five chiral centers corresponding to the C_2–C_6 portion of erythronolide A (**2**).

Further applications of these lactaldehyde equivalents in natural products synthesis will be reported in due course.

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Supplementary Material Available: ORTEP plots of compounds **12b**, **12d**, and **17**; physical properties and methods of purification for esters **3**–**5** and aldols **7**–**12** and **17** (includes ^1H NMR and ^{13}C NMR spectra and combustion analysis results) (8 pages). Ordering information is given on any current masthead page.

Nitrone Cycloaddition. A New Approach to β-Lactams

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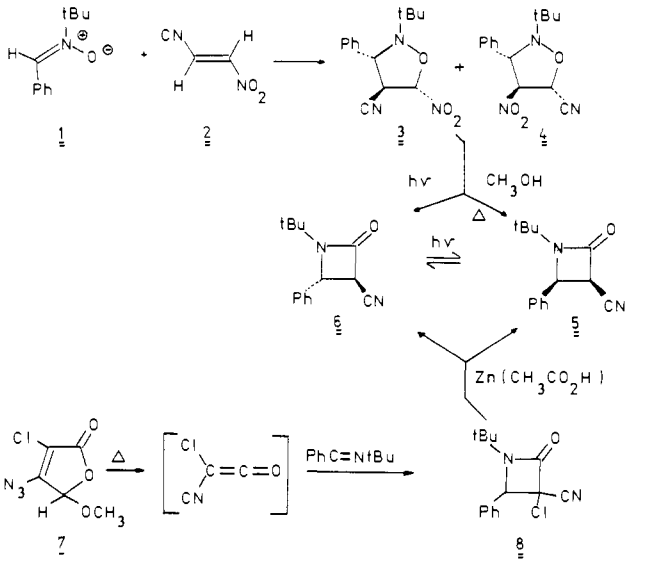
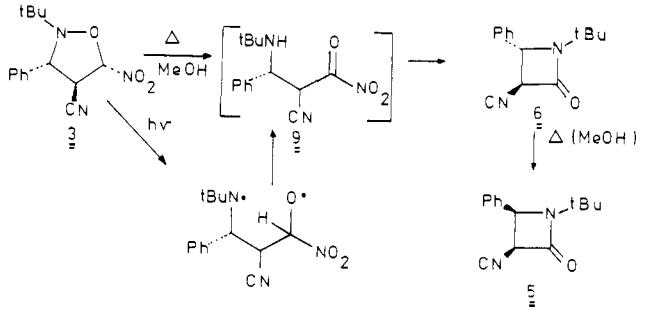
Because of their central role in the treatment of bacterial infection, the β-lactam antibiotics have received a great deal of attention since their discovery.[2] Considerable ingenuity has been demonstrated over the years in devising syntheses for the β-lactam system which forms the most salient feature of the penicillin and cephalosporin antibiotics.[3] This class of heterocycles has traditionally been prepared by the cyclization of β-aminopropanoic acid derivatives,[4] intramolecular Michael addition,[5] cycloaddition of heterocumulenes,[6] ring expansion of three-membered rings,[7] and ring contraction of five-membered rings.[8] New methods of constructing the four-membered lactam ring continue to be of interest in connection with the synthesis of analogues of the naturally occurring antibiotics.[9] In this report we describe a new procedure for the preparation of β-lactams. The key feature of the synthetic method involves 1,3-dipolar cycloaddition of a nitrone to a nitro-substituted olefin followed by a subsequent reorganization of the resulting 5-nitroisoxazolidine.

The reaction of phenyl-*N*-*tert*-butylnitrone (**1**) with *trans*-1-cyano-2-nitroethylene (**2**) gave rise to a mixture of two regioisomeric isoxazolidines **3** and **4** in quantitative yield (Scheme I). The major 5-nitro-substituted regioisomer **3** (60%), mp 76–77 °C, was separated by fractional crystallization from hexane [NMR ($CDCl_3$, 90 MHz) δ 1.00 (s, 9 H), 4.20 (dd, 1 H, J = 7.5 and 2.7 Hz), 4.25 (d, 1 H, J = 7.5 Hz), 5.65 (d, 1 H, J = 2.7 Hz), and 7.30 (s, 5 H); C^{13} NMR (20 MHz, $CDCl_3$) 26.0 (CH_3), 50.2 (C_4), 59.9 (*t*-Bu), 69.2 (C_3), 102.5 (C_5), 116.1 (CN)]. The minor 5-cyano regioisomer **4** (40%), mp 56–57 °C [NMR ($CDCl_3$, 90 MHz) δ 1.00 (s, 9 H), 4.60 (d, 1 H, J = 6.0 Hz), 5.19 (dd, 1 H, J = 6.0 and 1.5 Hz), 5.48 (d, 1 H, J = 1.5 Hz), and 7.20 (m, 5 H); C^{13} NMR (20 MHz, $CDCl_3$) 26.1 (CH_3), 59.6 (*t*-Bu), 66.7 (C_2), 68.3 (C_3), 98.8 (C_1), and 115.8 (CN)] was isolated by medium-pressure silica gel chromatography. Heating a sample of isoxazolidine **3** in methanol gave *cis*-β-lactam **5** in quantitative yield, mp 91–92 °C [NMR ($CDCl_3$, 90 MHz) δ 1.15 (s, 9 H), 4.10 (d, 1 H, J = 6.0 Hz), 4.75 (d, 1 H, J = 6.0 Hz), and 7.32 (s, 5 H)].[10] A similar reorganization occurred when isoxazolidine **3** was subjected to ultraviolet irradiation using 2537-Å light. In this case, however, the only product isolated was *trans*-β-lactam **6**, mp 180–181 °C [NMR ($CDCl_3$, 90 MHz) δ 1.25 (s, 9 H), 3.65 (d, 1 H, J = 3.0 Hz), 5.80 (d, 1 H, J = 3.0 Hz), and 7.40 (s, 5 H)]. Extended photolysis of either *cis*-**5** or *trans*-β-lactam **6** resulted in photoisomerization leading to a photostationary state ratio of 1:1. *trans*-β-Lactam **6** was smoothly converted to the thermodynamically more stable cis isomer **5** on heating in methanol with a trace of base. The structure of the β-lactams (i.e., **5** and **6**) were unambiguously established by comparison with independently synthesized samples. This was accomplished by heating 4-azido-3-chloro-5-methoxy-2(5*H*)-furanone (**7**) in the presence of *N*-benzylidene-*tert*-butylamine followed by reduction of the resulting chlorocyano-2-azetidinone **8** with zinc in acetic acid. Moore and co-workers have previously demonstrated that furanone **7** undergoes cleavage to chlorocyano ketene[11] which, in turn, is known to undergo [2 + 2] cycloaddition with C–N double bonds.[12,13]

Scheme I



Scheme II



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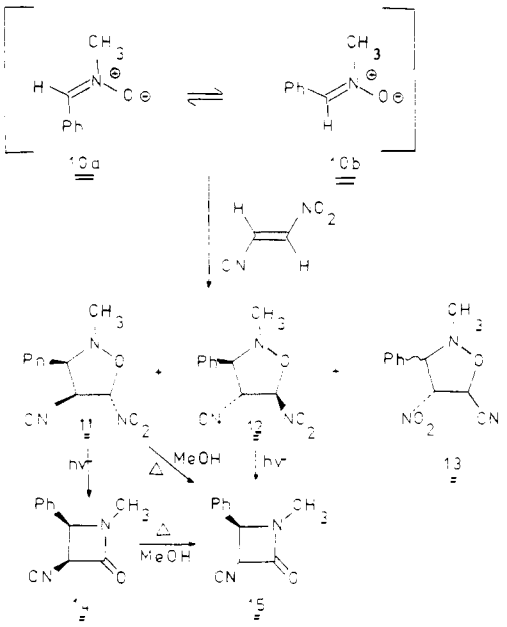
Scheme III



The ready conversion of the 5-nitroisoxazolidine regioisomer (i.e., **3**) to the β-lactam ring is most easily rationalized by the mechanism outlined in Scheme II. The nitrogen–oxygen bond of **3** is expected to be cleaved readily, since such heteroatom–heteroatom bonds are known to be relatively weak.[14,15] Thus, removal of the acidic proton adjacent to the nitro group followed by N–O bond cleavage and subsequent cyclization of the transient acyl nitro intermediate **9** nicely accommodates the formation of the β-lactam system.[16] The formation of *cis*-lactam **5** from the thermolysis of **3** in methanol reflects thermodynamic rather than kinetic factors. We have demonstrated this by heating a pure sample of **6** in methanol and recovering only the cis isomer. In this case, steric crowding about the β-lactam ring is minimized by having both the cyano and phenyl groups trans to the very large *tert*-butyl group. This would account for the greater thermodynamic stability of the *cis* isomer.[17] Photolysis of isoxazolidine **3** results in N–O bond scission which is followed by internal hydrogen transfer and subsequent cyclization of intermediate **9**.[18] It should be noted that the exclusive formation of lactam **6** from the irradiation of **3** fixes the stereochemistry of the phenyl and cyano groups as being trans in the cycloadduct.

In an effort to further establish the generality and scope of the nitrone-based synthesis of β-lactams, the cycloaddition of *C*-phenyl-*N*-methylnitrone (**10**) with *trans*-1-cyano-2-nitroethylene was investigated. In this case, a mixture of three isomeric cycloadducts was produced with properties similar to those observed for the *N*-*tert*-butylisoxazolidines. Two of these (i.e., **11** and **12**) derive from one regiochemical mode of cycloaddition of **10** to the π bond, while the other (i.e., **13**) derives from the alternate mode of addition (vide infra, Scheme III). To account for the formation of the two diastereomeric cycloadducts **11** and **12**, we assume that the trans isomer (**10a**) of phenyl-*N*-methylnitrone is in equilibrium with a small amount of the cis form (**10b**) and that the two transition states leading to **11** and **12** are of comparable energy. This is not the case with the corresponding *tert*-butylnitrone **1**, presumably as a consequence of steric factors.

The major 5-nitro substituted regioisomer **11** (mp 125–126 °C, 60%) was converted to *cis*-β-lactam **14** on photolysis with 2537-Å light [NMR ($CDCl_3$, 90 MHz) δ 2.85 (s, 3 H), 4.45 (d, 1 H, J = 6.0 Hz), 4.90 (d, 1 H, J = 6.0 Hz), 7.3–7.6 (m, 5 H)]. In marked contrast, heating a sample of **11** in methanol produced the isomeric *trans*-lactam **15**, mp 87–88 °C [NMR ($CDCl_3$, 90 MHz) 2.80 (s, 3 H), 3.80 (d, 1 H, J = 3.0 Hz), 4.75 (d, 1 H, J = 3.0 Hz), and 7.3–7.6 (m, 5 H)]. The structural assignment for β-lactams **14** and **15** was confirmed by comparison with independently synthesized samples.[19] *cis*-Lactam **14** was converted into the thermodynamically more stable trans isomer **15** on refluxing in methanol. The irradiation of the minor regioisomer **12** was also studied and was found to produce *trans*-β-lactam **15** as the exclusive ring contracted product. It should be noted that the distribution of β-lactams in the methyl series differs significantly from the encountered with the *tert*-butyl system. It is our belief that the difference in thermodynamic stability of the two lactam systems is chiefly controlled by the size of the substituent group on nitrogen.

In conclusion, we have shown that the 1,3-dipolar cycloaddition of nitrones with a nitroethylene derivative results in the production of regioisomeric adducts, one of which undergoes ready ring contraction to the β-lactam ring. We are continuing to explore the scope and mechanistic features of the reaction and will report additional findings at a later date.

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Regiocontrolled Hydration of 2-Butyne-1,4-diol Derivatives To Give 4,5-Dihydro-3(2*H*)-furanones. Practical Synthesis of Bullatenone and Geiparvarin

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Although the transformation of symmetrically substituted 2-butyne-1,4-diol derivatives into dihydro-3(2*H*)-furanones is well established and most promising in a practical sense,[1] this process has not been used for the synthesis of furanone derivatives,[2] in general, due mainly to the lack of regiocontrol in the hydration of the carbon–carbon triple bond.[3] Herewith we report a solution

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