Stereocontrolled Construction of Hydroazulenones by Sequential Anionic Oxy-Cope Rearrangement–S_N' Allylic Ether Displacement

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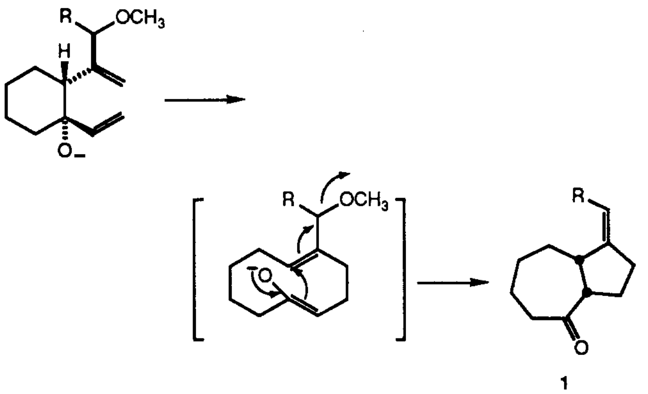
Summary: The possibility of generating hydroazulenone frameworks in stereocontrolled fashion is demonstrated with a 4α-methoxy-2-norcaren-3-yl example. This optically pure system illustrates in an especially revealing way the stereochemical issues surrounding assembly of the ketonic products.

Sir: We recently described the first example of intramolecular S_N' displacement of methoxide by enolate ions and hinted at the latent synthetic potential of this transformation.[2] In this paper, we demonstrate how this technology can be applied to the expedient elaboration of hydroazulenones based on the mechanistic paradigm illustrated in Scheme I. Broad application of this fundamental strategy to the stereocontrolled synthesis of carbocyclic frameworks typified by 1 can be envisioned. The latter, of course, constitute the backbone of guaianolide and pseudoguaianolide systems.[3] The protocol defined by Scheme I offers several advantages over strategies previously devised for assembling functionalized hydroazulene networks.[4] In order to make clear the stereochemical templating that is necessary to establish the several chiral centers in a given product, the results given by four stereoisomeric optically pure examples are detailed herein.

Scheme I



The readily available (−)-(1*R*,6*S*)-$\Delta^{4(10)}$-caren-*trans*-3-ol,[5] $[\alpha]^{20}_D$ −119.8° (*c* 2.47, $CHCl_3$), was *O*-methylated (NaH, MeI) and ozonolyzed to given norcaranone **2**, which upon treatment with $LiN(i\text{-}Pr)_2$ and *N*-phenyltriflimide[6] underwent completely regiocontrolled conversion to enol triflate **3a**[7] (Scheme II). Transformation into vinyl stannane **3b** was accomplished according to Wulff et al.,[8] thereby providing a nucleophilic 4α-methoxy-substituted 2-norcaren-3-yl system. Following transmetalation of **3b** with methyllithium[9] and condensation with (±)-2-chlorocyclohexanone,[10] the pair of diastereomeric chlorohydrins **4** and **5** were isolated in a 1:1 ratio (45%). The stereochemical course of this 1,2-addition was observed to be entirely controlled by the neighboring halogen atom. The absolute configurations shown were ascertained by X-ray analysis of **5**. The proper ensemble of necessary structural components was then arrived at by individual exposure of **4** and **5** to 3 equiv of vinylmagnesium bromide. This reagent promotes initial pinacol rearrangement (viz., 1,2-migration of the 2-norcarenyl unit) with liberation of a cyclohexanone carbonyl that is captured by a second equivalent of the organometallic. The divinyl alcohol pairs **6**/**7** and **9**/**8** were isolated in ratios approximating 2:1 (43–82% combined yields after MPLC).[11] The diminished steric control in the second step permitted access to all four stereoisomers. The individual assignments to **6** and **7** follow directly from ^1H NMR comparison with their desmethoxy counterparts, for which crystallographic corroboration is available. The case for **8** and **9** rests upon X-ray results acquired for the first of these alcohols.

When **6** was heated with KH in tetrahydrofuran, it underwent smooth rearrangement to **10** and **11** during 2 h.[12] As shown in Scheme III, **6** is so configured that both vinyl appendages are equatorially disposed in A; further, their mutual approach is not sterically impeded by the heavily substituted cyclopropane ring. Electrocyclization via this chair transition state produces the *trans,trans*-cyclodecadiene B. In B, the two double bonds are nicely proximate, thereby enabling *frontside* transannular S_N' displacement[13] of methoxide to operate. This process defines in precise manner all five stereogenic centers in **10**, a hydroazulenone that is capable of further equilibration with **11**.[14]

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[1] The Ohio State University Postdoctoral Fellow, 1988–1989.

[2] Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331.

[3] (a) Heathcock, C. H. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; John Wiley and Sons, Inc.: New York, 1973; Vol. 2, p 197. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *Ibid.* Vol. 5, 1983.

[4] Sworin, M.; Lin, K.-C. *J. Am. Chem. Soc.* **1989**, *111*, 1815 and pertinent references cited therein.

[5] (a) Gollnick, K.; Schroeter, S.; Ohloff, G.; Schade, G.; Schenck, G. *Chem. Ber.* **1965**, *687*, 14. (b) Paquette, L. A.; Ross, R. J.; Shi, Y.-J. submitted for publication.

[6] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313.

[7] Structures assigned to all compounds were in accord with individual infrared, 300-MHz ^1H NMR, 75-MHz ^{13}C NMR, and high-resolution mass spectra. Key intermediates have also given acceptable combustion analysis data. All recorded yields are based upon isolated material of >97% purity.

[8] (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277. (b) See also Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

[9] Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.

[10] (a) Wender, P. A.; Sieburth, S. McN.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967. (b) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771.

[11] The identical reactions in the desmethoxyl series result in 1,2-addition of vinyl exclusively trans to the norcarenyl substituent. Therefore, the ether oxygen plays an important role in directing entry of this nucleophile, the effect being particularly evident in the relative proportion of **9**.

[12] Quenching of the reaction mixtures with ethanol at −78 °C delivered **10** and **11** in a 1:1 ratio. Alternative use of saturated aqueous NH_4Cl solution at the same temperature gave more **11** than **10** (ratio 2:1, 71% yield). Independent equilibration of **10** and **11** with NaOMe in methanol at 20 °C also led to a 2:1 predominance of transfused isomer **11**.

[13] Review: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

[14] The stereochemical features of **10**, **11**, and **13** were deduced by 2D COSY ^1H-^1H chemical shift correlation at 500 MHz. Details of these analyses will be amplified upon in the full paper.

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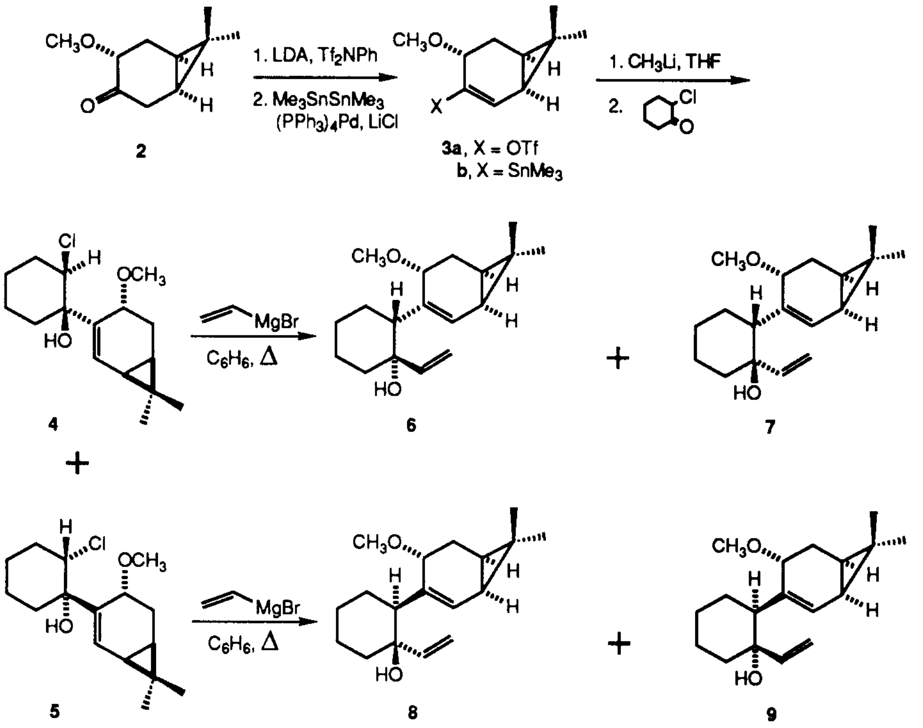
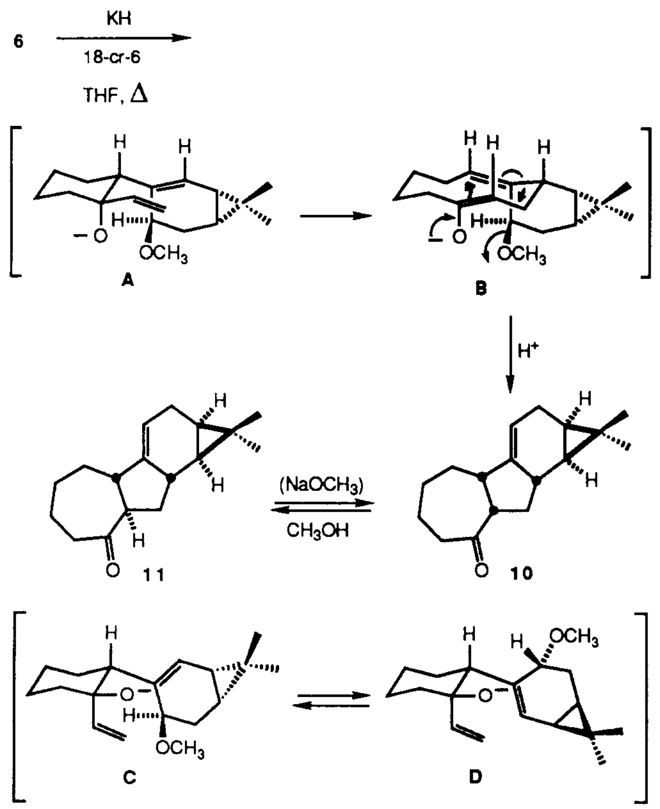
Scheme II



Scheme III



By comparison, the topography intrinsic to **7** is not as sterically conducive to [3.3] sigmatropy. In conformation C, the two π-termini are not all in adequate proximity for bonding. The chair alternative D poses a different dilemma. The combination of diminished accessibility to the syn face of the norcarene double bond *and* steric screening by the solvated alkoxide substituent is apparently not easily surmounted. As a consequence, **7** does not isomerize.

When **8** was heated analogously for 5 h, conversion to ketones **12** and **13** occurred (Scheme IV).[14,15] This isomerization signaled that its potassium alkoxide chooses to adopt conformation E despite the need to accomplish C–C bond formation syn to the dimethylcyclopropane ring (note, however, the axial alkoxide substituent). The 35% efficiency of this conversion and the co-production of **14** (36%) are a likely reflection of this steric feature. Once F is accessed, its trans,trans geometry once again (as in B) permits subsequent transannular *backside* allylic ether displacement. When admixed with sodium methoxide in methanol, **12** was transformed completely into **13**.

The conversion of **8** to **14** can be concisely rationalized as initially proceeding via transition state G, a simple rotamer of E (Scheme IV). The stereochemical outcome of the ensuing structural change is H, a *cis,trans*-cyclodecadiene. Since arrival at a medium ring having this geometry effectively precludes transannular conjoining of two olefinic centers because of the large interconnective gap that now exists,[16] H is not capable of subsequent S_N' reaction. In this instance, protonation ultimately delivers **14**.

The initial ring expansion in **9** seemingly utilizes a transition-state geometry (I) akin to that found in G (Scheme V). Subsequent arrival at J provides no other option but protonation to again deliver **14** (67%).

The acquisition of stereoisomers **10**–**13** illustrates the scope and stereoselectivity of the present method.[17] The success of this strategy is, of course, necessarily dependent upon assembling functional group arrays where the attainment of termini proximity is not problematic (as in **7**).

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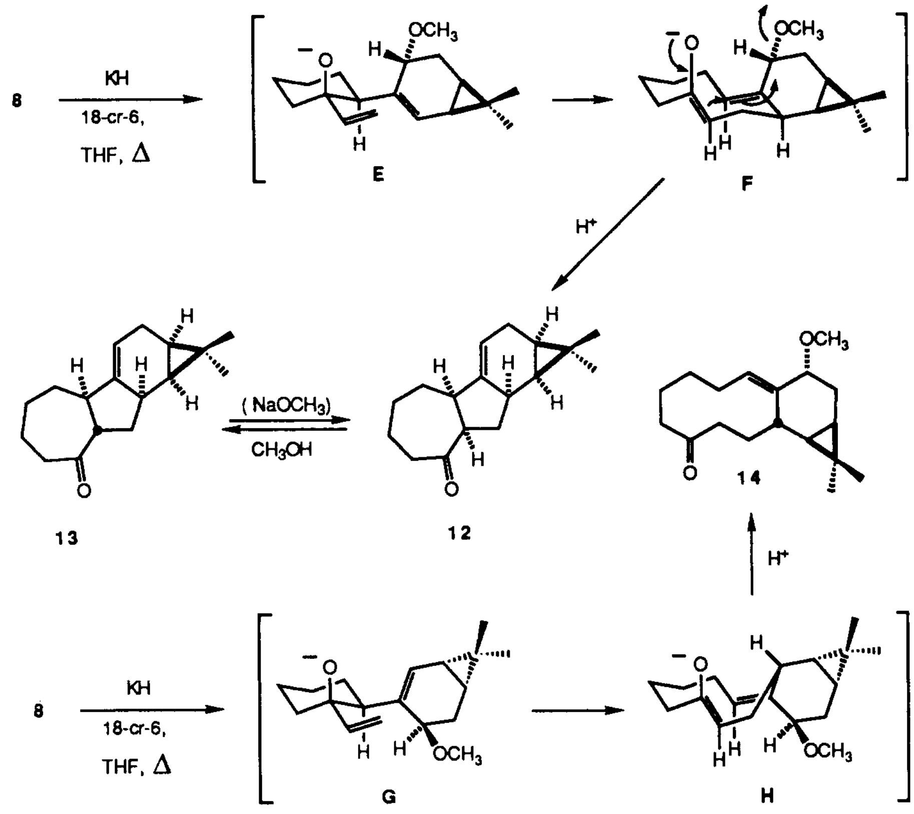
(15) Quenching of these reaction mixtures ethanol at −78 °C gave rise to **12** and **13** in a 1:3 ratio. When saturated aqueous NH_4Cl solution was employed under otherwise identical conditions, only **13** was isolated.

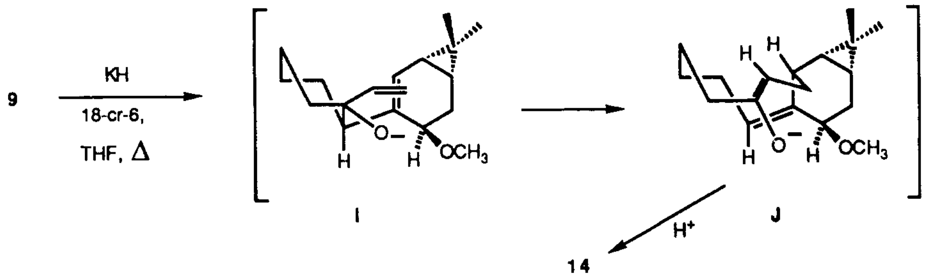
(16) Evaluation of the trans 1,5-enols of *cis*- and *trans*-cyclodecen-5-one by means of the MODEL program with complete energy minimization gave the following transannular gaps for potential cyclization: trans,trans isomer, 2.86 Å; cis,trans isomer, 3.20 Å.

(17) The yields in examples less sterically congested than those described herein are significantly improved.

Scheme IV



Scheme V



Furthermore, a kinetic predisposition for generation of an intermediate *cis,trans*-cyclodecadiene [as seen for **8** (in part) and **9**] must be recognized as conducive to stalemating the medium-ring enolate anion from entering into transannular bonding. The best scenario features evolution of a *trans,trans*-cyclodecadiene such as B and F where ideal stereoalignment is available for S_N' ejection of methoxide ion. We note in conclusion that chairlike transition states carrying an axial oxyanionic bond (see A and E) are a necessary prelude to these two-step processes. The relative importance of this structural feature[18,19] in other contexts is presently under investigation.

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[18] Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632.

[19] Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.*, in press.