Stereocontrolled Construction of Carbocyclic Rings by Sequential Cationic Cyclization–Pinacol Rearrangements

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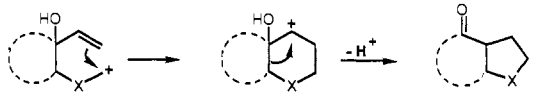
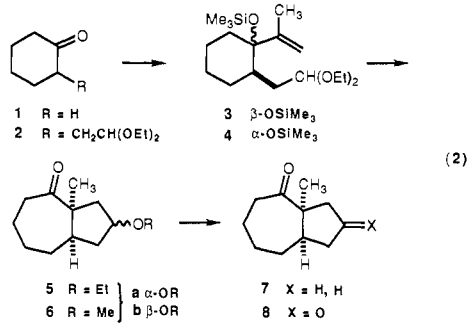
We recently reported a new synthesis of oxygen heterocycles that is believed to take place by a cationic cyclization–pinacol rearrangement pathway (eq 1, X = O).[1] In this communication



(1)

we report the development of a "ring-enlarging cyclopentane annulation" based on this mechanistic paradigm (eq 1, X = CH_2). Bicyclic and tricyclic ring systems containing five-, six-, seven-, and eight-membered carbocyclic rings can be assembled efficiently and with high stereocontrol with this chemistry. The intrinsic preference for cationic cyclizations to form six-membered rings via ordered transition states of chair topography[2] is exploited in this new method for preparing fused cyclopentanoids.[3]

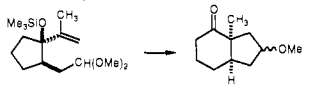
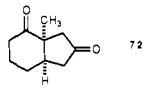
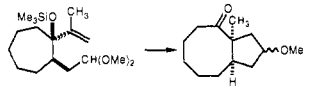
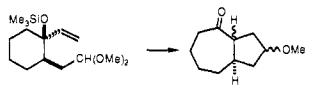
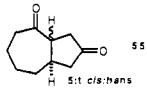
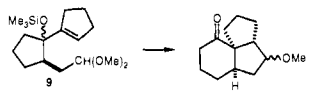
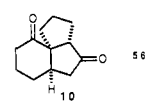
The sequence is illustrated by the transformation of cyclohexanone to the *cis*-octahydroazulenones **5** and **6**, as summarized in eq 2. Alkylation of cyclohexanone with 1,1-diethoxy-2-



(2)

bromoethane, as described by Cuvigny,[4] gave **2**, which upon treatment with (2-propenyl)lithium (−78 °C, THF) and then Me_3SiCl (23 °C, DMF, imidazole) provided a 6:1 mixture of the allylic silyl ethers **3** and **4** in 85% yield.[5-8] The key rearrangement was occasioned by treatment of this mixture of stereoisomers (0.3 M in CH_2Cl_2) with 1.1 equiv of $SnCl_4$ (−78 → −23 °C, quench at −23 °C with excess Et_3N and then MeOH).[9] Purification of the resulting product on silica gel afforded the *cis*-octahydroazulenones **5b** and **5a** in a ratio of 5:1 and 90% yield. Individual rearrangement of the separated acetals **3** and **4** confirmed that each stereoisomer afforded the cis-fused bicyclic product *exclusively*.[10] The stereochemical assignments for **5a** and **5b** followed directly from ^1H NMR NOE experiments carried out with the separated epimers.[11] In addition, chemical evidence for the cis ring fusion was obtained by sequential treatment of the methoxy hydroazulenones **6a** and **6b** (formed as a 1:5 mixture in similar overall yield from cyclohexanone and 1,1-dimethoxy-2-bromoethane) with Me_2BBr[12] and then $(n\text{-}Bu)_3SnH$ to give the *cis*-octahydroazulen-4-one **7**.[13] Oxidation of a 1:2 mixture of **6a** and **6b** with RuO_4[14] afforded a single dione **8** in 80% yield,[5] providing further confirmation that the rearrangement products were methoxy epimers.

Table I[a]

Rearrangement[b]	Yield, %[c]	Isomer ratio,[c] α:β	Dione	Yield[d] Overall, %
	82	4:1[e]		72
	75[f]	1:5		
	80	g		55
			5:1 *cis:trans*	
				56
9			10	
3-OSiMe$_3$	80	h		
α-OSiMe$_3$	70	2:1[i]		

[a] In CH_2Cl_2, [substrate] = 0.2–0.35 M, [$SnCl_4$] = 1.1 equiv, −78 → −23 °C. [b] After purification on silica gel. Stereochemical assignments were typically made by ^1H 2D COSY and ^1H 2D NOE experiments at 500 MHz. [c] By capillary GC analysis of the crude reaction product. [d] From the stereoisomeric mixture of silyl ethers produced in the addition of the vinyllithium reagent to the corresponding ketone. [e] A similar isomer ratio was produced from a 1:1 mixture of stereoisomeric starting acetals. [f] A stereoisomeric keto ether and an unknown product were found also in yields of 6% and 3%, respectively. [g] A mixture of four stereoisomeric keto ethers (53:30:10:7). A mixture of structurally related keto alcohols was also isolated in 8% yield. [h] The product was a 1:1 mixture of stereoisomeric keto ethers and keto alcohols. [i] No keto alcohols were isolated.

The broad scope and efficiency of this method are illustrated by the results summarized in Table I. Cis-fused hydrindans, hydroazulenes, and bicyclo[6.3.0]undecanes that contain functionality in both carbocyclic rings can be prepared readily in this fashion. The cis stereochemical outcome was anticipated to derive from a favored chair topography for the cyclization and rearrangement steps.[1,15] The rearrangement **9** → **10** (see Table I) was explored as a model study for the synthesis of the unusual *lycopodium* alkaloid megellanine (**11**).[16,17] It is notable that the

(1) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748. Herrinton, P. M.; Hopkins, M. H.; Mishra, P.; Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 3711.

(2) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5968. Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

(3) A number of π-cyclization terminators have been introduced for biasing cationic π-cyclizations toward forming five-membered-ring products. For an early discussion of this problem, see: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.

(4) Latchevegne, M.; Valette, G.; Cuvigny, T. M. *Tetrahedron* **1979**, *35*, 1745.

(5) Yields refer to isolated products obtained after chromatographic purification. New compounds showed IR, ^1H NMR, ^{13}C NMR, and high-resolution mass spectra in accord with their assigned structures.

(6) The major stereoisomer is assigned on the basis that vinyl Grignard and alkyllithium reagents typically add to 2-alkylcyclopentanones, 2-alkylcyclohexanones, and 2-alkylcycloheptanones preferentially from the ketone face opposite the alkyl substituent.[7]

(7) Marcou, A.; Normant, H. *Bull. Soc. Chim. Fr.* **1965**, 3491. Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107. Battioni, J. P.; Capman, M. L.; Chodkiewicz, X. *Bull. Soc. Chim. Fr.* **1969**, 976. Christl, M.; Roberts, J. D. *J. Org. Chem.* **1972**, *37*, 3443.

(8) Care must be exercised to prevent the intermediate hydroxy acetal from cyclizing to a bicyclic acetal. For example, this transformation occurs readily upon vacuum distillation, even when carried out in the presence of K_2CO_3.

(9) We have not yet extensively examined other Lewis acids. The conversion **3** → **5** can be accomplished in 75% yield in the presence of excess $Me_3SiOSO_2CF_3$. Direct rearrangement of the corresponding hydroxy acetals occurs in lower yield.

(10) No signals assignable to the trans stereoisomers were apparent in the 500-MHz ^1H NMR spectrum of the crude product mixture. Acetal **3** afforded a 6:1 mixture of **5b** and **5a**, respectively, while **4** afforded these epimers in a 1.3:1 ratio.

(11) That ^1H NOE's for cis vicinal hydrogens in five-membered rings are larger than those for trans vicinal hydrogens forms the basis for these assignments: Nakanishi, K.; Schooley, D. A.; Koreeda, M.; Miura, I. *J. Am. Chem. Soc.* **1972**, *94*, 2865.

(12) Guidon, Y.; Therien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680.

(13) House, H. O.; Gaa, P. C.; Van Derveer, D. *J. Org. Chem.* **1983**, *48*, 1661. House, H. O.; Nomura, G. S.; Van Derveer, D.; Wissinyer, J. E. *J. Org. Chem.* **1986**, *51*, 2408. House, H. O.; Yau, C. C.; Van Derveer, D. *J. Org. Chem.* **1979**, *44*, 3031.

(14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. Chong, J. M.; Sharpless, K. B. *Ibid.* **1985**, *50*, 1560.

(15) This aspect will be developed in detail in a subsequent full account of this study.

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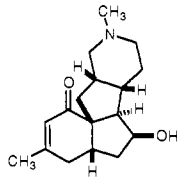

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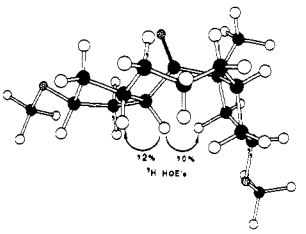

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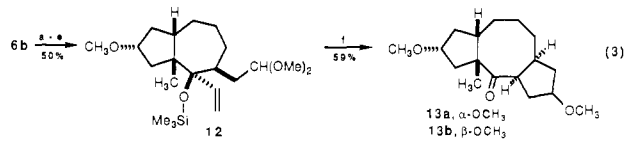
method reported here allows three of the four rings of this alkaloid target to be assembled with *complete* stereocontrol in only five steps from cyclopentanone and, moreover, directly introduces oxidation in the tricyclic product at the two desired sites. The structure of the crystalline dione **10** (mp 56 °C, from hexane) was confirmed by a single-crystal X-ray diffraction study.[18]

Since the products of acetal cyclization–pinacol rearrangements contain a ketone, the sequence reported here can be carried out in an iterative fashion to elaborate two new five-membered rings and accomplish a net two-carbon ring expansion of the starting ketone. The construction of the dicyclopentacyclooctane ring system, a tricyclic skeleton found in a number of biologically important sester- and diterpenes such as the fusicoccins and ophiobolins,[19] illustrates this sequence. Hydroazulenone **6b**, readily available from cyclohexanone (see eq 2), was first elaborated by the efficient stereocontrolled sequence summarized in eq 3 to



(3)

[a] KHMDS, 0°C, THF; $CH_2{=}CHCH_2I$, -78° to -50°C. [b] OsO_4, $NaIO_4$, dioxane-H_2O (3:1), 23°C. [c] MeOH, TsOH (cat.), 23°C. [d] $CH_2{=}CHLi$ (15 equiv), THF, -78° to 23°C. [e] $Me_3SiCH_2CO_2Et$ (20 equiv), Bu_4NF (cat.), 23°C. [f] $SnCl_4$ (1.1 equiv), CH_2Cl_2, -78° to -23°C.

provide **12** as a single diastereomer.[20] Rearrangement of **12** occurred smoothly in the presence of $SnCl_4$ to give the *cis,-anti,cis*-dicyclopentacyclooctanones **13a** and **13b** in a 1:2 ratio and 59% yield after separation on silica gel. The most stable conformation of **13b**, as determined by ^1H NMR NOE experiments and molecular mechanics calculations (MM2), is depicted in structure **14**.

In summary, a wide variety of carbocyclic ring systems can be assembled efficiently and with excellent stereocontrol by the sequential acetal cyclization–pinacol rearrangement strategy reported here. This new chemistry significantly broadens the range of precursors potentially available for assembling carbocyclic skeleta since cyclopentane annulation is coupled with expansion of a preexisting ring. The studies described here, together with our earlier reports[1] and recent disclosures by Trost[22] and Sworin,[23] clearly establish the utility of reaction designs that employ pinacol rearrangements to terminate cationic cyclizations.

Acknowledgment. This research was supported by a NIH Jarvis Neuroscience Investigator Award (NS-12389). NMR, mass spectral, and X-ray instrumentation employed in this study were purchased with the assistance of NSF Shared Instrumentation Grants. We especially wish to acknowledge Dr. Joseph Ziller for carrying out the X-ray analysis of **10**, Dr. Shoumo Chang for assistance with 2D NMR experiments, and Dr. Matthew Abelman for numerous insightful suggestions.

Supplementary Material Available: A typical procedure for the rearrangement step and experimental data for the X-ray diffraction study of **10** (7 pages). Ordering information is given on any current masthead page.

(16) Castillo, M.; Loyola, L. A.; Morales, G.; Singh, I.; Calvo, C.; Holland, M. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2893. Loyola, L. A.; Morales, G.; Castillo, M. *Phytochem.* **1979**, *18*, 1721.

(17) These alkaloids have not been prepared by total synthesis. Two approaches were recently disclosed. See: St. Laurent, D. R.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 3861. Mehta, G.; Rao, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1578.

(18) R_F = 5.9%, R_{wF} = 6.5%. Details are provided as Supplementary Material.

(19) For a review, see: Cordell, J. *Phytochemistry* **1974**, *13*, 2343. Leading references to recent synthesis efforts in this area can be found in: Rigby, J. H.; Senanayake, C. *J. Org. Chem.* **1987**, *52*, 5635.

(20) The stereochemical outcome of these transformations is consistent with existing precedent;[21] the stereochemistry of the acetal side chain was rigorously established by 2D ^1H NOE experiments.

(21) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081.

(22) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556.

(23) Sworin, M.; Neumann, W. L. *J. Org. Chem.* **1988**, *53*, 4894.

Three-Dimensional Heteronuclear NMR of ^{15}N-Labeled Proteins

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The introduction of two-dimensional (2D) NMR[1] has made it possible to determine solution structures of small proteins.[2] Although the 2D approach greatly reduces spectral overlap, many ambiguities remain in the analysis of 2D protein NMR spectra because of coincident or nearly coincident chemical shifts. Commonly used procedures to solve this type of problem rely on the fact that the chemical shifts of many protons show different pH and temperature dependence. Another, more elegant approach utilizes 3D NMR[3-6] to remove the problem of degenerate chemical shifts. Homonuclear 3D techniques, combining *J* connectivity and NOE information, have recently been demonstrated for small proteins, clearly demonstrating the power of this approach.[6,7] However, for proteins larger than about 15 kD, the *J* connectivity transfer step in such a 3D experiment rapidly looses its efficiency, severely decreasing sensitivity. Here the use of a very sensitive 3D experiment is demonstrated for unraveling the regular protein NOESY spectrum. This method requires ^{15}N labeling of the protein, a relatively simple procedure for bacterially overexpressed proteins. High-quality 3D NMR spectra can be obtained in a few days, without excessive demands for data processing or data storage.

The NOESY–HMQC pulse scheme we utilized (Figure 1) is slightly different from the scheme proposed very recently by Fesik and Zuiderweg,[8] permitting observation of NOE's to CαH protons that resonate very close to the H_2O resonance. The t_1 and t_3 dimensions represent the time variables in a regular NOESY experiment; during the t_2 dimension the NH protons are labeled with their ^{15}N chemical shifts. Therefore, a projection of the 3D spectrum onto the F_1,F_3 plane corresponds to the regular amide region of a 2D NOESY spectrum. However, individual F_1,F_3

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(1) Ernst, R. R.; Bodenhausen, G.; Wokaun, A. *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*; Clarendon: Oxford, 1987.
(2) Wuethrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986.
(3) Griesinger, C.; Sørensen, O. W.; Ernst, R. R. *J. Magn. Reson.* **1987**, *73*, 574.
(4) Griesinger, C.; Sørensen, O. W.; Ernst, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 7227.
(5) Vuister, G. W.; Boelens, R. *J. Magn. Reson.* **1987**, *73*, 328.
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(7) Vuister, G. W.; Boelens, R.; Kaptein, R. *J. Magn. Reson.* **1980**, *80*, 176.
(8) Fesik, S. W.; Zuiderweg, E. R. P. *J. Magn. Reson.* **1988**, *78*, 588.