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Pseudosymmetry in Azabicyclo[2.1.1]hexanes. A Stereoselective Construction of the Bicyclic Core of Peduncularine

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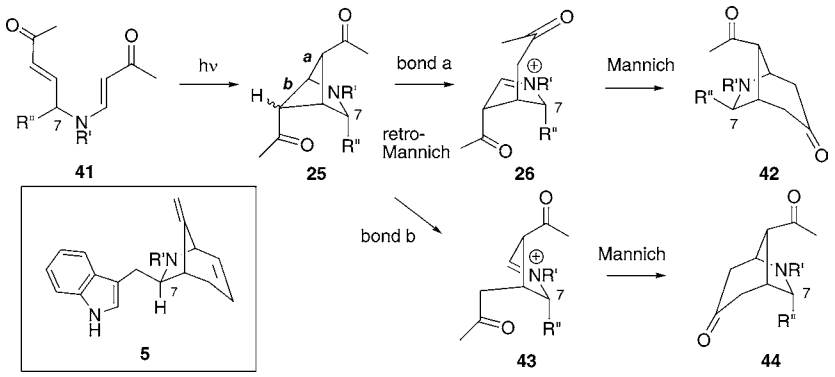
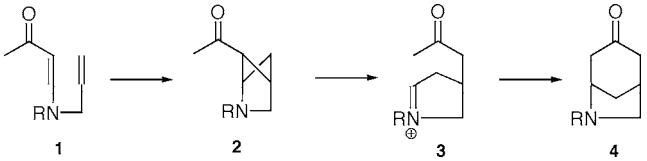
ABSTRACT



Intramolecular photocycloaddition of 41 or its equivalent leads to the formation of photoadduct 25. While retro-Mannich fragmentation of the "b" bond in 25 leads to the formation of 44 (via 43), with the incorrect relative stereochemistry for the synthesis of peduncularine 5, selective fragmentation of the "a" bond in 25 leads to the formation of 42 (via 26) with the correct relative stereochemistry for the synthesis of 5.

The inversion of configuration at a stereogenic center permits the transformation of a relative stereochemical relationship in a given structure. We report herein that such a net inversion of configuration can be achieved via recognition of the pseudosymmetry of the photoadduct **2** in the crossed vinylogous amide photocycloaddition cascade that we have recently described[1] (Scheme 1). We have developed this concept in the course of the application of the photochemical cascade outlined in Scheme 1 to an approach to the synthesis of the *Aristotelia* alkaloid peduncularine **5**,[2,3] as outlined retrosynthetically in Scheme 2. We reasoned that the target structure **5** could be obtained by reduction and dehydration of ketone **6**, which should be available from Mannich closure of unsaturated ketoiminium **7**, the product of the retro-Mannich fragmentation of photoadduct **8**. We envisioned that **8** could be obtained on irradiation of **9**, the absolute

Scheme 1. Synthesis of Azabicyclooctanones via Vinylogous Amide Photocycloaddition



[†] Recipient of the Eli Lilly Graduate Predoctoral Fellowship, 2002−2003.

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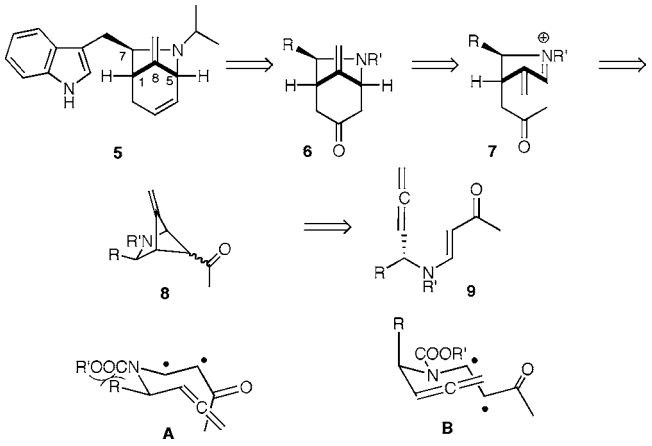
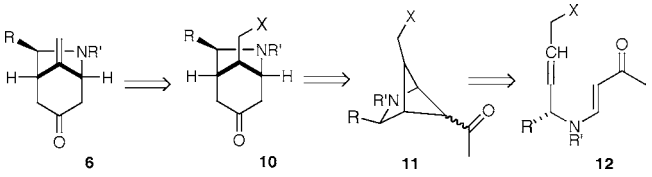
Scheme 2. Retrosynthetic Analysis for the Synthesis of Peduncularine



stereochemistry of which would be readily obtained from L-tryptophan. Photocycloaddition of **9** should proceed stereoselectively to give **8** with R′ = COOR′ based on our analysis of conformations A and B. A[1,3] strain as indicated in A should promote the pseudoaxial orientation of the indolylmethyl group R, leading to the stereochemical outcome represented in **8**.

Scheme 3. Revised Retrosynthetic Analysis with an Allene Surrogate



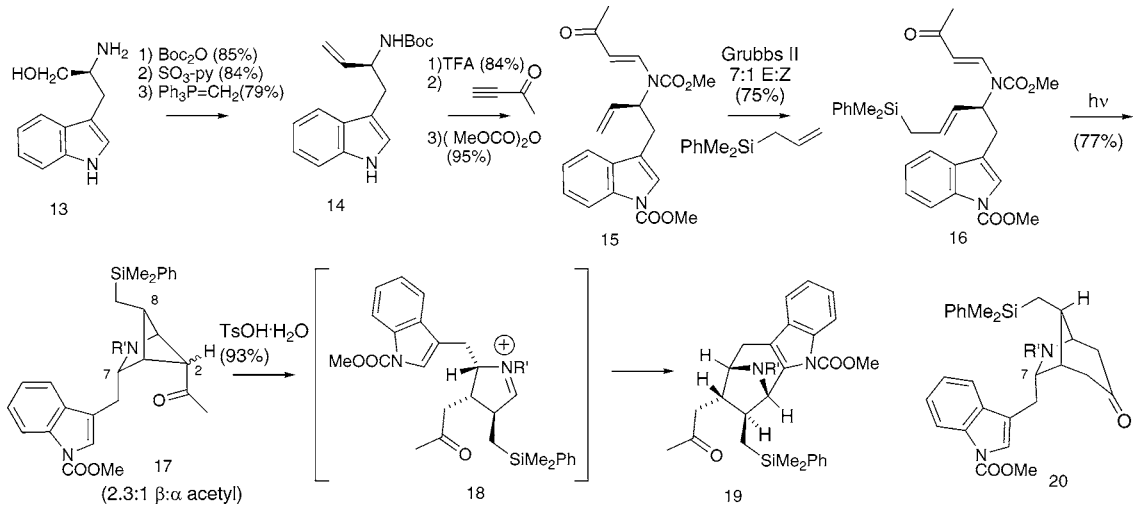
We have recently established that the methylene-substituted photoadducts **8** that result from the crossed photocycloaddition of allenes with vinylogous imides, i.e., **9**, cannot be readily converted to the azabicyclo[3.2.1]octanone ring system, i.e., **6**, a result that can be attributed to the instability of the unsaturated iminium intermediate **7** that results from the retro-Mannich fragmentation of **8**. We have therefore modified the retrosynthetic analysis to include a surrogate (XCH_2) for the exocyclic methylene in **6**, i.e., **10** (Scheme 3).

The synthesis of the requisite photosubstrate corresponding to **12** is outlined in Scheme 4. Boc protection of L-tryptophanol[4] **13** followed by Parikh−Doering oxidation and Wittig methylenation of the derived aldehyde afforded *N*-Boc vinyltryptamine **14**. Boc removal, followed by reaction of the resulting primary amine with 3-butyn-2-one and carboxylation of the resulting vinylogous amide with dimethyl pyrocarbonate gave vinylgous imide **15**. Cross-metathesis of **15** with allyl phenyldimethylsilane in the presence of the second-generation Grubbs catalyst[5] afforded **16**, as a 7:1 mixture of *E:Z* stereoisomers in 75% yield. Irradiation of (*E*)-**16** afforded **17** as a 2.3:1 ratio of acetyl epimers, both of which contain the incorrect C-7 relative stereochemistry for the synthesis of peduncularine. Attempted isomerization of **17** to **20** via retro-Mannich fragmentation of **17** followed by Mannich closure gave none of the desired bicyclic ketone **20** but instead afforded the Pictet−Spengler product **19** in excellent yield.

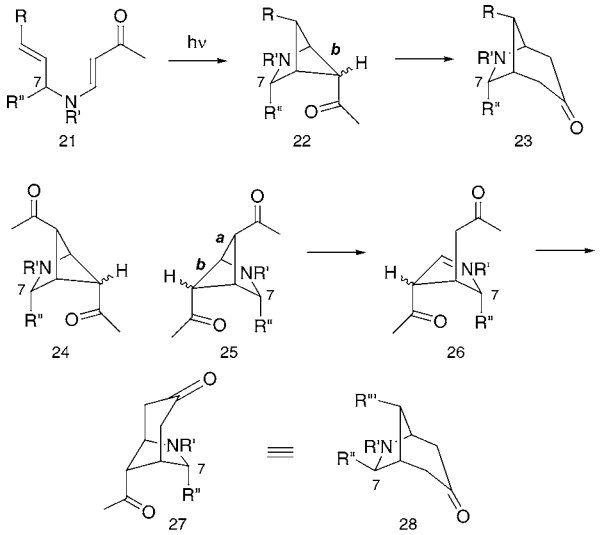
These studies established both the incompatibility of the indole moiety with the retro-Mannich/Mannich cascade and the selective formation of the undesired C-7 stereochemistry in the formation of photoadduct **17**. The application of the vinylogous imide photoaddition sequence to the synthesis of peduncularine therefore depends on the "epimerization" of the C-7 stereocenter in **17**. Although **17** is formed as a mixture of epimers at the C-2 acetyl-bearing carbon, only the indicated C-8 stereochemistry in **17** was observed.

This analysis led us to a pseudosymmetry approach to stereochemical control in this system. In the prototypical crossed photocycloaddition, as indicated in Scheme 5,

Scheme 4. Synthesis and Photocycloaddition of **16**



Scheme 5. Pseudosymmetry in the Azabicyclohexane Photoadduct

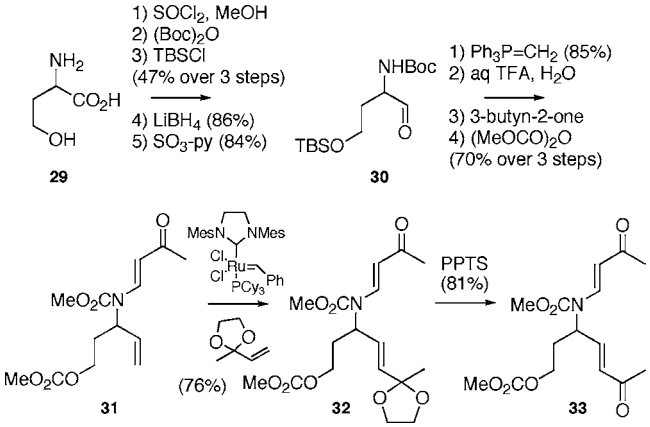


irradiation of **21** should lead to the selective formation of **22**, based on the formation of **17** from **16** (Scheme 4). Retro-Mannich fragmentation of **22** followed by Mannich closure would generate the azabicyclic ketone **23** with the undesired C-7 stereochemistry. We note however that an element of symmetry, i.e., pseudosymmetry, can be introduced if R = Ac in **22** as shown in **24**. Retro-Mannich fragmentation of **25**, the enantiomer of **24**, could then proceed through one of two possible regiochemical pathways, via the fragmentation of bond "a" or bond "b" of **25**, respectively. In the case of **22**, only the "b" bond fragmentation pathway is available. However, retro-Mannich cleavage of the "a" bond in **25** could generate ketoiminium **26**. Mannich closure of **26** would then afford **27**, which can be redrawn as **28**, the azabicyclic ketone with the requisite C-7 stereochemistry for the synthesis of peduncularine. The acetyl group in **27**, shown as R‴ in **28**, would then serve as the precursor for the exocyclic methylene of peduncularine.

Finally, the ready formation of Pictet−Spengler product **19** in Scheme 4 at the expense of the desired Mannich cyclization suggested that an indole precursor or surrogate should be used to preclude the formation of products corresponding to **19** (Scheme 4).

To test the viability of the pseudosymmetry approach to the synthesis of the peduncularine ring system, we prepared photosubstrates **32** and **33** as outlined in Scheme 6. Esterification of D,L-homoserine (in which the hydroxyethyl group was intended to faciliate the introduction of the indole moiety after the photochemical cascade), followed by carbamate formation [$(Boc)_2O$], silyl ether formation, ester reduction, and Parikh−Doering oxidation, gave aldehyde **30**, which,

Scheme 6. Preparation of Photosubstrates **32** and **33**

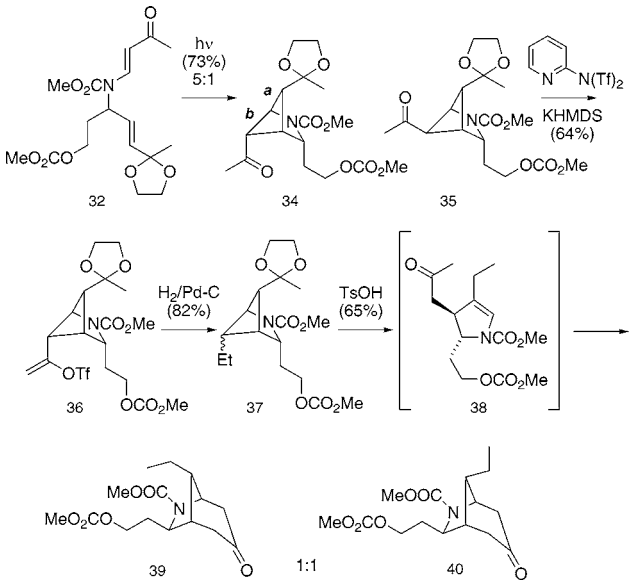


on Wittig methylenation, deprotection, reaction with butynone, and protection of the resulting vinylogous amide with dimethylpyrocarbonate, afforded **31**. Cross-metathesis reaction of **31** with 2-methyl-2-vinyl-1,3-dioxolane in the presence of the second-generation Grubbs catalyst afforded selectively protected **32**, which gave **33** upon removal of the ketal protecting group.

Irradiation of **33** (Scheme 6) should generate a photoadduct corresponding to **25** (Scheme 5) that would allow us to examine the regioselectivity of the retro-Mannich fragmentation of **25** (via bond "a" or "b"). Alternatively, irradiation of **32** would give **34** (Scheme 7), a selectively protected analogue of **25**. Manipulation of the "b" acetyl moiety in **34**, followed by liberation of the "a" acetyl group, would lead to selective fragmentation of the "a" bond in **25** (or **34**, Scheme 7).

Although irradiation of **33** led to none of the desired bisacetyl photoadduct corresponding to **25** (Scheme 5),

Scheme 7. Pseudosymmetry Approach to the Stereoselective Construction of the Peduncularine Ring System



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photocycloaddition of **32** gave a good yield of a 5:1 mixture of **34** and **35**, epimeric only at the acetyl-bearing carbon (Scheme 7). Elaboration of **34**/**35** to the bicyclic ring system of peduncularine then proceeded via enol triflate formation using Comins' reagent to give **36**, followed by reduction to give **37**. Treatment of **37** with *p*TsOH·H_2O in ethanol led to the formation of a 1:1 mixture of **39** and **40**, epimeric at the ethyl bearing carbon but with the requisite C-7 stereochemistry for the synthesis of peduncularine.

We have demonstrated that the pseudosymmetry analysis leads to the establishment of the stereochemically controlled synthesis of the peduncularine ring system. The application of this approach to the synthesis of peduncularine and related compounds is currently underway in our laboratory, and our results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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