Chemistry of Zerumbone. 1. Simplified Isolation, Conjugate Addition Reactions, and a Unique Ring Contracting Transannular Reaction of Its Dibromide

Takashi Kitayama* and Tadashi Okamoto

Department of Agricultural Chemistry, Faculty of Agriculture, Kinki University, Nara 631-8505, Japan

Richard K. Hill

Department of Chemistry, University of Georgia, Athens, Georgia 30602

Yasushi Kawai and Sho Takahashi

Institute for Chemical Research, Kyoto University, Uji 611-0011, Japan

Shigetomo Yonemori

Research Institute of Tropical Agriculture, University of Ryukyu, Taketomi, Okinawa 907-1541, Japan

Yukio Yamamoto

Graduate School of Human and Environmental Studies, Kyoto University, Sakyo, Kyoto 606-8501, Japan

Kouichi Ohe and Sakae Uemura

Graduate School of Engineering, Kyoto University, Sakyo, Kyoto 606-8501, Japan

Seiji Sawada

Kyoto University of Education, Fushimi, Kyoto 612-0863, Japan

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Zerumbone (**1**) was isolated from fresh rhizomes of *Zingiber zerumbet* Smith in yields of 0.3−0.4% by simple steam distillation and recrystallization. **1** accepted 2 equiv of hydrogen cyanide at the C6 and C9 double bonds of the cross-conjugated dienone system to give a mixture of diastereomers **3a**−**d**. In the presence of potassium cyanide, the dominant isomer **3a** was isomerized to a mixture of **3a**−**d**. Under controlled conditions, **1** added one mole of methanol regio- and stereoselectively at the C6 double bond to give adduct **4a**. With potassium cyanide, **4a** was transformed to the mixture of **3a**−**d**. **1** took up one mole of bromine at C6 double bond to give a diastereomeric mixture of adducts **5a** and **5b**. Treatment of **5a** with potassium cyanide gave a mixture of cyclopropanecarboxylic acid **6a** and **6b**. This unique ring-contracting cyclopropane formation is pictured as a sequential Favorskii type reaction. α-Cyclodextrin improved the selectivity and yields of the reactions conducted in an aqueous medium.

Introduction

Zerumbone[1a] (**1**, 2,6,9-humulatrien-8-one, or 2,6,9,9-tetramethyl-[2*E*,6*E*,10*E*]-cycloundeca-2,6,10-trien-1-one, Scheme 1) is a cyclic sesquiterpene found as the main component of the essential oil of a wild ginger, *Zingiber zerumbet* Smith. It was first isolated in 1960,[1b] structurally elucidated in 1965,[2] and later characterized by NMR[3] and X-ray.[4] The ginger plant propagates by rhizome in one-year cycles, is widespread in Southeast Asia, India, and Okinawa, and has found use as spice and ethnomedicines.[5] Despite the abundance of the plant and the interesting three-membered ring in **1**, the difficulty of isolation and resulting short supply have limited studies on the fundamental[6] as well as applied and pharmaceutical chemistry of zerumbone.[7]

Zerumbone contains three double bonds; an isolated one at C2, and two at C6 and C9 which are part of a cross-conjugated dienone system. Of these the C6 double bond appears least hindered, being furthest from the *gem*-dimethyl substituents at C11. The X-ray structure[4]

* Corresponding author. Tel: +81+742-43-7273 ext. 3302, fax: +81-742-43-1445; e-mail: kitayama@nara.kindai.ac.jp.

(1) (a) *In this article the nomenclature of the derivatives of zerumbone with an unaltered skeleton follows that of humulane. (b) Dev, S. *Tetrahedron*. **1960**, *8*, 171−180.

(2) Damodaran, N. P.; Dev, S. *Tetrahedron* **1965**, 1977−1981.

(3) Dev, S.; Anderson J. E.; Cormer, V.; Damodaran, N. P.; Roberts, J. D.; *J. Am. Chem. Soc.* **1968**, *90*, 1246−1248.

(4) Hall, S. R.; Nimgirawath, S.; Raston, C. L.; Sittatrakul, A.; Thadaniti, S.; Thirasasana, N.; White, A. H. *Aust. J. Chem*. **1981**, *34*, 2243−2247.

(5) In *Thai Medical Plants*; Fransworth, N. R.; Bunyapraphatsara, N.; Ed.; Prachachon: Bangkok, Thailand, 1992; pp 261−263.

(6) (a) Damodaran, N. P.; Dev, S. *Tetrahedron* **1968**, *24*, 4113−4122. (b) Chhabra, B. R.; Dhillon, R. S.; Wadia, M. S.; Kalsi, P. S. *Indian J. Chem*. **1975**, *13*, 222−224. (c) Matthes, H. W. D.; Luu, B.; Ourisson, G. *Tetrahedron* **1982**, *38*, 3129−3135. (d) Kodama, M.; Shiobara, Y.; Sumitomo, H.; Mitani, K.; Ueno, K. *Chem. Pharm. Bull.* **1987**, *35*, 4039−4042. (e) Nakatani, N.; Jitoe, A.; Masuda, T.; Yonemori, S. *Agric. Biol. Chem*. **1991**, *55*, 455−460.

(7) (a) Matthes, H. W. D.; Luu, B.; Ourisson, G. *Phytochemistry* **1980**, *19*, 2643−2650. (b) Ozaki, Y.; Kawahara, N.; Harada, M. *Chem. Pharm. Bull.* **1991**, *39*, 2353−2356.

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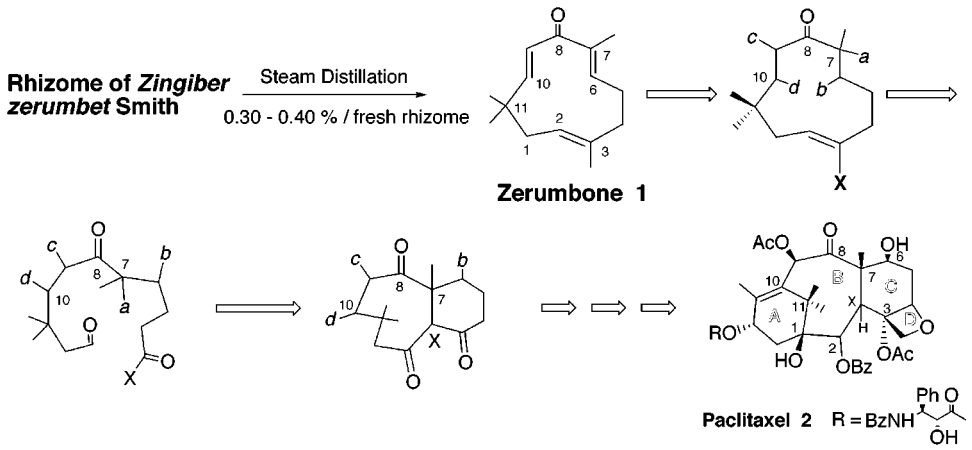
Scheme 1



reveals that the dienone system lies in a slightly distorted plane which is perpendicular to that of the isolated double bond.

As depicted in Scheme 1, the carbon skeleton of zerumbone can be imagined as a synthetic precursor of the B/C ring system of paclitaxel (**2**),[8] whose potent anticancer activity has captured the imagination of synthetic chemists. Addition of function groups *a*−*d* to the conjugated double bonds, insertion of an additional carbon (X) between C2 and C3, and connection of X with C7 could construct a bicyclic precursor suitable for further elaboration to **2**. This possible relationship encouraged us to pursue a practical method of isolation of **1** and examine addition reactions of the double bonds. We also report a conformational analysis of **1** and a novel intramolecular ring contractive rearrangement of zerumbone dibromide.

Results and Discussion

Fresh rhizomes of *Zingiber zerumbet* Smith were harvested initially in Thailand[9] in August 1995; subsequent collections have been made each October in Okinawa. Steam distillation of the sliced rhizomes yielded crystalline **1** in 0.3−0.4% yield. The high content of this solid terpene is comparable to that of camphor from the camphor tree (*Cinnamomum camphora*). Compared to the previous low-yield multistep extraction methods,[1−6] this simplified procedure makes **1** readily available from a widespread natural source and enabled us to explore its chemistry.

Conjugate Addition Reactions. Treated with excess aqueous KCN, **1** underwent conjugate addition at both conjugated double bonds nonstereoselectively, affording a mixture of four diastereomers **3a**−**d** in a ratio of 4.0: 3.6:1.5:1.0 in 95% yield. The low selectivity of addition implies that cyanide is a particularly reactive nucleophile under these conditions. The dominant stereoisomer **3a** could be made almost the sole product when the addition was carried out at low temperature in the presence of α-cyclodextrin and worked up after only 50% of **1** had been consumed.

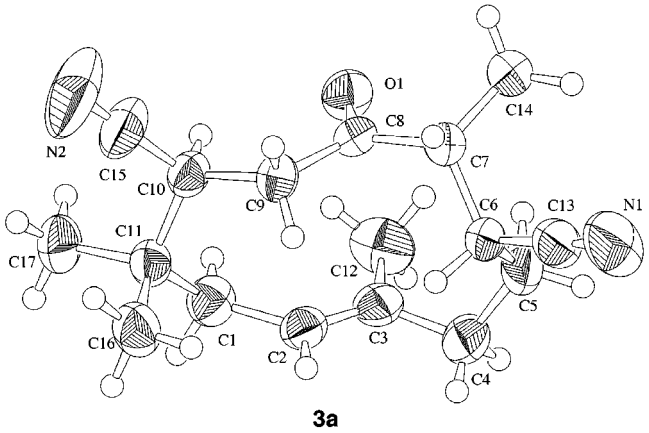


Figure 1. ORTEP drawing of the crystal structure of dominant isomer **3a**.

On exposure to aqueous KCN, isomer **3a** was converted to a mixture of **3a**−**d** in the same ratio as above. When K^{13}CN was used in this isomerization, no labeled cyano groups were incorporated into the products, showing that isomerization is due to exchange of the acidic hydrogens at C7 and C9 rather than reversible conjugate addition. It appears that the diastereomeric mixture of addition products results from a thermodynamically controlled equilibrium catalyzed by cyanide ion.

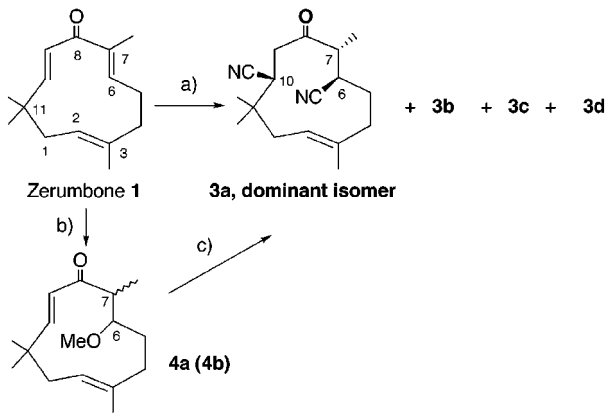
The structure of the major isomer **3a** was determined by single-crystal X-ray analysis (Figure 1), which shows that the two cyano groups are located on one face of the ring while the two methyl groups at C3 and C7 lie on the opposite face. The configuration of **3a** appears to minimize the repulsions among these functional groups. We believe that the slight predominance of **3a** results from the steric effect of the C3 methyl group; by shielding one face of the dienone system, this methyl may control the successive proton addition to C7 and then cyanide addition to C10.

In methanol with a catalytic amount of base or acid, only 1 equiv of methanol added to **1** specifically at C6, affording a single diastereomer **4a** in yields of 60−70%. Prolonged reaction times led to the gradual formation of its epimer **4b**. The flexible nature of the large ring made it impossible to determine the configuration of **4a** by NMR methods, even though NOEs of almost the same value (0.8%) were observed between the methoxy protons and those at C6 and C7, and no NOE was seen between the C7 methyl protons and the methoxy protons at C6.

(8) In *Taxane Anticancer Agents, Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds., American Chemical Society: Washington, DC, 1995.

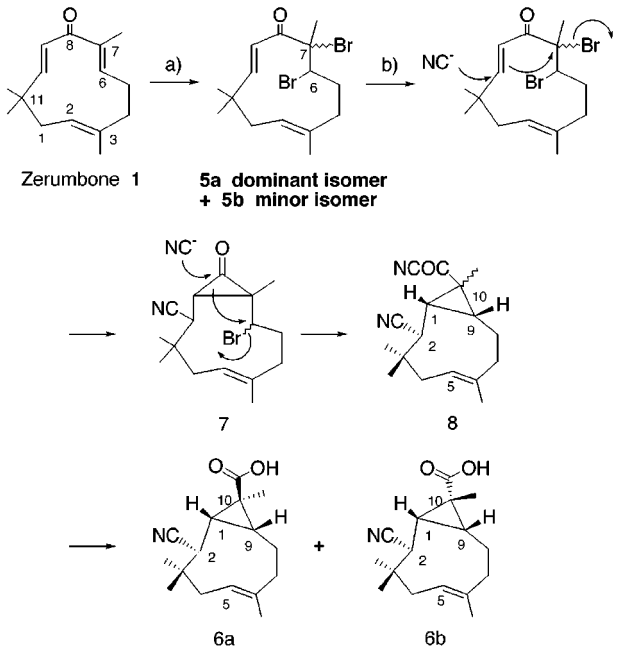
(9) Fresh rhizome of the ginger (13.5 kg) was harvested in Suratthani, Thailand, on Aug 1995. Sliced and air-dried material (3.6 kg) gave 36 g of **1** by methanol extraction followed by fractionation with hexane (1.0% of air-dried material).

Scheme 2[a]



[a] (a) KCN, MeCN−H_2O, 35−40 °C, 4 days, 95%, diastereomer ratio of **3a**−**d** 4.0:3.6:1.5:1.0; α-CD, 15−20 °C, 50% consumption of **1**, sole isomer of **3a**, 50%; (b) MeOH, *t*-BuOK, or BF_3, 15−20 °C, 15 h, 60% consumption of **1**, 60%; (c) KCN, MeCN−H_2O, 10−15 °C, 20 h, 100%.

Scheme 3[a]



[a] (a) Br_2, CCl_4, −10−0 °C, 30 min, 95%, diastereomer ratio of **5a**:**5b** 9.2:0.8; (b) KCN, α-CD, MeCN−H_2O, 10−15 °C, 80%, diastereomer ratio of **6a**:**6b** 9.0:1.0.

In an attempt to add cyanide ion to the remaining conjugated double bond, treatment of **4a** with KCN resulted quantitatively in the mixture of the four diastereomeric dinitriles **3a**−**d** in the same ratio observed above (Scheme 2). The smooth substitution of cyano for methoxy group represents a reversal of the addition of methanol, and again illustrates the strong affinity of cyanide for conjugate addition.

At 0 °C, 1 equiv bromine added to the C6 conjugated double bond of zerumbone, giving a mixture of dibromides **5a** and **5b** in a ratio of 9.2:0.8 in 95% yield (Scheme 3). Surprisingly, no addition to the isolated double bond at C2 or the C9 conjugated double bond was observed under these conditions. Given that it is the site of epoxidation by peracid,[6c] the unreactivity of the C2 isolated double bond toward bromine is unexpected. The NOE (2.4%) observed between the C6 proton and the C7 methyl protons in the minor isomer **5b** (though not in **5a**) is insufficient to permit an assignment of configuration, for the reason mentioned above.

Several other nucleophiles were tested. Although a reverse aldol reaction has been reported on treatment of **1** with alkali at high temperature,[2] no reaction was observed with sodium hydroxide or sodium acetate under mild conditions. Thiols and amines gave addition products which will be discussed elsewhere. The addition of various nucleohphiles shows that the conjugated double bond at C6 is most reactive, followed by the other conjugated double bond at C9.

Favorskii Rearrangement. In an attempt to effect conjugate addition of cyanide to the conjugated C9 double bond in **5**, the dibromide mixture **5a**,**b** was treated with aqueous KCN at room temperature in the presence of α- or *β*-cyclodextrin. The unexpected result was the formation of a 9:1 mixture of bicyclic carboxylic acids **6a** and **6b** in a total yield of 80% (Scheme 3). The same product mixture was obtained when the starting material was pure **5a** or **5b**. The structures of **6a** and **6b** were confirmed by X-ray analysis (Figure 2).

This unique ring-contracting transannular reaction can be described as a Favorskii rearrangement, involving the successive generation of two cyclopropane rings, initiated by conjugate addition of cyanide ion to C10. The resulting carbanion at C9 displaces the bromine at C7, forming the cyclopropanone intermediate **7**. Nucleophilic addition of a second cyanide ion to the carbonyl group opens the strained cyclopropanone to generate another carbanion at C9, which now displaces the remaining bromine, creating the final cyclopropane ring. The acyl cyanide **8** is rapidly hydrolyzed to afford the acid **6**.

With a reliable source of zerumbone now available, we look forward to examining other aspects of the rich chemistry of this naturally occurring medium ring system.

Experimental Section

General Methods. Melting points (mp) were uncorrected. NMR spectra were obtained at 270 and 500 MHz for proton, and at 68 and 125 MHz for C13 in a 7:3 mixture of $CDCl_3$ and CCl_4 with TMS as the internal standard unless otherwise noted. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were obtained by direct injection. Analytical and preparative HPLC was done on a system connecting a column of Wakosil-II 5C18 HC (150 × 8 mm) or Wakosil 5C18 HC (300 × 8 mm) monitored at 215 nm, eluting with a mixture of acetonitrile and water (7: 3), unless otherwise noted. Chemicals were commercially available reagent grades from Wako, Japan.

Extraction and Purification of Zerumbone (1). Sliced fresh rhizome (7.5 kg) of *Zingiber zerumbet* Smith, harvested in October 1996 in the Okinawa Islands, Japan, was placed in a stainless steel container (20 L) and subjected to steam distillation until the distillate contained no oil drops. The distillate was kept for one or two days at room temperature, and gave a crystalline solid of essential oil on the water surface. The solid was separated by filtration and recrystallized from hexane to afford **1** in a yield of 27.8 g (0.37% based on fresh rhizome). The yield of total essential oil was 39.0 g (0.52%).

Zerumbone (1): mp 66.0−66.5 °C (ref 64.5 °C)[1]; IR ($CHCl_3$), 3005, 1638 cm^{-1}; ^1H NMR: δ 1.07 (s, 3H, CH_3 at C11), 1.21 (s, 3H, CH_3 at C11), 1.54 (s, 3H, CH_3 at C3), 1.80 (s, 3H, CH_3 at C7), 1.85−1.93 (m, 1H, H at C1), 2.22−2.35 (m. 4H, H

(10) Altomare, A.; Cascarano G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343−350.

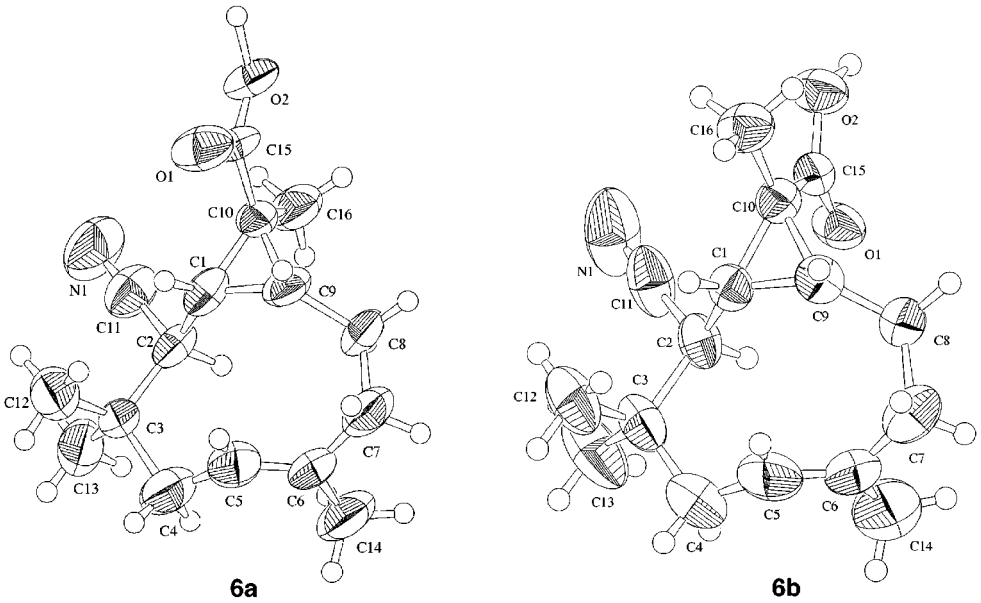


Figure 2. ORTEP drawing of the crystal structure of bicyclic carboxylic acids **6a** and **6b**.

at C1, 4 and 5), 2.42−2.48 (m, 1H, H at C5), 5.23 (bd, 1H, J = 15.2 Hz, H at C2), 5.85 (d, 1H, J = 16.2 Hz, H at C10), 5.97 (d, 1H, J = 16.2 Hz, H at C9), 6.01 (bd, 1H, J = 11.5 Hz, CH at C6); ^{13}C NMR: δ 11.8 (CH_3 at C7), 15.2 (CH_3 at C3), 24.2 (CH_3 at C11), 24.4 (C5), 29.4 (CH_3 at C11), 37.9 (C11), 39.4 (C4), 42.4 (C1), 125.0 (C2), 127.1 (C9), 136.3 (C3), 137.9 (C7), 149.0 (C6), 160.9 (C10), 204.4 (C8); MS m/z: 218.2 (M^+), 135.1, 107.1, 91.1, 79.1, 67.1, 53.1; HRMS m/z calcd mass for $C_{15}H_{22}O$ 218.1670, found 218.1691. Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.79; H, 10.15.

Methanol Extraction and Purification of 1 below 15 °C, and Its Optical Rotation. Fresh rhizome (100 g, sliced into 5 mm cubes) was immersed in methanol (300 mL) at 10−15 °C for 6 days. The solution was concentrated under reduced pressure below 15 °C to one-third the volume. The concentrate was extracted with hexane (50 mL × 2). The hexane layer was kept to stand at 10−15 °C for 4 days to obtain a crystalline precipitate. The precipitate was recrystallized in hexane: yield 250 mg (0.25%); $[\alpha]^{15}_D$ (c = 2.1 in methanol) 0.000.

Reaction of 1 with Potassium Cyanide. A mixture of **1** (3.2 g, 14 mmol) and potassium cyanide (3.0 g, 45 mmol) in acetonitrile:water (50: 20 mL) was stirred for 4 days at 35−40 °C. The solution was concentrated on a rotary evaporator, and the residue was fractionated with water and ethyl acetate (EtOAc). The EtOAc extract was concentrated to a crystalline mass (**3a**−**d**, 3.5 g, 95%) with a diastereomer ratio (by ^{1}H NMR) of 4.0:3.6:1.5:1.0, respectively. The solid was recrystallized from EtOAc:hexane to yield a dominant diastereomer **3a**. The mother liquor was chromatographed on silica gel and eluted with a hexane EtOAc gradient with little separation of the other diastereomers.

Reaction of 1 with KCN in the Presence of α-Cyclodextrin. A mixture of **1** (0.11 g, 0.50 mmol), KCN (0.20 g, 3.0 mmol), and α-CD (0.50 g) in acetonitrile:water (3.0 mL each) was stirred at 15−20 °C for 2 days. The solution was extracted with EtOAc. The extract was concentrated to a solid (0.12 g, 95%), which was shown to be a 1:1 mixture of **1** and **3a**. The solid was washed with hexane to remove **1** (60 mg, recovered yield 45%). The remainder was almost pure **3a** in a yield of 60 mg (50%).

Dominant Diastereomer 3a, [6*R,7*R**,10*S**]-(2*E*)-6,10-Dicyanohumulan-2-en-8-one**: yield 1.20 g, 37%; mp. 160−161 °C; IR (KBr) 2233, 1726 cm^{-1}; ^{1}H NMR: δ 1.16 (s, 3H, CH_3 at C11), 1.22 (d, 3H, J = 7.0 Hz, CH_3 at C7), 1.27 (s, 3H, CH_3 at C11), 1.44 (s, 3H, CH_3 at C3), 1.84−1.91 (m, 3H, H at C4 and 5), 2.12−2.21 (dd, 2H, J = 10.6 and 14.9 Hz, H at C1 and 4), 2.49 (dd, 1H, J = 3.2 and 19.4 Hz, H at C9), 2.83−2.86 (m, 2H, H at C6 and 7), 3.25 (dd, 1H, J = 3.0 and 4.6 Hz, H at C10), 3.38 (dd, 1H, J = 5.1 and 19.4 Hz, H at C9), 5.12 (dd, 1H, J = 4.0 and 10.5 Hz, H at C2); NOE 4.6% between protons at C6 and C7; ^{13}C NMR: δ 11.0 (CH_3 at C7), 16.2 (CH_3 at C3), 21.4 (CH_3 at C11), 24.4 (C5), 31.9 (CH_3 at C11), 33.2 (C7), 33.3 (C10), 35.8 (C11), 39.0 (C4), 40.9 (C9), 41.3 (C1), 45.8 (C6), 121.4 (CN at C6), 121.6 (CN at C10), 122.1 (C2), 135.9 (C3), 202.0 (C8); HRMS m/z calcd mass for $C_{17}H_{24}N_2O$ 272.18885, found 272.1889. Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 75.10; H, 9.02; N, 10.31.

Crystallographic Studies of 3a. A colorless prismatic crystal, crystal size 0.20 × 0.18 × 0.70 mm, monoclinic, space group $P2_1/c$ (no. 14), a = 14.488(3), b = 6.170(2), c = 18.844(3) Å, b = 109.93(1) °, V = 1583.6(7) Å^3, Z = 4, D_c = 1.142 g/cm^3, μ(Cu Kα) = 5.55 cm^{-1} was used for data collection. The intensity data were measured on a Rigaku AFC7R diffractometer using Cu−Kα radiation at a temperature of 21 °C by a $\omega-2\theta$ scan technique. The structure was solved by direct methods (SIR92)[10] and expanded using Fourier techniques (DIRDIF94).[11] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 1966 observed reflections ($I > 1.50\sigma(I)$) and 278 variable parameters and gave R = 0.054 and Rw = 0.092. The value of the goodness of fit indicator was 1.09.

Reaction of 3a with KCN. A mixture of **3a** (100 mg, 0.36 mmol) and KCN (20 mg, 0.30 mmol) in acetonitrile:water solution (2 and 1 mL, respectively) was stirred at 35−40 °C for 6 days. The solution was concentrated to dryness and then extracted with $CDCl_3$. Finally, the extract was submitted for NMR analysis. ^{1}H and ^{13}C NMR showed a diastereomer mixture of **3a**−**d** in a ratio of 5.0:3.2:0.8:0.5.

Reaction of 3a with ^{13}C-Labeled Sodium Cyanide. The same reaction was conducted with ^{13}C-labeled sodium cyanide (Na^{13}CN, 95% enrichment). ^{1}H and ^{13}C NMR spectra showed a diastereomeric mixture of **3a**−**d**, which was almost the same observed as above, and no isotopomers were enriched with ^{13}C.

Reaction of 1 with Methanol in the Presence of Potassium *tert*-Butoxide. 1 (0.22 g, 1.0 mmol) was stirred in methanol (15 mL) with a trace amount of potassium *tert*-butoxide at 10−15 °C for 15 h. At this stage, ^{1}H NMR of the solution showed a mixture of **1** and methanol adduct **4a** in a ratio of 4:6. The solution was fractionated between hexane and water. The organic layer was concentrated and chromato-

(11) Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M.; The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.

graphed on silica gel (Si-60) using hexane to separate **4a** in a yield of 0.12 g (50%). A longer reaction time afforded a diastereomeric mixture of **4a** and **4b**.

Reaction of 1 with Methanol in the Presence of BF_3 Etherate. The same mixture as above was treated with BF_3 etherate instead of potassium *tert*-butoxide. ^{1}H NMR of the solution showed a 1:1 mixture of **1** and methanol adduct **4a**. The solution was treated by the procedure above to separate **4a** in a yield of 80 mg (45%).

MeOH Adduct 4a as Dominant Isomer. (2*E*,9*E*)-6-Methoxy-2,9-humuradien-8-one: IR (neat) 1693, 1627 cm^{-1}; ^{1}H NMR: δ 0.96 (d, 3H, J = 6.6 Hz, CH_3 at C7), 1.00−1.11 (m, 1H, H at C5), 1.15 (s, 3H, CH_3 at C11), 1.19 (s, 3H, CH_3 at C11), 1.29−1.33 (m, 1H, H at C5), 1.37 (s, 3H, CH_3 at C3), 1.83−1.92 (m, 2H, H at C1 and 4), 2.07 (dd, 1H, J = 6.0 and 7.0 Hz, H at C1), 2.22 (t, 1H, J = 12.4 Hz, H at C4), 3.04−3.07 (m, 1H, H at C7), 3.41 (s, 3H, OCH_3 at C6), 3.65−3.68 (m, 1H, H at C6), 5.07 (dd, 1H, J = 4.6 and 6.9 Hz, H at C2), 6.04 (d, 1H, J = 16.2 Hz, H at C9), 6.18 (d, 1H, J = 16.2 Hz, H at C10); NOE 4.6% between protons at C6 and C7; ^{13}C NMR: δ 6.1 (CH_3 at C7), 16.2 (CH_3 at C3), 22.9 (CH_3 at C11), 28.1 (C5), 28.9 (CH_3 at C11), 38.5 (C4), 39.9 (C11), 41.2 (C1), 49.2 (C7), 56.8 (OCH_3 at C6), 82.2 (C6), 121.8 (C2), 127.9 (C9), 138.1 (C3), 151.4 (C10), 200.7 (C8); HRMS *m*/*z* calcd mass for $C_{16}H_{26}O_2$ 250.1931, found 250.1929.

Reaction of 4a with KCN. A mixture of **4a** (50 mg, 0.20 mmol) and KCN (35 mg, 0.50 mmol) in acetonitrile and water (1.0 and 0.5 mL, respectively) was stirred at 10−15 °C for 20 h. The product was a mixture of **3a**−**d** in a ratio of 4.2:3.7:1.4:0.9, which was almost the same ratio obtained in the reaction of **1** with KCN.

Reaction of 1 with Bromine. Bromine (0.75 g, 4.7 mmol) in CCl_4 (10 mL) was added dropwise at −15 to −10 °C to a stirred solution of **1** (1.0 g, 4.6 mmol) in toluene (5 mL). The final addition of bromine was titrated by measuring the presence of unsaturated C6 proton in **1** by ^{1}H NMR. The solution was concentrated under reduced pressure to yield crystalline dibromide **5a**,**b** (1.65 g, 95%) in a diastereomer ratio of 9.2: 0.8 by ^{1}H NMR. The dominant isomer **5a** was recrystallized from EtOAc:hexane in a yield 1.4 g (85%), and the minor isomer **5b** (0.1 g, 5%) was separated by silica gel (Si-60) chromatography, eluting with a hexane:EtOAc gradient.

Dominant Isomer 5a. (2*E*,9*E*)-6,7-Dibromo-2,9-humuradien-8-one: mp 99.0−99.5 °C; IR (KBr) 1695, 1629 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.18 (s, 3H, CH_3 at C11), 1.24 (s, 3H, CH_3 at C11), 1.29 (dd, 1H, J = 10.0 and 15.1 Hz, H at C1), 1.41 (s, 3H, CH_3 at C3), 1.84 (s, 3H, CH_3 at C7), 1.80−1.94 (m, 2H, H at C4 and 5), 2.10−2.25 (m, 3H, H at C1, 4, and 5), 4.34 (d, 1H, J = 7.0 Hz, H at C6), 5.09 (dd, 1H, J = 4.8 and 11.6 Hz, H at C2), 6.32 (d, 1H, J = 16.2 Hz, H at C10), 6.62(d, J = 16.2 Hz, 1H, H at C9); ^{13}C NMR (DMSO-d_6): δ 17.2 (CH_3 at C3), 20.9 (CH_3 at C7), 23.6 (CH_3 at C11), 29.4 (CH_3 at C11), 35.3 (C1), 37.5 (C4), 40.1 (C11), 40.8 (C5), 61.3 (C6), 71.4 (C7), 122.8 (C2), 125.3 (C9), 137.3 (C3), 155.3 (C10), 191.9 (C8); HRMS *m*/*z* calcd mass for $M^+ - {}^{81}Br$, $C_{15}H_{22}O^{81}Br$ 299.0880, found 299.0844. Anal. Calcd for $C_{15}H_{22}OBr_2$: C, 47.64; H, 5.86. Found: C, 47.42; H, 5.88.

Minor Isomer 5b. (2*E*,9*E*)-6,7-Dibromo-2,9-humuradien-8-one: mp 99.5−100.5 °C; IR (KBr) 1701, 1620 cm^{-1}; ^{1}H NMR: δ 1.18 (s, 3H, CH_3 at C11), 1,25 (s, 3H, CH_3 at C11), 1.44 (s, 3H, CH_3 at C3), 1.54 (dd, 1H, J = 10.8 and 16.2 Hz, H at C1), 1.85−2.05 (m, 2H, H at C4 and 4), 2.06 (s, 3H, CH_3 at C7), 2.15−2.30 (m, 3H, H at C1, 4 and 5), 4.19 (d, 1H, J = 7.3 Hz, H at C6), 5.06 (dd, 1H, J = 4.8 and 11.6 Hz, H at C2), 6.10 (d, 1H, J = 15.9 Hz, H at C10), 6.41 (d, 1H, J = 15.9 Hz, H at C9); NOE 2.4% between protons at C6 and at CH_3 at C7; ^{13}C NMR: δ 17.0 (CH_3 at C3, 23.2 (CH_3 at C7), 28.9 (CH_3 at C11), 31.0 (CH_3 at C11), 36.7 (C1), 38.1 (C4), 40.3 (C11), 41.0 (C5), 60.9 (C6), 79.5 (C7), 122.0 (C2), 122.4 (C9),138.0 (C3), 156.0 (C10), 190.9 (C8); HRMS *m*/*z* calcd mass for $C_{15}H_{22}O$-$^{81}Br_2$ 379.9960, found 379.9996. Anal. Calcd for $C_{15}H_{22}OBr_2$: C, 47.64; H, 5.86. Found: C, 47.36; H, 5.88.

Reaction of 5 with KCN in the Presence of α-CD. A solution of diastereomer mixture of **5a**,**b** (1.9 g, 5.0 mmol), KCN (0.75 g, 1.2 mmol), and α-CD (1.5 g) in acetonitrile and water (40 and 20 mL, respectively) was stirred for 12 h at 10−15 °C. The alkaline solution was extracted with EtOAc (10 mL × 2 times). The water layer was acidified with HCl and extracted with EtOAc (10 mL × 3 times). The organic layer was concentrated to a crystalline residue (1.30 g), which was recrystallized from EtOAc:hexane to yield dominant diastereomer **6a** (0.56 g). The mother liquor was chromatographed on silica gel to separate additional **6a** (0.28 g) and minor diastereomer **6b** (0.21 g), in a total yield of 1.1 g, 80%.

Dominant Isomer 6a. [1*R,2*S**,9*R**,10*S**]-Bicyclo[7.1.-0]-2-cyano-3,3,6,10-tetramethyl-(5*E*)-decene-1-carboxylic acid**: yield 63% based on **5**; mp > 210 °C; IR (KBr) 3200−2500 (b), 2230, 1681 cm^{-1}; ^{1}H NMR: δ 0.90 (qq, 1H, J = 12.5 Hz, H at C7), 1.23 (s, 3H, CH_3 at C3), 1.26 (s, 3H, CH_3 at C10), 1.29 (s, 3H, CH_3 at C3), 1.50 (ddd, 1H, J = 4.0, 9.5 and 12.5 Hz, H at C9), 1.66 (s, 3H, CH_3 at C6), 1.78 (d, 1H, J = 10.5 Hz, H at C2), 1.91 (t, 1H, J = 10.0 Hz, H at C1), 1.99−2.04 (m, 2H, H at C4 and 7), 2.08 (t, 1H, J = 12.0 Hz, H at C8), 2.17 (dd, 1H, J = 4.0 and 11.5 Hz, H at C8), 2.25 (t, 1H, J = 13 Hz, H at C4), 5.26 (bdd, 1H, J = 1.5 and 12.5 Hz, H at C5); ^{13}C NMR: δ 9.8 (CH_3 at C10), 16.7 (CH_3 at C3), 23.5 (C7), 23.6 (C10), 24.5 (CH_3 at C3), 31.1 (C1), 32.7 (overlapped, CH_3 at C3, C9), 36.7 (C2), 37,8 (C8), 38.2 (C3), 41.3(C4), 120.9 (CN at C2), 122.1 (C5), 134.4 (C6), 182.4 (COOH at C10). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.15; H, 9.08; N, 5.38.

Crystallographic Studies of 6a. A colorless prismatic crystal, crystal size 0.30 × 0.20 × 0.08 mm, orthorhombic, space group *Pbca* (no.61), a = 31.20(1), b = 11.01(2), c = 8.828-(8) Å, V = 3031(7) Å^3, Z = 8, D_c = 1.145 g/cm^3, μ(Cu Kα) = 5.91 cm^{-1} was used for data collection. The intensity data were measured on a Rigaku AFC7R diffractometer using Cu−Kα radiation at a temperature of 20 °C by a ω−2θ scan technique. The structure was solved by direct methods (SHELXS86)[12] and expanded using Fourier techniques (DIRDIF92).[13] All the calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 978 observed reflections (I > 1.50σ-(I)) and 173 variable parameters and gave R = 0.098 and Rw = 0.098. The value of the goodness of fit indicator was 1.55.

Minor Isomer 6b. [1*R,2*S**,9*R**,10*R**]-Bicyclo[7.1.0]-2-cyano-3,3,6,10-tetramethyl-(5*E*)-decene-1-carboxylic acid**: yield 16% based on **5**, recrystallized from EtOAc, mp 190−191 °C; IR (KBr) 3200−2500 (b), 2230, 1681 cm^{-1}; ^{1}H NMR: δ 1.18 (s, 3H, CH_3 at C3), 1.23−1.43 (m, 1H, H at C9), 1.30 (s, 3H, CH_3 at C3), 1.35−1.39 (dd, 1H, J = 6.0 and 12.0 Hz, H at C1), 1.45 (s, 3H, CH_3 at C10), 1.59−1.68 (m, 1H, H at C8), 1.68 (s, 3H, CH_3 at C6), 1.90−2.00 (m, 3H, H at C4, 7 and 8), 2.27−2.22 (qd, 1H, J = 12.5 Hz, H at C7), 2.25 (t, 1H, J = 13.0 Hz, H at C 4), 2.45 (d, 1H, J = 10.0 Hz, H at C2), 5.10 (dd, 1H, J = 1.9 and 12.5 Hz, H at C5); ^{13}C NMR: δ 16.7 (CH_3 at C6), 21.9 (C8), 23.3 (CH_3 at C10)), 24.1 (CH_3 at C3), 25.3 (C10), 32.7 (CH_3 at C3), 36.1 (C1), 36.7 (C3), 37.4 (C2), 38.6 (C9), 38.7 (C7), 41.4 (C4), 121.3 (CN at C2), 121.7 (C5), 135.3 (C6), 178.1 (COOH at C10).

Crystallographic Studies of 6b. A colorless prismatic crystal, crystal size 0.22 × 0.20 × 0.62 mm, monoclinic, space group $P2_1/c$ (no. 14), a = 6.532(2), b = 14.889(2), c = 15.723(2) Å, b = 98.41(2)°, V = 1512.6(5) Å^3, Z = 4, D_c = 1.148 g/cm^3, μ(Cu Kα) = 5.92 cm^{-1} was used for data collection. The intensity data were measured on a Rigaku AFC7R diffractometer using Cu−Kα radiation at a temperature of 21 °C by a ω−2θ scan technique. The structure was solved by direct methods (SIR92)[10] and expanded using Fourier techniques (DIRDIF94).[11] All calculations were performed using the teXsan crystallographic software package. The final cycle of

(12) Sheldrick, G. M. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: Oxford, UK, 1985; pp 175−189.

(13) Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. The DIRDIF program system, Technical Report of the Crystallography Laboratory; University of Nijmegen: The Netherlands, 1992.

full-matrix least-squares refinement was based on 1501 observed reflections ($I > 3.00\sigma(I)$) and 212 variable parameters and gave $R = 0.062$ and $Rw = 0.094$. The value of the goodness of fit indicator was 1.26.

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Supporting Information Available: X-ray experimental details for **3a**, **6a**, and **6b** tables of crystallographic data, atomic coordinates, anisotropic thermal parameters, bond lengths and angles, and torsion angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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