Table I. Kinetic Isotope Effect in the Wittig Reaction of Benzophenone-*carbonyl*-^{14}C with Isopropylidenetriphenylphosphorane in THF at 0 °C

no.	fraction of reaction	molar radioactivity,[a] mCi/mol	$^{12}k/^{14}k$
1	0	0.4831 ± 0.0009	
2	0.189	0.4893 ± 0.0006	1.057
3	0.330	0.4933 ± 0.0011	1.051
4	0.447	0.4986 ± 0.0005	1.053
5	0.561	0.5048 ± 0.0007	1.054
6	0.667	0.5103 ± 0.0003	1.050
			av 1.053 ± 0.002

[a] Errors are the standard deviations from the averages of multiple radioactivity measurements.

method) were sufficiently short for accurate integrals. The effect of NOE on the relative intensity of the signals was determined at −60 °C and calibrated. We estimated that the reproducibility of the intensity was ca. 5%, and the results from the kinetic treatment should be taken qualitatively.[10] Kinetic analysis was made on the basis of the reaction scheme shown in eq 1. Three differential equations were obtained in a usual manner. From these the following three equations were assumed for a very small Δt:

$$A_{t+\Delta t} = A_t + (-k_1A_tB_t + k_2C_t)\Delta t$$

$$C_{t+\Delta t} = C_t + (k_1A_tB_t - k_2C_t - k_3C_t)\Delta t$$

$$D_{t+\Delta t} = D_t + k_3C_t\Delta t$$

Here, A_t, B_t, C_t, and D_t refer to the concentration of ylide, ketone, oxaphosphetane, and triphenylphosphine oxide at t, respectively. Starting from the initial conditions of $t = 0$, three quantitites, $A_{t+\Delta t}$, $C_{t+\Delta t}$, and $D_{t+\Delta t}$, were calculated step by step for a small increment of Δt.

Competition Experiments. A pair of ketones (normally the parent and a substituted benzophenone, 0.14 mmol each) and dibenzyl ether (0.05 mmol, internal standard) were placed in a flame-dried, serum-capped test tube and dissolved in 2 mL of dry THF. A part (0.8 mL) of the solution was withdrawn and used for calibration in the GLC analysis. To the rest of the solution was added 1 mL of the ylide solution (0.1 mmol) by means of a hypodermic syringe at 0.0 °C, and the resulting solution was allowed to react for 1 h. The solution was worked up in the usual manner and subjected to GLC analysis (1-m glass column packed with 3% PEG-HT). The relative intensity of the ketones to the internal standard was used to determine the fraction of reaction, f, and the rate ratio was calculated according to the equation

$$k_A/k_B = \log\,(1 - f_A)/\log\,(1 - f_B)$$

Carbon-14 KIE Determination. A THF solution of benzophenone-*carbonyl*-^{14}C (0.4 M, 20 mL) containing dibenzyl ether (internal standard) was divided into six parts and transferred with a stainless steel needle into flame-dried test tubes capped with rubbed septa. To these solutions were added preset amounts of ylide solution (1.0 M); the molar ratio of ylide to ketone was in the range 0.2–0.7. The solutions were allowed to react for 1 h at 0 °C and worked up as usual, and then the fractions of reaction were determined by GLC. The unreacted benzophenone was recovered from the reaction mixture and purified by repeated recrystallization from hexane. Radioactivities were measured by a liquid scintillation counter (Beckman LS 9000) as reported previously.[11] KIE was calculated by using an equation of Tong and Yankwich.[12] The results are listed in Table I.

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(10) For kinetic experiments by use of ^{31}P NMR, see: Sawada, M.; Takai, Y.; Chong, C.; Hanafusa, T.; Misumi, S. *Tetrahedron Lett.* **1985**, *26*, 5065; *Anal. Chem.* **1986**, *58*, 231, and ref 3.

(11) Yamataka, H.; Tamura, S.; Hanafusa, T.; Ando, T. *J. Am. Chem. Soc.* **1985**, *107*, 5429.

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Force-Field Modeling of the Stereoselective Michael Additions of an Optically Active Amine and Its Lithium Amide to Acrylates

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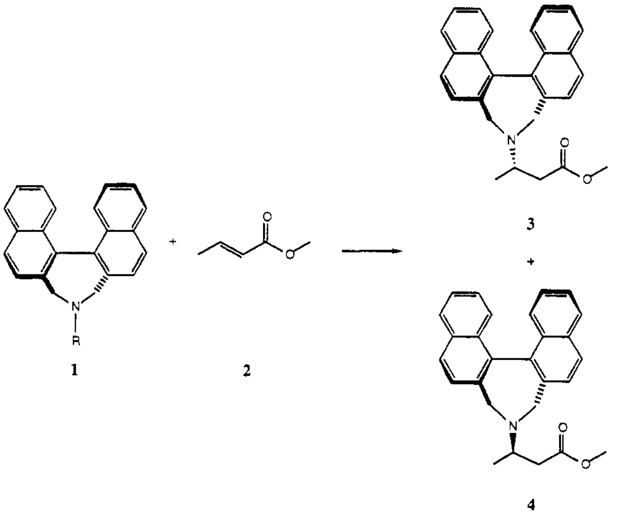
One of us recently reported the asymmetric Michael additions of chiral amine 1 and the corresponding lithium amide to methyl crotonate.[2a] Thermal addition of amine 1 (R = H) gave a 61% diastereomeric excess (de) of **3** as the kinetic product, with slow equilibration to a 1:1 mixture of **3** and **4**. The corresponding lithium amide, **1** (R = Li), however, gave the opposite diastereomer, **4**, with very high selectivity (97–98% de). In order to understand the origins of these stereoselectivities, we sought a relatively accurate three-dimensional model of the respective transition states for these reactions. We have had some success in adapting Allinger's MM2[3] for this purpose[4] and undertook a similar investigation here. Since only limited experimental data were available, we could not develop transition-state parameters in a systematic manner. Our approach was to develop a reasonable model and to test it against the available data. We set out to create a force field that could help rationalize the origin of these phenomena and provide a method of prediction for related cases.[2b]



Method of Calculation

Allinger's MM2 force field[3] was used for this study. Standard parameters were used whenever possible, but some new parameters had to be introduced for these calculations. The original force field does not have parameters for two sp^2-hybridized carbons that are formally singly bonded, such as present in the binaphthyl moiety

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(1) Present address: Department of Chemistry, University of California, Berkeley, CA 94720.

(2) (a) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820. (b) D'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.

(3) (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982. (b) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (c) Quantum Chemistry Program Exchange (QCPE), No. 395, Indiana University, Bloomington, IN.

(4) (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108–1117. (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

0022-3263/88/1953-3879$01.50/0

Table I. Parameter List for Michael Additions[a]

Torsional Parameters

2	1	8	31	0.000	0.000	0.000	31	30	3	7	0.000	10.379	0.303
1	8	31	30	0.000	0.000	0.000	31	30	3	6	0.000	16.250	0.000
1	8	31	5	0.000	0.000	0.000	30	3	6	1	3.530	2.300	−3.530
8	31	1	5	0.000	0.000	0.000	30	3	6	20	0.000	0.000	0.000
8	31	30	3	0.000	0.000	0.000	31	30	3	1	0.150	10.379	0.000
8	31	30	5	0.000	0.000	0.000	5	30	3	6	0.000	16.250	0.000
1	8	31	1	0.000	0.000	0.000	5	30	3	7	0.000	10.370	0.000
5	1	8	31	0.000	0.000	0.000	30	3	1	6	0.000	0.000	0.000
23	8	31	1	0.000	0.000	0.000	30	3	1	1	0.000	0.000	−0.110
23	8	31	30	0.000	0.000	0.000	30	3	1	5	0.000	0.000	−0.250
23	8	31	5	0.000	0.000	0.000	5	30	31	5	0.000	0.000	0.000
1	2	29	5	0.000	15.000	0.000	5	30	31	3	0.000	0.000	0.000
1	2	29	29	−0.270	15.000	0.000	5	31	3	1	0.000	0.000	0.000
1	1	2	29	−0.440	0.240	0.600	7	3	1	6	−5.0	7.50	0.000
2	29	29	2	0.900	3.000	0.400	3	1	6	21	−5.0	7.50	0.090
5	2	29	5	0.000	15.000	0.000	23	7	3	6	0.000	0.000	0.000[b]
5	2	29	29	0.000	15.000	−1.060	23	7	3	30	0.000	0.000	0.000[b]
2	29	29	5	1.300	0.550	−0.500	8	23	7	3	0.000	0.000	0.000[b]
5	29	29	5	1.000	0.500	0.750	1	31	30	23	0.000	0.000	0.000[b]
2	1	2	29	0.100	0.000	0.500	1	8	23	7	0.000	0.000	0.000[b]
5	1	2	29	0.000	0.000	−0.240	7	23	8	31	0.000	0.000	0.000[b]

Stretch Parameters

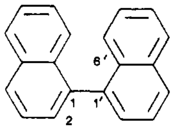
8	31	2.000	2.000	30	31	4.400	1.3944
5	29	4.600	1.101	3	30	4.400	1.509
2	2	8.067	1.390	5	30	4.600	1.093
2	29	8.067	1.390	5	31	4.600	1.093
29	29	5.950	1.460	23	7	0.500	2.000[b]

Bending Parameters

1	8	31	0.630	109.5	31	30	5	0.36	121.1
23	8	31	0.500	109.5	30	3	7	0.50	124.5
8	31	1	0.570	109.5	30	3	6	0.70	113.5
8	31	30	1.045	110.7	7	3	6	0.80	122.0
8	31	5	0.500	108.8	30	31	5	0.36	121.1
1	2	29	0.550	121.400	30	3	1	0.40	115.0
2	29	5	0.360	120.000	5	31	5	0.32	113.06
2	29	29	0.430	120.000	5	30	3	0.24	120.0
5	29	29	0.360	120.000	23	7	3	0.335	106.5[b]
5	2	29	0.360	120.000	8	23	7	0.100	130.0[b]
31	30	3	0.60	117.6					

[a] Atom types are as follows: type 29 is the 1,1′ singly bonded atoms of the binaphthyl moiety; type 30 is the carbon atom α to the carbonyl and is also α to the atom being attacked; type 31 is the olefinic carbon atom being attacked which is β to the carbonyl carbon. All remaining parameters are defined from the internal MM2 parameter list just as if atom types 29, 30, and 31 are equivalent to atom type 2. For instance, the bond length parameter for the 1–31 bond is identical with the type 1–2 bond. [b] Parameters for the anionic Michael addition involving the six-centered transition state.

of 1. The value of the dihedral angle between the two aromatic planes in 1 was expected to have an important influence on the stereoselectivity of this Michael addition. Therefore, a set of parameters (see Table I) defining the 1–1′ bond in 1 was introduced that gave reasonable results for the known molecular structure of 1,1′-binaphthalene, as shown below.



	calcd	exptl[5]
torsion angle (2-1-1′-6′) (deg)	63.6	68.6
bond length (1-1′) (Å)	1.486	1.474

For modeling the attack of the neutral amine 1 (R = H) on ester 2, a tetrahedral attack angle (N–C(sp^2)–C(sp^2)) and a transition-state N- - -C bond length of 2.0 Å were assumed.[6] These were fixed and not allowed to vary; the remaining geometrical features were optimized. The new parameters that were introduced into MM2 are shown in Table I. Local minima of this transition structure model were located by the unconstrained optimization of trial structures at various values of the H–N- - -C(sp^2)–C(sp^2) torsion angle (ω). The newly introduced parameters were varied to some extent to ascertain that the qualitative results were not critically dependent on the exact value of the chosen parameters. The s-cis conformation of the crotonate was chosen for the calculations, since this conformation is slightly favored for acrylate esters.[7] The results given here employed the parameters in Table I.

Results

The relative steric energies of the transition structure models for the addition of 1 (R = H) to 2 as a function of the dihedral angle ω are plotted in Figure 1. The energy curve for the transition structures leading to diastereomer 3 shows two minima at torsion angles of 150 and 330°, whereas the analogous curve leading to diastereomer 4 shows two local minima at torsion angles of ca. 60 and 250°. When only these local minima are included in a simple

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(5) Kerr, K. A.; Robertson, J. M. *J. Chem. Soc. B* **1969**, 1146.

(6) The use of the 2.0-Å N- - -C forming bond length is arbitrary but was chosen because the N- - -C(sp^2) forming bond length should be longer than the N- - -C(sp) forming length found by transition-state calculations: (a) Houk, K. N.; Strozier, R. W.; Rozeboom, M. D.; Nagase, S. *J. Am. Chem. Soc.* **1982**, *104*, 323. (b) Minato, T.; Fujimoto, H.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1621–1626.

(7) Loncharich, R. J.; Swartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14–23.

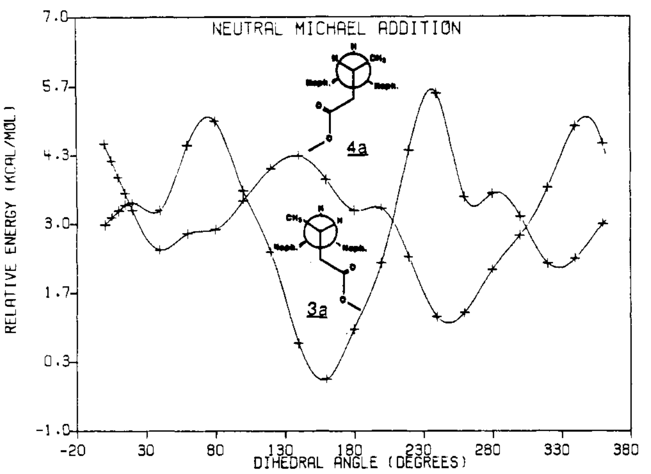
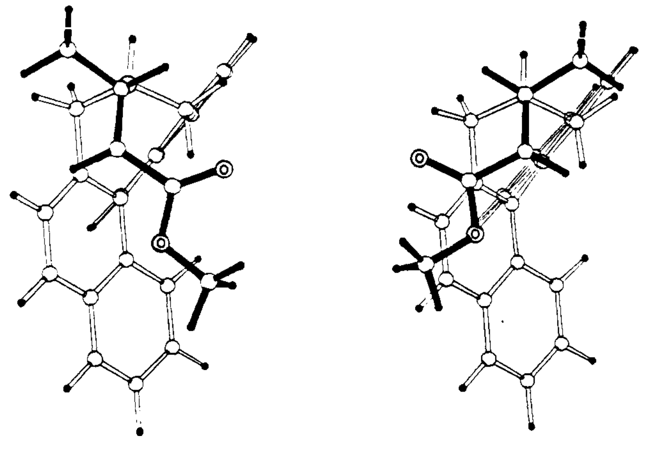


Figure 1. Relative steric energies for model transition structures of the reaction of **1** with **2** as a function of the torsion angle ω. Transition structure **3a** gives product **3**, and **4a** gives **4**.



3a **4a**

Figure 2. Transition structures (torsion angle ω restricted to 180°) for the neutral Michael addition.

Boltzmann distribution calculation, a kinetic product ratio of 4:1 for the diastereomers **3** and **4** is predicted. This result is in good agreement with the initial 4.1:1 ratio of **3** and **4** found experimentally.[2a]

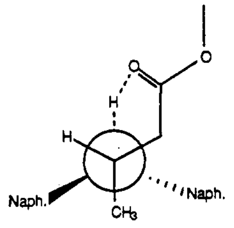
According to this model, the orientations of the ester and olefinic methyl groups of the crotonate with respect to the aryl groups of **1** are responsible for the energetic differentiation of the diastereomeric transition structures. The two 180° conformations are shown in Figure 2. These drawings are Newman projections viewing from the carbon being attacked toward the amine nitrogen. Structure **3a** has the ester group directed away from the protruding naphthalene moiety and has the methyl group in a relatively unhindered position; a favorable steric energy results. The preference of a torsion angle (ω) of 150° (versus 180°) is probably due to interactions of the methyl group with the naphthalene moiety. The potential energy curve for the diastereomeric transition structures affording **4** does not have even a local minimum in this region ($\omega \simeq 180^\circ$) since this would place the ester group and naphthalene moiety in close proximity and would also produce an unfavorable position of the methyl group, as shown in **4a** of Figure 2.

The lowest energy transition structure leading to **4** has a torsion angle of 250°. In this conformation, the ester group and the naphthalene group directed backward interfere only slightly, and the methyl group is relatively far removed from any unfavorable interactions with the other aromatic moiety. The methine group of the crotonate deviates 10° from the eclipsed conformation with the methylene group of the amine. This slight deviation, from a purely eclipsed conformation, lowers the energy of steric interaction between these two alkyl groups. The methylene hydrogens of the amine point away from (almost perpendicular) the interacting groups, reducing a potentially large steric interaction to give a minimum on the energy curve for the transition structure leading to diastereomer **4**.

Calculations for the analogous neutral Michael addition to the two faces of methyl acrylate and methyl isocrotonate support the notion that the relative orientations of both the ester and olefinic methyl groups are important factors for the observed stereoselectivity. The potential energy curves for methyl acrylate are similar to the ones displayed in Figure 1, but the face selectivity is reduced to approximately half that found for **2**. This suggests that the relative positions of ester and naphthalene moieties are important, if not the whole story. No stereoselectivity, however, is predicted in the case of methyl isocrotonate, since the ester and methyl groups are of approximately equal importance as contributors to the steric energy of the transition structures.

The experimental finding of a 1:1 thermodynamic product ratio for **3** and **4** can also be reasonably reproduced, since the two diastereomeric products are calculated to have nearly identical steric energies.

The ionic reaction of **1** (R = Li) with methyl crotonate (**2**) (which afforded preferentially the opposite diastereomer **4**) was modeled through the assumed six-center transition states **5** and **6**.[8] This is a rather drastic simplification, since H in our model replaces Li$^+$ and its accompanying ligands and solvent molecules! Our model assumes that the Li$^+$ primarily fixes the shape of the transition state, but itself has no steric influence. We were fully prepared to try more elaborate models, but this simple one provides an acceptable, if only tentative, solution to problem of the origin of stereoselectivity in these cases.



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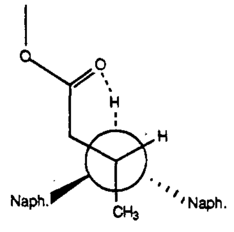

6

The structures obtained by this model, **5** and **6**, are similar to the structures **3a** ($\omega \simeq 300^\circ$) and **4a** ($\omega \simeq 60^\circ$), respectively. The relative energies and shapes of the potential energy curves for **3a** and **4a** in these regions show that the anionic Michael addition transition structure favors **6**, making **4** the kinetic product of the reaction. This calculation was reinforced through a number of calculations using various values for the bending parameters of the newly introduced C=O–H and O–H–N bending modes. All these computations gave lower energies (0.4–3.6 kcal) for **6** when compared to **5**.

The origin of this difference can be understood qualitatively in the following way. To convert **4a** in Figure 2 into **6** requires a clockwise rotation of the crotonate moiety. This results in a decrease in energy as both the methyl and ester groups move into less crowded regions of space. On

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[8] Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

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.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research.

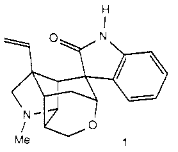
Registry No. 1 (R = H), 97551-09-2; 1 (R = Li), 115118-41-7; 2, 18707-60-3.

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).



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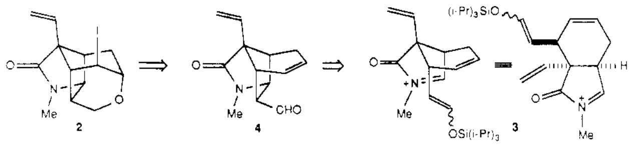
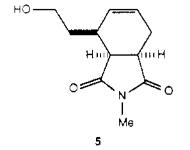
Scheme I



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.



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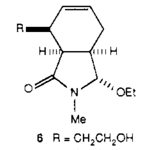
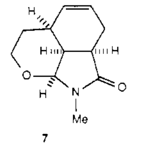


6 R = CH_2CH_2OH
8 R = CH_2CHO
9 R = $CH{=}CHOSi(i\text{-}Pr)_3$



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(1) Part 1: Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.

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(4) (a) Autry, R. L.; Tahk, F. C. *Tetrahedron* **1968**, *24*, 3337. (b) Johnson, R. S.; Lovett, T. O.; Stevens, T. S. *J. Chem. Soc. C* **1970**, 796. (c) Fleming, I. In *New Trends in Natural Product Chemistry*; *Studies in Organic Chemistry*; Atta-ur-rahman, Le Quesne, P. W., Eds.; Elsevier: Amsterdam, 1986; Vol. 26, p 83. (d) Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett.* **1987**, *28*, 1035. (e) Oh, T.; Overman, L. E. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, DC; ORGN 135.

(5) (a) Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274. (b) Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *Ibid*, **1976**, *98*, 6317.

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(8) This compound showed satisfactory spectra and analytical data. Spectral data may be found in the supplementary material.

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