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Asymmetric Silyl Nitronate Cycloadditions with Bornane-10,2-Sultam Derivatives

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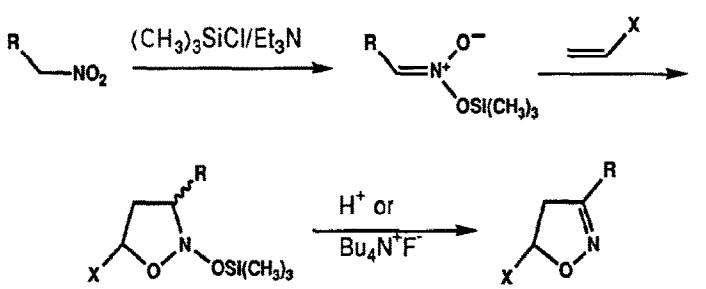
Abstract: Asymmetric silyl nitronate cycloadditions with *N*-acryloyl (2*R*)-bornane-10,2-sultam, *N*-acryloyl (2*S*)-bornane-10,2-sultam, and *N*-methacryloyl (2*R*)-bornane-10,2-sultam have been studied. The asymmetric silyl nitronate cycloaddition/elimination methodology provides a general route for the asymmetric synthesis of 2-isoxazolines.

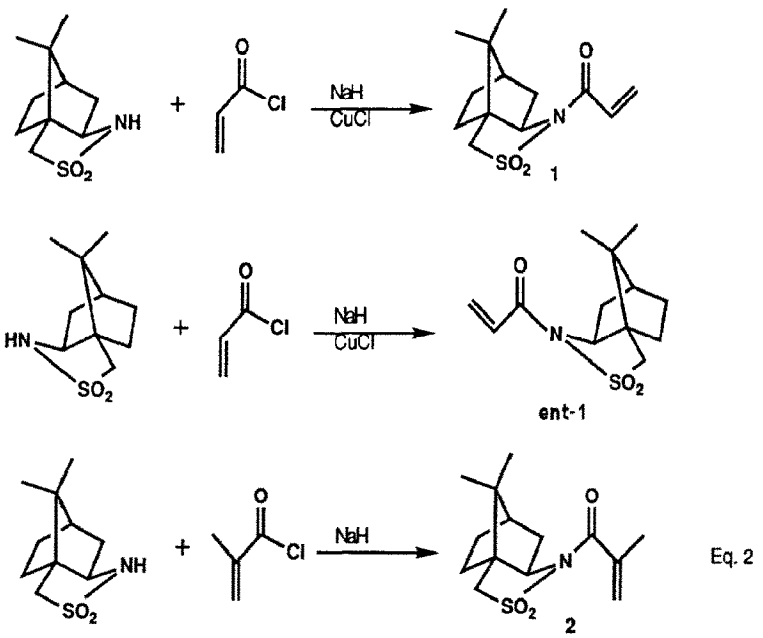
Silyl nitronates are prepared from primary and secondary nitro compounds by the deprotonation of the acidic α-proton, followed by *O*-silylation.[1,2] They show promising synthetic applicabilities as reagents in the nitro-aldol reactions and in 1,3-dipolar cycloadditions.[3] Even though the *N*-trimethylsilyloxyisoxazolidine cycloadducts of silyl nitronates to olefins have proved to be versatile intermediates that can be transformed to isoxazolines, isoxazoles, pyridazins, pyridazones, hydroxyfurans, hydroxy-1,4-diketones, cyclopentenones,[2d,e] the thermolabile, moisture sensitive silyl nitronates are much less used in organic synthesis than nitrile oxides or nitrones. With the exploratory work by Torssell and coworkers,[2] silyl nitronates can be considered as synthetic equivalents of nitrile oxides in their reactions with olefinic dipolarophiles. The resulting *N*-trimethylsilyloxyisoxazolidines are readily transformed into 2-isoxazolines upon treatment with acid or tetrabutylammonium fluoride.[4] Moreover, it has been found that it is advantageous to carry out the sequence of silylation, cycloaddition and silanol elimination to 2-isoxazoline as a one pot reaction (Eq. 1).[2d]



Eq. 1

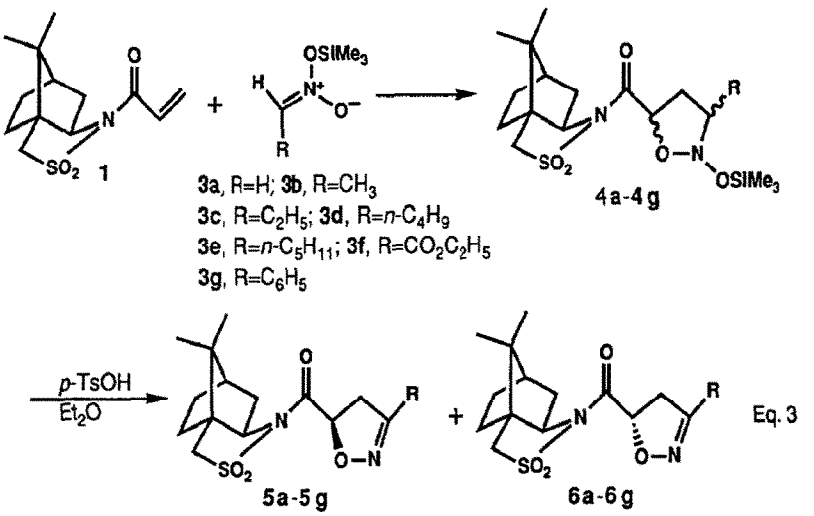
Asymmetric nitrile oxide cycloadditions with a wide variety of dipolarophiles have been studied, but little has been done on asymmetric silyl nitronate cycloadditions before our recent work.[5] Asymmetric silyl nitronate cycloadditions would be useful for the preparation of optically active 2-isoxazolines, which can be further converted to the optically active β-hydroxy carbonyls, γ-amino alcohols, β, γ-unsaturated ketones, and other compounds with important functional groups. Thus, these asymmetric cycloadditions provide the central intermediates for organic synthesis in optically active form. This paper enters into details on the asymmetric silyl nitronate cycloadditions with the Oppolzer's chiral sultam derivatives.[6]

For asymmetric dipolar cycloadditions, there are two conceptual approaches which differ in the placement of a chiral auxiliary on either the dipole or the dipolarophile.[7] In general the chiral dipolarophile approach is superior to the chiral dipole approach in stereoselectivity. Therefore the proper choice of the chiral dipolarophile is essential to the success of the asymmetric cycloadditions. Based on the results of asymmetric nitrile oxide cycloadditions,[8] we chose the Oppolzer's chiral sultam derivatives as the chiral dipolarophiles for the asymmetric silyl nitronate cycloadditions. *N*-Acryloyl (2*R*)-bornane-10,2-sultam (**1**) and *N*-acryloyl (2*S*)-bornane-10,2-sultam (**ent-1**) were prepared by the deprotonation of (2*R*)- and (2*S*)- bornane-10,2-sultam with NaH in toluene, respectively, followed by addition of acryloyl chloride. The yields were rather low due to their propensity toward polymerization under these conditions.[9] To improve the yield, several conditions for acryloylation were surveyed. The best result so far (52% isolated yield) was obtained by the inverse addition of the toluene solution of the deprotonated sultam to the toluene solution of acryloyl chloride in the presence of catalytic amount of copper (I) chloride.[10] On the other hand, *N*-methacryloyl (2*R*)-bornane-10,2-sultam (**2**) was prepared in high yield (95% isolated yield) by the deprotonation of (2*R*)-bornane-10,2-sultam with NaH in toluene, followed by addition of methacryloyl chloride (Eq. 2).



Eq. 2

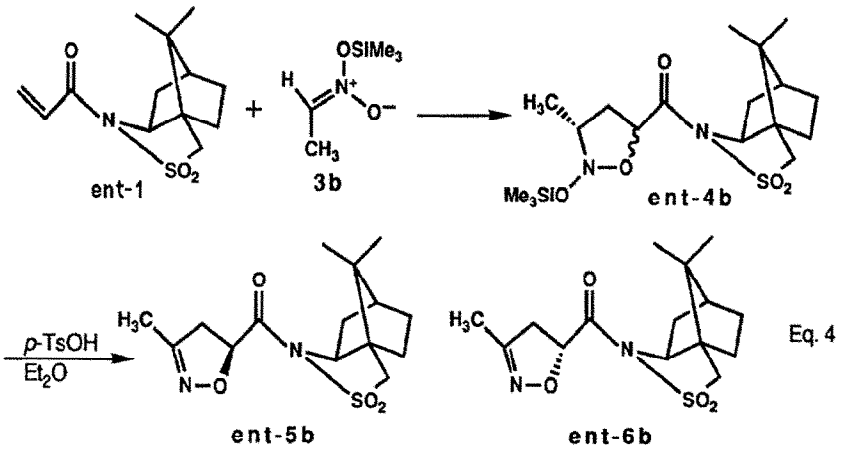
The cycloadditions of *N*-acryloyl (2*R*)-bornane-10,2-sultam (**1**) with in situ-generated silyl nitronates **3a-3g** gave the diastereomeric mixtures of *N*-trimethylsilyloxyisoxazolidines **4a-4g** (Eq. 3). The silyl nitronates **3a-3g** were generated by *O*-silylation of the corresponding primary nitro compounds using trimethylsilyl chloride and triethylamine at room temperature. Examination of the 300 MHz ^{1}H NMR of the crude reaction products showed the presence of four diastereomers in the cycloadditions of **1** with silyl nitronates **3c-3g**. However, only two diastereomers out of four possible isomers of *N*-trimethylsilyloxyisoxazolidine **4b** were formed in the cycloaddition of **1** with methyl substituted silyl nitronate **3b**. The major cycloadduct **4bm** was separated by chromatography in 75% yield. *p*-Toluenesulfonic acid catalyzed elimination of trimethylsilyl alcohols from *N*-trimethylsilyloxyisoxazolidines **4a-4g** produced the diastereomeric mixtures (**5a-5g** and **6a-6g**) of 2-isoxazolines.

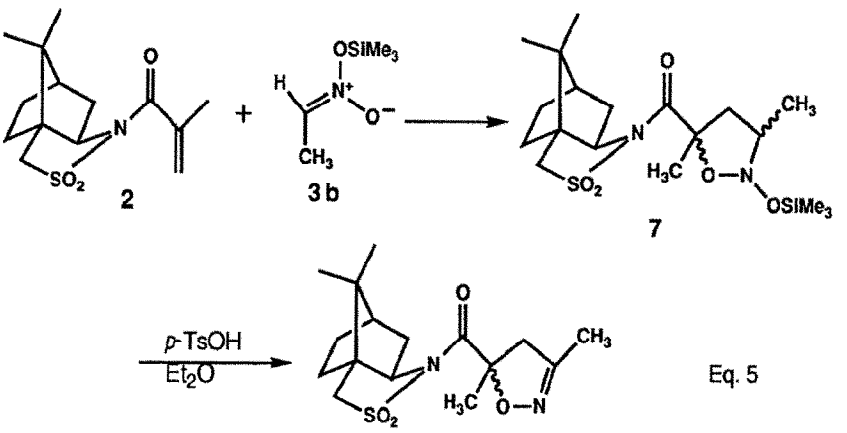


The cycloaddition of *N*-acryloyl (2*S*)-bornane-10,2-sultam (**ent-1**) with silyl nitronate **3b** also resulted in only two diastereomeric mixtures of **ent-4b** through *endo* transition states[5] and the major cycloadduct **ent-4bm** was separated and purified. Many attempts were made to grow single crystals of the major cycloadducts **4bm** and **ent-4bm** for X-ray crystallography. Finally, the X-ray crystal structure of the major cycloadduct **ent-4bm** was obtained.[11] This X-ray analysis not only provided the confirmation of the absolute stereochemistry of the major cycloadduct **ent-4bm** but also the insight for the transition states of silyl nitronate cycloadditions. Treatment of **ent-4b** with *p*-toluenesulfonic acid in ether gave the diastereomeric mixture of **ent-5b** and **ent-6b** (Eq. 4).

The cycloaddition of *N*-methacryloyl (2*R*)-bornane-10,2-sultam (**2**) with silyl nitronate **3b**, followed by elimination of trimethylsilyl alcohol from the resulting *N*-trimethylsilyloxyisoxazolidines **7** provided the diastereomeric mixture of 2-isoxazolines **8** (Eq. 5). The reaction was very slow and the diastereomeric ratio between the major cycloadduct and the minor cycloadduct of **8** was 67:33. Not only is **2** less reactive than **1** or **ent-1**, it is also significantly less selective. Curran and Heffner recently reported the asymmetric nitrile

oxide cycloaddition with **ent-2**.[10] They rationalized the reduced reactivity and the reduced stereoselectivity of **ent-2** in terms of the nonplanar ground state conformation deduced from the X-ray crystal structure of **ent-2**. Our experimental and X-ray crystallographic results[12] of **2** support their rationalization.





The results of a series of experiments are summarized in Table 1. A brief survey of solvent effects indicated that better diastereoselectivities were observed in nonpolar solvents such as toluene or hexane, while dichloromethane provided the lower diastereomeric ratio (82:18). This result parallels the solvent effect in asymmetric nitrile oxide cycloadditions.[8a,b] In toluene or hexane, useful levels of asymmetric induction (ca. 90:10) were consistently observed, regardless of the substituent on the silyl nitronate. The diastereomeric ratios between the major 2-isoxazoline products **5a**-**5g** and the minor ones **6a**-**6g** were determined by ^{1}H NMR using the chiral shift reagent Eu(hfc)$_3$ and capillary GC.

The cycloaddition of **1** with the silyl nitronate **3a** derived from nitromethane provided the 2-isoxazoline **5a** in good yield (entry 1). Fulminic acid (formonitrile oxide) cycloaddition of **1** will afford the same product **5a**. The classical method of generation of unstable fulminic acid is by acidification of its salts.[13] The

fulminates are all very toxic and potentially explosive. They are quite sensitive to shock and heat. Moreover, the use of fulminates is restricted to reactants soluble in water. Another possible route for fulminic acid is the dehydration method of nitromethane. However, the Mukaiyama procedure[14] fails for nitromethane. Thus, the unsubstituted silyl nitronate **3a** from nitromethane is a good, convenient synthetic alternative of the fulminic acid and will be greatly used for the synthesis of the 3-unsubstituted-2-isoxazoline heterocycles.

Table 1. Silyl Nitronate Cycloadditions with Bornane-10,2- Sultam Derivatives

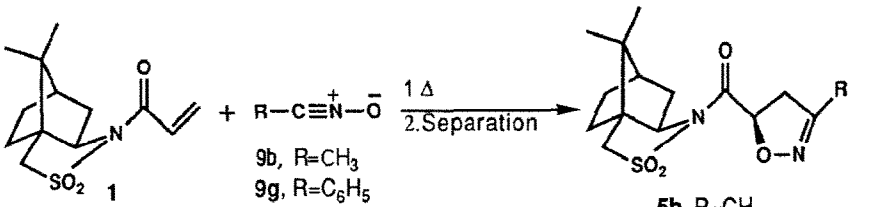
				Δ^2-Isoxazoline Products	
Entry	Sultam	Silyl Nitronate[a]	Solvent	Major 5/Minor 6 [b,c]	Yield[d,e]
1	**1**	**3a**, R=H	Toluene	89/11	96%(57%)
2	**1**	**3b**, R=CH_3	Toluene	89/11(93:7)	95%(75%)[h]
3	**1**	**3b**, R=CH_3	Hexane	88/12	
4	**1**	**3b**, R=CH_3	CH_2Cl_2	82/18	
5	**1**	**3c**, R=C_2H_5	Toluene	89/11(90:10)	96%(81%)
6	**1**	**3d**, R=C_4H_9	Toluene	89/11	93%(61%)
7	**1**	**3e**, R=C_5H_{11}	Toluene	90/10	94%(69%)
8	**1**	**3f**, R=$CO_2C_2H_5$	Toluene	89/11	85%(60%)
9	**1**	**3g**, R=C_6H_5	Tol/CH_2Cl_2	85/15	81%(50%)[i]
10	**ent-1**[f]	**3b**, R=CH_3	Toluene	88/12	96%(79%)
11	**2**	**3b**, R=CH_3	Toluene	67/33[g]	

a) Generated by the Torssell method by *O*-silylation of the primary nitro compound using trimethyl silyl chloride and triethylamine at room temperature. b) Ratios determined by ^{1}H NMR. c) The ratios in parentheses were determined by capillary GC. d) Isolated yield based on the sultam after chromatographic purification. e) The yield in parentheses represents the isolated yield of the major cycloadduct **5**. f) The enantiomeric sultam (**ent-1**) was used and enantiomeric products (**ent-4b**, **ent-5b**, and **ent-6b**) were obtained. g) The ratio between the major and minor products of 2-isoxazoline **8**. h) Isolated yield of the isoxazolidine product **4bm**. i) NMR yield.

Torssell reported that the yields of silyl nitronates of higher homologues than nitropropane or sterically hindered primary nitroalkanes were low.[2b] In the cycloadditions of the silyl nitronates of *n*-butyl and *n*-pentyl substituents, **3d** and **3e**, respectively, this kind of low yielding problem was readily solved. By using excess (5 equivalents) of *n*-nitropentane and *n*-nitrohexane, the cycloadditions of **1** with **3d** and **3e** gave the 2-isoxazoline products **5d** and **5e**, respectively, in good yields (entry 6 and 7). Aromatic (entry 9) and ester functionalized silyl nitronate (entry 8) also cycloadded smoothly with the chiral dipolarophile **1**. The antipodal chiral dipolarophile **ent-1** produced the enantiomeric 2-isoxazoline products **ent-5** and **ent-6** in the similar way (entry 10). Thus, the absolute stereochemistry of the final 2-isoxazoline product could be decided by the choice of the chiral dipolarophile **1** or its antipode **ent-1**. The series of examples presented demonstrates the generality of this asymmetric silyl nitronate cycloaddition/elimination methodology for the asymmetric synthesis of 2-isoxazolines.

The absolute stereochemistry of the newly generated C5 stereogenic center of the major cycloadduct **5**

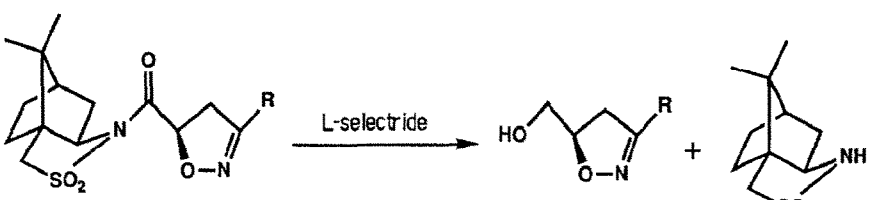
was rigorously determined as *R* by the chemical correlation method, the comparison of the optical rotations, and X-ray crystallography. The cycloadditions of **1** with nitrile oxides **9b** and **9g**, and chromatographic separation of the major cycloadducts gave 2-isoxazoline products **5b** and **5g**, respectively (Eq. 6). The absolute stereochemistry of the C5 stereogenic center of the major nitrile oxide cycloadduct has been already determined as *R*.[8b] The major products **5b** and **5g** of the cycloaddition/elimination sequence of silyl nitronates **3b** and **3g** were identical in all aspects with the major cycloadducts of nitrile oxides **9b** and **9g**, respectively. Therefore, we could assign the absolute stereochemistry of the C5 stereogenic centers of the major silyl nitronate cycloadducts **5b** and **5g** as *R*.



Eq. 6

The X-ray crystal structure of the major cycloadduct of **ent-4bm** clearly shows that the absolute stereochemistry of the C5 stereogenic center of the major cycloadduct between the antipodal chiral dipolarophile **ent-1** and silyl nitronate **3b** is *S*. This implies that the absolute stereochemistry of the C5 center of the major cycloadduct **4bm** between the chiral dipolarophile **1** and silyl nitronates **3b** is *R*. The X-ray crystallographic result further confirms our previous stereochemical assignments of the C5 stereogenic centers.

Additional evidences for the assignments of the absolute stereochemistry of the C5 stereogenic centers come from the comparison of the optical rotations of the optically active 2-isoxazoline alcohols with those of the authentic compounds prepared by asymmetric nitrile oxide cycloadditions.[8b] The optically active 2-isoxazoline alcohols **10b** and **10c** were prepared by L-selectride reduction of the major product **5b** and **5c**, respectively (Eq. 7). The optical rotations are in accord with the literature values[8b] of the corresponding compounds whose absolute stereochemistry of the C5 centers is *R*. The comparison of optical rotations and NMR (^{1}H and ^{19}F) study of the Mosher's ester[15] of **10b** indicate that the 2-isoxazoline alcohol is more than 98% enantiomerically pure.



Eq. 7

Thus, all three methods show that the absolute stereochemistry of the C5 centers of the major products **5a-5g** from the chiral dipolarophile **1** is *R*. The C5 stereogenic center is governed by the facial selectivity in the silyl nitronate cycloadditions. The stereochemical outcomes suggest that the major products arise from the top side attack of silyl nitronates to the favored ground state conformer of the chiral dipolarophile **1** or its antipode **ent-1**.[5,8b]

The optically active 2-isoxazoline alcohols **10b** and **10c** are good chiral building blocks for the asymmetric synthesis of natural products and their synthetic applications to the biofunctional molecules such as nonactin and tetranactin will be reported in due course.

Experimental

Apparatus ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz FT-NMR spectrometer in deuteriochloroform and chemical shifts are expressed in ppm. IR spectra were recorded on BOMEM FT-IR M100-C15 spectrometer. Mass spectra were recorded on KRATOS MS 25 RFA instrument. Optical rotations were measured on JASCO DIP-140 and DIP-360 polarimeters. Melting points were determined on Haake Buchler melting point appratus and are uncorrected. Capillary GC data were recorded on Varian 3300 GC. Microanalyses were performed at Korea Basic Science Center in Seoul, Korea.

Chemicals Dichloromethane, toluene, and hexane were distilled over calcium hydride and stored under nitrogen. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone ketyl before use. (2*R*)-Bornane-10,2-sultam and (2*S*)-bornane-10,2-sultam were purchased from Oxford chirality and Aldrich. Phenyl nitromethane was prepared by the substitution reaction of benzyl bromide with silver nitrite in 86% yield and other primary nitro compounds used for the generation of silyl nitronates were purchased from Aldrich. The materials obtained from commercial suppliers were used without further purification.

N-Acryloyl (2*R*)-bornane-10,2-sultam (**1**)

To a suspension of dry, oil-free NaH (1.2 g, 50 mmol) and toluene (160 mL) was added (2*R*)-bornane-10,2-sultam (6.27 g, 29 mmol). After 1h at room temperature, CuCl (272 mg, 2.7 mmol) was added. This mixture was added using a cannula to a solution of acryloyl chloride (4.4 mL, 54 mmol) in toluene (60 mL). After 15 min, the reaction mixture was quenched with H_2O and extracted with EtOAc. The extract was passed through silica gel, concentrated under reduced pressure, and purified by flash chromatography (1:4 EtOAc/hexane) to yield pure **1** (4.08 g, 52%): mp 191-193 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.18 (3H, s), 1.34-1.48 (2H, m), 1.88-1.96 (3H, m), 2.09-2,19 (2H, m), 3.45 (1H, d, J = 13.8 Hz), 3.50 (1H, d, J = 13.8 Hz), 3.94 (1H, dd, J = 7.4, 5.2 Hz), 5.85 (1H, dd, J = 10.3 Hz, 1.6 Hz), 6.49 (1H, dd, J = 16.8, 1.6 Hz), 6.87 (1H, dd, J = 16.7, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.8, 26.5, 32.9, 38.4, 44.7, 47.8, 48.5, 53.1, 65.1, 127.8, 131.2, 163.8; IR (KBr) 2964, 1675, 1416, 1325, 1133, 978 cm^{-1}; MS m/e 269 (M^+), 205, 190, 162, 134, 55; Anal. Calcd for $C_{13}H_{19}NO_3S$ (269.36): C, 57.97; H, 7.11; N, 5.20. Found: C, 57.99; H, 6.92; N, 5.08.

N-Acryloyl (2*S*)-bornane-10,2-sultam (**ent-1**)[10]

Prepared from (2*S*)-bornane-10,2-sultam by a similar procedure as for **1**: ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, s), 1.18 (3H, s), 1.38-1.47 (2H, m), 1.89-1.93 (3H, m), 2.12-2.17 (2H, m), 3.46 (1H, d, J = 13.8 Hz), 3.50 (1H, d, J = 13.8 Hz), 3.94 (1H, dd, J = 7.5, 5.2 Hz), 5.85 (1H, dd, J = 10.3, 1.6 Hz), 6.51 (1H, dd, J = 16.7, 1.6 Hz), 6.88 (1H, dd, J = 16.7, 10.3 Hz). The spectral data are identical with those previously described.[10]

N-Methacryloyl (2*R*)-bornane-10,2-sultam (**2**)

To a suspension of dry, oil-free NaH (200 mg, 8.34 mmol) and toluene (28 mL) was added (2*R*)-bornane-10,2-sultam (802 mg, 3.72 mmol). After 1h 20 min at room temperature, methacryloyl chloride (582 μL, 5.95 mmol) was added. After 1 h 40 min, the reaction mixture was quenched with H_2O and extracted with ether. The extract was dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (1:4 EtOAc/hexane) to afford pure **2** (1.03 g, 97%): mp 145-146 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, s), 1.23 (3H, s), 1.42 (2H, m), 1.90-2.05 (5H, m), 3.40 (1H, d, J = 13.6 Hz), 3.49 (1H, d, J = 13.6 Hz), 4.02 (1H, dd, J = 7.4, 5.0 Hz), 5.67 (2H, m); ^{13}C NMR ($CDCl_3$) δ 18.7, 19.9, 21.3, 26.5, 33.3, 38.3, 45.3, 47.7, 48.0, 53.5, 65.5, 124.3, 139.0, 171.3; IR (KBr) 2960, 1673, 1632, 1326, 1195, 1130, 1115, 1066, 979 cm^{-1}; Anal. Calcd for $C_{14}H_{21}NO_3S$ (283.38): C, 59.34; H, 7.47; N, 4.94. Found: C, 59.48; H, 7.46; N, 4.85.

N-[[(3*S*)-3-Methyl-2-[(trimethylsilyl)oxy]-(5*R*)-5-isoxazolidinyl]carbonyl]-(2*R*)-bornane-10,2-sultam (**4bm**)

To a solution of nitroethane (161 μL, 2.24 mmol), trimethylsilyl chloride (434 μL, 3.42 mmol), and toluene (6 mL) was added triethyl amine (474 μL, 3.42 mmol). After 15 min at room temperature, *N*-acryloyl (2*R*)-bornane-10,2-sultam (**1**) (75.6 mg, 0.28 mmol) was added. After 24 h, the reaction mixture was diluted with Et_2O and washed with H_2O. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (1:5 EtOAc/hexane) to give the pure product (88 mg, 75%): mp 123-124 °C; ^{1}H NMR ($CDCl_3$) δ 0.17 (9H, s), 0.97 (3H, s), 1.18 (3H, s), 1.20 (3H, d, J = 6.5 Hz), 1.26-1.44 (2H, m), 1.90 (3H, m), 2.05-2.15 (2H, m), 2.36-2.47 (2H, m), 3.44 (1H, d, J = 13.8 Hz), 3.47-3.56 (2H, m), 3.90 (1H, dd, J = 7.9, 5.1 Hz), 5.36 (1H, dd, J = 9.5 , 3.4 Hz); ^{13}C NMR ($CDCl_3$) δ -0.6, 13.8, 19.9, 20.9, 26.4, 33.0, 36.6, 38.3, 44.7, 47.8, 48.8, 53.1, 65.4, 67.3, 77.8, 170.1; IR (KBr) 2957, 1689, 1340, 1250, 1136, 849 cm^{-1}; MS m/e 416 (M^+), 147, 135, 93, 84, 75, 55, 43; Anal. Calcd for $C_{18}H_{32}N_2O_5SSi$ (416.61): C, 51.89; H, 7.74; N, 6.72. Found: C, 52.15; H, 7.74; N, 6.57.

N-[[(3*R*)-3-Methyl-2-[(trimethylsilyl)oxy]-(5*S*)-5-isoxazolidinyl]carbonyl]-(2*S*)-bornane-10,2-sultam (**ent-4bm**)

To a solution of nitroethane (212 μL, 2.95 mmol), trimethylsilyl chloride (564 μL, 4.44 mmol), and toluene (10 mL) was added triethyl amine (615 μL, 4.44 mmol). After 15 min at room temperature, *N*-acryloyl (2*S*)-bornane-10,2-sultam (**ent-1**) (100 mg, 0.37 mmol) was added. After 24 h, the reaction mixture was diluted with Et_2O and washed with H_2O. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (1:5 EtOAc/hexane) to give the pure product (99 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 0.17 (9H, s), 0.97 (3H, s), 1.18 (3H, s), 1.20 (3H, d, J = 6.5 Hz), 1.26-1.45 (2H, m), 1.90 (3H, m), 2.02-2.16 (2H, m), 2.37-2.46 (2H, m), 3.44 (1H, d, J = 13.8 Hz), 3.49-3.59 (2H, m), 3.90 (1H, dd, J = 7.8, 5.0 Hz), 5.36 (1H, dd, J = 9.3, 3.5 Hz); $[\alpha]_D^{16}$ = -19.2 (c 0.56,

$CHCl_3$). The structure was also analyzed by X-ray crystallography.[11]

General procedure for the synthesis of 2-isoxazoline products **5a-5g**

To a solution of nitroalkane (60.4 mmol), trimethylsilyl chloride (90.5 mmol), and toluene (150 mL) was added triethyl amine (90.5 mmol). After 15 min at room temperature, *N*-acryloyl (2*R*)-bornane-10,2-sultam (**1**) (12.1 mmol) was added. After 24 h, the reaction mixture was diluted with Et_2O and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude mixture of *N*-trimethylsilyloxyisoxazolidine. To an etheral (120 mL) solution of the isoxazolidine mixture was added *p*-TsOH (1.2 mmol). After 1 h, the reaction mixture was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. The extract was concentrated under reduced pressure and purified by flash chromatography to afford the pure product.

N-[(4,5-Dihydro-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5a**)

^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.19 (3H, s), 1.22-1.46 (2H, m), 1.89-1.94 (3H, m), 2.03-2.16 (2H, m), 3.26 (1H, ddd, J = 17.9, 11.2, 1.7 Hz), 3.41 (1H, ddd, J = 17.9, 6.9, 1.9 Hz), 3.45 (1H, d, J = 13.8 Hz), 3.53 (1H, d, J = 13.8 Hz), 3.92 (1H, dd, J = 7.7, 5.0 Hz), 5.48 (1H, dd, J = 11.1, 6.8 Hz), 7.14 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.8, 26.4, 32.9, 38.1, 39.5, 44.7, 47.9, 49.0, 52.9, 65.3, 145.1, 168.2; IR (CH_2Cl_2) 2955, 1693 (C=O), 1331, 1267, 1236, 1218, 1164, 1133, 832 cm^{-1}; $[\alpha]_D^{16}$ = -26.3 (c 0.23, $CHCl_3$).

N-[(4,5-Dihydro-3-methyl-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5b**)

mp 146-148 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.18 (3H, s), 1.31-1.45 (2H, m), 1.90 (3H, m), 1.99 (3H, s), 2.03-2.21 (2H, m), 3.20 (1H, dd, J = 17.6, 10.8 Hz), 3.29 (1H, dd, J = 17.5, 6.9 Hz), 3.44 (1H, d, J = 13.8 Hz), 3.51 (1H, d, J = 13.8 Hz), 3.91 (1H, dd, J = 7.7, 5.0 Hz), 5.49 (1H, dd, J = 10.7, 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.8, 20.8, 26.4, 32.9, 38.1, 42.4, 44.7, 47.9, 49.0, 52.9, 65.3, 76.9, 154.6, 168.7; IR (CH_2Cl_2) 2954, 1693 (C=O), 1328, 1268, 1235, 1218, 1163, 1133, 861 cm^{-1} MS m/e 326 (M^+), 179, 151, 135, 107, 93, 84, 79, 67, 56; $[\alpha]_D^{16}$ = -27.4 (c 0.20, $CHCl_3$); Anal. Calcd for $C_{15}H_{22}N_2O_4S$ (326.41): C, 55.20; H, 6.79; N, 8.58. Found: C, 55.63; H, 6.68; N, 8.48.

N-[(4,5-Dihydro-3-ethyl-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5c**)

mp 72-74 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, s), 1.14-1.19 (6H, m), 1.34-1.45 (2H, m), 1.88-1.93 (3H, m), 2.03-2.21 (2H, m), 2.37 (2H, q, J = 7.6 Hz), 3.21 (1H, dd, J = 17.3, 10.7 Hz), 3.30 (1H, dd, J = 17.3, 6.9 Hz), 3.44 (1H, d, J = 13.8 Hz), 3.52 (1H, d, J = 13.8 Hz), 3.91 (1H, dd, J = 7.7, 5.0 Hz), 5.47 (1H, dd, J = 10.7, 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 10.7, 19.8, 20.7, 20.8, 26.4, 32.8, 38.1, 40.8, 44.7, 47.8, 49.0, 52.9, 65.3, 76.7, 159.2, 168.7; IR (CH_2Cl_2) 2961, 1688 (C=O), 1329, 1269, 1233, 1163, 1133, 862 cm^{-1}; $[\alpha]_D^{16}$ = -24.3 (c 0.43, $CHCl_3$); Anal. Calcd for $C_{16}H_{24}N_2O_4S$ (340.44): C, 56.45; H, 7.11; N, 8.23. Found: C, 56.47; H, 7.13; N, 8.01.

N-[(4,5-Dihydro-3-*n*-butyl-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5d**)

^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 0.97 (3H, s), 1.17 (3H, s), 1.29-1.44 (4H, m), 1.49-1.59 (2H, m), 1.67-1.92 (3H, m), 2.02-2.15 (2H, m), 2.34 (2H, t, J = 7.3 Hz), 3.19 (1H, dd, J = 17.2, 10.6 Hz), 3.27 (1H, dd, J = 17.2, 6.8 Hz), 3.43 (1H, d, J = 13.8 Hz), 3.52 (1H, d, J = 13.8 Hz), 3.91 (1H, dd, J = 7.7, 5.0 Hz), 5.47 (1H, dd, J = 10.6, 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.8, 20.8, 22.2, 26.3, 26.7, 28.3, 32.8, 38.1, 41.0, 44.6, 47.8, 49.0, 52.9, 65.2, 76.6, 158.2, 168.7; IR (CH_2Cl_2) 2956, 1695 (C=O),

1327, 1267, 1134, 1067, 866 cm^{-1}; MS m/e 368 (M^+), 179, 135, 126, 70, 57, 41; $[\alpha]_D^{16}$ = -21.6 (c 0.54, $CHCl_3$).

N-[(4,5-Dihydro-3-*n*-pentyl-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5e**)

^1H NMR ($CDCl_3$) δ 0.88 (3H, m), 0.96 (3H, s), 1.17 (3H, s), 1.24-1.45 (6H, m), 1.56 (2H, m), 1.87-1.92 (3H, m), 2.02-2.15 (2H, m), 2.33 (2H, t, J = 7.5 Hz), 3.19 (1H, dd, J = 17.3, 10.7 Hz), 3.27 (1H, dd, J = 17.3, 6.9 Hz), 3.90 (1H, dd, J = 7.7, 5.0 Hz), 5.45 (1H, dd, J = 10.7, 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.8, 20.8, 22.2, 25.9, 26.3, 27.0, 31.2, 32.8, 38.0, 40.9, 44.6, 47.6, 49.0, 52.9, 65.2, 76.6, 158.2, 168.7; IR (CH_2Cl_2) 2957, 1695 (C=O), 1331, 1266, 1133, 1067, 864 cm^{-1}; MS m/e 382 (M^+), 179, 140, 71, 55, 43; $[\alpha]_D^{16}$ = -23.2 (c 0.43, $CHCl_3$).

N-[(4,5-Dihydro-3-ethoxycarbonyl-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5f**)

^1H NMR ($CDCl_3$) δ 0.97 (3H, s), 1.17 (3H, s), 1.31-1.46 (5H, m), 1.85-1.94 (3H, m), 2.02-2.17 (2H, m), 3.40-3.62 (4H, m), 3.90 (1H, dd, J = 7.7, 5.0 Hz), 4.32 (2H, q, J = 7.2 Hz), 5.69 (1H, dd, J = 11.4, 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.8, 20.8, 26.3, 32.8, 37.6, 38.0, 44.6, 47.7, 49.1, 52.9, 62.2, 65.3, 79.5, 151.0, 159.7, 167.0; IR (CH_2Cl_2) 2947, 1716 (C=O), 1336, 1253, 1141, 917 cm^{-1}; MS m/e 385 (M^+), 179, 151, 142, 114, 96, 93, 79, 70, 67, 55, 43; $[\alpha]_D^{16}$ = -24.9 (c 0.49, $CHCl_3$).

N-[(4,5-Dihydro-3-phenyl-(5*R*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**5g**)

^1H NMR ($CDCl_3$) δ 0.99 (3H, s), 1.13-1.47 (5H, m), 1.87-1.95 (3H, m), 2.05-2.19 (2H, m), 3.44-3.75 (4H, m), 3.95 (1H, dd, J = 7.6, 5.0 Hz), 5.70 (1H, dd, J = 11.1, 7.0 Hz), 7.41 (3H, m), 7.68 (2H, m); ^{13}C NMR ($CDCl_3$) δ 19.8, 20.9, 22.8, 26.4, 29.6, 32.9, 38.1, 38.8, 44.7, 47.9, 49.1, 53.0, 65.3, 77.8, 127.0, 128.6, 128.7, 130.3, 155.9, 168.3; IR (CH_2Cl_2) 2935, 1701 (C=O), 1451, 1285, 1130, 885 cm^{-1}; MS m/e 388 (M^+), 179, 146, 135, 118, 103, 83, 77, 69, 55; $[\alpha]_D^{16}$ = -25.7 (c 0.35, $CHCl_3$).

N-[(4,5-Dihydro-3-methyl-(5*S*)-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**6b**)

mp 173-175 °C; ^1H NMR ($CDCl_3$) δ 0.96 (3H, s), 1.11 (3H, s), 1.32-1.47 (2H, m), 1.89 (3H, m), 1.98 (3H, s), 2.09-2.14 (2H, m), 2.97 (1H, dd, J = 17.6, 7.0 Hz), 3.38 (1H, dd, J = 17.6, 11.7 Hz), 3.47 (2H, s), 3.91 (1H, m), 5.53 (1H, dd, J = 11.7, 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5, 19.8, 20.8, 26.3, 32.7, 38.0, 44.3, 44.6, 47.8, 49.1, 52.8, 65.2, 77.0, 153.8, 168.8; IR (KBr) 2959, 1714 (C=O), 1326, 1280, 1234, 1133, 1056 cm^{-1}; MS m/e 326 (M^+), 216, 179, 151, 135, 107, 93, 84, 79, 67, 56; $[\alpha]_D^{26}$ = -56.2 °C (c 1.0, $CHCl_3$).

N-[(4,5-Dihydro-3-methyl-(5*S*)-5-isoxazolyl)carbonyl]-(2*S*)-bornane-10,2-sultam(**ent-5b**)

To a solution of nitroethane (425 μL, 5.92 mmol), trimethylsilyl chloride (1.13 mL, 8.88 mmol), and toluene (15 mL) was added triethyl amine (1.23 mL, 8.88 mmol). After 15 min at room temperature, *N*-acryloyl (2*S*)-bornane-10,2-sultam (**ent-1**) (200 mg, 0.74 mmol)was added. After 24 h, the reaction mixture was diluted with Et_2O and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To an etheral (12 mL) solution of the crude product was added a catalytic amount of *p*-TsOH. After 1 h, the reaction mixture was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. The extract was concentrated under reduced pressure and purified by flash chromatography (1:2 EtOAc/hexane) to afford pure **ent-5b** (190 mg, 79%): ^1H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.19 (3H, s), 1.31-1.46 (2H, m), 1.90 (3H, m), 2.00 (3H, s), 2.04-2.21 (2H, m), 3.20 (1H, dd, J = 17.6, 10.8 Hz), 3.30 (1H, dd, J = 17.6, 6.9 Hz), 3.45 (1H, d, J = 13.8 Hz), 3.51 (1H, d, J = 13.8 Hz), 3.91 (1H, dd, J = 7.7, 5.0 Hz), 5.49 (1H, dd, J = 10.7, 6.9 Hz).

N-[(4-Hydro-3,5-dimethyl-5-isoxazolyl)carbonyl]-(2*R*)-bornane-10,2-sultam (**8**)

To a solution of nitroethane (161 μL, 2.24 mmol), trimethylsilyl chloride (434 μL, 3.36 mmol), and toluene (6 mL) was added triethyl amine (474 μL, 3.36 mmol). After 15 min at room temperature, *N*-metharyloyl (2*R*)-bornane-10,2-sultam (**2**) (81 mg, 0.28 mmol) was added. The reaction temperature was raised to 60 °C and additional 2 mL of toluene was added. After 24 h, the reaction mixture was diluted with Et_2O and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To an etheral (5 mL) solution of the crude product was added a catalytic amount of *p*-TsOH. After 1 h, the reaction mixture was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. The extract was concentrated under reduced pressure and purified by flash chromatography (1:2 EtOAc/hexane) to give the mixture (67:33) of **8** and recovered starting sultam **2** (46 mg, 57%). The spectral data were determined from the mixture of **8**: Major isomer; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.20 (3H, s), 1.37 (2H, m), 1.67 (3H, s), 1.85-2.12 (5H, m), 1.98 (3H, s), 3.37-3.73 (4H, m), 4.01 (1H, dd, J = 7.6, 5.0 Hz). Minor isomer; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.20 (3H, s), 1.37 (2H, m), 1.70 (3H, s), 1.85-2.12 (5H, m), 1.98 (3H, s), 3.37-3.73 (4H, m), 4.06 (1H, dd, J = 7.7, 4.9 Hz).

(5*R*)-5-Hydroxymethyl-3-methyl-2-isoxazoline (**10b**)

To a THF (115 mL) solution of **5b** (1.44 g, 4.1 mmol) was added a THF solution (1.0 M) of L-selectride (16.4 mL, 16.4 mmol). After 30 min at room temperature, the reaction mixture was quenched by sequencial additions of H_2O (2.6 mL), EtOH (9 mL), 3N aqueous NaOH (12 mL), and 30% aqueous H_2O_2 (8 mL) at 0 °C. The reaction mixture was extracted with Et_2O (x1) and CH_2Cl_2 (x3). The extract was dried over $MgSO_4$, concentrated under reduced pressure, and separated by flash chromatography (1:1 Et_2O/CH_2Cl_2) to afford pure **10b** (398 mg, 84%). (2*R*)-Bornane-10,2-sultam (864 mg, 98%) was also recovered: ^{1}H NMR ($CDCl_3$) δ 1.97 (3H, s), 2.08 (1H, br. s), 2.80 (1H, dd, J = 16.8, 7.3 Hz), 2.95 (1H, dd, J = 16.8, 10.6 Hz), 3.54 (1H, dd, J = 12.2, 4.5 Hz), 3.74 (1H, dd, J = 12.2, 3.2 Hz), 4.65 (1H, m); ^{13}C NMR ($CDCl_3$) δ 13.0, 40.0, 63.7, 80.1, 155.9; IR (neat) 3385, 2916, 1635, 1436, 1386, 1330 cm^{-1}; MS m/e 155 (M^+), 84, 68, 56, 51, 42, 39; $[\alpha]_D^{27}$ = -170.3 (c 1.1, $CHCl_3$). The spectral data of MTPA ester of **10b**: ^{1}H NMR ($CDCl_3$) δ 1.94 (3H, s), 2.70 (1H, dd, J = 17.2, 7.3 Hz), 3.01 (1H, dd, J = 17.2, 10.8 Hz), 3.53 (3H, s), 4.38 (2H, m), 4.79 (1H, m), 7.40 (3H, m), 7.51 (2H, m); ^{19}F NMR ($CDCl_3$) δ -72.6.

(5*R*)-5-Hydroxymethyl-3-ethyl-2-isoxazoline (**10c**)

To a THF (50 mL) solution of **5c** (1.2 g, 3.5 mmol) was added a THF solution (1.0 M) of L-selectride (15 mL, 15 mmol). After 20 min at room temperature, the reaction mixture was quenched by sequencial additions of H_2O (2 mL), EtOH (6 mL), 3N aqueous NaOH (7 mL), and 30% aqueous H_2O_2 (5 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, concentrated under reduced pressure, and separated by flash chromatography (1:1 Et_2O/CH_2Cl_2) to afford pure **10c** (385 mg, 85%). (2*R*)-Bornane-10,2-sultam (696 mg, 92%) was also recovered: ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, t, J = 7.5 Hz), 1.89 (1H, br. s), 2.36 (2H, q, J = 7.5 Hz), 2.84 (1H, dd, J = 17.0, 7.6 Hz), 2.98 (1H, dd, J = 17.0, 10.6 Hz), 3.54-3.60 (1H, m), 3.74-3.80 (1H, m), 4.62-4.71 (1H, m); ^{13}C NMR ($CDCl_3$) δ 10.7, 21.1, 38.2, 63.6, 79.9, 160.5; IR (neat) 3384, 2928, 1637, 1436, 1378, 1350, 1301, 1062, 874 cm^{-1}; MS m/e 129 (M^+), 98, 70, 56, 42; $[\alpha]_D^{27}$ = -159.7 (c 1.05, $CHCl_3$).

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11. We have recently published the X-ray crystal structure of **ent-4bm**.[5] Thermal parameters, bond lengths and angles are available from the Cambridge Crystallographic Data Centre.
12. The X-ray crystal structure of *N*-methacryloyl (2*R*)-bornane-10,2-sultam (**2**) was obtained at X-ray crystallographic laboratory in this department. We thank Prof. Kimoon Kim and Mr. D. Whang for the X-ray crystallographic work.
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