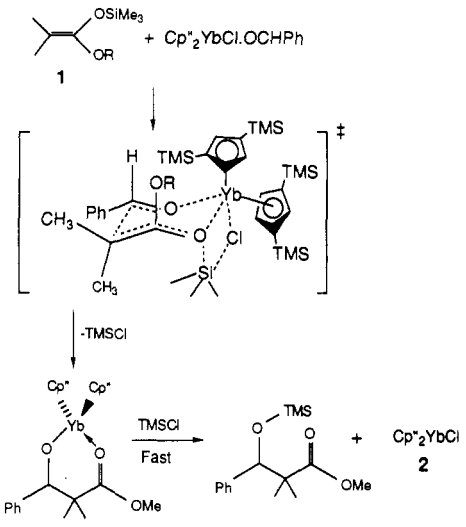
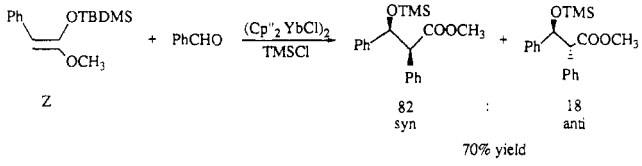
Scheme I



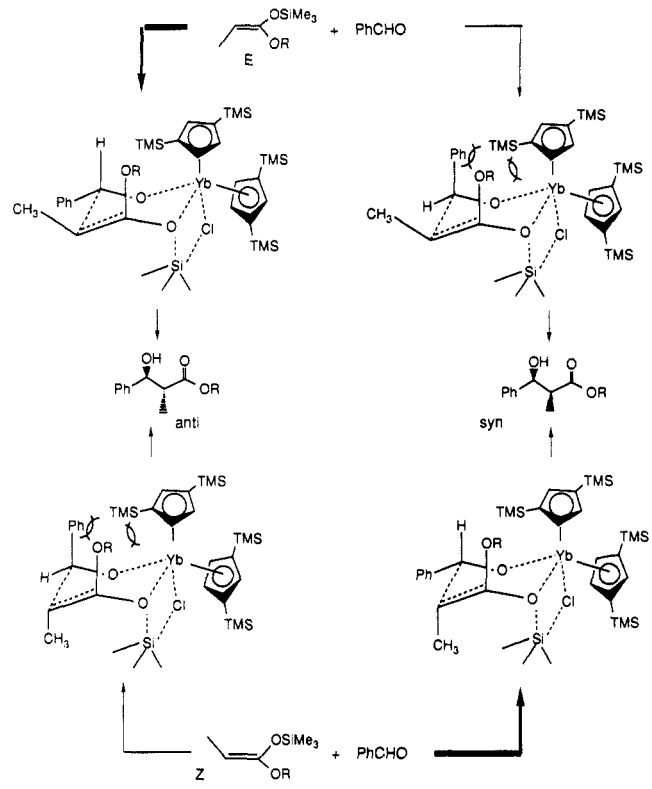
isomer is readily available from methyl phenylacetate and gave the result:



The reactions of the silyl enol ethers of various propionate esters with either TMS or TBDMS groups are summarized in Table I. From these data it appears that the *E* isomers react with >95% diastereoselection whereas that of the *Z* isomers is about 80–90%. The results are readily rationalized by a mechanism that is consistent with kinetic studies.[13] The use of other Lewis acids in such reactions generally gives poor diasterioselection.[14]

The ytterbium compound **2** is a dimer in inert solvents but forms a solvated monomer in donor solvents such as THF.[15] Color changes and the IR spectrum indicate that **2** forms a complex with the aldehyde, $Cp''_2YbCl{\cdot}OCHR$, which undergoes rate-determining reaction with the silyl enolate to give a hypothesized internally coordinated Yb intermediate. The latter rapidly reacts with the TMSCl present to give the product which is hydrolyzed on workup. This mechanism is shown in Scheme I and is consistent with the kinetic observation that the rate is independent of the concentration of TMSCl so long as some is present.[13]

Scheme II



On the basis of this mechanism, the stereochemical results are readily rationalized by the transition-state structures in Scheme II. The favored pathway in each case is shown by the heavy arrow. This scheme is an obvious application of the Zimmerman–Traxler model[16] as extended to the Mukaiyama addition by Chan et al.[17] The organolanthanide compound **2** thus shows promise as a useful addition of the growing armory of reagents for promoting stereocontrolled aldol-type addition reactions. With many possibilities for structural modification of the cyclopentadienyl ligands, the central lanthanide metal and the leaving halide, much further refinement of the reagent is clearly possible and is currently in progress.

Acknowledgment. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the Department of Energy, under Contract Number DE-AC03-76SF00098.

(13) Reported at the 1st International Conference on f-Elements, Leuven, Belgium, Sept. 6, 1990; Streitwieser, A.; Gong, L. *Eur. J. Solid State Inorg. Chem.*, in press.
(14) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.
(15) Gong, L.; Streitwieser, A., Jr.; Zalkin, A. *J. Chem. Soc., Chem. Commun.* **1987**, 460.
(16) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1020.
(17) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, *20*, 4029.

Total Synthesis of *dl*-Stenine

Cheng-yi Chen and David J. Hart*

Department of Chemistry, The Ohio State University, 120 W. 18th Ave., Columbus, Ohio 43210

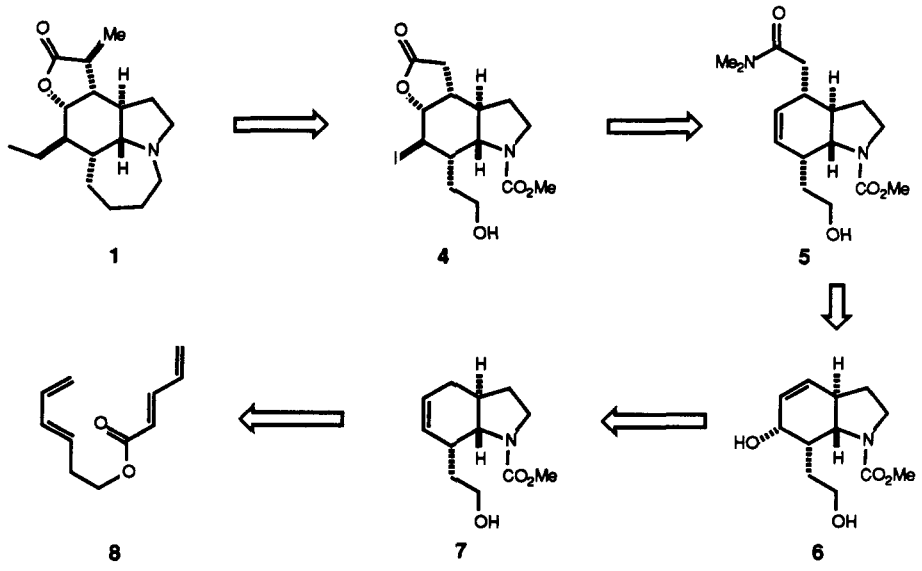
Received October 8, 1990

Summary: Intramolecular Diels–Alder cycloadduct **10** was converted to the *Stemona* alkaloid stenine (**1**) via a reaction sequence that features a Curtius rearrangement (**12** → **13**), Eschenmoser–Claisen rearrangement (**19** → **20**) and stereoselective free radical allylation (**4** → **21**).

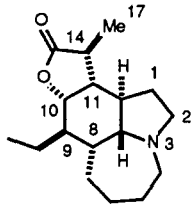
The roots of *Stemona tuberosa* and *Stemona japonica* have long been used in Chinese folk medicine as insecti-

0022-3263/90/1955-6236$02.50/0

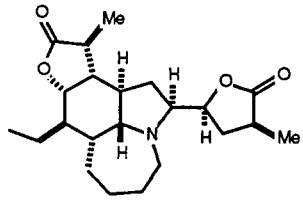
Scheme I



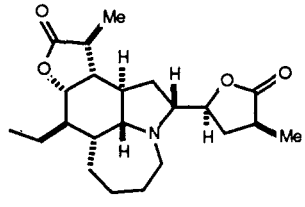
cidal, antiparasitic, and antitussive agents. At least 14 alkaloids have been isolated from these plants and their structures have been determined by a combination of X-ray crystallographic and degradative techniques.[1] Among them, stenine (1), tuberostemonine (2), tuberostemonine A (3) are structurally related.[2,3] Although the biological activity of stenine (1) has not been reported, tuberostemonine (2) inhibits neuromuscular transmission in crayfish and may be a useful tool in the field of neuropharmacology.[4] Although several approaches to this triad of alkaloids have been described, no total syntheses have been accomplished.[5-7] This paper presents the first total synthesis of stenine (1) using a strategy that we hope to extend to a synthesis of 2.



1



2



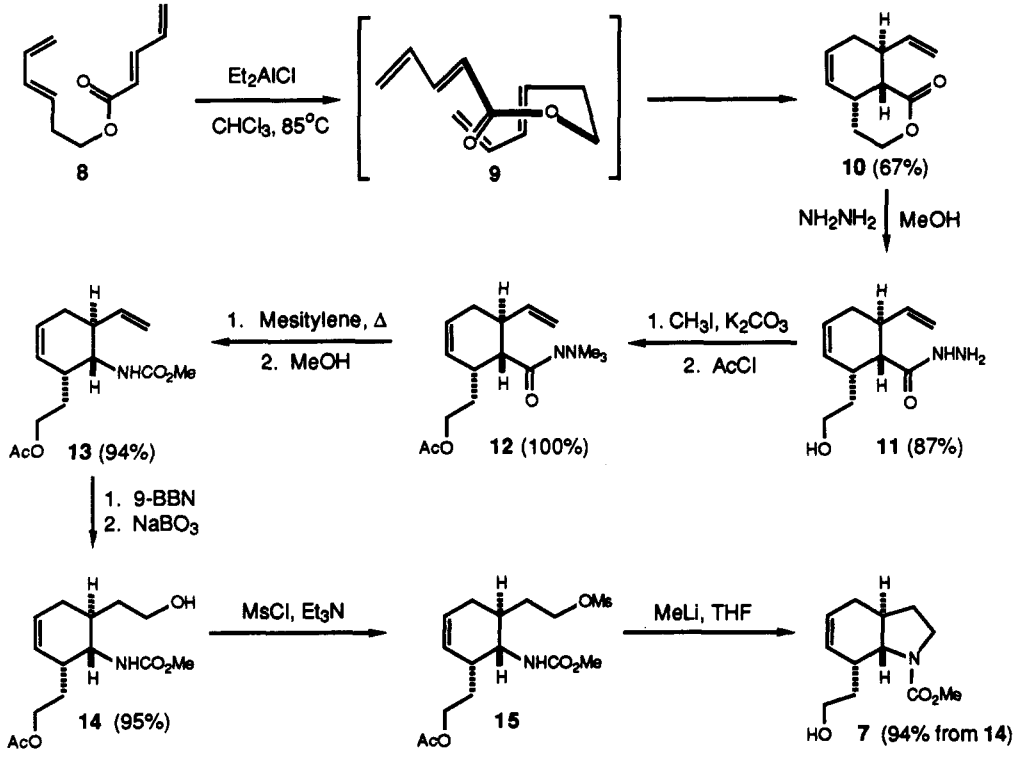
3

Stenine (1) contains seven stereogenic centers, and it was our hope that the synthesis would introduce these in a systematic fashion. Thus, our approach to stenine (1) is outlined antithetically in Scheme I. It was felt that iodolactone 4 would be a reasonable precursor to stenine (1). We planned to form the seven-membered ring in the later stages of the synthesis. The C(14) methyl group was to be introduced using an alkylation, while the ethyl group was to be introduced using an intermolecular free-radical carbon–carbon bond-forming reaction. It was anticipated that iodolactone 4 would be prepared from the tertiary amide 5, which in turn would be prepared from 6 using an Eschenmoser–Claisen rearrangement. The terminal hydroxyl group in intermediate 7 was to serve as a handle for introduction of the cyclohexenol moiety in intermediate 6, and the cyclohexene ring in 7 was to be constructed using a Diels–Alder reaction.

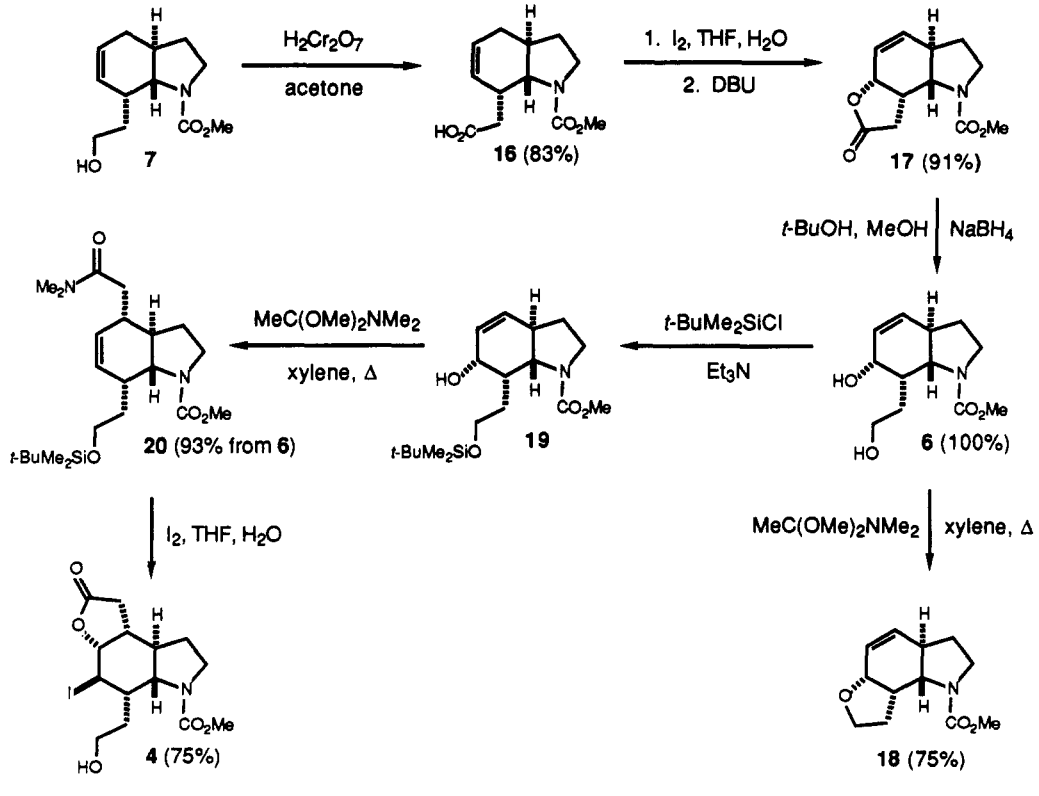
After investigating several unsuccessful routes to 7 using intermolecular Diels–Alder reactions, we settled on the route outlined in Scheme II. Thus, treatment of (*E*)-2,4-pentadienoyl chloride[8] with the lithium alkoxide of (*E*)-3,5-hexadienol[9] gave a 98% yield of tetraene 8. Treatment of 8 with diethylaluminum chloride in chloroform at 85 °C gave cycloadduct 10 (67%) as a single stereoisomer. This reaction presumably takes place via endo-chair transition state 9.[10] Treatment of lactone 10 with hydrazine in carefully degassed methanol gave hydrazide 11 in 87% yield after a single recrystallization. Methylation of 11 in the presence of potassium carbonate gave the corresponding aminimide and acetylation of the free hydroxyl group gave 12 in quantitative yield.[11] Thermolysis of 12 at 160 °C in mesitylene, followed by addition of anhydrous methanol afforded carbamate 13 (94%).[12] The synthesis of hexahydroindole 7 was com-

(1) Goetz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1976; Vol. IX, pp 545–551 and references cited therein.
(2) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull.* **1967**, *15*, 768.
(3) Harada, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1967**, 460.
(4) Shinozaki, H.; Ishida, M. *Brain Res.* **1985**, *334*, 33.
(5) Haruna, M.; Kobayashi, T.; Ito, K. *Tennen Yuki Kagobutsu, Toronkai Koen Yoshishu* **1977**, *27*, 200; *Chem. Abstr.* **1986**, *105*, 79195k.
(6) Xiang, L.; Kozikowski, A. P. *Syn. Lett.* **1990**, *2*, 279.
(7) For a synthesis of croomine, a structurally unrelated stemona alkaloid, see: Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
(8) Davies, C. R.; Davies, J. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2390.
(9) Martin, S. F.; Tu, C.-Y.; Chou, T. S. *J. Am. Chem. Soc.* **1980**, *102*, 5274.
(10) For a review of intramolecular Diels–Alder reactions, see: Ciganek, E. *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1984; Vol. 32, pp 1–374. Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.
(11) For a review of the chemistry of aminimides, see: McKillip, W. J.; Sedor, E. A.; Culbertson, B. M.; Wawzonek, S. *Chem. Rev.* **1973**, *73*, 255.
(12) Masuyama, A.; Tsuchiya, K.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2855. Benecke, H. P. *Tetrahedron Lett.* **1977**, 997. Benecke, H. P.; Wickel, J. H. *Tetrahedron Lett.* **1972**, 289.

Scheme II



Scheme III



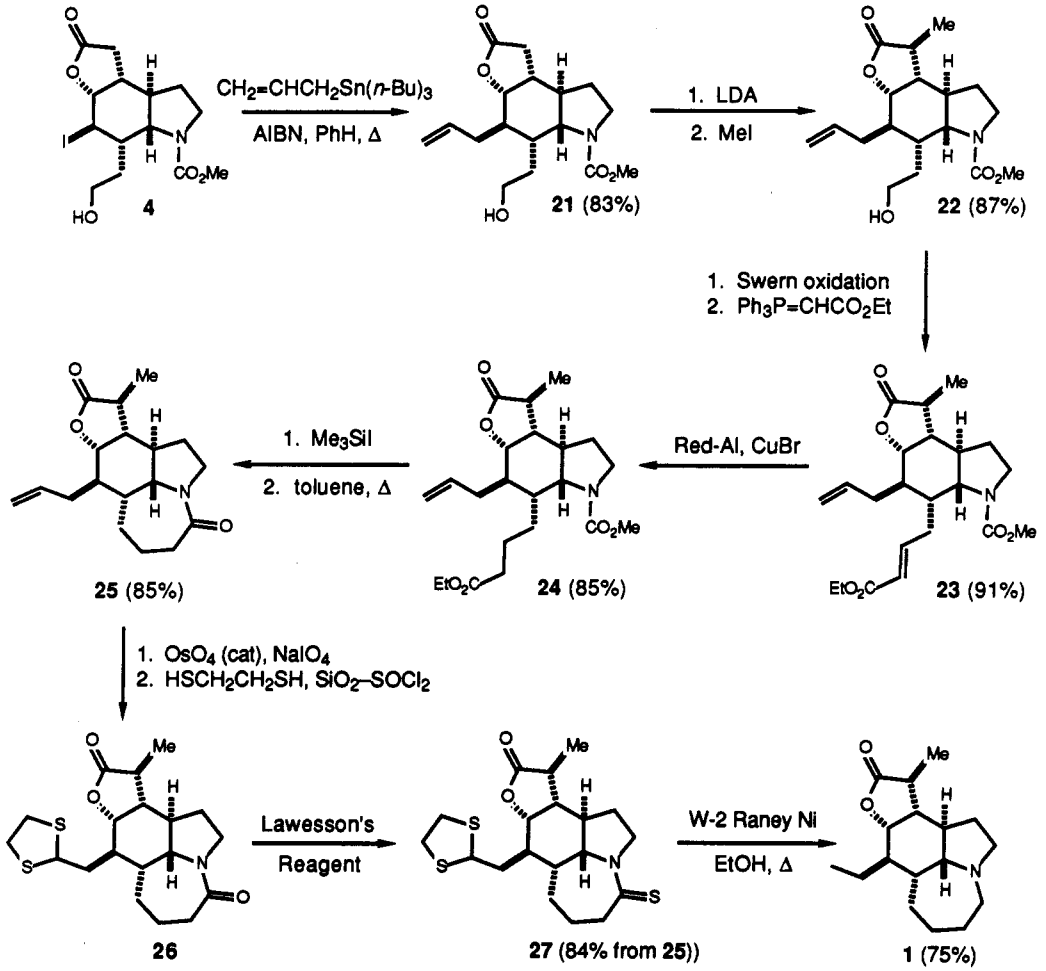
pleted using a straightforward reaction sequence. Thus, hydroboration–oxidation of 13 gave primary alcohol 14 in 95% yield.[13] Conversion of the alcohol to the corresponding mesylate and treatment of this material (15) with methyllithium gave 7 in 94% overall yield from 14.

The conversion of 7 to tricycle 4 was accomplished using the seven-reaction sequence outlined in Scheme III. Thus, oxidation of 7 using Jones reagent gave carboxylic acid 16 (83%).[14] A halolactonization–elimination sequence con-

(13) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280, 5281. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483.

(14) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

Scheme IV



verted **16** into **17** in 91% overall yield.[15] Although the stereochemical course of reactions to this point of the synthesis had been reasonably well established using NMR spectroscopy, assignments were put on a firm basis by performing an X-ray crystallographic analysis of **17**.[16] Continuing with the synthesis, reduction of lactone **17** using sodium borohydride gave diol **6** (100%).[17] Direct installation of the C(11) side chain using **6** was problematic as treatment of this diol with *N,N*-dimethylacetamide dimethyl acetal gave tetrahydrofuran **18** in 75% yield. Thus, the primary hydroxyl group was protected and the resulting allylic alcohol **19** was subjected to the Eschenmoser–Claisen conditions to give the desired amide **20** (93%).[18] Treatment of **20** with iodine in aqueous tetrahydrofuran completed the preparation of **4** in 75% yield.[19]

The conversion of iodolactone **4** into stenine (**1**) is outlined in Scheme IV. Allylation of **4** gave a single product in 83% yield.[20] This material was initially assigned structure **21** based on steric grounds, and the structure was later established by X-ray crystallography (vide infra). Alkylation of **21** once again gave a single stereoisomer, assigned structure **22**, in 87% yield.[21] The stereochemical relationship between C(10) and C(14) in **22** was established by difference NOE studies that indicated a cis relationship between the C(14) methyl group and C(10) hydrogen. Swern oxidation of **22** followed by a Wittig reaction gave unsaturated ester **23** in 91% yield and reduction of the conjugated double bond using Red-Al–CuBr gave ester **24** (85%).[22,23] The carbamate was removed using iodotrimethylsilane,[24] and the resulting amino ester was warmed in toluene for 12 h to afford lactam **25** in 85% overall yield. The structure of **25** was established by X-ray crystallography.[16] Johnson–Lemieux oxidation[25] of **25** followed by treatment of the resulting aldehyde with 1,2-ethanedithiol and silica gel impregnated with thionyl chloride[26] gave thioacetal **26**. Treatment of **26** with Lawesson's reagent gave thiolactam **27** (84% from **25**).[27] Reduction of **27** using W-2 Raney Ni[28] in ethanol at room temperature completed the synthesis of racemic stenine (**1**) in 75% yield. Although we were unable to

(15) For reviews on the halolactonization, see: Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171. Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 411–501.

(16) X-ray crystallographic analyses of compounds **17** and **25** were performed by Dr. Judith C. Gallucci at The Ohio State University Department of Chemistry Crystallographic Facility.

(17) Soai, K.; Oyamada, H.; Takse, M.; Okawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.

(18) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425.

(19) Faffaut, R. F. *J. Am. Chem. Soc.* **1952**, *74*, 4460.

(20) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

(21) Marshall, J. A.; Wuts, P. G. M. *J. Am. Chem. Soc.* **1978**, *100*, 1627.

(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(23) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.

(24) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.

(25) Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(26) Kamitori, T.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427.

(27) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(28) Kornfeld, E. C. *J. Org. Chem.* **1951**, *16*, 131. Wolfrom, M. L.; Karabinos, J. V. *J. Am. Chem. Soc.* **1944**, *66*, 909.

obtain an authentic sample of stenine, the ^1H NMR, IR, and MS of racemic stenine were in agreement with values reported for the natural product and the ^{13}C NMR spectrum was consistent with the assigned structure.[29]

In summary, a synthesis of stenine (1) has been accomplished in 25 steps and 5% overall yield from tetraene 8. Application of this strategy to the synthesis of tuberostemonine is underway.

(29) We thank Professor M. Haruna (Meijo University, Nagoya, Japan) for supplying a 400-MHz ^1H NMR spectrum of (-)-1 for the purpose of comparison with our 300-MHz ^1H NMR spectrum of *dl*-1.

Acknowledgment. We thank the National Institutes of Health (GM-27647) for their generous support, Dr. Charles Cottrell and Mr. Richard Weisenberger for assistance in recording NMR and Mass Spectra at The Ohio State University Chemical Instrumentation Center, and Mr. Carl Engleman for recording NMR spectra at The Ohio State University NMR Facility.

An Unexpected Reversal of Fluorine Substituent Effects in the Biomethylenation of Two Positional Isomers: A Serendipitous Discovery

Peter H. Buist* and Robert A. Pon

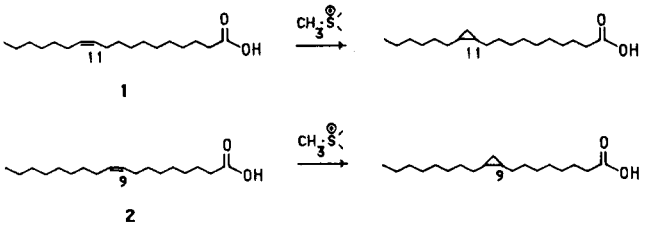
The Ottawa-Carleton Chemistry Institute, Department of Chemistry, Carleton University, Ottawa, Ontario K1S 5B6, Canada

Received September 7, 1990

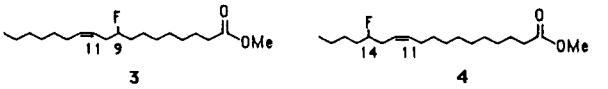
Summary: The mechanism of biological cyclopropyl fatty acid biosynthesis as it occurs in *Lactobacillus plantarum* has been probed using fluorine substituent effects. It has been shown that the pattern of rate retardations induced by homoallylic fluorine substitution is numerically the same but opposite in sense for two series of olefinic fatty acid substrates bearing the double bond at either the 9- or the 11-position.

The bacterium, *Lactobacillus plantarum*, is capable of methylenating both the *cis*-11-octadecenoic (*cis*-vaccenic) acid (1) produced by its own biosynthetic machinery as well as the *cis*-9-octadecenoic (oleic) acid (2) it meets in its natural environment.[1] The cyclopropyl products are dead-end metabolites and accumulate to such an extent that by the end of the growth cycle of this microorganism, some 80% of the cellular olefinic fatty acids have been methylenated. While considerable information has been gained on the cyclopropane synthase[2] the mechanistic details of this intriguing transformation are obscure and controversial. The current working hypothesis views this reaction as a genetic variation on a theme of olefin methylation/proton elimination which has been extensively elaborated on the sidechains of sterols[3] (See Scheme I). We have sought evidence for the existence of the putative carbocationic intermediate with the help of fluorine substituent effects—an approach which has been successful in the study of isoprenoid bioalkylations.[4] Thus we have shown that fluorine substitution at the 12-position of oleic acid has a substantially greater rate-retarding effect on biomethylenation than fluorine substitution at the 7-position.[5] It was while attempting to reproduce this result with the corresponding *cis*-fluorovaccenate series, that we stumbled upon a surprising result—namely that the pattern of fluorine-induced rate retardations is reversed as we now document.

Methyl *cis*-9-fluorovaccenate (3) and methyl *cis*-14-fluorovaccenate (4) were synthesized in racemic form using



precisely the same methodolgy as was used for the preparation of the fluorooleates referred to above.[5] All analytical data for the two homoallylically fluorinated vaccenates was satisfactory, and the compounds were judged to be pure by several chromatographic critera including capillary GC, GC/MS, and reverse-phase HPLC.



The two racemic[6] fluorinated substrates along with the parent compound were administered separately at a concentration of 40 mg/L to growing cultures of *L. plantarum* ATCC 8014. Growth of the microorganism proceeded to a similar extent in each set of experiments, and the degree of methylenation of each olefinic substrate was determined by analyzing the extracted fatty acid fraction via capillary GC as previously reported.[5]

When the results of the *cis*-vaccenate feedings are compared with the results of the oleate feedings,[5] an unexpected picture emerges as graphically illustrated in Figure 1. It is immediately obvious that the pattern of fluorine substituent effects is reversed when the double bond of the substrate is at the 11-position rather than at the 9-position. What is striking is that the numerical values obtained yield a near perfect "mirror image" pattern of rate retardations.

The simplest explanation for this phenomenon is that both substrates are visiting the same active site but are presenting *opposite* faces of the double bond to SAM—the

(1) Polacheck, J. W.; Tropp, B. E.; Law, J. H.; McCloskey, J. A. *J. Biol. Chem.* **1966**, *241*, 3362.
(2) Law, J. H. *Acc. Chem. Res.* **1971**, *4*, 199.
(3) Lederer, E. *Q. Rev.* **1969**, *23*, 453.
(4) Poulter, C. D.; Rilling, H. C. *Acc. Chem. Res.* **1978**, *11*, 306.
(5) Buist, P. H.; Findlay, J. M.; Leger, G.; Pon, R. A. *Tetrahedron Lett.* **1987**, *28*, 3891.

(6) We were able to show by capillary GC analysis[5] that *L. plantarum* does not discriminate between the two enantiomers of methyl 7-fluorooleate. Unfortunately our capillary GC system was unable to resolve any diastereomeric fluorocyclopropanes which were in all likelihood also present in the fluorovaccenate series.

0022-3263/90/1955-6240$02.50/0