the other hand, structure **3a** in Figure 2 is near an energy minimum, and the counterclockwise crotonate rotation required to form the chelated transition state analogous to **5** forces the methyl near the proximal naphthalene unit and the ester near a CH_2 group. In **6**, the crotonate can slant to the left, occupying the uncrowded region of space, while in **5**, either the methyl or the ester must occupy more crowded regions.

Conclusions

A model for the stereoselective Michael additions of **1** with methyl crotonate has been devised that can rationalize the experimental results: (1) formation of diastereomer **3** is preferred for the neutral reaction, (2) thermal equilibration gives a 1:1 mixture of **3** and **4**, and (3) reversed selectivity occurs under anionic conditions. The restrictions with respect to the dihedral angle ω that are imposed in the anionic six-center transition structures are responsible for the formation of opposite diastereomers for the neutral and anionic Michael additions according to this model.

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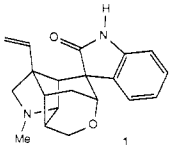
Registry No. **1** (R = H), 97551-09-2; **1** (R = Li), 115118-41-7; **2**, 18707-60-3.

Communications

Synthetic Studies toward Gelsemine. 2.[1] Preparation of the Tetracyclic Skeletal Part by Way of a Highly Stereospecific Intramolecular Reaction of a Silyl Enol Ether with an *N*-Acyliminium Ion

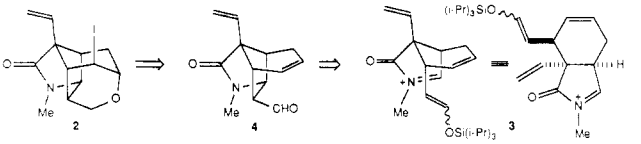
Summary: The tetracyclic skeletal part of the oxindole alkaloid gelsemine (**1**) was prepared from (*E*)-3,5-hexadien-1-ol in nine steps, including as the key step an unprecedented stereospecific cyclization reaction of a triisopropylsilyl enol ether with an *N*-acyliminium ion intermediate to give a tricyclic aldehyde (**3** → **4**).

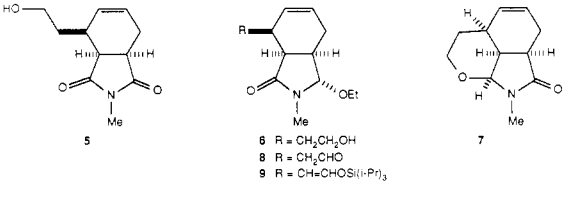
Sir: Gelsemine (**1**) is the principal alkaloid constituent of *Gelsemium sempervirens* (Carolina or yellow jasmine, Loganiaceae), a plant with a long medicinal history.[2] The structure of gelsemine was fully elucidated in 1959.[3] Since then, a number of synthetic approaches toward this unique alkaloid were published,[4] but a total synthesis has not been realized to date. Recently, we disclosed our strategy for the construction of gelsemine.[1] In the present paper we describe the synthesis of **2**, which possesses the tetracyclic skeletal part of gelsemine. The key step in this synthesis is the stereospecific ring closure of *N*-acyliminium intermediate **3**, containing an *E* silyl enol ether, to tricylcic aldehyde **4** (Scheme I).



Diels–Alder cycloaddition of (*E*)-3,5-hexadien-1-ol[5] with *N*-methylmaleimide (1 equiv, toluene, reflux, 24 h) gave pure endo-adduct **5** as a crystalline solid (mp 61–64 °C) in 92% yield.[1] Acid-assisted partial reduction[1,6] of imide **5** ($NaBH_4$ (excess), ethanol, H_2SO_4 (cat.), 0 °C, 2 h), immediately followed by ethanolysis (6 N H_2SO_4 in ethanol, 20 °C, 20 h) furnished a complex mixture of products,[1] which mainly contained the desired ethoxy lactam **6** and tricycle **7**, the latter resulting from reduction of the alternative carbonyl group followed by intramolecular ether formation (ratio **7**/**8** ca. 70/30). Because isolation of pure **6** from the ethanolysis product mixture appeared to be difficult on large scale, the crude mixture was carried on and subjected to oxidation (CrO_3, pyridine, CH_2Cl_2, 4.5 h, 20 °C).[7] Aldehyde **8**[8] was readily obtained pure from the resulting mixture by flash chromatography, in 44% overall yield from **5**. Treatment of **8** with triisopropylsilyl triflate[9] (TIPSOTf, 1.1 equiv) in the presence of Et_3N (1.25 equiv, Et_2O, 19 h, 20 °C) gave a ca. 50/50 ratio of (*E*)-**9** and (*Z*)-**9** in virtually quantitative yield. The *E*/*Z* ratio, which appeared to be of crucial significance (vide infra), could be improved to 70/30 by using CH_2Cl_2 as the reaction medium. The TIPS enol ethers **9** were completely stable toward flash chromatography, but could not be separated.

Scheme I





5 6 R = CH_2CH_2OH 8 R = CH_2CHO 9 R = $CH{=}CHOSi(i\text{-}Pr)_3$ 7

(1) Part 1: Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.
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(8) This compound showed satisfactory spectra and analytical data. Spectral data may be found in the supplementary material.
(9) (a) Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643. (b) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

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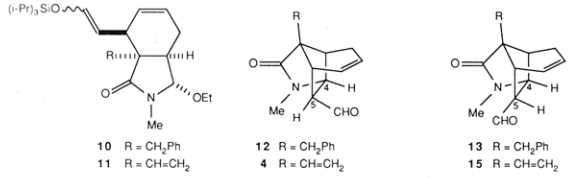
Table I. Results of the Cyclization of Silyl Enol Ether 10 in CH_2Cl_2 at 20 °C

entry	E/Z ratio of **10**	Lewis acid (equiv)	reaction time, h	total yield,[a] %	product ratio **12/13/14**[b]	stereoselectivity (**12** + **14**)/**13**[b]
1	<10:90	$SnCl_4$ (1.9)	20	50	6:88:6	12:88
2	<10:90	$TiCl_4$ (2.4)	22	58	6:82:12	18:82
3	<10:90	$BF_3{\cdot}OEt_2$ (1.1)	0.6	92	6:91[c]:3	9:91
4[d]	>90:10	$BF_3{\cdot}OEt_2$ (2.5)	2.0	90	44:11:45	89:11
5	>90:10	$BF_3{\cdot}OEt_2$ (1.1)	0.45	79	67:10:23	90:10
6	>90:10	$BF_3{\cdot}OEt_2$ (1.01)	0.15	80	84:6:10	94:6

[a] Isolated yield of the inseparable mixture after flash chromatography. [b] Determined from ^1H NMR spectra. [c] Contained 14% of its diethyl acetal. [d] The reaction was started at 0 °C, and then the reaction mixture was allowed to warm up.

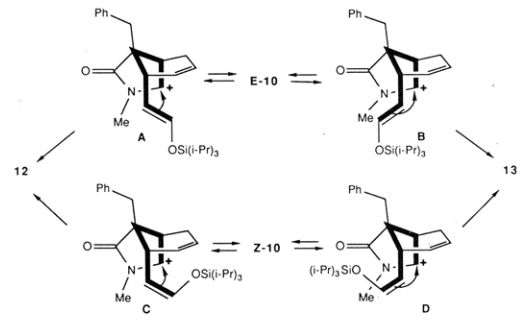
The next task was the introduction of the vinyl substituent by way of enolate chemistry.[10] Our hope that the TIPS enol ether would now function as a good aldehyde protecting group was fully realized. Lactam **9** was cleanly converted into its lithium enolate (1.1 equiv of LDA, THF, −78 °C, 30 min) in view of the following alkylation results. Treatment of the enolate with benzyl bromide furnished a well-separable mixture of (*E*)-**10**[8] and (*Z*)-**10**[8] in 87% yield. Quenching the enolate with 2-(phenylseleno)-ethanal[11] led to a mixture of aldol products, which as crude mixture was directly converted into the desired vinyl compound **11** (5 equiv of Et_3N, 3 equiv of $MeSO_2Cl$, CH_2Cl_2)[12] in ca. 70% yield. Unfortunately, (*E*)-**11** and (*Z*)-**11** were inseparable.



10 R = CH_2Ph **12** R = CH_2Ph **13** R = CH_2Ph
11 R = $CH{=}CH_2$ **4** R = $CH{=}CH_2$ **15** R = $CH{=}CH_2$

Although the intermolecular reaction of silyl enol ethers with *N*-acyliminium ions was well-known,[13] the intramolecular variant was unknown at the commencement of this study.[14,15] To gain information on the feasibility and the stereochemical aspects of the desired process **3** → **4** (Scheme I), we first subjected the individual isomers of benzyl compound **10** to Lewis acidic conditions. The results (Table I) show that $BF_3{\cdot}OEt_2$ is a very satisfactory Lewis acid. Generally, three products were obtained, which could not be separated by flash chromatography. However, integration of the aldehydic proton signals in the ^1H NMR spectra readily revealed the ratio of **12**[8] and **13**.[8] The assignment of the stereochemistry at C-5 of these rigid molecules is based on the magnitude of the vicinal coupling constant between H-4 and H-5, i.e., 0 Hz in **12** and 3 Hz in **13**.[16] Reduction ($NaBH_4$) of the mixture of entry 4 (Table I) gave a new mixture from which secondary alcohol **14**[8] was easily separable, so that its structure could also be established.[17] Compound **14** obviously arises from

Scheme II



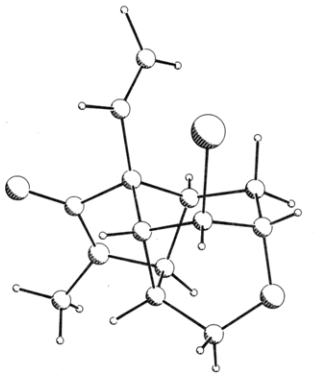


Figure 1. Crystal structure of tetracycle **2**.

acid-induced further cyclization of **12** in a Prins reaction.[18] This is also evident from Table I (entries 4–6) as longer reaction times give more of **14** at the expense of **12**.

The most important conclusion to be drawn from Table I is that a good yield of desired aldehyde **12** can be obtained by starting from pure *E* silyl enol ether. *Most remarkably, the N-acyliminium cyclization appears to be highly stereospecific, i.e., (E)-10 gives mainly aldehyde 12 and (Z)-10 mainly its C-5 isomer 13.*[19] To the best of our knowledge, such a stereochemical outcome is unprecedented for this type of a 5-Exo-Trig cyclization.[20,21] It is most probably associated with the special structure of our cyclization substrates and can be rationalized as follows (Scheme II). In the mechanism of cyclization,[21,22] the

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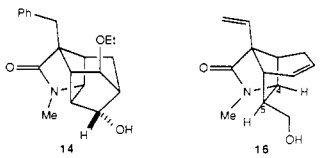
(14) For a review on intramolecular *N*-acyliminium reactions, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(15) For an example of the use of an ordinary iminium ion in this manner, see: Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801.
(16) With the MM2 force field the H-4,H-5 dihedral angle in this tricyclic skeleton was calculated to amount to 92° in **12** and 38° in **13**.
(17) This compound was obtained as a single isomer. The stereochemistry of the hydroxy and ethoxy groups could be unambiguously established from the magnitudes of the vicinal coupling constants in the pertinent five-membered ring of this rigid molecule.
(18) See, e.g.: Andersen, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144.
(19) The somewhat lower stereospecificity of entry 2 (Table I) may be due to epimerization at C-5, followed by irreversible Prins cyclization. Calculations using the MM2 force field indicated that **13** is ca. 1 kcal/mol more stable than **12**.
(20) Silyl enol ethers usually show little stereospecificity in Lewis acid mediated reactions with aldehydes or ketals; see: (a) Heathcock, C. H.; Davidson, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027. (b) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.
(21) For comparable 5-Exo-Trig olefin cyclizations, see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 369. (b) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.
(22) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744.

π-complexes A–D are considered as intermediates, which very much resemble the transition-state structures. Our results (Table I) show that (*E*)-**10** preferably cyclizes through A and (*Z*)-**10** favors the pathway through D. That A is more favorable than B can be understood by realizing that the atoms participating in the mechanism of five-membered-ring formation (boldface bonds in Scheme II) adopt a chair conformation in A vs a boat in B.[21,22] The same reasoning in comparing C and D gives the wrong answer, however. That D is preferred over C can be explained by invoking a severe steric interaction between the silyloxy function and the cyclohexene ring in C.

The *N*-acyliminium cyclization of the inseparable 70/30 *E*/*Z* mixture of **11** (BF_3·OEt_2, CH_2Cl_2, 20 °C, 5 min) gave a 70/30 mixture of the aldehydes **4** and **15**, respectively, showing that the stereospecificity is independent of the nature of the bridgehead substituent. Without purification, the aldehyde mixture was immediately reduced ($NaBH_4$, EtOH) to alcohols **16** and its C-5 epimer in 70% overall yield from **11**. Recrystallization of the latter mixture provided pure **16**[8] (mp 97–98 °C), which exhibited a singlet for H-4 in its ^1H NMR spectrum, proving the stereochemistry at C-5.[16] Definitive structural proof was obtained as follows. Treatment of **16** with iodine (Na_2CO_3, MeCN, 20 °C, 5 days) furnished tetracycle **2**[8] in 49% yield,[23] as a crystalline solid (mp 141–143 °C). This compund was subjected to a single-crystal X-ray diffraction study (Figure 1),[24] which nicely revealed the expected tetracyclic structure with an axial iodine substituent in a chair cyclohexane ring, and a boat-like tetrahydropyran ring.



In conclusion, we have developed an efficient route (nine steps from (*E*)-3,5-hexadien-1-ol) to the tetracyclic skeletal part of gelsemine. Our current studies are concerned with the introduction of the oxindole moiety[25] starting from **16**, and we hope to eventually accomplish the total synthesis of this intriguing alkaloid.

Acknowledgment. We thank K. Goubitz and D. Heijdenrijk of the Laboratory of Crystallography, University of Amsterdam, for the X-ray structural determination, C. Kruk and his staff for this help in obtaining and interpreting the NMR spectra, and Fang Ya for the purification of alcohol **16**. Use of the services and facilities of the Dutch CAOS/CAMM Center, under grant numbers SON-11-20-700 and STW-NCH-44.0703, is gratefully acknowledged.

Registry No. 1, 509-15-9; (±)-**2**, 115095-85-7; (±)-**5**, 115095-74-4; (±)-**8**, 115095-75-5; (±)-(*E*)-**9**, 115095-76-6; (±)-(*Z*)-**9**, 115095-77-7; (±)-(*E*)-**10**, 115095-78-8; (±)-(*Z*)-**10**, 115095-79-9; (±)-(*E*)-**11**, 115095-80-2; (±)-(*Z*)-**11**, 115095-81-3; (±)-**12**, 115095-82-4; (±)-**13**, 115182-33-7; (±)-**13** (diethyl acetal), 115095-83-5; (±)-**14**, 115095-86-8; (±)-**16**, 115095-84-6; (±)-5-*epi*-**16**, 115182-34-8; (*E*)-$HO(CH_2)_2CH{=}CHCH{=}CH_2$, 73670-87-8; *N*-methylmaleimide, 930-88-1.

(23) The remaining 51% consisted mainly of starting material and aldehyde **4**, apparently formed by means of iodine-mediated oxidation; the corresponding tetrahydrofuran was not found.

(24) Details of the X-ray study may be found in the supplementary material.

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Supplementary Material Available: Spectral data of compounds **2**, **8**, (*E*)-**10**, (*Z*)-**10**, **12–14**, and **16** and details of the single-crystal X-ray structure determination of **2** (7 pages). Ordering information is given on any current masthead page.

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Highly Diastereoselective Deprotonation and Substitution of Chiral 5,6-Dihydro-4*H*-1,2-oxazines

Summary: Deprotonation of the chiral 1,2-oxazine **1** by *n*-butyllithium provides a carbanion which reacts highly diastereoselectively with electrophiles affording the substituted 1,2-oxazines **2**. The overall substitution occurs under retention of configuration in most cases investigated. These remarkable results are in accord with recent ab initio calculations.

Sir: 5,6-Dihydro-4*H*-1,2-oxazines (herein abbreviated as 1,2-oxazines) are highly promising heterocyclic intermediates for the construction of polyfunctional compounds.[1] They are most easily prepared by [4 + 2] cycloaddition of nitrosoalkenes to (electron-rich) olefins.[2] C-4-substituted derivatives should be available by conversion of 1,2-oxazines to carbanions and subsequent reaction with appropriate electrophiles. This reaction sequence is well-known for oxime ethers[3] and the related isoxazolines.[4] Indeed, Shatzmiller has reported on the regiochemistry of the deprotonation of 5,6-dihydro-3-methyl-4*H*-1,2-oxazine.[5] To our best knowledge no other lithiated 1,2-oxazines have been studied. In this paper we disclose our results with the chiral 6-(trimethylsilyl)methyl-substituted 1,2-oxazine **1**,[1h] which demonstrate that deprotonation and reactions

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