Molecular Mechanics Calculations and the Stereochemical Course of Intramolecular Dipolar Cycloadditions of Nitrile Oxides†,[1]

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The intramolecular nitrile oxide cycloaddition of a series of 4-vinyl N-substituted β-lactams has been investigated. The synthesis of the olefinic nitrile oxides involves treating a 4-vinylazetidinone with a dibromoalkane. The resulting bromo lactam was converted to the corresponding nitro compound, which was then treated with a mixture of phenyl isocyanate and triethylamine. The nitrile oxides were not isolated but spontaneously underwent intramolecular cycloaddition to give fused six- and seven-membered ring systems. Two different transition states are possible for the cycloaddition. In the case of the six-membered ring, the reaction proceeds exclusively via a chair transition state leading to a cis cycloadduct. The transition state involved in the formation of the seven-membered ring is much more flexible and can produce the trans cycloadduct as well. MMX calculations of the energy relationships between the cis and trans isomers of the cycloadducts are in good agreement with the experimental results. The ratio of diastereomeric products from the INOC reaction appears to correlate with product stabilities, in accord with a late transition state.

The stereochemical course of intramolecular [4 + 2]-cycloaddition chemistry has been a problem of considerable current interest.[2,3] An analysis of various transition-state conformations represents a standard method for predicting product outcome and evaluating the relative merits of competing reaction pathways. This is particularly true in intramolecular Diels–Alder chemistry where issues of regio- and stereochemistry are determined by subtle conformational factors.[4-6] Usually, the relative importance of the two stereochemical pathways, exo and endo, are apparent from the ratio of cis- and trans-fused products. Results of previous studies indicate that endo or exo transition-state preferences of intramolecular Diels–Alder reactions can be markedly influenced by substituents.[7-9] The ratio of diastereomeric products obtained from intramolecular Diels–Alder reactions has been correlated with stabilities of boat-chair conformers as calculated by molecular mechanics.[10,11]

Among [4 + 2] cycloadditions, intramolecular 1,3-dipolar cycloadditions are of considerable value and have been applied successfully in the synthesis of many classes of compounds including important natural products.[3,12-22] Often in such syntheses it is desirable to be able to predict the stereochemical outcome of the cyclizations, yet little is known[13] about the factors influencing stereoselectivity of substituents during such ring closures and how to predict them. No definitive MM2 calculations have been reported that permit stereochemical correlations in intramolecular nitrile oxide–olefin cycloadditions.[23] During the course of our studies dealing with the unsaturated nitrile oxide β-lactam system,[24] we became interested in determining whether the product distribution of the INOC reaction could be correlated with molecular mechanics calculations as was done with intramolecular Diels–Alder chemistry.[11]

Results of Synthetic Experiments

The synthesis of the desired olefinic nitrile oxides 4 commenced with the 4-vinyl β-lactam 1 available from isoprene and chlorosulfonyl isocyanate. We were able to introduce additional functionality into 1 by monoalkylation with a dibromoalkane using a heterogeneous system of potassium hydroxide powder and tetrabutylammonium

† Dedicated with respect and affection to Professors Alan R. Katritzky and Edward C. Taylor on the occasion of their 60th and 65th birthdays, respectively.

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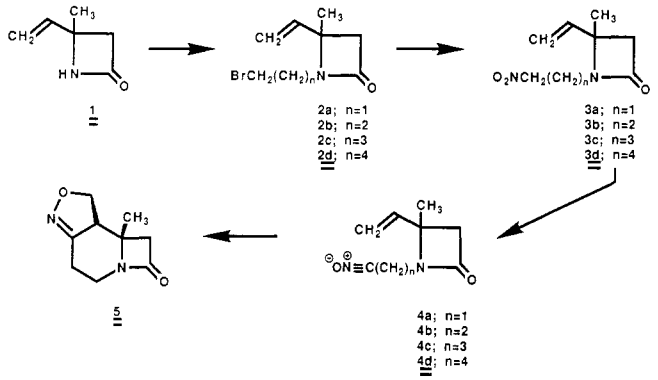
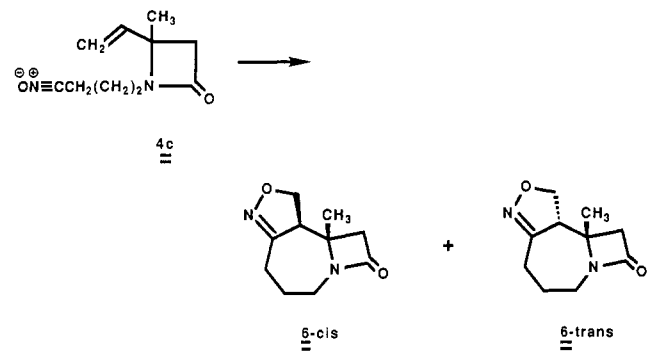
bromide. Reaction of the bromo lactams **2** with sodium nitrite provided the unsaturated nitro lactams and conversion of **3** into **4** was accomplished by means of phenyl

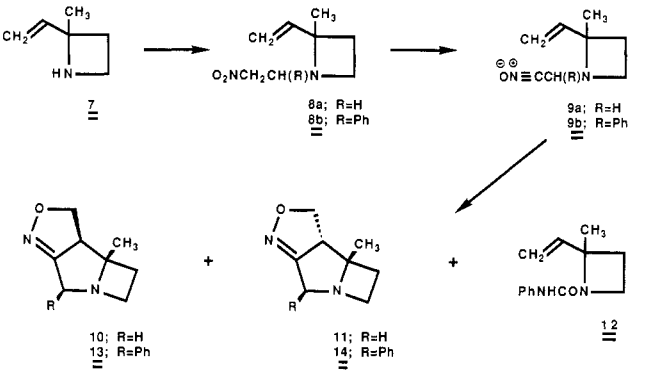


isocyanate–triethylamine.[25] The nitrile oxides **4b** and **4c** were not isolated but spontaneously underwent the intramolecular nitrile oxide–olefin cycloaddition to produce in good yield the fused six- and seven-membered ring systems **5** and **6**, respectively. Attempts to produce the analogous fused five- and eight-membered ring compounds were not successful; in the case of **4a**, a retro-Michael addition took place to give vinyl lactam **1**, while in the case of **4d** polymerization of the nitrile oxide occurred. It was found that ring closure with formation of a six-membered ring occurred stereospecifically to produce only isomer **5** while ring closure to a seven-membered ring gave a 40:60 mixture of stereoisomers *cis*-**6** and *trans*-**6**. Structure proof was provided by ^1H and ^{13}C NMR and mass spectra. The stereochemical cis assignment to the methyl and the methylene side chain is based on NOE experiments (ca. 8% enhancement).



In order to assess the stereochemical influence of a substituent further removed from the double bond, we decided to study the nitrile oxide–vinylazetidine system **9**. The monoalkylation route, employed successfully with vinyl β-lactams **1**, did not proceed well with the more basic vinylazetidine **7**. Hence, we investigated two other pathways to **9**: (a) Michael addition of **7** to a vinyl nitro compound and (b) nucleophilic displacement of an α-bromo aldoxime with **7**; both nitro and aldoxime functions can be readily converted to nitrile oxides.[26]

Reaction of **7** (available from **1** by AlH_3 reduction)[27] with nitroethene proceeded readily at 0 °C to give **8a** in 80% yield. In an analogous manner, Michael addition of **7** to β-nitrostyrene produced **8b** in quantitative yield as a 1:1 mixture of diastereomers. Treatment of **8a** with phenyl

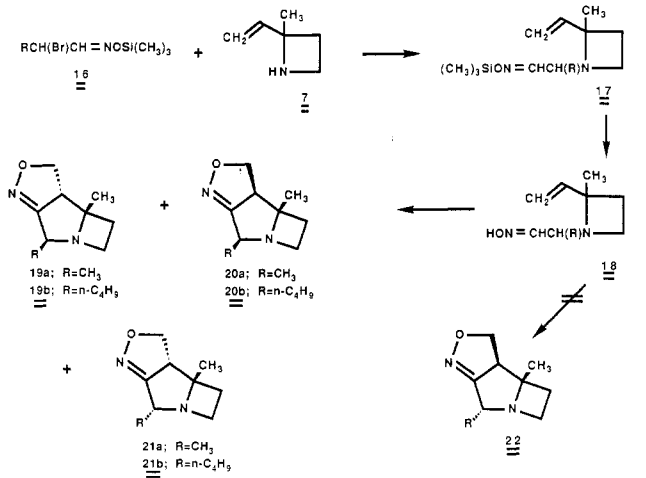


isocyanate and triethylamine led via **9a** to a mixture of cis and trans tricyclic azetidines **10** and **11** in a ratio of 2:3 and in 50% yield, the remainder being the phenylurea **12**. The formation of **12** may be due to a competitive retro-Michael addition regenerating **7**, which in turn is trapped by phenyl isocyanate.

Conversion of nitro olefin **8b** to the tricyclic isoxazolines **13** and **14** (1:2) proceeded on treatment with phenyl isocyanate and triethylamine likewise without isolation of the intermediate nitrile oxide **9b**.

Interestingly, both stereoisomers **13** and **14** isolated from the intramolecular cycloaddition of **9b** had only the *cis* phenyl-methyl configuration in spite of the fact that the starting nitro olefin **9b** was a 1:1 mixture of diastereomers. From this we surmise that ring closure to the *trans*-phenylmethyl isomers was unfavorable. Indeed this is borne out by an examination of models, which indicate steric interactions between the α-oriented phenyl and the hydrogen at C-4, at least in the transition state leading to the cis,trans isomer **22**. In the ring closure of both **9a** and **9b**, there is a preference of trans stereochemistry between the methyl and the methylene of the oxazoline ring (**11** and **14** are the predominant isomers).

The second pathway to nitrile oxides **9** is based on our recent discovery[28] that α-bromination of oximes can be carried out on their silyl derivatives to produce **16**. Nucleophilic displacement of the halogen in these *O*-silyl α-bromo aldoximes **16** by the azetidine **7** led to the silylated oxime products **17**. The latter were smoothly desilylated on chromatography over silica gel or in the presence of fluoride ions to produce **18** as a 1:1 mixture of diastereomers.



The unsaturated oximes **18** were converted via **9** to the cycloaddition products by treatment with sodium hypo-

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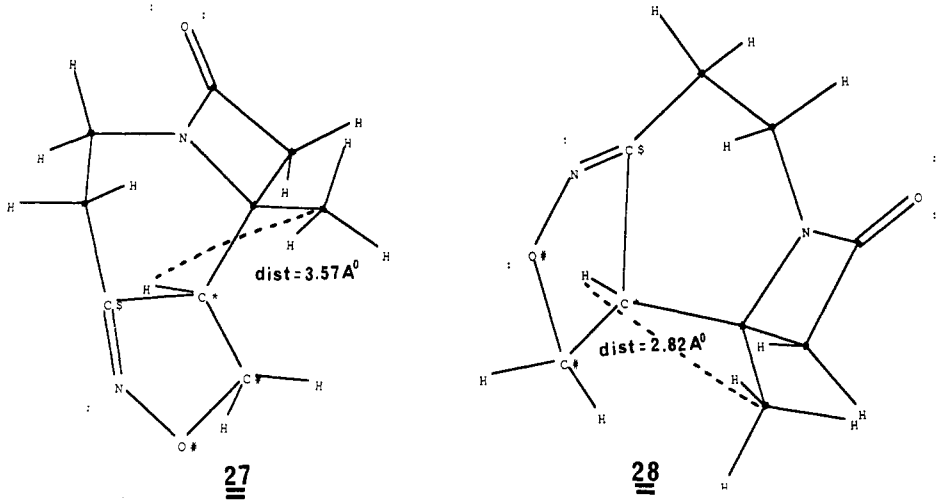

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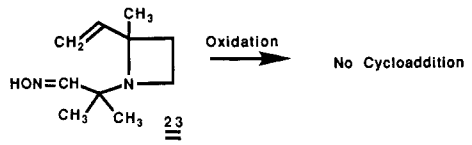
Figure 1. Transition states used in molecular modeling for the INOC reaction leading to cycloadducts *cis*-**5** and *trans*-**5**.

chlorite. The major products were the stereoisomers possessing the R and methyl groups in a cis configuration. Conspicuously absent in all three cases (R = Me, Bu, Ph) was the trans isomer corresponding to **22**, indicating again the unfavorable interactions described above. In the case of R = Me and R = Bu, a third isomer **21** was also present but it was absent when R was a larger substituent (i.e., phenyl). The configuration of the isomers was established by ^1H and ^{13}C NMR and by NOE experiments (see Experimental Section). In all of the cis Me:CH_2 compounds (i.e., **10**, **13**, **20**), the methylene protons absorb near 4.6 ppm while in the trans isomers (i.e., **11**, **14**, **19**, and **21**) these protons are found near 3.8 ppm. Consistent with the unfavorable interactions is the fact that the dimethyl derivative **23** failed to undergo the intramolecular cycloaddition since in this case one of the methyl groups would necessarily interfere in the transition state for cyclization.



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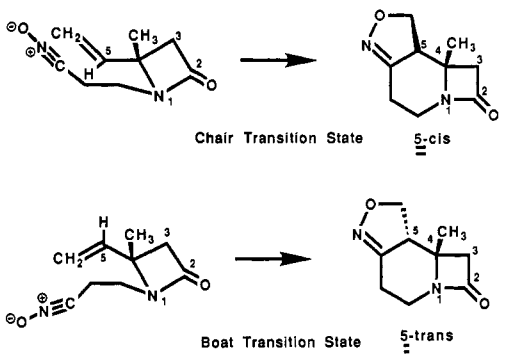
MMX Calculations

Over the past 15 years, molecular mechanics has developed into an important technique for the calculation of molecular properties.[29] This method has seen increasing use in the prediction of favored geometries and the reactive stereochemistry of conformationally mobile systems,[30] transition state geometries,[31] and product vs reactant energies.[32] The force fields and parameters developed by Allinger and co-workers and utilized through the MM2 program[29] have proved to be powerful tools in synthetic organic chemistry.[33] Molecular mechanics treats molecular strain energy by using a classical model in which the strain energy is expressed as a sum of energies associated with particular molecular deformations. We have used the MMX88 program as parameterized by Gajewski and Gilbert[34] and implemented in the program Model 2.92[35] to calculate the total energy of the various systems examined.

Scheme I



Inspection of molecular models of the nitrile oxide system indicates that two different transition states are possible for the cycloaddition (Scheme I). If the INOC reaction proceeds through a chair transition state, then the methyl at C-4 and the hydrogen at positions 5 will be trans, hence the C-4 methyl and C-5 methylene in product **5** will be cis. Alternatively, if the reaction is proceeding through a boat transition state, then the methyl and hydrogen at these positions will be cis to each other. In fact, the distribution of products was found to vary as a function of the connecting chain length. The INOC reaction for n = 2 gave only the six-membered ring cis stereoisomer (i.e., **5**). Ring closure to the seven-membered ring, on the other hand, gives **6** as both cis and trans isomers (2:3). Cycloaddition does not occur in the case of the eight-membered ring. A reasonable explanation to accommodate these results is that the six-membered ring is formed via the chair transition state which leads to the cis stereochemistry. The transition state involved in formation of the seven-membered ring is much more flexible and can therefore lead to trans products as well.

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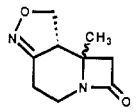
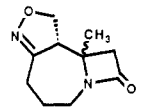
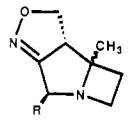
(33) For recent examples, see: Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275. Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249. Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058.
(34) MMX88 is available from Serena Software, 489 Serena Lane, Bloomington, IN 47401. Calculations were performed on a VAX 11/785 (version 4.3). We are indebted to Professor J. Gajewski of the University of Indiana for a prerelease version of this program.
(35) We thank Professor Kosta Steliou of the University of Montreal for many fruitful discussions, helpful advice, and providing a copy of the extensively rewritten Still Model program.

Table I. Molecular Mechanics Calculations of the INOC Reaction

			total energy, kcal/mol			
			cis	trans	TE	cis/trans[f]
	5	gs[a]	53.93	56.94	3.01	100:1
		ts[b]	43.13	44.67	1.54	
	6	gs	64.82	65.43	0.61	2:3
		ts	53.81	54.04	0.23	
	10, 11	R = H				
		ts	45.59	44.17	−1.42	2:3
	19, 20	R = CH_3				
		ts	50.69[c]	50.48[d,e]	−0.21	1:2

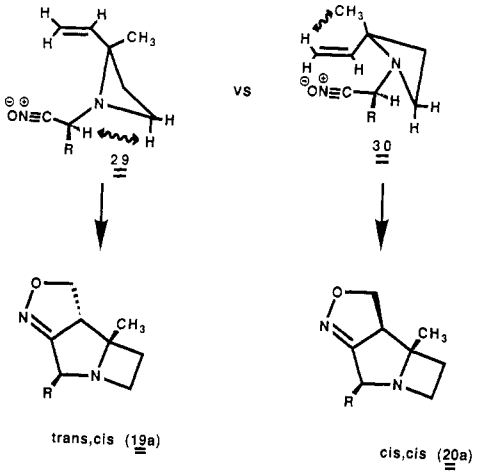
[a] Ground state. [b] Transition state. [c] cis,cis isomer. [d] trans,cis isomer. [e] trans,trans isomer has a value of 50.93 kcal/mol. [f] Experimental ratio determined by NMR.

The relative energy differences of these transition states were estimated by calculating the transition state total energy by using the MMX88 program. This program is parameterized for transition-state carbon (C$,C#,C*) as well as transition-state oxygen (O#). Transition-state bond orders of 0.3 were entered, which gave transition-state bond lengths and torsional angles very similar to those obtained from the more rigorous nitrile oxide calculations.[23] The structures pictured in Figure 1 were employed in our modeling studies. Although **27** and **28** (Figure 1) may differ from the actual transition-state geometry, the calculated energies still reflect the relative transition-state energies as both products are formed via the same dipole. At the very least, these computations provide a qualitative insight about various transition-state conformers.

The MMX calculations of the energy relationships between the cis and trans isomers of the cycloadducts are in good agreement with the experimental results. For example, in the six-membered ring system the MMX calculations predict a cis to trans ratio of 80:20, equivalent to a difference of ca. 1.5 kcal/mol between the two isomers. Since the intramolecular cycloaddition of the six-membered ring system exclusively affords the cis isomer, it is clear that the two-plane orientation approach leading to this isomer has significantly fewer nonbonded interactions than the one leading to the trans isomer. This is of some interest since very high levels of diastereoselection (≥20:1) are usually not attained in most nitrile oxide cycloadditions, because the nonbonded interactions responsible for the diastereoselection are generally of insufficient magnitude. This is readily apparent in the seven-membered series, where both sets of isomers are formed with an energy difference of only 0.23 kcal/mol.

The trends identified for the transition states parallel those found for the ground states. Calculations were carried out on the lowest energy conformations of the two regioisomeric cycloadducts and the results showed the same ordering of diastereo and conformational preferences. For the INOC reaction of **4b**, the cis isomer was found to be 3.0 kcal/mol more stable than the trans isomer. In the case of the seven-membered ring the cis isomer **6** was calculated to be more stable by 0.6 kcal/mol. Thus the preference for the chair or boat transition state in the internal cycloaddition parallels the ground-state preference observed for the isolated cycloadducts. The energy difference between the two transition-state conformations is smaller than the ground-state energy difference between the two diastereomeric forms of the product. This diminution of energy differences may be a result of a "loose" transition state for the nitrile oxide cycloaddition. Regardless of the origin of the differences, the results demonstrate the parallel between transition-state and product stabilities in the INOC reaction.

We have also probed the stereochemical effect during cycloaddition of a substituent near the nitrile oxide center. Here we are dealing with an azetidine, so it is difficult to compare this to the azetidinone case. Furthermore, the closure is to a five-membered ring. The stereochemical predictions of the MMX calculations for these intramolecular additions are compared to experiment in Table I. Certain trends are evident from inspection of the data. Most striking is the much larger amount of the trans cycloadduct. The computed energy difference between transition states **29** and **30** when R = H corresponds to 1.42



kcal/mol. A preference for the trans,cis isomer **19a** is found experimentally both when R = H and with the corresponding methyl compound (R = CH_3) and is correctly predicted by the MMX calculations. It seems reasonable to invoke allylic $A^{1,3}$ strain which is present in the transition state (i.e., **30**) leading to the cis product (**20a**) to explain the trans over cis preference. When the substituent R is near the nitrile oxide center, we also find a preference for the R group to be cis to the methyl substituent. We believe this to be due to steric interactions on the α side between an azetidine H and the R group if the latter is α. Indeed, neither was isomer **22** isolated in the INOC reaction nor did ring closure occur from the dimethyl analogue **23**. If these cycloadditions proceeded

via a reactant-like transition state, we would not expect the R substituent to significantly effect the product ratio. A product-like transition state, on the other hand, would tend to favor the trans,cis isomer according to molecular mechanics calculations.

In conclusion, the results of these studies support previous findings that transition-state preferences of intramolecular [4 + 2] cycloadditions can be markedly influenced by substituents. The ratio of diastereomeric products from the INOC reaction appears to correlate with product stabilities, in accord with a late transition state.

Experimental Section[36]

General Procedure for the Formation of *N*-Bromoalkyl Substituted 4-Methyl-4-vinyl-2-azetidinones 2. *N*-(2′-Bromoethyl)-4-methyl-4-vinyl-2-azetidinone (2a). To a stirred solution of vinylazetidinone 1[37] (555 mg, 5 mmol), 1.3 g (7 mmol) of 1,2-dibromoethane, and 177 mg (0.55 mmol) of tetrabutylammonium bromide in dry tetrahydrofuran (25 mL) was added freshly powdered potassium hydroxide (314 mg, 5.5 mmol) at 20 °C.[38] After being stirred for 12 h, the mixture was filtered, the tetrahydrofuran was evaporated, and the residue was taken up in 50 mL of methylene chloride. The methylene chloride solution was washed with water (3 × 40 mL) and brine (1 × 30 mL) and dried over sodium sulfate and the solvent was removed under reduced pressure to leave behind a colorless oil. Purification of this oil by flash chromatography (silica gel, ethyl acetate/petroleum ether (1:6, then 1:3, and 1:2 as eluent)) gave pure **2a** (650 mg, 60%) and unreacted **1** (160 mg, 29%) (respectively in the later two fractions). **2a**: IR 1740 cm^{-1}; mass spectra (*m/e*) 220, 218 (M^+), 138, 124, 109, 107, 96, 95, 82, 68, 66; NMR ($CDCl_3$) δ 1.56 (s, 3 H), 2.88 (s, 2 H), 3.46 (m, 4 H), 5.27 (dd, 1 H, *J* = 10.5 and 0.5 Hz), 5.29 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.97 (dd, 1 H, *J* = 17.5 and 10.5 Hz); ^{13}C NMR δ 21.2 (q), 28.4 (t), 41.9 (t), 50.8 (t), 57.8 (s), 116.6 (t), 140.0 (d), 166.6 (s).

***N*-(3′-Bromopropyl)-4-methyl-4-vinyl-2-azetidinone (2b).** From 555 mg of **1** and 1.1 g (5.5 mmol) of 1,3-dibromopropane as outlined for **2a** there were obtained after flash chromatography 900 mg (78%) of **2b** and 65 mg (12%) of **1**: IR 1740 cm^{-1}; mass spectra (*m/e*) 232, 234 (M^+), 173, 152, 124, 110, 95, 82, 68, 67; NMR ($CDCl_3$) δ 1.52 (s, 3 H), 2.15 (q, 2 H, *J* = 7.0 Hz), 2.83 (s, 2 H), 3.20 (dt, 2 H, *J* = 7.0 and 2.0 Hz), 3.44 (t, 2 H, *J* = 7.0 Hz), 5.27 (dd, 1 H, *J* = 10.5 and 0.5 Hz), 5.29 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.93 (dd, 1 H, *J* = 17.5 and 10.5 Hz); ^{13}C NMR δ 21.0, 30.52, 31.54, 38.65, 50.5, 57.5, 116.3, 140.0, 166.82.

***N*-(4′-Bromobutyl)-4-methyl-4-vinyl-2-azetidinone (2c).** From 555 mg of **1** and 1.11 g (5.2 mmol) of 1,4-dibromobutane as outlined for **2a** there was obtained after flash chromatography (ethyl acetate/petroleum ether (1:3)) 1.04 g (85%) of **2c** as a colorless oil: IR 1745 cm^{-1}; mass spectra (*m/e*) 246, 166, 135, 124, 110, 96, 82, 68; NMR ($CDCl_3$) δ 1.52 (s, 3 H), 1.65–1.78 (m, 2 H), 1.85–1.98 (m, 2 H), 2.83 (s, 2 H), 3.10 (t, 1 H, *J* = 7.0 Hz), 3.43 (t, 1 H, *J* = 7.0 Hz), 5.25 (dd, 1 H, *J* = 11.0 and 0.5 Hz), 5.27 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.94 (dd, 1 H, *J* = 17.5 and 11.0 Hz); ^{13}C NMR δ 21.1, 27.4, 30.1, 32.9, 38.94, 50.55, 57.5, 116.2, 140.3, 166.6.

***N*-(5′-Bromopentyl)-4-methyl-4-vinyl-2-azetidinone (2d).** Azetidinone **2d** was obtained in 80% yield following the procedure described for **2a**: NMR **2d** δ 1.50 (s, 3 H), 1.4–1.52 (m, 2 H), 1.53–1.66 (m, 2 H), 1.82–1.96 (m, 2 H), 2.82 (s, 2 H), 3.07 (t, 2 H, *J* = 6.5 Hz), 3.39 (t, 2 H, *J* = 6.5 Hz), 5.24 (dd, 1 H, *J* = 10.5 and 0.5 Hz), 5.26 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.93 (dd, 1 H, *J* = 17.5 and 10.5 Hz); ^{13}C NMR **2d** δ 21.1, 25.7, 28.0, 32.1, 33.36, 39.75, 50.52, 57.5, 116.04, 140.4, 166.65.

***N*-(3′-Nitropropyl)-4-methyl-4-vinyl-2-azetidinone (3b).** To a solution of (bromopropyl)azetidinone **2b** (231 mg, 1 mmol) in dry dimethylformamide (30 mL) under argon was added sodium nitrite (276 mg, 4 mmol) and stirring was continued at 20 °C for 12 h. The mixture was poured into 100 mL of ice–water and extracted with chloroform (4 × 50 mL). Drying and evaporation of the solution furnished **3b** as a light yellow oil which was purified by flash chromatography (silica, eluant: ethyl acetate/petroleum ether (30:70)) to provide 115 mg (58%) of pure **3b**: mass spectra (*m/e*) 199 (MH^+), 198, 183, 168, 151, 124, 112, 95, 88, 82, 68; NMR ($CDCl_3$) δ 1.47 (s, 3 H), 2.24 (q, 2 H, *J* = 7.0 Hz), 2.81 (s, 3 H), 3.12 (t, 2 H, *J* = 7.0 Hz), 4.43 (t, 2 H, *J* = 7.0 Hz), 5.23 (dd, 1 H, *J* = 10.5 and 0.5 Hz), 5.25 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.88 (dd, 1 H, *J* = 17.5 and 10.5 Hz); ^{13}C NMR δ 20.8 (q), 26.4 (t), 36.8 (t), 50.5 (s), 57.6 (t), 72.9 (t), 116.7 (t), 139.6 (d), 166.96 (s).

1-(4′-Nitrobutyl)-4-methyl-4-vinyl-2-azetidinone (3c). This compound was obtained in 55% yield by using the same procedure as was described for the preparation of **3b**: IR 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (s, 3 H), 1.58–1.73 (m, 2 H), 2.0–2.12 (m, 2 H), 2.84 (s, 3 H), 3.13 (m, 2 H), 4.43 (t, 2 H, *J* = 7.0 Hz), 5.26 (dd, 1 H, *J* = 10.5 and 0.5 Hz), 5.27 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.92 (dd, 1 H, *J* = 17.5 and 10.5 Hz); ^{13}C NMR δ 20.9 (q), 24.75 (t), 25.6 (t), 38.75 (t), 50.44 (t), 57.54 (s), 74.75 (t), 116.4 (t), 139.95 (d), 166.6 (s). Compounds **3a** and **3d** were prepared in a similar manner. **3a**: NMR δ 1.49 (s, 3 H), 2.85 (s, 2 H), 3.10 (m, 2 H), 3.81 (m, 2 H), 5.26 (dd, 1 H, *J* = 10.0 and 0.5 Hz), 5.27 (dd, 1 H, *J* = 17.0 and 1.0 Hz), 5.91 (dd, 1 H, *J* = 17.0 and 10.0 Hz); ^{13}C NMR δ 20.74, 45.0, 50.0, 57.7, 60.4, 116.6, 139.5, 166.1. Attempts to purify **3a** by chromatography on silica gel led to decomposition. **3d**: NMR δ 1.50 (s, 3 H), 1.36–1.51 (m, 2 H), 1.55–1.70 (m, 2 H), 1.97–2.12 (m, 2 H), 2.82 (s, 2 H), 3.0–3.13 (m, 2 H), 4.39 (t, 2 H, *J* = 6.5 Hz), 5.23 (dd, 1 H, *J* = 10.5 and 0.5 Hz), 5.25 (dd, 1 H, *J* = 17.5 and 0.5 Hz), 5.92 (dd, 1 H, *J* = 17.5 and 10.5 Hz); ^{13}C NMR δ 21.0, 23.8, 26.7, 28.0, 39.4, 50.5, 57.5, 75.3, 116.2, 140.2, 166.65.

4′,5′-Dihydroisoxazolo[4,3-*c*]-2′-oxoazetidino[2,1-*d*]-2,3-*cis*-2-methylpiperidine (5). To a solution of **3b** (60 mg, 0.3 mmol) in dry chloroform (10 mL) at room temperature was added phenyl isocyanate (83 mg, 0.7 mmol), followed by triethylamine (10 mg, 0.1 mmol). The mixture was stirred for 10 h during which time diphenylurea separated as a solid which was filtered. The filtrate was washed with water (1 × 20 mL) and dried (sodium sulfate), and the solvent was removed under reduced pressure to leave a semisolid which was chromatographed (silica, chloroform) to yield 48 mg (90%) of **5** as colorless needles, mp 127–128 °C (from methylene chloride–petroleum ether): IR 1740 cm^{-1}; mass spectra (*m/e*) 180 (M^+), 179, 151, 138, 137, 124, 111, 110, 108, 97, 96, 84, 81, 68, 67; NMR ($CDCl_3$) δ 1.34 (s, 3 H), 2.46 (dddd, 1 H, *J* = 13.5, 11.5, 7.5 and 1.0 Hz), 2.77 (m, 1 H), 2.88 (m, 1 H), 2.92 (br s, 2 H), 3.38 (ddd, 1 H, *J* = 11.5, 7.5 and 1.0 Hz), 4.21 (dd, 1 H, *J* = 9.5 and 7.5 Hz),[39] 4.35 (dd, 1 H, *J* = 11.5 and 9.5 Hz); ^{13}C NMR δ 17.3 (q), 23.9 (dd), 35.6 (dd), 51.7 (t), 55.6 (s), 57.2 (d), 68.7 (dd), 155.1 (s), 163.8 (s). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.92; H, 6.94; N, 15.50.

4′,5′-Dihydroisoxazolo[4,3-*d*]-2′-oxoazetidino[2,1-*d*]-2-methylhexahydroazepine (*cis*-6 and *trans*-6). From **3c** (64 mg, 0.3 mmol) after a 6-h reaction time as described for **5** there was isolated a 2:3 mixture of diastereomers *cis*-**6** and *trans*-**6**: IR 1745 cm^{-1}; mass spectra (*m/e*) 194 (M^+), 193, 166, 138, 110, 68, 67. NMR ($CDCl_3$) *cis*-,6 δ 1.39 (s, 3 H), 1.90 (m, 2 H), 2.70 (m, 1 H), 2.76 (d, 1 H, *J* = 12.5 Hz), 2.84 (dd, 1 H, *J* = 12.5 and 1.5 Hz), 2.85 (m, 1 H), 3.06 (m, 1 H), 3.53 (dd, 1 H, *J* = 11.0 and 6.0 Hz), 3.84 (m, 1 H), 4.14 (dd, 1 H, *J* = 9.0 and 6.0 Hz),[39] 4.35 (dd, 1 H, *J* = 11.0 and 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 18.2, 24.7, 26.4, 41.0, 49.7, 57.3, 61.0, 70.5, 158.2, 167.8; NMR *trans*-**6** δ 1.48 (s, 3 H), 1.90 (m, 2 H), 2.36 (ddd, 1 H, *J* = 14.0, 10.0 and 4.5 Hz), 2.64 (d, 1 H, *J* = 15.0 Hz), 2.86 (2 H), 3.01 (d, 1 H, *J* = 15.0 Hz), 3.38 (dd, 1 H, *J* = 10.0 and 3.5 Hz),[39] 3.85 (ddd, 1 H, *J* = 11.0, 6.0 and 6.0 Hz), 4.19 (dd, 1 H, *J* = 9.0 and 3.5 Hz), 4.34 (dd, 1 H, *J* = 10.0 and 9.0 Hz); ^{13}C NMR δ 24.52 (q), 25.4 (dd), 25.7 (dd), 40.1 (dd), 45.65 (dd), 57.5 (d), 58.2 (s), 72.0 (dd), 158.6 (s), 166.5 (s). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.22. Found: C, 62.00; H, 7.34.

4′,5′-Dihydroisoxazolo[4,3-*d*]azetidino[1,2-*a*]-2-methylpyrrolidines (10, 11). To a solution of nitroethylene (40 mg, 0.55 mmol) at −10 °C was added a sample of 7[27] (50 mg, 0.5 mmol). The reaction mixture was stirred for 30 min. Evaporation of the solvent under reduced pressure gave **8a** as a colorless oil:

(36) All ^1H and ^{13}C NMR spectra are correlated by decoupling and off-resonance experiments.

(37) Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, *36*, 2841.

(38) This procedure was adapted from Reuschling, D.; Dietsch, H.; Linkies, A. *Tetrahedron Lett.* **1978**, 615.

(39) Irradiation at the frequency of the angular methyl group increased the intensity of this signal by 6–10% (NOE).

IR 1740 and 1455 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.85–1.95 (m, 1 H), 2.08 (m, 1 H), 2.9–3.32 (m, 4 H), 4.30 (t, 2 H, J = 6.0 Hz), 5.07 (dd, 1 H, J = 11.0 and 1.5 Hz), 5.15 (dd, 1 H, J = 17.5 and 1.5 Hz), 5.98 (dd, 1 H, J = 17.5 and 11.0 Hz); ^{13}C NMR δ 20.3, 31.3, 48.3, 49.4, 74.2, 113.2, 142.6. This compound was dissolved in chloroform (5 mL) and a solution containing phenyl isocyanate (140 mg, 1 mmol) and then triethylamine (20 mg, 0.2 mmol) was added. The resulting mixture was stirred for 4 h. Filtration, followed by removal of the solvent, led to the isolation of a dark brown residue which was flash chromatographed (eluant: chloroform/methylene chloride (7:3)) to give a 2:3 mixture of **10** to **11** (32 mg, 42%): NMR **10** ($CDCl_3$) δ 1.19 (s, 3 H), 2.05–2.39 (m, 2 H), 3.58–3.80 (m, 2 H), 3.21 (d, 1 H, J = 16.0 Hz), 3.32 (q, 1 H, J = 9.0 Hz), 3.68 (d, 1 H, J = 16.0 Hz), 4.05 (dd, 1 H, J = 10.5 and 8.0 Hz),[39] 4.55 (dd, 1 H, J = 10.5 and 8.0 Hz), 4.58 (t, 1 H, J = 10.5 Hz); ^{13}C NMR δ 24.0, 31.4, 50.1, 53.3, 61.9, 68.6, 70.7, 171.1; NMR **11** ($CDCl_3$) δ 1.46 (s, 3 H), 2.05–2.40 (m, 2 H), 2.79 (dt, 1 H, J = 10 and 8.5 Hz), 3.58–3.80 (m, 2 H), 3.20 (d, 1 H, J = 14.5 Hz), 3.55 (d, 1 H, J = 14.5 Hz), 3.74 (t, 1 H, J = 10.5 Hz),[39] 4.18 (dd, 1 H, J = 10.5 and 8.5 Hz), 4.53 (dd, 1 H, J = 10.5 and 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 25.7, 30.0, 48.6, 50.1, 62.4, 68.2, 71.1, 166.8; mass spectra, CI (m/e) 153 (MH^+), 136, 120, 94.

General Procedure for the Preparation of *O*-Trimethylsilyl 2-Bromo Aldoximes 16. Preparation of 16a. To a stirred solution of propanal oxime (0.73 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in dry carbon tetrachloride (30 ml) at 0–5 °C was added dropwise trimethylsilyl chloride (1.08 g, 10 mmol) in carbon tetrachloride (5 mL). The mixture was slowly brought to room temperature and was stirred under argon for 2 h. The solution was filtered and the triethylamine hydrochloride salt was washed with carbon tetrachloride (2 × 10 mL). To the combined filtrate was added freshly crystallized and dried *N*-bromosuccinimide (1.78 g, 10 mmol) and benzoyl peroxide (0.120 g, 0.5 mmol). The stirred suspension was heated at reflux for 3.5 h or irradiated for 2 h using two 100-W lamps under an argon atmosphere. The solution was filtered and the filtrate was washed with a 10% sodium thiosulfate solution (1 × 20 mL) and water (2 × 20 mL) and dried over sodium sulfate. Removal of the solvent under reduced pressure gave **16a** as a colorless oil (2.2 g, 95%): bp 50–52 °C (10 mm) NMR ($CDCl_3$) (3:1 ratio of *Z*:*E* isomers) δ 0.21 and 0.22 (2 s, 9 H), 1.74 (d, 3 H, J = 7.5 Hz), 1.83 (d, 3 H, J = 7.5 Hz), 4.74 (q, 1 H, J = 7.5 Hz), 5.29 (dq, 1 H, J = 8.0 and 7.5 Hz), 7.01 (d, 1 H, J = 8.0 Hz), 7.62 (d, 1 H, J = 7.5 Hz); mass spectra (m/e) 226, 224 (MH^+), 223, 210, 208, 154, 152, 144, 128, 117, 91, 72.

In the same manner compounds **16b–d** were prepared: NMR **16b** ($CDCl_3$) (90%, 2.3:1 mixture of *Z*:*E* isomers) δ 0.22 (s, 9 H), 0.9 (t, 3 H, J = 7.0 Hz), 1.2–1.55 (m, 4 H), 1.72–2.05 (m, 2 H), 4.56 and 5.23 (2 dt, 1 H, J = 8.0 and 8.0 Hz), 7.01 and 7.53 (2 d, 1 H, J = 8.0 Hz); NMR **16c** (60%, 1:1 ratio of *Z*:*E* isomers) δ 0.22 and 0.23 (2 s, 9 H), 5.63 and 5.70 (2 d, 1 H, J = 8.0 Hz), 7.82 and 7.90 (2 d, 1 H, J = 8.0 Hz), 7.1–7.60 (m, 5 H); NMR **16d** (98%) δ 0.21 (s, 9 H), 1.91 s, 6 H), 7.7 (s, 1 H).

2-(2′-Methyl-2′-vinyl-1′-azetidinyl)hexanal *O*-(Trimethylsilyl)oxime (17b). To a solution containing **16b** (160 mg, 0.6 mmol) in carbon tetrachloride (15 mL) at 0 °C was added a sample of **7** (58 mg, 0.6 mmol) followed by triethylamine (62 mg, 0.61 mmol). After being stirred for 0.5 h, the mixture was filtered and the solvent was removed under reduced pressure to furnish **17b** (168 mg, 99%) as a mixture of four isomers in a ratio of 2:2:1:1: [^1H NMR of mixture: δ 7.1–7.25 (4 d, 1 H), 6.01–6.25 (m, 1 H), 5.0–5.16 (m, 2 H), 3.02–3.3 (m, 3 H), 2.08–2.2 (m, 1 H), 1.7–1.9 (m, 1 H), 1.05–1.6 (m, 6 H), four singlets at 1.34, 1.34, 1.41, 1.41 (3 H), 0.88 (m, 3 H), 0.2 (4 s, 9 H)]. This mixture was used in the next step without further purification.

4′,5′-Dihydroisoxazolo[4,3-*d*]azetidino[1,2-*a*]-2-methyl-5-butylpyrrolidines 19b, 20b, and 21b. The silylated oxime **17b** (168 mg) was mixed with silica gel (2 g) in methylene chloride (10 mL) and stirred at 25 °C for 0.5 h. Chromatography of the mixture over alumina provided the free oxime **18b**, which was dissolved in methylene chloride (20 mL). To this mixture was added a solution of sodium hypochlorite (9%, 0.9 mL, 1 mmol) dropwise at 0 °C. The solution was stirred for 1 h, the organic layer was concentrated under reduced pressure, and the aqueous portion was extracted with methylene chloride (2 × 5 mL). The combined organic extracts were washed with water (2 × 10 mL) and a saturated salt solution (1 × 10 mL) and dried (sodium sulfate) and the solvent was removed to leave behind a light yellow oil. The latter was chromatographed on silica gel (chloroform) to give a 3:2:2 mixture of three isomers (75 mg, 60%). Chromatography using a chloroform/methylene chloride mixture (80:20 and 100:0) provided separation of **19b** and **21b** as pure products and **20b** as a major component in a mixture of **19b**, **20b**, and **21b**; mass spectra, CI (m/e) 209 (M^+H), 207, 191, 179, 168, 151, 138, 124, 98, 86, 84, 70, 68; NMR **19b** δ 0.89 (t, 3 H, J = 7.5 Hz), 1.20–1.80 (m, 6 H), 1.49 (s, 3 H), 2.04 (ddd, 1 H, J = 12.0, 10.0 and 8.0 Hz), 2.30 (ddd, 1 H, J = 12.0, 10.0 and 5.5 Hz), 2.82 (ddd, 1 H, J = 10.0, 10.0 and 8.0 Hz), 3.18 (t, 1 H, J = 8.0 Hz), 3.66 (ddd, 1 H, J = 10.0, 10.0 and 5.5 Hz), 3.87 (t, 1 H, J = 11.5 Hz), 4.20 (ddd, 1 H, J = 11.5, 9.5 and 0.5 Hz), 4,54 (dd, 1 H, J = 11.5 and 9.5 Hz); ^{13}C NMR δ 13.9, 23.3, 25.0, 28.2, 31.4, 33.4, 48.3, 60.7, 63.5, 68.1, 71.9, 169.0; NMR **21b** δ 0.90 (t, 3 H), 1.2–1.8 (m, 6 H), 1.45 (s, 3 H), 2.16 (m, 2 H), 3.03 (q, 1 H, J = 9.5 Hz), 3.21 (ddd, 1 H, J = 9.5, 8.0 and 5.5 Hz), 3.74 (t, 1 H, J = 6.0 Hz), 3.75 (t, 1 H, J = 11.5 Hz), 4.19 (dd, 1 H, J = 11.5 and 9.0 Hz), 4.56 (dd, 1 H, J = 11.5 and 9.0 Hz); ^{13}C NMR δ 13.9, 22.7, 24.6, 25.3, 29.2, 30.1, 41.5, 58.4, 62.2, 67.4, 71.9, 169.0 ppm; NMR **20b** δ 0.89 (t, 3 H, J = 7.0 Hz), 1.23–1.78 (m, 6 H), 1.20 (s, 3 H), 2.12 (ddd, 1 H, J = 11.5, 9.0 and 3.5 Hz), 2.28 (ddd, 1 H, J = 11.5, 9.0 and 9.0 Hz), 3.28 (dt, 1 H, J = 8.0 and 1.0 Hz), 3.39 (q, 1 H, J = 9.0 Hz), 3.75 (ddd, 1 H, J = 9.0, 9.0 and 3.5 Hz), 4.04 (dd, 1 H, J = 11.5 and 9.0 Hz), 4.46 (dd, 1 H, J = 11.5 and 9.0 Hz), 4.63 (dt, 1 H, J = 11.5 and 1.0 Hz); ^{13}C NMR δ 14.0, 22.6, 24.8, 28.9, 31.0, 34.6, 53.2, 62.8, 63.6, 68.0, 70.6, 173.1; mass spectra, CI (m/e) 209 (MH^+), 207, 179, 98, 86, 84, 70. Anal. (mixture of isomers) Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 68.34; H, 9.75; N, 13.55.

2-(2′-Methyl-2′-vinyl-1-azetidinyl)propanal *O*-(Trimethylsilyl)oxime (17a). From **16a** (90 mg, 0.4 mmol) following the same procedure as outlined above for **17b** there was obtained crude **17a** as a light yellow viscous oil (95 mg, 99%); ^1H NMR of mixture of isomers 7.58, 7.43, 7.38, and 7.03 (4 d, 1 H), 6.1–6.5 (m, 1 H), 5.2–5.5 (m, 2 H), 3.3–4.1 (m, 3 H), 2.2–2.7 (m, 2 H), 1.88, 1.87, 1.85, 1.84 (4 s, 3 H), 1.75, 1.74, 1.32, and 1.22 (4 d, 3 H), 0.2 (s, 9 H). This material was used in the next step without further purification.

2-(2′-Methyl-2′-vinyl-1′-azetidinyl)propanal Oxime (18a). A crude sample of **17a** (95 mg) in methylene chloride (10 mL) was stirred with silica gel (1 g) for 1 h at 20 °C and was then flash chromatographed (silica gel eluant: (chloroform/ethyl acetate (9:1)) to give the free oxime **18a** as a 1:1 mixture of two diastereomers (yield 54 mg, 80%): ^1H NMR of mixture 7.25 and 7.19 (2 d, 1 H, J = 8.0 Hz), 6.18 and 6.12 (2 t, 1 H, J = 11.0 Hz), 5.06–5.18 (m, 2 H), 3.32–3.45 (m, 1 H), 3.05–3.31 (m, 2 H), 2.04–2.20 (m, 1 H), 1.81–1.94 (m, 1 H), 1.40 and 1.37 (2 s, 3 H), 1.08 and 1.06 (2 d, J = 4.0 Hz, 3 H); ^{13}C NMR δ 153.03 and 152.69, 142.69 and 142.59, 113.6 and 113.51, 66.84 and 66.56, 54.97 and 54.86, 47.00 and 46.88, 30.15 and 29.72, 21.41 and 20.76, 16.88 and 16.38.

4′,5′-Dihydroisoxazolo[4,3-*c*]azetidino[1,2-*a*]-2,5-dimethylpyrrolidines 19a, 20a, and 21a. To a stirred solution of **18a** (54 mg, 0.32 mmol) in methylene chloride (10 mL) was added dropwise an aqueous sodium hypochlorite solution (9%, 0.5 mL, 0.6 mmol). The mixture was stirred at 0 °C for 0.5 h and at room temperature for another 1.5 h. Workup as for **19b** gave a pale yellow oil which was chromatographed on alumina (chloroform eluant) to give 28 mg (52%) of a mixture of **19a**, **20a**, and **21a** (3:2:1) as an oil: mass spectra (m/e) 166 (M^+), 165, 151, 137, 121, 108, 97, 94, 82, 70, 69, 68, 67. Further separation was achieved by flash chromatography (chloroform, alumina). NMR **19a**: δ 1.25 (d, 3 H, J = 7.0 Hz), 1.51 (s, 3 H), 1.98–2.35 (m, 2 H), 2.80 (ddd, 1 H, J = 10.0, 9.5 and 8.0 Hz), 3.43 (q, 1 H, J = 8.0 Hz), 3.65 (ddd, 1 H, J = 9.5, 9.5 and 5.5 Hz), 3.92 (t, 1 H, J = 10.0 Hz),[39] 4.21 (dd, 1 H, J = 10.0 and 9.0 Hz), 4.55 (dd, 1 H, J = 11.0 and 9.0 Hz); ^{13}C NMR δ 19.8, 24.9, 31.6, 48.2, 58.1, 60.4, 68.04, 71.0, 169.5. NMR **20a** δ 1.22 (s, 3 H), 1.31 (d, 3 H, J = 7.0 Hz), 1.98–2.35 (m, 2 H), 3.34 (q, 1 H, J = 7.0 Hz), 3.41 (q, 1 H, J = 9.0 Hz), 3.77 (ddd, 1 H, J = 8.5, 8.5 and 3.5 Hz), 4.10 (dd, 1 H, J = 11.0 and 8.0 Hz),[39] 4.50 (dd, 1 H, J = 11.0 and 8.0 Hz), 4.64 (dt, 1 H, J = 11.0 and 1.0 Hz); ^{13}C NMR δ 20.4, 24.8, 30.9, 52.6, 58.3, 62.4, 68.2, 71.2, 173.9. Mass spectra, EI (m/e) 166 (M^+), 151, 137, 121, 108, 97, 94, 82, 70, 69, 68. NMR **21a**: δ 1.26 (d, 3 H, J = 7.0 Hz), 1.45 (s, 3 H), 1.98–2.35 (m, 2 H), 3.01 (q, 1 H, J =

10.0 Hz), 3.18 (ddd, 1 H, J = 10.0, 10.0 and 5.5 Hz), 3.76 (t, 1 H, J = 11.0 Hz), 3.88 (q, 1 H, J = 7.0 Hz), 4.21 (dd, 1 H, J = 11.0 and 9.0 Hz), 4.58 (dd, 1 H, J = 11.0 and 9.0 Hz); ^{13}C NMR δ 9.3, 25.1, 30.2, 41.3, 53.14, 62.0, 67.4, 72.4, 169.6.

4′,5′-Dihydroisoxazolo[4,3-*c*]azetidino[1,2-*a*]-2,5-*syn*-2-methyl-5-phenylpyrrolidines 13 and 14. Method A: Via Oxime 17c Obtained by Reaction of 7 with 16c. From **16c** following the procedure described for **17b** there was obtained crude **17c** which was dissolved in methylene chloride (15 mL) and treated with solid tetrabutylammonium fluoride (118 mg, 0.45 mmol). After being stirred at 20 °C for 0.5 h, the mixture was cooled to 0 °C and to it was added dropwise with vigorous stirring an aqueous sodium hypochlorite solution (0.5 mL, 0.6 mmol). The mixture was stirred for 1.5 h at 20 °C, and after the usual workup, the reisude was chromatographed (chloroform as eluant) to furnish 35 mg (38%) of a 1:2 mixture of the two diastereomers **13** and **14**. The spectra were identical with those of **13** and **14** isolated below.

Method B: Via Nitro Olefin 8b Obtained by Michael Addition of 7 to β-Nitrostyrene. To a solution of **7** (50 mg, 0.52 mmol) in chloroform (5 mL) at 20 °C was added β-nitrostyrene (76 mg, 0.51 mmol). NMR monitoring of the reaction mixture after 1 h indicated the quantitative formation of **8b**.[27] To this solution was added phenyl isocyanate (143 mg, 1.2 mmol) followed by triethylamine (20 mg, 0.2 mmol). The mixture was kept at 20 °C for 6 h. The solution was then diluted with methylene chloride (10 mL) and filtered, and the solvent was removed from the filtrate to give a light brown oil. The latter was chromatographed (ethyl acetate/petroleum ether (20:80 and 40:60)) to give a mixture of **13** and **14** (*ratio* 1:2, *yield* 46 mg, 41%) and **12** (52 mg, 49%): NMR **12** δ 1.63 (s, 3 H), 2.0–2.33 (m, 2 H), 3.86 (m, 1 H), 4.00 (m, 1 H), 5.29 (d, 1 H, J = 11.0 Hz), 5.39 (d, 1 H, J = 17.5 Hz), 5.92 (br s, 1 H), 6.18 (dd, 1 H, J = 17.5 and 10.0 Hz); ^{13}C NMR δ 23.0, 30.9, 43.0, 67.9, 114.5, 118.9, 122.6, 128.8, 138.7, 142.1 and 154.9; NMR **13** δ 1.34 (s, 3 H), 2.24 (ddd, 1 H, J = 12.5, 9.0 and 3.5 Hz), 2.36 (ddd, 12.5, 8.5 and 8.5 Hz), 3.56 (q, 1 H, J = 8.5 Hz), 3.89 (ddd, 1 H, J = 8.5, 8.5 and 3.5 Hz), 4.13 (dd, 1 H, J = 11.5 and 9.0 Hz), 4.47 (s, 1 H), 4.54 (dd, 1 H, J = 11.0 and 9.0 Hz), 4.76 (dt, 1 H, J = 11.5 and 1.0 Hz), 7.2–7.5 (m, 5 H); ^{13}C NMR δ 25.3 (t), 30.4 (q), 48.7 (dd), 60.6 (d), 65.6 (d), 68.9 (s), 71.1 (dd), 167.9 (s); mass spectra, CI (m/e) 229 (MH^+), 211, 199, 151, 118, 110, 96, 82 and 70; NMR **14** δ 1.42 (s, 3 H), 2.12 (ddd, 1 H, J = 13.0, 9.5 and 8.0 Hz), 2.39 (ddd, 1 H, J = 13.0, 10.5 and 5.5 Hz), 3.03 (ddd, 1 H, J = 10.5, 9.5 and 8.0 Hz), 3.65 (t, 1 H, J = 11.0 Hz),[39] 3.84 (ddd, 1 H, J = 9.5, 9.5 and 5.5 Hz), 4.24 (dd, 1 H, J = 10.0 and 9.0 Hz), 4.46 (br s, 1 H), 4.51 (dd, 1 H, J = 11.0 and 9.0 Hz), 7.2–7.5 (m, 5 H); ^{13}C NMR **14** δ 24.8 (q), 31.0 (dd), 53.6 (dd), 62.7 (d), 67.0 (d), 68.4 (s), 71.1 (dd), 172.6 (s).

2-Methyl-2-(2′-methyl-2′-vinyl-1′-azetidinyl)propanal Oxime (23). To a solution of **7** (40 mg, 0.4 mmol) and 2-bromo-2-methylpropanal *O*-(trimethylsilyl)oxime (95 mg, 0.4 mmol) in dry tetrahydrofuran (5 mL) at 0 °C was added tetrabutylammonium fluoride (118 mg, 0.45 mmol). The solution turned blue and the color faded within 5–10 min. After 20 min at 20 °C, the solvent was removed under reduced pressure and the resulting viscous material was taken up in methylene chloride (20 mL). The mixture was washed with water (3 × 20 mL) and a saturated salt solution (1 × 20 mL) and dried (sodium sulfate) and the solvent was removed to leave **23** as a clean product (yield 62 mg, 83%): ^{1}H NMR δ 1.08 (s, 3 H), 1.10 (s, 3 H), 1.32 (s, 3 H), 1.75–1.84 (m, 1 H), 1.9–2.03 (m, 1 H), 3.2–3.3 (m, 2 H), 4.95 (dd, 1 H, J = 11.0 and 1.0 Hz), 5.0 (dd, 1 H, J = 17.5 and 1.0 Hz), 6.13 (dd, 1 H, J = 17.5 and 11.0 Hz), 7.47 (s, 1 H); ^{13}C NMR δ 24.1, 24.3, 24.4, 30.7, 42.3, 56.5, 67.6, 112.0, 128.3, 155.8. Treatment of **23** with sodium hypochlorite as described for the formation of **19b–21b** led only to polymeric material.

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