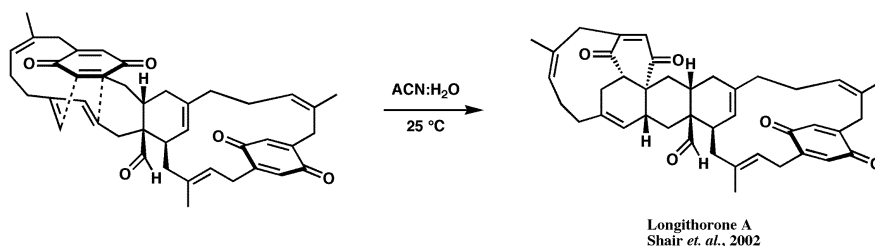
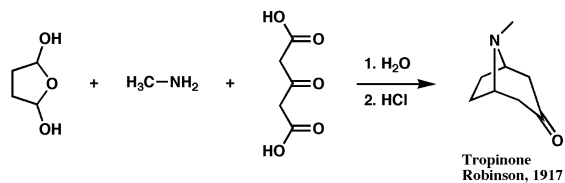


Biomimetic Synthesis of Natural Products

Literature Seminar
Eric Ashley, Stoltz Research Group
January 5, 2004



What is Biomimetic Synthesis? Who Benefits from these Studies?

A synthesis or synthetic sequence is considered biomimetic if it imitates a proposed biosynthetic pathway. A more strict definition requires that the reagents utilized for the reactions must be similar to those found in biological systems, and that the conditions must be physiologically relevant. Generally, the biosynthetic proposal must have a firm basis in known biochemical pathways, such as the biosynthesis of terpenes, polyketides, phenylpropanoids, alkaloids, or peptides.

Scientists interested in the biosynthesis of natural products often defend biomimetic synthesis as a method for proving or disproving biosynthetic proposals. Such evidence, however, is only circumstantial, and is often challenged by proponents of alternative biosynthetic routes. As a case in point, two different biosynthetic proposals have been supported by biomimetic syntheses of polyethers such as monensin. The success of both "biomimetic" routes prevents either from strongly supporting the proposed biosynthesis.

The results of biomimetic reactions have also provided evidence of enzyme participation in certain biosynthetic steps. For example, reactions that require elevated temperatures or strong reagents, or that proceed with diminished or alternative selectivity, are often cited as evidence that an enzyme conducts the reaction *in vivo*.

Synthetic chemists may be the primary beneficiaries of biomimetic studies. Biosynthetic proposals routinely result in highly efficient and elegant syntheses of otherwise daunting natural products.

Lead reviews: *Angew. Chem. Int. Ed.* **2004**, *43*, 160-181.

Nat. Prod. Rep. **2000**, *17*, 349-366.

Angew. Chem. Int. Ed. **2003**, *42*, 3078-3115.

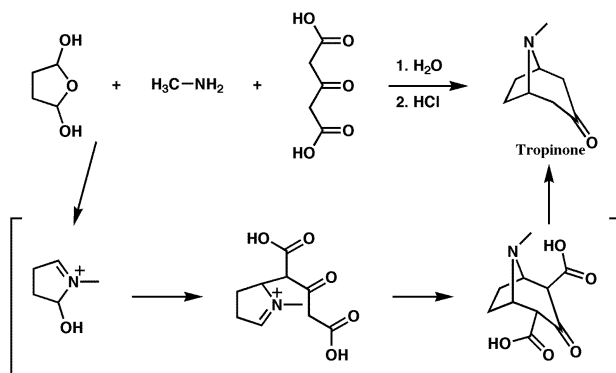
A Scifinder search for "biomimetic synthesis" refined for journal type=review lists 372 references.

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The First Biomimetic Synthesis

Sir Robert Robinson coined the term "biomimetic synthesis" in his 1917 paper describing his synthesis of Tropinone from succinaldehyde, methyl amine, and acetone dicarboxylic acid.

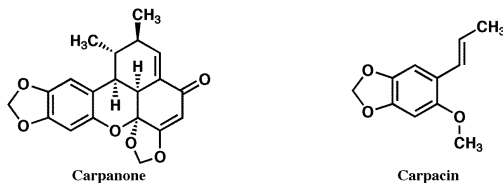


Although the full biosynthesis of tropinone remains unclear, studies indicate that a pyrrolinium moiety is attacked and cyclized by an acetate derived unit similar to Robinson's acetonedicarboxylic acid.

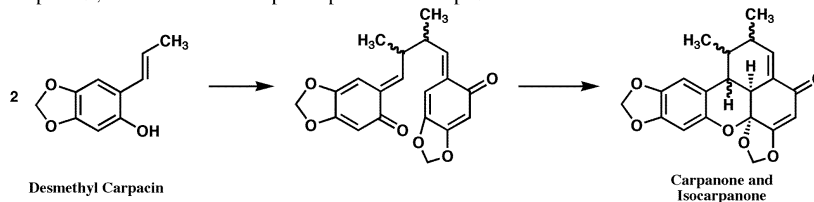
J. Chem. Soc. **1917**, 111, 762-768 and 876-899.
Nat. Prod. Rep. **2001**, 18, 494-502.

Carpanone

The hexacyclic lignan carpanone has the molecular formula $C_{22}H_{18}O_6$, indicating that it could be a dimer of a simpler C_{11} compound. The authors of the isolation paper note that carpacin is found in the same plant as carpanone. Interestingly, natural carpanone shows no optical activity. Furthermore, a minor isolate, isocarpanone, seems to differ from carpanone only by relative stereochemistry.



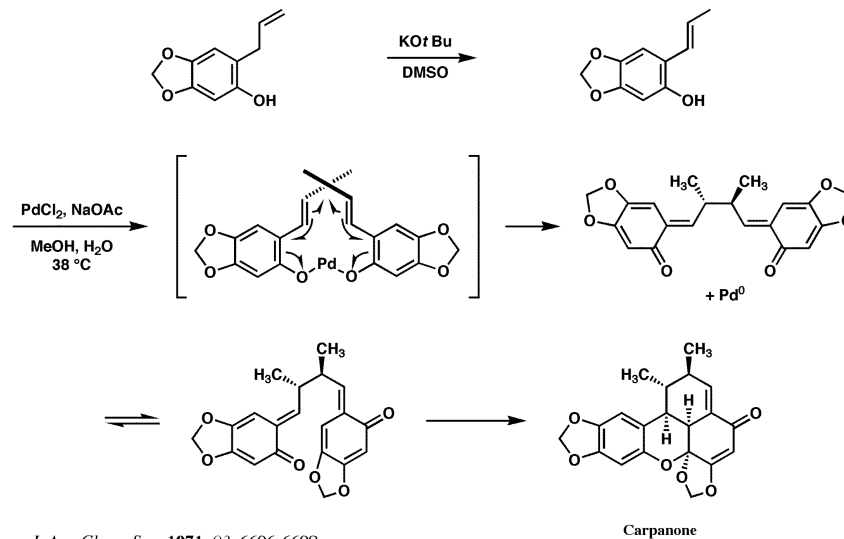
The authors therefore suggested that both carpanone and isocarpanone could arise via $\beta\beta$ -phenolic coupling of desmethyl carpacin followed by Diels-Alder cyclization. The C_2 coupled product provides carpanone, while the meso compound provides isocarpanone.



Tetrahedron Lett. **1969**, 59, 5159-5162.

Carpanone

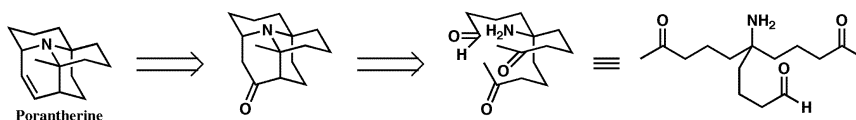
Only two years after the isolation and biosynthetic hypothesis had been published, Chapman completed the total synthesis of carpanone via a biomimetic route.



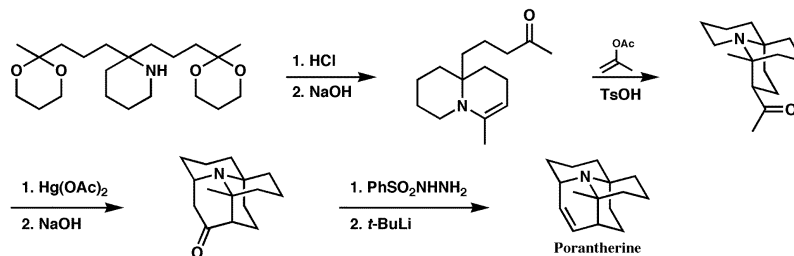
J. Am. Chem. Soc. **1971**, 93, 6696-6698.

Porantherine

The alkaloid porantherine is likely polyketide in origin. Successive mannich cyclizations of a tricarbonyl precursor (or its equivalent) were proposed to yield the natural product



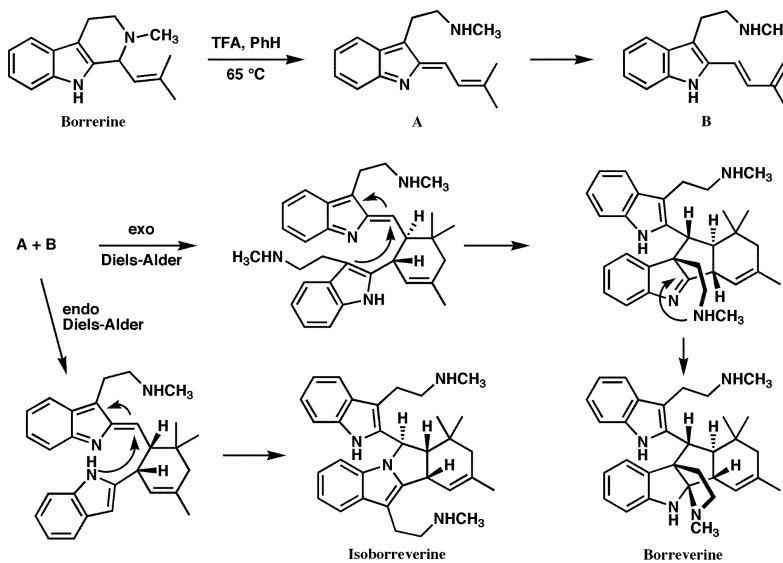
Synthetically, Ryckman began with with the functionalized piperidine, and employed a late stage oxidation to generate the aldehyde equivalent.



J. Am. Chem. Soc. **1987**, *109*, 4940-4948.

A similar strategy was pursued by E. J. Corey: *J. Am. Chem. Soc.* **1974**, *96*, 6516-6517.

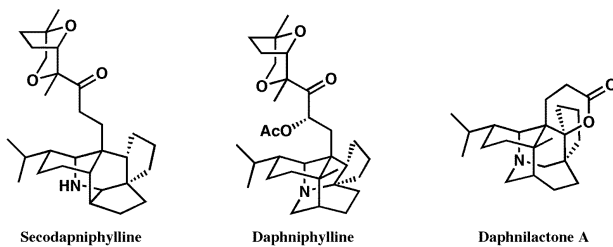
Borreverine and Isoborreverine



Dimers Borreverine and Isoborreverine are found with Borrerine. Warming Borrerine under acidic conditions leads to both dimers. Further heating causes equilibration that favors Isoborreverine.

J. Chem. Soc., Chem. Commun. **1978**, 826-828.

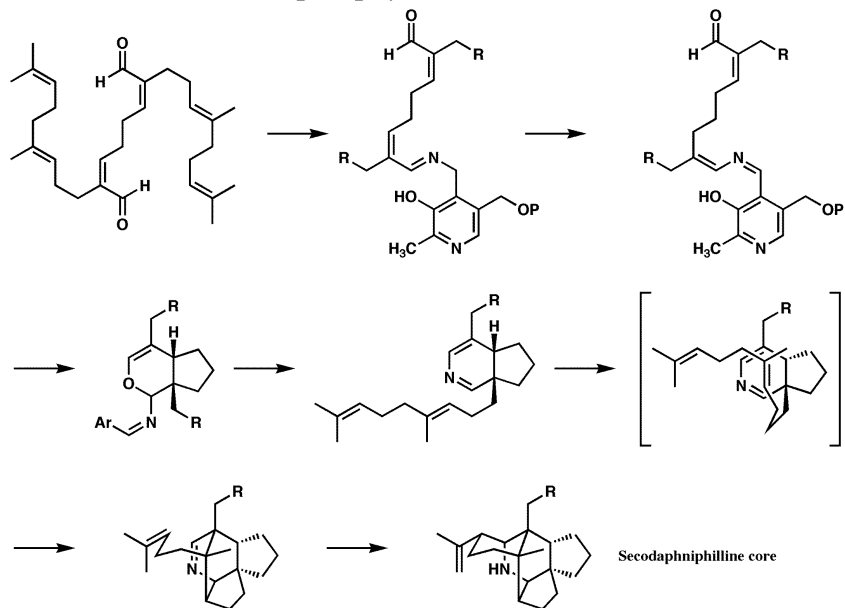
Daphniphyllum Alkaloids



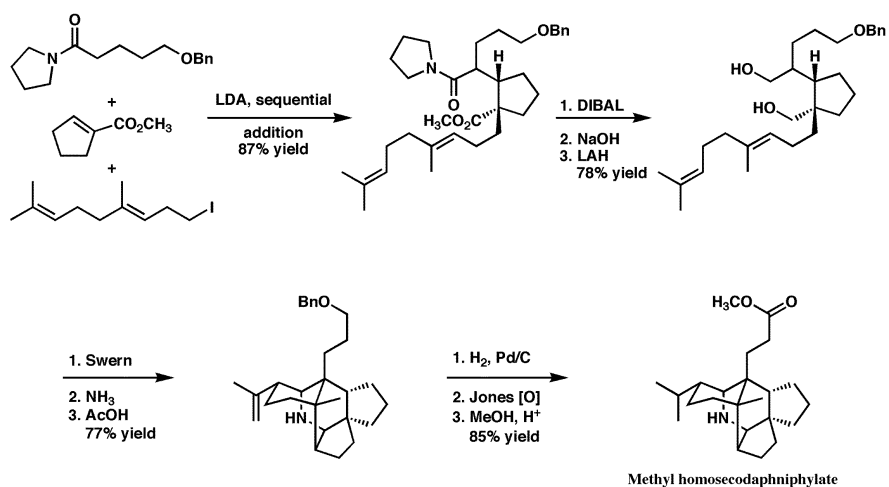
The daphniphyllum alkaloids, three of which are shown, were known to be derived from squalene. Heathcock proposed the conversion of squalene to a dialdehyde, which is converted to the secodaphniphylline skeleton by condensation with an ammonia equivalent followed by a series of cyclization reactions. A ring opening/ring closing isomerization provides the daphniphylline structure, and ring opening followed by condensation with a formaldehyde equivalent leads to the daphnilactone core. Heathcock's work on these molecules exemplifies his later comment on biomimetic synthesis: "For all natural products, there exists a synthesis from ubiquitous biomolecules. The inherent interconnectivity of natural products implies that a truly biomimetic total synthesis represents a general solution not to the preparation of a compound but to the preparation of all similarly derived natural products (discovered and undiscovered)."

Pure Appl. Chem. **1989**, *61*, 289-292.
Org. Lett. **2001**, *3*, 4323-4324.

Daphniphyllum Alkaloids

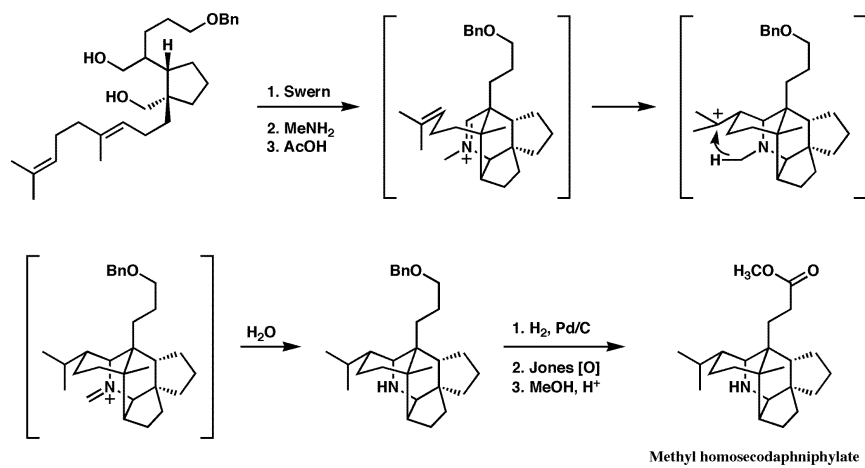


Daphniphyllum Alkaloids



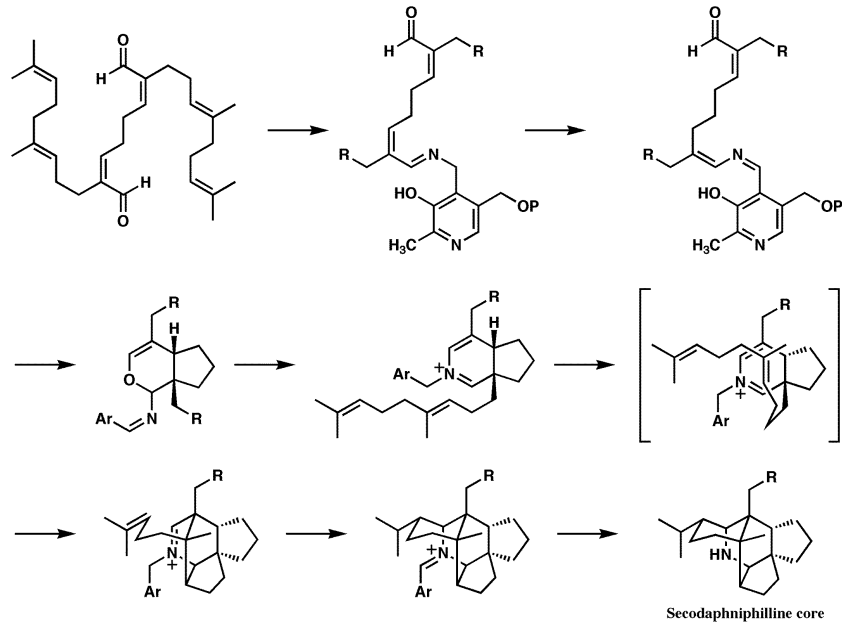
J. Am. Chem. Soc. **1988**, *110*, 8734-8736.

Daphniphyllum Alkaloids



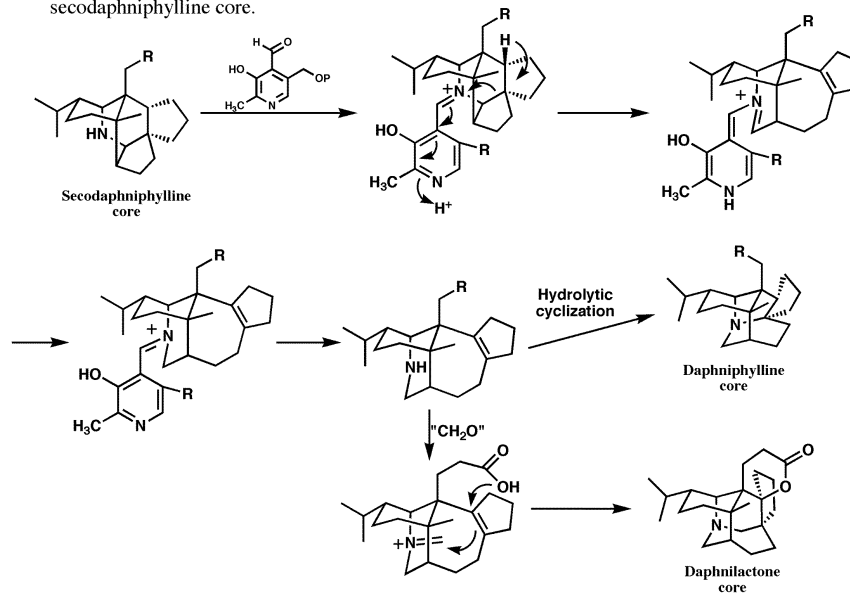
Interestingly, a mistaken utilization of methylamine rather than ammonia provided the saturated pentacycle.
J. Org. Chem. **1992**, *57*, 2544-2553.

Daphniphyllum Alkaloids

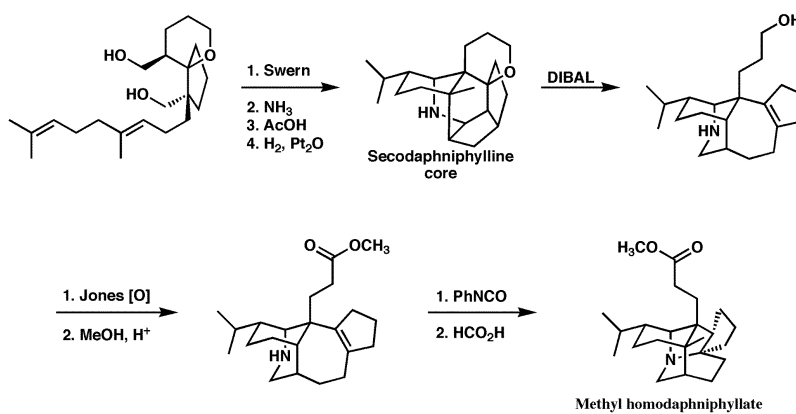


Daphniphyllum Alkaloids

Heathcock proposed that the daphniphylline and daphnilactone structures would arise from the secodaphniphylline core.



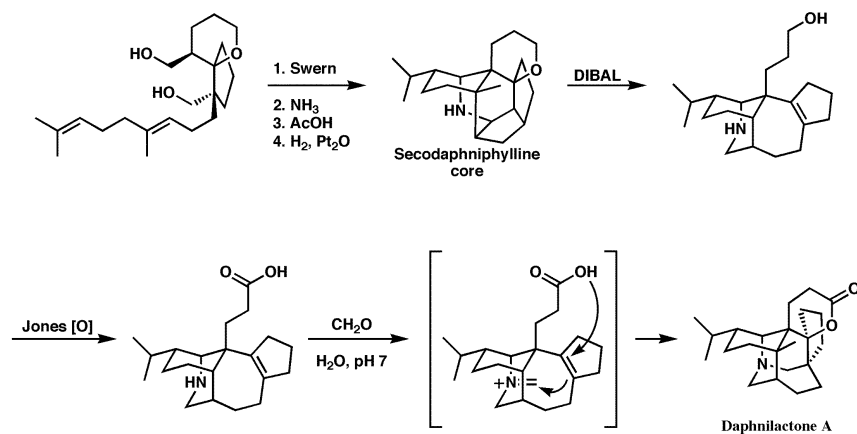
Daphniphyllum Alkaloids



Heathcock was able to fragment the secodaphniphylline core by inserting a leaving group at the 6,5 ring fusion. After formation of a urea, ring closure under acidic conditions provided the daphniphylline core.

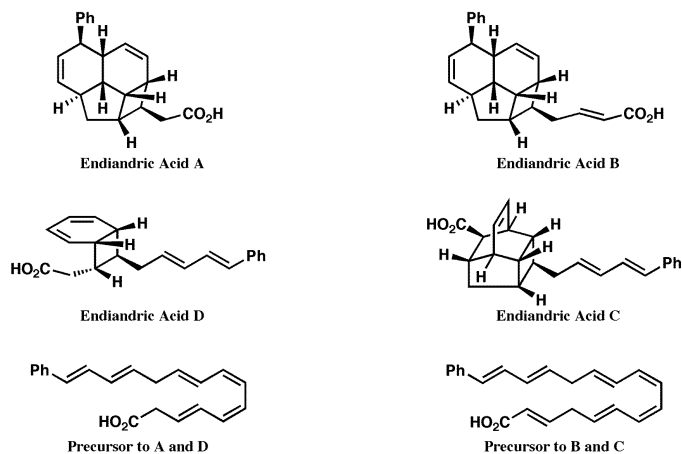
J. Org. Chem. **1992**, *57*, 2585-2594.

Daphniphyllum Alkaloids



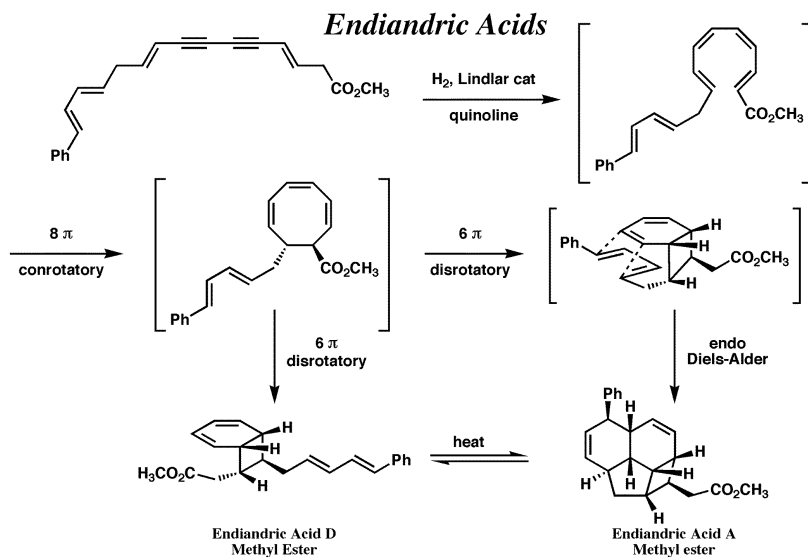
Alternatively, treatment of the ring opened compound with formaldehyde leads directly to daphnilactone A.

Endiandric Acids



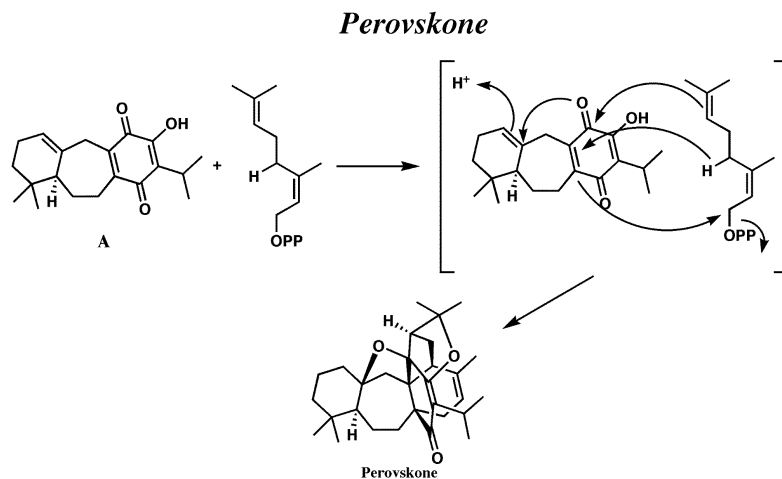
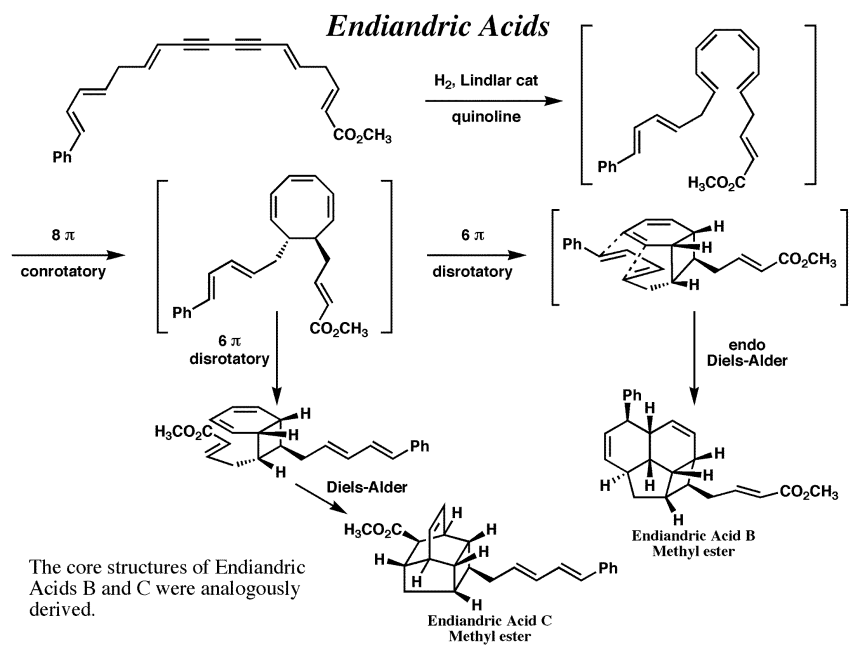
Endiandric Acids A-D were isolated from a variety of Lauraceae trees indigenous to Australia. The natural products were racemic mixtures. Banfield proposed that these compounds could arise via a series of pericyclic reactions from the acyclic, polyketide-derived polyenes shown.

J. Chem. Soc., Chem. Commun. **1980**, 902-903.

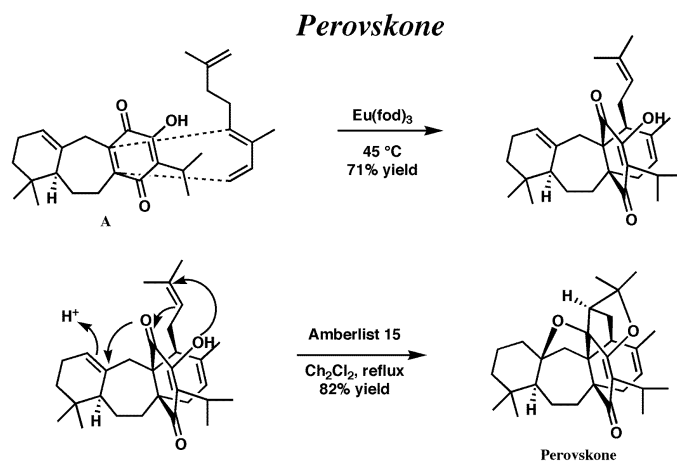


Nicolaou synthesized the polyene and found that it rapidly converted to the natural product core structures. Further, the two products interconvert when heated.

J. Am. Chem. Soc. **1982**, *104*, 5558-5560 and 5560-5562.

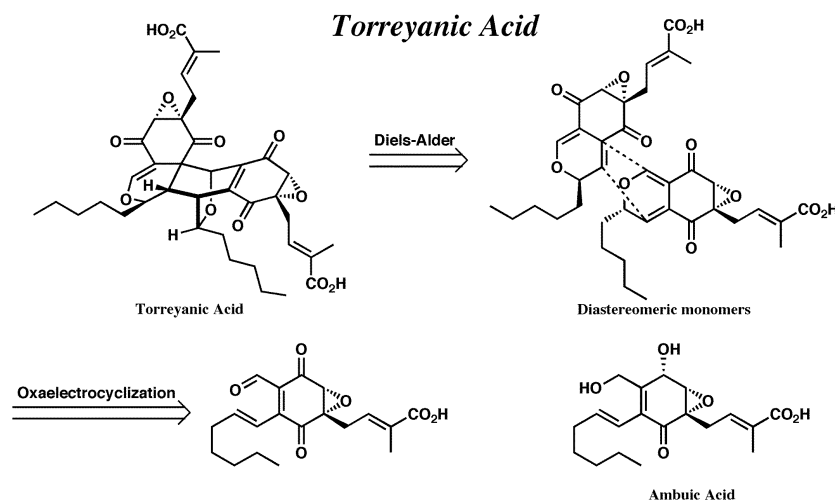


J. Org. Chem. **1992**, *57*, 4339-4340.



The essence of the biosynthetic proposal was carried out by treating A with *trans*- α -ocimene under Lewis acidic conditions to promote the Diels Alder cyclization. Subsequent treatment with protic acid formed the natural product.

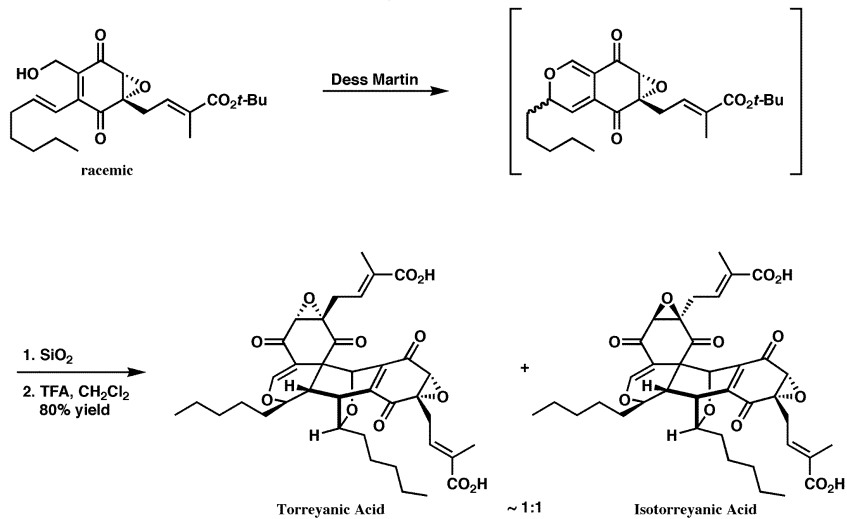
J. Am. Chem. Soc. **1994**, *116*, 4979-4980.



In the isolation paper, Clardy noted that Torreyanic Acid could arise by a Diels-Alder dimerization of diastereomeric monomers. Both diastereomers could arise via electrocyclization of an epoxyquinone aldehyde. In the biomimetic synthesis paper, Porco notes that Ambuic Acid was isolated from the same source, further supporting the proposed biosynthesis

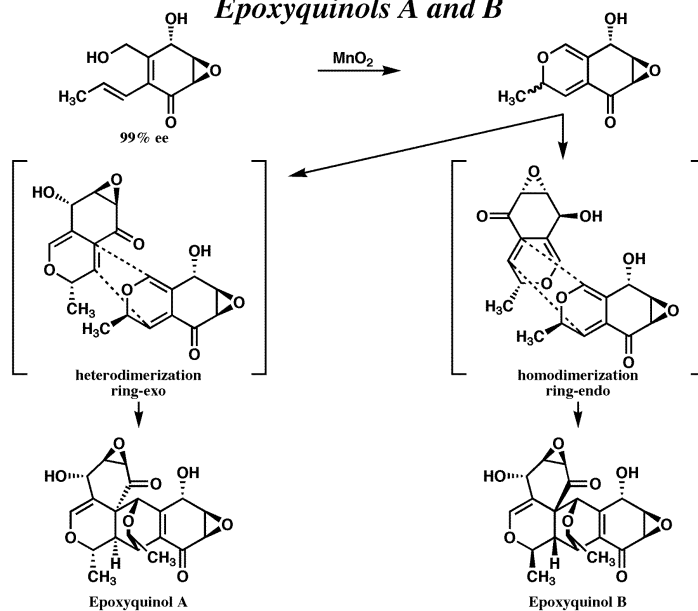
J. Org. Chem. **1996**, *61*, 3232-3233.
J. Am. Chem. Soc. **2000**, *122*, 10484-10485.

Torreyanic Acid



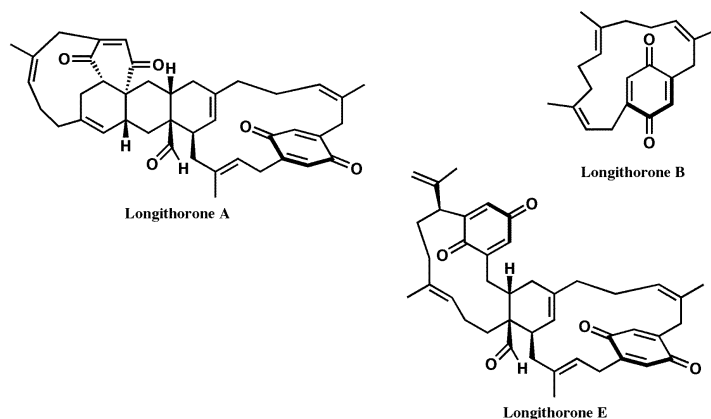
Oxidation of the racemic alcohol lead cleanly to the pyran as a mixture of diastereomers. The pentyl side chains provided the expected facial selectivity in the Diels-Alder cyclization, but the dimerization of monomers from enantiomeric series allowed the formation of Isotorreyanic Acid.

Epoxyquinols A and B



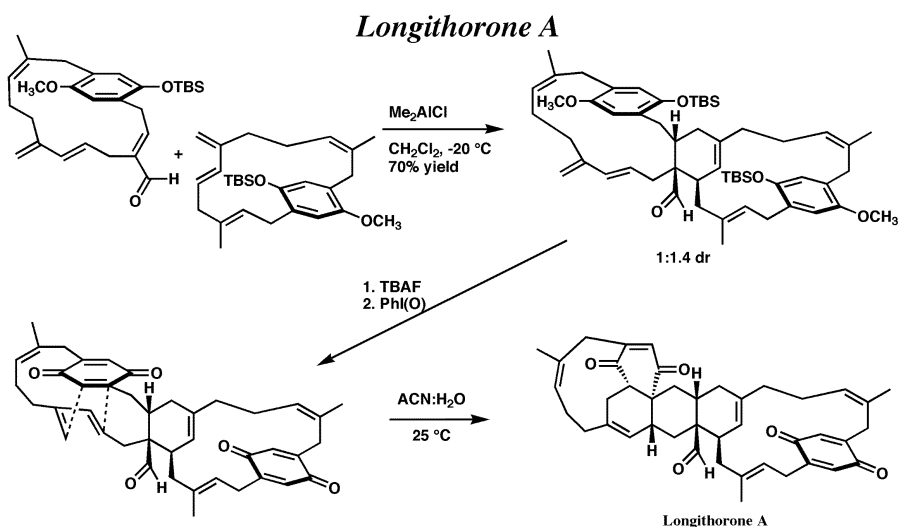
Angew. Chem. Int. Ed. 2002, 41, 3192-3194.

Longithorone A



The unique, polycyclic terpene-derived natural product Longithorone A was identified by the isolation chemists as a probable dimer of cyclo-fanesylated benzoquinones. A subsequent transannular Diels-Alder reaction was proposed for construction of the remaining cyclohexanes. In a subsequent paper, the authors disclosed several monomeric structures (e.g. Longithorone B) as well as dimers that had not undergone transannular cyclization (e.g. Longithorone E).

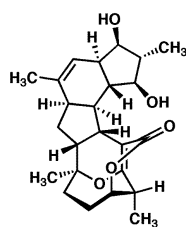
J. Am. Chem. Soc. **1994**, *116*, 12125-12126.
J. Org. Chem. **1997**, *62*, 3810-3819.



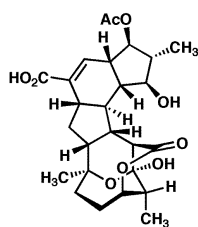
To test the biosynthetic hypothesis, Shair synthesized the requisite paracyclophanes. The first Diels-Alder reaction required lewis acid catalysis and failed to provide good facial selectivity, indicating that a dielsalderase enzyme may be involved in the biosynthesis. The transannular cyclization proceeded without forcing conditions

J. Am. Chem. Soc. **2002**, *124*, 773-775.

FR182877

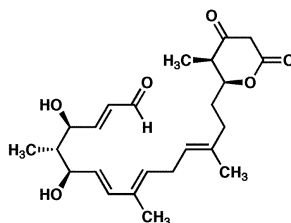


FR182877



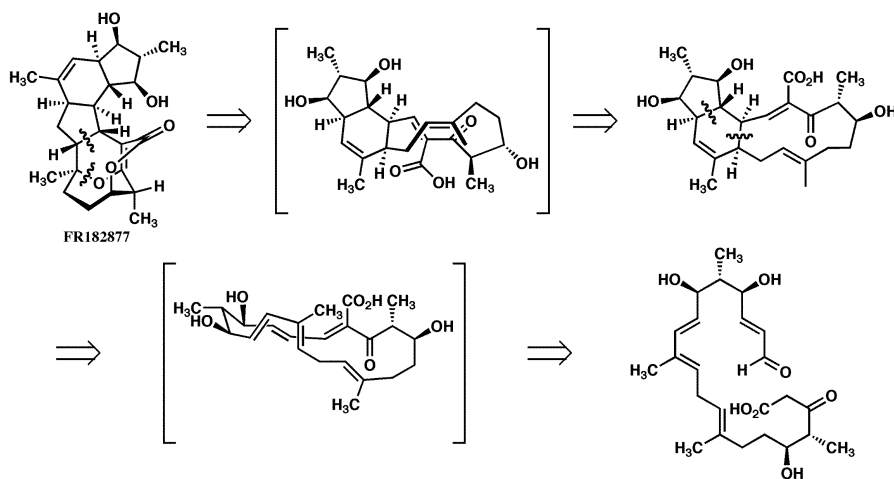
Hexacyclinic acid

FR182877 and the related natural product hexacyclinic acid were isolated separately in 1998 and 2000, respectively. Isotope feeding studies showed that hexacyclinic acid is derived from alternating acetate and propionate units via a polyketide pathway. In 1999, Soresen proposed that FR182877 could arise from an acyclic precursor via a polycyclization pathway that proceeded through Diels-Alder, Knoevenagel, and hetero Diels-Alder reactions. An endo transition state in the first Diels-Alder would lead to FR182877, while an exo pathway would provide hexacyclinic acid.



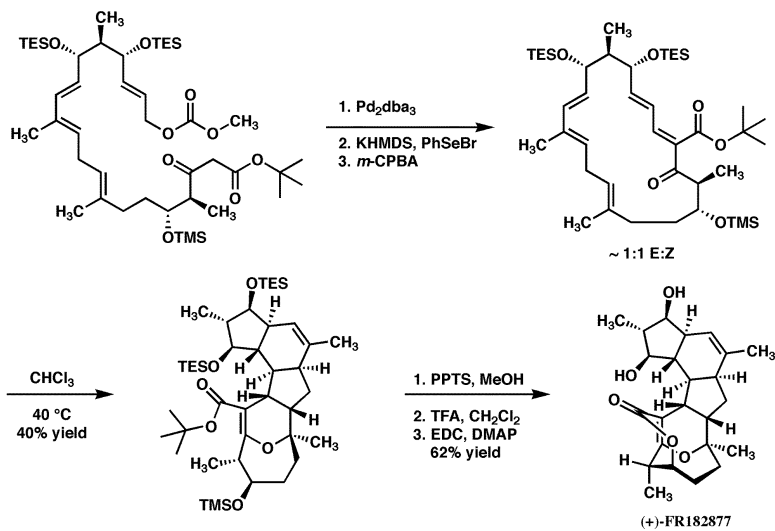
Org. Lett. **1999**, *1*, 645-648.

FR182877



After extensive experimentation, it was realized that macrocycle formation was necessary prior to pericyclic cyclization. Further, the lactone ring could not be installed until the pentacyclic core had been formed. The biosynthetic proposal was modified accordingly and reported with the total synthesis.

FR182877



Vosburf, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552-4553.

A nearly identical synthesis was subsequently reported by Evans and Starr. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787-1790.