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Synthesis of *N*,4-diaryl substituted β-lactams via Kinugasa cycloaddition/rearrangement reaction

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ABSTRACT

The methodology of construction of *N*,4-diaryl substituted β-lactam framework, based on the Kinugasa cycloaddition/rearrangement sequence is presented. The series of protected chiral propargyl alcohols was treated with diaryl nitrones to afford mainly the *cis*-**I** adduct, providing direct access to the highly-functionalized azetitidin-2-one derivatives with a well-defined stereochemistry. Under the optimized reaction conditions, the unprotected chiral propargylic alcohols were also found to be suitable precursors of β-lactams. The absolute configuration of adducts was determined by CD or HPLC-CD technique, which was shown to be reliable method of determination of the configuration at C-4 of 4-aryl-substituted azetidin-2-ones. Epimerization of the *cis* adduct to the respective *trans* isomer could be easily done by the oxidation of hydroxyl group next to the four-membered β-lactam ring to the ketone, followed by a base-mediated epimerization of the malonyl fragment.

1. Introduction

The *N*,4-diaryl substituted β-lactams **1**–**8** represent a group of compounds exhibiting a wide range of interesting biological activities, such as cholesterol absorption inhibition (compounds **1**–**4**),[1–7] antifungal (compound **5**),[8] analgestic (compound **6**),[9] and anticancer (compounds **7** and **8**).[10,11] All reported to-date methodologies of their synthesis have been based on a construction of the β-lactam ring via cyclocondensation of suitable substituted benzylidene-anilines and ketene, ester, or amide enolates.[12–17] In many cases, compounds **1**–**8** have been obtained as racemic mixtures. Moreover, their full relative configuration has not always been assigned.

The knowledge of an absolute configuration of chiral centers present in biologically active compounds as well as an ability of rational asymmetric construction of these centers are essential preconditions for the successful exploration of future applications of these compounds. In the case of β-lactam syntheses via cyclocondensation of esters or amides with imines, the control of stereoconfiguration of newly formed stereogenic centers in the four-membered ring has been usually accomplished either by the use of R^1 as a chiral auxiliary or R^2 as the defined chiral fragment that can be transformed later into desired C-3 substituent (Scheme 1).

Recently, we have reported a formal synthesis of Ezetimibe **1**,[18] a powerful cholesterol absorption inhibitor.[1,2] The crucial step of the reported synthesis is based on the Cu(I)-mediated Kinugasa cycloaddition/rearrangement cascade reaction between terminal acetylene derived from L-glyceraldehyde acetonide **9** and suitable *C*,*N*-diarylnitrone **10** (Scheme 2). The adduct **11** with (3*R*,4*S*) configuration at the azetidinone ring was obtained with a high stereoselectivity. The diol side chain was subsequently deprotected and subjected to the glycolic cleavage followed by the base-induced isomerization at C-3 carbon atom to afford the (3*S*,4*S*)-aldehyde **12**. The transformation of aldehyde **12** into Ezetimibe was previously demonstrated by the Schering-Plough Process group (Scheme 2).[19]

The effectiveness of transformation of **9** and **10** into the aldehyde **12** prompted us to investigate general possibilities of application of Kinugasa reaction as a method of the synthesis of selected *N*,4-diaryl substituted β-lactams. Considering the structures of compounds **1**–**8** and the possible transformations of substituents at C-3 of synthesized azetidinones, we decided to limit the selection of investigated compounds to acetylenes derived from L-glyceraldehyde (**14a**), (*S*)-malic acid (**14b**) and substituted propargyl alcohols (**15a**–**e**), and *C*,*N*-diaryl-nitrones: either unsubstituted or with *p*-protected oxygen atom in the benzylidene fragment, or else *p*-fluoroaniline (**13a**–**f**).

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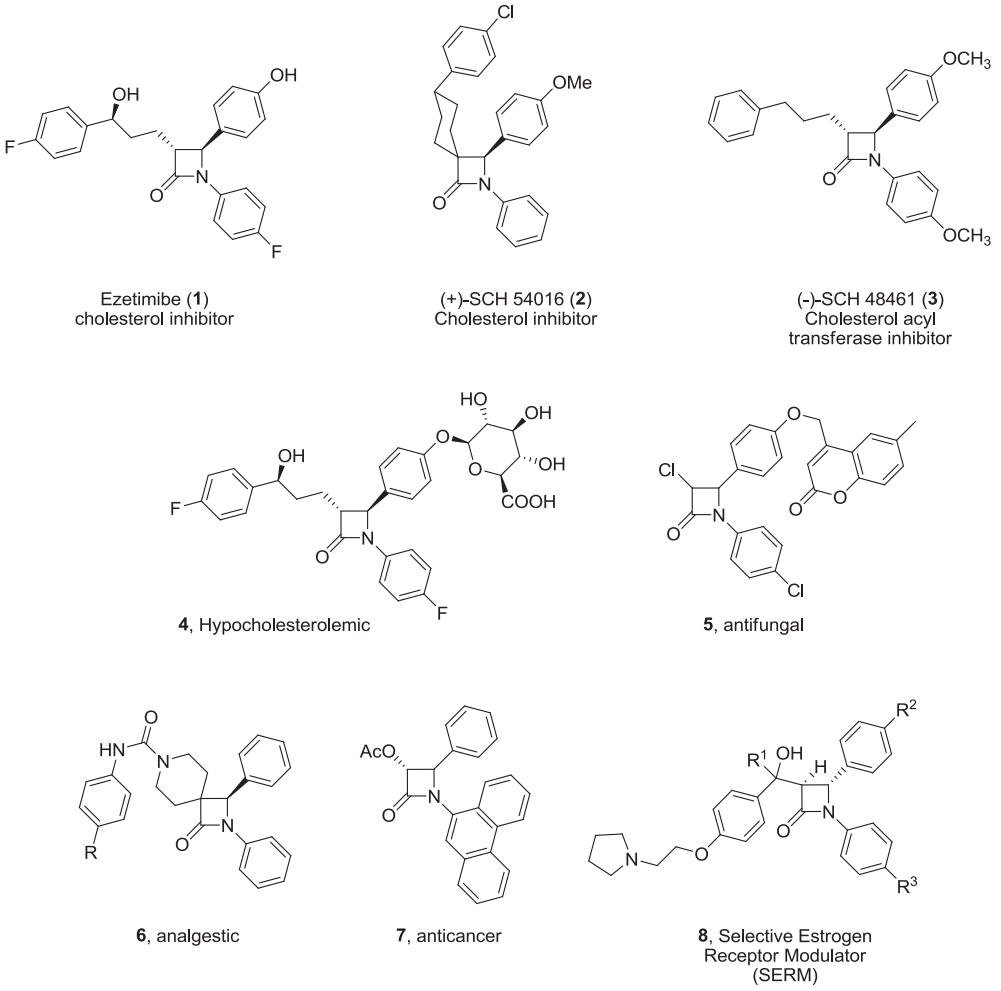
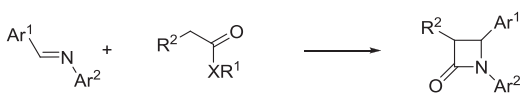


2. Results and discussion

Preliminary investigation of Kinugasa reaction between diaryl nitrones and terminal acetylenes indicated that the yield of reaction depends on the nature of both aryl substituents. This observation corresponds well with our previous work on the Friedel–Crafts reaction between acyl-iminium cation generated from 4-vinyloxy- or 4-acyloxy-azetidin-2-one and nucleophilic arenes, such as anisol (Scheme 3).[20] It has been shown that the initially formed 4-anisyl-azetidinone in the presence of Lewis acid underwent rapid opening of the four-membered ring by the second molecule of the nucleophile to form diaryl-substituted propionamides. Similarly, Carreira[21,22] observed β-lactam ring opening/cyclization cascade during attempts to reduce β-lactams containing electron-rich substituent at C4. This transformation involves the ring opening of azetidine leading to a benzylic carbocation as an intermediate, which is facilitated by electron-rich substituent of arene.

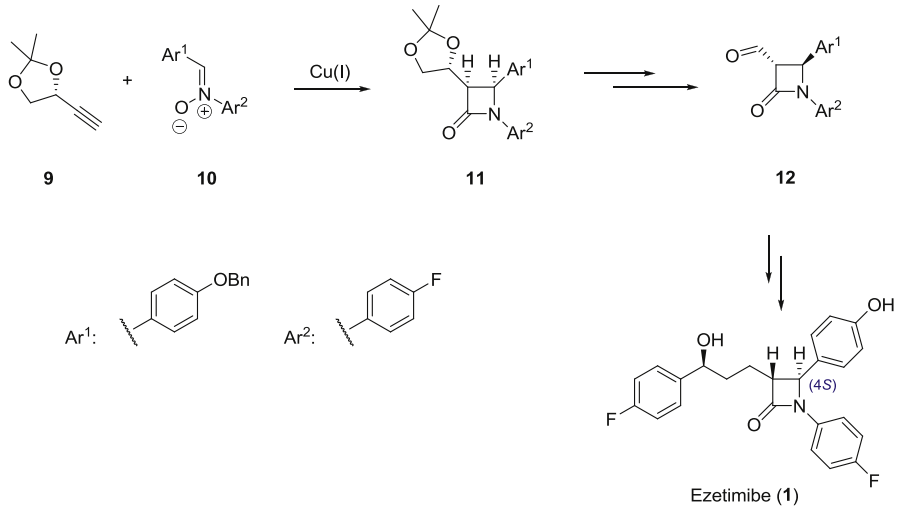
To shed more light on the reaction pathway, a representative group of *C*,*N*-diaryl-nitrones **13a**–**f** (Chart 1) was obtained utilizing a modified literature method,[23] which involved reduction of nitroaryls to corresponding hydroxylamines followed by the condensation with substituted benzaldehydes in the presence of methanesulphonic acid as a catalyst. This procedure offers an advantage over classical method, based on the condensation of an aryl hydroxylamine and substituted benzaldehyde in ethanol at reflux, since it allows to easily scale-up the preparation. The optimized conditions allowed preparation of nitrones **13b**–**f** in a 40–67% yield.



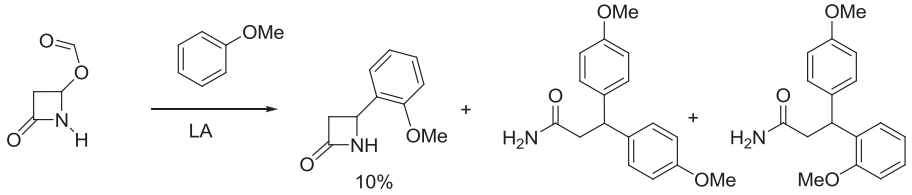
Scheme 1.

The other synthons for Kinugasa reaction, namely terminal acetylenes **14a**,**b**, were obtained by a one-pot procedure from corresponding aldehydes by treatment with Bestmann–Ohira reagent.[24,25] Alcohol **15a** was synthesized starting from phenethylaldehyde by the known sequence of reactions involving Horner–Emmons olefination with triethyl phosphonoacetate, reduction of the ester group to an alcohol, enantioselective epoxidation, exchange of hydroxyl group into chlorine atom and finally a rearrangement of the respective chloroepoxide to the product **15a** with 84% ee.[26] Alternatively, alcohol **15a** could be obtained following a shorter synthetic sequence based on the enantioselective addition of 2-methyl-3-butyn-2-ol to phenethylaldehyde, mediated by $Zn(OTf)_2$/*N*-methylephedrine complex and subsequent elimination of acetone in the presence of base to afford **15a** with 82% ee.[27] Propargylic alcohols **15b** and **15c** are commercially available and were used without further purification (Chart 2).

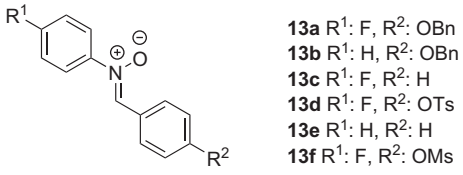
Kinugasa reactions of nitrones **13a**–**f** and acetylenes **14** and **15** were performed under standard reaction conditions in the presence of CuI (1 equiv) and Et_3N (4 equiv) in acetonitrile at rt. Recently, we have found that the use of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) offered better selectivity and yield than that obtained with Et_3N,[18]



Scheme 2.

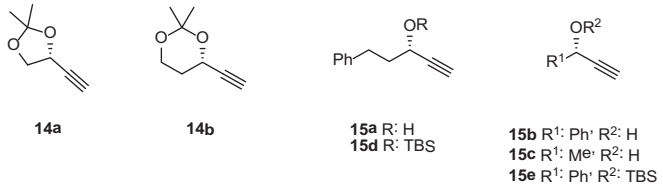


Scheme 3.



13a R^1: F, R^2: OBn
13b R^1: H, R^2: OBn
13c R^1: F, R^2: H
13d R^1: F, R^2: OTs
13e R^1: H, R^2: H
13f R^1: F, R^2: OMs

Chart 1.



14a **14b**

15a R: H
15d R: TBS

15b R^1: Ph, R^2: H
15c R^1: Me, R^2: H
15e R^1: Ph, R^2: TBS

Chart 2.

and we repeated reactions in the presence of TMG. The results are summarized in Tables 1 and 2. The absolute configuration of β-lactams was assigned by combination of NMR, CD, and X-ray analysis. Since the latter methodology has a general value for assignment of the absolute configuration for all 4-aryl-azetidin-2-ones we present a detailed discussion in the next section (*vide infra*).

In comparison with the previously investigated reactions of non-racemic acetylenes, such as **14a**, with cyclic nitrones,[28–30] the Kinugasa reactions involving *C*,*N*-diaryl imine oxides offered a lower level of stereoselectivity, reflected by the detection of four possible isomeric β-lactam products (Scheme 4). Such a result is not entirely surprising since Kinugasa reaction is a complex reaction cascade, which consists of cycloaddition-rearrangement followed by the enolate protonation (Scheme 5). Nevertheless, the collected

Table 1
The Kinugasa reaction of chiral acetylenes **14a**,**b** and diaryl nitrones[a]

Entry	Acetylene	Nitrone	Product	dr (*cis*-**I**:*trans*-**I**): (*cis*-**II**:*trans*-**II**)[b]	Yield of *cis*-**I** isomer (overall yield)[c] [%]
1	**14a**	**13a**	**16**	(9.7:2.7):(1:1)	41 (61)
2	**14a**	**13b**	**17**	(4.1:1.0):(3.5:0)	62[d] (95)
3	**14a**	**13c**	**18**	(5.3:2.5):(1.3:1.0)	55[e] (62)
4	**14a**	**13d**	**19**	(7.1:1.0):(1.0:1.6)[f]	45
5	**14a**	**13d**	**19**	(9.3:1.0):(1.3:1.9)	54[g]
6	**14a**	**13d**	**19**	(2.9:1.4):(1.0:0)	30[h]
7	**14a**	**13e**	**20**	(4.8:1):(1.1:17)	48 (82)
8	**14a**	**13f**	**21**	(5.0:1.0):(1.0:2.0)	60
9	**14b**	**13a**	**22**	(4.8:1.0):(1.2:1.8)	41 (75)
10	**14b**	**13c**	**23**	(6.3:1.0):(1.0:1.6)	57[i] (62)

[a] Standard conditions: nitrone (2 equiv), acetylene (1 equiv), CuI (1 equiv), TMG (2 equiv) in MeCN at rt.
[b] Determined by ^{1}H NMR and HPLC.
[c] The overall yield was determined by ^{1}H NMR of crude reaction mixture in $CDCl_3$ in the presence of trichloroethylene as an internal standard.
[d] Inseparable by chromatography mixture of **17**-*cis*-**I** and **17**-*trans*-**I** in ratio 3:1.
[e] Mixture of isomers in ratio 7.3:2.5:1 (**18**-*cis*-**I**:**18**-*trans*-**I**:**18**-*trans*-**II**), **18**-*cis*-**II** is more polar and was lost during the purification.
[f] TMG (4 equiv) was used.
[g] Reaction performed with 2 equiv of TMG.
[h] Reaction performed with 4 equiv of Et_3N.
[i] Mixture of isomers in ratio 7.7:1.0:1.5 (**23**-*cis*-**I**:**23**-*trans*-**II**:**23**-*trans*-**I**).

data show that the first step of cascade, cycloaddition, exhibits the preference of acetylene to approach to the *si* side of the nitrone and therefore to yield products with the (*S*) configuration at C-4 of azetidinone ring (**16**–**27** *cis*-**I** and **16**–**27** *trans*-**I**, Schemes 4 and 6). Interestingly, the protonation of (4*S*)-enolates proceeds with a higher selectivity, providing mostly *cis*-**I** products, whereas protonation of corresponding (4*R*)-enolates tends to yield a mixture of equal amounts of *cis*-**II** and *trans*-**II** azetidinones or with a slight excess of latter one.

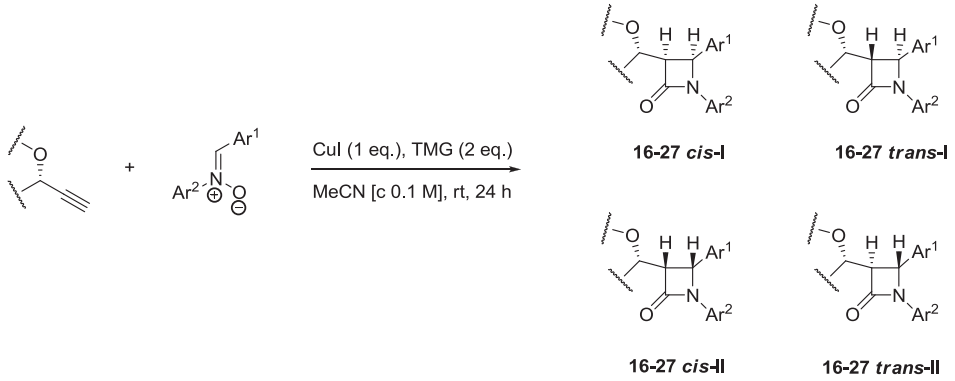
Table 2
The Kinugasa reaction of unprotected propargylic alcohols[a]

Entry	Acetylene	Nitrone	Product	Diastereoisomers ratio *cis*-**I**:*trans*-**I**:*cis*-**II**:*trans*-**II**[b,c]	Yield [%]
1	**15c**	**13e**	**24**	42:10:26:22	62[d]
2	**15b**	**13e**	**25**	45:26:18:11	65[d]
3	**15e**	**13e**	**26**	—	n.r.
4	**15a**	**13a**	**27**	42:9:26:23	57[d]

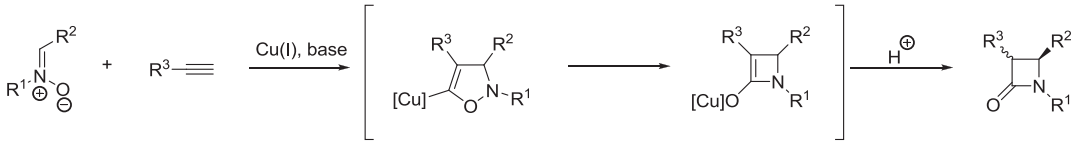
n.r.—no reaction.
[a] Standard conditions: nitrone (2 equiv), acetylene (1 equiv), CuI (1 equiv), TMG (2 equiv) in MeCN at rt.
[b] Determined by ^{1}H NMR and/or HPLC of crude mixture.
[c] For *cis/trans* description see Scheme 4.
[d] Isolated yield (mixture of isomers).

(Table 1, entry 2) in a high overall yield. For nitrone **13a** both effects are additive, therefore the reaction with this compound proceeded stereoselectively but with a moderate yield only (Table 1, entry 1).

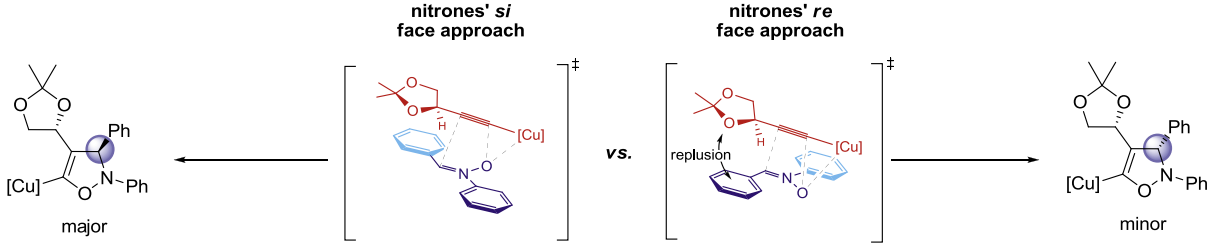
Next, we explored the use of unprotected chiral propargylic alcohols. It should be noted that such acetylenes have not been reported yet as reactants in Kinugasa reaction. First, we choose alcohol **15c** and the simplest nitrone **13e**. Gratifyingly, we found that formation of β-lactam proceeded in a good overall yield (62%) by using 2 equiv of copper iodide(I) (Table 2, entry 1). Unfortunately, chromatographically inseparable mixture of four possible isomers was formed. The absolute configuration of respective adducts was confirmed by HPLC-CD technique to indicate **24**-*cis*-**I** (for stereo description see Scheme 4) adduct as a major product (for



Scheme 4.



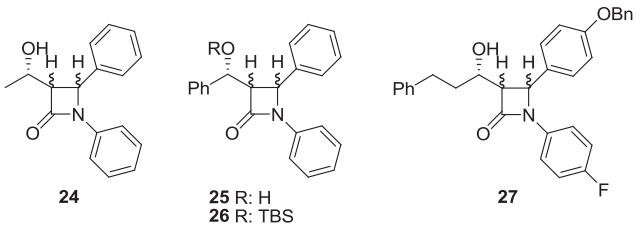
Scheme 5.



Scheme 6.

Additionally, as indicated by data presented in Table 1, both the yield and the stereoselectivity of these reactions are strongly related to the electronic nature of the nitrone. This can be easily followed comparing the results of the reaction of acetylene **14a** with nitrones **13b**, **13c**, and **13e** (Table 1, entries 2, 3, and 7). The reaction with nitrone bearing the *p*-fluorophenyl substituent at the nitrogen atom (**13c**) proceeded with a higher selectivity, to afford predominantly **18**-*cis*-**I** product, but with a lower overall yield in comparison with analogous reaction involving nitrone **13e**. On the other hand, the reaction of acetylene **14a** with nitrone **13b**, bearing a nucleophilic aryl in the benzylidene fragment, proceeded with a lack of selectivity to afford mixture of *cis*- and *trans*-azetidinones the determination of configuration *vide infra*). Somewhat better diastereoselectivity was obtained using alcohol **15b** with respect to (4*S*):(4*R*) ratio. The same result, in comparison to alcohol **15c**, was obtained with alcohol **15a** bearing a long side chain with nitrone **13a**. However, in contrast to outcome of other reactions, the final adducts were isolated as two mixtures: both *cis* diastereomers **27**-*cis*-**I**, **27**-*cis*-**II** and both *trans* ones **27**-*trans*-**I**, **27**-*trans*-**II**. Rather surprisingly, we did not observe formation of any products during the reaction with the silyl-protected analogs **15d** and **15e**, probably due to the steric reasons.

All biologically active *N*,4-diaryl-β-lactams **1**,**3**,**4**,**8** have the trans substituted four-membered ring, whereas Kinugasa reaction

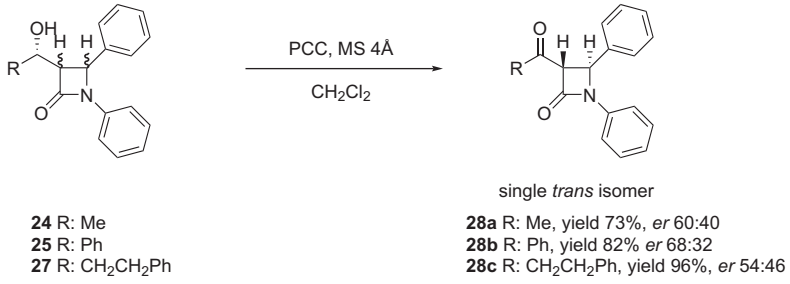


provides adducts with the *cis*-configuration. Epimerization of the cis adducts to the respective trans isomers could be achieved by the oxidation of the side-chain hydroxyl group to the ketone in **24**, **25** or **27** (Scheme 7), or by deprotection of the diol in the side chain followed by a silylation of the terminal group and oxidation of the secondary hydroxyl (such as alcohol **29**, Scheme 8). Subsequently, the base-catalyzed epimerization provided trans substituted β-lactam ring. In the case of the *vic*-diol derived from glyceraldehyde, glycolic cleavage led to the aldehyde, which easily epimerized in the presence of a base. Recently, this strategy has been exploited by us during the formal synthesis of Ezetimibe[18] and presently is demonstrated by formation of *trans* substituted β-lactams (see Scheme 2).

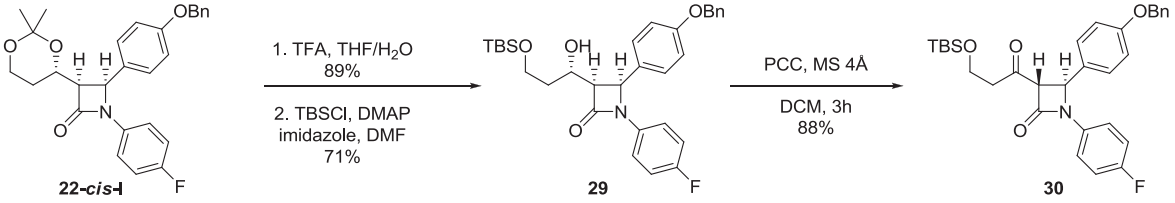
stressed that, the hydroxyl group at the side chain can be restored after epimerization by subsequent reduction of the keto function (Scheme 9).[31–39]

3. Determination of an absolute configuration

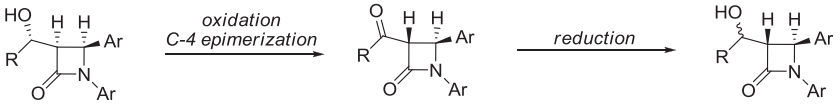
Chiroptical methods, and the electronic circular dichroism spectroscopy (ECD) in particular, appear to be convenient, sensitive, and fast techniques for the stereochemical assignments of azetidinones and their polycyclic derivatives in a solution as well as in the solid state.[40–42] Based on a broad variety of experimental data supported by the X-ray and computational studies, several sector and helicity rules for the correlation between the structure and Cotton effect (CE) signs of $n\rightarrow\pi^*$ transition have been established.[43–46] These rules allow to connect a negative CE associated with the $n\rightarrow\pi^*$ amide transition and the (4*R*) absolute configuration of azetidinones and a positive CE of the same excitation with their (4*S*) absolute configuration. Thus, we decided to use the ECD spectroscopy for a determination of the absolute stereochemistry at C4 carbon atom of compounds **16**-*cis*-**I**, **16**-*trans*-**I**, **16**-*cis*-**II**, **20**-*cis*-**I**, and **17**-*cis*-**I** isolated in a pure form from the reaction mixtures. It is important to note, however, that direct application of *CIP* rules for the stereochemistry designation at C4 in investigated compounds



Scheme 7.



Scheme 8.



Scheme 9.

The removal of a stereogenic center in the side chain of crude mixture of Kinugasa adducts by oxidation followed by a base epimerization led to the partially racemized product as a consequence of the ratio of (4*R*,4*S*) Kinugasa products (*cis*-**I**+*trans*-**I**:*cis*-**II**+*trans*-**II**). Moreover, bearing in mind that biologically active *N*,4-diarylazetidinones **1**,**3**–**5**,**7**,**8** have *trans* substituted β-lactam ring, the practical selectivity of the Kinugasa reaction depends on a ratio (*cis*-**I**+*trans*-**I**):(*cis*-**II**+*trans*-**II**) adducts because a base epimerization transforms all adducts *cis* into corresponding *trans* ones. Consequently in the case of target oriented synthesis only partial separation of the post reaction mixture is necessary. It should be may lead to a change of (*R*) and (*S*) descriptors depending on the identity of substituents without accompanying change of the actual stereochemical arrangement at C4 carbon atom. Therefore, for the azetidinones studied we decided to use the D and L nomenclature system, as defined in Fig. 1. According to this system, compounds with a positive 240 nm CE belong to the L series (**ii** in Fig. 1), whereas the negative sign of this CE indicates the membership of the D series (**i** in Fig. 1). Thus, compounds **16**-*cis*-**I**, **16**-*trans*-**I**, **20**-*cis*-**I**, and **17**-*cis*-**I** with a negative CE, appearing at around 240 nm, were attributed to the D series, whereas compound **16**-*cis*-**II** characterized by a positive CE at the same spectral range was assigned to the L series.

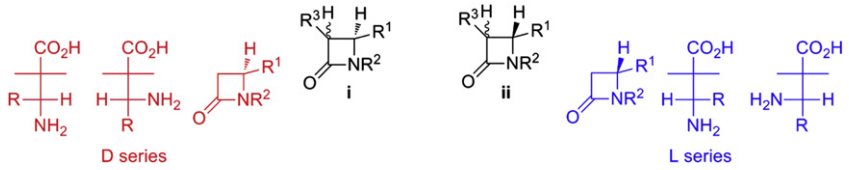


Fig. 1. Definition of the D- and L-series.

Regarding the absolute configuration, the (4*S*) configuration can be assigned to compounds **16**-*cis*-**I**, **16**-*trans*-**I**, **17**-*cis*-**I**, and **20**-*cis*-**I** from the D series, whereas the (4*R*) absolute configuration can be ascribed to the representative of the L series, compound **16**-*cis*-**II**. This assignment is additionally corroborated by the X-ray data of compounds **16**-*cis*-**I**, **18**-*cis*-**I**, and **23**-*cis*-**I** where the (4*S*) absolute configuration was independently confirmed (Fig. 2).[47]

The stereochemical analysis of crude post-reaction mixtures consisting of adducts with a different ratio of enantiomers or diastereoisomers was performed using the high-performance liquid chromatography with a circular dichroism detection in addition to the customary UV detection (on-line HPLC-CD). The combination of this methodology and NMR spectroscopy allowed for the full configurational assignment without the need to separate pure components from reaction mixtures. In the case of compound **28a** enantiomeric resolution was performed by HPLC-CD. The chromatogram of **28a** shows the presence of both enantiomers in the reaction mixture (Fig. 3, left). The assignment of the absolute configuration at C4 was made on the basis of the full LC-CD spectra recorded in the stop-flow mode. As shown in the Fig. 3 (right), the CD curves are almost mirror-shaped.

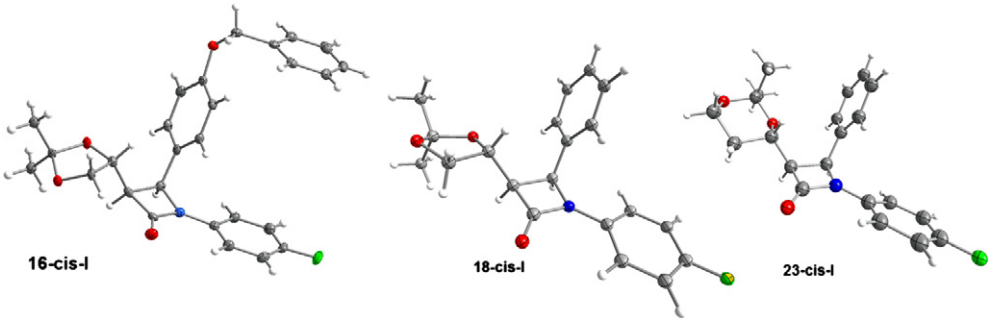


Fig. 2. Crystal structures of compound **16**-*cis*-**I**, **18**-*cis*-**I**, and **23**-*cis*-**I**.

To confirm that the same molecular species are present in a solid state and in a solution, ECD spectra of **16**-*cis*-**I** and **16**-*cis*-**II** were measured both in solid state as well as in the solution and then compared. The results obtained for the solid state measurement are in a good agreement with the respective data recorded in solution, as can be seen in Fig. 3. This conformity indicates that the solute–solvent interactions, which may affect the ECD spectra considerably due to both conformational and vicinal effects, are negligible and strongly suggests that the observed CD is largely a molecular property. Therefore, the analysis of the CD data for the purpose of determination of the absolute configuration of azetidinones **16**–**25** can be performed on the basis of chiroptical data obtained for solutions.

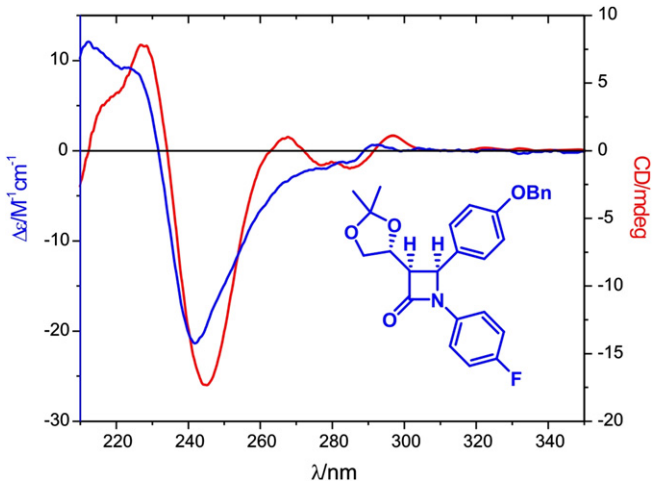


Fig. 3. Experimental ECD spectra for **16**-*cis*-**I** in acetonitrile solution (blue line) in $\Delta\varepsilon$ (M^{-1} cm^{-1}) and in KCl matrix (red line) in mdeg.

The positive sign of the CE at around 240 nm for the faster eluting peak indicates that it is belonging to the L series, whereas the negative CE in the same spectral region points to the membership of D series for the slower eluting peak. The stereochemical assignment at C3 carbon atom was done by comparing the coupling constants of protons (H3 and H4) located at C3 and C4 carbon atoms in the ^{1}H NMR spectrum (of reaction mixture). Coupling constant equal to 2.4 Hz indicates a *trans* relationship of both protons. Thus, the (3*R*,4*R*) absolute configuration can be attributed to the faster eluting enantiomer, whereas (3*S*,4*S*) absolute configuration to the slower eluting enantiomer.

The same combined procedure of LC-CD and NMR when applied to the mixture of enantiomers **28c** allowed to assign the absolute configuration at their C3 and C4 carbon atoms. The faster eluting peak is characterized by a positive CE at 250 nm while the slower eluting peak has a negative CE at 249 nm. Therefore, compound **28c** corresponding to the first peak could be attributed to the D series and compound *ent*-**28c**, related to the slower eluting peak, to the L series. The detailed ECD spectra recorded in the flow-stop mode and ^{1}H NMR coupling constants analysis leading to the assignment of (3*R*,4*R*) and (3*S*,4*S*) absolute configuration, respectively, are provided in the Supplementary data.

Much more complex and difficult was the stereochemical analysis of diastereomeric mixtures of **18**, **22**, **23**, and **24**. All these mixtures consisted of four components, with three-components differing in polarity only marginally. In all studied cases, the fourth compound has a significantly different retention time. A detailed discussion leading to the determination of absolute stereochemistry of all four

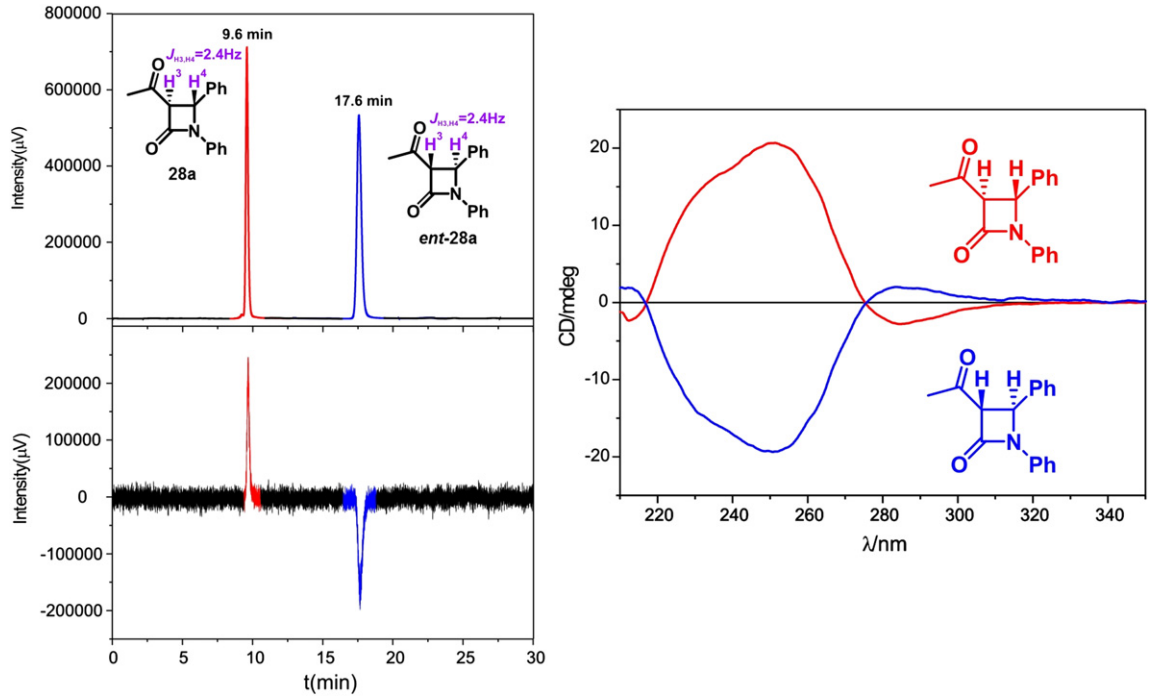


Fig. 4. Stereochemical assignment of the two enantiomers of **28a** by coupling of HPLC-CD with NMR spectroscopy; left: chromatogram of the **28a** mixture; right: CD spectra of **28a** (red line) and *ent*-**28a** (blue line) recorded in the stop-flow mode (Chiralpak® AD-H column, eluent *i*-PrOH/hexane 9:91 (v/v), flow 0.8 mL/min, detection at 250 nm).

components is presented here using as an example mixture **23**. For the first pass a mixture of MTBE/*n*-hexane 3:7 (v/v) as an eluent was used. Under these conditions, we could separate only the slowest component (Fig. 5, chromatogram 1). In its ECD spectrum recorded in the stop-flow mode the positive sign of the decisive CE at around 250 nm indicated the membership of the L-series. In addition, the coupling constant equal to 6.1 Hz in its ^{1}H NMR spectrum pointed to a *cis* arrangement of protons at C3 and C4. Based on the combined on-line HPLC-CD and NMR analysis the (3*S*,4*R*) absolute configuration could be ascribed to the slowest component of the mixture **23**.

Next, the mixture of remaining three-components was separated using an MTBE/*n*-hexane 15:85 (v/v) as eluant with a flow rate of 1 mL/min and UV/CD detection at $\lambda_{UV,CD}$=245 nm. Applying the stop-flow mode we were also able to register their individual ECD spectra (Fig. 5). The fastest and third consecutive components both had a negative CD in the $n\rightarrow\pi^*$ β-lactam amide transition spectral range, which allowed the assignment of both constituents to the D-series. The second fastest peak belonged to the component with a positive CE in the crucial spectral range thus indicating its membership in the L-series. The NMR coupling constant value equal to 2.4 and 2.6 Hz, measured for the fastest and the second fastest peaks of chromatogram, respectively, was indicative of the trans arrangement of protons at carbon atoms C3 and C4. On this basis, the (3*S*,4*S*) and (3*R*,4*R*) can be ascribed to the fastest and the second fastest peaks, respectively. The slowest peak was characterized by a *cis* orientation of protons at carbons C3 and C4, as indicated by the coupling constant of 5.6 Hz in its NMR spectrum. Accordingly, the (3*R*,4*S*) absolute configuration was assigned to this component of the reaction mixture. Thus, using HPLC-CD methodology combined with ^{1}H NMR analysis we could assign the absolute configuration of all four components of the reaction mixture without separation of individual components in a pure form.

Applying a similar combined HPLC-CD/NMR methodology we were able to fully characterize stereochemically all components of the other reaction mixtures. The analysis of **22** allowed to establish the absolute configuration of its four components in order from fastest to slowest eluting as follows: (3*R*,4*S*); (3*R*,4*R*); (3*S*,4*S*); (3*S*,4*R*), respectively. In the case of **18** and **24** the absolute configuration was assigned to be (3*S*,4*R*); (3*R*,4*R*); (3*S*,4*S*); and (3*R*,4*S*) in the order of elution from fastest to slowest, respectively.

Details of HPLC-CD and NMR analysis for all compounds are given in the experimental part and in Supplementary data.

In summary, the presented on-line HPLC-CD methodology, supported by ^{1}H NMR spectroscopy, proved to be a very valuable tool to determine the absolute configuration of the individual constituents of complex multi-component mixtures. One of the main advantages of such an approach is that it does allow to perform the full structural analysis without the need to isolate in a pure form the individual components of the mixture. It is particularly useful in cases where a separation or a purification of a multi-component mixture by traditional chromatography is very difficult or impossible. In addition, this methodology can be considered as a method of choice for fast assignment of the three dimensional structure when tested compounds are not sufficiently stable. For these reasons, it seems that the on-line HPLC-CD detection with the stop-flow mode will find an increased use both in the laboratories of modern organic chemistry and pharmaceutical chemistry as well.

4. Summary

The presented methodology enables an easy access to *N*,4-diaryl β-lactams with the defined configuration of C3 and C4 stereogenic centers, starting from readily available, inexpensive chiral acetylenes. All reactions are characterized by a moderate to good diastereoselectivity, and it could be further modulated by changing the electronic properties of the nitrone. The best results, from the point of selectivity, were obtained for nitrones bearing electron-withdrawing group (e.g., Ts or Ms). Bearing in mind that interesting *N*,4-diaryl-azetidinones have trans substituted β-lactam ring, the practical selectivity of the Kinugasa reaction depends on a ratio (*cis*-**I**+*trans*-**I**):(*cis*-**II**+*trans*-**II**) adducts. It was also demonstrated for the first time that the unprotected chiral propargylic alcohol could be utilized in the Kinugasa reaction. The respective

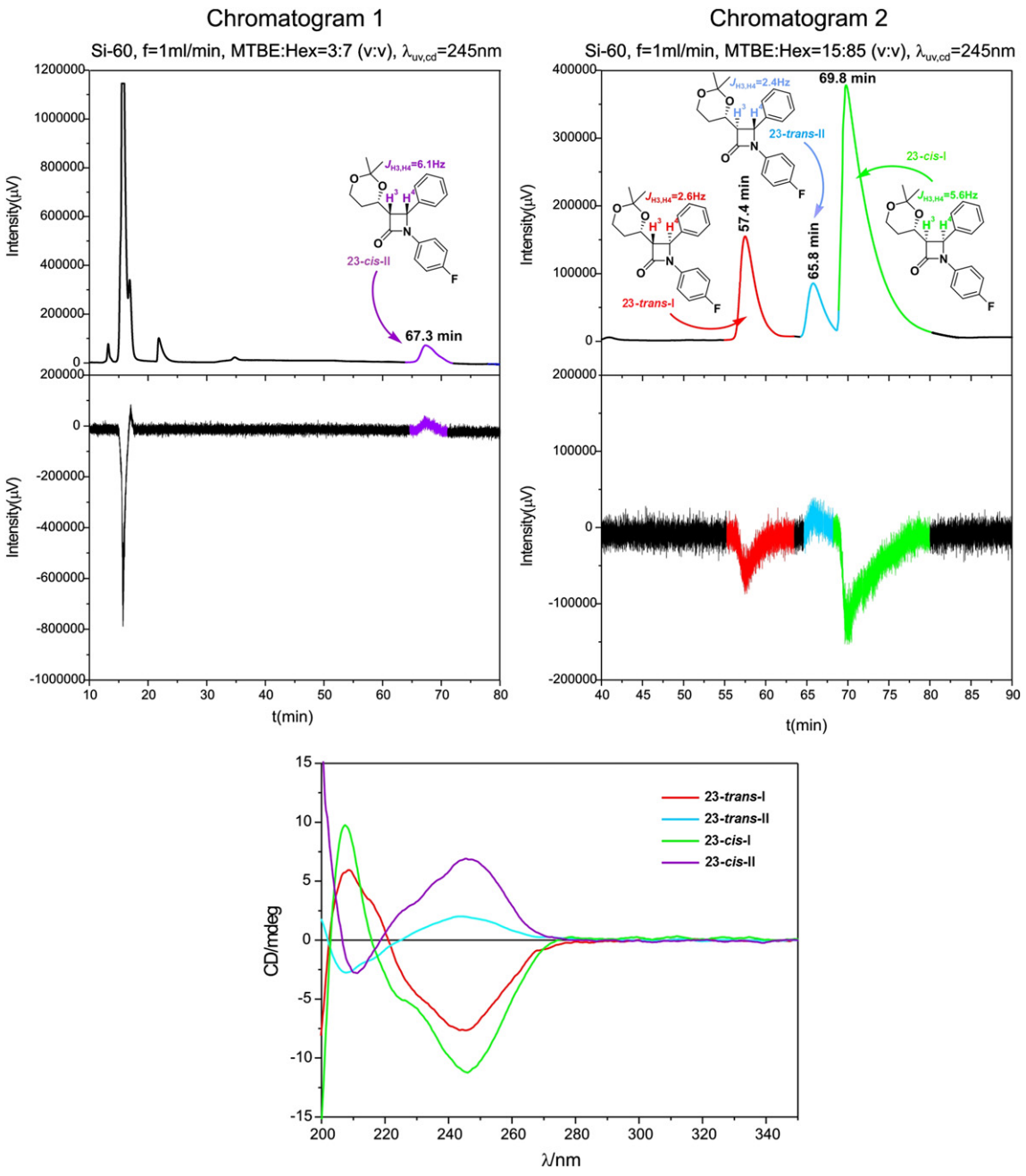


Fig. 5. Stereochemical assignment of the four diastereoisomers of **23** by coupling of HPLC-CD with NMR spectroscopy; top: two chromatograms of the **23** mixture; bottom: CD spectra of **23**-*trans*-**I** (red line), **23**-*trans*-**II** (blue line), **23**-*cis*-**I** (green line), and **23**-*cis*-**II** (violet line) recorded in the stop-flow mode (LiChrospher® Si60 column and mixtures of MTBE/*n*-hexane as the mobile phase with a flow rate of 1 mL/min).

adducts were subsequently oxidized/epimerized by treatment with PCC affording pure derivatives of *trans* azetidinone, which is a common framework of many antibiotics.

5. Experimental procedures

5.1. General

The NMR spectra were recorded on Varian VNMRS 500 MHz and Varian VNMRS 600 MHz spectrometers. Chemical shifts are reported in δ units and coupling constants are reported in hertz. High resolution mass spectra (HRMS) were taken using AMD-604 spectrometer (for electron ionization, 70 eV) or on Mariner spectrometer (for electrospray ionization). Infrared spectra were recorded on Jasco-V670 spectrophotometer. Optical rotatory was recorded on Jasco P-2000 polarimeter. Melting points were determined on a hot-stage apparatus and are uncorrected.

HPLC-CD measurements were performed with the Jasco HPLC system equipped with a PU-2089 quaternary gradient pump, the UV-2075 UV-detector and Jasco J-815 spectropolarimeter as a CD-detector. The 1 mg sample was dissolved in 1 mL of mobile phase and filtered through a 0.45 μm Nylon syringe filter. Injection volumes for all samples were 20 μL. Separations were performed with LiChrospher® Si60 column (5 μm, 250×4.6) using mixtures of MTBE and hexane as a mobile phase with a flow rate in range 0.8–1.0 mL/min or with Daicel Chiralpak® AD-H or Daicel Chiracel® OD-H chiral column (5 μm, 250×4.6) using mixtures of *i*-PrOH and hexane as a mobile phase with a flow rate in range 0.6–0.8 mL/min.

All solvents were dried and purified by known techniques.[48] *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) was purchased from

Sigma–Aldrich and used without further purification. Nitrones **13a**[18] and **13e**[49] were prepared following literature procedures. Merck silica gel, 230–400 mesh was used for flash column chromatography.

*5.1.1. N-Phenyl-α-(4-benzyloxyphenyl)nitrone (**13b**).* Nitrone **13b** was synthesized following literature procedure[18] starting from *N*-phenylhydroxylamine (5.46 g, 50.0 mmol), *p*-benzyloxybenzaldehyde (10.61 g, 50.0 mmol), CH_3SO_3H (4 drops), and acetone (100 mL). Nitrone **13b** was obtained as a off-white solid (6.1 g, 40%). Mp 157–159 °C (acetone); IR (film): 3050, 3035, 1603, 1550 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 8.42–8.38 (m, 2H), 7.84 (s, 1H), 7.78–7.74 (m, 2H), 7.48–7.31 (m, 8H), 7.08–7.04 (m, 2H), 5.13 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) 160.7, 149.0, 136.4, 134.1, 131.1, 129.6, 129.1, 128.7, 128.2, 127.5, 124.0, 121.7, 114.9, 70.1; HRMS (EI) *m*/*z* calcd for $C_{20}H_{17}NO_2$: 303.1259; found: 303.1252.

*5.1.2. N-(4-Fluorophenyl)-α-phenylnitrone (**13c**).* Nitrone **13c** was synthesized following literature procedure[18] starting from *N*-(*p*-fluorophenyl)-hydroxylamine (5.95 g, 46.8 mmol), benzaldehyde (4.7 mL, 46.8 mmol), CH_3SO_3H (3 drops), and acetone (70 mL). Nitrone **13c** was obtained as a off-white solid (4.8 g, 50%). Mp 170–171 °C (EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.45–8.36 (m, 2H), 7.88 (s, 1H), 7.84–7.76 (m, 2H), 7.56–7.45 (m, 3H), 7.20–7.12 (m, 2H), 5.13 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.0 (J_{CF} 248.8 Hz), 145.3, 134.5, 131.1, 128.8 (J_{CF} 40.0 Hz), 123.7 (J_{CF} 8.8 Hz), 116.0 (J_{CF} 22.5 Hz); HRMS (EI) *m*/*z* calcd for $C_{13}H_{10}FNO$: 215.0746; found: 215.0737; El. Anal. calcd for $C_{13}H_{10}FNO$: C 72.55; H 4.68, F 8.83, N 6.51. Found: C 72.68, H 4.54, N 6.63, F 8.74.

*5.1.3. N-(4-Fluorophenyl)-α-(4-tosyloxyphenyl)nitrone (**13d**).* Nitrone **13d** was synthesized following literature procedure[18] starting from *N*-(*p*-fluorophenyl)-hydroxylamine (2.75 g, 21.6 mmol), *p*-tosyloxybenzaldehyde (5.96 g, 21.6 mmol), CH_3SO_3H (1 drop), and acetone (50 mL). Nitrone **13d** was obtained as a white solid (5.58 g, 67%). Mp 172–174 °C (acetone); IR (film): 3097, 3060, 1596, 1504, 1380 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) 8.51 (s, 1H), 8.48–8.44 (m, 2H), 7.98–7.94 (m, 2H), 7.77–7.74 (m, 2H), 7.49–7.46 (m, 2H), 7.42–7.36 (m, 2H), 7.18–7.14 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) 162.4 (d, J_{CF} 205.0 Hz), 149.6, 146.0, 144.7 (d, J_{CF} 2.4 Hz), 132.5, 131.2, 130.4, 130.3, 130.1, 128.3, 123.8 (d, J_{CF} 7.5 Hz), 122.1, 115.9 (d, J_{CF} 19.3 Hz), 21.2; ^{19}F NMR (470 MHz, DMSO-d_6) δ: −111.3 (m); El. Anal. calcd for $C_{20}H_{16}FNO_4S$ C, 62.33; H, 4.18; F, 4.93; N, 3.63; S, 8.32. Found: C, 61.93; H, 4.32; F, 5.13; N, 3.52.

*5.1.4. N-(4-Fluorophenyl)-α-(4-mesyloxyphenyl)nitrone (**13f**).* Nitrone **13f** was synthesized following literature procedure[18] starting from *N*-(*p*-fluorophenyl)-hydroxylamine (3.18 g, 25.0 mmol), *p*-mesyloxybenzaldehyde (5.00 g, 25.0 mmol), CH_3SO_3H (1 drop), and acetone (50 mL). Nitrone **13f** was obtained as a white solid (3.18 g, 41%). Mp 158–160 °C (acetone); IR 1603, 1506, 1373 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) 8.61–8.57 (m, 2H) overlapping 8.59 (s, 1H), 8.02–7.97 (m, 2H), 7.51–7.47 (m, 2H), 7.43–7.37 (m, 2H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) 162.4 (d, J_{CF} 205.1 Hz), 149.8, 144.8, 132.5, 130.6, 130.1, 123.8 (d, J_{CF} 7.5 Hz), 122.3, 115.9 (d, J_{CF} 19.3 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) −111.7 (m); HRMS (EI) *m*/*z* calcd for $C_{14}H_{12}FNO_4S$: 309.0471; found: 309.0472.

5.2. Kinugasa reaction—general procedure

The Schlenk flask was charged with copper(I) iodide (1 mmol), purged with argon and degassed MeCN (5 mL), followed by *N*,*N*,*N*′,*N*′-tetramethylguanidine (2 mmol) were added. After cooling to 0 °C, acetylene (1 mmol) was added and the yellow mixture was stirred for 15 min. The second Schlenk flask was charged with nitrone (1.5–2 mmol), purged with argon and degassed MeCN was added (5 mL). Subsequently, solution of copper acetylide was cannulated into suspension of nitrone. After stirring for 20 h at rt under argon atmosphere, the reaction mixture was diluted with AcOEt (10 mL) and H_2O (10 mL). Aqueous phase was separated and washed with AcOEt (2×50 mL). Combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The diastereoisomer ratio of β-lactamic products was assigned by ^1H NMR and HPLC of crude reaction mixture. The products was isolated by column chromatography on silica gel (hexane/AcOEt mixtures). Pure *cis*-**I** isomers were obtained by recrystallization from EtOH.

*5.2.1. Azetidinone **16**-cis-**I**.* Mp 150–152 °C (EtOH); $[\alpha]_D^{25}$ −74 (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ: 7.20 (m, 2H), 7.12 (m, 2H), 7.06 (m, 2H), 7.01 (m,1H), 7.86 (d, *J* 14 Hz, 2H), 6.69 (d, *J* 14 Hz, 2H), 6.61 (m, 2H), 4.55 (m, 2H), 4.45 (d, *J* 5.8 Hz, 1H), 4.13 (dd, *J* 8.5, 6.5 Hz, 1H), 3.94 (dd, *J* 8.5, 6.1 Hz, 1H), 3.81 (dt, *J* 9.4, 6.1 Hz, 1H), 3.33 (dd, *J* 9.4, 5.8 Hz, 1H), 1.30 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 162.9, 159.7, 158.8 (d, J_{CF} 241.5 Hz), 158.1, 136.9, 134.2 (d, J_{CF} 2.6 Hz), 128.3, 128.0, 126.3, 118.4 (d, J_{CF} 7.6 Hz), 115.6 (d, J_{CF} 22.5 Hz), 115.3, 114.8, 108.5, 71.0, 69.6, 67.3, 58.7, 57.0, 26.8, 25.1; ^{19}F NMR (470 MHz) δ: −117.4 (m); IR (film): 1748, 1510 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{26}NO_4FNa$ [M+Na^+] 470.1738; found: 470.1754; El. Anal. calcd for $C_{27}H_{26}NO_4F$, C 72.47, H 5.86, N 3.13, F 4.25; found: C 72.39, H 5.78, N 3.15, F 4.32.

*5.2.2. Azetidinone **17**-cis-**I**.* Mp 142 °C (EtOH); $[\alpha]_D^{25}$ −94.5 (*c* 0.62, $CHCl_3$); IR (film): 2989, 1747, 1612, 1599 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.44–7.36 (m, 4H), 7.35–7.25 (m, 5H), 7.24–7.19 (m, 2H), 7.09–7.04 (m, 1H), 6.99–6.94 (m, 2H), 5.29 (d, *J* 5.4 Hz, 1H), 4.01–3.93 (m, 2H), 3.89–3.83 (m, 1H), (dd, *J* 9.0, 6.0 Hz, 1H), 1.36 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.8, 158.7, 137.4, 136.7, 129.1, 128.6, 128.4, 128.0, 124.0, 117.2, 114.9, 108.6, 70.1, 70.0, 67.3, 58.1, 57.1, 26.8, 25.4; HRMS (EI) *m*/*z* calcd for $C_{27}H_{27}NO_4$: 429.1940; found: 429.1934.

*5.2.3. Azetidinone **18**-cis-**I**.* $[\alpha]_D^{25}$ +77.9 (*c* 0.66, CH_2Cl_2); mp 113–115 °C (EtOH); ^1H NMR (600 MHz, $CDCl_3$) δ: 7.40–7.24 (m, 7H), 7.00–6.92 (m, 2H), 5.30 (d, *J* 5.5 Hz, 1H), 3.97 (dd, *J* 8.4, 5.8 Hz, 1H), 3.93 (dd, *J* 8.4, 6.6 Hz, 1H), 3.84 (ddd, *J* 9.2, 6.6, 5.8 Hz, 1H), 3.79 (dd, *J* 9.2, 5.5 Hz, 1H), 1.34 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 163.4, 159.1 (d, J_{CF} 243.8 Hz), 133.8, 133.6, 128.6, 128.4, 127.1, 118.6 (d, J_{CF} 7.9 Hz), 115.9 (d, J_{CF} 22.7 Hz), 108.6, 70.8, 67.3, 58.2, 57.6, 26.8, 25.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −117.6 (m); IR (film) *v*: 1750, 1511 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}NO_3FNa$ [M+Na^+] 364.1325; found 364.1330.

*5.2.4. Azetidinone **19**-cis-**I**.* Mp 157–159 °C (EtOH/hexane); $[\alpha]_D^{25}$ −81.6 (*c* 0.53, $CHCl_3$); IR ($CHCl_3$): 2986, 2935, 1752, 1511, 1373 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.68 (br d, *J* 7.8 Hz, 2H), 7.28 (br d, *J* 7.8 Hz, 2H), 7.24–7.19 (m, 4H), 7.02–6.94 (m, 4H), 3.77–3.70 (m, 2H), 2.44 (s, 3H), 1.33 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.3 (d, J_{CF} 202.4 Hz), 136.7 (d, J_{CF} 13.6 Hz), 129.8 (d, J_{CF} 30.8 Hz), 115.2 (d, J_{CF} 85.6 Hz), 84.5, 73.4, 61.4, 39.1, 30.4; ^{19}F NMR (376 MHz) δ −117.8 (m); HRMS (EI) *m*/*z* calcd for $C_{27}H_{26}O_6NFS$: 511.1465; found: 511.1443.

*5.2.5. Azetidinone **20**-cis-**I**.* Mp 153–155 °C (EtOH); $[\alpha]_D^{25}$ −125.1 (*c* 0.57, $CHCl_3$); IR (film): 1749, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.19 (m, 9H), 7.06–6.98 (m, 1H), 5.29 (d, *J* 5.2 Hz, 1H), 3.97–3.87 (m, 2H), 3.83–3.71 (m, 2H), 1.31 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 137.4, 134.1, 129.1, 128.5, 128.3, 127.2, 124.1, 117.1, 108.6, 70.9, 67.3, 57.9, 57.4, 26.8, 25.3; HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}O_3N$: 323.1521; found: 323.1536.

*5.2.6. Azetidinone **21**-cis-**I**.* Mp 148–151 °C (EtOH); $[\alpha]_D^{25}$ −81.7 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$): 2987, 2938, 1750, 1510, 1371 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.38–7.33 (m, 2H), 7.32–7.22 (m, 4H), 5.33 (d, *J* 4.8 Hz, 1H), 4.05–4.01 (m, 1H), 3.94–3.89 (m, 1H), 3.81–3.75 (m, 2H), 3.16 (s, 3H), 1.34 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ: 163.0, 159.2 (d, J_{CF} 202.3 Hz), 148.9, 133.4, 133.3 (d, J_{CF} 2.1 Hz), 128.9, 122.2, 118.5 (d, J_{CF} 6.5 Hz), 116.1 (d, J_{CF} 18.9 Hz), 108.0, 70.7, 67.3, 58.3, 56.9, 37.6, 26.8, 25.2; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{22}NO_6FS$: 458.1044; found: 458.1056.

5.2.7. Azetidinone ***22****-cis-****I****.* $[\alpha]_D^{25}$ −76 (*c* 0.38, CH_2Cl_2); mp 128–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.43–7.15 (m, 9H), 6.97–6.88 (m, 4H), 5.17 (d, *J* 5.5 Hz, 1H), 5.06 (s, 2H), 3.82–3.74 (m, 3H), 3.57 (dd, *J* 10.6, 5.6 Hz, 1H), 1.82–1.73 (m, 2H), 1.10 (s, 3H), 0.54 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 163.9, 158.9 (d, J_{CF} 243.5 Hz), 158.6, 136.7, 133.7, 128.6, 128.0, 127.3, 126.3, 118.6 (d, J_{CF} 7.8 Hz), 115.8 (d, J_{CF} 22.7 Hz), 114.6, 98.0, 69.9, 64.7, 59.5, 59.4, 57.3, 29.7, 29.4, 17.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −117.9 (m); IR (CH_2Cl_2) *v*: 1751, 1511 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{28}FNO_4Na$ [M+Na$^+$] 484.1900; found 484.1896.

5.2.8. Azetidinone ***23****-cis-****I****.* $[\alpha]_D^{25}$ −108.6 (*c* 0.55, CH_2Cl_2); mp 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.24 (m, 7H), 6.97–6.91 (m, 2H), 5.23 (d, *J* 5.6 Hz, 1H), 3.83–3.74 (m, 3H), 3.63 (dd, *J* 10.6, 5.6 Hz, 1H), 1.85–1.73 (m, 2H), 1.12 (s, 3H), 0.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.8, 159.0 (d, J_{CF} 243.7 Hz), 134.2, 133.6 (d, J_{CF} 2.8 Hz), 128.2, 127.5, 118.6 (d, J_{CF} 7.8 Hz), 115.8 (d, J_{CF} 22.7 Hz), 98.0, 64.7, 59.5, 59.4, 57.7, 29.7, 29.4, 17.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −117.8 (m); IR (film): 1754, 1509 cm^{-1}; HRMS *m*/*z* calcd for $C_{21}H_{22}NO_3FNa$ [M+Na$^+$] 378.1476; found 378.1489.

5.2.9. Azetidinones ***24****.* To a suspension of CuI (723.7 mg, 3.80 mmol, 2.0 equiv) in CH_3CN (19 mL), (*S*)-but-3-yn-2-ol (133.2 mg, 1.90 mmol) was added dropwise at 0 °C. After 15 min, nitrone **13e** (449.7 mg, 2.28 mmol) was added as a solid at this temp, and stirring was continued for 16 h at rt. The reaction mixture was diluted with water (40 mL) and aq ammonia (40 mL), and extracted with EtOAc (2×30 mL). The combined extracts were washed with brine (2×10 mL), dried over $MgSO_4$, and evaporated. The reside was purified by chromatography on silica (10% EtOAc/DCM) to give a product as a white solid (314.7 mg, 62%, mixture of four disatereoisomer in a ratio *cis*-**I**:*cis*-**II**:*trans*-**I**:*trans*-**II** 4.2:2.6:2.2:1). The configuration of a mixture of diastereoisomers was confirmed by UV-CD HPLC analysis: LiChrospher® Si60 20% MTBE in hexane, 1 mL/min; t_R 143.5 min (**24**-*cis*-**I**), 154.8 min (**24**-*trans*-**II**), 176.0 min (**24**-*trans*-**I**), 191.0 min (**24**-*cis*-**II**); IR (film): 3456, 3063, 2970, 2927, 1746, 1599 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.43–7.37 (m, 1H), 7.35–7.11 (m, 6H), 7.00–6.92 (m, 1H), 5.19 (d, *J* 5.4 Hz, 0.32×1H), 5.12 (d, *J* 6.0 Hz, 0.18×1H), 5.03 (d, *J* 2.4 Hz, 0.16×1H), 4.82 (d, *J* 2.4 Hz, 0.08×1H), 4.31–4.24 (m, 0.20×1H), 4.21–4.13 (m, 0.13×1H), 3.79–3.70 (m, 0.52×1H), 3.51 (dd, *J* 10.2, 6.0 Hz, 0.32×1H), 3.42 (dd, *J* 7.8, 5.4 Hz, 0.18×1H), 3.07 (dd, *J* 6.0, 2.4 Hz, 0.08×1H), 3.05 (dd, *J* 4.8, 2.4 Hz, 0.16×1H), 1.33 (d, *J* 6.0, 0.12×3H), 1.28–1.27 (m, 0.63×3H), 0.83 (d, *J* 6.0 Hz, 0.25×3H); ^{13}C NMR (150 MHz): 166.6, 165.9, 165.7, 164.6, 138.0, 137.6, 137.4, 137.4, 137.3, 137.1, 134.7, 134.5, 134.4, 134.0, 131.0, 130.6, 129.9, 129.7, 129.2, 129.1, 129.0, 129.0, 129.0, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 127.0, 127.0, 125.9, 125.9, 67.2, 66.3, 66.0, 65.1, 64.9, 63.9, 62.1, 60.3, 57. 7, 57.5, 56.8, 29.6, 22.6, 21.6, 21.3, 20.9; HRMS (EI) *m*/*z* calcd for $C_{23}H_{27}NO_5$: 267.1259; found: 267.1265.

5.2.10. Azetidinones ***25****.* To a suspension of CuI (190 mg, 1 mmol) and TMG (250 μL, 2 mmol) in MeCN (5 mL), (*R*)-1-phenylprop-2-yn-1-ol (132 mg, 1 mmol) was added dropwise at 0 °C. After 15 min, a solution of nitrone **13e** (394 mg, 2 mmol) in MeCN (5 mL) was added at this temp, and stirring was continued for 20 h at rt. The reaction mixture was diluted with water (10 mL) and aq ammonia (10 mL), and extracted with EtOAc (2×15 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$, and evaporated. The reside was purified by chromatography on silica (20% AcOEt/hexane) to give a product as a yellow solid (214 mg, 65%, mixture of four diastereoisomer in a ratio *cis*-**I**:*cis*-**II**:*trans*-**I**:*trans*-**II** 0.52:0.12:0.31:0.05). The configuration of a mixture of diastereoisomers was confirmed by UV-CD HPLC analysis: LiChrospher® Si60 column, 30% MTBE in hexane, 1 mL/min; t_R 11.5, 13.4, 15.5, and 60.2 min; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48–6.65 (m, 15H), 5.38 (d, *J* 4.0 Hz, 0.31×1H), 5.34 (d, *J* 5.8 Hz, 0.12×1H), 5.16 (d, *J* 2.5 Hz, 0.31×1H), 5.13 (d, *J* 7.2 Hz, 0.05×1H), 5.09 (d, *J* 6.0 Hz, 0.52×1H), 4.81 (d, *J* 2.5 Hz, 0.05×1H), 4.69 (d, *J* 10.0 Hz, 0.12×1H), 4.67 (d, *J* 9.0 Hz, 0.52×1H), 4.01 (dd, *J* 10.0, 5.8 Hz, 0.12×1H), 3.99 (dd, *J* 9.0, 6.0 Hz, 0.52×1H), 3.44 (dd, *J* 7.2, 2.5 Hz, 0.05×1H), 3.43 (dd, *J* 4.0, 2.5 Hz, 0.31×1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 166.3, 165.5, 141.1, 140.1, 137.6, 137.5, 137.1, 134.7, 134.5, 133.7, 130.9, 130.6, 129.9, 129.2, 129.1, 129.1, 129.0, 129.0, 128.9, 128.8, 128.6, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.9, 127.4, 126.8, 126.6, 125.7, 125.5, 124.1, 123.9, 121.7, 117.3, 117.2, 117.10, 117.07, 71.4, 70.1, 69.7, 66.9, 61.6, 59.7, 58.3, 57.6, 55.7, 46.0, 31.9, 29.7, 29.3, 22.7, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{19}NO_2Na$ [M+Na$^+$] 352.1308; found 352.1318.

5.2.11. Azetidinones ***27****.* To a suspension of CuI (380.9 mg, 2.0 mmol) in anhydrous CH_3CN (2 mL), TMG (0.25 mL, 2.0 mmol) was added followed by solution of (*S*)-5-phenylpent-1-yn-3-ol (160.2 mg, 1.0 mmol) in CH_3CN (2 mL) at 0 °C. After 15 min at this temp, nitrone **13e** (417.8 mg, 1.3 mmol) was added and stirred for 16 h at rt. Then reaction mixture was diluted with water (40 mL) and extracted with EtOAc (2×15 mL). The combined organic extracts were washed with 10% solution of citric acid (2×10 mL), brine (1×20 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (30–40% MTBE/hexane) to give a mixture of azetidinones **27**-*cis*-**I** and **27**-*cis*-**II** in ratio 67:33 (180.3 mg; based on ^{1}H NMR) and **27**-*trans*-**I** and **27**-*trans*-**II** in ratio 46:54 (90.3 mg; after crystallization from EtOH/hexanes; based on ^{1}H NMR); total yield 56%). The configuration of a mixture of diastereoisomers was confirmed by UV-CD HPLC analysis: LiChrospher® Si60 column, 30% MTBE in hexane, 0.8 mL/min; t_R 27.7 (**27**-*trans*-**I**), 29.5 (**27**-*trans*-**II**), 57.1 (**27**-*cis*-**II**), and 74.7 (**27**-*cis*-**I**) min; Mixture of azetidinones **27**-*trans*-**I** and **27**-*trans*-**II** IR (film): 3443, 3029, 2930, 1743, 1510 cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ: 7.32–7.23 (m, 2H), 7.18–6.99 (m, 10H), 6.94–6.89 (m, 1H), 6.84–6.80 (m, 1H), 6.72–6.67 (m, 2H), 6.62–6.56 (m, 2H), 4.82 (d, *J* 2.6 Hz, 0.46×1H), 4.64–4.55 (m, 1H), 4.47 (d, *J* 2.6 Hz, 0.54×1H), 3.89–3.80 (m, 0.54×1H), 3.71–3.64 (m, 0.46×1H), 2.89 (dd, *J* 5.6, 2.4 Hz, 0.46×1H), 2.84 (dd, *J* 4.6, 2.4 Hz, 0.54×1H), 2.70–2.39 (m, 2H), 2.13 (d, *J* 5.2 Hz, 0.54×1H), 1.99–1.86 (m, 0.46×1H +1H), 1.75–1.64 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ: 165.3, 165.1, 159.9, 159.0, 158.9, 157.9, 141.6, 141.5, 136.9, 136.8, 134.3, 134.2, 130.2, 129.7, 128.5, 128.4, 128.4, 128.4, 127.9, 127.7, 127.56, 127.2, 127.2, 125.9, 118.3, 118.3, 115.7, 115.5, 115.4, 115.4, 69.7, 68.7, 67.8, 66.5, 65.9, 57.2, 56.3, 37.1, 36.8, 31.8, 31.7; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{28}NO_3FNa$ [M+Na$^+$] 504.1945; found 504.1946. Mixture of azetidinones **27**-*cis*-**I** and **27**-*cis*-**II** IR (film): 3463, 3028, 2923, 1744 cm^{-1}; ^{1}H NMR (600 MHz, benzene-d_6) δ: 7.21–6.95 (m, 14H), 6.83–6.79 (m, 2H), 6.67–6.56 (m 4H), 4.63–4.54 (m, 2H), 4.43 (d, *J* 5.7 Hz, 0.67×1H), 4.19 (d, *J* 5.8 Hz, 0.33×1H), 3.63–3.57 (m, 0.67×1H), 3.53–3.48 (m, 0.33×1H), 3.26 (dd, *J* 10.4, 5.7 Hz, 0.67×1H), 3.26 (dd, *J* 10.4, 5.7 Hz, 0.33×1H), 2.80–2.74 (m, 0.67×1H), 2.65–2.59 (m, 2.57–2.50 (m, 1H), 2.44–2.33 (m, 1H), 1.92–1.85 (m, 0.67×1H), 1.53–1.46 (m, 0.33×1H), 1.24–1.15 (m, 1H); ^{13}C NMR (150 MHz, benzene-d_6) δ: 166.1, 163.8, 159.6, 159.0, 159.0, 158.0, 141.9, 141.6, 136.8, 136.7, 134.2, 133.9, 128.5, 128.4, 128.2, 128.2, 128.0, 127.3, 126.4, 125.8, 125.7, 125.5, 118.4, 118.4, 118.3, 118.2, 115.7, 115.5, 115.2, 114.9, 69.8, 69.7, 67.2, 66.8, 61.2, 59.4, 57.2, 56.9, 36.9, 36.4, 31.6, 31.2, 31.2; HRMS (ESI) *m*/*z* calcd for [M+Na$^+$] $C_{31}H_{28}FNO_3Na$: 501.1945; found 501.1959.

5.2.12. Azetidinone ***28a****.* To a solution of a mixture of alcohols **24** (185.8 mg, 0.70 mmol) in DCM (10 mL), molecular sieves 4 Å

(224.8 mg) and PCC (224.8 mg, 0.70 mmol) were added and stirred for 4.5 h at rt. Then reaction mixture was passed through pad of Florisil (10 mL), washed with 20% EtOAc/hexanes (20 mL) and evaporated. The crude product was chromatographed on silica (10 g, 10% EtOAc/hexanes) to give ketone **28a** a colorless oil (135.2 mg, 73%). Er 3:2 by HPLC, Daicel Chiralpak® AD-H column, 2% *i*-PrOH in hexane, 1.0 mL/min (Fig. 4); IR (film): 3065, 3033, 1754, 1716, 1501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.30 (m, 5H), 7.29–7.21 (m, 4H), 7.09–7.02 (m, 1H), 5.48 (d, *J* 2.4 Hz, 1H), 4.14 (d, *J* 2.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.8, 160.2, 137.1, 136.5, 129.2, 129.1, 128.7, 126.1, 117.0, 71.8, 55.5, 29.9; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{15}NO_2Na$ [M+Na^+]: 265.3065; found: 265.3069.

*5.2.13. Azetidinone **28b**.* To a solution of a mixture of alcohols **25** (100 mg, 0.30 mmol) in CH_2Cl_2 (5 mL), molecular sieves 4 Å (200 mg), and PCC (196 mg, 0.91 mmol) were added and stirred for 3 h at rt. Then reaction mixture was diluted with Et_2O and passed through pad of Celite and evaporated to give ketone **28b** as a yellowish oil (81 mg, 82%). Er 69:31 by HPLC: Daicel Chiracel® OD-H column, eluent 10% *i*-PrOH/hexane, 1.0 mL/min; t_R 8.4 and 9.6 min ^1H NMR (600 MHz, $CDCl_3$) δ: 7.60 (t, *J* 7.4 Hz, 1H), 7.51 (t, *J* 7.8 Hz, 2H), 7.46–7.42 (m, 2H), 7.39 (t, *J* 7.4 Hz, 2H), 7.36–7.22 (m, 5H), 7.06 (t, *J* 7.4 Hz, 1H), 5.77 (d, *J* 2.5 Hz, 1H), 4.83 (d, *J* 2.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 190.5, 160.0, 137.3, 136.8, 135.7, 134.0, 129.4, 129.3, 129.1, 128.8, 128.74, 126.2, 124.3, 117.1, 68.9, 55.8, 29.7; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{17}NO_2Na$ [M+Na^+] 350.1152; found 350.1162.

*5.2.14. Azetidinone **28c**.* To a solution of alcohol **27** (282.2 mg, 0.59 mmol) in dichloromethane (10 mL), molecular sieves 4 Å (380 mg) and PCC (380.0 mg, 0.56 mmol) were added, and stirred for 3 h at rt. Then reaction mixture was passed through pad of Florisil (5 g), washed with 20% EtOAc/hexanes (20 mL) and evaporated to give ketolactam **28c** as a colorless oil (270.1 mg, 96%). IR (film): 3063, 3030, 2931, 1754, 1713 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.43–7.36 (m, 4H), 7.35–7.31 (m, 1H), 7.28–7.17 (m, 9H), 6, 98–6.92 (m, 4H), 5.37 (d, *J* 2.4 Hz, 1H), 5.05 (s, 2H), 4.08 (d, *J* 2.4 Hz, 1H), 3.15–3.08 (m, 1H), 3.00–2.92 (m, 2H), 2.91–2.83 (m, 1H); ^{13}C NMR (125 MHz) δ 200.3, 160.1, 159.2, 159.2 (d, J_{CF} 242.7 Hz), 140.4, 136.6, 133.4, 128.7, 128.5, 128.4, 128.3, 128.1, 127.5, 127.5, 126.3, 118.6 (d, J_{CF} 8.0 Hz), 116.3 (d, J_{CF} 22.7 Hz), 115.6 71.4, 70.1, 55.4, 44.2, 29.1; HRMS (EI) *m*/*z* calcd for $C_{31}H_{26}NO_3FNa$: 502.1789; found: 502.1783. UV-CD HPLC Daicel Chiralpak® AD-H, 30% *i*-PrOH in hexane, 0.6 mL/min, t_R 31.3 min (3*R*,4*R*), 74.8 min (3*S*,4*S*).

*5.2.15. Azetidinone **29**.* To a suspension of ketal **22**-*cis*-**I** (1.0 g, 2.2 mmol) in a mixture of THF and water (2:1, 45 mL), TFA (3.0 mL, 39.6 mmol) was added and stirred in 30 °C (temp of oil bath) for 3 h. Then THF was evaporated on rotavapor, whereas solid material had precipitated. Crystals were filtrated of and the residue was recrystallized from MeOH to afford diol as a white solid (828 mg, 89%). Mp 154–155 °C (MeOH); $[\alpha]_D^{25}$ −97.3 (*c* 0.93, MeOH); IR (KBr) *v*: 3387, 3233, 1741, 1509, 1219 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.51–7.20 (m, 9H), 7.04–6.89 (m, 4H), 5.25 (d, *J* 5.5 Hz, 1H), 5.05 (s, 2H), 3.88 (m, 1H), 3.82–3.63 (m, 3H), 2.17–2.04 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.9, 159.0 (d, J_{CF} 244.0 Hz), 158.9, 136.5, 133.4 (d, J_{CF} 2.6 Hz), 128.6, 128.5, 128.1, 127.5, 126.0, 118.6 (d, J_{CF} 7.9 Hz), 115.7 (d, J_{CF} 22.7 Hz), 115.2, 70.1, 66.3, 60.6, 59.9, 57.8, 36.7; HRMS (ESI) *m*/*z* calcd for [M+Na^+] $C_{25}H_{24}FNO_4Na$: 444.1582; found 444.1601.

To a solution of diol (211 mg, 0.5 mmol) in anhydrous DMF (10 mL), TBSCl (83 mg, 0.6 mmol), imidazole (37 mg, 0.6 mmol), and catalytic amount of DMAP (6 mg, 0.1 mmol) were added. The reaction mixture was stirred for 16 h at rt, and quenched with satd solution of $NaHCO_3$ (1 mL) and water (10 mL), and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica (20% EtOAc/hexanes) to give alcohol **29** as a colorless oil (189 mg, 71%). $[\alpha]_D^{25}$ −70.8 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) *v*: 3483, 1748, 1511, 1249, 1248, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.51–7.18 (m, 9H), 7.08–6.88 (m, 4H), 5.24 (d, *J* 5.6 Hz, 1H), 5.06 (s, 2H), 3.96–3.84 (m, 2H), 3.83–3.75 (m, 1H), 3.73–3.62 (m, 1H), 2.79 (br s, 2H), 2.22–2.09 (m, 1H), 1.84–1.71 (m, 1H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.6, 158.9, 159 (d, J_{CF} 243.4 Hz), 136.7, 133.7 (d, J_{CF} 2.6 Hz), 128.6, 128.5, 128.1, 127.5, 126.3, 118.6 (d, J_{CF} 7.8 Hz), 115.8 (d, J_{CF} 22.6 Hz), 115.0, 70.1, 67.0, 61.7, 60.8, 57.8, 36.2, 25.8, 18.1, −5.5, −5.6; HRMS (ESI) *m*/*z* calcd for [M+Na^+] $C_{31}H_{38}FNO_4NaSi$: 558.2446; found: 558.2468.

*5.2.16. Azetidinone **30**.* To a suspension of PCC (65 mg, 0.3 mmol) and MS 4 Å (1 mg per 1 mg, 65 mg) in DCM (1 mL), alcohol **29** (53.6 mg, 0.1 mmol) was added and the mixture was stirred for 3 h. Then reaction mixture was diluted with Et_2O (5 mL), stirred for additional 30 min, filtrated through Celite, and evaporated. The residue was chromatographed on silica (10% EtOAc/hexanes) to give ketolactam **30** as a colorless oil (47.0 mg, 88%). $[\alpha]_D^{25}$ +10.6 (*c* 0.44, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.47–7.17 (m, 9H), 7.04–6.89 (m, 4H), 5.40 (d, *J* 2.5 Hz, 1H), 5.03 (s, 2H), 4.23 (d, *J* 2.5 Hz, 1H), 4.04–3.86 (m, 2H), 2.97–2.75 (m, 2H), 0.79 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.4, 160.2, 159.2 (d, J_{CF} 244.0 Hz), 159.1, 136.6, 133.5 (d, J_{CF} 2.7 Hz), 128.6, 128.4, 128.1, 127.5, 127.4, 118.6 (d, J_{CF} 7.9 Hz), 115.9 (d, J_{CF} 22.8 Hz), 115.57, 72.05, 70.08, 58.36, 55.30, 45.56, 25.75, 18.12, −5.54, −5.56; HRMS (ESI) *m*/*z* calcd for [M+Na^+] $C_{31}H_{36}FNO_4NaSi$: 556.2290; found: 556.2281.

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Supplementary data

The CD spectra and chromatograms of presented in this work azetidinones can be found. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.007. These data include MOL files and InChiKeys of the most important compounds described in this article.

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