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Unraveling the C_2-Symmetric Azatetraquinane System. Simple, Enantioselective Syntheses

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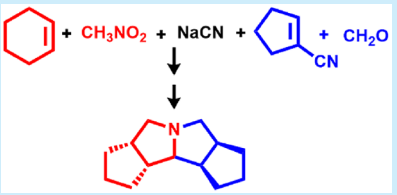
ABSTRACT: Concise stereocontrolled synthetic routes to the C_2-symmetric azatetraquinane **1** (or, also, the enantiomer) are described. The successful execution of the synthesis involved innovation in the methodology for [3+2] cycloaddition and stereochemical control.



This paper describes the enantioselective synthesis of the previously unknown C_2-symmetric azatetraquinane **1** and its enantiomer, an interesting synthetic challenge for multiple reasons. The various possible linear azatetraquinanes have not previously been made by synthesis. It is not easy to assess the viability of the many conceivable synthetic pathways to **1**, with stereocontrol as a major obstacle, especially with the five contiguous stereocenters.[1] In contrast, there have been many successful synthetic approaches to bicyclic and tricyclic quinanes, including natural products such as the alkaloids of the pyrrolizidine family **2**,[2] terpenoids containing the triquinane core (**3**),[3] and the nonlinear tetraquinane diterpenoids such as the crinipellin family (Figure 1).[4]

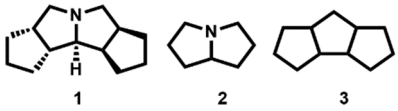
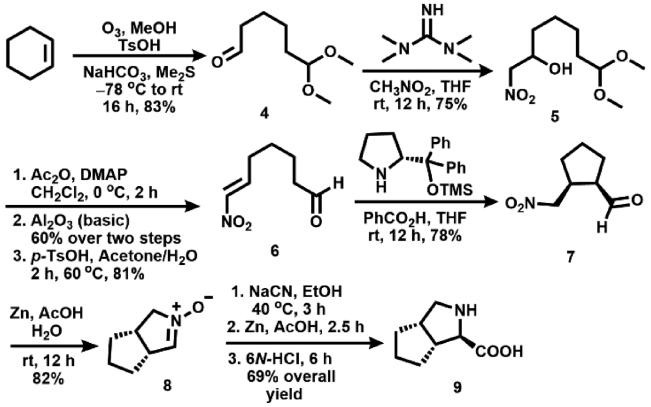


Figure 1. Linear quinanes.

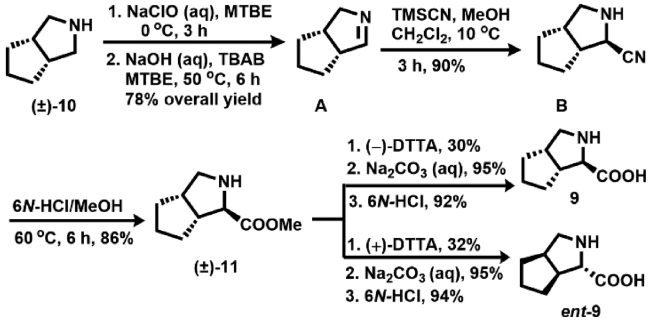
Our synthesis of the chiral azatetraquinane **1** utilized the chiral bicyclic nitrone **8**, which was constructed enantioselectively from cyclohexene as outlined in Scheme 1. The key steps are the catalytic enantioselective cyclization of the unsaturated nitro aldehyde **6** to form **7** and the reductive cyclization of **7** to the nitrone **8**.[5] Conversion of **8** to the (*R*)-amino acid **9** involved cyanide addition, N−O cleavage, and hydrolysis of cyano to COOH. Full experimental details can be found in the Supporting Information. The nitro aldehyde **6** was similarly transformed using *S*-diphenylprolinol TMS ether as catalyst into *ent*-**7**, from which the *S*-amino acid *ent*-**9** was made by the method outlined in Scheme 1.

The chiral *R*-*α*-amino acid **9** could also be obtained by resolution of the (±)-methyl ester **11** via the nicely crystalline salt with (−)-*R*,*R*-di-*p*-toluoyl tartaric acid [(−)-DTTA] using methanol/acetone as the solvent, and subsequent hydrolysis in hot 6 N HCl (Scheme 2).[6] The *α*-amino acid *ent*-**9** was made

Scheme 1. Enantioselective Route to Key Bicyclic Intermediates for the Synthesis of 1



Scheme 2. Pathway to the Chiral (*R*)-*α*-Amino Acid 9 from Bicyclic Amine 10 by Resolution of (±)-Methyl Ester 11



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similarly via the salt with (+)-*S*,*S*-di-*p*-toluoyl tartaric acid (see the Supporting Information for details). The racemic methyl ester **11** was synthesized from the bicyclic amine **10**.[6,7]

A potentially simple synthesis of the azatetraquinane **1** from the chiral *α*-amino acid **9** using an azomethine ylide-olefin [3+2] cycloaddition step, e.g., **9** → **1** (Figure 2), is actually extremely challenging because the scope of such additions is very limited.[8]

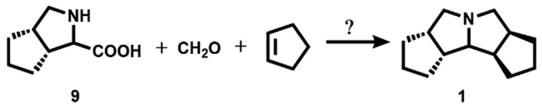


Figure 2. Simple but hypothetical route for the synthesis of **1**.

We devoted a very considerable amount of time and effort to the synthesis of the tricyclic lactone **12** from the amino acid **9** (or ester **11**) because that substance might serve as a useful precursor for the azomethine ylide **13** (Figure 3), but to no avail. The insolubility of the amino acid **9** in aprotic solvents is one obstacle to the generation of lactone **12** or azomethine ylide **13** from paraformaldehyde. The synthesis of the lactone **12** from various formaldehyde equivalents using a benzene-soluble salt with triethylamine also failed.

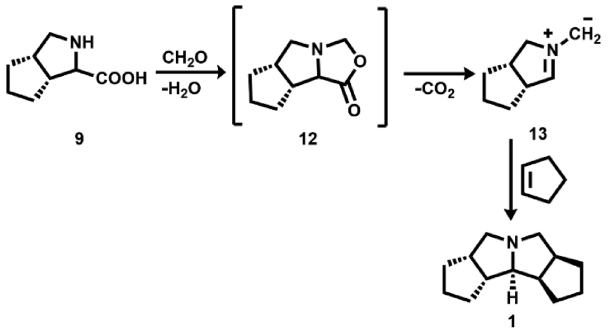
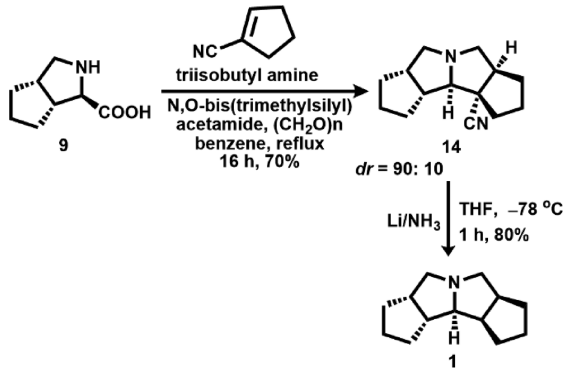


Figure 3. Hypothetical [3+2] cycloaddition route for the conversion of **9** to **1** in a single step.

In addition, the use of various literature procedures[8] for generating azomethine ylides failed to form **1** from excess cyclopentene and **9**, most likely because the azomethine ylide **13** is insufficiently reactive. The desired [3+2] cycloaddition reaction also failed to take place with the more electrophilic olefinic substrates 1-methoxycarbonyl cyclopentene, 2-cyclopentenone, and cyclopentadiene under a variety of conditions. Fortunately, it was possible to obtain the desired [3+2] cycloaddition product **14** from 1-cyanocyclopentene[9] and in situ-generated azomethine ylide **13** in modest yield using racemic amino acid, a tertiary amine, and paraformaldehyde at reflux in benzene or toluene. More than 40 experiments were performed to ascertain the most favorable conditions for the synthesis of the amino nitrile adduct **14**. Freshly sublimed paraformaldehyde in a large excess in benzene at reflux worked best and afforded higher yields of **14** than CH_2O gas (generated externally from paraformaldehyde and Amberlyst sulfonic acid resin in diglyme at 80 °C and added as a slow stream with N_2 gas as the carrier) or the Eschenmoser-type CH_2O equivalent $i\text{-}Pr_2N^+{=}CH_2Cl^-$ or chloromethyl trifluoroethyl ether. Triisobutylamine and trimethallylamine were superior to diisopropylethyl amine, and triethylamine was nonviable as a tertiary amine component. The use of bis-trimethylsilyl acetamide (2 equiv) as a scavenger of water led to a cleaner reaction and higher yields. Under optimum conditions (see Scheme 3 and the Supporting Information), the [3+2] cycloaddition reaction of racemic **9**, paraformaldehyde, and 1-cyanocyclopentene afforded the racemic adduct **14** as a 90:10 mixture of *anti*- and *syn*-[3+2] adducts in 70% yield.

Scheme 3. An Expeditious Synthesis of the C_2-Symmetric *anti*-Azatetraquinane 1



The pure racemic *anti*-adduct **14** was readily obtained by flash column chromatography on silica gel using hexane/acetone as the eluent. Reductive decyanation of **14** with excess lithium in liquid ammonia/THF at −78 °C occurred smoothly to give the desired racemic *anti*-azatetraquinane **1** in 80% yield as shown in Scheme 3.[10] The achiral C_s-symmetric diastereomer of **1** (Figure 4) having the terminal rings *syn* to one another was similarly made from the (minor) diastereomer of **14** (see the Supporting Information).

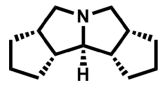


Figure 4. C_s diastereomer of **1**.

Enantiomerically pure *R*-amino acid **9** was analogously converted into the chiral levorotatory tetracyclic nitrile **14** and then into the chiral C_2-symmetric dextrorotatory azatetraquinane **1**, as summarized in Scheme 3 and detailed in the Supporting Information. Similarly, the levorotatory *ent*-**1** was synthesized starting from *S*-amino acid **9**.[11,12]

The stereochemistry of **14**, with terminal rings *anti* to one another in the major [3+2] cycloaddition product, follows from its conversion to the C_2-symmetric, chiral tetracyclic product **1** rather than the diastereomer of **1** described above having a terminal-ring-*syn* structure, which has C_s symmetry and is thus achiral (see the Supporting Information).

The pre-transition state assembly for the formation of **14** may reasonably be represented by the approximation shown in Figure 5 in which the cyano group projects away from (and is *exo* to) the bicyclic ylide moiety.

An important takeaway from the success of the process outlined in Scheme 3 is that cyano can be uniquely useful in azomethine-ylide cycloadditions to C=C, both serving as an activating and removable group and broadening the range of applicability.

The guidance provided by structure **14** led us to speculate that the reaction of the *R*-amino acid **9**, paraformaldehyde, and 1,2-dicyanocyclopentene (**E**) might be even more *exo*

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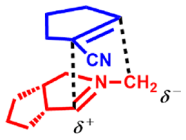
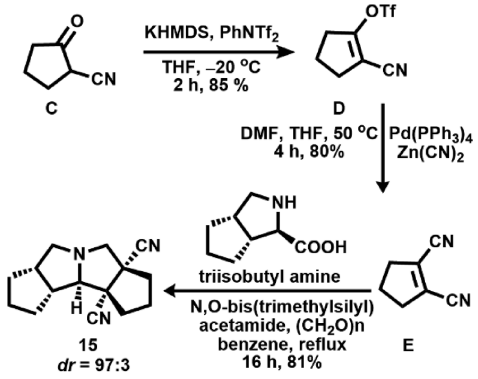


Figure 5. Three-dimensional pre-transition state assembly for the formation of the major (CN *exo*) [3+2] cycloadduct **14**.

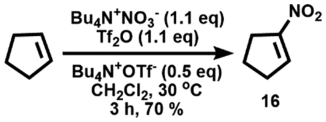
diastereoselective. It was gratifying to find that this reaction proceeded smoothly with 97:3 diastereoselectivity to give, after flash chromatographic purifications on silica gel, the pure adduct **15** in 81% yield (see Scheme 4). 1,2-Dicyanocyclopentene was synthesized from 2-cyanocyclopentanone (**C**) via the route shown in Scheme 4. Reaction of **15** with Li/liquid ammonia did not lead to bis-decyanation but instead to a cyclic amidine by reductive coupling of the two *cis* cyano groups. The double reductive decyanation of **15** remains an interesting challenge.

Scheme 4. Highly Diastereoselective Synthesis of Tetracyclic Dinitrile 15



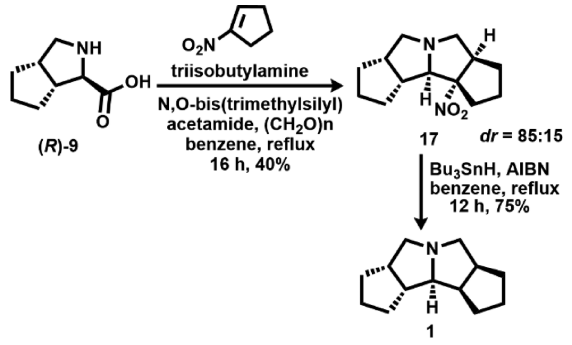
Another pathway for the synthesis of the chiral azatetraquinane **1** from the *R*-amino acid **9** was developed using 1-nitrocyclopentene as the olefinic component. To facilitate this approach, we developed the new route to 1-nitrocyclopentene (**16**) that is shown in Scheme 5. Although several preparations of **16** have been reported previously, these suffer from drawbacks such as the need for multiple steps or use of NO gas under pressure or ultrasound irradiation.[13] As shown in Scheme 5, slow addition of triflic anhydride to a solution of cyclopentene, tetrabutylammonium nitrate, and tetrabutylammonium triflate in CH_2Cl_2 at 30 °C produces **16** directly (via triflyl nitrate) in a smooth, easily executed, and controlled process that can readily be applied to many olefinic substrates.

Scheme 5. Convenient Synthesis of 1-Nitrocyclopentene

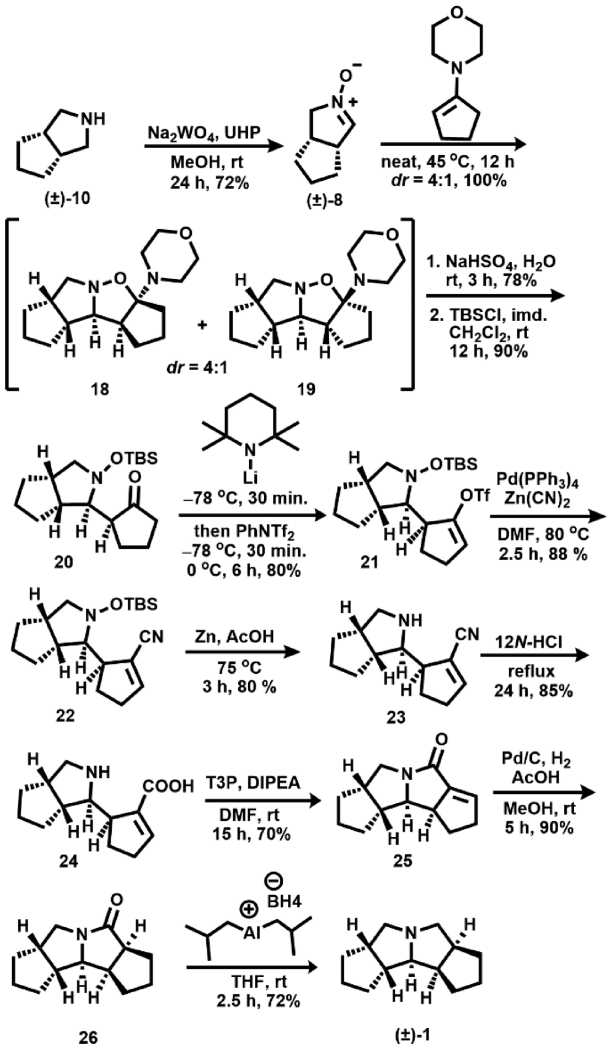


Under the optimum reaction conditions for the conversion of 1-cyanocyclopentene to the tetracycle **14** (Scheme 3), 1-nitrocyclopentene could be transformed into the desired tetracyclic [3+2] adduct **17** in 40% overall yield with 85:15 diastereoselectivity. Pure **17** was readily obtained by flash chromatography on silica gel in 35% yield. Reductive removal of the nitro group from adduct **17** was accomplished by heating with tri-*n*-butyltin hydride in benzene at reflux with azo-bisisobutyronitrile (AIBN) as the radical initiator for the replacement of NO_2 by H (Scheme 6).

Scheme 6. Synthesis of C_2-Symmetric *anti*-Azatetraquinane 1 via Tetracyclic Adduct 17



Scheme 7. Synthesis of (±)-1 via the (±)-Nitrone 8



We have also investigated an approach to the synthesis of **1** using the nitrone **8** (as the racemate) instead of azomethine ylide **13**, taking advantage of the fact that the former can be a weakly electrophilic reagent in contrast to the latter, which is

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strongly nucleophilic. This strategy led to another successful synthesis of the *anti*-azatetraquinane **1** by the route shown in Scheme 7. The reaction of the (±)-nitrone **8** with the morpholine enamine of cyclopentanone without solvent at 45 °C proceeded quantitatively to form the diastereomeric [3+2] cycloadducts **18** and **19** with a predominance of the desired *anti*-tetracycle **18** by 4:1 as shown in Scheme 7. The labile mixture was directly transformed into the tricyclic cyclopentanone derivative **20**, which was easily obtained as the pure diastereomer by flash column chromatography on silica gel, as described in detail in the Supporting Information. Ketone **20** was converted via the vinyl triflate **21**[14] to the α,β-unsaturated nitrile **22**,[15] which was then reduced to the amino nitrile **23**, hydrolysis of which gave the amino acid **24**. The synthesis of (±)-**1** by this route was completed by lactamization to **25**[16] and two-stage reduction.[17] This route also provides access to chiral **1** and *ent*-**1** starting with chiral nitrone **8**.

In summary, the studies reported herein have significantly expanded the scope of [3+2] azomethine ylide cycloaddition to C=C and have demonstrated an especially succinct route for the enantioselective synthesis of the novel azatetraquinane **1**. They have also emphasized that the development of [3+2] cycloaddition methodology via azomethine ylides lags far behind [4+2] cycloaddition technology and that further research in this area is needed to find improvements such as that reported herein utilizing cyano (or nitro) as an activating and removable group.

Finally, this work nicely exemplifies an unsettling paradox of synthesis: the simpler a new-found synthetic pathway, the more obvious it appears in retrospect, though finding that simplest route is very demanding.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00387.

Experimental procedures and characterization data for novel reactions and products, including copies of ^{1}H and ^{13}C NMR spectra and HPLC data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(11) The following $[\alpha]_D^{23}$ optical rotation values were measured for the chiral synthetic products [c = 1.0, $CHCl_3$ (precision ± 0.2)]: **14**, −21.4; *ent*-**14**, +21.4; **1**, +10.8; *ent*-**1**, −10.8.

(12) The cyano-substituted azatetraquinane **14** and its enantiomer *ent*-**14** were readily separated by HPLC using a chiral technologies AS-H column with 10% *i*-PrOH/90% hexane for elution and with retention times of 6.7 and 11.6 min, respectively.

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