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An Approach to the Isoschizozygane Alkaloid Core Using a 1,4-Dipolar Cycloaddition of a Cross-Conjugated Heteroaromatic Betaine

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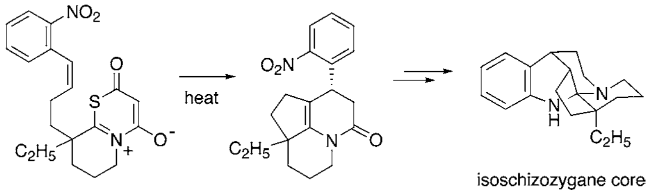
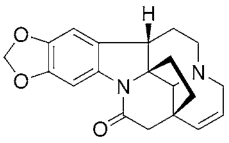
ABSTRACT

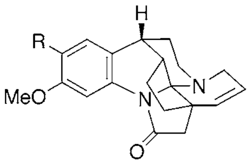


A new strategy for the synthesis of the isoschizozygane alkaloid core has been developed that is based on a 1,4-dipolar cycloaddition reaction of a cross-conjugated heteroaromatic betaine. The resulting cycloadduct undergoes loss of COS, and further reduction delivers a 5*a*-aza-acenaphthylene intermediate that was transformed into the isoschizozygane skeleton upon treatment with acid.

The schizozyganes represent a small group of hexacyclic indoline alkaloids[1] that were obtained from the twigs of the East African monotypic shrub *Schizozygia caffaeoides*.[2,3] In addition to the major alkaloid schizozygine (**1**),[4] a pair of minor alkaloids were isolated,[5] and their structures were established as isoschizogaline (**2**) and isoschizogamine (**3**) on the basis of extensive NMR studies.[3] A partial biosynthetic pathway was invoked to explain the formation of their unusual aminal-containing ring system[3] by assuming attack of the indoline nitrogen on a transient iminium ion derived from the schizozygane skeleton.[6] The resulting aziridinium ion intermediate could then be reductively opened to provide the isoschizozygane core.[3] The striking structural features of the isoschizozyganes, alongside their interesting biological properties,[7] have combined to make these natural products challenging targets for synthesis. Heathcock and Hubbs were the first to describe a concise synthesis of (±)-isoschizogamine,[8] and more recently Magomedov presented an alternative strategy to the cyclopenta[*b*]quinoline core using a formal hetero Diels−Alder reaction.[9] In this paper, we describe a different synthetic approach to the isoschizozygane alkaloids which uses an intramolecular 1,4-dipolar cycloaddition reaction of a cross-conjugated heteroaromatic betaine[10] to construct the novel hexacyclic skeleton. Our initial retrosynthetic analysis was based on our earlier work dealing with the intramolecular [3+2]-cycloaddition of thioiso-



1; schizozygine



2; R = H; isoschizogaline
3; R = OMe; isoschizogamine

Figure 1.

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[1] Saxton, J. E. In *Indoles, Part Four, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1984; Chapter IX, pp 437−486.

[2] Renner, U.; Kernweisz, P. *Experientia* **1963**, *19*, 244.

[3] Hájicek, J.; Taimr, J.; Budesinsky, M. *Tetrahedron Lett.* **1998**, *39*, 505.

[4] Renner, U.; Fritz, H. *Helv. Chim. Acta* **1965**, *48*, 308.

[5] Renner, U. *Lloydia* **1964**, *27*, 406.

[6] Kompis, I.; Hesse, M.; Schmid, H. *Lloydia* **1971**, *34*, 269.

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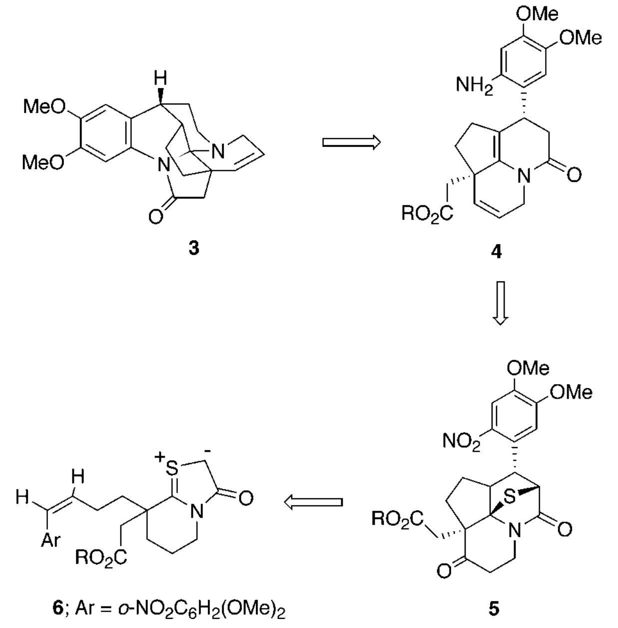
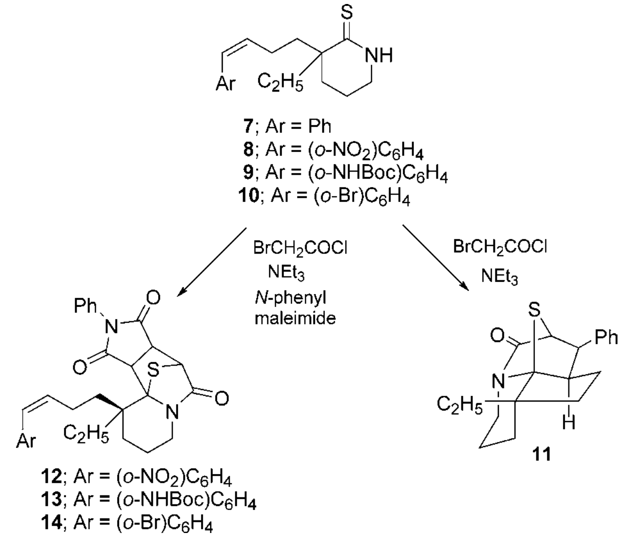
münchnones across tethered π-bonds[11] and is illustrated in Scheme 1. We assumed that the hexacyclic skeleton of isoschizogamine (**3**) could be formed from a compound of type **4** by a sequence of enamide protonation, acyl-iminium ion cyclization, and lactamization. Enamide **4** may be generated by extrusion of sulfur from cycloadduct **5** followed by reduction of both the nitro and keto groups and a subsequent dehydration. The key cycloadduct **5** should be accessible from an intramolecular dipolar cycloaddition of the 1,3-dipole present in the mesoionic betaine **6**.

Scheme 1



To test the feasibility of the retrosynthetic strategy outlined in Scheme 1, our initial efforts were focused on model substrates. Several *cis*-aryl alkenyl-substituted piperidinethiones were prepared by Castro−Stevens coupling[12] of the acetylenic NH-lactams followed by nickel boride-catalyzed hydrogenation of the alkynyl group[13] and subsequent conversion to the thiolactams using Lawesson's reagent.[14] Treatment of the simple phenyl-substituted thiolactam **7** with bromoacetyl chloride and triethylamine at 25 °C gave the desired cycloadduct **11** in 85% yield as a single diastereomer corresponding to endo-cycloaddition (Scheme 2). Assignment of the stereochemistry of cycloadduct **11** is based on its spectroscopic properties and also by analogy to related cycloadditions using isomünchnones where X-ray data had been obtained.[15]

Scheme 2



Unfortunately, all of our attempts to induce an analogous reaction using the closely related *ortho*-nitro-substituted thioamide **8** failed to give any signs of an internal cycloadduct. Similar experiments were carried out using the related *o*-NHBoc and *o*-Br aryl piperidinethiones **9** and **10**. In both of these cases no product attributable to intramolecular cycloaddition could be detected.[16] Whereas the reaction of the *cis*-aryl alkenyl-substituted piperidinethiones **8**−**10** failed to produce an internal cycloadduct, reaction in the presence of *N*-phenylmaleimide proved fruitful. Bimolecular cycloaddition occurred in 75−80% yield, providing a 1:1 mixture of diastereomeric cycloadducts (i.e., **12**−**14**), thereby establishing that the expected 1,3-dipole was indeed being formed.

The interaction of two reacting groups in the same molecule has always been of paramount concern to organic chemists.[17] The geometric requirements for interaction are generally evaluated through systems that have the reacting centers connected together by a few intervening atoms. This linkage provides a cyclic transition state that imposes distinct restrictions upon the bond angles at the reacting centers.[18] The ultimate success of the intramolecular thioisomünchnone cycloaddition of **8** will be critically dependent on the relative rate of the internal cycloaddition as compared to unproductive decomposition pathways. Conformational factors in the transition state play an important role in achieving the required two-plane orientation approach necessary for the cycloaddition. It would appear that the presence of an ortho

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(8) Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315.

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(10) Padwa, A.; Coats. S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651.

(11) (a) Padwa, A.; Harring, S. R.; Hertzog, D. L.; Nadler, W. R. *Synthesis* **1994**, 993. (b) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123. (c) Heidelbaugh, T. M.; Liu, B.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4757.

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(13) Brown, C. A.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 1003.

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(15) (a) Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418. (b) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072.

(16) Several unidentifiable products were formed that appear to be derived by addition of adventitious water across the thioisomünchnone dipole followed by ring opening and subsequent coupling with unreacted dipole.

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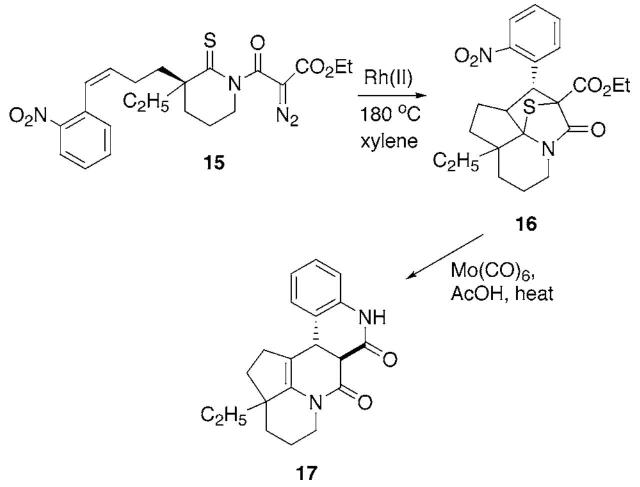
(18) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

substituent on the aromatic ring of the above systems twists the dipole sufficiently away from the preferred transition state for cycloaddition so that other pathways compete.

To overcome this problem, we thought it would be advantageous to study a more highly activated dipole, especially one that can be employed at a higher temperature for the cycloaddition. The formation and dipolar trapping of thioisomünchnones via the interaction of rhodium carbenoids derived from diazo thioamides have not been investigated to the same extent as that of the corresponding isomünchnone system.[19] The advantage of using this method to generate the dipole is that the reaction can be carried out at much higher temperatures (i.e., 180 °C). Our hope was that we might be able to induce the internal cycloaddition to occur using the *o*-phenyl-nitro-substituted diazo thioamide system **15**. We were pleased to find that the Rh(II)-catalyzed reaction of **15** in xylene at 180 °C provided cycloadduct **16** in 83% yield (Scheme 3). In an attempt to remove the sulfur atom, we exposed a sample of **16** to molybdenum hexacarbonyl in acetic acid according to a method developed by Alper and Blias for the reduction of thiols.[20] Under these conditions, however, compound **16** was converted to lactam **17** by reduction of both the sulfur bridge and nitro group, and the resulting anilino group then underwent a subsequent lactamization reaction with the adjacent ester functionality.

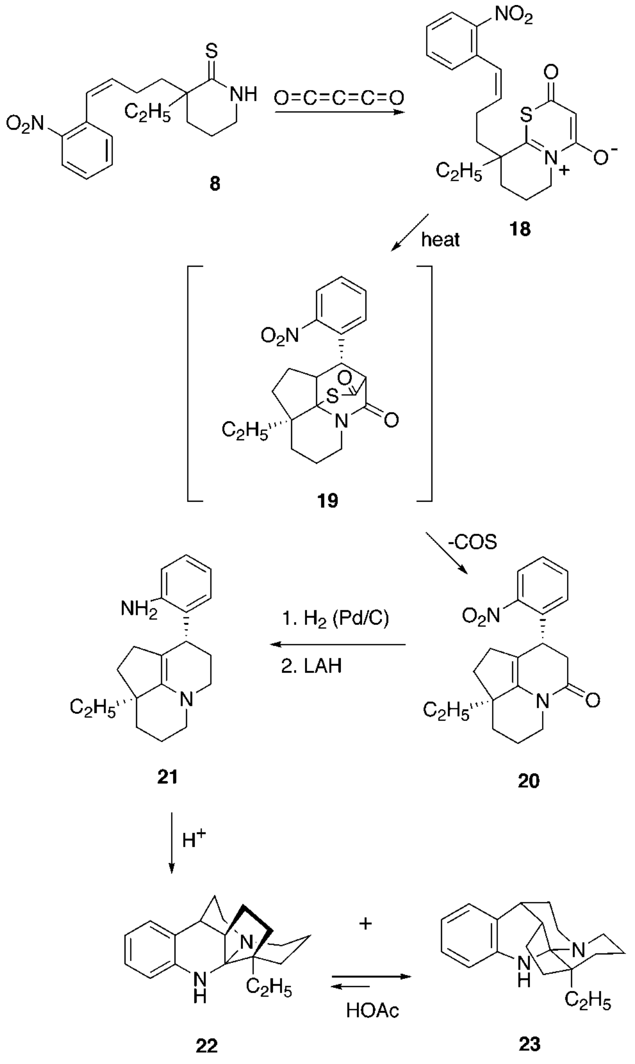
Scheme 3



At this point in time we reasoned that it might be possible to avoid the difficulties associated with the presence of the extra carboethoxy group in cycloadduct **16** by employing a 1,4-dipole for construction of the structural backbone of the isoschizozygane class of alkaloids. In contrast to 1,3-dipoles, much less in known about the cycloaddition behavior of 1,4-dipoles. This class of reactive intermediates attracted little synthetic attention until the elements of a 1,4-dipole were incorporated into a cross-conjugated heteroaromatic betaine by cyclo-condensation of an appropriately substituted monoprotic amidine or thioamide with a 1,3-bielectrophile derived from malonic acid.[21,22] Although several intermolecular 1,4-dipolar cycloadditions have been described in the literature,[23] applications of the intramolecular type are still rare but have significant synthetic potential.[24]

The synthesis of 5*a*-aza-acenaphthylen-5-one **20** commenced from the easily available thiolactam **8** (Scheme 4).

Scheme 4



Generation of the bright yellow isolable betaine **18** was accomplished by the reaction of **8** with carbon suboxide[25] at 25 °C for 5 h. Heating a sample of **18** at 120 °C for 3 h in toluene afforded **20** as a single diastereoisomer in 66%

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[20] Alper, H.; Blais, C. *J. Chem. Soc., Chem. Commun.* **1980**, 169.

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yield as a pale yellow solid whose formation is easily accounted for by extrusion of COS[26] from the originally formed cycloadduct **19** followed by a hydrogen shift. Catalytic reduction of the nitro functionality (H_2, Pd/C) in **20** to the corresponding amino group was followed by enamide reduction using LAH. The transient enamine **21** was treated with acid to furnish a 3:2-mixture of diastereomeric aminals **22** and **23**. The formation of the two observed diastereomers can be explained by protonation of the two diastereotopic faces of the double bond in the initially formed enamine **21**.[8] Treatment of either isolated isomer with acetic acid resulted in an equilibrated 1:6 mixture of **22** and **23** with the major diastereomer possessing the correct core skeleton of the isoschizozygane family of alkaloids.

In summary, an efficient approach to the core skeleton of the isoschizozyganes was accomplished by an intramolecular 1,4-dipolar cycloaddition reaction of a cross-conjugated heteroaromatic betaine intermediate. Application of this strategy to the synthesis of isoschizogamine is currently underway and will be reported at a later date.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (GM 059384) and the National Science Foundation (CHE-0450779).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[26] Carbonyl sulfide was identified when it was trapped in an alcoholic solution of piperidine where it formed the corresponding salt. See: Seibert, W. *Angew. Chem.* **1959**, *71*, 194.