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A NEW STEREOSPECIFIC ANNULATION

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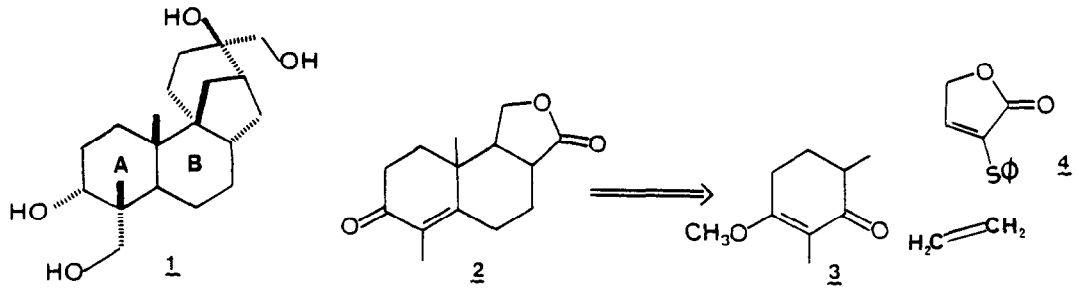
Summary: A new, high yield, two-step annulation method has been developed which features stereospecific formation of three contiguous asymmetric centers.

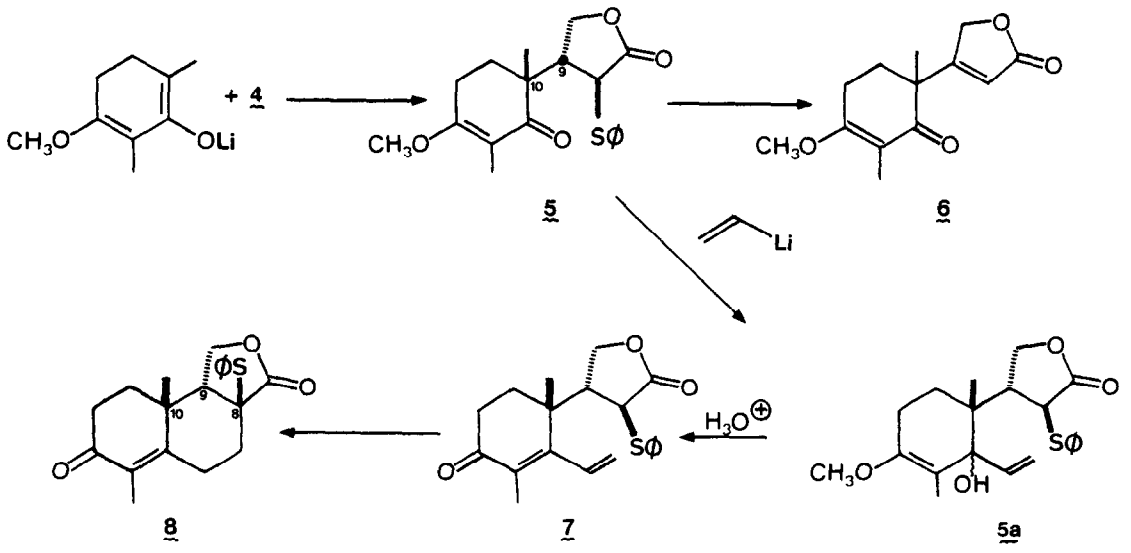
Since the pioneering work of Robinson, annulation reactions have continued to play a central role in organic chemistry.[2] Several annulation methodologies have been developed in recent years, but only a few of these address the point of stereocontrol of substituents attached to the newly formed ring.[3] We now report a new annulation methodology, developed during the course of studies directed toward aphidicolin (1)[4] total synthesis,[5] which features complete stereocontrol at three contiguous carbon centers.



As a model for the construction of the A,B rings of aphidicolin, we sought to prepare the tricyclic keto lactone 2. We envisioned that 2 might be prepared from three components, vinylogous ester 3, α-thiophenyl butenolide (4),[6] and a two-carbon fragment which might be utilized to complete the B ring.

We have found that the lithium dienolate of 3 (LDA/THF/-78 °C) reacts rapidly with 4 in THF at -95 °C to provide the adduct 5[7] as a single diastereomer in 96% yield.[8] The trans stereochemistry of α and β butyrolactone substituents was confirmed by oxidation[9] of 5 to the corresponding sulfoxide followed by thermal elimination to provide butenolide 6. The stereochemistry at C-9 and C-10 was determined as described below.

Scheme I

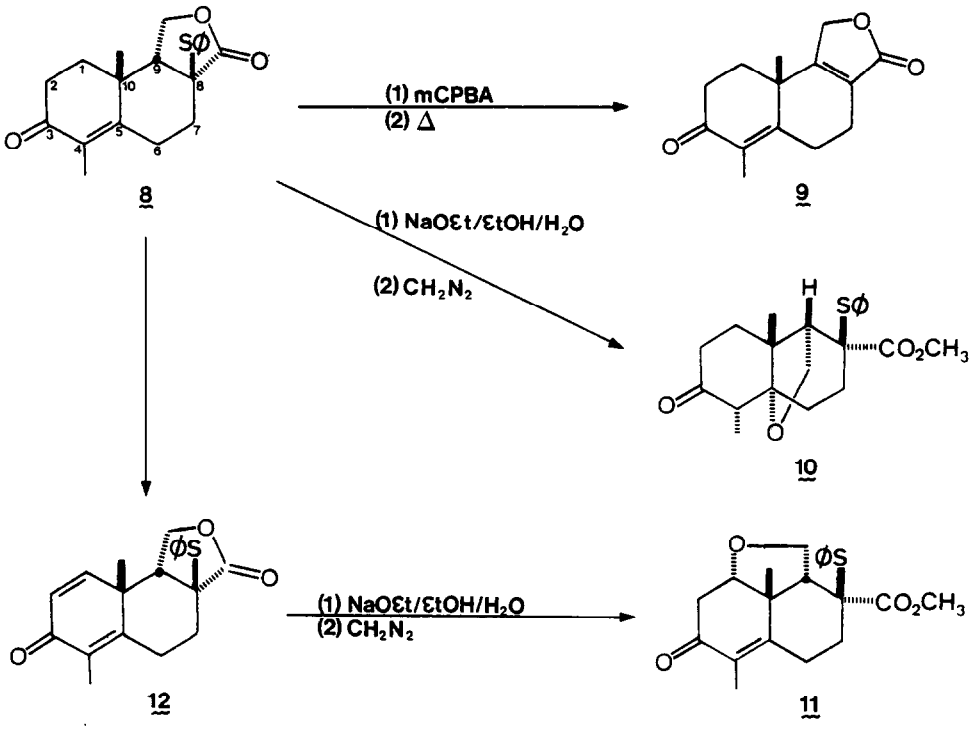


Addition of vinyllithium to 5 (2 eq., THF, 0 °C, 30 min)[10] provided the hydroxy diene 5a in 70% yield.[8] Treatment of 5a with 3% $HClO_4$/THF (30 min, 0 °C) gave dienone 7[7] quantitatively.[8] Under basic conditions ($NaOCH_3$, CH_3OH, 25 °C, 1 h), 7 cyclized[11] to the tricyclic enone 8,[7] again in quantitative yield.[8] This annulation sequence (Scheme I) may be performed in two synthetic operations in 67% overall yield: (a) Michael addition followed by in situ treatment of the enolate of 5 with vinyllithium and subsequent acidification to provide 7; (b) cyclization of 7 to the enone 8.

The stereochemical features of this transformation were elucidated as shown in Scheme II. Oxidation of sulfide 8 to the corresponding sulfoxide was followed by thermal elimination to provide butenolide 9[7] as the only product. This sequence unambiguously establishes the cis relationship[9] between C-8 thiophenyl and C-9 hydrogen in 8.

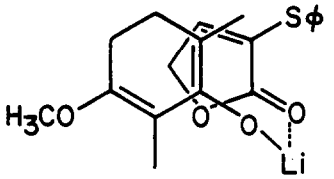
Furthermore, hydrolysis of the butyrolactone moiety of 8 followed by esterification with diazomethane provided the cyclic ether 10,[7] suggesting a cis relationship between C-9 hydrogen and C-10 methyl in butyrolactone 8. This suggestion was confirmed by the following results. Conversion of 8 to the corresponding dienol TMS ether (LDA/THF/-78 °C/TMSCl) was followed by treatment with palladium acetate to afford dienone 12.[7] Hydrolysis of 12 as before and subsequent esterification then gave cyclic ether 11[7] in high yield. Formation of 11 (equatorial H at C-1) is only possible when C-10 methyl and C-9 hydrogen are cis to one another.

Scheme II



8 9 10 12 11

The stereospecificity of the Michael addition leading to 5 is noteworthy.[12] We currently rationalize this result by invoking a lithium ion chelated transition state such as 13.[13,14]



13

Studies designed to address this hypothesis are in progress. The application of this methodology to aphidicolin total synthesis is also underway.

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References and Notes.

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(8) Yields refer to isolated, spectrally and chromatographically homogeneous material.

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(10) The first equivalent of vinyllithium serves to deprotonate the lactone moiety to provide the corresponding enolate which is inert to addition of vinyllithium.

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(13) A similar hypothesis has been advanced to rationalize the stereoselectivity of the Michael addition of phenmenthyl propionate enolate to E and Z methyl crotonates.[10c] These authors, however, apparently failed to consider the ground state conformational preferences of E and Z methyl crotonates, an ambiguity which is absent in the case of thiophenyl butenolide.

(14) This process does not appear to fully conform to the general topological rules proposed by Seebach; see Seebach, D.; Golinski, J. Helv. Chim. Acta. 1981, 64, 1413.

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