# [1.3], [3.3] and Tandem [1.3]–[3.3] Rearrangements of 11- and 12-Membered Trienolides

**Khalid M. Khan and David W. Knight***

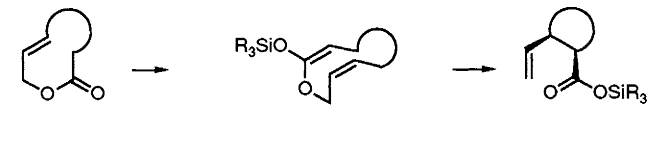
*Department of Chemistry, University Park, Nottingham NG7 2RD, UK*

The bis-*O*-silyl enolates **5** derived from lactones **4** rearrange *via* a tandem [1.3]–[3.3] mechanism leading to the cyclopentane acids **8**, whereas the higher homologue **13** is similarly converted into the cyclodecene **15** by a [1.3] process; by contrast, *O*-silyl enolates of the less substituted lactones **21** and **25** undergo exclusively [3.3] rearrangements.

The alicyclic version [**1** → **2** → **3**] of the enolate Claisen rearrangement[1] leads only to the *cis* diastereoisomers **3** when the (*Z*)-lactones **1** contains 12 atoms or less,[2] *via* a boat-like transition state **2** imposed on the intermediate (*E*)-enolates by the constraints of the relatively short bridge connecting the distal ends of the diene system.[3] To extend this methodology further, we have examined rearrangements of more highly functionalized substrates such as the keto-lactone **4a**, which can be prepared by a retro-aldol fragmentation,[4] rather than the more usual method of lactonization of the corresponding ω-hydroxy-acids.[2,3,5] In the event, the rearrangement took an unexpected pathway which is the subject of this paper.

Enolization and *O*-silylation [3 equiv. lithium diisopropylamide (LDA), tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA), −78 °C; *tert*-butyldimethylsilyl chloride (TBDMSCl)] of the lactone **4a** led to an isolable bis-*O*-silyl enolate **5a** which appeared to be a single kinetic regioisomer. This, to our surprise,[2] resisted rearrangement until refluxed in xylene and gave, after desilylation (HF–MeCN), a single acid in 53% yield, after chromatography and crystallisation. This was not the expected[6] cycloheptene derivative **6a** but rather the cyclopentanecarboxylic acid **8a**,† the structure of which was confirmed by X-ray analysis.[7] A reasonable mechanism consists of an initial [1.3] rearrangement of the bis-enolate **5a** leading to a cyclononadiene carboxylate **7a** which, given the (*E*)-stereochemistry of the ketone enolate shown, could rearrange further by a [3.3]-Cope process *via* a boat conformation (*cf.* **2**) to give the final product. Attempts to intercept derivatives of the cyclononadiene **7a** were unsuccessful, indicating that the Cope rearrangement occurs more rapidly than the [1.3] process. The alternative tandem combination of a [3.3] followed by a [1.3] rearrangement appears to lack an appropriate driving force for the second step. [1.3] Rearrangements of *O*-silyl enolates have previously been observed in the lactone derivatives **9** leading to the cyclopropane acids **10**;[8] earlier examples include the lithio enolates of benzyl esters,

† Satisfactory analytical and spectroscopic data have been obtained for all isolated compounds.

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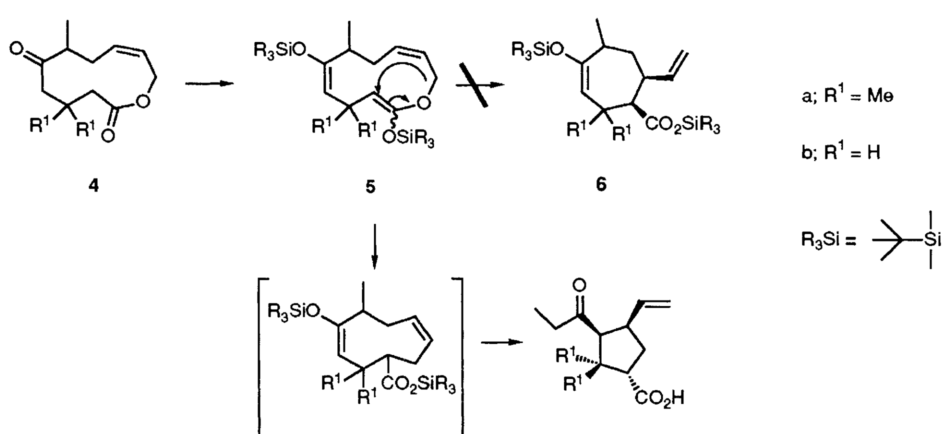


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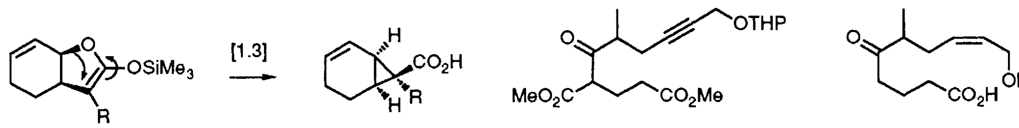


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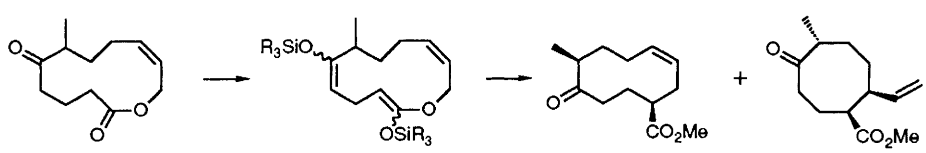
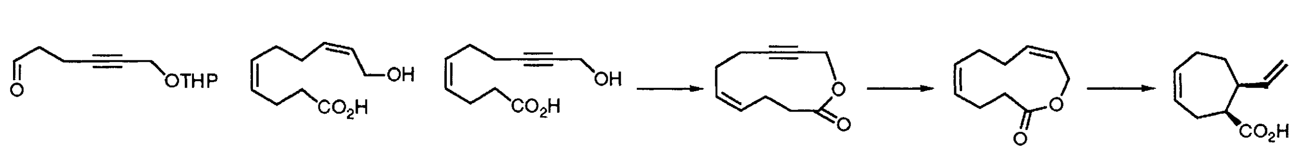
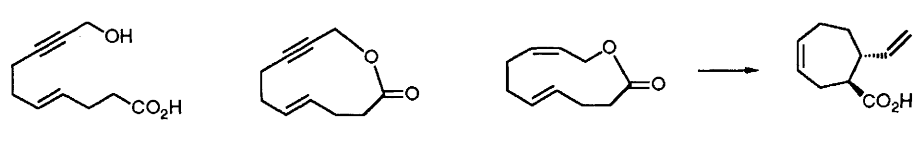



13 14 15 16




17 18 19 20 21 22




23 24 25 26

where the [3.3] process would disrupt the aromaticity of the aryl ring.[9] The actual mechanism of the [1.3] rearrangement is not clear; a concerted process with inversion at carbon seems most likely[10] although a fragmentation–recombination mechanism is possible.[11]

To determine if the *gem*-dimethyl group was responsible for the [1.3] rearrangement of bis-enolate **5a**, we prepared the lactone **4b**. As the retro-aldol approach[4] failed, we homologated methyl 3-oxopentanoate by coupling the derived dianion[12] with the tetrahydropyran-2-yl (THP) ether of 4-chlorobut-2-yn-1-ol followed by Michael addition[13] to methyl acrylate. Decarboxylation[14] of the resulting diester **11**,† deprotection, Lindlar reduction and ester hydrolysis gave the hydroxy acid **12**† which was lactonized using Mukaiyama's reagent.[5,15] Rearrangement of lactone **4b**† as described above resulted in the isolation (66%) of the cyclopentane acids **8b**† and its all-*cis* epimer† in a ratio of 78 : 22. Thus, although the *gem*-dimethyl substituent of lactone **4a** is not the primary cause of the [1.3] rearrangement, it does influence the stereoselectivity of the overall process.

Further evidence for the tandem [1.3]–[3.3] process was obtained from rearrangement of the 12-membered lactone **13**,†‡ the kinetic bis-*O*-silyl enolate **14** of which cannot undergo a [3.3]-Cope rearrangement. Thermolysis in xylene of enolate **14**, generated as described above, and esterification ($CH_2N_2$) led to two esters in a ratio of 3 : 1 (76% total yield).§ The major component was the [1.3] rearrangement product **15**,† indicating the validity of the [1.3]–[3.3] mechanism; a weak NOE effect suggested that this was the *cis* diastereoisomer. The second, minor, product was the cyclooctanecarboxylate **16**.† The *cis*-stereochemistry of the vinyl and carboxylate groups was assigned by comparison with methyl *cis*-2-vinylcyclooctanecarboxylate.[2] The assignment of the methyl group stereochemistry as *trans* is tentative and based on the involvement of a boat-like transition state **2** in which it would be equatorial.[2,3] The minor product **16** could arise because the extra carbon in the intermediate bis-enolate **14**, relative to bis-enolates **5**, allows some overlap of the distal ends of the 1,5-diene fragment. Alternatively, the two products could arise *via* different enolate geometries; to gain more insight into this, the lactones **21** and **25** were prepared as mimics of, respectively, the (*E*)- and (*Z*)-ketone enolate geometries in the bis-enolates **5**.

The hydroxy acid **18**† was prepared by Wittig reaction between aldehyde **17**† and the triphenylphosphorane derived from ethyl 4-bromoacetate [KN(TMS), −78 °C, THF], Lindlar reduction and hydrolysis; unfortunately, lactonization[15] produced an isomeric mixture. However, a similar cyclization of the *acetylenic* hydroxy acid **19**† gave a 53% yield of the lactone **20**† which was converted into the lactone **21**† by Lindlar reduction. Enolization (1.5 equiv. LDA, TBDMSCl, −78 °C) afforded an *O*-silyl enolate which, to our surprise, rearranged at ambient temperature to give the *cis*-cycloheptene acid **22**† (67%) as a single diastereoisomer, the structure of which was deduced by comparative spectroscopic data.[2] No traces of either [1.3] or tandem [1.3]–[3.3] rearrangement products were found. The formation of acid **22** is consistent with the intermediacy of an (*E*)-enolate which rearranges *via* a boat conformation **2**.[2,3] This suggested that the (*Z*)-silyl enolates of the initial keto-lactones **4**, related to the (*E*, *Z*) lactone **25**, were involved in the tandem [1.3]–[3.3] processes. Lactone **25** was also prepared from aldehyde **19** by reaction with vinylmagnesium bromide, orthoester Claisen rearrangement[16] and deprotection to give the (*E*)-hydroxy acid **23**† in excellent overall yield. Direct lactonization[15] of this provided the enynolide **24** (45%) which was converted into the (*E*, *Z*) lactone **25**† by Lindlar reduction. Sequential enolization, *O*-silylation and heating in THF led to the *trans* cycloheptene acid **26**,† the product, once again, of a [3.3] rearrangement, according to all spectral and analytical data. As it is not clear at which stage the necessary double bond isomerization occurs, it is difficult to draw conclusions regarding the geometry of the intermediate enolate. However, isomerization to the (4*Z*) isomer prior to rearrangement is precluded if the (*E*)-*O*-silyl enolate was formed as this would lead to the *cis* product **22**. These latter transformations lead to the conclusion that the unusual [1.3] rearrangements of the *O*-silyl enolates obtained from lactones **4** and **13** are caused by the presence of the silyloxy function derived from the ketone group; possibly the flanking methyl substituent also plays a key role in this. Efforts to further define these transformations are in progress.

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‡ Prepared as described for lactone **4b** from methyl 3-oxopentanoate, but using (*Z*)-5-iodo-1-(tetrahydropyran-2′-yloxy)pent-2-ene in the dianion alkylation step.

§ Separation was achieved by reversed-phase HPLC using a C-18 RadPack eluted with 45% water in methanol.

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