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The Stereochemically Controlled Synthesis of Spirocyclic Ethers and Lactones with Medium-Sized (7-, 8-, and 12-Membered) Carbocyclic Rings by Phenylthio Migration: 1-Oxaspiro[4.n]alkanes and Alkan-2-ones with n = 6, 7, and 11.

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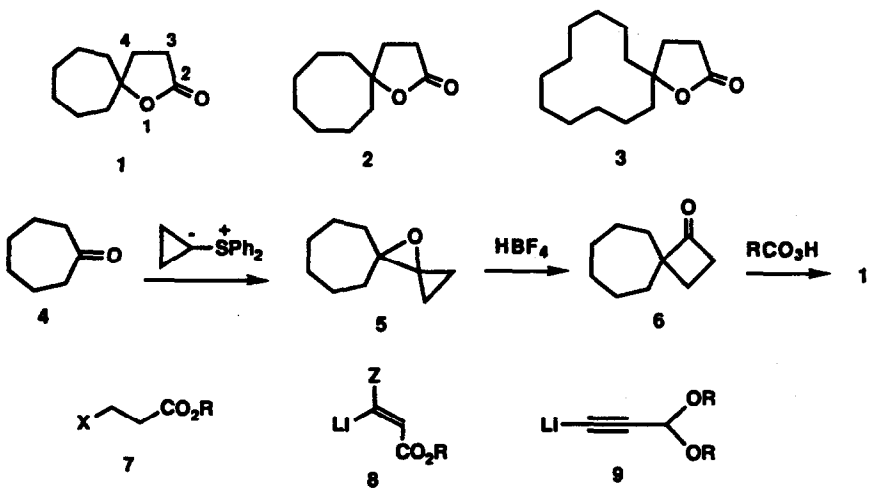
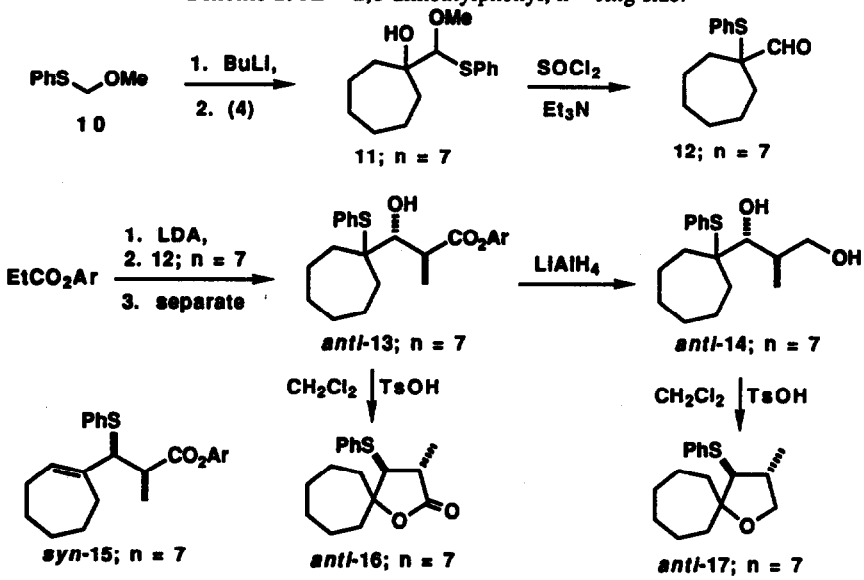
Abstract: 3-Methyl-4-phenylthio-1-oxaspiro[4.6]undecanes, [4.7]dodecanes, [4.11]hexadecanes and the corresponding 2-ones (lactones) can be made from cyclohepta-, octa-, and dodecanone by chain extension to the 2-phenylthiocarbaldehyde, stereoselective aldol reaction and stereospecific phenylthio migration with control over the relative (3,4-*syn* or *anti*) and absolute (*R* or *S* at positions 3 and 4) stereochemistry.

Trost's general synthesis[1] of spirocyclic lactones from cyclic ketones, e.g. **4**, by a single chain extension to **5**, rearrangement to **6** and oxidation, gives excellent yields of 1-oxaspiro[4.6]undecan-2-one **1** from cycloheptanone **4**. Other workers have used chain extensions with halides[2] such as **7** with SmI_2, or acrylates **8**; Z = PhS etc.,[3] or versions of **9** with various masked carbonyl groups[4] to make spirocyclic lactones with medium-sized carbon rings, such as 1-oxaspiro[4.7]dodecan-2-one **2** or 1-oxaspiro[4.11]hexadecan-2-one **3**. The few reported two-stage chain extensions[5] rely on carbonylation of a metal complex to introduce the carbonyl group of the lactone. None of these methods can easily be used to introduce chiral centres into the lactone ring (C-3 and C-4).



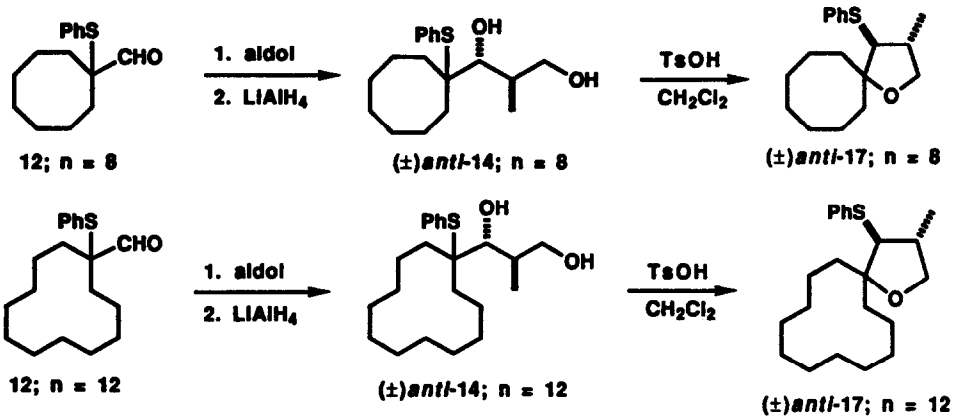
We report the first syntheses of single diastereoisomers and enantiomers of substituted ring systems **1** to **3** and the related ethers with chiral centres in the heterocyclic ring. Our approach[6] initially extends the chain by addition of $PhSCH_2OMe$ **10** to the cyclic ketone. Rearrangement[7] of adduct **11** to a 2-PhS-carbaldehyde **12** and a second chain extension by stereoselective aldol reaction gives **13**. Two chiral centres can be introduced in the aldol reaction with control over relative and absolute stereochemistry and transformed stereospecifically with inversion at the migration terminus (C-4) during cyclisation with PhS migration via an episulfonium (thiiranium) ion which captures an intramolecular nucleophile. This approach using Heathcock's *anti* aldol reaction[8] from cycloheptanone (scheme 1) , reduction to the diol **14** and rearrangement in acid, gave the spirocyclic ether 3-methyl-4-phenylthio-1-oxaspiro[4.6]undecane **17**; n = 7 (100%). Direct acid-catalysed rearrangement of the aldol *anti*-**13**; n = 7 gave a mixture of the allyl sulphide *syn*-**15**; n = 7 (45%) and the lactone 3-methyl-4-phenylthio-1-oxaspiro[4.6]undecan-2-one *anti*-**16**; n = 7 (44%): the hindered aryl ester participates less effectively than the oxazolidinone in the cyclisation of **19** below.

Scheme 1: Ar = 2,6-dimethylphenyl, n = ring size.

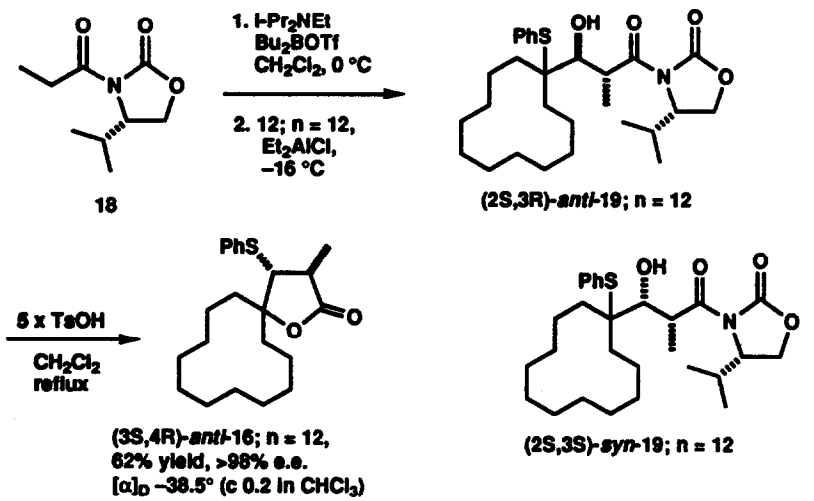


Formation of **11** and rearrangement to give **12** are both successful with medium sized carbocyclic rings, n = 8 and n = 12, leading to the spirocyclic ethers 3-methyl-4-phenylthio-1-oxaspiro[4.n]alkanes **17** (scheme 2). Heathcock's *anti* selective aldol reaction[8] with the lithium enolate of 2,6-dimethylphenyl propionate gives good yields of the racemic *anti* aldols **13**; n = 8 and 12. This stereoselective aldol reaction seems to be particularly suitable for aldehydes with large substituents next to the carbonyl group. The steric hindrance caused by the conformationally flexible medium ring is perhaps less of a problem in aldehydes **12** as the PhS group at C-2 of the aldehyde increases reactivity by adopting a Felkin conformation with the C-SPh bond parallel to the p orbitals of the carbonyl group. Reduction to the diols *anti*-**14**; n = 8 and 12 followed by acid catalysed rearrangement gave the spirocyclic ethers *anti*-**17**; n = 8 (76%) and 12 (100%) in good yield. The *anti* stereochemistry was deduced from NOE experiments. The lactones **16**; n = 8 and 12 can again be formed in poor yield by rearrangement of the aldols **13**: racemic *anti*-**16**; n = 12 was used in the determination of the optical purity of the (3*S*, 4*R*) enantiomer below.

Scheme 2; Synthesis of 3-Methyl-4-phenylthio-1-oxaspiro[4.7]dodecane (racemic *anti*-**17**; n = 8) and 3-Methyl-4-phenylthio-1-oxaspiro[4.11]hexadecane (racemic *anti*-**17**; n = 12)

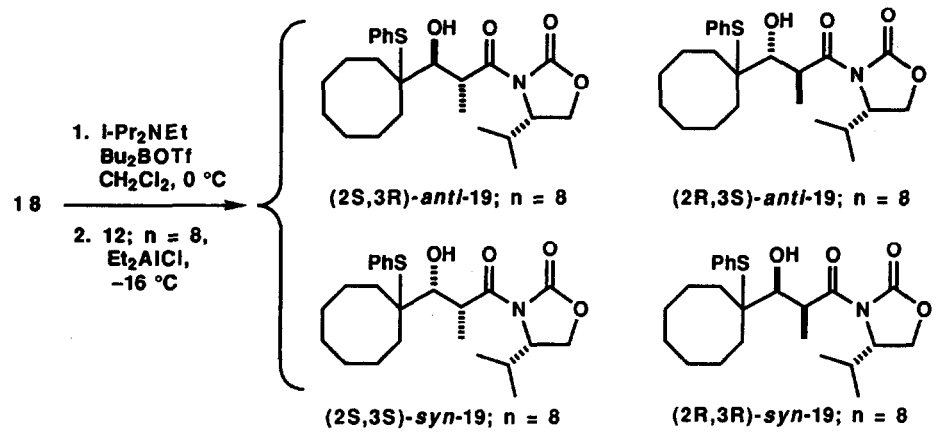


Heathcock's Lewis acid-catalysed aldol procedure[9] with the Evans valine-derived chiral auxiliary **18** was usefully diastereoselective. With 3.0 equivalents of the Lewis acid (Et_2AlCl) two aldol products (2S,3R)-*anti*-**19**; n = 12 and (2S,3S)-*syn*-**19**; n = 12 were formed in a 70:30 ratio. As expected,[9] increasing the amount of Lewis acid to 6.0 equivalents improved the selectivity to 84:16 and the major (2S,3R)-*anti* product was isolated in 58% yield. Cyclisation of this major product in excess acid gave the spirocyclic lactone (and recovered chiral auxiliary) in one step. The enantiomeric excess was determined by NMR, in comparison with racemic *anti*-lactone, with Pirkle's chiral solvating agent 1-(9-anthryl)-2,2,2-trifluorethanol.



The same procedure was much less successful with the eight-membered ring compounds. The aldol reaction of **18** with **12**; n = 8 gave a mixture of all four diastereoisomers of **19**; these were separated by column chromatography and identified by ^1H and ^{13}C NMR. The *syn* or *anti* aldol relationship is deduced from the

coupling constant between the hydrogen atoms on C-2 and C-3: $J_{2,3}$ 8.4 and 8.6 Hz for the two *anti* aldols and $J_{2,3}$ 5.5 and 4.9 Hz for the two *syn* aldols. The *anti*:*syn* ratio (HPLC) was 64:36 and hardly changed with amount of Lewis acid, while the diastereofacial selectivity was 44:20 for the *anti* and 21:15 for the *syn* aldols. The major product could be isolated in 32% yield, but this is not a practical method. The eight-membered ring also induces anomalous results in simple PhS migrations.[10]



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