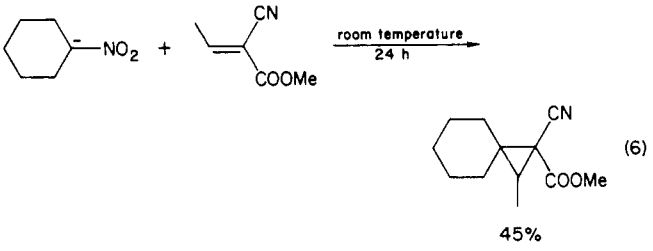
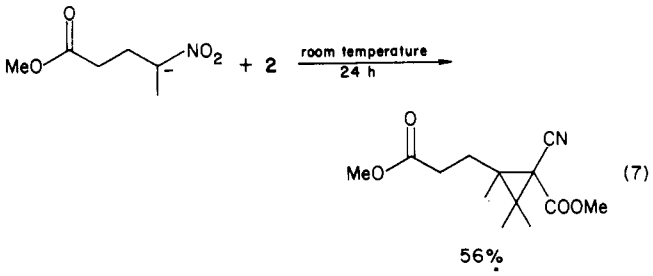
and cheap; the nitronate is stable and easy to handle.

As the α-anion of 2-nitropropane is much more stable than the α-anion of ketones, the reaction of the potassium salt of 2-nitropropane with alkenes substituted with only one keto group is thermodynamically unfavored for the formation of cyclopropanes. Nevertheless, *gem*-dimethylcyclopropanes were obtained in 5–10% yields even in such cases. The present alkylidene transfer reaction is not limited to the examples presented above but can be further extended. When nitro cycloalkanes are used, spiro compounds are prepared as in eq 6. Nitro compounds



(6)

45%



(7)

56%

having other functional groups also follow this reaction, as, for example, methyl 4-nitropentanoate, which results in the regioselective formation of cyclopropanes. When primary nitroalkanes were used, primary alkyl groups could be transfered in 50–60% yields. Only alkenes were successful substrates, activated by two electron-withdrawing groups. The stereochemistry of the present alkylidene transfer reaction is noteworthy. The stereochemistry of alkenes was retained in the course of the reaction when they were prepared by the Knoevenagel reaction. This means that the reaction proceeds via the similar intermediates as those of the Knoevenagel reaction.[8] The studied reaction of nitro groups so closely parallels the sulfone cyclopropanation.[9] The former method has merits over the latter one in that various alkyl groups are transfered regioselectively.

Thus, the nitro group at allylic, benzylic, and tertiary positions is especially readily replaced by intramolecular nucleophiles to form cyclopropanes. This fact strongly suggests that the present ring closure proceeds via single-electron transfer as in other reactions of nitro compounds with nucleophiles.[10] Further studies are currently in progress on the mechanism of the ring closure along with the synthetic application of the present reaction.

Registry No. 1-K, 96914-56-6; **2**, 6666-75-7; (*E*)-**3**, 96914-59-9; (*Z*)-**3**, 96914-73-7; **4**, 5330-61-0; **5**, 3377-21-7; **6**, 96914-60-2; **7**-K, 96914-57-7; (*Z*)-**10**, 96914-62-4; (*E*)-**10**, 96914-63-5; **11**, 96914-64-6; $PhCH(K)NO_2$, 66045-11-2; $(CH_3)_2CH(K)NO_2$, 28273-55-4; (*E*)-$CH_3CH{=}C(CN)CO_2Me$, 51977-58-3; $(CH_3)_2C{=}C(CN)_2$, 13166-10-4; (*E*)-$(CH_3)_2CHCH_2CH{=}C(CN)CO_2Me$, 96914-67-9; (*E*)-$PhCH{=}C(CN)CO_2Me$, 14533-86-9; $CH_3CH{=}C(CO_2Me)_2$, 17041-60-0; (*E*)-$(CH_3)_2CHCH_2CH{=}C(CN)SO_2Ph$, 96914-69-1; (*E*)-CH3CH=CHC(O)Ph, 35845-66-0; (*E*)-PhCH=CHC(O)Ph, 614-47-1; $MeO_2C(CH_2)_2C(K)CH_3NO_2$, 96914-58-8; 3-cyano-2,2-dimethyl-1-(1-heptenyl)-3-(methoxycarbonyl)cyclopropane, 96914-61-3; nitrocyclohexane potassium salt, 12385-03-4; methyl 1-cyano-2-methylspiro[2.5]octan-1-oate, 96914-65-7; 3-cyano-1,1,2,2-tetramethyl-3-(methoxycarbonyl)cyclopropane, 96914-64-6; 3,3-dicyano-1,1,2,2-tetramethylcyclopropane, 1195-70-6; *trans*-1-cyano-1-(methoxycarbonyl)-2,2,3-trimethylcarbonyl)cyclopropane, 96914-68-0; *trans*-1-cyano-2,2-dimethyl-1-(methoxycarbonyl)-3-phenylcyclopropane, 96914-63-5; 1,1-dimethyl-2,2-bis(methoxycarbonyl)-3-methylcyclopropane, 24512-15-0; *trans*-1-cyano-2,2-dimethyl-3-isobutyl-1-(phenylsulfonyl)cyclopropane, 96914-70-4; *trans*-1-benzoyl-2,2-dimethyl-3-methylcyclopropane, 96914-71-5; *trans*-1-benzoyl-2,2-dimethyl-3-phenylcyclopropane, 50299-81-5; methyl *trans*-1-cyano-2,2,3-trimethyl-1-[(methoxycarbonyl)-cyclopropyl]propionate, 96914-72-6.

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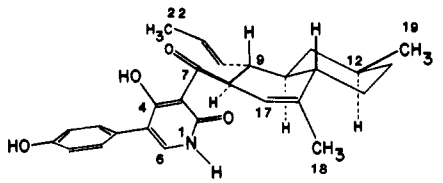
Total Synthesis of (±)-Ilicicolin H

Summary: The first total synthesis of ilicicolin H (**1**) is described. An intramolecular Diels–Alder strategy provides high regio- and stereoselectivity.

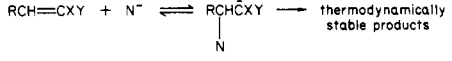
Sir: Extracts from the mycelium of the imperfect fungus, *Cylindrocladium ilicicola*, have led to the isolation and characterization of the novel antifungal antibiotic known as ilicicolin H (**1**).[2] Bassianin, tenellin, and funiculosin



Ilicicolin H **1**

have been identified as related members of this family of natural products,[3] and extensive biosynthetic studies of tenellin and ilicicolin H have established a unique ring expansion rearrangement leading to these α-pyridone metabolites.[4] These studies present a convergent route

(8) See: Apeloig, Y.; Miriam, K.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 2784. Tanikaga, R.; Tamura, T.; Nozaki, Y.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1984**, *87*.



(9) Trost, B. M.; Melvin, L. S., Jr. "Sulfur Ylides"; Academic Press: New York, 1975. Campbell, R. V. M.; Crobie, L.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1971**, 218.

(10) The nitro group at allylic, benzylic, and tertiary positions is readily denitrated by radical reactions, see: Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705. Nucleophilic substitution of tertiary nitroalkanes with stabilized carbanions proceeds via single-electron-transfer processes, see: Kornblum, N.; Erickson, A. S. *J. Org. Chem.* **1981**, *46*, 1047 and references therein. The synchronous process also cannot be excluded for the present cyclization.

(1) Alfred P. Sloan Fellow (1983–1986).

(2) Matsumoto, M.; Minato, H. *Tetrahedron Lett.* **1976**, 3827.

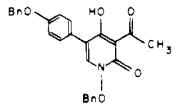
(3) Wat, C.-K.; McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4090. Ando, K.; Matsuura, I.; Nawata, Y.; Endo, H.; Sasaki, H.; Okytomi, T.; Sachi, T.; Tamura, G. *J. Antibiot.* **1978**, *31*, 533.

(4) Tanabe, M.; Urano, S. *Tetrahedron* **1983**, *24*, 3569. Leete, E.; Kowanko, N.; Newmark, R. A.; Vining, L. C.; McInnes, G.; Wright, J. L. C. *Tetrahedron Lett.* **1975**, 4103. McInnes, A. G.; Smith, D. G.; Walter, J. A.; Vining, L. C.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1974**, 282.

0022-3263/85/1950-2807$01.50/0

for the total synthesis of **1** with utilization of a unique intramolecular Diels–Alder cycloaddition of a bis-diene substrate, occurring with high regio- and stereoselectivity.[5]

We have previously reported a total synthesis of tenellin, which provided the heterocyclic pyridin-2-one **2** in excellent overall yield.[6] A convergent pathway to ilicicolin H (**1**) was visualized via Claisen condensation of the protected pyridone with an acyclic α,β-unsaturated aldehyde, affording a C-8→C-17 linkage (ilicicolin numbering). Thus, we sought to assemble the precursor tetraene **3**, containing the pyridone nucleus, with an intramolecular cycloaddition at a late stage of the synthesis to complete formation of the *trans*-decalin system.



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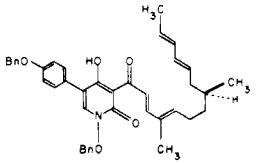
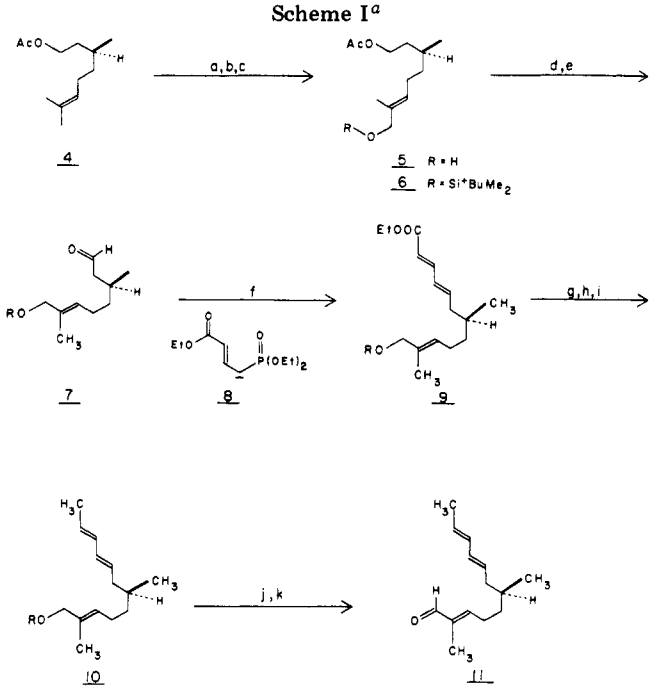


3

Preparation of the prerequisite bis-diene **3** is illustrated in Scheme I, beginning with racemic citronellol acetate.[7] Selenium dioxide oxidation of **4** gave the alcohol **5** and varying amounts of its corresponding aldehyde.[8] The crude product was treated with sodium borohydride, yielding the desired alcohol **5** in 68% yield. Protection of the allylic hydroxyl as its *tert*-butyldimethylsilyl ether gave **6**, and saponification of the acetate followed by oxidation with pyridinium chlorochromate provided aldehyde **7** in 80% yield. Condensation with the preformed phosphonate anion **8** of ethyl 4-(diethoxyphosphinyl)crotonate (1.3 equiv) at −78 °C with subsequent warming to room temperature (2 h) afforded the unsaturated ethyl ester **9** in 73% yield with exclusive *E* stereochemistry.[9] Modification

Scheme I[a]



4 **5** R = H **6** R = Si^{t}BuMe$_2$ **7** **8** **9** **10** **11**

[a] (a) SeO_2 (catalytic amount), *t*-BuOOH (2.5 equiv), CH_2Cl_2, 22 °C; (b) then $NaBH_4$, MeOH, 68%; (c) ClSi/*t*-BuMe$_2$, imidazole, DMF, 0 °C, 95%; (d) LiOH, MeOH, 22 °C, 95%; (e) PCC, CH_2Cl_2, 22 °C, 1 h, 85%; (f) ethyl 4-(diethylphosphono)crotonate, LDA, THF, −78 °C → rt over 2 h, 73%; (g) Dibal, CH_2Cl_2, −78 °C, 10 min, 89%; (h) LiH, SO_3·pyridine, 22 °C, 2 h; (i) then $LiAlH_4$ added, 22 °C, 16 h, 60%; (j) *n*-$Bu_4N^+F^-$, THF, 22 °C, 96%; (k) PCC, CH_2Cl_2, 22 °C, 1 h, 82%.

of this reaction using lithium chloride and DBU as a base in acetonitrile gave greatly reduced yields of diene **9**.[10] Alternatively, standard Wittig reactions with the corresponding (3-carbethoxy-2-propenylidene)triphenylphosphorane gave high yields of mixtures of *E,E*, *E,Z*, and *Z,E* dienes, in which the desired *E,E* geometry represented the major (60%) component.[11]

The ethyl ester of **9** was transformed into a methyl group by initial reduction to the corresponding allylic alcohol, conversion to its sulfate, and further reduction with lithium aluminum hydride, affording the diene **10**.[12] Similar attempts with the allylic mesylate, tosylate, and bromide gave mixtures containing overreduction and diene rearrangement products. Removal of silyl ether protection and subsequent oxidation gave the unsaturated aldehyde **11** for Claisen condensation with the dianion of the 3-acetyl-4-hydroxypyridin-2-one **2**. Choice of base, solvent, and temperature proved to be crucial for success in the condensation procedure. Solid potassium *tert*-butoxide (3 equiv, freshly sublimed) was added to a tetrahydrofuran solution of aldehyde **11** (4 equiv) and pyridone **2** (1.0 equiv) at −40 °C. Additional quantities of base (potassium *tert*-butoxide; three times at 30-min intervals; 1.0 equiv each) were added to drive the reaction to completion at 4 h and led to the isolation of tetraene **3** in 72% yield after preparative chromatography (silica gel, 25% EtOAc in hexanes).

(5) Williams, D. R.; Gaston, R. D.; Horton, I. B. *Tetrahedron Lett.* **1985**, *26*, 1391.

(6) Williams, D. R.; Sit, S.-Y. *J. Org. Chem.* **1982**, *47*, 2846.

(7) All compounds were purified and fully characterized by infrared, nuclear magnetic resonance (360 MHz), and high resolution mass spectral data and/or combustion elemental analyses. The stereochemistry expressed in Scheme I is depicted as relevant to the natural product **1**. All synthetic compounds are to be considered racemic. A partial listing of data for key intermediates includes the following. **9**: ^{13}C NMR (90.8 MHz, $CDCl_3$) δ −5.28, 13.4, 14.3, 18.4, 19.4, 25.0, 25.9, 32.6, 36.3, 40.4, 60.0, 68.6, 77.2, 119.2, 124.4, 129.6, 134.3, 143.2, 144.9, 167.2. **Tetraene 3**: ^1H NMR (360 MHz, $CDCl_3$) δ 0.93 (d, 3 H, J = 6.5 Hz), 1.20–1.40 (m, 1 H), 1.40–1.62 (m, 2 H), 1.73 (d, 3 H, J = 6.5 Hz), 1.95 (s, 3 H), 2.00–2.17 (m, 2 H), 2.21–2.46 (m, 2 H), 5.07 (s, 2 H), 5.29 (s, 2 H), 5.39–5.62 (m, 2 H), 5.92–6.11 (m, 3 H), 7.00 (AA'BB', $\Delta\nu_{AB}$ = 47.8 Hz, J = 8.6 Hz, 4 H), 7.11 (s, 1 H), 7.28–7.51 (m, 10 H), 7.64 (d, 1 H, J = 15.3 Hz), 8.02 (d, 1 H, J = 15.3 Hz), 17.60 (s, 1 H). **Ilicicolin H (1)**: ^1H NMR (360 MHz, $CDCl_3$) δ 0.56 (apparent q, 1 H, J = 12.1 Hz), 0.90 (d, 3 H, J = 6.5 Hz), 0.95–1.10 (m, 2 H), 1.21–1.47 (m, 2 H), 1.56 (d, 3 H, J = 6.3 Hz), 1.66 (s, 3 H), 1.67–1.90 (m, 3 H), 2.55 (apparent q, 1 H, J = 10.2, J = 10.0, J = 9.2 Hz), 4.96 (m, 1 H), 5.15 (br s, 1 H), 5.19 (ddq, 1 H, J = 15.2, J = 9.2, J = 1.0 Hz), 5.26 (d, 1 H, J = 1.0 Hz), 5.50 (dq, 1 H, J = 15.2, J = 6.3 Hz), 7.07 (AA'BB', $\Delta\nu_{AB}$ = 152.2 Hz, J_{AB} = 8.5 Hz, 4 H), 7.31 (s, 1 H), 10.6 (br s, 1 H), 16.76 (s, 1 H). Irradiation at δ 0.56 gave an altered multiplet at δ 1.35 and 1.75. Irradiation at δ 1.35 resulted in an altered multiplet at δ 0.56 and at 2.55. Irradiation at δ 1.75 gave an altered multiplet at δ 0.56 and 0.98: IR (CCl_4) 3600, 3400–3100, 1655, 1610 cm^{-1}; high resolution MS calcd for $C_{27}H_{31}NO_4$ 433.225, found 433.225. Complete details will be provided in the full account of this work.

(8) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. Camps, F.; Coll, J.; Parente, A. *Synthesis* **1978**, 215.

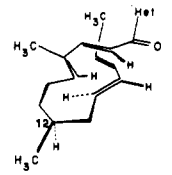
(9) Although complete analysis of ^1H NMR data for the olefinic protons was not possible because of some overlap in chemical shifts, the *E,E* stereochemistry of the diene was assured from **9** [^1H NMR (360 MHz) δ 7.26 (dd, 1, J = 15.4, 10.1 Hz, H_b), 6.15 (m, 2 H, H_c and H_d), 5.97 (d, 1, J = 15.4 Hz, H_a), 5.38 (dt, 1, J = 7.0, 1.1 Hz)] and allylic alcohol **9a** [δ 6.22 (dd, 1, J = 15.0, 10.4 Hz, H_b), 6.05 (dd, 1, J = 15.0, 10.4 Hz, H_c), 5.65–5.77 (m, 2 H, H_a and H_d), 5.38 (br t, J = 7 Hz, H_{15})]. Other recent reports featuring condensations of phosphonocrotonate **8** include the following: Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503. Roush, W. R.; Peseckis, S. M.; Walts, A. E. *Ibid.* **1984**, *49*, 3429.

(10) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(11) Reactions of 2-butenylidene-1-triphenylphosphorane with aldehyde **7** (*n*-BuLi, THF, −78 °C) gave mixtures of geometric isomers of diene **10**, containing the *Z*(C9-10), *E*(C20-21) isomer as the major component (~60%).

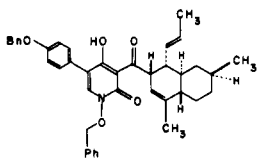
(12) Corey, E. J.; Achiwa, K. *J. Org. Chem.* **1969**, *34*, 3667.

Diels–Alder reactions of the bis-diene **3** presented two opportunities of diene–dienophile pairing for conversion to an octahydronaphthalene system. In addition, each diene–dienophile pair could interact in four diastereotopic endo- and exo-bridged transition states. Upon heating in *o*-dichlorobenzene (reflux for 5 min), a remarkably facile cycloaddition was observed solely from the exo-bridged transition state available from conformer **12**. Trans-fused



12

decalins **13** and **14** demonstrate the exclusive formation of a chair conformer in the cyclohexane (B) ring with the remote C-12 methyl substituent in an equatorial disposition. Preparative thin-layer chromatography (silica gel, 25% EtOAc in hexanes) afforded **13** and **14** in an approximately 5:1 ratio, respectively, in 80% yield. This mixture was generally utilized for further transformations to ilicicolin H (**1**).[13]



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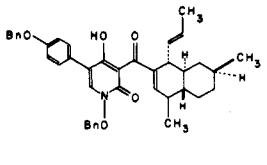

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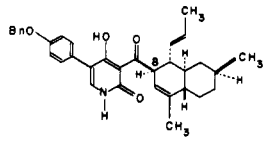

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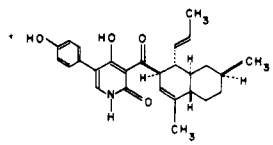

1

Finally, the synthesis was completed upon treatment of **13** and **14** with excess strong base (LDA, THF, –78 °C, 20 min), promoting deprotonation of the benzyl ether of the heterocyclic hydroxamic acid with subsequent loss of benzaldehyde and net reduction at N-1. Thus, the benzyloxy unit served as an excellent protecting group for the α-pyridone.[14] Quenching the reaction with cold aqueous acetic acid afforded **15** with solely the desired C-8 configuration. The remaining benzyl ether was efficiently removed upon treatment with boron trichloride in methylene chloride (–78 °C, 1 min, MeOH quench, 60% yield), providing racemic ilicicolin H (**1**) as confirmed by comparisons with authentic natural product.[15]

Acknowledgment. We thank the Alfred P. Sloan Foundation and the National Institutes of Health (AI 17668) for generous support of our research and acknowledge assistance of the National Science Foundation for purchase of high field NMR (CHE81-05004) and high-resolution mass spectrum instrumentation (CHE81-11957).

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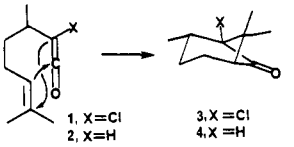
Intramolecular [2 + 2] Cycloadditions of Ketenes. 2. Synthesis of Chrysanthenone, β-Pinene, β-*cis*-Bergamotene, and β-*trans*-Bergamotene[1]

Summary: Vinylketenes prepared from geranoyl and farnesoyl chloride by treatment with triethylamine react to give bicyclo[3.1.1]heptanones which can be converted to β-pinene and the β-bergamotenes by Wolff–Kishner reduction.

Sir: The stereospecific [2 + 2] cycloaddition of ketenes to alkenes is a valuable method for the synthesis of cyclobutanones and compounds that can be derived from them; it is one of the few general methods for carbofunctionalization of alkenes. We have recently initiated a program to develop the intramolecular [2 + 2] cycloaddition of ketenes and alkenes into a general synthetic method.[1,3] We found that the electronic effects of substituents on the double bond rather than the connectivity patterns control the regiochemistry of the cycloaddition. Chloroketene **1**, prepared by treatment of the corre-



sponding acid chloride with NEt_3 in benzene at reflux, cyclized to give a 55% yield of the bicyclo[3.1.1]heptanone **3**. Activation of the ketene by the chloro substituent is necessary since ketene **2** does not give **4**. The intramolecular cycloaddition of **1** to **3** provides a remarkably simple route to the pinane skeleton. Unfortunately, **3** does not possess suitable functionality for the synthesis of naturally occurring pinane derivatives. We therefore turned our attention to substituents other than chloride which would facilitate cycloaddition.

Vinylketene **7** was an attractive possibility because available evidence indicated that vinylketenes undergo both intermolecular[4] and intramolecular[5] [2 + 2] cycloadditions more readily than simple alkylketenes. Furthermore, **7** should be easily prepared since treatment of geranoyl chloride (**6**) with NEt_3 and MeOH in benzene gives methyl γ-geranate, presumably via the vinylketene **7**.[6] The intramolecular cycloaddition of **7** would give **8**,

(13) Longer reaction times led to increased amounts of the α,β-unsaturated isomer **14**. The slightly less polar **13** is colorless, whereas **14** is yellow under visible light. High-field NMR did not unambiguously allow assignment of C-8 stereochemistry of structure **13**.

(14) This scheme of N-protection may be generalized for heterocycles which can function as effective leaving groups. Potassium *tert*-butoxide in tetrahydrofuran cleanly removes the benzyloxy unit of **2** and tetraene **3** at 0 °C.

(15) We thank Dr. Makoto Matsumoto, Shionogi Research Laboratory, Ltd., Fukushima-ku, Osaka, 553, Japan, for generously providing a sample of ilicicolin H.

(1) For Part 1 of this series, see: Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194.

(2) Fellow of the Alfred P. Sloan Foundation 1979–1983; Dreyfus Teacher-Scholar 1982–1987.

(3) For a complementary study, see: Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192.

(4) Danheiser, R. L., Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670 and ref 7 therein.

(5) See ref 3. The vinylketenes in this paper give cycloadducts with an endocyclic double bond. The main role of the double bond in these cases may be to restrict rotational freedom resulting in a less negative entropy of activation for the cycloaddition.

(6) Bedoukian, R. H.; Wolinsky, J. *J. Org. Chem.* **1975**, *40*, 2154.

0022-3263/85/1950-2809$01.50/0