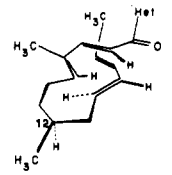
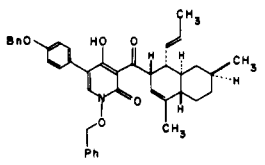
Diels–Alder reactions of the bis-diene **3** presented two opportunities of diene–dienophile pairing for conversion to an octahydronaphthalene system. In addition, each diene–dienophile pair could interact in four diastereotopic endo- and exo-bridged transition states. Upon heating in *o*-dichlorobenzene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

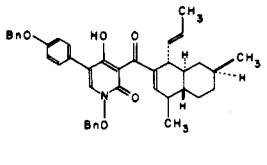


12

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]



13



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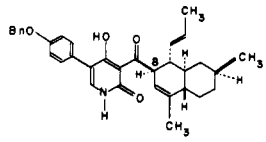

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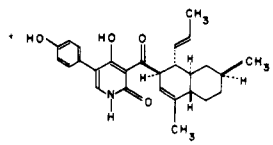

1

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]

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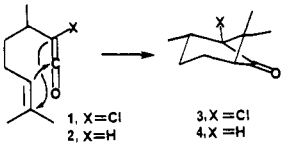
Intramolecular [2 + 2] Cycloadditions of Ketenes. 2. Synthesis of Chrysanthenone, β-Pinene, β-*cis*-Bergamotene, and β-*trans*-Bergamotene[1]

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.

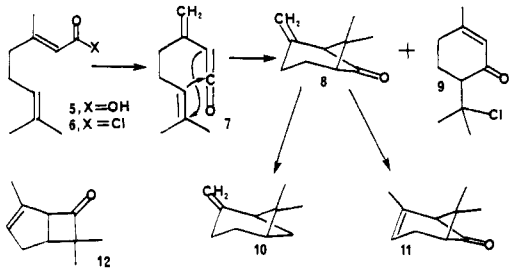
(3) For a complementary study, see: Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192.

(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



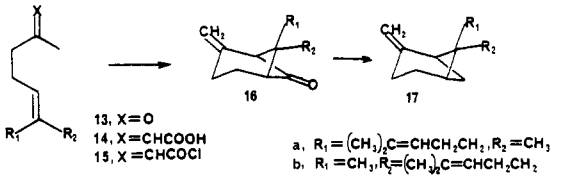
which can easily be converted to β-pinene (**10**) and chrysanthenone (**11**).

Treatment of geranic acid (**5**)[7a] with oxalyl chloride in benzene (5 equiv, 2 h, 25 °C) gave the acid chloride **6**, which was treated with NEt_3 (3 equiv) in toluene (0.03 M) at reflux for 1 h to give a 43% yield of 7,7-dimethyl-2-methylenebicyclo[3.1.1]heptan-6-one (**8**)[8] in 43% yield and **9** in 7% yield.[9] The selective formation of **7** from **6** appears to result primarily from the greater kinetic acidity of the methyl protons rather than the *E* geometry of the double bond.[10]

The structure of **8** was unambiguously established by isomerization to give chrysanthenone (**11**)[11] in quantitative yield with hydrogen and palladium on calcium carbonate[12] and by Wolff–Kishner reduction (10 equiv $NH_2NH_2{\cdot}H_2O$, TEG, 105 °C, 1 h; 150 °C, 30 min; 30 equiv KOH, 185 °C, 1 h) to give β-pinene (**10**) in 70% yield. The intramolecular cycloaddition of **7** to give **8** is thus the key step in three-step syntheses of chrysanthenone[13] (43% overall yield) and β-pinene[14] (30% overall yield) from the simple acyclic precursor geranic acid.

Beereboom has reported that treatment of geranic acid with Ac_2O and NaOAc at reflux gives a 28% yield of filifolone (**12**).[15] Based on our results, it is likely that the vinylketene **7** is formed which cyclizes to give **8** as the kinetic product, which undergoes acid-catalyzed rearrangement[16] to give filifolone.

This intramolecular cycloaddition reaction appeared to offer a very attractive route to β-*cis*-bergamotene (**17a**) and β-*trans*-bergamotene (**17b**). The bicyclo [3.1.1] ring



system has made the bergamotenes challenging synthetic targets. Gibson and Erman have prepared β-*cis*- and α-*cis*-bergamotene in 12 steps from β-pinene.[17b] Corey, Cane, and Libit have prepared α-*trans*- and β-*trans*-bergamotene in 21 steps from geranyl acetate.[18a] Larsen and Monti have prepared α-*trans*- and α-*cis*-bergamotene in 13 steps.[14c]

Nerylacetone[7b] (**13a**) was converted to a 9:1 mixture of *E,Z*- and *Z,Z*-farnesic acid (**14a**) by the Horner–Emmons Wittig reaction[19] followed by basic hydrolysis. The crude acid (**14a**) was converted to the acid chloride **15a** (NaH, 2 equiv oxalyl chloride, benzene), which was treated with NEt_3 in toluene at reflux as above to give **16a**[8] (30% from **13a**) uncontaminated with **16b**. The isomer with an endocyclic double bond was isolated in 3% yield. Wolff–Kishner reduction of **16a** as described above for 8 gave a 65% yield of β-*cis*-bergamotene (**17a**) whose spectral data are identical with those previously reported.[17] β-*cis*-Bergamotene is therefore available from nerylacetone in five steps in 19% overall yield.

In a similar manner geranylacetone[7b] (**13b**) was converted to a 9:1 mixture of *E,E*- and *Z,E*-farnesic acid (**14b**)[19] and thence to **16b**[8] in 38% overall yield. Initial attempts at Wolff–Kishner reduction of **16b** to give **17b** were unsuccessful due to the increased steric hindrance caused by the larger side chain. Fortunately, Wolff–Kishner reduction with anhydrous hydrazine gave a 40% yield of β-*trans*-bergamotene (**17b**) whose spectral data are identical with those previously reported.[18] β-*trans*-Bergamotene is therefore available from geranylacetone in five steps in 15% overall yield.

These results clearly indicate the power of the intramolecular [2 + 2] cycloaddition reaction of ketenes to generate efficiently bicyclic terpenes that are otherwise relatively inaccessible. We are continuing our examination of the scope and limitations of this cycloaddition reaction and are exploring routes to the more complex sesquiterpenes copaene, ylangene, and longipinene using **16b** as a starting material.

(7) Commercially available from (a) Bedoukian Research Inc. and (b) Fluka Chemical Corp.

(8) NMR ($CDCl_3$) **8**: δ 1.07 (s, 3), 1.20 (s, 3), 2.62 (ddd, 1, *J* = 7.2, 5.7, 2.5 Hz), 3.15 (d, 1, *J* = 7.2 Hz), 4.63 (s, 1), 4.80 (s, 1). **16a**: δ 1.18 (s, 3), 2.68 (ddd, 1, *J* = 6.9, 4.8, 1.5 Hz), 3.22 (d, 1, J = 6.9 Hz). **16b**: δ 1.03 (s, 3), 2.72 (ddd, 1, *J* = 7.2, 3, 3 Hz); 3.22 (d, 1, *J* = 7.2 Hz). IR (neat) **8**, **16a**, **16b**: 1777 cm^{-1}.

(9) All new compounds were characterized by IR, 300-MHz ^1H and 75-MHz ^{13}C NMR, and elemental analysis.

(10) A similar sequence of reactions carried out on the *Z* isomer of **5** gave a 15% yield of **8** uncontaminated with **11**. The lower yield probably results from the instability of the *Z* acid chloride.

(11) The IR and ^1H and ^{13}C NMR data are identical with the literature data. Swiggar, A. A.; Silverstein, R. M. "Monoterpenes: Infrared, Mass, ^1H and ^{13}C NMR Spectra and Kovats Indices"; Aldrich Chemical Co.: Milwaukee, WI, 1981; p 11.

(12) Widmark, G. *Acta Chem. Scand.* **1955**, *9*, 941. Brown, C. A. *Synthesis* **1978**, 754 and references cited therein.

(13) Chrysanthenone has previously been prepared by partial synthesis from verbenone: Hurst, J. J.; Whitham, G. H. *J. Chem. Soc.* **1960**, 2864.

(14) For previous syntheses of α- or β-pinene, see: (a) Crowley, K. J. *Tetrahedron* **1965**, *21*, 1001. (b) Thomas, M. T.; Fallis, A. G. *J. Am. Chem. Soc.* **1976**, *98*, 1227. (c) Larsen, S. D.; Monti, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 8015.

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(16) Erman, W. F.; Treptow, R. S.; Bazukis, P.; Wenkert, E. *J. Am. Chem. Soc.* **1971**, *93*, 657. These authors propose a similar mechanism for the formation of **12** except that the vinyl ketene with a *Z* trisubstituted double bond is proposed to give **11**, which rearranges to **12**.

(17) (a) Hogg, J. W.; Terhune, S. J.; Lawrence, B. M. *Cosmet. Perfum.* **1974**, *89*, 66. (b) Gibson, T. W.; Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 4771.

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