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Type 2 Intramolecular *N*-Acylnitroso Diels–Alder Reaction: Stereoselective Synthesis of Bridged Bicyclic Oxazinolactams

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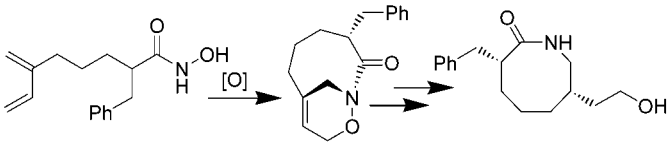
ABSTRACT



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The type 2 intramolecular *N*-acylnitroso Diels–Alder reaction has been employed for the synthesis of substituted bridged bicyclic oxazinolactams. Upon oxidation of hydroxamic acid 6, a 3-benzylated oxazinolactam (7) was synthesized with *complete* diastereoselectivity. Elaboration of cycloadduct 7 liberated a *cis*-3,7-disubstituted azocin-2-one (9).

Medium-ring nitrogen heterocycles occur in many natural and unnnatural products and possess a broad spectrum of medicinal and biological properties.[1] Azocin-2-ones (eight-membered lactams), in particular, have been used as sedatives and anti-convulsant and anti-hypertensive agents.[2] More recently, disubstituted azocin-2-ones have been prepared as peptide analogues to mimic the type VI β-turn conformation of natural polypeptides.[3] The preparation of eight-membered rings by conventional cyclization methods of acyclic precursors has presented considerable challenges to chemists due to unfavorable enthalpic and entropic factors.[4] Current synthetic methodology for the preparation of this class of compounds still remains substrate specific, and general solutions for the regio-functionalization and stereocontrolled synthesis have not been well established.[5] Increasing interest in eight-membered heterocycles has resulted in progress toward synthesizing functionalized azocin-2-ones.[6]

We have been developing hetero type 2 intramolecular Diels−Alder (IMDA) methodology for the synthesis of medium ring heterocycles.[7−9] Type 2 connectivity in the IMDA cycloaddition[10] provides an opportunity to control both regio- and stereochemistry. As part of this program, *N*-acylnitroso dienophiles have been employed for the preparation of bridged bicyclic molecules.[11] For example,

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(2) Thorsett, E. D. et al. *J. Med. Chem.* **1986**, *29*, 251−260.
(3) (a) Derrer, S.; Davies, J. E.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2943−2956. (b) Derrer, S.; Davies, J. E.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957−2967.
(4) (a) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117−3125. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.
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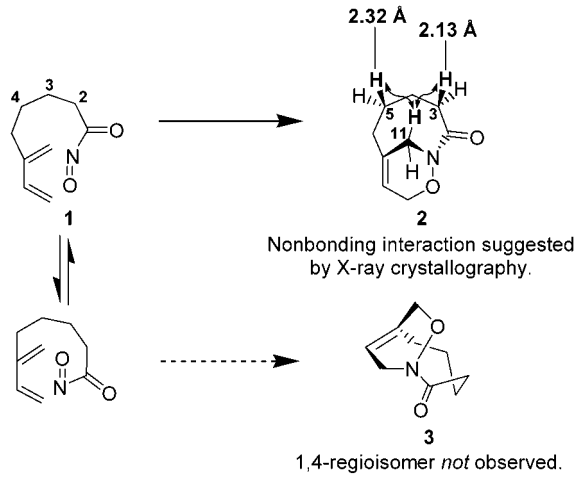
upon oxidation of *N*-hydroxy-6-methylene-7-octenamide, the corresponding *N*-acylnitroso intermediate **1** undergoes spontaneous intramolecular cycloaddition to form the bridged bicylic oxazinolactam (**2**) as a *single* regioisomer (Scheme 1). The cycloadduct contains both a bridgehead olefin and a

Scheme 1



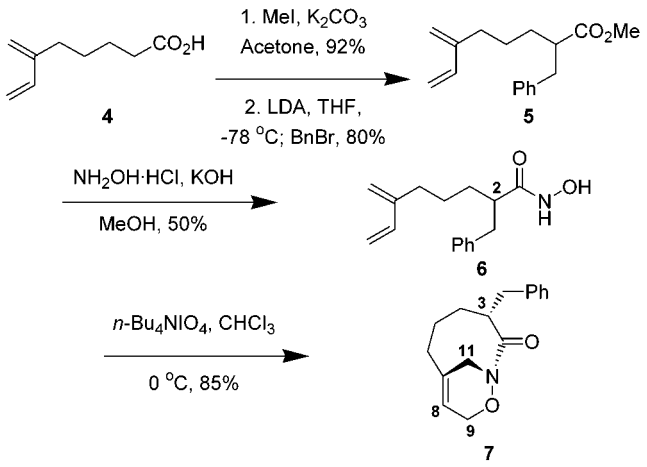
bridgehead oxazinolactam functional group. In contrast, the corresponding *intermolecular* Diels−Alder reaction gives an equal mixture of regioisomers.[11] The origin of the regioselectivity of the intramolecular cycloaddition can be explained in part by consideration that the estimated energy of the 1,3-regioisomer (*meta* cycloadduct, **2**) is 2.7 kcal mol^{-1} lower than the 1,4-regioisomer (*para* cycloadduct, **3**).[12] A portion of this difference in strain energy can be manifested in the competing transition states leading to cycloadduct formation.

In view of the importance of complex medium-ring heterocycles, we are developing methods for their stereo- and enantioselective synthesis. Specifically, we have examined the effect of tether substituents on the diastereoselectivity of the *N*-acylnitroso cycloaddition. The introduction of substituents has been found to influence the π-facial selectivity of the type 2 IMDA reaction.[13] We report the synthesis of a series of substituted hydroxamic acid precursors. The cycloaddition reaction of these precursors proceeded readily upon oxidation and resulted in moderate to complete diastereoselectivity. These processes provide a stereocontrolled entry into functionalized bridged bicyclic oxazinolactams.

A concerted cycloaddition involves continuous overlap between the π orbitals of the 2-substituted butadiene and those of the nitroso dienophile.[14] Since the strained cycloadduct has relatively low conformational flexibility, the structure of the bridgehead oxazinolactam (**2**) can be used to approximate the [4 + 2] cycloaddition transition state.[15] Analysis of the X-ray crystal structure of oxazinolactam **2** revealed a close contact between the *endo* proton at C11 and the *syn* hydrogen at C3 (Scheme 1). This intimate proton interaction suggested that substituents at position C2 in the Diels−Alder precursor could introduce a bias in the stereoselectivity of the ensuing cycloaddition step.[16]

The synthesis of an α-benzylated hydroxamic acid **6** was undertaken to examine the effect (Scheme 2). Esterification

Scheme 2



of 6-methylene-7-octenoic acid **4**[8] followed by alkylation (LDA, THF, −78 °C; BnBr) provided ester **5**. Conversion of **5** to hydroxamic acid **6** was accomplished by treatment with NH_2OH·HCl and KOH in MeOH. Addition of hydroxamic acid **6** to a $CHCl_3$ solution of *n*-Bu_4NIO_4 led to the isolation of cycloadduct **7** in 85% yield as a *single diastereomer* (100% ds).[17]

The 1,3-regiochemistry of cycloadduct **7** was determined by two-dimensional homonuclear COSY experiments. Individual off-diagonal signals allowed differentiation between the two sets of diastereotopic protons at C9 (4.85 and 4.40 ppm) and C11 (4.07 and 3.66 ppm). The assignments of the C9 protons were based on their unique cross-peaks that correlated with the C8 vinylic hydrogen at 5.51 ppm. The assignments of the C11 protons were strengthened in the following stereochemical determination of cycloadduct **7** using NOE analysis.

Irradiation of the C3 methine proton at 2.55 ppm resulted in enhancement of the *syn* proton at C11 at 4.07 ppm

(12) Calculations were performed with GAUSSIAN 98. The structures were optimized using the implemented B3LYP functional and 6-31G* basis set.

(13) Shea, K. J.; Gauthier, D. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 7311−7314.

(14) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192−5200.

(15) MMFF calculations suggested that the ground-state conformation of cycloadduct **2** is approximately 6.1 kcal mol^{-1} lower in strain energy than the nearest local minimum conformation.

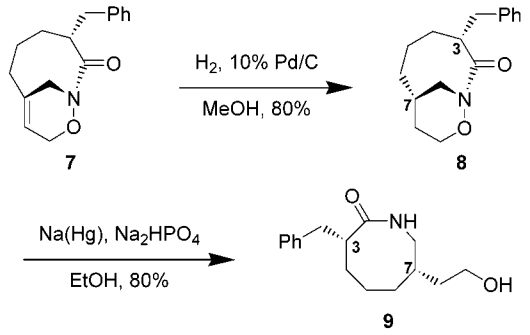
(16) The carbon atoms α, β, and δ to the hydroxamic acid functionality are referred to positions C2, C3, and C4, respectively. In accordance to the IUPAC system, the corresponding atoms in the cycloadduct have changed to positions C3, C4, and C5. See the numbering system shown in Scheme 1.

(17) The diastereoselectivity of all cycloadditions in this study was determined by comparing the spectroscopic ratio of the C8 vinylic protons in crude reaction mixtures by ^{1}H NMR.

(6.0%).[18] Enhancement of the methine proton at C3 (3.6%) was also observed in the converse experiment by irradiating the same C11 hydrogen. This establishes the benzyl substituent at C3 is in an *anti* relationship with respect to the methylene bridge (C11).

Elaboration of cycloadduct **7** was carried out to corroborate the stereochemical and regiochemical assignments by the conversion to an azocin-2-one (Scheme 3). Catalytic hydrogenation of cycloadduct **7** afforded saturated bicyclic oxazinolactam **8** in 80% yield.[19] Irradiation of the methine proton (2.63 ppm) at C3 α to the benzyl group resulted in the enhancement of the *syn* proton (4.14 ppm) of the methylene bridge, consistent with the stereochemistry observed in precursor **7**. Na(Hg) amalgam reduction of **8**, induced cleavage of the N−O bond and provided a *cis*-3,7-disubstituted azocin-2-one (**9**) as a *single diastereomer* in 80% yield.

Scheme 3

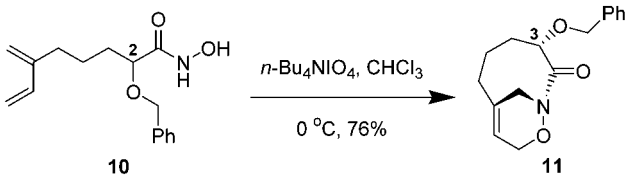


Assignment of the *cis* configuration in **9** from reduction of **8** is based on the assumed configurational integrity of the stereocenters at C3 and C7 during cleavage of the N−O bond. The structure of an azocin-2-one **9** was suggested by the presence of hydroxyethyl and benzyl fragments in ^{1}H NMR. In addition, when lactam **9** was subjected to CIMS, a molecular ion involving the loss of 45 amu was observed, consistent with the fragmentation of a $-CH_2CH_2OH$ group. These results establish that formation of **9** derived from elaboration of a bicyclo[5.3.1] adduct (1,3-regioisomer), oxazinolactam **7** (Scheme 3). The formation of oxazinolactam **7**, an *anti* diastereomer, is consistent with the transition-state model based on the structure of the cycloadduct.

Rationalization of stereoselectivity of the cycloaddition is based on steric interactions that develop in our working model for the transition state. Since heteroatom substituents are also used in this study, other factors such as dipole−dipole interactions could also contribute to the stereoselectivity of the reaction. To evaluate the importance of this factor, we have synthesized 2-benzyloxy hydroxamic acid derivative **10**.

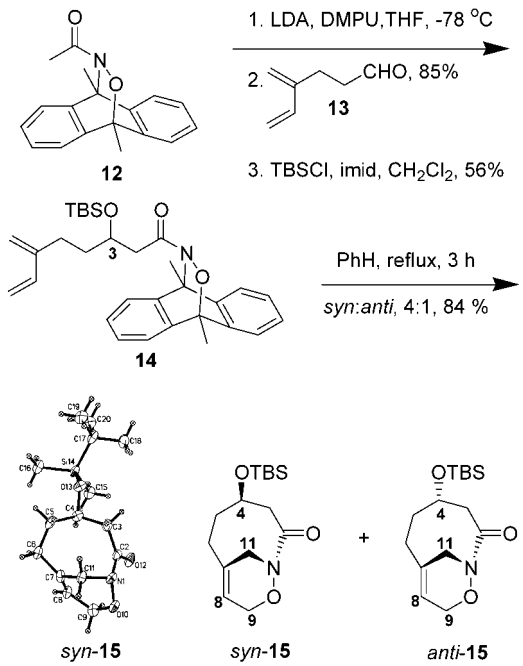
Oxidation and cycloaddition of **10** produced a single *anti* diastereomer **11**, 100% ds (Scheme 4). In the transition state for this cycloaddition, the *syn* product would be favored due to dipole−dipole repulsion. Since the *anti* product is found exclusively with carbon and oxygen substituents in both reactions, it appears that sterics dominate the origin of stereoselectivity in 2-substituted derivatives.

Scheme 4



The influence of substituents at tether position C3 is less clear in the competing cycloaddition transition states that lead to formation of *syn* and *anti* products. The requisite Diels−Alder precursor **14** was synthesized by aldol addition of the enolate of 9,10-dimethylanthracene adduct **12**[20] to 4-methylene-5-hexen-1-al **13**[21] (Scheme 5). The corresponding secondary alcohol was protected as a *tert*-butyldimethylsilyl ether (**14**). The Diels−Alder precursor was generated

Scheme 5



(18) NOE experiments were conducted using the DPFGSE method with mixing times (D8) of 0.5 s.

(19) Addition to bridgehead olefins occurs with complete *exo*-facial selectivity. See: (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683−1715. (b) Shea, K. J.; Beauchamp, P. S.; Lind, R. S. *J. Am. Chem. Soc.* **1980**, *102*, 4544−4546. (c) Shea, K. J.; Fruscella, W. M.; Carr, R. C.; Burke, L. D.; Cooper, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 447−452. (d) Whitney, J. M.; Parnes, J. S.; Shea, K. J. *J. Org. Chem.* **1997**, *62*, 8962−8963.

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in situ by heating adduct **14** in benzene to reflux. The subsequent intramolecular cycloaddition led to the formation of two diastereomers in a 4:1 ratio in 84% combined yield. Purification by silica gel column chromatography allowed the separation of *syn*-**15** and *anti*-**15**. Analysis of the X-ray crystal structure of the major product established the *syn* stereochemistry (*syn*-**15**) between the silyloxy group at C4 and the methylene bridge (C11).

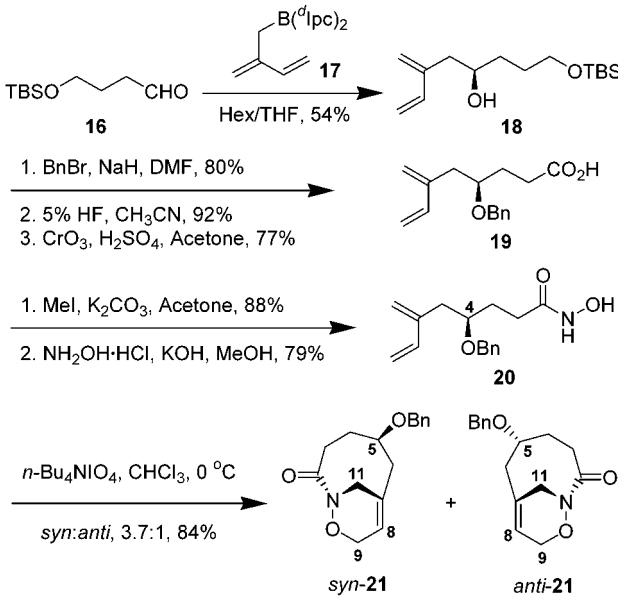
In the COSY spectrum of the minor product (*anti*-**15**), the presence of cross-peaks between the C8 vinylic proton (5.43 ppm) and the C9 hydrogens (4.28 and 4.76 ppm) establishes their proximity. The ^{1}H NMR of *anti*-**15** revealed an AB system for the two diastereotopic protons at C11 (3.67 and 3.97 ppm). The *anti* stereochemistry of the cycloadduct was assigned on the basis of a 3.9% signal enhancement of the C11 *syn* hydrogen at 3.97 ppm by irradiating the C4 methine proton at 4.72 ppm. The C3 substitution in the Diels−Alder precursor exerted only a moderate (4:1) influence at 80 °C on the diastereoselectivity of cycloaddition in favor of the *syn* product (*syn*-**15**).

Inspection of the X-ray crystal structure of oxazinolactam **2** also revealed a close contact between the *endo* proton at C11 and the *syn* hydrogen at C5 (Scheme 1). The contact is less than that between the C11 *endo* proton and the C3 *syn* hydrogen. Nevertheless, substitution at position C4 in the tether may also lead to a diastereoselective cycloaddition.

The 4-benzyloxyhydroxamic acid **20** was targeted for synthesis (Scheme 6). Enantioselective isoprenylation[22] of 4-(*tert*-butyldimethylsiloxy)butanal **16**[23] with diisopinocampheylborane **17** gave homoallylic alcohol (*R*)-(−)-**18** in 92% ee.[24] Alcohol protection, desilation, and Jones oxidation afforded carboxylic acid **19**. Esterification followed by treatment with basic hydroxylamine furnished hydroxamic acid **20**. Subsequent oxidation of Diels−Alder precursor **20** with *n*-Bu_4NIO_4 in $CHCl_3$ at 0 °C provided two diastereomers in a 3.7:1 ratio favoring *syn*-**21** in 84% combined yield. The two cycloadducts were separated by preparative thin-layer chromatography using $CHCl_3$/ethyl acetate (9:1, v/v).

The basis of the structural assignments of *syn*- and *anti*-**21** was analogous to those used to identify cycloadducts **7** (Scheme 2) and *anti*-**15** (Scheme 4). The stereochemistry of cycloadducts **21** was secured by NOE analysis. In *syn*-**21**, irradiation of the benzilic protons at 4.53 ppm resulted in the enhancement of the C11 *syn* proton at 3.67 ppm (4.1%). Saturating either the C5 methine proton (4.01 ppm) or the C11 *syn* proton did not give increase in the intensity of the

Scheme 6



reciprocal proton signals. These NMR results allowed the assignment of a *syn* relationship of the benzyloxy group at C5 with respect to the methylene bridge (C11). In the minor product (*anti*-**21**), enhancement of the C11 *syn* proton at 3.75 ppm was observed by irradiating the C5 methine proton at 3.88 ppm (3.2%), consistent with the *anti* stereochemistry assigned in the cycloadduct.

In contrast with the 2-substituted Diels−Alder precursor, substitution at position C4 of hydroxamic acid **20** induced a slight bias in the cycloaddition favoring the formation of *syn*-**21**. This observed diastereoselectivity is opposite to that predicted on the basis of the structure of the cycloadduct and calls attention to the limitation of this model.

In summary, we have developed approaches for the introduction of substituents at positions C3−5 in oxazinolactams by the type 2 intramolecular *N*-acylnitroso Diels−Alder reaction. Complete diastereoselectivity for the C2 substituted precursor was observed, leading to the formation of an *anti*-substituted oxazinolactam. The substituted bridged bicyclic oxazinolactams will form the basis of the synthesis of complex hetereocycles.

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(24) Determined as (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) derivative on capillary GC.