An Entry to the Carbapenem Antibiotic Scaffold via the Asymmetric Kinugasa Reaction

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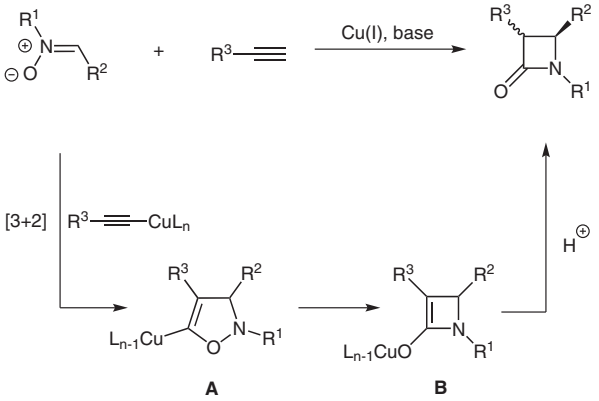
Abstract: The copper(I)-mediated reaction between five-membered cyclic nitrones and terminal acetylenes, leading to the assembly of the basic skeleton of carbapenem antibiotics is described. The diastereoselectivity of this cycloaddition–rearrangement cascade, a process known as the Kinugasa reaction, with respect to the structure and configuration of both substrates, as well as the reaction conditions, are discussed. Application of the described methodology to sugar-derived nitrones offers an attractive entry toward thienamycin and related compounds.

Key words: β-lactams, Kinugasa reaction, carbapenem antibiotics, nitrones, acetylenes

1 Introduction

The copper(I)-mediated reaction between nitrones and terminal acetylenes, discovered in 1972 by Kinugasa and Hashimoto,[1] represents a direct and simple method for the formation of β-lactams.[2] As shown in Scheme 1, the Kinugasa reaction involves a cycloaddition–rearrangement cascade process catalyzed by copper(I) ions, and proceeds in the presence of an organic base. The initially formed copper–alkyne π-complex undergoes deprotonation. Next, the activated triple bond takes part in a 1,3-dipolar cycloaddition with a nitrone to provide five-membered isoxazoline **A**. The rearrangement of isoxazoline copper complex **A** into copper enolate **B** and subsequent protonation leads to the formation of a β-lactam ring. The protonation of intermediate enolate **B** in the second step occurs from the less-shielded side of the β-lactam ring. Consequently, the major product displays the relative *cis*-configuration of protons in the four-membered ring. There are striking similarities between the first step of the Kinugasa reaction and the well-known cycloaddition of azides to terminal acetylenes, a process known as the click reaction.[3]

Although the first examples of the Kinugasa reaction were described in the 1970s,[1,4] almost three decades passed before the reaction received further attention and detailed investigation. Nevertheless, the number of reports related to this particular approach toward the direct formation of 2-azetidinones, both diastereo-[5–7] and enantioselective[8–12] variants, is limited. Moreover, in most cases, *C*,*N*-diarylnitrones have been utilized,[5–12] whilst examples of reactions involving aliphatic nitrones are scarce.[4]



Scheme 1 Mechanism of the Kinugasa reaction

The first enantioselective intermolecular Kinugasa reaction, using phenyl-substituted reactants **1** and **2** and bisoxazoline ligands **3** as a source of chirality, was reported in 1995 by Miura and co-workers.[8] However, the products were obtained with relatively poor selectivity (*cis*/*trans* >66:34, ee for the *cis*-diastereomer of up to 40%). Improved results (up to 85% ee) were reported by Tang et al.[13] for the copper(II)–trisoxazoline ligand complex **4**. Promising enantioselectivity [*cis*/*trans* >95:5, ee (*cis*) 70–90%) was observed by Lo and Fu for identical reactants, but using ferrocenyl catalyst **5**.[9a] The same group also described the first example of an intramolecular enantioselective Kinugasa reaction using compound **6**.[9b] The corresponding tricyclic products were obtained with good stereoselectivity (74%, ee 88%).[9b] Other highly efficient copper catalysts with chiral HETPHOX ligands **7**[11] and IndaBOX ligands **8**[10,12] have also been described (Figure 1).

In 2002, Basak and co-workers[5a] reported the first diastereoselective version of the Kinugasa cascade involving reactions of acetylenes with a chiral auxiliary. The reaction between chiral oxazolidinyl propynes **9** and *C*,*N*-diarylnitrones provided only one set of *cis*/*trans*-azetidinones **10** in a moderate yield and poor *cis*/*trans* ratio, which typically did not exceed 1:3 (Scheme 2). Hsung et al.,[6] in 2008, demonstrated that chiral oxazolidinone-derived ynamides **11** were efficient reagents for the diastereoselective Kinugasa reaction involving *C*,*N*-diarylnitrones, to pro-

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Biographical Sketches

Marek Chmielewski (fourth from left) is Vice President of the Polish Academy of Sciences, elected for the term 2011–2014. He received his M.Sc. from the Department of Chemistry, Warsaw University of Technology, and Ph.D. from the Institute of Organic Chemistry of the Polish Academy of Sciences (Warsaw) in 1972, under the supervision of Prof. A. Zamojski. He received a D.Sc. (Habilitation) from the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw) in 1981. Subsequently, he completed two long-term research stays at Purdue University with R. L. Whistler (1973–74), and at Southern Illinois University in Carbondale with J. N. BeMiller (1979–81). Since 1984 he has been a Professor at the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw). He has also been a visiting Professor in the U.S.A., Spain and France. He is engaged in the fields of stereocontrolled syntheses of β-lactam antibiotics and transformations of carbohydrates into amino and imino sugars with special attention directed toward asymmetric addition and cycloaddition reactions. His other fields of interest include the synthesis of glycosyl hydroperoxides with the aim of performing enantioselective epoxidations and solid-phase organic synthesis.

Bartłomiej Furman (first from left) was born in Radom, Poland in 1969. He studied chemistry at the Warsaw University of Technology. In 1998, he obtained his doctorate under the guidance of Professor Marek Chmielewski at the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw). After post-doctoral studies with Horst Kunz (Mainz University), he realized Habilitation under the direction of Marek Chmielewski in 2006 and was promoted to Associate Professor in 2008. He has received the Polish Science Award for Young Scientists (1999) and the Prime Minister Award (1999). His scientific interests involve stereocontrolled synthesis, the development of new methodologies and the synthesis of bioactive compounds.

Margarita Jurczak (third from left) studied chemistry at the University of Warsaw. In 1977, she completed her Ph.D. thesis in organic chemistry under the supervision of Professor W. Sobótka at the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw). After a post-doctoral stay at Louvain la Neuve University, (Belgium, 1980–81), she again joined the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw), where she is currently in an Assistant Research position. She is interested in the application of nitrones in organic synthesis.

Olga Staszewska-Krajewska (second from left) was born in Warsaw, Poland in 1969. She studied chemistry at Warsaw University. In 2000, she obtained her doctorate under the guidance of Professor Marek Chmielewski at the Institute of Organic Chemistry in Warsaw. She is mainly involved in the application of modern NMR techniques for determination of the structures, relative configurations and conformations of small organic molecules, in particular, bioactive chiral β-lactams, small heterocycles and sugars.

Magdalena Maciejko (fifth from left) studied organic chemistry at Warsaw University and the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw), under the supervision of Professor Bartłomiej Furman. In 2010, she joined the Institute of Organic Chemistry (Warsaw) and is currently a Ph.D. student working on the application of sugar-derived nitrones in the Kinugasa reaction.

Sebastian Stecko (sixth from left) obtained his M.Sc. degree in chemical technology from the Silesian University of Technology, Gliwice, Poland. In 2008, he obtained his doctorate at the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw), under the supervision of Professor Marek Chmielewski. After post-doctoral studies with Siegfried Blechert (Technical University Berlin) in 2011, he commenced his independent research at the Institute of Organic Chemistry (Warsaw). His scientific interests involve stereocontrolled synthesis, the development of new methodologies and the synthesis of bioactive compounds.

vide 3-amino-β-lactams **12** in good yields and with high stereoselectivities (Scheme 2).

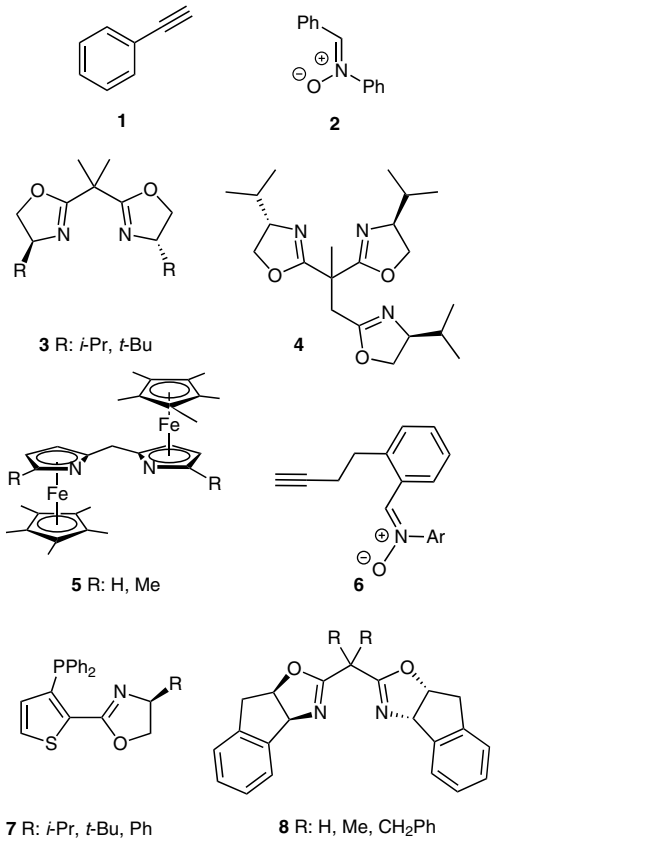
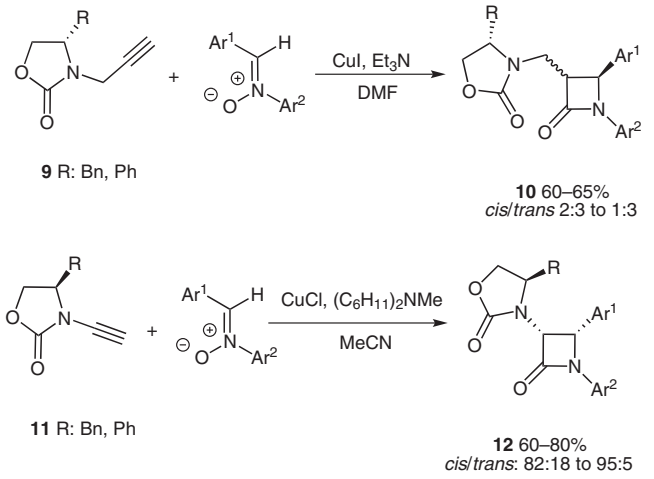


Figure 1 Structures of various substrates and complexes employed in the Kinugasa reaction



Scheme 2 Examples of diastereoselective Kinugasa reactions

2 Diastereoselective Kinugasa Reactions with Chiral Cyclic Nitrones and Achiral Acetylenes

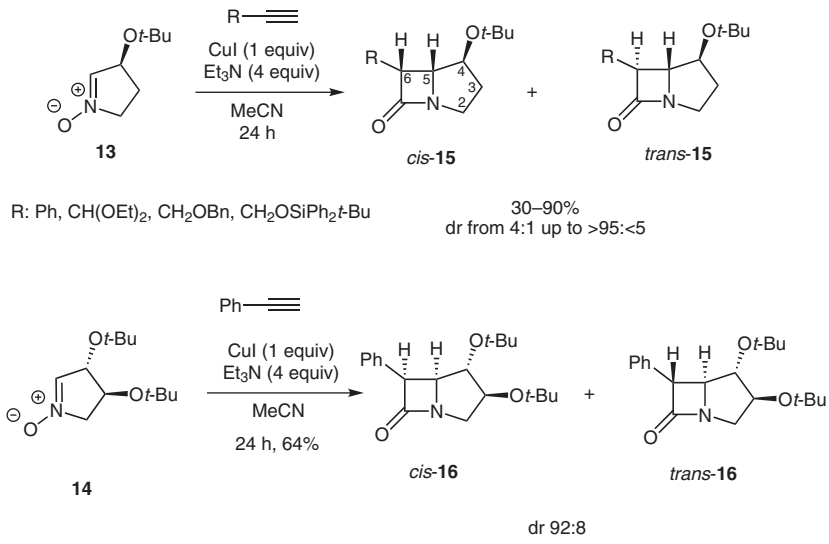
In contrast to the examples of the diastereoselective Kinugasa reaction described so far, we focused our attention on the reactions of chiral cyclic nitrones **13** and **14**,[14,15] derived from malic and tartaric acids,[16] respectively, with simple achiral acetylenes (Scheme 3). These studies were a continuation of our ongoing research on the applications of nitrones in the synthesis of bioactive molecules,[17] including β-lactams.[18] The main reasons for the selection of nitrones **13** and **14** were due to their availability, stability, and ability to form products possessing the basic skeleton of the highly active carbapenem antibiotics. To some extent, our concept was related to the well-known pioneering approach of Tufariello toward carbapenems based on the 1,3-dipolar cycloaddition of a cyclic nitrone to a crotonate.[19] Moreover, it was intriguing that cyclic aliphatic nitrones had been used only once in the Kinugasa reaction, by Ding and Irwin, in 1976.[4]

The yields of the desired Kinugasa products (compounds **15** and **16**, Scheme 3) varied from poor, for aliphatic acetylenes, to moderate and good for aryl acetylenes.[14a] Interestingly, somewhat better results were observed for certain aliphatic acetylenes bearing oxygen atoms.[14c] The effectiveness of these reactions could be further enhanced slightly, in several cases, by the addition of hydrazine,[14a] or N,N-ligands, such as 2,2′-bipyridine or 1,10-phenanthroline.[14c]

All the investigated reactions with nitrones **13** and **14** provided only one set of *cis*/*trans*-azetidinones with a high preference for the formation of the *cis*-isomers, *cis*-**15** or *cis*-**16**. On the basis of the proposed stereochemical model of the Kinugasa reaction (Figure 2), the resulting geometry of the carbapenam skeleton depends strongly on the first step of the cascade, which is the 1,3-dipolar cycloaddition of the nitrone to the triple bond of the copper acetylide. The approach of the reactants in the cycloaddition step is controlled by the substituent located next to the double bond in the nitrone, whereas protonation of the intermediate enolate in the second step occurs from the less-shielded side of the bicyclic skeleton. Consequently, the major product displays the relative *cis*-orientation of protons in the four-membered β-lactam ring.

The 5,6-*cis*/*trans* ratio depends on the structure of the starting acetylene as well as the type of amine base used.[14a] For example, the reaction of phenylacetylene (**1**) with nitrone **13** in the presence of triethylamine as the base provided a mixture of *cis*-**15**/*trans*-**15** in a diastereomeric ratio of about 4:1 (Scheme 3, R = Ph). However, when a bulkier base was utilized (e.g., DIPEA), isomer *cis*-**15** was obtained predominantly (dr >95:5).

Owing to the presence of a protected hydroxy group in the five-membered ring, and potential for variation of the sub-



Scheme 3 Reactions of chiral cyclic nitrones with simple achiral acetylenes

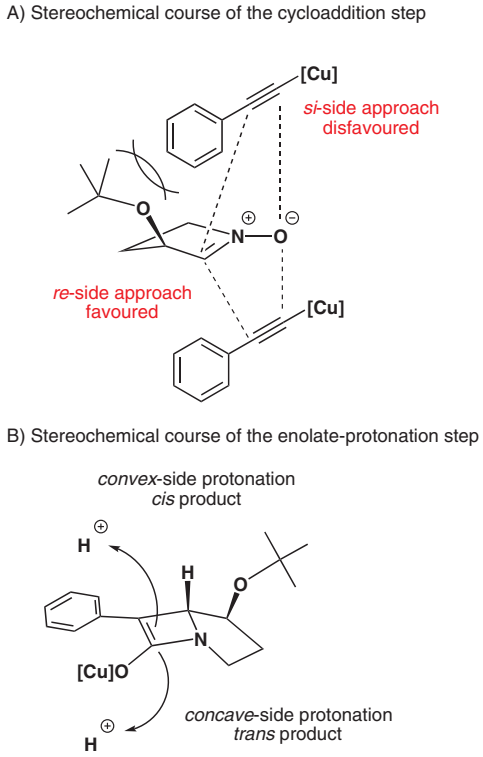
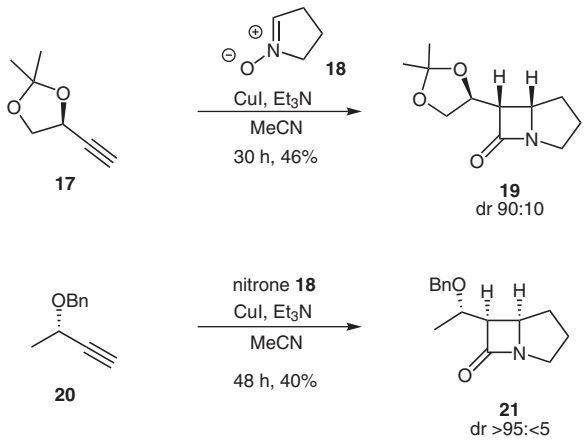


Figure 2 Proposed stereochemical model of the Kinugasa reaction

stituents at C-6 of the carbapenam skeleton (depending on the acetylene used), further transformation of the initially formed adducts, or introduction of new substituents should be possible.

3 Diastereoselective Kinugasa Reactions of Chiral Acetylenes with an Achiral Cyclic Nitrone

The reactions of chiral acetylenes, for example D-glyceraldehyde-derived compound **17** or acetylene **20** prepared from L-lactic acid, with achiral nitrone **18** proceeded with excellent diastereoselectivities to afford the corresponding carbapenams **19** and **21** in moderate yields (40–46%, Scheme 4).[14b] It should be noted, however, that the unsubstituted nitrone **18** was less stable than its substituted congeners **13** and **14**, and therefore extension of the reaction time may lead to the formation of side products.



Scheme 4 Reactions of chiral acetylenes with achiral nitrone **18**

The observed direction of asymmetric induction can be rationalized using the stereochemical model presented in Figure 3.[14b] During the cycloaddition step the nitrone attacks from the less hindered side of the acetylene. The final protonation of the enolate occurs to a significant

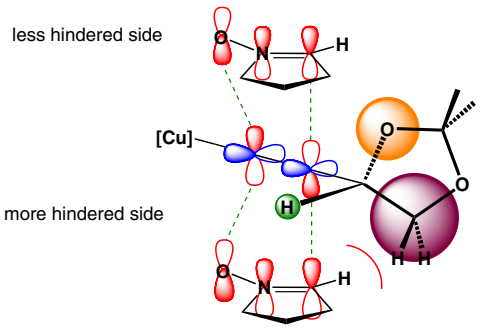


Figure 3 Stereochemical model of the asymmetric induction in the reactions depicted in Scheme 4

degree from the convex side of the intermediate (see Figure 2, B) to provide the *cis*-substituted β-lactam ring.

4 Double Asymmetric Induction in Kinugasa reactions Involving Cyclic Nitrones

Studies on the double asymmetric induction in Kinugasa cascades with both a chiral acetylene and a cyclic nitrone were a natural extension of our work (Scheme 5).[14b] For example, in the case of matched pair **13** and **17**, only *cis*-carbapenam **22** was obtained, whereas for the mismatched pair, **17** and *ent*-**13**, two diastereoisomers, *cis*-**23** and *trans*-**23**, were formed in a 9:1 ratio.

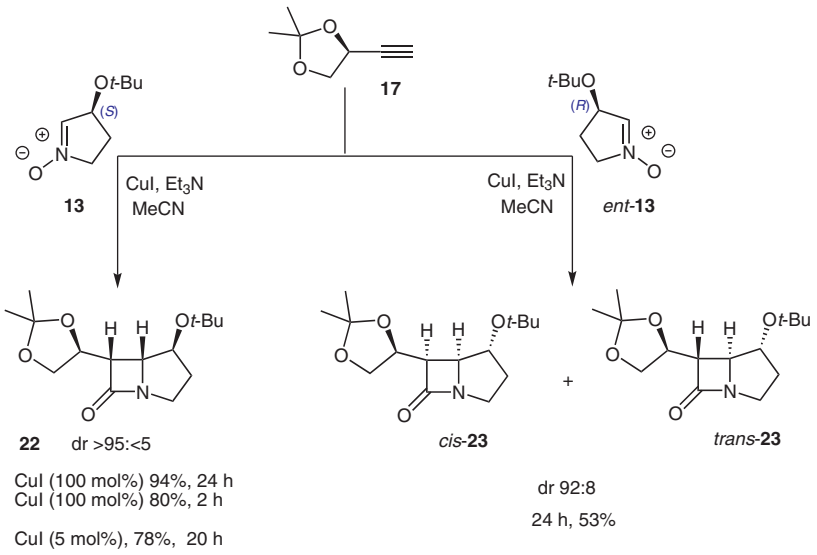
The stereochemical outcome of the reactions in which both the reactants (acetylene and nitrone) were chiral, can be rationalized on the basis of previous observations (Figure 2).[14b] The most important feature is that the first 1,3-dipolar cycloaddition step proceeds almost exclusively *anti* to the *tert*-butoxy group of the nitrone. The influence of the stereogenic center of the acetylene can be disregarded in this step. It also had an insignificant effect on the protonation step, and only in the case of mismatched pairs was the influence of the acetylene stereogenic center manifested by the formation of a small amount of the *trans*-isomer. Nevertheless, it should be noted that since the Kinugasa reaction proceeds in the presence of a base, the fact that formation of the *trans*-isomer may occur via subsequent base-catalyzed epimerization at C-6 (α to the β-lactam carbonyl group) cannot be ignored.

The question of configuration of all the carbapenams obtained during our studies was resolved by NMR spectroscopy, X-ray diffraction analysis, and by chirooptical methods. As demonstrated previously, the chirooptical methods, and particularly electronic circular dichroism spectroscopy (ECD), supported by time-dependent density functional theory (TD-DFT) calculations, are convenient, sensitive, and fast techniques for the stereochemical assignment of azetidinones and their polycyclic derivatives in both solution and solid states.[14c,20]

5 Structure Effect of the Acetylene on the Kinugasa Reaction

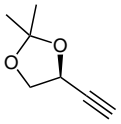
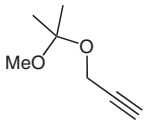
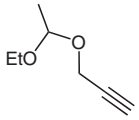
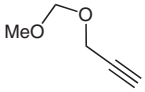
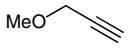
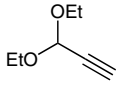
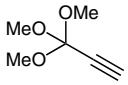
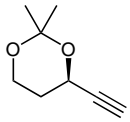
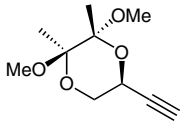
During studies on the effects of the structure of the acetylene on the course of the Kinugasa reaction, it was found that some acetylenes displayed enhanced reactivity providing the corresponding 2-azetidinones in high yields and in short reaction times (Table 1, acetylenes **17** and **28**).[14c]

It can be postulated that the high reactivities observed for compounds **17** and **28** correlate with the specific structures of these molecules. The copper(I) complexes of terminal acetylenes are usually highly aggregated species, engaging in a range of σ- and π-interactions.[21,22] Although the precise nature of the reactive alkynyl copper species is still not clear, some recent experimental and computational results have revealed that dinuclear copper(I) acetylides display enhanced reactivity in 1,3-dipolar cycloaddition reactions (e.g., copper-mediated azide–alkene cycloaddition).[3,23,24]



Scheme 5 Double asymmetric induction in Kinugasa cascades with both a chiral acetylene and a chiral nitrone

Table 1 Structure Effect of Acetylenes on the Kinugasa Reaction

Acetylene	CuI (mol%)	Time (h)	Yield (%)
	100	24	94 (60)[a]
	100	2	80 (47)[a]
	5	24	78
	5	2	80
17			
	100	24	75
	100	2	46
	5	24	30
24			
	100	24	41
	100	2	nd
	5	24	nd
25			
	100	24	40
	100	2	nd
	5	24	nd
26			
	100	24	45 (55)[a]
	100	2	12
	5	24	nd
27	5	2	nd
	100	24	72 (94)[a]
	100	2	62 (68)[a]
	5	24	58 (97)[a]
	5	2	60[a]
28			
	100	24	31 (36)[a]
	100	2	10
	5	24	nd
	5	2	nd
29			
	100	24	55 (52)[a]
	100	2	55
	5	24	35 (36)[a]
	5	2	36
30			
	100	24	56 (30)[a]
	100	2	57
	5	24	49 (31)[a]
	5	2	31
31			

[a] In the presence of 1,10-phenanthroline (100 or 5 mol%); nd = not determined.

Bearing in mind these previous reports[23,24] and our own experimental observations,[14c] it can be concluded that in the case of acetylenes **17** and **28**, some additional coordination effect might occur that disables their deactivating high aggregation ability, which consequently enhances their reactivity toward the Kinugasa cascade.

The enhancement of the Kinugasa reaction rate for acetylenes derived from glyceraldehyde **17**, and propargyl aldehyde acetal **28**, is probably the result of formation of a highly reactive rigid dinuclear copper(I) complex in which each copper ion is coordinated to one or both oxygen atoms of the acetylene molecule, and to both triple bonds (Figure 4).[14c]

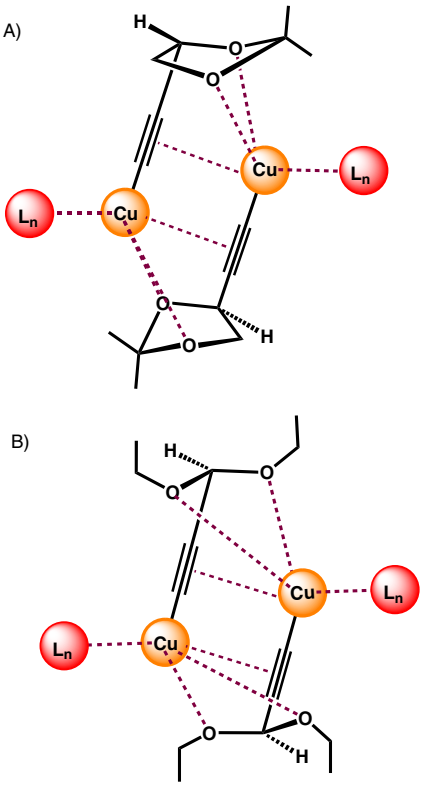


Figure 4 Possible structures of the rigid dinuclear copper(I) complexes formed from acetylenes **17** and **28**

The rigid structure of the dioxolane ring stabilizes the acetylide conformation and enables optimum interaction between the oxygen atoms and the copper ion. Such coordination is less effective in the case of more flexible structures (Table 1, compounds **24**–**26**). It has been demonstrated that a phenyl ring can replace one of the oxygen atoms to provide coordination of the copper ion by the aromatic sextet.[14c] However, it should be noted that two nucleophilic centers are necessary for the effective coordination of the copper ion, and thus to activate the triple bond for the cycloaddition reaction with nitrones (cf. acetylenes **17** and **28**).[14c]

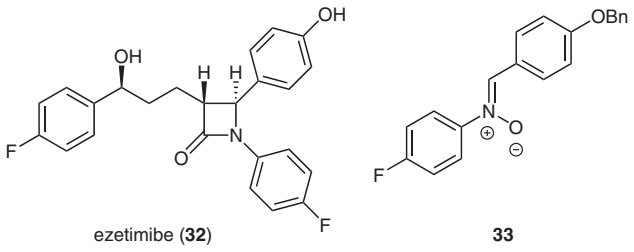
The existence of a specific coordination effect of the copper(I) ion would appear to be confirmed by reactions with an external ligand, for example, 1,10-phenanthroline. The significant increase in the reaction yield in the case of acetylene **28** may indicate the occurrence of synergistic effects of both oxygen atoms and the N,N-ligand. In contrast, addition of 1,10-phenanthroline to the reaction of nitrone **13** and acetylene **27** resulted in only a slight enhancement in the yield. The opposite effect imparted by

1,10-phenanthroline in the case of acetylene **17** could possibly be explained assuming interference with the 1,3-dioxolane ring effect, probably due to competitive coordination of the metal ion. A similar situation, that is, competitive coordination of copper(I) can occur if an additional oxygen atom is introduced to the acetylene molecule (compare substrates **28** and **29**). This result further confirms the important role of the oxygen atoms and their location in the acetylene molecule.

The general message from the above results is that successful Kinugasa reactions require the use of highly active acetylenes. This ensures that formation of the 2-azetidinone is fast enough to inhibit other possible side reactions. Consequently, in such cases, the catalyst loading can be decreased to 5 mol% to afford the desired products in acceptable yields without any decrease in the diastereoselectivity (Table 1).[14c] On the other hand, the low-active acetylenes require extended reaction times, which can promote side processes. We also observed deoxygenation of the nitrones mediated by the copper(I) complex and acetylene coupling to give diacetylenes. Accordingly, the yields were lower and the reactions could not be performed effectively in a catalytic manner.

Based on our observations, as well as the reported cases of copper-mediated acetylene–azide cycloaddition proposed by Sharpless,[25] we have suggested a plausible catalytic cycle for the investigated cascade process.[14c]

The encouraging obtained results for the glyceraldehyde-derived acetylene **17**[14c] prompted further studies on the synthetic potential of this compound as a precursor for ezetimibe (**32**),[26–29] a strong cholesterol absorption inhibitor that reduces the levels of low-density lipoprotein (LDL) in the plasma. Consequently, we focused our attention on the Kinugasa reactions involving readily available *C*,*N*-diarylnitrone **33** (Figure 5) and related compounds.[27,29]



ezetimibe (**32**) **33**

Figure 5 Structures of ezetimibe (**32**) and *C*,*N*-diarylnitrone **33**

6 Kinugasa Reactions Involving Sugar-Derived Nitrones toward the Synthesis of Carbapenems

The good stereoselectivities afforded by Kinugasa reactions with simple five-membered nitrones enabled an attractive entry into the carbapenem antibiotic skeleton (see structures **34**–**36**, Figure 6), notwithstanding the moderate yields realized at the time.[2]

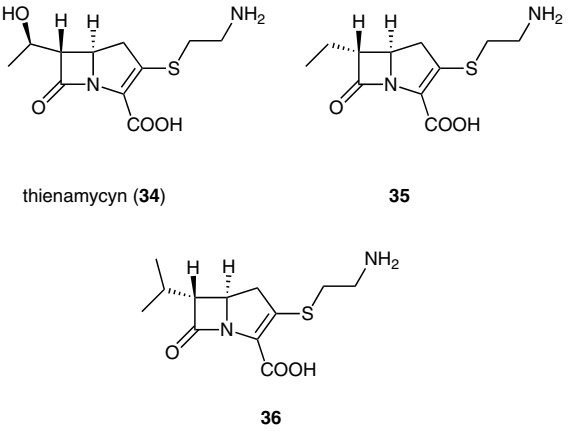


Figure 6 Carbapenem antibiotics

Bearing in mind the therapeutic value of compounds **34**–**36**, we focused our attention on acetylenes **17**, **28**, and **37**–**42**, which should allow easy access to the side chains present in carbapenem antibiotics, and to nitrones available from L- and D-arabinose, and 2-deoxy-D-ribose (Figure 7).[30–32] Several of our attempts to reproduce the published procedure[33] for the synthesis of sugar-derived cyclic nitrones did not lead to the desired products.

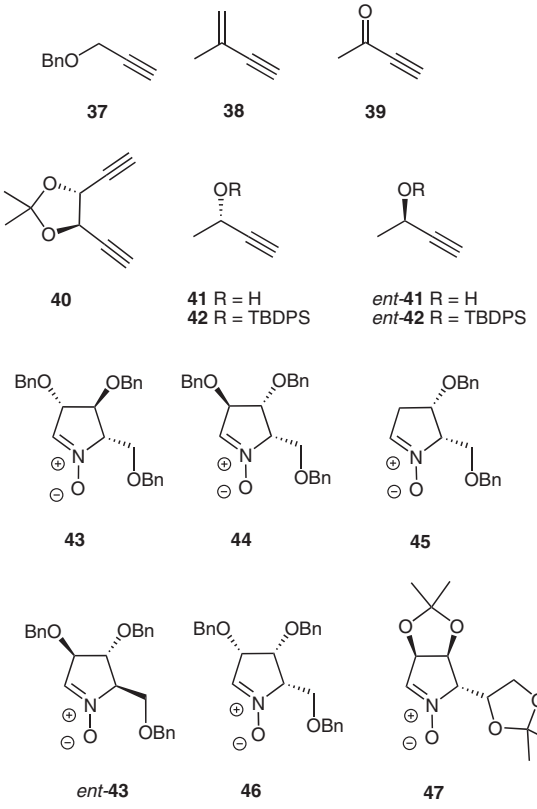


Figure 7 Structures of acetylenes **37**–**42** and nitrones **43**–**47**

Nitrones **43**-**47** were selected in order to achieve high diastereoselectivity in the Kinugasa reaction, and to obtain compounds that could be easily transformed into the five-

membered 2-carboxypyrrolidine ring present in carbapenems. Very recently, Kinugasa reactions involving nitrones **43**, **44**, **46**, and **47** with sugar-derived acetylenes were reported by Khangarot and Kaliappan.[7]

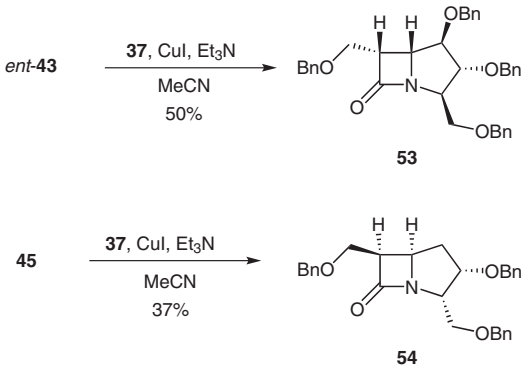
The structures and configurations of all the synthesized carbapenams were assigned using ^{1}H NMR spectroscopy. In addition to the standard correlations and NOE effects, characteristic features including the upfield shifts of the protons located on carbon atoms next to the nitrogen atom and *syn* to the unshared electron pair were evident.[34]

The stereoselectivities of the Kinugasa reactions involving sugar-derived nitrones **43**–**47** and achiral acetylenes (e.g. **28**, **37**, and **38**) depend on the substitution pattern in the former. In contrast to the simple nitrones **13** and **14**, the outcome of the process is governed not only by the substituent next to the double bond (position C-3), but can also be influenced by the group attached to the C-5 atom.

With nitrones **43** and *ent*-**43**, bearing both 3-OBn and 5-CH_2OBn groups on the same face of the dipole, the Kinugasa cascade provides single diastereoisomers **48** and *ent*-**48**, respectively, as a result of the *anti* approach of the acetylide of **28** to both substituents (Scheme 6). However, when the substituents occupied opposite sides of the nitrone plane, as in nitrone **44**, an antagonistic effect of both groups on the asymmetric induction would be expected. Indeed, such an internal mismatch effect was observed in the reaction of nitrone **44** with acetylene **28**, which provided a mixture of two *cis*-carbapenams, **49** and **50**. The benzyloxy substituent next to the double bond (C-3) of the nitrone played a significant role in the stereocontrol and the *cis*-isomer **49**, resulting from the *anti* approach of the acetylide, was the major product (Scheme 6).

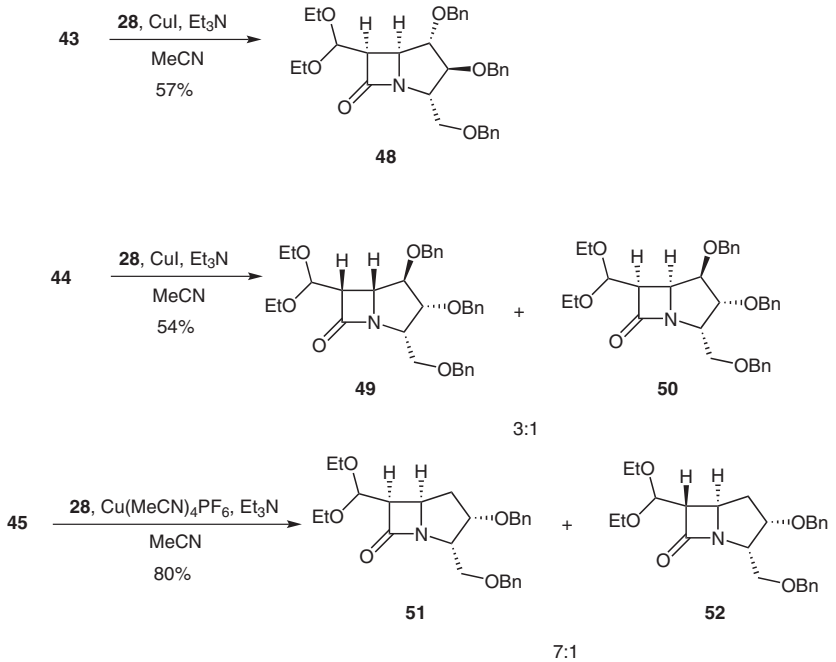
The benzyloxymethyl group at C-5 is responsible for determining the diastereoselectivity only when there is no substituent at C-3 on the nitrone, as for example in compound **45**, derived from 2-deoxyribose. Its reaction with acetylene **28** afforded carbapenam **51** preferentially, however, a trace amount of the corresponding *trans*-product **52** was also isolated (Scheme 6).

A similar situation was apparent with acetylene **37**, obtained from propargyl alcohol. Addition of **37** to nitrone *ent*-**43** gave the *cis*-adduct **53**. The same outcome was observed for the reaction between nitrone **45** and acetylene **37**, which provided carbapenam **54**, exclusively (Scheme 7).



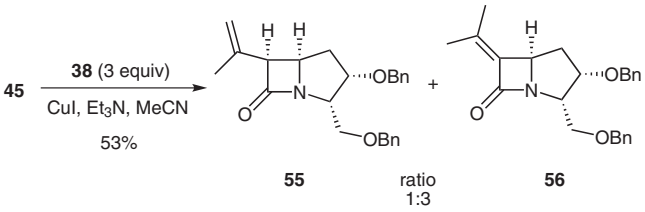
Scheme 7 Synthesis of carbapenams **53** and **54**

The reaction of commercially available acetylene **38** with 2-deoxyribose-derived nitrone **45** provided the expected product **55** along with the double bond migration product **56** (Scheme 8), which was the major component following work-up. This partial shift of the double bond can be



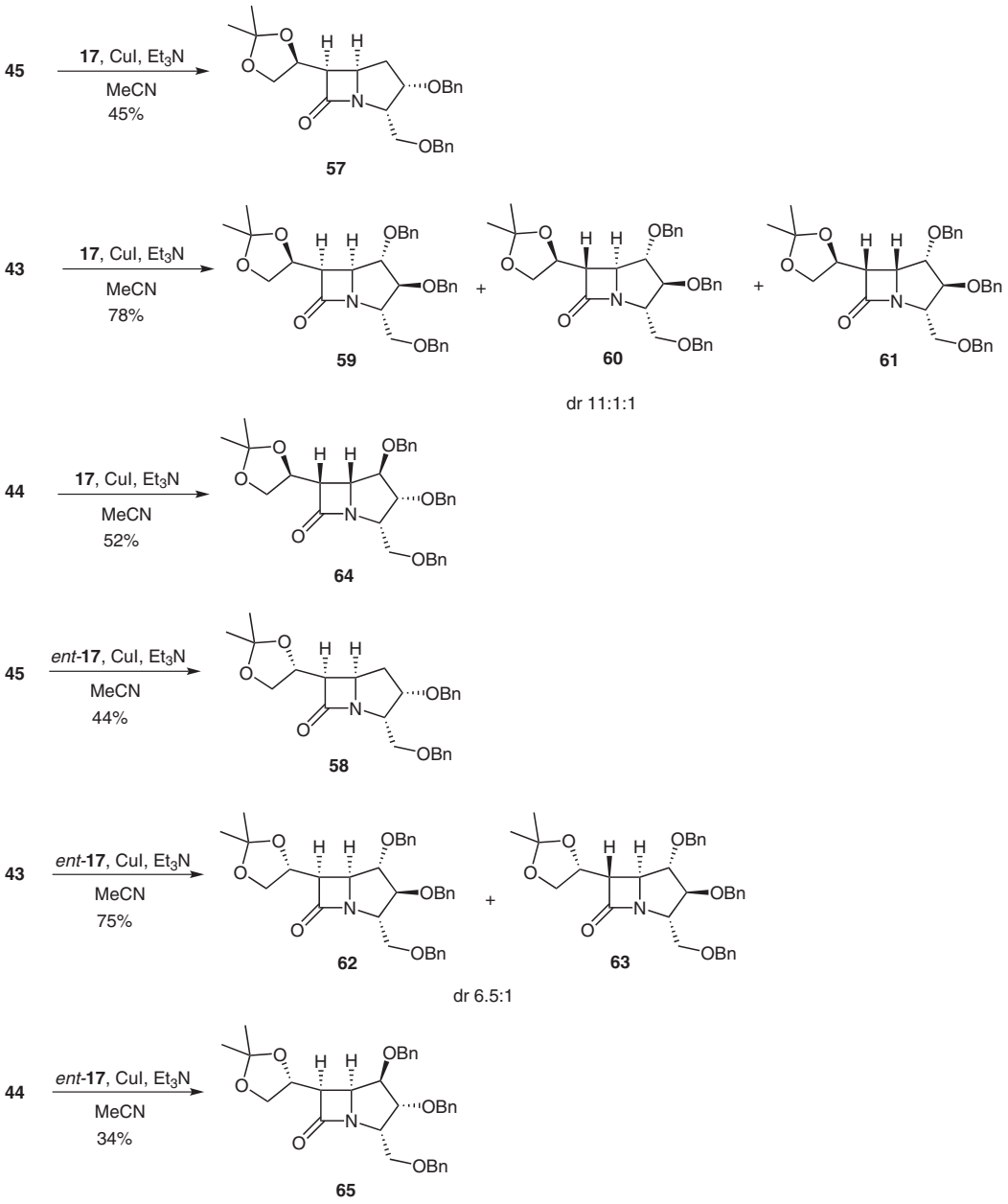
Scheme 6 Stereoselectivities of the Kinugasa reactions involving sugar-derived nitrones **43**–**45**

ascribed to the basic conditions of Kinugasa reaction. It should be noted that an *exo* double bond can be easily transformed into a hydroxy, amino or isopropyl group via a sequence of reactions involving *cis*-hydroxylation, followed by glycolic cleavage and standard transformation of the keto group, or hydrogenation of the double bond.[35,36] Unfortunately, commercially available acetylene **39** did not provide any defined product under Kinugasa reaction conditions.



Scheme 8 Synthesis of carbapenams **55** and **56**

Reactions in which both the acetylenes (**17**/*ent*-**17**, **41**/*ent*-**41** and **42**/*ent*-**42**) and nitrones (**43**/*ent*-**43**, **44** and **45**) were chiral, demonstrate interesting cases of double asymmetric induction (Scheme 9). Since the stereochemical pathway all of these reactions proceeded in a similar fashion, we have discussed in detail only those involving acetylenes **17**/*ent*-**17**, with the exception of the reactions of acetylenes **41**/*ent*-**41** and **42**/*ent*-**42** with nitrone **45**, because the latter substrates enable access to the basic skeleton of the carbapenem antibiotics. The results of other reactions can be found in the Supporting Information.

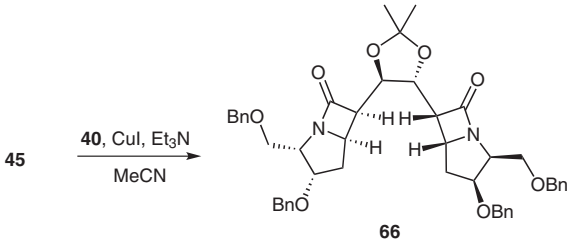


Scheme 9 Kinugasa reactions of chiral acetylenes and nitrones

As was demonstrated previously,[14b] in cases in which both substrates were chiral, the configuration of the stereogenic center present in the acetylene molecule played only a secondary role. The stereoselectivity depends mostly on the nature of the substituents and configurations of the nitrones at C-3 and C-5 . The case in which the nitrone did not possess a benzyloxymethyl group is similar to the situation discussed above for nitrones **13** and **14** having a 3-*tert*-butoxy substituent. When the nitrone does not have a large substituent at C-3 (e.g., nitrone **45**), the benzyloxymethyl substituent at C-5 determines the stereoselectivity of the reaction. The acetylene approaches the nitrone *anti* to that group regardless of the configuration of the nitrone stereogenic center. This was observed when nitrone **45** reacted with acetylenes **17** and *ent*-**17** to afford compounds **57** and **58** as the only products (Scheme 9).

A more complicated situation arises when the nitrone possesses substituents at both C-3 and C-5 (as in **43** and **44**). Matched and mismatched relationships between the configurations of both substituents on the five-membered ring of the nitrone (benzyloxymethyl and benzyloxy groups) need be taken into consideration. If both substituents are on the same side of the ring (**43**/*ent*-**43** – matched situation) the product of *anti* addition is formed with a high preference. However, when both substituents are on opposite sides of the ring (mismatched situation), the stereochemistry of the acetylene fragment can influence the composition of the isomeric products since it fits with both configurations at C-3 and C-5 of the nitrone. It should be recalled that the preferred *cis*-product can always be accompanied by the *trans*-isomer, which can be assigned to base-mediated epimerization at the position α to the β-lactam carbonyl group. The tendency for epimerization to occur depends on the base used, but can also be attributed to the structure and configuration of the acetylene fragment. However, the latter process cannot be reasonably or adequately rationalized. The above-mentioned observations were manifested in the reactions of **17**/*ent*-**17**, **41**/*ent*-**41**, and **42**/*ent*-**42** with nitrones **43**/*ent*-**43** and **44**.

In the reaction of chiral acetylene **17** and nitrone **43**, *anti*/*cis*-**59** was obtained as the major product. It was, however, accompanied by trace amounts of adduct *trans*-**60** and alternative *cis*-isomer **61**. The formation of these trace products could be due to the influence of the stereogenic center of the dioxolane fragment. In the case of *ent*-**17** and nitrone **43**, the configurations of all the stereogenic centers influenced asymmetric induction toward the same outcome, and therefore *anti*/*cis* adduct **62** was formed along with a trace amount of the epimerized product **63**.

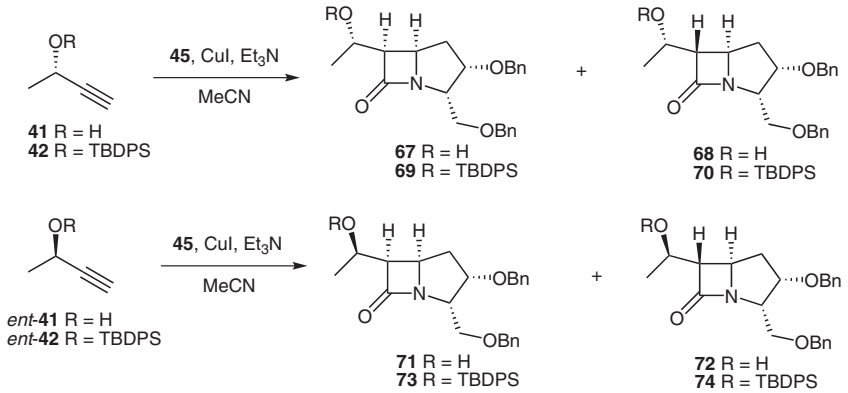


Scheme 10 Formation of bis-adduct **66**

Interesting double addition was observed in the case of acetylene **40** derived from D-tartaric acid (Scheme 10). The bis-substituted product **66** was formed with high stereoselectivity via reaction of two of the same matched pairs. A similar double addition involving diaryl nitrone **33** and **40** was investigated previously with the aim of developing an attractive entry to ezetimibe (**32**), but without success.[27]

The reaction of the chiral acetylene **41 (**derived from L-lactic acid) with nitrone **45** led to the *cis*-diastereomeric product **67** in a low yield (27%), accompanied by a trace amount of the *trans* isomer **68** (Scheme 11). A much improved result was obtained for the reaction of O-protected acetylene **42** with the same nitrone (**45**). Carbapenam **69** along with a small amount of the *trans* isomer **70** were obtained in 74% overall yield (**69**:**70**, dr = 7:1).

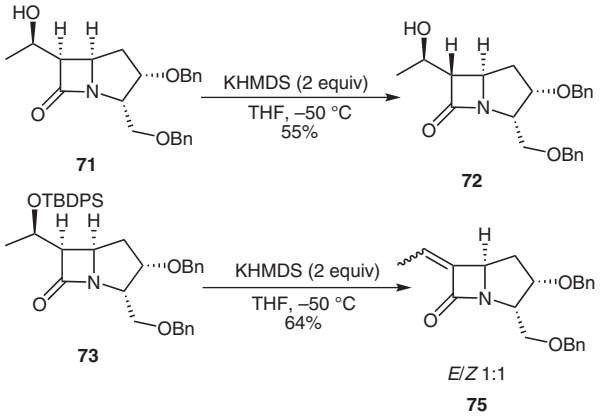
Different results were obtained from the reactions of acetylene *ent*-**41**, derived from D-lactic acid. The mismatched situation of nitrone **45** and the acetylene led to the formation of isomers *cis*-**71** and *trans*-**72** in a ratio of about 2:1, and an overall yield of 30%. In contrast to the reaction of the *O*-silyl protected acetylene derived from L-lactic acid,



Scheme 11 Kinugasa reactions of chiral acetylenes **41**/*ent*-**41**, **42**/*ent*-**42** and nitrone **45**

42, the reaction of *ent*-**42** with nitrone **45** proceeded in a lower yield (17%) compared to that of the free alcohol *ent*-**41** to afford a mixture of diastereoisomers **73** and **74** in a ratio of about 3.3:1 (Scheme 11).

Bearing in mind the configuration of the antibiotic, thienamycin (**34**) and related compounds **35** and **36**, the *trans*-isomer **72** had the desired configuration of the stereogenic centers in the four-membered ring and hydroxyethyl side chain. Thus, the reactions of nitrones **43**–**45** provide mostly *cis*-azetidinones, and we decided to explore a method for the epimerization at C-3 to afford the corresponding *trans*-product bearing the same absolute configurations at C-5, C-6 and C-1′ as those found in active antibiotics, for example, carbapenems **34**–**36**. After screening various bases, we found that in the presence of two equivalents of potassium hexamethyldisilazide (KHMDS), the *cis*-isomer **71** could be epimerized at C-6 of the carbapenam skeleton to provide the desired isomer **72** (Scheme 12) in 55% yield. On the other hand, base-mediated epimerization of the corresponding silyl-protected compound **73** yielded a 1:1 (*E*/*Z*) mixture of elimination products **75**.



Scheme 12 Successful epimerization of carbapenam **71** and formation of elimination products **75**

7 Conclusion

In conclusion, we have shown that the diastereoselective Kinugasa reaction involving five-membered cyclic nitrones derived from pentofuranoses, and simple non-chiral and chiral acetylenes provides an interesting entry into carbapenam antibiotics. The reactions proceeded in moderate to good yields and displayed high levels of diastereoselectivity affording mostly one predominant *cis*-product. It should be noted that the configuration at the bridgehead carbon atom, which is essential for the biological activity of the target antibiotic, can be easily controlled by the substituents and the configurations of the groups next to the double bond of the nitrone. Bearing in mind the structures and configurations of carbapenem antibiotics, the nitrone derived from 2-deoxyribose provided the most attractive products having appropriate substitution on the pyrrolidine ring, which enables the introduction of side chains in subsequent reaction steps, as well as the correct configurations at the bridgehead carbon atom. It was demonstrated that epimerization (*cis* into *trans*) at C-6 of the carbapenam skeleton could be easily achieved in the presence of potassium hexamethyldisilazide.

Thin-layer chromatography was performed on Merck silica gel 60 F254 (20 cm × 20 cm, × 0.2 cm) aluminum sheets. Column chromatography was carried out using Merck silica gel (230–400 mesh). Optical rotations were measured using a JASCO P-2000 digital polarimeter. Infrared spectra were recorded on an FT-IR-1600 Perkin-Elmer spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-NMR-vnmrs 600 spectrometer using deuterated solvents and TMS as the internal standard. Chemical shifts are reported as δ values in ppm and coupling constants are quoted in Hz. High-resolution mass spectra were recorded on an ESI-TOF Mariner Spectrometer (Perspective Biosystem). HPLC was carried out on an Hitachi Chromatograph with a DAD detector equipped with an LiChrospher® Si60 analytical column (250 × 4.6, 5 μm). Detailed characterization data of selected carbapenams is provided below. Full data for all other newly synthesized compounds can be found in the Supporting Information.

Kinugasa Reaction; General Procedure

To a suspension of CuI (0.5 mmol, 95 mg) in degassed anhyd MeCN (3 mL) was added Et_3N (280 μL, 2.0 mmol). After cooling to 0 °C, a soln of acetylene (0.5 mmol) in MeCN (1 mL) was added and the obtained mixture was stirred for 15 min. Next, a soln 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. The cooling bath was removed and the mixture stirred at r.t. under an N_2 atm. The progress of the reaction was monitored by TLC. Upon completion of the reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel. The diastereoisomeric ratio was determined by HPLC or ^{1}H NMR spectroscopy of the crude reaction mixture

(2*S*,3*S*,4*S*,5*S*,6*R*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (48)

Reaction of acetylene **28** with nitrone **43** afforded compound **48** in 57% yield.

Colorless oil; $[\alpha]_D$ +33 (*c* 1, CH_2Cl_2); R_f = 0.52 (hexanes–EtOAc, 2:1).

IR (film): 2975, 2868, 1773, 1100 cm^{-1}.

^{1}H NMR (600 MHz, C_6D_6): δ = 0.92 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.07 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 3.18–3.23 (m, 1 H, $CHHCH_3$), 3.34–3.51 (m, 5 H, CH_2OBn, $CHHCH_3$, CH_2CH_3), 3.66 (dd, *J* = 6.1, 2.7 Hz, 1 H, H-5), 3.75 (dd, *J* = 8.2, 6.1 Hz, 1 H, H-6), 4.22–4.30 (m, 3 H, 3 × C*H*HPh), 4.33–4.42 (m, 5 H, H-3, H-4, 3 × C*H*HPh), 4.52 (m, 1 H, H-2), 4.83 [d, *J* = 8.1 Hz, 1 H, $CH(OEt)_2$], 7.00–7.30 (15 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.5, 15.7, 55.5, 56.2, 58.3, 62.1, 63.0, 67.8, 72.5, 73.7, 74.3, 80.5, 86.1, 98.3, 127.1, 127.3, 127.5 (× 2), 127.6 (× 2), 127.7, 127.8, 127.9, 128.1, 128.2, 137.8, 138.4, 138.5, 177.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{39}NO_6Na$: 568.2670; found: 568.2719.

(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (49) and (2*S*,3*R*,4*R*,5*S*,6*R*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (50)

Reaction of acetylene **28** with nitrone **44** afforded compounds **49** and **50** in 54% combined yield in a ratio of ~3:1.

Compound 49
Colorless oil; $[\alpha]_D$ –46 (*c* 1, CH_2Cl_2); R_f = 0.73 (hexanes–EtOAc, 2:1).

IR (film): 2928, 2870, 1770, 1103 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ = 0.91 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.06 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 3.16–3.24 (m, 1 H, CH_2CH_3), 3.30 (m, 3 H, CH_2CH_3), 3.51 (dd, *J* = 6.2, 2.5 Hz, 1 H, H-5), 3.60 (dd, *J* = 9.0, 6.2 Hz, 1 H, H-6), 3.61–3.65 (m, 1 H, H-2), 4.05 (dd, *J* = 4.2, 2.2 Hz, 1 H, H-3), 4.11 (dd, *J* = 9.7, 4.4 Hz, 1 H, CHOBn), 4.25–4.28 (m, 1 H, H-4), 4.31–4.42 (m, 7 H, 3 × CH_2Ph, CHOBn), 4.81 [d, *J* = 9.0 Hz, 1 H, $CH(OEt)_2$], 7.00–7.21 (15 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.0, 15.2, 55.7, 58.7, 59.6, 63.0, 63.8, 64.6, 71.4, 71.9, 73.1, 80.3, 85.8, 99.1, 127.2, 127.3, 127.4, 127.5, 127.6 (× 2), 127.7, 127.8, 127.9, 128.1, 128.2, 137.8, 138.2, 138.5, 174.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{39}NO_6Na$: 568.2669; found: 568.2661.

Compound 50
Colorless oil; $[\alpha]_D$ +30 (*c* 1, CH_2Cl_2); R_f = 0.53 (hexanes–EtOAc, 2:1).

IR (film): 2928, 2869, 1769, 1100 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ = 1.12–1.17 (m, 6 H, 2 × CH_2CH_3), 3.21–3.23 (m, 1 H, 1 × CH_2CH_3), 3.49–3.58 (m, 2 H, CH_2CH_3), 3.60–3.67 (m, 4 H, $CHCH_3$, CH_2OBn, H-6), 3.89 (dd, *J* = 5.8, 3.3 Hz, 1 H, H-5), 4.00–4.04 (m, 1 H, H-4), 4.07–4.09 (m, 1 H, H-2), 4.22–4.26 (m, 1 H, H-3), 4.39–4.58 (m, 6 H, CH_2Ph), 5.03 [d, *J* = 8.1 Hz, 1 H, $CH(OEt)_2$], 7.20–7.35 (15 H, ArH).

^{13}C NMR (150 MHz, C_6D_6): δ = 15.3, 15.5, 53.5, 57.2, 59.3, 61.1, 63.0, 67.8, 71.5, 72.7, 73.3, 80.5, 85.1, 98.3, 127.1, 127.3, 127.5 (× 2), 127.6 (× 2), 127.7, 127.8, 127.9, 128.1, 128.2, 137.8, 138.4, 138.5, 177.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{39}NO_6Na$: 568.2675; found: 568.2661.

(2*S*,3*S*,5*R*,6*R*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (51) and (2*S*,3*S*,5*R*,6*S*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-(diethoxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (52)
Reaction of acetylene **28** with nitrone **45** afforded compounds **51** and **52** in 55% combined yield and in a ratio of ~ 4:1. When the reaction was performed in the presence of $Cu(MeCN)_4PF_6$ instead of CuI, the dr was 7:1 and the yield was 80%.

Compound 51
Colorless oil; $[\alpha]_D$ +10 (*c* 1, CH_2Cl_2); R_f = 0.68 (hexanes–EtOAc, 2:1).

IR (film): 2971, 2867, 1764, 1098 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ = 0.99 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.05 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.87 (ddd, *J* = 13.5, 7.5, 5.5 Hz, 1 H, H-4b), 1.98 (ddd, *J* = 13.5, 6.7, 3.6 Hz, 1 H, H-4a), 3.31–3.50 (m, 5 H, 2 × OCH_2CH_3, H-6), 3.60 (dd, *J* = 9.5, 5.4 Hz, 1 H, CHOBn), 3.64 (d, *J* = 9.5, 6.3 Hz, 1 H, CHOBn), 3.71–3.75 (m, 1 H, H-5), 4.07–4.12 (m, 2 H, H-2, H-3), 4.17 (d, *J* = 12.0 Hz, 1 H, OCHHPh), 4.21 (d, *J* = 12.0 Hz, 1 H, OCHHPh), 4.28 (d, *J* = 12.0 Hz, 1 H, OCHHPh), 4.33 (d, *J* = 12.0 Hz, 1 H, OCHHPh), 4.53 [d, *J* = 6.2 Hz, 1 H, $CH(OEt)_2$], 6.98–7.30 (10 H, ArH).

^{13}C NMR (150 MHz, C_6D_6): δ = 15.07, 15.09, 32.3, 53.5, 54.9, 60.8, 61.7, 62.4, 68.3, 71.9, 72.9, 82.9, 99.3, 127.4, 127.5, 127.6, 127.7, 128.3, 128.4, 137.9, 138.3, 175.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{33}NO_5Na$: 462.2251; found: 462.2273.

Compound 52
Colorless oil; $[\alpha]_D$ +4.4 (*c* 1, CH_2Cl_2); R_f = 0.31 (hexanes–EtOAc, 2:1).

IR (film): 2975, 2868, 1764, 1095 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ = 1.01 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.06 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.33–1.36 (m, 1 H), 1.92 (ddd, *J* = 13.2, 5.8, 2.8 Hz, 1 H, CHH, H-4b), 3.02 (dd, *J* = 5.5, 2.2 Hz, 1 H, H-5), 3.30–3.41 (m, 2 H, OCH_2CH_3), 3.48–3.57 (m, 2 H, OCH_2CH_3), 3.60 (dd, *J* = 9.4, 5.6 Hz, 1 H, CHOBn), 3.66 (dd, *J* = 9.3, 7.4 Hz, 1 H, CHOBn), 3.89 (m, 1 H, H-2), 3.92 (ddd, *J* = 8.1, 5.9, 2.2 Hz, 1 H, H-5), 4.02–4.13 (m, 3 H, 2 × CH_2Ph, H-3), 4.23–4.32 (m, 2 H, CH_2Ph), 4.67 [d, *J* = 5.4 Hz, 1 H, $CH(OEt)_2$], 7.00–7.24 (10 H, ArH).

^{13}C NMR (150 MHz, C_6D_6): δ = 15.2, 15.3, 36.2, 53.4, 60.1, 61.6, 62.1, 62.7, 67.8, 72.3, 73.2, 83.9, 99.8, 127.4, 127.5, 127.6, 127.7, 128.3, 128.4, 137.8, 138.3, 175.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{33}NO_5Na$: 462.2251; found: 462.2271.

(2*S*,3*S*,5*R*,6*R*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (57)
Reaction of acetylene **17** with nitrone **45** afforded compound **57** in 45% yield.

Colorless oil; $[\alpha]_D$ +56.0 (*c* 1, CH_2Cl_2); R_f = 0.41 (hexanes–EtOAc, 2:1).

IR (film): 2931, 2870, 1751, 1062 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 8.3 Hz, 6 H, 2 × CH_3), 2.06–2.08 (m, 1 H, H-4a), 2.25–2.29 (m, 1 H, H-4b), 3.48 (dd, *J* = 3.6, 3.4 Hz, 1 H, H-6), 3.63–3.65 (m, 2 H, CH_2OBn), 3.89–3.97 (m, 2 H, H-5, H-5′a), 4.00 (dd, *J* = 8.1, 6.1 Hz, 1 H, H-5′b), 4.08 (dd, *J* = 11.3, 5.6 Hz, 1 H, H-2), 4.22 (ddd, *J* = 9.4, 6.1, 3.7 Hz, 1 H, H-4′), 4.38 (dd, *J* = 11.7, 5.8 Hz, 1 H, H-3), 4.51–4.57 (m, 4 H, 2 × CH_2Ph), 7.28–7.34 (10 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.0, 26.3, 31.6, 52.7, 53.7, 60.2, 67.6, 67.8, 72.2, 72.3, 73.3, 82.2, 110.3, 127.5, 127.6, 127.7, 128.3, 128.4, 138.0, 138.3, 176.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{31}NO_5Na$: 460.2095; found: 460.2095.

(2*S*,3*S*,5*R*,6*R*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-[(*R*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (58)
Reaction of acetylene *ent*-**17** with nitrone **45** afforded compound **58** in 44% yield.

Colorless oil; $[\alpha]_D$ +130 (*c* 1, CH_2Cl_2); R_f = 0.53 (hexanes–EtOAc, 2:1).

IR (KBr): 2942, 2857, 1767, 1062 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.94 (ddd, *J* = 13.6, 7.2, 5.8 Hz, 1 H, H-4a), 2.29 (ddd, *J* = 6.5, 4.3, 1.6 Hz, 1 H, H-4b), 3.47 (dd, *J* = 9.5, 5.4 Hz, 1 H, H-6), 3.62–3.68 (m, 2 H, CH_2OBn), 3.85 (dd, *J* = 8.3, 3.8 Hz, 1 H, H-5′a), 4.02–4.07 (m, 2 H, H-2, H-5), 4.15–4.17 (m, 2 H, H-4′, H-5′b), 4.35 (dd, *J* = 10.2, 5.5 Hz, 1 H, H-3), 4.49–4.59 (m, 4 H, 2 × CH_2Ph), 7.26–7.32 (10 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.4, 26.8, 31.9, 54.0, 54.3, 60.9, 67.7, 68.2, 71.4, 72.3, 73.3, 83.1, 109.2, 127.5 (× 2), 127.6, 127.8, 128.3, 128.4, 137.8, 138.2, 176.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{31}NO_5Na$: 460.2095; found: 460.2112.

(2*S*,3*S*,4*S*,5*S*,6*R*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (59), (2*S*,3*S*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (60) and (2*S*,3*S*,4*S*,5*R*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (61)

Reaction of acetylene **17** with nitrone **43** afforded compounds **59**, **60** and **61** in 78% combined yield in a ratio of ~ 11:1:1.

Compound 59

Colorless oil; $[\alpha]_D$ +11 (*c* 1, CH_2Cl_2); R_f = 0.30 (hexanes–EtOAc, 2:1).

IR (film): 2934, 2867, 1769, 1098 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ = 1.17 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 2.92 (dd, *J* = 5.5, 3.9 Hz, 1 H, H-6), 3.27 (dd, *J* = 9.9, 4.5 Hz, 1 H, CH*H*OBn), 3.36 (dd, *J* = 9.7, 5.7 Hz, 1 H, C*H*HOBn), 3.42–3.45 (m, 1 H, H-5), 3.56 (dd, *J* = 7.9, 5.9 Hz, 1 H, H-5′a), 3.84 (dd, *J* = 7.9, 4.0 Hz, 1 H, H-5′b), 3.94 (ddd, *J* = 9.8, 5.9, 4.0 Hz, 1 H, H-4′), 4.12–4.16 (m, 1 H, H-2), 4.16–4.24 (m, 2 H, CH_2Ph), 4.32–4.51 (m, 5 H, 2 × CH_2Ph, H-3), 4.63–4.67 (m, 1 H, H-4), 7.02–7.25 (15 H, ArH).

^{13}C NMR (600 MHz, $CDCl_3$): δ = 26.4, 54.2, 58.6, 60.3, 60.7, 67.5, 68.9, 72.1, 72.2, 72.4, 73.1, 82.7, 88.2, 110.3, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 137.5, 137.6, 137.9, 174.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2530; found: 566.2513.

Compound 60

Colorless oil; $[\alpha]_D$ +24 (*c* 1, CH_2Cl_2); R_f = 0.41 (hexanes–EtOAc, 2:1).

IR (film): 2924, 2858, 1767, 1092 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.23 (dd, *J* = 7.4, 2.3 Hz, 1 H, H-6), 3.47 (d, *J* = 6.4 Hz, 2 H, CH_2OBn), 3.69 (dd, *J* = 3.8, 2.6 Hz, 1 H, H-5), 3.74 (dd, *J* = 8.4, 6.2 Hz, 1 H, H-5′a), 3.81–3.83 (m, 1 H, H-4), 4.08 (dd, *J* = 8.4, 6.3 Hz, 1 H, H-5′b), 4.17 (ddd, *J* = 13.0, 6.5, 3.2 Hz, 1 H, H-2), 4.27–4.33 (m, 1 H, H-3), 4.38 (dd, *J* = 13.4, 6.3 Hz, 1 H, H-4′), 4.47–4.60 (m, 6 H, 3 × CH_2Ph), 7.21–7.40 (15 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.3, 26.8, 59.2, 59.7, 62.7, 67.5, 68.5, 71.9, 72.0, 73.2, 73.5, 85.6, 87.9, 109.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 137.3, 137.5, 137.9, 174.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2513; found: 566.2533.

Compound 61

Colorless oil; $[\alpha]_D$ +19.6 (*c* 1, CH_2Cl_2); R_f = 0.60 (hexanes–EtOAc, 2:1).

IR (film): 2925, 2859, 1767, 1096 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.44–3.50 (m, 2 H, CH_2OBn), 3.56 (dd, *J* = 10.7, 5.6 Hz, 1 H, H-6), 3.82–3.86 (m, 2 H, H-5′a, H-5), 4.04 (dd, *J* = 8.8, 6.1 Hz, 1 H, H-5′b), 4.16–4.20 (m, 1 H, H-2), 4.21–4.22 (m, 1 H, H-4), 4.28–4.31 (m, 1 H, H-3), 4.33–4.35 (m, 1 H, H-4′), 4.42–4.62 (m, 6 H, CH_2Ph), 7.20–7.36 (15 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.3, 27.0, 56.3, 60.2, 62.4, 68.2, 68.3, 71.5, 71.6, 72.2, 73.1, 82.4, 88.1, 108.9, 127.6 (× 2), 127.7 (× 2), 127.8, 127.9, 128.2, 128.3, 128.4, 137.3, 137.6, 137.9, 175.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2513; found: 566.2513.

(2*S*,3*S*,4*S*,5*S*,6*R*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*R*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (62) and (2*S*,3S,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*R*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (63)

Reaction of acetylene *ent*-**17** with nitrone **43** afforded compounds **62** and **63** in 75% combined yield in a ratio of ~ 6.5:1.

Compound 62

Colorless oil; $[\alpha]_D$ +55.5 (*c* 1, CH_2Cl_2); R_f = 0.55 (hexanes–EtOAc, 2:1).

IR (film): 2934, 2868, 1767, 1097 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 3.47–3.51 (m, 2 H, CH_2OBn), 3.58 (dd, *J* = 10.7, 5.5 Hz, 1 H, H-6), 3.83–3.88 (m, 2 H, H-5, H-5′a), 4.05 (dd, *J* = 8.7, 6.0 Hz, 1 H, H-5′b), 4.19–4.25 (m, 2 H, H-2, H-4), 4.29–4.32 (m, 1 H, H-3), 4.36 (m, 1 H, H-4′), 4.43–4.62 (m, 6 H, CH_2Ph), 7.00–7.23 (15 H, ArH).

^{13}C NMR (600 MHz, C_6D_6): δ = 26.9, 56.8, 60.4, 62.4, 68.2, 68.3, 71.2, 71.7, 71.8, 72.8, 82.5, 88.1, 108.6, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 137.6, 138.3, 174.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2519; found: 566.2533.

Compound 63

Compound **63** was not isolated in pure form; R_f = 0.58 (hexanes–EtOAc, 2:1).

^1H NMR (600 MHz, $CDCl_3$): δ (selected signals from a diastereoisomeric mixture) = 3.35 (dd, *J* = 4.2, 2.9 Hz, 1 H), 3.65 (dd, *J* = 6.4, 2.9 Hz, 1 H).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2519; found: 566.2525.

(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (64)

Reaction of acetylene **17** with nitrone **44** afforded compound **64** in 52% yield.

Colorless oil; $[\alpha]_D$ +25.0 (*c* 1, CH_2Cl_2); R_f = 0.48 (hexanes–EtOAc, 2:1).

IR (film): 2921, 2854, 1765, 1099 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 3.40 (dd, *J* = 10.8, 5.4 Hz, 1 H, H-6), 3.61–3.65 (m, 1 H, H-2), 3.70 (dd, *J* = 5.4, 3.8 Hz, 1 H, H-5), 3.76 (dd, *J* = 8.5, 5.7 Hz, 1 H, H-5′a), 3.84 (dd, *J* = 8.5, 6.1 Hz, 1 H, H-5′b), 4.00 (dd, *J* = 9.7, 4.3 Hz, 1 H, C*H*HOBn), 4.08 (dd, *J* = 9.8, 5.9 Hz, 1 H, CH*H*OBn), 4.15–4.18 (m, 1 H, H-4′), 4.20 (dd, *J* = 5.1, 3.6 Hz, 1 H, H-3), 4.33–4.34 (m, 1 H, H-4), 4.46–4.65 (m, 6 H, 3 × CH_2Ph), 7.23–7.35 (15 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.2, 27.0, 55.6, 58.8, 62.8, 64.2, 68.2, 71.8, 72.1, 72.2, 73.3, 79.8, 86.0, 108.8, 127.4, 127.6, 127.7, 127.8 (× 2), 127.9, 128.34, 128.36, 128.4, 137.6, 137.9, 138.0, 174.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2519; found: 566.2520.

(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-[(*R*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-1-azabicyclo[3.2.0]heptan-7-one (65)

Reaction of acetylene *ent*-**17** with nitrone **44** afforded compound **65** in 34% yield.

Colorless oil; $[\alpha]_D$ +43 (*c* 1, CH_2Cl_2); R_f = 0.53 (hexanes–EtOAc, 2:1).

IR (film): 2933, 2869, 1765, 1098 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.24 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.49 (dd, *J* = 9.8, 5.6 Hz, 1 H, H-6), 3.62–3.68 (m, 2 H, CH_2OBn), 3.76 (dd, *J* = 8.7, 5.7 Hz, 1 H, H-5′a), 3.92 (dd, *J* = 5.6,

3.7 Hz, 1 H, H-5), 4.04–4.10 (m, 2 H, H-5′b, H-2), 4.22–4.24 (m, 2 H, H-3, H-4), 4.49–4.56 (m, 6 H, 3 × CH_2Ph), 4.76–4.79 (m, 1 H, H-4′), 7.27–7.37 (m, 15 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.4, 27.1, 53.4, 56.5, 59.1, 67.6, 69.1, 71.0, 71.7, 73.0, 73.3, 80.6, 85.7, 108.6, 127.0, 127.6, 127.7, 127.8, 127.9, 128.4, 128.5, 128.6, 137.3, 137.6, 138.1, 176.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{37}NO_6Na$: 566.2513; found: 566.2520.

(2*S*,3*S*,5*R*,6*R*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-1′-hydroxyethyl]-1-azabicyclo[3.2.0]heptan-7-one (67) and (2*S*,3*S*,5*R*,6*S*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-[(*S*)-1′-hydroxyethyl]-1-azabicyclo[3.2.0]heptan-7-one (68)

Reaction of acetylene **41** with nitrone **45** afforded compounds **67** and **68** in 27% combined yield in a ratio of about 8:1.

Compound 67

Colorless oil; $[\alpha]_D$ +115 (*c* 1, CH_2Cl_2); R_f = 0.3 (hexanes–acetone, 2:1).

IR (film): 2929, 2866, 1755, 1096 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.69 (ddd, *J* = 13.3, 8.0, 5.0 Hz, 1 H, H-4a), 1.95 (ddd, *J* = 13.5, 6.2, 3.0 Hz, 1 H, H-4b), 2.89 (dd, *J* = 9.1, 5.4 Hz, 1 H, H-6), 3.60 (dd, *J* = 9.2, 5.0 Hz, 1 H, C*H*HOBn), 3.65–3.70 (m, 2 H, CH*H*OBn, H-1′), 3.74–3.76 (m, 1 H, H-5), 3.98–4.02 (m, 2 H, H-2, H-3), 4.10–4.21 (m, 2 H, CH_2OBn), 4.25–4.35 (m, 2 H, CH_2OPh), 7.01–7.30 (10 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.8, 31.9, 54.6, 57.7, 60.8, 63.8, 68.3, 71.8, 73.0, 83.5, 127.2, 127.3, 127.4, 127.5 (× 2), 127.8, 128.0, 128.1, 128.2, 177.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{27}NO_4Na$: 404.1832; found: 404.1830.

Compound 68

Colorless oil; $[\alpha]_D$ +85 (*c* 1, CH_2Cl_2); R_f = 0.32 (hexanes–acetone, 2:1).

IR (film): 2934, 2865, 1754, 1098 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ = 0.92 (ddd, *J* = 13.2, 8.1, 5.1 Hz, 1 H, H-4a), 1.05 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.83 (ddd, *J* = 13.2, 6.0, 2.9 Hz, 1 H, H-4b), 2.51 (dd, *J* = 5.5, 2.1 Hz, 1 H, H-6), 3.55–3.61 (m, 2 H, H-5, C*H*HOBn), 3.65 (dd, *J* = 9.5, 7.6 Hz, 1 H, CH*H*OBn), 3.69–3.72 (m, 1 H, H-1′), 3.88–3.91 (m, 1 H, H-2), 4.00–4.02 (m, 1 H, H-3), 4.08–4.36 (m, 4 H, 2 × CH_2Ph), 7.21–7.35 (10 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.9, 34.7, 52.6, 61.4, 62.4, 68.3, 71.5, 72.0, 73.2, 79.2, 127.5, 127.6, 127.7, 128.4, 138.22, 138.23, 138.3, 169.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{27}NO_4Na$: 404.1832; found: 404.1831.

(2*S*,3*S*,5*R*,6*R*)-3-(Benzyloxy)-2-[(benzyloxy)methyl)]-6-[(*R*)-1′-hydroxyethyl]-1-azabicyclo[3.2.0]heptan-7-one (71) and (2*S*,3*S*,5*R*,6*S*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-6-[(*R*)-1′-hydroxyethyl]-1-azabicyclo[3.2.0]heptan-7-one (72)

Reaction of acetylene *ent*-**41** with nitrone **45** afforded compounds **71** and **72** in 30% combined yield in a ratio of ~ 2:1.

Compound 71

Colorless oil; $[\alpha]_D$ +25 (*c* 1, CH_2Cl_2); R_f = 0.35 (hexanes–acetone, 2:1).

IR (film): 2929, 2865, 1753, 1092 cm^{-1}.

^{1}H NMR (600 MHz, C_6D_6): δ = 0.94 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.38 (ddd, *J* = 12.7, 7.7, 5.3 Hz, 1 H, H-4a), 1.61 (ddd, *J* = 13.3, 6.6. 3.6 Hz, 1 H, H-4b), 2.83 (dd, *J* = 8.0, 5.6 Hz, 1 H, H-6), 3.47–3.52 (m, 1 H, H-5), 3.56 (dd, *J* = 9.1, 5.0 Hz, 1 H, CH*H*OBn), 3.58–3.67 (m, 2 H, C*H*HOBn, H-1′), 3.95–4.01 (m, 2 H, H-2, H-3), 4.10–4.18 (m, 2 H, CH_2Ph), 4.25–4.33 (m, 2 H, CH_2Ph), 7.00–7.26 (10 H, ArH).

^{13}C NMR (150 MHz, C_6D_6): δ = 21.4, 31.0, 53.9, 56.7, 60.4, 64.6, 68.1, 71.9, 72.9, 83.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 178.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{27}NO_4Na$: 404.1838; found: 404.1845.

Compound 72

Colorless oil; $[\alpha]_D$ +34 (*c* 1, CH_2Cl_2); R_f = 0.26 (hexanes–acetone, 2:1).

IR (film): 2924, 2859, 1756, 1099 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.61 (ddd, *J* = 13.2, 8.1, 5.1 Hz, 1 H, H-4a), 2.39 (ddd, *J* = 13.3, 5.7, 2.8 Hz, 1 H, H-4a), 2.86 (dd, *J* = 6.9, 1.9 Hz, 1 H, H-6), 3.62 (dd, *J* = 9.5, 6.1 Hz, 1 H, CH*H*OBn), 3.69 (dd, *J* = 9.7, 6.9 Hz, 1 H, C*H*HOBn), 3.88 (ddd, *J* = 9.9, 5.7, 1.9 Hz, 1 H, H-5), 4.08–4.12 (m, 1 H, H-2), 4.14–4.18 (m, 1 H, H-1′), 4.39–4.41 (m, 1 H, H-3), 4.44–4.66 (m, 4 H, CH_2Ph), 7.26–7.38 (10 H, ArH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.9, 36.4, 54.3, 61.6, 63.7, 66.3, 67.9, 72.3, 73.3, 84.2, 127.4, 127.5, 127.7, 127.8, 128.3, 128.4, 137.8, 138.2, 176.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{27}NO_4Na$: 404.1838; found: 404.1832.

Epimerization; Typical Procedure

A soln of *cis*-2-azetidinone **71** (100 mg, 0.26 mmol) in anhyd THF (10 mL) was cooled to –55 °C and treated with a soln of KHMDS (520 μL, 0.52 mmol, 1 M in THF). The progress of the reaction was monitored by TLC. After stirring for 5 h, the resulting mixture was diluted with Et_2O (25 mL) followed by the addition of H_2O (10 mL). The organic phase was dried over Na_2SO_4, evaporated and the residue chromatographed on silica gel (hexane–*i*-PrOH, 9:1) to afford *trans*-azetidinone **72** (54 mg, 55%).

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Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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