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Spiro- and Bridged-Ring Forming Electrophile Induced -> Oxime -> Nitrone Cycloaddition Cascades. Multiplication of Chirality

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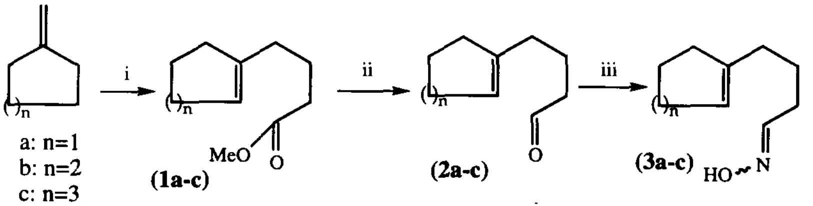
Abstract: Electrophile induced 6-exo-trig spirocyclisation of oximes onto 5-, 6- or 7-membered cycloalkenes occurs stereo- and regio- specifically in good yield. Bridged - ring forming cyclisations creating bicyclo-[3.3.1]- and bicyclo-[3.2.1]-ring systems also occur in good yield. Chiral bridged-ring systems have been synthesised, *via* the latter processes, that involve multiplication of chiral centres from one to six and seven in one pot reactions. © 1997 Elsevier Science Ltd.

As part of an ongoing research program developing new cascade reaction we have recently reported a range of electrophile induced oxime -> nitrone -> cycloaddition cascades[1]. We now report that phenylselenyl bromide is an excellent reagent for effecting stereo- and regio-specific spiro- and bridged- ring forming cyclisation of oximes onto proximate alkenes.

Spirocyclisation: A series of 5-7 membered δ-alkenyl aldehydes (**2a-c**) were prepared from the appropriate methylenecycloalkenes via ene reaction and reduction as outlined in Scheme 1[2] and these were converted to their oximes. Oximes (**3a-c**) were obtained as 1:1 E/Z-isomer mixtures in 54-59% overall yield from (**1a-c**).

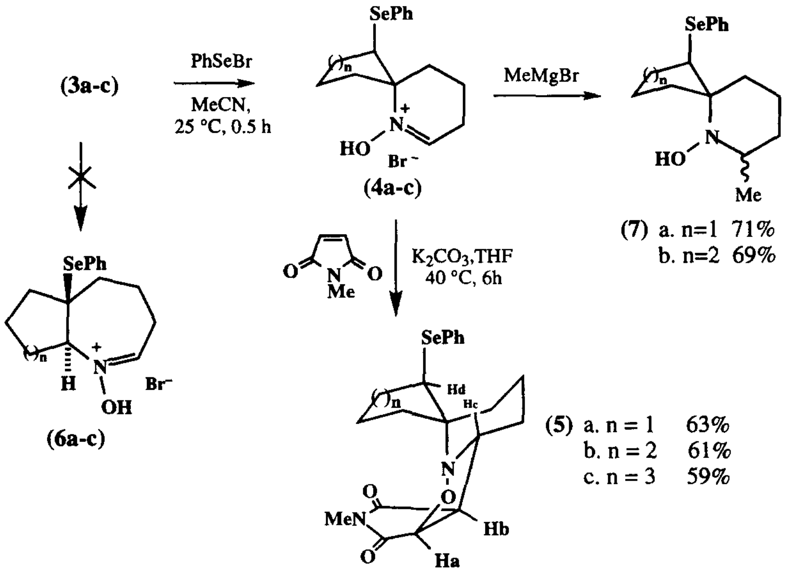


Reagents and conditions: i) $CH_2=CHCO_2Me$, $AlCl_3$, benzene, r.t., 48h. ii) DIBAL-H toluene, -78 °C, 1h, iii) $NH_2OH.HCl$, CH_3COONa, MeCN, H_2O, r.t., 3h.

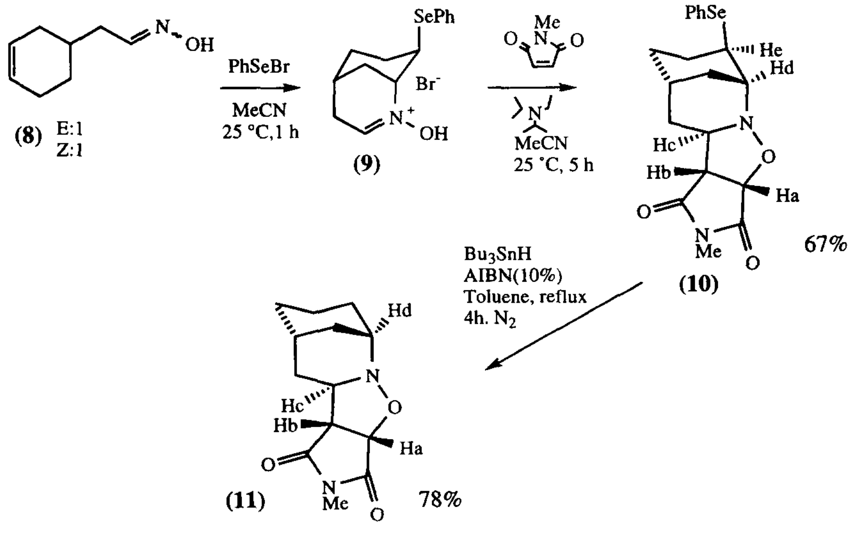
Scheme 1

Electrophile mediated cyclisation of (**3a-c**) was explored using PhSeBr induced 6-exo-trig cyclisation. The spirocyclic nitrone salts (**4a-c**) were the exclusive products. The alternative 7-endo-trig cyclisations which would produce 5/7-, 6/7- and 7/7 -bicyclic nitrone salts (**6a-c**) were not observed. Neutralisation of the nitrone salts (with K_2CO_3 or Hunig's base) and cycloaddition to N-methylmaleimide (NMM) afforded cycloadducts (**5a-c**) as single stereoisomers in 59-63 % overall yield from (**3a-c**). The stereochemistry of (**5a-c**) was determined by n.O.e spectroscopy, ^{2}D-COSY studies and X-ray crystal structure determination. Interestingly, the X-ray crystal structure of (**5c**) shows the presence of two different conformations of the 7-membered ring[3].

Reaction of **(4a)** and **(b)** with excess methylmagnesium bromide (2.5 equiv.) gave the corresponding hydroxylamines **(7a)** and **(b)** as 1:1 mixtures of diastereoisomers (^{1}H n.m.r.) in 69-71% overall yield from **(3a)** and **(3b)**.

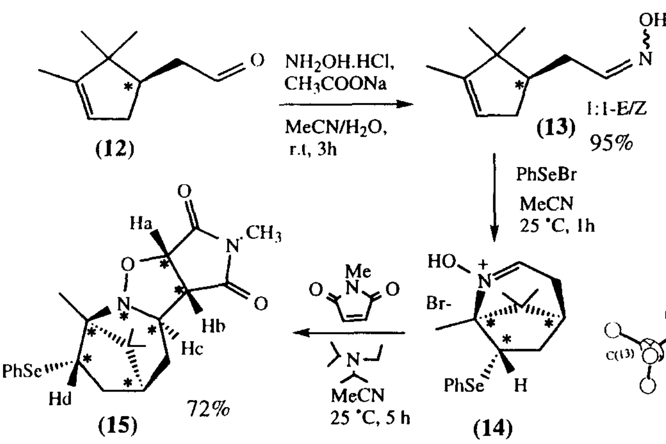


Bridged-Rings Systems: Formation of bridged ring nitrones was first evaluated with oxime **(8)**, prepared as a 1:1 E/Z-isomer mixture in 93% overall yield.[4] An analogous cyclisation (PhSeBr) - cycloaddition sequence furnished the nitrone salt **(9)** first and then cycloadduct **(10)**. Cycloadduct **(10)** was obtained as a 4:1 mixture of isomers (^{1}H n.m.r.) in 67% overall yield from oxime **(8)**. The minor isomer appears to be associated with an equatorial SePh moiety (^{1}H n.m.r.). The stereochemistry of the major isomer **(10)** was determined by n.O.e and ^{2}D-COSY studies.



Removal of the PhSe group using Bu_3SnH(1mol eq.) /AIBN(10 mol)% gave the desired product **(11)** in 78 % yield as a single exo-isomer containing five stereocentres, indicating that the observed 4:1 mixture of isomers of **(10)** arises from the PhSe group. The stereochemistry of **(11)** was assigned from n.O.e. data, ^{2}D-COSY studies and X-ray crystallography.

Syntheses of optically active bridged-ring systems involving multiplication of stereocentres from one to six or seven in high yielding one pot reactions have also been achieved by analogous sequences from chiral non racemic oximes. Thus the known literature rearrangement of (-)-α-pinene epoxide[5] was used to prepare **(12)** and this was converted to its oxime **(13)**. The optically active oxime was a colourless liquid which comprised a 1:1 mixture of E- and Z- isomers. The versatility of the electrophile induced cyclisation process is demonstrated by the cyclisation of **(13)** to **(14)** despite the potential for steric inhibition by the gem-dimethyl group. Cycloaddition of **(14)** with NMM in the presence of Hunig's base afforded a single cycloadduct formulated as (**15**, $[\alpha]_D$ +67 (c=0.8, $CHCl_3$) in 72% overall yield from **(13)**. The stereochemistry of product **(15)** was determined by n.O.e. spectroscopy, ^{2}D-COSY studies and X-ray crystallography (Figure).This sequence results in the multiplication of chiral centres from one to seven.



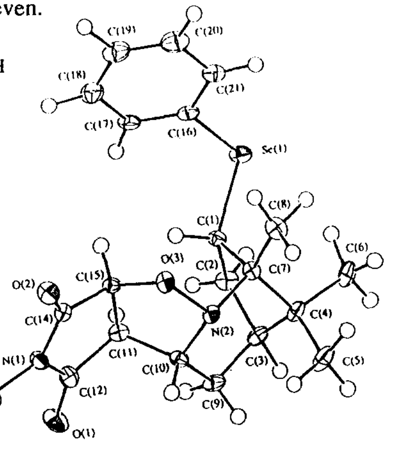
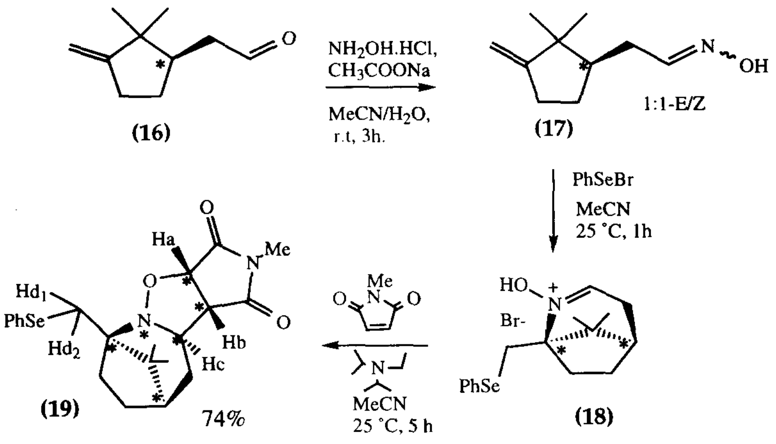


Figure: X-Ray Crystal Structure of (15)

Bridged-ring formation via cyclisation of a chiral oxime onto an exo-methylene group was studied next. Thus (*1 R*)-(2,2-dimethyl-3-methylenecyclopentyl)-1-acetaldehyde **(16)** was prepared from 6,6-dimethylbicyclo[3.1.1]-hept-2-ene-2-ethanol (Nopol) according to the literature procedure[5]. The oxime **(17)** was obtained as a 1:1 E/Z-isomer mixture which reacted (MeCN, r.t, 1h) with PhSeBr to give the nitrone salt **(18)**. Liberation of free base using Hunig's base followed by reaction with NMM (MeCN, r.t, 10h) gave a single exo-cycloadduct (**19**, $[\alpha]_D$ -64.0 (c=0.2, $CHCl_3$) [74%, from **(17)**]. In this sequence multiplication of chiral centres from one to six has been achieved in a one pot process. The stereochemistry of the cycloadduct was determined from n.O.e data, ^{2}D-COSY studies and X-ray crystallography.



In summary, the technically simple, electrophile induced, oxime -> nitrone -> cycloaddition sequence occurs highly regio- and stereo-selectively and provides a major increase in molecular complexity.

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