Formal [3 + 2] Cycloaddition Reaction of [1,4]Oxazin-2-ones and α-Alkynyl Ketones via a Tandem Mukaiyama-Aldol Addition/ Aza-Cope Rearrangement

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Introduction

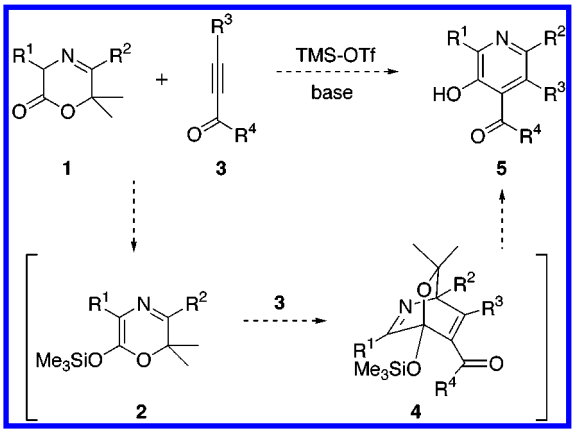
In the course of our investigations on carbonyl-alkyne-exchange (CAE) reactions,[1−7] we were interested in the use of [1,4]oxazin-2-ones[8] **1** as precursors for cyclic heterodienes for the synthesis of vitamin B_6 analogues **5** starting from **1** and acetylenic ketones[9] **3** as depicted in Scheme 1. Silyl enol ether formation would give cyclic aza dienes **2**, which should react in a [4 + 2] cycloaddition with acetylenic ketones **3** to give bicyclic adducts **4**. Electrocyclic extrusion of acetone finally should lead to 3-hydroxypyridines **5**. An alternative strategy starting from 5-trimethylsiloxy oxazoles and olefins described by Takagaki et al.[10] leading to vitamin B_6 analogues of type **5** constituted further motivation for this approach.

Results and Discussion

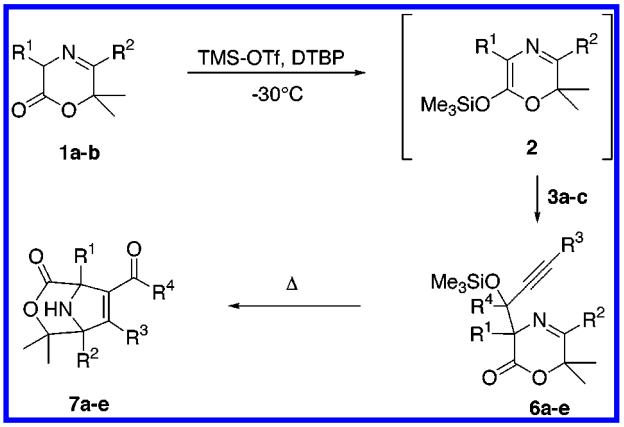
Although we were aware of the inherent difficulties of Diels−Alder reactions with aza dienes,[11,12] we expected a similar increase of reactivity of cyclic as compared to acyclic aza dienes as has been observed in CAE reactions of the parent all-carbon dienes.[7]

Thus, treatment of, e.g., **1a** ($R^1 = R^2 =$ Me) with **3a** ($R^3 = CO_2Me$, $R^4 =$ Ph), trimethylsilyl triflate (TMS-OTf), and 2,6-di-*tert*-butylpyridine (DTBP) in CH_2Cl_2 at −30 °C resulted in formation of a new product with the same molecular weight as **4** (Scheme 1). Analysis of 2D NMR spectra, however, revealed that not a [4 + 2] cycloaddition had taken place but rather a Mukaiyama-aldol[13−15]addition

Scheme 1



Scheme 2



of the silyl enol ether **2** to the carbonyl group of acetylenic ketones **3** to form adducts **6** as shown in Scheme 2. Products of type **6** turned out to be relatively unstable. After some days, transformation of **6a** into bicyclic derivative **7a** had taken place as confirmed by 2D NMR experiments and X-ray crystallography. An ORTEP stereoplot of **7a** ($R^1 = R^2 =$ Me; $R^3 = CO_2Me$; $R^4 =$ Ph) is depicted in Figure 1 of the Supporting Information. The bicyclic pyrrolidine **7a** actually corresponds to the product of a formal [3 + 2] cycloaddition of **1a** and **3a**. This finding was astonishing inasmuch as during our investigations of [3 + 2] cycloadditions of [1,4]oxazin-2-ones we discovered that acetylenic ketones are poor dipolarophiles due to numerous side reactions.[16] Under standard reaction conditions for [3 + 2] cycloaddition reactions (Ag(I) catalysis[17]), **7a** could be isolated in 19% yield only.

To elucidate the mechanism of this unusual rearrangement, we studied the influence of substituents R^2 and R^3 on product formation. Optimized reaction conditions for the Mukaiyama-aldol reaction were found by using 2.2 equiv of TMS-OTf and 2.5 equiv of 2,6-di-*tert*-

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Table 1. Sequential Mukaiyama−Aldol/Rearrangement Reactions

entry	R^1	R^2	R^3	R^4	Mukaiyama aldol (yield, %)[a]	rearrangement (yield, %)[a]
a	Me	Me	CO_2Me	Ph	**6a** (90)	**7a** (88)
b	Me	Me	CO_2Et	Ar[b]	**6b** (60)[c]	**7b** (94)
c	Me	Me	$SiMe_3$	Ph	**6c** (95)[d]	**7c** (59)
d	Me	Ph	CO_2Me	Ph	**6d** (44)[c]	**7d** (50)
e	Me	Ph	$SiMe_3$	Ph	**6e** (92)[e]	**7e** (55)

[a] Isolated yields. [b]3,4,5-trimethoxyphenyl. [c]Ratio of diastereomers not determined. [d]2:1 mixture of diastereoisomers. [e]3:2 mixture of diastereoisomers.

butylpyridine in CH_2Cl_2 at temperatures ranging between −40 and −25 °C. At temperatures above −20 °C, Michael addition of the silyl enol ether to the acetylenic ketone became an important side reaction. The experimental results are summarized in Table 1.

1,2-Addition of the silyl enol ether of oxazinones **2** to acetylenic ketones **3** and concomitant silyl transfer to yield the tertiary alcohols **6** as mixtures of diastereomers (Table 1) proceeded usually in good yields. Products **6** were stable enough to be isolated and purified by chromatography on SiO_2. The ratio of diastereoisomer formation could be determined by NMR in cases where the silylated alkyne **3c** ($R^3 = SiMe_3$, $R^4 = Ph$) was used (Table 1, entries c and e). The NMR spectra of **6a**, however, indicated the formation of only one diastereomer. Rearrangement to the formal [3 + 2] adducts **7** was achieved by heating solutions of these primary adducts.

The nature of substituents R^3 attached to the alkyne seemed to have no major effect on the rearrangement. Compared to the carbomethoxy-substituted compounds **6a**,**b**,**d** it was observed that the rearrangement of the TMS-substituted derivatives **6c** and **6e** proceeded more slowly (see the Experimental Section) and that the diastereomers rearranged at slightly different rates as qualitatively observed by TLC.

The polarity of the solvent appeared to play only a minor role since rearrangements proceeded at similar rates in chloroform, 1,2-dichloroethane, or 1,4-dioxane/H_2O.

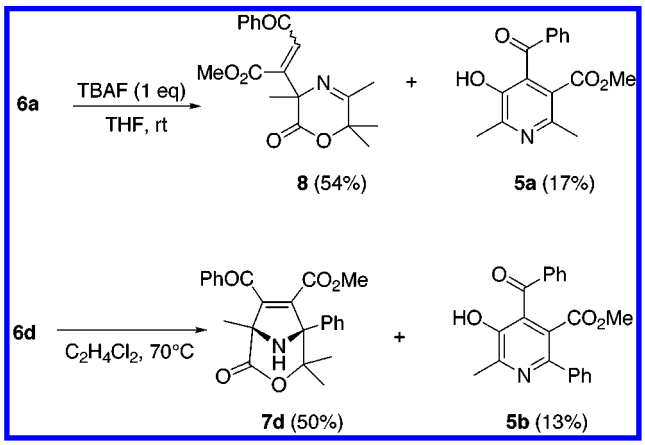
In two cases, the originally targeted nicotinic acid derivatives **5a** and **5b** could be isolated, however, only as byproducts in low and irreproducible yields (see Scheme 3).

A number of experiments were carried out in an attempt to determine the factors that influence the rate and the course of the rearrangements. Thus, adduct **6c** was exposed to several different reaction conditions as summarized in Scheme 4.

Addition of pyridinium *p*-toluenesulfonate (PPTS) in a variety of solvents regenerated **1a** and the hydrolyzed alkyne probably via a retro-aldol reaction. Treatment of **6c** with silver nitrate in a mixture of ethanol and water and trapping of the silver complex with sodium cyanide[18] gave **9** where the trimethylsilyl group was replaced by a hydrogen. This adduct underwent rearrangement to **10** under thermal conditions. The bicyclic derivative **10** could also be obtained by treatment of rearranged product **7c** with tetrabutylammonium fluoride (TBAF) in THF at room temperature.

On the other hand, exposure of **6c** to a catalytic amount of potassium carbonate in MeOH resulted in the clean

Scheme 3

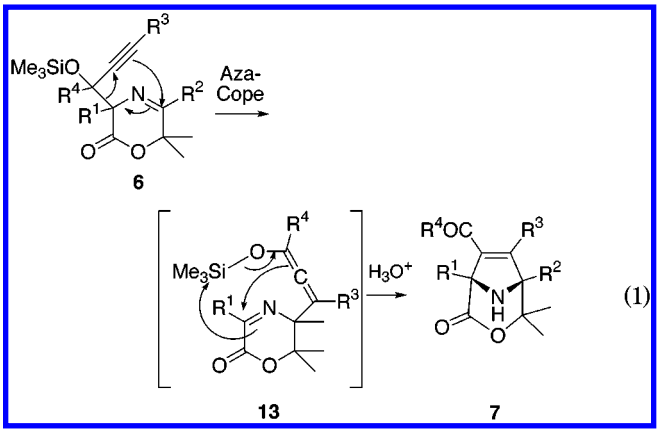


formation of **11** via a retro-aldol reaction and subsequent 1,4-addition to the alkyne followed by addition of MeOH. Product **11** was also obtained by treatment of **1a** and **3c** with K_2CO_3 in MeOH. At room temperature, Michael adducts (*E*)-**12** and (*Z*)-**12** were isolated in a ratio of 7.5:1. At 40 °C, however, addition of methanol and thus formation of **11** was observed.

Interestingly, treatment of **6c** with tetrabutylammonium fluoride in THF at −78 °C led again to the formation of (*Z*)-**12** and (*E*)-**12**, however, in favor of the thermodynamically less stable *cis*-olefin (*Z*)-**12** in a *Z*/*E* ratio of 5:1.

In summary, neither basic or acidic conditions nor the addition of a Ag(I) salt enhanced the rate of the aza-Cope rearrangement. The best reaction conditions giving satisfactory yields of rearranged products **7** were found by heating the intermediate adducts **6** in dioxane/water (40:1) at 90 °C.

For the conversion of the Mukaiyama-aldol adducts **6** into **7** two mechanisms can be postulated. The first possibility is depicted in eq 1 and involves a 2-aza-Cope rearrangement to yield the allenic silyl enol ether **13** followed by an intramolecular Mukaiyama aldol addition to the resulting imine. Analogous oxy-Cope rearrangements have been reported in the literature.[19−21]



This two-step mechanism would also offer an alternative pathway to the one shown in Scheme 1 for the

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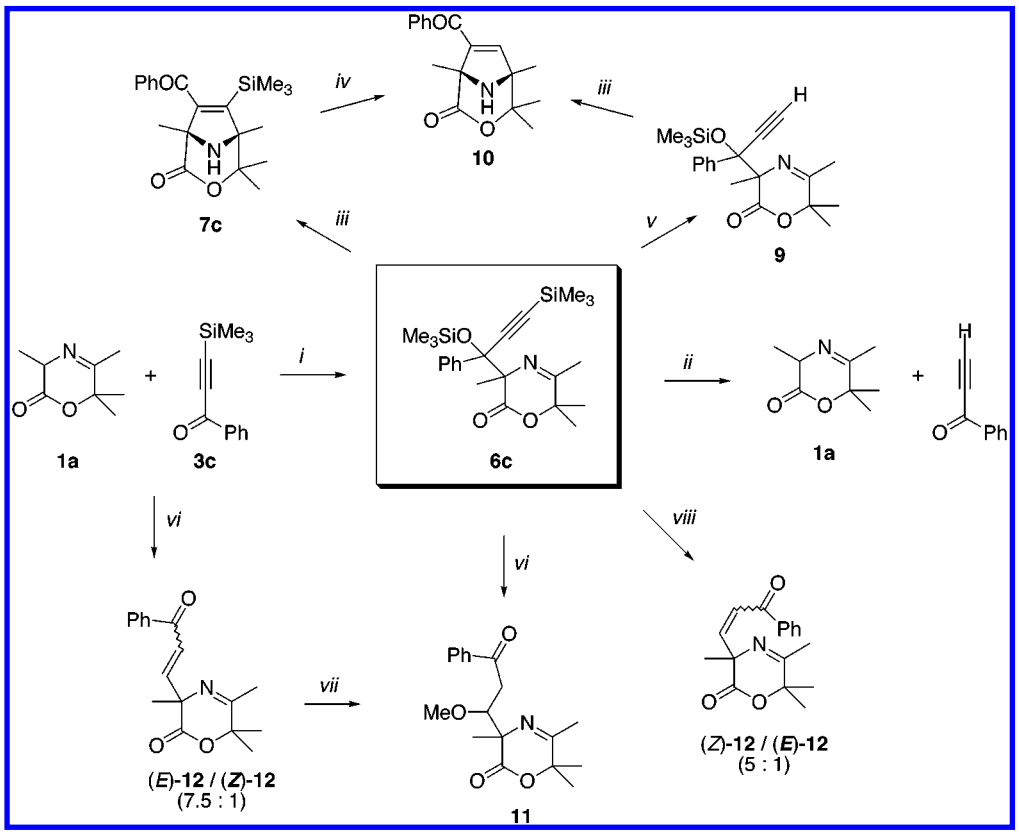
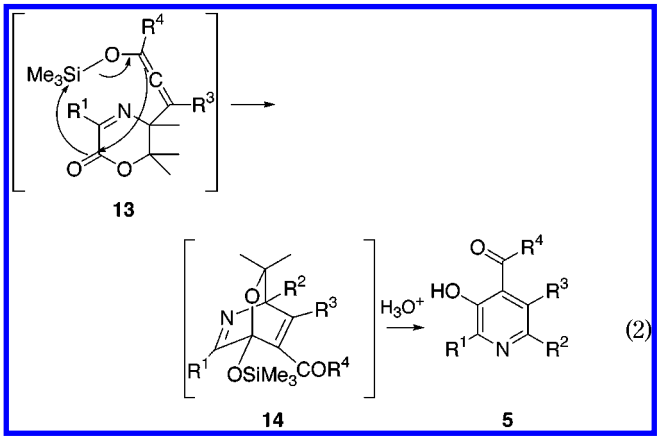
Scheme 4[a]



[a] Reagents and conditions: (i) TMS-Tf, DTBP, $CHCl_2$; (ii) H_3O^+; (iii) dioxane/H_2O, Δ; (iv) TBAF, THF, rt; (v) $AgNO_3$, NaCN, EtOH; (vi) cat. K_2CO_3, MeOH, rt; (vii) cat. K_2CO_3, MeOH, 40 °C; (viii) TBAF, THF, −78 °C.

formation of the observed nicotinic acid derivatives **5a** and **5b**. Thus, rearrangement of **13** into bicyclic intermediate **14**, the intermediate of the corresponding CAE reaction (Scheme 1), elimination of acetone, and aromatization would explain the formation of **5a** and **5b** (cf. eq 2).



An alternative possibility for the formation of the bicyclic pyrrolidine derivatives would involve a concerted mechanism in which in intramolecular migration of the trimethylsilyl group from oxygen to nitrogen would be accompanied by a simultaneous [1,2]-C−C bond migration of the oxazinone moiety to the adjacent triple bond.

From the experimental results, it is difficult to rule out one of these two mechanisms. Nevertheless, we favor the first mechanism because it offers a consistent rational for the observation of both the main bicyclic products, the occasionally occurring pyridine side products, and the transformations described in Scheme 4. The fact that the hydrolysis product of **13** was never detected might suggest that the 2-aza-Cope rearrangement rather than the aldol addition constitutes the rate-determining step.

Unfortunately, so far no reaction conditions have been found that would favor the formation of the desired pyridine derivatives.

Summary

In summary, we have found a novel reaction between silyl enol ethers derived from [1,4]oxazin-2-ones **1** and acetylenic ketones **3** yielding interesting bicyclic pyrrolidine derivatives **7** in good yields. Compounds of type **7** correspond to the regiochemically less favored products obtained from a [3 + 2] cycloaddition reaction between the two starting materials. A putative mechanism involving a Mukaiyama-aldol reaction followed by a 2-aza-Cope rearrangement rationalizes the formation and the regiochemical outcome of bicyclic pyrrolidine derivatives **7** as well as the formation of nicotinic acid derivatives **5a** and **5b**, which were formed as byproducts. The structures of the novel compounds of type **7** were confirmed by an X-ray structure of **7a**.

Experimental Section

General Methods. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 0.25 mm plates. Visualization was accomplished using ultraviolet light or the following stain: (a) 1% $KMnO_4$, 2% $NaHCO_3$ in H_2O, or (b) *o*-toluidine (320 mg), acetic acid (60 mL), and KI (2 g) dissolved in H_2O (1 l). Chromatography was performed using E. Merck

silica gel 60 (230−400 mesh). Solvent systems are reported as volume percent mixtures. Chloroform was filtered over alox prior to use, and CH_2Cl_2 was distilled from CaH and stored under Ar. Liquid reagents were distilled prior to use. All other reagents were purchased from Fluka or Aldrich and used without further purification.

General Procedure for Mukaiyama Aldol Reactions. To a stirred solution of oxazinone **1** (0.5 mmol) in dry CH_2Cl_2 (2 mL) at −30 °C under Ar were added ynone **3** (1.2 equiv) and di-*tert*-butylpyridine (2.5 equiv). TMS-OTf (2.2 equiv) was added dropwise, and the reaction mixture was stirred between −30 and −20 °C. After completion of the reaction, the mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was dried ($MgSO_4$), and the solvents were evaporated.

4-Phenyl-4-(3,5,6,6-tetramethyl-2-oxo-3,6-dihydro-2*H*-[1,4]oxazin-3-yl)-4-trimethylsilanyloxybut-2-ynoic Acid Methyl Ester (6a). Treatment of **1a** (500 mg, 3.22 mmol) with **3a** (728 mg, 1.2 equiv), di-*tert*-butylpyridine (1.59 mL, 2.5 equiv), and TMS-OTf (1.28 mL, 2.2 equiv) (24 h at −20 °C) according to the general procedure gave after chromatography on SiO_2 (90 g, hexane/ether 2:3, ether, ether/EtOAc) 1.2 g (90%) of **6a** (containing traces of **7a**) and 125 mg (10%) of the Michael-addition product.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5−7.45 (m, 2 arom. H); 7.35−7.25 (m, 3 arom. H); 3.83 (s, 3 H, $COOCH_3$); 1.97 (s, 3H, C(9)-H_3); 1.61 (s, C(3)H_3); 1.48 (s, C(11)H_3); 1.19 (s, C(12)H_3); 0.12 (s, 9H, $SiMe_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.52 (1); 167.40 (8); 153.68 (7); 139.42 (arom C); 128.38 (arom C); 127.94 (arom C); 127.26 (arom C); 87.78; 83.66 (10); 80.29 (6); 79.86 (4); 67.48 (2); 52.78 (COOMe); 28.16 (11); 26.60 (12); 23.87 (3); 22.16 (9); 1.24 ($SiMe_3$).

IR (film): 1736s; 1717s; 1685m; 1066m.

MS (EI): 415 (1, M^+); 400 (2, $[M - CH_3]^+$); 342 (3), 261 (100); 227 (22); 105 (40).

(1*S,5*R**)-7-Benzoyl-1,4,4,5-tetramethyl-2-oxo-3-oxa-8-azabicyclo[3.2.1]oct-6-ene-6-carboxylic Acid Methyl Ester (7a). 6a** was dissolved in $CHCl_3$ and heated to reflux for 5 h. Crystallization from hexane/EtOAc gave 730 mg (66%) of pure **7a** (plus 150 mg from mother liquor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.8−7.75 (m, 2 arom. H); 7.65−7.55 (m, 1 arom. H); 7.5−7.4 (m, 2 arom. H); 3.45 (s, 3H, $COOCH_3$); 2.48 (br, NH); 1.66 (s, C(10)H_3); 1.60 (s, C(9)H_3); 1.44 (s, C(12)H_3); 1.43 (s, C(11)H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.74 (13); 166.87 (2); 162.93 (14); 159.91 (7); 140.78 (6); 135.37; 134.28; 128.99; 128.70; 90.06 (4); 71.18 (1); 71.01 (5); 51.99 ($COOCH_3$); 24.96 (10);23.87 (11); 19.64 (9); 16.96 (12).

IR (KBr): 1729s; 1653s; 1594m.

MS (EI): 343 (5, M^+); 248 (100, $[M - C_3H_6O]^+$); 256 (48); 225 (72); 162 (10); 105 (28).

4-(3,5,6,6-Tetramethyl-2-oxo-3,6-dihydro-2*H*-[1,4]oxazin-3-yl)-4-(3,4,5-trimethoxyphenyl)-4-trimethylsilanyloxybut-2-ynoic Acid Ethyl Ester (6b) and (1*S,5*R**)-7-(3,4,5-Trimethoxybenzoyl)-1,4,4,5-tetramethyl-2-oxo-3-oxa-8-azabicyclo[3.2.1]oct-6-ene-6-carboxylic Acid Ethyl Ester (7b).** **1a** (100 mg, 0.644 mmol) was treated according to the general procedure with **3b** (282 mg, 1.5 equiv), di-*tert*-butylpyridine (360 μL, 2.5 equiv), and TMS-OTf (247 μL, 2.2 equiv) (3 h at −20 °C) to give after chromatography on SiO_2 (20 g, hexane/EtOAc 2:1 → 1:1, EtOAc) 25 mg (9%) of **7b**, 198 mg (∼60%) of **6b** (containing traces of **7b**), and 90 mg (30%) of 1,4-adduct.

6b was dissolved in $CHCl_3$ and heated to reflux for 5 h. Filtration over SiO_2 gave 160 mg (94%) of pure **7b** as a white foam.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.04 (s, 2 arom. H); 4.1−3.9 (m, OCH_2CH$_3$); 3.92 (s, 3 H, OCH_3); 3.88 (s, 6 H, 2 OCH_3); 2.5 (br, NH); 1.67 (s, CH_3); 1.58 (s, CH_3); 1.46 (s, CH_3); 1.45 (s, CH_3); 0.92 (t, 3H, OCH_2CH_3, J = 7.1).

IR (KBr): 1743s; 1721s; 1660m; 1416s; 1335s; 1128s.

MS (ISP): 465 (25, $[M + NH_4]^+$); 448 (100, $[M + H]^+$).

3,5,6,6-Tetramethyl-3-(1-phenyl-3-trimethylsilanyl-1-trimethylsilanyloxyprop-2-ynyl)-3,6-dihydro[1,4]oxazin-2-one (6c) and (1*S,5*R**)-7-Benzoyl-1,4,4,5-tetramethyl-6-trimethylsilanyl-3-oxa-8-azabicyclo[3.2.1]oct-6-en-2-one (7c).** **1a** (100 mg, 0.644 mmol) was treated according to the general procedure with **3c** (165 mg, 1.2 equiv), di-*tert*-butylpyridine (318 μL, 2.5 equiv), and TMS-OTf (256 μL, 2.2 equiv) (5 h at −30 °C and overnight at −20 °C). Chromatography on SiO_2 (15 g, hexane/ether 2:1 → 1:1) gave 263 mg (95%) of **6c** as a 2:1 (A:B) mixture of diastereomers.

A 350 mg (0.81 mmol) portion of **6c** was dissolved in dioxane/water (40:1) and heated to 95 °C for 3 d. Evaporation of the solvent and chromatography on SiO_2 gave 171 mg (59%) of **7c**.

Spectroscopic data of diastereomeric mixture of **6c**:

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.6−7.5 (m, 2 arom. H); 7.3−7.2 (m, 3 arom. H); 2.07 (s, A, CH_3); 1.95 (s, B, CH_3); 1.56 (s, B, CH_3); 1.53 (s, A, CH_3); 1.44 (s, A CH_3); 1.42 (s, B CH_3); 1.30 (s, A CH_3); 1.25 (s, B CH_3); 0.24 (s, 9H, B, $OSiMe_3$); 0.22 (s, 9H, A, $OSiMe_3$); 0.09 (s, 9H, A, $SiMe_3$); 0.07 (s, B, 9H, $SiMe_3$).

Spectroscopic data of **7c**:

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.8−7.75 (m, 2 arom H); 7.65−7.55 (m, 1 arom H); 7.5−7.35 (m, 3 arom H); 2.29 (br, NH); 1.63 (s, CH_3); 1.49 (s, CH_3); 1.44 (s, CH_3); 1.29 (s, CH_3); 0.11 (s, 9H, $SiMe_3$).

IR (KBr): 1730s; 1654s; 1595m; 1127s; 841s.

MS (ISP): 375 (65, $[M + NH_4]^+$); 358 (100, $[M + H]^+$).

4-Phenyl-4-(3,6,6-trimethyl-2-oxo-5-phenyl-3,6-dihydro-2*H*-[1,4]oxazin-3-yl)-4-trimethylsilanyloxybut-2-ynoic Acid Methyl Ester (6d), Methyl (1*S,5*R**)-7-Benzoyl-1,4,4-trimethyl-2-oxo-5-phenyl-3-oxa-8-azabicyclo [3.2.1]oct-6-ene-6-carboxylate (7d), and 4-Benzoyl-5-hydroxy-6-methyl-2-phenylnicotinic Acid Methyl Ester (5b). 1b** (109 mg, 0.5 mmol) was treated according to the general procedure with **3a** (94 mg, 1.2 equiv), di-*tert*-butylpyridine (280 μL, 2.5 equiv), and TMS-OTf (199 μL, 2.2 equiv) (3.5 h at −40 °C). Chromatography on SiO_2 (20 g, hexane/EtOAc 5:1 → 2:1) gave 105 mg (44%) of **6d** together with 40 mg (20%) of 1,4-adduct.

6d (105 mg, 0.22 mmol) was dissolved in dichloroethane and heated to 70 °C overnight. Evaporation of the solvent and chromatography on SiO_2 gave 44 mg (50%) of **7d** and 8 mg (10%) of **5b**.

Spectroscopic data of diastereomeric mixture of **6d**:

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.6−7.2 (m, 10 arom H); 3.82 (s, A, OCH_3); 3.80 (s, B, OCH_3); 1.71 (s, A, CH_3); 1.63 (s, B, CH_3); 1.60 (s, B, CH_3); 1.58 (s, A, CH_3); 1.55 (s, A + B, CH_3); 1.45 (s, B, CH_3); 1.29 (s, A, CH_3); 0.15 (s, 9H, A, $OSiMe_3$); 0.10 (s, 9H, A, $OSiMe_3$).

MS (ISP): 495 (60, $[M + NH_4]^+$); 478 (100, $[M + H^+]$).

Spectroscopic data of **7d**:

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.8−7.75 (m, 4 arom H); 7.65−7.55 (m, 1 arom H); 7.5−7.3 (m, 5 arom H); 3.27 (s, 3H, $COOCH_3$); 3.05 (br, NH); 1.81 (s, CH_3); 1.62 (s, CH_3); 1.43 (s, CH_3).

IR (MIR): 1735s; 1651m; 1250m.

MS (EI): 373 (5, $[M - CH_3OH]^+$); 346 (36, $[M - COOCH_3]^+$); 319 (58); 286 (100); 230 (14); 105 (14).

Spectroscopic data of **5b**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.5 (br, OH); 7.75−7.65 (m, 2 arom H); 7.6−7.5 (m, 1 arom H); 7.5−7.3 (m, 7 arom H); 3.00 (s, 3 H, $COOCH_3$); 2.67 (s, 3H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ 198.55 (C=O); 167.27 (COOMe); 152.10; 149.05; 148.27; 139.31; 137.20; 133.72; 129.20; 128.50; 128.32; 128.28; 125.58; 123.97; 51.92 (OMe); 19.81 (Me).

MS (ISN): 464 (10, $[M + OAc]^+$); 346 (100, $[M - H^+]$).

3,6,6-Trimethyl-5-phenyl-3-(1-phenyl-3-trimethylsilanyl-1-trimethylsilanyloxyprop-2-ynyl)-3,6-dihydro[1,4]oxazin-2-one (6e) and (1*S,5*R**)-7-Benzoyl-5-phenyl-1,4,4-trimethyl-6-trimethylsilanyl-3-oxa-8-azabicyclo[3.2.1]oct-6-en-2-one (7e). 1b** (140 mg, 0.644 mmol) was treated according to the general procedure with **3c** (165 mg, 1.2 equiv), di-*tert*-butylpyridine (318 μL, 2.5 equiv), and TMS-OTf (256 μL, 2.2 equiv) (5 h at −30 °C and overnight at −20 °C). Chromatography on SiO_2 (15 g, hexane/ether 2:1 → 1:1) gave 292 mg (92%) of **6e** as a 2:3 mixture of diastereoisomers.

A 60 mg (0.12 mmol) portion of **6e** was dissolved in dichloroethane and heated to reflux overnight to give after chromatography 28 mg (55%) of **7e**.

Spectroscopic data of diastereomeric mixture of **6e**:

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.7−7.5 (m, 4 arom H); 7.5−7.15 (m, 6 arom H); 1.69 (s, A, CH_3); 1.67 (s, B, CH_3); 1.59 (s, B, CH_3); 1.56 (s, A, CH_3); 1.48 (s, A CH_3); 1.30 (s, B CH_3); 0.26 (s, 9H, B, $OSiMe_3$); 0.23 (s, 9H, A, $OSiMe_3$); 0.12 (s, 9H, B, $SiMe_3$); 0.07 (s, A, 9H, $SiMe_3$).

Spectroscopic data of **7e**:

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.85−7.8 (m, 2 arom H); 7.6−7.3 (m, 5 arom H); 7.3−7.2 (m, 1 arom H); 7.1−7.05 (m, 2 arom H); 2.9 (br., NH); 1.88 (s, CH_3); 1.81 (s, CH_3); 1.40 (s, CH_3); 0.02 (s, 9H, $SiMe_3$).

MS (ISP): 437 (100, $[M + NH_4]^+$); 420 (95, $[M + H]^+$).

3,5,6,6-Tetramethyl-3-(1-phenyl-1-trimethylsilanyloxy-prop-2-ynyl)-3,6-dihydro[1,4]oxazin-2-one (9). To a solution of **6c** (100 mg, 0.23 mmol) in EtOH (1 mL) was added at rt under Ar a solution of $AgNO_3$ (104 mg, 0.61 mmol) in EtOH/water (3:1). The mixture was stirred at rt for 1 h. NaCN (30 mg, 0.61 mmol) was added, and the white suspension was stirred for another 30 min. The mixture was poured on brine and extracted with ether. The organic layer was dried ($MgSO_4$), and the solvents were evaporated. The product was purified by chromatography on SiO_2 (20 g, hexane/EtOAc 1:1) to give 30 mg (37%) of **9** as a mixture of diastereomers.

^{1}H NMR (250 MHz, $CDCl_3$): 7.45−7.4 (m, 2 arom H); 7.25−7.15 (m, 3 arom H); 2.79 (s, 1 acetylene H); 1.87 (s, CH_3); 1.53 (s, CH_3); 135 (s, CH_3); 1.11 (s, CH_3); 0.0 (s, 9 H, $OSiMe_3$).

MS (ISP): 358 (100, $[M + H]^+$).

(1*S,4*R**)-7-Benzoyl-1,4,4,5-tetramethyl-3-oxa-8-azabicyclo[3.2.1]oct-6-en-2-one (10).** To a solution of **6c** (14 mg, 39 μmol) in THF was added at rt under Ar TBAF (1 M solution in THF, two drops). The mixture was stirred at rt for 1 h, poured on brine, and extracted with ether. The organic layer was dried ($MgSO_4$), and the solvents were evaporated. The product was purified by chromatography on SiO_2 (2 g, hexane/EtOAc 1:1) to give 10 mg (89%) of **10**.

^{1}H NMR (250 MHz, $CDCl_3$): 7.85−7.75 (m, 2 arom H); 7.65−7.55 (m, 1 arom H); 7.5−7.4 (m, 2 arom H); 6.76 (s, 1 olef H); 2.3 (br, NH); 2.04 (s, CH_3); 1.64 (s, CH_3); 1.58 (s, CH_3); 1.46 (s, CH_3).

MS (ISP): 571 (15, $[2M + H]^+$); 286 (100, $[M + H]^+$).

3-(1-Methoxy-3-oxo-3-phenylpropyl)-3,5,6,6-tetramethyl-3,6-dihydro[1,4]oxazin-2-one (11). To a solution of **6c** (100 mg, 0.23 mmol) in MeOH (1 mL) was added at rt under Ar K_2CO_3 (3−4 crystals). The mixture was stirred at rt overnight, poured on brine, and extracted with ether. The organic layer was dried ($MgSO_4$), and the solvents were evaporated. The product was purified by chromatography on SiO_2 (20 g, hexane/EtOAc 1:1) to give 50 mg (68%) of **11**.

^{1}H NMR (250 MHz, $CDCl_3$): 8.0−7.9 (m, 2 arom H); 7.6−7.4 (m, 3 arom H); 4.51 (dd, 1 aliph H, J = 2.6, 6.3 Hz); 3.75 (s, 3 H, OMe); 3.18 (dd, 1 aliph H, J = 16.6, 6.3 Hz); 3.03 (dd, 1 aliph H, J = 2.6, 16.6 Hz); 1.99 (s, CH_3); 1.44 (s, CH_3); 1.37 (s, CH_3); 1.31 (s, CH_3).

MS (ISP): 635 (20, $[2M + H]^+$); 318 (100, $[M + H]^+$).

(*E*)- and (*Z*)-3,5,6,6-Tetramethyl-3-(3-oxo-3-phenylpropenyl)-3,6-dihydro[1,4]oxazin-2-one ((*E*)- and (*Z*)-12). To a solution of **1a** (100 mg, 0.23 mmol) and **3c** (156 mg, 1.2 equiv) in MeOH (1 mL) was added at rt. under Ar K_2CO_3 (3−4 crystals). The mixture was stirred at rt for 2 h, poured on brine, and extracted with ether. The organic layer was dried ($MgSO_4$), and the solvents were evaporated. The product was purified by chromatography on SiO_2 (10 g, hexane/EtOAc 1:1) to give 130 mg (71%) of a 7.5:1 mixture of (*E*)-**12** and (*Z*)-**12**. The isomers were not separated.

Spectroscopical data for (*E*)-**12**:

^{1}H NMR (250 MHz, $CDCl_3$): 7.95−7.9 (m, 2 arom H); 7.65−7.4 (m, 3 arom H); 7.13 (d, 1 olef H, J = 15.6 Hz); 7.01 (d, 1 olef H, J = 15.6 Hz); 2.18 (s, CH_3); 1.74 (s, CH_3); 1.61 (s, CH_3); 1.52 (s, CH_3).

MS (ISP): 303 (100, $[M + NH_4]^+$); 286 (25, $[M + H]^+$).

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Supporting Information Available: ^{1}H NMR and 2D NMR spectra of compounds **6a** and **7a**, and an ORTEP diagram (Figure 1) and X-ray structure data for compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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