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Asymmetric Kinugasa Reaction of Cyclic Nitrones and Nonracemic Acetylenes

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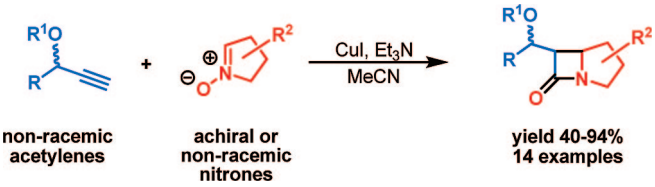
Received January 19, 2009



Kinugasa reactions between chiral acetylenes and five-membered nitrones, achiral and bearing a stereogenic center in both enantiomeric forms, proceed in moderate to good yield with high diastereoselectivity affording mostly one dominant product. The first step of the reaction is controlled by the configuration of the nitrone, whereas the protonation of intermediate enolate in the second step depends mainly on the configuration of the bridgehead carbon atom formed in the first step. In the case of the mismatched pair, the configuration at the C-6 center of the carbapenam skeleton may also be affected by the configuration of the stereogenic center in the acetylene portion.

Introduction

The β-lactam antibiotics represent a powerful tool against bacterial infections. Owing to their attractive biological activity, the synthesis and properties of mono- and polycyclic systems containing the β-lactam ring have been extensively investigated.[1] The history of β-lactams goes back to 1907 when Staudinger discovered the imine−ketene cycloaddition.[2] Unil then, a number of methodologies for the construction of a β-lactam ring, both in diastereo- and enantioselective fashion, were developed.[3]

The copper(I)-mediated reaction between nitrones and terminal acetylenes, discovered in 1972 by Kinugasa and Hashimoto,[4] represents a direct and simple method of the β-lactam ring formation (Scheme 1). While the Kinugasa reaction has shown a great potential in 2-azetidinone synthesis,[5−15] there are only a few reports detailing the related diastereo-[9−11] and enantioselective protocols.[12−15]

Very recently, we reported a diastereoselective version of the Kinugasa reaction involving nonracemic cyclic nitrones, derived from malic and tartaric acids, and simple achiral acetylenes.[11] Such reactions displayed high diastereoselectivity leading to one dominant product. On the basis of the proposed stereochemical model of the reaction,[11] it has been shown that the stereochemical outcome of the Kinugasa reaction depends on the first step,

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(2) Staudinger, H. *Ann. Chem.* **1907**, *356*, 51.

(3) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837. (b) Deshmukh, A. R. A. S.; Bhwal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanti, A. *Curr. Med. Chem.* **2004**, *11*, 1889. (c) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. (d) Alcaide, B.; Almendros, P.; Argoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.

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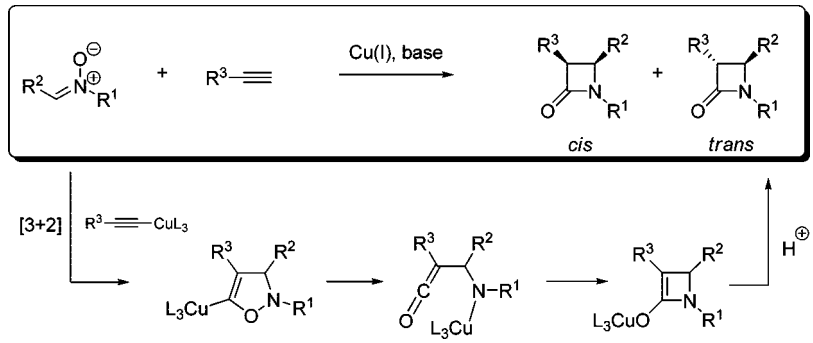
10.1021/jo900121x CCC: $40.75
Published on Web 03/26/2009

SCHEME 1. Postulated Mechanisms of the Kinugasa Reaction[12c]

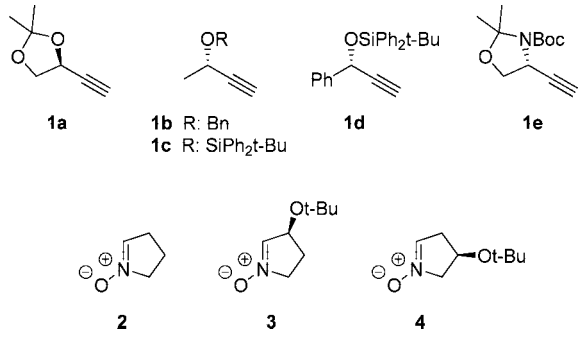


1,3-dipolar cycloaddition. The addition is controlled by the substituent present in the nitrone, whereas the protonation of intermediate enolate in the second step occurs from the less shielded side of carbapenam skeleton. Consequently, the major product displays the relative *cis*-orientation of protons in the four-membered β-lactam ring.[11] Good stereoselectivity of these reactions opens an attractive entry to the carbapenam skeleton notwithstanding the moderate yield.

Results/Discussion

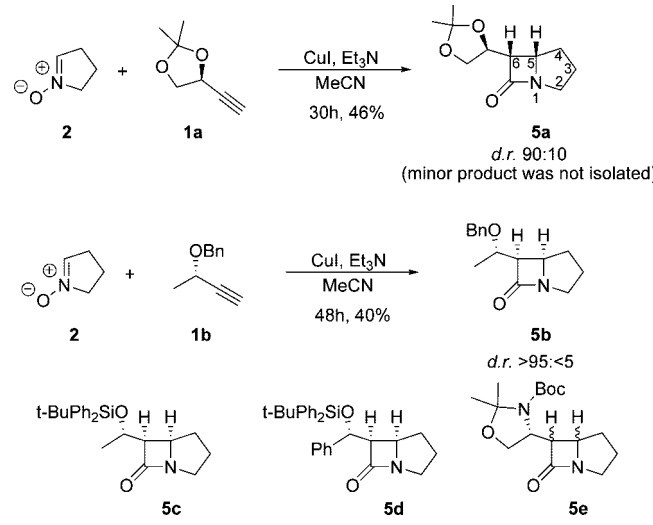
The interesting preliminary results[11] prompted us to further investigate the Kinugasa reactions involving chiral, optically pure acetylenes and five-membered ring nitrones, both nonchiral or with a stereogenic center.

The present paper describes our studies on the asymmetric induction observed in reactions between acetylenes **1a**−**e** and the achiral nitrone **2**, as well as chiral nitrones in both enantiomeric forms **3/3-*ent*** and **4/4-*ent***. The results thus obtained, together with previously reported studies,[11] made possible to propose the stereochemical pathway of the reaction in both matched and mismatched variants.



The acetylene **1a** was prepared from D-glyceraldehyde[16] by treatment with the Bestmann−Ohira reagent.[17] The acetylenes **1b**−**d** were obtained starting from the commercially available (*S*)-3-butyn-2-ol and (*R*)-1-phenyl-2-propyn-1-ol, using standard silylation or benzylation protocols.[18] The compound **1e** was obtained from Garner's aldehyde following the procedure described for the acetylene **1a**.[19] The nonchiral nitrone **2** was synthesized from 1,4-dibromobutane following the literature procedure[20] whereas the chiral nitrones **3/3ent** and **4/4-*ent*** were prepared from the corresponding L- and D-malic acids, according to the Brandi methodology.[21]

SCHEME 2



As shown in Scheme 2, reactions between nitrone **2** and acetylenes **1a** and **1b** proceeded with excellent diastereoselectivity, affording the corresponding carbapenams **5a** and **5b** in moderate yield (∼50%). The relative configuration of H-5 and H-6 protons in both products was proven using $^3J_{H5-H6}$ coupling constants and was found to be *cis* for both of them.[22] The absolute configuration at the newly introduced stereogenic centers in **5a** - **5d** was assigned using $^3J_{H6-H1'}$, by analogy to compounds **12** and **13a**, and is discussed later. The high diastereoselectivity was observed also for reactions involving silylated acetylenes **1c** and **1d**. The detected *cis* products **5c** and **5d** were unstable, however, and decomposed during isolation and purification steps. Their structure and configuration were based only on MS and selective NMR data recorded for crude compounds and the assignment was made by analogy to **5a** and **5b**. In the case of acetylene **1e**, the target carbapenam **5e** was even less stable and only traces of product were detected in the reaction mixture (mass spectrometry analysis) albeit

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(18) (*S*)-3-Butyn-2-ol and (*R*)-1-phenyl-2-propyn-1-ol do not react in the Kinugasa reaction at all.
(19) Garner, Ph.; Park, J. M. *Org. Synth.* **1992**, *70*, 18.
(20) Cordero, F.; Machetti, F.; De Sarlo, F.; Brandi, A. *Gazz. Chim. Ital.* **2007**, *127*, 25.
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(22) (a) Effenberger, F.; Fischer, P.; Prossel, G.; Kiefer, G. *Chem. Ber.* **1971**, *104*, 1987. (b) Effenberger, F.; Fischer, P.; Prossel, G. *Chem. Ber.* **1971**, *104*, 2002.
(23) The range of $^3J_{H5-H6}$ coupling constant values for *cis*-β-lactams is 5.0−6.5 Hz, whereas for *trans*-β-lactams it amounts to 2−2.5 Hz.

complete consumption of the acetylene was observed during the reaction. The low stability of the adducts was probably caused by the β-elimination process followed by further decomposition of the molecule.[22]

As already mentioned, both reactions presented in Scheme 2 afforded the products in moderate yields. It should be underlined that relatively low yield is a characteristic feature of the Kinugasa reaction due to a dual character of copper acetylide which may react either as dipolarophile or as nucleophile.[12] For this reason, the addition of organocopper compound to the imine can also occur as a side reaction.[12] Moreover, additional side processes such as the Cu(I)-mediated deoxygenation of the nitrone[24] or Glasser coupling[25] are also possible. In investigated cases, the low yield may also be caused by the known low stability of the nitrone **2**.[26] Previously, we have reported that addition of hydrazine increased the reaction yield.[11] This works, however, for phenylacetylene only, while other acetylenes, particularly those with protected oxygen or nitrogen functions, do not show such effect.

The outcome of the reactions, in case where both reactants (acetylene and nitrone) are chiral, can be explained on the basis of the previous observations. The most important one is that the first 1,3-dipolar cycloaddition step involving nitrone **3**/**3-*ent*** proceeds exclusively *anti* to the *tert*-butoxy group. The reaction of **1c** with the nitrone **3** led to two carbapenams **6a** and **6b** in a 9:1 ratio, respectively, whereas nitrones' enantiomeric form (**3-*ent***) afforded solely the *cis* isomer **7** (Table 1). In contrast to the reactions described earlier, the products derived from **1c**, as well as **1d**, do not decompose during isolation and purification steps. The high stereoselectivity was obtained in the case of pair **3-*ent*/1b**, whereas two products **8a** and **8b** in a 4:1 ratio were isolated from the postreaction mixture between nitrone **3** and acetylene **1b**. Similarly to pairs **1c**/**3-*ent*** and **1b**/**3-*ent***, the reaction of **3-*ent*** with **1d** yielded product **11**, exclusively. The analogous reaction involving the nitrone **3** afforded a mixture of two β-lactams **10a** and **10b**. The stereochemical outcome of this reaction is similar to the reaction of **3** with acetylene **1b** and **1c** (formation of **10a** and **10b**). According to these results, all reactions of acetylenes **1b**−**d** with **3-*ent*** represent the matched pairs of reactants, whereas those involving the nitrone **3** and the same acetylenes are mismatched pairs.

Due to the inverse absolute configuration at the stereogenic center next to the triple bond in acetylene **1a** (derived from D-glyceraldehyde) in comparison with **1b**−**d**, the opposite stereochemical preferences were noticed for the reactions with nitrones **3** and **3-*ent***. In the case of the former, a single product **12** was obtained, whereas the latter afforded the mixture of **13a** and **13b** in a 92:8 ratio. The overlapping of diagnostic signals in NMR spectra of the minor product **13b** did not allow for the assignment of configuration at C-5 and C-6 atoms, it was assigned by analogy to other cases. It should be underlined that in contrast to other currently investigated cases, the reaction between **3** and **1a** leading to **12** proceeded with the remarkably high yield, exceeding 90%.

Comparison of the NMR spectral data of compounds **12** and **13a** allowed, by analogy, to assign the absolute configuration to all products obtained (**5**−**15**). It has been shown previously[11] that owing to the influence of the *tert*-butoxy group, the dominant product of addition to the nitrone **3** has *syn* location of the H-4 and H-5 protons. Bearing in mind coupling constants within the β-lactam skeleton (0−2 Hz for *anti* and 4−6 Hz for *syn*); consequently, it is straightforward to assign the absolute configuration at the C-6 carbon atom, as well. These assignments were independently supported by the NOEs taken for both compounds (see the Supporting Information), which for **12** show a spin−spin interaction between H-4 and H-1′ protons whereas such interactions were not observed between H-4−H-5 and H-6−H-1′. For compound **13a**, protons H-6 and H-1′ shows spin−spin interaction, whereas such interactions were not observed between H-4 proton and H-5, and H-1′. Carbapenam **12** (6*S*,1′*S*) is characterized by $^3J_{H6-H1'} = 10.1$ Hz whereas **13a** (6*R*,1′*S*) having alternative relation of both protons by $^3J_{H6-H1'} = 2$ Hz, similarly **8a** shows $^3J_{H6-H1'} = 4.7$ Hz, whereas **9** shows $^3J_{H6-H1'} = 8.5$ Hz. Consequently, on the basis of the large coupling constants $^3J_{H6-H1'}$ (10.3, 10.0, 9.4, and 8.0 Hz for **5a**, **5b**, **5c**, and **5d**, respectively), we were able to assign theirs configurations at C-5 and C-6 carbon atoms.

Finally, reactions involving acetylene **1a** and nitrones **4** and **4-*ent*** were performed. The reaction of matched pair (**1a**/**4**) afforded compound **14**, whereas in the case of the mismatched pair (**1a**/**4-*ent***) two products **15a** and **15b** were isolated. Configuration assignments for **14** and **15a**,**b** were made by analogy to **12** and **13a**. The results of this reaction indicate that in this case, the *tert*-butoxy group influences also the direction of asymmetric induction, although the stereogenic center of the nitrone is moved away from the reaction center. The previously studied reaction of the nitrone **4** with phenylacetylene led to a mixture of two *cis* products in ca. 3:1 ratio.[11]

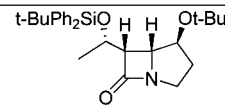
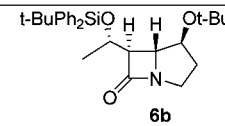
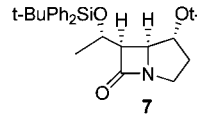
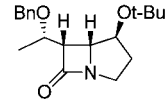
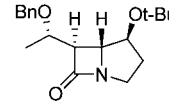
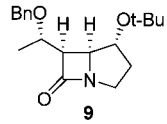
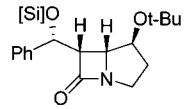
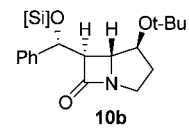
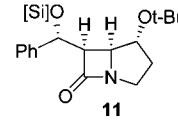
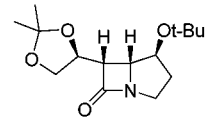
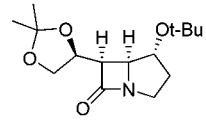
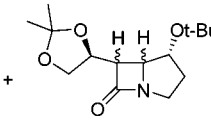
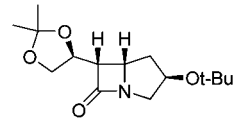
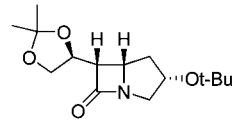
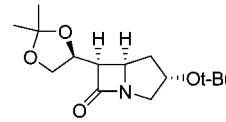
Similarly to the reaction involving Garner's acetylene **1e** and the nitrone **2**, which led to decomposition products, the reactions of the same acetylene **1e** with nitrones **3** and **3-*ent*** did not provide expected adducts either; we were unable to detect any defined product.

Currently, there is no reasonable explanation for the significant enhancement of the yield recorded in the case of reaction between **1a** and **3**. We assigned this phenomenon to coordination of the copper atom at the isoxazoline or/and enolate step by the oxygen atoms of the 1,3-dioxolane moiety. Such extra stabilization may accelerate the rate of the Kinugasa reaction with respect to the other possible side reactions and consequently causes formation of the desired carbapenam in very high yield (in 80% after 2 h and over 90% after 24 h).

Very recently, we pointed out that the stereochemical course of the Kinugasa reaction between nonracemic nitrones **3**, **4**, and achiral acetylenes,[11] depends on the initial cycloaddition step. As it is shown in Figure 1, the cycloaddition of the acetylene from the *si* side of the nitrone (*anti* approach with respect to *t*-BuO substituent) is more favorable due to steric hindrance of the nitrones' *re* side. The subsequent generation of stereogenic center at C-6 depends on the configuration at previously created bridgehead carbon atom (C-5) and proceeds through a protonation of the intermediate enolate (afforded after rearrangement of the isoxazoline) from its convex or concave side. Experimental observations revealed high preference of convex-side

(24) Singh, S. K.; Reddy, M. S.; Mangle, M.; Ganesh, K. R. *Tetrahedron* **2007**, *63*, 126.
(25) Siemsen, O.; Livingstone, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
(26) (a) Torssell, K. B., *Nitrile Oxide, Nitrones and Nitronates in Organic Chemistry*; VCH Publishers, Inc.: New York, 1998. (b) Grigor'ev, I. A. In *Nitrile Oxide, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons: New York, 2008. (c) Merino, P. In *Science of Synthesis*; Padwa, A., Ed.; George Thieme: New York, 2004; Vol. 27, p 511.

TABLE 1. Double-Asymmetric Induction in Kinugasa Reaction of Nitrones 3/3-*ent* and 4/4-*ent* with Acetylenes 1a−e[a]

Ent.	Acetylene	Nitrone	Time [h]	Yield [%][b]	Product(s)	*d.r.* ratio[c]
1	**1c**	**3**	24	52	 **6a**  **6b**	90:10
2	**1c**	**3-*ent***	24	54	 **7**	>95:<5
3	**1b**	**3**	24	48	 **8a**  **8b**	80:20
4	**1b**	**3-*ent***	24	42	 **9**	>95:<5
5	**1d**	**3**	22	62	 **10a**  **10b**	70:30
6	**1d**	**3-*ent***	20h	75	 **11**	>95:<5
7	**1a**	**3**	24	94 (80[d])	 **12**	>95:<5
8	**1a**	**3-*ent***	24	53	 **13a** +  **13b**	92:8[e]
9	**1a**	**4**	24	45	 **14**	>95:<5
10	**1a**	**4-*ent***	24	50	 **15a**  **15b**	1:2

[a] Standard conditions: acetylene (0.5 mmol), CuI (0.5 mmol), Et_3N (2 mmol), and nitrone (1 mmol) in MeCN at rt. [b] All are isolated yields. [c] The dr was determined by using ^1H NMR or/and HPLC. [d] After 2 h. [e] Configuration of **13b** was not assigned due to the overlap of diagnostic signals. [f] Only traces of product was detected by mass spectrometry.

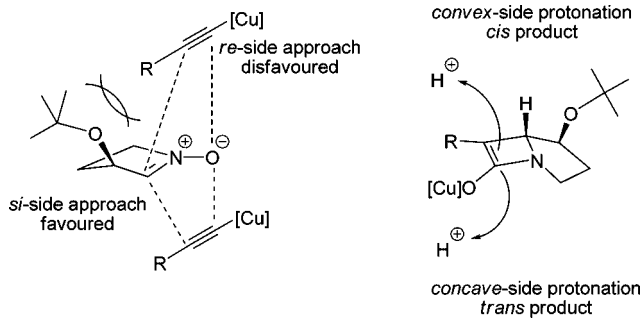


FIGURE 1. Stereochemical outcome of the Kinugasa reaction.

protonation (leading to 5,6-*cis* products) what can be easily explained by steric factors.

Inspection of the data collected in Scheme 2 and Table 1 indicates that the stereochemical outcome of Kinugasa reaction of nonracemic acetylenes **1a**−**d** with nonchiral nitrone **2** is controlled by the initial cycloaddition step. Parts a and b of Figure 2 demonstrate this influence of the acetylenes' chiral center on the asymmetric induction. Three distinct trajectories of the approach of the nitrone **2** to acetylide are possible. Following the observed configuration at the C-5 and C-6 atoms for compounds **5a**−**d**, as well as for other compounds discussed, the attack of the nitrone from the bottom side of the acetylene is preferred to that from the top, due to the lower degree of steric repulsion between the nitrone and a medium substitutent (Figure 2a). It can be assumed that the alternative back-side approach (Figure 2b) is also less favorable. The replacement of the achiral nitrone **2** by its chiral analogue **3** or **3-*ent*** eliminates the asymmetric inductive effect of the acetylene stereogenic center completely, and products of *anti* approach with respect to the *t*-BuO group are observed exclusively. Its influence decreases slightly when the *t*-BuO group at the nitrone is transposed from C-3 to C-4 (compare Table 1, entries 8 and 10). In this case, however, the *anti* approach product is also the major one.

Based on assignments of the configuration at C-5 and C-6 carbon atoms of carbapenams **5a** and **5b**, as well as other afforded carbapenams, it can be concluded that the stereochemical outcome of the final protonation step of the intermediate enolate (Scheme 1) is controlled to the great degree by the configuration at C-5. Certainly, the influence of the side-chain stereogenic center cannot be excluded entirely, and its minor effect can be considered through the Felkin−Ahn model (Figure 2c). Two possible conformations of the side chain in the intermediate enolate are depicted in Figure 2c. For the lowest energy conformer **A**, both convex and concave approaches should be disfavored, the former one due to steric repulsion of the large group L (i.e., for **1b**, L = OBn; for **1c**, L = $OSiPh_2$-*t*-Bu) and the latter one (Felkin−Ahn approach) due to hindrance of the fused five-membered ring. In the case of higher energy conformer **B** (2 kcal/mol),[27] the steric repulsion at the convex side are minimized, and it can be assumed that a protonation proceeds from this side (*anti*-Felkin−Ahn approach), as can be seen from our experimental results. Such an approach, leading to 5,6-*cis* product, predominates, and the formation of 5,6-*trans* cabrapenams (minor products) was noticed only in cases of mismatch pairs (Table 1, entries 3 and 5).

Conclusions

We have shown that the diastereoselective Kinugasa reaction involving five-membered nitrones, except the unstable nonsubstituted nitrone, and simple chiral acetylenes provides an interesting entry to carbapenams. The reactions displayed high diastereoselectivity affording mostly one dominant product and usually proceeded in a moderate yield. In certain cases, however,

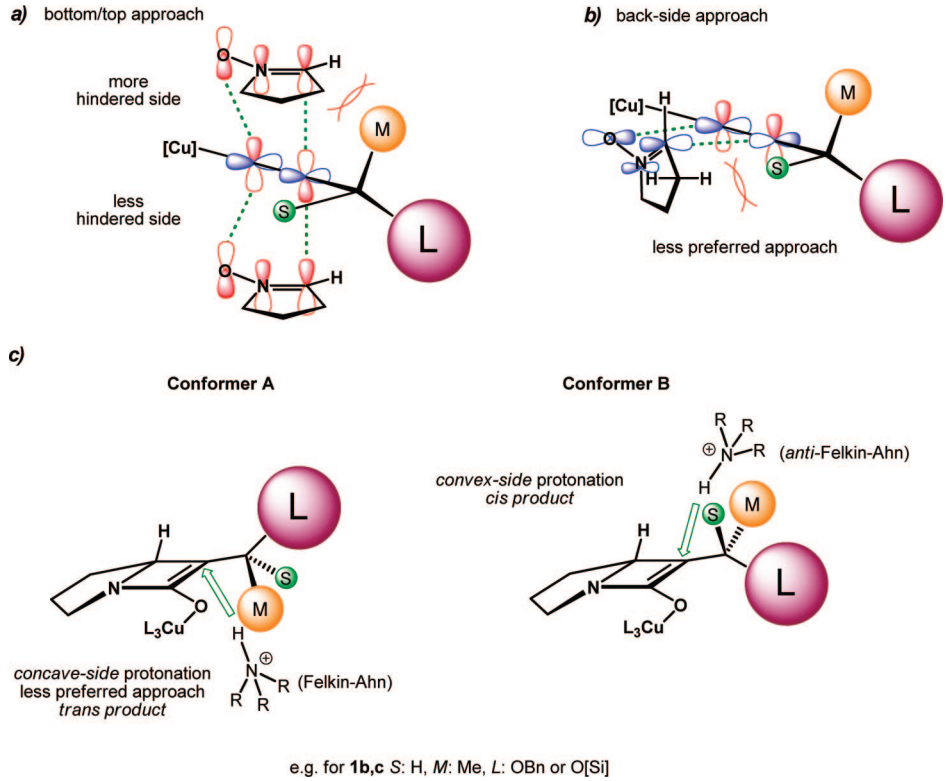


FIGURE 2. Stereochemical models of Kinugasa reaction involving nonchiral nitrone **2** and chiral acetylenes.

particularly for the matched pairs, the observed yield was high. Based on the proposed mechanism, it is possible to explain the stereochemical pathway of the reaction and to predict the geometry of synthesized products. The 1,3-dipolar cycloaddition step is controlled first of all by the configuration of the nitrone. The geometry of the acetylene controls the configuration only in the case of reaction with achiral nitrone. The protonation of intermediate enolate in the second step depends for the most part on the configuration of the bridgehead carbon atom formed in the first step. In the case of the mismatched pair, the configuration at the C-6 atom of the carbapenam skeleton may also be affected by the geometry of the acetylene portion, and this influence can be explained by the Felkin−Anh model. Consequently, the major product exhibits the relative *cis* orientation of protons in the four-membered β-lactam ring.

Experimental Procedures

Reaction of Nitrones with Acetylenes. General Procedure. To a suspension of CuI (0.5 mmol, 95 mg) in dry, degassed MeCN (3 mL) was added 280 μL (2.0 mmol) of triethylamine. After the mixture was cooled to 0 °C, a solution of acetylene (0.5 mmol) in 1 mL of MeCN was added, and the obtained mixture was stirred for 15 min. Then a solution of nitrone (1 mmol) in MeCN (1−2 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 nitrogen atmosphere. The progress of the reaction was monitored by TLC. Subsequently, the solvent was removed under diminished pressure, and the residue was purified by column chromatography on silica gel or Florisil. The diastereoisomeric ratio (Table 1) was assigned by HPLC or ^{1}H NMR.

(5*S*,6*S*,4′*S*)-6-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-azabicyclo-[3.2.0]heptan-7-one (5a): colorless oil; $[\alpha]_D$ −146.5 (*c* 0.87, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.12 (1H, dd, *J* 8.4, 6.0 Hz), 3.97 (1H, ddd, *J* 10.3, 6.0, 6.0 Hz), 3.87 (1H, dd, *J* 8.4, 6.0 Hz), 3.33 (1H, m, H-5), 3.13 (1H, dd, *J* 10.3, 5.2 Hz), 2.35 (1H, m), 1.50−1.38 (3H, m), 1.34−1.27 (4H, m), 1.23 (3H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 176.1, 109.0, 71.6, 68.6, 55.3, 54.7, 45.7, 29.7, 27.1, 25.7, 25.6; IR (film) 1749 cm^{-1}; HR MS (ESI) calcd for $C_{11}H_{17}NO_3Na$ [M + Na$^+$] 234.1101, found 234.1097. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.50; H, 8.09; N, 6.61.

(5*R*,6*R*,1′*S*)-6-(1′-Benzyloxy)ethyl-1-azabicyclo[3.2.0]heptan-7-one (5b): colorless oil; $[\alpha]_D$ +200.0 (*c* 0.94, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.40−7.10 (5H, Ph), 4.34 (1H, d, *J* 11.6 Hz), 4.07 (1H, d, *J* 11.6 Hz), 3.50 (1H, dq, *J* 10.0, 6.0 Hz), 3.37−3.29 (2H, m), 3.18 (1H, dd, *J* 10.0, 5.3 Hz), 2.43 (1H, m), 1.53−1.23 (7H, m); ^{13}C NMR (125 MHz, C_6D_6, without Ph carbon atoms) δ 177.0, 71.1, 70.2, 56.9, 56.2, 45.2, 29.7, 26.1, 18.2; IR (film) 1761 cm^{-1}; HR MS (ESI) calcd for [M + Na$^+$] $C_{15}H_{19}NO_2Na$ 268.1313, found 268.1310. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.40; H, 7.80; N, 5.69.

(5*R*,6*R*,1′*S*)-6-(1′-*tert*-Butyldiphenylsilyloxy)ethyl-1-azabicyclo-[3.2.0]heptan-7-one (5c): ^{1}H NMR (500 MHz, C_6D_6) selected signals from spectra of crude product δ 4.04 (1H, dq, *J* 9.4, 6.1 Hz), 3.18 (1H, dd, *J* 9.4, 5.1 Hz), 1.34 (3H, d, *J* 6.1 Hz); IR (film) 1758 cm^{-1}; HR MS (ESI) *m*/*z* calcd for [M + Na$^+$] $C_{24}H_{31}NO_2SiNa$ 416.2016, found 416.2023.

(5*R*,6*R*,1′*S*)-6(1′-*tert*-Butyldiphenylsilyloxy)benzyl-1-azabicyclo-[3.2.0]heptan-7-one (5d): ^{1}H NMR (500 MHz, C_6D_6) selected signals from spectra of crude product δ 5.01 (1H, d, *J* 8.0 Hz), 3.60 (1H, dd, *J* 8.0, 5.2 Hz); IR (film) 1760 cm^{-1}; HR MS (ESI) *m*/*z* calcd for [M + Na$^+$] $C_{29}H_{33}NO_2SiNa$ 478.2173, found 478.2192.

(4*S*,5*R*,6*S*,1′*S*)-4-*tert*-Butoxy-6-(1′-*tert*-butyldiphenylsilyloxy)-ethyl-1-azabicyclo[3.2.0]heptan-7-one (6a): colorless oil; $[\alpha]_D$ −37.9 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.10−7.20 (10H, m), 4.16 (1H, dq, *J* 8.4, 6.1 Hz), 3.82 (1H, m), 3.48 (1H, ddd, *J* 11.4, 7.8, 5.8 Hz), 3.38 (dd, *J* 5.8, 4.2 Hz), 3.28 (1H, dd, *J* 8.4, 5.8 Hz), 2.72 (1H, m), 1.70 (1H, m), 1.51 (1H, m), 1.27 (9H, s), 1.07 (3H, d, *J* 6.1 Hz), 0.90 (9H, s); ^{13}C NMR (125 MHz, C_6D_6, without Ph carbon atoms) δ 177.4, 73.7, 71.4, 67.3, 61.6, 58.9, 44.2, 38.6, 28.5, 27.3, 23.6, 19.5; IR (film) 1761 cm^{-1}; HR MS (ESI) calcd for $C_{28}H_{39}NO_3NaSi$ [M + Na$^+$] 488.2591, found 488.2590; HPLC hexane/2-propanol 95:5, flow 1 mL/min, t_R 4.0 min. Anal. Calcd for $C_{28}H_{39}NO_3Si$: C, 72.21; H, 8.44; N, 3.01. Found: C, 72.29; H, 8.43; N, 3.00.

(4*S*,5*R*,6*R*,1′*S*)-4-*tert*-Butoxy-6-(1′-*tert*-butyldiphenylsilyloxy)-ethyl-1-azabicyclo[3.2.0]heptan-7-one (6b): colorless oil; $[\alpha]_D$ −23.8 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6, without protons of Ph group) δ 4.40 (1H, d, *J* 12.0 Hz), 4.26 (1H, dd, *J* 12.0 Hz), 3.67 (1H, dq, *J* 7.4, 6.2 Hz), 3.56−3.49 (2H, m), 3.43 (1H, ddd, *J* 14.0, 7.6, 6.5 Hz), 2.75 (1H, dd, *J* 7.4, 2.3 Hz), 2.79 (1H, ddd, *J* 14.0, 7.6, 6.5 Hz), 1.73−1.63 (2H, m), 1.23 (3H, d, *J* 6.2 Hz, Me), 0.99 (9H, s), 0.87 (9H, s); ^{13}C NMR (125 MHz, C_6D_6, without Ph carbon atoms) δ 176.1, 74.5, 73.5, 73.4, 70.7, 62.1, 62.1, 44.5, 38.3, 28.5, 28.0, 18.7; IR (film) 1767 cm^{-1}; HR MS (ESI) calcd for $C_{19}H_{27}NO_3Na$ [M + Na$^+$] 488.2591, found 488.2588; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 6.1 min. Anal. Calcd for $C_{28}H_{39}NO_3Si$: C, 72.21; H, 8.44; N, 3.01. Found: C, 72.18; H, 8.42; N, 3.00.

(4*R*,5*S*,6*R*,1′*S*)-4-*tert*-Butoxy-6-(1′-*tert*-butyldiphenylsilyloxy)-ethyl-1-azabicyclo[3.2.0]heptan-7-one (7): colorless oil; $[\alpha]_D$ +65.0 (*c* 2.2, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.10−7.20 (10H, m), 4.93 (1H, m), 4.45 (1H, dq, *J* 4.1, 6.5 Hz), 3.83 (1H, ddd, *J* 11.5, 8.0, 3.2 Hz), 3.76 (1H, dd, *J* 6.0, 2.5 Hz), 3.13 (1H, dd, *J* 6.0, 4.1 Hz), 2.95 (1H, ddd, *J* 11.5, 9.3, 6.7 Hz), 2.70 (1H, m), 1.78 (1H, m), 1.28 (9H, s), 1.24 (9H, s), 1.05 (3H, d, *J* 6.5 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 177.6, 73.6, 71.3, 67.4, 64.0, 59.6, 45.2, 39.8, 28.9, 27.4, 26.7, 21.9, 19.5; IR (film) 1767 cm^{-1}; HR MS (ESI) calcd for $C_{28}H_{39}NO_3SiNa$ [M + Na$^+$] 488.2591, found 488.2575; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 4.3 min. Anal. Calcd for $C_{28}H_{39}NO_3Si$: C, 72.21; H, 8.44; N, 3.01. Found: C, 72.19; H, 8.48; N, 2.99.

(4*S*,5*R*,6*S*,1′*S*)-6-(1′-Benzyloxy)ethyl-4-*tert*-butoxy-1-azabicyclo-[3.2.0]heptan-7-one (8a): colorless oil; $[\alpha]_D$ +13.3 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.6−7.20 (5H, Ph), 4.41 (1H, d, *J* 11.8 Hz), 4.23 (1H, d, *J* 11.8 Hz), 4.10 (1H, m), 3.58 (1H, ddd, *J* 11.0, 8.1, 3.7 Hz), 3.53 (1H, dq, *J* 6.3, 4.7 Hz), 3.47 (1H, dd, *J* 6.0, 2.9 Hz), 3.13 (1H, dd, *J* 6.0, 4.7 Hz), 2.75 (1H, m), 1.92 (1H, m), 1.50 (1H, m), 1.23 (3H, d, *J* 6.3 Hz), 1.00 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 176.9, 71.9, 71.1, 70.7, 63.3, 57.6, 45.0, 39.1, 28.5, 28.0, 18.5; IR (film) 1764 cm^{-1}; HR MS (ESI) calcd for $C_{19}H_{27}NO_3Na$ [M + Na$^+$] 340.1883, found 340.1868; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 8.0 min. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.92; H, 8.59; N, 4.39.

(4*S*,5*S*,6*S*,1′*S*)-6-(1′-Benzyloxy)ethyl-4-*tert*-butoxy-1-azabicyclo-[3.2.0]heptan-7-one (8b): colorless oil; $[\alpha]_D$ −66.5 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.50−7.00 (5H, Ph), 3.67 (1H, dq, *J* 7.4, 6.2 Hz), 3.53 (1H, m) 3.49 (1H, dd, *J* 4.2, 2.5 Hz), 3.44 (1H, ddd, *J* 14.0, 7.6, 6.5 Hz), 2.75 (1H, dd, *J* 7.4, 2.5 Hz), 2.70 (1H, ddd, *J* 14.0, 7.6, 6.5 Hz), 1.73−1.60 (2H, m), 1.23 (3H, d, *J* 6.2 Hz), 0.99 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 176.1, 74.5, 73.5, 73.4, 70.7, 62.1, 62.1, 44.5, 38.3, 28.4, 18.8; IR (film) 1760 cm^{-1}; HR MS (ESI) calcd for $C_{19}H_{27}NO_3Na$ [M + Na$^+$] 340.1883, found 340.1897; HPLC hexane/i-propanol 95/5, flow 1 mL/min, t_R 9.2 min. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.87; H, 8.55; N, 4.45.

(4*R*,5*S*,6*R*,1′*S*)-6-(1′-Benzyloxy)ethyl-4-*tert*-butoxy-1-azabicyclo-[3.2.0]heptan-7-one (9): colorless oil; $[\alpha]_D$ +124.5 (*c* 2.5, CH_2Cl_2);

(27) The conformational analysis was carried out with the MM+ force field, and the obtained geometries were reoptimized by using DFT calculations at the B3LYP/6-31+G(d) theory level.

^{1}H NMR (500 MHz, C_6D_6) δ 7.30−7.00 (5H, Ph), 4.32 (1H, d, *J* 11.4 Hz), 4.23 (1H, m), 4.08 (1H, d, *J* 11.4 Hz), 3.67−3.60 (2H, H-2a), 3.50 (1H, dq, *J* 8.5, 6.1 Hz), 3.21 (1H, dd, *J* 8.5, 5.9 Hz), 2.79 (1H, m), 1.69 (1H, m), 1.57 (1H, m), 1.22 (3H, d, *J* 6.1 Hz), 0.99 (9H, s); ^{13}C NMR (125 MHz, C_6D_6, without Ph carbon atoms) δ 178.1, 73.8, 71.7, 71.0, 70.2, 64.3, 58.2, 45.7, 39.5, 28.4, 18.2; IR (film) 17601 cm^{-1}; HR MS (ESI) calcd for $C_{19}H_{27}NO_3Na$ [M + Na$^+$] 340.1883, found 340.1882; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 5.5 min. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.87; H, 8.56; N, 4.40.

(4*S*,5*R*,6*S*,1′*R*)-4-*tert*-Butoxy-6-(1′-*tert*-butyldiphenylsilyloxy)-benzyl-1-azabicyclo[3.2.0]heptan-7-one (10a): colorless oil; $[\alpha]_D$ −15.7 (*c* 3.6, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.10−7.20 (15H, m), 4.73 (1H, d, *J* 10.4 Hz), 4.07 (1H, dd, *J* 10.4 Hz, 6.5 Hz), 3.71 (1H, br dd, *J* 11.6, 7.1 Hz), 3.59 (1H, br d, *J* 5.4 Hz), 3.39 (1H, d, *J* 6.5 Hz), 2.75 (1H, ddd, *J* 11.6, 11.4, 5.3 Hz), 1.34−1.26 (2H, m), 1.24 (9H, s), 1.09 (9H, s); ^{13}C NMR (125 MHz, C_6D_6, without Ph carbon atoms) δ 179.4, 73.6, 72.7, 70.4, 63.4, 58.5, 45.9, 38.9, 27.8, 27.3, 19.7. 19.2; IR (film) 1758 cm^{-1}; HR MS (ESI) calcd for $C_{33}H_{41}NO_3NaSi$ [M + Na$^+$] 550.2753, found 550.2751; HPLC hexane/2-propanol 98/2, flow 1 mL/min, t_R 5.9 min. Anal. Calcd for $C_{33}H_{41}NO_3Si$: C, 75.10; H, 7.83; N, 2.65. Found: C, 75.07; H, 7.84; N, 2.63.

(4*S*,5*R*,6*R*,1′*R*)-4-*tert*-Butoxy-6-(1′-*tert*-butyldiphenylsilyloxy)-benzyl-1-azabicyclo[3.2.0]heptan-7-one (10b). The sample contained inseparable impurities (purity ∼90% according to HPLC): colorless oil; ^{1}H NMR (500 MHz, C_6D_6, without protons of Ph groups) δ 7.05 (1H, br s), 6.88 (1H, d, *J* 1.5 Hz), 4.39 (1H, dd, *J* 3.6, 1.5 Hz), 3.76 (1H, m), 3.62 (1H, ddd, *J* 11.6, 7.3, 4.9 Hz), 2.90 (1H, m) 1.64−1.52 (2H, m), 1.26 (9H, s), 0.92 (9H, s); IR (film) 1745 cm^{-1}; HR MS (ESI) calcd for $C_{28}H_{39}NO_3NaSi$ [M + Na$^+$] 488.2591, found 488.2611; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 4.8 min.

(4*R*,5*S*,6*R*,1′*R*)-4-*tert*-Butoxy-6-(*tert*-butyldiphenylsilyloxy)-benzyl-1-azabicyclo[3.2.0]heptan-7-one (11): colorless oil; $[\alpha]_D$ +344.1 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.00−6.80 (15H, m), 5.37 (1H, d, *J* 3.3 Hz), 4.98 (1H, m), 3.76 (1H, ddd, *J* 11.5, 7.9, 3.2 Hz), 3.65 (1H, dd, *J* 6.1, 2.4 Hz), 3.48 (1H, dd, *J* 6.1, 3.3 Hz), 2.86 (1H, ddd, *J* 11.5, 9.2, 6.5 Hz), 2.15 (1H, m), 1.73 (1H, m), 1.19 (9H, s), 1.08 (9H, s); ^{13}C NMR (125 MHz, C_6D_6, without Ph carbon atoms) δ 177.6, 74.0, 73.8, 71.5, 64.7, 59.7, 45.3, 39.8, 28.9, 27.4, 19.7; IR (film) 1759 cm^{-1}; HR MS (ESI) calcd for $C_{33}H_{41}NO_3NaSi$ [M + Na$^+$] 550.2748, found 550.2730; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 6.3 min. Anal. Calcd for $C_{33}H_{41}NO_3Si$: C, 75.10; H, 7.83; N, 2.65. Found: C, 75.05; H, 7.80; N, 2.67.

(4*S*,5*R*,6*S*,4′*S*)-4-*tert*-Butoxy-6-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-azabicyclo[3.2.0]heptan-7-one (12): colorless oil; $[\alpha]_D$ −77.5 (*c* 0.78, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.15 (1H, ddd, *J* 6.3, 2.7, 2.2 Hz), 4.04 (1H, dd, *J* 8.5, 6.0 Hz), 3.88 (1H, ddd, *J* 10.1, 6.0, 5.8 Hz), 3.77 (1H, dd, *J* 8.5, 6.0 Hz), 3.60 (1H, dd, *J* 5.7, 2.2 Hz), 3.54 (1H, ddd, *J* 11.8, 7.5, 3.1 Hz), 3.16 (1H, dd, *J* 10.1, 5.7 Hz), 2.75 (1H, ddd, *J* 11.6, 9.84, 6.9 Hz), 1.70−1.58 (2H, m), 1.28 (3H, s), 1.19 (3H, s), 1.11 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 176.4, 109.1, 74.0, 71.8, 70.7, 68.7, 63.1, 55.5, 45.6, 39.5, 28.3, 27.0, 25.5; IR (film) 1763 cm^{-1}; HR MS (ESI) calcd for $C_{15}H_{25}NO_4Na$ [M + Na$^+$] 306.1676, found 306.1681; HPLC hexane/2-propanol 95/5, flow 1 mL/min, t_R 16 min. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.56; H, 8.88; N, 4.93.

(4*R*,5*S*,6*R*,4′*S*)-4-*tert*-Butoxy-6-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-azabicyclo[3.2.0]heptan-7-one (13a): colorless oil; $[\alpha]_D$ +8.3 (*c* 1.40, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.52 (1H, m), 4.08 (1H, dd, *J* 9.8, 7.8 Hz), 3.96 (1H, ddd, *J* 9.8, 5.8, 2.0 Hz), 3.64 (1H, dd, *J* 7.8, 5.8 Hz), 3.54 (1H, ddd, *J* 14.2, 8.1, 5.3 Hz), 3.44 (1H, dd, *J* 5.6, 3.9 Hz), 2.84 (1H, dd, *J* 5.6, 2.0 Hz), 2.76 (1H, m), 2.09 (1H, m), 1.67 (1H, m), 1.49 (3H, s), 1.32 (3H, s), 1.10 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 175.4, 110.3, 73.6, 72.7, 71.2, 67.8, 62.7, 51.8, 44.6, 38.9. 28.5, 26.9, 26.2; IR (film) 1766 cm^{-1}; HR MS (ESI) calcd for $C_{15}H_{25}NO_4Na$ [M + Na$^+$] 306.1676, found 306.1683. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.56; H, 8.90; N, 4.93.

(3*R*,5*S*,6*S*,4′*S*)-4-*tert*-Butoxy-6-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-azabicyclo[3.2.0]heptan-7-one (14): colorless oil; $[\alpha]_D$ −123.2 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.11 (1H, dd, *J* 8.2, 6.0 Hz), 4.06 (1H, ddd, *J* 10.0, 6.0, 5.9 Hz), 3.99 (1H, m), 3.82 (1H, d, *J* 8.2, 5.9 Hz), 3.76 (1H, m), 3.65 (1H, d, *J* 11.8, 5.8 Hz), 3.15 (1H, dd, *J* 10.0, 5.3 Hz), 2.60 (1H, dd, *J* 11.8, 3.6 Hz), 1.74−1.69 (2H, m), 1.30 (3H, s), 1.24 (3H, s), 0.91 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 175.6, 109.1, 75.8, 73.5, 71.9, 68.6, 55.1, 54.4, 53.83, 35.1, 28.1, 27.1, 25.7; IR (film) 1758 cm^{-1}; HR MS (ESI) calcd for $C_{15}H_{25}NO_4Na$ [M + Na$^+$] 306.1676, found 306.1661. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.54; H, 8.86; N, 4.90.

(3*S*,5*S*,6*S*,4′*S*)-4-*tert*-Butoxy-6-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-azabicyclo[3.2.0]heptan-7-one (15a): colorless oil; $[\alpha]_D$ −103.6 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.61 (1H, ddd, *J* 10.0, 8.5, 7.7 Hz), 4.22 (1H, dd, *J* 7.7, 6.1 Hz), 3.99 (1H, dd, *J* 8.5, 6.1 Hz), 3.74 (1H, dddd, *J* 5.6, 4.7, 4.4, 2.8 Hz), 3.52 (1H, dd, *J* 12.0, 2.8 Hz), 3.45 (1H, dt, *J* 8.0, 5.3 Hz), 3.32 (1H, dd, *J* 10.0, 5.3 Hz), 2.45 (1H, dd, *J* 12.0, 4.7 Hz), 1.87 (1H, ddd, *J* 14.1, 5.3, 4.4 Hz), 1.64 (1H, ddd, *J* 14.1, 8.0, 5.6 Hz), 1.40 (3H, s), 1.27 (3H, s), 0.91 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 176.2, 108.7, 75.7, 73.7, 72.2, 68.6, 57.4, 54.7, 54.2, 34.7, 28.1, 27.2, 25.8; IR (film) 1760 cm^{-1}; HR MS (ESI) calcd for. $C_{15}H_{25}NO_4Na$ [M + Na$^+$] 306.1676, found 306.1677. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.55; H, 8.87; N, 4.95.

(3*S*,5*R*,6*R*,4′*S*)-4-*tert*-Butoxy-6-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-azabicyclo[3.2.0]heptan-7-one (15b): colorless oil; $[\alpha]_D$ +20.2 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.30 (1H, dq, *J* 7.2, 6.2 Hz), 4.01 (1H, dd, *J* 9.3, 7.8 Hz), 3.84 (1H, dd, *J* 11.7, 6.3 Hz), 3.70 (1H, ddd, *J* 9.3, 5.9, 2.2 Hz), 3.60 (1H, dd, *J* 7.8, 5.9 Hz), 3.44 (1H, ddd, *J* 8.2, 5.8, 4.7 Hz), 2.76 (1H, dd, *J* 5.8, 2.2 Hz), 2.61 (1H, dd, *J* 11.7, 6.2 Hz), 2.23 (1H, ddd, *J* 14.3, 7.2, 4.7 Hz), 1.58 (1H, ddd, *J* 14.3, 8.2, 6.2 Hz), 1.51 (3H, s), 1.33 (3H, s), 1.03 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 175.9, 110.2, 74.6, 73.4, 72.4, 67.8, 54.1, 53.4, 53.3, 34.4, 28.1, 27.1, 26.3; IR (film) 1759 cm^{-1}; HR MS (ESI) calcd for $C_{15}H_{25}NO_4Na$ [M + Na$^+$] 306.1676, found 306.1680. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.59; H, 8.90; N, 4.92.

Acknowledgment. Financial support for this work was provided through the Polish Ministry of Science and Higher Education Grant No. N N204 156036.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5**−**15**; NOE experiments for **12** and **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900121X