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Tetrahedron
Tetrahedron 61 (2005) 493–500

Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides

Ming-Chang P. Yeh,* Chi-Fen Jou, Wei-Tzou Yeh, Da-Yu Chiu and N. Ravi Kumar Reddy

Department of Chemistry, National Taiwan Normal University, 88 Ding-Jou Road, Section 4, Taipei 117, Taiwan, ROC

Received 3 September 2004; accepted 12 October 2004

Abstract—Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene- and -1,3,5-triene-tethered nitrile oxides gave tricyclic isoxazolines as a single stereoisomer in most cases. The relative stereochemistry of tricycle-fused isoxazolines resulting from 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides is *cis–cis*, whereas from cyclohepta-1,3,5-triene-tethered nitrile oxides the *cis–trans* isomer predominates.

1. Introduction

Cycloaddition of nitrile oxide and olefin produces isoxazoline derivatives, which has played an important role for the construction of five-membered heterocycles. The isoxazoline ring has been revealed to be a latent precursor for a variety of difunctional compounds like γ-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles and unsaturated oximes,[1] therefore the heterocycles has been utilized for construction of natural products having such functionalities.[2] On the other hand, the intramolecular cycloaddition is useful synthetic strategy to yield bicyclic compounds, which often proceeds with high regio- and stereoselectivity. When nitrile oxides were used as the intramolecular 1,3-dipole, bicyclic isoxazolines were produced.[3–5] For example, norbonadiene-tethered nitrile oxides underwent intramolecular cycloaddition to afford good yields of highly regio- and stereoselective tetracyclic compounds.[6] Recently, we are interested in the intramolecular cycloaddition of conjugated dienes with nitrile oxides because of highly stereoselective polycyclic products as new building blocks for synthesis of naturally occurring materials. Surprisingly, reports on the intramolecular cycloaddition of conjugated dienes and nitrile oxides are rare.[7] This report describes synthesis of cyclo-1,3-diene- and 1,3,5-triene-tethered nitrile oxides by treatment of the corresponding aldoximes with *n*-BuLi and *N*-chlorosuccinimide (NCS), and the intramolecular 1,3-dipolar cycloaddition.

Keywords: Aldoximes; Isoxazolines; Cyclohexa- and cyclohepta-1,3-dienes; Cyclohepta-1,3,5-trienes.
* Corresponding author. Tel.: +886 2 29350750; fax: +886 2 29324249; e-mail: cheyeh@scc.ntnu.edu.tw

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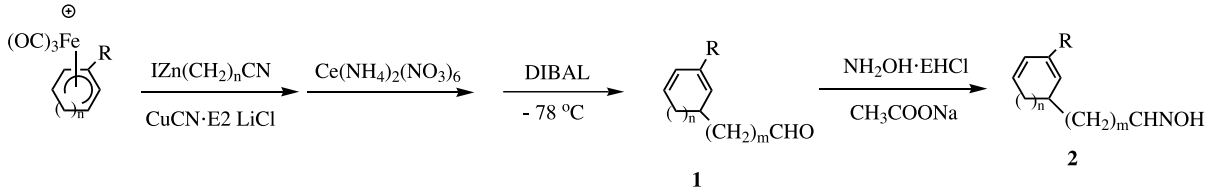
doi:10.1016/j.tet.2004.10.078

2. Results and discussion

Cyclo-1,3-dienaldoximes were synthesized according to the literature procedures.[8–11] As shown in Scheme 1, the starting cyclohexa-1,3-dienaldoximes **2a–f** were prepared starting from addition of functionalized zinc–copper reagents to (η^5-cyclohexadienyl)tricarbonyliron cation salt. Treating cyclohexa-1,3-dienals **1a–f**[8,9] with NH_2-OH·HCl and CH_3COONa in MeOH at 30 °C afforded **2a–f** (entries 1–6, Table 1). Cyclohepta-1,3-dienaldoximes **2g–h** (entries 7–8, Table 1) were synthesized in the similar fashion starting from (η^5-cycloheptadienyl)tricarbonyliron cation salt.[8,10] Cyclohepta-1,3,5-triene derivatives **3a–c** (entries 10–12, Table 1) were synthesized starting from the corresponding zinc–copper reagents and (η^7-cycloheptatrienyl)tricarbonylchromium cation salt (Scheme 2).[8,11]

Dienaldoxime **2a** in CH_2Cl_2 solution (0.03 M) was treated with NCS (1.3 mol equiv) at 30 °C for 2 h followed by slow addition of triethylamine (1.5 mol equiv) at 0 °C. The reaction was stirred at 30 °C for 24 h and led in 45% yield to tricyclic isoxazoline **4** (entry 1, Table 1). The other method was employed to produce the corresponding nitrile oxide using *n*-BuLi as base. Reaction of *n*-BuLi (1.1 mol equiv) with **2a** at 0 °C for 30 min followed by addition of NCS (1.3 mol equiv, 0.03 M in THF) gave a light yellow solution. The yellow solution was stirred at 30 °C for 3 h under nitrogen to give compound **4** as the only diastereomer isolated in 64% (entry 1, Table 1) after chromatographic purification. Thus, the use of the C-5 tethered cyclohexa-1,3-dienaldoxime allowed controlling the stereochemistry of three contiguous asymmetric centers of the tricycle-fused isoxazolines in a single step. Moreover, the current reaction



a : R = H, m = 2, n = 1

b : R = H, m = 3, n = 1

d : R = $SiMe_2Ph$, m = 3, n = 1
e : R = $SiMe_2Ph$, m = 4, n = 1
g : R = H, m = 2, n = 2

h : R = H, m = 3 , n = 2

Scheme 1.

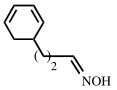
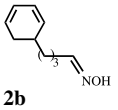
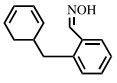
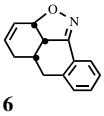
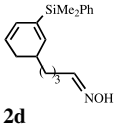
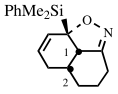
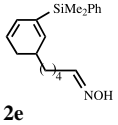
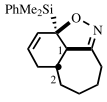
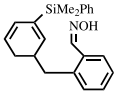
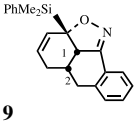
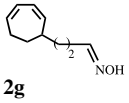
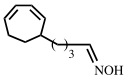
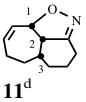
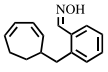
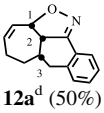
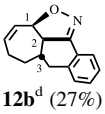
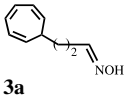
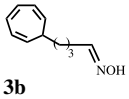
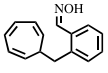
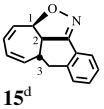
condition (*n*-BuLi, NCS, and cyclo-1,3-dienaldoxime, 30 °C, 3 h) for 1,3-dipolar cycloaddition is easier than those of alkene analogs, which normally required higher temperatures (80–110 °C) and longer hours (15–48 h).[6] NMR studies provided the initial evidence for support of the structural assignments. The ^{1}H NMR spectrum of compound **4** exhibited a multiplet at δ 5.96 assigned to the vinyl H at C-7 (Scheme 3); a broad doublet at δ 5.76 assigned to the vinyl H at C-6; a doublet of doublets, centered at δ 4.92 assigned to the methine H at C-7a; a doublet of doublets at δ 3.83 assigned to the methine H at C-7b. The C-13 NMR spectrum exhibited a signal at δ 170.1 assigned to C-2a (iminyl); two signals at δ 130.7 and 125.2 assigned to two vinyl carbons (C-6 and C-7); and a signal at δ 74.6 assigned to C-7a. The relative stereochemistry for **4** was assigned by NOESY (nuclear Overhauser enhancement spectroscopy) measurements. For example, cross peaks for **7a** and **7b** and **7b** and **4a** in the NOSEY spectrum indicated that *cis–cis* relative stereochemistry for the three fused methine protons. The stereochemical outcome suggested that the dipole is aligned to the face of the cyclohexadiene in which the tethering chain resides (Scheme 3). This stereoselectivity is consistent to those of 1,3-dipolar cycloaddition of cyclohexene-tethered nitrile oxides.[4c] Under the same reaction condition, tricyclic isoxazolines **5** (70%) and **6** (66%) were produced from intramolecular 1,3-dipolar cycloadditions of **2b** (entry 2, Table 1) and **2c** (entry 3, Table 1), respectively. The *cis–cis* relative stereochemistry assigned for both **5** and **6** was based on NOSEY measurements and comparison of their coupling constants of fused methine protons with the corresponding data of **4**.

Several entries in Table 1 deserve special mention. Substrates with a bulky dimethylphenylsilyl group at the C-3 position of the cyclohexa-1,3-diene ring, **2d–f** (entries 4–6, Table 1), also underwent intramolecular dipolar cycloaddition to produce **7** (39%), **8** (25%), and **9** (48%), respectively, as the only diastereomeric product in each case. Since norbornadiene derivative, **16**, with a trimethylsilyl group at the olefinic carbon failed to give cycloadducts after stirring in toluene at 90 °C for 96 h (Eq. 1),[11] it is reasonable to state that cyclo-1,3-diene-tethered nitrile oxides are more reactive substrates than unconjugated norbornadiene analogs. The *cis* relationship for the dimethylphenylsilyl group and H_1 of **7** is fixed by syn cycloaddition of the olefin with the tethered nitrile oxide. The relative stereochemistry for H_1 and H_2 assigned as *cis* came from the coupling constant of 5.2 Hz for H_1–H_2, which is close to those of the same methine protons of **5** (6.5 Hz) and **6** (5.2 Hz). The *cis–cis* stereochemistry was secured by X-ray diffraction analysis of **7**. Similarly, the relative configuration for the two fused methine protons of **9** determined to be *cis* was based on the coupling constant of 4.7 Hz for H_1–H_2. However, a coupling constant of 10.4 Hz for H_1–H_2 of **8** suggested a *trans* relationship between H_1 and H_2. This assignment was further confirmed by comparison of the coupling constant with those of *trans* methine fused protons of **12b** and **13–15** (see below). The stereochemical course of formation of tricyclic isoxazoline **8** indicated that the tether with four methylene carbons may be long enough for the dipole to align to the dipolarophile on the opposite face of the cyclohexadiene ring (Scheme 4).

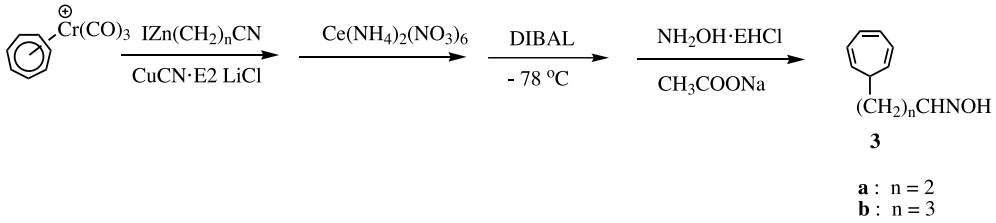
Increasing the ring size by one with the cyclohepta-1,3-diene derivatives **2g** (entry 7, Table 1) and **2h** (entry 8, Table 1) also underwent 1,3-dipolar cycloaddition to provide tricyclic isoxazolines **10** (70%) and **11** (60%), respectively, as the only stereoisomer in each case. The *cis–cis* configurations of **10** and **11** were secured by X-ray diffraction analysis. Surprisingly, 1,3-dipolar cycloaddition of cyclohepta-1,3-diene containing an aromatic nitrile oxide, **2i**, generated a mixture of diastereomers **12a** (50%) and **12b** (20%) (entry 9, Table 1). The structure for **12a** was established using coupling constants of H_1–H_2 and H_2–H_3. The centered H_2 of **12a** exhibited as a doublet of doublets with coupling constants of 11.2 and 4.4 Hz which are close to those of **10** (11.0, 7.5 Hz) and **11** (10.8, 5.3 Hz). However, the ^{1}H NMR spectrum of **12b** revealed a triplet for H_2 at δ 3.25, with a coupling constant of 12.1 Hz. The large coupling constant indicated a *cis* relationship between H_1 and H_2 and a *trans* relationship between H_2 and H_3 in the tricycle-fused isoxazoline **12b**. Rigorous proof of the structures were accomplished by X-ray diffraction analysis of **12a** and **12b**. The generation of both diasteroisomers **12a** and **12b** suggested that 1,3-dipolar cycloaddition of **2i** occurred on both faces of the cycloheptadiene ring.

Under the same reaction condition, cyclohepta-1,3,5-triene-tethered nitrile oxides **3a–3c** (entries 10–12, Table 1) afforded tricyclic isoxazolines **13** (15%), **14** (80%), and **15** (68%), respectively, as a single stereoisomer in each case. The structures for **13–15** were established as *cis–trans* by

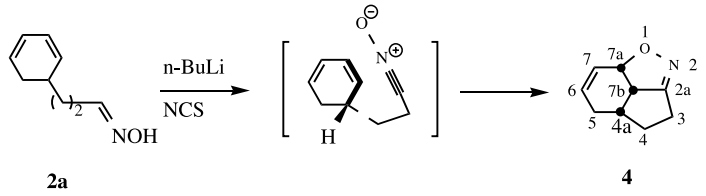
Table 1. Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides

Entry[a]	Dienaldoximes	Cycloadducts		Yield[b]
1	 **2a**	 **4**		64%[a]
2	 **2b**	 **5**		70%[a]
3	 **2c**	 **6**		66%[a]
4	 **2d**	 **7**[d]		39%[c]
5	 **2e**	 **8**		25%[c]
6	 **2f**	 **9**		48%[c]
7	 **2g**	 **10**[d]		70%[a]
8	 **2h**	 **11**[d]		60%[a]
9	 **2i**	 **12a**[d] (50%)	 **12b**[d] (27%)	77%[a]
10	 **3a**	 **13**[d]		15%[c]
11	 **3b**	 **14**[d]		80%[a]
12	 **3c**	 **15**[d]		68%[a]

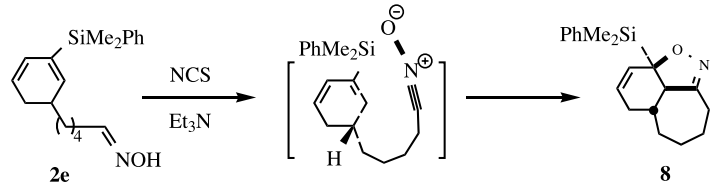
[a] Cyclizations were carried out in THF using *n*-BuLi (1.2 equiv) and NCS at 30 °C for 3 h.
[b] Isolated yields after column chromatography.
[c] Cyclizations were carried out in THF using Et_3N (1.2 equiv) and NCS at 30 °C for 24 h.
[d] The structure is confimed by X-ray diffraction analysis.



Scheme 2.

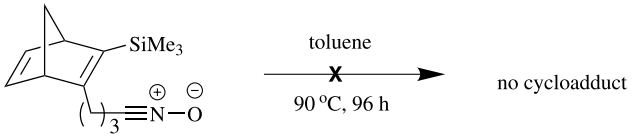


Scheme 3.



Scheme 4.

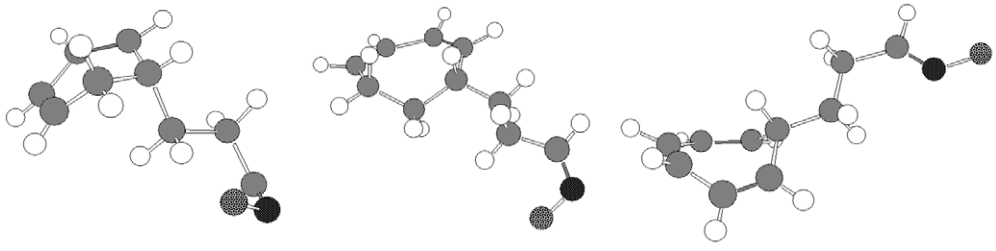
comparison of their ^{1}H NMR spectral data with the corresponding data of **12b**. Rigorous proof of the structures was accomplished by X-ray diffraction analysis of **13**–**15**. The result suggested that 1,3-dipolar cycloaddition of cyclohepta-1,3,5-triene-tethered nitrile oxides occurred on the β-face of the ring. The different stereochemical outcome between cyclic diene and triene analogs may be explained by computer-based modeling methods. Molecular modeling of the cyclohepta-1,3,5-triene derivative **3a** reveals that all six sp^2 carbons of the ring are nearly on the same plane and the C-7 carbon locates above the plane. Thus, the tethered dipole could add to the dipolarophile on the β-face of the ring to give the *cis–trans* diastereomer (Fig. 1). While tethered nitrile oxides of cyclic diene analogs (**2a** and **2g**) locating at the α-face of the ring would approach to the olefine from α-face (Fig. 1).



(1)

3. Conclusion

The reactions outlined herein demonstrate that intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene- and 1,3,5-triene-tethered nitrile oxides can be an effective method for synthesis of tricycle-fused isoxazolines in



2a **2g** **3a**

Figure 1.

diastereoselective fashion. Specially, it is a synthetic advantage that the tricycle-fused isoxazolines contain a masked allyl alcohol. In the particular reaction cases demonstrated in this work, products having an α-silyl allyl alcohol functionality masked in the fused isoxazolines are generated. Moreover, tricyclic isoxazolines containing a conjugated diene in a seven-membered ring would be expected to demonstrate still higher levels of synthetic utility.

4. Experimental

4.1. General

All reactions were run under a nitrogen atmosphere in oven-dried glassware unless otherwise indicated. Anhydrous solvents or reaction mixtures were transferred via an oven-dried syringe or cannula. Tetrahydrofuran (THF) was dried by passing through two sequential columns of activated alumina.[12] Aldehydes **1a–b**[8,11] were prepared according to literature procedures. Flash column chromatography, following the method of Still, was carried out with silica gel (230–400 mesh) using the indicated solvents.[13] ^{1}H nuclear magnetic resonance (NMR) spectra were obtained with 400 and 500 MHz spectrometers. The chemical shifts are reported in parts per million with either tetramethylsilane (0.00 ppm) or $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded frequency of 100 and 125 MHz with $CDCl_3$ (77.0 ppm) as the internal standard. Mass spectra were acquired at an ionization potential of 70 eV and are reported as mass/charge (*m*/*e*) with percent relative abundance. High-resolution mass spectra (HRMS) were obtained with a double-focusing mass spectrometer.

4.2. Typical procedures for intramolecular 1,3-dipolar cycloaddition via sequential additions of hydroxylamine hydrochloride, *N*-chlorosuccinimide, and *n*-BuLi to cyclo-1,3-diene-tethered aldehydes

In a typical procedure, to a 100 mL round bottom flask under nitrogen was added NaOAc (0.63 g, 7.71 mmol), $NH_2OH\cdot HCl$ (0.54 g, 7.71 mmol) and MeOH (10 mL). To the reaction mixture at 30 °C, aldehyde **1a** (0.70 g, 5.14 mmol in 10 mL of MeOH) was added via syringe and was stirred at 30 °C for 2 h. The reaction mixture was concentrated. The resulting mixture was diluted with 50 mL of CH_2Cl_2 and 50 mL of water. The reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The resultant solution was washed with water (3×50 mL) and brine (2×100 mL), dried over anhydrous magnesium sulfate (5.0 g), and concentrated to give the crude mixture (0.70 g, 4.63 mmol, 90%). Flash column chromatography of the crude mixture produced aldoximes as a mixture of Z and E isomers and was used without further separation. To a 100 mL Shlenk flask under nitrogen was added aldoxime **2a** (0.10 g, 0.66 mmol) in 22 mL of THF. To the reaction mixture at −78 °C, *n*-BuLi (0.34 mL, 2.5 M, 0.86 mmol) was added slowly and was stirred at 30 °C for 30 min.[14] To the reaction mixture at 0 °C, NCS (0.11 g, 0.86 mmol) in 15 mL of THF was added slowly via syringe to give a light yellow solution. The reaction mixture was quenched with 30 mL of saturated aqueous ammonium chloride after aldoxime **2a** was no longer appeared on TLC (ca. 3 h). The reaction mixture was extracted with EtOAc (3× 30 mL). The resultant solution was washed with water (3× 50 mL) and brine (2×100 mL), dried over anhydrous magnesium sulfate (5.0 g), and concentrated to give the crude mixture.

4.2.1. Cycloadduct 4. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2a** (0.10 g, 0.66 mmol) using *n*-BuLi (0.34 mL, 2.5 M, 0.86 mmol) and NCS (0.11 g, 0.86 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **4** (0.062 g, 0.42 mmol, 64%) as a yellow oil: IR (CH_2Cl_2) 3052, 2944, 2872, 1652, 1439, 1422, 1391, 1282, 1267, 1256, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.76 (br d, J=10.0 Hz, 1H), 4.92 (dd, J=9.9, 3.7 Hz, 1H), 3.83 (dd, J=9.5, 8.0 Hz, 1H), 2.37 (m, 4H), 2.19 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 130.7, 125.2, 74.6, 54.5, 35.4, 29.2, 24.5, 19.8; MS (EI) *m*/*z* 149.1 (M^+, 30), 132.1 (14), 117.1 (16), 95.0 (11), 91.0 (100), 79.1 (22), 77.0 (19), HRMS (EI) *m*/*z* calcd for $C_9H_{11}NO$ 149.0841, found 149.0842. The relative stereochemistry for **4** was determined by NOESY (nuclear Overhauser enhancement spectroscopy) measurements. Cross peaks for **7a** and **7b** and **7b** and **4a** in the NOSEY spectrum showed a *cis–cis* relationship among these protons.

4.2.2. Cycloadduct 5. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2b** (0.20 g, 1.21 mmol) using *n*-BuLi (0.58 mL, 2.5 M, 1.45 mmol) and NCS (0.21 g, 1.57 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **5** (0.14 g, 0.85 mmol, 70%) as a yellow oil: IR (CH_2Cl_2) 3060, 2942, 2855, 1732, 1657, 1434, 1422, 1394, 1282, 1267, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (ddd, J=10.0, 6.4, 2.1 Hz, 1H), 5.76 (dt, J=11.0, 4.4 Hz, 1H), 5.04 (dd, J=11.0, 4.4 Hz, 1H), 3.33 (dd, J=10.9, 6.5 Hz, 1H), 2.75 (dd, J=11.1, 3.6 Hz, 1H), 2.38 (m, 1H), 2.08 (m, 2H), 1.74 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 132.5, 124.7, 74.4, 48.8, 31.0, 28.6, 24.6, 24.3, 18.7; MS (EI) *m*/*z* 163.1 (M^+, 75), 146.1 (26), 131.1 (21), 117.0 (20), 109.0 (21), 105.1 (36), 91.0 (100), 79.0 (46); 77.0 (30); HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0996. The relative stereochemistry for **5** was determined by NOESY measurements.

4.2.3. Cycloadduct 6. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2c** (0.30 g, 1.40 mmol) using *n*-BuLi (0.67 mL, 2.5 M, 1.68 mmol) and NCS (0.23 g, 1.68 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **6** (0.20 g, 0.86 mmol, 66%) as a yellow solid: mp 108–110 °C; IR (CH_2Cl_2) 3061, 2986, 2927, 1732, 1610, 1483, 1462, 1438, 1424, 1375, 1282, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J=7.9 Hz, 1H), 7.34 (dt, J=7.4, 1.3 Hz, 1H), 7.25 (m, 2H), 6.01 (ddd, J=10.2, 5.9, 1.9 Hz, 1H), 5.72 (dt, J=10.2, 4.2 Hz, 1H), 5.20 (br d, J= 9.5 Hz, 1H), 3.64 (dd, J=9.6, 5.2 Hz, 1H), 3.16 (dd, J= 16.9, 5.6 Hz, 1H), 2.83 (dd, J=16.9, 1.9 Hz, 1H), 2.69 (m,

1H), 2.04 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 136.3, 132.0, 130.5, 129.8, 126.8, 126.0, 125.2, 123.9, 76.3, 47.4, 35.3, 28.5, 25.2; MS (EI) *m/z* 211.1 (M^+, 100), 194.1 (43), 165.1 (41), 116.1 (83), 79.1 (48), 77.0 (32); HRMS (EI) *m/z* calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0998. The relative stereochemistry for **6** was determined by NOESY measurements.

4.2.4. Cycloadduct 7. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2d** (0.26 g, 0.87 mmol) using NCS (0.20 g, 1.46 mmol) and triethylamine (0.15 mL, 1.07 mmol) in CH_2Cl_2 for 24 h was purified by flash-column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **7** (0.10 g, 0.34 mmol, 39%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **7**: mp 89–90 °C; IR (CH_2Cl_2) 3627, 2944, 2854, 1684, 1635, 1428, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.31 (m, 3H), 5.91 (ddd, J=10.1, 5.8, 2.3 Hz, 1H), 5.62 (ddd, J=10.1, 2.9, 1.5 Hz, 1H), 3.03 (d, J=5.2 Hz, 1H), 2.76 (m, 1H), 2.02 (m, 2H), 1.96 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.65 (m, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 0.40 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 135.2, 134.4, 129.6, 129.4, 127.7, 126.2, 76.5, 51.4, 30.4, 29.0, 24.6, 24.2, 18.1, −5.6, −6.1; MS (EI) *m/z* 297.2 (M^+, 8), 255.2 (5), 229.2 (10), 213.1 (4), 153.1 (5), 152.1 (13), 151.1 (100), 137.1 (11), 135.1 (36); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NOSi$ 297.1549, found 297.1550. Anal. Calcd for $C_{18}H_{23}NOSi$: C, 72.68; H, 7.79; N, 4.71. Found: C, 72.98; H, 7.84; N, 4.78. The relative stereochemistry for **7** was confirmed by X-ray diffraction analysis.

4.2.5. Cycloadduct 8. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2e** (0.60 g, 1.91 mmol) using NCS (0.38 g, 2.87 mmol) and triethylamine (0.29 mL, 2.09 mmol) in CH_2Cl_2 for 24 h was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **8** (0.15 g, 0.48 mmol, 25%) as a yellow oil: IR (CH_2Cl_2) 3629, 2927, 2862, 1830, 1636, 1602, 1427 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.40 (m, 3H), 5.91 (br s, 2H), 2.83 (d, J=10.4 Hz, 1H), 2.48 (ddd, J=16.8, 12.2, 4.3 Hz, 1H), 2.15 (dt, J=17.0, 4.3 Hz, 1H), 1.94–1.78 (m, 4H), 1.40 (m, 2H), 1.30 (m, 1H), 1.25 (m, 1H), 1.24 (m, 1H), 0.36 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 134.9, 134.5, 129.4, 127.7, 127.5, 125.9, 81.0, 54.6, 36.8, 35.3, 30.9, 27.9, 26.9, 24.8, −6.3, −6.9; MS (EI) *m/z* 311.2 (M^+, 0), 213.1 (5), 152.1 (10), 151.1 (100), 137.0 (4), 136.1 (4), 135.1 (31), 107.0 (4), 91.0 (9); HRMS (EI) *m/z* calcd for $C_{19}H_{25}NOSi$ 311.1705, found 311.1700. The relative stereochemistry for **8** was determined by the coupling constant between the centered and the adjacent fused methine protons.

4.2.6. Cycloadduct 9. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2f** (0.43 g, 1.25 mmol) using triethylamine (0.20 mL, 1.37 mmol) and NCS (0.20 g, 1.50 mmol) in CH_2Cl_2 for 24 h was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **9** (0.21 g, 0.60 mmol, 48%) as a yellow oil: IR (CH_2Cl_2) 3684, 3070, 3025, 2921, 2838, 1768, 1609, 1460, 1428, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=7.6 Hz, 1H), 7.67 (m, 2H), 7.40 (m, 3H), 7.31 (dt, J=7.5, 1.3 Hz, 1H), 7.23 (m, 2H), 5.89 (ddd, J=10.1, 5.48, 2.12 Hz, 1H), 5.65 (dd, J=10.2, 2.1 Hz, 1H), 3.40 (d, J=4.7 Hz, 1H), 3.03 (dd, J=16.7, 4.6 Hz, 1H), 2.73 (dd, J=16.8, 1.9 Hz, 1H), 2.21 (m, 1H), 1.96 (dt, J=18.0, 5.9 Hz, 1H), 1.76 (ddt, J=18.0, 11.3, 2.5 Hz, 1H), 0.52 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 136.2, 134.9, 134.4, 134.1, 130.2, 129.8, 129.5, 127.8, 126.6, 126.1, 125.4, 125.3, 78.4, 50.4, 35.7, 28.6, 25.2, −5.4, −5.7; MS (EI) *m/z* 345.1 (M^+, 0), 255.2 (1), 299.0 (3), 213.0 (1), 153.0 (3), 152.0 (10), 151.0 (100), 137.0 (5), 135.0 (20), 85.9 (7), 83.9 (11); HRMS (EI) *m/z* calcd for $C_{22}H_{23}NOSi$ 345.1549, found 345.1542. The relative stereochemistry for **9** was determined by the coupling constant between the centered and the adjacent fused methine protons.

4.2.7. Cycloadduct 10. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2g** (0.20 g, 1.21 mmol) using *n*-BuLi (0.58 mL, 2.5 M, 1.45 mmol) and NCS (0.19 g, 1.45 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **10** (0.14 g, 0.85 mmol, 70%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **10**: mp 82–84 °C; IR (CH_2Cl_2) 3053, 2928, 2873, 1739, 1654, 1422, 1286, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J=11.2, 6.8, 3.1 Hz, 1H), 5.53 (ddd, J=11.2, 3.6, 1.8 Hz, 1H), 5.08 (dd, J=11.2, 4.5 Hz, 1H), 3.93 (dd, J=11.0, 7.5 Hz, 1H), 2.37 (m, 6H), 1.89 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 132.9, 126.5, 80.1, 60.9, 39.1, 35.7, 30.6, 28.8, 20.1; MS (EI) *m/z* 163.1 (M^+, 9), 146.1 (11), 117.1 (18), 105.1 (19), 91.0 (100), 88.0 (21), 79.1 (26), 70.0 (53), 61.0 (69); HRMS (EI) *m/z* calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0999. The relative stereochemistry for **10** was confirmed by X-ray diffraction analysis.

4.2.8. Cycloadduct 11. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2h** (0.18 g, 1.0 mmol) using *n*-BuLi (0.50 mL, 2.5 M, 1.2 mmol) and NCS (0.16 g, 1.2 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **11** (0.12 g, 0.67 mmol, 60%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **11**: mp 66–68 °C; IR (CH_2Cl_2) 3052, 2939, 2896, 1605, 1438, 1422, 1280, 1266, 1260 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dt, J=12.0, 3.6 Hz, 1H), 5.78 (ddt, J=12.0, 5.8, 2.0 Hz, 1H), 4.80 (dd, J=11.0, 7.5 Hz, 1H), 3.30 (dd, J=10.8, 5.3 Hz, 1H), 2.75 (dd, J=11.5, 4.2 Hz, 1H), 2.43 (br d, J=11.5 Hz, 1H), 2.22 (m, 2H), 2.12 (m, 1H), 1.81 (m, 2H), 1.60 (m, 3H), 1.39 (d, J=11.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 137.5, 122.2, 57.7, 37.7, 32.3, 31.7, 26.3, 25.9, 22.1; MS (EI) *m/z* 177.1 (M^+, 30), 148.1 (21), 134.1 (20), 117.1 (25), 105.1 (37), 91.0 (100), 79.1 (54), 67.1 (54); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1148. The relative stereochemistry for **11** was confirmed by X-ray diffraction analysis.

4.2.9. Cycloadduct 12a. The crude mixture obtained from

intramolecular 1,3-dipolar cycloaddition starting from oxime **2i** (0.30 g, 143 mmol) using *n*-BuLi (0.69 mL, 2.5 M, 1.7 mmol) and NCS (0.23 g, 1.7 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **12a** (0.15 g, 0.66 mmol, 50%) and **12b** (0.08 g, 0.36 mmol, 27%) both as white solids. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **12a**: mp 119–121 °C; IR (CH_2Cl_2) 3052, 2928, 2858, 1720, 1613, 1484, 1460, 1436, 1422, 1364, 1282, 1266, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J=7.6$ Hz, 1H), 7.30 (m, 1H), 7.40 (m, 1H), 7.31 (td, $J=7.4$, 1.3 Hz, 1H), 5.80 (m, 1H), 5.58 (ddd, $J=11.6$, 4.2, 2.5 Hz, 1H), 5.30 (br d, $J=11.3$ Hz, 1H), 3.83 (dd, $J=11.2$, 4.4 Hz, 1H), 3.20 (dd, $J=16.0$, 4.5 Hz, 1H), 2.76 (dd, $J=16.0$, 2.5 Hz, 1H), 2.56 (m, 1H), 2.23 (m, 1H), 2.17 (m, 1H), 1.67 (m, 1H), 1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 136.4, 132.4, 130.2, 129.3, 127.0, 126.7, 125.8, 125.0, 80.8, 52.4, 39.1, 35.3, 29.7, 29.1; MS (EI) *m/z* 225.1 (M^+, 53), 195.1 (30), 167.1 (31), 165.1 (30), 115.0 (29), 91.0 (100), 77.0 (28), 65.0 (17), HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1154. The relative stereochemistry for **12a** was confirmed by X-ray diffraction analysis.

4.2.10. Cycloadduct 12b. Mp 120–122 °C; IR (CH_2Cl_2) 3051, 2928, 2858, 1721, 1613, 1484, 1462, 1436, 1424, 1364, 1278, 1266, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J=6.2$ Hz, 1H), 7.22 (m, 3H), 5.63 (m, 3H), 3.25 (t, $J=12.1$ Hz, 1H), 2.86 (dd, $J=12.3$, 4.3 Hz, 1H), 2.70 (dd, $J=12.3$, 9.8 Hz, 1H), 2.21 (m, 3H), 1.77 (m, 1H), 1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.7, 131.8, 129.9, 128.5, 126.5, 126.2, 125.8, 125.3, 80.3, 52.8, 37.1, 35.4, 28.0, 25.2; MS (EI) *m/z* 225.1 (M^+, 100), 194.1 (19), 183.1 (23), 170.0 (73.67), 165.1 (37), 115.0 (61), 91.0 (83), 81.1 (67), 77.0 (63), 65.0 (25), HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1151. The relative stereochemistry for **12b** was confirmed by X-ray diffraction analysis.

4.2.11. Cycloadduct 13. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **3a** (0.20 g, 1.23 mmol) using NCS (0.20 g, 1.47 mmol) and triethylamine (0.19 mL, 1.35 mmol) in CH_2Cl_2 for 24 h was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **13** (0.03 g, 0.70 mmol, 15%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **13**: mp 84–86 °C; IR (CH_2Cl_2) 3683, 3065, 2988, 1739, 1640, 1422, 1270 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, $J=12.0$, 2.2 Hz, 1H), 6.10 (dd, $J=10.0$, 3.9 Hz, 1H), 5.95 (m, 2H), 4.97 (d, $J=10.6$ Hz, 1H), 3.45 (t, $J=11.0$ Hz, 1H), 2.59 (m, 2H), 2.28 (m, 2H), 2.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 134.3, 133.0, 126.4, 79.0, 66.6, 41.3, 30.9, 29.2, 21.4; MS (EI) *m/z* 161.1 (M^+, 21), 144.1 (47), 143.1 (19), 117.1 (22), 116.1 (36), 115.1 (30), 105.1 (18), 104.1 (19), 91.1 (100), 79.1 (24), 77.0 (37); HRMS (EI) *m/z* calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0840; Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.44; H, 5.73; N, 8.59. The relative stereochemistry for **13** was confirmed by X-ray diffraction analysis.

4.2.12. Cycloadduct 14. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **3b** (0.30 g, 1.69 mmol) using *n*-BuLi (0.88 mL, 2.5 M, 2.20 mmol) and NCS (0.27 g, 2.03 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **14** (0.24 g, 1.36 mmol, 80%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **14**: mp 66–68 °C; IR (CH_2Cl_2) 3683, 3471, 3056, 2936, 2855, 1605, 1421, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (dd, $J=11.7$, 2.08 Hz, 1H), 5.93 (m, 2H), 5.81 (dd, $J=10.2$, 4.4 Hz, 1H), 4.98 (d, $J=11.1$ Hz, 1H), 3.07 (t, $J=11.5$ Hz, 1H), 2.74 (dd, $J=10.2$, 4.3 Hz, 1H), 2.26 (m, 1H), 2.16 (td, $J=12.8$, 5.4 Hz, 1H), 2.04 (m, 2H), 1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 137.7, 132.3, 126.3, 125.2, 79.8, 62.4, 40.7, 30.3, 26.4, 25.0; MS (EI) *m/z* 175.1 (M^+, 16), 147.1 (36), 146.1 (36), 129.0 (20), 119.1 (30), 117.1 (30), 115.0 (30), 107.0 (59), 91.0 (97), 79.0 (100), 77.0 (48); HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ 175.0997, found 175.0996; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.42; H, 7.55; N, 7.96. The relative stereochemistry for **14** was confirmed by X-ray diffraction analysis.

4.2.13. Cycloadduct 15. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **3c** (0.30 g, 1.33 mmol) using *n*-BuLi (0.70 mL, 2.5 M, 1.73 mmol) and NCS (0.21 g, 1.60 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **15** (0.20 g, 0.91 mmol, 68%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **15**: mp 104–106 °C; IR (CH_2Cl_2) 3057, 2990, 2893, 1614, 1462, 1438, 1355, 1277, 1269, 1260, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, $J=7.6$ Hz, 1H), 7.31 (td, $J=7.4$, 1.5 Hz, 1H), 7.23 (m, 2H), 6.26 (dd, $J=11.8$, 1.6 Hz, 1H), 6.01 (m, 2H), 5.93 (m, 1H), 5.28 (d, $J=12.0$ Hz, 1H), 3.87 (t, $J=12.6$ Hz, 1H), 3.04 (m, 2H), 2.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 138.1, 136.5, 136.4, 130.0, 128.8, 128.2, 126.6, 125.7, 125.6, 125.3, 80.0, 65.6, 37.4, 35.0; MS (EI) *m/z* 223.1 (M^+, 100), 194.1 (51), 180.1 (30), 178.1 (46), 169.0 (45), 165.0 (40), 115.0 (45), 107.0 (93), 91.0 (58), 79.0 (80), 77.0 (41); HRMS (EI) *m/z* calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0999; Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.67; H, 5.68; N, 6.24. The relative stereochemistry for **15** was confirmed by X-ray diffraction analysis.

Crystallographic data crystallographic data (excluding structure factors) for the structures **7**, **10**, **11**, **12a**, **12b**, **13**–**15** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 248696-248703, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was supported by grants from National Taiwan Normal University (ORD 92-2) and National Science Council (NSC 92-2113-M-003-009).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.078

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