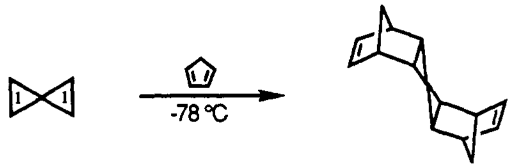
Confirmation that **1** was produced as a discrete species was provided by the isolation of the Diels-Alder adduct **6**. Thus when the walls of the liquid nitrogen trap used to collect **1** were coated with cyclopentadiene, compound **6** was isolated in 10% yield as a colorless oil. The structure of **6** is based on the $^1H$ and $^{13}C$ NMR spectra, which compare favorably with data from other cyclopropene adducts.[6,7,14] The $C_2$ symmetry of **6** leads, as expected, to seven $^{13}C$ NMR signals for the norborenyl carbons.



**1** **6**

Studies to confirm the anticipated properties[3,4] of **1** are in progress. These results will be reported shortly.

**Acknowledgment**. We gratefully acknowledge the Robert A. Welch Foundation for support of this work. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

**Supplementary Material Available:** Experimental procedures including complete characterization of **1–6** and $^1H$ and $^{13}C$ NMR spectra of **2** and **4–6** (6 pages). Ordering information is given on any current masthead page.

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## New Approach to *Strychnos* Alkaloids. Stereocontrolled Total Synthesis of (±)-Dehydrotubifoline[1]

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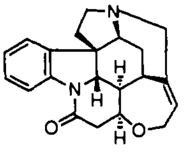
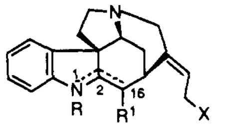
*Received February 11, 1991*

Only modest progress has been recorded in the arena of *Stychnos* alkaloid total synthesis since the exceptional preparation of strychnine (**1**) by the Woodward group over 35 years ago.[2]



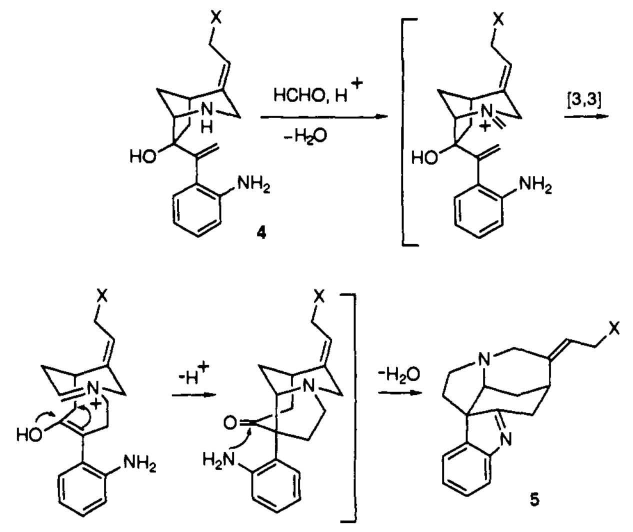
**strychnine (1)**



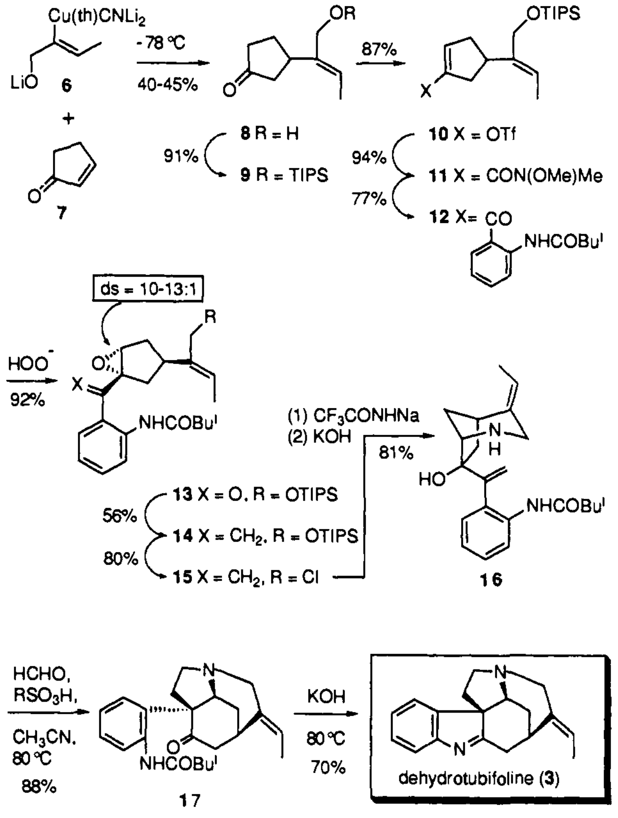
**akuammicine (2)**
R = X = H , R$^1$ = CO$_2$Me ; 2,16-dehydro
**dehydrotubifoline (3)**
R = : , X = R$^1$ = H ; 1,2-dehydro

Notably few method for assembling the core pentacyclic strychnan skeleton (exemplified in **2** and **3**) of this large and diverse alkaloid family have been developed.[3,4] In this communication we report a conceptually new approach to *Strychnos* alkaloids, which is characterized by the concise evolution of the strychnan skeleton (**5**) by "aza-Cope–Mannich"[1,5] rearrangement of a 2-azabicyclo[3.2.1]octane precursor **4** (Scheme I).

**Scheme I**



**Scheme II**[a]



[a] TIPS = $(i\text{-Pr})_3Si$; Tf = $SO_2CF_3$; th = 2-thienyl.

The required cis relationship of the styrene and amine functionality on the 2-azabicyclo[3.2.1]octane ring was secured by assembling the key cyclization precursor **16** from intramolecular aminolysis of cyclopentene epoxide **15** (Scheme II).[6] This latter intermediate was prepared in nine steps from 2-cyclopentenone as outlined in Scheme II. The elements of the bridging E ring and its (*Z*)-ethylidene appendage were initially introduced by

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(1) Synthesis Applications of Cationic Aza-Cope Rearrangements. 22. Part 21: Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598.

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(3) For recent reviews, see: (a) Husson, H. P. In *Indoles: Monoterpene Indole Alkaloids*; Saxon, J. E., Ed.; Wiley: New York, 1983; Chapter 7. (b) Bosch, J.; Bonjoch, J. In *Studies in Natural Products Chemistry. Volume 1. Stereoselective Synthesis (Part A)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; pp 31–88.

(4) For recently reported alternate approaches to *Strychnos* alkaloids of the strychnan-type, see: (a) Amat, M.; Alvarez, M.; Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Lavilla, R.; Garcias, X.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 3453 and references therein. (b) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. (c) Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624. (d) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696.

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(6) For background studies leading to this strategy, see: Marquis, R. W., Jr. Ph.D. Dissertation, University of California, Irvine, 1989.

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treating (*Z*)-2-bromo-2-buten-1-ol[7] sequentially (−78 °C, ether–THF) with 3 equiv of *t*-BuLi, 1 equiv of lithium thienylcyanocuprate,[8] 2 equiv of $Me_3SiCl$[9] and 1 equiv of 2-cyclopentenone. Chromatographic purification provided cyclopentanone **8** in 40–45% yield.[10] Protection of the primary alcohol of **8** as a triisopropylsilyl (TIPS) ether[11] and subsequent regioselective enolization (−78 °C, THF) of **9**[12] with Masamune's base[13] provided, after in situ triflation[14] ($Tf = SO_2CF_3$), the enol triflate **10**. This intermediate was contaminated with ca. 10% of its double-bond regioisomer.[15] Carbonylation of **10** [5% $Pd(PPh_3)_4$, CO (1 atm), DMF, 55 °C][16] in the presence of *N*,*O*-dimethylhydroxylamine provided amide **11**. Acylation of **11**[17] with the aryllithium dianion prepared from 2-(trimethylacetamido)bromobenzene[18] gave enone **12** in an overall yield of 63% from cyclopentanone **9**.

Enone **12** was epoxidized with good facial selectivity (10–13:1) at −23 °C (*t*-BuOOH, Triton B) to give **13**, which afforded styrene **14** upon subsequent reaction with 3 equiv of (methylene)triphenylphosphorane (THF, −78 → 23 °C). Desilylation of **14** with $(n\text{-}Bu)_4NF$ followed by chlorination of the liberated alcohol (MsCl, DMF, LiCl, −23 → 23 °C) afforded the allylic chloride **15**. Although direct bis-aminolysis of **15** with $NH_3$ was not clean, the desired cyclization was accomplished by sequential treatment of **15** (DMF, 23 °C) with the sodium salt of trifluoroacetamide,[19] followed by cleavage of the resulting bicyclic amide with KOH ($EtOH–H_2O$, 80 °C). This sequence delivered the azabicyclic amine **16** in 35% overall yield from enone **12**.

The pivotal rearrangement of **16** was occasioned under standard mild conditions [paraformaldehyde (1.5 equiv), camphorsulfonic acid (1.0 equiv), $Na_2SO_4$ (2 equiv), $CH_3CN$ at reflux][1] to provide a single crystalline product **17** in 88% yield. Hydrolysis of this intermediate with a large excess of KOH in $EtOH–H_2O$ (2:1) at reflux provided, in 70% yield, (±)-dehydrotubifoline (**3**). The synthetic product was indentical with an authentic sample prepared by acid treatment of natural akuammicine.[20]

The chemistry outlined herein defines a short, highly stereocontrolled, new strategy for preparing *Strychnos* alkaloids. The overall yield of (±)-dehydrotubifoline from 2-cyclopentenone was 6%, and this conversion was accomplished in only 12 chemical operations. Besides the key aza-Cope–Mannich rearrangement step (**16** → **17**), other notable transformations include 1,4-addition of a 1-hydroxy-2-butenyl cuprate (**7** → **8**) and formation of an unsaturated *N*-methyl-*N*-methoxyamide by palladium-catalyzed carbonylation–aminolysis of an enol triflate (**10** → **11**). The extension of this approach to the preparation of strychnine and other complex *Strychnos* alkaloids is under investigation.

**Acknowledgment**. The support of PHS Grant NS-12389 is gratefully acknowledged as is fellowship support for J.M.F. from the American Cancer Society (PF-3171). NMR and mass spectra were determined at Irvine with spectrometers acquired with the assistance of NSF shared instrumentation grants. We thank Dr. Susan Vice for her early efforts on this project, Mr. Steven Knight for optimizing the preparation of **10** and **11**, and Professor E. Wenkert and J. Lēvy for samples of natural akuammicine.

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[7] Readily available in 90% overall yield from methyl *trans*-crotonate by bromination, dehydrobromination ($Et_3N$, pentane, reflux), and $(i\text{-}Bu)_2AlH$ (−78 °C, $CH_2Cl_2$) reduction.

[8] Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

[9] (a) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

[10] Yields are reported for isolated compounds purified by flash chromatography on silica gel. All new compounds showed $^1H$ NMR, $^{13}C$ NMR, IR, and high-resolution mass spectra in complete accord with their assigned structures.

[11] Ogilvie, K. K.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, 2865.

[12] For an alternate, longer preparation of **9**, see ref 6.

[13] Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

[14] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

[15] These isomers have been separated by careful chromatography on silica gel (hexane) to give **10** in 71% yield and >40:1 isomeric purity. In early experiments this mixture was carried forward, and subsequent purified intermediates contained only a few percent of the undesired regioisomer.

[16] For the preparation of simple α,β-unsaturated amides in this way, see: Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

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# Spectra of the Solvated Electron in the Presence of Sodium Cation in Tetrahydrofuran and in Its α,α′-Methylated Derivatives[†]

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We report the first optical absorption spectra of a solvated electron with clearly resolved structures. The results presented in this communication were obtained via time-resolved pulse radiolysis experiments on tetrahydrofuran (THF), mixed *cis*- and *trans*-2,5-dimethyltetrahydrofuran (2,5-DMTHF), and 2,2,5,5-tetramethyltetrahydrofuran (2,5-TMTHF) solutions containing millimolar concentrations of sodium salts.

It has been known for quite some time that the properties of the solvated electron in solutions of electrolytes in moderately polar solvents differ considerably from its properties in the same solvents but in the absence of electrolytes.[1,2] Specifically, for sodium salts in tetrahydrofuran (THF), the absorption maximum occurs at 880 nm (1.41 eV), compared with 2120 nm (0.58 eV) for $e^-_{sol}$ in neat THF.[3] This phenomenon is attributed to the formation of a new species $(e^-,M^+)$.[4] The magnitude of the spectral shift is not a monotonic function of the radius of the bare cation[5] and is, for example, smaller for lithium than for sodium. It appears to depend critically on the degree of solvation of the alkali-metal cation, which controls the equilibrium distance between the positive charge and the electron.

In this study we investigated the influence of the structure of the solvent molecule on the spectral and kinetic properties of the $(e^-,Na^+)$ moiety. 2,5-DMTHF and 2,5-TMTHF were selected as interesting media since their dipole moments and dielectric constants are similar to those of unsubstituted THF, yet their ability to tightly solvate alkali-metal cations is significantly diminished as a result of the steric hindrance generated by the presence of two or four methyl groups in the α positions.

Our time-resolved pulse radiolysis experiments were performed on purified samples of the above ethers that contained 5–20 mM sodium salts. Tetraphenylboron sodium was used as the source

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[†] Work performed under the auspices of the Office of Basic Energy Sciences, Division of Chemical Science, US-DOE, under Contract No. W-31-109-ENG-38.

[1] Klosterboer, J. G.; Gilling, L. J.; Rettschnick, R. P. H.; Van Voorst, J. D. W. *Chem. Phys. Lett.* **1971**, *8*, 457.

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[3] Bockrath, B.; Dorfman, L. M. *J. Phys. Chem.* **1973**, *77*, 1002.

[4] The species $(e^-,M^+)$ is often regarded as an "ion pair" composed of the solvated electron and the solvated metal cation. However, it should be pointed out that there is no experimental evidence (results of the present study included) that would prove the validity of this structure and would rule out the possibility of a spherically symmetric, hydrogen-like, geometry of the $(e^-,M^+)$ moiety, with the solvated metal cation residing in the center and the electron delocalized over its solvation shell. Therefore, in our description of $(e^-,M^+)$, we will refrain from using the term "ion pair", which implies a nonconcentric, axial arrangement of the components.

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