.; Justice, R. M.; Kinnick, M. D.; Morin, J. M., Jr.; Paschal, J. W.; Ternansky, R. L. *Tetrahedron Lett.* **1993**, *34*, 3051–3054; (g) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210–9216; (h) Jackson, B. G.; Pedersen, S. W.; Fisher, J. W.; Misner, J. W.; Gardner, J. P.; Staszak, M. A.; Doecke, C.; Rizzo, J.; Aikins, J.; Farkas, E.; Trinkle, K. L.; Vicenzi, J.; Reinhard, M.; Kroeff, E. P.; Higginbotham, C. A.; Gazak, R. J.; Zhang, T. Y. *Tetrahedron* **2000**, *56*, 5667–5677; (i) Lee, J. C.; Kim, G. T.; Shim, Y. K.; Kang, S. H. *Tetrahedron Lett.* **2001**, *42*, 4519–4521; (j) Misner, J. W.; Fisher, J. W.; Gardner, J. P.; Pedersen, S. W.; Trinkle, K. L.; Jackson, B. G.; Zhang, T. Y. *Tetrahedron Lett.* **2003**, *44*, 5991–5993.
5. (a) Cooper, R. D. G. *Am. J. Med.* **1992**, *92*, S2–S6; (b) DeSante, K. A.; Zeckel, M. L. *Am. J. Med.* **1992**, *92*, S16–S19; (c) Hyslop, D. L. *Am. J. Med.* **1992**, *92*, S65–S69; (d) Hyslop, D. L.; Bischoff, W. *Am. J. Med.* **1992**, *92*, S86–S94; (e) Iravani, A.; Bischoff, W. *Am. J. Med.* **1992**, *92*, S95–S100; (f) McCarty, J. *Am. J. Med.* **1992**, *92*, S74–S79; (g) McCarty, J.; Ruoff, G. E.; Jacobson, K. D. *Am. J. Med.* **1992**, *92*, S80–S85; (h) Moellering, R. C.; Jacobs, N. F. *Am. J. Med.* **1992**, *92*, S1; (i) Therasse, D. G. *Am. J. Med.* **1992**, *92*, S20–S25; (j) Zeckel, M. L. *Am. J. Med.* **1992**, *92*, S58–S64.
6. (a) Chmielewski, M.; Stecko, S.; Mames, A.; Furman, B. *J. Org. Chem.* **2008**, *73*, 7402–7404; (b) Chmielewski, M.; Stecko, S.; Mames, A.; Furman, B. *J. Org. Chem.* **2009**, *74*, 3094–3100; (c) Chmielewski, M.; Mames, A.; Stecko, S.; Mikolajczyk, P.; Soluch, M.; Furman, B. *J. Org. Chem.* **2010**, *75*, 7580–7587; (d) Maciejko, M.; Stecko, S.; Staszewska-Krajewska, O.; Jurczak, M.; Furman, B.; Chmielewski, M. *Synthesis* **2012**, 2825–2839.
7. Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466–467.
8. Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198–2199.
9. Khangarot, R. K.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2011**, *2011*, 6117–6127.
10. Grigor'ev, I. A. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, 2008.
11. Stecko, S.; Michalak, M.; Stodulski, M.; Mucha, Ł.; Parda, K.; Furman, B.; Chmielewski, M. *Synthesis* **2012**, 2695–2698.
12. Cordero, F. M.; Machetti, F.; De Sarlo, F.; Brandi, A. *Gazz. Chim. Ital.* **1997**, *127*, 25–29.
13. (a) Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736–1744; (b) Murahashi, S. I.; Shiota, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265–268.
14. Ashoorzadeh, A.; Archibald, G.; Caprio, V. *Tetrahedron* **2009**, *65*, 4671–4680.
15. (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246; (b) Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331–2333; (c) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054–3056; (d) Bunlaksananusorn, T.; Lecourt, T.; Micouin, L. *Tetrahedron Lett.* **2007**, *48*, 1457–1459; (e) Serizawa, M.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2008**, *19*, 921–931; (f) Ji, D. M.; Xu, M. H. *Tetrahedron Lett.* **2009**, *50*, 2952–2955.
16. (a) Łysek, R.; Borsuk, K.; Chmielewski, M.; Kałuża, Z.; Urbańczyk-Lipkowska, Z.; Klimek, A.; Frelek, J. *J. Org. Chem.* **2002**, *67*, 1472–1479; (b) Frelek, J.; Kowalska, P.; Masnyk, M.; Kazimierski, A.; Korda, A.; Woźnica, M.; Chmielewski, M.; Furche, F. *Chem.—Eur. J.* **2007**, *13*, 6732–6744; (c) Chmielewski, M.; Cierpucha, M.; Kowalska, P.; Kwit, M.; Frelek, J. *Chirality* **2008**, *20*, 621–627; (d) Frelek, J.; Łysek, R.; Borsuk, K.; Jagodziński, J.; Furman, B.; Klimek, A.; Chmielewski, M. *Enantiomer* **2002**, *7*, 107–114; (e) Woźnica, M.; Masnyk, M.; Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M.; Frelek, J. *J. Org. Chem.* **2010**, *75*, 7219–7226; (f) Kwit, M.; Skowronek, P.; Gawronski, J.; Frelek, J.; Woźnica, M.; Butkiewicz, A. *In Comprehensive Chiroptical Spectroscopy*; John Wiley & Sons: 2012; pp 37–72.
17. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center, Cambridge, UK, as a supplementary publications: **16** (CCDC 898221), **22a** (CCDC 898220).