BF_3–Et_2O/1 h), and treatment with α-bromo-γ-butyrolactone (DMF/CsF/120 °C/1 h[10] or KF-Celite/CH_3CN/60 °C/14 h). The lactone **4** was then reacted with PhSeNa by the same procedure as described for the model experiment to afford the phenylselenide **9** (X = Se)[5] in 81% yield after distillation (bp 210–220 °C at 0.1 torr) (Scheme III). Oxidative elimination of the phenylseleno group from **9** (X = Se) occurred readily again to give the rather unstable naphthylbutenoate **10**[5] in 72% yield, which on treatment with methanolic Na_2CO_3 was cyclized to yield the key dihydrofuran intermediate **11**,[5] bp 160–165 °C at 1.0 torr, in 91% yield (an overall yield of 54% from **4**). Similarly, transformation of **4** to **11** was carried out via the phenyl sulfide **9** (X = S)[5] in comparable yield.

Now, oxidative removal of the acetonide group of **11** with silver(II) oxide generated a 2-hydroxybutyrate side chain, giving the nanaomycin A precursor **12**, mp 87–88 °C, in 80–90% yield. Formation of the dihydropyran ring was then achieved according to the method of Li,[3h,i] i.e., reaction of **12** with zinc and hydrochloric acid in THF for 5 min, addition of excess acetaldehyde to the reaction mixture and heating at 60 °C for 4 h, and oxidation of the resulting product with silver(I) oxide. The pyranojuglone **13** (cis isomer of nanaomycin A methyl ester) obtained in 51% yield was identified by comparison of the spectral data with those of the authentic sample synthesized by an alternative route by us.[3e] Isomerization of **13** to the trans isomer with sulfuric acid followed by saponification[3c,h] afforded (±)-nanaomycin A in 66% yield.

The synthetic route to **1** has several advantages over the reported ones beginning with naphthalenediols.[3c,f,h] The highest overall yield has been achieved even though each step has not been optimized. Multigram quantities of the antibiotic can be prepared from commercially available reagents and in an operationally simple manner.

Registry No. (±)-**1**, 73804-47-4; (±)-**4**, 86309-79-7; **5**, 481-39-0; (±)-**6**, 86309-80-0; (±)-**7** (X = Se), 86309-81-1; (±)-**7** (X = S), 86309-82-2; **8**, 86309-83-3; (±)-**9** (X = Se), 86309-84-4; (±)-**9** (X = S), 86309-85-5; **10**, 86309-86-6; (±)-**11**, 86309-87-7; (±)-**12**, 86309-88-8; (±)-*cis*-**13**, 78340-70-2; (±)-*trans*-**13**, 73804-46-3; 1-naphthol, 90-15-3; (±)-α-bromo-γ-butyrolactone, 86362-17-6; 1,4,5-naphthalenetriol, 481-40-3; 1,4,5-naphthalenetriol 4,5-acetonide, 86309-89-9; acetaldehyde, 75-07-0.

(10) Clark, J. H.; Miller, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 498.

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Received February 23, 1983

Facile Bridged Bicycloalkane Synthesis via Intramolecular Nitrone-Olefin Cycloaddition

Summary: Exocyclic nitrones smoothly participate in intramolecular cycloaddition reactions to provide bridged bicycloalkanes. The application of this methodology in the first total synthesis of the antifertility agent (±)-7,12-secoishwaran-12-ol is also discussed.

Sir: The development of effective approaches to bridged bicycloalkanes is an important topic in organic synthesis.[1]

Scheme I

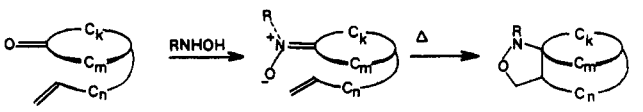
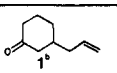
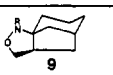
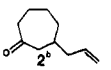
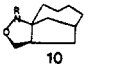
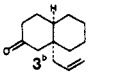
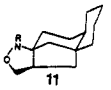
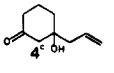
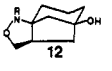
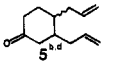
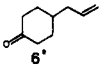
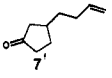
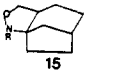
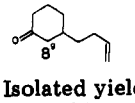
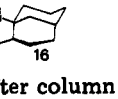


Table I. Cyclizations of Alkenylcycloalkanones Mediated by Alkylhydroxylamines

cycloalkanone	bridged bicycloalkane	temp, °C/ time, h	yield,[a] % (R)
		80/3	84 (Me) 100 (Bz) 74 (Ph)
		80/3	84 (Me) 82 (Bz)
		80/2	94 (Bz)
		80/3	66 (Me) 70 (Bz)
		80/5	75 (Me) 90 (Bz)
		111/36	48 (Bz)
		111/24	50 (Bz)
		111/48	46 (Me)

[a] Isolated yield after column chromatography. [b] Prepared by adding allyltrimethylsilane to the corresponding cycloalkenone in the presence of $TiCl_4$ as described by: Sakurai, H.; Hosomi, A. *J. Am. Chem. Soc.* **1977**, *99*, 1673. [c] Prepared by addition of excess allylmagnesium bromide to the sodium enolate of cyclohexane-1,3-dione (20%). [d] Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. [e] Conia, J. M.; Moinet, G. *Bull Soc. Chim. Fr.* **1969**, 500. [f] Conia, J. M.; Beslin, P. *Ibid.* **1969**, 483.

This structural type is manifest in a wide variety of natural products. In addition, the fragmentation or rearrangement of bridged bicycloalkanes is an established protocol for the synthesis of other ring systems.[2] We now describe a new approach to bridged bicycloalkanes and document the potential of this methodology in the first total synthesis of the antifertility agent (12*S*)-7,12-secoishwaran-12-ol.[3]

(1) A particularly novel approach to these ring systems has been reported recently and underscores the continuing interest in this area: Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784.

(2) Some notable examples include the following. (a) Bicyclo[2.2.1]-heptane → prostaglandins E_2 and $F_{2\alpha}$: Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Bicyclo[2.2.1]heptane → ambrosin and damsin: Grieco, P. A.; Majetich, G. F.; Ohfune, Y. *Ibid.* **1982**, *104*, 4226. (c) Bicyclo[2.2.2]octane → trichodermol: Still, W. C.; Tsai, M.-Y. *Ibid.* **1980**, *102*, 3654. (d) Bicyclo-[2.2.2]octane → eriolanin: Roberts, M. R.; Schlessinger, R. H. *Ibid.* **1981**, *103*, 724. (e) Bicyclo[3.2.1]octane → hinesol: Marshal, J. A.; Brady, S. F. *Tetrahedron Lett.* **1969**, 1387. (f) Bicyclo[3.3.1]nonane → ophiobolin ring system: Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *42*, 3633. (g) Bicyclo[4.3.1]decane → bulnesol: Marshal, J. A.; Partridge, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 1090.

(3) (a) Pakrashi, A.; Chakrabarty, B.; Dasgupta, A. *Experientia* **1976**, *32*, 394. (b) Pakrashi, S. C.; Ghosh Dastidur, P. P.; Basu, S.; Achari, B. *Phytochemistry* **1977**, *16*, 1103. (c) Pakrashi, A.; Shaha, C. *Experientia* **1977**, *33*, 1498. (d) Pakrashi, S. C.; Ghosh Dastidur, P. P.; Chakrabarty, S.; Achari, B. *J. Org. Chem.* **1980**, *45*, 4765.

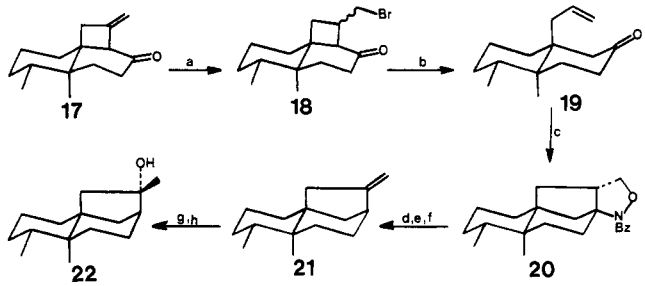
0022-3263/83/1948-2632$01.50/0

The conceptualization of our approach to bridged bicycloalkanes is illustrated in Scheme I. It was hoped that an appropriate cycloalkanone appended with an olefin side chain could be converted in situ to the corresponding exocyclic nitrone which could then participate in an intramolecular cycloaddition[4] to provide a bridged bicycloalkane fused to an isoxazolidine.[5,6] The merit of this strategy was immediately apparent. First, a variety of bridged bicycloalkanes would become available by varying the size of the cycloalkanone as well as the length and positioning of the alkenyl side chain. Second, the isoxazolidine ring provides a useful handle for the introduction of functionality typically found in bridged bicyclic natural products, for example, on the carbon adjacent to the bridgehead position (hydroxyl or methylene) and, more importantly, at the bridgehead position (hydroxyl or hydrogen).

The various cycloalkanones that have been subjected to the standard cyclization conditions are shown in Table I. The cycloalkanone and a hydroxylamine (1.1 equiv) are heated in the appropriate aromatic solvent (benzene, toluene, or xylenes) with azeotropic removal of water for the indicated time period. The yields in Table I refer to isolated yields after evaporation of the solvent and flash chromatography (silica gel, 15% EtOAc/hexane). Full spectral data for compounds **9–22** are available in the supplementary material.

Some general comments are in order. First, in all cases only one diastereomer is produced from a single cycloalkanone as evidenced by the corresponding ^{13}C NMR spectrum and/or a clean AB pattern for the oxymethylene protons in the ^1H NMR spectrum. Molecular models indicate that the exo transition states should be preferred over the highly strained endo transition states wherein dipole–olefin orbital overlap is virtually inaccessible. Therefore, the bicycloalkanes are most likely fused with exocyclic isoxazolidines as shown. Further support for these stereochemical assignments is based on the conversion[7] of isoxazolidines **9** and **15** to the known *exo*-bicyclo[3.2.1]octane-6-carboxylic acid[10] and *exo*-bicyclo[3.2.1]octane-2-carboxylic acid,[11] respectively. Second, the reaction is successful with cycloalkanones substituted with either 3-(2-propenyl) or 3-(3-butenyl) side chains, although the latter examples (e.g., **7** and **8**) require higher temperatures to effect cyclization and are lower yielding, presumably reflecting destabilizing interactions encountered from a boatlike conformation of the bridging atoms in the exo mode of cycloaddition.[12] Third, yields are not appreciably affected by the nature of the alkyl group on the alkylhydroxylamine. Finally, sensitive compounds such as the β-hydroxycyclohexanone **4** tolerate the reaction conditions.

Scheme II



With the general success of this methodology now assured, its application in natural product synthesis was next investigated. An attractive candidate for this purpose is (12*S*)-7,12-secoishwaran-12-ol (**22**). This interesting sesquiterpene was recently isolated by Pakrashi and coworkers from *Aristolochia indica* Linn. (Aristolochiaeceae)[3a,b] and shown to have 100% interceptive activity in mice at a single dose of 100 mg/kg[3c]. As a part of their structural characterization studies, these workers found that the exocyclic olefin **21** and secoishwaranol (**22**) could be interconverted.[3d] Thus, the total synthesis could be reduced to the preparation of olefin **21** which in turn was expected to be easily derivable from the intramolecular nitrone–olefin cycloadduct **20**.

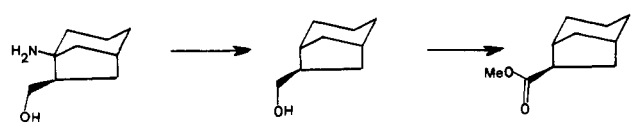
An obvious point of departure for the preparation of the cycloaddition substrate **19** is the known ketone **17**[13] which requires only the formal addition of H_2 to the cyclobutane α-keto carbon–vinyl carbon sigma bond. To this end, photochemically initiated anti-Markovnikov addition of HBr to olefin **17** gave a mixture of bromides.[14] Reductive fragmentation (excess Li, NH_3/THF) of the crude mixture of bromides proceeded smoothly to the desired keto olefin **19** (Scheme II) in 60% yield for the two steps.[15] To our

(4) For reviews of this intramolecular cycloaddition reaction see: (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 376. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (c) Padwa, A. *Ibid.* **1976**, *15*, 123. (d) Black, D. St. C; Crozier, F; Davis, V. C. *Synthesis* **1975**, 205.

(5) In a pioneering series of invesgiations which defined the scope of the intramolecular nitrone–olefin cycloaddition reaction, LeBel reported the preparation of some bridged bicycloalkanes. However, the examples in this study employed less readily available substrates which had a reversal of functionality in comparison with those described above, namely, *cycloalkenes* appended with *aldehydic* side chains. For an account of this work, see: LeBel, N. A. *Trans. N. Y. Acad. Sci.* **1965**, *27*, 858.

(6) A similar strategy for the preparation of *fused* bicycloalkanes has recently been reported. See: Takahashi, S.; Kusumi, T.; Sato, Y.; Inouyl, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1777.

(7) Hydrogenation of isoxazolidine **9** (R = CH_2Ph) with Pearlman's catalyst ($Pd(OH)_2$, H_2 at 1 atm) afforded the amino alcohol i (73%; mp 75 °C) which was "hydrodeaminated" (5 equiv of NH_2OSO_3H, 5 mL of 2.5 M NaOH, 65 °C; 92%)[8] to give the carbinol ii. Oxidation of ii using the Sharpless procedure ($RuCl_3{\cdot}nH_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O; 92%)[9] and esterification (CH_2N_2) of the resulting carboxylic acid gave the ester iii which was identical with an authentic sample.[10] Isoxazolidine **15** (R = CH_2Ph) was similarly converted to *exo*-bicyclo[3.2.1]octane-2-carboxylic acid (mp 47–79°C) and the corresponding benzylamine salt (mp 139–140 °C) whose melting points were similar to those reported previously.[11]



(8) Dolduras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *100*, 341.

(9) Carlsen, P. H. J.; Katsuki, R.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(10) Moriarty, R. M.; Chien, C. C.; Adams, T. B. *J. Org. Chem.* **1979**, *44*, 2210. In our hands, the Wolf–Kishner reduction of *endo*-3-oxobicyclo[3.2.1]octane-6-carboxylic acid proceeded with concomitant epimerization of the carboxy function. This conclusion is based on the following evidence: treatment of the corresponding ester with LDA followed by $C_5H_5NH_+$ ^-OTs gave a new ester in addition to the recovered starting ester in a ratio of 3:1. Separation (HPLC) and treatment of the new ester with NaOMe in MeOH gave complete conversion to the original ester. Furthermore, the protons α to the original and new esters resonate in the 360-MHz ^1H NMR spectra at δ 2.66 (br dd, J = 9.0, 5.1 Hz) and 2.93 (br ddd, J = 11.7, 6.2, 6.0 Hz), respectively, in accord with the expected chemical shift differences and coupling for similar endo and exo protons in bridged bicyclic systems. Cf.: Marshall, J. L.; Walter, S. R. *J. Am. Chem. Soc.* **1974**, *96*, 6358.

(11) Cantello, B. C. C.; Mellor, J. M.; Scholes, G. *J. Chem. Soc. C* **1971**, 2915.

(12) The reaction fails completely when an additional methylene is present in the side chain, e.g., 3-(4-pentenyl)cyclohexanone.

(13) This ketone was prepared in connection with a total synthesis of ishwarane. See: Kelly, R. B.; Zamecnik, J.; Beckett, B. A. *Can. J. Chem.* **1972**, *50*, 3455.

(14) House, H. O.; Chu, C.-Y.; Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1977**, *42*, 1709.

(15) The reductive cleavage of γ-bromo ketones has been observed previously. See: (a) Baker, K. M.; Davis, B. R. *Tetrahedron* **1968**, *24*, 1655. (b) Oppolzer, W.; Gorrichon, L.; Bird, T. G. C. *Helv. Chim. Acta* **1981**, *64*, 186.

surprise, attempted cyclization of ketone **19** through the agency of benzylhydroxylamine in benzene or toluene was unsuccessful. On closer inspection it was soon realized that ketone **19** was reluctant to form the requisite nitrone. Fortunately, replacement of the solvent with ethanol and addition of a drying agent (anhydrous Na_2SO_4) delivered a single isoxazolidine, **20** (reflux 8 h; mp 116 °C; 80%). Scission of both the N–O and N–benzyl bonds in **20** was performed by catalytic hydrogenation (H_2, 1 atm; $Pd(OH)_2$; 100% yield) to provide an amino alcohol which was then "hydrodeaminated" by using the commendable procedure of Dolduras and Kollonitsch[8] (5 equiv of NH_2OSO_3H, 6 equiv of NaOH, 68% EtOH, 65 °C, 5h; 65% yield). The resulting alcohol was dehydrated upon employment of the Grieco protocol[16] (ArSeCN, Ph_3P, THF; O_3; 65% yield) to provide the desired olefin **21**. Epoxidation (MCPBA, CH_2Cl_2 aqueous $NaHCO_3$; 67% yield),[17] and subsequent reduction ($LiAlH_4$, Et_2O; 90% yield) then furnished (±)-7,12-secoishwaran-12-ol (mp 116–117 °C) which was identical with an authentic sample (TLC, IR, 360-MHz ^1H NMR, ^{13}C NMR).

The work reported herein broadens the utility of the intramolecular nitrone cycloaddition reaction. This reaction has found extensive application in the synthesis of *alkaloids* and other nitrogen-containing natural products.[4] It is now apparent that this reaction can be further exploited in the synthesis of various *terpenes*.[18] In addition, the bridgehead nitrogen substituent of these cycloadducts is strategically positioned to trigger rearrangement or fragmentation to other ring systems. These possibilities and further application of this methodology in natural product synthesis are under investigation.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation (Grant No. CHE-8205144), and the University of Nebraska Research Council for financial and material support. High-field (360 MHz) ^1H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant No. CHE-80-24328). We are most grateful to Professor S. C. Pakrashi for furnishing an authentic sample of (12*S*)-7,12-secoishwaran-12-ol.

Supplementary Material Available: Full spectral data for compounds **9–22** (8 pages). Ordering information is given on any current masthead page.

(16) Grieco, P. S.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(17) An isomeric epoxide was also isolated in 8% yield.

(18) To our knowledge, the only exception is the synthesis of α-bisabolol reported independently by two groups. (a) Schwartz, M. A.; Swanson, G. C. *J. Org. Chem.* **1979**, *44*, 953. (b) Iwashita, T.; Kusum, T.; Kakisawa, H. *Chem. Lett.* **1979**, 947.

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