

Tandem Photocycloaddition–Retro-Mannich Fragmentation of Enaminones. A Route to Spiropyrrolines and the Tetracyclic Core of Koumine

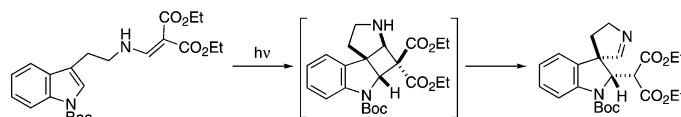
James D. White* and David C. Ihle

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@oregonstate.edu

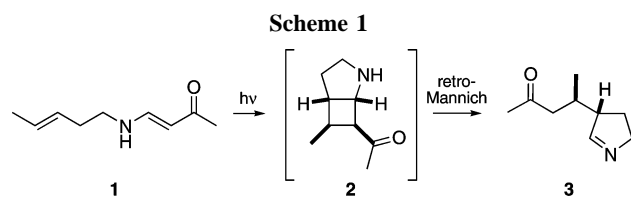
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ABSTRACT



Intramolecular [2 + 2] photocycloaddition of β -aminoalkylidene malonates gives transiently a cyclobutane which undergoes retro-Mannich fragmentation to a Δ^1 -pyrroline. The tandem sequence, exemplified in two series based on tryptamine and aminoethyl-1,4-cyclohexadiene, leads to a spiroindolopyrroline skeleton and to the nonindolenine portion of koumine.

Enaminones (vinylogous amides) are photochemically reactive, and when irradiated they undergo [2 + 2] cycloaddition with an alkene to generate a cyclobutane.^{1,2} The intramolecular variant of this photocycloaddition (Scheme 1) is also



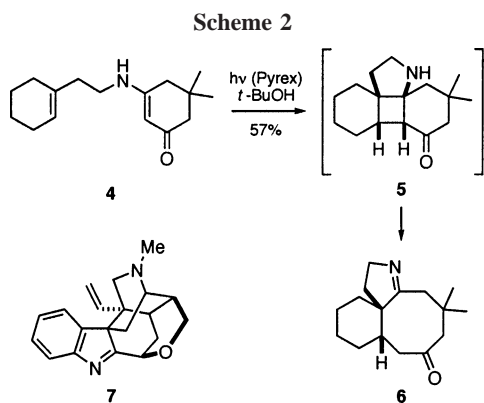
known.^{3–5} Ring strain generated in the conversion of **1** to **2** can lead to fragmentation of the cyclobutane via a retro-

Mannich reaction, with the result that a Δ^1 -pyrroline (**3**) is formed in a stereodefined manner.

The overall conversion **1** \rightarrow **3** is the intramolecular nitrogen counterpart of a process first described by De Mayo, in which an enolic β -diketone undergoes [2 + 2] photocycloaddition with an alkene followed by retro-aldol fragmentation of the intermediate cyclobutane to produce a 1,5-diketone.⁶ An early example of the process shown in Scheme 1 was reported by Schell, who showed that irradiation of **4** through Corex glass led initially to tetracycle **5** and then to the cyclooctanone **6** (Scheme 2).⁷ Application of this tandem sequence has been made by Winkler in syntheses of several alkaloids, including mesembrine,⁸ perhydrohistrionicotoxin,⁹ vindorozine,¹⁰ and manzamine A,¹¹ and Swindell has used the method for construction of the taxane BC subunit.¹²

(1) Bohme, E. H.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1965**, 2441.
 (2) Cantrell, T. S. *Tetrahedron* **1971**, 27, 1227.
 (3) Wiesner, K.; Musil, V.; Wiesner, K. J. *Tetrahedron Lett.* **1968**, 5643.
 (4) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, 40, 2702.
 (5) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E.; Thiessen, W. E. *J. Org. Chem.* **1979**, 44, 1380.

(6) De Mayo, P. *Acc. Chem. Res.* **1971**, 4, 41.
 (7) Schell, F. M.; Cook, P. M. *J. Org. Chem.* **1984**, 49, 4067.
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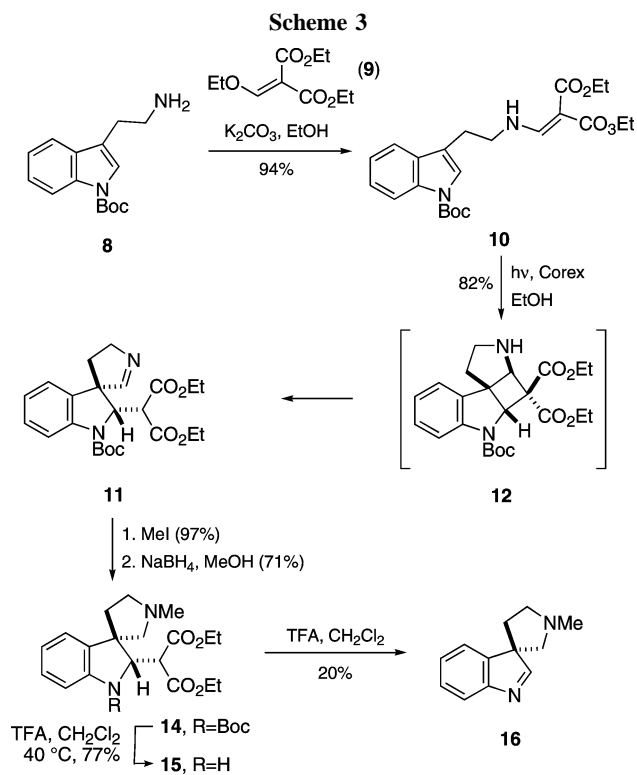


However, the scope of the intramolecular photocycloaddition–retro-Mannich process has received less attention than the De Mayo reaction despite the opportunities it presents for preparing a diverse set of nitrogen heterocycles with good stereocontrol.

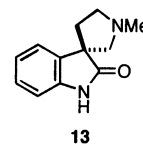
We now report the results of a study which demonstrate that the intramolecular [2 + 2] photocycloaddition–retro-Mannich construct can be applied to substrates based on tryptamine and β -phenethylamine templates. Among other attributes, this chemistry has provided entry to the core structure of the indolenine alkaloid koumine (**7**).¹³

Our initial studies focused on the intramolecular photocycloaddition of β -amino-substituted alkylidene malonates on the premise that a sequence akin to that in Scheme 1 would yield a product in which the ester groups could be differentiated and therefore modified in selective fashion. The protected tryptamine **8** was condensed with diethyl β -ethoxymethylidene malonate (**9**) under basic conditions to afford **10**,¹⁴ which was irradiated through Corex glass with a 450 W Hanovia mercury lamp (Scheme 3). After 7 h, reaction was complete and the spiroindolopyrrolidine **11** was isolated in high yield. The intermediate tetracycle **12** could not be detected in this reaction, presumably because retro-Mannich fragmentation occurred as soon as **12** was formed, but a subsequent experiment provided circumstantial evidence that **12** was indeed the initial product from **10** (vide infra). Only a single stereoisomer of **11** was produced from **10**, reflecting the uniquely defined configuration around the tetrasubstituted cyclobutane of **12**. This result appears to eliminate a stepwise radical mechanism initiated by attack of the photoexcited alkylidene malonate at the indole 3-position.

Alkaloids of the spiroindolopyrrolidine family,¹⁵ such as the oxindole coerulecine **13**,¹⁶ generally bear a methyl substituent on the pyrrolidine nitrogen. Introduction of this



methyl substituent into **11** was accomplished by N-alkylation with methyl iodide followed by reduction of the resulting iminium iodide with sodium borohydride to furnish **14**.



Removal of the Boc protection from **14** with trifluoroacetic acid afforded a good yield of **15**, but also led to a minor amount of spiroimine **16** in which the malonate residue was absent. The latter product is apparently the result of a further retro-Mannich fragmentation of **15**.

A useful extension of the sequence shown in Scheme 3 would be incorporation of an alkyl substituent at C2 of the spiroindolopyrrolidine **15** since this could potentially offer a new route to the family of Strychnos alkaloids¹⁷ that includes, for example, akuammicine (**17**).¹⁸ To that end, protected tryptamine **8** was condensed with alkylidene malonate **18** to give **19** (Scheme 4). Irradiation of **19** through Pyrex again afforded a single spiroimine **20**, presumably via cyclobutane **21**. Reduction of **20** with sodium cyanoborohydride yielded **22** as a single epimer resulting from delivery of hydride to the less hindered face of the imine.

Our strategy for assembling the nonindolenine portion **23** of koumine (**7**) envisioned cyclization of octahydroisoquino-

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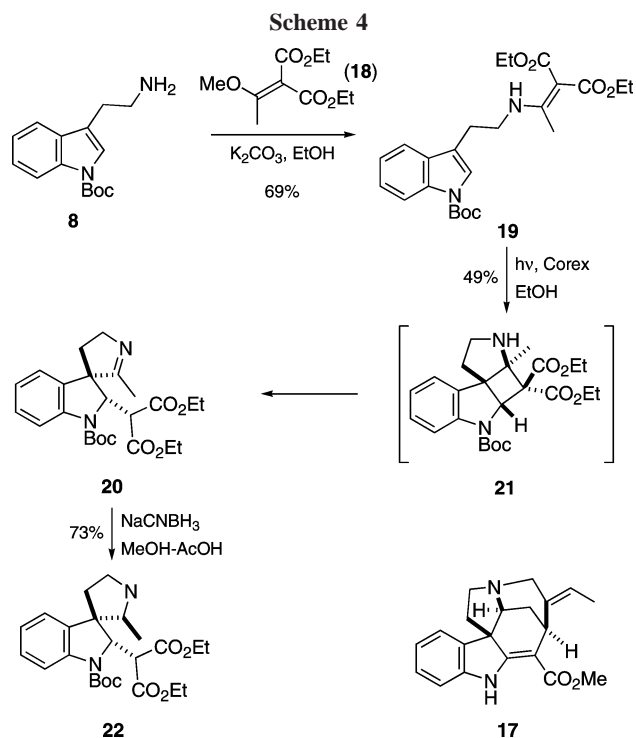
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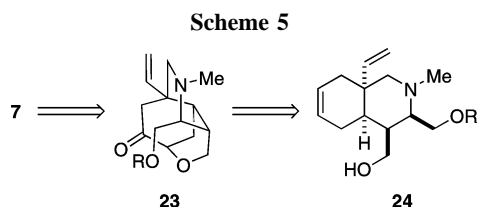
(14) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 2224.

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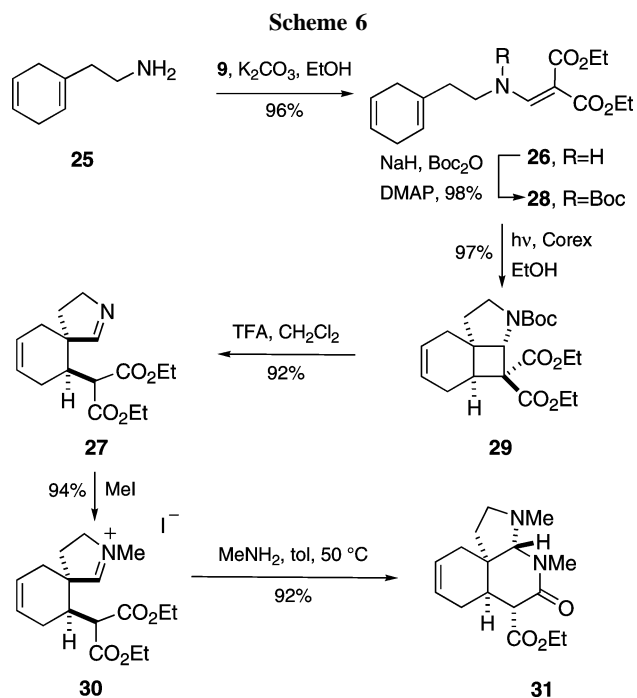


line **24**, which we believed could be constructed via a photocycloaddition–retro-Mannich approach similar to that developed with tryptamine (Scheme 5). In this case, our

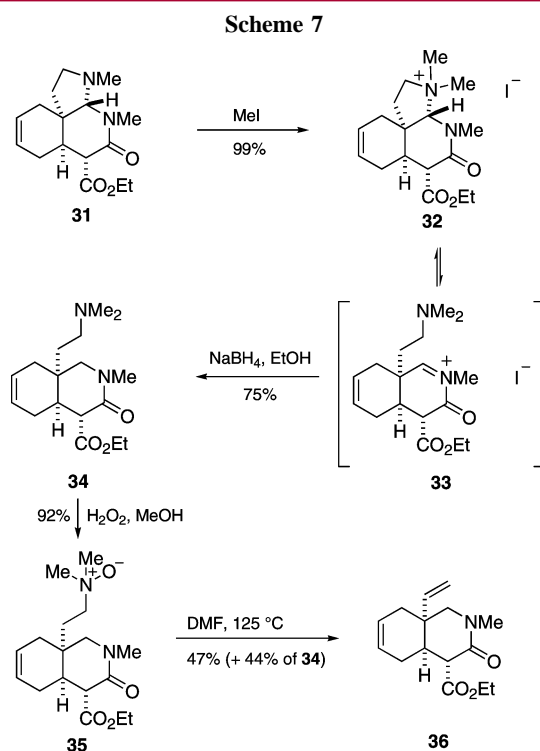


starting point was the Birch reduction product **25**¹⁹ of β -phenethylamine, which was condensed with **9** to furnish **26** (Scheme 6). Irradiation of **26**, as expected, produced spiroimine **27** (61% yield), but it was found that the yield of this process could be improved if **26** was first converted to its Boc derivative **28**. When the latter was irradiated through Corex rather than Pyrex glass, the cyclobutane **29** could be isolated in nearly quantitative yield. Subsequent removal of the Boc protection from **29** caused spontaneous retro-Mannich fragmentation to **27**. To activate **27** for cyclization to a precursor for **24**, the imine nitrogen was first methylated and the resultant methiodide **30** was treated with methylamine in warm toluene. The product **31**, obtained in high yield, was the result of initial formation of an aminal followed by intramolecular acylation by one of the two ethyl esters to give a δ -lactam.

With **31**, there was now an opportunity to employ the fused pyrrolidine of this tricycle as the progenitor of the angular

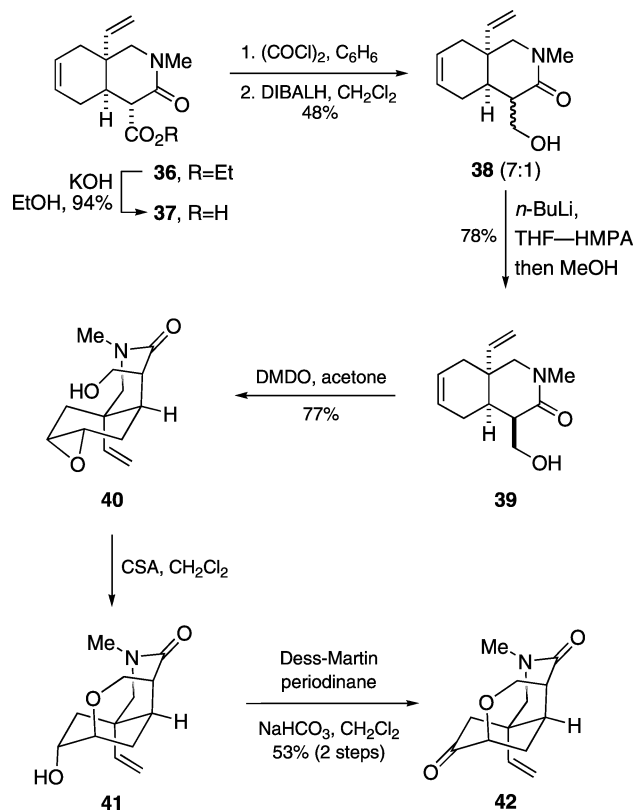


vinyl substituent needed for **24**. The basic pyrrolidine nitrogen of **31** was alkylated with methyl iodide in the expectation that the resultant quaternary iodide **32** would exist in equilibrium with acyliminium iodide **33** (Scheme 7). In practice, reduction with sodium borohydride in situ after treatment of **31** with methyl iodide afforded tertiary amine **34** in excellent yield. Conversion of **34** to its *N*-oxide



(19) Wimalasena, K.; Alliston, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 1220.

Scheme 8



35 was straightforward, but Cope elimination²⁰ of **35** in hot DMF yielded isoquinoline **36** accompanied by a significant quantity of **34** resulting from deoxygenation.²¹ The latter was recycled through **35** to augment the yield of **36**.

(20) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.

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It was now necessary to invert the configuration of the ester carbon of **36** in order to set in place an endo primary alcohol that could be used to construct the tricyclic ether **23**. This was accomplished by saponification of **36**, conversion of the resulting carboxylic acid to its acyl chloride, and reduction with diisobutylaluminum hydride, a sequence that avoided unwanted reduction of the lactam carbonyl (Scheme 8). The mixture of primary alcohols **38** produced in this manner²² was isomerized to endo alcohol **39** via its dianion followed by reprotonation at low temperature. Treatment of **39** with dimethyldioxirane²³ afforded exo epoxide **40** with only a trace of product resulting from epoxidation of the vinyl group, and exposure of **40** to camphorsulfonic acid resulted in clean cyclization to cyclic ether **41**. This alcohol was oxidized²⁴ in situ to ketone **42**, which now stands ready for homologation of the lactam carbonyl, Fischer indolization, and final intramolecular alkylation at the indole β carbon to reach koumine.^{25,26}

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Supporting Information Available: Experimental procedures, characterization data, and representative ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) The stereochemistry of the resulting alcohols was determined by cyclization with mercury(II) acetate. The exo primary alcohol underwent intramolecular oxymercuration exclusively at the vinyl group, whereas **39** yielded the product of oxymercuration at the cyclohexene double bond.

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(26) For a formal synthesis of (+)-koumine, see: (a) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895. (b) Bailey, P. D.; McLay, N. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 441.