Progress in Hydroazulene Synthesis

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Recently developed stereoselective synthetic routes to hydroazulenes are reviewed. Three principal synthetic approaches have been employed:
1. Rearrangements of bicyclic compounds containing cyclohexane rings;
2. Cleavage of tricyclic compounds;
3. Olefin cyclizations.

Die in neuerer Zeit entwickelten stereoselektiven Synthesen von Hydroazulen wenden im wesentlich die folgenden drei Reaktionstypen an:
1. Umlagerungen von bicyclischen Verbindungen, die Cyclohexan-Ringe enthalten;
2. Spaltung von tricyclischen Verbindungen;

In 1936, Pfau and Plattner formulated a satisfactory structure for azulene, a deep blue C_{10}H_{8} aromatic hydrocarbon which had mystified and intrigued chemists for nearly seventy-five years\(^2\). Subsequently, numerous synthetic routes to azulene and its derivatives were developed which relied upon the dehydrogenation of bicyclo[5.3.0]decanes (hydroazulenes) as the final step\(^3\). In recent years, hundreds of hydroazulenic sesquiterpenes have been isolated from plant sources and, despite their rather complex nature, many have been structurally elucidated\(^4\). Representative examples are shown below.

While their role in plant physiology is still obscure, certain hydroazulenic sesquiterpenes are of interest as aroma chemicals\(^5\) and potential medicinal agents\(^6,7\). These considerations coupled with the inherent chemical challenges of these complex molecules have provided stimulus for chemists to actively seek new efficient synthetic routes to hydroazulenes. The earlier schemes noted above are, for the most part, devoid of steric selectivity and are therefore useless as potential routes to chiral hydroazulenes\(^8\). The main problem of stereochemical control derives from the inherent conformational complexities of substituted cyclopentane and cycloheptane rings\(^9\).


\(^3\) A. E. SCHEINDAL, J. Amer. Chem. Soc. 37, 167, 1537 (1915).


Both systems undergo pseudorotation through conformers which differ only slightly in energy. Thus, conformational predictions are often extremely crude for such systems and reactions which allow equilibration of chiral centers frequently lead to gross mixtures of all possible diastereoisomers. This situation has in large part dictated the tactics of more recent stereoselective approaches to hydroazulenes wherein conformationally well-defined ring systems (usually cyclohexane derivatives) are employed for stereochemical control prior to a hydroazulene forming rearrangement step.

1. Routes Involving Skeletal Rearrangements of Bicyclic Compounds

The most common version of this approach involves the rearrangement of a bicyclo[4.4.0]decane derivative through 1,2-migration of the central C—C bond. The photochemical conversion of santonin to isophotosantonic lactone (Scheme A) is an early example.²

An especially facile version of this approach utilizes vicinal hydroxy sulfonate derivatives which undergo a pinacolic-type rearrangement under mild conditions to give hydroazulenic products in high yield (Scheme C).³, ¹⁴

Scheme C

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Appropriately functionalized bicyclo[4.3.1]decanes have been shown to rearrange efficiently to hydroazulenes upon solvolysis (Scheme D)¹². In this case, the bridged ring system provides a rigid framework for the introduction of chiral centers which either remain unaltered or change predictably in the rearrangement step.

Scheme D

In the foregoing examples of solvolytic rearrangements, the observed migration of only one of the several carbon atoms adjacent to the leaving group must be governed by two factors:
- group migration leading to the more stable cation intermediate (oxo > 3' > 2' > 1');
- antiperiplanar relationship of migrating and leaving groups.

Solvolytic rearrangements of 1-substituted bicyclo[4.4.0]decanes have also been employed with great success in hydroazulene synthesis (Scheme B)⁸, ¹³

Scheme B

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These requirements are illustrated in Scheme E. Reactions a and b. In each case, migration of only one of the two antiperiplanar groups (C-5 vs C-3 in Reaction a and C-2 vs C-4 in Reaction b) is preferred. These processes lead to tertiary cations as opposed to primary (e.g., C-10 vs C-2 in Reaction a) or secondary (e.g., C-1 vs C-5 in Reaction b).

Considering the above arguments, one would expect solvolytic rearrangements of bicyclo[4.3.0]nonyl-carbonyl systems, as shown below, to give mixtures of products (Scheme F). Here, rotation of the C-1/C-10 bond permits three geometrically favorable alkyl shifts, each of which affords a tertiary cation.

Scheme F

However, a double bond in the 5,6-position has been found to exert a marked directing effect on such solvolysis reactions. In the following example (Scheme G), a total predominance of hydroazulene product was realized. This result is attributable to a change in mechanism for the solvolysis step which can now take place via homoallylic participation and subsequent cyclopropylcarbonyl rearrangement.

Scheme G

2. Routes Involving Cleavage of Tricycles

In principle, any reaction which generates a cycloheptane ring could be employed in hydroazulene synthesis. For example, certain bicyclo[3.3.1]octanones have been found to give cycloheptenecarboxylates upon base cleavage. Recently, cyclopentane-fused analogs of such systems have been converted to the corresponding hydroazulencarboxylates along similar lines (Scheme H).

Scheme H

3. Routes Involving Olefin Cyclizations

Cation-initiated olefin cyclization reactions have also found applications in hydroazulene synthesis. One promising approach involves closure of the cycloheptane ring via acid treatment of appropriate unsaturated aldehydes (Scheme I) available from bicyclo[4.3.0]nonane precursors. This highly selective ring closure yields the exocyclic olefin with trans-related CH₃ and OH. Steric (anti CH₃/OH should be of lower energy than syn CH₃/OH) and stero-electronic factors undoubtedly control this cyclization. The trans orientation also allows for intramolecular proton removal by the carbonyl oxygen as shown below.

Scheme I

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Transannular cyclodecadiene cyclizations have been postulated as key steps in hydroazulene biosynthesis. Accordingly, a cycloeca-1,5-diene is thought to interact with an electrophilic moiety at one of the trisubstituted double bonds whereupon cyclization takes place to give hydroazulenic products (Scheme J). Presumably, enzymes control the entire process thus enabling selective anti-Markownikoff attack by the external electrophile at one of the two chemically similar double bonds.

Scheme J

A variation on the biogenetic proposal wherein one of the cyclodecadiene double bonds is activated through epoxidation has recently been shown to afford hydroazulenic products. In this approach, mild acid treatment promotes epoxide cleavage with transannular participation to give hydroazulenes (Scheme K).

Scheme K

Interestingly, the isomeric cyclodecene epoxide affords only hydronaphthalenic cyclization products upon similar treatment (Scheme L). In this case, six-membered ring formation can take place through tertiary cation intermediates, a pathway not available to the above isomeric epoxide.

Scheme L

Certain epoxycyclodecenes have also been found to undergo thermal cyclizations (Scheme M) to give hydroazulenes isomeric with those obtained in the acid-catalyzed process.

Scheme M

Several years ago, we decided to examine cyclo-
decadiene cyclizations of the type shown in Scheme N, whereby the selective electrophilic activation of one double bond could be achieved through the use of an allylic leaving group. The intermediate allyl cation would expectedly display characteristics of both a 1,6- and 1,5-cyclodecadiene. Cyclization of such a species via a tertiary cation would then afford a bicyclo[5.3.0]decane derivative. A priori, several problems might be foreseen with regard to synthetic applications of this scheme. In the first place, the allylic cation has two electrophilic centers either one of which could interact (at least hypothetically) with the transannular double bond (regioselectivity). Secondly, each of the aforementioned cyclization reactions generates three asymmetric centers and the question of stereoselectivity must be considered.

Scheme N

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An appropriate model system for initial study, 3-hydroxy-6-methyl-trans, trans-cyclodec-1,6-diene (2) was readily prepared through successive treatment of the unsaturated keto-mesyate 1 with excess diborane and base (Scheme O). The p-nitrobenzoate derivative 3 underwent solvolysis in buffered aqueous dioxane to give, in 80% yield, an unsaturated tertiary alcohol 4 whose gross structure was elucidated through hydrogenation, dehydration, and ozonolysis leading to the known ketone 5.27 The stereochemistry of the solvolysis product 4 was surmised through synthetic correlations with the aforementioned hydrogenation product.28

![Scheme O](image)

The cyclization of cyclodecadienyl p-nitrobenzoate 3 is thus both stereoselective and regioselective. These findings can be formulated in terms of transition-state requirements for the various cyclization modes as shown in Scheme P. Accordingly, ionization of the p-nitrobenzoate may afford the sickle cation or an isomeric W-cation.29 1,5-Cyclization of the sickle cation would lead to a highly strained trans-cycloheptene intermediate whereas 1,7-cyclization would give an energetically more favorable cis-cycloheptene. In the case of the W-cation, both the 1,5- and the 1,7-cyclization pathways lead to high-energy trans-cycloheptene intermediates. Regioselectivity could therefore be controlled by the geometry of the allylic cation.30

The observed trans-ring fusion of the solvolysis product 4 may be explained on the basis of steric interactions which develop during formation of the 1,7 carbon-carbon bond. Of the two possible arrangements, cis-eclipsed H-1 and H-7 vs trans-staggered H-1 and H-7, the latter (depicted in Scheme P) appears more favorable. Attack of water at the less hindered face of the bicyclic cation as indicated in Scheme P completes the stereochemical picture.

![Scheme P](image)

3-Hydroxy-6-methyl-trans, trans-cyclodec-1,6-diene (2):
To a 0.35 M solution (150 ml) of borane in tetrahydrofuran was added a solution of keto-mesyate 1 (4.68 g) in tetrahydrofuran (100 ml) over a period of 10 min. The solution was stirred at 0° for 1 hr and at room temperature for 1 hr and then methanol (26 ml) was added dropwise. The solution was treated with 2 M methanolic sodium methoxide (190 ml) and stirred at room temperature for 19 hr and at reflux for 20 min. The mixture was poured into saturated sodium chloride solution. The product was isolated via ether extraction (2.4 g = 80% of crude product) and purified by chromatography on neutral Woelm alumina (75 g, Grade III); yield: 1.86 g; b. p. 100°/0.02 mm; the product crystallized upon distillation. Two recrystallizations from pentane yielded an analytical sample; m. p. 46.5°-48°.

6-Hydroxy-6-methyl-trans-bicyclo[5.3.0]dec-2-ene (4):
A solution of 3-(4-nitrobenzoyl oxy)-6-methyl-trans, trans-cyclo dec-1,6-diene31 (3; 963 mg; m. p. 74-75°) and sodium hydrogen carbonate (505 mg) in 3:1 dioxane/water (200 ml) was stirred at reflux for 52 hr. The product was isolated via ether extraction and was purified by short-path distillation; yield: 434 mg (87%); b. p. 70°/0.005 mm. The oily product contained 78% of alcohol 4 and 10% unidentified hydrocarbons according to G. L. C. analysis. An analytical sample was secured via preparative G. L. C.

![Scheme Q](image)

The dimethylcyclo decadienyl p-nitrobenzoate 6, prepared along the lines indicated in Scheme P has recently been found to yield the anti, trans, syn-hydroazulenol 7 upon solvolysis in aqueous dioxane buffered with sodium hydrogen carbonate31. This finding is of particular interest from a stereochemical point of view insofar as this product closely resembles the guaiazulenes (e.g., bulnesol,15 aromadendrene6) in its substitution pattern.
The foregoing cyclooctadienyl cyclization reactions have been viewed as ionic dissociative processes although both the regioselectivity and stereoselectivity of the reaction could be accomodated by a concerted (S$_{n2}$') reaction pathway.$^{22}$ This possibility was excluded by careful examination of the solvolytic behavior of an allylic isomer of p-nitrobenzoate 3. As seen in Scheme R, a common intermediate would require similar product distributions from both allyl isomers while an S$_{n2}$ reaction pathway would lead to isomeric hydroazulenes from each system. The cycloeca-1,5-dienol 12 was prepared from the epoxy-ketone 8 as shown in Scheme S.$^{33}$ The fragmentation of mesylate 11 was effected with lithium aluminum hydride in tetrahydrofuran in order to preclude a possible base-catalyzed cis-trans isomerization of the conjugated enone which formed upon alkoxide-initiated fragmentation.$^{34}$ Subsequent work (Scheme U) showed this precaution to be unnecessary.

Scheme R

The p-nitrobenzoate 13 underwent solvolysis in buffered aqueous dioxane to give a mixture of products similar in composition to that obtained previously from the isomeric p-nitrobenzoate 3. This finding supports the dissociative pathway depicted in Scheme P but does not completely exclude the possibility of differing mechanistic pathways (S$_{n2}'$ and S$_{n2}$) leading to a common hydroazulenic cation.

Scheme S

The presence of a cis allylic double bond in p-nitrobenzoate 13 introduces the possibility of U-cation formation as shown in Scheme T. This cation, in contrast to the corresponding sickle cation, could undergo cyclization at either C-5 or C-7 to give isomeric hydroazulenic products containing cis-cycloheptene double bonds. Our findings indicate that either the U-cation is not a favored intermediate or, if formed, it does not undergo 1,5-cyclization.

Scheme T

6-Hydroxy-1,6-dimethyl-trans-bicyclo[5.3.0]dec-2-ene (17):
A solution of 7-hydroxy-2,7-dimethyl-trans-cis-cycloeca-1,5-diene (15; 267 mg) in acetic acid (3 ml) saturated with sodium acetate was stirred at room temperature for 16 hr. The product was isolated via ether extraction; yield of crude acetate 16; 276 mg. This material was treated with a solution of lithium aluminum hydride (180 mg) in ether (5 ml) to give 244 mg of a clear oil. Purification was effected by preparative layer chromatography on silica gel; yield: 188 mg (70%); m.p. 75.5–78. The analytical sample was secured upon crystallization from pentane; m.p. 77.5–78.5.
The apparent selectivity observed in the cyclization of \( p \)-nitrobenzoate \( 13 \) prompted an extension of the synthesis outlined in Scheme S to angularly methylated hydroazulenes related to the pseudoguanolides (e.g., ambrosin\(^7\)). To that end, the hydroxy mesylate \( 11 \) was treated with sodium \( t \)-butoxide to give the cyclodecadienone \( 14 \) (Scheme U). The geometry of the conjugated double bond was shown to be cis through reduction of the ketone group with lithium aluminum hydride/aluminum chloride\(^{35} \) to give the cyclodecadienol \( 12 \). Addition of methylthiolium to ketone \( 14 \) afforded the tertiary alcohol \( 15 \). This material smoothly cyclized in glacial acetic acid/sodium acetate at room temperature to give (70\% yield) the hydroazulenyl acetate \( 16 \).

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\begin{align*}
\text{Scheme U} \\
\text{The structure of the derived crystalline alcohol } 15 \text{ was confirmed through independent synthesis of its hydrogenation product } 23 \text{ as shown in Scheme V. The known hydroazulene } 18^{28} \text{ afforded a 40:60 mixture of } \text{cis} \text{ and } \text{trans} \text{ ketones } 19 \text{ and } 21 \text{ upon addition of lithium dimethylcopper.}^{29} \text{ The distinct shielding of the angular methyl group by the carbonyl group observed in the N.M.R. spectrum of the } \text{trans} \text{ isomer } 21 (\delta = 0.70 \text{ ppm}) \text{ as opposed to the } \text{cis}-\text{isomer } 19 (\delta = 1.17 \text{ ppm}) \text{ supports the stereochemical assignments.}^{30} \text{ A similar trend was noted in the related exocyclic olefins } 20 (\delta = 1.02 \text{ ppm}) \text{ and } 22 (\delta = 0.73 \text{ ppm}) \text{ secured via treatment of the ketones with triphenylphosphonium methyldi in ethereal solution. Epoxidation of the } \text{trans} \text{-fused isomer } 22 \text{ with 3-chloroperoxybenzoic acid and subsequent reduction of the epoxide } 24 \text{ afforded the alcohol } 23, \text{ also obtained via hydrogenation of the solvolytically derived alcohol } 17. \text{ The } \text{cis}-\text{fused hydroazulene } 20, \text{ upon epoxidation and reduction, yielded alcoholic material which clearly differed (I.R., N.M.R., G.L.C.) from alcohol } 23. 
\end{align*}
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Scheme V

Thus far, cyclodecadienols have proved to be attractive intermediates for hydroazulene synthesis via solvolysis-cyclization reactions. The apparent regio- and stereoselectivity of such reactions is particularly gratifying but additional studies are needed to clarify the controlling factors. A systematic analysis of potential routes to a dimethylhydroazulene framework appropriate for further elaboration to guaine-type molecules is shown in Scheme W. The center column depicts all possible cyclodecadienol precursors which could give allylic cations leading to such a system. Each precursor, in principle, could afford two isomeric allylic cations, sickle or W from \text{trans} allylic derivatives (top four structures of center column) and sickle or U from \text{cis} allylic derivatives (bottom four structures of center column). It should be noted that two different sickle cations can be generated. In one case, the lower numbered (5,6) bond is \text{cis} and the higher numbered (6,7) bond is \text{trans}. This is designated \text{ct} (cf. the second column of structures in Scheme W). In the second case, the 5,6-bond is \text{trans} and the 6,7-bond is \text{cis}. This isomer is designated as \text{tc} (cf. the fourth column of structures in Scheme W). The \text{ct} cations are geometrically constrained to undergo 1,7-cyclization to the aforementioned guaine precursor (first column) whereas the \text{tc} cations must undergo 1,5-cyclization to give an unwanted isomer (fifth column). The hypothetical U-cations (second column) can theoretically undergo either 1,5- or 1,7-cyclization while the W-cations (fourth row) cannot cyclize. This analysis suggests that the most promising approach to the desired guaine pre-

\footnotesize{26 cf. J. A. MARSHALL, Synthesis 1971, 229.}
\footnotesize{27 W. HÜCKEL, L. SCHNITZSPAHN, Liebgis Ann. Chem. 505, 274 (1932).}
30 For an indication of the steric stability of allylic radicals, see P. D. BARTLETT, L. K. MONTGOMERY, B. STOFFE, J. Amer. Chem. Soc. 86, 616 (1964).}
cursor (column 1) would be through the 1,6-cis, trans derivative (column 3, row 1) or the 1,6-trans, trans derivative (column 3, row 4). The undesired hydroazulene cation (column 5), on the other hand, should be best secured from the 1,5-cis, trans (column 3, row 2) or the 1,5-trans, trans (column 3, row 3) derivatives. In each case, the geometry of the 1,2-double bond could influence the ring-fusion stereochemistry.

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31 W. F. Huffman, unpublished work.