The Isoxazoline Route to the Molecules of Nature

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Over the past few years we have been concerned with further developing nitrile oxide cycloaddition chemistry as a tool for natural product total synthesis. While studies regarding the preparation of these reactive dipoles and extensive investigations of their scope and mode of reactivity have been made over the years,[1] the actual utilization of these compounds in synthesis appears to be a more recent phenomenon.[2]

The ability of nitrile oxides to react with olefins was first recorded by Weygand in 1927.[3] Beginning in 1946 Quilico and his associates carried out extensive studies of fulminic acid and its derivatives,[4] and in 1961 Huisgen categorized the nitrile oxides as being members of a broader class of 1,3 dipoles that were capable of undergoing [3 + 2] cycloaddition reactions.[5] On the chemical time scale then, the [3 + 2] dipolar cycloaddition reaction as a reaction type represents a younger breed of concerted $\pi_4S + \pi_2S$ process than does the Diels–Alder reaction. It is thus no wonder that [3 + 2] cycloaddition reactions find little mention in most undergraduate organic textbooks[6] and that the number of syntheses completed using such methodology are at present fairly meager. Much has been done to exploit the characteristics and idiosyncrasies of the Diels–Alder reaction, but, in contrast, much yet remains to be discovered regarding dipolar cycloaddition reactions.

In this brief synopsis of recent advances in nitrile oxide chemistry, we will attempt to show the amazing versatility of isoxazolines generated from nitrile oxides and olefins for the construction of a variety of natural product systems. We note here that the fully aromatic counterparts of the isoxazolines, the isoxazoles,[7] have also proven to be important vehicles in synthesis, for reductive cleavage of the heterocyclic ring reveals an enamino ketone or a 1,3-dicarbonyl system. Further reduction can give rise to an amino ketone that loses ammonia to afford an enone.[8]

The isoxazoline ring represents a fairly responsive heterocyclic system, too, for its interaction with the appropriate sort of reagent can yield access to (a) γ-amino alcohols, (b) β-hydroxy ketones (and thus α,β-unsaturated ketones, allylic alcohols, 1,3-diols, and 1,3-dienes), (c) β-hydroxy nitriles, acids, and esters, and (d) α,β- and β,γ-unsaturated oximes.

We shall illustrate the first three types of transformations using examples generated in our own laboratories. The last transformation type d is due to Jäger, and the reader is directed to the appropriate references.

γ-Amino Alcohols.

The production of γ-amino alcohols requires that both the C=N bond and the N–O bond of the isoxazoline be reduced. Depending on the nature of the reducing agent, it is possible to effect this conversion through either the intermediacy of an isoxazolidine (e.g.,

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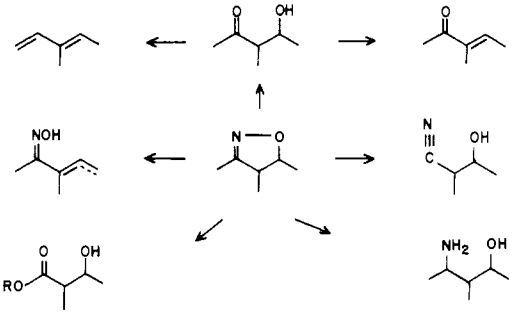
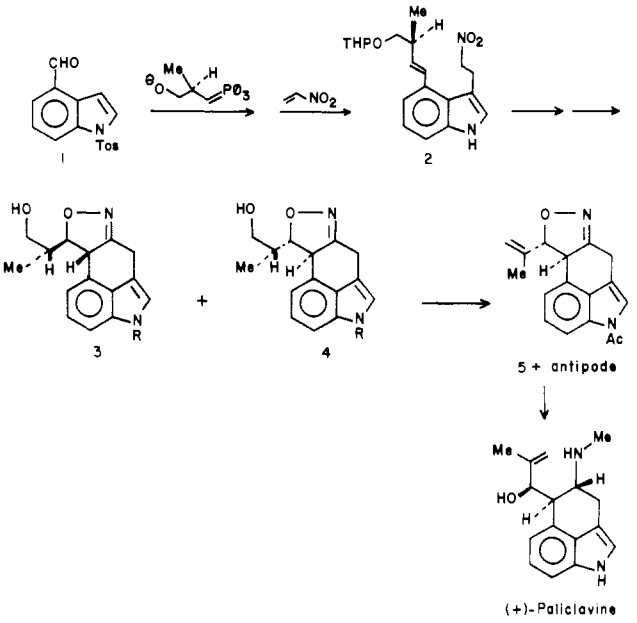
Scheme I



Scheme II



(1) Ch. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag, New York (1971).
(2) A. P. Kozikowski in "Comprehensive Heterocyclic Chemistry", A. R. Katritzky, Ed., Pergamon Press, Oxford (1984).
(3) C. Weygand and E. Bauer, *Justus Liebigs Ann. Chem.*, **459**, 123 (1927).
(4) A. Quilico and G. Speroni, *Gazz. Chem. Ital.*, **76**, 148 (1946).
(5) R. Huisgen, *Proc. Chem. Soc.*, 357 (1961). For a thorough discussion of regioselectivity in nitrile oxide cycloaddition reactions, see: K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
(6) In the fourth edition of "Organic Chemistry" by R. T. Morrison and R. N. Boyd, the only topics associated with the term cycloadditions are the addition reactions of carbenes, the Diels–Alder reaction, and [2 + 2] cycloadditions.
(7) N. K. Kochetokov and S. D. Sokolov, *Adv. Heterocycl. Chem.*, **2**, 365 (1963); B. J. Wakefield and D. J. Wright, *ibid.*, **25**, 147 (1979). More recently the isoxazole ring has also been used to gain access to β-hydroxy ketones. See, for example: P. G. Baraldi, A. Barco, S. Benetti, F. Moroder, G. P. Pollini, and D. Simoni, *J. Org. Chem.*, **48**, 1297 (1983) and references therein.
(8) G. Stork, M. Ohashi, H. Kamachi, and H. Kakisawa, *J. Org. Chem.*, **36**, 2784 (1971).
(9) V. Jäger and H. Grund, *Angew. Chem., Int. Ed. Engl.*, **15**, 50 (1976). V. Jäger and W. Schwab, *Tetrahedron Lett.*, 3129 (1978); V. Jäger, V. Buss, and W. Schwab, *ibid.*, 3133 (1978).

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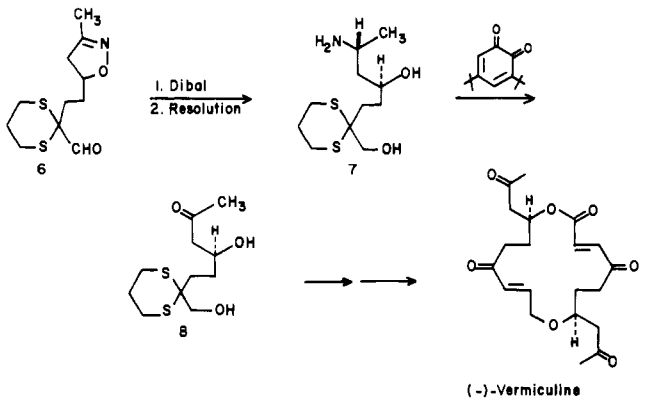
Scheme III



with $Me_3O^+BF_4^-/NaBH_4$ or LAH) or a β-hydroxy imine (e.g., with sodium/alcohol).[10,11] Since the complete saturation of an isoxazoline results in retention of a nitrogen atom, this conversion would seem to be of primary importance in the synthesis of alkaloid systems.

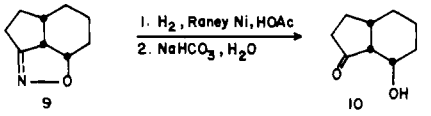
To date, we have been able to use transformation (a) to synthesize the ergot alkaloids chanoclavine[11] and paliclavine[12] and to prepare an intermediate for use in a projected lysergic acid synthesis. The key step in these synthetic undertakings involved the intramolecular nitrile oxide cycloaddition (INOC) reaction of a 3,4-disubstituted indole bearing a nitroethyl group at C-3 and an unsaturated appendage at C-4. In the paliclavine synthesis, the starting 3,4-disubstituted indole **2** contained all of the elements required for conversion to the final product. Additionally, this indole was built in optically active form, for we had hoped that because of the antiperiplanar effect,[12] the nitrile oxide would add opposite the larger "allylic" group and thus display diastereoselection in the cycloaddition process. Unfortunately, a 1.1:1 mixture of diastereomers **3** and **4** was generated. These could, however, be separated at the stage of their mesylates, and thus upon dehydration of the primary alcohol the pure antipodes were in hand (Scheme II).

The optically active phosphonium salt employed at the start of the synthesis had served as a convenient (but nonrecoverable) resolving agent. After *N*-methylation and reduction of the isoxazolinium salt, the isoxazolidine was cleaved with aluminum amalgam (hydrogenation could not be used this time due to the presence of the C=C bond) to deliver paliclavine. While this synthesis is blighted by the poor diastereoselection found in the [3 + 2] cycloaddition process, it did serve to further catalyze our interest in this phenomenon, and it has led us to investigate this issue in much greater detail.

In connection with these syntheses, we note that Jäger and co-workers have undertaken a detailed study of the stereochemistry of reduction of 3,4-, 3,5-, and 3,4,5-substituted isoxazolines. Lithium aluminum hydride generally serves as the best reducing agent in terms of overall yield and diastereoselectivity (~3:1).[10]

A final example of the isoxazoline → γ-amino alcohol conversion is found in Burri's synthesis of the dilactone antibiotic vermiculine. The product amino alcohol **7** resulting from the stereospecific DIBAL reduction of **6** was oxidized to the β-hydroxy ketone **8** by using 3,5-di-*tert*-butyl-*o*-benzoquinone (Scheme III).[13] This transformation represents an indirect method for converting an isoxazoline to a β-hydroxy ketone, the topic of the next section.

Scheme IV

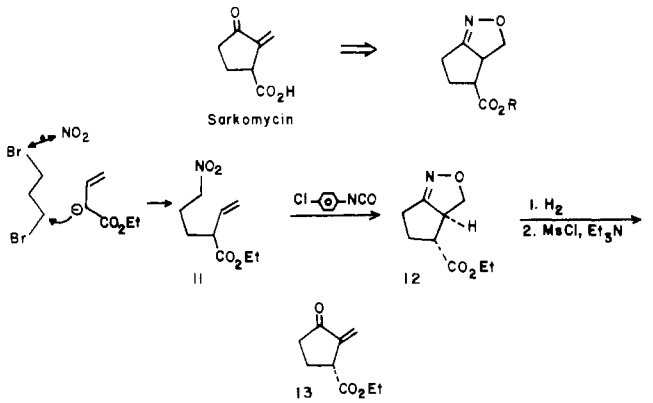


β-Hydroxy Ketones, α,β-Unsaturated Ketones, and 1,3-Dienes

N–O Bond Cleavage Methods. In this ring scission process, the N–O bond of the isoxazoline is cleaved to reveal initially a β-hydroxy imine that is then hydrolyzed to β-hydroxy ketone. While a number of reductive methods have been devised to bring about this transformation, the choice of the precise reaction conditions does depend on the type of functionality present within the substrate and on the necessity of preserving asymmetry at C-4 (isoxazoline ring numbering). Raney nickel/acetic acid has been reported by Wollenberg to effect the following N–O cleavage reaction (**9** → **10**) (Scheme IV).[14] When these conditions were applied to the isoxazoline prepared from acetonitrile oxide and cyclopentene, a chromatographically separable mixture of the cis and trans isomers of 2-acetylcyclopentanol resulted. Since the pure cis isomer was found not to undergo epimerization in the presence of acetic acid, it was reasoned that epimerization must occur at the β-hydroxy imine stage via the tautomeric enamine. By employing a stronger mineral acid (weaker conjugate base) in the hydrogenation brew, it would seem that rapid protonation of the imine with addition of water would lead to a carbinolamine that could break down to β-hydroxy ketone without epimerization. Indeed, hydrogenation of this isoxazoline with W-2 Raney nickel and 4 equiv of concentrated HCl in 5:1 methanol–water gave exclusively the cis product. Since aluminum(III) is known to catalyze imine hydrolysis and since aluminum chloride undergoes hydrolysis to release HCl, we have studied in greater detail a catalyst system comprised of Raney nickel and aluminum chloride in methanol and water. In most cases studied to date, the conversion of isoxazoline to β-hydroxy ketone occurred cleanly and with complete stereospecificity.[15a] In a few instances, the use of boron trichloride in place of the aluminum chloride has proven advantageous.[17,30,31]

(10) V. Jäger and V. Buss, *Liebigs Ann. Chem.*, 101 (1980); V. Jäger, V. Buss, and W. Schwab, *ibid.*, 122 (1980).
(11) A. P. Kozikowski and H. Ishida, *J. Am. Chem. Soc.*, **102**, 4265 (1980).
(12) A. P. Kozikowski and Y. Y. Chen, *J. Org. Chem.*, **46**, 5248 (1981).
(13) K. F. Burri, R. A. Cardone, W. Y. Chen, and P. Rosen, *J. Am. Chem. Soc.*, **100**, 7069 (1978). For an elegant application of the type a transformation to biotin, see: P. N. Confalone, E. D. Lollar, G. Pizzolato, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **100**, 6291 (1978).
(14) R. H. Wollengerg and J. E. Goldstein, *Synthesis*, 757 (1980).
(15) (a) A. P. Kozikowski and M. Adamczyk, *Tetrahedron Lett.*, **23**, 3123 (1982). (b) P. S. Bailey, "Ozonation in Organic Chemistry", Vol. II, Academic Press, New York (1982). (c) The cleavage of isoxazolines to β-hydroxy ketones by Ti^{3+} has also been reported: S. H. Andersen, N. B. Das, R. D. Jorgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma, and K. B. G. Torssell, *Acta Chem. Scand., Ser. B*, **B36**, 1 (1982); S. K. Mukerji, K. K. Sharma, and K. B. G. Torssell, *Tetrahedron*, **39**, 2231 (1983); S. H. Andersen, K. K. Sharma and K. B. G. Torssell, *ibid.*, **39**, 2241 (1983). (d) For an important study on the use of boric acid in isoxazoline hydrogenations, see D. P. Curran, *J. Am. Chem. Soc.*, **105**, 5826 (1983). (e) BF_3·OEt_2 as an additive: S. F. Martin and B. Dupre, *Tetrahedron Lett.*, **24**, 1337 (1983).

Scheme V



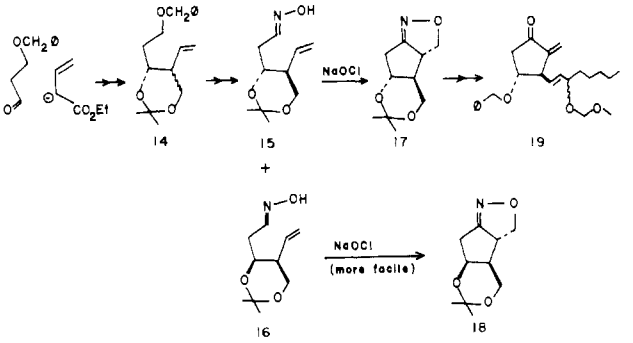
Our second method for unmasking isoxazolines recognizes the structural relationship of these heterocycles to oximes. Oximes can generally be converted in moderate to good yield to their corresponding carbonyl compounds by ozonolysis.[15b] On exposing a variety of isoxazolines to a stream of ozone followed by a dimethyl sulfide quench, the pure β-hydroxy ketones were isolated. No epimerization was found to occur under these reaction conditions.[15a]

Five-Membered Ring Synthesis. Armed with these methods, we have now begun a program to illustrate the far reaching consequences of the nitrile oxide cycloaddition/N–O bond cleavage approach to natural product synthesis. We have begun in a relatively simple way by demonstrating the applicability of such chemistry to the construction of cyclopentanoids, such as the methylenecyclopentanone sarkomycin.[16a] As shown through the retrosynthetic analysis below, the α,β-unsaturated ketone portion of this molecule represents nothing more than the demasked form of an isoxazoline (Scheme V).

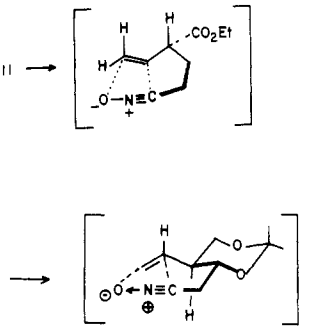
Generation of the nitrile oxide containing a tethered olefin from the corresponding nitro compound **11** by Mukaiyama's method[16b] led via the INOC process to the isoxazoline **12**. Cleavage of its N–O bond and dehydration then gave sarkomycin ethyl ester.

Sarkomycin does in a sense represent the prototype of a prostaglandin. To further demonstrate the importance of our method of five-membered ring synthesis, we have also examined the cycloaddition reactions of **15** and **16**, intermediates similar to that used in the sarkomycin synthesis but carrying an additional oxygen substituent.[17] Conversion of each of the chromatographically separable alcohols available from debenzylation of **14** separately to its aldehyde and thence to its oxime afforded the desired nitrile oxide precursors. The stereochemically correct oxime **15** was treated with NaOCl to effect nitrile oxide formation with cyclization to the isoxazoline **17**. The wrong isomer **16** also cyclized in good yield (and at a faster rate) to afford **18**. To further transform **17** to a prostaglandin, one only need recognize the structural relationship of our material to that of intermediate **19** generated by Stork in one of his many elegant syntheses of the prostaglandins.[18] After installation of the lower side chain the isoxazoline was cleaved (Raney Ni/BCl_3/MeOH/H_2O) to β-hydroxy ketone and the alcohol dehydrated to provide the Stork-like intermediate. The ability to effect N–O bond cleavage in this instance without reduction of the carbon–carbon double bond and with minimal hydrogenolysis of the oxygen protecting groups is noteworthy (Scheme VI).

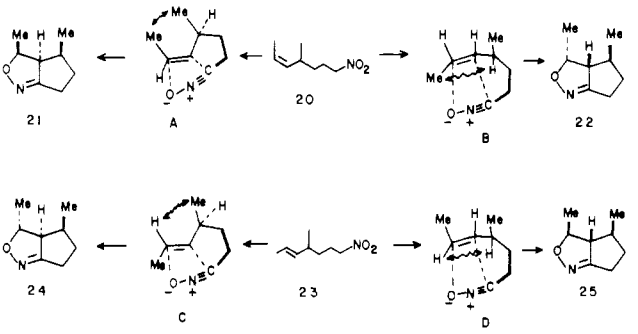
Scheme VI



Scheme VII



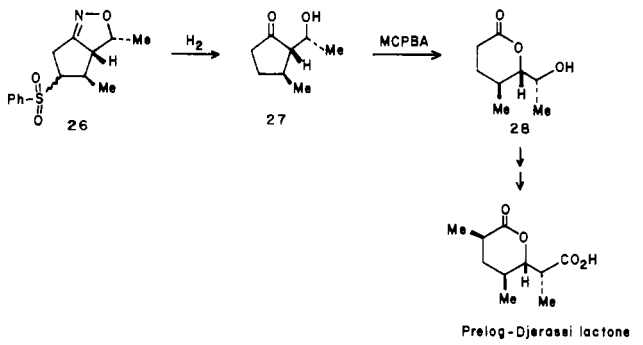
Scheme VIII



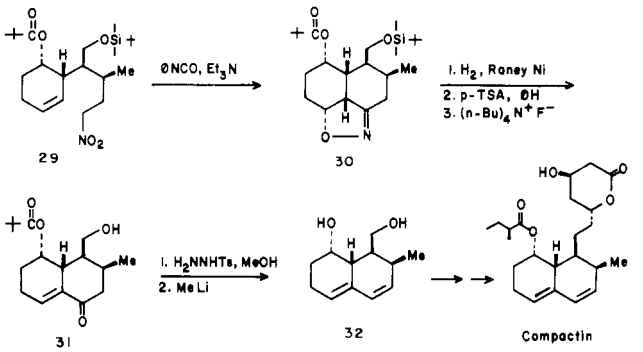
Stereocontrol in the INOC Process. In the sarkomycin synthesis, we observed the production of only a single isoxazoline from the INOC process. The stereochemical outcome of this reaction is presumed to be a consequence of reaction through that transition state which minimizes $A^{1,3}$ strain. In the prostaglandin work, on the other hand, the production of a single isoxazoline product appears to be a consequence of the geometric constraints imposed on the transition state by the presence of the dioxane ring (Scheme VII). An even more dramatic example of the ability of $A^{1,3}$ strain to control diastereoface selectivity during a [3 + 2] cycloaddition reaction was seen with the (*Z*)-nitroalkene **20**. This material was found to give only a single isoxazoline when exposed to phenyl isocyanate and triethylamine. As can be seen from the transition-state drawings, transition-state A is sterically more congested due to the serious methyl–methyl interaction. Transition-state B is consequently of lower energy, and cycloaddition occurs to deliver only the isoxazoline **22**.

(16) (a) A. P. Kozikowski and P. D. Stein, *J. Am. Chem. Soc.*, **104**, 4023 (1982). (b) T. Hoshino and M. Mukaiyama, *ibid.*, **82**, 5339 (1960).
(17) A. P. Kozikowski and P. D. Stein, *J. Org. Chem.*, **49**, 2301 (1984).
(18) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745, 6260 (1975).

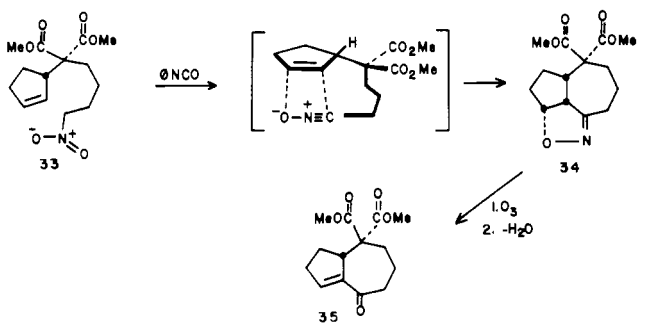
Scheme IX



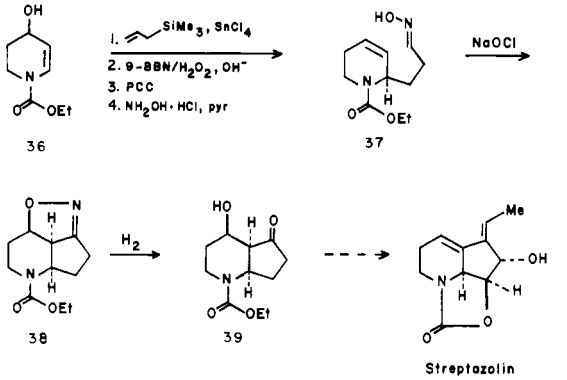
Scheme X



Scheme XI



Scheme XII



In contrast, when the (*E*)-nitroalkene **23** was subjected to the cyclization conditions, a 3:1 mixture of isomers favoring **25** was produced, a result of the smaller steric difference between the transition states C and D (Scheme VIII).[19]

Thus, it is indeed possible to control the relative stereochemical disposition of three contiguous centers via the INOC process. We suggest that this stereocontrolled synthesis of isoxazoline structures should find use in both macrolide and ansamycin synthesis, for cleavage of the N–O bond of **26** (Raney Ni, $AlCl_3$), proceeds with concomitant desulfonylation to yield a single cyclopentanone derivative. Subjection of **27** to Baeyer–Villiger conditions then provides the δ-lactone **28**.[20] As can readily be discerned, this δ-lactone resembles closely the Prelog–Djerassi lactone, an important degradation product of several naturally occurring macrolides (Scheme IX).

We also suggest that the location of an asymmetric center at other positions of the emerging carbocyclic ring may permit the control of face selectivity in these cycloaddition reactions as well. Molecular mechanics calculations are presently being carried out in collaboration with Professor Houk's group that are intended to define a precise transition-state picture for these INOC reactions. While the transition-state pictures are still crude, the predictions based on such models do in most cases completely mirror our experimental results. Once the MMII calculations have been perfected, it should be possible to know a priori whether a particular INOC reaction will proceed with a desirable degree of steroselectivity.

Fused Carbocycles. The INOC route to carbocyclics is also being tested in the area of decalin synthesis. An approach to the hexahydronaphthalene portion of the hypocholesterolemic agent compactin has been completed. We have constructed the nitro compound **29** and shown that it will undergo the INOC process to give stereospecifically **30** (Scheme X).

Hydrogenation of the N–O bond and acid-catalyzed dehydration of the β-hydroxy ketone yielded enone **31**. Tosylhydrazone formation followed by methyllithium treatment gave the diene **32**. Thus, through this synthesis we have demonstrated the ability of the isoxazoline ring to function as a masked form of a 1,3-diene.[21]

While it would appear that the construction of both five- and six-membered rings is a matter of fairly routine predictability, one might perhaps approach the construction of seven and larger membered carbocyclic rings via the INOC process with greater apprehension. We have at present found, however, that it is possible to gain access to the hydroazulene ring system through such chemistry. The cycloaddition reaction of **33** gives a single crystalline isoxazoline **34** in >80% yield. Minimization of nonbonded interactions in the transition state controls product stereochemistry (cis-ring fusion). An intermediate such as **34** might well provide a very simple entry to the guaianolides and pseudoguaianolides for ozonolytic unraveling of the isoxazoline ring provides a β-hydroxy ketone that readily dehydrates to the enone **35** (Scheme XI).[22]

Fused-Ring Heterocycles. An efficient means for crafting the skeleton of the unique antimetabolite streptazolin illustrates the INOC route to fused-ring heterocycles. The required nitrile oxide precursor **37** is prepared in straight order from the hydroxytetrahydropyridine **36** by reaction with allyltrimethylsilane

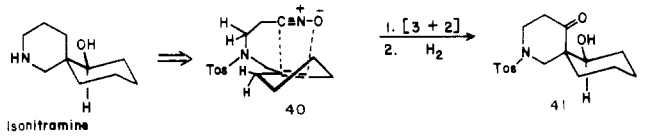
(19) A. P. Kozikowski and Y. Y. Chen, *Tetrahedron Lett.*, **23**, 2081 (1982).

(20) S. Goldstein, unpublished results from the University of Pittsburgh.

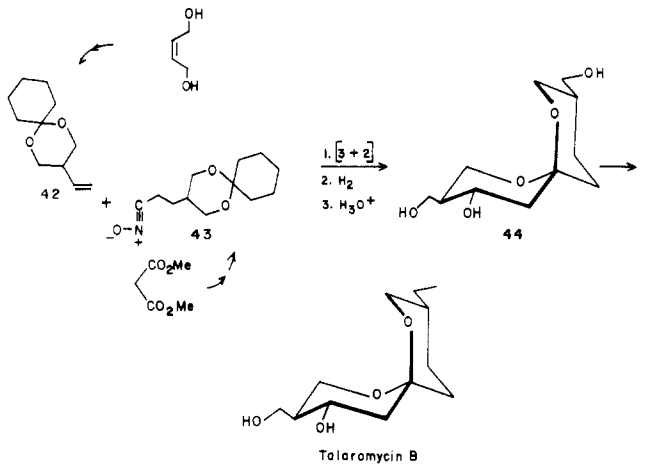
(21) C. S. Li, unpublished results.

(22) A. P. Kozikowski and B. Mugrage, *Tetrahedron Lett.*, **24**, 3705 (1983). For the preparation of 9-, 13-, 15-, and 16-membered lactones by the INOC reaction, see: M. Asaoka, M. Abe, T. Mukuta, and H. Takei, *Chem. Lett.*, 215 (1982).

Scheme XIII



Scheme XIV



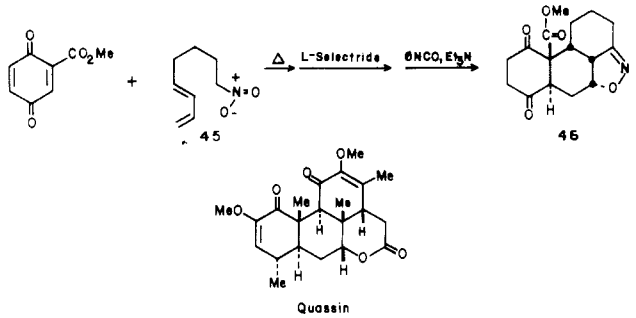
in the presence of stannic chloride. Exposure of the desired oxime to sodium hypochlorite yields stereospecifically the isoxazoline **38** (90%). Hydrogenolysis then provides the azahydrindanone **39**, an appropriately functionalized precursor to streptazolin (Scheme XII).[23]

Spirocycles. Spirocycles represent yet another skeletal type that can be accommodated by nitrile oxide cycloaddition chemistry. The newly isolated alkaloid isonitramine, a compound related structurally to the histrionicotoxins, suggests an INOC-based dissection in which the nitrile oxide is tethered to an olefinic unit through a heteroatom (Scheme XIII). The nitro group derived nitrile oxide **40** does indeed furnish the desired spirocycle **41** after hydrogenation, albeit in a yield of (at present) a modest 30% for the cycloaddition step. In this particular instance, the trisubstituted nature of the double bond undergoing addition, its unfavorable regio-directing character, and significant nonbonded interactions in the transition state may be responsible for the incursion of nonproductive side reactions.[24]

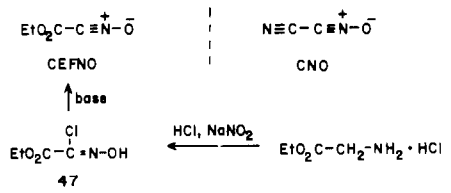
Within this general area of spirocycle synthesis, it would also appear that the isoxazoline → β-hydroxy ketone conversion should provide a valuable entry to naturally occurring spiroketal systems. The simple structure embodied by the toxin talaromycin B serves to illustrate this point. Reaction of the symmetrical nitrile oxide **43** with the symmetrical alkene partner **42** generates the expected isoxazoline. Hydrogenolysis of this intermediate and subsequent acid treatment of the β-hydroxy ketone provide the spiroketal **44**. Such an intermediate need only have one of its hydroxymethyl groups transformed to ethyl in order to complete the synthetic scheme.[25] Certainly, the assembly of more complex spiroketals, such as those present in the milbemycins, should also be feasible through a related strategy. In these cases, the preparation of both the

(23) A. P. Kozikowski and P.-u. Park, *J. Org. Chem.*, **49**, 1674 (1984).
(24) A. P. Kozikowski and P.-W Yen, *Tetrahedron. Lett.*, submitted for publication.
(25) A. P. Kozikowski and J. G. Scripko, *J. Am. Chem. Soc.*, **106**, 353 (1984).

Scheme XV



Scheme XVI



nitrile oxide precursor and its olefin partner in chiral form would be mandatory (Scheme XIV).

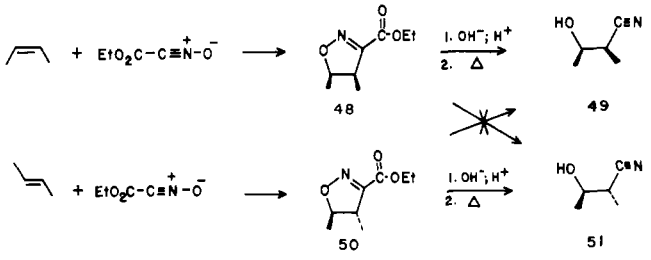
Polycycles. Lastly, we have begun to delve into the preparation of a new class of molecules that should permit the rapid construction of condensed ring systems via tandem Diels–Alder—dipolar cycloaddition chemistry (i.e., the [4 + 2] + [3 + 2] cycloaddition process). The execution of such a notion requires only that we be able to prepare easily nitroalkyl-substituted butadienes (or furans). As illustrated below for 8-nitro-1,3-octadiene, thermal cycloaddition with carbomethoxy-*p*-benzoquinone, L-Selectride (Aldrich) reduction of the activated double bond of the cycloadduct, and phenyl isocyanate/triethylamine initiated dipolar cycloaddition afford the stereodefined tetracycle **46**, a compound possessing five centers of asymmetry.[26] Such chemistry should find applications in the steroid area as well as in the development of routes to the antileukemic principles, the quassinoids (Scheme XV).

A Route to β-Hydroxy Nitriles, Acids, and Esters

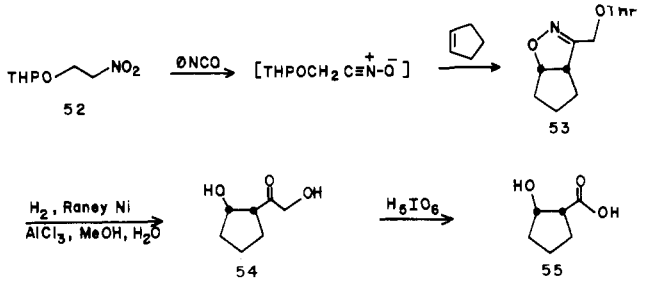
We have investigated the use of two old yet relatively unappreciated reagents, carbethoxyformonitrile oxide (CEFNO) and cyanogen *N*-oxide (CNO) for the stereospecific functionalization of olefins.[27] While the latter reagent has been shown to cycloadd to several different olefins, the difficulty in procuring the starting material, chloral hydrate, required for its preparation led us to look more seriously at carbethoxyformonitrile oxide. This reagent is generated by treating the crystalline precursor, ethyl chlorooximidoacetate (**47**) with either aqueous sodium carbonate or triethylamine in ether. The chloro oxime is itself easily prepared from glycine ester hydrochloride by treatment with hydrochloric acid and sodium nitrite (Scheme XVI). By using a large excess of olefin to dipole in the [3 + 2] cycloaddition reactions with CEFNO, high yields of cycloadducts can be achieved even with olefins generally regarded to be poor dipolarophiles. A 78% isolated yield of the isoxazoline from cyclohexene can be

(26) A. P. Kozikowski, K. Hiraga, J. P. Springer, B. C. Wang, and Z.-b. Xu, *J. Am. Chem. Soc.*, **106**, 1845 (1984).
(27) A. P. Kozikowski and M. Adamczyk, *J. Org. Chem.*, 48, 366 (1983).

Scheme XVII



Scheme XVIII



achieved if a 1:20 ratio of dipole to dipolarophile is employed.[28]

For conversion of these isoxazolines to β-hydroxy nitriles, the isoxazoline esters were simply saponified and the free acids heated at a temperature 5–10 °C above their melting points. The β-hydroxy nitriles generated by this precedented decarboxylative ring-opening reaction were generally contaminated by small amounts of the corresponding cyano aldehyde (or ketone) (removable by sodium bisulfite treatment).

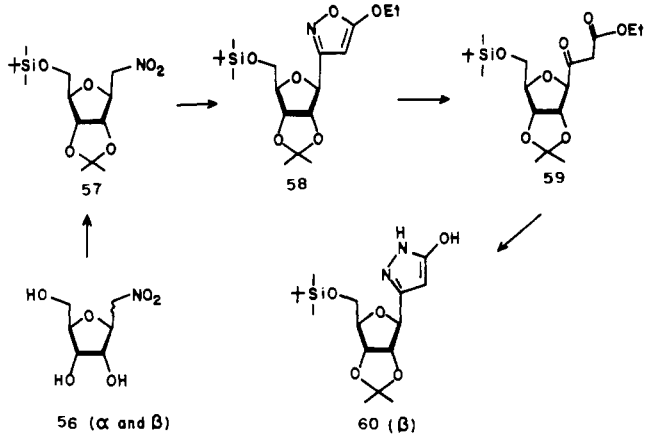
Most pertinent to the development of this [3 + 2] approach to β-hydroxy nitriles was the finding that pyrolysis of the isoxazoline acids prepared from *trans*- and *cis*-2-butene occurred without any crossover in stereochemistry. Decarboxylative ring opening thus takes place without epimerization of the nitrile bearing carbon. (**48** → **49**; **50** → **51**) (Scheme XVII).

In further study of such methodology for olefin functionalization, we also realized that the commercially available reagent 2-nitroethanol could provide a related (lower oxidation level) type of nitrile oxide that should function in a very similar fashion to CEFNO. By protecting the hydroxyl group of 2-nitroethanol as its tetrahydropyranyl ether and then reacting this derivative **52** with phenyl isocyanate in the presence of the appropriate olefin, high yields of the expected cycloadducts were generated.[27,29] These isoxazolines (**53**) were readily converted to their corresponding β-hydroxy acid derivatives (**55**) through a simple two-step process involving aluminum chloride hydrogenolysis with concomitant cleavage of the tetrahydropyranyl group followed by periodic acid oxidation (Scheme XVIII).

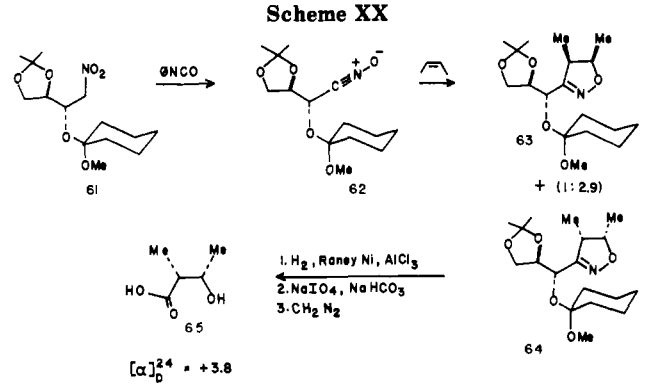
The utility of nitrile oxides containing an α-oxygen substituent in carbon–carbon bond-forming processes (both intra- and intermolecular) led us to consider building optically active nitrile oxides derived from sugars or sugar fragments. The known ribofuranosylnitromethanes **56**α and **56**β were converted to their 2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl derivatives and then reacted with phenyl isocyanate/triethylamine in the presence of ethoxyacetylene. The

(28) G. Zinner and H. Gunther, *Chem. Ber.*, **98**, 1353 (1965).
(29) A. P. Kozikowski and A. K. Ghosh, *Tetrahedron Lett.*, **24**, 2623 (1983).

Scheme XIX



Scheme XX

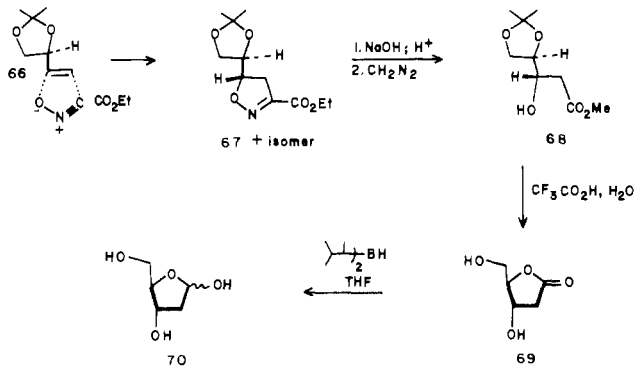


product derived from the β-isomer not only constitutes a new species of C-nucleoside analogue, but additionally it can serve as a valuable precursor to a host of other *C*-nucleoside structures. Hydrogenolysis of its N–O bond affords the β-keto ester **59**. This uniquely generated product engages in a double condensation reaction with bis-nucleophiles, such as hydrazine, to deliver a new *C*-nucleoside derivative, the pyrazole **60** (Scheme XIX).[30]

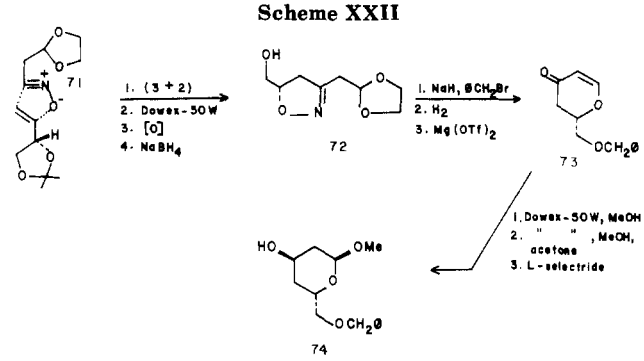
Stereocontrol in Intermolecular Cycloadditions. If we now return to the β-hydroxy acid synthesis, it would seem, based on the foregoing discussions, that one might be able to develop a diastereoselective route to such part structures by using a nitroethanol derivative derived from a sugar fragment. On condensing (*R*)-glyceraldehyde acetonide with nitromethane employing potassium fluoride as base, two β-hydroxy nitro compounds are produced in a 4:1 ratio. The major product is that produced via a Felkin-type transition state, and protection of its free hydroxy group as a methoxycyclohexane ketal yielded the desired precursor **61**. Conversion of **61** to its nitrile oxide **62** in the presence of several mono- and disubstituted olefins gave good yields of cycloadducts. Only with the disubstituted products was any degree of diastereoselection observed. While the diastereomeric excesses are not high, it is nonetheless interesting to observe that some chirality transfer does obtain for a cylindrically symmetrical nitrile oxide. Since the diastereomeric products can generally be separated by column chromatography, we believe that this chemistry may provide in some instances a useful alternative to both microbiological and aldol methods for optically active β-hydroxy

(30) A. P. Kozikowski and S. Goldstein, *J. Org. Chem.*, **48**, 1139 (1983).

Scheme XXI



Scheme XXII



acid synthesis.[31] Further fine tuning of such reagents may well be possible (Scheme XX).

There does, of course, exist an alternative method for achieving the chiral-selective assembly of β-hydroxy carboxylic acids or nitriles by intermolecular cycloaddition pathways. This would involve adding an achiral nitrile oxide component (e.g., CEFNO) to a chiral olefin bearing an allylic asymmetric center in a diastereoselective fashion. While the extent of such diastereoselection appears to be small when there is little to distinguish the allylic groups on a steric or electronic basis as in the paliclavine synthesis, we have observed that an allylic oxygen substituent can, on the other hand, serve as a useful control element for achieving such diastereofacial selectivity. This type of stereocontrol is best illustrated through a simple synthesis of 2-deoxy-D-ribose. Optically active (+)-(*S*)-isopropylidene-3-butene-1,2-diol (**66**) was reacted with carbethoxyformonitrile oxide to afford an 80:20 mixture of diastereomeric cycloadducts (**67**; major isomer). These products were separated by chromatography, and the major isomer converted to 2-deoxy-D-ribose (**70**) as displayed in the scheme (Scheme XXI).[32]

The extent of diastereofacial selection in the addition of the nitrile oxide derived from **52** to olefin **66** was even higher than observed with CEFNO (>94%). In comparison with current aldol technology, it is informative to note that the anion of methyl acetate has been reported to react with isopropylidene-D-glyceraldehyde to afford an 85:15 mixture of the erythro and threo isomers.[33,34]

Finally, by combining the unique ability of the nitrile oxide derived from 3-nitropropionaldehyde ethylene acetal to serve as a formylketene equivalent (in the Diels–Alder sense) in the elaboration of olefins to dihydropyran-4-ones with such diastereofacial selectivity, one can design a chiral selective approach to a protected version of the compactin lactone (see structures **29–32** above and the corresponding text).[35] The isoxazoline **72**, a degradation product of the first-formed isoxazoline, was hydrogenated, and the resulting β-hydroxy ketone subjected to a magnesium triflate promoted cyclocondensation reaction. Axial addition of methanol to **73**, deketalization, and reduction then provided the desired product **74**, a compound prepared previously in racemic form by a Diels–Alder process.[36] Nitrile oxide **71** and its derivatives thus appear to hold tremendous potential for the synthesis of carbohydrates and carbohydrate-related materials (Scheme XXII).

In summation, it seems that nitrile oxide cycloaddition chemistry can serve as a powerful tool for crafting the diverse molecules of Nature. Not only can one build a variety of carbocyclic and heterocyclic ring systems through its agency, but, additionally, one can begin to exploit diastereofacial selective cycloaddition reactions in a rational way so as to achieve a satisfactory solution to the problem of acyclic stereocontrol. The nitrile oxides thus serve as remarkably mild reagents in effecting carbon–carbon bond forming reactions with the simultaneous incorporation of manipulatable heteroatom functionality.[37]

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(31) A. P. Kozikowski, Y. Kitagawa, and J. P. Springer, *J. Chem. Soc., Chem. Commun.*, 1460 (1983).

(32) A. P. Kozikowski and A. K. Ghosh, *J. Am. Chem. Soc.*, **104**, 5788 (1982).

(33) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. J. VanDerveer, *J. Org. Chem.*, **45**, 3846 (1980). For other comparisons, see ref 32.

(34) Reasonable levels of diastereoselection are also observed with the *tert*-butyldimethylsilyl ether of 3-buten-2-ol. A. P. Kozikowski and A. K. Ghosh, *J. Org. Chem.*, **49**, 2762 (1984).

(35) A. P. Kozikowski and C. S. Li, *J. Org. Chem.*, in press.

(36) S. Danishefsky, J. F. Kerwin, and S. Kobayashi, *J. Am. Chem. Soc.*, **104**, 358 (1982).

(37) Due to space limitations I could not adequately cover the important work of other investigators. To them I apologize in advance. Attention is called to ref 2 and to a recent article [V. Jäger and R. Schohe, *Tetrahedron*, **40**, 2199 (1984)] for more detailed referencing in the nitrile oxide cycloaddition area.