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A Formal Synthesis of Ezetimibe via Cycloaddition/Rearrangement Cascade Reaction†

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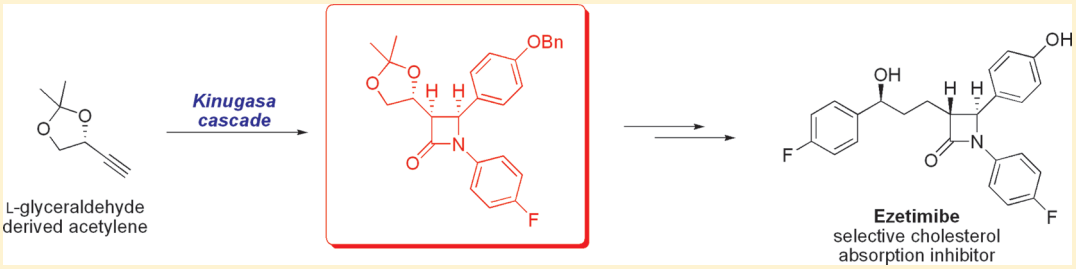
Supporting Information

ABSTRACT:



A formal synthesis of a powerful cholesterol inhibitor, ezetymibe **1**, is described. The crucial step of the synthesis is based on Cu(I)-mediated Kinugasa cycloaddition/rearrangement cascade reaction between terminal acetylene derived from acetonide of L-glyceraldehyde and suitable *C,N*-diarylnitrone. The adduct with (3*R*,4*S*) configuration at the azetidinone ring, obtained with high stereoselectivity, was subsequently subjected to deprotection of the diol side chain followed by glycolic cleavage and base-induced isomerization at the C3 carbon atom to afford the (3*S*,4*S*) aldehyde, which has been already transformed into ezetimibe by the Schering–Plough group.

Ezetimibe (**1**) is a strong cholesterol absorption inhibitor that reduces plasma low-density lipoprotein fraction (LDL-C).[1] Owing to the clinical attractiveness of ezetimibe (**1**), its synthesis became a target for many academic and industrial laboratories. To date, several synthetic routes for the preparation of ezetimibe have been described, mainly over past few years.[2−11] The reported methodologies are usually based on the construction of the β-lactam ring via a cyclocondensation between diaryl imine and ester or amide enolate (Scheme 1). The essential factor of the reported syntheses is the formation of three stereogenic centers present in **1** with the correct absolute configuration. The configuration of the chiral center in the side chain is usually accomplished either at the beginning or at the end of the reaction sequence, by the enantioselective reduction of phenone carbonyl group (for instance via CBS method[10b] or by treatment with (−)-DIP chloride[7a]). The control over configuration of the remaining two stereogenic centers in the β-lactam ring is usually achieved by the use of R^1 (Scheme 1) as a chiral auxiliary, except for instances when the (*S*)-β-hydroxy-γ-butyrolactone[10b] or the (*S*)-6-(4-fluorophenyl)tetrahydro-2*H*-pyran-2-one[11] was used as the ester component. In the latter case, however, the stereochemical pathway of the reaction has not been discussed and no information on the diastereomeric excess of the desired product has been provided.[11]

Among numerous direct methodologies leading to the chiral β-lactams,[12,13] the Cu(I)-mediated cycloaddition/rearrangement cascade process of nitrones with terminal alkynes that proceeds in the presence of base (known as Kinugasa reaction[14]) has received increased attention during the past decade.[15,16]

Recently, we have demonstrated that the reaction of cyclic aliphatic nitrones with terminal acetylenes, both achiral or enantiomerically defined, led to the formation of β-lactam ring with a high *cis*-stereoselectivity (Scheme 2).[16] The yield of desired products varies from poor (for aliphatic acetylenes) to moderate and good for aryl acetylenes. Interestingly, somewhat better results have been observed for certain aliphatic acetylenes bearing oxygen atoms.[16a] The acetylene derived from the acetonide of glyceraldehyde has been found to be a particularly attractive substrate for Kinugasa reaction (Scheme 2).[16a]

Encouraging results for the glyceraldehyde-derived acetylene **2**/***2ent*** prompted further studies on the potential of this compound as a precursor for ezetimibe (**1**) following the proposed synthetic reaction sequence (Scheme 3). Consequently, we focused our attention on the Kinugasa reactions involving readily available *C,N*-diarylnitrone **3a**.

We considered the synthesis of ezetimibe (**1**) via Schering–Plough intermediate **5**, for which the transformation leading to the target molecule **1** has been reported.[10b] The key features of the retrosynthetic analysis are shown in Scheme 3. The aldehyde **5** with *trans* configuration at carbon atoms C3 and C4 would be prepared by the deprotection of 1,2-diol fragment of **4**, followed

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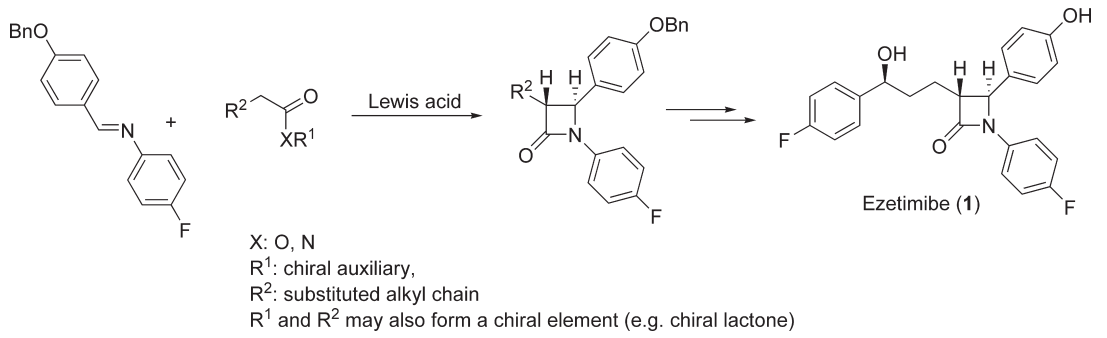
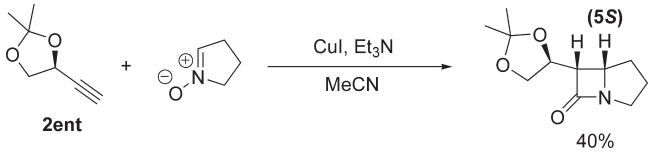
Scheme 1



Scheme 2



by a glycolic cleavage and epimerization at the C3 stereogenic center in the *cis* aldehyde by treatment with a weak base.

Considering our previous observations that acetylene derived from D-glyceraldehyde **2*ent*** reacted with nonchiral 1,2-pyrroline-*N*-oxide to produce corresponding carbapenam with the (5*S*) configuration (Scheme 2),[16a] we expected that **2*ent*** with nitrone **3a** should yield the *cis* substituted adduct (**4*ent***) also with (4*S*) configuration, opposite to that present in ezetimibe (**1**). Indeed, appropriate experiment returned the predicted stereochemistry.

Consequently, as the substrate of the synthesis we selected the readily available isopropylidene L-glyceraldehyde, which was transformed into corresponding acetylene **2** by treatment with Bestman–Ohira reagent according to the known procedure.[16a] The second component of the Kinugasa reaction, the nitrone **3a**, was obtained in 60% yield by the standard procedure using *p*-benzyloxybenzaldehyde and *p*-fluorophenylhydroxylamine (prepared from 4-fluoro-1-nitrobenzene).[17]

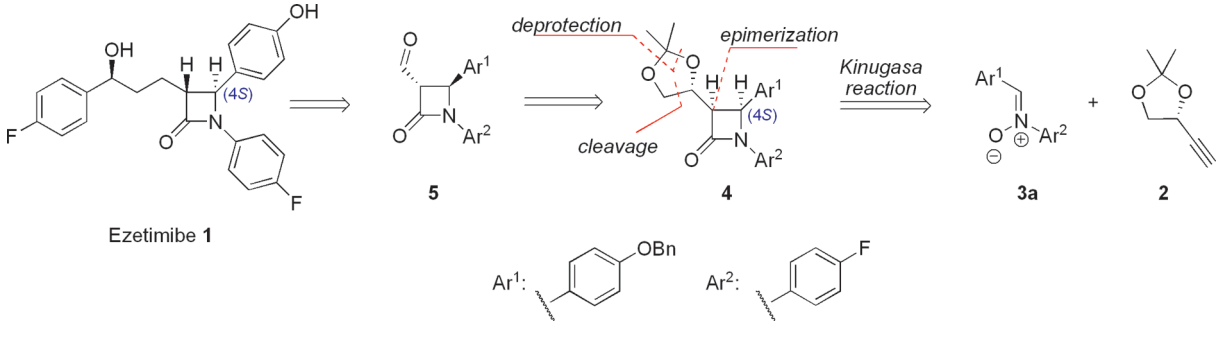
The Kinugasa cycloaddition/rearrangement cascade between nitrone **3a** and acetylene **2** under our standard conditions (2 equiv of nitrone with respect to acetylene, 1 equiv of CuI, 4 equiv of Et_3N in MeCN) provided the desired *cis*-azetidinone **4** along with two other isomers: *trans* isomer **6** and alternative *cis* product **7** in a ratio of 50:25:25, respectively (Scheme 4).

The configuration of the major product **4** was assigned by ^{1}H NMR ($J_{3,4}$ = 5.8 Hz, and $J_{3,1'}$ = 9.4 Hz) and was also unequivocally confirmed by the X-ray structure analysis. The second *cis* isomer **7** did not formed crystals suitable for X-ray measurement, but analysis of ^{1}H NMR coupling constants provided unambiguous evidence of its absolute configuration ($J_{3,4}$ = 6.1 Hz and $J_{3,1'}$ = 6.6 Hz). Isolation of the *trans* isomer **6** in a pure form was difficult because its polarity is close to that of the major reaction product. An analytical sample was obtained via repeated preparative HPLC (the sample with 93% diasteroisomeric purity was obtained). The *trans* substitution of the β-lactam ring in **6** was assigned following analysis of its ^{1}H NMR spectrum where a small $J_{3,4}$ = 2.4 Hz coupling constant was observed. The absolute configuration of stereogenic centers in **6** was substantiated by comparison of the CD spectra of compounds **4**, **6**, **7**, and **4*ent*** (see Supporting Information). Under the initial reaction conditions, the presence of a fourth possible isomer (**8**) was not detected. During subsequent optimization of the Kinugasa reaction conditions, compound **8** was found in certain cases; however, the attempts to isolate it failed. Nevertheless, the careful analysis of NMR spectra of crude postreaction mixtures led to identification of the well-separated diagnostic signals of H3 and H4 protons ($J_{3,4}$ = 2.5 Hz and $J_{3,1'}$ = 6.0 Hz) that were indicative of the existence of alternative *trans* adduct **8**.

Due to lower than expected[16a] stereoselectivity of the Kinugasa reaction, further optimization of this process was performed by varying copper(I) source, base type, solvent, and other reaction conditions. Selected results are collected in Table 1.

The choice of solvents for the reaction is restricted to the polar aprotic ones. The surprisingly low solubility of nitrone **3a** in organic solvents (even in alcohols) was found to be the main

Scheme 3



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Scheme 4

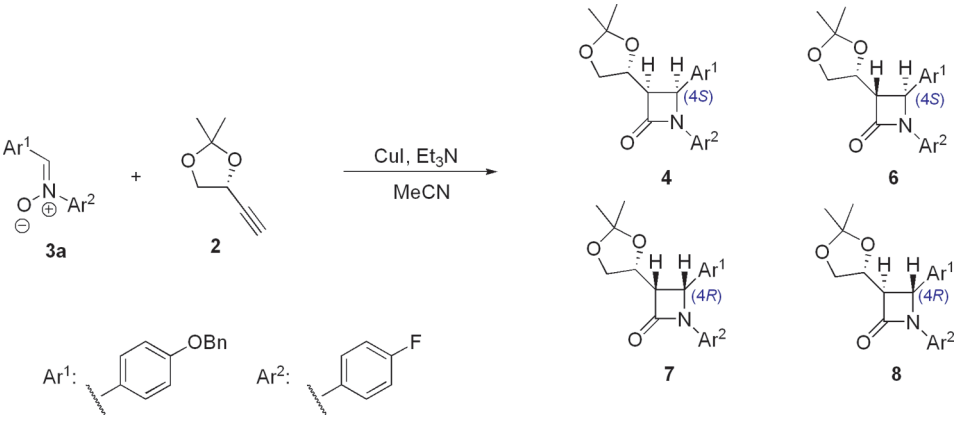


Table 1. Kinugasa Reaction of Nitrone 3a and L-Glyceraldehyde-Derived Acetylene 2[a]

entry	copper salt (equiv)	base[b] (equiv)	nitrone **3** (eqiuv)	(**4**:**6**):(**7**:**8**)[c]	yield **4** (**4** + **6**)	overall
1	CuI (1.0)	Et_3N (4)	1.6	(59:23):(1:17)	28 (32)	39
2	CuI (1.0)	TMG (2)	1.6	(68:19):(7:7)	41 (53)	61
3	CuI (1.0)	Et_3N (4)	1.1	(62:22):(8:8)	37 (50)	60
4	$Cu(Et_3N)I$ (1.0) [d]	TMG (2)	1.1	(57:25):(9:9)	37 (54)	66
5	$Cu(MeCN)_4PF_6$ (1.0)	Et_3N (4)	1.1	(48:30):(20:2)	28 (45)	58
6	CuI (1.0)	(*i*-Pr)$_2$NEt (4)	1.2	(61:21):(14:4)	30 (40)	49
7	CuI (0.1)	Et_3N (4)	1.1	(40:32):(25:3)	19 (35)	48
8	CuI (0.1)	TMG (2)	1.2	(65:20):(8:7)	44 (58)	67
9	$Cu(Et_3N)_4I$ (1.0)[d]	TMG (2)	1.2	(54:11):(21:14)	25 (30)	45

[a] Reactions performed in MeCN at room temperature. [b] TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine. [c] Determined by ^{1}H NMR and HPLC. [d] Prepared in situ.

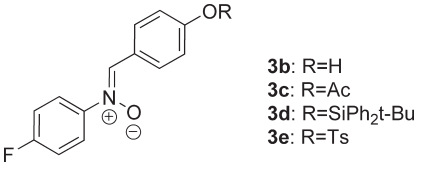
problem of the reaction. Acetonitrile is the solvent of choice that provided the optimal combination of solubility and an acceptable reaction rate. The higher solubility of the nitrone was observed when a mixture of MeCN with HMPA in ratio 1:1 was used; however, its use did not improve the overall yield.

Replacement of CuI by other copper(I) salts, such as CuCl, CuBr, CuOAc, or $CuSO_4$/sodium ascorbate, resulted in reduction of yield of desired products. Moreover, the copper-mediated deoxygenation of the nitrone **3a** to the corresponding imine constituted a significant side process and necessitated the use 1.2−2 equiv excess of the nitrone with respect to the acetylene.

An exchange of Et_3N by other bases, for instance, *i*-Pr_2NEt or *c*-Hex_2NMe or DABCO, decreased the efficiency of the reaction. Only the *N*,*N*,*N*′,*N*′-tetramethylguanidine offered a higher yield of desired products **4** and **6**. However, in contrast to reactions performed in the presence of triethylamine, the formation of the second *trans* isomer **8** was observed. *N*,*N*,*N*′,*N*′-Tetramethylguanidine afforded also the best diastereoselectivity: dr = 68:19:7:7 for **4**, **6**, **7**, and **8**, respectively.

The surprisingly low stereoselectivity of the reaction of **3a** with **2** suggested that such result might be triggered by the electronic properties of the nitrone itself. When acetylene **2** was subjected to the reaction with diphenylnitrone **9**, the azetidinone **10** was isolated as a single product in a good yield (Scheme 5).

Bearing in mind that the electronic properties of nitrone **3a** might affect the course of the Kinugasa reaction, we explored the use of nitrones **3b**−**e** with alternative *O*-protection of the phenol group. The nonsubstituted phenol **3b**, its *O*-acetyl derivative **3c**, and *O*-silyl ether **3d** were ineffective substrates for the reaction. Moreover, the nitrone **3d** underwent desilylation under reaction conditions. Only the *O*-tosylated compound **3e** reacted well, providing corresponding β-lactams, but no improvement of the selectivity and yield was observed.



Recently, we have shown that 4-(*p*-methoxy-aryl)-substituted azetidin-2-ones are particularly sensitive to the nucleophilic reagents in the presence of acid catalysts and undergo addition of the nucleophile to the C4 carbon atom with opening of the four-membered β-lactam ring.[18] Henceforth, the assessment of reasons for lower than expected yield and selectivity of the Kinugasa reaction involving **3a**−**e** should take into account observation that substitution in both aryls in adducts **4** and **6**−**8** can promote a similar reactivity. Better results found for the nitrone **9** support such an assumption.

The transformation of **4** into ezetimibe (**1**) precursor **5** is shown in Scheme 6. It should be noted that the *trans* isomer **6** has the same configuration at C4 of the azetidin-2-one ring as ezetimibe **1**, so from the synthetic point of view both stereoisomers **4** and **6** are precursors for the target molecule and can be used for the next steps without separation.

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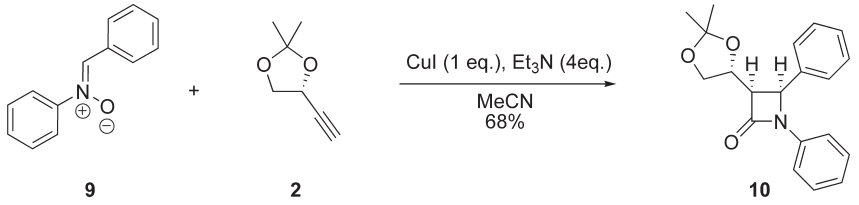
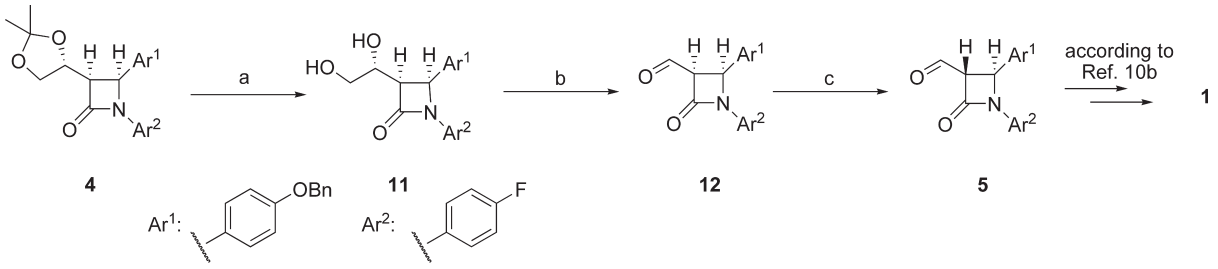
Scheme 5



Scheme 6[a]



[a] Reagents and conditions: (a) CF_3COOH, THF/H_2O; (b) 2.4 equiv of $NaIO_4$ (on silica), CH_2Cl_2, 2 h, 0 °C; (c) 20 equiv of $NaHCO_3$, CH_2Cl_2, 3 h, 0 °C, 82−86% (after 2 steps, *cis* (**12**):*trans* (**5**) = 1:6.2−8.8).

Deprotection of **4** proceeded smoothly in THF/H_2O (2:1) in the presence of 10 equiv of trifluoroacetic acid to give diol **11** in 76% yield. The rate of hydrolysis can be accelerated in the presence of microwave irradiation (200 W, 3 min) affording diol **11** in 70%.

Initial attempts to cleave the 1,2-diol moiety were performed according to the Schering−Plough procedure.[10b] However, when diol **11** was treated with $NaIO_4$ in $MeCN/H_2O$ solution followed by the standard work up to afford **12**, the desired aldehyde was accompanied by decomposition products. This may be caused by a reactive β-dicarbonyl fragment present in **12**. Moreover, probable formation of the hydrate by **12** could have made the isolation product more difficult, consequently leading to a low yield of the overall transformation. To overcome these difficulties, we turned our attention to the method reported by Shrig et al.[19] This alternative protocol, applying silica gel-supported $NaIO_4$ in anhydrous dichloromethane, should exclude formation of a hydrate. Indeed, glycolic cleavage with above method, followed by the epimerization of initially formed *cis* aldehyde with solid sodium bicarbonate (20 equiv), directly after the oxidation step, yielded crude aldehyde products (82−85%) as a mixture of C-3 epimers *cis* **12** and *trans* **5** in a ratio of about 1:8.5, respectively. Due to instability of **5** this compound should be used directly in further steps leading to ezetimibe (**1**).

Transformation of compound **5** into ezetimibe (**1**) has already been reported by the Schering−Plough group.[10b] This sequence involved Mukayiama reaction of **5** with silyl enol ether of *p*-fluoro-acetophenone to afford an enone, which was hydrogenated followed by a stereoselective reduction of the carbonyl group in the presence of a chiral ligand (*R*)-2-methyl-CBS-oxaborolidine.[10b]

In summary, we have described a novel approach for synthesis of β-lactamic cholesterol absorption inhibitors, particularly ezetimibe **1**. The key step of the newly presented synthesis is the formation of *N*,4-diaryl-substituted azetidin-2-one ring via copper(I)-catalyzed Kinugasa reaction. The presented methodology is the first example of an application of the Kinugasa reaction in a target-oriented synthesis. Taking into account the inexpensive starting materials and simple steps that do not require special preparative procedures, our methodology leading to **5** offers certain advantages over Schering−Plough's synthesis.[10b] Moreover, Kinugasa reaction involving diaryl nitrones offers an attractive approach to the recently reported family of new anticancer β-lactams.[20]

EXPERIMENTAL SECTION

Syntheses of Nitrones 3a−e

General Method,[17] Step 1. To a suspension of *p*-fluoronitrobenzene (300 mmol, 31.8 mL) in a solution of NH_4Cl (390 mmol, 20.9 g) in water (600 mL) at 60 °C was added zinc powder in 1.0−1.5 g portions (39.2 g, 600 mmol), keeping the temperature of the reaction mixture in the range of 60−65 °C. When zinc addition was completed, the mixture was stirred for an additional 15 min at 60 °C. Then zinc oxide was filtered (with the use of a Schott funnel, porosity G3) and washed with water (3 × 50 mL, water temp 70 °C), to the resulting solution was added solid NaCl (205 g), and the solution was cooled to 0 °C. After 30 min the yellow precipitate was filtered, washed with cold water (∼0 °C, 2 × 40 mL), and dried in vacuo (2.5 mbar) for 1 h. The crude 4-fluorophenylhydroxylamine was used directly in the next step without further purification.

Step 2. To a solution of crude 4-fluorophenylhydroxylamine (10 mmol) in acetone (10 mL) were added *p*-benzyloxybenzaldehyde (10 mmol) and catalytic amount of CH_3SO_3H (10 mol %) at room temperature. After 2 h, the resulting precipitate was filtered, washed with acetone, and dried in vacuo.

***N*-(4-Fluorophenyl)-α-(4-benzyloxyphenyl)nitrone (3a).** Off-white solid; yield 60%. Mp 193−195 °C (acetone); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49−8.47 (m, 2H), 8.42 (s, 1H), 7.99−7.95 (m, 2H), 7.50−7.45 (m, 2H), 7.44−7.32 (m, 5H), 7.13 (d, J = 5.0 Hz, 2H), 5.20 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2 (d, J_{CF} = 245.6 Hz), 159.9, 144.8 (d, J_{CF} = 2.4 Hz), 136.6, 133.0, 130.9, 128.4, 127.9, 127.8, 124.1, 123.6 (d, J_{CF} = 9.3 Hz), 115.7 (d,

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J_{CF} = 22.9 Hz), 114.7, 69.4; HR MS (ESI) *m/z* calcd for $C_{20}H_{16}NO_2F$-Na [M + Na^+] 344.1057, found 344.1055. Anal. Calcd for $C_{20}H_{16}FNO_2$: C, 74.75; H, 5.02; F, 5.91; N, 4.36. Found: C, 74.76; H, 5.08; F, 6.03; N, 4.40.

***N*-(4-Fluorophenyl)-α-(4-hydroxyphenyl)nitrone (3b).** Light pink solid; yield 61%. Mp 216−217 °C (acetone); IR (film) 3186 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.39−8.35 (m, 2H), 8.33 (s, 1H), 7.97−7.92 (m, 2H), 7.38−7.32 (m, 2H), 6.91−6.86 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.0 (d, J_{CF} = 204.4 Hz), 159.8, 144.8 (d, J_{CF} = 2.0 Hz), 133.4, 131.2, 123.5 (d, J_{CF} = 7.4 Hz), 122.5, 115.7 (d, J_{CF} = 19.1 Hz), 115.3; HRMS (EI) *m/z* calcd for $C_{13}H_{10}O_2NF$: 231.0696, found 231.0688. Anal. Calcd for $C_{13}H_{10}FNO_2$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.50; H, 4.37; N, 6.04.

***N*-(4-Fluorophenyl)-α-(4-acyloxyphenyl)nitrone (3c).** Light yellow solid; yield 57%. Mp 166−169 °C (acetone); IR (film) 1756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43−8.39 (m, 2H), 7.86 (s, 1H), 7.76−7.71 (m, 2H), 7.21−7.16 (m, 2H), 7.15−7.09 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.9 (d, J_{CF} = 246.4 Hz), 152.1, 145.0 (d, J_{CF} = 3.2 Hz), 133.4, 130.3, 128.1, 123.5 (d, J_{CF} = 8.7 Hz), 121.8, 115.9 (d, J_{CF} = 23.2 Hz), 114.7, 21.1; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}FNO_3Na$ [M + $Na]^+$ 296.0693, found 296.0690. Anal. Calcd for $C_{15}H_{12}FNO_3$: C, 65.93; H, 4.43; N, 5.13. Found: C, 65.91; H, 4.40; N, 5.08.

***N*-(4-Fluorophenyl)-α-(4-*tert*-butyldiphenylsilyloxyphenyl)-nitrone (3d).** Yellowish solid; yield 45%. Mp 109−112 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (2H, m), 7.74−7.70 (5H, m), 7.40−7.24 (7H, m), 7.14 (2H, m), 6.85 (2H, m), 1.11 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190,8, 164,0 (d, J_{CF} = 250 Hz), 158,5, 144,7, 136,2, 132,9, 132,1, 130,9, 128,7, 124,3, (d, J_{CF} = 9 Hz), 120,9, 116,4 (d, J_{CF} = 23 Hz), 114,3, 26,4. HRMS (ESI) *m/z* calcd for $C_{29}H_{28}NO_2FSiNa$ [M + $Na]^+$ 492.1756, found 492.1754. Anal. Calcd for $C_{29}H_{28}FNO_2Si$: C, 74.17; H, 6.01; N, 2.98. Found: C, 74.15; H, 5.98; N, 3.00.

***N*-(4-Fluorophenyl)-α-(4-tosyloxyphenyl)nitrone (3e).** White solid; yield 67%. Mp 172−174 °C (acetone); ^1H NMR (600 MHz, DMSO-d_6) δ 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 (150 MHz, DMSO-d_6) δ 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; HRMS (ESI) *m/z* calcd for $C_{20}H_{16}NO_4FSNa$ [M + $Na]^+$ 408.0682, found 408.0679. Anal. Calcd for $C_{20}H_{16}FNO_4S$: C, 62.33; H, 4.18; F, 4.93; N, 3.63. Found: C, 61.93; H, 4.32; F, 5.13; N, 3.52.

Synthesis of 2-Azetidinone 4. A Schlenk flask was charged with copper(I) iodide (4.53 g, 23.8 mmol) and purged with argon, and degassed MeCN (120 mL)and *N,N,N′,N′*-tetramethylguanidine (47.6 mmol, 5.48 g, 6 mL) were added. After cooling to 0 °C, acetylene **2** (23.8 mmol, 3.0 g) was added, and the yellow mixture was stirred for 15 min. A second Schlenk flask was charged with nitrone **3a** (28.56 mmol, 9.18 g) and purged with argon, and degassed MeCN was added (120 mL). Subsequently, a solution of copper acetylide was cannulated into the suspension of nitrone **3a**. After stirring for 16 h at room temperature under argon atmosphere, the reaction mixture was diluted with AcOEt (100 mL) and H_2O (100 mL). The aqueous phase was separated and washed with AcOEt (2 × 50 mL). The combined organic phases were washed with brine, dried (anhydr Na_2SO_4), and concentrated. The diasteroisomer ratio of crude products mixture was assigned by HPLC (hexane/MTBE, 7:3 v/v, 1 mL/min, det 223 nm; t_R = 11.7 min for **4**, 13.2 min for **6**, 14.5 min for **8** and 42.3 min for **7**), and the ratio was 68:19:7:7 for **4**, **6**, **7**, and **8**, respectively. The product was isolated by column chromatography on silica gel (hexane/AcOEt 6:1) to afford adduct **4** (4.37 g, 41%) accompanied by **6** (1.28 g, 12%), and **7** (0.47 g, 5%). The second *trans* isomer was not isolated.

Azetidinone 4. Mp 150−152 °C (EtOH); $[\alpha]^{25}_D$ −74 (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.20 (2H, m), 7.12 (2H, m), 7.06 (2H, m), 7.01 (m,1H), 7.86 (2H d *J* = 14 Hz), 6.69 (2H d *J* = 14 Hz), 6.61 (2H, m), 4.55 (2H, m), 4.45 (1H,d *J* = 5.8 Hz),4.13 (1H, dd *J* = 8.5, 6.5 Hz), 3.94 (1H, dd *J* = 8.5, 6.1 Hz), 3.81 (1H, dt *J* = 9.4, 6.1 Hz), 3.33 (1H, dd *J* = 9.4, 5.8 Hz), 1.30 (3H, s), 0.93 (3H, s); ^{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; 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. 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.

Azetidinone 6. A sample (12 mg) with 93% diasteroisomeric purity was obtained by repetitive preparative HPLC (optical rotation not recorded). ^1H NMR (600 MHz, C_6D_6) δ 7.42−7.336 (4H, m); 7.28−7.22 (5H, m), 6.98−6.90 (4H, m), 4.90 (1H, d, *J* = 2.4 Hz), 4.52−4.47 (1H, m), 4.12−4.06 (2H, m), 3.30 (1H, dd, *J* = 3.9, 2.4 Hz), 4.42 (3H, s), 1.39 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 159.1, 159.0 (d, J_{CF} = 244 Hz), 136.7, 133.7 (d, J_{CF} = 2.4 Hz), 129.3, 128.6, 128.1, 127.5, 127.3, 118.5 (d, J_{CF} = 7.9 Hz), 115.8 (d, J_{CF} = 22.6 Hz), 115.8, 110.0, 72.5, 70.1, 66.2, 61.7, 57.3, 26.4, 25.7; IR (film) 1749, 1511 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_4NFNa$ [M + Na^+] 470.1738, found 470.1741.

Azetidinone 7. Mp 104−107 °C; $[\alpha]^{25}_D$ = +74.8 (*c* 0.51, CH_2Cl_2); IR (film): 1748, 1510, 1372 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.31−7.27 (m, 2H), 7.21−7.17 (m, 2H), 7.14−7.10 (m, 2H), 7.09−7.04 (m, 1H), 6.86−6.82 (m, 2H), 6.73−6.69 (m, 2H), 6.69−6.63 (m, 2H), 4.61 (s, 2H), 4.28 (d, *J* = = 6.0 Hz, 1H), 3.87−3.81 (1H, dt, *J* = 7.7, 6.6, 6.0 Hz), 3.48 (1H, pseudo dd, *J* = 8.1, 7.9 Hz), 3.29 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.14 (pseudo dd, *J* = = 6.6, 6.1 Hz, 1H), 1.49 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 163.8, 159.3, 158.7 (d, J_{CF} = 201.1 Hz), 137.2, 134.8 (d, J_{CF} = 2.3 Hz), 128.9, 128.8, 128.4, 128.1, 128.0, 127.7, 126.6, 118.7 (d, J_{CF} = 6.4 Hz), 116.1, 115.9 (d, J_{CF} = 22.4 Hz), 109.9, 72.5, 70.1, 68.2, 58.0, 56.9, 26.9, 26.1; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_4NFNa$ [M + $Na]^+$ 470.1738, found 470.1756. Anal. Calcd for $C_{27}H_{26}NO_4F$: C, 72.47; H, 5.86; N, 3.13, F 4.25. Found: C, 72.41; H, 5.86; N, 3.09, F 4.29.

Azetidinone 10. To a suspension of CuI (190 mg, 1.0 mmol) in anhydrous CH_3CN (10 mL) were added Et_3N (0.56 mL, 4.0 mmol) and acetylene **2** (126 mg, 1.0 mmol) at 0 °C. After 15 min nitrone **9**[20] was added (395 mg, 2.0 mmol, 2.0 eqiuv) as a solid, and the mixture was stirred for 16 h at rt. Then solvent was evaporated, and the residue was chromatographed on silica gel (60 mL, 10% EtOAc/hexanes) to give an off-white solid (218 mg, 68%). Mp 153−155 °C (EtOH);$[\alpha]^{25}_D$ = −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.

Diol 11. To a solution of acetonide **4** (933 mg, 2.1 mmol) in a mixture of THF (20 mL) and water (10 mL) was added CF_3CO_2H (1.60 mL), and the mixture was kept at 50 °C for 6 h (TLC analysis showed complete consumption of substrate, 50% EtOAc/hexanes). Then the organic solvents were evaporated, and a white solid was formed. After filtration, the crude diol was recrystallized from EtOH to give a product as a white, thin neeedles (702 mg, 76%). Mp 210−212 °C (EtOH); $[\alpha]^{25}_D$ −52.1 (*c* 0.7, acetone); IR (film) 3369, 1726, 1512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 7.42−7.27 (m, 5H), 7.25−7.19 (m, 4H), 6.98−6.88 (m, 2H), 5.25 (d, *J* = 5.5 Hz, 1H), 5.01 (s, 2H), 3.81−3.74 (m, 1H), 3.71−3.65 (m, 1H), 3.62−3.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 164.7, 158.9 (d, J_{CF} = 242.5 Hz), 158.7, 136.4, 133.1 (d, J_{CF} = 2.5 Hz), 128.3, 128.2, 127.7,

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127.2, 125.8, 118.5 (d, J_{CF} = 7.5 Hz), 115.5 (d, J_{CF} = 22.5 Hz), 69.8, 67.3, 64.6, 57.4, 57.1; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{22}O_4FNNa$ [M + Na^+] 430.1425, found 430.1416. Anal. Calcd for $C_{24}H_{22}FNO_4$: C, 70.75; H, 5.44; F, 4.66; N, 3.44. Found: C, 70.74, H, 5.45; F, 4.88, N, 3.42.

Aldehyde 5. To a vigorously stirred suspension of diol **11** (330 mg, 0.81 mol) in anhydrous CH_2Cl_2 (15 mL), cooled to 0 °C, was added silica gel-supported $NaIO_4$ reagent (1.78 g, 2.13 mmol), and the mixture was stirred for 2 h at this temperature. Then silica was filtered and washed with anhydrous CH_2Cl_2 (2 × 5 mL), and the solvent was evaporated to give a white solid (285 mg). ^{1}H NMR indicated the ratio of diastereisomers as *trans*:*cis* (**12**:**5**) = 7.8:1 (based on integration of aldehyde hydrogen atom). Selected diagnostic signals for **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 2.4 Hz, C*H*O), 5.36 (d, *J* = 6.0 Hz, H-4); 3.40 (dd, *J* = 6.0, 2.4 Hz, H-3); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{18}FNO_3Na$ [M + Na]$^+$ 398.1168, found 398.1172. To the crude mixture of aldehydes in anhydrous CH_2Cl_2 (15 mL) was added $NaHCO_3$ (1.36 g, 16.2 mmol, 20.0 eqiuv) at 0 °C, and the mixture was stirred for 3 h at this temp. The solid was filtered, and the solvent was evaporated to give a mixture of *trans*:*cis* diastereoisomers in a ratio of 8.5:1 (based on integration of aldehyde hydrogen atom). Selected ^{1}H NMR data for aldehyde **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (d, *J* = 1.2 Hz, C*H*O), 5.40 (d, *J* = 2.4 Hz, H-4), 4.23 (dd, *J* = 2.4, 1.2 Hz, H-3); the spectral data are in agreement with those reported.[10b] The aldehyde **5** is unstable and was used directly in next steps of the synthesis according to the Schering−Plough protocol.[10b]

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra; CD spectra of **4**, ***4ent***, **6**, and **7**; CIF file of compound **4**.[21] This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

†Dedicated to Professor Janusz Jurczak in the year of his 70th birthday.

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